



US 20080091249A1

(19) United States

(12) Patent Application Publication

Wang

(10) Pub. No.: US 2008/0091249 A1

(43) Pub. Date: Apr. 17, 2008

(54) PHOTOBIMODULATION APPARATUS
WITH ENHANCED PERFORMANCE AND
SAFETY FEATURES

(75) Inventor: Sean Xiaolu Wang, Wilmington,
DE (US)

Correspondence Address:
BWT PROPERTY, INC.
19 SHEA WAY, SUITE 301
NEWARK, DE 19713

(73) Assignee: **BWT PROPERTY, INC.**,
Newark, DE (US)

(21) Appl. No.: 11/869,222

(22) Filed: Oct. 9, 2007

Related U.S. Application Data

(60) Provisional application No. 60/828,982, filed on Oct.
11, 2006.

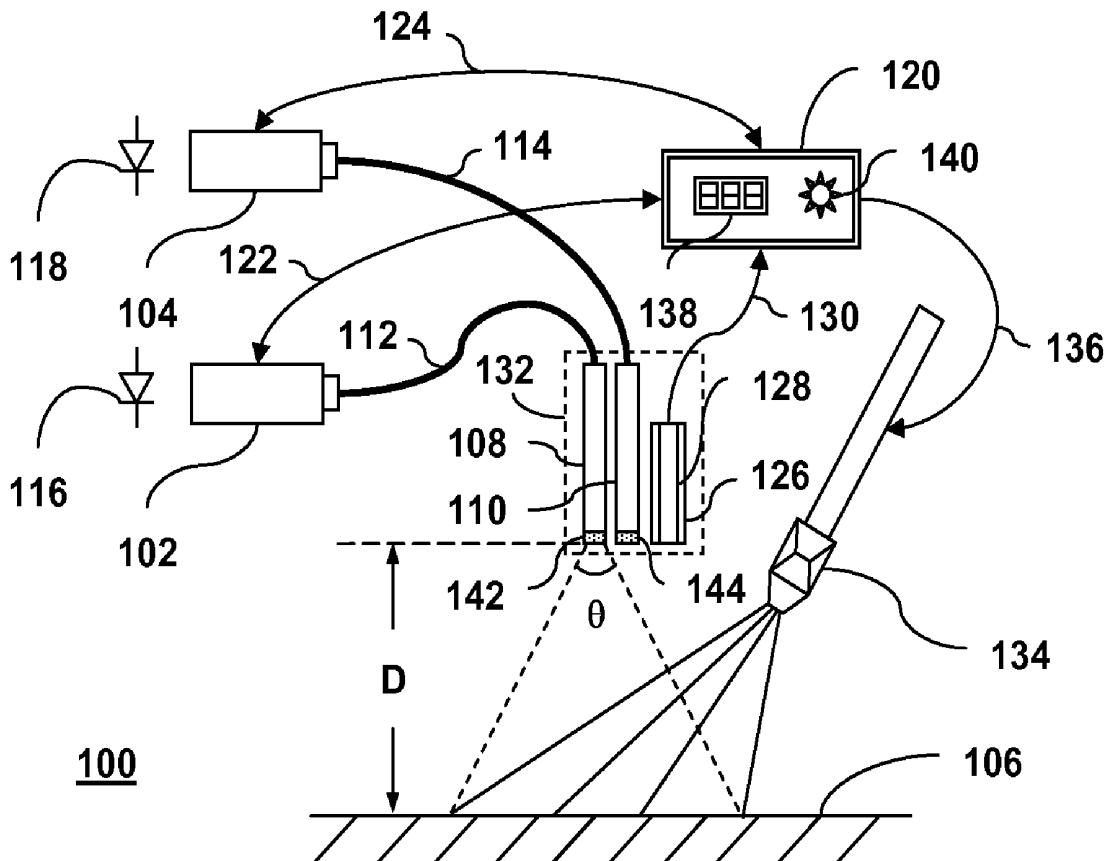
Publication Classification

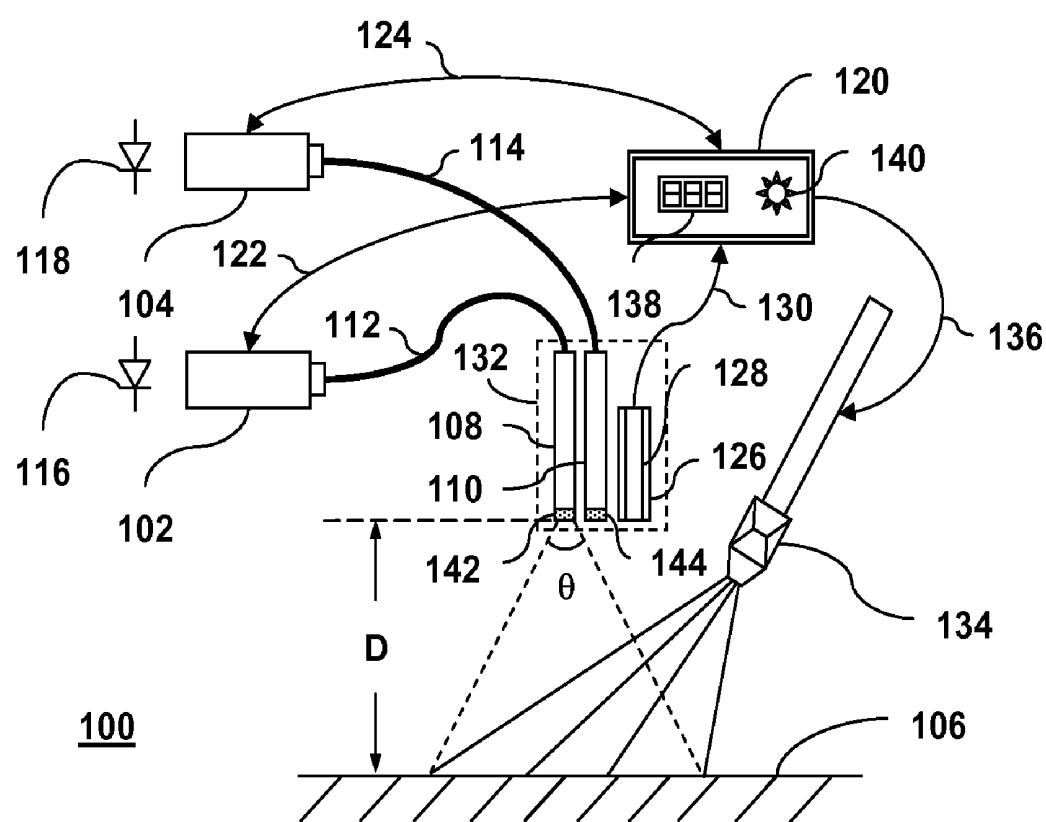
(51) Int. Cl.
A61B 18/18 (2006.01)

(52) U.S. Cl. 607/88

ABSTRACT

A photobiomodulation apparatus providing precise light intensity, light dosage, and tissue temperature control so as to enhance the safety of the photobiomodulation treatment process and improve the comfort level of the patient.



**FIG. 1**

PHOTOBIMODULATION APPARATUS WITH ENHANCED PERFORMANCE AND SAFETY FEATURES

REFERENCE TO RELATED APPLICATIONS

[0001] This application claims an invention which was disclosed in Provisional Patent Application No. 60/828,982, filed Oct. 11, 2006, entitled "Photobiomodulation Apparatus with Enhanced Performance and Safety Features." The benefit under 35 USC §119(e) of the above mentioned United States Provisional Applications is hereby claimed, and the aforementioned applications are hereby incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates generally to a photobiomodulation apparatus and more specifically to a photobiomodulation apparatus with enhanced performance and safety features.

BACKGROUND

[0003] Photobiomodulation or photobiostimulation relates to treatment of living tissue with certain wavelength of light to aid tissue regeneration, resolve inflammation, relieve pain, and boost the immune system. Clinical applications include soft tissue injuries, chronic pain, wound healing, nerve regeneration, and possibly even resolving viral and bacterial infections.

[0004] Photobiomodulation is generally performed with a laser light source. Depending on the area of the treatment site, the power of the laser may range from several milliwatts to tens of watts. The involvement of high power lasers place a safety issue as high light intensity may cause overheating, denaturizing, or even carbonization of the tissue. Here light intensity is defined as the total laser power divided by the area of the treatment site. For photobiomodulation applications, where the treatment site is relatively large, it is actually the light intensity that sets the tissue damage threshold.

[0005] In PCT patent application No. WO 01/78830, Casey et al. discloses a photobiomodulation treatment apparatus that incorporates a thermo-graphic device, such as an infrared camera to detect infrared radiation emitted by the targeted tissue and produce a thermograph. The thermograph is used to control the laser output energy to impart precisely controlled light dosage to the targeted tissue. The Casey patent application fails to teach a method for light intensity control.

[0006] In U.S. patent application No. 2004/0162596, Altshuler et al. discloses a method for modulating the efficacy of photobiomodulation by controlling the temperature in the targeted region and/or its surrounding volume. The method comprises the steps of measuring the temperature of the targeted region and modifying the heat delivered to or extracted from the targeted region to keep its temperature within a pre-defined threshold. The method does not comprise any step for light intensity control.

[0007] In U.S. Pat. No. 6,475,211, Chess et al. discloses a method and apparatus for treatment of biologic tissue with simultaneous radiation and temperature modification. The temperature modification, which is performed by a vortex tube, helps to reduce pain and other side effects caused by

the light radiation. The Chess patent does not provide any clue for controlling the intensity of the radiation light source.

[0008] There thus exists a need in the art for a photobiomodulation apparatus with precise light intensity, dosage, and tissue temperature control so as to enhance the performance as well as safety of the treatment process and improve the comfort level of the patient.

SUMMARY OF THE INVENTION

[0009] According to one aspect of the present invention, there is provided a plurality of sensor elements in the photobiomodulation apparatus to monitor the treatment process. Such sensor elements include photo detectors to monitor the power of the lasers, distance measurement devices to monitor the distance between the laser output port and the treatment site, as well as remote temperature sensors to monitor the temperature of the treatment site.

[0010] According to another aspect of the present invention, there is provided a temperature modulation unit in the photobiomodulation apparatus to control the temperature of the targeted tissue during the treatment process.

[0011] According to yet another aspect of the present invention, there is provided at least two laser units in the photobiomodulation apparatus. The two laser units have different output powers and beam divergence angles to treat targeted tissue with different areas. Yet in another possible configuration, the two laser units have different output wavelengths, resulting in different absorption coefficient and penetration depth in the targeted tissue. The light dosage at different depth of the tissue can thus be controlled by controlling the light intensity of each laser unit.

[0012] According to yet another aspect of the present invention, there is provided a control unit in the photobiomodulation apparatus. The control unit can respond to the sensor signal produced by the sensor elements, control the status of the laser units and the temperature modulation unit, as well as send alarm signal to the operator of the photobiomodulation apparatus in case the light intensity or the tissue temperature exceeds a pre-defined range.

BRIEF DESCRIPTION OF THE FIGURES

[0013] The accompanying figures, where like reference numerals refer to identical or functionally similar elements throughout the separate views and which together with the detailed description below are incorporated in and form part of the specification, serve to further illustrate various embodiments and to explain various principles and advantages all in accordance with the present invention.

[0014] FIG. 1 illustrates one exemplary embodiment of the photobiomodulation apparatus.

[0015] Skilled artisans will appreciate that elements in the figures are illustrated for simplicity and clarity and have not necessarily been drawn to scale. For example, the dimensions of some of the elements in the figures may be exaggerated relative to other elements to help to improve understanding of embodiments of the present invention.

DETAILED DESCRIPTION

[0016] Before describing in detail embodiments that are in accordance with the present invention, it should be observed that the embodiments reside primarily in combinations of method steps and apparatus components related to. Accordingly, the apparatus components and method steps have been

represented where appropriate by conventional symbols in the drawings, showing only those specific details that are pertinent to understanding the embodiments of the present invention so as not to obscure the disclosure with details that will be readily apparent to those of ordinary skill in the art having the benefit of the description herein.

[0017] In this document, relational terms such as first and second, top and bottom, and the like may be used solely to distinguish one entity or action from another entity or action without necessarily requiring or implying any actual such relationship or order between such entities or actions. The terms "comprises," "comprising," or any other variation thereof, are intended to cover a non-exclusive inclusion, such that a process, method, article, or apparatus that comprises a list of elements does not include only those elements but may include other elements not expressly listed or inherent to such process, method, article, or apparatus. An element proceeded by "comprises . . . a" does not, without more constraints, preclude the existence of additional identical elements in the process, method, article, or apparatus that comprises the element.

[0018] FIG. 1 illustrates one exemplary embodiment of the present invention. The photobiomodulation apparatus 100 comprises two laser units 102 and 104. The laser unit 102 has a relatively high output power level of several watts to several tens of watts. The laser unit 104 has a relatively low output power level of several milliwatts to several hundreds of milliwatts. The types of the lasers used may include but are not limited to diode lasers, fiber lasers, solid state lasers, and gas lasers. The output wavelength of the laser units may range from ultraviolet, visible to near infrared or even mid-infrared. The light of the two laser units 102 and 104 is delivered to the targeted tissue 106 through individual output wands 108 and 110, respectively. The wands 108 and 110 may have different numerical apertures for laser beam divergence angle control. For example, the wand 108 associated with the high power laser unit 102 may have a relatively larger numerical aperture so that the corresponding laser beam have a larger divergence angle (θ) to cover a large-area treatment site. Meanwhile, the wand 110 associated with the low power laser unit 104 may have a relatively smaller numerical aperture so that the corresponding laser beam can be utilized to treat small-area tissue. This double-laser design avoids the safety problem when a high power laser is used to treat a small-area target, in which case the light intensity of the laser beam has a chance to exceed the safety level. The two laser units 102 and 104 are connected with their output wands 108 and 110 through optical fibers (or other forms of optical waveguides) 112 and 114, respectively. In case where the two output wands 108 and 110 are designed as detachable elements, a wand identification mechanism such as those disclosed by Kelsoe et al. in U.S. Pat. No. 5,085,492 may be introduced to prevent wand misconnection. In this exemplary embodiment, two photo detectors 116 and 118 are used to measure the output power (P) of the corresponding laser units 102 and 104 and the measured power level is sent to a central control unit 120 through electrical connections 122 and 124, respectively. The central control unit 120 can control the on/off status, drive current (or power level) of the two laser units 102 and 104 through the same electrical connections 122 and 124.

[0019] The photobiomodulation apparatus 100 further comprises a distance measurement unit 126 and a remote

temperature sensor 128. The distance measurement unit 126 can be a simple caliper, or more preferably a laser or ultrasound distance measurement device, which measures the distance (D) between the output port of the wand 108 and 110 to the targeted tissue 106. The measured distance data are sent to the central control unit 120 through an electrical connection 130. The size (A) of the laser beam on the targeted tissue can be calculated as:

$$A = \pi \cdot (D \cdot \tan(\theta/2))^2$$

where D is the measured distance value, and θ is the divergence angle of the laser beam set by the numerical aperture of the output wand 108 and 110. Thus the light intensity (I) of the laser beam can be determined as:

$$I = P/A$$

where P is the output power of the laser units 102 and 104 measured by the photo detectors 116 and 118. The obtained light intensity can be displayed to the operator by a display unit 138 on the central control unit 120. The light dosage, which is a product of the light intensity (I) and the duration time (T) of treatment process, can be automatically controlled by the central control unit 120 or be manually controlled by the operator. In case the light intensity exceeds a safety level or is beyond a predefined optimum range for photobiomodulation, the central control unit 120 may send a warning signal to the operator through an indicator 140. The operator can thus correct the light intensity by adjusting the power of the laser units 102, 104 and/or the distance between the wand 108, 110 and the targeted tissue 106. When the light intensity exceeds above a pre-defined safety level, the central control unit 120 may automatically shut down the laser units 102 and 104.

[0020] The remote temperature sensor 128 is preferably an infrared thermometer, which is capable of measuring the average tissue temperature for the treatment site. The accuracy for the temperature sensor 128 is preferably better than 1 degree Celsius ($^{\circ}$ C.). The measured temperature data are also sent to the central control unit 120 through the electrical connection 130. When the tissue temperature exceeds a pre-defined range, a warning message is generated by the indicator 140. The central control unit 120 may shut down the laser units 102 and 104 in case the tissue temperature is too high. In this exemplary embodiment, the output wands 108, 110, the distance measurement unit 126, and the temperature sensor 128 may be integrated together to form a common output port 132 for ease of operation. To further enhance the uniformity of the laser beam, optical diffusers 142, 144 may be attached in front of the output wands 108, 110 to homogenize the laser beam.

[0021] The photobiomodulation apparatus 100 further comprises a temperature modulation unit 134 to control the temperature of the targeted tissue 106. The temperature modulation unit 134 can be a dynamic cooling device as disclosed by Nelson et al. in U.S. Pat. No. 5,814,040 or a vortex tube as disclosed by Chess et al. in U.S. Pat. No. 6,475,211, both are hereby incorporated by reference. When a high intensity laser is used in the photobiomodulation process to produce high penetration depth into the tissue, the surface temperature of the tissue may exceed a safety level due to excessive heat generation. In this case, the temperature modulation unit 134 may deliver cold material to the treatment site to keep the tissue temperature below the safety level. The central control unit 120 can control the heat extraction rate of the temperature modulation unit 134

through an electrical connection 136 based on the measured light intensity on the tissue 106 and the tissue temperature measured by the remote temperature sensor 128. In another case, the temperature control unit 134 may also deliver warm material to the treatment site to modulate the efficacy of photobiomodulation.

[0022] In a slight variation of the present embodiment, the photobiomodulation apparatus comprises a plurality of laser units with different output wavelengths. The light of the plurality of laser units may be applied simultaneously or alternatively on the targeted tissue. Since the absorption rate and penetration depth of the laser light is mainly determined by its wavelength, the light dosage at different depth of the tissue can thus be controlled by controlling the light intensity of each laser unit. For example, the laser light with high penetration depth and low penetration depth may be applied alternatively or be mixed in certain ratio on the target tissue so that more even treatment effects can be obtained for different depth of the tissue than in the case where only one laser wavelength is used. As another advantage, the multiple-wavelength operation mode avoids the heat accumulation problem at a specific depth of the tissue where the light absorption rate has the maximum value at one laser wavelength.

[0023] In another variation of the present embodiment, the output power of the laser units may be modulated to produce a pulsed light output. The light intensity of the laser units can thus be controlled by varying the duty cycle of the power modulation to keep the average light intensity as well as the temperature of the targeted tissue below a safety threshold.

[0024] In yet another variation of the present embodiment, the photobiomodulation apparatus further comprises another photo detector to monitor the radiation emitted by the tissue in case it is carbonized by the laser beam. The central control unit may shut down the laser units when such a radiation is detected to protect the targeted tissue.

[0025] In the foregoing specification, specific embodiments of the present invention have been described. However, one of ordinary skill in the art appreciates that various modifications and changes can be made without departing from the scope of the present invention as set forth in the claims below. For example, the laser units in the disclosed photobiomodulation apparatus may be replaced by light emitting diodes (LEDs). Accordingly, the specification and figures are to be regarded in an illustrative rather than a restrictive sense, and all such modifications are intended to be included within the scope of present invention. The benefits, advantages, solutions to problems, and any element(s) that may cause any benefit, advantage, or solution to occur or become more pronounced are not to be construed as a critical, required, or essential features or elements of any or all the claims. The invention is defined solely by the appended claims including any amendments made during the pendency of this application and all equivalents of those claims as issued.

What is claimed is:

1. An apparatus for performing photobiomodulation on a targeted tissue, the apparatus comprising:

at least one light source to produce light emission from an output port to the targeted tissue, wherein said light emission has a divergence angle set by the properties of said light source and output port;
at least one photo detector to measure the optical power of said light emission;

a distance sensor to measure the distance between the output port and the targeted tissue;

a temperature sensor to monitor the temperature of the targeted tissue;

a temperature modulation unit to control the temperature of the targeted tissue; and

a central control unit to control the status of said light source and temperature modulation unit based on the information obtained from said photo detector, distance sensor, and temperature sensor.

2. The apparatus of claim 1, wherein the central control unit measures the light intensity on the targeted tissue based on the divergence angle and optical power of the light emission along with the distance between the output port and the targeted tissue.

3. The apparatus of claim 2, wherein the central control unit controls a drive current of the light source to keep the measured light intensity within a pre-defined range.

4. The apparatus of claim 2, wherein the light source is modulated to produce a light intensity modulation, and wherein the central control unit controls a duty cycle of said intensity modulation to keep the measured average light intensity within a pre-defined range.

5. The apparatus of claim 1, wherein the central control unit controls the temperature modulation unit to keep the tissue temperature within a pre-defined range.

6. The apparatus of claim 2, wherein the central control unit sends alarm signal to an operator when the measured light intensity and/or the tissue temperature exceed a pre-defined range.

7. The apparatus of claim 2, wherein the central control unit automatically shut down the light source when the measured light intensity and/or the tissue temperature are greater than a pre-defined safety level.

8. The apparatus of claim 1, wherein the light sources comprise at least two laser units, and wherein the optical power of the two laser units can be adjusted independently during the photobiomodulation process.

9. The apparatus of claim 8, wherein one laser unit has a relatively higher optical power to treat large-area tissue and the other laser unit has a relatively smaller optical power to treat small-area tissue.

10. The apparatus of claim 8, wherein the two laser units have different output wavelengths to treat tissue at different depth.

11. The apparatus of claim 1, further comprising a photo detector to monitor the radiation emitted by the targeted tissue in case it is carbonized by the light emission produced by the light source, and wherein the central control unit automatically shut down the light source when said radiation is detected.

12. A method for performing photobiomodulation on a targeted tissue, the method comprising the steps of:

providing at least one light source to produce light emission;

delivering said light emission from an output port to the targeted tissue;

monitoring the light intensity on the targeted tissue by measuring the optical power of the light emission and the distance between the output port and the targeted tissue;

controlling the light intensity on the targeted tissue to
keep it within a pre-defined range;
providing a temperature sensor to monitor the temperature
of the targeted tissue;

controlling the temperature of the targeted tissue to keep
it within a pre-defined range.

* * * * *

WO 2009/121158 A2

(12) PEDIDO INTERNACIONAL PUBLICADO SOB O TRATADO DE COOPERAÇÃO EM MATÉRIA DE PATENTES (PCT)

(19) Organização Mundial da Propriedade Intelectual

Secretaria Internacional

(43) Data de Publicação Internacional
8 de Outubro de 2009 (08.10.2009)

PCT

(10) Número de Publicação Internacional

WO 2009/121158 A2

(51) Classificação Internacional de Patentes :
A61N 5/06 (2006.01)Castelo de Windsor nº475-Apto 302, Bairro Castelo, 31330-180 Belo Horizonte - Minas Gerais (BR). **DEL-VECCCHIO, Sara** [BR/BR]; Rua João Hallak nº306, Bairro Matozinhos, 36305-024 São João Del Rey - Minas Gerais (BR). **FERRARI SANTOS CORRÊA, Maurício** [BR/BR]; Rua Marte, nº101 - Apto 104, Bairro Jardim Riacho das Pedras, 32241-250 Contagem - Minas Gerais (BR). **DE BARROS SILVEIRA, Lívio** [US/US]; Rua Paulo Piedade Campos, nº703 - Apto 201, Bairro Estoril, 30455-250 Belo Horizonte - Minas Gerais (US). **GONÇALVES TEIXEIRA, Alexandre** [BR/BR]; Rua Castelo de Windsor nº475 - Apto 302, Bairro Castelo, 31330-180 Belo Horizonte - Minas Gerais (BR). **PINOTTI BARBOSA, Marcos** [BR/BR]; Rua Ramalhete nº 55- Apto 201, Bairro Anchieta, 30310-310 Belo Horizonte - Minas Gerais (BR).(21) Número do Pedido Internacional :
PCT/BR2009/000100(22) Data do Depósito Internacional :
1 de Abril de 2009 (01.04.2009)

(25) Língua de Depósito Internacional : Português

(26) Língua de Publicação : Português

(30) Dados Relativos à Prioridade :
PI0801418-3 1 de Abril de 2008 (01.04.2008) BR
014090001516 30 de Março de 2009 (30.03.2009) BR(74) Mandatário : **CORREA CREPALDE MEDEIROS, Juliana**; UNIVERSIDADE FEDERAL DE MINAS GERAIS - UFMG [BR/BR]; Av. Antônio Carlos, 6627, Reitoria - 7º Andar, Sala 7005, Campus UFMG - Pampulha, 31270-901 Belo Horizonte - Minas Gerais (BR).(71) Requerente (para todos os Estados designados, exceto US) : **UNIVERSIDADE FEDERAL DE MINAS GERAIS - UFMG** [BR/BR]; Av. Antônio Carlos, 6627, Reitoria - 7º Andar, Sala 7005, Campus UFMG - Pampulha, 31270-901 Belo Horizonte - Minas Gerais (BR).

(72) Inventores; e

(75) Inventores/Requerentes (para US únicamente) :
RODRIGUES DE ARAÚJO, Angélica [BR/BR]; Rua

(81) Estados Designados (sem indicação contrária, para todos os tipos de proteção nacional existentes) : AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW,

(Continua na página seguinte)

(54) Title : PHOTOBIMODULATION APPARATUS FOR PREVENTING AND TREATING MAMMARY TRAUMA AND NON-INFECTIOUS TEAT INJURIES

(54) Título : DISPOSITIVO FOTOBIMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECIOSAS DOS TETOS

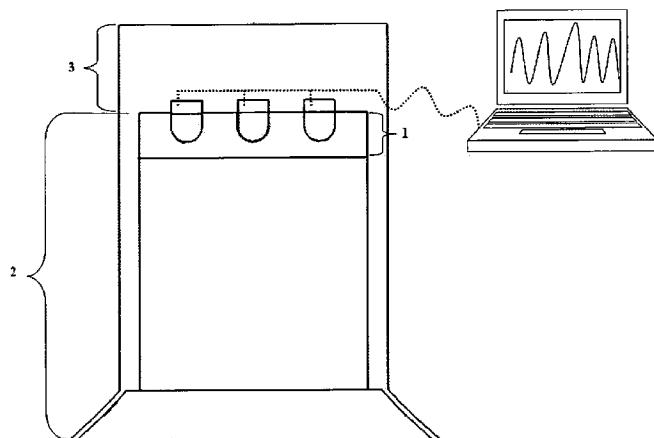


Figura 1

(57) Abstract : The present invention relates to a device that makes use of photobiostimulation principles for treating mammary traumas (fissures and cracks) in clinical and household environments, with the aim of helping tissue cicatrization of noninfected mammary injuries as well as minimizing sequels (pain and hindrances to breastfeeding) arising in such circumstances. This device can also be used in veterinary medicine for preventing and treating teat injuries, as a way to prevent traumatic teat lesions resulting from the (manual or mechanical) milking process, and for treating noninfectious teat injuries, in this way minimizing the sequels thereof (pain, compromised milking process, reduced milk production, changes in the physico-chemical composition and quality of the milk, as well as costs and economic losses).

(57) Resumo :

(Continua na página seguinte)



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, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

- (84) **Estados Designados** (*sem indicação contrária, para todos os tipos de proteção regional existentes*) : ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ,

UG, ZM, ZW), Eurasiático (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europeu (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publicado:

- *sem relatório de pesquisa internacional; será republicado após receção do mesmo (Regra 48.2(g))*

A presente patente de invenção apresenta um dispositivo que utiliza os princípios da fotobioestimulação, para o tratamento de traumas mamilares (fissuras e rachaduras), para uso em ambientes clínico e domiciliar, com o objetivo de auxiliar o processo de cicatrização tecidual de lesões mamilares não infectadas e minimizar as seqüelas (dor e impedimento a prática da amamentação) decorrentes destas condições. Este dispositivo pode ser utilizado também em medicina veterinária, para prevenção e tratamento de lesões dos tetos, com a função de prevenir lesões traumáticas dos tetos consequentes do processo de ordenha (manual ou mecânica) e tratar lesões não-infectadas dos tetos, minimizando as seqüelas decorrentes destas condições (dor, comprometimento do processo de ordenha, redução da produção leiteira, modificações na composição fisico-química e na qualidade do leite bem como custos e perdas econômicas).

“DISPOSITIVO FOTOBIOMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECCIOSAS DOS TETOS”

A presente patente de invenção apresenta um dispositivo que 5 utiliza os princípios da fotobioestimulação, para o tratamento de traumas mamilares (fissuras e rachaduras), para uso em ambientes clínico e domiciliar, com o objetivo de auxiliar o processo de cicatrização tecidual de lesões mamilares não infectadas e minimizar as seqüelas (dor e impedimento à prática da amamentação) decorrentes destas condições. Este dispositivo pode ser 10 utilizado também em medicina veterinária, para prevenção e tratamento de lesões dos tetos, com a função de prevenir lesões traumáticas dos tetos consequentes do processo de ordenha (manual ou mecânica) e tratar lesões não-infectadas dos tetos, minimizando as seqüelas decorrentes destas 15 condições (dor, comprometimento do processo de ordenha, redução da produção leiteira, modificações na composição físico-química e na qualidade do leite bem como custos e perdas econômicas).

Segundo a literatura (POTTER, Women's experiences of managing mastitis, 2005), o melhor tratamento para os traumas mamilares ainda é a prevenção. Orientações de cuidados com a mama e sobre técnicas 20 adequadas para amamentação, dadas durante o período gestacional e/ou no puerpério, têm sido a principal ferramenta para se evitar o aparecimento das fissuras e rachaduras do mamilo (Ministério da Saúde, MANUAL DE PROMOÇÃO DO ALEITAMENTO MATERNO, 1997; SNOWDEN *et al.*, Treatments for breast engorgement during lactation, 2001; COTTERMAN, Reverse pressure 25 softening: a simple tool to prepare areola for easier latching during engorgement, 2004). Estas medidas, entretanto, não são, na maioria das vezes, eficazes para solucionar o problema quando este já se encontra instalado.

Com o intuito de promover a cura das fissuras e das rachaduras 30 do mamilo é comum a aplicação tópica de substâncias cicatrizantes (naturais ou químicas), o uso de modalidades físicas (compressas quentes ou frias e o ultra-som) e da acupuntura (MCLACHLAN, Ultrasound treatment for breast engorgement: a randomised double blind trial. 1991; ZIEMER *et al.*, Evaluation

of a dressing to reduce nipple pain and improve nipple skin condition in breast-feeding women, 1995; KVIST et al., Effects of acupuncture and care intervention on the outcome of inflammatory symptoms of the breast in lactating women, 2004). Os resultados destas terapias, entretanto, nem sempre são satisfatórios. Como consequência, têm-se riscos à saúde e ao bem-estar da mulher e de seu lactente. O desenvolvimento de mastite e abscessos e a dificuldade ou a interrupção da amamentação são as principais complicações decorrentes do não fechamento das lesões mamárias (ALMEIDA, Amamentação: um híbrido de natureza e cultura, 1999; BIANCUZZO, Sore nipples: prevention and problem solving, 2000). A dor nas mamas, comum nestes quadros, faz com que o ato de amamentar torne-se fonte de conflito e sofrimento materno, inviabilizando o estabelecimento de um vínculo satisfatório entre a mãe e o bebê (MASS, Breast pain: engorgement, nipple pain and mastitis, 2004).

O leite é considerado o mais nobre dos alimentos, por sua composição rica em proteína, gordura, carboidratos, sais minerais e vitaminas. Além de suas propriedades nutricionais, o leite proporciona nutrientes e proteção imunológica, a baixo custo, para o neonato e oferece elementos anticarcinogênicos, presentes na gordura, como o ácido linoléico conjugado, esfingomielina, ácido butírico, α -caroteno, vitaminas A e D (MULLER, 2002). Devido a essas características, o sistema agro-industrial do leite tem enorme importância social, sendo um dos mais importantes do país (OLIVEIRA et al., 1999).

A atividade leiteira é praticada em todo o território nacional em mais de um milhão de propriedades rurais e, somente na produção primária, gera mais de três milhões de empregos, agregando mais de seis bilhões ao valor da produção agropecuária nacional (VILELA et al., 2002).

Apesar do grande valor social e econômico agregado ao leite, os processos de desenvolvimento e consolidação da indústria de laticínios no Brasil ainda ocorrem de forma lenta. Do ponto de vista tecnológico, a qualidade da matéria prima é um dos maiores entraves a esse crescimento. Fatores zootécnicos, associados ao manejo, à alimentação, ao potencial genético dos rebanhos, e àqueles relacionados à obtenção e à armazenagem do leite têm

influenciado a qualidade do leite in natura (KITCHEN, 1981) e, consequentemente, o seu aproveitamento industrial.

Dentre estes, uma das causas extremamente prejudiciais à composição e características físico-químicas do leite, é a mastite (KITCHEN, 1981; SCHÄELIBAUM, 2000). Esta é uma das mais complexas e dispendiosas afecções que acometem os animais da indústria leiteira, devido a sua alta prevalência (estima-se que 17 a 20% da população mundial de vacas leiteiras tenham mastite em pelo menos um dos quartos do úbere) e aos prejuízos econômicos e sociais que a mesma acarreta (BRANT e FIGUEIREDO, 1994).

Os maiores prejuízos à produção de leite no mundo (redução da quantidade e comprometimento da qualidade do leite produzido ou mesmo perda total da capacidade secretora da glândula mamária) são causados por esta afecção, a qual constitui cerca de 25% do valor gerado por todas as outras doenças de importância econômica. Estimativas feitas em vários países calculam que as perdas por mastite sejam de 10 a 15% da produção total, podendo chegar em algumas regiões a 70%. Destes, 8% se deve ao descarte de leite; 8% aos medicamentos e à assistência veterinária; 14% às mortes e ao descarte do animal, o que significa também a perda de material genético (RIBEIRO *et al.*, 2003).

A mastite pode ainda comprometer a saúde pública pela veiculação de microorganismos patogênicos ao consumidor. Ao nível social, a mastite é preocupante por agravar problemas sociais como desnutrição, mortalidade infantil e fome (COSTA, s.d.-A; COSTA, s.d.-B.).

A etiologia da mastite é complexa e multivariada, o que torna necessário o desenvolvimento de programas para controle e, principalmente, prevenção da doença (HURLEY e MORIN, s.d.). Entre as principais medidas de controle estão o monitoramento dos índices de mastite, a pré e a pós imersão dos tetos em solução anti-séptica, o conforto ambiental, o tratamento dos animais ao secar, o tratamento medicamentoso dos casos clínicos, o descarte dos animais com infecções crônicas e a higiene, manejo e manutenção dos equipamentos de ordenha (CULLOR, 1983; PHILPOT & NICKERSON, 1991; NICKERSON *et al.*, 1995; NICKERSON, 1998; HILLERTON, 1996; MÜLLER,

1999; FONSECA e SANTOS, 2000). No que diz respeito à prevenção, é consenso na literatura que a manutenção da saúde e da integridade da pele do teto é o ponto chave (MICHEL et al, 1974; HAMANN, 1987; NICKERSON, 1994; NEIJENHUIS et al., 2001). Segundo O'SHEA et al. (1987) e LEWIS et 5 al.(2000), as lesões e alterações da pele, particularmente as da região do esfíncter do teto, aumentam o risco de desenvolvimento da doença por favorecerem a penetração de microorganismos patogênicos para o úbere.

Lesões das mais variadas (EDWARDS et al., 2000; HILLERTON et al, 2001; NEIJENHUIS, et al.; 2001; SANTINE and BRITO, 2004; OHNSTAD, 10 s.d) e com graus de gravidade diversos acometem as papilas mamárias, especialmente das fêmeas grandes produtoras de leite (BRISTOL, 1989; BLOOD et al., 1995) e há muitos anos vêm sendo um problema para os médicos veterinários e os produtores de leite (FARNSWORTH, s.d.).

O advento dos equipamentos para ordenha mecânica e o amplo 15 uso de substâncias para lavagem e anti-sepsia do úbere (RASMUSSEN and MADSEN, 2000) adicionaram aos convencionais problemas de lesões do teto ocasionados por pisadas/cortes em arames ou por fatores climáticos, a possibilidade de traumas por efeitos mecânicos e químicos. A ocorrência maior destas afecções diz respeito à formação de fistulas e rachaduras teciduais. Na 20 presença de tais condições, a proteção química e física dada pela integridade e flexibilidade da pele e da musculatura lisa do esfíncter externo do teto deixam de existir, tornando vulnerável a saúde e funcionalidade do úbere (SIEBER e FARNSWORTH, 1981; NEIJENHUIS et al., 2000).

O canal do teto representa uma importante linha de defesa do 25 corpo contra infecções (GIRAUDO, 1996). Este canal encontra-se normalmente fechado por um anel muscular (esfíncter do teto) no período entre ordenhas, e é bloqueado por um tampão de queratina derivada das células da parede do canal. Esta queratina tem atividade antimicrobiana, mas sua principal função é a de agir como uma barreira física contra microorganismos patogênicos 30 (JONES e BAILEY, 1998). A ordenha ou o ato de mamar remove este tampão e torna flácido o esfíncter, fazendo com que o canal do teto fique mais suscetível a infecções por um período de até duas horas. Depois deste, a musculatura tende a retomar seu tônus e o tampão de queratina é novamente formado

(VAZ, s.d.).

Existem vários fatores que podem impedir o retorno do tônus do esfíncter à normalidade, como produtos químicos (desinfetantes) com ação cáustica e ordenhadeira com excesso de vácuo ou com pulsação excessivamente rápida (VAZ, s.d.; SAINSBURY, 1998). Estes fatores podem provocar uma hiperqueratose na extremidade do canal do teto, o que dificulta o seu fechamento. Esta lesão se caracteriza por um anel esbranquiçado e ligeiramente elevado ao redor do orifício (NEYENHUIS *et al.*, 2001). Em casos extremos, pode haver necrose da abertura, com rachaduras ou fistulas que se irradiam dela e que podem servir de abrigo para os agentes patogênicos (VAZ, s.d.).

Mudanças na condição do teto podem ocorrer a curto, médio e longo prazo (MEIN *et al.*, 2001; REINEMANN, s.d.). As mudanças a curto prazo na condição dos tetos tais como: 1-alterações da coloração (róseo para avermelhado ou azulado), 2- volume (aumento), 3- forma (flexível e maleável para rígido), 4- grau de abertura do orifício do teto, geralmente ocorrem em resposta ao próprio processo de ordenha. Sob boas condições de ordenha, o teto pode levar até algumas horas para recuperar totalmente sua integridade. Falhas na máquina ou no gerenciamento da ordenha e/ou nos intervalos entre as mesmas são consideradas causas primárias de exacerbação das mudanças a curto prazo na condição do teto (MEIN *et al.*, 2001).

As mudanças a médio prazo referem-se a alterações teciduais e danos vasculares (hemorragias petequiais ou em grande escalas) do teto que em poucos dias ou semanas, tornam-se visíveis. Essas podem ser decorrentes da ordenhadeira (falha na pulsação, vácuo e sobreordenha), da ação de agentes químicos (rigidez e perda da elasticidade) sobre o teto ou de condições climáticas adversas (pele escamada e seca devido diminuição da hidratação). Essas condições podem se interrelacionar favorecendo ao aparecimento de fissuras e/ ou rachaduras do teto, principalmente em sua porção distal (MEIN *et al.*, 2001).

As mudanças a longo prazo são caracterizadas pela presença de hiperqueratose na porção distal do teto. Essas são descritas pela presença de um anel de queratina de qualquer espessura circundando o orifício do teto

associado ou não a rugosidades neste anel (NEYENHUIS *et al.*, 2001). Os fatores que mais influenciam a hiperqueratose em relação às condições ambientais adversas incluem o tamanho do canal do teto, estágio de lactação e interações entre máquina e processo de ordenha (MEIN *et al.*, 2001).

5 Diferentes métodos têm sido propostos para promover a prevenção e o tratamento das lesões dos tetos. A utilização de substâncias tópicas anti-sépticas e cicatrizantes e bandagens do teto têm promovido resultados satisfatórios, mas somente em algumas situações. O uso de medicamentos é normalmente uma opção considerável (LANGONI *et al.*, 2000),
10 mas estes apresentam como desvantagens o alto custo e a possibilidade de deixar resíduos no leite, impossibilitando a utilização do mesmo (WATTIAUX, s.d.). Frente a isto, o estudo e o desenvolvimento de novas estratégias que possam prevenir e potencializar a cura das lesões traumáticas não-infecciosas dos tetos fazem-se necessários. Apesar do melhor tratamento para as lesões
15 do teto ainda ser a prevenção, estratégias que sejam efetivas em tratá-las também são de extrema importância, pois quanto mais rápido ocorrer o retorno à funcionalidade normal do úbere, menores serão os riscos de complicações, como por exemplo, o desenvolvimento de estenoses e da própria mastite.

Estudos recentes têm demonstrado que a radiação tecidual com
20 fontes de luz (como por exemplo, LASER's – *Light Amplification by Stimulated Emission of Radiation*, em português, amplificação da Luz por emissão estimulada de radiação – e LED's – *Light Emitting Diode*, em português, diodo emissor de luz) parece ser uma estratégia efetiva para a prevenção das lesões traumáticas do teto e para favorecer o processo de cicatrização tecidual das
25 mesmas, principalmente por estimular o fluxo sanguíneo e a produção de colágeno na área irradiada (SCHAFFER *et al.*, 2000; LAGAN *et al.*, 2000; LUCAS *et al.*, 2003; TAKEZAKI *et al.*, 2006). Os efeitos da terapia fotobiomoduladora são decorrentes da absorção da luz por cromóforos presentes nas células tais como os citocromos-C oxidase presentes nas
30 mitocôndrias (KARU *et al.*, 2004).

Os benefícios fotobiomoduladores do LASER e do LED de baixa intensidade têm sido observados em condições tais como osteoartrite, radiculopatias, tendinites e, principalmente, no tratamento de feridas cutâneas

em animais (KANA *et al.*, 1981; SOARES *et al.*, 1989; MATERA *et al.*, 2003) e humanos (CORRÊA *et al.*, 2003; SIQUEIRA *et al.*, 2004). O incremento à produção de ATP, o estímulo à proliferação e a ação dos fibroblastos e das células epiteliais bem como a microcirculação local são algumas das principais 5 justificativas fisiológicas para o uso da radiação luminosa para a terapêutica cicatricial (MESTER, 1974; CASTRO *et al.*, 1983; BAXTER, 1994; WEISS *et al.*, 2005; VINCK *et al.*, 2003).

Tatarunas *et al.* (1998) avaliaram a ação do LASER As-Ga, 904 nm, em feridas cirúrgicas de pele de felinos. Foram utilizados 63 animais 10 divididos em 3 grupos: A- irradiados com 4 J/cm^2 , B- irradiados com 2 J/cm^2 , C- controle, não irradiados. A aplicação foi realizada de modo pontual, com a caneta mantida perpendicular e contatando levemente a ferida. As aplicações foram realizadas no 2º, 4º, 8º e 15º dias de pós-operatório de ovariohisterectomia. O estudo concluiu que o LASER As-Ga nas dosagens de 2 15 e 4 J/cm^2 atuou positivamente na cicatrização por primeira intenção de feridas cirúrgicas em pele de felinos, tendo a dose de 2 J/cm^2 se mostrado vantajosa em relação à de 4 J/cm^2 .

Say *et al.* (2003) realizaram um estudo experimental em seres humanos, com o objetivo de comparar a eficácia do LASER de diferentes 20 comprimentos de onda no tratamento de úlceras cutâneas venosas crônicas. O estudo foi realizado com quatro indivíduos, sendo dois submetidos à aplicação de LASER He-Ne, 632,8 nm, dose de 4 J/cm^2 e os outros dois à terapêutica com LASER As-Ga, 904 nm, na mesma dose. Os resultados, avaliados através 25 de registros fotográficos e mensuração da área da ferida, demonstraram que o LASER promoveu aceleração do processo de cicatrização das úlceras, sendo o As-Ga mais eficaz no tratamento destas lesões.

Hopkins *et al.* (2004) utilizando vinte e dois voluntários, induziram ulcerações na pele da parte anterior do antebraço com diâmetro de 1,27 cm². Essas lesões cutâneas foram irradiadas com LASER tipo 46-diodo, 30 820nm, dose de 8 J/cm^2 e tempo de aplicação de 5 segundos, durante 10 dias. Por meio da análise de registros fotográficos, as feridas foram avaliadas pela contração, coloração e presença de brilho. Os autores perceberam que no

6º, 8º e 10º dia de aplicação, as ulcerações do grupo de intervenção com laser apresentavam menor tamanho, evoluíram do vermelho para o rosa claro e tornaram-se mais homogêneas em relação ao grupo controle. Estes achados corroboram com outros dados da literatura, os quais apontam o LASER de baixa potência como acelerador do processo de reparo tecidual.

Estudos sobre os efeitos da terapia com luz no manejo das lesões dos tetos são raros na literatura. Todavia, grupos de pesquisadores russos têm observado resultados satisfatórios para utilização desta terapia no tratamento de lesões do mamilo em humanos (ALEKSEENKO *et al.*, 1987; KOVALEV, 1990). Estes resultados juntamente com os efeitos positivos decorrentes da interação luz-tecidos sugerem que a radiação luminosa pode ser uma alternativa promissora para a prevenção e o tratamento de lesões não-infecciosas do teto.

Frente a isso, o desenvolvimento de novas estratégias que sejam efetivas em tratar as fissuras e os traumas mamilares, e para minimizar os problemas e inconvenientes decorrentes dos traumas dos tetos é de extrema importância.

Nas buscas realizadas em bancos de patentes no Brasil e no exterior, não foram encontrados documentos que descrevessem a aplicação do dispositivo para traumas mamilares e para traumas dos tetos, nem uma configuração específica para este fim.

De maneira geral, as patentes existentes contemplam apenas a utilização de componentes químicos para a assepsia e compostos para tratamento das lesões. Duas patentes utilizam luz, todavia uma delas (US 2008/0000426 A1) trata-se de um dispositivo não-invasivo para o diagnóstico de mastite e a outra patente (US 6276297 B1) retrata um dispositivo para desinfecção dos componentes do sistema de ordenha, incluindo as teteiras e a limpeza dos tetos. O primeiro dispositivo avalia a reflexão da luz pelo tecido do teto e com base nesses dados identifica a presença ou não de mastite. Entretanto, esta patente não contempla tratamento da mastite pela utilização de luz. O segundo dispositivo utiliza luz com comprimento de onda na faixa do ultravioleta (100-280 nm) para destruição de bactérias e garantir a assepsia dos componentes e dos tetos. Também não contempla a fotobioestimulação como

forma de tratamento.

A praticidade do equipamento, a possibilidade de uso em ambiente clínico ou de campo (ambos sob a supervisão e/ou orientação de um profissional da medicina veterinária) juntamente com as características do projeto do dispositivo, possibilitam aplicações de curta duração para prevenção e/ou tratamento não-invasivos das lesões não-infecciosas do teto. Este fato torna-se importante nos casos em que interferências na rotina de manejo e cuidado do animal não são desejáveis como, por exemplo, na indústria leiteira.

A patente US05958966 descreve um dispositivo e um método para tratamento de câncer de próstata baseado na fotobioestimulação, e envolve um anticorpo que é ligado ao antígeno da próstata.

A patente US06881405 descreve biomoduladores, que regulam diferenciação e proliferação celular, assim como métodos de uso para tratamentos de várias condições patológicas, como por exemplo, câncer, desordem imunológica e doenças vasculares; estimular cicatrização tecidual após lesões; para vacinações; estimular a produção de moléculas importantes; e produzir retalhos vasculares para transplantes.

A patente US06933287 descreve um método para tratamento de tumor com radiação, no qual o tumor é sensibilizado através de um agente sensibilizante tumoral.

O “DISPOSITIVO FOTOBIMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECCIOSAS DOS TETOS”, objeto da presente patente, foi desenvolvido com a finalidade de minimizar os problemas (dificuldade de cicatrização e dor) e inconvenientes (interrupção da amamentação) decorrentes dos traumas mamilares, bem como para minimizar os problemas e inconvenientes decorrentes dos traumas dos tetos para a atividade leiteira.

O projeto do dispositivo fotobiomodulador levou em consideração a morfologia e a anatomia da mama humana, agregando conforto à usuária durante a aplicação e a possibilidade de uso em diferentes formatos e tamanhos de mama, uma vez que a unidade de posicionamento pode ser anatomicamente ajustada à mama. No caso da aplicação em animais, considerou-se a morfologia e a anatomia dos tetos, o que possibilita sua

aplicação em diferentes tamanhos de teto, agregando facilidade de manuseio e operação ao profissional responsável.

O equipamento pode ser confeccionado em material esterilizável, o que permite e favorece adequada assepsia a cada aplicação.

5 Tal fato é de fundamental importância para o controle e prevenção de infecções, principalmente quando se trata de feridas abertas. Adicionalmente, para aplicacao em humanos, há a possibilidade de fixação do dispositivo sobre a mama, por meio de suporte anatomicamente ajustável ao tronco superior, confeccionado em material antialérgico e lavável, o que favorece o posicionamento do dispositivo fotobiomodulador e facilita a sua aplicação. A praticidade do equipamento juntamente com a possibilidade de uso em ambiente domiciliar, além do clínico (ambos sob a supervisão e orientação fisioterapêutica), contribuem para a maior aderência da paciente ao tratamento, o que, indiretamente, favorece a melhores resultados no controle da dor e 10 cicatrização tecidual.

15

Para a aplicação em animais, há a possibilidade de fixação do dispositivo no teto por pressão ou por meio de suporte externo, anatomicamente ajustável ao animal, confeccionado em material antialérgico e lavável, não restritivo.

20 O dispositivo fotobiomodulador baseia-se nos princípios da fotobioestimulação, já consagrados na literatura (MESTER et al., Laser stimulation of wound healing, 1974; KARU, Photobiological fundamentals of low-power LASER therapy, 1987; HARRIS, Biomolecular Mechanisms of LASER biostimulation, 1991; WHELA et al., Medical applications of space light-emitting diode technology-space station and beyond, 1999; ORTIZ et al., 25 LASER de baixa intensidade: efeitos sobre os tecidos biológicos, 2001; WHELAN et al., Light Emitting Diode Medical Application from deep space to deep sea, 2001; KARU et al, Photobiological modulation of cell attachment via cytochrome e oxidase, 2004; KARU; KOLYAKOV, Exact Action spectra of cellular responses relevant to phototherapy, 2005; WEISS et al., Clinical 30 experience with light-emitting diode (LED) photomodulation, 2005). Segundo este princípio, fontes de luz com comprimentos de onda na faixa espectral do vermelho ao infravermelho próximo, não restritivo, são capazes de modular a atividade das células biológicas de tecidos lesionados. Estas fontes podem ser

polarizadas ou não-polarizadas, de padrão plano ou esférico, coerentes ou não-coerentes, contínuas ou pulsáteis, não restritivas. Podem compor uma configuração óptica/mecânica adequada para a obtenção dos parâmetros ópticos necessários à bioestimulação, utilizando elementos ópticos como por exemplo, lentes, espelhos, divisores de feixes, entre outros. Qualquer que seja o tipo de luz utilizada e os elementos ópticos empregados, a radiação resultante emitida pelo dispositivo fotobiomodulador não deve se capaz de elevar a temperatura dos tecidos biológicos a níveis suficientes para indução de respostas termofisiológicas (LANZAFAME *et al.*, Temperature-controlled 830nm Low-level Laser Therapy of experimental pressure ulcers, 2004) e óculos de proteção individual, com filtro específico para o comprimento de onda emitido pelo dispositivo fotobiomodulador, deverão ser utilizados pela usuária e pelo profissional da área de saúde durante a aplicação, para prevenção de possíveis danos oculares.

A intensidade/potência de emissão da luz, o comprimento de onda, o tempo de aplicação, a freqüência, o modo do pulso, o tempo de tratamento, entre outros parâmetros, podem ser controlados de forma a atender a diferentes padrões de tratamento de modo a otimizar a aplicação do dispositivo.

Foram utilizados comprimentos de onda na faixa espectral do vermelho (622nm) ao infravermelho próximo (950nm). Um sistema indicativo de funcionamento da fonte emissora, visual e/ou auditivo, auxilia o usuário acerca do tempo necessário para a aplicação bem como o alerta para o correto funcionamento do dispositivo. O controle do tempo poderá ser realizado via temporizador, ou sistema embutido microcontrolado, ou dispositivos eletrônicos ou ainda por uma interface de comunicação com microcomputador. O ajuste da intensidade poderá ser feito através da seleção do modo de emissão da luz e/ou do número de fontes luminosas a ser utilizadas para a aplicação.

As figuras abaixo relacionadas ilustram o dispositivo fotobiomodulador, objeto da presente patente de invenção, nos quais:

A figura 1 mostra o dispositivo montado com a configuração do corpo em formato cilíndrico.

A figura 2 mostra o dispositivo montado com a configuração do corpo em formato cônico.

A figura 3 mostra a vista frontal da unidade de posicionamento da mama para as configurações cilíndrica e cônica.

5 A figura 5 mostra, (a) é a vista frontal e (b) é a vista de topo.

As figuras 4, 6, 7, 8, 9 e 10 apresentam as seguintes vistas: em (a) vista frontal do dispositivo completo; (b) vista do corte apresentado em (a);

(c) vista de topo e (d) vista frontal do dispositivo sem a unidade de proteção.

Quando necessário apresentam também a vista lateral em (a) e um corte

10 auxiliar na unidade de iluminação em (d). Os componentes do dispositivo devem ser confeccionados de forma a resistirem ao processo de assepsia bem como aos impactos provenientes da movimentação do animal durante a aplicação do dispositivo.

O dispositivo fotobiomodulador pode ser montado em configurações apropriadas, não restritivas, como por exemplo, corpo em

15 formato cilíndrico, (Figura 1) e/ou corpo em formato cônico (Figura 2). Qualquer uma das configurações será composta por um corpo principal, subdividido em três unidades principais, não restritivas, sendo a unidade emissora de luz (1), a unidade de posicionamento (2) da mama e a unidade de controle (3).

20 A unidade emissora de luz (1) compreende a(s) fonte(s) luminosa(s) que emitirá(ão) a intensidade de luz nos comprimentos de onda necessários para a bioestimulação, bem como outros possíveis elementos ópticos, conforme descrito anteriormente. Pode ser composta por fontes luminosas que emitem luz nos comprimentos de onda necessários ao tratamento, de qualquer espécie

25 como LED (em português, diodo emissor de luz), laser, lâmpadas incandescentes, fluorescentes, entre outras, não restritivo. O acionamento desta unidade é realizado pela unidade de controle (3).

A unidade de posicionamento (2) da mama, pode possuir formatos cônicos (Figura 3A) ou circular (Figura 3B) ou outra geometria que

30 seja favorável ao posicionamento do dispositivo fotobiomodulador na mama humana, evitando, desta forma, desconforto para as usuárias. A superfície interna da unidade de posicionamento (2) da mama poderá receber um recobrimento e/ou acabamento apropriado (como por exemplo, espelhado,

opaco) de modo a possibilitar o melhor direcionamento dos raios luminosos ao tecido lesionado, otimizando a eficiência do dispositivo durante a bioestimulação.

Uma vez que os efeitos fisiológicos/terapêuticos decorrentes da interação luz-tecido são provenientes de processos atérmicos e que é indesejável o aumento da temperatura tecidual durante a aplicação do dispositivo fotobiomodulador, pode ser necessária a medição da temperatura da área irradiada para maior controle e segurança do tratamento. Para tanto, pode-se instalar um ou mais sensores/transdutores de temperatura, preferencialmente ao longo da periferia da unidade de posicionamento (2). A tecnologia utilizada para o sensor/transdutor de temperatura pode ser termopar, termistor, por resistência elétrica, por sensor de fibra óptica ou outro efeito de modulação da luz, não restritivo. Também pode ser desejável a medição de outras grandezas tais como intensidade luminosa, impedância tecidual e imagem durante a aplicação do dispositivo, para maior controle e segurança durante as aplicações.

Essas informações poderão ser utilizadas para acompanhamento e/ou aprimoramento das aplicações clínicas ou para pesquisas científicas. Para tanto poderão ser empregados sensores/transdutores para medição de intensidade luminosa e/ou impedância tecidual e/ou micro-câmeras acoplados à unidade de posicionamento (2). As informações obtidas por esses sensores, como por exemplo, às imagens, poderão ser utilizadas para estudo da área das lesões e acompanhamento da evolução do processo de cicatrização dos traumas mamilares.

A unidade de controle (3) é responsável pelo funcionamento do dispositivo fotobiomodulador, acionando a unidade emissora de luz (1), quando necessário. Ela é composta por um circuito eletroeletrônico dividido em três blocos: ("A") fonte de alimentação; ("B") sinalizador e ("C") controle e temporizador, cujas funções são descritas a seguir.

O bloco "A" refere-se à fonte de alimentação responsável por fornecer aos demais blocos a tensão adequada para operação do equipamento. Este bloco pode ser implementado utilizando elementos armazenadores de energia (como pilhas, baterias entre outros) ou pela

transformação da energia fornecida pelas concessionárias de energia e/ou geradores de forma a adequar a energia às necessidades do dispositivo.

O bloco “B” é responsável pela sinalização, visual e/ou sonora, indicando se o equipamento está energizado, se está emitindo luz e o possível 5 término do tempo da aplicação. Este pode ser composto por display de cristal líquido e/ou LED e/ou beep.

O bloco “C” é responsável pelo controle da emissão da luz, permitindo a escolha do modo de emissão da luz previamente selecionado. Esse bloco também pode ser responsável pela contagem do tempo da 10 aplicação. Deste modo, um cronômetro programável, poderá fazer a contagem (crescente e/ou decrescente), registrar o tempo de exposição e enviar ao bloco “B” o momento do fim da contagem. Este bloco também pode apresentar a interface para comunicação com computador, o qual poderá receber os parâmetros de funcionamento do dispositivo, por exemplo, tempo de aplicação 15 e modo de emissão, assim como ser capaz de adquirir os sinais dos sensores/transdutores (temperatura, intensidade luminosa, impedância tecidual e imagem), podendo armazenar esses dados para posterior processamento.

O dispositivo, assim constituído, traz uma série de características consideradas adequadas e vantajosas do ponto de vista de 20 proporcionar um tratamento não-invasivo para traumas mamilares, sem contato direto com a região lesada e de comprovada eficácia em estudos pilotos (ARAÚJO et al, Development of a led cluster device able to treat mammila injury emitting in the infrared wavelength, 2007), trazendo como principais benefícios o controle da dor e o aprimoramento do processo de cicatrização 25 tecidual.

O dispositivo fotobiomodulador também pode ser montado em configurações apropriadas que melhor se adaptem à anatomia do teto e ao tipo e localização da lesão, ao tipo de material a ser confeccionado e ao tipo de fixação ao teto, como por exemplo, corpo em formato tubular cilíndrico, de base 30 arredondada (Figura 4) ou reta (Figuras 5 a 10), de seção transversal circular, ou outra geometria favorável, não restritivas. Qualquer uma das configurações será composta por um corpo principal, subdividido em três unidades principais, não restritivas: (1) a unidade emissora de luz, mostrada com configurações exemplificadas nas Figuras 4d, 6d, 7d, 8d, 9d e 10d, não restritivas; (2) a

unidade de posicionamento e fixação primária no teto, a qual compreende a porção superior do dispositivo; e (3) a unidade de controle, a qual ficará à parte das unidades anteriores. Também para qualquer uma das configurações descritas pode-se utilizar um único corpo principal, procedendo-se a aplicação de um teto por vez ou uma estrutura composta por vários corpos, permitindo-se a aplicação do tratamento concomitantemente em todos os tetos do animal, como por exemplo, a apresentada na Figura 5, não restritivo.

A unidade emissora de luz (1) compreende a(as) fonte(es) luminosa(as) que emitirá(ão) a intensidade de luz nos comprimentos de onda na faixa espectral do vermelho ao infravermelho próximo, não restritiva, e intensidade/potência necessários para a bioestimulação, bem como outros possíveis elementos ópticos, conforme descrito anteriormente. Nesta unidade, as fontes luminosas estarão dispostas radialmente ao longo de todo corpo principal, ou em outro posicionamento que seja adequado à anatomia do teto, 5 ao tipo e localização da lesão, aos parâmetros de emissão e ao tipo de geometria escolhida. Podem ser fixadas ao longo da mesma linha da seção transversal (Figuras 6 e 7) ou intercaladas nesta (Figuras 4,5,8,9 e 10), não restritivo. As fontes de luz poderão estar localizadas em todas as superfícies do corpo, incluindo a base, (Figura 4), ou somente nas superfícies laterais (Figuras 10 5 a 10), não restritivos. A fixação das fontes luminosas poderá ser realizada de diferentes formas, dispostas em um conjunto auxiliar (4), o qual será fixado ao corpo principal da Figura 4, ou diretamente ao próprio corpo principal (5) da Figura 6 e também nas demais, ou qualquer outro tipo de fixação que melhor atenda às características da fonte de luz e da geometria utilizadas. Pode ser 15 composta por fontes luminosas que emitam luz nos comprimentos de onda necessários ao tratamento, de qualquer espécie como LED, LASER, lâmpadas incandescentes, fluorescentes, fibra óptica, não restritivas. O número de fontes luminosas, o posicionamento e a ativação das mesmas bem como o(s) comprimento(s) de onda a ser (em) utilizado(s) poderão ser combinados de 20 forma a melhor atender o tratamento desejado. O acionamento desta unidade é realizado pela unidade de controle (3) de maneira conjunta ou independente para determinados grupos de fontes luminosas. A superfície interna da unidade emissora (1) poderá receber um recobrimento e/ou acabamento apropriado (como por exemplo espelhado ou opaco) de modo a possibilitar o melhor 25

direcionamento dos raios luminosos ao tecido lesionado, otimizando a eficiência do dispositivo durante a fotobioestimulação.

A unidade emissora pode contemplar uma unidade de proteção a qual garantirá a integridade das conexões elétricas bem como das próprias fontes luminosas durante o manuseio do dispositivo, como por exemplo, a apresentada pelo item (6) nas Figuras 4, 6, 7, 8, 9 e 10. Esta unidade de proteção acompanhará a geometria das unidades principais podendo ser fixada por meio de união roscada, soldada (Figura 4), quando se tratar de corpos metálicos ou poliméricos, por encaixe, pressão ou outro tipo de fixação que seja apropriado a outros materiais. Pode se fixar ao próprio sistema de fixação do teto, o qual poderá fazer parte do corpo principal (Figuras 6, 7, 8 e 9) ou ser um componente independente deste (Figuras 4 e 10). A fixação destas unidades também pode ser realizada com o auxílio de um anel externo (9) a estas como, por exemplo, ilustrado nas Figuras 9 e 10, ou outra configuração mais apropriada. A unidade de proteção também visa garantir a segurança do aplicador do dispositivo e do próprio animal quanto a possíveis panes elétricas.

A unidade de posicionamento (2) e fixação do teto, pode possuir formatos com seção cônica (7) da Figura 7 ou reta (8) nas Figuras 5,6,8,9 e 10, ou outra geometria que seja favorável ao posicionamento do dispositivo fotobiomodulador na extremidade superior do teto, evitando, desta forma, desconforto e estresse do animal durante a aplicação do dispositivo bem como outras lesões ao teto. Esta unidade pode ser confeccionada em material polimérico, antialérgico e esterilizável de modo a garantir a fixação e o correto posicionamento do dispositivo. Conforme dito anteriormente, esta unidade pode ser confeccionada integrada ao corpo principal, formando um corpo único, ou de maneira independente, sendo posteriormente montada sobre o corpo principal, de acordo com o material e o processo de fabricação a ser utilizado. Um aparato auxiliar externo de suporte e fixação do dispositivo ao teto pode ser confeccionado contemplando a fixação do dispositivo em outra porção do corpo do animal ou em algum aparato inerente ao processo de ordenha ou do ambiente comum do animal, quando possível. Em outros casos, pode-se inclusive, aproveitar o sistema de vácuo inerente ao processo de ordenha, para realizar a fixação do dispositivo, devendo o dispositivo sofrer as modificações

necessárias para garantir a integridade do mesmo e a utilização do sistema.

O ajuste da intensidade/potência poderá ser feito através da seleção do modo de emissão da luz e/ou do número de fontes luminosas a ser utilizados para a aplicação, não restritivo, o qual estará consequentemente interrelacionado ao controle dos demais parâmetros conforme descrito em seqüência.

A seleção do(s) comprimento(s) de onda poderá ser feita através da ativação de uma determinada fonte luminosa ou de um grupo de fontes as quais possuam o(s) comprimento(s) de onda necessário(s) ao tratamento, não restritivo. Uma combinação de diferentes comprimentos de onda poderá ser utilizada de forma a garantir a eficiência e otimização do tratamento, uma vez que, dessa forma, várias células envolvidas no processo de reparo poderão ser conjuntamente estimuladas.

Os parâmetros do pulso, no caso da utilização de luz pulsátil, como, por exemplo, a duração, a freqüência e o modo do pulso, poderão ser controlados eletronicamente a partir de circuitos integrados e/ou lógicas digitais, não restritivo.

O controle do tempo poderá ser realizado via temporizador, ou sistema embutido microcontrolado, ou dispositivos eletrônicos ou ainda por uma interface de comunicação com microcomputador.

Um sistema indicativo de funcionamento da(s) fonte(s) emissora(s), visual e/ou auditivo, auxiliará o usuário acerca do tempo necessário para a aplicação bem como o alertará para o correto funcionamento do dispositivo. De maneira similar, um sistema indicativo da quantidade de carga da fonte de energia utilizada, visual e/ou auditivo, permitirá o controle do uso do dispositivo.

REIVINDICAÇÕES

1. "DISPOSITIVO FOTOBIMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECCIOSAS DOS TETOS", caracterizado por utilizar os princípios da fotobioestimulação compreendendo uma unidade emissora de luz (1), uma unidade de posicionamento (2) da mama ou teto e uma unidade de controle (3).
2. "DISPOSITIVO FOTOBIMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECCIOSAS DOS TETOS", de acordo com a reivindicação 1, caracterizado pela unidade emissora de luz (1) compreender fontes luminosas que emitem luz com comprimentos de onda variando entre 600nm a 950nm, na faixa espectral do vermelho ao infravermelho, não restritivo.
3. "DISPOSITIVO FOTOBIMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECCIOSAS DOS TETOS", de acordo com a reivindicação 2, caracterizado pela fonte luminosa poder ser polarizada ou não-polarizada, de padrão plano ou esférico, coerente ou não-coerente, contínua ou pulsátil, não restritiva.
4. "DISPOSITIVO FOTOBIMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECCIOSAS DOS TETOS", de acordo com a reivindicação 1, caracterizado pela unidade de posicionamento (2) da mama possuir formato cônico, circular, sem restrições quanto ao formato.
5. "DISPOSITIVO FOTOBIMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECCIOSAS DOS TETOS", de acordo com a reivindicação 4, caracterizado por ser fixado sobre a mama por meio de um suporte anatomicamente ajustável ao tronco.
6. "DISPOSITIVO FOTOBIMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECCIOSAS DOS TETOS", de acordo com a reivindicação 1,

caracterizado pela unidade de posicionamento (2) do teto possuir corpo em formato tubular cilíndrico, de base arredondada ou reta, de seção transversal circular, ou outra geometria favorável, não restritivas.

- 5 7. "DISPOSITIVO FOTOBIMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECTUOSAS DOS TETOS", de acordo com a reivindicação 6, caracterizado por ser fixado ao teto por pressão ou por suporte auxiliar externo adaptado ao animal ou a algum aparato do processo de ordenha ou do ambiente comum do animal e por ser um dispositivo anatomicamente adaptável, aplicável, isolada ou simultaneamente, para todo e qualquer tamanho de teto.
- 10 8. "DISPOSITIVO FOTOBIMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECTUOSAS DOS TETOS", de acordo com a reivindicação 1, caracterizado pela unidade de controle (3) compreender um circuito eletrônico responsável por controlar o acionamento da unidade emissora de luz (1), a intensidade e a potência da luz irradiada, o comprimento de onda, frequência e modo do pulso, a duração do pulso, o tempo de aplicação e fornecer a tensão adequada para operação.
- 15 9. "DISPOSITIVO FOTOBIMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECTUOSAS DOS TETOS", de acordo com a reivindicação 8, caracterizado por compreender sensores para medição da temperatura da área irradiada, instalados preferencialmente ao longo da periferia da unidade de posicionamento (2).
- 20 10. "DISPOSITIVO FOTOBIMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECTUOSAS DOS TETOS", de acordo com a reivindicação 8, caracterizado por compreender sensores/transdutores e microcâmeras, para medição de parâmetros como intensidade luminosa, impedância tecidual e para aquisição de imagens da região tratada.
- 25
- 30

11. "DISPOSITIVO FOTOBIMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECCIOSAS DOS TETOS", de acordo com as reivindicações 9 e 10, caracterizado por compreender uma interface de comunicação com um computador para aquisição e processamento dos sinais dos sensores/transdutores e visualização de resultados em display.
12. "DISPOSITIVO FOTOBIMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECCIOSAS DOS TETOS", caracterizado por ser anatomicamente adaptável e aplicável para todo e qualquer tamanho de mama ou teto de animais.
13. "DISPOSITIVO FOTOBIMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECCIOSAS DOS TETOS", caracterizado por atuar de forma não-invasiva e sem contato com as lesões do mamilo.
14. "DISPOSITIVO FOTOBIMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECCIOSAS DOS TETOS", caracterizado por poder ser utilizado em ambientes clínico, domiciliar ou de campo.
15. "DISPOSITIVO FOTOBIMODULADOR PARA PREVENÇÃO E TRATAMENTO DE TRAUMAS MAMILARES E LESÕES NÃO-INFECCIOSAS DOS TETOS", caracterizado pela unidade de posicionamento (2) ser confeccionada em material antialérgico e lavável.
16. "DISPOSITIVO DE RADIAÇÃO LUMINOSA PARA PREVENÇÃO E TRATAMENTO DE LESÕES NÃO-INFECCIOSAS DOS TETOS", caracterizado por utilizar os princípios da fotobiomodulação para prevenção e tratamento de lesões, aprimoramento do processo cicatricial e controle da dor mamilos humanos ou teto de animais.

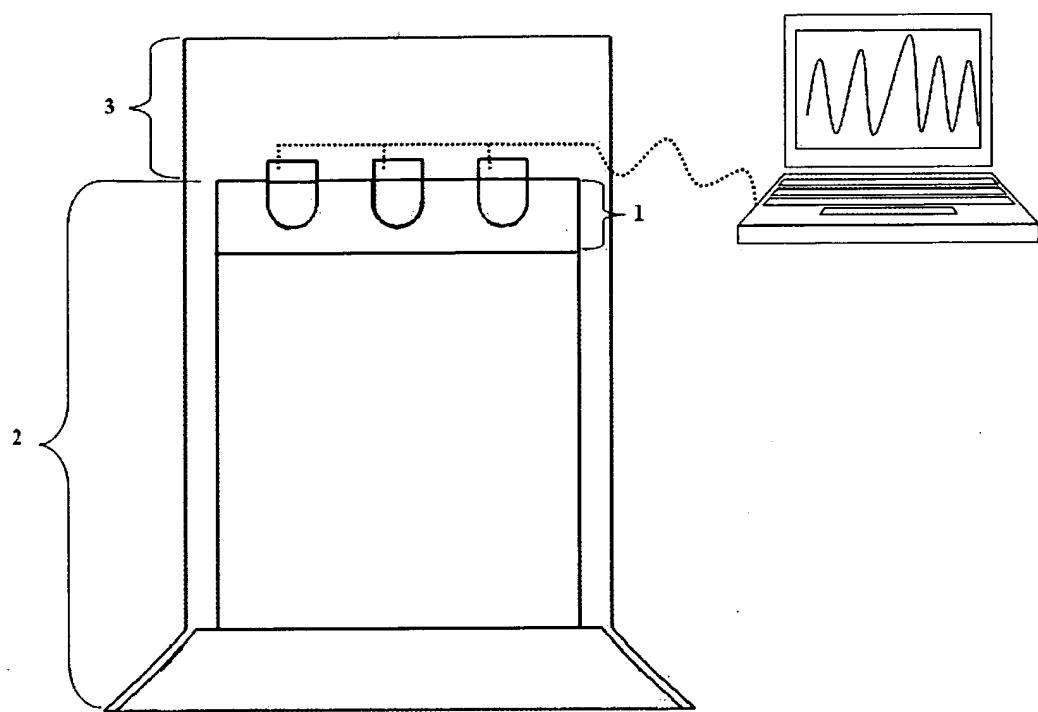


Figura 1

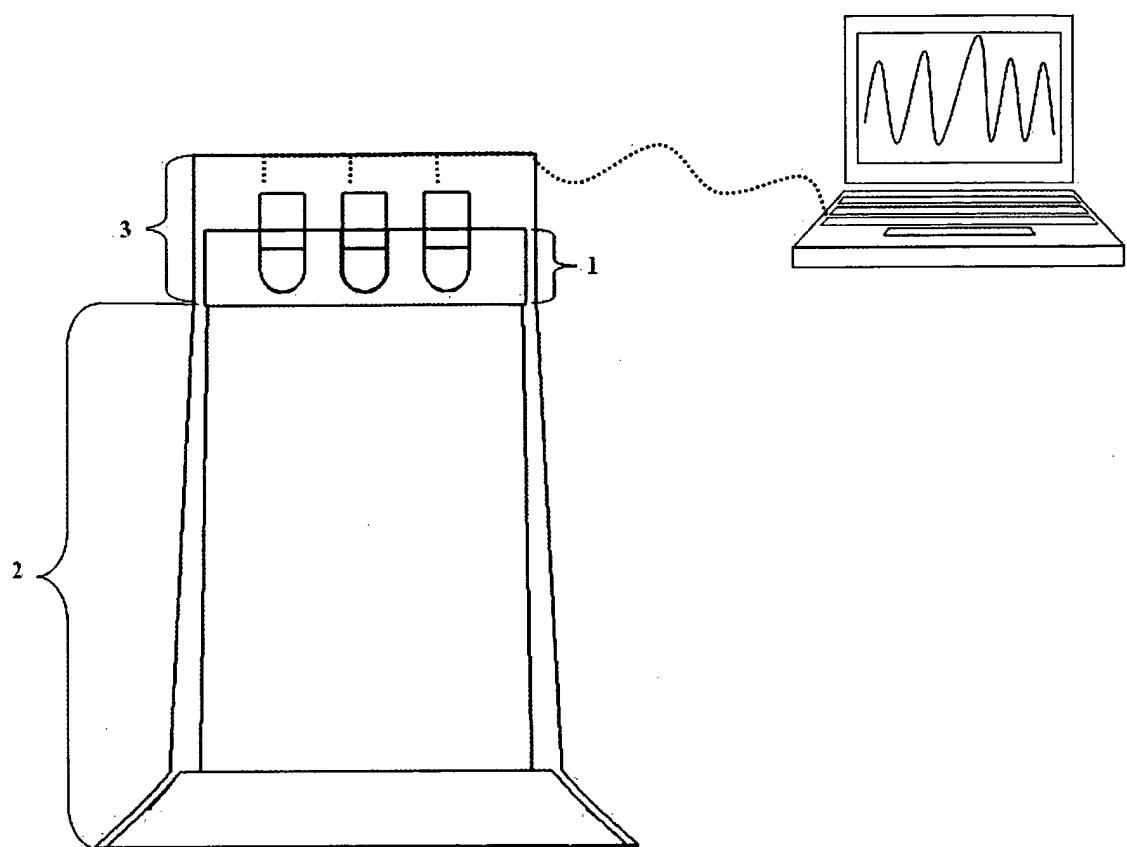


Figura 2

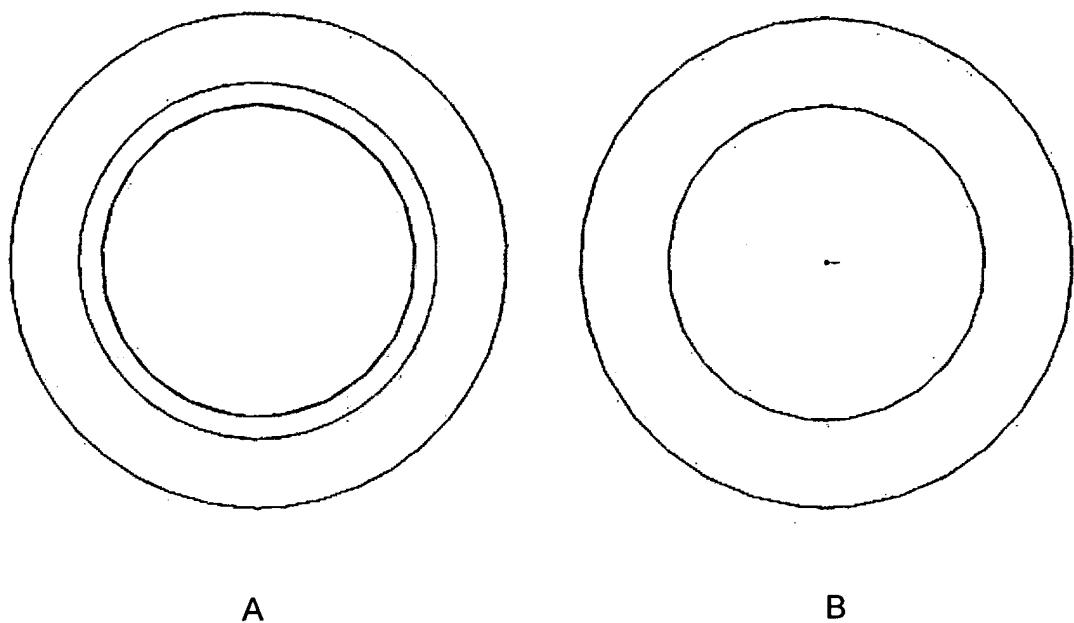


Figura 3

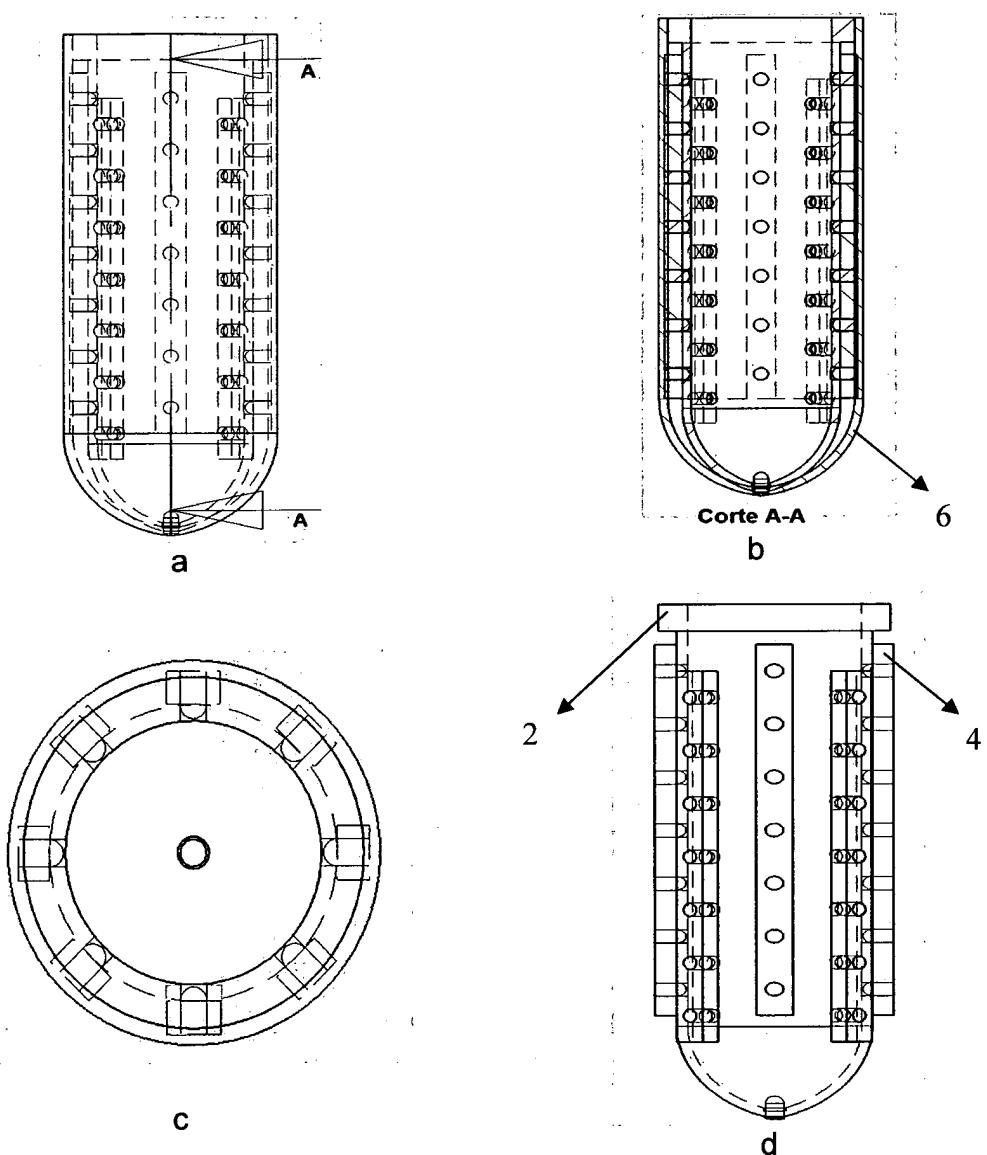


Figura 4

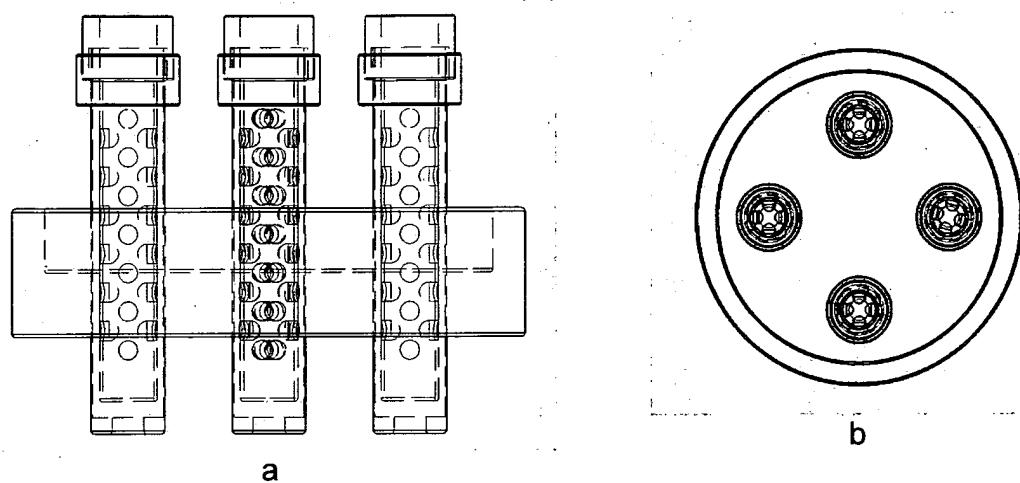


Figura 5

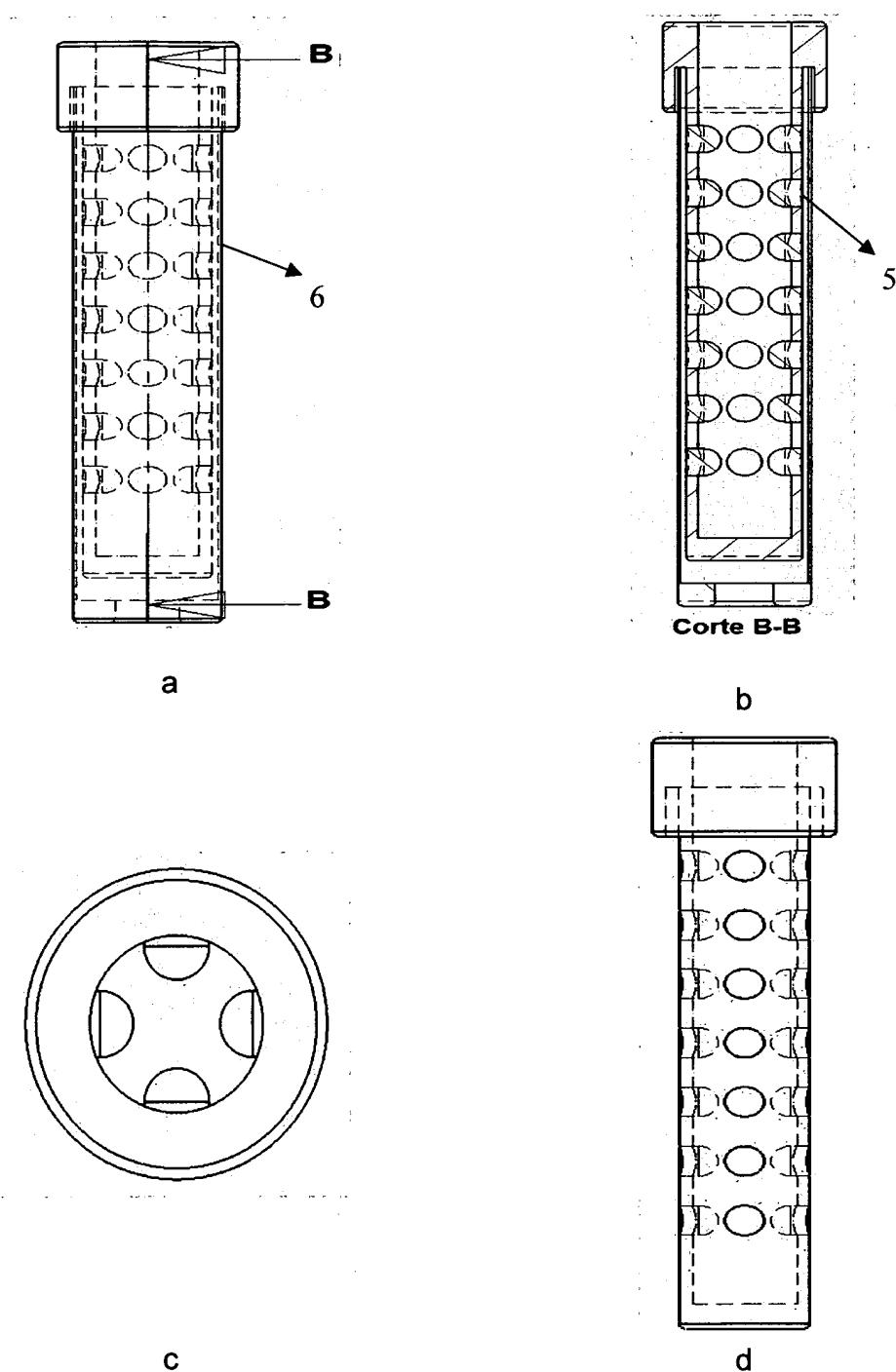
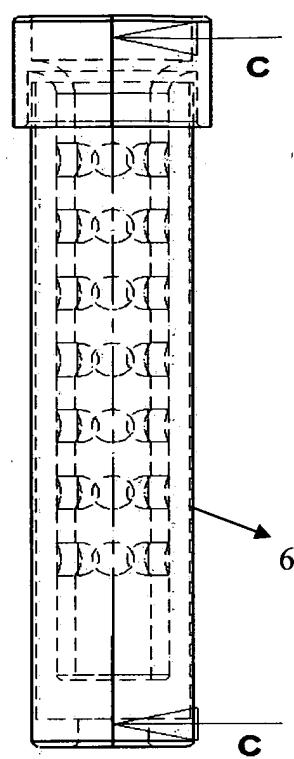
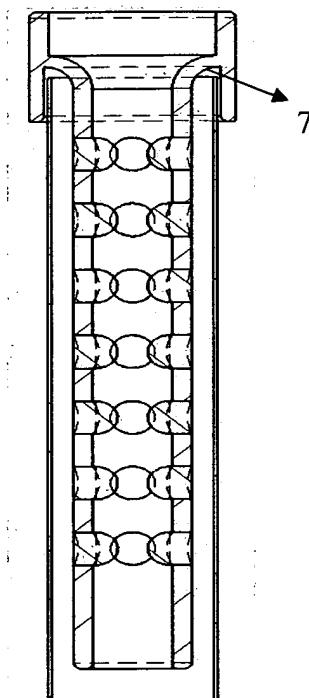


Figura 6

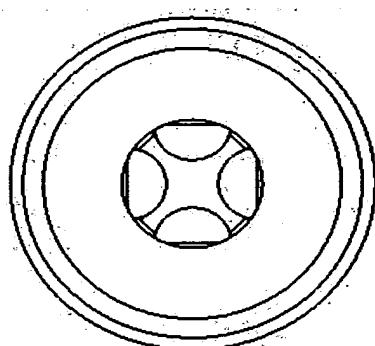


a

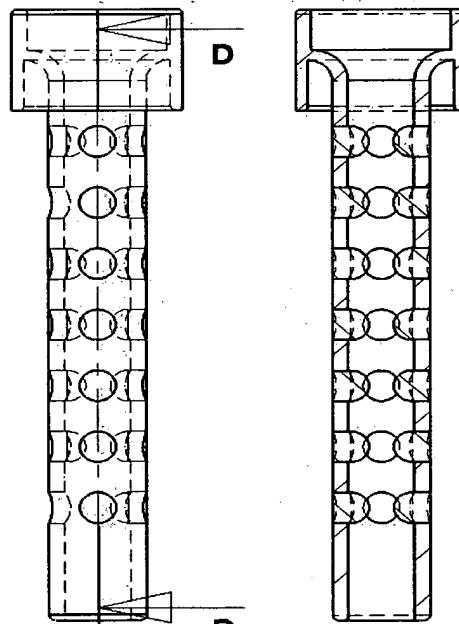


Corte C-C

b



c



d

Corte D-D

Figura 7

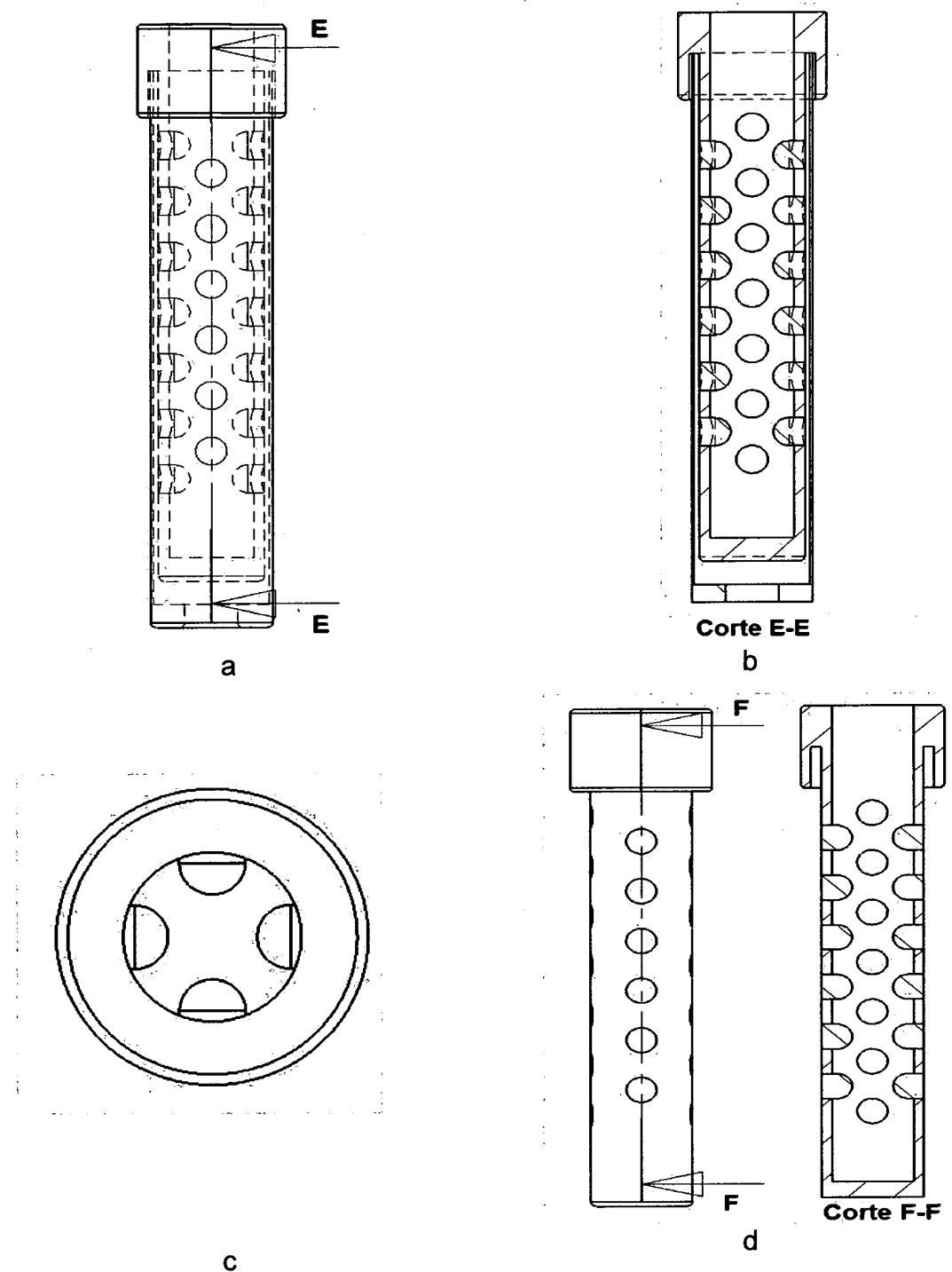


Figura 8

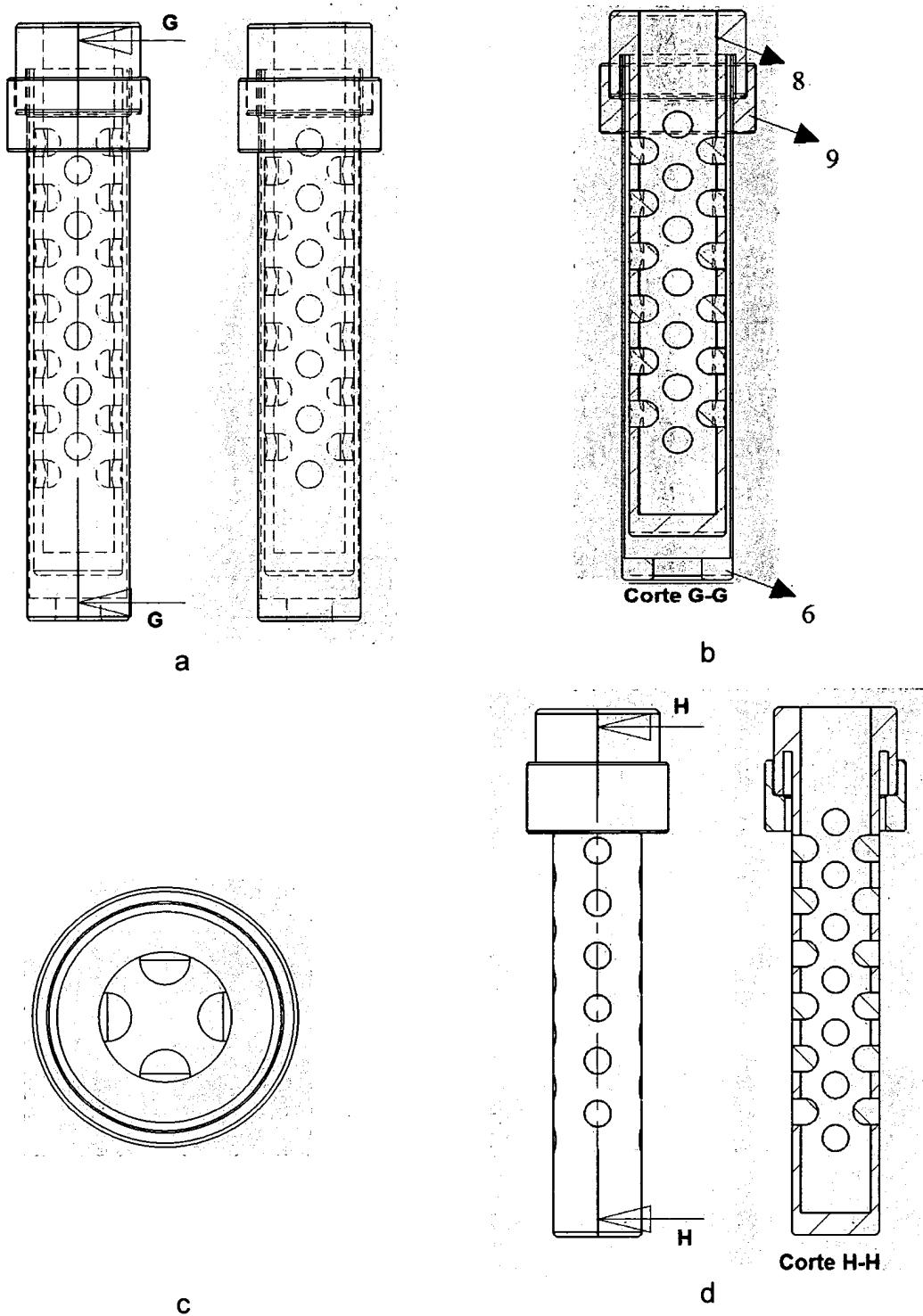


Figura 9

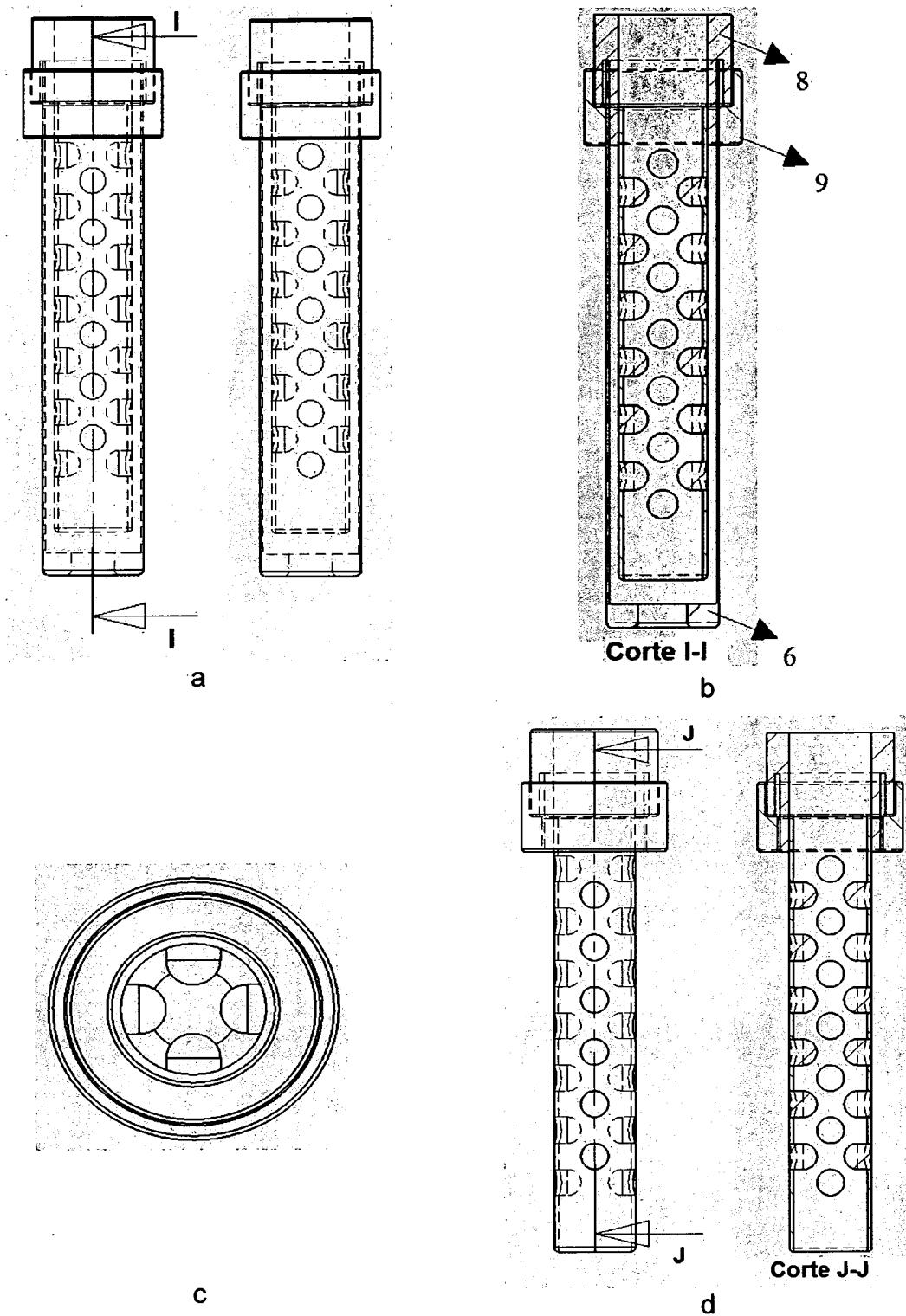


Figura 10



US 20050197681A1

(19) United States

**(12) Patent Application Publication
Barolet et al.**

(10) Pub. No.: US 2005/0197681 A1

(43) Pub. Date: Sep. 8, 2005

(54) **METHOD AND DEVICE FOR THE TREATMENT OF MAMMALIAN TISSUES**

Related U.S. Application Data

(60) Provisional application No. 60/541,936, filed on Feb. 6, 2004.

(75) Inventors: **Daniel Barolet**, Rosemere (CA);
Mathieu Auclair, Ste-Dorothee (CA);
Annie Boucher, Montreal (CA)

Publication Classification

Correspondence Address:

DARBY & DARBY P.C.

P. O. BOX 5257

NEW YORK, NY 10150-5257 (US)

(73) Assignee: **Lumiphase inc.**, Mont Royal (CA)

(21) Appl. No.: 11/053,603

(22) Filed: **Feb. 7, 2005**

(51) Int. Cl.⁷ A61H 21/00
(52) U.S. Cl. 607/86

(52) U.S. GR. 607,300
(53) ABSTRACT

ABSTRACT

A method and device for causing a predetermined physiological change in a mammalian tissue. The method includes irradiating the tissue with a radiation having a power density in the tissue substantially larger than an activation threshold power density, the tissue being irradiated under conditions suitable to cause the predetermined physiological change. The device can emit radiation and forms to the anatomy of a patient. The device can both cool the patient and treatment head using one cooling system.

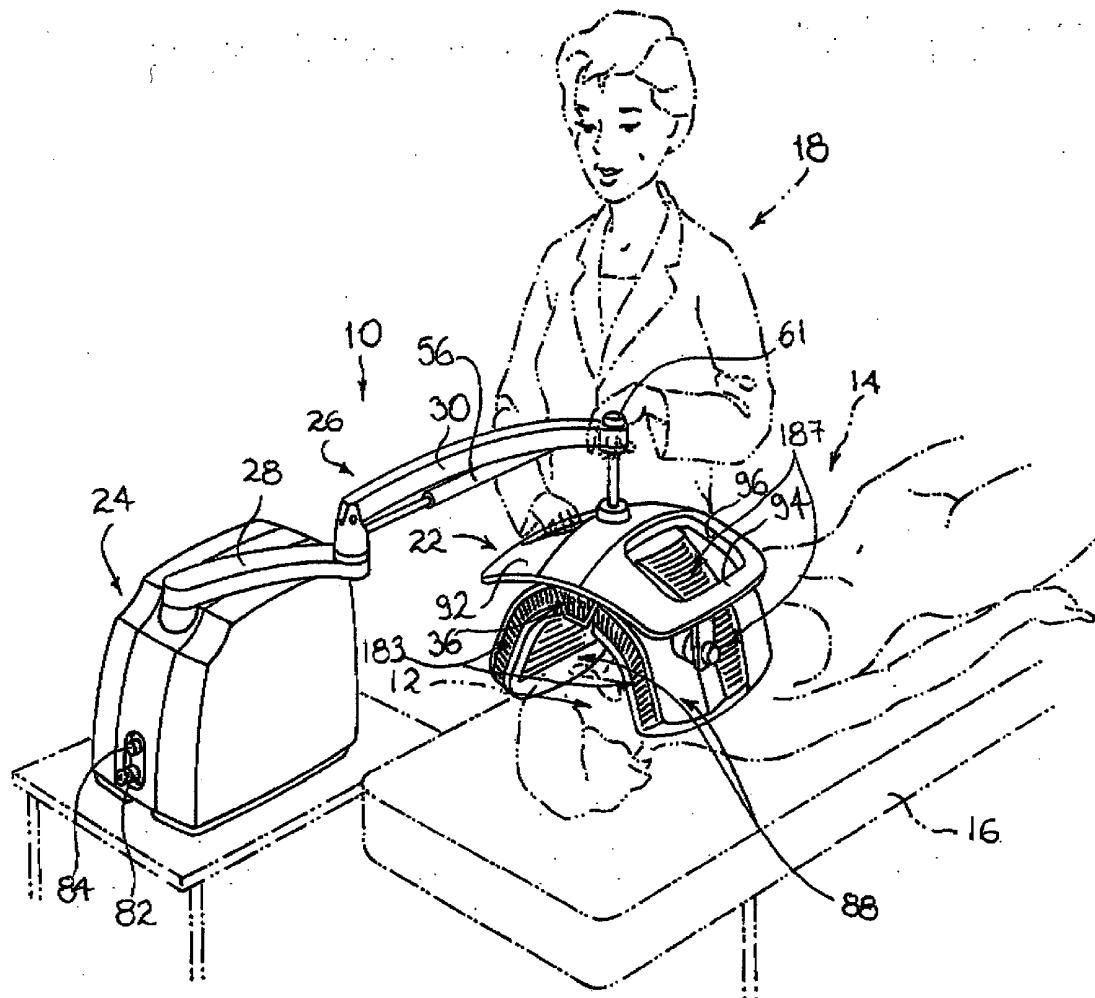
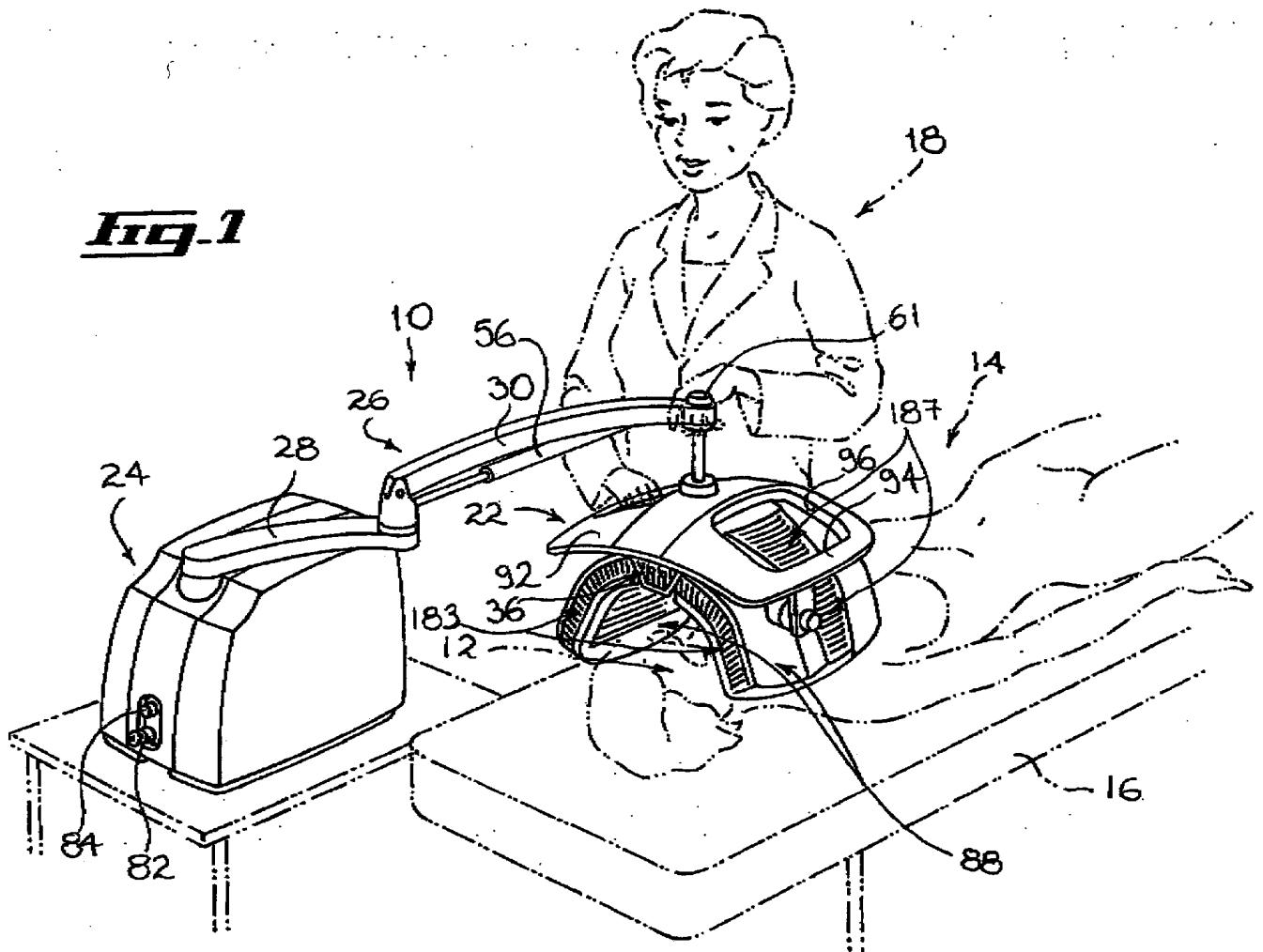


Fig. 1



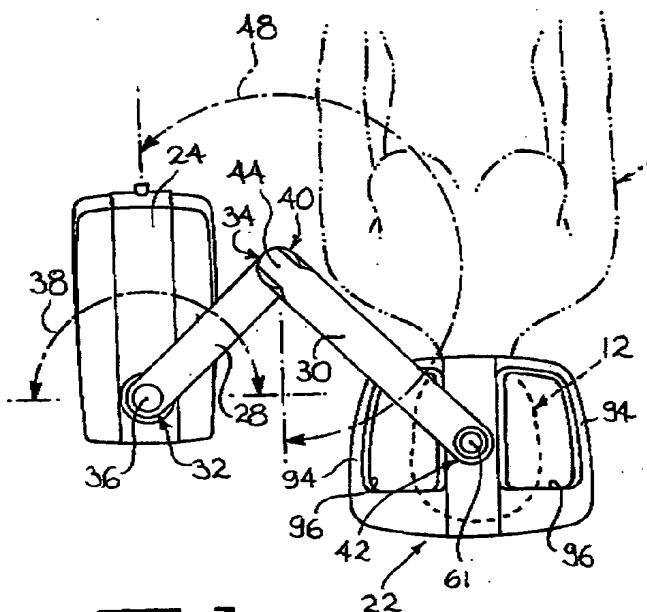


Fig-2

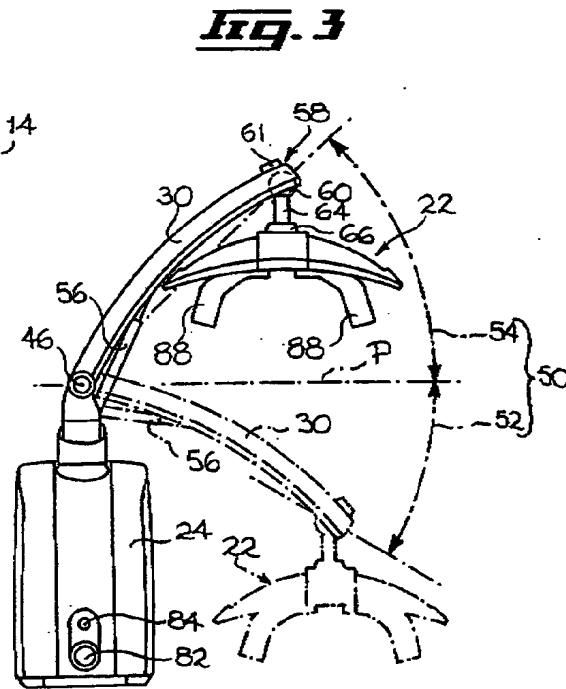


Fig. 3

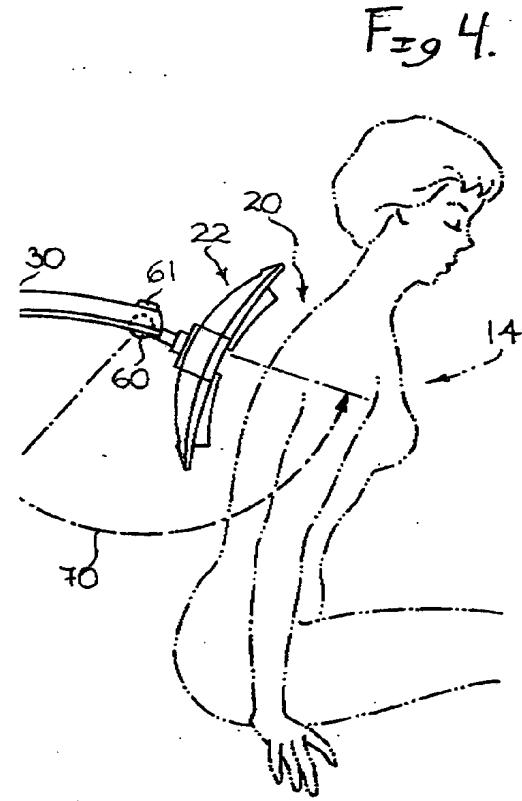
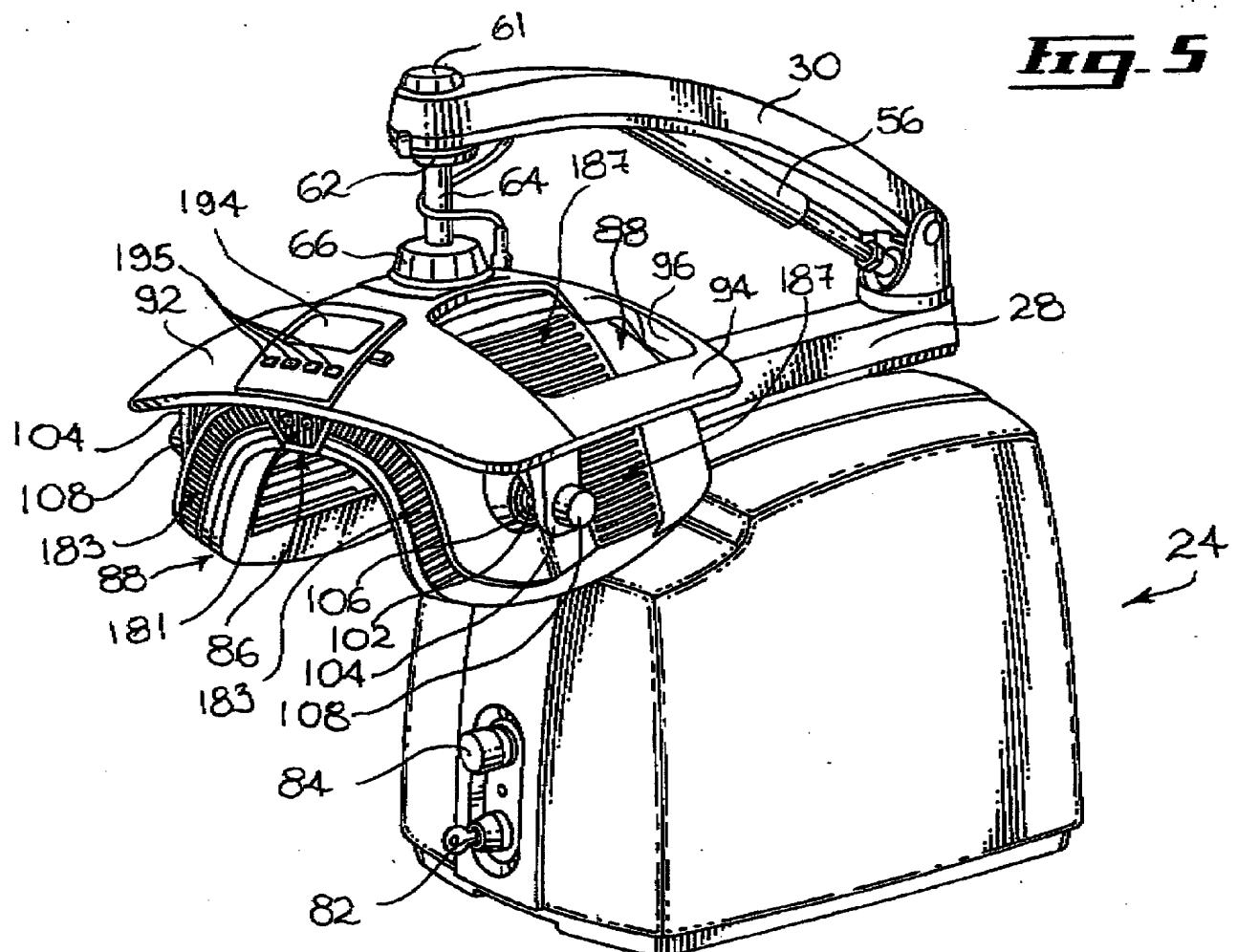


Fig 4.

FIG. 5



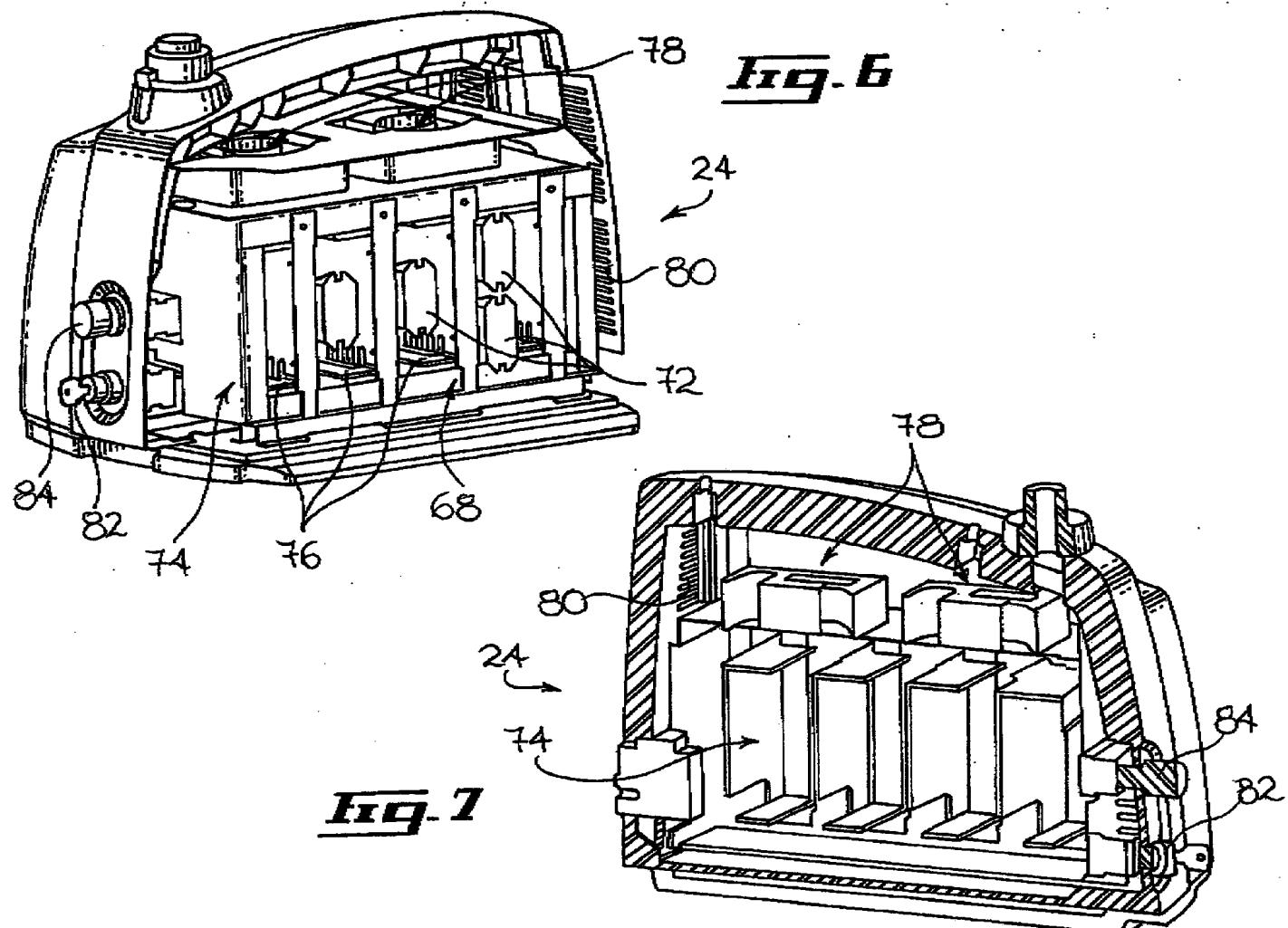
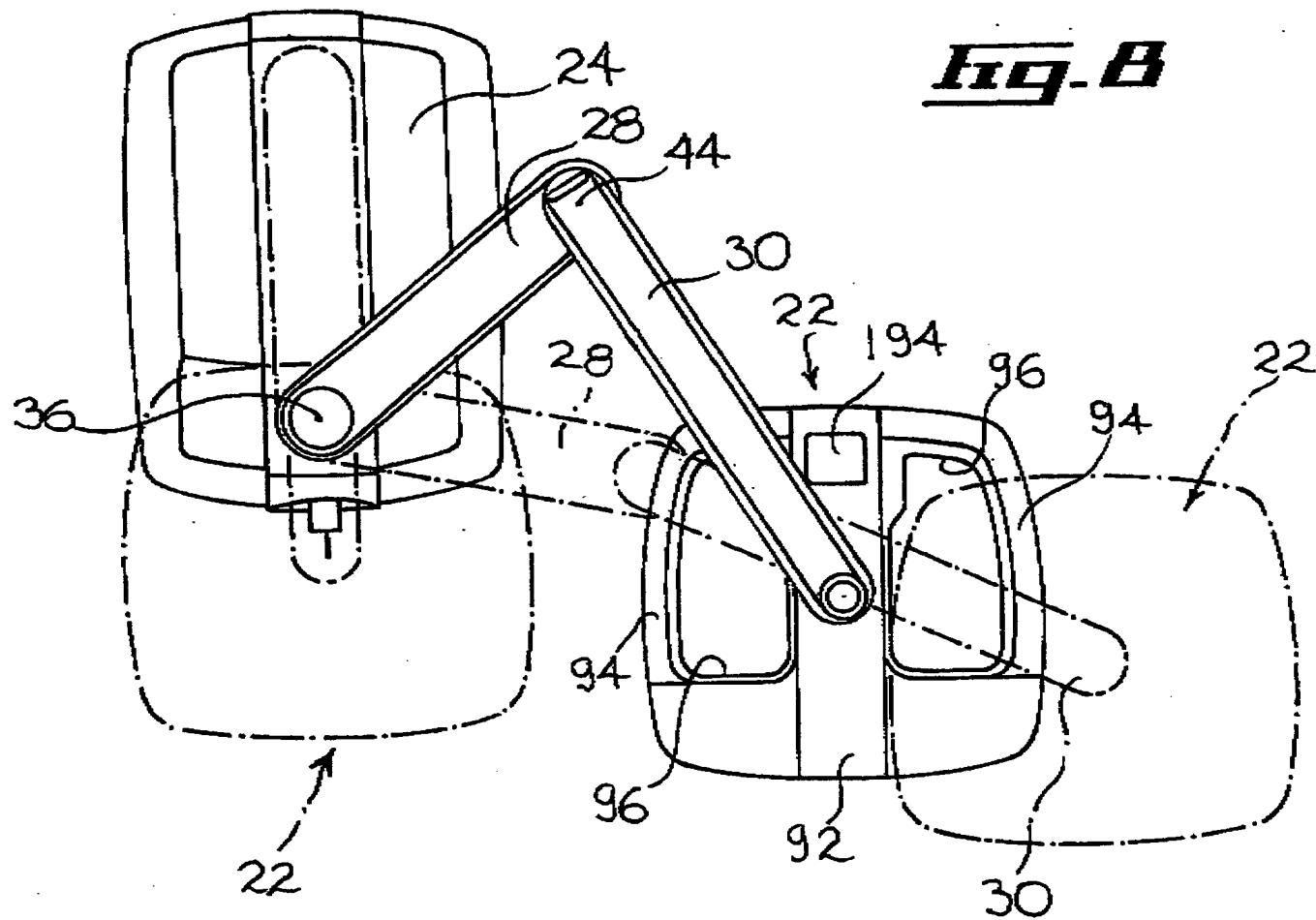
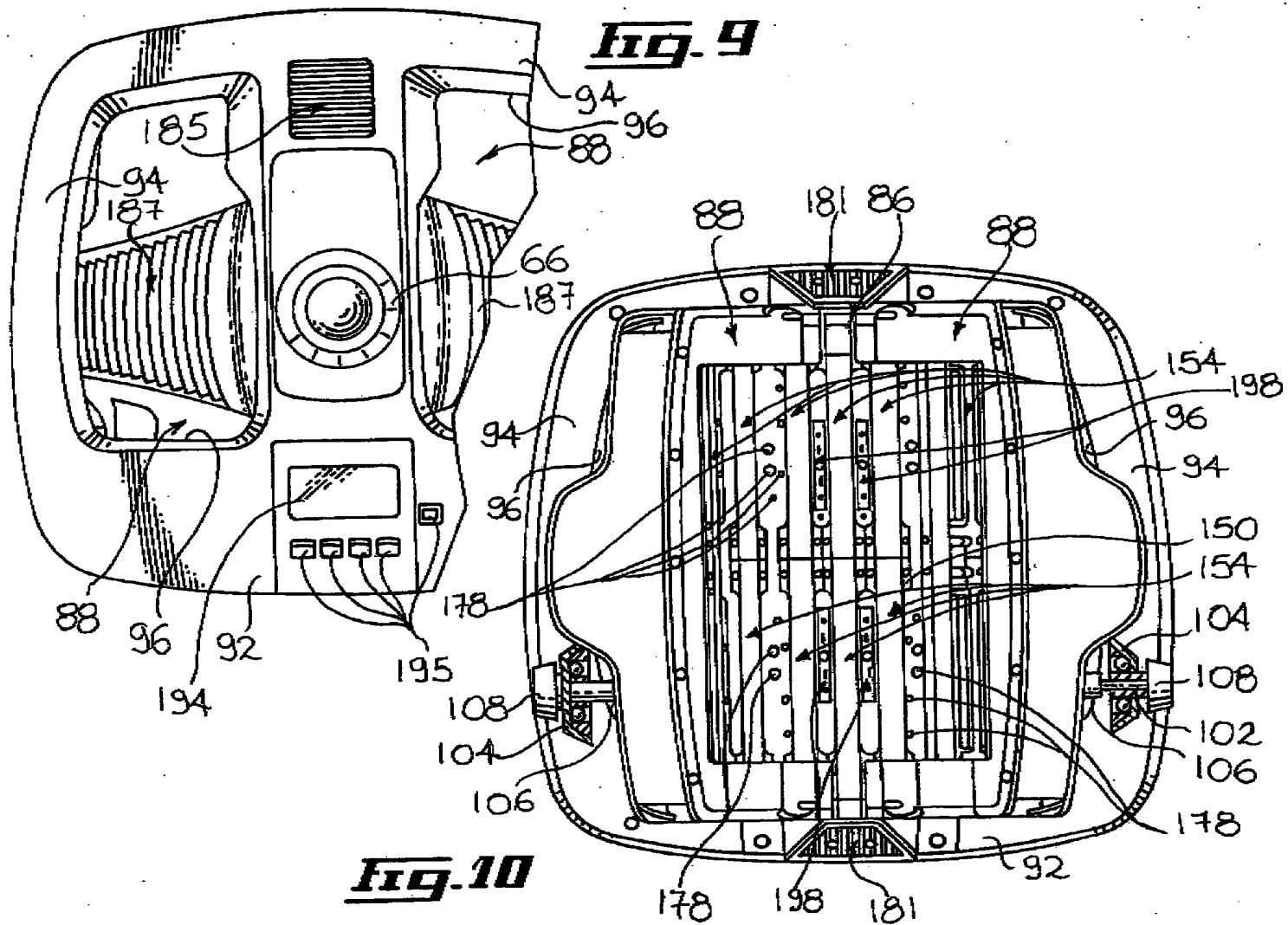


FIG. B





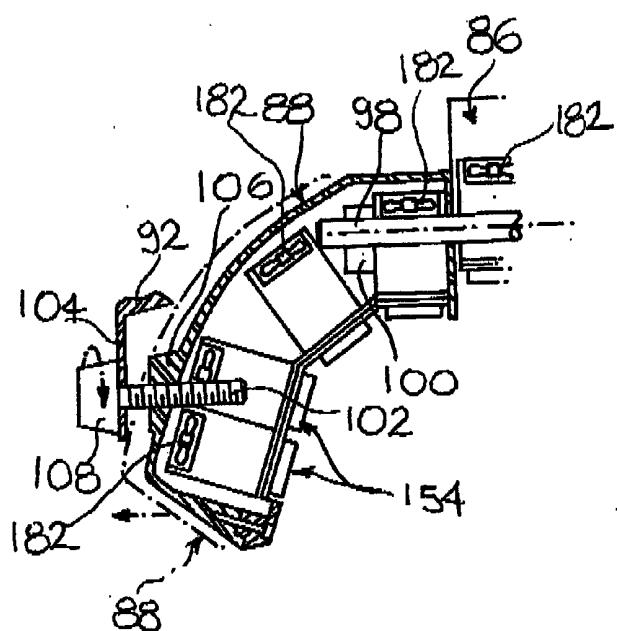


FIG. 11

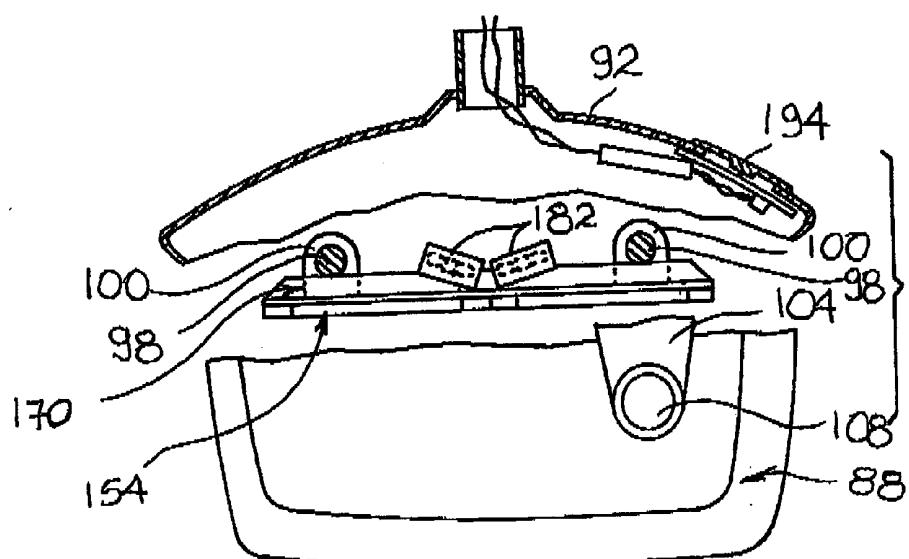


FIG. 12

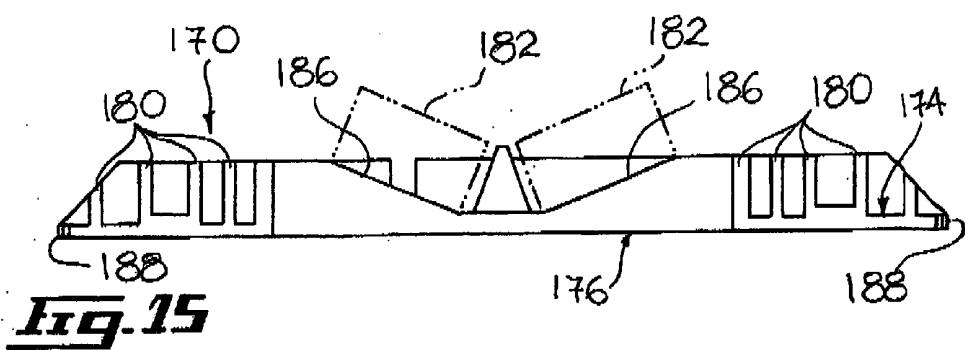
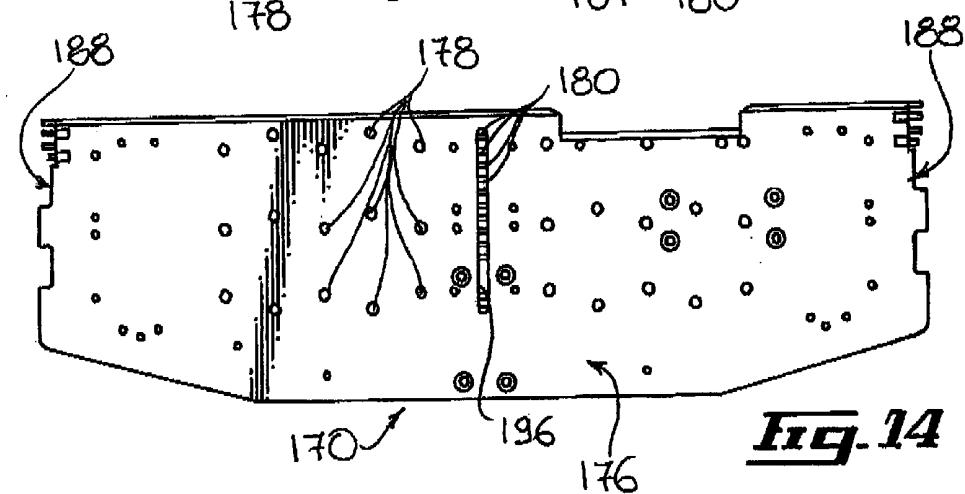
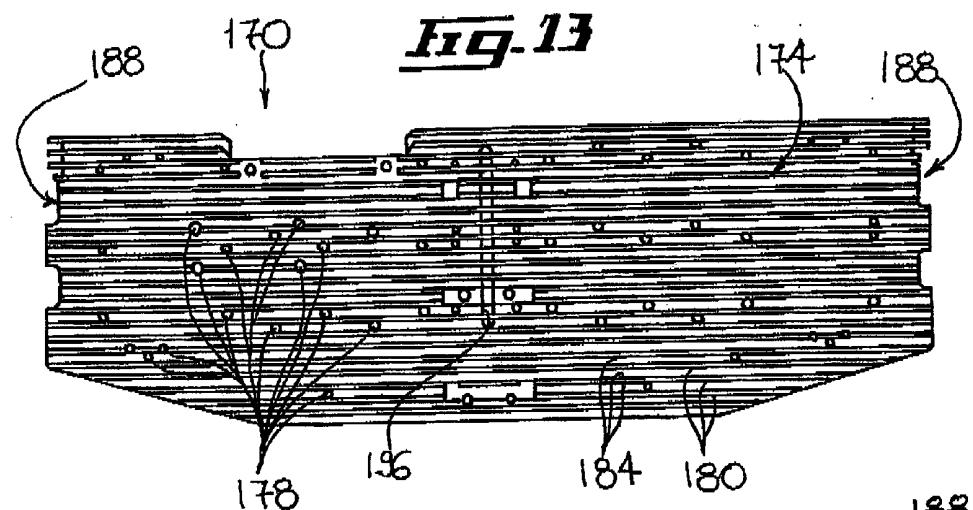


Fig. 16

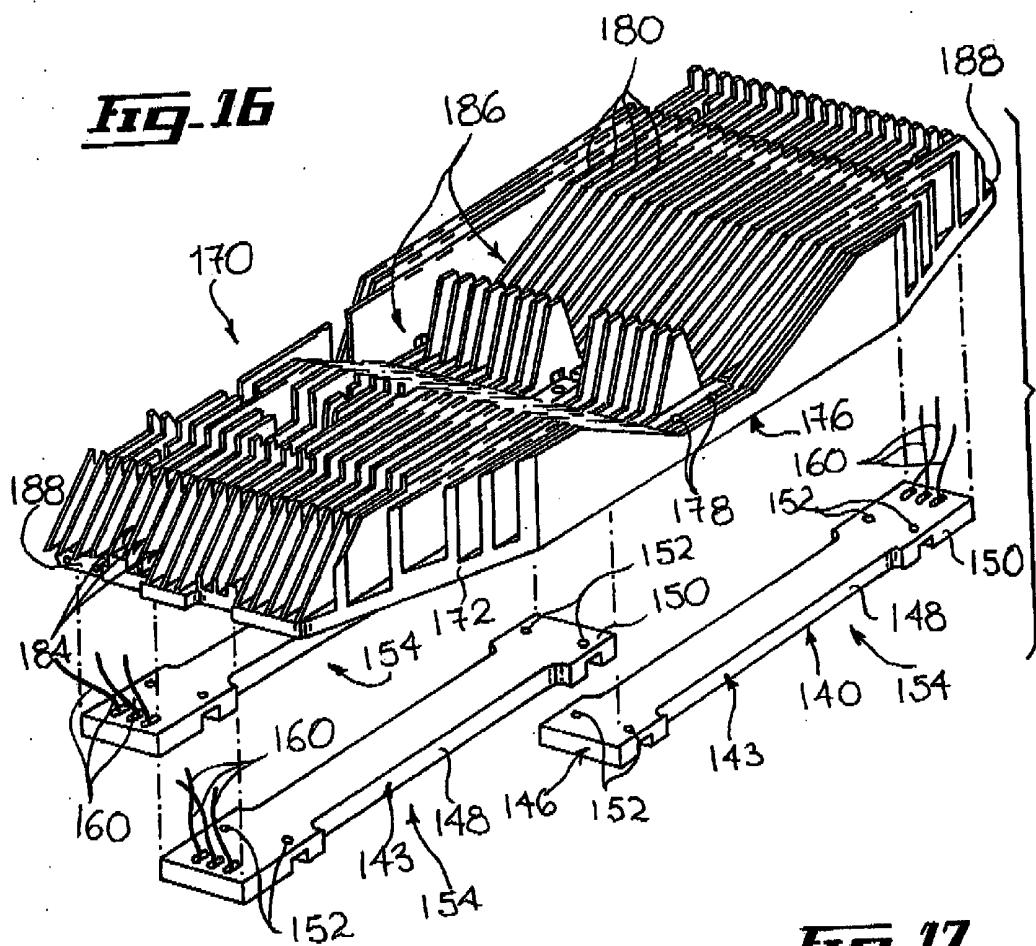
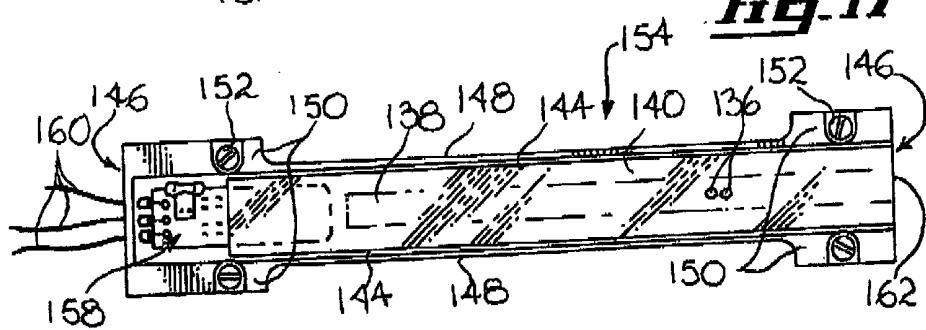
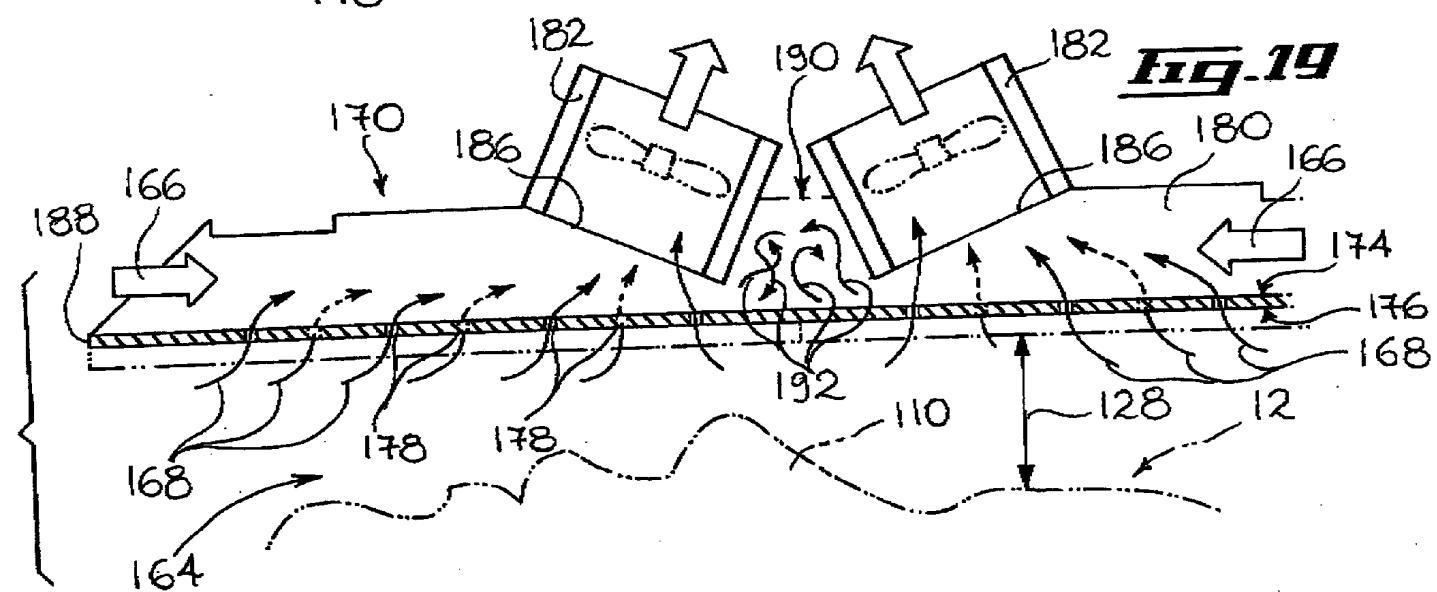
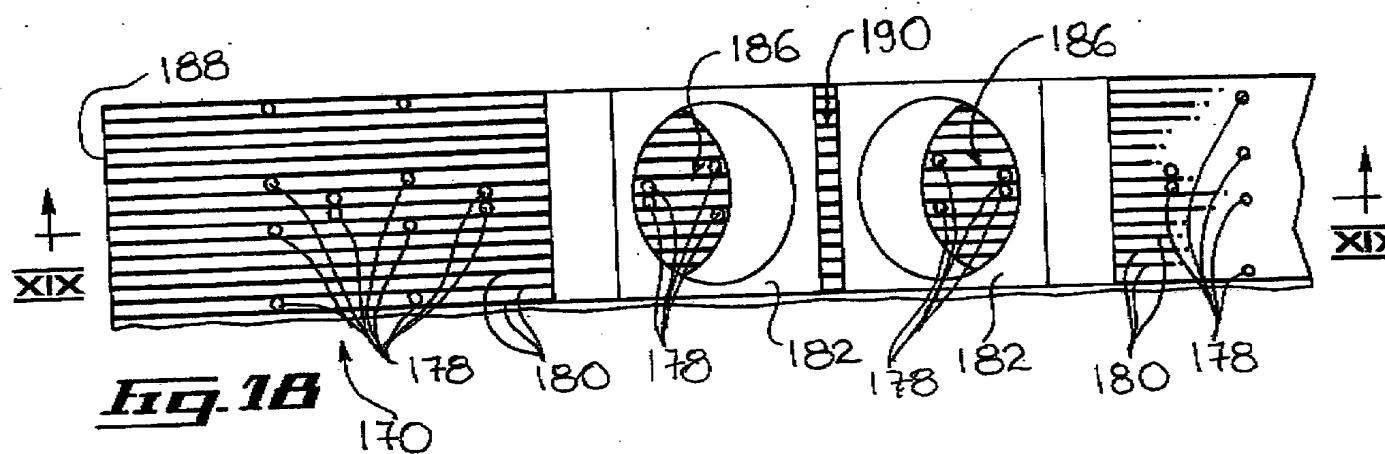
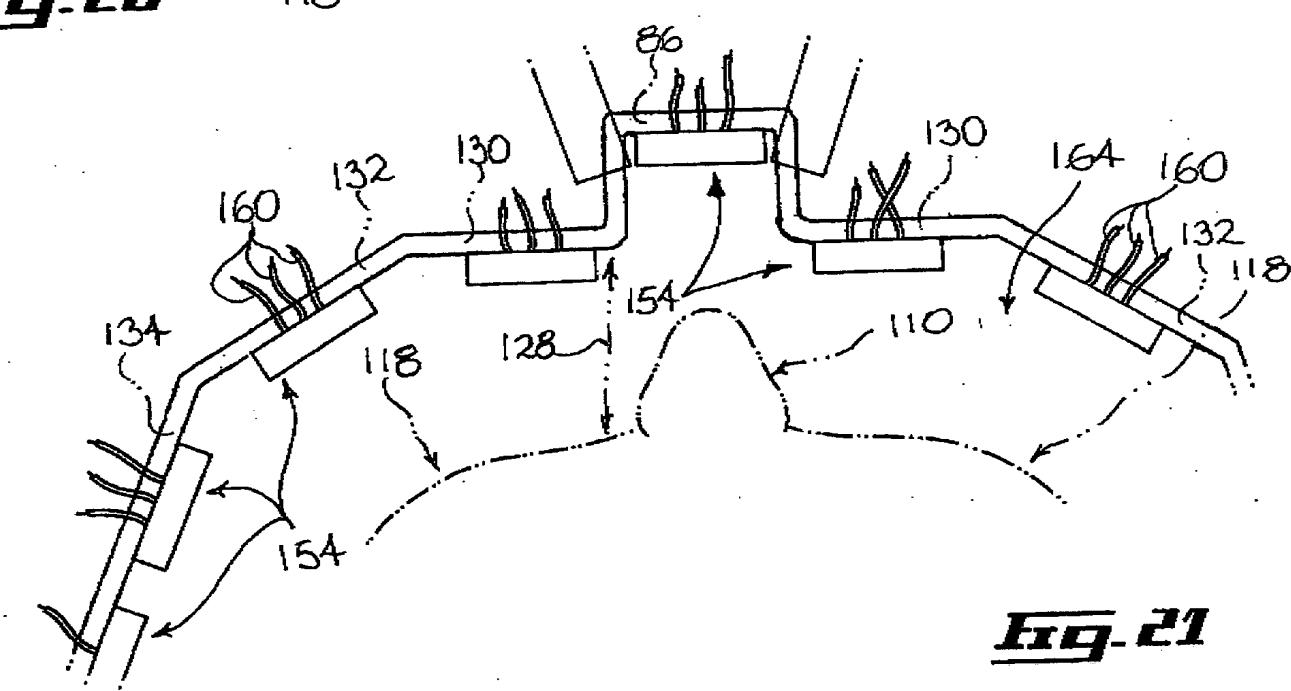
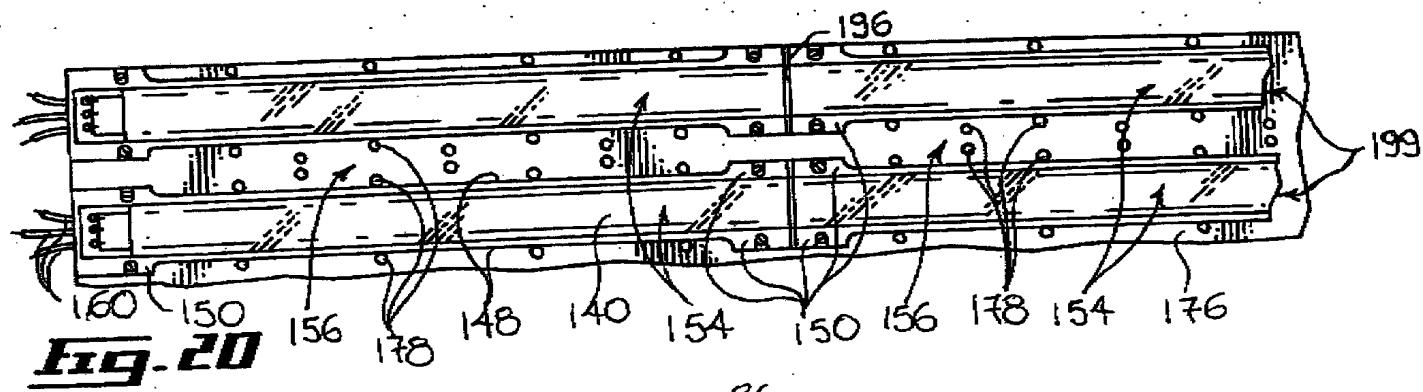
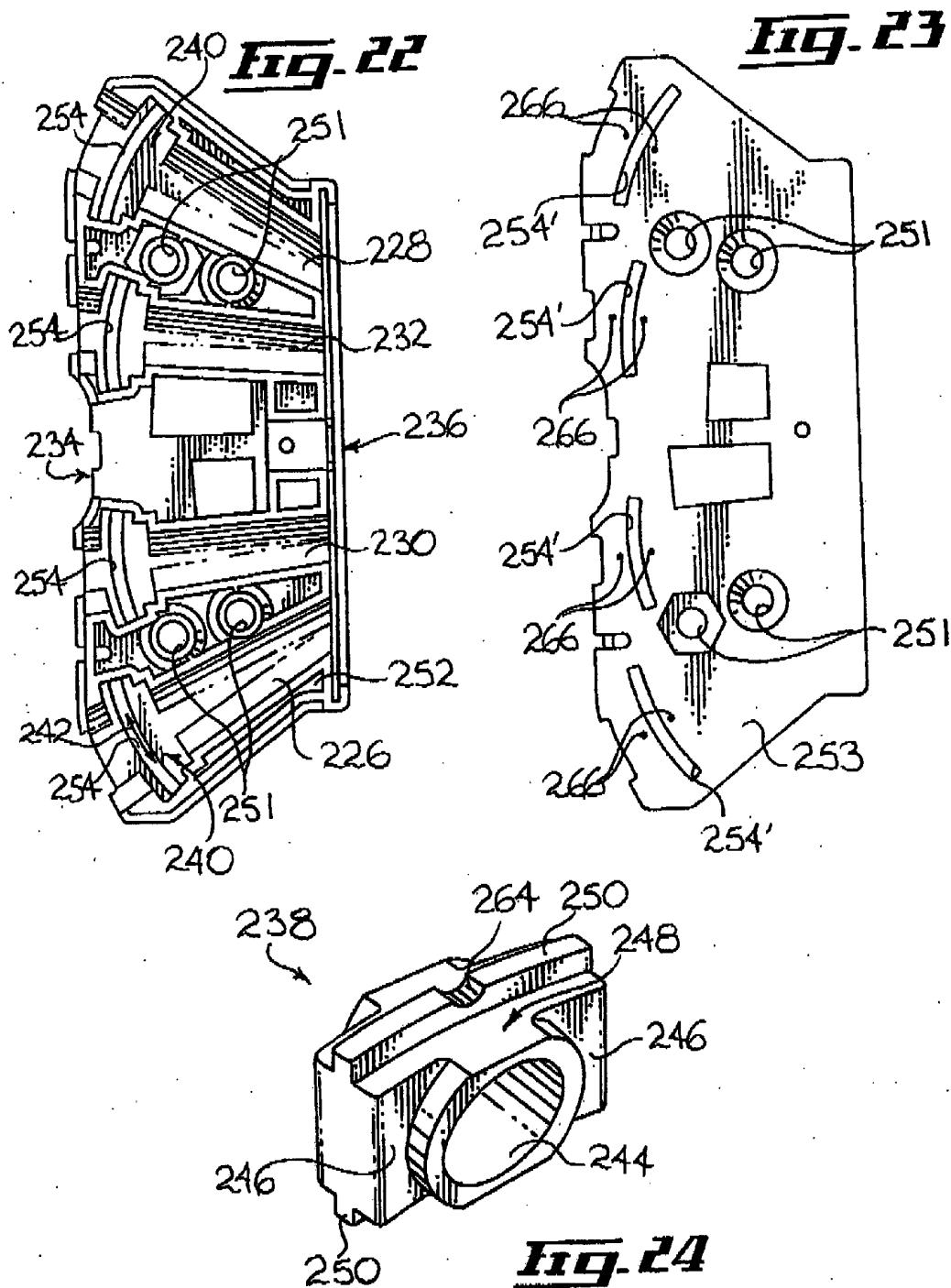


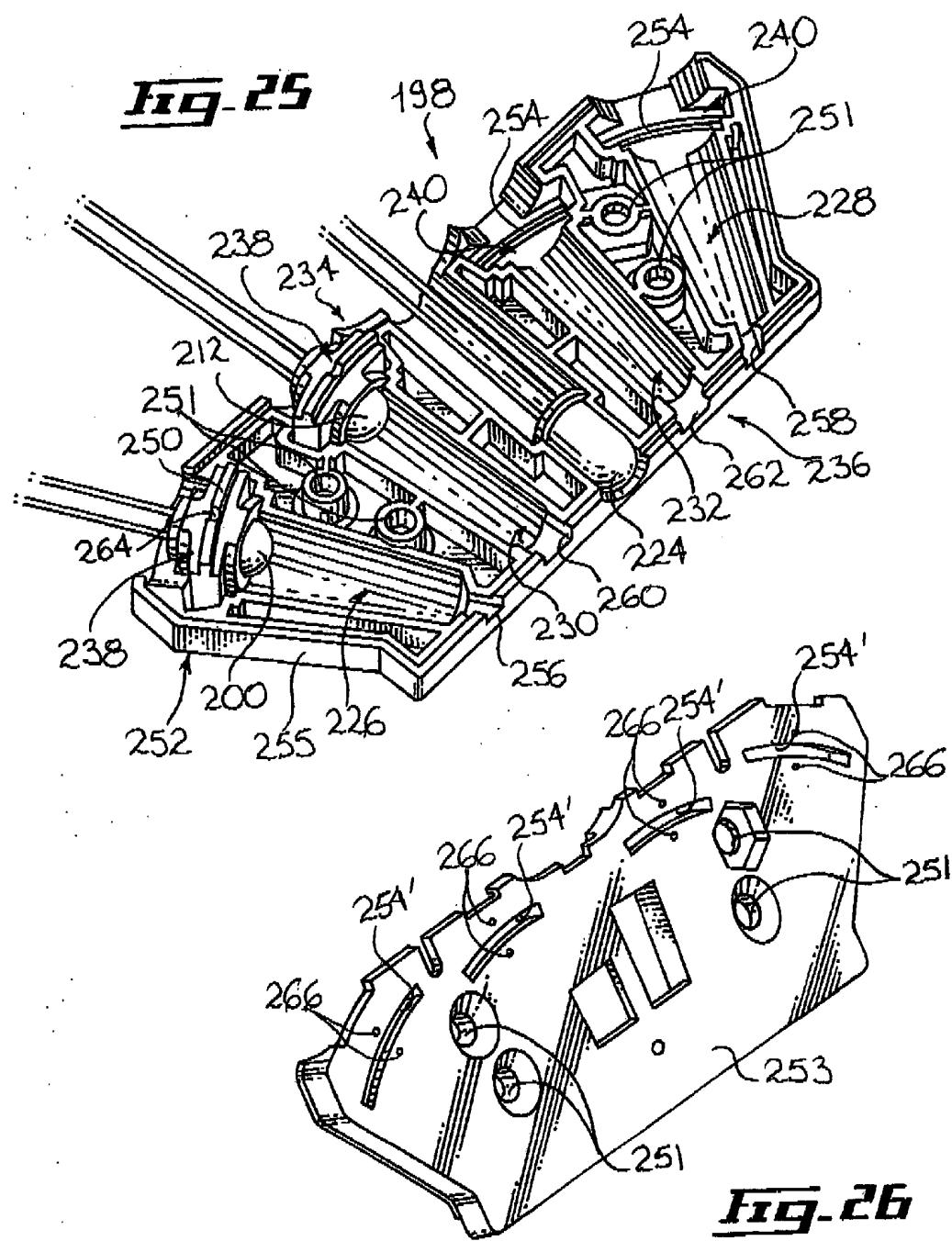
Fig. 17

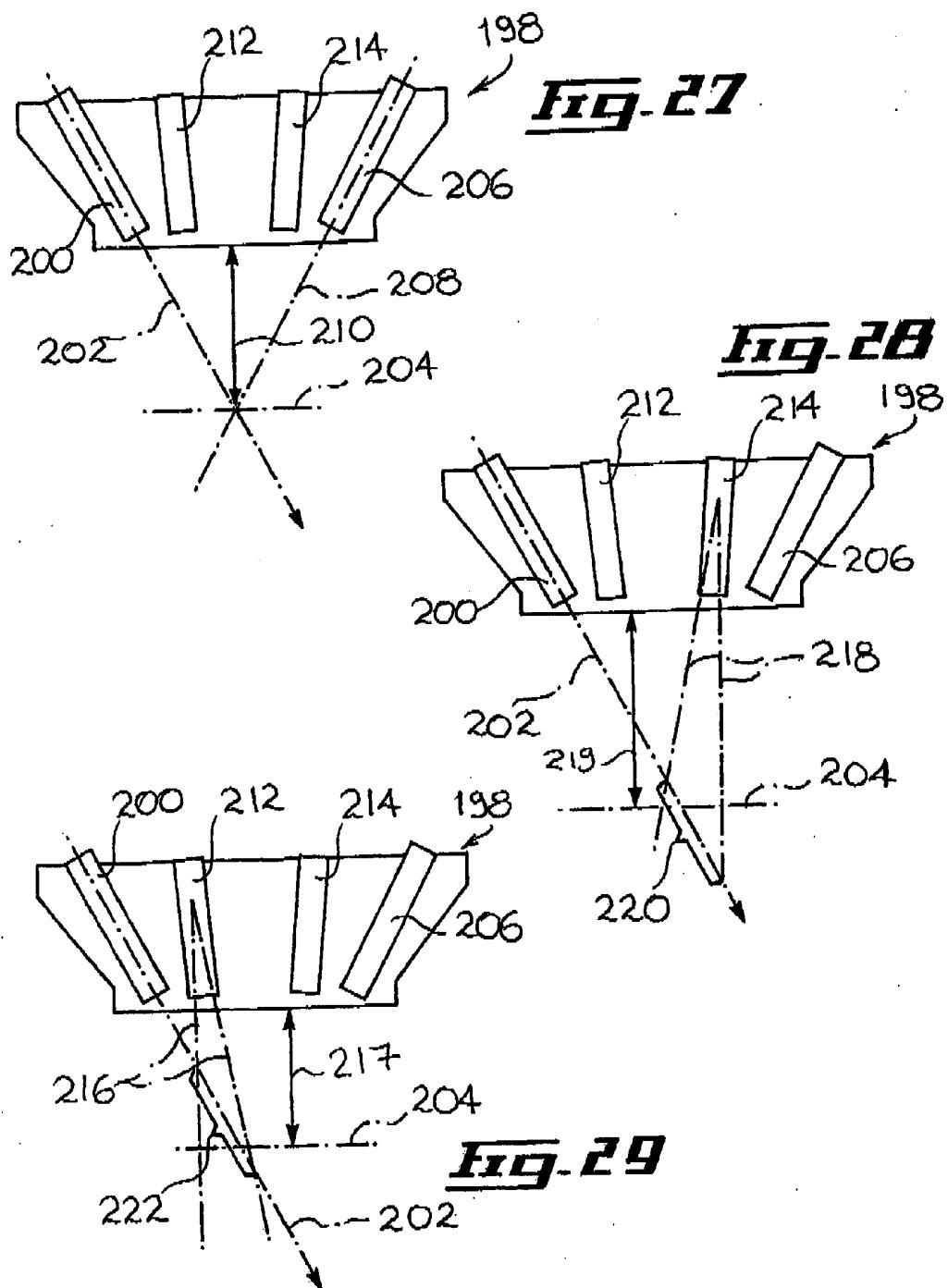












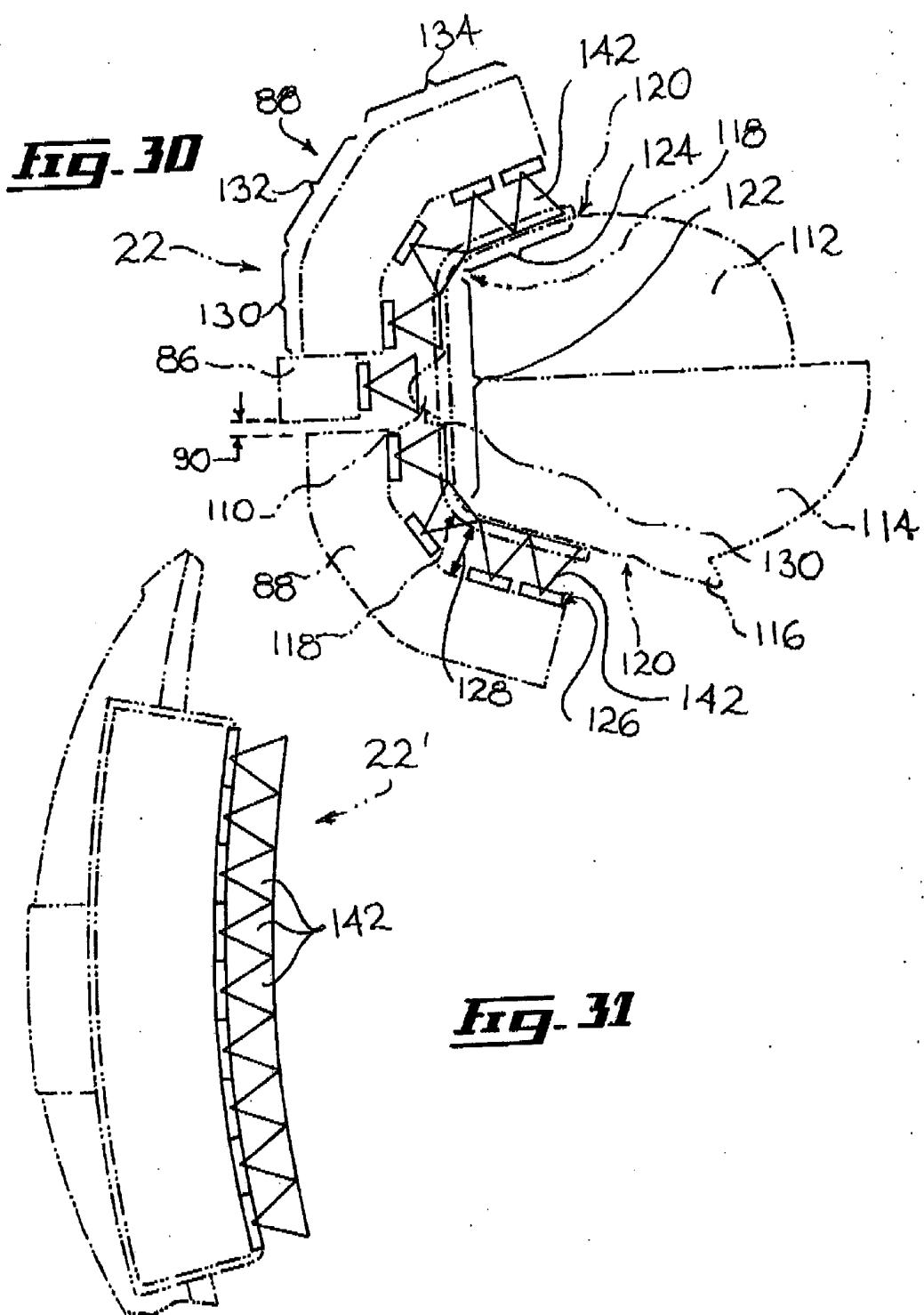


FIGURE 32

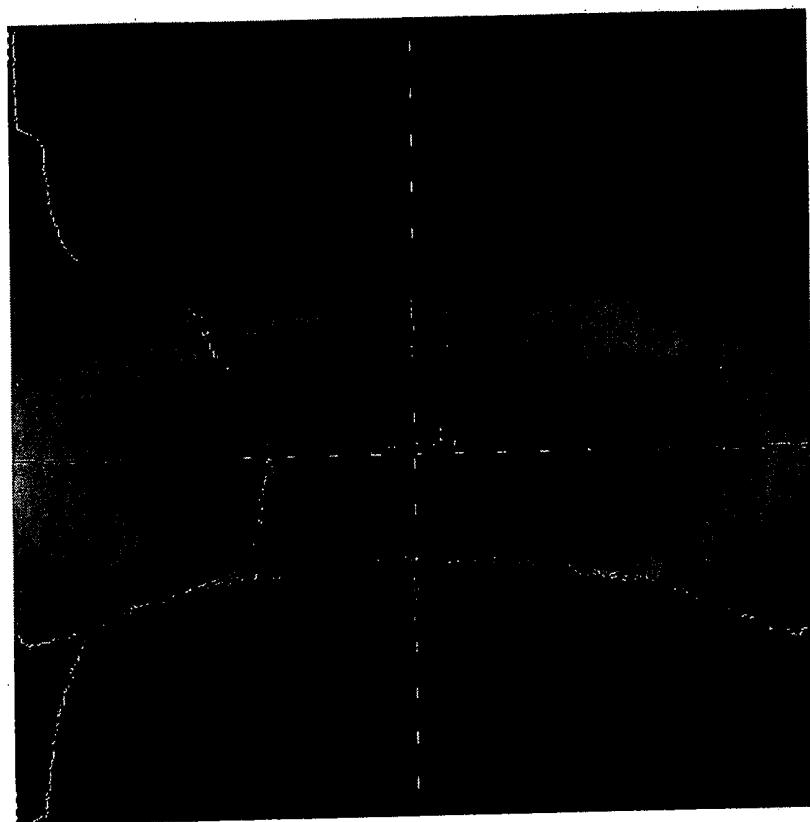
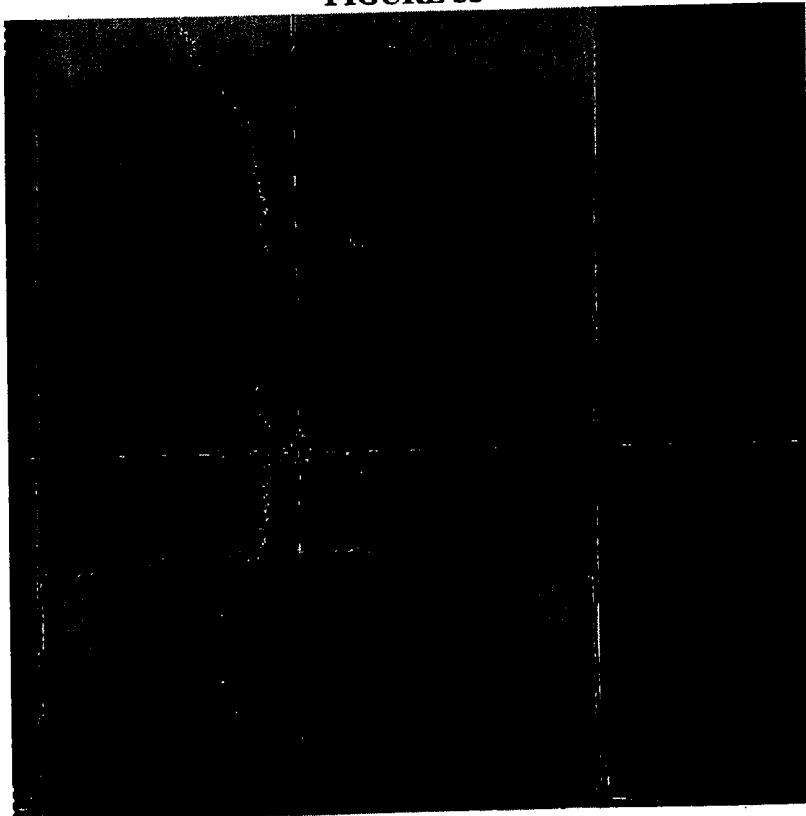
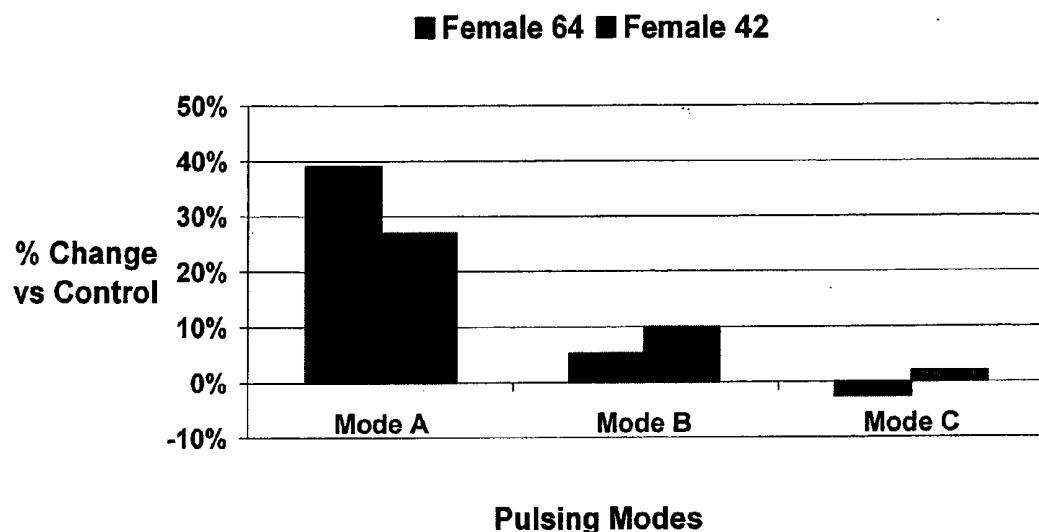


FIGURE 33



Percent Change in Average Procollagen Secretion vs Control (11 Treatments/1 Month)*



Pulsing Modes

Figure 34

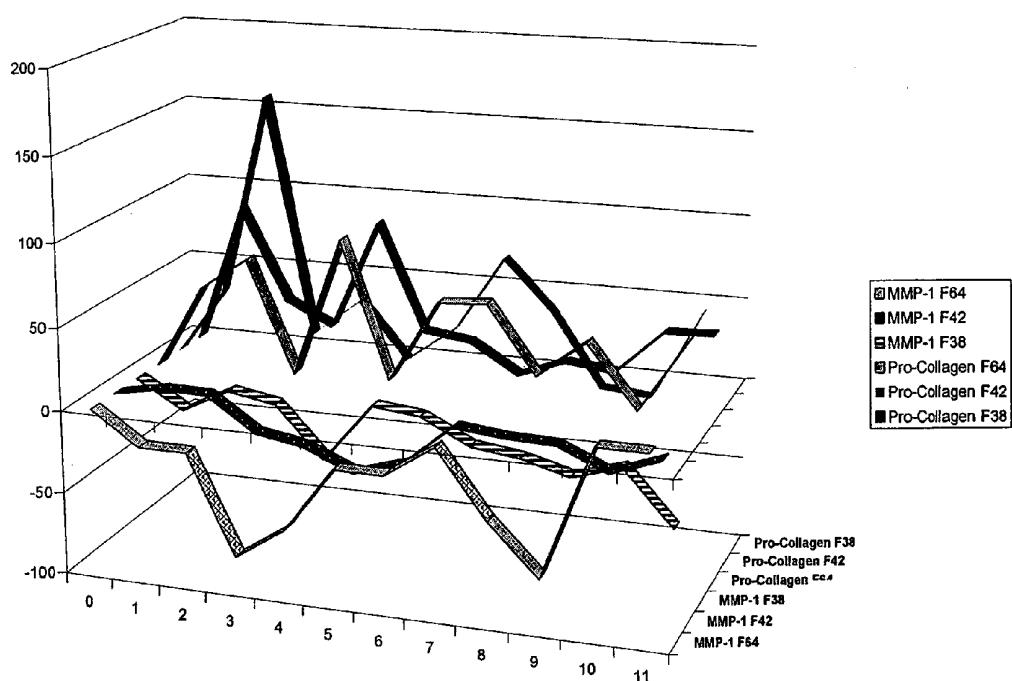


Figure 35

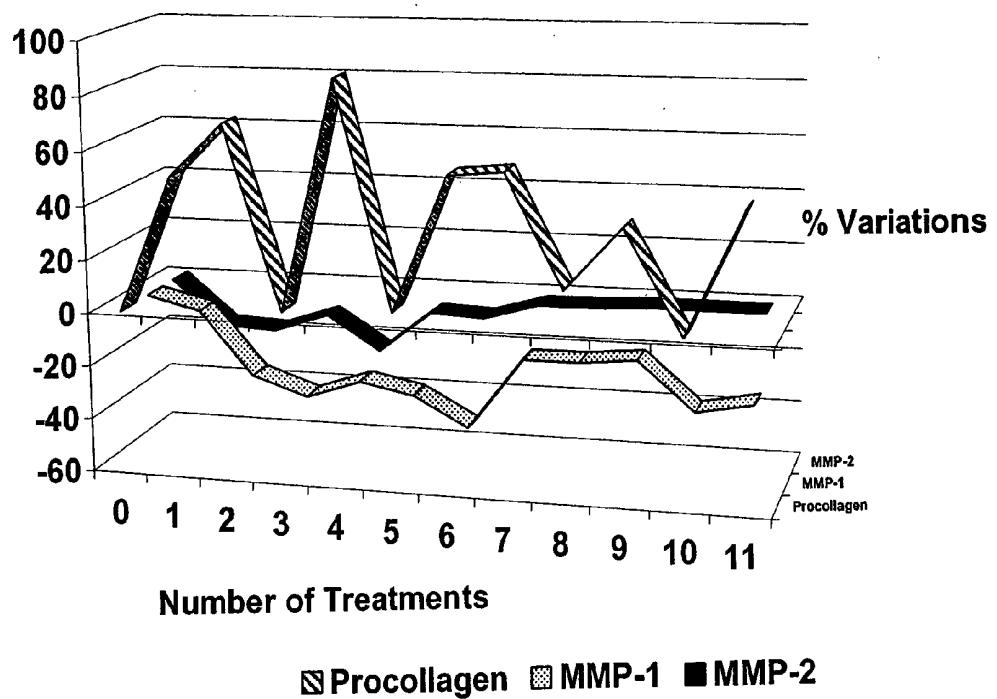


Figure 36

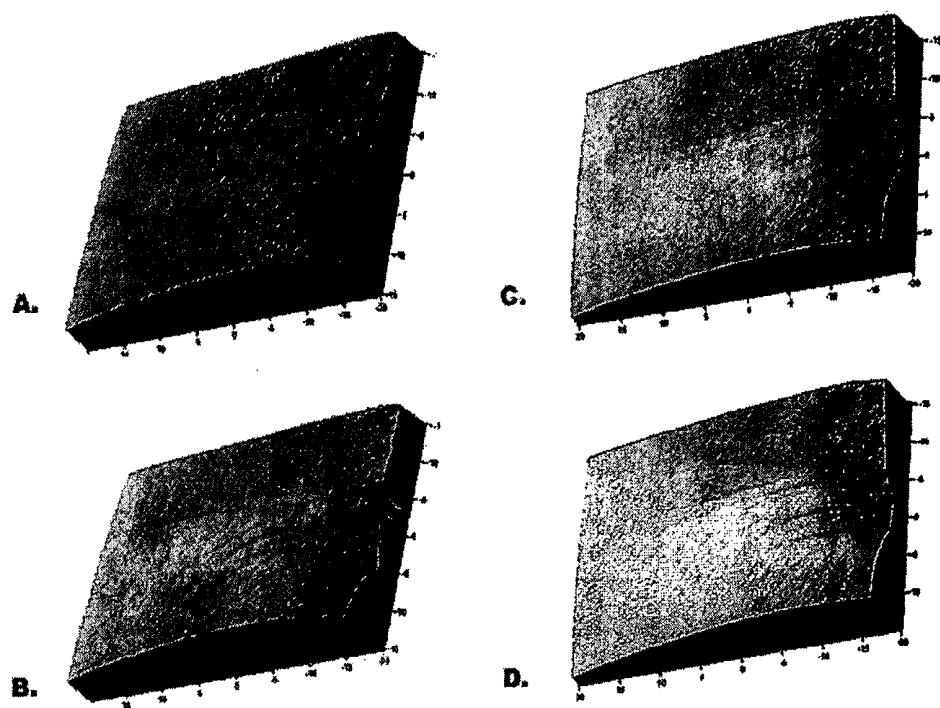


Figure 37

Fig. 38

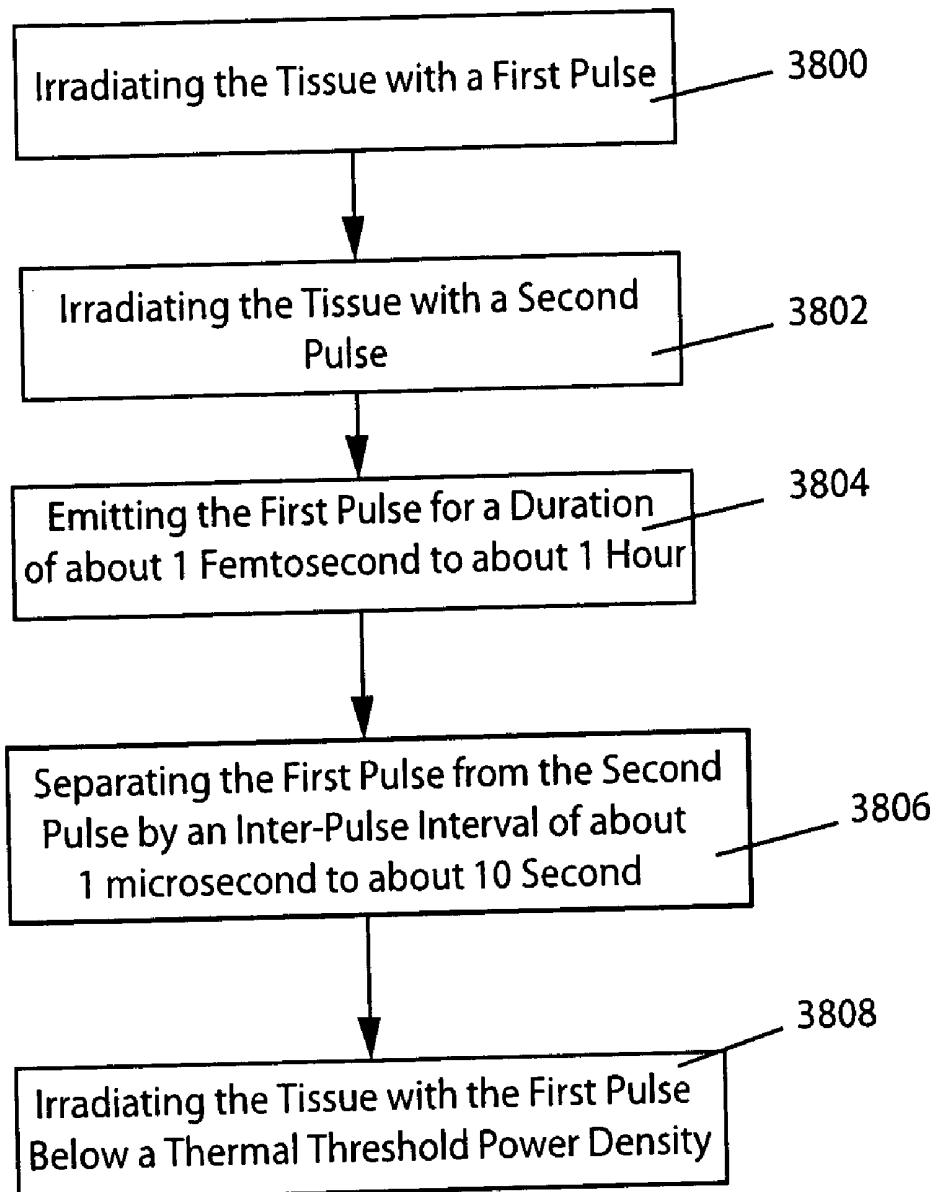


Fig. 39

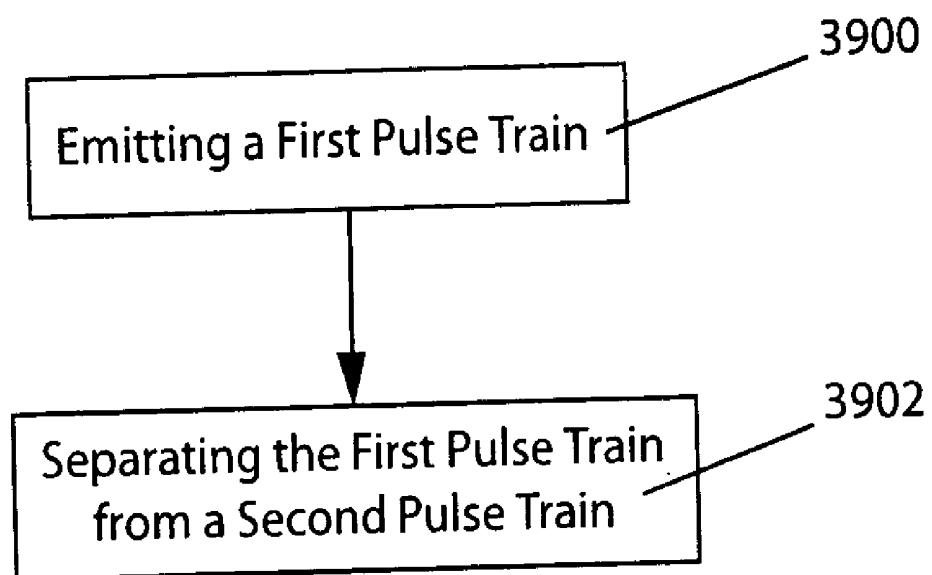


Fig. 40

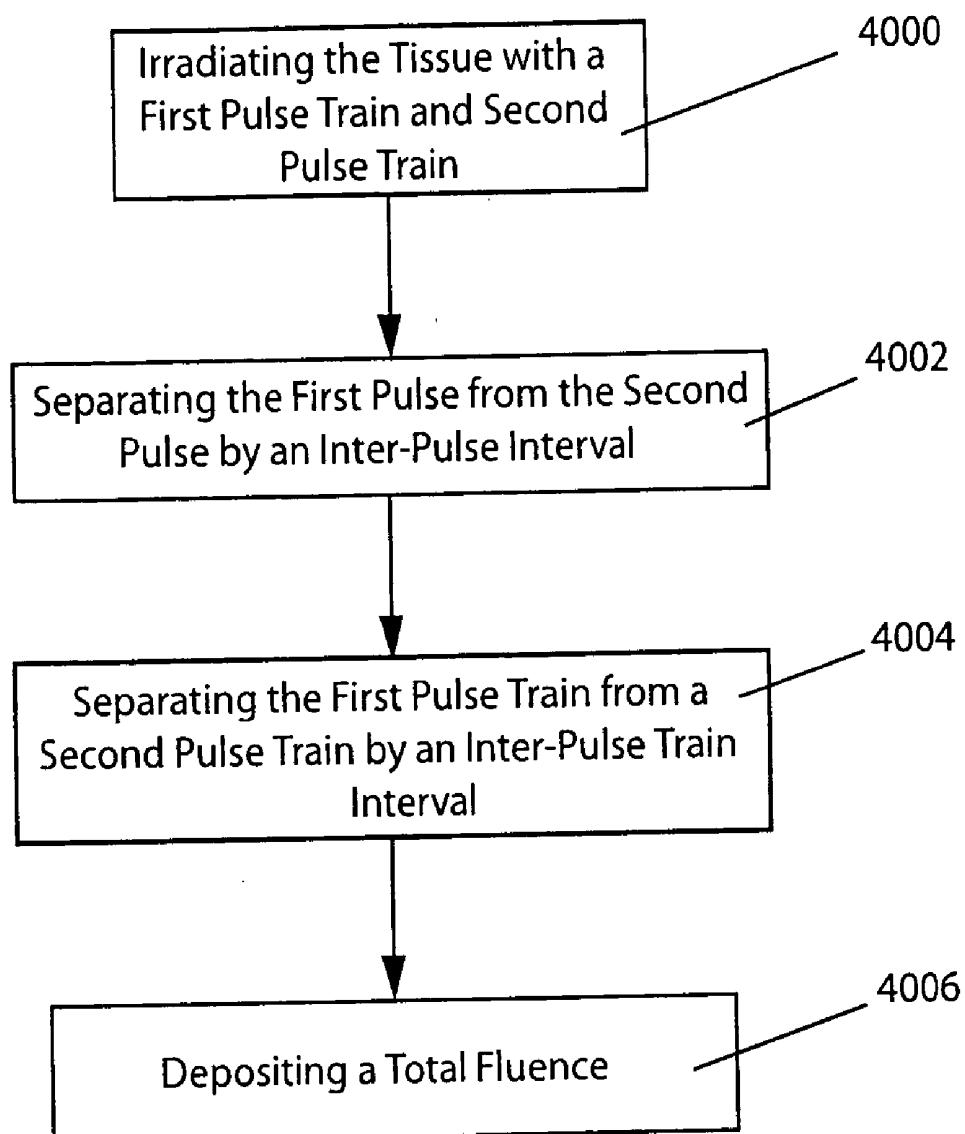


Fig. 41a

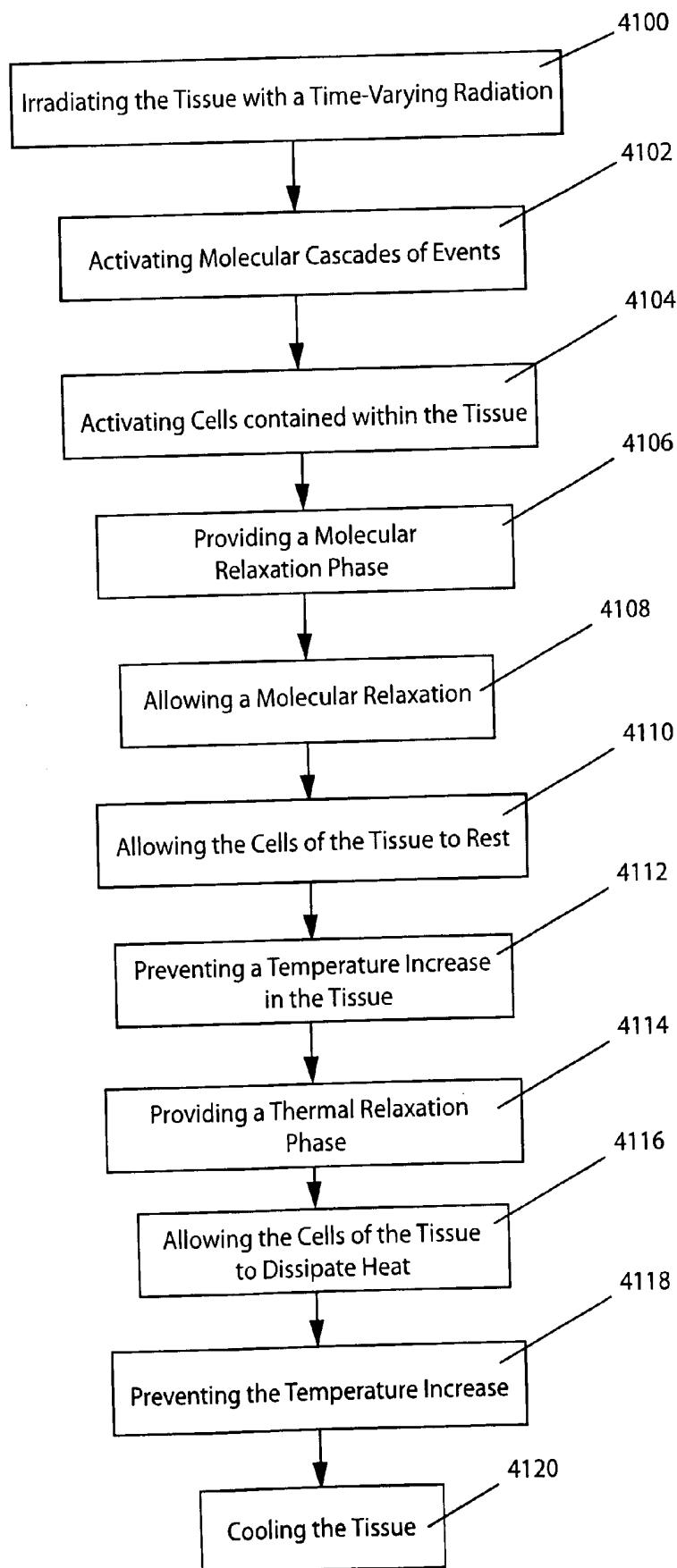


Fig. 41b

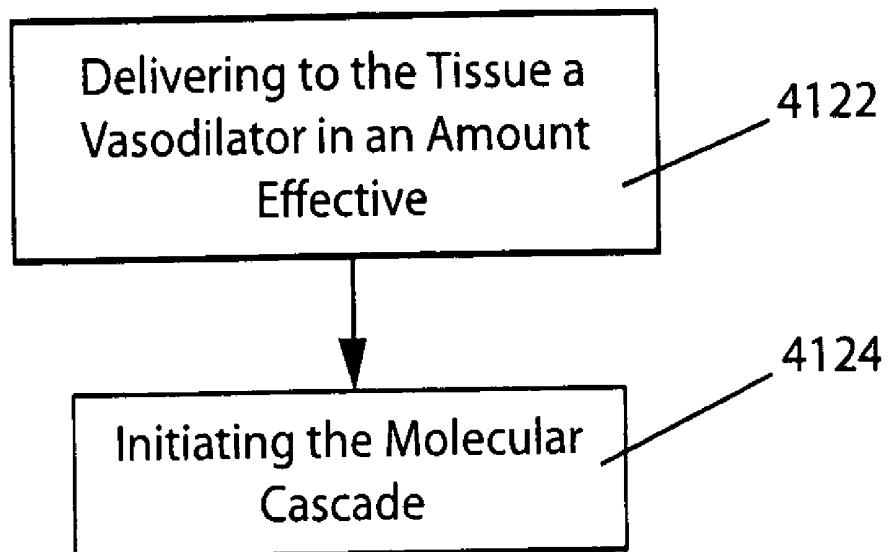
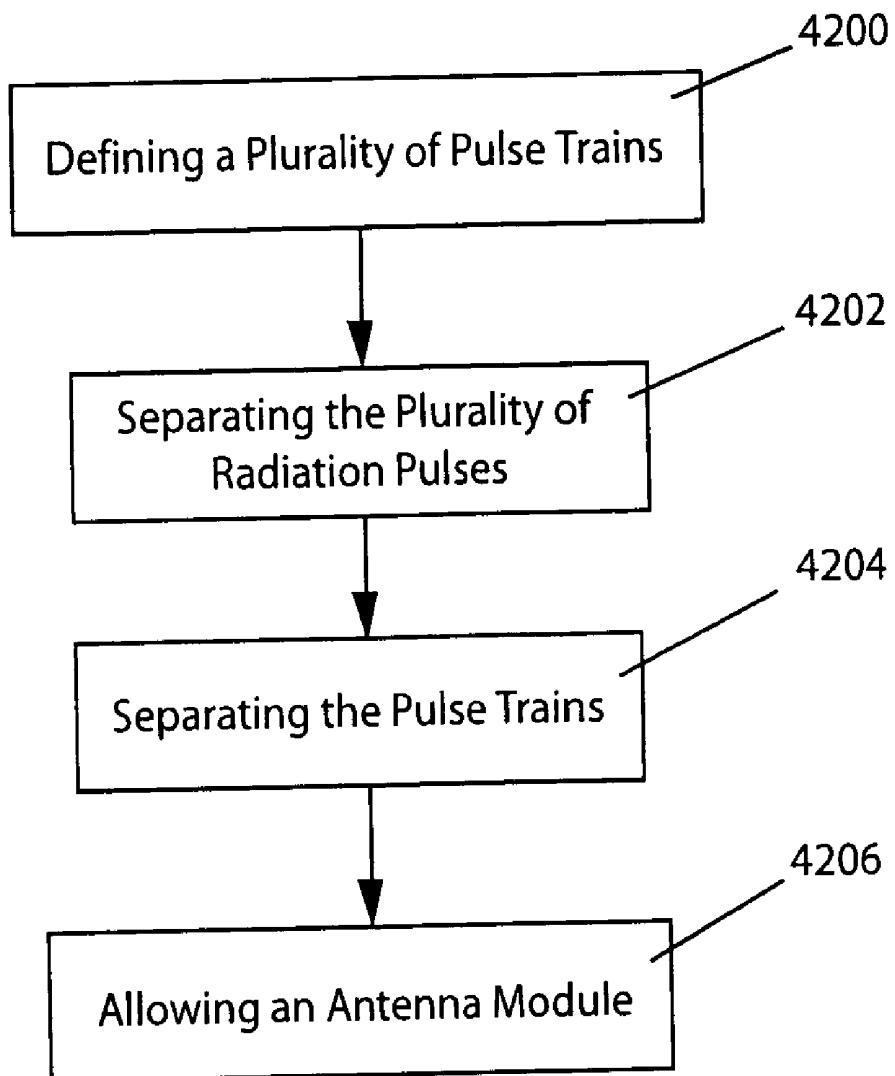


Fig. 42



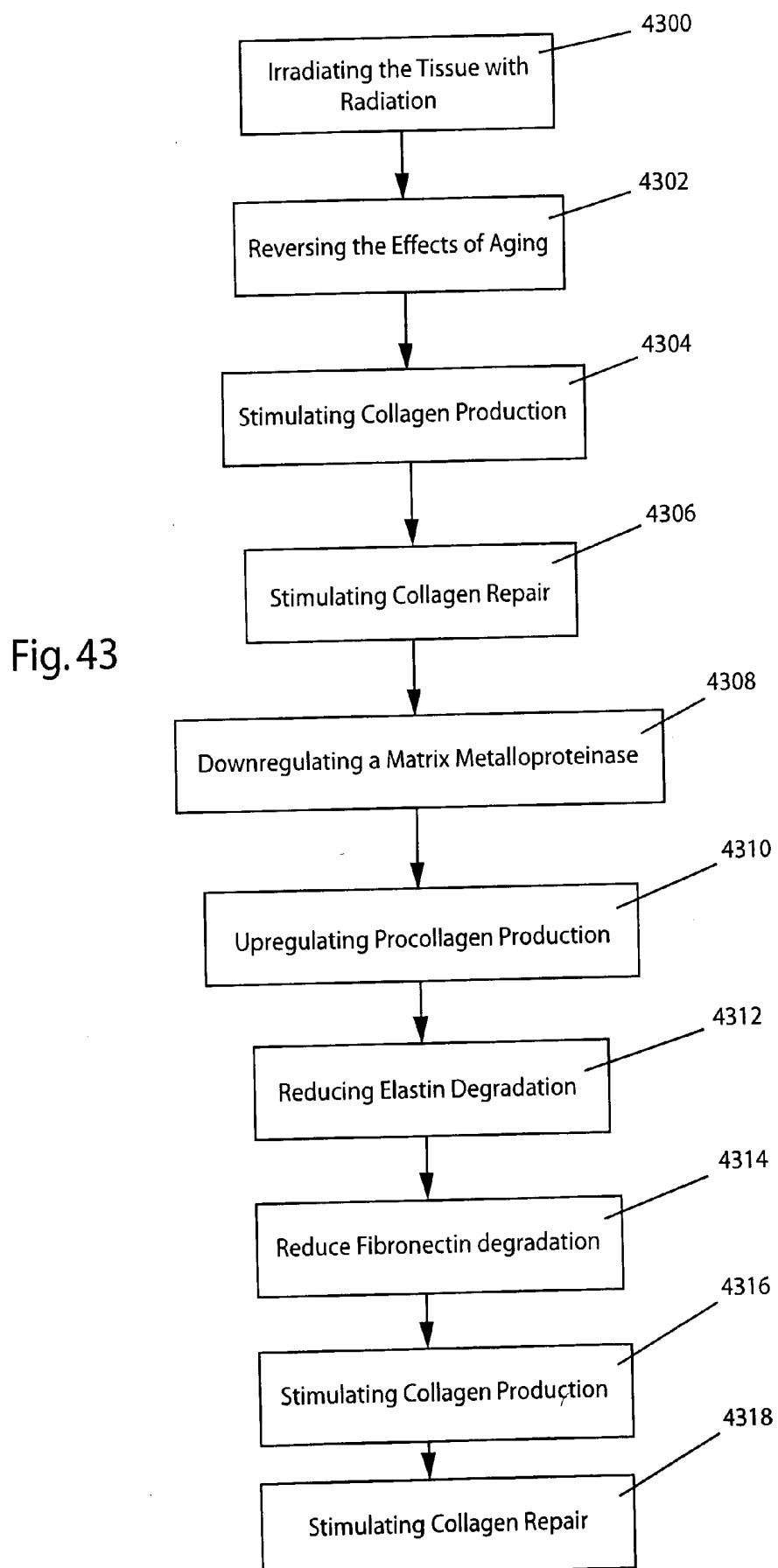


Fig. 44

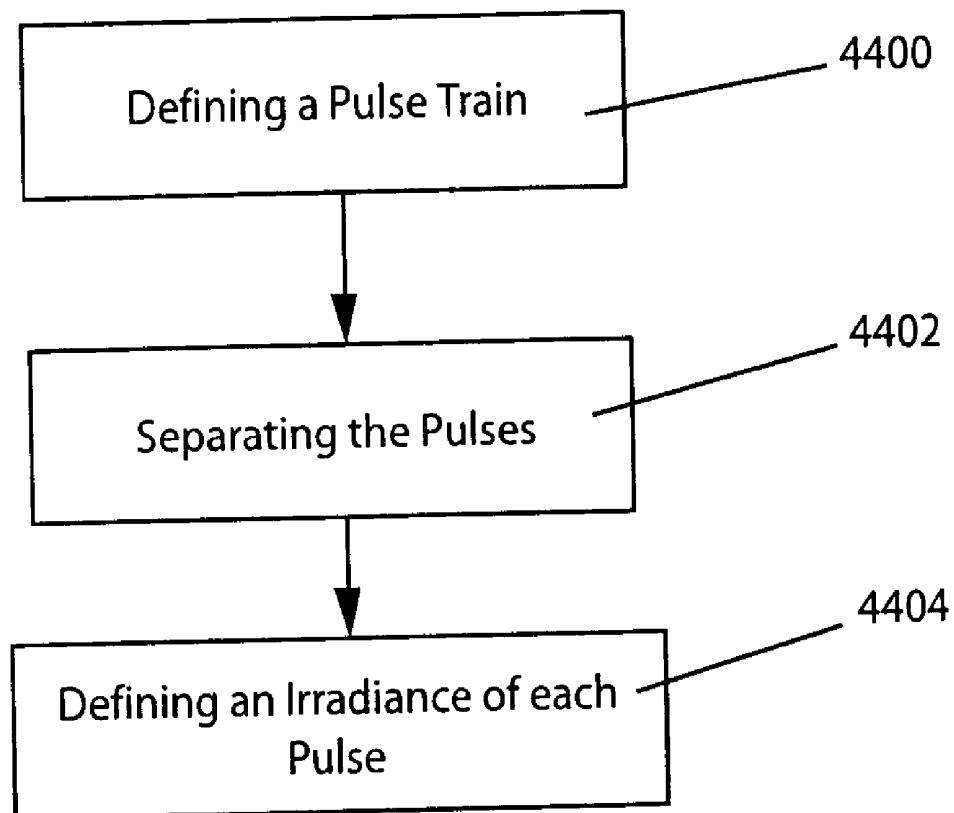


Fig. 45a

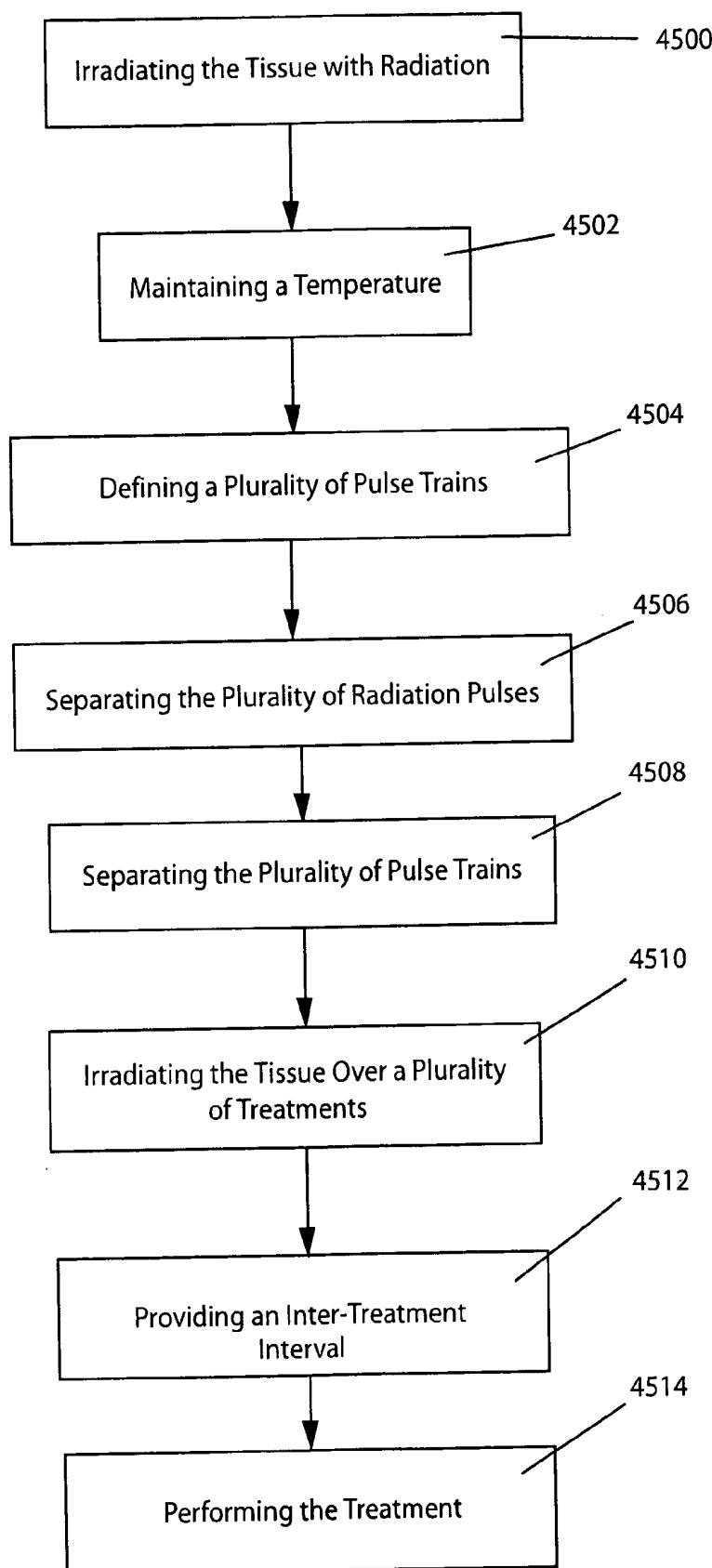


Fig. 45b

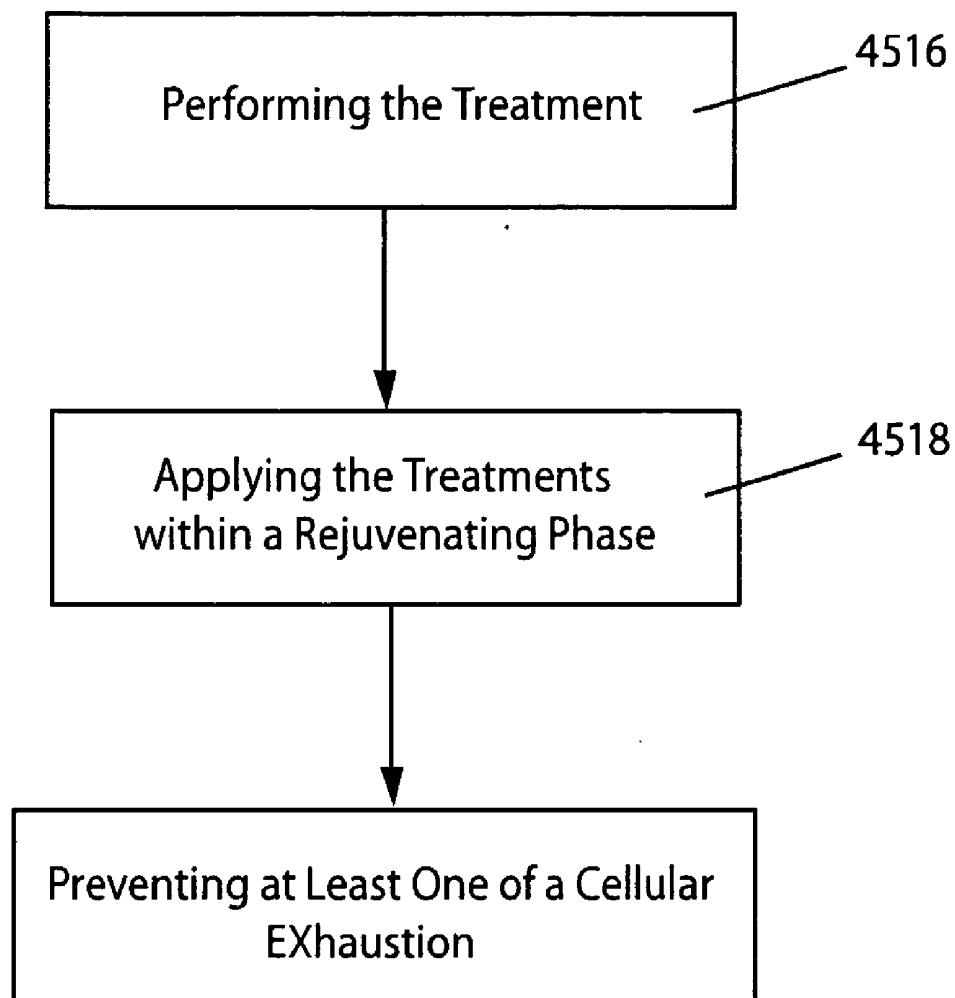


Fig. 46

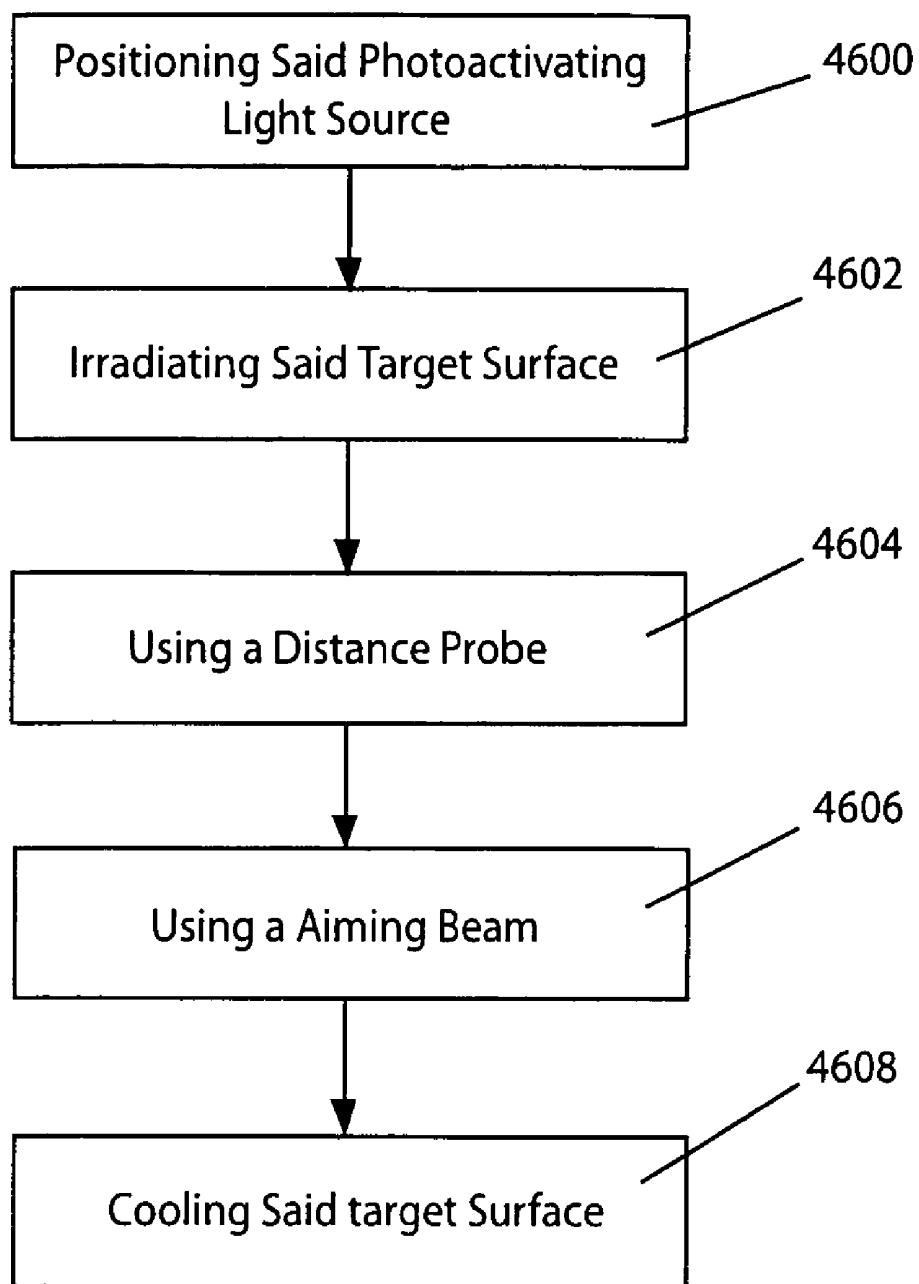
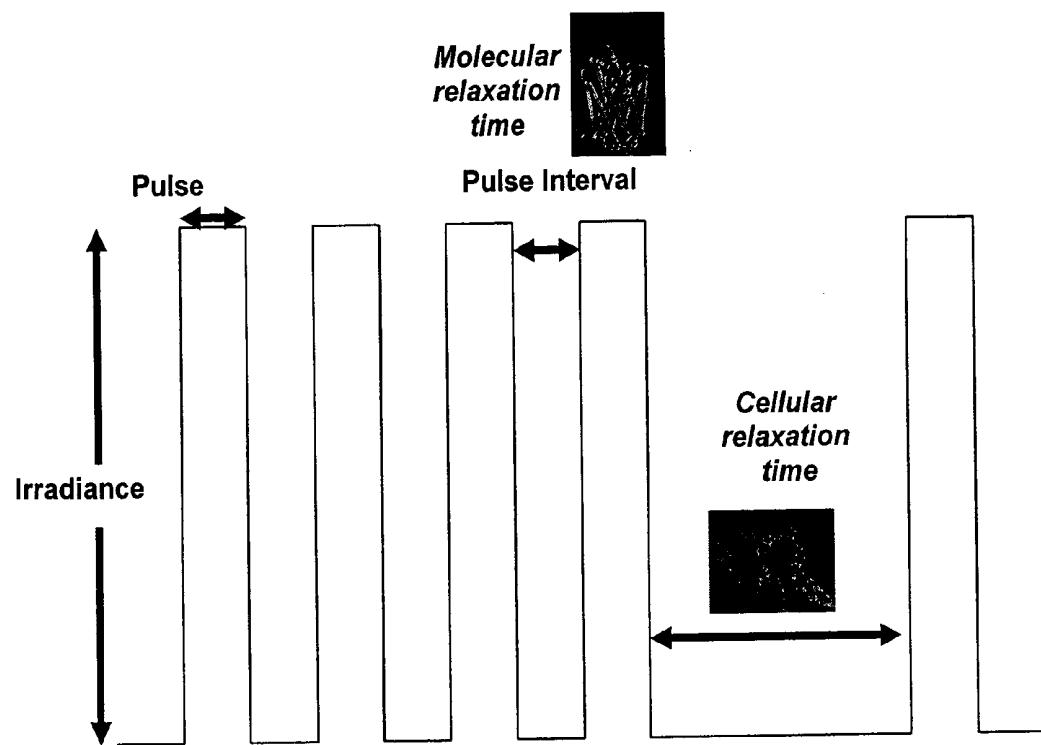


FIGURE 47



METHOD AND DEVICE FOR THE TREATMENT OF MAMMALIAN TISSUES

FIELD OF THE INVENTION

[0001] The present invention relates to the field of treatment of living tissue such as the dermatological treatment of skin, and is particularly concerned with a method and a device for the treatment of mammalian tissues.

BACKGROUND OF THE INVENTION

[0002] With aging demographics, dermatological treatments in general and in particular dermatological treatments for slowing the effects of aging are becoming increasingly popular.

[0003] It is known that aging of the skin shifts the balance between collagen production and breakdown, which leads to wrinkles, facial sag and rough skin texture. Stimulating skin cells to produce collagen can partly reverse this process. Stimulating collagen synthesis in aged skin is shown to reduce wrinkles and improve skin texture. The benefit of stimulating a person's own collagen production is that collagen is deposited in an orderly, structured manner and that there is no risk of allergy, immune reaction or injection-induced infection.

[0004] Some prior art methods for reducing the effects of aging on the skin were based on thermally injuring the skin with associated disadvantages. The first era of a different approach called low level laser radiation therapy and photobioactivation occurred in the 1960s and 1970s. Some lasers available were then tested for a biological effect. Largely anecdotal observations were made at the time.

[0005] The second era began in the 1980s. During this period, proper controls were used to discriminate the placebo effect from significant results. People became interested in the wavelengths of the radiation produced by the lasers, and began to investigate the photobiological basis of the therapeutic use of laser radiation.

[0006] A third era has recently started. More data on the photobiological basis of existing phototherapies are now available, and more is known about the photoactivation of enzymes and membranes. Some prior art methods and devices of photoinduction have been proposed. However, they have heretofore yielded relatively unsatisfactory results.

[0007] In view of the above, there is a need in the industry to provide a novel method and a novel device for the treatment of mammalian tissues.

[0008] The present description refers to a number of documents, the content of which is herein incorporated by reference in their entirety.

SUMMARY OF THE INVENTION

[0009] In a broad aspect, the invention provides a method for causing a predetermined physiological change in a mammalian tissue. The method includes irradiating the tissue with a radiation having a power density in the tissue substantially larger than an activation threshold power density, the tissue being irradiated under conditions suitable to cause the predetermined physiological change.

[0010] Advantageously, the claimed invention is relatively easy to perform and relatively safe. The claimed invention is furthermore relatively painless when performed *in vivo* and gives clinically significant results in relatively few treatments.

[0011] The invention is relatively well adapted to enhance physiological processes and causes relatively few side effects.

[0012] In another broad aspect, the invention provides a method for treating a mammalian skin tissue, the method including irradiating the tissue with radiation defining a pulse train including a plurality of radiation pulses, wherein:

[0013] a. the radiation has a wavelength of from about 400 nanometers to about 1500 nanometers;

[0014] b. the pulses each have a duration of from about 1 femtosecond to about 1 hour;

[0015] c. the pulses are separated from each other by an inter-pulse interval, the inter-pulse interval being of from about 1 microsecond to about 10 seconds; and

[0016] d. the power density of each pulse in the tissue is of from about 0.1 mW/cm² to about 10 W/cm².

[0017] In yet another broad aspect, the invention provides a method for altering the physiology of a mammalian tissue, the method including irradiating the tissue with radiation defining a plurality of pulse trains, each pulse train including a plurality of radiation pulses having a predetermined pulse duration, the pulses being separated from each other by an inter-pulse time interval, the pulse trains being separated from each other by an inter-train time interval, the inter-train interval being substantially larger than the inter-pulse interval.

[0018] In yet another broad aspect, the invention provides a method for altering the physiology of a mammalian tissue, the method including irradiating the tissue with a time-varying radiation according to a power density temporal profile suitable for both activating molecular cascades of events and activating cells contained within the tissue.

[0019] In yet another broad aspect, the invention provides a method for regenerating an extracellular matrix in mammalian tissue, the method including irradiating the tissue with radiation under conditions suitable to regenerate the extracellular matrix.

[0020] In yet another broad aspect, the invention provides a method for improving tissue integrity in mammalian tissue, the method including irradiating the tissue with radiation under conditions suitable to improve tissue integrity in the mammalian tissue.

[0021] In yet another broad aspect, the invention provides a method for reducing damages previously caused to a mammalian skin tissue, the method including irradiating the tissue with radiation presenting a power density temporal profile such that the radiation has a power density within the tissue that is above an activation threshold at least over a predetermined time interval, the predetermined time interval being such that the temperature of the tissue remains below an overheating temperature above which the radiation is ineffective to reduce the damages previously caused to the mammalian skin tissue.

[0022] Examples of such damages include damages caused by aging and pathologies, such as eczema, psoriasis and many others.

[0023] In accordance with the present invention, there is also provided a photoactivation device for modulating the physiology of a target biological activity by directing a photoactivating beam of light having a predetermined set of photoactivating light parameters on a target surface, the device comprising: a photoactivating light source for emitting the photoactivating beam of light; a positioning means operatively coupled to the photoactivating light source for allowing selective positioning of the photoactivating light source relative to the target surface; a position evaluating means for evaluating the position of the photoactivating light source relative to the target surface.

[0024] In accordance with the present invention, there is further provided a photoactivation device for modulating the physiology of a target cellular activity by directing photoactivating light having a predetermined set of photoactivating light parameters on a treatment area of a target human body; the device comprising: a treatment head, the treatment head including a photoactivating light source for emitting photoactivating light, the treatment head also including a treatment area cooling means for cooling the treatment area.

[0025] Typically, the treatment head is spaced from the treatment area by a treatment head-to-treatment area spacing, the treatment area cooling means including a cooling air flowing means for creating a treatment area air flow flowing at least partially in the treatment head-to-treatment area spacing for cooling the treatment area. Conveniently, treatment head also includes a light source cooling means for cooling the photoactivating light source.

[0026] In accordance with the present invention, there is further provided a method of photoactivating mammalian tissue using a photoactivating device, the photoactivating device including a photoactivating light source adapted to generate a photoactivating beam of light having a predetermined set of light parameters, the mammalian tissue defining a target surface adapted to be irradiated by the photoactivating beam of light, the method comprising the steps of: positioning the photoactivating light source and the mammalian tissue relative to each other so that the photoactivating light source and the target surface are at a predetermined operational distance relative to each other; irradiating the target surface with the photoactivating beam of light while the photoactivating light source is spaced from the target surface by the operational distance; wherein the operational distance is such that the photoactivating beam of light photoactivates the biological tissue. Typically, the method includes using a distance probe for adjusting the distance between the photoactivating light source and the target surface towards the operational distance.

[0027] Conveniently, the method further comprises the step of: using an aiming beam of light emanating from an aiming device operatively coupled to the photoactivating light source for aiming the photoactivating light source towards the target surface prior to using the distance probe for adjusting the distance between the photoactivating light source and the target surface towards the operational distance.

[0028] In accordance with the present invention, there is yet still provided a method of photoactivating mammalian

tissue using a photoactivating device, the photoactivating device including a photoactivating light source adapted to generate a photoactivating beam of light having a predetermined set of light parameters, the mammalian tissue defining a target surface adapted to be irradiated by the photoactivating beam of light, the method comprising the steps of: irradiating the target surface with the photoactivating beam of light emanating from the photoactivating light source; cooling the target surface so as to maintain the target surface at a temperature below a predetermined thermal threshold. Typically, the cooling of the target surface includes using a cooling flow of air for convectively cooling the target surface.

BRIEF DESCRIPTION OF THE DRAWINGS

[0029] Embodiments of the present invention will now be disclosed, by way of example, in reference to the following drawings in which:

[0030] FIG. 1, in an elevational view, illustrates a photoactivation device in accordance with an embodiment of the present invention being used for treating the face area of an intended patient;

[0031] FIG. 2, in a partial top view with sections taken out, illustrates a photoactivation device in accordance with an embodiment of the present invention being used for treating the face area of an intended patient;

[0032] FIG. 3, in a side view, illustrates a photoactivation device in accordance with an embodiment of the present invention, the photoactivation device being shown with its arm assembly in full lines in a raised position and in phantom lines in a lowered position;

[0033] FIG. 4, in a partial elevational view with sections taken out, illustrates a photoactivation device in accordance with an embodiment of the present invention being used for treating the back area of an intended patient;

[0034] FIG. 5, in a perspective view, illustrates a photoactivation device in accordance with an embodiment of the present invention;

[0035] FIG. 6, in a partial perspective view with sections taken out, illustrates the base portion of a photoactivation device in accordance with an embodiment of the present invention, the base portion of the photoactivation device being shown with part of its base casing removed therefrom;

[0036] FIG. 7, in a partial cross-sectional view with sections taken out, illustrates part of the base portion shown in FIG. 6 with some of its components removed therefrom;

[0037] FIG. 8, in a top view, illustrates a photoactivation device in accordance with an embodiment of the present invention, the photoactivation device being shown with its arm assembly moved between a retracted and an extended position;

[0038] FIG. 9, in a partial top view with section taken out, illustrates part of the treatment head of a photoactivation device in accordance with an embodiment of the present invention;

[0039] FIG. 10, in a bottom view, illustrates a treatment head part of a photoactivation device in accordance with an embodiment of the present invention;

[0040] FIG. 11, in a partial transversal cross-sectional view with sections taken out, illustrates some of the components of the treatment head of a photoactivation device in accordance with an embodiment of the present invention;

[0041] FIG. 12, in a partial longitudinal cross-sectional view with sections taken out, illustrates some of the components of the treatment head of a photoactivation device in accordance with embodiment of the present invention;

[0042] FIG. 13, in a top view, illustrates a heat sink component part of a photoactivation device in accordance with embodiment of the present invention;

[0043] FIG. 14, in a bottom view, illustrates the heat sink component shown in FIG. 13;

[0044] FIG. 15, in a schematic elevational view, illustrates the heat sink component shown in FIGS. 13 and 14;

[0045] FIG. 16, in a perspective view, illustrates the heat sink component shown in FIGS. 13 through 15 having photoactivating light sources about to be attached thereto, the heat sink component and the photoactivating light sources being part of a photoactivation device in accordance with an embodiment of the present invention;

[0046] FIG. 17, in a bottom view, illustrates a lighting module part of a photoactivation device in accordance with an embodiment of the present invention;

[0047] FIG. 18, in a schematic top view with sections taken out, illustrates part of a the heat sink shown in FIGS. 13 through 15 with air fan casings mounted thereon;

[0048] FIG. 19, in a longitudinal cross-sectional view taken along arrows XIX-XIX of FIG. 18, illustrates the heat sink and air fan casings shown in FIG. 18;

[0049] FIG. 20, in a partial bottom view with sections taken out, illustrates a set of lighting modules mounted on a heat sink, the lighting modules and the heat sink being part of a photoactivation device in accordance with an embodiment of the present invention;

[0050] FIG. 21, in a schematic and partial transversal cross-sectional view with sections taken out, illustrates the face of an intended patient positioned underneath a treatment head part of a photoactivation device in accordance with an embodiment of the present invention;

[0051] FIG. 22, in a top cross-sectional view, illustrates part of the casing of a distance probe, the distance probe being part of a photoactivation device in accordance with an embodiment of the present invention;

[0052] FIG. 23, in a bottom view, illustrates a complementary part to the casing shown in FIG. 22;

[0053] FIG. 24, in a perspective view, illustrates an attachment component part of a distance probe, the distance probe being part of a photoactivation device in accordance with an embodiment of the present invention;

[0054] FIG. 25, in a partial perspective view with sections taken out, illustrates some of the internal components of a distance probe, the distance probe being part of a photoactivation device in accordance with an embodiment of the present invention;

[0055] FIG. 26, in a partial perspective view with sections taken out, illustrates a complementary section of the distance probe partly shown in FIG. 25;

[0056] FIG. 27, in a schematic elevational view, illustrates a distance probe positioned at a target distance relative to a target tissue;

[0057] FIG. 28, in a schematic elevational view, illustrates a distance probe positioned at a greater distance than a target distance relative to a target tissue;

[0058] FIG. 29, in a schematic elevational view, illustrates a distance probe positioned closer to a target tissue than a target distance;

[0059] FIG. 30, in a schematic cross-sectional view, illustrates a treatment head part of a photoactivation device in accordance with an embodiment of the present invention, the treatment head being shown treating two juxtaposed sagittal half-head sections respectively of a woman in the 5th percentile and of a man in the 95th percentile in terms of size, the women and men sagittal half-head sections being shown transversally sectioned about a mid-plane taken adjacent the level of the nose;

[0060] FIG. 31, in a partial schematic elevational view, illustrates an alternative treatment head such as that shown in FIG. 4;

[0061] FIG. 32, in a top view illustrates the typical lighting pattern created by a lighting module part of a photoactivation device in accordance with an embodiment of the present invention;

[0062] FIG. 33, in a top view, illustrates the lighting pattern typically created by three adjacent lighting modules;

[0063] FIG. 34 illustrates a percent change in average procollagen in control experiment compared to over one-month (11 treatments) irradiation for two human reconstructed skin samples further to irradiation with radiation presenting a power density temporal profile according to the invention; in vitro treatment of normal human reconstructed skin was performed by a pulsed LED light source for 3 times a week during 4 consecutive weeks;

[0064] FIG. 35 illustrates a percent variation in procollagen and MMP-1 activity over a one-month period punctuated with the 11 LED treatments relating to FIG. 34;

[0065] FIG. 36 illustrates a percent variation in procollagen, MMP-1 and MMP-2 activities over a one-month period punctuated with the 11 LED treatments relating to FIG. 34;

[0066] FIG. 37A illustrates PRIMOS computerized pre-and post-treatment pictures of the right crowfeet area of a human subject for in vivo pulsed radiation treatments according to the invention (12 treatments were performed); Pre-treatment picture color-coded topography of the right crowfeet area; Darker areas indicate deeper wrinkle surface;

[0067] FIG. 37B illustrates PRIMOS computerized pre-and post-treatment pictures of the right crowfeet area of a human subject for in vivo pulsed radiation treatments according to the invention (12 treatments were performed); In addition to topography, skin texture and pore size can also be appreciated before treatment in phaseshift mode photography of the right crowfeet area;

[0068] FIG. 37C illustrates PRIMOS computerized pre-and post-treatment pictures of the right crowfeet area of a human subject for in vivo pulsed radiation treatments according to the invention (12 treatments were performed); Post-treatment color-coded topography after twelve treatments. Improvements in wrinkle depth and number are clearly noticeable when compared with pre-treatment color-coded topography (FIG. 37A);

[0069] FIG. 37D illustrates PRIMOS computerized pre-and post-treatment pictures of the right crowfeet area of a human subject for in vivo pulsed radiation treatments according to the invention (12 treatments were performed); Post-treatment phaseshift mode photography after twelve treatments, exhibiting a smoother surface/tighter skin and noticeable reduction in pore size;

[0070] FIG. 38 is a flow chart illustrating a method of the present invention;

[0071] FIG. 39 is a flow chart illustrating another method of the present invention;

[0072] FIG. 40 is a flow chart illustrating a further embodiment of a method of the present invention;

[0073] FIG. 41 is a flow chart illustrating another method of the present invention;

[0074] FIG. 42 is a flow chart illustrating a further method of the invention;

[0075] FIG. 43 is a flow chart illustrating an embodiment of the method;

[0076] FIG. 44 is a flow chart illustrating another embodiment;

[0077] FIG. 45 is a flow chart illustrating a further method embodiment;

[0078] FIG. 46 is a flow chart illustrating a method of use of the present device; and

[0079] FIG. 47 is a graph illustrating irradiance vs. time of the present methods and device.

DETAILED DESCRIPTION

[0080] Referring to FIG. 1, there is shown in a schematic perspective view, a photoactivation device in accordance with an embodiment of the present invention, generally designated by the reference numeral 10. The photoactivation device 10 is adapted to be used mainly for modulating the physiology of a target biological activity by directing photoactivating light having a predetermined set of photoactivating light parameters on a treatment area of a target human body. Although throughout the text the examples of photoactivation result mainly in photoinduction of the physiology of a target biological activity, it should be understood that photoactivation could result in photoinhibition of the target biological activity without departing from the scope of the present invention

[0081] In FIG. 1, the photoactivation device 10 is shown being used for treating the face area 12 of an intended patient 14 lying on a treatment bed 16. The photoactivation device 10 is shown being operated by a nearby standing operator 18. It should, however, be understood that the photoactivation device 10 could be used in other contexts such as for treating other treatment areas without departing from the

scope of the present invention. For example, FIG. 4 illustrates a photoactivation device 10 being used for treating the upper back region 20 of a sitting patient 14.

[0082] Photoactivation device 10 includes a treatment head 22. The treatment head 22, in turn, includes a photoactivating light source for emitting photoactivating light. The photoactivation device 10 also includes a device base 24 for supporting the device 10 on a supporting surface such as a table top, a floor or the like. The device 10 further includes a base-to-head arm assembly 26 for mechanically coupling the treatment head 22 to the device base 24 and allowing selective movement of the treatment head 22 relative to the device base 24.

[0083] As shown more specifically in FIGS. 1 through 5 and 8, the base-to-head arm assembly 26 typically includes an assembly first arm 28 and an assembly second arm 30. The assembly first arm 28 defines a first arm first end 32 and a longitudinally opposed first arm second end 34. As shown more specifically in FIG. 2, the assembly first arm 28 is pivotally coupled substantially adjacent the first arm first end 32 to the device base 24 for pivotal movement relative thereto about a substantially vertical first arm rotation axis 36 through a predetermined first arm rotation range 38.

[0084] FIG. 2 illustrates the first arm rotation range 38 as having a value of approximately 180 degrees. It should, however, be understood that the first arm rotation range 38 could have other values without departing from the scope of the present invention.

[0085] The assembly second arm 30 defines a second arm first end 40 and a longitudinally opposed second arm second end 42. The assembly second arm 30 is pivotally coupled substantially adjacent the second arm first end 40 to the assembly first arm 28 for pivotal movement relative thereto about both a substantially vertical second arm vertical rotation axis 44 and a substantially horizontal second arm horizontal rotation axis 46. Rotation of the assembly second arm 30 about the second arm vertical rotation axis 44 is allowed through a predetermined second arm horizontal rotation range 48 shown in FIG. 2. Rotation of the assembly second arm 30 about the horizontal rotation axis 46 is allowed through a predetermined vertical rotation range 50 illustrated in FIG. 3.

[0086] The second arm horizontal rotational range 48 is shown in FIG. 2 as having a value of approximately 225 degrees. The second arm vertical rotation range 50 is illustrated in FIG. 3 as having an overall value of approximately 75 degrees with a first segment 52 thereof spanning generally downwardly approximately 30 degrees from an horizontal reference plane P and a second segment 54 thereof spanning generally upwardly approximately 45 degrees from the horizontal reference plane P.

[0087] It should, however, be understood that the second arm horizontal and vertical rotation ranges 48, 50 and the first and second segments 52, 54 of the second arm vertical rotation range 50 could have other values without departing from the scope of the present invention. Also, although the assembly first and second arms 28, 30 typically have a length respectively of approximately 32 cm and 82 cm, the assembly first and second arms 28, 30 could have other dimensional values without departing from the scope of the present invention.

[0088] The base-to-head arm assembly 26 typically also includes a weight compensating assembly or means mechanically coupled to the assembly second arm 30 for at least partially compensating for the weight of the treatment head 22 and preventing the assembly second arm 30 from pivoting about the second arm horizontal rotation axis 46 under the weight of the treatment head 22. In the embodiments shown throughout the Figures, the weight compensating means includes a pneumatic cylinder 56. It should, however, be understood that the weight compensating means may take any other suitable form such as that of a resiliently deformable member, strategically positioned compensating weights or the like without departing from the scope of the present invention.

[0089] The base-to-head arm assembly 26 typically further includes an arm-to-head universal-type mechanical coupling or swivel 58 extending between the assembly second arm 30 substantially adjacent the second arm second end 42 and the treatment head 22 for mechanically coupling the latter and allowing the treatment head 22 to pivot and rotate relative to the assembly second arm 30. The base-to-head arm assembly 26 typically still further includes an arm-to-head releasable locking assembly or means for releasably locking the treatment head 22 in a head operational position relative to the assembly second arm 30. The arm-to-head swivel and the arm-to-head locking means may take any suitable form without departing from the scope of the present invention. In one embodiment of the invention, the arm-to-head mechanical coupling 58 includes a swivel ball 60 mounted within a corresponding swivel socket 62 so as to form a ball and socket-type joint. A swivel spacing segment 64 extends from the swivel ball 60 for attachment to the treatment head 22.

[0090] The arm-to-head mechanical coupling 58 is typically of the universal-type allowing the treatment head 22 to swivel through a three-dimensional swivel range 70. Although the swivel range 70 is shown in 4 has having a value of approximately 115 degrees in one plane, it should be understood that the swivel range 70 also acts across multiple planes wherein the swivel range for each plane can be the same or different values. Thus, treatment head 22 can be swivelled into and out of the plane illustrated in FIG. 4. Additionally, the swivel ranges can have other values without departing from the scope of the present invention. The arm-to-head mechanical coupling 58 typically also allows the treatment head 22 to rotate relative to a head rotational axis extending substantially co-axially with the longitudinal axis of the swivel spacing component 64. Thus, mechanical coupling 58 can allow treatment head 22 to spin on one axis, permitting treatment head 22 to be orientated to any angle in relation to the base 24, as well as second arm 30.

[0091] The arm-to-head releasable locking means typically include means for increasing the friction between the swivel socket 62 and the swivel ball 60 through the use of a knob 61 or the like. The arm-to-head releasable locking means may take any other suitable form including the use of temperature-dependent memory alloys adapted to change configuration for selectively frictionally engaging the swivel ball 60.

[0092] The device 10 also typically includes an arm-to-head releasable electrical coupling 66 extending between base-to-head arm assembly 26 and the treatment head 22 for

releasably electrically coupling the latter. Preferably, the arm-to-head releasable electrical coupling 66 allows for quick, easy and ergonomic coupling of treatment head 22 to a portion of the base-to-head arm assembly 26 such as to the swivel spacing component 64. This, in turn, allows for customisation of the treatment head 22 depending on the area being treated, the desired type of photoactivation effect or other operational parameters.

[0093] For example, FIGS. 1, 2, 3, 5, 21 and 30 illustrate a substantially arc-shaped treatment head 22 adapted for treating the face region 12 of an intended patient 14 whereas FIGS. 4 and 31 illustrate a generally concave yet relatively more flattened treatment head 22 adapted for treating the back region 20 of an intended patient 14. Further, the arc shaped treatment head 22 can be used to partially surround and treat appendages such as the arms and legs of the intended patient 14 or other bodyparts such as the buttocks or individual breasts of the intended patient 14. Further, the "flattened" treatment head 22' can be used for treating the chest and sides of patient 14 and can be sized to treat a larger surface area. It should be understood that other types of treatment heads 22 having other configurations could also be used without departing from the scope of the present invention.

[0094] As illustrated more specifically in FIGS. 6 and 7, the device base 24 typically protectively houses at least part of a device power supply generally referred to by the reference numeral 68. The power supply 68 includes at least one and typically four power supply units 72 mounted within a conventional Faraday-type cage 74. The Faraday-type cage 74 also houses at least one and typically four relay components 76.

[0095] A device base venting assembly or means is typically provided for venting the components housed within the device base 24. The device base venting assembly or means typically includes at least one and preferably two base venting fans 78 mounted on the Faraday cage 74. The device base fans 78 are adapted to convectively cool the components housed within the device base 24 by drawing air through a base venting grid 80.

[0096] An on-off switch 82 and an emergency stop switch 84 typically extend from the device base 24 for allowing an intended user respectively to turn the device 10 on and off and to quickly turn the device 10 off in case of an emergency.

[0097] Referring now more specifically to FIGS. 9 through 12, 21 and 30, there is shown, in greater details, some of the features of a treatment head 22 intended for use in treating a human face area. Typically, such treatment head 22 includes at least two and preferably three head sections. Each of the head sections is typically provided with a photoactivating light source 154 for emitting photoactivating light. Typically, at least two of the head sections are movable relative to each other. As will be hereinafter disclosed in greater details, in situations wherein at least two of the head sections are movable relative to each other, each of the movable head sections also includes a section positioning means operatively coupled to a corresponding section photoactivating light source 154 for allowing selective positioning of the corresponding section photoactivating light source 154 relative to a corresponding target surface section.

[0098] In other words, the target surface on which photoactivating light is directed is typically dividable into target

surface sections and the treatment head is dividable into corresponding head sections each having a corresponding section photoactivating light source 154. Furthermore, the individual head sections and, hence, their corresponding individual section photoactivating light source 154 are allowed to move relative to each other in order to provide optimal treatment to the individual target surface sections.

[0099] As illustrated schematically in FIG. 30, the treatment head 22 intended to be used for treating a human face area 12 typically includes a central head section 86 and a pair of lateral head sections 88. The lateral head sections 88 are positioned on each side of the central section 86. Furthermore, at least one of the lateral head sections 88 and preferably both lateral head sections 88 are laterally displaceable relative to the central head section 86. To illustrate the relative movement between the lateral head sections 88 and the central head section 86, the lateral head section 88 appearing in the top part of FIG. 30 is shown as being in a proximal relationship relative to the central head section 86 while the lateral head sections 88 appearing in the lower part of FIG. 26 is shown as being spaced relative to the central head section 86 by a central-to-lateral head section spacing 90. This allows the lateral head sections 88 to maintain the same distance from the face area 12 regardless of the size and/or shape of the patient's 14 face.

[0100] As illustrated more specifically in FIGS. 1, 2 and 8 through 12, the treatment head 22 typically includes a head base 92. The head base 92 typically defines a graspable head base handle section. In the embodiments shown throughout the Figures, the graspable head base handle section includes a pair of handle segments 94 delimited, at least in part, by corresponding adjacent handle section apertures 96 positioned on each side of the head base 92. The handle segments 94 are conveniently configured and sized for being graspable by the hand of an intended operator 18 to allow manual positioning of the treatment head 22.

[0101] Typically, the central head section 86 is fixedly attached to the head base 92. The central and lateral head sections 86, 88 are typically provided with cooperating lateral guiding assemblies or means operatively coupled therebetween for guiding the lateral movement of the lateral head sections 88 relative to the central head section 86. Also, the treatment head 22 is typically further provided with lateral moving assemblies or means operatively coupled between the head base 92 and the lateral head sections 88 for laterally moving the lateral head sections 88 relative to the central head section 86.

[0102] As illustrated more specifically in FIGS. 11 and 12, the lateral guiding assembly or means typically include at least one guiding rod 98 and preferably two guiding rods 98 attached to the central head section 86 and extending laterally therefrom on opposite sides of the latter. The lateral guiding assembly or means also includes corresponding guiding sleeves 100 attached to each lateral head section 88. Each one of the guiding sleeves 100 defines a corresponding guiding channel for slideably receiving a corresponding section of a corresponding guiding rod 98.

[0103] As illustrated more specifically in FIGS. 10 and 11, the lateral moving assembly or means typically includes a pair of lateral moving screws 102 (only one of which is shown in FIG. 11). Each of the lateral moving screws 102 is mechanically coupled to the head base 92 for rotation

relative thereto and threadably coupled to a corresponding lateral head section 88 for moving the latter upon rotation thereof.

[0104] As shown more specifically in FIGS. 1, 5, 10 and 11, the head base 92 is typically provided with a pair of screw spacing arms 104 extending therefrom for rotatably receiving one of the lateral moving screws 102. Also, each of the lateral head sections 88 is typically provided with a corresponding lateral threaded section 106 for threadably engaging with a corresponding lateral moving screw 102.

[0105] Each lateral moving screw 102 is typically provided with a lateral screw knob 108 for facilitating manual rotation thereof. Upon rotation of a given lateral screw knob 108, the threaded coupling between the corresponding lateral moving screw 102 and the corresponding lateral threaded section 106 causes the corresponding lateral head section 88 to move relative to the corresponding spacing arm 104 and, hence, relative to the central head section 86.

[0106] In at least one embodiment of the invention, the treatment head 22 is configured and sized so as to conform substantially to the geometry of a target human face 12. Typically, the treatment head 22 is configured and sized so as to conform substantially to the geometry of a target human face 12 when the target human face 12 has anthropometric or dimensional values located between that of the lower 5th percentile of women and the higher 95th percentile of men.

[0107] FIG. 30 schematically illustrates two juxtaposed sagittal half-head sections respectively of a woman in the 5th percentile and of a man in the 95th percentile in terms of size. The women and men sagittal half-head sections 112, 114 are shown transversally sectioned about a mid-plane taken adjacent the level of the nose 110. The women half-head section 112 appears on the top part of FIG. 30 and the men half-head section 114 appears on the lower part of FIG. 30. FIG. 30 hence illustrates the variation of size that needs to be accounted for in order for the treatment head 22 to accommodate size range differences when treating head sizes having a value between that of the 5th percentile of women and the 95th percentile of men.

[0108] The human face includes a pair of ears 116 (only one of which is shown in FIG. 30) and a pair of eyes (not shown). Each of the eyes defines a laterally disposed periorbital region 118 while each of the ears 116 defines a corresponding temporal periauricular region 120. Typically, the lateral periorbital region 118 corresponds to the region of the zygomatic process and is the region wherein rhytids or wrinkles commonly referred to as crow's feet typically appear.

[0109] For example, with reference to FIG. 30, the human face 12 typically defines a central face region 122 extending substantially in the area located between the lateral periorbital regions 118. The human face also defines a pair of lateral face regions 124, each extending substantially in the region located between one of the lateral periorbital regions 118 and a corresponding temporal periauricular region 120.

[0110] As illustrated more specifically in FIGS. 21 and 30, the treatment head 22 typically defines a head proximal surface 126 adapted to face the target human face 12. The head proximal surface 126 is configured and sized so as to be at a substantially constant head surface-to-target surface

operational distance **128** relative to the target human face **12** substantially throughout the treatment area thereof.

[0111] Typically, the treatment head **22** is configured and sized so that the photoactivating light source **154** is at a substantially constant light source-to-target surface operational distance relative to the target human face **12** substantially throughout the treatment area thereof. Hence, for a photoactivating light source **154** having a relatively constant fluence, the treatment head **22** is configured and sized so as to deliver a photoactivating light having a substantially constant target irradiance (or optical power density) on the treatment area. The lateral movement of the lateral head sections **88** hence typically allows the treatment head **22** to deliver the photoactivating light with substantially constant target irradiance on the target human face **12** when the target human face **12** has anthropometric values located between the 5th percentile of women and the 95th percentile of men.

[0112] Further, the central head section **86** is typically adapted to deliver photoactivating light to the nose region and, hence, is typically outwardly offset relative to the lateral head sections **88**. Also, typically, at least one of the lateral head sections **88** and preferably both the lateral head sections **88** have a substantially arc-shaped cross-sectional configuration. Each lateral head section **88** is typically configured and sized for delivering photoactivating light to a corresponding area extending laterally from the nose **110** to a corresponding temporal periauricular region **120**.

[0113] As illustrated more specifically in FIGS. 21 and 30, in at least one embodiment of the invention, each of the lateral head sections **88** defines a lateral head section first segment **130** for delivering photoactivating light to a corresponding lateral face section first segment extending from a first position located laterally substantially adjacent to the nose **110** to a second position located laterally substantially proximal to a corresponding lateral periorbital region **118**.

[0114] Each lateral head section **88** also defines a lateral head section second segment **132** for delivering photoactivating light to a corresponding lateral face section second segment extending substantially across the corresponding lateral periorbital region **118** from the second position to a third position located laterally to the corresponding lateral periorbital region **118**. Each lateral head section **88** further defines a lateral head section third segment **134** (only a portion of which is shown in FIG. 21) for delivering photoactivating light to a corresponding lateral face section third segment extending substantially from the third position to the corresponding temporal periauricular region **120**.

[0115] Typically, the lateral head section first, second and third segments **130**, **132** and **134** are provided with first, second and third segment light sources. The first, second and third segment light sources are positionable at a substantially constant light source-to-target surface operational distance relative to the target human face **12** substantially throughout the treatment area thereof.

[0116] In the embodiments shown throughout the FIGS., the lateral head section first and second segments **130**, **132** are both provided with at least one row of photoactivating light sources **154** and the lateral head section third segment **134** is provided with a pair of laterally adjacent rows of photoactivating light sources **154**. Typically, the rows of photoactivating light sources **154** of the lateral head section

first, second and third segments **130**, **132** and **134** provide a substantially constant fluence with a substantially constant beam size and beam divergence. Optionally, some or all of these and other optical parameters may be customized without departing from the scope of the present invention.

[0117] Referring now more specifically to FIGS. 16 and 17, there is shown some of the features of a typical photoactivating light source **154**. In at least one embodiment of the invention, the photoactivating light source **154** is of the Chip On Board type (COB) including an electronic light generating component mounted directly on the mounting surface of a corresponding Printed Circuit Board (PCB). Typically, the electronic light generating component includes at least one LED and preferably a substantially elongated LED matrix **138**. In FIG. 17 only a pair of LEDs **136** making up the LED matrix **138** is shown. Also, the LEDs **136** are shown enlarged relatively to the remainder of the LED matrix **138**. Furthermore, the LEDs **136** are shown having a substantially disc-shaped cross-sectional configuration. It should however be understood that other types of LEDs **136** could be used without departing from the scope of the present invention. For example, typically, the LED matrix **138** consists of a substantially flat LED strip. It should also be understood that other types of light generating components could be used without departing from the scope of the present invention.

[0118] In an embodiment, LED matrix **138** consists of rows and columns of LEDs. The matrix can have an equal or unequal number of rows and columns. Additionally, each row and column can have a varying number of LEDs as compared to an adjacent row or column. Each row or column can light simultaneously or light in a "cascade" fashion. The LEDs can cascade so quickly as to be preserved as simultaneously by the human eye. LED matrix can be designed to configure to a specific region or shape of the treatment head **22** to provide light rays without unnecessary exposure. Further, sections of the LED matrix do not necessarily all light for every treatment and alternating rows and columns can light or some not light at all for a specific treatment.

[0119] Typically, the photoactivating light source **154** also includes a lens optically coupled to the electronic light generating component **138** for guiding the photoactivating light rays **142** (shown schematically in FIGS. 30 and 31) emitted by the electronic light generating component **138** so that the photoactivating light source **154** emits photoactivating light according to a predetermined light emission pattern. In the example shown throughout the Figures, the lens is used for focusing the photoactivating light rays **142**. It should, however, be understood that the lens could also be used for dispersing the photoactivating light rays **142** depending on the type of light generating component being used.

[0120] Typically, the lens includes a substantially elongated lens plate **140**. The lens plate **140** is typically maintained in a spaced relationship relative to the LED matrix **138** by a Chip On Board casing **143**.

[0121] The lens plate **140** defines a pair of longitudinally extending lens plate side edges **144**. The Chip On Board casing **143** typically has a substantially elongated configuration defining a pair of longitudinally opposed Chip On Board casing longitudinal ends **146**. The Chip On Board

casing 143 also has a pair of longitudinally extending Chip On Board casing side walls 148.

[0122] Each of the Chip On Board casing side walls 148 is typically in a substantially proximal relationship relative to a corresponding lens plate side edge 144. The Chip On Board casing side walls 148 diverge laterally outwardly adjacent the casing longitudinal ends 146 so as to form corresponding Chip On Board casing attachment flanges 150.

[0123] The Chip On Board casing attachment flanges 150 are typically provided with attachment apertures 152 extending therethrough for receiving conventional attachment components such as screws adapted to be used for mounting corresponding Chip On Board casing 143 to a suitable supporting surface as will be hereinafter disclosed in greater details.

[0124] As illustrated more specifically in FIG. 20, the photoactivating light sources 154 are typically grouped in pairs positioned in side by side and contiguous relationship relative to each other with their respective attachment flanges 150 in a proximal relationship relative to each other. In such a configuration, the remainder of the corresponding adjacent casing side walls 148 of laterally adjacent photoactivating light sources 154 delimit a Chip On Board casing cooling channel 156 therebetween for allowing the flow of a cooling fluid therethrough as will be hereinafter explained in greater details.

[0125] Each photoactivating light source 154 typically also includes control electronics 158 typically positioned adjacent one of the Chip On Board casing longitudinal ends 146. Chip On Board cables 160 typically extend from an undersurface of the Chip On Board casing 143 for allowing connection thereof to a suitable connector. Sealing of the photoactivating light source module is typically provided by a self-adhesive tape 162 located at the Chip On Board Casing longitudinal end 146 opposite the electronic controls 158.

[0126] Typically, each photoactivating light source 154 is designed for emitting pulsed photoactivating light having a target irradiance of substantially greater than 0.04 W/cm^2 , a target fluence of approximately between 0.05 and 10 J/cm^2 and a predetermined pulsing pattern. More specifically, the target irradiance typically has a value of approximately 0.05 W/cm^2 at the centre of LED array and the target fluence has a value of approximately 4 J/cm^2 . Specifically, an embodiment utilizes a target fluence of 4.5 J/cm^2 and greater. Another embodiment is a fluence between 4.5 and 10 J/cm^2 .

[0127] The photoactivating light emitted by the photoactivating light sources 154 typically has a wavelength value of approximately between 600 nm and 700 nm . More specifically, the photoactivating light typically has a peak wavelength value of approximately $660 \text{ nm} \pm 10 \text{ nm}$.

[0128] The pulsing pattern of the photoactivating light sources 154 typically includes a pulse width of approximately 0.0005 seconds and a pulse interval of approximately 0.00015 seconds. The predetermined pulsing pattern also typically includes pulse trains of between approximately 3 and 5 pulses with pulse train intervals of approximately 0.00155 seconds. It should be understood that other pulsing patterns could be used without departing from the scope of the present invention.

[0129] Typically, with a target irradiance of approximately 0.05 W/cm^2 at the centre of LED array and a target fluence of approximately 4.5 J/cm^2 , the head surface-to-target surface operational distance 128 has a value of approximately $2.5 \text{ cm} \pm 1$ to 3 mm . It should however be understood that the head surface-to-target surface operational distance 128 could have another value without departing from the scope of the present invention.

[0130] The above factors are interrelated and all combine to produce different irradiances. For example, an LED array having a power density 0.05 W/cm^2 , a pulse width of 0.005 seconds, a pulse interval of 0.00015 seconds, having a 4 pulse pulse train with pulse train intervals of 0.00155 seconds for a total of 160 seconds generates a total irradiance of 500 W/cm^2 . Changing any one of the parameters can alter the irradiance or altering different parameters can result in the same irradiance.

[0131] Typically, although by no means exclusively, the photoactivating light source pointing tolerance has a value of approximately ± 3 degrees and a beam divergence (FWHM) of approximately 50 ± 5 degrees. The spectral width (FWHM) has a value of approximately $30 \pm 5 \text{ nm}$. The lens plate 140 is typically of the cylindrical type, with, for example, UL94 V-2 polycarbonate used as lens material.

[0132] FIGS. 32 and 33 illustrate respectively a typical irradiance pattern produced by a single photoactivating light source 154 and three laterally adjacent photoactivating light sources 154 respectively. As can be seen from these Figures, the optical power density or irradiance is substantially constant throughout the lighting range.

[0133] Typically, the maximum to minimum deviation is in the order of 15% along the length of the photoactivating light source 154. Also, preferably, the photoactivating light sources 154 are designed so that the irradiance or optical power density remains relatively constant throughout the lifetime thereof. For example, the photoactivating light sources 154 may be designed so that the irradiance does not fall to less than 85% of initial irradiance after $2,000$ hours of operation. It should be understood that other types of photoactivating light sources having other optical, mechanical, electrical or interface characteristics could be used without departing from the scope of the present invention.

[0134] As mentioned previously, the head proximal surface 126 is typically spaced relative to the target human face 12 by a head surface-to-target surface operational distance 128. As illustrated more specifically in FIG. 19, the treatment head 22 and the treatment area hence typically define a treatment head-to-treatment area spacing 164 there between.

[0135] Typically, the treatment head 22 also includes a treatment area cooling assembly or means for cooling the treatment area. In one embodiment of the invention, the treatment area cooling assembly or means includes a cooling air flowing assembly or means for creating a treatment area air flow 168 flowing at least partially in the treatment head-to-treatment area spacing 164 for cooling the treatment area. The treatment area air flow 168 is adapted to cool the treatment area by convectively cooling the treatment area and/or evacuating heat from the treatment head-to-treatment area spacing 164. The treatment area air flow 168 is also adapted to allow for evacuation of carbon monoxide and/or other by-products produced by the breathing of the intended patient 14.

[0136] In the embodiment shown throughout the FIGS. the treatment area air flow 168 is induced by sucking or pulling air away from the treatment head-to-treatment area spacing 164. In an alternative embodiment of the invention, the treatment area air flow 168 is induced by blowing air into the treatment head-to-treatment area spacing 164. Regardless of whether the treatment area air flow 168 is induced by blowing cooling air into the treatment head-to-treatment area spacing 164 or by sucking or pulling heated air away from the treatment head-to-treatment area spacing 164, the cooling air may optionally be pre-cooled to further enhance its cooling effect. Both blowing cooling air at a patient 14 or pulling heated air away from a patient 14, will result in a cooling effect on the patient's 14 skin. This can comfort the patient as well as cool the skin to prevent overheating or burning the patient 14.

[0137] Also, optionally, the cooling air may be mixed with various agents such as therapeutic agents, photoactivation promoting agents or the like. Furthermore, the cooling air may optionally mixed with anaesthetic agents such as sedating agents for at least partially sedating the patient, local anaesthetic agents for at least partially providing a local anaesthesia of the treatment site or the like.

[0138] Typically, the treatment head 22 also includes a light source cooling assembly or means for cooling the photoactivating light sources 154. Typically, the light source cooling assembly or means includes a device cooling air flowing assembly or means for creating a light source air flow 166 for convectively cooling the photoactivating light sources 154 and associated components. In the embodiment shown throughout FIGS. 13-20, the device cooling air flowing assembly or means also creates the treatment area air flow 168 for cooling the treatment area. More specifically, the light source air flow 166 creates a vacuum for inducing the treatment area air flow 168. Alternatively, the light source air flow 166 and the treatment area air flow 168 may be induced separately.

[0139] As illustrated more specifically in FIGS. 16, 18 and 19, the photoactivating light sources 154 are typically thermally coupled to a heat sink 170. The cooling air flowing assembly or means allows the light source air flow 166 to cool the heat sink 170 and to create a vacuum across the heat sink 170 for inducing the treatment area air flow 168. The heat sink 170 includes a heat sink base plate 172. The heat sink base plate 172 defines a heat sink base plate first surface 174 and an opposed heat sink base plate second surface 176. The heat sink base plate 172 has at least one, and preferably a plurality of air flow apertures 178 extending therethrough. The air flow apertures 178 can be disposed in a predetermined pattern to form a specific air flow or can be randomly placed.

[0140] The cooling air flowing assembly or means allows the light source air flow 166 to flow over at least a portion and preferably most of the heat sink base plate first surface 174 so as to create a vacuum drawing the treatment area air flow 168 from the heat sink base plate second surface 176 through the air flow apertures 178.

[0141] The heat sink 170 typically also includes heat dissipating fins 180 extending from the heat sink base plate first surface 174. The heat dissipating fins 180 define fin channels 184 therebetween. The cooling air flowing assembly or means allows the light source air flow 166 to flow at

least partially between the heat dissipating fins 180. Typically, the cooling air flowing assembly or means includes at least one air fan 182 in fluid communication with the fin channels 184.

[0142] As illustrated more specifically in FIGS. 15, 16, 18 and 19, the heat dissipating fins 180 are configured so as to define at least one and preferably two fan receiving recesses 186. The fan receiving recesses 186 are adapted to at least partially receive corresponding venting air fans 182. The fan receiving recesses 186 are typically configured, positioned and sized so that at least one and preferably both air fans 182 are positioned at an angle relative to both the heat sink base plate 172 and the heat dissipating fins 180.

[0143] Typically, the treatment head 22 includes a plurality of heat sinks 170 positioned in a side-by-side relationship relative to each other. Each heat sink 170 has a corresponding heat sink base plate 172 and each heat sink base plate 172 has a substantially elongated configuration extending between a pair of longitudinally opposed base plate longitudinal ends 188. The heat dissipating fins 180 extend substantially longitudinally along corresponding heat sink base plates 172.

[0144] The fan receiving recesses 186 are typically positioned substantially intermediate the plate longitudinal ends 188. As shown more specifically in FIGS. 18 and 19, the air fans 182 are positioned so as to be in a substantially symmetrically opposite relationship relative to each other. Each air fan 182 is positioned so as to draw a corresponding light source air flow portion from a corresponding base plate longitudinal end 188.

[0145] As shown more specifically in FIG. 19, each pair of air fans 182 defines a fan-to-fan spacing 190 therebetween. The air fans 182 are configured, sized and positioned so that a portion of the cooling air that they draw will penetrate in the fan-to-fan spacing 190 according to a flow pattern schematically represented and designated by the reference numeral 192. The flow pattern 192 of the air drawn by the air fans 182 in the fan-to-fan spacing 190 is such that it allows cooling of the portion of the heat sink base plate 172 located thereunderneath. Alternately, air fans 182 can be disposed in base 24 or a separate housing (not illustrated) and placed in fluid communication with the heat sinks 170 and perform the same function as if placed in the fan receiving recesses 186.

[0146] As illustrated more specifically in FIGS. 10 and 20, the Chip On Board casings 143 are mounted on the heat sink base plate second surface 176 with the Chip On Board casing cooling channels 156 substantially in register with at least some of the air flow apertures 178 so as to allow the flow of air from the sink base plate first surface 174 to the sink base plate second surface 176. As illustrated more specifically in FIG. 19, when the air fans 182 draw the light source air flow 166 over the heat sink base plate first surface 174, a vacuum is created in the air flow apertures 178. This vacuum draws the treatment area air flow 168 from the heat sink base plate second surface 176, through both the Chip On Board casing cooling channels 156 and the corresponding air flow apertures 178 in register therewith so that the treatment area air flow 168 eventually merges with the light source air flow 166 over the heat sink base plate first surface 174.

[0147] As illustrated more specifically in FIG. 20, the treatment head 22 typically includes rows 199 of photoac-

tivating light sources 154 in substantially side-by-side and contiguous relationships relative to each other. Each row 199 is typically formed by juxtaposing a pair of photoactivating light sources 154 with their respective longitudinal axis in a substantially co-linear relationship relative to each other. Optionally, an air flowing slot 196 extends through the heat sink base plate 172 between longitudinally adjacent photoactivating light sources 154.

[0148] As illustrated more specifically in **FIG. 11**, the central head section 86 and the lateral head sections 88 are each provided with independent sets of strategically positioned optical probes air fans 182. Air sucked into the casings formed respectively by the central head section 86 and the lateral head sections 88 is adapted to flow through corresponding pairs of longitudinally opposed central and lateral air inlet grids 181, 183 (only one inlet grid 181, 183 part of each pair of air inlet grids 181, 183 is illustrated in **FIG. 5**).

[0149] As illustrated more specifically in **FIG. 9**, air flowing out of the casing formed by the central head section 86 is adapted to flow through a corresponding central air outlet grid 185 located substantially longitudinally opposite the screen 194. As illustrated more specifically in **FIGS. 1, 5 and 9**, air flowing out of the casing formed by each lateral head section 88 is adapted to flow through a corresponding substantially radially disposed lateral air outlet grid 187.

[0150] In an alternative embodiment of the invention, the heat dissipating assembly or means includes as a so-called heat spreader. The latter pertains to a member which channels heat from a semi-conductor die to leads which exit the die package. A heat sink and a heat spreader may also be used together to cool the device. It should be understood that yet other forms of heat dissipating means could be used without departing from the scope of the present invention.

[0151] The photoactivation device 10 typically further includes a position evaluating assembly or means for evaluating the position of the photoactivating light source relative to the target surface. Typically, the photoactivation device 10 also includes an information providing assembly or means for providing information regarding the position of the photoactivating light source relative to the target surface.

[0152] As illustrated more specifically in **FIGS. 5 and 8**, the information providing means typically includes a visual display such as an LCD screen 194 or the like for providing a visual display regarding the position of the photoactivating light source relative to the target surface. It should be understood that other types of visual display means could be used without departing from the scope of the present invention. Also, the information providing assembly or means may use audio, tactile or other sensory modes or combinations thereof to provide information regarding the position of the photoactivating light source relative to the target surface without departing from the scope of the present invention.

[0153] In at least one embodiment of the invention, the information providing means includes a direction indicating means for providing information regarding the direction the photoactivating light source should be moved to reach a predetermined target position relative to the target surface. In at least one embodiment of the invention, the direction indicating means includes an electronic circuitry coupled to

the position evaluating means for displaying arrows indicating to an intended user the direction in which the treatment head 22 should be moved to reach a predetermined target position relative to the target surface. Typically, optimal positioning of the treatment head 22 is achieved by simply following step-by-step "real time" optical instructions provided on the LCD screen 194.

[0154] The treatment head 22 is typically provided with control buttons 195 or the like, conveniently located substantially adjacent the LCD screen 194 for controlling the display parameters, operational parameters or any other suitable parameters. Optionally such parameters could also be controlled using a remote control (not shown). Optionally, the parameters could also be controlled using other type of user interfaces such as through voice command or the like without departing from the scope of the present invention.

[0155] In at least one embodiment of the invention, the photoactivation device 10 includes an actuating means for taking a predetermined course of action depending on the position of the photoactivating light source relative to the target surface or other operational parameters. For example, the actuating means may include an automatic positioning means for automatically repositioning the photoactivating light source towards a predetermined target position relative to the target surface.

[0156] In at least one embodiment of the invention, the position evaluating means allows for evaluation of the three-dimensional coordinates of the photoactivating light source relative to the target surface. In another embodiment of the invention, the position evaluating means allows for evaluation only of the distance between the photoactivating light source and the target surface.

[0157] Typically, the position evaluating means includes at least one and preferably a plurality of non-contacting probes for evaluating the distance between the photoactivating light source and the target surface without contacting the target surface. The non-contacting probes are typically optical probes although other parameters such as temperature, sound waves or the like could be used without departing from the scope of the present invention.

[0158] In at least one embodiment of the invention, the photoactivation device 10 also includes an aiming means operatively coupled to the position evaluating means for allowing aiming of the position evaluating means towards a target position located on the target surface. The aiming means may take any suitable form including a visible aiming beam of light for visibly pointing towards the target position.

[0159] Referring now- more specifically to **FIGS. 22 through 29**, there is shown in greater details an optical probe 198 part of a typical position evaluating assembly or means in accordance with an embodiment of the present invention. As shown schematically in **FIG. 27**, the optical probe 198 includes a distance probe light source 200 for projecting a probe light ray along a projection optical axis 202 towards the target surface 204. The optical probe 198 also includes a distance probe target sensor 206 for sensing the probe light ray travelling along a target sensor optical axis 208 once the probe light ray has been reflected by the target surface 204.

[0160] The distance probe light source 200 and the distance probe target sensor 206 are configured, sized and

positioned so that the projection optical axis 202 and the target sensor optical axis 208 are angled relative to each other and intercept each other on the target surface 204 substantially only when the target surface 204 is spaced from the photoactivating light source by a predetermined target-to-photoactivating light source spacing distance 210. In other words, the distance probe light source 200 and the distance probe target sensor 206 are positioned, configured and sized so that the distance probe target sensor 206 will only receive or be able to sense the probe light ray projected by the distance probe light source 200 and reflected by the target surface 204 when the target surface 204 is spaced from the photoactivating light source 200 by the predetermined target-to-photoactivating light source spacing distance 210 or within a predetermined range thereof.

[0161] Hence, the optical probe 198 is configured so that when the photoactivating light source is spaced from the target surface 204 by the predetermined target-to-photoactivating light source spacing distance 210, the target sensor optical axis 208 and the projection optical axis 202 are angled relative to each other and intercept each other substantially on the target surface 204 allowing the distance probe target sensor 206 to sense the probe light ray.

[0162] The optical probe 198 typically includes at least one distance probe offset sensor for sensing the probe light ray when the latter travels along an offset sensor optical axis. In the embodiment shown throughout the Figures, the optical probe 198 includes both a distance probe near sensor 212 and a distance probe far sensor 214 for sensing the probe light ray when the latter travels along respectively a near sensor optical axis 216 and a far sensor optical axis 218.

[0163] As illustrated more specifically in FIG. 28, the distance probe light source 200 and the distance probe far sensor 214 are configured, sized and positioned so that the probe light ray is reflected from the target surface 204 so as to travel along the far sensor optical axis 218 when the photoactivating light source is spaced from the target surface 204 by a far spacing distance 219 within a predetermined far spacing range. Similarly, as illustrated in FIG. 29, the distance probe light source 200 and the distance probe near sensor 212 are configured, sized and positioned so that the probe light ray is reflected from the target surface 204 so as to travel along the near sensor optical axis range 216 when the photoactivating light source is spaced from the target surface 204 by a near spacing distance 217 located within a predetermined near spacing range.

[0164] The near and far sensors 212 and 214 are typically configured so as to be able to sense or be activated by light rays emanating from within predetermined corresponding angular optical range 216, 218 corresponding to the predetermined near and far spacing ranges. Typically, the near, far and target spacing ranges are substantially contiguous relative to each other so as to form a substantially continuous operational spacing range.

[0165] Typically, the distance probe light source 200 allows for the emission of a probe light ray having a frequency located within the infra-red spectrum. Accordingly, the distance probe target, near and far sensors 206, 212 and 214 are typically adapted to sense or be activated by light rays in the infra-red spectrum. The infra-red spectrum may be particularly useful for distance probing with darker skinned patients. It should, however, be understood that the

distance probe light source 200 could be used for emitting probe light rays within other frequency ranges without departing from the scope of the present invention.

[0166] Typically, the optical probe 198 also includes an aiming assembly or means operatively coupled to the position evaluating assembly or means for allowing aiming of the probe light ray towards a target position located on the target surface 204. Typically, the aiming means includes a visible aiming beam of light for visibly pointing towards the target surface. The aiming beam of light may be produced by any suitable means such as an aiming LED 224 shown in FIG. 25. As illustrated more specifically in FIGS. 22 through 26, the optical probe 198 typically includes an optical probe casing. The optical probe casing, in turn, includes a light source cavity 226 for protectively receiving at least part of the distance probe light source 200, a target sensor cavity 228 for protectively receiving at least part of the distance probe target sensor 206, a near sensor cavity 230 for protectively receiving at least part of the distance probe near sensor 212 and a far sensor cavity 232 for protectively receiving at least part of the distance probe far sensor 214.

[0167] The optical probe casing is typically configured and sized for housing the distance probe light source 200, the distance probe near sensor 212, the distance probe far sensor 214 and the distance probe target sensor 206 in sequential side-by-side order and in an angled relationship relative to each other. Typically, the optical probe casing defines a casing input end 234 and a substantially opposed casing output end 236.

[0168] The light source cavity 226 has a generally elongated configuration and extends through the optical probe casing substantially from the casing input end 234 to the casing output end 236. The light source cavity 226 typically has a substantially frusto-conical configuration tapering towards the casing output end 236.

[0169] Typically, the optical probe 198 further includes a light source alignment assembly or means for allowing adjustment of the direction of the projection optical axis 202 relative to the optical probe casing. Typically, the distance probe target sensor 206, the distance probe far sensor 214 and the distance probe near sensor 212 are also provided with substantially identical or different angle adjustment means. As illustrated more specifically in FIG. 25, the light source alignment assembly or means typically includes a probe light source mounting component 238 for mounting the distance probe light source 200 on the optical probe casing. Also, the light source cavity 226 typically has a light source mounting section 240 located substantially adjacent the casing input end 234 for receiving the light source mounting component 238 and allowing selective movement thereof within the light source mounting section 240. Typically, the light source cavity 226 defines a cavity longitudinal axis and the light source mounting section 240 is configured and sized for allowing selective movement of the light source mounting component 238 therein along a substantially arc-shaped adjustment trajectory 242.

[0170] As shown more specifically in FIG. 24, the light source mounting component 238 typically includes a substantially cylindrical light source receiving channel 244 for receiving the distance probe light source 200 and a pair of substantially radial mounting component guiding flanges 246. The light source mounting component 238 defines a

pair of opposed and substantially flat mounting component guiding surfaces 248 (only one of which is shown in FIG. 24). At least one of the mounting component guiding surfaces 248 is provided with a corresponding guiding tongue 250 extending substantially outwardly therefrom.

[0171] As illustrated more specifically in FIG. 22, 23, 25 and 26, the optical probe casing defines a pair of opposed probe casing main walls 252, 253 maintained in a spaced-apart relationship relative to each other by a casing peripheral wall 255 extending therebetween. The casing main walls 252, 253 are adapted to be releasably assembled together using conventional attachment components such as screws, bolts or the like (not shown) extending through corresponding casing wall attachment apertures 251.

[0172] As illustrated in FIG. 25, adjacent to the casing output end 236, the casing peripheral wall 255 is provided with a light source output aperture 256 and a casing target aperture 258 both extending therethrough in optical communication respectively with the light source cavity 226 and the target sensor cavity 228. Similarly, the casing peripheral wall is also provided with a near optical slot 260 and a far optical slot 262 extending therethrough in optical communication respectively with the near sensor cavity 230 and the far sensor cavity 232.

[0173] At least one and preferably both casing main walls 252, 253 have guiding grooves 254, 254' formed respectively therein for guidingly receiving a corresponding guiding tongue 250. Typically, the guiding grooves 254' formed in the casing main wall 253 extend therethrough so as to allow access to the corresponding guiding tongues 250 without requiring disassembly of the casing main wall 252, 253.

[0174] Typically, the guiding tongues 250 that are inserted in corresponding guiding grooves 254' are provided with corresponding tongue notches 264 formed therein. The tongue notches 264 are adapted to allow insertion therein of a substantially pointed object. The substantially pointed object, in turn, is adapted to be used for facilitating the sliding of the guiding tongue 250 along the guiding grooves 254, 254' during adjustment of the alignment of the direction of the projection optical axis 202, the target sensor optical axis 208, the projection optical axis 202, the near sensor optical axis 216 and/or the far sensor optical axis 218 relative to the optical probe casing.

[0175] The light source alignment assembly or means typically further includes an alignment locking assembly or means for releasably locking the probe light source mounting components 238 in their respective aligned relationship relative to their respective light source mounting sections 240. The alignment locking assembly or means typically includes locking apertures 266 formed in the casing main wall 253 substantially adjacent the guiding grooves 254'. The alignment locking assembly or means typically also includes locking screws or the like (not shown) threadably insertable in corresponding locking apertures 266.

[0176] Each locking screws is configured, sized and positioned so that a distal tip thereof is adapted to frictionally contact a corresponding mounting component guiding surface 248 for frictionally preventing the movement of a corresponding probe light source mounting component 238 in its corresponding light source mounting section 240.

[0177] As illustrated more specifically in FIG. 10, the position evaluating assembly or means typically includes a set of strategically positioned optical probes 198. Although the optical probes 198 shown in FIG. 10 are only visible in the central head section 86, typically, the central head section 86 and the lateral head sections 88 are each provided with independent sets of strategically positioned optical probes 198 so as to allow for independent assessment of their respective position relative to the target surface.

[0178] Typically, the optical probes 198 are positioned in the casing cooling channels 156. It should however be understood that the optical probes 198 could be otherwise located without departing from the scope of the present invention.

[0179] Also, other types of position measuring or evaluating means could be used without departing from the scope of the present invention. In an alternative embodiment of the invention (not shown), the position measuring means includes a light source for directing a measuring beam towards the target surface and a photodetector positioned to receive a portion of the measuring beam reflected from the target surface.

[0180] A beam splitter is positioned between the light source and the target surface to reflect a portion of the light source measuring beam to a monitor photodetector. The monitor photodetector receives the reflected beam and provides an output signal representative of the position of the beam splitter reflected beam and, hence, the position of the light source with respect to an idealised position.

[0181] In one embodiment, the photodetector develops a monitor output signal representative of the deviation between an idealised centre line and an actual centre line of the light source. The monitor output signal may be employed for display purposes. The monitor output signal may also be employed with positioning means to displace the light source from its actual position towards the ideal position so as to reduce the measurement error associated with the actual position of the light source.

[0182] Optionally, the device 10 may further be provided with sensing means for sensing environmental and/or target tissue parameters that may have an influence on the value of the optimal head surface-to-target surface operational distance 128 and/or the optimal power density and/or the optimal value for other operational parameters. For example, the device 10 may optionally be further provided with a temperature sensor, a skin pigmentation or color sensor, a skin thickness sensor or the like.

[0183] The device 10 is optionally further provided with means for allowing optimal adjustment of selected operational parameters for achieving a predetermined photoinduced effect. The means for allowing optimal adjustment of selected operational parameters typically allows for global or localised adjustment of the selected operational parameters.

[0184] Light-based radiation therapy is effective in a number of clinical situations, but the photobiological basis of this therapy remains, at least in part, misunderstood. Wavelengths both in the visible (380-700 nm (nanometers)) and infrared regions (700-1000 nm) of the electromagnetic spectrum are effective in such therapies, often providing similar

clinical results, despite dramatic differences in their photochemical and photophysical properties.

[0185] It is established that the amplitude of laser light stimulation in biological tissues depends on a set of at least four parameters, besides the wavelength of light: 1. light intensity threshold (Irradiance or I_0), 2. beam cross section (spot size), 3. total irradiation time (Δt_{tot}) and 4. energy dose (fluence). The relevant parameters for modulation are interrelated according to this equation:

$$\text{Fluence} = I_{\text{stim}} \times \Delta t_{\text{tot}}$$

$$\text{where } I_{\text{stim}} \geq I_0$$

[0186] In biological tissues, light intensities lower than threshold values I_0 do not produce modulatory effects, even under prolonged irradiation time Δt_{tot} . Fluence and power density, also referred to as irradiance, are then independent from each other as allowed through the use of non-constant power densities as a function of time. The effective range of fluence in the above equation is given by the Arndt-Shultz curve showing different modes of cell reaction at different levels of energy density (57).

[0187] Besides the above-mentioned parameters, beam repetition frequencies in periodic time-varying irradiations also have extended influence on the activation/inhibition of biological tissues. Direct effects of pulse frequency received support on the experimental side from the observation-of additional Ca²⁺ uptake in macrophage (58) and an enhanced chemiluminescence in murine splenocytes (59) after irradiation with pulsed semiconductor lasers of suitable pulse duration and repetition frequency. There has also been support from the clinical side (15).

[0188] By far, the majority of laser applications in dermatology use laser-induced heating. In contrast to photoactivation/inhibition, heating does not require any particular thermal photon energy. "Selective photothermolysis" uses heat at a higher level. This approach changed the scope of lasers in dermatology over the 15 years since its formulation (56). This term was coined to describe site-specific, thermally mediated injury of microscopic, specific tissue targets by selectively absorbed pulses of light (55, 56). Such confined energy coagulates the target (i.e. oxyhemoglobin in blood vessels, melanin in pigmented cells) without injury to the surrounding skin.

[0189] Therefore, exposure duration and relaxation time are relatively important in the well-established selective photothermolysis concept. The so-called thermal relaxation time (TRT) or time required for significant cooling of a small target structure plays a major role in selective photothermolysis. Thermal conduction dominates the cooling of microscopic structures in skin. However, more microscale radiational cooling studies are needed (55). When the laser exposure is less than the TRT, maximal thermal confinement will occur.

[0190] The quantum yield of a photochemical reaction is the probability that photochemistry will occur when the energy of light is absorbed by the system. Hence, the true photochemical sensitivity of a system is the product of two probabilities: the probability that light of a given wavelength will be absorbed and the probability that the absorbed light will be responsible of a chemical change. Therefore, once a therapeutic benefit has been found for a given wavelength of

light, the optimum energy parameters and the optimum number of treatments to achieve a clinical benefit must be determined.

[0191] The light activation of enzymes is one of the fastest growing fields of photobiology, and several reviews on this subject have been published (7-9). Enzymes are catalysts. In principle, one photon can activate one enzyme molecule, which in turn can process many thousands of substrate molecules. The activation of enzymes provides a huge amplification factor for initiating a biological response with light. Such remarkable amplification potential may explain why low level laser radiation therapy is effective. If the effect of one photon can be amplified biologically, then not a lot of photons are required to produce a physiological effect. Proper parameters of light stimulating a given enzyme and leading to the beneficial therapeutic effect must be optimized and established. There are a number of ways suggested, both direct and indirect, to light-activate or inhibit an enzyme.

[0192] 1. Activate (Produce) the Substrate

[0193] For example, if a cell is exposed to UV radiation, the photochemical damage that occurs in the DNA will be repaired by a set of DNA repair enzymes that have become active due to the presence of their substrates, damaged DNA.

[0194] 2. Activate the Enzyme-Substrate Complex

[0195] In another example taken from UV radiation photobiology, the photoreactive enzyme (DNA photolyase) recognizes one type of DNA damage as its substrate, i.e., the cyclobutane-type pyrimidine dimer, and combines with these dimers in the dark. Activation occurs when the enzyme-substrate complex becomes exposed to visible light, the energy of the light being then used by the enzyme to split the dimer to yield repaired DNA.

[0196] 3. Activate the Enzyme Directly

[0197] This is generally accomplished by stimulating a conformational change in the enzyme molecule itself or in an attached photochromic inhibitor of the enzyme. There are many examples of each of these mechanisms (7-9).

[0198] 4. Induce the Synthesis of the Enzyme

[0199] This would occur by gene activation. For example, when bacteria are UV irradiated, a whole group of DNA repair enzymes are induced. Some of these induced enzymes are not present in detectable concentrations prior to induction, while other enzymes are present in small amounts but are induced to higher amounts by UV irradiation. Laser radiation at 633 nm has been shown to stimulate collagen synthesis in cutaneous wounds by enhancing the synthesis of Type I and Type II procollagen mRNA levels (10).

[0200] Therefore, the light activation of enzyme can occur by several diverse mechanisms. The first two mechanisms mentioned, i.e., the radiation-triggered production of the substrate, and the irradiation of the enzyme-substrate complex do not result in amplification of the bioreaction since one absorbed photon is needed for each photochemical event to take place. For that reason, a high level of radiation is required for these events.

[0201] The last two mechanisms, i.e., the direct activation of an enzyme and the induction of the synthesis an enzyme,

result in more chemical changes than the number of photons absorbed, and are produced by lower levels of radiation than the two processes mentioned above. Therefore, these last two mechanisms of enzyme activation are strong candidates for the photobiological basis of low level laser radiation therapy in the visible region of the spectrum.

[0202] The absorption of radiation in the infrared region results in molecular rotations (rotation of the whole molecule about some axis) and molecular vibrations (the stretching or bending of bonds resulting in the displacement of atomic nuclei relative to each molecule, but not affecting the equilibrium positions of nuclei). Thus, infrared radiation would not be expected to cause chemical changes in molecules, although reaction rates might be increased due to heating.

[0203] If the biological effect of low level visible light therapy is through photochemistry (probably the photoactivation of enzymes), and the biological effect of infrared radiation is through molecular rotations and vibrations, how can light-based radiation therapy produce similar clinical responses when either visible radiation or infrared radiation is used? For example, Abergel and coworkers (12, 13) found that the irradiation of fibroblasts in culture either at 633 nm or at 904 nm stimulated the synthesis of collagen. In separate studies, both 633 nm radiation (14) and 1060 nm radiation (15) were beneficial in reducing the pain of rheumatoid arthritis.

[0204] To explain the biostimulation effect of low level radiation at 633 nm; Karu (1) proposed a chain of molecular events starting with the absorption of light by a photoreceptor, which leads to signal transduction and amplification, and finally results in the photoresponse. In Karu's model, light is absorbed by components of the respiratory chain (i.e. flavine dehydrogenases, cytochromes and cytochrome oxidase), which causes an activation of the respiratory chain and the oxidation of the NAS pool, which leads to changes in the redox status of both the mitochondria and the cytoplasm. This in turn has an effect on membrane permeability/transport, with changes in the Na/H ratio and increases in Na/K'-ATPase activity, which has an effect on the Ca⁺⁺ flux. The Ca⁺⁺ flux affects levels of cyclic nucleotides, which modulates DNA and RNA synthesis, modulating cell proliferation (i.e. biostimulation).

[0205] This also suggests an explanation for why radiation at 904 nm can produce biological effects similar to those produced by radiation at 633 nm. In Karu's model, radiation at 633 nm initiates, probably by photoactivating enzymes in the mitochondria, a cascade of molecular events leading to the photoresponse. Radiation at 904 nm produces the same final response, but initiates the response at the membrane level (probably through photophysical effects on Ca⁺⁺ channels) at about halfway through the total cascade of molecular events that leads to biostimulation.

[0206] Calcium ions are intracellular messengers in many signal-transducing systems. The intracellular levels of Ca⁺⁺ are advantageously kept low because phosphate esters are prevalent and calcium phosphates are very insoluble. The cytosolic level of Ca⁺⁺ in unexcited cells is several orders of magnitude less than the extracellular concentration. Thus, the cytosolic Ca⁺⁺ concentration can be abruptly raised for signaling purposes by transiently opening calcium channels in the plasma membrane or in an intracellular membrane (16-23).

[0207] In a recent paper, Karu (1) makes the following statement: "the magnitude of the laser biostimulation effect depends on the physiological state of the cell at the moment of irradiation". This explains why the effect is not always detectable, as well as the variability of the results reported in the literature.

[0208] For example, it has been established that irradiation accelerated the proliferation of slowly growing HeLa subpopulations. In medicine, laser treatment appears to work in cases of severe damage (e.g. trophic ulcers), and the effect of light on normally regenerating wounds may be insignificant (if there is any). Light only stimulates cell proliferation if the cells are growing poorly at the time of the irradiation. Thus, if a cell is fully functional, there is nothing for laser radiation to stimulate, and no therapeutic benefit will be observed. A similar analogy is that patients will not show a beneficial effect of vitamin therapy if they already receive an adequate supply of vitamins in their daily diets.

[0209] The interaction between living tissue and cells and radiations has been extensively studied. Non-limiting examples of such studies are found in references 1-60, A1-A7 and B1-B7.

[0210] The following text proposes a number of mechanisms through which the claimed invention achieves desired effects. However, some embodiments of the invention achieve the desired effect through alternative mechanisms. Accordingly, the proposed mechanisms should not be interpreted to restrict the scope of the appended claims that do not claim such mechanisms.

[0211] In a first aspect, the claimed invention includes a method for treating a mammalian tissue, such as for example a mammalian skin tissue, the method including irradiating the tissue with radiation defining a pulse train including a plurality of radiation pulses. The radiation has a wavelength of from about 400 nanometers to about 1500 nanometers, the pulses each have a duration of from about 1 femtosecond to about 1 hour, the pulses are separated from each other by an inter-pulse interval, the inter-pulse interval being of from about 1 microsecond to about 10 seconds, and the power density of each pulse in the tissue is of from about 0.1 mw/cm² to about 10 W/cm². All the parameters describing the radiation are either adjusted independently from each other or adjusted in combinations causing synergistic effects within the tissue.

[0212] The exact values for the various pulse parameters depend on the effect that is sought. Examples of more specific values and of effects that are sought are given hereinbelow.

[0213] In one of these examples, the pulses each have a duration of from about 100 microsecond to about 10 milliseconds. In a very specific example of implementation, the pulses each have a duration of from about 250 microsecond to about 1 millisecond.

[0214] In another of these examples, the inter-pulse interval is of from about 10 microseconds to about 10 milliseconds. In a very specific example of implementation, the inter-pulse is of from about 100 microseconds to about 500 microseconds.

[0215] While the pulse duration and the inter-pulse intervals may be considered separately from each other, it is also

within the scope of the invention to consider synergistic effects related to these two parameters.

[0216] For example, the ratio of the pulse duration divided by the pulse interval takes any suitable value. In a specific example of implementation, the ratio of the pulse duration divided by the pulse interval is within the interval of from about 0.1 to about 10. In a very specific example of implementation, the ratio of the pulse duration divided by the pulse interval is within the interval of from about 0.5 to about 2. Within this last interval, and non-limitatively, a ratio of the pulse duration divided by the pulse interval of about 1 has been found to produce desired effects in the skin while being technologically achievable.

[0217] A specific example of a suitable power density of each pulse in the tissue is a power density contained within the interval of from about 30 mW/cm² to about 100 mW/cm².

[0218] In a specific example of implementation, the method includes irradiating the tissue with radiation defining a plurality of pulse trains, each pulse train including a plurality of radiation pulses. For example, each pulse train includes from 2 to 100 pulses. The pulse trains are separated by inter-train time intervals wherein no pulses are produced, the inter-train intervals lasting from about 1 microsecond to about 1 second.

[0219] The term pulse is to be broadly interpreted. For example, the pulses need not be of a substantially uniform power density with a substantially total absence of power density within the inter-pulse intervals, even if such pulses are an example of pulses suitable for use in some embodiments of the invention.

[0220] Indeed, each pulse may present a time evolution leading to pulses having any suitable time evolution. Also, during the inter-pulse interval, the power density is substantially smaller than a power density within each pulse, but not necessarily zero. Examples of such power density during the inter-pulse intervals are given hereinbelow.

[0221] In a non-limiting specific example of implementation, the inter-train intervals last from about 500 microseconds to about 2.25 milliseconds and each pulse train includes from 4 to 10 pulses. The ratio of the inter-train interval to the inter-pulse interval is of from about 2 to about 10, and in a very specific example of implementation, the ratio of the inter-train interval to the inter-pulse interval is of about 3.

[0222] As described in further details hereinbelow, the above-described method for treating a mammalian tissue finds applications, among other applications, to the production of desired effects in a mammalian skin tissue. For example, the radiation power density temporal profile causes a predetermined physiological change in a mammalian skin tissue.

[0223] In the context of this specific example, it has been found that it is beneficial to pulse treat the skin, i.e. it is valuable that the light source is not energized for the whole duration (continuous wave) of the treatment but is rather pulsed, leaving time for the skin to rest between pulses and intervals. Furthermore, it has been found that it is often necessary to stop the pulsing sequence for a greater amount of time after a predetermined number of light pulses have already been emitted.

[0224] In one example, the radiation is produced using Light Emitting Diodes (LEDs) which obey a predetermined duty cycle. Of course, should LEDs not necessitating a predetermined duty cycle be used, many constraints regarding the irradiation are removed.

[0225] In addition, it has been found that a specific example of a desired physiological effect, namely an increase in collagen production, is favoured by pulsed radiation such as the pulsed radiation described hereinabove. This beneficial effect of pulsed radiation is also present in many other situations.

[0226] More specifically, in the context of increase in collagen production, it has been found that the exposure duration ("time on") is a factor to be relatively closely monitored, but that the component of the sequential pulsing of the present invention is the pulse relaxation time or pulse interval ("time off"). Shorter pulse intervals seem to improve the metabolic pathways resulting in healthier skin cells. Then, after a predetermined number of pulses within the pulse train, it is advantageous in some tissues to provide a downtime to let the light skin rest. This downtime is provided by the inter-train interval.

[0227] Target response selectivity is made possible not only by picking the appropriate pulse durations, but also by picking the proper inter-pulse interval assuming that all other established parameters are held constant (fluence, irradiance, treatment time, wavelength, spot size, working distance, etc.). In a specific and non-limiting example of implementation, the target within which a response is sought includes a chromophore, but alternative targets are within the scope of the invention.

[0228] In the context of increased collagen production, the pulse train typically includes more than three pulses of substantially equal pulse duration, separated by substantially equal inter-pulse intervals wherein substantially no power is provided within the tissue. Each pulse train is separated from a subsequent pulse train by the inter-pulse interval.

[0229] More specifically, and non-limitatively, it has been found interesting to use three or more pulses of 250-1000 μ sec (microseconds) by pulse trains separated by 100-500 psec intervals. Pulse train intervals of suitable durations are used to separate pulse trains, as dictated by the duty cycle of the LEDs used and physiological parameters, both at the cellular and at the molecular level.

[0230] While in many embodiments of the invention the pulse durations, inter-pulse intervals, number of pulses within each pulse train and inter-train intervals are substantially constant within each treatment, it is within the scope of the invention to have treatments wherein these parameters are not constant over the whole treatment.

[0231] The number of pulses to be administered during a session depends on many parameters such as the power density desired, the energy density delivered by the LEDs or other light source used, the wavelength, and the spot size, for example. As will be apparent to one skilled in the art, the number of pulses by pulse train is variable and depends on the exact effect that is sought.

[0232] It has also been found that pulsed radiation similar to the pulsed radiation described hereinabove is usable to treat other skin conditions that are not related to collagen

production. For example, it appears possible to treat cheloids by photoinhibition and atrophic scars through photoactivation. It is also believed possible to treat acne, eczema, psoriasis, vitiligo, rosacea, hair regrowth, exogenous pigments, dermal melanosis, some adnexial tumors and cutaneous hyperpigmentation via the proposed method. Therefore, the above-described irradiation of the skin is usable for many dermatological conditions. A proposed and non-limiting mechanism through which these treatments may work includes modulating a skin cell activity.

[0233] In addition, using pulsed radiation defined by suitable pulse and radiation parameters leads to a stimulation of collagen production that is substantially larger than a collagen production produces by a continuous mode stimulation. A proposed, non-limiting, and non-binding, mechanism that may cause this effect includes a reduction in cellular exhaustion and provides optimal dermal fibroblast stimulation as well as collagenase inhibition.

[0234] The above-described method for treating a mammalian skin tissue and results obtained therefrom also suggest a method for altering the physiology of a mammalian tissue, the method including irradiating the tissue with radiation defining a suitable radiation power density profile. The radiation power density profile is any suitable power density temporal profile, such as, non-limitatively, a power density temporal profile including a plurality of pulse trains, each pulse train including a plurality of radiation pulses having a predetermined pulse width and being separated from each other by an inter-pulse time interval, the pulse trains being separated from each other by an inter-train time interval, the inter-train interval being substantially larger than the inter-pulse interval.

[0235] Examples of suitable values for ratio of the inter-train interval to the inter-pulse interval and the number of pulses within each pulse train have been mentioned hereinabove.

[0236] In an example of implementation, a minimal power density of the radiation within the tissue during each pulse is at least about two times as large as a maximal power density of the radiation within the tissue during each inter-pulse interval. In another example, a minimal power density of the radiation within the tissue during each pulse is at least about ten times as large as a maximal power density of the radiation within the tissue during each inter-pulse interval. In yet other examples of implementation, a minimal power density of the radiation within the tissue during each pulse is at least about 100 times or at least about 10000 times as large as a maximal power density of the radiation within the tissue during each inter-pulse interval. Suitable values of pulse duration, power density of each pulse in the tissue, ratio of the pulse duration divided by the pulse interval have also been mentioned hereinabove.

[0237] The above-described irradiations also find applications in causing a predetermined physiological change in a mammalian tissue, the tissue being irradiated with a radiation having a power density in the tissue substantially larger than an activation threshold power density, the tissue being irradiated under conditions suitable to cause the predetermined physiological change.

[0238] In an embodiment, the activation threshold power density is a power density: below which the predetermined

physiological change is substantially absent from the mammalian tissue upon the mammalian tissue being irradiated with the radiation and above which the predetermined physiological change is substantially present in the mammalian tissue upon the mammalian tissue being irradiated with the radiation.

[0239] However in alternative embodiments of the invention, an activation threshold is relatively hard to define as the presence of the predetermined physiological change is progressively observed as a function of the power density. In these cases, the activation threshold is a power density above which the predetermined physiological change is observed in the tissue at a level that is large enough to be clinically significant.

[0240] In an embodiment of the invention, the power density is below a thermal threshold power density over which a temperature of the irradiated tissue increases to temperature greater than a predetermined overheating temperature. Over the predetermined overheating temperature, the predetermined physiological change is substantially inhibited at least in part, substantially totally inhibited or even substantially reversed.

[0241] The definition of a thermal threshold is a consequence, among other factors, of a thermal inertia of the irradiated tissue. Indeed, the irradiated tissue has a thermal diffusion coefficient and a heat capacity that buffer an increase in temperature upon deposition of heat within the tissue.

[0242] To achieve a relatively high power density (or intensity), within the limits of a non-thermal treatment, there is a need to generate a relatively high intensity over a relatively short treatment time. Then, the thermal inertia and thermal conduction coefficient of the tissue achieve a relatively high power density without causing a potentially harmful temperature increase in the tissue.

[0243] The suggested non-thermal light-based treatment described hereinabove is a therapeutic strategy established with the specific concern that supra-physiologically, a temperature rise potentially reduces or impedes the normal metabolism within the tissue. For example, in mammalian skin tissue, such supra-physiological temperature rises potentially reduce or impede collagen metabolism and potentially promote collagen degradation.

[0244] Aside the fact that triple helices of type I collagen melt just several degrees above body temperature (B1, B2), a thermal treatment where a skin temperature increase (for example, superior by 2° C. to the maximal non-pathological temperature of the skin) is maintained, being repeated or not, can enhance the production of collagen degrading-enzymes, collagenases (such as metalloproteinases (MMP)).

[0245] If the temperature of the tissue increases sufficiently, a heat shock induces the expression of MMP-1 at the mRNA and protein levels in a temperature-dependent manner (B3). Also, it was found that heat treatment increases MMP-12 mRNA and protein expression in human skin (B4). MMP can trigger dermal collagen degradation to reverse collagen metabolism. Evidence points out that proteolytic enzymes like MMP-1/MMP-2 would add to and already poorer collagen production by degrading collagen at the pace it is newly produced (B5). Moreover, occurring fragmentation of type 1 collagen by collagenases would act as to

promote collagen loss both in aged and photodamaged skin, as the damaged protein would downregulate collagen synthesis by cells naturally able to produce collagen (B6, B7).

[0246] In addition, skin hyperthermia has a potential to promote an inflammatory state with increased redness (rubor), heat (calor), swelling (tumor), and pain (dolor). The redness and heat are caused by the increased blood supply to the heated area. Blood vessels and capillaries become vasodilated providing extravasation of various leukocytes involved in the initiation and maintenance of inflammation. It is preferable to substantially minimize these side effects.

[0247] Finally, enzymatic activity would be challenged by supraphysiological temperature at the treatment site. Heat sets off protein denaturation, which implies lost of enzymatic function. Collagen synthesis would be compromised with a potential risk of fibrosis. Furthermore, high intensity, or high power density, light sources result in the deoxygenation of tissue and possible hyperthermia.

[0248] In an example wherein the tissue is a skin tissue, a relatively high power density brings the targeted tissue to its physiological threshold of activation and triggers a cascade of events leading, for example, to enhanced procollagen production. However, these beneficial effects are cancelled and even reversed if the skin reaches the overheating temperature.

[0249] Non-thermal reactions initiate molecular conformational changes and metabolic activation relatively quickly. A suitable fluence (dose or quantity of energy reaching the skin) is delivered, in a relatively short treatment time without any substantial increase in the skin temperature.

[0250] In this case, power density and fluence become independent variables. Indeed, there is a need to achieve the power density activation threshold independently of the required total fluence. Only a relatively high power density can provide such high fluence with substantially no heat being delivered to the skin. As already mentioned, the condition of a relatively small increase in skin temperature is advantageous as supra-physiological skin surface temperature has a potential to prevent proper photobiochemical reactions from happening.

[0251] In a specific embodiment of the invention, the power density required for cellular activation is between 30 and 100 mW/cm² at tissue. Since the intensity for a suitable activation of fibroblasts within the skin tissue is relatively sensible to the power density, there is a need for a relatively accurate method of delivering the radiation into the tissue. In a specific example of implementation, a novel optical positioning system, described elsewhere in this document, is used to provide a relatively very precise working distance between the light source and the surface of the skin for optimal beam intensity delivery. However, it is within the scope of the invention to irradiate the tissue using any alternative suitable apparatus.

[0252] Prolonged but insufficient power density irradiation will have substantially no physiological benefit since the power density activation threshold is not surpassed. In addition, as described in further details hereinbelow, pulsing patterns must be elaborated to minimize cellular exhaustion.

[0253] As also further detailed hereinbelow, no adverse effects have so far been linked to the above-described

method, especially in an embodiment of the invention wherein the radiation is produced by Light Emitting Diodes (LEDs). This is probably due to a substantial absence of thermal damage during treatment. Any other suitable interval of power density may be used, depending on the exact tissue and duration of irradiation.

[0254] In alternative embodiments of the invention, the activation threshold is about 0.1 mW/cm². In other alternative embodiments of the invention, the activation threshold is about 10 mW/cm². In yet other alternative embodiments of the invention, the activation threshold is about 30 mW/cm².

[0255] Also, in alternative embodiments of the invention, the thermal threshold is about 10 mW/cm², about 100 mW/cm², about 1 W/cm², and/or about 1 kW/cm². The thermal threshold is linked to both the thermal inertia of the tissue and to the power density temporal pattern of the radiation, among other factors.

[0256] In a specific embodiment of the invention, the activation threshold power density is about 30 mW/cm² and the thermal threshold power density is about 100 mW/cm².

[0257] In one embodiment, the overheating temperature is about 2° Celsius over a maximal non-pathological in-vivo temperature of the mammalian tissue. In other embodiments of the invention, the overheating temperature is about 0.5° Celsius over a maximal non-pathological in-vivo temperature of the mammalian tissue. In yet other embodiments of the invention, the overheating temperature is about 0.1° Celsius over a maximal non-pathological in-vivo temperature of the mammalian tissue.

[0258] The exact overheating temperature depends on many factors. For example, the overheating temperature depends of a balance between beneficial effects of the radiation and harmful effects of the radiation. Control of the temperature of the skin is achieved at least in part through a suitable temporal pattern of power density. Another manner of controlling skin temperature includes cooling the skin, for example through convection. Another manner of cooling the skin includes vasodilating the skin blood vessels, for example through the administration of a suitable vasodilating substance.

[0259] The embodiments focus mainly on applications to mammalian skin tissue. However, in alternative embodiments application can be performed on any other suitable tissue.

[0260] Also, other parameters of the radiation must be suitably adjusted to achieve an expected photoresponse. For example, the fluence (for example in J/cm²) or total dose of energy released over a definite amount of time is such a parameter. Fluence and power density are independent variables which ought to be considered, especially for medical applications. For instance, bearing in mind equal fluence delivered, irradiance values under the threshold point, even under prolonged irradiation time, would very likely produce minimal results in biostimulatory effects. Consequently, an accurate working distance is required so as to provide the needed irradiance to ensure successful collagen production by targeted dermal fibroblasts.

[0261] As mentioned hereinabove, the physiological effect includes for example stimulating collagen production by

fibroblasts contained within the skin tissue. In another example, the physiological effect includes reversing skin damages caused by aging, for example by reversing damages caused to an extracellular matrix of the skin by aging. Yet another physiological effect includes modulating an apoptosis response of the skin tissue.

[0262] In another aspect of the invention, the above-described radiation temporal power density profile is suitable to provide a method for altering the physiology of a mammalian tissue. More specifically, this method includes irradiating the tissue with a time-varying radiation according to a temporal power density profile suitable for both activating molecular cascades of events and activating cells contained within the tissue.

[0263] In specific embodiments of the invention, the power density temporal profile of the radiation is selected so that at least one of the following effects are produced:

[0264] initiating molecular-scale events within the tissue leading to the desired physiological effect;

[0265] stimulating cell-scale events within the cells of the tissue;

[0266] allowing a cellular relaxation so as to prevent cell exhaustion during the irradiation;

[0267] allowing a molecular relaxation so as to allow reversible molecular conformational changes to be reversed;

[0268] preventing a temperature increase in the tissue above a thermal threshold at which a cascade of events triggered by radiation and leading to the desired alteration of the physiology of a mammalian tissue is reversed; and/or

[0269] preventing a temperature increase in the tissue above a thermal threshold above which tissue damage occurs.

[0270] In other embodiments of the invention, the power density temporal profile of the radiation is selected so that two or more of the above-mentioned effects occur. The reader skilled in the art will readily appreciate that a suitable choice of radiation, including a suitable chaise of radiation power density temporal profile leads to potentially synergistic effects.

[0271] In a specific embodiment of the invention, cell-scale events include progressively increasing a mitochondrial activity level within the cells of the tissue while the resting periods substantially prevent cell exhaustion.

[0272] An example of a tissue wherein the above-described effects has been observed to occur is a skin tissue wherein the irradiation stimulates collagen production by fibroblasts. However, it is within the scope of the invention to apply radiation to achieve a desired physiological effect in any other suitable tissue. Also, it is within the scope of the invention to irradiate both in vivo tissue and in vitro tissues.

[0273] In a specific example relating to skin tissue, experimental results suggest that to successfully enhance dermal collagen production leading to clinically significant results, a combination of the following achieves a suitable activation of dermal fibroblasts by non-thermal, non-coherent LED light.

[0274] A sequential pulsing mode with predetermined time on and time off provides resting periods during irradiation of dermal fibroblasts. While preventing cell exhaustion, this pulsing mode contributes to energize the metabolic pathways for optimal signal transduction and amplification.

[0275] Pulse duration of between about 250 and about 1000 μ sec have been shown to produce interesting results, but other pulse durations are within the scope of the invention. It is hypothesized that such pulse durations meet the necessary time for the antenna molecule to initiate the molecular cascade of events probably taking place within the mitochondria and leading to the cell response. This molecular cascade of events is initiated further to an antenna molecule receiving at least one photon contained within the radiation and likely occurs in the mitochondria of cells of the tissue.

[0276] Pulse intervals of about 100 to about 500 μ sec have also been shown to produce suitable effects. This order of magnitude of pulse intervals substantially enhances molecular photobiochemical reactions within the mitochondria as it provides resting phases between pulses in order to achieve reversible molecular conformational changes that will ultimately generate signal transduction and amplification leading to an expected gene expression.

[0277] Regarding the pulse trains, they each include from 4 to 10 pulses in this example. The number of pulse needed to bring the cell to the needed level of activation within the pulse train seems to be an important parameter. For values larger than 10, the cell probably sees the pulse trains as a quasi-continuous-wave modes and little or no further stimulatory effects are triggered in this particular example.

[0278] Pulse train intervals of about 750 μ sec to about 2250 μ sec are suitable. In a specific example, the inter-pulse interval is at least 3 times the pulse duration. This relatively long lag time between pulse trains seems to have an effect in preventing cell exhaustion through avoidance of mitochondrial depletion that brings the cell to a higher level of gene expression.

[0279] The number of pulses within each pulse train is large enough to bring the cells to a suitable level of activation while preventing the cell to each a steady-state of activation.

[0280] Another observed effect of pulse trains similar to the above-described pulse trains is a regeneration of an extracellular matrix in mammalian tissue. To that effect, the tissue is irradiated with radiation under conditions suitable to regenerate the extracellular matrix. For example, the tissue is a skin tissue.

[0281] In this case, it has been observed that a suitable radiation leads to an at least partial reversal of the effects of aging within the skin tissue. Various mechanisms whereby this reversal is effected include a stimulation in collagen production within the tissue, a stimulation of collagen repair within the extracellular matrix, a downregulation of a matrix metalloproteinase (MMP) gene expression within the cells of the tissue, an upregulation of procollagen production within the cells of the tissue, a reduction in elastin degradation within the extracellular matrix and a reduction fibronectin degradation within the extracellular matrix, among others.

[0282] Indeed, a suitable radiation seems to restores extra-cellular matrix (ECM) equilibrium in the dermis. In aging skin, collagen production decreases while degradation increases. External signs of aging such as uneven pigmentation and wrinkles, thinning skin, lack of firmness and dullness result from a reduction in collagen, a protein that gives the skin its suppleness as well as its ability to repair itself.

[0283] Free radicals are known to attack the collagen. As collagen diminishes, the skin's ability to regenerate and heal itself declines. Normally, healthy collagen gives the skin its softness and resiliency. But damaged collagen molecules become stiff and inflexible, making the skin appear old. Besides collagen, other dermal extracellular matrix components like elastin become altered and damaged. Hence the term elastosis describes age and sun related histopathological morphological alterations in the upper dermis.

[0284] Free radicals can also stimulate production in the body of collagen-digesting enzymes. When the skin is exposed to ultraviolet light, free radicals activate transcription factors, chemical messenger molecules normally present in the cells. When activated, the transcription factors migrate to the nucleus of the cell and stimulate DNA to produce collagen-digesting enzymes. These begin to leave tiny defects in the skin, which eventually turn into wrinkles.

[0285] Lastly, free radicals also cause inflammation. This occurs at the cellular level and is not visible to the naked eye. Inflammation can happen in a number of ways. It can be the result of the oxidation of enzymes produced as a defence mechanism by the body in response to exposure to trauma such as sunlight or chemicals. Anti-inflammatory effects of suitable irradiation, such as irradiations defined by above-discussed parameters, counteract such skin damage.

[0286] In addition, matrix metalloproteinase (MMP) activity is highly regulated in skin tissue. It plays a key role in dermal extracellular matrix turnover. MMPs are a large family of proteolytic enzymes, which are involved in the degradation of many different components of the extracellular matrix. The MMPs have been classified into different groups including collagenases, gelatinases, stromelysins, and others. There is increasing evidence indicating that individual MMPs have important roles in aging skin.

[0287] While the above suggests that completely stopping collagen degradation would provide an ideal treatment against aging, controlled degradation of extracellular matrix (ECM) is in fact essential for the homeostasis of the dermis. However, recent evidence suggests that this homeostasis is out of balance in aging and photoaged skin. Downregulation of MMP gene expression combined with upregulation of procollagen production are therefore two components that may lead a successful anti-aging photoinduction.

[0288] More specifically, as described in more details in the examples found hereinbelow, the role of MMP-1 or collagen degrading enzyme using a non-ablative non-thermal LED therapy has been thoroughly studied since most dermal extracellular matrix is composed of collagen.

[0289] In addition, new research indicates that another matrix metalloproteinase (MMP), MMP-2, is a strong marker for other dermal matrix degrading enzyme activity. MMP-2 or Gelatinase-A is able to degrade elastin, fibronectin, type IV collagen, and gelatins but shows no activity

against laminin or interstitial collagens. Also, these enzymes are thought to act co-operatively with the collagenases to effect the complete degradation of interstitial collagens. Gelatinase-A is widely expressed in-adult tissues and constitutively expressed in many connective tissue cells with poor regulation by growth factors (GF).

[0290] Induction of MMP expression by agonists requires transduction of a signal from the extracellular space to the MMP genes. This is achieved by agonist binding to cell membrane receptors, and in some cases cytoplasmic receptors, activation of cellular tyrosine kinase signal transduction cascades, transcription factor activation and induction of MMP transcription. Conversely, downregulation of MMP gene expression that may be triggered, for example using the above described tissue irradiation, has a potential to lead to aging reversal in skin tissue.

[0291] The above-described irradiation may also be approached as leading to a method for improving cellular integrity in mammalian tissue, the method comprising irradiating the tissue with radiation under conditions suitable to improve cellular integrity in the mammalian tissue. For example, the method comprises stimulating collagen production within the skin tissue.

[0292] Briefly, non-coherent, non-thermal visible/near infrared light was observed to restore cellular integrity of aged and photoaged fibroblasts, regaining their full potential and basal metabolic collagen secretion level. A goal of such a therapy is to reverse the constantly declining collagen production level over the years and increase it towards a basal level by using a predetermined number of radiation treatments over a period of time.

[0293] More specifically, the claimed invention includes a method wherein a tissue is irradiated over a plurality of treatments and the treatments are provided with an inter-treatment time interval therebetween. Further, within each treatment, the power density temporal profile during the treatment defines a plurality of pulse trains, each pulse train including a plurality of radiation pulses having a predetermined pulse duration and being separated from each other by an inter-pulse time interval. The pulse trains being separated from each other by an inter-train time interval, the inter-train interval being substantially larger than the inter-pulse interval and the irradiation is performed under conditions suitable for substantially reducing damages previously caused to a mammalian skin tissue.

[0294] In a specific example the treatments are applied within a rejuvenating phase wherein the tissue is substantially rejuvenated. Optionally, the treatments are further applied during a maintenance phase following the rejuvenating phase, the maintenance phase including treatments that substantially maintain the rejuvenation of the tissue.

[0295] In some embodiments of the invention, the inter-treatment time interval during the maintenance phase is substantially larger than the inter-treatment time interval during the rejuvenating phase. Some of these latter embodiments are such that the inter-treatment time interval during the maintenance phase is substantially larger than the duration of the rejuvenating phase.

[0296] The inter-treatment time intervals are adjusted in any suitable manner. For example, the inter-treatment time interval during the rejuvenating phase is from about 1

minute to about 1 year. In other examples, the inter-treatment time interval during the rejuvenating phase is from about 1 hour to about 1 month. In yet other examples, the inter-treatment time interval during the rejuvenating phase is from about 1 day to about 1 week. In yet other examples, the inter-treatment time interval during the rejuvenating phase is from about 3 days to about 4 days.

[0297] The inter-treatment time interval during the maintenance phase is also adjusted in any suitable manner and is, for example and non-limitatively, from about 1 day to about 5 years. In other examples, the inter-treatment time interval during the maintenance phase is from about 1 month to about 1 year. In yet other examples, the inter-treatment time interval during the maintenance phase is about 1 year.

[0298] In some specific embodiments of the invention, the rejuvenating phase includes from 5 to 20 treatments with an inter-treatment time interval during the rejuvenating phase of from about 1 day to about 1 week. In this example, a suitable example of an inter-treatment time interval during the maintenance phase is from about 1 month to about 1 year. Maximizing the inter-treatment interval during the maintenance phase while maintaining the treatment efficiency is advantageous to a patient undergoing the treatment.

[0299] Embodiments of the rejuvenating phase include from 2 to 1000 treatments, 2 to 50 treatments, and 5 to 20 treatments. In a specific embodiment of the invention, a rejuvenating phase including 12 treatments has been shown to give acceptable results.

[0300] For each treatment, the radiation is provided according to a power density temporal profile similar to the above-described power density temporal profiles. Another parameter that also needs to be determined is the total fluence of each treatment. A fluence of 4.5 J/cm^2 or greater has been shown to give acceptable results, especially below 10 J/cm^2 but other fluences are also within the scope of the invention. For example, the fluence of each treatment can be from about 1 mJ/cm^2 to about 20 kJ/cm^2 , about 1 J/cm^2 to about 50 J/cm^2 , and from about 4 J/cm^2 to about 10 J/cm^2 .

[0301] In a specific example, 3 to 50 treatments, each irradiating the tissue with a fluence having a value of from about 1 to about 30 J/cm^2 are performed over a period of from about 1 day to about 1 year. Afterwards, maintenance therapy is performed to help preserve skin appearance. In a very specific example of implementation, between 4 and 10 J/cm^2 are deposited in the skin at a rate of two treatments per week for six week. Afterward, a single similar annual treatment helps in conserving the improvements caused to the skin.

[0302] A possible mechanism for this action follows from Karu (1) who stated that the magnitude of the laser bio-stimulation effect depends on the physiological condition of the cell at the moment of irradiation. Light would only stimulate cell proliferation if the cells are growing poorly at the time of the irradiation. Cell conditions are to be considered since laser/light exposures would restore and stimulate procollagen production, energizing the cell to its own maximal biological potential.

[0303] Therefore, a suitable irradiation therapy regenerates at least in part cellular integrity of aged and photoaged fibroblasts, enabling them to eventually regain their full

potential and basal metabolic collagen secretion level, or at least to improve these factors. The goal of such therapy is to reverse at least in part the constantly declining collagen production level over the years and bring it back to basal level by using a predetermined number of treatments over a relatively short period of time. Maintenance therapy is then the key to keep the best overall skin appearance.

[0304] More generally, the invention provides a method for reducing damages previously caused to a mammalian skin tissue, the method comprising irradiating the tissue with radiation presenting a temporal power density profile such that the radiation has a power density within the tissue that is above an activation threshold at least over a predetermined time interval, the predetermined time interval being such that the radiation causes an increase in temperature within the tissue of at most 2° Celsius .

[0305] In a specific example of implementation, the radiation presents a temporal power density profile substantially preventing a cellular exhaustion, the cellular exhaustion being a state of the cells wherein the cells are unable to respond to further irradiation. More specifically, the radiation presents a temporal power density profile substantially preventing mitochondrial exhaustion.

[0306] In some embodiments of the invention, the temporal power density profile of the radiation stimulates the skin tissue so as to repair damages to the extracellular matrix of the skin tissue. For example, the mammalian skin tissue is human skin tissue.

[0307] Examples of damages previously caused to a mammalian skin tissue include a degradation of extracellular collagen, a degradation of extracellular elastin, a degradation of extracellular fibronectin and a reduction in collagen secretion by fibroblasts contained within the skin tissue, among others.

[0308] In yet another aspect of the invention, non-thermal, non-coherent close/near Infrared (IR) light therapy is effective against apoptosis. Indeed, a substantially rejuvenated tissue includes cells that are less likely to experience apoptosis than the cells were prior to the irradiation. The diminution in the likelihood of apoptosis is caused at least in part by a reversal of an aging process or at least in part by a reversal of damages caused by environmental factors.

[0309] With regards to the an application of the invention to reversal of aging, it is known that aging of the skin shifts the balance between collagen production and breakdown, which leads to wrinkles, facial sag and rough skin texture. Stimulating skin cells to produce collagen can partly reverse this process. Stimulating collagen synthesis in aged skin was shown to reduce wrinkles and improve skin texture. The benefit of stimulating a person's own collagen production is that collagen is deposited in an orderly, structured manner and that there is no risk of allergy, immune reaction or injection-induced infection.

[0310] It has been found that it is possible to stimulate the collagen production by subjecting the skin to light in the 635-805 nm (nanometers) range. It has also been found that by using a non-thermal light source, such as for example a Light Emitting Diode (LED), it is possible to minimize the risks of leaving treatment marks. Furthermore, it has been found that light can be shone directly onto the skin without necessity of removing a skin layer, thereby yielding a non-ablative method.

[0311] It has also been found that the production of collagen is a natural photobiochemical reaction similar to plant photosynthesis. To maximize benefits of LED therapy on skin, a topical formulation may optionally be used during treatment, such as a specially formulated topical formulation may be used as an adjunct therapy to promote collagen synthesis with powerful antioxidants to inactivate free radicals including vitamins (A, B₅, C, E) and essential nutrients.

[0312] Thirdly, it has also been found that it is beneficial to pulse treat the skin, i.e. it is valuable that the light source is not energized for the whole duration (continuous wave) of the treatment but is rather pulsed, leaving time for the skin to rest between pulse and intervals. Furthermore, it has been found that it is often necessary to stop the pulsing sequence for a greater amount of time after a predetermined number of light pulses have already been emitted. Indeed, as will be obvious to one skilled in the art, LEDs must obey a predetermined duty cycle. Of course, should LEDs not necessitating a predetermined duty cycle be used, the train of pulses could be repetitive, as will be described hereinbelow.

[0313] It has also been found that the sequential pulsing mode described hereinabove may be used to treat other skin conditions that are not related to collagen production. For example, it appears possible to treat cheloids by photoinhibition and atrophic scars through photoactivation. It is also believed possible to treat acne, eczema, psoriasis, vitiligo, rosacea, hair regrowth, exogenous pigments, dermal melanosis, some adnexial tumors and cutaneous hyperpigmentation via the proposed method. It is therefore believed that the Sequential Pulsing Mode according to the present invention, by turning skin cells on and off and its effects on the skin may be used for many dermatologic conditions.

[0314] Even though wavelength is an important parameter in irradiation of tissues, it is less specific to activate the fibroblast. Several known absorption peaks can activate the fibroblast. 660 nm wavelength is one of the peak absorption spectrum of the fibroblast (49).

[0315] The present invention also relates to a non-ablative, non-thermal method for the treatment of skin by photoactivation of procollagen and/or photoinhibition of collagenase (such as MMP-1). The method involves projecting photoinduction light having predetermined photoinduction light parameters on a target treatment area of the skin and, hence, using photons to trigger photobiochemical reactions within the skin.

[0316] Typically, the photoinduction light has wavelength values between 600 and 700 nm, for example with a peak at 660 nm. Indeed, reported evidence shows that normal and abnormal human fibroblast cell lines exhibit higher cell counts when exposed to a 660 nm light source. The 660 nm wavelength is also associated with photosynthesis in plants wherein the latter use chlorophyll to convert sun light into cellular building blocks. Furthermore, 660 nm provides a relatively optical penetration into the skin. The increased depth of penetration of higher wavelengths provides differ-

ences in specific protein expression and greater proliferating capacity by dermopapillary vs. deeper reticular fibroblast. In human skin, a penetration depth at 660 nm is 2.23 mm, enough to reach the dermis.

[0317] It should, however, be understood that other wavelengths could be used for overall increased collagen synthesis or other applications without departing from the scope of the present invention.

[0318] In some embodiments of the invention, the above-described irradiations are performed using a suitable laser-based device. However, LED light therapy is an effective alternative to lasers. LEDs are available in multiple wavelengths, can be arranged in large, flat arrays (allowing treatment of large areas) and produce no thermal effects (no pain and virtually no side effects for the patient). Furthermore, LED therapy is considered low risk therapy by the FDA as opposed to laser therapy that can actually damage the eye with their pinpoint beam of laser light (15).

EXAMPLE 1

[0319] This example describes in further details an the use of an innovative non-ablative, non-thermal LED system for skin rejuvenation in an in vitro model using human reconstructed skin.

[0320] Benefits associated with the enhancement of homologous collagen production with a light source for the treatment of aging skin in healthy patients involve the stimulation of specific subcellular photoreceptors located in the mitochondria of mammalian cells like dermal fibroblasts. The mitochondrial target or antenna molecule seems to be the last enzyme of the respiratory chain, the cytochrome c oxidase. Medical literature covering the use of light to activate dermal fibroblast collagen synthesis remains sparse, although stimulation of the fibroblast would result in a clinically relevant effect. Hence, critical parameters must be considered to boost collagen secretion using pulsed LED light source. For instance, specific wavelengths were suggested to induce increased growth characteristics in fibroblasts. Normal and abnormal human fibroblast cell lines exhibit significantly higher cell counts when exposed to 660 nm wavelengths (A1).

[0321] The fluence, or total dose of energy distributed over a given amount of time, is another important characteristic influencing light therapy, as well as irradiance or the total light intensity reaching the cell. In fact, cellular threshold irradiance must be exceeded in order to induce a proper physiological stimulation, in this case, collagen synthesis.

[0322] Fluence and irradiance are independent variables to be considered in order to generate a specific physiological effect. Even prolonged but insufficient irradiance exposure will have no physiological benefit since the irradiance threshold is not surpassed. In addition, pulsing patterns must be elaborated to avoid possible cellular exhaustion, implying that required patterns of sequential exposures must be rigorously tested, to allow resting time to fibroblasts in between stimulations, over the entire treatment span. Finally, very

precise positioning or working distance is mandatory to assure optimal beam delivery intensity covering the treatment area, so as to achieve maximum physiological effects. Therefore, many variables will influence the success and efficacy of LED therapy.

[0323] In vitro testing of pulsed sequence parameters and monitoring of procollagen and MMP-1 secretion on multi-age human primary fibroblasts monolayer and human reconstructed skin are reported hereinbelow. Also, the results are obtained and discussed in the context of seeking an optimization of an innovative non-thermal and relatively powerful pulsed LED light source for skin rejuvenation.

[0324] The fibroblast is the major dermis cell type, producing and secreting procollagen and elastic fibers (A2, A3). Procollagen is terminally cleaved by proteolytic enzymes into collagen that aggregates and becomes cross-linked, these tightly cross-linked collagen fibers providing tensile strength and resistance to shear and other mechanical forces.

[0325] LED therapy offers an innovative strategy to optimize the capacity of the cell to produce collagen and promote dermal softness, resiliency, suppleness, and increased skin repair ability, while also triggering the basic energy process in mitochondria to activate colour sensitive cytochrome systems playing a central role in the bioenergetics of the cell (12, 32, 54, 50).

[0326] Karu (A8) stated that the magnitude of the laser biostimulation effect depends on the physiological condition of the cell at the moment of irradiation. Light would only stimulate cell proliferation if the cells were growing poorly at the time of the irradiation. Cell conditions are to be considered since laser/light exposures would restore and stimulate procollagen production, energizing the cell to its own maximal biological potential. No adverse effect has so far been linked to LED therapy, most probably due to absence of thermal damage during treatment.

[0327] An objective of the present study is to evaluate the efficacy of an innovative LED technology on in vitro stimulation of normal human reconstructed skin. Eleven (11) LED exposures of determined sequential pulsing rates were performed over a one-month period on fibroblasts from reconstructed skin from three adult females of 38, 42 and 64 years old (F38, F42, F64).

[0328] Procollagen dosages increased while percentages of total activity of matrix metalloproteinase-1 (MMP-1) decreased proportionally. Hence, pulsed LED light exposures seem to significantly reverse photoaging damage while boosting collagen production and reducing collagenase (MMP-1) activity.

[0329] The pulsed LED light source tested in this study is an innovative non-ablative non-thermal light source using photons to trigger photobiochemical reactions, stimulating skin collagen. Critical light pulsing parameters impacting on the success of LED therapy have been evaluated and determined during the in vitro development process on human reconstructed skin of this high power density, new light therapy device. Therefore, examples of power density temporal profiles that are suitable to achieve the desired results were determined.

[0330] II. Protocol

[0331] In Vitro Experiments: Human Fibroblast Monolayer and Human Reconstructed Skin Model

[0332] Cell culture media. Keratinocytes were grown in complete DME-HAM medium: a combination of Dulbecco-Vogt modification of Eagle's medium (DME) with Ham's F12 in a 3:1 proportion (Gibco), supplemented with 5% Fetal Clone II serum (FCSII) (HyClone, Logan, United States), 10 ng/mL epidermal growth factor (Austral biologicals, San Ramon, United States), 24.3 μ g/mL adenin (Sigma), 5 μ g/mL insulin (Sigma), 5 μ g/mL transferrin (Roche), 2×10^{-9} M 3,3'5' triiodo-L-thyronin (Sigma), 0.4 μ g/mL hydrocortisone (Calbiochem, La Jolla, United States), 100 IU/mL penicillin G (Sigma), and 25 μ g/mL gentamycin (Schering, Pointe-Claire, Canada). Fibroblasts were cultured in DME containing 10% fetal calf serum (FCS) (HyClone), 100 IU/mL penicillin G, and 25 μ g/mL gentamycin.

[0333] Cell isolation. Human epidermal keratinocytes and dermal fibroblasts were isolated from normal skin specimens; keratinocytes are mainly found in the epidermis while fibroblasts are localized in the dermis. Skin specimens were collected from healthy adult females of 38, 42 and 64 years old during either reductive breast surgery (F38, F42) or face-lift (F64). Procedures for cell isolation were initiated within three hours following the surgery according to previously published methods (A5, A6). Briefly, skin specimens were washed five times with a phosphate buffer saline supplemented with 100 IU/ml penicillin G and 25 μ g/ml gentamicin. Specimens were then cut in 3 mm wide strips and kept overnight at 4° C. in Hepes buffer containing 500 μ g/ml thermolysin. The epidermis was mechanically separated from the dermis with forceps; keratinocytes dissociated from the epidermis though incubation of the epidermal fragments under agitation at 37° C., for 30 minutes, with 0.05% trypsin-0.1% EDTA in PBS. Following trypsin inactivation (addition of culture medium containing 10% serum and centrifugation), keratinocytes were expanded in the presence of irradiated 3T3 fibroblasts in T75 flasks and subsequently frozen until further use. Fibroblasts were dissociated from the remaining dermis fragments following incubation in a collagenase H solution, at 37° C., under agitation. After centrifugation, fibroblasts were also plated in T75 flasks for expansion and subsequently frozen until further use. Three different fibroblast primary cell lines (F34, F42, and F64) and one keratinocyte cell line were used in this study.

[0334] Light source. The various light sources tested were supplied by OPUSMED inc. and were gas sterilized prior to handling in the tissue culture laboratory. Herein, three different low energy LED light sources (wavelengths of 635, 660 and 805 nm) and six different sequential pulsing modes, for each light source reaching a total of 18 distinct tested modes were investigated. During this study, total fluence was kept steady at 4 J/cm². Light intensity or irradiance delivered to the skin was also kept constant at 50 mW/cm², for a total exposure time of 160 seconds, including various time on and time off sequences (pulsed pattern). Modes A, B and C are also referred to as modes 1, 4 and 6 hereinbelow.

TABLE 1

TESTED PARAMETERS	TESTING RANGE	Mode 1	Mode 2	Mode 3	Mode 4	Mode 5	Mode 6
Pulse duration	0 to 10^6 μ sec	500	500	500	500	250	250
Inter-pulse interval (time off)	0 to 10^6 μ sec	150	100	50	100	100	50
# Pulse per Train	1 to 100 Units	4	4	4	8	4	4
Inter-train Interval	0 to 10^6 μ sec	1550	1700	1850	3300	700	850
Power density	3 to 600 W/m ²	500	500	500	500	500	500
Total Treatment Time	0 to 999 sec	160	160	160	160	160	160

[0335] During the course of this experiment, six light pulsing patterns were tested. For each mode, key parameters combined altogether, including time on and time off intervals, sequential pulsing train characteristics, irradiance and total treatment time are described.

[0336] Photoinduction of Human Fibroblasts

[0337] Briefly, dermal fibroblasts isolated from normal human skin specimens were expanded and seeded in 25 cm² culture flasks for four weeks to form sheets. Two fibroblast sheets were then superimposed to form a reconstructed dermal equivalent, after which human epidermal keratinocytes were expanded and seeded on top of the dermal equivalent and cultured for 1 week under submerged conditions. Cultivation of the cell system at the air/liquid interface took place for an additional 4 weeks. Finally, LED treatments were performed over reconstructed skin 3 times a week, for 4 consecutive weeks. Supernatants were collected prior to each treatment and 24 hours after the final treatment. Experiments were done using different normal human reconstructed skin and each test point was performed in triplicate. Determination of procollagen and MMP-1 concentrations in harvested supernatants was respectively assessed with specific ELISA and activity assay systems. LED Treatment Parameters. From previous initial preliminary results obtained from in vitro tests performed on human primary fibroblasts monolayer (data not shown), eighteen (18) well-responding pulsing LED modes were kept for further testing on complete normal human reconstructed skin (dermis and epidermis). Subsequently, in vitro response regarding procollagen and MMP-1 secretions were evaluated using eleven (11) consecutive LED exposures performed with the best sequential mode A (at a determined pulse sequence already tested and optimized in vitro, over a one-month period, on human reconstructed skin from, among others, three healthy 38, 42 and 64 year old females (F38, F42, F64). Duration of treatment was determined by total fluence.

[0338] Cell culture media: Keratinocytes were grown in complete DME-HAM: a combination of Dulbecco-Vogt modification of Eagle's medium (DME) with Ham's F12 in a 3:1 proportion (Gibco), supplemented with 5% Fetal Clone II serum (HyClone, Logan, United States), 10 μ g/mL epidermal growth factor (Austral biologicals, San Ramon, United States), 24.3 μ g/mL adenin (Sigma), 5 μ g/mL insulin (Sigma), 5 μ g/mL transferrin (Roche), 2x10⁻⁹ M 3,3'5' triodo-L-thyronin (Sigma), 0.4 μ g/mL hydrocortisone (Calbiochem, La Jolla, United States), 10-10 M cholera toxin

(ICN biomedicals), 100 IU/mL penicillin G (Sigma), and 25 μ g/mL gentamycin (Schering, Pointe-Claire, Canada). Fibroblasts were cultured in DME, 10% fetal calf serum (HyClone), 100 IU/mL penicillin G, and 25 μ g/mL gentamycin.

[0339] Cell isolation: The skin is composed of two important layers: the epidermis mainly composed of keratinocytes and the dermis that is composed of fibroblasts in a connective tissue matrix. Human epidermal keratinocytes and dermal fibroblasts were isolated from normal skin specimens. The skin specimens were removed during reductive breast surgery of two healthy adult females (F38 and F42), a face-lift (F64) and during the circumcision of a healthy newborn. The isolation procedures were initiated within three hours following the surgery according to previously published methods elaborated in our laboratory. Briefly, the skin specimens were washed five times with a phosphate buffer saline supplemented with 100 IU/ml penicillin G and 25 μ g/ml gentamicin. The specimens were then cut in 3 mm wide strips and kept overnight at 4° C. in Hepes buffer containing 500 μ g/ml thermolysin. The epidermis was mechanically separated from the dermis with forceps. The keratinocytes were dissociated from the epidermis by incubating the epidermal fragments under agitation at 37° C. for 30 minutes with 0.05% trypsin-0.1% EDTA in PBS. After the inhibition of the trypsin by addition of medium containing 10% serum and centrifugation, keratinocytes were expanded in the presence of irradiated 3T3 fibroblasts in T75 flasks and subsequently frozen until further use. Fibroblasts were dissociated from the remaining dermis fragments by incubation in a collagenase H solution at 37° C. under agitation. After centrifugation, the fibroblasts were plated in T75 flasks for expansion, subsequently frozen until further use. Production of tissue-engineered reconstructed skin equivalent. Dermal fibroblasts were cultivated in fibroblast medium containing 50 μ g/mL of sodium ascorbate (Sigma) for four weeks to form sheets. After the fibroblast sheets were peeled from the bottom of the dishes, two of these sheets were then superimposed and cultured; the surface area of the construct was maintained by stainless anchoring ring for one week. After a week of dermal equivalent maturation, 1x10⁶ keratinocytes were seeded on top of the reconstructed dermal equivalents. After 7 days of maturation under submerged conditions, the cell system was then brought to the air-liquid interface and cultivated in complete DME-HAM with 5% serum and 50 μ g/mL of sodium ascorbate, and without EGF for an additional three weeks. Culture medium was changed three times a week.

[0340] Cell count and viability: The cells were counted manually (hemacytometer) and/or electronically (Coulter counter). Cell viability was determined using the trypan blue exclusion test.

[0341] Histological analysis: Biopsies of untreated and treated skin equivalents were fixed at least 24 hours in a Bouin solution (ACP, Canada) and embedded in paraffin. Five Em thick cross-sections were stained with Masson's trichrome. Pictures were taken at the 40x objective with a digital camera (CoolSnap RS Photometrics, Roper Scientific, Munich, Germany) for each condition.

[0342] III. Results

[0343] LED sequential pulsing modes for ideal in vitro reconstructed skin stimulation were evaluated. Several modes were tested, with sequential time on and time off to provide cell resting periods in between pulses. Various pulsed LED light durations as well as intervals distanced by a short resting gap were applied to human reconstructed skin, which generated diverse procollagen and MMP-1 productions profiles. Three final modes (A, B and C) were selected from among the most efficient pulsing modes tested in vitro. Clinical response seems to be wavelength dependent with increased depth of penetration at higher wavelengths relating to differences in specific protein expression and greater proliferating capacities by dermal papillary versus deeper reticular fibroblasts (A2, A3). In human skin, penetration depth at 660 nm is 2.23 mm, enough to reach the whole papillary layer in the dermis (A7). Certain pulsing modes stimulated some reconstructed skin with predilection, leaving others without physiological effect. Tests were conducted to find the sequencing pulsing mode offering the best procollagen secretion over control, for a wide proportion of tested human reconstructed skin. FIG. 1 shows the representative average procollagen secretion versus control obtained after 11 pulsed LED light source treatments, achieved over a one-month period, at three different sequential pulsing modes, for two selected reconstructed skins, F42 and F64. Demonstrating a strong stimulation power over procollagen production for 2 reconstructed skins of different age, the sequential pulsing mode designated mode A was selected for further coming in vitro collagen synthesis analysis. This pulsed pattern proved to be optimal for all reconstructed skin tested. Procollagen production and inhibition of MMP-1 activity were also assessed over a one-month period, after 11 LED treatments in Mode A. FIG. 2 shows inversely proportionate patterns of total secretion following comparison of procollagen and MMP-1 concentrations during pulsed LED light therapy for F38, F42 and F64 reconstructed skin. All experiments were performed in triplicate.

[0344] IV. Discussion and Conclusion

[0345] Many parameters ought to be considered for efficacious stimulation of collagen synthesis. First, non thermal LED high-power density maximizes new collagen production by dermal fibroblasts by promoting procollagen synthesis. Collagenase (MMP-1) inhibition patterns, which could appear inversely proportional to procollagen synthesis events, are also observed on human reconstructed skin. This, combined with increased procollagen production, decreased MMP-1 activity supports the accumulation of additional dermal collagen. The cell becomes energized by such light treatments and accumulation of new collagen is possible.

[0346] As seen in FIG. 1, selected pulsing modes could suggest an age dependent response. The biological potentiality of the targeted cells seems to influence final results. As stated by Karu, the magnitude of biostimulation effect depends on the pre-treatment physiological conditions of the cell. The sequential pulsing mode selected for further analysis corresponds to the pulsing pattern promoting procollagen secretion for the widest tested population sample. Modes B and C generated procollagen production in the younger skin equivalent (F42), but no procollagen secretion was noticed for the oldest skin specimen, F64. Mode A increased procollagen synthesis in both reconstructed skins and generated an increase in procollagen synthesis of up to 40%.

[0347] Clinical response is thought to be wavelength dependent with increased depth of penetration at higher wavelengths. A deeper skin penetration may lead to differences in specific protein expression. In vitro, dermal papillary fibroblasts exhibit better growth potentials than dermal reticular fibroblasts (A2). At 660 nm, with increased depth of penetration, the stimulation covers the whole dermal papillary layer, providing the expected biological response in papillary fibroblasts. Other than wavelength, augmentation in protein synthesis seems to be associated with a combination of key parameters, as stated earlier.

[0348] Moreover, while such LED treatment increase type I procollagen production, it appears to inhibit in an inversely proportional manner the production of metalloproteinase (MMP), collagen degrading enzyme found in aging skin. Indeed, as free radicals are known to attack the collagen. As collagen diminishes, the skin's ability to regenerate and heal itself declines. The term elastosis describes age and sun related histopathological morphological alterations in the upper dermis. Free radicals can stimulate production in the body of collagen-digesting enzymes, such as collagenase and metalloproteinase (MMP).

[0349] Matrix metalloproteinase (MMP) activity is highly regulated. It plays a key role in dermal extracellular matrix turnover. Matrix metalloproteinases (MMPs) are a large family of proteolytic enzymes, which are involved in the degradation of many different components of the extracellular matrix. The MMPs have been classified into different groups including collagenases, gelatinases, stromelysins, and others. There is increasing evidence indicating that individual MMPs have important roles in aging skin. Controlled degradation of extracellular matrix (ECM) is essential for the homeostasis of the dermis. Recent evidence suggests that this homeostasis is out of balance in aging and photoaged skin. Downregulation of MMP gene expression combined with upregulation of procollagen production are key components for successful anti-aging photoinduction. The role of MMP-1 or collagen degrading enzyme using such ablative non-thermal LED therapy has been thoroughly studied since most dermal extracellular matrix is composed of collagen. Another matrix metalloproteinase, MMP-2, is a strong marker for other dermal matrix degrading enzyme activity. MMP-2 or Gelatinase-A is able to degrade elastin, fibronectin, type IV collagen, and gelatins but shows no activity against laminin or interstitial collagens. Also, these enzymes are thought to act co-operatively with the collagenases to effect the complete-degradation of interstitial collagens. Downregulation of MMP gene expression is triggered by the above-described treatments (FIG. 1 and 2).

[0350] Furthermore, both efficacy and safety of LED therapy were confirmed in vivo with a clinical study involving 53 patients. In fact, twelve (12) treatments led to a significant improvement in the appearance of wrinkles, skin tone and texture.

EXAMPLE 2

[0351] This example relates to a periorbital rhytid improvement by non-ablative, non-thermal led photoinduction.

[0352] Stimulating skin cells to produce collagen can partly reverse wrinkles, facial sag, rough skin texture, and external signs of aging such as thinning skin, lack of firmness and dullness resulting from a reduction in collagen. Healthy collagen gives the skin its softness, resiliency, suppleness as well as its ability to repair itself (50, 54). On the other hand, damaged collagen molecules become stiff and inflexible, and the skin appears old. Increasing stimulation of collagen synthesis in aging skin is realistic and can substantially improve the appearance of fine lines and even deeper wrinkles when performed correctly. However, this procedure requires a comprehensive approach for which there is little reported clinical experience to date. A review of the literature indicates that the efficacy of LLLT (Low Level Laser Therapy) for skin rejuvenation has not been established. Experiments using light-emitting diodes (LEDs) to invigorate in vitro fibroblast proliferation, growth factor synthesis, collagen production and angiogenesis suggest faster wound healing. Indeed, non-ablative LED therapy induces extracellular matrix changes, amplifies pro-collagen I and collagen I expressions, while structural protein changes are also observed in fibroblast tissue cultures, skin biopsies and open wounds (A1, 12, 32). Those metabolic modulations are thought to correlate with clinical improvement in photoaged skin. As stated in EXAMPLE 1, following eleven (11) LED exposures of determined pulse sequences performed over a one-month period on dermal fibroblast skin equivalents from healthy 38, 42 and 64 year old females (F38, F42, F64), it was observed that procollagen dosages augmented while total activity of matrix metalloproteinase-1 (MMP-1) decreased proportionally. Hence, pulsed LED light exposures seem to significantly catalyze resistance to photoaging damages by amplifying collagen production and decreasing collagenase (MMP-1) activity, resulting in overall increased collagen synthesis.

[0353] The tissue irradiation method tested is performed with a non-ablative non-thermal light source using photons to induce photobiochemical reactions, triggering skin collagen synthesis. The pulsed LED light source combines relatively high-power density and critical parameters that must be considered for successful collagen formation. For example, wavelength is a key parameter ensuring proper biological stimulation.

[0354] Reported evidence shows that normal and abnormal human fibroblast cell lines exhibit significantly higher cell counts when exposed to 660 nm light source (A1). Likewise, the fluence or total dose of energy released over a definite amount of time is another important determinant of efficacious LED therapy. Light intensity or irradiance delivered to the skin is also a leading factor to induce the anticipated stimulatory effects. In fact, threshold intensity must be exceeded to promote collagen production.

[0355] Biologically, fluence and irradiance are independent variables which ought to be considered, especially for medical applications. For instance, bearing in mind equal fluence delivered, irradiance values under the threshold point, even under prolonged irradiation time, would never produce biostimulatory effects. In addition, LED pulsing patterns may be thought to avoid cellular exhaustion leading to cell unresponsiveness or even apoptosis, which implies that specific triggering pulsing features must be rigorously tested and established.

[0356] Finally, optical positioning is another key requirement to precisely monitor an accurate working distance so as to provide the needed irradiance to ensure efficacious collagen production by dermal fibroblasts, as light energy propagation is carefully oriented and delivered over the skin surface.

[0357] An objective of the present example is to evaluate the efficacy and safety of an LED technology for non-ablative wrinkle reduction, focused on periorbital rhytides. LED therapy, either used alone or in combination with topical therapy improved significantly the appearance of skin tone and texture and reduced the appearance of wrinkles.

[0358] Clinical Study: IRB Services (FDA approved independent ethical review committee) reviewed the ethical aspects of the study. Informed consent was obtained after explanation of potential risks involved. Fifty-three (53) patients were recruited, selected according to the Fitzpatrick Classification of Wrinkling and Degree of Elastosis.

TABLE 2

Mild Elastosis Class I Subtype (Subtype 1)	Mild Elastosis Class I (Subtype 2)	Mild Elastosis Class I (Subtype 3)	Moderate Elastosis Class II (Subtype 4)	Moderate Elastosis Class II (Subtype 5)	Moderate Elastosis Class II (Subtype 6)
n = 5	n = 21	n = 16	n = 6	n = 1	n = 0

[0359] Table 2 outlines the patient distribution according to Fitzpatrick Classification.

[0360] Class I: Mild Elastosis Subtype 1-2-3: Fine textural changes with subtly accentuated skin lines.

[0361] Class II: Moderate Elastosis Subtype 4-5-6: Distinct papular elastosis, dyschromia.

[0362] A double-blind, side-by-side comparison study with photoaged patients (mean age=44.4 years old, for n=40), Fitzpatrick skin types I, II, and III, treated 12 times over a 4-week period with an LED device on periorbital rhytides was performed (Table 2). Patients were evaluated by digital photographs and PRIMOS profilometry performing Phaseshift Rapid In-Vivo Measurements of Skin (3D in-vivo optical skin imaging) to quantify precise clinical improvements (60).

[0363] To maximize the benefits of the treatment, a topical regular moisturizer without active ingredients was applied daily, combined with LED treatment.

[0364] Treatment parameters:

[0365] Treatment site: Periorbital area (crowfeet)

[0366] Treated side: Randomly assigned, with no cooling method: sequentially pulsed LED treatment of a few seconds with total fluence >4 J/cm² on one side.

[0367] Untreated control side: Randomly assigned, with no cooling method: few minutes total fluence of 0 J/cm² on the contralateral (sham) side.

[0368] Schedule: A total of 3 treatments per week, for 4 consecutive weeks (12 treatments in total).

[0369] The parameters relating to irradiation are summarized in Table 3.

TABLE 3

PARAMETERS	UNITS	MODE 1
Pulse duration (time on)	Microseconds (μ sec)	500
Inter-pulse Interval (time off)	Microseconds (μ sec)	150
# Pulse per Pulse Train	Units	4
Inter-train Interval	Microseconds (μ sec)	1550
Power density	W/m ²	500
Total Treatment Time	Seconds	160

[0370] The parameters above combined altogether to achieve the optimal light pulsing mode.

[0371] The measurements taken during and after the experiment were 3D surface topography (PRIMOS: GFM Germany) readings were taken at Week 0 (pre-treatment), 4 and 12. Surface pre-treatment topography measurements compared to post-treatment measurements (Resolution +/- 1 micron (10^{-6} m)). Before and after pictures were computer-matched prior to results analysis. Further, the pictures were reviewed at quartile scale blinded observer clinical analysis of digitalized pictures at Week 0, 4 and 12 (week 0=pre-treatment pictures). Before and after assessment of the degree of clinical improvement: 0-25% Fair, 26-50% Good, 51-75% Very good, 76-100% Excellent.

[0372] Results

[0373] Most subjects involved in the clinical study reported subjective improvement in the quality and visual

aspect of their skin. An overall enhancement of 58% was obtained in the global appearance of the skin, 8 weeks after the final treatment. Other clinical results included reduction in skin roughness, pore size and redness. No adverse effect or discomfort has been linked to the treatment, most probably due to the absence of thermal damage during treatment. A light redness could have occurred following treatment, usually vanishing an hour post-treatment. Moreover, no allergy, immune reaction or infection was noticed. Enhancement of skin appearance was lightly noticeable right after LED exposure, but enhancement in wrinkle reduction and improved pore size, firmness, softness, resiliency and suppleness were observed up to 4 months post-treatment.

[0374] An objective method providing more accurate quantification of facial wrinkles was used in this study. PRIMOS Software analysis was performed over pre- and post-treatment matched pictures (prior to analysis, all pictures were matched either manually or with the software application, ensuring rigorous comparison). Afterward, the average maximum height for a given profile, the Rz value ($Rz=(1/N)*[(H_1+H_2+\dots+H_N)-(L_1+L_2+\dots+L_N)]$), was calculated as the mean peak-to-valley height, highs and lows (H and L) from the profile lines, providing a measurement of wrinkle severity (B6).

[0375] After twelve treatments, the mean improvement of the Rz value reaches 24.6 μ m for 41 patients (n=41, results of 8 remaining participants are currently being analyzed), implying that the average wrinkle depth of the studied crowfeet area is reduced by 24.6 μ m (data not shown).

[0376] Compared pre

[0377] and post-treatment Rz values reached up to a 225.2 μ m variation for one study participant (age=46 years old), proving an important wrinkle reduction after therapy. A representative sample of PRIMOS pre- and post-treatment pictures are shown in FIGS. 4A to 4D.

[0378] Table 4 gives more specific details regarding the study cohort average percent improvement following treatment of the right crowfeet area with the following the 12 treatments. Quantitative improvements are measures by comparison of both pre and post treatment PRIMOS Ra and Rz values.

TABLE 4

Patient ID	Age	Gender	Fitzpatrick wrinkle classification system	Fitzpatrick phototype classification system	Post-treatment improvements in wrinkle score (%)			Overall Skin Improvement (%)
					Rz (%)	Ra (%)		
P1	39	F	I.1	2	Y	25	14	70
P2	38	M	I.2	3	Y	17	31	80
P3	41	F	I.2	2	Y	17	22	40
P4	48	F	II.5	2	Y	-14	-7	40
P5	45	F	I.3	2	N	8	7	30
P6	40	F	I.2	3	Y	29	14	40
P7	40	F	I.2	2	Y	9	4	40
P8	41	M	I.3	3	Y	26	14	80
P9	59	F	II.4	1	Y	40	30	40
P10	61	F	II.4	1	Y	21	22	45
P11	44	F	I.2	2	N	14	24	60
P12	44	M	I.3	3	Y	30	23	70

TABLE 4-continued

Patient ID	Age	Gender	Fitzpatrick wrinkle classification system	Fitzpatrick phototype classification system	Post-treatment improvements in wrinkle score (%)	Rz (%)	Ra (%)	Overall Skin Improvement (%)
P13	62	F	I.3	2	Y	16	9	40
P14	48	F	II.4	2	Y	-8	2	60
P15	53	F	I.3	2	Y	37	31	90
P16	37	F	I.2	1	N	30	22	45
P17	40	F	I.2	3	N	30	48	40
P18	43	F	I.2	3	N	0	0	20
P19	44	F	I.1	3	Y	40	44	80
P20	46	F	I.1	2	Y	10	5	40
P21	44	F	I.2	3	Y	33	34	70
P22	40	F	I.2	3	N	10	11	30
P23	49	F	I.3	2	N	11	16	35
P24	43	F	I.3	3	Y	11	19	80
P25	43	F	I.3	2	Y	14	11	45
P26	52	F	II.4	2	Y	6	1	40
P27	39	F	I.3	3	Y	-13	-7	20
P28	45	F	I.2	2	Y	20	19	70
P29	57	F	II.4	3	Y	49	56	70
P30	33	F	I.2	2	N	6	7	55
P31	53	F	I.3	3	N	23	27	55
P32	41	F	I.3	2	N	38	42	60
P33	46	F	I.3	3	Y	51	38	100
P34	41	F	I.2	3	N	20	12	35
P35	39	F	I.3	3	N	12	8	40
P36	41	F	I.2	1	N	20	19	35
P37	41	F	I.3	1	Y	15	11	80
P38	37	F	I.1	1	N	13	12	35
P39	58	F	II.4	2	N	-7	-2	80
P40	42	F	I.3	2	N	3	1	20
AVERAGE IMPROVEMENT (%)								
								52

[0379] Table 4 illustrates that the study cohort average percent improvement following treatment of the right crowfeet area with the LumiPhase-R (12 treatments). Quantitative improvements are measures by comparison of both pre and post treatment PRIMOS Ra and Rz values.

[0380] This example shows that LED therapy goes beyond the concept of thermal injury to achieve a clinical response. The testes therapy was shown to promote new collagen formation and improvement in skin tone, texture and fine lines, noticeably enhancing overall appearance by 58% in a significant number of patients (n=49). In addition, lack of adverse effects confirms that this new non-ablative non-thermal light source is safe and efficacious.

[0381] The therapy can be used alone or in combination with skin rejuvenation regimens. Thus, it can serve as a complementary treatment to other skin rejuvenation therapies or topical agents that also enhance collagen production. Indeed, topical cosmeceutical agents have been observed to act as adjuncts to non-ablative rejuvenation. A potent synergy between LED therapy and topical agents seems to increase skin resiliency and firmness. During the course of this study, regular moisturizing cream without active ingredients was applied daily before bedtime on the crowfeet area.

[0382] The main advantages of the tested therapy are numerous when compared to low-level lasers. First, this device allows for treatment of larger surfaces with more accuracy, using several LED arrays. Moreover, the optical positioning system ensures, through optimal and uniform

beam delivery over the skin surface, a relatively precise light release so a suitable quantity of photons are then reaching the targeted cells.

[0383] Furthermore, the tested treatment head has been designed like a facial mask, allowing for more adequate matching of the facial contours, thereby increasing the system's overall performance and convenience. In addition, a greater clinical response is to be anticipated from tested light therapy since photons are delivered via a unique sequential mode that seems to prevent fibroblast exhaustion by providing different resting intervals between pulses. This, in turn, favours a potent cell response during the complete treatment. Finally, wrinkle reduction and other skin improvements obtained within this study can be related to therapy's relatively high-power density which maximizes procollagen synthesis by dermal fibroblasts. Over a very short treatment time, a high intensity is delivered, generating an optimal physiological effect, in a relatively safe and relatively painless manner. It is important to note that the tested is effective for a wide range of skin colours, even for dark complexion patients. However, phototypes V & VI would probably loose much irradiance through interference with their high melanin content at the dermo-epidermal junction.

[0384] Herein, average reduction of wrinkle depth is evaluated at 24.6 μm for n=41 patients, which suggests in vivo that new collagen secretion is filling fine lines and moderate wrinkles. A great clinical response is achieved following treatments on the crowfeet area, and additional improvement is likely after more treatment sessions, in a

cumulative manner. Treatment of contiguous facial areas could intensify overall skin improvements. A significant increase in skin firmness and resiliency is also to be expected for the periorbital area.

[0385] Referring to FIG. 38, a method of photoactivating mammalian tissue causing a predetermined physiological change is illustrated. The steps include irradiating the tissue with a first pulse having a power density above an activation threshold power density (step 3800). The activation threshold power density is a power density below which the predetermined physiological change is substantially absent from the mammalian tissue upon the mammalian tissue being irradiated with the radiation.

[0386] Further, above which the predetermined physiological change is substantially present in the mammalian tissue upon the mammalian tissue being irradiated with the radiation.

[0387] The tissue is irradiated with a second pulse (step 3802) and the first pulse is emitted for a duration of about 1 femtosecond to about 1 hour (step 3804). The first and second pulses are separated by an inter-pulse interval of about 1 microsecond to about 10 seconds (step 3806). Typically the first and second pulses have a wavelength of about 400 nanometers to about 1500 nanometers and a power density of about 0.1 mW/cm² to about 10 W/cm², and more specifically about 30 mW/cm² to about 100 mW/cm².

[0388] In further embodiments, the activation threshold power density can be about 0.1 mW/cm², about 10 mW/cm², and/or about 50 mW/cm². The inter-pulse interval can be about 10 microseconds to about 5 milliseconds or about 100 microseconds to about 0.5 milliseconds. Duration of the first and subsequent pulses can be about 100 microseconds to about 5 milliseconds or about 250 microseconds to about 1 millisecond. Typically, all the pulses are emitted by at least one light emitting diode (LED). Another embodiment includes the step of emitting the first pulse for about 250 microseconds to about 1 millisecond and the inter-pulse interval is from about 100 microseconds to about 0.5 millisecond.

[0389] The physiological effect of the photoactivation method can include at least one of stimulating collagen production by fibroblasts contained within the skin tissue, substantially reversing at least in part skin damages caused by aging, reversing at least in part damages caused to an extracellular matrix of the skin by aging, and modulating an apoptosis response of the skin tissue.

[0390] An embodiment utilizes ratios of key factors, including a ratio of the duration divided by the inter-pulse interval can be about 0.1 to about 10 and about 0.5 to about 2. Another embodiment is the power density of radiation within the tissue is below one of about 10 percent and about 1 percent of the activation threshold power density during the inter-pulse interval.

[0391] Furthermore, a minimal power density of the radiation within the tissue during each pulse can be about two times, about ten times, about 100 times, and about 10,000 times as large as a maximal power density of the radiation within the tissue during the inter-pulse interval.

[0392] Another method of photoactivation included the steps of irradiating the tissue with a first pulse having a

power density below a thermal threshold power density (step 3808). The thermal threshold power density is a value over which a temperature of the irradiated tissue increases to a temperature greater than a predetermined overheating temperature. The thermal threshold power density can be about 10 mW/cm², about 100 mW/cm², about 1 W/cm², and about 1 kW/cm². The overheating temperature can be about 2° C., about 0.5° C., and about 0.1° C. over a maximal non-pathological in-vivo. temperature of the mammalian tissue. Further, the activation threshold power density is about 30 mW/cm² and the thermal threshold power density is about 100 mW/cm².

[0393] FIG. 39 illustrates a method wherein at least two pulse trains are utilized. Each pulse train includes a first pulse and a second pulse. The method includes emitting a first pulse train (step 3900) and separating the first pulse train from a second pulse train by an inter-pulse train interval of about 1 microsecond to about 1 second (step 3902). The inter-pulse train interval is one of 500 microsecond to about 1 second, about 750 microseconds to about 2,250 microseconds, and about 500 microseconds to about 2.25 milliseconds. Other embodiments of the inter-pulse train interval are about 2 to about 10 and specifically, about 3.

[0394] A number of pulses emitted within each pulse train can be 2 to 100 pulses, 4 to 10 pulses, and 3 to 10 pulses, all of which are within the duty cycle of the light source, specifically the LED.

[0395] Another method of photoactivating mammalian tissue causing a predetermined physiological change is illustrated in FIG. 40. The tissue can be irradiated with a first pulse train and a second pulse train, each pulse train having at a first pulse and a second pulse (step 4000). The first pulse can be separated from the second pulse by an inter-pulse interval (step 4002) and the first pulse train can be separated from a second pulse train by an inter-pulse train interval (step 4004). In embodiments, the inter-pulse train interval can be about 1 microsecond to about 1 second, 500 microsecond to about 1 second, about 750 microseconds to about 2,250 microseconds, or about 500 microseconds to about 2.25 milliseconds. Further, a ratio of the inter-pulse train interval to the inter-pulse interval is about 2 to about 10, and specifically the ratio of the inter-train pulse interval to the inter-pulse interval is about 3. Other embodiment include a number of pulses within each pulse train is one of 2 to 100 pulses, 4 to 10 pulses, and 3 to 10 pulses.

[0396] Other steps include of depositing a total fluence from the first and second pulse trains to the tissue of about 0.001 J/cm² to about 20,000 J/cm² (step 4006). Alternately, the total fluence can be about 4 J/cm² to about 10 J/cm².

[0397] Turning to FIG. 41, a method of photoactivating mammalian tissue causing a predetermined physiological change is illustrated. The steps include irradiating the tissue with a time-varying radiation including a power density temporal profile (step 4100). The irradiating step can include activating molecular cascades of events (step 4102) and activating cells contained within the tissue (step 4104). A molecular relaxation phase can be provided (step 4106) and includes additional methods. Molecular relaxation can be allowed wherein a reversible molecular conformational changes are reversed at least in part so that the molecular cascades of events are reactivatable (step 4108) and allow-

ing the cells of the tissue to rest so as to prevent at least in part cell exhaustion during the irradiation (step 4110).

[0398] Further embodiments include preventing a temperature increase in the tissue above an overheating temperature (step 4112) at which the cascade of events triggered by the radiation are substantially reversed. A thermal relaxation phase can be provided (step 4114) that includes allowing the cells of the tissue to dissipate heat (step 4116) so as to remain substantially below the overheating temperature. Further, temperature increases can be prevented by one or more methods (step 4118), including by a thermal inertia of the tissue, cooling the tissue (step 4120) which can include active convective cooling and delivering to the tissue a vasodilatator (step 4122) in an amount effective to cause a vasodilatation within the tissue.

[0399] Embodiments include power density temporal profiles remaining below a thermal threshold above which the temperature within the tissue is likely to increase above the overheating temperature. Additionally, the molecular cascade of events can be initiated by receiving, by an antenna molecule, least one photon contained within the radiation (step 4124). Further, the molecular cascade of events occurs partly in the mitochondria of the cells of the tissue and include reversible conformational changes that are reversed during the molecular relaxation phases. Activating the cells can also include progressively increasing a mitochondrial activity level within the cells of the tissue.

[0400] Further to the above embodiments FIG. 42 illustrates a method of defining a plurality of pulse trains (step 4200), each pulse train including a plurality of radiation pulses having a predetermined pulse duration. The plurality of radiation pulses can be separated by an inter-pulse interval (step 4202) and the pulse trains can be separated by an inter-pulse train interval (step 4204), the inter-pulse train interval being substantially larger than the inter-pulse interval. Another step can be allowing an antenna molecule to initiate the molecular cascades of events (step 4206).

[0401] An embodiment configures the plurality of pulses within each pulse train to a number of pulses to bring the cells to a suitable level of activation. Alternately, or in addition, the number of pulses within each pulse train can be a number preventing the cells from substantially reaching a steady state of activation (i.e. 4 to 10 pulses). The inter-train interval can provide cellular relaxation phases and allows the cells of the tissue to rest so as to prevent at least in part at least one of cell exhaustion and mitochondrial exhaustion during the irradiation. Specifically, an example of an inter-train interval is about 750 microseconds and about 2,250 microseconds.

[0402] Another method is illustrated in FIG. 43, and is a method for regenerating an extracellular matrix in mammalian tissue by irradiating the tissue with radiation to regenerate the extracellular matrix (step 4300). The radiation can perform at least one of partially reversing the effects of aging within the skin tissue (step 4302), stimulating collagen production within the tissue (step 4304), stimulating collagen repair within the extracellular matrix (step 4306), downregulating a matrix metalloproteinase (MMP) gene expression within the cells of the tissue (step 4308), upregulating procollagen production within the cells of the tissue (step 4310), reducing elastin degradation within the extracellular matrix (step 4312), reducing fibronectin degradation

within the extracellular matrix (step 4314), stimulating collagen production within the tissue (step 4316) and stimulating collagen repair within the extracellular matrix (step 4318).

[0403] FIG. 44 illustrates defining a pulse train (step 4400) including a plurality of radiation pulses wherein the pulses each have a duration of from about 250 microsecond to about 1 millisecond, separating the pulses from each other by an inter-pulse interval (step 4402), the inter-pulse interval is about 100 microseconds to about 500 microseconds; and defining an irradiance of each pulse in the tissue of about 30 mW/cm² to about 100 mW/cm² (step 4404).

[0404] Turning now to FIG. 45, a method for reducing damages previously caused to a mammalian skin tissue, include the steps of irradiating the tissue with radiation having a power density temporal profile having a power density within the tissue greater than an activation threshold over a predetermined time interval (step 4500), and maintaining a temperature of the tissue below an overheating temperature by selecting the predetermined time interval (step 4502). In an embodiment, the overheating temperature is about 5° C. above a maximal non-pathological in-vivo tissue temperature.

[0405] Further, steps of defining a plurality of pulse trains, each pulse train including a plurality of radiation pulses having a predetermined pulse duration (step 4504), separating the plurality of radiation pulses by an inter-pulse interval (step 4506) and separating the plurality of pulse trains by an inter-train interval, the inter-train interval being substantially larger than the inter-pulse interval (step 4508). These steps are similar to the similar steps above. The embodiment can also include irradiating the tissue over a plurality of treatments, wherein a treatment includes one or more pulse trains (step 4510), providing an inter-treatment time interval between treatments (step 4512) and performing the treatment to substantially reduce damages previously caused to the mammalian skin tissue (step 4514).

[0406] A further embodiment includes applying the treatments within a rejuvenating phase wherein the tissue is substantially rejuvenated (step 4516). A maintenance phase can follow the rejuvenating phase and including steps of substantially maintaining the rejuvenation of the tissue (step 4518). Alternate embodiments include the inter-treatment time interval during the maintenance phase is larger than an inter-treatment time interval during the rejuvenating phase. Also, the inter-treatment time interval during the maintenance phase can be larger than the duration of the rejuvenating phase. In specific embodiments, the inter-treatment time interval during the rejuvenating phase is one of about 1 minute to about 1 year, about 1 hour to about 1 month, about 1 day to about 1 week, and about 3 days to about 4 days. Another embodiment can be where the inter-treatment time interval during the maintenance phase is from about 1 day to about 5 years, about 1 month to about 1 year, and about 1 year.

[0407] The rejuvenating phase includes at least one of 2 to 1000 treatments, 2 to 50 treatments, 5 to 20 treatments, and 12 treatments. The inter-treatment time interval during the rejuvenating phase can be about 1 day to about 1 week and wherein the inter-treatment time interval during the maintenance phase is about 1 month to about 1 year. Another

embodiment of the method includes substantially preventing at least one of a cellular exhaustion and a mitochondrial exhaustion (step 4520).

[0408] As above, in FIG. 43, radiation can partially reverse the effects of aging within the skin tissue, stimulate collagen production within the tissue, stimulate collagen repair within the extracellular matrix, downregulate a matrix metalloproteinase (MMP) gene expression within the cells of the tissue, upregulate procollagen production within the cells of the tissue, reduce elastin degradation within the extracellular matrix, reduce fibronectin degradation within the extracellular matrix, stimulate collagen production within the tissue, and stimulate collagen repair within the extracellular matrix.

[0409] Pulse train embodiment include the same features as above, including about 4 to about 10 pulses, the pulses within each pulse train lasting about 250 microseconds to about 1 millisecond, the inter-pulse interval is about 100 microseconds to about 0.5 millisecond, and the inter-train interval is about 500 microseconds to about 1 second. The fluence of each treatment is one of about 1 mJ/cm² to about 1 kJ/cm², about 1 J/cm² to about 50 J/cm², and about 4 J/cm² to about 10 J/cm².

[0410] The substantially rejuvenated tissue can include cells that are less likely to experience apoptosis than the cells were prior to the irradiation. Reducing a likelihood of apoptosis can be performed by at least one of reversing an aging process, and reversing environmental factors.

[0411] Another method includes applying an active topical formulation to the skin prior to irradiation. The active topical formulation promotes collagen synthesis and can include antioxidants and a vitamin selected from the set consisting of vitamins A, B₅, C and E.

[0412] The radiation described in the embodiments above can be suitable for treating at least one of cheloids by photoinhibition, atrophic scars through photoactivation, acne, eczema, psoriasis, vitiligo, rosacea, promoting hair regrowth, removing at least in part exogenous pigments in the skin, dermal hypermelanosismelanosis, an adnexial tumor, cutaneous hyperpigmentation, smoothing wrinkles, reducing a thinning skin, reducing a lack of firmness of the skin, and reducing dullness of the skin.

[0413] FIG. 46 illustrates method of photoactivating mammalian tissue using a photoactivating device. The photoactivating device includes a photoactivating light source adapted to generate a photoactivating beam of light having a predetermined set of light parameters. All of the parameters are discussed above in detail. The mammalian tissue defines a target surface adapted to be irradiated by the photoactivating beam of light. The method includes the steps of positioning the photoactivating light source and the mammalian tissue relative to each other so that the photoactivating light source and the target surface are at a predetermined operational distance relative to each other (step 4600). Once positioned, irradiating the target surface with the photoactivating beam of light while the photoactivating light source is spaced from the target surface by the operational distance (step 4602). Typically, the operational distance is such that the photoactivating beam of light photoactivates the biological tissue.

[0414] Another embodiment includes using a distance probe for adjusting the distance between the photoactivating

light source and the target surface towards the operational distance (step 4604). Alternately or in conjunction with, an operator can use an aiming beam of light emanating from an aiming device operatively coupled to the photoactivating light source for aiming the photoactivating light source towards the target surface prior to using the distance probe for adjusting the distance between the photoactivating light source and the target surface towards the operational distance (step 4606).

[0415] Further embodiments include cooling the target surface so as to maintain the target surface at a temperature below a predetermined thermal threshold (step 4608). The cooling step can also use a cooling flow of air for convectively cooling the target surface (step 4610). Additionally, the cooling step can also cool the photoactivating light source (step 4612).

[0416] FIG. 47 illustrates an irradiance verses time graph of pulse intervals. The figure illustrates the pulse duration, pulse interval and, importantly, the cellular relaxation time.

[0417] Although the present invention has been described hereinabove by way of preferred embodiments thereof, it can be modified, without departing from the spirit and nature of the subject invention as defined in the appended claims.

Endnotes

[0418] 1. Karu, T. (1988). Molecular mechanism of the therapeutic effect of low-intensity laser radiation. Lasers in Life Science 2, 53-74

[0419] 2. Smith, K. C. (ed.) (1989). The Science of Photobiology, 2nd edn. Plenum Press, NY

[0420] 3. Walker, J. B., Akhanjee, L. K., Cooney, M. M., Goldstein, J., Tamayoshi, S. and Segal-Gidan, F. (1988). Laser therapy for pain of trigeminal neuralgia. Clinical Journal of Pain 3,183-187

[0421] 4. Moore, K. C., Hira, N., Kumar, P. S., Jayakumar, C. S. and Ohshiro, T. (1988). A double blind crossover trial of low level laser therapy in the treatment of postherpetic neuralgia. Laser Therapy 1, 7-9

[0422] 5. Walker, J. (1983). Relief from chronic pain by low power laser irradiation. Neuroscience Letters 43, 339-344

[0423] 6. Tyce, G. M., (1985). Biochemistry of serotonin. Serotonin and the Cardiovascular System (ed Canhoutte, P. M.) pp. 1-13, Raven Press, NY

[0424] 7. Hug, D. H., (1978). The activation of enzymes with light. Photochemical and Photobiological Reviews 3, 1-33

[0425] 8. Hug, D. H., (1981). Photoactivation of enzymes. Photochemical and Photobiological Reviews 6, 87-138

[0426] 9. Hug, D. H., (1991). Photobioinduction of enzymes. Journal of Photochemistry and Photobiology in press

[0427] 10. Saperia, D., Glassberg, E., Lyons, R. F., Abergel, R. P., Baneux, P., Castel, J. C., Dwyer, R. M., and Uitto, J. (1986). Demonstration of elevated Type I and Type II procollagen mRNA levels in cutaneous wounds treated with helium-neon laser. Proposed

- mechanism for enhanced wound healing. *Biochemical and Biophysical Research Communications* 138, 1123-1128
- [0428] 11. Smith, K. C. and Hanawalt, P. C.(1969). *Molecular Photobiology*, Academic Press, NY
- [0429] 12. Abergel, R. P., Meeker, C. A., Lam, T. S., Dwyer, R. M., and Uitto, J. (1984). Control of connective tissue metabolism by lasers: recent developments and future prospects. *Journal of the American Academy of Dermatology* 11, 1142-1150
- [0430] 13. Lam, T. S., Abergel, R. P., Meeker, C. A., Castel, J. C., Dwyer, R. M., and Uitto, J. (1986). Laser stimulation of collagen synthesis in human skin fibroblast cultures. *Lasers in Life Science* 1, 61-77
- [0431] 14. Walker, J. B., Akhanjee, L. K., Cooney, M. M., Goldstein, J., Tamayoshi, S. and Segal-Gidan, F. (1987). Laser therapy for pain of rheumatoid arthritis. *Clinical Journal of Pain* 3, 54-59
- [0432] 15. Goldman, J. A., Chiapella, J., Casey, H., et al. (1980). Laser therapy of rheumatoid arthritis. *Lasers in Surgery and Medicine* 1, 93-101
- [0433] 16. Whitfield, J. F., Boynton, A. L., MacManus, J. P., Rixon, R. H., Sikorska, M., Tsang, B., Walker, P. R., and Swierenga, S. H. H. (1980). The roles of calcium and cyclic AMP in cell proliferation. *Growth Regulation by Ion Fluxes* (ed. Leffert, H. I.) *Annals of the New York Academy of Sciences* 339, 216-240
- [0434] 17. Watson, J. D., Hopkins, N. H., Roberts, J. W., Steitz, J. A., and Weiner, A. M. (1987). *Molecular Biology of the Gene* 4th edn, Vol II, Chapter 25, *The Control of Cell Proliferation*, pp. 962-1005. Benjamin/Cummings, Menlo Park, Calif.
- [0435] 18. Agency for Health Care Policy and Research. Treatment of pressure ulcers; clinical guideline number 15. AHCPR Publication No.95-0652 1994;1-125.
- [0436] 19. Basford JR. Low intensity laser therapy: still not an established clinical tool. *Lasers in Surgery & Medicine* 1995. 1995(16):331-42.
- [0437] 20. Bihari I, Mester AR. The biostimulative effect of low level laser therapy of long-standing crural ulcers using helium neon laser, helium neon plus infrared lasers, and noncoherent light: preliminary report of a randomized double-blind comparative study. *Laser Therapy* 1989; 1(2):97-8.
- [0438] 21. Bradley M, Nelson EA, Petticrew M, et al. Wound dressings for the treatment of pressure sores (Protocol for a Cochrane Review). In *The Cochrane Library*, Issue 2, 1999. Oxford:Update Software.
- [0439] 22. Cambier DC, Vanderstraeten G. Low-level laser therapy: The experience in Flanders. *European Journal of Physical Medicine & Rehabilitation* 1997(7):102-5.
- [0440] 23. Cho C Y, Lo J S. Dressing the part. *Dermatology Clinics* 1998(16):25-47.
- [0441] 24. Crous L, Malherbe C. Laser and ultraviolet light irradiation in the treatment of chronic ulcers. *Physiotherapy* 1988(44):73-7.
- [0442] 25. Cullum N, Roe B. Leg ulcers. Jan. 1, 1995: 1st edition. Scutari Projects, Royal College of Nursing. Middlesex, U.K.
- [0443] 26. Falanga V. Special issue on wound healing: An overview. *Journal of Dermatologic Surgery & Oncology*. 1993(19):689-90.
- [0444] 27. Flemming K, Cullum N. Laser therapy for the treatment of venous leg ulcers (Cochrane Review). In *The Cochrane Library*, Issue 1, 1999. Oxford: Update Software.
- [0445] 28. Galletti G. Low power laser therapy: a non-invasive highly effective therapeutic modality. *Laser Therapy* 1997;9:131-36.
- [0446] 29. Gogia P P. Physical therapy modalities for wound management. *Ostomy Wound Management* 1996;42(1):46-8.
- [0447] 30. Gogia P P. Physical therapy intervention in wound management. In: *Chronic Wound Care* 2nd ed. Wayne, PA: Health Management Publications, Inc. 1997:251-59.
- [0448] 31. Gogia P P, Marquez R R. Effects of helium-neon laser on wound healing. *Ostomy Wound Management* 1992;38(6):38-41.
- [0449] 32. Gupta A K, Filonenko N, Salansky N, et al. The use of low energy photon therapy (LEPT) in venous leg ulcers: a double-blind, placebo-controlled study. *Dermatologic Surgery* 1998;24(12):1383-86.
- [0450] 33. Jovell A J, Navarro-Rubio MD. Evaluacion de la evidencia científica. *Medicina Clinica* 1995(105):740-43.
- [0451] 34. Kane D, Krasner D. Wound healing and wound management. In: *Chronic Wound Care* 2nd ed. Wayne, PA: Health Management Publications, Inc. 1997:1-4.
- [0452] 35. Keast D H, Orsted H. The basic principles of wound care. *Ostomy Wound Management* 1998;44(8):24-31.
- [0453] 36. Kleinman Y, Simmer S, Braksma Y, et al. Low level laser therapy in patients with venous ulcers: early and long-term outcome. *Laser Therapy* 1996(8):205-8.
- [0454] 37. Landau Z. Topical hyperbaric oxygen and low energy laser for the treatment of diabetic foot ulcers. *Archives of Orthopaedic & Trauma Surgery* 1998(117):156-58.
- [0455] 38. Lundeberg T, Malm M. Low-power HeNe laser treatment of venous leg ulcers. *Annals of Plastic Surgery* 1991 :27(6):537-39.
- [0456] 39. Maim M, Lundeberg T. Effect of low power gallium arsenide laser on healing of venous ulcers. *Scandinavian Journal of Plastic & Reconstructive Surgery & Hand Surgery* 1991;25(3):249-51.
- [0457] 40. Mitton C, Hailey D. *Hyperbaric oxygen treatment in Alberta*. Edmonton. Alberta Heritage Foundation for Medical Research, April 1998.

- [0458] 41. Nussbaum EL, Biemann I, Mustard B. Comparison of ultrasound/ultraviolet-C and laser for treatment of pressure ulcers in patients with spinal cord injury. *Physical Therapy* 1994;74:812-23.
- [0459] 42. Ovington L G. Dressings and adjunctive therapies: AHCPR Guidelines Revisited. *Ostomy Wound Management* 1999;45(1A(Suppl)):94S-106S.
- [0460] 43. Regional Wound Care Guidelines Working Group CHA. Regional wound care guidelines. Edmonton. Capital Health Authority, 1998.
- [0461] 44. Scottish intercollegiate guidelines network (SIGN). The care of patients with chronic leg ulcer. *A National Clinical Guideline* 1998. Edinburgh, U.K. SIGN Secretariat, Royal College of Physicians.
- [0462] 45. Shuttleworth E, Banfield K. Wound care. light relief, low-power laser therapy. *Nursing Times* 1997(93):74-78.
- [0463] 46. Singer A J, Clark R A F. Cutaneous wound healing. *New England Journal of Medicine* 1999;341(10):738-46.
- [0464] 47. Telfer J, Filonenko N, Salansky N. Low energy laser therapy for leg ulcers [Abstract]. *Lasers in Surgery & Medicine*. 1993.
- [0465] 48. University of Delaware PTGs. Lasers and physical therapy care. <http://copland.udel.edu/~7179/index1.htm> Aug. 1, 1999.
- [0466] 49. Webb C, Dyson M, Lewis W H. Stimulatory effect of 660 nm low level laser energy on hypertrophic scar-derived fibroblasts: possible mechanisms for increase in cell counts. *Lasers in Surgery and Medicine* 1998(22):294-301.
- [0467] 50. Wheeland R G. Lasers for the stimulation or inhibition of wound healing. *Journal of Dermatologic Surgery & Oncology* 1993(19):747-52.
- [0468] 51. Zhang C and Wong-Riley M. Depolarization stimulation upregulates GA-binding protein in neurons: a transcription factor involved in the bigenomic expression of cytochrome oxidase subunits. *Eur J Neurosci* 12, 1013-1023 (2000a).
- [0469] 52. Zhang C and Wong-Riley M. Synthesis and degradation of cytochrome oxidase subunit mRNAs in neurons: Differential bigenomic regulation by neuronal activity. *J Neurosci Res* 60, 338-344 (2000b).
- [0470] 53. Wong-Riley, M. T. Bai, X. Buchmann, E. Whelan, H. T. "Light-emitting diode treatment reverses the effect of TTX on cytochrome oxidase in neurons" *Neurochemistry*. 12(14):3033-7,2001.
- [0471] 54. Whelan, H. T. Smits, R. L. Buchmann, E. V. Whelan, N. T. Turner, S. G. Margolis, D. A. Cevenini, V. Stinson, H. Ignatius, R. Martin, T. Cwiklinski, J. Philippi, A. F. Graf, W. R. Hodgson, B. Gould, L. Kane, M. Chen, G. Caviness, J. "Effect of NASA light-emitting diode (LED) irradiation on wound healing" *Journal of Clinical Laser Medicine & Surgery*.19(6):305-13,2001.
- [0472] 55. Goldman, M., Cutaneous laser surgery: The art and science of selective photothermolysis. 2nd edition, Mosby, pp. 8-9.
- [0473] 56. Anderson R R, Parrish J A: Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation, *Science* 220:524, 1983.
- [0474] 57. Sommer A P et al., Biostimulatory windows in low-intensity laser activation: Lasers, Scanners, and NASA's Light-Emitting Diode Array System, *J of Clin Laser Med & Surg*, vol 19:1;2001 , pp 29-33.
- [0475] 58. Young SR et al., Effect of light on calcium uptake by macrophages, *Laser Ther.* 1991; 3, 1-5.
- [0476] 59. Karu T et al., Changes in oxidative metabolism of murine spleen following laser and superluminous diode (660-950 nm) irradiation: effects of cellular composition and radiation parameters. *Lasers Surg. Med.*, 193:13, 453-462.
- [0477] 60. Friedman P M, Skover G R, Payonk G, et al. 3D in-vivo optical skin imaging for topographical quantitative assessment of non-ablative laser technology. *Dermatol Surg.* 2002 March; 28(3):199-204.
- [0478] A1) Webb C, Dyson M, Lewis W H. Stimulatory effect of 660 nm low level laser energy on hypertrophic scar-derived fibroblasts: possible mechanisms for increase in cell counts. *Lasers Surg Med* 1998; 22(5):294-301.
- [0479] A2) Harper R A, Grove G. Human skin fibroblasts derived from papillary and reticular dermis: differences in growth potential in vitro. *Science* 1979 May 4; 204(4392):526-7.
- [0480] A3) Schonherr E, Beavan L A, Hausser H, et al. Differences in decorin expression by papillary and reticular fibroblasts in vivo and in vitro. *Biochem J* 1993 Mar. 15; 290 (Pt 3):893-9.
- [0481] A4) Karu, T. Molecular mechanism of the therapeutic effect of low-intensity laser radiation. *Lasers in Life Science* 1988; 2, 53-74.
- [0482] A5) Auger F. A., Rémy-Zolghadri M., Grenier G., Germain L.: "A truly New Approach For Tissue Engineering: The LOEX Self-Assembly Technique". In: Stem cell transplantation and tissue engineering, A. Haverich, H. Graf, eds, Springer-Verlag, Berlin. Chapter 6: 73-88, 2002.
- [0483] A6) Germain L., Moulin V., Berthod F., Lopez C. A., Goulet F., Auger F. A.: "Multiple applications of tissue-engineered human skin". In: Cultured human keratinocytes and tissue engineered skin substitutes R. E. Horch, A. M. Munster, B. M. Achauer, eds. Georg Thieme Verlag, Stuttgart, Germany. pp. 91-98, 2001.
- [0484] A7) Simpson C R, Kohl M, Essenpreis M, Cope M. Near infrared optical properties of ex-vivo human skin and subcutaneous tissues measured using the Monte Carlo inversion technique. *Phys Med Biol* 1998 43: 2465-2478.
- [0485] B1) Privalov P L. Stability of proteins. Proteins which do not present a single cooperative system. *Adv Protein Chem.* 1982;35:1-104.
- [0486] B2) Piez K A. Structure and assembly of the native collagen fibril. *Connect Tissue Res.* 1982;10(1):25-36.
- [0487] B3) Chi-Hyun P., Min J L, Jungmi A., Sangmin K., Hyeon H K, Kyu H K., Hee C E., and Jin H C. Heat Shock-induced Matrix Metalloproteinase (MMP)-1 and

MMP-3 Are Mediated through ERK and JNK Activation and via an Autocrine Interleukin-6 Loop *J Invest Dermatol* 2004, 123: 6, 1012-1019.

[0488] B4) Chen Z, Seo J Y, Kim Y K, Lee S R, Kim K H, Cho K H, Eun H C, Chung J H. Heat modulation of tropoelastin, fibrillin-1, and matrix metalloproteinase-12 in human skin in vivo. *J Invest Dermatol*. 2005 January;124(1):70-8.

[0489] B5) Chung J H, Seo J Y, Choi H R, Lee M K, Youn C S, Rhie G, Cho K H, Kim K H, Park K C, Eun H C. Modulation of skin collagen metabolism in aged and photoaged human skin in vivo. *J Invest Dermatol*. 2001 November;117(5):1218-24.

[0490] B6) Varani J, Spearman D, Perone P, Fligiel S E, Datta S C, Wang Z Q, Shao Y, Kang S, Fisher G J, Voorhees J J. Inhibition of type I procollagen synthesis by damaged collagen in photoaged skin and by collagenase-degraded collagen in vitro. *Am J Pathol*. 2001 March;158(3):931-42.

[0491] B7) Fligiel S E, Varani J, Datta S C, Kang S, Fisher G J, Voorhees J J. Separation of retinoid-induced epidermal and dermal thickening from skin irritation. *J Invest Dermatol*. 2003 May;120(5):842-8.

We claim:

1. A method of photoactivating mammalian tissue causing a predetermined physiological change, comprising the steps of:

irradiating the tissue with a first pulse having a power density above an activation threshold power density;

irradiating the tissue with a second pulse;

emitting the first pulse for a duration of about 1 femtosecond to about 1 hour; and

separating the first pulse from the second pulse by an inter-pulse interval of about 1 microsecond to about 10 seconds.

2. The method as described in claim 1, wherein the first pulse has a wavelength of about 400 nanometers to about 1500 nanometers and the power density is about 0.1 mW/cm² to about 10 W/cm².

3. The method as defined in claim 1, wherein the power density is from about 30 mW/cm² to about 100 mW/cm².

4. The method as defined in claim 1, wherein the activation threshold power density is one of about 0.1 mW/cm², about 10 mW/cm², and about 50 mW/cm².

5. The method as defined in claim 1, wherein the inter-pulse interval is one of about 10 microseconds to about 5 milliseconds and about 100 microseconds to about 0.5 milliseconds.

6. The method as defined in claim 1, wherein the duration is one of about 100 microseconds to about 5 milliseconds and about 250 microseconds to about 1 millisecond.

7. The method as defined in claim 1, further comprising the step of emitting the first pulse for about 250 microseconds to about 1 millisecond and the inter-pulse interval is from about 100 microseconds to about 0.5 millisecond.

8. The method as defined in claim 1, wherein the first pulse is emitted by at least one light emitting diode (LED).

9. The method as defined in claim 1 wherein a physiological effect of the photoactivation includes at least one of stimulating collagen production by fibroblasts contained within the skin tissue, substantially reversing at least in part

skin damages caused by aging, reversing at least in part damages caused to an extracellular matrix of the skin by aging, and modulating an apoptosis response of the skin tissue.

10. The method as defined in claim 1, wherein a ratio of the duration divided by the inter-pulse interval is one of about 0.1 to about 10 and about 0.5 to about 2.

11. The method as defined in claim 1, wherein the power density of radiation within the tissue is below one of about 10 percent and about 1 percent of the activation threshold power density during the inter-pulse interval.

12. The method as defined in claim 1, further comprising a minimal power density of the radiation within the tissue during each pulse is one of about two times, about ten times, about 100 times, and about 10,000 times as large as a maximal power density of the radiation within the tissue during the inter-pulse interval.

13. The method as defined in claim 1, further comprising the steps of:

irradiating the tissue with the first pulse having a power density below a thermal threshold power density over which a temperature of the irradiated tissue increases to a temperature greater than a predetermined overheating temperature.

14. The method as defined in claim 13, wherein the thermal threshold power density is one of about 10 mW/cm², about 100 mW/cm², about 1 W/cm², and about 1 kW/cm².

15. The method as defined in claim 13, wherein the overheating temperature is one of about 2° C., about 0.5° C., and about 0.1° C. over a maximal non-pathological in-vivo temperature of the mammalian tissue.

16. The method as defined in claim 13, wherein the activation threshold power density is about 30 mW/cm² and the thermal threshold power density is about 100 mW/cm².

17. The method as defined in claim 13, further comprising at least two pulse trains, each pulse train including the first pulse and the second pulse, further comprising the steps of:

emitting a first pulse train; and

separating the first pulse train from a second pulse train by an inter-pulse train interval of about 1 microsecond to about 1 second.

18. The method as defined in claim 17, wherein the inter-pulse train interval is one of 500 microsecond to about 1 second, about 750 microseconds to about 500 milliseconds, and about 500 microseconds to about 2.25 milliseconds.

19. The method as defined in claim 17, wherein a ratio of the inter-pulse train interval to the inter-pulse interval is about 2 to about 10.

20. The method as defined in claim 17, wherein the ratio of the inter-pulse train interval to the inter-pulse interval is about 3.

21. The method as defined in claim 17, wherein a number of pulses within each pulse train is one of 2 to 100 pulses, 4 to 10 pulses, and 3 to 10 pulses.

22. A method of photoactivating mammalian tissue causing a predetermined physiological change, comprising the steps of:

irradiating the tissue with a first pulse train and a second pulse train, each pulse train having at a first pulse and a second pulse;

separating the first pulse from the second pulse by an inter-pulse interval; and

separating the first pulse train from a second pulse train by an inter-pulse train interval.

23. The method as defined in claim 22, wherein the inter-pulse train interval is one of about 1 microsecond to about 1 second, 500 microsecond to about 1 second, about 750 microseconds to about 500 milliseconds, and about 500 microseconds to about 2.25 milliseconds.

24. The method as defined in claim 22, wherein a ratio of the inter-pulse train interval to the inter-pulse interval is about 2 to about 10.

25. The method as defined in claim 22, wherein the ratio of the inter-train pulse interval to the inter-pulse interval is about 3.

26. The method as defined in claim 22, wherein a number of pulses within each pulse train is one of 2 to 100 pulses, 4 to 10 pulses, and 3 to 10 pulses.

27. The method as defined in claim 22, further comprising the step of depositing a total fluence from the first and second pulse trains to the tissue of about 0.001 J/cm² to about 20,000 J/cm².

28. The method as defined in claim 27, wherein the total fluence is about 4 J/cm² to about 10 J/cm².

29. A method for photoactivating mammalian tissue, comprising the steps of:

irradiating the tissue with a time-varying radiation including a power density temporal profile, wherein the irradiating step includes:

activating molecular cascades of events; and

activating cells contained within the tissue.

30. The method as defined in claim 29, further comprising the step of providing a molecular relaxation phase comprising at least one of:

allowing a molecular relaxation wherein reversible molecular conformational changes are reversed at least in part so that the molecular cascades of events are reactivatable; and

allowing the cells of the tissue to rest so as to prevent at least in part cell exhaustion during the irradiation.

31. The method as defined in claim 29, further comprising the step of preventing a temperature increase in the tissue above an overheating temperature at which the cascade of events triggered by the radiation are substantially reversed.

32. The method as defined in claim 31, further comprising the step of providing a thermal relaxation phase including the step of allowing the cells of the tissue to dissipate heat so as to remain substantially below the overheating temperature.

33. The method as defined in claim 31, further comprising the step of preventing the temperature increase by a thermal inertia of the tissue.

34. The method as defined in claim 29, further comprising the step of cooling the tissue.

35. The method as defined in claim 34, wherein the cooling step includes cooling the tissue by through active convective cooling.

36. The method as defined in claim 34, wherein cooling the tissue includes delivering to the tissue a vasodilatator in an amount effective to cause a vasodilatation within the tissue.

37. The method as defined in claim 31, wherein the power density temporal profile remains below a thermal threshold above which the temperature within the tissue is likely to increase above the overheating temperature.

38. The method as defined in claim 29 further comprising the step of initiating the molecular cascade of events including the step of receiving, by an antenna molecule, least one photon contained within the radiation.

39. The method as defined in claim 29 wherein the molecular cascade of events occurs partly in the mitochondria of the cells of the tissue.

40. The method as defined in claim 30, wherein the molecular cascade of events includes reversible conformational changes that are reversed during the molecular relaxation phases.

41. The method as defined in claim 29, wherein activating the cells includes progressively increasing a mitochondrial activity level within the cells of the tissue.

42. The method as defined in claim 29, further comprising the steps of:

defining a plurality of pulse trains, each pulse train including a plurality of radiation pulses having a pre-determined pulse duration;

separating the plurality of radiation pulses by an inter-pulse interval; and

separating the pulse trains by an inter-pulse train interval, the inter-pulse train interval being substantially larger than the inter-pulse interval.

43. The method as defined in claim 42, further comprising the step of allowing an antenna molecule to initiate the molecular cascades of events.

44. The method as defined in claim 42, wherein the plurality pulses within each pulse train is a number of pulses to bring the cells to a suitable level of activation.

45. The method as defined in claim 44, wherein the number of pulses within each pulse train is a number preventing the cells from substantially reaching a steady state of activation.

46. The method as defined in claim 42, wherein the number of pulses within each pulse train is from 4 to 10 pulses.

47. The method as defined in claim 42, further comprising the step of providing the inter-train interval to provide cellular relaxation phases and allowing the cells of the tissue to rest so as to prevent at least in part at least one of cell exhaustion and mitochondrial exhaustion during the irradiation.

48. The method as defined in claim 42, wherein the inter-train interval is about 750 microseconds and about 500 milliseconds.

49. A method for regenerating an extracellular matrix in mammalian tissue, comprising the step of irradiating the tissue with radiation to regenerate the extracellular matrix.

50. The method as defined in claim 49, wherein the radiation performs at least one of the steps of:

partially reversing the effects of aging within the skin tissue;

stimulating collagen production within the tissue;

stimulating collagen repair within the extracellular matrix;

downregulating a matrix metalloproteinase (MMP) gene expression within the cells of the tissue;
upregulating procollagen production within the cells of the tissue;
reducing elastin degradation within the extracellular matrix;
reducing fibronectin degradation within the extracellular matrix;
stimulating collagen production within the tissue; and
stimulating collagen repair within the extracellular matrix.

51. The method as defined in claim 49, further comprising the steps of:

defining a pulse train including a plurality of radiation pulses wherein the pulses each have a duration of from about 250 microsecond to about 1 millisecond;
separating the pulses from each other by an inter-pulse interval, the inter-pulse interval is about 100 microseconds to about 500 microseconds; and
defining an irradiance of each pulse in the tissue of about 30 mW/cm² to about 100 mW/cm².

52. A method for reducing damages previously caused to a mammalian skin tissue, comprising the steps of:

irradiating the tissue with radiation having a power density temporal profile having a power density within the tissue greater than an activation threshold over a pre-determined time interval; and
maintaining a temperature of the tissue below an overheating temperature by selecting the predetermined time interval.

53. The method as defined in claim 52, wherein the overheating temperature is about 5° C. above a maximal non-pathological in-vivo tissue temperature.

54. The method as defined in claim 52, further comprising the steps of:

defining a plurality of pulse trains, each pulse train including a plurality of radiation pulses having a pre-determined pulse duration;
separating the plurality of radiation pulses by an inter-pulse interval; and
separating the plurality of pulse trains by an inter-train interval, the inter-train interval being substantially larger than the inter-pulse interval.

55. The method as defined in claim 54, further comprising the steps of:

irradiating the tissue over a plurality of treatments, wherein a treatment includes one or more pulse trains;
providing an inter-treatment time interval between treatments; and
performing the treatment to substantially reduce damages previously caused to the mammalian skin tissue.

56. The method as defined in claim 55, further comprising the step of applying the treatments within a rejuvenating phase wherein the tissue is substantially rejuvenated.

57. The method as defined in claim 56, further comprising the steps of applying a maintenance phase following the

rejuvenating phase, the maintenance phase including steps of substantially maintaining the rejuvenation of the tissue.

58. The method as defined in claim 57, wherein an inter-treatment time interval during the maintenance phase is larger than an inter-treatment time interval during the rejuvenating phase.

59. The method as defined in claim 58, wherein the inter-treatment time interval during the maintenance phase is larger than a duration of the rejuvenating phase.

60. The method as defined in claim 57, wherein the inter-treatment time interval during the rejuvenating phase is one of about 1 minute to about 1 year, about 1 hour to about 1 month, about 1 day to about 1 week, and about 3 days to about 4 days.

61. The method as defined in claim 57 wherein the inter-treatment time interval during the maintenance phase is from about 1 day to about 5 years, about 1 month to about 1 year, and about 1 year.

62. The method as defined in claim 57, wherein the rejuvenating phase includes at least one of 2 to 1000 treatments, 2 to 50 treatments, 5 to 20 treatments, and 12 treatments.

63. The method as defined in claim 57, wherein the inter-treatment time interval during the rejuvenating phase is about 1 day to about 1 week and wherein the inter-treatment time interval during the maintenance phase is about 1 month to about 1 year.

64. The method as defined in claim 57, further comprising the step of substantially preventing at least one of a cellular exhaustion and a mitochondrial exhaustion.

65. The method as defined in claim 57, wherein the radiation performs at least one of the steps of:

partially reversing the effects of aging within the skin tissue;
stimulating collagen production within the tissue;
stimulating collagen repair within the extracellular matrix;
downregulating a matrix metalloproteinase (MMP) gene expression within the cells of the tissue;
upregulating procollagen production within the cells of the tissue;
reducing elastin degradation within the extracellular matrix;
reducing fibronectin degradation within the extracellular matrix;
stimulating collagen production within the tissue; and
stimulating collagen repair within the extracellular matrix.

66. The method as defined in claim 55, wherein each pulse train includes about 4 to about 10 pulses,

wherein the pulses within each pulse train lasting about 250 microseconds to about 1 millisecond,

wherein the inter-pulse interval is about 100 microseconds to about 0.5 millisecond, and

wherein the inter-train interval is about 500 microseconds to about 1 second.

67. The method as defined in claim 66, wherein the fluence of each treatment is one of about 1 mJ/cm² to about 1 kJ/cm², about 1 J/cm² to about 50 J/cm², and about 4 J/cm² to about 10 J/cm².

68. The method as defined in claim 56, wherein the substantially rejuvenated tissue includes cells that are less likely to experience apoptosis than the cells were prior to the irradiation.

69. The method as defined in claim 68, further comprising the steps of reducing a likelihood of apoptosis by at least one of reversing an aging process, and reversing environmental factors.

70. The method as defined in claim 56, further comprising the steps of applying an active topical formulation to the skin prior to irradiation.

71. The method as defined in claim 70, wherein the active topical formulation promotes collagen synthesis.

72. The method as defined in claim 71, wherein the active topical formulation includes at least one of antioxidants and a vitamin selected from the set consisting of vitamins A, B₅, C and E.

73. The method as defined in claim 52, wherein the radiation is suitable for treating at least one of cheloids by photoinhibition, atrophic scars through photoactivation, acne, eczema, psoriasis, vitiligo, rosacea, promoting hair regrowth, removing at least in part exogenous pigments in the skin, dermal hypermelanosis, an adnexial tumor, cutaneous hyperpigmentation, smoothing wrinkles, reducing a thinning skin, reducing a lack of firmness of the skin, and reducing dullness of the skin.

74. A method of photoactivating mammalian tissue using a photoactivating device, said photoactivating device including a photoactivating light source adapted to generate a photoactivating beam of light having a predetermined set of light parameters, said mammalian tissue defining a target surface adapted to be irradiated by said photoactivating beam of light, said method comprising the steps of:

positioning said photoactivating light source and said mammalian tissue relative to each other so that said photoactivating light source and said target surface are at a predetermined operational distance relative to each other; and

irradiating said target surface with said photoactivating beam of light while said photoactivating light source is spaced from said target surface by said operational distance; wherein said operational distance is such that said photoactivating beam of light photoactivates said biological tissue.

75. A method as recited in claim 74 further comprising the step of:

using a distance probe for adjusting the distance between said photoactivating light source and said target surface towards said operational distance.

76. A method as recited in claim 75 further comprising the step of:

using an aiming beam of light emanating from an aiming device operatively coupled to said photoactivating light source for aiming said photoactivating light source towards said target surface prior to using said distance probe for adjusting the distance between said photoactivating light source and said target surface towards said operational distance.

77. A method as recited in claim 74 further comprising the step of:

cooling said target surface so as to maintain said target surface at a temperature below a predetermined thermal threshold.

78. A method as recited in claim 77 wherein the cooling of said target surface includes using a cooling flow of air for convectively cooling said target surface.

79. A method as recited in claim 77 further comprising the step of also cooling said photoactivating light source.

80. A method of photoactivating mammalian tissue using a photoactivating device, said photoactivating device including a photoactivating light source adapted to generate a photoactivating beam of light having a predetermined set of light parameters, said mammalian tissue defining a target surface adapted to be irradiated by said photoactivating beam of light, said method comprising the steps of:

irradiating said target surface with said photoactivating beam of light emanating from said photoactivating light source; and

cooling said target surface so as to maintain said target surface at a temperature below a predetermined thermal threshold.

81. A method as recited in claim 80 wherein the cooling of said target surface includes using a cooling flow of air for convectively cooling said target surface.

82. A method as recited in claim 80 further comprising the step of also cooling said photoactivating light source.

83. A photoactivation device for modulating the physiology of a target biological activity by directing a photoactivating beam of light having a predetermined set of photoactivating light parameters on a target surface, said device comprising:

a photoactivating light source for emitting said photoactivating beam of light;

a positioning means operatively coupled to said photoactivating light source for allowing selective positioning of said photoactivating light source relative to said target surface; and

a position evaluating means for evaluating the position of said photoactivating light source relative to said target surface.

84. A device as recited in claim 83 further comprising an information providing means for providing information regarding the position of said photoactivating light source relative to said target surface.

85. A device as recited in claim 84 wherein said information providing means includes a visual display component for providing a visual display indicative of the position of said photoactivating light source relative to said target surface.

86. A photoactivation device for modulating the physiology of a target cellular activity by directing photoactivating light having a predetermined set of photoactivating light parameters on a treatment area of a target human body; said device comprising:

a treatment head, said treatment head including a photoactivating light source for emitting photoactivating light, said treatment head also including a treatment area cooling means for cooling said treatment area.

87. A photoactivation device as recited in claim 86 wherein said treatment head is spaced from said treatment area by a treatment head-to-treatment area spacing, said treatment area cooling means including a cooling air flowing means for creating a treatment area air flow flowing at least partially in said treatment head-to-treatment area spacing for cooling said treatment area.

88. A photoactivation device as recited in claim 86 wherein said treatment head also includes a light source cooling means for cooling said photoactivating light source.

89. A photoactivation device as recited in claim 88 wherein said light source cooling means includes a cooling air flowing means for creating a light source air flow for convectively cooling said photoactivating light source.

90. A photoactivation device as recited in claim 89 wherein said cooling air flowing means also creates a treatment area air flow for cooling said treatment area.

* * * * *



US 20040260367A1

(19) United States

(12) Patent Application Publication

De Taboada et al.

(10) Pub. No.: US 2004/0260367 A1

(43) Pub. Date: Dec. 23, 2004

(54) DEVICE AND METHOD FOR PROVIDING PHOTOTHERAPY TO THE HEART

(76) Inventors: Luis De Taboada, Carlsbad, CA (US); Jackson Streeter, Reno, NV (US)

filed on Jan. 31, 2002. Provisional application No. 60/410,080, filed on Sep. 12, 2002. Provisional application No. 60/549,679, filed on Mar. 3, 2004.

Publication Classification

Correspondence Address:
KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614 (US)

(51) Int. Cl. 7 A61N 5/06

(52) U.S. Cl. 607/88; 607/89

(57) ABSTRACT

(21) Appl. No.: 10/818,947

(22) Filed: Apr. 6, 2004

Related U.S. Application Data

(63) Continuation-in-part of application No. 10/328,153, filed on Dec. 23, 2002.

(60) Provisional application No. 60/345,177, filed on Dec. 21, 2001. Provisional application No. 60/353,638,

A method for treating a patient's heart is provided. The method includes providing a light source which emits light having an initial power density. The method further includes positioning the light source relative to the patient's heart with intervening tissue of the patient between the light source and the patient's heart. The method further includes directing light onto cardiac tissue of the patient's heart from the light source through the intervening tissue without damaging the intervening tissue. The cardiac tissue is irradiated by an efficacious power density of light for an efficacious period of time.

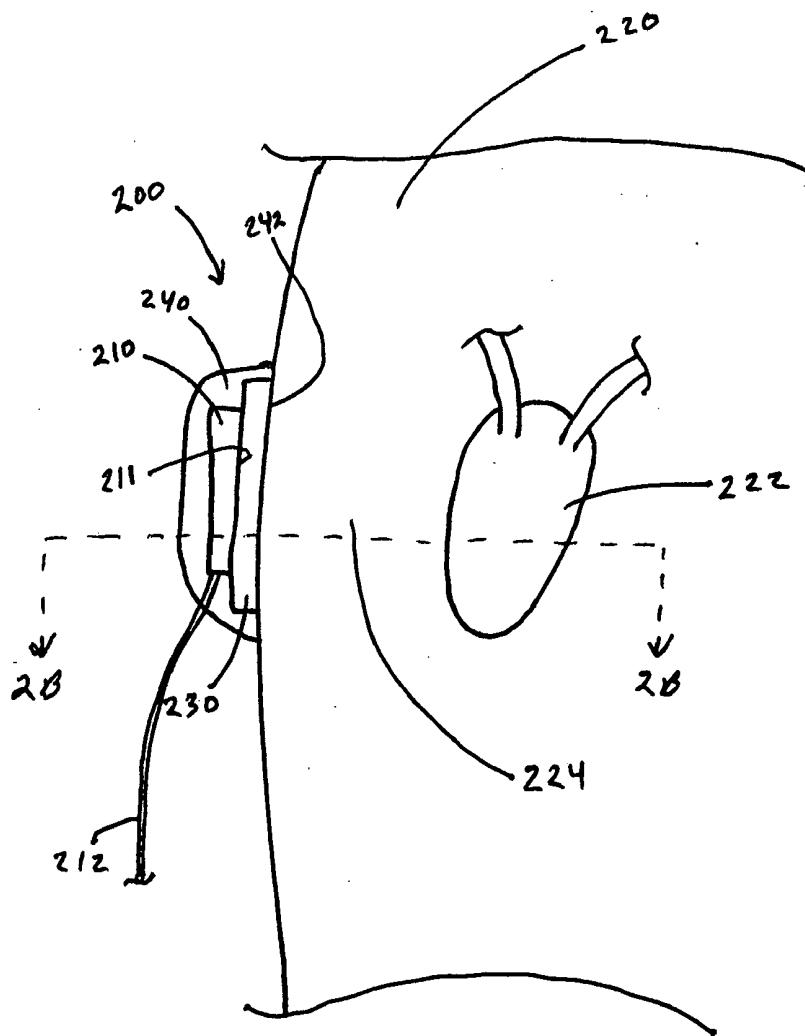


Figure 1:

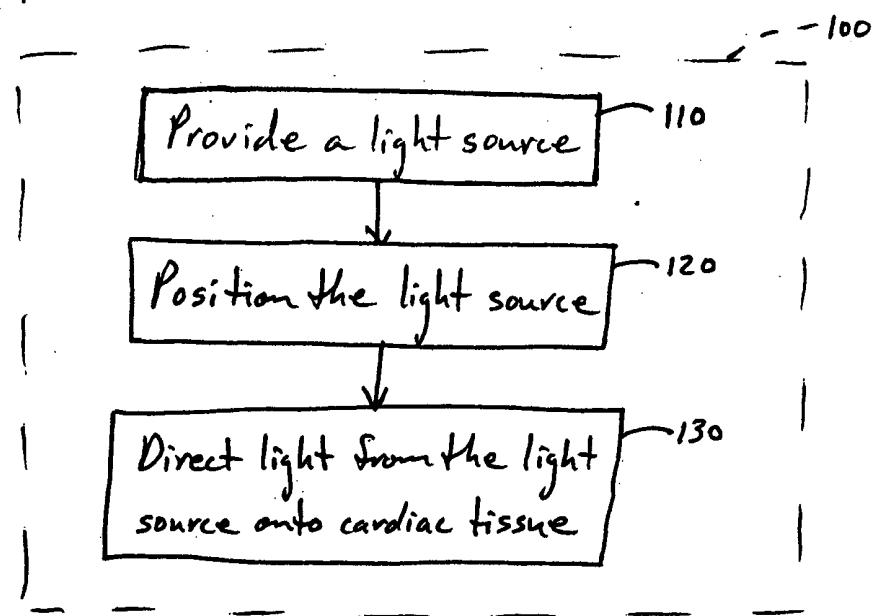


Figure 2A:

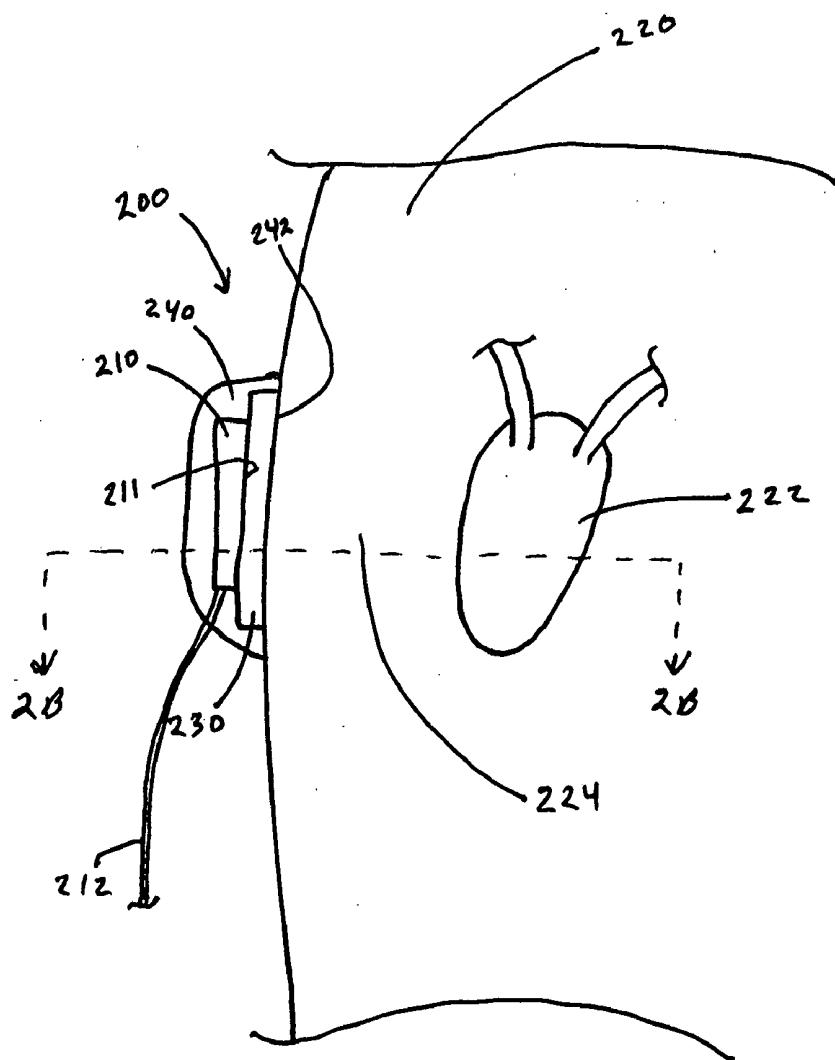


Figure 2B:

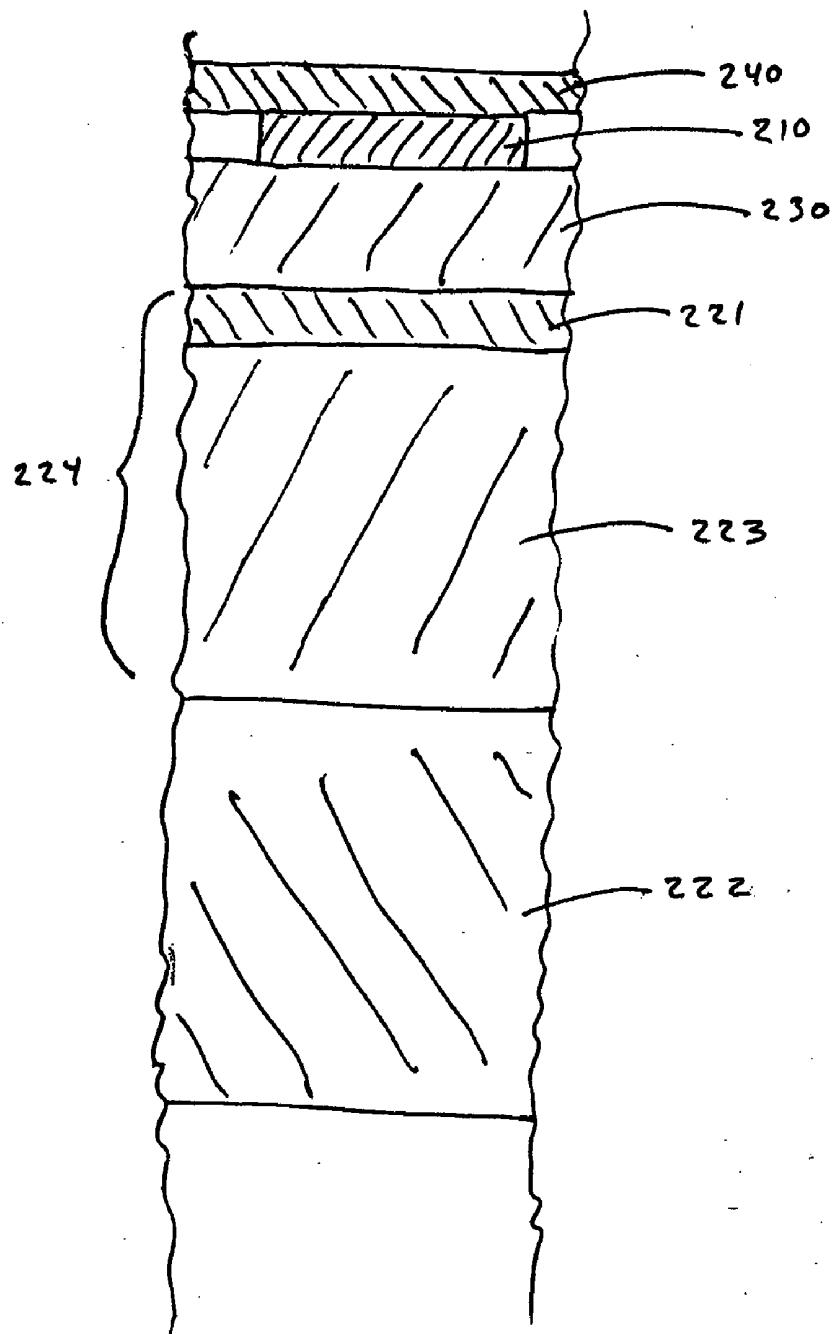


Figure 3:

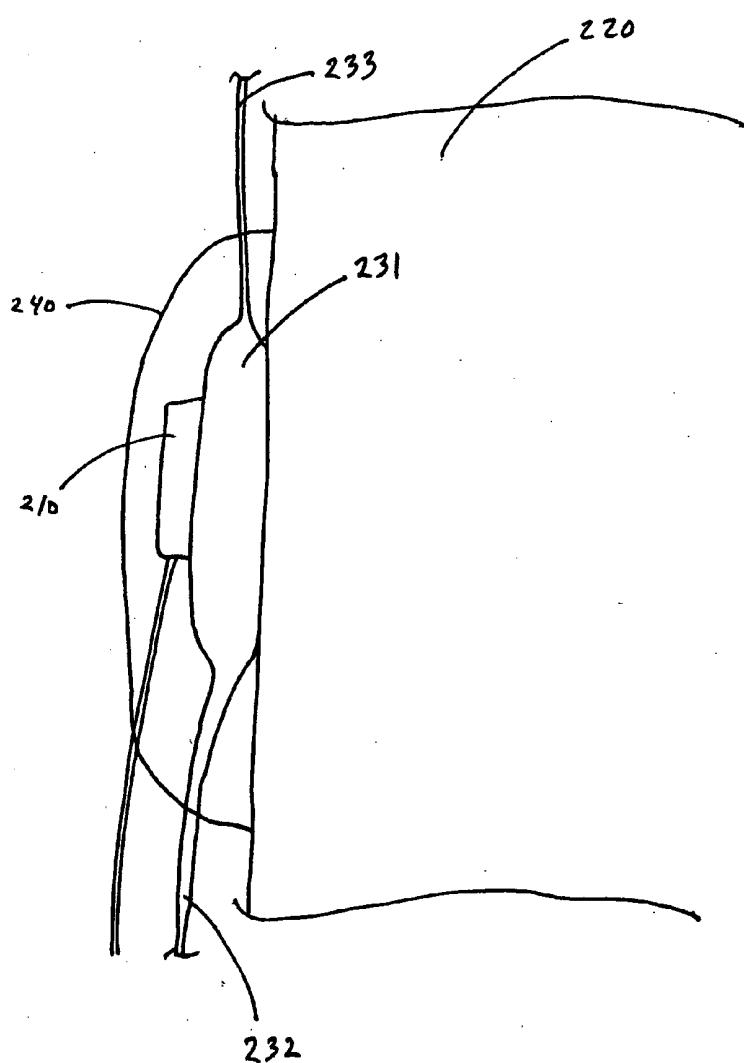


Figure 4A:

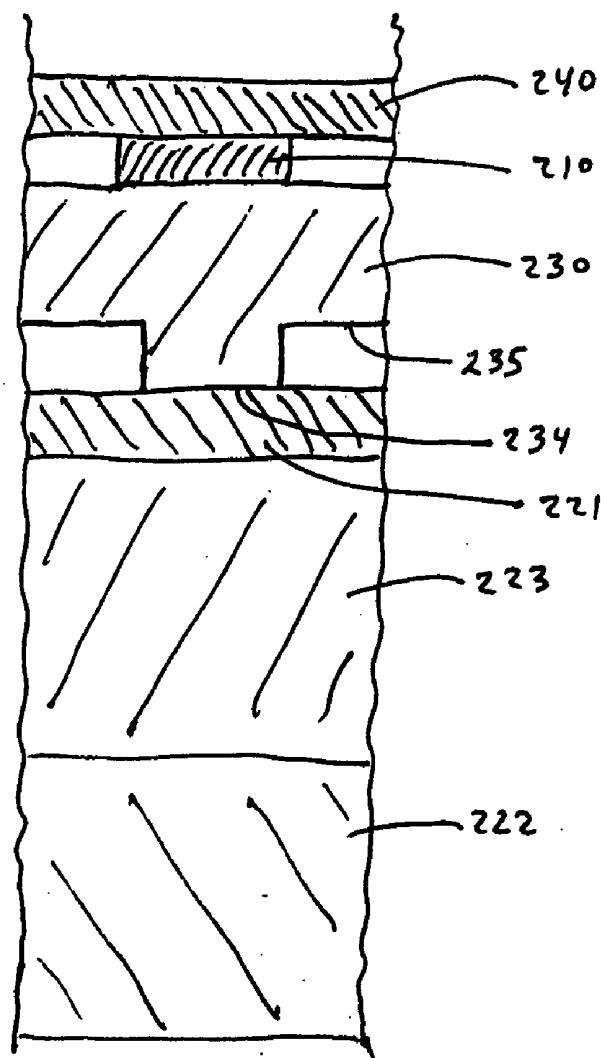
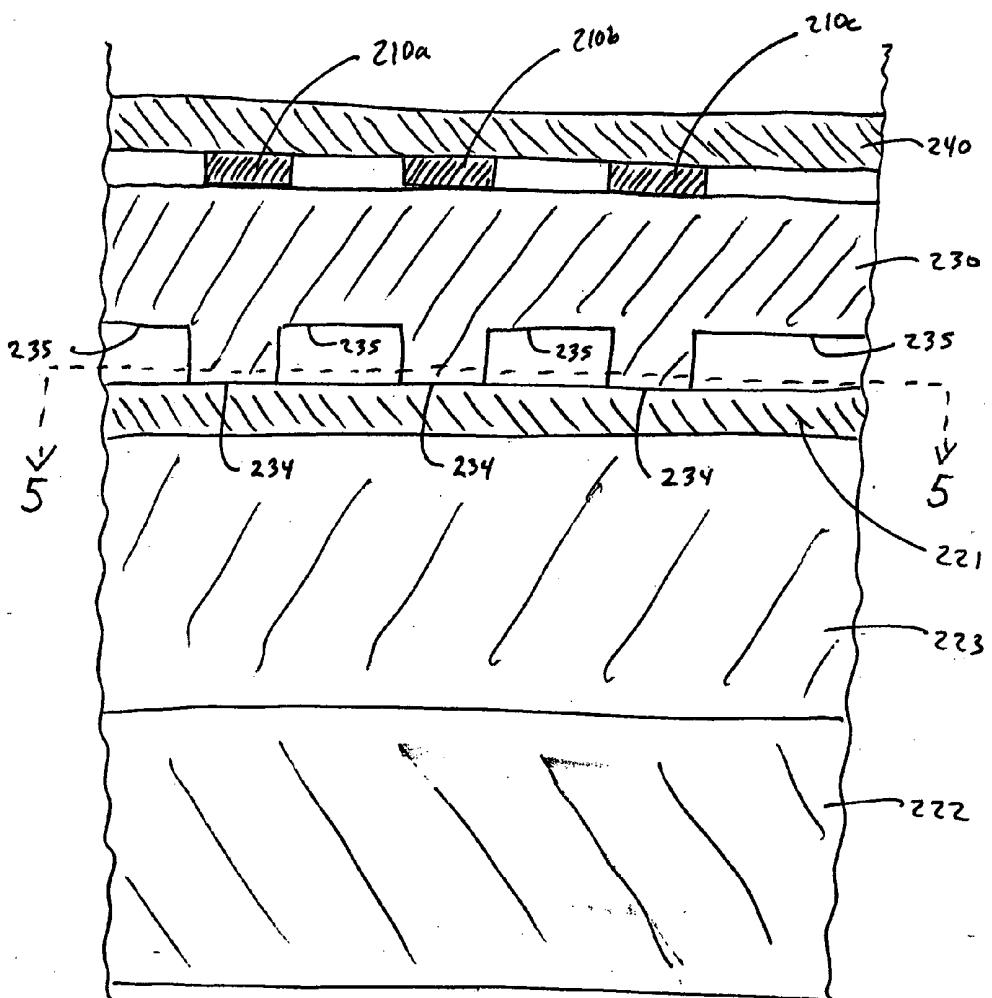


Figure 4B:



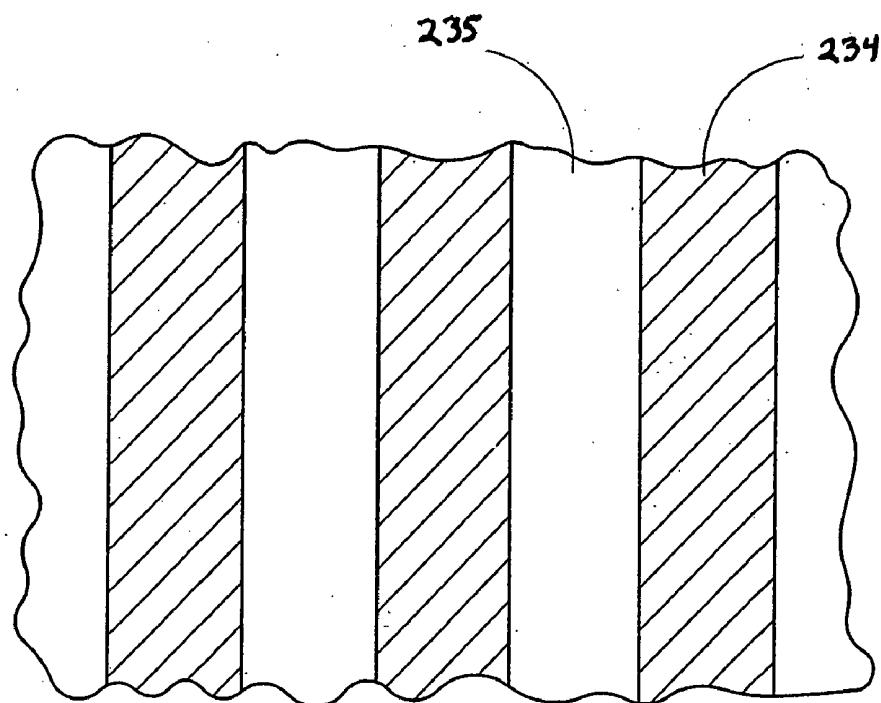


FIG. 5A

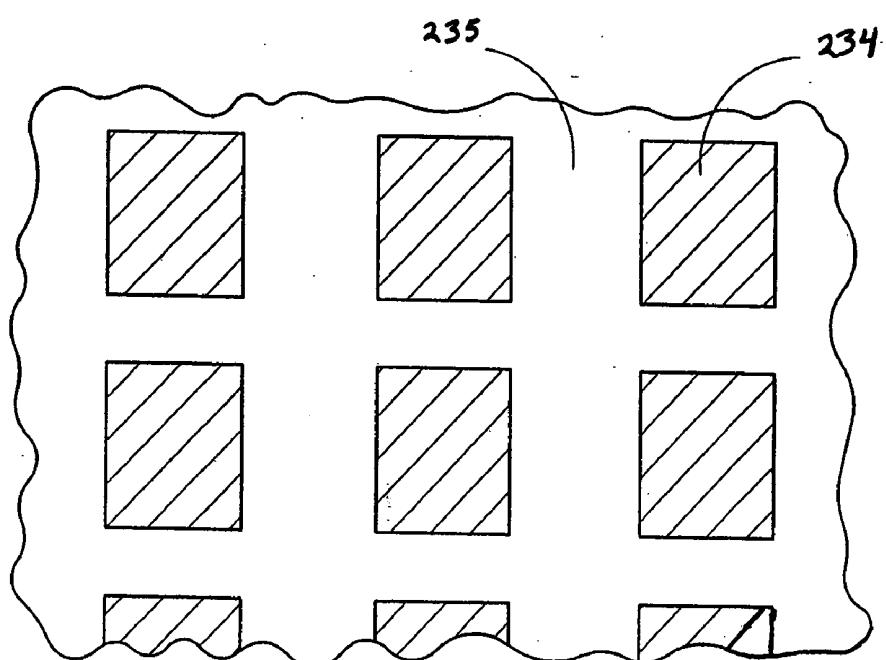
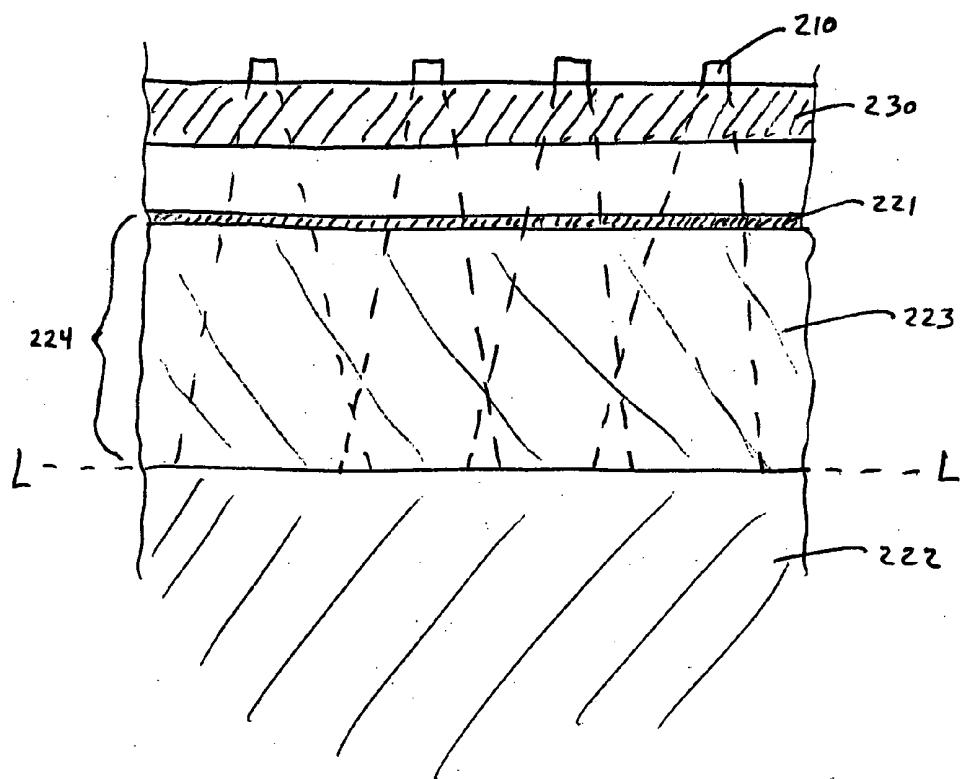


FIG. 5B

Figure 6A:



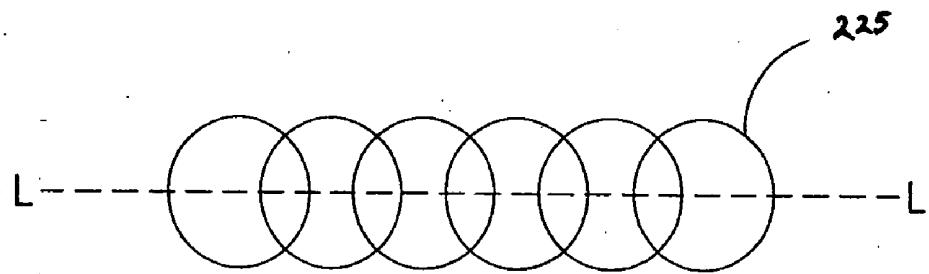


FIG. 6B

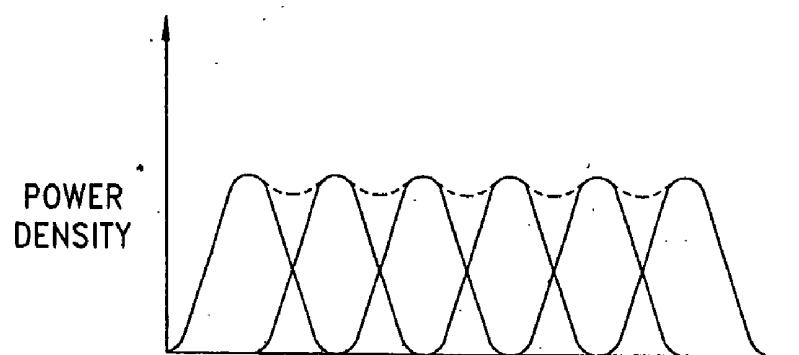


FIG. 6C

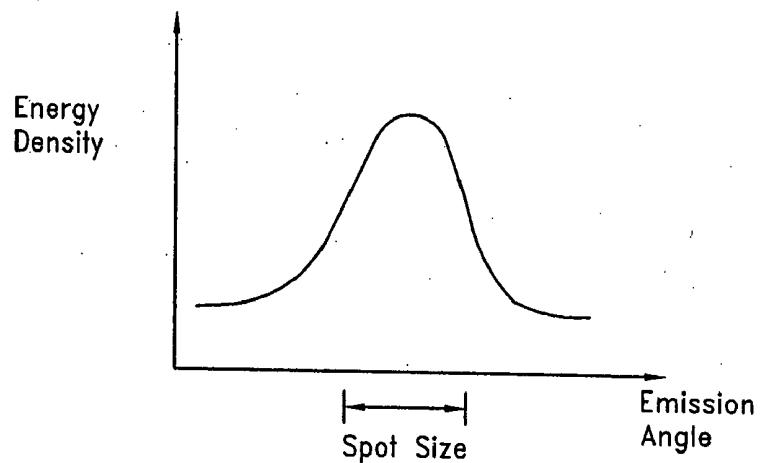


FIG. 7A

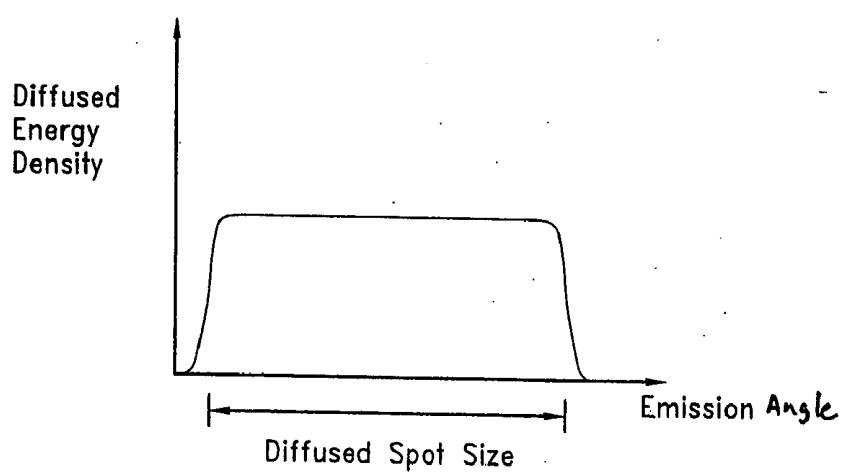
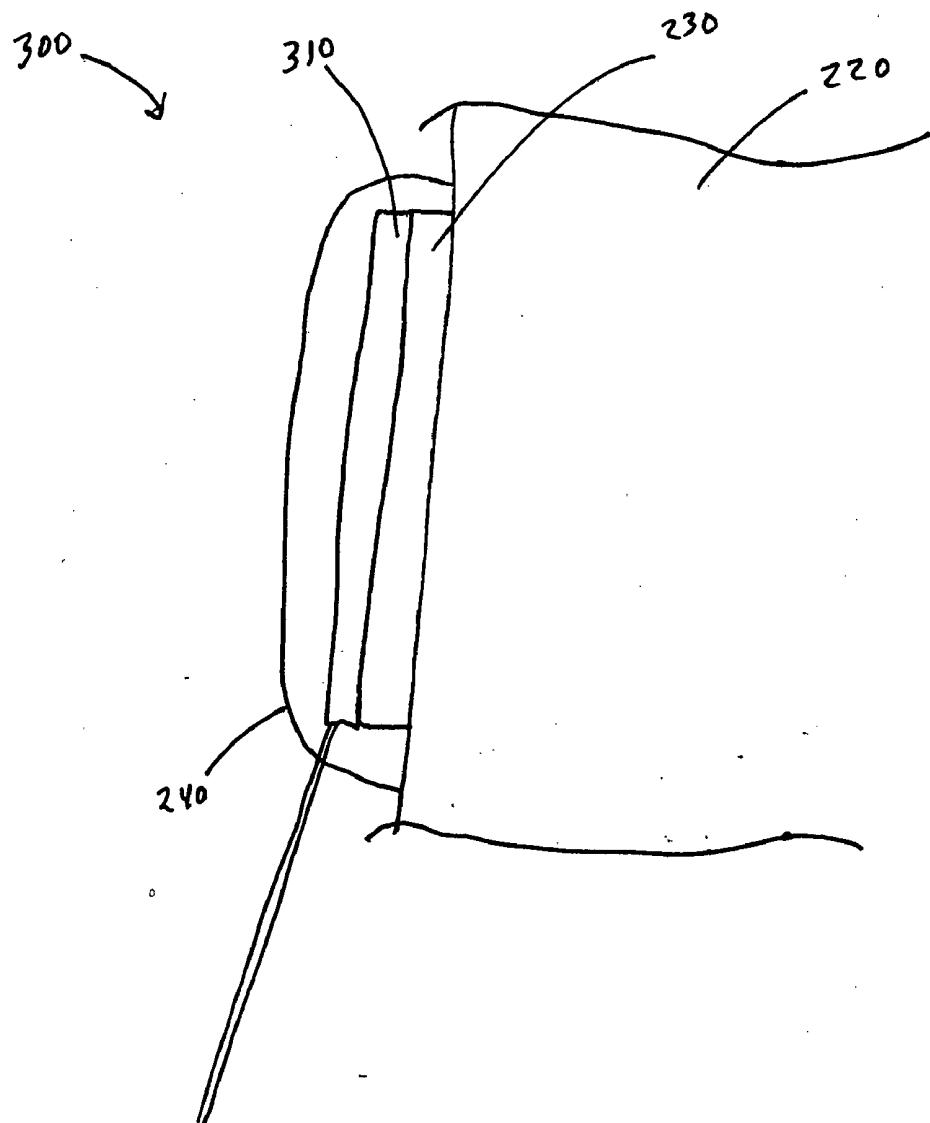


FIG. 7B

Figure 8A:



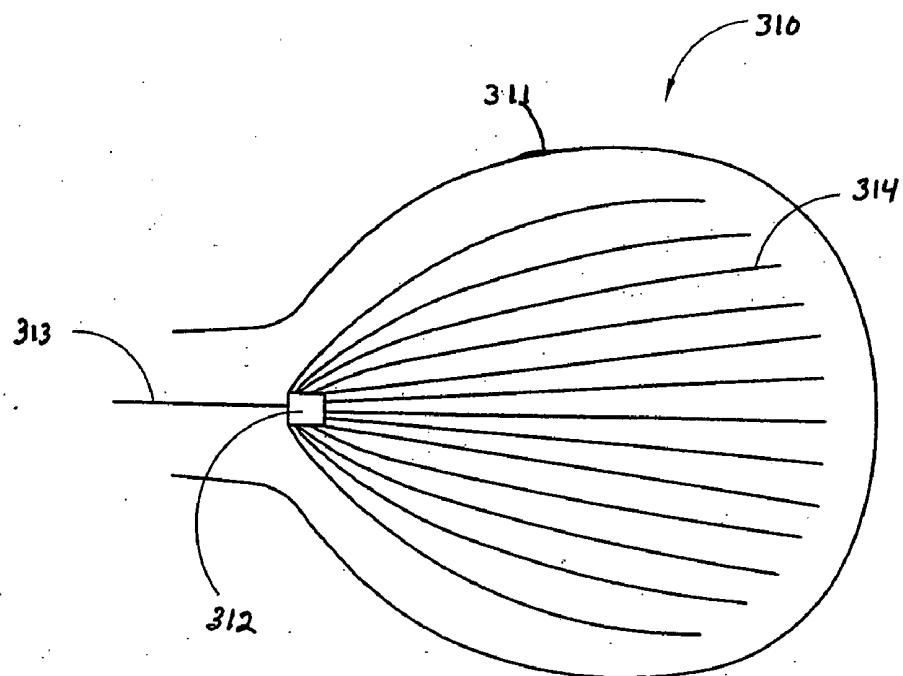


Figure 8B

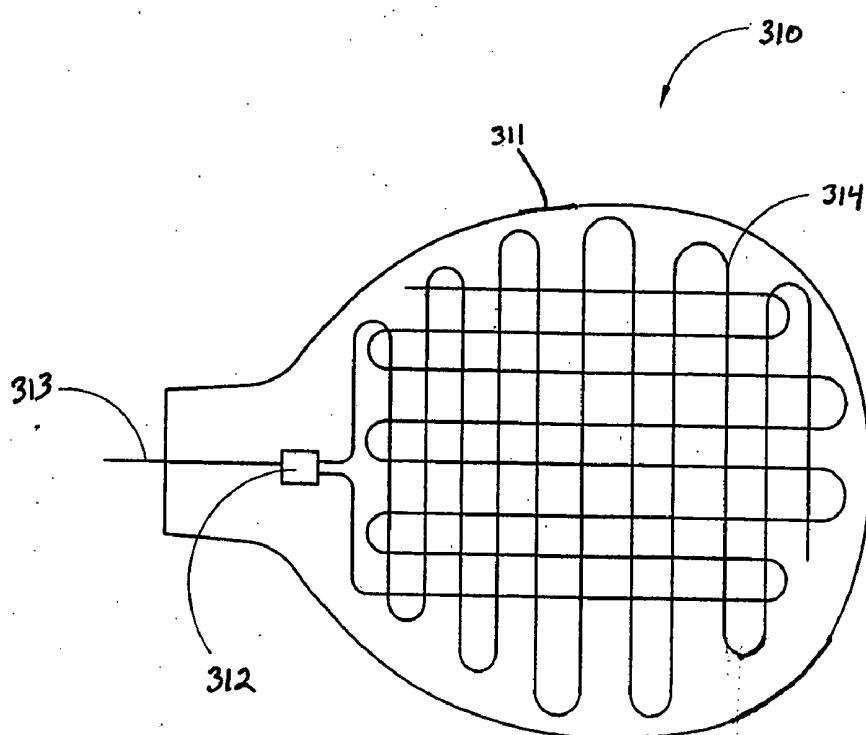


Figure 8C

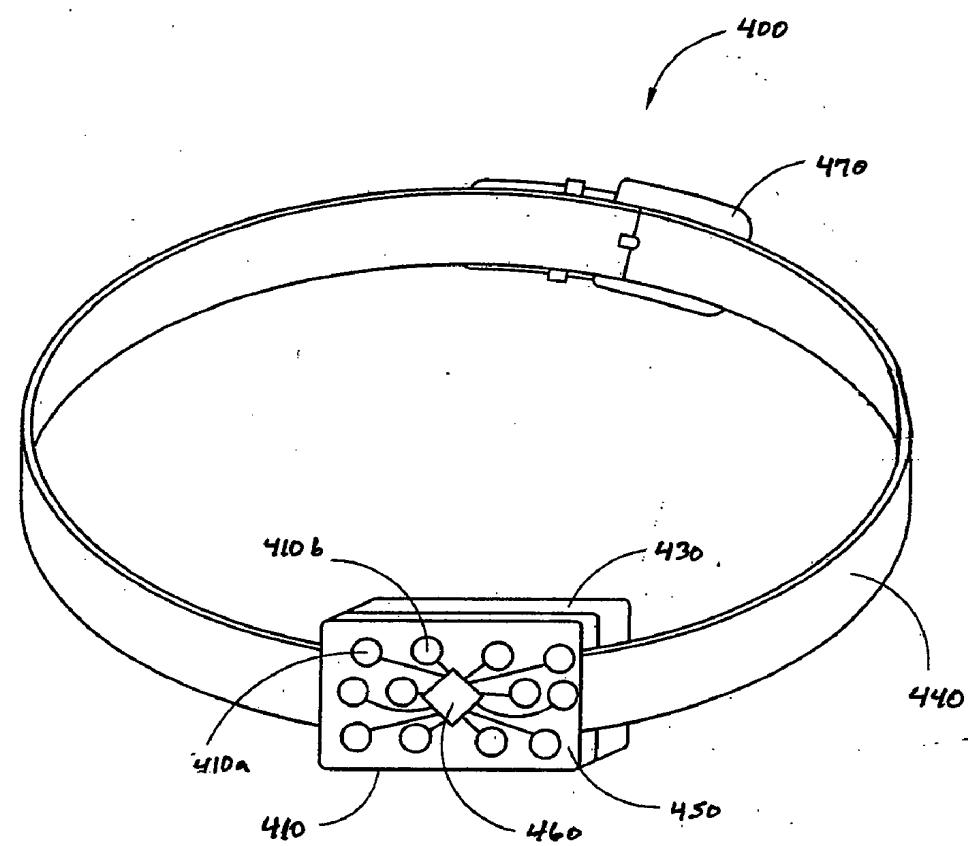


Figure 9

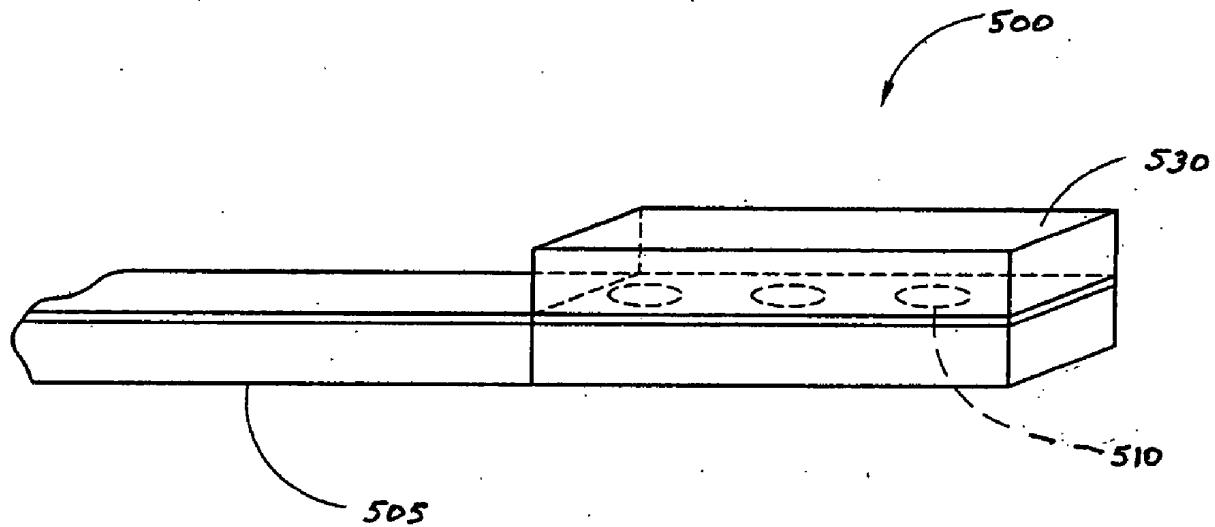


Figure 10

Figure 11A:

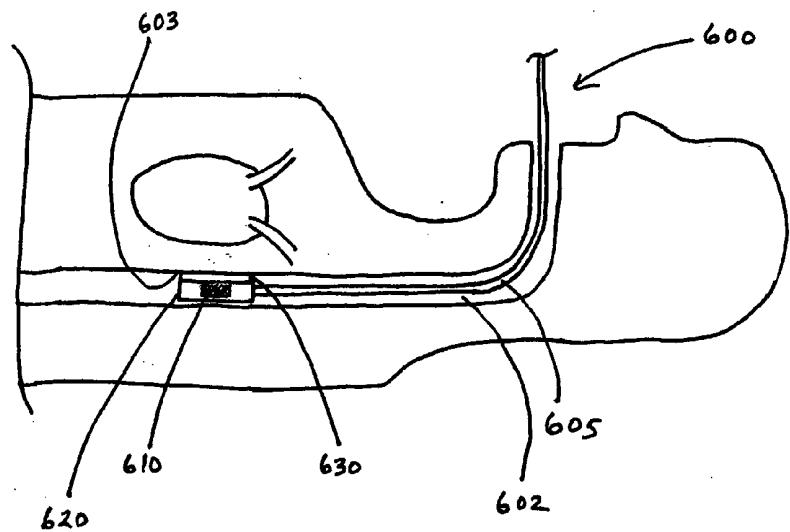


Figure 11B:

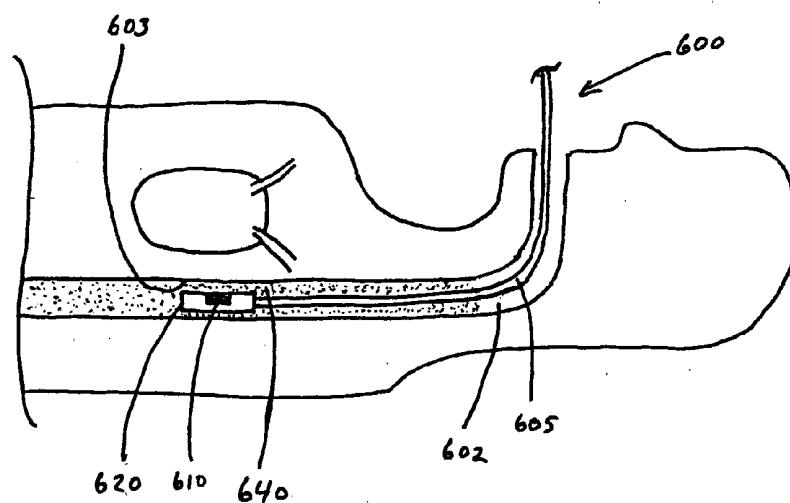


Figure 12:

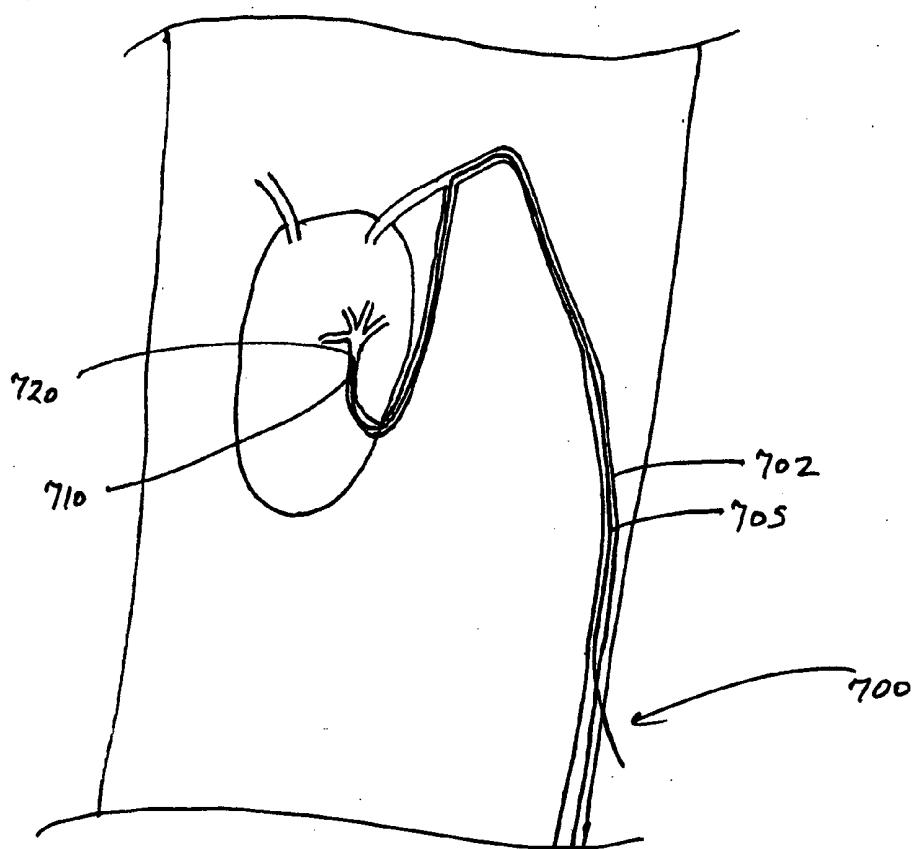


Figure 13A:

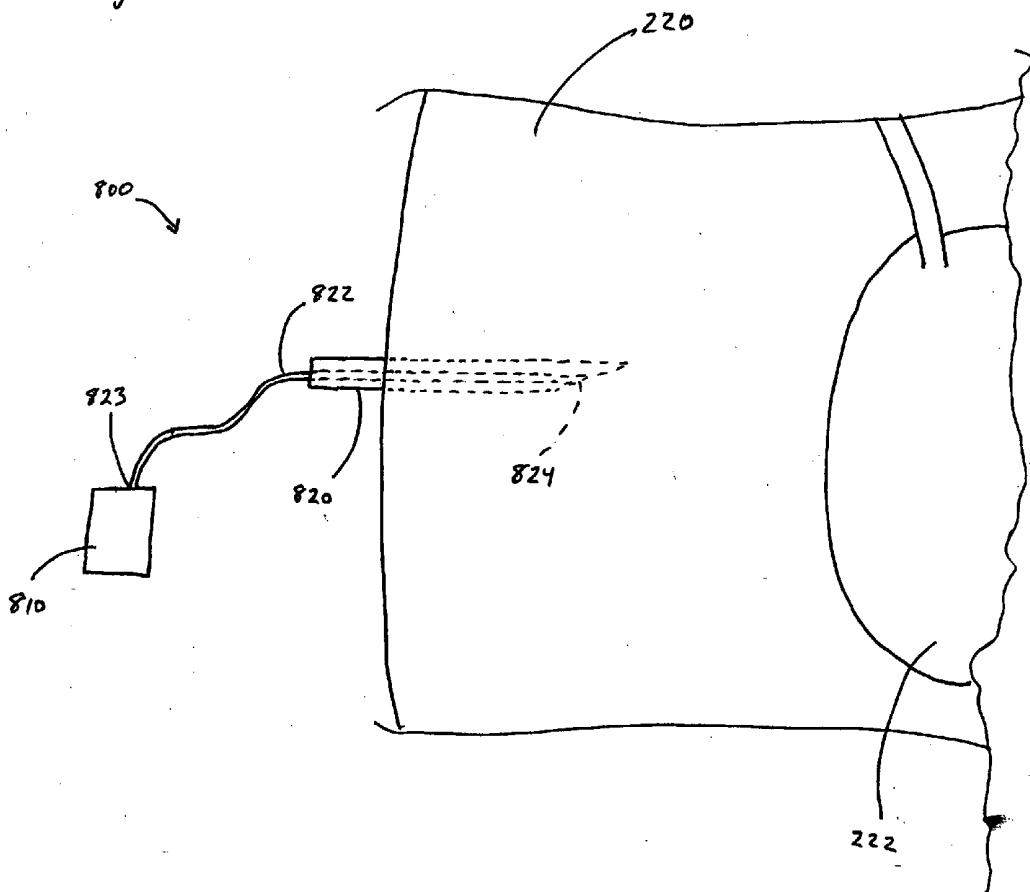
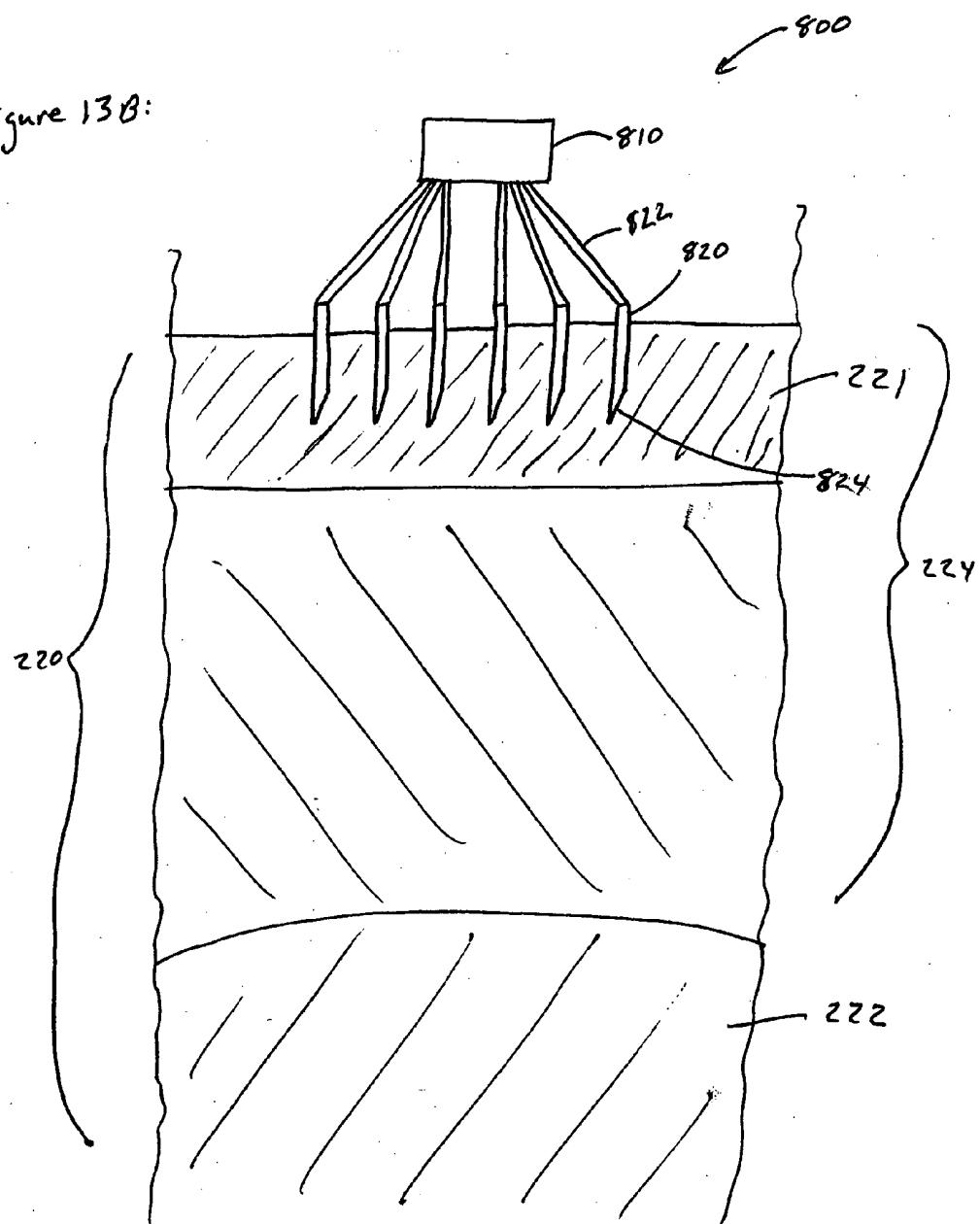


Figure 13B:



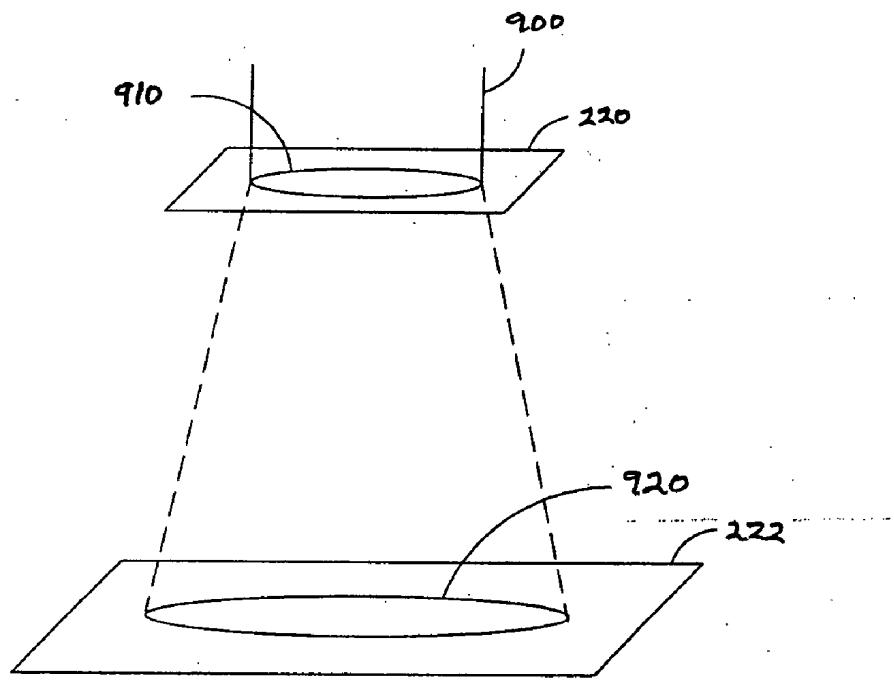


Figure 14A

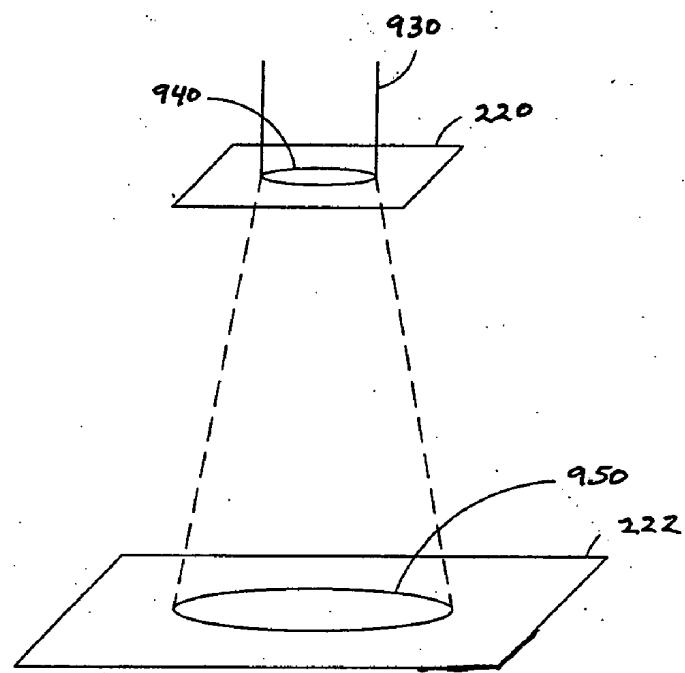


Figure 14B

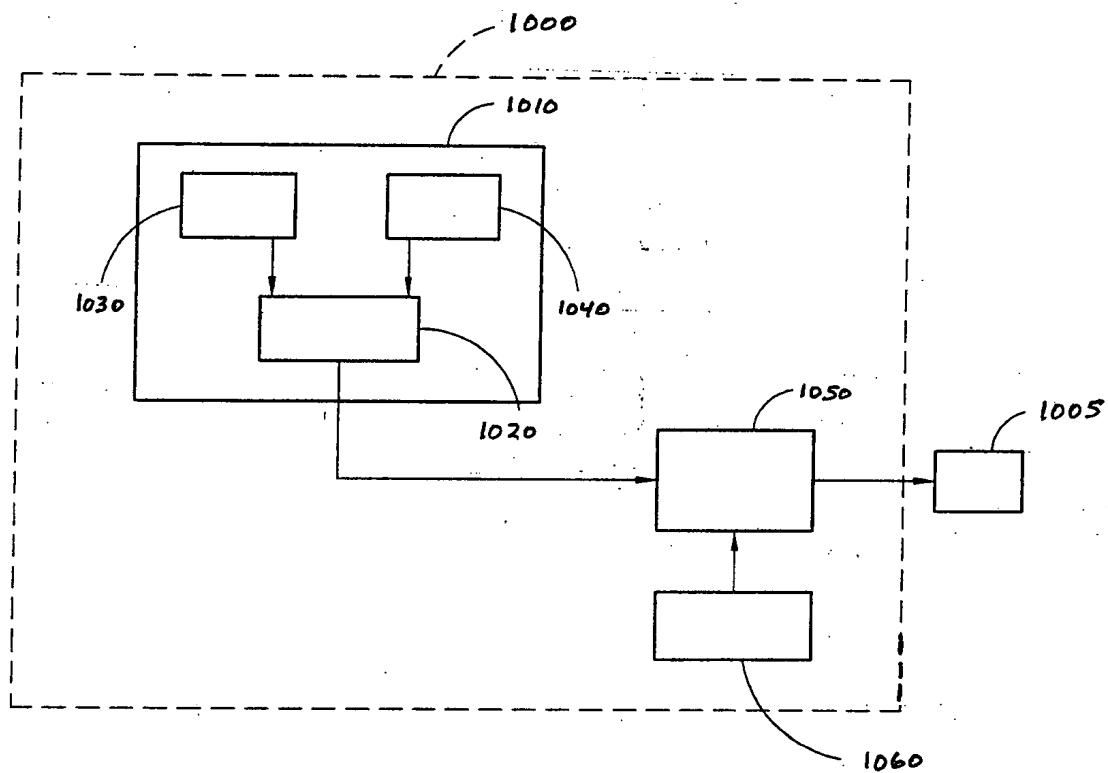


Figure 15

DEVICE AND METHOD FOR PROVIDING PHOTOTHERAPY TO THE HEART**CLAIM OF PRIORITY**

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 10/328,153, filed Dec. 23, 2002, which is incorporated in its entirety by reference herein and which claims benefit to U.S. Provisional Application No. 60/345,177, filed Dec. 21, 2001, U.S. Provisional Application No. 60/353,638, filed Jan. 31, 2002, and U.S. Provisional Application No. 60/410,080, filed Sep. 12, 2002, each of which is incorporated in its entirety by reference herein. This application also claims benefit to U.S. Provisional Application No. 60/549,679, filed Mar. 3, 2004, which is incorporated in its entirety by reference herein.

BACKGROUND OF THE INVENTION**[0002] 1. Field of the Invention**

[0003] The present invention relates in general to phototherapy, and more particularly, to novel apparatuses and methods for phototherapy of cardiac tissue.

[0004] 2. Description of the Related Art

[0005] Myocardial ischemia refers to the condition of oxygen deprivation in heart muscle ("myocardium") that is produced by some imbalance in the myocardial oxygen supply-demand relationship. Myocardial infarction ("MI"), also known as "heart attack", refers to the death of cells in an area of heart muscle as a result of oxygen deprivation due to obstruction of the blood supply, typically due to occlusion of one or more coronary arteries or branches. Occlusion usually stems from clots that form upon the sudden rupture of an atherosomatous plaque through the sublayers of a blood vessel, or when the narrow, roughened inner lining of a sclerosed artery leads to complete thrombosis. Approximately 1.5 million myocardial infarctions (MIs) occur annually, and nearly 500,000 deaths result from ischemic heart disease. The United States alone loses billions of dollars annually to medical care and lost productivity due to cardiovascular disease including myocardial infarction.

[0006] Treatment after MI depends on the extent to which the cells have been deprived of oxygen. Complete oxygen deprivation produces a zone of infarction in which cells die and the tissue becomes necrotic, with irretrievable loss of function. However, immediately surrounding the area of infarction is a less seriously damaged region of tissue, the zone of ischemia, in which cells have not been irretrievably damaged by complete lack of oxygen but instead are merely weakened and at risk of dying. If adequate collateral circulation develops, the extended zone may regain function within 2 to 3 weeks. The zone of infarction and the zone of ischemia, are both identifiable using standard diagnostic techniques such as electrocardiography, echocardiography and radionuclide testing.

[0007] Therapeutic strategies in treating MI are directed at reducing the final extent of the infarcted region by preserving viable tissue and if possible retrieving surviving but at-risk cells. Known treatment methods for myocardial infarction include surgical interventions and pharmacologic treatments. A combination of therapeutic approaches is sometimes advisable. Selection of the appropriate therapy depends on a number of factors, including the degree of

coronary artery occlusion, the extent of existing damage if any, and fitness of the patient for surgery. Surgical interventions include coronary artery bypass surgery and percutaneous coronary procedures such as angioplasty, artherectomy and endarterectomy. Pharmacologic agents for treating MI include inhibitors of angiotensin converting enzyme (ACE) such as captopril, quinapril and ramipril, thrombolytic agents including aspirin, streptokinase, t-PA and anistreplase, β -adrenergic antagonists, Ca^{++} channel blockers, and organic nitrates such as nitroglycerin. However, surgical interventions are invasive and can increase the risk of stroke, and pharmacologic agents carry the risk of eliciting serious adverse side effects and immune responses.

[0008] High energy laser radiation is now well accepted as a surgical tool for cutting, cauterizing, and ablating biological tissue. High energy lasers are now routinely used for vaporizing superficial skin lesions and, and for making deep cuts. Examples of such procedures include transmyocardial laser revascularization (TMLR) and percutaneous transmyocardial laser revascularization (PTMR). In TMLR, a laser is inserted through a chest incision and used to drill approximately 15-30 transmural channels from the epicardial to the endocardial surfaces through the left ventricular myocardium in an attempt to improve local perfusion to ischemic myocardial territories not being reached by diseased arteries. In PTMR, the laser is introduced via a catheter. Other examples include laser ablation or cauterization of cardiac tissue to stop atrial fibrillation.

[0009] For a laser to be suitable for use as a surgical laser, it must provide laser energy at a power sufficient to heat tissue to temperatures over 50° C. Power outputs for surgical lasers vary from 1-5 W for vaporizing superficial tissue, to about 100 W for deep cutting.

[0010] In contrast, low level laser therapy involves therapeutic administration of laser energy to a patient at vastly lower power outputs than those used in high energy laser applications, resulting in desirable biostimulatory effects while leaving tissue undamaged. In rat models of myocardial infarction and ischemia-reperfusion injury, low energy laser irradiation reduces infarct size and left ventricular dilation, and enhances angiogenesis in the myocardium. (See, e.g., Yaakobi et al., *J. Appl. Physiol.*, Vol. 90, pp. 2411-19 (2001)).

[0011] Against the background, a high level of interest remains in finding new and improved therapeutic methods for the treatment of myocardial infarction. In particular, a need remains for relatively inexpensive and non-invasive approaches to treating myocardial infarction that also avoid the limitations of drug therapy.

SUMMARY OF THE INVENTION

[0012] In certain embodiments, a method for treating a patient's heart is provided. The method comprises providing a light source which emits light having an initial power density. The method further comprises positioning the light source relative to the patient's heart with intervening tissue of the patient between the light source and the patient's heart. The method further comprises directing light onto cardiac tissue of the patient's heart from the light source through the intervening tissue without damaging the intervening tissue. The cardiac tissue is irradiated by an efficacious power density of light for an efficacious period of time.

[0013] In certain embodiments, a method for treating a patient's heart is provided. The method comprises introducing light of an efficacious power density onto a target area of the heart by directing light having an initial power density through intervening tissue of the patient. The light has a plurality of wavelengths, and the efficacious power density is at least 0.01 mW/cm² at the target area.

[0014] In certain embodiments, a method for treating a patient's heart following a myocardial infarction is provided. The method comprises applying low-level light therapy to the heart no earlier than about two hours following the myocardial infarction.

[0015] In certain embodiments, a method provides a cardioprotective effect in a patient having a ischemic event in the heart. The method comprises identifying a patient who has experienced an ischemic event in the heart. The method further comprises estimating the time of the ischemic event. The method further comprises commencing administration of a cardioprotective effective amount of light energy to the heart no less than about two hours following the time of the ischemic event.

[0016] In certain embodiments, a method for treating a patient's heart is provided. The method comprises directing an efficacious power density of light through intervening tissue of the patient to a target area of the heart concurrently with applying an electromagnetic field to the heart. The electromagnetic field has an efficacious field strength.

[0017] In certain embodiments, a method for treating a patient's heart is provided. The method comprises directing an efficacious power density of light through intervening tissue of the patient to a target area of the heart concurrently with applying an efficacious amount of ultrasonic energy to the heart.

[0018] In certain embodiments, a therapy apparatus for treating a patient's heart is provided. The therapy apparatus comprises a light source having an output emission area positioned to irradiate a portion of the heart with an efficacious power density and wavelength of light through intervening tissue. The therapy apparatus further comprises an element interposed between the light source and the intervening tissue. The element is configured to inhibit temperature increases at the intervening tissue caused by the light.

[0019] In certain embodiments, a therapy apparatus for treating a patient's heart is provided. The therapy apparatus comprises a light source configured to irradiate at least a portion of the heart with an efficacious power density and wavelength of light. The therapy apparatus further comprises a biomedical sensor configured to provide real-time feedback information. The therapy apparatus further comprises a controller coupled to the light source and the biomedical sensor. The controller is configured to adjust said light source in response to the real-time feedback information.

[0020] In certain embodiments, a therapy apparatus for treating a patient's heart is provided. The therapy apparatus comprises an implantable light source configured to irradiate at least a portion of the heart with an efficacious power density and wavelength of light.

[0021] In certain embodiments, a method of treating a patient's heart is provided. The method comprises implant-

ing a light source within the patient. The method further comprises irradiating at least a portion of the heart with an efficacious power density and wavelength of light from the implanted light source.

[0022] In certain embodiments, a therapy apparatus for treating a patient's heart is provided. The therapy apparatus comprises a light source configured to irradiate at least a portion of the patient's blood with an efficacious power density and wavelength of light prior to the blood flowing to the heart.

[0023] In certain embodiments, a method of treating a patient's heart is provided. The method comprises irradiating at least a portion of the patient's blood with an efficacious power density and wavelength of light. The method further comprises allowing the irradiated blood to flow to the heart.

[0024] For purposes of summarizing the present invention, certain aspects, advantages, and novel features of the present invention have been described herein above. It is to be understood, however, that not necessarily all such advantages may be achieved in accordance with any particular embodiment of the present invention. Thus, the present invention may be embodied or carried out in a manner that achieves or optimizes one advantage or group of advantages as taught herein without necessarily achieving other advantages as may be taught or suggested herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] FIG. 1 is a flow diagram of a method of treating a patient's heart in accordance with embodiments described herein.

[0026] FIGS. 2A-2B schematically illustrate an embodiment of a therapy apparatus comprising a light source configured to be placed outside the patient's torso.

[0027] FIG. 3 schematically illustrates an embodiment of a therapy apparatus with an element which comprises a container coupled to an inlet conduit and an outlet conduit for the transport of a flowing material through the element.

[0028] FIGS. 4A and 4B schematically illustrate embodiments of a therapy apparatus with an element with a portion spaced away from the torso and a portion contacting the skin of the torso and configured to facilitate the blanching of the skin of the torso.

[0029] FIGS. 5A and 5B schematically illustrate cross-sectional views of two embodiments of the element in accordance with FIG. 4B taken along the line 5-5.

[0030] FIGS. 6A-6C schematically illustrate an embodiment in which light emitted by the light sources propagates from the light sources through the intervening tissue, including the skin of the torso, to the heart and disperses in a direction generally parallel to the skin.

[0031] FIGS. 7A and 7B schematically illustrate the diffusive effect on the light by the element.

[0032] FIGS. 8A-8C schematically illustrate embodiments of the therapy apparatus with a light source comprising a light-emitting blanket.

[0033] FIG. 9 schematically illustrates an embodiment of the therapy apparatus with a light source, an element, and a

flexible strap configured for securing the therapy apparatus over an area of the patient's torso.

[0034] FIG. 10 schematically illustrates an embodiment of the therapy apparatus with a handheld probe.

[0035] FIGS. 11A and 11B schematically illustrate embodiments of a therapy apparatus configured to be inserted into the esophagus of the patient.

[0036] FIG. 12 schematically illustrates an embodiment of a therapy apparatus configured to be inserted into a blood vessel of the patient.

[0037] FIG. 13A schematically illustrates an embodiment of a therapy apparatus configured to avoid a portion of intervening tissue between the therapy apparatus and the heart.

[0038] FIG. 13B schematically illustrates an embodiment of the therapy apparatus with a plurality of needles.

[0039] FIGS. 14A and 14B schematically illustrates two light beams having different cross-sections impinging a patient's torso and propagating through the patient's torso to irradiate a portion of the patient's heart.

[0040] FIG. 15 is a block diagram of a control circuit comprising a programmable controller.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0041] Low level light therapy ("LLLT") or phototherapy involves therapeutic administration of light energy to a patient at lower power outputs than those used for cutting, cauterizing, or ablating biological tissue, resulting in desirable biostimulatory effects while leaving tissue undamaged. For example, as described by U.S. Pat. No. 6,214,035 to Streeter, which is incorporated in its entirety by reference herein, LLLT can be used to improve cardiac microcirculation after cardiac surgeries, such as coronary bypass or angioplasty, by applying a low level of laser energy directly to a region of ischemic myocardium before closing the surgical incision.

[0042] In non-invasive or minimally-invasive phototherapy, it is desirable to apply an efficacious amount of light energy to the internal tissue to be treated without highly traumatic incisions (e.g., using light sources positioned outside the body). However, absorption of the light energy by intervening tissue can limit the amount of light energy delivered to the target tissue site, while heating the intervening tissue. In addition, scattering of the light energy by intervening tissue can limit the power density or energy density delivered to the target tissue site. Brute force attempts to circumvent these effects by increasing the power and/or power density applied to the outside surface of the body can result in damage (e.g., burning) of the intervening tissue.

[0043] Non-invasive or minimally-invasive phototherapy methods are circumscribed by setting selected treatment parameters within specified limits so as to preferably avoid damaging the intervening tissue. A review of the existing scientific literature in this field would cast doubt on whether a set of undamaging, yet efficacious, parameters could be found. However, certain embodiments, as described herein, provide devices and methods which can achieve this goal.

[0044] FIG. 1 is a flow diagram of a method 100 of treating a patient's heart in accordance with embodiments described herein. In an operational block 110, a light source is provided which emits light having an initial power density. In an operational block 120, the light source is positioned relative to the patient's heart with intervening tissue of the patient between the light source and the patient's heart. In an operational block 130, light from the light source is directed onto cardiac tissue of the patient's heart without damaging the intervening tissue. The cardiac tissue is irradiated by an efficacious power density of light for an efficacious period of time.

[0045] Providing a Light Source

[0046] The light source provided in the operational block 110 preferably generates light in the visible to near-infrared wavelength range. In certain embodiments, the light source comprises one or more laser diodes, which each provide coherent light. In embodiments in which the light from the light source is coherent, the emitted light may produce "speckling" due to coherent interference of the light. This speckling comprises intensity spikes which are created by constructive interference and can occur in proximity to the target tissue being treated. For example, while the average power density may be approximately 10 mW/cm², the power density of one such intensity spike in proximity to the cardiac tissue to be treated may be approximately 300 mW/cm². In certain embodiments, this increased power density due to speckling can improve the efficacy of treatments using coherent light over those using incoherent light for illumination of deeper tissues.

[0047] In other embodiments, the light source provides incoherent light. Exemplary light sources of incoherent light include, but are not limited to, incandescent lamps or light-emitting diodes. A heat sink can be used with the light source (for either coherent or incoherent sources) to remove heat from the light source and to inhibit temperature increases at the torso.

[0048] In certain embodiments, the light source generates light which is substantially monochromatic (i.e., light having one wavelength, or light having a narrow band of wavelengths). To maximize the amount of light transmitted to the heart, the wavelength of the light is selected in certain embodiments to be at or near a transmission peak (or at or near an absorption minimum) for the intervening tissue, which in certain embodiments corresponds to a peak in the transmission spectrum of tissue at about 820 nanometers. In certain such embodiments, the light emitted by the light source has a wavelength at which the absorption by intervening tissue is below a damaging level. In other embodiments, the wavelength of the light is preferably between about 590 nanometers and about 3000 nanometers, more preferably between about 780 nanometers and about 1064 nanometers, and most preferably between about 780 nanometers and about 840 nanometers. In still other embodiments, wavelengths of 630, 790, 800, 808, 810, 820, or 830 nanometers can be used. It has also been found that an intermediate wavelength of about 739 nanometers appears to be suitable for penetrating the intervening tissue, although other wavelengths are also suitable and may be used.

[0049] In other embodiments, the light source generates light having a plurality of wavelengths. In certain such embodiments, each wavelength is selected so as to work

with one or more chromophores within the target tissue. Without being bound by theory, it is believed that irradiation of chromophores increases the production of ATP in the target tissue, thereby producing beneficial effects. In certain embodiments, the light source is configured to generate light having a first wavelength and light having a second wavelength. In certain such embodiments, the light having the first wavelength is transmitted concurrently with the light having the second wavelength to the target cardiac tissue. In certain other such embodiments, the light having the first wavelength is transmitted sequentially with the light having a second wavelength to the target cardiac tissue.

[0050] In certain embodiments, the light source includes at least one continuously emitting GaAlAs laser diode having a wavelength of about 830 nanometers. In another embodiment, the light source comprises a laser source having a wavelength of about 808 nanometers. In still other embodiments, the light source includes at least one vertical cavity surface-emitting laser (VCSEL) diode. Other light sources compatible with embodiments described herein include, but are not limited to, light-emitting diodes (LEDs) and filtered lamps.

[0051] The light source is capable of emitting light energy at a power sufficient to achieve a predetermined power density at the cardiac target tissue. The subsurface power densities are selected to be effective at producing the desired biostimulative effects on the tissue being treated. In certain embodiments, phototherapy of tissue achieved by irradiating the target cardiac tissue with average power densities of light of at least about 0.01 mW/cm² and up to about 1 W/cm². In various embodiments, the average power density at the cardiac tissue is at least about 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, or 90 mW/cm², respectively, depending on the desired clinical performance. In certain embodiments, the cardiac tissue is irradiated with an average power density of preferably about 0.01 mW/cm² to about 100 mW/cm², more preferably about 0.01 mW/cm² to about 50 mW/cm², and most preferably about 2 mW/cm² to about 20 mW/cm². In still other embodiments, the efficacious average power density at the cardiac tissue being irradiated is between about 10 mW/cm² and about 150 mW/cm². Other levels of power densities at the cardiac tissue being irradiated are compatible with embodiments described herein.

[0052] Taking into account the attenuation of energy as it propagates from the skin surface, through body tissue, bone, and fluids, to the subdermal target tissue, initial average power densities preferably between about 10 mW/cm² to about 10 W/cm², or more preferably between about 100 mW/cm² to about 500 mW/cm², will typically be used to attain the selected power densities at the subdermal target tissue. Higher average power densities can be used in accordance with embodiments described herein. To achieve such surface power densities, the light source is preferably capable of emitting light energy having a total power output of at least about 25 mW to about 100 W. Light sources with higher total power outputs can be used in accordance with embodiments described herein. In various embodiments, the total power output is limited to be no more than about 30, 50, 75, 100, 150, 200, 250, 300, 400, or 500 mW, respectively. Higher total power outputs can be used in accordance with embodiments described herein. In addition, the light sources of certain embodiments are operated in continuous-wave

(CW) mode, while in other embodiments, the light sources are pulsed with peak power outputs.

[0053] In certain embodiments, the light source comprises a plurality of sources used in combination to provide the total power output. The actual power output of the light source is preferably controllably variable. In this way, the power of the light energy emitted can be adjusted in accordance with a selected average power density at the subdermal tissue being treated.

[0054] Certain embodiments utilize a light source that includes only a single laser diode that is capable of providing about 25 mW to about 100 W of total power output. In certain such embodiments, the laser diode can be optically coupled to the patient via an optical fiber or can be configured to provide a sufficiently large spot size to avoid power densities which would burn or otherwise damage the intervening tissue. In other embodiments, the light source utilizes a plurality of sources (e.g., laser diodes) arranged in a grid or array that together are capable of providing at least about 25 mW to about 2000 W of total power output. The light source of other embodiments may also comprise sources having power capacities outside of these limits.

[0055] In certain embodiments, the efficacious period of time over which the tissue is being irradiated by the efficacious power density of light is approximately one second, and up to approximately one hour. In various embodiments, the efficacious period of time is at least about 1, 3, 5, 10, 15, 20, 30, 45, 60, 120, 180, 300, 600, 900, 1200, or 3600 seconds, depending on the desired clinical performance. In certain embodiments, the cardiac tissue is irradiated for a time period of preferably about 1 second to about 5 minutes, more preferably about 1 second to about 3 minutes, and most preferably about 3 seconds to about 3 minutes. Other period of time for irradiation are compatible with embodiments described herein. In certain embodiments, the efficacious power density and the efficacious period of time are selected to achieve an efficacious energy density at the target tissue site being treated. In certain such embodiments, the efficacious energy density is in a range between approximately 0.01 mJ/cm² and approximately 27,000 mJ/cm².

[0056] Other parameters can also be varied in the use of phototherapy in accordance with embodiments described herein. These other parameters can contribute to the light energy that is actually delivered to the treated tissue and may play key roles in the efficacy of phototherapy. Certain embodiments include irradiating a selected portion of the heart, while other embodiments irradiate the entire heart. Certain embodiments irradiate the selected portion of the heart or the entire heart by multiple irradiations of selected small portions of the heart in series.

[0057] Positioning the Light Source: Outside the Patient's Torso

[0058] The phototherapy methods for the treatment of the heart described herein may be practiced and described using, for example, a laser therapy apparatus such as that shown and described in U.S. Pat. No. 6,214,035, U.S. Pat. No. 6,267,780, U.S. Pat. No. 6,273,905 and U.S. Pat. No. 6,290,714, which are all incorporated in their entirety by reference herein, as are the references incorporated by reference therein.

[0059] FIGS. 2A-2B schematically illustrate an embodiment of a therapy apparatus 200 comprising a light source

210 configured to be placed outside the patient's torso **220**. In such embodiments, positioning the light source **210** in the operational block **120** comprises placing the light source **210** outside the patient's torso **220** and interposing an element **230** between the light source **210** and the torso **220**. The element **230** inhibits temperature increases at the torso **220** for an efficacious power density at the cardiac tissue being irradiated. In certain embodiments, the element **230** is part of the therapy apparatus **200**, while in other embodiments, the element **230** is separate from the therapy apparatus **200**.

[0060] In certain embodiments, positioning the therapy apparatus **200** on the patient's chest provides access to irradiate selected anterior portions of the heart. In other embodiments, irradiation access to selected posterior portions of the heart is provided by placing the therapy apparatus **200** on the patient's back. Other positions of the therapy apparatus **200** can be used to provide irradiation access to other selected portions of the heart.

[0061] In the embodiment illustrated by FIG. 2A, the therapy apparatus **200** comprises a light source **210** having an output emission area **211** positioned to irradiate a portion of the heart **222** with an efficacious power density and wavelength of light through intervening tissue **224**. The therapy apparatus **200** further comprises an element **230** interposed between the light source **210** and the intervening tissue **224**. The element **230** is configured to inhibit temperature increases at the intervening tissue **224** caused by the light.

[0062] As used herein, the term "element" is used in its broadest sense, including, but not limited to, as a reference to a constituent or distinct part of a composite device. In certain embodiments, the element **230** is configured to contact at least a portion of the patient's torso **220**, as schematically illustrated in FIGS. 2A and 2B. In certain such embodiments, the element **230** is in thermal communication with and covers at least a portion of the torso **220**. In other embodiments, the element **230** is spaced away from the torso **220** and does not contact the torso **220**.

[0063] In certain embodiments, the light passes through the element **230** prior to reaching the torso **220** such that the element **230** is in the optical path of light propagating from the light source **210**, through the skin **221**, and through the bones, tissues, organs, arteries, veins, and fluids of the torso **220** (schematically illustrated in FIG. 2B by the region **223**) to the heart **222**. In certain embodiments, the light passes through a transmissive medium of the element **230**, while in other embodiments, the light passes through an aperture of the element **230**. As described more fully below, the element **230** may be utilized with various embodiments of the therapy apparatus **200**.

[0064] In certain embodiments, the light source **210** is disposed on the interior surface of a housing **240** which fits securely onto the patient's torso **220**. The housing **240** provides structural integrity for the therapy apparatus **200** and holds the light source **210** and element **230** in place. Exemplary materials for the housing **240** include, but are not limited to, metal, plastic, or other materials with appropriate structural integrity. The housing **240** may include an inner lining **242** comprising a stretchable fabric or mesh material, such as Lycra or nylon. The inner lining **242** is configured to contact the torso **220** while remaining outside the propagation path of the light from the light source **210** to the heart

222. In certain embodiments, the light source **210** is configured to be removably attached to the housing **240** in a plurality of positions so that the output emission area **211** of the light source **210** can be advantageously placed in a selected position for treatment of a selected portion of the heart **222**. In other embodiments, the light source **210** can be an integral portion of the housing **240**.

[0065] The light source **210** illustrated by FIG. 2A comprises at least one power conduit **212** coupled to a power source (not shown). In some embodiments, the power conduit **212** comprises an electrical conduit which is configured to transmit electrical signals and power to an emitter (e.g., laser diode or light-emitting diode). In certain embodiments, the power conduit **212** comprises an optical conduit (e.g., optical waveguide) which transmits optical signals and power to the output emission area **211** of the light source **210**. In certain such embodiments, the light source **210** comprises optical elements (e.g., lenses, diffusers, and/or waveguides) which transmit at least a portion of the optical power received via the optical conduit **212**. In still other embodiments, the therapy apparatus **200** contains a power source (e.g., a battery) and the power conduit **212** is substantially internal to the therapy apparatus **200**.

[0066] In certain embodiments, the patient's torso **220** comprises hair and skin which cover the patient's chest. In other embodiments, at least a portion of the hair is removed prior to the phototherapy treatment, so that the therapy apparatus **200** substantially contacts the skin of the torso **220**.

[0067] In certain embodiments, the element **230** is configured to contact the patient's torso **220**, thereby providing an interface between the therapy apparatus **200** and the patient's torso **220**. In certain such embodiments, the element **230** is coupled to the light source **210** and in other such embodiments, the element **230** is also configured to conform to the contours of the torso **220**. In this way, the element **230** positions the output emission area **211** of the light source **210** relative to the torso **220**. In certain such embodiments, the element **230** is mechanically adjustable so as to adjust the position of the light source **210** relative to the torso **220**. By fitting to the torso **220** and holding the light source **210** in place, the element **230** inhibits temperature increases at the torso **220** that would otherwise result from misplacement of the light source **210** relative to the torso **220**. In addition, in certain embodiments, the element **230** is mechanically adjustable so as to fit the therapy apparatus **200** to the patient's torso **220**.

[0068] In certain embodiments, the element **230** provides a reusable interface between the therapy apparatus **200** and the patient's torso **220**. In such embodiments, the element **230** can be cleaned or sterilized between uses of the therapy apparatus **200**, particularly between uses by different patients. In other embodiments, the element **230** provides a disposable and replaceable interface between the therapy apparatus **200** and the patient's torso **220**. By using pre-sterilized and pre-packaged replaceable interfaces, certain embodiments can advantageously provide sterilized interfaces without undergoing cleaning or sterilization processing immediately before use.

[0069] In certain embodiments, the element **230** comprises a container (e.g., a cavity or bag) containing a material (e.g., gel). The container can be flexible and configured to con-

form to the contours of the torso 220. Other exemplary materials contained in the container of the element 230 include, but are not limited to, thermal exchange materials such as glycerol and water. The element 230 of certain embodiments substantially covers a localized portion of the torso 220 in proximity to the irradiated portion of the torso 220.

[0070] In certain embodiments, at least a portion of the element 230 is within an optical path of the light from the light source 210 to the torso 220. In such embodiments, the element 230 is substantially optically transmissive at a wavelength of the light emitted by the output emission area 211 of the light source 210 and is configured to reduce back reflections of the light. By reducing back reflections, the element 230 increases the amount of light transmitted to the heart 222 and reduces the need to use a higher power light source 210 which may otherwise create temperature increases at the torso 220. In certain such embodiments, the element 230 comprises one or more optical coatings, films, layers, membranes, etc. in the optical path of the transmitted light which are configured to reduce back reflections.

[0071] In certain such embodiments, the element 230 reduces back reflections by fitting to the torso 220 so as to substantially reduce air gaps between the torso 220 and the element 230 in the optical path of the light. The refractive-index mismatches between such an air gap and the element 230 and/or the torso 220 would otherwise result in at least a portion of the light propagating from the light source 210 to the heart 222 to be reflected back towards the light source 210.

[0072] In addition, certain embodiments of the element 230 comprise a material having, at a wavelength of light emitted by the light source 210, a refractive index which substantially matches the refractive index of the torso 220 (e.g., about 1.3), thereby reducing any index-mismatch-generated back reflections between the element 230 and the torso 220. Examples of materials with refractive indices compatible with embodiments described herein include, but are not limited to, glycerol, water, and silica gels. Exemplary index-matching gels include, but are not limited to, gels available from Nye Lubricants, Inc. of Fairhaven, Mass. and "Scan Ultrasound Gel," Ref. 11-08, from Parker Laboratories, Inc. of Fairfield, N.J.

[0073] In certain embodiments, the element 230 is configured to cool the torso 220 by removing heat from the torso 220 so as to inhibit temperature increases at the torso 220. In certain such embodiments, the element 230 comprises a reservoir (e.g., a chamber or a conduit) configured to contain a coolant. The coolant flows through the reservoir near the torso 220. The torso 220 heats the coolant, which flows away from the torso 220, thereby removing heat from the torso 220 by active cooling. The coolant in certain embodiments circulates between the element 230 and a heat transfer device, such as a chiller, whereby the coolant is heated by the torso 220 and is cooled by the heat transfer device. Exemplary materials for the coolant include, but are not limited to, water or air.

[0074] In certain embodiments, the element 230 comprises a container 231 (e.g., a flexible bag) coupled to an inlet conduit 232 and an outlet conduit 233, as schematically illustrated in FIG. 3. A flowing material (e.g., water, air, or glycerol) can flow into the container 231 from the inlet

conduit 232, absorb heat from the torso 220, and flow out of the container 231 through the outlet conduit 233. Certain such embodiments can provide a mechanical fit of the container 231 to the torso 220 and sufficient thermal coupling to prevent excessive heating of the torso 220 by the light. In certain embodiments, the container 231 can be disposable and replacement containers 231 can be used for subsequent patients.

[0075] In still other embodiments, the element 230 comprises a container (e.g., a flexible bag) containing a non-flowing material which does not flow out of the container but is thermally coupled to the torso 220 so as to remove heat from the torso 220 by passive cooling. Exemplary materials include, but are not limited to, water, glycerol, and gel. In certain such embodiments, the non-flowing material can be pre-cooled (e.g., by placement in a refrigerator) prior to the phototherapy treatment to facilitate cooling of the torso 220.

[0076] In certain embodiments, the element 230 is configured to apply pressure to at least a portion of the skin 221 of the torso 220 in the optical path of the light. By applying sufficient pressure, the element 230 can blanch the portion of the skin 221 by forcing at least some blood out the optical path of the light. The blood removal resulting from the pressure applied by the element 230 to the skin 221 decreases the corresponding absorption of the light by blood in the skin 221 of the torso 220. As a result, temperature increases due to absorption of the light by blood at the skin 221 of the torso 220 are reduced. As a further result, in certain embodiments, the fraction of the light transmitted to the subdermal target tissue of the heart 222 is increased.

[0077] FIGS. 4A and 4B schematically illustrate embodiments of the element 230 configured to facilitate the blanching of the skin 221 of the torso 220. In the cross-sectional view of a portion of the therapy apparatus 200 schematically illustrated in FIG. 4A, certain element portions 234 contact the skin 221 and other element portions 235 are spaced away from the skin 221. The element portions 234 contacting the skin 221 provide an optical path for light to propagate from the light source 210 to the torso 220. The element portions 234 contacting the skin 221 also apply pressure to the skin 221, thereby forcing blood out from beneath the element portion 234. FIG. 4B schematically illustrates a similar view of an embodiment in which the light source 210 comprises a plurality of light sources 210a, 210b, 210c.

[0078] FIG. 5A schematically illustrates one embodiment of the cross-section along the line 5-5 of FIG. 4B. The element portions 234 contacting the skin 221 comprise ridges extending along one direction, and the element portions 235 spaced away from the skin 221 comprise troughs extending along the same direction. In certain embodiments, the ridges are substantially parallel to one another and the troughs are substantially parallel to one another. FIG. 5B schematically illustrates another embodiment of the cross-section along the line 5-5 of FIG. 4B. The element portions 234 contacting the skin 221 comprise a plurality of projections in the form of a grid or array. More specifically, the portions 234 are rectangular and are separated by element portions 235 spaced away from the skin 221, which form troughs extending in two substantially perpendicular directions. The portions 234 of the element 230 contacting the skin 221 can be a substantial fraction of the total area of the element 230.

[0079] FIGS. 6A-6C schematically illustrate an embodiment in which light emitted by the light sources 210 propagates from the light sources 210 through the intervening tissue 224, including the skin 221, of the torso 220 to the heart 222 and disperses in a direction generally parallel to the skin 221, as shown in FIG. 6A. While FIG. 6A shows the light sources 210 and the element 230 spaced away from the torso 220, in other embodiments, the element 230 contacts the torso 220. The light sources 210 are preferably spaced sufficiently far apart from one another such that the light emitted from each light source 210 overlaps with the light emitted from the neighboring light sources 210 at the heart 222. FIG. 6B schematically illustrates this overlap as the overlap of circular spots 225 at a reference depth at or below the surface of the heart 222. FIG. 6C schematically illustrates this overlap as a graph of the power density at the reference depth of the heart 222 along the line L-L of FIGS. 6A and 6B. Summing the power densities from the neighboring light sources 210 (shown as a dashed line in FIG. 6C) serves to provide a more uniform light distribution at the tissue to be treated. In such embodiments, the summed power density is preferably less than a damage threshold of the heart 222 and above an efficacy threshold.

[0080] In certain embodiments, the element 230 is configured to diffuse the light prior to reaching the torso 220. FIGS. 7A and 7B schematically illustrate the diffusive effect on the light by the element 230. An exemplary energy density profile of the light emitted by a light source 210, as illustrated by FIG. 7A, is peaked at a particular emission angle. After being diffused by the element 230, as illustrated by FIG. 7B, the energy density profile of the light does not have a substantial peak at any particular emission angle, but is substantially evenly distributed among a range of emission angles. By diffusing the light emitted by the light source 210, the element 230 distributes the light energy substantially evenly over the area to be illuminated, thereby inhibiting "hot spots" which would otherwise create temperature increases at the torso 220. In addition, by diffusing the light prior to its reaching the torso 220, the element 230 can effectively increase the spot size of the light impinging the skin 221 of the torso 220, thereby advantageously lowering the power density at the torso 220, as described more fully below. In addition, in embodiments with multiple light sources 210, the element 230 can diffuse the light to alter the total light output distribution to reduce inhomogeneities.

[0081] In certain embodiments, the element 230 provides sufficient diffusion of the light such that the power density of the light is less than a maximum tolerable level of the torso 220 and heart 222. In certain other embodiments, the element 230 provides sufficient diffusion of the light such that the power density of the light equals a therapeutic value at the target tissue. The element 230 can comprise exemplary diffusers including, but are not limited to, holographic diffusers such as those available from Physical Optics Corp. of Torrance, Calif. and Display Optics P/N SN1333 from Reflexite Corp. of Avon, Conn.

[0082] In certain embodiments in which a plurality of light sources 210 are used, the light sources 210 are selectively activated individually or in groups to provide predetermined irradiation patterns on the torso 220. These irradiation patterns can comprise irradiated areas and non-irradiated areas, which in certain embodiments, are varied as functions of time. In addition, the light sources 210 can be pulsed in

selected groups or all together. This selective irradiation can be used to reduce the thermal load on particular locations of the torso 220 by limiting the amount of irradiation to any one particular area of the torso 220. Thus, the thermal load at the torso 220 due to the absorption of the light can be distributed across the torso 220, thereby avoiding unduly heating one or more portions of the torso 220. In certain embodiments, the irradiated area is a substantial fraction of the total area of the heart, and in other embodiments, the irradiated area includes the total area of the heart. As described more fully below, in certain embodiments, the selective irradiation can be used to reduce the amount of scattering and absorption of the light by the lungs during the treatment procedure.

[0083] FIG. 8A schematically illustrates another embodiment of the therapy apparatus 300 which comprises the housing 240 and a light source comprising a light-emitting blanket 310. FIG. 8B schematically illustrates an embodiment of the blanket 310 comprising a flexible substrate 311 (e.g., flexible circuit board), a power conduit interface 312, and a sheet formed by optical fibers 314 positioned in a fan-like configuration. FIG. 8C schematically illustrates an embodiment of the blanket 310 comprising a flexible substrate 311, a power conduit interface 312, and a sheet formed by a plurality of optical fibers 314 woven into a mesh. The blanket 310 is preferably positioned within the housing 240 so as to cover an area of the torso 220 corresponding to a portion of the heart 222 to be treated.

[0084] In certain such embodiments, the power conduit interface 312 is configured to be coupled to an optical fiber conduit 313 which provides optical power to the blanket 310. The optical power interface 312 of certain embodiments comprises a beam splitter or other optical device which distributes the incoming optical power among the various optical fibers 314. In other embodiments, the power conduit interface 312 is configured to be coupled to an electrical conduit which provides electrical power to the blanket 310. In certain such embodiments, the power conduit interface 312 comprises one or more laser diodes, the output of which is distributed among the various optical fibers 314 of the blanket 310.

[0085] In certain other embodiments, the blanket 310 comprises an electroluminescent sheet which responds to electrical signals from the power conduit interface 312 by emitting light. In such embodiments, the power conduit interface 312 comprises circuitry configured to distribute the electrical signals to appropriate portions of the electroluminescent sheet.

[0086] The side of the blanket 310 nearer the torso 220 is preferably provided with a light scattering surface, such as a roughened surface to increase the amount of light scattered out of the blanket 310 towards the torso 220. The side of the blanket 310 further from the torso 220 is preferably covered by a reflective coating so that light emitted away from the torso 220 is reflected back towards the torso 220. This configuration is similar to configurations used for the "back illumination" of liquid-crystal displays (LCDs). Other configurations of the blanket 310 are compatible with embodiments described herein.

[0087] In certain embodiments, the light source 210 generates light which cause eye damage if viewed by an individual. In such embodiments, the apparatus 200 can be configured to provide eye protection so as to avoid viewing

of the light by individuals. For example, opaque materials can be appropriately placed to block the light from being viewed directly. In addition, interlocks can be provided so that the light source **210** is not activated unless the apparatus **200** is in place, or other appropriate safety measures are taken.

[0088] Another suitable phototherapy apparatus in accordance with embodiments described here is illustrated in FIG. 9. The illustrated therapy apparatus **400** includes a light source **410**, an element **430**, and a flexible strap **440** configured for securing the therapy apparatus **400** over an area of the patient's torso. The light source **410** can be disposed on the strap **440** itself, or in a housing **450** coupled to the strap **440**. The light source **410** preferably comprises a plurality of diodes **410a, 410b, . . .** capable of emitting light energy having a wavelength in the visible to near-infrared wavelength range. The element **430** is configured to be positioned between the light source **410** and the patient's torso **220**.

[0089] The therapy apparatus **400** further includes a power supply (not shown) operatively coupled to the light source **410**, and a programmable controller **460** operatively coupled to the light source **410** and to the power supply. The programmable controller **460** is configured to control the light source **410** so as to deliver a predetermined power density to the target cardiac tissue. In certain embodiments, as schematically illustrated in FIG. 9, the light source **410** comprises the programmable controller **460**. In other embodiments the programmable controller **460** is a separate component of the therapy apparatus **400**.

[0090] In certain embodiments, the strap **440** comprises a loop of elastomeric material sized appropriately to fit snugly onto the patient's torso **220**. In other embodiments, the strap **440** comprises an elastomeric material to which is secured any suitable securing means **470**, such as mating Velcro strips, buckles, snaps, hooks, buttons, ties, or the like. The precise configuration of the strap **440** is subject only to the limitation that the strap **440** is capable of maintaining the light source **410** in a selected position so that light energy emitted by the light source **410** is directed towards the targeted cardiac tissue.

[0091] In the exemplary embodiment illustrated in FIG. 9, the housing **450** comprises a layer of flexible plastic or fabric that is secured to the strap **440**. In other embodiments, the housing **450** comprises a plate or an enlarged portion of the strap **440**. Various strap configurations and spatial distributions of the light sources **410** are compatible with embodiments described herein so that the therapy apparatus **400** can treat selected portions of cardiac tissue.

[0092] In still other embodiments, a therapy apparatus **500** for delivering the light energy includes a handheld probe **505**, as schematically illustrated in FIG. 10. The probe **505** includes a light source **510** and an element **530** as described herein.

[0093] Positioning the Light Source: Within the Torso

[0094] FIGS. 1A and 11B schematically illustrate embodiments of a therapy apparatus **600** configured to be inserted into the esophagus **602** of the patient. The therapy apparatus **600** comprises a flexible probe **605** and a light source **610** located on a distal end **620** of the probe **605**. In certain embodiments, as illustrated by FIG. 11A, the distal

end **620** of the probe **605** is configured to contact a surface **603** of the esophagus **602**. In certain such embodiments, the distal end **620** of the probe **605** further comprises an element **630** interposed between the light source **610** and the surface **603** of the esophagus **602**. As described above in relation to embodiments positioned outside the torso, the element **630** is configured to inhibit temperature increases at the esophagus **602** for an efficacious power density at the cardiac tissue.

[0095] In certain other embodiments, as illustrated by FIG. 11B, the esophagus **602** contains a material **640** which serves as the element **630**. In certain embodiments, the material **640** (e.g., water) has a refractive index which substantially matches the refractive index of the inside surface **603** of the esophagus **602**, thereby reducing any index-mismatch-generated back reflections between the distal end **620** and the esophagus **602**. In addition, the material **640** can provide cooling to the esophagus **602** to inhibit temperature increases. The material **640** can also advantageously diffuse the light from the light source **610**.

[0096] By inserting the therapy apparatus **600** into the esophagus **602**, the therapy apparatus **600** can treat portions of the heart which are not accessible by other embodiments described herein. For example, upon insertion into the esophagus **602**, the light source **610** of the therapy apparatus **600** is closer to the cardiac tissue to be irradiated than in embodiments with a light source positioned outside the torso. Thus, the therapy apparatus **600** can provide phototherapy using lower initial power densities since there is less intervening tissue to absorb or scatter the light. In addition, such embodiments can more easily irradiate selected posterior portions of the heart.

[0097] FIG. 12 schematically illustrates an embodiment of a therapy apparatus **700** configured to be inserted into a blood vessel **702** of the patient. The therapy apparatus **700** comprises a catheter **705** and a light source **710** located on a distal end **720** of the catheter **705**. In certain embodiments, the catheter **705** is introduced into either an artery or a vein and positioned so that the light source **710** is in proximity to cardiac tissue. The catheter **705** is introduced interfemorally in certain embodiments by inserting the catheter **705** into a femoral artery. The catheter **705** is introduced interclavicularly in certain other embodiments by inserting the catheter **705** into a clavicular artery. By placing the light source **710** in proximity to the cardiac tissue to be irradiated, such embodiments avoid having the light absorbed or scattered by intervening tissue such as the lungs. An exemplary catheter is described by U.S. Pat. No. 6,443,974 issued to Oron et al., which is incorporated in its entirety by reference herein.

[0098] FIG. 13A schematically illustrates an embodiment of a therapy apparatus **800** configured to avoid a portion of intervening tissue between the therapy apparatus **800** and the heart **222**. The therapy apparatus **800** comprises at least one light source **810** which comprises at least one needle **820**. In certain embodiments, the needle **820** comprises an optical fiber **822** that has a first end **823** optically coupled to the light source **810**, as illustrated in FIG. 13A. The needle **820** is positioned so that a second end **824** of the optical fiber **822** is inserted into the torso **220**. By transmitting light from the light source **810** into the torso **220**, such embodiments avoid scattering or absorption by a portion of the intervening tissue of the torso **220**.

[0099] In certain embodiments, the needle **820** is inserted through at least a portion of the skin of the patient's torso

220. In certain such embodiments, the second end **824** of the optical fiber **822** is past the skin **221** of the torso **220**, thereby avoiding scattering or absorption by the skin **221** of light transmitted to the heart **222**. In other embodiments, the second end **824** is inserted deeper into the torso **220**, past portions of bone, muscles, and other tissue, so that these tissues do not scatter or absorb the light transmitted from the therapy apparatus **800** to the heart **222**. In still other embodiments, the second end **824** is inserted such that the needle **820** does not puncture the pericardium surrounding the heart **222**. Other positions of the needle **820** are compatible with embodiments described herein.

[0100] FIG. 13B schematically illustrates an embodiment of the therapy apparatus **800** with a plurality of transdermal needles **820**. In the embodiment illustrated by FIG. 13B, each needle **820** itself is optically transmissive at the wavelength of light from the light source **810**. Thus, each needle **820** serves as a portion of an optical fiber **822** with a second end **824** inserted into the torso **220**. In certain embodiments, each needle **820** comprises a lumen or other conduit through which the light from the light source **810** is transmitted into the torso **220**.

[0101] Each needle **820** extends through at least a portion of the skin **221** of the torso **220**. In such embodiments, the light emitted from the second end **824** of the optical fiber **822** avoids scattering or absorption by the outermost layers of the skin **221**. In certain such embodiments, the needles **820** extend approximately halfway through the muscle wall of the chest to be within approximately 3 millimeters of bone. The needles **820** are preferably biocompatible and strong enough to withstand the insertion process.

[0102] Exemplary needles **820** in accordance with embodiments described herein include silicon microneedles, such as those described by U.S. Pat. No. 5,928,207 issued to Pisano et al. and U.S. Pat. No. 6,187,210 issued to Lebouitz et al., each of which is incorporated by reference herein. Other exemplary microneedles are described by Brazile et al. in "Active Microneedles with Integrated Functionality," Technical Digest of the 2000 Solid-State Sensor and Actuator Workshop, Hilton Head Isl., S.C., 06/04-08/00, Transducer Research Foundation, Cleveland (2000), pp. 199-202, which is incorporated in its entirety by reference herein.

[0103] In certain embodiments, phototherapy is performed by directly irradiating the cardiac tissue after a sufficient opening has been made in the chest. In certain such embodiments, the opening is made for a cardiac bypass surgical procedure. The phototherapy can provide a cardio-protective, healing-accelerating mechanism. The phototherapy can be performed before, during, after, or a combination thereof, the bypass surgical procedure. In other embodiments, the opening is made expressly for placing the therapy apparatus in proximity to the heart **222**. In certain such embodiments, the intervening tissue is at a minimum, while in other embodiments in which the therapy apparatus contacts the target cardiac tissue, the intervening tissue is effectively nonexistent.

[0104] In still other embodiments, at least a portion of the therapy apparatus is implanted within the torso **220** in proximity to the heart **222**. Such "pacemaker"-type embodiments can deliver light to a selected portion of the heart **222** while minimizing the scattering and absorption by intervening tissue. Such embodiments can implant a light source

comprising a small laser or one or more battery-operated light-emitting diodes and use the light source to irradiate a selected portion of the heart.

[0105] In other embodiments, the blood can be irradiated within an artery (e.g., by placing a laser or an optical fiber within the artery). The irradiated blood then has more ATP which gets to the heart. In other embodiments, the blood can be removed from the body, irradiated outside the body, and returned to the body to carry ATP to the heart.

[0106] Directing Light Onto Cardiac Tissue: Power Density

[0107] Phototherapy for the treatment of cardiac tissue after a myocardial infarction (MI) is based in part on the discovery that power density (i.e., power per unit area or number of photons per unit area per unit time) and energy density (i.e., energy per unit area or number of photons per unit area or power density multiplied by the exposure time) of the light energy applied to tissue are significant factors in determining the relative efficacy of low level phototherapy. Contrary to previous understanding in the prior art, efficacy is not as directly related to the total power or the total energy delivered to the tissue. This discovery is particularly applicable with respect to treating and saving surviving but endangered cardiac tissue in a zone of danger surrounding the primary infarct after an MI. Preferred methods described herein are based at least in part on the finding that, given a selected wavelength of light energy, it is the power density and/or the energy density of the light delivered to cardiac tissue (as opposed to the total power or total energy delivered to the cardiac tissue) that appears to be important factors in determining the relative efficacy of phototherapy in treating patients after experiencing an MI.

[0108] Without being bound by theory, it is believed that light energy delivered within a certain range of power densities and energy densities provides the desired biostimulative effect on the intracellular environment, such that proper function is returned to previously nonfunctioning or poorly functioning mitochondria in at-risk cardiac cells. The biostimulative effect may include interactions with chromophores within the target tissue, which facilitate production of ATP thereby feeding energy to injured cells which have experienced decreased blood flow due to the MI. Because MIs correspond to blockages or other interruptions of blood flow to portions of the heart, it is thought that any effects of increasing blood flow by phototherapy are of less importance in the efficacy of phototherapy for MI victims. Further information regarding the role of power density and exposure time in phototherapy is described by Hans H.F.I. van Breugel and P. R. Dop Bär in "Power Density and Exposure Time of He-Ne Laser Irradiation Are More Important Than Total Energy Dose in Photo-Biomodulation of Human Fibroblasts In Vitro," Lasers in Surgery and Medicine, Volume 12, pp. 528-537 (1992), which is incorporated in its entirety by reference herein.

[0109] In embodiments described herein, an efficacious power density of light is directed onto cardiac tissue. In certain such embodiments, a cardioprotective-effective power density of light is provided to a patient that has experienced an ischemic event in the heart, thereby providing a cardioprotective effect.

[0110] As used herein, the term "cardiodegeneration" refers to the process of cardiac cell destruction resulting

from primary destructive events such as MI, as well as from secondary, delayed and progressive destructive mechanisms that are invoked by cells due to the occurrence of the primary destructive event. Primary destructive events include disease processes or physical injury or insult, including MI, but also include other diseases and conditions such as physical trauma or acute injury or insult. Secondary destructive mechanisms include any mechanism that leads to the generation and release of molecules toxic to cardiac cells, including apoptosis, depletion of cellular energy stores because of changes in mitochondrial membrane permeability, release or failure in the reuptake of excessive glutamate, reperfusion injury, and activity of cytokines and inflammation. Both primary and secondary mechanisms contribute to forming a “zone of danger” for cardiac cells, wherein the cardiac cells in the zone have at least temporarily survived the primary destructive event, but are at risk of dying due to processes having delayed effect.

[0111] As used herein, the term “cardioprotection” refers to a therapeutic strategy for slowing or preventing the otherwise irreversible loss of cardiac cells due to cardiodegeneration after a primary destructive event, whether the cardiodegeneration loss is due to disease mechanisms associated with the primary destructive event or secondary destructive mechanisms.

[0112] As used herein, the term “cardioprotective-effective” refers to a characteristic of an amount of light energy. A cardioprotective-effective amount of light energy achieves the goal of preventing, avoiding, reducing, or eliminating cardiodegeneration. In certain embodiments, a cardioprotective-effective amount is a power density of the light energy measured in mW/cm^2 , while in other embodiments, a cardioprotective-effective amount is an energy density of the light energy measured in mJ/cm^2 .

[0113] Thus, in certain embodiments, a method of phototherapy involves delivering a cardioprotective-effective amount of light energy having a wavelength in the visible to near-infrared wavelength range to a target area of the patient’s heart 222. In certain embodiments, the target area of the patient’s heart 222 includes the area of infarct, i.e. to cardiac cells within the “zone of danger.”

[0114] In other embodiments, the target area includes portions of the heart 222 not within the zone of danger. In certain such embodiments, irradiation of healthy cardiac cells outside the zone of danger can treat and save surviving but endangered cardiac cells in the zone of danger surrounding the infarcted area. Without being bound by theory, it is believed that irradiation of healthy tissue in proximity to the zone of danger increases the production of ATP and copper ions in the healthy tissue and which then migrate to the injured cells within the region surrounding the infarct, thereby producing beneficial effects. Additional information regarding the biomedical mechanisms or reactions involved in phototherapy is provided by Tiina I. Karu in “*Mechanisms of Low-Power Laser Light Action on Cellular Level*”, Proceedings of SPIE Vol. 4159 (2000), Effects of Low-Power Light on Biological Systems V, Ed. Rachel Lubart, pp. 1-17, which is incorporated in its entirety by reference herein.

[0115] The significance of the power density used in phototherapy has ramifications with regard to the devices and methods used in phototherapy treatments of cardiac tissue, as schematically illustrated by FIGS. 14A and 14B,

which show the effects of scattering by intervening tissue. Further information regarding the scattering of light by tissue is provided by V. Tuchin in “*Tissue Optics: Light Scattering Methods and Instruments for Medical Diagnosis*”, SPIE Press (2000), Bellingham, Wash., pp. 3-11, which is incorporated in its entirety by reference herein.

[0116] FIG. 14A schematically illustrates a light beam 900 impinging a portion 910 of a patient’s torso 220 and propagating through the patient’s torso 220 to irradiate a portion 920 of the patient’s heart 222. In the exemplary embodiment of FIG. 14A, the light beam 900 impinging the torso 220 has a circular cross-section with a radius of 2 centimeters and a cross-sectional area of approximately 12.5 cm^2 . For comparison purposes, FIG. 14B schematically illustrates a light beam 930 having a significantly smaller cross-section impinging a smaller portion 940 of the torso 220 to irradiate a portion 950 of the heart 222. The light beam 930 impinging the torso 220 in FIG. 14B has a circular cross-section with a radius of 1 centimeter and a cross-sectional area of approximately 3.1 cm^2 . The cross-sections and radii of the light beams 900, 930 illustrated in FIGS. 14A and 14B are exemplary; other light beams with other parameters are also compatible with embodiments described herein. In particular, similar considerations apply to focussed beams, collimated beams, or diverging beams, as they are similarly scattered by the intervening tissue.

[0117] As shown in FIGS. 14A and 14B, the cross-sections of the light beams 900, 930 become larger while propagating through the torso 220 due to scattering from interactions with tissue. The light beams 900, 930 propagate through various tissue portions, each with a characteristic angle of dispersion, with the light beams 900, 930 experiencing an effective angle of dispersion. Assuming that the effective angle of dispersion is 15 degrees and the irradiated cardiac tissue of the heart 220 is 7 centimeters below the surface of the torso 220, the resulting area of the portion 920 of the heart 222 irradiated by the light beam 900 in FIG. 14A is approximately 45.6 cm^2 . Similarly, the resulting area of the portion 950 of the heart 222 irradiated by the light beam 930 in FIG. 14B is approximately 24.8 cm^2 .

[0118] Irradiating the portion 920 of the heart 222 with a power density of 10 mW/cm^2 corresponds to a total power within the portion 920 of approximately 456 mW ($10 \text{ mW/cm}^2 \times 45.6 \text{ cm}^2$). Assuming only approximately 0.5% of the light beam 900 is transmitted between the surface of the torso 220 and the heart 222, the incident light beam 900 at the surface of the torso 220 will have a total power of approximately 91200 mW ($456 \text{ mW}/0.005$) and a power density of approximately 7300 mW/cm^2 ($91200 \text{ mW}/12.5 \text{ cm}^2$). Similarly, irradiating the portion 950 of the heart 222 with a power density of 10 mW/cm^2 corresponds to a total power within the portion 950 of approximately 248 mW ($10 \text{ mW/cm}^2 \times 24.8 \text{ cm}^2$), and with the same 0.5% transmittance, the incident light beam 950 at the surface of the torso 220 will have a total power of approximately 49600 mW ($248 \text{ mW}/0.005$) and a power density of approximately 15790 mW/cm^2 ($49600 \text{ mW}/3.1 \text{ cm}^2$). These calculations are summarized in Table 1.

TABLE 1

	2 cm Spot Size (FIG. 14A)	1 cm Spot Size (FIG. 14B)
<u>Surface of Torso:</u>		
Area	12.5 cm ²	3.1 cm ²
Total power	91200 mW	49600 mW
Power density	7300 mW/cm ²	15790 mW/cm ²
<u>Heart:</u>		
Area	45.6 cm ²	24.8 cm ²
Total power	456 mW	248 mW
Power density	10 mW/cm ²	10 mW/cm ²

[0119] These exemplary calculations illustrate that to obtain a desired power density at the heart 222, higher total power at the surface of the torso 220 can be used in conjunction with a larger spot size at the surface of the torso 220. Thus, by increasing the spot size at the surface of the torso 220, a desired power density at the heart 222 can be achieved with lower power densities at the surface of the torso 220 which can reduce the possibility of overheating the torso 220. In certain embodiments, the light can be directed through an aperture to define the illumination of the torso 220 to a selected smaller area.

[0120] Directing Light Onto Cardiac Tissue: Other Parameters

[0121] In certain embodiments, delivering the cardioprotective amount of light energy includes selecting an initial power density of the light energy at the torso 220 corresponding to the predetermined efficacious power density at the target area of the heart 222. As described above, light propagating through tissue is scattered and absorbed by the tissue. Calculations of the initial power density to be applied to the torso 220 so as to deliver a predetermined efficacious power density to the selected target area of the heart 222 preferably take into account the attenuation of the light energy as it propagates through the skin and other tissues, such as bone and lung tissue. Factors known to affect the attenuation of light propagating to the heart 222 include, but are not limited to, skin pigmentation, the presence and color of hair over the area to be treated, amount of fat tissue, body size, breast size, the presence of bruised or scarred tissue, amount of pericardial fluid, presence of other materials (e.g., sutures) in the intervening tissue, and the location of the target area of the heart 222, particularly the depth of the area relative to the surface of the torso 220. For example, for higher levels of skin pigmentation (with correspondingly higher absorptions), the power density applied to the torso 220 should be higher so as to deliver a predetermined power density of light energy to a selected portion of the heart 222. In addition, the power density selected to be applied to the target area of the patient's heart 222 can depend on other factors, including, but not limited to, the wavelength of the applied light, the type and location of the injury to the heart 222, and the patient's clinical condition.

[0122] The target area of the patient's heart 222 to be irradiated can be previously identified by using standard medical imaging techniques. In certain embodiments, treatment includes calculating an initial power density which corresponds to a preselected power density at the target area of the patient's heart 222. The calculation of certain embodi-

ments includes some or all of the factors listed above that affect the penetration of the light energy through the torso 220 and thus the power density at the target area. The power density of light energy to be delivered to the target area of the patient's heart 222 may also be adjusted to be combined with any other therapeutic agent or agents, especially pharmaceutical cardioprotective agents, to achieve the desired biological effect. In such embodiments, the selected power density can also depend on the additional therapeutic agent or agents chosen. The power density and other parameters of the applied light are then adjusted according to the results of the calculation.

[0123] These other parameters can include the timing pattern of the phototherapy. In certain embodiments, the light energy is preferably delivered for at least one treatment period of at least about five minutes, and more preferably for at least one treatment period of at least ten minutes. In other embodiments, the treatment proceeds continuously for a period of about 10 seconds to about 2 hours, more preferably for a period of about 1 minute to about 10 minutes, and most preferably for a period of about 1 minute to about 5 minutes.

[0124] In certain embodiments, the light energy is pulsed during the treatment period, while in other embodiments, the light energy is continuously applied during the treatment period. If the light is pulsed, the pulse widths are preferably at least about 10 nanoseconds, and are more preferably in a range between approximately 100 microseconds and approximately 20 milliseconds. In certain embodiments, the pulses occur at a frequency of up to about 100 kHz. Continuous wave light may also be used.

[0125] In certain embodiments, the treatment may be terminated after one treatment period, while in other embodiments, the treatment may be repeated for at least two treatment periods. The time between subsequent treatment periods is preferably at least about five minutes, more preferably at least about 1 to 2 days, and most preferably at least about one week. In certain embodiments in which treatment is performed over the course of multiple days, the therapy apparatus is wearable over multiple concurrent days. The length of treatment time and frequency of treatment periods can depend on several factors, including the functional recovery of the patient and the results of imaging analysis of the infarct. In certain embodiments, one or more treatment parameters can be adjusted in response to a feedback signal from a device (e.g., electrocardiogram or magnetic resonance imaging) monitoring the patient.

[0126] In certain embodiments, the therapy pattern is selected to reduce the amount of scattering and absorption of the light by the lungs during the treatment procedure. Lung tissue surrounds a large fraction of the heart 222 and the lung tissue can be a significant source of scatter and absorption. For example, the lungs are substantially opaque at wavelengths of approximately 810 nanometers. However, during breathing, the lungs move back and forth such that the fraction of the heart 222 occluded from a light source by the lungs varies. Thus, in certain embodiments, irradiation occurs during those portions of the breathing cycle at which the lungs comprise a minimum fraction of the intervening tissue between the light source and the heart 222.

[0127] The thrombolytic therapies currently in use for treatment of MI are typically begun within a few hours of the MI. However, many hours often pass before a person who

has suffered an MI receives medical treatment, so the short time limit for initiating thrombolytic therapy excludes many patients from treatment. In contrast, phototherapy treatment of MI appears to be more effective if treatment begins no earlier than several hours after the ischemic event has occurred. Consequently, the present methods of phototherapy may be used to treat a greater percentage of MI patients.

[0128] In certain embodiments, a method provides a cardioprotective effect in a patient that had an ischemic event in the heart. The method comprises identifying a patient who has experienced an ischemic event in the heart. The method further comprises estimating the time of the ischemic event. The method further comprises commencing administration of a cardioprotective effective amount of light energy to the heart. The administration of the light energy is commenced no earlier than about two hours following the time of the ischemic event. In certain embodiments, phototherapy treatment can be efficaciously performed preferably within 24 hours after the ischemic event occurs, and more preferably no earlier than three hours following the ischemic event, and most preferably no earlier than five hours following the ischemic event. In certain embodiments, one or more of the treatment parameters can be varied depending on the amount of time that has elapsed since the ischemic event.

[0129] Without being bound by theory, it is believed that the benefit in delaying treatment occurs because of the time needed for induction of ATP production, and/or the possible induction of angiogenesis in the region surrounding the infarct. Thus, in accordance with one preferred embodiment, the phototherapy for the treatment of MI occurs preferably about 6 to 24 hours after the onset of MI symptoms, more preferably about 12 to 24 hours after the onset of symptoms. It is believed, however, that if treatment begins after about 2 days, its effectiveness will be greatly reduced.

[0130] In certain embodiments, the phototherapy is combined with other types of treatments for an improved therapeutic effect. Treatment can comprise directing light through the torso 220 of the patient to a target area of the heart 222 concurrently with applying an electromagnetic field to the heart. In such embodiments, the light has an efficacious power density at the target area and the electromagnetic field has an efficacious field strength. For example, the therapy apparatus can also include systems for electromagnetic treatment, e.g., as described in U.S. Pat. No. 6,042,531 issued to Holcomb, which is incorporated in its entirety by reference herein. In certain embodiments, the electromagnetic field comprises a magnetic field, while in other embodiments, the electromagnetic field comprises a radio-frequency (RF) field. As another example, treatment can comprise directing an efficacious power density of light through the torso 220 of the patient to a target area of the heart 222 concurrently with applying an efficacious amount of ultrasonic energy to the heart 222. Such a system can include systems for ultrasonic treatment, e.g., as described in U.S. Pat. No. 5,054,470 issued to Fry et al., which is incorporated in its entirety by reference herein.

[0131] Directing Light Onto Cardiac Tissue: Therapy Apparatus Control

[0132] FIG. 15 is a block diagram of a control circuit 1000 comprising a programmable controller 1010 coupled to a light source 1005 according to embodiments described

herein. The control circuit 1000 is configured to adjust the power of the light energy emitted by the light source 1005 to generate a predetermined energy delivery profile, such as a predetermined subsurface power density, to the target area of the heart 222. In certain embodiments, the control circuit 1000 is also configured to adjust other parameters of the phototherapy, including but not limited to, pulsing of the light, number, frequency, and duration of treatment periods, pattern of irradiation applied to the patient, wavelengths of the light, and the magnitude, timing, and duration of the application of other sources of energy (e.g., magnetic, RF, ultrasonic) to the heart.

[0133] In certain embodiments, the programmable controller 1010 comprises a logic circuit 1020, a clock 1030 coupled to the logic circuit 1020, and an interface 1040 coupled to the logic circuit 1020. The clock 1030 of certain embodiments provides a timing signal to the logic circuit 1020 so that the logic circuit 1020 can monitor and control timing intervals of the applied light. Examples of timing intervals include, but are not limited to, total treatment times, pulselength times for pulses of applied light, and time intervals between pulses of applied light. In certain embodiments, the light source 1005 can be selectively turned on and off to reduce the thermal load at the torso 220 and to deliver a selected power density to the target cardiac tissue. In addition, in embodiments using a plurality of light sources, the light sources can be selectively activated to provide a predetermined pattern of irradiation.

[0134] The interface 1040 of certain embodiments provides signals to the logic circuit 1020 which the logic circuit 1020 uses to control the applied light. The interface 1040 can comprise a user interface or an interface to a sensor monitoring at least one parameter of the treatment. In certain such embodiments, the programmable controller 1010 is responsive to signals from the sensor to preferably adjust the treatment parameters to optimize the measured response. The programmable controller 1010 can thus provide closed-loop monitoring and adjustment of various treatment parameters to optimize the phototherapy. The signals provided by the interface 1040 from a user are indicative of parameters that may include, but are not limited to, patient characteristics (e.g., skin type, fat percentage), selected applied power densities, target time intervals, and power density/timing profiles for the applied light.

[0135] In certain embodiments, the logic circuit 1020 is coupled to a light source driver 1050. The light source driver 1050 is coupled to a power supply 1060, which in certain embodiments comprises a battery and in other embodiments comprises an alternating current source. The light source driver 1050 is also coupled to the light source 1005. The logic circuit 1020 is responsive to the signal from the clock 1030 and to user input from the user interface 1040 to transmit a control signal to the light source driver 1050. In response to the control signal from the logic circuit 1020, the light source driver 1050 adjusts and controls the power applied to the light source 1005. Other control circuits besides the control circuit 1000 of FIG. 15 are compatible with embodiments described herein.

[0136] In certain embodiments, the logic circuit 1020 is responsive to signals from a sensor monitoring at least one parameter of the treatment to control the applied light. For example, certain embodiments comprise a temperature sen-

sor thermally coupled to the torso **220** to provide information regarding the temperature of the torso **220** to the logic circuit **1020**. In such embodiments, the logic circuit **1020** is responsive to the information from the temperature sensor to transmit a control signal to the light source driver **1050** so as to adjust the parameters of the applied light to maintain the temperature at the torso **220** below a predetermined level. Other embodiments include exemplary biomedical sensors including, but not limited to, an electrocardiograph sensor, a blood flow sensor, a blood gas (e.g., oxygenation) sensor, an ATP production sensor, or a cellular activity sensor. Such biomedical sensors can provide real-time feedback information to the logic circuit **1020**. In certain such embodiments, the logic circuit **1020** is responsive to signals from the sensors to preferably adjust the parameters of the applied light to optimize the measured response. The logic circuit **1020** can thus provide closed-loop monitoring and adjustment of various parameters of the applied light to optimize the phototherapy.

EXAMPLE

Phototherapy on Neurons

[0137] While the following description recounts the irradiation of neurons with an efficacious power density of light, it serves as an example of the phototherapy technique in general. An *in vitro* experiment was done to demonstrate one effect of phototherapy on neurons, namely the effect on ATP production. Normal Human Neural Progenitor (NHNP) cells were obtained cryopreserved through Clonetics of Baltimore, Md., catalog # CC-2599. The NHNP cells were thawed and cultured on polyethyleneimine (PEI) with reagents provided with the cells, following the manufacturers' instructions. The cells were plated into 96 well plates (black plastic with clear bottoms, Becton Dickinson of Franklin Lakes, N.J.) as spheroids and allowed to differentiate into mature neurons over a period of two weeks.

[0138] A Photo Dosing Assembly (PDA) was used to provide precisely metered doses of laser light to the NHNP cells in the 96 well plates. The PDA included a Nikon Diaphot inverted microscope (Nikon of Melville, N.Y.) with a LUDL motorized x,y,z stage (Ludl Electronic Products of Hawthorne, N.Y.). An 808 nanometer laser was routed into the rear epi-fluorescent port on the microscope using a custom designed adapter and a fiber optic cable. Diffusing lenses were mounted in the path of the beam to create a "speckled" pattern, which was intended to mimic *in vivo* conditions after a laser beam passed through human skin. The beam diverged to a 25 millimeter diameter circle when it reached the bottom of the 96 well plates. This dimension was chosen so that a cluster of four adjacent wells could be lasered at the same time. Cells were plated in a pattern such that a total of 12 clusters could be lasered per 96 well plate. Stage positioning was controlled by a Silicon Graphics workstation and laser timing was performed by hand using a digital timer. The measured power density passing through the plate for the NHNP cells was 50 mW/cm².

[0139] Two independent assays were used to measure the effects of 808 nanometer laser light on the NHNP cells. The first was the CellTiter-Glo Luminescent Cell Viability Assay (Promega of Madison, Wis.). This assay generates a "glow-type" luminescent signal produced by a luciferase reaction with cellular ATP. The CellTiter-Glo reagent is added in an

amount equal to the volume of media in the well and results in cell lysis followed by a sustained luminescent reaction that was measured using a Reporter luminometer (Turner Biosystems of Sunnyvale, Calif.). Amounts of ATP present in the NHNP cells were quantified in Relative Luminescent Units (RLUs) by the luminometer.

[0140] The second assay used was the alamarBlue assay (Biosource of Camarillo, Calif.). The internal environment of a proliferating cell is more reduced than that of a non-proliferating cell. Specifically, the ratios of NADPH/NADP, FADH/FAD, FMNH/FMN and NADH/NAD, increase during proliferation. Laser irradiation is also thought to have an effect on these ratios. Compounds such as alamarBlue are reduced by these metabolic intermediates and can be used to monitor cellular states. The oxidization of alamarBlue is accompanied by a measurable shift in color. In its unoxidized state, alamarBlue appears blue; when oxidized, the color changes to red. To quantify this shift, a 340PC microplate reading spectrophotometer (Molecular Devices of Sunnyvale, Calif.) was used to measure the absorbance of a well containing NHNP cells, media and alamarBlue diluted 10% v/v. The absorbance of each well was measured at 570 nanometers and 600 nanometers and the percent reduction of alamarBlue was calculated using an equation provided by the manufacturer.

[0141] The two metrics described above, (RLUs and % Reduction) were then used to compare NHNP culture wells that had been lasered with 50 mW/cm² at a wavelength of 808 nanometers. For the CellTiter-Glo assay, 20 wells were lasered for 1 second and compared to an unlased control group of 20 wells. The CellTiter-Glo reagent was added 10 minutes after lasering completed and the plate was read after the cells had lysed and the luciferase reaction had stabilized. The average RLUs measured for the control wells was 3808+/-3394 while the laser group showed a two-fold increase in ATP content to 7513+/-6109. The standard deviations were somewhat high due to the relatively small number of NHNP cells in the wells (approximately 100 per well from visual observation), but a student's unpaired t-test was performed on the data with a resulting p-value of 0.02 indicating that the two-fold change is statistically significant.

[0142] The alamarBlue assay was performed with a higher cell density and a lasing time of 5 seconds. The plating density (calculated to be between 7,500-26,000 cells per well based on the certificate of analysis provided by the manufacturer) was difficult to determine since some of the cells had remained in the spheroids and had not completely differentiated. Wells from the same plate can still be compared though, since plating conditions were identical. The alamarBlue was added immediately after lasering and the absorbance was measured 9.5 hours later. The average measured values for percent reduction were 22%+/-7.3% for the 8 lasered wells and 12.4%+/-5.9% for the 3 unlased control wells (p-value=0.076). These alamarBlue results support the earlier findings in that they show a similar positive effect of the laser treatment on the cells.

[0143] Increases in cellular ATP concentration and a more reduced state within the cell are both related to cellular metabolism and are considered to be indications that the cell is viable and healthy. These results are novel and significant in that they show the positive effects of laser irradiation on cellular metabolism in *in-vitro* neuronal cell cultures.

[0144] The explanations and illustrations presented herein are intended to acquaint others skilled in the art with the invention, its principles, and its practical application. Those skilled in the art may adapt and apply the invention in its numerous forms, as may be best suited to the requirements of a particular use. Accordingly, the specific embodiments of the present invention as set forth are not intended as being exhaustive or limiting of the invention.

What is claimed is:

1. A method of treating a patient's heart, the method comprising:

providing a light source which emits light having an initial power density;

positioning the light source relative to the patient's heart with intervening tissue of the patient between the light source and the patient's heart; and

directing light onto cardiac tissue of the patient's heart from the light source through the intervening tissue without damaging the intervening tissue, the cardiac tissue being irradiated by an efficacious power density of light for an efficacious period of time.

2. The method of claim 1, wherein the efficacious power density is an average power density of at least about 0.01 mW/cm².

3. The method of claim 1, wherein the efficacious power density is an average power density of at least about 10 mW/cm².

4. The method of claim 1, wherein the efficacious power density is an average power density between about 10 mW/cm² and about 150 mW/cm².

5. The method of claim 1, wherein the light has a wavelength between about 590 nanometers and about 3000 nanometers.

6. The method of claim 1, wherein the light has a wavelength between about 780 nanometers and about 1064 nanometers.

7. The method of claim 1, wherein the light has a wavelength between about 780 nanometers and about 840 nanometers.

8. The method of claim 1, wherein the light source emits light having a first wavelength and light having a second wavelength, the light having the first wavelength being transmitted concurrently with the light having the second wavelength to the cardiac tissue.

9. The method of claim 1, wherein the light source emits light having a first wavelength and light having a second wavelength, the light having the first wavelength being transmitted sequentially with the light having the second wavelength to the cardiac tissue.

10. The method of claim 1, wherein the light emitted by the light source is pulsed.

11. The method of claim 1, wherein the light has an initial average power density between about 10 mW/cm² and about 10 W/cm² prior to being transmitted through the intervening tissue.

12. The method of claim 1, wherein positioning the light source comprises placing the light source outside the patient's torso and interposing an element between the light source and the torso, the element inhibiting temperature increases at the torso for an efficacious power density at the cardiac tissue.

13. The method of claim 1, wherein positioning the light source comprises placing the light source within the patient's esophagus.

14. The method of claim 1, wherein the light source comprises at least one needle which provides a conduit for light from the light source, and positioning the light source comprises inserting the needle through at least a portion of the skin of the patient's torso.

15. The method of claim 1, further comprising a catheter with the light source located on a distal end of the catheter, wherein positioning the light source comprises introducing the catheter into an artery or a vein such that the light sensor is in proximity to cardiac tissue.

16. The method of claim 15, wherein the catheter is introduced interfemorally.

17. The method of claim 15, wherein the catheter is introduced interclavicularly.

18. The method of claim 1, wherein directing light onto cardiac tissue is performed during portions of the patient's breathing cycle in which the patient's lungs comprise a minimum fraction of the intervening tissue.

19. The method of claim 1, further comprising directing the light onto the cardiac tissue for at least one treatment period of at least about ten minutes.

20. The method of claim 1, further comprising directing the light onto the cardiac tissue for at least one treatment period of at least about five minutes.

21. The method of claim 1, further comprising directing the light onto the cardiac tissue for a first treatment period and for a second treatment period commenced subsequent to the completion of the first treatment period.

22. The method of claim 21, wherein commencement of the second treatment period occurs at least about five minutes after completion of the first treatment period.

23. The method of claim 21, wherein commencement of the second treatment period occurs at least one week after completion of the first treatment period.

24. A method for treating a patient's heart, the method comprising introducing light of an efficacious power density onto a target area of the heart by directing light having an initial power density through intervening tissue of the patient, wherein the light has a plurality of wavelengths, and the efficacious power density is at least 0.01 mW/cm² at the target area.

25. The method of claim 24, further comprising determining the initial power density to be introduced so as to deliver the efficacious power density, said determining based on at least one characteristic indicative of attenuation of light by the intervening tissue.

26. The method of claim 25, wherein the characteristic is selected from a group consisting of: skin pigmentation, presence and color of hair over the target area, amount of fat tissue, body size, breast size, presence of bruised or scarred tissue, amount of pericardial fluid, presence of other materials within the intervening tissue, and the location of the target area of the heart.

27. A method of treating a patient's heart following a myocardial infarction, the method comprising applying low-level light therapy to the heart no earlier than about two hours following the myocardial infarction.

28. The method of claim 27, wherein the low-level light therapy is applied to the heart no earlier than three hours following the myocardial infarction.

29. A method of providing a cardioprotective effect in a patient having a ischemic event in the heart, the method comprising:

identifying a patient who has experienced an ischemic event in the heart;

estimating the time of the ischemic event; and

commencing administration of a cardioprotective effective amount of light energy to the heart no less than about two hours following the time of the ischemic event.

30. The method of claim 29, wherein commencing administration of a cardioprotective effective amount of light energy to the heart occurs no less than about three hours following the time of the ischemic event.

31. The method of claim 29, wherein commencing administration of a cardioprotective effective amount of light energy to the heart occurs no less than about five hours following the time of the ischemic event.

32. A method for treating a patient's heart, the method comprising directing an efficacious power density of light through intervening tissue of the patient to a target area of the heart concurrently with applying an electromagnetic field to the heart, the electromagnetic field having an efficacious field strength.

33. The method of claim 32, wherein the electromagnetic field is a magnetic field.

34. The method of claim 32, wherein the electromagnetic field is a radio-frequency (RF) field.

35. A method for treating a patient's heart, the method comprising directing an efficacious power density of light through intervening tissue of the patient to a target area of the heart concurrently with applying an efficacious amount of ultrasonic energy to the heart.

36. A therapy apparatus for treating a patient's heart, the therapy apparatus comprising:

a light source having an output emission area positioned to irradiate a portion of the heart with an efficacious power density and wavelength of light through intervening tissue; and

an element interposed between the light source and the intervening tissue, the element configured to inhibit temperature increases at the intervening tissue caused by the light.

37. The therapy apparatus of claim 36, further comprising a controller coupled to the light source and configured to selectively energize the light source.

38. The therapy apparatus of claim 37, wherein the controller is configured to selectively energize the light source so as to irradiate a predetermined area of the heart.

39. The therapy apparatus of claim 38, wherein the predetermined area of the heart is a substantial fraction of the total area of the heart.

40. The therapy apparatus of claim 36, wherein the light source provides coherent light.

41. The therapy apparatus of claim 40, wherein the coherent light emitted by the light source has intensity spikes due to speckling from coherent interference.

42. The therapy apparatus of claim 36, wherein the light source comprises a laser diode.

43. The therapy apparatus of claim 36, wherein the light source comprises a plurality of laser diodes.

44. The therapy apparatus of claim 36, wherein the light source comprises a light-emitting diode.

45. The therapy apparatus of claim 36, wherein the light source comprises a light-emitting blanket placed outside the patient's torso.

46. The therapy apparatus of claim 45, wherein the blanket comprises a plurality of optical fibers.

47. The therapy apparatus of claim 45, wherein the blanket comprises an electroluminescent sheet.

48. The therapy apparatus of claim 36, wherein the light source is positioned outside the patient's torso and the element is configured to contact the patient's torso.

49. The therapy apparatus of claim 48, wherein the element provides a disposable and replaceable interface between the therapy apparatus and the patient's torso.

50. The therapy apparatus of claim 48, wherein the element comprises a bag containing a material and is configured to conform to contours of the torso.

51. The therapy apparatus of claim 48, wherein at least a portion of the element is in an optical path of the light from the light source to the torso.

52. The therapy apparatus of claim 51, wherein the element is substantially optically transmissive at the wavelength and is configured to reduce back reflections of the light.

53. The therapy apparatus of claim 51, wherein the element is configured to fit to the torso so as to substantially reduce air gaps in the optical path of the light between the torso and the element.

54. The therapy apparatus of claim 51, wherein the element comprises a material having a refractive index which substantially matches a refractive index of the torso.

55. The therapy apparatus of claim 54, wherein the material comprises glycerol.

56. The therapy apparatus of claim 54, wherein the material comprises silica gel.

57. The therapy apparatus of claim 48, wherein the element is coupled to the light source and is configured to conform to the torso so as to position the output emission area of the light source relative to the torso.

58. The therapy apparatus of claim 48, wherein the element is coupled to the light source and is mechanically adjustable so as to adjust a position of the light source relative to the torso.

59. The therapy apparatus of claim 48, wherein the element is configured to cool the torso by removing heat from the torso.

60. The therapy apparatus of claim 59, wherein the element comprises a reservoir configured to contain a coolant which flows through the reservoir near the torso, is heated by the torso, and which flows away from the torso.

61. The therapy apparatus of claim 60, wherein the coolant circulates between the element and a heat transfer device, whereby the coolant is heated by the torso and cooled by the heat transfer device.

62. The therapy apparatus of claim 60, wherein the coolant comprises water.

63. The therapy apparatus of claim 60, wherein the coolant comprises air.

64. The therapy apparatus of claim 59, wherein the element comprises a non-flowing material which is thermally coupled to the torso.

65. The therapy apparatus of claim 64, wherein the non-flowing material is pre-cooled prior to treatment of the heart.

66. The therapy apparatus of claim 64, wherein the non-flowing material comprises a gel.

67. The therapy apparatus of claim 48, wherein the element is configured to apply pressure to at least a portion of the skin of the torso in the optical path of the light, thereby blanching the portion of the skin of the torso and decreasing absorption of the light by the portion of the skin of the torso.

68. The therapy apparatus of claim 36, wherein the element is configured to diffuse the light prior to reaching the torso.

69. The therapy apparatus of claim 36, wherein the element comprises at least one needle which provides a conduit for light from the light source, the needle being configured to be inserted through at least a portion of the skin of a patient's torso.

70. The therapy apparatus of claim 36, further comprising a flexible probe wherein the light source is located on a distal end of the probe, the probe configured to be inserted into the patient's esophagus.

71. The therapy apparatus of claim 70, wherein the element comprises water contained in the esophagus.

72. A therapy apparatus for treating a patient's heart, the therapy apparatus comprising:

a light source configured to irradiate at least a portion of the heart with an efficacious power density and wavelength of light;

a biomedical sensor configured to provide real-time feedback information; and

a controller coupled to the light source and the biomedical sensor, the controller configured to adjust said light source in response to the real-time feedback information.

73. The therapy apparatus of claim 72, wherein the biomedical sensor comprises an electrocardiograph sensor, a blood flow sensor, a blood oxygenation sensor, an ATP production sensor, an electrocardiogram sensor, or a cellular activity sensor.

74. A therapy apparatus for treating a patient's heart, the therapy apparatus comprising an implantable light source configured to irradiate at least a portion of the heart with an efficacious power density and wavelength of light.

75. A method of treating a patient's heart, the method comprising:

implanting a light source within the patient; and
irradiating at least a portion of the heart with an efficacious power density and wavelength of light from the implanted light source.

76. A therapy apparatus for treating a patient's heart, the therapy apparatus comprising a light source configured to irradiate at least a portion of the patient's blood with an efficacious power density and wavelength of light prior to the blood flowing to the heart.

77. A method of treating a patient's heart, the method comprising irradiating at least a portion of the patient's blood with an efficacious power density and wavelength of light and allowing the irradiated blood to flow to the heart.

* * * * *



US 20100280563A1

(19) **United States**

(12) **Patent Application Publication**

Norlin-Weissenrieder et al.

(10) **Pub. No.: US 2010/0280563 A1**

(43) **Pub. Date: Nov. 4, 2010**

(54) **DEVICE AND METHOD FOR DETECTING
AND TREATING A MYOCARDIAL
INFARCTION USING
PHOTOBIMODULATION**

(86) PCT No.: **PCT/SE07/00194**

§ 371 (c)(1),
(2), (4) Date: **May 20, 2010**

(76) Inventors: **Anne Norlin-Weissenrieder,
Stockholm (SE); Leda Henriquez,
Bandhagen (SE); Hans
Strandberg, Sundbyberg (SE); Eva
Hartström, Hasselby (SE); Mikael
Sjögren, Fjardhundra (SE); Annika
Naeslund, Bromma (SE); Johan
Eckerdal, Knivsta (SE)**

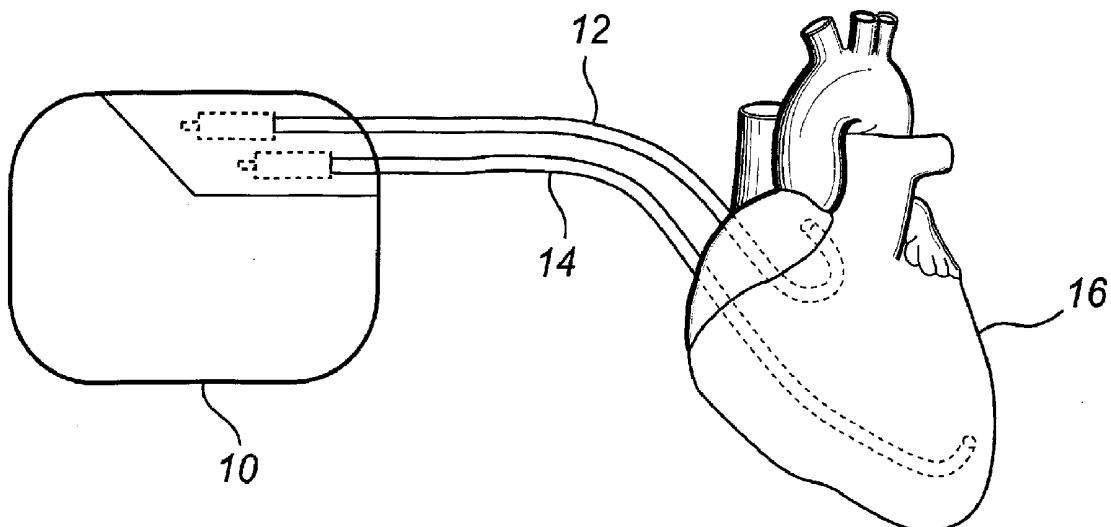
Publication Classification

(51) **Int. Cl.
A61N 1/362** (2006.01)

(52) **U.S. Cl. 607/3**

(57) **ABSTRACT**

In an implantable medical device and a method for treating cardiac tissue of a heart of a patient with therapeutic light, a myocardial infarction is detected and a location the myocardial infarction is identified. A therapy session is initiated by selectively activating one or more of a number of light emitting units arranged in at least one medical lead connectable to the implantable medical device, to emit therapeutic light toward the detected location of the myocardial infarction upon detection of an occurrence of the myocardial infarction.



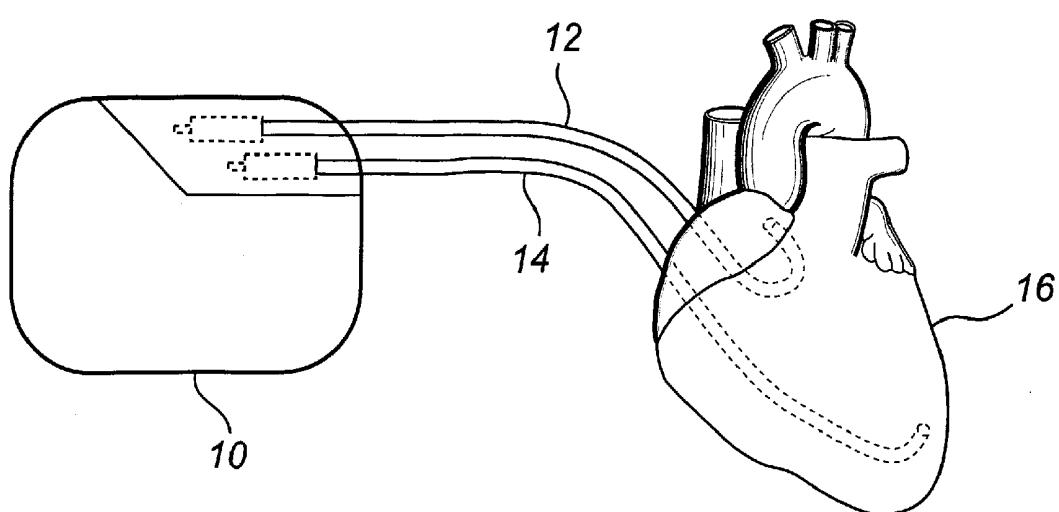


Fig. 1

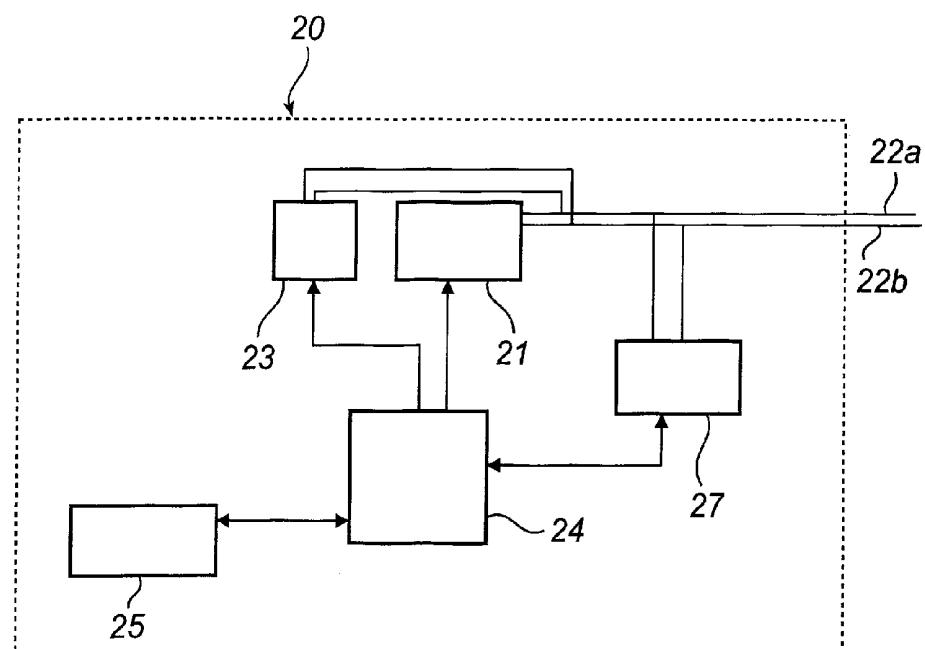


Fig. 2a

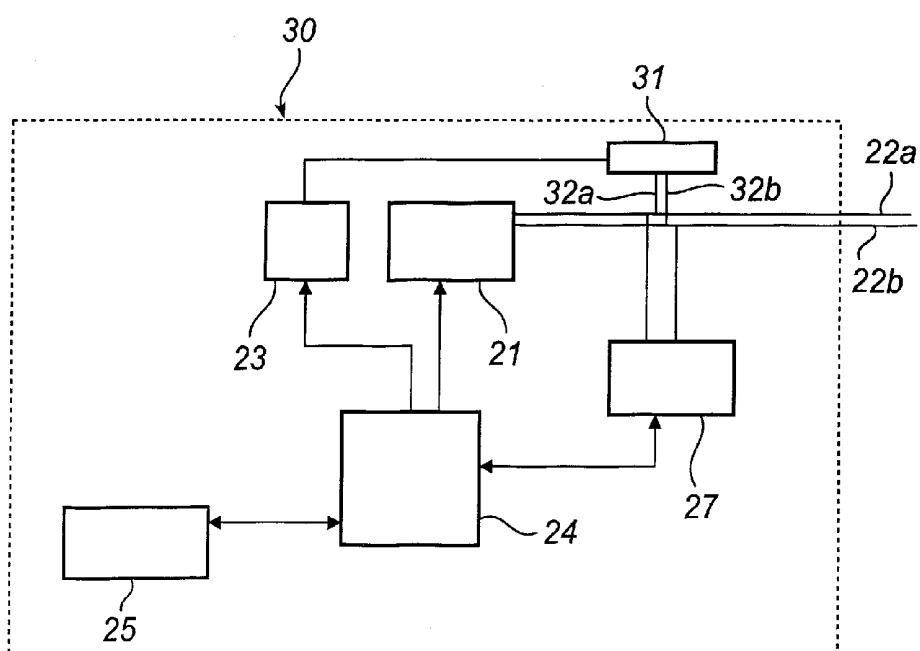


Fig. 2b

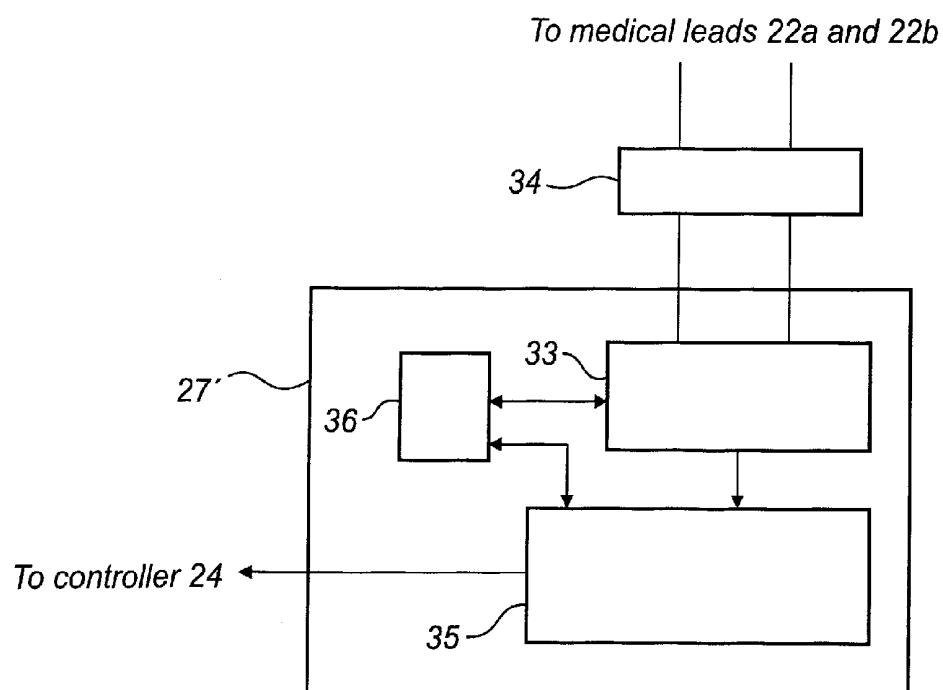


Fig. 3a

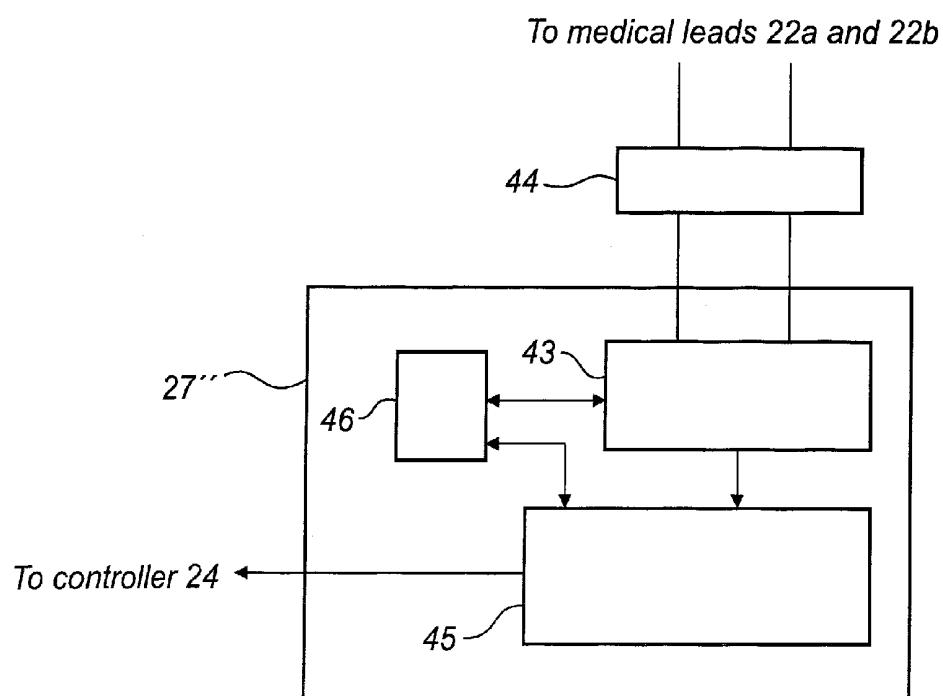


Fig. 3b

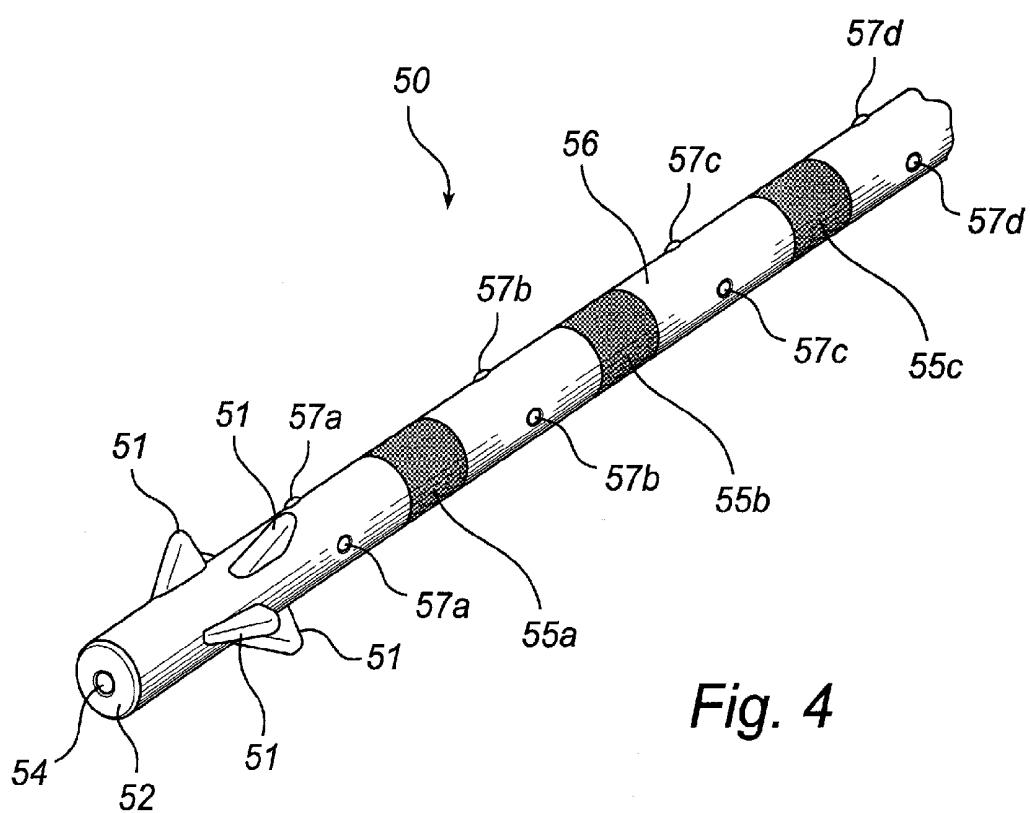


Fig. 4

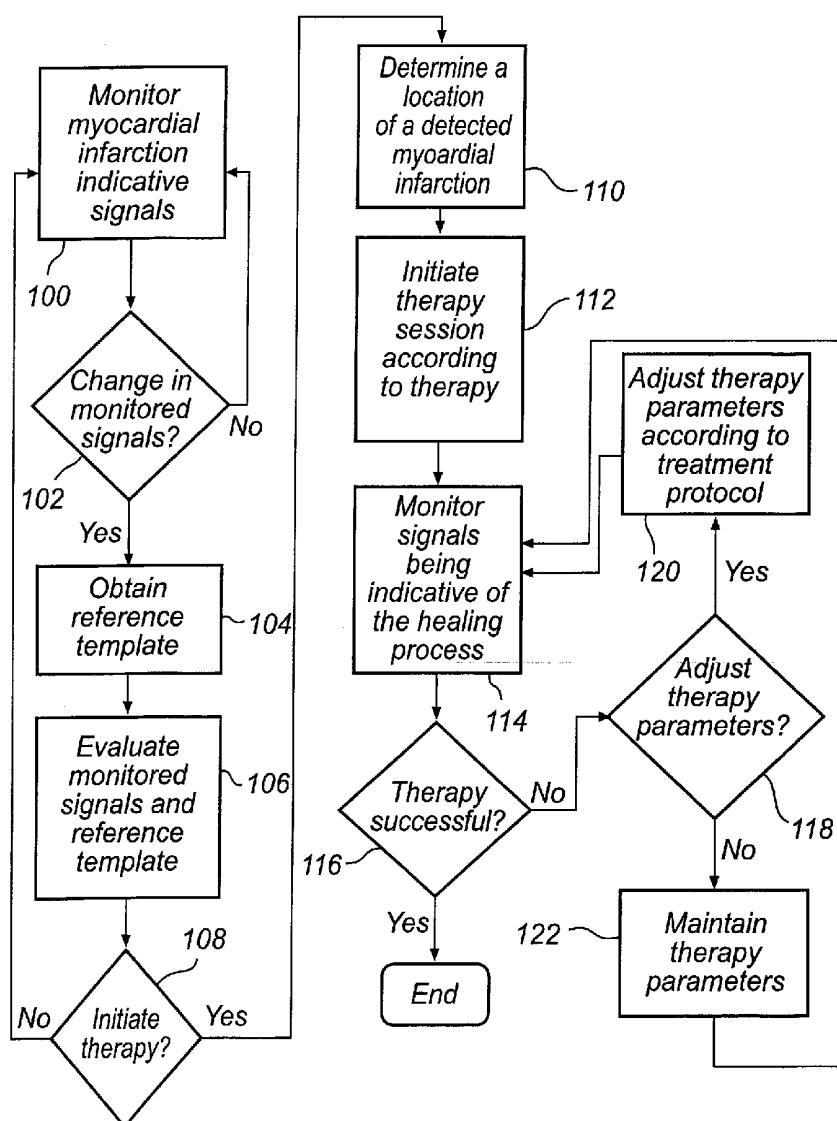


Fig. 5

DEVICE AND METHOD FOR DETECTING AND TREATING A MYOCARDIAL INFARCTION USING PHOTOBIMODULATION

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

[0002] The present invention generally relates to cardiac pacing systems and, in particular, to methods and medical devices for detecting and treating myocardial infarctions.

[0003] 2. Description of the Prior Art

[0004] Due to the in general poorer medical status of pacemaker and ICD patients they are subjected to an increased risk of myocardial infarction (MI). The term myocardial infarction refers to the death of myocardial or heart tissue caused by a partial or complete blockage of one of the arteries that supply blood to the heart (coronary arteries), resulting in an interruption in the blood supply to the heart. In the classical acute MI there is a sudden occlusion of a coronary artery due to thrombosis resulting in the death of part of either the right or left ventricular wall. The thrombus occurs due to atherosomatous changes in the blood vessel wall.

[0005] When heart tissue is deprived of blood-borne oxygen for longer than 30 minutes (called ischemia), it begins to die. Ischemia causes electrical instability within the chambers of the heart, preventing the heart from adequately pumping blood throughout the body.

[0006] Cardiac repair after MI is a complex process involving diverse inflammatory components, extracellular matrix remodelling and responses of the cardiomyocytes to ischemia. After necrosis of the cardiomyocytes and a long inflammatory phase, the ischemic zone is subsequently replaced by fibrotic tissue. This permanent damage of the heart muscle increases the risk of developing congestive heart failure (CHF).

[0007] It is critical to begin treatment of the areas affected by ischemia as soon as possible after the myocardial infarction. Intensive research over the last 20 or more years has demonstrated that prompt treatment can decrease damage from a heart attack and increase the chance for survival. If such therapy is initiated within 1 hour of the onset of symptoms, less irreparable damage may occur.

[0008] In light of this, a number of approaches have been made to detect and/or to treat myocardial infarction in implantable medical devices such as pacing devices. For example, in EP 467 695 A2 a method and apparatus for detecting and treating myocardial infarctions in antitachyarrhythmia and bradycardia pacing devices are disclosed. Electrical activity of the patient's heart is sensed and signalled in order to detect the presence of an MI and a thrombolytic drug is released into the bloodstream upon such detection. Thus, this solution improves the supply of blood at the detection of an MI but, however, it does not treat potential damages of the cardiac tissue caused by the MI.

[0009] In EP 1 384 433, by the same applicant, a monitor for early detection of an ischemic heart disease of a patient using intracardiac impedance is shown. According to this solution, the impedance changes due to the increased stiffness of the cardiac tissue caused by the ischemic heart disease are detected. However, EP 1 384 433 is not concerned with the treatment of a detected ischemia.

[0010] Furthermore, EP 1 690 566, U.S. Pat. No. 6,604,000 and U.S. Pat. No. 6,256,538 also present implantable medical

devices incorporating an ischemia detector responsive to measured intracardiac impedance.

[0011] US 2004/0260367 shows a method for treating a detected myocardial infarction of a patient's heart. According to this solution, a light source adapted to generate therapeutic light in the visible to near-infra-red wavelength range using so called low level light therapy ("LLLT") or phototherapy is positioned relative to the patient's heart on the torso of the patient. The therapeutic light penetrates the intervening tissue and the cardiac tissue is irradiated according to a treatment protocol. Thus, the solution according to US 2004/0260367 is impaired with the problem that a detection of the myocardial infarction and a determination of the location of the myocardial infarction are required before the treatment can be initiated. As discussed above, the heart tissue begins to die if it is deprived of blood-borne oxygen for longer than 30 minutes and hence it is critical to begin treatment of the areas affected by ischemia as soon as possible after the myocardial infarction. Therefore, the cardiac tissue may already have been affected with damages, which may be irreparable, when the treatment can be initiated.

[0012] Thus, there remains a need within the art of a method and medical device that are capable of detecting the occurrence and location of a myocardial infarction and initiating a treatment of the cardiac tissue suffering from the myocardial infarction subsequently to the detection.

SUMMARY OF THE INVENTION

[0013] An object of the present invention is to detect the occurrence and location of a myocardial infarction is detected and to administer a treatment to the cardiac tissue suffering from the myocardial infarction is initiated.

[0014] According to another object of the present invention, the occurrence and location of a myocardial infarction is automatically detected and a treatment of the cardiac tissue suffering from the myocardial infarction is automatically initiated subsequently to the detection.

[0015] According to a further object of the present invention, a commencement of a myocardial infarction and the location of the myocardial infarction can be detected at an early stage.

[0016] According to an aspect of the present invention, there is provided an implantable medical device including a pulse generator emits cardiac stimulating pulses and that is connectable to at least one medical lead for delivering the pulses to cardiac tissue of a heart of a patient. The implantable medical device has a myocardial infarction detection means, which myocardial infarction detection unit that detects a myocardial infarction and identifies a location of the myocardial infarction. Further, the implantable medical device has therapy circuitry connected to a number of light emitting units arranged in the at least one medical lead adapted to emit therapeutic light, and a control circuit connected to the myocardial infarction detection unit and to the light emitting units, the control circuit being configured to initiate a therapy session in which one or more of the light emitting units is/are selectively activated to emit the therapeutic light toward a detected location of the myocardial infarction upon detection of an occurrence of the myocardial infarction.

[0017] According to a second aspect of the present invention, there is provided a method for treating cardiac tissue of a heart of a patient with therapeutic light using an implantable medical device including a pulse generator adapted to pro-

duce cardiac stimulating pacing pulses and being connectable to at least one medical lead for delivering the pulses to cardiac tissue of a heart of a patient. The method includes the steps of intracorporeally detecting a myocardial infarction and identifying a location of the myocardial infarction, and initiating a therapy session by selectively activating one or more of a number of intracorporeally placed light emitting units arranged in the at least one medical lead to emit therapeutic light toward the detected location of the myocardial infarction upon detection of an occurrence of the myocardial infarction.

[0018] According to a third aspect of the present invention, there is provided a computer-readable medium, directly loadable into an internal memory of an implantable medical device according to the first aspect of the present invention, encoded with software code that causes the implantable medical device to perform steps in accordance with a method according to the second aspect of the present invention.

[0019] The invention utilizes the technique photobiomodulation, also called Low Level Laser Therapy (LLLT), Cold Laser Therapy (CLT), Laser Biomodulation, phototherapy or Laser therapy, wherein certain wavelengths of light at certain intensities are delivered for a certain amount of time. More specifically, the present invention is based on the insight of using such therapeutic light to treat cardiac tissue after a myocardial infarction. This is based upon the findings that photobiomodulation has been proven to be a successful therapy in wound healing see, for example, "Effect of NASA light-emitting diode irradiation on wound healing", H. T. Whelan et al., Journal of Clinical Laser Medicine and Surgery, 19, (2001) p 305. It was also confirmed by Whelan et al. that the cell growth of various cell types in human and rat could be increased by up to 200% by irradiation of light of certain wavelengths. Furthermore, it has also been shown, for example, in "Low energy laser irradiation reduces formation of scar tissue after myocardial infarction in rats and dogs", U. Oron, et al., Circulation, 103, (2001), p 296, that light therapy improves the regeneration of the cardiac cells and decreases the scar tissue formation following a myocardial infarction.

[0020] Thus, the present invention provides a number of advantages, for example, an occurrence and location of a myocardial infarction can be detected at an early stage and the treatment of the myocardial infarction can thus be initiated at an early stage. This is of high importance since it has been shown that it is critical to initiate the treatment of the areas of cardiac tissue affected by ischemia as soon as possible after the myocardial infarction. Intensive research over the last 20 or more years has demonstrated that prompt treatment may decrease damage from a heart attack and increase the chance for survival. If a therapy is initiated within 1 hour of the onset of the infarct, less irreparable damage may occur. A further advantage of the present invention is that the regeneration of cardiac cells after a myocardial infarction is improved.

[0021] According to an embodiment, the therapy circuit is adapted to activate the light emitting unit or units to emit the therapeutic light according to a treatment protocol, wherein the treatment protocol includes treatment parameters comprising: emitting intervals of the therapeutic light, intensity of the emitted therapeutic light, wavelength of the emitted light, and/or intermittence of the emitted therapeutic light.

[0022] In one embodiment, each of the light emitting units is formed by at least one light emitting diode. The light emitting units, according to other embodiments, may be arranged in an array along an outer surface of a lead body of respective medical lead.

[0023] According to an embodiment of the present invention, the electrodes are arranged in an array along the outer surface of a lead body of respective medical lead.

[0024] In a further embodiment, each of the light emitting units includes at least one optical fiber adapted to conduct light emitted from at least one light source arranged in the implantable medical device, and the therapy circuit selectively activates the at least one light source and/or at least one optical fibre such that light conducted in one or more optical fibres emanates from the one or more optical fibers toward the detected location.

[0025] The at least one light source may be a laser source adapted to emit coherent and monochromatic light having a wavelength in the range of 600 nm-1000 nm. Furthermore, in one embodiment, an intensity of 1-500 mW/cm² and a total dosage of about 1-4 J/cm² are applied. In another embodiment, an intensity of 6-50 mW/cm² and a total dosage of about 1-4 J/cm² may be applied.

[0026] According to an embodiment of the present invention, the myocardial infarction detection unit includes an impedance measuring circuit connected to the electrodes arranged in the medical leads. The impedance measuring device is adapted to apply excitation current pulses between respective electrode pairs including at least a first and at least a second electrode and to measure the impedance in the tissues between the at least first and the at least second electrode of the electrode pairs to the excitation current pulses. Further, the myocardial infarction detection means includes a myocardial infarct detector adapted to evaluate the measured impedances by detecting changes in the impedances being consistent with a myocardial infarction and to determine a location of the myocardial infarction using the evaluation. The impedance measuring circuit may measure the impedance between a number of different combinations of electrodes. The impedance measuring circuit may be adapted to periodically initiate impedance measuring sessions according to a myocardial infarction monitoring protocol, wherein the impedance between different pairs of electrodes is measured according to a predetermined sequence (e.g. one pair after another during consecutive cardiac cycles or all pairs simultaneously during a number of consecutive cardiac cycles) to be able to detect and locate a myocardial infarction. That is, during each impedance measuring session, a number of impedance measurements from the different electrode pairs are obtained. Consequently, it is possible to continuously monitor the cardiac tissue to enable a reliable detection of the occurrence and location of a myocardial infarction.

[0027] According to embodiments of the present invention, the myocardial infarct detector compares measured impedances with a stored reference impedance template to detect an occurrence of a myocardial infarction and a location of the myocardial infarction from the result of the comparison. The template may alternatively be obtained or created by the myocardial infarction detection means during a period when no changes of the monitored signals, e.g. impedance or electrical activity of the cardiac tissue, are of a sufficient magnitude to indicate the possibility of the commencement of a condition such as a myocardial infarction. Such a template may also be updated periodically by performing new measurements of the impedance and/or the electrical activity.

[0028] In one example, impedance value ratios for a cardiac cycle is determined by determining a maximum impedance and a minimum impedance, respectively, measured by the impedance measuring circuit during a cardiac cycle. Further,

an impedance value ratio being below a predetermined impedance value ratio threshold is determined to be consistent with a myocardial infarction; and the impedance value ratio being smallest of the impedance value ratios being below the predetermined impedance value ratio threshold is determined to indicate the location of the myocardial infarction.

[0029] Alternatively, or as a complement to the impedance value ratio determination, the myocardial infarct detector may be adapted to calculate a respective maximum time derivative of the measured impedance curves, to determine a maximum impedance time derivative being below a predetermined impedance time derivative threshold to be consistent with a myocardial infarction and to determine the maximum impedance time derivative being lowest of the maximum impedance time derivatives being below the predetermined impedance time derivative threshold to indicate the location of the myocardial infarction.

[0030] In yet another embodiment of the present invention, the myocardial infarction detection unit has an intracardiac electrogram measuring circuit connected to the electrodes of respective medical leads and which measuring circuit is adapted to measure intracardiac electrograms using one or more electrodes of the medical leads. Furthermore, the myocardial infarction detection unit includes a myocardial infarct detector adapted to evaluate the intracardiac electrograms to detect changes being consistent with a myocardial infarction and to determine a location of the myocardial infarction using the evaluation. A reference template, which template may be a stored reference impedance template, may be used in this evaluation. The template may alternatively be obtained or created by the myocardial infarction detection means during a period when no changes of the monitored signals, e.g. the electrical activity of the cardiac tissue, are of a sufficient magnitude to indicate the possibility of the commencement of a condition such as a myocardial infarction. Such a template may also be updated periodically by performing new measurements of the electrical activity. Consequently, it is possible to continuously monitor the cardiac tissue to enable a reliable detection of an occurrence and location of a myocardial infarction.

[0031] In a specific embodiment of the present invention, the myocardial infarct detector is adapted to determine a ST segment elevation being above a predetermined ST segment threshold as being consistent with the occurrence of a myocardial infarction and determine the intracardiac electrogram having the largest ST segment elevation of the ST segments being above a predetermined ST segment threshold as indicating the location of the myocardial infarction.

[0032] Furthermore, according to embodiments of the present invention, a combination of impedance measurements and intracardiac electrograms is used to detect an occurrence and location of a myocardial infarction. For example, both ST segment elevations and maximum impedance time derivatives may be used to detect myocardial infarctions. Thereby, it is possible to obtain a more reliable detection of the myocardial infarction and the location of the myocardial infarction.

[0033] At an infarction, certain hormones or chemical substances are released or are produced in a higher concentration than normal, for example, creatine phosphatase, FABP (Fatty Acid Bonding Proteins), LDH (Lactic Dehydrogenase), or GOT (Glutamic-Oxalatic Transaminase). In one embodiment of the present invention, this is utilized by

arranging a sensor in the implantable medical device or in the medical leads adapted to sense such a hormone or substance. A semiconductor sensor may be used where a reactance material is applied on a surface of the sensor, which reactance material is specific to react with the substance of interest.

[0034] According to embodiments of the present invention, signals being indicative of the healing process of the myocardial infarction is monitored, continuously or periodically, during the therapy session to determine whether the therapy has been successful and should be ended or whether the therapy parameters, i.e. the parameter of the treatment protocol, should be adjusted in order to make the treatment more potent during a certain phase of the healing process or to make the treatment less potent. A more potent treatment may be a higher degree of intensity of light or a constant intensity of light but with a changed intermittence, i.e. longer periods of light delivery or a more frequent light delivery with a constant period of light delivery. A less potent treatment may instead be a lower degree of intensity of light or a constant intensity of light but with a changed intermittence, i.e. shorter periods of light delivery or a less frequent light delivery with a constant period of light delivery.

[0035] According to one embodiment of the present invention, the myocardial infarct detector, after an initiation of a therapy session, monitors impedances obtained by at least an electrode pair indicating the location of the myocardial infarction to determine whether the impedances indicate that the therapy session should be terminated and/or the treatment parameters should be adjusted or maintained.

[0036] Furthermore, the myocardial infarct detector may be adapted to determine impedance value ratios for successive cardiac cycles and to determine that the therapy session should be terminated if a predetermined number of the impedance value ratios are found to be above the impedance value ratio threshold.

[0037] In another embodiment, the myocardial infarct detector may be adapted to calculate maximum time derivatives of the measured impedance curves for successive cardiac cycles and to determine that the therapy session should be terminated if a predetermined number of the maximum impedance time derivatives are found to be above a predetermined impedance time derivative threshold.

[0038] According to further embodiments, the myocardial infarct detector is adapted to monitor intracardiac electrograms obtained by at least an electrode pair indicating the location of the myocardial infarction to determine whether the intracardiac electrograms indicate that the therapy session should be terminated and/or the treatment parameters should be adjusted or maintained.

[0039] In a certain embodiment, the myocardial infarct detector is adapted to determine ST segments for successive cardiac cycles and determine that the therapy session should be terminated if a predetermined number of the ST segment elevations are found to be below a predetermined ST segment elevation threshold.

[0040] Moreover, according to other embodiments of the present invention, a combination of impedance measurements and intracardiac electrograms is used to determine whether the therapy should be terminated or whether the therapy parameters should be adjusted or maintained. For example, both ST segment elevations and maximum impedance time derivatives may be used to evaluate the therapy. Thereby, it is possible to obtain a more reliable judgement of the healing process and the therapy.

[0041] According to an embodiment of the present invention, the implantable medical device is provided with a power transmission unit that operates by inductive coupling in order to provide the implantable medical device with additional energy for a healing process. A receiver coil with a rectifier is arranged in the implantable medical device. An external sending coil is arranged to emit AC-fields in frequencies of a few kHz to about 500 kHz. This additional energy may be supplied directly to the light emitting means, for example, the diodes or may be used to charge a re-chargeable battery of the implantable medical device.

[0042] In a further embodiment, a warning system is arranged in the implantable medical device adapted to notify the patient (e.g. by means of a beep signal or a generated vibration) and/or a care institution such a hospital. For example, the hospital can be notified via message transmitted via an RF (Radio Frequency) unit of the implantable medical device and telecommunication system containing, inter alia, information related to the patient and a detected myocardial infarction stored in the implantable medical device. A decision at the hospital how to proceed with the treatment of the infarct can be based on the transmitted information collected by the sensors of the implantable medical device. For example, medical personnel is able to tune the light therapy by programming the device and the device can be provided with additional power or energy can be supplied from an external power source shortly after the onset of the infarct. The patient is also able to contact medical personnel via a home monitoring equipment installed at his/hers home at notification of a detection of an infarct.

[0043] In one embodiment of the present invention, the light emitting units are activated such that therapeutic light is emitted according to a treatment protocol including treatment parameters comprising one, more or all of: emitting intervals of the therapeutic light, intensity of the emitted therapeutic light, wavelength of the emitted light, intermittence of the emitted therapeutic light, or treatment periods. The protocol may thus comprise a predetermined treatment scheme. In an alternative embodiment, the treatment is varied in dependence of one or more treatment response parameters.

[0044] In embodiments of the present invention, the light emitting units emit coherent and monochromatic light having a wavelength in the range of 600 nm-1000 nm. Furthermore, an intensity of 1-500 mW/cm² and a total dosage of about 1-4 J/cm² may be used.

[0045] As will be apparent to those skilled in the art, steps of the method of the present invention, as well as preferred embodiment thereof, are suitable to realize as a computer program or an encoded computer readable medium.

BRIEF DESCRIPTION OF THE DRAWINGS

[0046] The features that characterize the invention, both as to organization and to method of operation, together with further objects and advantages thereof, will be better understood from the following description used in conjunction with the accompanying drawings. It is to be expressly understood that the drawings is for the purpose of illustration and description and is not intended as a definition of the limits of the invention. These and other objects attained, and advantages offered, by the present invention will become more fully apparent as the description that follows is read in conjunction with the accompanying drawings.

[0047] FIG. 1 schematically shows an embodiment of a pacemaker system in which an implantable medical device in accordance with the present invention may be implemented.

[0048] FIG. 2a schematically illustrates an embodiment of the implantable medical device according to the present invention.

[0049] FIG. 2b schematically illustrates another embodiment of the implantable medical device according to the present invention.

[0050] FIG. 3a schematically illustrates an embodiment of the myocardial infarction detection unit in accordance with the present invention.

[0051] FIG. 3b schematically illustrates another embodiment of the myocardial infarction detection unit in accordance with the present invention.

[0052] FIG. 4 schematically illustrates an embodiment of a medical lead in accordance with the present invention.

[0053] FIG. 5 is high-level flow chart of an embodiment of the method for treating a myocardial infarction with therapeutic light using an implantable medical device according to the present invention.

[0054] In the following, the present invention will be discussed in the context of medical systems including at least an implantable pacemaker, and medical leads such as an atrial lead and a ventricular lead.

[0055] With reference first to FIG. 1, a pacemaker system is shown that includes an implantable pacemaker 10 connectable to an atrial lead 12 and a ventricular lead 14 including electrodes for providing therapy to a heart 16 of a patient. The leads 12, 14 are implanted into the heart 16 via veins and are fixated at the cardiac tissue by means of, for example, helical screws.

[0056] Turning now to FIGS. 2a, an embodiment of an implantable medical device, e.g. a pacemaker or an ICD, according to the present invention will be discussed. The implantable medical device 20 comprises a housing (not shown) being hermetically sealed and biologically inert. Normally, the housing is conductive and may, thus, serve as an electrode. The pacemaker 20 is connectable to one or more pacemaker leads, where only two are shown in FIGS. 2a and 2b, namely a ventricular lead 22a implanted in the right ventricle of the heart (not shown) and one atrial lead 22b implanted in the right atrium of the heart (not shown).

[0057] The leads 22a and 22b can be electrically coupled to the pacemaker 20 in a conventional manner. The leads 22a, 22b carry one or more electrodes, such as a tip electrode or ring electrodes, arranged to, inter alia, measure the impedance or transmit pacing pulses for causing depolarization of cardiac tissue adjacent to the electrode(-s) generated by a pace pulse generator 21 under influence of a controller or controlling circuit 24 including a microprocessor. The controller 24 controls, inter alia, pace pulse parameters such as output voltage and pulse duration.

[0058] Moreover, a storage unit 25 is connected to the controller 24, which storage unit 25 may include a random access memory (RAM) and/or a non-volatile memory such as a read-only memory (ROM). The storage unit 25 is connected to the controller 24. Detected signals from the patient's heart are processed in an input circuit (not shown) and are forwarded to the controller 24 for use in logic timing determination in known manner.

[0059] Furthermore, the implantable medical device 20 has a myocardial infarction detection unit 27, which will be described below in more detail with reference to FIGS. 3a and

3b. The myocardial infarction detection unit 27 is configured to process detected signals from the patient's heart to detect whether a myocardial infarction has occurred and may also, if such an infarction is detected, determine or identify a location of the detected myocardial infarction within the heart. Information from the myocardial infarction detection unit 27 such as detection of a myocardial infarction and the location may be forwarded to the controller 24. The myocardial infarction detection unit 27 is connected to the electrodes arranged in the medical leads 22a, 22b, for example, a number of ring electrodes arranged along the medical leads and tip electrodes, see FIG. 4.

[0060] In this embodiment, a plurality of light emitting units (see FIG. 4) are incorporated in one or all of the leads 22a, 22b and connected to the controller 24. In one embodiment, the light emitting units are formed of light emitting diodes that are arranged at a periphery of the tube-shaped leads 22a and 22b in an array along a longitudinal direction of the leads. The light emitting diodes emit monochromatic light having a wavelength of 600-1000 nm. The light emitting diodes are connected to a therapy circuit 23, which is adapted to, under control of the controller 27, selectively activate one or more of the diodes. Upon a detection of a myocardial infarction and at determination of a location within the heart of such an infarction, the myocardial infarction detection unit 27 may forward this information to the controller 24, which, in turn, may activate selected diodes via the therapy circuit 23 according to a treatment protocol. One or more of the diodes may be selected, based on the determination of the location of the myocardial infarction, and activated to emit therapeutic light towards the detected myocardial infarction. The treatment protocol may include predetermined or adjustable treatment parameters such as emitting intervals of the therapeutic light, intensity of the emitted therapeutic light, wavelength of the emitted light, and intermittence of the emitted therapeutic light.

[0061] The implantable medical device 20 is powered by a battery (not shown), which supplies electrical power to all electrical active components of the implantable medical device 20 including the light emitting units arranged in the medical leads 22a and 22b and the myocardial infarction detection unit 27. The implantable medical device 20 may also be provided with means for power transmission via inductive coupling in order to provide the implantable medical device 20 with additional energy for a healing process. A receiver coil (not show) with a rectifier is arranged in the implantable medical device 20. An external sending coil is arranged to emit AC-fields in frequencies of a few kHz to about 500 kHz. This additional energy may be supplied directly to the light emitting units, for example, the diodes or may be used to charge a re-chargeable battery of the implantable medical device 20.

[0062] The implantable medical device 20 further has a communication unit (not shown), for example, an RF telemetry circuitry for providing RF communications. Thereby, for example, data contained in the storage means 25 can be transferred to an external programmer device (not shown) via the communication unit and a programmer interface (not shown) for use in, for example, analyzing system conditions, patient information, etc.

[0063] Moreover, the implantable medical device 20 may further have a notifying device (not shown) adapted to, at detection of an occurrence of a myocardial infarction, notify said patient of the event that a myocardial infarct has been

detected and/or that therapy has been initiated. In one embodiment, the notifying device is a vibration unit adapted to vibrate in the event that a myocardial infarct has been detected and/or that therapy for treating such an infarct has been initiated and thereby notify the patient.

[0064] Referring to FIG. 2b, a further embodiment of the implantable medical device according to the present invention will be discussed. Like parts in the implantable medical device shown in FIG. 2a and FIG. 2b will be denoted with the same reference numerals and descriptions thereof will be omitted since they have been described above with reference to FIG. 2a. A light source 31 is arranged in the implantable medical device 30, for example, a laser adapted to emit monochromatic light having a wavelength of 600-1000 nm. The light source 31 is connected to a number of optical fibers 32a arranged in the ventricular lead 22a and a number of optical fibers 32b arranged in the atrial lead 22b. The optical fibers 32a, 32b are arranged to conduct light emitted by the light source 31 such that the conducted therapeutic light emanates from the optical fibers 32a, 32b toward the cardiac tissue. The optical fibers 32a, 32b are arranged such that light can be applied cardiac tissue along the periphery of the medical leads 22a, 22b. That is, distal ends of respective optical fibers 32a, 32b are arranged in arrays along the outer periphery of the medical leads 22a, 22b see FIG. 4. Furthermore, the light source 31 has a selector circuit adapted to, under influence of the controller 27, select one or more of the optical fibers 32a, 32b to conduct light during a therapy session such that therapeutic light can be applied to an identified location of a myocardial infarction.

[0065] Referring now to FIGS. 3a and 3b, embodiments of the myocardial infarction detection means will be discussed in more detail. With reference first to FIG. 3a, an embodiment of the myocardial infarction detection means adapted to determine an occurrence of a myocardial infarction and to determine the location of the myocardial infarction using measured impedances, for example, transcardiac impedances will be described. The myocardial infarction detection unit 27 has an impedance measuring circuit 33 connected to the electrodes incorporated in the medical leads 22a and/or 22b, which will be described in more detail below with reference to FIG. 4. In one embodiment, each medical lead carries ring electrodes arranged along the respective lead and a tip electrode and the impedance measuring circuit 33 may be connected to the electrodes via a switching device 34. The switching device 34 may be arranged in the implantable medical device 20 and are adapted to switch an applied current to a selected electrode(-s) of the medical lead(-s) 22a, 22b. Those skilled in the art may design such a switching device based on the switching device described in U.S. Pat. No. 5,423,873, the teaching of which hereby are incorporated by reference in its entirety. Hence, the impedance measuring circuit 33 may, for example, measure the impedance between a first ring electrode of the first medical lead 22a and the housing the implantable medical device, a first ring electrode of the first medical lead 22a and a second ring electrode of the first medical lead 22a, a first ring electrode of the first medical lead 22b and a first ring electrode of the second medical lead 22b, and a first ring electrode of the second medical lead 22b and a second ring electrode of the second medical lead 22b. The impedance measuring circuit 33 is adapted to apply excitation current pulses between respective electrode pair including at least a first and at least a second electrode, as mentioned above, to measure the impedance in the tissues

between the at least first and the at least second electrode of the respective electrode pairs to the excitation current pulses. The impedance measuring circuit 33 is adapted to periodically initiate impedance measuring sessions according to a myocardial infarction monitoring protocol, wherein the impedance between different pairs of electrodes is measured according to a predetermined sequence (e.g. one pair after another during consecutive cardiac cycles or all pairs simultaneously during a number of consecutive cardiac cycles) to be able to detect and locate a myocardial infarction. That is, during each impedance measuring session, a number of impedance measurements from the different electrode pairs are obtained. For example, a measurement including four electrode pairs will provide four impedance values.

[0066] Furthermore, myocardial infarction detection means 27 comprises a myocardial infarct detector 35 adapted to evaluate the measured impedances by detecting changes in the impedances that is consistent with a myocardial infarction and to determine a location of the myocardial infarction using the evaluation. In one embodiment, the myocardial infarct detector 35 is adapted to compare the measured impedances with a reference impedance template stored in a template memory 36 to detect an occurrence of a myocardial infarction and a location of the myocardial infarction from the result of the comparison. Alternatively, the reference impedance template may be stored in the storage means 25. Moreover, the reference template can be obtained and created before the parameter monitoring session is initiated, e.g. the impedance measurement session, and updated periodically. In one embodiment, the impedance measurements sessions are synchronized with the heartbeats of the patients, for example, at the end of diastole.

[0067] The myocardial infarct detector 35 may be adapted to determine impedance value ratios for each cardiac cycle by determining a maximum impedance and a minimum impedance for each electrode pair during the cardiac cycle. By comparison with the template, it is possible to identify whether a myocardial infarction has occurred. For example, an impedance value ratio being below an impedance value ratio threshold is determined to be consistent with a myocardial infarction. Further, by comparing the impedance value ratios being below the threshold, a location of the myocardial infarction can be determined. In this embodiment, the impedance value ratio being smallest is determined to indicate the location of the myocardial infarction. That is, the electrode pair providing the impedance measurement curve having the smallest difference between the maximum impedance value and the minimum impedance value during a cardiac cycle is determined to be the electrode pair being closest to the detected myocardial infarction and, hence, the location of the myocardial can be determined. The myocardial infarct detector 35 is adapted to send an instruction or message to the controller 24 informing the controller 24 that a myocardial infarction has been detected and the location of the myocardial infarction, i.e. as defined by the electrode pair being determined to be closest to the detected myocardial infarction.

[0068] In another embodiment of the present invention, the myocardial infarct detector 35 is adapted to calculate a maximum time derivative of each measured impedance curve, i.e. for each electrode pair. By comparing the calculated maximum time derivatives with the template, it is possible to identify whether a myocardial infarction has occurred. For example, a maximum impedance time derivative being below a predeter-

mined impedance time derivative threshold is determined to be consistent with a myocardial infarction. Further, in this embodiment, the maximum impedance time derivative being the lowest of the maximum impedance time derivatives being below the impedance time derivative threshold is determined to indicate the location of the myocardial infarction. That is, the electrode pair providing the impedance measurement curve having the lowest maximum impedance time derivative is determined to be the electrode pair being closest to the detected myocardial infarction. The myocardial infarct detector 35 is adapted to send an instruction or message to the controller 24 informing the controller 24 that a myocardial infarction has been detected and the location of the myocardial infarction, i.e. as defined by the electrode pair being determined to be closest to the detected myocardial infarction.

[0069] Those skilled within the art appreciate that there are a number of other conceivable variations or alternatives to the embodiments described above.

[0070] For example, the morphology of the obtained impedance curves may be compared with an impedance template to determine the occurrence and location of a myocardial infarction. In one embodiment, the part of the impedance curve at systole, i.e. after the QRS-complex, is studied and compared with a reference curve obtained with the same electrode configuration at normal conditions, i.e. at conditions when no myocardial infarction is present.

[0071] Moreover, the myocardial infarct detector may be adapted to, after an initiation of a therapy session, monitor impedances obtained by at least the electrode pair that indicated the location of the myocardial infarction to determine whether the obtained impedances indicate that the therapy session should be terminated and/or whether treatment parameters should be adjusted. The therapy parameters can be adjusted during the treatment procedure. For example, a higher light intensity can be used during an initial therapy period and the light intensity can be reduced during a second period after the initial period. Alternatively, a constant light intensity but an adjusted intermittence can be utilized, e.g. the periods of light delivery can be adjusted or shorter intervals between the periods of light delivery are used.

[0072] In one embodiment, the myocardial infarct detector is adapted to determine impedance value ratios for successive cardiac cycles and to determine that the therapy session should be terminated if a predetermined number of the impedance value ratios are found to be above a predetermined impedance value ratio threshold. Alternatively, the therapy parameters can be adjusted, for example, shorter intervals between the periods of light delivery can be used if a predetermined number of the impedance value ratios are found to be below a predetermined impedance value ratio threshold.

[0073] In a further embodiment, the myocardial infarct detector is adapted to calculate maximum time derivatives of the measured impedance curves for successive cardiac cycles and to determine that the therapy session should be terminated if a predetermined number of the maximum impedance time derivatives are found to be above a predetermined impedance time derivative threshold. Alternatively, the therapy parameters can be adjusted, for example, shorter intervals between the periods of light delivery can be used if a predetermined number of the impedance value ratios are found to be below a predetermined impedance value ratio threshold.

[0074] Turning now to FIG. 3b, an embodiment of the myocardial infarction detection unit 27" adapted to determine an occurrence of a myocardial infarction and to determine the location of the myocardial infarction using electrical activity of the heart of the patient impedances will be described. The myocardial infarction detection unit 27" 27' includes a sensor 43 that senses electrical activity of the heart including an intracardiac electrogram measuring circuit connected to electrodes incorporated in the medical leads 22a and/or 22b, which will be described in more detail below with reference to FIG. 4. In one embodiment, each medical lead has a number of ring electrodes arranged along the respective lead and a tip electrode and the means for sensing electrical activity 43 may be connected to the electrodes via a switching device 44. The switching device 44 may be arranged in the implantable medical device 20 and is adapted to switch between selected electrode(-s) of the medical lead(-s) 22a, 22b to obtain signals indicative of the electrical activity of the heart from different electrode(-s) and/or combination of electrodes. Those skilled within the art may design such a switching device based on the switching device described in U.S. Pat. No. 5,423,873, the teachings of which are incorporated herein by reference. Thereby, the electrical activity of the heart can be measured using different electrodes and/or combination of electrodes, for example, at a first ring electrode of the first medical lead 22a and a second ring electrode of the first medical lead 22a, at a first ring electrode of the first medical lead 22a and at a first ring electrode of the second medical lead 22b, and/or at a first ring electrode of the second medical lead 22b and at a second ring electrode of the second medical lead 22b. The electrical activity sensor 43 is adapted to perform sensing sessions according to a myocardial infarction monitoring protocol, wherein the electrical activity at different sensors, electrodes and/or combinations of electrodes are measured according to a predetermined sequence (e.g. one electrode after another during consecutive cardiac cycles or a number of electrodes simultaneously during a number of consecutive cardiac cycles) to be able to sense electrical activity and obtain intracardiac electrograms for different electrodes and/or combinations of electrodes.

[0075] Furthermore, the myocardial infarction detection unit 27" includes a myocardial infarct detector 45 adapted to evaluate the obtained intracardiac electrograms to detect changes being consistent with a myocardial infarction and to determine a location of the myocardial infarction using the evaluation. In one embodiment, the myocardial infarct detector is adapted to determine a ST segment elevation of each obtained intracardiac electrogram and compare them with a reference template stored in a template memory 46 to detect an occurrence of a myocardial infarction and a location of the myocardial infarction from the result of the comparison. Alternatively, the reference impedance template may be stored in the storage unit 25. Moreover, the reference template can be obtained and created before the parameter monitoring session is initiated, e.g. the impedance measurement session, and updated periodically.

[0076] In this embodiment, it is determined whether the ST segment elevation is above a predetermined ST segment threshold and in such a case; it is determined to be consistent with the occurrence of a myocardial infarction. The intracardiac electrogram having the largest ST segment elevation of the ST segments being above the predetermined ST segment threshold is determined to indicate the location of the myocardial infarction. That is, the electrode and/or electrode com-

bination providing the intracardiac electrogram curve having the largest ST segment elevation during a cardiac cycle is determined to be the electrode and/or electrode combination being closest to the detected myocardial infarction and, hence, the location of the myocardial can be determined. The myocardial infarct detector 45 is adapted to send an instruction or message to the controller 24 informing the controller 24 that a myocardial infarction has been detected and the location of the myocardial infarction, i.e. as defined by the electrode and/or electrode combination being determined to be closest to the detected myocardial infarction. In one embodiment, the amplitude of a cardiac signal is measured during a short interval after the detection of R-wave. For example, the interval is about 40-150 ms after the R-wave detection. Measured amplitude is compared with a predetermined reference amplitude value and when the measured amplitude exceeds the reference value, a myocardial infarction is indicated.

[0077] Moreover, the myocardial infarct detector may be adapted to, after an initiation of a therapy session, monitor intracardiac electrograms obtained by at least an electrode and/or an electrode combination indicating the location of the myocardial infarction to determine whether obtained intracardiac electrograms indicate that the therapy session should be terminated and/or the treatment parameters should be adjusted. For example, a higher light intensity can be used during an initial therapy period and the light intensity can be reduced during a second period after the initial period. Alternatively, a constant light intensity but an adjusted intermittence can be utilized, e.g. the periods of light delivery can be adjusted or shorter intervals between the periods of light delivery are used.

[0078] The myocardial infarct detector may be adapted to determine ST segments for successive cardiac cycles after the initiation of the therapy session and to determine that therapy session should be terminated if a predetermined number of the obtained ST segment elevations are found to be below a predetermined ST segment elevation threshold. Alternatively, the therapy parameters can be adjusted, for example, shorter intervals between the periods of light delivery can be used if a predetermined number of the impedance value ratios are found to be above a predetermined impedance value ratio threshold.

[0079] According to a further embodiment of the present invention, the myocardial infarction detection means 27 comprises circuitry for detecting the occurrence and location of a myocardial infarction using both impedances and intracardiac electrogram. In this case, the occurrence and location of a myocardial infarction can be detected by using impedances and the healing process can be monitored by means of intracardiac electrograms, for example, by evaluating the ST elevation.

[0080] With reference to FIG. 4, an embodiment of a medical lead in accordance with the present invention will be described. The medical lead 50 comprises a number of tines 51 for fixating the lead 50 at the cardiac tissue.

[0081] An annular tip electrode 52 is arranged at the tip of the lead and will, after the implantation, abut against the cardiac tissue. A light emitting diode 54 is arranged at the centre of the tip portion of the lead. Further, an array of ring electrodes 55a-55c are arranged along an outer periphery 56 of the medical lead. An array of light emitting diodes 57a-57d is arranged along the outer periphery 56.

[0082] Turning now to FIG. 5, a high-level flow chart of an embodiment of the method for treating a myocardial infarction of a heart of a patient with therapeutic light using an implantable medical device according to the present invention is shown. At step 100, signals indicative of a myocardial infarction is monitored, for example, impedances of cardiac tissue or electrical activity for determining intracardiac electrograms as discussed above. This monitoring, i.e. the measuring or sensing sessions can be initiated at periodic intervals or can be performed continuously. At step 102, a determination is constantly or at regular intervals made in the myocardial infarct detector 35, 45 as to whether there has been any change in the signal being monitored of sufficient magnitude to indicate the possibility of an occurrence of a myocardial infarction. If no change, or if the magnitude of the change is too small, the algorithm returns to step 100. According to an embodiment, the algorithm waits for a predetermined period of time before it returns to step 100.

[0083] On the other hand, if a change that indicates the occurrence of a myocardial infarction is detected, the algorithm proceeds to step 104 where a reference template is obtained. The reference template may be a predetermined template stored in the template memory 36, 46, in the memory of the implantable medical device 20, or a template obtained and created by using measurements performed during a period when no myocardial indicative change in the monitored signals is detected. This created template may be updated periodically. Then, at step 106, the obtained data, e.g. the morphology of the impedance curves, a maximum impedance time derivative for the different impedance curves, or a ST elevation of the different intracardiac electrograms, are compared with the reference template. At step 108, it is checked whether the comparison indicates a deviation such that an occurrence of a myocardial infarction can be established and, thus, whether a delivery of therapy is justified. If the comparison indicates that the deviation is not sufficient to justify an initiation of a therapy, the algorithm returns to step 100.

[0084] If the deviation indicates that therapy should be initiated, the algorithm proceeds to step 110, where a location of the established myocardial detection is determined by using the obtained data, for example, the impedance curves or the intracardiac electrograms as described above. For example, the ST elevation being the largest or the minimum difference between the maximum impedance value and the minimum impedance value indicate which electrode and/or electrode combination that is closest to the detected myocardial infarction. Then, at step 112, a therapy session is initiated in accordance with a therapy protocol, which may include predetermined or adjustable treatment parameters such as emitting intervals of the therapeutic light, intensity of the emitted therapeutic light, wavelength of the emitted light, or intermittence of the emitted therapeutic light. The therapy protocol may be stored in the storage unit 25 of the implantable medical device 20 or in the memory of the myocardial detection means 27', 27".

[0085] At step 114, signals being indicative of the healing process are continuously monitored after the initiation of the therapy session. As described above, impedance signals and/or intracardiac electrograms may be used for this determination. At step 116, it is determined whether the therapy should be terminated based on the therapy protocol. If yes, the therapy is ended. On the other hand if no, the algorithm proceeds to step 118, where it is checked whether the therapy

parameters should be adjusted. For example, shorter intervals between the periods of light delivery can be used if a predetermined number of the impedance value ratios, i.e. for a number of successive cardiac cycles, are found to be within a predetermined impedance value ratio interval or if the ST elevation, i.e. for a number of successive cardiac cycles, is found to be within a predetermined ST elevation value interval. If yes, the algorithm proceeds to step 120, where the therapy parameters are adjusted in accordance with the therapy protocol. Then, the algorithm returns to step 114, where the therapy is continued with the new adjusted parameters.

[0086] Alternatively, the algorithm may proceed to step 112, where a new therapy session is initiated with the new adjusted parameters. On the other hand, if it is determined that the therapy parameters should not be adjusted at step 118, the algorithm proceeds to step 122 where the therapy parameters are maintained. Thereafter, the algorithm returns to step 114, where the therapy is continued with the maintained therapy parameters. Alternatively, the algorithm may proceed to step 112, where a new therapy session is initiated with the maintained parameters.

[0087] The present invention applies to implantable medical devices such as implantable pacemakers including biventricular pacemakers, pacemakers capable of delivering pacing to the atrium, the ventricle, or both the atrium and the ventricle (i.e. left ventricle and/or right ventricle), as well as devices, which are capable of delivering one or more cardioversion or defibrillation shocks.

[0088] In a further embodiment of the present invention, the control circuit 24 is adapted to, at detection of an occurrence of a myocardial infarction, send a notification to a medical care institution, e.g. a hospital or a care centre, via a communication unit of the medical device 10, 20, 30 and at least one external radio communication network such as wireless LAN ("Local Area Network"), GSM ("Global System for Mobile communications"), or UMTS ("Universal Mobile Telecommunications System"). For a given communication method, a multitude of standard and/or proprietary communication protocols may be used. For example, and without limitation, wireless (e.g. radio frequency pulse coding, spread spectrum frequency hopping, time-hopping, etc.) and other communication protocols (e.g. SMTP, FTP, TCP/IP) may be used. Other proprietary methods and protocols may also be used. The notification may include at least the patient identity, the occurrence of a myocardial infarction and/or the location of the detected infarct within the heart. The communication unit may be adapted to communicate with an extracorporeal communication device, e.g. mobile phone, a pager or a PDA ("Personal Digital Assistant"), which is adapted to receive the notification and to transmit it via said communication network further to the medical care institution. Alternatively, the communication unit may be adapted to communicate with a home monitoring unit located in the home of the patient. The home monitoring unit is adapted to communicate with the care institution via a telephone link. Furthermore, the notification may include a geographical location of the patient, for example, by means of a GPS ("Global Positioning System") unit arranged in the communication device. Thereby, it is possible for the care institution to obtain an early notification of the infarct of a patient and, additionally, the position of the patient and hence the patient can be given care at an early stage of an infarction.

[0089] In a further embodiment of the present invention, an extracorporeal therapy unit may be connected to a medical lead according to the present invention for supplying, for example, power to the light emitting means or, in case of light conducting optical fibres in the medical lead for supplying therapeutic light. Furthermore, an extracorporeal therapy unit comprising a lead in form of a guide wire including light emitting means in accordance with the present invention may be used to treat the detected infarct since the medical personnel controlling the therapy unit may be provided with the location of the detected infarct via the implanted medical device.

[0090] Although modifications and changes may be suggested by those skilled in the art, it is the intention of the inventors to embody within the patent warranted heron all changes and modifications as reasonably and properly come within the scope of their contribution to the art.

We claim as our Invention:

1. An implantable medical device comprising:
a pulse generator that emits cardiac stimulating pacing pulses;
a medical lead connected to said pulse generator that delivers said pulses in vivo to cardiac tissue of the heart of a patient;
a myocardial infarction detection unit that detects a myocardial infarction and identifies a location of said myocardial infarction;
a therapy circuit connected to a plurality of light emitting units carried by said medical lead, each of said light emitting units being operated by said therapy circuit to emit therapeutic light; and
a control circuit connected to said myocardial infarction detection unit and to said therapy circuit, said control circuit being configured to initiate a therapy session via said therapy circuit, in which one or more of said plurality of light emitting is/are selectively activated to emit said therapeutic light toward the detected location of the myocardial infarction upon detection of an occurrence of the myocardial infarction.

2. The implantable medical device according to claim 1, wherein said therapy circuit is configured to activate said light emitting units to emit said therapeutic light according to a treatment protocol.

3. The implantable medical device according to claim 2, wherein said treatment protocol includes treatment parameters comprising: emitting intervals of said therapeutic light, intensity of said emitted therapeutic light, wavelength of said emitted light, and intermittence of said emitted therapeutic light.

4. The implantable medical device according to claim 1, wherein each of said plurality of light emitting units comprises at least one light emitting diode.

5. The implantable medical device according to claim 1, wherein said light emitting units are arranged in an array arranged along an outer surface of a lead body of said medical lead.

6. The implantable medical device according to claim 1, wherein each of said plurality of light emitting units comprises at least one optical fibre fiber that conducts light emitted from at least one light source said implantable medical device, and wherein said therapy circuit selectively activates said at least one light source and/or at least one optical fiber to

cause light conducted in one or more optical fiber to emanate from said one or more optical fiber toward said detected location.

7. The implantable medical device according to claim 6, wherein the at least one light source is a laser source.

8. The implantable medical device according to claim 1, wherein said medical lead comprises a plurality of electrodes, and wherein said myocardial infarction detection unit comprises:

- an impedance measuring circuit connected to said electrodes and configured to:
apply excitation current pulses between respective electrode pairs including at least a first and at least a second electrode; and
measure the impedance in the tissues between said at least first and said at least second electrode of said electrode pairs to the excitation current pulses; and
a myocardial infarct detector that evaluates said measured impedances by detecting changes in said impedances associated with the myocardial infarction and to determine the location of said myocardial infarction using said evaluation.

9. The implantable medical device according to claim 8, wherein said myocardial infarct detector configured to compare measured impedances with a stored reference impedance template to detect the occurrence of the myocardial infarction and the location of said myocardial infarction from a result of the comparison.

10. The implantable medical device according to claim 9, wherein said myocardial infarct detector configured to:

- determine impedance value ratios for a cardiac cycle by determining a maximum impedance and a minimum impedance, respectively, measured by the impedance measuring circuit during a cardiac cycle;
- determine an impedance value ratio being below a predetermined impedance value ratio threshold to be consistent with a myocardial infarction; and
- determine the impedance value ratio being smallest of the impedance value ratios being below said predetermined impedance value ratio threshold to indicate the location of the myocardial infarction.

11. The implantable medical device according to claim 9, wherein said myocardial infarct detector is configured to:

- calculate a respective maximum time derivative of the measured impedance curves;
- determine a maximum impedance time derivative being below a predetermined impedance time derivative threshold to be consistent with a myocardial infarction; and
- determine the maximum impedance time derivative being lowest of the maximum impedance time derivatives being below said predetermined impedance time derivative threshold to indicate the location of the myocardial infarction.

12. The implantable medical device according to claim 1, wherein said medical lead comprises a plurality of electrodes, and wherein said myocardial infarction detection unit comprises:

- an intracardiac electrogram measuring circuit connected to said electrodes that measures intracardiac electrograms using respective pairs of said electrodes; and
a myocardial infarct detector that evaluates said intracardiac electrograms to detect changes consistent with a

myocardial infarction and to determine the location of said myocardial infarction using said evaluation.

13. The implantable medical device according to claim 12, wherein said myocardial infarct detector is configured to:

determine a ST segment elevation being above a predetermined ST segment threshold as being consistent with the occurrence of a myocardial infarction; and determine the intracardiac electrogram having the largest ST segment elevation of the ST segments being above a predetermined ST segment threshold as indicating the location of said myocardial infarction.

14. The implantable medical device according to claim 8, wherein said myocardial infarct detector is, after an initiation of a therapy session, configured to:

monitor impedances obtained by at least an electrode pair indicating the location of said myocardial infarction to determine whether said impedances indicate that said therapy session should be terminated and/or said treatment parameters should be adjusted.

15. The implantable medical device according to claim 14, wherein said myocardial infarct detector is adapted configured to:

determine impedance value ratios for successive cardiac cycles; and

determine that said therapy session should be terminated if a predetermined number of said impedance value ratios are found to be above said impedance value ratio threshold.

16. The implantable medical device according to claim 14, wherein said myocardial infarct detector is configured to:

calculate maximum time derivatives of the measured impedance curves for successive cardiac cycles; and determine that said therapy session should be terminated if a predetermined number of said maximum impedance time derivatives are found to be above a predetermined impedance time derivative threshold.

17. The implantable medical device according to claim 12, wherein said myocardial infarct detector is configured to:

monitor intracardiac electrograms obtained by at least an electrode pair indicating the location of said myocardial infarction to determine whether said intracardiac electrograms indicate that said therapy session should be terminated and/or said treatment parameters should be adjusted.

18. The implantable medical device according to claim 17, wherein said myocardial infarct detector is configured to:

determine ST segments for successive cardiac cycles; and determine that said therapy session should be terminated if a predetermined number of said ST segment elevations are found to be below a predetermined ST segment elevation threshold.

19. The implantable medical device according to claim 1, wherein each of said light emitting units emits coherent and monochromatic light.

20. The implantable medical device according to claim 1, wherein each of said light emitting unit emits light having a wavelength in the range of 600 nm-1000 nm.

21. The implantable medical device according to claim 1 comprising a communication unit, and wherein said control circuit is configured to, upon detection of an occurrence of a myocardial infarction, send a notification to a medical care institution via said communication unit of and at least one external communication network, said notification including

at least an identity of the patient and information related to a detected myocardial infarction.

22. The implantable medical device according to claim 21, wherein said communication unit 30) is configured to communicate with an extracorporeal communication device, said communication device being configured to receive said notification and to transmit said notification via said communication network to said medical care institution.

23. The implantable medical device according to claim 22, wherein said extracorporeal communication device is a mobile phone, a pager or a PDA ("Personal Digital Assistant").

24. The implantable medical device according to claim 21, wherein said communication unit of said medical device is configured to communicate with an extracorporeal home monitoring unit connected to said at least one communication network, said home monitoring unit being adapted to receive said notification and to transmit said notification via said communication network to said medical care institution.

25. The implantable medical device according to claim 1, further comprising a notifying device configured to, upon detection of an occurrence of myocardial infarction, notify said patient that the myocardial infarct has been detected and/or that therapy has been initiated.

26. The implantable medical device according to claim 25, wherein said notifying device is a vibration unit.

27. A method for treating cardiac tissue of a heart of a patient with therapeutic light using an implantable medical device including a pulse generator that emits cardiac stimulating pacing pulses and connectable to at least one medical lead for delivering said pulses in vivo to cardiac tissue of a heart of a patient, comprising the steps of:

detecting in vivo a myocardial infarction and identifying a location of said myocardial infarction; and

automatically initiating an in vivo therapy session by selectively activating one or more of a plurality of light emitting units carried said at least one medical lead to emit therapeutic light detected location of the myocardial infarction upon detection of an occurrence of the myocardial infarction.

28. The method according to claim 27, further comprising the step of:

selectively activating said light emitting units to emit said therapeutic light according to a treatment protocol.

29. The method according to claim 28, wherein said treatment protocol includes treatment parameters comprising: emitting intervals of said therapeutic light, intensity of said emitted therapeutic light, wavelength of said emitted light, and intermittence of said emitted therapeutic light.

30. The method according to claim 27 comprising forming each of said plurality of light emitting units as at least one light emitting diode.

31. The method according to claim 27, comprising arranging said light emitting units in an array arranged along an outer surface of a lead body of said medical lead.

32. The method according to claim 27, further comprising the step of:

emitting said therapeutic light via at least one optical fiber that conducts light from at least one light source in said implantable medical device to cause said conducted therapeutic light to emanate from said at least one optical fiber toward the detected location of the myocardial infarction upon detection of the occurrence of the myocardial infarction.

- 33.** The method according to claim **32**, comprising employing a laser source as said at least one light source.
- 34.** The method according to claim **27**, wherein the step of detecting a myocardial infarction and identifying a location of said myocardial infarction comprises the steps of:
- applying excitation current pulses between respective electrode pair including at least a first and at least a second electrode;
 - measuring the impedance in the tissues between said at least first and said at least second electrode of said electrode pairs to the excitation current pulses;
 - evaluating said measured impedances by detecting changes in said impedances being consistent with a myocardial infarction; and
 - determining a location of said myocardial infarction using said evaluation.
- 35.** The method according to claim **34**, wherein the step of evaluating comprises the step of:
- comparing measured impedances with a stored reference impedance template to detect an occurrence of a myocardial infarction and a location of said myocardial infarction from the result of the comparison.
- 36.** The method according to claim **35**, wherein the step of comparing comprises the steps of:
- determining impedance value ratios for a cardiac cycle by determining a maximum impedance and a minimum impedance, respectively, measured by the impedance measuring circuit during a cardiac cycle;
 - determining an impedance value ratio being below a predetermined impedance value ratio threshold to be consistent with a myocardial infarction; and
 - determining the impedance value ratio being smallest of the impedance value ratios being below said predetermined impedance value ratio threshold to indicate the location of the myocardial infarction.
- 37.** The method according to claim **35**, wherein the step of comparing comprises the steps of:
- calculating a respective maximum time derivative of the measured impedance curves;
 - determining a maximum impedance time derivative being below a predetermined impedance time derivative threshold to be consistent with a myocardial infarction; and
 - determining the maximum impedance time derivative being lowest of the maximum impedance time derivatives being below said predetermined impedance time derivative threshold to indicate the location of the myocardial infarction.
- 38.** The method according to claim **27**, wherein said medical lead comprises a plurality of electrodes, and further comprising the steps of:
- measuring intracardiac electrograms using respective pairs of said electrodes; and
 - evaluating said intracardiac electrograms to detect changes being consistent with a myocardial infarction and to determine a location of said myocardial infarction using said evaluation.
- 39.** The method according to claim **38**, wherein the step of evaluating comprises the steps of:
- determining a ST segment elevation being above a predetermined ST segment threshold as being consistent with the occurrence of a myocardial infarction; and
 - determining the intracardiac electrogram having the largest ST segment elevation of the ST segment elevations

- being above a predetermined ST segment threshold as indicating the location of said myocardial infarction.
- 40.** The method according to claim **35**, further comprising the step of:
- monitoring impedances obtained by an electrode pair indicating the location of said myocardial infarction to determine whether said impedances indicate that said therapy session should be terminated and/or said treatment parameters should be adjusted.
- 41.** The method according to claim **40**, further comprising the steps of:
- determining impedance value ratios for successive cardiac cycles; and
 - determining that said therapy session should be terminated if a predetermined number of said impedance value ratios are found to be above said impedance value ratio threshold.
- 42.** The method according to claim **40**, further comprising the steps of:
- calculating maximum time derivatives of the measured impedance curves for successive cardiac cycles; and
 - determining that said therapy session should be terminated if a predetermined number of said maximum impedance time derivatives is found to be above a predetermined impedance time derivative threshold.
- 43.** The method according to claim **35**, further comprising the step of:
- monitoring intracardiac electrograms obtained by an electrode pair indicating the location of said myocardial infarction to determine whether said intracardiac electrograms indicate that said therapy session should be terminated and/or said treatment parameters should be adjusted.
- 44.** The method according to claim **43**, further comprising the steps of:
- determining ST segments for successive cardiac cycles; and
 - determining that said therapy session should be terminated if a predetermined number of said ST segment elevations are found to be below a predetermined ST segment threshold.
- 45.** The method according to claim **27** comprising, from said light emitting unit emitting coherent and monochromatic light.
- 46.** The method according to claim **27** comprising, from said light emitting unit emitting light having a wavelength in a range of 600 nm-1000 nm.
- 47.** The method according to claim **27**, further comprising the step of, upon detection of an occurrence of the myocardial infarction, sending a notification to a medical care institution via a communication unit of said medical device and at least one external communication network, and including in said notification including at least an identity of the patient and information related to a detected myocardial infarction.
- 48.** The method according to claim **47**, wherein the step of sending a notification comprises the steps of:
- communicating with an extracorporeal communication device and, at said communication device receiving said notification and transmitting said notification via said communication network to said medical care institution.
- 49.** The method according to claim **48** comprising employing, as said extracorporeal communication device, a mobile phone, a pager or a PDA (“Personal Digital Assistant”).

50. The method according to claim 48, wherein the step of sending a notification comprises the step steps of:

communicating with an extracorporeal home monitoring unit connected to said at least one communication network and, at said home monitoring unit, receiving said notification and transmitting said notification via said communication network to said medical care institution.

51. The method according to claim 27, further comprising the step of, upon detection of an occurrence of the myocardial infarction, automatically notifying said patient that the myocardial infarct has been detected and/or that therapy has been initiated.

52. The method according to claim 51, comprising notifying the patient via a vibration unit.

53-59. (canceled)

60. A computer-readable medium encoded with programming instructions, said medium being loadable into a control

unit of an implantable medical device comprising a pulse generator that emits cardiac stimulation pulses and at least one medical lead connected to the pulse generator for delivering the stimulating pulses in vivo to cardiac tissue of a heart of a patient, and a plurality of light emitting units carried by the at least one medical lead, said programming instructions causing said control unit to:

detect in vivo a myocardial infarction and to identify a location of the myocardial infarction; and

initiate an in vivo therapy session by selectively activating one or more of said light emitting units to emit therapeutic light toward the detected location of the myocardial infarction upon detection of an occurrence of the myocardial infarction.

* * * * *



US 20100168806A1

(19) **United States**

(12) **Patent Application Publication**

Norlin-Weissenrieder et al.

(10) **Pub. No.: US 2010/0168806 A1**

(43) **Pub. Date: Jul. 1, 2010**

(54) **DEVICE AND METHOD FOR TREATING
CARDIAC TISSUE OF A HEART OF A
PATIENT WITH THERAPEUTIC LIGHT
USING PHOTOBIMODULATION**

(86) PCT No.: **PCT/SE2006/001375**

§ 371 (c)(1),
(2), (4) Date: **Mar. 9, 2010**

(76) Inventors: **Anna Norlin-Weissenrieder,
Stockholm (SE); Leda Henriquez,
Vallingby (SE); Hans Stranberg,
Sundbyberg (SE); Eva Harström,
Hasselby (SE); Mikael Sjögren,
Fjardhundra (SE); Annika
Naeslund, Bromma (SE); Johan
Eckerdal, Knivsta (SE)**

Publication Classification

(51) **Int. Cl.**

A61N 1/05 (2006.01)
A61N 5/06 (2006.01)
A61N 1/362 (2006.01)

(52) **U.S. Cl.** **607/3; 607/122; 607/88; 607/92**

(57) **ABSTRACT**

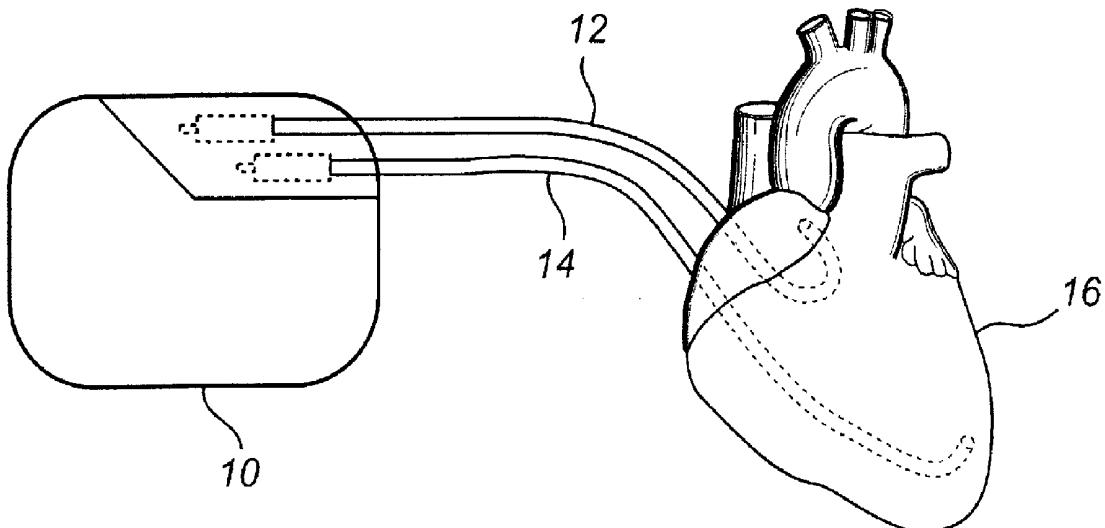
Correspondence Address:

**SCHIFF HARDIN, LLP
PATENT DEPARTMENT
233 S. Wacker Drive-Suite 6600
CHICAGO, IL 60606-6473 (US)**

(21) Appl. No.: **12/516,834**

(22) PCT Filed: **Nov. 30, 2006**

For treatment of cardiac tissue of a heart of a patient with therapeutic light using an implantable medical device connectable to at least one medical lead carrying electrodes and at least one fixation element that fixes the lead at a fixation area of the cardiac tissue, therapeutic light is emitted toward the at least one fixation area of cardiac tissue and/or toward a contact area between the at least one electrode and cardiac tissue using an intracorporeal light emitter.



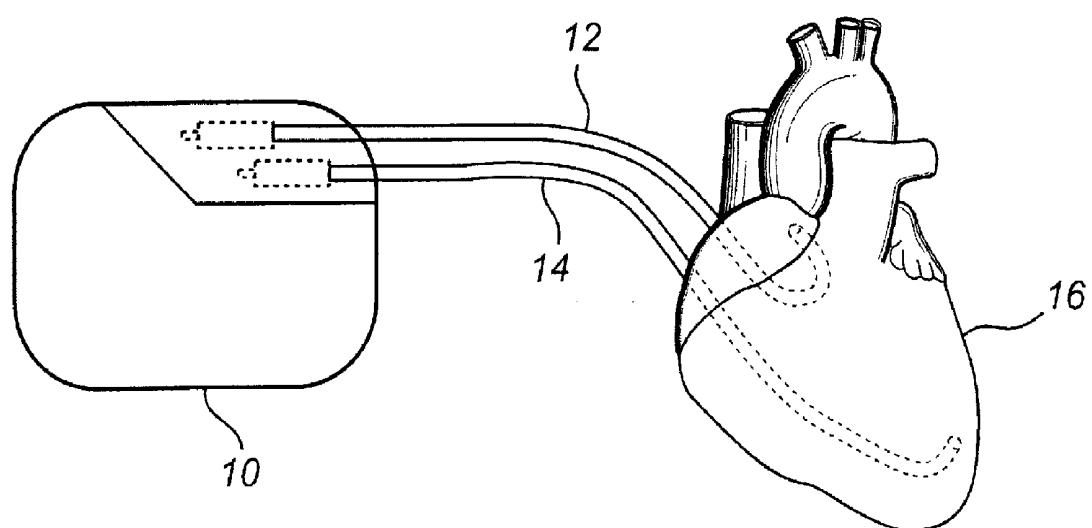


Fig. 1

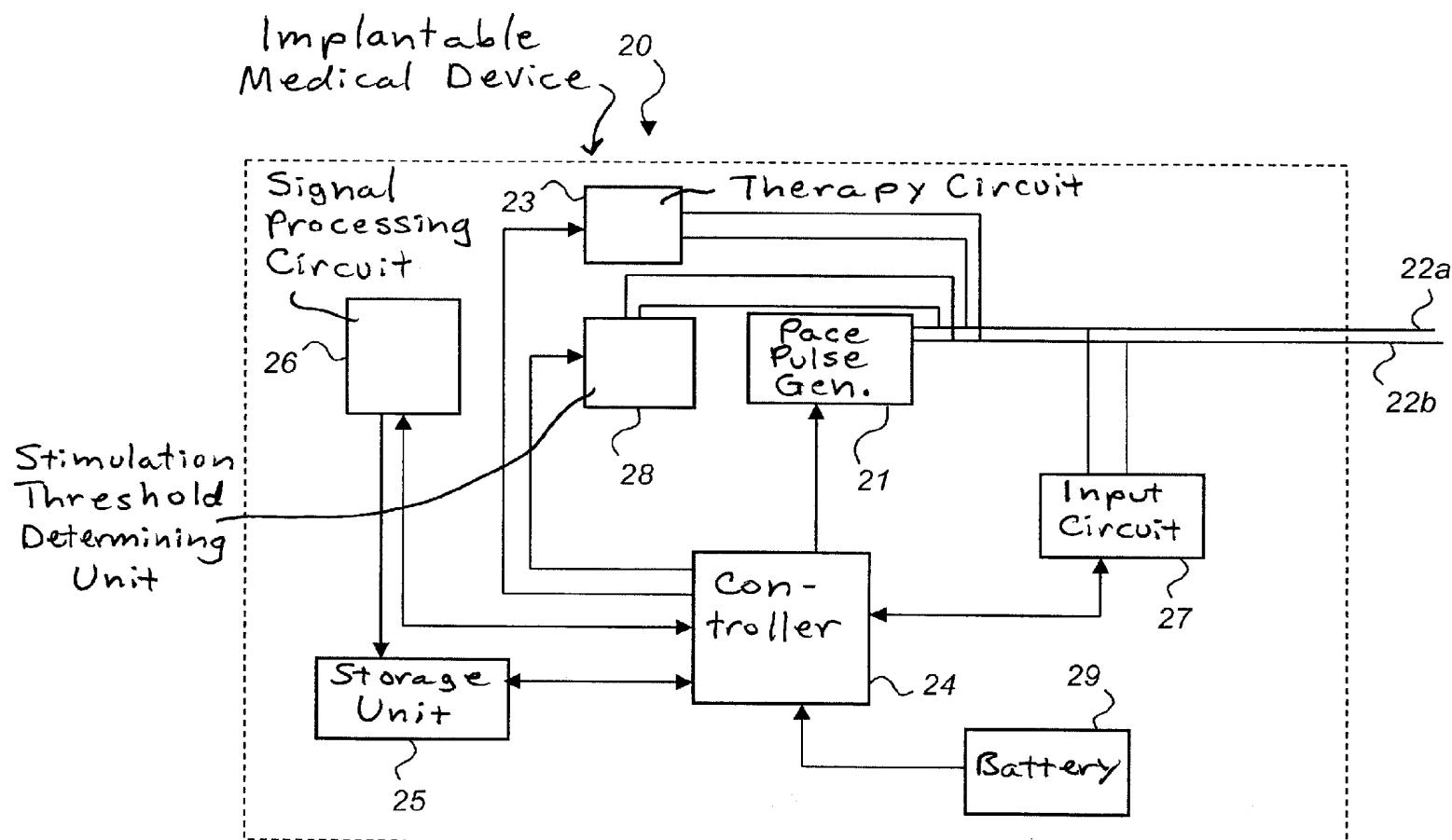


Fig. 2a

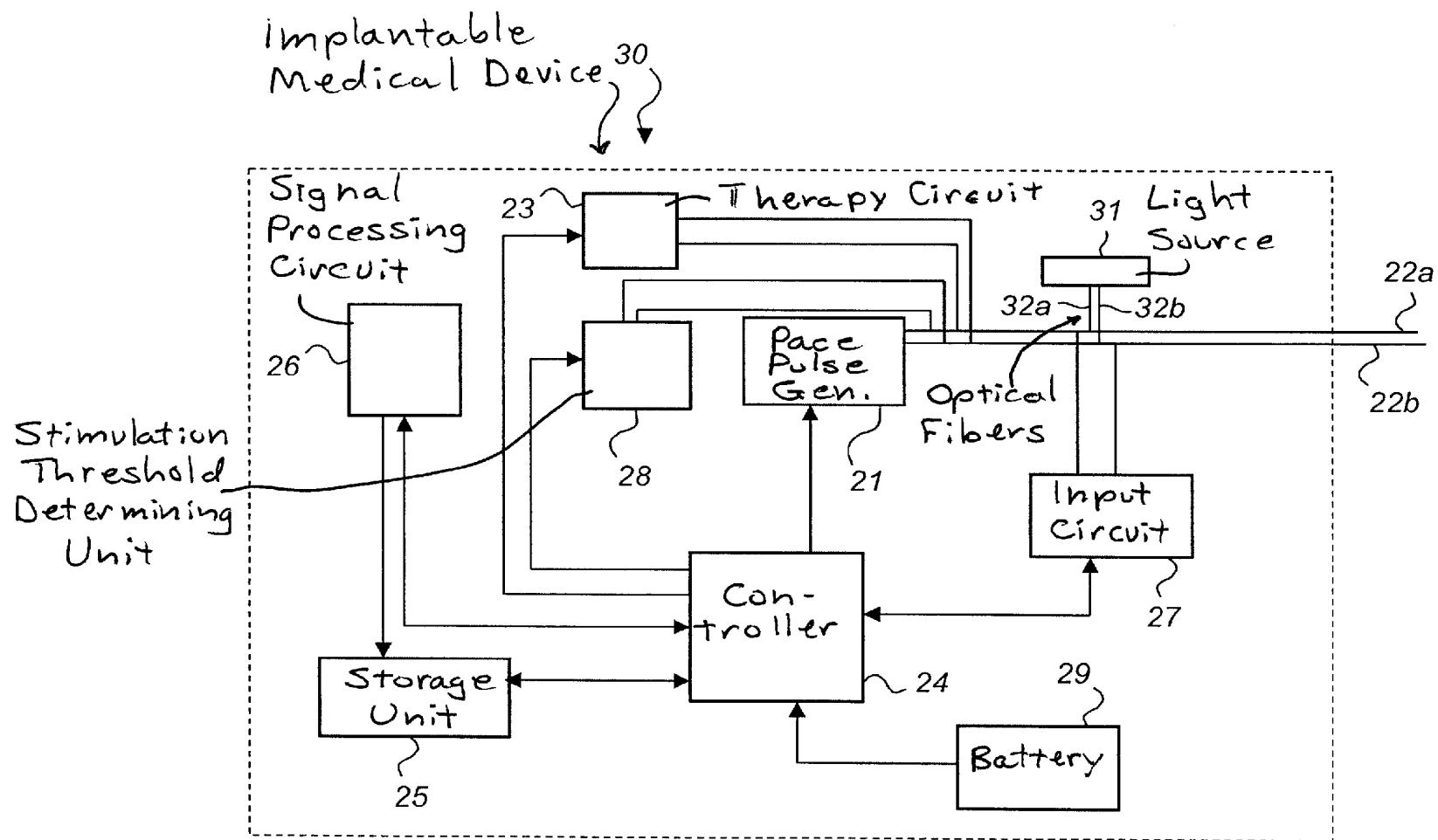


Fig. 2b

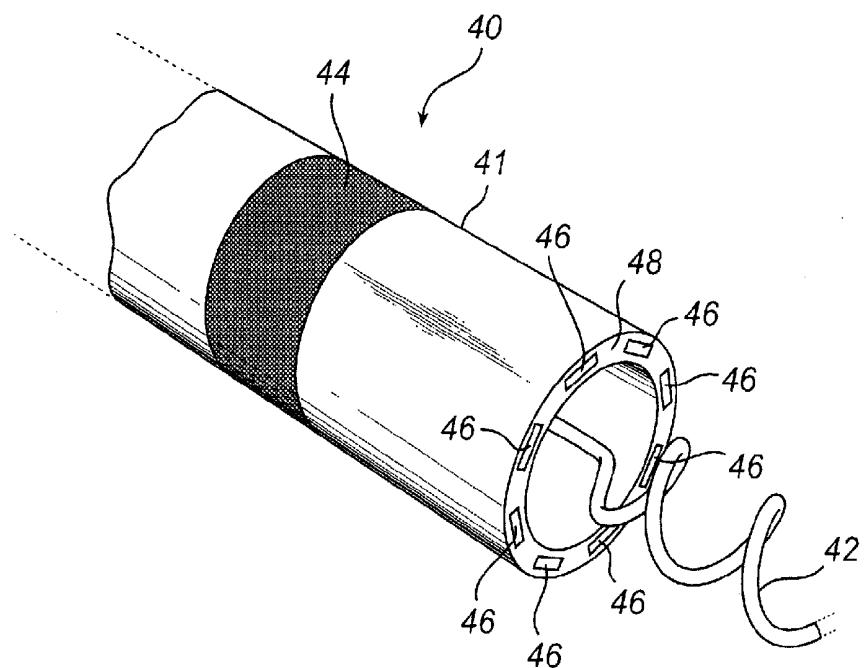


Fig. 3

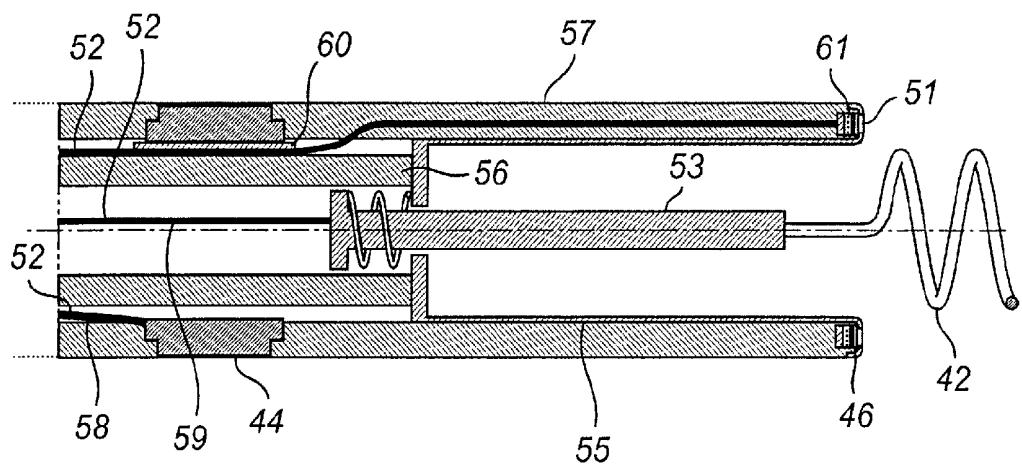


Fig. 4

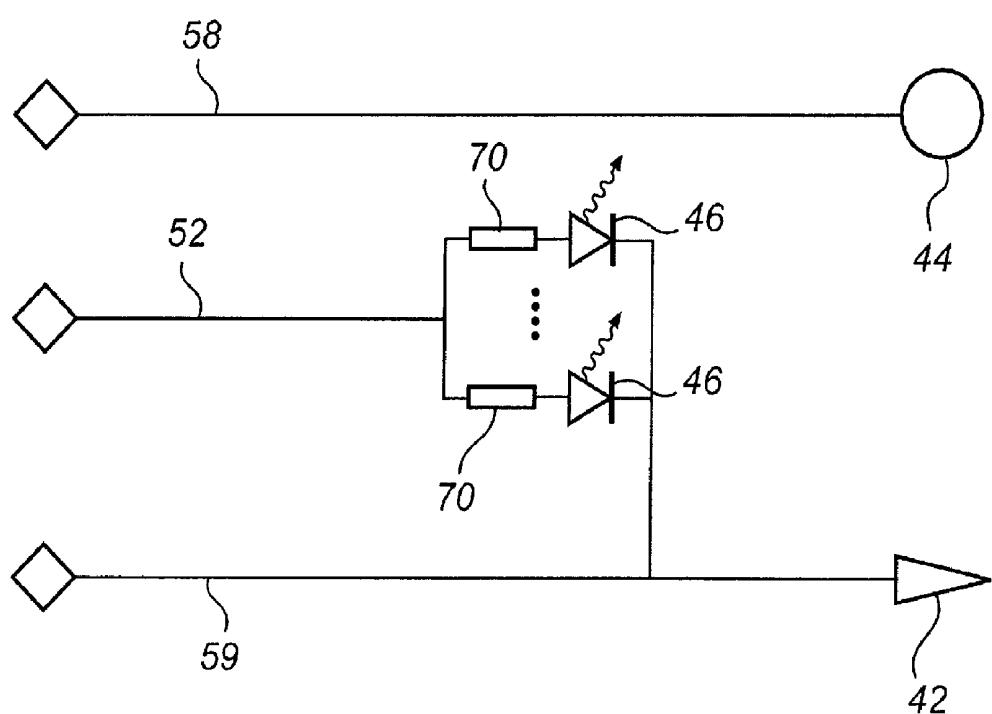


Fig. 5

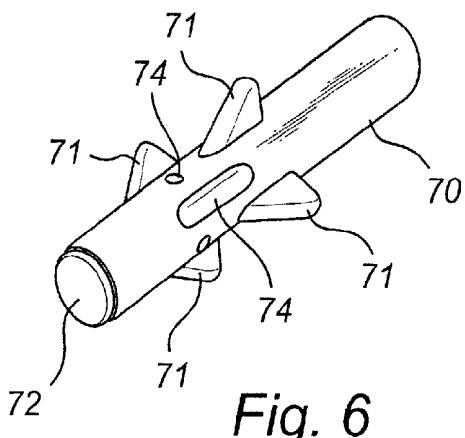


Fig. 6

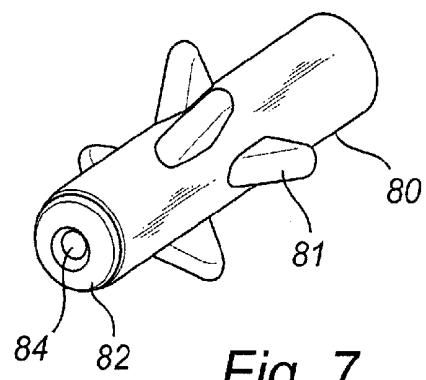


Fig. 7

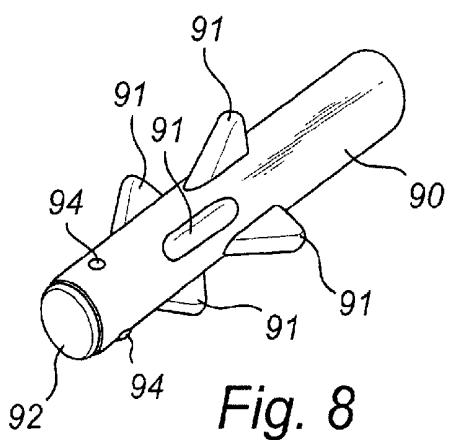


Fig. 8

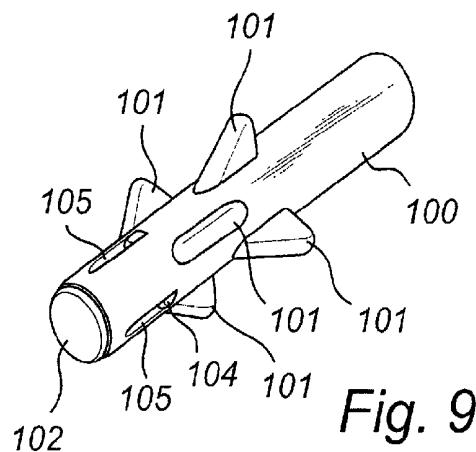


Fig. 9

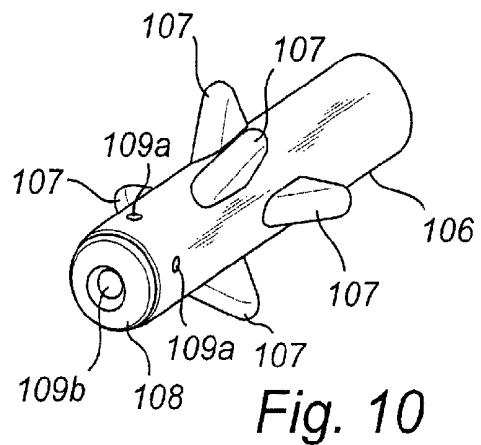


Fig. 10

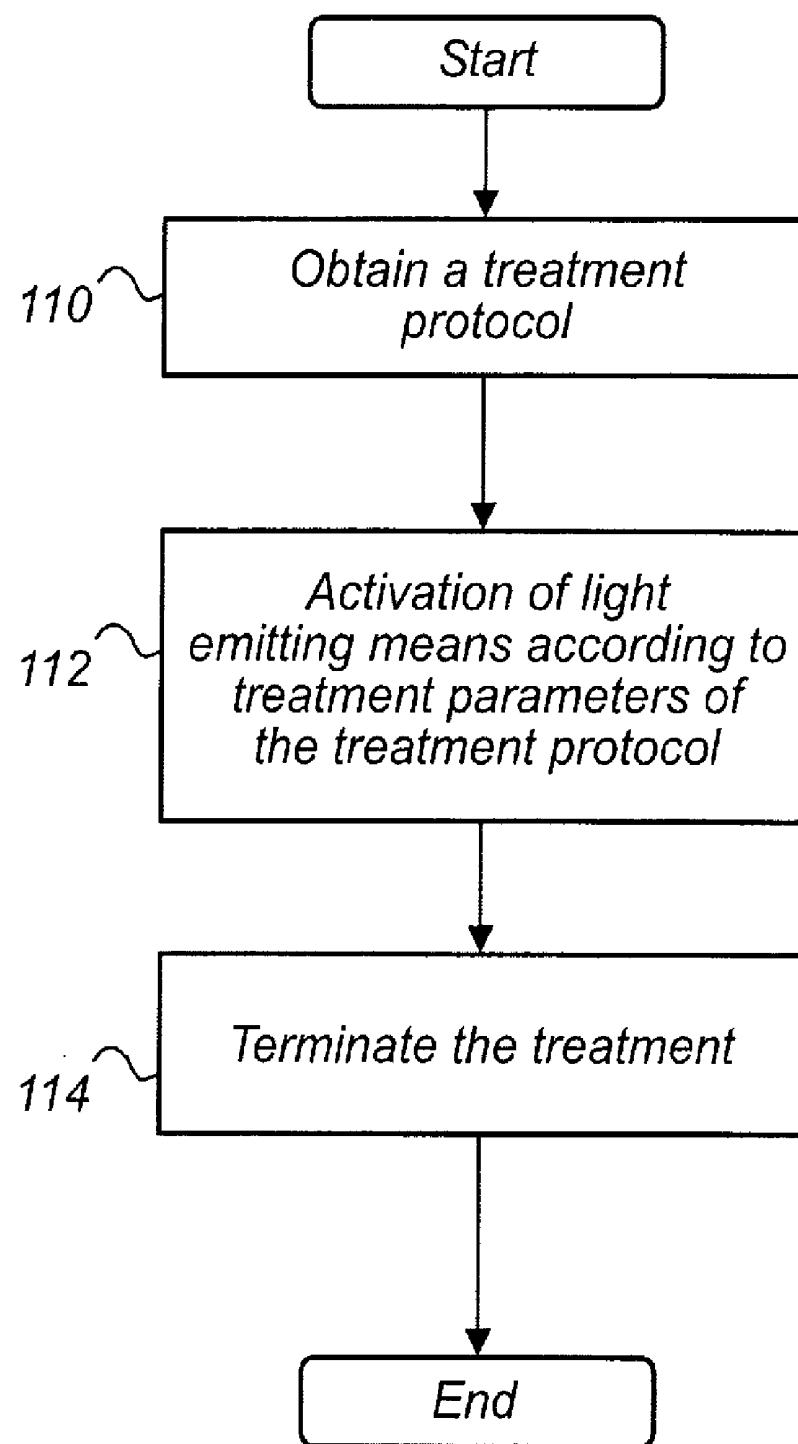


Fig. 11

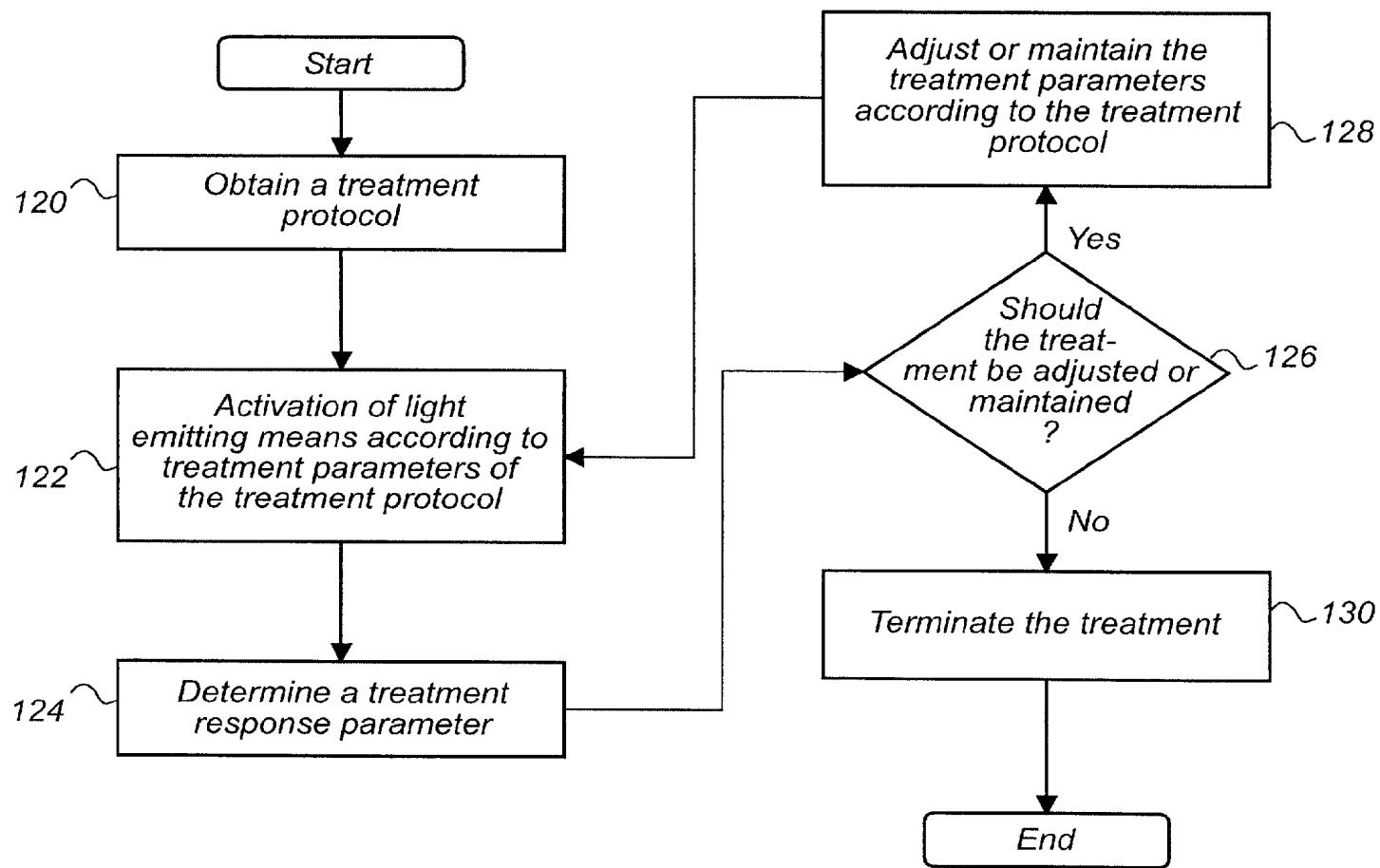


Fig. 12

DEVICE AND METHOD FOR TREATING CARDIAC TISSUE OF A HEART OF A PATIENT WITH THERAPEUTIC LIGHT USING PHOTOBIMODULATION

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

[0002] The present invention generally relates to cardiac pacing systems and, in particular, to methods, implantable medical devices, and a medical lead for treatment of cardiac tissue of a heart of a patient with therapeutic light using an implantable medical device.

[0003] 2. Description of the Prior Art

[0004] In pacemaker applications it is of high importance to design electrode surfaces with good biocompatibility in order to reduce the inflammatory responses. The amount and character of the inflammation affects the thickness of the scar tissue that encapsulates the electrode as a result of the healing and down regulation of the inflammation responses. Poor healing results in a thick scar tissue and hence the pacemaker is required to supply stimulation pulses of higher energy to be able to stimulate the healthy cardiac cells shielded by the scar tissue. The fact that the electrical field in one location decreases with the square of the distance to the source illustrates the importance to keep the fibrous tissue as thin as possible. Thus, to increase and ensure high efficiency of the pacemaker it is necessary to ensure a thin fibrous capsule formation around the electrode.

SUMMARY OF THE INVENTION

[0005] Thus, an object of the present invention is to provide a method, an implantable medical device and a computer program product for improving the healing of the trauma following the implantation of the cardiac electrode into the cardiac tissue.

[0006] Another object of the present invention is to provide a method, an implantable medical device and a computer program product for reducing a stimulation threshold at a contact area of the cardiac electrode.

[0007] A further object of the present invention is to provide a method, an implantable medical device and a computer program product for improving regeneration of cardiac cells after an implantation of cardiac electrodes.

[0008] According to an aspect of the present invention there is provided a medical lead that is connectable to an implantable medical device including a pulse generator adapted to produce cardiac stimulating pacing pulses. The medical lead has at least one fixation element that fixes the lead at at least one fixation area of cardiac tissue of the patient, at least one electrode for delivering the pulses to cardiac tissue of a heart of a patient when connected to the implantable medical device, and at least one intracorporeal light emitter that emits therapeutic light toward the at least one fixation area and/or toward at least one contact area of the cardiac tissue where the at least one electrode substantially abuts against the cardiac tissue.

[0009] According to a second aspect of the present invention there is provided an implantable medical device including a pulse generator adapted to produce cardiac stimulating pacing pulses. The implantable medical device is connectable to at least one lead carrying electrodes for delivering the pulses to cardiac tissue of a heart of a patient and at least one fixation element that fixes the lead at at least one fixation area

of cardiac tissue of the patient. Furthermore, the implantable medical device has at least one intracorporeal light emitter that emits therapeutic light toward the at least one fixation area and/or toward at least one contact area of the cardiac tissue where the at least one electrode substantially abuts against the cardiac tissue.

[0010] According to a third aspect of the present invention, there is provided a method for treating cardiac tissue of a heart of a patient with therapeutic light using an implantable medical device including a pulse generator adapted to produce cardiac stimulating pacing pulses. The implantable medical device is connectable to at least one lead carrying electrodes for delivering said pulses to cardiac tissue of a heart of a patient and at least one fixation element that fixes lead at at least one fixation area of cardiac tissue of the patient. The method includes the step of emitting therapeutic light toward the at least one fixation area of cardiac tissue and/or toward a contact area of the cardiac tissue where said the at least one electrode substantially abut against the cardiac tissue.

[0011] According to yet another aspect of the present invention, there is provided a medical system that includes an implantable medical device according to the second aspect of the present invention and at least one lead according to the first aspect of the present invention.

[0012] According to a further aspect of the present invention there is provided a computer-readable medium, directly loadable into an internal memory of an implantable medical device according to the second aspect of the present invention, encoded with software code for causing the implantable medical device to perform steps in accordance with the method according to the third aspect of the present invention.

[0013] The invention utilizes the technique photobiomodulation, also called Low Level Laser Therapy (LLLT), Cold Laser Therapy (CLT), Laser Biomodulation, phototherapy or Laser therapy, wherein certain wavelengths of light at certain intensities are delivered for a certain amount of time. More specifically, the present invention is based on the insight of using such therapeutic light to treat cardiac tissue at an implantation site of a cardiac electrode and/or an electrode contact area of the cardiac tissue. This is founded upon the findings that photobiomodulation has been proven to be a successful therapy in wound healing see, for example, "Effect of NASA light-emitting diode irradiation on wound healing", H. T. Whelan et. al., Journal of Clinical Laser Medicine and Surgery, 19, (2001) p 305. It was also confirmed by Whelan et. al. that the cell growth of various cell types in human and rat could be increased by up to 200% by irradiation of light of certain wavelengths. Furthermore, it has also been shown, for example, in "Low energy laser irradiation reduces formation of scar tissue after myocardial infarction in rats and dogs", U. Oron, et. al., Circulation, 103, (2001), p 296, that light therapy improves the regeneration of the cardiac cells and decreases the scar tissue formation following a myocardial infarction.

[0014] Thus, the present invention provides a number of advantages, for example, the healing of the trauma following the implantation of the cardiac electrode into the cardiac tissue can be improved and enhanced. Furthermore, the stimulation threshold at a contact area of the cardiac electrode can be reduced significantly. A further advantage of the present invention is that the regeneration of cardiac cells after an implantation of cardiac electrodes is improved.

[0015] According to one embodiment, the light emitter is at least one light emitting diode. The at least one light emitting diode may be arranged at a distal tip portion of the medical lead

adjacent to the fixation element or to an electrode. In other embodiments, the light emitter is arranged at an outer periphery of the medical lead, for example, in proximity of fixation means arranged at the outer periphery, e.g. tines.

[0016] In a further embodiment, the medical lead includes at least one optical fiber that conducts light from at least one light source arranged in the implantable medical device such that the conducted therapeutic light emanates from the at least one optical fiber toward at least one fixation area and/or toward at least one contact area between an electrode and cardiac tissue.

[0017] According to embodiments of the present invention, measurable indicators of the healing process are monitored and obtained, continuously or regularly, and in one embodiment, a stimulation threshold is measured or calculated. The fact that during the damage and healing time of 1-4 weeks, the threshold value normally first increases significantly from the value at the implantation and then returns to about the initial value. The treatment can be delivered according to predetermined time schedule, utilizing the above mentioned healing process, or based on feedback from the healing process using, for example, the stimulation threshold such that a variation of the measured thresholds indicates a variation of treatment parameters, for example, an intensity of light. The treatment can be completed when the reduction of the threshold values has ceased. For example, average threshold values can be determined and compared periodically with preceding average values (e.g. an average over a 24 hour period) to obtain a trend over the development of the stimulation threshold, i.e. over the healing process. In the beginning, a trend with increasing values will be obtained and, then one or a few peak values will be identified and altered when the average values will start to decrease. When the decline of the trend has come to an end, the treatment will be stopped. The treatment may be more potent during the phase with increasing threshold values and may be maintained or decreased at the identification of the peak value or values. A more potent treatment may be a higher degree of intensity of light or a constant intensity of light but with a changed intermittence, i.e. longer period of light delivery or a more frequent light delivery with a constant period of light delivery.

[0018] In one embodiment of the present invention, the light emitting means are activated such that therapeutic light is emitted according to a treatment protocol including treatment parameters comprising one, a number of or all of: emitting intervals of the therapeutic light, intensity of the emitted therapeutic light, wavelength of the emitted light, intermittence of the emitted therapeutic light, or treatment periods. The protocol may thus comprise a predetermined treatment scheme. In an alternative embodiment, the treatment is varied in dependence of one or more treatment response parameters.

[0019] According to another embodiment, the at least one treatment response parameter is a stimulation threshold at a contact area between an electrode and the cardiac tissue.

[0020] In embodiments of the present invention, the light emitting means are adapted to emit coherent and monochromatic light having a wavelength in the range of 600 nm-1000 nm. Furthermore, an intensity of 6 to 50 mW/cm² and a total dosage of about 1 to 4 J/cm² may be used.

[0021] As realized by the person skilled in the art, steps of the methods of the present invention, as well as preferred embodiment thereof, are suitable to realize as a computer program or a computer readable medium.

[0022] The features that characterize the invention, both as to organization and to method of operation, together with further objects and advantages thereof, will be better understood from the following description used in conjunction with the accompanying drawings. It is to be expressly understood that the drawings are for the purpose of illustration and description and is not intended as a definition of the limits of the invention. These and other objects attained, and advantages offered, by the present invention will become more fully apparent as the description that now follows is read in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] FIG. 1 schematically shows a pacemaker system including an implantable medical device and medical leads in accordance with the present invention.

[0024] FIG. 2a schematically illustrates an embodiment of the implantable medical device according to the present invention.

[0025] FIG. 2b schematically illustrates another embodiment of the implantable medical device according to the present invention.

[0026] FIG. 3 is a projection view of an embodiment of a medical lead according to the present invention.

[0027] FIG. 4 is a cross-sectional view of the medical lead shown in FIG. 3.

[0028] FIG. 5 is a circuit diagram illustrating a supply circuit for the diodes of the medical lead shown in FIGS. 3 and 4.

[0029] FIG. 6a is a projection view of another embodiment of a medical lead according to the present invention.

[0030] FIG. 7a is a projection view of a further embodiment of a medical lead according to the present invention.

[0031] FIG. 8a is a projection view of yet another embodiment of a medical lead according to the present invention.

[0032] FIG. 9a is a projection view of still another embodiment of a medical lead according to the present invention.

[0033] FIG. 10a is a projection view of a further embodiment of a medical lead according to the present invention.

[0034] FIG. 11 is a high-level flow chart of an embodiment of the method for treating cardiac tissue of a heart of a patient with therapeutic light using an implantable medical device according to the present invention.

[0035] FIG. 12 is a high-level flow chart of another embodiment of the method for treating cardiac tissue of a heart of a patient with therapeutic light using an implantable medical device according to the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0036] In the following, the present invention will be discussed in the context of medical systems comprising at least an implantable pacemaker such as a bi-ventricular pacemaker, and medical leads such as an atrial lead and a ventricular lead.

[0037] With reference first to FIG. 1, a pacemaker system has an implantable bi-ventricular pacemaker 10 connectable to an atrial lead 12 and a ventricular lead 14 including electrodes for providing therapy to a heart 16 of a patient. The leads 12, 14 are implanted into the heart 16 via veins and are fixed at the cardiac tissue by means of, for example, helical screws. As discussed above, the helical screw and/or the electrodes will cause tissue damages, which entail, inter alia,

increased stimulation threshold values. This will, in turn, lead to an impaired therapy and an impaired ability to detect heart signals. The healing process of the damaged tissue will eventually improve the therapy, e.g. due to a reduced stimulation threshold.

[0038] According to the invention, a light emitter is arranged such that therapeutic light is emitted at areas of damaged cardiac tissue following an implantation, e.g. at fixation areas of the helical screws and/or at the contact areas of the electrodes, which will be discussed in more detail below.

[0039] Turning now to FIGS. 2a and 2b, an embodiment of an implantable medical device, e.g. a bi-ventricular pacemaker, according to the present invention will be discussed. The implantable medical device 20 has a housing (not shown) being hermetically sealed and biologically inert. Normally, the housing is conductive and may, thus, serve as an electrode. The pacemaker 20 is connectable to one or more pacemaker leads. Only two leads are shown in FIGS. 2a and 2b; namely a ventricular lead 22a implanted in the right ventricle of the heart (not shown) and one atrial lead 22b implanted in the right atrium of the heart (not shown).

[0040] The leads 22a and 22b can be electrically coupled to the pacemaker 20 in a conventional manner. The leads 22a, 22b comprises one or more electrodes, such as a tip electrode or a ring electrode, arranged to, inter alia, measure the impedance or transmit pacing pulses for causing depolarization of cardiac tissue adjacent to the electrode (-s) generated by a pace pulse generator 21 under influence of a controller or controlling circuit 24 including a microprocessor. The controller 24 controls, inter alia, pace pulse parameters such as output voltage and pulse duration.

[0041] Moreover, a storage unit 25 is connected to the controller 24. The storage unit 25 may include a random access memory (RAM) and/or a non-volatile memory such as a read-only memory (ROM). The storage unit 25 is connected to the controller 24 and a signal processing circuit 26. Detected signals from the patient's heart are processed in an input circuit 27 and are forwarded to the controller 24 for use in logic timing determination in known manner.

[0042] In this embodiment, light emitting means (see, for example, FIGS. 3 and 4) is arranged at a distal tip of the leads 22a, 22b and is connected to the controller 24. In one embodiment, the light emitter in form of a light emitting diode is arranged at the periphery of each of the ends of tube-shaped leads. The light emitting diodes are adapted to emit monochromatic light having a wavelength of 600-1000 nm. The light emitting diodes are connected to a therapy circuit 23 adapted to activate the diodes under control of the controller 24. After implantation, the tube-shaped ends will abut the cardiac tissue and emitted light from the diodes will penetrate into the cardiac tissue at and around the electrode tips. The controller 24 is hence adapted to activate the diodes via the therapy circuit 23 according to a treatment protocol, which may include predetermined or adjustable treatment parameters such as emitting intervals of the therapeutic light, intensity of the emitted therapeutic light, wavelength of the emitted light, and intermittence of the emitted therapeutic light.

[0043] Furthermore, a stimulation threshold determining unit 28 is arranged in the implantable medical device 20 connected to the electrodes of the leads 22a, 22b. The stimulation threshold determining unit 28 is adapted to determine stimulation threshold values of the at least one contact area of the electrodes using pacing responses of at least one applied

stimulation pulse. For example, the controller 24 may perform a stimulation threshold test procedure including applying at least one stimulation pulse via at least one the electrodes, for example, a series of stimulation pulses having stepwise increased voltage. The stimulation threshold determining unit 28 may measure the pacing responses of the applied stimulation pulses and determine stimulation threshold values of the contact area (-s) of using the pacing responses. Moreover, the stimulation threshold determining unit 28 may be adapted to determine an average stimulation threshold value (-s) using pacing responses of series of stimulation pulses applied during a period of time having a predetermined length. This average stimulation threshold value (-s) may be compared with average stimulation threshold values for at least one preceding period of time to determine a trend of the simulation threshold values, which average stimulation threshold values and/or trend of average stimulation threshold values may be used to adjust treatment parameters of the treatment protocol.

[0044] Thus, the stimulation threshold may be used as an indicator of the healing process. During the therapy period, e.g. 1-4 weeks after the implantation, the threshold value will normally increase significantly from the value at the implantation and will eventually decrease to the implantation value. Therefore, a suitable way of identifying when the therapy should be finished is when the reduction of the threshold value has ceased. This is, according to the embodiment of the invention described above, measured by averaging the threshold values over predetermined period of times, for example, over twenty-four hours and is compared with corresponding average values for preceding twenty-four hour periods. In the beginning of the healing process, the values will disclose an increasing trend, i.e. gradually increase over time, and eventually the values will begin to decrease gradually. When the decreasing of the values has ceased, the therapy is determined to be finished.

[0045] The therapy parameters can be adjusted during the treatment procedure. For example, a higher light intensity can be used during the increasing trend of the average values and the light intensity can be reduced during the decreasing trend. Alternatively, a constant light intensity but an adjusted intermittence can be utilized, e.g. the periods of light delivery can be adjusted or shorter intervals between the periods of light delivery are used.

[0046] The implantable medical device 20 is powered by a battery 29, which supplies electrical power to all electrical active components of the implantable medical device 20 including the light emitting means and stimulation threshold determining unit 28. The implantable medical device 20 further comprises a communication unit (not shown), for example, an RF (Radio Frequency) telemetry circuitry for providing RF communications. Thereby, for example, data contained in the storage unit 25 can be transferred to an external programmer device (not shown) via the communication unit and a programmer interface (not shown) for use in analyzing system conditions, patient information, etc.

[0047] Referring to FIG. 2b, a further embodiment of the implantable medical device according to the present invention will be discussed. Like parts in the implantable medical device shown in FIG. 2a and FIG. 2b will be denoted with the same reference numerals and descriptions thereof will be omitted since they have been described above with reference to FIG. 2a. A light source 31 is arranged in the implantable medical device 30, for example, a laser adapted to emit mono-

chromatic light having a wavelength of 600-1000 nm. The light source 31 is connected to a first optical fiber 32a arranged in the ventricular lead 22a and a second optical fiber 32b arranged in the atrial lead 22b. The optical fibers 32a, 32b are arranged to conduct light emitted by the light source such that the conducted therapeutic light emanates from the optical fibers 32a, 32b toward at least one fixation area of the fixation means of the cardiac tissue and/or at least one contact area of the cardiac tissue of the at least one electrode. This will be discussed in more detail below with reference to FIG. 5

[0048] With reference to FIGS. 3, 4, and 5, an embodiment of a medical lead according to the present invention will be discussed. The tube-like medical lead 40, e.g. the ventricular lead 22a or the atrial lead 22b discussed above, has a tip screw or helicoidal electrode 42, which may be fixed or extensible, and a ring electrode 44. Furthermore, a number of light emitting diodes 46 are arranged at the periphery 48 of the tube-like end 41 of the lead 40. At an implantation of the lead 40 into the heart of a patient, the helicoidal electrode is screwed into the cardiac tissue and the periphery 48 of the lead will abut against the cardiac tissue. During a treatment procedure when therapeutic light is applied to the tissue, it will penetrate into the tissue substantially at and about the helicoidal electrode 42.

[0049] In FIG. 4, a cross-sectional view of the electrode tip of the lead according to the present invention shown in FIG. 3 is illustrated. The tip screw electrode 42 of the lead 40 is, at implantation, screwed in to the cardiac tissue such that the light emitting diodes 46 will abut against the cardiac tissue. In this embodiment, the light emitting diodes 46 are protected from direct contact with body fluids and/or cardiac tissues by means of transparent elements 51, which according to one embodiment may be glass windows. The diodes 46 may be arranged at an angle such that the emitted light is centred towards the helicoidal electrode 42. Alternatively, the transparent elements 51 may be designed as prisms to achieve the centring of the emitted light. Each light emitting diode 46 is supplied with current via an electric conductor 52, which conductors 52, in turn, are connected to the therapy circuit 23.

[0050] The helicoidal electrode 42 is attached to a movable shaft 53 and a connector spring 54 is arranged between the shaft 53, a mapping collar 55, and an inner insulating tube 56. An outer insulating tube 57 forms the outer housing of the lead 40. The ring electrode 44 is connected to an electrical conductor 58 and via the conductor 58 to, inter alia, the pace pulse generator 21 and/or the stimulation threshold determining means 28. Furthermore, the helicoidal electrode 42 is connected to an electrical conductor 59 and via the conductor 59 to, inter alia, the pace pulse generator 21 and/or the stimulation threshold determining means 28. The ring electrode 44 is isolated from the electric conductor 52 with an insulation sheet 60.

[0051] The light emitting diodes 46 is connected to the mapping collar 55 and to a connection ring 61, which in one embodiment is an electrically conducting rubber flange. The electrically conducting ring 61 has two functions; to mechanically press the diodes 46 such that an adequate electrical connection is achieved and to provide an electrical resistance at the supply to the diodes 46, see FIG. 5, to distribute the current to each of the diodes 46 in an even manner.

[0052] The electrical conductors 52, 58, 59 are preferably arranged as helicoidal wires.

[0053] With reference to FIG. 5, an embodiment of a connection circuit for the electrodes 42, 44 and light emitting diodes 46. In FIG. 4, one electric conductor 58 to the light emitting diodes was shown. However, each diode 46 could be connected to and supplied via one conductor. In FIG. 5, the diodes 46 are supplied with one conductor 58 via resistance elements 68 for current distribution, for example, 1-100 ohm.

[0054] The light emitting diodes are preferably designed to provide a light treatment at an intensity 6-50 mW/cm² and a total dosage of 1-4 J/cm² per day.

[0055] Referring now to FIGS. 6-10, further embodiments of the present invention will be discussed. In FIG. 6, a medical lead 70 with a number of tines 71 for fixating the lead 70 at the cardiac tissue is shown. A tip electrode 72 will, after the implantation, abut against the cardiac tissue. Furthermore, a number of light emitting diodes 74 are arranged at the outer surface of the tube-like lead 70 such that emitted therapeutic light can be applied at fixation areas of the tines 71 in the cardiac tissue.

[0056] In FIG. 7, a further embodiment of the medical lead according to the present invention is shown. The medical lead 80 is provided with a number of tines 81 for fixating the lead 80 at the cardiac tissue. An annular tip electrode 82 is arranged at the tip of the lead and will, after the implantation, abut against the cardiac tissue. A light emitting diode 84 is arranged at the centre of the tip portion of the lead. When implanted, the light emitting diode can emit therapeutic light at a contact area between the electrode 82 and the cardiac tissue.

[0057] In FIG. 8, yet another embodiment of the medical lead according to the present invention is shown. The medical lead 90 is provided with a number of tines 91 for fixating the lead 90 at the cardiac tissue. A tip electrode 92 will, after the implantation, abut against the cardiac tissue. Furthermore, a number of light emitting diodes 94 are arranged at the outer surface or periphery of the tube-like lead 90 such that emitted therapeutic light can be applied or directed at fixation areas of the tines 91 in the cardiac tissue.

[0058] According to still another embodiment of the medical lead in accordance with the present invention, see FIG. 9, the medical lead 100 is provided with a number of tines 101 for fixating the lead 100 at the cardiac tissue and a tip electrode 102 that will abut against the cardiac tissue after the implantation. Moreover, a number of light emitting diodes 104 are arranged at the outer surface of the tube-like lead 100. Each diode 104 is arranged in a groove 105 such that emitted therapeutic light can be applied at fixation areas of the tines 101 in the cardiac tissue and at a contact area between the electrode 102 and the cardiac tissue.

[0059] Referring now to FIG. 10, yet another embodiment of the present invention will be described. The medical lead 106 is provided with a number of tines 107 for fixating the lead 106 at the cardiac tissue and a tip electrode 108 that will abut against the cardiac tissue after the implantation. Moreover, a number of light emitting diodes 109a are arranged at the outer surface of the tube-like lead 106 and a light emitting diode 109b is arranged at the centre of the tip portion of the lead.

[0060] As the person skilled within the art easily realizes, there are a number of conceivable variation to the embodiments described above with reference to FIG. 6-10. For example, the medical lead can be provided with a diode at the centre of the tip portion of the lead and diodes arranged in respective grooves.

[0061] Turning now to FIG. 11, high level flow chart of an embodiment of the method for treating cardiac tissue of a heart of a patient with therapeutic light using an implantable medical device, such as a pacemaker of the type described above, will be discussed.

[0062] After a treatment procedure is initiated, the controller 24 obtains, at step 110, a treatment protocol including treatment parameters comprising: emitting intervals of the therapeutic light, intensity of the emitted therapeutic light, wavelength of the emitted light, intermittence of the emitted therapeutic light, and treatment periods. This protocol may be stored in the storage means 25 of the implantable medical device 20, 30. Alternatively, the treatment protocol may be transferred wirelessly to the controller via the communication unit (not shown) from an external programmer workstation. Furthermore, the treatment protocol may be predetermined and/or adapted to the patient. The protocol may also be updated and/or adjusted during a therapy, as will be discussed below, as a response of the applied therapy or upon instructions from, for example, a physician received via the communication unit and the programmer workstation. The therapy may be initiated upon receiving an instruction from the physician received via the communication unit and the programmer workstation.

[0063] Thereafter, at step 112, at least one light emitting means, e.g. the light emitting diodes discussed above, is activated in accordance with the treatment protocol. The light therapy is in this embodiment performed in accordance with a predetermined treatment protocol. For example, during a first initial period (e.g. 1-2 weeks), the treatment may be more potent by using a high degree of brightness, or a lower degree of brightness and a changed intermittence, i.e. longer periods of applied light or a more frequent delivery of light with a shorter period of applied light. After this initial period, the treatment can be adjusted during a second period of time (e.g. 1-2 weeks) in that the potency of the therapy is lowered, for example, by using a lower degree of brightness, or a lower degree of brightness and a changed intermittence, i.e. shorter periods of applied light or a more frequent delivery of light with a shorter period of applied light. Subsequently, at step 114, the therapy is terminated.

[0064] With reference instead to FIG. 12, high level flow chart of another embodiment of the method for treating cardiac tissue of a heart of a patient with therapeutic light using an implantable medical device, such as a pacemaker of the type described above, will be discussed.

[0065] After a treatment procedure is initiated, the controller 24 obtains, at step 120, a treatment protocol including treatment parameters comprising: emitting intervals of the therapeutic light, intensity of the emitted therapeutic light, wavelength of the emitted light, intermittence of the emitted therapeutic light, and treatment periods. This protocol may be stored in the storage means 25 of the implantable medical device 20, 30. Alternatively, the treatment protocol may be transferred wirelessly to the controller via the communication unit (not shown) from an external programmer workstation. Furthermore, the treatment protocol may be predetermined and/or adapted to the patient. The protocol may also be updated and/or adjusted during a therapy, as will be discussed below, as a response of the applied therapy or upon instructions from, for example, a physician received via the communication unit and the programmer workstation. The therapy

may be initiated upon receiving an instruction from the physician received via the communication unit and the programmer workstation.

[0066] Thereafter, at step 122, at least one light emitting means, e.g. the light emitting diodes discussed above, is activated in accordance with the treatment protocol. The light therapy is in this embodiment performed with continuous feedback from healing process. It is continuously checked, at regular intervals, whether a stimulation threshold at a contact area between an electrode and the cardiac tissue satisfies predetermined criteria. Hence, the healing process is continuously monitored in order to adjust the therapy to the healing process such that a variation of measured thresholds provides information whether, for example, the intensity of light or brightness of light should be adjusted or whether the treatment should be terminated.

[0067] At step 124, a treatment response parameter is determined or calculated, which in this embodiment is a stimulation threshold. This can be done, for example, by applying at least one stimulation pulse via at least one electrode, measuring pacing responses of the at least one applied stimulation pulse; and determining stimulation threshold values of the at least one contact area of the electrode using the pacing responses. In one embodiment, an average stimulation threshold value is determined using pacing responses of stimulation pulses applied during a period of time having a predetermined length. Furthermore, these average values can be used to determine a trend of the stimulation threshold values over time.

[0068] According to one embodiment, initial treatment parameters are used during a period with increasing threshold values, the treatment parameters are adjusted when a decreasing trend has been identified or at the occurrence of a number of peak values, and the treatment is terminated when the decreasing trend has levelled or has come to an end. In a certain embodiment, the parameters of the initial treatment is set such that the treatment is made with a high degree of brightness, or a lower degree of brightness and a changed intermittence, i.e. longer periods of applied light or a more frequent delivery of light with a shorter period of applied light. When a decreasing trend has been identified or at the occurrence of a number of peak values, the treatment is adjusted such that the potency of the therapy is lowered, for example, by using a lower degree of brightness, or a lower degree of brightness and a changed intermittence, i.e. shorter periods of applied light or a more frequent delivery of light with a shorter period of applied light. Finally, the treatment is terminated when the decreasing trend has levelled or has come to an end. Thus, at step 124, an average stimulation threshold value is determined or calculated. Subsequently, at step 126, the present average value is compared with previously calculated threshold to determine the trend. If it is found that the treatment parameters should be adjusted or maintained, for example, in accordance with the description given above, the algorithm proceeds to step 128 where the parameter or parameters is/are adjusted or maintained. Then, the algorithm returns to step 122. On the other hand, if it is found that the treatment should be terminated, the algorithm proceeds to step 130 where the treatment is terminated.

[0069] As those skilled within the art will realize, there are a number of alternative and conceivable variations of the above-described method, for example, in regard to the monitoring of the healing process.

[0070] Although an exemplary embodiment of the present invention has been shown and described, it will be apparent to those having ordinary skill in the art that a number of changes, modifications, or alterations to the inventions as described herein may be made. Thus, it is to be understood that the above description of the invention and the accompanying drawings is to be regarded as a non-limiting example thereof and that the scope of protection is defined by the appended patent claims.

We claim as our invention:

1-41. (canceled)

42. An implantable medical lead comprising:
an elongate lead body configured for in vivo implantation in a subject, said lead body having first and second lead body ends;
an electrical conductor extending in said lead body, said electrical conductor having a first conductor end at said first lead body end configured for electrical connection to a pulse generator to receive electrical stimulating pulses therefrom, and having a second conductor end approximately coextensive with said second lead body end;
at least one electrode connected to said second conductor end configured for in vivo exposure to cardiac tissue of the subject to deliver said stimulating pulses to said tissue at a contact area where said electrode abuts said tissue;
a fixation element carried by said lead body at said second lead body end, said fixation element being configured to interact with said tissue in a fixation area to hold said electrode against said tissue in said contact area; and
at least one light emitter carried by said lead body at said second lead body end that emits biomodulating light in vivo, said light emitter being located at said second lead body end, relative to said electrode and to said fixation element, to cause said biomodulating light to be emitted toward at least one of said fixation area and said contact area.

43. A medical lead as claimed in claim **42** wherein said light emitter is configured for connection to a control circuit that activates said light emitter to emit said biomodulating light according to a treatment protocol.

44. A medical lead as claimed in claim **43** wherein said light emitter is operable by said control circuit according to a treatment protocol comprising treatment parameters selected from the group consisting of emission duration of said biomodulating light, intensity of said biomodulating light, a wavelength of said biomodulating light, and times between emission of said biomodulating light.

45. A medical lead as claimed in claim **42** wherein said light emitter comprises at least one light emitting diode.

46. A medical lead as claimed in claim **45** wherein said lead body has a tip at said second lead body end, and wherein said at least one light emitting diode is located at said tip adjacent to said fixation element.

47. A medical lead as claimed in claim **46** wherein said at least one light emitting diode is located at said tip adjacent to said electrode.

48. A medical lead as claimed in claim **42** wherein said light emitter comprises at least one optical fiber carried in said lead body and configured for optical communication with a light source of said biomodulating light.

49. A medical lead as claimed in claim **42** wherein said electrical conductor is configured for connection to a stimula-

tion threshold determining unit that determines a stimulation threshold value for said contact area dependent on response of said tissue to at least one delivered electrical stimulation pulse.

50. A medical lead as claimed in claim **49** wherein said stimulation threshold determining unit is configured to determine an average stimulation threshold value from a plurality of responses of said tissue to a plurality of delivered stimulation pulses during a period of time having a predetermined duration.

51. A medical lead as claimed in claim **50** wherein said stimulation threshold determining unit is configured to compare said average stimulation threshold value for a current period of time with at least one preceding average stimulation threshold value obtained during a preceding period of time, to determine a trend of said stimulation threshold values.

52. A medical lead as claimed in claim **51** wherein said light emitter is configured for connection to a control circuit that activates said light emitter to emit said biomodulating light according to a treatment protocol, and wherein said control circuit is supplied with at least one of said average stimulation threshold value and said trend, and is configured to adjust said treatment protocol dependent on said at least one of said average stimulation threshold value and said trend.

53. A medical lead as claimed in claim **42** wherein said light emitter is configured to emit coherent and monochromatic light as said biomodulating light.

54. A medical lead as claimed in claim **42** wherein said light emitter is configured to emit biomodulating light having a wavelength in a range between 600 nm and 1000 nm.

55. An implantable medical device comprising:
a pulse generator configured for in vivo in a subject, that emits electrical stimulation pulses;
an elongate lead body configured for in vivo implantation in the subject, said lead body having first and second lead body ends;
an electrical conductor extending in said lead body, said electrical conductor having a first conductor end at said first lead body end configured for electrical connection to said pulse generator to receive said electrical stimulating pulses therefrom, and having a second conductor end approximately coextensive with said second lead body end;
at least one electrode connected to said second conductor end configured for in vivo exposure to cardiac tissue of the subject to deliver said stimulating pulses to said tissue at a contact area where said electrode abuts said tissue;
a fixation element carried by said lead body at said second lead body end, said fixation element being configured to interact with said tissue in a fixation area to hold said electrode against said tissue in said contact area; and
at least one light emitter carried by said lead body at said second lead body end that emits biomodulating light in vivo, said light emitter being located at said second lead body end, relative to said electrode and to said fixation element, to cause said biomodulating light to be emitted toward at least one of said fixation area and said contact area.
56. An implantable medical device as claimed in claim **55** wherein said light emitter is configured for connection to a control circuit that activates said light emitter to emit said biomodulating light according to a treatment protocol.

57. An implantable medical device as claimed in claim **56** wherein said light emitter is operable by said control circuit according to a treatment protocol comprising treatment parameters selected from the group consisting of emission duration of said biomodulating light, intensity of said biomodulating light, a wavelength of said biomodulating light, and times between emission of said biomodulating light.

58. An implantable medical device as claimed in claim **55** wherein said light emitter comprises at least one light emitting diode.

59. An implantable medical device as claimed in claim **58** wherein said lead body has a tip at said second lead body end, and wherein said at least one light emitting diode is located at said tip adjacent to said fixation element.

60. An implantable medical device as claimed in claim **59** wherein said at least one light emitting diode is located at said tip adjacent to said electrode.

61. An implantable medical device as claimed in claim **55** wherein said light emitter comprises at least one optical fiber carried in said lead body and configured for optical communication with a light source of said biomodulating light.

62. An implantable medical device as claimed in claim **55** wherein said electrical conductor is configured for connection to a stimulation threshold determining unit that determines a stimulation threshold value for said contact area dependent on response of said tissue to at least one delivered electrical stimulation pulse.

63. An implantable medical device as claimed in claim **62** wherein said stimulation threshold determining unit is configured to determine an average stimulation threshold value from a plurality of responses of said tissue to a plurality of delivered stimulation pulses during a period of time having a predetermined duration.

64. An implantable medical device as claimed in claim **63** wherein said stimulation threshold determining unit is configured to compare said average stimulation threshold value for a current period of time with at least one preceding average stimulation threshold value obtained during a preceding period of time, to determine a trend of said stimulation threshold values.

65. An implantable medical device as claimed in claim **64** wherein said light emitter is configured for connection to a control circuit that activates said light emitter to emit said biomodulating light according to a treatment protocol, and wherein said control circuit is supplied with at least one of said average stimulation threshold value and said trend, and is configured to adjust said treatment protocol dependent on said at least one of said average stimulation threshold value and said trend.

66. An implantable medical device as claimed in claim **55** wherein said light emitter is configured to emit coherent and monochromatic light as said biomodulating light.

67. An implantable medical device as claimed in claim **55** wherein said light emitter is configured to emit biomodulating light having a wavelength in a range between 600 nm and 1000 nm.

68. A method for stimulating tissue in vivo comprising the steps of:

implanting an elongate lead body in vivo in a subject, said lead body having first and second lead body ends; connecting a first conductor end of an electrical conductor extending in said lead body at said first lead body end, to a pulse generator to receive electrical stimulating pulses

therefrom, said electrical conductor having a second conductor end approximately coextensive with said second lead body end;

placing at least one electrode connected to said second conductor end in in vivo exposure to cardiac tissue of the subject and delivering said stimulating pulses to said tissue at a contact area where said electrode abuts said tissue;

providing a fixation element carried by said lead body at said second lead body end, and causing said fixation element to interact with said tissue in a fixation area to hold said electrode against said tissue in said contact area; and

emitting biomodulating light in vivo from at least one light emitter carried by said lead body at said second lead body end, and locating said light emitter at said second lead body end, relative to said electrode and to said fixation element, to cause said biomodulating light to be emitted toward at least one of said fixation area and said contact area.

69. A method as claimed in claim **68** comprising connecting said light emitter to a control circuit and, from said control circuit, activating said light emitter to emit said biomodulating light according to a treatment protocol.

70. A method as claimed in claim **69** comprising operating said light emitter by said control circuit according to a treatment protocol comprising treatment parameters selected from the group consisting of emission duration of said biomodulating light, intensity of said biomodulating light, a wavelength of said biomodulating light, and times between emission of said biomodulating light.

71. A method as claimed in claim **68** comprising employing at least one light emitting diode as said light emitter.

72. A method as claimed in claim **71** wherein said lead body has a tip at said second lead body end, and comprising locating said at least one light emitting diode at said tip adjacent to said fixation element.

73. A method as claimed in claim **72** comprising locating said at least one light emitting diode at said tip adjacent to said electrode.

74. A method as claimed in claim **68** wherein said light emitter comprises at least one optical fiber carried in said lead body and comprising placing said at least one optical fiber in optical communication with a light source of said biomodulating light.

75. A method as claimed in claim **68** comprising connecting said electrical conductor to a stimulation threshold determining unit and, in said stimulation threshold determining unit, determining a stimulation threshold value for said contact area dependent on response of said tissue to at least one delivered electrical stimulation pulse.

76. A method as claimed in claim **75** comprising, in said stimulation threshold determining unit, determining an average stimulation threshold value from a plurality of responses of said tissue to a plurality of delivered stimulation pulses during a period of time having a predetermined duration.

77. A method as claimed in claim **76** comprising, in said stimulation threshold determining unit, comparing said average stimulation threshold value for a current period of time with at least one preceding average stimulation threshold value obtained during a preceding period of time, to determine a trend of said stimulation threshold values.

78. A method as claimed in claim **77** comprising connecting said light emitter to a control circuit and, from said control

circuit, activating said light emitter to emit said biomodulating light according to a treatment protocol, and supplying said control circuit with at least one of said average stimulation threshold value and said trend and, in said control circuit, adjusting said treatment protocol dependent on said at least one of said average stimulation threshold value and said trend.

79. A method as claimed in claim **68** comprising, from said light emitter, emitting coherent and monochromatic light as said biomodulating light.

80. A method as claimed in claim **68** comprising, from said light emitter, emitting biomodulating light having a wavelength in a range between 600 nm and 1000 nm.

81. A computer-readable medium encoded with programming instructions, said medium being loadable into a processor of an implantable medical device having an elongate lead body configured for in vivo implantation in a subject, said lead body having first and second lead body ends, a pulse generator, an electrical conductor extending in said lead body, said electrical conductor having a first conductor end at said

first lead body end connected to said pulse generator to receive electrical stimulating pulses therefrom, and having a second conductor end approximately coextensive with said second lead body end, at least one electrode connected to said second conductor end configured for in vivo exposure to cardiac tissue of the subject to deliver said stimulating pulses to said tissue at a contact area where said electrode abuts said tissue, a fixation element carried by said lead body at said second lead body end, said fixation element being configured to interact with said tissue in a fixation area to hold said electrode against said tissue in said contact area, and at least one light emitter carried by said lead body at said second lead body end that emits biomodulating light, said light emitter being located at said second lead body end, relative to said electrode and to said fixation element, said programming instructions operating said processor to cause said biomodulating light to be emitted toward at least one of said fixation area and said contact area.

* * * * *