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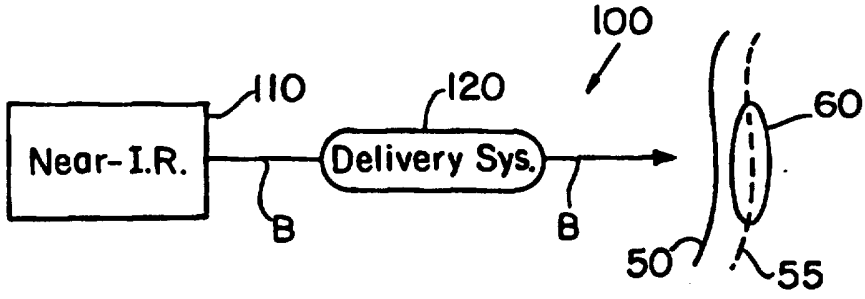
(54) Title: NEAR-INFRARED SELECTIVE PHOTOTHERMOLYSIS FOR VASCULAR TARGETS

(57) Abstract

Near-infrared selective photothermolysis for the treatment of ectatic blood vessels, for example, blood vessels of a portwine stain birthmark, leg veins, or vessels contributing to psoriasis. This technique is especially applicable to deeper lying blood vessels in view of the better penetration of the near-infrared light. Consequently, vessels below a dermal/epidermal boundary can be reached. Near-infrared is defined as a range of approximately 700 to 1,200 nm. The optimal colors are near 760 or between 980 to 990 nm for most populations.



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NEAR INFRARED SELECTIVE PHOTOTHERMOLYSIS FOR VASCULAR TARGETS

Background of the Invention

Vascular lesions, comprising enlarged or ectatic blood vessels, pigmented lesions, and tattoos have been successfully treated with lasers for many years. In the process called selective photothermolysis, the targeted structure, the lesion tissue or tattoo pigment particles, and the surrounding tissue are collectively irradiated with laser light. The wavelength or color of this laser light, however, is chosen so that its energy is preferentially absorbed into the target. Localized heating of the target resulting from the preferential absorption leads to its destruction.

Most commonly in the context of vascular lesions, such as portwine stains for example, hemoglobin of red blood cells within the ectatic blood vessels serves as the laser light absorber, *i.e.*, the chromophore. These cells absorb the energy of the laser light and transfer this energy to the surrounding vessels as heat. If this occurs quickly and with enough energy, the surrounding vessels reach a temperature to denature their proteins. The fluence, Joules per square centimeter, to reach the denaturation of the vessels is calculated to be that necessary to raise the temperature of the targeted volume within the vessel to about 70°C before a significant portion of the absorbed laser energy can diffuse out of the vessel. The fluence must, however, be limited so that the surrounding tissue is not also denatured.

However, simply selecting the necessary fluence is not enough. The intensity and pulse duration of the laser light must also controlled for selectivity by both minimizing diffusion into the surrounding tissue during the pulse while avoiding localized vaporization. Boiling and vaporization are desirably avoided since they lead to mechanical, rather than chemical, damage--which can increase injury and hemorrhage in tissue surrounding the lesion. These constraints suggest that the pulse duration should be longer with a correspondingly lower intensity to avoid vaporization. The situation becomes more complex if the chromophore is the blood cell hemoglobin within the lesion blood vessels, since the vessels are an order of magnitude larger than the blood cells. Radiation must be added at low intensities so as to not vaporize the small cells, yet long enough to heat the blood vessels by thermal diffusion to the point of denaturation while minimizing damage to the surrounding tissue.

Long pulse flashlamp excited dye lasers have been used as the light source. These lasers have the high spectral brightness required for selective photothermolysis and can be tuned to the alpha absorption band of hemoglobin. Colors in the range of 577 to 585nm are absorbed well by the chromophore, the red blood cells in the blood vessels relative to the melanin in the surrounding tissue.

Summary of the Invention

Selective photothermolysis performed with conventional flashlamp excited dye lasers results in suboptimal therapy. The thermal relaxation time constant is a measure of a structure's ability to retain heat. For blood vessels, the constants are on

the order of milliseconds; red blood cells have thermal relaxation time constants of microseconds. A pulse duration that is much longer than the thermal relaxation time constant for red blood cells enables heat to diffuse to the surrounding vessels, and when pulse duration is also less than or equal to the vessel's constant, the heat is localized within the vessel to avoid damage to surrounding tissue. In fact, theory dictates that the optimum length of the light pulse should be the thermal relaxation time of the vessels. Larger vessels, greater than 30 microns, consequently should be treated with pulse durations of 0.5 msec and longer. Commercially available dye lasers are limited in pulse durations to approximately 0.5 msec and shorter, however. Since the vessel relaxation time increases as the square of its diameter, the usefulness of these dye lasers quickly diminishes for larger vessels. As a result, in selective photothermolysis treatment, many times higher than optimum fluences must be used to compensate for the pulse duration limitations. This leads to temporary hyperpigmentation, *viz.*, purpura.

Moreover, conventional light frequencies further limit the efficacy of photothermolysis. The molar extinction coefficient, a measure of a chemical's optical absorption characteristics, is approximately 0.2 for both melanin and hemoglobin in the range of 577 to 585nm. This limits the effective penetration depth of light, and the depth to which vessels can be treated, to less than 0.5 mm for fair Caucasian skin, as an example. This is above the dermal/epidermal layer.

In summary, conventional the dye laser treatment techniques work exceptionally well on vascular lesions comprised of vessels less than 30 microns in diameter and located above the dermal/epidermal junction. On the negative side, it fails to properly heat larger vessels and can not reach deeper vessels, penetration being limited because of the high absorption. These represent serious drawbacks since the worst case scenario of deep and large vessels is a ubiquitous characteristic of skin.

The near infrared portion of the electro-magnetic spectrum, designated for the purposes of this description as stretching from approximately 700 to 1400 nm, provides regions of favorable ratios between competing melanin and hemoglobin absorption. The use of these wavelengths for the treatment of vessels has been universally ignored as an alternative to the 577-585 nm wavelengths because of the poor hemoglobin absorption characteristics in this area. This conclusion, however, fails to recognize that the ratio between the absorption characteristics of the hemoglobin and the melanin is the principle variable in achieving selectivity, not net absorption. Moreover, in the treatment of deeper lying vessels, the poor absorption characteristics can actually be an asset since it enables deeper overall penetration of the laser light.

In light of the above, in general, according to one aspect, the invention is directed to selective photothermolysis for the treatment of vascular targets in which near-infrared radiation is used.

In specific embodiments, this technique is used to treat non-ectatic vessels or ectatic blood vessels, such as blood vessels of a portwine stain birthmark. The invention, however, also encompasses the treatment of leg veins and psoriasis, which is affected by blood flow through vessels. This technique is especially applicable to deeper lying blood vessels in view of the better penetration of the near infrared light. Consequently, vessels below a dermal/epidermal boundary can be reached.

In specific embodiments a few different wavelength ranges are possible. Generally, the near-infrared light is in the range of approximately 700 to 1,400 nm the upper end of the range being limited by water absorption. More specifically, the range can be limited to 750 to 780 nm. The best color is 760 nm, however. Alternatively, a general range of 980 to 990 nm is also effective.

The laser light is preferably generated by one of an alexandrite, titanium sapphire, chromium doped fluoride, or semiconductor diode laser and conveyed to the patient via an optical fiber delivery system for transmitting the laser light to a patient.

In general according to another aspect, the invention features a near-infrared selective photothermolysis device for treatment of vascular targets. This device comprises a laser system for generating near-infrared laser light pulse having a duration of greater than 0.2 milliseconds and a delivery system for transmitting the laser light pulse to a patient.

In specific embodiments, the laser system includes an alexandrite, titanium sapphire, chromium doped fluoride or semi-conductor diode-type laser. If the pulse duration or power output of the selected laser device is inadequate individually, the light pulses from multiple diode lasers, for example, can be combined. Time-multiplexing achieves long effective pulse durations when individual devices have limited durations. Consequently, effective pulse durations of between 1 and 10 msec are achievable when individual laser diodes only produce pulses of 0.5 msec. Combinations of simultaneously generated beams increase effective power.

In general according to still another aspect, the invention features a method for treating a vascular target. This method comprises irradiating the target with near-infrared laser light pulses. The duration of these pulses is controlled to approximately match a thermal relaxation time of the targeted vessels. The near-infrared wavelengths stretch from approximately 700 to 1,400 nm.

The above and other features of the invention including various novel details of construction and combinations of parts, and other advantages, will now be more particularly described with reference to the accompanying drawings and pointed out in the claims. It will be understood that the particular method and device embodying the invention is shown by way of illustration and not as a limitation of the invention. The principles and features of this invention may be employed in various and numerous embodiments without the departing from the scope of the invention.

Brief Description of the Drawings

In the accompanying drawings, reference characters refer to the same parts throughout the different views. The drawings are not necessarily to scale; emphasis has instead been placed upon illustrating the principles of the invention. Of the drawings:

Fig. 1 schematically shows a near-infrared selective photothermolysis device of the invention using a single laser;

Fig. 2 is a plot of the molar extinction coefficient as a function of wavelength, in nanometers, for oxyhemoglobin HbO_2 (solid line), deoxyhemoglobin Hb (dotted line), bilirubin (dashed line), and DOPA-melanin (the apparently exponentially falling solid line);

Fig. 3 schematically shows a near-infrared selective photothermolysis device of the invention using multiple laser diodes or diode arrays; and

Fig. 4 is a plot of TiS laser output as a function of time for different levels of flashlamp excitation, showing that relaxation oscillation is not a factor for long pulse durations.

Detailed Description of the Preferred Embodiments

Turning now to the drawings, a near-infrared selective photothermolysis device 100, constructed according to the principles of the present invention, is illustrated in Fig. 1. This device 100 is generally similar to that found in the prior art except to the extent that it includes a radiation source that generates light pulses in the near-infrared region of the electromagnetic spectrum. More completely, a laser system 110 generates a beam of near-infrared light B, *i.e.*, in the range of 700-1400 nm. The beam of light B is coupled into a delivery system 120, such as a single

optical fiber, and transported to the skin 50 of a patient. Because this light beam B is in the near-infrared region of the spectrum, it can achieve substantial penetration beyond a dermal/epidermal boundary 55 to treat underlying vascular targets 60. This target 60 could be of one of many different types such as portwine stain birthmarks, hemangiomas, telangiectasia, idiopathic vulvodynia, leg veins, and the vascular flow contributing to psoriasis. Further, it could also be vessels in simple wrinkles, caused by age or sun exposure, or blood vessels in scar tissue.

The pulse duration of the light beam B is matched to the thermal relaxation time of the targeted vessels. Generally, this requires durations greater than 0.2 msec. For vessels of 30 microns in diameter and larger, as are present in portwine stains of adult patients, the duration should ideally exceed 0.2 msec. usually 0.5 msec, whereas pulse durations of 1 msec to 10 msec should be selected, if the vessels are larger than 100 microns.

Referring to Fig. 2, there are a number of specific ranges within the near-infrared that will be especially effective in treating vascular lesions. (Because the molecular weights of melanin are poorly defined, the spectrum shown is the optical density on a scale of 0 to 1.5 for a 1.5 mg% solution of DOPA-melanin.) Fig. 2 is a plot of the molar extinction coefficient as a function of wavelength in nanometers.

For an acceptable degree of selectivity in fair Caucasian skin, the ratio between the molar extinction coefficient of the hemoglobin and the melanin should be at least 0.05. The ratio of combined deoxyhemoglobin

(Hb) and oxyhemoglobin (HbO_2) absorption to melanin absorption (DOPA-melanin) is generally favorable, 0.05 or greater, between 700 and 1,200 nm. If the deoxyhemoglobin Hb is specifically targeted, the wavelength range of 700 to 1,000 nm of the laser beam B is acceptable. The deoxyhemoglobin absorption peaks in the range of 750 to 780 nm with the best ratios at approximately 760 nm.

The total absorption of hemoglobin is less in the near-infrared than the conventional range of 577-585 nm. Therefore, fluences of the light beam B required to treat ectatic vessels are higher than fluences used with conventional shorter wavelengths. Therefore, the light beam B generally provides fluences of between 2 and 20 J/cm^2.

The laser system 110 can comprise several candidate lasers that will generate the near-infrared laser light around 760 nm. For example, alexandrite is tunable within the range of 720-790nm. Also tunable titanium sapphire (TiS) produces light in the range of 720-950 nm. These two lasers appear to be the best candidates since they are highly developed under current technology. Other tunable chromium doped fluoride lasers such as $LiCaAlF_6$, $LiCaGaF_6$, $LiSrAlF_6$, and $LiSrGaF_6$ in addition to semiconductor diode lasers are also potential alternatives.

Alexandrite lasers are particularly well adapted to selective photothermolysis since pulse generation in the range of 3 to 10 msec is possible. This pulse duration is most appropriate for the treatment of vessels of 100 microns and larger, which are ineffectively treated by currently available

technology. These lasers, however, exhibit a very spiky behavior in the so-called normal mode of operation. This results from relaxation oscillation.

Semiconductor diode lasers do not store energy in a metastable upper laser level and consequently do not show the spiky behavior. The individual power output is, however, too low to reach the necessary fluences which are necessary to treat most vessels. Implementation of diode lasers requires the combination of beams from many lasers to reach the more than 100 watts needed. Such an embodiment is schematically shown in Fig. 3 in which the outputs from three diode lasers 210, 212, 214 of the laser system 205 are combined into a single beam and coupled into the delivery system 220. The diode lasers 210-214, or TiS lasers, are coordinated by a synchronizer 230 that controls their respective times of light generation. Alternatively, if still more power is required the diode lasers 210, 212, 214 are alternatively replaced with separate arrays of diodes. In either case, the delivery system 220 is preferably liquid core flexible light guide instead of a single glass optical fiber. These liquid core guides have large apertures, typically 5mm and still retain flexibility. Thus, beams from the several diode lasers, or several arrays, are directly focused onto the liquid light guide, greatly simplifying the transfer optics between the laser diodes and the skin containing the targeted vessels.

Another device for combining many beams from diode lasers is specifically disclosed in U.S. Pat. Appl. Ser. No. 08/163,160, entitled, "Fault Tolerant Optical System Using Diode Laser Array," of which the present

inventor is a co-inventor and which is incorporated herein by this reference. This application is directed to the use of corrective micro-optics to mate a two-dimensional diode array with a masked-produced two-dimensional array of collimator micro-lens and mass-produced transformer sets.

The TiS laser is another viable candidate. In tests, these lasers have produced 1 to 5 msec pulses and did not exhibit the spiky behavior that is characteristic of flashlamp excited solid state laser systems. Most solid state lasers have an upper state lifetime of approximately 100 μsec. In the TiS laser, however, this lifetime is only 3 μsec. As a result, if the TiS lasing medium is pumped hard, as for example how dye lasers are pumped, the upper state becomes saturated and will not store any more energy after about 2-3 μsec. This neutralizes most relaxation oscillation pulsing. For example, as shown in Fig. 4, four different levels of flashlamp excitation are demonstrated, 2,000, 1,800, 1,600, and 1400 V.D.C. The resulting pulse durations of two to three msec do not exhibit strong relaxation oscillation pulsing characteristics. The pulses tended to be limited in duration to approximately 3 msec, however, by thermal lensing effects.

If individual TiS lasers are not capable of producing the necessary pulse durations, the laser system 110 of Fig. 3 may time multiplex the outputs of several lasers as taught in U.S. Pat. Serial No. 08/329,195, filed on October 26, 1994, entitled "Ultra Long Pulsed Dye Laser for Treatment of Ectatic Vessels and Method Therefor," of which the present inventor is a co-inventor and which is incorporated herein by this

reference. Specifically, the synchronizer 230 of Fig. 3 sequentially triggers each of the diode or TiS lasers 210-214 to thereby generate effective pulse durations. Alternatively or additionally, to achieve high effective power output, the synchronizer 230 simultaneously triggers all of some of the lasers 210-214.

The deoxyhemoglobin HbO_2 can be specifically targeted, which has a favorable absorption range between 800 and 1200nm. The best absorption ratios exist between 980 and 990 nm. Here, the molar extinction coefficient of the oxyhemoglobin HbO_2 peaks and the coefficient ratio of oxy-hemoglobin to melanin actually exceeds 0.1. This is a desirable range for diode laser treatment. 50 watt fiber coupled continuous wave diode lasers, stand alone and fully developed, are commercially available. These state of the art diode laser arrays can produce 100 watts in a quasi-continuous wave mode. The pulse duration of these modes is typically around 400 μsec. Therefore, in the treatment of larger vessels time-multiplexed arrays of diode lasers, as described above, are necessary.

While this invention has been particularly shown and describe with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended claims.

CLAIMS

I claim:

1. Near infrared selective photothermolysis for the treatment of vascular targets.

2. A selective photothermolysis process for treatment of vascular targets, comprising:
generating near-infrared light pulses; and
irradiating tissue of a patient with the pulses to selectively affect the vascular targets contained in the tissue.

3. A process as claimed in either of Claims 1 or 2, further comprising targeting ectatic blood vessels for treatment.

4. A process as claimed in any of the preceding claims, further comprising generating near-infrared light pulses with a pulse duration of greater than 0.2 milliseconds.

5. A process as claimed in any of the preceding claims, further comprising generating the near-infrared light pulses with a pulse duration within a range of 1 to 50 milliseconds.

6. A process as claimed in any of the preceding claims, further comprising generating the near-infrared light pulses with a wavelength within a range of approximately 700 to 1,400 nm.

7. A process as claimed in any of the preceding claims, further comprising generating the near-

infrared light pulses with a wavelength within a range of approximately 700 to 1000nm.

8. A process as claimed in any of the preceding claims, further comprising generating the near-infrared light pulses with a wavelength within a range of approximately 750 to 780 nm.

9. A process as claimed in any of the preceding claims, further comprising generating the near-infrared light pulses with a wavelength of approximately 760 nm.

10. A process as claimed in any of Claims 1-5, further comprising generating the near-infrared light pulses with a wavelength within a range of approximately 800 to 1200 nm.

11. A process as claimed in any of Claims 1-5, further comprising generating the near-infrared light pulses with a wavelength within a range of approximately 980 to 990 nm.

12. A process as claimed in any of the preceding claims, further comprising targeting vessels below a dermal/epidermal boundary.

13. A process as claimed in any of the preceding claims, further comprising generating the near-infrared light pulses with an alexandrite laser.

14. A process as claimed in any of Claims 1-12, further comprising generating the near-infrared light pulses with a titanium sapphire laser.

15. A process as claimed in any of Claims 1-12, further comprising generating the near-infrared light pulses with a chromium doped fluoride laser.

16. A process as claimed in any of Claims 1-12, further comprising generating the near-infrared light pulses with a semiconductor diode laser.

17. A process as claimed in any of the preceding claims, further comprising transmitting the near-infrared light pulses to the patient with an optical fiber delivery system.

18. A near-infrared selective photothermolysis device for treatment of vascular targets, the device comprising:

a laser system for generating near-infrared laser light pulses having durations greater than 0.2 milliseconds; and

a delivery system for transmitting the laser light pulses to the vascular targets of a patient.

19. A device as claimed in Claim 18, wherein the vascular targets comprise ectatic blood vessels.

20. A device as claimed in either of Claims 18 or 19, wherein the laser light pulses have a wavelength in a range of approximately 700 to 1400 nm.

21. A device as claimed in either of Claims 18 or 19, wherein the laser light pulses have a wavelength in a range of approximately 700 to 1000 nm.

22. A device as claimed in either of Claims 18 or 19, wherein the laser light pulses have a wavelength in a range of approximately 750 to 780 nm.

23. A device as claimed in either of Claims 18 or 19, wherein the laser light pulses have a wavelength in a range of approximately 760 nm.

24. A device as claimed in either of Claims 18 or 19, wherein the laser light pulses have a wavelength in a range of approximately 800 to 1200 nm.

25. A device as claimed in either or Claims 18 or 19, wherein the laser light pulses have a wavelength in a range of approximately 980 to 990 nm.

26. A device as claimed in either of Claims 18 or 19, wherein the laser system comprises an Alexandrite laser.

27. A device as claimed in either of Claims 18 or 19, wherein the laser system comprises a titanium sapphire laser.

28. A device as claimed in either of Claims 18 or 19, wherein the laser system comprises a chromium doped fluoride laser.

29. A device as claimed in either of Claims 18 or 19, wherein the laser system comprises a semi-conductor diode laser.

30. A device as claimed in any of Claims 18-29 wherein the laser system comprises plural lasers.

31. A device as claimed in any of Claims 18-30, wherein the delivery system comprises an optical fiber for combining and delivering light from the lasers.

32. A device as claimed in any of Claims 18-31, wherein the laser system time-multiplexes the lasers.

33. A device as claimed in any of Claims 18 - 32, wherein an effective pulse duration of a light pulse from the time-multiplexed lasers is between 1 and 10 msec.

34. A device as claimed in any of Claims 18- 33, wherein the laser system simultaneously triggers the lasers to increase effective power levels.

35. A method for treating vasculature, comprising:

irradiating the vasculature with near-infrared laser light pulses; and

controlling a duration of the pulses to approximately match a thermal relaxation time of blood vessels of the vasculature.

36. A method as claimed in Claim 35, wherein the laser light pulses have a wavelength in a range of approximately 700 to 1,400 nm.

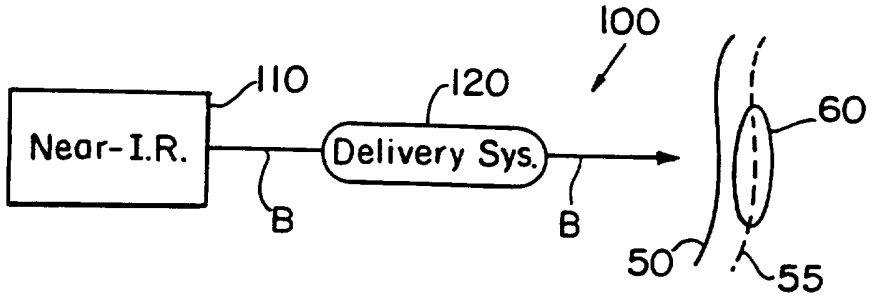


FIG. 1

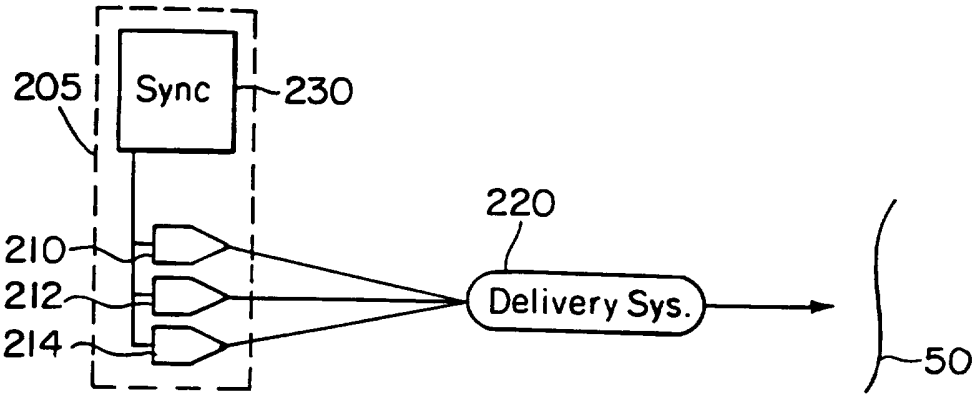


FIG. 3

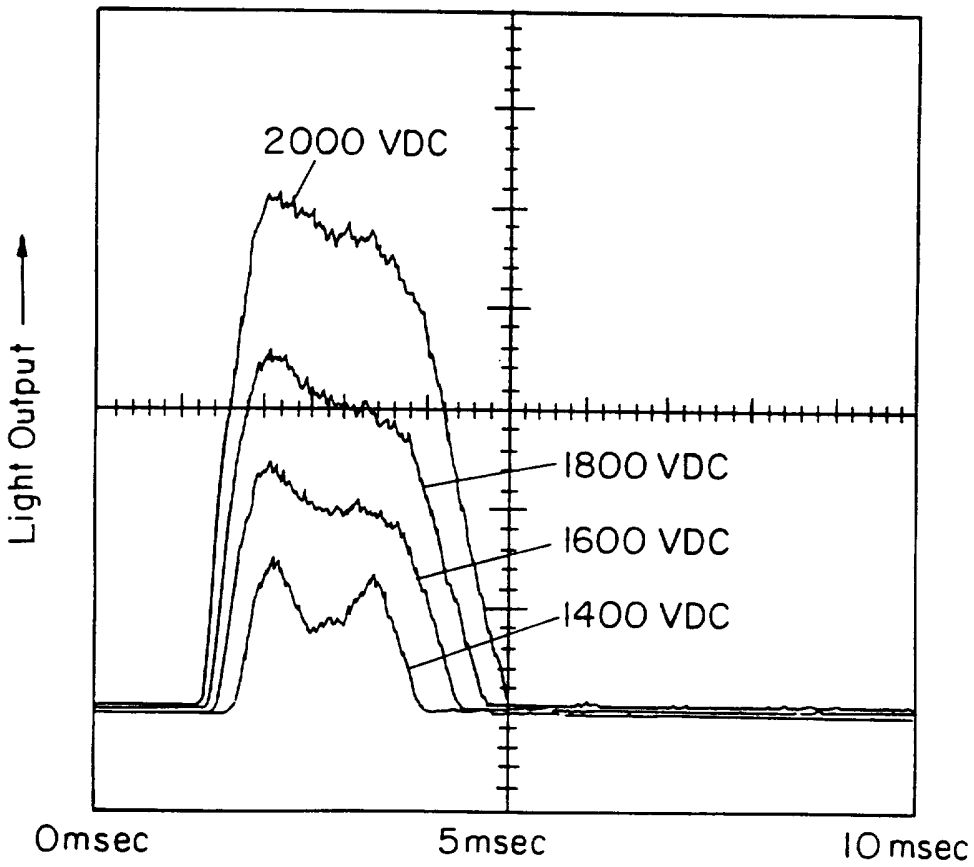
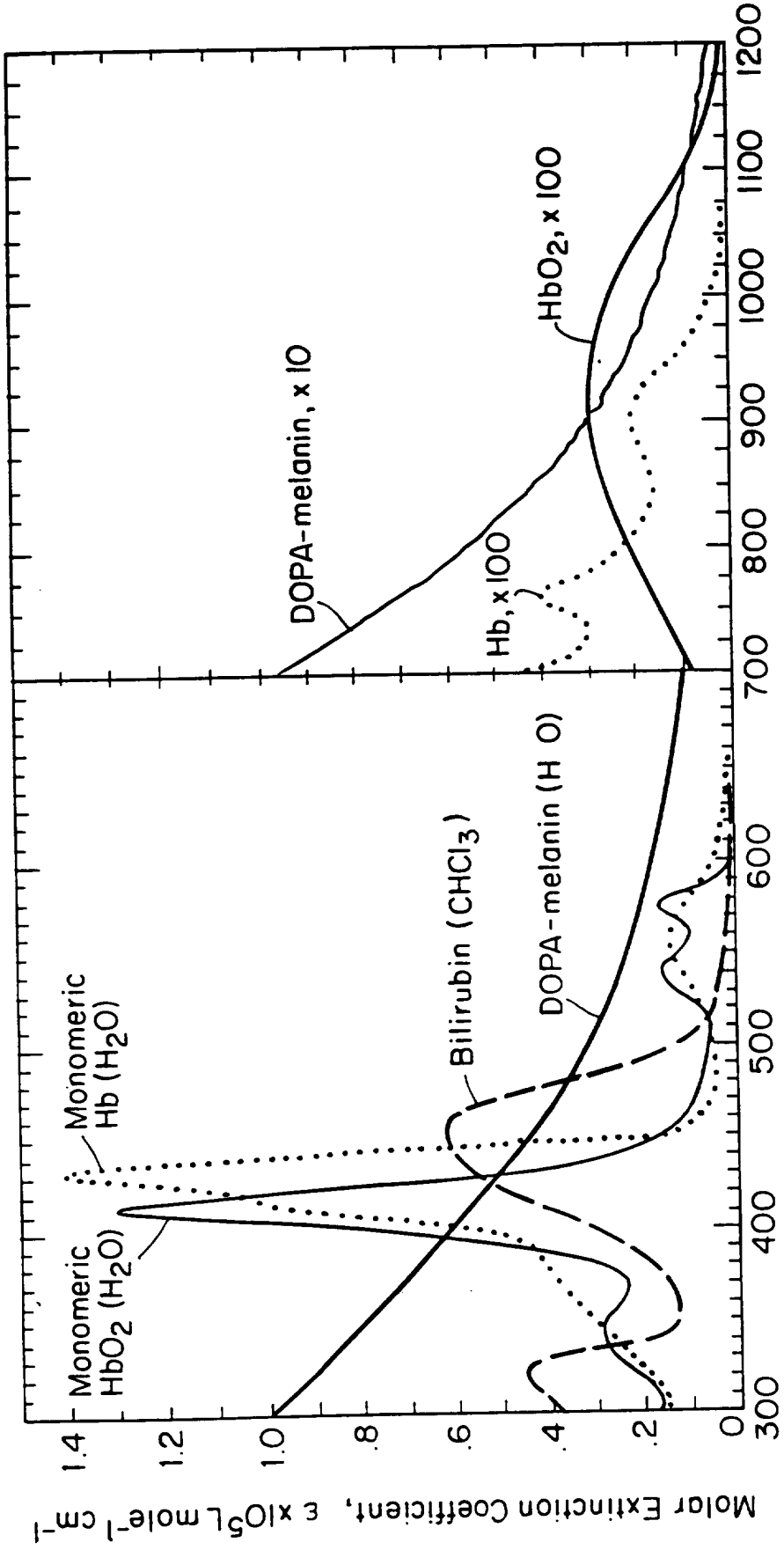


FIG. 4


Molar Extinction Coefficient, ε x10⁵L mole⁻¹ cm⁻¹
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1.2
1.0
.8
.6
.4
.2
0
300
400
500
600
700
800
900
1000
1100
1200
Wavelength, nm
Monomeric HbO2 (H2O)
Monomeric Hb (H2O)
Bilirubin (CHCl3)
DOPA-melanin (H O)
DOPA-melanin, x 10
HbO2, x 100
Hb, x 100

FIG. 2

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 95/16243

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61N5/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61N A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,91 13652 (CANDELA LASER CORPORATION) 19 September 1991	1,2
A	see page 1, line 1 - line 20 see page 6, line 23 - line 31	6-11, 13-15, 18, 20-25, 27,28, 30-34
Y	see abstract	3,13,14

Y	US,A,5 071 416 (HELLER) 10 December 1991	13,14
A	see claims 3,4	26,27

Y	US,A,5 057 104 (CHESS) 15 October 1991	3
A	see abstract	19

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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1

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 1996	22. 04. 96

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 344 418 (GHAFFARI) 6 September 1994 see column 3, line 45 - line 47	1,2,18
A	WO,A,91 18646 (OMEGA) 12 December 1991 see claim 1	1,2,18
A	WO,A,92 03977 (MASSACHUSSETS) 19 March 1992 see page 20, line 5 - page 21, line 10 see page 23, line 27 - page 25, line 19	1-34
A	EP,A,0 297 360 (ALLIED-SIGNAL) 4 January 1989 see abstract	1
A	WO,A,92 06739 (THE GENERAL HOSPITAL) 30 April 1992 see claims 1-7	1,2,18
A	EP,A,0 413 025 (SUMITOMO) 20 February 1991 see claim 1	1,2,18

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/16243

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. [X] Claims Nos.: 35 and 36
because they relate to subject matter not required to be searched by this Authority, namely:
Method for treatment of human or animal by surgery, therapy rule 39.1 (iv)

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

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

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

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

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

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

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

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 95/16243

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