(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 November 2006 (16.11.2006)

PCT

(10) International Publication Number
WO 2006/119971 A1

(51) International Patent Classification:
A61N 5/06 (2006.01) *A61N 5/067* (2006.01)

(21) International Application Number:
PCT/EP2006/004339

(22) International Filing Date: 9 May 2006 (09.05.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/679,015 9 May 2005 (09.05.2005) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/119971 A1

(54) Title: METHODS FOR PEELING AND INCREASING TURNOVER OF SKIN WITH HIGH-FLUENCY, INTENSE PULSED LIGHT

(57) Abstract: The present invention relates to the use of a high- fluency, intense pulsed light source for inducing the expression of TGF-β in skin cells, resulting in the release of extracellular matrix proteins such as tenascin, and an increase in the concentration of fibroblasts and plasma cells. As the high-fluency, intense pulsed light source methodology disclosed herein produces an artificial wound which stimulates the immune system and extracellular matrix formation, the present invention relates to the use of a high-fluency intense pulsed light source alone, or in combination with laser or radiof requency, for dermatologic treatment and plastic surgery treatment.

METHODS FOR PEELING AND INCREASING TURNOVER OF SKIN WITH HIGH-FLUENCY, INTENSE PULSED LIGHT

Background of the Invention

Light therapy is an emerging field, wherein light emitting diodes and other emitters of electromagnetic radiation are used to treat various medical conditions such as acne, hair growth stimulation, hair growth inhibition, scar reduction and removal, wrinkle reduction, etc.

Dermabrasion, chemical peeling, and laser and flashlamp skin resurfacing have been established to attain their therapeutic effects by stimulating a wound-healing response that leads to an increase in dermal collagen (Tsai, et al. (1995) *Dermatol. Surg.* 21:539-4; Nelson, et al. (1995) *J. Am. Acad. Dermatol.* 32:472-8; Menaker, et al. (1999) *Dermatol. Surg.* 25:440-4; Fournier, et al. (2001) *Dermatol. Surg.* 27:799-806; Goldberg and Cutler (2000) *Lasers Surg. Med.* 26:196-200; Zelickson and Kist (2000) *Lasers Surg. Med.* 12:17). For example, the nonablative laser is able to generate dermal temperature increase of 30-40°C while limiting thermal injury to the epidermis (Lask, et al. (1997) *SPIE Proc.* 2970:338-49). The dermal heat may eventually result in activation of fibroblasts to produce a long term healing response and subsequent collagen remodeling (Lask, et al. (1997) *supra*; Fitzpatrick, et al. (1996) *Arch. Dermatol.* 132:395-405). Shorter wavelength technologies have been hypothesized to induce a heat-mediated cytokine activation (Goldberg (2000) *J. Cutan. Laser Ther.* 2:59-61).

Further, U.S. Patent Application Serial No. 10/119,772 describes the manipulation of collagen, fibroblast, and fibroblast-derived cell levels in mammalian tissue using a plurality of pulses from at least one source of narrowband,

multichromatic electromagnetic radiation (*e.g.*, from a light emitting diode, a laser, a fluorescent light source, an organic light emitting diode, a light emitting polymer, a xenon arc lamp, a metal halide lamp, a filamentous light source, an intense pulsed light source, a sulfur lamp, and combinations thereof) having a dominant emissive wavelength of from about 300 nm to about 1600 nm, and wherein said pulses have a duration of from about 0.1 femtoseconds to about 100 seconds, the interpulse delay between said pulses is from about 0.1 to about 1000 milliseconds, and the energy fluence received by said tissue is less than about 10 joule per square centimeter.

Summary of the Invention

The present invention is a method for increasing the proliferation or turnover of at least one layer of skin by exposing skin to a high-fluency, intense pulsed light source.

The present invention is also a method for stimulating sloughing of the stratum corneum of the epidermis by exposing skin to a high-fluency, intense pulsed light source.

Brief Description of the Drawings

Figure 1 illustrates the relative expression of TN and TGF-β in the follicular bulb (Figure 1A), germinative epidermis (Figure 1B) and in plasma cells (Figure 1C) up to approximately 4 months after treatment with an intense pulsed light source.

Detailed Description of the Invention

It has now been shown that a high-fluency, intense pulsed light source can induce the expression of TGF-β in

skin cells, resulting in the release of extracellular matrix proteins such as tenascin, and an increase in the concentration of fibroblasts and plasma cells. Further, increased expression of Ki67 is observed in both dermal and epidermal layers, indicative of increased proliferation of these skin cells. As the high-fluency, intense pulsed light source methodology disclosed herein produces an artificial wound (*i.e.*, not occurring by natural means such as by accident) thereby stimulating the immune system and extracellular matrix formation, the present invention relates to the use of a high-fluency intense pulsed light source for dermatologic treatment and plastic surgery treatment. Such dermatologic treatment includes increasing the turnover of at least one layer of human or mammalian skin and stimulating sloughing of the outer layer of the epidermis.

To demonstrate the utility of high-fluency intense pulsed light in dermatologic treatment, pigs were treated with 40 flashes (6.5-21 ms) of light having a wavelength ranging from 565 to 695 nm and a fluency of 35-60 J/cm^2. With higher fluency, erythema was observed. Using a wavelength of 640 nm, pulse time between 4.2 to 4.8 milliseconds (ms) and energy of 35 J/cm^2, negligible erythema was observed. While no blisters were identified, hair on the pigs was burnt and transient depigmentation was observed, but disappeared after some time.

Biopsy samples taken from the irradiated pigs were stained for the presence of TGF-β1 and tenascin. One day after radiation, the appearance of TGF-β1 in the basal epidermal layer and the follicular bulb was detected. Fibroblasts and plasma cells were also strongly positive. After 1 week, the outermost epidermis, endothelial vessels, follicular bulb, fibroblasts and plasma cells were

intensely stained (Figure 1). TGF-β1 immunoreactivity decreased after 2 weeks, reaching a level similar to that found on the first day of treatment. After one month, the expression of TGF-β reached a peak value and then began to slowly fall in the second and third month. Subsequently, TGF-β1 levels began to increase and on day 120 elevated levels were observed.

Tenascin was visible below the epidermal germ layer and around the hair follicles. At about 7-10 days after radiation, the biopsies showed a strong increase in tenascin expression (Figure 1). Tenascin was found to be localized in the papillar dermis, the epidermal layer and also in the depths of the dermis, while in the endothelial vessels and the follicular bulb there was a sharp decrease. Biopsies showed a sharp decrease in tenascin immunoreactivity after one month, but this gradually recovered in the germinative epidermis, papillar dermis and the follicular bulb in the second month, but not in the endothelial vessels and plasma cells, where it was absent. In the third month, tenascin levels gradually increased.

The Ki67 protein is expressed in all phases of the cell cycle except G0 and serves as a marker for cell proliferation (Schluter, et al. (1993) J. Cell Biol. 123:513-522). Upon exposure to high-fluency, intense pulsed light, both dermal and epidermal layers were found to exhibit an increase in the expression of Ki67, indicative of an increase in cell proliferation.

In view of the role of TGF-β in cellular proliferation (Lee, et al. (1993) *J. Burn Care Rehabil.* 14:319-35; Mustoe, et al. (1997) *Science* 237:1333-6; Beck, et al. (1991) *Growth Factors* 5:295-304) and the instant findings which demonstrate that high-fluency, intense pulsed light increases TGF-β levels and Ki67 levels in the dermal and

epidermal layers of skin of a subject, the present invention embraces the use of a high-fluency, intense pulsed light source in a method for increasing the proliferation and turnover of at least one layer of skin in a subject. In carrying out such a method, the skin of the subject is exposed to an effective amount of high-fluency, intense pulsed light so that TGF-β and Ki67 expression is increased thereby stimulating proliferation and turnover of skin cells. Depending on the wavelength of light, the proliferation and turnover of one or more layers of skin is contemplated. For example, the use of a dominant wavelength emission in the range of about 500 nm will be useful for increasing the proliferation and turnover of epidermal layers of skin, whereas light having a wavelength of about 600 nm to about 660 nm can be used for increasing the proliferation and turnover of epidermal and dermal layers of skin.

An effective amount of light, in the context of this method of the invention, is an amount which stimulates or increases the turnover of skin, *e.g.*, from 28-30 days as found in a normal human subject to less than 28 days (*e.g.*, 20-25 days) upon exposure to high-fluency, intense pulsed light. Suitable effective amounts or parameters associated with high-fluency, intense pulsed light which achieve the desired effect are disclosed herein and can vary with the desired layers to be treated.

The epidermis is composed of many layers including the horny layer (stratum corneum), the clear layer (stratum lucidum), granular layer (stratum granulosum), prickle-cell layer (stratum spinosum); and basal layer (stratum basale). In the basal layer of the epidermis, new cells are constantly being reproduced, pushing older cells to the surface. As skin cells move farther away from their source

of nourishment, they flatten and shrink. They lose their nuclei, move out of the basal layer to the stratum corneum which is composed of about 15 to 20 cell layers, and turn into keratin. After serving a brief protective function, the keratinocytes are imperceptibly sloughed off. This process is called keratinization and takes about 4 weeks. By increasing proliferation and turnover of skin cells, high-fluency, intense pulsed light is also useful for accelerating the natural process of sloughing.

Accordingly, the present invention is also a method for stimulating sloughing of the stratum corneum of the epidermal layer using an effective amount of high-fluency, intense pulsed light. An effective amount of said light is an amount which results in an increase in the amount or rate of sloughing of stratum corneum cells. For example, an adult human sheds approximately 10 grams of skin cells a day, and therefore an increase in the amount of skin cells sloughed per day would be indicative of high-fluency, intense pulsed light exposure stimulating skin cell sloughing.

As used herein, fluency is defined as the power level of the radiation reaching target tissue. In the context of the instant methods, a high-fluency radiation source produces about 3 to 90 joule per square centimeter (J/cm^2) of tissue. In one embodiment of the present invention, high-fluency of about 10 to 50 J/cm^2 is employed. In particular embodiments, high-fluency of about 35 J/cm^2 is employed.

For purposes of the present invention, any device that emits intense pulsed light in a bandwidth of ± about 100 nanometers around a dominant wavelength can be can be used in accordance with the methods disclosed herein. Generally, any intense pulsed light source capable of exposing the

target tissue with from about 3 to 90 J/cm^2 of energy in the desired wavelength (generally within the range of from about 435 nm to about 1900 nm) will be able to achieve the desired result. It is contemplated that the tissue penetration depth for intact skin may be different than the tissue penetration depth for ulcerated or burned skin and may also be different for skin that has been abraded or enzymatically peeled or that has had at least a portion of the stratum corneum removed. Thus, the wavelength used for any particular application can vary.

By way of illustration, light having a dominant wavelength emission in the range of about 500 nm may be more suitable for exposing epidermal layers of skin as such a short wavelength has limited depth of penetration, whereas light having a wavelength of about 600 nm to about 660 nm can more easily penetrate to a greater depth, if treatment of the lower dermal layers or even deeper is desired. Accordingly, the selection of the dominant wavelength of the radiation emitter is also dependent on the depth of treatment desired. Suitable wavelengths for inducing TGF-β are in the range of 590 to 690 nm. As a wavelength of 640 nm was found to minimize erythema, a dominant wavelength of 640 nm is particularly suitable for use in the methods of the instant invention.

Exposure time is another aspect of intense pulsed light which can vary with the desired effect and the target cell, tissue or organ. In general, pulse lengths can vary from less than one picosecond to several seconds with interpulse intervals of a few picoseconds to a few hundred milliseconds. In particular embodiments, the pulse length is in the range of 0.1 to 500 milliseconds and the interpulse interval in the range of 20 to 60 milliseconds. To maximize skin turnover and sloughing, while minimizing

erythema, pulse durations of from about 4.2 to 4.8 milliseconds with an interpulse interval of about 20 milliseconds are particularly suitable.

Similarly, the number of pulses (also referred to as repetitions or flashes) per treatment can also be varied. For example, large numbers of pulses may be less effective at inducing cell proliferation than a smaller numbers of pulses. In general, a treatment regime can include between 10 and 100 pulses. In particular embodiments, the number of pulses per treatment is in the range of 40. Further, a treatment can be repeated multiple times over a given period of time (*e.g.*, weeks or months) to achieve the desired result.

Further, light penetration into the target tissue can be optimized by varying the treatment head of the intense pulsed light source. For example, a large spot size diminishes the scattering of the light beam. Treatment head size can vary from 8-10 mm x 20-45 mm. A particularly suitable treatment head is in the range of 8 mm x 34-35 mm.

By changing the different parameters of the flashlamp, namely energy, wavelength, pulse duration etc., efficient treatment for a variety of diseases or conditions can be achieved with a high degree of selectivity and safety. In a particular embodiment of the present invention, a high-fluency, intense pulsed light source used in accordance with the instant methods has an emissive wavelength of from about 435 nm to about 1900 nm, wherein the pulses have a duration of from about 2 ms to about 30 ms, and the energy fluence received by the tissue is about 3 to 90 joule per square centimeter.

Suitable flashlamp systems which can be used for carrying out the methods disclosed herein include, but are not limited to, the IPL™ Quantum, VASCULIGHT™, and LUMENIS

ONE™, PHOTODERM™ and EPILIGHT™ systems as well as those disclosed in GB 2,293,648; EP 0 565 331; U.S. Patent No. 5,405,368; and WO 91/15264. For example, the VASCULIGHT™ (ESC Medical Systems Ltd., Yokneam, Israel) and IPL™ Quantum (ESC Sharplan, Yokneam, Israel) systems are based on the principal of selective photothermolysis. In contrast to laser systems, these flashlamps use non-coherent light of a broad-band spectrum in the range of 435-1900 nm. By applying different cut-off filters (*e.g.*, 515, 550, 570, 590, 615, 645, 695, and 795 nm), a specific part of the shorter wavelengths can be cut off. The pulse duration ranges between 2-5 ms (VASCULIGHT™) and 6-26 ms (IPL™ Quantum). Further, fluence ranges between 3-90 J/cm^2 (VASCULIGHT™) and 5-45 J/cm^2 (IPL™ Quantum) can be achieved. Other suitable intense pulsed light sources or flashlamps which can be used in accordance with the parameters disclosed herein are well-known to those of skill in the art.

In particular embodiments, a water-containing gel or solution is used between the skin and the intense pulsed light source probe during treatment to facilitate optical coupling of the light and facilitate heat transfer from the epidermis to the gel.

Advantageously, the methods of the present invention can be carried out without blistering, significant erythema or damage to the underlying tissues. Thus, it is contemplated that the methods of the instant invention will be useful for facilitating epidermal renewal in subjects with acne, large pores, age spots, sun-damaged skin, burns, etc. The methods of the present invention will also be useful in the treatment of psoriasis, eczema (neurodermitis), viral warts, precancerous solar keratosis

or skin lesions, skin ulcers (diabetic, pressure, venous stasis), and the like.

It is further contemplated that the high-fluency, intense pulsed light source as disclosed herein can be combined, either serially or simultaneously with another light or wavelength source (*e.g.*, laser or radiofrequency) to carry out the methods disclosed herein. The high-fluency, intense pulsed light source and other light or wavelength source can be used together to work synergistically, or combined, wherein each has its own effect. Suitable parameters for radiofrequency include a fluence in the range of about 0.5 J/cm^2 to about 500 J/cm^2; a wavelength in the range of about 300 nm to about 1200 nm; a frequency in the range of 500 kHz to 300 MHz; and a spot size in the range of 1 mm^2 to 10 cm^2.

The invention is described in greater detail by the following non-limiting examples.

Example 1: Animal Model

Male, dark-haired pigs were randomly selected for analysis. An intra muscular injection of Azopyrone (0.5 mg/kg) was administered to initiate anesthesia. The anesthesia was maintained with halothane (3-4%) and nitrous oxide. The back region of the pigs, *i.e.*, between their forelegs and hind legs, and the abdomen was shaved to achieve a maximum penetration depth. The area was washed with hibiscub. Treatment sites were outlined by West Indian ink applied to the skin with hypodermic needles. Four marks outlined a 40 x 20cm^2 treatment area. No ointment was applied pre- or post-operatively in the treatment area. No chemical or mechanical debridement was performed during follow up examinations. Buprenorphine, 0.05-0.1 mg/kg i.p., was given soon after the treatment to minimize pain. The

animals were euthanized 120-360 days after treatment using intravenous nembutal (100-150 mg/kg).

Example 2: High-Fluency, Intense Pulsed Light Method

A stencil was placed on the back of the pigs to treat the same surface every time. The pigs underwent general anesthesia for 15-30 minutes (5 times for the treatment and 5 times for the biopsies). In total there were 40 flashes per pig, per treatment. A VASCULIGHT™ system with 590 and 695 nm filters and a QUANTUM™ system with 565 and 640 nm filters were used. Pulse times were 6.5 to 21 milliseconds and the fluence was 35 to 60 J/cm^2. An entire surface of 40 x 2.8 cm^2 was treated per pig. The treatment took 4 to 5 minutes with an interval of 4 weeks between treatments. Treatment regimes are listed in Table 1.

TABLE 1

Wavelength (nm)	Pulse Time (ms)	Energy (J/cm^2)	Delay Between Pulses (ms)	Pulse Mode
550	5 & 3	40	20	Double Pulse
590	7 & 7	40	60	Double pulse
645	4 & 2.5	35	20	Double pulse
695	7 & 7 & 7	60	60	Triple pulse
565	4.2 & 5.4	40	20	Double pulse
640	4.2 & 4.8	35	20	Double pulse

Biopsies were performed immediately following light treatment and again on the second, seventh, fourteenth and twenty-eighth post-operative day. In the second month, one week after the last biopsy, the pigs were radiated again and after 3 weeks biopsies were performed. This was continued for four months. A total amount of 240 biopsies were thus taken. Full-thickness, 3-mm punch biopsies were obtained from each treated site. Tissue specimens were

fixed in formalin, embedded in paraffin, sectioned and stained with hematoxylin and eosin for light microscopic examination.

Pigs were followed daily during the first week. After that they were seen and evaluated after 1, 2, 3, 6, 12, and 30 weeks. They were examined for presence of crust formation, swelling, bleeding, erythema, wound healing, scar formation, depigmentation and loss of hair. Photographs were taken before and after treatment.

Example 3: Immunohistochemistry

Tissue blocks of pig skin biopsy were fixed in 4% neutral-buffered paraformaldehyde at 4°C for 4 to 12 hours. The specimens were then routinely processed for paraffin embedding at 56°C. Paraffin sections measuring 4 μm were used for light microscopy and immunohistochemical analysis.

Paraffin sections were deparaffinized and rehydrated. Immunohistochemical demonstration of tenascin and TGF-β antigens was performed on these sections with the avidin-biotin peroxidase (ABC) method. Briefly, these sections were processed through the following incubation steps: hydrogen peroxide 3% in methanol for 30 minutes to block endogenous peroxidase; normal goat serum for TGF-β1 and normal horse serum for tenascin, diluted 1:75 v/v, for 30 minutes to 1 hour to reduce non-specific background staining; incubation with primary antibody anti-TGF-β1 (Santa Cruz Biotechnology, Inc., Santa Cruz, CA) and with primary antibody anti-tenascin (Sigma, St Louis, MO) overnight at 4°C; biotinylated secondary goat anti-rabbit IgG (for TGF-β1), and horse anti-mouse IgG (for tenascin), diluted 1:200 v/v, for 30 minutes to 1 hour (Vector Labs, Burlingame, CA); ABC complex for 1 hour (VECTASTAIN® ABC kit, Vector Labs); and histochemical visualization of

peroxidase using 3',3'-diaminobenzidine hydrochloride as chromogen (Sigma, St. Louis, MO) for 5 minutes in a dark room. Sections were then rinsed in tap water, counterstained with hematoxylin, dehydrated and mounted with EUKITT® (Kindler GmbH & Co., Freiburg, Germany).

For the above immunohistochemical procedures controls included omission of the primary or secondary antibody which resulted in negative staining and the use of human placenta as positive control for tenascin and TGF-β1 antibodies.

Example 4: Statistical Analysis

The statistical analysis of the data was descriptive. The data is presented as contingency tables to detect association between technical and clinical parameters. Exact Fisher tests were used to evaluate the homogeneity of the tables, p-values below 0.05 are considered significant.

What is claimed is:

1. A method for increasing the proliferation or turnover of at least one layer of skin comprising exposing skin to a high-fluency, intense pulsed light source thereby increasing the proliferation or turnover of at least one layer of the skin.

2. The method of claim 1, further comprising exposing the skin to laser or radiofrequency.

3. A method for stimulating sloughing of the stratum corneum of the epidermis comprising exposing skin to a high-fluency, intense pulsed light source thereby stimulating sloughing of the stratum corneum of the epidermis.

4. The method of claim 3, further comprising exposing the skin to laser or radiofrequency.

5. An apparatus for carrying out the method of any of claims 1 to 4.

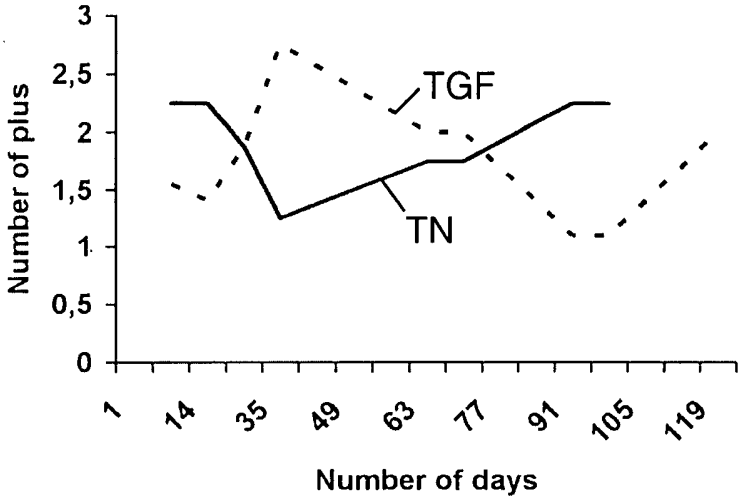

FIG. 1A

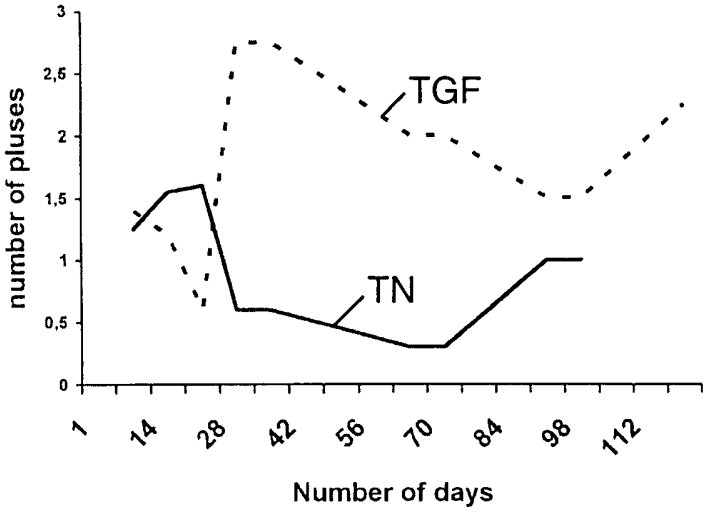

FIG. 1B

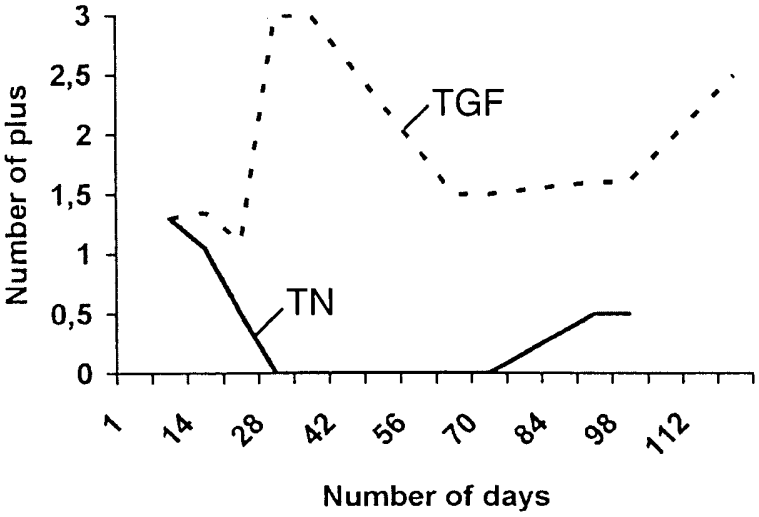

FIG. 1C

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/004339

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61N5/06
ADD. A61N5/067

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61N

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/033040 A (PALOMAR MEDICAL TECHNOLOGIES, INC) 22 April 2004 (2004-04-22) page 2, line 21 - line 30; table 3 page 5, line 8 - line 20 page 15, line 30	5
X	EP 0 320 080 A (DIAMANTOPOULOS, COSTAS; ALEXANDROU, ALEX PANIKOS; OMEGA UNIVERSAL LIMI) 14 June 1989 (1989-06-14) page 6, line 10 - line 22 page 8, line 29 page 10, line 43 - line 45	5
X	US 2003/004556 A1 (MCDANIEL DAVID H) 2 January 2003 (2003-01-02) paragraphs [0009], [0010], [0015], [0016], [0058]	5

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 August 2006	21/08/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rodríguez Cossío, J

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/004339

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/020197 A (JOHNSON & JOHNSON CONSUMER COMPANIES, INC; COLE, CURTIS; SKOVER, GREGO) 23 February 2006 (2006-02-23) page 11, line 20 - page 14, line 1	5
X	US 6 887 260 B1 (MCDANIEL DAVID H) 3 May 2005 (2005-05-03) column 2, line 48 - column 3, line 8	5
X	WO 99/27863 A (THERMOLASE CORPORATION; TANKOVICH, NIKOLAI INANOVICH; KOLINKO, VLADIMA) 10 June 1999 (1999-06-10) page 19	5
X	EP 0 925 807 A (THERMOLASE CORPORATION) 30 June 1999 (1999-06-30) paragraph [0013]	5
X	US 2005/180140 A1 (GEORGE DAVID S ET AL) 18 August 2005 (2005-08-18) paragraph [0020]	5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/004339

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-4
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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

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

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

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

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

2. [ ] As all searchable claims could be searched without effort justifying an additional 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/EP2006/004339

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