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(71) Applicant *(for all designated States except US)*: **STEBA MAOR SA** [LU/LU]; 7 Place du Théâtre, L-2613 Luxembourg (LU).

(72) Inventor; and
(71) Applicant : **ABENHAIM, Lucien** [FR/GB]; 1-10 Summer Street, London Bedfordshire EC1 R5 (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **CHARBIT, Suzy** [FR/FR]; Bât. 7, 25, Square Edison, F-94000 Creteil (FR). **GAILLAC, Bertrand** [FR/FR]; 22 rue des Vinaigriers, F-75010 Paris (FR).

(74) Agents: **L'HELGOUALCH, Jean** et al.; Cabinet Sueur & L'Helgoualch, Le Centralis, 63 avenue du Général Leclerc, F-92340 Bourg-la-Reine (FR).

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(54) Title: FOCAL PHOTODYNAMIC THERAPY METHODS

(57) Abstract: Improved methods of treating prostate cancer by vascular-targeted photodynamic therapy, and improved methods of planning treatment,are presented using a light density index to plan and guide effective treatment.

FOCAL PHOTODYNAMIC THERAPY METHODS

1. BACKGROUND

[0001] Some men with early prostate cancer seek an alternative to whole gland therapy, on the one hand, and active surveillance without therapeutic intervention, on the other. Selective therapies that treat the cancer while preserving normal prostate tissue are increasingly sought. Such selective therapies include tumor-targeted approaches capable of discriminating neoplastic from benign tissue, and focal therapies, in which selectivity is achieved by spatially-directed focal ablation.

[0002] Among focal therapies, photodynamic therapy (PDT) – in which a photosensitizing agent is administered systemically and is photoactivated locally to the tumor site – has become an increasingly attractive option given the development of a new generation of photosensitizing agents with improved properties. Notable among these new agents are metal-containing derivatives of bacteriochlorophylls, two of which have been advanced into human clinical trials in the past decade, Pd-Bacteriopheophorbide (padoporfin; WST09; TOOKAD®)— *see* Koudinova *et al.*, "Photodynamic therapy with Pd-Bacteriopheophorbide (TOOKAD): successful *in vivo* treatment of human prostatic small cell carcinoma xenografts," *Int. J. Cancer* 104(6):782-9 (2003); Weersink *et al.*, "Techniques for delivery and monitoring of TOOKAD (WST09)-mediated photodynamic therapy of the prostate: clinical experience and practicalities," *J Photochem Photobiol B.* 79(3):211-22 (2005); Trachtenberg *et al.*, "Vascular targeted photodynamic therapy with palladium-bacteriopheophorbide photosensitizer for recurrent prostate cancer following definitive radiation therapy: assessment of safety and treatment response," *J Urol.* 178(5):1974-9 (2007); Trachtenberg *et al.*, "Vascular-targeted photodynamic therapy (padoporfin, WST09) for recurrent prostate cancer after failure of external beam radiotherapy: a study of escalating light doses," *BJU Int.* 102(5):556-62 (2008); Madar-Balakirski *et al.*, "Permanent occlusion of feeding arteries and draining veins in solid mouse tumors by vascular targeted photodynamic therapy (VTP) with Tookad," *PLoS One* 5(4):e10282 (2010) — and more recently, an improved anionic derivative thereof, Palladium 3^1-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1-(2-sulfoethyl) amide (WST11; STAKEL®; TOOKAD® Soluble™), *see* Mazor *et al.*, "WST-11, A Novel Water-soluble Bacteriochlorophyll Derivative: Cellular Uptake, Pharmacokinetics,

Biodistribution and Vascular-targeted Photodynamic Activity Using melanoma Tumors as a Model," *Photochemistry & Photobiology* 81:342-351 (2005); Brandis *et al.*, "Novel Water-soluble Bacteriochlorophyll Derivatives for Vascular-targeted Photodynamic Therapy: Synthesis, solubility, Phototoxicity and the Effect of Serum Proteins," *Photochemistry & Photobiology* 81:983-993 (2005); Ashur *et al.*, "Photocatalytic Generation of Oxygen Radicals by the Water-Soluble Bacteriochlorophyll Derivative WST-11, Noncovalently Bound to Serum Albumin," *J. Phys. Chem. A* 113:8027-8037 (2009).

[0003] One of the challenges facing photodynamic therapy is the need to define a prospective treatment plan that will direct the placement of optic fibers so as to deliver a treatment-effective light dose in the desired three dimensional volume of prostate tissue, without causing unacceptable collateral damage to other structures, such as the urethra and rectum. The complex interaction among light, photosensitizer, and oxygen, as well as the heterogeneity in light and drug distribution in the prostate, make current approaches to treatment planning computationally intense. Davidson *et al.*, "Treatment planning and dose analysis for interstitial photodynamic therapy of prostate cancer," *Phys. Med. Biol.* 54:2293-2313 (2009). The computational requirements preclude real-time intra-operative adjustment.

[0004] A second challenge arises from the clinical observation that there exists a treatment-effective threshold light dose, and that this threshold dose appears to vary widely among patients who receive the same photosensitizer and in whom fiber placement and light dose were planned according to the same algorithm. Davidson *et al.*, "Treatment planning and dose analysis for interstitial photodynamic therapy of prostate cancer," *Phys. Med. Biol.* 54:2293-2313 (2009). This poses a challenge in selecting light dosages in advance of treatment, and thus in planning effective therapy.

[0005] There exists, therefore, a continuing need for methods by which the treatment-effective threshold dose can be defined in advance of treatment. There exists a further need for treatment planning software that incorporates such treatment-effective threshold dose calculation into the planning algorithm.

2. SUMMARY

[0006] Using the photosensitizing agent, Palladium 3^1-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1-(2-sulfoethyl) amide (WST11; TOOKAD® Soluble™), we have discovered that a Light Density Index ("LDI") can be calculated that predicts the efficacy of photodynamic therapy of prostate tumors. The prediction of efficacy has been validated by MRI as early as 1 week post-treatment, and further confirmed by negative biopsy at 6 months post-treatment. The LDI can be used to define a treatment-effective threshold light dose from historical data, providing a readily-calculable dose parameter that can be used in prospective treatment planning to increase likelihood of successful treatment, without adding significantly, and potentially reducing, computational complexity while increasing likelihood of therapeutic success.

[0007] Accordingly, in a first aspect, a method of treating prostate cancer is provided. The method comprises systemically administering a photosensitizing agent to a patient having a prostate tumor, and then activating the photosensitizing agent by delivering light of appropriate wavelength through at least one optical fiber positioned proximal to the tumor, wherein the administered light dose is at or above a prior-determined treatment-effective light density index (LDI) threshold.

[0008] In various embodiments, the treatment-effective LDI threshold is prior-determined from historical data obtained using the same photosensitizing agent. In certain embodiments, the historical data are obtained using the same photosensitizing agent, administered at the same systemic dosage, at times from historical data obtained using the same photosensitizing agent, administered at the same systemic dosage, and same wavelength of delivered light.

[0009] In various typical embodiments, the photosensitizing agent is administered intravenously.

[0010] In certain embodiments, the photosensitizing agent is Palladium 3^1-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1-(2-sulfoethyl) amide, or pharmaceutically acceptable salts thereof, including the dipotassium salt. Palladium 3^1-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1-(2-sulfoethyl) amide, or pharmaceutically acceptable salts thereof, is in certain embodiments administered intravenously at 3 – 6 mg/kg, including at a dose of 4 mg/kg. In certain embodiments

using this photosensitizing agent, the dose of light delivered is 200 J/cm and the LDI threshold is 1.0.

[0011] In some embodiments, the activating light is delivered through a plurality of optical fibers, typically positioned using a perineal brachytherapy template. Typically, the light is delivered at a wavelength that approximates an absorption maximum of the systemically administered photosensitizing agent.

[0012] In a related aspect, an improvement is presented to methods of photodynamic treatment of prostate cancer in which a photosensitizing agent is administered systemically and then activated by delivery of light of appropriate wavelength through at least one optical fiber positioned proximal to the tumor. The improvement comprises delivering a light dose at or above a prior-determined treatment-effective light density index (LDI) threshold.

[0013] In a further aspect, the treatment-effective light density index threshold is used in improved methods of planning patient-specific photodynamic treatment of prostate cancer, including planning of vascular-targeted photodynamic treatment of prostate cancer. The improvement comprises setting the total length of illuminating fiber to be used for treatment based upon the planned treatment volume (PTV) and a prior-determined treatment-effective light density index threshold.

[0014] In typical embodiments, the total length of illuminating fiber is calculated as the product of PTV and a prior-determined treatment-effective light density index threshold, or scalar multiple thereof. The treatment-effective LDI threshold is typically prior-determined from historical data from use of the same photosensitizing agent, often from historical data in which the same photosensitizing agent, administered at the same systemic dosage, was used. In certain embodiments, the treatment-effective LDI threshold is determined from historical data from use of the same photosensitizing agent, administered at the same systemic dosage, same wavelength of delivered light, and same light density.

[0015] In a further aspect, a computer program product for treatment planning is presented. The program product comprises a computer usable medium having computer readable program code embodied therein, the computer readable program code adapted to

be executed by a computer to implement a method for producing an improved patient-specific treatment plan for photodynamic therapy of prostate cancer. The computer-executed method comprises the step of setting the total length of illuminating fibers needed for effective therapy based upon the planned treatment volume (PTV) and a prior-determined treatment-effective light density index threshold.

[0016] In some embodiments, the total length of illuminating fibers is calculated as the product of PTV and prior-determined treatment-effective light density index threshold, or scalar multiple thereof. The treatment-effective LDI threshold is, in some embodiments, prior-determined from historical data in which the same photosensitizing agent was used as that intended for the use being planned. In various embodiments, the treatment-effective LDI threshold is prior-determined from historical data obtained from use of the same photosensitizing agent, administered at the same systemic dosage, and from the same photosensitizing agent, administered at the same systemic dosage, same wavelength of delivered light, and same light density.

[0017] In a further aspect, an assistance method, implemented by computer, for the planning of treatment of a patient by photodynamic therapy is presented, in which a predefined photosensitizing agent must be administered to the patient, and then subjected to illumination at a predetermined wavelength through at least one illuminating fiber designed to be introduced over a length of insertion into the treatment area. The assistance method comprises calculating the planned treatment volume, PTV, of the treatment area; determining a treatment-effective light density index, LDI, threshold; and setting then the total length of said at least one illuminating fiber to be used for treatment based upon the planned treatment volume, PTV, and said prior-determined treatment-effective light density index threshold

3. DETAILED DESCRIPTION

[0018] Using the photosensitizing agent, Palladium 3^1-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1-(2-sulfoethyl) amide (WST11; TOOKAD® Soluble™), we have discovered that a Light Density Index ("LDI") can be calculated that predicts the efficacy of photodynamic therapy of prostate tumors. The prediction of efficacy has been validated by MRI as early as 1 week post-treatment, and further confirmed by negative

biopsy at 6 months post-treatment. The LDI can be used to define a treatment-effective threshold light dose from historical data, providing a readily-calculable dose parameter that can be used in prospective treatment planning to increase likelihood of successful treatment, without adding significantly, and potentially reducing, computational complexity, while concomitantly increasing likelihood of therapeutic success.

[0019] Accordingly, in a first aspect, a method of treating prostate cancer is provided. The method comprises systemically administering a photosensitizing agent to a patient having a prostate tumor, and then activating the photosensitizing agent by delivering light of appropriate wavelength through at least one optical fiber positioned proximal to the tumor, wherein the administered light dose is at or above a prior-determined treatment-effective light density index (LDI) threshold.

[0020] LDI

[0021] The Light Density Index ("LDI") is calculated as

$LDI = \Sigma(n)L/PTV,$

where $\Sigma(n)L$ is the total length of all illuminating fibers and PTV is the planned treatment volume. In typical embodiments, the length of all illuminating fibers is measured in centimeters, and the planned treatment volume is measured in milliliters.

[0022] The patient-specific PTV used in calculating the LDI is planned using known treatment planning approaches. In some embodiments, the PTV is derived by volume reconstruction from a series of MRI images of the patient's prostate, typically a transverse series, on a plurality of which, typically on all of which, the tumor margin has been outlined. The outline of the tumor margin on sectional images is typically performed by a radiologist or surgeon, although in certain embodiments discrimination of the tumor margin is performed by image recognition software, which is typically thereafter reviewed by a radiologist or surgeon. Volume reconstruction is performed using standard digital image processing techniques and algorithms. In typical embodiments, the PTV is planned to include an additional enveloping volume to ensure that treatment is sufficient to fully include the actual tumor margin. In such embodiments, the treatment planning software typically adds the user-chosen or software-predetermined margin to each two-dimensional sectional image in which the tumor margin has been circumscribed. In some

embodiments, the margin can be added after the volume reconstruction, although this computationally more complex approach is presently not preferred. In some embodiments, the PTV is calculated according to the methods described in Davidson *et al.*, "Treatment planning and dose analysis for interstitial photodynamic therapy of prostate cancer," *Phys. Med. Biol.* 54:2293-2313 (2009).

[0023] Treatment-effective LDI threshold

[0024] The treatment-effective LDI threshold is determined prior to treatment. In typical embodiments, the treatment-effective LDI threshold is prior-determined from historical clinical data.

[0025] In typical embodiments, the treatment-effective LDI threshold is determined by first correlating the magnitude of the treatment LDI for each of a series of historical patients with one or more later-observed patient-specific outcomes. The later-observed outcomes are chosen from art-accepted outcomes, including clinical outcomes, such as post-treatment survival, change in tumor stage or grade, or more typically, from radiologic and/or pathologic outcomes that are art-recognized as useful surrogates, such as evidence of tissue necrosis on post-treatment MRI, or percentage of negative biopsies post-treatment.

[0026] In some embodiments, the treatment LDI is calculated from historical data using the actual treated volume (ATV) instead of the historical prospective PTV. The ATV is usefully calculated from the area of necrosis observed on post-treatment MRI images, such as MRI images taken at 1 week post-treatment, 1 month post-treatment, 2 months post-treatment, 3 months post-treatment, and/or 6 months post-treatment. In certain embodiments, the ATV is derived by volume reconstruction from a series of post-treatment MRI images of the patient's prostate, typically a transverse series, on a plurality of which, typically on all of which, the margins of the necrotic area, or hypoperfused area, has been outlined. The outline of the necrotic or hypoperfused area on sectional images is typically performed by a radiologist or surgeon, although in certain embodiments, discrimination of the margin is performed by image recognition software, which is typically thereafter reviewed by a radiologist or surgeon. Volume reconstruction is performed using standard digital image processing techniques and algorithms.

[0027] In typical embodiments, standard statistical approaches will be applied to the correlated treatment LDI and outcome data to determine a treatment-effective threshold that provides a desired degree of statistical confidence. For example, in Example I, below, we identify a treatment-effective LDI threshold having a P value of < 0.01 with respect to predicting necrosis volume on MRI at 1 week post-treatment as a percentage of the PTV, and also having a P value < 0.01 with respect to the percentage of negative biopsies at 6 months post-treatment. Any chosen treatment-effective LDI threshold may provide different magnitudes of statistical significance with respect to different outcomes.

[0028] Because the treatment-effective LDI threshold may differ depending on the choice of photosensitizing agent, its systemic dosage, and the irradiating wavelength delivered locally to the prostate, the treatment-effective LDI threshold is usefully derived from historical data drawn from prior clinical use of the same photosensitizing agent to be used in the subject patient. In some embodiments, the historical data are from use of the same photosensitizing agent, administered at the same systemic dosage, to be used in the subject patient. In some embodiments, the historical data are from use of the same photosensitizing agent, administered at the same systemic dosage, and irradiated with the same wavelength to be used in the subject patient. In addition, because the treatment-effective LDI threshold may differ depending on the light density (*e.g.*, in Joules/cm) delivered through each fiber, the treatment-effective LDI threshold is usefully derived from historical data drawn from prior clinical use of the same light density to be used in the subject patient.

[0029] The prior-determined treatment-effective LDI threshold does not require recalculation from historical data for each patient to be treated. In typical embodiments, the treatment-effective LDI threshold will be treated as a constant, typically user-entered, by treatment planning algorithms. However, it is contemplated that the treatment-effective LDI threshold will be recalculated on a periodic basis as additional historical data become available, such as the data on additional patients, and/or additional outcome data on patients included in the prior calculation. Furthermore, in certain embodiments, the treatment-effective LDI threshold will be calculated separately for defined subpopulations of historical patients, and the treatment-effective LDI threshold used for

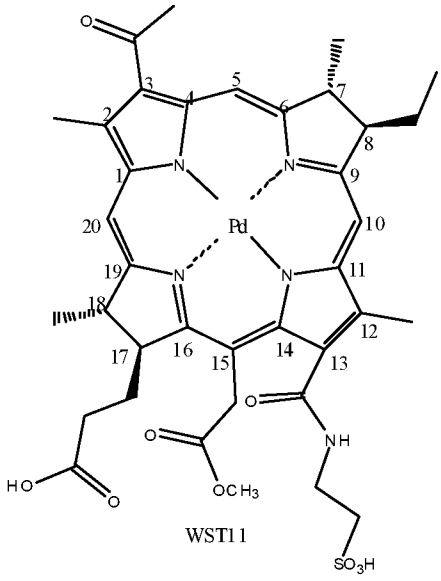
administering treatment to a given patient will be chosen based on the patient's similarity to the historical subpopulation.

[0030] Photosensitizing agents

[0031] The efficacy of the LDI parameter to predict treatment efficacy was demonstrated using the photosensitizing agent, Palladium 3^1-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1-(2-sulfoethyl) amide (WST11; TOOKAD® Soluble™) as the dipotassium salt.

[0032] Thus, in a preferred embodiment of the methods of this aspect of the present invention, the photosensitizing agent is Palladium 3^1-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1-(2-sulfoethyl) amide, or a pharmaceutically acceptable salt thereof. The WST11 compound in its un-ionized form has the structure given below, in formula (Ia), in which the tetrapyrrole carbons are numbered according to standard IUPAC nomenclature:

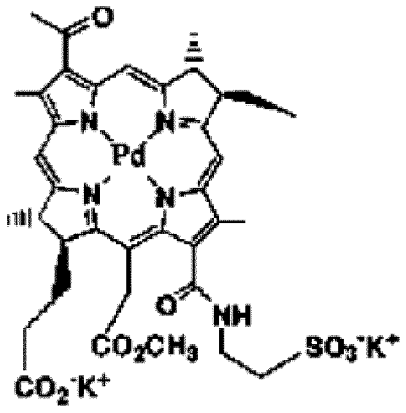
(Ia)



WST11

[0033] In various embodiments, pharmaceutically acceptable WST11 salts usefully include a counterion selected from monovalent and divalent alkaline and alkaline earth metal cations, such as one or more of K^+, Na^+, Li^+, and Ca^{2+}. In an embodiment that is at present particularly preferred, the dipotassium salt is used, as shown in Formula Ib:

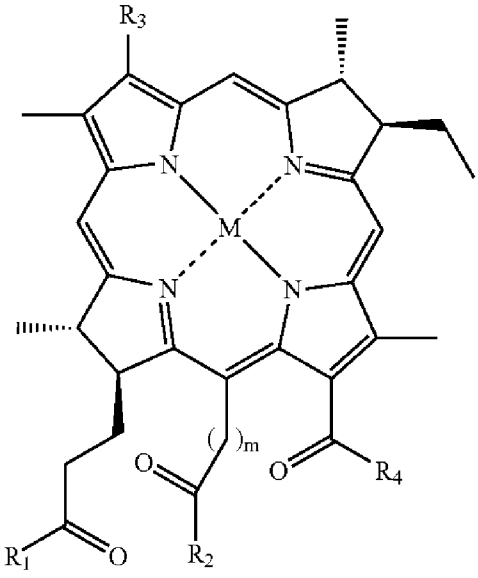
(Ib)



[0034] The compounds of formulae Ia and Ib are prepared according to known procedures. See WO 2004/045492 and US pre-grant application publication no. US 2006/01422260 A1, the disclosures of which are incorporated herein by reference in their entireties.

[0035] In other embodiments, the photosensitizing agent is a compound of Formula II:

(II)



wherein

M represents 2H or a metal atom selected from divalent Pd, Pt, Co, Sn, Ni, Cu, Zn and Mn, and trivalent Fe, Mn and Cr;

R_1, R_2, and R_4 each independently is Y-R_5;

Y is O, S or NR_5R_6;

R_3 is selected from $–CH=CH_2$, $-C(=O)-CH_3$, -C(=O)-H, $-CH=NR_7$, $-C(CH_3)=NR_7$, $-CH_2-OR_7$, $-CH_2-SR_7$, $-CH_2-NR_7R'_7$, $-CH(CH_3)-OR_7$, $-CH(CH_3)-SR_7$, $-CH(CH_3)-NR_7R'_7$, $-CH(CH_3)$Hal, $-CH_2$-Hal, $-CH_2-R_7$, $-CH=CR_7R'_7$, $-C(CH_3)=CR_7R'_7$, $-CH=CR_7$Hal, $-C(CH_3)=CR_7$Hal, and $-C\equiv CR_7$;

R_5, R_6, R_7 and R'_7 each independently is H or is selected from the group consisting of:

(a) C_1-C_{25} hydrocarbyl optionally containing one or more heteroatoms, carbocyclic or heterocyclic moieties, and/or optionally substituted by one or more functional groups selected from the group consisting of halogen, oxo, OH, SH, CHO, NH_2, $CONH_2$, a negatively charged group, and an acidic group that is converted to a negatively charged group at the physiological pH;

(b) a residue of an amino acid, a peptide or of a protein; and

(c) when Y is O or S, R_5 may further be R_8^+;

m is 0 or 1; and

R_8^+ is H^+ or a cation;

provided that:

(i) at least one, preferably two, of R_5, R_6, R_7 and R'_7 is a hydrocarbon chain as defined in (a) above substituted by a negatively charged group or by an acidic group that is converted to a negatively charged group at the physiological pH; or

(ii) at least one, preferably two, of R_1, R_2, and R_4 is OH, SH, $O^-R_8^+$ or $S^-R_8^+$; or

(iii) at least one of R_1, R_2, and R_4 is OH, SH, $O^-R_8^+$ or $S^-R_8^+$ and at least one of R_5, R_6, R_7 and R'_7 is a hydrocarbon chain substituted by a negatively charged group or by an acidic group that is converted to a negatively charged group at the physiological pH; or

(iv) at least one of R_1, R_2, and R_4 is OH, SH, $O^-R_8^+$ or $S^-R_8^+$ and at least one of R_5, R_6, R_7 and R'_7 is a residue of an amino acid, a peptide or of a protein; or

(v) at least one of R_5, R_6, R_7 and R'_7 is a hydrocarbon chain substituted by a negatively charged group or by an acidic group that is converted to a negatively charged group at the physiological pH and at least one of R_5, R_6, R_7 and R'_7 is a residue of an amino acid, a peptide or of a protein;

but excluding the compounds of formula I wherein M is as defined, R_3 is $-C(=O)CH_3$, R_1 is OH or OR_8^+ and R_2 is $-OCH_3$, and the compound of formula II wherein M is 2H, R_3 is $-C(=O)CH_3$, R_1, R_2 and R_4 are OH, and m is 0 or 1.

[0036] In various embodiments of photosensitizing agents of formula II, the negatively charged groups are selected from the group consisting of COO^-, COS^-, SO_3^-, and/or PO_3^{2-}. In various embodiments, the acidic groups that are converted to negatively charged groups at physiological pH are selected from the group consisting of COOH, COSH, SO_3H, and/or PO_3H_2. In certain embodiments, R_1 is $Y\text{-}R_5$; Y is O, S or NH; and R_5 is a hydrocarbon chain substituted by functional groups selected from OH, SH, SO_3H, NH_2, $CONH_2$, COOH, COSH, PO_3H_2. In selected embodiments, R_5 is the residue of an amino acid, a peptide or a protein. Usefully, M is a divalent palladium atom.

[0037] In certain embodiments of photosensitizing agents of formula II,

M represents 2H, divalent Pd, Cu, or Zn or trivalent Mn;

R_1 is $-O^-R_8^+$, $-NH-(CH_2)_n-SO_3^-R_8^+$, $-NH-(CH_2)_n-COO^-R_8^+$;$-NH-(CH_2)_n-PO_3^{2-}(R_8^+)_2$; or $Y\text{-}R_5$ wherein Y is O, S or NH and R_5 is the residue of an amino acid, a peptide or a protein;

R_2 is C_1-C_6 alkoxy such as methoxy, ethoxy, propoxy, butoxy, more preferably methoxy;

R_3 is $-C(=O)-CH_3$, $-CH=N-(CH_2)_n-SO_3^-R_8^+$;$-CH=N-(CH_2)_n-COO^-{}_8^+$;$-CH=N-(CH_2)_n-PO_3^{2-}(R_8^+)_2$;$-CH_2-NH-(CH_2)_n-SO_3^-R_8^+$;$-NH-(CH_2)_n-COO^-R_8^+$; or $-NH-(CH_2)_n-PO_3^{2-}(R_8^+)_2$;

R_4 is $-NH-(CH_2)_n-SO_3^-R_8^+$;$-NH-(CH_2)_n-COO^-R_8^+$;$-NH-(CH_2)_n-PO_3^{2-}(R_8^+)_2$;

R_8^+ is a monovalent cation such as K^+, Na^+, Li^+, NH_4^+, more preferably K^+; and

m is 1, and n is an integer from 1 to 10, preferably 2 or 3.

[0038] In certain embodiments of photosensitizing agents of formula II,

M is divalent Pd;

R_1 is $-O^-R_8^+$, $-NH-(CH_2)_n-SO_3^-R_8^+$, or Y-R_5 wherein Y is O, S or NH and R_5 is the residue of an amino acid, a peptide or a protein;

R_2 is C_1-C_6 alkoxy, preferably methoxy;

R_3 is $-C(=O)-CH_3$, $-CH=N-(CH_2)_n-SO_3^-R_8^+$; or $-CH_2-NH-(CH_2)_n-SO_3^-R_8^+$;

R_4 is $-NH-(CH_2)_n-SO_3^-R_8^+$; $NH-(CH_2)_n-COO^-R_8^+$; $NH-(CH_2)_n-PO_3^{2-}-(R_8^+)_2$;

R_8^+ is a monovalent cation, preferably K^+;

m is 1, and n is 2 or 3.

[0039] The compounds of Formula II may be synthesized according procedures described in WO 2004/045492 and US pre-grant application publication no. US 2006/01422260 A1, the disclosures of which are incorporated herein by reference in their entireties.

[0040] In typical embodiments, the photosensitizing agent is administered intravenously. In certain embodiments, the photosensitizing agent is administered by intravenous infusion. In other embodiments, the photosensitizing agent is administered as an intravenous bolus.

[0041] In certain embodiments in which the photosensitizing agent is WST11, or pharmaceutically acceptable salt thereof, the photosensitizing agent is administered intravenously at a dose of about 2 – 6 mg/kg. In certain embodiments, the WST11 or salt thereof is administered intravenously at a dose of about 2 mg/kg, 3 mg/kg, about 4 mg/kg, about 5 mg/kg, even about 6 mg/kg. In one series of embodiments, the photosensitizing agent is Palladium 3^1-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1-(2-sulfoethyl) amide dipotassium salt administered intravenously at 4 mg/kg.

[0042] Light wavelength

[0043] The wavelength of light delivered will be appropriate for the chosen photosensitizing agent, and in typical embodiments will approximate an absorption maximum of the agent.

[0044] In embodiments in which the photosensitizing agent is WST11 or salt thereof, the wavelength will typically be between about 670 to about 780 nm. In various embodiments, the wavelength will be about 750 nm, including about 753 nm.

[0045] In another aspect, an improvement is provided to methods of photodynamic treatment planning. The improvement comprises setting the total length of illuminating fiber to be used for treatment based upon the planned treatment volume (PTV) and a prior-determined treatment-effective light density index threshold. As would be understood, the length of illuminating fiber refers to the length of optical fiber that is positioned in the prostate tissue and capable of delivering light to the tissue.

[0046] In typical embodiments, the total length of all illuminating fiber is calculated as the product of a prior-determined treatment-effective LDI threshold x PTV, or scalar transformation thereof. In typical embodiments, the LDI threshold and PTV are determined as above-described. In certain embodiments, the total length of all illuminating fiber is provided by a single fiber. More typically, the total length of all illuminating fiber is contributed by a plurality of fibers. In some embodiments, all fibers are of identical length. In other embodiments, the fibers differ in length.

[0047] The improvement can used in conjunction with existing methods of treatment planning that are designed to optimize the placement of optical fibers for photodynamic therapy of prostate cancer. In some embodiments, for example, the total length of all illuminating fiber calculated as above-described is used in conjunction with light diffusion-based treatment planning methods, such as that described in Davidson *et al.*, "Treatment planning and dose analysis for interstitial photodynamic therapy of prostate cancer," *Phys. Med. Biol.* 54:2293-2313 (2009). In other embodiments, the total length of all illuminating fiber calculated as above-described is used in conjunction with other treatment planning algorithms.

[0048] By establishing the total length of illuminating fiber, the improvement usefully reduces the number of variables to be considered, reducing computing complexity, while ensuring that the optimized fiber placement delivers a light dose that is above the therapeutic threshold. Thus, the improvement can usefully be incorporated into software used to plan photodynamic treatment.

[0049] Thus, in another aspect, a computer program product is provided, comprising a computer usable medium having computer readable program code embodied therein, the computer readable program code adapted to be executed by a computer to implement a method for producing a patient-specific treatment plan for photodynamic therapy of

prostate cancer, the method comprising a step of setting the total length of illuminating fiber to be used for treatment based upon the planned treatment volume (PTV) and a prior-determined treatment-effective light density index threshold. In typical embodiments, the PTV and prior-determined treatment-effective light density index threshold are calculated as above-described, and the total length of illuminating fiber is calculated as the product of a prior-determined treatment-effective LDI threshold x PTV, or scalar transformation thereof.

[0050] Further advantages and features are shown in the following Example, which is presented by way of illustration and is not to be construed as limiting the scope of the present invention.

4. EXAMPLES

Example 1: Light density index predicts early efficacy of focal vascular targeted photodynamic treatment of prostate cancer

[0051] Materials and Methods

[0052] Palladium 3^1-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1-(2-sulfoethyl) amide dipotassium salt was prepared as described in WO 2004/045492 and US 2006/0142260, the disclosures of which are incorporated herein by reference in their entireties.

[0053] Men with low risk organ-confined prostate cancer (Gleason 3 +3 on minimum 10 core TRUS biopsy) were recruited into two consecutive studies: PCM201 (a dose escalation study) or PCM203 (a confirmatory study). The vascular-targeted photodynamic therapy ("VTP") procedure, carried out under general anesthesia, involved administration of TOOKAD® Soluble intravenously at 4 mg/kg, which was then activated by low power laser light delivered locally to the prostate via a brachytherapy-style transperineal template with a light density of 200 J/cm. Planned treatment volume ("PTV", in mls) was determined by the location of tumor on biopsy and by MRI, and varied in volume from less than one lobe, to the whole prostate.

[0054] The Light Density Index ("LDI") was calculated as LDI = Σ(n)L/PTV, where Σ(n)L is the total length of all illuminating fibers (in cm), and PTV is the planned treatment volume, in mls.

[0055] Early treatment effect was determined as the proportion of the PTV which showed lack of uptake of gadolinium on 1 week MRI. This was also correlated with the result of 6 month transrectal ultrasound (TRUS)-guided biopsy (positive or negative for any cancer).

[0056] The correlation between LDI and the volume of tissue necrosis at day 7 and with the rate of negative biopsies at Month 6 was assessed in search of a threshold.

[0057] Results

[0058] 90 men were treated with a TOOKAD® Soluble dose of 4mg/kg and a light dose of 200J/cm in the two studies. Of these 89 were analyzable for LDI. Results using an LDI threshold of 1 are presented below.

	Treatment effect on 1 week MRI as % of PTV (n lobes)		**% of negative biopsies (6 months) (n lobes))**	
	PCM201	PCM203	PCM201	PCM203
LDI <1	59 (17)	60 (22)	31 (4/17)	N/A
LDI≥ 1	95 (12)	94 (28)	83 (10/12)	N/A
P	<0.01	<0.01	<0.01	-

(N/A – not yet available)

[0059] Conclusion

[0060] LDI is a reliable predictor of treatment effect using TOOKAD® Soluble VTP, both in terms of effect seen on 1 week MRI, and 6 month biopsy.

[0061] While various specific embodiments have been illustrated and described, it will be appreciated that various changes can be made without departing from the spirit and scope of the invention(s).

WHAT IS CLAIMED IS:

1. A method of treating prostate cancer, comprising:

systemically administering a photosensitizing agent to a patient having a prostate tumor;

activating the photosensitizing agent by delivering light of appropriate wavelength through at least one optical fiber positioned proximal to the tumor,

wherein the dose of light delivered is at or above a prior-determined treatment-effective light density index (LDI) threshold.

2. The method of claim 1, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent.

3. The method of claim 2, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent, administered at the same systemic dosage.

4. The method of claim 3, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent, administered at the same systemic dosage, and same wavelength of delivered light.

5. The method of any one of claims 1 – 4, wherein the photosensitizing agent is Palladium 3^1-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1-(2-sulfoethyl) amide, or pharmaceutically acceptable salts thereof.

6. The method of claim 5, wherein the photosensitizing agent is Palladium 3^1-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1-(2-sulfoethyl) amide dipotassium salt.

7. The method of any one of claims 1 – 6, wherein the photosensitizing agent is administered intravenously.

8. The method of claim 7, wherein the photosensitizing agent is Palladium 3^1-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1-(2-sulfoethyl) amide, or pharmaceutically acceptable salts thereof, administered intravenously at 3 – 6 mg/kg.

9. The method of claim 8, wherein the photosensitizing agent is administered at a dose of 4 mg/kg.

10. The method of claim 9, wherein the dose of light delivered is 200 J/cm and the LDI threshold is 1.0.

11. The method of any one of claims 1 - 10, wherein light is delivered through a plurality of optical fibers.

12. The method of claim 11, wherein the optical fibers are positioned using a brachytherapy template.

13. The method of any one of claims 1 – 12, wherein light is delivered at a wavelength that approximates an absorption maximum of the systemically administered photosensitizing agent.

14. In a method of photodynamic treatment of prostate cancer in which a photosensitizing agent is administered systemically and then activated by delivery of light of appropriate wavelength through at least one optical fiber positioned proximal to the tumor, the improvement comprising:

delivering a light dose at or above a prior-determined treatment-effective light density index (LDI) threshold.

15. The method of claim 13, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent.

16. The method of claim 15, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent, administered at the same systemic dosage.

17. The method of claim 16, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent, administered at the same systemic dosage, and same wavelength.

18. The method of any one of claims 14 – 17, wherein the photosensitizing agent is Palladium 3^1-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1-(2-sulfoethyl) amide, or pharmaceutically acceptable salts thereof.

19. The method of claim 18, wherein the photosensitizing agent is Palladium 3^1-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1-(2-sulfoethyl) amide dipotassium salt.

20. The method of any one of claims 14 – 19, wherein the photosensitizing agent is administered intravenously.

21. The method of claim 20, wherein the photosensitizing agent is Palladium 3^1-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1-(2-sulfoethyl) amide, or pharmaceutically acceptable salts thereof, administered intravenously at 3 – 6 mg/kg.

22. The method of claim 21, wherein the photosensitizing agent is administered at a dose of 4 mg/kg.

23. The method of claim 22, wherein the light is delivered at 200 J/cm and the LDI threshold is 1.0.

24. The method of any one of claims 14 - 23, wherein light is delivered through a plurality of optical fibers.

25. The method of claim 24, wherein the optical fibers are positioned using a brachytherapy template.

26. The method of any one of claims 14 – 25, wherein light is delivered at a wavelength that approximates an absorption maximum of the systemically administered photosensitizing agent.

27. In a method of planning photodynamic therapy of prostate cancer in a patient, the improvement comprising:

setting the total length of illuminating fiber to be used for treatment based upon the planned treatment volume (PTV) and a prior-determined treatment-effective light density index threshold.

28. The method of claim 27, wherein the total length of illuminating fiber is calculated as the product of PTV and prior-determined treatment-effective light density index threshold or scalar multiple thereof.

29. The method of claim 28, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent.

30. The method of claim 29, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent, administered at the same systemic dosage.

31. The method of claim 30, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent, administered at the same systemic dosage, and same wavelength of delivered light.

32. The method of claim 31, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent, administered at the same systemic dosage, same irradiating light wavelength, and same light density.

33. A computer program product comprising a computer usable medium having computer readable program code embodied therein, the computer readable program code adapted to be executed by a computer to implement a method for producing a patient-specific treatment plan for photodynamic therapy of prostate cancer, the method comprising:

setting the total length of illuminating fibers needed for effective therapy based upon the planned treatment volume (PTV) and a prior-determined treatment-effective light density index threshold.

34. The computer program product of claim 33, wherein the total length of illuminating fibers is calculated as the product of PTV and prior-determined treatment-effective light density index threshold, or scalar multiple thereof.

35. The computer program product of claim 34, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent.

36. The computer program product of claim 35, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent, administered at the same systemic dosage.

37. The computer program product of claim 36, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent, administered at the same systemic dosage, and same wavelength of delivered light.

38. The computer program product of claim 37, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent, administered at the same systemic dosage, same irradiating light wavelength, and same light density.

39. Assistance method, implemented by computer, for the planning of treatment of a patient by photodynamic therapy, in which a predefined photosensitizing agent must be administered to the patient, and then subjected to illumination at a predetermined wavelength through at least one illuminating fiber designed to be introduced over a length of insertion into the treatment area, **characterized in that** it includes the following steps:

calculating the planned treatment volume, PTV, of the treatment area;

determining a treatment-effective light density index, LDI, threshold; and then

setting the total length of said at least one illuminating fiber to be used for treatment based upon the planned treatment volume, PTV, and said prior-determined treatment-effective light density index threshold.

40. The assistance method of claim 39, wherein the total length of illuminating fiber is calculated as the product of PTV and prior-determined treatment-effective light density index threshold or scalar multiple thereof.

41. The method of claim 40, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent.

42. The assistance method of claim 41, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent, administered at the same systemic dosage.

43. The assistance method of claim 42, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent, administered at the same systemic dosage, and same wavelength of delivered light.

44. The assistance method of claim 43, wherein the treatment-effective LDI threshold is prior-determined from historical data from use of the same photosensitizing agent, administered at the same systemic dosage, same irradiating light wavelength, and same light density.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/054060

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

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SEAN R H DAVIDSON ET AL: "Treatment planning and dose analysis for interstitial photodynamic therapy of prostate cancer; Treatment planning and analysis for prostate PDT", PHYSICS IN MEDICINE AND BIOLOGY, TAYLOR AND FRANCIS LTD. LONDON, GB, vol. 54, no. 8, 21 April 2009 (2009-04-21) , pages 2293-2313, XP020149927, ISSN: 0031-9155, DOI: 10.1088/0031-9155/54/8/003 page 2298; figure 1	33-44

X	US 2011/034971 A1 (SVANBERG SUNE [SE] ET AL) 10 February 2011 (2011-02-10) paragraph [0180]	33-44

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 April 2012	10/05/2012

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2012/054060

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

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

1. [X] Claims Nos.: 1-32
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 therapyRule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

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

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

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

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

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

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

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

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

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/054060

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2011034971 A1	10-02-2011	AT 467439 T	15-05-2010
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		US 2011034971 A1	10-02-2011
		WO 2008020050 A1	21-02-2008