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(71) Applicant: THE PENN STATE RESEARCH FOUNDATION [US/US]; 304 Old Main, University Park, Pennsylvania PA 16802 (US).

(72) Inventor; and

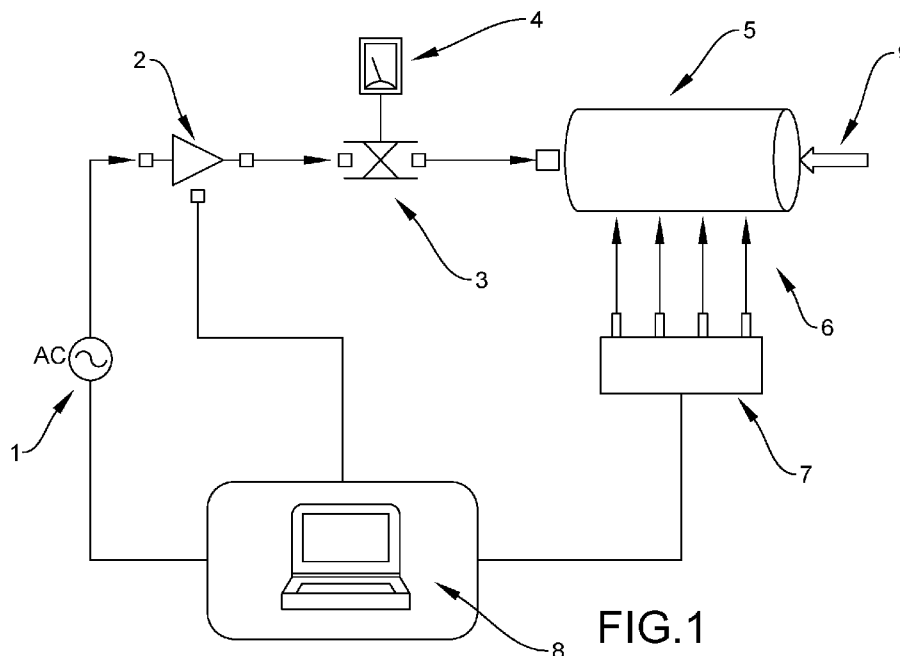
(71) Applicant: SPADAFORA, Carmenza [PA/PA]; Building 28, City of Knowledge, Panama City (PA).

(72) Inventor: STOUTE, Jose Antonio; Penn State University College of Medicine, 500 University Drive, Hershey, Pennsylvania PA 17033 (US).

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(54) Title: DEVICE FOR THE TREATMENT OF MALARIA



(57) Abstract: Device for the treatment of malaria A method and device for the treatment of malaria which comprises applying microwave energy to a patient under non-thermal conditions. The non-thermal conditions are achieved by applying the microwave energy under conditions that the normal heating effects of microwaves are not significant. For example, microwave energy may be switched on in pulses lasting less than 6 seconds.

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a
patent (Rule 4.17(ii))*
- *of inventorship (Rule 4.17(iv))*

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Device for the treatment of malaria

This invention relates to a device for the treatment of malaria and, in particular, a system for the treatment of malaria using electromagnetic energy in the microwave spectrum.

Malaria is an infectious disease widespread in many tropical and subtropical regions. *Plasmodium falciparum*, the causative agent of the most devastating form of malaria, causes serious public health problems worldwide. According to the World Health Organization (Fact Sheet: World Malaria Report 2016), in 2015 there were 212 million new cases of malaria worldwide and an estimated 429,000 malaria deaths worldwide. To date, the most effective ways to control malaria have been the use of drugs to treat the disease and insecticides to control the transmission.

Due to the spread of resistance to both types of molecules, there is a need for a new safe and effective treatment for malaria.

The present invention relates to the use of microwave energy in the treatment of malaria.

Microwave irradiation is known to be used in the treatment of cancer, by means of thermal ablation. It has previously been suggested that microwave thermal ablation could also be used to treat malaria.

[American Journal of Tropical Medicine and Hygiene (2009), 81(5), Suppl. 1, 44-45. 58th Annual Meeting of the American Society of Tropical Medicine and Hygiene, ASTMH, Washington, DE, United States]

However, thermal ablative therapy, for example when used for the treatment of cancer, does carry risks. The high temperatures produced in microwave thermal ablation can cause collateral thermal damage in the

human body, including haemorrhage. The treatment can also cause abscess formation.

It has now been surprisingly found that the non-thermal use microwave energy significantly inhibits the growth of *Plasmodium falciparum*, without affecting mammalian cells, and is therefore useful in the treatment of malaria.

Accordingly, the present invention provides a method for the treatment of malaria which comprises applying microwave energy to a patient, sufficient to reduce the level of malarial parasites in the patient under non-thermal conditions.

In a further aspect, the invention provides a device for the treatment of malaria in a patient, comprising a microwave generator, an applicator connected to the microwave generator and a control means adapted to cause the generator to provide pulses of microwave energy to the patient through the applicator sufficient to reduce the level of malarial parasites in the patient under non-thermal conditions.

The term 'treatment' when used herein includes prevention and prophylaxis.

The non-thermal use of microwaves means that the tissues of the patient subjected to microwave energy do not significantly rise in temperature. In particular, the method and device of this invention may comprise the application of microwave energy under conditions wherein the temperature of the tissue of a patient does not exceed 50°C. Suitably, the temperature does not exceed 45°C, preferably not in excess of 42°C.

The non-thermal conditions may be achieved by applying the microwave energy in sufficiently short pulses, so that the normal heating effects of

microwaves are not significant. For example, microwave energy may be switched on in pulses lasting less than 6 seconds, suitably from 3 to 5 seconds, preferably about 5 seconds.

- 5 Following each pulse of microwave energy, the energy is switched off for an interval before the next pulse. The interval allows the tissues to cool between pulses of microwave energy. The period of the interval should however be sufficiently short to allow continuity in the application of microwave energy.

10

The period of each cycle, comprising one pulse and one interval, is generally called a duty cycle, and is expressed in terms of the pulse period as percentage of the overall cycle. In the present invention, it is suitable to use from a 10% duty cycle to a 25% duty cycle. The duration
15 of each duty cycle may be, for example, from 15 seconds to one minute, suitably from 20 seconds to 40 seconds. Thus, the interval between pulses may be from 10 to 50 seconds, suitably from 15 to 40 seconds, preferably from 18 to 30 seconds.

- 20 Each cycle is then successively repeated to provide a treatment period sufficient to allow the microwave energy to reduce the level of malarial parasites. The treatment period is suitably from 20 minutes to one hour, for example 20 minutes to 50 minutes, preferably from 25 minutes to 45 minutes. During the treatment period, there may be multiple cycles of
25 pulse/interval. For example, there may be from 25 to 150 cycles in one treatment period. It is convenient to have from 50 to 120 cycles per treatment period.

- The part of the electromagnetic spectrum defined as microwaves have
30 frequencies from 300 MHz to 300 GHz. In this invention, frequencies within this range can be used, in particular from 300 MHz to 200 GHz, for example from 300 MHz to 100 GHz. It is suitable to use the conventional

microwave frequency of 2.45 GHz, which is often chosen because it falls within the band (2.4 to 2.5 GHz) that is not reserved for communication purposes. However, other frequencies may also be used.

5 The device of this invention comprises a microwave generator, an applicator connected to the microwave generator and a control means. The purpose of the applicator is to transmit the microwaves to the patient. It is possible to connect one applicator, or a plurality of applicators to the microwave generator. For example, two or three
10 applicators may be connected. One suitable type of applicator is a waveguide resonator, comprising an enclosure or cavity, into which the patient's body, or part thereof, is inserted. Waveguides are well known in the art and may be of a size and shape suitable to accommodate the patient's body or part thereof. The waveguide should be closed at least on
15 one side. Alternatively, the applicator may be an open delivery system such an antenna, or a transmission line. The applicator may comprise a ceramic cap, to apply the microwave energy directly onto or into the tissues. Preferably the tip of the applicator is designed for single use to reduce the risk of cross-infection.

20

Because the malaria parasites are present in the blood, the microwave energy may be applied to any suitable part of the patient's body, for example the torso, arms, legs, hands or feet. Alternatively, the applicator may be in the form of a probe or needle to provide the microwave energy
25 within the body or into a vein.

30

The connection between the microwave generator and the applicator may be a simple cable, such as a coaxial cable, or may contain further components, such as an amplifier.

The control means is adapted to cause the generator to provide pulses of microwave energy. In its simplest form, the control means may comprise

a simple mechanical switch system, which may be manual or programmable. Suitably, the control means is programmable, either mechanically or preferably an electronically, such as in the form of a computer. The control means is generally programmed to provide pre-determined sequence of pulses and interval periods suitable for the treatment. In addition, the control means may also be used to control other variables of the treatment, such as treatment period, frequency and power of the microwave energy. The control means may be attached to the microwave generator or situated in the connection between the microwave generator and the applicator.

The microwave energy power employed in this invention is such to prevent the patient's body temperature to rise significantly. Suitably the power may be from 3 to 8 Watts.

The above-mentioned parameters of power, pulse times, interval times and treatment times may be varied to maintain non-thermal conditions and achieve the most effective reduction in the level of malarial parasites in the patient.

Patients may preferably be treated in two or more sessions, for example at daily intervals or every other or every third day.

The level of malarial parasites in the blood can be measured by known techniques, by microscopy or by flow cytometry. Parasite species that affect humans are *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale* and *Plasmodium knowlesi*.

The temperature of the tissues may be measured by a temperature monitoring sensor or probe.

Although this invention is not limited by mechanism of action, our data suggest that the non-thermal microwave energy targets the food vacuole leading to release of intracellular calcium and acidification of the cytoplasm; an opening of calcium channels plays a critical role in this process. There is also a contribution of autophagy in the death of the parasites treated with non-thermal microwave energy.

Our data also show that the microwave treatment according to this invention induces morphological changes that are visible under light microscopy and detectable by flow cytometry, with an increase in reactive oxygen species and lipid peroxidation generation followed by a decrease in cytoplasmic pH, caspase activation and DNA fragmentation.

Furthermore, we have also found that the ability of the parasite *P. falciparum* to synthesize haemozoin after treatment with microwave energy is not affected. That is, the non-thermal microwave treatment of this invention differs in the mechanism of action of known antimalarials such as chloroquine and mefloquine.

Thus, the use of non-thermal microwave non-microwave energy will act in synergy with antimalarial substances.

Accordingly, in a further aspect of this invention, there is provided an antimalarial substance for use in a method for the treatment of malaria which comprises administering the antimalarial substance to a patient and applying microwave energy to the patient, sufficient to reduce the level of malarial parasites in the patient under non-thermal conditions.

Because the non-thermal microwave energy acts by different mechanism from most antimalarial substances, the microwave energy may be applied prior to, concomitant with, or subsequent to, the administration of the

antimalarial substance. Preferably, however, the microwave energy is applied subsequent to the administration of the antimalarial substance.

5 The antimalarial substance may be a known antimalarial substance, or a substance subsequently found to possess antimalarial activity. For example, the antimalarial substance may be: an aryl amino-alcohol compound, such as quinine, quinidine, mefloquine, halofantrine, lumefantrine, piperazine, or tafenoquine; an amino-quinoline such as chloroquine, primaquine, or amodiaquine; an antifolate compound, such as
10 pyrimethamine, proguanil, chlorproguanil, trimethoprim, a sulphone or sulphonamide; an artemisinin compound or derivative such as artemisinin, dihydroartemisinin, artemether, artesunate or artelinic acid; a naphthoquinone, such as atovaquone; an iron chelating agent such as desferrioxamine; or an antimicrobial with antimalarial activity, such as
15 tetracycline, doxycycline, clindamycin, azithromycin, or fluoroquinolones. The antimalarial substance may also be a combination of compounds, such as atovaquone in combination with proguanil.

20 The antimalarial substance may be administered by a route that is suitable to allow absorption of, such as orally, intravenously, intramuscularly, subcutaneously, sublingually, buccally, rectally, vaginally, nasally, topically or transdermally.

25 Prior to, concomitant with, or subsequent to administration of the antimalarial substance, the non-thermal microwave energy is applied to the patient, as described herein.

One embodiment of the present invention will now be described with reference to the accompanying drawings in which:
30 Fig 1 is a schematic representation of a device according to this invention.

A signal generator 1 provides a microwave signal, which is transmitted to a signal amplifier 2. The signal then passes through a coupler 3 having a power indicator 4. The coupler 3 is connected to a waveguide applicator 5, operating at 2.45 GHz. Temperature sensors are connected to an optical fibre thermometer 7. The microwave generator 1, amplifier 2, and thermometer 7 are all connected to a control means in the form of a computer 8.

In operation, a body part, such as a limb, head, neck or torso of a patient suffering from malaria is introduced into the waveguide 5 in the direction shown by the arrow 9. The temperature sensors 6 are attached to the patient. The software on the computer 8 allows a user to control the exposure parameters of pulse and interval times, as well as monitor the temperature, to ensure a non-thermal irradiation.

The invention is further illustrated by *in vitro* data generated in the following Example.

Example 1

Experimental methods

(a) Parasites and cultures

The malaria parasite strain HB3 of *P. falciparum* was cultivated following the method described by Haynes et al. [Culture of human malaria parasites *Plasmodium falciparum*. Nature 263, 767–9 (1976).] with some modifications. In brief, we used O+ erythrocytes in complete medium that consisted of RPMI 1640 supplemented with 25 mM HEPES, 0.2% sodium bicarbonate, and 10% serum. Blood was obtained from donors under a human protocol approved by the local human use committee. Cultures were maintained at 37 °C in a gas mixture of 5% CO₂, 5% O₂ and 90% N₂ at 2% hematocrit and synchronized with alanine and thermal cycling as described by Almanza et al [Automated Synchronization of *P. falciparum*

using a Temperature Cycling Incubator. Curr Trends Biotech Pharm 1130–1133 (2011).].

(b) Microwave exposure system

5 The microwave exposure system consisted of a signal generator, a signal amplifier, a power reflectometer, a waveguide applicator and four optical fiber probes connected to a digital thermometer. All were connected to a computer equipped with custom software BioEMC (Bio Electro Magnetic Compatible) which allowed the user to control all of the exposure
10 parameters as well as store the results of each experiment.

(c) Microwave exposure conditions

Experiments were conducted at a frequency of 2.45 GHz. For the resonant cavity, 150 ul of 0.9% saline was placed at the bottom of a 17 x 100 mm
15 polypropylene tube (Karter Scientific). A small styrofoam holder was placed on top of the saline and a 250 ul polypropylene tube (KeL Scientific KS-3858-WC25) with 200 ul of blood sample was placed in the holder. The cavity was tuned to always obtain the lowest reflected power and thus maximize the absorption of energy by the sample.
20

(d) Growth assays

Following exposure of duplicate samples containing trophozoite or early schizont-synchronized cultures with 2% parasitemia were seeded in 96-well plates for 72 hrs. The growth was monitored for from 24 hrs to up to
25 72 hrs by microscopy or by flow cytometry. For microscopy, Giemsa-stained thin smears were prepared and the number of infected erythrocytes in at least 1,000 erythrocytes was counted. The microscopist was always blinded to the experimental treatment of each sample. For flow cytometry, samples were stained with 2 µg/ml Hoechst 33342
30 (Invitrogen, Carlsbad, CA, USA) for 15 min prior to transferring a 125 ul aliquot to 125 ul of 4% paraformaldehyde in PBS. Samples were stored at 4°C until acquisition. A CyFlow Space cytometer (Partec, Görlitz,

Germany) was used for acquisition by exciting the samples with a UV laser. The data were analyzed with the FloMax version 2.7 (Quantum Analysis GmbH, Munster, Germany). The change in growth was calculated as (24 h parasitemia - 0 h parasitemia) / 24 h parasitemia.

5

The results are shown in Table 1

Table 1

Power 12W				Power 10W			
Irradiation time	Pulse on (seconds)	interval (seconds)	parasite survival (%)	Irradiation time	Pulse on (seconds)	interval (seconds)	parasite survival (%)
20 minutes	5	40	80.45	20 minutes	5	40	100
	5	30	78.98		5	30	100
	5	25	78.5		5	25	97.85
	5	18	65.5		5	18	98.78
	5	15	65.67		5	15	98.75
25 minutes	5	40	75.35	25 minutes	5	40	100
	5	30	77.45		5	30	100
	5	25	54.4		5	25	96.35
	5	18	47.2		5	18	93.86
	5	15	50.35		5	15	93.5
30 minutes	5	40	47.36	30 minutes	5	40	95.5
	5	30	46.21		5	30	93.45
	5	25	37.56		5	25	94.36
	5	18	38.45		5	18	88.78
	5	15	35.15		5	15	87.9
45 minutes	5	40	18.55	45 minutes	5	40	87.56
	5	30	18.45		5	30	88.45
	5	25	17		5	25	83.9
	5	18	12		5	18	77.5
	5	15	13.5		5	15	77.2

10

CLAIMS

1. A device for the treatment of malaria in a patient, comprising a
5 microwave generator, an applicator connected to the microwave generator and a control means adapted to cause the generator to provide pulses of microwave energy to the patient through the applicator sufficient to reduce the level of malarial parasites in the patient under non-thermal conditions.
- 10 2. A device as claimed in claim 1 wherein the temperature of the tissue of a patient is maintained less than 42 degrees Celsius.
3. A device as claimed in claim 1 or claim 2 wherein microwave energy is
15 switched on in pulses lasting less than 6 seconds.
4. A device as claimed in any one of claims 1 to 3 wherein the interval between pulses is from 18 to 30 seconds.
- 20 5. A device as claimed in any one of claims 1 to 4 wherein the treatment period is from 25 minutes to 45 minutes.
6. A device as claimed in any one of claims 1 to 5 wherein the applicator is a waveguide.
- 25 7. An antimalarial substance for use in a method for the treatment of malaria which comprises administering the antimalarial substance to a patient and applying microwave energy to the patient, sufficient to reduce the level of malarial parasites in the patient under non-thermal

conditions.

8. A method for the treatment of malaria which comprises applying microwave energy to a patient, sufficient to reduce the level of malarial parasites in the patient under non-thermal conditions.
9. A method as claimed in claim 8 wherein the temperature of the tissue of a patient does not exceed 42 degrees Celsius.
10. A method as claimed in claim 8 or claim 9 wherein microwave energy is switched on in pulses lasting less than 6 seconds.
11. A method as claimed in any one of claims 8 to 10 wherein the interval between pulses is from 18 to 30 seconds.
12. A method as claimed in any one of claims 8 to 11 wherein the treatment period is from 25 minutes to 45 minutes.

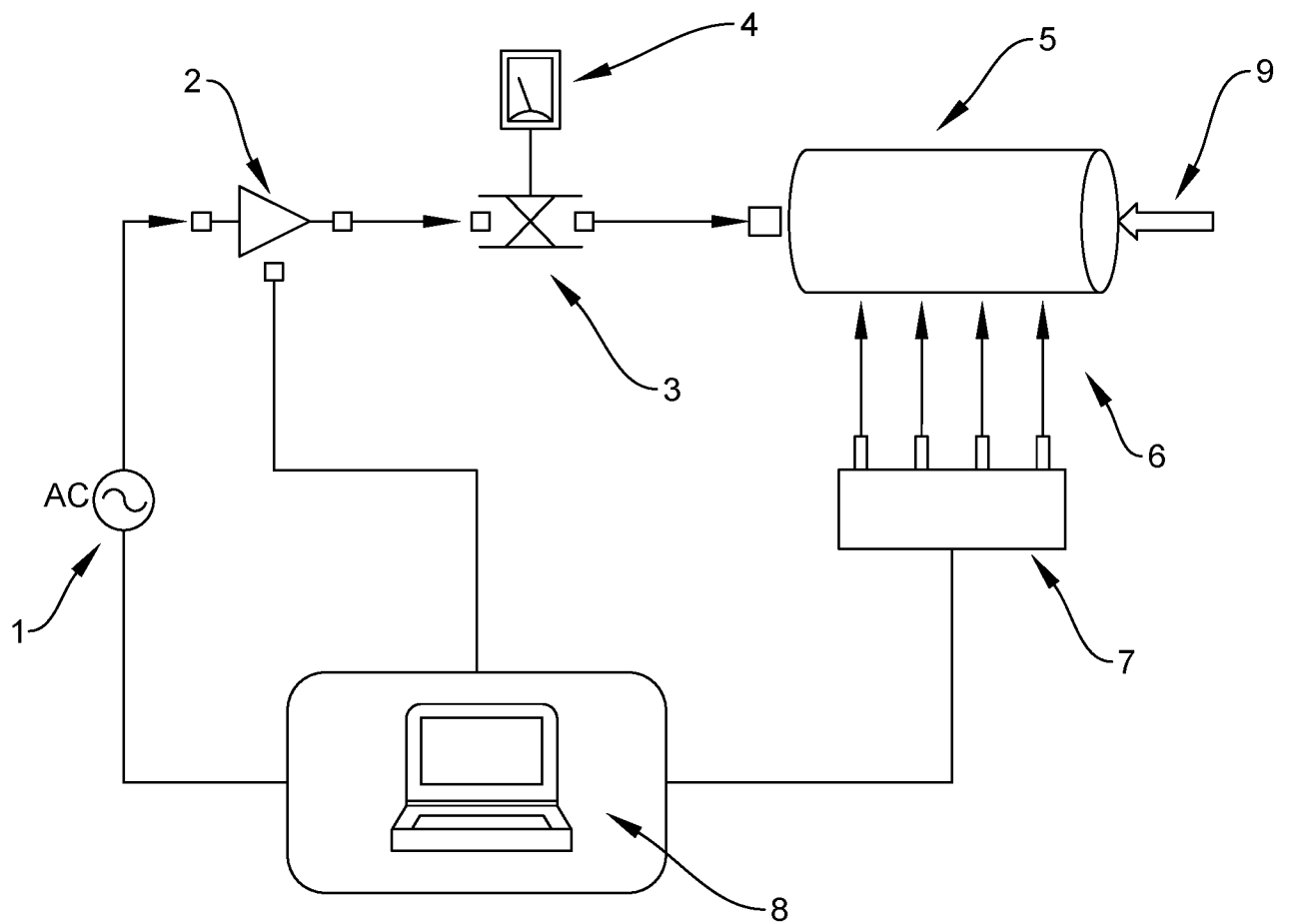


FIG.1

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2020/051554

A. CLASSIFICATION OF SUBJECT MATTER INV. A61N5/02 A61N5/04 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 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 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	C T NADOVICH ET AL: "Microwave Exposure System for In Vitro and In Vivo Studies", PROCEEDINGS OF THE 2014 COMSOL CONFERENCE IN BOSTON, 1 January 2014 (2014-01-01), XP055691483, DOI: 10.13140/2.1.2922.7843 the whole document -----	1-3,6
X	US 4 228 805 A (ROSEN ARYE ET AL) 21 October 1980 (1980-10-21) abstract; figure 1 column 2, line 21 - column 5, line 53 -----	1-3
X	US 9 669 231 B1 (CLARK GEORGE [US] ET AL) 6 June 2017 (2017-06-06) abstract; figure 1 column 5, line 12 - column 6, line 32 column 11, line 61 - column 14, line 67 -----	1-5
-/--		
☒ 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	
7 May 2020	26/05/2020	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Beck, Ewa	

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2020/051554

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 105 213 174 A (WANG JIANXIN) 6 January 2016 (2016-01-06) the whole document -----	1-3
X	REX DALTON: "Central America: Panama's big ambition", NATURE, vol. 469, 26 January 2011 (2011-01-26), pages 462-463, XP055691307, the whole document -----	1,2
X	"Promising new microwave treatment for malaria", youtube, 30 August 2011 (2011-08-30), page 4 pp., XP054980447, Retrieved from the Internet: URL:https://www.youtube.com/watch?v=ZtH-q5Ysh4 [retrieved on 2020-05-06] the whole document -----	1,2
A	JP 2010 195760 A (NAGAURA YOSHIKI; NAGAURA KUMIKO; NAGAURA ZENICHIRO) 9 September 2010 (2010-09-09) the whole document -----	1-6
X	US 2004/181114 A1 (HAINFELD JAMES F [US] ET AL) 16 September 2004 (2004-09-16) abstract; claims 1,22 paragraph [0040] -----	7
A	CISKA VERBAANDERD ET AL: "Repurposing Drugs in Oncology - chloroquine andhydroxychloroquine as anti-cancer agents", 20171123, vol. 11, no. 781, 23 November 2017 (2017-11-23), pages 1-35, XP002784324, DOI: 10.3332/ECANCER.2017.781 the whole document -----	7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2020/051554

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

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

1. ☒ Claims Nos.: 8-12
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 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:

see additional sheet

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-7

There are two inventions as follows:

1.1. claims: 1-6

A device for the treatment of malaria in a patient, comprising a microwave generator, an applicator connected to the microwave generator and a control means adapted to cause the generator to provide pulses of microwave energy to the patient through the applicator sufficient to reduce the level of malarial parasites in the patient under non-thermal conditions, wherein the interval between pulses is from 18 to 30 seconds.

1.2. claim: 7

An antimalarial substance for use in a method for the treatment of malaria which comprises administering the antimalarial substance to a patient and applying microwave energy to the patient, sufficient to reduce the level of malarial parasites in the patient under non-thermal conditions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2020/051554

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4228805	A	21-10-1980	JP S587290 B2 09-02-1983
			JP S5570238 A 27-05-1980
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			WO 2004112590 A2 29-12-2004
