



(51) International Patent Classification:

H05H 1/24 (2006.01)

A61N 1/44 (2006.01)

A61B 18/04 (2006.01)

(21) International Application Number:

PCT/EP2020/066802

(22) International Filing Date:

17 June 2020 (17.06.2020)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

PCT/IB2019/000782

17 June 2019 (17.06.2019)

IB

(71) Applicants: INSERM (INSTITUT NATIONAL DE LA SANTÉ ET DE LA RECHERCHE MÉDICALE)

[FR/FR]; 101, rue de Tolbiac, 75013 PARIS (FR). SOR-

BONNE UNIVERSITE [FR/FR]; 21 Rue de l'Ecole de Médecine, 75006 PARIS (FR).

(72) Inventors: **FOUASSIER, Laura**; INSERM-Sorbonne Université, UMRS 938, 27 rue de Chaligny, 75012 PARIS (FR). **DUFOUR, Thierry**; LPP, Equipe Plasmas froids, 4 Place Jussieu, Tour 34, Etage 4, Porte LPP, Office 417, 75006 PARIS (FR). **JUDEE, Florian**; 966 rue de la Cote Blanche, 58600 GARCHIZY (FR). **PLEDEL, Sylvain**; LPP (UMR 7648), 4 Place Jussieu, Tour 34, Etage 4, Porte LPP, 75006 PARIS (FR). **VAQUERO, Javier**; INSERM-Sorbonne Université, UMRS 938, 27 rue de Chaligny, 75012 PARIS (FR).

(74) Agent: **PLASSERAUD IP**; 66 rue de la Chaussée d'Antin, 75440 PARIS CEDEX 09 (FR).

(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,

(54) Title: MEDICAL DEVICE FOR APPLYING PLASMA

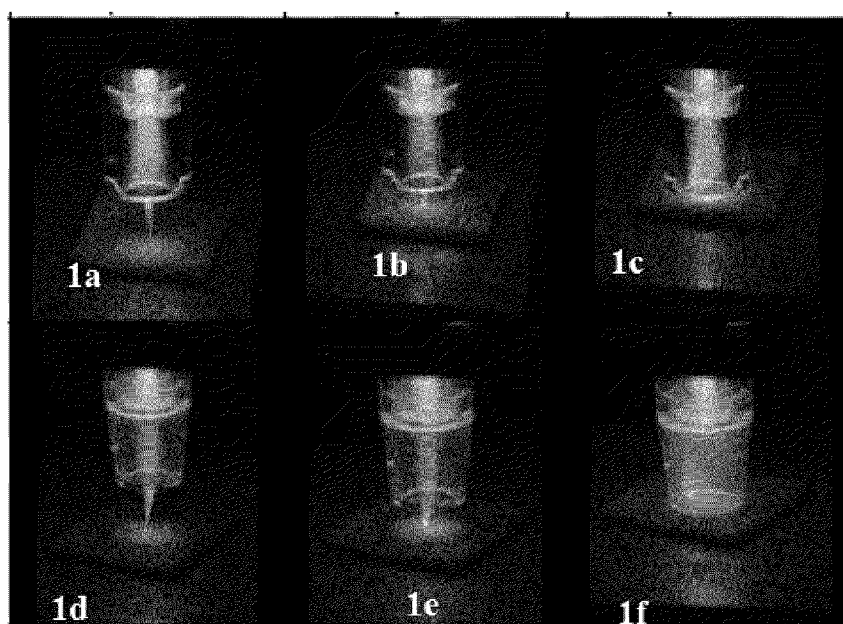


Figure 1

(57) **Abstract:** The present invention relates to medical device configured for applying a plasma jet on a target, wherein the medical device comprises a tip configured to homogenize and enlarge the plasma in contact with the target. Based on a study of porcine and murine models, the inventors have clearly demonstrated that cold plasma drive to anti-tumor effects without causing deleterious consequences (burnings). In order to enhance this effect, the inventors further developed a removable tip which in more to homogeneize and enlarge plasma ensures a better control of its physico- chemical properties over treatment time. In another aspect, the invention relates to method of treatment of cholangiocarcinoma comprising irradiating a tumor with a cold plasma jet. In yet another aspect, the invention relates to method for manufacturing a removable tip according to the present invention.



DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

MEDICAL DEVICE FOR APPLYING PLASMA

The present invention relates to the field of cancer therapy and more specifically to the field of plasma therapy.

Cold atmospheric plasmas are weakly ionized gases containing
5 energetic and chemical transient species (electrons, ions, metastables, radicals)
while presenting radiation, gas flowing and electromagnetic field properties. In
laboratory, they can be easily generated by supplying electrical power to a
device containing either one or two electrodes. The electrode connected to the
high voltage power supply is commonly referred as the exciting (or powered)
10 electrode while the second optional electrode is referred as the counter-
electrode and is usually brought to the ground. As a result, a non-linear and
high magnitude electric field can be generated to create electrical discharges
that partially ionize the gas into cold plasma. Of the most commonly cold
plasma devices used in laboratories, the dielectric barrier discharge (DBD)
15 appears ubiquitous owing to its low manufacturing and implementation costs,
as well as its great versatility in regard of the many diversified applications
like ozone generation, incoherent excimer UV radiation, air purification,
surface modifications, etc.

In these DBDs, one electrical insulating layer, typically a dielectric
20 material like quartz or alumina is utilized as a barrier to prevent arcing from
plasma current. Whatever their 1 or 2 electrode(s) configurations, two types of
DBD can be distinguished: (i) the non-flowing DBDs where the powered
electrode is enwrapped by an insulator material and where plasma remains
confined in the interelectrode region (ii) gas-flowing DBDs where plasma is
25 located in this region as well as further away: in the post-electrode region.
There, the ionized gas is referred as a plume to design its emissive properties
although long lifetime radicals can propagate much further away in the post-
discharge without emitting any radiation. The gas-flowing DBDs are more
commonly referred as plasma jets and more specifically as atmospheric
30 pressure plasma jets (APPJ) if they operate in ambient air. One can distinguish
two types of APPJ configurations: (i) APPJ devices with a single metal
electrode biased to the exciting potential (typically high voltage) while the

counter-electrode is the biological target (grounded or floating potential) exposed to plasma, (ii) APPJ devices with two metal electrodes (exciting electrode and counter electrode) while the biological target can eventually play a role of third electrode. Among the 'two-electrodes APPJ' successfully applied upon *in vivo* experiments, the plasma gun (PG) is composed of an outer ring electrode and an inner pin electrode directly in contact with the gas/plasma. Another configuration of interest, referred in this article as plasma Tesla jet (PTJ), presents two distant ring electrodes located on the outer tube.

Due to its metastable nature at atmospheric pressure, applying cold plasma uniformly on a large targeted area (typically a few square centimeters) and over a long period time is often uneasy and drives to non-homogeneous treatment of this target. Such instabilities are particularly true in the case of two-electrode DBDs due to the lack of parallelism between the two electrodes as well as to boundary effects. In the case of an APPJ, the plasma plume interacts with the ambient air and generates radicals as well as long lifetime reactive species. Owing to the relative humidity in the ambient air, the gaseous densities of these latter species is rarely controlled. Moreover, the chemical composition of the ambient air being essentially limited by a N_2/O_2 ratio close to 3.7, the gaseous chemistry operating in the plasma plume remains limited. Surprisingly, in the field of plasma medicine, reactive species are often considered as one of the main reason of therapeutic effects demonstrated upon *in vitro* and *in vivo* experiments.

Due to the difficulties inherent to its application, therapeutic use of cold plasma is a field which remains still largely unexplored.

Since plasma jet devices have already successfully demonstrated antitumor effects, there is a need to provide technological incrementations to enlarge and homogenize the plasma plume upon its interaction with a tumor, with the aim to cover it entirely.

To that end, a first aspect of the present invention relates to a medical device configured for exposing a target tumor to a plasma jet, wherein the medical device comprises a tip configured to enlarge and homogenize the plasma jet in contact with the exposed target.

Obviously, this interestingly allows improving the quality, the versability and the reproducibility of the plasma therapy.

Typical medical devices used to generate cold plasma include dielectric barrier devices. For instance, such device can comprise a dielectric tube in which at least one
5 gas such as helium is injected. Two distant metallic rings are maintained around the tube and a voltage is applied on them so as to create an electric field in the tube, located between the electrodes. The potential difference is chosen so as to ionize the gas flowing inside the tube and thus to generate a flowing cold plasma which propagates outside the tube for a short distance, forming a so-called “plasma jet”, which can also be
10 referred to as a *plasma plume* when considering the plasma which goes beyond the electrodes.

In order to enlarge and to homogenize the plasma jet, the invention provides a tip which can be set up between the tube’s end and the tumor tissue to be treated.

Preferably, the target tumor has an external location. As a matter of fact,
15 although cold plasma can penetrate skin to a certain extent, or be applied through surgery, the invention is easier to use on external tissues, whether lesions, tumors or inflamed. As a consequence, exemplary target tumors of choice for the present invention comprise melanoma and ectopic tumors such as cholangiocarcinoma.

Cholangiocarcinoma (CCA) is a heterogeneous group of aggressive
20 malignancies that can emerge at every point of the biliary tree from the canals of Hering into the liver to the main bile duct. CCA is the second most frequent type of primary liver cancer and ~3% of all gastrointestinal neoplasia. Cholangiocarcinoma are generally asymptomatic in early stages, they are diagnosed when the disease has already metastasized, drastically complicating their therapeutic treatment options. Surgical
25 resection is the only effective therapy, but it can only be applied in 20% of patients and the 5 year survival rate remains as low as 15%–40%. Most of the patients who cannot benefit from surgery undergo a palliative treatment with a combination of gemcitabine and oxaliplatin platinum salt (GEMOX), the only chemotherapy validated for advanced unresectable CCA (Valle et al 2010). In case of tumor progression after this first line of
30 treatment, there is no other treatment approved to date. Tumor size and other features (anatomical location, vascular and lymph node invasion and metastasis) condition the

potential surgical and/or radiological options but chances of recurrence are very high. Owing to these limitations, the emergence of new therapeutic options is eagerly needed.

Preferably, the tip comprises a hollow cavity configured to be in contact with the target tumor. This cavity can be of any shape and allows confining the plasma plume
5 from the ambient atmosphere, thus preventing the plasma jet to dissipate or to interact with the oxygen of the atmosphere without control, thus allowing the plasma to be homogenously applied to the treated zone.

The shape of the cavity can be designed and engineered to encompass the size of the tumor, taking into account its topography and improve the effectiveness of the
10 exposure. Indeed, the effectiveness depends both on the exposure time and on the electrical power of the plasma. Although the electrical power cannot be easily measured with high accuracy, it is largely correlated with the gas partial pressure per surface of exposure and to the plasma, both of which can be controlled by the shape of the tip.

Preferably, the cavity is a cone-shaped, a truncated cone-shaped or a gradual
15 curve-shape cavity. Such shapes will allow smoothly increasing or decreasing the section of tumor tissue exposed to the plasma.

As such, the cavity can present a sectional area which increases outward; such cavity will be referred to as A-shaped cavity and allows increasing the surface of exposure. The term outward is to be understood as meaning from the plasma generation
20 device toward the lesion to be exposed.

Alternatively, the cavity presents a sectional area which decreases outward; such cavity will be referred to as V-shaped cavity and allows concentrating the plasma when the surface of exposure can be decreased. The term outward is to be understood as meaning from the plasma generation device toward the lesion to be exposed.

25 The tip can be made of any material which does not conduct electrical charges and preferably biocompatible such as polymers, most of 3D-printable materials, etc.

Preferably, the cold plasma is to present a gas temperature lower than 40°C to not induce drying effects of the tissues although these effects are time-dependant and although thermal effects might be intended for other applications where hyperthermia
30 could play a therapeutic role. In all cases, the gas temperature cannot exceed the

temperature at which the insulator material constituting the tip starts to induce a change of its state (typically vitreous transition temperature, melting temperature, etc.).

Preferably, the tip is removable. As a matter of fact, depending on the size and on the location of the target tumors, it may be necessary or interesting to opt for a different tip. Furthermore, a removable tip could be interestingly installed on pre-existing medical devices.

The tip can comprise lateral micro-holes, preferably lateral micro-holes presenting a diameter comprised between 0.1 mm to 10 mm with a typical size of 1 mm. These holes can be drilled to ensure two functions: first, when the tip is in perfect contact with the target (no possible gas leakage), the surpressure of gaseous plasma contained into the cavity can be evacuated through these holes; second, offering the opportunity to connect through these holes captors that will monitor parameters of interest in real time (e.g. chemical composition, gas temperature, etc.).

The invention also relates to a method of treatment of cholangiocarcinoma comprising irradiating a tumor with a cold plasma jet.

The tumor can e.g. be exposed to the cold plasma jet for a duration comprised between a few seconds to several minutes.

The plasma jet plume is preferably confined so as to prevent ionization of ambient air, although some lateral holes can be drilled into the tip to enable the plasma gas to be released in the air and therefore to prevent any surpressure or transient plasma phenomena propagating at counter-flow.

The method according to the present invention preferably comprises using a medical device according to the invention.

The present invention also relates to a removable tip for a medical device according to the invention.

The present invention also relates to a method for manufacturing a removable tip according to the present invention.

The invention can be better understood at the reading of the detailed examples below, which constitute non-limitative embodiments of the present invention and at the examining of the annexed drawing, on which:

- 5 - Figure 1 shows different medical devices according to the invention exposing an ex-vivo target to a plasma jet,
- Figure 2 is an infrared photography of a plasma jet device treating a target tumor, and
- Figure 3 is a flowchart representing the volumic growth of tumors with and without plasma treatment.

10 It is understood that the described embodiments are not restrictive and that it is possible to make improvements to the invention without leaving the framework thereof.

 In case of the present embodiment, a cold plasma operating at atmospheric pressure was generated in a dielectric barrier device in which a
15 flow of helium was flowing at a rate of 1L per minute. In order to ionize the flowing helium, the dielectric barrier device was powered by a AC high-voltage electric generator. The pulses presented an amplitude of 8000V and were delivered at a frequency of 10kHz for a duty cycle of 14%.

 Post-mortem porcine skin samples presenting a dimension comprised
20 between 3.5 and 4.5 cm² were used for the sake of this embodiment. The exposure time was set to 2 minutes.

 The samples were placed on a metal plate connected to a resistance and a capacitor mounted in parallel so as to mimic the electrical response of the animal model under plasma exposure.

25 If no tip was used, the diameter of the plasma plume in contact with the targeted tissue was lower than 2mm. Adding a tip with either an A-shaped or a V-shaped cavity allowed to significantly increase the diameter of the plume upon its contact with the target.

 The A-shaped tip allowed to triple the diameter whereas the V-shaped
30 tip allowed to multiply it by five.

Depending on the topology and size of the targeted tumor, it is possible to engineer a tip which can cover the whole tumor volume so as to provide a homogenous treatment. Without any tip, the plasma must be moved above the tumor so as to effectively scan the whole region to be treated. Such step is
5 inconvenient, potentially dangerous, and renders the treatment heterogeneous.

Figure 1 shows a cold plasma jet generated with an A-shaped tip (1a, 1b, 1c) and with a V-shaped tip (1d, 1e, 1f) and applied to a target sample at different distances. Fig1a and 1d correspond to a gap of 10 mm between the extremity of the tip and the target sample, fig 1b and 1e correspond to a gap of
10 5mm and fig 1c and 1f correspond to a gap lower than 1 mm.

It shows that in order to obtain an optimal effect, the tip should be applied right on the target sample. Otherwise, the homogenization and spreading of the plasma plume do not occur in the tip cavity whilst the plasma jet keeps propagating in a thin ray that focuses on the sample tissue.

15 Figure 2 is an infrared photography which allows mapping the temperature of the plasma jet. Figure 2a corresponds to a set-up without any tip, figure 2b to a set-up with an A-shaped tip, and figure 2c to a set-up with a V-shaped tip.

These pictures clearly show that the gas temperature of plasma stays
20 well under 30°C, thus preventing any burns of the target sample and authorizing treatment times potentially larger than a few minutes.

The current therapeutic effect of the plasma has been evidenced even without any tip in a subcutaneous xenograft tumor model performed with EGI-1 cholangiocarcinoma cells.

25 A few days after injection of tumor cells under mice skin, the proliferation of these cells has been high enough to create a tumor exhibiting a measurable volume that mimicks human tumor (Vaquero et al 2018). As shown in Figure 3, when tumor volumes reach an approximate volume as high as 200 mm³, two successive PG treatments are achieved at days 13 and 20 for an
30 exposure time of 1 min, repetition frequency of 1 kHz and D_{cycle}=14%. The tumor volumes remain the same versus time whatever the control and plasma groups. Then, after leaving a 14 d refractory period, the tumors are treated

using the PTJ at days 34 and 41 with the same aforementioned plasma conditions. However in that latter case, there was a strong reduction of tumor growth in the plasma group compared with the control group. At day 48, tumor volumes remain limited to 1250 mm^3 for mice belonging to the plasma group versus 1730 mm^3 for mice belonging to the control group. Besides, the p-value between these two tumor volumes is lower than 0.05, hence underlining the significant therapeutic effect of the plasma therapy. Experiments have not been carried out further to respect ethical protocols limiting tumor volume to less than 2000 mm^3 for the two groups.

Altogether, the dermal toxicity test and the xenograft tumor experiments show that the PTJ is as safe as the PG and displays *in vivo* antitumor properties. The PTJ properties are more interesting since PTJ effect appears the day after PTJ treatment, i.e. at day 35 in the *in vivo* experiment and that this effect is obtained at a very advanced stage of tumor development.

To understand why one of the two plasma sources validates an anti-tumor effect and not the other, we propose to briefly compare them at the light of the usual cold plasma properties, i.e. radiative, thermal, chemical, electrical and gas flow properties. The gas temperature (neutral species) is always close to 305 K ($\pm 6 \text{ K}$) whatever the plasma source (with the exception of the arc regime which cannot be applied on living organisms). Therefore, we assume that for such a low value, the temperature cannot induce antitumor effect owing to the absence of such results with the PG. Regarding flow properties, it has been shown that profiles may significantly differ if the target is changed but not when the PG is replaced with the PTJ. Again, in our own experimental conditions, the impact of flow properties can be considered as negligible to induce antitumor effects. The radiative properties are stronger with PG than with PTJ whereas more chemical species may be produced with PTJ, likely to explain the tumor size reduction. In our *in vivo* experiments, the tumors were ectopically grafted on mice, i.e. covered by a thin skin layer likely to mitigate the diffusion of exogeneous radicals from plasma. Since reactive species can be delivered several millimeters into tissues (Szili et al 2018), it is important to identify if those detected with PTJ and PG are likely to induce antitumor effects:

– The hydroxyl (OH) radical is known as the most electrophilic ROS with high reactivity. It can cause oxidative damage to DNA, proteins and lipids as long as it is produced in their vicinity (Hadi et al 2010, Cadet and Davies 2017). In our research works, even if OH radicals are significantly produced with the two APPJ, their therapeutic potential remains questionable in inducing antitumor effects.

– Low concentrations of extracellular singlet oxygen can inactivate catalase on the membrane of tumor cells and thus abrogate the antioxidant activity of one of the central molecules of tumor cells (Riethmüller et al 2015). Although produced in low amounts with our APPJ, the role of O radical as antitumoral agent must not be underestimated. In the vicinity of inactivated catalase, it could prevent NO from oxidation and prevent H₂O and peroxynitrite (constantly produced outside of tumor cells) to be decomposed (Bauer 2016). Then, the subsequent protonation of peroxynitrite into peroxynitrous acid can enable the production of intracellular NO₂ and hydroxyl radicals.

– To the best of the authors knowledge, the H radical is not described in the literature as a candidate likely to induce strong anticancer effects. For these reasons, H radicals can reasonably be considered as playing a negligible role in the demonstrated antitumor effects.

– As reminded by D. Graves (2014), nitric oxide (NO) is a biologically significant molecule that can induce several pivotal effects, e.g. immune modulation of tumor growth, modulation of angiogenesis and inhibition of cell respiration (Janakiram and Rao 2015, Morbidelli et al 2019). Although NO has not been investigated in the preset study, further works could be carried out to generate it on purpose, as selectively as possible.

Finally, the plasma electrical properties are also assumed to play an important role in the antitumor effect. Depending on whether PG or PTJ is used on the same target, the resulting $V=f(t)$ profiles could highlight substantial differences (change in voltage polarity, change in pulses duration, ...).

CLAIMS

1. Medical device configured for exposing a target tumor to a plasma jet, wherein the medical device comprises a tip configured to homogenize and enlarge the plasma jet in contact with the exposed target.

5 2. Medical device according to claim 1, wherein the target tumor has an external location.

3. Medical device according to claim 2, wherein the target tumor is a melanoma or a cholangiocarcinoma.

10 4. Medical device according to any of claim 1 or 3, wherein the tip comprises a hollow cavity configured to be in contact with the target tumor.

5. Medical device according to claim 4, wherein the hollow cavity is a cone-shaped, a truncated cone-shaped cavity or a gradual curve-shaped cavity.

6. Medical device according to claim 4 or 5, wherein the cavity presents a sectional area which increases outward.

15 7. Medical device according to claim 4 or 5, wherein the cavity presents a sectional area which decreases outward.

8. Medical device according to any of claims 1 to 7, wherein the cold plasma is to present a temperature inferior to 30°C.

20 9. Medical device according to claims 1 to 8, wherein the tip comprises lateral micro-holes , preferably lateral micro-holes presenting a diameter comprised between 0.1 mm to 10 mm

10. Medical device according to claims 1 to 9, wherein the tip is removable.

11. Method of treatment of cholangiocarcinoma comprising irradiating a tumor with a cold plasma jet.

25 12. Method of treatment according to claim 11, wherein the plasma jet is confined so as to prevent ionization of ambient air.

13. Method of treatment according to claim 11 to 12, wherein the method comprises using a medical device according to any of claim 1 to 10.

14. Removable tip for a medical device according to any of claims 1 to 10.

15. Method for manufacturing a removable tip according to claim 14.

DRAWINGS

1/2

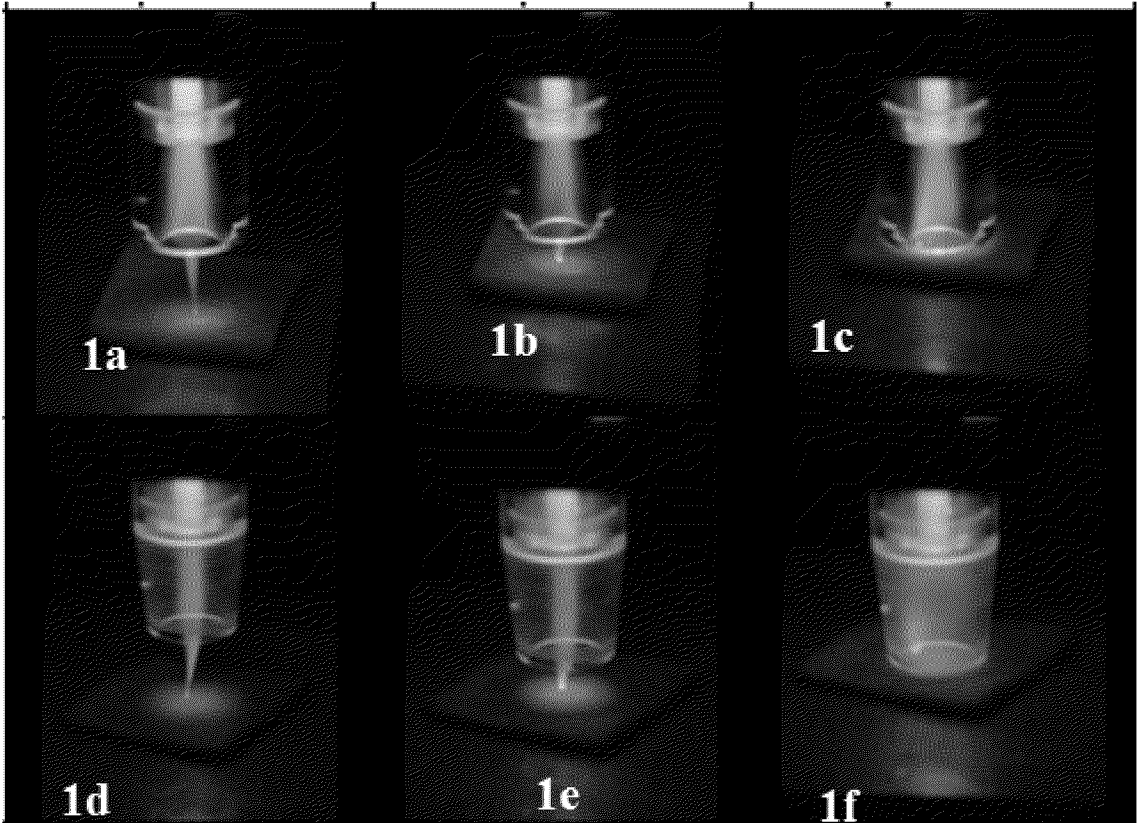


Figure 1

5

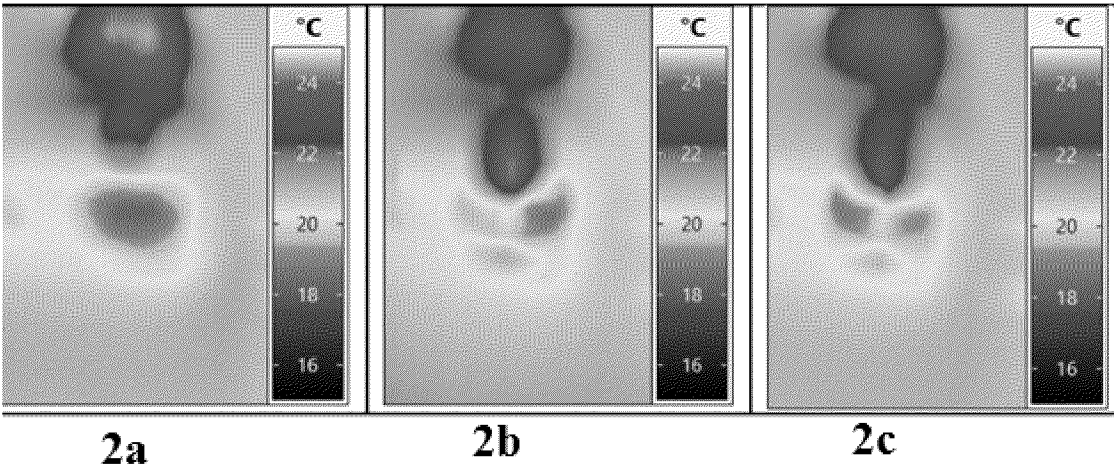


Figure 2

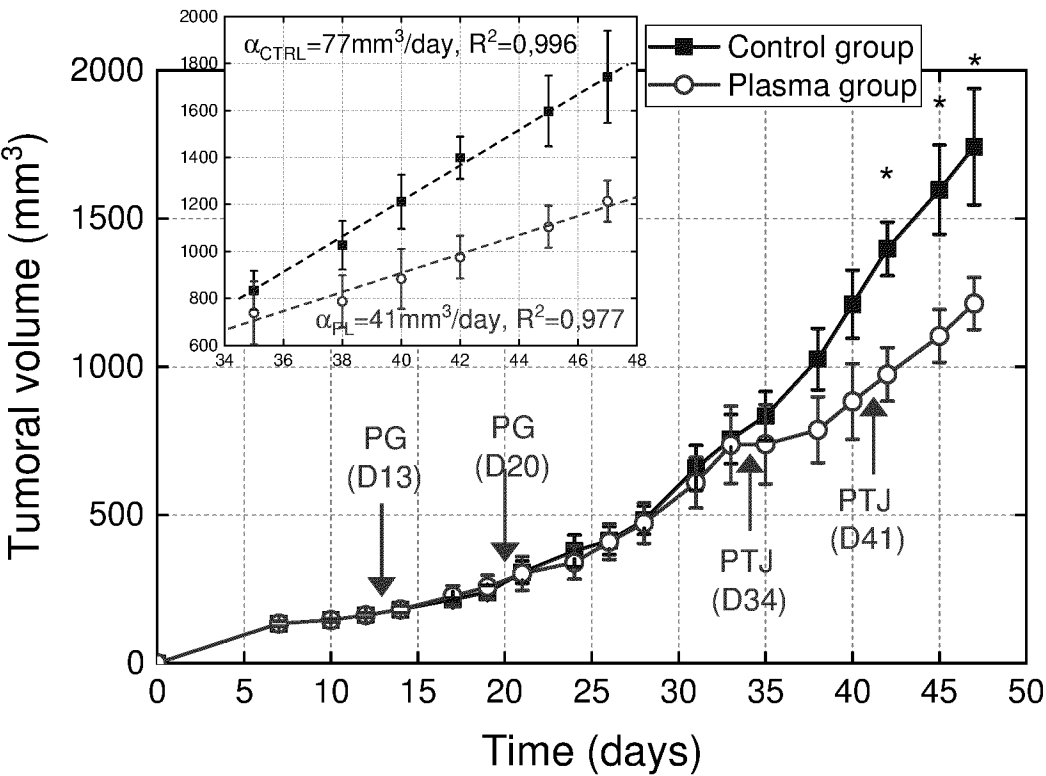


Figure 3

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2020/066802

A. CLASSIFICATION OF SUBJECT MATTER

INV. H05H1/24 A61B18/04 A61N1/44
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)

H05H 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	US 9 192 776 B2 (HUMMEL ROBERT M [US]; WATSON GREGORY A [US] ET AL.) 24 November 2015 (2015-11-24) figures 1A, 1B, 10 column 1, line 21 - line 59 column 6, line 9 - column 6, line 26 column 10, line 2 - column 10, line 53 -----	1-10, 14, 15
X	US 2010/125267 A1 (LEE KEUN HO [KR] ET AL) 20 May 2010 (2010-05-20) figures 1, 6 paragraph [0002] paragraph [0025] - paragraph [0028] paragraph [0042] - paragraph [0043] ----- -/-	1-8, 10, 14, 15



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

17 August 2020

Date of mailing of the international search report

01/09/2020

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

Clemente, Gianluigi

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/066802

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 2 328 389 A1 (OKINO AKITOSHI [JP]; MIYAHARA HIDEKAZU [JP]) 1 June 2011 (2011-06-01) paragraph [0010] - paragraph [0011] paragraph [0030] - paragraph [0037] figures 3,4,6 -----	8
A	US 7 608 839 B2 (UNIV MCGILL [CA]) 27 October 2009 (2009-10-27) column 13, line 31 - column 14, line 23 column 16, line 57 - line 67 -----	8
A	F JUDÉE ET AL: "Atmospheric pressure plasma jets applied to cancerology: correlating electrical configuration with in vivo toxicity and therapeutic efficiency", JOURNAL OF PHYSICS D: APPLIED PHYSICS, vol. 52, no. 24, 5 April 2019 (2019-04-05), page 245201, XP055668219, GB ISSN: 0022-3727, DOI: 10.1088/1361-6463/ab0fbb the whole document -----	1-9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2020/066802

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.: 11-13
because they relate to subject matter not required to be searched by this Authority, namely:
The subject-matter of Claims 11-13 defines a method of treatment of the human body by therapy. The EPO in its function as International Search Authority is therefore not required to search said subject-matter (Art.17(2)(a)(i) and R.39 PCT).
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/EP2020/066802

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 9192776	B2	24-11-2015	EP 2755716 A1 23-07-2014
			EP 2756514 A1 23-07-2014
			EP 2756515 A1 23-07-2014
			EP 2756516 A1 23-07-2014
			EP 2756517 A1 23-07-2014
			EP 2756739 A1 23-07-2014
			EP 2756740 A1 23-07-2014
			EP 2758979 A2 30-07-2014
			EP 2854268 A1 01-04-2015
			US 2013068226 A1 21-03-2013
			US 2013068732 A1 21-03-2013
			US 2013069530 A1 21-03-2013
			US 2013071286 A1 21-03-2013
			US 2013072858 A1 21-03-2013
			US 2013072859 A1 21-03-2013
			US 2013072860 A1 21-03-2013
			US 2013072861 A1 21-03-2013
			US 2015127079 A1 07-05-2015
			US 2015221476 A1 06-08-2015
			US 2017136253 A1 18-05-2017
			US 2017156200 A1 01-06-2017
			US 2019254154 A1 15-08-2019
			WO 2013040454 A1 21-03-2013
			WO 2013040469 A1 21-03-2013
			WO 2013040473 A1 21-03-2013
			WO 2013040476 A1 21-03-2013
			WO 2013040477 A1 21-03-2013
			WO 2013040481 A1 21-03-2013
			WO 2013040486 A1 21-03-2013
			WO 2013052261 A2 11-04-2013
US 2010125267	A1	20-05-2010	KR 20100054368 A 25-05-2010
			US 2010125267 A1 20-05-2010
EP 2328389	A1	01-06-2011	CN 102172105 A 31-08-2011
			EP 2328389 A1 01-06-2011
			JP 4611409 B2 12-01-2011
			JP 2010061938 A 18-03-2010
			KR 20110056393 A 27-05-2011
			MY 155509 A 30-10-2015
			SG 193813 A1 30-10-2013
			US 2011156590 A1 30-06-2011
			WO 2010027013 A1 11-03-2010
US 7608839	B2	27-10-2009	CA 2547043 A1 08-02-2007
			US 2007029500 A1 08-02-2007