



- (51) **International Patent Classification:**
A61B 18/14 (2006.01) *A61B 1/00* (2006.01)
A61B 18/00 (2006.01)
- (21) **International Application Number:**
PCT/EP2017/064280
- (22) **International Filing Date:**
12 June 2017 (12.06.2017)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
PA 2016 70426 14 June 2016 (14.06.2016) DK
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- (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,

(54) **Title:** ADD-ON CAP AND SYSTEM FOR ELECTROPORATION

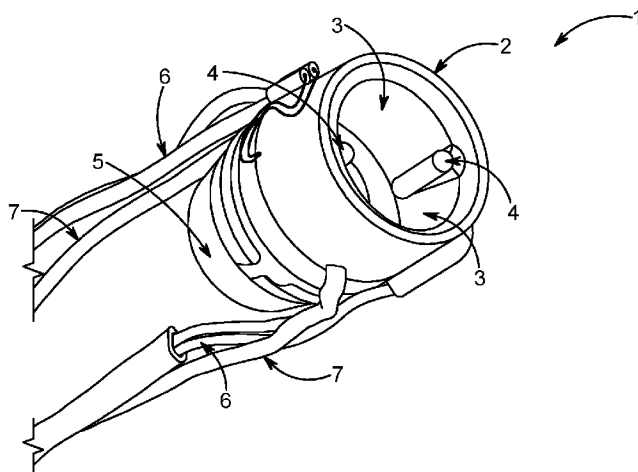


FIG. 1

(57) **Abstract:** The present disclosure relates to an add-on cap for electroporation of tissue comprising: at least one closed sidewall, such as a cylindrical sidewall; a proximal open end; a distal open end; the at least one closed sidewall and the proximal and distal open ends defining a hollow body having an internal volume; two electrodes on opposite sides of the internal volume, the electrodes configured to apply an electric field for electroporation of tissue inside the internal volume, wherein the proximal open end is adapted to be sealingly engaged to a tip of an instrument, such as an endoscope. The disclosure further relates to a system for electroporation of tissue comprising the add-on cap and an endoscope. The disclosure also relates to a method for electroporation of tissue using the cap mounted on the tip of the endoscope, comprising the steps of: positioning the distal open end of the add-on cap adjacent to tissue to be treated with electroporation, wherein the positioning is visually assisted by imaging through the add-on cap from the distal open end to the proximal



CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, 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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, 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).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

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

open end; applying vacuum in the internal volume through the proximal open end of the add-on cap, thereby aspirating tissue into the internal volume; and electroporating the aspirated tissue by applying an electric field between the electrodes of the add-on cap.

Add-on cap and system for electroporation

The present disclosure relates to an add-on cap for an instrument, such as an endoscope, for electroporation of tissue. The disclosure further relates to a system for electroporation of tissue, comprising the add-on cap, and to a method for
5 electroporation of tissue.

Background of invention

Electroporation is a medical and molecular biology technique in which an electric field is applied to cells or molecules in order to increase the permeability of the cell membrane, allowing chemicals, drugs, or DNA to be introduced into the cell.

10 Electroporation has a number of possible fields of application, and can be used both reversibly and irreversibly. In a typical electroporation process, short and intense electric pulses are generated to transiently permeabilize the cell membrane.

In reversible electroporation, which may be used in relation to for example chemotherapy, the electric field is below an electric field threshold and allows the cell to
15 repair after the treatment. Reversible electroporation may involve getting a substance, such as a drug or gene, into a cell or molecule that is normally not permeable for this substance without inducing cell death. The electric field threshold for a cell is individual for the cell. In irreversible electroporation the electric field is greater than the electric field threshold, which creates permanent nanopores in the cell membrane disrupting
20 the cellular homeostasis. As a consequence the cell dies by apoptosis.

Reversible electroporation is known and performed both *in vitro* and *in vivo*. *In vivo* electroporation is typically performed using needle electrodes that are inserted into for example a tumor and surrounding tissue. One device for reversible electroporation is the Cliniporator system. Irreversible electroporation may also be performed *in vivo*.

25 One device for irreversible electroporation is the NanoKnife system which also uses needle or spear like electrodes.

WO 2011/030322 describes an apparatus for carrying out research experiments and prophylactic or treatment procedures on tissue comprising a chamber for receiving
30 tissue and a receiver for receiving an instrument such as an endoscope. Vacuum draws tissue into the chamber, in which electroporation is applied by means of electrodes.

Summary of invention

The present disclosure relates to an improved add-on cap for electroporation of tissue comprising: at least one closed sidewall, such as a cylindrical sidewall; a proximal open end; a distal open end; the at least one closed sidewall and the proximal and distal open ends defining a hollow body having an internal volume; and two electrodes on opposite sides of the internal volume, the electrodes configured to apply an electric field for electroporation of tissue inside the internal volume, wherein the proximal open end is adapted to be sealingly engaged to a tip of an instrument, such as an endoscope.

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Since the cap with two internal electrodes has two open ends, of which one can be sealingly engaged with the tip of the instrument, the cap can easily be attached and used with an endoscope to perform electroporation, while providing visibility both when positioning the device before the electroporation and during the electroporation by imaging tissue that is aspirated into the cap from the inside of the cap. If a vacuum generator is connected to the internal volume through the endoscope, the tissue can be treated inside the cap without the need for needle electrodes while the process is observed from the inside of the cap.

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The presently disclosed add-on cap can be attached directly to the tip of an endoscope. The term endoscope is to be construed as any endoscope, including rigid and flexible endoscopes. Preferably the at least one closed sidewall and the open ends of the cap form a combined receiver for the instrument and internal volume for electroporation of tissue, such that the add-on cap extends in an axial direction of the instrument. The cap may therefore have a substantially cylindrical shape with two open ends, wherein the proximal open end fits an endoscope. Electric wiring to the electrodes may be provided by means of cables on the outside of the closed sidewall, wherein the cables are connected to the electrodes through holes in the closed sidewall. By arranging the cables on the outside, the cap with cables can be easily attached to the tip of the endoscope by threading the proximal open end over the tip. The cables can then run along the endoscope on the outside of the endoscope and can for example be clipped onto the endoscope. This setup further improves both the visibility inside the internal volume and the possibilities of additional (action) inside the internal volume, such as biopsy and/or chemotherapy by injection, during electroporation.

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The present disclosure further relates to a system for electroporation of tissue comprising: an endoscope; the presently disclosed add-on cap adapted to be mounted on the tip of the endoscope and extending in an axial direction of the endoscope; and
5 an electric current generator.

The present disclosure further relates to a method for electroporation of tissue using the presently disclosed system, wherein the add-on cap is mounted on the tip of the endoscope, comprising the steps of: positioning the distal open end of the add-on cap adjacent to tissue to be treated with electroporation, wherein the positioning is visually
10 assisted by imaging through the add-on cap from the distal open end to the proximal open end; applying vacuum in the internal volume through the proximal open end of the add-on cap, thereby aspirating tissue into the internal volume; and electroporating the aspirated tissue by applying an electric field between the electrodes of the add-on cap.
15 The imaging can be provided through a normal lens of the endoscope. In one embodiment the method comprises the steps of: before electroporation of the aspirated tissue, measuring the impedance between the two electrodes and comparing against a predetermined impedance threshold; and, based on the comparison, determine if electroporation is to be started. The combination of visual observation of the cap
20 throughout the process of positioning the cap and aspiration of tissue and measuring the impedance between the electrodes provides an efficient way of ensuring that the electroporation is performed correctly. Measuring the impedance may provide information about the contact between the electrodes and the aspirated tissue, and about the characteristics of the material, which may be further used to inform the user
25 of a result of a treatment.

Description of drawings

Fig. 1 shows a first embodiment of the presently disclosed add-on cap for electroporation.

Fig. 2 shows the add-on cap of fig. 1 from a different angle.

30 **Fig. 3** shows the add-on cap of figs. 1-2 from a different angle.

Fig. 4 shows a second embodiment of the presently disclosed add-on cap for electroporation.

Fig. 5 shows the add-on cap of fig. 4 mounted on the tip of a gastroscope.

35 **Fig. 6** shows a view from the inside of the presently disclosed add-on cap for electroporation, the cap being position in the bowel cavity.

Fig. 7 shows a view from the inside of the presently disclosed add-on cap for electroporation, wherein intestinal mucosa is aspirated into the cap.

Fig. 8 shows a view from the inside of the presently disclosed add-on cap for electroporation, wherein intestinal mucosa is aspirated into the cap and a sclerotherapy
5 needle is used to inject a substance into the aspirated tissue.

Fig. 9 shows a view from the inside of the presently disclosed add-on cap for electroporation, wherein a biopsy forceps is used to collect a sample of the intestinal mucosa.

Detailed description of the invention

10 The present disclosure relates to a cap for electroporation of tissue comprising:

- at least one closed sidewall, such as a cylindrical sidewall; a proximal open end; a distal open end; the at least one closed sidewall and the proximal and distal open ends defining a hollow body having an internal volume;
- two electrodes on opposite sides of the internal volume, the electrodes
15 configured to apply an electric field for electroporation of tissue inside the internal volume,

wherein the proximal open end is adapted to be sealingly engaged to a tip of an instrument, such as an endoscope.

20 The terms 'proximal' and 'distal' in the present disclosure are defined in relation to the instrument i.e. the proximal end of the cap is located towards the instrument and the distal end of the cap is located towards the tissue.

The fact that the cap has two open ends, of which one can be sealingly engaged with
25 the tip of the instrument such as an endoscope, makes it possible to attach it to the tip of the scope such that an electroporation process can be performed while the user has visibility through the cap. The prior art device disclosed in WO 2011/030322 has one receiver for receiving an instrument and one chamber, wherein the receiver and chamber are radially offset. In the presently disclosed cap, a closed sidewall forms a
30 hollow body with two open ends, of which one is directly attached around the tip of the instrument. Thereby, the user will have visibility throughout an electroporation process. In a first phase, during positioning of the cap, the user will have visibility through the cap, which forms an extension of the scope. In contrast to the device in WO
2011/030322, the user is able to see the tissue in front of the cap. The visibility can be
35 provided by means of standard imaging capabilities of e.g. an endoscope. In a second

phase tissue is drawn into the cap by means of a vacuum generator connected through the endoscope. In the second phase the user is able to observe the tissue being drawn into the cap from the inside of the cap. In a third phase electroporation is performed by applying an electric field through the electrodes in the hollow body. The add-on cap can therefore be mounted directly on the tip of an instrument and used without being further adapted to an existing system. Preferably, the cap is provided with cables connected to the electrodes. In one embodiment the cables are mounted on the outside on the closed sidewall and connected to the electrodes through holes in the closed sidewall. By arranging the cables on the outside, the cap with cables can be easily attached to the tip of the endoscope by threading the proximal open end over the tip. The cables can then run along the endoscope on the outside of the endoscope and can for example be clipped onto the endoscope. The presently disclosed add-on cap may therefore be seen as a device capable of providing electroporation to an endoscope without need for further integration, while allowing visual observation of both the positioning and the actual electroporation through the cap.

Preferably, the at least one closed sidewall and the two open ends of the cap form a combined receiver for the instrument and internal volume for electroporation of tissue, such that the add-on cap extends in an axial direction of the instrument. In one embodiment the longitudinal axis of the add-on cap is an extension of the longitudinal axis of the instrument when the cap is attached to the instrument. In this configuration there is direct visibility from the proximal open end to the distal open end. The sidewall may be formed as an extension of the instrument. The distal open end may be an opening substantially perpendicular to an axial extension of the instrument.

'Vacuum' may generally be referred to a pressure much less than atmospheric pressure. In relation to the present invention, 'vacuum' is construed broadly as an at least partial vacuum (imperfect vacuum) with the intention that the vacuum is capable of drawing tissue into the cap. In one embodiment the proximal open end is sealingly engaged to the instrument such that vacuum can be applied in the internal volume through the proximal open end. In this regard the internal volume of the cap may be seen as a closed volume during electroporation since the proximal end is sealingly engaged to the tip of the instrument and the distal end open end is typically sealed by tissue that is drawn into the cap. The internal volume may therefore be substantially sealed from both open ends when vacuum is applied through the proximal open end and tissue is drawn into the internal volume through the distal open end.

There are several options and scenarios for using the cap for electroporation. One option is that a substance, such as a drug, is added to the circulatory system. During the electroporation process the permeability of the cell membrane is increased, which
5 allows the substance in the circulatory system to be translocated into the cell. A second option is to fill the internal volume with a liquid comprising chemicals, drugs, a gene therapy vector, siRNA, or DNA to be introduced into the cell through the proximal open end while tissue is inside the cap and blocks the distal open end of the cap. Adenoviral CRISPR-Cas vector delivery may also be done using this option. During this process it
10 is possible to observe the treatment from the scope from the inside of the cap. A third option, which is possible with the presently disclosed add-on cap for electroporation, is to use an injection needle through the add-on cap to inject a substance in the tissue. Also in this scenario it is an advantage that the injection can be observed visually through the cap.

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Physical properties of the cap

The cap may be dimensioned to fit a number of instruments, such as an endoscope, including gastroscopes, colonoscopes, cystoscopes, nephroscopes, bronchoscopes, sigmoideoscopes and borescopes. The diameter of the cap, in particular the diameter
20 of the sidewall, may be for example 1-20 mm, or 5-20 mm, or 10-20 mm, or 5-15 mm, or 5-10 mm. In one embodiment, suitable for gastroscopes for use in the stomach and duodenum, the cap has an outer diameter of 8.8 mm. In another embodiment, suitable for colonoscopes for use in the large intestine, the cap has an outer diameter of 13.2 mm. In one embodiment, suitable for flexible cystoscopes for use in the urinary bladder and ureter, the cap has an outer diameter of 2.7 mm. Other possible and known outer
25 diameters of caps are 13.9 mm and 14.9 mm.

The length of the cap, i.e. the distance between the two open ends, may be for example in the range of 1-20 mm, or 5-20 mm, or 10-20 mm, or 5-15 mm, or 5-10 mm.
30 A suitable length can be said to depend on the diameter of the sidewall and also has to take into account the visibility through the cap from the inside of the cap. A longer cap will have less visibility outside the cap than a shorter. On the other hand, a longer cap has a larger internal volume, which may be useful for example for treating more tissue. Therefore a suitable combination of diameter and length may be a diameter between 5
35 and 15 mm and a length between 5 and 15 mm.

Preferably, the proximal end of the add-on cap fits an exterior surface of a distal end of the instrument. In this regard the at least one closed sidewall may be shaped such that it can be snapped or threaded onto the tip of the instrument, which typically has a circular cross-section. The open proximal end may therefore be substantially circular and the at least one closed sidewall may be a substantially cylindrical closed surface. The proximal and distal open ends may then be represented by a top and bottom part of a cylinder. The at least one closed sidewall and the open ends may form an endoscopic cap. The hollow body, or at least a proximal section of the closed sidewall, may be tapered and/or conical and/or funnel shaped in order to be sealingly attached around the tip of the instrument. The closed sidewall may furthermore be seen as an extension of the instrument in an axial direction of the instrument when the cap is mounted on the instrument.

Although there are two electrodes on opposite sides of the internal volume on the inside of the closed sidewall it may be possible in some embodiments to further increase the visibility by using a transparent cap. The presently disclosed add-on cap may be therefore be a transparent endoscopic cap, such as a hollow transparent cylinder. The add-on cap may be made of a plastic material and/or silicone and may have a smooth exterior surface to avoid that tissue is damaged.

Other shapes and cross-sections of the cap are also possible. For example the hollow body may have a substantially rectangular three-dimensional shape. A cross section of the hollow body may also be elliptical or form a polygon, preferably an equilateral and/or convex polygon, a polygon such as a triangle, square, pentagon, hexagon, or a heptagon.

Temperature sensor(s), impedance measurement, electric properties

The presently disclosed add-on cap for electroporation of tissue may further comprise at least one temperature sensor in the internal volume. Preferably, the at least one temperature sensor is mounted on the inside of the at least one closed sidewall between the two electrodes. Generated heat is a factor to take into account for *in vivo* electroporation. If too much heat is dissipated, surrounding tissue in the body may be damaged. The fact that the add-on cap may provide a closed internal volume during electroporation when tissue is drawn into the cap protects surrounding tissue during the process. A temperature sensor may be placed on the inside of the at least one closed sidewall between the two electrodes where it does not interfere with the process and

the visibility through the cap. A temperature sensor may keep the user informed whether there is any risk of damage of surrounding tissue throughout the electroporation process. If the measured temperature is above a predetermined temperature threshold, the electroporation can be stopped manually or automatically.

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In one embodiment two temperature sensors are mounted on opposite sides of the internal volume between the two electrodes. Two sensors on opposite sides provide additional security by avoiding that only the temperature on one side is measured and the temperature is accidentally higher on the other side.

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In a further embodiment of the add-on cap the two electrodes are configured to measure an impedance between the two electrodes. The two electrodes may be planar electrodes mounted on the inside of the at least one closed sidewall. Impedance is defined as the frequency domain ratio of the voltage to the current. Impedance can be said to be an AC property which cannot be measured as easily as a resistance. Measurements of impedance may be carried out at one frequency, or the variation of device impedance over a range of frequencies may be of interest. For the present add-on cap the impedance may for example be carried out a measurement frequency of approximately 50 kHz.

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The electroporation process may be used both for reversible and irreversible electroporation. The applied voltage is not limited to any voltage range but may be between 30 and 400 V. The applied pulses may have a length of 10 μ s to 1000 μ s, more preferable between 200 μ s and 800 μ s, even more preferable between 500 μ s and 700 μ s, such as 600 μ s. The time between the pulses may be 10 ms to 1000 ms, preferably between 10 ms and 500 ms, more preferably between 10 and 200 ms.

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System for electroporation of tissue

The present disclosure further relates to a system for electroporation of tissue comprising:

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- an endoscope;
- an add-on cap as described above, the add-on cap adapted to be mounted on the tip of the endoscope and extending in an axial direction of the endoscope; and
- an electric current generator.

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5 The endoscope may be a gastroscope, or a colonoscope, or a cystoscope, or a nephroscope, or a bronchoscope, or a borescope. The system may further describe a vacuum generator in connection with the internal volume through the proximal open end of the add-on cap. Endoscopes typically have internal channels which can be used to apply a vacuum.

10 The system may further comprise means (a device) for measuring an impedance. The system may further comprise processing means and/or a processing module. The processing module could be a computer or part of a computer. The processing module may be configured to measure and process the impedance between the two electrodes. The impedance can then be compared against a predefined threshold in order to determine if electroporation can be started. The impedance check can be automatic and and/or may also involve an indication to the user whether the measured impedance is above or below the threshold.

15 The processing module may also be configured to compare a temperature measured by the temperature sensor(s) against a predetermined temperature threshold.

20 The add-on cap and system may comprise a pair of cables. The cables connected to the electrodes may be positioned on the outside of the endoscope along the endoscope. By arranging the cables on the outside, the cap with cables can be easily attached to the tip of the endoscope by threading the proximal open end over the tip. The cables can then run along the endoscope on the outside of the endoscope and can for example be clipped onto the endoscope.

25 The system may further comprise a biopsy forceps for taking a sample from the tissue and/or a hypodermic needle for injecting a substance into the tissue. The presently disclosed add-on cap enables visibility inside the internal volume during electroporation.

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Method for electroporation of tissue

The present disclosure further relates to a method for electroporation of tissue using the system according to the present disclosure, wherein the add-on cap is mounted on the tip of the endoscope, the method comprising the steps of:

35 a) positioning the distal open end of the add-on cap adjacent to tissue to be treated with electroporation, wherein the positioning is visually assisted by

- imaging through the add-on cap from the distal open end to the proximal open end;
- b) applying vacuum in the internal volume through the proximal open end of the add-on cap, thereby aspirating tissue into the internal volume; and
- 5 c) electroporating the aspirated tissue by applying an electric field between the electrodes of the add-on cap.

The method may use any variant of the presently disclosed add-on cap and system. The steps are sequential. One advantage in relation to the devices and methods that are known in the art is that the whole process may be visually assisted by an imaging modality from the inside of the cap.

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Since the system may comprise a processing module configured to measure and process the impedance between the two electrodes, it is possible to measure the impedance and compare against a predefined threshold to verify that the electrodes have good contact with the tissue before the electroporation starts. In one embodiment electroporation is started if the measured impedance is below the predefined impedance threshold. The method may further comprise the steps of:

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- i. before electroporation of the aspirated tissue, measuring the impedance between the two electrodes and comparing against a predetermined impedance threshold;
- 20 ii. based on the comparison, determine if electroporation is to be started.

Steps i) and ii) are preferably performed sequentially between steps b) and c). If the measured impedance is above a predefined impedance threshold it may show that the contact between the electrodes and tissue is not satisfactory. In this case the distal open end may be repositioned to have a better position or angle. In one embodiment the steps a-b and i-ii may be iteratively repeated until the tissue is arranged such that the measured impedance is below the predefined impedance threshold.

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The method may further comprise the step of measuring the temperature inside or outside the add-on cap during electroporation. If the temperature exceeds a predefined temperature threshold the electroporation may be stopped or interrupted in order not to damage surrounding tissue (step c).

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Detailed description of drawings

The invention will in the following be described in greater detail with reference to the accompanying drawings. The drawings are exemplary and are intended to illustrate some of the features of the presently disclosed add-on cap and system for
5 electroporation, and are not to be construed as limiting to the presently disclosed invention.

Fig. 1 shows a first embodiment of the presently disclosed add-on cap (1) for
10 electroporation. The cap has a closed sidewall (2) two electrodes (3) on opposite sides of the internal volume. In the example there are two temperature sensors (4) on opposite sides of the internal volume between the two electrodes (3). A proximal open end (5) is designed to be sealingly engaged to fit the tip of an endoscope. A first pair of cables (6) are connected to the temperature sensors (4) and a second pair of cables (7) are connected to the electrodes (3).

15 Fig. 2 shows the add-on cap (1) of fig. 1 from a different angle. It can be seen that a proximal section (14) of the closed sidewall (2) is slightly tapered to fit the tip of an endoscope. The cap also has a distal section (15) which may be transparent. Tissue may be drawn into the cap through the distal open end (8).

20 Fig. 3 shows the add-on cap (1) of figs. 1-2 from a different angle. The closed sidewall (2) has a substantially circular cross-section.

Fig. 4 shows a second embodiment of the presently disclosed add-on cap (1) for
25 electroporation. This embodiment does not have any temperature sensors. The sidewall (2) is substantially cylindrical.

Fig. 5 shows the add-on cap (1) of fig. 4 mounted on the tip of a gastroscope (9). It can
30 be noted that the first pair of cables (6) connected to the temperature sensors (4) and the second pair of cables (7) connected to the electrodes (3) are placed outside the gastroscope (9).

Fig. 6 shows a view from the inside of the presently disclosed add-on cap (1) for
35 electroporation, the cap being position in the bowel cavity (10). The cap has a closed sidewall (2) and two electrodes (3) on opposite sides of the internal volume. This is a typical view during positioning of the device. The distance between the rim (11) and the

lens of the imaging in the endoscope determines the angles in which visibility is provided during positioning of the device.

5 Fig. 7 shows a view from the inside of the presently disclosed add-on cap (1) for electroporation, wherein intestinal mucosa (12) is aspirated into the cap. It can be noted that the distal open end (8) is thereby substantially sealed.

10 Fig. 8 shows a view from the inside of the presently disclosed add-on cap (1) for electroporation, wherein intestinal mucosa (12) is aspirated into the cap and a sclerotherapy needle (13) is used to inject a substance into the aspirated tissue. The process is observed from the inside of the cap (1).

15 Fig. 9 shows a view from the inside of the presently disclosed add-on cap (1) for electroporation, wherein a biopsy forceps (14) is used to collect a sample of the intestinal mucosa (12). The process is assisted by imaging from the inside of the cap (1).

Claims

1. An add-on cap for electroporation of tissue comprising:
 - at least one closed sidewall, such as a cylindrical sidewall; a proximal open end; a distal open end; the at least one closed sidewall and the proximal and distal open ends defining a hollow body having an internal volume;
 - two electrodes on opposite sides of the internal volume, the electrodes configured to apply an electric field for electroporation of tissue inside the internal volume,wherein the proximal open end is adapted to be sealingly engaged to a tip of an instrument, such as an endoscope.
2. The add-on cap according to any of the preceding claims, wherein the at least one closed sidewall and the open ends form a combined receiver for the instrument and internal volume for electroporation of tissue.
3. The add-on cap according to any of the preceding claims, wherein the add-on cap is adapted to be mounted on the tip of an oblong instrument, such as an endoscope, the add-on cap extending in an axial direction of the instrument.
4. The add-on cap according to claim 3, wherein a longitudinal axis of the add-on cap is an extension of a longitudinal axis of the instrument.
5. The add-on cap according to any of claims 3-4, wherein the add-on cap provides direct visibility from the proximal open end to the distal open end.
6. The add-on cap according to any of claims 3-5, wherein the distal open end is an opening substantially perpendicular to an axial extension of the instrument.
7. The add-on cap according to any of the preceding claims, wherein the two electrodes are configured to measure an impedance between the two electrodes.
8. The add-on cap according to any of the preceding claims, wherein the two electrodes are planar electrodes mounted on the inside of the at least one closed sidewall.

9. The add-on cap according to any of the preceding claims, further comprising at least one temperature sensor.
- 5 10. The add-on cap according to claim 9, wherein the at least one temperature sensor is mounted on the inside of the at least one closed sidewall between the two electrodes.
- 10 11. The add-on cap according to any of claims 9-10, wherein two temperature sensors are mounted on opposite sides of the internal volume between the two electrodes.
- 15 12. The add-on cap according to any of the preceding claims, further comprising cables connected to the two electrodes.
13. The add-on cap according to claim 9, wherein the cables are mounted outside the closed sidewall and connect to the electrodes through holes in the closed sidewall.
- 20 14. The add-on cap according to any of the preceding claims, wherein the proximal open end is sealingly engaged to the instrument such that vacuum can be applied in the internal volume through the proximal open end.
- 25 15. The add-on cap according to claim 14, wherein tissue to be treated with electroporation is drawn into the internal volume through the distal open end by the generated vacuum.
- 30 16. The add-on cap according to claim 15, wherein the internal volume is substantially sealed from both open ends when vacuum is applied through the proximal open end and tissue is drawn into the internal volume through the distal open end.
- 35 17. The add-on cap according to any of the preceding claims, wherein a proximal end of the add-on cap fits an exterior surface of a distal end of the instrument.

18. The add-on cap according to any of the preceding claims, wherein the at least one closed sidewall is a substantially cylindrical closed surface.
- 5 19. The add-on cap according to any of the preceding claims, wherein the proximal and distal open ends are represented by a top and bottom of a cylinder.
20. The add-on cap according to any of the preceding claims, wherein the at least one closed sidewall and the open ends form an endoscopic cap.
- 10 21. The add-on cap according to claim 20, wherein the endoscopic cap is transparent, such as a hollow transparent cylinder.
22. The add-on cap according to any of the preceding claims, wherein the hollow body is tapered and/or conical and/or funnel shaped.
- 15 23. The add-on cap according to any of the preceding claims, wherein the at least one closed sidewall is one closed surface extending in an axial direction of the instrument.
- 20 24. The add-on cap according to any of the preceding claims, wherein the hollow body is rectangular.
- 25 25. The add-on cap according to any of the preceding claims, wherein a cross-section of the hollow body is elliptical.
26. The add-on cap according to any of the preceding claims, wherein a cross-section of the hollow body forms a polygon, preferably an equilateral and/or convex polygon, a polygon such as a triangle, square, pentagon, hexagon, or a heptagon.
- 30 27. A system for electroporation of tissue comprising:
- an endoscope;
 - an add-on cap according to any of the preceding claims, the add-on cap adapted to be mounted on the tip of the endoscope and extending in an axial direction of the endoscope; and
 - an electric current generator.
- 35

28. The system according to claim 27, wherein the endoscope is a gastroscope, or a colonoscope, or a cystoscope, or a nephroscope, or a bronchoscope, a sigmoideumscope or a borescope.
- 5
29. The system according to any of claims 27-28, further comprising a vacuum generator in connection with the internal volume through the proximal open end of the add-on cap.
- 10
30. The system according to any of claims 27-29, further comprising means for measuring an impedance between the two electrodes of the add-on cap.
31. The system according to any of claims 27-30, further comprising processing means configured to compare a temperature measured by the temperature sensor against a predetermined temperature threshold.
- 15
32. The system according to any of claims 27-31, further comprising processing means configured to compare an impedance between the two electrodes on opposite sides of the internal volume against a predetermined impedance threshold.
- 20
33. The system according to any of claims 27-32, wherein the cables connected to the electrodes are positioned on the outside of the endoscope along the endoscope.
- 25
34. The system according to any of claims 27-33, further comprising a biopsy forceps for taking a sample from the tissue and/or a hypodermic needle for injecting a substance into the tissue.
- 30
35. A method for electroporation of tissue using the system according to any of claims 27-34, wherein the add-on cap is mounted on the tip of the endoscope, comprising the steps of:
- 35
- a) positioning the distal open end of the add-on cap adjacent to tissue to be treated with electroporation, wherein the positioning is visually assisted by imaging through the add-on cap from the distal open end to the proximal open end;

- b) applying vacuum in the internal volume through the proximal open end of the add-on cap, thereby aspirating tissue into the internal volume; and
- c) electroporating the aspirated tissue by applying an electric field between the electrodes of the add-on cap.

5

36. The method according to claim 35, wherein the steps are sequential.

37. The method according to any of claims 35-36, further comprising the steps of:

10

- i. before electroporation of the aspirated tissue, measuring the impedance between the two electrodes and comparing against a predetermined impedance threshold;
- ii. based on the comparison, determine if electroporation is to be started.

15

38. The method according to claim 37, wherein electroporation is started if the measured impedance is below the predefined impedance threshold.

20

39. The method according to any of claims 35-38, further comprising the step of repositioning the distal open end of the add-on cap adjacent to tissue if the measured impedance is above a predefined impedance threshold.

25

40. The method according to any of claims 35-39, further comprising the step of iteratively repeating steps a)-b) and i)-ii) until the tissue is arranged such that the measured impedance is below the predefined impedance threshold.

30

41. The method according to any of claims 35-40, further comprising the step of measuring the temperature inside or outside the add-on cap during electroporation.

42. The method according to claim 41, wherein the electroporation is interrupted if the temperature exceeds a predefined temperature threshold.

1/5

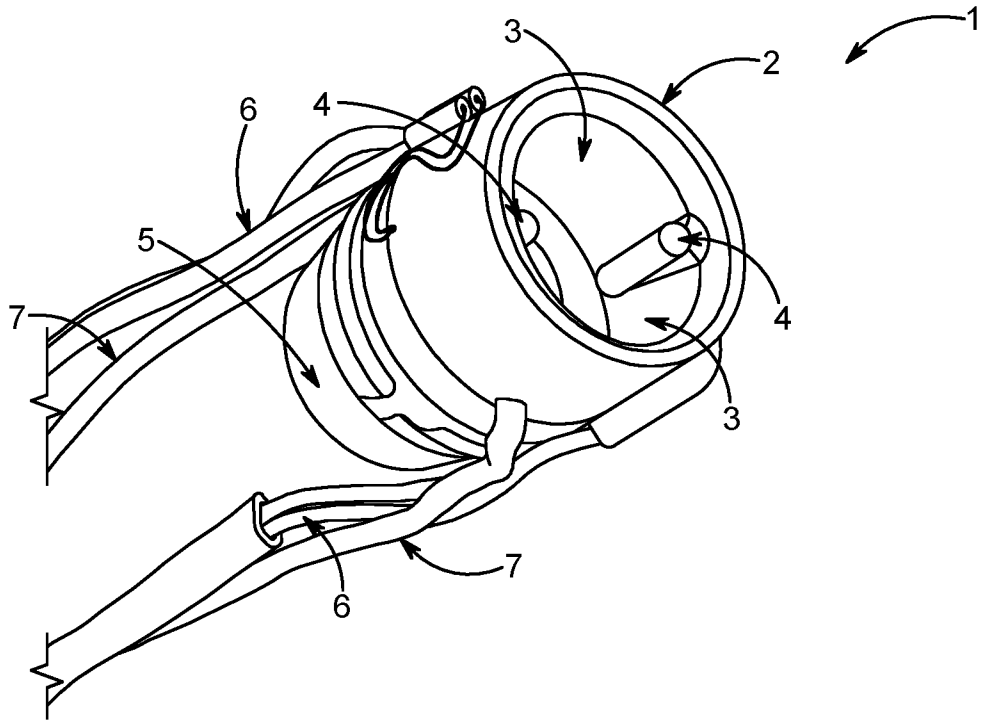


FIG. 1

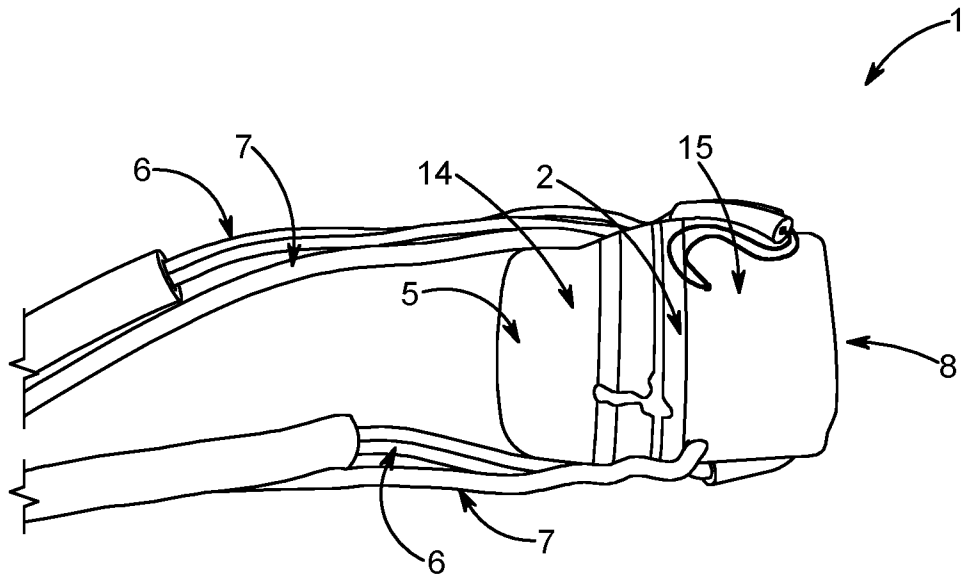


FIG. 2

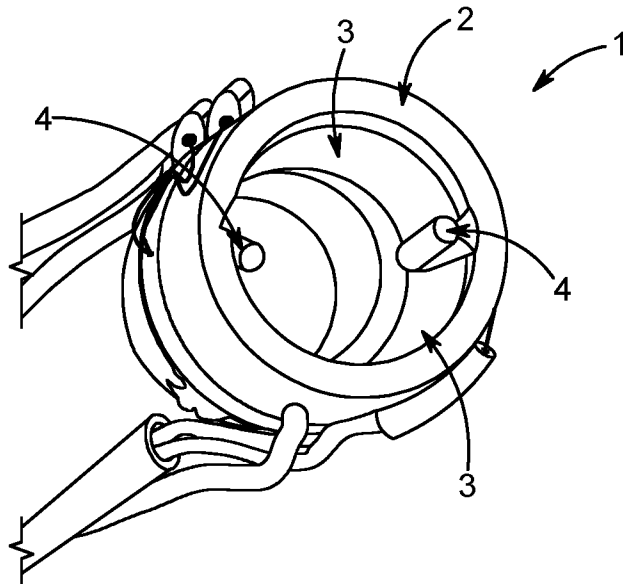


FIG. 3

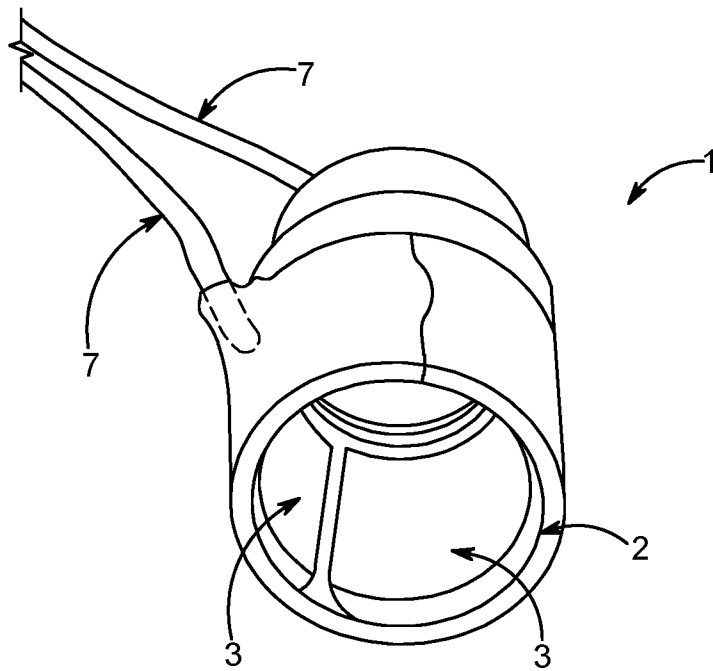


FIG. 4

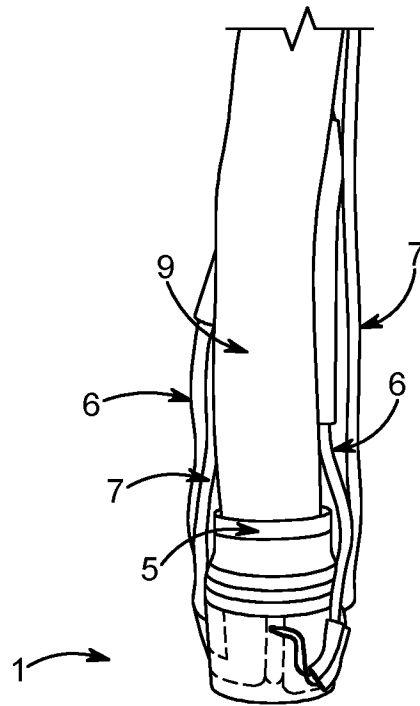
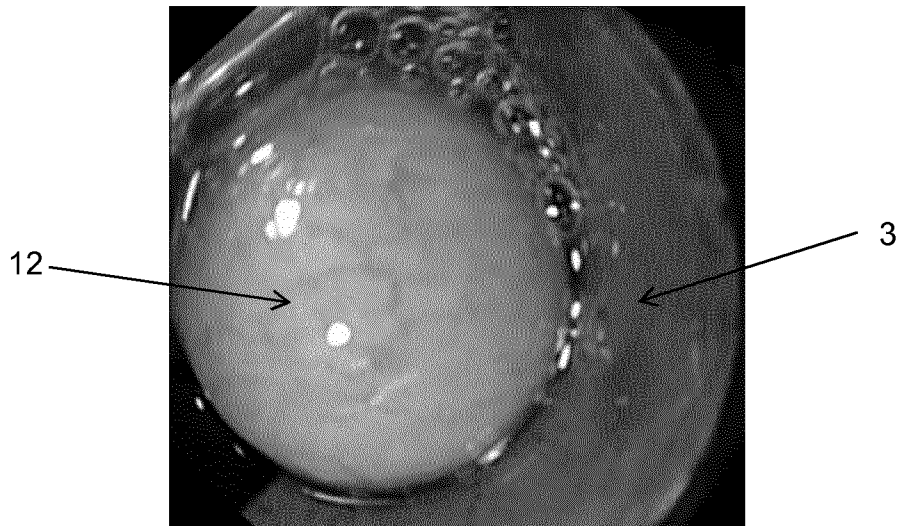
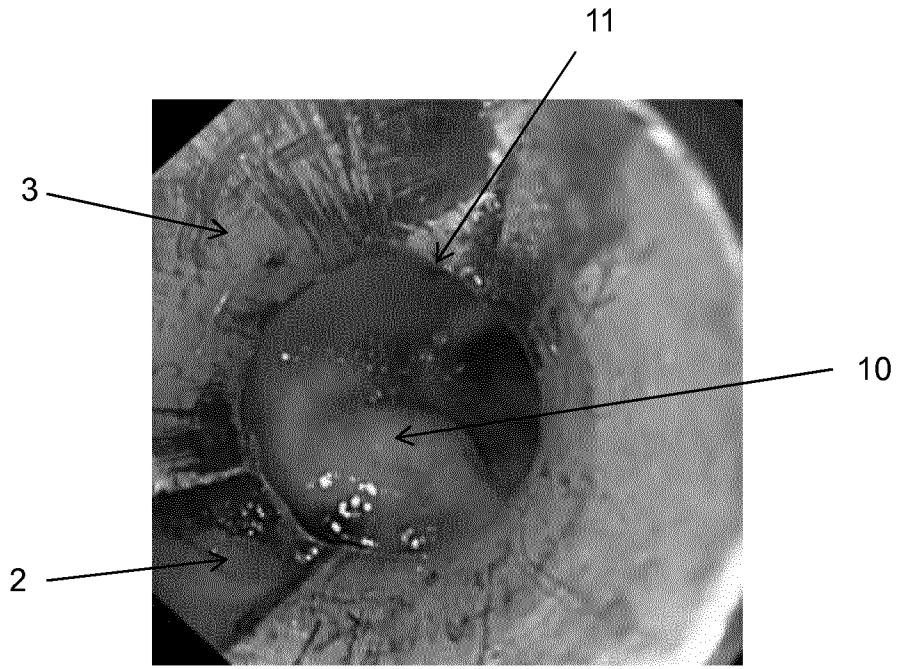


FIG. 5



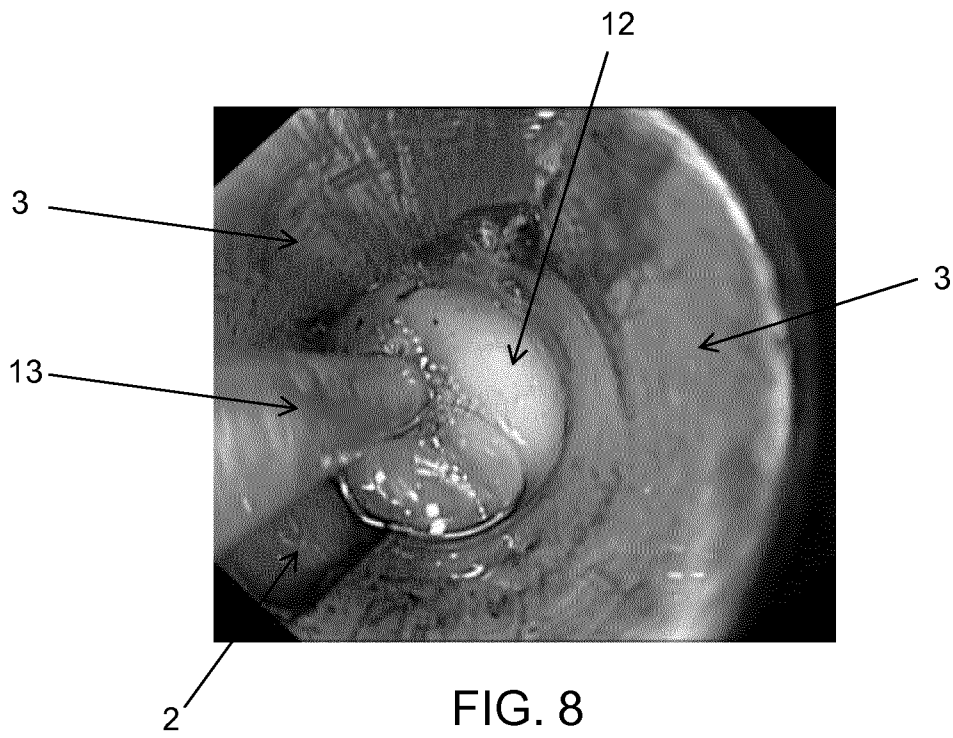


FIG. 8

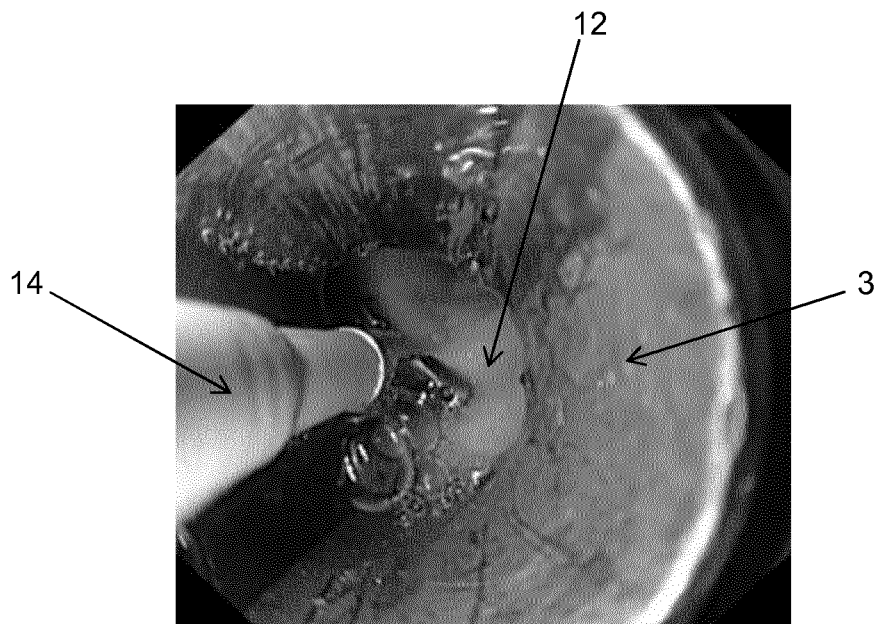


FIG. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/064280

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B18/14 A61B18/00 A61B1/00
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)
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 6 086 583 A (OUCHI TERUO [JP]) 11 July 2000 (2000-07-11)	1-8, 12-30, 32-34
Y	abstract; figures 1-49 columns 5-13	9-11,31
X	US 2015/073409 A1 (WATSON JOHN PAUL [US] ET AL) 12 March 2015 (2015-03-12)	1-13,17, 20-23, 27,28, 30-34
X	US 2005/080411 A1 (OUCHI TERUO [JP]) 14 April 2005 (2005-04-14)	1-7, 12-30, 32-34
	the whole document	
	-/--	

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 13 September 2017	Date of mailing of the international search report 22/09/2017
------------------------------------------------------------------------------------	----------------------------------------------------------------------

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 Lins, Stephanie
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/064280

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016/058464 A1 (NGUYEN MAN MINH [US] ET AL) 3 March 2016 (2016-03-03) the whole document	1-8, 12-30, 32-34
A	----- US 2007/179535 A1 (MORRISSEY ANTHONY [IE] ET AL) 2 August 2007 (2007-08-02) abstract; figures 1-17 paragraphs [0097] - [0099]	1-34
Y	----- US 2014/012247 A1 (BAKOS GREGORY J [US] ET AL) 9 January 2014 (2014-01-09) abstract; figures 1-23 paragraphs [0039] - [0094]	9-11,31
A	----- US 2012/172784 A1 (SODEN DECLAN [IE]) 5 July 2012 (2012-07-05) the whole document	1-34

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2017/064280

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.: 35-42
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 surgery
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:

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/EP2017/064280

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
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专利名称(译)	用于电穿孔的附加帽和系统		
公开(公告)号	EP3468494A1	公开(公告)日	2019-04-17
申请号	EP2017733989	申请日	2017-06-12
[标]申请(专利权)人(译)	奥胡斯大学 地区日德兰		
申请(专利权)人(译)	AARHUS UNIVERSITET 地区日德兰		
当前申请(专利权)人(译)	AARHUS UNIVERSITET 地区日德兰		
[标]发明人	OERNTOFT MAI BRITT WORM GEERT TORBEN LYSKJAER IBEN CALLESEN MORTEN MOEBJERG UHRE VIBEKE RASMUSSEN MAD S KRISTOFFER HEILSKOV		
发明人	ØRNTOFT, MAI-BRITT, WORM GEERT, TORBEN LYSKJÆR, IBEN CALLESEN, MORTEN, MØBJERG UHRE, VIBEKE RASMUSSEN, MAD S KRISTOFFER, HEILSKOV		
IPC分类号	A61B18/14 A61B18/00 A61B1/00		
CPC分类号	A61B1/00087 A61B1/00089 A61B1/00101 A61B1/00137 A61B1/2676 A61B1/2736 A61B1/307 A61B1/31 A61B18/1492 A61B2018/00291 A61B2018/00494 A61B2018/005 A61B2018/00511 A61B2018/00541 A61B2018/00559 A61B2018/00613 A61B2018/00642 A61B2018/00648 A61B2018/00678 A61B2018/00708 A61B2018/00791 A61B2018/00875 A61B2018/00982 A61B2018/142 A61B2018/1495 A61N1/05 A61N1/327		
优先权	201670426 2016-06-14 DK		
外部链接	Espacenet		

摘要(译)

本发明涉及一种用于组织电穿孔的附加帽，包括：至少一个封闭的侧壁，例如圆柱形侧壁；近端开口端；远端开口端；所述至少一个封闭侧壁和所述近端和远端开口端限定具有内部容积的中空主体；在内部容积的相对侧上的两个电极，电极被配置为施加电场以用于内部容积内的组织的电穿孔，其中近端开口端适于密封地接合到器械的尖端，例如内窥镜。本公开还涉及用于组织电穿孔的系统，其包括附加帽和内窥镜。本发明还涉及一种使用安装在内窥镜尖端上的帽进行组织电穿孔的方法，包括以下步骤：将附加帽的远端开口端定位在待电穿孔组织附近，其中定位通过从远端开口端到近端开口端的附加帽成像，在视觉上辅助；通过附加帽的近端开口端在内部容积中施加真空，从而将组织吸入内部容积中；通过在附加帽的电极之间施加电场来对吸入的组织进行电穿孔。