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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 December 2007 (21.12.2007)

PCT

(10) International Publication Number
WO 2007/144004 A1

(51) International Patent Classification:
A61B 18/14 (2006.01)

(21) International Application Number:
PCT/DK2007/050069

(22) International Filing Date: 12 June 2007 (12.06.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2006 00788 12 June 2006 (12.06.2006) DK
60/812,601 12 June 2006 (12.06.2006) US

(71) Applicant *(for all designated States except US)*: **REGION HOVEDSTADEN v/HERLEV HOSPITAL** [DK/DK]; Herlev Ringvej 75, DK-2730 Herlev (DK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GEHL, Karen Julie** [DK/DK]; Herlev Ringvej 75, DK-2730 Herlev (DK). **VIDEBÆK, Karsten** [DK/DK]; Toftager 24, St. Valby, DK-4000 Roskilde (DK).

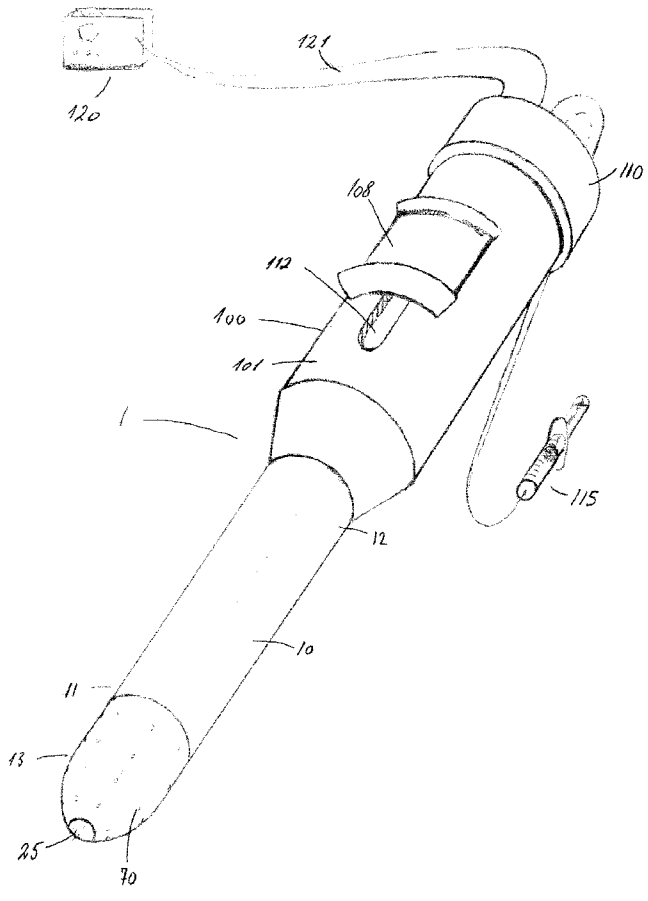
(74) Agent: **PLOUGMANN & VINGTOFT A/S**; Sundkrogsgade 9, Post Box 831, DK-2100 Copenhagen Ø (DK).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: ELECTRODE INTRODUCER DEVICE



(57) Abstract: An electroporation device 1 comprising a handle section 100; an elongate introducer shaft 10 connected to said handle section 100, said introducer shaft 10 having a distal tip 13; and a set of electrodes 60 having respective distal ends 61, each electrode 60 being slidably arranged within said introducer shaft 10 from a retracted position, where said distal ends 61 are enclosed within said introducer shaft 10, to an exposed position, where said distal ends 61 extend from said distal tip 13; wherein said electrode distal ends 61 are deflectable away from a longitudinal axis L of said shaft 10 when deployed/extended to their extended position, such that at least one planar projection taken in a plane perpendicular to said longitudinal axis L of a distance D1 between a pair of distal ends 61 of said electrodes 60 is larger than a maximal extent D2 of a cross-section of said introducer shaft 10, said cross-section taken in a plane perpendicular to said longitudinal axis L at a distal end 11 of said introducer shaft 10.

WO 2007/144004 A1

Published:
— *with international search report*

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

ELECTRODE INTRODUCER DEVICE

The present invention concerns a device and a method for electroporation, in general and more specifically the present invention concerns a device and method for administering therapeutical molecules, such as a drug, an isotope or genetic material enhanced by electric pulses causing electroporation of and/or electrophoretic effects in a target region of a patient's body.

BACKGROUND OF THE INVENTION

In the treatment of diseases in the brain, e.g. brain cancer, as well as diseases in other anatomical areas of a body, physical access to a diseased tissue region may be a challenge. This is especially the case if the diseased region lies deep within the body of the patient. Furthermore, efficient delivery and subsequent uptake of therapeutic molecules, such as a drug or genetic compound, to an anatomical target tissue is often a problem.

Electroporation is a known method used to deliver drugs and genetic material to various biologic tissues, where the uptake of these substances into tissue cells is enhanced through the application of electric pulses of specific amplitude. The delivery of drugs by electroporation is also known as electro-chemotherapy (ECT) and the delivery of genes as Electro Gene Transfer (EGT). In ECT and EGT applications, electroporation is used to create a transient permeabilization of the cell membranes in a target tissue area with the purpose of enhancing the uptake of the chemotherapeutic agents as well as the uptake and expression of genetic materials.

In addition to the delivery of therapeutic molecules, electroporation has a stand-alone application that is known as irreversible electroporation (IRE). In IRE, the amplitude of electric pulses is increased beyond the levels used in ECT and EGT, which creates a permanent permeabilization of the cell membranes in a target tissue area with the purpose of promoting cell death through cell leakage.

In order to provide an efficient electroporation two or more electrode poles have to be brought into – or into close vicinity of – the region to be treated (target region). Examples of devices used for Electroporation are known from US 5 674

267 and US 6 278 895. These devices consist of an array of needle-type electrodes arranged as individual electrodes inserted via some external plate-shaped element providing a fixed distance between and relative position of the individual needles. If the target region is situated in a remote region of the body, such as the deeper regions of the brain, the placement of electrodes may in itself be harmful to intervening tissue through which the electrodes need to traverse in order to be located in the desired region. Furthermore, a large access area must be available, and for applications in the brain this will entail creating a large hole in the patient's skull. Therefore, it is evident that the mentioned prior art devices are only well-suited for treatment in target regions in close proximity to an outer surface of the body, because an attempt to treat deeper-lying regions would cause excessive trauma to the intervening tissue.

OBJECT OF THE INVENTION

There is thus a need for an electroporation device and an electroporation method that overcomes the shortcomings of the presently known devices and methods. It is an object of the present invention to provide such a device and method. It is a further object of the invention to provide an electroporation device which can be manoeuvred to deeper-lying regions of the body or to regions that are otherwise difficult to access, and to do so with the least amount of injury to the tissue. E.g. for applications in the brain, it is an objective to provide a device necessitating the smallest possible entry hole while providing the largest possible electric field. A further object of the invention is to provide an electroporation device capable of delivering an improved, flexible and more efficient electric field in order to enhance the transfer of e.g. a drug, isotopes, genetic materials or other therapeutical molecules through cell membranes of a target tissue/region. By providing an improved, more efficient and more readily controlled electrical field, the energy applied through electrodes to the tissue may be reduced. Thereby, unintended damages to the tissue, especially the tissue immediately surrounding the electrodes may be reduced. There is furthermore a need for a device constituting an alternative to the known devices.

SUMMARY OF THE INVENTION

These and other objectives of the invention are obtained by an electroporation device comprising a handle section; an elongate introducer shaft connected to said handle section, said introducer shaft having a distal tip; and a set of electrodes having respective distal ends, each electrode being slidably arranged within said introducer shaft and said tip from a retracted position, where said distal ends are enclosed within said introducer shaft, to an exposed position, where said distal ends extend from said distal tip; wherein said electrode distal ends are deflectable away from a longitudinal axis of said shaft when deployed/extended to their extended position, such that at least one planar projection taken in a plane perpendicular to said longitudinal axis of a distance between a pair of distal ends of said electrodes is larger than a maximal extent of a cross-section of said introducer shaft, said cross-section taken in a plane perpendicular to said longitudinal axis L at a distal end of said introducer shaft.

A significant advantage of the presently described device is that it allows insertion of multiple electrodes to a sub-surface tissue region or target region of a patient's body while causing minimal tissue displacement and damage to intervening tissue. This advantageous effect is obtained due to the small outer extent/diameter or profile of the invasive portion, i.e. the shaft or at least the distal part thereof, of the present device in a direction transversal to the direction of insertion.

The device according to the invention allows sub-surface generation of a pattern of electrode end points (distal ends) resembling e.g. a planar or spatial ellipse or ellipsoidal shape or any other regular or irregular spatial geometric shape that will provide an efficient electric field of controllable shape, suitable for the varying anatomical/geometric shapes of the target regions found in real patients. Furthermore, this can be obtained under such sub-surface circumstances (deeper-lying / difficultly accessible regions) as is not possible with prior art devices, through the sub-surface deployment of multiple electrodes that are angled away from the introducer shaft and comprise respective un-insulated end-points, preferably placed in an equidistant relationship, that may circumscribe the outer periphery of such an ellipsoid or other geometric shape in the target region.

In an embodiment of the electroporation device, the deflection of said distal ends of said electrodes, when in their extended position, is provided by a curving of distributor channels provided in said distal tip. Alternatively or additionally, the deflection of said distal ends of said electrodes, when in their extended position, is provided by tension characteristics of at least a section (in an elongate direction) of said electrodes, i.e. by a biasing of said electrode or electrode section. Alternatively or additionally said electrodes are formed in a material comprising a shape memory alloy.

In one embodiment the distal tip may alternatively or additionally be formed with a substantially smooth, rounded, non-cutting shape with a substantially smooth, non-cutting transition to the introducer shaft proper. Thus, the device has no sharp edges, and injuries to the tissue can be minimized.

In an embodiment the distal tip is connectable to said introducer shaft. Alternatively the tip is formed integrally with the shaft.

In yet another embodiment each of said electrode distal ends can be advanced individually to their extended positions. Thereby, the extended distribution of the electrodes, and thus the shape of the electrical field, may be adapted to the individual target tissue. Alternatively, the electrodes may be advanced or extended from the tip in subsets of electrodes or as one set of electrodes, e.g. such that the length of the individual electrodes are adapted to the target tissue shape.

In yet another embodiment the electrodes are extendable such that said distal ends are extendable to form a spatial distribution around a volume of target tissue/a target region. In one embodiment thereof, the distal ends are extendable to form a substantially spherical distribution pattern. Alternatively at least a subset of said distal ends is extendable to form an ellipsoid pattern in a plane parallel to said longitudinal axis of the introducer shaft.

In any of the above mentioned embodiments said electrodes may be slideably arranged in electrically insulated guide channels formed in the shaft and tip.

Alternatively or additionally, said electrodes may be provided with an electric insulation coating, the distal-most part of the electrode distal ends being un-insulated to form point electrodes.

The sub-surface generation of an electric field having a geometric shape resembling an ellipse or other three-dimensional shape will provide a more homogeneous tissue coverage. The subsequent application of short and intense electric pulses to two or more of these, preferably equidistant, electrodes will result in a potential difference between the positive and the negative electrodes and a resulting electric field will be generated between these two or more electrodes.

According to an advantageous embodiment of the invention said introducer shaft further comprises a delivery channel through which a dose of therapeutical molecules can be administered, said delivery channel extending through the length of said shaft and terminating through said distal tip. The delivery channel is provided through the shaft along an elongate axis thereof in order to accommodate the delivery of a dose of therapeutical molecules to the region in the vicinity of the tip of the shaft when the device is inserted into the region of a target tissue. Thus, local administration of therapeutic molecules to a target region can be enhanced. However, it is understood that the device may also be applied in combination with systemic administration of therapeutical molecules, where the electroporation will enhance local uptake of therapeutic molecules in tissue cells in the region/vicinity of the electrodes.

In an embodiment said delivery channel is connectable to an external therapeutic molecule delivery system comprising a therapeutic molecule reservoir and pumping means for administering said therapeutic molecules through said delivery channel. Alternatively, the handle part comprises a therapeutic molecule delivery system comprising a therapeutic molecule reservoir and pumping means for administering said therapeutic molecules through said delivery channel. In either embodiment of the device comprising a delivery channel said device may further be adapted to for introducing e.g. a surgical tool or an ultrasound probe through said delivery channel. This adaptation may comprise a suitable sizing of the delivery channel and/or suitable connection means between the device and the

surgical tool. In an alternative embodiment a separate channel may be provided in the shaft for the insertion of a surgical tool or an ultrasound probe.

In one embodiment said introducer shaft has a circular cross section with an outer diameter of 15 mm or less, preferably of 10 mm or less, more preferably of 5 mm or less. However, other cross sections may be provided as well, e.g. oval. in this case the above mention dimensions may apply to the maximal extent across the cross section.

In yet another embodiment the introducer shaft may comprise an outer tube and an inner electrode assembly guide received in said outer tube, and where said electrodes are slideably arranged in electrode guide channels formed in said inner electrode assembly guide. In an embodiment said electrode guide channels are formed in a set of cylindrical guide sheaths that are received in semi-open channels distributed in a longitudinal direction along the periphery of said inner electrode assembly guide. In another embodiment, the introducer shaft may be provided by a multitude of electrode guide channel tubes, each configured to receive one or more electrodes.

The introducer shaft may in one embodiment be rigid. However, in other embodiments the introducer shaft may be flexible and/or steerable, the latter embodiment especially being suitable for insertion through body cavities / transvenous applications.

Such flexible and/or steerable applications may be endoscopic or catheter-based applications in natural channels or lumens in the body, where a flexible/steerable shaft 10 is desirable. Introduction of the device may be through natural anatomical openings or through suitable entry sites such as for instance the femoral artery. Alternatively or additionally, laparoscopic applications through an opening in the abdominal cavity or other areas of the anatomy are envisioned, where the shaft may be introduced via an introducer such as a laparoscope with a working channel or a similar introducer sheath. Such an introducer may, e.g. have a cutting edge, or a removable trocar with a trocar tip that may be removed after insertion of the introducer to facilitate insertion.

In an embodiment, the shaft is substantially straight. However, in other embodiments the shaft may be curved, in order to provide the opportunity to be used in particular anatomic regions (e.g. for tumours of the head and neck) or to circumvent e.g. fragile tissue regions.

Preferably the device comprises 10 or more electrodes. Thus, the electrodes, in extended position, may be spatially distributed to enhance the formation of a spatial electrical field The device, in yet other embodiments comprises 12, 16 or more electrodes.

The device, in yet another embodiment comprises 32 electrodes. In one particular embodiment, said electrodes are slideably arranged within guide channels distributed in groups of four in each of eight cylindrical guide sheaths.

In respect to all of the previously mentioned embodiments an electric stimulus generator may be integrated into the handle section of the device. Alternatively, the device comprises means for connecting/attaching the device electrodes to an external electric stimulus generator.

In one embodiment each electrode or group of electrodes is individually assignable to pass an electrical current, such that the emission of electric stimuli can be provided from individual electrodes or groups of electrodes. Thus an enhanced control of an induced electrical field may be provided. The control or assignment of the individual electrodes or groups of electrodes may be provided by a suitable electronic control unit provided either in the handle part of the device, in the external electronic stimulus generator or as a stand-alone unit.

The tip of the introducer shaft may be a rounded, smooth, atraumatic tip adapted for spreading tissue, thus causing minimal damage to the tissue through which it is to be moved. This is advantageous especially for intravenous applications or applications in e.g. the brain. However, the tip may in other embodiments be provided with a sharpened or cutting tip or a pointed tip that is e.g. suitable for percutaneous applications.

The object of the invention is further obtained by an electroporation method comprising the steps of providing an electroporation device, the device comprising an elongate introducer shaft having a distal tip; and a set of electrodes having respective distal ends, each electrode being slidably arranged within said introducer shaft from a retracted position, where said distal ends are enclosed within said introducer shaft, to an extended position, where said distal ends extend from said distal tip; the method further comprising the steps of inserting said introducer shaft through tissues of a body and bring said distal tip into a vicinity of a target region of tissue to be treated, while said electrodes are in said retracted position; extending said electrodes to said extended position, such that said electrode distal ends are deflected away from a longitudinal axis of said shaft in such a way that at least one planar projection taken in a plane perpendicular to said longitudinal axis of a distance between a pair of distal ends of said electrodes is larger than a maximal extent of a cross-section of said introducer shaft, said cross-section taken in a plane perpendicular to said a longitudinal axis at a distal end of said introducer shaft; administering a dose of therapeutic molecules to said body; and applying through said electrodes one or more electric pulses, e.g. in a specific sequence to the target region tissue to create a transient permeabilization of cell membranes of tissue in said target region.

In one embodiment of the electroporation method according to the invention said dose of therapeutic molecules is administered systemically. In another embodiment of the electroporation method according to the invention said dose is administered locally in the vicinity of the target region. Such local administration may advantageously be delivered before, during or after extending said electrodes, through a delivery channel extending through the length of said shaft and terminating through said distal tip. Alternatively said dose may be delivered locally through a suitable addition injection/infusion device.

The object of the invention may further be obtained by one aspect of a method of generating an electric field in a target region of a patient, comprising the steps of inserting into the vicinity of the target region a set of electrodes, having respective distal ends, enclosed (in a first retracted position) within a single elongate introducer shaft having a distal tip; extending at least a pair of said electrodes to a position extended from their position within said shaft, such that

said electrode distal ends are deflected away from a longitudinal axis of said shaft in such a way that at least one planar projection taken in a plane perpendicular to said longitudinal axis of a distance between a pair of distal ends of said electrodes is larger than a maximal extent of a cross-section of said introducer shaft, said cross-section taken in a plane perpendicular to said a longitudinal axis at a distal end of said introducer shaft; and applying through said electrodes one or more electric pulses to the target tissue.

In an embodiment of this aspect of the method of generating an electric field in a target tissue of a patient, the electrodes are point electrodes which are positioned such that when a sequence of electric pulses is applied through some or all of said electrodes an ellipsoid or spatially ellipsoid electric field is generated between some of or all the points that are positioned in the tissue. In a further embodiment said ellipsoid or spatial ellipsoid field is generated by positioning said point electrodes in an ellipsoid or spatially ellipsoid configuration at least partly surrounding or enclosing said target tissue. In yet another embodiment said point electrode distal ends are positioned in substantially circular parallel layers, where the position of the point electrodes in a section perpendicular to said circular layers defines an ellipsoid configuration. In a further embodiment the electric field is generated in the tissue by applying a sequence of electric pulses between at least sixteen point electrodes in at least four essentially parallel, consecutive layers comprising at least four point electrodes in each layer and such that said sequence comprises the steps of generating at least some pulses travelling from at least one of the electrodes in first positive layer of point electrodes to at least one of the electrodes in a first negative layer of point electrodes placed in equidistant relation to the electrodes in the first layer, while other pulses simultaneously travel from at least one of the electrodes in a second positive layer to at least one of the electrodes in a second layer of point electrodes, respectfully.

The object of the invention is further obtained by another aspect of a method of generating an electric field in a target tissue of a patient, comprising the steps of inserting into the vicinity of a target tissue a set of point electrodes, having respective electrically conductive distal ends, and positioning said electrode distal ends in a spatial formation surrounding or enclosing at least partly said target

tissue; applying through said point electrodes a sequence of electric pulses to the target tissue.

In an embodiment of this other aspect of the method of generating an electric field in a target tissue of a patient, the point electrodes are positioned such that when a sequence of electric pulses is applied through said electrodes an ellipsoid or spatially ellipsoid electric field is generated in the tissue. In a further embodiment said ellipsoid or spatial ellipsoid field is generated by positioning said point electrodes in an ellipsoid or spatially ellipsoid configuration at least partly surrounding or enclosing said target tissue. In yet an embodiment said point electrode distal ends are positioned in substantially circular parallel layers and where the position of the point electrodes in a section perpendicular to said circular layers defines an ellipsoid configuration. In a further embodiment the electric field is generated in the tissue by applying a sequence of electric pulses between at least sixteen point electrodes in at least four essentially parallel, consecutive layers comprising at least four point electrodes in each layer and such that said sequence comprises the steps of generating at least some pulses travelling from at least one of the electrodes in a first positive layer of point electrodes to at least one of the electrodes in a first negative layer of point electrodes placed in equidistant relation to the electrodes in the first layer, while other pulses simultaneously travel from at least one of the electrodes in a second positive layer to at least one of the electrodes in a second negative layer of point electrodes, respectively.

The invention is advantageously applied in electro–chemotherapy, electro gene therapy especially for treatment of brain cancers, and other diseases of the brain. The present disclosure describes the invention from this point of view, but it is understood that the device according to the invention may also be adapted for applications in the treatment of diseases of e.g. the liver, lung, kidney or other soft or hard tissues. The invention may further be applied in the field of irreversible electroporation.

The device and method may be applied to treatment of humans as well as animals.

In the present document the term shaft should be taken to mean an elongate structure that is either rigid or flexible/bendable/steerable, and either substantially straight or forming a uniform curve at least over a section of the length of the shaft.

DESCRIPTION OF THE DRAWINGS

In the following the invention will be described in further detail with reference to the drawing. The figures show ways of implementing the present invention and are not to be construed as being limiting to other possible embodiments falling within the scope of the attached claim set.

- Fig. 1 shows a perspective view of an electrode introducing electroporation device according to an embodiment of the invention.
- Fig. 2 shows, in a perspective view, a distal end of an embodiment of an introducer device according to the invention;
- Fig. 3 shows a section through a distal end of the introducer device shown in Fig. 2, the electrodes being in a retracted position;
- Fig. 4 shows a section through a distal end of the introducer device shown in Fig. 2, the electrodes being in an advanced position;
- Fig. 5 shows a perspective view of a distal end of the introducer device shown in Fig. 2, with an indication of the range of the advanced electrodes;
- Fig. 6 shows a partly cut-out sectional view of an electrode introducer device according to another embodiment of the invention
- Fig. 7 shows, in an exploded, sectional view, a distal end of an introducer shaft of a the introducer device shown in Fig. 6;
- Fig. 8, in an exploded view, shows details of the introducer device shown in Fig. 6;
- Fig. 9, in a frontal view, shows a distal tip of a device according to one embodiment of the invention, with two layers of extended electrode distal ends visible;
- Fig. 10 shows some of the electrodes extending from the distal tip of the device shown in Fig. 9, indicating a pulse emitting pattern between these electrodes; and

– Fig. 11 shows the resulting pattern of the electric field induced in a target tissue by the pulse emitting pattern indicated in Fig. 10.

EMBODIMENTS OF THE INVENTION

In fig. 1 an electrode introducing electroporation device 1 according to an embodiment of the invention is shown. The device 1 comprises a handle section 100 and an elongate introducer shaft 10 preferably having a length suitable for accessing deeper-lying tissue regions. The length of the shaft 10 may be adapted for the intended use. The shaft 10 is attached to the handle section 100, and has a proximal end 12 adjacent to the handle section 100 and a distal end 11. The shaft may in one embodiment be fixedly attached to the handle section. In other embodiments the shaft may be detachably mounted to the handle section 100, and may comprise suitable means for establishing temporary connections, e.g. for conducting electrical pulses. A distal tip 13, that is preferably shaped to permit the creation of a channel through intervening layers of tissue while causing minimal damage to said tissue, is disposed at the distal end 11 of said shaft 10. The distal tip 13 has a rounded, non-cutting shape. In other embodiments (not shown) the distal tip may be provided with a cutting edge or a pointed tip, i.e. a sharpened tip. These latter embodiments are e.g. well-suited for percutaneous applications. In either case, the distal tip 13 may be formed integrally with the introducer shaft 10 or it may be a formed as a separate part coupled to the distal end 11 of the introducer shaft 10. With a removable/detachable tip 13, and/or a detachable shaft 10, the length and thereby the reach of the device, may be adapted, by a suitable choice of shaft. Further, this allows for use of use of single-use only parts for the parts that are inserted into a patient. Thereby, the need for disinfection of the parts to be inserted into a patient may be eliminated.

The introducer shaft 10 comprises a centrally located delivery channel 20 (see Fig. 3) provided through the shaft 10 from the proximal end 12 to the distal end 11 along a longitudinal axis, L, of said shaft 10, and terminating through said distal tip 13, said channel 20 having a proximal end 22 and a distal end 21. At the distal end 21 of the channel 20 one or more outlets 25 are provided in the distal tip 13 in order to administer an amount of fluid/medical compound adjacent to the distal tip 13. In the embodiments shown in the figures a single outlet 25 is provided,

however, the channel 20 may split up into a multitude of minute channels at the distal end 21, each having an outlet at the distal tip 13. The proximal end 22 of the channel 20 extends through the shaft 10 to the handle section 100, and is adapted for connection to a drug/genetic material delivery means (115) comprising a storage of a drug/medicament and/or means (e.g. a pump or a piston or the like) for advancing said medicament from said storage and through said channel 20 to a target tissue. In a simple form the delivery means may be provided by a syringe 115, connected to the delivery channel 20 via the handle section 100, e.g. by a tubing.

In an alternative embodiment (not shown), the channel 20 may be configured to receive an elongate delivery system, e.g. in the form of a tubing, that may reach from the storage means into the region to be treated. Such a delivery system may comprise a syringe connected to said tubing, in such a way that the channel is adapted to receive e.g. a distal section of said tubing.

In yet another alternative embodiment (not shown), the device 1 may provide an integrated therapeutic molecule delivery system comprising delivery means with advancing/pumping means and/or a storage for a medicament/drug, isotope or a genetic material solution, being integrated in the handle section 100.

The electroporation device 1 and the delivery channel 20 may also be configured by e.g. appropriate coupling means and/or dimensioning to receive and guide for instance an ultrasound probe, a surgical tool or another tool for minimally invasive manipulation of tissue. Thus the device 1 can be used in a flexible way, where for example it is not necessary to remove the device 1 and replace it with another specialized surgical tool, if the operator/surgeon encounters unexpected obstacles/difficulties prior to, during or following the electroporation process.

The shaft 10 further comprises a plurality of guide channels 50 (see Figs. 3 and 4), distributed around the central channel 20, and extending from the proximal end 12 to the distal end 11 of said shaft 10, and through the distal tip 13. Each guide channel 50 is adapted for guiding one or more elongate electrodes 60 that are movable relative to the shaft 10 between a first retracted position, as shown in Fig. 3, and a second extended position, as shown in Fig. 4.

In an alternative embodiment (not shown) each guide channel 50 may be provided, at least along a section of the shaft 10, by individual tubes, the shaft 10, in said section being formed by the set of individual tubes.

Each electrode 60 has a proximal end 62, extending into the handle section 100, a distal end 61 and an intermediate region 63 electrically connecting the proximal end 62 and the distal end 61 of each electrode 60.

The proximal ends 62 of the electrodes 60 are configured to act as connectors, thus providing a means of connecting the electrodes 60 to an electric stimulus generator 120 that supplies single electric pulses or sequences of electric pulses according to electroporation protocols for drug and gene delivery. The electric pulses are intended to generate an electric field for the purpose of creating transient permeabilization of cell membranes and/or an electrophoretic effect in the vicinity of the distal ends 61 of said electrodes 60 when the introducer device 1 is placed in or close to a target tissue area and the electrodes 60 are forwarded to an extended position, see further regarding the use of the device below.

The electrodes 60 are connectable to an external electric stimulus generator 120 via an electronic connector (cable) 121 at the handle section 120 as shown in Fig. 1. In an alternative embodiment an electric stimulus generator 120 may be formed integrated with the introducer device, preferably in the handle section 100.

The configuration of the proximal ends 62 of the electrodes 60 further permits movement of the electrodes 60 between a first retracted position and a second extended position in a deployment sequence that will be further described below.

The intermediate regions 63 of the electrodes 60 are movably received in said electrode guide channels 50 running through the introducer shaft from the proximal end 12 to the distal end 11 at the distal tip 13. Preferably, each electrode 60 has its own channel 50 to support and protect it and insulate it from the other electrodes 60, as shown in Figs 2-4, but multiple channels 50 may be bundled together in electrode assemblies, for example as shown in Fig. 6. Said

electrode guide channels 50 permit longitudinal movement of the electrodes 60 between the first retracted position and the second extended position.

Electrode end points at the distal ends 61 of the electrodes 60 are movably received in distributor channels 70 formed in the distal tip 13, and extending to the outer surface of said distal tip 13. Each distributor channel 70 further communicates with a corresponding guide channel 50 in the shaft proper 10. Thus, movement of the electrodes 60 in a longitudinal direction (with respect to the longitudinal axis of the shaft 10) between a first retracted position where the distally disposed end points 61 of the electrodes 60 are concealed within the distal tip 13, and a second extended position, where the end points 63 of the electrodes 60 are extended from the distal tip 13, is allowed.

In an alternative embodiment (not shown), the device may only have distributor channels 70 formed in the distal tip 13, the electrodes 60 being contained in a hollow shaft 10, the individual channels 50 being left out.

While positioned in the first retracted position, which is the default mode of the device 1, the end points at the distal ends 61 of the electrodes 60 are held in storage in the distributor channels 70 in the distal tip 13, thus permitting the minimally invasive insertion of the device 1, i.e. with minimal damage to surrounding tissue.

The distributor channels 70 are shaped to ensure deployment of the distal ends 61 of the electrodes 60 in a predetermined pattern where a largest distance D1 (See Fig. 5) between a pair of oppositely arranged electrode end points 61, in a plane transversal to the longitudinal axis of the introducer shaft is larger than the diameter – or the largest extension D2 of the introducer shaft 10/distal tip 13 – in a plane perpendicularly to the longitudinal axis of the introducer shaft 10. Thus, it is made possible to access deeper lying tissues, e.g. within the brain, trough a single channel using a single introducer shaft 10, spreading the intervening tissues during the insertion, and, when the tip 13 reaches the target tissue, the electrodes can be extended through and/or around the target tissue. This allows an operator (surgeon) to treat a target tissue region or volume which has a cross-sectional dimension/extent larger than the diameter of a cross-section of the

introducer shaft 10, where the cross-section is taken in a plane perpendicular to the longitudinal axis of the introducer shaft 10. In order to provide the above described distribution of the distal ends 61 of the electrodes 60, the distributor channels 70 are formed such that at least some of the distributor channels 70 curve outwardly, i.e. away from a longitudinal centre axis L of the introducer shaft 10 (as seen from their connection to the distal end 11 of the corresponding guide channels 50 in the shaft 10 and towards the outer surface of the distal tip 13 where the distributor channels 70 terminates). Each of the distributor channels 70, or sets of distributor channels 70may be provided with a different individual shape/deflection/curving in order to ensure a specific pattern or distribution of the extended electrodes 60 during use.

Alternatively, the deflection away from said longitudinal axis L may be provided by e.g. a pre-tensioning or biasing of said electrodes 60. Such tensioning may be provided by a suitable choice of materials, e.g. a shape memory alloy such as Nitinol, or by forming the (flexible) electrode e.g. in a bent shape, such that when it is arranged in a straight guide channel 50 of the shaft 10 it is held in tension. The individual electrodes 60 or set of electrodes may have an individual biasing such that the electrodes may, when extended from their retracted position in the shaft 10/tip 13 form a desired spatial pattern around the target tissue.

Further, the desired spatial distribution of the part of the electrodes extending from the tip 13 may be provided by a combination of the shape of the tip distributor channels 70 and a biasing of the electrodes 60.

In use, the electronic connection means (not shown) at the proximal ends 62 of the electrodes 60 are connected to a suitable electric stimulus generator 120. The shaft 10 of the introducer device 1 is then inserted, e.g. through a bore hole in a patient's skull or an incision in the patient's skin and introduced to the target region of the patient's body. The precise location of the target region and thereby for the bore/incision may be identified by means of ultrasound, CT, MR or another suitable means, and the correct position of the tip 13 of the introducer shaft 10 (post insertion) may be verified by similar means prior to, during or after deployment of the electrodes. When a correct position of the tip 13 of the introducer shaft 10 has been obtained relative to the target tissue, an operator

may deliver a suitable chemotherapeutic agent, in fluid or liquid form, or a dose of genetic material or other substance through the delivery channel 20 and into the tissue region to be treated.

Before, during or after delivery of the drug or genetic material through the delivery channel, the operator may deploy some or all the elongate electrodes 60 in a desired pattern. Deployment is performed by actuating a suitable deployment mechanism at the handle section 100 or at the proximal end 12 of the shaft 10, and results in the longitudinal motion of all or some the electrodes 60 along the axis of the introducer shaft 10 from the first retracted position – as shown in Fig. 3 – to the second advanced position, e.g. as shown in Fig. 4. The distributor channels 70 in the distal tip 13 may be shaped to provide each individual electrode 60 with a unique path through the tissue, when advanced from the tip 13, which enables the creation of an electrode pattern where a distance D1 between oppositely arranged electrode end points 61 in a plane transversal to the longitudinal axis of the introducer shaft 10 is larger than a diameter D2 (or the largest extent of the shaft 10 in a section perpendicular to the longitudinal axis of the shaft 10 if the shaft is not of circular cross section) of the introducer shaft 10 in the same transversal plane.

Upon deployment of some or all of the electrodes to their extended position, an operator may actuate the electric stimulus generator 120 to deliver one or more pulses, e.g. a sequence of short and intense pulses to the tissue to be treated (target tissue). To ensure a suitable distribution of pulses and the thereby induced electric fields in the target tissue, pulses may be assigned to alternating specific electrodes 60 in a sequential pattern that may be tailored to suit the anatomy of the individual region of the body to be treated and/or the geometry of the specific malignant target tissue. Such assignment may be obtained for instance by suitable manipulation of the electric stimulus generator, e.g. through programmable electronic control means.

Upon pulse delivery, the operator may retract the elongate electrodes 60 to their retracted position by suitably manipulating the deployment mechanism in the handle section 100, and the device may be removed from the body of the patient. Alternatively, the operator may reposition the device 1 after having retracted the

elongate electrodes 60, potentially permitting multiple pulse applications covering a larger area in a single device insertion.

The electrode introducer device 1 shown in Figs. 2-5 is depicted as having eight guide channels 50, distributor channels 70 and electrodes 60. However, a device according to the invention may be provided with any number of electrodes 60. The distribution of the guide channels 50 over a cross-section of the introducer shaft 10 shown in Figs. 2-5, is such that the electrodes all run in a plane parallel to the longitudinal axis of the introducer shaft 10. However, the electrodes 60 and their guide (and distributor) channels 50 (70) may be located around the entire circumference of the channel 20 in the shaft 10, surrounding the delivery channel 20 in other patterns as well.

Each electrode is formed in an electrically conductive material. Parts of the electrodes may be formed with an electrically insulating coating or sheathing, such that only the most distal ends 61 (points) of the electrodes 60 are un-insulated. Thus, the electric pulses will create an electric field spanning the distance from point to point (distal end 61 to distal end 61), and a readily controllable firing pattern and thus a more controllable and accurate electric field may thus be generated by suitable selection and assignment of electrodes. For completeness it is to be understood that the entire length or part of the entire length of the electrodes 60 may also be electrically un-insulated, provided that the guide channels 50 and the distributor channels 70 are formed in an electrically insulating material.

As shown in Fig. 5 the device may be configured such that the distal ends 61 of the electrodes 60 may form an ellipsoid field E that is the result of this electrode 60 pattern. A target tissue could be imagined situated within the ellipsoid area E, shown in the figure. Some of the electrodes 60 are thus advanced through the target tissue when guided to their extended position. In other embodiments of the invention it can be imagined that electrode patterns can be formed, such that a target area can be surrounded by electrode points (distal ends) 61 in various three-dimensional patterns, e.g. a spherical or spherically elliptic or ellipsoid pattern.

As can be appreciated from Fig. 5, a device according to the invention may be adapted with sets of electrodes 60 that may be extendable to different distances from the distal tip 13 along the longitudinal axis of the shaft 10, such that the distal ends 61 of each set are positioned in a common plane perpendicular to the longitudinal axis of the shaft 10. In Fig. 5 four sets of two electrodes extend to different distances from the distal tip 13, thus forming the above mentioned ellipsoid shape E.

Further, some of the electrodes 60 may be formed in such a way that they undertake a curved path through the tissue such that when advanced forward towards their extended position they will initially be deflected away from the central longitudinal axis L of the shaft 10, and will then reflect back such that the distal tip closes in on the central, longitudinal axis of the shaft 10, when advanced further. Thus, when fully extended, such an electrode 60 will describe a gently U-shaped or substantially, softened Ω-shaped curve. This may be accomplished by providing electrodes in an elastic material or a shape memory alloy such as Nitinol or by providing different section (lengthwise) of the electrodes with different biases (pre-tensionings).

Yet further, guiding channels may be shaped to impose on the electrodes certain paths through the tissue. For instance, it may be advantageous to impose on the electrodes a strictly linear path through the tissue, as the electrodes will then be able to withstand much higher loads without buckling – as opposed to electrodes given a curving path.

The deployment mechanism for the electrodes 60 may be manually driven or motorized (e.g. electronically controlled). The deployment mechanism may be adapted to advance all electrodes simultaneously as a set, or individually, or in groups (subsets) of electrodes 60. When the electrodes are advanced simultaneously, different electrode patterns may be achieved through a predetermined composition of electrodes of suitable lengths, shapes (by tensioning, alternative cross-sections predisposing the wire for certain directions of movement or by adequate shaping of guide channels) and materials. The device 1 according to the invention may further be controlled by an electronic control unit (not shown), either incorporated in the device 1 or connectable to the

device 1 through a cable or a wireless connection. In the wireless configuration, a suitable power supply is preferably located inside the device. The electronic control unit may be programmable, such that a desired electrode pattern may be programmed prior to a surgical procedure.

In alternative embodiments (not shown), and as mentioned above, a partially disposable device variation of the above described embodiments is proposed, with a disposable introducer shaft 10 and non-disposable (re-usable) handle section 100 comprising a deployment mechanism with interfaces to electrodes formed in the disposable introducer shaft 10 and a electronic connections that may be customized to individual electrical stimulus generators 120.

The shaft may in all embodiments be formed in a plastic or metallic material such as titanium, stainless steel or an injection moulded polymeric material. The outer diameter of the shaft is preferably five (5) millimetres or smaller, preferably between gauge 17 to 14 incl. The wall thickness of the shaft is preferably between 0.05 mm and 0.25 mm. The guide channels 50, 70 may be formed in a suitable material, e.g. formed in a thermoplastic elastomer or a similar electrically insulating material. The electrodes 60 may be formed in an electrically conductive material such as titanium, stainless steel or the like

In the following, an aspect of the invention, suited in particular for applications within the brain, e.g. in the treatment of brain cancer or genetic deficiencies will be described in further detail with reference to Figs. 6-8. Like references will be used for similar parts, with respect to the aspects of the invention shown in the previous drawings. The electrode introducer device 1 comprises an introducer shaft 10 and a handle section 100. The introducer shaft 10 is intended for insertion into the body of the patient and is fixedly attached to the handle section 100.

In alternative embodiments a partially disposable device is proposed, with a disposable introducer shaft 10 and non-disposable (re-usable) handle section 100 comprising a deployment mechanism with interfaces to electrodes formed in the disposable introducer shaft 10 and a connector that may be customized to individual electric stimulus generators 120.

The introducer shaft 10 comprises the following:

- An outer tube 15 having a proximal end 11 and a distal end 12 which is preferably formed in a plastic or metallic material such as titanium, stainless steel or an injection moulded polymeric material. The outer diameter D2 of this tube is preferably five (5) millimetres or smaller. The wall thickness of said outer tube is preferably between 0.05 mm and 0.25 mm and the length of the tube is preferably between 50 mm and 500 mm depending on the particular application.

- An inner electrode assembly guide 16 that is preferably formed in a thermoplastic elastomer or a similar electrically insulating material. The inner electrode assembly guide 16 is placed in an inner lumen of the outer tube 15. The electrode assembly guide 16 has a flattened proximal end and a flattened distal end comprising faces that lie perpendicular to the longitudinal axis. This electrode assembly guide 16 comprises eight straight, semi-open channels 17 distributed in a circular pattern around and partially sunk into an outer periphery of the electrode assembly guide 16 and running in parallel tracks from the proximal end 12 to shortly before the distal end 11. In addition, the electrode assembly guide 16 has a central bore/delivery channel 20 providing a fluid channel and/or a working channel for surgical instruments. The outer periphery of the electrode assembly guide 16 fits within the lumen of the outer tube.

- Eight electrode assemblies each comprising a cylindrical guide sheath 30. The guide sheaths 30 are preferably formed in a thermoplastic elastomer or a similar electrically insulating material, and are received in the straight semi-open channels 17 in the electrode assembly guide 16 and firmly attached therein. The cylindrical guide sheaths 30 have a flattened proximal 32 and distal end 31. The interior of each electrode assembly guide sheaths 30 comprises four mutually electrically insulated electrode channels 50 running in parallel from the proximal 32 to the distal 31 end, and distributed in a pattern that resembles a square with the electrode channels 50 placed in the corners. The proximal end of each electrode channel 50 comprises an electrode support zone with a slightly increased diameter for the first approximately 20 mm, to receive a corresponding

supporting sheath that is mounted on the proximal end 62 of each electrode 60. Further, the electrode assemblies comprise a total of thirty-two elongate, preferably cylindrical electrodes 60 formed in an electrically conductive material such as titanium, stainless steel or the like, each electrode having proximal ends 62, distal ends 61 and intermediate zones 63. Approximately 20 mm from the proximal 62 end of each electrode 60, a supporting sheath (not shown) 20 mm long may in be provided, the sheat surrounding a part of the intermediate zone 63 of the electrode 60. This supporting sheath is meant to lend support to the individual electrodes to prevent buckling or bending during the deployment sequence and is configured to slide into the electrode support zone (of the electrode channels 50 on the guide sheaths 30) when the electrode is moved from its retracted to its advanced position during deployment. Each electrode 60 is preferably covered with an electrically insulating layer except on the distal tip which is left without insulation. Yet further, the electrodes 60 are grouped in groups of four, and each group of electrodes is inserted in a cylindrical guide sheath 30, one electrode in each electrode channel 50. Insertion is done so that the proximal ends 62 of the electrodes 60 protrude approximately 30 mm from the proximal ends of the guide sheaths 30, whereas the distal ends 61 of the electrodes 60 protrude approximately 40 mm from the distal ends of the guide sheaths 30.

- Eight alignment bushings 80, each configured to receive and guide four electrodes 60 and each with a proximal end 82 and a distal end 81 and four alignment channels 83. The alignment bushings 80 are placed in extension of each of the eight electrode assemblies (guide sheaths 30), and are configured to interface with said assemblies and guide sheaths 30 and to receive the four elongate electrodes 60 where they emerge from the distal ends 31 of said assemblies/guide sheaths 30 in a manner to prevent electrode buckling or bending during the deployment sequence. To achieve this, the proximal end 82 of each alignment bushing 80 is configured to align the four alignment channels 83 with the four electrode channels 50 of the electrode assemblies/guide sheaths 30. The path of the alignment channels 83 of each alignment bushing 80 is configured to change the pattern of the elongate electrodes from the square pattern configuration

when emerging from the electrode assemblies/guide sheaths 30 to a linear pattern when they emerge from the alignment bushing 80. Since the eight electrode assemblies/guide sheaths 30 are distributed in a circular pattern and the eight alignment bushings 80 are placed in extension of the assemblies, a radial pattern may be created by suitably orienting the alignment bushings 80.

- A distal tip 13 that is an immediate extension of, and aligned with, the electrode assembly guide 16. The distal tip 13 comprises eight elongate, roughly triangular spacer units 40, each with a proximal end 42 and a tapered, rounded distal end 41, a rounded outer surface 43 and an inner section with two faces 44a, 44b. One face 44b is smooth and one face 44a comprises four distributor grooves 70 that run from the proximal end 42 towards the distal end 41 while curving towards the outer rounded surface 43 of the spacer unit 40, each in a predetermined unique curve. The faces 44a, 44b meet in a 45 degree angle to create a wedge. A rounded cut-out 45 takes away the sharpened end of the wedge. The proximal ends 42 of the spacer units 40 have a reduced height and are inserted into the distal end 11 of – and held tightly together by – the outer tube 15 while the distal ends 41 of the spacer units 40 meet to form a torpedo-shaped tip 13. When all eight wedge-shaped spacer units 40 are held together by the outer tube 15, the rounded cut-outs 45 create a central bore 46 aligned with the delivery channel 20 of the electrode assembly guide 16. The spacer units 40 are oriented so that the smooth face 44b of one spacer unit 40 rests against the face 44a comprising four distributor grooves 70 of the neighbouring spacer unit 40, thus creating four distributor channels 70 per spacer unit 40, for a total of 32 channels. Each distributor channel 70 is configured to receive a specific elongate electrode 60 where it emerges from its respective alignment bushing 80 and to permit its longitudinal movement between a first retracted and a second advanced position (in the same manner as shown in Figs. 3 and 4 respectively). In their first retracted positions, all electrodes 60 are placed with their distal ends 61 entirely within the distributor channels 70. When the electrodes are advanced as part of a deployment sequence, the distal ends 61 of the electrodes 60 are moved out of the distributor channels 70 to protrude

from the distal tip 13. As the grooves and thus the channels 70 lead towards the rounded outer surface 43 of each spacer unit 40 (and thus are deflected away from the longitudinal axis of the introducer shaft 10) and each in its own angle, each electrode is given its own path and emerges from the distal tip 13 in its own direction when advanced. Thus, by providing 32 electrodes that may be moved between a first retracted and a second advanced position, each with a unique path that leads away from the distal tip 13 and ends in a unique point it is possible to generate a three-dimensional pattern of electrode points 60 as previously described.

- A round adaptor plate 90, fixedly attached to the proximal ends 62 of the elongate electrodes 60 and placed proximally to the proximal end of the electrode assembly guide 16. The adaptor plate 90 is longitudinally movable between a first retracted and a second advanced position. The proximal ends 62 of the elongate electrodes are inserted in holes 92 in the adaptor plate 90 that are placed in a pattern resembling that of the electrodes 60 when they emerge from the guide sheaths 30 and the supporting sheath of each electrode is fixedly attached to the adaptor plate 90. The adaptor plate 90 further comprises a central hole 93 that is aligned with the delivery channel 20 of the electrode assembly guide 16, as well as two guide pins 91 that are placed oppositely to each other on – and protruding from – the outer periphery of the adaptor plate 90.

The handle section 100 comprises the following:

- A generally cylindrical housing 101 that is preferably formed in plastic or another suitable material. The housing comprises two half sections, each having an inner and an outer surface, a proximal end, a distal end and an intermediate zone.

- A deployment slider 102 that is preferably made of plastic or a similar non-conductive material and is movable between a first retracted and a second advanced position within and relative to said housing 101. The deployment slider 102 has a proximal end 104 and a distal end 104 and is in operative

connection with the adaptor plate by means of two connecting clamps 105. Said connecting clamps 105 are configured to engage the guide pins 91 of the adaptor plate 90 and are slidably held in grooves 109 in the housing 101. The distal end of the deployment slider comprises 32 connections 106 that are configured to receive the proximal ends 62 of the electrodes 60 as they emerge from the adaptor plate 90. Said connections 106 are electrically connected to the distal ends of flexible leads (not shown) that conduct electric pulses from the electric stimulus generator 120 to the electrodes 60. The proximal ends of said leads are connected to a connector plug that constitutes an interface to an electric stimulus generator 120. The deployment slider 102 further comprises a central bore 107 aligned with the central hole 93 in the adaptor plate 90, as well as two or more finger grips 108 that protrude radially away from the outer surface of the housing 101, through openings in the same. Said finger grips 108 permit an operator to move the deployment slider 102 between a first retracted position and a second advanced position, in order to advance the electrodes 60. The distal half ends of the housing 101 are fixedly attached to the introducer shaft 10 so that the proximal part of the shaft 10, as well as the adaptor plate 90 and the deployment slider 102, all lie within the housing 101. Towards the distal part of the inner surface of each half section of the housing 101 is a groove 109 that is configured to receive one of two connecting clamps 105 of the deployment slider 102. In a proximal continuation of said groove 109 is placed a motion control slot 112 (see Fig. 1) that runs to the proximal end of each half section. The motion control slot 112 is configured to receive one of two finger grips 108 of the deployment slider 102 and permit longitudinal motion of the slider 102 between a first retracted and a second advanced position. The proximal end of the housing 101 is threaded to receive an end cap 110 that serves the dual purpose of closing the handle section 101 and holding the proximal ends of the two half sections of the housing 101 together. Further, one half section comprises an outlet configured to receive the leads 121, 122 as they emerge from the deployment slider 102.

- An end cap 110 that comprises an outer shell with a threading on its inner surface and an inner support cylinder that has a circumference

corresponding with the circumference of the inner surface of the housing. The end cap further comprises a central hole 111 that is aligned with the central bore in the deployment slider 102 and is configured to receive the tubing of the drug dispenser.

In use, the connector plug of the device is connected to a suitable electric stimulus generator 120. The device 1 is then inserted through a bore hole in the patient's skull and introduced to the target region of the patient's body/brain. The precise location may be identified by means of ultrasound, CT, MR or another suitable means, and the correct position of the introducer shaft 10 prior to deployment may be verified by similar means. As described above, in other embodiments, the stimulus generator may be integrated in the handle section.

When a correct position of the introducer shaft 10 has been obtained, an operator may deliver a suitable chemotherapeutic agent or dose of genetic material through the central channel 111, 107, 93, 20 and into the tissue region to be treated. Delivery is done by inserting the elongate, length-adjusted and properly dulled needle of a syringe 115 in the central hole of the end cap and advancing it until no further motion is possible. The operator may then empty the syringe barrel 115 by pressing the syringe plunger, whereupon the liquid in the syringe is expelled into the tissue to be treated.

Before, during or upon delivery, the operator may deploy the elongate electrodes 62 in a predefined pattern. Deployment is done by moving the deployment slider 102 from its first retracted position towards its second advanced position until further movement is prevented by the end of the motion control slots 112. Said movement results in the motion of the electrodes 60 from the first retracted to the second advanced position. The distributor channels 70 in the distal tip 13 are shaped to provide each individual electrode 60 with a unique, preferably essentially linear path through the tissue and a unique end-point, and the goal is to enable the creation of an electrode pattern that may have a larger diameter (or maximum extent in a plane perpendicular to the longitudinal axis of the shaft 10) than the introducer shaft 10 and may ensure optimal distribution of the short and intense pulses and the thereby derived electric fields in the tissue to be treated. In one particular preferred embodiment the un-insulated electrode tips (distal

ends 61) are positional and positioned with their end-points at least partially surrounding or enclosing the target region of tissue in such a way that the distal ends 61 describe or define the outer periphery of a spherical/spatial ellipse. In said preferred embodiment the 32 electrodes are organized in four layers, each layer having a different diameter and consisting of eight electrodes 60 with their end-points (distal ends 61) describing a circular pattern in a plane perpendicular to the axis of the introducer shaft 10.

Upon deployment, an operator may activate the electric stimulus generator 120 to deliver a sequence of preferably short and intense electric pulses, for example square-wave pulses, to the tissue to be treated. To ensure a suitable distribution of pulses and the consequent electric fields in the tissue to be treated (target tissue), pulses may be assigned to alternating specific electrodes 60 in a pattern that may be tailored to suit the anatomy of the individual region of the body to be treated and/or the geometry of the specific malignant target tissue. In an embodiment, at least some of the end-points 61 of the electrodes 60 are placed in equidistant relation to other electrode end points 61, and at least some pulses are assigned to equidistant pairs of electrodes. Thus, a homogenous or heterogeneous, controllable three-dimensional electric field can be created in the target tissue.

In a further embodiment the un-insulated electrode 60 tips are positionable in such a pattern that their end-points 61 outline an outer periphery of an ellipsoid or an ellipse in a plane taken parallel to the longitudinal axis of the shaft 10 – corresponding to what is illustrated by reference E in Fig.5. In this embodiment, and as further shown in Fig. 9, the 32 electrodes 60 are organized in four substantially parallel layers (in a plane perpendicular to the longitudinal axis of the shaft 10) numbered a-d, (a being the top-most (with respect to the distal tip 13)/most-distal layer (with respect to the user/surgeon)) consisting of eight electrodes numbering 1-8 in each layer, with their end-points describing an elliptical or a circular pattern perpendicular to the axis of the introducer shaft. In Fig. 9, the top layer a and bottom layer d of electrodes 60 has been left out, for the purpose of clarity, such that the b (b1-b8) and c (c1-c8) layers are shown.

The efficiency of the electroporation may be enhanced by adapting a controlled pulse emitting sequence, thus creating a controlled electric field. In one suggested pulse sequence, at least some of the pulses assigned travel from electrodes in layer a to electrodes in layer c that are placed in equidistant relation to the electrodes in layer a, while others simultaneously travel between equidistant pairs in layer b and layer d. In one particular firing sequence, pulses travel from positive electrodes a1 and a2 to negative electrodes c6 and c5, and simultaneous pulses travel from positive electrodes b1 and b2 to negative electrodes d6 and d5, as illustrated in Fig. 10 where only the mentioned electrode distal ends 61 are shown, the other 24 being removed for the sake of clarity. The pulses will travel the shortest possible way (assuming uniform electric resistance in the target tissue) wherefore the electric field can be shaped and controlled by the positioning of the electrodes such that firing between the electrodes in different layers can be made between equidistant positive and negative pairs of electrode ends (61) (point electrodes). Thus, an elongate, three-dimensional electric field F is generated, as shown in Fig. 11. The position of the field may be altered to cover the largest possible tissue volume by sequentially changing the assignment of pulses to other equidistant positive and negative electrodes in a suitable pattern.

Upon pulse delivery, the operator may retract the elongate electrodes 60 to their first retracted position by moving the deployment slider 102 from the second advanced position to the first retracted position whereby the electrodes are retracted to their default position within the distal tip 13, and the device 1 may be removed from the body of the patient. Alternatively, the operator may reposition the device after having retracted the elongate electrodes 60, potentially permitting multiple pulse applications covering a larger area in a single device insertion.

In either of the above embodiments a separate channel (not shown) or a portion of the delivery channel 20 may be used to deliver a saline solution to enhance the Electroporation process by increasing tissue conductivity. A saline solution may also be introduced via the delivery channel 20 proper. In either case suitable means for connecting the channel 20 to a source of saline solution may preferably be provided at the handle section.100

As described above, the cross-sectional shape of the electrodes is preferably essentially circular. However, in other embodiments, other cross sectional shapes may be applied. The diameter and cross-sectional shape of the distributor channels 70 are in any event preferably dimensioned for the desired electrode diameter and cross-sectional shape, in order to provide the best possible support for the electrodes, without limiting their ability to be moved from their retracted position to their extended position (and back).

In either of the above described embodiments, the electrode diameter is preferably 0.4 mm or smaller, such as 0.3 mm, 0.25 mm including electrically insulating coating. The diameter of the electrodes 60 is typically correlated to the stiffness of the electrodes, such that the thicker the electrode, the stiffer the electrode. For some applications a stiff electrode may be necessary, e.g. if the tissue is tough. In soft tissue a less stiff electrode may be applied.

Also depending on the application, the tip of the electrodes may be configured such that it may cut through tissue or it may be smooth in order to more gently spread the tissue.

Further, the electrodes may biased (e.g. pre-tensioned) in such a way that their geometrical configuration in their extended state varies with the extent to which they have been extended beyond the distal tip 13 of the shaft 10. This may be applied be providing the electrodes 60 with different tension characteristics along the lengthwise direction of the electrodes. Thus, a very flexible electroporation device may be obtained.

In the description above and in the drawings, the delivery channel 20 has been illustrated to be centrally located within the shaft 10. However the delivery channel 20 may be asymmetrically located within the shaft, with respect to its cross sectional position. In other embodiments (not shown) the single delivery channel 20 may be replaced by a plurality of smaller delivery channels, each having an outlet at the tip 13. Thereby a more even distribution of an injected therapeutic molecule solution can be obtained.

As described above, a surgical tool or the like may be inserted via the delivery channel 20. The invention also concerns a combination of an electroporation device having a delivery channel according to any of the embodiments described above and an therapeutic molecule solution injection device. The therapeutic molecule solution injection device comprises an elongate hollow part adapted for the delivery channel 20, and a steerable outlet tip. The elongated hollow part is adapted in length, such that the steerable outlet tip can be extended beyond the tip 13 of the electroporation device. The steerable outlet tip may be used to administer a dose of therapeutic molecule solution in a precise location in the target tissue.

Alternatively, or in addition to the combination with therapeutic molecule solution injection device, the electroporation device may have a steerable tip 13. This may be provided by having control rods or strings extending through the shaft 10 to the tip 13, the tip e.g. being pivotally mounted at the distal end of the shaft 10, pivotably about an axis either parallel to the elongate axis of the shaft or perpendicular (or at another angle) to the axis of the shaft. The extent to which the tip 13 may be steered is of course dependant on the stiffness of the electrodes, and a flexible alignment between the channels 50 in the shaft and the channels 70 in the tip 13. By providing a steerable tip 13, the flexibility and reach of the electroporation device may be enhanced, since for also a larger target tissue volume, a single entry hole/channel, formed by the shaft 10 through the surrounding (healthy) tissue is necessary. Thus the reach of the electrodes may be expanded by a turning of the tip 13 or a combination of a turning of the shaft and a tipping of the tip 13 (when the electrodes are in retracted position in the shaft) Thereby the applied electrical field can be repositioned, in a sequence until the entire target tissue may be covered. Further the direction of the outlet of the delivery channel may be altered in order to provide for a more precise delivery of a therapeutical molecule solution. The steerable tip 13 may be combined with the above mentioned therapeutic molecule solution injection device in order to further enhance the reach and flexibility of the drug delivery. However, the steerable tip 13 may also be applied in embodiments without a delivery channel, i.e. embodiments suitable for systemic introduction of drugs or for irreversible electroporation.

The electrodes may also be prepared with/covered by/impregnated with a drug or DNA molecule compound that may be dissolvable in an electrical field. Thereby, a drug etc. may be released from the electrodes when an electrical field is applied to the target tissue via the electrodes. Thereby the delivery channel 20 may be spared. However, the drug impregnated electrodes may also be used with embodiments having a delivery channel 20 in order to release multiple drugs or in order to save the delivery channel for e.g. a field enhancing saline solution as described above.

CLAIMS

1. An electroporation device (1) comprising
   - a handle section (100);
   - an elongate introducer shaft (10) connected to said handle section (100), said introducer shaft (10) having a distal tip (13); and
   - a set of electrodes (60) having respective distal ends (61), each electrode (60) being slidably arranged within said introducer shaft (10) and said tip (13) from a retracted position, where said distal ends (61) are enclosed within said introducer shaft (10), to an exposed position, where said distal ends (61) extend from said distal tip (13);

   wherein said electrode distal ends (61) are deflectable away from a longitudinal axis (L) of said shaft (10) when deployed/extended to their extended position, such that at least one planar projection taken in a plane perpendicular to said longitudinal axis (L) of a distance (D1) between a pair of distal ends (61) of said electrodes (60) is larger than a maximal extent (D2) of a cross-section of said introducer shaft (10), said cross-section taken in a plane perpendicular to said longitudinal axis (L) at a distal end (11) of said introducer shaft (10).

2. An electroporation device (1) according to claim 1, wherein the deflection of said distal ends (61) of said electrodes (60), when in their extended position, is provided by a curving of distributor channels (70) provided in said distal tip (13).

3. An electroporation device (1) according to claim 1 or 2, wherein the deflection of said distal ends (61) of said electrodes (60), when in their extended position, is provided by a biasing of at least a section of said electrodes (60).

4. An electroporation device (1) according to any of the claims 1-3, wherein said electrodes (60) are formed in a material comprising a shape memory alloy.

5. An electroporation device (1) according to any of claims 1-4 wherein the distal tip (13) is formed with a substantially smooth, rounded, non-cutting shape with a substantially smooth, non-cutting transition to the introducer shaft (10).

6. An electroporation device (1) according to any of claims 1-5 wherein the distal tip (13) is detachable from said introducer shaft (10).

7. An electroporation device (1) according to any of claims 1-6, wherein each of said electrodes (60) can be advanced individually or in sets to their extended positions.

8. An electroporation device (1) according to any of claims 1-7, wherein said electrodes (60) are extendable such that their distal ends (61) form a spatial distribution around a volume of target tissue.

9. An electroporation device (1) according to claim 8, wherein said electrodes (60) are extendable such that their distal ends (61) form a substantially spherical distribution pattern.

10. An electroporation device (1) according to claim 8, wherein a subset of said electrodes (60) are extendable, such that their distal ends (61) form an ellipsoid pattern (E) in a plane parallel to said longitudinal axis (L) when extended.

11. An electroporation device (1) according to any of claims 1-10, wherein said electrodes (60) are slideably arranged in electrically insulated guide channels (50).

12. An electroporation device (1) according to any of claims 1-10, wherein said electrodes (60) are provided with an electric insulation coating, the distal-most part of the electrode (60) distal ends (61) being un-insulated to form point electrodes.

13. An electroporation device (1) according to any of claims 1-12, wherein said introducer shaft (10) further comprises a delivery channel (20) through which a dose of therapeutical molecules can be administered, said delivery channel (20) extending through the length of said shaft (10) and terminating through said distal tip (13).

14. An electroporation device (1) according to claim 13, wherein said delivery channel (20) is connectable to an external therapeutic molecule delivery system (115) comprising a therapeutic molecule reservoir and pumping means for administering said therapeutic molecules through said delivery channel (20).

15. An electroporation device (1) according to claim 13, wherein the handle part (100) comprises a therapeutic molecule delivery system comprising a therapeutic molecule reservoir and actuating means for administering said therapeutic molecules through said delivery channel (20).

16. An electroporation device (1) according to any of claims 14-15, wherein said device (1) is further adapted to for introducing a surgical tool or an ultrasound probe through said delivery channel (20).

17. An electroporation device (1) according to any of the previous claims, wherein said introducer shaft (10) has a circular cross section with an outer diameter (D2) of 15 mm or less, preferably of 10 mm or less, more preferably of 5 mm or less.

18. An electroporation device (1) according to any of the previous claims, wherein the introducer shaft (10) comprises an outer tube (15) and an inner electrode assembly guide (16) received in said outer tube (15), and where said electrodes (60) are slideably arranged in electrode guide channels (50) formed in said inner electrode assembly guide (16).

19. An electroporation device (1) according to claim 18, wherein said electrode guide channels (50) are formed in a set of cylindrical guide sheaths (30) that are received in longitudinal semi-open channels (17) distributed radially along the periphery of said inner electrode assembly guide (16).

20. An electroporation device (1) according to any of the previous claims comprising 32 electrodes (60).

21. An electroporation device (1) according to claim 20, wherein said electrodes (60) are slideably arranged within guide channels (50) distributed in groups of four in each of eight

cylindrical guide sheaths (30).

22. An electroporation device (1) according to any of the previous claims, wherein an electric stimulus generator is integrated into the handle section (100) of the device (1).

23. An electroporation device (1) according to any of the claims 1-21, having means for attaching the device (1) electrodes (60) to an external electric stimulus generator.

24. An electroporation device (1) according to claim 22 or 23, wherein each electrode (60) is individually assignable, such that the emission of electric stimuli can be provided from individual electrodes (60).

25. An electroporation method comprising the steps of

- providing an electroporation device (1) comprising
  - an elongate introducer shaft (10) having a distal tip (13); and
  - a set of electrodes (60) having respective distal ends (61), each electrode (60) being slidably arranged within said introducer shaft (10) from a retracted position, where said distal ends (61) are enclosed within said introducer shaft (10), to an extended position, where said distal ends (61) extend from said distal tip (13);
- inserting said introducer shaft (10) through tissues of a body and bring said distal tip (13) into a vicinity of a target region to be treated, while said electrodes (60) are in said retracted position;
- extending said electrodes (60) to said extended position, such that said electrode distal ends (61) are deflected away from a longitudinal axis (L) of said shaft (10) in such a way that at least one planar projection taken in a plane perpendicular to said longitudinal axis (L) of a distance between a pair of distal ends (61) of said electrodes (60) is larger than a maximal extent of a cross-section of said introducer shaft (10), said cross-section taken in a plane perpendicular to said a longitudinal axis (L) at a distal end (11) of said introducer shaft (10); and

- applying through said electrodes (60) one or more electric pulses to the target region tissue to create a permeabilization of cell membranes of tissue in said target region.

26. An electroporation method according to claim 25, wherein each of said electrodes (60) are extended such that their distal ends (61) form a spatial distribution at least partly around a volume of target tissue.

27. An electroporation method according to claim 25 or 26, wherein said electrodes (60) are extended individually or in sets to their extended positions to a spatial configuration of the distal (61) at least partially surrounding a target tissue.

28. An electroporation method according to any of claims 25-27, wherein said electrodes (60) are extended such that their distal ends (61) form a substantially spherical distribution pattern.

29. An electroporation device (1) according to any of claims 25-27, wherein a subset of said electrodes (60) are extendable, such that their distal ends (61) form an ellipsoid pattern (E) in a plane parallel to a longitudinal axis (L) of the shaft (10) when extended.

30. An electroporation method according to any of claims 25-29, comprising a step of administering a dose of therapeutic molecules to said body prior to, while or after applying through said electrodes (60) one or more electric pulses to create a transient permeabilization of cell membranes of tissue in said target region.

31. An electroporation method according to any of claims 25-30, wherein said dose of therapeutic molecules is administered systemically.

32. An electroporation method according to any of claims 25-30, wherein said dose is administered locally in the vicinity of the target region.

33. An electroporation method according to claim 32, wherein said dose is delivered before, during or after extending said electrodes (60), through a delivery channel (20) extending through the length of said shaft (10) and terminating through said distal tip (13).

34. A method of generating an electric field in a target region of a patient, comprising the steps of

- inserting into the vicinity of the target region a set of electrodes (60), having respective distal ends (61), enclosed within a single elongate introducer shaft (10) having a distal tip (13);
- extending at least a pair of said electrodes (60) to an extended position, such that said electrode distal ends (61) are deflected away from a longitudinal axis (L) of said shaft (10) in such a way that at least one planar projection taken in a plane perpendicular to said longitudinal axis (L) of a distance between a pair of distal ends (61) of said electrodes (60) is larger than a maximal extent of a cross-section of said introducer shaft (10), said cross-section taken in a plane perpendicular to said a longitudinal axis (L) at a distal end (11) of said introducer shaft (10); and
- applying through said electrodes (60) one or more electric pulses to the target tissue.

35. A method of generating an electric field in a target tissue of a patient, comprising the steps of

- inserting into the vicinity of a target tissue a set of point electrodes (60), having respective electrically conductive distal ends (61), and positioning said electrode distal ends (61) in a spatial formation surrounding or enclosing at least partly said target tissue;
- applying through said point electrodes (60) one or more electric pulses to the target tissue.

36. A method according to claim 35, wherein the point electrodes are positioned such that when a sequence of electric pulses is applied through said electrodes an ellipsoid or spatially ellipsoid electric field is generated in the tissue.

37. A method according to claim 36, wherein said ellipsoid or spatial ellipsoid field is generated by positioning said point electrodes in an ellipsoid or spatially ellipsoid configuration at least partly surrounding or enclosing said target tissue.

38. A method according to claim 36 or 37, wherein said point electrode distal ends (61) are positioned in substantially circular parallel layers and where the position of the point electrodes in a section perpendicular to said circular layers defines an ellipsoid configuration.

39. A method according to claim 38, wherein the electric field is generated in the tissue by applying a sequence of electric pulses between at least sixteen point electrodes (61) in at least four essentially parallel, consecutive layers a, b, c, d, comprising at least four point electrodes (61) in each layer a, b, c, d, and wherein said sequence comprises the steps of generating at least some pulses travelling from a first positive layer a of point electrodes to a first negative layer of point electrodes c placed in equidistant relation to the electrodes in the first layer a, while other pulses simultaneously travel from a second positive layer b to a second negative layer of point electrodes d, respectively.

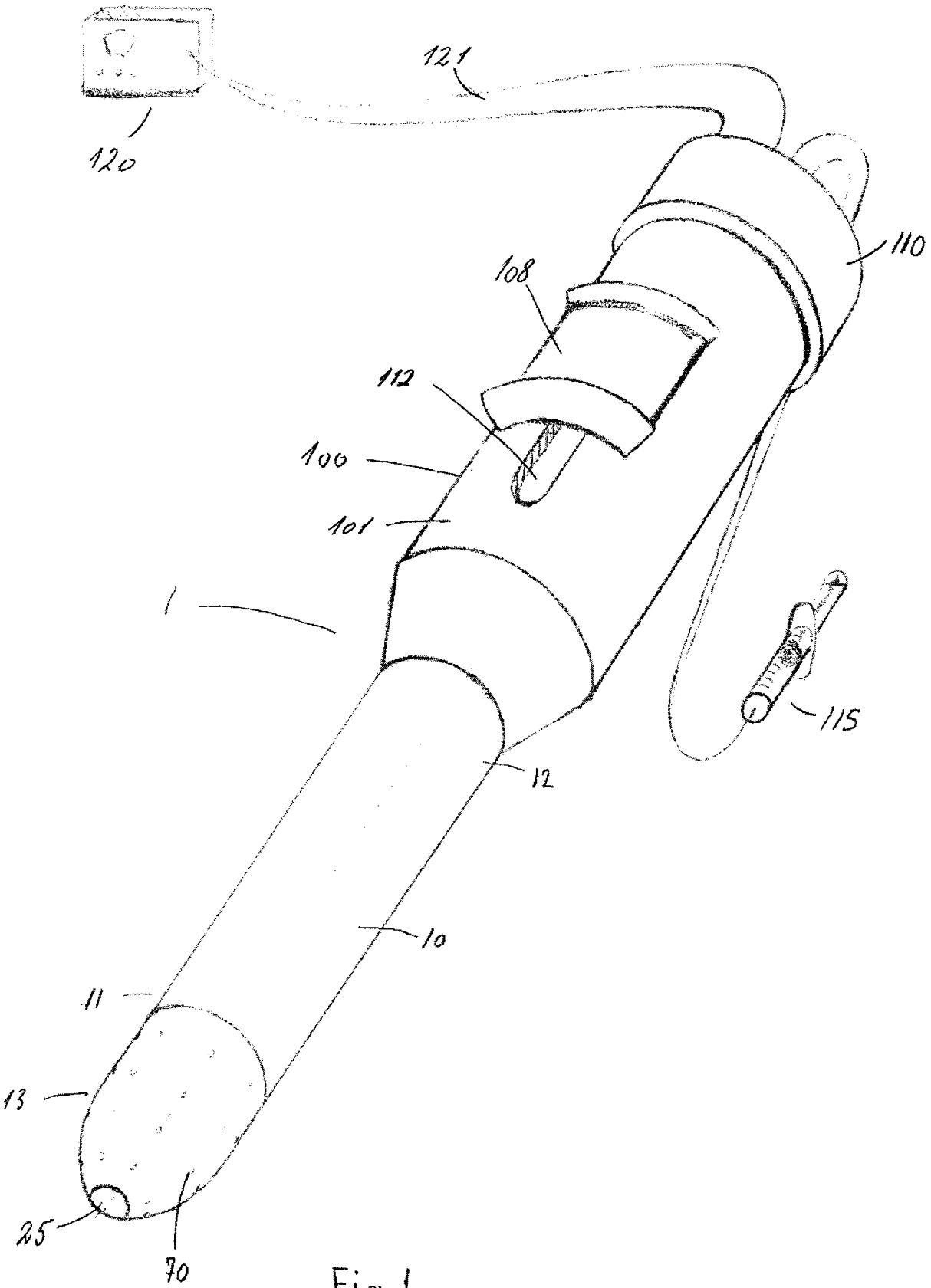


Fig. 1

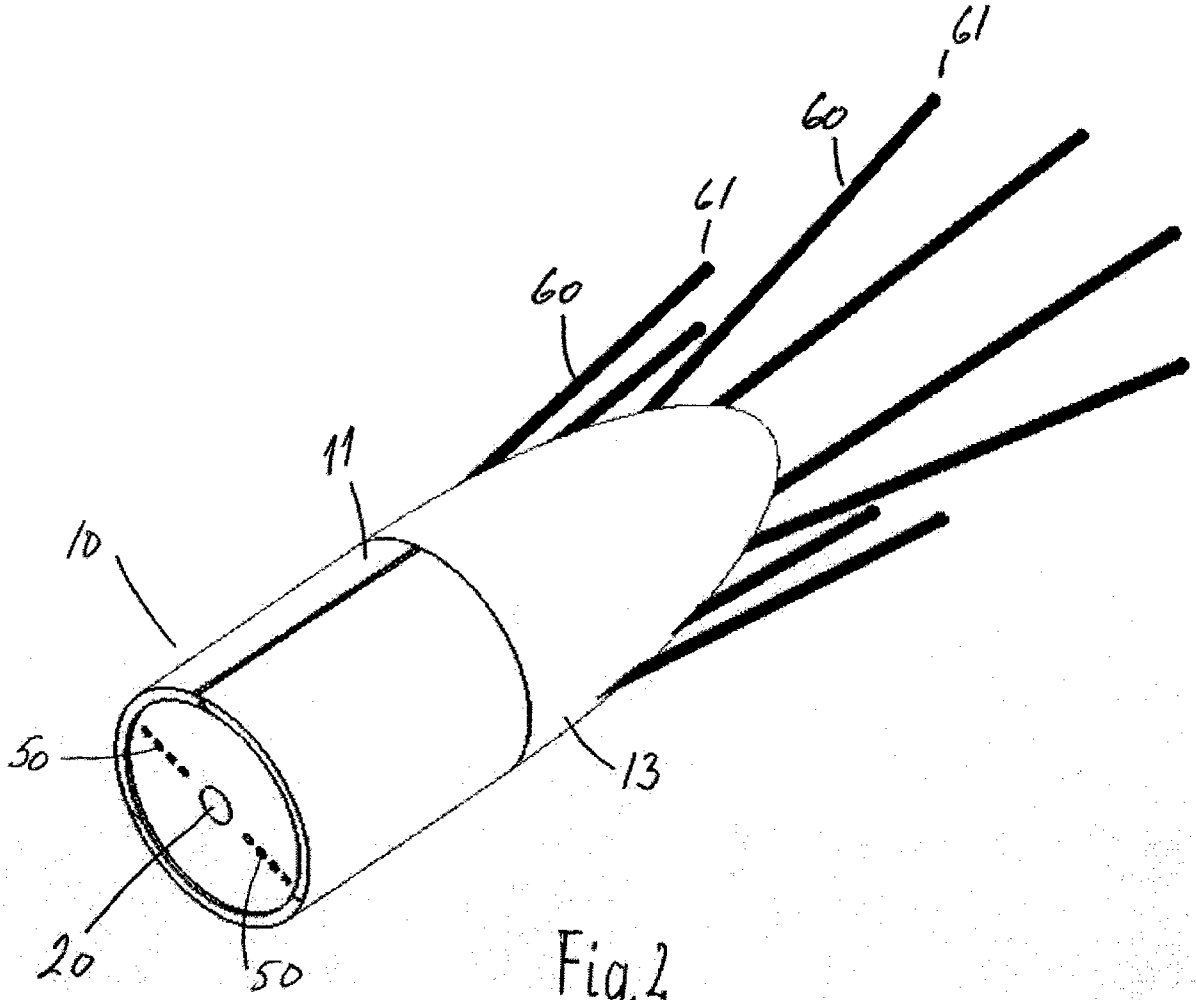


Fig. 2

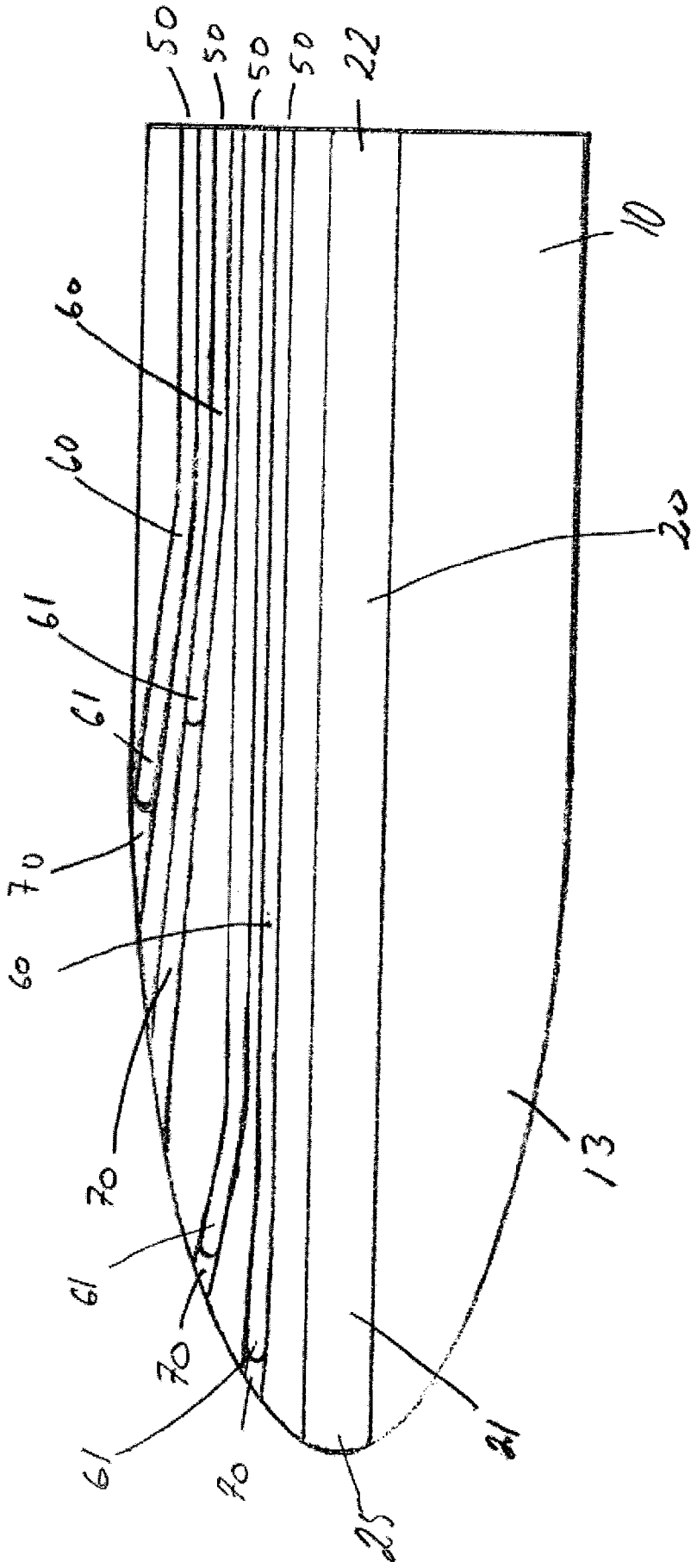


Fig. 3

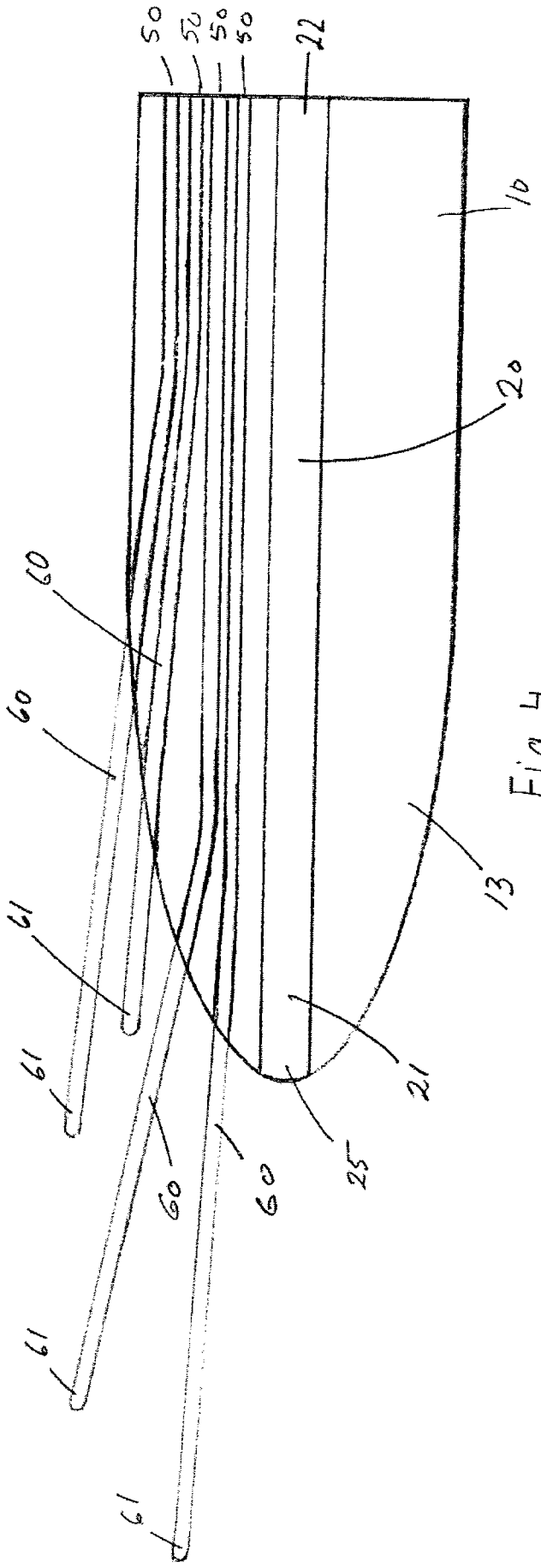


Fig. 4

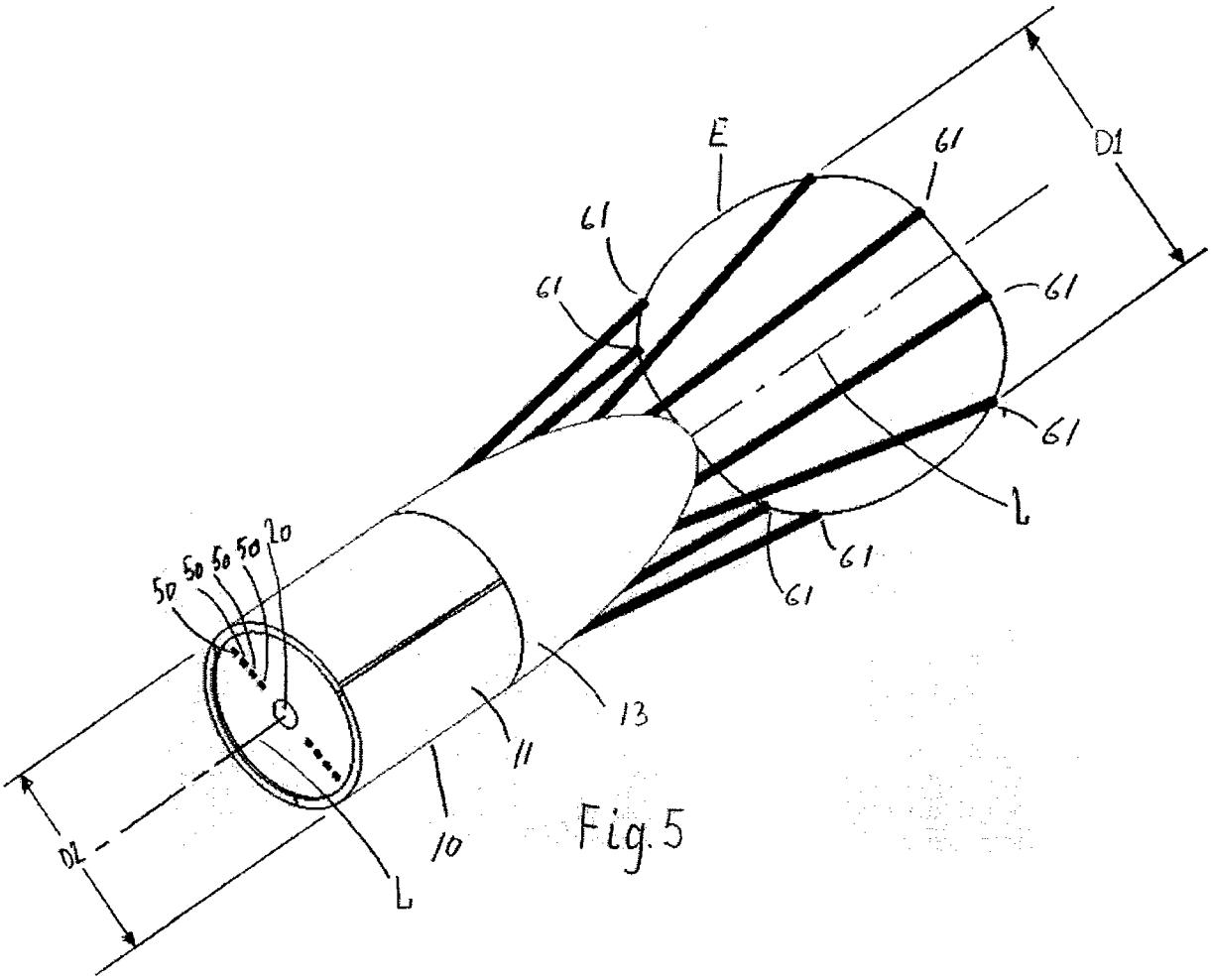


Fig. 5

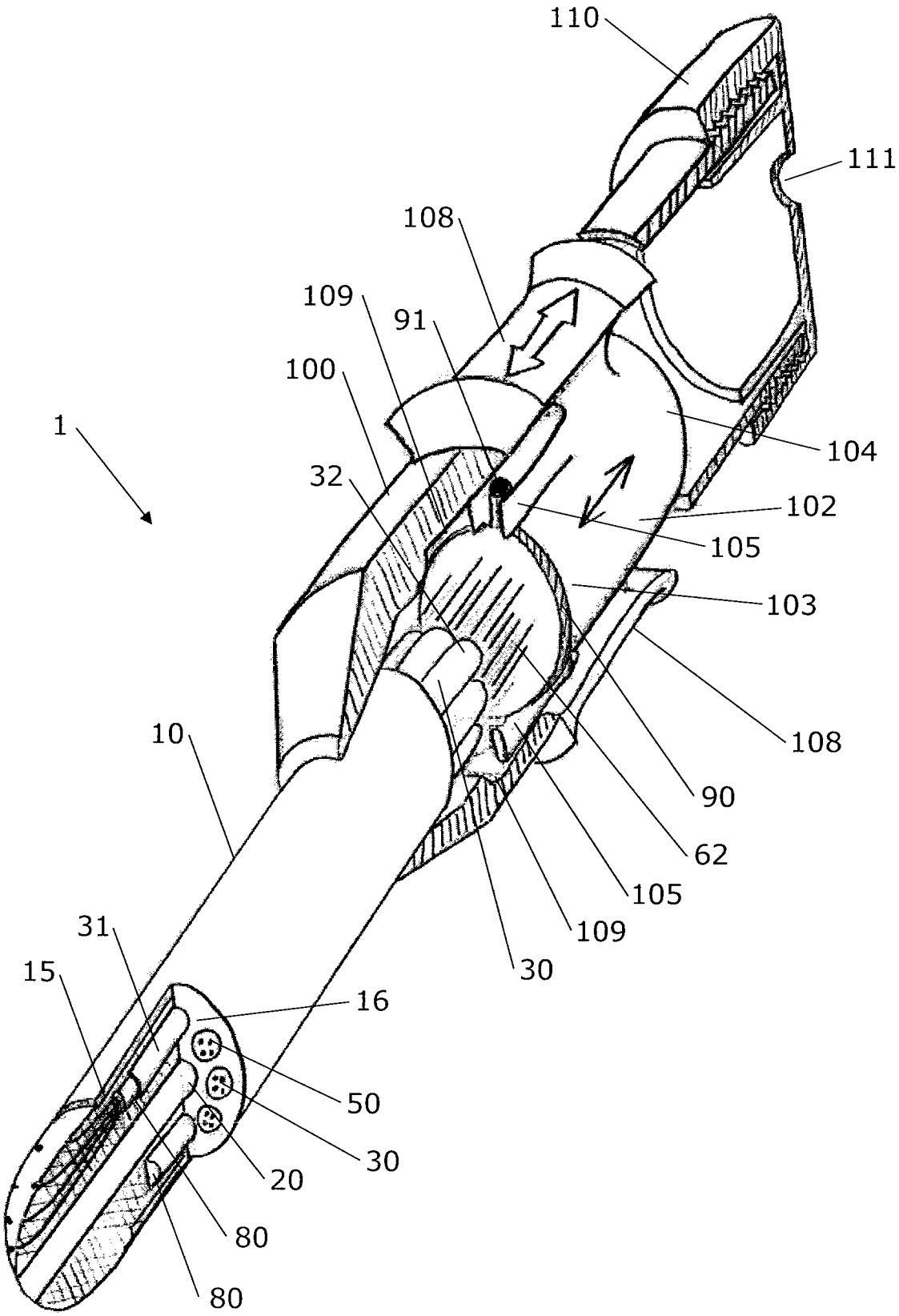

110
111
108
109
91
100
1
104
32
102
105
103
108
10
90
62
105
109
30
31
15
16
50
30
20
80
80

Fig. 6

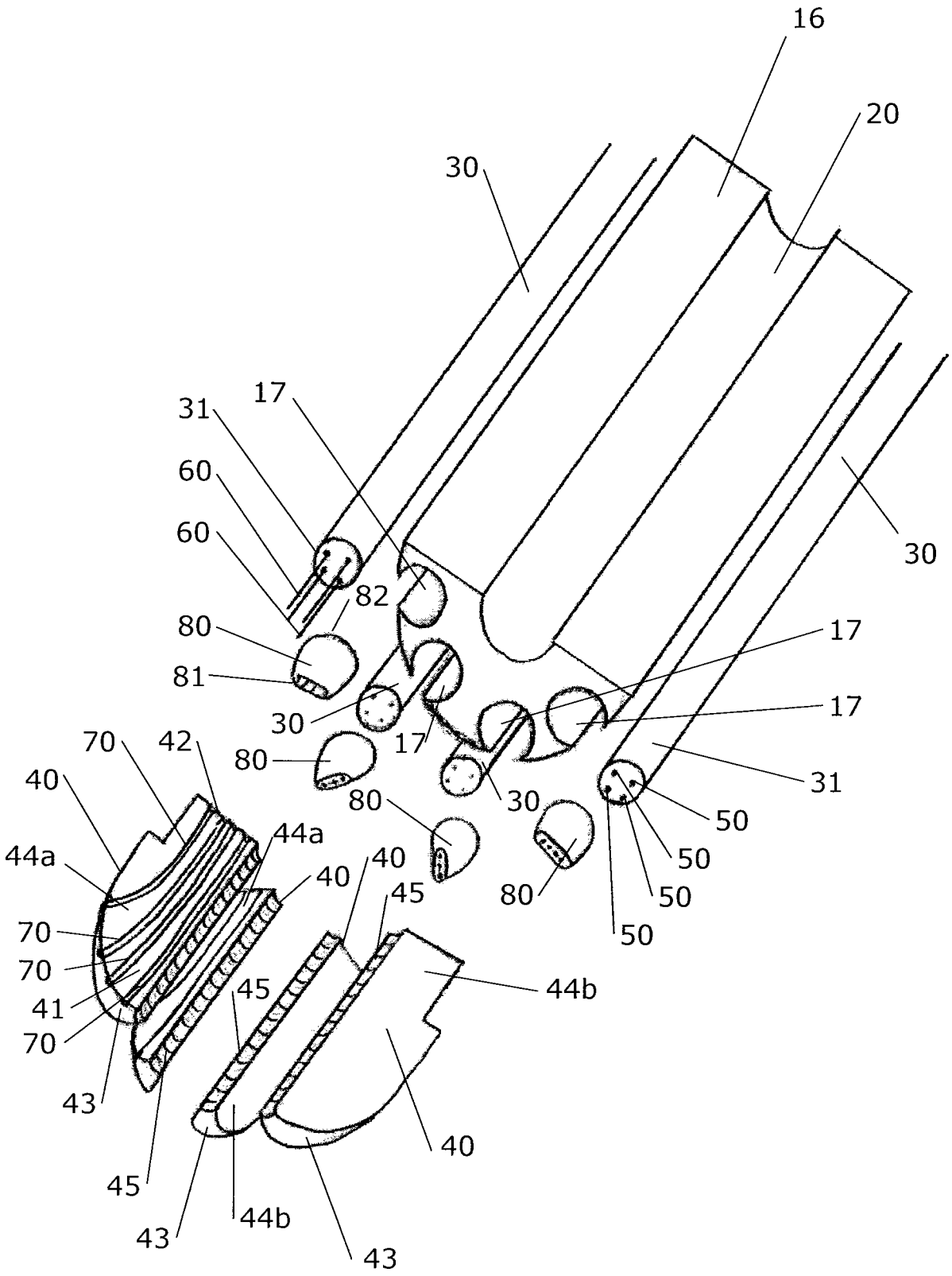

16
20
30
17
31
60
60
82
80
81
30
17
17
70
42
80
40
80
30
31
50
44a
44a
40
40
45
50
50
50
70
70
41
70
45
44b
43
45
40
43
44b
43

Fig. 7

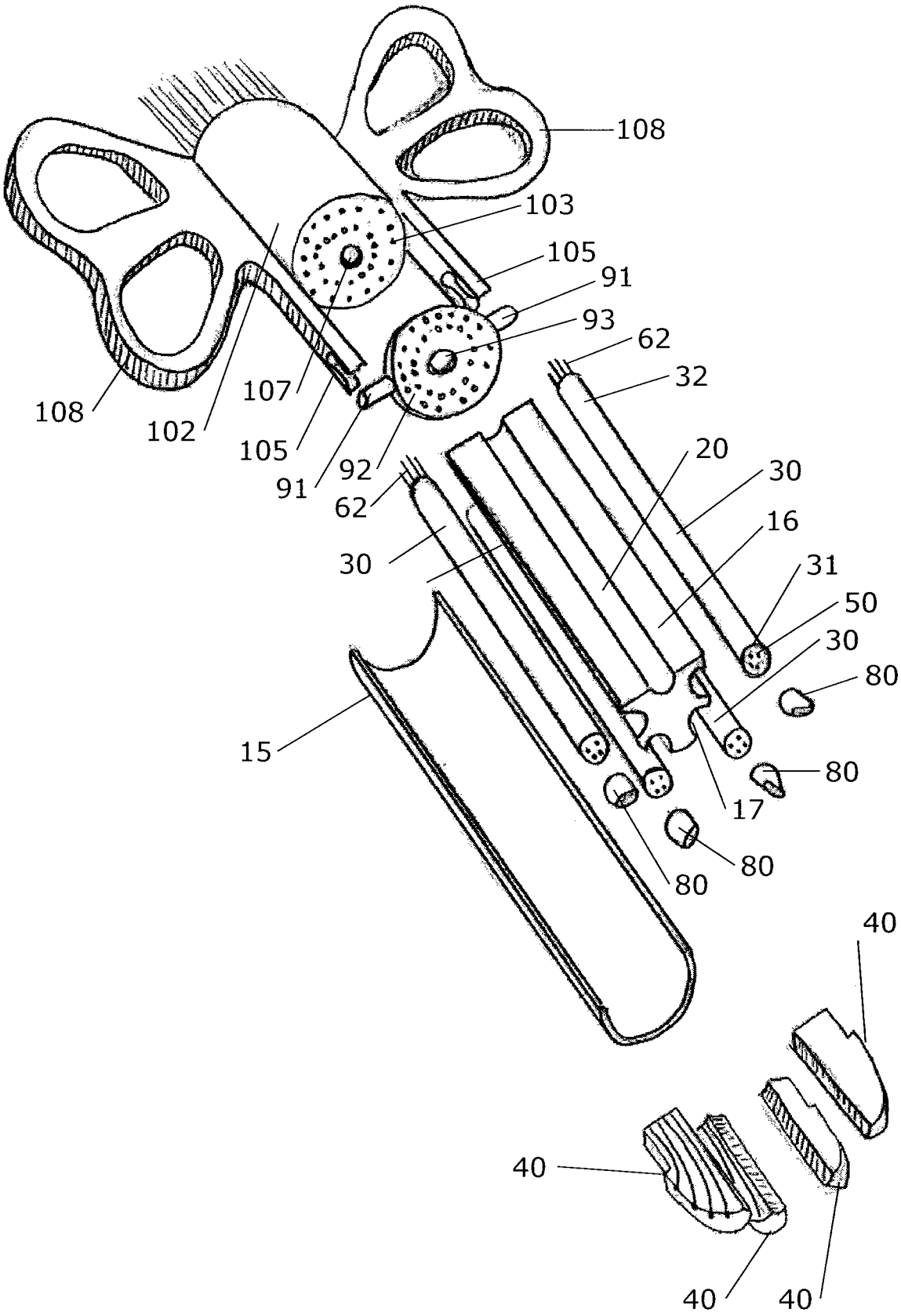

108
103
105
91
93
62
32
107
108
102
105
91
92
62
20
30
16
30
31
50
30
80
15
80
17
80
80
40
40
40
40

Fig. 8

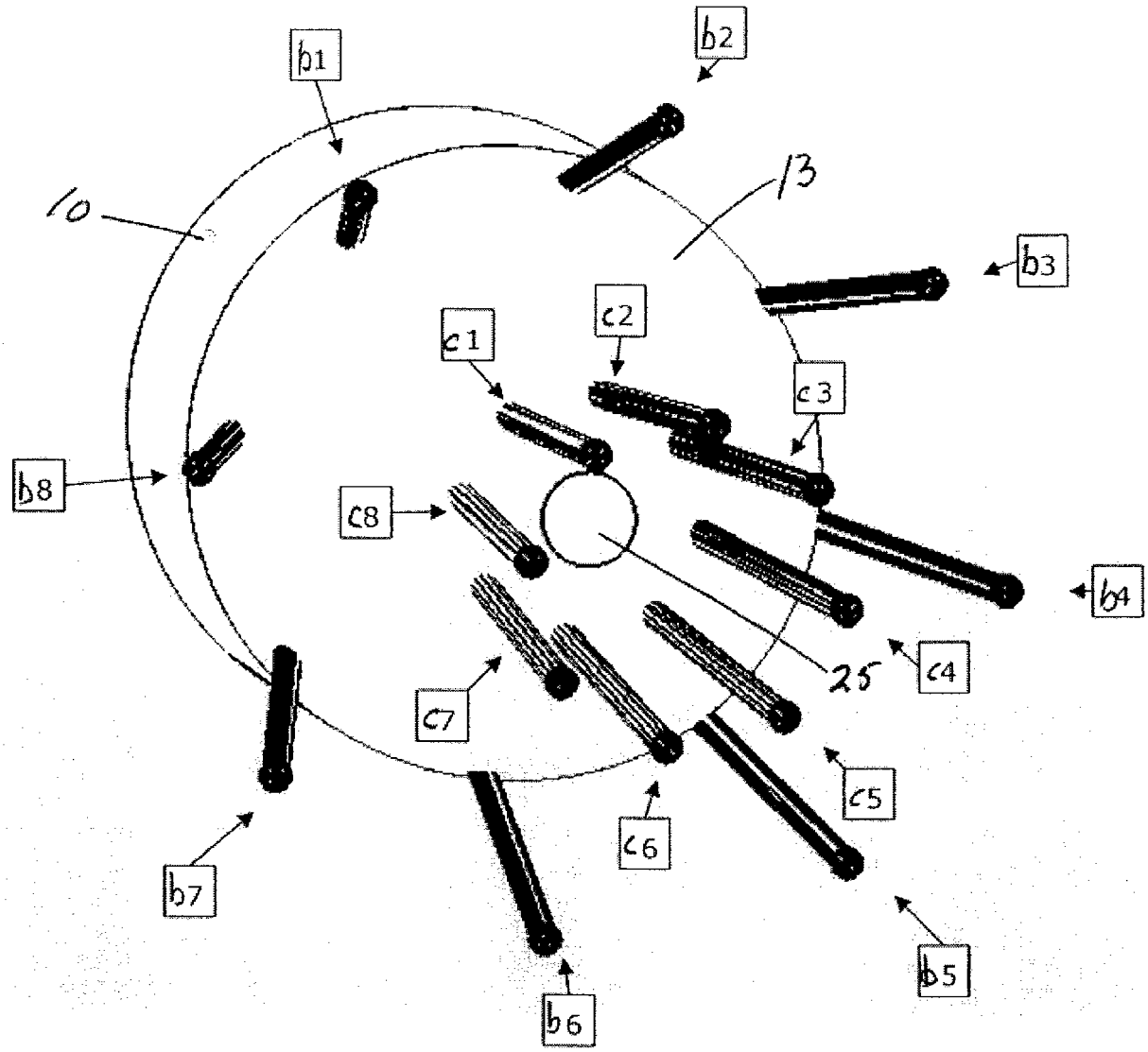


Fig. 9

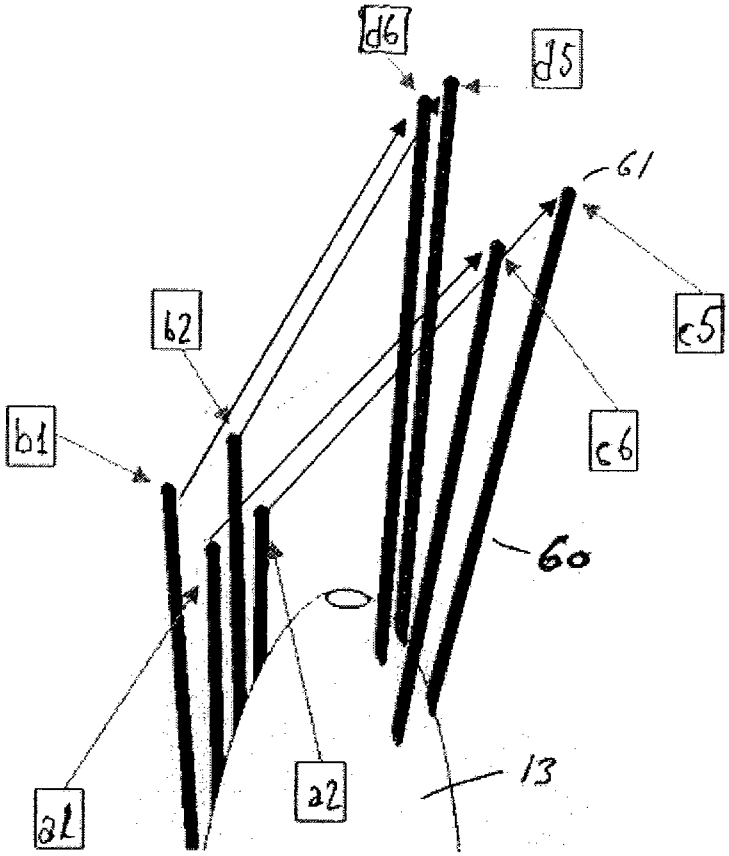


Fig. 10

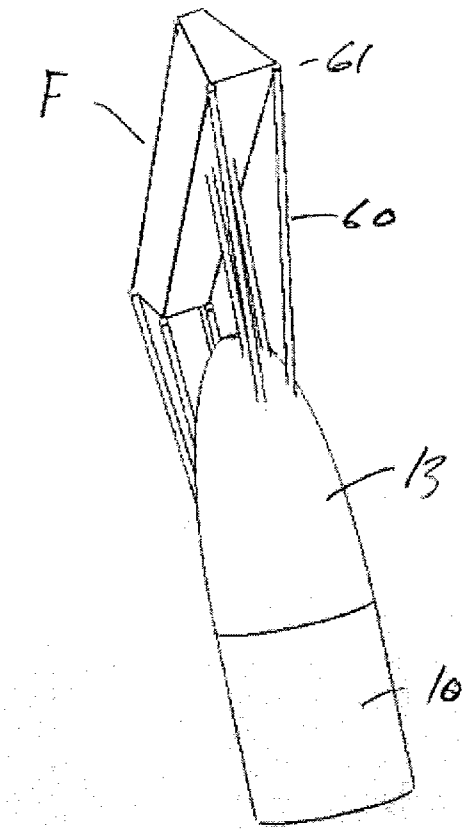


Fig 11

INTERNATIONAL SEARCH REPORT

International application No
PCT/DK2007/050069

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B18/14

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 practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/059328 A1 (DANIEL STEVEN A [US] ET AL) 25 March 2004 (2004-03-25) paragraphs [0073], [0075] - [0078], [0086], [0105], [0107], [0109], [0152], [0173], [0178], [0181]; figures 10,12A,28	1-24
X	US 2003/212394 A1 (PEARSON ROB [US] ET AL) 13 November 2003 (2003-11-13) the whole document	1-24

☐ 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 document but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 September 2007	21/09/2007

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK2007/050069

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

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

1. [X] Claims Nos.: 25-39
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

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

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

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

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

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

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

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

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

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/DK2007/050069

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004059328 A1	25-03-2004	CA 2434151 A1	18-07-2002
		EP 1363700 A2	26-11-2003
		JP 2004523272 T	05-08-2004
		WO 02054941 A2	18-07-2002
		US 2002133148 A1	19-09-2002
US 2003212394 A1	13-11-2003	US 2007112342 A1	17-05-2007