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(54) **ADAPTIVE, MULTI-INJECTION PORT, DOUBLE BALLOON CATHETER FOR ORGAN-BASED LOCAL DELIVERY OF GENE THERAPY**

(71) Applicant: **Wisconsin Alumni Research Foundation**, Madison, WI (US)

(72) Inventors: **John Booske**, McFarland, WI (US); **Paul Laeseke**, Madison, WI (US); **Susan Hagness**, Madison, WI (US)

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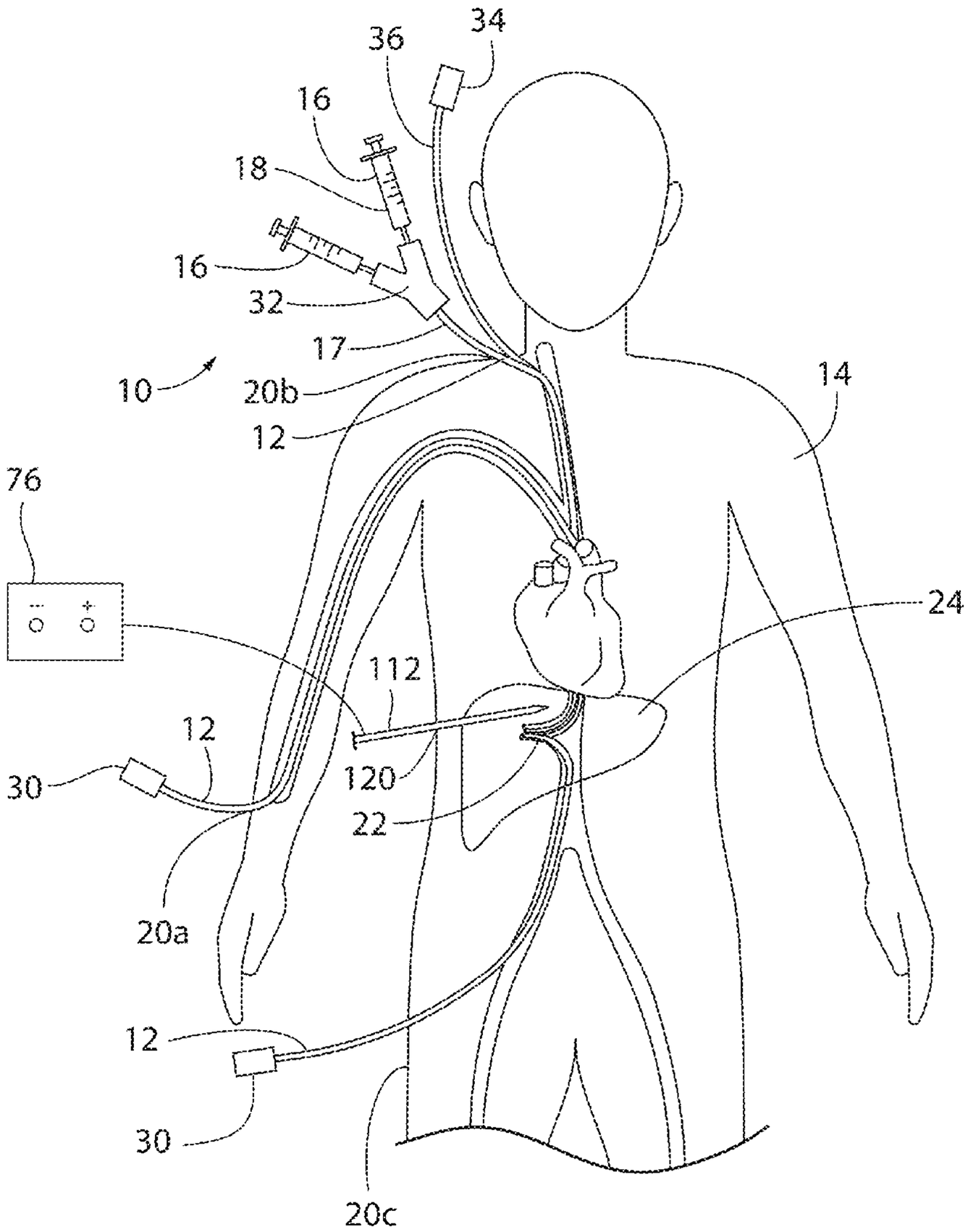
(57) **ABSTRACT**

A "localizable" systemic gene therapy system is provided substantially increasing the transfection efficiency of the gene vectors into targeted tissue cells and substantially reducing the escape of the gene vectors from the targeted tissue volume, such as would waste the vectors, promote undesired immune reactions, and/or incur prohibitive costs for the required dose of gene-containing virus vectors. In this regard, the invention provides a means to simultaneously achieve local cell membrane permeability for virus vector transport and gene-containing vector injection in a portion of a vascularized organ. It includes a double-balloon catheter that create a finite contained volume in a blood vessel for the introduction of vectors with reduced loss along with a percutaneously inserted needle electrode providing increased cell membrane permeability for virus vector transport of the cells by creating an electric field in the same location where the vectors are injected.



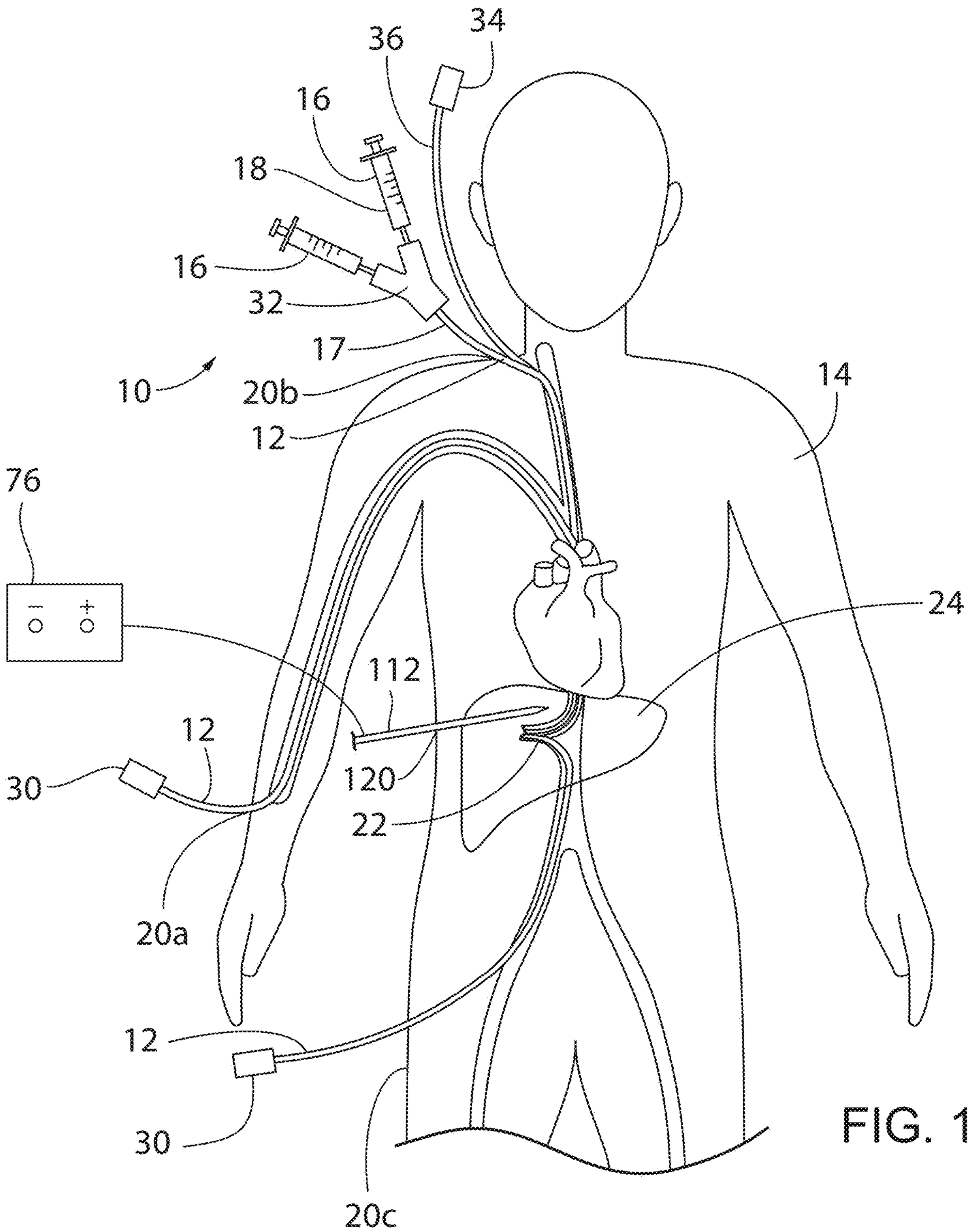


FIG. 1

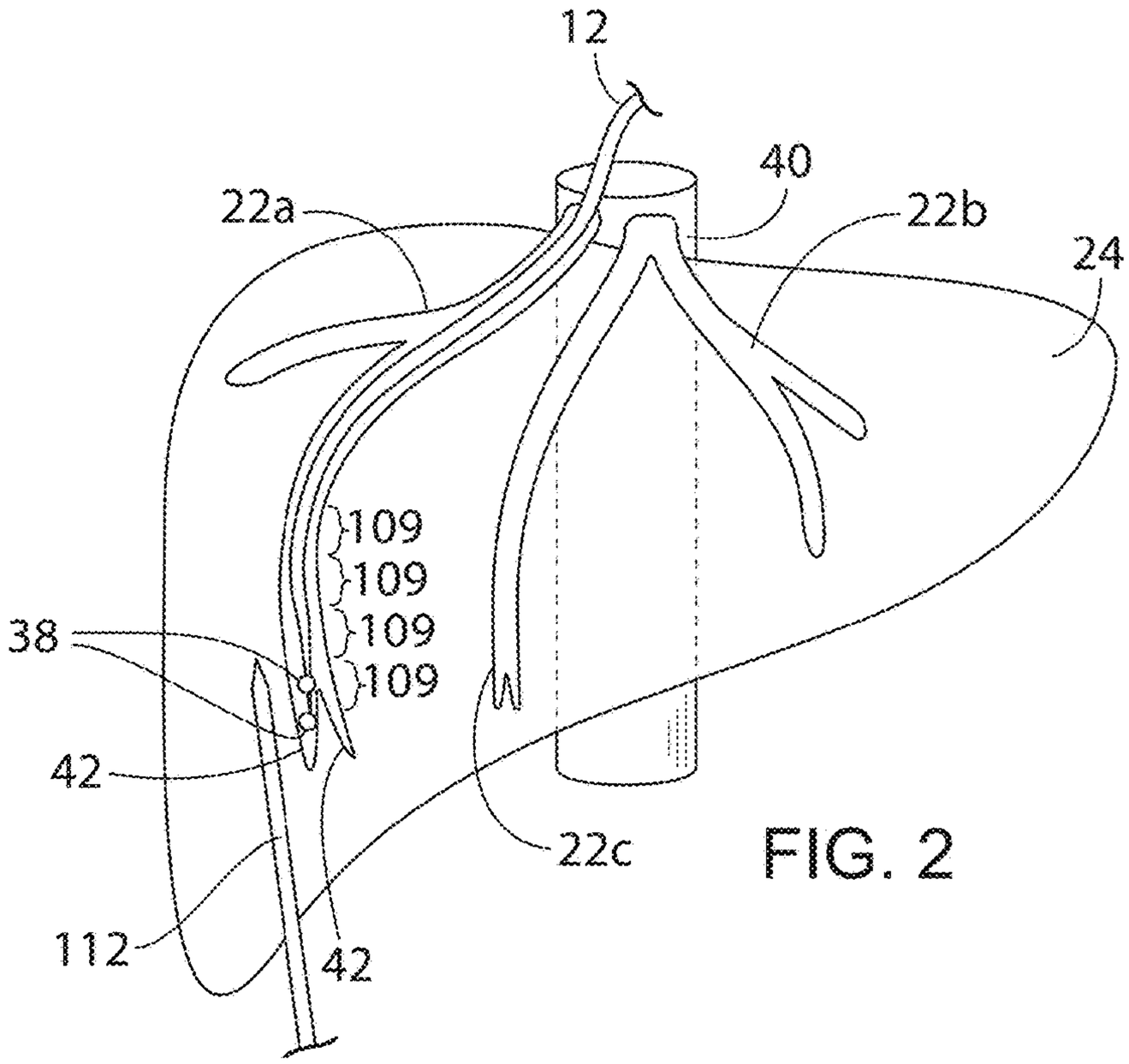

12
40
22a
22b
24
109
109
109
109
38
42
22c
112
42

FIG. 2

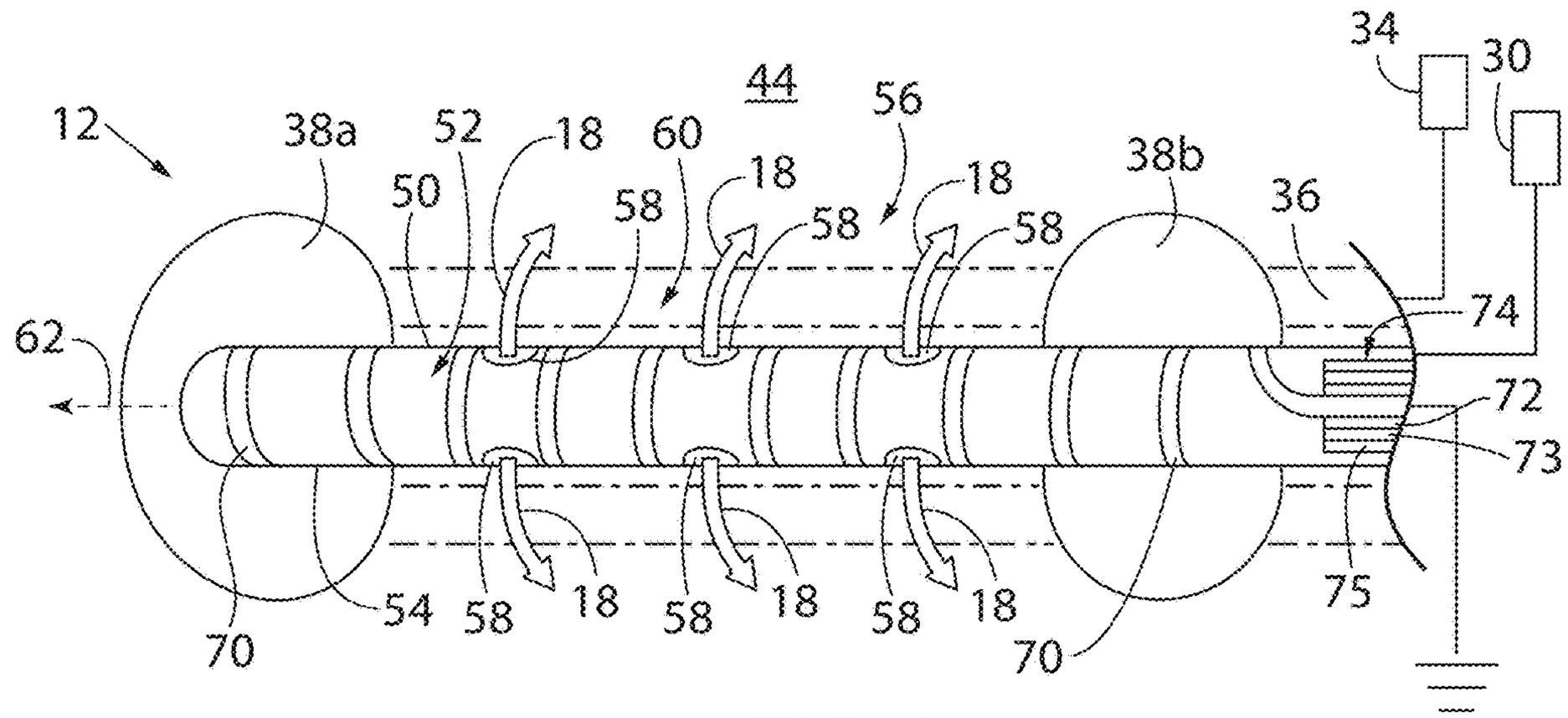

34
30
44
56
12
38a
52
18
60
18
18
38b
36
50
58
58
58
74
62
72
73
54
58
18
58
18
58
18
75
70
70

FIG. 3

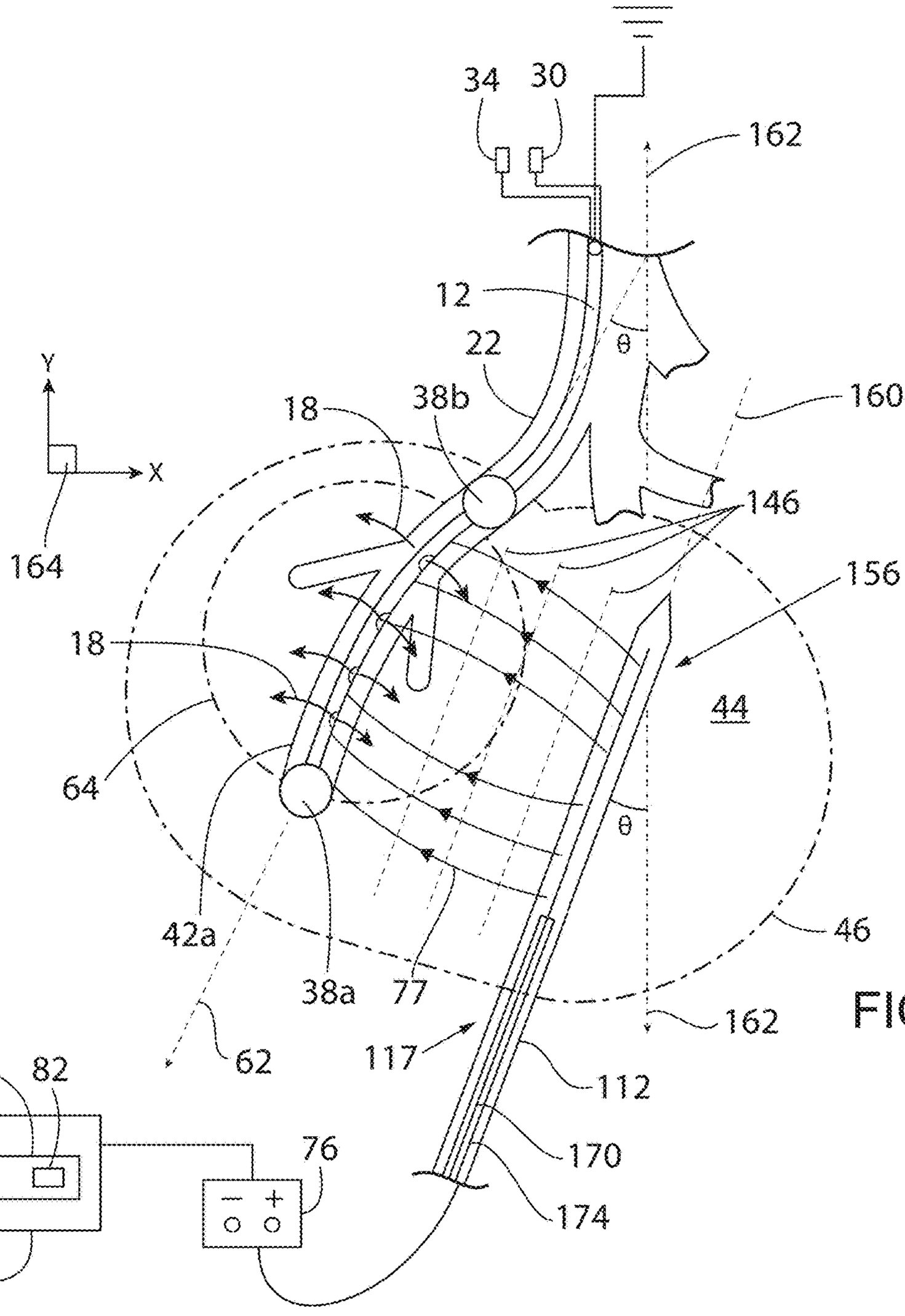

34
30
162
12
22
θ
Y
X
38b
18
160
164
146
156
18
44
64
θ
42a
38a
77
46
162
62
117
112
84
82
78
76
170
174
80

FIG. 4

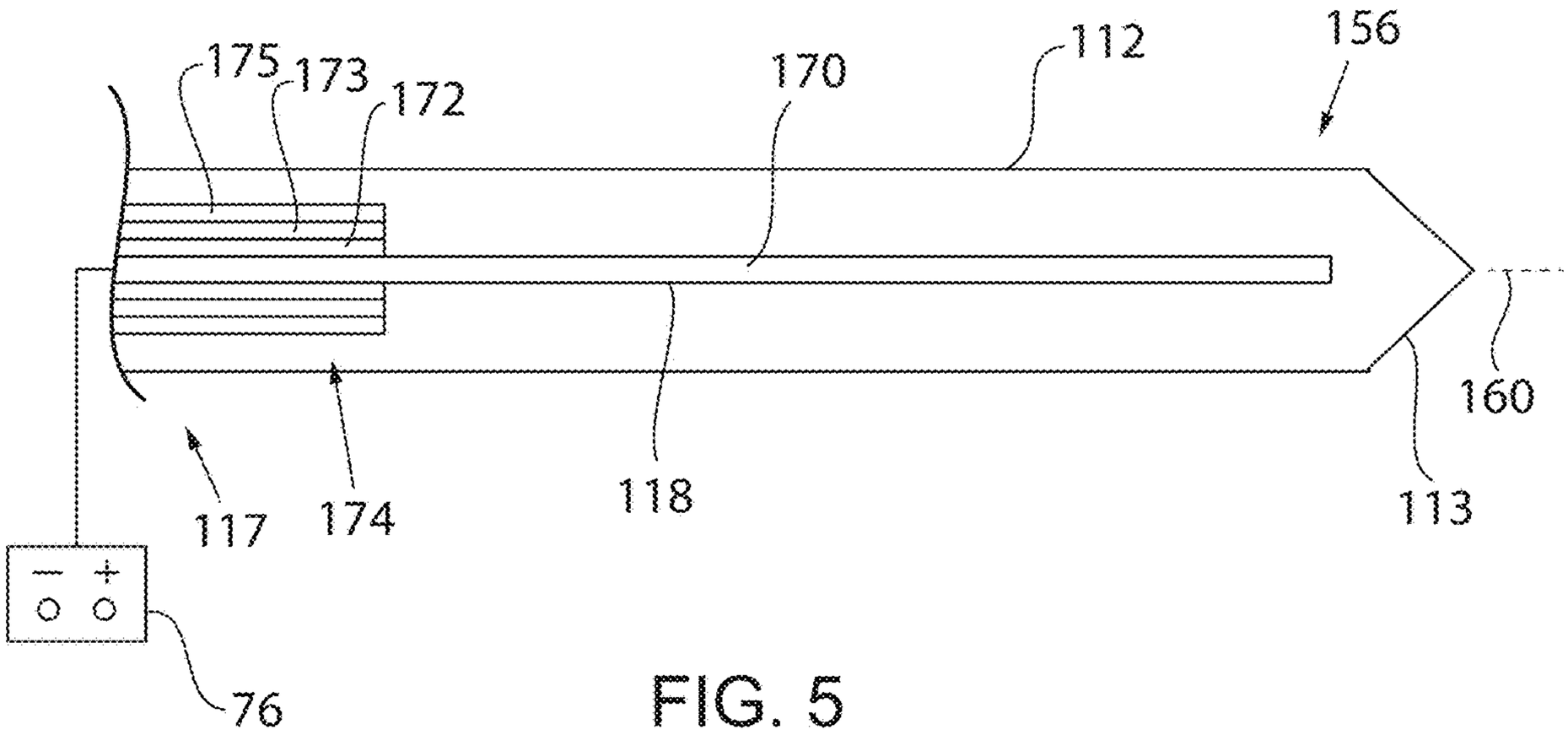


FIG. 5

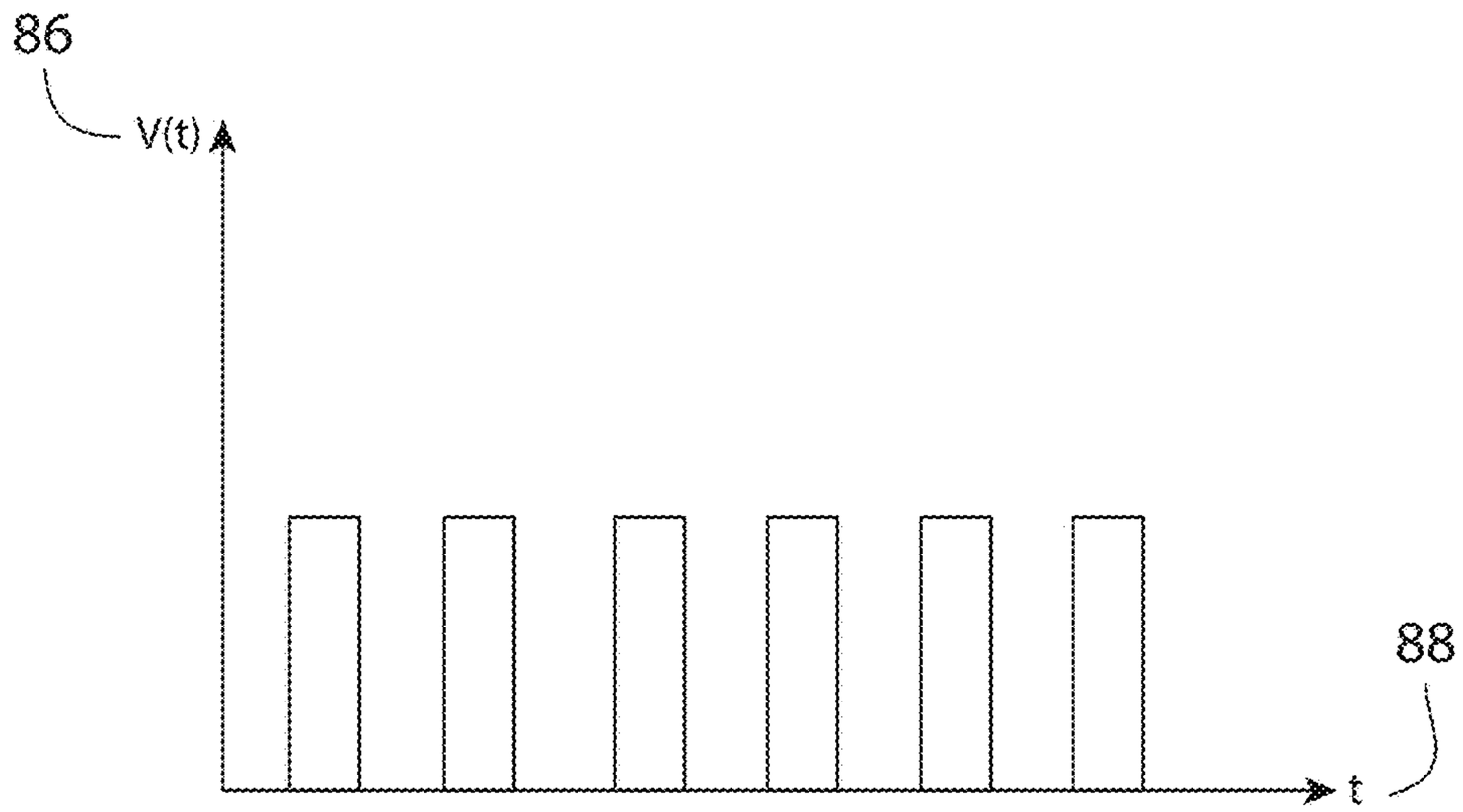


FIG. 6

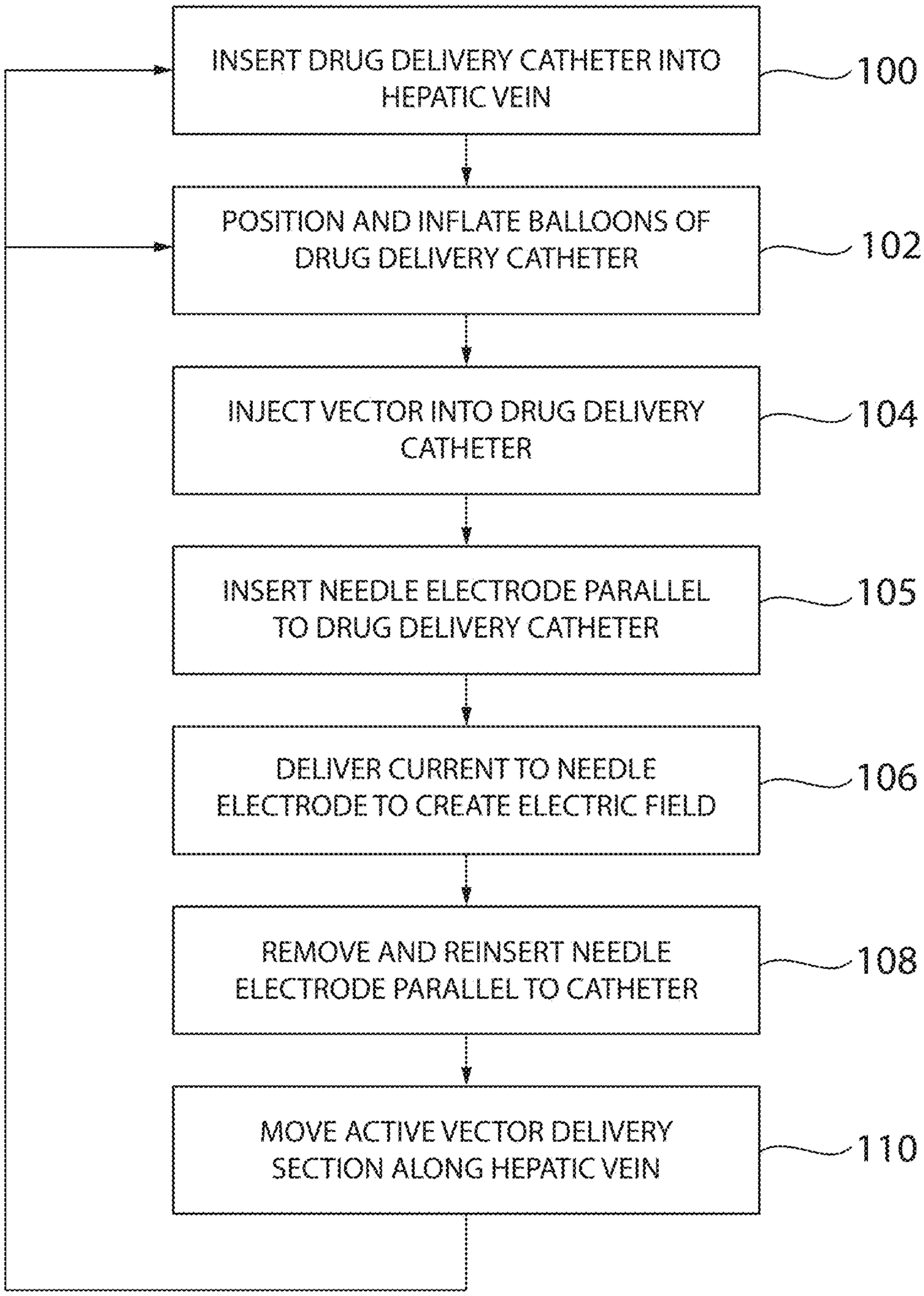

INSERT DRUG DELIVERY CATHETER INTO HEPATIC VEIN
100
POSITION AND INFLATE BALLOONS OF DRUG DELIVERY CATHETER
102
INJECT VECTOR INTO DRUG DELIVERY CATHETER
104
INSERT NEEDLE ELECTRODE PARALLEL TO DRUG DELIVERY CATHETER
105
DELIVER CURRENT TO NEEDLE ELECTRODE TO CREATE ELECTRIC FIELD
106
REMOVE AND REINSERT NEEDLE ELECTRODE PARALLEL TO CATHETER
108
MOVE ACTIVE VECTOR DELIVERY SECTION ALONG HEPATIC VEIN
110

FIG. 7

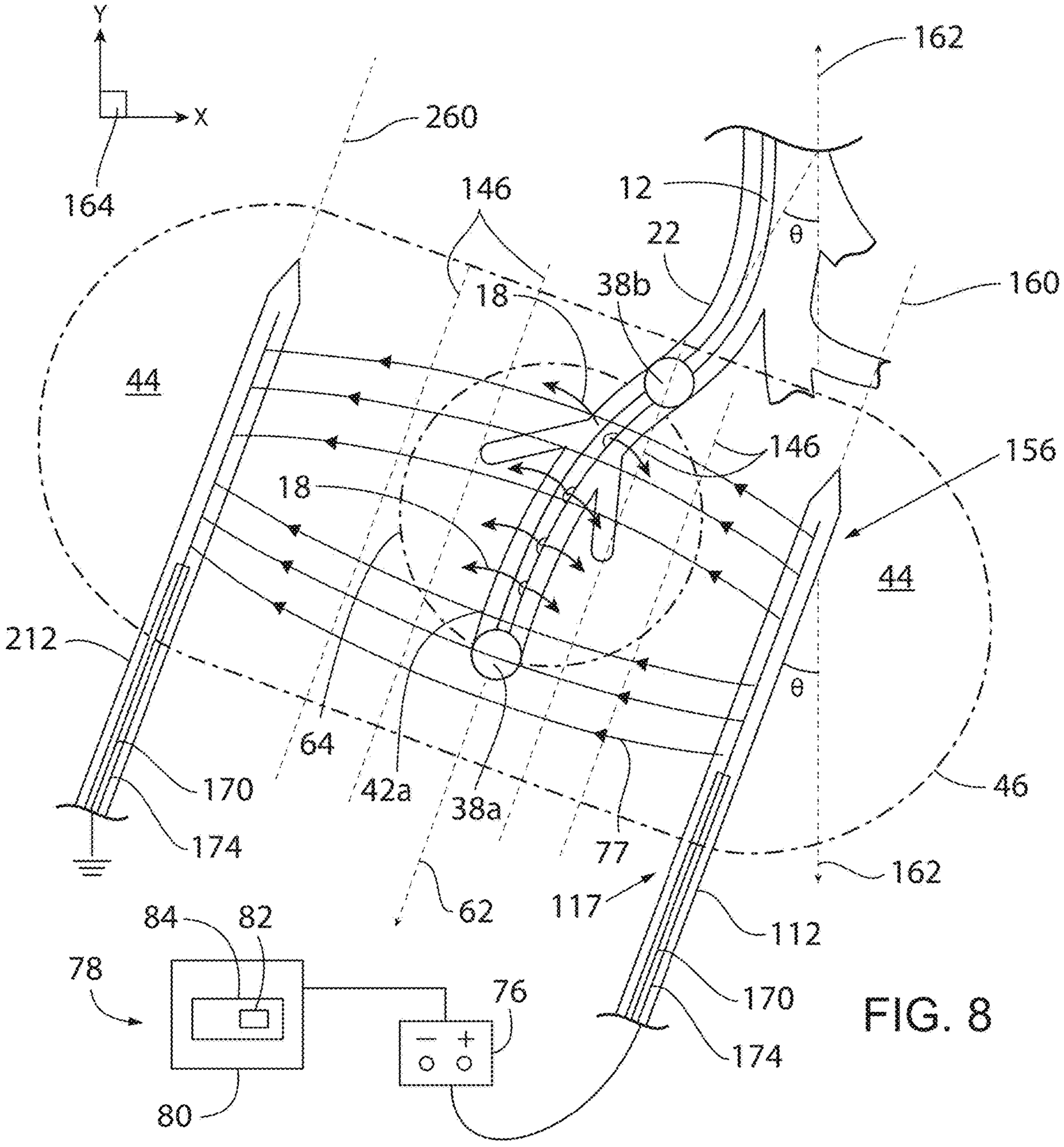

Y
X
164
260
146
12
22
38b
18
θ
162
160
44
146
156
18
212
64
170
42a
38a
77
174
θ
46
162
84
82
62
117
112
78
76
170
80
174

FIG. 8

ADAPTIVE, MULTI-INJECTION PORT, DOUBLE BALLOON CATHETER FOR ORGAN-BASED LOCAL DELIVERY OF GENE THERAPY

CROSS REFERENCE TO RELATED APPLICATION

Background of the Invention

[0001] The present invention relates to a method and apparatus for drug or gene therapy, and more particularly, an improved drug or gene therapy delivery system using electrical stimulation to enhance uptake into cells.

[0002] Genetic mutation based metabolic diseases significantly reduce quality of life for hundreds of millions of people in the world and account for 70% of child hospitalizations and 10% of adult hospitalizations. There are hundreds of such diseases, including diabetes, cystic fibrosis, sickle cell anemia, hemophilia, and thalassemia. Many of them involve the liver due to its central role in metabolism.

[0003] Gene therapy is a promising treatment strategy for these diseases, potentially curing them by inserting functional genes (i.e., a functional portion of a DNA sequence) into a portion of cells within the target organ, for example, liver cells, thus correcting the inherited metabolic discrepancy. Only a small fraction of liver cells (hepatocytes) need to be converted, for example, about 5% in the liver, in order to produce therapeutic gene products sufficient to cure Type 1 diabetes. Gene therapy is also being actively investigated for curing diseases involving vascularized tissue mass bodies, e.g., cancer tumors.

[0004] A carrier, or vector, of genes or gene fragments, such as a virus capsid, can be used to deliver foreign, functional genes into cells. By transferring the functional gene into a virus that either enters the cell membrane through endocytosis (viruses without a lipid envelope) or binds to receptors on the cell membrane and fuses with the cell membrane thus releasing the genetic material (viruses with a lipid envelope), genes can be introduced into the cell. Depending on the virus used to deliver the gene, the viral genetic material either integrates into a chromosome of the cell or persists episomally without integration within the nucleus of the cell and expresses the introduced gene to treat the genetic defect.

[0005] Systemic gene therapy, which delivers functional genes via the circulatory system, has been found to be a successful delivery method for functional genes in small mammals (smaller than an average dog). However, this treatment has not been found to be scalable to large mammals for three reasons:

[0006] First, inefficient transduction of target cells necessitates large, cost-prohibitive gene vector doses. The larger size of the animal and more extensive blood flow pathways necessitates much larger doses of expensive vectors in order to convert the necessary amount of hepatocytes for effective therapy.

[0007] Second, the patient may have pre-existing antibodies that neutralize a virus capsid used as a gene vector rendering therapeutic attempt less effective or ineffective.

[0008] Third, systemic injection of such large quantities of the virus vector can trigger adaptive immunity that destroys not only the virus but also the genetically modified cells.

[0009] Compensating for these problems by introducing large amounts of vector is impractical because of the high expense of producing the vector and the inherent risks associated with injecting large amounts of virus into a human patient.

SUMMARY OF THE INVENTION

[0010] The present invention provides a "localizable" liver gene therapy system substantially reducing the escape of the gene vectors from the tissue mass or organ, e.g., the liver, such that the waste of vector through systemic dilution is minimized, which would also limit the undesired immune reactions. In this regard, the invention describes a two inflatable balloon catheter that delivers a volume of vectors into a contained length of blood vessel to precisely deliver a high concentration of virus to the surrounding tissue. The high concentration of virus to a small, contained volume of tissue increases the uptake of vectors with reduced vector loss. While the contained length of vector delivery would seem to be counter to the intent of treating a large amount of tissue, parallel electrodes used in conjunction with vector delivery produce increased cell membrane permeability for viral vector transport in the tissue region between the electrodes offsetting this localization of vector delivery and improving uptake of the vector.

[0011] For example, a drug delivery catheter is inserted into a venous access site for hepatic vein catheterization. The medical professional may visualize the hepatic vein using computed tomography (CT) scan, ultrasound, or x-ray (fluoroscopy) guidance to advance the catheter into a blood vessel of the liver. A pair of inflated balloons flanking an active delivery section of the catheter may secure the location and position of the catheter's active delivery section. Gene therapy, e.g., viral vectors are then injected through the catheter to pass outward through egress holes in the active delivery section of the catheter to define a gene delivery area in the surrounding tissue.

[0012] Next, a separate minimally invasive needle electrode is inserted parallel to the catheter intravenously or through a blood vessel to create an electric field. A voltage relative to another electrode, e.g., located on the outside of the catheter wall, is delivered as a pulse to the needle electrode to create an electric field in the gene delivery area outside of the catheter. This results in an improved transduction rate of the viral vectors into the hepatic cells and therefore improved conversion of the hepatocytes with smaller vector doses.

[0013] The present invention provides a therapeutic delivery system comprising a catheter providing a distal end having a first and second inflatable balloon spaced apart along the distal end to define an intervening catheter section and at least one passageway through a delivery lumen of the intervening catheter section for the delivery of a therapeutic substance to a therapy site. A first electrical conductor is supported by and extends along the outside of the catheter along a first axis. A second electrical conductor insertable percutaneously through tissue of the therapy site extends substantially parallel to the intervening catheter section of the catheter along a second axis and is connected to a power supply delivering an electric voltage to the second electrical conductor relative to the first electrical conductor, configured to increase cell membrane permeability. The second electrical conductor includes an inner and outer coaxial conductive element and the outer coaxial conductive element is absent across from the first electrical conductor to

allow for creation of an electrical field outside of the catheter, between the first and second electrical conductors.

[0014] It is thus a feature of at least one embodiment of the invention to use one or more thin needle electrodes inserted percutaneously near the liver (through tissue or within a vein) to create an electric field more precisely in the small drug delivery area to avoid adverse effects related to large vector doses.

[0015] The distance between the catheter and the second electrical conductor may be approximately 5 to 30 mm.

[0016] It is thus a feature of at least one embodiment of the invention to simplify the placement of the active electrode in close proximity to the drug delivery catheter without having to insert the active electrode through a blood vessel.

[0017] The first electrical conductor may be molded into a wall of the catheter and extend outside of the wall of the catheter. The first electrical conductor may be attached to the outer surface of the wall of the catheter. The first electrical conductor may form a helix.

[0018] It is thus a feature of at least one embodiment of the invention to use the catheter as the grounded return electrode without interfering with the delivery of therapeutics.

[0019] The first electrical conductor may be grounded.

[0020] It is thus a feature of at least one embodiment of the invention to use a separate needle electrode device to act as the active electrode which may be inserted around the grounded return electrode, simplifying the creation of an electric field in three dimensional space.

[0021] The second electrical conductor may be copper plated steel, stainless steel, chromium, tantalum, titanium, gold, platinum, nickel, zirconium, copper, and alloys of these metals, with an outer diameter less than 0.7 mm.

[0022] It is thus a feature of at least one embodiment of the invention to allow the thin, minimally invasive needle to be inserted into the tissue at a desired angle commensurate with the catheter angle independent of the position or angle of any blood vessels.

[0023] The equipotential lines of the electric field in a plane containing the first and second axes may be substantially evenly spaced and parallel between the first and the second electrical conductors.

[0024] It is thus a feature of at least one embodiment of the invention to create uniform electric fields which are equally applied to the cells of the drug delivery area to more accurately determine optimal electrical stimulation protocols.

[0025] A position of at least one of the first and second inflatable balloon may be movable along a length of the catheter.

[0026] It is thus a feature of at least one embodiment of the invention to adjust the length of the active delivery area of the catheter to accommodate variations in the organ or tissue delivery site and to adjust for different drug delivery applications using a standardized catheter assembly or kit of catheters of different lengths.

[0027] At least one therapeutic substance may comprise at least one of a drug or gene therapy.

[0028] It is thus a feature of at least one embodiment of the invention to optimize delivery of viral vector using electric field pulses of low duration to induce holes (increase permeability) in the cell membrane without affecting cell viability.

[0029] The present invention also provides a method for delivering one or more therapeutic substances to a patient, comprising: providing a catheter comprising a distal end having a first and second inflatable balloon spaced apart along the distal end to define an intervening catheter section and at least one passageway through a delivery lumen of the intervening catheter section for the delivery of at least one therapeutic substance to a therapy site, a proximal end having a therapeutic injection port, and a first electrical conductor extending along the catheter; providing a second electrical conductor insertable extending substantially parallel to the intervening catheter section of the catheter, wherein the second electrical conductor includes an outer coaxial conductive element and wherein the outer coaxial conductive element is absent from the second electrical conductor across from the intervening catheter section to allow for the creation of an electrical field across the first and second electrical conductors; inserting the catheter at a first insertion site into a blood vessel of a patient along a first axis; inserting the second electrical conductor at a second insertion site through tissue of the therapy site substantially parallel to the intervening catheter section of the catheter along a second axis; injecting the at least one therapeutic substance into the therapeutic injection port of the catheter and through the delivery lumen of the intervening catheter section to deliver the at least one therapeutic substance into surrounding cells; and delivering an electrical charge to the second electrode to produce a voltage across the first and second electrical conductors configured to increase cell membrane permeability of the surrounding cells.

[0030] It is thus a feature of at least one embodiment of the invention to separate the application of voltage to a thin minimally invasive needle electrode which may be easily inserted through tissue at various angles to more closely match the angle of the drug delivery catheter held within the blood vessel.

[0031] The second electrical conductor may be inserted approximately 5 to 30 mm from the catheter.

[0032] It is thus a feature of at least one embodiment of the invention to increase the strength of the electric field between electrodes at lower voltage to optimize cell membrane permeability.

[0033] The second electrical conductor may be inserted at approximately the same angle with respect to a longitudinal axis of the patient as an angle of the catheter with respect to the longitudinal axis of the patient.

[0034] It is thus a feature of at least one embodiment of the invention to produce a substantially uniform electric field between short linear sections or "stations" along the blood vessel.

[0035] The method may further produce an electric field wherein the equipotentials of the electric field in a plane containing the first and second axes are substantially evenly spaced and parallel between the first and the second electrical conductors.

[0036] It is thus a feature of at least one embodiment of the invention to accurately determine electric field strength to calculate electric stimulation protocols for cell membrane opening to minimize cell death.

[0037] The method may further provide moving a position of at least one of the first and second inflatable balloon to vary a length of the intervening catheter section.

[0038] It is thus a feature of at least one embodiment of the invention to treat the majority of the length of the organ or sub-organ by adjusting the active delivery section of the catheter.

[0039] The method may further provide removing the second electrical conductor from the second insertion site and inserting the second electrical conductor at a third insertion site through tissue substantially parallel to the intervening catheter section of the catheter.

[0040] It is thus a feature of at least one embodiment of the invention to apply voltage around the circumference of the catheter in order to create an electric field in the entire volume of the liver.

[0041] The present invention also provides a method for delivering one or more therapeutic substances to a patient, comprising: providing a catheter comprising a distal end having an intervening catheter section and at least one passageway through a delivery lumen of the intervening catheter section for the delivery of at least one therapeutic substance at a therapy site, and opposite a proximal end having a therapeutic injection port; providing a first electrical conductor extending along the catheter wherein the first electrical conductor includes an outer coaxial conductive element; providing a second electrical conductor extending substantially parallel to the first electrical conductor, wherein the second electrical conductor includes an outer coaxial conductive element; wherein the outer coaxial conductive element of the first and second electrical conductors is absent across from the intervening catheter section to allow for creation of an electrical field across the first and second electrical conductors; inserting the catheter at a first insertion site into a blood vessel of a patient along a first axis; inserting the first electrical conductor percutaneously at a second insertion site through tissue of the therapy site substantially parallel to the intervening catheter section of the catheter along a second axis; inserting the second electrical conductor percutaneously at a third insertion site through tissue of the therapy site substantially parallel to the intervening catheter section of the catheter along a third axis; injecting the at least one therapeutic substance into the therapeutic injection port of the catheter and through the delivery lumen of the intervening catheter section to deliver the at least one therapeutic substance into surrounding cells of the therapy site; and delivering an electrical charge to at least one of the first and second electrical conductor to produce a voltage across the first and second electrical conductors configured to increase cell membrane permeability of the surrounding cells of the therapy site.

[0042] It is thus a feature of at least one embodiment of the invention to use multiple percutaneous electrodes to produce an electric field around the drug therapy site (in three dimensional space) without sequentially removing needle electrodes.

[0043] These particular objects and advantages may apply to only some embodiments falling within the claims and thus do not define the scope of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0044] FIG. **1** is a front view of a human receiving intravenous gene delivery through catheterization of a hepatic vein of the liver through alternative venous access sites of the body;

[0045] FIG. **2** is a perspective view through the liver of the human of FIG. **1** after insertion of a drug delivery catheter in the hepatic vein of the liver and a needle electrode inserted proximate to the catheter through tissue;

[0046] FIG. **3** is a side elevation view of the drug delivery catheter of FIG. **1** inserted within the hepatic vein and having an active delivery portion flanked by occlusion balloons and a grounded electrode extending on an exterior of the wall of the catheter to effectuate an electric field with an active electrode of the needle electrode (not shown);

[0047] FIG. **4** is a schematic view showing the drug delivery catheter inserted into a lower hepatic vein of the liver and providing dispersion of viral vectors from the inner lumen of the catheter into a gene delivery area while the needle electrode is inserted parallel to the catheter to create an electric field between the catheter and the needle electrode;

[0048] FIG. **5** is a cross section view of the needle electrode of FIG. **1** having a conductor with an unshielded portion to effectuate an electric field with the grounded electrode of the drug delivery catheter;

[0049] FIG. **6** is a chart showing a pattern of electrical field pulses delivered to the conductor of the needle electrode;

[0050] FIG. **7** is a flow chart showing the method steps of gene therapy according to the present invention; and

[0051] FIG. **8** is a schematic view of an alternative embodiment showing the drug delivery catheter being flanked by a pair of needle electrodes inserted in parallel to create an electric field between the needle electrodes and across the drug delivery area.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0052] Referring now to FIG. **1**, a gene therapy delivery system **10** may include at least one drug delivery catheter **12**, and preferably one drug delivery catheter **12**, inserted within the body to deliver fluids containing genes to a target organ of a human patient **14** for transduction into cells. The fluids may be intravenously injected by a syringe **16** or a pump (not shown) into a proximal end **17** of the drug delivery catheter **12** extending outside of the body and into a catheter insertion site. The fluids may include viral vectors **18**, for example, retroviruses, lentiviruses, adenoviruses, adeno-associated viruses, and the like containing functional genes for gene therapy. Viral vectors **18** are generally larger than gene plasmids and therefore are more difficult to transport across cell membranes.

[0053] While the present invention is illustrated as a gene therapy delivery system **10**, it is understood that the delivery system **10** may also be used to deliver drugs to, for example, tissue or tumor site.

[0054] The drug delivery catheter **12** may be inserted into a peripheral or central vein of the human patient **14** through a venous access site **20***a-c* allowing for catheterization of a hepatic vein **22** of the liver **24** of the human patient **14**, for example, inserted at the antecubital vein **20***a*, the jugular vein **20***b*, or the femoral vein **20***c*, as seen as alternative insertion sites in FIG. **1**. In one embodiment, the drug delivery catheter **12** may be inserted at an incision inside the neck of the human patient **14** proximate to the jugular vein **20***b* and then drawn downward through the hepatic vein **22** into the liver **24**. The medical professional may use a guide wire (not shown) to facilitate placement of the drug delivery catheter **12** allowing the drug delivery catheter **12** to be installed over the guide wire after placement of the guide wire. This catheterization process may also be facilitated by real-time visualization by a medical professional through CT scan, ultrasound, or x-ray (fluoroscopy) guidance.

[0055] Referring also to FIG. **3**, the drug delivery catheter **12** may include at least one proximal port **30**, for example, two proximal ports **30** connected by a Y connector **32**, allowing different fluids to be injected into the drug delivery catheter **12**. The drug delivery catheter **12** may also provide a separate balloon inflation port **34** and balloon inflation tube **36** co-extending with and substantially parallel to the drug delivery catheter **12** to provide inflation of one or more balloons **38** of the drug delivery catheter **12**, as further described below. The balloon inflation port **34** may also include a valve controlling flow through the tube **36** to inflate or deflate the balloons **38** as desired.

[0056] While it is shown that the drug delivery catheter **12** is installed into the hepatic vein **22** of the liver **24** of the human patient **14** for gene therapy, it is understood that the drug delivery catheter **12** may also catheterize other organs or tissues of the human patient **14** such as the kidney or pancreas.

[0057] Referring now to FIG. **2**, the drug delivery catheter **12** may be fed by the medical professional through the inferior vena cava **40** of the liver **24** and into one of the upper hepatic veins **22** of the liver **24**, for example, the right hepatic vein **22***a* (as shown catheterized), left hepatic vein **22***b*, or middle hepatic vein **22***c*. The drug delivery catheter **12** may be further fed from the upper hepatic veins **22** into one of the lower blood vessels **42** branching from the upper hepatic veins **22** and which contact surrounding hepatic tissue cells **44** of the liver **24**. For example, as shown, the drug delivery catheter **12** may be fed into one of the upper hepatic veins **22** and terminate in a lower blood vessel **42**.

[0058] A separate fine needle electrode **112** may be fed into the liver **24** percutaneously by puncturing the abdominal skin at an insertion site **120** outside the liver **24** and advancing through liver tissue to extend substantially parallel to a section of the drug delivery catheter **12** within the lower blood vessel **42** to share adjacent tissue therebetween. In this manner, the drug delivery catheter **12** and needle electrode **112** are placed in relatively close proximity, about 5-30 mm or about 5-25 mm or about 5-20 mm or about 5-15 mm or about 5-10 mm, allowing a generally uniform electric field **46** to be created between the drug delivery catheter **12** and the needle electrode **112** as further discussed below.

[0059] Referring now to FIGS. **2** and **3**, the drug delivery catheter **12** may have a construction facilitating dispersion of the viral vector **18** via the drug delivery catheter **12** as well as increase cell membrane permeability for viral vector transport of the hepatic cells **44** as described below.

[0060] The drug delivery catheter **12** may include a thin, flexible tube having an outer wall **50** made from a medical grade material such as vinyl, rubber latex, and silicone. The outer wall **50** has sufficient flexibility to flex with flexure of the drug delivery catheter **12** without holding a bent shape and without changing the stiffness of the outer wall **50**. The outer wall **50** may have an outer diameter of 1.5-3 mm and an inner dimeter of 0.8-2.5 mm. The drug delivery catheter **12** may be consistent with a 5 French gauge catheter, 6 French gauge catheter, 7 French gauge catheter, 8 French gauge catheter or 9 French gauge catheter.

[0061] The drug delivery catheter **12** may come in varied lengths and outer diameters to accommodate the size of the receiving blood vessels and the distance between the access site **20***a-c* and the drug delivery site.

[0062] The outer wall **50** may provide an inner lumen **52** allowing for the flow of fluids therethrough. For example, the internal lumen **52** may allow for the passage of the viral vectors **18** from the proximal port **30** extending outside the body to a terminal end **54** of the drug delivery catheter **12** positioned within the lower blood vessel **42**. The terminal end **54** may be a straight end terminating at a rounded enclosed tip or catheter cap. The terminal end **54** may also support a distal balloon **38***a* as further described below.

[0063] When installed within the lower blood vessel **42**, a distal end **56** of the drug delivery catheter **12** may provide an active section **60** delivering the viral vector **18** out through the outer wall **50** and into the lower blood vessel **42** and further flanked by spaced apart balloons **38**, as further discussed below. The outer wall **50** of the drug delivery catheter **12** may include one or more exit ports **58** within the active section **60** of the drug delivery catheter **12** allowing for the egress of viral vectors **18** injected into the drug delivery catheter **12**, flowing through the inner lumen **52**, and flowing outward into the surrounding hepatic cells **44**. The exit ports **58** may be approximately 0.1-0.4 mm in diameter or may be approximately ¼ to ½ of the inner diameter of the drug delivery catheter **12**. It is understood that any number of exit ports **58** may be included within the catheter outer wall **50** depending on the desired length of the active section **60**, and in any configuration around a circumference of the outer wall **50**.

[0064] The exit ports **58** may be linearly aligned along a longitudinal axis **62** of the drug delivery catheter **12**, or alternatively, the exit ports **58** may be staggered in varying positions around a circumference of the outer wall **50** along the longitudinal axis **62** of the drug delivery catheter **12**. The exit ports **58** may extend along substantially the entire length of the active section **60**. For example, a single exit port **58** may be centered longitudinally within the active section **60** or more than one exit ports **58** may be spaced symmetrically about the center of the active section **60** and extend along substantially the entire length of the active section **60**.

[0065] Alternatively, the outer wall **50** may be a porous material having microscopic holes allowing the viral vectors **18** to permeate through the outer wall **50** of the tube and disseminate into the surrounding hepatic cells **44**.

[0066] Generally, it is understood that the active section **60** allows for the egress of the viral vectors **18** from the inner lumen **52** of the drug delivery catheter **12** into the hepatic tissue cells **44** surrounding the active section **60** of the drug delivery catheter **12**.

[0067] The dispersion of viral vectors **18** volumes may be contained by at least two balloons **38**, and preferably a pair of balloons **38***a*, **38***b*, spaced apart and flanking the active section **60** of the drug delivery catheter **12** delivering the viral vector **18**. A distal balloon **38***a* may be positioned at or near the terminal end **54** of the drug delivery catheter **12** and a proximal balloon **38***b* may be positioned upstream from the terminal end **54** on the proximal side of the active section **60**.

[0068] The balloons **38** may be integrally molded with the drug delivery catheter **12**, for example, built within or as part of the outer wall **50** of the drug delivery catheter **12**, or may be bonded to the outer wall **50** of the drug delivery catheter **12**, for example, by a curable adhesive sealing an outer perimeter of the balloon **38** material to the outer wall **50** to create an airtight seal.

[0069] In certain embodiments, the distal balloon **38***b* and/or proximal balloon **38***a* may be movable or repositionable to allow the gene delivery area **64** bounded between the

inflated balloons **38***a*, **38***b* to vary. In this respect, the distal balloon **38***b* and proximal balloon **38***a* may be repositionable along the length of the drug delivery catheter **12** and inflated to expand at various locations along the drug delivery catheter **12** in order to vary the gene delivery area **64** of the active section **60**. Some of the proximal exit ports **58** may be "cut off" or removed from the active section **60** of the drug delivery catheter **12**, for example, by moving the proximal balloon **38***a* toward the distal balloon **38***b* to prevent the egress of viral vectors **18** from exit ports **58** outside of the active section **60**. Conversely, the number of proximal exit ports **58** may be increased by moving the proximal balloon **38***a* away from the distal balloon **38***b* to increase the number of exit ports **58** in the active section **60**. Both the distal balloon **38***b* and proximal balloon **38***a* may be movable or repositionable, for example, to reposition the gene delivery area **64** along the length of the drug delivery catheter **12**. Alternatively, the distal balloon **38***b* may be fixed in position at the terminal end **54** of the drug delivery catheter **12** while the proximal balloon **38***a* is moved to vary the length of the active section **60**.

[0070] The balloons **38***a* may be separate from the drug delivery catheter **12** in order to be separately movable to desired locations along the longitudinal axis **62** and then expand out through longitudinally spaced openings in the outer wall **50** or co-expand with the outer wall **50** to hold the lower blood vessel **42**.

[0071] The balloon **38** may be made of a material which resiliently deforms under radial pressure, for example, polyethylene (PE), nylon, polyamide, polyether block amides (PEBAX), polyethylene terephthalate (PET), silicone, POC, polypropylene, polyether block PBT and the like. The balloon **38** may include multiple layers and/or be coextruded and may also include additional fiber reinforcements. The size of the balloons **38** may vary depending on the size of the receiving lower blood vessel **42**.

[0072] The pair of balloons **38***a*, **38***b* may be inflated simultaneously by injecting gas or liquid such as air, saline or iodinated contrast medium into the balloon inflation port **34** at the proximal end **17** of the drug delivery catheter **12** and through the balloon inflation tube **36** extending longitudinally with the drug delivery catheter **12**. The balloon inflation tube **36** may be integrated with the drug delivery catheter **12**, for example, molded into the outer wall **50** of the drug delivery catheter **12**, bonded to the drug delivery catheter **12**, or separate from the drug delivery catheter **12**. It may be desired to include a separate balloon inflation tube **36** from the inner lumen **52** to independently control inflation or deflation of the balloons **38***a*, **38***b* while also using the inner lumen **52** as a fluid channel for the delivery of viral vectors **18**. In this respect gas or liquid may flow through a balloon lumen that is separate from the inner lumen **52** of the drug delivery catheter **12**. Alternatively, the gas or liquid may flow through the same tube as the inner lumen **52** of the drug delivery catheter **12**.

[0073] The balloon **38** may be constructed as described above, and as described in U.S. Pat. Nos. 8,603,064 and 7,060,051, both of which are hereby incorporated by reference.

[0074] The balloons **38***a*, **38***b* may secure the positioning of the drug delivery catheter **12** within the lower blood vessel **42** by engaging the inner walls of the lower blood vessel **42** thus anchoring the drug delivery catheter **12** to the lower blood vessel **42** when inflated, and then deflated for removal of the drug delivery catheter **12** from the lower blood vessel **42** and from the body.

[0075] The balloons **38***a*, **38***b* also provide additional benefit by localizing the dispersion of the viral vectors **18** to a gene delivery area **64** substantially longitudinally bounded by the pair of inflated balloons **38***a*, **38***b*. In this respect, when viral vector **18** is injected into the inner lumen **52** of the drug delivery catheter **12**, the inflated balloons **38***a*, **38***b* prevent the viral vector **18** from flowing downstream or upstream through the lower blood vessel **42**. Therefore, the viral vectors **18** are encouraged to be absorbed into the nearby surrounding hepatic tissue, or may flow into smaller lateral vessels and capillaries to then be absorbed into the nearby surrounding hepatic tissue, instead of returning up the vein toward the proximal port **30** or down the vein from the terminal end **54** of the drug delivery catheter **12**.

[0076] The inflated balloons **38***a*, **38***b* also block blood flow between the inflated balloons **38** during gene delivery.

[0077] Referring to FIGS. **3** and **4**, the drug delivery catheter **12** may support a grounded, return electrical conductor **70**, extending coaxially within the internal lumen **52** along the longitudinal axis **62** of the drug delivery catheter **12**. The electrical conductor **70** may also be coaxially positioned so that it does not block or obscure any of the exit ports **58**, for example, it may be molded or partially molded into or onto the outer wall **50** of the drug delivery catheter **12** so that the electrical conductor **70** extends along the longitudinal axis **62** of the drug delivery catheter **12**, for example, linearly or in a helix formation (as shown in FIG. **3**). The outer dimension of the electrical conductor **70** is less than the thickness of the outer wall **50** of the drug delivery catheter **12** to be integrated into the outer wall **50** or may be attached to the inner or outer surface of the outer wall **50**. The electrical conductor **70** may extend substantially an entire length of the drug delivery catheter **12**, however, terminating before reaching the terminal end **54** of the drug delivery catheter **12**, or before the distal balloon **38***b*.

[0078] The electrical conductor **70** may include one or more electrodes (contacting the surrounding tissue and fluid) extending to the exterior or outside of the outer wall **50**. It is understood that any number of electrodes may be formed outside and along the drug delivery catheter **12**. In a preferred embodiment, the electrical conductor **70** includes one or more electrodes molded or attached to the outer surface of the outer wall **50** to better achieve targeted electric field intensities with the least amount of voltage. It is understood that the electrical conductor **70** may be embedded within the outer wall **50** or positioned inside the outer wall **50** but include electrodes that extend to the outside of the outer wall **50** to receive current.

[0079] The electrical conductor **70** is configured to be grounded, or be at zero volts relative to the earth, and may be copper plated steel, stainless steel, chromium, tantalum, titanium, gold, platinum, nickel, zirconium, copper, alloys of these metals, and any other biocompatible electrically conducting metal, with or without an outer dielectric insulator permitting free passage of the electrical field but blocking electrical current flow and chemical reaction between the fluid and the material of the electrical conductor **70**.

[0080] In an alternative embodiment, the electrical conductor **70** may be a return electrode connected to a power source to apply a voltage (i.e., potential difference) between the electrical conductor **70** and the needle electrode **112** as

described further below. In this respect, the electrical conductor **70** may be at a negative voltage.

[0081] Optionally, the electrical conductor **70** may be shielded above the active section **60**, or above the proximal balloon **38***a*, by an insulator **72** layer, an outer conductor **73** layer, and an insulator shield or jacket **75**. The outer conductor **73** layer and the electrical conductor **70** are connected to ground potential. In this respect, the electric field is restricted to the dielectric and does not extend into the shielded section **74**. For example, a shielded portion **74** may be a shielded cable, such as a coaxial cable, or a layered medical tubing with the electrical conductor **70** surrounded by a tubular insulating layer **72**, for example, a solid plastic or a foam plastic such as solid polytetrafluoroethylene (PTFE) or solid polyethylene (PE) dielectric, and further surrounded by a tubular outer conductor **73**, for example, a metal braided shield such as braided copper, aluminum or stainless steel wire, which may be plated or multi-layered, and may be further surrounded by an insulating shield or jacket **75**, for example, a solid plastic such as polyvinyl chloride (PVC) which may be sealed around the outer conductor **73** to prevent reaction with fluids and the like.

[0082] The electrical conductor **70** may extend into the active section **60** with the insulator **72**, outer conductor **73**, and insulator jacket **75** removed. In this respect, the electric fields in the shielded portion **74** above the active section **60** are reduced and do not extend into the surrounding hepatic tissue cells **44** outside of the active section **60** of the drug delivery catheter **12**. Alternatively, the electrical conductor **70** may remain insulated in the active section **60** with only the outer conductor **73** and insulator jacket **75** removed. In this respect, the electrical conductor **70** is not exposed to chemical reaction with the hepatic tissue cells **44**. It is understood that the shielded portion **74** may still have an outer dimension less than the inner diameter of the outer wall **50** of the drug delivery catheter **12** to provide clearance therearound for flow of viral vector **18**.

[0083] The drug delivery catheter **12** as described herein may include features of the two balloon catheter described in U.S. Pat. No. 10,918,861, also assigned to the present applicant, hereby incorporated by reference.

[0084] Referring to FIGS. **4** and **5**, one or more separate needle electrodes **112** may be inserted into the hepatic tissue cells **44** such that it extends substantially parallel to the longitudinal axis **62** of the electrical conductor **70** and acts as the active electrode. The needle electrode **112** may support an antenna providing an active electrical conductor **170** having a length that is approximately the entire length of the needle electrode **112** but is shielded at the proximal end **117** by an outer dielectric insulator **118**.

[0085] The active electrical conductor **170** may be a wire configured to carry electrical charge and may be copper plated steel, stainless steel, chromium, tantalum, titanium, gold, platinum, nickel, zirconium, copper, alloys of these metals, and any other biocompatible electrically conducting metal, with or without an outer dielectric insulator **118** permitting free passage of the electrical field but blocking electrical current flow and chemical reaction between the material of the active electrical conductor **170** and bodily fluid and surrounding tissue. The outer dielectric insulator **118** may be Teflon or another insulating material, as described below, shielding the active electrical conductor **170** at the proximal end **117** and exposing the active electrical conductor **170** at the distal end **156** to serve as the active electrode. The active electrical conductor **170** may be exposed to provide a single active electrode at the distal end **156** or an array of electrodes alternating with the insulating material.

[0086] In one embodiment, the proximal end **117** of the active electrical conductor **170** may be shielded by an insulator **172** layer, an outer conductor **173** layer, and an insulator shield or jacket **175**. The outer conductor **173** layer may be connected to a ground potential while the active electrical conductor **170** is connected to a power source **76**. In this respect, the electric field is restricted to the dielectric and does not extend from a shielded section **174**. For example, the shielded portion **174** may be a shielded cable, such as a coaxial cable, or a layered medical tubing with the active electrical conductor **170** surrounded by a tubular insulating layer **172**, for example, a solid plastic or a foam plastic such as solid polytetrafluoroethylene (PTFE) or solid polyethylene (PE) dielectric, and further surrounded by a tubular outer conductor **173**, for example, a metal braided shield such as braided copper, aluminum or stainless steel wire, which may be plated or multi-layered, and may be further surrounded by an insulating shield or jacket **175**, for example, a solid plastic such as polyvinyl chloride (PVC) which may be sealed around the outer conductor **173** to prevent reaction with fluids and the like.

[0087] The active electrical conductor **170** may extend across from the active section **60** of the drug delivery catheter **12** with the insulator **172**, outer conductor **173**, and insulator jacket **175** removed. In this respect, the electric fields are contained primarily to the length of the active section **60** of the coextending parallel drug delivery catheter **12**. Alternatively, the active electrical conductor **170** may remain insulated in the active section **60** with only the outer conductor **173** and insulator jacket **175** removed. In this respect, electrical current is blocked from flowing into the surrounding hepatic tissue cells **44** and the active electrical conductor **170** is not exposed to chemical reaction with the hepatic tissue cells **44**.

[0088] The needle electrode **112** has a beveled tip **113** allowing the sharp point to pierce the abdominal skin and be inserted percutaneously through the tissue mass of the liver **24**.

[0089] In certain embodiments, the needle electrode **112** may be the active electrical conductor **170** surrounded by a hollow cannula. The hollow cannula may be made of medical grade plastic tubing made of stiff plastic medical grade material such as silicone, polyvinylchloride, polyethylene, and polyurethane. The hollow cannula has a beveled tip allowing the sharp point to pierce the abdominal skin. In this construction, the hollow cannula may be inserted through a vein of the liver **24** to be placed in close proximity, about 5-30 mm or about 5-25 mm or about 5-20 mm or about 5-15 mm or about 5-10 mm, to the drug delivery catheter **12**. However, the hollow cannula does not need to be inserted coextensive with the drug delivery catheter **12**, or at the venous access site **20***a-c*, or through the hepatic vein **22**, but may be fed through a vein of the liver **24** to be positioned along the active section **60** of the drug delivery catheter **12**.

[0090] In this respect, the present invention provides a needle electrode **112** (or hollow cannula) that may be easily inserted in parallel along the drug delivery catheter **12** either through tissue or a vein of the liver **24** without needing to catheterize the hepatic vein **22** coextensive with the drug delivery catheter **12**.

[0091] The needle electrode **112** is thin and minimally invasive to facilitate precise placement of the electrode. The needle electrode **112** (or hollow cannula) has an outer diameter of approximately 0.1 to 1.5 mm or approximately 0.1 to 0.7 mm or approximately between 0.2 and 0.4 mm, and desirably approximately less than 1.5 mm or approximately less than 0.7 mm or approximately less than 0.4 mm to minimize discomfort to the patient.

[0092] Referring also to FIG. **6**, the needle electrode **112** may be used in conjunction with a pulse generator **76** to provide a pulsed electrical charge to the active electrical conductor **170**. For example, the pulse generator **76** may deliver a direct current (DC) **77** in the form of a repeated pulse or burst (e.g., pulse biased positive or negative) of an appropriate current amplitude and duration to the active electrical conductor **170** to create a voltage (i.e., potential difference) between the potential of the active electrical conductor **170** and the ground potential of the electrical conductor **70**. An electric pulse may be applied to the active electrical conductor **170** receiving direct current **77** while the electrical conductor **70** acts as the return, grounded electrode.

[0093] As mentioned above, in an alternative embodiment, the electrical conductor **70** of the drug delivery catheter **12** may be connected to a power source and be at a negative voltage to act as the negative return electrode.

[0094] Turning briefly to FIG. **8**, in an alternative embodiment, the electrical conductor **70** of the drug delivery catheter **12** may be omitted and replaced with a second needle electrode **212** with a similar construction as the needle electrode **112**), and used in conjunction with the needle electrode **112**, to act as the active or return electrode and create an electric field between the needle electrode **112** and the second needle electrode **212**. The second needle electrode **212** may be connected to the pulse generator **76** to produce a pulsed electrical charge, e.g., acting as the active electrode or alternating with the needle electrode **112** as the active electrode and return electrode, or to create a ground potential when acting as the return electrode to the needle electrode **112** as shown.

[0095] The second needle electrode **212** is inserted along an axis **260** parallel to the axis **160**. In this arrangement, the needle electrode **112** and second needle **212** may extend substantially in parallel to flank the gene delivery area **64** and thus create an electric field over the gene delivery area **64**. The needle electrode **112** and second needle **212** may or may not be in parallel with the drug delivery catheter **12** while the needle electrode **112** and second needle electrode **212** are desirably in parallel to produce parallel and equidistant electric field equipotentials **146**. The needle electrode **112** and second needle electrode **212** are in close proximity, about 5-30 mm or about 5-25 mm or about 5-20 mm or about 5-15 mm or about 5-10 mm in maximize the electric field strength therebetween.

[0096] Alternatively, the second needle electrode **212** could also be used with the electrical conductor **70** of the drug delivery catheter **12** and the needle electrode **112**, acting as an additional active electrode to supplement the needle electrode **112** and making it easier to create an electric field in the three dimensional space of the gene delivery area **64** without removing the first needle electrode **112**. Although two needle electrodes are shown in FIG. **8**, it is understood that any number of additional needle electrodes, including one, two, three or more needle electrodes, may be used and inserted into hepatic cells **44** of the patient.

[0097] Pulse generators **76** suitable for in vivo cell membrane opening for viral vector transport as taught herein are sold by ECM under the trade name "830 square wave electroporation system". Other pulse generators **76** are also commercially available and may be used with the present invention.

[0098] As illustrated in FIG. **5**, the electric pulses may be repeated square pulses created by the pulse generator **76**. It is understood that the electric pulses may take other shapes such as spikes or round waves. An electronic control circuit **78** may communicate with the pulse generator **76** to receive a preset voltage output and pulse length from the medical professional. The electronic control circuit **78** may hold, for example, a microprocessor **80** for executing a program **82** held in a stored memory **84**.

[0099] The microprocessor **80** may also receive input data from the medical professional such as a distance between internal electrical conductor **70** and active electrical conductor **170**, or a cross-sectional area between internal electrical conductor **70** and active electrical conductor **170**, and execute the program **82** held in the stored memory **84** to output a voltage output **86** and pulse duration **88** to be used for effective pulse delivery, for example, using a lookup table. It is understood that internal electrical conductor **70** may be inserted along longitudinal axis **160** angled within the lower blood vessel **42** at an angle θ with respect to a longitudinal axis **162** of the human patient **14** and thus the needle electrode **112** will be inserted in a corresponding angle θ to be close to parallel with the active section **60** of the drug delivery catheter **12**. Therefore, the distance between the electrical conductor **70** and the active electrical conductor **170** is the same along the active section **60**.

[0100] The voltage output **86** may be selected so that the electric field **46** created between the internal electrical conductor**70** and active electrical conductor **170** achieves or exceeds an efficacious electric field strength. For example, if the electric field **46** is too high, this can result in cell death through irreversible cell membrane opening. Alternatively, if the electric field strength is too low, the transmembrane potential required to permeabilize the cell membrane (typically 0.7 V) cannot be reached.

[0101] The pulse duration **88** may also be selected so that the electric field **46** created between the internal electrical conductor **70** and active electrical conductor **170** achieves or exceeds an efficacious electric field **46** strength. For example, if the pulse length is too short, (microseconds), the membrane capacitance may not charge up high enough to reach the required transmembrane potential. An efficacious electric field **46** strength may be coextensive with the gene delivery area **64**.

[0102] It has been found that for gene delivery (compared to drug delivery), a combination of low electric field strength and long pulse length has been effective. For example, electric field intensities between 100-200 V/cm and pulse durations of 38-100 msec; and electric field intensities between 200-275 V/cm and pulse duration of about 50 msec have been found to be effective. Other parameters, which determine the efficacy of the delivery of viral vectors **18** into hepatic cells **44** are field strength, pulse length, shape of the pulse and number of pulses.

[0103] The electrical conductor **70** and active electrical conductor **170** are desirably parallel and equidistant so that

the electric field equipotentials **146** in a plane **164** containing the longitudinal axis **62** of the delivery catheter **12** and longitudinal axis **160** of the needle electrode **112**, are evenly spaced and parallel across the electrical conductor **70** and active electrical conductor **170** simplifying the determination of the electric field strength, pulse length, shape of the pulse and number of pulses.

[0104] The parameters used may be similar to those of electroporation described in *Methods in Molecular Medicine*, Vol. 37: Electrically Mediated Delivery of Molecules to Cells, Edited by: M. J. Jaroszeski, R. Heeller, and R. Gilbert, Humana Press, Inc., Totowa, NJ, and hereby incorporated by reference.

[0105] Referring now to FIG. **7**, as noted above, the present invention uses a drug delivery catheter **12** of desired length and outer diameter inserted into the lower blood vessel **42** and a separate needle electrode **112** inserted along and parallel to the drug delivery catheter **12** to provide more efficient gene delivery eliminating the need for to catheterize neighboring blood vessels in close proximity. Such a procedure can use a single minimally invasive vascular catheter **12** catheterizing one or more lower blood vessels **42** of the liver **24** to perform direct gene delivery into the target liver with greater efficacy. To further enhance the efficiency of gene delivery for a large tissue area, the electrical conductor **70** of the catheter **12** and an active electrical conductor **170** of a separately inserted needle electrode **112** simultaneously increase cell membrane permeability for viral vector transport the hepatic cells **44** between adjacent electrodes to open temporary pores in the cell membrane allowing the vector **18** to readily enter the cells.

[0106] As indicated by process block **100**, the drug delivery catheter **12** may be inserted through a venous access site **20***a-c*, for example, the jugular vein **20***b*, through a small incision at the neck of the human patient **14**. The medical professional may use a guidewire and/or real-time visual imaging such as CT scan, ultrasound, or x-ray (fluoroscopy) to assist with the catheterization of the hepatic vein **22** of the right hepatic vein **22***a*.

[0107] As indicated by process block **102**, once the catheter **12** is properly positioned within the lower blood vessel **42** of the right hepatic vein **22***a* of the liver **24** (desirably spanning the majority of the length of the liver), the balloons **38***a*, **38***b* may be repositioned to define an active section **60** delivering the viral vector **18** to a desired gene delivery area **64**. The balloons **38** are inflated by injecting gas or fluid such as air, iodinated contrast or saline through the balloon inflation port **34** and through the inflation tube **36** in order to secure the catheter **12** in position, prevent further blood flow between the balloons **38***a*, **38***b*, and to isolate the gene delivery area **64**. The balloons **38***a*, **38***b* of each drug delivery catheter **12** may inflate simultaneously and to a similar extent such that the inflated balloons **38***a*, **38***b* of each respective drug delivery catheter **12** are a similar size. In this respect the balloons **38***a*, **38***b* of the drug delivery catheter **12** may be a different size from the balloons **38***a*, **38***b* of the drug delivery catheter **12** to accommodate for different inner diameter sizes of the lower blood vessel **42**.

[0108] Optionally, saline may be injected (retrograde flush) into the proximal ports **30** of the catheter **12** to wash the inner lumen **52** and gene delivery area **64** from obstructive blood and tissues or antibodies.

[0109] Then, as indicated by process block **104**, the viral vector **18** may be injected (retrograde flush) into the proximal ports **30** of the catheter **12** in order to fill the inner lumen **52** of the catheter **12** with the viral vector **18** and to disseminate the vector **18** through the exit ports **58** of the outer wall **50** of the catheter **12**, and further through the vascular walls of the lower blood vessels **42**, and into the gene delivery area **64** surrounding the catheter **12**. It is understood that the gene delivery area **64** may comprise of regions emanating from and surrounding the active section **60** of the drug delivery catheter **12**.

[0110] Then, as indicated by process block **105**, the needle electrode **112** is precisely inserted percutaneously through liver tissue or a vein of the liver **24** using visual imaging such as CT scan, ultrasound, or x-ray to extend parallel to the active section **60** of the drug delivery catheter **12** and approximately 5-30 mm away from the active section **60** of the drug delivery catheter **12** to create an electric field **46** in the area between and around the needle electrode **112** and drug delivery catheter **12** overlapping with the gene delivery area **64**. In an alternative embodiment, if a second needle electrode **212** is inserted percutaneously through liver tissue or a vein of the liver **24** as seen in FIG. **8**, the electric field **46** is created in the area between the needle electrode **112** and the second needle electrode **212** overlapping with the gene delivery area **64**.

[0111] As indicated by process block **106**, the medical professional may consider the location and distance between the catheter **12** and needle electrode **112** using visual imaging such as CT scan, ultrasound, or x-ray to determine a desired voltage output **86** and pulse duration **88** to be outputted by the pulse generator **76**. The medical professional may program the pulse generator **76** to elicit a direct current **77** in short pulses, for example, square waves as illustrated in FIG. **6**, to the needle electrode **112** to therefore create an electric field **46** between and surrounding the catheter **12** and the needle electrode **112**. It is understood that the electric field **46** may comprise of a region surrounding the drug delivery catheter **12** and the needle electrode **112** and primarily extending across the drug delivery catheter **12** and needle electrode **112**, the tissue area coextensive or greater than the gene delivery area **64**.

[0112] Next, as indicated by process block **108**, the needle electrode **112** may be repositioned, or a second needle electrode **212** inserted and positioned, radially around the active section **60** of the drug delivery catheter **12** and process block **106** repeated one or more times to further create a uniform electric field around the circumference of the drug delivery catheter **12** and to create an electric field in the three-dimensional space of the gene delivery area **64** of the liver.

[0113] Furthermore, as indicated by process block **110**, the drug delivery catheter **12** may be withdrawn (or advanced) within the lower blood vessel **42** in order to repeat the drug delivery steps **102**, **104** and electrical stimulation steps **105** and **106** at various longitudinal stations **109**, as seen in FIG. **2**, along the length of the lower blood vessel **42**. Alternatively, the balloons **38***a*, **38***b* may be repositioned to define a new active section **60** at the different stations **109**. Since the blood vessels are generally non-linear over an extended length, the drug delivery step **104** and electrical stimulation steps **105**, **106**, **108** may be reperformed at short longitudinal stations **109** along the length of the blood vessels to ensure a substantially uniform electric field is applied to the new

gene delivery area **64**. In this respect, the needle electrode **112** is also repositioned parallel to the new active section **60** at the different stations **109**.

[0114] Next, as indicated by returning to process block **100**, the drug delivery catheter **12** may be removed from the lower blood vessel **42** of the right hepatic vein **22***a*, and the drug delivery catheter **12** may be withdrawn and inserted into a lower blood vessel **42** of the middle hepatic vein **22***b* in a similar manner as described in process blocks **100** and **102**. The drug delivery steps **102**, **104** and electrical stimulation steps **105**, **106**, **108** may also be repeated in the new gene delivery area **64** at the new hepatic vein location. These steps may also be repeated for a lower blood vessel **42** of the left hepatic vein **22***c* to provide treatment over substantially the entire liver.

[0115] The increase of cell membrane permeability for viral vector transport of the gene delivery area **64** provided by the electric field **46** allows for the hepatic cells **44** in the gene delivery area **64** to be more susceptible to viral intake. In this respect, the catheter **12** and needle electrode **112** allows for simultaneous or nearly simultaneous delivery of genes to cells with increased cell membrane permeability for viral vector transport of the cells extending between the drug delivery catheter **12** and needle electrode **112**. It is contemplated that the drug delivery described above may be performed once or may be conducted as repeated treatments as necessary.

[0116] It is understood that the gene therapy delivery system **10** may be performed on any mammal and of any size, for example, both small and large mammals.

[0117] It is understood that "drug", "gene", "viral vector", and "vector" are used interchangeably, and "drug therapy" and "gene therapy" are used interchangeably to describe the delivery of therapeutic substances which are not intended to be limiting.

[0118] It is understood that "transduction", "transducing", "transfection", and "transfecting" are used interchangeably to describe the insertion of genes or DNA into cells and are not intended to be limiting.

[0119] It is understood that "tissue", "tissue mass", "tissue cells" "organ", "liver", "tumor", "tumor site" are used interchangeably to describe the target or site within the body receiving gene therapy and are not intended to be limiting.

[0120] Certain terminology is used herein for purposes of reference only, and thus is not intended to be limiting. For example, terms such as "upper", "lower", "above", and "below" refer to directions in the drawings to which reference is made. Terms such as "front", "back", "rear", "bottom" and "side", describe the orientation of portions of the component within a consistent but arbitrary frame of reference which is made clear by reference to the text and the associated drawings describing the component under discussion. Such terminology may include the words specifically mentioned above, derivatives thereof, and words of similar import. Similarly, the terms "first", "second" and other such numerical terms referring to structures do not imply a sequence or order unless clearly indicated by the context.

[0121] When introducing elements or features of the present disclosure and the exemplary embodiments, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of such elements or features. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements or features other than those specifically noted. It is further to be understood that the method steps, processes, and operations described herein are not to be construed as necessarily requiring their performance in the particular order discussed or illustrated, unless specifically identified as an order of performance. It is also to be understood that additional or alternative steps may be employed.

[0122] References to "a microprocessor" and "a processor" or "the microprocessor" and "the processor," can be understood to include one or more microprocessors that can communicate in a stand-alone and/or a distributed environment(s), and can thus be configured to communicate via wired or wireless communications with other processors, where such one or more processor can be configured to operate on one or more processor-controlled devices that can be similar or different devices. Furthermore, references to memory, unless otherwise specified, can include one or more processor-readable and accessible memory elements and/or components that can be internal to the processor-controlled device, external to the processor-controlled device, and can be accessed via a wired or wireless network.

[0123] It is specifically intended that the present invention not be limited to the embodiments and illustrations contained herein and the claims should be understood to include modified forms of those embodiments including portions of the embodiments and combinations of elements of different embodiments as come within the scope of the following claims. All of the publications described herein, including patents and non-patent publications, are hereby incorporated herein by reference in their entireties.

[0124] To aid the Patent Office and any readers of any patent issued on this application in interpreting the claims appended hereto, applicants wish to note that they do not intend any of the appended claims or claim elements to invoke 35 U.S.C. 112(f) unless the words "means for" or "step for" are explicitly used in the particular claim.

What we claim is:

1. A therapeutic delivery system comprising:

a catheter providing a distal end having a first and second inflatable balloon spaced apart along the distal end to define an intervening catheter section and at least one passageway through a delivery lumen of the intervening catheter section for the delivery of a therapeutic substance to a therapy site;

a first electrical conductor supported by and extending along the catheter along a first axis; and

a second electrical conductor insertable percutaneously through tissue of the therapy site to extend substantially parallel to the intervening catheter section of the catheter along a second axis and connected to a power supply delivering an electric voltage to the second electrical conductor relative to the first electrical conductor, configured to increased cell membrane permeability;

wherein the second electrical conductor includes an inner and outer coaxial conductive element and wherein the outer coaxial conductive element is absent across from the first electrical conductor to allow for creation of an electrical field outside of the catheter, between the first and second electrical conductor.

2. The therapeutic delivery system of claim **1**, wherein a distance between the catheter and the second electrical conductor is approximately 5 to 30 mm.

3. The therapeutic delivery system of claim **1**, wherein the first electrical conductor is molded into a wall of the catheter and extended outside of the catheter.

4. The therapeutic delivery system of claim **3**, wherein the first electrical conductor forms a helix.

5. The therapeutic delivery system of claim **1**, wherein the first electrical conductor is grounded.

6. The therapeutic delivery system of claim **1**, wherein the second electrical conductor has an outer diameter less than 1.5 mm.

7. The therapeutic delivery system of claim **1**, wherein equipotentials of the electric field in a plane containing the first and second axes are substantially evenly spaced between the first and the second electrical conductors.

8. The therapeutic delivery system of claim **1**, wherein equipotentials of the electric field in a plane containing the first and second axes are substantially parallel between the first and the second electrical conductors.

9. The therapeutic delivery system of claim **1**, wherein a position of at least one of the first and second inflatable balloon may be movable along a length of the catheter.

10. The therapeutic delivery system of claim **1**, wherein at least one therapeutic substance comprises at least one of a drug or gene therapy.

11. A method for delivering one or more therapeutic substance to a patient, comprising:

providing a catheter comprising a distal end having a first and second inflatable balloon spaced apart along the distal end to define an intervening catheter section and at least one passageway through a delivery lumen of the intervening catheter section for the delivery of at least one therapeutic substance at a therapy site, and opposite a proximal end having a therapeutic injection port, and a first electrical conductor extending along the catheter;

providing a second electrical conductor extending substantially parallel to the intervening catheter section of the catheter, wherein the second electrical conductor includes an outer coaxial conductive element and wherein the outer coaxial conductive element of the second electrical conductor is absent across from the intervening catheter section to allow for creation of an electrical field across the first and second electrical conductors;

inserting the catheter at a first insertion site into a blood vessel of a patient along a first axis;

inserting the second electrical conductor percutaneously at a second insertion site through tissue of the therapy site substantially parallel to the intervening catheter section of the catheter along a second axis;

injecting the at least one therapeutic substance into the therapeutic injection port of the catheter and through the delivery lumen of the intervening catheter section to deliver the at least one therapeutic substance into surrounding cells of the therapy site; and

delivering an electrical charge to the second electrical conductor to produce a voltage across the first and second electrical conductors configured to increase cell membrane permeability of the surrounding cells of the therapy site.

12. The method of claim **11**, further comprising inserting the second electrical conductor approximately 5 to 30 mm from the catheter.

13. The method of claim **11**, wherein the second electrical conductor is inserted at approximately the same angle with respect to a longitudinal axis of the patient as an angle of the catheter with respect to the longitudinal axis of the patient.

14. The method of claim **11**, further comprising producing an electric field in a plane containing the first and second axes wherein equipotentials of the electric field are substantially evenly spaced between the first and the second electrical conductors.

15. The method of claim **11**, further comprising producing an electric field wherein equipotentials of the electric field in a plane containing the first and second axes are substantially parallel between the first and the second electrical conductors.

16. The method of claim **11**, further comprising moving a position of at least one of the first and second inflatable balloon to vary a length of the intervening catheter section.

17. The method of claim **11**, further comprising

removing the second electrical conductor from the second insertion site; and

inserting the second electrical conductor at a third insertion site through tissue substantially parallel to the intervening catheter section of the catheter.

18. The method of claim **11**, further comprising grounding the first electrical conductor.

19. The method of claim **11**, wherein the blood vessel is located within a vascularized organ, tissue, or tumor.

20. A method for delivering one or more therapeutic substance to a patient, comprising:

providing a catheter comprising a distal end having an intervening catheter section and at least one passageway through a delivery lumen of the intervening catheter section for the delivery of at least one therapeutic substance at a therapy site, and opposite a proximal end having a therapeutic injection port;

providing a first electrical conductor extending along the catheter wherein the first electrical conductor includes an outer coaxial conductive element;

providing a second electrical conductor extending substantially parallel to the first electrical conductor, wherein the second electrical conductor includes an outer coaxial conductive element;

wherein the outer coaxial conductive element of the first and second electrical conductors is absent across from the intervening catheter section to allow for creation of an electrical field across the first and second electrical conductors;

inserting the catheter at a first insertion site into a blood vessel of a patient along a first axis;

inserting the first electrical conductor percutaneously at a second insertion site through tissue of the therapy site substantially parallel to the intervening catheter section of the catheter along a second axis;

inserting the second electrical conductor percutaneously at a third insertion site through tissue of the therapy site substantially parallel to the intervening catheter section of the catheter along a third axis;

injecting the at least one therapeutic substance into the therapeutic injection port of the catheter and through the delivery lumen of the intervening catheter section to deliver the at least one therapeutic substance into surrounding cells of the therapy site; and

delivering an electrical charge to at least one of the first and second electrical conductor to produce a voltage

across the first and second electrical conductors configured to increase cell membrane permeability of the surrounding cells of the therapy site.

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