

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)



WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

PCT

<p>(51) International Patent Classification<sup>6</sup> : <b>A61N 1/30</b></p>	<p><b>A1</b></p>	<p>(11) International Publication Number: <b>WO 98/47562</b></p> <p>(43) International Publication Date: 29 October 1998 (29.10.98)</p>
<p>(21) International Application Number: PCT/US98/08183</p> <p>(22) International Filing Date: 23 April 1998 (23.04.98)</p> <p>(30) Priority Data: 08/845,553 US 24 April 1997 (24.04.97)</p>	<p>(71) Applicant: ICHOR MEDICAL SYSTEMS, INC. [US/US]; Building 2, 3550 General Atomics Court, San Diego, CA 92121 (US).</p> <p>(71)(72) Applicant and Inventor: BERNARD, Robert, M. [US/US]; P.O. Box 9960, Rancho Santa Fe, CA 92067 (US).</p> <p>(74) Agent: WESSEMAN, James, C.; The Law Offices of James C. Weseman, Suite 1600, 401 West A Street, San Diego, CA 92101 (US).</p>	<p>(81) Designated States: AU, CA, JP, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report.</i></p>
<p>(54) Title: ELECTRODES AND ELECTRODE ARRAYS</p>		

(57) Abstract  
Electrodes and electrode array apparatus and systems for *in vivo* delivery of electrical waveforms rendering therapeutic benefit to the patient are disclosed.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

<b>AL</b>	Albania	<b>ES</b>	Spain	<b>LS</b>	Lesotho	<b>SI</b>	Slovenia
<b>AM</b>	Armenia	<b>FI</b>	Finland	<b>LT</b>	Lithuania	<b>SK</b>	Slovakia
<b>AT</b>	Austria	<b>FR</b>	France	<b>LU</b>	Luxembourg	<b>SN</b>	Senegal
<b>AU</b>	Australia	<b>GA</b>	Gabon	<b>LV</b>	Latvia	<b>SZ</b>	Swaziland
<b>AZ</b>	Azerbaijan	<b>GB</b>	United Kingdom	<b>MC</b>	Monaco	<b>TD</b>	Chad
<b>BA</b>	Bosnia and Herzegovina	<b>GE</b>	Georgia	<b>MD</b>	Republic of Moldova	<b>TG</b>	Togo
<b>BB</b>	Barbados	<b>GH</b>	Ghana	<b>MG</b>	Madagascar	<b>TJ</b>	Tajikistan
<b>BE</b>	Belgium	<b>GN</b>	Guinea	<b>MK</b>	The former Yugoslav Republic of Macedonia	<b>TM</b>	Turkmenistan
<b>BF</b>	Burkina Faso	<b>GR</b>	Greece			<b>TR</b>	Turkey
<b>BG</b>	Bulgaria	<b>HU</b>	Hungary	<b>ML</b>	Mali	<b>TT</b>	Trinidad and Tobago
<b>BJ</b>	Benin	<b>IE</b>	Ireland	<b>MN</b>	Mongolia	<b>UA</b>	Ukraine
<b>BR</b>	Brazil	<b>IL</b>	Israel	<b>MR</b>	Mauritania	<b>UG</b>	Uganda
<b>BY</b>	Belarus	<b>IS</b>	Iceland	<b>MW</b>	Malawi	<b>US</b>	United States of America
<b>CA</b>	Canada	<b>IT</b>	Italy	<b>MX</b>	Mexico	<b>UZ</b>	Uzbekistan
<b>CF</b>	Central African Republic	<b>JP</b>	Japan	<b>NE</b>	Niger	<b>VN</b>	Viet Nam
<b>CG</b>	Congo	<b>KE</b>	Kenya	<b>NL</b>	Netherlands	<b>YU</b>	Yugoslavia
<b>CH</b>	Switzerland	<b>KG</b>	Kyrgyzstan	<b>NO</b>	Norway	<b>ZW</b>	Zimbabwe
<b>CI</b>	Côte d'Ivoire	<b>KP</b>	Democratic People's Republic of Korea	<b>NZ</b>	New Zealand		
<b>CM</b>	Cameroon		Republic of Korea	<b>PL</b>	Poland		
<b>CN</b>	China	<b>KR</b>	Republic of Korea	<b>PT</b>	Portugal		
<b>CU</b>	Cuba	<b>KZ</b>	Kazakstan	<b>RO</b>	Romania		
<b>CZ</b>	Czech Republic	<b>LC</b>	Saint Lucia	<b>RU</b>	Russian Federation		
<b>DE</b>	Germany	<b>LI</b>	Liechtenstein	<b>SD</b>	Sudan		
<b>DK</b>	Denmark	<b>LK</b>	Sri Lanka	<b>SE</b>	Sweden		
<b>EE</b>	Estonia	<b>LR</b>	Liberia	<b>SG</b>	Singapore		

DescriptionElectrodes and Electrode ArraysTechnical Field

5 The present invention relates to the delivery of electrical waveforms and, more particularly, to the design of electrodes and electrode arrays for efficiently delivering electrical waveforms *in vivo*.

Background of the Invention

10 There exists a broad range of potential applications for the *in vivo* delivery of electrical waveforms, including bone repair, dermal wound healing, nerve regeneration, transport and delivery of therapeutic agents, and the like. Certain known techniques utilizing such electrical waveforms are generally referred to as iontophoresis, electro-osmosis, electroporation, and electropermeabilization. As there is limited understanding of the phenomenon known as electroporation, the terms electroporation and electropermeabilization are often used interchangeably.

15 Iontophoresis involves the application of electric currents to drive or repel oppositely charged particles through tissue. Iontophoretic devices have been known since the early 1900's. U.S. Pat. Nos. 3,991,755; 4,141,359; 4,398,545 and 4,250,878 disclose examples and some applications of such devices.

20 Electro-osmosis occurs when an electric field is applied parallel to a charged surface in contact with a solution. The net ion movement causes a hydrodynamic flow of all molecules which are nearby in the solution (Dimitrov *et al.* (1990)). During electroporation, the transport of therapeutic agent across the cell membrane is commonly believed to involve diffusion, the movement of molecules from areas of higher concentration to areas of lower concentration. This transmembrane movement into the cytosol of electroporated cells may be enhanced by electro-osmosis (Sowers  
25 (1992) pp. 120-125).

30 Electroporation refers to the application of electric fields of sufficient intensity and duration as to induce transient increases in cell membrane permeability. The cell membrane is a selectively permeable barrier that greatly inhibits the penetration of many therapeutic agents into the cytosol. As a comparative example, Mir *et al.* (1992)

report a 10,000-fold increase in the cytotoxic activity of bleomycin, a normally impermeable chemotherapeutic agent, in the electroporated cells.

5 Rols *et al.* (1990) describe electroporation as a threshold dependent phenomenon in that electric field intensity must be higher than a critical threshold to induce cell permeability. They further report that the extent and duration of membrane permeabilization is dependent on pulse duration and number. Provided that the electric field strength was not too high and the pulse duration not too long, electroporation of the cell membrane appears reversible (Zimmerman (1986) pg 177). Thus there exists an opportunity for the use of electroporation of cell membranes to achieve therapeutic benefits. In order to achieve success, the electric fields propagated in tissue by the delivery of specific electrical waveforms must apply sufficient transmembrane voltage and pulse duration to induce cell membrane permeability, yet not exceed inherent upper limits leading to cell lysis (death).

15 Other than transdermal or transcutaneous applications, the *in vivo* electroporation of cell membranes is a relatively limited field. In U.S. Pat. No. 5,273,525 to Hofmann, and U.S. Pat. No. 5,389,069 to Weaver, a description is given of a two electrode system for acute placement during tissue electroporation.

20 Nishi, *et al.* (1996), Ceberg, *et al.* (1994), Salford, *et al.* (1993) and Okino, *et al.* (1987) also describe two electrode systems for tissue electroporation. Where described therein, the electrodes are of rod type (needle) construction, acutely placed in tissue, and spaced approximately 0.5-2cm apart. However, the prior art does not provide clear guidance as to the need for uniformity in the electric field propagation. Additionally, there are not known to be methods for the confinement of threshold level field intensities to the targeted tissue.

25 As depicted in Figure 1, panel A, the electric field propagated in tissue by a two electrode system **20a-20b** as described in the prior art would be considerably weaker in the region of tissue that is proximal to the midpoint between the electrodes (represented as the dashed box **22**). In fact, the field strength in the tissue will weaken geometrically as the distance from either electrode **20a**, **20b** is increased (panel B), and the field strength in the mid-region of tissue will also weaken geometrically as the distance "L" between the two electrodes is increased. As electroporation is considered to be a threshold-dependent phenomenon, with inherent upper limits due to the risk of

30

cell lysis, a two electrode system is poorly suited to establish uniform electric field coverage, i.e., uniform electroporation, in the tissue targeted for treatment.

Plate-type electrodes **24a**, **24b** aligned in parallel (see Figure 2) have been proposed to provide a uniform electric field **26** for electrochemotherapy delivered transcutaneously (U.S. Pat. No. 5,468,223 to Mir), and U.S. Pat. No. 5,439,440 to Hofmann describes an electrode for *in vivo* electroporation as spaced apart parallel arrays of needle electrodes **28a**, **28b**, **28c**, **28d** mounted on a dielectric support member **30** (see Figure 3). This design allows adjustments in needle depth and spacing between the parallel arrays (separated by distance L), but not the spacing of electrodes within each array **32**. As disclosed, the array design has features that suggest similarity to the plate-type electrodes of Figure 2. However, in order to approach electric field uniformity (field **26** in Figure 2), the spacing **32** between adjacent electrodes **28a**, **28b** in the same array would need to be in the range of 0.25 L or less. The anatomy of the tissue involved may limit the number of electrodes that can be spaced within the targeted region. If the spacing between adjacent electrodes on the array is much greater than 0.25 L, then the same field uniformity problems noted previously will remain for this array design. Furthermore, although the needle arrays are described as adjustable in depth, there is no disclosure providing a means to confine the field effects for deep tissue applications in the third dimensional axis relative to the electrode arrays.

Thus, it would be desirable to provide a means to propagate electric fields of adequate intensity for a three dimensional region of tissue so as to achieve uniform electroporation, while mitigating electric field-induced cell lysis. In addition, there is a need to confine such therapeutic field effect to the targeted region of tissue.

It is also considered desirable to provide the means to implement effective *in vivo* therapies utilizing electroporation that rely on: (i) adequate transmembrane voltages, i.e., adequate electric field intensities, propagated throughout a predetermined region of tissue, (ii) minimization of cell lysis due to electrical waveform delivery, most likely to occur in the electrode milieu where electric field intensities are the greatest, (iii) confinement of therapeutic electric field effects to the predetermined region of tissue, and (iv) adequate concentration of therapeutic agents in the extracellular space of the cells in the tissue being treated.

### Disclosure of the Invention

The present invention provides electrode and electrode array apparatus which facilitates the efficient delivery of electrical waveforms, and particularly delivery to a predetermined three dimensional region of tissue within a patient. Electrical waveforms of certain parameters, comprising many different therapeutic objectives and techniques, may be efficiently delivered through the present invention, while minimizing the risk of trauma to the patient.

In one aspect, the invention provides an electrode array having at least three individually addressable electrodes disposed so as to form a triangle in a plane intersecting the electrodes.

In another aspect of the invention, a system is provided wherein the electrode array is located *in situ* in a patient. When combined with elongate electrodes having defined conductive regions, the system defines a predetermined treatment region within the tissue of the patient.

A further aspect of the invention provides an elongate electrode apparatus having a means for connecting the electrode to a source of electrical signals, an electrically conductive region located distal to the connecting means, and an electrically nonconductive region located proximal to the connecting means.

The invention also provides an efficient means of expanding the electrode array "cell," or any alternative cell design, into a multi-cell grid for controlled electric field propagation in an expanded cross sectional area of the predetermined region. Penetrating the tissue, and designed for electric field confinement along one axis of the predetermined region, individual electrodes may be of varying lengths and proportions, comprising a distal electrically-conductive portion and a proximal electrically-nonconductive portion.

In certain embodiments, one can separately control each individual electrode, in order to achieve the desired therapeutic effect while minimizing attendant tissue trauma.

### Brief Description of the Drawings

Figure 1, panel A is a two dimensional schematic view depicting the field lines and approximate electric field intensity for a two electrode model, wherein the intra-electrode distance is  $L$  and the dashed box positioned midway between the two electrodes indicates the region of lowest electric field strength, and panel B is a graphic representation of the relationship between the distance from the electrode and the electric field strength;

Figure 2 is a schematic view depicting the field lines and approximate electric field strength for a plate electrode model, wherein the plates generate approximately uniform fields in the central region and weaker fringe electric fields at the edges;

Figure 3 depicts an electrode array of the prior art which includes spaced apart parallel arrays of needle electrodes mounted on a dielectric support member;

Figure 4 depicts an electrode array configuration in accordance with the invention, exemplified as a tricell array mounted on a dielectric support member;

Figure 5 depicts the electric field generated in the array of Figure 4 in a characteristic trilobe pattern, wherein the shaded area indicates the region where the electric field strength exceeds the electroporation threshold;

Figure 6 depicts three interlocking trilobe field patterns resulting from the sequentially shifting electric field activation of the array of Figure 4;

Figure 7 illustrates a box array of needle electrodes with a core electrode mounted on a dielectric support member;

Figure 8 illustrates a box array of needle electrodes without a core electrode mounted on a dielectric support member;

Figure 9 depicts a hexagonal electrode array of needle electrodes mounted on a dielectric support member;

Figure 10 depicts the expansion of the tricell array of Figure 4 into a trigrid pattern of interlocking tricells;

Figure 11 depicts the use of a four channel control means to activate the tricells in a trigrid, so as to provide the interlocking trilobe field patterns of Figure 6;

Figure 12 depicts the individual trilobe field patterns resulting from the four channel control means used to activate the tricells in a trigrid, with the arrows indicating the polarity along coincident lines;

Figure 13 depicts the expansion of the box array of Figure 7 into a multi cell grid pattern of overlapping cells;

Figure 14 depicts the expansion of the box array of Figure 8 into a multi cell grid pattern of overlapping cells;

5 Figure 15 depicts the expansion of the hexagonal array of Figure 9 into a multi cell grid pattern of overlapping cells;

Figure 16 depicts the placement of an electrode array of the invention *in situ* in the brain of a patient;

10 Figure 17 depicts cascaded electrical signal pulses of increasing electric field intensity;

Figure 18 depicts the cascaded pulses of Figure 17, followed by pulses creating electric fields of decreasing intensity;

Figure 19 is a Kaplan-Meier survival chart for the experimental subjects described in example 2;

15 Figure 20 is a Kaplan-Meier survival chart for the experimental subjects described in example 3;

Figure 21 is a Kaplan-Meier survival chart for the experimental subjects described in example 4; and

20 Figure 22 is a Kaplan-Meier survival chart for the experimental subjects described in example 5.

### Detailed Description of the Invention

The present invention provides apparatus and systems which facilitate the efficient delivery of electrical waveforms, and particularly such waveform delivery to a predetermined three dimensional region of tissue within a patient. Electrical waveforms of certain parameters, comprising many different therapeutic objectives and techniques, may be efficiently delivered through the present invention, while minimizing the risk of surgical trauma to the patient.

In one aspect, the invention provides an electrode array having at least three individually addressable electrodes disposed so as to form a triangle in a plane intersecting the electrodes. The electrodes can be provided in any form capable of conducting an electrical signal and establishing an electric field between oppositely-charged electrodes. Desirably, such electrodes will be of surgical quality, bio-compatible, and capable of withstanding the demands of implantation and use in a patient. Materials commonly employed in the construction of such electrodes include nickel titanium, gold, silver, stainless steel, platinum, platinum iridium alloys, graphite, ceramic, and the like.

In certain embodiments, and in one aspect of the invention, the electrodes will be elongate, for example rod electrodes **34a**, **34b**, **34c** (see Figure 4), so as to simplify the surgical implantation of the electrode in the patient. Representative of such rod electrodes are needles such as acupuncture needles, which are usually of surgical quality, strength and (presumptively) bio-compatible stainless steel construction. However, it has been found that the relatively sharp point of such a needle electrode may provoke arcing of the electric field, particularly at the electrode delivering the electrons in the propagation of the electric field (i.e. the "pulse electrode"). Thus it has been found desirable to provide a rod electrode where the point of the electrode distal from the source of electrical signals includes a radius of curvature sufficient to substantially eliminate arcing at the electric field strengths utilized in the practice of the present invention, for example in the range of 0.1 to 1mm. It has also been found that the diameter of the rod electrode has a similar effect on arcing potential, due in part to the relationship of the electrode diameter to the radius of curvature of the point. Therefore, the rod electrode itself will desirably also be of sufficient diameter to satisfy the arcing-reduction conditions as well.

Such elongate electrodes will desirably include a means for connecting to a source of electrical signals **36** and a non-conductive region **38** located proximal to the signal source. In this context the term "non-conductive" is taken to mean that the electrode does not permit an electric field to propagate radially from the electrode in the non-conductive region, while allowing the electrical signal or waveform to proceed axially or longitudinally through the non-conductive region. Such electrodes will also include a conductive region **40** located distal from the signal source. Optionally, there can be a plurality of conductive and non-conductive regions established in the electrode **34**, for example where the distal-most region of the electrode is provided as a non-conductive region **41**, in order to more precisely define the conductive region **40**. Conveniently, these electrode regions **38**, **40** (and optionally region **41**) can be provided by shielding portions of the electrode **34** with a dielectric material, for example, with plastic, Teflon<sup>®</sup>, ceramic, graphite, polyimide, and the like. Alternatively, the electrode may be of composite construction, for example where the cross sectional diameter of the electrode is maintained relatively constant in order to facilitate insertion of the electrode **34** into the tissue of the patient.

In addition to facilitating surgical implantation, such an electrode **34** with a nonconductive region **38** (and optionally region **41**) will permit the establishment of a predetermined region of tissue for treatment, where two of the dimensions are established by the geometry of the electrode array, and the third dimension is established by the length of the conductive region **40** of the electrode **34**, i.e. the "effective electrode length."

For example, as also depicted in Figure 4, one aspect of the invention is a three electrode array (termed a "tricell") comprising three elongate electrodes of predetermined length, disposed approximately parallel to each other, and spatially oriented in the "X" and "Y" dimensions of a three dimensional predetermined region, desirably in the approximate geometrical shape of an equilateral triangle. The "Z" or third dimension of the predetermined region is dependent on the effective electrode length established by the conductive region(s).

Thus, in another aspect of the invention, a system is provided wherein the present electrode array is located *in situ* in a patient. When combined with elongate electrodes having defined conductive regions establishing effective electrode lengths,

the system defines a predetermined treatment region within the tissue of the patient. This predetermined treatment region can then be subject to the electropermeabilization effects of the electric fields, promoting the introduction of therapeutic agents into cells within the region.

5           Although the present invention can be readily applied in any environment in which the delivery of electrical waveforms is considered desirable, the invention is particularly suited for the delivery of electrical waveforms *in vivo* to patients expected to benefit from such treatment. Such therapeutic uses presently include bone repair, dermal wound healing, nerve regeneration, transport and delivery of therapeutic agents,  
10           and the like. For example, the invention will find use in aiding in the administration of therapeutic agents in situations in which such administration has been considered problematic. Among these situations are included chemotherapy, and particularly chemotherapeutic treatment of brain tumors.

          As used herein, the term "therapeutic agent" includes pharmacological agents,  
15           chemotherapeutic agents, nucleic acids, genes, antibodies and all other compositions which provide therapeutic benefit to a patient in need of treatment. One therapeutic application of electroporation consists of infusion of an anti-cancer drug into the patient, and electroporation of the drug into the tumor cells by applying electric fields between the electrodes.

20           The present invention provides an array of individual electrodes organized into a geometry which efficiently delivers electrical waveforms to a predetermined region of tissue within a patient. One aspect of this efficiency is to maximize the electrical waveform intensity and uniformity for a given intra-electrode distance while minimizing the actual number of electrodes which must be placed in order to insure  
25           complete coverage of the predetermined treatment region

          In overview, the present invention thus provides an apparatus comprising an electrode array of a pre-determined geometry which can be implanted as a system *in situ* in a patient. The electrodes are each connected through conductive cables to a high voltage switching device, for example a Cyto Pulse™ PA-101 sequencer (available  
30           from Cyto Pulse Sciences, Inc., Columbia, Maryland) with software modifications to permit simultaneous activation of multiple electrodes. The switching device will in turn be connected to a suitable power supply or pulse generator, for example, a

Cyto Pulse™ PA 2000 or PA 4000 power supply, or a BTX™ T820 power supply (available from Genetronics, San Diego, California). Also provided will be a means for individually addressing the electrodes so that electric fields can be propagated between preselected electrodes in a pattern which insures thorough coverage of the predetermined tissue region. The switching of electrical signals between the individual electrodes can be accomplished by numerous means, e.g. manually, mechanically, electrically, or by means of a circuit controlled by a programmed digital computer. However, the precise mechanism used in switching the electrical signals between individual electrodes will largely be chosen as a matter of convenience. Thus, in certain embodiments, one can separately control each individual electrode, in order to achieve the desired therapeutic effect while minimizing attendant tissue trauma, as disclosed in U.S. Patent Application Serial No. 08/476,714, the entire contents of which is incorporated herein by this reference.

As noted previously, the amplitude of the waveform applied to the array is based on the intra-electrode distance and should be selected so as to propagate electric field strengths sufficient to obtain the intended therapeutic benefits. Once the intra-electrode distance is determined and the settings for the power supply are selected, the present array will allow for the efficient delivery of the electrical waveforms to the predetermined tissue region within the patient.

In operation, an array as described above is disposed within the tissue of a host patient so as to adequately define the intended region for therapeutic treatment. Once the array is established and connected to the pulse generator, electric signals are directed to the electrodes in order to propagate electric fields of predetermined amplitude and duration through the tissue between the electrodes. The parameters of the signal are generally selected so that the tissue between the electrodes is subjected to electric fields strengths of high intensity and short duration. The voltage will be adjusted so that the generated field has the desired intensity. These fields will make the membranes of preselected cells in the tissue transiently permeable in order to permit the therapeutic agents to enter the cells in the predetermined region. This transient increase in permeability is believed to result from the temporary formation of pores within the cell membranes large enough to permit migration of the agent through the membrane and into the cytosol.

As illustrated in Figure 4, the present array can be desirably established as conductive rod electrodes 34a, 34b, 34c, optionally mounted on an insulated or dielectric carrier or support member 45 and held in a predetermined geometry while allowing the electrodes to be inserted to a desired depth in the tissue. Alternatively, the electrodes can be implanted individually, and then optionally affixed to a support or directly to the patient (as depicted schematically in Figure 16). Desirably, the electrodes can be provided with a penetration stop so that the predetermined depth of insertion can be achieved in minimal time. Optionally, the geometry of the array established on the carrier can be subject to adjustment for intra-electrode distance, and a distance spacing sensor may be used to generate a signal either to the operator or directly to the pulse generator so that voltage adjustments can be made in order to establish the desired electric field.

In operation, an array as above described is selected and optionally mounted on a suitable carrier which can then be stereotaxically positioned in relationship to the patient so as to facilitate the accurate and rapid establishment of the electrode array in situ in the patient. In certain embodiments of the invention, acute placement of the electrodes will be made into the peripheral regions of the cavity remaining after surgical resection of a tumor mass. Electrode array geometry can be maintained by a support, while electrode placement and depth would be determined by the surgeon. The therapeutic agent will then be infused into the patient either systemically or by direct injection into the vasculature of the predetermined tissue region or directly into the tissue itself, or by methods as described in Application Serial No. 08/476,714.

The function of the pulse or signal generator is to generate a predetermined electrical waveform which, when applied to the electrodes, results in the propagation of electric fields of the predetermined amplitude and duration through the tissue that is positioned between the electrodes. Preferably, these waveforms are applied repeatedly so as to optimize the electropermeability effect.

In the practice of the invention, two elements are ordinarily controlled to provide the intended benefits: i) the electrical waveform parameters delivered by the signal generator, and ii) the electrical state of each individual electrode within the array during the delivery of the waveform.

The electrical waveform parameters which can be controlled include the type of waveform, the signal amplitude, and the pulse duration. These individual parameters determine the characteristics of a single pulse. In certain embodiments it is desirable to vary these characteristics between pulses. Pulse-to-pulse variability dictates that one or more individual parameters, such as amplitude, be manipulated from one pulse to the next in order to increase safety or therapeutic efficacy. For example, Figure 18 depicts a pulse train wherein a high amplitude pulse **46** is followed by a series of lower amplitude pulses **48**. Pulse sequences determine the manner in which individual pulses are integrated. In this regard, the number of, and time interval between, individual pulses in a sequence is regulated, as well as the number of pulse sequences in a course of therapeutic treatment (e.g. **46**, **46'**, **46''** in Figure 18).

Control of the electrical state of the individual electrodes involves a system capable of individually addressing electrodes within an array. One embodiment of such control would incorporate a high voltage switching device wherein the electrical state of each electrode is controlled by an individual switch. Each switch would have three settings: i) pulse positive (+), ii) pulse negative (-), and iii) open (i.e. off). Together these switches could be electrically activated in any of numerous possible combinations. Although an array of "tricells" can be pulsed in a "trigrig" pattern with only four channels (as depicted in Figure 11), system flexibility in establishing alternative array patterns suggests the use of individual switches for each electrode in the array.

Where desirable, the integrated control of these and other elements of the invention can be accomplished by utilizing microprocessor or digital computer technologies. Additionally, data pertaining to realtime waveform delivery can be digitized and acquired for evaluation and verification of proper system function. Desirably, such data could be stored within the local system until uploaded to a central computer for further use.

Electric fields will be established within the target tissue by delivery of electrical waveforms to preselected electrodes. The parameters of the signal will define the electric field strength  $E$  (in kV/cm) within the tissue. Each protocol and tissue will have its own characteristics which determine the critical field strength for optimum therapeutic effect. This tissue variation is due to cell size, membrane composition and the individual characteristics of the cell membrane itself. Generally, the required field

strength varies inversely with the size of the cells contained within the tissue. Mammalian tissue generally requires field strengths of between approximately 0.2 kV/cm to 3 kV/cm for electroporation.

5 The electrical waveform provided by the generator can be an exponentially decaying pulse, a square pulse, a unipolar oscillating pulse train or a bipolar oscillating pulse train. Square pulses are generally sufficient to implement the majority of techniques. The electric field strength can desirably be between 0.2 kV/cm to 20 kV/cm, more commonly 0.5 kV/cm to 3 kV/cm. The pulse duration can be from 100 nanoseconds to 100 milliseconds and there can be from 1 to 10,000 pulses per 10 second. Of course, the waveform, strength and pulse duration will be dependent on the tissue in the predetermined region and the type of therapeutic agent that is to permeate the cells via electroporation.

In certain embodiments, the present invention provides an apparatus and system for the transport and delivery of therapeutic agents *in vivo* to a predetermined region of 15 tissue within the host. Such transport and delivery consists of, in part: i) the localized circulatory extravasation of systemically administered therapeutic agents; (ii) the local extracellular infusion of therapeutic agents; (iii) the distribution and concentration of therapeutic agent within the predetermined region of tissue; (iv) the electroporation of cell membranes within the predetermined region of tissue; and (v) the transport of the 20 therapeutic agents into the cytosol of the electroporated cells within the predetermined region of tissue.

As discussed above, one embodiment of the electrode array, representing a single electrode cell (a tricell as depicted in Figure 4), is comprised of three 25 individually addressable penetrating electrodes ordinarily of approximately uniform predetermined lengths, desirably of biologically compatible construction and with electrically nonconductive proximal regions and electrically conductive distal regions; such electrically conductive distal regions defining the effective electrode length. In certain embodiments, the effective electrode length of each individual electrode may be different and will be of a predetermined value in order to confine the electric field 30 effects to the predetermined region for tissue treatment. Such predetermination of electrode length shall be of sufficient value as to assure appropriate consideration for

the weakened electric field effects encountered at either end of the electrode, as depicted in Figure 2 (i.e. the field-fringe effect 33).

Of particular benefit, in embodiments dependent on electric field threshold to achieve desired therapeutic effect, such as electroporation, is the manner in which the waveforms are applied to a trigonous portion of the predetermined treatment region through the tricell (see Figure 5). When applying an electrical waveform by configuring one primary 42 and two secondary electrodes 44a, 44b in each tricell (where the polarity of the primary electrode can be either + or -), the electric field lines converge 43, resulting in relatively uniform, threshold-level field intensities throughout the trigonous region or "trilobe" adjacent to the primary electrode. In a similar manner, the other two electrode configurations can be sequentially pulsed, resulting in three interlaced "trilobes" yielding complete therapeutic coverage of the tricell (see Figure 6). Selected alternative electrode array geometries are depicted in Figures 7, 8 and 9, each having distinct disadvantages when compared to the tricell.

In one embodiment, wherein an electroporation protocol is administered, the voltage applied to electrode pairs is reported in the literature as a function of the distance, "L", between those pairs, typically in kV/cm (see Figures 4, 7, 8 and 9). Based upon the literature pertaining to tissue electroporation, it appears that higher voltage commensurate with larger L is more problematic than smaller voltage and the corresponding smaller L, suggesting that one practicing *in vivo* electroporation cannot simply expand L to any desired distance and expect an overall satisfactory therapeutic effect. Cell lysis due to high electric field strengths around the electrode tract must be considered, as well as the weakened state of the electric field midway between electrode pairs (see Figure 1); a weakening that is more prevalent in electrode array geometries other than the present tricell array.

Additionally, an optimal efficiency of electrodes used per tissue volume treated must be achieved in order to minimize surgical complications correlated to the number of electrodes implanted and the requisite time spent occupying the operating room. Thus, the present invention also provides an efficient means of expanding the electrode array tricell, or any alternative cell design, into a multi-cell grid for controlled electric field propagation in an expanded cross sectional area of the predetermined region. In order to alleviate many of these potential treatment complications, a tricell as depicted

in Figure 4 can be expanded in a multi-cell pattern (i.e., a "trigrig") to provide therapeutic coverage of the "X" and "Y" dimension of a predetermined treatment region which exceeds the linear dimension L (see Figure 10). When compared to other electrode designs configured with the same L (see Figures 13, 14 and 15), the trigrig offers considerable advantages in uniformity of electric field coverage and efficiency when directly comparing the number of electrodes required to treat a given predetermined treatment region. This advantage is an important consideration in any clinical/surgical application. One benefit of this expansion into a trigrig is that once the basic tricell is established, each additional electrode placed in the array creates at least one and possibly two additional cells in the array grid.

Of further benefit in certain embodiments is the manner in which the trigrig can be pulsed in a tricell-interlocking manner, as depicted in Figure 12. This pattern provides complete therapeutic coverage of the predetermined treatment region with only three pulse combinations (see Figure 6), and requires only four electrode channels (see Figure 11) regardless of the number of electrodes in the complete array. Overall tissue trauma during surgery is thus minimized, a unique characteristic of the trigrig array.

Utilizing information provided by MRI, CT scan, or other methods, the optimal trigrig pattern and effective electrode length can be determined, thus defining the predetermined region targeted for treatment. In either tricell or trigrig fashion, these electrodes may be placed acutely for single treatment or chronically for a series of treatments to the same predetermined region in the patient.

To mitigate cell lysis associated with the more intense electric fields around the electrodes (inherent to some embodiments), a localized hyperconductance of the extracellular fluids may be desirable in order to partially shunt or shift field intensities away from the electrode milieu and toward the more central portions of L in the predetermined region. This may be accomplished by direct injection of hyperconductive solutions by local injection, or by infusion through a hollow core in the electrode. Alternatively, in certain embodiments, such as electroporation, electrical pulse parameters determined to be of therapeutic benefit may be adapted in such a way as to initially induce localized increases in the conductance of the electrode milieu. One method of inducing such effect is a cascaded pulse sequence (see Figure 17) where applied voltages are cascaded from lower values initially **50**, being progressively

increased in each subsequent round 52, 54, and reaching optimal therapeutic pulse parameters in a final round of pulsing.

In embodiments involving Iontophoresis, electrically charged therapeutic agents are desirably distributed through and concentrated within the predetermined region by means of electrical waveforms delivered through the individually addressable electrodes of the present invention.

During electroporation, the transmembrane delivery of therapeutic agent into the cytosol of the permeabilized cells is commonly believed to occur by diffusion.

Electroosmosis may enhance this transmembrane delivery. In one embodiment, electrical waveforms of a lesser intensity (48, 48', 48'' in Figure 18) are delivered through the individually addressable electrodes of the present invention, after the electroporation waveforms have been delivered and before cell membrane resealing, in order to enhance the transport of the extracellular therapeutic agents into the cytosol of the electroporated cells.

The following examples serve to illustrate certain preferred embodiments and aspects of the present invention and are not to be construed as limiting the scope thereof.

### Experimental

In the experimental disclosure which follows, all weights are given in grams (g), milligrams (mg), micrograms ( $\mu\text{g}$ ), nanograms (ng), or picograms (pg), all amounts are given in moles (mol), millimoles (mmol), micromoles ( $\mu\text{mol}$ ), nanomoles (nmol),  
5 picomoles (pmol), or femtomoles (fmol), all concentrations are given as percent by volume (%), proportion by volume (v:v), molar (M), millimolar (mM), micromolar ( $\mu\text{M}$ ), nanomolar (nM), picomolar (pM), femtomolar (fM), or normal (N), all liquid volumes are given in liters (L), milliliters (mL), or microliters ( $\mu\text{L}$ ), all solid volumes are given in cubic centimeters (cc), and linear measurements are given in  
10 millimeters (mm), micrometers ( $\mu\text{m}$ ), or nanometers (nm), unless otherwise indicated.

The following examples demonstrate the practice of the present invention in delivering electrical waveforms to tumor tissue.

#### Example 1: Tumor model used in survival studies.

The experimental brain tumor model employed in the following examples was  
15 the 9L gliosarcoma in the female Fischer rat. Tumor implants consisted of 200,000 9L gliosarcoma cells suspended in  $2.3\mu\text{L}$  of Dulbecco's Phosphate Buffered Saline with 2% rat serum. After anesthetization by intra peritoneal injection of a ketamine/xylazine mixture, the scalp was shaved and swabbed with Betadine<sup>®</sup> solution. After placement in a stereotaxic apparatus, a 1cm incision was made in the scalp above bregma. A burr  
20 hole was drilled in the skull 1mm anterior and 3mm lateral of bregma. The injection needle was lowered stereotactically 4mm deep, into the right caudate nucleus. After slow injection of the cells (4 minutes for  $2.3\mu\text{L}$ ), the needle was raised and the burr hole was sealed with bone wax. After careful irrigation of the area, the wound was closed with surgical staples.

Example 2: Single Treatment - Triangle Electrode Array (Tricell).

On the eighth day post implantation (tumor mass approximately 0.02cc), the rats were again anesthetized with an i.p. injection of a ketamine/xylazine mixture. After placement in the stereotaxic apparatus, the scalp was again disinfected with Betadine®.

5 Another incision was made in the scalp and the burr hole was located. An electrode array comprising three elongate rod electrodes oriented in an approximate equilateral triangle was then placed in the stereotaxic arm. The array was then placed around the burr hole so that each electrode was approximately equidistant from the implant hole. New burr holes were drilled to accommodate the electrodes. The array was then  
10 lowered with the stereotaxic arm to a depth of 5mm.

The femoral vein of the animal was then exposed and 1 unit of bleomycin per kg of bodyweight was injected intravenously over approximately fifteen seconds. After 30 minutes to allow circulation of the bleomycin, the animals were exposed to a regimen of brief high voltage pulses. Each pulse had an amplitude of 450 volts (1 kV/cm based  
15 on the established electrode spacing) and a duration of 100 $\mu$ s. Four pulses were applied at each of three single-primary-two secondary electrode combinations (see Figure 5). After completion of the pulse regimen, the electrode array was slowly extracted, the burr holes sealed with bone wax, and the incision sealed with surgical  
20 staples.

**Results:** In Figure 19, a Kaplan-Meier survival chart illustrates the survival rates for 26 animals treated as described. The x-axis represents days of survival and the y-axis represents the percentage of subject alive on the selected day. As Figure 19 demonstrates, 120 days after implant 43% of the treated animals survived, and showed no outward signs of the presence of a tumor mass. The dashed line represents a control  
25 group which received no treatment.

After 120 days, five of the 11 surviving subjects were sacrificed by cardiac perfusion with 150mL of formalin. The brains of three subjects were then sectioned horizontally at 1mm, 2mm, and 4mm with a thickness of 5 $\mu$ m. The tissue sections were stained with hematoxylin and eosin. Pathological examination revealed that no  
30 viable tumor cells remained in any of the tissue sections.

Example 3: Multiple Treatments - Triangle Electrode Array (Tricell)

Several survival studies have been performed to determine the benefit of multiple treatments. The tumor model from Example 1 was again employed for these experiments. Animal subjects were treated on day eight post-implantation with the protocol outlined in Example 2 for the triangle electrode arrays. On day eleven, the animals were re-anesthetized and, after reopening the scalp and removing the bone wax plugs, the electrodes were lowered into the existing burr holes. The identical treatment procedure was then performed on the animal.

**Results:** In Figure 20, a Kaplan-Meier survival chart illustrates the survival rates for the multiple treatment groups. Fifteen animals received the two treatment procedure as described. As Figure 20 demonstrates, 120 days after implant 87% of the treated animals survived, and showed no outward signs of the presence of a tumor mass. The dashed line represents a control group which received no treatment.

The brains of six of the 13 surviving subjects were then prepared according to the histological procedure of Example 2. Pathological examination of the tissue sections revealed no residual tumor.

Example 4: Multiple Treatments with Multicell Array (Trigrid)

In order to demonstrate the concept of expanding individual cells into a grid format a two-cell triangle (interlocked tricells) was tested on the tumor model from Example 1. Four electrodes were arranged into two approximately equilateral triangles with sides of 3mm. The preparation procedure from example 3 was followed for each subject. The electrode array was lowered to a depth of 5 mm. The pulsing regimen was based on the trigrid pulsing pattern outlined in Figure 12.

"Tri-grid" pulsing: Thirty minutes after the injection of the bleomycin agent, the array was pulsed four times in each of three combinations with a magnitude of 300 volts (1 kV/cm based on electrode spacing) and a pulse duration of 100 $\mu$ sec. The electrodes were pulsed so that each "cell" was configured with a single primary and two secondary electrodes. All four of the electrodes were active in each configuration, creating an interlocking triangle array.

**Results:** In Figure 21, a Kaplan-Meier survival chart illustrates the survival rates for the animals treated as described. As Figure 21 demonstrates, 120 days after implant 75% of the treated animals survived, and showed no outward signs of the presence of a tumor mass. The dashed line represents a control group which received no treatment.

The brains of the six surviving subjects were then prepared according to the histological procedure of Example 2. Pathological examination of the tissue sections revealed no residual tumor.

Example 5: Protocols for Control Subjects

Three control protocols were performed to compare with the treatment groups. All subjects were implanted according to the procedure outlined in Example 1. The first group of 35 rats received no treatment (Drug (D) -, Electrical Pulsing (EP) -).

5 The second group of eight rats were treated on day eight post implant in accordance with the procedure of Example 2, except they did not receive the therapeutic agent (D-, EP+). The third group of eight rats were treated on day eight post implant in accordance with the procedure of Example 2, except they did not receive the electrical pulses (D+, EP-).

10 **Results:** In Figure 22, a Kaplan-Meier survival chart illustrates the survival rates for the animals in the control protocols. As Figure 22 demonstrates, no animals from any of the control protocols survived beyond 32 days after implant. There was no significant difference in survival between any of the groups (D- EP-, D- EP+, D+, EP-), demonstrating that both the therapeutic agent and the electrical pulse regimen are  
15 necessary for significant increase in survival.

All patents and patent applications cited in this specification are hereby incorporated by reference as if they had been specifically and individually indicated to be incorporated by reference.

20 Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be apparent to those of ordinary skill in the art in light of the disclosure that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

REFERENCES

## U.S. Patent Documents:

3,991,755	11/1976	Vernon, <i>et al.</i>	128/172.1
4,141,359	2/1979	Jacobsen, <i>et al.</i>	128/172.1
4,250,878	8/1981	Jacobsen, <i>et al.</i>	128/172.1
4,398,545	8/1993	Wilson	128/798
5,019,034	5/1991	Weaver, <i>et al.</i>	604/20
5,215,088	6/1991	Normann, <i>et al.</i>	128/642
5,273,525	12/1993	Hofmann	604/21
5,298,017	3/1994	Theeuwes, <i>et al.</i>	604/20
5,304,120	4/1994	Crandell, <i>et al.</i>	604/52
5,389,069	2/1995	Weaver	604/21
5,439,440	8/1995	Hofmann	604/20
5,468,223	11/1995	Mir	604/51

**Other Publications:**

- Ceberg, *et al.*, *Anti-Cancer Drugs* **5**:463-466 (1994).  
Dimitrov, *et al.*, *Biochim. Biophys. Acta* **1022**:381-392 (1990)  
Mir, *et al.*, *C.R. Acad. Sci. Paris t. 314*, **3**:539-544 (1992)  
Nishi, *et al.* *Cancer Res.* **56**:1050-1055 (1996)  
Okino, *et al.* *Jpn J. Cancer Res.* **78**:1319-1321 (1987)  
Rols, *et al.* *Biophysical J.* **58**:1089-1098 (1990)  
Salford, *et al.* *Biochem. Biophys. Res. Comm.* **194**, **2**:938-943 (1993)  
Sowers in "Guide to Electroporation and Electrofusion," D. Chang ed.,  
Academic Press, San Diego (1992).  
Zimmerman in "Rev. Physiol. Biochem. Pharmacol." **105**:177, Springer-Verlag, New  
York (1986).

Claims:

- 5 1. An apparatus for the delivery of electrical waveforms comprising  
an electrode array having at least three individually addressable  
electrodes disposed so as to form a triangle in a plane intersecting said  
electrodes; and  
electrical signal generating means operatively connected to said  
individually-addressable electrodes for delivering electrical waveforms to said  
electrodes and thereby generating electroporation-inducing electrical fields  
10 between said electrodes.
2. An apparatus as recited in claim 1 wherein the electrodes are elongate.
3. An apparatus as recited in claim 2 wherein the elongate electrodes are  
15 oriented in approximately parallel directions.
4. An apparatus as recited in claim 1 wherein the triangle is of  
approximately equilateral geometry.
- 20 5. An apparatus as recited in claim 1 wherein each of said electrodes  
comprises an electrically conductive region and an electrically nonconductive region.
- 25 6. An apparatus as recited in claim 1 wherein said array comprises at least  
four electrodes disposed so as to form two interconnected triangles in a plane  
intersecting said electrodes.

7. A system for the delivery of electrical waveforms to a patient comprising an electrode array adapted to be implanted in a patient and having at least three individually addressable electrodes disposed so as to form a triangle in a plane intersecting said electrodes; and

5 electrical signal generating means operatively connected to said individually-addressable electrodes for delivering electrical waveforms to said electrodes and thereby generating electroporation-inducing electrical fields between said electrodes.

10 8. A system as recited in claim 7 wherein the electrodes are elongate.

9. A system as recited in claim 8 wherein the elongate electrodes are oriented in approximately parallel directions.

15 10. A system as recited in claim 7 wherein the triangle is of approximately equilateral geometry.

11. A system as recited in claim 7 wherein each of said electrodes comprises an electrically conductive region and an electrically nonconductive region.

20 12. A system as recited in claim 11 wherein the electrically conductive region of said electrodes and the geometry of said array define a predetermined treatment area for said patient.

25 13. A system as recited in claim 7 wherein said array comprises at least four electrodes disposed so as to form two interconnected triangles in a plane intersecting said electrodes.

14. An apparatus for the delivery of electrical waveforms comprising an electrode array having at least four individually addressable electrodes disposed so as to form a plurality of triangles in a plane intersecting said electrodes wherein each such triangle shares a common side with an adjacent triangle.

5

15. An apparatus for the delivery of electrical waveforms comprising an electrical waveform generator which generates waveforms of sufficient intensity and duration so as to increase the permeability of a biological cell membrane subjected to said waveform; and

10

an electrode array operatively connected to said generator and having at least three individually addressable electrodes disposed so as to form a triangle in a plane intersecting said electrodes.

16. An apparatus for the delivery of electrical waveforms comprising an electrical waveform generator which generates waveforms of sufficient intensity and duration so as to increase the permeability of a biological cell membrane subjected to said waveform; and

15

an electrode array operatively connected to said generator and having at least four individually addressable electrodes disposed so as to form a plurality of triangles in a plane intersecting said electrodes and wherein each such triangle shares a common side with an adjacent triangle.

20

17. An apparatus as recited in claim 16 wherein, in each electrode triangle a single primary electrode is in electrically conductive communication with two secondary electrodes.

25

18. An apparatus for the delivery of electrical waveforms comprising an elongate electrode having a proximal end and a distal end and comprising:

means for connecting the proximal end of said electrode to a source of electrical signals,

5 an electrically conductive region located distal to said connecting means, and

an electrically nonconductive region located adjacent to said connecting means.

10 19. An apparatus for the delivery of electrical waveforms comprising an electrode array having at least three individually addressable electrodes according to claim 18 which are disposed so as to form a triangle in a plane intersecting said electrodes, whereby the disposition of the electrodes and the electrically conductive regions of the electrodes determine a three-dimensional region wherein the electrical  
15 waveforms propagate an electric field therebetween.

20 20. A system for the delivery of electrical waveforms to a patient comprising an electrode array according to claim 19 adapted to be disposed in a patient so that a three-dimensional region of tissue is established wherein the electrical waveforms propagate an electric field substantially confined to said region.

FIG. 1A

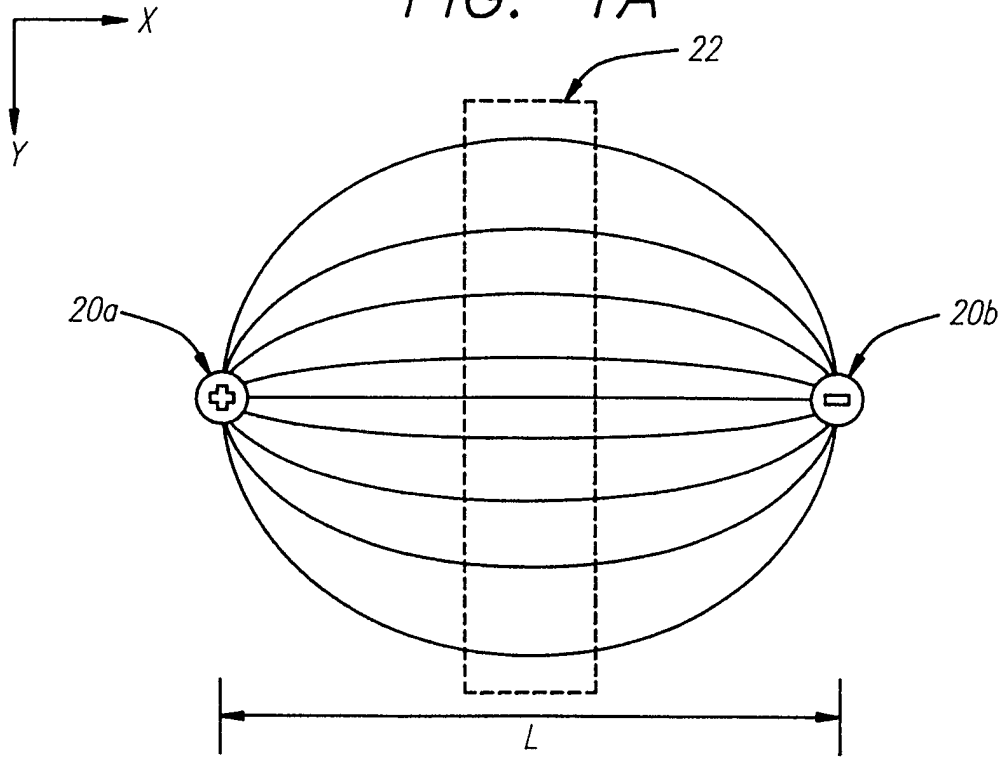
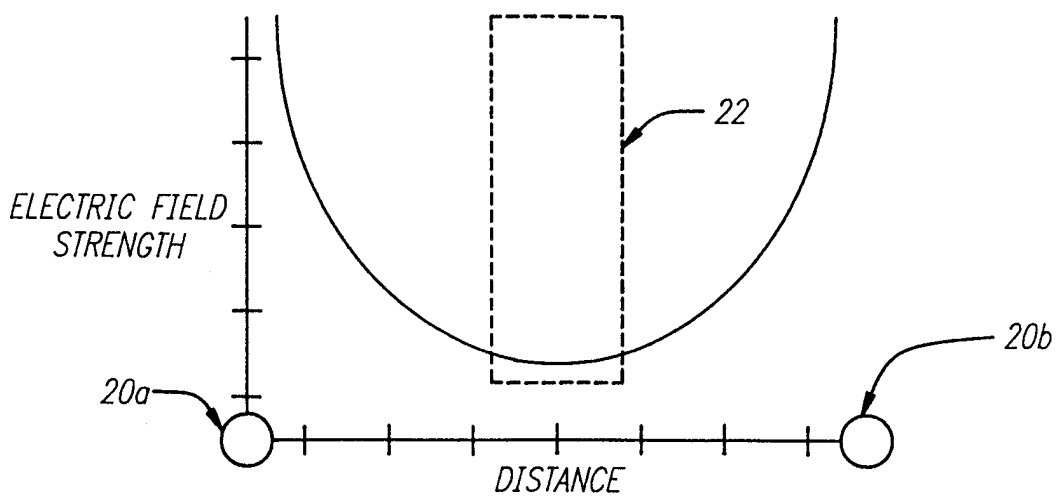


FIG. 1B



2/14

FIG. 2

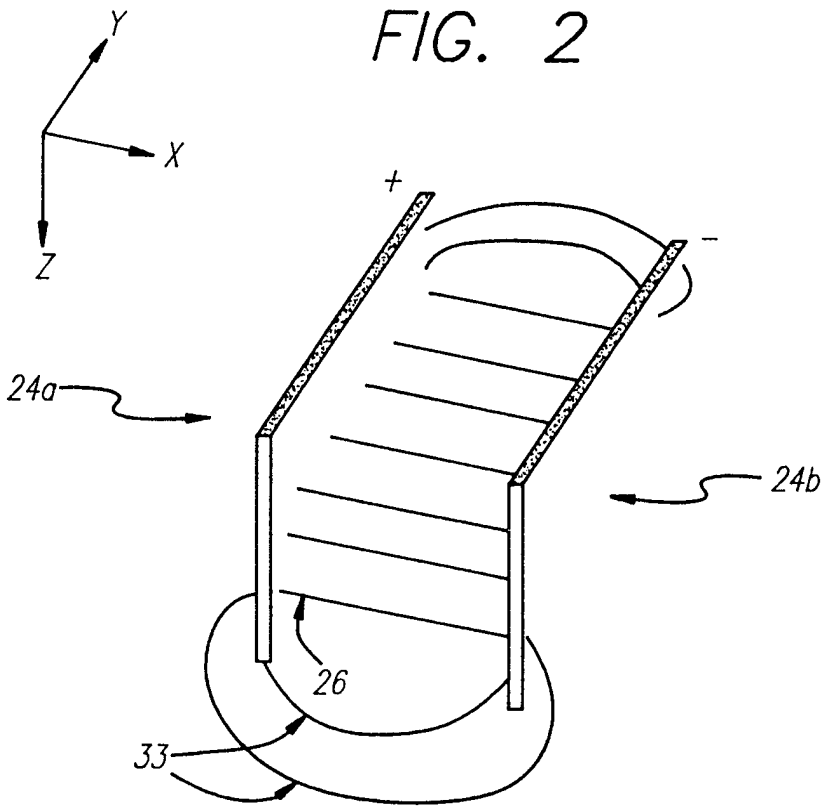
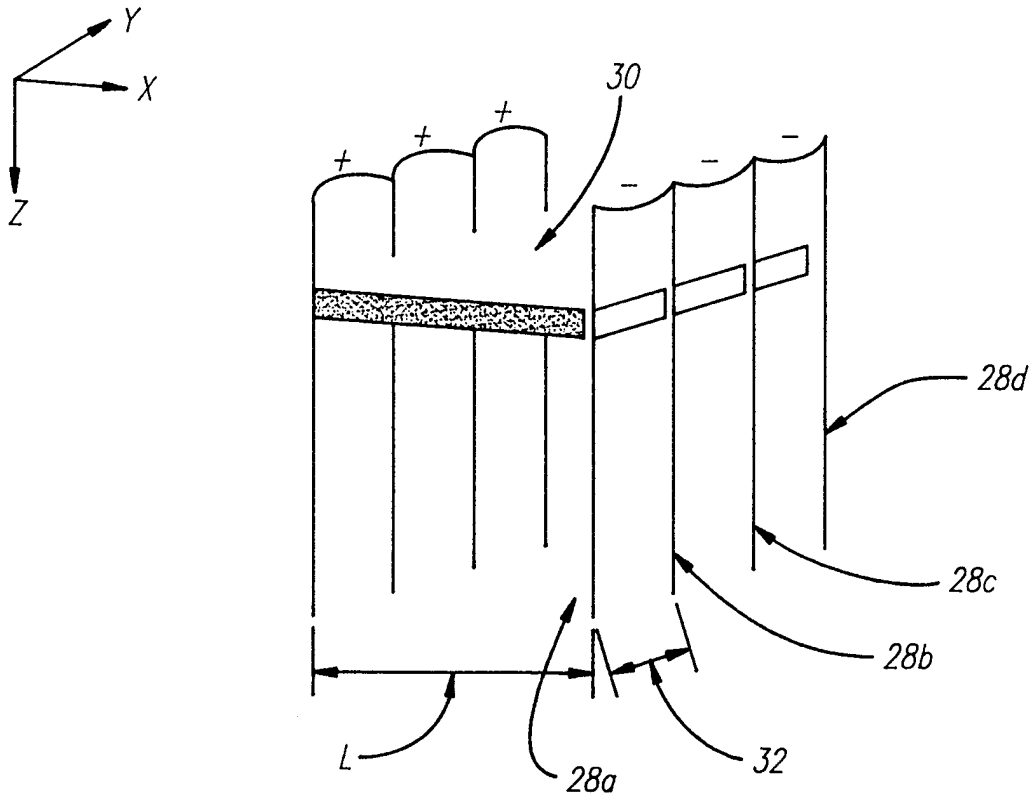


FIG. 3



SUBSTITUTE SHEET (RULE 26)

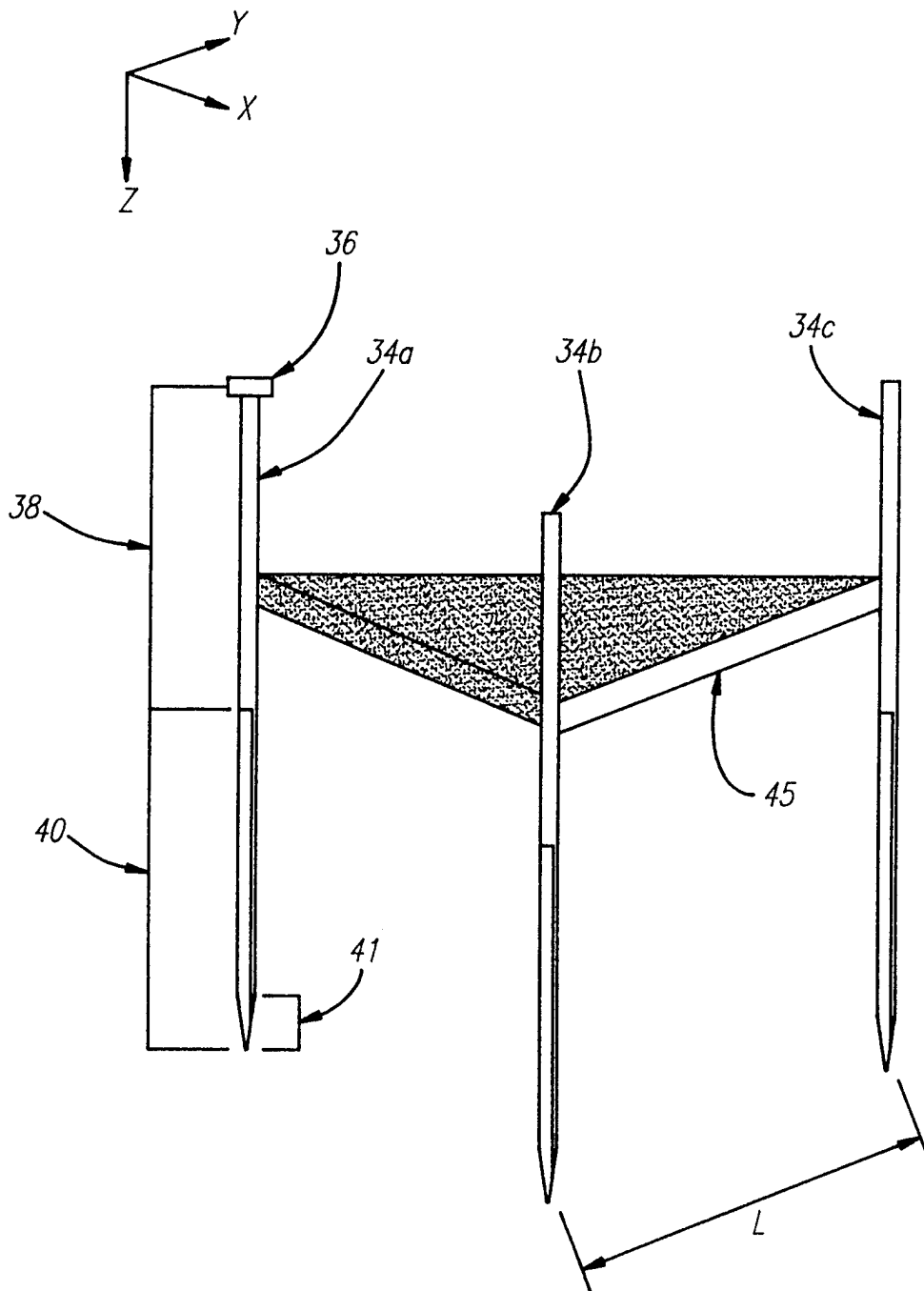


FIG. 4

FIG. 5

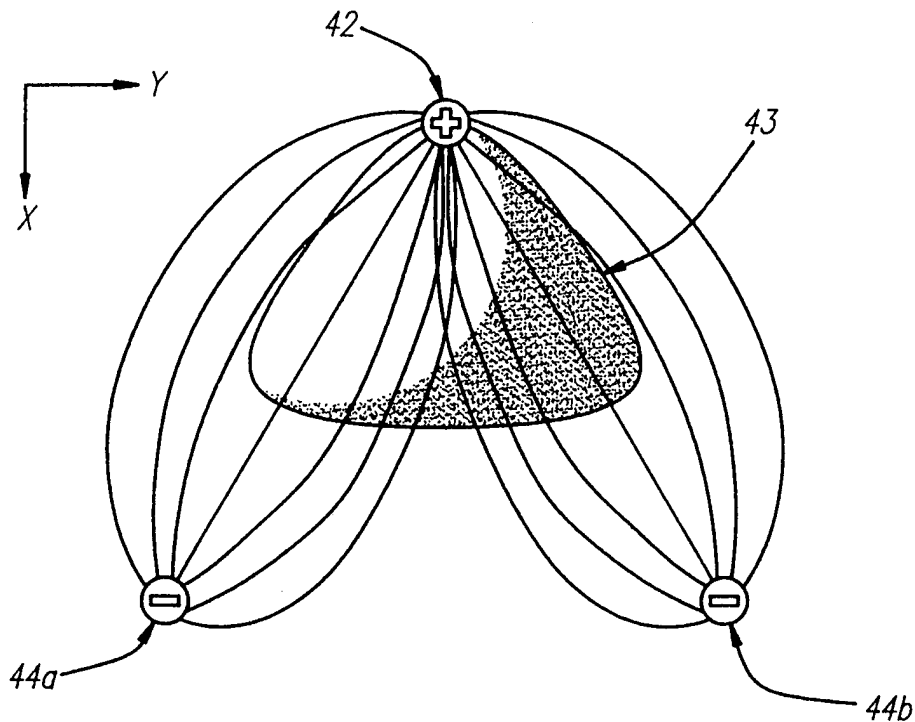
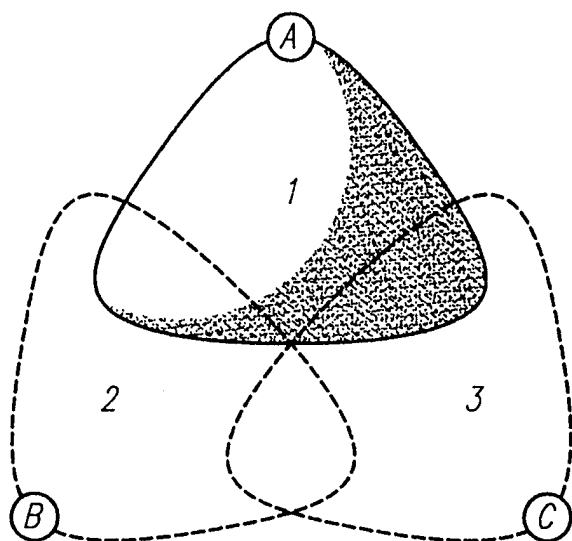


FIG. 6



TRICELL ELECTRODE STATES

	A	B	C
COMB. 1	+	-	-
COMB. 2	-	+	-
COMB. 3	-	-	+

5/14

FIG. 7

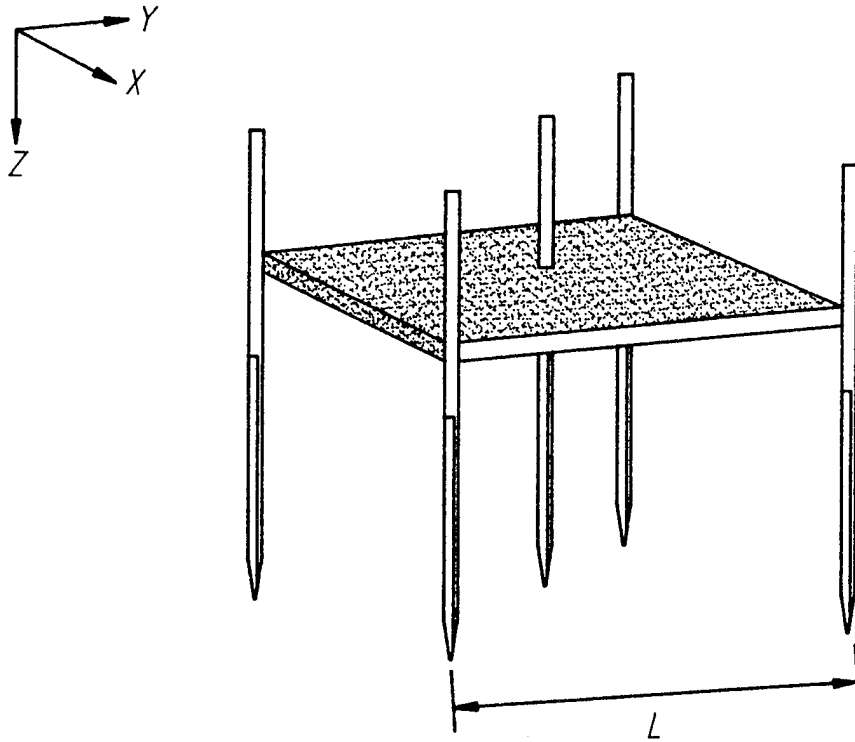


FIG. 8

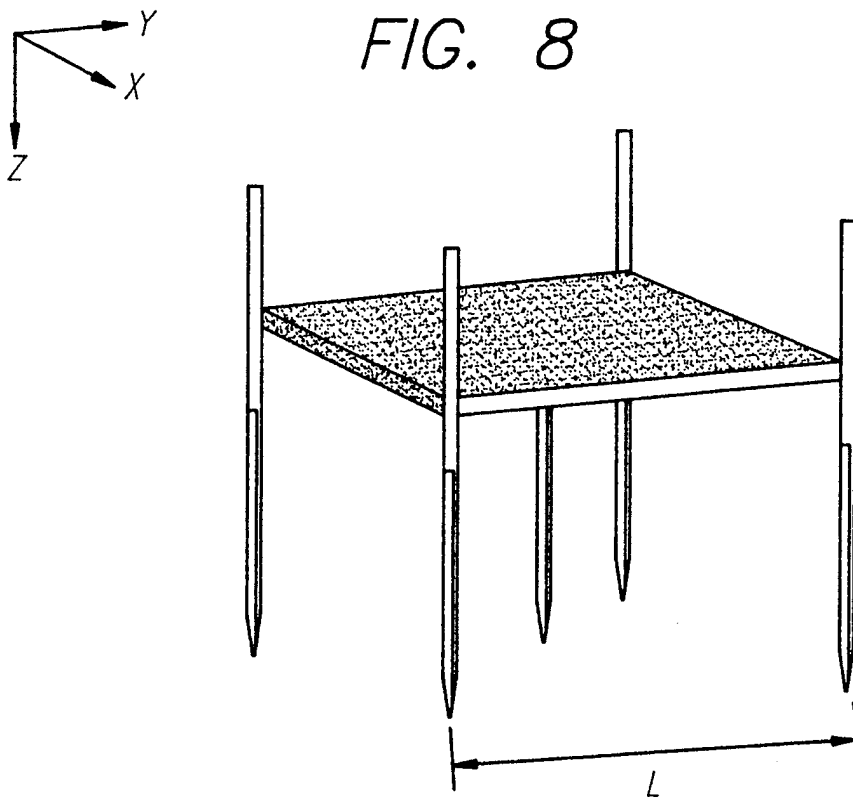


FIG. 9

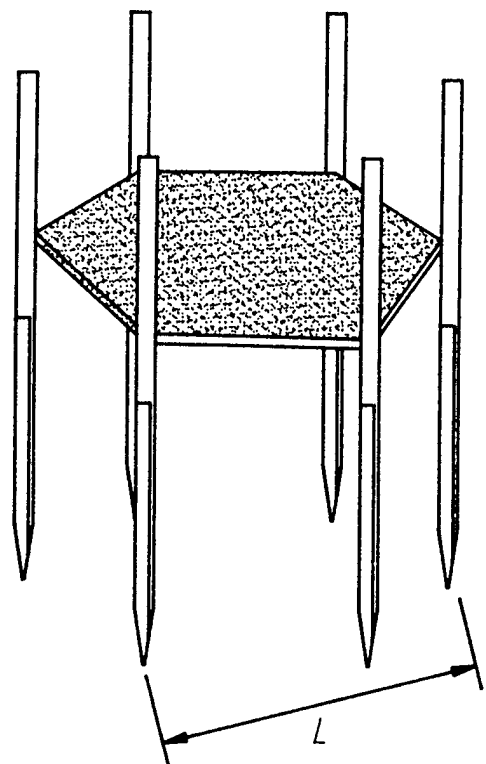
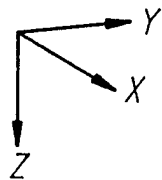


FIG. 10

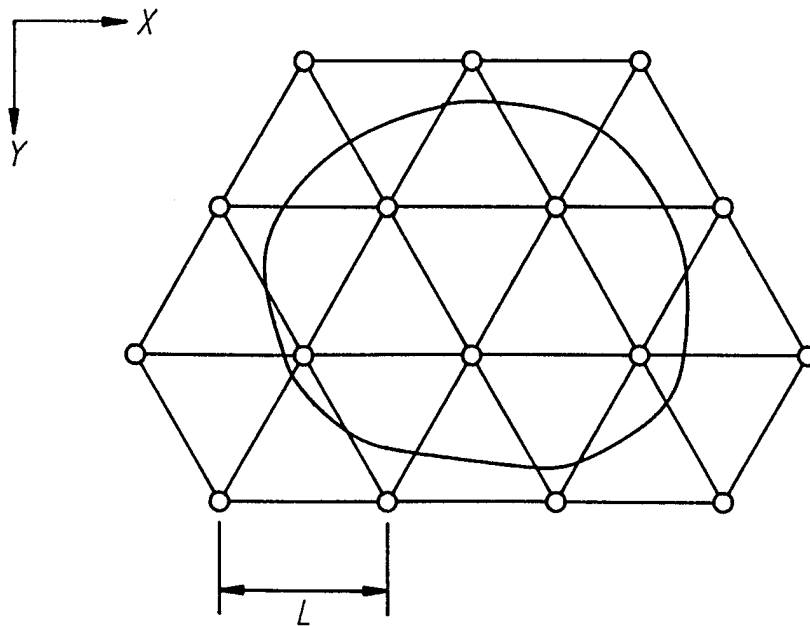
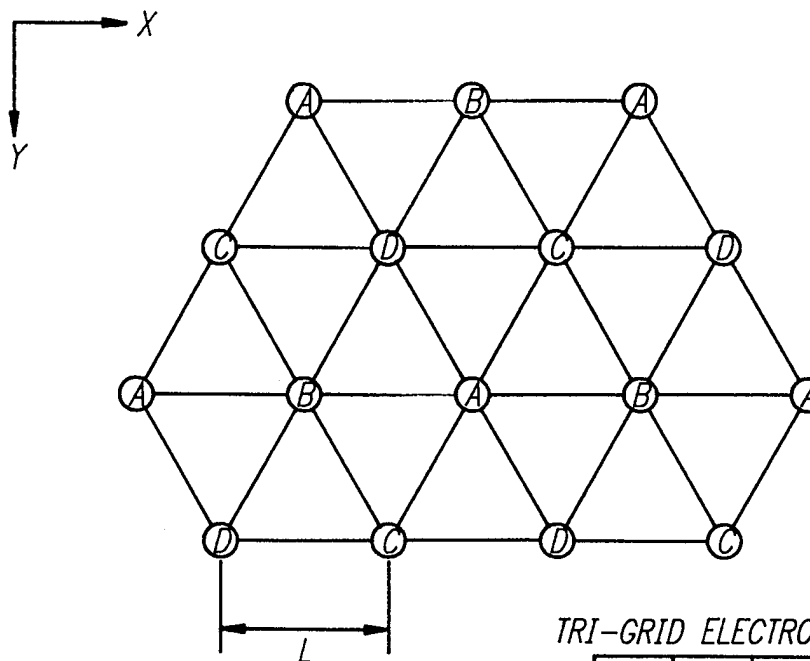


FIG. 11

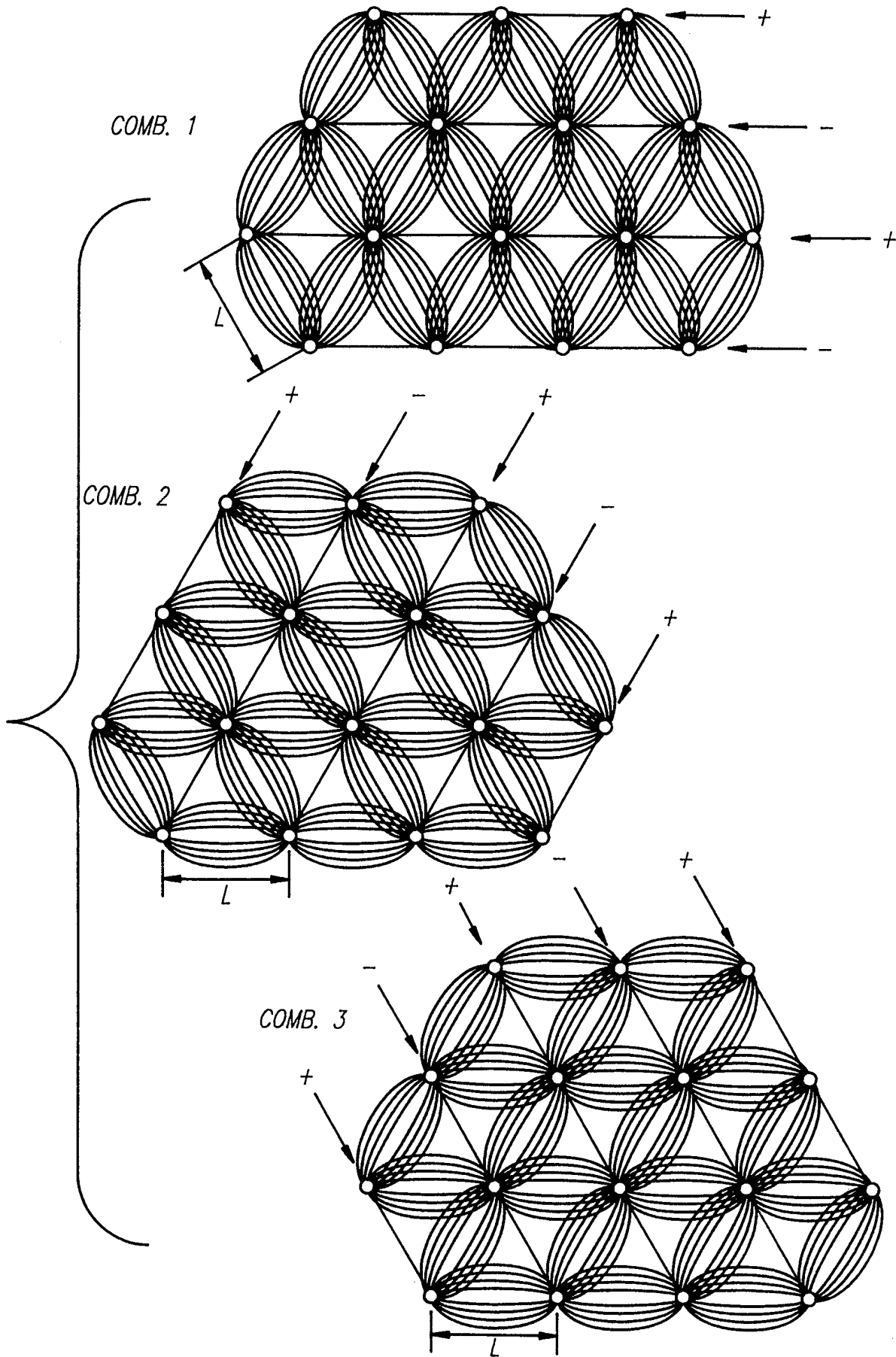


TRI-GRID ELECTRODE STATES

	A	B	C	D
COMB. 1	+	+	-	-
COMB. 2	+	-	+	-
COMB. 3	+	-	-	+

FIG. 12

8/14



9/14

FIG. 13

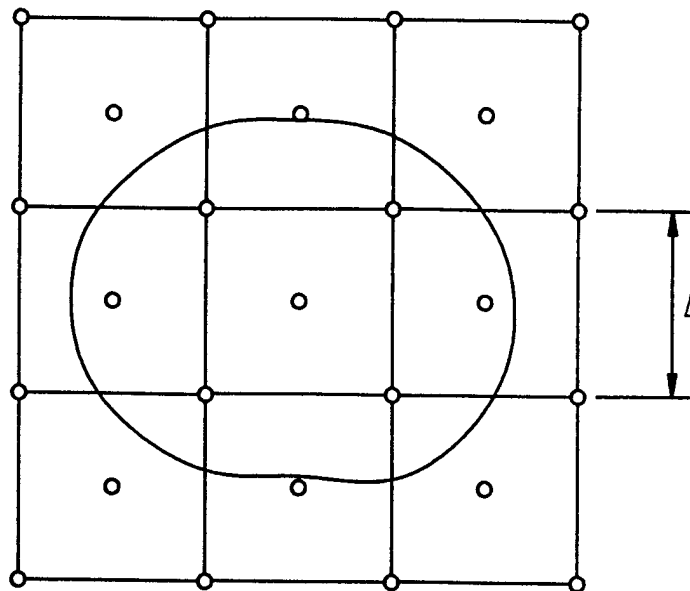


FIG. 14

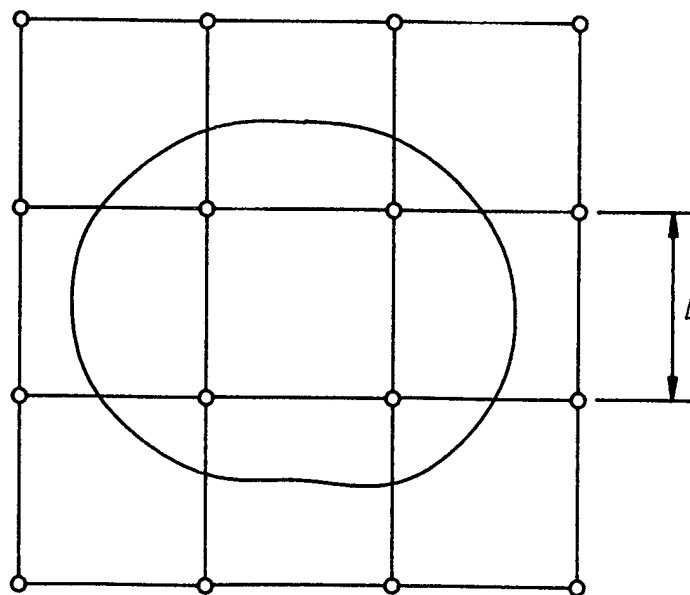


FIG. 15

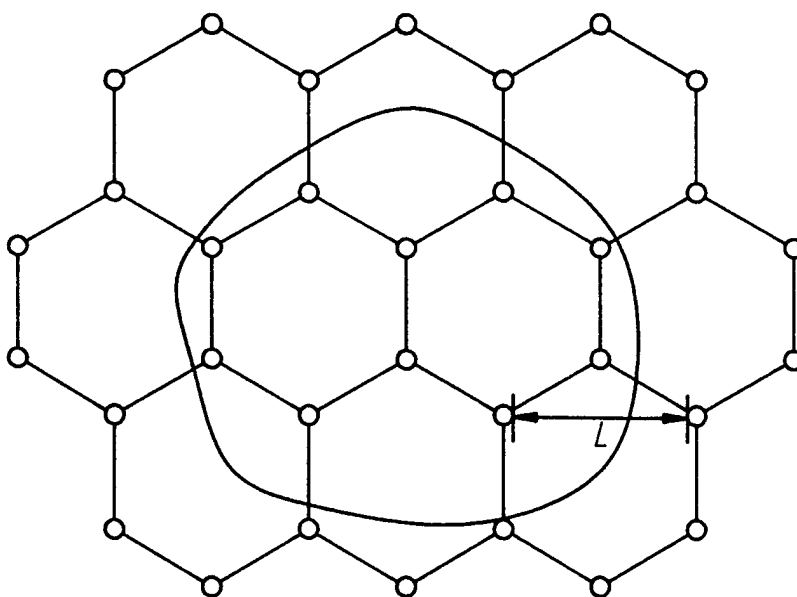


FIG. 16

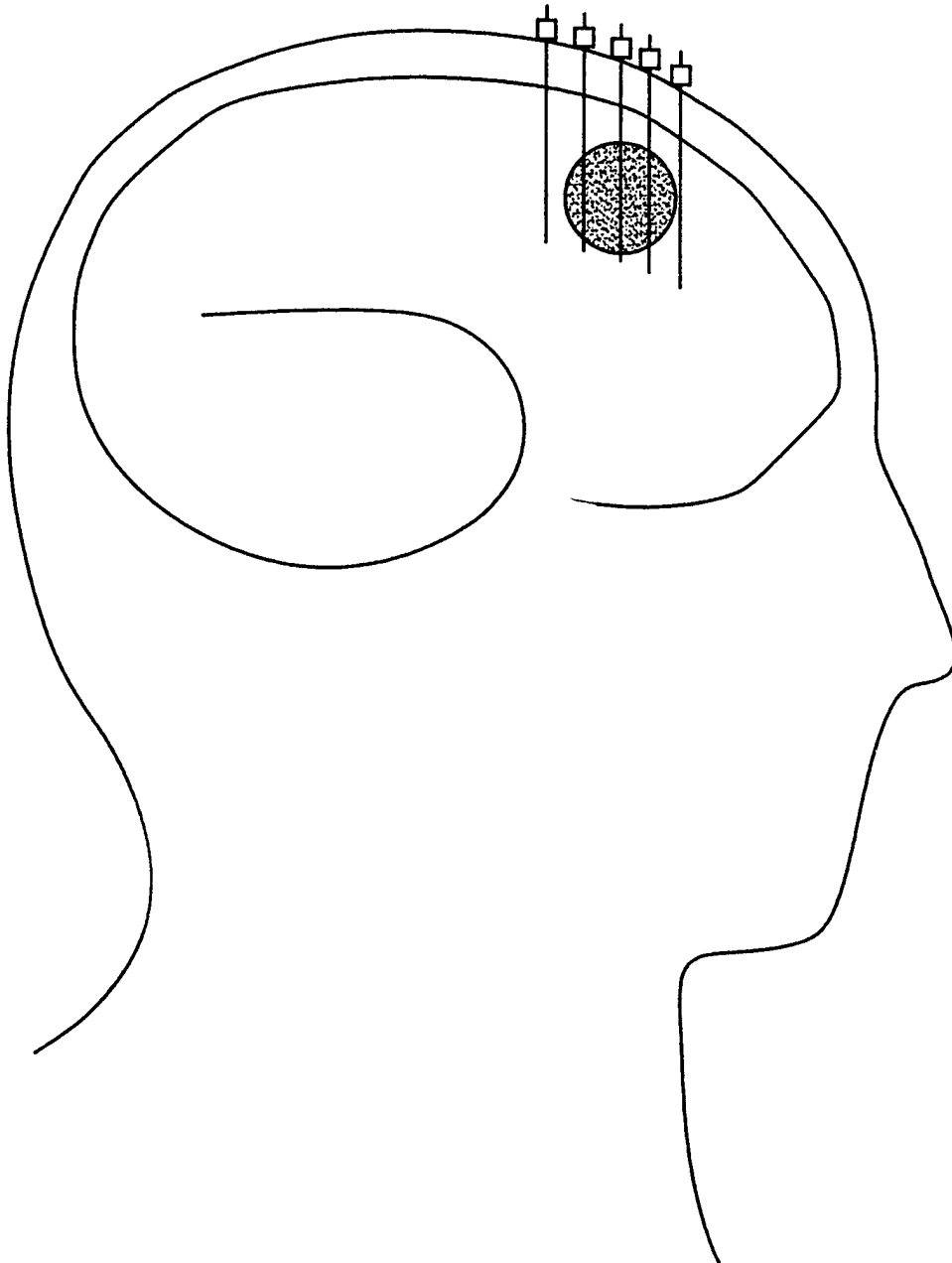


FIG. 17

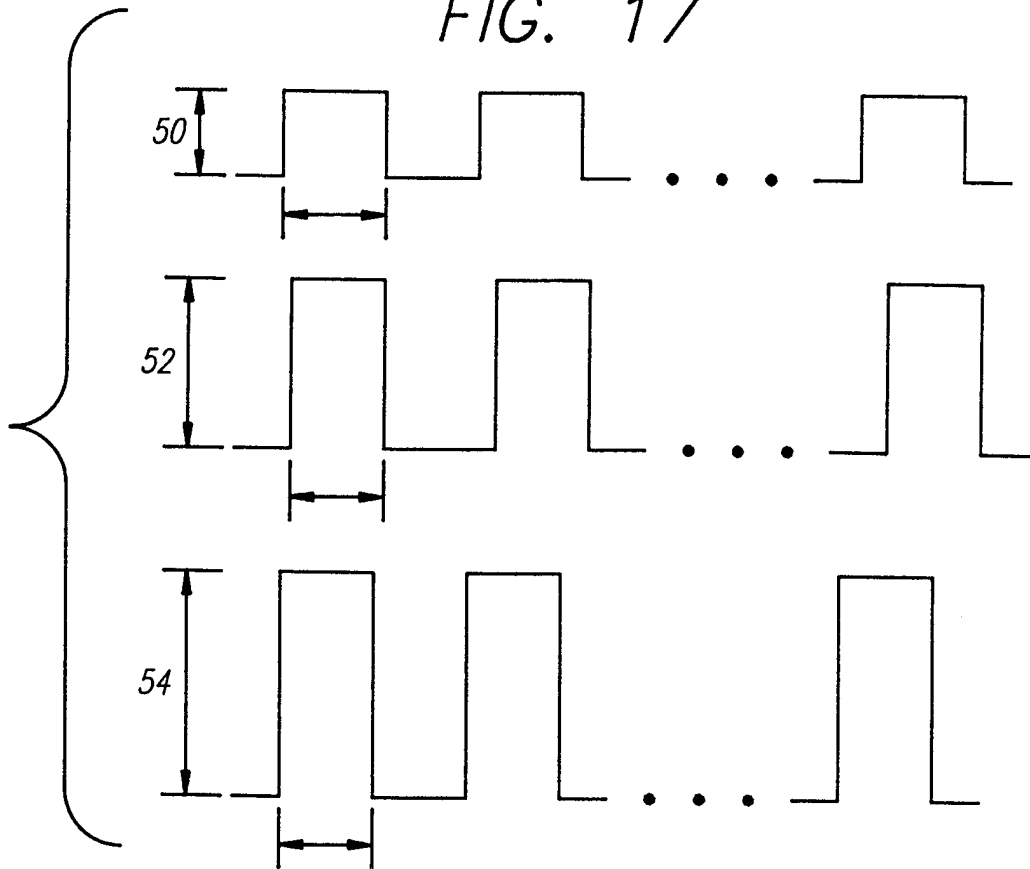


FIG. 18

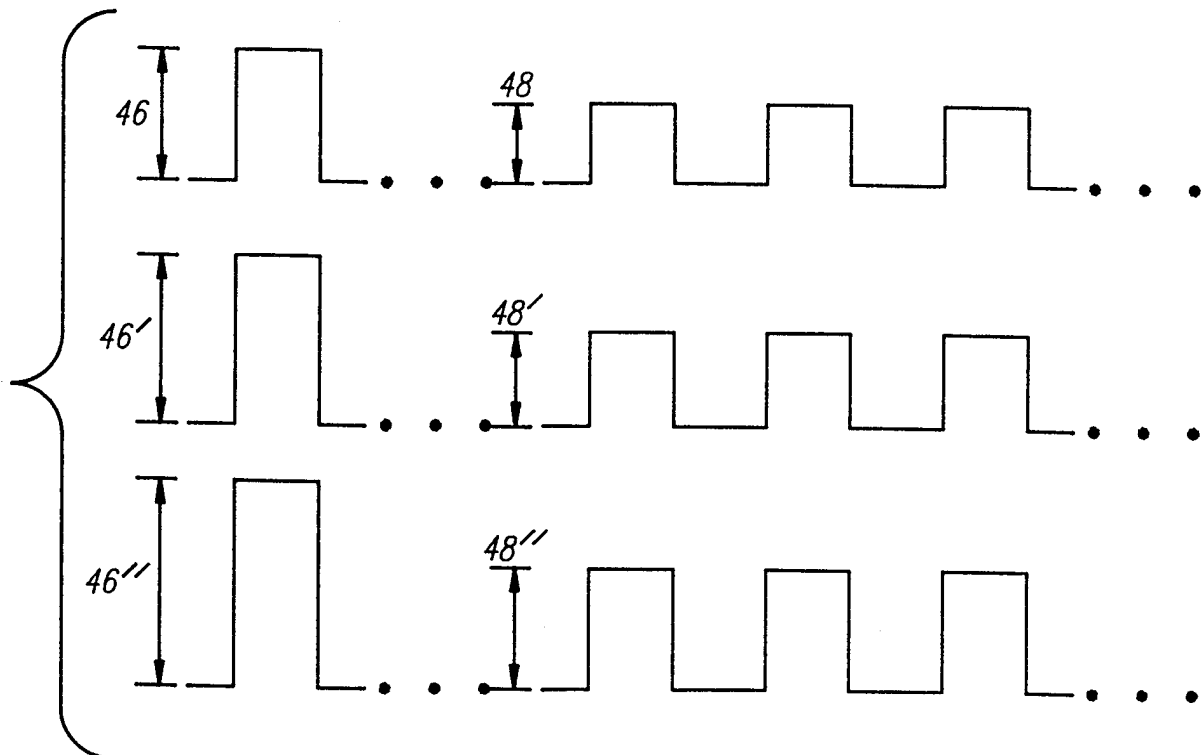
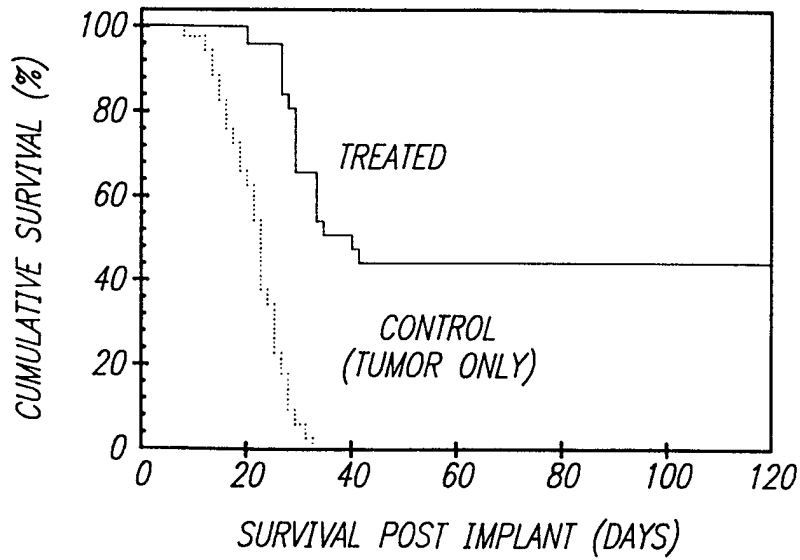


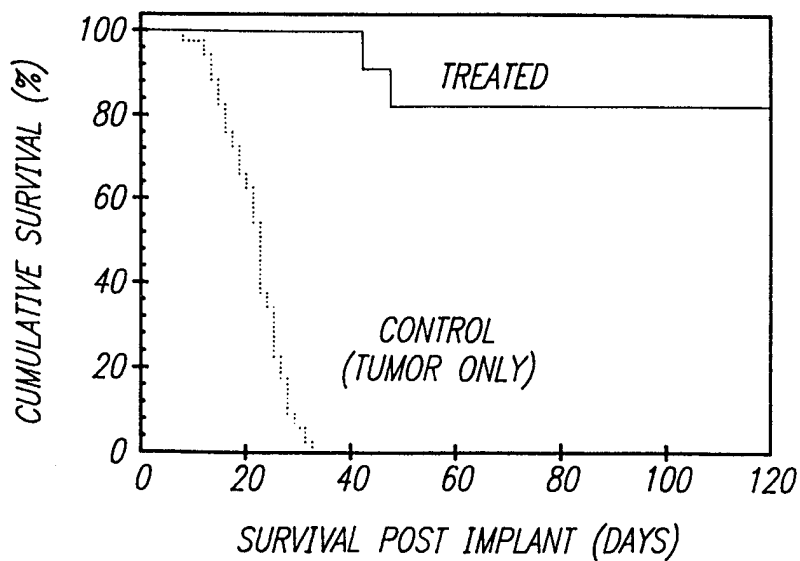
FIG. 19



NOTE: DATA POOLED FROM 4 GROUPS.

TREATED GROUP:  
26 ANIMALS TREATED  
11 ANIMALS > 120 DAYS.

FIG. 20



NOTE: DATA POOLED FROM 3 GROUPS.

TREATED GROUP:  
15 ANIMALS TREATED  
13 ANIMALS > 120 DAYS.

FIG. 21

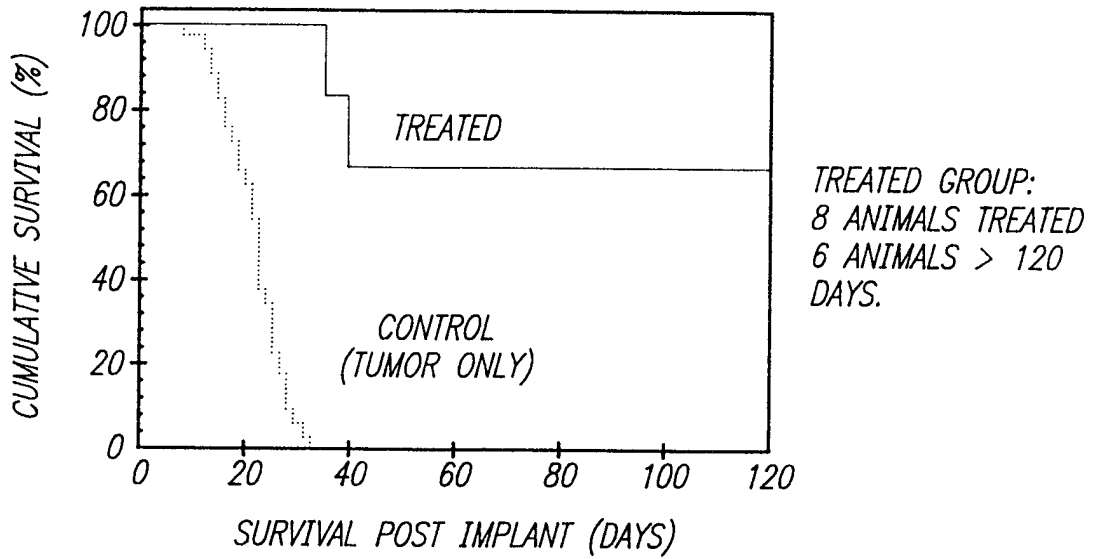
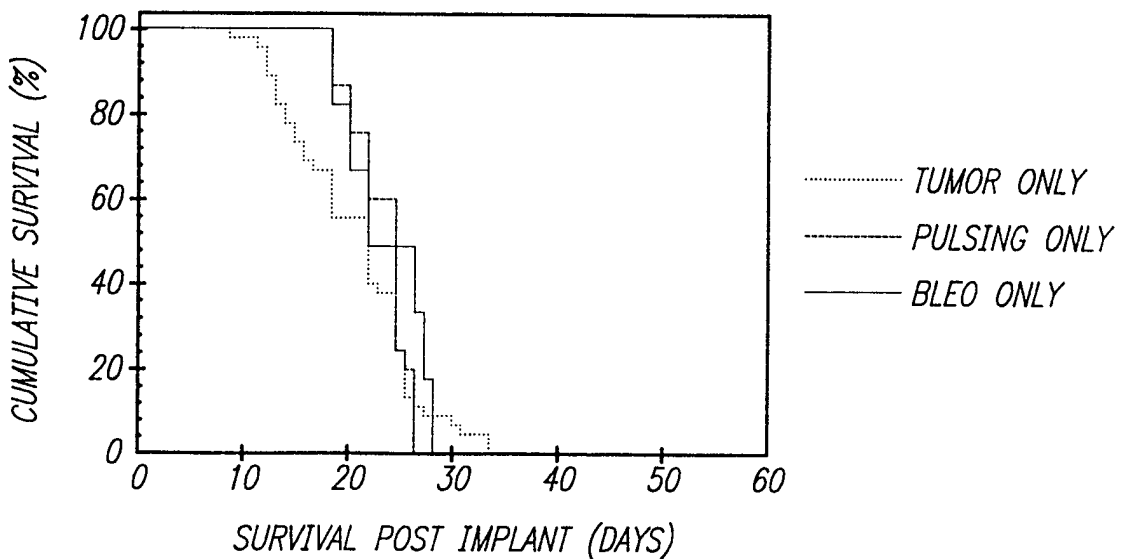
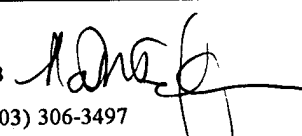


FIG. 22



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/08183

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(6) :A61N 1/30 US CL :607/116 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) U.S. : 607/116, 148, 152, 153; 604/20, 21; 128/907		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched NONE		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) APS		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, E	US 5,704,908 A (HOFMANN ET AL) 06 January 1998, column 3, lines 30-50.	1-20
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:	"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	
"A" document defining the general state of the art which is not considered to be of particular relevance	"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	
"E" earlier document published on or after the international filing date	"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	
"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)	"&" document member of the same patent family	
"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		
Date of the actual completion of the international search 15 JULY 1998	Date of mailing of the international search report <b>05 AUG 1998</b>	
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JEFF JASTRZAB  Telephone No. (703) 306-3497	