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Palti

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(54) **APPARATUS FOR DESTROYING DIVIDING CELLS**

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This patent is subject to a terminal disclaimer.

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A61N 1/00 (2006.01)

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See application file for complete search history.

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(57) **ABSTRACT**

An apparatus is provided for selectively destroying dividing cells in living tissue formed of dividing cells and non-dividing cells. The dividing cells contain polarizable intracellular members and during late anaphase or telophase, the dividing cells are connected to one another by a cleavage furrow. The apparatus includes a generator and insulated electrodes for subjecting the living tissue to electric field conditions sufficient to cause movement of the polarizable intracellular members toward the cleavage furrow in response to a non-homogeneous electric field being induced in the dividing cells. The non-homogeneous electric field produces an increased density electric field in the region of the cleavage furrow. The movement of the polarizable intracellular intracellular members towards the cleavage furrow causes the breakdown thereof which results in the destruction of the dividing cells, while the non-dividing cells of the living tissue remain intact.

37 Claims, 12 Drawing Sheets

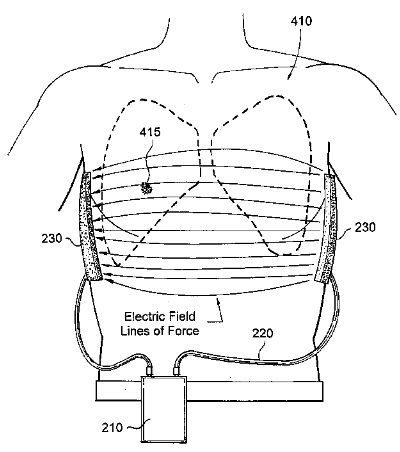

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FIG. 1A

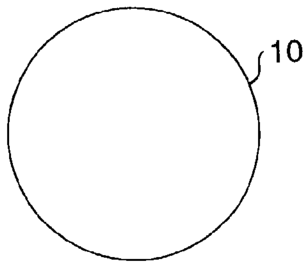


FIG. 1B

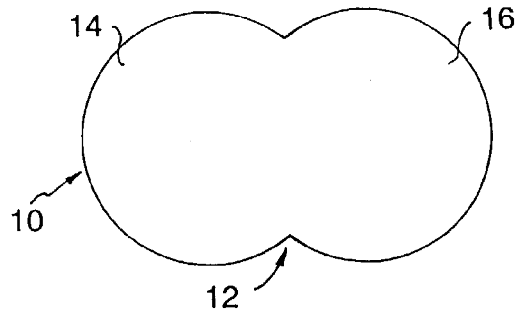


FIG. 1C

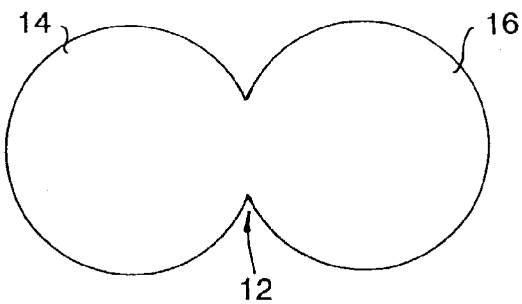


FIG. 1D

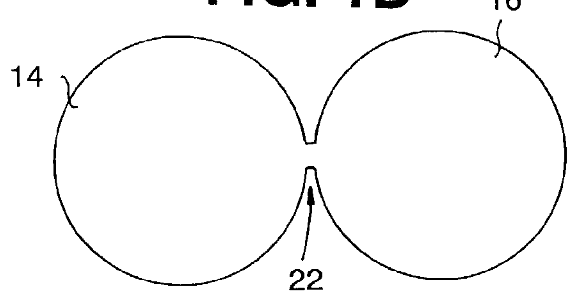


FIG. 1E

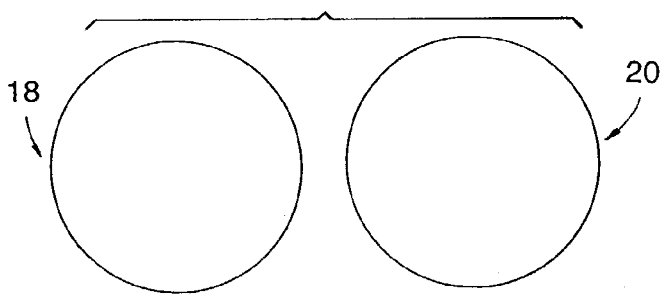
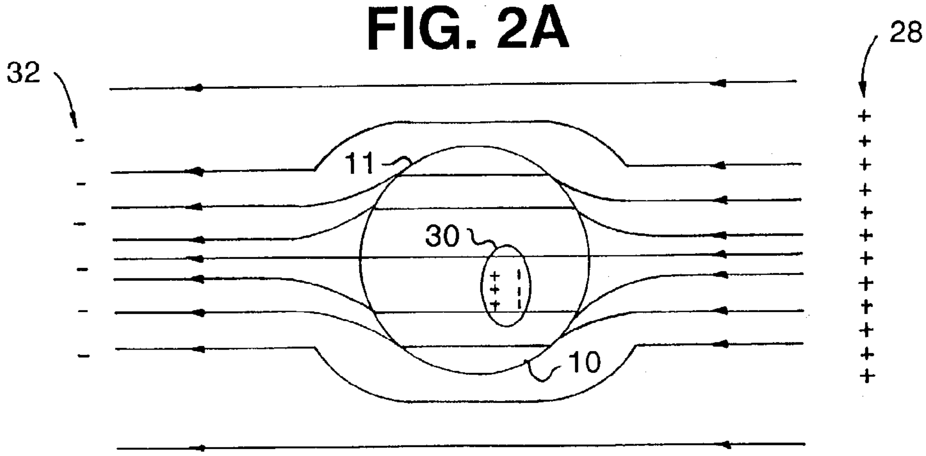


FIG. 2A



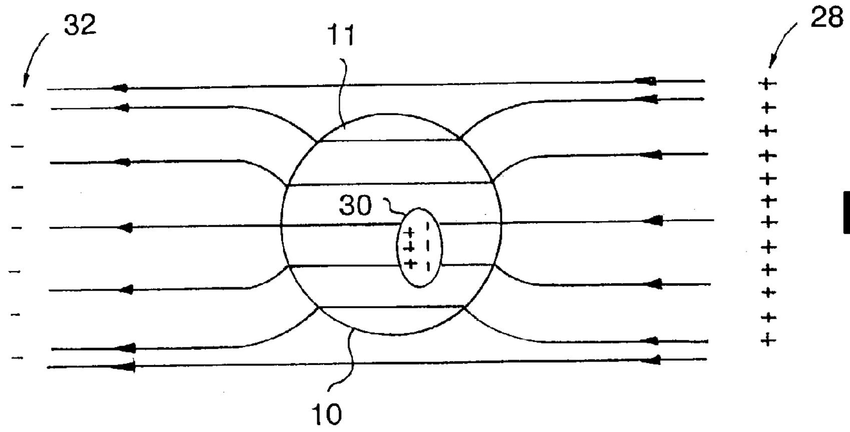


FIG. 2B

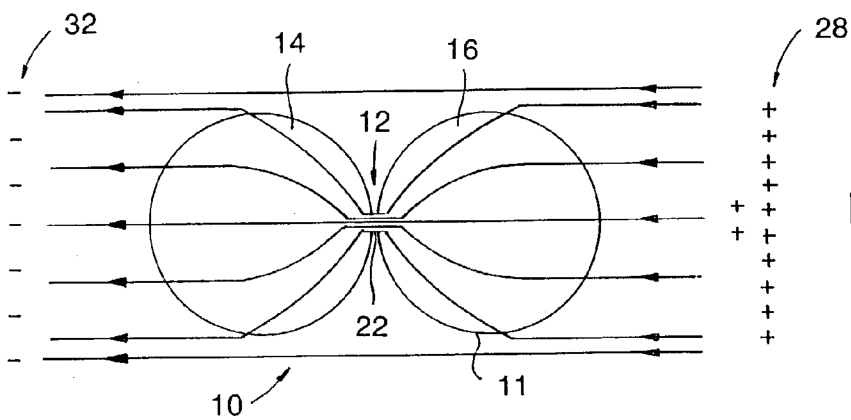


FIG. 3A

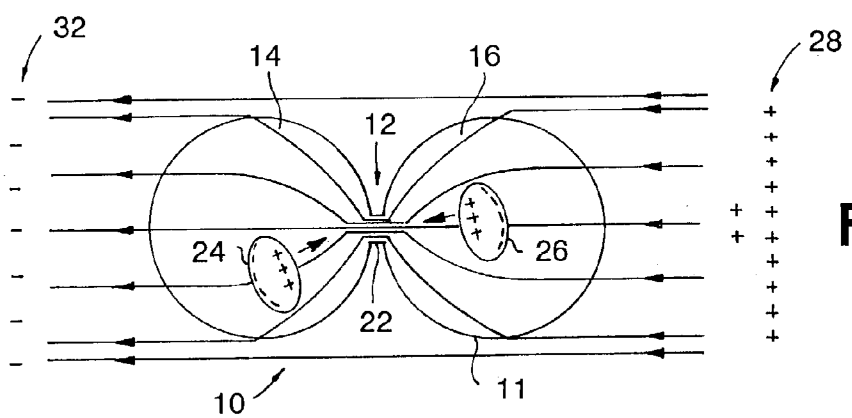


FIG. 3B

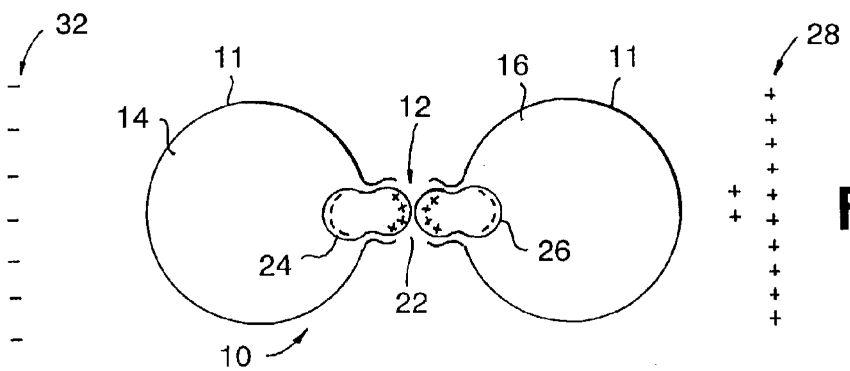


FIG. 3C

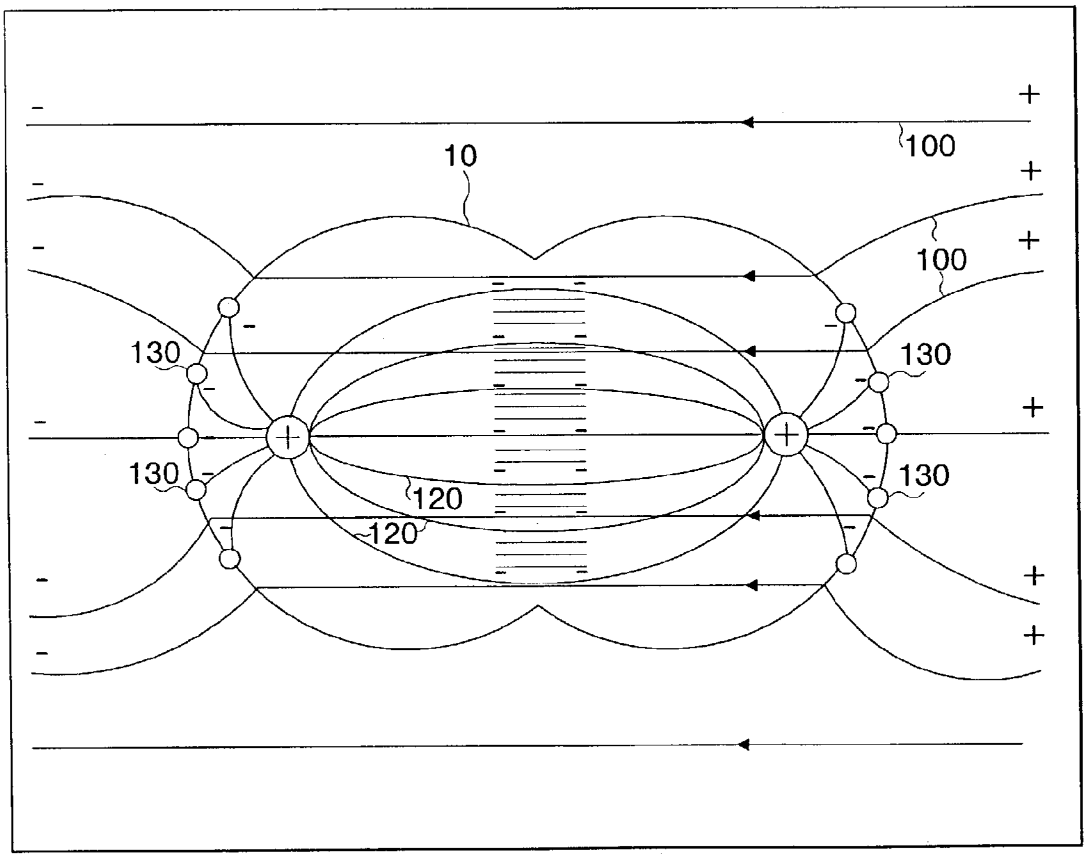


FIG. 4

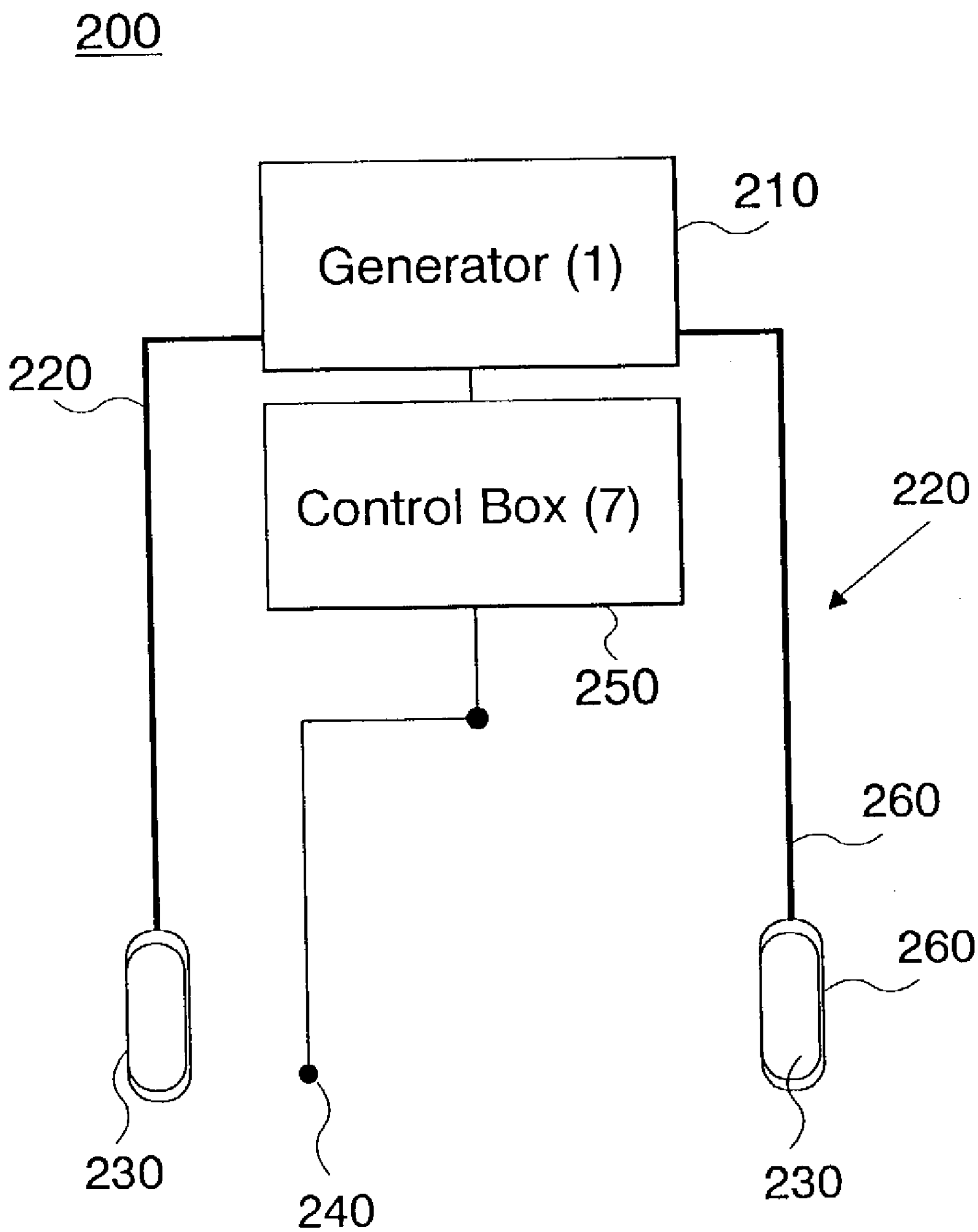

200
210
Generator (1)
220
Control Box (7)
220
250
260
260
230
240
230

FIG. 5

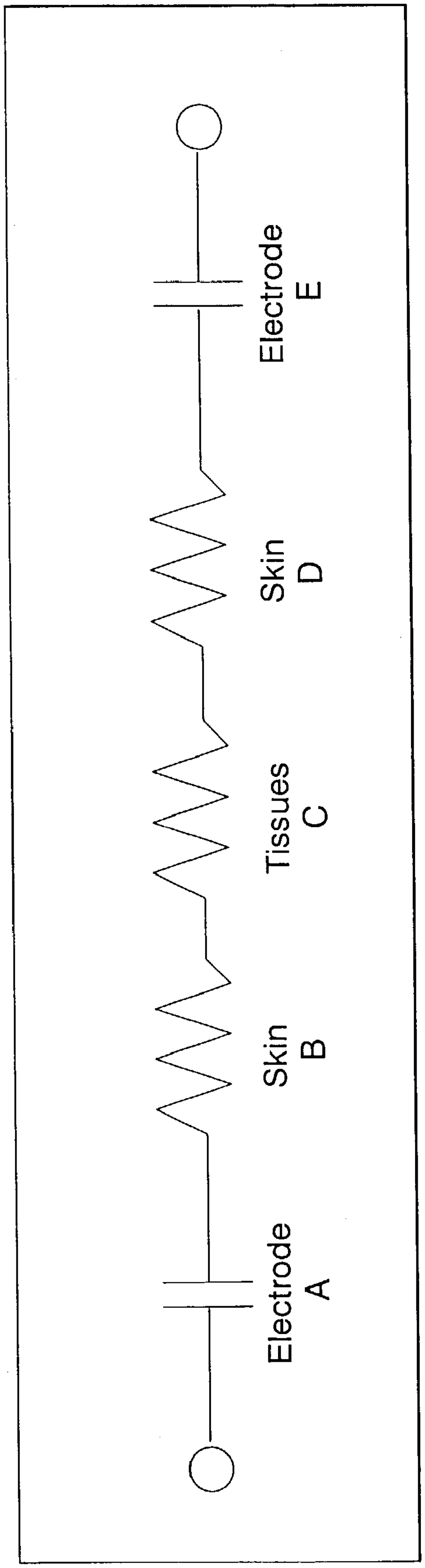


FIG. 6

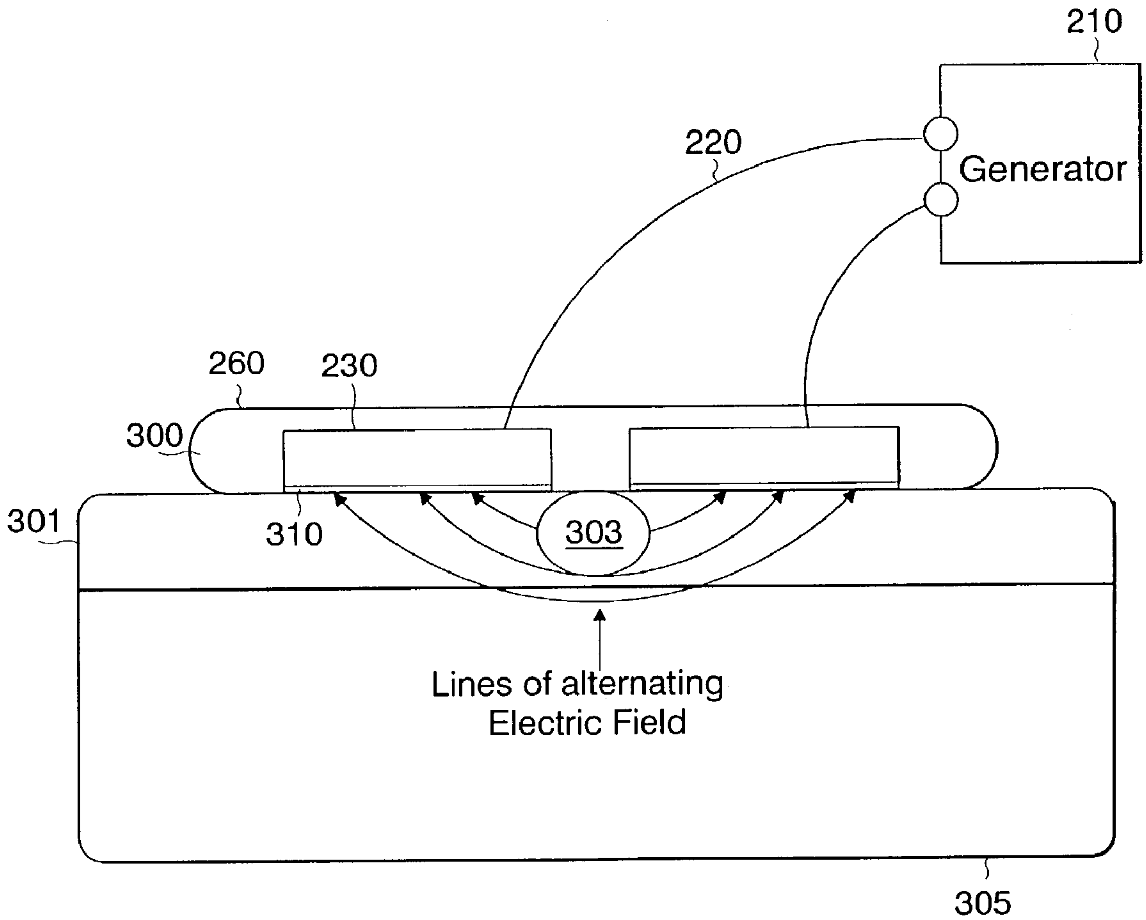

210
220
Generator
260
230
300
301
310
303
Lines of alternating
Electric Field
305

FIG. 7

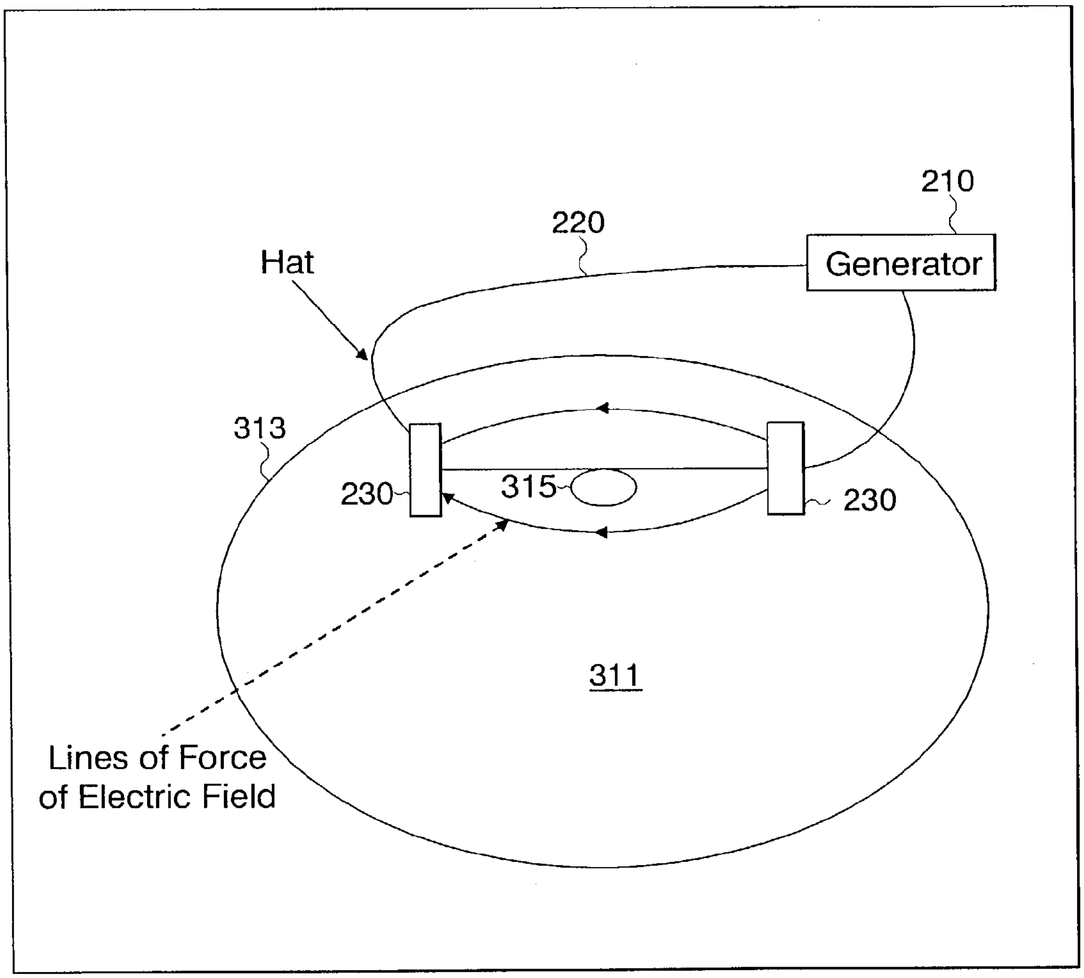

210
220
Generator
Hat
313
230
315
230
311
Lines of Force
of Electric Field

FIG. 8

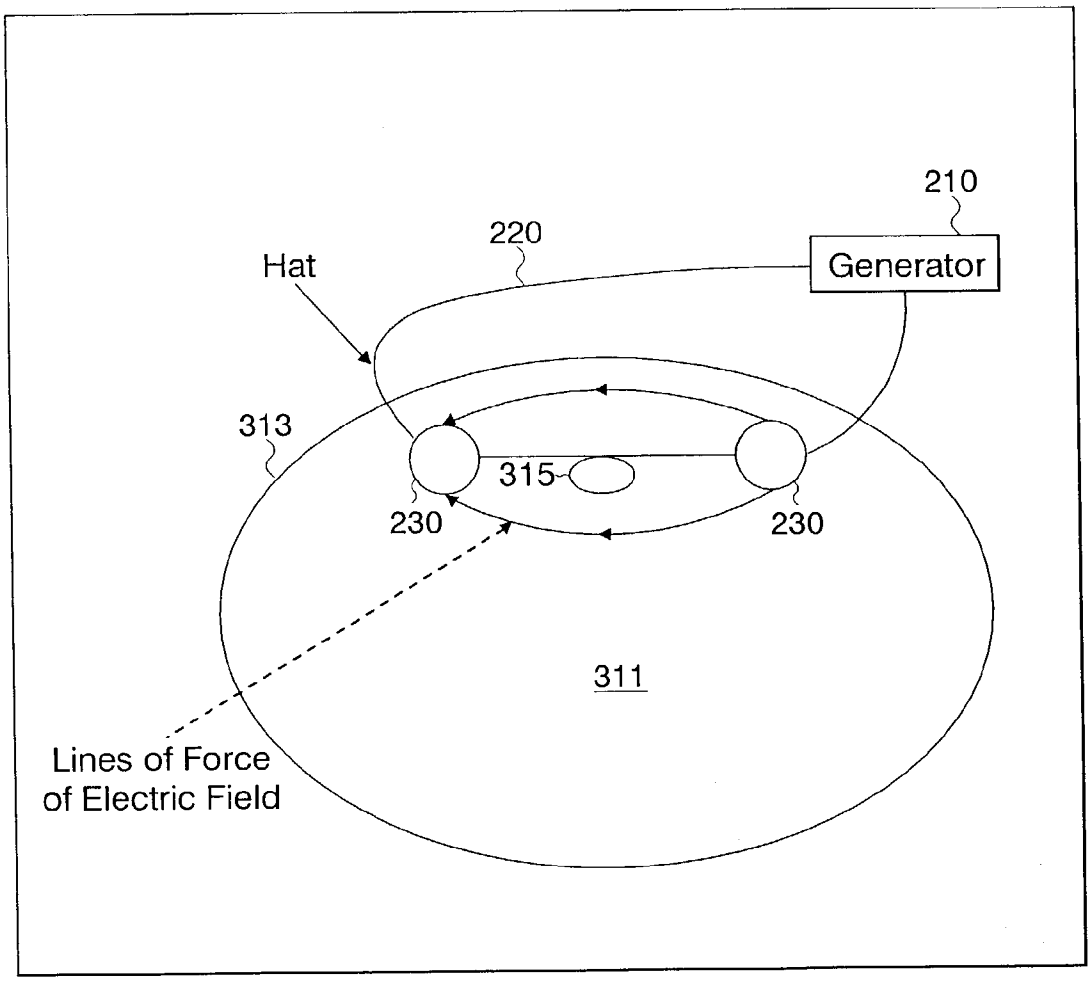

210
220
Hat
Generator
313
315
230
230
311
Lines of Force
of Electric Field

FIG. 9

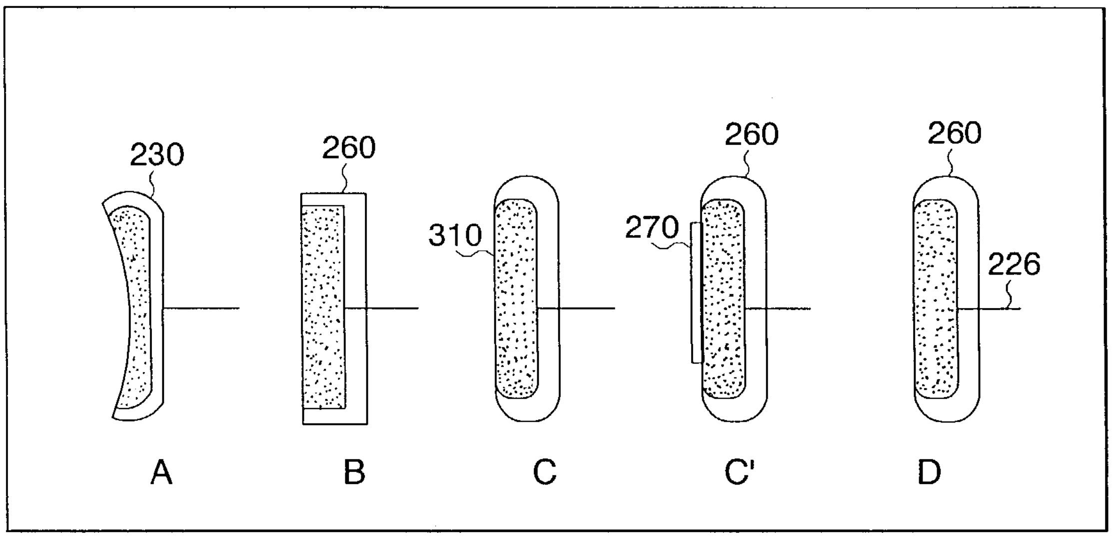
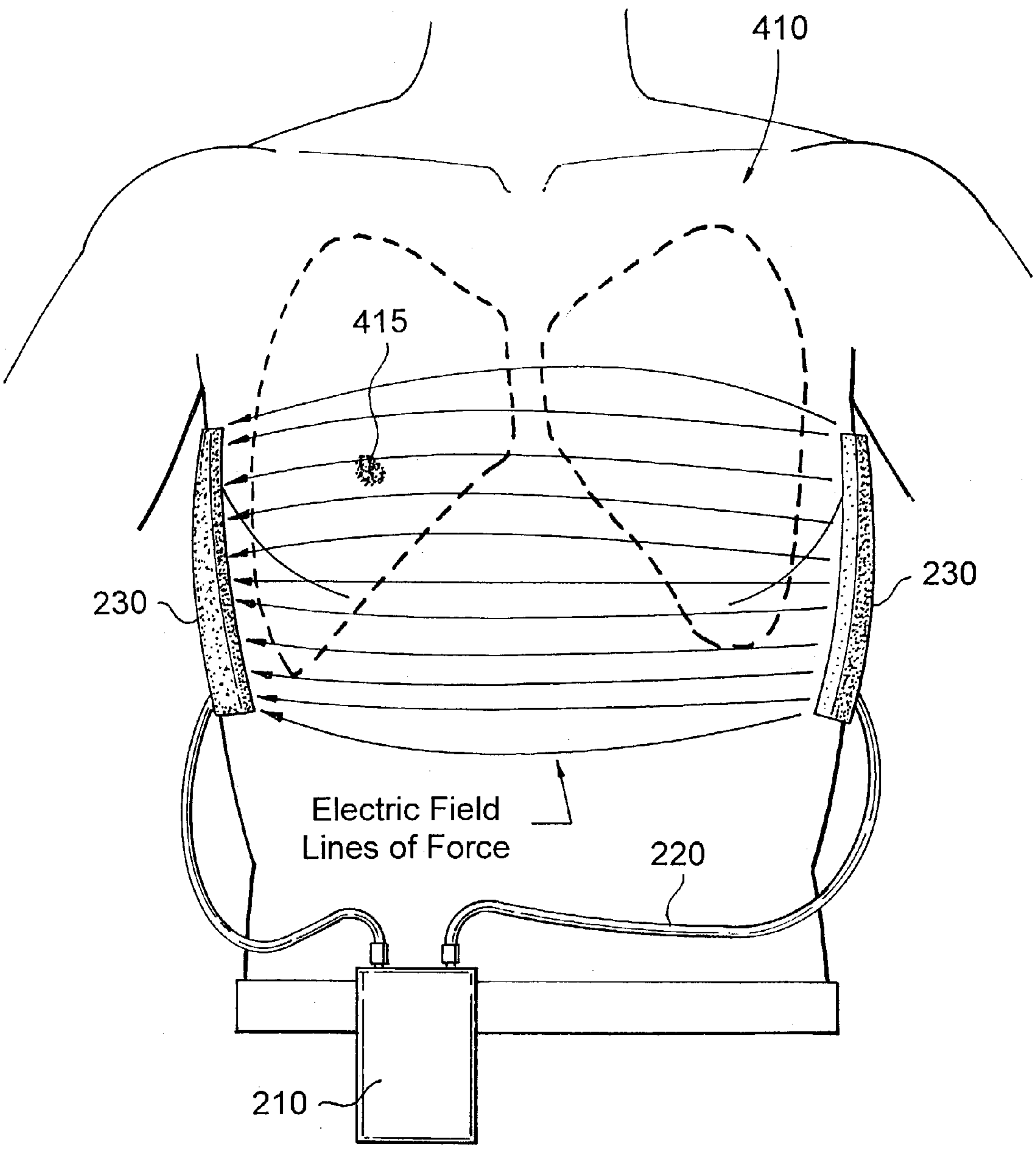
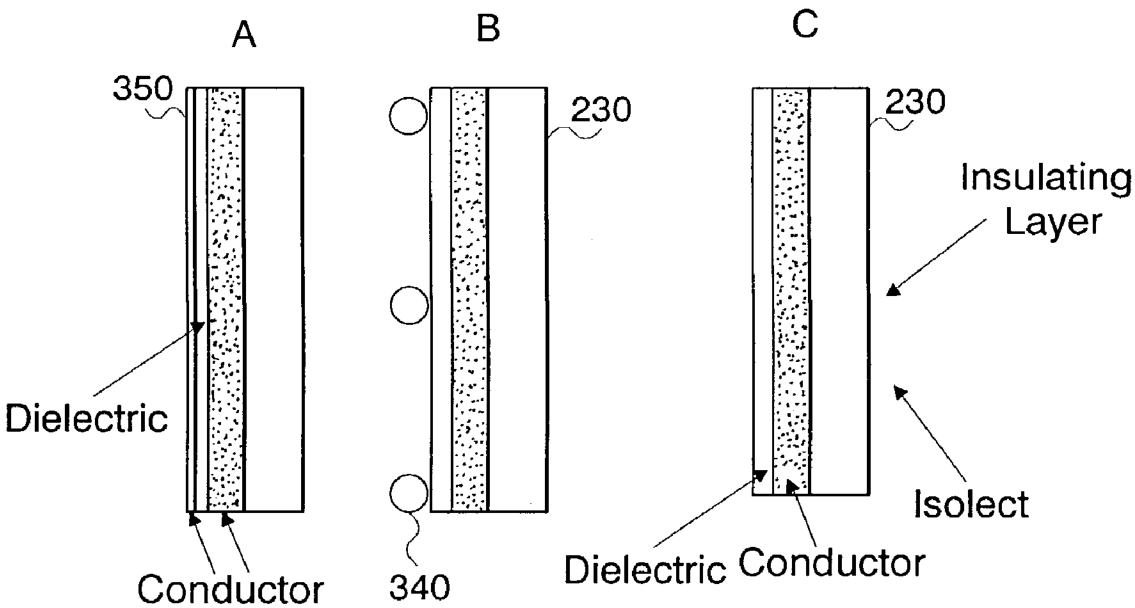


FIG. 10

FIG. 11





Cross Section of Isolect With and Without a Protecting Net

FIG. 12

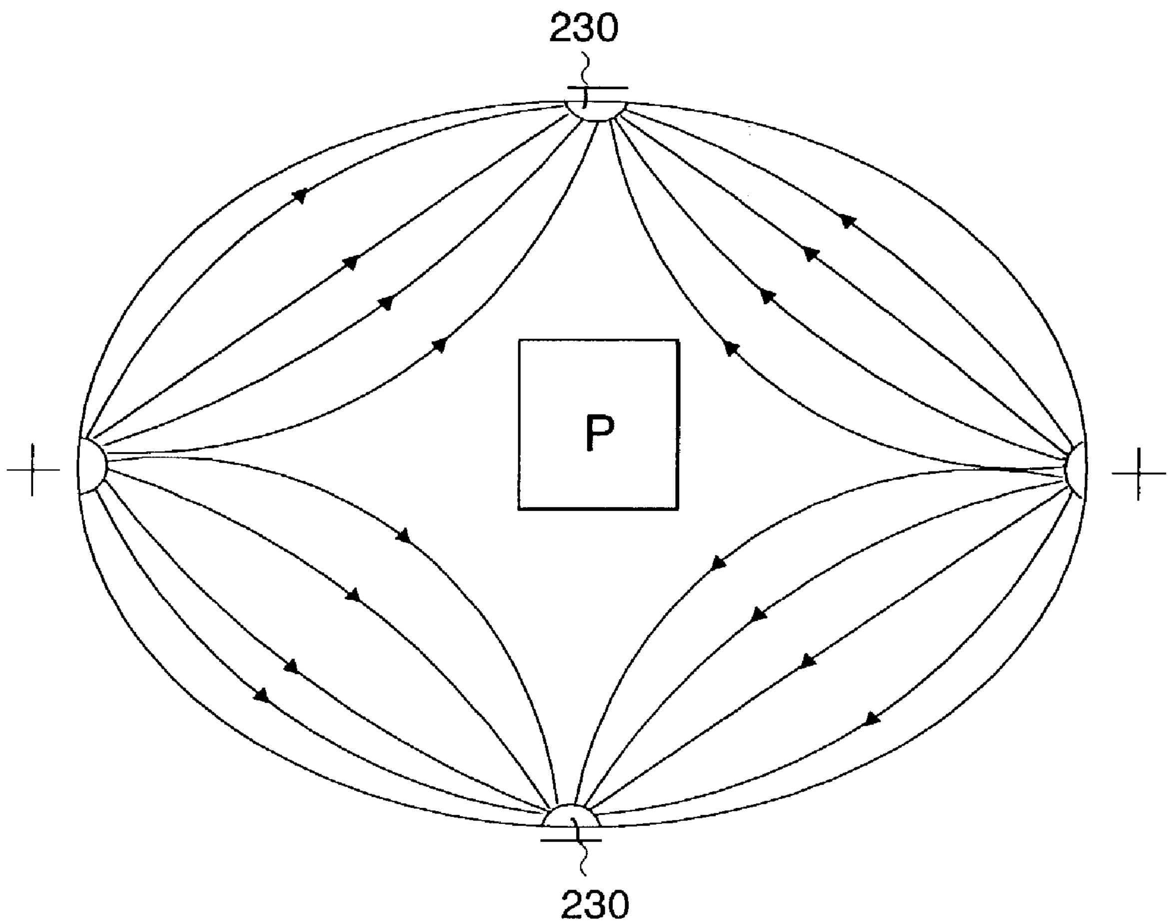


FIG. 13

APPARATUS FOR DESTROYING DIVIDING CELLS

TECHNICAL FIELD

This invention concerns selective destruction of rapidly dividing cells, and more particularly, to an apparatus for selectively destroying dividing cells by applying an electric field having certain prescribed characteristics.

BACKGROUND

All living organisms proliferate by cell division, including cell cultures, microorganisms (such as bacteria, mycoplasma, yeast, protozoa, and other single-celled organisms), fungi, algae, plant cells, etc. Dividing cells of organisms can be destroyed, or their proliferation controlled, by methods that are based on the sensitivity of the dividing cells of these organisms to certain agents. For example, certain antibiotics stop the multiplication process of bacteria.

The process of eukaryotic cell division is called "mitosis", which involves nice distinct phases (see Darnell et al., *Molecular Cell Biology*, New York: Scientific American Books, 1986, p. 149). During interphase, the cell replicates chromosomal DNA, which begins condensing in early prophase. At this point, centrioles (each cell contains 2) begin moving towards opposite poles of the cell. In middle prophase, each chromosome is composed of duplicate chromatids. Microtubular spindles radiate from regions adjacent to the centrioles, which are closer to their poles. By late prophase, the centrioles have reached the poles, and some spindle fibers extend to the center of the cell, while others extend from the poles to the chromatids. The cells then move into metaphase, when the chromosomes move toward the equator of the cell and align in the equatorial plane. Next is early anaphase, during which time daughter chromatids separate from each other at the equator by moving along the spindle fibers toward a centromere at opposite poles. The cell begins to elongate along the axis of the pole; the pole-to-pole spindles also elongate. Late anaphase occurs when the daughter chromosomes (as they are not called) each reach their respective opposite poles. At this point, cytokinesis begins as the cleavage furrow begins to form at the equator of the cell. In other words, late anaphase is the point at which pinching the cell membrane begins. During telophase, cytokinesis is nearly complete and spindles disappear. Only a relatively narrow membrane connection joins the two cytoplasms. Finally, the membranes separate fully, cytokinesis is complete and the cell returns to interphase.

In meisosis, the cell undergoes a second division, involving separation of sister chromosomes to opposite poles of the cell along spindle fibers, followed by formation of a cleavage furrow and cell division. However, this division is not preceded by chromosome replication, yielding a haploid germ cell.

Bacteria also divide by chromosome replication, followed by cell separation. However, since the daughter chromosomes separate by attachment to membrane components; there is no visible apparatus that contributes to cell division as in eukaryotic cells.

It is well known that tumors, particularly malignant or cancerous tumors, grow uncontrollably compared to normal tissue. Such expedited growth enables tumors to occupy an ever-increasing space and to damage or destroy tissue adjacent thereto. Furthermore, certain cancers are characterized by an ability to transmit cancerous "seeds", including single

cells or small cell clusters (metastasises), to new locations where the messastatic cancer cells grow into additional tumors.

The rapid growth of tumors, in general, and malignant tumors in particular, as described above, is the result of relatively frequent cell division or multiplication of these cells compared to normal tissue cells. The distinguishably frequent cell division of cancer cells is the basis for the effectiveness of existing cancer treatments, e.g., irradiation therapy and the use of various chemo-therapeutic agents. Such treatments are based on the fact that cells undergoing division are more sensitive to radiation and chemo-therapeutic agents than non-dividing cells. Because tumors cells divide much more frequently than normal cells, it is possible, to a certain extent, to selectively damage or destroy tumor cells by radiation therapy and/or chemotherapy. The actual sensitivity of cells to radiation, therapeutic agents, etc., is also dependent on specific characteristics of different types of normal or malignant cell types. Thus, unfortunately, the sensitivity of tumor cells is not sufficiently higher than that many types of normal tissues. This diminishes the ability to distinguish between tumor cells and normal cells, and therefore, existing cancer treatments typically cause significant damage to normal tissues, thus limiting the therapeutic effectiveness of such treatments. Furthermore, the inevitable damage to other tissue renders treatments very traumatic to the patients and, often, patients are unable to recover from a seemingly successful treatment. Also, certain types of tumors are not sensitive at all to existing methods of treatment.

There are also other methods for destroying cells that do not rely on radiation therapy or chemotherapy alone. For example, ultrasonic and electrical methods for destroying tumor cells can be used in addition to or instead of conventional treatments. Electric fields and currents have been used for medical purposes for many years. The most common is the generation of electric currents in a human or animal body by application of an electric field by means of a pair of conductive electrodes between which a potential difference is maintained. These electric currents are used either to exert their specific effects, i.e., to stimulate excitable tissue, or to generate heat by flowing in the body since it acts as a resistor. Examples of the first type of application include the following: cardiac defibrillators, peripheral nerve and muscle stimulators, brain stimulators, etc. Currents are used for heating, for example, in devices for tumor ablation, ablation of malfunctioning cardiac or brain tissue, cauterization, relaxation of muscle rheumatic pain and other pain, etc.

Another use of electric fields for medical purposes involves the utilization of high frequency oscillating fields transmitted from a source that emits an electric wave, such as an RF wave or a microwave source that is directed at the part of the body that is of interest (i.e., target). In these instances, there is no electric energy conduction between the source and the body; but rather, the energy is transmitted to the body by radiation or induction. More specifically, the electric energy generated by the source reaches the vicinity of the body via a conductor and is transmitted from it through air or some other electric insulating material to the human body.

In a conventional electrical method, electrical current is delivered to a region of the target tissue using electrodes that are placed in contact with the body of the patient. The applied electrical current destroys substantially all cells in the vicinity of the target tissue. Thus, this type of electrical method does not discriminate between different types of cells within the target tissue and results in the destruction of both tumor cells and normal cells.

Electric fields that can be used in medical applications can thus be separated generally into two different modes. In the first mode, the electric fields are applied to the body or tissues by means of conducting electrodes. These electric fields can be separated into two types, namely (1) steady fields or fields that change at relatively slow rates, and alternating fields of low frequencies that induce corresponding electric currents in the body or tissues, and (2) high frequency alternating fields (above 1 MHz) applied to the body by means of the conducting electrodes. In the second mode, the electric fields are high frequency alternating fields applied to the body by means of insulated electrodes.

The first type of electric field is used, for example, to stimulate nerves and muscles, pace the heart, etc. In fact, such fields are used in nature to propagate signals in nerve and muscle fibers, central nervous system (CNS), heart, etc. The recording of such natural fields is the basis for the ECG, EEG, EMG, ERG, etc. The field strength in these applications, assuming a medium of homogenous electric properties, is simply the voltage applied to the stimulating/recording electrodes divided by the distance between them. These currents can be calculated by Ohm's law and can have dangerous stimulatory effects on the heart and CNS and can result in potentially harmful ion concentration changes. Also, if the currents are strong enough, they can cause excessive heating in the tissues. This heating can be calculated by the power dissipated in the tissue (the product of the voltage and the current).

When such electric fields and currents are alternating, their stimulatory power, on nerve, muscle, etc., is an inverse function of the frequency. At frequencies above 1–10 KHz, the stimulation power of the fields approaches zero. This limitation is due to the fact that excitation induced by electric stimulation is normally mediated by membrane potential changes, the rate of which is limited by the RC properties (time constants on the order of 1 ms) of the membrane.

Regardless of the frequency, when such current inducing fields are applied, they are associated with harmful side effects caused by currents. For example, one negative effect is the changes in ionic concentration in the various "compartments" within the system, and the harmful products of the electrolysis taking place at the electrodes, or the medium in which the tissues are imbedded. The changes in ion concentrations occur whenever the system includes two or more compartments between which the organism maintains ion concentration differences. For example, for most tissues, $[Ca^{++}]$ in the extracellular fluid is about 2×10^{-3} M, while in the cytoplasm of typical cells its concentration can be as low as 10^{-7} M. A current induced in such a system by a pair of electrodes, flows in part from the extracellular fluid into the cells and out again into the extracellular medium. About 2% of the current flowing into the cells is carried by the Ca^{++} ions. In contrast, because the concentration of intracellular Ca^{++} is much smaller, only a negligible fraction of the currents that exits the cells is carried by these ions. Thus, Ca^{++} ions accumulate in the cells such that their concentrations in the cells increases, while the concentration in the extracellular compartment may decrease. These effects are observed for both DC and alternating currents (AC). The rate of accumulation of the ions depends on the current intensity ion mobilities, membrane ion conductance, etc. An increase in $[Ca^{++}]$ is harmful to most cells and if sufficiently high will lead to the destruction of the cells. Similar considerations apply to other ions. In view of the above observations, long term current application to living organisms or tissues can result in significant damage. Another major problem that is associated with such electric fields, is due to the electrolysis process that takes place at the electrode surfaces. Here charges are transferred between the metal (electrons) and the electrolytic solution (ions) such that charged active radicals are formed. These can cause significant damage to organic molecules, especially macromolecules and thus damage the living cells and tissues.

In contrast, when high frequency electric fields, above 1 MHz and usually in practice in the range of GHz, are induced in tissues usually by means of insulated electrodes or transmission of e.m. waves, the situation is quite different. These type of fields generate only capacitive or displacement currents, rather than the conventional charge conducting currents. Under the effect of this type of field, living tissues behave mostly according to their dielectric properties rather than their electric conductive properties. Therefore, the dominant field effect is that due to dielectric losses and heating. Thus, it is widely accepted that in practice, the meaningful effects of such fields on living organisms, are only those due to their heating effects, i.e., due to dielectric losses.

In U.S. Pat. No. 6,043,066 ('066) to Mangano, a method and device are presented which enable discrete objects having a conducting inner core, surrounded by a dielectric membrane to be selectively inactivated by electric fields via irreversible breakdown of their dielectric membrane. One potential application for this is in the selection and purging of certain biological cells in a suspension. According to the '066 patent, an electric field is applied for targeting selected cells to cause breakdown of the dielectric membranes of these tumor cells, while purportedly not adversely affecting other desired subpopulations of cells. The cells are selected on the basis of intrinsic or induced differences in a characteristic electroporation threshold. The differences in this threshold can depend upon a number of parameters, including the difference in cell size.

The method of the '066 patent is therefore based on the assumption that the electroporation threshold of tumor cells is sufficiently distinguishable from that of normal cells because of differences in cell size and differences in the dielectric properties of the cell membranes. Based upon this assumption, the larger size of many types of tumor cells makes these cells more susceptible to electroporation and thus, it may be possible to selectively damage only the larger tumor cell membranes by applying an appropriate electric field. One disadvantage of this method is that the ability to discriminate is highly dependent upon cell type, for example, the size difference between normal cells and tumor cells is significant only in certain types of cells. Another drawback of this method is that the voltages which are applied can damage some of the normal cells and may not damage all of the tumor cells because the differences in size and membrane dielectric properties are largely statistical and the actual cell geometries and dielectric properties can vary significantly.

What is needed in the art and has heretofore not been available is an apparatus for killing dividing cells, wherein the apparatus better discriminates between dividing cells, including single-celled organisms, and non-dividing cells and is capable of selectively destroying the dividing cells or organisms with substantially no affect on the non-dividing cells or organisms.

SUMMARY

An apparatus for use in a number of different applications for selectively destroying cells undergoing growth and division is provided. This includes, cell, particularly tumor cells, in living tissue and single-celled organisms. The apparatus can be incorporated into a number of different configurations (e.g., as a skin patch or embedded internally within the body) to eliminate or control the growth of such living tissue or organisms.

A major use of the present apparatus is in the treatment of tumors by selective destruction of tumor cells with substantially no affect on normal tissue cells, and thus, the exemplary apparatus is described below in the context of selective destruction of tumor cells. It should be appreciated however, that for purpose of the following description, the term "cell" may also refer to a single-celled organism (eubacteria, bacteria, yeast, protozoa), multi-celled organisms (fungi, algae, mold), and plants as or parts thereof that are not normally classified as "cells". The exemplary apparatus enables selective destruction of cells undergoing division in a way that is more effective and more accurate (e.g., more adaptable to be aimed at specific targets) than existing methods. Further, the present apparatus causes minimal damage, if any, to normal tissue and, thus, reduces or eliminates many side-effects associated with existing selective destruction methods, such as radiation therapy and chemotherapy. The selective destruction of dividing cells using the present apparatus does not depend on the sensitivity of the cells to chemical agents or radiation. Instead, the selective destruction of dividing cells is based on distinguishable geometrical and structural characteristics of cells undergoing division, in comparison to non-dividing cells, regardless of the cell geometry of the type of cells being treated.

According to one exemplary embodiment, cell geometry-dependent selective destruction of living tissue is performed by inducing a non-homogenous electric field in the cells using an electronic apparatus.

It has been observed by the present inventor that, while different cells in their non-dividing state may have different shapes, e.g., spherical, ellipsoidal, cylindrical, "pancake-like", etc., the division process of practically all cells is characterized by development of a "cleavage furrow" in late anaphase and telophase. This cleavage furrow is a slow constriction of the cell membrane (between the two sets of daughter chromosomes) which appears microscopically as a growing cleft (e.g., a groove or notch) that gradually separates the cell into two new cells. During the division process, there is a transient period (telophase) during which the cell structure is basically that of two sub-cells interconnected by a narrow "bridge" formed of the cell material. The division process is completed when the "bridge" between the two sub-cells is broken. The selective destruction of tumor cells using the present electronic apparatus utilizes this unique geometrical feature of dividing cells.

When a cell or a group of cells are under natural conditions or environment, i.e., part of a living tissue, they are disposed surrounded by a conductive environment consisting mostly of an electrolytic inter-cellular fluid and other cells that are composed mostly of an electrolytic intra-cellular liquid. When an electric field is induced in the living tissue, by applying an electric potential across the tissue, an electric field is formed in the tissue and the specific distribution and configuration of the electric field lines defines the paths of electric currents in the tissue, if currents are in fact induced in the tissue. The distribution and configuration of the electric field is dependent on various parameters of the tissue, including the geometry and the electric properties of the different tissue components, and the relative conductivities, capacities and dielectric constants (that may be frequency dependent) of the tissue components.

The electric current flow pattern for cells undergoing division is very different and unique as compared to non-dividing cells. Such cells including first and second sub-cells, namely an "original" cell and a newly formed cell, that are connected by a cytoplasm "bridge" or "neck". The currents penetrate the first sub-cell through part of the membrane ("the current source pole"); however, they do not exit the first sub-cell through a portion of its membrane closer to the opposite pole ("the current sink pole"). Instead, the lines of current flow converge at the neck or cytoplasm bridge, whereby the density of the current flow lines is greatly increased. A corresponding, "mirror image", process that takes place in the second sub-cell, whereby the current flow lines diverge to a lower density configuration as they depart from the bridge, and finally exit the second sub-cell from a part of its membrane closes to the current sink.

When a polar or a polarizable object is placed in a non-uniform converging or diverging field, electric forces act on it and pull it towards the higher density electric field lines. In the case of dividing cell, electric forces are exerted in the direction of the cytoplasm bridge between the two cells. Since all intercellular organelles are polarizable, and most macromolecules are polar (have a dipole moment) they are all force towards the bridge between the two cells. The field polarity is irrelevant to the direction of the force and, therefore, an alternating electric having specific properties can be used to produce substantially the same effect. It will also be appreciated that the concentrated electric field present in or near the bridge or neck portion in itself exerts strong forces on charges and natural dipoles and can lead to the disruption of structures associated with these members.

The movement of the cellular organelles towards the bridge disrupts the cell structure and results in increased pressure in the vicinity of the connecting bridge membrane. This pressure of the organelles on the bridge membrane is expected to break the bridge membrane and, thus, it is expected that the dividing cell will "explode" in response to this pressure. The ability to break the membrane and disrupt other cell structures can be enhanced by applying a pulsating alternating electric field that has a frequency from about 50 KHz to about 500 KHz. When this type of electric field is applied to the tissue, the forces exerted on the intercellular organelles have a "hammering" effect, whereby force pulses (or beats) are applied to the organelles numerous times per second, enhancing the movement of organelles of different sizes and masses towards the bridge (or neck) portion from both of the sub-cells, thereby increasing the probability of breaking the cell membrane at the bridge portion. The forces exerted on the intracellular organelles also affect the organelles themselves and may collapse or break the organelles.

According to one exemplary embodiment, the apparatus for applying the electric field is an electronic apparatus that generates the desired electric signals in the shape of waveforms or trains of pulses. The electronic apparatus includes a generator that generates an alternating voltage waveform at frequencies in the range from about 50 KHz to about 500 KHz. The generator is operatively connected to conductive leads which are connected at their other ends to insulated conductors/electrodes (also referred to as isolects) that are activated by the generated waveforms. The insulated electrodes consist of a conductor in contact with a dielectric

(insulating layer) that is in contact with the conductive tissue, thus forming a capacitor. The electric fields that are generated by the present apparatus can be applied in several different modes depending upon the precise treatment application.

In one exemplary embodiment, the electric fields are applied by external insulated electrodes which are constructed so that the applied electric fields can be of a local type or of a widely distributed type. This embodiment is designed to treat skin tumors and lesions that are close to the skin surface. According to this embodiment, the insulated electrodes can be incorporated into a skin patch that is applied to a skin surface. The skin patch can be a self-adhesive flexible patch and can include one or more pairs of the insulated electrodes.

According to another embodiment, the apparatus is used in an internal type application in that the insulated electrodes are in the form of plates, wires, etc., that are inserted subcutaneously or deeper within the body so as to generate an electric field having the above desired properties at a target area (e.g., a tumor).

Thus, the present apparatus utilizes electric fields that fall into a special intermediate category relative to previous high and low frequency applications in that the present electric fields are bio-effective fields that have no meaningful stimulatory effects and no thermal effects. Advantageously, when non-dividing cells are subjected to these electric fields, there is no effect on the cells; however, the situation is much different when dividing cells are subjected to the present electric fields. Thus, the present electronic apparatus and the generated electric fields target dividing cells, such as tumors or the like, and do not target non-dividing cells that is found around in healthy tissue surrounding the target area. Furthermore, since the present apparatus utilizes insulated electrodes, the above mentioned negative effects, obtained when conductive electrodes are used, i.e., ion concentration changes in the cells and the formation of harmful agents by electrolysis, do not occur with the present apparatus. This is because, in general, no actual transfer of charges takes place between the electrodes and the medium, and there is no charge flow in the medium where the currents are capacitive.

It should be appreciated that the present electronic apparatus can also be used in applications other than treatment of tumors in the living body. In fact, the selective destruction utilizing the present apparatus can be used in conjunction with any organism that proliferates division and multiplication, for example, tissue cultures, microorganisms, such as bacteria, mycoplasma, protozoa, fungi, algae, plant cells, etc. Such organisms divide by the formation of a groove or cleft as described above. As the groove or cleft deepens, a narrow bridge is formed between the two parts of the organism, similar to the bridge formed between the sub-cells of dividing animal cells. Since such organisms are covered by a membrane having a relatively low electric conductivity, similar to an animal cell membrane described above, the electric field lines in a dividing organism converge at the bridge connecting the two parts of the dividing organism. The converging field lines result in electric forces that displace polarizable elements within the dividing organism.

The above, and other objects, features and advantages of the present apparatus will become apparent from the following description read in conjunction with the accompanying drawings, in which like reference numerals designate the same elements.

BRIEF DESCRIPTION OF THE DRAWING FIGURES

FIGS. **1**A–**1**E are simplified, schematic, cross-sectional, illustrations of various stages of a cell division process;

FIGS. **2**A and **2**B are schematic illustrations of a non-dividing cell being subjected to an electric field;

FIGS. **3**A, **3**B and **3**C are schematic illustrations of a dividing cell being subjected to an electric field according to one exemplary embodiment, resulting in destruction of the cell (FIG. **3**C) in accordance with one exemplary embodiment;

FIG. **4** is a schematic illustration of a dividing cell at one stage being subject to an electric field;

FIG. **5** is a schematic diagram of an apparatus for applying an electric according to one exemplary embodiment for selectively destroying cells;

FIG. **6** is a simplified schematic diagram of an equivalent electric circuit of insulated electrodes of the apparatus of FIG. **5**;

FIG. **7** is a schematic illustration of a skin patch incorporating the apparatus of FIG. **5** and for placement on a skin surface for treating a tumor or the like;

FIG. **8** is a schematic illustration of the insulated electrodes implanted within the body for treating a tumor or the like;

FIG. **9** is a schematic illustration of the insulated electrodes implanted within the body for treating a tumor or the like;

FIGS. **10**A–**10**D are schematic illustrations of various constructions of the insulated electrodes of the apparatus of FIG. **5**;

FIG. **11** is a schematic illustration of two insulated electrodes being arranged about a human torso for treatment of a tumor container within the body, e.g., a tumor associated with lung cancer;

FIGS. **12**A–**12**C are schematic illustrations of various insulated electrodes with and without protective members formed as a part of the construction thereof; and

FIG. **13** is a schematic illustration of insulated electrodes that are arranged for focusing the electric field at a desired target while leaving other areas in low field density (i.e., protected areas).

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Reference is made to FIGS. **1**A–**1**E which schematically illustrate various stages of a cell division process. FIG. **1**A illustrates a cell **10** at its normal geometry, which can be generally spherical (as illustrated in the drawings), ellipsoidal, cylindrical, "pancake-like" or any other cell geometry, as is known in the art. FIGS. **1**B–**1**D illustrate cell **10** during different stages of its division process, which results in the formation of two new cells **18** and **20**, shown in FIG. **1**E.

As shown in FIGS. **1**B–**1**D, the division process of cell **10** is characterized by a slowly growing cleft **12** which gradually separates cell **10** into two units, namely sub-cells **14** and **16**, which eventually evolve into new cells **18** and **20** (FIG. **1**E). A shown specifically in FIG. **1**D, the division process is characterized by a transient period during which the structure of cell **10** is basically that of the two sub-cells **14** and **16** interconnected by a narrow "bridge" **22** containing cell material (cytoplasm surrounded by cell membrane).

Reference is now made to FIGS. **2**A and **2**B, which schematically illustrate non-dividing cell **10** being subjected to an electric field produced by applying an alternating electric potential, at a relatively low frequency and at a relatively high frequency, respectively. Cell **10** includes intracellular organelles, e.g., a nucleus **30**. Alternating electric potential is applied across electrodes **28** and **32** that can be attached externally to a patient at a predetermined region, e.g., in the vicinity of the tumor being treated. When cell **10** is under natural conditions, i.e., part of a living tissue, it is disposed in a conductive environment (hereinafter referred to as a "volume conductor") consisting mostly of electrolytic inter-cellular liquid. When an electric potential is applied across electrodes **28** and **32**, some of the field lines of the resultant electric field (or the current induced in the tissue in response to the electric field) penetrate the cell **10**, while the rest of the field lines (or induced current) flow in the surrounding medium. The specific distribution of the electric field lines, which is substantially consistent with the direction of current flow in this instance, depends on the geometry and the electric properties of the system components, e.g., the relative conductivities and dielectric constants of the system components, that can be frequency dependent. For low frequencies, e.g., frequencies lower than 10 KHz, the conductance properties of the components completely dominate the current flow and the field distribution, and the field distribution is generally as depicted in FIG. **2**A. At higher frequencies, e.g., at frequencies of between 10 KHz and 1 MHz, the dielectric properties of the components becomes more significant and eventually dominate the field distribution, resulting in field distribution lines as depicted generally in FIG. **2**B.

For constant (i.e., DC) electric fields or relatively low frequency alternating electric fields, for example, frequencies under 10 KHz, the dielectric properties of the various components are not significant in determining and computing the field distribution. Therefore, as a first approximation, with regard to the electric field distribution, the system can be reasonably represented by the relative impedances of its various components. Using this approximation, the intercellular (i.e., extracellular) fluid and the intracellular fluid each has a relatively low impedance, while the cell membrane **11** has a relatively high impedance. Thus, under low frequency conditions, only a fraction of the electric field lines (or currents induced by the electric field) penetrate membrane **11** of the cell **10**. At relatively high frequencies (e.g., 10 KHz–1 MHz), in contrast, the impedance of membrane **11** relative to the intercellular and intracellular fluids decreases, and thus, the fraction of currents penetrating the cells increases significantly. It should be noted that at very high frequencies, i.e., above 1 MHz, the membrane capacitance can short the membrane resistance and, therefore, the total membrane resistance can become negligible.

In any of the embodiments described above, the electric field lines (or induced currents) penetrate cell **10** from a portion of the membrane **11** closest to one of the electrodes generating the current, e.g., closest to positive electrode **28** (also referred to herein as "source"). The current flow pattern across cell **10** is generally uniform because, under the above approximation, the field induced inside the cell is substantially homogeneous. The currents exit cell **10** through a portion of membrane **11** closest to the opposite electrode, e.g., negative electrode **32** (also referred to herein as "sink").

The distinction between field lines and current flow can depend on a number of factors, for example, on the frequency of the applied electric potential and on whether electrodes **28** and **32** are electrically insulated. For insulated electrodes applying a DC or low frequency alternating voltage, there is practically no current flow along the lines of the electric field. At higher frequencies, the displacement currents are induced in the tissue due to charging and discharging of the electrode insulation and the cell membranes (which act as capacitors to a certain extent), and such currents follow the lines of the electric field. Fields generated by non-insulated electrodes, in contrast, always generate some form of current flow, specifically, DC or low frequency alternating fields generate conductive current flow along the field lines, and high frequency alternating fields generate both conduction and displacement currents along the field lines. It should be appreciated, however, that movement of polarizable intracellular organelles according to the present invention (as described below) is not dependent on actual flow of current and, therefore, both insulated and non-insulated electrodes can be used efficiently. Several advantages of insulated electrodes are that they have lower power consumption and cause less heating of the treated regions.

According to one exemplary embodiment of the present invention, the electric fields that are used are alternating fields having frequencies that are in the range from about 50 KHz to about 500 KHz, and preferably from about 100 KHz to about 300 KHz. For ease of discussion, these type of electric fields are also referred to below as "TC fields", which is an abbreviation of "Tumor Curing electric fields", since these electric fields fall into an intermediate category (between high and low frequency ranges) that have bio-effective field properties while having no meaningful stimulatory and thermal effects. These frequencies are sufficiently low so that the system behavior is determined by the system's Ohmic (conductive) properties but sufficiently high enough not to have any stimulation effect on excitable tissues. Such a system consists of two types of elements, namely, the intercellular, or extracellular fluid, or medium and the individual cells. The intercellular fluid is mostly an electrolyte with a specific resistance of about 40–100 Ohm*cm. As mentioned above, the cells are characterized by three elements, namely (1) a thin, highly electric resistive membrane that coats the cell; (2) internal cytoplasm that is mostly an electrolyte that contains numerous macromolecules and micro-organelles, including the nucleus; and (3) membranes, similar in their electric properties to the cell membrane, cover the micro-organelles.

When this type of system is subjected to the present TC fields (e.g., alternating electric fields in the frequency range of 100 KHz–300 KHz) most of the lines of the electric field and currents tend away from the cells because of the high resistive cell membrane and therefore the lines remain in the extracellular conductive medium. In the above recited frequency range, the actual fraction of electric field or currents that penetrates the cells is a strong function of the frequency.

FIG. **3** schematically depicts the resulting field distribution in the system. As illustrated, the lines of force, which also depict the lines of potential current flow across the cell volume mostly in parallel with the undistorted lines of force (the main direction of the electric field). In other words, the field inside the cells is mostly homogeneous. In practice, the fraction of the field or current that penetrates the cells is determined by the cell membrane impedance value relative to that of the extracellular fluid. Since the equivalent electric circuit of the cell membrane is that of a resistor and capacitor in parallel, the impedance is a function of the frequency. The higher the frequency, the lower the impedance, the larger the fraction of penetrating current and the smaller the field distortion.

As previously mentioned, when cells are subjected to relatively weak electric fields and currents that alternate at high frequencies, such as the present TC fields having a frequency in the range of 50 KHz–500 KHz, they have no effect on the non-dividing cells. While the present TC fields have no detectable effect on such systems, the situation becomes different in the presence of dividing cells.

Reference is now made to FIGS. **3**A–**3**C which schematically illustrate the electric current flow pattern in cell **10** during its division process, under the influence of alternating fields (TC fields) in the frequency range from about 100 KHz to about 300 KHz in accordance with one exemplary embodiment. The field lines or induced currents penetrate cell **10** through a part of the membrane of sub-cell **16** closer to electrode **28**. However, they do not exit through the cytoplasm bridge **22** that connects sub-cell **16** with the newly formed yet still attached sub-cell **14**, or through a part of the membrane in the vicinity of the bridge **22**. Instead, the electric field or current flow lines—that are relatively widely separated in sub-cell **16**—converge as they approach bridge **22** (also referred to as "neck" **22**) and, thus, the current/field line density within neck **22** is increased dramatically. A "mirror image" process takes place in sub-cell **14**, whereby the converging field lines in bridge **22** diverge as they approach the exit region of sub-cell **14**.

It should be appreciated by persons skilled in the art that homogeneous electric fields do not exert a force on electrically neutral objects, i.e., objects having substantially zero net charge, although such objects can become polarized. However, under a non-uniform, converging electric field, as shown in FIGS. **3**A–**3**C, electric forces are exerted on polarized objects, moving them in the direction of the higher density electric field lines. It will be appreciated that the concentrated electric field that is present in the neck or bridge area in itself exerts strong forces on charges and natural dipoles and can disrupt structures that are associated therewith.

In the configuration of FIGS. **3**A and **3**B, the direction of movement of polarized objects is towards the higher density electric field lines, i.e., towards the cytoplasm bridge **22** between sub-cells **14** and **16**. It is known in the art that all intracellular organelles, for example, nuclei **24** and **26** of sub-cells **14** and **16**, respectively, are polarizable and, thus, such intracellular organelles are electrically forced in the direction of the bridge **22**. Since the movement is always from lower density currents to the higher density currents, regardless of the field polarity, the forces applied by the alternating electric field to organelles, such as nuclei **24** and **26**, are always in the direction of bridge **22**. A comprehensive description of such forces and the resulting movement of macromolecules of intracellular organelles, a phenomenon referred to as "dielectrophoresis" is described extensively in literature, e.g., in C. L. Asbury & G. van den Engh, Biophys. J. 74, 1024–1030, 1998, the disclosure of which is hereby incorporated by reference in its entirety.

The movement of the organelles **24** and **26** towards the bridge **22** disrupts the structure of the dividing cell and, eventually, the pressure of the converging organelles on bridge membrane **22** results in the breakage of cell membrane **11** at the vicinity of the bridge **22**, as shown schematically in FIG. **3**C. The ability to break membrane **11** at bridge **22** and to otherwise disrupt the cell structure and organization can be enhanced by applying a pulsating AC electric field, rather than a steady AC field. When a pulsating field is applied, the forces acting on organelles **24** and **26** have a "hammering" effect, whereby pulsed forces beat on the intracellular organelles towards the neck **22** from both sub-cells **14** and **16**, thereby increasing the probability of breaking cell membrane **11** in the vicinity of neck **22**.

A very important element, which is very susceptible to the special fields that develop within the dividing cells is the microtubule spindle that plays a major role in the division process. In FIG. **4**, a dividing cell **10** is illustrated, at an earlier stage as compared to FIGS. **3**A and **3**B, under the influence of external TC fields (e.g., alternating fields in the frequency range of about 100 KHz to about 300 KHz), generally indicated as lines **100**, with a corresponding spindle mechanism generally indicated at **120**. The lines **120** are microtubules that are known to have a very strong dipole moment. This strong polarization makes the tubules susceptible to electric fields. Their positive charges are located at the two centrioles while two sets of negative poles are at the center of the dividing cell and the other pair is at the points of attachment of the microtubules to the cell membrane, generally indicated at **130**. This structure forms sets of double dipoles and therefore they are susceptible to fields of different directions. It will be understood that the effect of the TC fields on the dipoles does not depend on the formation of the bridge (neck) and thus, the dipoles are influenced by the TC fields prior to the formation of the bridge (neck).

Since the present apparatus (as will be described in greater detail below) utilizes insulated electrodes, the above-mentioned negative effects obtained when conductive electrodes are used, i.e., ion concentration changes in the cells and the formation of harmful agents by electrolysis, do not occur when the present apparatus is used. This is because, in general, no actual transfer of charges takes place between the electrodes and the medium and there is no charge flow in the medium where the currents are capacitive, i.e., are expressed only as rotation of charges, etc.

Turning now to FIG. **5**, the TC fields described above that have been found to advantageously destroy tumor cells are generated by an electronic apparatus **200**. FIG. **5** is a simple schematic diagram of the electronic apparatus **200** illustrating the major components thereof. The electronic apparatus **200** generates the desired electric signals (TC signals) in the shape of waveforms or trains of pulses. The apparatus **200** includes a generator **210** and a pair of conductive leads **220** that are attached at one end thereof to the generator **210**. The opposite ends of the leads **220** are connected to insulated conductors **230** that are activated by the electric signals (e.g., wavefons). The insulated conductors **230** are also referred to hereinafter as isolects **230**. Optionally and according to another exemplary embodiment, the apparatus **200** includes a temperature sensor **240** and a control box **250** which are both added to control the amplitude of the electric field generated so as not to generate excessive heating in the area that is treated.

The generator **210** generates an alternating voltage waveform at frequencies in the range from about 50 KHz to about 500 KHz (preferably from about 100 KHz to about 300 KHz) (i.e., the TC fields). The required voltages are such that the electric field intensity in the tissue to be treated is in the range of about 0.1 V/cm to about 10 V/cm. To achieve this field, the actual potential difference between the two conductors in the isolects **230** is determined by the relative impedances of the system components, as described below.

When the control box **250** is included, it controls the output of the generator **210** so that it will remain constant at the value preset by the user or the control box **250** sets the output at the maximal value that does not cause excessive heating, or the control box **250** issues a warning or the like when the temperature (sensed by temperature sensor **240**) exceeds a preset limit.

The leads **220** are standard isolated conductors with a flexible metal shield, preferably grounded so that it prevents the spread of the electric field generated by the leads **220**. The isolects **230** have specific shapes and positioning so as to generate an electric field of the desired configuration, direction and intensity at the target volume and only there so as to focus the treatment.

The specifications of the apparatus **200** as a whole and its individual components are largely influenced by the fact that at the frequency of the present TC fields (50 KHz–500 KHz), living systems behave according to their "Ohmic", rather than their dielectric properties. The only elements in the apparatus **200** that behave differently are the insulators of the isolects **230** (see FIGS. **7**–**9**). The isolects **200** consist of a conductor in contact with a dielectric that is in contact with the conductive tissue thus forming a capacitor.

The details of the construction of the isolects **230** is based on their electric behavior that can be understood from their simplified electric circuit when in contact with tissue as generally illustrated in FIG. **6**. In the illustrated arrangement, the electric field distribution between the different components is determined by their relative electric impedance, i.e., the fraction of the field on each component is given by the value of its impedance divided by the total circuit impedance. For example, the potential drop on element $\Delta V_A = A/(A+B+C+D+E)$. Thus, for DC or low frequency AC, practically all the potential drop is on the capacitor (that acts as an insulator). For relatively very high frequencies, the capacitor practically is a short and therefore, practically all the field is distributed in the tissues. At the frequencies of the present TC fields (e.g., 50 KHz to 500 KHz), which are intermediate frequencies, the impedance of the capacitance of the capacitors is dominant and determines the field distribution. Therefore, in order to increase the effective voltage drop across the tissues (field intensity), the impedance of the capacitors is to be decreased (i.e., increase their capacitance). This can be achieved by increasing the effective area of the "plates" of the capacitor, decrease the thickness of the dielectric or use a dielectric with high dielectric constant. There a number of different materials that are suitable for use in the intended application and have high dielectric constants. For example, some materials include: lithium nibate ($LiNbO_3$), which is a ferroelectric crystal and has a number of applications in optical, pyroelectric and piezoelectric devices; yittrium iron garnet (YIG) is a ferrimagnetic crystal and magneto-optical devices, e.g., optical isolator can be realized from this material; barium titanate ($BaTiO_3$) is a ferromagnetic crystal with a large electro-optic effect; potassium tantalate ($kTaO_3$) which is a dielectric crystal (ferroelectric at low temperature) and has very low microwave loss and tunability of dielectric constant at low temperature; and lithium tantalate ($LiTaO_3$) which is a ferroelectric crystal with similar properties as lithium niobate and has utility in electro-optical, pyroelectric and piezoelectric devices. It will be understood that the aforementioned exemplary materials can be used in combination with the present device where it is desired to use a material having a high dielectric constant.

In order to optimize the field distribution, the isolects **230** are configured differently depending upon the application in which the isolects **230** are to be used. There are two principle modes for applying the present electric fields (TC fields). First, the TC fields can be applied by external isolects and second, the TC fields can be applied by internal isolects.

Electric fields (TC fields) that are applied by external isolects can be of a local type or widely distributed type. The first type includes, for example, the treatment of skin tumors and treatment of lesions close to the skin surface. FIG. **7** illustrates an exemplary embodiment where the isolects **230** are incorporated in a skin patch **300**. The skin patch **300** can be a self-adhesive flexible patch with one or more pairs of isolects **230**. The patch **300** includes internal insulation **310** (formed of a dielectric material) and the external insulation **260** and is applied to skin surface **301** that contains a tumor **303** either on the skin surface **301** or slightly below the skin surface **301**. Tissue is generally indicated at **305**. To prevent the potential drop across the internal insulation **310** to dominate the system, the internal insulation **310** must have a relatively high capacity. This can be achieved by a large surface area; however, this may not be desired as it will result in the spread of the field over a large area (e.g., an area larger than required to treat the tumor). Alternatively, the internal insulation **310** can be made very thin and/or the internal insulation **310** can be of a high dielectric constant. As the skin resistance between the electrodes (labeled as A and E in FIG. **6**) is normally significantly higher than that of the tissue (labeled as C in FIG. **6**) underneath it (1–10 KΩ vs. 0.1–1 KΩ), most of the potential drop beyond the isolects occurs there. To accommodate for these impedances (Z), the characteristics of the internal insulation **310** (labeled as B and D in FIG. **6**) should be such that they have impedance preferably under 100 KΩ at the frequencies of the present TC fields (e.g., 50 KHz to 500 KHz). For example, if it is desired for the impedance to be about 10K Ohms, such that over 1% of the applied voltage falls on the tissues, for isolects with a surface area of 10 mm^2, at frequencies of 200 KHz, the capacity should be on the order of 10^{-10} F, which means that using standard insulations with a dielectric constant of 2–3, the thickness of the insulating layer **310** should be about 50–100 microns. An internal field 10 times stronger would be obtained with insulators with a dielectric constant of about 20–50.

Since the insulating layer can be very vulnerable, etc., the insulation can be replaced by very high dielectric constant insulating materials, such as titanium dioxide (e.g., rutil), the dielectric constant can reach values of about 200. One must also consider another factor that effects the effective capacity of the isolects **230**, namely the presence of air between the isolects **230** and the skin. Such presence, which is not easy to prevent, introduces a layer of an insulator with a dielectric constant of 1.0, a factor that significantly lowers the effective capacity of the isolects **230** and neutralizes the advantages of the titanium dioxide (routil), etc. To overcome this problem, the isolects **230** can be shaped so as to conform with the body structure and/or (2) an intervening filler **270** (as illustrated in FIG. **1**C), such as a gel, that has high conductance and a dielectric constant, can be added to the structure. The shaping can be pre-structured (see FIG. **10**A) or the system can be made sufficiently flexible so that shaping of the isolects **230** is readily achievable. The gel can be contained in place by having an elevated rim as depicted in FIG. **10**C. The gel can be made of gelatins, agar, etc., and can have salts dissolved in it to increase its conductivity. FIGS. **10**A–**10**C illustrate various exemplary configurations for the isolects **230**. The exact thickness of the gel is not important so long as it is of sufficient thickness that the gel layer does not dry out during the treatment. In one exemplary embodiment, the thickness of the gel is about 0.5 mm to about 2 mm.

In order to achieve the desirable features of the isolects **230**, the dielectric coating of each should be very thin, for example from between 1–50 microns. Since the coating is so thin, the isolects **230** can easily be damaged mechanically. This problem can be overcome by adding a protective feature to the isolect's structure so as to provide desired protection from such damage. For example, the isolect **230** can be coated, for example, with a relatively loose net **340** that prevents access to the surface but has only a minor effect on the effective surface area of the isolect **230** (i.e., the capacity of the isolects **230** (cross section presented in FIG. **12**B). The loose net **340** does not effect the capacity and ensures good contact with the skin, etc. The loose net **340** can be formed of a number of different materials; however, in one exemplary embodiment, the net **340** is formed of nylon, polyester, cotton, etc. Alternatively, a very thin conductive coating **350** can be applied to the dielectric portion (insulating layer) of the isolect **230**. One exemplary conductive coating is formed of a metal and more particularly of gold. The thickness of the coating **350** depends upon the particular application and also on the type of material used to form the coating **350**; however, when gold is used, the coating has a thickness from about 0.1 micron to about 0.1 mm. Furthermore, the rim illustrated in FIG. **10** can also provide some mechanical protection.

However, the capacity is not the only factor to be considered. The following two factors also influence how the isolects **230** are constructed. The dielectric strength of the internal insulating layer **310** and the dielectric losses that occur when it is subjected to the TC field, i.e., the amount of heat generated. The dielectric strength of the internal insulation **310** determines at what field intensity the insulation will be "shorted" and cease to act as an intact insulation. Typically, insulators, such as plastics, have dielectric strength values of about 100V per micron or more. As a high dielectric constant reduces the field within the internal insulator **310**, a combination of a high dielectric constant and a high dielectric strength gives a significant advantage. This can be achieved by using a single material that has the desired properties or it can be achieved by a double layer with the correct parameters and thickness. In addition, to further decreasing the possibility that the insulating layer **310** will fail, all sharp edges of the insulating layer **310** should be eliminated as by rounding the corners, etc., as illustrated in FIG. **10**D using conventional techniques.

FIGS. **8** and **9** illustrate a second type of treatment using the isolects **230**, namely electric field generation by internal isolects **230**. A body to which the isolects **230** are implanted is generally indicated at **311** and includes a skin surface **313** and a tumor **315**. In this embodiment, the isolects **230** can have the shape of plates, wires or other shapes that can be inserted subcutaneously or a deeper location within the body **311** so as to generate an appropriate field at the target area (tumor **315**).

It will also be appreciated that the mode of isolects application is not restricted to the above descriptions. In the case of tumors in internal organs, for example, liver, lung, etc., the distance between each member of the pair of isolects **230** can be large. The pairs can even by positioned opposite sides of a torso **410**, as illustrated in FIG. **11**. The arrangement of the isolects **230** in FIG. **11** is particularly useful for treating a tumor **415** associated with lung cancer. In this embodiment, the electric fields (TC fields) spread in a wide fraction of the body.

In order to avoid overheating of the treated tissues, a selection of materials and field parameters is needed. The isolects insulating material should have minimal dielectric losses at the frequency ranges to be used during the treatment process. This factor can be taken into consideration when choosing the particular frequencies for the treatment. The direct heating of the tissues will most likely be dominated by the heating due to current flow (given by the I*R product).

The effectiveness of the treatment can be enhanced by an arrangement of isolects **230** that focuses the field at the desired target while leaving other sensitive areas in low field density (i.e., protected areas). The proper placement of the isolects **230** over the body can be maintained using any number of different techniques, including using a suitable piece of clothing that keeps the isolects at the appropriate positions. FIG. **13** illustrates such an arrangement in which an area labeled as "P" represents a protected area. The lines of field force do not penetrate this protected area and the field there is much smaller than near the isolects **230** where target areas can be located and treated well. In contrast, the field intensity near the four poles is very high.

The following Example serves to illustrate an exemplary application of the present apparatus and application of TC fields; however, this Example is not limiting and does not limit the scope of the present invention in any way.

EXAMPLE

To demonstrate the effectiveness of electric fields having the above described properties (e.g., frequencies between 50 KHz and 500 KHz) in destroying tumor cells, the electric fields were applied to treat mice with malignant melanoma tumors. Two pairs of isolects **230** were positioned over a corresponding pair of malignant melanomas. Only one pair was connected to the generator **210** and 200 KHz alternating electric fields (TC fields) were applied to the tumor for a period of 6 days. One melanoma tumor was not treated so as to permit a comparison between the treated tumor and the non-treated tumor. After treatment for 6 days, the pigmented melanoma tumor remained clearly visible in the non-treated side of the mouse, while, in contrast, no tumor is seen on the treated side of the mouse. The only areas that were visible discernable on the skin were the marks that represented the points of insertion of the isolects **230**. The fact that the tumor was eliminated at the treated side was further demonstrated by cutting and inversing the skin so that its inside face was exposed. Such a procedure indicated that the tumor has been substantially, if not completely, eliminated on the treated side of the mouse. The success of the treatment was also further verified by pathhistological examination.

The present inventor has thus uncovered that electric fields having particular properties can be used to destroy dividing cells or tumors when the electric fields are applied to using an electronic device. More specifically, these electric fields fall into a special intermediate category, namely bio-effective fields that have no meaningful stimulatory and no thermal effects, and therefore overcome the disadvantages that were associated with the application of conventional electric fields to a body. It will also be appreciated that the present apparatus can further include a device for rotating the TC field relative to the living tissue. For example and according to one embodiment, the alternating electric potential applies to the tissue being treated is rotated relative to the tissue using conventional devices, such as a mechanical device that upon activation, rotates various components of the present system.

While the invention has been particularly shown and described with reference to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details can be made without departing from the spirit and scope of the invention.

What is claimed is:

1. An apparatus for selectively destroying dividing cells in living tissue, the dividing cells having polarizable or polar intracellular members, the apparatus comprising:

a first insulated electrode having a first conductor and a first insulating layer, wherein the first insulated electrode is configured for placement against the living tissue with the first insulating layer disposed between the first conductor and the living tissue so as to insulate the first conductor from the living tissue;

a second insulated electrode having a second conductor and a second insulating layer, wherein the second insulated electrode is configured for placement against the living tissue with the second insulating layer disposed between the second conductor and the living tissue so as to insulate the second conductor from the living tissue; and

an electric field source for applying an alternating electric potential across the first and second conductors,

wherein the amplitude and frequency of the electric field source and the capacitance of the insulating layers are such that, when the electrodes are placed against the living tissue and the alternating electric potential is applied across the first and second conductors, an electric field is induced in the living tissue, the induced electric field having characteristics such that passage of the electric field through the dividing cells in late anaphase or telophase transforms the electric field into & non-homogenous electric field that produces an increased density electric field in a region of a cleavage furrow of the dividing cells, the non-homogeneous electric field produced within the dividing cells being of sufficient intensity to move the polarizable intracellular members toward the cleavage.

2. The apparatus of claim **1**, wherein the electric field is of sufficient frequency so that the non-homogeneous electric field produced in the dividing cells defines electric field lines which generally converge at a region of the cleavage furrow, thereby defining the increased density electric field, resulting in destruction of the dividing cells as a result of the polarizable intracellular members movement toward the furrow.

3. The apparatus of claim **1**, further including:

a first conductive lead operatively connecting the first electrode to the electric field source; and

a second conductive lead operatively connecting the second electrode to the electric field source.

4. The apparatus of claim **1**, wherein the first electrode includes a first dielectric member that is in contact with the first conductor, the first dielectric member for placement against the living tissue to form a capacitor.

5. The apparatus of claim **4**, wherein the second electrode includes a second dielectric member that is in contact with the second conductor, the second dielectric member for placement against the living tissue to form a capacitor.

6. The apparatus of claim **5**, wherein each of the first and second dielectric members is formed of a layer of titanium dioxide.

7. The apparatus of claim **5**, wherein each of the first and second dielectric members comprises a dielectric coating having a thickness between about 5 microns to about 50 microns.

8. The apparatus of claim **7**, further including: a loose net disposed around the dielectric coating for restricting access to a surface of the dielectric coating while only having a minimal effect on a surface area of the dielectric coating.

9. The apparatus of claim **7**, further including: a thin conducting coating disposed on the dielectric coating for contacting the tissue.

10. The apparatus of claim **9**, wherein the conducting coating is formed of gold.

11. The apparatus of claim **5**, wherein at least one of the first and second electrodes includes an intervening filler disposed on the respective dielectric member thereof, the intervening filler being formed of a material that has high conductance and a high dielectric constant.

12. The apparatus of claim **11**, wherein the intervening filler comprises a gel formed of at least one material selected from the group consisting of gelatins and agar.

13. The apparatus of claim **12**, wherein the gel includes salt dissolved therein to increase the conductivity of the gel.

14. The apparatus of claim **11**, wherein the intervening filler is contained within the dielectric member by a rim formed as part of the dielectric member.

15. The apparatus of claim **1**, wherein the alternating electric potential has a frequency of between about 50 KHz to about 500 KHz.

16. The apparatus of claim **1**, wherein the alternating electric potential has a frequency of between about 100 KHz to about 300 KHz.

17. The apparatus of claim **1**, wherein the electric field is a substantially uniform electric field prior to passing through the dividing cells.

18. The apparatus of claim **1**, wherein the electric field source comprises a generator that generates an alternating voltage waveform at frequencies between about 50 KHz to about 500 KHz.

19. The apparatus of claim **18**, wherein each of the first and second electrodes are activated by the alternating voltage waveform.

20. The apparatus of claim **18**, wherein the voltage waveform is selected so that an electric field intensity in tissue to be treated is between about 0.1 V/cm to about 10.0 V/cm.

21. The apparatus of claim **1**, further including:

a control box operatively connected to the electric field source; and

a temperature sensor coupled to the control box, wherein the control box and the temperature sensor control the amplitude of the electric field generated so that excessive heating in a treated area is prevented.

22. The apparatus of claim **1**, wherein the first and second electrodes are adapted to be inserted within a body.

23. The apparatus of claim **22**, wherein the first and second electrodes are incorporated into a structure that is adapted to be inserted subcutaneously within the body.

24. The apparatus of claim **1**, wherein the first and second electrodes are configured for placement on opposite sides of a torso with the dividing cells being associated with a tumor that is formed within the body at a location between the first and second electrodes.

25. A skin patch for selectively destroying dividing cells that are in a localized area of living tissue, the dividing cells having polarizable or polar intracellular members, the skin patch including:

a skin patch body for placement on the living tissue over the localized area of dividing cells, the skin patch body comprising: a first insulated electrode having a first conductor and a first insulating layer disposed between the first conductor and the living tissue so as to insulate the first conductor from the living tissue; and a second insulated electrode having a second conductor and a second insulating layer disposed between the second conductor and the living tissue so as to insulate the second conductor from the living tissue; and

an electric field source for applying an alternating electric potential across the first and second conductors, wherein the amplitude and frequency of the electric field source and the capacitance of the insulating layers are such that, when the skin patch body is placed against the living tissue and the alternating electric potential is applied across the first and second conductors, an electric field is induced in the living tissue, the induced electric field having characteristics such that passage of the electric field through the dividing cells in late anaphase or telophase transforms the electric field into a nonhomogenous electric field that produces an increased density electric field in a region of a cleavage furrow of the dividing cells, the non-homogeneous electric field produced within the dividing cells being of sufficient intensity to move the polarizable intracellular members toward the cleavage furrow.

26. The skin patch of claim **25**, wherein the electric field is of sufficient frequency so that the non-homogeneous electric field produced in the dividing cells defines electric field lines which generally converge at a region of the cleavage furrow, thereby defining the increased density electric field, resulting in destruction of the dividing cells as a result of the polarizable intracellular members movement toward the furrow.

27. The skin patch of claim **25**, wherein the alternating electric potential has a frequency of between about 50 KHz to about 500 KHz.

28. The skin patch of claim **25**, wherein the alternating electric potential has a frequency of between about 100 KHz to about 300 KHz.

29. The skin patch of claim **25**, wherein the electric field is a substantially uniform electric field prior to passing through the dividing cells.

30. The skin patch of claim **29**, wherein each of the first and second electrodes are activated by the alternating voltage waveform.

31. The skin patch of claim **29**, wherein the voltage waveform is selected so that an electric field intensity in tissue to be treated is between about 0.1 V/cm to about 10.0 V/cm.

32. The skin patch of claim **25**, wherein the electric field source comprises a generator that generates an alternating voltage waveform at frequencies between about 50 KHz to about 500 KHz.

33. The skin patch of claim **25**, further including:

a control box operatively connected to the electric field source;

and a temperature sensor coupled to the control box, wherein the control box and the temperature sensor control the amplitude of the electric field generated so that excessive heating in a treated area is prevented.

34. The skin patch of claim **25**, further comprising: at least one additional insulated electrode having a corresponding conductor that is coupled to the electric field source.

35. The skin patch of claim **34**, wherein all of the insulated electrodes are arranged to focus the electric field at a target within the localized area of the living tissue while also forming a protected area which has a low electric field density.

36. An apparatus for selectively destroying dividing cells in living tissue, the dividing cells having polarizable or polar intracellular members, the apparatus comprising:

a first insulated electrode having a first conductor and a first insulating layer, wherein the first insulated electrode is configured for placement against the living tissue with the first insulating layer disposed between the first conductor and the living tissue so as to insulate the first conductor from the living tissue;

a second insulated electrode having a second conductor and a second insulating layer, wherein the second insulated electrode is configured for placement against the living tissue with the second insulating layer disposed between the second conductor and the living tissue so as to insulate the second conductor from the living tissue; and

an electric field source for applying an alternating electric potential across the first and second conductors,

wherein the amplitude an& frequency of the electric field source and the capacitance of the insulating layers are such that, when the electrodes arc placed against the living tissue and the alternating electric potential is applied across the first and second conductors, an electric field is induced in the living tissue, the induced electric field having characteristics such that (a) passage of the electric field through the dividing cells in late anaphase or telophase kills a significant portion of the dividing cells, and (b) passage of the electric field through non-dividing cells leaves the non-dividing cells substantially unharmed.

37. A skin patch far selectively destroying dividing cells that are in a localized area of living tissue, the dividing cells having polarizable or polar intracellular members, the skin patch including:

a skin patch body for placement on the living tissue over the localized area of dividing cells, the skin patch body comprising: a first insulated electrode having a first conductor and a first insulating layer disposed between the first conductor and the living tissue so as to insulate the first conductor from the living tissue; and a second insulated electrode having a second conductor and a second insulating layer disposed between the second conductor and the living tissue so as to insulate the second conductor from the living tissue; and

an electric field source for applying an alternating electric potential across the first and second conductors,

wherein the amplitude and frequency of the electric field source and the capacitance of the insulating layers are such that, when the skin patch body is placed against the living tissue and the alternating electric potential is applied across the first and second conductors, an electric field is induced in the living tissue, the induced electric field having characteristics such that (a) passage of the electric field through the dividing cells in late anaphase or telophase kills a significant portion of the dividing cells, and (b) passage of the electric field through non-dividing cells leaves the non-dividing cells substantially unharmed.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,136,699 B2
APPLICATION NO. : 10/263329
DATED : November 14, 2006
INVENTOR(S) : Yoram Palti

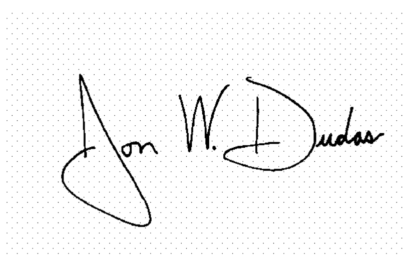
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 17
Line 25, change "&" to --a--.

Column 20
Line 17, change "an&" to --and--.
Line 19, change "arcl" to --are--.
Line 30, change "far" to --for--.

Signed and Sealed this

Twentieth Day of March, 2007



JON W. DUDAS
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

(68)	PATENT NO.	:	7,136,699
(45)	ISSUED	:	November 14, 2006
(75)	INVENTOR	:	Yoram Palti
(73)	PATENT OWNER	:	Novocure Limited
(95)	PRODUCT	:	NovoTFF-100A System

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. 7,136,699 based upon the regulatory review of the product NovoTFF-100A System by the Food and Drug Administration. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 689 days

from May 20, 2023, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156.

I have caused the seal of the United States Patent and Trademark Office to be affixed this 16th day of March 2016.

Michelle K. Lee
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office