Evolution of Using the Electric Field in Medical Applications

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ABSTRACT

Direct-current electric fields and exogenous alternating electric fields have long been examined for their biological effects, which vary from implications for embryonic development to influences on wound healing. The employ electric fields to cure tumors is the main topic of this essay. This article focuses on the clinical effects of tumor treating fields, a type of AEF, on the therapy of cancers including glioblastoma and mesothelioma. We give a summary of TT Fields' typical mode of action, which is their capacity to interfere with specifically dividing cells generate and segregate their mitotic spindles. Even if the operation of TT Fields can be largely explained by this common mechanism, it is by no means all-inclusive. The direct impact of exogenously applied AEFs on DNA as well as their Mainstream theory does not take into account the ability to alter the permeability and functionality of cancer cell membranes.. In order to give readers a more thorough understanding of how AEFs affect cell membranes, this review provides a summary of the most recent research. It provides a summary of three mechanical theories that possibly explain the more recent observations on the effects of AEFs made using the gated ion channel voltage, bio electrorheological, and electroporation model. There were inconsistencies between TTFields for all three proposed models' effective frequency range and field strength. Through theoretical investigations into how different electric fields affect cellular membranes depending on the presence or absence of a disease, the external microenvironment, and the structure of the tissue or cell, we resolved these differences. Finally, potential experimental approaches to confirm these results are described. Clinical advantages will eventually materialize.

Keywords: *voltage-gated ion channel, tumor treatment fields, glioblastoma, pulse electric fields (PEFs), bioelectrorheology, cell membrane, electroporation.*

INTRODUCTION

Biology has inspired a lot of research studies. A well-known example is the Luigi Galvani experiment, in which electricity generated by lightning or stationary electricity made frog legs twitch. [1,2]. Techniques for measuring the slope of biological tissue in physical parameters as voltage and current have improved, and researchers have discovered that exposure to electromagnetic fields can cause morphological changes in organisms, according to advances in tools for measuring drop of physical factors in biological molecular and picturing technology. A variety of Morphometric methods, including embryological enhancement and repairing a wound, can be triggered by events [2-4]. Electromotive force (EMF) exposure frequencies for biologically relevant exposure can scale with very low frequency close to (0-300 Hz) through medium values between (3x10 Hz-4x10^2 kHz) to elevate and very elevating frequencies (1x 10 ^{6} Hz to 10 10^9 Hz, as in Diagram 1 [2,5]).

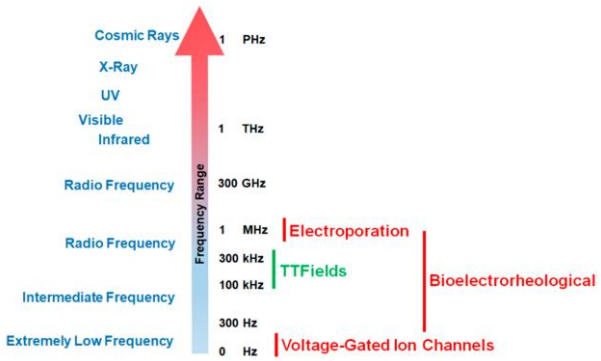

Diagram 1. Action operating frequencies of channel of Voltage-Gated calcium (VGCCs), Tumor-repairing fields, the bio electrorheological mode , and the electroporation mode along the electromagnetic spectrum. While Ca channels function at very low power, TTFields operates in the range of intermediate frequencies, as indicated in the figure. Contrarily, electroporation often works at microwave frequency bands whereas radio to middle frequency range of the bioelectrorheological model.

Various electromagnetic frequency scales provide various molecular consequences (Diagram 1). Reduce frequencies, such as those between 0 and 300 Hz, for point frequently cause membrane depolarization and subsequently excite the heart, muscles, nerves, and are various tissues [2]. A different fabric, for instance]. High power fields, which have a frequency of 120 MHz, are the other end of the spectrum. to cause the cells to undergo reversible elongation and rotatory motion as a result of stress brought on by illustration [6]. The method of electro process which involves using a microbiology technique called The frequency scale from 1 Hz - 1 MHz [7] is used for a broad variety of electrical pulses that quickly pores transmission pores.

Tumor fields are replacing electric fields of medium frequency ($1x10^2$–$4x10^2$ kHz). Cancer related treatment fields (TTFields) have been extensively researched for many years [8–10]. Glioblastoma, the most typical and deadly basic brain cancer in big [10,11], has been treated with these electric fields. based on phase's outcomes . This type of AEF therapy was noticed in a phase 2 clinical test to be superior in order to adjuvant temozolomide alone in extending the median total survival and individuals with newly diagnosed conditions had progression-free survival by 4.9 months and 2.7 months, respectively.

The electromagnetic spectrum's effective operating wavelength scales for voltage connected with calcium channels, tumor repairing the, and the electroporation mode. As seen calcium Channels function at more less frequencies, while TTFields is in the range of intermediate frequencies. The bioelectrorheological model roles between intermediate and radio frequencies, in contrast to electro proses . Different electromagnetic wave scale will result in various molecular tissue reactions (Diagram 1). Small power , including those between 0 and 300 Hz, have a tendency to stimulate all tissues [2].

On the other side of the wavelength , it was discovered that high power as 120 $x10^6$ Hz produce reversible rotation and elongation in the cells as a result of stress brought on by field aberrations [6]. Moving electric lines of medium frequency ($1x10^2$–$4x10^2$ kHz), also known as tumor repair area in relation to cancer have been thoroughly exanimated for a long time [8–10].

The all typical and deadly basic brain cancer in abigs, glioblastoma was treated using these electric fields [10, 11]. This type of treatment was noticed in the United State according to findings of a phase 2 clinical experiment that demonstrated the combination of 200 kHz TTFields.

It is noteworthy that in the gliobastoma patient arm receiving 200 KHz TT Fields, the rate of all survival throughout a 5-year period increased from 5% to 13% [12]. The first-line treatment of malignant pleural mesothelioma (MPM) that is unresectable, locally advanced, or metastatic when combined with pemetrexed and platinum-based chemotherapy was approved by the Food and Drug Administration in 2019 under its humanitarian set exemption [13].

Pemetrexed and cisplatin were tested in a 2003 phase 2 clinical experimental study against comparable historical controls of (12.1–5.7) months [14], The median overall survival in this first -arm phase 1 clinical investigation was 18.2 - 7.6 months, respectively [13].Notably, a phase III clinical research with open sings that was randomized, controlled, and conducted on MPM patients and published in 2016 showed a median total survival of 65 weeks in the original arm (pemetrexed). Thus, the repair of cancer by electric Fields is a novel, verified treatment that might serve as an alternative sample in anti-cancer therapies [16]).

The disruptive effect of TT Fields on bathtub dimers, which serve as the foundation for microtubules and contain inherent dipole moments., that together form the mitotic spindle, is one of the anti-tumor processes that is effective, but the mechanism is still not fully known [8]. In cells that are actively dividing, the mitotic spindle's normal function is compromised. [18] by applying exogenous TTFields, which prevent reproduction, to force microtubular filaments to align along electric field lines. [8,9,19]. (Diagram2A). As a result of these disturbances, tissue that is able to reject mitosis may experience apoptosis. [8,9,19], can also result in abnormal mitotic tissue death, abnormal chromosomal segregation, and abnormal mitotic cell death.

Numerous proof of concept studies have been conducted over the past ten years. and pertinent technological advancements [8,19], ultimately resulted in a commercial, clinical TT Fields device being approved by the FDA for the therapy of newly diagnosed and recurrent glioblastoma [11,12,19-23]. (biopsy, partial, or gross total), location (the United States vs. a country outside the United States)[12]. Notably, in the glioblastoma patient arm receiving 200 kHz TT Fields, sirvivulous intake increased from 5% to 13% throughout a 5-year period. [12]. The FDA most recently approved 150 kHz frequency in 2019 with regard to its humanitarian device exemption for the first-line therapy of locally advanced, incurable malignant pleural tumors when used in conjunction with pemetrexed and chemotherapy with a platinum basis [13].

Compared to analogous historical data from a 2003 phase 2 clinical trial investigating pemetrexed's compatibility [14], In this first arm phase 1 clinical test, the median OS and PFS were (18.2 - 7.6) months and respectively [13].Notably, a phase 2 clinical research with randomized controlled open-label design conducted on patients and published in 2016 noticed a 16.1-month median total survival in its original group [15]. So, the Fields method of treating cancer is a brand-new, proven method that could serve as a second spaceman in the fight against tumors (near surgery, radiation therapy, chemotherapy [16]).

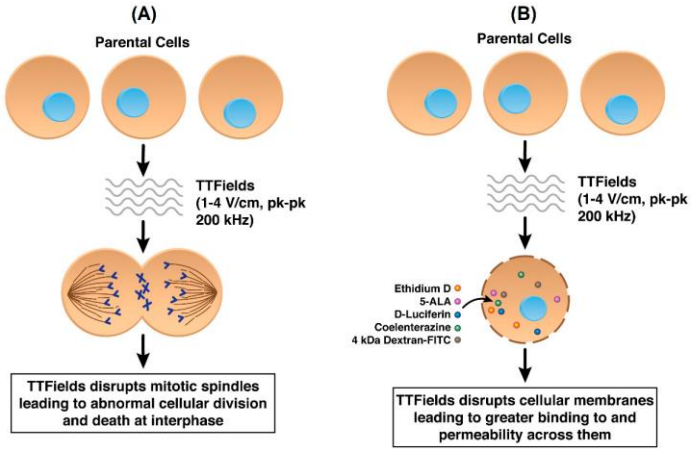

Diagram 2 (A) The typical mode of action of TTFields in tumor tissue involves how the formation of the mitotic spindle intersects. (B) TT Fields disrupt the plasma membranes of cancer cells, increasing their permeability.

But it is generally accepted that Generally speaking, non-static electric field therapy and specific treatment fields, exhibit an increased number of mechanisms. AEFs may also alter other structures in addition to microtubules. Protein synthesis that occurs during mitosis, such as that of septins [24,25].Studies have been conducted to determine how AEFs affect DNA replication. Causing autophagy and having an effect on the survival and operation of immune cells [5]. We have recently observed that irradiating TT Fields in connected with a novel anti-tumor Human glioma development was synergistically reduced by the drug withaferin A. cells [26]. We proposed that the reason for this synergistic impact is improved accessibility. Glioblastoma cells by transiently increasing the translocation of withaferin A membrane permeability of malignant cells (Figure 2B). scanning electron microscopy has demonstrated. (SEM), TT Fields cause cancer cell membranes to develop fenestrae by raising the

Size and quantity of post-exposure membrane holes that were noticed [27]. This final finding demonstrates that tumor tissues differ naturally from homologous cells in terms of their physical and chemical properties. This might provide some insight into why non-cancer cells react to AEFs differently.. In fact, it is known that tumor tissues have a resting membrane potential that is significantly more depolarized than non-tumor tissues [28–31].

Comparatively, tumor tissues are more malleable than Since non tumor tissues ' changed membrane makeup makes them susceptible to malignancy, According to reports, cells respond to fluid shear stress differently than other types of neoplastic cells [32–34]. Additionally, changes in membrane ion channel expression This demonstrates how ion channel alterations could be distributed, and function in cancer cells function as indicators for the development of tumors [35]. The features of tumor tissues can be affected by AEFs, as will be discussed in more detail in the next sections. Additionally, these traits have an impact on tumor therapy. It was discovered that these consequences only occurred in cancer cells and not in non-cancerous tissues [27].

It may be possible to identify improvements in the efficiency of grouping chemotherapy with repair fields by adding a form and possibly strongly attaching it.

The data and shape of fenestrae in tumor tissue membranes are improved by treatment by understanding the interactions between variables such as frequency, field intensity, and duration. .It is essential for us to create usable models in order to comprehend such optimization of the interactions between TT Fields and biological membranes, or between AEFs generally.

According to earlier simulation studies [36], zoom of the fixed symbol may occur near the immature partitions during cell division. In fact, biological and initial clinical tests have demonstrated that TT Fields affect mitosis in dividing cells [8,37]. On the other hand, we observe that considerable signal zooming at the wavelength of the

Treatment Fields could occur at the location of membrane pores or channels or in the regions in cellular gaps between Tissue collecting. As a result, the majority of this zoom occurs close to the cell membrane, where the majority of the anticipated typical effects of Treatment Fields will manifest.

We provide three models to clarify how cellular responses to intermediate frequency AEFs are affected. membrane permeability is affected by membranes (Diagram 3). First, EMF gradients imposed by AEFs may increase ionic and molecular permeability by physical forcing of channel to assume open case. This may have an impact on cellular membrane permeability. Second, according to the "bioelectrorheological model," shown in Diagram 3B, non-static electric power with a frequency range of 1 x10 3 to 1 x106 Hz can potentially subject membranes to cutting stress, leading to membrane deformation and power moving in permeability. Third, reversible electro processes and AEFs, in particular Treatment Fields, have a lot in common (Diagram 3C). The next sections provide a detailed definition of each model's features and an explanation of how elements from each model can be combined to provide a synthesis that explains how AEFs and TT Fields alter cell membranes in cancer.

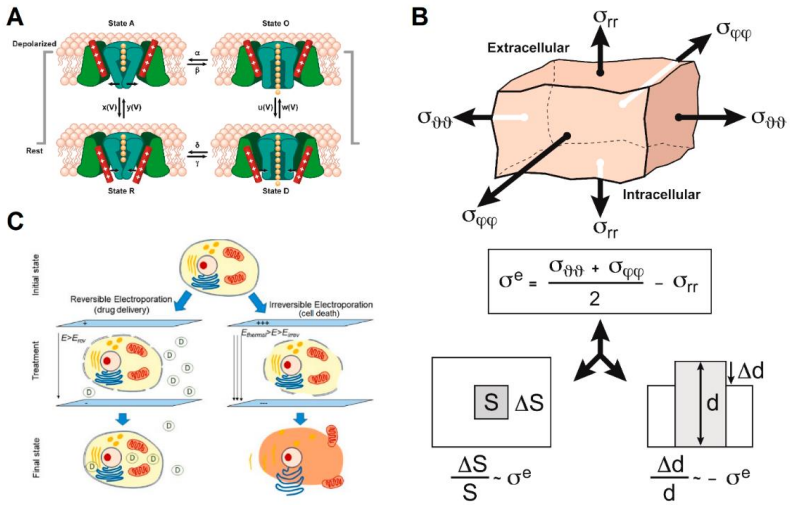

Diagram 3. Three theories that might explain how non-static electric fields influence the behavior and neutrality of cell membranes include: How AEFs impact ion channel physical potential (A). (B) mode (derived by [40]). The electro processing mode (C) (reprinted by reference [41]).

In the future, all artificially produced electric plus magnetic fields will collectively be referred to as "electromagnetic fields.". As a result, we are constantly exposed to electromagnetic spectrum with different wavelength configurations. For domestic electric and commercial power transmission and distribution, respectively, The typical sources include appliances with intermediate wavelengths for many different products, including phones, and energy frequencies with hertz high power and close to 1 GHz. Human organic material is somewhat conductible.

When an electric unit is provided directly to an organic object or when that object is exposed to an electric field that changes as the current travels through it. The body may become aroused or emit heat if the impact electric field or the associated current are also powerful. Rather than produced heat is primarily responsible for the detrimental health effects when a high frequency applied field is present.

Each bodily tissue in a human has a significantly different conductivity. Additionally, it is influenced by the applied field's frequency. Muscles' conductivity rises (and their permittivity falls) with power, usually near 0.2 resistant per meter for low frequencies between static current and power close to 0.8 resistant per meter for high power refer to gigahertz [42]. These magnitudes are considerably less than those of a sample , But despite this, a human's dominating electrical behavior is inverse resistivity for evidence in low-power locations because the resulting loss

is greater than 1.. Recently, one of the many fascinating areas of inquiry has emerged: the extent to which a human biological exposed to a non-ionizing field creates an electric potential or current.. Background concerns regarding electromagnetic fields' potential health impacts, as well as their usefulness in new study areas or medical treatments, are both present.

The former is frequently referred to as an "EMF issue." Numerous epidemiological investigations have been conducted on a broad scale to look for a connection between diseases and power-frequency electromagnetic fields, primarily magnetic fields. Recently, findings from comparable epidemiological studies including cell phones operating at frequencies about 1 GHz have been reported. The backdrop for the latter area of interest includes studies on how to modify tissue membranes with employing a pulsed elevate electric power, as well as medical therapies similar hyperthermia and accelerating the healing of fractured bones

However, their calculations are only of a technical character. We can calculate these values with the greatest accuracy feasible within a computer's capabilities. Because of the quick development numerical analysis of high-speed, high-capacity computers, the Recently, methods for calculating electric fields have achieved outstanding progress.

This has made it possible to quantitatively evaluate the distributions of the heat created by high-frequency electromagnetic waves furthermore to the high wavelength non-ionizing waves' generated electric plus and current. Several divisions on the order can now be calculated for these numbers. It should be noted, however, that due to the complex, minute features of the human body, accurate simulation is not possible.

The following subjects related to the impact of electricity with current on a human organic are briefly discussed in this article: Basic field calculation formulas (Effects of non-ionizing radiation, computations techniques, the test institute, and power study volunteers are only a few examples. The study directly corresponding to biological and medicinal methods., as was already indicated, but we do not cover these topics in this review. At a conference titled Evaluation of Electric Field and Current in a Human Body Induced by Electromagnetic Fields.

FUNDAMENTAL CALCULATION FORMULAS MAXWELL'S EQUATIONS

all electromagnetic field phenomena should be considered. The ensuing phases, however, are drastically varied depending on the field's power, which is typically. This phenomenon known as "electromagnetic waves" seldom appears when electric and magnetic fields coexist in a specific ratio as they move across space at a high frequency, where we may evaluate electric or magnetic fields separately. The essential formulas or equations used for the

$$E = -dB/dt \quad \text{..... [1]}$$

$$H = J + dD/dt \quad \text{.....[2]}$$

An electric field may be produced inside the human body when the frequency is reduced by either an external magnetic field or a source of external voltage that changes over time. When a given current distribution is known, equation two can be used to compute the magnetic field if the external magnetic potential is present. Equation one's integral form is

$$\int E.\, dl = -\, d/dt \int_s B.\, ds \quad \text{.....[3]}$$

According to equation three , an electric field is typically created in a single loop when a magnetic field induces conduction (also known as "electromagnetic induction"). In the event that an electric wave is used to irradiate a metal, an eddy current occurs, which primarily flows on the surface. The human body is in a similar problems .

however, is only caused if the magnetic wave does not exist or if it does not change over time and is replaced by an external voltage.. The following equation describes this induction, which is known as "electrostatic induction":

$$rot\ \boldsymbol{E} = 0 \quad (4)$$

Equation (4) is a representation of the crucial equation known as Laplace's equation., which expresses electrostatic waves , by equivalently stating that the electric wave is provided by an unbounded potential based on the experimental resistance, the created electric field subsequently generates the current density shown below as:

$$\boldsymbol{J} = \sigma \boldsymbol{E} \quad (5).$$

A very crude example of a low frequency is a closed sphere with a harmonic resistivity that persists under a steady magnetic field. In relation to the induced current density J, the fundamental parameters are expressed as

$$J = j\pi\sigma f\, rB. \quad (6)$$

where r is the displacement from the sphere's mid and f is frequency. The induced current is so little when calculating induction inside a human body that its secondly impact on the (original field can be disregarded. Since a person's body has the same permeability . the initial magnetic field is not distorted or disturbed by their presence. These characteristics allow us to estimate the non-ionizing radiation influence on the vicinity of the human body. Contrarily, the impact of the existence of a human form on non-ionizing radiation results in a significant modification of the initial wave, necessitating the inclusion of additional information in the computation.

Equations (1) and (2) result in a repeated relationship where a changing electric field generates a new magnetic field, and the cycle continues in an angularly rising frequency potential with no initial current. The field then changes into a non-ionizing radiation and travels over space at the velocity of an optical wave.. The sole coordinate shared by both the electric and magnetic waves is parallel to the direction of transmission. feature resistance, which in vacuum is approximately 120 (= 377), is the ratio of these magnitudes. But it should be noted that this straightforward relationship only applies to electromagnetic waves that are far away the source .

When using high frequency, Identifying the heating magnitude caused by Joule's heating in a bodily component is the major objective of the computation The amount of electric wave that the tissue has absorbed is shown by this value.. The term "SAR" (Specific Absorption Rate) refers to the amount of electricity absorbed per unit mass and is written as:

$$SAR = \sigma E2/\rho \quad (7)$$

Where the electric wave in the appropriate molecular is represented with symbol E and the density 3. The Impact of Magnetic Fields Extremely high frequency electromagnetic waves, such UV, X, and rays, can directly ionize or modify the chemical composition of irradiated materials. This is because the wavelength , when viewed as a single particle, has a high energy. The correlation between the frequency and this potential The frequency of these ionizing waves is 3 10^6 GHz and a wavelength smaller than 100 nanometers in order to be able to ignore the effect at gigahertz-level frequencies.

The possible consequences of an electric wave rather than current formed in a person's tissue are broadly categorized as excitation and heating based on the frequency, as was established in part one. The border is thought to be located at roughly 100 x10^3Hz. Below this frequency, excitation appears to be more significant, but heating is more crucial above this potential . It is well known that a variety of electrical waves, as opposed to controlling biological activities within the persons organic, The permitted crucial induced impact are largely contrasted with reference to these internal (endogenous) occurrences. The bulk of standards and suggestions mentioned thus far used current density as their limit magnitude.

In 1998, the International Commission on Non-Ionizing Radiation Protection issued the guidelines [44] . According to them, the fundamental limit of current density in proximity to the back of the body at frequencies between 4 Hz and 1 kHz is 0.01 Amperes. This percentage is one out of five lower for the general public. These figures were estimated using data from numerous cell- and animal-based investigations.

On the other hand, the IEEE Standards for reduce frequency location less than 3×10^3 Hz, which were published in 2002 .Based on the hypothesis that the impact of an electromagnetic wave on another person's body, rather than flowing current, is the primary cause of electrical excitation [45],

As previously mentioned in the preceding sections, the major effect of high frequency is thought to be heating. The electromagnetic energy that is taken in by human tissue is what heats things up. Measure of the thermal impact caused by the absorption of high-frequency electromagnetic power.

ANALYTICAL TECHNIQUES

In traditional texts on electricity and magnetism, numerous analytical techniques are described. They are only relevant to a small number of such straight forward configurations and circumstances, like for a dipole source. The "strictly accurate ones" that are free of setup faults and are used to confirm the accuracy of the results for the setup are significant examples of these solved problems. as well as to investigate how the pertinent components have an effect. It should be noticed , however, that more analytic solves are produced, necessitating the use of computers, inevitably mixed up with some degree of Setup mistakes.

MEMBERS

One noteworthy aspect of the Committee is that it is made up of knowledgeable experts who work in every frequency range of cellular phones, from low (power) to high frequency. The chairperson, secretaries, and assistant secretary positions were filled by the authors of this paper. 23 people made up the overall number of members, excluding a few participants who were not members. Survey on the current state of research, paragraph 5.3 The group's initial task was to review and talk about the individual members' research projects.

SURVEY ON THE STATE OF RESEARCH AT THE MOMENT

Surveying and debating the individual members' research was the first phase of the activity. Induction from overhead power lines, electrical equipment, mobile phones, high-frequency near-field, lightning stroke current, hyperthermia, and IH (induction heating) appliances are just a few of the examples given in a questionnaire survey of the Committee members that received 18 responses. FEM 4, FDTD 7, Impedance Method 2, and approximately 14 other calculation techniques were among the 14 calculation experiences that were used. 14 of the software products used in these techniques were original creations of each member's organization, and 5 were commercial products.

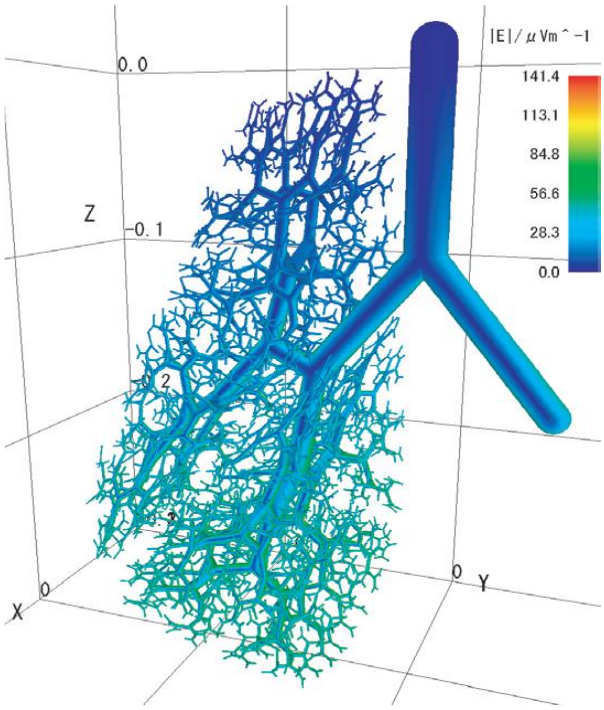

Diagram 4: A lung model for the quick multipole surface charge technique with roughly 2000 terminals [6]

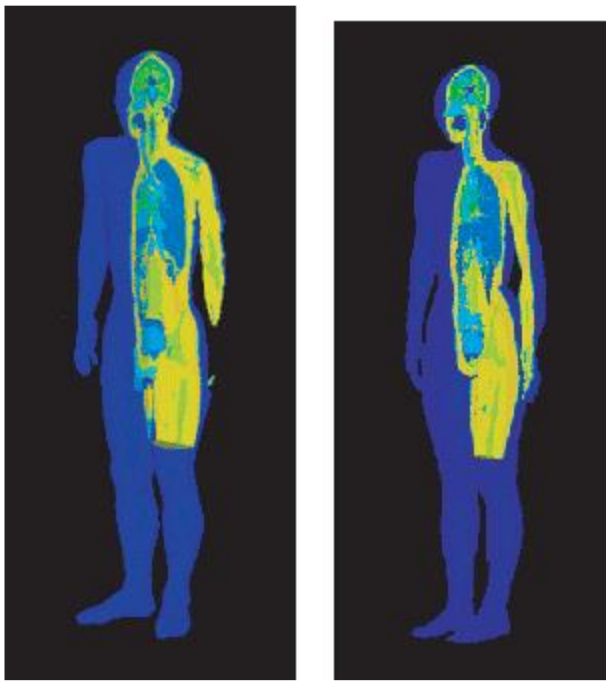

Diagram 4: Demonstrates the "TARO" adult male and "HANAKO" adult female in NICT people styles.

FRESH AREAS FOR STUDY

Recently, the term "electroporation" has gained popularity as a new area of study [46]. This effect happens when a cell membrane receives additional potential energy. More specifically, the inverse resistivity is produced when power is applied for at least a brief period of time at a rate greater than 300 micro Amperes.

It is claimed that in addition to the Joules-heating effect, which has been traditionally regarded to be dominant, electroporation also plays a significant role in the cases of electric shocks.

High potential are used in experimental studies to produce electroporation, which results in a variety of novel and fascinating events at the cellular level. Even the relationship between electromagnetic fields' impacts on human health and human evolution is discussed in a publication as a result [47].

The latter is hypothesized to be caused by an effect like lightning strikes in nature. Since electroporation is essentially an electromagnetic event, a thorough computation is crucial at the cellular level. Additionally, we would like to emphasize the need of collaboration among experts in diverse domains of engineering, biology, physiology, and medicine for the study of electroporation.

DISCUSSION

In an effort to maximize treatment effectiveness without increasing toxicity, current cancer treatment procedures frequently integrate Versatile therapeutic techniques, such as resection, radiation, and chemotherapy. Despite this approach, people with glioblastoma have this excruciating tumor, and the frequent side effects of treatment have a significant impact on peoples' quality of life. Preclinical investigations, aircraft studies, a new Phase 2, and a planned scattered clinical study all support the utility of electric wave therapy in recurrent glioblastoma when compared to various chemotherapy regimens.

Despite early it will happen findings, there are still few clinical research investigating the effectiveness of AEFs. In contrast, numerous years of clinical studies have supported the efficacy of the current radiation and chemotherapy regimens. However, AEF therapy is a whole new approach to the management of brain malignancies. By adjusting elements like as intensity and energy, ideal electric wave therapy has the potential to provide individualized care in the future and improve clinical outcomes. The outcomes of patients with malignancies who currently have poor prognoses are predicted to improve as the region of neurooncology advances. Thanks to substantial improvements in currently available medications rather than the development of fresh techniques Although electric wave therapy is not expected to be a cure-all for brain tumors, it does have the potential to be incorporated into multimodal neurooncology therapies in the close to future. These repairs were expected to improve patients' quality of life while decreasing adverse effects from existing treatment alternatives and increasing the number of patients who would still be alive.

CONCLUSION

Early on (days 2-4) and 1-1.5 months following BC surgery, two medical rehabilitation programs reduced discomfort and postoperative edema and enhanced shoulder joint movement. reducing severe lymphostasis and raising standard of living.

The requirement that general magnetic treatment procedures be covered in rehabilitation courses in addition to physical therapy, exposure to an alternating low-frequency electrostatic field It was revealed that there were exercises, balancing treatment, and private classes with a medical psychologist. In general Overall, a significant and lasting therapeutic impact was obtained in comparison to the patient group. who received physiotherapeutic placebo treatments, highlighting the wisdom of individuals with breast cancer who are in the rehabilitation stages are exposed to physical forces.

REFERENCES

[1] Bresadola, M. Medicine and science in the life of Luigi Galvani (1737–1798). Brain Res. Bull. 1998, 46, 367–380.
[2] Funk, R.H.; Monsees, T.; Özkucur, N. Electromagnetic effects—From cell biology to medicine. Prog. Histochem. Cytochem. 2009, 43, 177–264.
[3] Levin, M. Bioelectromagnetic in morphogenesis. Bioelectromagnetic 2003, 24, 295–315.

[4] McCaig, C.D.; Zhao, M. Physiological electrical fields modify cell behaviour. BioEssays 1997, 19, 819–826.

[5] Karanam, N.K.; Story, M.D. An overview of potential novel mechanisms of action underlying Tumor Treating Fields-induced cancer cell death and their clinical implications. Int. J. Radiat. Biol. 2020, 1–11.

[6] Fueredi, A.A.; Ohad, I. Effects of high-frequency electric fields on the living cell. I. Behaviour of human erythrocytes in high- frequency electric fields and its relation to their age. Biochim. Biophys. Acta 1964, 79, 1–8.

[7] Novickij, V.; Ruzgys, P.; Grainys, A.; Šatkauskas, S. High frequency electroporation efficiency is under control of membrane capacitive charging and voltage potential relaxation. Bioelectrochemistry 2018, 119, 92–97.

[8] Giladi, M.; Schneiderman, R.S.; Voloshin, T.; Porat, Y.; Munster, M.; Blat, R.; Sherbo, S.; Bomzon, Z.; Urman, N.; Itzhaki, A.; et al. Mitotic Spindle Disruption by Alternating Electric Fields Leads to Improper Chromosome Segregation and Mitotic Catastrophe in Cancer Cells. Sci. Rep. 2016, 5, 18046.

[9] Kirson, E.D.; Gurvich, Z.; Schneiderman, R.; Dekel, E.; Itzhaki, A.; Wasserman, Y.; Schatzberger, R.; Palti, Y. Disruption of Cancer Cell Replication by Alternating Electric Fields. Cancer Res. 2004, 64, 3288–3295.

[10] Kirson, E.D.; Schneiderman, R.S.; Dbalý, V.; Tovaryš, F.; Vymazal, J.; Itzhaki, A.; Mordechovich, D.; Gurvich, Z.; Shmueli, E.; Goldsher, D.; et al. Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields). BMC Med. Phys. 2009, 9, 1–13.

[11] Stupp, R.; Taillibert, S.; Kanner, A.A.; Kesari, S.; Steinberg, D.M.; Toms, S.A.; Taylor, L.P.; Lieberman, F.; Silvani, A.; Fink, K.L.; et al. Maintenance Therapy with Tumor-Treating Fields Plus Temozolomide vs. Temozolomide Alone for Glioblastoma. JAMA 2015, 314, 2535–2543.

[12] Stupp, R.; Taillibert, S.; Kanner, A.; Read, W.; Steinberg, D.M.; Lhermitte, B.; Toms, S.; Idbaih, A.; Ahluwalia, M.S.; Fink, K.; et al. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs. Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma. JAMA 2017, 318, 2306–2316.

[13] Ceresoli, G.L.; Aerts, J.G.; Dziadziuszko, R.; Ramlau, R.; Cedres, S.; van Meerbeeck, J.P.; Mencoboni, M.; Planchard, D.; Chella, A.; Crinò, L.; et al. Tumour Treating Fields in combination with pemetrexed and cisplatin or carboplatin as first-line treatment for unresectable malignant pleural mesothelioma (STELLAR): A multicentre, single-arm phase 2 trial. Lancet Oncol. 2019, 20, 1702–1709.

[14] Vogelzang, N.J.; Rusthoven, J.J.; Symanowski, J.; Denham, C.; Kaukel, E.; Ruffie, P.; Gatzemeier, U.; Boyer, M.; Emri, S.; Manegold, C.; et al. Phase III Study of Pemetrexed in Combination With Cisplatin Versus Cisplatin Alone in Patients With Malignant Pleural Mesothelioma. J. Clin. Oncol. 2003, 21, 2636–2644.

[15] Zalcman, G.; Mazieres, J.; Margery, J.; Greillier, L.; Audigier-Valette, C.; Moro-Sibilot, D.; Molinier, O.; Corre, R.; Monnet, I.; Gounant, V.; et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): A randomised, controlled, open-label, phase 3 trial. Lancet 2016, 387, 1405–1414.

[16] Hottinger, A.F.; Stupp, R.; Homicsko, K. Standards of care and novel approaches in the management of glioblastoma multiforme. Chin. J. Cancer 2014, 33, 32–39.

[17] Davies, A.M.; Weinberg, U.; Palti, Y. Tumor treating fields: A new frontier in cancer therapy. Ann. N. Y. Acad. Sci. 2013, 1291, 86–95.

[18] Hottinger, A.F.; Pacheco, P.; Stupp, R. Tumor treating fields: A novel treatment modality and its use in brain tumors. Neuro Oncol. 2016, 18, 1338–1349.

[19] Tuszynski, J.A.; Wenger, C.; Friesen, D.E.; Preto, J. An Overview of Sub-Cellular Mechanisms Involved in the Action of TTFields. Int. J. Environ. Res. Public Heal. 2016, 13, 1128.

[20] Chaudhry, A.; Benson, L.; Varshaver, M.; Farber, O.;Weinberg, U.; Kirson, E.D.; Palti, Y. NovoTTF™-100A System (Tumor Treating Fields) transducer array layout planning for glioblastoma: A NovoTAL™ system user study. World J. Surg. Oncol. 2015, 13, 1–7.

[21] Stupp, R.; Wong, E.T.; Kanner, A.A.; Steinberg, D.; Engelhard, H.; Heidecke, V.; Kirson, E.D.; Taillibert, S.; Liebermann, F.; Dbalý, V.; et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent

glioblastoma: A randomised phase III trial of a novel treatment modality. Eur. J. Cancer 2012, 48, 2192–2202.

[22] Mrugala, M.M.; Engelhard, H.H.; Tran, D.D.; Kew, Y.; Cavaliere, R.; Villano, J.L.; Bota, D.A.; Rudnick, J.; Sumrall, A.L.; Zhu, J.-J.; et al. Clinical Practice Experience With NovoTTF-100A™ System for Glioblastoma: The Patient Registry Dataset (PRiDe). Semin. Oncol. 2014, 41, S4–S13.

[23] Gallego, O. Nonsurgical Treatment of Recurrent Glioblastoma. Curr. Oncol. 2015, 22, 273–281.

[24] Wong, E.T.; Lok, E.; Swanson, K.D. Alternating Electric Fields Therapy for Malignant Gliomas: From Bench Observation to Clinical Reality. Prog. Neurol. Surg. 2018, 32, 180–195.

[25] Gera, N.; Yang, A.; Holtzman, T.S.; Lee, S.X.; Wong, E.T.; Swanson, K.D. Tumor Treating Fields Perturb the Localization of Septins and Cause Aberrant Mitotic Exit. PLoS ONE 2015, 10, e0125269.

[26] Chang, E.; Pohling, C.; Beygui, N.; Patel, C.B.; Rosenberg, J.; Ha, D.H.; Gambhir, S.S. Synergistic inhibition of glioma cell proliferation by Withaferin A and tumor treating fields. J. Neuro Oncol. 2017, 134, 259–268.

[27] Chang, E.; Patel, C.B.; Pohling, C.; Young, C.; Song, J.; Flores, T.A.; Zeng, Y.; Joubert, L.-M.; Arami, H.; Natarajan, A.; et al. Tumor treating fields increases membrane permeability in glioblastoma cells. Cell Death Discov. 2018, 4, 1–13.

[28] Lobikin, M.; Chernet, B.; Lobo, D.; Levin, M. Resting potential, oncogene-induced tumorigenesis, and metastasis: The bioelectric basis of cancer in vivo. Phys. Biol. 2012, 9, 065002.

[29] Marino, A.A.; Iliev, I.G.; Schwalke, M.A.; González, E.; Marler, K.C.; Flanagan, C.A. Association between Cell Membrane Potential and Breast Cancer. Tumor Biol. 1994, 15, 82–89.

[30] Tokuoka, S.; Morioka, H. The membrane potential of the human cancer and related cells. I. Gan 1957, 48, 353–354.

[31] Yang, M.; Brackenbury, W.J. Membrane potential and cancer progression. Front. Physiol. 2013, 4, 185.

[32] Barnes, J.M.; Nauseef, J.T.; Henry, M.D. Resistance to Fluid Shear Stress Is a Conserved Biophysical Property of Malignant Cells. PLoS ONE 2012, 7, e50973.

[33] Huang, Q.; Hu, X.; He, W.; Zhao, Y.; Hao, S.; Wu, Q.; Li, S.; Zhang, S.; Shi, M. Fluid shear stress and tumor metastasis. Am. J. Cancer Res. 2018, 8, 763–777.

[34] Sok, M.; Šentjurc, M.; Schara, M.; Stare, J.; Rott, T. Cell membrane fluidity and prognosis of lung cancer. Ann. Thorac. Surg. 2002, 73, 1567–1571.

[35] Lastraioli, E.; Iorio, J.; Arcangeli, A. Ion channel expression as promising cancer biomarker. Biochim. Biophys. Acta (BBA) Biomembr. 2015, 1848, 2685–2702.

[36] Wenger, C.; Giladi, M.; Bomzon, Z.; Salvador, R.; Basser, P.J.; Miranda, P.C. Modeling Tumor Treating Fields (TTFields) application in single cells during metaphase and telophase. In Proceedings of the 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), Milan, Italy, 25–29 August 2015; Institute of Electrical and Electronics Engineers (IEEE): Piscataway, NJ, USA, 2015; Volume 2015, pp. 6892–6895.

[37] Wong, E.T.; Lok, E.; Swanson, K.D. An Evidence-Based Review of Alternating Electric Fields Therapy for Malignant Gliomas. Curr. Treat. Options Oncol. 2015, 16, 40.

[38] Hering, S.; Beyl, S.; Stary, A.; Kudrnac, M.; Hohaus, A.; Guy, R.H.; Timin, E.; Beyl, S.; Guy, H.R. Pore stability and gating in voltage-activated calcium channels. Channels 2008, 2, 61–69.

[39] Hering, S.; Zangerl-Plessl, E.-M.; Beyl, S.; Hohaus, A.; Andranovits, S.; Timin, E.N. Calcium channel gating. Pflüger Arch. Für Die Gesammte Physiol. Des Menschen Tiere 2018, 470, 1291–1309.

[40] Pawłowski, P.; Fikus, M. Bioelectrorheological model of the cell. Analysis of the extensil deformation of cellular membrane in alternating electric field. Biophys. J. 1993, 65, 535–540.

[41] López-Alonso, B.; Hernáez, A.; Sarnago, H.; Naval, A.; Güemes, A.; Junquera, C.; Burdío, J.M.; Castiella, T.; Monleón, E.; Gracia-Llanes, J.; et al. Histopathological and Ultrastructural Changes after Electroporation in Pig Liver Using Parallel-Plate Electrodes and High-Performance Generator. Sci. Rep. 2019, 9, 2647.

[42] Tenforde TS, Kaune WT. Interaction of extremely low frequency electric and magnetic fields with humans. Health Physics 1987; 53(6):585–606.

[43] Takuma T, et al. at a symposium entitled. Evaluation of electric field and current in a human body induced by electromagnetic fields. 1-S6-1 ~ 1-S6-8 (in Japanese), Annual Meeting of the IEEJ, at Tokushima (2005-3).

[44] ICNIRP. Guidelines for limiting exposure to time-varying electric, magnetic, and electromagnetic fields (up to 300 GHz). Health Physics 1998; 74(4):494–522.

[45] IEEE C 95.6–2002. Standards for safety levels with respect to human exposure to electromagnetic fields, 0 to 3 kHz, 2002.

[46] Joshi RP, Schoenbach KH. Electroporation dynamics in biological cells subjected to ultrafast electrical pulses: A numerical simulation study. Physical Review E 2000; 62:1025–1033.

[47] Weaver JC. Electroporation of biological membranes from multicellular to nano scales. IEEE Transactions on Dielectrics and Electrical Insulation 2003; 10(5):754–768.