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Geon Oh,[1,2] Yunhui Jo,[3] Yongha Gi,[1] Jinyoung Hong,[1] Jonghyun Kim,[4] Boram Lee,[2] and Myonggeun Yoon[1,4,a)]

AFFILIATIONS

[1] Department of Bioengineering, Korea University, Seoul, Republic of Korea
[2] Department of Radiation Oncology, Inha University School of Medicine, Incheon, Republic of Korea
[3] Institute of Global Health Technology (IGHT), Korea University, Seoul, Republic of Korea
[4] FieldCure Ltd., Seoul, Republic of Korea

[a)] **Author to whom correspondence should be addressed:** radioyoon@korea.ac.kr. **Present address:** Department of Bio-medical Engineering, Korea University 145 Anam-ro, Seongbuk-gu, Seoul 02841, Republic of Korea. **Telephone**: +82-2-3290-5651. **Fax:** +82-2-940-2829

ABSTRACT

This study was designed to investigate the correlation between the impulse by dielectrophoretic force applied inside a dividing cell during alternating electric fields therapy and the inhibition of cell proliferation. Distributions of the electric field and dielectrophoretic force inside a dividing cell were calculated using the finite element method of COMSOL Multiphysics. Based on the results, the average magnitude of the impulse by the dielectrophoretic force applied to the cleavage furrow inside a dividing cell placed in various directions was calculated as a function of electric field intensity at an extracellular reference point. The simulation results showed that the average magnitude of the impulse to the cleavage furrow inside a dividing cell ranged from 1.51×10^{-9} to 1.49×10^{-7} N s when tumor treating fields with an intensity ranging from 0.1 to 1 V/cm is applied at an extracellular reference point for 6 h. To verify the relationships between the impulse by the dielectrophoretic force and the inhibition of cell proliferation, the survival fractions of the four cancer cell lines were determined as a function of intensity and time duration of the electric field. The correlation between the magnitude and application time of the electric field and the survival fractions of the four cell lines showed similar trends *in vitro*. These results suggest that both the dielectrophoretic force and the time required for the force to act are proportionally related to the inhibitory effect on dividing cells, enabling this impulse to be used as a reference to quantify the inhibition of cell proliferation.

I. INTRODUCTION

Tumor treating fields (TTFs) are alternating electric fields with low electric field magnitude (<2.5 V/cm) and a specific frequency band (100–300 kHz) that inhibit the proliferation of tumor cells. The effectiveness of TTFs has been demonstrated in preclinical *in vitro* and *in vivo* experiments, as well as in clinical trials.[1–3] TTFs in cancer treatment were found to have fewer side effects than other types of cancer treatments, with TTFs reported to synergize with radiation therapy, chemotherapy, and immunotherapy, methods frequently used to treat cancers in clinical practice.[4–9] These findings have suggested that TTFs may become a new technology for cancer treatment.[10,11]

TTFs are thought to inhibit the division of tumor cells mainly through dielectrophoresis induced by an inhomogeneous alternating electric field, which causes a defect in cytokinesis.[12–14] In dielectrophoresis, non-polarized particles are subjected to dielectrophoretic (DEP) forces when exposed to a non-uniform alternating electric field, with these DEP forces depending on the voltage and frequency of the electric field, as well as the permittivity and conductivity of the medium.[15] Dividing cancer cells give rise to daughter cells separated by a narrow furrow, and application

of an uneven alternating electric field can result in a relatively high electric field gradient in this furrow, resulting in a greater DEP force.[16]

A recent clinical study of TTFs therapy in 340 patients with brain tumors showed that prognosis was significantly better in patients with a power loss density (a parameter associated with the magnitude of an applied electric field) above than 0.77 mW/cm^3 in the tumor.[17] In addition, prognosis was significantly better in patients with compliance (a parameter associated with the application time of an electric field) above than 75%.[17] These results indicated that the ability of TTFs to inhibit cell proliferation is proportional not only to the magnitude of the electric field, which is proportional to the DEP force, but also to the time of application of the electric field. Moreover, recent *in vivo* and *in vitro* studies have shown similar trends, with the ability of TTFs to inhibit cell proliferation being a function of both applied field magnitude and time.[18–20] These findings suggest that a reference value for quantifying the inhibitory effect of TTFs therapy on cell division should include parameters associated with the magnitude of the applied electric field, an indicator of DEP force, and the duration of electric field application, an indicator of the time required for the DEP force to act on dividing cells.

In physics, the magnitude of change in momentum transferred to an object following application of an external force was found to be determined by the product of the external force and the duration of its application, defined as the impulse.[21] In the context of dividing cells as the objects receiving the external force, and the force acting on them (i.e., the impulsive force) being the DEP force, the magnitude of the impulse received by the dividing cells can be defined as the product of the DEP force and the time duration of treatment.

In the present study, simulations were used to calculate the magnitudes of the impulse by the DEP force applied to the cleavage furrow inside a dividing cell for various frequencies of electric fields and cell orientations. In addition, to verify the connection between the results in the simulation and the results when an actual alternating electric field is applied to cancer cells, TTFs were applied to several cancer cell lines under various conditions *in vitro*, and the correlations between the impulse by dielectrophoretic force applied inside a dividing cell and the inhibitory effect on dividing cells were analyzed.

II. METHODS AND MATERIALS

A. Cellular level simulation of TTFs

1. Cellular level computational modeling of TTFs

Based on a finite element mesh, the distribution of electric fields was calculated using COMSOL Multiphysics software (www.comsol.com).[22] In all calculations, the relative permittivity of both the cytoplasm and medium was set at 80, the relative permittivity of the membrane was 9.8, the cell diameter was 10 μm, the membrane thickness was 5 nm, and the conductivities of the membrane, cytoplasm, and media were 5.0 × 10^{-6}, 0.6, and 1.3 s/m, respectively (Table I).[13,23–25] Because the electrical quasi-static approximation of Maxwell's equations could be applied to TTFs, solving Laplace's equations yielded the electric potential V,[26]

TABLE I. Simulation conditions.

Parameter	Value
Radius of particle	1.0 μm
Membrane thickness	5.0 nm
Relative permittivity of the membrane	9.8
Conductivity of the membrane	5.0 ×10^{-6} s/m
Relative permittivity of the cytoplasm	80
Conductivity of the cytoplasm	0.6 s/m
Relative permittivity of the media	80
Conductivity of the media	1.3 s/m

$$\vec{J} = \sigma\vec{E} + j\omega\vec{D}, \tag{1}$$

$$\vec{D} = \varepsilon\vec{E}, \tag{2}$$

$$\vec{J} = \sigma\vec{E} + j\omega\varepsilon\vec{E}, \tag{3}$$

$$\vec{E} = -\nabla V, \tag{4}$$

where $\vec{J}$ is the current density (A/m^2), σ is the electrical conductivity (s/m), $\vec{E}$ is the electric field (V/m), j is the imaginary unit, ω is the angular frequency, $\vec{D}$ is the electric displacement field (C/m^2), ε is the permittivity, and V is the electric potential (V). Equation (1) describes the total current density ($\vec{J}$) as the sum of the displacement current density ($j\omega\vec{D}$) and the electric field ($\vec{E}$) multiplied by the electrical conductivity (σ). Equation (2) shows that the electric displacement field is equal to the electric field ($\vec{E}$) multiplied by the permittivity (ε). Substituting Eq. (2) into $\vec{D}$ in Eq. (1) yields Eq. (3). Equation (4) shows that the electric field magnitude is equal to the negative gradient of the electric potential (V).[27]

2. Impulse by dielectrophoretic force of TTFs

The DEP force exerted by the inhomogeneous distribution of an electric field in a cell is calculated based on the interaction between the dipole and the inhomogeneous electric field. The force applied inside a microscopic polarizable particle could be calculated using the following equation:[12]

$$\langle\vec{F}\rangle = 2\pi r^3\varepsilon_m R_e[K(\omega)]\vec{\nabla}E_{rms}{}^2, \tag{5}$$

where $\langle\vec{F}\rangle$ is the expectation value of the dielectrophoretic force vector, $\vec{\nabla}$ is the divergence of the variable, r is the radius of the particle to which the force is applied, E_{rms} is the root mean square value of the electric field, ε_m is the dielectric constant of the cytoplasm of that cell, and $R_e[K(\omega)]$ is the real component of the Clausius–Mossotti factor.[28,29]

The impulse applied by the DEP force inside a microscopic cell for the time duration of TTFs could be calculated using the following equation:

$$\langle\text{Impulse}\rangle = \langle\vec{F}\rangle\Delta t, \tag{6}$$

TABLE II. Characteristics of the cell lines used in this study.

Cell line	Organism	Tissue	Disease
U373	*Homo sapiens*, human	Brain	Glioblastoma
B16F10	*Mus musculus*, mouse	Skin	Melanoma
AGS	*Homo sapiens, human*	Stomach	Gastric carcinoma
HPAF-II	*Homo sapiens*, human	Pancreas	Ductal adenocarcinoma

where ⟨Impulse⟩ and $\langle \vec{F} \rangle$ are the expectation value of the impulse and the dielectrophoresis force vector, respectively, and Δt is the time duration of TTFs.

B. *In vitro* experiments with TTFs

1. Experimental setup for TTFs

Alternating electric fields (AC-EFs) with an intensity of 0.6–1.2 V/cm and a frequency of 150 kHz were generated between a pair of insulated electrodes connected to a function generator (AFG-2112, Good Will Instrument Co. Ltd., New Taipei City, Taiwan) and a high-voltage amplifier (A303, A. A. Lab Systems Ltd., Ramat Gan, Israel). The magnitude of actual voltages ranged from 150 to 350 V_{pp} corresponding to intensities of 0.6, 0.9, and 1.2 V/cm in cell culture media. To ensure that the cells were under the influence of AC electric fields, a pair of insulated electrodes was attached to the bottom of each culture dish. The magnitude of the electric field in each experiment was adjusted according to the treatment condition. To confirm that the conditions of the AC-EFs were adequately applied, voltage and frequency were measured with an oscilloscope (GDS-2102A, Good Will Instrument Co. Ltd.) before, during, and after each experiment. The temperature was monitored using a thermometer (TES-1300, TES Electrical Electronic Corp.) every time the AC-EFs were applied; no significant increases in temperature due to the electric fields were observed [Fig. 4(a)].

2. Cell culture

The effects of TTFs on four cancer cell lines, AGS, HPAF-II, U373, and B16F10, were evaluated (Table II). The AGS and

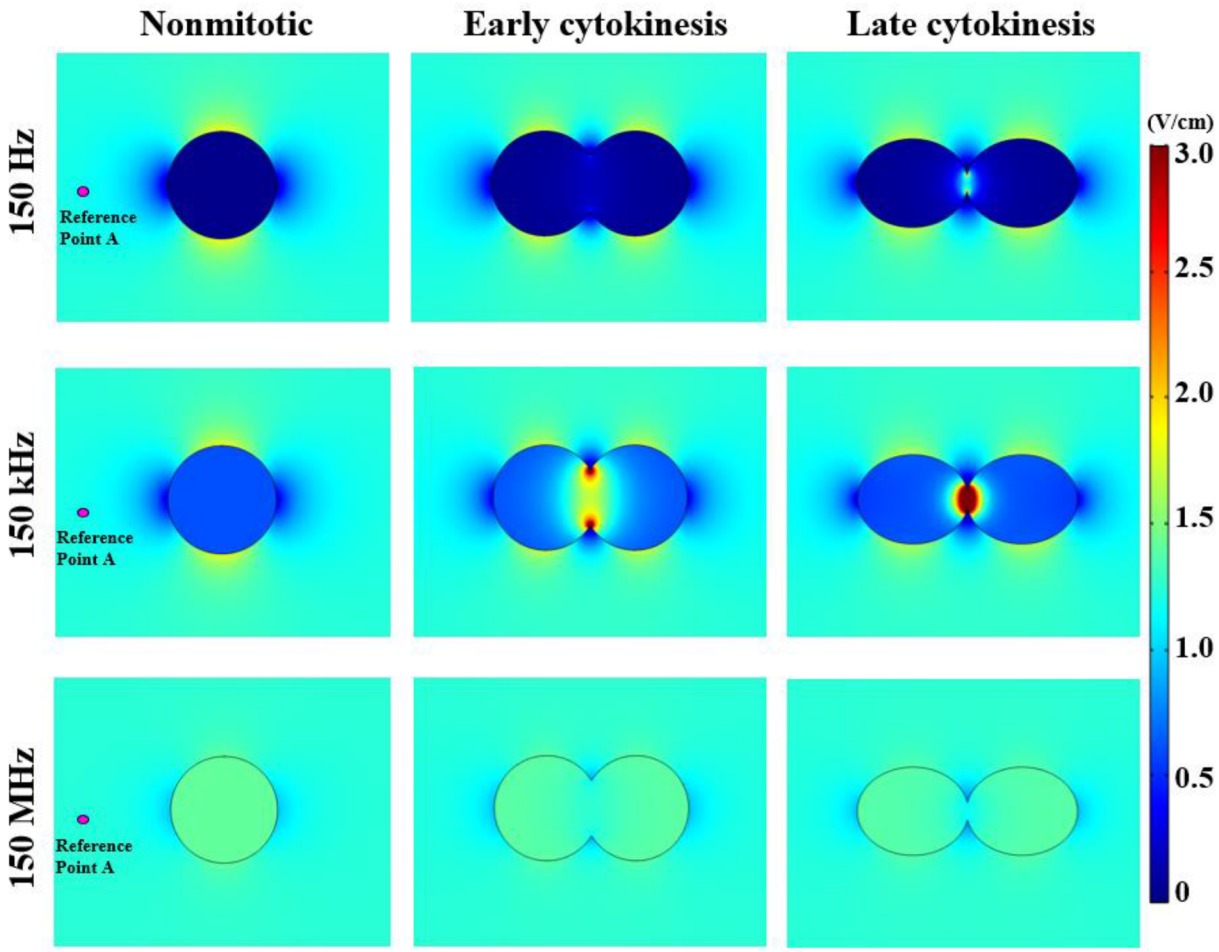

FIG. 1. Cellular level distribution of the applied electric fields at several frequency bands (rows) to dividing cells in various stages of the cell cycle (columns).

HPAF-II cell lines were purchased from the American Type Culture Collection (ATCC; Manassas, VA, USA), and U373 and B16F10 cell lines were obtained from the Korean Cell Line Bank (Seoul, Korea). All cells were cultured in accordance with the supplier's instructions.

3. Colony formation assay

TTFs were applied 3–24 h/day for 3 days according to appropriate treatment conditions. After culture for 14–20 days, the resulting colonies were stained with 0.4% Crystal Violet (Sigma, St. Louis, MO, USA). The plating efficiency was defined as the percentage of seeded cells that formed colonies under specific culture conditions. The survival fraction was calculated using the following formula: survival fraction = colonies counted/(cells seeded × plating efficiency/100) [Fig. 4(b)].

III. RESULTS

A. Cellular level simulation of TTF treatment

To investigate the physical effects of the frequencies of the AC-EFs inside dividing cells, AC-EFs of frequencies of 150 Hz,

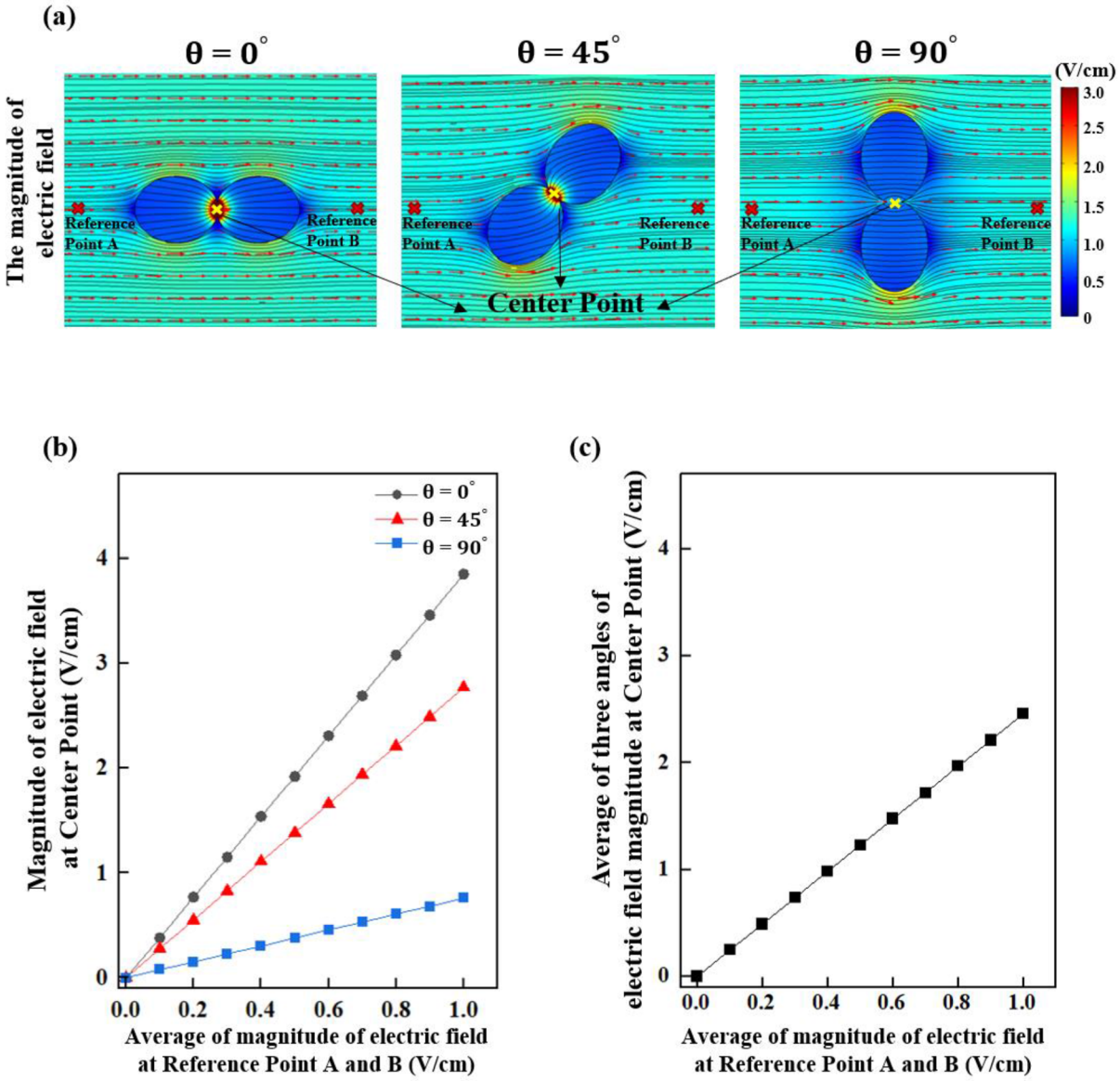

FIG. 2. (a) Distribution of the applied electric field inside dividing cells during late cytokinesis, when the angle (**θ**) between the direction of the applied electric field and the direction of cell orientation was set at 0°, 45°, and 90°. (b) Magnitude of the electric field applied to the Center point at each angle when the magnitude of the electric field at Reference point A and B ranged from 0.1 to 0.1 V/cm. (c) Average magnitudes of the electric field applied to the Center Point at the three angles.

150 kHz, and 150 MHz with an intensity of 1.2 V/cm at an extracellular reference point A were applied to cells at each of the three major stages of cell division: nonmitotic, early cytokinesis, and late cytokinesis.[30] When dividing cells in a nonmitotic state were exposed to an AC-EF of frequency 150 Hz, the intensity of the electric field inside the cell was almost zero. This intensity increased as the frequency increased, with the intensity of the electric field inside the cell being similar to that outside the cell at a frequency of 150 MHz (column 1 in Fig. 1). Furthermore, as the cells progressed through cytokinesis, the application of electric fields at frequencies of 150 Hz and 150 MHz resulted in a distribution of electric fields inside the cells almost similar to that in the

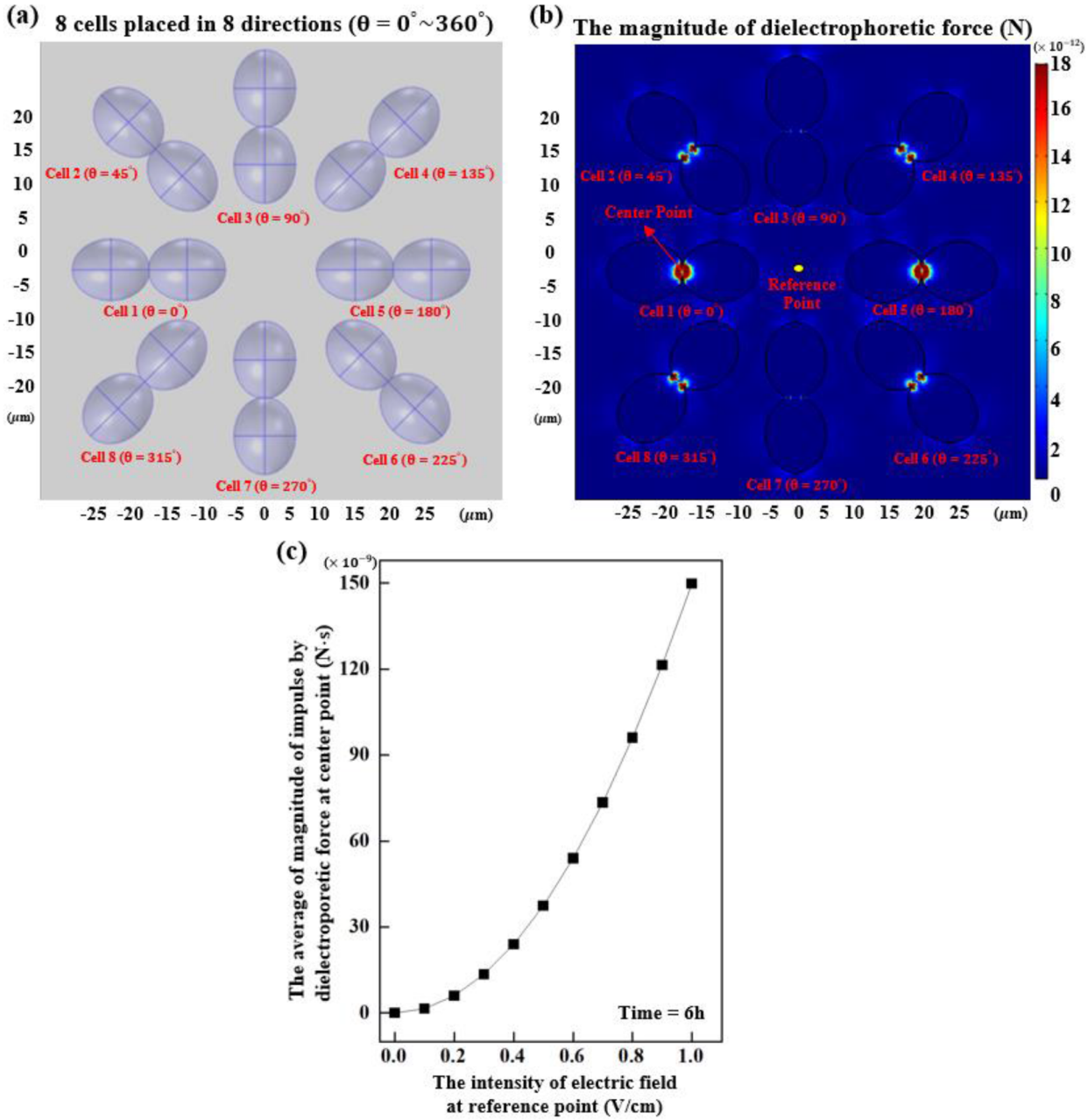

FIG. 3. (a) Illustration of eight dividing cells oriented in eight different directions. (b) Distribution of dielectrophoretic forces inside the eight dividing cells. (c) Relationship between the intensity of electric field measured at the reference point (x axis) and the average of the impulse by dielectrophoretic forces measured at the center point of the eight dividing cells (y axis).

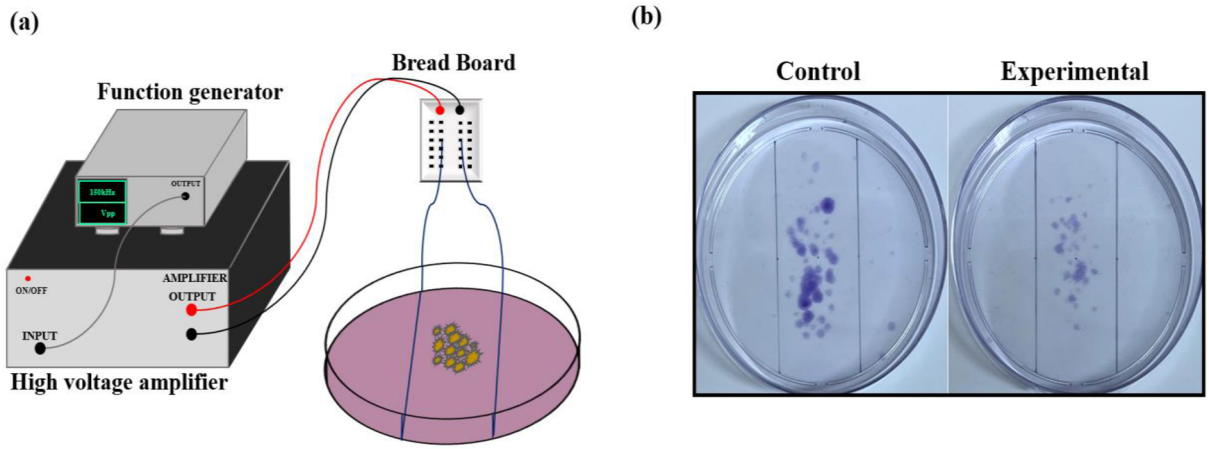

FIG. 4. (a) Schematic diagram of the experimental setup. (b) Results of colony formation assays in the control and experimental groups.

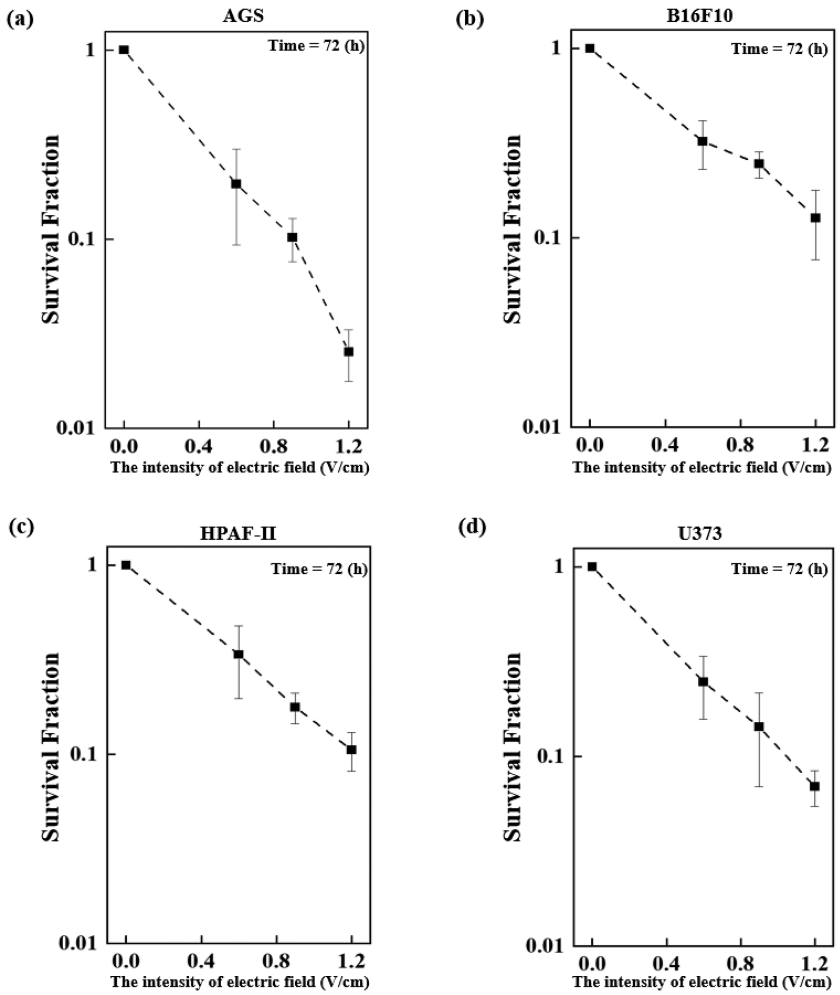

FIG. 5. Relationships between the intensity of electric field and the survival fractions of four tumor cell lines, (a) AGS, (b) B16F10, (c) HPAF-II, and (d) U373, after 72 h of TTFs treatment.

nonmitotic state. However, at a frequency of 150 kHz, the cleavage furrows of the dividing cells during early cytokinesis showed a high intensity of electric field (E > 1.6 V/cm), with these intensities further increasing during late cytokinesis (E > 3.0 V/cm) (columns 2 and 3 in Fig. 1).

To evaluate the effect of cell orientation on the distribution of applied electric field intensities, AC-EFs were applied at a frequency of 150 kHz, the frequency that had shown the largest distribution of electric field intensities inside the cells (Fig. 1). AC-EFs were subsequently applied to cells in late cytokinesis at angles (θ) of 0°, 45°, and 90° between the direction of the applied electric field and the direction of cell orientation, and the distributions of electric field intensities inside the cells were evaluated. The intensity of the electric field at the center of the cleavage furrows of dividing cells gradually decreased as the angle increased from 0° to 90° [Fig. 2(a)]. Moreover, simulation of the electric field with the intensity ranging from 0 to 1.0 V/cm at reference points A and B outside the cell showed that the electric field strength at 90° was 19.74% of that at 0° [Fig. 2(b)]. Figure 2(c) shows a graph of the arithmetic mean of the electric field intensity at the center in the three directions under the same conditions.

Because cells in an actual microscopic environment are randomly distributed in various directions, a real environment was simulated by applying an electric field to eight dividing cells at angles ranging from 0 to 360° in 45° intervals [Fig. 3(a)]. The intensity of the DEP force applied to the center point of the cleavage furrow inside each dividing cell was calculated as a function of the intensity of the electric field to a reference point outside the eight dividing cells

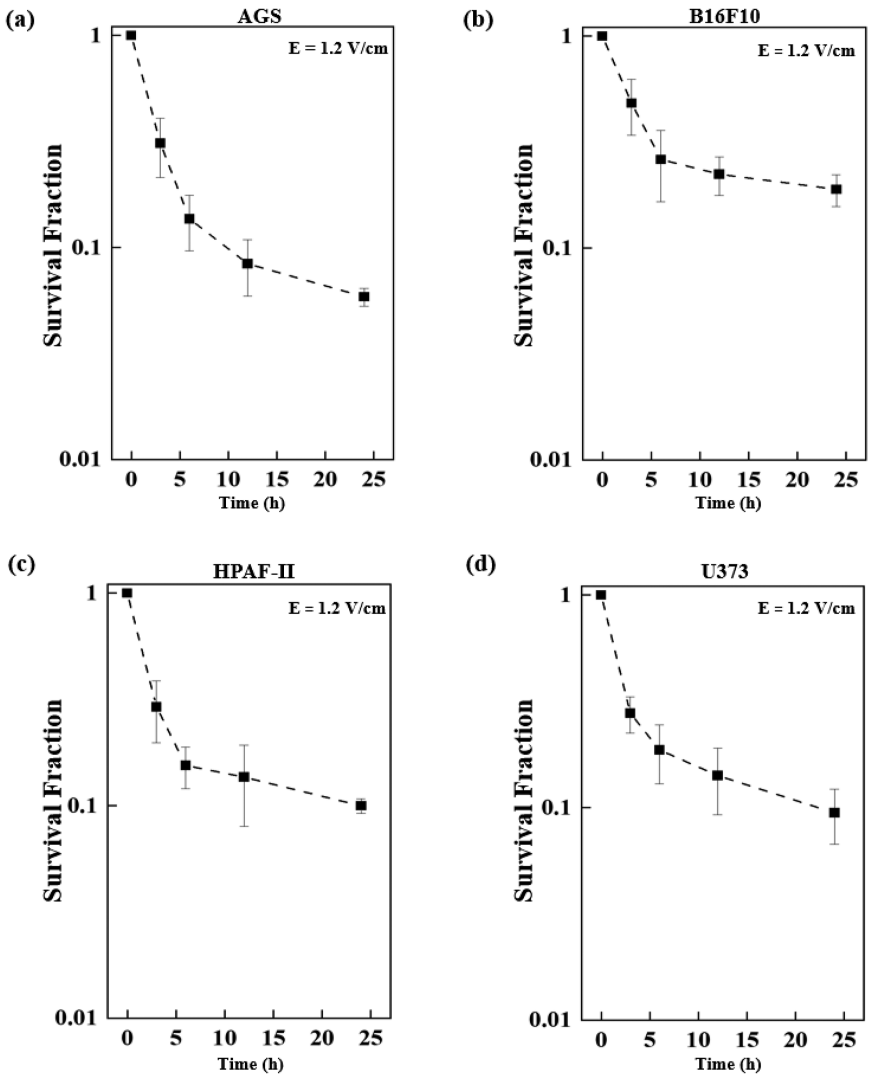

FIG. 6. Relationships between time duration of electric fields and the survival fractions of four tumor cell lines (a) AGS, (b) B16F10, (c) HPAF-II, and (d) U373, after 72 h of TTFs treatment.

[Fig. 3(b)]. Simulation results showed that the DEP forces applied to the center of the cleavage furrow of eight dividing cells placed in different directions values ranged from 1.45×10^{-13} to 1.60×10^{-11} N when 1.0 V/cm of electric field intensity is applied at the reference point [Fig. 3(b)]. Figure 3(c) shows that the average magnitude of the impulse to the cleavage furrow inside a dividing cell ranged from 1.51×10^{-9} to 1.49×10^{-7} N s when TTFs with an intensity ranging from 0.1 to 1 V/cm are applied at an extracellular reference point for 6 h. These simulation results suggest that the average impulse delivered to the randomly oriented cells is proportional to the intensity of the electric field at an extracellular reference point and time duration of TTFs.

B. *In vitro* experiments with TTFs

To determine the correlation between the impulse due to TTFs and the inhibition of cell proliferation *in vitro*, electric fields at an extracellular reference point in culture media with intensities of 0.6, 0.9, and 1.2 V/cm were applied to four cancer cell lines, AGS, B16F10, U373, and HPAF-II cells, for 3, 6, 12, and 24 h, followed by a 24 h period when the electric field was not applied, with the procedure repeated for three days (total 72 h). When the time duration of the electric field at an extracellular reference point is fixed, the survival fraction decreased in proportion to the increase in intensities of electric fields in culture media, with the four tumor cell lines displaying similar trends despite differences in the slopes of their declines (Fig. 5). In the same way, when the intensity of the electric field in culture media is fixed, the survival fraction decreased in proportion to the increase in the time duration of electric fields (Fig. 6). This experimental evidence suggests that both the intensity and the time duration of the applied electric field in culture media are proportionally related to the inhibitory effect on dividing cells, resulting in a proportional relationship between the impulse inside a dividing cell and inhibitory effect of TTFs.

IV. DISCUSSION

TTFs have been shown to markedly affect dividing cells, particularly tumor cells. Clinical studies have demonstrated the efficacy of TTFs in treating cancer.[7,10] Evaluations of the mechanism by which TTFs inhibit cell division[12–14] have identified the dielectrophoresis phenomenon as the main mechanism of action of TTFs.[11,12,14,23] The present study therefore focused specifically on the mechanism by which the dielectrophoresis phenomenon inhibits cell division.

The simulation study found that applying an AC-EF at specific frequencies (150 kHz in this simulation) to a dividing cell in the late cytokinesis stage resulted in a maximum electric field intensity of the electric field inside the cell when the angle between the direction of the field and cell orientation was 0°. The simulation results also showed that the intensity of the AC-EF at an extracellular reference point is proportional to the electric field intensity inside the cell, which results in the DEP force inside a dividing cell. In addition, *in vitro* study suggests that both the intensity of the applied electric field in culture media and the time duration are proportionally related to the inhibitory effect on dividing cells. Therefore, a proposed physical quantity, the magnitude of impulse generated by the DEP force, may be a measure of the inhibitory effect of TTFs on cell division.

To quantify the inhibitory effect of TTFs on cell division, it may be necessary to calculate the impulse generated by the DEP force accurately. However, it is very hard to calculate or measure this quantity since cells in an actual microscopic environment are randomly distributed in various directions with various stages of cell cycles. This limitation may be overcome by measuring the macroscopic quantity, which is proportional to the impulse generated by the DEP force by the AC-EF. Our results showed that the quantity obtained by multiplying the intensity of the applied electric field at an extracellular reference point, an indicator of DEP force, by the duration of electric field application, an indicator of the time required for the DEP force to act on dividing cells, is proportionally related to the DEP force by the AC-EF.

The macroscopic quantity that is proportional to the magnitude of impulse by the DEP force applied inside a microscopic cell for the time duration of TTFs can be practically calculated based on $E_{rms}\Delta t$, where E_{rms} is the rms value of the electric field at an extracellular reference point and Δt is the time duration of TTFs. The quantity, $E_{rms}\Delta t$, has several advantages. First, it is measurable and calculable macroscopically. Second, it can be used as a prognostic factor of the inhibitory effect of TTFs on cell division since it is proportional to the impulse generated by the DEP force by the AC-EF. The disadvantage of this quantity is that it has no meaningful physical units. To overcome this problem, one may consider $E_{rms}\Delta t$ as the rms value of impulse per unit charge, which is located at an extracellular reference point. Although $E_{rms}\Delta t$ can be used as a measure of the inhibitory effect, further research is needed to understand how each of the two variables is related to the inhibitory effect *in vitro* and *in vivo*.

Furthermore, it is crucial to clarify the difference between the previously proposed metrics and the newly proposed metric based on impulse to quantify the cytostatic effect of alternating electric fields. In a previous study, a metric to quantify the effect of TTF therapy was proposed by multiplying the power loss density and the time duration based on the proportional relationship between *in vitro* experiments and clinical trial results.[19] Although the authors showed that the absorbed energy is proportional to the cytostatic effect of alternating electric fields based on empirical data, there was little information about the mechanism of why the absorbed energy is related to the effect of TTFs. On the other hand, in this study, we proposed a metric to quantify the cell division inhibition effect of TTF therapy based on the fact that DEP force, which is known to be the main mechanism of the inhibition effect of proliferation in TTF therapy. In other words, based on a theoretically principled approach rather than an empirical approach, a new reference quantity representing the value called the impulse by DEP force is proposed in the study. We believe that this new metric can be considered as more representative of the cell division inhibition effect of TTFs because it is derived based on the underlying mechanism of TTFs.

In conclusion, the present study used cellular-level simulations and *in vitro* experiments with four tumor cell lines to confirm that impulse by DEP force is a single variable that represents both the DEP force, the primary mechanism of action of TTFs, and the application time of the DEP force. These findings have important implications for future studies aimed at understanding the fundamental mechanism by which TTFs inhibit cell division based on dielectrophoretic phenomena. In addition, impulse by DEP force

may be a valuable tool for evaluating the inhibitory effect of TTFs on cell proliferation, which may help optimize treatment protocols and improve cancer therapy outcomes.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Ethics Approval

This study did not require ethical board approval because it did not contain human or animal trials.

Author Contributions

G.O. and Y.J. contributed equally to this work.

Geon Oh: Data curation (equal); Formal analysis (equal); Software (equal); Writing – original draft (equal). **Yunhui Jo**: Resources (equal); Validation (lead); Writing – review & editing (equal). **Yongha Gi**: Software (equal). **Jinyoung Hong**: Investigation (equal). **Jonghyun Kim**: Software (equal). **Boram Lee**: Writing – review & editing (equal). **Myonggeun Yoon**: Conceptualization (lead).

DATA AVAILABILITY

The data that support the findings of this study are available within the article.

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