ACCSCIENCE PUBLISHING

Tumor Discovery

ORIGINAL RESEARCH ARTICLE

Development and validation of a comprehensive tumor treating fields system for glioblastoma therapy: From prototype design to preclinical evaluation

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Abstract

Glioblastoma multiforme (GBM) is an aggressive and lethal brain tumor with limited treatment options and poor prognosis. Standard therapies such as surgery, radiation, and chemotherapy provide modest survival benefits but are often ineffective against tumor recurrence. Tumor treating fields (TTF) therapy has emerged as a promising non-invasive treatment modality that uses alternating electric fields to disrupt cancer cell division and inhibit tumor growth. However, the optimization and practical implementation of TTF systems remain challenging due to limitations in field penetration, electrode design, and treatment efficacy. In this study, we designed and developed a novel TTF prototype system to enhance electric field transmission and optimize therapeutic efficiency. The system incorporates high-dielectric ceramic electrodes made of barium titanate zirconate, allowing for superior field penetration. We evaluated the system through a series of *in vitro* and *in vivo* experiments. *In vitro*, GBM cells exposed to the TTF system exhibited significant reductions in proliferation, with higher field intensities yielding greater inhibition. *In vivo*, using a rat GBM model, we observed marked tumor suppression, as validated by bioluminescence imaging and magnetic resonance imaging. Survival analysis further demonstrated prolonged lifespan in TTF-treated rats compared to controls. Our findings highlight the potential of this novel TTF system to improve GBM treatment outcomes. This study provides a comprehensive framework for future advancements in TTF therapy, paving the way for clinical translation and further integration with conventional and emerging cancer therapies.

Keywords: Glioblastoma multiforme; Tumor therapy; Tumor treating fields; Electric field therapy; System design

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1. Introduction

Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor in adults, representing approximately 15% of all brain tumors.[1-3] Despite

aggressive treatment approaches, including surgery, radiation, and chemotherapy, the prognosis for GBM patients remains dismal, with a median survival time of only 12 – 15 months.[4] The challenges in treating GBM lie in its highly invasive nature, rapid proliferation, and resistance to standard therapies. Current therapies are often limited by the blood-brain barrier, which restricts the delivery of chemotherapeutic agents, as well as the tumor's heterogeneity, which leads to treatment failure and recurrence.[5]

The standard treatment regimen for GBM, known as the Stupp protocol, includes maximal safe surgical resection followed by radiotherapy and concurrent temozolomide chemotherapy.[6,7] Although this approach slightly extends survival,[8] the 5-year survival rate of patients typically remains below 10%, underscoring the urgent need for novel therapeutic strategies. Moreover, extensive infiltration of GBM into healthy brain tissue renders complete surgical removal nearly impossible, necessitating adjuvant therapies capable of targeting residual tumor cells without causing significant toxicity to the surrounding brain structures.[9]

Tumor treating fields (TTF) have emerged as a promising non-invasive therapeutic modality for GBM, offering an alternative mechanism to target tumor growth.[10-12] TTF utilizes low-intensity, alternating electric fields at intermediate frequencies (100 – 300 kHz) to disrupt the mitotic process of rapidly dividing tumor cells.[13] These fields interfere with microtubule polymerization, alignment of chromosomes, and other essential mitotic functions, leading to apoptosis.[14,15] The U.S. Food and Drug Administration (FDA) has approved the use of TTF therapy through devices like the Optune system, further validating its potential in GBM treatment. Clinical trials have demonstrated the ability of TTF therapy to prolong overall survival and progression-free survival in GBM patients when combined with standard chemoradiation.[16-18] However, the full potential of TTF has yet to be realized, as current systems are limited in their flexibility to adjust field parameters, and few studies have explored the detailed engineering behind the design and optimization of TTF systems.

Despite its promising efficacy, TTF therapy is constrained by several limitations, including patient adherence to continuous treatment (at least 18 h/day),[19] variability in treatment response due to anatomical and tumor heterogeneity,[19] and potential skin irritation from electrode placement.[20] In addition, the precise biophysical mechanisms underlying TTF therapy remain an active area of research, with emerging studies investigating its broader impact on cell signaling pathways, immune modulation, and the tumor microenvironment.[21-26] Understanding these mechanisms is crucial for refining TTF parameters to enhance its therapeutic effectiveness and integrate it with other emerging treatments, such as immunotherapy and targeted drug delivery systems.

To address these limitations, our study presents the design, development, and preclinical evaluation of a novel TTF system, focusing on key components such as electrical signal regulation, transmission, and corresponding therapeutic effects. We designed the system to generate highly controlled electric fields and incorporated it with high-dielectric ceramic electrodes composed of barium titanate zirconate,[27-29] which have superior electric field transmission properties compared to conventional electrodes. By evaluating the performance of this system through *in vitro* glioblastoma cell experiments and *in vivo* rat models, we demonstrate its efficacy in inhibiting tumor growth. Furthermore, we provide a comprehensive guide to the technical design of the system to further democratize TTF research more accessible with the hope to deepen innovation in the field.

This study contributes valuable insights into the optimization of TTF therapy for clinical use, particularly in enhancing the effectiveness of electric field-based cancer treatments. In addition, we explore how electric field intensity, frequency, and electrode design impact treatment outcomes, providing data that could inform future advancements in personalized TTF therapy. Our approach integrates interdisciplinary expertise in engineering, materials science, and oncology, positioning this study as a crucial step toward improving the clinical application of TTF therapy. By systematically analyzing treatment parameters and their biological effects, we aim to bridge the gap between experimental and clinical applications, ultimately refining TTF therapy as a viable component of multimodal GBM treatment strategies.

Beyond the immediate implications for GBM treatment, the principles underlying TTF therapy may hold broader applications in other malignancies, including lung,[30,31] pancreatic,[32,33] and ovarian[34,35] cancers. Future research should explore the feasibility of expanding TTF technology to different cancer types, optimizing electrode configurations, and integrating real-time monitoring systems to enhance treatment precision. By advancing TTF system design and understanding its mechanistic effects, we hope to contribute to the development of more effective, personalized, and patient-friendly cancer therapies.

2. Materials and methods

2.1. Materials and instruments

The reagents used in the cell experiments comprised glioblastoma cells (Cyagen Biosciences), Dulbecco's

Modified Eagle medium (Procell Life Science and Technology Co., Ltd.), penicillin-streptomycin (Procell Life Science and Technology Co., Ltd.), fetal bovine serum (ExCell Bio). The reagents used in the rat experiments comprised C6-LUC glioma cells (Cyagen Biosciences), isoflurane (RWD Life Science Co., Ltd.), D-Luciferin Potassium Salt (Rhone Reagents), and Sprague-Dawley (SD) rats sourced from Hangzhou Qizhen Experimental Animal Technology Co., Ltd. All rats were male, aged between 6 and 8 weeks. Ceramic electrodes were acquired from the Flexible Bioelectronics Division, Institute of Flexible Electronics Technology of THU.

The instruments used for the electrode test comprised Bruker D8 Discover X-ray diffractometer (XRD), Zeiss Sigma 300 scanning electron microscope, and Agilent 4294A precision impedance analyzer. The instruments used for the rat experiments comprised stereotaxic apparatus (Blue Star B/S, Anhui Zhenghua Biological Instrument Co., Ltd.), multimode small animal *in vivo* imaging system (AniView 600, Guangzhou Boluoteng Biotechnology Co., Ltd.), small animal anesthesia machine (Model H1670401-200L, RWD Life Science Co., Ltd.), small animal magnetic resonance imaging (MRI) system (7.0T MRI, Bruker Biospin GmbH PharmaScan7016), and constant-temperature drying oven (Model DHP-9082, Ningguo Shaying Scientific Instrument Co., Ltd.).

2.2. Cell experiments

Four round glass slides were placed in the TTF cell experimental device. Three milliliters of cell suspension (density 2×10^5 cells/mL) was applied evenly on a slide, and incubated at 37°C. The TTF-treated group was subjected to the alternating electric field with specific parameters (field strength and frequency). Control cells received no electric field stimulation but were otherwise cultured under identical conditions. The slides were taken out at specified times, and the cells were digested and counted. Cell morphology and proliferation rates were recorded at each time point, and changes in cell density were analyzed to assess the effect of TTF on cell growth.

2.3. Rat tumor model

Rats were acclimatized in a specific pathogen-free (SPF)-grade environment at a controlled temperature of 20 – 26°C and humidity of 40 – 70%, with a 12-h light-dark cycle. The rats were provided sterilized corn cob bedding, along with free access to food and water for 7 days. Following acclimation, the rats were divided into two groups: the control group and the TTF treatment group, with three rats in each group.

The glioblastoma model[36,37] was established by stereotaxic injection of C6-LUC cells. The rats were anesthetized using isoflurane and secured in a stereotaxic frame. The C6-LUC cells, harvested during their exponential growth phase, were prepared at a concentration of 5×10^5 cells in 5 μL PBS. The cells were injected into the right striatum at coordinates 1 mm posterior to bregma, 3 mm lateral to the midline, and 4.5 mm deep from the skull surface. After injection, the skull was sealed with bone wax, and the incision was sutured and disinfected. The rats were then returned to the SPF environment for recovery.

2.4. TTF treatment

Three days post-injection, TTF treatment was administered. Electrode patches were affixed to the shaved scalp of anesthetized rats, positioned orthogonally to create intersecting electric fields. The TTF system was activated for >20 h daily, with continuous treatment until day 20. The electric field parameters were set to 2 V/cm at 200 kHz, matching the *in vitro* settings. Every 4 days, the electrodes were removed, the skin was disinfected, and fresh electrodes were attached.

Rats were monitored daily for general health, and the skin reactions at the electrode sites were recorded. Bioluminescent imaging was conducted on days 10, 12, 14, 16, and 18 using an *in vivo* imaging system following intraperitoneal injection of D-luciferin. MRI scans were performed on day 19 using a T2-TurboRARE sequence to confirm tumor size. On day 19, blood samples were collected for complete blood count and biochemical analysis.

3. Results

A block diagram is a graphical representation of a system's architecture, showing key components and their interactions. It provides a high-level overview of the system's functionality, which is crucial for understanding how different subsystems work together. In this study, the overall design block diagram of the TTF system is shown in Figure 1A, including a Signal Generator, Signal Amplifier, and Control Module. The Signal Generator produces a 200 kHz sine wave, amplified by the Signal Amplifier, and modulated through a Microcontroller Unit-controlled Control Module to adjust signal intensity and frequency for each of the 36 output channels. This modular design allows independent control over each electrode's output, enabling precise application of electric fields. In the cell culture experiments, four electrodes are arranged orthogonally, providing alternating electric fields every second, as depicted in the inset of Figure 1A.

A printed circuit board (PCB) is the backbone of modern electronic systems, providing mechanical support and electrical connections for components. It

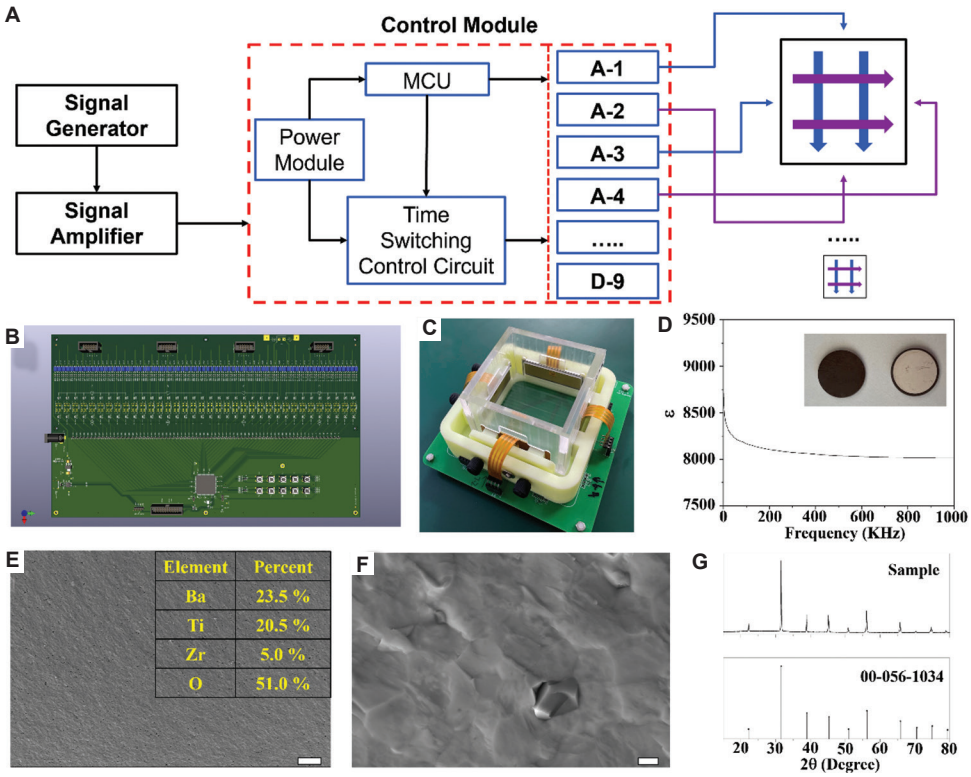


Figure 1. Overview of TTF system. (A) The overall design block diagram of the TTF system. (B) The PCB layout of the Control Module. (C) An actual photograph of the TTF system used in the cell experiments. (D) The measurements of the ceramic electrode across different frequencies; the inset shows the front and back of a ceramic electrode, with the back silver plated. (E and F) SEM images and EDS analysis showing the cross-sectional morphology of the ceramic electrode. Scale bars: 100 μm (e); 2 μm (f). (G) The XRD pattern of the ceramic electrode.
Abbreviations: EDS: Energy dispersive spectrometry; PCB: Printed circuit board; SEM: Scanning electron microscopy; TTF: Tumor treating fields; XRD: X-ray diffractometry.

consists of multiple layers of insulating material and conductive traces that facilitate signal transmission. In this study, the PCB layout is shown to illustrate how the Control Module distributes electric signals precisely to each electrode. The Control Module's PCB layout, shown in Figure 1B, highlights the intricate design needed to manage the precise delivery of the electric fields to each electrode. Figure 1C presents the prototype used in the cell experiments, demonstrating the physical implementation of the system with orthogonally positioned ceramic electrodes. A key feature of the system is the high-dielectric ceramic electrodes, which have a relative dielectric constant exceeding 8000 at 200 kHz, significantly higher than the reported electrodes[6] (Figure 1D). The superior dielectric properties ensure effective electric potential transmission during treatment. The electrode's cross-sectional morphology, analyzed by the scanning electron microscope, reveals a uniform structure, and the energy dispersive spectrometer confirms the primary composition as barium titanate zirconate (Figure 1E and 1F). The XRD analysis (Figure 1G) further validates the crystalline structure of the ceramic electrodes, matching the standard PDF card 00-056-1034, confirming the suitability for stable and efficient electric field generation. The combination of these images confirms the successful design and fabrication of the TTF system, ensuring effective electric field delivery during therapy.

In the cell culture experiments, a well-defined electrode arrangement was used to apply alternating electric fields to glioblastoma cells, allowing for a controlled investigation of TTF effects on cell proliferation. The schematic diagram of the experimental setup helps illustrate how electric fields interact with cells. The glioblastoma cells (U251) were exposed to varying electric field intensities using the TTF system. The experimental setup is illustrated in Figure 2A, where four circular cell culture slides were placed under orthogonally arranged electrodes to apply the electric fields in alternating directions. Finite element analysis is a numerical method used to simulate and analyze physical phenomena such as electric fields, thermal distribution, and mechanical stress. In Figure 2B, the electric field distribution across the culture area was simulated using the finite element analysis software (COMSOL Multiphysics),

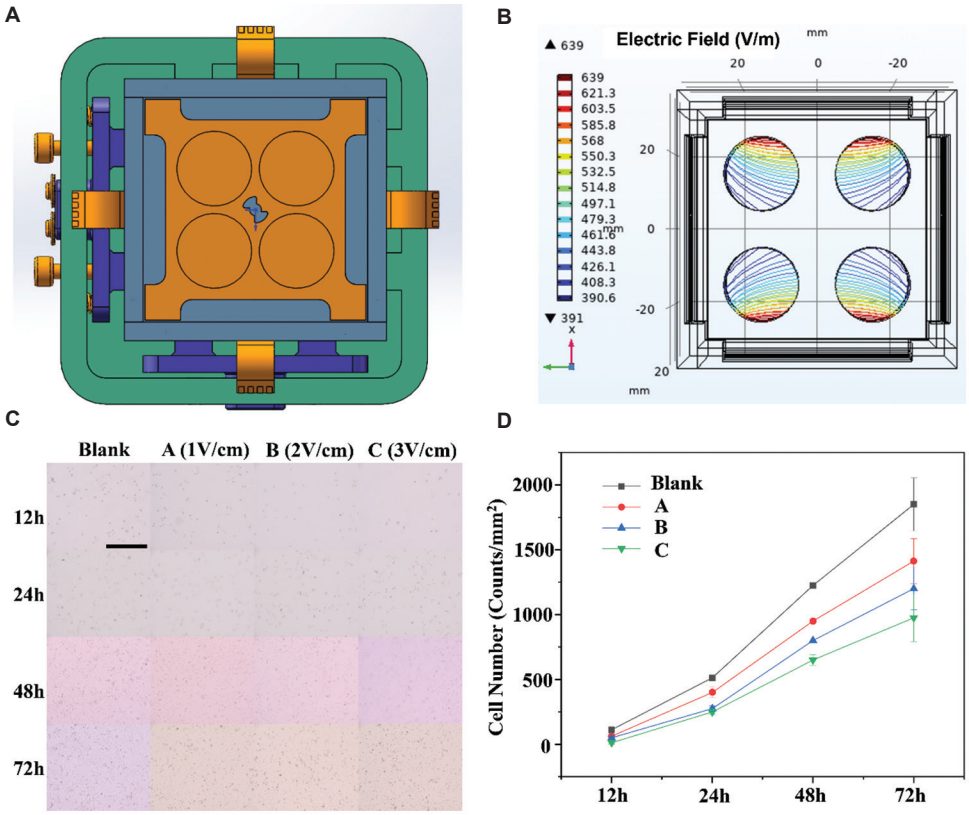


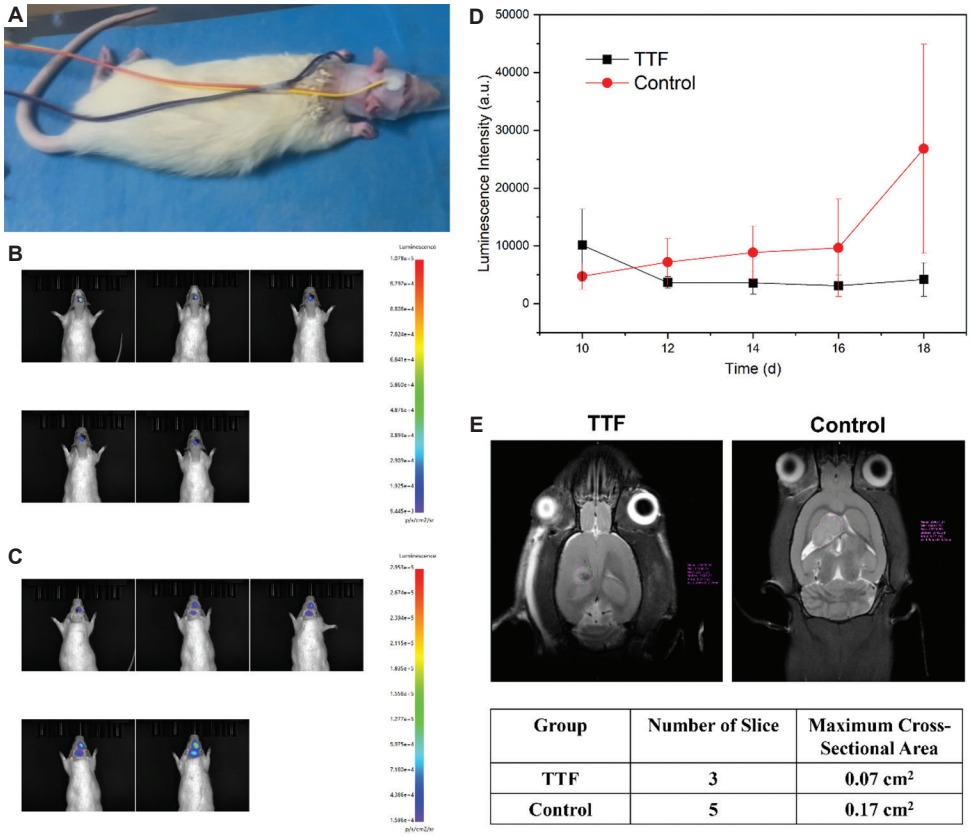
Figure 2. Cell experiments of TTF therapy. (A) The top view of the cell experiment prototype design, showing the placement of round cell culture glass slides and the orthogonal electric field application. (B) The finite element simulation of the electric field distribution using Comsol software. (C) Images of U251 cells cultured under different electric field intensities and at various time points (12, 24, 48, and 72 h). Scale bar: 0.5 mm. (D) The quantitative analysis of adherent cell counts.
Abbreviation: TTF: Tumor treating fields.

confirming the uniform application of the field over the cells.

The visual comparison of cell morphology across different electric field strengths shows a significant reduction in cell proliferation, especially at higher field intensities. Figure 2C presents micrographs of cells treated under 1, 2, and 3 V/cm electric fields at 12, 24, 48, and 72-h intervals. A marked decrease in cell number and altered cell morphology were observed at all-time points in the TTF-treated group, with the highest intensity (3 V/cm) showing the most pronounced effects. After 72 h, cell counts revealed a 35% reduction in proliferation at 2 V/cm and a 50% reduction at 3 V/cm compared to the control group (Figure 2D). These results demonstrate that the TTF system significantly inhibited glioblastoma cell growth *in vitro*. The inhibitory effect appeared to be both time- and intensity-dependent, with higher electric field intensities resulting in greater inhibition of cell proliferation.

For the *in vivo* experiments, a rat glioblastoma model was established to evaluate the efficacy of TTF therapy. The ethical approval (202404A010) from the Ethics Review Committee was obtained before the research. Figure 3A shows the placement of four electrode patches on the rat's head, positioned orthogonally to ensure comprehensive electric field coverage. C6-LUC glioblastoma cells, derived from the rat C6 glioma cell line by stably integration of a constitutive firefly luciferase expression construct, were injected into the brain, and TTF therapy was applied at 2 V/cm for >20 h/day for a period of 20 days.

Tumor growth was monitored using bioluminescence imaging at multiple time points-days 10, 12, 14, 16, and 18 post-inoculation (Figure 3B and 3C). Bioluminescence intensity served as an indicator of tumor size, with stronger signals representing larger tumors. Comparison between the TTF-treated and control groups revealed significant tumor suppression in the treated group over time (Figure 3D). By day 18, tumor luminescence intensity was reduced by more than 5 times in the TTF-treated group compared to controls. In addition, MRI scans performed on day 18 (Figure 3E) provided further validation of the tumor size reduction, with TTF-treated rats exhibiting smaller tumor



Group	Number of Slice	Maximum Cross-Sectional Area
TTF	3	0.07 cm^2
Control	5	0.17 cm^2

Figure 3. Rat experiments of TTF therapy. (A) The setup for the TTF treatment on the rat's head with 4 electrode patches placed on both sides of the head. (B and C) The bioluminescence images of rats from the TTF-treated group and the control group, respectively, over several days. (D) The comparative graph of bioluminescence intensity between the treatment and control groups. (E) MRI scans from day 18 showing reduced tumor size in TTF-treated rats compared to rats in the control group.
Abbreviations: MRI: Magnetic resonance imaging; TTF: Tumor treating fields.

cross-sectional areas compared to controls. These results demonstrate the effectiveness of the TTF system in slowing tumor progression in the glioblastoma rat model.

During TTF therapy, additional physiological parameters were monitored to assess treatment safety and tolerability in the glioblastoma rat model. Figure 4A shows the detailed process of electrode placement on the rats, ensuring proper alignment for optimal electric field delivery. Body weight changes were tracked throughout the experiment, as shown in Figure 4B, indicating that TTF-treated rats maintained a relatively stable body weight compared to the control group, suggesting minimal adverse effects on overall health. To assess potential thermal damage from the electrode patches, temperature measurements were recorded at the electrode-skin interface during TTF treatment (Figure 4C). The data showed no significant increase in skin temperature over time, confirming that the treatment did not induce thermal injury. However, some mild skin damage was observed at the electrode attachment sites on days 8, 10, and 12 (Figure 4D), where local redness and slight erosion occurred. These skin lesions were manageable and did not progress to severe injury, demonstrating the favorable overall safety profile of the TTF system despite some localized effects.

4. Discussion

The present study successfully developed and validated a novel TTF system for GBM therapy, demonstrating significant efficacy in both *in vitro* and *in vivo* models. Our findings contribute to the growing body of research supporting the therapeutic potential of TTF while also introducing innovative elements in device design, electric field optimization, and biological impact assessment. In this section, we discuss the implications of our findings, the limitations of the study, and potential future directions for improving TTF therapy in clinical applications.

4.1. Mechanism of action and optimization

Our TTF system operates at a frequency of 200 kHz and an intensity of 2 V/cm, which are consistent with clinically

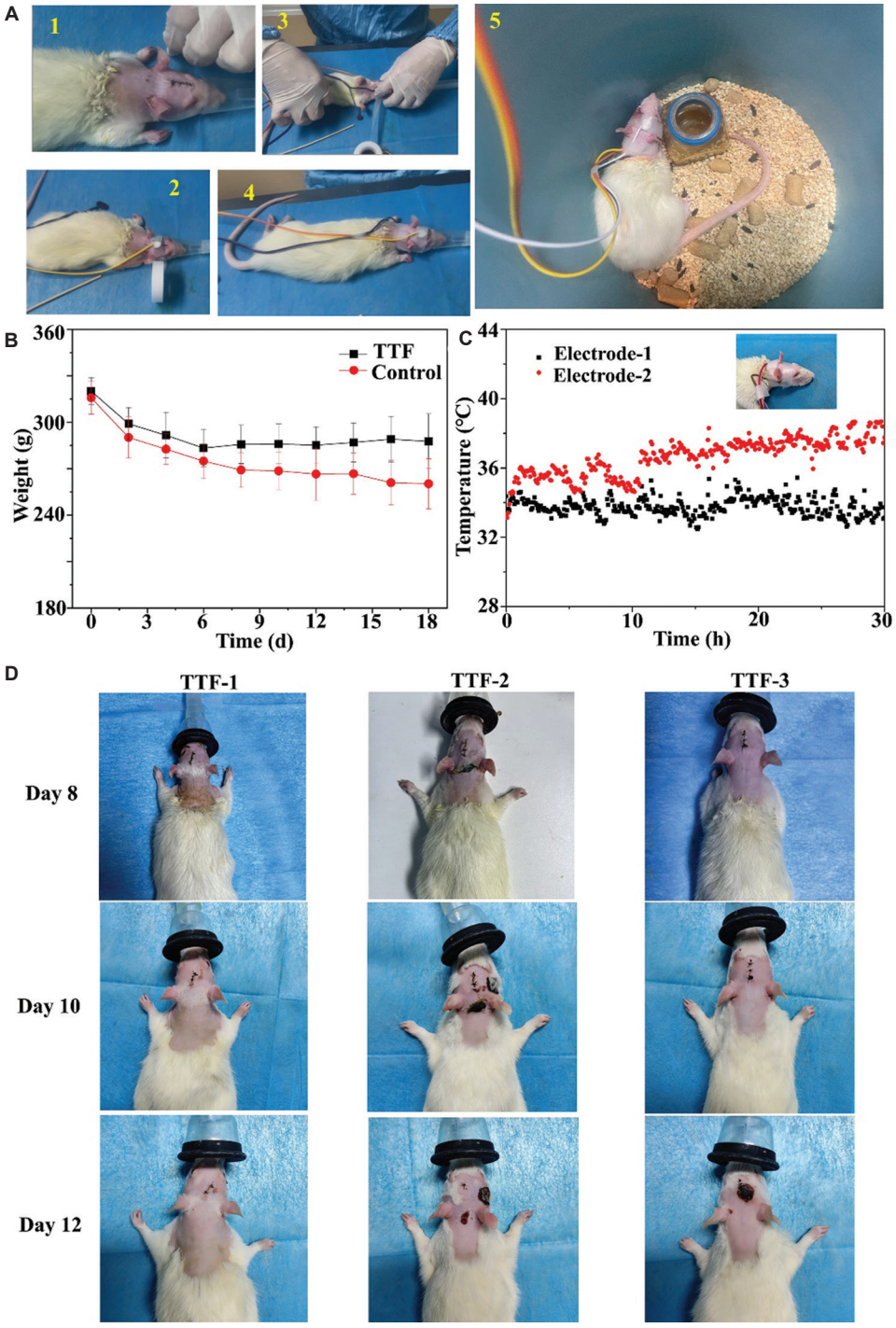


Figure 4. Safety of TTF therapy. (A) The electrode installation process and treatment setup for rats undergoing TTF therapy. (B) The change in body weight over time for both control and TTF-treated groups. (C) The temperature profile at the electrode-skin interface during TTF therapy. (D) The skin condition of rats in the treatment group on days 8, 10, and 12.
Abbreviation: TTF: Tumor treating fields.

approved TTF parameters. Our device incorporates high-dielectric ceramic electrodes made of barium titanate zirconate, which significantly improves electric field transmission and uniformity. These improvements are crucial as uniform and precise electric field distribution enhances therapeutic efficacy while minimizing unwanted side effects. Furthermore, the modular design of our control system allows independent manipulation of electric field

parameters, offering the flexibility to optimize treatment for individual patients or different tumor types.

The observed inhibition of glioblastoma cell proliferation and tumor progression in our models aligns with previous research indicating that alternating electric fields disrupt mitotic spindle formation, interfere with tubulin polymerization, and induce apoptosis in rapidly dividing cancer cells. Importantly, the *in vitro* findings demonstrated a dose-dependent response, with higher electric field intensities leading to greater tumor suppression. This suggests the potential for further optimizing field strength and exposure duration to maximize efficacy while maintaining safety.

4.2. Comparison with existing TTF devices

At present, the FDA-approved Optune system represents the benchmark for TTF therapy. However, it is limited by its relatively static field distribution and reliance on external wearable electrodes. Our system's integration of high-dielectric ceramic electrodes addresses these limitations by ensuring more efficient electric field penetration and a more homogenous distribution over tumor-affected areas. In addition, our system's control module enables dynamic field modulation, which could provide greater adaptability in treating heterogeneous and irregularly shaped tumors.

Moreover, while the Optune system has demonstrated survival benefits when combined with temozolomide chemotherapy, its efficacy remains suboptimal for some patient populations. Our system presents an opportunity to explore combination therapies, such as pairing TTF with immunotherapies, targeted inhibitors, or gene therapies. This combinatorial approach could further enhance treatment outcomes and extend survival benefits beyond what is currently achievable with standard TTF therapy.

4.3. Safety and tolerability considerations

One of the primary concerns associated with TTF therapy is the potential for adverse effects such as skin irritation and discomfort at electrode attachment sites. Our study monitored physiological responses in rat models and observed only mild skin irritation, which did not progress to severe tissue damage. This suggests that our electrode design minimizes localized heating and mechanical stress. Future research should focus on developing bioadaptive materials that further reduce skin irritation and improve patient compliance.

In addition, concerns regarding TTF's effects on normal brain tissue and neural function remain largely unexplored. While TTF selectively targets rapidly dividing cells, understanding its long-term impact on the surrounding neural microenvironment is essential. Investigating whether TTF influences neuroinflammation, neuronal plasticity, or cognitive function could inform strategies to enhance safety and mitigate any potential neurotoxicity.

4.4. Future directions and clinical translation

Despite promising preclinical results, translation of our newly developed TTF system into clinical practice requires further experimental validation. Future studies should include large-scale animal models with longer treatment durations to assess long-term efficacy and safety. In addition, clinical trials will be necessary to determine whether the advantages observed in our preclinical models translate into meaningful benefits for GBM patients.

One promising direction is the integration of real-time monitoring and feedback control in TTF therapy. Advanced sensor technologies and machine learning algorithms could be employed to personalize treatment based on tumor response dynamics. This precision medicine approach could optimize electric field parameters in real time, maximizing therapeutic effects while minimizing unnecessary exposure.

Another avenue for exploration is the combination of TTF therapy with other modalities such as hyperthermia, photodynamic therapy, and nanomedicine-based drug delivery. These synergies may enhance tumor sensitivity to TTF while overcoming some of the resistance mechanisms associated with conventional treatments. In addition, investigating TTF's applicability to other aggressive cancers, such as pancreatic or lung cancers, could broaden its clinical impact.

5. Conclusion

Our study presents a comprehensive and systematic approach to the development and evaluation of an advanced TTF therapy system for GBM. By incorporating high-dielectric ceramic electrodes and a modular control system, we demonstrated improvements in electric field transmission and therapeutic efficacy compared to existing TTF devices. The preclinical results showed that our system effectively inhibited glioblastoma cell proliferation *in vitro* and reduced tumor growth *in vivo*, supporting its potential as a novel approach for GBM treatment.

Importantly, our study also highlighted the need for further validation of the therapy system to establish its clinical significance. While our device demonstrated promising results in preclinical models, additional studies are required to assess its comparative efficacy, safety profile, and ease of integration into standard treatment regimens. The findings suggest that while improved electrode materials and field modulation strategies may offer advantages, these benefits must be rigorously tested in larger, more diverse experimental models.

Looking ahead, future research should focus on optimizing electric field parameters, exploring combination therapies, and integrating real-time monitoring for adaptive treatment strategies. Clinical translation will require rigorous trials to validate the safety and effectiveness of this technology in human patients. If successfully implemented, our TTF system could represent a significant advancement in glioblastoma treatment, offering a non-invasive and highly adaptable therapeutic option for improving patient outcomes. Overall, this study contributes valuable insights into the engineering and biological aspects of TTF therapy, paving the way for further innovations in electric field-based cancer treatments.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Zhiyong Wang
Formal analysis: Han Lv
Investigation: Xindong Wang
Methodology: Xindong Wang
Writing–original draft: Xindong Wang
Writing–review & editing: Han Lv, Xian Wang

Ethics approval and consent to participate

The study is approved by Ethics Review Committee of Hangzhou Yanqu Information Technology Co., Ltd. (approval no.: 202404A010).

Consent for publication

Not applicable.

Availability of data

All datasets on which the conclusions of this paper rely have been presented in the main manuscript.

References

1. Yalamarty S, Filipczak N, Li, X, *et al.* Mechanisms of resistance and current treatment options for glioblastoma multiforme (GBM). *Cancers (Basel)*. 2023;15(7):2116.

doi: 10.3390/cancers15072116

2. Saqib M, Zahoor A, Rahib A, *et al.* Clinical and translational advances in primary brain tumor therapy with a focus on glioblastoma-A comprehensive review of the literature. *World Neurosurg X*. 2024;24:100399.

doi: 10.1016/j.wnsx.2024.100399

3. Stupp R, Taillibert S, Kanner A, *et al.* Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: A randomized clinical trial. *JAMA*. 2017;318(23):2306-2316.

doi: 10.1001/jama.2017.18718

4. Stupp R, Wong E, Kanner A, *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(14):2192-2202.

doi: 10.1016/j.ejca.2012.04.011

5. Wong E, Lok E, Swanson K. Clinical benefit in recurrent glioblastoma from adjuvant NovoTTF-100A and TCCC after temozolomide and bevacizumab failure: A preliminary observation. *Cancer Med.* 2015;4(3):383-391.

doi: 10.1002/cam4.421

6. Kirson E, Dbalý V, Tovarys F, *et al.* Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. *Proc Natl Acad Sci U S A*. 2007;104(24): 10152-10157.

doi: 10.1073/pnas.0702916104

7. Warren K, Liu L, Liu Y, *et al.* The impact of timing of concurrent chemoradiation in patients with high-grade glioma in the era of the stupp protocol. *Front Oncol.* 2019;9:186.

doi: 10.3389/fonc.2019.00186

8. Pless M, Weinberg U. Tumor treating fields: Concept, evidence and future. *Expert Opin Investig Drugs.* 2011;20(8):1099-1106.

doi: 10.1517/13543784.2011.583236

9. Gutin P, Wong E. Noninvasive application of alternating electric fields in glioblastoma: A fourth cancer treatment modality. *Am Soc Clin Oncol.* 2012;32:126-131.

doi: 10.14694/EdBook_AM.2012.32.122

10. Cao Q, Hajosch A, Kast R, *et al.* Tumor Treating Fields (TTFields) combined with the drug repurposing approach CUSP9v3 induce metabolic reprogramming and synergistic anti-glioblastoma activity *in vitro*. *Br J Cancer.* 2024;130(8):1365-1376.

doi: 10.1038/s41416-024-02608-8

11. Rominiyi O, Vanderlinden A, Clenton S, *et al.* Tumour treating fields therapy for glioblastoma: Current advances

and future directions. *Br J Cancer.* 2021;124(4):697-709.

doi: 10.1038/s41416-020-01136-5

12. Stupp R, Taillibert S, Kanner A, *et al.* Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: A randomized clinical trial. *JAMA*. 2015;314(23):2535-2543.

doi: 10.1001/jama.2015.16669

13. Guo X, Yang X, Wu J, *et al.* Tumor-treating fields in glioblastomas: Past, present, and future. *Cancers (Basel).* 2022;14(15):3669.

doi: 10.3390/cancers14153669

14. Moser J, Salvador E, Deniz K, *et al.* The mechanisms of action of tumor treating fields. *Cancer Res.* 2022;82(20):3650-3658.

doi: 10.1158/0008-5472.Can-22-0887

15. Voloshin T, Schneiderman R, Volodin A, *et al.* Tumor treating fields (TTFields) hinder cancer cell motility through regulation of microtubule and acting dynamics. *Cancers (Basel).* 2020;12(10):3016.

doi: 10.3390/cancers12103016

16. Chen W, Wang Y, Zhao B, *et al.* Optimal therapies for recurrent glioblastoma: A Bayesian network meta-analysis. *Front Oncol.* 2021;11:641878.

doi: 10.3389/fonc.2021.641878

17. Taphoorn M, Dirven L, Kanner A, *et al.* Influence of treatment with tumor-treating fields on health-related quality of life of patients with newly diagnosed glioblastoma: A secondary analysis of a randomized clinical trial. *JAMA Oncol.* 2018;4(4):495-504.

doi: 10.1001/jamaoncol.2017.5082

18. Fabian D, Guillermo M, Alnahhas I, *et al.* Treatment of glioblastoma (GBM) with the addition of tumor-treating fields (TTF): A review. *Cancers.* 2019;11(2), 174.

doi: 10.3390/cancers11020174

19. Mun E, Babiker H, Weinberg U, *et al.* Tumor-treating fields: A fourth modality in cancer treatment. *Clin Cancer Res.* 2018;24(2):266-275.

doi: 10.1158/1078-0432.CCR-17-1117

20. Anadkat M, Lacouture M, Friedman A, *et al.* Expert guidance on prophylaxis and treatment of dermatologic adverse events with Tumor Treating Fields (TTFields) therapy in the thoracic region. *Front Oncol.* 2022;12:975473.

doi: 10.3389/fonc.2022.975473

21. Pan J, Eskandar T, Ahmed Z, *et al.* Biophysical and biological mechanisms of tumor treating fields in glioblastoma. *J Cancer Sci Clin Ther.* 2024;8(3):265-270.

doi: 10.26502/jcsct.5079249

22. Berkelmann L, Bader A, Meshksar S, *et al.* Tumour-treating fields (TTFields): Investigations on the mechanism of action by electromagnetic exposure of cells in telophase/cytokinesis. *Sci Rep.* 2019;9(1):7362.

doi: 10.1038/s41598-019-43621-9

23. Li X, Yang F, Rubinsky B. A theoretical study on the biophysical mechanisms by which tumor treating fields affect tumor cells during mitosis. *IEEE Trans Biomed Eng.* 2020;67(9):2594-2602.

doi: 10.1109/TBME.2020.2965883

24. Farmani A, Mahdavinezhad F, Scagnolari C, *et al.* An overview on tumor treating fields (TTFields) technology as a new potential subsidiary biophysical treatment for COVID-19. *Drug Deliv Transl Res.* 2022;12(7):1605-1615.

doi: 10.1007/s13346-021-01067-5

25. Carrieri F, Smack C, Siddiqui I, *et al.* Tumor treating fields: At the crossroads between physics and biology for cancer treatment. *Front Oncol.* 2020;10:575992.

doi: 10.3389/fonc.2020.575992

26. Xiang X, Liu H, Tao X, *et al.* Glioblastoma behavior study under different frequency electromagnetic field. *iScience.* 2023;26(12):108575.

doi: 10.1016/j.isci.2023.108575

27. Tewatia K, Sharma A, Sharma M, *et al.* Factors affecting morphological and electrical properties of Barium Titanate: A brief review. *Mater Today Proc.* 2021;44:4548-4556.

doi: 10.1016/j.matpr.2020.10.813

28. Liu W, Kong F, Liang Y, *et al.* Strategy to achieve both enhanced dielectric tunability and reduced dielectric loss in the barium zirconium titanate ceramics. *Ceram Int.* 2024;50(18):31759-31766.

doi: 10.1016/j.ceramint.2024.05.354

29. Sumona H, Sultan M, Urmi S, *et al.* Investigation of structural, electrical and optical properties of lanthanum and zirconium doped barium titanate ceramics. *Mater Sci Eng B.* 2023;298:116844.

doi: 10.1016/j.mseb.2023.116844

30. Barsheshet Y, Voloshin T, Brant B, *et al.* Tumor treating fields (TTFields) concomitant with immune checkpoint inhibitors are therapeutically effective in non-small cell lung cancer (NSCLC) *in vivo* model. *Int J Mol Sci.* 2022;23(22):14073.

doi: 10.3390/ijms232214073

31. Pless M, Droege C, von Moos R, *et al.* A phase I/II trial of tumor treating fields (TTFields) therapy in combination with pemetrexed for advanced non-small cell lung cancer. *Lung Cancer.* 2013;81(3):445-450.

doi: 10.1016/j.lungcan.2013.06.025

32. Giladi M, Schneiderman R, Porat Y, *et al.* Mitotic disruption and reduced clonogenicity of pancreatic cancer cells

in vitro and *in vivo* by tumor treating fields. *Pancreatology.* 2014;14(1):54-63.

doi: 10.1016/j.pan.2013.11.009

33. Jo Y, Oh G, Gi Y, *et al.* Tumor treating fields (TTF) treatment enhances radiation-induced apoptosis in pancreatic cancer cells. *Int J Radiat Biol.* 2020;96(12):1528-1533.

doi: 10.1080/09553002.2020.1838658

34. Vergote I, von Moos R, Manso L, *et al.* Tumor treating fields in combination with paclitaxel in recurrent ovarian carcinoma: Results of the INNOVATE pilot study. *Gynecol Oncol.* 2018;150(3):471-477.

doi: 10.1016/j.ygyno.2018.07.018

35. Lok E, San P, White V, *et al.* Tumor treating fields for ovarian carcinoma: A modeling study. *Adv Radiat Oncol.* 2021;6(4):100716.

doi: 10.1016/j.adro.2021.100716

36. Wu H, Yang L, Liu H, *et al.* Exploring the efficacy of tumor electric field therapy against glioblastoma: An *in vivo* and *in vitro* study. *CNS Neurosci Ther.* 2021;27(12):1587-1604.

doi: 10.1111/cns.13750

37. Wu H, Wang C, Liu J, *et al.* Evaluation of a tumor electric field treatment system in a rat model of glioma. *CNS Neurosci Ther.* 2020;26(11):1168-1177.

doi: 10.1111/cns.13441