



Review

Advances and Perspectives on Bioelectronic and Atomic Nanogenerators for Anticancer Therapy

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Abstract: Nowadays, due to improvements in living standards, more attention is reserved to all-around disease prevention and health care. In particular, research efforts have been made for developing novel methods and treatments for anti-cancer therapy. Self-powered nanogenerators have emerged in recent years as an attractive cost-effective technology to harvest energy or for biosensing applications. Bioelectronic nanogenerators can be used for inducing tissue recovery and for treating human illness through electrical stimulation. However, there is still a lack of comprehensive cognitive assessment of these devices and platforms, especially regarding which requirements must be satisfied and which working principles for energy transduction can be adopted effectively in the body. This review covers the most recent advances in bioelectronic nanogenerators for anti-cancer therapy, based on different transducing strategies (photodynamic therapy, drug delivery, electrical stimulation, atomic nanogenerators, etc.), and the potential mechanisms for tissue repair promotion are discussed. The prospective challenges are finally summarized with an indication of a future outlook.

Keywords: nanogenerators; anti-cancer therapy; tumor; piezoelectric; triboelectric; pyroelectric; atomic nanogenerators; bioelectronic



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1. Introduction

In recent years, cancers, tumors, and oncogenic diseases have increases in frequency and leading millions of people to death [1–3]. The main current treatments to contrast this burden consist either of a surgical resection or chemotherapy and radiotherapy. In the first case, the removal of cancerous tumors does not provide a permanent solution to the disease; in fact, they recur in 30–50% of cases [4]. In the case of chemo/radio-therapies, the treatments can inhibit the recurrence of cancerogenic conditions, facilitating the cancer regression [5,6], but they have various levels of effectiveness and their impact affects also non-cancerous dividing cells, implying a non-specifically spread toxicity. Novel treatments are thus urgently needed with higher efficiency and accuracy, fewer side effects and permanent effectiveness. Recently, new therapies have been proposed, including drug delivery through nanocarriers, gas therapy [7], electrical stimulation [8], nanozyme-based catalytic therapy [9], photodynamic therapy [10–12], sonodynamic therapy [13], etc. The common element of these treatments consists of delivering anti-cancer agents in a localised and specific manner. To this purpose, microdevices or nanodevices that can be manipulated and controlled accurately are increasingly needed: these can take the form of nanocarriers (nanoparticles, nanoparticles-embedded liposomes, etc.) or smart bioelectronic patches that can deliver anti-cancer drugs or electrical signals for actuating biochemical effects

against the propagation of cancers. All these strategies and unconventional therapeutic platforms need to be connected to a power source or ideally self-powered. Nanogenerators have emerged as a useful and effective technology for supplying electrical power to other systems: distributed networks of these devices harvesting energy provide a promising alternative that can complement standard power plants [14–17]. Invented in 2006 by Wang's group [18], they can convert energy from the available sources (i.e., mechanical, thermal, biochemical, etc.) into electrical energy [18,19], due to intrinsic properties of their constituent materials and at the microscale/nanoscale, against conventional bulky systems for energy generation [15,20–22], especially chemical batteries which need periodic recharging, are unsuitable for being installed in hostile places and have a limited lifetime [23–27]. They are mostly employed to scavenge energy from the environments and natural resources of clean energy [14,15,20,22,28–34], e.g., environmental vibrations, wind flows, water waves, ocean currents, impacts of rainfalls, human biomechanics (voluntary movements, heartbeat, breathing, blood circulation, etc.) but also for sensing human motion [35–37], monitoring physiological parameters [35,38–42], for supplying implantable biomedical devices [38,43,44] or wearable systems for robotics [45–47]. The recent advancements in electronics, i.e., miniaturization, multifunctionality, property-tunability, softness, flexibility, conformality, and design adaptability, have fueled the rapid and continuous development of different types of nanogenerators, with novel materials [16,48,49] and applications [35–39,50–56]. The most common nanogenerators developed over the years are based on the piezoelectric, pyroelectric, and triboelectric effects [15,48,57], which intrinsically lead to charge generation upon the application of a mechanical strain, deformation, stress, temperature change, or friction between two dissimilar materials [15,58,59]. These devices have gained attractive properties, e.g., light weight, flexibility, simplicity of designs, durability, and cost-effectiveness. Additionally, their biocompatibility has made them suitable for being implanted and powering devices for stimulation or drug delivery for many diseases, including cancers [60].

In the context of cancer treatment, the word “nanogenerator” also refers to another strategy to specifically target and wipe out cancer cells without any side effects. Atomic nanogenerators have been proposed by McDevitt et al. [61], consisting of single atoms of a radioactive isotope housed inside a molecular cage which is attached to a monoclonal antibody targeted to specific forms of cancer. After injecting these constructs into the body and internalising them into cancer cells, tumors may be shrunk without toxicity owing to the decaying activity of the radioactive isotope, which releases ultimately high-energy alpha particles that destroy cancer cells.

In this review, different types of nanogenerators (bioelectronic and atomic) used for anti-cancer therapy are described and classified. Section 2 provides an overview of the main unconventional strategies for cancer therapies, with a highlight on the working principles that are aimed at killing cancer cells and reducing the propagation/size of the tumor (Figure 1). Atomic nanogenerators are presented as a specific category of molecular-size carriers that generate energy in the form of particles to bombard and kill cancer cells. State-of-the-art bioelectronic nanogenerators and self-powered platforms are instead described in Section 3, with a focus on the targeted application and on the respective operation modes and materials. Finally, the applicative perspectives and future challenges are discussed, with the aim to suggest improvements in the design and implementation of next-generation nanogenerators for the treatment of cancers.

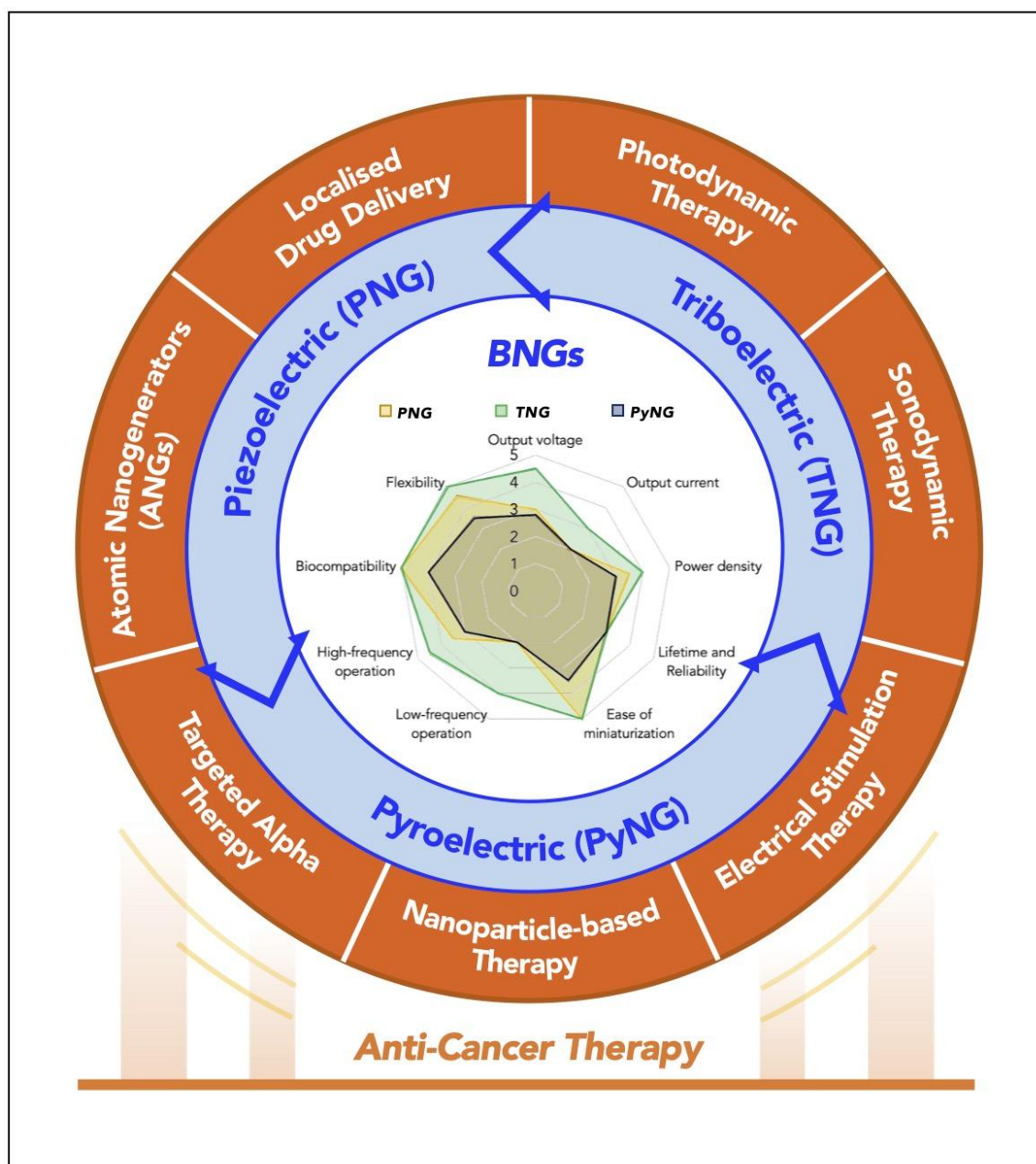


Figure 1. Illustrations of the unconventional strategies for anti-cancer therapy: localized drug delivery, photodynamic therapy, sonodynamic therapy, electrical stimulation therapy, nanoparticle-based therapy, targeted alpha therapy, and atomic nanogenerators. BNGs: Bioelectronic nanogenerators.

2. Unconventional Strategies for Anti-Cancer Therapy

2.1. Localised Drug Delivery (LDD)

Localized drug delivery (LDD) has emerged as an unconventional yet highly effective strategy for anti-cancer therapies, offering a means to enhance therapeutic efficacy while minimizing systemic side effects [62] (Figure 2). This approach involves the direct administration of therapeutic agents to the tumor site, ensuring higher concentrations of the drug at the target location and reducing exposure to healthy tissues. Traditional systemic therapies often lead to significant adverse effects due to the non-specific distribution of drugs throughout the body. In contrast, localized drug delivery systems (LDDS) aim to provide a more targeted treatment modality, improving patient outcomes and quality of life. One of the primary advantages of localized drug delivery is its ability to stabilize embedded drug molecules and preserve their anticancer activity [63]. By directly ad-

ministering drug-loaded implants or formulations at the tumor site, LDDS can achieve controlled and prolonged release of therapeutic agents. This sustained release ensures that adequate drug concentrations are maintained over time, allowing for effective diffusion into cancer cells as they divide. Various formulations have been developed for localized delivery, including hydrogels, nanoparticles, polymeric films, and wafers [64]. For instance, injectable hydrogels have gained popularity due to their ability to release drugs topically at the tumor site while minimizing systemic toxicity. These hydrogels can be engineered to respond to specific stimuli in the tumor microenvironment, such as pH or temperature changes, allowing for smart release mechanisms that further enhance therapeutic efficacy. Another significant aspect of localized drug delivery is its potential to load and release water-insoluble chemotherapeutics effectively. Many traditional chemotherapeutic agents suffer from poor solubility, limiting their effectiveness when administered systemically. However, by utilizing advanced delivery systems such as polymeric nanoparticles or liposomes, these drugs can be encapsulated and delivered directly to tumors [65]. This method not only improves the solubility of the drugs but also enhances their bioavailability at the target site. Brachytherapy exemplifies a successful application of localized drug delivery in cancer treatment [62,66]. This technique involves implanting radioactive seeds directly into or near a tumor, providing targeted radiation therapy while minimizing exposure to surrounding healthy tissues. Brachytherapy has shown efficacy in various cancers, including prostate and breast cancer, significantly reducing recurrence rates and improving patient survival outcomes. For example, studies have indicated that brachytherapy applied at surgical resection sites can decrease local recurrence rates in lung cancer patients from 19% to just 2%, demonstrating its effectiveness as a localized treatment option [67]. Recent advancements in LDDS technology have also focused on developing systems that allow for real-time monitoring and adjustment of drug release profiles [68]. These innovations include smart polymers that can alter their properties in response to environmental changes within the tumor microenvironment. Such systems enable clinicians to tailor treatment regimens based on individual patient needs, optimizing therapeutic outcomes. Despite its numerous advantages, localized drug delivery is not without challenges. One significant hurdle is ensuring adequate penetration of therapeutic agents into solid tumors, which often exhibit heterogeneous structures and varying degrees of vascularization [65,69]. Researchers are actively investigating methods to enhance drug diffusion within tumors, such as using combination therapies that incorporate mechanical or electrical stimulation alongside localized delivery systems. Moreover, regulatory approval processes for new LDDS technologies can be complex and time-consuming. Extensive preclinical and clinical trials are necessary to demonstrate safety and efficacy before these innovative treatments can be widely adopted in clinical practice. With ongoing advancements in formulation technologies and a deeper understanding of tumor biology, LDDS has the potential to revolutionize cancer treatment paradigms and improve patient outcomes significantly.

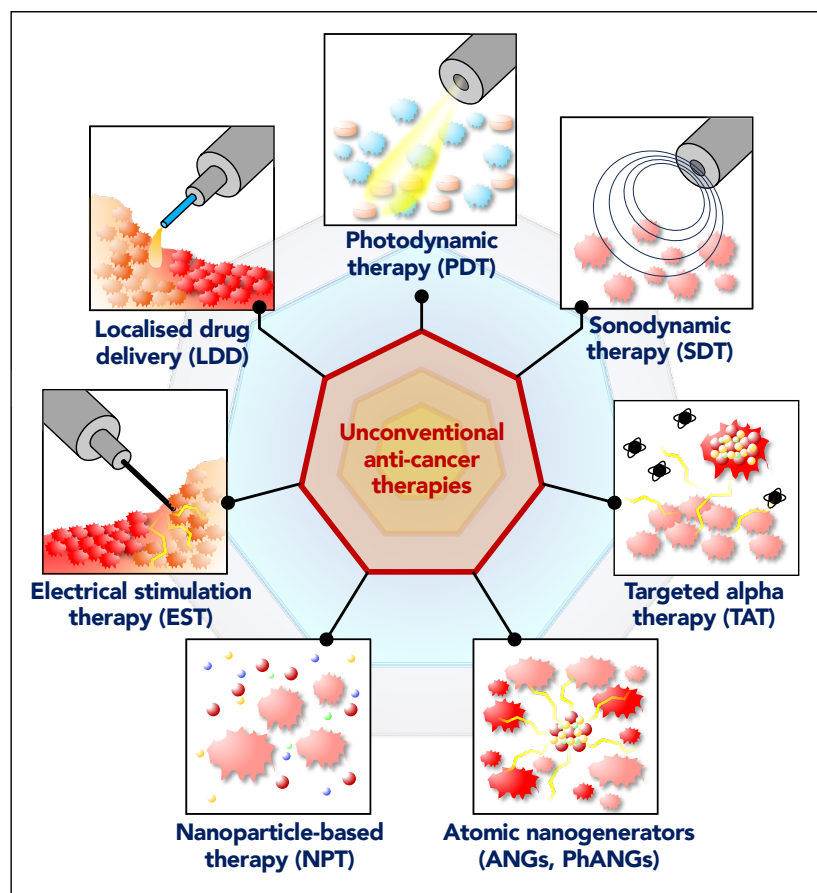


Figure 2. Illustration of the unconventional anti-cancer therapies treated in this manuscript: localized drug delivery (LDD), photodynamic therapy (PDT), sonodynamic therapy (SDT), targeted alpha therapy (TAT), electrical stimulation therapy (EST), nanoparticle-based therapy (NPT), atomic nanogenerators (ANGs, PhANGs). The insets result from assembly of clipart images to illustrate the main working principle.

2.2. Photodynamic Therapy (PDT)

To induce photodynamic therapy (PDT), optical illumination is used to activate selectively some light-sensitive anti-cancer drugs (photosensitizers, PSs) [12,70–73] (Figure 2). PDT is characterized by its minimally invasive nature and high precision, allowing for localized treatment that minimizes damage to surrounding healthy tissues.

The fundamental mechanism of PDT involves the administration of a PS that preferentially accumulates in cancer cells [74]. Upon exposure to specific wavelengths of light, typically from lasers or light-emitting diodes (LEDs), the activated photosensitizer generates reactive oxygen species (ROS), including singlet oxygen and free radicals. These ROSs play a crucial role in inducing cellular damage, leading to apoptosis or necrosis of cancer cells. The effectiveness of PDT is contingent upon several factors, including the type of PS used, the light source's wavelength and intensity, and the tumor's oxygenation status [75]. PSs can be classified into first, second, and third generations based on their chemical properties and mechanisms of action. First-generation PSs, such as hematoporphyrin derivatives, have been widely used but are limited by poor solubility and inadequate tumor targeting [76]. In contrast, second-generation PSs have improved pharmacokinetics and selectivity for tumor tissues. Recent advancements in third-generation PSs leverage nanotechnology to enhance delivery and activation efficiency by utilizing nanocarriers that improve solubility, stability, and targeting capabilities. One significant advantage of PDT is its ability to induce not only direct cytotoxic effects on tumor cells but also to disrupt

tumor vasculature. The generation of ROS can damage endothelial cells lining blood vessels within tumors, leading to thrombosis and reduced blood supply. This vascular disruption further contributes to tumor necrosis and enhances the overall therapeutic effect. Additionally, PDT has been shown to elicit an immune response against tumors [77,78]. The localized destruction of cancer cells can release tumor antigens into the surrounding tissue, stimulating an immune reaction that may help eliminate residual cancer cells even at distant sites.

Despite its advantages, PDT faces challenges that limit its clinical application. One major hurdle is the depth of light penetration in tissues; conventional light sources struggle to reach deeper tumors effectively [79]. Light delivery on the targeted cancerous area can be carried out through optical fibers or fiber-optic probes, similar to several other examples of implantable optical endoscopy probes for applications in optogenetics or laser therapy [80–84]. The main limitations for the long-term therapeutic applicability of this approach include the tight tethering, the risk of skin damage and the complexity of the operation [85]. To overcome these issues, novel miniaturized implantable devices have been proposed that can deliver light through integrated LEDs with spatial and temporal accuracy and, ideally, via wireless operation [86–88].

Furthermore, hypoxic conditions within tumors can significantly reduce the efficacy of PDT since oxygen is a critical component for ROS generation. Strategies to enhance oxygen delivery to tumors include using oxygen carriers such as perfluorocarbons or designing photosensitizers that can generate ROS under low-oxygen conditions. Clinical applications of PDT have expanded over the years. It has been approved for treating various cancers, including nonmelanoma skin cancer, oesophageal cancer, bladder cancer, and certain head and neck cancers. The versatility of PDT allows it to be used not only for curative purposes but also for palliative care to relieve symptoms associated with advanced cancers. Recent advancements in PDT research are focusing on integrating it with other treatment modalities, such as immunotherapy and targeted therapies. For instance, photoimmunotherapy combines PSs with immune checkpoint inhibitors or monoclonal antibodies to enhance anti-tumor immunity while leveraging the cytotoxic effects of PDT. In conclusion, PDT represents a significant advancement in cancer treatment strategies by offering a targeted approach that minimizes systemic toxicity while maximizing therapeutic efficacy. With ongoing research aimed at overcoming current limitations and improving treatment protocols through innovative technologies and combination therapies, PDT holds great promise as a vital tool in modern oncology.

2.3. Sonodynamic Therapy (SDT)

Sonodynamic therapy (SDT) is a cancer treatment based on low-intensity ultrasounds that are locally amplified by sono-sensitizers [89–91] (Figure 2). The propagation of ultrasounds is very efficient and compatible with biological tissue due to its non-radiative properties. Additionally, ultrasounds transfer energy *in vivo* independently from the environment [92–96].

This non-invasive approach offers significant advantages over traditional cancer therapies, particularly in its ability to penetrate deep tissues while minimizing systemic toxicity. The fundamental principle of SDT involves the administration of a sonosensitizing agent, which is a non-toxic chemical that becomes activated upon exposure to low-intensity ultrasound. When ultrasound waves are applied to the sensitized tissue, they generate reactive oxygen species (ROS) through various mechanisms, including cavitation, thermal effects, and mechanical stress. These ROSs are crucial for inducing cytotoxic effects within cancer cells, leading to apoptosis or necrosis.

Ultrasonic waves are usually delivered non-invasively using an ultrasound transducer placed on the skin or inserted endoscopically for deeper tumors. A coupling medium like ultrasound gel ensures efficient transmission. SDT typically uses low-intensity ultrasound in the 20 kHz-to-3 MHz range, depending on penetration depth and cavitation effects. Lower frequencies (20–500 kHz) enable deeper penetration and stronger cavitation, while higher frequencies (500 kHz–3 MHz) provide more localized effects. Frequencies around 0.5–1 MHz are commonly used to balance penetration and therapeutic efficiency in activating sonosensitizers for cancer treatment.

One of the key benefits of SDT is its capacity for deep tissue penetration, which allows it to target tumors that are otherwise difficult to reach with other therapies such as PDT. While PDT relies on light activation that can be limited by tissue opacity, ultrasound can effectively penetrate several centimeters into biological tissues, making SDT particularly suitable for treating solid tumors located deeper within the body. This characteristic not only enhances the therapeutic efficacy but also broadens the range of cancers that can be treated using this technique. The mechanisms by which SDT induces cancer cell death are multifaceted. One primary mechanism is the cavitation effect, where the rapid formation and collapse of microbubbles in response to ultrasound create shock waves and shear forces that disrupt cellular structures [90,97]. This mechanical damage can compromise cell membranes and organelles, leading to cell death. Additionally, the energy released from cavitating bubbles can facilitate the production of ROS, which further exacerbates cellular damage by oxidizing critical biomolecules such as lipids, proteins, and DNA [98]. Recent advancements in nanotechnology have significantly enhanced the effectiveness of SDT. Nanoparticles are being developed as sonosensitizers or carriers for existing sensitizers, improving their solubility, stability, and targeting capabilities [99–101]. For example, mesoporous silica nanoparticles can be loaded with chemotherapeutic agents alongside sonosensitizers, allowing for a dual-action approach where both drug delivery and sonodynamic effects occur simultaneously [102]. This combination not only increases the precision of treatment but also enhances overall therapeutic outcomes. Moreover, studies have indicated that SDT can elicit an immune response against tumors. The localized destruction of cancer cells releases tumor antigens into surrounding tissues, potentially stimulating systemic anti-tumor immunity. This phenomenon has been referred to as the “abscopal effect”, where treatment at a primary tumor site leads to the regression of distant metastases [103]. This aspect of SDT is particularly promising as it suggests that this therapy could not only target primary tumors but also help in controlling metastatic disease.

Several challenges remain in optimizing SDT for clinical use. One major hurdle is the need for effective sonosensitizers that can achieve high specificity and efficacy within tumor environments. Additionally, understanding the precise mechanisms by which ultrasound activates these sensitizers is crucial for maximizing therapeutic efficacy and minimizing side effects. Ongoing research aims to elucidate these mechanisms while developing new formulations and delivery systems that enhance the performance of SDT. In conclusion, sonodynamic therapy represents a cutting-edge strategy in cancer treatment that leverages ultrasound and sonosensitizers to induce targeted cell death with minimal side effects. Its ability to penetrate deep tissues and activate therapeutic agents selectively positions it as a valuable addition to existing cancer treatment modalities. As research continues to advance in this field, SDT holds great promise for improving patient outcomes and expanding treatment options for various malignancies.

2.4. Electrical Stimulation Therapy (EST)

Electrical stimulation represents a recent approach for numerous applications in the field of minimally invasive therapeutic devices. Electrical impulses are, in fact, the con-

stituents of cognitive and skeletal functions for human beings and all animals [104,105]. Together with natural electrical impulses, the application of external impulses can be harnessed to address several medical disorders. Extracellular excitation (applied through electrodes) can generate or inhibit neural signals [106], or they can contribute to enhancing tissue regeneration processes for treatments of bone fractures [107–109], muscular dystrophy [110,111], hair loss [112–115], bladder control dysfunction [116–121], or skin wounds [122–126]. Bioelectronic nanogenerators or electronic skins are the most widely adopted devices for delivering electrical stimulation therapy (EST) for regenerative medicine applications [40–49], whereas neural dust platforms are generally used for other conditions, where peripheral nerves are considered [50–58]. The most recent devices for EST consist of electrodes patterned onto flexible or stretchable substrates, and they can be coupled with other functionalities, e.g., for aiding the delivery of drugs or of light with specific wavelengths.

In the context of anti-cancer therapy, EST has emerged as a promising approach, leveraging the application of electric fields to induce cell death in cancerous tissues (Figure 2). This method capitalizes on the unique responses of cancer cells to electrical inputs, which can disrupt cellular functions, promote apoptosis, and enhance the efficacy of conventional treatments.

One of the primary mechanisms through which electrical stimulation induces cancer cell death is by triggering apoptosis, a programmed cell death pathway that is often dysregulated in cancer cells. Recent studies have demonstrated that applying alternating current (AC) electric fields can activate bio-nanoantennae—nanostructures designed to facilitate electron transfer within cells. These bio-nanoantennae are typically created using conductive or semiconductive nanomaterials, such as gold, silver, carbon-based nanostructures, or piezoelectric nanocrystals, which can efficiently respond to external electric fields. They are often synthesized through chemical vapor deposition, electrodeposition, or self-assembly techniques to achieve optimal shape and conductivity. Once fabricated, these nanostructures are delivered to tumor sites via targeted nanoparticle carriers, functionalized with ligands or antibodies that ensure selective accumulation in cancerous tissues. Upon exposure to AC electric fields, the bio-nanoantennae enhance localized electron transfer, potentially modulating redox reactions, generating ROS, or interfering with cellular signaling pathways, ultimately contributing to cancer cell inhibition or death.

For instance, when redox mediators such as zinc porphyrin are used in conjunction with electrical stimulation, they can regulate electron transport and induce quantum biological tunneling, effectively triggering apoptosis in patient-derived cancer cells like glioblastoma (GBM) [127,128]. The application of a resonant electrical input has been shown to enhance mitochondrial activity and facilitate the release of cytochrome c, a key player in the apoptotic cascade. This process results in increased caspase activity, which is indicative of apoptosis, thereby selectively targeting and killing cancer cells while sparing normal tissues [129].

Electrical stimulation has also been found to significantly suppress the energy metabolism of cancer cells, leading to rapid cell death. By inducing changes in mitochondrial function and disrupting the electron transport chain (ETC), ES creates an energy crisis within cancer cells. This phenomenon has been described as a “domino effect”, where the initial electrical input leads to mitochondrial dysfunction and subsequent depletion of ATP levels [130]. Studies indicate that this disruption impedes critical metabolic pathways, resulting in cellular stress and eventual apoptosis or necrosis. The Young’s modulus of cancer cell membranes decreases due to cytoskeletal damage caused by electrical stimulation, further contributing to cell death by compromising membrane integrity [131].

Electroporation is another critical mechanism through which electrical stimulation induces cell death [132]. This process involves applying short bursts of high-voltage electric fields to create temporary pores in the cell membrane, allowing for increased permeability. In the context of cancer treatment, electroporation can facilitate the uptake of therapeutic agents or induce direct cell death by compromising cellular homeostasis.

Pulse streams, used in high-frequency irreversible electroporation (H-FIRE), improve tissue penetration while minimizing side effects. In contrast, AC electric fields, such as Tumor-Treating Fields (TTFields), are applied continuously at 100–500 kHz with low intensity (1–3 V/cm), disrupting cancer cell division without causing membrane poration, making them a non-invasive alternative to electroporation-based treatments. Nanosecond-pulsed electric fields (nsPEFs) extend this concept by generating numerous nanopores across all cellular membranes—a phenomenon known as supra-electroporation. This unique characteristic allows nsPEFs to induce significant cytotoxic effects across various tumor types by creating large numbers of pores that disrupt both plasma and intracellular membranes [133,134]. The rapid formation and subsequent collapse of these pores can lead to apoptosis or necrosis depending on the intensity and duration of the electric field applied [135].

In addition to direct effects on cancer cells, electrical stimulation can modulate the immune response against tumors. High-frequency electrical stimulation has been shown to enhance immune activity by promoting cytokine release and increasing the infiltration of immune cells into tumor sites. This dual action not only attacks cancer cells directly but also recruits the body's immune system to recognize and eliminate tumor cells more effectively. For example, studies have demonstrated that combining electrical stimulation with immunotherapeutic agents can reduce tumor sizes in immune-competent mouse models while having minimal effects in immune-deficient models [136]. This suggests that ES may enhance the effectiveness of immunotherapies by improving drug delivery through electroporation or by stimulating an endogenous immune response.

The application of electrical stimulation for inducing cancer cell death holds significant promise for clinical translation. Several devices have been developed that utilize these principles, including bioelectronic nanogenerators that provide continuous bioelectrical stimulation at tumor sites. These devices can be designed for minimally invasive implantation and can operate autonomously without external power sources, making them suitable for long-term treatment regimens. Moreover, combining electrical stimulation with existing therapies such as chemotherapy or radiotherapy may enhance overall treatment efficacy while reducing side effects associated with systemic drug delivery. For instance, studies have indicated that applying electrical fields during chemotherapy can increase drug uptake in tumor cells while simultaneously inducing stress responses that sensitize them to treatment [137,138].

2.5. Nanoparticle-Based Therapy (NPT)

Nanoparticle-based therapy (NPT) has emerged as a revolutionary approach in the fight against cancer, offering innovative solutions that address the limitations of traditional treatment modalities such as chemotherapy, radiation, and surgery (Figure 2). The unique properties of nanoparticles (NPs)—including their size, surface area, and ability to be engineered for specific functions—enable them to enhance drug delivery, improve therapeutic efficacy, and reduce side effects [139–143].

Nanoparticles can be designed to deliver therapeutic agents directly to cancer cells with high specificity. The mechanisms of action primarily rely on two targeting strategies: passive targeting and active targeting [144]. Passive targeting exploits the enhanced permeability and retention (EPR) effect, which is a phenomenon observed in tumors due to their

abnormal vasculature and poor lymphatic drainage [145,146]. This allows nanoparticles to accumulate preferentially in tumor tissues when administered systemically. The size of the nanoparticles plays a crucial role in this process; typically, particles ranging from 10 to 100 nanometers are optimal for effective accumulation in tumors. Active targeting, on the other hand, involves modifying the surface of nanoparticles with ligands that specifically bind to receptors overexpressed on cancer cells [147,148]. These ligands can include antibodies, peptides, or small molecules such as folic acid or transferrin. By functionalizing nanoparticles with these targeting moieties, researchers can enhance the selectivity of drug delivery systems, ensuring that therapeutic agents are released primarily at tumor sites while minimizing exposure to healthy tissues. Once the NPs reach the tumor microenvironment, they can release their payload through various mechanisms. For instance, stimuli-responsive nanoparticles can be engineered to release drugs in response to specific environmental cues such as pH changes, temperature fluctuations, or enzymatic activity prevalent in tumors. This controlled release enhances therapeutic efficacy while reducing systemic toxicity.

The use of NPT offers several significant advantages over conventional cancer treatments [149,150]. First, it provides improved pharmacokinetics: NPs can enhance the solubility and stability of poorly soluble drugs, improving their bioavailability and pharmacokinetics. This is particularly beneficial for hydrophobic chemotherapeutic agents that often face challenges in achieving therapeutic concentrations in plasma. Second, they help reduce side effects, in fact, by delivering drugs specifically to cancer cells, nanoparticle-based therapies can significantly reduce side effects associated with systemic chemotherapy. Traditional chemotherapy often affects rapidly dividing healthy cells, leading to adverse effects such as nausea, hair loss, and immunosuppression. Targeted delivery minimizes these effects by sparing normal tissues. Third, many cancers develop resistance to conventional therapies through various mechanisms such as drug efflux pumps or altered apoptotic pathways. Nanoparticles can be designed to circumvent these resistance mechanisms by co-delivering multiple therapeutic agents or using combination therapies that target different pathways simultaneously. Fourth, NPs can be engineered for various applications beyond drug delivery. They can be used for imaging purposes (theranostics), combining diagnostic and therapeutic functions within a single platform. This capability allows for real-time monitoring of treatment responses and tumor progression. Fifth, NPs have shown promise in enhancing immunotherapy by delivering immune-modulating agents directly to tumors or by acting as adjuvants that stimulate immune responses against cancer cells. By improving antigen presentation and T-cell activation, nanoparticle-based therapies can potentially increase the effectiveness of existing immunotherapies [151]. Furthermore, numerous studies have demonstrated the efficacy of NP formulations for delivering traditional chemotherapeutic agents such as doxorubicin and paclitaxel. For example, liposomal formulations of doxorubicin (Doxil) have been approved for treating breast cancer and Kaposi's sarcoma due to their improved pharmacokinetics and reduced cardiotoxicity compared to free doxorubicin [152,153].

NPs are also employed in gene therapy applications where they serve as carriers for nucleic acids such as DNA or RNA. These carriers facilitate the delivery of therapeutic genes or RNA interference molecules directly into cancer cells, enabling targeted genetic modifications that can inhibit tumor growth [154–156].

Additionally, NPs can be used in conjunction with radiation therapy to enhance its effectiveness. For instance, gold nanoparticles have been shown to increase localized radiation dose deposition due to their high atomic number, resulting in improved tumor control while sparing surrounding healthy tissues [157–160]. Beyond their high-Z properties, AuNPs also possess a high surface area-to-volume ratio, leading to an enhanced density of

free electrons at the nanoparticle interface. This contributes to increased secondary electron emission upon radiation exposure, amplifying localized energy deposition and DNA damage in cancer cells. While this effect is primarily due to physical dose enhancement, AuNPs also exhibit plasmonic properties, i.e., their conduction electrons collectively oscillate when exposed to specific electromagnetic fields, such as visible or near-infrared light. However, in the context of radiation therapy, plasmonic resonance plays a minor role compared to direct dose enhancement via secondary electron generation.

Besides regulatory hurdles, there are three main challenges for the extensive implementation of NPs in anti-cancer therapies. First, producing NPs at scale while maintaining consistent quality is a significant challenge. Standardized manufacturing processes need to be developed to ensure reproducibility and reliability across batches. Secondly, while many nanoparticles are designed with biocompatible materials, concerns regarding long-term toxicity and biodistribution remain. Comprehensive studies are essential to evaluate the safety profiles of these formulations over extended periods. Finally, the heterogeneous nature of tumors poses challenges for effective targeting using nanoparticles. Variability in receptor expression among different tumor cells may limit the effectiveness of targeted therapies; thus, strategies must be developed to account for this heterogeneity.

2.6. Targeted Alpha Therapy (TAT) and Atomic Nanogenerators (ANGs)

Targeted alpha therapy (TAT) is an innovative cancer treatment modality that utilizes the unique properties of alpha-emitting radionuclides, such as actinium-225 (^{225}Ac), thorium-227 (^{227}Th), and radium-223 (^{223}Ra), to deliver localized cytotoxic effects directly to tumor cells (Figure 2). The fundamental principle behind atomic nanogenerators (ANGs) is their ability to emit high-energy alpha particles that have a short range in biological tissues, typically around 40 to 100 micrometers [61,161,162]. This limited range allows for the effective destruction of malignant cells while sparing surrounding healthy tissue, thereby minimizing systemic toxicity, a significant advantage over conventional radiation therapies.

The mechanism of action for ANGs involves the decay of radioactive isotopes, which emit alpha particles that cause direct damage to the DNA of cancer cells [163,164]. Alpha particles are highly ionizing and can create dense clusters of ionization events along their path, leading to substantial damage to cellular structures. This damage can lead to cell death through various pathways, including apoptosis and necrosis. The high linear energy transfer (LET) associated with alpha particles (approximately $80\text{ keV}/\mu\text{m}$) results in a potent cytotoxic effect, making these radionuclides particularly effective against highly proliferative tumor cells. Research has shown that even minimal amounts of these radionuclides can achieve significant therapeutic outcomes, as they can kill cancer cells at very low activity levels, often measured in becquerels or picocuries [165,166].

One of the most compelling aspects of ANGs is their ability to be engineered for targeted delivery. By conjugating these radionuclides with monoclonal antibodies or peptides that specifically bind to tumor-associated antigens, researchers can enhance the selectivity of the treatment. This targeted approach ensures that the radioactive payload is delivered precisely to the tumor site, maximizing therapeutic efficacy while reducing off-target effects. For example, the use of ^{225}Ac -labeled prostate-specific membrane antigen (PSMA) ligands has shown promising results in treating metastatic castration-resistant prostate cancer (mCRPC) [167,168]. Clinical studies have demonstrated impressive treatment responses in patients who had previously undergone extensive therapies, highlighting TAT as a salvage treatment option. In addition to antibody conjugation, NPs have been developed as carriers for radionuclides. These NPs can encapsulate alpha-emitting isotopes and facilitate their delivery directly to tumor cells. For instance, gold nanoparticles have been explored as carriers for ^{225}Ac due to their biocompatibility and ability to enhance

radiation effects through the photoelectric effect [169–171]. The combination of localized radiation from alpha emissions and enhanced absorption characteristics leads to improved therapeutic outcomes.

Moreover, ANGs can be combined with other therapeutic modalities to enhance their effectiveness further. For instance, integrating TAT with immunotherapy or chemotherapy could create a synergistic effect that improves overall treatment outcomes [172–174]. The localized destruction of tumor cells by alpha particles can release tumor antigens into the microenvironment, potentially stimulating an immune response that targets residual cancer cells. This dual approach not only addresses the primary tumor but also helps manage metastatic disease. Recent studies have shown that combining TAT with immune checkpoint inhibitors can lead to enhanced anti-tumor immunity. For example, when ^{225}Ac -labeled antibodies are used alongside PD-1 inhibitors, there is an observed increase in T-cell activation and proliferation within the tumor microenvironment [175]. This not only enhances direct cytotoxic effects on cancer cells but also promotes systemic immune responses against distant metastases.

Clinical applications of ANGs have expanded over the years. They have been approved for treating various cancers, including non-Hodgkin lymphoma, prostate cancer, and certain types of neuroendocrine tumors. The versatility of TAT allows it to be used not only for curative purposes but also for palliative care to relieve symptoms associated with advanced cancers. For instance, ^{223}Ra has been approved for treating bone metastases in prostate cancer patients. Clinical trials have demonstrated that patients receiving ^{223}Ra experience significant reductions in pain and improved quality of life compared to those receiving standard care alone [176–178]. Similarly, ^{225}Ac -PSMA therapy has shown remarkable efficacy in mCRPC patients with previously limited treatment options.

Despite their advantages, several challenges remain in the clinical application of ANGs. One significant hurdle is the limited availability and production of certain alpha-emitting radionuclides. The production process for isotopes like ^{225}Ac is complex and often requires specialized facilities such as nuclear reactors or particle accelerators. Additionally, there are concerns regarding radiation safety and the management of radioactive waste associated with these therapies. Ongoing research is focused on optimizing production methods and developing new isotopes with favorable decay characteristics and availability. For example, researchers are exploring alternative production routes for ^{225}Ac using neutron capture reactions or accelerator-based methods that may offer more sustainable production options [179]. Furthermore, understanding patient-specific factors that influence treatment responses is crucial for improving outcomes with atomic nanogenerators. Genetic mutations and variations in DNA repair mechanisms can affect how tumors respond to radiation therapy. Identifying biomarkers that predict sensitivity or resistance to TAT could help tailor treatments to individual patients, enhancing efficacy and minimizing adverse effects. Current research efforts are oriented towards addressing radionuclide availability and patient stratification.

2.7. Photoactivatable Atomic Nanogenerators (PhANGs)

Besides ANGs of alpha particles, other types of nanogenerators can be adopted in anti-cancer therapy to produce reactive species. The common nonmetal reactive species are based on oxygen, nitrogen, carbon, and sulfur, and they include a collective term of non-radical molecular forms (hydrogen peroxide (H_2O_2), CO, etc.) and radicals, i.e., atoms, ions, or molecules that contain unpaired electrons in the outermost electron orbitals, such as alkyl radical [180], nitric oxide ($\bullet\text{NO}$) [181], peroxyxynitriteanion (ONOO^-) [182], hydroxylradical ($\bullet\text{OH}$) [183], chlorine radical ($\bullet\text{Cl}$) [184], and superoxide radical anion ($\text{O}\bullet^{2-}$) [185].

Cancer cells exhibit elevated levels of reactive species, and, to maintain redox balance, they must produce higher amounts of endogenous antioxidants. This flexible ability to alter redox status can diminish the effectiveness of chemotherapy and radiotherapy against malignant tumor cells. Interestingly, some experimental findings indicate that reactive species may have a preferential inhibitory effect on cancer cells compared to normal cells due to the direct suppression of endogenous antioxidants by reactive species within cancer cells. Despite the inherent advantages of reactive species-based nanomedicine, therapies utilizing these species face several limitations [186]: (1) their dependence on oxygen restricts therapeutic efficacy in hypoxic tumors; (2) the short absorption wavelengths of photoactivatable nanogenerators hinder their ability to target deep-seated tumors; and (3) undesirable side effects resulting from the nonspecific distribution of nanogenerators continue to pose challenges. In light of these issues, researchers are focusing on designing and developing theranostic platforms that integrate reactive species-based monotherapy with synergistic therapies involving other treatment strategies. The generation of reactive species in cells can arise from internal stimuli (specific metabolic processes or pathological conditions) or external stimuli (physicochemical or biochemical reactions initiated by reactive species generators). Light-activated reactive species generators (or photoactivatable atomic nanogenerators, PhANGs) are promising therapeutic candidates due to their noninvasive nature and the ability to control their activity in a spatiotemporal manner for biomedical applications (Figure 2).

In the context of reactive species containing oxygen, PhANGs are often combined with PDT, offering two types of mechanisms [186]. The oxygen-dependent type-II PDT can transfer the photon energy to the PhANGs by exciting them from the ground state to the singlet state and to the triplet state, which eventually transfers the energy to the molecular oxygen for generating singlet oxygen. In contrast, the oxygen-independent type I PDT can generate superoxide radical anions and hydrogen peroxide without the involvement of molecular oxygen. Both types of PDT can induce both apoptotic and necrotic death of the tumor cells.

As an example, Liu et al. [187] developed an oxygen-independent radical nanogenerator, PI/FBC, through the co-assembly of iodized polymer PI and near-infrared (NIR) photosensitizer FBC. This system has been further evaluated as a remotely controllable platform for generating free radicals to enhance antitumor efficacy. The PI/FBC radical nanogenerator can be activated by NIR light to produce ROS by transferring energy to oxygen while also inducing the formation of toxic iodine radicals through electron transfer to PI. Importantly, this radical nanogenerator is controllable and unaffected by oxygen concentration, distinguishing it from traditional tumor treatments. Additionally, due to the strong NIR emission from FBC, the distribution of the PI/FBC radical nanogenerator can be monitored without the need for additional imaging agents.

Zheng et al. [186] proposed a comprehensive review of PhANGs and, more specifically, different examples of organic and inorganic photosensitizers for PDT.

Reactive nitrogen species (RNS), particularly nitric oxide ($\bullet\text{NO}$) and its various metabolites, such as peroxynitrite anion (ONOO^-), have also emerged as critical players in cancer therapy. As a vital biological regulatory molecule, $\bullet\text{NO}$ is involved in numerous physiological and pathological processes, making it closely related to the development and progression of various diseases, including cancer. Similar to ROS, $\bullet\text{NO}$ exhibits a concentration-dependent behavior that can be both beneficial and detrimental. For example, at concentrations below $0.2\ \mu\text{mol}$, $\bullet\text{NO}$ can promote angiogenesis within solid tumors, facilitating their growth [186]. Conversely, at concentrations exceeding $1\ \mu\text{mol}$, $\bullet\text{NO}$ can exert toxic effects on cells, leading to cell death and tumor regression when maintained at therapeutic levels. The antitumor mechanisms of $\bullet\text{NO}$ are multifaceted. It influences

the energy metabolism of cancer cells, which can result in tumor suppression. Additionally, $\bullet\text{NO}$ can react with reactive oxygen radicals, generating nitrogen/oxygen-based free radicals that damage DNA structures. This damage is critical for inducing apoptosis in cancer cells. Furthermore, $\bullet\text{NO}$ promotes macrophage activation to enhance the immune response against tumors and inhibits metastasis by downregulating platelet aggregation. It also plays a role in activating tumor suppressor genes like p53, which further contributes to cancer cell apoptosis and reduces the expression of P-glycoprotein (P-gp), a protein often associated with drug resistance. As a primary source of RNS in biological systems, $\bullet\text{NO}$ possesses high reactivity in the presence of other radicals and can oxidize or nitrate local biomolecules. This characteristic allows for precise anti-cancer therapy through controlled release mechanisms at tumor sites. However, the creation of a precisely controllable NO generation system suitable for clinical use has proven challenging. Guo et al. [188] presented intelligent near-infrared (NIR) laser-triggered NO nanogenerators designed for the treatment of multidrug-resistant (MDR) cancer. These nanogenerators are created by integrating photothermal agents and heat-sensitive NO donors into a single nanoparticle. They can absorb 808 nm NIR photons and convert them into sufficient heat to trigger the release of NO. The produced NO molecules effectively reverse multidrug resistance by inhibiting the expression of P-glycoprotein, leading to increased intracellular accumulation of doxorubicin and heightened toxicity to MDR cancer cells in vitro. Additionally, through surface modification with targeting ligands, these nanoparticles selectively accumulate in tumor tissue. The therapeutic efficacy of the nanogenerators is confirmed in a humanized MDR cancer model, where in vivo experiments demonstrate their excellent tumor suppression capabilities with minimal side effects upon NIR laser exposure.

Various other strategies have been developed for the delivery of $\bullet\text{NO}$, including bonding methods such as R-O-NO, R-S-NO, R-N-NO (where R represents an alkyl group), and metal-NO complexes. These bonding strategies enable light-activated nanotherapeutic platforms to achieve controlled $\bullet\text{NO}$ release through external light irradiation. The application of $\bullet\text{NO}$ as monotherapy is relatively uncommon due to its concentration-dependent therapeutic effects. However, combination therapies involving $\bullet\text{NO}$ have been extensively researched. Current studies on $\bullet\text{NO}$ -based treatments primarily focus on four key pathways: (i) inducing cytotoxicity at high concentrations, (ii) chemotherapy sensitizer, (iii) radiotherapy sensitizer, and (iv) phototherapy sensitizer. The growing body of research on the integration of $\bullet\text{NO}$ therapy with other treatment modalities underscores the importance of exploring innovative cancer treatment methods. For instance, Chen et al. [189] developed a tumor-specific nanogenerator for peroxynitrite (ONOO^-) by encapsulating cisplatin and sodium nitroprusside within poly(D,L-lactide-co-glycolide) polymersomes to enhance drug delivery and improve chemotherapy outcomes. Following a series of catalysis involving nicotinamide adenine dinucleotide phosphate oxidases and glutathione reduction, this nanogenerator, referred to as PMCS, can selectively generate ONOO^- within the tumor environment. The produced ONOO^- not only significantly increases vascular permeability but also enhances the accumulation and penetration of PMCS into the tumor by activating matrix metalloproteinases that degrade the extracellular matrix. In addition to endocytosis, PMCS releases cisplatin to trigger apoptosis in tumor cells. Furthermore, free cisplatin released from dead cells can rapidly affect neighboring tumor cells through the ONOO^- -mediated upregulation of the copper transporter, thereby further enhancing the efficacy of chemotherapy.

Carbon-containing reactive species (RCS), particularly carbon monoxide (CO) and various alkyl radicals, have garnered significant attention for their potential as ANGs in anti-cancer therapy. CO, a notable carbon-centric derivative, exhibits unique properties that make it an intriguing candidate for therapeutic applications. It is well-established

that CO has a binding affinity for hemoglobin (Hb) that is 220 times greater than that of oxygen, which can disrupt the oxygen-carrying capacity of Hb in the bloodstream and lead to poisoning effects. Beyond its toxicological implications, CO also plays a role as an endogenous signaling molecule with diverse biomedical functions, including regulating blood pressure, reducing inflammation, and sensitizing tumor cells to chemotherapy while impairing mitochondrial respiration. Due to these multifaceted roles, the investigation of CO as a therapeutic agent has gained considerable momentum. However, to mitigate the inherent toxicity associated with CO, it is crucial to develop strategies for its targeted delivery to tumor sites, ensuring controlled release upon demand. Various nanocarriers have been engineered to support CO donors, such as Ru carbonyl, Fe carbonyl, and Mn carbonyl, enabling effective transport and release of CO specifically at the tumor location. For instance, Zhang et al. [190] utilized gold nanocages (AuNCs) as PhANG to encapsulate the CO donor iron pentacarbonyl ($\text{Fe}(\text{CO})_5$) under anaerobic conditions to prevent premature leakage and oxidation during circulation. Under 808 nm laser irradiation, the AuNCs converted light into heat energy, facilitating the decomposition of $\text{Fe}(\text{CO})_5$ into CO and iron. The released CO subsequently interfered with mitochondrial respiration, induced autophagy in cancer cells, and damaged lysosomes. Additionally, the iron produced from this reaction underwent a Fenton reaction in the acidic environment of lysosomes, generating cytotoxic hydroxyl radicals that further enhanced anti-cancer efficacy. Beyond its direct effects on mitochondrial function and tumor growth inhibition, CO can also enhance the efficacy of chemotherapy. Small molecule chemosensitizers are often employed to increase tumor cell sensitivity to chemotherapeutic agents. Research indicates that CO can act as a chemosensitizer while also exhibiting anti-inflammatory properties. For example, Zhang et al. [191] developed a multifunctional CO nanogenerator based on partially oxidized tin disulfide nanosheets (POS NSs), which were modified by targeting ligand-functionalized polymers to improve tumor specificity. The POS NSs effectively loaded doxorubicin (DOX), allowing for the generation of CO upon 561 nm laser irradiation through catalyzing CO_2 . This process not only sensitized tumor cells to DOX treatment but also induced hyperthermia upon laser exposure for photothermal ablation of tumors. The resultant CO release reduced inflammatory responses associated with photothermal therapy (PTT), demonstrating the potential of CO in enhancing therapeutic outcomes. Similarly, Shen et al. developed MCM@PEG-CO-DOX nanoparticles by oxidizing ferrocene compounds to create carbonized magnetic nanoparticles (MC), which were then modified with iron-based metal-organic frameworks (MOFs) to serve as carriers for both the CO donor $\text{Mn}(\text{CO})_5\text{Br}$ and DOX. Upon 808 nm laser irradiation, these nanoparticles produced photothermal effects that triggered the release of both $\bullet\text{NO}$ and DOX. The combination of these therapies elicited significant tumor suppression effects due to their synergistic action. Moreover, recent studies have shown that CO can enhance oxygen consumption in mitochondria, creating a hypoxic environment conducive to activating hypoxia-activated prodrugs. For instance, Li et al. [192] developed a theranostic nanoplatfrom using mesoporous Prussian blue nanoparticles (m-PB NPs) as carriers for tirapazamine (TPZ) and iron pentacarbonyl ($\text{Fe}(\text{CO})_5$). By modifying these nanoparticles with polyallylamine hydrochloride and polyacrylic acid to prolong blood circulation time and promote accumulation at tumor sites, they demonstrated that NIR light irradiation induced cleavage of coordination bonds in $\text{Fe}(\text{CO})_5$, releasing CO. The subsequent increase in aerobic respiration led to enhanced activation of TPZ within hypoxic tumor cells, resulting in improved antitumor efficacy. Furthermore, studies have indicated that multidrug resistance (MDR), often mediated by P-glycoprotein (P-gp)-dependent drug efflux mechanisms in cancer cells, poses significant challenges to chemotherapy efficacy. Various strategies have been proposed to overcome P-gp-mediated drug resistance. However, recent research has revealed that CO can effectively

reverse this resistance by disrupting mitochondrial function and inhibiting ATP-dependent drug efflux mechanisms. In addition to enhancing chemotherapy effectiveness, CO has also been explored for optimizing PDT against hypoxic tumors. Wang et al. [193] synthesized a nano-photosensitizer based on the diketopyrrolopyrrole nucleus (DPP-NF), incorporating a light-responsive •NO donor and pH-sensitive groups into its structure. The DPP-NF nanoparticles could be activated under weakly acidic lysosomal conditions to generate reactive oxygen species for PDT while enabling photothermal conversion under laser irradiation. Upon exposure to 660 nm light, released •NO was able to induce DNA damage in tumor cells while overcoming the low efficiency of PDT in hypoxic environments. In conclusion, carbon-containing reactive species like carbon monoxide offer promising avenues for cancer treatment through their unique mechanisms of action and ability to synergize with existing therapies. By leveraging advanced nanotechnology platforms designed for controlled release and targeted delivery of CO, researchers aim to optimize therapeutic outcomes while minimizing side effects associated with traditional cancer treatments.

3. Bioelectronic Nanogenerators for Anti-Cancer Therapy

3.1. Bioelectronic Nanogenerators (BNGs): Materials and Mechanisms

Bioelectronic nanogenerators for implantable use against cancer are generally based on patches made of functional materials. Most commonly, these materials include insulators/dielectrics, conductive layers/electrodes, and/or electromechanically active materials, such as piezoelectrics. Piezoelectricity and triboelectricity are the most widely adopted mechanisms to generate charges, thus electrical energy, which can be directly used for electrical stimulation or for supplying other connected devices. In this section, the main principles of piezoelectric and triboelectric materials are outlined.

3.1.1. Piezoelectric Materials and Nanogenerators

Piezoelectric nanogenerators are based on two electrodes and a piezoelectric material sandwiched between them (Figure 3a). The latter can directly convert applied strain energy into electrical energy, with high output power density [58,194,195]: under an applied mechanical strain, the center of negative and positive ions in the microstructure is no longer overlapped, resulting in a nonzero dipole moment that generates a piezoelectric potential and thus an electric current in an external circuit [196]. Conversely, an electric voltage applied onto a piezoelectric material will generate a displacement or a deformation, which is useful for actuation or to generate acoustic waves [197]. Piezoelectrics are usually produced in the form of nanostructured layers [198–200] or as thin films [201–205], and they can be ceramic or polymeric [196,197]. Thin-film ceramic piezoelectric materials can be deposited onto rigid and soft substrates, such as polyimide, poly(ethylene naphthalate), etc. [59]. There exist several choices for selecting a piezoelectric material: besides lead zirconate titanate ($\text{PbZr}_{1-x}\text{Ti}_x\text{O}_3$, PZT) and its derivatives, which are highly performing but also toxic due to the presence of lead, other ceramic lead-free alternatives are potassium sodium niobate (KNN) [206], lithium niobate (LiNbO_3) [207], barium titanate (BaTiO_3) [208], zinc oxide (ZnO) [201,209], or aluminium nitride (AlN) [210,211]. For instance, ZnO has a wurtzite microstructure: under normal conditions, Zn^{2+} and O^{2-} ions are arranged in a tetrahedron structure along the c-axis, but upon the application of outer stress, a non-centrosymmetric structure is formed and a piezoelectric potential is generated [212–214]. LiNbO_3 is a cheap epitaxially grown piezoelectric material exploited for acoustic and optical devices [215], characterized by chemical inertness, heat resistance, lower dielectric constants than other piezo-ceramics [216], and thin-film processability [207]. AlN also emerged, together with ZnO, as a lead-free highly performing material [22,217–221]. It can be synthesized by sputtering deposition in the form of transparent micrometric films on

flexible substrates [32,41,210,222,223] with attractive properties, e.g., temperature and humidity resistance [224], chemical stability [225,226], and biocompatibility [59,202]. Finally, piezo-polymers are an alternative solution to achieve flexibility and maintain piezoelectric performances. Poly(vinylidene fluoride) (PVDF) and its co-polymers [42,227] are widely used because they are lightweight, soft, and suitable for being employed in fluid flows or for wearable/implantable patches [42,228,229]. Although compared to other inorganic piezo-materials they have high dissipation factors, high dielectric constants, poor heat resistance, and damped performances [230], PVDF derivatives have high piezoelectric coefficient compared to other polymers, excellent chemical resistance, and ease of fabrication, such as electrospinning [42].

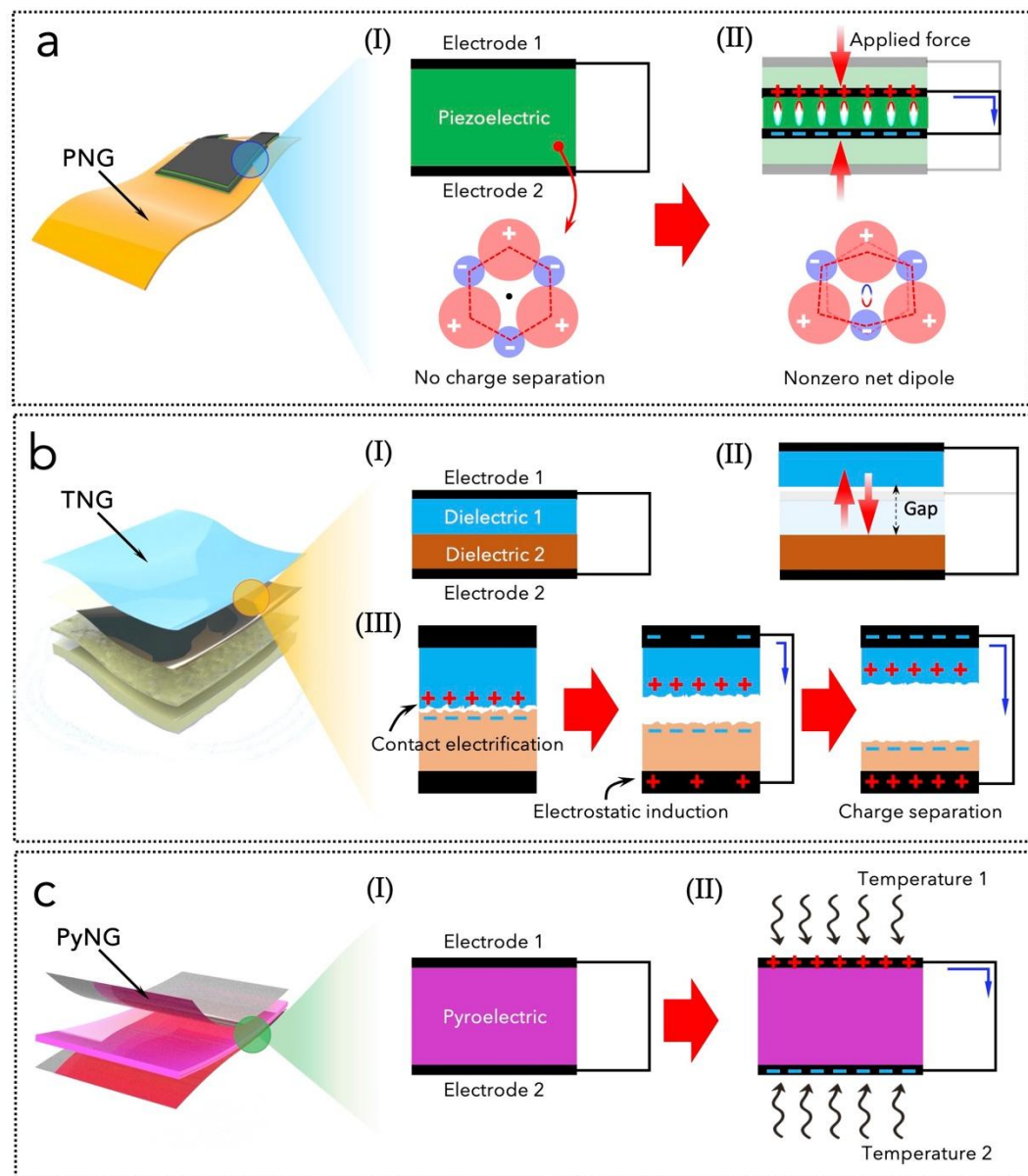


Figure 3. Illustrations of the fundamental working principles of piezoelectric (a), triboelectric (b), and pyroelectric nanogenerators (c). (a,b) Reprinted from [19], MDPI, Creative Commons Attribution (CC BY) license.

3.1.2. Triboelectric Materials and Nanogenerators

Triboelectric nanogenerators are based on coupling the triboelectrification effect with the electrostatic induction effect. Triboelectricity, i.e., the generation of triboelectric surface

charge densities, occurs during the relative contact (in vertical or horizontal mode) of two dissimilar materials [231–233]. Electrostatic induction induces the redistribution of charges from these materials to some conductive or metal electrodes, which allows for the generation of electrical power through an external circuit (Figure 3b) [234–237]. Triboelectric materials are classified based on their triboelectric polarity, i.e., their capability of attaining electrons or positive charges on the surface, which is responsible for the material's surface charge density. The materials' polarity depends on the electron affinity and the work function, as established in the triboelectric series [234,238,239]. Contact electrification consists of generating and redistributing surface charges at the contact interface between two materials. This process occurs at the interfaces, so it strongly depends on the materials' morphology and surface properties, e.g., it is enhanced by different nanostructuring/patterning techniques that change the surface roughness, the porosity, and the wettability [240–246]. Common examples of flexible triboelectric materials are polyimide, polytetrafluoroethylene, polyethyleneterephthalate, polydimethyl siloxane, and parylene C (poly(para-xylylene)) [22,41,247–257]. Triboelectric nanogenerators rely on the vertical or horizontal sliding contact between two materials connected to two electrodes: the charges generated during friction can be collected through an external circuit and produce current and voltage. Compared to electromagnetic generators, they are lightweight, low-density, cost-effective, and highly scalable, and they do not need bulky architectures, e.g., with coils or magnets [16,31,35,40,232,258–261]. Triboelectric nanogenerators can be divided into four basic operation modes. The first one is the lateral sliding mode, which consists of two electrode layers, two triboelectric materials, and the connecting wires. The second one is the vertical contact-separation mode, consisting of two triboelectric materials in front of each other with metal electrodes on the back of each one; the cycling contact and separation between the two materials generates surface charges that are transferred by induction to the electrodes. The third one is the single-electrode mode that presents a triboelectric layer with only one electrode to collect energy from a moving object without connecting leads. The fourth one is the freestanding triboelectric-layer mode, which includes a free-moving object and two electrode layers that are not in complete contact with the frictional object.

3.1.3. Pyroelectric Materials and Nanogenerators

Pyroelectric nanogenerators (PyNGs) convert thermal energy into electrical energy due to changes in the polarity of the material's crystalline microstructure due to a change in temperature. This change in the internal spontaneous polarization strength is responsible for a flow of electrons that can be collected in an external circuit (Figure 3c). When the temperature of a pyroelectric material changes, it induces a variation in the polarization of the material. This change can be due to external heat sources or ambient temperature fluctuations. As the material's polarization changes, bound charges are displaced within the material, leading to the generation of an electric field. This electric field drives charge carriers towards the electrodes of the nanogenerator, producing a measurable electric current. The generated electrical energy can be harnessed for powering small devices or stored for later use. The efficiency of energy conversion is influenced by factors such as material composition, temperature range, and structural design [262]. This property implies that these nanogenerators can be widely used in temperature-controlled closed-loop drug delivery systems. The development of PyNGs has garnered significant interest due to their potential applications in energy harvesting from ambient heat sources, such as body heat and environmental temperature variations. The materials employed in PyNGs can be broadly categorized into ceramics and polymers. Ceramic pyroelectrics include traditional lead-based ceramics, such as PZT, that are well-known for their high pyroelectric coefficients and energy density, making them effective for energy harvesting applications.

However, environmental concerns regarding lead have prompted a shift towards lead-free alternatives. Recent advancements have focused on materials such as sodium bismuth titanate (NBT) and potassium niobate (KNbO_3), which offer comparable pyroelectric properties with enhanced environmental compatibility [263,264]. For instance, NBT-based ceramics have demonstrated high energy density and stability under varying temperatures [264]. Among polymers, as for its piezoelectric properties, PVDF is widely used due to its excellent flexibility and high pyroelectric response. Variants such as P(VDF-TrFE) have been engineered to optimize their pyroelectric performance, achieving significant energy conversion efficiencies [265].

Combining polymers with nanostructured materials, such as metal oxides or carbon nanotubes, has been shown to enhance the overall performance of PyNGs, as well as of PNGs, by improving mechanical properties and increasing surface area for charge generation [266].

PyNGs are emerging as a promising power source for implantable medical devices, addressing the limitations of conventional battery systems. Recent advancements have also focused on hybrid systems that combine pyroelectric materials with piezoelectric elements to enhance energy harvesting efficiency. The flexibility and small size of these nanogenerators enable them to conform to the body's contours, making them ideal for applications such as pacemakers and wearable health monitoring devices [267–270]. The development of PyNGs is accelerating the creation of self-powered biomedical systems that can monitor health conditions in real time while minimizing invasive procedures. As research progresses, these nanogenerators hold significant potential to revolutionize the field of implantable electronics by providing a reliable and sustainable power source that leverages the body's inherent thermal energy.

3.2. BNGs for Localised Anti-Cancer Drug Delivery

When drugs are utilized for disease prevention, diagnosis, and treatment, they must be formulated into suitable dosage forms. The effectiveness of a drug is typically assessed based on the rationality, precision, safety, and efficacy of these dosage forms. Drug dosage forms have evolved through five generations. The first generation includes pastes or pills containing active pharmaceutical ingredients that can be administered either externally or orally. As clinical demands and administration methods expanded, the second generation emerged, comprising aerosols, capsules, tablets, and injections. The third generation introduced controlled drug delivery systems (DDS), which maintain effective drug concentrations in vivo over extended periods after one or more doses, overcoming limitations related to timing and frequency of administration. The fourth generation focuses on targeted DDS that enhance drug accumulation in specific organs, tissues, and cells, thereby minimizing toxicity and side effects while improving therapeutic outcomes. Targeted DDS are particularly prevalent in tumor therapy. The fifth generation includes pulsed DDS that automatically release drugs in sync with the body's physiological rhythms during disease episodes. Self-powered technology based on nanogenerators BNGs offers practical solutions to these challenges [271].

A self-powered system operates independently of an external power source. In the intelligent-controlled DDS, self-powered devices can generate electric power to address the energy requirements for drug release control with output regulated by the design of the NG's structure and function. Furthermore, biodegradable BNGs not only mitigate surgical risks but also reduce the overall size and complexity of drug delivery devices.

Chemotherapy is a commonly employed treatment for cancer. However, it is associated with limited therapeutic efficacy and significant side effects. As a result, there is a pressing need for drug delivery systems that can target specific sites, enhancing drug

delivery to tumors while reducing off-target effects and overall drug dosages, thereby minimizing adverse reactions [272]. The integration of BNGs into localized anti-cancer drug delivery systems represents a significant advancement in anti-cancer therapy, enabling precise and controlled release of therapeutic agents directly at tumor sites. These devices harness biomechanical energy from the body to generate electricity, which can power drug delivery mechanisms, enhancing the efficacy of treatments while minimizing systemic side effects [273,274].

For these applications, BNGs typically operate based on the triboelectric effect or piezoelectric effect, converting mechanical energy from body movements or physiological processes into electrical energy. This electricity can be used to drive various drug delivery systems, allowing for real-time control over drug release. For instance, the generated electric field can stimulate the release of chemotherapeutic agents from encapsulated carriers, such as liposomes or hydrogels, directly into the tumor microenvironment. The ability to modulate drug release in response to external stimuli, such as changes in temperature or electric fields, enhances treatment precision and can significantly improve therapeutic outcomes [275,276].

The application of BNGs in anti-cancer therapy is particularly promising due to their ability to deliver localized treatment while minimizing systemic exposure [277]. Recent studies have demonstrated that these devices can effectively enhance the therapeutic efficacy of chemotherapeutic agents like doxorubicin (DOX) by controlling their release rates through applied electric fields. Recently, red blood cells (RBCs) have gained attention as potential carriers for targeted drug delivery due to their biological origin, intrinsic biocompatibility, ease of access, long circulation time (approximately 120 days in humans), and stable, flexible membranes [278,279]. Notably, RBCs fall within the optimal size range for the enhanced permeation and retention (EPR) effect observed in tumors, facilitating their accumulation at tumor sites [280]. For example, a biodegradable triboelectric nanogenerator (BI-TENG) was shown to generate an electric field that accelerated DOX release from red blood cells, leading to improved targeting of tumour cells while reducing off-target effects [276] (Figure 4a).

Another triboelectric BNG (TNG)-supported RBC drug delivery system has been developed to enable controlled and localized delivery of DOX with improved efficiency [281] (Figure 4b). This system utilizes polytetrafluoroethylene (PTFE) and titanium as the friction layers in the encapsulated magnet-TNG (MTNG). The application of an electric field generated by the MTNG significantly enhances the release of DOX. In vivo studies demonstrated that when RBCs loaded with DOX (D@RBC) were injected into tumor-bearing mice, the DOX signal at the liver was initially high but decreased significantly over time. In contrast, the signal at the tumor site increased during the first 48 h and only slightly decreased at 72 and 96 h, indicating effective targeting. On day 30 post-treatment, tumors in the MTNG + D@RBC group exhibited significantly reduced volumes compared to other groups, highlighting the superior therapeutic efficacy of this combined approach in vivo.

Moreover, these devices can also be integrated with other therapeutic modalities such as photothermal therapy or immunotherapy. By combining localized drug delivery with additional treatment strategies, BNGs can create a synergistic effect that enhances overall treatment efficacy against tumors. Future research should focus on optimizing device design for better integration with existing cancer therapies and exploring novel materials that could enhance performance. Additionally, advancements in wireless technology may allow for remote control over drug delivery systems, providing clinicians with greater flexibility in managing patient care.

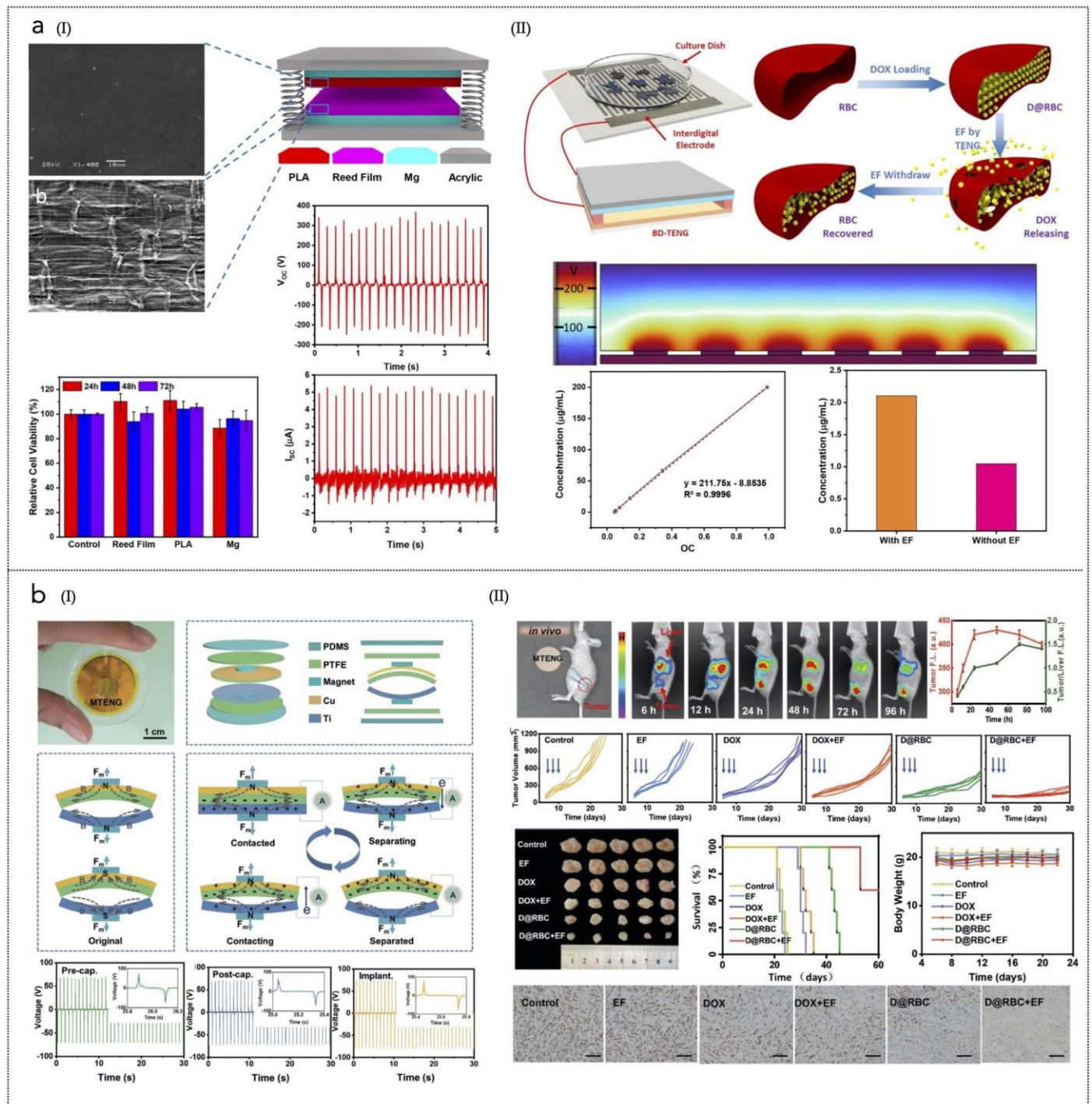


Figure 4. (a) (I) Illustration of the prototype TNG with SEM images of the biodegradable film and PLA and reed film. The plots show the electrical signals with an outside force, V_{oc} , I_{sc} , and cell viability after 3 days of culture in media supplemented with several biodegradable films. (II) BI-TENG-controlled constructs used to control DOX release: DOX standard concentration curve and D&RBC before and after electric field stimulation are shown in the plots. Reprinted from [276], Springer Nature, Creative Commons Attribution 4.0 International License. (b) (I) Schematic diagram, device structure and output performance of the MTENG. Working principle of the MTENG; V_{oc} of the MTENG before and after encapsulation; V_{oc} of the MTENG after encapsulation and implanted subcutaneously in streaky pork. (II) MTENG-controlled RBC DDS in vivo. The images show blood

circulation and accumulation to tumors of the D@RBCs obtained by in vivo imaging system at 6, 12, 24, 48, 72, and 96 h, respectively. The in vivo tumor growth curve is shown; blue arrows indicate the treatment time point: Day 6, Day 8, and Day 10. The other images of the harvested tumors in various groups after 1 month. At the bottom, the Ki67 immunohistochemistry images of the tumors in various groups are shown (scale bar: 200 μm), together with the survival curves of the mice in various groups, and the body weight of the mice. Reprinted with permission from [281]. Copyright 2019, Wiley-VCH GmbH.

3.3. BNGs for Photodynamic Anti-Cancer Therapy

Despite its advantages, PDT faces several challenges, including inadequate localization of photosensitizers (PSs), limited light penetration in deep tissues, and the development of treatment resistance. PDT operates on the principle that when a photosensitizer is activated by specific wavelengths of light, it generates ROS, which can induce cell death in cancerous tissues. The effectiveness of PDT is contingent upon the precise delivery of light to the tumor site and the adequate concentration of PSs within the tumor. Traditional PDT methods often struggle with light penetration, especially in deep-seated tumors, leading to suboptimal therapeutic outcomes. Furthermore, the lack of targeted delivery can result in systemic toxicity and reduced efficacy due to off-target effects.

To address these limitations, the integration of BNGs into PDT systems offers a novel approach that enhances treatment efficacy [282,283]. In fact, BNGs can provide a self-powered system that ensures sustained illumination of PSs directly at the tumor site, thereby enhancing ROS production and improving treatment outcomes. Recent advancements in piezoelectric and triboelectric BNGs have demonstrated their potential to facilitate localized PDT by generating electrical energy from physiological movements or external stimuli.

A notable example is the development of an implantable micro-scale LED device that enables on-demand activation of PSs deep within tumor tissues. This device consists of multiple micro-LEDs arranged in a needle-like structure, allowing for direct implantation into tumor cores. By emitting mild visible light, this system minimizes inflammatory responses while promoting immunogenic cell death (ICD) in tumor cells. Studies have shown that this approach effectively enhances antitumor immunity while reducing adverse effects associated with intense light exposure [284].

Another innovative approach involves a fully implantable wireless optoelectronic system that integrates PDT with hyperthermia and real-time tumor size monitoring (Figure 5a). Utilizing micro inorganic LEDs (μ -LEDs), this system can emit programmable light intensities tailored to individual patient needs. The ability to monitor tumor size continuously allows for adaptive treatment strategies, optimizing therapeutic efficacy while minimizing damage to surrounding healthy tissues [285].

A self-powered PDT therapeutic tablet has been developed that synergizes with ferroptosis inducers to enhance cancer treatment outcomes (Figure 5b). This device leverages the Fenton reaction to generate additional ROS during PDT while simultaneously increasing oxidative stress within cancer cells. Experimental results indicate a significant tumor inhibition rate, showcasing the potential for combining NG technology with PDT to overcome challenges related to hypoxia and inadequate PS penetration [286].

Research has also explored human motion-driven self-powered PDT systems that autonomously manage irradiation modes based on patient activity levels. This approach allows for continuous treatment without requiring external power sources, making it particularly advantageous for outpatient settings where patient mobility is crucial [287].

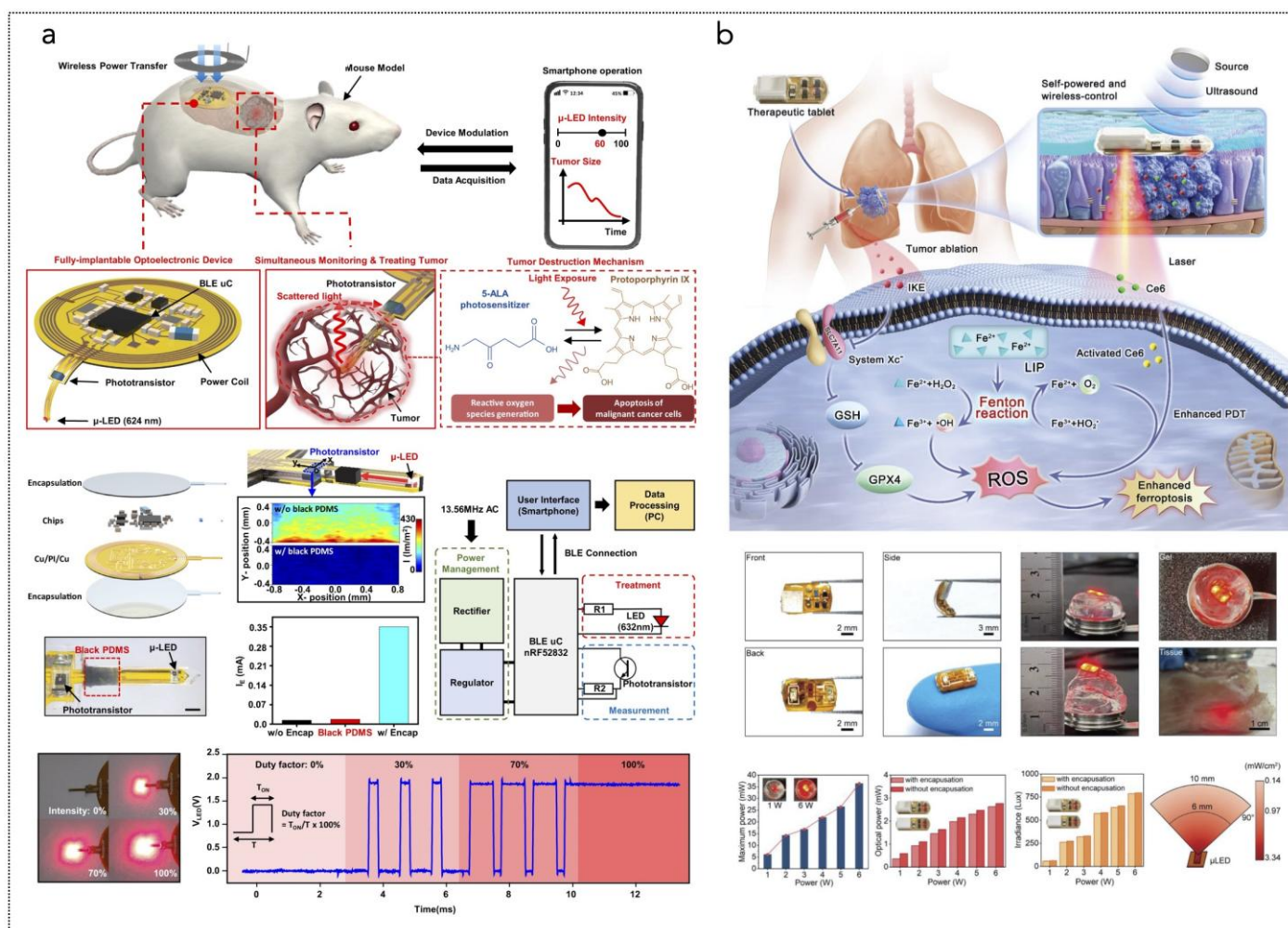


Figure 5. (a) Overall concept of cancer treatment and monitoring system including device schematic, principle of device operation that enables fully programmable μ -LED intensity control and real-time monitoring of tumor size, and chemical mechanism of PDT. The device includes PDMS/SiO₂/polyethylene C encapsulation layers and a probe part containing black PDMS for blocking internally reflected light; Scale bar, 1 mm. The block diagram of electronic components for wireless operation includes wireless power transfer, light delivery control, photocurrent measurement, and wireless communication with a smartphone. Pulse width modulation of the μ -LEDs with intensity of 0%, 30%, 70%, and 100% is shown, together with forward voltage of the μ -LED when duty factor is sequentially changed to 30%, 70%, and 100% from 0%. Reprinted from [285], Springer Nature, Creative Commons Attribution 4.0 International License. (b) Ferroptosis inducer IKE, when combined with photodynamic therapy, presents a novel approach to cancer treatment. IKE induces ferroptosis in tumor cells by locally inhibiting the SLC7A11-GSH-GPX4 signaling pathway. Concurrently, iron ions accumulate in the body and enhance the cellular hypoxic environment through the Fenton reaction. The therapeutic tablet is minimally invasively implanted into the primary lung cancer site, and ultrasound drives the μ LEDs to activate the photosensitizer chlorin e6 (Ce6), utilizing oxygen supplied by IKE to enhance photodynamic therapy, generate reactive oxygen species (ROS), and deplete glutathione (GSH). The accumulation of ROS leads to ferroptosis in lung cancer cells due to the formation of lipid peroxides. Reprinted from [286], Wiley-VCH GmbH. Creative Commons Attribution 4.0 International License.

While both BNGs for PDT and localized drug delivery systems aim to enhance therapeutic efficacy and minimize side effects, they operate through different mechanisms and have distinct advantages. Localized drug delivery aims to reduce systemic toxicity by concentrating drug action within the tumor environment. However, it may not address issues related to hypoxia or insufficient ROS generation inherent in traditional chemotherapy

methods. On the other hand, ING-enhanced PDT specifically targets cancer cells through ROS generation while potentially stimulating immune responses against tumors.

Several challenges remain regarding the integration of BNGs into PDT, such as (i) ensuring that BNG materials are biocompatible to minimize adverse reactions upon implantation; (ii) guaranteeing durability over extended periods to maintain consistent therapeutic effects without requiring surgical replacement; (iii) navigating through extensive preclinical and clinical trials to demonstrate safety and efficacy.

3.4. BNGs for Sonodynamic Anti-Cancer Therapy

BNGs are revolutionizing SDT, which is an advantageous cancer treatment strategy over conventional therapies, owing to its minimally invasive approach, targeted tumor destruction, and reduced side effects. The effectiveness of SDT is often hindered by challenges such as insufficient penetration of ultrasound waves into deeper tissues and the need for effective delivery systems for sensitizers. Recent developments in BNG technology have shown great promise in enhancing SDT by providing a self-powered mechanism that improves the localization and activation of therapeutic agents directly at tumor sites.

Another promising application involves a nanoparticle formulation based on a cathepsin B-degradable co-polymer that carries hematoporphyrin (HPNP) [288]. This system has demonstrated significant improvements in cellular uptake and antitumor efficacy when used in conjunction with ultrasound exposure. In studies focused on pancreatic ductal adenocarcinoma (PDAC), the HPNP formulation exhibited enhanced sonodynamic effects, leading to considerable reductions in tumor volume within just 24 h post-treatment. The ability of this formulation to respond to specific conditions within the tumor microenvironment—such as elevated levels of proteolytic enzymes—facilitates targeted drug release and enhances overall treatment outcomes.

Moreover, recent investigations have explored liposomal nanosystems designed to function as sonodynamic immune adjuvants [289,290]. These systems aim to modulate the tumor microenvironment (TME) by increasing oxygen availability and inducing immunogenic cell death (ICD) alongside ferroptosis. By integrating these capabilities into a single platform, researchers have reported significant improvements in antitumor responses both *in vitro* and *in vivo*. The combination of BNGs with such advanced nanosystems allows for more effective modulation of the TME, addressing critical barriers to successful cancer treatment.

The incorporation of BNGs into SDT not only enhances therapeutic efficacy but also offers distinct advantages compared to localized drug delivery systems. While localized drug delivery primarily focuses on delivering chemotherapeutic agents directly to tumors, often utilizing carriers like liposomes or nanoparticles, BNG-enhanced SDT leverages ultrasound's power to activate sensitizers and generate ROS on demand. By providing a self-powered solution, BNGs ensure that therapeutic agents remain active at the tumor site for extended periods, thereby enhancing their effectiveness while minimizing systemic toxicity [291–293].

BNGs can also be used to enhance the effectiveness of low-intensity electric stimulation, which can diminish multidrug resistance in cancer and induce notable anti-proliferative effects by disrupting calcium (Ca^{2+}) and potassium (K^+) homeostasis and influencing the organization of mitotic spindles. Introducing piezoelectric materials may favor directly these electric stimuli specifically toward malignant cells to preserve the proliferation and function of healthy cells [294]. As demonstrated, Marino et al. [295] introduced a method based on ultrasound-sensitive piezoelectric NPs to remotely deliver electric stimulation to glioblastoma cells (Figure 6a). Barium titanate NPs have been functionalized with an antibody targeting the transferrin receptor (TfR) to achieve dual targeting of both the blood-brain

barrier and glioblastoma cells. The remote ultrasound-mediated piezo-stimulation significantly reduced the proliferation of glioblastoma cells *in vitro*, and when combined with a sub-toxic concentration of temozolomide, it enhanced sensitivity to chemotherapy while producing remarkable anti-proliferative and pro-apoptotic effects. Cafarelli et al. [296] comprehensively reviewed the fundamental mechanisms of acoustically mediated piezoelectric stimulation, exploring the current challenges that prevent the full adoption of this technology in clinical practice, such as piezoelectric properties measurement, control of the ultrasound dose *in vitro*, modeling and measuring the piezo effects, knowledge on the triggered bioeffects, therapy targeting, biocompatibility studies, and control of the ultrasound dose delivered *in vivo*.

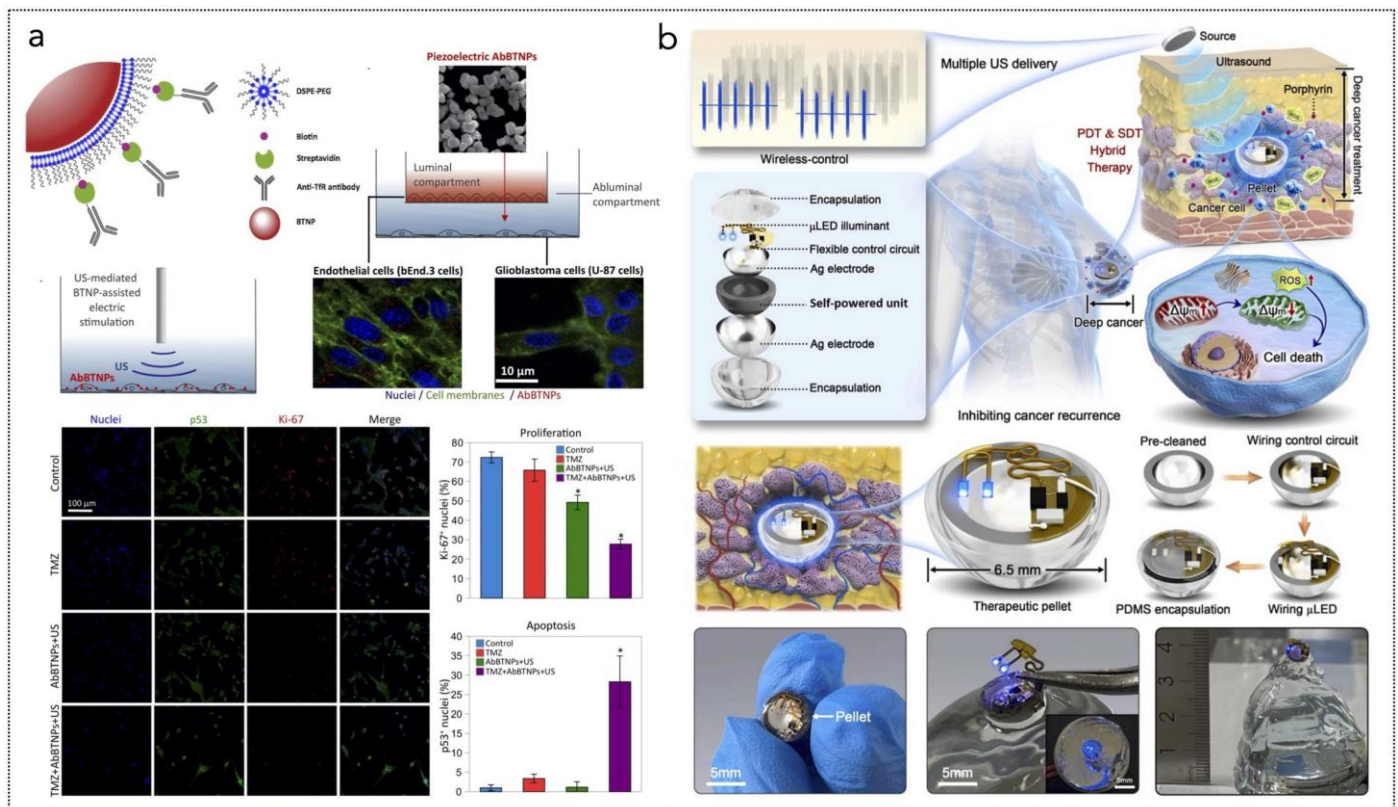


Figure 6. (a) Illustration of barium titanate NP functionalization with antibody against transferrin receptor (TfR). The scheme shows the NP crossing through a static 3D model of the blood brain barrier and chronic piezoelectric stimulation of glioblastoma cells. At the bottom, CLSM imaging of Ki-67 and p53 expression in different experimental conditions for NP-assisted piezoelectric stimulation to improve anticancer efficacy of TMZ. Reprinted with permission from [295]. Copyright 2018, Elsevier. (b) Design and structure of implantable self-powered therapeutic pellet, with an integrated μLED with flexible serpentine electrode, with wireless PDT/SDT hybrid therapy for inhibiting cancer recurrence. Reprinted with permission from [297], Copyright 2022, Elsevier.

Hybrid systems have been recently introduced that combine SDT with PDT for cancer treatment. For instance, Guan et al. [297] proposed an innovative implantable self-powered therapeutic pellet designed for wireless hybrid therapy combining PDT and SDT to prevent cancer recurrence and reduce tumor size (Figure 6b). The pellet features a compact design that integrates a self-powered unit, an LED light source, and a control circuit, allowing it to be directly implanted at the tumor site. This self-powered unit captures ultrasound energy through the piezoelectric effect, enabling the delivery of therapeutic light doses to tissues for PDT while simultaneously facilitating direct SDT. In preclinical mouse models, this hybrid PDT/SDT approach has demonstrated significant efficacy in treating breast

cancer, outperforming treatments that utilize either PDT or SDT alone, and shows promise for future clinical applications in humans. The system effectively addresses key limitations of current advanced technologies by achieving: (i) deep tissue treatment within the body; (ii) hybrid therapy that optimizes the activation of sensitizers; and (iii) wireless control over therapeutic dosimetry. Additionally, further research on this implantable self-powered therapeutic pellet for wireless PDT/SDT hybrid therapy, both in vitro and in vivo, could provide valuable insights into the interactions between established clinical cancer treatments and emerging precision therapies.

3.5. BNGs for Cancer Treatment Through Bioelectrical Stimulation

BNGs represent a promising frontier in cancer treatment, leveraging bioelectrical stimulation to directly kill cancer cells or inhibit their proliferation. These innovative devices are designed to harvest energy from the body's own physiological movements, such as breathing, heartbeat, or muscle contractions, to power localized electrical stimulation. This approach is particularly advantageous as it eliminates the need for external power sources, enabling minimally invasive, self-sustained cancer therapies. The recent literature highlights several strategies and device architectures that have been explored to harness the potential of BNGs for oncological applications [298].

The mechanisms by which bioelectrical stimulation exerts anticancer effects are multifaceted. Electrical fields can disrupt the cell cycle, inhibit mitosis, and induce apoptosis in cancer cells. They can also alter the tumor microenvironment, reducing hypoxia and promoting immune cell infiltration. For instance, studies have shown that low-intensity electrical stimulation can enhance the efficacy of immunotherapies by increasing the expression of antigens on cancer cells, making them more recognizable to immune cells.

Pan et al. [136] presented an optically microprinted flexible interdigital electrode with a gold-plated polymer microneedle array, fabricated by combining optical 3D microprinting and electroless plating processes, to generate AC electric fields for cancer treatment (Figure 7a). EST induced necrotic cell death through mitochondrial Ca^{2+} overload and increased intracellular ROS production, leading to the release of damage-associated molecular patterns that activated the immune response and potentiated immunogenic cell death.

Low-intensity electric stimulation offers an alternative treatment capable of inhibiting the proliferation of various tumor cell lines [299]. In more detail, this type of stimulation hinders cell division by impacting K^+ channels, specifically through the overexpression of the inward rectifier K^+ channel Kir3.2 [300], and by disrupting cytoskeletal structures during cell division, particularly through disorganization of the mitotic spindle [301]. Additionally, low-intensity and low-frequency AC stimulation has been shown to significantly enhance the effects of chemotherapy in glioblastoma treatment during clinical trials [302]. AC not only influences cancer cell proliferation without the use of drugs but also reduces multidrug resistance by interfering with the plasma membrane translocation of MDR1, a P-glycoprotein (P-gp) whose overexpression is linked to chemotherapy resistance [303]. However, since AC stimulation can also affect the proliferation of non-malignant cells, such as human astrocytes, it is crucial to specifically target electric stimuli to cancer cells. In this context, piezoelectric nanomaterials have emerged as promising tools for wireless, non-invasive, and targeted electric stimulation of cells and tissues. Owing to the remote ultrasound-mediated activation of these piezo-nanotransducers, various cell types can be successfully stimulated. Marino et al. [304] presented an innovative piezoelectric nanoplateform consisting of Barium titanate NPs functionalized with anti-HER2 antibodies (Ab-BTNPs), which specifically target HER2-positive cancer cells. The anti-proliferative effects of remote piezoelectric stimulation on SK-BR-3 breast cancer cells were assessed through cell cycle progression analysis, evaluation of proliferation markers, and measure-

ment of metabolic activity in cell cultures. Additionally, intracellular Ca^{2+} levels, mitotic spindle development, and K^{+} channel expression at the gene level were assessed.

Moreover, bioelectrical stimulation can impair angiogenesis, depriving tumors of their blood supply and hindering growth. Angiogenesis is closely linked to inflammatory processes as it facilitates nutrient supply and waste removal to maintain physiological homeostasis. Conversely, pathological angiogenesis can occur due to dysregulated inflammatory processes, leading to chronic inflammation [305]. During inflammation, there is a significant interaction between immune and endothelial cells, with several studies indicating that these immune/endothelial cell interactions promote cancer development. In the tumor microenvironment, cancer cells secrete and activate various growth factors, including VEGF, FGFb, EGF, and TGFb, to stimulate angiogenesis [306,307].

Sen et al. [308] showed that the angiogenic behavior of human cerebral microvascular endothelial cells can be inhibited by using nudin-3a-loaded ApoE-functionalised polymeric piezoelectric NPs, remotely responsive to ultrasounds. The electrical stimulation favoured the inhibition of tumor-induced angiogenesis, specifically vessel formation, endothelial cell migration and invasion, and angiogenesis-related cytokines production.

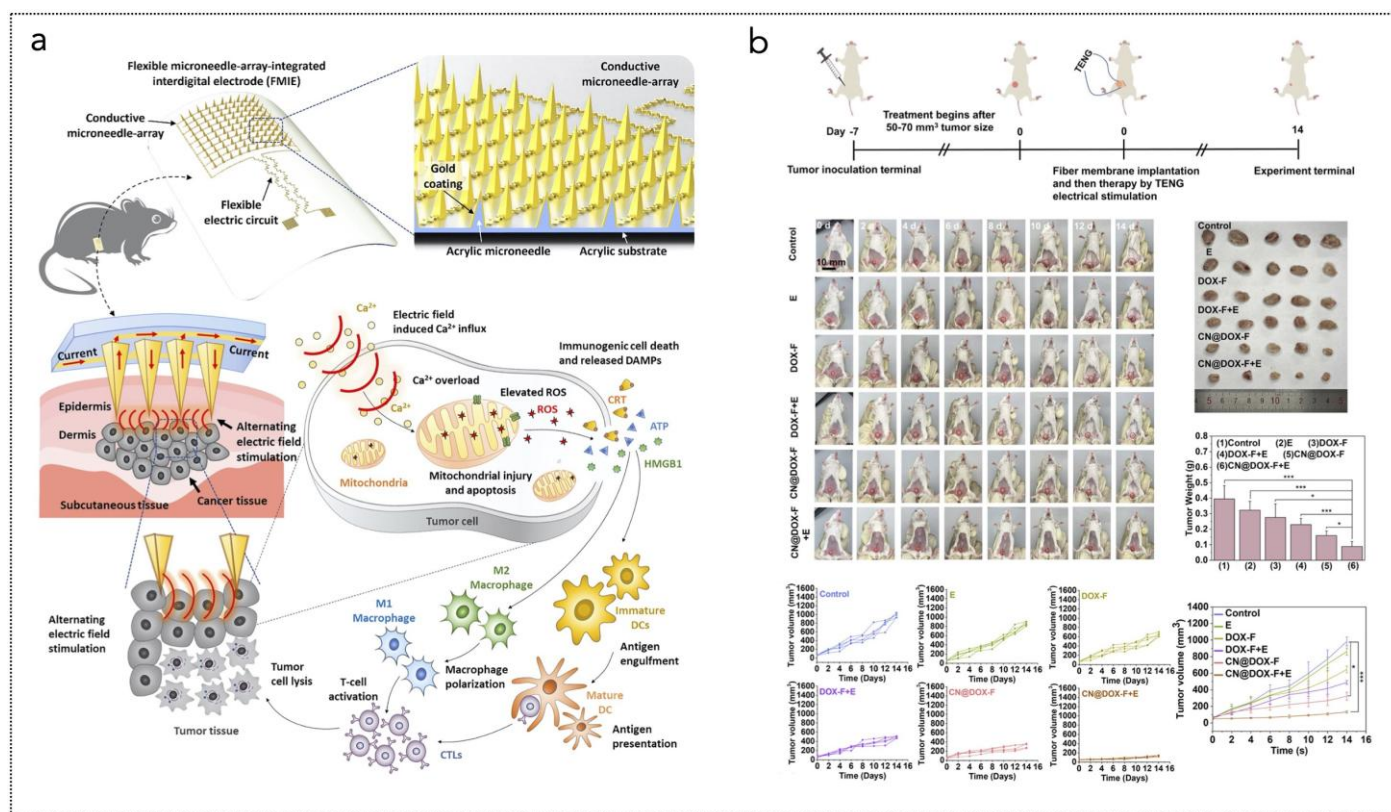


Figure 7. (a) Schematic of the gold-plated polymer microneedle array for electrically stimulated cancer immunomodulation. Reprinted with permission from [136], Copyright 2023, Elsevier. (b) In vivo cancer therapy on the subcutaneous 4T1 tumor-bearing BALB/c mice: schematic illustration of the cancer therapy with the TENG-assisted catalytic and chemotherapeutic system, together with the photographs of the representative mice in different groups during the 14 days of treatment. The plots show the mean tumor weights after the excision on day 14, and the tumor volume change of the mice during the treatment. Reprinted with permission from [8], Copyright 2023, American Chemical Society.

These mechanisms underscore the potential of bioelectronic nanogenerators to serve as versatile tools in cancer treatment, combined with other therapies as well. For instance, Zheng et al. [8] presented a self-driven electrical stimulation-enhanced cancer catalytic

therapy combined with chemotherapy by integrating a human-powered TNG with an implantable and biodegradable gelatin/polycaprolactone nanofibrous patch (Figure 7b). This patch is designed to incorporate DOX and graphitic carbon nitride (g-C₃N₄). Notably, the peroxidase (POD)-like activity of g-C₃N₄, which facilitates the generation of hydroxyl radicals, can be significantly amplified through self-driven electrical stimulation. Concurrently, DOX is released to enhance the therapeutic effect, particularly in the weakly acidic conditions typical of the tumor microenvironment.

Das et al. [131] described, in detail, different approaches of electrotherapy and electrochemotherapy for cancer treatment.

Table 1 reports some representative examples of BNGs for anti-cancer therapy, as proposed in previous works. It should be noted that, in many cases, it is challenging to categorize systems, devices, or approaches within the aforementioned groups of BNGs or ANGs. For example, some approaches rely on the ultrasound activation of piezoelectric nanomaterials for bioelectrical stimulation of cancer cells. These can fall into the category of EST but also NPT, and, anyway, they can be associated with the physical principle of PNGs, although the piezoelectric effect here is used in the reverse direction. Thus, Table 1 can serve as a reference for showcasing practical examples of approaches for anti-cancer therapies.

Table 1. Representative examples of BNGs for anti-cancer therapy, proposed in previous works and classified in terms of the materials used, the targeted application, the underlying working principle. The colors correspond to different applications: green (localized drug delivery); yellow (photodynamic therapy); blue (sonodynamic therapy); orange (electrical stimulation therapy); grey (nanoparticle-based therapy); and pink (atomic nanogenerators). Some systems can deliver multiple synergistic therapies or can fall into multiple categories.

	Type of Device/Approach	Working Principle	Materials	Stage of Research	Ref.
LOCALISED DRUG DELIVERY	Biodegradable TNG connected to an interdigitated electrode	The TNG is used as the power source to stimulate the electric field to increase the speed of the drug delivery system release of doxorubicin (DOX) from RBCs, facilitating the precise killing of cancer cells, and the DOX release rate returns to normal after the applied field is stopped.	PLA, Reed film, Mg Rice paper, ginkgo biloba	Device scale In vivo	[276]
	Magnet TNG in a drug delivery system	The contacting-mode TNG can ensure high and consistent electricity for enhancing the release of DOX from RBCs.	PTFE, PDMS, magnet, Cu, Ti	Device scale In vivo	[281]
	Disk TNG within a self-powered drug delivery system	The disk-shaped TNG provides a current source for the self-powered drug delivery system and electrically stimulates cells seeded in the gap between the electrodes, facilitating also the uptake of DOX from cancer cells.	PMMA, polyamide, PVDF, Cr/Ag, Au	Device scale In vitro	[309]
	Implantable, biodegradable, wireless TNG	With the excitation of ultrasound to the TNG, it can generate an alternating current voltage and concurrently release the loaded anti-mitotic drugs into tumor tissues, which synergistically disrupts the assembly of microtubules and filament actins, induces cell cycle arrest, and finally enhances cell death. The drug carrier incorporated into the TNG is based on carbonaceous metal-organic framework zeolitic imidazolate framework-8 (ZIF-8) NPs.	Polycaprolactone, Mg	Device scale In vivo	[275]
PHOTODYNAMIC THERAPY	Fully implantable, wireless, flexible optoelectronic system	The system is capable of continuous and effective cancer treatment by fusing PDT and hyperthermia and enabling tumor size monitoring in real time. It exploits inorganic μ -LEDs that emit light with a wavelength of 624 nm, and precisely monitors the tumor size by Si phototransistor during a long-term implantation	Cu, polyimide PDMS, μ LED	Device scale In vivo	[285]
	PyNG for specific mitochondria-targeting	The PyNG is used for chemo-photodynamic therapy against HepG2 malignant liver tumors. A superb ROS production and tumor cell elimination capability is disclosed via mitochondria-targeting and hypoxia-relieving performances. The PyNG, based on the heat-conducting coating of poly-dopamine, is integrated in a drug delivery system for the co-release of DOX and EGCG.	Barium titanate Poly-dopamine (PDA)	In vitro	[310]
	Twinning structured PNG for self-powered PDT	Powered by energy harvested from body motion, the system realizes effective tumor tissue killing and inhibition.	Parylene/PET, Cu, Ag, PVDF	Device scale In vivo	[287]
	PNG for PDT/SDT low-dose/long-term cancer treatment	Implantable self-powered therapeutic pellet that provides wireless PDT/SDT hybrid therapy for low-dose/long-term cancer recurrence inhibition and tumor regression. The miniature pellet contains an integrated self-powered unit, a light-emitting diode illuminant, and a control circuit.	Ag Polyimide	Device scale In vivo	[297]
	PNG coupled with a self-powered wireless drug/light injector	The device comprises a semi-invasive pedestal with a micro light emitting diode (μ -LED) and a syringe needle, as well as a detachable actuator that contains a drug reservoir, a thermally-driven pump, and a wireless control circuit. The device can be wirelessly controlled to deliver on-demand dosages of drugs and light into the tumor under the skin, producing ROS species and inducing cancer cell apoptosis.	Magnet μ LED	Device scale In vivo	[311]

Table 1. Cont.

	Type of Device/Approach	Working Principle	Materials	Stage of Research	Ref.
	PNG for piezo-catalytic treatment of hypoxic tumors	The system includes acid-degradable Janus-type multicompartamental carriers able to separately encapsulate piezocatalytic Au nanoparticle-coated poly(ethylene glycol)-modified zinc oxide nanorods (Au@P-ZnO NRs) and O ₂ -generating catalase (CAT). The sequential release by the Janus carriers significantly increased the intracellular ROS levels under hypoxia conditions upon ultrasound irradiation owing to the O ₂ supplied by the CAT.	Poly(ethylene glycol)ZnO Au	Device scale In vivo	[312]
SONODYNAMIC THERAPY	PNG based on iron-doped and oxygen-deficient piezoelectric nanosheets	Due to the existence of oxygen defects introduced through Fe doping, the bandgap of BWO-Fe is significantly narrowed so that BWO-Fe can be more easily activated by exogenous ultrasound (US). The oxygen defects acting as the electron traps inhibit the recombination of US-induced electrons and holes. More importantly, the dynamically renewed piezoelectric potential facilitates the migration of electrons and holes to the opposite side and causes energy band bending, which further promotes the production of reactive oxygen species and induces the tumor cells' apoptosis.	Bismuth tungstate nanosheets Fe	In vivo	[313]
	Ultrasound-activated Au/ZnO-based Trojan PNG	Firstly, the ZnO-nanogenerators will generate a piezoelectric potential difference of about 140 mV by ultrasonic excitation when targeted (by MLS moiety) to the mitochondria, disrupting the mitochondrial membrane potential for electrostimulation. Secondly, the nanogenerators enhance greatly multiple enzyme-like activities of Au nano-components for enhanced tumor catalytic therapy	ZnO, Au Poly(ethylene glycol)	In vitro	[13]
	PNG based on ultrasonic-responsive piezoelectric NPs for treatment of glioblastoma	The remote ultrasound-mediated piezo-stimulation significantly reduced the proliferation of glioblastoma cells in vitro, and when combined with a sub-toxic concentration of temozolomide, it enhanced sensitivity to chemotherapy while producing remarkable anti-proliferative and pro-apoptotic effects.	Barium titanate	In vitro	[295]
	Wireless, battery-free therapeutic dot for piezo-PDT	The therapeutic dot is implanted directly inside the tissue around the tumor and wirelessly controlled by ultrasound (US), allowing dual activation of electron-hole pairs from the nanocomposites via US and ultraviolet light (UV). The internally generated piezoelectric field minimizes electron-hole recombination, maximizing ROS induction within tumor cells.	Au, ZnO nanorods Poly(ethylene glycol)	In vivo	[291]

Table 1. Cont.

	Type of Device/Approach	Working Principle	Materials	Stage of Research	Ref.
ELECTRICAL STIMULATION THERAPY	Human-driven TNG coupled with implantable and biodegradable nanofibrous patch	The nanofibrous patch incorporates doxorubicin (DOX) and graphitic carbon nitride (g-C ₃ N ₄), in which the peroxidase (POD)-like activity of g-C ₃ N ₄ to produce hydroxyl radical (•OH) can be distinctly enhanced by the self-driven electrical stimulation for 4.12-fold, and simultaneously DOX can be released to synergize the therapy.	PDMS, TiO ₂ , Nitrile, Al Gelatin, polycaprolactone	Device scale In vivo	[8]
	Optically microprinted flexible interdigital electrode with an Au-plated polymer microneedle array	The flexible microneedle-array-integrated interdigital electrode is fabricated by combining optical 3D microprinting and electroless plating processes. Electrical stimulation of cancer cells induced necrotic cell death through mitochondrial Ca ²⁺ overload and increased intracellular reactive oxygen species (ROS) production. This led to the release of damage-associated molecular patterns that activated the immune response and potentiated immunogenic cell death (ICD).	Au, acrylic	Device scale In vivo	[136]
	AC stimulation electrodes in tumor cell cultures	Low frequency, low intensity alternating current electrical stimulation drastically enhances chemotherapeutic efficacy in MDR1 drug-resistant malignant tumors.	Stainless steel leads	In vitro	[299]
	Ultrasound-activated piezoelectric nanoparticles (NPs)	Chronic piezoelectric stimulation results in the ability to inhibit cancer cell proliferation by upregulating the expression of the gene encoding Kir3.2 inward rectifier potassium channels, by interfering with Ca ²⁺ homeostasis, and by affecting the organization of mitotic spindles during mitosis.	Barium titanate NPs	In vitro	[304]
	Electrodes for nano-pulsed electrical stimulation	The study is conducted on a mouse malignant melanoma model. After stimulation, the number of T lymphocytes as measured in the spleen increased, indicating that the therapy stimulates the immune system of the animal to attack the tumor.	Metal leads	In vivo	[314]
NANOPARTICLE-BASED THERAPY	Magnetostrictive-piezoelectric triggered tumor therapy	The system initiates an intratumoral magneto-driven and piezoelectric-catalyzed reaction using core-shell structured CoFe ₂ O ₄ -BiFeO ₃ magnetostrictive-piezoelectric nanoparticles under an alternating magnetic field. The NPs catalyze the generation of (ROS), in particular superoxide radicals (•O ₂ [−]) and hydroxyl radicals (•OH).	CoFe ₂ O ₄ -BiFeO ₃	In vivo	[315]
	Piezoelectric oral microrobots for targeted catalytic and immunotherapy of colorectal cancer	The microrobots consist of Veillonella atypica (VA) cells whose surface is loaded with <i>Staphylococcus aureus</i> cell membrane-coating BaTiO ₃ nanocubes via click chemical reaction. Following oral administration, the microrobots accurately targeted orthotopic colorectal cancer. Under in vitro ultrasonic stimulation, the piezoelectric particles catalyze two reduction reactions (O ₂ → •O ₂ [−] and CO ₂ → CO) and three oxidation reactions (H ₂ O → •OH, GSH → GSSG, and LA → PA) simultaneously, effectively inducing immunogenic death of tumor cells.	Barium titanate NPs	Device scale In vivo	[316]
	Janus-type nanocarriers with piezoelectric nanomaterials	The acid-degradable Janus-type multicompartamental carriers are able to separately encapsulate piezocatalytic gold nanoparticle-coated poly(ethylene glycol)-modified zinc oxide nanorods and O ₂ -generating catalase. The sequential release by the Janus carriers significantly increased the intracellular ROS levels under hypoxia conditions upon ultrasound irradiation owing to the O ₂ supplied by the catalase.	Au, ZnO nanorods, Poly(ethylene glycol)	In vivo	[312]
	Engineered NPs carrying photosensitizers	The NPs can be specifically activated within tumors by conjugating antibodies against programmed death ligand 1 (PDL1) with matrix metalloproteinase protein 2 (MMP-2)-sensitive NPs that carry a photosensitizer, ICG (MMP-2 is highly expressed in tumors). When used in conjunction with localized near-infrared radiation that activates the photosensitizer to produce ROS, the effect of limiting the growth and metastasis of murine tumors is enhanced.	αPDL1/ICG nanocomplexes Epigallocate 3-O-gallate (dEGCG) Poly(ethylene glycol)	In vivo	[317]

Table 1. Cont.

	Type of Device/Approach	Working Principle	Materials	Stage of Research	Ref.
ATOMIC NANOGENERATORS	Liquid metal nanodroplet-based NO nanogenerator	The liquid metal nanodroplet (LMND)-based NO nanogenerator (LMND@HSG) is stabilized by a bio-reducible guanylated hyperbranched poly(amido amine) (HSG) ligand. Mechanically, the tumor microenvironment specifically triggers a cascade process of glutathione elimination, ROS generation, and NO release.	EGaIn	In vivo	[318]
	Calcium phosphate ANG for NO production	The calcium phosphate nanotheranostic system (GCAH) is constructed for effective synergistic cancer starvation/gas therapy and it is obtained by a facile biomineralization strategy using glucose oxidase (GOx) as a biotemplate, followed by loading of L-Arginine (L-Arg) and modification of hyaluronic acid (HA) to allow special selectivity for glycoprotein CD44 overexpressed cancer cells. The system only exhausts the glucose nutrients in tumor region by the GOx-triggered glucose oxidation, while the generated H ₂ O ₂ can oxidize L-Arg into NO under acidic tumor microenvironment for enhanced gas therapy.	Calcium phosphate	In vivo	[319]
	Ultrasound and laser-promoted dual-gas ANG	In this nanogenerator, calcium carbonate–polydopamine–manganese oxide NPs undergo reactive decomposition in a moderately acidic tumor, resulting in the generation of calcium, manganese ions, carbon dioxide (CO ₂), and oxygen (O ₂). Calcium and manganese ions act as adjuvants that trigger an immune response. The cancer cell membrane rupture caused by sudden bursts of bubbles (CO ₂ and O ₂) under ultrasound stimulation and the photothermal properties of polydopamine also contributed to the anti-tumor effect.	Calcium carbonate Polydopamine Manganese oxide	In vivo	[320]
	ANG for Ca ²⁺ production	The ANG is based on calcium phosphate (CaP)-doped hollow mesoporous copper sulfide. This generates Ca ²⁺ directly and persistently in the lysosomes (low pH). Near-infrared light radiation can accelerate Ca ²⁺ generation from the basic Ca ²⁺ nanogenerator by disturbing the crystal lattice of hollow mesoporous copper sulfide via NIR-induced heat. Curcumin can facilitate Ca ²⁺ release from the endoplasmic reticulum to the cytoplasm and inhibit the expelling of Ca ²⁺ in the cytoplasm through the cytoplasmic membrane.	Calcium phosphate-doped hollow mesoporous copper sulfide	In vivo	[321]

4. Conclusions: Challenges and Outlook

The advent of bioelectronic BNGs and ANGs has opened new frontiers in cancer treatment, offering innovative approaches that leverage the unique properties of these devices for therapeutic applications. These technologies have demonstrated significant potential in enhancing anti-cancer therapies through localized energy delivery and targeted treatment mechanisms. BNGs (PNGs, TNGs, and PyNGs) and ANGs differ significantly in their applicability, performance, and compatibility for anti-cancer therapy. Piezoelectric and triboelectric nanogenerators generate electricity from mechanical stimuli, making them well-suited for localized drug delivery, electrical stimulation therapy, and nanoparticle-based therapy, where controlled activation is beneficial. Pyroelectric nanogenerators, which convert thermal fluctuations into electrical energy, are more relevant for photodynamic and sonodynamic therapy, leveraging temperature variations for therapeutic activation. These BNGs are biocompatible, utilizing materials like polymers and ceramics, and are fabricated through scalable techniques such as electrospinning and nanolithography. However, they may suffer from limited stability and inconsistent energy output in dynamic biological environments. ANGs, in contrast, rely on nuclear decay, offering sustained energy generation for applications like targeted alpha-therapy and photodynamic therapy. Their stability and long-lasting power output make them advantageous for deep-tissue treatments, but their potential radioactive side effects and limited material options (radioisotopes) pose challenges in clinical translation. Fabrication is more complex, involving isotope enrichment and encapsulation strategies for safety. While BNGs provide versatile and safer alternatives, ANGs offer superior longevity and penetration depth, making them preferable for specific long-term or deeply embedded cancer therapies.

However, several challenges and bottlenecks must be addressed to realize the full potential of these technologies in clinical settings.

4.1. Material Limitations

One of the primary challenges facing the effective implementation of bioelectronic and atomic nanogenerators in anti-cancer therapy is the availability and performance of suitable materials. The materials used in the fabrication of BNGs must exhibit biocompatibility, mechanical robustness, and efficient energy conversion properties. For instance, while polymers such as polycaprolactone and gelatin are commonly used in the design of nanofibrous patches for drug delivery, their mechanical properties may not always meet the demands of long-term implantation or repeated mechanical stress. Additionally, the development of novel materials with enhanced piezoelectric or triboelectric properties is crucial for improving the output performance of these devices. Research into biodegradable materials that can withstand harsh biological environments while maintaining their functional integrity over time is essential for advancing these technologies.

4.2. Size Requirements

Another critical consideration for the successful application of bioelectronic and atomic nanogenerators in anti-cancer therapy is the optimization of system size to balance functionality and biocompatibility. BNGs must be small enough ($< \text{few cm}^2$) to be minimally invasive while still generating sufficient energy to power therapeutic mechanisms, such as localized drug release or electrical stimulation. Miniaturization should not compromise structural integrity, requiring precise engineering to ensure durability under physiological conditions. Furthermore, the integration of nanogenerators with implantable or wearable platforms demands careful design to accommodate power requirements without increasing patient discomfort. Atomic nanogenerators, in particular, must be designed at the sub-nanometer to nanometer scale to harness anti-cancer effects at the cellular scale while

maintaining stability within biological environments. Their ultra-small size allows for targeted delivery at the cellular level, but challenges arise in ensuring biosafety.

Achieving an optimal balance between size, efficiency, and stability is key to enhancing the clinical viability of these technologies.

4.3. Power Management Challenges

Power management remains a significant bottleneck for the effective use of bioelectronic nanogenerators in anti-cancer therapies. The output generated by these devices often involves low voltages and currents, which can complicate signal extraction and utilization. Designing efficient power management circuits that can optimize energy harvesting, storage, and distribution is critical for ensuring that these devices operate effectively within the biological context. Moreover, hybrid systems that combine different energy harvesting mechanisms (such as piezoelectric and triboelectric) can introduce additional complexity in circuit design, necessitating innovative solutions to maximize efficiency while minimizing losses.

4.4. Reliability and Durability

Reliability is another critical factor influencing the successful implementation of nanogenerators in cancer therapies. These devices are expected to undergo continuous mechanical deformation or friction during operation, which can lead to material fatigue and failure over time. Ensuring the durability of all components involved in the fabrication process is essential for long-term functionality. Furthermore, packaging solutions must be developed to protect these devices from environmental factors such as humidity, biofouling, and chemical exposure that could compromise their performance. Advanced encapsulation techniques that provide hermetic sealing while allowing for biocompatibility are necessary to enhance device longevity.

4.5. Integration with Existing Therapies

Integrating BNGs and ANGs with existing cancer treatment modalities poses another challenge. While these technologies hold promise for enhancing localized treatment efficacy, their successful integration into established therapeutic protocols requires extensive research to understand how they interact with other treatments such as chemotherapy or immunotherapy. For instance, combining TAT with nanogenerator technology could potentially enhance therapeutic outcomes by improving drug delivery or stimulating immune responses; however, understanding the timing, dosage, and potential interactions between therapies is essential for optimizing patient outcomes.

4.6. Regulatory Hurdles

Navigating regulatory pathways presents a significant barrier to the clinical translation of bioelectronic and atomic nanogenerators. The approval process for medical devices can be lengthy and complex, requiring extensive preclinical studies to demonstrate safety and efficacy before they can be tested in human trials. As these technologies are often at the intersection of multiple scientific disciplines—materials science, engineering, biology, and medicine—establishing clear regulatory guidelines tailored to their unique characteristics will be crucial for facilitating their development and adoption.

4.7. Cost-Effectiveness

Despite their advantages over conventional therapies, concerns regarding the cost-effectiveness of bioelectronic and atomic nanogenerators remain a significant challenge. While these technologies may offer long-term savings through improved patient outcomes and reduced side effects, initial development costs can be high due to complex fabrication

processes and specialized equipment requirements. Developing scalable manufacturing techniques that reduce production costs while maintaining quality will be essential for making these technologies accessible to a broader range of healthcare settings.

4.8. Biocompatibility Issues

Biocompatibility is a crucial consideration when developing bioelectronic nanogenerators for cancer therapy. The materials used must not elicit adverse immune responses or toxicity when implanted in human tissues. Extensive biocompatibility testing is required to ensure that any materials used in device fabrication do not cause inflammation or other negative reactions within the body. Furthermore, as research progresses toward using biodegradable materials for temporary implants, understanding how these materials degrade over time without releasing harmful byproducts will be essential.

In summary, while BNGs and ANGs hold tremendous promise as unconventional strategies against cancer through enhanced localized treatment mechanisms, several challenges must be addressed before they can be effectively implemented in clinical practice. By focusing on material innovation, power management optimization, reliability studies, integration with existing therapies, regulatory pathways, cost-effectiveness considerations, and biocompatibility issues, researchers can pave the way for these advanced technologies to transform cancer treatment paradigms significantly. As advancements continue in this field, these technologies and approaches may become integral components of comprehensive cancer care strategies aimed at improving patient outcomes while minimizing side effects associated with traditional therapies.

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