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# Applications for Pulse Power using Nanosecond Pulsed Electric Fields (nsPEFs) in Cell Biology and Cancer Treatment

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**Keywords:** Apoptosis; Calcium mobilization; Mitochondria membrane potential; Electroporation; Basal cell carcinoma; Squamous cell carcinoma; Melanoma; Hepatocellular carcinoma; Pancreatic carcinoma

When engineers, physicists and molecular cell biologists began working together, pulse power technology evolved from uses in weaponry and high energy physics to applications in basic science and medicine, including cancer treatment. Pulse power technology uses capacitors with high voltage, fast discharge capabilities that serve as power pulse compression devices. The high voltage is released in nanoseconds into cancer cells or tumors, which are forced to respond to high power, low energy and non-thermal stimuli. Since nsPEFs do not exist in nature, eukaryotic cells evolved without such stimuli; therefore, it is of specific interest to determine how cells respond to these stimuli. As might be expected, responses to nsPEFs are distinct from those induced by previously known forms of cellular stresses [1].

A common example of the pulse power concept comes from storage of 1 joule (J) of energy and releasing it in extremely short times. Released in one second, one microsecond or one nanosecond, the peak power is one watt, one megawatt (one million watts, MW) or one gigawatt (a billion watts, GW), respectively. A one nanosecond pulse delivery yields 1.34 million horsepower. This is equivalent to the power of one of the three main shuttle rockets at lift off; however, it is delivered for just one nanosecond. How do tumor cells respond to this kind of power? This has been one of the focuses of the Frank Reidy Research Center for Bioelectrics and ten other Institutions that are presently part of the Bioelectrics Consortium, which began in 2005 by Old Dominion University in Norfolk, Virginia, Kumamoto University in Kumamoto, Japan and Institute for Pulsed Power and Microwave Technology at the Forschungszentrum Karlsruhe, Germany. So how are high pulse power physics and engineering developing new methods to treat cancer without chemotherapeutic cocktails, ionizing radiation, targeted small molecular weight inhibitors and neutralizing antibodies? However, this does not exclude possibilities that nsPEFs could be used in combination with these modalities [2].

Nanosecond pulsed electric fields charge membranes throughout the cell. One response is to form nanopores in plasma membranes and organelle membranes. Unlike conventional electroporation pores, nsPEFs generate large numbers of nanopores in all cell membranes–a phenomenon called supra-electroporation [3,4]. The presence of such nanopores was demonstrated experimentally as voltage-sensitive and inward-rectifying membrane pores [5]. There is emerging evidence that other structures may be directly and/or indirectly affected, such as enzymes and other proteins [6,7]. In any event, nsPEFs initiates distress signaling on a background of oncogenic signaling in cancer treatment. When electric fields are high enough, cell signaling leads to caspase-dependent apoptosis as well as caspase-independent mechanisms of cell death [8].

NsPEFs are delivered to cells between electrodes in cuvettes or on microscope slides and responses are analyzed such as changes in the mitochondria membrane potential by flow cytometry [9] or calcium mobilization with fluorescent microscopy [10], respectively. For cancer treatment, pulses are delivered after surrounding tumors with needle, plate or suction electrodes. For complete clearance of tumors, it has been suggested that every tumor cell must receive a lethal threshold electric field. However, given a potential for an immune response, this recommendation may not be absolute, as will be presented below.

One interest over the last decade has been tumor elimination in several cancers that are readily approachable with external electrodes. These include melanoma [11,12], squamous cell carcinoma [13] and basal cell carcinoma [14,15]. NsPEFs have also been effective against hepatocellular carcinoma [16] and pancreatic carcinoma [17]. Treating these cancers will advance this technology to internal organs using laparoscopy and catheter electrodes.

Another interest understands what effects pulse waveform components have on cell structures. This is especially true for pulse fast rise and fall times, or in the frequency domain, high frequency components and what effects they have on plasma membranes versus intracellular structures such as mitochondria [9]. Results indicate that 600 ns pulses with fast rise-fall times (15 ns) have greater effects to decrease the mitochondria membrane potential ($\Delta\Psi m$) and viability than slow rise-fall time (150 ns) pulses do. Under these conditions, extracellular calcium is necessary, but not sufficient for loss of $\Delta\Psi m$ and cell death; influx of extracellular calcium and dissipation of $\Delta\Psi m$ are both required for loss of cell viability.

Another perspective seeks to compare *in vitro and in vivo* efficacy and mechanisms of nsPEFs, especially for cell death and tumor clearance. In this comparison, a relationship holds constant for ectopic mouse B16f10 melanoma and ectopic Hepa1-6 HCC. When lethal conditions are compared by the product of pulse duration, electric field and pulse number, about a 30-fold greater product is required *in vivo* compared to *in vitro*. This relationship also holds true for orthotopic rat N1-S1 HCC cells and tumors. This should allow prediction of *in vivo* tumor-eliminating conditions from *in vitro* studies. Based on recent studies, cell death is induced, in part, by intrinsic apoptosis mechanisms *in vitro* [8] and *in vivo* [18].

A recently realized and exciting nsPEF property for effective cancer treatment is the possibility for an immune response after nsPEF treatment. Mice with successfully treated Hepa1-6 HCC tumors

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exhibited protection against a second challenge injection of the same tumor cells, while tumors were readily formed in naïve, aged-matched control mice [19]. Other evidence from UV-induced melanomas indicates that when mice treated with nsPEFs were compared to mice treated with tumor excision, the nsPEF-treated mice were superior at rejecting secondary tumor challenges. Also $CD4^+$-T cells were present within treated tumors [20]. Additional evidence from an orthotopic N1-S1 HCC model also supports nsPEF-induced immune responses [21].

A major problem with advancing nsPEF technology is tight funding circumstances and proposing an unconventional treatment approach compared to individualized, targeted drug therapies. For nsPEFs, patient individualized treatments are not necessary; however presently, not all tumor types can be treated with nsPEFs. Most targeted and conventional cancer therapies, which require months of treatment, have only been temporarily successful before resistances occur. Cell death responses to nsPEFs appear to be much quicker, suggesting that changes for resistance developments should be lower. So far, all cancer cells and normal cells are susceptible when electric fields are sufficiently high. Then susceptible cells include cancer cells, host cells supporting tumor growth and cancer stem cells, which are not vulnerable to treatments that target rapidly dividing cells and may be responsible for some recurrences. In addition, providing further evidence for immune responses after nsPEF treatment should change perspective about this seemingly unconventional cancer treatment.

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