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## Concepts of Cancer and a Novel Cancer Therapy: Treating Tumors as an Aggressive Organ

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Cancer may be one of the oldest diseases on earth. Since advances in medicine have significantly increased our lifespan, cancer has now become one of our biggest “natural” enemies. At the start of the “war on cancer” 40 years ago, we had some basic misconceptions about cancer. When Payton Rous, father of the Rous sarcoma oncovirus, won the Nobel Prize in 1966, he criticized the concept that cancer could be caused by somatic mutations, espousing the idea that all cancers were caused by viruses [1,2]. As late as 1978 Isaiah Fidler, a Houston oncologist, reported that cancer included “one cause, one mechanism and one cure” [3]. It was just a matter of finding the right cytotoxins in the right combination [4]. We had not yet realized that cancer could be identified at base-pair resolutions [5]. In *The Art of War* [6], Sun Tzu, who considered war a necessary evil, prophesized “Know your enemy”. Given our present and growing knowledge of our enemy cancer, we should not have to consider cancer a necessary evil. Since the beginning of this millennium, we have gained a much better understanding of this enemy. Nevertheless, we are still challenged by cancer’s limitless replicative potential [7,8] and its seemingly illimitable power to survive, evade, invade and metastasize.

A major problem for cancer therapy is that it exhibits hundreds of different genotypes defined by substantial numbers of mutations in a wide variety of genes/proteins. To simplify this diversity, Hanahan and Weinberg [7,8] defined eight major cancer hallmarks that control cell homeostasis and proliferation. These include self-sufficiency in growth signals, insensitivity to growth-inhibitory (anti-growth) signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis, reprogramming energy metabolism and evasion of immune surveillance. They also considered that unstable genomes and inflammation could advance multiple cancer hallmarks.

More recently Vogelstein et al. [5] defined a cancer genome landscape, describing cancers as “pathway diseases” with two to eight mutations in genes that provide selective growth advantages to tumors referred to as “driver” mutations. These come from a class of 12 signaling pathways that regulate three core cellular processes: cell fate, cell survival and genome maintenance. With knowledge of cancer’s molecular mechanisms, treatment strategies using mutation-specific, small molecule drugs or monoclonal antibodies have been developed to specifically target some cancers as defined in cancer hallmarks and “driver gene” pathways. One example is the treatment of B-RAF oncoprotein, a major participant in a driver pathway in melanoma, which provides self-sufficiency of growth signals [9,10]. However, tumors treated with B-RAF inhibitors, like other approaches using these strategies, often develop resistance after treatment and tumors reappear. This is a common cancer therapeutic inadequacy. Furthermore, BRAF mutations in colorectal cancers are not responsive to these inhibitors [11]. Thus, new treatment modalities are needed to treat cancer, especially ones that can effectively ablate tumors and enhance immune mechanisms. My laboratory is investigating a relatively new therapy that modifies two cancer hallmarks without drugs: evasion of apoptosis and sustained angiogenesis [12]; however, the latter could be considered an anti-vascular effect. More recently,

we have found that this novel treatment approach may also address another cancer hallmark, evasion of immune surveillance. The strategy, discussed below, uses pulsed power technology that delivers nanosecond pulsed electric fields (nsPEFs) directly to tumors.

During developmental and homeostatic cell death, apoptosis is anti-inflammatory and immunologically silent or tolerogenic [13]. Although some studies show that necrotic cells can provoke an immune response [14-17], a number of recent studies indicate that caspase-dependent processes are important for immunogenicity [18]. In chemotherapy-induced cell death, some (anthracyclins), but not all (mitomycin C) caspase-inducing chemotherapeutic agents initiate immunogenic cell death [19]; thus, not all caspase-mediated apoptosis programs have the same impact on immune mechanisms. Apoptosis has been shown to induce maturation of dendritic cells leading to T-cell activation and immunity [20] and that apoptotic cells not only undergo degradation, but also deliver processed antigen to dendritic cells for cross-presentation [21]. Immunogenic cell death has obvious advantages for cancer treatment. In the last several years, it has been realized that there is a relatively specific set of cell death mechanisms that plays roles in immunogenic cell death. These include changes in cell surface membranes (externalized calreticulin binds to CD91 on dendritic cells enhancing engulfment), release of soluble factors that interact with a series of dendritic cell receptors to enhance antigen presentation to T-cells (HMGB1 binding toll-like receptors and ATP binding to purinergic P2RX7 stimulating IL-1 $\beta$ ) and activation of the immune system against cancer [18]. Thus, there is increasing evidence that it is important to understand mechanisms of tumor cell death because they can provide a means to enhance immune responses and prevent recurrences through immunogenic cell death, whether by apoptosis and/or necrosis.

The approach for *in vivo* cancer treatment in my laboratory and others using nsPEFs [22-25] departs from targeting specific cancer “drivers” with mutation-specific targeted drugs, although treatment with nsPEFs should render most “drivers” inoperable. In evaluating effects of nsPEFs, they do affect several cancer hallmarks as indicated above. However, nsPEFs target the whole tumor as an organ at the primary site.

At the first international Evolution and Cancer Conference in June of 2011, Steven Neuberg, a social psychologist from Arizona State University in Tempe pointed out that a more apt metaphor for

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cancer than “foreign invaders” is cancer as “criminal gangs” who as local residence have gone bad, slowly exploit the environment around them for their own gain. “Cancers are not outside the body, they come from within us”, he said [26]. In this concept, the criminal gang (the cancer) within the local community (cancer microenvironment) coerces the local population (“educating” supporting host cells) to use their resources (growth factors, signaling molecules) to thwart the authorities (evading immune surveillance) and support the gang’s criminal activity (the tumor behaving as an organ). Thus, the presence of cancer supplies a new, demanding organ, more aggressive than other organs in your body. Studies in my laboratory are investigating possibilities that nsPEF ablation goes beyond eliminating tumors at the primary site by alerting the immune system to the “criminal gang’s” cancer activities, thereby providing a protective, vaccine-like effect and preventing recurrences [27].

Pulsed power technology with nsPEFs ablates cancer by a non-thermal, non-drug procedure. Using pulsed power, which has been used for decades in weaponry and high power physics, provides an innovative progression of pulsed power to application in basic science and cancer treatment, among other utilizations [28]. An example of pulsed power principles inherent in nsPEFs is to compare storage of one joule of energy released in one second (1 watt) versus released in one microsecond (1 megawatt) or one nanosecond (1 gigawatt). The latter is enough power to light an intermediate-sized city for that nanosecond. The high power eliminates cells by programmed cell death. It does not immediately “blow cells away”; cell death is delayed and mechanisms are definable and quantifiable *in vitro* [29-35] and *in vivo* [12,27,36,37]. Cells ultimately die by programmed cell death mechanisms that include both caspase-dependent (or -associated) and caspase-independent cell death, which requires further characterization.

We continue to develop a local treatment modality with nsPEFs using an orthotopic rat N1-S1 hepatocellular carcinoma (HCC) model with the likelihood to enhance immune function [27,37]. In the world population, incidence and mortality rates of HCC are nearly equal, symptoms and diagnoses generally occur at advanced stages and prognoses are usually poor. Diagnoses of younger people have increased in the US mostly due to increases in hepatitis C and B infections. However, early diagnoses are more common due to greater awareness, new screening approaches and high-resolution imaging of the liver, providing more definitive diagnoses [38]. Presentation and treatment considerations of HCC are unique compared to other cancers because the prognosis not only depends on tumor size, but also on underlying diseases such as cirrhosis or other hepatic functional maladies [39]. Major problems for HCC treatment include less than 20% patient eligibility for resection because of underlying liver disease and/or tumor position near vital structures. Furthermore, there are no management strategies that avoid multiple treatments and prevent recurrences. These problems are resolvable because nsPEF treatment has sharply defined treatment zones determined by the electrode design, which only affects tissues within electrodes surrounding the tumor. This requires a single treatment and after ablation offers a protection or resistance to further tumor growth [27]. It therefore appears to vaccinate against the same cancer, thereby preventing recurrences.

There are a number of alternative treatments to surgery and drugs with several relatively new technologies for treating HCC using thermal approaches (radiofrequencies, microwaves, cryoablation), chemical techniques (percutaneous ethanol / acetic acid), radiological methods (ionizing radiation, transarterial chemoembolization and radioembolization), high frequency ultrasound (HIFU) treatment

and irreversible electroporation [40-45]. However, while some of these methods have had some success, all of these most often require multiple treatments and recurrences are common. Thermal and chemical methods of ablation are taken from 16<sup>th</sup> century medicine when Ambroise Pare, a self-taught “surgeon”, described charring tumors with a coal-heated soldering iron or scorching them with a paste of sulfuric acid [46]. Patients with HCC are generally spared chemotherapeutic drug treatment, because HCCs are notoriously resistant to chemotherapeutic agents and radiation. Even the new oral multi-kinase inhibitor sorafenib for advanced HCC has only rather modest clinical efficacy extending survival by only 7-10 months [47,48].

There are numerous advantages for using nsPEF ablation as a means for cancer therapy as opposed to other physical and chemical methods, radiofrequency ablation (RFA), radiation or chemotherapeutic agents. (However, nsPEFs have been shown in combination with gemcitabine to provide synergistic cytotoxic responses [49]). nsPEF ablation (1) targets multiple programmed cell death mechanisms that evade apoptosis induction and promote angiogenesis [12,36], two well-known cancer hallmarks; (2) can induce cell death in the absence of FADD, caspase-8 and APAF-1, which bypasses cancer-causing mutations that block death receptor pathways and caspase activation [32]; (3) targets mitochondria-mediated programmed cell death [30,32,50,51] even in the presence of Bcl-xl overexpression, which protects mitochondria [Beebe et al., unpublished]; (4) provides well-defined treatment zones that focus treatments to the tumor and marginal tissue surrounded by electrodes, which minimizes damage to healthy surrounding tissue [52]; (5) exhibits broad specificity for cell death induction in tumor masses and the microenvironment, which includes rapidly growing tumor cells, slower growing host cells that collaborate with tumor cells and cancer stem cells; (6) requires a single treatment lasting about 17 minutes with rapid tumor disappearance [27], which avoids long treatment times that allow chances for resistance-causing mutations that lead to recurrences; (7) exhibits minimal local and systemic side effects; (8) induces local infarction of small vessels [12,36] and transiently reduces blood flow to tumors, yet recovers to allow inflow of immune cells [27]; and (9) provides a protective, vaccine-like effect in ectopic mouse and orthotopic rat models for HCC [27]; this shows that this protective effect is independent of species or tumor location. We hypothesize that this is likely due to enhanced immune surveillance from cells undergoing nsPEF-induced cell death, thus addressing another cancer hallmark [27].

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