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Nanopulse stimulation can reverse immunosuppression and activate immunity memory in two orthotopic cancer models

Nanopulse Stimulation (NPS) is a pulsed power technology that delivers non-thermal, high-power, nanosecond duration pulses to cells and tumors. Innate and adaptive immunity are scheduled NPS responses. In orthotopic models of rat N1-S1 liver and mouse 4T1-Luc breast cancers, NPS induces an in situ vaccination such that animals are immune to challenge injections post-treatment. Significant for tumor elimination and immunity, NPS causes electric field intrusion into intracellular domains, with mitochondria as primary sensors. In both cancer models, NPS resolves the immunosuppressive tumor microenvironment (TME). In the 4T1-Luc model, TGFβ+ and 4-1BB+ activated T-regulatory cells (Tregs), myeloid-derived suppressor cells (MDSC), and tumor-associated macrophages (TAMs) are selectively eliminated with concomitant M-1 macrophage polarization and Tregs shifting from an activated to a naïve identity. With increases in resident memory T cells, the effector T cell / Treg ratio increases, demonstrating mechanisms for adaptive immunity. The rat liver model also showed specific increases in two activated natural killers (NK) cell phenotypes, one of which returned during the challenge-response.

In contrast, in the ectopic B16f10 melanoma model, NPS was less effective in eliminating tumors and inducing vaccine effects. NPS began to dismantle the B16f10 TME and initiate an immune response with increases in various activated, effector, and memory T cells, NKs, and M1 macrophages. However, the initial decreases in immunosuppressive cells are followed by the combined effects of persistent T regulatory cells and M2 TAMs along with various expression markers, including exhaustion signatures that potentiated the suppressive TME

We are now directed to resolve this return of immunosuppression to the TME. We have combined NPS with gene electron delivery (GET) of an IL-12-plasmid. This approach did not induce a better vaccine effect. Our ongoing approach is to inject carbon nanotube (CNTs) functionalized with anti-PD-L1. CNT alone deceased NPS conditions by 3-fold *in vitro.*

Recent Publications

1. Stephen J Beebe, et.al, (2022): Photodynamic Therapy of Inorganic Complexes for the Treatment of Cancer. Photochemistry and Photobiology 98 (1), 17-41
2. Stephen J Beebe (2021): Effects of usEPs on Plasma Membranes—Pores, Channels, and Repair. Ultrashort Electric Pulse Effects in Biology and Medicine, 33-75
3. Stephen J Beebe (2021): Effects of usEPs on DNA, Nuclear, and Subnuclear Compartments. Ultrashort Electric Pulse Effects in Biology and Medicine, 159-174

Biography

Stephen J Beebe received his BS degree in Zoology, Ohio University, Athens (1970), and Ph.D. in Medical Sciences (Pharmacology), Toledo University School of Medicine (1982). He was a Post-Doctoral Fellow / Associate, Department of Molecular Physiology and Biophysics, Vanderbilt (1982-1987), and a Fulbright and Marshal Scholar at the National Hospital and Institute for Medical Biochemistry, Oslo, Norway (1987-1989). At the Eastern Virginia Medical School (1989-2007), he was an Assistant Professor, Jones Institute for Reproductive Medicine, Department of Obstetrics and Gynecology (1989-1994), and an Associate Professor in the Departments of Pediatric and Physiological Sciences (1994-2007). He is now a Professor in the Frank Reidy Research Center for Bioelectrics, Old Dominion Univ., Norfolk, VA (2007-present).

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