Editorial
Plasma and Cancer Treatment

THE INTERNATIONAL Workshop on Plasma for Cancer Treatment, IWPCT, is an international workshop that focuses on basic and clinical research into the interaction of low temperature plasmas (LTP) with cancer cells and tumors. It was founded in 2014 by Prof. M. Keidar and Prof. M. Laroussi as a venue for researchers to present their cutting edge research on the application of LTP for cancer treatment, or "plasma oncology." The first IWPCT was held in March 2014 in Washington, DC, USA, under the co-chairmanship of M. Laroussi (Old Dominion University, Norfolk, VA, USA) and M. Keidar (George Washington University, Washington, DC, USA). The second workshop, IWPCT-2, was held in March 2015 in Nagoya, Japan under the chairmanship of Prof. M. Hori (Nagoya University, Nagoya, Japan). IWPCT-3 was held again in Washington, DC, USA, in April 2016 under the co-chairmanship of Dr. J. Canady (Jerome Canady Research Institute, Takoma Park, MD, USA) and Dr. J. Sherman (George Washington University). The fourth workshop, IWPCT-4, was held on March 27–28, 2017 at the Institut Curie, Paris, France, under the co-chairmanship of Dr. J. Santos-Sousa (Universite Paris-Sud, Orsay, France) and Dr. P.-M. Girard (Institut Curie). IWPCT-4 was technically co-sponsored by the IEEE-NPSS and full papers based on the oral presentations given at the workshop were submitted and peer-reviewed for eventual inclusion in this issue of TRPMS.

The cancer application of LTP (or plasma oncology) is a vibrant topic of research within the field of biomedical applications of LTP, known today as plasma medicine. Plasma medicine research started in the mid-1990s with experiments on the inactivation of bacteria on biotic and abiotic surfaces and in media. Since then the field has grown and expanded into potential applications for new therapies in wound healing, dentistry, and cancer treatment. Also, within the last decade several LTP sources have been approved for cosmetic and other medical use: for example, in 2008 the FDA approved the Rhytec Portrait (plasma jet) for use in dermatology. Other plasma devices for various medical applications, such as the Bovie J-Plasma and the Canady Helios Cold Plasma and Hybrid Plasma Scalpel are today in use in USA. In U.K., the Adtec MicroPLaSter (developed in collaboration with the Max Planck Institute) was approved for clinical trials in 2008. In Germany, the kINPen (developed by INP, Greifswald) received medical certification class IIa in 2013. The PlasmaDerm device (CINOGY GmbH Duderstadt, Germany) operates as a dielectric barrier discharge in open air and was also approved in Germany.

Starting around the mid-2000s several investigators reported on successful tests which showed that LTP can destroy cancerous cells *in vitro* and *in vivo* 1)–4). These include cancer cell lines such as glioblastoma, carcinoma, leukemia, melanoma, and others. In addition, several reports showed preliminary evidence that LTP kills cancer cells in a selective manner. This gave the research community an impetus to thoroughly investigate LTP as a potential future therapy for some types of cancers.

Investigators reported that the effects of LTP on biological cells are mediated by reactive oxygen and nitrogen species (RONS) 5). In cancer cells these mechanisms of action include the induction of apoptosis, cell cycle arrest at the S-phase, DNA damage/double-strand breaks, and increase of the intracellular concentrations of ROS. Research by various groups showed that RONS generated by LTP react with cell membranes and can even penetrate the cells and induce subsequent reactions within the cells that can trigger cell signaling cascades, which can ultimately lead to apoptosis. In fact LTP delivers not only reactive species but it also can exhibit large enough electric fields that are suspected to also play a role, such as in cellular electroporation which in turn can allow large molecules to enter the cells. Another interesting approach that has been researched in the last few years is to use plasma activated media (PAM) instead of directly applying LTP to cancer cells 6). By exposing liquid media to LTP investigators have shown that species generated by the plasma react inside the gas-liquid boundary and create secondary longer lived species that can diffuse into the liquid and "activate" it 7). Concentrations of species such hydrogen peroxide and peroxynitrite have been measured in the liquid and correlated with the effects of PAM on cancer cells 8). One of the advantages of PAM is that it can be stored and used at a later time (up to several hours).

This issue contains papers discussing the latest results on the application of LTP to various cancer cell lines, including those associated with brain cancer (glioblastoma), breast cancer, and skin cancer (melanoma). The fundamental and applied studies presented in this issue cover both direct LTP application and treatment by plasma activated media modalities. In addition, one paper considers immunogenic response to LTP and another discusses a model-based control of plasma jets, an important issue to be considered in the design of plasma sources intended for medical applications.

To conclude, the guest editors would like to thank all the authors for their valuable contributions and the reviewers for their time and efforts. Special thanks go to the

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M. LAROUSSI, *Guest Editor*

D. GRAVES, *Guest Editor*

M. KEIDAR, *Guest Editor*

APPENDIX
RELATED WORK

1) M. Keidar *et al.*, "Cold plasma selectivity and the possibility of a paradigm shift in cancer therapy," *Brit. J. Cancer*, vol. 105, no. 9, pp. 1295–1301, 2011.
2) M. Vandamme *et al.*, "Antitumor effects of plasma treatment on U87 glioma xenografts: Preliminary results," *Plasma Process. Polym.*, vol. 7, nos. 3–4, pp. 264–273, 2010.
3) J. Schlegel, J. Köritzer, and V. Boxhammer, "Plasma in cancer treatment," *Clin. Plasma Med.*, vol. 1, no. 2, pp. 2–7, 2013.
4) M. Laroussi, S. Mohades, and N. Barekzi, "Killing of adherent and non-adherent cancer cells by the plasma pencil," *Biointerphases*, vol. 10, 2015, Art. no. 029410.
5) D. B. Graves, "The emerging role of reactive oxygen and nitrogen species in redox biology and some implications for plasma applications to medicine and biology," *J. Phys. D Appl. Phys*., vol. 45, no. 26, 2012, Art. no. 263001.
6) F. Utsumi *et al.*, "Effect of indirect nonequilibrium atmospheric pressure plasma on anti-proliferative activity against chronic chemo-resistant ovarian cancer cells in vitro and in vivo," *PLoS ONE*, vol. 8, no. 12, 2013, Art. no. e81576.
7) X. Lu *et al.*, "Reactive species in non-equilibrium atmospheric-pressure plasmas: Generation, transport, and biological effects," *Phys. Rep.*, vol. 630, pp. 1–84, May 2016.
8) S. Mohades, N. Barekzi, H. Razavi, V. Maramuthu, and M. Laroussi, "Temporal evaluation of antitumor efficiency of plasma activated media," *Plasma Process. Polym*., vol. 13, p. 1206, 2016.