Epithelial-to-mesenchymal transition enhances cancer cell sensitivity to cytotoxic effects of cold atmospheric plasmas in breast and bladder cancer systems

*Peiyu Wang [1, 2], Renwu Zhou [4], Patrick Thomas [1, 2], Susmita Mandal [5], Mohit K. Jolly [5], Derek J. Richard [1,2], Bernd H. A. Rehm [6], Kostya (Ken) Ostrikov [7], Xiaofeng Dai [3], Elizabeth D. Williams [1, 2], Erik W. Thompson [1, 2, *]*

1, Queensland University of Technology, School of Biomedical Sciences, Brisbane 4059, Australia
2, Translational Research Institute, Woolloongabba, Queensland 4102, Australia;
3, Wuxi School of Medicine, Jiangnan University, Wuxi 214122, China
4, School of Chemical and Biomolecular Engineering, The University of Sydney, NSW 2006, Australia
5, Centre for BioSystems Science and Engineering, Indian Institute of Science, Bangalore 560012, India
6, Centre for Cell Factories and Biopolymers, Griffith Institute for Drug Discovery, Griffith University, Nathan, QLD 4111, Australia
7, Queensland University of Technology, School of Chemistry and Physics, Brisbane 4000, Australia
*Correspondence: *e2.thompson@qut.edu.au* (E.W.T), t: +61 (0)7 3443 7365

Cold atmospheric plasma (CAP) has emerged as a highly selective anti-cancer agent, most recently in the form of plasma-activated medium (PAM). Since epithelial mesenchymal transition (EMT) has been implicated in metastasis and resistance to various cancer therapies, we assessed whether EMT status associated with PAM response. Mesenchymal breast cancer cell lines as well as the mesenchymal variant in an isogenic EMT/MET human breast cancer cell system (PMC42-ET/LA), were more sensitive to PAM treatment than their epithelial counterparts, contrary to their responses to other therapies. The same trend was seen in luminal bladder cancer model (TSU-Pr1/B1/B2) and the basal 5637 bladder cancer cell line. Three-dimensional spheroid cultures of the bladder cancer cell lines were less sensitive to the PAM treatment compared to their 2-dimensional counterparts; however incrementally better responses were seen in more mesenchymally-shifted cell lines. This study provides evidence that PAM preferentially inhibits mesenchymally-shifted carcinoma cells, which have been associated with resistance to other therapies. Thus, PAM may represent a novel treatment that can selectively inhibit triple-negative breast cancers, which tend to be more mesenchymal, and may be selectively active against metastasis. Our approach may potentially be utilized for other aggressive cancers exhibiting EMT and opens new opportunities for CAP and PAM as a promising new onco-therapy.