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**Adaptive plasma for cancer therapy: physics, mechanism and applications<sup>1</sup>**

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One of the most promising applications of cold atmospheric plasma (CAP) is the cancer therapy. The uniqueness of plasma is in its ability to change composition in situ. Plasma self-organization could lead to formation of coherent plasma structures. These coherent structures tend to modulate plasma chemistry and composition, including reactive species, the electric field and charged particles. Formation of coherent plasma structures allows the plasma to adapt to external boundary conditions, such as different cells types and their contextual tissues. In this talk we will explore possibilities and opportunities that the adaptive plasma therapeutic system might offer. We shall define such an adaptive system as a plasma device that is able to adjust the plasma composition to obtain optimal desirable outcomes through its interaction with cells and tissues. The efficacy of cold plasma in a pre-clinical model of various cancer types such as lung, bladder, breast, head, neck, brain and skin has been demonstrated. Both *in-vitro* and *in-vivo* studies revealed that cold plasmas selectively kill cancer cells. Recently mechanism of plasma selectivity based on aquaporin hypothesis has been proposed. Aquaporins (AQPs) are the confirmed membrane channels of H<sub>2</sub>O<sub>2</sub> and other large molecules. We have demonstrated that the anti-cancer capacity of plasma could be inhibited by silencing the expression of AQPs. Additional possible cell feedback mechanism was recently discovered. It is associated with production of reactive species during direct CAP treatment by cancer cells. Selective production of hydrogen peroxide by different cells can lead to adaptation of chemistry at the plasma-cell interface based on the cellular input. In particular we have found that the discharge voltage is an important factor affecting the ratio of reactive oxygen species to reactive nitrogen species in the gas phase and this correlates well with effect of hydrogen peroxide production by cells.

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