

Plasma biological applications: Issues and challenges linked to plasma/target interactions

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The last decade has seen an impressive increase of the research dedicated to the biological applications of low temperature atmospheric pressure plasmas. Medical applications are tacking an increasing place underlined by many clinical trials. Biological applications extended to agriculture and, more recently, to cosmetic. Despite the huge number of experiments, there are still numerous challenges to overcome linked to the nature of the encountered target (biological tissues and materials, organs and their direct environment, liquids) that have a direct effect on the produced plasma itself and on the generated species.

The extremely strong coupling between the plasma characteristics and those of the target (e.g. ref. [1, 2]), plays a very important role in the results observed during treatments. A variation in the chemical or physical characteristics of the target will involve significant differences in the gas flow, the local temperature, or the induced electric field, resulting *de facto* in variations in the production of the reactive species. It also concerns the transposition of the results between the *in vitro* and the *in vivo* experiments that are carried out under extremely different conditions, especially concerning the equivalent electric circuit of the reactor / plasma / biological target assembly. These problems directly affect the identification of the processes involved and currently limit the possibility of a definition of a "dose" in plasma treatments. In addition, a study recently reported in [3] led to think over non-sustainable tumor response. The loss of effectiveness under long-term plasma treatment of cancer tissue opens questions about plasma application and protocol. It must be considered that the treated area is morphologically and chemically changing over the time, from activated surrounding to more normal tissues that are less humid and bacteriologically cleaner. This aspect is of particular importance for the development of efficient systems and protocols for any plasma therapeutic approaches. It induce a in real-time in situ control of plasma production and at longer term a protocol adaptation taking into account the biological target evolution.

We will discuss the induced changes in gas flow and plasma characteristics, as well as changes induced in microenvironment of living targets. We will emphasize on the fact that plasma diagnostics must be performed in real treatment conditions. We will also tackle the main issues and challenges linked to the control of the multimodal action of non-equilibrium cold plasmas on living organisms.

[1] T. Darny, J.M. Pouvesle, J. Fontane *et al*, PSST, 26 105 001 (2017)

[2] T. Darny, J.M. Pouvesle, V. Puech *et al*, PSST, 26 045 008 (2017)

[3] H.R. Metelmann, C. Seebauer, V. Miller *et al*, Clinical Plasma Medicine 9, 6 (2018)

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