OFES Town Hall Whitepaper

Cold Atmospheric Plasmas and their Interface with Biology

Michael Kong, Old Dominion University, Norfolk, Virginia, USA

Oral presentations and primary workshop are desired.

1. Research Frontier and Scientific Challenge:

Reaction chemistry of cold atmospheric pressure plasmas (CAP) is unique with its breadth and depth enabled by rapid collisions (up to 10^{12} Hz) of more than one hundred particles, all initiated and modulated by electrons. Little evidence, if any, exists of similar reaction chemistry created without plasmas. The importance of CAP in biology is well recognized within the field of plasmas, but less so by that of biology and medicine. The current understanding of plasma medicine needs to be much more advanced to establish that CAP-induced signaling is a unique and realistic route to controlled manipulating of many cellular functions. Significantly new research agendas are also needed in the translation space. Take drug development as an example, two common FDA questions are (1) the chemical identity of the drug and (2) the dose range of safety and effectiveness. There is little evidence that translational questions such as these could be readily addressed from current research activities in cold atmospheric plasmas and plasma biomedicine. New research frontiers must include translation-relevant scientific challenges.

Synergy of reactive oxygen species (ROS) and reactive nitrogen species (RNS) is a hallmark of CAP chemistry and is widely considered as a key indicator of why plasma chemistry is unique. Scientifically, it is exceptionally challenging to pinpoint chemical identities of a plasma treatment regimen when synergy is the dominant theme. Does the solution lie in persistent diligence and increased investment? In molecular biology, the concept of gene expression profiling is used to measure the activity of thousands genes simultaneously and create a globe picture of cellular functions. This has inspired the concept of materials genome as a way to catalogue different types of materials. A similar concept of plasma chemistry genome is then plausible by profiling ROS/RNS. Here, a concentration baseline is needed to identify which ROS/RNS are likely to contribute to a plasma-induced biological event, similar to the baseline of gene expression. For manipulation of cell functions, it is useful to note that physiological levels of endogenous ROS/RNS in cells are usually from 100pM (e.g. NO) to a few μM (e.g. H_2O_2). These are the levels for plasma-induced aqueous species around which to induce preferential changes in cellular functions without undue tissue damage. This implies that concentrations of relevant gaseous plasma species may need to be as low as a few to a few tens ppb, already below the detection limit of some of the current plasma diagnostics (e.g. laser-induced fluorescence). Clearly, the lack of precision diagnostics has knock-on effects on our ability to decipher chemical identities of CAP and their effective and safe dose rage.

Of the above challenges and those discussed at recent international conferences and in literature, a priority may be established based on what could be realistically achieved with the most advanced of plasma science and what needs significant participation and possibly leadership from the biology community. The following are proposed as key knowledge gaps as the target of scientific challenges:

- Profile of plasma species in terms of their concentrations (as a measure of the identity of CAP chemistry and as the basis with which to develop CAP dose profile);
- Transfer functions of reactive plasma species from gas phase to liquid phase and then to cells;
- ROS/RNS impacts on structures (hence functions) of biomolecules;
- Well-engineered CAP system capable of precision delivery of ROS/RNS at sub-ppm level

Ultimately, significant advances in addressing these scientific challenges and others would lead to a well-engineered CAP technology with a catalog of different combinations of ROS, RNS and other quantities in the form of an identity profile and an dose profile, thus giving a clear landscape of the accessible plasma chemistry and its quantitative classification. With a capability of precision control of delivered plasma species, the ROS/RNS profile catalog can then be used to explore the benefits of CAP to many different

diseases with clarity and confidence. In turn, these would collectively help identify the uniqueness of CAP-enabled therapies and biotechnologies.

2. Approaches and Research Capabilities to Advance Research Frontier:

With research challenges set in the translation space, effective approaches will need to consider factors relevant to and methodologies appropriate for biology. There are already exciting examples of embracing such changes, for example modeling of how gaseous plasma species interact with liquid, biofilm and liquid-covered tissues and of how ROS affect lipids and cell membranes. The former extends the capability of classical plasma global and fluid models, whereas the latter introduces the recent advance in molecular dynamics simulation. Once fully validated, these modeling studies help establish a quantitative understanding of and relevant control strategies for transport of gaseous plasma species into cell and tissue containing liquid. These have considerable upward scope, for example in providing atomic details of how plasma ROS/RNS affect dynamically specific proteins that are key to certain human diseases. Here, validation and benchmarking face two challenges, namely the lack of knowledge of relevant reaction coefficients and the need to introduce and develop new experimental methodologies for the liquid-phase (and account for the presence of cells and tissues).

A great deal of work is needed in order to establish a well-reasoned recommendation list for specific approaches for advance the research frontier and required research tools and capabilities. The most important component in identifying such approaches is to engage representatives of the biology community who have keen interest in plasma technologies, and the most significant research tool or capability is an interdisciplinary research facility for plasma biomedicine. The benefits of the latter have been unambiguously established in Germany and South Korea. These are likely to be the most enabling for the advance of the field. Some progresses have already been made, for example, the use electron paramagnetic resonance for liquid-phase ROS/RNS concentration measurements and the introduction of ROS/RNS knockout using ROS/RNS scavengers. The lack of reaction coefficients in the liquid phase may be addressed, alone with other techniques, quantum chemistry modeling.

3. Impact on Plasma Science and Potential for Societal Benefits:

Cold atmospheric pressure plasmas represent the newest member of the low-temperature gas plasma family, and investigations of CAP interface with biology will advance plasma science with new understanding, diagnostics and simulation tools, and new methodologies to catalogue plasma-materials interactions. The need to achieve sub-ppm precision will help enhance plasma science as a quantitatively controllable science. A significant broadening of the scope of current plasma science is the expansion to the liquid phase. In the gas phase, classical low-temperature plasma physics is underpinned by electron energy distribution function (EEDF) and ion energy distribution function (IEDF) with which to unravel and understand most chemical reactions. In the liquid phase, solvated electrons are much fewer in quantities and with little kinetic energy. As a result, reaction chemistry is no longer dictated by EEDF. An example of new plasma questions may be how plasmas mediate the dynamics of the electron donors and acceptors in liquid and indeed in cell-containing media. A new horizon of plasma science is emerging.

At present, cold atmospheric plasmas have established their merits for tissue ablation and coagulation, disinfection, wound healing, and therapies for some cancers. Plasma-based tissue ablation and coagulation are performed routinely in Europe and United States, whereas plasma-enabled decontamination of flexible endoscopes is a few years from the market and several phase-II clinical trails have been completed successfully for plasma treatment of chronic wounds. Infectious diseases are a major cause of death, and according to Centers for Disease Control and Prevention (CDC) the annual cost for antibiotics resistance caused infection is $55bn in 2013. Similar strong cases could be made in other applications of CAP, such as control of food spoilage and wastage, for which the direct economic cost is $750bn pa according to Food And Agriculture Organization (FAO) of the United Nation. There is a very strong and compelling case of major societal benefit for research in plasma biology.