Plasma Medicine

by Michael R. Wertheimer and Sylvain Coulombe

Plasma Medicine (PM) is a relative newcomer among traditional areas of plasma processing science, but it has been expanding very rapidly in recent years; it now implicates researchers and users not only from plasma-related sciences and technology, but also increasingly from biology, microbiology, medical and dental research, and even clinical practice of medicine and dentistry. Among tangible proofs that PM has now become quite well established are the following:

(i) In June of 2012 the *4th International Conference on Plasma Medicine* (ICPM-4) was held in Orléans, France; it attracted 280 attendees, 100 more than its predecessor, ICPM-3, held 2 years prior, and three times more than ICPM-2.

(ii) The *International Society of Plasma Medicine* (http://www.plasmamed.org/) was founded in 2009.

(iii) Two young journals, "*Plasma Medicine*" (Begell House Inc., Publishers) and "*Clinical Plasma Medicine*" (Elsevier GmbH) now cater specifically to researchers in this field. Very recently, a book entitled "*Plasma Medicine: Applications of Low-Temperature Gas Plasmas in Medicine and Biology*" [1] appeared in print, the first dedicated specifically to this field.

However, the discipline of PM goes much further back in time: it may, in fact, be considered an agglomeration of several distinct areas of research and applications, some of them advanced to the point of therapeutic practice and industrial implementation. As schematically represented in Figure 1, these are:

(a) Plasma sources designed for biomedical and therapeutic uses;

(b) Sterilization and decontamination aided by "cold" plasmas;

(c) Two- and three-dimensional solid surfaces designed for the immobilization of bio-molecules and / or living cells for cell-culture or "tissue engineering";

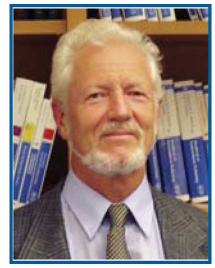
(d) Finally, the actual use of gas-discharge plasmas on living cells or tissues, for biological research or clinical treatments.

We shall start by listing recent review articles of a general nature, through which the interested reader may rapidly acquire an overview of PM. Following this, we briefly address each of the areas identified above separately, highlighting what we believe to be the most important developments and trends for the future.

As already mentioned, the literature related to the various component-fields that comprise PM has been growing exponentially in recent years. Beside the two above-mentioned new journals exclusively devoted to PM, many articles (including review papers) can be found in "traditional" journals that regularly publish plasma-related research results. For example, three entire issues of the journal *Plasma Processes and Polymers (PPaP)* were devoted to PM, namely Vol. 5, No. 6 (August 2008); Vol. 7, No. 3–4 (March 2010); and Vol. 9, No. 6 (June 2012). A review article in the first, by G. Fridman *et al.*, is entitled "*Applied plasma medicine*" [2], while the lead-review article in the second, by G. Lloyd *et al.*, is entitled "*Gas plasma: medical uses and developments in wound care*" [3]; another important contribution, by A. von Keudell *et al.*, bearing the title "*Inactivation of bacteria and biomolecules by low-pressure plasma discharges*" [4] reports very extensive results obtained in the course of a multi-year "BIODECON" project funded by the European Commission. That same topic, "plasma sterilization and decontamination", is the theme of eight articles that comprise the third (2012) special issue of *PPaP* mentioned above, Vol. 9, No. 6, pp 559–629. Similarly, a review article by M.G. Kong *et al.*, entitled "*Plasma medicine: an introductory review*" [5] kicks off an issue of the *New Journal of Physics* (Vol. 11, No.11, November 2009) containing numerous articles with the common theme "Focus on Plasma Medicine".

Let us now address salient features of each of the four sub-fields of PM, (a) to (d) above; we point out principal unanswered questions and anticipated future trends.

(a) Plasma sources for PM. Figure 2 is a mosaic of images depicting plasma sources being used for PM research, but also for therapeutic applications, several of them in Greifswald, Germany, where an important collaboration exists between the Leibniz-Institute for Plasma Science and Technology e.V. (INP Greifswald) and neighbouring medical faculties [6]. These sources all have certain features in common, namely that the generated plasma discharges are "cold" (gas temperature is near-ambient) and that they operate at atmospheric pressure. Gases being used to feed these plasma sources are generally the noble gases (Ar or He), or air. However,



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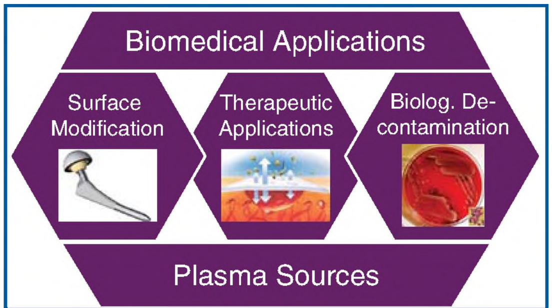

Fig. 1 Schematic representation of the main areas comprising “Plasma Medicine“ (Plasma uses in the Life Sciences). Courtesy of Prof. Dr. K.-D. Weltmann, INP, Greifswald, Germany.

at least one source that is already approved world-wide for PM with human patients operates at somewhat higher temperature, namely the *PlasmaJet* system [3], illustrated in Figure 3: Here, a fine beam of neutral Ar plasma, manipulated by a skilled surgeon, releases both thermal and kinetic energy upon contact with diseased tissue. More will be said about it in (d) below. A final illustration in this section, Figure 4, shows a 2.45 GHz microwave-powered “plasma-jet” that was developed at the Max-Planck Institute for extraterrestrial physics (MPE) in Munich, Germany, extensively studied and used by G. Morfill *et al.* [5,7]: a flow of several standard litres per minute (slm) of Ar passing through the discharge zone is directed downstream to the area of the patient’s body being treated (Fig. 4a). Here too, more will be said in section (d) below.

(b) Sterilization and decontamination. Bacteria, bacterial spores, endotoxins, harmful proteins such as prions, and other undefined organic matter can all be found on surgical instruments, catheters and endoscopes after medical use. If these expensive devices are to be reused for health-care, they must be subjected to increasingly rigorous sterilization procedures, for example those described in the ISO EN 15883 standard. Just like synthetic organic photoresists used in lithographic steps during the manufacture of integrated circuits [8], these biologically-derived organic solids can be volatilized and removed by low-temperature plasma treatments, or at least deactivated and rendered harmless [4,9,10], using either suitable low- or atmospheric-pressure plasma devices (see also *PPaP* 9(6), 2012). Near-ambient temperature of treatment is important, because many medical devices include plastic parts, or are thermally sensitive for other reasons. Although related journal- and patent literature goes back to the 1960s, and there even exists since many years a commercial device (Johnson & Johnson “Sterad-100S”) that uses plasma to destroy residues of the actual sterilizing agent, H_2O_2 [9,10], much current work is still aimed at better understanding of the complex mechanisms that involve the plasmas’ various neutral and ionized active species as well as energetic photons, as they interact with the targeted biological systems. Only very recently has a first fully plasma-based industrial process, in the pharmaceutical domain, been announced [11]; this constitutes a major step forward for the many researchers in this field.

(c) Substrates for cell-culture and tissue engineering. Commercial cell-culture ware, for example Petri dishes, are made of medical-grade poly(styrene); in order for their surfaces to be “wettable” and thereby to promote cell adhesion and –proliferation, the manufacturers subject those products to surface-modification by plasma-induced “grafting” of oxygen- (and sometimes

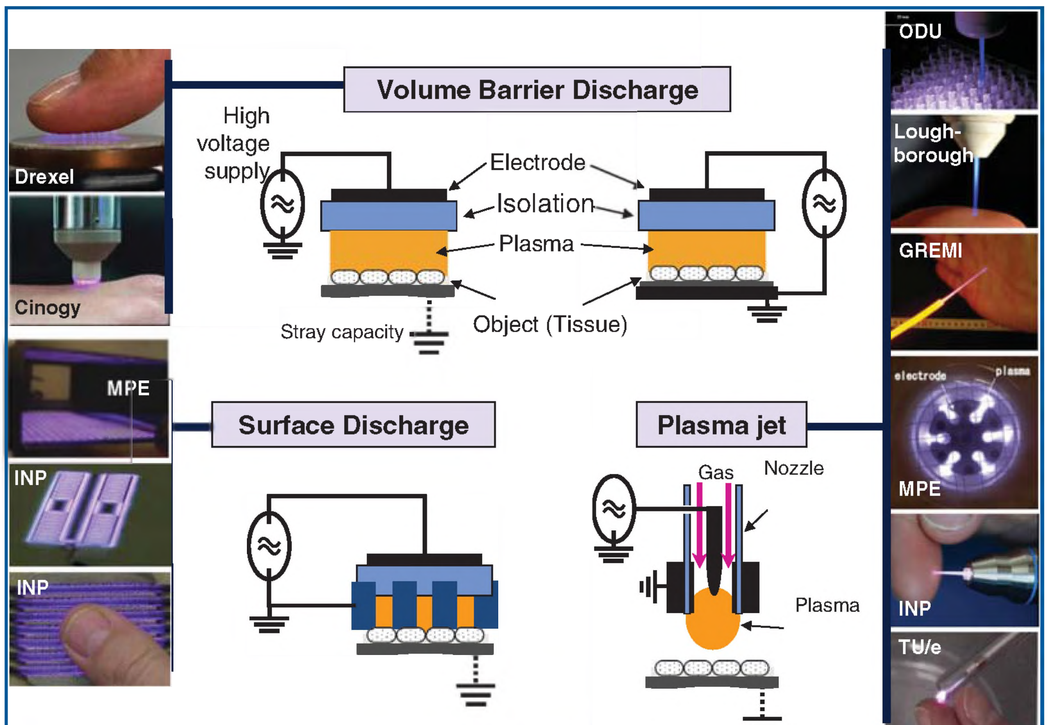

Fig. 2 Plasma sources developed in various laboratories, including INP Greifswald, Germany (see text). Courtesy of Prof. Dr. K.-D. Weltmann; see also ref. [6].

Fig. 3 PlasmaJet System (Plasma Surgical, Inc., Abingdon, UK); from [3], with permission.

biodegradable polymers such as poly(lactide): Wyrwa and coworkers[13] used electrospinning to create non-woven scaffolds comprised of sub-µm fibres, which were subsequently coated with an ultra-thin layer of plasma-polymerized allylamine. The coated structures were found to promote adhesion and spreading of human MG-63 osteoblast cells, the eventual aim being to grow a bone-like 3D solid structure from which the original polymer scaffold was removed by bio-degradation. An Italian-British collaboration is pursuing a similar methodology, but using instead a highly porous 3D scaffold made of poly(caprolactone)[14].

nitrogen-)-containing polar functional groups. In a recent review article, Siow *et al.*[12] describe the now enormous body of world literature wherein plasmas are used both for grafting but also for deposition of thin organic coatings, to generate chemically reactive surfaces for biomolecule immobilization and cell colonization. These techniques are now also being applied to the domain of tissue engineering on three-dimensional (3D) structures, for example ones made of

(d) Clinical Plasma Medicine. Just like gas-discharge plasma is capable of destroying prokaryotic cells (bacteria), it can have *beneficial* effects on healthy eukaryotic cells (mammalian cells), or it can be made to preferentially destroy cancerous cells, for example by inducing apoptosis[15]. Plasma is now increasingly used therapeutically in endoscopic surgery (see below) and other medical protocols, for example applied in direct contact with living tissues to deactivate pathogens (e.g. bacteria or bio-films); to stop bleeding without damaging healthy tissue; to disinfect wounds (for example, chronic ulcers, see below) and to assist wound-healing; to treat dermatological disorders, including wrinkling of skin, and in certain dental applications (e.g. whitening of teeth, root-canal treatments, among others). Let us briefly return to Fig. 3: The hand-held jet can act like a "plasma scalpel" that incises diseased tissue, including deep inside the human body for treatments of endometriosis, Barrett's disease, and numerous others[3]. The mechanical agitation of the flowing gas stream dissipates excess liquid in the operative field, while the plasma jet's thermal energy cuts the (dried) tissue and rapidly coagulates the thin, superficial layers, thereby minimizing blood-loss. The microwave-driven cold atmospheric Ar plasma illustrated in Fig. 4 was demonstrated to be a very safe and effective add-on therapy in patients with chronic infected wounds[3,16]: A 5 min. therapy regimen led to 34% higher

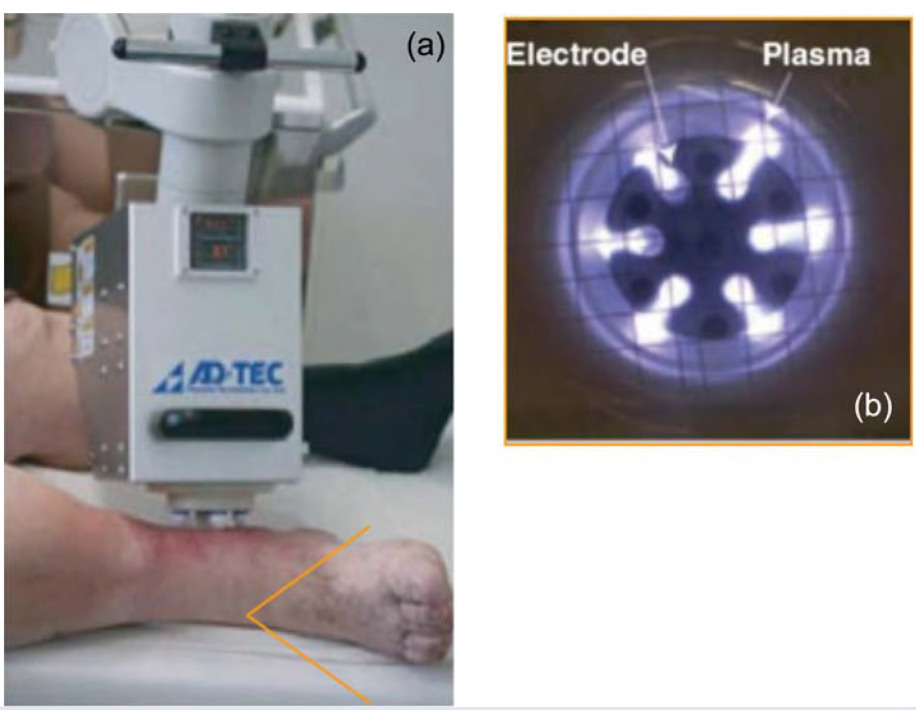

Fig. 4 (a) Microwave-powered plasma torch applied to patient with a chronic leg wound; (b) view into the torch during operation; from [7], with permission.

germ reduction in 291 applications on 36 patients, compared to controls. Subsequent studies revealed that 2 min. treatments were just as effective (40%, 70 applications, 14 patients); the beneficial effects were found to be independent of the bacterial species and their resistance levels. No side-effects occurred and the treatments were well tolerated, even by elderly patients.

In a recent topical review article, Graves[7] examines the emerging role of reactive oxygen and nitrogen species (ROS and RNS, respectively) in redox biology, in general, but more specifically in therapeutically highly promising situations like those listed above. Although the synergistic interplays between plasma chemistry and biology are daunting, he concludes on the optimistic note that progress in science and technology often occurs at the boundaries between seemingly unrelated fields: the present ones (RONS, redox biology, medicine) fall well within this category. In another recent review entitled "*The 2012 Plasma Roadmap*"[17], a two-page sub-section is devoted to PM; its author, G. Kroesen concurs by stating that "*we have to establish a multi-disciplinary scientific community to generate this required understanding*".

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