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PLASMA PROCESSES AND POLYMERS

WHITE PAPER

White paper on plasma for medicine and hygiene: Future in plasma health sciences

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Plasma Science and Technology offer their valuable contribution to human health since more than 50 years, after decades of experiences in the field of biomaterials; and more than a decade in using plasmas for therapeutic uses in medicine. Current knowledge as well as key challenges and opportunities for the human health have been intensely discussed during the Future in Plasma Science II (FIPS II) workshop in February 2016 in Greifswald, Germany. This contribution summarizes the major outcomes of the meeting and the current literature and consensus with an emphasis on major challenges in the fields of Plasma Science and Technology for improving human health.

KEYWORDS
cell biology, decontamination, plasma oncology, plasma parameters, smart materials

1 | INTRODUCTION

Plasma Science and Technology is blessed with a wealth of opportunities and potential applications exploitable in Biology and Medicine for human health.[1] The intrinsic motivation of cold plasma-related research in Plasma Medicine, Sterilization/Decontamination, and Biomedical Materials is to see its translation into Health Science. Despite

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the beauty and uniqueness of plasma technologies at low (LP) and atmospheric (AP) pressure, they actually show many challenges at the same time in many fields, most of all in Biology and Medicine, sometimes also beyond Science and Technology, as in the case of Ethic issues. Owing to the nature of medical-oriented plasma research, these challenges are multidisciplinary spread across different fields, such as: i) plasma physics, chemistry, and engineering; ii) chemistry of liquids; iii) material chemistry and engineering; iv) surface and thin film science; and v) cell and redox biology in medical and clinical science. Challenges in process standardization and authority accreditation procedures also exist, to have plasma-based products, protocols, and therapies accepted. We expect that these challenges will be overcome as it happened for other technologies that are introduced in the clinical field from time to time. To discuss the status, the advancements, and the challenges in the field, the Future in Plasma Science II (FIPS) workshop in February 2016 in Greifswald, Germany, was setup to provide a platform for exchanging ideas and collaborations. Within the subsection "Plasmas for Health Sciences," five major fields were identified in need of communal efforts to tackle prominent obstacles essential to move forward in those topics: 1. plasma-based biomedical materials; 2. plasma decontamination; 3. plasma biology; 4. plasma wound healing; and 5. plasma oncotherapy. Common to all topics is the central aim to exploit the uniqueness of plasma experimental conditions and resulting chemical species for each application. This requires the identification of key active plasma parameters and components on the one hand, and the dedicated control of those on the other.

The second key to successful plasma applications is the transdisciplinary exchange and research. For instance, translating a plasma-based protocol or a plasma-modified material into the clinics requires expertise in physics, chemistry, biology, medicine, and regulatory affairs. Connecting to the communities that work in one or at the interphases of several of these fields substantiates plasma medical research. For example, AP cold plasmas ignited in air generate Reactive Oxygen/Nitrogen Species (RONS), which were subject of investigations for decades in the field of redox biology and medicine, and still are. The field of Biomaterials Science and Technology, in continuous scientific and technological evolution, shows also similar examples. Surface Science, and Technology, were surface modification plasma techniques are embedded, has completely redesigned the significance, the vision and the products in Biomaterials Science and Technology, when it became clear that surface chemistry and morphology of biomedical materials could influence the response of living tissues to prostheses, implants and other devices, thus determining their fate and that of the patient.[2]

Plasma Medicine also links well to the fields of cellular and molecular biology, biomaterials, and application-specific clinical disciplines. Accordingly, many publications on plasmas added new perspectives in such adjacent communities and vice versa. This has recently extended to the fields of bioelectrics and photodynamic therapy (PDT), which respectively use either transient electric fields whose features are quite close to those delivered in the vicinity of plasma jets or DBD[3,4] or ROS resulting from the light activation of targeted photosensitizers. These two communities have long experienced and simulated the interaction of ROS with membranes and the different ways extracellular stimuli may finally trigger intracellular effects (e.g., cell permeabilization, pore formation, endocytosis, polar molecules arrangement along electric field lines, or ROS attachment).

This opinion article describes the need and challenges currently associated with plasma-related medical research across different disciplines. Despite these needs, it is worthwhile mentioning that the field is advancing and consolidating, especially regarding positive outcomes reported by different groups around the world in the newest field of Plasma medicine. A visualization artist graphed some key points during the discussions at the FIPS workshop (Figure 1).

2 | PLASMAS FOR MEDICINE AND HYGIENE

2.1 | Plasma-based synthesis of biomedical surfaces

Humans use non-biological materials to suture and replace organs and functions since ever,[5] with continuous improvements of the quality of all kind of materials, metals first, then polymers mostly after World War II. Most often, though, they were first developed for certain uses (e.g., Titanium alloys for engineering, PolyMethylMetaAcrylate as glass substitutes) and only later, in few cases, translated to biomedical practices (e.g., Titanium in orthopedic and dental implants, PMMA in Intra Ocular Lenses [IOLs]). Indeed, before the 1950s there were few precedents of collaboration between medical doctors and engineers or material scientists. Most implants had high probability of failure as the concepts of sterilization, biocompatibility, and foreign body reaction were still poorly understood or unknown. The terms biomaterial and biocompatibility were defined and redefined during the development of the discipline. Late in the 20th century biomedical materials could finally be designed, tested and produced directly for their effective use in medicine.[2] Biomaterials Science and Technology is now a complex, still evolving interdisciplinary academic and industrial field where topics like surface modification and nanotechnology, for example, are fully assimilated, continuously producing newer products to save millions of lives and improve the quality of more.

In the 1960sit became clear that the outmost layer of biomaterials plays a key role in addressing the biological

FIGURE 1 Comic of the discussion. Current challenges in the research field "Plasma for Medicine and Hygiene" visualized during the discussions at the workshop

responses of cells, blood, tissues, and bacteria at the interface with the biological environment in vitro (cell culture plates, test tubes), ex vivo (catheters, dialysis systems), and in vivo (prostheses, implantable devices). Success or failure of biomaterials is determined by the response of the biological environment to their surface chemistry and morphology, among other factors. In certain cases, the interactions have to be encouraged but controlled for example, for inducing the osseo-integration of an implant in a bone tissue; in others they have to be discouraged and/or fought, for example, for avoiding bacterial colonization of prostheses during and after surgery. In most cases surface characterization and surface modification techniques, plasma processes among them, came useful to address the in vitro responses of biosystems to biomaterials. Translation in vivo is undoubtedly more complicated, as more interactions and reactions (e.g., that of the immune system of the host) have to be controlled.

One of the first bio-oriented paper on plasma processing of materials was published in 1969,[6] dealing with the grafting of amino groups onto various polymers with NH_3 and N_2/H_2fed LP RF (13.56 MHz) Glow Discharges. Those experiments aimed to the ionic immobilization of heparin through surface-grafted ionizable $-NH_2$ groups, for obtaining stable heparin–coated blood-compatible materials. In those same years LP plasmas boosted the miniaturization of Microprocessors in Microelectronics, a trend that still continues, doubling their performances every 1.5–2 years.[7] Indeed, cold AP plasmas in the 1970's were certainly known, but their use for surface modification processes was not under development yet. LP cold plasmas, instead, were being used more and more in Microelectronics and Semiconductor industries for their ability to provide anisotropic etching of materials when coupled with proper lithographic approaches. As then LP and AP cold plasma processes have been constantly investigated and developed for adapting the surface of biomaterials to the best biological response for several purposes. Tuning surface properties with no alteration of the bulk, stable surfaces, intrinsic processes sterility, and minimal wastes are benefits of plasma processes for biomedical companies with respect to other technologies.

Etching, deposition, and grafting plasma processes have been utilized in several possible implementations of

biomaterials. Rising the hydrophilic character of hydrophobic polymer surfaces for better and faster cell colonization, spreading, and growth is probably the easiest level of plasma-alteration to imagine in this contest. When properly optimized to limit the recovery of the natural substrate hydrophobicity[8] AP/LP grafting plasma treatments of polar chemical groups result in stable hydrophilic polymer surfaces. These processes provide since the late 1970s probably the best known biomedical product of plasma technology so far, the disposable Cell-Culture PolyStyrene (CCPS) Petri dishes.[9] The surface hydrophilization of soft silicone-hydrogel Contact Lenses for reduced uptake of lipids from the tears, and improved comfort for prolonged wear is another biomedical example of a successful bio-oriented plasma process,[10] among many others. Biomaterials nowadays are investigated, developed, and produced in a wide variety of chemical compositions and shapes, stable or biodegradable, from simple flat sheets to complex shapes such as small caliber tubes, nano/micro particles, porous membranes for filters and dialysis, and porous scaffolds for Regenerative Medicine, where the homogeneity of the surface modification is usually a very important issue. Combined experiments of plasma processes, surface analysis, and in vitro biological tests[11] are necessary for optimizing plasma-modified surfaces around all those substrates before animal and clinical tests in case of in vivo applications.

Several plasma-synthesized surfaces are available today that are in the process to be or are already translated in commercial products. The following list on surface functionalization is certainly not complete: cell-adhesive,[12] non-fouling cell repulsive;[13,14] hydrophilic hydrogel-like;[15] functionalized for biomolecule immobilization;[16] drug releasing;[17–19] and resistant to bacterial growth.[20,21] The term non fouling is referred to the ability of certain surfaces, generally highly hydrated, to repel cells, bacteria and biomolecules and avoid their adhesion; Surfaces with anti-bacterial properties may certainly be developed with the LP/AP plasma deposition of non-fouling coatings,[13,14] for example, with Polyethylene Oxide (PEO)-like structure; release properties of antibacterial compounds can be added to the coatings by means of proper LP/AP plasma processes,[18,20,21] for the implementation of local killing properties against bacteria. Silver ions and antibiotics are among the compounds use in these coatings.

The development of anti-bacterial surfaces on prostheses, for example, would limit the onset of infections around implanted prostheses during the recovery time after surgery, in an aging society with multi-morbidities. Overall LP/AP surface modification processes are used in the fabrication of several biomedical devices, and it is expected that the development of newer plasma- synthesized surfaces will expand the use of plasmas in Biomaterials Science and Technology. Recently investigated processes include the deposition of nano and nano/bio-composite coatings from aerosol-assisted AP plasma processes[17,18] plasma processing of scaffolds with micrometric porosity[22–25] and the deposition of free-standing ultra-thin "nanofilms."[26]

2.2 | Plasma decontamination

The application of plasma to inactivate or kill microorganisms is one of the earliest objects of research in the field of plasma use for medicine and hygiene. Starting with Menashi's patent in 1968,[27] a lot of research work was done especially in low-pressure application for antimicrobial treatment of materials and devices.[28–32] With the enhanced availability of cold atmospheric pressure plasma devices in the middle of the 1990s, its usability for antimicrobial treatments was investigated at length, too.[33–35] Even if for these efforts in many cases the term "plasma sterilization" was claimed, a real plasma-based sterilization process or device, respectively, is not available yet. Several devices on the market combine low-pressure hydrogen peroxide gas treatment with plasma.[36] However, it was demonstrated that the effectivity of these processes is mainly based on the activity of hydrogen peroxide.[37] The only industry-scale pure plasma-based low-pressure decontamination process that was introduced in 2012 is aimed on the re-sterilization of sterile packaging materials as part of a pharmaceutical filling and packaging process.[38] It is, therefore, not fully comparable with the "classical" heat, radiation, or toxic gas-based sterilization procedures as required by the pharmacopoeia and other regulations for final sterilization of products and devices. Consequently, it has to be stated that, because of several practical and regulatory reasons, plasma processes are very likely not suitable to replace or equally complement classical sterilization processes.[39] However, there is a huge chance to use plasma processes for specific decontamination of medical devices with increased risk where sterilization by heat, radiation, or toxic gases is not effective. One of the most important problems here are non-cellular infection-transmitting agents like prion proteins or amyloid fibrils, which are held responsible for neurodegenerative diseases like Transmissible Spongiform Encephalopathy (TSE) or Alzheimer's disease, respectively. Several studies could demonstrate the effectivity of plasma to inactivate and destroy such agents.[40–42] Consequently, there should be a huge potential to use plasma processes to improve reprocessing procedures of medical devices, for example, surgical instruments that are potentially contaminated with that kind of agents being resistant to conventional sterilization. Plasmas and/or plasma-generated reactive species can penetrate into small cavities. Above all atmospheric pressure plasma processes are advantageous for integration into continuous manufacturing and reprocessing lines and can be adapted to specific geometries of intricate products like endoscopes.[43] Consequently, together with other measures specific and customized application of atmospheric pressure plasma is promising to get final products

that are microbiologically safe for the designated use.[39] Such specific applications have to be identified with regard to industrial as well as regulatory needs.

A more recent field of research on atmospheric pressure plasma application is the field of hygiene above all in the clinical environment.[44,45] Especially because of its ability to inactivate and/or kill multidrug resistant pathogens and also viruses,[46–48] plasma could open up new chances to fight against the growing problem of hospital-acquired and transmitted infections.[49] One field currently under discussion is plasma application in hand disinfection.[44,50] Much more challenging is the plasma application on larger body surfaces for sanitation of patients populated with MRSA.[51] Moreover, there are promising approaches for plasma-based decontamination and purification of air. This is not limited to microorganisms but may also include the inactivation or removal of other dangerous or at least unwanted air pollutants including nitrogen oxides or volatile organic compounds.[44,52,53] Similarly, plasma can be used both for microbiological decontamination but also for removal of organic substances, for example, drugs, from wastewater.[44,54–59] This is based on the well-known transfer of chemical reactivity into water by atmospheric-pressure plasma treatment.[55,60] Finally, several promising technical concepts are available for effective decontamination or cleaning of surfaces by plasma devices.[61,62] All these different plasma applications will be not only applicable in hospital environment but at least partially also in public domains or at home where needed. However, even if there is a lot of experimental experience with promising results to use plasmas to clean air, clean water, or clean surfaces, respectively, there are only few practical applications realized yet. Possibly, similar to plasma applications for device treatment as described above, also these plasma applications will be less successful as stand-alone systems but rather as part of integrated holistic systems of hygiene management of hospitals, but also of other facilities like nurseries, schools, or rest homes. Including innovative approaches of antimicrobial treatment of food,[63,64] plasma has a huge potential to contribute effectively to prevent transfer and dissemination of bacterial infections.

The real market potential for plasma-based devices or processes depends on the decisive question, if and to what extent plasma is able to solve problems in the field of hygiene that cannot be adequately solved by conventional techniques and procedures. Besides some more or less niche applications, the most important field could be its effectiveness to inactivate multidrug resistant pathogens. Antimicrobial resistance is estimated to be a key health and macroeconomic challenge worldwide.[65] Therefore, one of the main research tasks in plasma decontamination should be to prove that there is really no development of resistance in microorganisms following plasma treatment. Answering this question could be the breakthrough to open the market for plasma technology in the field of hygiene.

2.3 | Plasma biology

Applying plasmas to cells and tissues exposes them to a tunable, complex, and plasma source dependent multicomponent system. Not enough, plasma components change on the way from the source (over liquids) to the target as well as once in direct contact with the target (e.g., tissue).[66,67] The unique features of cold plasmas are the generation of various highly reactive, charged particles, UV radiation, and in some situations transient electric fields that all occur simultaneously. While in many biological in vitro experiments excess liquid involuntarily decreases this complexity to allow pinpointing mechanism at work in some instances, we see at least seven challenges in plasma biology and tissue treatment:

- dissection of single and synergistic effects of different plasma components;
- identification and technical control of key biologically relevant plasma species;
- elucidation of the role of intracellular and membrane-bound redox enzymes to translate information from oxidized sites into biological responses;
- determination of the mode of penetration in deep tissue of plasma triggered effects;
- for plasma-treated liquids, the understanding on how these species can be "battery-stored" in a way unique to plasma-derived components;
- creating standards in the field of plasma medicine that allow translating results from one plasma source to another;
- setup of suitable tissue-like models that allow to investigate plasma-medical effects.

Coming back to the main challenges to translate plasma delivery on biological targets to a new, safe, and efficient medical alternative or adjuvant treatment, the following paths and recent reports may be relevant to consider. First way to try to discriminate the specific or combinatory role of plasma components is to analyze biological results obtained with direct plasma treatment in comparison with indirect methods based on either plasma afterglow or effluent or those involving plasma-treated solutions. Unfortunately, there still exists a questioning situation both on:

The composition of plasma activated solutions: which mainly reveals the coexistence of hydrogen peroxide, nitrite, and nitrate[68–70] but probably need more detailed analysis dealing with the presence of other traces or solvated ions or electrons. The persistence over long periods, up to several days, of plasma-treated solution reactivity is another often reported but not fully documented features likely to help in the understanding of the processes underlying such indirect plasma treatments.

The delivery of plasma or afterglow with some plasma devices: An archetypical questioning situation exists for

instance dealing with the "reference COST plasma jet."[70] The successful development of this user's friendly and fully characterized tool for biological applications may nevertheless lead to confusion and misunderstanding when trying to translate results obtained with this device in comparison with those achieved with another plasma source, such as most of plasma jets or dielectric barrier discharges. The reason being that the "COST plasma jet" delivers a so called "plasma afterglow or effluent" a not a full plasma with all the potentially "active components," such as charged particles and transient electric field. The characterization and standardization of any plasma source to be used for applications where a target is set in front of the plasma device, either a tissue or a solution to be plasma activated, is undoubtedly much more challenging than with pure afterglow devices. It was demonstrated drastic interactions exists between plasma device and target potentially leading to huge modulation of plasma features.[66,71–73] Researchers should try to clarify the status of the plasma source they use and standard diagnostics should be suggested for this issue.

The identification of short-lived species with state of the art diagnostic tools but also the very strong spatial gradients connected with fantastic pH variation other layers of only a few hundreds of nanometers in depth,[74] are examples of very challenging issues to face to get more insights on plasma liquid interaction and tentatively plasma penetration very specific nature. Short-lived species and strong gradients delivered most of time in pulsed regime would probably trigger unique chemical and biological processes. First comparative assessments between plasma-treated liquids derived from different plasma sources with the same cell line have been reported.[75] If not considered as a competitive analysis between different plasma sources, which probably besides their efficiency for a specific biological action also have their own intrinsic unique features in some protocols, this is a very new and promising approach. Finally, the translation from in vitro experiments to pre-clinical and eventually clinical research requires the design of somehow realistic tissue mimicking targets and more animal experiments.[76–78] These can provide accurate biological reactions under plasma stimuli (e.g., oxygen tension, blood flow modulations, and recruitment of immune system cells and stem cells) and allows more investigating more realistic plasma-derived target modifications.

Nevertheless, translational studies have been attempted and reported from the very early development of "plasma medicine" works around the world, regardless of the availability and validation of such mimicking targets. The following sections will illustrated this for two promising topics, wound healing and cancer treatment.

2.4 | Plasma wound healing

As immediate effect of research in plasma biology, plasma medicine means the application of physical plasma for medical therapies. Whereas some well-established electrosurgical techniques for cauterization as well as tissue cutting and sealing are based mostly on thermal plasma effects,[79] research for medical application of cold atmospheric plasma starting in the middle of the 1990s was focused particularly on wound healing.[80–82] In April 2012 in a German workshop on clinical plasma medicine was stated that plasma application in dermatology as well as plastic and aesthetic surgery would have the best prospect to succeed.[83] At this time, this statement was rather a prognosis or vision. However, now plasma application in wound healing is on its way to clinical reality. Cold atmospheric plasma application in this medical field is based on two important biological plasma effects:

- Inactivation of a broad spectrum of microorganisms including multidrug resistant ones
- Stimulation of cell proliferation and angiogenesis and, as a result, promotion of tissue regeneration

Besides a huge number of in vitro tests using a broad spectrum of microorganisms as well as cell cultures and tissue models, both effects were demonstrated in vivo by animal experiments[84–94] as well as clinical trials.[95–104] Moreover, recent work demonstrated a pronounced increase of microcirculation in tissue following plasma treatment.[105–108] Many chronic wounds are hypoxic,[109] and a plasma-triggered local increase in blood supply may contribute to healing responses.

The concept of plasma-supplemented wound healing combines cleaning and antisepsis on wound surface with stimulation of tissue regeneration in deeper wound areas.[110] Consequently, cold atmospheric plasma is mainly used for treatment of chronic wounds, that is, wounds with stagnation of the healing process occurring in many adults with vascular disease or diabetes and are attributed to chronic venous insufficiency, arterial disease, prolonged pressure, or neuropathy. Chronic wounds are in most cases characterized by both persistent infections and an inability of dermal and/or epidermal cells to respond to physiological reparative stimuli.[111] However, there are promising efforts in acute wound healing, too.[112,113] Here, plasma application is particularly useful in risk patients to prevent chronification, for example, in case of immunosuppression, circulatory disorders, or problematic sutures. Infection prevention and support of wound healing in fields with increased contamination or infection risk (skin folds, inguinal region) as well as antiseptic treatment of primary and secondary wounds to prevent postoperative wound infections are other meaningful indications for plasma treatment of acute wounds.

Three devices for direct application of cold atmospheric plasma are CE certified as medical devices class II, mainly for the purpose of treatment of chronic wounds as well as pathogen-based skin diseases: the argon-driven cold atmospheric plasma jet kINPen MED (neoplas tools GmbH, Greifswald, Germany), the dielectric barrier discharge-based device PlasmaDerm (CINOGY GmbH Duderstadt, Germany), and the microwave-driven argon plasma torch SteriPlas (ADTEC, Hunslow,UK).[114–116] These devices are increasingly used in clinics as well as by practicing doctors above all as last resort in chronic wounds where conventional wound treatment fails. In the great majority of such cases, the wound healing process can be revived up to full closure of such often long-term persisting wounds. Highly effective eradication of antimicrobial resistant bacteria (MRSA etc.) is reported just as reduction of pain. No acute or long-term complications became known. However, there are several open questions remaining related to clinical practice:

- Intensity and/or duration of single treatment
- Frequency of treatment (daily, weekly, . . .)
- Duration of therapy, definition of the clinical end point of treatment:
- Wound decontamination?
- Initial stimulation of healing?
- Complete healing?
- Individual and/or disease-dependent differences in therapy scheme
- Treatment mode:
- Uniform treatment of complete wound
- Specific treatment of different wound regions: edge versus central wound region

Solution of these questions will further optimize plasma treatment schemes but needs a close coordination of experimental and clinical research.

It has to be pointed out that the certification of the devices mentioned above is based on comprehensive physical, biological, pre-clinical, and clinical characterization.[117] This has to be demanded for all other medical plasma devices on the market to guarantee safety and reliability of therapeutic plasma applications!

The growing success of cold plasma application in wound healing is encouraging for further effort in research in plasma medicine. Two of the most pressing challenges are:

Development of more application adapted plasma devices offering effect-directed modification of plasma composition and adapted device geometries, for example, for large-area applications or applications in visceral cavities;

Monitoring and control of plasma performance during application in relation to therapeutic efficacy by a continuously available parameter or set of parameters.

Together with ongoing basic research on molecular mechanisms of plasma-cell and plasma-tissue interaction and the role of single components of the "plasma cocktail" for specific biological effects, further clinical research will open up new possibilities of cold atmospheric plasma application in dermatology, ophthalmology, dentistry, cardiology, and other fields of medicine. Together with continued and increasing clinical success this will lead to establish plasma medicine as a self-contained medical field like laser medicine some decades ago.[118]

2.5 | Plasma OncoTherapy

Studies in Plasma OncoTherapy increase with pace. Plasmas readily induce apoptosis in eukaryotic cells. Much attention has been given toward a selectivity of plasma in tumor over healthy cells. However, cell death is omnipresent in the body, also in tumors. For example, tumors frequently secrete FAS-L to drive anticancer T lymphocytes into apoptosis.[119] Moreover, some memory lymphocytes are highly sensitive toward hydrogen peroxide and hence plasma whereas others memory types are not.[120–122] Different memory cell types derive from similar naïve T cells illustrating that not only the amount of oxidants but also processes such as redox signaling provide some degree "selectivity" in response to plasmas. Regardless of the malignancy of a given cell type, this signaling translates redox information in proteins and thiol groups into distinct biological responses.[123] Some cancer cell types readily undergo apoptosis in response to oxidants.[124] Others have altered redox signaling cascades, making them withstand much higher species concentrations then the surrounding tissue.[125] This puts the idea of a universal selectivity of plasmas on cancers on standby. Yet, gold standard tumor therapy is not very selective either. Chemotherapy kills also non-malignant, rapidly dividing cells, for example in hair follicles or the gut. Radiotherapy causes DNA damage in cells adjacent to tumors (e.g., immune cells or stroma), too. What is more recognized today is that there are requirements for how a cell should die. Benefits of an immunogenic cell death (ICD) in apoptosis or necrosis have been suggested.[126–128] Here, the host immune response is indicated as final effector. This is important for any oncological treatment including plasma because 90% of tumor patients die because of hard-to-reach metastasis. Bulk tumor mass can often be removed surgically with ease. From a clinician's point of view, there are only very few indications where plasma could or should be used to remove bulk tumor mass, for example, when tumors are present on major blood vessels.[129] The future in Plasma OncoTherapy is therefore to induce ICD in tumors to help dendritic cells find, eat, and present cancer cell antigen to elicit robust T cell immune responses.[130] ICD is an accepted intellectual framework in oncology and immunology. It elegantly and retrospectively

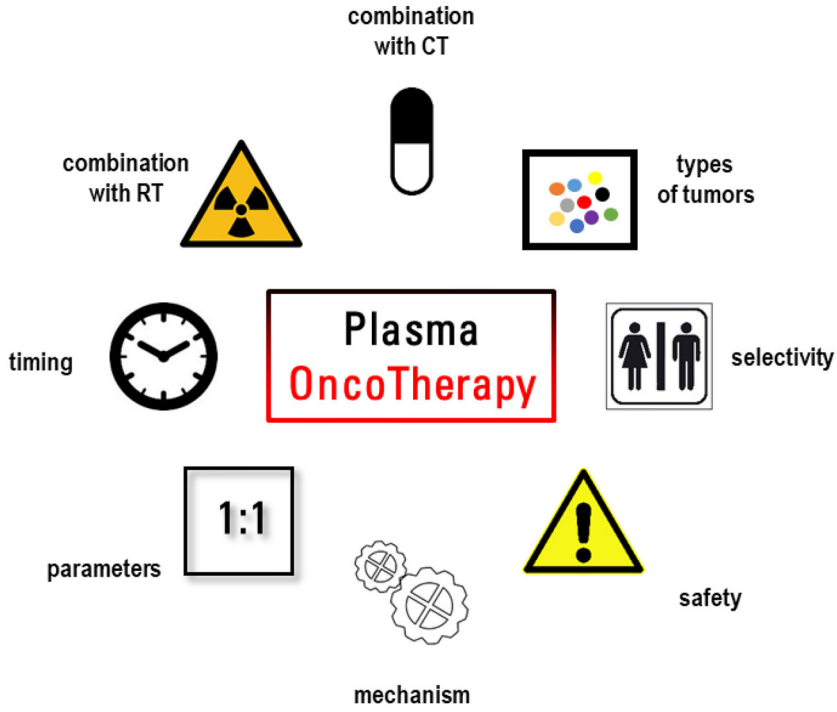

FIGURE 2 Plasma OncoTherapy.Six central needs in Plasma OncoTherapy are shown. Types of tumors should be identified that show are highly susceptible to plasma treatment should be identified. In this regard, the plasma parameters may extend or limit applications in distinct cancer types. Combinational approach with radio and chemotherapy should be undertaken. Clinical protocols need to be studied to elucidate the optimal timing of a plasma treatment (e.g. stand-alone or before, in between, or after chemotherapy). Finally, understanding the central biological effector mechanisms will help to optimize plasmas with regard to antitumor activity

explains why there is a clinical benefit of some chemotherapeutic drugs over others, and why radiotherapy can induce antitumor immune responses in tumor regions that have not been treated (abscopal effect). Off note, the so far only available proof-of-principle experiment for ICD needs to be carried out in vaccination experiments in mouse studies using murine cell lines.[131]

Plasma OncoTherapy currently faces three main challenges: what is the ideal anticancer plasma setting, which types of tumors in combination with what plasma give the desired response with regard to (immunogenic) cell death, and how exactly and at which stage of clinical cancer intervention should plasma actually be applied. First reports suggested immunogenic cell death in vitro and in vivo upon plasma treatment.[132–137] Urgently investigated should be the biological anticancer mechanism of cold plasmas with regard to biochemical events as well as synergistic or possibly even antagonistic effects with radio or chemotherapy (Figure 2). In studies, chemotherapeutic agents should be selected that are employed clinically in a given type of tumor on a regular basis. Finally, studies in Plasma Oncotherapy should be motivated by clearly describing at which point of care plasma is hypothesized to be useful (e.g., early tumor stages as replacement therapy, adjuvant therapy, palliative setting). It is understood that only fruitful interaction with clinicians can help to guide a plasma application into plasma medicine, eventually. Driven from experience with authorities regarding official approvement of plasma applications in dermatology, this will be most likely i) one plasma source with a fixed parameter settings ("one doctor, one button" principle); ii) indicated for one type of tumor (with others potentially following once established); and iii) within one specific treatment regimen (e.g., adjuvant therapy in stage IV metastatic pancreatic cancer in patients receiving chemotherapeutic gemcitabine). Hence, Plasma OncoTherapy should further look into clinical needs to design feasible concepts that in future possibly generate a patients' benefit using this promising technology.

3 | CONCLUSIONS

Plasma Science and Technology have probably reached their maturity in several grounds, and offer today a great number of solutions and products in numerous fields. In the strategic area of human Health, though, probably the application of plasma processes has still large margins of improvements, particularly for the in vivo testing of plasma-processed biomaterials, for the full understanding of the effects of

plasma-generated RONS and other species on biomolecules, cells, biological liquids and tissues, and for the full development of plasma-based therapies in Wound Healing, Cancer Treatments and other clinical specializations. For the close future, we auspicate and expect significant advancements of bio-oriented knowledge in Plasma Science and Technology, and sincerely believe that relevant plasma-based therapeutic approaches will be developed soon, with noticeable fundamental, clinical, and economic impact on human Health Care.

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