# PLASMA MEDICINE

## Applications of Low-temperature Gas Plasmas in Medicine and Biology

The introduction of low-temperature plasma technology to medical research and to the healthcare arena in general is set to revolutionize the way we cure diseases. This innovative medium offers a valid and advantageous replacement of traditional chemical-based medications. Its application in the inactivation of pathogens, in particular, avoids the recurrent problem of drug resistant micro-organisms.

This is the first book dedicated exclusively to the emerging interdisciplinary field of plasma medicine. The opening chapters discuss plasmas and plasma chemistry, the fundamentals of non-equilibrium plasmas, and cell biology. The rest of the book is dedicated to current applications, illustrating a plasma-based approach to wound healing, electrosurgery, cancer treatment, and even dentistry.

The text provides a clear and integrated introduction to plasma technology and has been devised to answer the needs of researchers from different communities. It will appeal to graduate students and physicists, engineers, biologists, medical doctors, and biochemists.

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To the memory of my father, Habib Laroussi, and
to my mother, Manana (Jeloul) Laroussi. Mounir Laroussi
Michael Kong dedicates this book to his wife, Dr. Hailan Chen.
To my granddaughter, Anny. Gregor Morfill
Wilhelm Stloz dedicates this book to his wife, Karola.

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# Foreword

### A surgeon's perspective

The hallmark of healthcare in the twenty-first century is "revolution" – in literally all aspects and fields. Information-age technologies are being adopted, clinical practice is fiercely focused on patient safety, and financial constraints have imposed a cost–benefit mandate that has never been seen before. Throughout all this turmoil, the one consistent driver has been the rapid development of new technologies.

Plasma physics has been an important and growing field for decades, with many applications in the non-healthcare industries. Literally hundreds of applications are in daily use, though the most common revolve around sterilization, debridement, surface etching, etc. Recently, the discovery of the biologic effects of plasma has gained enormous interest. Simultaneously, healthcare has advanced basic biologic science into the molecular and nanotechnology arena – a domain that is the core of plasma physics. The result has been an outpouring of new discoveries by the combination of the two fields, which has become known as plasma medicine.

Major findings continue to rapidly accelerate progress, not linearly but logarithmically. The introduction of dielectric barrier discharge and low-temperature plasma jets has eliminated the need for many restrictive constraints, such as high temperature, vacuum, high energy, and noble gas, resulting in the development of prototype instruments that can be used effectively in "normal" conditions of room temperature, free air, and atmospheric pressure in a low-power, handheld instrument. This permits the generation of a tissue-tolerant plasma (TTP) that is clinically relevant, as well as cost effective.

The other component of the revolution is the combining of information with energy – information (computers etc.) can control energy with great precision, and energy (spectral analysis etc.) can generate information. This combinatorial feed-back loop holds the promise to replace numerous physical objects with energy–information interaction. For example, instead of using alcohol, iodine, or merthiolate to sterilize supplies, the application of plasma energy can achieve the same results (sterilization) without physical supplies. No more need for ordering, waiting for delivery, maintaining inventory, distribution throughout the hospital, storage until use, and reordering when utilized. Monitoring the generation of energy, it will be possible to precisely control the amount of energy to accomplish the sterilization without tissue injury using the TTP. In a handheld plasma instrument, it may be possible to attain the same sterility without the huge logistical chain and cost as described above. Plasma sterilization would be available whenever needed, at the point of care and in real time, without the need to reorder more supplies. This would dramatically improve the delivery, efficiency, cost effectiveness, and safety of patient care.

To date, six basic science foundations have been identified in the plasma cloud and are in the process of validation. These are: (1) reactive chemical species such as nitric oxide, reactive oxygen species, oxygen singlets, ozone; (2) free ions; (3) ultraviolet (UV) and near-infrared (NIR) light; (4) visible light (V); (5) high temperatures; and (6) electromagnetic radiation (EM). Each of these differently generated forms of energy has profound biological effects. In addition, the ability to control the amount/type of components of the energy generated can be regulated through adjusting the amount/type/source of input energy, pulse duration/width/frequency, use of free air/noble gas, the constituents of the surrounding medium (air, liquid, etc.), static/dynamic field, etc. Thus, the opportunities are vast, if not unlimited, in the variety of combinations of energy that can be used to create a desired effect.

Of particular importance are the biologic effects of plasma that have clinical significance. Pioneering investigations have demonstrated the following effects: the plasma to cell and tissue interactions, where the new discoveries (which are still ongoing) of how the ionic cloud of free ions and reactive species (NO, $H_2O_2$, etc.) can exert control over many important biologic processes in wound healing, inflammation, sterilization, and so on; the ability to selectively turn on and turn off specific molecules (such as cytokines, interferon, and prothrombin); the acceleration of stem cell replication; and the induction of specific epigenetic phenomena, which results in increased wound healing, activation of coagulation, induction of angiogenesis, etc. As new biologic effects are discovered, it will be important to "tune" the specific components of the plasma cloud to produce the precise combination of energy types to generate a particular clinical effect.

There are three medical clinical investigational areas at this time: sterilization and treatment of skin infections (primarily fungus, tenia pedis antibiotic-resistant infections, etc.), the accelerated healing of chronic wounds, and modification of surfaces of orthopedic implants for biocompatibility. The remainder of the research is in the laboratory basic sciences. As new effects are discovered, rigorous technology transition and commercialization will be needed in order for new applications to quickly emerge.

It is worthwhile to speculate on a number of medical needs that might be possible to achieve using plasma medicine, based on the known physical and biologic effects. For example, it might be possible to continuously sterilize supplies, instruments, and equipment while they are being used. If a plasma could be distributed over the surface of an instrument or supply continuously while performing a surgical or medical procedure, there would be no need to sterilize instruments or run quality checks in the factory but rather they could be shipped non-sterile at substantial cost savings. Every day there is a significant loss of supply usage because the supply or disposable instrument becomes out of date or contaminated before or during a procedure, requiring the opening of a new sterile replacement, thereby increasing the cost for the procedure. Finally, it may be possible to monitor the instrument by measuring the change in the plasma characteristics. This concept could be also applied to sterilization (or maintenance of sterility) of the many types of catheters that are inserted into the body, such as intravenous catheters, chest tubes, and Foley urinary catheters. The cost saving in this application alone would be incalculable.

The field of plasma medicine is in its infancy, and, therefore, many new discoveries are needed to grow this science to its full potential. The first society, the International Society of Plasma Medicine, was formed only a few years before the publication of this book, but has grown substantially to provide the necessary scientific forum where presentations of the science can be made, confirmation of results discussed, and publication of proceedings can be made in their official journal, the *Journal of Plasma Medicine*. The founding of this society and its journal represents the codifying and institutionalization of a new field of science and provides legitimacy to the emerging field of plasma medicine.

This book represents one of the first attempts to describe and understand the potential use of plasma as applied to medicine. The examples above demonstrate just a few of the new opportunities that are yielded by the application of plasma medicine. Certainly, many other opportunities beyond those speculated will be discovered, though some of them will be proven to be ineffective – but that is the hard science. However, the basic hypothesis is sound: replacement of physical objects with energy can significantly improve the quality, efficiency, safety, and cost of healthcare. What now remains is the discovery and validation of these potential opportunities and, more importantly, the development and commercialization into clinical products of the "low-hanging-fruit" applications of plasma in medicine.

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## A physicist's perspective

The success of pioneering sponsored studies that applied cold plasmas and pulsed power to medical challenges has become the highlight of my entire quarter-century of service as Program Manager for Plasma Physics at the US Air Force Office of Scientific Research (AFOSR). No other program that I sponsored has equaled the lasting impact on society that these breakthroughs presaged. It is not surprising that a vibrant young community of talented scientists and engineers continues to grow around the globe in addressing the questions and promises of this new field. This book does our community a great service by capturing the state-of-the-art of this fascinating topic.

Non-equilibrium "cold" plasmas were of great interest to the US Air Force long before my office at AFOSR launched bold new initiatives in this area in the late 1980s. Eminent scientists at the US Air Force Materials and Propulsion Laboratories at Wright-Patterson Air Force Base, Ohio, made great contributions for decades in understanding how to optimally produce and utilize such plasmas for military applications.

The new AFOSR programs, however, shifted the primary emphasis to low-temperature air plasmas, a logical focus given the atmospheric operating environment of most USAF systems. Early programs enabled researchers to finely quantify and explain the dramatic broadband microwave absorption properties of lightly ionized layers of collision-dominated cold air plasmas. The military implications were clear, but practical applications were restricted by the enormous power requirements for air plasma generation techniques accepted at that time. This impasse was overcome by the major AFOSR-sponsored discovery that trains of repetitive short-pulse-length power bursts can efficiently sustain air plasmas. In addition, for some applications, simply switching to tailored gas mixtures, rather than ambient air, bypassed the issue completely.

The target of AFOSR cold plasma programs evolved in an exciting new direction in the mid-1990s. At that time, leading-edge researchers at the University of Tennessee-Knoxville (including one of this book's authors, M.L.)

began examining the useful effects of atmospheric-pressure plasmas on biological systems.

The earliest AFOSR-sponsored work in this field demonstrated the easily reproducible ability of such plasma to *rapidly* kill a variety of common bacteria. In a few minutes, lightly ionized cold air plasmas virtually obliterated thriving colonies of bacteria *without the excessive heat and/or harsh chemicals* typical of medically accepted sterilization techniques. This opened the door to a remarkable new approach for sterilizing (for example) human skin with minimum trauma to living skin cells. Serious wounds could be bathed in sterilizing plasma streams eliminating the bacteria that otherwise slow the healing process. In hospital operating theaters (including military field units) a patient's exposed tissue could be similarly bathed in sterilizing continuous streams of cold plasma in order to reduce the chances of postoperative infections, a major cause of hospital deaths. Furthermore, hospitals (including military field hospitals) could use cold plasma "baths" to rapidly sterilize medical implements, not limited to metal tools but also encompassing plastic and even fabric items.

The biological sterilization utility of cold plasmas took a further leap in the late 1990s when they were shown to lyse (break open) dormant spores. Specifically, anthrax spores were destroyed in a matter of minutes, opening the door to future military (and civilian) use of cold plasmas to decontaminate surfaces harboring such deadly pathogens. After the turn of the century it was further demonstrated that the plasma lysing of spores exposed their internal genetic material to rapid biochemical analysis in order to identify harmful versus benign contaminants.

This early work was generally accomplished by plasma scientists and engineers under sponsorship of a plasma physics program. Biologists and medical personnel were typically involved in a consulting capacity but this new research arena emerged from the physics as opposed to the biological/medical community.

This genesis bespeaks a fundamental challenge; cold plasma technology will not be embraced by the medical community until that community understands this "foreign" technology sufficiently enough to appreciate it. The overwhelming majority of medical professionals have their educational roots in biology, not physics. Plasma physics journal articles are practically indecipherable by biologists – and vice versa. Fortunately, this book makes it clear that those biology–medicine–physics barriers are being torn down. The door is clearly opening wider with each passing year. A cold plasma revolution in medical applications is in the offing.

This book performs a crucial service to the physics, biology, and medical communities by presenting new understanding in a shared terminology that can be fully appreciated by all three. The authors are internationally recognized experts in this growing field. Their book provides a much-needed, eye-opening overview of this exciting new discipline of plasma medicine.

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