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Cold Gas Plasma: An Emerging Technology for the Biomedical Arena

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Plasma is the most ubiquitous state of matter in the visible universe. The other three more familiar are the solid, liquid, and gaseous states, but these are estimated to constitute less than 1% of all the matter that we can see. The stars, the solar wind, intergalactic matter, and, closer to Earth, lightning are all plasma. Plasma is generally referred to as the fourth state of matter, but in fact some argue that it is the first state of matter. Right after the big bang matter was so hot that only the plasma state existed. It is only after the universe expanded and cooled enough that the gaseous, liquid, and solid states were formed. So, how is plasma produced artificially in the laboratory? The simplest way is to subject a gas to high electric fields. If there are few seed electrons already present in the gas, they get accelerated by the applied field to high kinetic energies. When these electrons collide with the atoms and molecules of the background gas they are able to knock off electrons and set them free. The atoms/molecules missing one or more electrons are called "ions." The newly freed electrons are accelerated by the applied electric field and, in their turn, enter into ionizing collisions with other atoms and molecules and free even more electrons. This is referred to as an "avalanche process" which leads to an exponential increase of the number of charged particles in the gas. With such a process we end up with a mixture of neutral atoms and molecules, ions, and electrons. To describe this "soup" of particles the American physicist Irving Langmuir used the term "plasma" for the first time in the late 1920s.

Plasma is the enabling technology in the semiconductor industry and without it computer chips cannot be manufactured. And of course, everyone knows about plasma TVs and fluorescent light tubes, the functions of which are based on plasma.

So, what does all this have to do with medicine? Well, the story goes like this. By the late 1980s and early 1990s scientists learned how to make plasma at atmospheric pressure (no vacuum necessary) and keep its temperature close to room temperature or at most not higher than 40°C. This kind of plasma is known as "cold" plasma. Figure 1 shows a photograph of a cold plasma generated in this author's laboratory using a plasma device called the dielectric barrier discharge. Using a plasma like the one shown in Figure 1 scientists showed that cold plasma can kill bacteria efficiently without damaging the substrate or dish containing the bacteria cells. As an illustrative example, Figure 2 shows a plot of bacteria kill rate after exposure to cold plasma. Encouraged by these findings, scientists then developed a variety of cold plasma sources to decontaminate surfaces and various media (including liquids) from biological contaminants, such as bacteria, fungi, and viruses. In addition, cold plasma was used to disinfect wounds and accelerate the wound healing process (see Figure 3). These early results were widely disseminated in the scientific literature and by the early years of the 21st century scientists from around the world took notice. Today, a global research community is active in this emerging scientific field, working on applications ranging from wound healing to cancer treatment. This multidisciplinary field that involves physics, engineering, biology, biochemistry, and medicine is known as "Plasma Medicine."

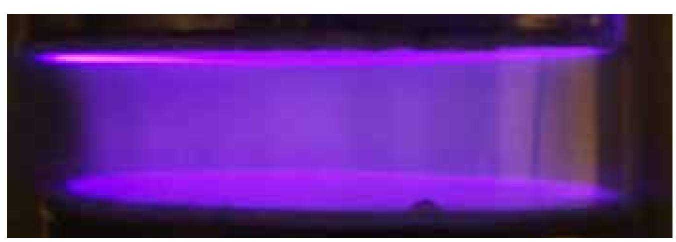

Fig. 1 Atmospheric pressure cold plasma generated by a dielectric barrier discharge. Photo courtesy M. Laroussi

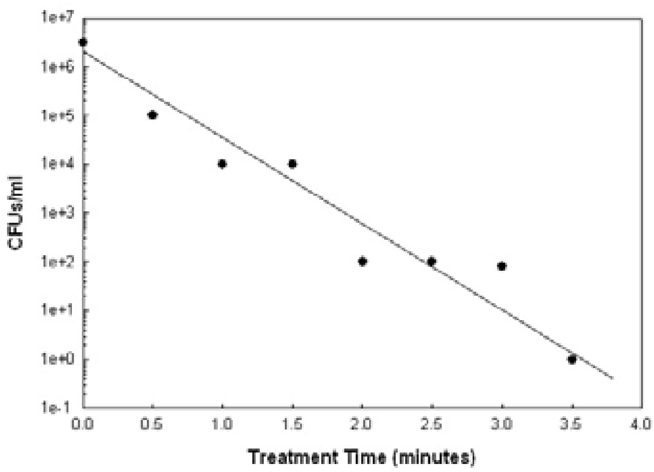

Fig. 2 Inactivation of E. coli bacteria under exposure to the cold plasma shown in Figure 1. The figure shows how the number of surviving bacteria cells decline as the exposure time to the plasma increases. The number of surviving cells decreases from more than a few millions initially to only a few cells after 3.5 minutes of plasma exposure.

Fig. 3 Images from a 61-year-old patient with venous ulcer, treated with argon plasma. Left image is before plasma treatment, middle image is after seven 2-minute plasma treatments, and right image is after eleven 2-minute plasma treatments. The condition of the wound drastically improved after the plasma treatment regimen. Photo courtesy Dr. Georg Isbary.

How Does Cold Plasma Affect Biological Cells?

Cold plasma produces many "agents" that can act on biological cells. These include charged particles, photons, and electric fields. But it is thought that most of the observed effects (inactivation of pathogens, proliferation of healthy cells, killing of cancer cells, etc.) are mediated by the reactive oxygen species (ROS) and reactive nitrogen species (RNS) generated by the plasma. ROS and RNS include hydroxyl, OH, atomic oxygen, O, superoxide, O_2^-, hydrogen peroxide, H_2O_2, and nitric oxide, NO. These chemical species are known to have specific biological effects. For example, OH radicals can react with and degrade unsaturated fatty acids, which make up the outer membrane of biological cells. Hydrogen peroxide, H_2O_2, is a very reactive oxidant molecule that can degrade proteins and break DNA strands. Nitric oxide, NO, is an intracellular messenger and regulator of biological functions. It affects the regulation of immune-deficiencies, cell proliferation, induction of phagocytosis (removal of pathogens by cells of the immune system), regulation of collagen synthesis, and angiogenesis (regeneration of new blood vessels). The reactive chemicals generated by plasma (ROS and RNS) can also enter the cell and increase its oxidative stress, which can lead to induction of programmed cell death (known as apoptosis). This is thought to be one of the mechanisms by which plasma kills cancer cells.

Why Cold Plasma for Medicine?

In the last two decades the healthcare field has been facing two severe challenges: 1. The increase of resistance to antibiotics by several strains of bacteria. In the United States alone thousands of patients with compromised immune systems die each year because of hospital-acquired infections (HAI) that could not be treated by conventional antibiotics. To date no bacterial resistance to cold plasma treatment has been reported; 2. Chronic wounds: Thousands of amputations occur per year because of the failure of conventional therapies to heal chronic wounds such as diabetic ulcers. Cold plasma has been found to play a beneficial role for the healing of chronic wounds. Several clinical trials have shown that cold plasma reduces the wound infection and stimulates the proliferation of healthy cells like fibroblasts and therefore speeds up the wound healing process.

Both *in vitro* and *in vivo* tests have shown that cold plasma can kill cancer cells and reduce tumors efficiently. This application is referred to as "plasma oncology." Investigators have tested a relatively large number of cancer cell lines with encouraging success, and clinical trials are being organized as of the time of the writing of this article. These activities are aimed at developing a new plasma-based cancer therapy, which does not have the side effects caused by other aggressive treatments such as chemotherapy. Cold plasma will most likely be the technological basis for an adjuvant therapy that follows surgery to kill remnant cancer cells that cannot be eliminated by surgery alone.

What Other Bio-applications Can Cold Plasma be Used For?

In addition to the potential of using cold plasma in medical therapies, other applications are being explored. For example, cold plasma has recently been used successfully in agricultural applications. Here, cold plasma has been employed for purposes including treatment/decontamination of fruits and legumes to extend shelf life, the modification of the wettability of the surfaces of seeds, and the enhancement of the germination speed and yield of plant seeds. Another timely application is the use of cold plasma to kill viruses. Here investigators have shown that cold plasma is effective against airborne viruses and in liquid droplets. This is of great relevance in the fight against viral-driven pandemics such as the COVID-19. One last example is the possibility of using cold plasma in space medicine. Here cold plasma can potentially be used in manned deep-space, long-duration, missions to decontaminate tools and gear from possible extraterrestrial microorganisms and to disinfect wounds or skin infections that astronauts may experience during such missions.

Suggested Reading:

1. M. Laroussi, "Non-Thermal Decontamination of Biological Media by Atmospheric Pressure Plasmas: Review, Analysis, and Prospects", *IEEE Trans. Plasma Sci.* **30**, pp. 1409-1415, (2002).

2. G. Fridman, G. Friedman, A. Gutsol, A. B. Shekhter, V. N. Vasilets, A. Fridman, "Applied plasma medicine", *Plasma Process. Polym.* **5**, 503-533, (2008).

3. T. von Woedtke, S. Reuter, K. Masur, K.-D. Weltmann, "Plasma for Medicine", *Phys. Repts.* **530**, (2013) 291.

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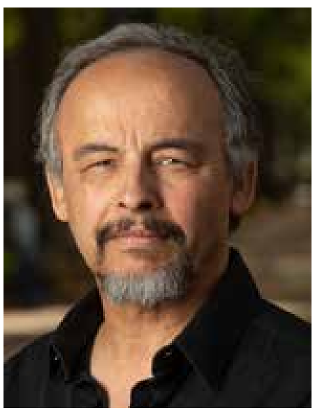

ABOUT THE AUTHOR

Dr. Mounir Laroussi is a Professor at the Electrical & Computer Engineering Department of Old Dominion University (ODU) and is the Director of ODU's Plasma Engineering & Medicine Institute (PEMI). Dr. Laroussi's research interests are in the physics and applications of non-equilibrium gaseous discharges including the biomedical applications of low temperature plasma (LTP). He designed and developed numerous novel LTP devices such as the resistive barrier discharge (RBD) and the plasma pencil. Dr. Laroussi conducted the first pioneering experiments on the use of low temperature atmospheric pressure plasmas for biomedical applications and contributed to the establishment of the interdisciplinary field of "Plasma Medicine". For his scientific achievements in the field of low temperature plasmas and their biomedical applications he was elevated to the grade of Fellow by IEEE in 2009 and was awarded the 2012 IEEE-NPSS Merit Award.