Further Research and Applications in the Field of Ozone Therapy: Much more than a "Therapeutic Unconventional Hypothesis"

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In light of the growing interest about ozone therapy, we were asked to update — both from a scientific and clinical point of view — the latest applications in the field of Human Medicine with this minireview.

In many conferences in which we are invited to participate as *lecturers*, we often observe how many Doctors and health professionals are increasingly drawn to listening to the most recent acquisitions in the field of Ozone Therapy. This testifies that the time is ripe for wider recognition of this therapeutic technique, as indeed was the case recently in the United Arab Emirates where, as a result of a conference organized in April of this year in Abu Dhabi (*http://www.lotusholistic.ae/ozone.html*), the authorities of HAAD (Health Authority Abu Dhabi) the specialization of *GP Ozone Therapist* has officially entered in the database of the allowed non-conventional or alternative therapies.

To our opinion, It is time that public opinion and health care professionals widen their horizons on ozone therapy. Indeed, this therapeutic approach must be considered not only a resource devoted to the resolution of *back pain* or *herniated disc*, but also as a systemic treatment useful in numerous pathological conditions or simply as a therapeutic prophylactic resource to prevent the damages of aging and to improve many functions of our bodies.

Before considering the merits of the latest scientific discoveries, allow us to introduce a new terminology regarding the pharmacological mechanism of action underlying the treatment with ozone, which can't be considered — according to classical schemes of pharmacology currently spread in the faculties of medicine — as a simple interaction between the molecule (drug) and the receptor (cellular membrane protein), but rather as "*Hormetic Stress*".

Our scientific conviction that a molecule like ozone, i.e. a strong oxidant, could induce benefits in various ailments, when used at low doses was believed to be an unconventional theory. We are now very happy to note how this concept could finally gain a certain scientific credibility. Indeed, in a recent paper the Nobelist Dr. James Watson proposed an unconventional view on oxidative stress and diabetes. The conventional view is that oxidative stress causes insulin resistance.

In March of this year, Dr. James Watson, who co-discovered the double helix structure of DNA, proposed an unconventional view on the cause of diabetes. [The Lancet, Volume 383, Issue 9919, Pages 841 - 843, 1 March 2014]. "*The fundamental cause, I suggest, is a lack of biological oxidants, not an excess*," he says. "*Physical exercise prompts the body to make large numbers of oxidants — molecules called reactive oxygen species, or ROS*," he continues, and that's why exercise is beneficial to our bodies. This hypothesis certainly needs to be tested. It could be that it's the balance that matters, and that disease results due to an imbalance on either side; i.e. both oxidative stress or oxidative deficiency (such as hypoxia), could lead to insulin resistance and other diseases. The idea that similar to brief exercise, the conditioning effects induced by small ozone doses, could be helpful for many of the biological functions of all the cells that burn oxygen to produce energy seems to be worthy of new and strong scientific studies dedicated to the matter.

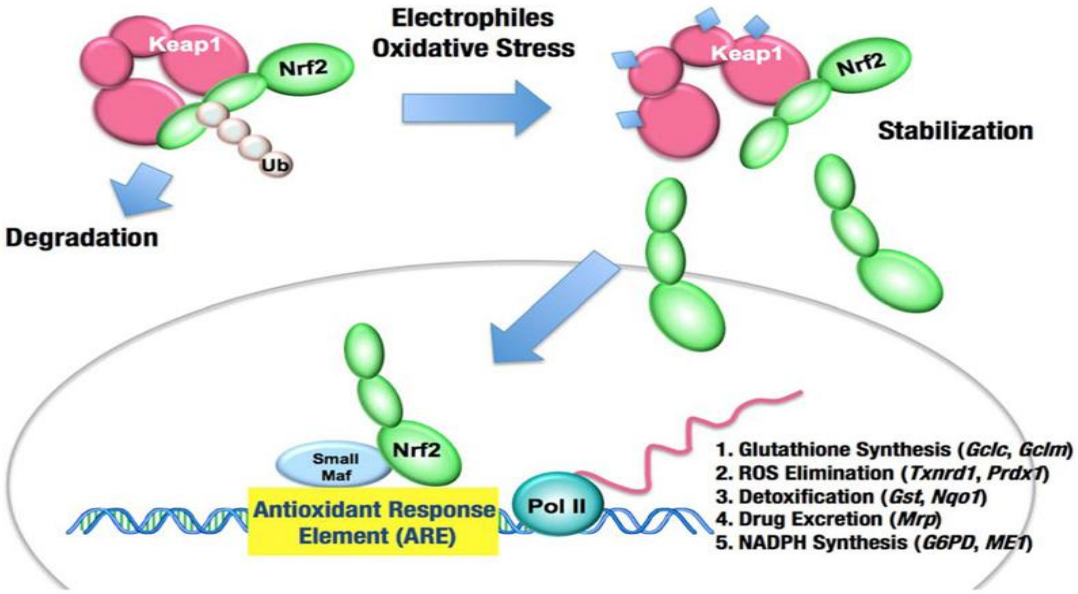
Like other Xenobiotics, agents not recognized in the metabolism of the body (from the Greek Xenos = Foreign and Bios = Life), such as *heat, mechanical trauma, ionizing radiation* or the same *foods* that we eat daily, even "ozone" molecule is able to influence the cellular functions.

Indeed, following the stress, cells promote protection mechanisms that defend from the specific damage induced by the same stressing agent. The term xenobiotic has been introduced only recently (Mason HS, North JC, Vanneste M. Fed Proc. 1965 Sep-Oct, 24 (5): 1172-1180), and the details are still lacking of adequate scientific support regarding the involved mechanisms. As is obvious, this is reflected negatively in regards to ozone therapy too, and makes understandable, but not reasonable, the lack of attention of health authorities devoted to the control of human health.

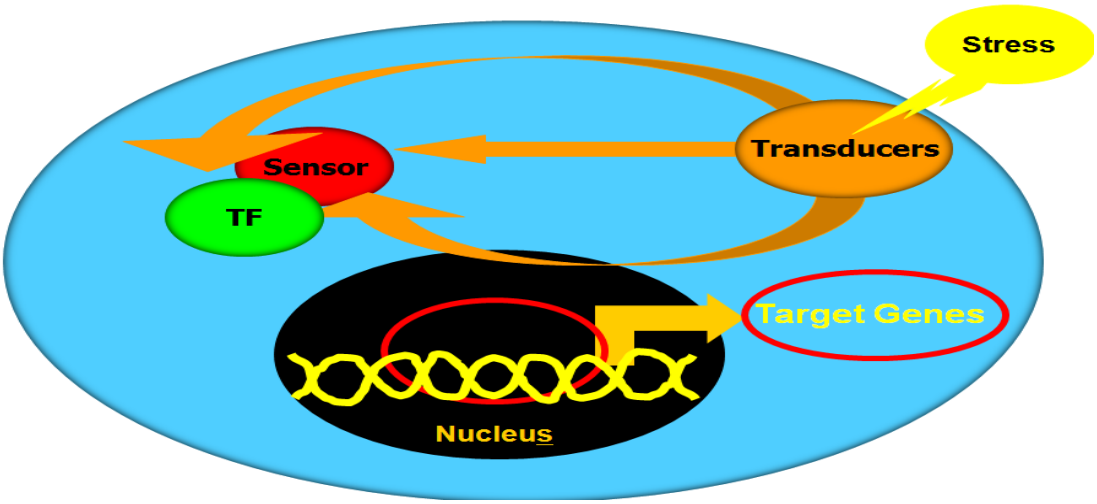
So the studies to date are mostly directed to the characterization of the Mode of Action of the Stress Response (MOA), understood as the definition of individual metabolic pathways activated at the cellular level by the various Xenobiotics. Ozone, like other agents, and unlike the common drugs that act on a specific receptor, induces small stress to the whole cell when used at low doses. This, in turn, triggers a series of intracellular metabolic processes and promotes a myriad of intracellular activities. As a consequence of these reactions, the defense mechanisms of the cell are alarmed and enhanced to improve functionality, explaining in part the surprising therapeutic actions of this gas. A recent study published in the prestigious Toxicological Sciences (Steven O. Simmons, Chun-Yang Fan, and Ram Ramabhadran, TOXICOLOGICAL SCIENCES 111 (2), 202-225 (2009)) has fully explained the biochemical mechanism with its intracellular mediators (*Transducers, Sensors and Transfer Factor*), where for each type of xenobiotic is possible to monitor the intracellular metabolic pathways (Fig. 1).

Pathway	TF	Sensor	Major transducers
Oxidative stress	Nrf2	Keap1	MAPK, ERK, p38, PKC
Heat shock response	HSF-1	Hsp90	CaMK2, CK2
DNA damage	p53	MDM2	ATM, JNK, Chk1, Chk2
Hypoxia	HIF-1	VHL	p38, PI3K
ER stress	XBP-1, ATF6, ATF4	BiP	IRE1α, S2P
Metal stress	MTF-1	None	PKC, CKII, TKs
Inflammation	NF-κB	IkB	IKK
Osmotic stress	NFAT5	None	p38, ATM, PKA

There is no doubt that this complexity makes us understand why it is not easy set up clinical trials demonstrating definitively the therapeutic power of these agents. On the other hand, any drug interaction, due to its direct bind with a receptor and consequent biological function activated, is easily measurable and statistically standardized. In short, the stimulus of Oxidative Stress, in the case of ozone, is able to activate Nrf2 protein (**Pecorelli et al**, Toxicol Appl Pharmacol. 2013 Feb 15;267(1):30-40. doi: 10.1016/j.taap.2012.12.001; **Re et al**, EJP, Eur J Pharmacol. 2014 Sep 16. pii: S0014-2999(14)00634-7. doi: 10.1016/j.ejphar.2014.08.029) which, moving in the nucleus, starts production from part of Target Genes of proteins that promote cell functions (Fig. 2), strengthening the defenses, and optimizing the underlying specific function.



We can now start to understand why following low doses ozone therapy we can observe positive effects, like aesthetics, if the conditioned cell is part of the skin tissue or a modulating effect on inflammation if the cell falls within the context of neuromuscular or bone tissues (Fig. 3).



It is time that he various ozone therapy societies, in Italy and internationally, start to increase their scientific weight, being now ozone therapy a common treatment in most of the continents and administered to millions of patients, with virtually no or few side effects (mostly of instrumental or iatrogenic origin). The lack of dedicated university courses and precise legislation at government level, make the sector unstable at present.

Ozone therapy, like other similar holistic approaches, could be included in the newly branch of Human Enhancement. This is one of the reasons that prompted some experts to establish a non-profit medical society for "*scientific research, bioethical analysis and the enhancement of human health*". Due to the increasingly long-lived population, the aim will be also to broaden the knowledge in the field of integrated and natural therapies in the aim of preventing aging and most of the pain pathologies of the elderly.

The Association, called *PotenziAttiva*, will also take care of the relationships between the various companies or individuals active in the field of complementary therapies. *PotenziAttiva* will also be active in studying the appropriate lifestyles and techniques for the prevention of rare diseases and aging. A website will be launched in the near future with both a public facing and member-only design.