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**Biophysical aspects of complexity  
in health and disease**

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## **“Electromagnetic homeostasis: the role of low-amplitude electromagnetic fields on life organization”.**

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The whole set of oscillatory frequencies of various substances, enzymes, cell membranes, nucleic acids, bioelectrical phenomena generated by the electrical rhythm of coherent groups of cells, cell to cell communication among population of host bacteria, forms an increasingly complex hierarchies of electromagnetic signals of different frequencies which cover the living being and represents a fundamental information network controlling the cell metabolism.

From this approach emerges the concept of “electromagnetic homeostasis”: i.e. the capability of the human body to maintain balance of highly complex electromagnetic interactions within, in spite of the external electromagnetic noisy environment. This concept may have an important impact on the actual definitions of health and disease.

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## **“Long-distance electrodynamic interactions among biomolecules”.**

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Living cells host a complex network of biochemical reactions, where the molecular players seem to know where to go and when.

A longstanding hypothesis surmises that these interactions could be driven by electrodynamic forces between biomolecular partners in these reactions. However electrodynamic interactions between biomolecules have eluded detection. Here, we provide theoretical and experimental confirmation of a crucial prerequisite for this hypothesis: the activation of a collective vibration of a macromolecule subject to an external supply of energy.

We first outline a theoretical model that describes out-of-equilibrium collective oscillations of a macromolecule as a classical phonon condensation phenomenon. Internal couplings among the normal modes of the molecule trigger a phase transition when the energy input rate exceeds some threshold, channeling the input energy into a coherent oscillation of the entire molecule.

Next, we report on the experimental evidence that this phenomenon is possible. This has been found for two different proteins, the Bovine Serum Albumin and the Red Phycoerythrin which displayed collective vibrations in the sub-THz domain when driven in a stationary out-of-thermal equilibrium state by means of optical pumping.

Finally, we report on the unprecedented experimental discovery of the activation of intermolecular electrodynamic interactions between proteins obtained through the cross-checking with two different and complementary experimental approaches, and in full agreement with theoretical predictions.

Our results could lead to a better understanding of the dynamics of biomolecular encounters and recognition in living cells by opening a broad domain of systematic investigations. We foresee the possibility of modulating biochemical reactions like enzymatic chains, DNA duplication and repair, and gene expression through externally applied electromagnetic fields, with numerous medical applications.



# **“Biophysical Concept for the new understanding of the interaction mechanism of ELF-EM pulses at Resonance frequencies with alive systems for medical applications and case studies”.**

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In this presentation the resonance interference interaction mechanism of applied extremely low frequency (ELF) electric pulses with the bioelectric signals generated during targeted metabolic process will be in some details discussed. The net result of the interference is the algebraic summation of the interfering signals which may lead to enhancement or inhibition of the metabolic process; depending on the mode of interaction. Based on this understanding, it was possible to control the metabolic activities of some alive systems such as microbes, fungi and cancer cells. Skin infections represent a significant burden of infection diseases. Complicated skin infections characteristically involve deeper skin structures or coexist in patients with immune suppression, infected burns, ulcer wounds and diabetic foot infection. These infections are likely to be multi-microbial. There is a world midst of an immerging crisis of antibiotic resistance for microbial pathogens. Therefore, it seems necessary to find out other alternative safe and efficient methods for the treatment of microbial infection diseases.

In this work a new noninvasive technique, using extremely low frequency (ELF) square electric pulses for the treatment of bacterial infected skin diseases. The frequency and duration time of exposure to these pulses were chosen depending on the resonance inhibiting frequency for the growth of the infecting bacteria according to our previous published work for in vitro and in vivo studies. The trial was expanded to diabetic foot treatment through clinical trial project with the Egyptian Ministry of Health and supported by the Egyptian Ministry of Defense. The trial was done at Almaza Military Hospital in Cairo, Egypt. In this method the subject is exposed to the ELF-EM field of strength 2.0 V/CM generated between two parallel copper plate electrodes connected to the pulse generator. The distance between the two electrodes is 150 cm. The exposure time and number of sits depended on the type/s of the infecting micro organism and the treated case condition. The clinical trial covered 150 patients. Some case results will be presented. Clinical investigations indicated no growth for bacteria and accelerate healing of the infected area after exposure for all ELF-EM treated cases. The main goal of the other part of this presentation is to study the effect of exposure of solid Ehrlich tumor implanted in mice to square wave magnetic field on growth characteristics and to realize the resonance mechanism. The results indicated that exposure to 4.5 Hz for 30 minutes is the inhibiting resonance frequency and whole body exposure of the animal can be a preventive agent on the metastasis of Ehrlich

tumor which occurred in some organs. In a recent publication for our group, a combination of bacteriolytic therapy with magnetic field for Ehrlich tumor treatment is discussed. In this experiment the efficiency of intra-tumoral injection of *Pseudomonas aeruginosa* bacteria in the cortex Of the tumor mass for two hours then the animal was whole body subjected to the inhibiting resonance frequency for the injected bacterial growth at 0.7 Hz magnetic field for one hour. The results indicated the progressive decrease of tumor volume during the course of the experiment which is interesting and promising result for medical application.

[N.B. A pannier for some treated cases will be presented]

### Pictures:



(Photos for some cases)

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## “DireWaves: Disarming resistant microbes with resonant waves.”

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Can we identify non-chemical methods to disarm antibiotic resistant microbes?  
Can weak, resonant electromagnetic fields (EMF) interfere with and disrupt antibiotic resistant microbes?

We here report on the status of the VILLUM Experiment project Direwaves. The aim of the project is to validate and further explore if biophysical means such as resonant EMFs can act as a complimentary approach in finding new treatment regimes against antibiotic resistant bacteria. Several studies have shown effects in *Pseudomonas aeruginosa* biofilm formation and growth of MRSA (1,2).

We have set up a bioresonance lab, including a shielded mu-metal chamber and an adjustable frequency generator system capable of generating weak (microTesla range), low-frequency (1-20 Hz) electromagnetic fields. A *Pseudomonas aeruginosa* biofilm assay is used to monitor physiological effects of resonant fields.

Preliminary data suggests that frequencies corresponding to the ion cyclotron resonance of Mg<sup>++</sup> and K<sup>+</sup> can inhibit biofilm formation up to 40% compared to untreated (no or ambient field). Ongoing studies aim to establish which frequency ranges and amplitudes that might be effective in disarming resistant microbes and work synergistically with existing antibiotics.

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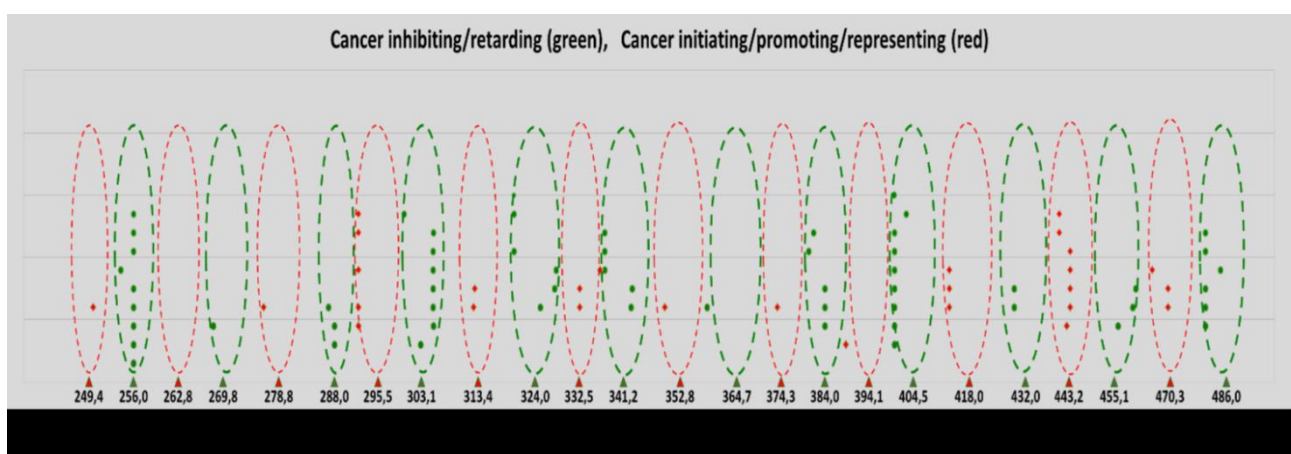
## “Searching for a Window effect in bioelectromagnetic interaction.”

**Ledda M.<sup>1\*</sup>, Lolli M.G.<sup>1</sup>, Grimaldi S.<sup>1</sup>, Lisi A.<sup>1</sup> and Foletti A.<sup>1-2</sup>**

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Fröhlich proposed that the functionality and sensitivity in living systems results from ordered states within the apparently chaotic motions and arrangements of biological molecules in order to build and maintain its coherence regardless the ceaseless response to external stimuli due to adaptive dynamics [1]. A consequence of this perspective is that metastable and far from equilibrium states may exist over large distances, thus suggesting a mechanism by which cells can be electrically or electromagnetically coupled each other [2-4], in addition to the short-range interaction due to biochemical signalling complementing classical cell biology [5]. This long-range biological biophysical way to communicate is based on occurrence of a resonance effect [6] and very likely may contribute to provide growth control in healthy tissue (coherence) [7] to enable electromagnetic homeostasis [8-9] but may be impaired in dysfunctional tissues as well as for instance in cancer due to loss of coherence [10-11]. According to this hypothesis the carcinogenesis could fit in a frequency pattern of electromagnetic (EM) waves, in which a gradual loss of cellular organization occurs. Geesink and Meijer in a recent paper hypothesized that cancer may be initiated and promoted at typical frequencies of electromagnetic waves positioned in decoherent frequency zones [12]. In contrast, the generation of cancer features can be inhibited and retarded by application of coherent frequencies. This hypothesis has been substantiated by collecting 200 different EM frequencies effects as emerging from 320 different published biomedical studies confirming the possible existence of so called “biological windows” in tissue interaction with electromagnetic cues as proposed by W.R. Adey some decades ago [13,14].



**Fig.1-** Calculated normalized EM frequencies that were experimentally applied to living cells systems are found to be patterned in 12 apparent bands of cell-sustaining coherent frequencies able to inhibit/retard cancer (green points) and cell-decaying decoherent frequencies able to initiate/promote/represent cancer (red squares), positioned between the cell-sustaining frequency bands. [12]

To address this working hypothesis, we planned to study the effects of ELF-MF (Extremely Low Frequency Magnetic Fields) on human epithelial colorectal adenocarcinoma cells (CaCo-2 cells) at three different individual frequencies chosen among those proposed by Geesink and Meijer algorithm [12]. In particular, we used two single cues proposed as cancer inhibiting frequencies (256 Hz and 303 Hz) and a single cue proposed as cancer initiating (443 Hz). CaCo-2 cells exposed to 256 Hz frequency at 100  $\mu$ T or 50  $\mu$ T showed a tiny and no statistical decrease of proliferation rate compared to control cells but a statistically significant increase in cellular mortality at day 3 or 4 as compared to control. CaCo-2 cells exposed to 303 Hz frequency at 100  $\mu$ T or 50  $\mu$ T showed a statistical decrease of proliferation rate at day 4 and no statistically significant changes of cellular mortality as compared to control. Finally, CaCo-2 cells exposed to 443 Hz 100  $\mu$ T frequency showed a tiny and no statistical increase of proliferation rate and the same cellular mortality compared to the control ones. These preliminary results showed that specific assumed inhibiting cues afforded an interesting increase of cellular mortality (256 Hz) or decrease in cellular proliferation (303 Hz) while supposed initiating cue (443) didn't affect neither proliferation neither mortality of this cell line. Many limitations emerge from these preliminary data warranting further systematic experiment in order to carefully identify the “biological windows” as for time exposure, intensity of magnetic field, specificity of initiating or inhibiting cues for different tissues, possible different effect on normal or cancer phenotypes of same cell type, and last but not least to plan the assessment of the translation of the results from the lab to the bedside for possible future integrative clinical applications.

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## **“Water mediates cancer.”**

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Cancer is connected with an extensive disruption of the cellular energy system. Mitochondrial dysfunction occurs in both Warburg effect cancer cells and fibroblasts associated with reverse Warburg effect cancer cells. However, the link between mitochondrial dysfunction and cancer has not yet been satisfactorily explained. Mitochondrial oxidative energy production decreases to about 50 % in comparison with healthy cells [1] and Warburg assumed that this disturbance triggers cancer mechanism. He wrote “The adenosine triphosphate synthesized by respiration therefore involves more structure than the adenosine triphosphate synthesized by fermentation” [2].

Mitochondrial dysfunction itself may be caused by inhibition of pyruvate transfer into mitochondrial matrix, by disturbed  $H^+$  ion transfer across inner mitochondrial membrane into cytosol, or by other defects causing decreased pH at the mitochondria.  $H^+$  ion pumping creates electrical potential on the mitochondrial inner membrane and a pH gradient. Due to mitochondrial dysfunction, both values are reduced [3].

At charged surfaces, water forms layers of exclusion zones (also called ordered water) with macroscopic thicknesses up to about 500  $\mu m$  [4, 5]. Properties of these layers depend on the electric field at the surface and pH value of the water solution. Formation of such layers at the region of hydrogen ions transferred from mitochondria proposed in [3] explains decreased and increased potential (in comparison with a real potential) measured at these organelles in healthy and cancer cells, respectively [6]. Measurements disclosed that polarization of the layer depends on pH and that positively and negatively charged particles can be excluded [4].

Due to changed inner arrangement of electrons in water molecules the layer releases a massive number of electrons at high value of pH [7]. If the actual mitochondrial membrane potential drops below a certain critical value due to mitochondrial dysfunction, the layer is repolarised and can release electrons which are transferred to the cytosol rim [3].

We suppose the released electrons form a conductive cloud which damps electric and electromagnetic activity of the inflicted cell, leading to lowered electromagnetic activity, disturbed coherence, decreased frequency of oscillations, and decreased level of biological functions [3]. In the reverse Warburg effect cancers, fibroblasts supply energy-rich metabolites to the associated cancer cell [8], resulting in its increased power of electromagnetic field, fluctuations due to shift of oscillations to an unstable nonlinear region, decreased frequency, and loss of coherence.



In both cases, field-control of chemical reactions might be corrupted [3, 9, 10] and a pathway to genome somatic mutations might open.

Warburg effect seems to be the central phenomenon in cancer initiation and cancer can be considered a disease of the cellular energy system, transforming tissue-bound cells to individual entities.

#### **Acknowledgement:**

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## **“Interactions of Electromagnetic Fields in Microwave Frequency Band with Biological Systems”.**

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This contribution is focused on interactions of electromagnetic fields in microwave frequency band with biological systems, mainly from the point of view of physics.

Approach to research of biological effects of microwave EM fields (both thermal and non-thermal) will be presented.

Basic known results of this research (both positive and negative biological effects of EM field) will be discussed here.

From it will result how the positive biological effects can be used in the area of applications of EM fields in medicine and biology.

In details will be described the use of microwave technology for cancer treatment by hyperthermia.

Principles of new type hyperthermia applicators (e.g. based on MTM technology, etc.) will be mentioned.

Last but not least, prospective use of microwave technology for medical diagnostics, e.g. microwave differential tomography, will be given.

## **“Wellbeing Complexity Needs Effective Information Support Tools”.**

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Quite recently researchers have been finding that higher air pollution levels are even correlated to lower math, verbal test scores and cognitive performance, according to a study of more than 25,000 people living throughout China [1]. The classic medicine approach sees Environmental medicine divided between integrative clinicians and occupational and environmental physicians based on their practice dynamics.

All clinicians face challenges in assessing toxicant loads, and an exposure history is seen as the most useful tool. Currently, standardised exposure assessment tools are used to advance the clinical practice of environmental medicine and expand its reach across other clinical disciplines [2]. As a matter of fact, nobody is realizing that it is a global emergence, not a local one only [3]. More advanced, effective tools are needed to face this new, imminent generational catastrophe effectively. But, at global level, nobody is taking care concretely of this dreadful problem apparently. Unfortunately, using the traditional medical approaches, deep functional damages are manifested only when it is too late to find an effective solution and recovering. Why? Because human beings are not equipped to become aware about their real wellbeing state from weak and superweak signals [4], especially of electromagnetic (EM) type [5,6].

We need to shift from a disease-focused to a wellbeing-focused paradigm by new advanced information support systems and tools. In fact, despite a fairly long history, the notions on information emission or fields have not gained a worthy recognition in the scientific community, due to the low sensitivity of past and present instrument control. But more examples are accumulating continuously.

In 2009, Luc. Montagnier showed that high dilutions of the DNA solution of some bacteria and viruses are sources of EM emission in the range of several hundred hertz to several kilohertz [7,8]. He used the results of these experiments to justify the revolutionary hypothesis according to which water, aquatic environments of living organisms can participate in the storage and transfer of genetic information.

EM signals are endogenously generated at different levels of the biological organization and, likely, play an active role in synchronizing internal cell function or local/systemic adaptive response. Consequently, each adaptive response can be

described by its specific electromagnetic pattern and, therefore, correlates with a unique and specific electromagnetic signature [9].

This new basic understanding allows to develop new biophysical, biomedical modelling and simulation systems. We present new technique that can overcome the past limitations.

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# **“Why there is not more research on electromagnetic cell communication?”**

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Funding of research on electromagnetic cell communication (ECC) as opposed to chemical cell communication has not yet received full attention.

Apart from funding there are also the researchers that need to be encouraged to study ECC.

Therefore, the goal of this workshop regards the simplicity of designing an ECC-experiment and summarises some of the promising results obtained so far.

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# **“Biophysical Aspects of Biological Organization Underpinning Health and Disease”.**

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So far, electromagnetic signals have been widely considered as an epiphenomenon or a by-product of the biochemical activity of the living organisms. In spite of this fact that a number of biophysical analysis has become part of biomedical investigations such as, for instance, electrocardiograms, electroencephalograms, evoked potentials, electromyographs, bio-impedentiometric analysis, evolving and becoming more and more sensitive and sophisticated techniques on which to rely into the daily clinical activity.

Today, eventually, we can consider the biophysical and biochemical aspects as a double aspect of the living being [1] reminding, somehow, the wave-particle duality characterizing the physics of the beginning of the last century in contemporary medical practice [2].

If we consider that biochemistry and biophysics are mutually interacting with each other, then we can also begin to be able to study the adaptive dynamics and consequently both the physiology and the pathophysiology also from a biophysical viewpoint.

Following previous intuitions, today we begin to consider that the endogenous electromagnetic activity can be the driver of the phenomena of embryological development, of cell differentiation along the physiological turnover, and during the reparative processes through stem cells commitment [3].

A number of constraints of such endogenous electromagnetic activity have been recently postulated in order to define the existence, nature, and function of such a coherent state, far from thermodynamic equilibrium, in biological systems till to become an essential condition for the existence of life.

According to these postulates:

- living cells generate an endogenous electromagnetic field and such a field is coherent.
- microtubules are non-linear oscillating structures generating an electromagnetic field in living cells.
- Mitochondrial activity establishes the conditions for the generation of this endogenous electromagnetic field.
- Synchronization, force effects for transport, interactions, morphology, and information transfer may be functions of the electromagnetic field.
- Even consciousness, instinct of self-preservation, and the central control function of the brain and less developed structures may depend on quantum electrodynamic processes.

- Disturbances of the energy processing system and the coherent electrodynamic state far from thermodynamic equilibrium may produce pathological states, including cancer [4].

Endogenous alternating electromagnetic fields contribute to self-tuning and self-regulation of metabolic processes and are essentially non-linear [5,6].

Furthermore, recent studies have shown that endogenous electromagnetic activity can even guide the activity of the cerebral cortex [7].

This process leads to the use of non-linear biophysical signalling to modulate both the biochemical and biophysical characteristics of the organism at once sustaining as well his inner coherence and complexity [8,9].

Indeed, endogenous electromagnetic signals seems to play a significant role in the synchronization of physiological activity along the ceaseless adaptive dynamics aimed to enable allostatis as well as in the effort to restore allostasis when allostatic load has been established in the effort to cope with both endogenous and external threatening in the attempt to keep stability through dynamic changes [10].

In this framework it become rather obvious to consider health and disease as dynamic and unavoidable parts of ceaselessly adaptive dynamics instead of separated entities to be defined and described as mutually independent.

Actually, to some extent, We need disease to strengthen health and overcome temporary frailty, and We need health to restore from disease and strengthen resilience to face successfully future adaptive dynamics [11].

Biochemical and biophysical dynamics become the two side of the same adaptive process mutually and synchronously interacting each other effectively and efficiently to preserve and enhance life.

Notably, if we consider the huge number of cells constituting a human organism [12] and, moreover the fast turnover [13] most of them underwent through the entire lifespan it is quite logical consider that only electromagnetic fields fulfil the requirements to keep the stability of the entire organism in real time without loss of coherence, energy or information.

Remarkably, it has been lately outlined that DNA electrodynamics may play a relevant role in chromatin regulation [14], moreover, endogenous bioelectric network [15] may store non-genetic information during both development and regeneration opening up to the possibility of modulating epigenetic regulation through biophysical methods [16].

So far, medicine relayed basically and uniquely on biochemical intervention in order to restore health. Today, it is possible, in addition, to rely on biophysical intervention [17] aimed to restore the self-regulation and self-regeneration capabilities of the organism itself by means of endogenous, external, or a combination of endogenous and external electromagnetic signals [18].

Medical practice could take useful benefit from the integration of biophysical protocols for the therapy and prevention of an increasing number of health burden both acute and chronic [19].

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# **“The Tissue Organization Field Theory in the Context of a Theory of Organisms”.**

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In 1999, Sonnenschein and Soto co-authored a book entitled THE SOCIETY OF CELLS (Bios-Taylor & Francis) in which they critically evaluated the status of research in the fields of control of cell proliferation and carcinogenesis. They concluded that a) the default state of all cells is proliferation and motility, and b) sporadic cancers (over 95% of clinical cases) and inborn errors of development (be they inherited or induced) represented by about 5% of cancers. Both types of cancers are anchored at the tissue level of biological organization. These are the core premises of their tissue organization field theory of carcinogenesis (TOFT).

In addition, Sonnenschein and Soto have defined cancer as “development gone awry”. As reflected in scholarly and lay publications, the TOFT is increasingly accepted by the cancer research and secular communities as the theory that more reliably explain cancers within an evolutionary relevant perspective.

For over a decade now, the Soto/Sonnenschein lab has developed a 3D model of the human breast responsive to the three mammatropic hormones, i.e. estrogens, progesterone and prolactin. In addition, they also developed experimental models to study the biophysical determinants of morphogenesis. As members of the ORGANISM group at the Ecole Normale Supérieure, in Paris, France, they have extended their scientific interest by exploring the theoretical implications of TOFT within biology at large in the context of a Theory of Organisms. Based on the organicist tradition, their Theory of Organisms postulates that: 1) the default state of all cells is proliferation with variation and motility, a notion rooted in the cell theory, 2) the principle of variation, which applies to morphogenesis and inheritance, and 3) the principle of organization, considered as the fundamental source of biological stability. A discussion of these topics will be presented.

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# “The cellular “electrome”: undervalued aspects”.

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## 1. Cellular electricity is inorganic ion-based

The analysis of the “strange phenomenon”, that we know as “electric current” started with the study of electric fishes, a story that is no longer in the collective memory. When it was discovered that electric current could also be observed and studied in bimetal constructs, the early batteries, electricity became a hot, world changing, topic. But how do electric fishes generate an electric current, sometimes so strong that it is deadly for its preys? Many years of research later, it became apparent that the current was produced in electric organs that are modified muscle or nerve cells.

But what is the difference between electric current from the socket and biological electric current? An electric current is a flow of charge through a conductor. In electricity from the socket, the current is carried by electrons, while biological electric current is carried by inorganic ions, the key ones being  $\text{Na}^+$ ;  $\text{K}^+$ ,  $\text{H}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ ,  $\text{HCO}_3^-$ ,  $\text{Cl}^-$ . Inorganic ions can be confined in structures lined by biological lipid membranes, while electrons cannot because of too small.

The same basic laws of electricity, Ohm’s law etc. apply to both types of electric current. Thus, biological electric current is based upon transmembrane and transcellular transport of inorganic ions. Transmembrane transport is achieved by the concerted action of ion pumps which transport specific ions against their concentration gradient, an energy demanding process, and the passive, downhill transport through ion channels.

How this system contributes to physiological processes is very well documented in neurobiology, e.g. action potentials, in muscle contraction, renal function etc.

## 2. Cells can drive a self-generated current through themselves: self-electrophoresis

A lesser known function is transcellular transport, with *self-electrophoresis* as a possibility. Prof. W.H. Telfer (Philadelphia) and his coworker Richard Woodruff were the discoverers. They studied a special case of oocyte development in the silk moth *Hyalophora cecropia*.

They were puzzled by the observation that in developing oocytes some types of macromolecules did not get distributed according to the principles of simple diffusion.

Instead, they were subject to electric-charge dependent unidirectional transport. Their explanation resulted in the concept that not only such oocyte-type, but in fact, all cells are miniature electrophoresis chambers, at least during part of their life cycle.

## 3. The vibrating probe technique

When cells drive an electric-ionic current through themselves, the current loop must be closed outside the cells. Prof. Lionel Jaffe (U.S.A.) developed a special tool to map the current pattern. It was named “the vibrating probe”.



It enabled to map the current pattern around an ameba, the *Drosophila* egg, plant roots, embryos etc.  $\text{Ca}^{2+}$  plays a key role in such currents. The data obtained highlighted the importance of *non-spherical symmetry* and *polarity* in biological systems.

#### **4. A recent unifying concept: The cellular self-generated electrome. Some implications for a better understanding of Death, the Soul, and the Cognitive memory system**

In the classical “mind-body” wording, “body” is usually associated with the “mass aspect” of living entities and “mind” with the “immaterial” one. Thoughts, consciousness and soul are classified as immaterial.

A most challenging question emerges: Can something that is truly immaterial, thus that in the wording of physics has no mass, exist at all? Many will answer: “No, impossible”.

My answer is that it is very well possible, that no esoteric mechanisms need to be invoked, but that this possibility is inherent to two well established but undervalued physiological mechanisms.

The first one is electrical in nature.

In analogy with “genome”, “proteome” etc. “electrome” (a novel term) stands for the totality of all *ionic* currents of any living entity, from the cellular to the organismal level.

Cellular electricity is truly vital. Death of any cell ensues at the very moment that it irreversibly (excluding regeneration) loses its ability to realize its electrical dimension.

The second mechanism involves communication activity that is invariably executed by sender-receiver entities that incessantly handle information. Information itself is immaterial (= no mass).

Both mechanisms are instrumental to the functioning of all cells, in particular to their still enigmatic cognitive memory system. Ionic/electrical currents associated with the (actin) cytoskeleton likely play a key role, but have been largely overlooked.

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## **“Both health and disease have their own biophysical patterns.”**

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The underlying rules for a natural system describing cellular automata are simple, but produce highly complex behaviour.

A mathematical basis for the spectra of discrete coherent and non-coherent electromagnetic (EM) frequencies was derived, in which the algorithm exhibits an information distribution according to ratios of 2:3 in 1:2 at a semi-harmonic manner.

The GM-model shows that energy both in animate systems and typical inanimate systems is semi-harmonic, quantized and discrete.

The particular EMF patterns were revealed by a meta-analysis of more than 500 biomedical publications that reported life-sustaining as well as life-decaying EMF frequencies.

The discrete eigenfrequency values can be related to bio-resonance of solitons also called polaron quasi particles in life systems as described by Fröhlich.

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# **“Electroconductive Properties of Microtubules, Actin and Kinesin: Physical Force, Energy, Power and Information Considerations.”**

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We provide an overview of the modeling performed at both atomistic and coarse-grained levels in order to gain insight into electrostatic and electro-conductive properties of the cytoskeleton.

Computer simulations and experimental measurements carried out for microtubules and actin filaments are presented.

Charge and dipole values for monomers and dimers as well as polymerized forms of these proteins are summarized.

Continuum approximations for cable equations describing actin filaments and microtubules compare favorably to measurements in buffer solutions showing soliton waves and transistor-like amplification of ionic signals.

In addition, experimental evidence for memristive behavior of microtubules supports their hypothesized role in memory storage and information processing.

Conductivity and capacitance of tubulin and microtubules have been measured and modeled. A dramatic change in conductivity occurs when tubulin forms microtubules.

In living cells, this signals a conductive phase transition coinciding with mitosis in dividing cells.

Finally, we provide estimates of the forces, energies and power involved in the action of electric fields on microtubules and kinesin motors.

These calculations are compared and contrasted with typical values experienced at a cell level.

We will also discuss how cytoskeleton can electromagnetically interact with the cell's exterior via its coupling with the ion channels and other membrane proteins.

## **“Impact of oscillating magnetic field on charge transport processes in the light of possible biological effects.”**

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We analyze the effect of oscillating magnetic field on the dynamics of electrons, self-trapped in nonlinear soliton states [1-3].

Such solitons are formed in macromolecules and provide charge transport in redox processes in living systems [4-7].

It is shown that in the presence of the oscillating magnetic field the dynamics of electrons in soliton states is qualitatively different from the dynamics of free electrons. The velocity of solitons and their cyclotron dynamical mass are calculated as functions of the intensity and frequency of magnetic field for different orientations of the field. The change of the soliton dynamics is reflected on the redox process and can have biological effects [8,9].

These results can explain the experimental data on the therapeutic effects of weak oscillating magnetic fields [10].

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# **"Electromagnetic Fields Couple to Endogenous Signalling Pathways of the Cell".**

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During the last two decades, elaborated studies could show that endogenous electrical fields and ion gradients arise in biological systems. The main driver of these phenomena is the membrane (resting) potential found in any cell type of the body including stem cells.

This potential comes from the segregation of charges by molecular machines like pumps, transporters and ion channels. Electric fields (EF) and electromagnetic fields (EMF) can spread out via gap junctions (GJ) to larger areas and trigger pathways for cell signaling, production of tissue factors, growth hormones, transmitters etc.

The situations, where we find endogenous EFs in an organism are those where fast changes in morphology happen: during embryonic development, in wound healing and in regeneration. EFs are also important as guiding cues for cell migration in early development, wound healing and regeneration. These often override chemical or topographic cues.

The organism uses this fast information medium because EF can spread out faster than diffusion of signaling factors, growth hormones or other molecules. Thus, EF has a pre-formative capacity in patterning and coordination.

Now, also the complete cascade of linking the endogenous EF into the canonical signaling pathways is well studied in many situations. EF can also spread via cell processes with GJ even within the very thin tunneling nanotubes (TNT).

These TNT were recently found also in very distantly located cells of adult tissues like the fibrocytes of connective tissue and in fascia. GJ are often precursors and pre-formative for classical synapses of nerve cells, which then are also chaperoning the further development and differentiation of organ development.

In sum, all these new findings proof that EF and EMF patterns in the organism represent an endogenous counterpart which is accessible for adequate EF, EMF and pulsed EMF in therapy.

## “Molecular Bioresonances in Biology and Medicine”.

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There is much evidence of existence of electromagnetic resonances within biological macromolecules, particularly proteins and DNA/RNA.

The whole area of biophotonics is related to ultra-weak photon emission from biological systems [1], particularly within the range of UVA, visible and infra-red spectrum.

In addition, there is also evidence of biomolecular resonances in much lower frequency ranges including KHz, MHz and GHz. However, so far there is no evidence or theory, how and if these macromolecular resonances are related to biological activity of macromolecules.

Here we present, the Resonant Recognition Model (RRM), which can explain that such emission, and particularly its specific frequencies, are critical for resonant activation of proteins and DNA/RNA.

The RRM is based on the findings that certain periodicities within the distribution of energy of delocalized electrons along protein (DNA/RNA) molecule are critical for their biological function and/or interaction with their targets [2-3].

If charge transfer through these macromolecules is introduced, then charge moving through macromolecular backbone can produce electromagnetic radiation, absorption and resonance with spectral characteristics corresponding to energy distribution. The frequency range of this radiation depends on charge velocity [2-9].

We applied this concept on number of proteins and DNA/RNA examples [2-5], as well as on some medical conditions like: Crigler-Najjar syndrome [6], pain [7] and influence of environmental light to health [8].

This concept has been also experimentally tested by predicting the electromagnetic frequencies for activation of L-Lactate Dehydrogenase [9].

The concept has also been tested independently on experimental measurements of photon emission from dying melanoma cells [10], as well as on photon emission from lethal and non-lethal Ebola strains [11].

These findings could be used, not only to understand biological processes and resonances in biomolecules, but also to influence these processes using either radiation or design of related molecules.

Thus, the RRM approach is promising tool for design and development of new techniques in pharmacology, drug design, biotechnology and medicine.

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## **“Aquaphotomics for Disease Diagnosis and Understanding”.**

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Aquaphotomics<sup>1</sup> is a new scientific field that explores water – light interaction as a two ways tool to investigate and stimulate biological and aqueous systems. It has been discovered<sup>2</sup> that water molecular structure presented as spectral pattern is a collective mirror image of the physiological condition of a system.

Near infrared spectral monitoring has been conducted for various biological systems<sup>3,4,5</sup>. Spectral patterns of healthy and diseased cells, plants, animals will be presented showing consistent changes in the water spectral pattern in transition from “healthy” to “unhealthy” state of the respective system.

Portable spectrophotometer has been designed to measure water spectral pattern non-invasively and in real time. It has been successfully used for diagnosis and results will be presented.

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## ***“Water Structuring in Aqueous Solutions Investigated by Delayed Luminescence”.***

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Water and life are closely linked. Liquid water is required for life to start and for life to continue. Moreover, water has a number of anomalous properties which have been related to the water's role in the chemistry of life [1]. Water molecules are “connected” by a weak bond, and the strangeness of water is a consequence of the extensive three-dimensional hydrogen bonding of water molecules to one another. There are two main hypotheses [2] concerning the hydrogen bonding of liquid water that divide water science: water forms (i) a continuum three-dimensional network of (more or less) distorted H-bonding around a near-tetrahedral local structure from one side, and (ii) the mixture of two distinct competing structural motifs, namely a low-density water (LDW) and a high-density water (HDW), on the other side.

Although the water anomalies are more evident in the supercooled region, recent experimental evidences at ambient conditions, where most important biological processes involving water occur, have been reported, as:

- the formation of massive ‘exclusion zone’ (EZ), where solutes are excluded, next to various hydrophilic surface [3];
- the observation by X-ray spectroscopy of two distinct, inter-converting structural species whose ratio depends on temperature [4];
- the observation by dielectric spectroscopy measurements of a Debye-like slow relaxation, associated to structural and/or dynamical inhomogeneities on length scales as large as 0.1 mm [5].

With the aim of using new experimental techniques that can provide different and complementary information, in this work water structuring has been investigated by measuring the time-resolved photo-induced Delayed Luminescence (DL) from suitable aqueous solutions. Indeed:

- DL intensity has been correlated to the dimension of the ordered structures where it has been measured [6];
- the DL phenomenon in biological systems has been connected with the formation and dissociation of non-linear coherent self-trapped (localised) electron states (solitons and electrosolitons [7].
- the water structure (formation of a dynamic quasi-lattice) and its polymorphism have been used to explain intrinsic luminescence of water [8].

In Literature it is reported that the water ordering effect can be enhanced by adding suitable solute. In aqueous salt solutions, in fact, addition of a solute to water causes a displacement of the HDW/LDW equilibrium because ions partition differently between contiguous micro-domains [9]. On the other hand, viscous liquid has showed effects that indicate the presence of structure for a quite long period. In this respect, the SOL–GEL technique based on a tetraethoxysilane (TEOS) precursor leads to the formation of a three dimensional silica network at or near room temperature and water elimination. Moreover, a recurring hypothesis in experimental and computational studies is that cryoprotectants, as glycerol, act by modifying water structure giving rise to the formation of nano-clusters of water surrounded by the matrix of solute molecules [10].

So we performed DL measurements from aqueous solutions of some salts [11, 12], TEOS [13] and glycerol [14], also on varying concentration and temperature, by using the dedicated equipment for fast ultraweak luminescence analysis ARETUSA developed at the Laboratori Nazionali del Sud (LNS-INFN), in Catania [11-14].

The measurements of DL showed:

- Evidence of a significant DL signal only for the aqueous solutions for which LDW clusters formation is foreseen, suggesting that LDW domains should be longer-lasting and/or larger and/or more ordered than HDW ones.
- The probability distribution function of decay time presents a maximum in the microsecond range for all the solutions, letting to suppose that LDW domains have lifetime of the same order of magnitude. This surprising result appears to be the first experimental evidence of so long lasting lifetimes of water's structures.
- The findings are correlated with experimental [3,4] and theoretical [10, 15] studies from other authors.

So, changes in the water structuring could be used as a simple tool to store and transfer the energy that is harnessed in biochemical processes. On the other hand the many physical and chemical properties of water, that have a crucial and unique role for life as we know it, are related to such low density structuring. In this respect, the possibility to explore the water structuring by using DL measurements could constitute a powerful tool of investigation of life's processes.

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## **“The Quantum-Mechanical Nature of Nociceptive Sensors”.**

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Pain can be generated by different phenomena, starting from mechanical damage to the breakdowns of different metabolic pathways in the organism.

Therefore, the mechanism responsible for pain signal generation must be common neuronal mechanism which has the property to receive extra- and intracellular signals of various physical, chemical and metabolic factors and generate abnormal membrane excitation.

As pain sensation can be changed upon the effect of extremely weak chemical and physical factors, having intensity even less than thermal threshold, it cannot be explained from the point of membrane theory excitation, which is based on the classical thermodynamic principals. Therefore, the mentioned common mechanism should have quantum-mechanical sensitivity.

On the basis of our data showing that the net water influx has activation effect on Na inward current in excitable membrane and the increase of cell hydration leads to elevation of the number of functionally active receptors and ionic channels in the membrane (Ayrapetyan et al. 1984, 1985, 1988), we hypothesize that the abnormal activation of osmotically driven net water uptake by cell is a primary mechanism for generation of membrane hyper-excitation.

The facts that both thermodynamic properties of membrane bathing aqua medium and cell metabolism have quantum-mechanical sensitivity allow us to consider the net water influx as a determining factor for quantum-mechanical sensitivity of nociceptive properties of the membrane.

To support the aforementioned hypothesis the experimental data on the comparative  
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study of  $^{45}\text{Ca}^{2+}$  and  $^{40}\text{Ca}^{2+}$  effect on cell hydration and pain thresholds (“hot plate”) of rats in different metabolic states of organism are presented.

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## **“The primo vascular system: a rediscovered vascular system in mammals – Biochemical and biophysical characteristics”.**

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In my talk I will give an overview of the rediscovery of a third vascular system in mammals (besides the blood and the lymphatic system): the primo vascular system (PVS).

The PVS comprises a three-dimensional network of vessels and nodes with a specific microstructure of the vessels. After reviewing the key discoveries about the PVS, I will report on my own PVS research conducted during my research stay in 2018 at Seoul National University, one of the main institutions investigating the PVS. Specific biochemical and biophysical aspects of the PVS will be explained in detail.

I will also discuss the potential significance of the PVS with respect to pathophysiology and medical applications.

# **"The Use of Extra-Low Frequency Pulsed Electromagnetic Field (PEMF) to Regulate Immunomodulatory Properties of Mesenchymal Stromal Cells and Macrophages"**

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An emerging body of evidence indicates the existence of a frequency-dependent interaction between extremely-low frequency (< 30 Hz) pulsed electromagnetic fields (PEMF) and cell signaling molecules along inflammatory pain pathways in both macrophages (Ms) and mesenchymal stem/stromal cells (MSCs).

Ms are not only involved in inflammatory and anti-infective processes, but also play an important role in maintaining tissue homeostasis.

MSCs are significant modulators of chronic inflammation and autoimmune disorders. During cell-communication processes, endogenous and exogenous signaling affects normal and pathological developmental conditions.

Our research shows exogenous influences such as PEMF therapeutically reduce pain and inflammation by modulating G-protein coupling receptors (GPCRs) to down-regulate pain-related second messenger cyclic adenosine monophosphate (cAMP), and inflammatory cytokines tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukins IL-1 $\beta$ , IL-3, IL-4, IL-6, IL-10, IL-17A, as well as the transcription factor nuclear factor kappa B (NF- $\kappa$ B).

Results using 5.1 Hz, 0.04 mT show PEMF can bring pain-associated inflammatory responses back to homeostasis by stabilizing anti-inflammatory cytokines and decreasing pro-inflammatory cytokines in Ms and MSCs.

# “Integrative Biophysical Management for Early Stage of Chronic Kidney Disease”.

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**Background:** Chronic Kidney Disease (CKD) and its clinical evolution are an emerging issue [1,3], due to an increasingly aging population [4] and has been recently correlated to allostatic load as an expression of cumulative biological risk [5-8]. Moreover, CKD is raising as a public health priority [9]. Therefore, the assessment of integrative strategies contributing to manage the decline in renal function is advisable. Previous evidence indicates that a biophysical integrated approach can significantly improve renal function [10-12]. Nevertheless, controlled trials assessing the clinical efficacy of this strategy were still lacking.

**Aim of the study-** The primary goal was to test the efficacy of a single session of biophysical therapy, delivered every three months over one year, on the outcome of estimated glomerular filtration rate in elderly patients.

**Methods-** This study was designed as a 12-month randomized controlled trial. Inclusion criteria were elderly patients (age starting from 70 years and above) affected by stage II/IIIb CKD, while exclusion criteria were diabetes or continuous assumption of steroidal or non-steroidal anti-inflammatory medications. Patients were then randomly assigned to either control or biophysical treatment. In addition to standard treatment with renin angiotensin aldosterone system (RAAS) inhibitors, the biophysical group received an electromagnetic information transfer through aqueous system procedure [13] every three months performed by a commercial available electromedical device (Med Select 729, Wegamed GmbH, Essen, Germany). Estimated glomerular filtration rate (eGFR), according to CKD-Epidemiology Collaboration formula [14], was calculated, through serum creatinine sampling, at enrollment, as baseline, and at the endpoint after one year.

**Statistical Analyses-** Statistical analysis was performed using MedCalc software (Mariakerke, Belgium) and Instat Software (GraphPad, San Diego, CA, USA). A p-value <0.05 was considered statistically significant. Student's paired t-test was used to compare mean differences in eGFR values in patients from baseline and 1 year while Student's unpaired t-test was used to compare differences in eGFR between male and female patients. Receiver operating characteristic curve (ROC) analysis was used to assess the ability of improvement in eGFR to discriminate patients who received biophysical treatment compared to control group.

**Results-** A total of 238 patients were included in this study, 118 (73.9±3.8 years) in the biophysical therapy group and 120 (74.6±4.2 years) in the control group. At baseline, mean eGFR was 69±11.8 ml/min in the biophysical group and 70.7±11.5ml/min in the control group. At the endpoint after one year, eGFR was 74.1±12.3 ml/min in the biophysical group, compared to 66.3±11.9 ml/min in the control group, with a statistically significant difference between groups (p<0.0001).

**Discussion-** The biophysical intervention significantly improved eGFR in this group of elderly patients and the improvement in eGFR in the biophysical treated group was independent of age, gender and antihypertensive treatment.

Remarkably, these results were obtained with only 4 single intervention session along one year, as the electromagnetic information through aqueous system procedure [13] allowed to extend the effects up to three months by self-administration of the treated aqueous solution by patients themselves at home.

**Conclusions-** This study suggests a potential contribution of a biophysical integrated strategy [15] to support renal function against its natural decline due to aging in the elderly. Biophysical therapy could represent an integrative, non-invasive, effective, safe, and cost-effective method useful to provide a personalized management [16] of individual patients in preventive medicine. Additionally, biophysical therapy allows to link personal care to population care in general practice [17] as a tool for personalized medicine. Further wider and longer clinical evaluations are needed to confirm these reports as well as to assess the possibility to extend this biophysical strategy to support renal function in early stage of Chronic Kidney Disease regardless the age of its onset starting the intervention at its beginning following previous reports [10-12].

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## **“Building a Personalized Biophysical Therapy Toolkit: work in progress”.**

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Stress burden is unanimously considered as the most important prognostic factor impacting overall morbidity and mortality [1,2]. Eventually, the cumulative effect of stress burden impairs allostasis and give rise to allostatic load [3-8]. Consequently, any procedure aimed to reduce allostatic load may be beneficial in order to decrease in general both morbidity and mortality [9] and in particular some of the component of the global burden of disease that are somehow stress-related. In contemporary medical practice we assume that biophysical and biochemical aspects of the biological organization are double aspect of the living being during adaptive dynamics and that we can study physiology and pathophysiology either from a biophysical or from a biochemical viewpoint or, better, from both simultaneously. Additionally, today we begin to consider that the endogenous electromagnetic activity can be the driver of aspects such embryological development, cell differentiation along the physiological turnover, and during the reparative processes through epigenetic effects [10]. Indeed, endogenous electrodynamic activity [11-14] seems to play a pivotal role in the short and long-range hierarchical synchronization of physiological activity along the ceaseless adaptive dynamics aimed to maintain allostasis as well as in the effort to restore allostasis when allostatic load is challenged due to pathophysiological cues. Consequently, the term electromagnetic homeostasis [15] has been, recently, suggested to describe these dynamics outlining a crucial role of electromagnetic signalling in order to establish and tuning the inner coherence of endogenous life rhythms [16]. A biophysical toolkit is now available to enable the management of an increasing number of disease burden ranging from pain in general [17], to low back pain [18], articular pain [19], knee osteoarthritis [20], neck pain and disability [21], early anxiety and depression states [22], refractory gynaecological infections [23], till to early stages of chronic kidney disease [24]. The reported biophysical strategy implemented an electromagnetic information transfer through aqueous system procedure [25] enabled by means of a biomedical wave generator (Medselect 729, Wega, Germany) operating in the low frequency range providing a carrying (1 Hz-20 KHz) and a modulating frequency (1-20 Hz) delivered at the earth magnetic field intensity (50  $\mu$ T). The procedure starts with the recording of a pattern of endogenous electromagnetic signals through a couple of electrodes placed on the patient (the site is varying according to the different aim of the treatment time by time) for a settled time. Then, the endogenous signals are continuously replayed and transferred back to the patient though an electromagnetic carpet on which the patient lay down in order to achieve a systemic effect, and through a couple of electromagnetic probes on specific locations in order to achieve a local effect at once according to selective and specific protocols. Simultaneously, all the output signals may be recorded on a commercially available microelements aqueous solution with dropper (Nomabit Base, Named, Italy) in order to allows the self-administration of the drops according to an incremental weekly plan as in previous reports. Remarkably, a single therapy session allows a self-treatment by the recorded drops lasting up to three months. Here we report two new possible clinical application of this biophysical procedure.

### **Biophysical management of allostatic load assessed through salivary alpha-amylase - a randomized placebo controlled pilot study.**

The first is pilot study aimed to assess the possible effect of a biophysical treatment through the EMITTAS procedure to affect salivary alpha-amylase as a marker of allostatic load [26-28]. A total of 24 patients were randomly assigned to a sham treatment or to a biophysical protocol including EMITTAS. Patients assigned to both groups received the Nomabit Base solution but the sham group received a non-recorded one as placebo. In order to maintain the homogeneity between the two groups in this study we rely only on the recording of patient's endogenous signals from the forehead and from the neck in correspondence of carotids arteries and none of the groups received the direct treatment. Therefore, we were able to evaluate the effect of the EMITTAS procedure itself independently from the direct effect of the biophysical delivery. Sampling of salivary alpha-amylase was performed at 8 am [29,30] for all patients at baseline the same day of the delivery of the procedure and after one month as end point. Mean salivary alpha-amylase was  $105 \pm 102$  U/ml at baseline and  $116,7 \pm 110$  U/ml at the endpoint in the sham group showing no statistically significant difference with  $p = 0.4$ , while in the biophysical EMITTAS group the salivary alpha-amylase was  $118 \pm 81$  U/ml at baseline and  $27.8 \pm 37$  U/ml at the endpoint showing a statically significant decrease  $P < 0.04$ .

Since salivary alpha-amylase is a reliable biomarker of allostatic load [26-28,31] we warrant further and larger study to assess the effectiveness of this procedure extending to three month the endpoint as for other studies. The possibility to impact allostatic load seems to be feasible by means of this biophysical strategy and seems also time effective and cost effective. Moreover, the salivary sampling could allow to easily collect wider groups of patients and not influence the stress levels being painless and self-sampled at home at replicable standardized time.

### **Biophysical management of leaky gut syndrome - an open label pilot study.**

The second report is about an open label pilot study aimed to assess a possible contribution of a biophysical intervention in the management of leaky gut syndrome. Leaky gut syndrome is an emerging clinical condition characterized by intestinal and/or extra-intestinal symptoms [32] that can be screened through a specific questionnaire in order to prescribe serum sampling to ascertain possible gluten-associated conditions [33]. As objective correlate of leaky gut syndrome it is now available the determination of serum zonulin [34-36].

A total of 245 patients with either intestinal either extraintestinal symptoms were examined in a general practice setting by mean of serum zonulin sampling. Among the total 154 patients (62,9%) turned out to be positive while the negative ones were 91 (37,1%). Among the positives 55 patients accepted to be part of an open label biophysical treatment integrating the EMITTAS procedure. At the endpoint, after 3 months, 43 of them (78,2%) had normalized serum zonulin level, while 12 (21,8%) resulted still above the threshold but with reduced serum zonulin levels. The biophysical treatment afforded normalization of serum zonulin in an interesting number of patient and could represent an integrative interventional perspective in leaky gut syndrome. Leaky gut syndrome has been recently connected to the pathophysiology of irritable bowel syndrome [37], inflammatory bowel disease [38], gastrointestinal autoimmune diseases [39], autoimmune disease in general [40] and diabetes mellitus [41]. Moreover, since leaky gut syndrome represent a challenging entity to cope with, biophysical treatment may represent a tailored integrative intervention aimed to restore intestinal permeability defects [42] allowing an effective and efficient subjective relief from symptoms, as well as an objective normalization or reduction of serum zonulin. The biophysical toolkit is therefore offering some new interesting clinical interventions for some of the emerging clinical syndromes practitioners and/or specialists has to face in their daily clinical activity fitting the concept of non-invasive, non-pharmacological, reliable, safe, effective, efficient, cost effective and personalized treatment.



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## “Biophysical Management of Anxiety and Stress: a Pilot Study”.

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**State of the art-** Anxiety and depression cause a dramatic impact on public health [1-4], therefore it is crucial to find cost effective strategies to cope with them. Integrating the knowledge from physics and biology, today living organisms can be considered as dynamic processes, far from equilibrium, connected and regulated by a continuous flow of substance, energy and information [5]. Preliminary studies showed a significant reduction of anxiety symptoms after biophysical treatments [6-8] suggesting a potential role of biophysical therapies in the management of their mild and moderate symptoms [8].

**Aim of the study-** The primary goal was to test the efficacy of a single session of biophysical therapy on symptoms related to stress, anxiety and depression.

**Materials and methods-** The study was designed as RCT. The inclusion criterion was a score of GAD-7 [9] greater than 5. One hundred patients were recruited and then were randomized to the intervention group (N=50) and to the placebo group (N=50). The intervention consisted in a single session of biophysical therapy performed by the Med Select 729 (Wegamed GmbH, Essen, Germany) simultaneously integrating the electromagnetic information through aqueous system procedure (Nomabit Base, Named, Italy) [10]; the placebo group followed the same identical procedure but without recording nor transmitting the signals. Both groups were assessed at T0 and after three months as endpoint (T1) with the following questionnaires: Depression Anxiety Stress Scale (DASS) [11,12]; Center for Epidemiologic Studies Depression Scale Revised [13,15]; WHO-QoL-Bref [15,16].

**Statistical Analyses-** Data were processed and analysed using the Statistical Package for Social Sciences (SPSS version 22.0; Chicago, IL, USA). Both parametric and non-parametric tests were used, in accordance with Shapiro–Wilk as a test for normality. Baseline group differences were assessed using Student’s *t*-test or Mann–Whitney *U* test to compare the two groups for continuous measures and  $\chi^2$  Test or Fisher’s Exact Test for categorical measures. GLM repeated measures multivariate ANOVA (RM-MANOVA) was used to analyse the main pre- and post- intervention effects and interactions both between and within experimental and control groups. A  $p < 0.05$  was considered statistically significant throughout all of the analyses.

**Results-** At baseline there were neither significant differences in socio demographics nor in clinical data between the two groups, except for marital status. The RM-MANOVA yielded a significant interaction between time and groups, with a greater reduction of DASS, CES-D and WHO-PHYSICAL scores in the intervention group.

**Discussion-** The biophysical intervention was proved to be effective in reducing anxiety, depression and stress and in improving physical quality of life. Remarkably, these results were obtained with only a single intervention session, as the electromagnetic information through aqueous system procedure allowed to extend the effects up to three months by self-administration of the treated aqueous solution by patients themselves at home.

**Conclusions-** These preliminary results suggest that a single biophysical intervention could be beneficial in reducing the global burden of symptoms related to stress, anxiety and depression and in improving physical quality of life. Additionally, it seems to be cost effective especially in mild and moderate symptoms of anxiety and depression. Further studies are needed in order to confirm these findings.

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# **“Spatio-temporal dynamics of spontaneous ultra-weak photon emission (autoluminescence) from human hands measured with an ultra-sensitive electron multiplying CCD camera setup”.**

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Biological tissue exhibits autoluminescence, i.e. a spontaneous ultra-weak photon emission (UPE) without photoexcitation.

In this study, we report UPE measurements on human hands using an electron-multiplying CCD (EMCCD) camera.

The images from left and right hands (2 subjects, 10 images in total) were taken on different dates.

We observed the following spatio-temporal aspects of the hand UPE images:

- (i) all images show clearly that human hands exhibit autoluminescence;
- (ii) (ii) there was large variability in the UPE intensity with respect to the factors: time (time of day, date), anatomical location on the hand, and individual subject;
- (iii) (iii) images taken on the same date (but at different times of day) showed a stronger similarity than images of the same subject taken on different dates;
- (iv) iv) the mean UPE intensity (averaged over 2 regions of interest at the right and left dorsum of the hands) correlated with the time of measurement (lower intensity at around noon).

Our study documents the feasibility of UPE imaging of hands with an EMCCD camera and shows that the spatio-temporal variability of the UPE pattern harbours information that seems to be correlated to internal and external factors.



## **“Non-thermal effects of radiofrequency electromagnetic fields exposure on neural stem cells”.**

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In literature there are many evidences suggesting the ability of high frequency (3 MHz - 300 GHz) electromagnetic fields to influence biological systems, interfering with some regulation and control processes. However, up to date, the action mechanisms are not well understood. It should be better clarified their connection with the characteristics of the impinging electromagnetic field, that is Specific Absorption Rate (SAR), exposure time (chronic or acute), frequency and type of modulation [1-3].

In these contribution, we present the first results assessing the non-thermal effects induced by exposure on primary Olfactory Ensheathing Cells (OECs) to continuous and amplitude modulated 900 MHz EMF, in far field condition and at different time expositions (10, 15, 20 minutes).

OECs are typical glial cells showing characteristics of stem cells.

They express several growth factors and are able to promote axonal regeneration and functional restoration in the injured sites of Central Nervous System.

Furthermore, it is known that a reduced functionality of olfactory system represents an early sign of neurodegeneration.

The OECs were isolated from olfactory bulb of 2-day old mouse pups [4] and divided into three groups (control, sham and tests). The control samples were kept in the incubator at 37 ° C in an environment of humidified air and CO<sub>2</sub> (95% -5%).



Sham and tests were placed in a thermostatic bath, appropriately realized, at 37°C for the duration of the exposure. As sham it is intended a sample treated as test samples but not exposed to EMFs. The tests were exposed in far-field conditions to EMFs at 900 MHz continuous (CW 900 MHz) and amplitude modulated at 50 Hz (AM 900 MHz), electromagnetic wave amplitude  $\sim 7$  V/m in both exposure modes, and at three exposure times: 10, 15 and 20 minutes.

The expression of the marker proteins of the OECs (S-100 and Nestin) and of the cytoskeletal proteins (GFAP and Vimentin) was evaluated by immunocytochemistry, as well as the cell viability by MTT test.

The experimental results showed that the exposure to CW 900 MHz and AM 900 MHz was able to induce a significant decrease in cell viability, changes in morphology and expression of the analyzed markers compared to the control cell cultures (incubator and sham). Surprisingly, these effects show a kinetic as function of exposure times and presence (AM 900 MHz) or absence (CW 900 MHz) of amplitude modulation.

Studies are now in progress to better clarify the molecular mechanisms induced by EMF on OECs, in order to highlight also the involvement of glutamate receptors.

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## **“Experimental evidence for a collective, coherent behaviour of water molecules in electrolytic solutions”.**

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We studied the water molecule organization in chlorides salts by using the methods of the classical Infra-Red spectroscopy.

A simple mathematical treatment of the data shows the emergence of a self-similar behaviour in concentrated solutions of strong electrolytes. I

n other words, beyond certain concentrations (whose exact value depends on the ion nature), the restructuring of the water-water interactions shows similar patterns at increasingly changing scales.

This observation implies a collective property of the system and cannot be anyhow related to the behaviour of independent molecules.

This shows that cooperative and coherent behaviours arise in aqueous solutions, even at physiological concentrations, and that the correct description of these systems cannot rely uniquely on the molecular model.

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## **“Electronically excited species formation during oxidative radical reaction in skin”.**

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Reactive oxygen species are formed during the oxidative metabolic processes which enhance to a toxic level under stress condition.

The condition is referred to as oxidative stress.

Under normal conditions, cells are capable of dealing with ROS using defense systems (non-enzymatic and enzymatic) but it can lead to an acute damage to cells/organs via the oxidation of cellular components under stress condition.

Oxidation of biomolecules is a well-studied mechanism of cellular injury in several of organisms and it is frequently used as an indicator of oxidative stress.

In the presented study, we have used the porcine ear/ porcine skin biopsies as an ex-vivo/in-vitro model system to represent human skin.

Results have been presented on the involvement of hydroxyl radical in the initiation of lipid peroxidation thereby leading to the formation of reactive intermediates followed by the formation of electronically excited species eventually leading to ultra-weak photon emission (Scheme I).

To understand the participation of different electronically excited species, the effect of a scavenger of singlet oxygen on photon emission in broad range of spectrum (visible to near-infrared region) was measured which showed its contribution.

The results have been supported based on measurement with interference filter reflecting a substantial contribution of triplet carbonyls in the photon emission.

Based on the results obtained, it is concluded that during the oxidative radical reactions, the ultra-weak photon emission is contributed by the formation of both triplet excited carbonyls and singlet oxygen.

The methods used in the current study is claimed to be a potential tool for non-invasive determination of the physiological and pathological state of human skin.

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## **“Delayed Luminescence in cancer research”.**

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The evaluation of optical properties of biological samples is gaining increasing interest both in scientific and applicable field due to the ability of used optical techniques to provide information on the biological status of the system under analysis in a fast and non-destructive way. In this context the Delayed Luminescence (DL) appears to be an excellent candidate for the development of a reliable and economical optical biopsy techniques.

The term Delayed Luminescence (DL) refers to the photo-induced ultra-weak luminescence emitted by systems, also biological, after the illumination source has been switched off. The DL has a spectral emission lying from the optical range to near infrared and its intensity is various orders of magnitude ( $10^3$ - $10^5$ ) lower than the usual Fluorescence or Phosphorescence. DL is by nature extremely polyphasic. Its lifetime spectrum extends from  $10^{-7}$  to more several seconds after the stimulation end. Indeed it is well known that relaxation from non-equilibrium state towards equilibrium of complex systems can be approximated by a power law, being such an approximation consistent with the idea of a distribution for relaxation kinetics [1]. Due to the low level of DL, we used the dedicated equipment for fast ultraweak luminescence analysis ARETUSA developed at the National Southern Laboratories of the National Nuclear Physics Institute (LNS-INFN), in Catania, Italy. The samples were excited by a nitrogen laser source emitting pulses at 337 nm. The re-emitted photons, in the wavelength range 350–850, nm are collected by a photomultiplier tube working in single photon counting mode. Spectral measurements were carried out by using broadband bandpass filters centered at 450 nm, 550 nm and 650 nm (50nm FWHM) inserted between sample and photomultiplier tube.

Improvement in experimental equipment as well as mathematical analysis of data have shown the possibility to use the DL in cancer research as tool to investigate the status of human cells and tissues, so showing the possibility to discriminate between normal and tumor conditions [2, 3]. The study performed on human leukemia Jurkat T-cells [4-5], on follicular and anaplastic human Thyroid cancer cells [6], on glioblastoma multiforme [7] gave the possibility to correlate DL to apoptosis and oxidative stress. The results pointed out the mitochondrial origin of this ultraweak luminescence and in particular to its correlation with the electron flow in the complex I of the mitochondrial respiratory chain [7, 8], whose natural biomarkers, NADH, flavins and singlet oxygen, emit respectively in blue, green-yellow and red regions. Worth to note that in addition to their established role in generating energy for the cell, mitochondria represent an essential component of many apoptotic pathways, and

features of DL have been correlated to apoptosis and oxidative stress. More recently in the framework of the research project ETHICS “Pre-clinical experimental and theoretical studies to improve treatment and protection by charged particles” funded by INFN, we studied DL emitted by non-tumorigenic breast epithelial cell line and metastatic breast cancer cell line in order to found possible correlations between Delayed Luminescence and in vitro damaging induced by ion irradiation. The experimental results showed not only DL dependence on cell line but also its ability to give early information of the effects induced by proton dose [9].

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## “Coherent Frequencies for a Diagnostic and Therapy ‘Tool-Kit’.”

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**Coherent frequencies:** Two oscillations are coherent if their waveforms can be superimposed in space and time. The degree of coherence between  $N$  oscillators is determined by a Poisson distribution; statistical fluctuations give the fractional bandwidth of the coherence as  $\sqrt{1/N}$ . Given enough coherent oscillators, their bandwidth reduction can enable the system to exceed thermal energy  $kT$  and their frequency become significant.

Coherence propagates by diffusion in water and water vapour with a velocity  $\sim m/s$ . If there is no interaction with the medium, its velocity is that of light  $\sim 300 Mm/s$ . Information is transmitted as modulation on the magnetic vector potential field component (A-field). The distance over which the coherence persists becomes the constant parameter making frequency proportional to velocity. This generates many interacting frequencies from optical through microwave to biological each being determined by velocity ratios the system will support.

The endogenous frequency of the healthy Heart Meridian has a bandwidth  $\sim ppm$ . It is stabilised through 384 MHz to a  $(149-127\text{ cm}^{-1})\ 22\text{ cm}^{-1}$  water-vapour-laser transition. Frequencies characterising chemicals also can appear in various parts of the spectrum. Above 1.42 GHz (molecular hydrogen resonance) and in the blue and shorter wavelengths coherently synchronised bio-systems can have superluminal inter-communication.

Coherent frequencies can be imprinted into water by mechanical succussion (momentum impulse) or an applied magnetic (B-field). Water memory requires proton precession to generate a local magnetic field such that proton magnetic resonance conditions can be satisfied for any frequency. This happens when a critical  $53\ \mu m$  domain of protons becomes coherent. Imprints can be erased by placing the water in a closed steel box to reduce the geomagnetic field to  $<380\text{ nT}$ . Frequency imprints are non-Abelian.

**Coherence in Diagnosis:** Acupuncture meridians and chakra points have characteristic endogenous frequencies. If a target organ is under stress, its frequency appears in the whole-body field. Scattered light from bio-systems is modulated by the frequencies of the scatterer. This modulation is retained in photographs, even after these have been transmitted over the internet. They can be extracted from light scattered from photographs (or print-outs) and used for diagnosis and therapy. Stress from environmental and other toxic chemicals or food allergens can be identified by frequencies.

**Coherence in Therapy:** Here, the *sine qua non* is that a coherent frequency can have a biological effect. It has chirality states, stimulatory or depressive of biological activity and there are frequencies which can switch between them. Homeopathic potencies and allergy neutralising dilutions have characteristic frequencies which can be matched to stress frequencies to find a *similiter*. Pharmaceuticals have their characteristic frequency signatures but chemistry is not the only way to create therapeutic frequencies. EMF generated frequencies are easy to adapt to drug resistant pathogens and can be distributed quickly over the internet. A *similiter* for Marie Curie derived from her photograph would have been a potency of radium bromide.

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## **“Treatment of neointimal hyperplasia using 5- Aminolevulinic Acid – loaded PESDA microbubbles- mediated blue laser photodynamic therapy”.**

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**Introduction:** Neointimal hyperplasia refers to proliferation and migration of vascular smooth muscle cells primarily in the tunica intima, resulting in the thickening of arterial walls and decreased arterial lumen space.

Neointimal hyperplasia is the major cause of restenosis after percutaneous coronary interventions such as stenting or angioplasty.

The term neointima is used because the cells in the hyperplastic regions of the vascular wall have histological characteristics of both intima and normal artery cells.

**Purpose:** In this study, we developed an experimental blue laser photodynamic therapy system, and investigated its effectiveness on neointimal hyperplasia regression in the rat carotid artery accompanied by 5- Aminolevulinic Acid - loaded microbubbles administration.

**Methods:** Briefly, rats underwent balloon dilatation injury at the common carotid artery. Histopathology results showed neointimal hyperplasia formation in all of the rats' arteries.

Then stenotic arteries of the treatment group at lesion region, treated with 5- Aminolevulinic Acid – loaded PESDA (Perfluorocarbon- Exposed Sonication Dextrose Albumin) microbubbles (100 ml/kg, 2-5 ×10<sup>5</sup> bubbles/ml) administration

accompanied by extracorporeally blue laser (441.6 nm, 120 J/cm<sup>2</sup>) photodynamic therapy. Foam cells density were evaluated in the treatment group compared with the other groups using histology.

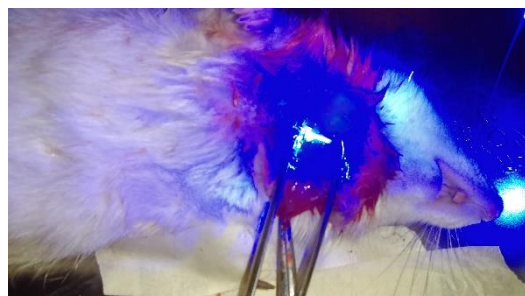
**Results:** Results from histopathology showed a significant reduction in the mean value for foam cells density within the early atherosclerotic lesion in the treatment group compared with the other groups ( $p < 0.05$ ).

**Conclusion:** Enhanced anti-inflammatory effect of 5-Aminolevulinic Acid-induced by low-level laser photodynamic therapy leads to an enhanced efferocytosis effect that can cause to a reduction in the foam cells density.

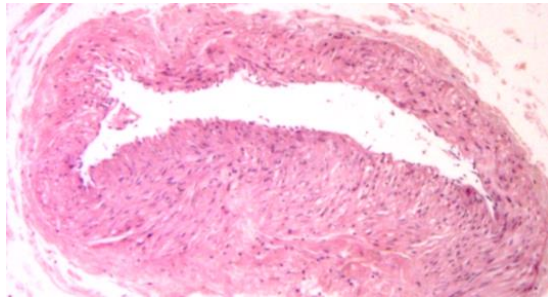
This protocol may be a potential treatment to neointimal hyperplasia.



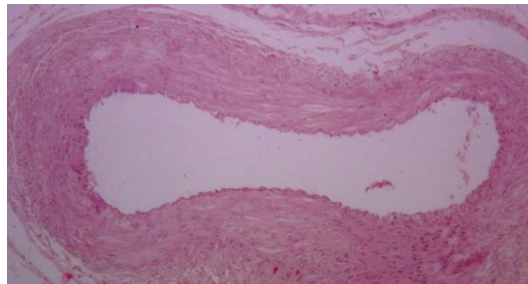
Preparation of 5- Aminolevulinic Acid - loaded PESDA microbubbles



Photodynamic therapy with blue laser



Neointimal hyperplasia in the rat carotid artery



Carotid artery after photodynamic therapy

**“Intermediate stage atherosclerosis regression in the rabbit abdominal aorta using Low- level confocal dual-pulse electrohydraulic shock wave- mediated sonodynamic therapy accompanied by 5- Aminolevulinic Acid - loaded PESDA microbubbles and high- dose atorvastatin administration”.**

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**Introduction:** Atherosclerotic lesions are considered intermediate by histological criteria when accumulations of lipid, cells, and matrix components, including minerals, are associated with macrophages foam cells-rich soft plaque formation, structural disorganization, repair, and thickening of the intima, as well as deformity of the arterial wall.

Lesions considered intermediate by their histology may or may not narrow the arterial lumen, may or may not be visible by angiography, and may or may not produce clinical manifestations.

Such lesions may be clinically significant even though the arterial lumen is not narrowed, because complications may develop suddenly.

**Purpose:** In this study, we developed an experimental Low- level confocal dual-pulse electrohydraulic shock wave therapy system, and investigated its effectiveness on intermediate stage atherosclerosis regression in the rabbit abdominal aorta accompanied by 5- Aminolevulinic Acid - loaded PESDA microbubbles and high-dose atorvastatin administration, wherein diagnostic B- mode ultrasound is combined with shock wave therapy system, with a goal of increased safety.

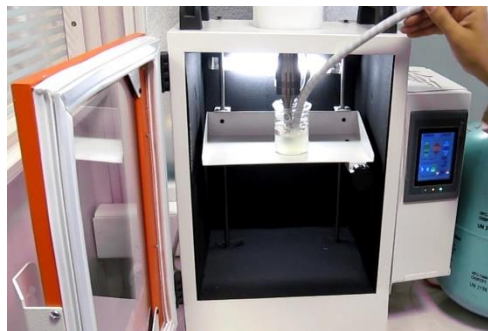


**Methods:** Briefly, rabbits underwent primary balloon dilatation injury at the abdominal aorta (approximately 1 cm superior to the iliac bifurcation) followed by a 1.5% cholesterol- rich diet injury for six weeks. Histopathology and ultrasonography results showed the formation of macrophages foam cells-rich soft plaque in all of the rabbits' arteries, resulting in vessel wall thickening and intermediate stage atherosclerosis formation.

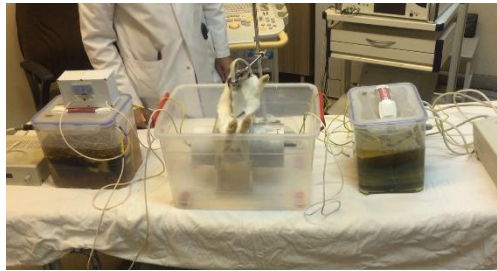
Then atherosclerotic arteries of the treatment group at lesion region, treated with 5- Aminolevulinic Acid- loaded PESDA (Perfluorocarbon- Exposed Sonication Dextrose Albumin) microbubbles (100 ml/kg,  $2-5 \times 10^5$  bubbles/ml) and high- dose (5mg/ kg/day) atorvastatin administration- mediated sonodynamic therapy using Low- level confocal dual-pulse electrohydraulic shock wave (8 Kv, 2 Hz and 12Kv, 0.5 Hz) therapy system. Foam cells density were evaluated in the treatment group compared with the other groups using histopathology.

**Results:** Results from ultrasound imaging concurrent with shock wave therapy, showed the collapsing of microbubbles and feasibility and acute safety of targeting stenotic region in the abdominal aorta. Also, histopathology results showed a significant reduction in the mean value for foam cells density, lumen wall mean thickness and percentage of luminal cross- sectional area of stenosis, in the treatment group compared with the other groups ( $p < 0.05$ ).

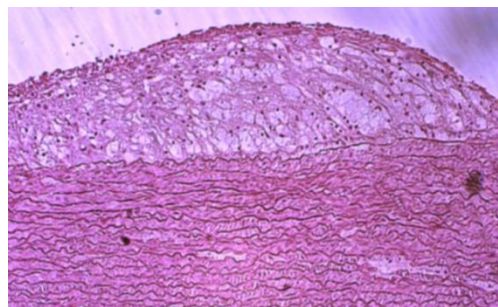
**Conclusion:** Enhanced anti- inflammatory effect of 5- Aminolevulinic Acid- induced by Low- level confocal dual-pulse electrohydraulic shock wave accompanied by Enhanced lipophilic effect of atorvastatin, induced by collapsed microbubbles due to targeted shock wave therapy, leads to an enhanced macrophages efferocytosis effect. Enhanced macrophages efferocytosis effect can cause to a reduction in the foam cells density and reduce intermediate stage atherosclerosis and significantly dilate the luminal cross- sectional area of stenosis. This protocol may be a potential treatment to intermediate stage atherosclerosis.



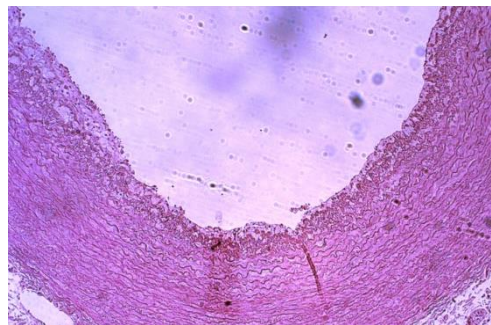
Preparation of 5- Aminolevulinic Acid - loaded PESDA microbubbles



Sonodynamic therapy with Low- level confocal dual-pulse  
electrohydraulic shock wave system



Intermediate stage atherosclerosis in the rabbit abdominal aorta



Abdominal aorta after sonodynamic therapy

# **“Resonance Detection System between Altered Biological Tissues and Determined Electromagnetic frequencies”.**

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The “TRIMprob” Bioscanner Tissue Resonance Interaction Method probe) is a not cumbersome, portable and usable everywhere revolutionary device that does not require chemical or radioactive contrast agents, photographic plates or other consumables. Also, for these characteristics the Bioscanner obtained the certification from the Istituto Superiore della Sanità (Higher Institute of Health) and from Ministero della Salute (Ministry of Health) inserted it in the list of the Medical Devices EC of Servizio Sanitario Nazionale (National Health Service).

The device detects malfunction of mitochondria and microtubules in the cell, but best results are obtained analysing the cancer cells. When the pathological tissues are hit by the electromagnetic waves of the device, they absorb some frequencies selectively in the UHF band and the device detects a drop of the corresponding spectral line. In the light of this discovery any kind of cancer, except for leukaemia, can be diagnosed by a harmless test, repeatable to infinity, to be made on dressed person, which show a diagnostic repeatability by a minimum of 70% to beyond 95%.

In Italy near fifty hospitals (But not yet in Emilia-Romagna) have started using it to detect cancer of the ovaries, of the rectal colon, of the thyroid, of the stomach-duodenum, of the bladder, of the prostate and breast, obtaining accuracy similar or superior to traditional medical tests (such as ultrasound, TAC, RMN, PET, biopsies, aspirated needle), often invasive or anyhow uncomfortable. Japan, Brazil, Malaysia, Turkey, Iran, United Kingdom, France, Belgium are already using the Trimprob in their hospital.

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