The use of ion resonance-like therapy with SEQEX electromedical devices as an integrated medical treatment for patients with neoplastic and autoimmune pathologies

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1) Why use ion resonance-like therapy?

The biological effects of SEQEX devices are based on studies conducted by the American scientist Abraham R. Liboff. In 1985 he hypothesized that the terrestrial magnetic field was able to interact with extremely low frequency and intensity electromagnetic fields (ELF-EMF) directly inside biological tissues, inducing a phenomenon resembling ion cyclotron resonance (*Liboff AF Geomagnetic cyclotron resonance in living things. J Biol Physics 1985;13:99-102*). He hypothesized that electromagnetic waves could modify the trajectories of key biological ions, like Ca++, Na+, K+, and Mg++, promoting their movement through the cell membrane. This transmembrane ionic movement activates specific intercellular processes. ELF-EMF waves acting in association with the geomagnetic field induce a physical response on a cellular level in a phenomenon known as "ion cyclotron resonance" (ICR) (*Liboff AR. Electric-field ion cyclotron resonance. Bioelectromagnetics. 1997;18:85-7*).
A series of studies demonstrated that the biological effects of ELF-EMF on the ionic channels of the cellular membrane are capable of activating the high voltage Ca++ channels while inhibiting the low voltage channels, with resulting effects on calmodulin, prostaglandin E, and arachidonic acid. They also activate the Na+ channels (*Piacentini R, Ripoli C, Mezzogori D, et al. Extremely low-frequency electromagnetic fields promote in vitro neurogenesis via upregulation of Ca(v)1-channel activity. J Cell Physiol. 2008; 215: 129–39 - Cui Y, Liu X, Yang T, Mei Y-A, Hu C. Exposure to extremely low-frequency electromagnetic fields inhibits T-type calcium channels via AA/LTE4 signaling pathway. Cell Calcium 2014;55:48–58 - He Y-L, Liu D-D, Fang Y-J, Zhan X-Q, Yao J-J, Mei Y-A. Exposure to Extremely Low-Frequency Electromagnetic Fields Modulates Na Currents in Rat Cerebellar Granule Cells through Increase of AA/PGE2 and EP Receptor-Mediated cAMP/PKA Pathway. Plos One January 2013, e543769*).
SEQEX devices enable the administration of extremely low intensity electromagnetic fields (ELF-EMF) to the entire organism using a mat that generates an electromagnetic field. Patients lie on the mat for a customization test, which quantifies the effectiveness of individual electromagnetic wave configurations administered by the device in order to customize treatment according to response. This involves measuring the impedance after the administration of each individual wave configuration in order to select and record the waveforms that induce maximum ionic mobilization. The electromagnetic waves selected by the device are recorded on a “smart card” and are subsequently administered to the subject for 27 minutes at least twice a week. It is preferable that treatment is repeated regularly for a minimum of 20 to 30 sessions. The intensity of terrestrial magnetism varies from 25 to 75 μTesla (0.25 to 0.75 gauss) between the poles and the equator. SEQEX emits an intensity of 20 μT (0.20 gauss) and frequencies within the range of 1 to 80 Hz (for comparison the frequency emitted by household electrical sockets is 40 to 60 Hz). These parameters underline the complete absence of potential toxicity of the device. It generates electromagnetic waves analogically, including wave harmonics which are important for modulating the biological effects on living organisms.

2) What are the main intracellular effects produced by ELF-EMF and exploited in therapy?

A) A number of in vivo and in vitro studies have demonstrated that ELF-EMF can **reduce oxidative stress** and equilibrate the oxidation reduction balance by promoting the activity of antioxidant enzymes. Oxidative stress occurs when the production of free radicals overwhelms the production of the organism's antioxidant systems (*Klebanoff S 1999, in Inflammation: Basic principles and clinical correlates – Gallin JI, and Snyderman R eds. - 3rd Ed. pp 721-68, Lippincott Williams & Wilkins, Philadelphia*). Free radicals are molecules particularly hungry for electrons, which they subtract from fats and proteins, damaging the cells to which these belong and altering their functions. Our production of free radicals rises in response to chronic inflammatory states, septic events, neoplasias, assumption of medications, and exposure to toxic agents (in particular cigarette smoke). When the production of free radicals is not balanced by the production of antioxidants, oxidative stress occurs. A number of studies have highlighted the capacity of ELF-EMF to abate oxidative stress. The first study was conducted at the University of Urbino by Prof. Ruggero Rossi in 2002. The research was only published in 2007 by his collaborators due to the untimely death of the professor (*Vallesi G, Raggi F, Ruffini F, et al.: Effects of cyclotronic ion resonance on human metabolic processes: a clinical trial and one case report. Electromagn Biol Med 2007;26:283-8*). It was subsequently observed that ELF-EMF are capable of enhancing the antioxidant activity of mitochondria (*Tunez I et al. Effect of transcranial magnetic stimulation on oxidative stress induced by 3-nitropropionic acid in cortical synaptosomes. Neurosci Res 2006;56:91–95*) by inducing intranuclear transduction of the NrF2 factor (nuclear factor-erythroid 2-related factor 2) capable of activating more than 500 cell protection genes (*Tasset I et al. Neuroprotective effects of extremely low-frequency electromagnetic fields on a Huntington's disease rat model: effects on neurotrophic factors and neuronal density. Neuroscience 2012;209:54-63*).

B) ELF-EMF have a **protective effect on cells** and can induce the production of heat shock proteins (HSPs), which are proteins that protect cells subjected to stress due to physical or chemical insult. These proteins intervene by assisting the completion of the tertiary structures of other proteins in cases in which "stressors" might compromise them. They are thus mediators capable of repairing other proteins and enabling their correct operation (*Perez FP, Zhou X, Morisaki J et al. Electromagnetic field therapy delays cellular senescence and death by enhancement of the heat shock response. Exp Gerontol 2008;43:307-16*) (*Carmody S, Wu XL, Lin H, et al. Cytoprotection by electromagnetic field‐induced hsp70: A model for clinical application. J Cell Biochem 2000;79:453-9*).

C) ELF-EMF produce an **anti-inflammatory effect** by reducing the production of proinflammatory cytokines. They also enhance the activity of the signal transducer Nrf2, which plays an essential role in the anti-inflammatory/antioxidant response, activating at least 500 cell protection genes and antioxidant enzymes. Nrf2 also competes with other signal transduction molecules like NF-kB, which instead induces activation of genes for the production of proinflammatory cytokines (TNF, IL1, IL6, etc.) and the expression of certain adhesion molecules required for activating inflammation.
ELF-EMF also directly inhibit activation of NFkB (*G Vianale et al.: Extremely low frequency electromagnetic field enhances human keratinocyte cell growth and*

decreases proinflammatory chemokine production. Br J Dermatol. 2008;158:1189-96) and reduce the activity of the Cox-2 inflammation mediator and proinflammatory cytokines like TNF-α and IL-1β (*Ross CL et al.: Electromagnetic Field Devices and Their Effects on Nociception and Peripheral Inflammatory Pain Mechanisms. Altern Ther Health Med. 2016;22:52-64*).

D) ELF-EMF have a **regenerative effect on tissue**, which is not limited to the regeneration of bone tissue, but includes the potential regeneration of numerous tissues through the stimulation of mesenchymal stem cells and their differentiation and maturation into the various cellular elements (neurological, cartilaginous, muscular, cutaneous, and mucosal tissue).
ELF-EMF promote the recovery of sensori-motor functions in rats subjected to hemisection of thoracic spinal cord (*Das S, et al. Exposure to ELF- magnetic field promotes restoration of sensori-motor functions in adult rats with hemisection of thoracic spinal cord. Electrom Biol Med 2012;31:180-94 –Yang Y et al. Acute neuroprotective effects of extremely low-frequency electromagnetic fields after traumatic brain injury in rats. Neuroscience Letters 2012;516:15–20*) and induce the differentiation of mesenchymal stem cells of rat bone marrow towards functional neurons (*Bai WF, Hu WC, Feng Y, et al. Fifty-Hertz electromagnetic fields facilitate the induction of rat bone mesenchymal stromal cells to differentiate into functional neurons. Cytother 2013;15: 961-70*).
ELF-EMF accelerate the healing of wounds in normal and diabetic rats through hyper-regulation of the release of FGF-2 (fibroblast growth factor) and prevent tissue necrosis in diabetic subjects following ischemic insult (*Callaghan MJ, et al. Pulsed electromagnetic fields accelerate normal and diabetic wound healing by increasing endogenous FGF–2 release. Plast Reconstr Surg. 2008; 121:130–41*). They can also selectively modulate the expression of genes involved in the process of wound healing, activating in particular mTOR (*Patruno A et al.: mTOR activation by PI3K/Akt and ERK signaling in short ELF-EMF exposed human keratinocytes. PLoS One. 2015 Oct 2;10(10):e0139644*).
Exposure to ELF-EMF at 50 Hz can promote the proliferation and differentiation of bone marrow mesenchimal stem cells by promoting the production of cytokines like G-CSF and GM-CSF (*Fan W, Quian F, Ma Q et al. 50 Hz electromagnetic field exposure promotes proliferation and cytokine production of bone marrow mesenchimal stem cells. Int J Clin Exp Med 2015;8:7394-404*), confirming the reduced use of myeloid growth factors in subjects suffering from Hodgkin's lymphoma undergoing chemotherapy (ABVD), demonstrated by our group (*E Rossi, MT Corsetti, S Sukkar, C Poggi. Extremely low frequency electromagnetic fields prevent chemotherapy induced myelotoxicity. Electromagn Biol Med 2007;26: 277–81*).

E) ELF-EMF have a **protective effect on the central nervous system** and are useful against neurodegenerative diseases and immunomediated diseases of the nervous system.
It was observed that they produce a neuroprotective effect on rats suffering from Huntington's Chorea, increasing the production of BDNF (Brain Derived Neurotropic Factor) and GDNF (Glial Derived Neurotropic Factor) (*Tasset I et al. Neuroprotective effects of extremely low-frequency electromagnetic fields on a Huntington's disease rat model: effects on neurotrophic factors and neuronal density. Neuroscience 2012;209:54-63*) and can increase dopamine levels in rats with Parkinson's disease (*Yang X The effect of repetitive transcranial magnetic stimulation on a model rat of Parkinson's disease. Neuroreport 2010;21:268–272*)

In studies on elderly patients affected by stroke, more rapid functional and psychological recovery was observed following exposure to ELF-EMF (*Cichoń N, et al.: Extremely low frequency electromagnetic field (ELF-EMF) reduces oxidative stress and improves functional and psychological status in ischemic stroke patients. Bioelectromagnetics. 2017;38:386-96*).
ELF-EMF modulate autoimmunity in autoimmune diseases of the central nervous system like multiple sclerosis, and slow neurodegenerative processes in patients with diseases like Alzheimer's. The beneficial effects appear to be mainly a result of lowering the oxidative stress, which is well known to be raised in both these pathologies (*Guerriero F et al.: Extremely low frequency electromagnetic fields stimulation modulates autoimmunity and immune responses: a possible immuno-modulatory therapeutic effect in neurodegenerative diseases. Neural Regen Res. 2016;11:1888-95*)

F) Subjects treated with ELF-EMF exhibit **improved mood, wellbeing, and behavior**.
ELF-EMF have a function similar to that obtained with neurofeedback since they are capable of inducing changes in brain signals by modulation of electroencephalographic waves (*Shafiel SA, et al. Local ELF-magnetic field: a possible novel therapeutic approach to psychology symptoms. Neurol Sci. 2014;35:1651-6*), and they can induce synchronization of neurons with consequent improvement in intellectual functions (*Azanza MJ, et al. Synchronization dynamics induced on pairs of neurons under applied weak alternating magnetic fields. Comp Biochem Physiol A Mol Integr Physiol. 2013;166:603-18*). The modification of electroencephalographic waves by ELF-EMF reduces anxiety and improves the sleep-wake cycle (*Amirifalah Z et al. Local exposure of brain central areas to a pulsed ELF magnetic field for a purposeful change in EEG. Clin EEG Neurosci. 2013;44:44-52*)

G) In vitro experiments have revealed an **inhibitory activity on certain neoplastic cell lines**. Crocetti et al. observed that by applying ELF-EMF to neoplastic and normal mammary cell cultures it was possible to selectively inhibit the growth of neoplastic cells, while normal cells did not demonstrate any slowing of growth and in fact their growth was slightly enhanced (*S Crocetti, Beyer C, Schade C, et al. Low intensity and frequency pulsed electromagnetic fields selectively impair breast cancer cell viability. 2013 PLoS online 8 (9), e72944*). The action of ELF-EMF was demonstrated on the granulocytic differentiation of promyelocytic leukemia cells treated with ATRA (*Provenzano AE, Amatori S, Nasconi MG et al. Effect of fifty-Hertz electromagnetic fields on granulocytic differentiation of ATRA-treated acute promyelocytic leukemia NB4 cells. Cell Phys Biochem 2018;46:389-400*). A synergic effect of ELF-EMF and doxorubicin was observed in the treatment of mice suffering from T-cell lymphoma (*B Říhová, T Etrych, M Šírová et al. Synergistic Effect of EMF-BEMER-type Pulsed Weak Electromagnetic Field and HPMA-bound Doxorubicin on Mouse EL4 T-cell Lymphoma. J Drud Target 2011;19:890-9*).

Ionic movement through the cell membranes modifies the homeostasis of the intra- and extra-cellular ions and induces a number of protective and curative effects on the cells of the entire organism.

For this reason ELF-EMF could be the first messenger capable of modulating the response of biological systems unbalanced by pathology and striving to recover homeostasis.

3) Can the inhibition of oxidative stress reduce the effectiveness of chemotherapy?

ROS have a protective effect on neoplastic cells. This is supported by the observation that patients suffering from neoplasia exhibit higher levels of generalized oxidative stress (*Toyokuni S, Okamoto K, Yodoi J, Hiai H. Persistent oxidative stress in cancer. FEBS Lett. 1995;358:1-3 - Djuric Z, Heilbrun LK, Simon MS, et al. Levels of 5-hydroxymethyl-2'-deoxyuridine in DNA from blood as a marker of breast cancer. Cancer. 1996;77:691-696 - Sentürker S, Karahalil B, Inal M, et al. Oxidative DNA base damage and antioxidant enzyme levels in childhood acute lymphoblastic leukemia. FEBS Lett. 1997;416:286-290*) and of oxidization within the neoplastic tissue, relative to normal tissue (*Malins DC, Holmes EH, Polissar NL, Gunselman SJ. The etiology of breast cancer: characteristic alterations in hydroxyl radical-induced DNA base lesions during oncogenesis with potential for evaluating incidence risk. Cancer. 1993;71:3036-3043 - Wang M, Dhingra K, Hittelman WN, Liehr JG, de Andrade M, Li D. Lipid peroxidation-induced putative malondialdehyde-DNA adducts in human breast tissues. Cancer Epidemiol Biomarkers Prev. 1996;5:705-710 - Chajes V, Lhuillery C, Sattler W, Kostner GM, Bougnoux P. Alpha-tocopherol and hydroperoxide content in breast adipose tissue from patients with breast tumors. Int J Cancer. 1996;67:170-175 - Carr I, Underwood JC. The ultrastructure of the local cellular reaction to neoplasia. Int J Cytol. 1974;37:329-47*).
Lowering oxidative stress has been shown not to reduce the effectiveness of chemotherapy, but instead to enhance it.
In 2005 Kennedy et al. studied 103 children suffering from acute lymphoblastic leukemia (ALL) and observed that the concentration of vitamin A, vitamin E, carotenoids, flavonoids, and the “ROS Absorption Capacity” were directly correlated with: a) lower reduction of chemotherapy doses, b) lower incidence of infection, c) improved quality of life, d) less delays in chemotherapy protocol programs, e) reduced days of hospitalization. Conversely, the quantity of 8-hydroxy-deoxyguanidine in the blood mononucleates (an expression of a state of cellular oxidation) showed an inverse trend. The authors concluded that children with ALL suffered less side effects in association with a diet rich in natural antioxidants. In other words, dietary supplementation promoted increased effectiveness of treatment, even in terms of prognosis and survival (*Kennedy DD, et al. Antioxidant status decreases in children with acute lymphoblastic leukemia during the first six months of chemotherapy treatment. Pediatr Blood Cancer 2005:44;378-85*). In a literature review study by Simone CB et al., 280 publications were examined on the use of antioxidants and incidental compromise of effectiveness of chemotherapy. These included in vitro and in vivo studies. In the 50 studies on humans, 5081 of 8521 patients received support from antioxidant substances, and relative to the controls these exhibited no interference with antitumoral therapeutic response. The various studies included administration of: vitamin A, vitamin C, vitamin E, selenium, cysteine, B group vitamins, vitamin D3, vitamin K3, glutathione, and melatonin as individual agents or in combinations. Other studies observed that antioxidants not only reduced the side effects of chemotherapy by protecting healthy tissue, but were also able to enhance the activity of the antineoplastic agents. In 15 studies in which 3738 patients assumed supports in association with chemoradiotherapy, a trend was observed for increased survival (*Simone CB, et al. Antioxidants and other nutrients do not interfere with chemotherapy or radiation therapy and can increase kill and increase survival. Altern Ther Health Med 2007;13:22-8 and 2007:13:40-7*). Other studies confirmed this observation (*Block KI, et al. Impact of antioxidant supplementation on chemotherapy efficacy: A systematic review of the*

evidence from randomized controlled trials. Cancer Treat Rev 2007;33:407-18 - Moss RW. Do antioxidants interfere with radiation therapy for cancer? Integr Cancer Ther 2007;6:281-92).

Some studies have demonstrated that free radicals can inhibit the action of chemotherapeutics, possibly inhibiting the apoptosis induced by chemotherapeutics on neoplastic cells (deactivation of the caspases and Fas receptor) and slowing the progress of the cellular cycle of neoplastic cells causing them to stop at the checkpoint, which interferes with the capacity of cytostatics to kill them (*Kagan VE, et al: The role for oxidative stress in apoptosis: Oxidation and externalization of phosphatidylserine is required for macrophages clearance of cells undergoing Fas-mediated apoptosis. J Immunol 2002; 169:487 - Shacter E, et al: Oxidative stress interferes with cancer chemotherapy: inhibition of lymphoma cell apoptosis and phagocytosis. Blood 2000; 96: 307*). It should be remembered that in the past certain synthetic antioxidants were used to reduce the side effects of chemotherapeutics without these interfering in any way with the antineoplastic effect (*Mell LK, et al. Int J Radiation Oncology Biol Phys 2007;68:111-8 - Moghrabi A, et al. Blood 2007;109:896-904 -Kangarloo SB, et al. Med Oncol 2004;21:9-20*).