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Beneficial Effects of Electromagnetic Radiation in Cancer

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1. Introduction

In the last three decades, a large number of studies have been arisen, which dealt with the effects of electromagnetic fields (EMFs) in biological systems (Aaron & Ciombor, 1993; Tao & Henderson, 1999; Tofani et al., 2002b; Walker et al., 2007). The EMFs have been used in very important technological applications that concern in diagnosis (e.g. MRI, X-rays, CT). A part of scientific community turned its interest to the application of EMFs in the treatment of various pathological conditions, mainly in experimental level, such as osteoporosis, the bone fractures, muscle regeneration, diabetes, arthritis and neurological disorders (Barker et al., 1984; Bassett et al., 1974a; Dortch & Johnson, 2006; Fischer et al., 2005; László et al., 2011; Otter et al., 1998; Tabrah et al., 1990; Wang et al., 2010). The last decades EMFs are gradually being used in the research field of one of the most deadly disease known to man, cancer.

Cancer constitutes one of the most serious causes of death worldwide and according to World Health Organization (WHO), it accounted for 7.6 million deaths (around 13% of all deaths) in 2008 (World Health Organization [WHO], 2011). Deaths from cancer are projected to continue rising to over 11 million in 2030.

The modern methods of cancer treatment include: chemotherapy, radiation therapy, surgery, immunotherapy, monoclonal antibody therapy etc. Clinicians select the suitable treatment for the patient, examining, apart from the general situation of his health, the type of cancer, the location and grade of the tumour as well as the stage of the disease. Certain types of cancer, due to their complexity, require combination of treatments. The patients, however, are called to face the side effects, which often accompany the therapeutic methods, such as fatigue, nausea and vomiting, loss of appetite, pain, hair loss, nerve and muscle effects, metastasis and many others. The final aim of the scientists is to increase the effectiveness of the existing treatments, eliminate the side effects and to improve as much as possible the quality of life of patient. Data provided by several studies support the possible development of new alternative forms of treatment, which in combination with the already existing ones, could contribute in the achievement of this aim.

Several epidemiological studies have implicated the EMFs with the induction of mutations, leukaemia and neurological and cardiovascular disorders (Ahlbom et al., 2001). Although

there are indications of the adverse effects of EMFs, the authors' opinion is that this is the one side of the coin. Therefore, the other side of the coin is the study of possible anticancer effects of EMFs; this constitutes a challenge.

There is data supporting the opinion that the use of EMFs has effects in the cell proliferation and in malignant tumours in animals (Tofani et al., 2001; Yamaguchi et al., 2006). It has also been reported that EMFs could act synergistically with chemotherapeutic agents (Gray et al, 2000; Ruiz Gómez et al., 2002), and reverse the resistance of cancer cells in chemotherapy (Hirata et al., 2001; Janigro et al., 2006). Certain clinical studies have shown that the application of EMFs in cancer patients, does not present side effects or toxicity (Barbault et al., 2009; Roncheto et al., 2004). Existed data, also indicate that they prolong the survival time of patients and inhibit the disease progression (Barbault et al., 2009; Kirson et al., 2007). Consequently, EMFs can be used as a low-cost, safe and adjuvant treatment of the existing anticancer therapy.

2. *In vitro* studies

Various *in vitro* techniques have been employed to examine the effects of EMFs on cancer as well as normal cells. These studies investigated whether exposure of cells to EMFs results in modulation of cell growth and also the type of cell death (apoptosis or necrosis). Data regarding the mechanism of action are scarce and will be discussed in more detail in a later paragraph (Section 7).

According to Chen Y.C. et al., exposure of HeLa (human cervical cancer) and PC-12 (rat pheochromocytoma) cells, for 72h continuously, to ELF-EMF of 1.2±0.1 mT, at 60 Hz, results in a significant decrease in cell proliferation, at about 18.4% and 12.9%, respectively (Chen Y.C. et al., 2010). The same effect on HeLa cells was also seen, after exposure to PEMF of 0.18T, at 0.8Hz, for 16h. A decrease, at about 15%, in cell proliferation, was observed 24h later (Tuffet et al., 1993). The application of ELF-EMF (at 50Hz) of different intensities and durations on PC-12 cells, results not only in a slight transient decrease of the proliferation rate but also in morpholigical differentiation (Morabito et al., 2010).

The ability of human colon adenocarcinoma cells to proliferate was tested, when ELF-EMF of 1.5mT peak and 1Hz or 25Hz, for 15min or 360min, was applied. Results revealed a significant decrease in cell growth, in cells exposed to 1Hz for 360min (Ruiz Gómez et al., 1999). The same research team studied the exposure of HCA-2/1cch (human colon adenocarcinoma) cells to 25 Hz, 1.5 mT, for 2h and 45 min. In presence of dexamethasone, a decrease of 55.84±7.35% of the relative cell number occurred (Ruiz Gómez et al., 2000).

The effects of static magnetic fields were also studied on cell proliferation. A 64h exposure under a 7T uniform static magnetic field leads to reduction of viable cell number by 19.04±7.32%, 22.06±6.19%, and 40.68±8.31% in three human cancer cell lines: the HTB 63 (melanoma), HTB 77 IP3 (ovarian carcinoma), and CCL 86 (lymphoma; Raji cells) cell line, respectively (Raylman et al., 1996). Furthermore, the static magnetic fields seem not to affect the proliferation of normal cell lines according to Tofani et al., 2001. Two transformed cell lines, WiDr (human colon adenocarcinoma) and MCF-7 (human breast adenocarcinoma), and the untransformed cell line, MRC-5 (embryonal lung fibroblast), were exposed to 3mT static MF, modulated in amplitude with 3mT ELF-MF, at 50 Hz, with a superimposition of

ELF magnetic field, for 20min. Both WiDr and MCF-7 cells, showed morphological evidence of increased apoptosis, while MRC-5 cells remained intact and did not show any increase in apoptosis (Tofani et al., 2001).

Apoptosis was determined as the cause of cell death after exposure to EMF according to a study by Hisamitsu et al. and another study by Simkó et al. In the first one, HL-60 and ML-1 (Human Myeloblastic Leukemia) cells undergo apoptosis (detected through ladder type-DNA fragmentation), after exposure at 50Hz, 45mT ELF-EMF for time periods of 1 and 2.5h. The same study revealed that normal human peripheral blood leukocytes did not undergo DNA fragmentation, when exposed to ELF-EMF under the same exposure conditions (Hisamitsu et al., 1997). Simkó et al. studied the effects of ELF-EMF in the SCL II (human squamous cell carcinoma) cells and AFC (human amniotic fluid) under different field intensities and durations. It was observed that when a 50Hz, 0.8-1.0mT EMF was applied, for 48h and 72h of continuous exposure, a significant increase in the frequency of micronucleus (MN) formation and induction of apoptosis in SCL II, occurred. Moreover, exposure of AFC cells did not reveal any significant differences, compared to control, at different EMF intensities and various exposure periods (Simkó et al., 1998).

SCOV3 (human ovarian carcinoma) cells undergo apoptosis, when exposed to a pulsed electric field of 10kV/cm, 100ns, 1 Hz, for 5min (Yao et al., 2008). The authors proposed that apoptosis induction was due to the increase of the intracellular concentration of Ca^{2+}. High resolution ^{1}H-NMR spectroscopy also revealed an apoptosis like behavior, when K562 (human muelogenous leukaemia) cells were exposed to ELF 50 Hz sinusoidal magnetic field of 1mT or 5mT, for 2h (Santini et al., 2005). Moreover, continuous exposure of SH-SY5Y (human neuroblastoma) cells to a 900MHz radiofrequency radiation (SAR: 1W/kg), for 24h, leads to significant reduction in the viability of neuroblastoma cells (Buttiglione et al., 2007), whereas exposure of human epidermoid cancer KB cells at a 1.95MHz non-thermal electromagnetic field (SAR 3.6±0.2 mW/g) induced a time-dependent apoptosis, which reached 45% after 3h of exposure (Caraglia et al., 2005).

In order to detect whether the potency of anticancer drugs (vincristine (VCR), mitomycin C (MMC), and cisplatin) was enhanced in the presence of a pulsed electromagnetic fields (PEMF) of 1.5mT, at 1 and 25Hz, Ruiz Gómez et al. used HCA-2/1cch (a multidrug resistant human colon adenocarcinoma [HCA]) cells, as a cancer model. Two different modes of exposure were implemented: (a) exposure to drug and PMF for 1h simultaneously and (b) drug exposure for 1 h, and then exposure to PEMF for the next 2 days (2 h/day). The results showed that vincristine's cytotoxicity was increased at 1Hz PEMF, while that of mitomycin C and cisplatin was significantly increased at 25Hz PEMF (Ruiz Gómez et al., 2002).

In another study, the experimental data obtained by Miyagi et al. indicated that when murine osteosarcoma cells, resistant to doxorubicin, were treated with DOX in the presence of 10 x 10^{-3} mT PEMF at 10Hz, the inhibition growth rate was significantly higher compared to both non-exposed resistant cells and those non-treated with doxorubicin (Miyagi et al., 2000). Similarly, the application of PEMFs (at 10Hz and intensity of 4G) increased doxorubicin (DOX) binding ability to nuclear DNA and inhibited cell growth of MOS/ADR1 (P-gp positive multidrug resistant murine osteosarcoma) cells. Also, data indicated that this type of field reversed the DOX resistance of the MOS/ADR1 cells (Hirata et al., 2001).

K562 (human muelogenous leukaemia) and U937 (histiocytic lymphoma) cells were tested for their viability under different modes of exposure. When cancer cells exposed to a 50Hz sinusoidal ELF-PEMF, it was observed that the electromagnetic field induced both apoptosis and necrosis. Furthermore, application of ELF-PEMF in the presence of the chemotherapeutic agent actinomycin-C (ACM) resulted in strong enhancement of the cytotoxic effect of ACM in cancer cells. (Traitcheva et al., 2003).

In a study of Chen et al., K562 cells were treated with cis-platin (DDP) under the exposure in a static magnetic field (SMF) of 8.8mT for 12h. It was found that the cytotoxic effect of DDP was enhanced in the presence of SMF, as well as the DNA breakage was increased. Also, as atomic force microscopy revealed, the cell surface ultrastructure was modified (Chen W.F. et al., 2010). In a similar study, K-562 cell line was also used in order to investigate the potential synergistic effects between adriamycin (ADM) and exposure to a moderate-intensity static magnetic field (SMF) of 8.8mT, for 12h. The cytotoxic effect of ADM was enhanced in the presence of SMF, through the significant inhibition of the metabolic activity (cell proliferation) of these cancer cells (Hao et al., 2011).

Additionally, BEL-7402 (human hematoma cell line) cells were treated with a variety of X-ray irradiation doses (0, 2, 4, 6, 8 and 10 Gy) combined to 100 Hz EMF (sine wave with a mean intensity of 0.7mT), for two or six exposure times (duration of each exposure session was 30mins, with 12h intervals). Two periods of EMF exposure combined with X-ray irradiation, at a dose of 2 Gy, increased the apoptosis rates of BEL-7402 cells, compared to those subjected to X-ray irradiation alone. Furthermore, six periods of EMF exposure caused higher apoptosis rates than two periods did. Thus, repetitive EMF exposure periods may cause accumulation of apoptotic effects in BEL-7402 cells (Jian et al., 2009).

3. *In vivo* studies

Several scientific teams have turned their interest to the effects of EMFs, in apoptosis, angiogenesis and tumour growth, blood flow and platelet adherence as well as in the transcription of genes that is related with the appearance of cancer, *in vivo* models.

In more detail, Syrian Golden hamsters bearing A-Mel-3 melanomas were exposed to SMFs with varying field strength (<600 mT) at different exposure times (1 min to 3h). Short time of exposure, at a magnetic flux density of 150mT, presented a significant reduction of red blood cell velocity and segmental blood flow in tumour microvessels. An extended exposure to SMFs (up to 3h), resulted in comparable reductions (Strieth et al., 2008). One year later the same scientific team used Syrian Golden Hamsters bearing syngenic A-Mel-3 melanomas, which were exposed to a SMF of 586mT for three hours. A deceleration of tumour growth was observed whereas angiogenesis was attenuated (Strelczyk et al., 2009).

Wang et al. used moderate-intensity and spatial gradient static magnetic fields (GSMF) (0.2–0.4 T, 2.09 T/m, 1–11 days) on two *in vivo* models, a chick chorioallantoic membrane (CAM) and a matrigel plug, in order to investigate their potential effects on angiogenesis. The *in vivo* findings revealed that GSMF caused reduction of vascular numbers and contents of hemoglobin, and inhibited vascularization (Wang et al., 2009).

In two independent experiments, exposure of nude mice bearing a subcutaneous human colon adenocarcinoma (WiDr), in static magnetic fields of intensity of 5.5 mT, daily for 70

min (first experiment) and for four consecutive weeks (second experiment), respectively, resulted in a significant increase of survival time as well as a significant inhibition of tumour growth. In addition, a reduction of cell proliferation and an increase of apoptosis in tumours of treated animals were observed. These findings were accompanied by the evidence of reduction of the expressed p53 (Tofani et al., 2002b).

Antitumour and immunomodulatory effects of pulsed magnetic fields have also been investigated in a study, which utilized the following conditions: pulse width = 238 μs, peak magnetic field = 0.25 T (at the center of the coil), frequency = 25 pulses/s, 1000 pulses/sample/day and magnetically induced eddy currents in B16-BL6 melanoma model mice = 0.79–1.54 A/m^2. Exposure of mice in pulsed magnetic fields lasted 16 days. The experimental data showed anticancer and immunomodulatory properties of pulsed magnetic stimulation such as decrease of tumour growth and elevated production of tumour necrosis factor (TNF-a) in mouse spleens (Yamaguchi et al., 2006). In addition, extremely low-frequency pulsed-gradient magnetic field (with the maximum intensity of 0.6–2.0 T, gradient of 10–100 T/m, pulse width of 20–200 ms and frequency of 0.16–1.34 Hz) presented antitumour and antiangiogenic properties, in exposed Kunming mice bearing murine tumour (Zhang et al., 2002). Analogous effects have also been determined in several other studies (de Seze et al., 2000; Williams et al., 2001).

While it is rendered known, henceforth, that low level electromagnetic fields present very interesting effects in physiology of cancer, particular attention has begun to be given in ELF-EMFs. Jimenez-Garcia et al. used male Fischer-344 rats, which were subjected to the modified resistant hepatocyte model and exposed to 4.5 mT - 120 Hz ELF-EMF. The results showed a decrease of more than 50% of the number and the area of γ- glutamyl transpeptidase-positive preneoplastic lesions, glutathione S-transferase placental expression, as well as a significant decrease of proliferating cell nuclear antigen, Ki-67, and cyclin D1 expression. These findings showed inhibition of preneoplastic lesions, through antiproliferative activity of ELF-EMF (Jimenez-Garcia et al., 2010).

Several studies come to prove the anticancer activity of certain electric fields. In one of them, low intensity, intermediate-frequency (100–300 kHz), alternating electric fields were used in *in vivo* treatment of tumours in C57BL/6 and BALB/c mice (B16F1 and CT-26 syngeneic tumour models, respectively) and induced significant slowing of tumour growth and extensive destruction of tumour cells within 3–6 days (Kirson et al., 2004). These findings have been extended by another study, in which additional animal tumour models (intradermal B16F1 melanoma and intracranial F-98 glioma) were used (Kirson et al., 2007). Mi et al. utilized 48 BALB/c mice, which were inoculated with U_{14} cervical cancer cells and then subjected in steep pulsed electric field (SPEF). The presented data indicated irreversible destruction of integrality of tumour cell, retardation of tumour growth and prolongation of survival time (Mi et al., 2004).

Certain studies have utilized chemotherapeutic agents for the study of synergistic phenomena between chemotherapy and electromagnetic fields. Female B6C3F1 mice, with transplanted mammary adenocarcinoma, were exposed to static magnetic or electric fields and presented significantly greater tumour regression compared to that of mice treated only with 10 mg/kg of adriamycin (Gray et al., 2000). Potential anticancer activity of magnetic field has also been investigated through similar study, in which nude mice, bearing a

subcutaneous human breast tumour (MDA-MB-435), were exposed for 70 min daily, for six consecutive weeks, to modulated MF (static with a superimposition of extremely low-frequency fields at 50 Hz), of total intensity of 5.5 mT. The anticancer activity of MF was compared to that of cyclophosphamide. The inhibition on spread and growth of lung metastases caused by MF was greater than that caused by cyclophosphamide. It is worth to mention that no toxic or abnormal effects were observed (Tofani et al., 2002a). Moreover, cisplatin, one of classic anticancer drugs, when used in combination with ELF-MF exposure, extended the survival time of immunocompetent mice bearing murine Lewis Lung carcinomas (LLCs) compared with that of mice treated only with cisplatin (Tofani et al., 2003).

4. Clinical studies

As described previously in sections 2 and 3, a large number of *in vitro* and *in vivo* studies, support the anticancer effects of EMFs. On the other hand, there is only a small number of data concerning the application of EMFs in clinical studies, which deal with cancer management.

Salvatore J, has designed and completed a Phase I clinical study, using a combination of static magnetic field (SMF) and antineoplastic chemotherapy, in patients with advanced malignancy (lung cancer, non-Hodgkin's Lymphoma, and colon/rectum cancer). The aim of this study was to establish the safety and toxicity of this combination and not the efficacy of treatment. Data were collected from 10 patients, by estimating the white blood cell and platelet count. There were no differences in the previous markers in control and participants during the treatment plan. Results from this work suggest that the combination is safe without increasing the severity of chemotherapy toxicity, and set the bases for the Phase II and III clinical trials. In these trials, the efficacy of a SMF as an anti-neoplastic agent either alone or in combination with chemotherapy, is going to be determined (Salvatore et al., 2003).

In another study of Barbault et al., it is proposed that a combination of tumour-specific frequencies may have a therapeutic effect. A total of 1524 frequencies, ranging from 0.1 to 114 kHz, were identified from 163 cancer patients, while a compassionate treatment was offered to 28 patients with advanced cancer (breast, ovarian pancreas, colon, prostate, sarcoma and other types of cancer). The patients received a total of 278.4 months of experimental treatment and the median treatment duration was 4.1 months per patient. None of the patients, who received experimental therapy, reported any side effects of significance. Two of the patients presented a complete and partial response to the treatment and four patients presented stable disease. A woman, with breast cancer, showed a complete disappearance of some lesions, according to PET-CT (Positron emission tomography - computed tomography), and significant improvement of the overall condition. Thus, the tumour-specific frequencies provide an effective and well tolerated treatment which may present antitumour properties in end-stage patients (Barbault et al., 2009).

Eleven patients with mean age of 60 years and with stage IV, locally advanced or metastatic disease (adenocarcinoma, duct carcinoma, squamous cell carcinoma and other types), were enrolled in a human pilot study conducted by Ronchetto et al. Patients were exposed for 5

days/week, over 4 weeks, according to two different static magnetic fields schedules: 20 min daily (4 patients) and 70 min daily (7 patients). Results showed that MF-exposed patients present mild or no side effects. Furthermore, this pilot study supports the evidence that human exposure to MF with specific physical characteristics is associated with a favourable safety profile and good tolerability (Ronchetto et al., 2004).

Kirson et al. has reported, that exposure of cancer cell lines and tumour bearing animals to low-intensity, intermediate-frequency (100–300 kHz), alternating electric fields, revealed significant anticancer effects *in vitro* and *in vivo* (Kirson et al., 2004). Based on these findings, he proceeded in a pilot clinical trial, including 10 patients with recurrent glioblastoma, using the above described fields. No serious adverse events were observed in all patients, after >70 months of cumulative treatment. The median time of disease progression and median overall survival were more than double than the reported medians of historical control patients. The authors concluded that this type of fields can be used as a safe and effective treatment for cancer patients (Kirson et al., 2007).

In 2008, Salzberg et al. designed a prospective, pilot study to investigate the safety and efficacy of low-intensity, intermediate-frequency electric fields in 6 patients (heavily pre-treated with several lines of therapy) with metastatic solid tumours, while no additional standard treatment option was available to them. A device was used to emit the frequencies 100–200 kHz, at a field intensity of 0.7 V/cm. A patient presented 51% reduction in tumour size, after 4 weeks of fields' treatment. Also, an arrest of tumour growth was seen in three patients, during treatment. Despite the small number of patients, this study revealed that this type of electric fields presented lack of toxicity and significant efficacy in patients' treatment (Salzberg et al., 2008).

In a recent phase I/II clinical study, 41 patients with advanced hepatocellular carcinoma (HCC), were subjected to very low levels of electromagnetic fields modulated at HCC-specific frequencies (410.2Hz-20365.3Hz). Patients were being administered with three-daily 60min outpatient treatments, till the disease progression or death. During treatment no NCI grade 2, 3 or 4 toxicities (grades based on National Cancer Institute Common Terminology Criteria (CTC) for adverse events), were observed, while most of the patients reported complete disappearance or decrease of pain shortly after treatment initiation. Four patients presented a partial response to the treatment, while 16 patients (39%) had a stable disease for more than 12 weeks. This type of EMFs provided a safe and well tolerated treatment, as well as evidence of antitumour effects in HCC-patients (Costa, 2011).

A brief description of the beneficial effects per EMF category is presented in Figure 1.

5. Studies of our research team

5.1 Studies in resonant frequencies

After several experimental studies, Benveniste concludes that "molecular signal could be mimicked by electromagnetic signals" (Benveniste, 2004). This means that an interaction between specific electromagnetic frequencies and molecules may exist, through the phenomenon of resonance. Our studies are based on this phenomenon, using only resonant frequencies derived from the initial target.

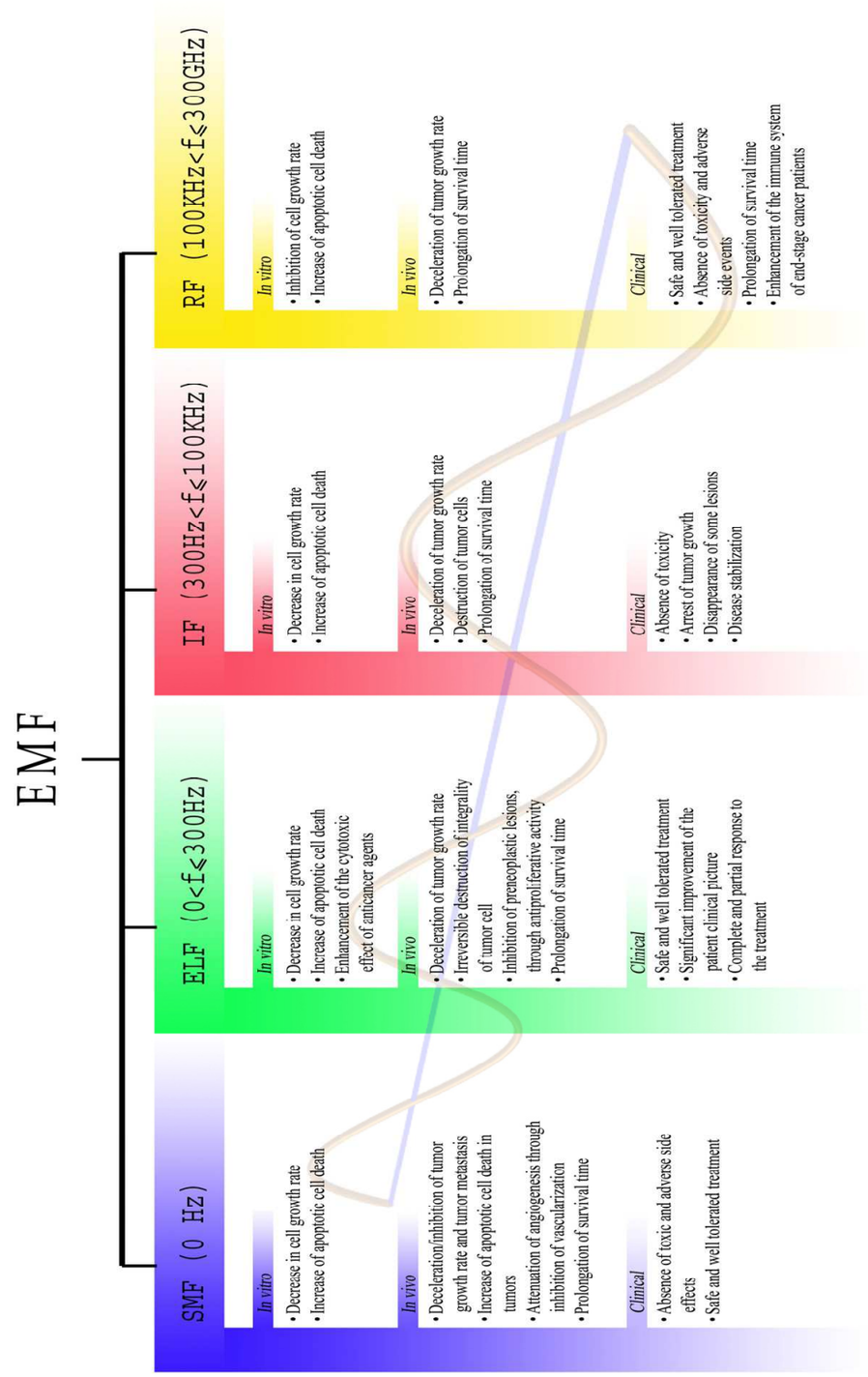

Fig. 1. Illustration of the beneficial effects per EMF category according to the level of the scientific research. Electromagnetic fields have been categorized according to Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). Abbreviations: EMF, electromagnetic fields; SMF, static magnetic field; ELF, extremely low frequency; IF, intermediate frequency; RF, radiofrequency; f, frequency

The investigation of the effects of electromagnetic radiation against various cancer cell lines as well as bearing tumour rat models has been subsumed in our research interests. A series of an *in vitro*, *in vivo* experiments and a clinical study have been published, dealing with the antitumour and immunomodulatory effects of resonant low intensity or intermediate or radiofrequency fields.

In 2006, our research group published an *in vitro* study, using low intensity radiofrequency electromagnetic field, causing no thermal effects, against leiomyosarcoma cells (LMS) and smooth muscle cells (SMC). A total of 492 frequencies, from 10 to 120 kHz, were used for the exposure of both cell lines to resonant EMFs. These frequencies were generated by a device, with the following characteristics: the intensity for electric field was 1.1 to 1.11 ± 0.01 V/m, for the magnetic field 0.0027 to 0.0029±0.00005 A/m and the power density of the electromagnetic field was 3.22 mWatt/m^2 approximately. During the EMF or sham exposure, all cell cultures were placed in a Faraday cage, at room temperature, in order to exclude the external electromagnetic field interactions. Both cell lines were exposed to the 492 resonant frequencies, for 45 min, for two consecutive sessions (at 72 h and 120h from zero time). After the first session of exposure (at 72h), LMS cell growth was significantly decreased, more than 98% ($P< 0.0001$ compared to the control cells). The remaining cells (2%) were cultured and re-exposed (at 120h-second session). Cells presented a remarkable resistance to EMFs, induced only a 20% decrease in proliferation, after the second session of exposure. Then the exposed LMS (from the second session) were preserved in liquid nitrogen for a short time period. After that, LMS cells were defrosted, cultured and exposed once again, at the same EMF pattern for two more sessions as described previously, in order to estimate the apoptosis and cell cycle arrest. Exposed cells presented a significant increase in apoptosis, compared to the control group (sham exposed). On the other hand, SMC did not present any significant alteration on their cell growth when exposed to EMFs. Data revealed that the specific electromagnetic spectrum of LMS cells causes cell death by apoptosis. Another point that has to be stated is that after repeated exposures, the phenotype of LMS cells was altered, and so, the initial electromagnetic resonance fingerprint should be reconsidered (Karkabounas et al., 2006).

Our *in vivo* study presents the effects of a resonant low intensity electromagnetic field, causing no thermal effects, on Wistar rats. LMS cells were exposed for two sessions as described previously according to the protocol of the *in vitro* experiment. Female Wistar rats were inoculated with, exposed (one group) and non-exposed (three groups) LMS cells to EMF. Animals belonging to experimental Group-II (EG-II) were inoculated with cells exposed to EMF and were not further exposed to irradiation. Animals which were inoculated with cells non-exposed to EMF, were randomly separated into three groups: The control Group-CG, in which animals were sham exposed, the experimental control Group-ECG, in which animals were exposed to a non-resonant EMF radiation pattern, for 5 h per day till the death of all animals and experimental Group-I, EG-I, in which animals were exposed to the resonant EMF radiation for 5 h per day, for a maximum of 60 days. Animals of both EG-II and EG-I demonstrated a significant prolongation of the survival time and a decreased tumour growth rate, in comparison to the animals of CG. Furthermore, the survival time of EG-I animals was found to be significantly longer compared to that of EG-II animals. Concluding, results revealed that exposure of tumour bearing Wistar rats to resonant electromagnetic frequencies caused significant prolongation of the survival time and decrease of tumour growth rate (Avdikos et al., 2007).

The aim of our recent study, published in 2011, was to investigate whether the coherent electromagnetic fields were able to enhance the immune system in end-stage cancer patients. Fifteen end-stage patients (5 male and 10 female) were recruited for this study while a complete medical history was received. No female patient was pregnant. All of them had completed their chemotherapy radiation, and/or adjuvant antioxidant treatment, at least 4 weeks, before participation in the study, while none of them received any medications. All patients were tested for the type of malignancy, by histology and CT (Computed Tomography) or MRI (Magnetic Resonance Imaging). Data from blood biochemistry, haematological analysis and tumour markers were also included in the study. All patients were exposed at radiofrequencies ranging from 600 kHz–729 kHz, for 8 h/day, 6 days/week for 4 weeks. The population of NK cells and cytotoxicity of NK T-lymphocytes versus K562 cancer cell line were estimated by flow cytometry, before and after exposure. Results revealed that no side effects were recorded in patients, while data from biochemical and haematological analysis remained stable. The populations of NK cells and NKT lympocytes and the NK cytotoxicity (at ratio of 12.5:1) against K562 cells were significantly increased in all exposed-patients ($p<0.001$). In conclusion, increase in number and cytotoxicity of NK cells seems to be critical for the prolongation of the survival time and quality of life of end-stage cancer patients (Evangelou et al., 2011).

5.2 ^{1}H-NMR-retrieved resonant frequencies from biological and chemical molecules

Every molecule emits specific frequencies ("fingerprint") providing a distinct electromagnetic spectrum. Based on this concept and on results of our previous *in vitro* and *in vivo* studies, in 2008, we have started a new set of experiments, in order to investigate the biological effects of specific molecules' resonant frequencies emission (RFRs-not to be confused with the abbreviation of radiofrequencies [RFs]), obtained from their ^{1}H-NMR spectrum analysis. We hypothesized that the emission of these RFRs could produce the same or similar effects with the molecules themselves, in cellular and animal systems. Molecules' RFRs were obtained by transforming the chemical shifts (in ppm) of their NMR spectra, using the equation given by Keeler (Keeler, 2005). The resultant set of frequencies constitutes, to our opinion, the above mentioned "fingerprint".

Two different experiments have been conducted, using a chemically-synthesized compound (SnMNA) with anticancer properties (Verginadis et al., 2011a), as well as morphine. In the first experiment, a set of RFRs (26 frequencies) was obtained from the ^{1}H-NMR spectrum analysis of the SnMNA complex. Leiomyosarcoma (LMS), human breast adenocarcinoma cells (MCF-7) and normal human fetal lung fibroblast (MRC-5), were exposed to SnMNA-RFRs, for 5h/day for two consecutive days. MTT assay was used for estimation of cell growth proliferation. Significant cell death ($p<0.01$) was observed in the two cancer cell lines, whereas there was no cytotoxic effect against MRC-5 cells. Additionally, tumour bearing Wistar rats, were exposed to the same SnMNA-RFRs, for 5h/day, till the first animal death. Experimental findings revealed significant prolongation of the mean survival time ($p<0.05$) and reduction of the mean tumour growth rate ($p<0.05$) of the exposed-animals, compared to the non-exposed or exposed ones to randomly selected non resonant frequencies (non-RFRs which possess the same energy to the corresponding RFRs) (control groups) (Evangelou et al., 2008; Verginadis et al., 2008). In the second experimental procedure, the analgesic effect of morphine-RFRs (45 frequencies obtained from ^{1}H-NMR

spectrum analysis) were evaluated using the hot-plate and the tail-flick test (analgesia tests). Healthy Wistar rats were exposed to morphine-RFRs for 5h and measurement of latency times were taken, after 1 and 5 hours of exposure, by both analgesia tests. Exposed to morphine-RFRs animals, presented significant increase in the analgesia ($p<0.05$) compared to those exposed to non-RFRs (Verginadis et al., 2011b). Preliminary results showed that, when animals were treated with naloxone (a μ-opioid receptor competitive antagonist of morphine) and after being exposed to morphine-RFRs, did not present any analgesia. The latter indicates that the morphine-RFRs analgesic effect is probably exerted through direct or indirect activation of the μ-opioid receptors.

6. Reproducibility

According to bibliography, there are scientific teams arguing about the reproducibility and variance of experimental findings, because of not clearly described protocols or not accurate application of them. Malyapa et al. (Malyapa et al., 1998) tried to replicate the work of Lai and Singh (Lai & Singh 1995) without any success, because there were significant differences in comet assay analyses. Two different research groups (Lacy-Hulbert et al., 1995; Saffer & Thurston, 1995) tried to replicate the work of Goodman (Goodman & Henderson, 1991; Goodman et al., 1992) with controversial results. Jin et al. (Jin et al., 1997), published the possible parameters, not being considered, which were responsible for the inability of these two groups of investigators to replicate Goodman's work: different HL60 cell populations, mRNA extraction procedure, the stability/variability of internal standards and sham exposure set-up.

There is a number of specific EMF-exposure parameters which have to be outlined in publications, such as used frequencies, duration and pattern of exposure (continuous and/or intermittent), pulse shape (pulsed or sinusoidal fields), intensity and depth of penetration. Also, the researchers should mention the specific intensity field at the target site and not at the surface or close to the generating device (Markov, 1994). Thus, in order to achieve reproducibility of the biological results, analytical experimental protocols and a complete report of the exposure conditions must be described.

7. Mechanism of action

The clarification of mechanisms of action of EMFs, on the cellular systems, has been proved difficult work for the scientists so far. Several models of interaction of cells with chemical phenomena, caused by EMFs, have been discussed, depending on the physical parameters of their emission. The complexity of problem increases, when different cellular types and different radiation "windows" are used, something that leads to different cellular responses. The diversity of these responses is referred to changes of free charges on cellular membrane, alterations of membrane-related proteins and enzymes, as well as to the activation of signal transduction pathways.

Little have been done for the determination of relationship between EMFs and their potential anticancer activity. Most studies that have dealt with this, lead to conclusions, which are limited in their findings. They do not propose any more general mechanisms, but even if they do so, there is no correlation between them.

As proposed by Chen Y et al., when cancer cells were exposed to ELF-EMF, their bioactivity was disturbed, resulting in an abnormal cell signal transduction process, which is possibly responsible for the inhibition mechanisms of cell growth. This can be assumed by the theoretical calculation, of the tangential ionic motion (such as K^+, Na^+, Ca^{2+} and Cl^-) in living cells, governed by the exposure in the time-variant MF and induced EF of the associated ELF-EMF. In theory, this calculation suggests that the oscillating motion of ions in the vicinity of the cell membrane with a net tangential displacement, could exert a significant electromagnetic force acting on the voltage sensors in the voltage-gated channels, screening ionic flux into or out of the cell membrane, which results in the failure of the signal transduction process and the inhibition of the cell growth (Chen Y.C. et al., 2010).

According to the study of Hisamitsu et al., HL-60 and ML-1 leukemic cells underwent ladder-type nucleosomal DNA fragmentation, when exposed to ELF-EMF of 50Hz and 45mT, for 1 and 2.5h. Several *in vitro* studies have associated the magnetic field exposure (50Hz, 22mT, for 1h) with increased intracellular Ca^{2+} concentration (Lindström et al., 1993; Walleczek & Budinger, 1992), which in turn affects endonuclease activity. Based upon reported data, Hisamitsu supports that the ladder type nucleosomal DNA fragmentation was caused by enhanced endonuclease activity, because of the elevated intracellular Ca^{2+} (Hisamitsu et al., 1997).

ELF-EMFs (4.5mT - 120Hz) have been proved to decrease the levels of expressed PCNA, involved in DNA replication and in the RAD6-dependent DNA repair pathway, of Ki-67, associated with DNA replication and of cyclin D, which participates in cell cycle progression. According to these results and to the authors' opinion, ELF-EMF influence the continuity of cell cycle and DNA synthesis of liver cancer cells, possibly via Ca^{2+} flow regulation or via radical chemistry interactions, under the reported conditions of radiation (Jimenez-Garcia et al., 2010).

Moreover, cell adhesion molecules (CAMs), are proteins located on the cell surface, involved in cell adhesion, the process of binding with other cells or with the extracellular matrix. A 50 Hz magnetic field (with a magnetic flux density of 0.5 mT) caused significant changes in cell growth, fibronectin and CD44 expression in MG-63, a human osteosarcoma cell line. In fact, there was a decrease in fibronectin receptor expression, whereas an increase in hyaluronan receptor expression was seen. CAMs are involved in cancer cell functions, such as proliferation and metastasis. Integrins and CD44 participate in the above processes, as members of CAMs. The adhesion of cells, via integrins regulates cellular shape, motility and cell cycle. Moreover, the levels of expressed CD44 influence cell–cell interactions, cell adhesion and migration. According to Rudzki and Jothy (Rudzki & Jothy, 1997) and proposed mechanism of action by Santini, it is indicated that MF influence these molecules' expression, responsible for the transmission of vital signals, in the growth and metastasis of cancer (Santini et al., 2003).

Furthermore, repetitive magnetic stimulation has been shown antitumour and immunomodulatory properties, since tumour necrosis factor (TNF-a) production was increased in mouse spleens, after exposure of B16-BL6 melanoma model mice to pulsed magnetic field. Yamaguchi et al. explanation and bibliography (Ashkenazi, 2002; Aggarwal, 2003), correlates TNF-a, which initiates the TNFR1–TRADD–FADD–Caspase-8–Caspase-3

apoptotic pathway, with the antitumour effects shown after pulsed magnetic field stimulation (Yamaguchi et al., 2006).

The most difficult part of explanation of EMFs' mechanism of action, regarding to their antineoplastic properties, is the connection of provided energy by EMFs in the cellular system and primary response of cancer cells, with some of "classical" signal transduction pathways contributing to cellular death. Various models of explanation of interaction between MFs and Ca^{2+} have been proposed, from physics viewpoint such as ion parametric resonance model by Lednev (Lednev, 1991) and ion interference model by Binhi (Binhi, 1997), but they do not cover the knowledge gap about the biochemical interaction site for MFs, in the cellular system. Gartzke and Lange supported that the ion-conducting actin filament bundle within microvilli, could play the role of the cellular target system for MF (Gartzke & Lange, 2002). The analytic description of the above mechanistic models does not fall into the aims of this paragraph.

8. Conclusion and recommendation for further work

As the applications of EMFs have influenced a lot of aspects of everyday life, life sciences and medicine were also meant to be influenced. At the present, however, the nature of their action on the cellular systems remains enigmatic, and particularly, in presence of such a complex disease, as is cancer. A continuously increasing number of studies come to prove the anticancer activity of EMF emission, but in a specific "window" of action, and explaining only certain mechanistic parts of it. A lot of pieces are still missing from the puzzle, because of the many parameters, such as the type of information being transmitted, the conditions of emission, the frequencies, the doses, the type of experimental cancers as well as the genetic material of cells, on which cellular response depends. Our research aims to outflank these "windows" of action, using resonant frequencies derived from the ^{1}H-NMR spectrum of biological and chemical molecules ("fingerprint") and to determine the molecular pathways which are triggered.

Based on our results so far, we have indications to support our hypothesis. Several experiments are in progress, investigating the possible signaling pathways triggered by interactions between RFRs emission and cancer cellular targets. Briefly, we are going to study the effects of RFRs, derived from anticancer agents with determined mechanism of action, on various cancer cell lines. Modulation of gene expression and specific signaling pathways activation, by RFRs, will provide us significant information about their mechanism of action and will support the idea that electromagnetic signals could imitate the molecular signal through the resonance phenomenon.

A new research horizon lies ahead of us, as the potential clinical application of EMFs could be proved an innovative, alternative or/and adjuvant therapeutic approach, in cancer treatment.

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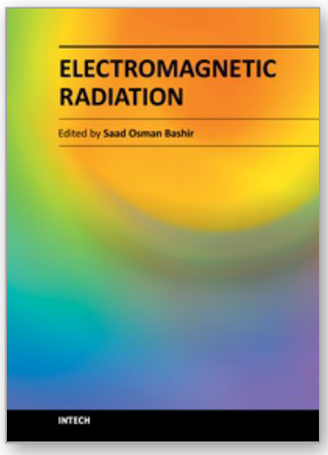

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The application of electromagnetic radiation in modern life is one of the most developing technologies. In this timely book, the authors comprehensively treat two integrated aspects of electromagnetic radiation, theory and application. It covers a wide scope of practical topics, including medical treatment, telecommunication systems, and radiation effects. The book sections have clear presentation, some state of the art examples, which makes this book an indispensable reference book for electromagnetic radiation applications.

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