1) WM topic and description

Diagnosis and treatment of cancer with very low level radiofrequency electromagnetic fields amplitude-modulated at tumor-specific frequencies

2) Comprehensive review (state-of-the-art)

Over the past century, there have been many attempts to diagnose and treat cancer with electromagnetic fields. While the use of high energy ionizing radiation has become a mainstay in the diagnosis (x-ray and computed tomography) and treatment (radiation therapy) of cancer, the use of low intensity, non-ionizing electromagnetic fields is much less common(*1*). More than 2 decades ago we pioneered the use of low and safe levels of radiofrequency electromagnetic fields (RF EMF) in the treatment of insomnia(*2*). Our original hypothesis was that administration of low and safe levels of electromagnetic fields by means of an antenna placed inside the mouth cavity would allow for safe delivery to the brain(*2*). Experiments conducted in healthy subjects (*3, 4*) demonstrated that a single modulation frequency (42.7 Hz) had a sleep inducing effect in healthy individuals. We tested the hypothesis that amplitude modulation of a carrier frequency such as 27.12 MHz, which is approved worldwide for medical use, could be used therapeutically for the treatment of sleep disorders and demonstrated that such an approach was both feasible and effective for the treatment of chronic insomnia(*5*).

In 2001 we hypothesized that the growth of tumor cells might be inhibited by a combination of specific modulation frequencies. We developed novel, noninvasive methods to determine whether patients with a diagnosis of cancer exhibited vascular responses that differed from those observed in healthy individuals. We found that cancer patients exhibited changes in pulse pressure upon exposure to RF EMF amplitude-modulated (AM) at very specific frequencies (*6*). We found that patients with early-stage disease have changes in pulse pressure to some but not the majority of tumor specific frequencies. On the other hand, patients with advanced, metastatic disease exhibit changes in pulse pressure to the majority of the corresponding tumor specific frequencies(*6*). Examination of healthy individuals did not reveal changes in pulse pressure to tumor specific frequencies(*1*). Identification of consistent and reproducible pulse pressure changes to specific frequencies among patients with the same tumor type led us to hypothesize that these frequencies might be implicated in their pathogenesis. We further hypothesized that administration of these frequencies might have a beneficial therapeutic effect. A feasibility study was designed in which 28 patients with advanced malignancies who had no curative therapeutic options were offered daily home treatment with intrabuccally administered 27.12 MHz AM RF EMF, which where modulated at specific frequencies that had been previously been identified in patients with the same type of tumor. Each tumor specific frequency was admitted for three seconds, starting from the lowest frequency and ending with the highest frequency. The sequence was repeated for one hour, three times a day.

Two of the seven patients with stage IV breast cancer had major responses following intrabuccal treatment to breast cancer specific frequencies. One patient with metastases to the bone and the adrenal gland had a complete response lasting 11 months. Another patient with metastases to the bone and liver had a partial response lasting 13.5 months. Both patients had ER/PR hormone refractory breast cancer. A patient with recurrent thyroid cancer metastatic to the lungs has had had stable disease for 8 years and 2 months and is still receiving treatment as of November 2014 (*1*). Disease stabilization was observed in one patient with mesothelioma for six month, one patient with non-small cell lung cancer for five-month, and one patient with pancreatic cancer for four months. All other patients had disease progression despite administration of tumor specific frequencies.

These exciting and unexpected results led to the design of a phase I/II study in advanced hepatocellular carcinoma(*7*). A total of 41 patients were offered treatment with hepatocellular carcinoma specific frequencies until progression or death. Objective response by RECIST (Response Evaluation Criteria In Solid Tumors) criteria was observed in four (9.8%) patients. In comparison the response rate in similar patients treated with sorafenib (Nexavar^{R}) is only 2.2%(*8*). Importantly, four (9.8%) patients had stable disease for more than 15 month, three (7.3%) had stable disease for more than 27 months, although several of them had received prior systemic treatment. One patient with disease progression at the time of enrollment had a near complete response lasting more than five years(*1, 7*). In comparison, none of the 137 patients treated with sorafenib had stable disease lasting longer than 15 month(*8*). Treatment was well tolerated in both studies with only grade 1 toxicity reported i.e. fatigue and mucositis(*9*). No patient experienced grade 2, grade 3 or grade 4 for toxicity even after 5 to 7 years of treatment. Complete blood counts and chemistry profiles obtained in these patients did not suggest any treatment related toxicity.

To begin to understand the mechanism of action of AM RF EMF we designed and conducted *in vitro* experiments using exposure systems replicating the exposure levels achieved in humans(*10*). These experiments showed that tumor specific frequencies have the capability to block the growth of corresponding tumor cells, e.g. breast cancer specific

frequencies were able to block the growth of breast cancer cells and hepatocellular carcinoma specific frequencies were able to block the growth of hepatocellular carcinoma cells. However, breast cancer specific frequencies did not block the growth of hepatocellular carcinoma cells and hepatocellular carcinoma specific frequencies did not affect the growth of breast cancer cells. Similarly, tumor specific frequencies did not affect the growth of noncancerous cells(*10*). These findings demonstrate that tumor specific frequencies identified in patients with cancer have the capability to have a direct impact on the growth of cancer cells. We have new preliminary data suggesting that calcium is a necessary mediator of AM RF EMF inhibition of cancer cell growth. These exciting findings suggest the existence of a novel receptor mechanism blocking cancer cell growth, which may be activated by radiofrequency electromagnetic fields when modulated within specific frequency "windows" (*11*).

The “windows phenomenon” was first identified in 1975 when the efflux of radioactive calcium ($^{45}Ca^{2+}$) from chick forebrains was found to occur upon exposure to specific modulation frequencies of a 147 MHz carrier wave at low exposure levels (1mW/cm^2)(*12*). These experiments were the first to identify significantly higher calcium efflux in samples exposed to an amplitude-modulated carrier wave when compared to an unmodulated carrier wave and non-irradiated samples. Moreover, these experiments also identified that within amplitude-modulation frequencies there are specific frequencies, which result in greater release of calcium from chick forebrains as compared to other frequencies in the same panel of exposure. Within the set of frequencies that triggered calcium efflux (6, 9, 11, 16 and 20 Hz) two frequencies (11 and 16 Hz) resulted in the highest amount of calcium efflux(*12*). The “windows phenomenon” has been confirmed by other investigators. Specifically, Blackman et al. identified calcium efflux from chick brains using a 50 MHz carrier wave, which was amplitude-modulated at 16 Hz and 50 Hz(*13, 14*). Additionally, Schwartz et al. were able to show that isolated frog hearts exposed to a 240 MHz carrier wave amplitude-modulated at 16Hz also exhibited movement of calcium ions akin to the forebrains of neonatal chicks(*15*). Taken together these results point to a common response (calcium efflux) that comes from a narrow band of specific amplitude-modulation frequencies of a non-specific carrier wave in both mammalian and amphibian tissues (50 MHz, 147 MHz & 240 MHz)(*13-18*).

3) Gaps and challenges

Both *in vitro* and animal studies conducted over the past two decades have shown that RF EMFs have an impact on calcium metabolism but only when amplitude modulated at specific frequencies. This nonlinear effect, which occurs at well-defined frequencies and exposure levels, is independent of the carrier frequency. Similarly, our clinical and laboratory investigations suggest that the growth of cancer cells may be effectively blocked when exposed to low and safe levels of AM RF EMF. However, our understanding of the biophysical demodulation mechanisms leading to shrinkage of tumors or stable disease in other patients is limited.

While the clinical studies have been conducted at various institutions and the radiological responses have been independently reviewed by US radiologists, laboratory experiments using cancer cell lines have not yet been independently replicated.

4) Objectives to be achieved

An in-depth understanding of the molecular mechanisms mediating in addition of cancer cell growth upon exposure to AM RF EMF is sorely needed. The following questions ought to be answered:

What are tumor-specific frequencies identified through changes in pulse pressure in patients with a diagnosis of cancer? What part of the vascular system reactivity to AM RF EMF is affected by the presence of cancer?

Can tumor-specific frequencies be used to diagnose specific forms of cancer, e.g. development of hepatocellular carcinoma in patients with chronic hepatitis B and/or C infection?

Which genetic features predicted response and duration of response to tumor-specific frequencies?

What is the biophysical demodulation mechanism leading to cancer cell growth arrest upon exposure to AM RF EMF?

What are the respective biological contributions of the electric and magnetic components in AM RF EMF?

Which components of the cell cycle is affected by AM RF EMF in cancer cells?

What is the role of calcium in AM RF EMF mediated cancer cell growth inhibition? Is there any similarity with the role of calcium as it relates to brain cells?

What is the mechanism of tumor shrinkage in vivo?

5) Proposed research activities

1) Development of validated *in vitro* and *in vivo* models for the molecular study of AM RF EMF effects on cancer cells. Multidisciplinary work including physician scientists, biologists, engineers and physicists will be necessary.
2) Characterization of the pulse pressure changes in patients with a diagnosis of cancer exposed to AM RF EMF, which are modulated at tumor-specific frequencies. Here again, collaboration between physician oncologists, cardiologists, engineer and physicists will be needed to fully characterize this new phenomenon.
3) Can tumor-specific frequencies be identified in animals that carry human tumor xenografts? Ongoing experiments will need to collaboration between biostatisticians analyzing the data generated from Doppler measurements.
4) Can tumor-specific frequencies be used to diagnose specific forms of cancer? Patients with chronic hepatitis B at risk of developing hepatocellular carcinoma would be a prime group of individuals to be studied. Collaboration between engineers and oncologists will be needed.

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