Effects of Magnetic Fields Created by Ultra-Low Radio Frequency Energy (*ul*RFE®) on Biological Systems - An Overview

Xavier Figueroa PhD, Yesenia Green PhD,

Donna Morgan Murray PhD, Mike Butters

EMulate Therapeutics, Inc.

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Introduction

Magnetic fields are a fundamental part of life. They play a role in bird migration and fish navigation, among other phenomena. The earth's magnetic field enables navigating with a compass. Magnetic fields exist whenever there is electric current; electricity provides a convenient means for creating magnetic fields for other uses, for example, in medicine.

Magnetic fields have been used for various medical purposes since at least 2500 BC. Animals and bacteria sense the earth's magnetic field. The search for how magnetic fields produce biological effects has driven exploration in a multitude of experimental systems, clinical studies, and the clinical use of FDA-approved devices. Various aspects of the effects of applied magnetic fields are understood, while others remain the subject of research. Even so, magnetic fields are used successfully for many medical applications, e.g., magnetic resonance imaging, to speed bone fracture repair, to increase the rate of wound healing, to decrease pain and to treat depression and obsessive-compulsive disorder. Today, there are numerous innovations involving magnetic fields that hold promise in a variety of life science applications.

Magnetic Fields

Magnetic fields arise from ferromagnetic materials, such as iron and nickel, or from electric current. For example, the earth's magnetic field is generated by the molten iron alloy in the outer core. Medical applications take advantage of the interconnection between electricity and magnetic fields.

Current in a wire produces a magnetic field [1]. The properties of the field depend on the properties of the current. If the current's amplitude does not change, it produces what is referred to as a static magnetic field. A current with changing amplitude produces an oscillating magnetic field. Both types of field have played a role in the biological investigations of magnetic field effects.

Radio Frequency Energy and Ultra-Low Radio Frequency Energy

Radiofrequency energy is an oscillating form of magnetic or electromagnetic radiation that transfers energy by radio waves. Radio Frequency Energy (RFE) lies in the frequency range between 0 kilohertz (kHz) to 300 gigahertz (GHz), while ultra-low radio frequency energy lies in the frequency range below 3 kHz [2]. The full RFE spectrum is non-ionizing radiation. In this paper, the term "*ul*RFE" means or refers to specific ultra-low radio frequency energy and RFE in the frequency range of 0 kHz to 22 kHz.

Proposed Mechanisms of Action

Biophysical models for the action of electromagnetic fields on cells have demonstrated how oscillating magnetic fields may impact cellular dynamics through the forcing of ions. According to the present theory, extremely low frequency fields in the range of 3 Hz – 30 kHz are the

most bioactive ones. The basic mechanism is the forced-vibration of all the free ions on the surface of a cell's plasma membrane [3].

Experimental evidence (Figure 1) also suggests that *ul*RFE can alter the structural confirmation of tubulin dimers similar to a chemical taxane, thereby increasing the binding affinity between dimers [4].

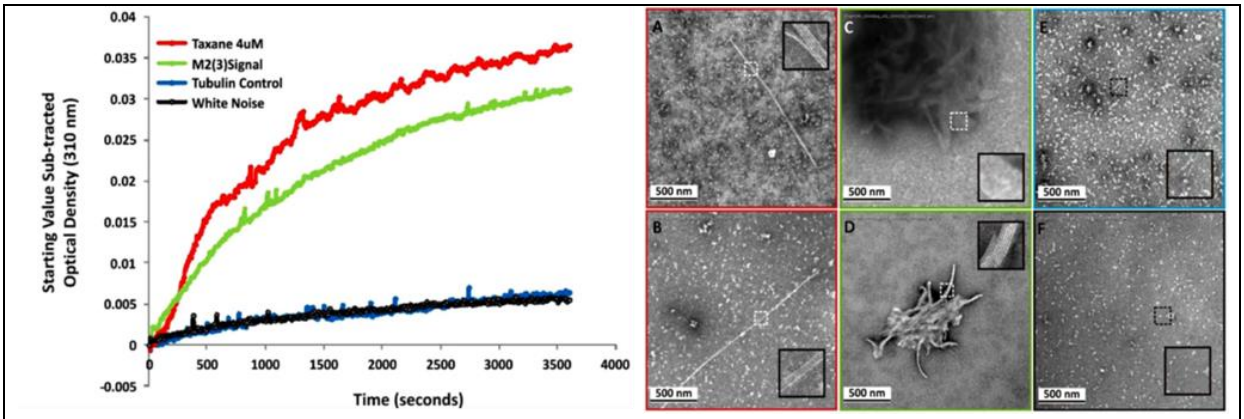

Figure 1 - Scanning electron microscopy (SEM) of tubulin polymerization assay. Samples taken from an experiment using taxane (A and B), M2(3) signal (C and D), GTP control (E) and a white noise control (F) runs. Micrographs are all magnified 21,000×, while insets are enlarged and zoomed micrographs taken at 52,000×. Dashed boxes represent the area of interest for the inset. The graph to the left of the micrographs is the tubulin polymerization assays from which the samples were taken for SEM imaging. Samples were taken at the end of the assay runs. Colored outlines around the micrograph represent the lines of the graph from which the samples were derived.

Several additional theories have driven the experimental search for the mechanism of the biological effects from oscillating magnetic fields.

One fundamental property of an oscillating magnetic field is that it can induce current flow in a conducting medium. This fundamental phenomenon of a magnetic field gives rise to the theory that a field-induced current may alter the behavior of a cell's membrane channel. For example, calcium or sodium ions can move across the cell membrane, and such a change may cause a nerve to fire. A current might alter the movement of calcium ions into the cell, which activates several pathways that influence the cell's physiology.

Another possible mechanism is that an oscillating magnetic field is capable of changing the binding properties of specific proteins and can alter properties within a cell, such as that of a protein known as calmodulin, which is regulated by calcium binding.

A third theory regarding the effect of oscillating magnetic fields is that they alter nitric oxide and reactive oxygen species. Nitric oxide is a regulator of several important regulatory pathways in cells. Alterations in reactive oxygen species change cell metabolism.

Unequivocal identification of the precise mechanism that elicits a specific outcome in a cell, tissue or patient is the subject of ongoing research.

Influences of the Earth's Magnetic Field

The Earth generates a magnetic field. Life on this planet has evolved surrounded by the geomagnetic environment generated by the Earth [5]. Animals as diverse as bats, worms, birds, sea turtles and lobsters can sense changes in the local magnetic environment [5, 6] and can use them for navigation [7] [8] and foraging [9].

The mechanism by which the Earth's magnetic field is sensed has not been unambiguously determined [5, 6]. In some organisms, specialized cells contain iron particles that may act as sensors. In other cases, no specialized protein or cell organelles have been identified to detect magnetic fields.

Device-Generated Magnetic Fields

Magnetic fields have been shown to alter the analgesic effects of opioids, produce analgesic responses, stimulate bone growth, reduce tissue swelling, and promote wound healing in both animal models and humans. Magnetic fields that enhance bone growth and aid in wound healing have been in clinical use for at least 40 years [10]. Pain reduction effects from the use of magnetic fields have been observed in studies of breast reconstruction [11] and breast reduction [12], post-cesarean operative recovery [13], and osteoarthritis [14]. In other studies using magnetic fields, analgesic and opioid use and edema were also reduced in breast reduction, breast reconstruction and post-caesarean patients. Devices generating magnetic fields are effective for treating major depression and obsessive-compulsive disorder, and such devices are recommended for treating the acute phase of depression in patients who are resistant and intolerant of other therapeutic options [15].

In concert with the clinical development of magnetic field use, researchers have attempted to define the underlying biological effects that lead to the field's therapeutic effects and to relate them to one or more of the underlying theories of magnetic field function. This work has included isolated protein systems, cells grown in culture, and organisms ranging from nematodes to mammals, as well as numerical modeling of the functions of the cell. Examples of these types of investigations are discussed next.

Changes in the expression of heat shock protein (HSP) have been detected in planaria [16, 17] and *C. elegans* [18, 19]. Exposure to low-frequency, low power (< 1000 mG) magnetic fields can induce stress-like effects in these model organisms, inducing changes in gene expression and protein function.

Pre-treatment of MS-1 cells with a magnetic field increased the heat shock proteins HSP70 and HSP90. A similar increase in HSPs in HL-60 [20], chicken embryos and SH-SY5Y neuroblastoma cells [21] have been reported.

Magnetic fields alter the behavior of the epidermal growth factor receptor (EGFR), an important regulator of cell growth. This receptor, when exposed to a magnetic field, forms clusters in the membrane, which leads to phosphorylation of the receptor and to activation of one of the receptor targets (Ras). These changes reflect what occurs when epidermal growth factor (EGF) binds to EGFR and indicate that the magnetic field activated the receptor in the absence of its natural activator EGF [22-27]. Proliferation and cell migration are affected by magnetic fields. The growth and migration of endothelial cells has been reported to be altered by magnetic fields.

Mice injected with a transformed cell line formed smaller tumors when treated with magnetic fields [28]. Additional studies in models of cancer demonstrate effects of magnetic fields [29-34].

Though a definitive answer to the question of how these fields exert their effects is not available, evidence that magnetic fields have beneficial effects in therapeutics is abundant.

***u*lRFE®**

EMulate Therapeutics, Inc. (www.emulatetx.com) has developed a patented (40 issued patents to date), proprietary technology using *u*lRFE® to produce therapeutic biological effects that have been demonstrated in plants, animals and now in humans. EMulate's *u*lRFE technology produces a broadband, multifrequency oscillating magnetic field, with frequencies from 0 kHz up to roughly 22 kHz, that is obtained from recordings of selected molecules derived using its proprietary Magnetic Interrogation Device System or "MIDS." While the details of the mechanism of action are not fully understood, recordings are hypothesized to capture noncovalent features of the recorded molecule that alter cellular behavior. EMulate's *u*lRFE technology is currently in clinical testing for adults and children with terminal brain cancer, using an oscillating magnetic field created by its *u*lRFE technology, derived from the molecule paclitaxel. The technology is also in preclinical testing and in initial human testing, using oscillating magnetic fields derived from other specific molecules, for use in patients suffering from chronic or acute pain and from central nervous system disorders.

Proof of Concept Experiments

Initial studies conducted at the University of California at San Diego looked at the effects of the paclitaxel signal (the A1A signal) on a GBM model in mice (U-87 MG), and at downregulating the CTLA-4 and PD1 (A2 signal) immune checkpoint inhibitor genes using the recordings of siRNA targeting the murine versions of the human genes played sequentially while exposing mice to the A2 magnetic field. Tumor growth in both models was reduced to a statistically significant degree when compared to the control mice (exposed to a white noise signal). The results demonstrated that the technology is flexible enough to record very different molecules to target specific pathways (data in preparation for publication).

In addition, the specificity of action in the biologic activity produced by *u*lRFE includes experiments conducted by independent labs (Swedish Neuroscience Institute and the University of California at San Francisco) targeting the epidermal growth factor receptor, EGFR, on glioblastoma cell line U-87 MG. A recording of a small inhibitor RNA (siRNA) targeting human EGFR was tested *in vitro*. At 48 and 72 hours., EGFR inhibition by specific *u*lRFE reduced the level of EGFR protein by 27% and 73%, respectively. These data indicate that certain *u*lRFE can inhibit gene expression at the transcriptional and protein levels, similar to what is observed with physical small interfering RNA (siRNA) inhibition [35]. Specific EGFR knockdown effect was detected in U-87 MG cells treated with *u*lRFE using an 80 gene PCR-based array.

Experiments conducted by EMulate® in *Chlamydomonas reinhardtii* using *u*lRFE derived from siRNA against MAA7 (tryptophan synthase beta) showed a decrease in mRNA levels for MAA7. In cells exposed to the *u*lRFE, an increase in cell growth was observed as compared to no *u*lRFE [36].

Experiments in the agricultural/botanical sector were done in collaboration with the Donald Danforth Plant Sciences Center, assessing the gene-regulating ability of a plant growth hormone (agrin), the effects of a recorded signal of agrin and the outcomes of a siRNA against

a highly conserved chlorophyl gene. A gene ontology screen, comparing physically treated plant and untreated plant to *ul*RFE-treated plants, demonstrated that the overlap in gene expression and gene suppression reached a statistically significant level ($P < 0.0001$) in overlap for both the agrin signal and the siRNA signal directed against a chlorophyl plant gene (data on file).

*ul*RFE has been tested in over 400 dogs (pets) with naturally occurring malignancies by Dr. Greg Ogilvie (Angel Care Cancer Center, LA; data on file).Interim review of the first 200 pets observed partial responses and complete responses in over 20 different solid, non-brain tumor types. No clinically important or significant toxicities (Grade 3 or 4) were observed.

Figure 2 – Representative case and process for treating active and growing tumors in canines.

An early case of a patient with a masse cell tumor treated only with *ul*RFE demonstrates cancer-free biopsy 8 weeks post treatment (Figure 2).

Terminal Brain Cancer in Adults and Children - A1A: Paclitaxel *ul*RFE; A2HU: Anti CTLA-4 & PD-1 *ul*RFE

Results from feasibility studies by EMulate using *ul*RFE derived from a specific chemotherapy drug (paclitaxel) in patients with recurrent glioblastoma [37] are encouraging and have shown a median overall survival (OS) of 7 months in a *ul*RFE-alone arm and 10 months in a *ul*RFE plus standard of care arm (Figure 3). The OS in patients treated with *ul*RFE alone was consistent with historical results using "active" chemotherapy agents alone, and OS increased by 3 months when used in combination with chemotherapy. The median progression-free survival (PFS) in this study was 10 weeks for *ul*RFE alone and 16 weeks for *ul*RFE plus standard of care. For comparison, the median OS for "active drugs" in this disease is 7.2 months, meaning *ul*RFE appears to have a similar effect to chemotherapy for this patient population in this study, without patients taking chemo. When *ul*RFE is added to "active drugs," overall survival (OS) improved to 10 months in this cohort of patients. PFS for historically active therapies is 9.1 weeks [38]. These data suggest that *ul*RFE is safe and feasible for the treatment of recurrent GBM. A study in newly diagnosed glioblastoma using the specific *ul*RFE is ongoing with encouraging results. (Data being prepared for publication)

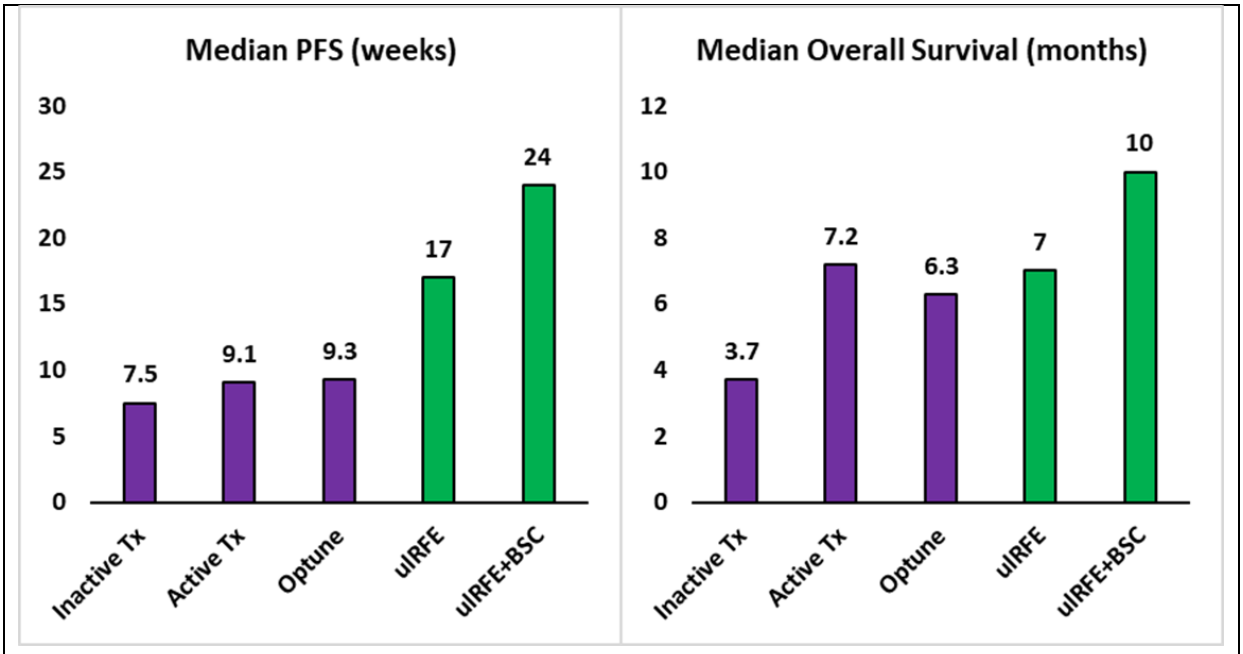

Figure 3 – Results of the feasibility (phase I-II) clinical trials testing the effects of therapies on glioblastoma multiforme (GBM). Optune is an FDA-cleared device for the treatment of recurrent GBM. ulRFE is EMulate Therapeutics' treatment signal tested on patients

diagnosed with recurrent GBM. Inactive Tx, historical clinical trials determined no efficacy for the tested treatment. Active Tx, historical clinical trial determined efficacy for the tested treatment. BSC, best standard of care. PFS, progression free survival.

In 2019, NAT-105 results were published [39]. NAT-105 was a Phase I study conducted in Australia where the EMulate's therapeutic device was programmed with the A2HU signal, a combination of two *ul*RFE signals: one derived by measuring and recording a CTLA-4-directed siRNA *ul*RFE signal, and the other derived by measuring and recording a PD-1-directed siRNA *ul*RFE signal. There were no serious adverse events and few adverse events attributed to the device; no adverse event led to discontinuation of Voyager. Due to the small number of patients treated (N=11), conclusions were not drawn from the clinical utility data. However, the fact that 30–50% of patients were alive 12 months after starting the EMulate device therapy was encouraging.

A pivotal (phase III) GBM study using A1A *ul*RFE is in development for initiation in the near future.

EMulate has deployed the A1A *ul*RFE for compassionate use in diagnosed cases of diffuse midline glioma/diffuse intrinsic pontine glioma (DMG/DIPG). DMG/DIPG is a rare (~1800 cases are diagnosed annually) and uniformly lethal disease and occurs almost exclusively in a pediatric population. DMG/DIPG represents the most common solid tumor in childhood and accounts for the highest number of cancer-related deaths in children. There are no approved therapies for DMG and median survival after diagnosis is only 6-9 months. Based on the recommendation of EMulate's medical advisors, a compassionate use trial was initiated. Cumulative results in these cases demonstrate that the *ul*RFE technology is safe and may increase survival in this population (Table 1) since 12 of the 14 patients treated survived more than 12 months.

	DMG/DIPG	Other Brain Cancers
# Patients Treated	14	2
Age, range (median)	4-28 years (8 years)	7-17 years
# Males/# Females	4/10	2/0
Weeks on treatment, range (median)	2-49 (19)	13-14
# Patieints with OS > 12 months	12	2

Table 1 – DMG/DIPG results for compassionate use of the *ul*RFE A1A signal. No severe adverse events were recorded.

A pivotal clinical trial is being prepared for DMG/DIPG using the A1A *ul*RFE.

Hapbee Technologies, Inc. (TSXV: HAPB) – Wellness Wearables

In 2019, EMulate created Hapbee Technologies, Inc. to utilize its *ul*RFE technology for the consumer wellness industry.

Initial rodent studies conducted at Crown Bio, an independent clinical research organization (CRO) for Hapbee Technologies demonstrated behavioral changes in mice that were exposed to oscillating magnetic fields derived from chemistries intended to either stimulate or suppress behavior (e.g., caffeine, nicotine, melatonin, CBD, THC and alcohol). Under controlled and blinded conditions, independent evaluators noted the mice reacting to the specific *ul*RFE in a manner consistent with reactions expected from using the compound from which the *ul*RFE was derived (Figure 4).

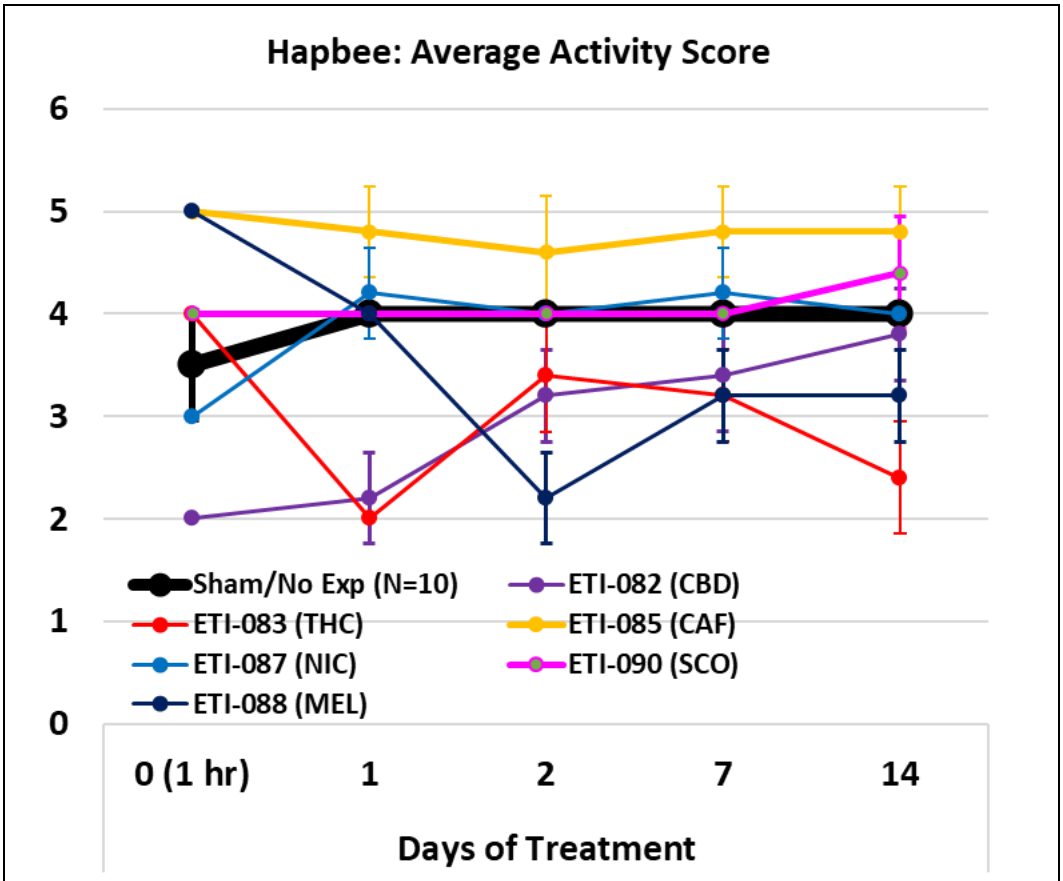

Figure 4 – Observational results of mice exposed continuously to the designated signals. A single observer rated mouse behavior in their home cages. Mice were rated at the same time every day on generalized activity (higher numerical value represents higher activity; lower numerical value represents lower activity. Cannabidiol (CBD), nicotine (NIC), melatonin (MEL), caffeine (CAF), scotch (SCO) and D-9-tetrahydrocannabinol (THC). Error bars are standard deviation.

These *ul*RFE signals are now part of the Hapbee catalog of products that are in the non-medical, commercial market space (Hapbee.com), which launched its first product to customers in late 2020.

The Potential of *ul*RFE for Pain Management and Mental Health Conditions. Enhanced Signals (stronger and faster acting effects)

In late 2020 and early 2021, EMulate generated *ul*RFE signals derived from compounds with known pain/inflammation reducing effects (fentanyl, CBD and naproxen among others) and from compounds with psychoactive potential activity (psylocibin and S-Duloxetine among others).

Pre-clinical screening tests at ANS Biotech, an independent CRO specializing in validated pre-clinical rodent pain models, tested several *ul*RFE signals (Figure 5). The *ul*RFE derived from fentanyl demonstrated a pain-reducing capability (102%) similar to (or better than) the physical ("gold standard") drug used as a positive control (U50-488H; 100%). In a rat model for neuropathic pain (Oxaliplatin), *ul*RFE derived from naproxen (72%), fentanyl (74%) and CBD (64%) achieved measurable pain-reducing effects compared to Duloxetine (100%).

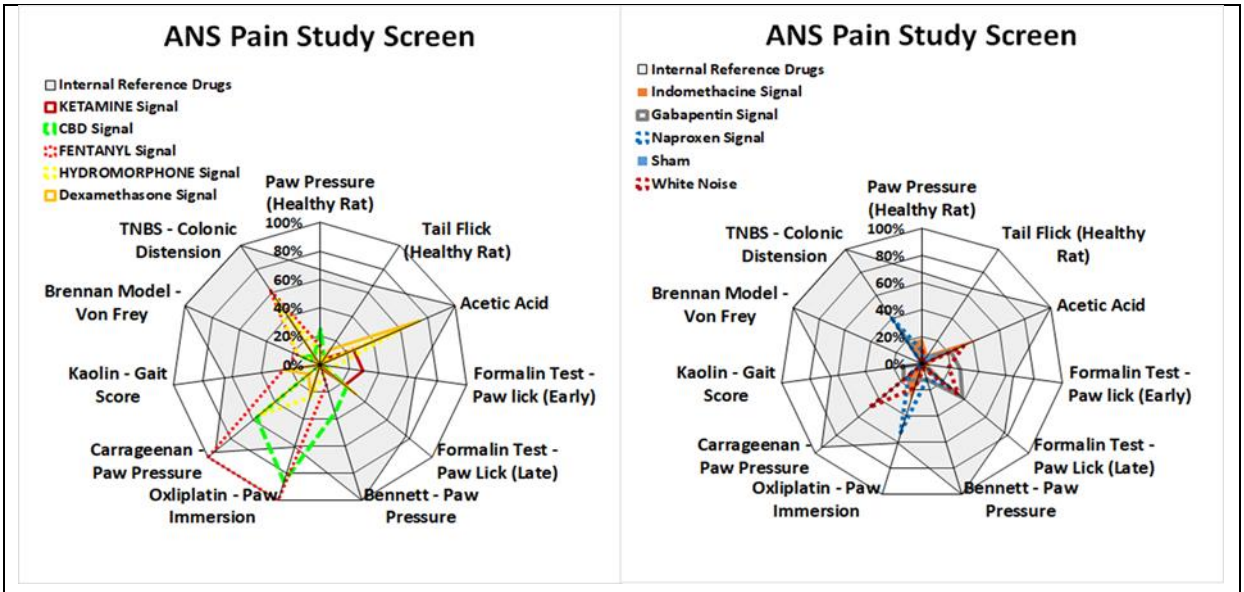

Figure 5 – ANS Pain Screen, the ALGOGram™. The radar plots represent the percentage level of pain reduction relative to a historical standard. Left, radar plot with the most active signals. Right, radar plot with controls (white noise, sham) and less active signals. Grey shaded area represents the maximal pain reduction with physical drugs used as positive controls (morphine, indomethacin, duloxetine and (-)U50,488H.

While conducting these screening assays, EMulate developed a proprietary technique which "modified" (i.e., enhanced) their signals. Anecdotally, volunteers observed that the effects from selective signals had a faster onset with a more pronounced effect.

Based on the initial pre-clinical pain results, follow-up confirmatory studies were conducted to replicate these findings with sufficient power to measure statistical significance (Figures 6, 7 &

8). In addition to replicating the effects with the *ul*RFE signals originally used in the screening tests, an additional arm of the study compared the unmodified (original) *ul*RFE signal to the modified signal of the same derivative to objectively determine if the new *ul*RFE variations were truly stronger.

Results confirmed that the new, modified signals were more effective than the original, unmodified signals.

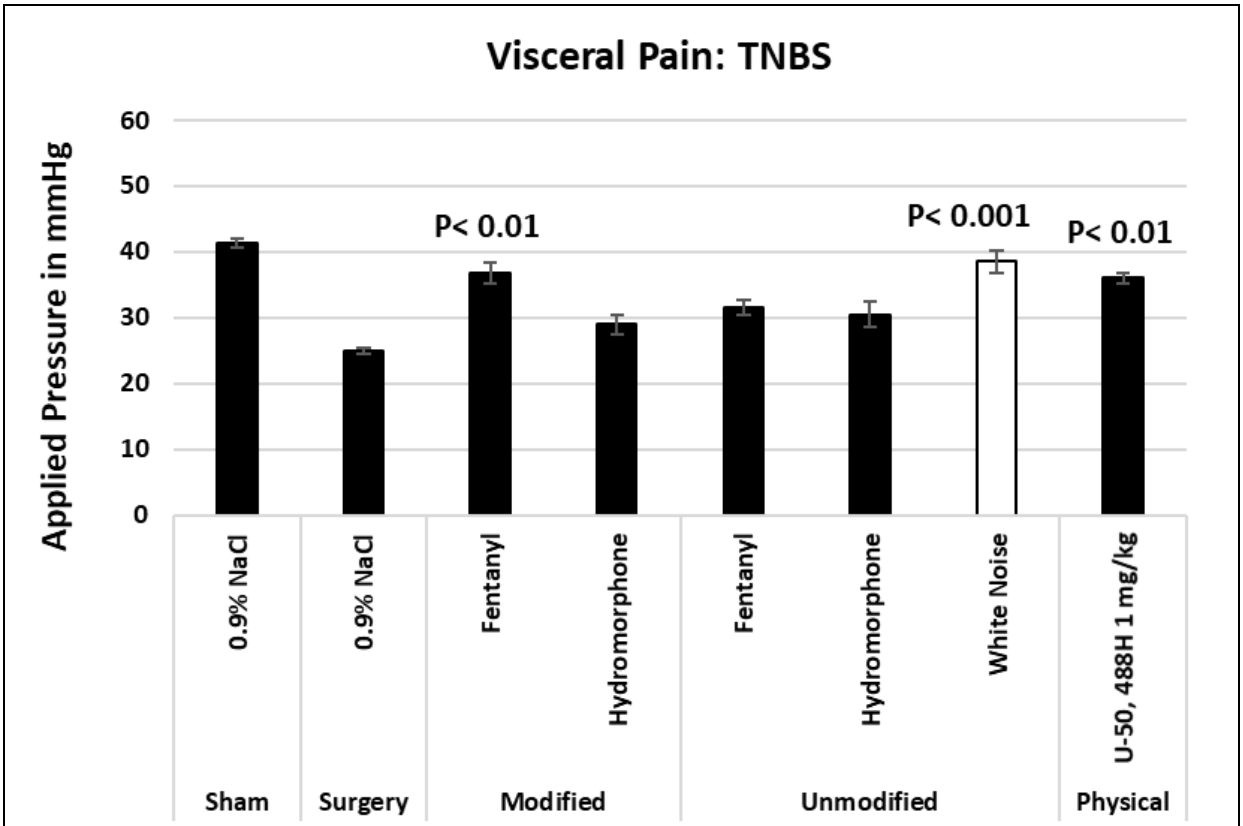

Figure 6 – TNBS colonic sensitivity model of visceral pain. The kappa-opioid agonist (U-50,488H) was used as a positive control for pain modulation. Columns are the amount of pressure (in mmHg) applied to balloon that induced a behavioral response during colonic distension. Error bars are standard error of the mean (s.e.m.). Alpha = 0.05 and adjusted for multiplicity of interaction compared to the control values.

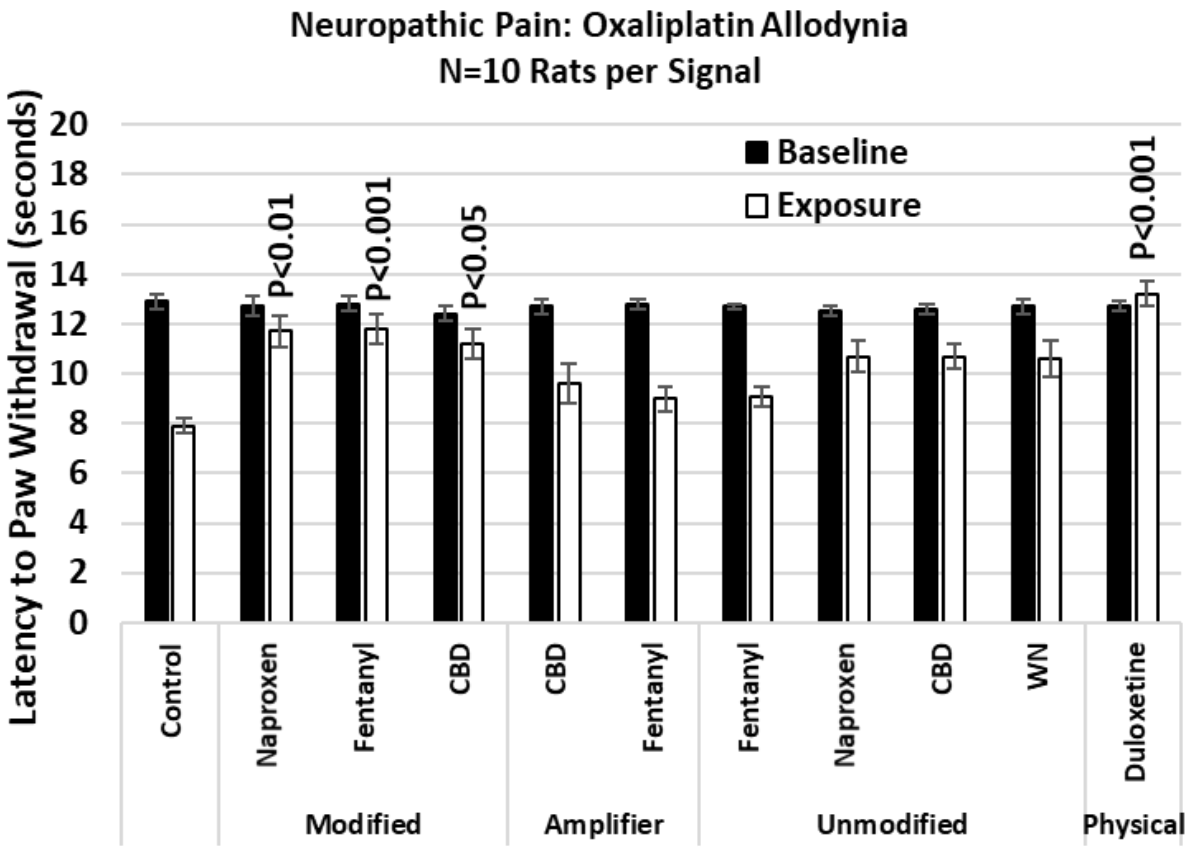

Figure 7 – Oxaliplatin induced neuropathic allodynia pain model. Duloxetine 100 mg/kg p.o. was used as a positive control for pain modulation. Black columns are the time-lag for leg withdrawal from a 10° C water bath (uninjected leg). White columns are the time-lag for leg withdrawal from the leg treated with oxaliplatin. Error bars are standard error of the mean (s.e.m.). Alpha = 0.05 and adjusted for multiplicity of interaction compared to the control values.

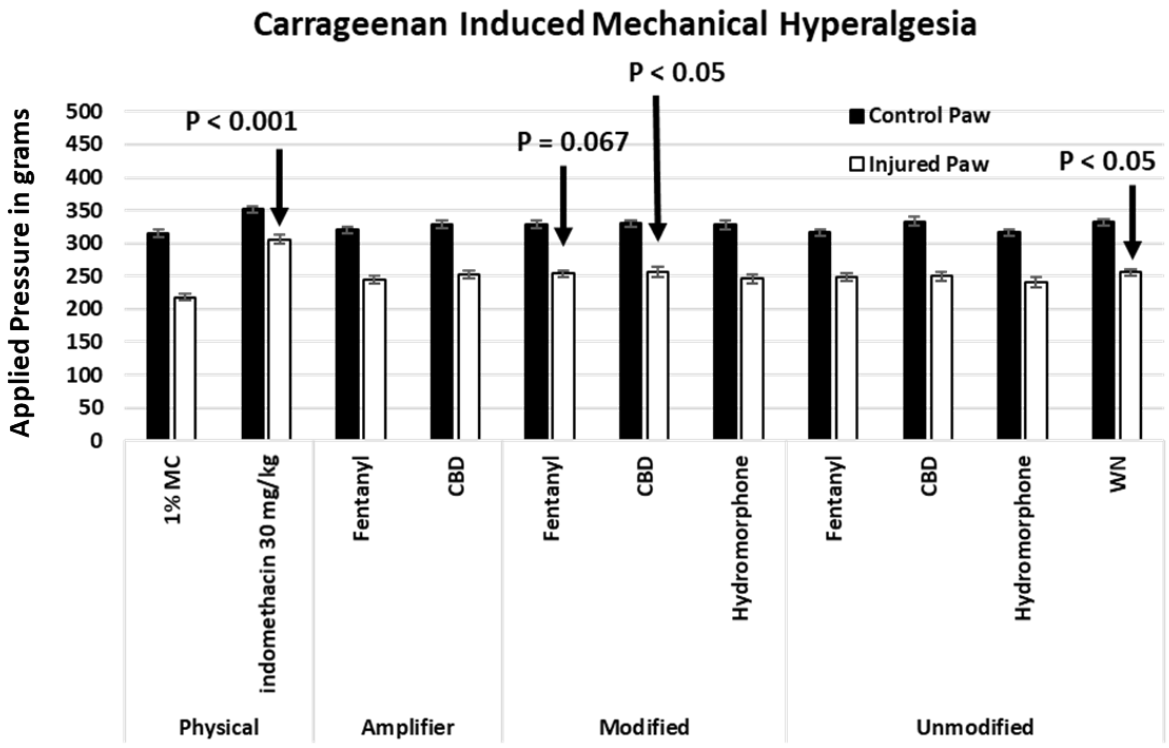

Figure 8 – Carrageenan induced mechanical hyperalgesia pain model. Indomethacin (p.o.) was used as a positive control for pain modulation. Black columns are the amount of pressure (in grams) applied before paw was lifted (uninjected left paw). White columns are the amount of pressure (in grams) applied before paw was lifted (injected right paw). Error bars are standard error of the mean (s.e.m.). Alpha = 0.05 and adjusted for multiplicity of interaction compared to the control values.

The white noise signal, which was used as a negative control to account for the generalized effect of a fluctuating magnetic field of similar magnitude, demonstrated a measurable and significant decrease in two of the pain models tested (visceral pain and mechanical hyperalgesia; Figure 6 & 8). This was a surprising finding, as the white noise signal has not previously demonstrated a meaningful effect in the initial screen we ran at ANS Biotech (Figure 4) and in other internal studies we have completed. Furthermore, the white noise showed no statistically significant effects on the other three pain models tested.

A possibility to account for the results of the white noise exposure is the known effect of stochastic resonance in biology. Exposure of the rats to the signals occurred in resin-type, tiered racks. Rat cages and cage coils were stacked on shelves at distances established to limit interference or coupling, but there remains the possibility that the magnetic fields could interact with one another. The cage setups for the visceral pain and mechanical hyperalgesia had a mixture of different signals on the same rack. The cage arrangement at ANS varied,

based on the test that was being run on the date of exposure and testing. The stochastic resonance effect is a known signal enhancement technique, in which white noise is introduced to a sub-threshold signal to elevate components of the signal above the noise threshold. Due to the proximity of the cages, there was a potential for one of the signals (modified fentanyl, as an example) to be near enough to the white noise cage coil for the stochastic resonance effect to occur. This is a potential confounding factor that could have led to one of the signals interacting and producing the pain inhibiting effects seen with white noise. EMulate intends to repeat the negative noise control portion of the pain study at some time in the future.

Additionally, encouraging anecdotal reports from human volunteers using one or more of the *ul*RFE pain reduction signals reported pain reduction between 70% - 100% within 11 – 30 minutes. An additional benefit that EMulate will explore is the potential for reduced or no addiction to using the product for patients. Human clinical trials for both acute and chronic pain indications are being planned for the near future.

A generalized toxicology and anxiety/depression screen was conducted at Porsolt SA, an independent CRO specializing in mental health pre-clinical animal models. *ul*RFE derived from psylocibin and S-duloxetine (Figure 9) among others were tested. Initial results demonstrated a statistically significant effect in reducing motor function with the psylocibin and S-duloxetine signals, comparable to diazepam at 2mg/kg (a mid-range dose). All assays were conducted by trained technicians that were blinded to the animals in the *ul*RFE field(s) as well as the compound source of the *ul*RFE.

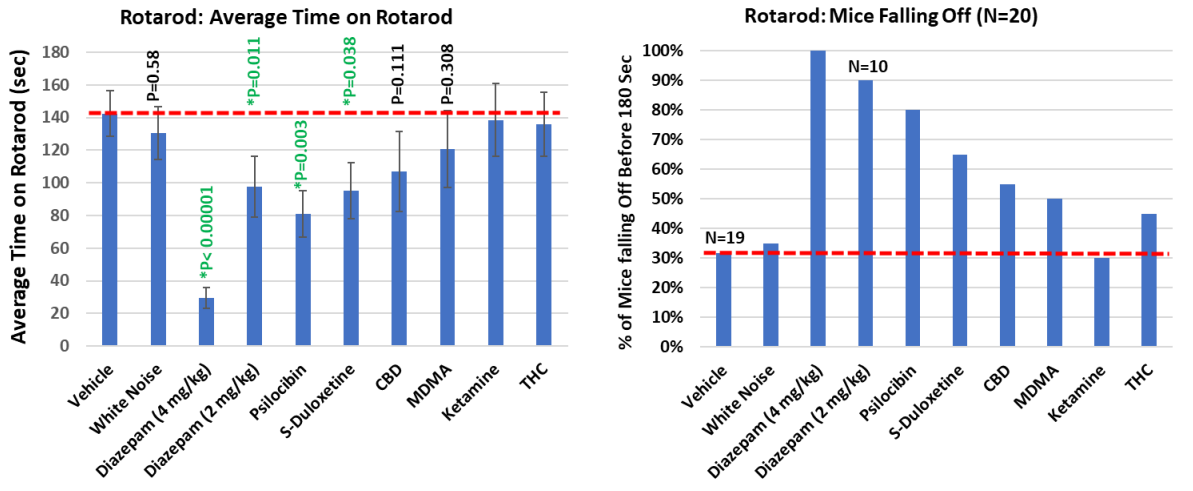

Figure 9 - Gross motor effects of ulRFE signals on mouse climbing ability. Diazepam (2 & 4 mg/kg) was used as a positive control to induce motor deficits. Signals tested were derived from psylocibin, duloxetine, cannabidiol (CBD), 3,4-Methylene dioxymethamphetamine (MDMA), D-9-tetrahydrocannabinol, (THC) and ketamine. Vehicle was a saline injection. Alpha was set at P = 0.05. Error bars are standard error of the mean (s.e.m.). Unless indicated, 20 mice per group were tested.

Summary

Multiple studies in a variety of systems confirm that magnetic fields can alter biological function. Therapeutically useful devices are or have been used presently in clinical practice, both in human and veterinary medicine. Treatment for bone growth, wound healing, arthritis pain and depression are among the clinical uses. Research aims to understand better how these magnetic fields produce their effects to further enable new and exciting therapeutic options for many diseases.

In multiple pre-clinical animal and agriculture models and in-human clinical studies, EMulate Therapeutics has observed that specific *ul*RFE demonstrates a measurable, objective and specific biological change. The magnetic fields generated by the EMulate *ul*RFE point to the flexibility and specificity of the technology. Feasibility (phase I/II) clinical trials in GBM and a compassionate use trial in DMG have shown excellent safety and preliminary and encouraging effectiveness in overall survival. Pre-clinical in vitro assays have demonstrated the ability to selectively reduce mRNA and protein expression in cell-culture for EGFR and in immuno-oncology targets. *ul*RFE derived from known pain inhibiting compounds have resulted in measurable reduction in pain scales in validated and objective pain models. Encouraging pre-clinical results in mental health models suggest that specific *ul*RFE may be able to help treat patients suffering from anxiety, depression, PTSD and other mental health conditions.

EMulate's technology has a broad range of applications in multiple areas of human and animal health conditions and may offer significant benefits over current treatments for many patients.

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