Pilla, A. 2009. Unified Mechanism for Pulsed Electromagnetic Field Bioeffects: Cellular, Animal and Clinical Evidence. Bioelectomagnetic Society Meetings June, Davos, Switzerland.

Introduction: The author proposed starting in 1972 that weak EMF signals could be configured to modulate ion binding at electrified cell membrane/aqueous interfaces using the electrochemical information transfer model. That model described all voltage dependent processes at the cell membrane in terms of electrical equivalent circuits, allowing the EMF signal to be configured according to the dielectric properties of responding pathways such as ion binding and membrane transport. This guided the configuration of the EMF signals now in routine clinical use for recalcitrant fractures. As the biological signaling pathways for tissue growth and repair have become more elucidated, the target pathway and its dielectric properties could be better defined, suggesting that, while the original bone repair signal is clearly within an effective dosimetry range, it is not configured for optimal dose. This may explain why lengthy daily treatments for up to several months are often required to reach a satisfactory clinical outcome. This work shows how more effective EMF signals may be configured a priori by using the dielectric properties of a two step ion binding pathway involving Ca2+ binding to calmodulin (CaM), followed by Ca/CaM binding to an enzyme such as nitric oxide synthase (NOS) which leads to transient nitric oxide (NO) release. Direct evidence that PEMF affects this pathway is provided for chondrocytes and neuronal cells in culture and in a rat thermal injury model of cardiac ischemia. Strong indirect clinical evidence is also presented for post-surgical pain relief, chronic wound repair, and for cardiac myopathy patients with chronic angina.

Materials And Methods: The proposed EMF transduction pathway relevant to tissue repair starts with Ca2+ binding to CaM followed by Ca/CaM binding to, and activating, constitutive nitric oxide synthase (cNOS = e(ndothelial)NOS or n(euronal)NOS) which catalyzes the release of the signaling molecule NO. Configuration of a PEMF signal which can modulate NO release by analysis of the kinetic equations describing this two step process in terms of its dielectric properties was performed. There results a two time constant electrical equivalent circuit analog which contains the time constants for Ca2+ binding to CaM and Ca/CaM binding to NOS. Quantization of these dielectric properties, using literature results for CaM-dependent enzyme kinetics, allows EMF signals to be configured to increase the surface concentration of bound Ca2+ above that due to background thermal fluctuations. Pulse modulated radio frequency signals (PEMF), in clinical use for wound repair and the reduction of pain and edema, were configured using the above approach. One such signal, consisting of a 1-5 msec burst of 27.12 MHz sinusoidal waves repeating at 1-5/sec with 0.01-0.05 G peak amplitude, was used to modulate NO release in perturbed neuronal cells and angiogenesis in a cardiac injury model in the rat. Existing studies using the original PEMF bone healing signal consisting of a 5 msec burst of 200/20 μsec bipolar pulses repeating at 5/sec, were analyzed according to the model for reported effects on DNA synthesis in articular chondrocytes and growth factor dependent angiogenesis in endothelial cells and wound healing in diabetic mice. A PEMF signal configured for the Ca/CaM/NO pathway was used in double blind

clinical studies for acute post-operative pain relief in breast surgery and for symptom relief in patients with cardiac myopathies exhibiting chronic angina.

Results: The PEMF signal configured to target the Ca/CaM pathway was applied to rat Achilles' tendon and cutaneous wound healing models, wherein healing rates, as assessed by tensile strength, were increased at 3 weeks by 59 and 69%, respectively. The PEMF bone healing signal increased DNA synthesis in articular chondrocytes by 150% via a Ca/CaM/NO pathway. This study systematically used CaM, NOS and cGMP inhibitors which, individually, eliminated the PEMF effect on DNA synthesis [4]. The PEMF signal increased NO release from neuronal cells, by up to 200%, when intracellular calcium was increased by glutamate or 6-OHDA in a cellular model of inflammation. PEMF increased angiogenesis by 200% in a thermal myocardial injury in a rat model. This effect was eliminated in rats who were fed L-NAME, a general NOS inhibitor [6]. PEMF significantly accelerated post surgical pain relief by 3X with a concomitant reduction in pain medications in a randomized double-blind study on breast augmentation patients. A similarly configured PEMF signal provided significant relief of angina pain (4X) and decreased physical limitations (2X) within three months, in a double blind study of patients with cardiac myopathies.

Conclusions: Taken together, all of the available evidence provides strong support for Ca/CaM-dependent transient NO production as an important PEMF transduction pathway for tissue repair. This allows a mechanism to be suggested. PEMF signals increase the rate of Ca2+ binding to CaM, which then catalyzes cNOS, e.g., eNOS, producing an immediate (seconds) production of NO which can orchestrate an anti-inflammatory response via increased blood and lymph flow. NO, in turn, regulates cGMP production (minutes) which cascades to the appropriate growth factor release dependent upon the stage of healing, e.g., FGF-2 for angiogenesis. This is summarized in the figure. Disruption of tightly regulated free cytosolic Ca2+ in cells is a signal for endogenous tissue repair and regeneration mechanisms. PEMF signals could modulate Ca/CaM which catalyzes eNOS, allowing the PEMF signal to modulate the release of NO from eNOS and potentially affect the entire tissue repair pathway from pain and edema to angiogenesis, bone and tissue regeneration and other regenerative actions. Resting cells (in homeostasis), in which there is no transient increase in cytosolic free Ca2+, do not appear to respond to PEMF, providing one explanation for the reports of no known side effects from PEMF therapies.