Driving Molecular Transport across Biological Membranes from Magnetic Nanoparticle/Pulsed Magnetic Field (Viktor Chikan)

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Our research aim is to investigate how magnetic nanoparticles and magnetic field combinations can be used to open up pores on various membranes to facilitate transport of various sized molecules. The research will address the underlying fundamental challenges that limit the efficient use of various types of magnetic fields for creating a biological response such as cell death, change in function. In this research, cell, bacterial and liposomal model systems will be investigated when nanoparticles are integrated into their structure and exposed to various types of magnetic fields such as short homogeneous and inhomogeneous magnetic pulses, linearly and circularly polarized magnetic fields, or small amplitude AC magnetic fields. The transport properties will be evaluated using fluorescence techniques based on permeability essays, electrochemical essays detecting small trace molecules and based on exploring the biological response of the system such as cell viability. Addition characterization techniques will be necessary to accurately survey the structure of these systems prior and post exposure to the magnetic fields. In this research, we will implement spectroscopic and microscopic techniques to explore spatial and dynamical aspects of the magnetic fields on proposed systems. Integration of fluorescence microscopy with electromagnet will allow studying the systems under the I influence of the magnetic fields. Spectroscopic method based on magnetic field transient Faraday rotation of the magnetic particles and dynamical measurements of ultrasonic intensities will explore the transfer of the magnetic field's energy into mechanical movement in the medium.

Background and Rationale: There is tremendous interest in developing methodologies to control biological processes at the cellular level remotely. A particularly intriguing concept is to regulate material transport across biologically important membranes by various external magnetic field stimuli. Magnetic nanoparticles are very promising materials for assisting, enhancing and localizing the effects of external magnetic fields for this purpose[1] Scientists are at the beginning stage in the exploration of magnetic beads or nanoparticles to control membrane transport. Building 'molecular drills' based on magnetic nanoparticles receives significant attention in recent years.[2]

Since 2007, the Chikan group has been active in magnetic hyperthermia research.[3] Magnetic hyperthermia treatment to eliminate cancer is based on heating cancer cells by applying few milli tesla amplitude alternating magnetic fields in the presence of magnetic nanoparticles inside the cancer tissue. A major concern of the effective use of magnetic hyperthermia is that the amount of heat necessary to eliminate cancer cells and tissues places tight requirements on the effective concentrations of the nanoparticles. Results from our collaborative effort and from others show that magnetic hyperthermia treatment is effective against cancer. As it has been shown the mechanical aspect of moving magnetic particles also contributes significantly to the effectiveness of magnetic hyperthermia treatments. [4] This observation provides a strong rationale for pursuing research on the mechanical aspect of the magnetic nanoparticles and its biological impact in the presence

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[1] *Journal of Magnetism and Magnetic Materials* **2005,** *293* (1), 483-496.

[2] ACS Applied Materials & Interfaces 2020, 12 (12), 13657-13670.

[3] *BMC Cancer* **2010,** *10* (1), 119.; *Int J Nanomedicine* **2012,** *7*, 297-306.; *Ther Deliv* **2015,** *6* (10), 1195-210.

[4] Naud, C.; Thébault, C.; Carrière, M.; Hou, Y.; Morel, R.; Berger, F.; Diény, B.; Joisten, H., Cancer treatment by magneto-mechanical effect of particles, a review. Nanoscale Advances 2020.

of various magnetic fields types. The Chikan lab has realized early on that to decease the potentially toxic side effects from large quantities of magnetic nanoparticles (few mg of NP/ml of cancer tissue) is to explore the effects of increased magnetic field strengths; therefore, our investigations focused on high magnetic field strengths(Few Tesla) and magnetic field gradients(Few Hundred Tesla/m) for mechanically manipulating magnetic nanoparticles.[5]

Discovery of drug Release from magnetic field induced ultrasound from magnetic nanoparticles: In order to understand the behaviors of cell membranes when exposed to short intense magnetic fields in the presence of magnetic nanoparticles, our research has focused on a liposomal model system consisting of phospholipids. The permeability changes in these liposomal drug delivery vehicles modified to incorporate the magnetic NP triggers,[6] which enabled us to make some important discoveries such as: 1) We have successfully demonstrated the ability to prepare liposomes loaded with model drug and triggerable magnetic particles to deliver drugs very rapidly (sub milliseconds), which is great gain over the traditional speed of liposomal drug delivery systems (minutes an hours). 2) The magneto liposomes when triggered with inhomogeneous pulsed magnetic fields release drug molecules. 3) We have discovered that the mechanism of drug release is the result of the ultrasound generation from small magnetic nanoparticles as shown in the Figure 1.[7] 4) The ultrasound is generated from the oscillation of particles (not heat) in the pulsed oscillating inhomogeneous magnetic fields as opposed to the much weaker magnetostriction effect due to homogeneous magnetic fields. Our group utilizing very low duty cycle intense magnetic pulses has achieved comparable drug delivery efficiencies to the results carrier out with magneto liposomes exposed to low amplitude continuous alternating magnetic field studies with 100% duty cycle electro magnets 6) In addition these scientific discoveries, we have developed several electromagnets[8] and power delivery system to produce not only homogeneous magnetic fields(~15-20 Tesla), but transient spatially homogeneous rotating magnetic fields (~few hundred milli Tesla) that will be used in the next phase of the proposal. Our newest pulsed magnet and the power delivery system has been integrated on a mobile cart to pursue collaborative studies in cell laboratories. The portable magnet will be replicated to extend collaborations with multiple laboratories simultaneously to increase the impact and applicability of this research and assist other groups to address their specific challenges in relation to induced molecular transport. **Application to Cancer therapy:** As previously stated, microporation induced by inhomogeneous magnetic pulses used in this work have been demonstrated within liposomes. In the next phase of our research, we wanted to

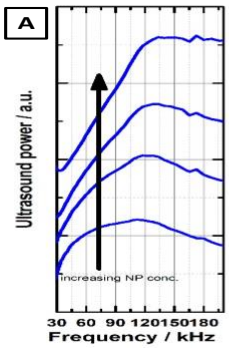


Figure 1 Ultrasound from colloidal iron oxide nanoparticles

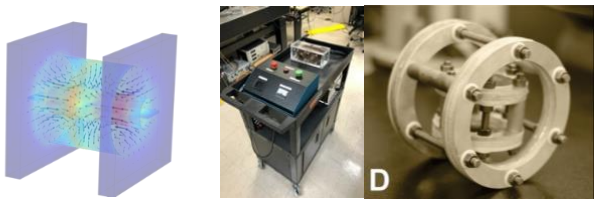


Figure 2 LEFT: COMSOL calculation of Inhomogeneous magnetic field inside anti Helmholtz coil used in cancer therapy. MIDDLE: Portable electromagnet and the integrated power delivery system for cell work. RIGHT: Rotating Pulsed Magnet from Chikan lab

[5] Podaru, G.; Chikan, V., Magnetic Nanomaterials: Applications in Catalysis and Life Sciences. In *Chapter 1 Magnetism in Nanomaterials: Heat and Force from Colloidal Magnetic Particles* Bossmann, S. H., Ed. The Royal Society of Chemistry: 2017; pp P007-P008.

[6] *J Phys Chem B* **2014,** *118* (40), 11715-22.

[7] *The Journal of Physical Chemistry C* **2016,** *120* (4), 2386-2391.

[8] *Rev Sci Instrum* **2015,** *86* (3), 034701.

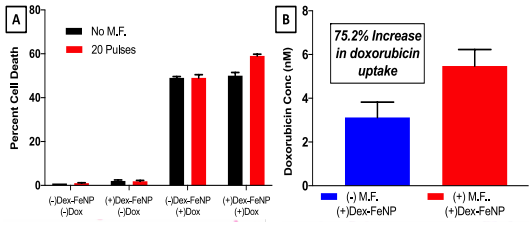


Figure 3 A Percentage of U-937 (human cancer cell line) cell death in combinational treatments in the presence or absence of dextrin-coated nanoparticles, doxorubicin, and or 0, 20, or 50 magnetic pulses applied Quantification via HPLC of doxorubicin uptake within U-937 human cancer cells in the presence of 0.0025 mg/mL of dextrin-coated IONPs, 20 magnetic pulses

explore if the reverse direction of molecular transport (relative to our earlier liposomal work) can be assisted with our approach combining pulsed magnetic fields and magnetic nanoparticles. This microporation technique is applied to facilitate the transport of a model therapeutic agent (doxorubicin) into the U937 cancer cell line.[9] We have shown that the commercially available glucose-coated magnetic nanoparticles accumulated in U937 cell lines prior to application of magnetic pulses and shown no adverse effects on cell viability. Our investigations explored the possibility of increase cell death while concurrently increasing accumulation of doxorubicin via MAFIA (Magnetic (MA) field (F), induced (I), action (A), herein referred to as MAFIA, in which inhomogeneous magnetic fields assisted by magnetic particles with targeting ligands increase drug uptake resulting in selective cell death). We have also demonstrated that other cell lines and drug types also show similar effects. The results from this work has been or under publication and a patent application has been submitted with the assistance of Kansas State University.

[9] *ACS Applied Nano Materials* **2020,** *3* (3), 2414-2420.