MAGNETIC NANOPARTICLE SYSTEMS FOR HYPERTHERMIC PREVENTION OF CANCEROUS FORMATIONS AND INFECTIOUS DISEASES IN BONE TISSUE GROWN ON MULTISCALE, BIOACTIVE POLYMERIC AND CERAMIC MATERIALS

Hyperthermia has been used in a variety of treatments of various diseases for several thousand years. Increasingly, it has been viewed as a promising form of cancer therapy, in addition or in combination with other widely used methods of cancer treatments, such as surgery, chemotherapy and radiotherapy. Mild hyperthermia in the range of 41C to 46 C stimulates immune system response to non-specific immunotherapy of cancers, and thermoablation of tumour cells to 46C to 56C leads to their necrosis, coagulation or carbonization, and thus to tumor destruction. However, thermoablation temperature range is too close to that of the normal cells, and thus requires unrealistic local temperature control. Hyperthermia takes advantage of enhanced sensitivity of poorly oxygenated (hypoxic) cancerous cells to temperatures in 42C to 45C range as compared to normal tissue cells. This is even more remarkable, as hypoxic cancerous cells are less sensitive to radiation. In this temperature range many intracellular processes involving structural and enzymatic proteins are modified, altering hypoxic cell growth and differentiation, and inducing apoptosis. In contrast, well oxygenated (euoxic) cancerous cells (that are not sensitive to heat) are more sensitive to radiation. Therefore, as clinical results confirm, a combination of hyperthermia with radiation therapy leads to substantial improvement in cancerous growth treatment. An added bonus is that heating interferes with repair of radiation-induced damage in the DNA of cancerous cells, thus further enhancing the overall therapeutic effect. Similar effects of hyperthermia are also reported in the case of other diseases, such as HIV.

Among a variety of heating modes, very few are capable of delivery of high heat energy to deeply located cancerous cells without destruction of the surrounding normal tissue. Moreover, only the use of micro- and nanoscale (as opposed to macroscopic) inductive mediators injected as particle dispersion allows accurate delivery of controlled heat to precisely specified locations in the body. The reason is that all other types of mediators may lead to uncontrolled heating of the body because of the tissue's intrinsic electrical conductivity, electrical field inhomogeneities caused by differences in the tissue dielectric permeability, and/or eddy currents. Thus, the product of the amplitude of the AC magnetic field H and frequency v of the current, Hv, should not exceed 4.85×10^8 A/ms for treatment sessions of one hour, with the frequency in the range from 50kHz to 10MHz, to avoid neuromuscular electrostimulation while still ensuring appropriate penetration depth of the fr-field.

The latest micro- and nanoscale mediators are developed in the form of injectable colloidal dispersions of magnetic particles that ensures accurate control and higher temperature homogeneity of the heating. In particular, the particle distribution in the tissue can be determined by MRI, and the particles can be specifically engineered for intake by cancerous cells, to selectively overheat only cancerous cells, including those of metastases in any region of the body. For multidomain ferro- anf ferri- magnetic particles, heating occurs due to hysteresis losses, while for single-domain (usually superparamagnetic) particles the energy comes from the AC magnetic field that induces rotations of magnetic moments to overcome the energy barrier $E=KV$ where K is the anisotropy constant and V is the volume of the magnetic core of a particle. The value of the specific absorption rate (SAR) of the magnetic material used in micro/nanoparticles (that is defined as the power of heating of magnetic material per gram) is of crucial importance: the higher the SAR the lower the injected dose of the suspention to the

patient. Currently, magnetic nanoparticles of 3 to 1500 nm in diameter feature cores of single and multidomain Fe_2O_3, γ- Fe_2O_3, Fe_3O_4, or ferrite, and shells (if any) of dextran or aminosilane groups, for biocompatibility. The dispersion media are either physiological solution or water.

More research has revealed that dextra shell may be attacked by enzymes in lysosomes, and dextran-shelled magnetic nanoparticles has been classified as unsuitable for intracellular magnetic fluid hyperthermia (MFH). Modification of magnetic nanoparticle with aminosilane groups allows not only solve the bioneutrality problem, but also help accumulating the particles in cancerous cells. Novel approaches to particle design for needs of MFH have been developed. In particular, it has been observed that manganese perovskite systems, such as $LaSrMnO_3$ of 20 to 180 nm in diameter, may be a key factor to precisely controlled MFH, as the superparamagnetic to paramagnetic transition in such systems depends on the composition and can be tailored to be precisely in the range of 42 C to 46C. Therefore, such systems allow precise control of a given amount of energy delivered to the cancerous cells regardless of the duration of the MFH session, as after the transition temperature is reached the particles become paramagnetic and can not absorb the rf-field energy any longer.

The major task of this project is to use manganese perovskite core-shell nanoparticle systems for hyperthermic prevention of cancerous formations and infectious diseases in bone tissue grown on artificial scaffolds, **such as multiscale, bioactive polymeric and ceramic materials**. The major tasks of the project fall under several thrusts.

1. **Synthesis and characterization** of several spherical $La_{1-x}Sr_xMnO_3$ - core / SiO_2-shell nanoparticle systems, with pre-designed amount of La and Sr atoms to ascertain the superpara- to paramagnetic transition temperature in the range of 45C to 50C. The core and shell diameters will be finely tuned to meet the hyperthermal therapy requirements of high SAR, energy delivery precision and controllability, and bioneutrality, at the same time.
2. **Homogeneous integration o**f the magnetic core-shell nanoparticle systems into the multiscale bioactive polymeric scaffold materials, novel calcium phosphate bioceramic surfaces, and nanoparticle-loaded e-spun nanofibers for therapeutic protein delivery; control of the particle mobility within/on such matrices.
3. **Enhancement** of durability of the scaffold-integrated magnetic nanoparticles to extend their therapeutic life-span.
4. **Investigation of therapeutic properties** of such magnetic nanoparticles in the bioactive polymeric and ceramic materials.

Integration of the magnetic nanoparticles into natural or artificially-grown bone tissue or joint surfaces presents a new cost-effective approach to bone cancer and infection prevention. A very simple and physically comfortable procedure will include periodic exposure of the magnetic nanoparticle-loaded bone/joint tissue to AC magnetic field for a prescribed amount of time, to ensure homogeneous suppression of cancerous cell growth at very early stages through entire depth of bone/joint tissue. Durability of the magnetic nanoparticles can be enhanced choosing an appropriate thickness of the silica shells to make the nanoparticle therapeutic longevity at least as long as that of the tissue scaffolds, so the cancerous cell growth prevention can be realized during entire lifecycle of the tissue.

Other uses of bone/joint tissue integrated magnetic nanoparticles include controlled warming of the tissue to enhance drug effects, metabolism and immune system response, and to control the rate of these processes through manipulations with the magnitude and frequency of the AC magnetic fields.