Tuning magnetism in shape-controlled hybrid nanoparticles for enhanced hyperthermia efficiency and heat-activated drug delivery.

Magnetic materials are known to play a significant role in biology and medicine. Biomedical nanomagnetics is a multidisciplinary area of research in science, engineering and medicine with broad applications in imaging, diagnostics and therapy.[1] Recent developments offer exciting possibilities in personalized medicine providing a truly integrated approach, since chemistry, materials science, physics, engineering, biology and medicine are incorporated. Biomedical applications require magnetic nanoparticles (MNPs) with several well-defined and reproducible structural, physical, and chemical features. The key idea of this proposal is to provide enhanced multifunctional co-operative heat-triggered magnetic carriers. These multifunctional nanoplatforms besides the magnetic core which is actually the driving force for magnetic hyperthermia, may be functionalized with extra action(s) triggered only during AC magnetic field exposure. Such magnetic nanoparticles can be a highly effective new nanoscale tool useful for a variety of systems that rely on heat induction, initiating from magnetic hyperthermia therapy but go beyond current modalities with add-on tools such as on-demand drug release and thermal activation of metabolic pathways within a single cell. Specifically, we will study the physics of self-assembly and magnetism at the nanoscale and unravel their interconnections in an effort to provide multifunctional enhanced heat-triggered MNPs.

Namely, **Synthesis is the 1st phase of this proposal and its objective is the facile, cost-effective, high-yield and systematic production of magnetic nanoparticles of the type MFe_2O_4 where M=Fe, Co, Mn.** Here, the Greek partner will employ single-phase ferrite nanoparticles with facile synthetic controls that result in uniform size, excellent crystallinity and size monodispersity and allow for optimal tuning of anisotropy constant *K*. Starting from the widely accepted in biomedicine iron oxides Fe_3O_4 and γ-Fe_2O_3 we intent to implement synthetic procedure and proceed on alternative ferrite nanoparticles selected based on their low inherent toxicity, ease of synthesis, physical and chemical stability but mainly due to tunable magnetic properties since $CoFe_2O_4$ is a representative hard material with $K=2.0\times10^5\ J{\cdot}m^3$ and $MnFe_2O_4$ is representative soft material with $K=3.0\times10^3$ $J{\cdot}m^3$ also a suitable enhanced MRI contrast agent.[2]

Accordingly, the **2nd phase´s (Properties) objective is to provide magnetic nanoparticles with tunable but reproducible magnetic features both at the nanoparticle level and also at collective assembly i.e. a novel approach in the significant enhancement of magnetic heat induction by means of modulating magnetism**. Structural, morphological and magnetic characterization at the intra/particle level (atomic resolution) is required to unravel the driving forces of anisotropy tuning and interaction intensities within an individual nanoparticle entity. X-ray diffraction, Microscopy techniques, Static and Dynamic Magnetometry will be employed by the German partner to comprehend the physics of the self-assembly and nanomagnetism while providing a valuable feedback to ultimate optimization of synthesis procedures. Interactions of particles with their chemical surrounding will also be studied, in order to stabilize an aqueous suspension. Eventually the Greek partner will deal with AC-magnetic hyperthermia response of optimum systems and in

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[1] *Biomedical Nanomagnetics: A Spin through possibilities in Imaging, Diagnostics, and Therapy, K. Krishnan, IEEE Trans. Magn.* ***46****, 2523 (2010).*

[2] *Monodisperse magnetic nanoparticles for theranostic applications, D. Ho, X. Sun, S. Sun. Accounts of Chemical Research* ***44****, 875 (2011).*

collaboration with the German partner will try to quantitatively correlate hyperthermia efficiency with particle properties (K, M_s, D) and field features (f, H_o). The combination of small particle size in conjunction with the ferromagnetic stability and high saturation magnetization is also crucial for improving the heating efficiency in magnetic hyperthermia and at the same time achieving higher signal sensitivity for better contrast in magnetic resonance imaging (MRI). Consequently, based on the experience and complementarity of Greek and German teams, we will coordinate a detailed structural and magnetic profile mapping and unravel the mechanisms to enhance heating efficiency by property tuning structural and physical properties at the nanoscale.

Eventually, based on the magnetic properties of individual nanoparticles, dipolar interactions directly associated with interparticle distances may also lead to enhanced magnetic features and further tuning of collective magnetic behavior and hyperthermia efficacy.[3, 4] Within this proposal, in an effort to overcome current limitations and constraints, we will focus on size regimes beyond the superparamagnetic limit but within the single-domain region in order to exploit a beneficial combinatory heating effect both from Néel relaxation and hysteresis losses. During this project's lifetime we intend to change the current worldwide belief that hyperthermia is a synergistic treatment modality mainly supporting invasive schemes such as X-ray therapy and chemotherapy strengthening the anti-tumor effect. Due to its non-invasive character, the remote control of its efficiency if properly combined with enhanced performance and the adequate heat-triggered modalities we would like eventually to reintroduce her as a radically novel integrated approach for future theranostics.

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[3] *Optimal size of nanoparticles for magnetic hyperthermia: A combined theoretical and experimental study, B. Mehdaoui, A. Meffre, J. Carrey, S. Lachaize, L. –M. Lacroix, M. Gougeon, B. Chaudret, M. Respaud, Adv. Func. Mater.* ***21****, 4573 (2011).*

[4] *Influence of dipolar interactions on hyperthermia properties of ferromagnetic particles, D. Serantes, D. Baldomir, C. Martinez-Boubeta, K. Simeonidis, M. Angelakeris, E. Natividad, M. Castro, D.-X. Chen, A. Sanchez, Ll. Balcells and B. Martínez, J. Appl. Phys.* ***108****, 073918 (2010).*