Synthesis and characterization of novel triple-layer nanoparticles with multimodal potential-first results

Z. Medarova[1], M. Yigit[1], C. Ran[1], M. Kumar[1], and A. Moore[1]

[1]MGH/HST Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Charlestown, MA, United States

Background. It is becoming increasingly clear that no single imaging modality carries all of the properties necessary for comprehensive quantitative diagnostics with high spatial and temporal resolution, high sensitivity of detection, and tomographic capability. Therefore, in order to collect truly thorough information through imaging, one needs to employ a multimodality approach. With this in mind, it is important to develop contrast agents that have innate multimodal properties and can be detected by different modalities. This is one problem addressed by the study described here. We have synthesized a nanoparticulate contrast agent that consists of elements detectable by computed tomography (CT), magnetic resonance imaging (MRI) and optical imaging (Raman microscopy) without the addition of ligands, such as optical dyes, paramagnetic ions, or iodine. An additional value of our study extends from the fact that the described contrast agent is clinically compatible and easily functionalized with a multitude of ligands without the need for complex chemistry.

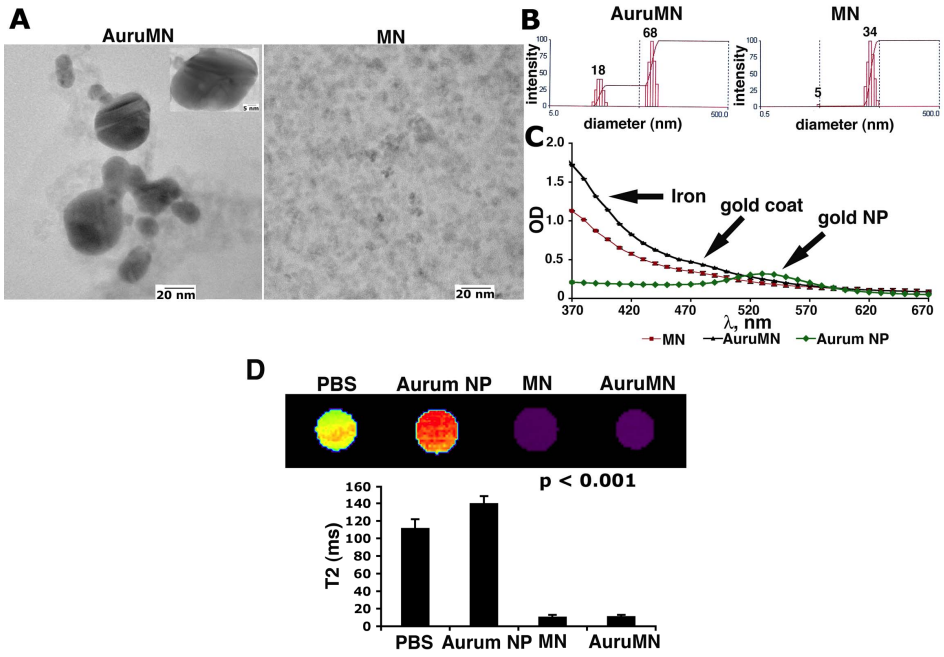

Figure 1. Dynamic light scattering (A) and transmission electron microscopy (B) of AuruMN and MN. C. UV-VIS spectrophotometry of AuruMN, MN, and gold nanoparticles (Aurum NP). D. MRI of AuruMN, MN, gold nanoparticles (Aurum NP) and buffer.

Methods and Materials. The contrast agent (AuruMN) represents a three-layer construct, consisting of a 3-5 nm core of iron oxide (detectable by MRI), covered with dextran-T10 for a resulting diameter of 10-30 nm, and coated with gold (compatible with detection by CT and Raman microscopy) for a final diameter of ~70 nm. Nanoparticle size was determined using dynamic light scattering and transmission electron microscopy. UV-VIS spectrophotometry was performed to obtain an indication of successful coating of the iron oxide with gold. Further confirmation was obtained through ICP elemental analysis. The relaxivity of the preparation was determined by NMR Spetroscopy. Its suitability for MRI was demonstrated by T2-weighted MR imaging at 9.4T, using the following parameters: T2 weighted spin echo (SE) pulse sequences- TR/TE = 3000/8, 16, 24, 32, 40, 48, 56, 64ms, FoV = 3.2x3.2 cm^2, matrix size 128 x 128, resolution 250 x 250 μm^2 and slice thickness = 0.5 mm. **Results** Transmission electron microscopy (Fig. 1A) and dynamic light scattering (Fig. 1B) showed that the nanoparticle suspension was fairly monodisperse with a median nanoparticle diameter of 68 nm for the prevalent AuruMN nanoparticle population, compared to 34nm for the precursor MN nanoparticles, not coated with gold. UV-VIS spectrophotometry detected an absorbance peak < 370nm representative of the iron oxide precursor and a small peak at about 500nm consistent with the formation of a gold coat (Fig. 1C). The presence of both iron and gold in the nanoparticle preparation was confirmed by ICP elemental analysis. The R2 and R1 relaxivities of AuruMN were comparable to those of the precursor MN nanoparticles (31.5 and 101.4 vs 36.4 and 117.6, respectively). MRI of nanoparticle phantoms revealed that AuruMN and MN nanoparticles are comparably suitable for detection using T2-weighed MR sequences (Fig. 1D).

Summary.

The nanoparticle preparation described here can find application in pre-clinical and clinical diagnostics and therapy. It represents a versatile platform based on which one can design a wealth of diagnostic/therapeutic agents through functionalization of the nanoparticles with targeting moieties, specific for chosen cells, tissues, or biological processes as well as with molecular therapeutic agents, e.g. small interfering RNAs, chemotherapeutic drugs, chemical inhibitors, etc. Similar nanoparticulate contrast agents with varying sizes can be synthesized and used for multimodal screening through magnetic resonance imaging, computed tomography, and optical imaging.