# Optimization of all-in-one thermo-responsive theranostic mesoporous silica nanoparticles for hepatocellular carcinoma

Marwa M.I. Rizk [1,2], Connor J.R. Wells [1], Pratik Gurnani [3], Gareth R. Williams [4], and Gemma-Louise Davies [1]

[1] Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK.

[2] Department of Pharmaceutics, Faculty of Pharmacy, Alexandria University, Alexandria, Egypt.

[3] Division of Molecular Therapeutics and Formulation, School of Pharmacy, University Park, University of Nottingham, Nottingham, NG7 2RD

[4] UCL School of Pharmacy, University College London, 29-39 Brunswick Square, London WC1N 1AX,

**Background:** Hepatocellular carcinoma (HCC) is commonly diagnosed in the late stages which limits the treatment options to only the FDA approved drug sorafenib. However, its low efficacy, poor solubility, and the toxic side effects are all obstacles that limit its performance. In addition, the lack of a proper diagnostic tool for either detecting the tumor in the early stages or to monitor the disease progression represents another barrier toward effective HCC treatment.

**Methods:** Our work aims to solve these problems by developing mesoporous silica nanoparticles (MSNs) that have the ability to enhance the therapeutic performance through, multi-drug combination. Therapeutic MSNs have been prepared and the effect of the pore size, internal pores' chemistry, scaling up and solvent polarity on both drug loading and entrapment efficiency of sorafenib tosylate and doxorubicin HCl has been studied.

In term of diagnosis, MRI active MSNs have been optimized by incorporating the MRI contrast agent gadolinium (Gd-DOTA) chelate to internal surfaces, at different locations where water gating can be exploited to provide an 'on/off' MRI signal switch for disease diagnostics. To achieve the gating, different molecular weight of the LCST thermo-responsive polymer (Poly(N-isopropylacrylamide)) have been synthesized and characterized using turbidimetry as well as dynamic light scattering to determine their cloud points (the temperature at which the polymer transfers from hydrated to dehydrated phase).

**Results:** Sorafenib loading into MSNs was highly affected by solvent polarity. The higher the polarity, the lower the drug loading, especially in the hydrophilic MSNs. In case of doxorubicin HCl, the loading capacity and entrapment efficiency were decreased 5 times upon scaling up. The diagnostic MSNs showed relaxivity values ($r_1$) (i.e. higher relative signal enhancement) of 13.7 and 10 times more, respectively, for core MSNs- Gd (GC) and edge MSNs-Gd (GE), than the commercially available Gd-DOTA chelate (Dotarem©) of $r_1$ 3.4 $mM^{-1}$ $s^{-1}$ at 1 T .The molecular weight of the synthesized LCST polymers were 2400-6800 kDa with a slight difference in the cloud points (34.5 - 35.5 $^{o}$C), and noticeable heating-cooling hysteresis.

**Conclusions:** MRI active mesoporous silica nanoparticles were successfully synthesized through covalent loading with $Gd^{3+}$-DOTA chelate in the interior surface of the pores. In addition, drug-loaded MSNs were prepared and the effect of the pore size, its chemistry, scaling up as well as solvent polarity on both drug loading and entrapment efficiency was studied. Future work will involve assessing the behavior of the grafted thermo-responsive polymers onto MSNs using DLS, turbidimetry, and 1H relaxometric measurements.