# pH-triggered 19F MRI for Lung Cancer Cell A549

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## Introduction

$^{19}$F MRI has been recognized as a powerful and noninvasive methodology for cancer diagnosis due to no background signal in biological tissues, and hence high-contrast images in vivo are very helpful to identify tumors. We developed a novel nanosized and pH-trigged biosensor, which encapsulates high-sensitive $^{19}$F MRI contrast agent in gold nanoparticles (AuNPs)-capped mesoporous silica nanoparticles (MSNs) platform (Fig. 1), and this biosensor is capable to specifically target to lung cancer cell (A549) for intracellular MRI.

## Materials and Methods

AuNPs have been employed to seal the nanopores of MSNs in order to inhibit premature $^{19}$F contrast agent ($C_6F_6$) release, AuNPs@MSNs are stable at pH 7.4 (Fig 2.a) but rapidly dissolve at pH <5.5 (Fig 2.b). AuNPs@MSNs specifically bind to the surface of the A549 cells through the folate functionalized AuNPs after internalization into target cells, and then the AuNPs lids are rapidly dissolved in the acidic intracellular compartments. After that, the $^{19}$F contrast agent is released into the cytosol from the MSNs. As a proof-of-concept demonstration, the specific targeting and endocytosis process of AuNPs@MSNs is observed using confocal laser scanning microscopy (not shown).

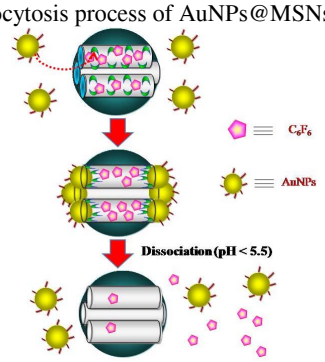


**Fig. 1.** Schematic of synthesis of pH-triggered $^{19}$F MRI biosensor. $^{19}$F MRI contrast agent encapsulated in AuNPs@MSNs release to the cytosol via selective dissolution of AuNPs in the acidic intracellular compartments of lung cancer cells

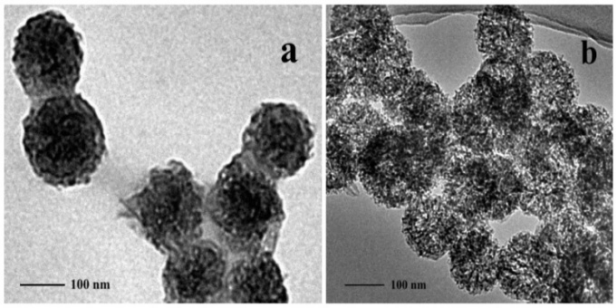


**Fig. 2.** TEM micrographs of (a)AuNPs@MSNs and (b) AuNPs@MSNs after incubation in pH 5.5 buffer solution, showing the dissolution of the AuNPs.

Acid functionalized gold nanoparticles (COOH-AuNPs) were synthesized via a modification of the procedure reported previously [1]. COOH-MSNs which have diameters of ~100 nm and 3.4 nm wide channel-like pores were first synthesized according to a procedure reported by Kim et al [2]. Then, to functionalize with amine group, the COOH-MSNs and 50 μL APTES was suspended in 20 mL of toluene and refluxed for 12 h. $C_6F_6$ was loaded in amines functionalized MSNs through π-π interactions between the APTES and $^{19}$F contrast agent ($C_6F_6$). As depicted in Fig.1, $C_6F_6$ is loaded in the mesopores of the MSNs and encapsulated with disulfide-linked AuNPs that physically block the $C_6F_6$ in from leaching out. In the end, the precipitate was centrifuged and washed several times with water (pH 7.4).

The transmission electron microscopy (TEM) analysis was conducted with a JEOL JEM-3010 transmission electron miscroscope operated at 200 kV. $^{19}$F MRI experiments were carried out on a Bruker Biospin 9.4T mico-imager. Echo times (TE) =200ms, TR=2000ms, matrix size = 64 × 64, slice thickness = 40 mm.

## Results and Discussion

Because of the core-shell structure of the AuNPs@MSNs, the pH-triggered $^{19}$F biosensors exhibited significant effect shielding of MRI (Fig 3.a). However, after incubation in A549 cell 60 min, the AuNPs lids were uncapped in response to the extracellular pH of solid tumor tissues where the pH was 0.4-1.0 units lower than the physiological one (pH=7.4), thus achieving appreciably enhanced $^{19}$F MR signal at the intracellular pH typical of tumor environments (Fig 3.b). AuNPs@MSNs in pH 5.5 buffer showed a rapid dissolution of AuNPs(Fig 3.c), resulting in a further enhancement of $^{19}$F MRI signal.

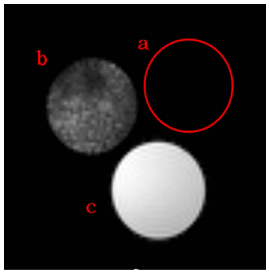


**Fig. 3.** $^{19}$F MRI of $C_6F_6$ AuNPs@MSN in (a) pH 7.4 PBS (b) A549 cell (c) pH 5.5 PBS incubation 60 min

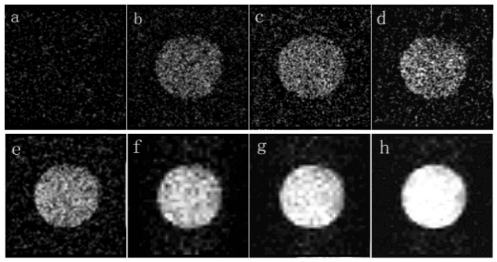


**Fig. 4.** $^{19}$F MRI of $C_6F_6$ AuNPs@MSN in lung cancer cell (A549) at different incubation time (a)0 min (b) 10 min (c)20 min (d)30 min (e)60 min (f)90 min (g)120 min (h)180 min

## Conclusion

We have shown that AuNPs lids on MSNs can be efficiently dissolved in the acidic intracellular compartments of cancer cells, inducing the $^{19}$F contrast agent release from the pores of the MSNs into the cytosol. Eventually, an appreciably enhanced $^{19}$F MRI signal could be detected at an extremely low concentration, which demonstrated the potential utility of these nanopaticles as high-sensitive MRI biosensors for tumors.

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**Reference** [1] Shizhen Chen et al, Biosensors and Bioelectronics 2011; 26: 4320– 4325. [2] Mi-Hee Kim et al, ACSNANO 2011; 5:3568–3576