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# Fluorescent core-shell alloy nanoparticles for cell targeting applications

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**Introduction:** We report the synthesis and characterization of gold-silver (Au/Ag) alloy core silica shell (Au/Ag@SiO<sub>2</sub>) nanoparticles (NPs) incorporating fluorescent molecules and functionalized with antibodies (Abs) to target cancer cells (Fig. 1). These multifunctional Au/Ag@SiO<sub>2</sub> NPs present various advantages: (1) The size of the Au/Ag core can produce tunable scattering signals due to local plasmonic resonance effect which can be easily collected by darkfield microscopy<sup>[1]</sup>; (2) The Abs-functionalized NPs can target cell surface receptors as contrast agent in flow cytometry (fluorescence and scattering channels)<sup>[2]</sup> due to high optical cross-section; (3) The field enhancement around the metallic core can increase the intensity of fluorescent molecules since they have a higher excitation and emission rate, generate more photons and are less vulnerable to photobleaching than unprotected fluorescent molecules<sup>[3]-[5]</sup>; (4) The combination of multiple NPs displaying characteristics signals in both darkfield and fluorescence channels can bring a significant improvement in terms of marker efficiency; (5) The SiO<sub>2</sub> shell should allow the incorporation and protection of a high number of fluorescent molecules and further ease the surface modification.

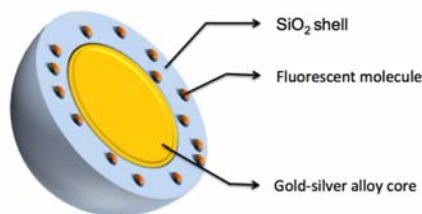


Fig. 1. Schematic representation of fluorescent Au/Ag@SiO<sub>2</sub> NPs.

**Material and Methods:** Fluorescent molecules (Fluorescein isothiocyanate (FITC), Rhodamine B isothiocyanate (RBITC) and CF 647) were incorporated in the SiO<sub>2</sub> shell after reaction with (3-aminopropyl)triethoxysilane (APTES) diluted with dimethylformamide (DMF) and triethylamine (as a catalyst) to form fluorescent precursors (FPs). Au/Ag@SiO<sub>2</sub> NPs were synthesized with tetraethyl orthosilicate (TEOS), ammonia solution, FPs and 60 nm citrate-capped (25/75 or 50/50) Au/Ag alloy NPs diluted in EtOH under continuous stirring for 24 h. Au/Ag@SiO<sub>2</sub> surface was modified with (3-mercaptopropyl)trimethoxysilane (MPTMS) to react with Abs (anti-CD44 and anti-EGFR as positive Abs, anti-Nectin2 as negative Abs) in presence of sulfo-succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate (sulfo-SMCC). Functionalized NPs were incubated with human HeLa cancer cells for 30 minutes in dark environment on ice.

**Results and Discussion:** Fluorescent tunable Au/Ag@SiO<sub>2</sub> NPs have been synthesized and characterized (Fig. 2). NPs containing 60 nm Au/Ag (25/75 or 50/50)<sup>[6]</sup> have been produced and visualized by TEM (Fig. 2A,B) since their different scattering peaks can be used in darkfield microscopy. The fluorescent molecules incorporated in the NPs showed clear signal compared to bare Au/Ag NPs and supernatant (Fig. 2C-E). Au/Ag@SiO<sub>2</sub> NPs containing FITC were then observed by darkfield and fluorescence microscopy (Fig. 2F,G). The scattering and fluorescent signals colocalized and the higher scattering intensity of NP clusters colocalized with brighter fluorescent signal. The fluorescent NPs targeting cancer cells was confirmed by flow cytometry (Fig. 3).

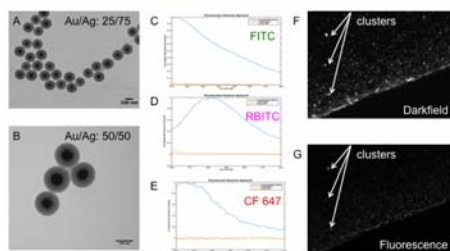
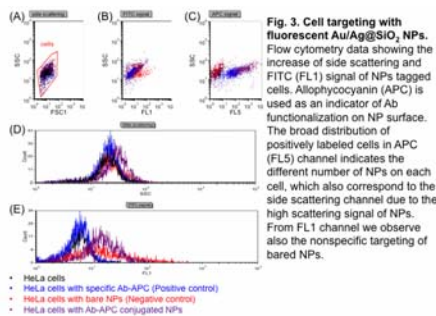


Fig. 2. Characterization of fluorescent Au/Ag@SiO<sub>2</sub> NPs. Structure of 60 nm Au/Ag (25/75 (A) and 50/50 (B)) core with 40 nm SiO<sub>2</sub> shell observed by TEM. The fluorescence spectra of FITC (C), RBITC (D) and CF 647 (E) incorporated in Au/Ag@SiO<sub>2</sub> NPs compared to the spectra of bare Au/Ag NPs and supernatant measured by UV-visible spectroscopy. Darkfield (F) and fluorescence (G) microscopy of Au/Ag@SiO<sub>2</sub> NPs containing FITC (60x magnification).



**Conclusion:** Fluorescent Au/Ag@SiO<sub>2</sub> NPs targeting different cell surface receptors were synthesized, characterized and used as contrast agent labeling cancer cells. The combination of scattering and fluorescence channels in flow cytometry from the proposed NPs incorporating different fluorescent molecules would allow multifunctional and multichromatic possibilities for in vitro and in vivo imaging.

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