



## **In Vitro and In Vivo Evaluations of A High Affinity and Specificity Photoacoustic Nanoparticle Targeting to Cancer**

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**Title:** In Vitro and In Vivo Evaluations of A High Affinity and Specificity Photoacoustic Nanoparticle Targeting to Cancer

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**Introduction:** Photoacoustic (PA) imaging is a hybrid modality, combining the high sensitivity of optical imaging and the high resolution of acoustic imaging, and thus offers a unique opportunity to improve the early detection of cancer cells. This work aims to develop a silica coated iron oxide (SIO) nanoparticle as a potent cancer cell selective PA contrast agent, with a high binding affinity and selectivity to the gastrin releasing peptide receptor (GRPR) which is overexpressed in many human cancers including prostate cancer, breast cancer and small cell lung cancer etc.

**Methods:** Silica coated iron oxide (IO) nanoparticle was synthesized and conjugated with bombesin (BBN) peptide and AlexaFluor750 (AF750) dye to form SIO-AF750-BBN. This hybrid nanoparticle was purified and characterized by Transmission Electron Microscopy (TEM), Fourier Transform Infrared Spectroscopy (FTIR), Atomic Force Microscopy (AFM) and electrochemistry. In vitro binding affinity was determined by a competitive IC<sub>50</sub> assay against the gold standard <sup>125</sup>I-Tyr4-BBN for GRPR on human prostate cancer PC-3 cells. In vivo evaluation was performed in mice bearing PC-3 tumors to explore the in vivo binding affinity and specificity, as well as the PA imaging efficacy, pharmacokinetics, and biodistribution of the SIO-AF750-BBN nanoparticle.

**Results and Discussion:** SIO-AF750-BBN has a core diameter of 9.7±0.7 nm and a silica coating thickness of 7.5±0.9 nm, and 4.6 AF750-BBN per nanoparticle. The photoacoustic signal strength of SIO-BBN-AF750 was examined and compared to SIO, IO, and AF750-BBN in near infrared (NIR) wavelength range of 680-970 nm. SIO-AF750-BBN showed the strongest PA enhancement with a peak at 740 nm, over the bare SIO or IO nanoparticle or the bare AF750-BBN molecule. In vitro cell binding experiment showed that SIO-AF750-BBN had a high binding specificity and affinity to the GRPRs, with an IC<sub>50</sub> = 19.3 ± 3.7 nM for PC-3 cells. In vivo NIRF imaging of SIO-AF750-BBN was performed in prostate cancer PC-3 tumor bearing mice 1-hour after tail vein injection, and showed a significantly higher intensity in tumor tissues in the uptake group than that of the receptor-blocking group, indicating a high in vivo binding specificity and sensitivity of SIO-AF750-BBN to GRPRs on PC-3 tumors. In vivo photoacoustic images were performed at 680-970 nm wavelength range pre- and 1-hour post-tail vein injections. The SIO-AF750-BBN uptake group showed the most photoacoustic signal enhancement especially in the tumor core, while the receptor-blocking group and the small molecule AF750-BBN group showed significantly lower PA signals (approximately 35% and 22% that of the SIO-AF750-BBN group, respectively, at 750 nm). The result shows the high in vivo photoacoustic sensitivity of SIO-AF750-BBN on the PC-3 tumors.

Conclusion: SIO-AF750-BBN is a promising nanoparticle for site-specific targeting and photoacoustic imaging of cancer cells expressing gastrin releasing peptide receptors such as prostate cancer.