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Radiolabeled TATE functionalized Gold Nanoparticles for potential use in imaging and therapy of Neuroendocrine tumors

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Background and Goal of the study
Peptide receptor radionuclide theranostics is a targeted approach for imaging and therapy of cancers. In this purview, a number of peptide based derivatives such as octreotide analogues, are in clinical use utilizing 68Ga/177Lu radionuclidic pair. The octreotide peptide such as 3-Tyr-Octreotate (TATE) used for peptide receptor targeting is an agonist peptide which enters the tumor cell via somatostatin receptor mediated transport across the cell membrane. However, rapid elimination of the radiopharmaceutical from blood limits the uptake of the radiopharmaceutical in the tumours. To effect improved target uptake, there is an interest to explore the performance of radiolabeled TATE functionalized gold nanoparticles, as the later are known to have higher blood residence period. Surface modified gold nanoparticles are known to enter living cells and are excellent candidate for utilization in biomedicines, mainly in cancers and carcinomas. The objective of the present work is to functionalize gold nanoparticles with TATE peptide along with DOTA chelator so as to radiolabel them with 68Ga/ 177Lu radionuclides and evaluate them for their theranostic potential.

Methodology
Commercially available DOTA-TATE was directly used to functionalize Gold nanoparticles. Briefly, DOTA-TATE (0.7 mM, 0.5 mL) solution in water was added and mixed with a solution of HAuCl4 (1mM) in TWEEN 80 (1mM). The resulting solution was then reduced rapidly with ice-cold NaBH4 (0.5 M, 1mL) to obtain the required 'TATE along with DOTA functionalized gold nanoparticles'. The obtained gold nanoconjugates were purified by dialysis, characterized and then used for labelling studies. The labelling protocol involved direct addition of purified gold nanoparticles to 68GaCl3/177LuCl3 activity (185 MBq) in 0.1M acetate buffer (pH 4-5), and the resulting reaction mixture was heated at 60℃ for 15-30 min to yield the radiolabeled TATE functionalized gold nanoparticles.

Results and Discussion
TATE having a disulphide linkage is expected to have affinity towards Au surface under reducing conditions. Such a formation was observed in the present experimental conditions and gold nanoparticles in wine red colour were obtained. The nanocolloidal solution using UV/Vis Spectroscopy gave a prominent peak at 512nm, thus confirming the nano-colloidal nature of the particle synthesized with size in the range 10-20 nm. The radiolabeling yield as determined by paper chromatography in 0.5M citrate buffer [Rf free MCl3 (M=68Ga/177Lu) =0.8-1.0; TATE functionalized Au-nanoparticle = 0-0.2] was observed to be >90 % for both the radiometals. In vitro experiments in AR42J cell lines are underway to evaluate the potential of the functionalized gold nanoparticles in comparison with the DOTA-TATE metal complexes in clinical use.

Conclusion
Water dispersible Gold NPs functionalized with TATE peptide along with DOTA chelator has been successfully synthesized. These have been successfully labelled with radiometals in reasonable yields. Further cell experiments are underway to evaluate the efficacy of the labelled Au nanoparticles.

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