# Silica Nanoparticles as a vehicle for $^{225}Ac/^{89}Zr$ delivery for use as a Theragnostic Agent in Targeted α-Therapy

**Background:** Neuroendocrine Tumors (NETs) are a derived from a group of cells that are have both "neuro" and "endocrine" properties. NETs are classified as an orphan disease as they make up ~2% of cancerous malignancy and have an occurrence of <200,000 new cases a year in the United States. These tumors can be present throughout the body; however they have a high incidence in the gastrointestinal and pulmonary systems.

Currently, only surgical removal of NETs has been curative. Surgical removal can only be applied to large distinct tumors and cannot be used for smaller metastatic lesions. NETspot ($^{68}$Ga-DOTATATE) was FDA approved in June 2016 for the imaging of neuroendocrine tumors using an otreotate derivative (DOTATATE), that includes the macrocyclic chelator DOTA (1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid), which targets the somatostatin receptor on NETs. Recently, $^{177}$Lu-DOTATATE (Luthera©) was FDA approved in January 2018 for the treatment of NETs employing peptide receptor radionuclide therapy (PRRT). This treatment has been associated with an increase in progression free survival and overall survival. Lutetium-177 is a beta emitter with a 6.6 day half-life and a maximum beta energy of 498 keV. Beta particles have low linear energy transfer (LET) (~0.2 keV/um) meaning they deposit their energy over a long path length resulting in dose to tissue millimeters in distance from the targeted tumor site. While this may be advantageous for larger tumors, smaller lesions treated with this modality result in a larger dose to healthy tissue and less absorbed dose to the tumor.

Targeted α-therapy (TAT) is a promising treatment method for small tumors and metastases. The high linear energy transfer of α-particles causes double strand DNA breaks inducing cell death. With traditional chelators, the recoil effect during α-decay causes the chelation bonds to break (daughter radionuclides can travel ~80 nm in tissue). This is a problem for α-emitters that have long decay chains, like $^{225}$Ac, because the radioactive daughter radionuclides are released from the tumor site. This decreases the dose delivered in the tumor site and increases the dose delivered to healthy tissue throughout the body. Silica nanoparticles (SNPs) are a promising solution as additional layers of silica or gold can be added after radiolabeling, increasing the retention of daughter radionuclides at the tumor site. Another challenge in working with $^{225}$Ac is the inability to image the biological agent. SNPs allow for the co-incorporation of PET radionuclide $^{89}$Zr and TAT radionuclide $^{225}$Ac resulting in a theragnostic agent (one that can be used to simultaneously image and treat the diseased cells). SNPs are also cheap, biologically inert, and can be functionalized with peptides to target specific receptors overexpressed in tumors.

**Methods:** Mesoporous silica nanoparticles (MSNPs) were synthesized using triethyl- and trimethyl-orthosilicate as silica precursors in the presence of a cationic surfactant (cetrimonium bromide). Experiments determining the optimal pH and temperature for the binding of $^{89}$Zr and $^{225}$Ac to MSNPs were carried out between pH 4.5 and 6.5 and temperature ranging from 25-75°C. Once optimal conditions were determined, binding kinetics were investigated to establish times required for radiolabeling. Furthermore, nanoparticles were synthesized utilizing the Stöber method (nonporous SNPs) to determine if $^{225}$Ac and $^{89}$Zr could be incorporated during nanoparticle production. Gold coating of MSNPs was obtained by surface amination followed by the attachment of small gold nanoparticles that acted as seeds for the formation of a gold metal layer produced by electroless (chemical reduction) plating using $HAuCl_4$ and $NH_2OH{\cdot}HCl$.

**Results:** Optimal conditions for radiolabeling both $^{89}$Zr and $^{225}$Ac were determined to be

ammonium acetate pH 5.5 at 75°C. Radiolabeling yields for the binding of $^{225}$Ac and $^{89}$Zr to MSNPs in ammonium acetate, pH 5.5, showed ~87% and ~80% radiochemical yield, respectively. Actinium-225 was co-incorporated into the Stöber SNPs with a radiochemical yield of 91%. A uniform gold coating was obtained on ~90% of the MSNPs. Further optimization is underway to improve coating yields or separate gold-coated SNPs from those without gold coating.

**Conclusions:** We have successfully radiolabeled MSNPs with both $^{225}$Ac and $^{89}$Zr and directly incorporated $^{225}$Ac into SNPs produced by the Stöber. Future studies will include analyzing the daughter retention efficiency of these nanoparticles in addition to the functionalization of these nanoparticles with the octreotide peptide for initial in vitro studies.

**Lay Abstract**

Neuroendocrine Tumors (NETs) are a derived from a group of cells that are have both “neuro” and “endocrine” properties. NETs are classified as an orphan disease as they make up ~2% of cancerous malignancy and have an occurrence of <200,000 new cases a year in the United States. These tumors can be present throughout the body; however, they have a high incidence in the gastrointestinal and pulmonary systems.

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Lutetium-177 is a beta emitter with a 6.6-day half-life. Beta particles deposit their energy over a long path length resulting in dose to tissue millimeters in distance from the targeted tumor site. While this may be advantageous for larger tumors, smaller lesions treated with this modality result in a larger dose to healthy tissue and minimal to the tumor site. Targeted α-therapy (TAT) is a promising treatment method for small tumors and metastases. While beta particles travel a long distance, α-particles have a lot of energy and travel a very short range (~100x smaller than that of beta particles) depositing ~10 times as much energy in a fraction (1/100) of the distance of beta particles. This high energy deposition results in irreparable DNA damage resulting in cell death. While targeted alpha therapy is promising a major issue with this type of therapy is the multiple daughter radionuclides. When alpha decay happens the daughters travel ~80nm detaching from the targeting vector (such as DOTATATE). This allows radioactivity to leave the tumor site and deposit dose throughout the body, decreasing the dose delivered to the tumor. Silica nanoparticles (SNPs) are a promising solution as additional layers of silica or gold can be added after radiolabeling, increasing the retention of daughter radionuclides at the tumor site. Another challenge in working with $^{225}$Ac is the inability to image the biological agent. SNPs allow for the co-incorporation of Positron Emission Tomography (PET) radionuclide $^{89}$Zr and TAT radionuclide $^{225}$Ac resulting in a theragnostic agent (one that can be used to simultaneously image and treat the diseased cells). SNPs are also cheap, biologically inert, and can be functionalized with peptides to target specific receptors overexpressed in tumors. This allows for the production of a theranostic agent; one that images and treats the cancer at the same time.