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

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Introduction

- Peptide receptor radionuclide therapy (PRRT) is used to selectively deliver radiation doses to induce apoptosis in cancer cells
- PRRT traditionally uses β- emitters because the daughter radionuclides of α emitters (like ^{225}Ac) are difficult to retain
- α particles have a higher linear energy transfer than β- particles which is more lethal to cells
  - 50-230 keV/μm vs. ~0.2 keV/μm
- Advantages of silica nanoparticles (SNPs) as a vehicle:
  - Trap metals and daughter radionuclides
  - Functionalized with peptides
  - Biologically inert
  - Co-incorporation of ^{89}Zr for PET imaging
- The resulting SNPs will be a theragnostic agent that can simultaneously treat and image tumors with ^{225}Ac and ^{89}Zr, respectively

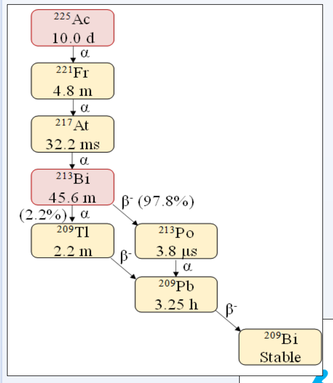


Figure 1: ^{225}Ac decay chain

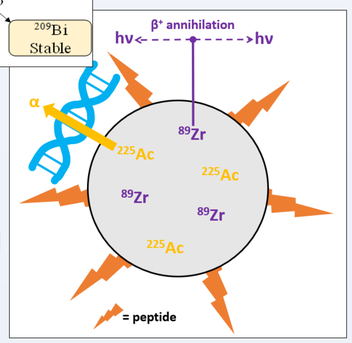
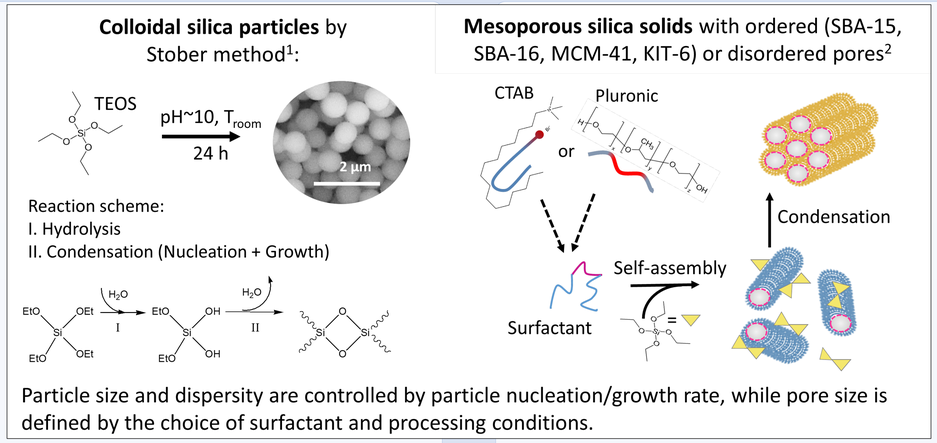


Figure 2: SNP functionalized with a peptide showing a doubles stranded DNA break induced by ^{225}Ac α-decay and PET imaging capabilities from ^{89}Zr

Objectives

- Produce SNPs that encapsulate both ^{225}Ac and ^{89}Zr
- Coat SNPs to help contain the radioactive daughters of ^{225}Ac
- Attach an octreotide peptide to the gold-coated SNPs for active targeting of Neuroendocrine Tumors.
- Study the in vitro and in vivo stability of the octreotide functionalized SNPs radiolabeled with ^{225}Ac and ^{89}Zr



Materials and Methods

Direct incorporation of ^{225}Ac was performed via the Stöber method.[1] This is shown on the left side of the above figure. Briefly, TEOS (Tetraethyl orthosilicate) is hydrolyzed and then reacts to form polymers, which then turn into nanoparticles. Particle size is controlled by growth rate. ^{225}Ac was added to this process to determine if ^{225}Ac would incorporate into the SNPs as they were formed.

Indirect incorporation of ^{225}Ac and ^{89}Zr was performed via incubation with mesoporous SNPs (MSNPs). The silanol groups are negatively charged at pH > 5 attracting positively charged ^{225}Ac and ^{89}Zr cations. Two types of MSNPs were studied: MSNPs made with the surfactant CTAB (Cetrimonium bromide) as the porogen[2] and MSNPs made with tannic acid as the porogen.[3] Effect of pH and temperature on radiolabeling yields were measured.

Optimum conditions for radiolabeling MSNPs with ^{225}Ac were determined to be in 0.1M Ammonium Acetate buffer pH 5.5 at 70°C. Radiolabeling of MSNPs was then studied at various time points for both the tannic acid and CTAB MSNPs. The radiolabeling of ^{89}Zr tannic acid and CTAB MSNPs was also studied under these conditions.

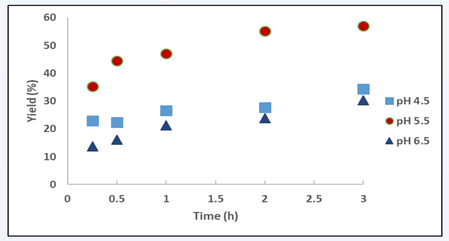
As the daughter radionuclides have ~70 keV kinetic energy simulations were performed to deterimine the distance traveled in SNPs. The recoil of the ^{221}Fr through silica with and without a gold coating was simulated using the monte carlo program SRIM (Stopping Range of Ions in Matter).

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 $NH_2OH{\cdot}HCl$.[4]

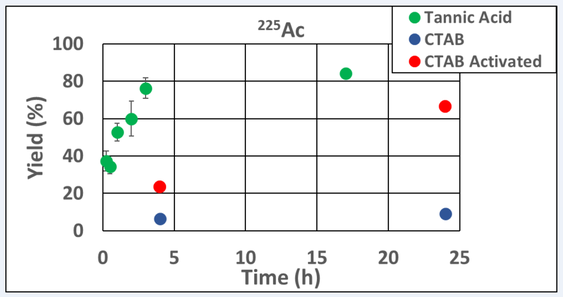
Results

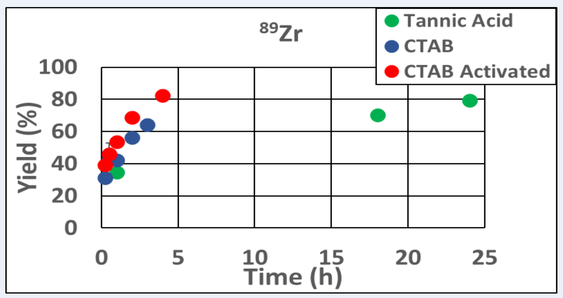
Direct incorporation of ^{225}Ac via the Stöber method was found to be 91%. Our nanoparticles were ~ 300nm in diameter. Experiments to minimize the particle size are currently underway.

The affect of pH on ^{225}Ac is shown below. Optimum pH was found to be pH 5.5.

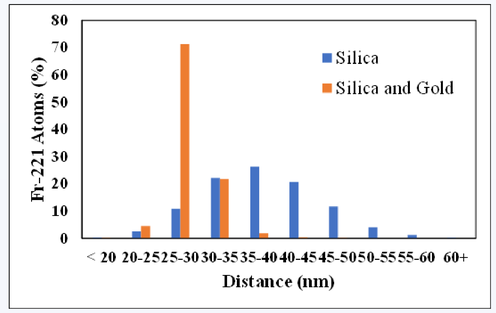


Radiolabeling yields of ^{89}Zr and ^{225}Ac into CTAB and Tannic Acid MSNPs are shown below. ^{89}Zr shows better binding affinity under all conditions compared to ^{225}Ac. Highest ^{225}Ac yields were achieved with the Tannic Acid MSNPs

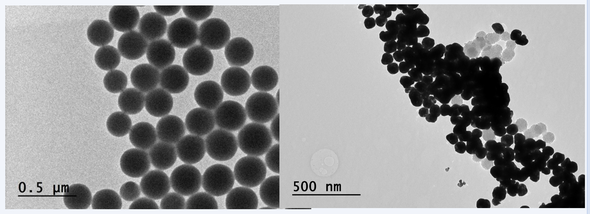




SRIM simulation of ^{221}Fr recoil is shown below. Based on these results a dense gold shell is necessary to limit the size of our SNPs to <100 nm



We were able to completely coat MSNPs with gold (figure below left uncoated/right coated). While most of the MSNPs were completely coated some MSNPs did not get coated at all. We are working to determine how we can coat all MSNPs or separate gold-coated from non-coated.



Conclusions

We have produced ^{225}Ac radiolabeled nanoparticles using both the direct and indirect methods. Furthermore, ^{89}Zr radiolabeling was verified under the same conditions for the indirect method. Direct incorporation of ^{89}Zr is in progress. We have also shown that a gold coating can be obtained on our MSNPs, which will help with daughter retention. Future work will evaluate ^{225}Ac daughter retention in both the direct and indirect methods with and without gold coating. Additionally, experiments are underway to attach the peptide to the nanoparticles for direct targeting.

References

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[3]Gao, Z. et al. Chem. Mater. 26, 2030-2037 (2014).

[4]Ignacio-de Leon et al. MRS Online Proceedings Library Archive 1502 (2013).

Acknowledgements

We would like to thank The Education and Research Foundation for Nuclear Medicine and Molecular Imaging and the Neuroendocrine Tumor Research Foundation for funding this research.