Gold Coated Nanoparticles as a vehicle for $^{225}Ac/^{89}Zr$ delivery for use as a Theragnostic Agent in Targeted a-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 nanoparticles (NPs) as a vehicle for Targeted Alpha Therapy (TAT):
  - Trap metals and daughter radionuclides
  - Functionalized with peptides
  - Co-incorporation of ^{89}Zr for PET imaging
- The resulting NPs will be a theragnostic agent that can simultaneously treat and image tumors with ^{225}Ac and ^{89}Zr, respectively

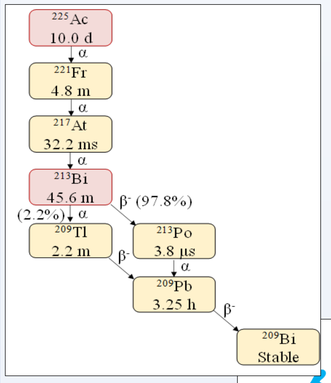


Figure 1: ^{225}Ac decay chain showing multiple alpha emitting daughters

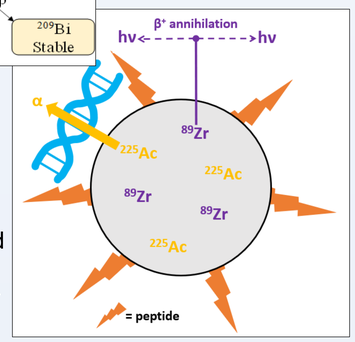


Figure 2: NP functionalized with a peptide showing a doubles stranded DNA break induced by ^{225}Ac α-decay and PET imaging capabilities from ^{89}Zr

Objectives

- Produce NPs that encapsulate both ^{225}Ac and ^{89}Zr
- Coat NPs with gold to help contain the radioactive daughters of ^{225}Ac
- Study the stability and daughter retention of ^{225}Ac loaded NPs
- Attach an octreotide peptide to the gold-coated NPs for active targeting of Neuroendocrine Tumors.

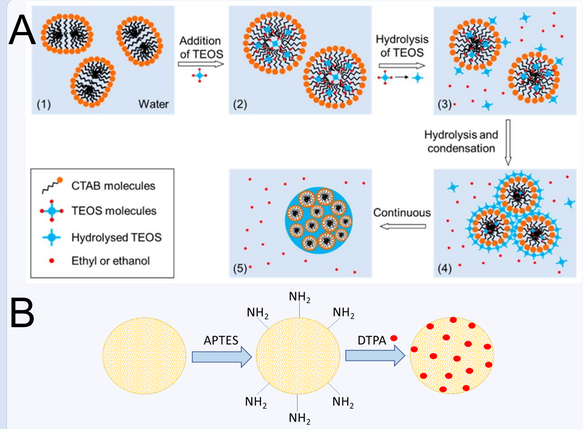


Figure 3: A) Synthesis of Mesoporous Silica Nanoparticles (MSNPs)[1] **B)** Attachment of DTPA to MSNPs

Materials and Methods

MSNPs were made with the surfactant CTAB (Cetrimonium bromide) as the porogen[2] aminated with APTES (3-aminopropyl)triethoxysilane) and functionalized with DTPA (Diethylenetriamine-pentaacetic acid). The DTPA was added to aid in ^{225}Ac radiolabeling (Figure 3).

DTPA functionalized MSNPs were radiolabeled with ^{225}Ac. Briefly, 1 mL of 2 mg/mL DTPA functionalized MSNPs were incubated with ^{225}Ac in ammonium acetate buffer pH 5.5 for 4 hours. At different time points radiolabeling yield was assessed via radioTLC with 0.1 M citrate pH 4.5 as a running buffer.

Iron oxide nanoparticles were also investigated due to their ability to be separated rapidly via magnetic precipitation accelerating the synthesis process (Figure 4).[3] Iron oxide nanoparticles were synthesized with ^{225}Ac and/or ^{89}Zr and radiolabeling yield assessed via magnetic precipitation and gamma analysis of the supernatant and nanoparticles. Chemical stability of ^{225}Ac radiolabeled iron oxide nanoparticles was investigated in PBS, HEPES, BSA, and 0.01, 0.1, and 1 M DTPA over 7 days. Gold coating of Iron oxide nanoparticles was also investigated by incubation iron oxide nanoparticles with $AuCl_3$ using trisodium citrate as a reducing agent.

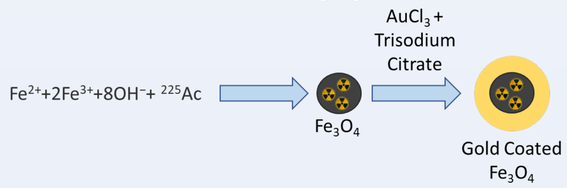


Figure 4: Synthesis of gold coated ^{225}Ac radiolabeled iron oxide nanoparticles

Results

DTPA functionalized MSNPs were successfully radiolabeled with ^{225}Ac. Radiolabeling yields of 83 ± 1 % were obtained after 4 hours (Figure 5). MSNPs were successfully coated with 25 nm of gold (Figure 6)

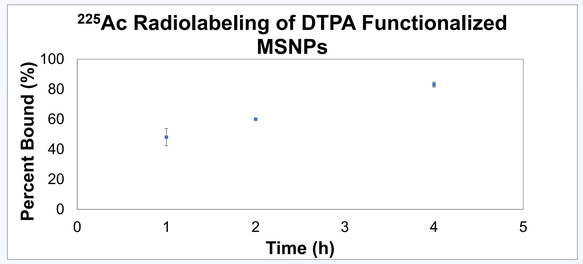


Figure 5: ^{225}Ac radiolabeling of DTPA functionalized MSNPs vs time

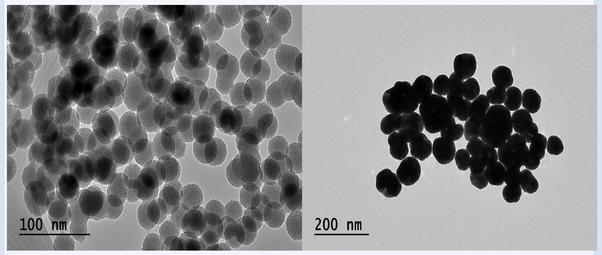


Figure 6: Left: 100 nm MSNPs Right: 100nm MSNPs coated with 25 nm of gold.

Iron oxide nanoparticles were successfully synthesized coincorporating both ^{89}Zr and ^{225}Ac with greater than 90% radiochemical yield. Radiolabeled nanoparticles showed good chemical stability in PBS, HEPES pH 7 and 1% BSA. Degradation of radiolabeled nanoparticles increased with increasing concentrations of DTPA, which was expected (Figure 7). Gold coating these nanoparticles is expected to increase chemical stability.

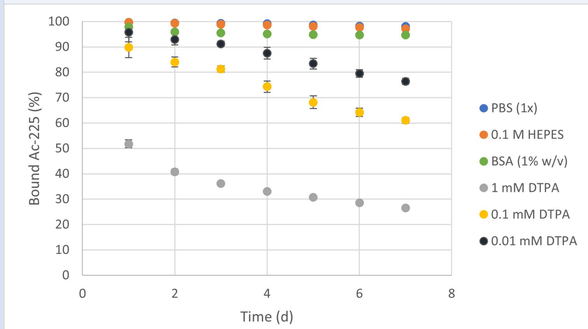
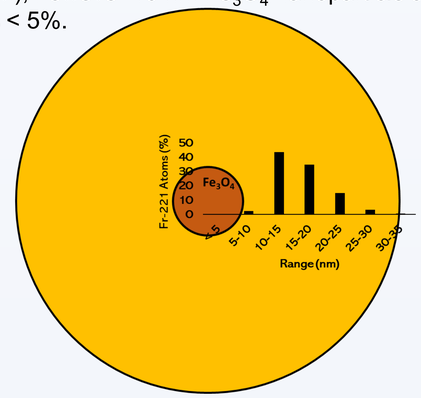


Figure 7: Chemical stability of radiolabeled iron oxide nanoparticles in PBS, 0.1M HEPES, 1% BSA, 0.01 M, 0.1 M and 1 M DTPA.

Gold coating of iron oxide nanoparticles is needed to contain the daughters of actinium. Initial attempts at gold coating have shown lots of aggregate formation and optimization is underway. Figure 8 shows a 10 nm iron oxide nanoparticles coated with 30 nm of gold is sufficient to trap > 99% of the first actinium daughter radionuclide ^{221}Fr when using the simulation code Stopping Range of Ions in Matter (SRIM), however 10 nm Fe_3O_4 nanoparticle alone traps < 5%.



Conclusions

We have successfully radiolabeled both DTPA functionalized MSNPs and iron oxide nanoparticles with ^{225}Ac and ^{89}Zr. Successful optimization of gold coating MSNPs has also been obtained. Iron oxide nanoparticles have shown good chemical stability in PBS, HEPES buffer and 1% BSA, however when contacted with various concentrations of DTPA degradation occurs. Gold coating these nanoparticles will increase chemical stability in addition to encapsulating the daughter radionuclides within. Next steps are to optimize gold coating of iron oxide nanoparticles and attaching octreotide peptides for targeting NET tumors.

References

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Acknowledgements

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