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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Background/Significance to NETS

Neuroendocrine Tumors (NETs) are a derived from a group of cells that are have both "neuro" and "endocrine" properties. 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 a-therapy (TAT) is a promising treatment method for small tumors and metastases. The high linear energy transfer of a-particles causes double strand DNA breaks inducing cell death. With traditional chelators, the recoil effect during a-decay causes the chelation bonds to break (daughter radionuclides can travel ~80 nm in tissue). This is a problem for a-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 and iron oxide nanoparticles (TNPs) are a promising solution as additional layers of 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. TNPs 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). TNPs are also cheap, biologically inert, and can be functionalized with peptides to target specific receptors overexpressed in tumors.

Materials and Methods

Silica and iron oxide nanoparticles (TNPs) were synthesized with and without a gold coating and radiolabeled with ^{89}Zr and or ^{225}Ac. Iron oxide nanoparticles were developed in addition to silica as a way to speed up the separation process, which can be done within minutes with a magnet as opposed to hours with centrifugation. Both ^{89}Zr and ^{225}Ac were successfully incorporated into iron oxide nanoparticles with > 95% radiochemical yield. Stability studies were performed on the radiolabeled iron oxide nanoparticles at 37°C and in PBS, 0.1 M HEPES pH 7.5 and 1mM DTPA in 0.1 M HEPES pH 7.5 and analyzed for ^{225}Ac retention over a period of 7 days. Gold coating of the iron oxide nanoparticles was performed by electroless reduction in a sodium

citrate solution and the particles were analyzed by TEM (transmission electron microscopy) with EDS (energy dispersive spectroscopy) for elemental analysis. Mesoporous silica nanoparticles were functionalized with DTPA and DOTA in attempts to improve ^{225}Ac radiolabeling yields.

Results

Both ^{89}Zr and ^{225}Ac were successfully incorporated into iron oxide nanoparticles with > 98% radiochemical yield. ^{225}Ac radiolabeled iron oxide nanoparticles were found to be stable at 37°C and in PBS and 0.1 M HEPES pH 7.5 for 7 days, however they decomposed in 0.1 mM DTPA in 0.1M HEPES pH 7.5 as expected. Coating with gold should improve the stability in DTPA and serve as a measure of extent of gold coating on the nanoparticles as we can't use TEM to analyze radioactive particles. Iron oxide nanoparticles were successfully coated with gold, however aggregate formation was observed.

Conclusions

We have successfully radiolabeled iron oxide nanoparticles with both ^{225}Ac and ^{89}Zr. Gold coating of the particles is successful but results in aggregate formation. Studies are underway to improve aggregate formation of these particles for stability and daughter retention studies. 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.