

Development of radiolabeled alginate micro- and nanoparticles for treatment of cancer

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Scientific Session

Part of:

SS22 Innovative strategies for Radiotracer Development: from Bench to Preclinical Testing 12:45 PM - 2:00 PM

International Best Abstract Award Winner Molecular Targeting Probes-Radioactive & Nonradioactive Oral

Info

Purpose/Background:

The development of radiotherapeutics is advancing rapidly in the field of cancer therapy. Progress in targeted delivery using antibodies or peptides, in combination with alpha-particle emitting radionuclides, is demonstrating efficacy and reduced collateral damage to normal tissue. The 100 μm range α -particle radiation offers a unique mechanism of action, confining the radiation to the tumor cells to which the radiopharmaceuticals bind. Radionuclides are bound to the targeting vector by a chelator. However, the large atomic size, recoil energy from the alpha particle emission, and the chemical differences between mother and daughter nuclides make it challenging to develop chelators that can stably bind alpha-emitting radionuclides. A stable chelator is crucial in targeted alpha therapy to prevent off-target toxicity from radionuclides released from the targeting molecule and to maximize the therapeutic efficacy.

In this study, we present the development of a new type of micro- or nanoparticle that can stably chelate alpha-emitting radionuclides. The particles are derived from the natural biopolymer alginate, which is a straight-chain polysaccharide found in seaweed and kelp. Alginate can bind and cross-link with multivalent cations such as calcium to form gels. We hypothesized that alginate could also form insoluble particles when complexed with calcium and additionally chelate radionuclides. Micrometer- or nanometer-sized particles can be functionalized by conjugating specific cell receptor-binding peptides to the particles. In this study, we conjugated RGD (Arginine-Glycine-Aspartic Acid) peptides to the particles. RGD binds to cell surface integrins, particularly the $\alpha\text{v}\beta 3$ integrin. In this study, we have used the alpha-emitter actinium-225 (^{225}Ac). Our goal is to use these functionalized, alpha-emitting particles to treat glioblastoma.

Methods:

Microparticles were made by utilizing spray dried sodium alginate and converting it to insoluble calcium alginate. The average size of these microparticles was 10-15 μm . These particles were further milled to < 600 nm in size using a Netzsch MicroCer mill. The particles were subsequently functionalized by conjugation of the RGD peptide using EDC/NHS chemistry. Initially, carbodiimide (EDC) activates carboxyl groups of alginate, which then react spontaneously with primary amines to form amide bonds. This reaction is mediated by N-hydroxysuccinimide (NHS).

Calcium alginate micro- and nanoparticles were incubated with actinium-225 chloride solution (Eckert & Ziegler) in secular equilibrium with daughters for 1 hour at room temperature. Radioactivity associated with calcium alginate particles was determined by a gamma counter (Cobra model 5000) with a 5.5" NaI scintillation crystal. Energy (KeV) windows were set to identify francium-221 and bismuth-213 gamma peaks of 218 and 440 Kev, respectively.

Results:

Radioactivity bound to the alginate particles incubated with ^{225}Ac as a function of time after first washing is shown in the figure. The red bars show radioactivity from ^{225}Ac , while the blue and green bars show the radioactivity from the decay daughters ^{221}Fr and ^{213}Bi , respectively. More than 95% of the available radioactivity from ^{225}Ac and daughters were associated with the particles at all time points.

Conclusion:

In this study, we demonstrated that alginate micro- and nanoparticles can stably chelate ^{225}Ac and its decay daughters for more than 30 days. The stable chelation of ^{225}Ac decay daughters by the alginate micro- and nanoparticles increases the total radioactive dose delivered to the cancer cells to which the particles bind, with 3 α - and 2 β -emissions. This stable chelation represents a significant and innovative advancement over current radionuclide chelators which cannot retain decay daughters. Actinium-RGD-alginate nanoparticles (ARAspheres) are now undergoing pre-clinical testing in a rodent model of glioblastoma.

