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Nanoparticles for the treatment of metastatic non small cell lung cancer with 225Ac

Non small cell lung cancer (NSCLC) is the most common form of primary lung neoplasia with nearly 40% of patients having metastasis at the time of diagnosis, resulting in a 5-year survival rate ranging from 13-36% in patients with nodal metastasis, and decreasing to as little as 2% for those with distant metastasis. Furthermore, pulmonary metastatic disease is the most common form of secondary lung tumors, being identified in 30-55% of all cancer patients. Targeted α-radiotherapy (TAT) agents have great potential for treating micro-metastatic disease, given their short, densely ionizing track length and high relative biologic effect (RBE). The use of in vivo alpha generators allows for multiple alpha decays from a single radioactive nucleus, but retaining the radioactive daughters at the target site throughout the decay process is a challenge. We present preclinical data describing a multilayered nanoparticle-antibody conjugate that can deliver multiple α radiations from the in vivo α-generator 225Ac at biologically relevant receptor sites while also containing the radioactive daughters at those sites. The layered nanoparticles (NP) consist of an 225Ac-doped (La0.5Gd0.5)PO4 core coated with four layers of GdPO4 and an outer layer of Au. These multi-shell particles combine the radiation resistance of crystalline lanthanide (Ln) phosphate to contain atoms of the therapeutic radionuclide and its radioactive daughters, the magnetic properties of gadolinium for facile separation during synthesis, and the chemistry of gold for attachment of targeting agents to the nanoparticle surface. In a proximity delivery model of cancer, 225Ac-NPs conjugated to mAb 201b resulted in a 73% decrease in the number of EMT6 colonies in the lung five days after treatment [1]. On biodistribution studies and SPECT/CT imaging, over 85% of the injected dose was delivered to the target tissue, and approximately 90% of the fourth daughter, 213Bi, was retained in the target 24 hours after injection. Competition assays demonstrated specific binding of the conjugated radiopharmaceutical to the target. Current studies are evaluating the application of these 225Ac nanoparticles to A549 NSCLC grown in a mouse orthotopic lung cancer model, while a spontaneous cancer model in canine patients is also being explored.

1. M.F. McLaughlin, J.D. Robertson, P.H. Pevsner, J.S. Wall, S. Mirzadeh, and J. Kennel, "LnPO4 Nanoparticles Doped with Ac-225 and Sequestered Daughters for Targeted Alpha Therapy,"Cancer Biotherapy and Radiopharmaceuticals 29(1), 34-41 (2014)

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