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Radioimmunotherapy Using Oxide Nanoparticles: Radionuclide Containment and Mitigation of Normal Tissue Toxicity

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Abstract

Radionuclides with specific emission properties can be incorporated into metal-chalcogenide and metal-oxide nanoparticles. Coupled to antibodies, these conjugates could be injected into the bloodstream to target and destroy non-solid tumors or target organs for radioimaging. In the first year of this project, two types of radioactive nanoparticles, CdTe:^{125m}Te and Y_2O_3:^{170}Tm were synthesized and coupled to antibodies specific to murine epithelial lung tissue. The nanoparticles successfully target the lung tissue *in vivo*. Some leaching of the radioisotope was observed. The coming year will explore other types of nanoparticles (other crystal chemistries) in order to minimize leaching.

Body of Report

Nanoparticles have been shown to couple to proteins and the resulting conjugates may find applications as targeted drug delivery systems or medical imaging diagnostic tools (Tiefenauer, Kuhne et al. 1993; Frey, Mantis et al. 1999; Akerman, Chan et al. 2002; Wang, Mamedova et al. 2002; Gao, Cui et al. 2004). These conjugates could be injected into the bloodstream to target and destroy non-solid tumors or target organs for Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) imaging (for a review of small molecule analogs see (Goldenberg 2002)). The nanoparticle based drugs may also mitigate unintentional radiotoxic effects by effectively sequestering and retaining the radionuclides and daughter products.

CdTe nanoparticles were selected for the first experiments because the techniques for synthesizing CdTe nanoparticles are well-developed and the surfaces can be easily modified to allow for protein coupling. The CdTe nanoparticles can be doped with small quantities of the radioisotope ^{125m}Te ($t_{1/2}$ = 58 days) which emits low energy 35.5 keV γ-rays with no complicating beta or alpha emission thus allowing for verification of antibody performance and nanoparticle fate within the test mice.

Cadmium telluride nanoparticles doped with ^{125m}Te were prepared based on the Peng method (Peng and Peng 2001) in which CdO reacts with ^{125m}Te metal within trioctylphosphine micelles at 250 ºC. A reaction time of 5 min affords homogeneous and unaggregated 5 nm diameter nanoparticles. The CdTe nanoparticle surfaces were derivatized by mercaptoacetic acid (Wuister, Swart et al. 2003).

The surface derivatized CdTe nanoparticles were reacted with the targeting antibodies (murine lung mouse antibodies, mAB 201B) using traditional protein coupling chemistry (Wang, Mamedova et al. 2002). The CdTe-antibody conjugates were then purified by gel filtration and column chromatography. A typical radiography gel was employed to determine the fractions of crosslinked antibody, heavy antibody-nanoparticle conjugates, and other impurities. The 200 kD fraction (one antibody plus one nanoparticle) was selected from the gel and injected into Balb/c female mice for *in-vivo* testing. The mice were sacrificed after 2 hours. Biodistribution analysis was performed by vivisection and ^{125m}Te counting of organs. Radioactivity in the skin, muscle, liver, spleen, kidney, intestines, heart, lung and blood was determined. For CdTe, approximately 60% of the injected dose targets the correct organ. For Y_2O_3 around 25% of the injected dose reached the target organ. Leaching was observed for some longer experiments (5 days post injection), however that was not unexpected for these nanoparticle as they were selected for surface chemistry not solubility.

FY06 will focus on the mitigation of leaching through the selection of less soluble nanoparticles. Candidate materials include CdTe/ZnS, ZrO_2, and Al_2O_3.

This project will benefit both DOE and the National Institutes of Health. The techniques developed here will have direct application to SPECT and PET imaging by providing a new delivery medium for radionuclides. The nanoparticle based delivery approach may also have specific application in lymphoma treatment, by allowing heavier and more toxic alpha-emitting metals to be delivered safely within a patient.

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