

Imaging of vascular targeted LaPO₄ nanoparticles doped with Ac-225

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Nanoparticles (NP) of diverse composition have been touted as potential carriers for various therapeutic drugs including radioisotopes. Targeting of relatively large constructs such as antibody or peptide coated NP has been shown to be efficient only when the target is a circulating lymphocyte or endothelial surface protein. In this application, the alpha emitter Ac-225 ($t_{1/2}$ 10 days) has been incorporated into LaPO₄ NP with the intent that the alpha cascade from three daughter radionuclides can provide a potent, site specific radioimmunotherapy. When Ac-225 is attached to targeting agents with standard chelation methods, the daughter radionuclides are released soon after the first decay occurs. The major aim of this NP application is to sequester the daughter radionuclides ²²¹Fr ($t_{1/2}$ 4 min), ²¹⁷At ($t_{1/2}$ 0.03 sec) and ²¹³Bi ($t_{1/2}$ 45 min) at the site of targeting. We show here by using micro SPECT/CT that ²²⁵Ac LaPO₄ NP coupled with MAb 201B to thrombomodulin, in a model of vascular targeting, accumulate rapidly in mouse lung after iv injection due to binding to the thrombomodulin expressed preferentially on lung endothelial cells. Specific targeting was demonstrated by showing that competition with excess unlabeled MAb or with NP targeted with control antibody resulted in NP being deposited chiefly in liver and spleen. Although most of the gamma rays from these radionuclides are too high in energy to be detected efficiently, micro SPECT with appropriate energy windows can be used to obtain dramatic images. Standard biodistribution techniques show that ~ 32% of the total injected dose of ²²⁵Ac LaPO₄ NP is bound in lung 1 hr postinjection yielding a value of %ID/g of >200. Simultaneous analyses of the biodistribution of ²²⁵Ac and ²¹³Bi demonstrate that more than half of the daughter radionuclides are retained in NP. We conclude that Ac-225 incorporated in LaPO₄ NP can be a potent radioimmunotherapeutic when targeted efficiently to the appropriate site and that specific delivery can be monitored by SPECT imaging.

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