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In vivo and in vitro analysis of In-111 and Cu-64 labeled PNA-peptides in mice

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The *B-cell lymphoma/leukemia-2 (bcl-2)* gene is overexpressed in non-Hodgkin's lymphoma. It produces a protein that blocks apoptosis and is strongly correlated with increased relapse rates after chemotherapy and poor overall survival. In this study, radiolabeled peptide nucleic acid (PNA) probes were delivered to bcl-2 mRNA-deficient and -rich tumor models in mice to determine whether the probes are specific for cells that express bcl-2 mRNA and to differentiate between positive and negative bcl-2 tumors. A peptide, Tyr^3-octreotate, was attached to the PNA to target somatostatin receptors on the surface of tumor cells, where the PNA can then be delivered into the cell and bind to bcl-2 mRNA. In vitro efflux studies of ^{111}In-DOTA-anti-*bcl-2*-PNA-Tyr^3-octreotate were performed in somatostatin receptor positive Mec-1 (*bcl-2* positive) and Ramos (*bcl-2* negative) cells. The cell associated radioactivity was 14.9% in Ramos cells, as compared with 60% in Mec-1 cells at 4 h post-injection, signifying that PNA is washed out of the Ramos cells while there is higher retention in Mec-1 cells. In in vivo studies, ^{111}In-DOTA-anti-bcl-2-PNA-Tyr^3-ocreotate and a modified compound, ^{64}Cu-DOTA-anti-bcl-2-PNA-T(s)-Tyr^3-octreotate, were injected into Ramos-bearing nude mice and Mec-1-bearing SCID mice, and organ uptakes were compared at 48 h post-injection. The results showed a 0.18% injected dose per gram of tissue (ID/g) tumor uptake with the ^{111}In labeled compound in Ramos mice and 1.33% ID/g in Mec-1 mice. The ^{64}Cu labeled compound in the Ramos mice showed a 0.69% ID/g tumor uptake and 1.12% ID/g in Mec-1 mice. Both studies showed a significantly lower tumor uptake in Ramos mice than in Mec-1 mice, concluding that the PNA in both compounds are specific for bcl-2 mRNA.