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In vitro evaluation of In-111-DOTA-anti-bcl-2-PNA-Tyr-3-octreotate in Chronic Lymphocytic Leukemia cells

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The B-cell lymphoma/leukemia-2 (bcl-2) gene is overexpressed in many cancers. This gene increases cell survival by blocking apoptosis, or programmed cell death. The objective of this study was to evaluate radiolabeled peptide nucleic acid (PNA)-peptide conjugates targeting bcl-2 gene expression. DOTA-anti-bcl-2-PNA-Tyr-3-octreotate conjugate was labeled with In-111. Uptake, internalization, and efflux studies were performed in the human chronic lymphocytic leukemia (CLL) cell line Mec-1, which expresses both somatostatin receptors and bcl-2 mRNA. In the conjugate, octreotate is the somatostatin receptor ligand. Receptor and mRNA binding were also evaluated. Internalization of In-111-DOTA-anti-bcl-2-PNA-octreotate increased from 58.29% at 1min to 67.9% at 15min and reached 81% at 4h, whereas the internalized In-111-DOTA-Tyr-3-octreotate in Mec-1 cells started from 31.1% at 1min and gradually increased to 49.28% and 66.1% at 15min and 4h, respectively. Efflux analysis of Mec-1-In-111-DOTA-anti-bcl-2-PNA-Tyr-3-octreotate showed that 84.9% of radioactivity remained in the cells after 1min incubation and 60.0% of cell associated radioactivity was retained 4h later. Analysis of In-111-DOTA-Tyr-3-octreotate showed the cell associated radioactivity dropped from 85.1% at 1min to 69.1% at 4h.The western blot assay study showed a 51.0% bcl-2 protein synthesis inhibition by treatment with DOTA-anti-bcl-2-PNA-Tyr-3-octreotate. As a result, a peptide conjugate, which contains two molecular functions, was developed. These functions are receptor mediated tumor cell delivery and oncogene mRNA targeting. This agent has the potential to be used for detection of tumor bcl-2 expression by non-invasive molecular imaging.