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Heterodimer Peptide Based on RGD and NPY Analog for Breast Tumor Targeting

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Heterodimer peptides targeting more than one receptor target can be advantageous as tumors can simultaneously express more than one receptor type. The design of heterodimer peptides can significantly increase the avidity and specificity of the contrast agent due to simultaneous binding to more than one type of receptor or at least one receptor independently, compared to their corresponding monospecific counterparts. A heterodimer molecule consisting of cyclic RGD and NPY analog motifs in a single probe is an attractive approach, as both receptors are overexpressed simultaneously in breast cancer. We hypothesize that a peptide ligand recognizing both αvβ3 integrin and NPY receptors will be advantageous because of its dual-receptor-targeting ability, which could enable the determination of disease location, monitoring of pathological and molecular changes associated with payload delivery, as well as a comprehensive view of the material behavior in vivo that can be utilized to guide therapeutic and diagnostic interventions. The HYNIC-cRGDfk-NPY peptide was radiolabeled with 99mTc using tricine/EDDA as co-ligand. The cellular-specific binding of [99mTc]HYNIC-cRGDfk-NPY was evaluated on different cell lines as well as with a blocking experiment on MCF-7 and MDA-MB231 (human breast cancer cells). The proof-of-concept of tumor-targeting was performed through ex vivo biodistribution in normal mice, MCF-7 and MDA-MB231 tumor-bearing mice also in SPECT/CT images. By using tricine/EDDA as a coligand, labeling yield was more than 97%. The in vitro cell uptake test showed that this radiolabeled peptide had a good affinity to MDA-MB231 and MCF-7 cells. The in vivo results showed a tumor/muscle ratio of 5.65 ± 0.94 for MCF-7 model, and 7.78 ± 3.20 for MDA-MB231 Also, tumor uptake was reduced significantly from 9.30% to 4.41% (MCF-7) and from 4.93 % to 2.3% (MDA-MB231) in blocking study whereas 500-fold molar excess of cold peptide was injected 30 min prior to the injection of related radioconjugated peptide suggesting the potencial of heterobivalent radioligand [99mTc]-HYNIC-cRDGfk-NPY to target breast tumors targeting.