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Evaluation of a new series of copper-64-nota-bombesin targeted radiopharmecuticals with PET imaging potential

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Tissue-specific radiopharmaceuticals having promise as diagnostic and therapeutic targeting vectors for human cancers is of significant interest. In recent years, our group and many others have focused upon design and development of targeting vectors having high selectivity and affinity for the gastrin-releasing peptide receptor (GRPr). GRP receptors are known to be over-expressed on a variety of malignancies including breast, lung, pancreatic, and prostate cancers. Bombesin (BBN), an amphibian analogue of mammalian GRP, has demonstrated the ability to bind with high affinity and specificity to the GRP receptor. In this study, we report the synthesis of the bifunctional chelating agent (BFCA) 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA) and conjugation to the biologically active BBN targeting vector. Bombesin conjugates were derived of the form, NOTA-X-BBN (X = GGG, SSS, ßAla, 5Ava, and 8Aoc). The unligated BBN [7-14] peptides with spacer groups were synthesized by solid-phase peptide synthesis (SPPS) and purified by reverse phase-high performance liquid chromatography (RP-HPLC). NOTA chelator was conjugated to the N-terminal primary amine of BBN manually. The final NOTA-X-BBN derivatives were purified by RP-HPLC and their chemical constitution verified. [^{64}Cu-NOTA-X-BBN]-conjugates were prepared by addition of $^{64}CuCl_2$ to a buffered solution containing the conjugate followed by purification *via* RP-HPLC. *In vivo* studies of [^{64}Cu-NOTA-8-Aoc-BBN]-conjugates in normal CF-1 mice showed receptor-specific uptake in normal pancreatic tissue, an organ known to express the GRPr in very high numbers. Furthermore, studies in human-prostate tumor-bearing mice have demonstrated the ability of [^{64}Cu-NOTA-8-Aoc-BBN] to undergo receptor-specific tumor uptake. Diagnostic positron emission tomography (PET) imaging using this conjugate was successful in resolving xenografted tumors in a mouse model. Both normal and tumor-bearing mice exhibited low liver accumulation of Cu-64, a known complication of ^{64}Cu-containing radiopharmaceuticals. Further studies are needed to verify the efficacy of [^{64}Cu-NOTA-8-Aoc-BBN] to target other human malignancies.