Radiolabeled Peptide for Diagnosis and Therapy - Wynn A. Volkert, Ph.D.
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Summary: A wide variety of radiolabeled peptides have been and are being designed and studied for in vivo targeting of cognate receptors that are uniquely or overexpressed on human cancer cells. This lecture highlights results obtained during the development process and progress made with two different peptide-receptor systems, i.e., bombesin (BB) analogues and alpha-melanocyte stimulating hormone (α-MSH) analogues. Radiotracers based on BB peptides target several human cancers (including prostate, breast and pancreatic cancers) while those based on α-MSH target melanoma tumors. These peptide systems have demonstrated important promise in experimental tumor bearing animal models. As a result, BB and α-MSH peptide conjugates labeled with a variety of radionuclides are being developed as potential radiopharmaceuticals for either molecular imaging or targeted radiotherapeutic applications in the clinical setting.

Objectives:

1. Summarize results of studies to design and characterize radiolabeled BB and α-MSH peptide conjugates at the chemical and in vitro levels.

2. Discuss strategies used for optimizing tumor uptake and pharmacokinetic properties of BB and α-MSH constructs.

Review results of studies in rodent animal models with various radionuclides during the phases of development of these types of radiotracers as diagnostic imaging or radiotherapeutic agents.

Radiolabeled peptides that specifically target cognate receptors that are uniquely or overexpressed on cancer cells have been designed and investigated by scientists across the globe for well over a decade (1-4). A wide variety of novel constructs have been and are being identified and developed for diagnostic and therapeutic applications in human cancer patients (4-8). The most outstanding example of successes in this arena resulted from development of radiolabeled peptides that are capable of high in vivo targeting of somatostatin receptor expression on cancerous tumors (1,4,9,10). This work has paved the way for exploration of radiotracer development with a multitude of other receptor systems. This presentation highlights strategies to design and characterize radiolabeled peptides that bind with high affinity and specificity to the bombesin (BB) family of receptors and the melanocortin-1 receptor to enable long term retention of the radiotracer in cancer cells. Results from selected studies with these radiolabeled peptides in rodent animal models to assess their potential for either to molecular imaging or targeting radiotherapeutic applications in humans is reviewed.
The bombesin receptor family is comprised of four receptor subtypes: neuromedin B receptor (BB1), gastrin releasing peptide (GRP) receptor (BB2), the orphan receptor subtype-(BB3) and the bombesin receptor subtype (BB4) (5). While the majority of the radiolabeled BB peptides emphasize targeting GRP receptors, there is increasing interest in developing radiotracers that also target the BB1 and BB3 subtypes (11-12). Many of the BB peptide-conjugates are analogues of the truncated bombesin [1-14] molecules in which the radiometallated chelate is linked to the N-terminal end of the peptide (5,12-17). BB conjugates labeled with a variety of radiometals (including Tc-99m, In-111, Cu-64, Re-188, Lu-177, and Y-90) have been evaluated for potential utilization for diagnostic or therapeutic applications. The majority of these radiolabeled BB analogues bind to the BB receptors found on the surface of human cancer cells in an agonistic manner to initiate receptor-mediated endocytosis to effect maximization of intracellular residualization. Variations of the chelate moiety, linker group and BB(7-14) binding region on the peptide targeting moiety provide for modifications in tumor uptake and retention, deposition in normal organs and pharmacokinetics. Radiolabeled BB analogues have been identified that hold promise for a diagnostic agent or for treatment of human cancers that overexpress BB receptors (including, breast, prostate and pancreatic) (4,5,7,11-13, 16,18). Examples of radiolabeled BB analogues that are capable of in vivo targeting of human cancerous tumors with high specificity will be discussed.

Clinical and pre-clinical results from targeted therapy studies with alpha emitting radionuclides have underscored their potential for the treatment of blood borne cancers as well as solid tumors and metastases (19-23). At the University of Missouri-Columbia, peptide targeted alpha-therapy has been examined for the treatment of melanoma. Early melanoma tumor diagnosis and prompt surgical removal are a patient’s best hope for a cure. Unfortunately, metastatic malignant melanoma is resistant to current chemotherapy and immunotherapy regimens, resulting in very poor survival statistics (24,25). A novel class of cyclic peptides was developed that target and are internalized by the melanocortin-1 receptor, over-expressed on melanoma cells (26,27). The melanoma-targeting peptide, DOTA-CCMSH, was radiolabeled with $^{212}$Pb, the parent radioisotope of the alpha-particle emitter $^{212}$Bi, for radiotherapy and $^{203}$Pb for a “match-pair” imaging agent. Biodistribution studies in B16/F1 melanoma bearing C57 mice demonstrated that $^{203}$Pb[DOTA]-CCMSH exhibited high tumor uptake and retention. The disappearance of whole-body radioactivity was rapid yielding high tumor to background ratios as illustrated in micro SPECT imaging studies. Pre-clinical therapy studies of B16/F1 and TXM-13 melanoma bearing mice were performed with $^{212}$Pb[DOTA]-CCMSH. The $^{212}$Pb labeled peptide was used for the radiotherapy studies since it delivers approximately 10x the dose per unit of administered activity compared to $^{212}$Bi[DOTA]-CCMSH alone (23,28). Treatment with 50 µCi and 100 µCi doses of $^{212}$Pb-[DOTA]-ReCCMSH prolonged the mean life of B16/F1 tumor mice from 14.6 to 22.0 days (P=0.004) and 28.0 days (p=0.002), respectively. The 200 µCi treatment group exhibited the best survival statistics (45.0 days mean survival, P=0.01). Forty-four percent of the mice receiving a 200 µCi dose and 20% of the mice from the 100 µCi treatment group were free of tumor and survived the entire 120-day study (28). Ongoing therapy studies of amelanonic TXM-13 human melanoma bearing scid mice confirm the anti-melanoma therapeutic effects of $^{212}$Pb-[DOTA]-ReCCMSH treatment. Mice treated with 50 µCi or 100 µCi of
\(^{212}\text{Pb-[DOTA]-ReCCMSH}\) showed significantly reduced tumor growth rates over the first 90 days of the study. Results from melanoma therapy studies using \(^{212}\text{Pb-[DOTA]-CCMSH}\) in both syngeneic and xenografted mouse melanoma animal models demonstrate the therapeutic efficacy of peptide-targeted alpha-therapy and highlight the clinical potential for the treatment of disseminated metastatic melanoma.


