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The magic bullet: Creating Indium-111 bombesin targeting vectors for use in diagnostic imaging of prostate and breast cancer

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Background: According to the American Cancer Society, over 68,000 men and women will die from prostate and breast cancer in this year alone. Prostate, breast and other cancers have been shown to express the BB2 receptor. For the past decade the Hoffman laboratory has been synthesizing radiopharmaceutical conjugates based on the Bombesin (BBN) peptide (Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2) that target the BB2 receptor for diagnosis and treatment of cancer. The radioconjugates are composed of a bombesin targeting vector, linking group, chelation moiety and a radioactive metal. One focus of our group is to investigate the efficacy of new Bombesin Targeting Vectors (BTV) which are derivatives of the BBN peptide. In the sixth position of the BTV is a D-phenylalanine amino acid. Our hypothesis is that the D-phenylalanine is responsible for significantly reducing kidney retention. Reduction of kidney retention is crucial for clinical radiotherapeutic applications because the kidney is often the dose limiting organ. In order to understand the structure function relationship of the D-phenylalanine in the BTV targeting vectors, we synthesized and evaluated the BTV peptide with the L-phenylalanine in the sixth position to determine what effect the stereochemistry has upon the in vitro receptor binding and in vivo pharmacokinetic properties of the peptide. **Methods:** The peptides were synthesized using solid phase peptide synthesis, purified using RP-HPLC, and characterized using electrospray mass spectrometry. Radiolabeling of the peptides was performed using $^{111}InCl_3$. In vitro cell binding assays and internalization and efflux studies were performed using the PC-3 human cancer cell line. In vivo pharmacokinetic studies were performed using CF-1 mice. Micro-SPECT (single photon emission computed tomography) imaging studies were performed in PC-3 SCID mice. **Results:** In vivo pharmacokinetic studies at 15 min post-injection gave 39.85 ± 5.07 %ID/g in the BB2 receptor expressing mouse pancreas for the L-Phe-BTV radioconjugate compared to 10.30 ± 0.34 for the D-Phe-BTV. Surprisingly, the kidney clearance for both radioconjugates was statistically identical. **Conclusion:** Incorporation of the L-Phe instead of the D-Phe into the sixth position of the BTV had no statistically significant effect upon the renal clearance of the radioconjugate. However, the change in stereochemistry from the L to the D-form had significant effects upon the in vivo uptake and retention of the radioconjugate. Further investigations will be conducted to understand the mechanism responsible for the difference in uptake and retention of the two Bombesin radioconjugates.