# Comparative pharmacokinetic and biodistribution studies of two novel [$^{177}$Lu]bombesin analogues for prostate cancer target therapy

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Prostate cancer is one of the most frequently diagnosed cancer in men in Brazil, second only to skin cancer. The National Cancer Institute estimates that 52 in 100,000 men will be diagnosed with prostate cancer in 2008, most of them over age 65 years. Treatment options have varied, being dependent upon stage and patient story, but once the tumour has metastasized, treatment become less effective and the cancer can progresses to a hormone refractory state characterized by high morbidity and mortality. Bombesin (BBN), a 14-aminoacid amphibian peptide homologue of mammalian gastrin-releasing peptide (GRP), has demonstrated the ability to bind with high affinity and specificity to GRP receptor, which are overexpressed on a variety of human cancers, including prostate cancer. The goal of the present work was to compare the radiolabeling with lutetium-177 ($^{177}$Lu) and the *in vivo* behavior in both normal *Balb-C* and *Nude* mice xenografted with PC3 prostate human cancer cells of new developed bombesin analogues – DOTA-X-BBN(6-14) (BBNp4) and DOTA-Y-BBN(6-14) (BBNp6), where X and Y are spacers of four and six aminoacids, respectively. Those spacers were inserted between the chelator and the binding sequence in other to improve *in vivo* properties.

Preliminary studies were done to establish the ideal labeling conditions for obtaining the highest yield of labeled BBNp4 and BBNp6. Instant thin layer chromatography (ITLC) and HPLC analysis were applied to determine free lutetium and the stability of the preparations was evaluated either after storing at 4ºC or incubation in human serum at 37ºC. Biodistribution, pharmacokinetics and single photon emission tomography studies were performed at different time intervals (5 min – 24 hours) after i.v. injection of the radiolabeled analogues in normal *Balb-C* mice and *Nude* mice with PC3 tumour xenografts .

Both analogues were successfully labeled with high yield (>98%) at optimized conditions and kept stable for more than 96 hours at 4ºC and 4 hours in human serum, but BBNp6 was more stable than BBNp4 in both analyzed conditions. *In vivo* studies

showed that plasma concentration decreased rapidly and the excretion was performed mainly by renal pathway for both developed analogues. BBNp4 and BBNp6 showed affinity for GRP receptors on PC-3 cells and the increment of two aminoacids in the spacer increased the *in vivo* uptake in PC-3 xenografts, but not in pancreas and intestine (GRP positive tissues). Moreover, the *in vivo* results were confirmed by single photon emission tomography.

Further studies are in development to evaluate the specificity and internalization of these analogues by prostate carcinoma PC-3 cells. Other modifications at the spacer will be also investigated to produce different analogues with improved pharmacokinetics and high specific receptor affinity.