



# AULA VIRTUAL de RADIOFARMACIA

Plataforma Virtual de Formación Continuada en Radiofarmacia

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## Lectura recomendada

### PEGylation of $^{99m}\text{Tc}$ -labeled bombesin analogues improves their pharmacokinetic properties

Simone Däpp, Elisa García Garayoa, Veronique Maes, Luc Brans, Dirk A. Tourwé  
Cristina Müller, Roger Schibli

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**Introduction:** Radiolabeled bombesin (BN) conjugates are promising radiotracers for imaging and therapy of breast and prostate tumors in which BN<sub>2</sub>/gastrin-releasing peptide (GRP) receptors are overexpressed. However, the low in vivo stability of BN conjugates may limit their clinical application. In an attempt to improve their pharmacokinetics and counteract their rapid enzymatic degradation, we prepared a series of polyethylene glycol (PEG)-ylated BN(7-14) analogues for radiolabeling with  $^{99m}\text{Tc}(\text{CO})_3$  and evaluated them in vitro and in vivo.

**Methods:** Derivatization of a stabilized (N<sup>Q</sup>His)Ac-BN(7-14)[Cha<sup>13</sup>,Nle<sup>14</sup>] analogue with linear PEG molecules of various sizes [5 kDa (PEG<sub>5</sub>), 10 kDa (PEG<sub>10</sub>) and 20 kDa (PEG<sub>20</sub>)] was performed by PEGylation of the ε-amino group of a β<sup>3</sup>hLys-βAla-βAla spacer between the stabilized BN sequence and the (N<sup>Q</sup>His)Ac chelator. The analogues were then radiolabeled by employing the  $^{99m}\text{Tc}$ -tricarbonyl technique. Binding affinity and internalization/externalization studies were performed in vitro in human prostate carcinoma PC-3 cells. Stability was investigated in vitro in human plasma and in vivo in Balb/c mice. Finally, single photon emission computed tomography (SPECT)/X-ray computed tomography studies were performed in nude mice bearing PC-3 tumor xenografts.

**Results:** PEGylation did not affect the binding affinity of BN analogues, as the binding affinity for BN<sub>2</sub>/GRP receptors remained high ( $K_d < 0.9$  nM). However, in vitro binding kinetics of the PEGylated analogues were slower. Steady-state condition was reached after 4 h, and the total cell binding was 10 times lower than that for the non-PEGylated counterpart. Besides, PEGylation improved the stability of BN conjugates in vitro and in vivo. The BN derivative conjugated with a PEG<sub>5</sub> molecule showed the best pharmacokinetics in vivo, i.e., faster blood clearance and preferential renal excretion. The tumor uptake of the  $^{99m}\text{Tc}$ -PEG<sub>5</sub>-Lys-BN conjugate was slightly higher compared to that of the non-PEGylated analogue (3.91%±0.44% vs. 2.80%±0.28% injected dose per gram 1 h postinjection, p.i.). Tumor retention was also increased, resulting in a



threefold higher amount of radioactivity in the tumor at 24 h p.i. Furthermore, decreased hepatobiliary excretion and increased tumor-to-nontarget ratios (tumor-to-blood: 17.1 vs. 2.1; tumor-to-kidney: 1.1 vs. 0.4; tumor-to-liver: 5.8 vs. 1.0, 24 h p.i.) were observed and further confirmed via small-animal SPECT images 1 h p.i.

**Conclusion:** PEGylation proved to be an effective strategy to enhance the tumor-targeting potential of  $^{99m}\text{Tc}$ -labeled BN-based radiopharmaceuticals and probably other radiolabeled peptides

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