radiocopper-ligand complex exhibits high in vivo stability. The appending carboxylic group enables this derivative to be conjugated to terminal amino groups in peptides. In this context, radiolabeled peptides based on bombesin derivatives represent interesting targeting vector molecules for certain varieties of cancer. This regulating peptide shows a high affinity to the gastrin-releasing peptide receptor (GRPR), which is overexpressed on a variety of tumors.

The present work reports the synthesis of bioconjugates, consisting of DMPTACN as copper chelator and stabilized bombesin derivatives as targeting vector molecules. These conjugates were radiolabeled with ^{64}Cu in the interest of developing tumor imaging agents for Positron Emission tomography (PET). In vitro binding characteristics of the [^{64}Cu]Cu-DMPTACN-bombesin conjugates in GRPR-overexpressing prostate cancer (PC-3) cells were evaluated. Biodistribution studies were performed in Wistar rats. Tumor accumulation was evaluated in NMRI nu/nu mice bearing the human prostate tumor PC-3 by small animal PET.

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Biodistribution of [^{111}In-DOTA^0,trp^8]SS-14 in sst$^+_{2/3/5}$-HEK tumor-bearing mice

Xanthippi Kotsaka[a], Aikaterini Tatsi[a,b], Panteleimon I. Marsouvanidis[a], Theodosia Maina[a], Paul Cordopatis[b], Eric P. Krenning[c], Marion de Jong[c], Berthold A. Nock[a]
[a]*COSTBM0607-WG2, IRRP, NCSR "Demokritos", Athens, Greece*
[b]*Patras University, Patras, Greece*
[c]*EMC University Rotterdam, Netherlands*

Since the five known sst$_{1\text{-}5}$ can be expressed together or in various combinations in many human tumors, research has lately been directed toward radiolabeled pansomatostatins displaying an expanded sst$_{1\text{-}5}$ affinity profile. Such radioligands may prove to be suitable for broader clinical indications than currently used sst$_2$-preferring radiopharmaceuticals, like OctreoScan ([^{111}In-DTPA^0]octreotide). We have previously reported on [DOTA^0,trp^8]SS-14, showing a pansomatostatin-like affinity profile. The ^{111}In-derived tracer, [^{111}In-DOTA^0,trp^8]SS-14, specifically localized in rsst$_2^+$ AR4-2J tumors in SCID mice. We now present first biodistribution data of [^{111}In-DOTA^0, trp^8] SS-14 in SCID mice bearing HEK tumors selectively expressing each of the hsst$_{2A}$, hsst$_3$ and hsst$_5$. For this purpose, suspension of HEK cells stably transfected with one of the hsst2A, hsst3 and hsst5 was inoculated subcutaneously in the flanks of SCID mice. Palpable masses grew at the inoculation site 14–20 days later, and biodistribution was conducted 4 h after injection of [^{111}In-DOTA^0, trp^8]SS-14 (2-3μCi, 100μL±excess sst$_{2A/3/5}$-blocker). Tumor uptake was suboptimal (0.5–1.5%ID/g), most probably due to insufficient radioligand stability and/or to low levels of sst$_{2A/3/5}$ expression in the HEK implants.

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Optimizing conditions for radiolabelling DTPA-bombesin analogues with In-111 at high specific activity

Priscilla Brunelli Pujatti, Jair Mengattim, Elaine B. de Araújo
IPEN/CNEN, São Paulo, Brazil

In designing radiometal-based peptides, an important factor to consider is the specific activity (SA) of the molecule. Low SA can compromise the uptake of the tracer in the tissue of interest *in vivo* and lead to physiological responses due to the presence of the cold peptide in the organism. However, very high SA can cause radiolysis of the compound, resulting in undesirable impurities. In this study, parameters influencing the kinetics of labelling of a DTPA-bombesin analogue (BETG$_5$) with ^{111}In were investigated and conditions were optimized to obtain the highest achievable SA. The effects of peptide mass, ^{111}In activity, temperature and time of reaction in radiolabelling yield and peptide integrity were systematically categorized applying ITLC-SG and HPLC as chromatography techniques. Kinetics of ^{111}In-labelling was optimal at pH 4.5, room temperature and 15 min of incubation. Higher radiochemical purities were obtained when 10 μg of BETG$_5$ reacted with 37–555 MBq of radiometal (maximum SA 111 GBq/μmol). ^{111}In-BETG$_5$ integrity analysis suggested that oxidation does not depend on radiolabelling conditions and can be avoided by the addition of methionine in radiolabelling medium. These optimized conditions will be applied to produce high specific activity DTPA-bombesin analogues for preclinical studies in healthy and tumour mice.

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In vivo characterization of dual isotope radiolabeled cell penetrating imaging probes activatable by tumoral matrix metalloproteinase-2

Sander Martinus Johannes van Duijnhoven[a], Marc S. Robillard[b], Klaas Nicolay[a], Holger Gruell[a,b]
[a]*Biomedical NMR, University of Technology Eindhoven, The Netherlands*
[b]*Philips Research Eindhoven, The Netherlands*

We developed dual isotope radiolabeled cell penetrating imaging probes (ACPPs) activatable by tumoral matrix metalloproteinase-2 (MMP-2), and assessed their in vivo biodistribution in tumor-bearing mice. These probes, in which the polycationic cell penetrating peptide domain and the polyanionic peptide domain [1] were labeled with ^{177}Lu and ^{125}I, respectively, showed a significant approximately threefold higher uptake in MMP-2 positive HT-1080 tumor compared to MMP-2 negative muscle (t test, P<.01). Interestingly, ACPP showed a significant higher tissue uptake relative to a negative control peptide with a scrambled linker in all tissues which resulted from uptake of the activated ^{177}Lu labeled cell penetrating peptide domain. Next, a radiolabeled cell penetrating peptide showed no significantly different tumor-to-tissue ratios compared to ACPP (P>.05). These data show that the MMP-2 sensitive ACPP is not activated in tissue specifically, but instead most likely in the blood, resulting in a nonspecific biodistribution of the activated ACPP. Therefore, the positive tumor-to-muscle ratio observed for ACPP is not a result of tumor-associated ACPP activation as suggested earlier for fluorescently labeled ACPPs [1].

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Reference

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Pb-212-labeled α-MSH analogue modified with a nuclear localization sequence for melanoma targeting☆

Xiuli Zhang[a], Fabio Gallazzi[b], Susan Deutscher[a], Thomas Quinn[a]
[a]*Biochemistry, University of Missouri, Columbia, MO, USA*
[b]*Research Cores, University of Missouri, Columbia, MO, USA*

The goal of this project was to evaluate the tumor-targeting potential of the peptide ^{212}Pb-DOTA-GPKKKRKVQA-Nle-EH-DPhe-RWGRPV-NH$_2$ that targets the MC1R, overexpressed on melanoma cells, in vitro and in vivo. The peptide DOTA-GPKKKRKVQA-Nle-EH-DPhe-RWGRPV-NH$_2$

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