Targeted alpha-therapy with ^{225}Ac-labeled PSMA ligands: A preclinical investigation on the fate of the decay nuclides

Alexander Wurzer[1], Baiqing Sun[1], Samaah Saleb[2], Julia Brosch-Lenz[1], Sebastian Fischer[1], Susanne Kossatz[1], Kerstin Hürkamp[2], Wei Bo Li[2], Alfred Morgenstern[3], Frank Bruchertseifer[3], Wolfgang Weber[1], Calogero D'Alessandria[1]

1 Nuklearmedizinische Klinik und Poliklinik, Klinikum rechts der Isar, Technical University of Munich, Ismaninger Straße 22, 81675 München, Germany.
2 Institute of Radiation Medicine, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany.
3 European Commission, Joint Research Centre, Karlsruhe, Germany.

Background: Alpha therapy with ^{225}Ac-labeled ligands targeting the prostate-specific membrane antigen (PSMA) has emerged as a promising treatment option for advanced prostate cancer. Due to alpha recoil, the alpha-emitting progeny is released from the PSMA-targeted molecule and can undergo redistribution, contributing to off-target toxicity in dose limiting organs. In the present study, biodistribution studies of [^{225}Ac]Ac-PSMA I&T were performed in mice, with the aim to investigate the pharmacokinetics of the radioligand compared to unbound progeny. The study was complemented by measurement of the cellular uptake and externalization kinetics of [^{225}Ac]Ac-PSMA I&T in comparison to its ^{177}Lu-labeled analogue. **Methods:** In vitro studies (IC_{50}, internalization, externalization) of [^{225}Ac]Ac-PSMA I&T and [^{177}Lu]Lu-PSMA I&T were performed on LNCaP and/or PC3Pip-cells. The lipophilicity of each radioligand was determined by the *n*-octanol/buffer method. Biodistribution studies of [^{225}Ac]Ac-PSMA I&T (10 min, 1 h, 24 h and 7 d p.i.) were conducted on LNCaP-tumor bearing NSG and healthy C57BL/6 mice. Equilibrium uptake was determined 24 h after dissection by separate quantification of ^{221}Fr (218 keV) and ^{213}Bi (440 keV). Tissues of interest (kidneys, salivary glands and tumor) were measured immediately after dissection until reaching equilibrium by determining the time-dependent activity distribution of ^{221}Fr and ^{213}Bi. **Results:** [^{225}Ac]Ac-PSMA I&T demonstrated similar cell binding characteristics and cellular retention compared to [^{177}Lu]Lu-PSMA I&T. In biodistribution studies [^{225}Ac]Ac-PSMA I&T displayed fast clearance from the blood pool mainly via the renal system and rapid tumor uptake. In tumor-bearing animals a higher liver uptake (2 %ID/g over 7 d) was found compared to the healthy control group (< 0.7% ID/g over 7 d). No redistribution of non-bound ^{221}Fr and ^{213}Bi was measured from tumor tissue after initial radioligand uptake. Compared to equilibrium a higher ^{213}Bi-uptake was found in kidneys and salivary glands at the time point of death: At 10 min and 1 h p.i., uptake in salivary glands was 1.6-fold and 8.0-fold higher, respectively, while uptake in kidneys was 2-fold higher at both time points. **Conclusion:** The PSMA-targeting characteristics and pharmacokinetics of [^{225}Ac]Ac-PSMA I&T are similar to its ^{177}Lu-labeled analogue. The progeny of [^{225}Ac]Ac-PSMA I&T is being trapped in tumor tissue. ^{213}Bi formed by alpha recoil was found to accumulate in salivary glands and the renal system, which could result in an increased dose to organs at risk. The effect of unbound progeny to the development of xerostomia and potential long-term side effects on the renal system warrant further investigation.

Acknowledgments: This work is supported by a CRIS Cancer - Prostate Cancer Foundation Young Investigator Award and the German Federal Office for Radiation Protection.

Disclosure: AW, SF and ME are listed as inventors in patent applications for some types of radiohybrid PSMA ligands.

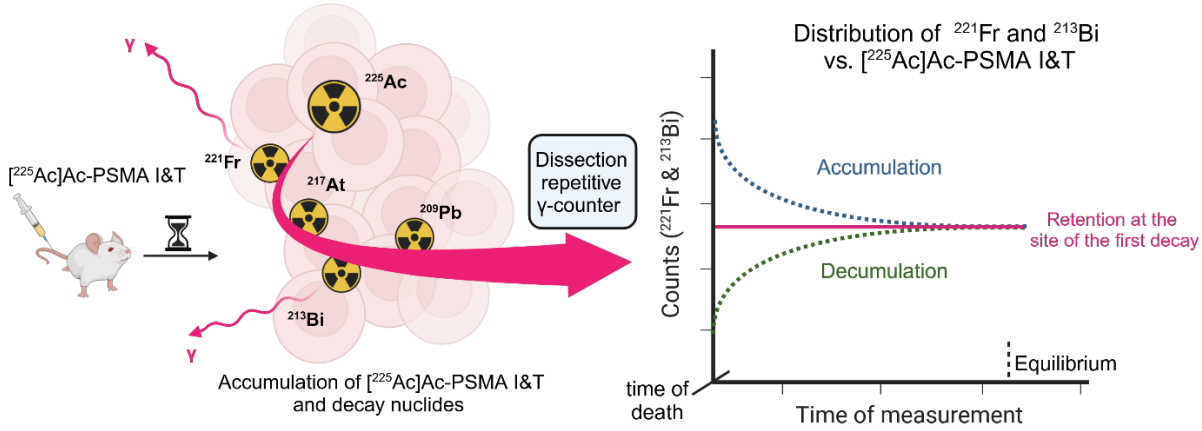

Figure 1. Determination of the fate of ^{225}Ac-progeny in biodistribution studies: Higher uptake at the time point of dissection compared to equilibrium indicates accumulation of unbound non-equilibrium nuclides within the organ. Lower uptake corresponds to a fast delocalization of the liberated progeny from the tissues after the first decay. A constant count rate indicates that the decay nuclides are remaining trapped within the analyzed organ at the site of the first decay.