Preclinical Development of Novel PSMA-Targeting Radioligands – Modulation of Albumin-Binding Properties to Improve Prostate Cancer Therapy

Christoph A. Umbricht[1], Martina Benešová[1,2], Susan Cohrs[1], Roger Schibli[1,2], Cristina Müller[1,2]

[1]Center for Radiopharmaceutical Sciences ETH-PSI-USZ, Paul Scherrer Institut, 5232 Villigen PSI; [2]Department of Chemistry and Applied Biosciences, ETH Zurich, 8093 Zurich

AIM OF THE STUDY The aim of this project was to design and investigate PSMA-targeting radiopharmaceuticals comprising different types of albumin binders (weak and strong) to improve treatment of metastatic castration-resistant prostate cancer.

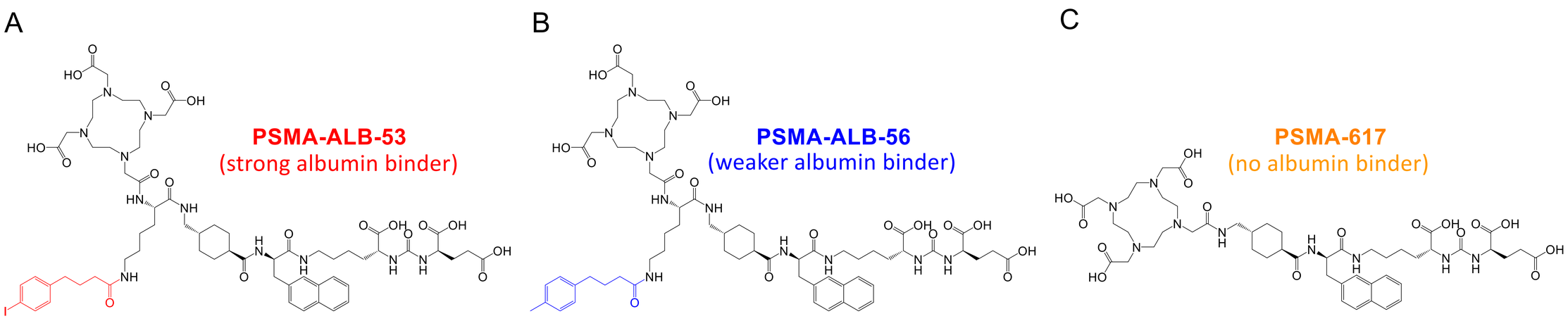

Figure 1: Chemical structures of (A) PSMA-ALB-53 with the stronger albumin-binding 4-(p-iodophenyl)-moiety highlighted in red, (B) PSMA-ALB-56 with the weaker albumin-binding p-(tolyl)-moiety highlighted in blue and (C) PSMA-617, a clinically-used PSMA ligand without dedicated albumin-binder.

RESULTS PSMA-ALB-53 and PSMA-ALB-56 *(Fig.1)* were radiolabeled with ^{177}Lu (β^--emitter for therapy) and evaluated in preclinical experiments. In vitro, both compounds showed PSMA-specific cell uptake, while ^{177}Lu-PSMA-ALB-53 exhibited 10-fold higher albumin binding properties in mouse and human serum compared to ^{177}Lu-PSMA-ALB-56 *(data not shown)*.

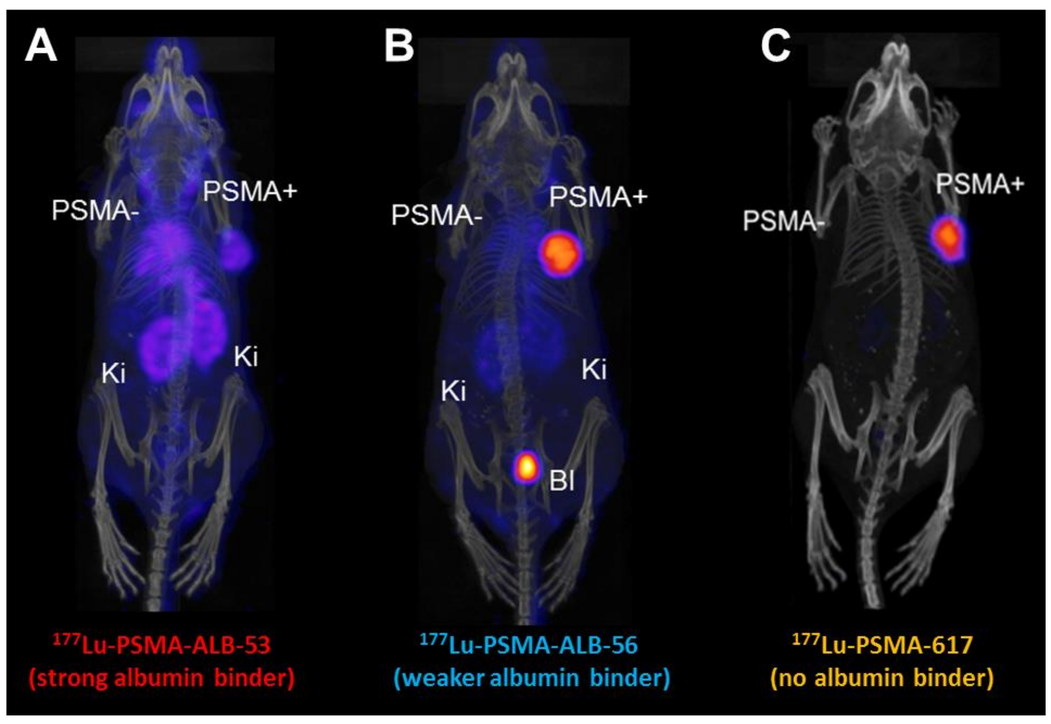

Figure 2: SPECT/CT scans of mice with prostate cancer xenografts, 24 h after injection of (A) ^{177}Lu-PSMA-ALB-53, (B) ^{177}Lu-PSMA-ALB-56 and (C) ^{177}Lu-PSMA-617. PSMA+ = PSMA-expressing tumor, PSMA- = PSMA-negative tumor, Ki = kidneys, Bl = bladder.

SPECT/CT scans of ^{177}Lu-PSMA-ALB-53 and ^{177}Lu-PSMA-ALB-56 showed significantly higher accumulation of radioactivity in PSMA-positive tumors than the clinically-used ^{177}Lu-PSMA-617. Clearance from blood and kidneys was faster for ^{177}Lu-PSMA-ALB-56 compared to ^{177}Lu-PSMA-ALB-53 *(Fig. 2).*

A preclinical therapy was performed in mice bearing PSMA-positive xenografts. Mice treated with ^{177}Lu-PSMA-ALB-56 (5 MBq/mouse) showed a reduced tumor growth relative to ^{177}Lu-PSMA-617 (5 MBq/mouse) resulting in complete tumor remission in four out of six mice at study end *(Fig. 3).* Median survival for ^{177}Lu-PSMA-ALB-56 could not be determined (n.d.) since more than 50% of animals were still alive after 84 days, while mice treated with ^{177}Lu-PSMA-617 or saline showed a clearly decreased median survival (*Fig. 4)*.

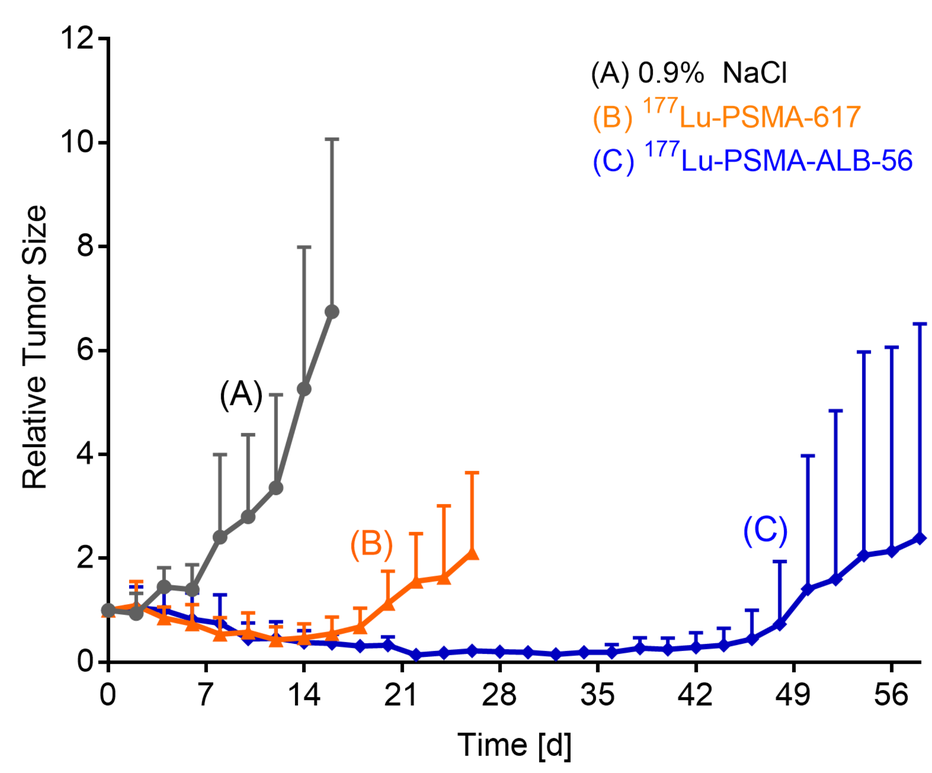

Figure 3: Relative tumor growth of tumor-bearing mice after the injection of (A) 0.9% NaCl, (B) 5 MBq ^{177}Lu-PSMA-617 or (C) 5 MBq ^{177}Lu-PSMA-ALB-56. Curves are shown until the first animal of the respective group had to be euthanized.

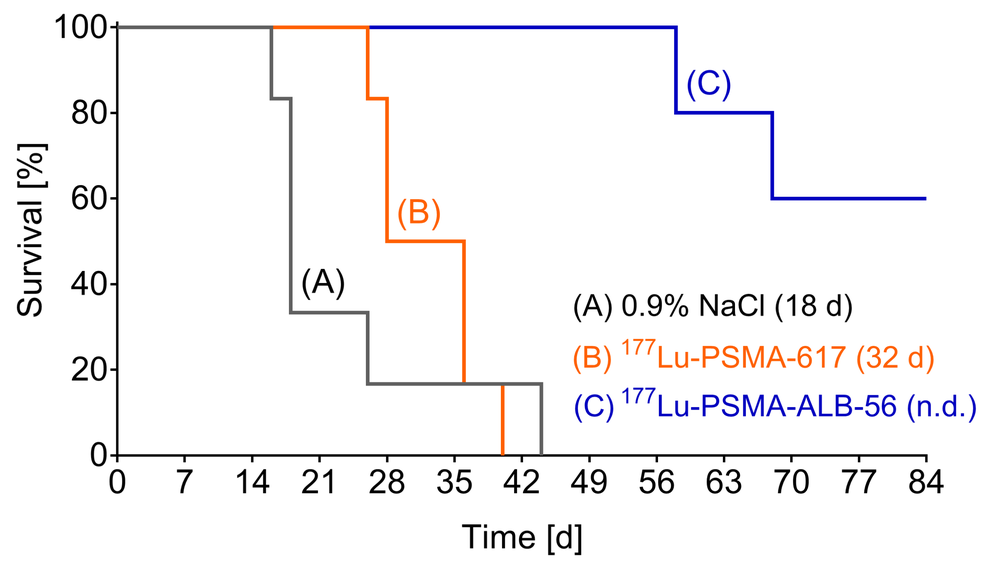

Figure 4: Median survival (indicated in brackets in days, n.d. = not determined) of tumor-bearing mice after the injection of (A) 0.9% NaCl, (B) 5 MBq ^{177}Lu-PSMA-617 or (C) 5 MBq ^{177}Lu-PSMA-ALB-56. The study was terminated at Day 84.

CONCLUSION The herein presented ^{177}Lu-PSMA-ALB-56 was more effective to treat tumors than the clinically-used ^{177}Lu-PSMA-617 resulting in complete tumor remission in the majority of mice at the end of the preclinical therapy study. These promising results warrant further investigations to assess the potential for a clinical application of ^{177}Lu-PSMA-ALB-56 and to potentially enable more efficient radionuclide therapy using lower quantities of radioactivity and/or less frequent applications.

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