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Specificity of PSMA-617 Radiotherapy for Prostate Cancer

Joseph A. Reddy, Melissa Nelson, LeCun Xu, Elaine Westrick, Marilynn Vetzel, Leroy Wheeler, Albert Felten, Hari K. Santhapuram, Iontcho Vlahov and Christopher P. Leamon

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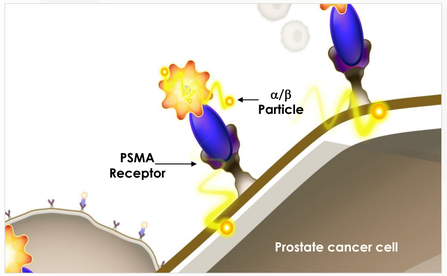
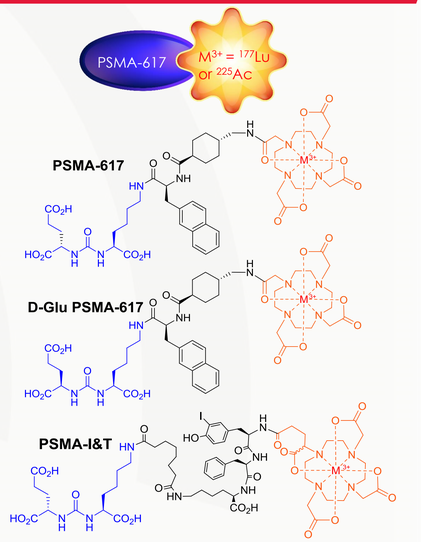
Introduction

Prostate-specific membrane antigen (PSMA) is a biomarker that is overexpressed on prostate cancer as well as on the neovasculature of many non-prostate solid tumors. Lately, several small molecular PSMA binding ligands chelated to various radionuclides have been studied for imaging and treatment of prostate cancer lesions. One such clinically tested agent is PSMA-617, a DOTA derivative of a PSMA-specific targeting ligand. In our hands, radiochemical yields of PSMA-617 labeled with either ^{177}Lu (β emitter) or ^{225}Ac (α emitter) were greater than 97%. Binding experiments with ^{177}Lu and ^{225}Ac chelates of PSMA-617 and D-Glu PSMA-617 (a predicted non-PSMA binding, D-glutamic acid isomer of PSMA-617) were performed using the PSMA-positive, 22RV1 cell line. PSMA-617, was found to bind in a concentration dependent manner with very high affinity, whereas the cellular association of D-Glu PSMA-617 was found to be > 60-fold lower. The *in vivo* biodistribution of these two agents were investigated in BALB/c *nu/nu* mice bearing subcutaneous 22RV1 xenografts. Organ distribution revealed specific PSMA-617 uptake in the 22RV1 tumors and the PSMA$^+$ kidneys, while the uptake of D-Glu PSMA-617 remained near background in both of these tissues. Different from tumor, PSMA-617 exhibited a rapid clearance from the kidneys to yield a high tumor-to-background contrast at 4 and 24 h post dose. Complementary antitumor activity studies were performed with ^{225}Ac-labeled PSMA-617. Here, significant tumor growth inhibition was observed without detectable hematologic or renal toxicity to the mice. These data provide additional support for a phase 3 prospective trial currently being planned to evaluate ^{177}Lu-PSMA-617 in patients with metastatic PSMA$^+$ prostate cancers, along with the continued clinical investigation of ^{225}Ac-PSMA-617 in a similar patient population.

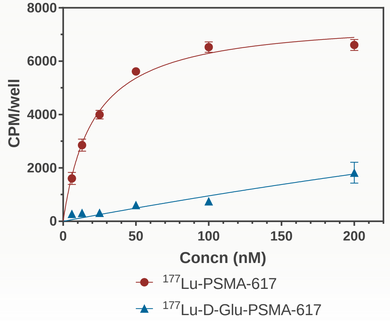
Advantage: Endocytosis is not critical for RLT therapy



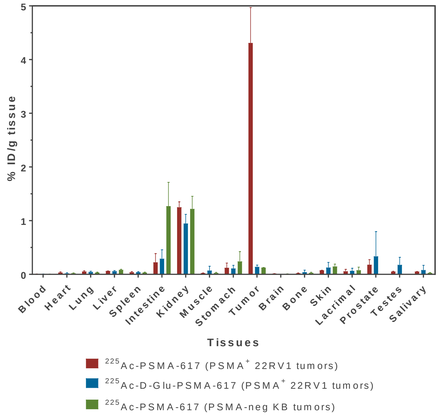
Structures of test articles



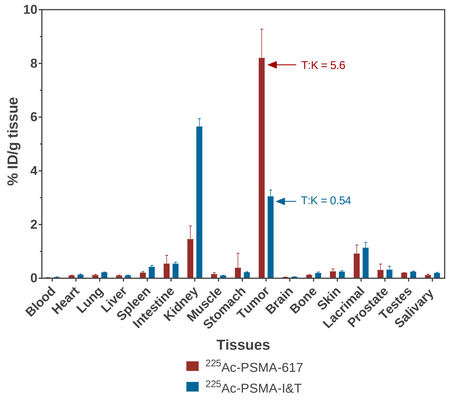
In vitro high affinity binding to PSMA$^+$ cells is stereo-specific



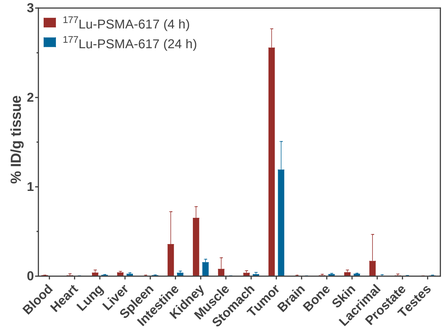
PSMA$^+$ tumor uptake requires an L-Glu containing ligand

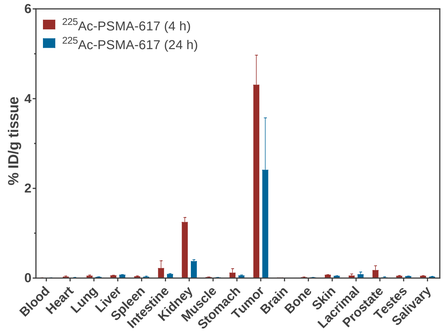


Tumor:kidney ratio significantly favors PSMA-617 over PSMA-I&T



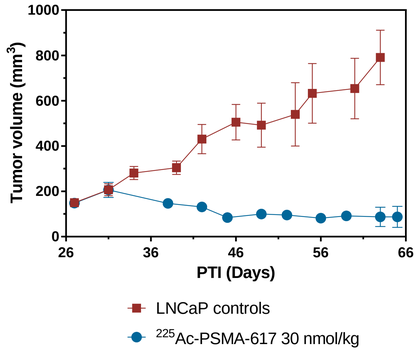
High T/NT ratios (4 & 24 h p.i.) for both ^{177}Lu and ^{225}Ac PSMA-617 chelates





T/NT ratios		Blood	Heart	Lungs	Liver	Spleen	Intestine	Kidney	Muscle	Skin	Salivary
^{177}Lu	4 h	238	77	89	65	179	12	4.0	65	80	
	24 h	1193	284	82	45	114	37	7.5	505	43	
^{225}Ac	4 h	853	197	106	70	153	53	3.6	199	57	84
	24 h	840	380	124	45	179	39	9.8	262	71	98

A single low dose of ^{225}Ac-PSMA-617 is highly active against PSMA$^+$ tumors



^{177}Lu-PSMA-617 clinical data

Pre and post ^{177}Lu-PSMA-617 treatment

M. Hofman. Lutetium-177 PSMA theranostics phase II trial. Presented at ESMO, Spain (2017)

Endocyte, Inc., 3000 Kent Avenue, West Lafayette, IN 47906