Preclinical evaluation of ^{212}Pb-based radiopharmaceutical therapy of prostate cancer

Sangeeta Ray (Banerjee), Ph. D.

Division of Nuclear Medicine and Molecular Imaging
The Russell H. Morgan Department of Radiology and Radiological Science
Johns Hopkins University, Baltimore, USA

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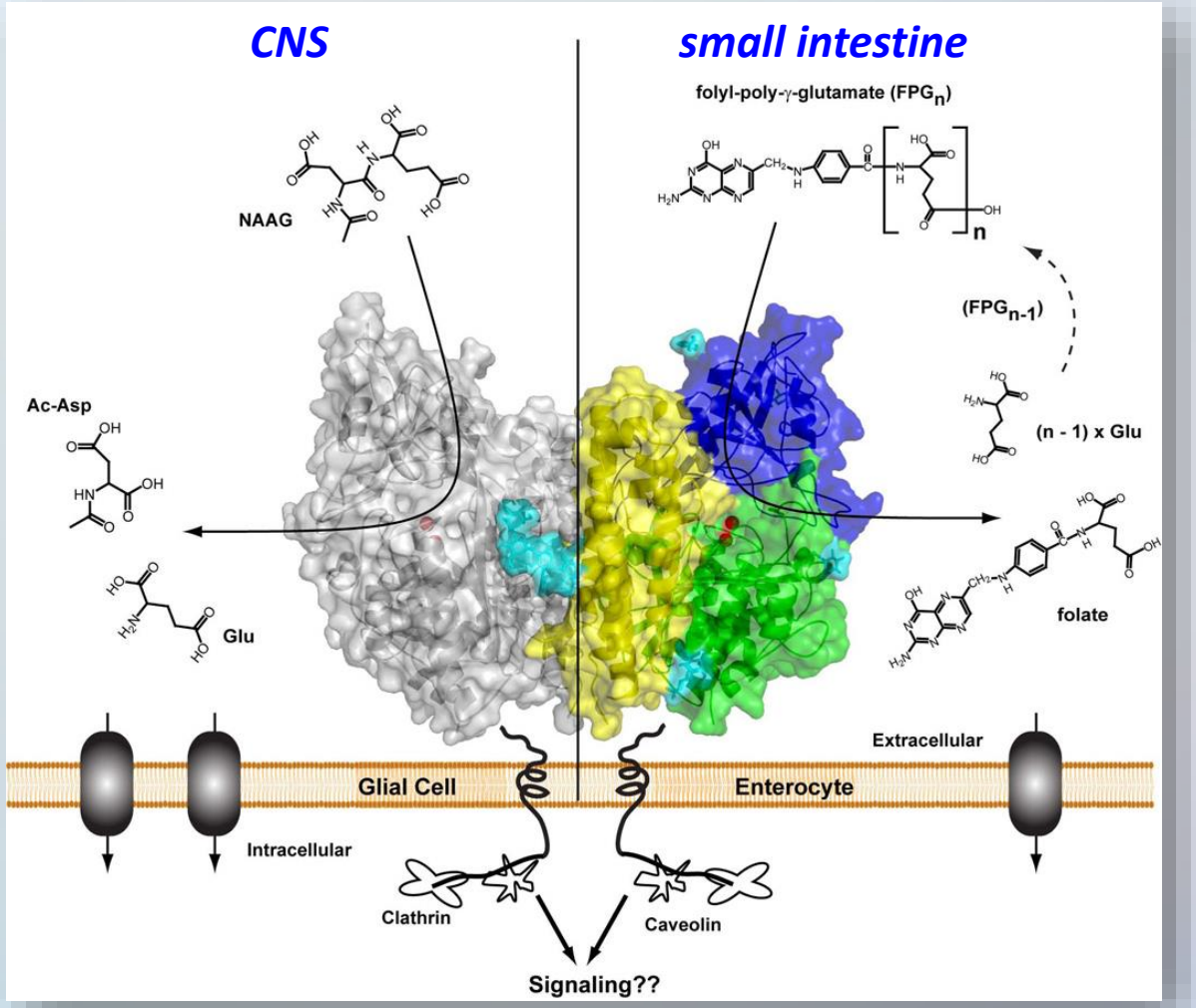
Prostate-Specific Membrane Antigen (PSMA)



- Type II transmembrane protein
- Associated with aggressive prostate cancer (85-95% late stage patients)
- Present in solid tumor neovasculatures
- Marker of androgen signaling

Curr Med Chem 2012;19: 856–870

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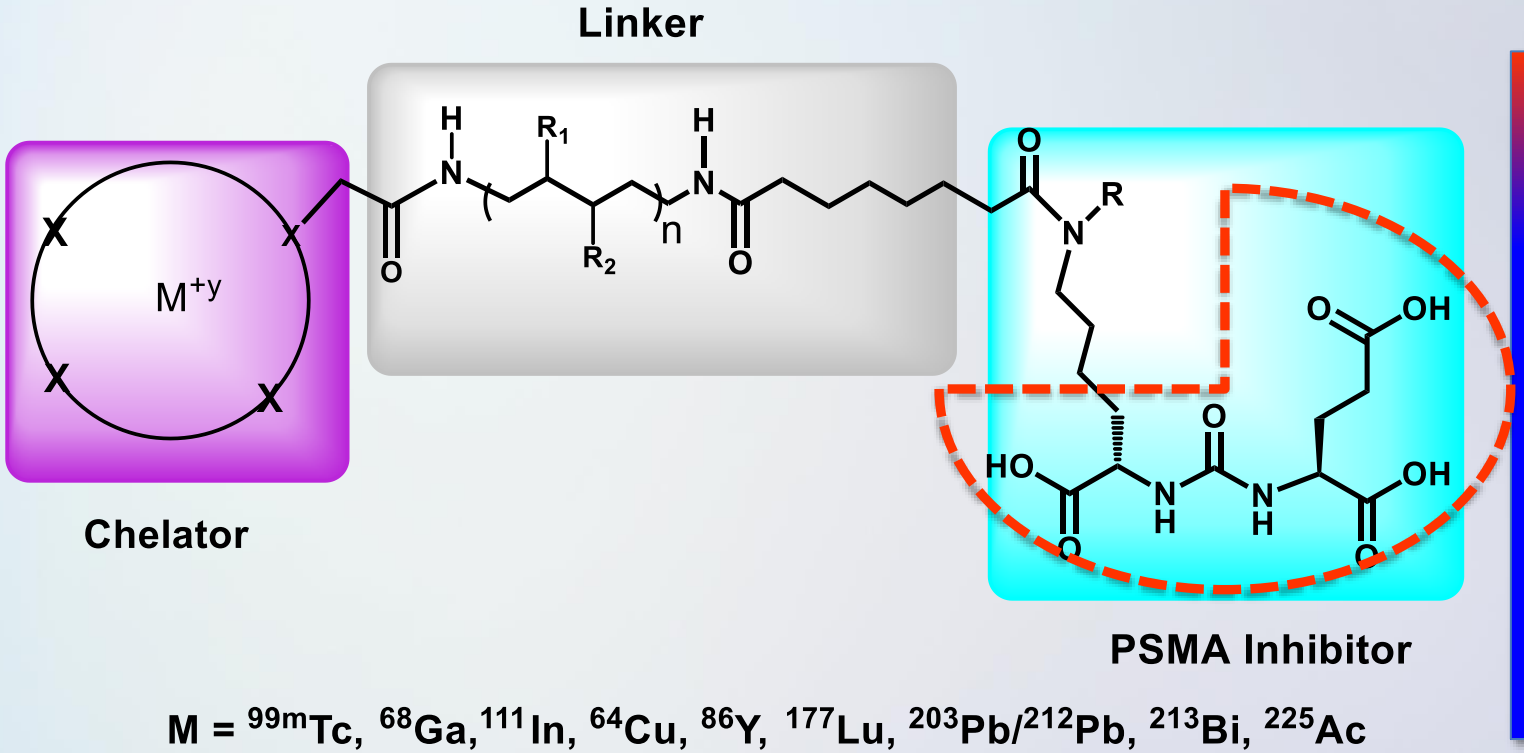
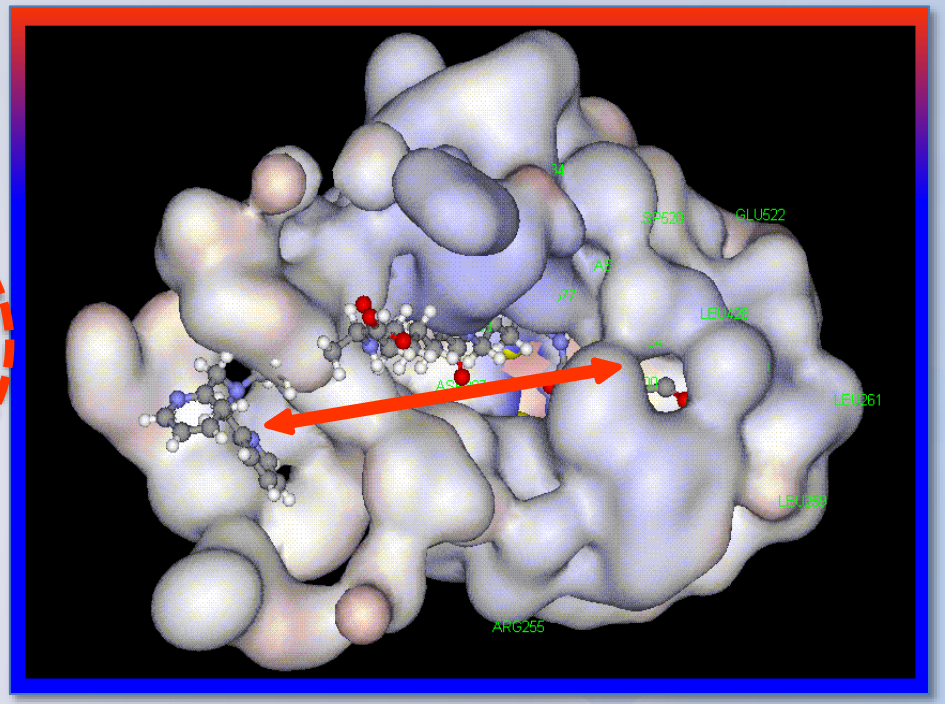
High-affinity radiometal-based agents

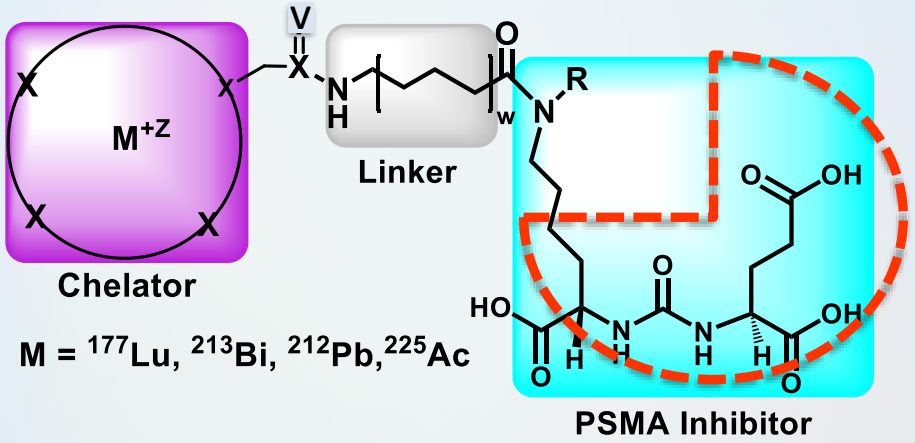




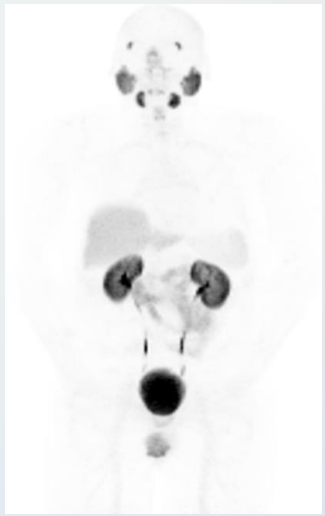
M = ^{99m}Tc, ^{68}Ga, ^{111}In, ^{64}Cu, ^{86}Y, ^{177}Lu, ^{203}Pb/^{212}Pb, ^{213}Bi, ^{225}Ac

Banerjee *et al.*
J Med Chem 2008, **J Med Chem 2010**, **Angew Chem Int Ed 2011**, **Oncotarget** 2011, **J Med Chem** 2013, **J Med Chem** 2014, **J Nucl Med** 2015, **Angew Chem Int Ed.** 2015, **Bioconjug Chem** 2016, **Biomacromolecules** 2017, **Chemistry** 2018, **Eur J Nucl Med Mol Imaging** 2019, **J Nucl Med** 2020

PSMA-based radiotherapeutics: Radiometals



gross recurrent disease



micrometastases

- To reduce toxicity in normal tissues
- Selection of radiometal to match the disease stage
- Risk/benefit of β- vs. α-particle radiometals
- 40–60% patient respond to ^{177}Lu-PSMA-617

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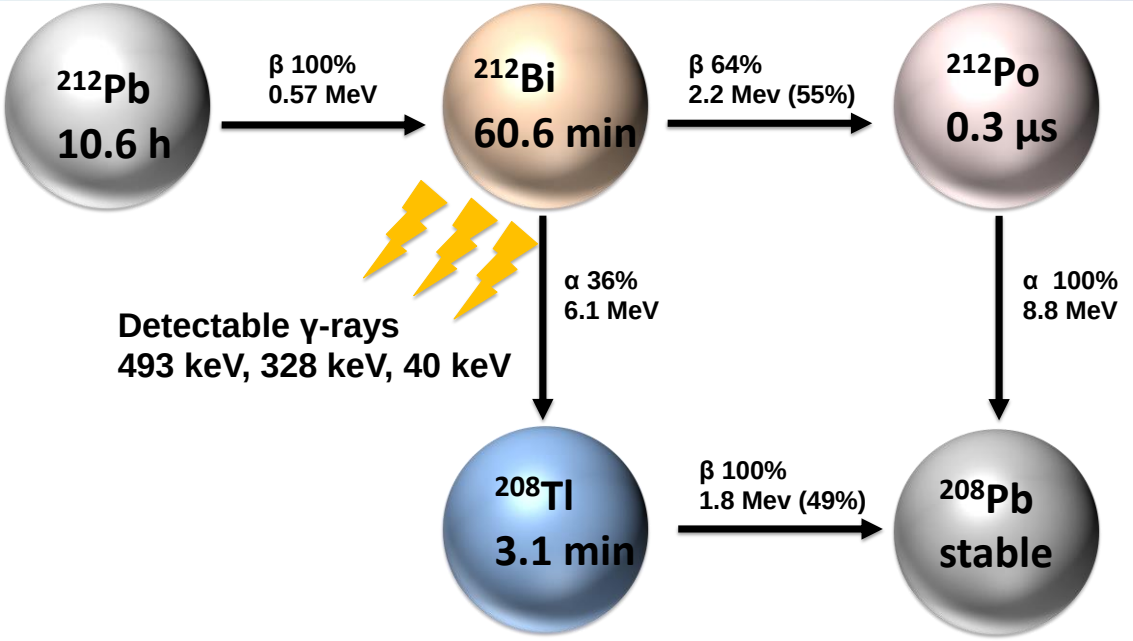
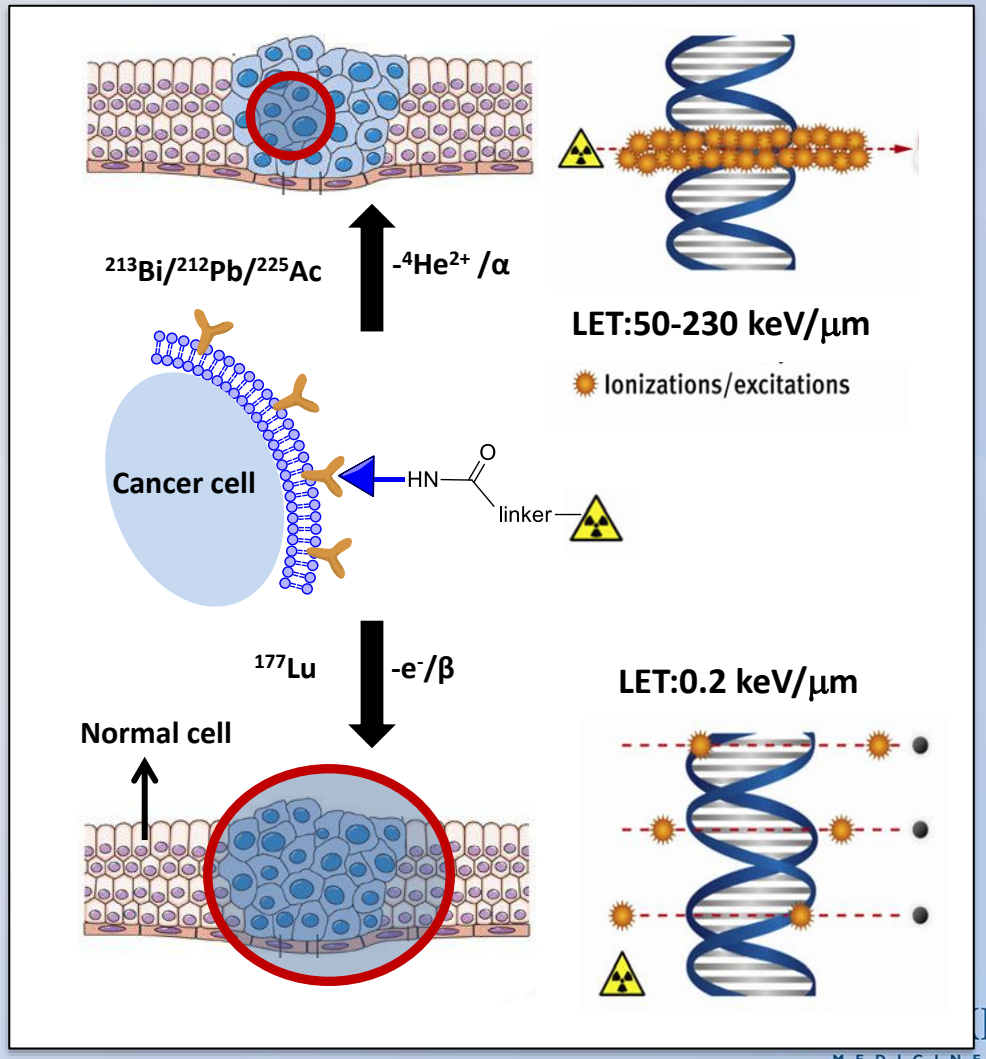
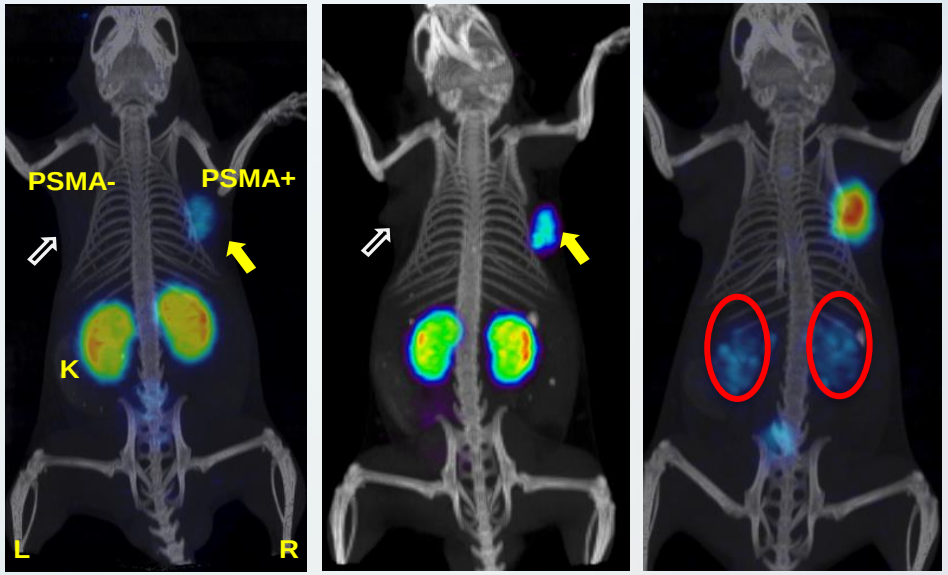
The decay chain of ^{212}Pb

- In vivo α-particle nanogenerator of ^{212}Bi
- Potential imaging (γ-ray) capabilities
- Half-life 10.6 hours

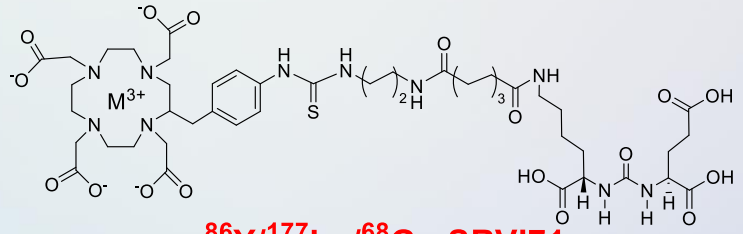




$^{86}Y/^{68}Ga$-labeled PET radiotracers



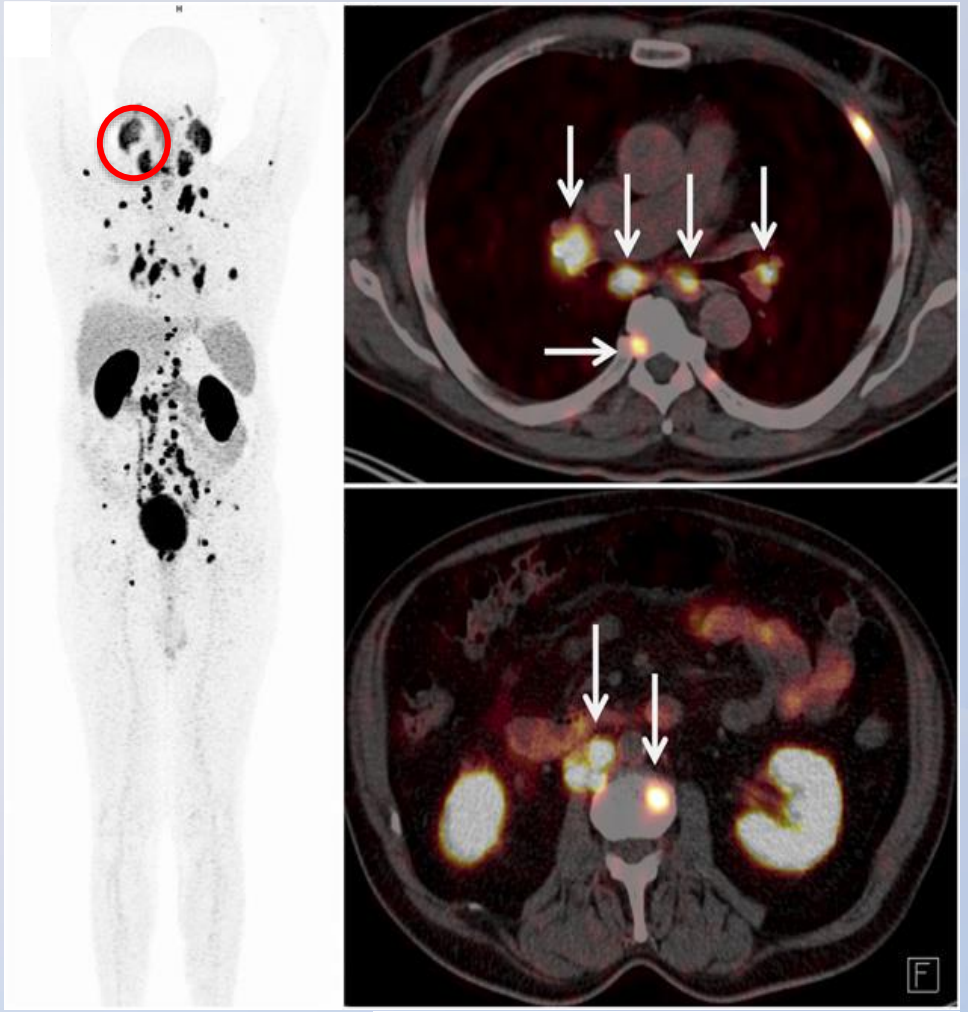
0.5 h 2 h 12 h



$^{86}Y/^{177}Lu/^{68}Ga$-SRVI71

J Nucl Med 2015;56:628-34; Angew Chem Int Ed. 2015;54:10778-82

Advanced Accelerator Applications (AAA-Novartis)



^{68}Ga-SRVI71

Courtesy: Dr. Richard Baum

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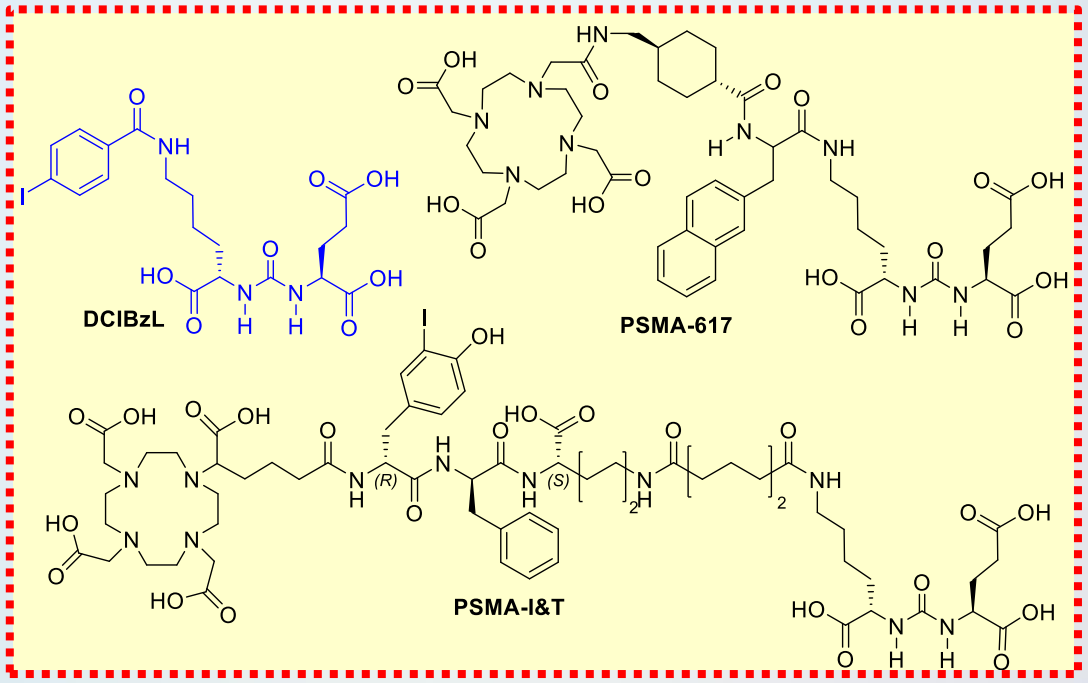
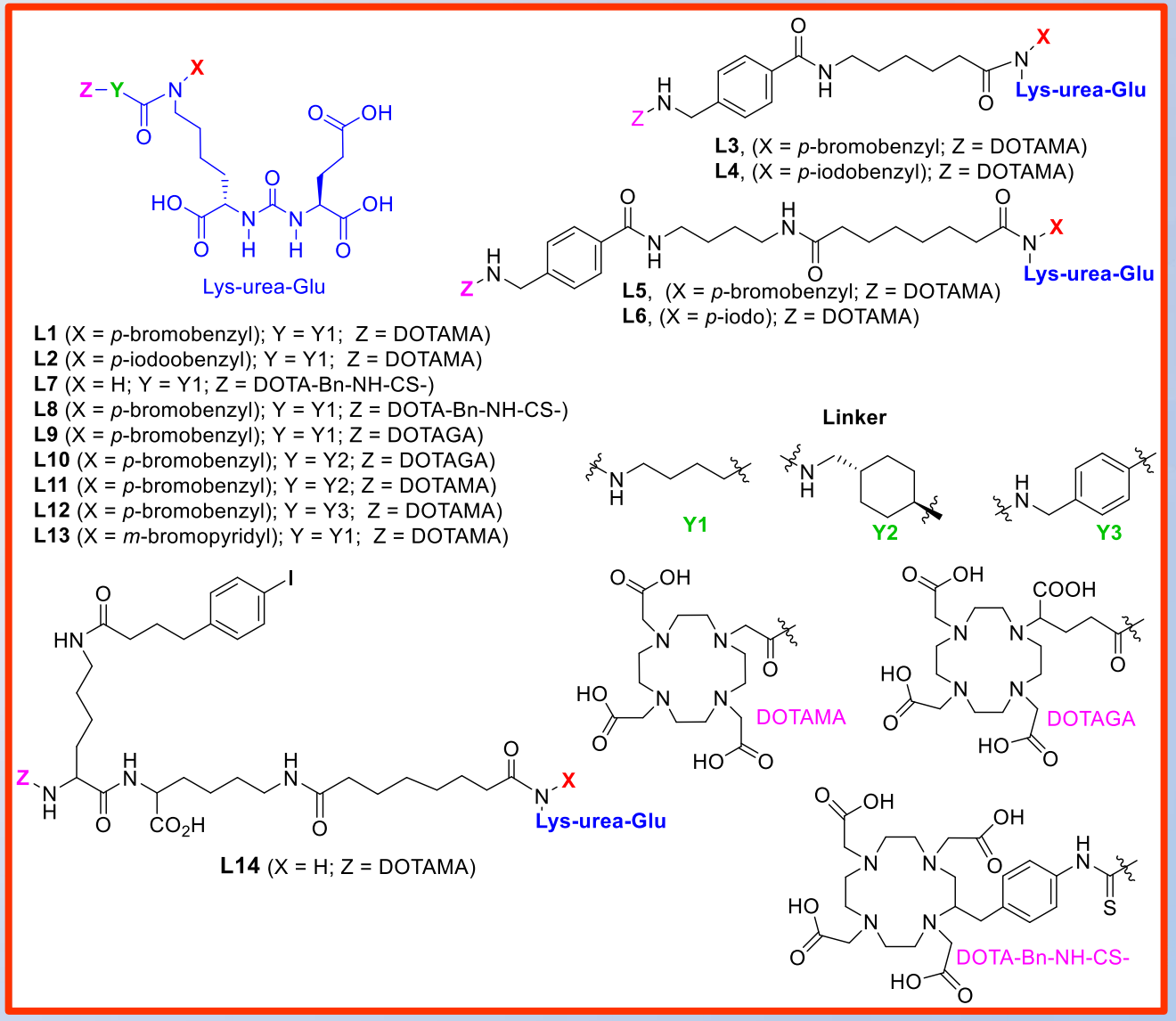
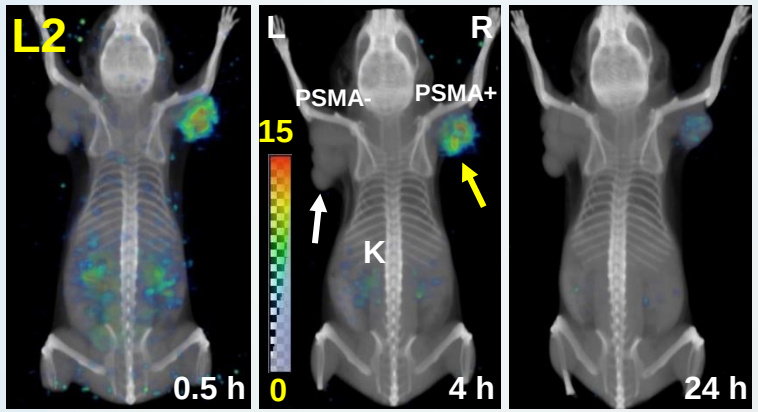
Structure-activity relationship study: ^{177}Lu-labeled compounds

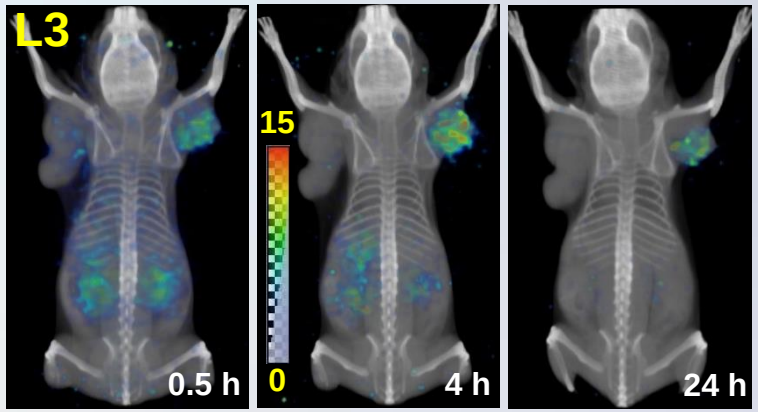


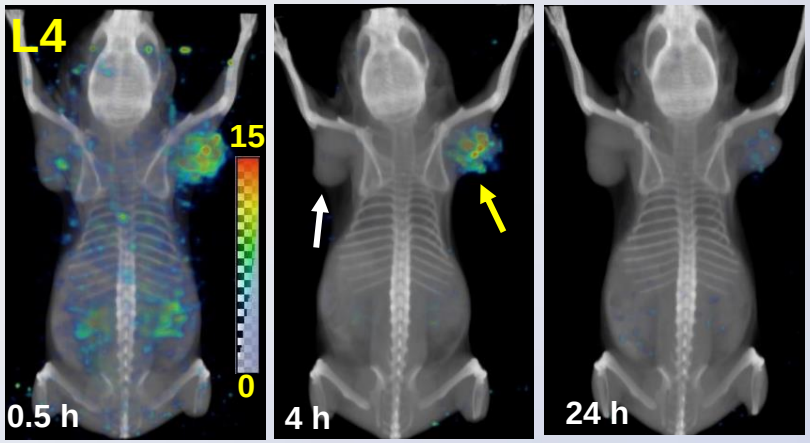


Banerjee et al.
Eur J Nucl Med Mol Imaging , 2019:46;2545–2557

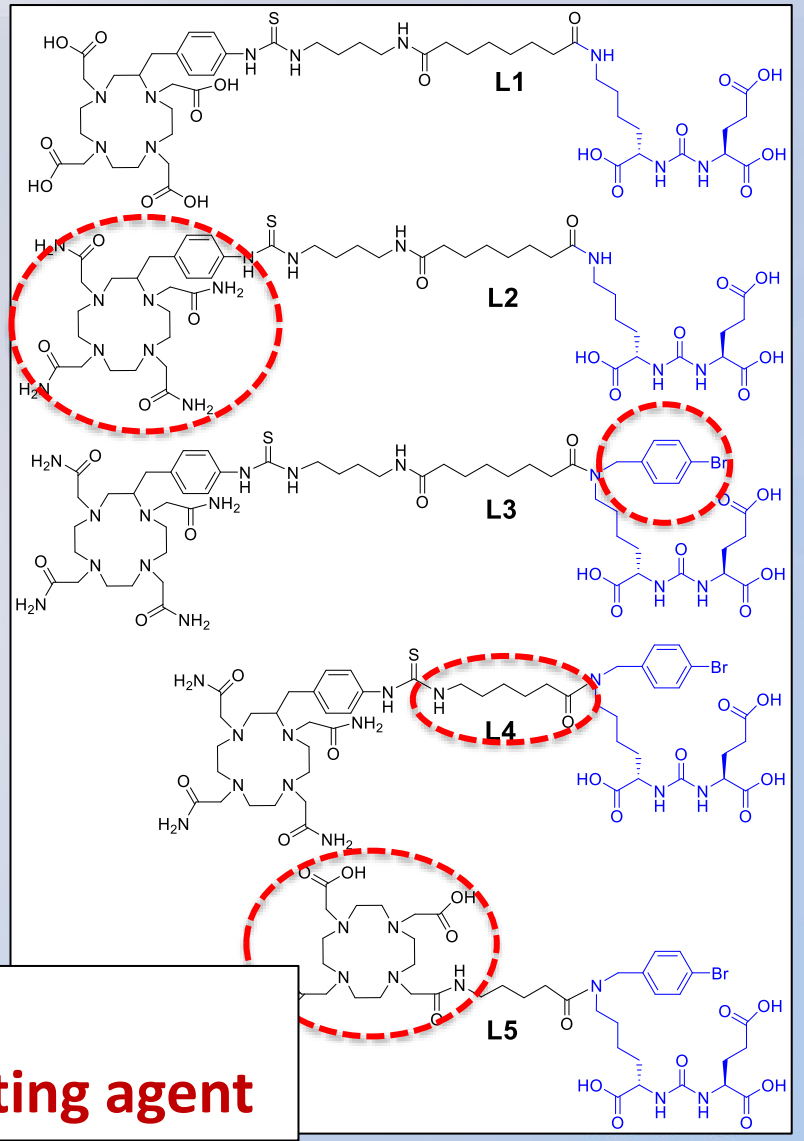
Preclinical evaluation by ^{203}Pb-labeled analogs







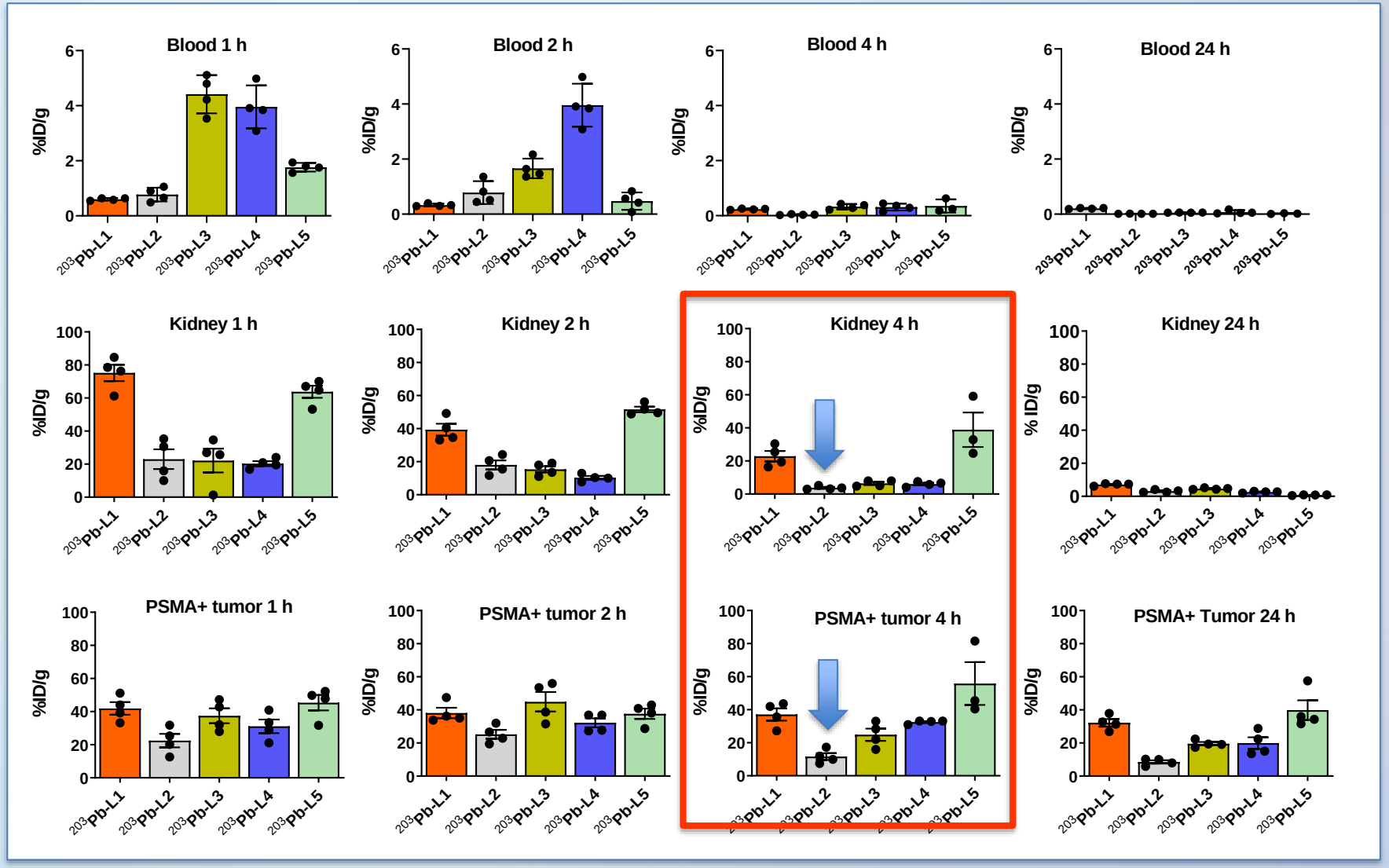
Compound	K_i (nM)
L1	0.2-0.5
L2	8.5-10.3
L3	5.8-9.5
L4	6.3-7.8
L5	0.2-0.4
Pb-L2	10.1-15.3
Pb-L3	11.1-17.1
Pb-L5	0.5-0.9
DCIBzL	0.01-0.06

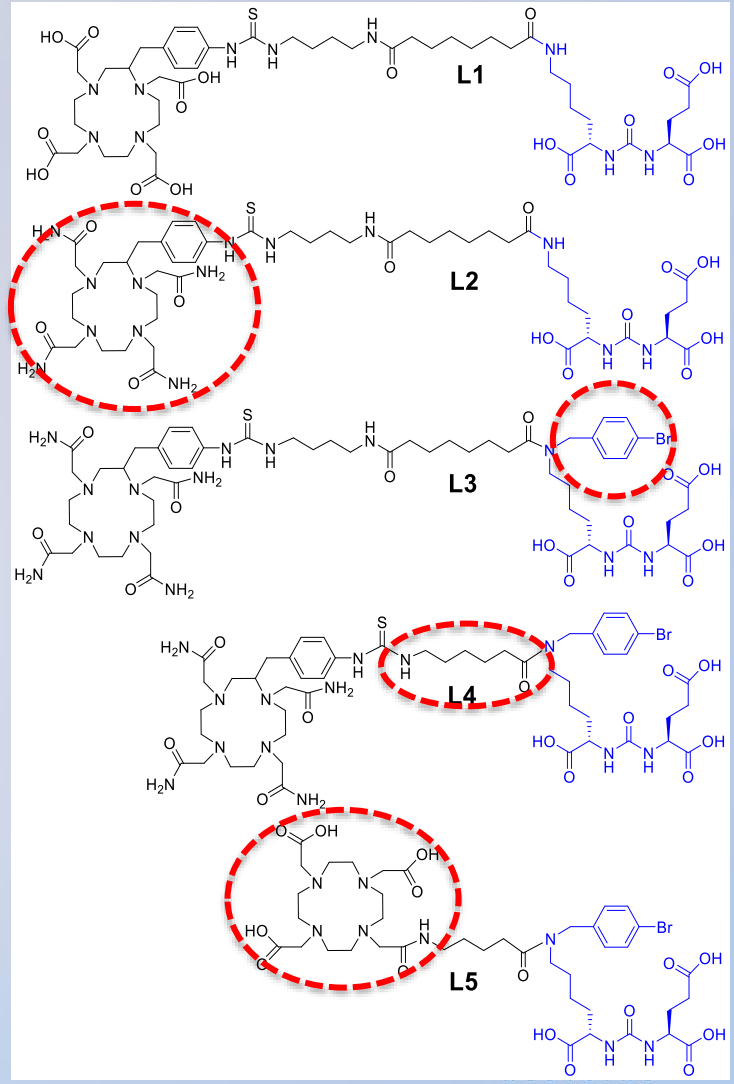


(*Banerjee* et al. J Nucl Med 2020)

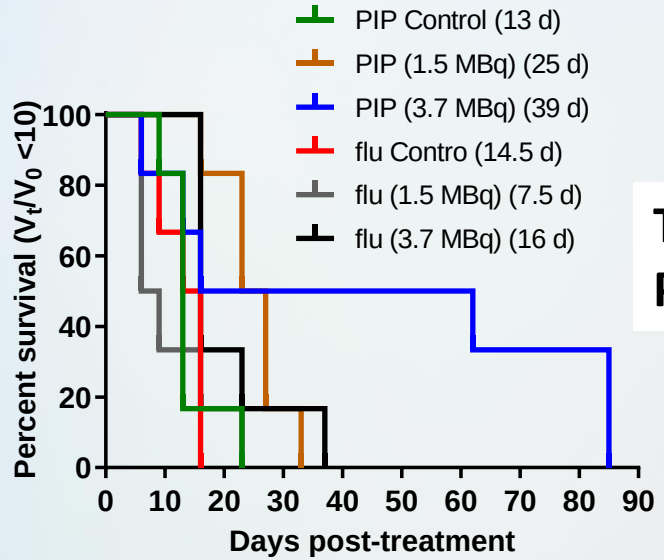
Fast renal clearance for ^{203}Pb-L2, ^{203}Pb-L3, ^{203}Pb-L4 with TCMC chelating agent

Time-dependent tissue uptake (^{203}Pb-labeled analogs)



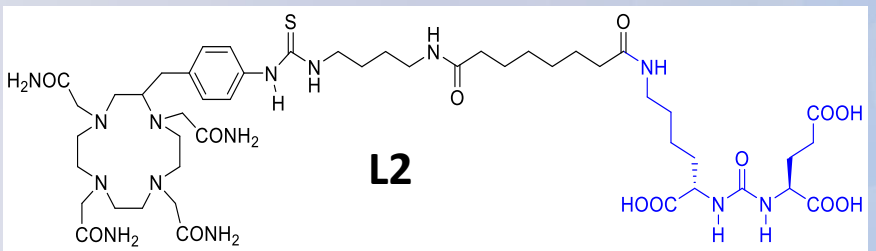


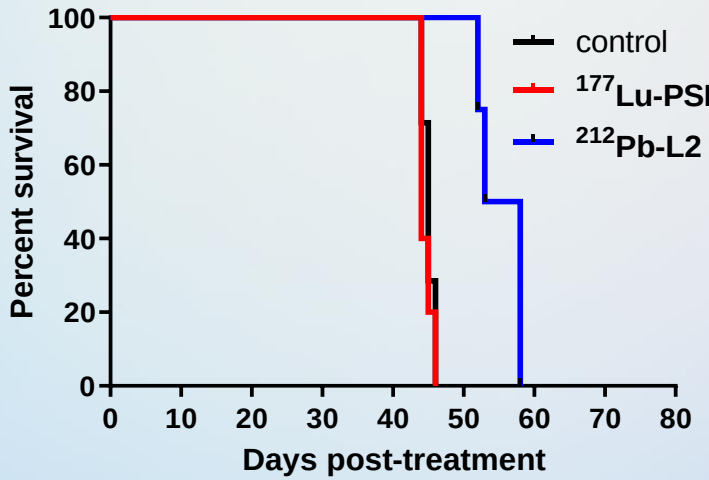
Radiopharmaceutical therapy: ^{212}Pb-L2



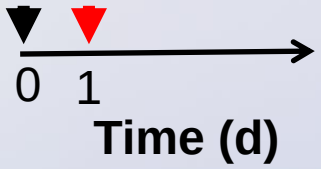
High treatment efficacy in PSMA+ flank tumor model and PSMA+ micrometastatic model (100 uCi, single administration)

Tumor model:
PSMA+/PSMA- PC3 flank





Study design



Cell Injection
Activity

Tumor model:
PSMA+ micrometastatic

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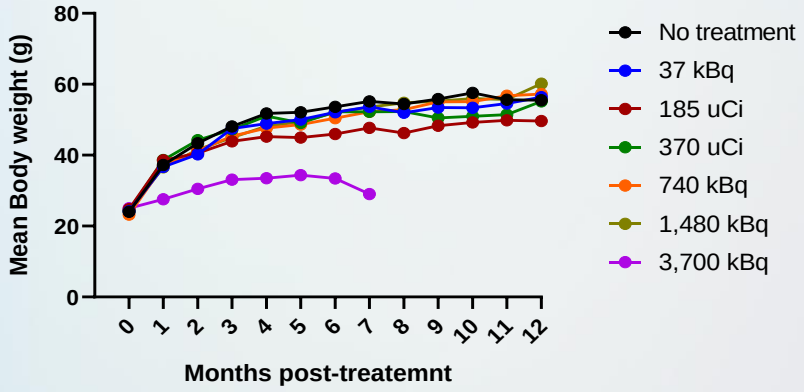
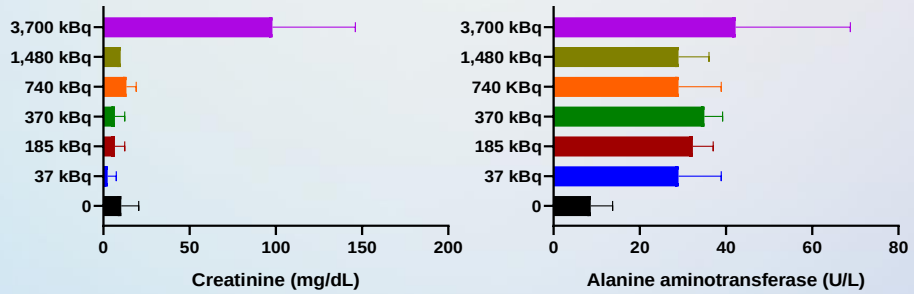
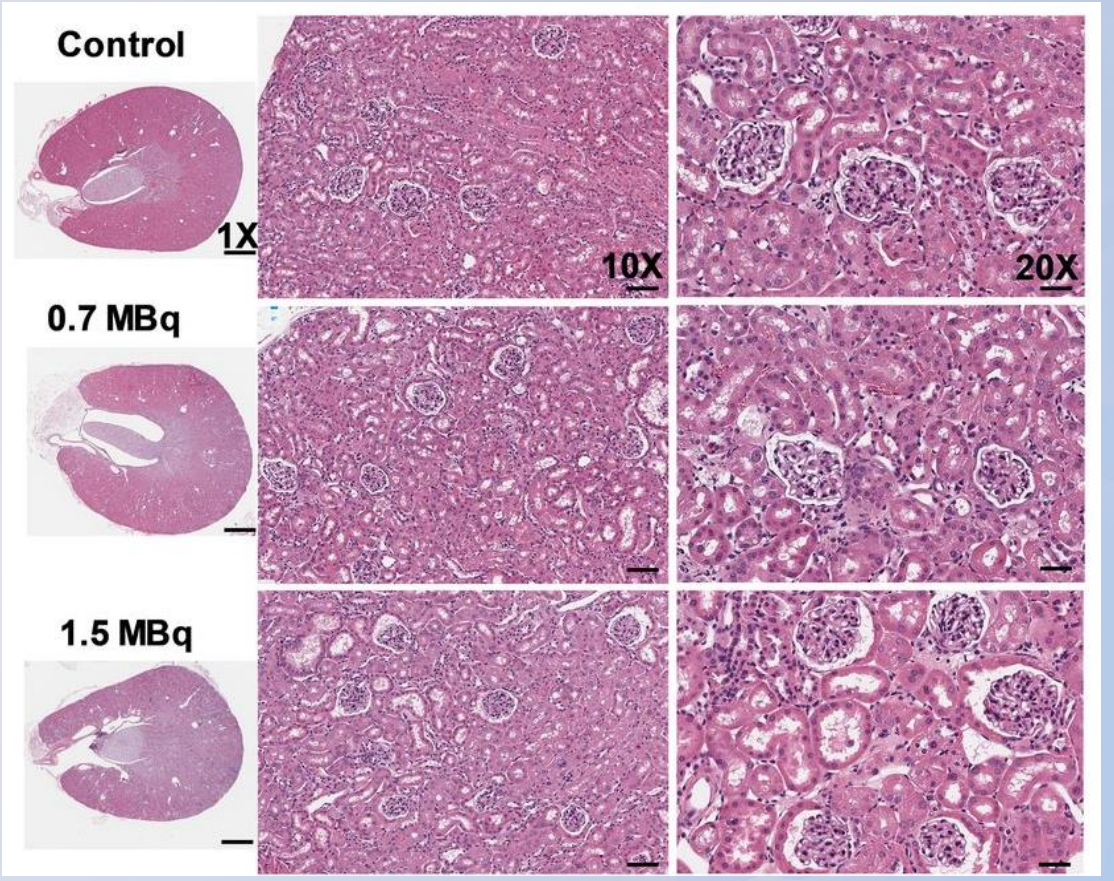
Long-term radiotoxicity data

Dose-limiting organ: kidney
Maximum tolerated activity: ~ 40 µCi (1.5 MBq)
No hematologic toxicity







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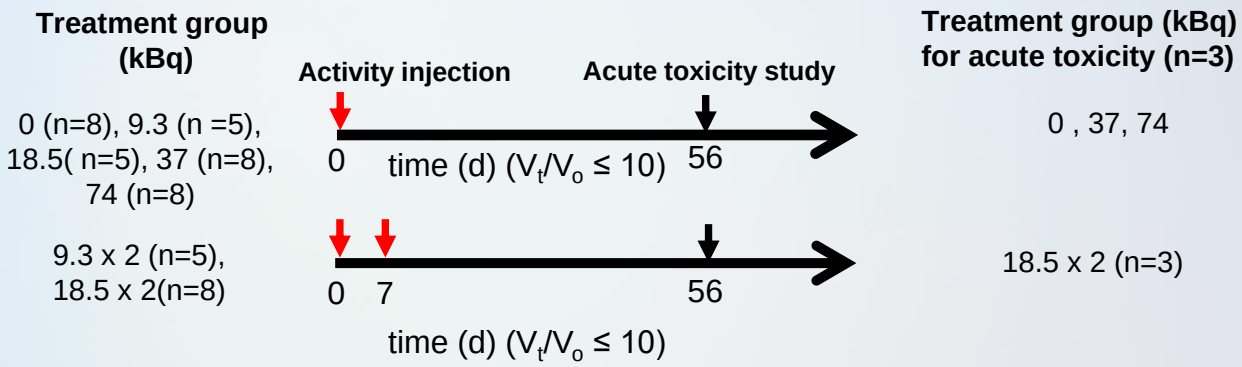
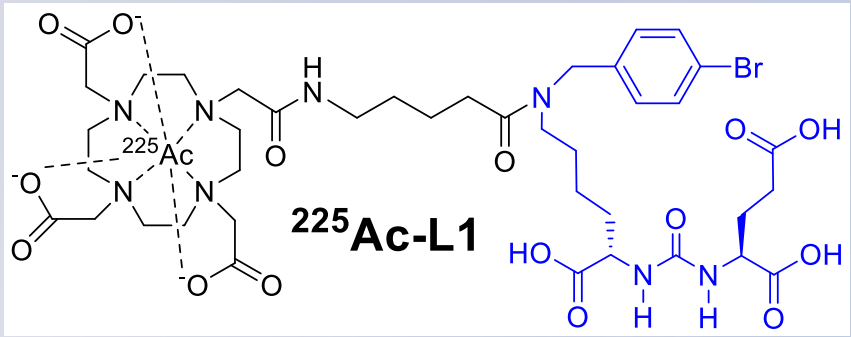
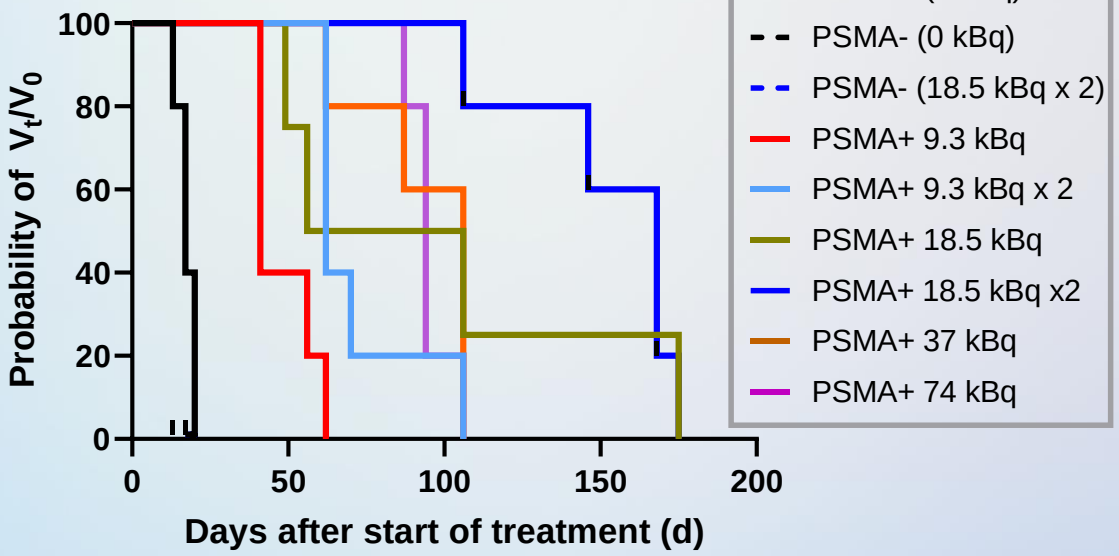
^{225}Ac-L1 treatment efficacy (flank tumor model)

Study design







Treatment group	Median $V_t/V_o \leq 10$ (d)
0 kBq (PSMA+)	17
0 kBq (PSMA-)	17
18.5 kBq x 2 (PSMA-)	17
9.3 kBq (PSMA+)	41
9.3 kBq x 2 (PSMA+)	62
18.5 kBq (PSMA+)	56
18.5 kBq x 2 (PSMA+)	168
37 kBq (PSMA+)	106
37 kBq x2 kBq (PSMA+)	94

Safe and effective activity
18.5 kBq × 2 (7 days apart)

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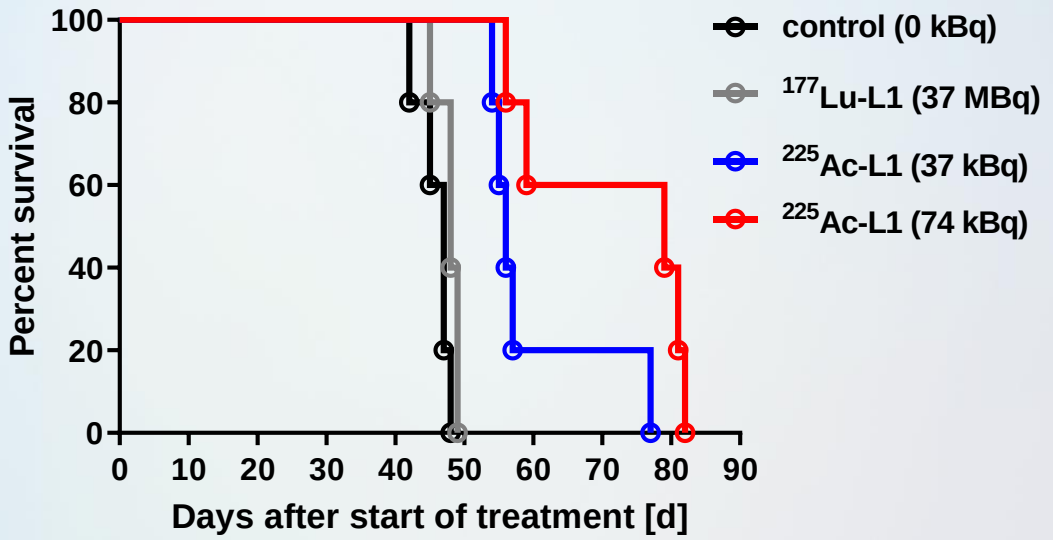
^{225}Ac-L1 vs.^{177}Lu-L1

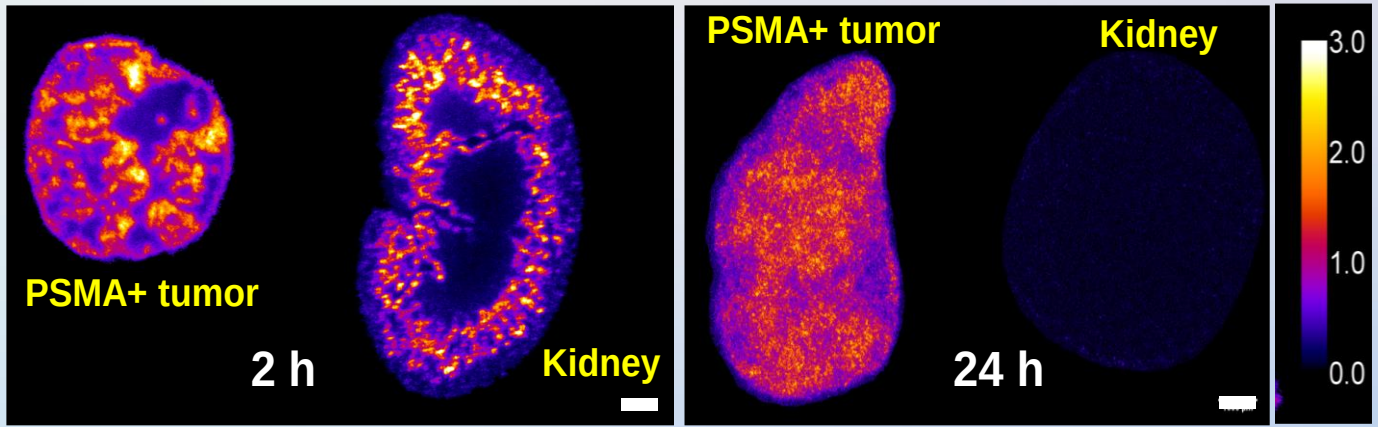


Treatment group	Median survival (d)
0 kBq	47
37 MBq	48
37 kBq	56
74 kBq	79

Tumor model:
PSMA+ micrometastatic

Higher efficacy of ^{225}Ac-L1 compared to ^{177}Lu-L1

Alpha-camera imaging



^{225}Ac-L1: Fast renal cortical clearance

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Summary

Significant therapeutic efficacy in PSMA+ PC3 PIP flank tumor model

Efficacy of α-particle emitting agents (^{212}Pb/^{225}Ac) in micrometastatic model

Optimized radiotheranostic agent, ^{68}Ga-/^{177}Lu-PSMA-R2 (NCT03490838)

Towards translation of ^{212}Pb as a clinical therapeutic; getting the lead in! (Brechbiel et al. 2011, Dalton Trans)

Development and dosimetry of ^{203}Pb/^{212}Pb-labelled PSMA ligands: bringing "the lead" into PSMA-targeted alpha therapy? (Santos et al. 2019, Eur J Nucl Med Mol Imaging)

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Acknowledgement

Our Team

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