UCSF Department of Radiology and Biomedical Imaging

Development of ^{134}Ce/La pa imaging surrogate for ^{225}Ac rad in prostate cancer

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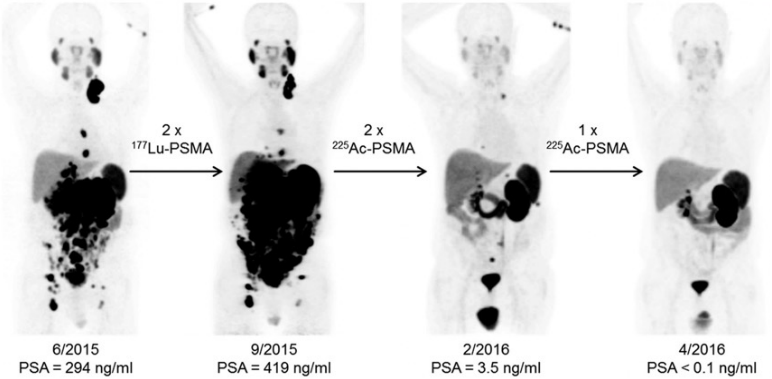
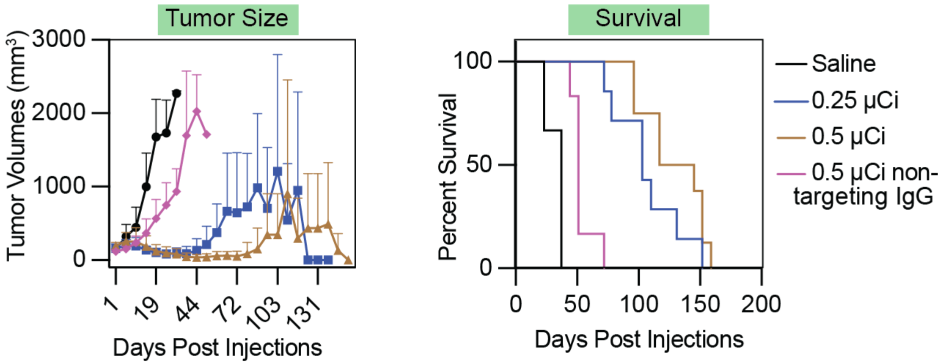
^{225}Ac radionuclide therapy

- ✓ Targeted alpha particle therapy with ^{225}Ac demonstrates great promise for cancer treatment
- ✓ For example, [^{225}Ac]PSMA-617 is effective in the treatment of PCa patients

[^{225}Ac]PSMA-617



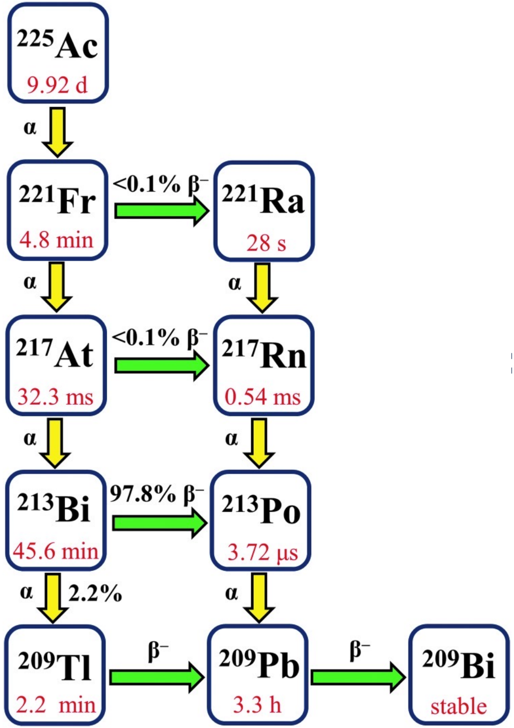
[^{225}Ac]DOTA-YS5: 22Rv1 tumors



- ✓ Difficult to directly measure the in vivo PK of ^{225}Ac labeled molecules

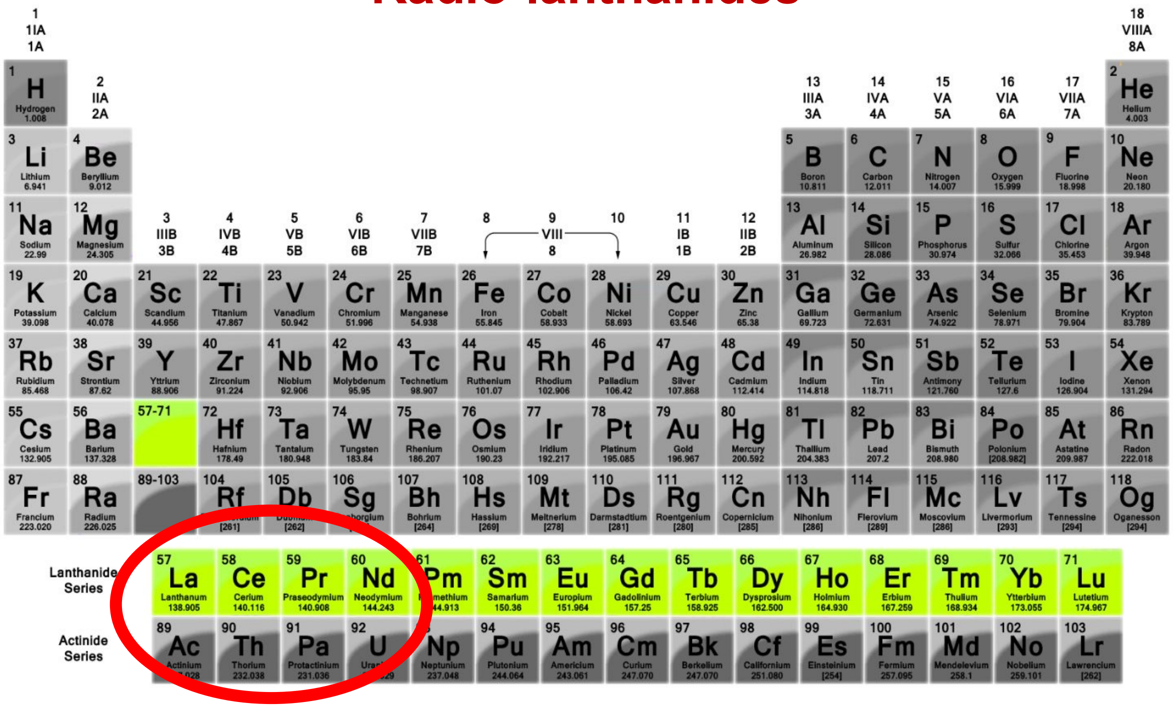
❖ Kratochwil K, et al., J Nuc Med. 2016, 57: 1941-1944
❖ Bidkar AP, et al., Clin Cancer Res. 2023, 29: 1916–1928

^{225}Ac Imaging?



✓ Two "Imageable" daughters; emits low-energy γ-rays, which are challenging to image with SPECT

Radio-lanthanides



- ✓ Actinium, Cerium, Lanthanum, Neodymium and Praseodymium
- ✓ Similar chemical properties
- ✓ Ionic radii (+3): Ac (1.12 Å), **La (1.03 Å), Ce (1.01 Å),** Pr (1.13 Å), Nd (1.11 Å)

Imaging Surrogates for 225Ac

Isotope	Half-life	Max β+ energy (MeV)	β+ branching ratio (%)	Challenges
$^{64}Cu/^{68}Ga/^{89}Zr$	12.7/1.1/78 h			dissimilar chemistry
^{130}La	8.7 m	4.29	71	High β+ energy; Short $t_{1/2}$; ^{130}Ba (0.1%)
^{131}La	59 m	1.89	23	Low β+ branching; ^{131}Ba (0.1%)
^{132}La	4.59 h	3.67	41	$t_{1/2}$; Long-lived daughter (10^{21} y)
^{133}La	3.91 h	1.02	7	$t_{1/2}$; Low β+ branching; 10.5 y daughter
$^{134}Ce/^{134}La$	77 h /6.5 m	2.71	64	
^{136}La	9.9 min	1.83	35	Short $t_{1/2}$; Low β+ branching

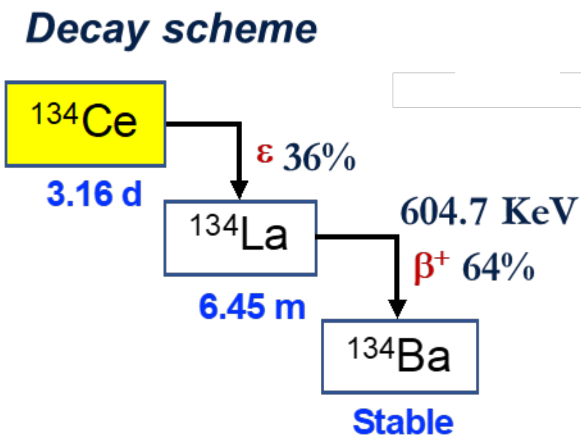
✓ $^{134}Ce/La$ pair may serve as a better PET imaging surrogate for ^{225}Ac therapy

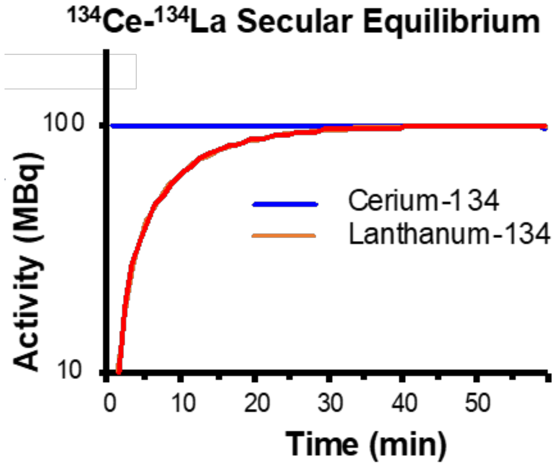
❖ Nelson BJB, et al., J Nuc Med. 2022, 63: 584-90

❖ Alicio-Sarduy E, et al., J Nuc Med. 2021, 62: 1012-5

^{134}Ce/La pair

✓ ^{nat}La (p, 6n) yielding ^{134}Ce





✓ ^{134}Ce/La is an in-situ generator

❖ Bailey TA, et al., Nature Chemistry, 2021,13: 284-289
❖ Lubberink M, Tolmachev V, et al., Phys. Med. Biol. 2002, 47: 615–29

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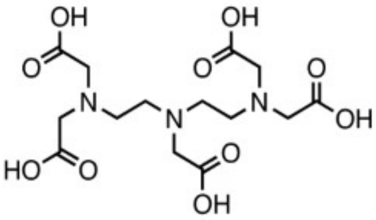
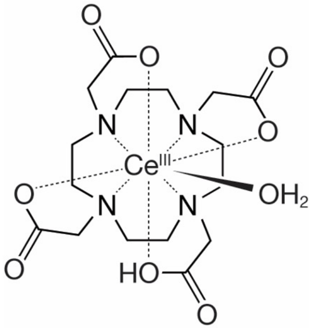
❖ $^{134}Ce/La$ pair (Abergel lab)



DTPA
(+3 metal chelator)



DOTA
(+3 metal chelator)

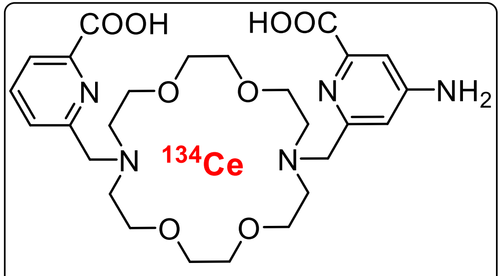
- ✓ DTPA & DOTA
- ✓ Higher molar ratios (1000:1, L:M)
- ✓ Higher Temp.(45 °C)

❖Bailey TA, et al., Nature Chemistry, 2021,13: 284-289
❖Bailey TA, et al., Nuclear Medicine and Biology, 2022, 28: 110–111

Objective

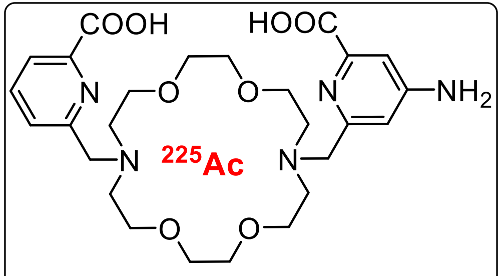
- ✓ Develop a robust radiolabeling method for chelation with ^{134}Ce, which can serve as a surrogate for $^{134}Ce/^{225}Ac$ theranostic agents.

- ✓ Utilize the developed methods for prostate cancer imaging using the small molecule PSMA-617, and prostate cancer targeting antibody YS5



^{134}Ce-Macropa.NH_2

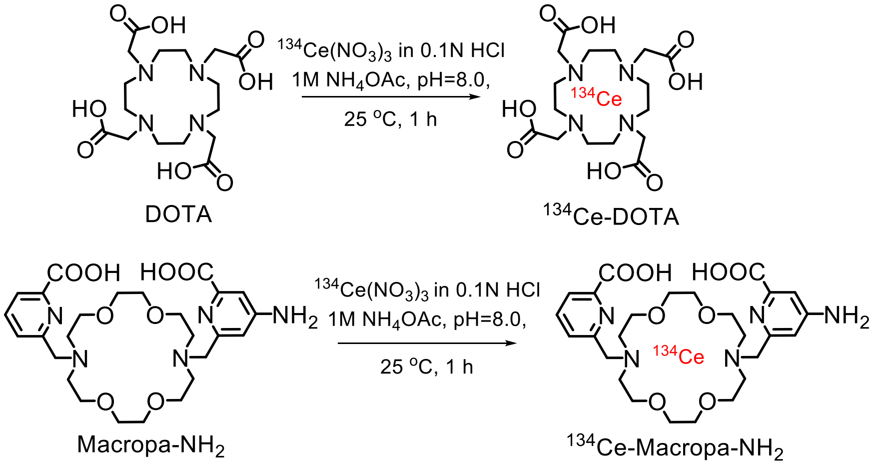
=

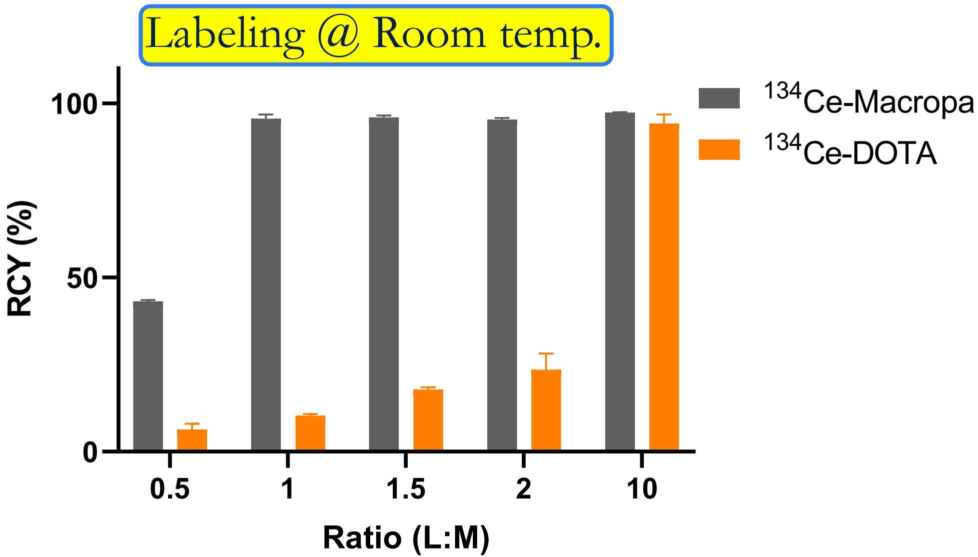


^{225}Ac-Macropa.NH_2

❖ Thiele NA, et al., Angew Chem. 2017,129:14904–14909

Model chelator studies: Macropa.NH_2 & DOTA





✓ Macropa.NH_2 is effective at a lower ligand-to-metal ratios than DOTA

TLC : C18, 10% NH_4Cl:MeOH (1:1)

❖ Bobba KN, et al., JNM, 2023, 00:1-7, DOI:10.2967/jnumed.122.265355

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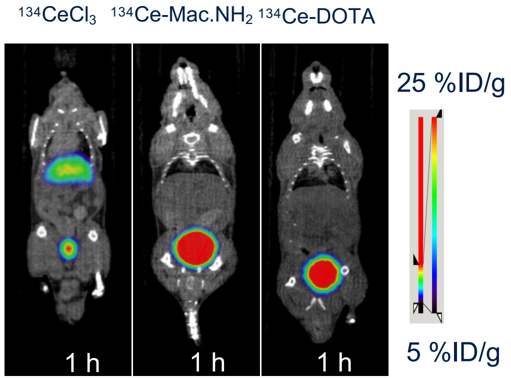
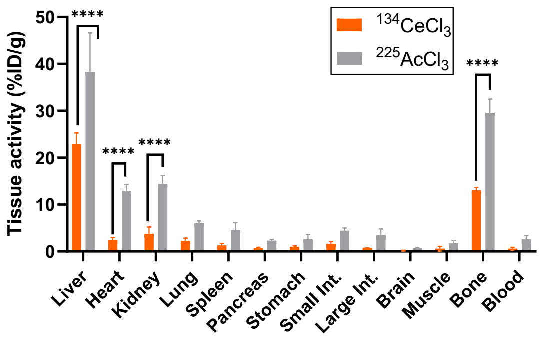
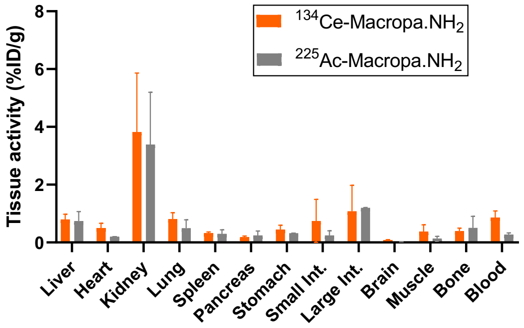
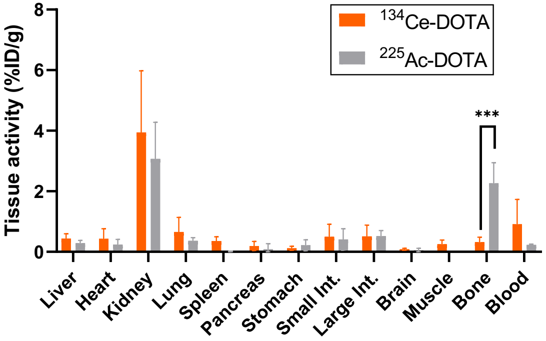
^{134}Ce-DOTA/Macropa.NH_2 in vivo







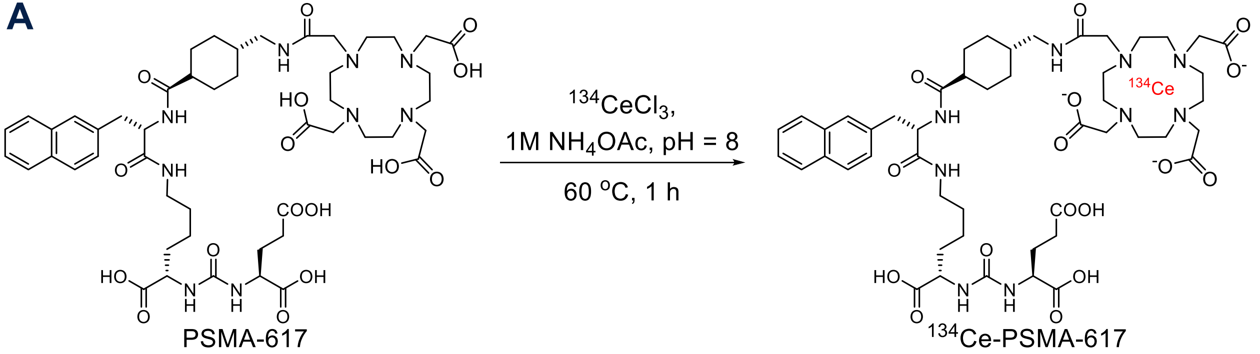


- ✓ High in vivo stability of ^{134}Ce-DOTA and Macropa.NH_2
- ✓ ^{225}Ac &^{134}Ce-DOTA/Macropa ex-vivo biodistribution are largely similar

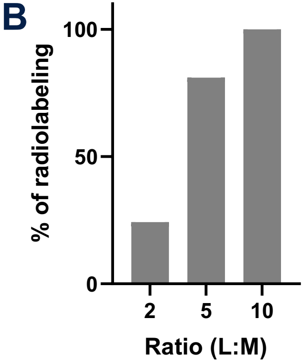
❖ Bobba KN, et al., JNM, 2023, 00:1-7, DOI:10.2967/jnumed.122.265355

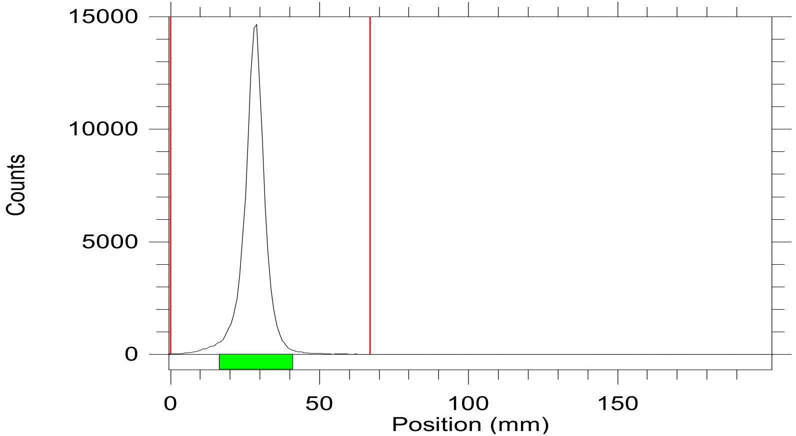
Radiolabeling of ^{134}Ce-PSMA-617

A



B

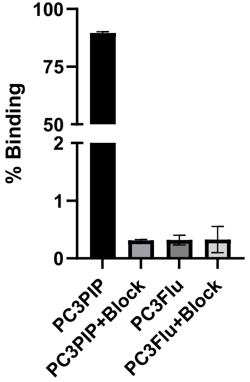




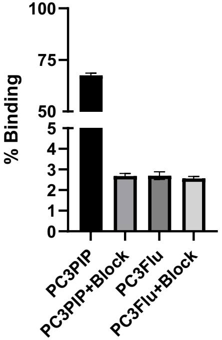
In vitro studies in PCa cells with ^{134}Ce-PSMA-617

❖ Cell binding

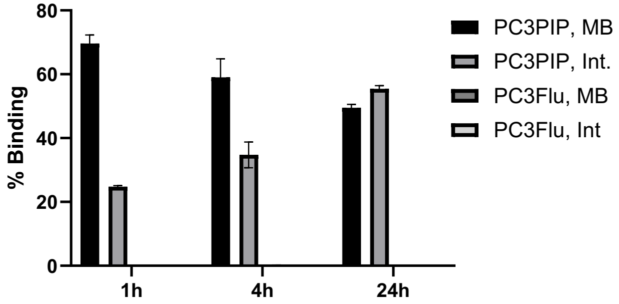
^{134}Ce-PSMA-617

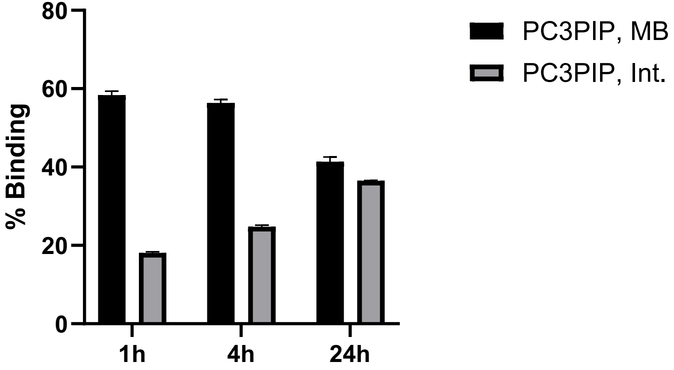


^{225}Ac-PSMA-617

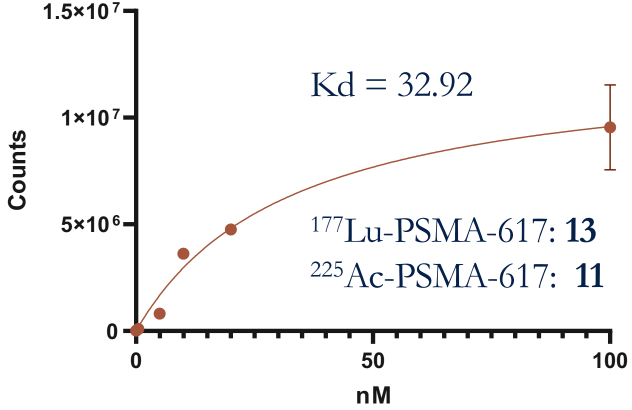


❖ Membrane bound and Internalization

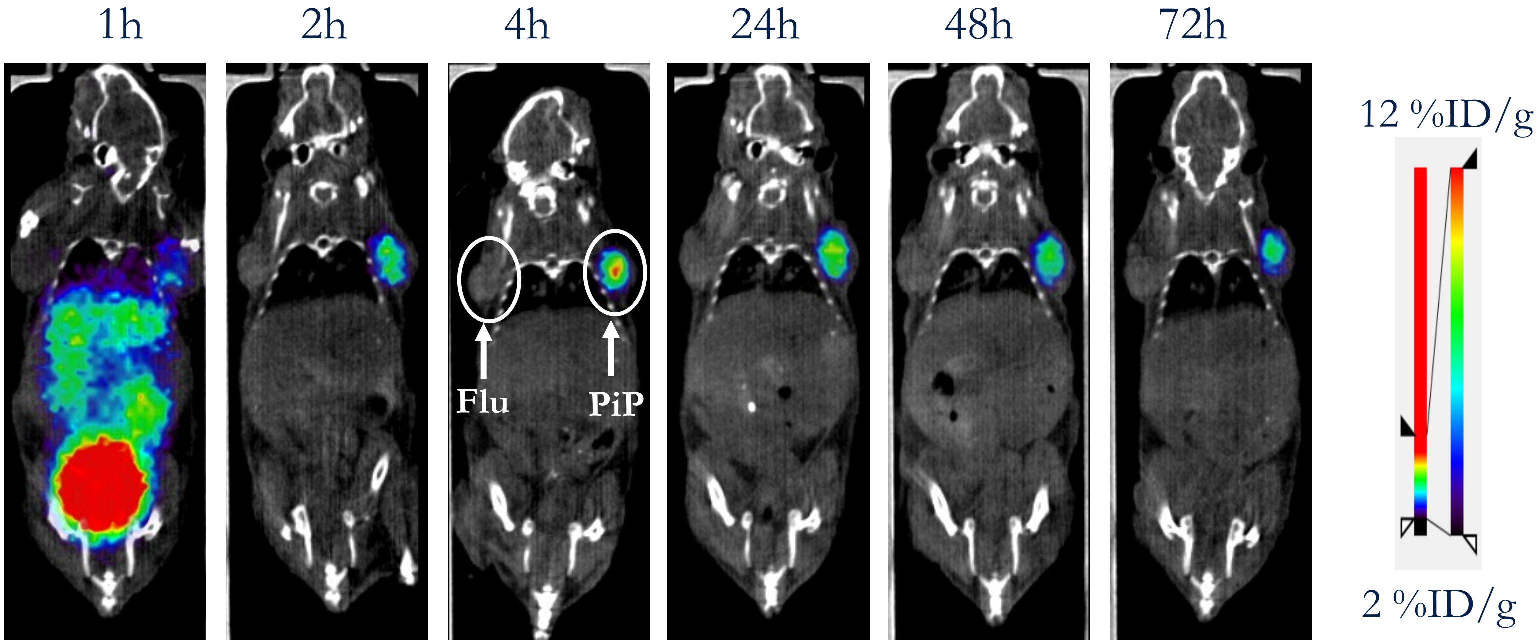




❖ Saturation binding assay

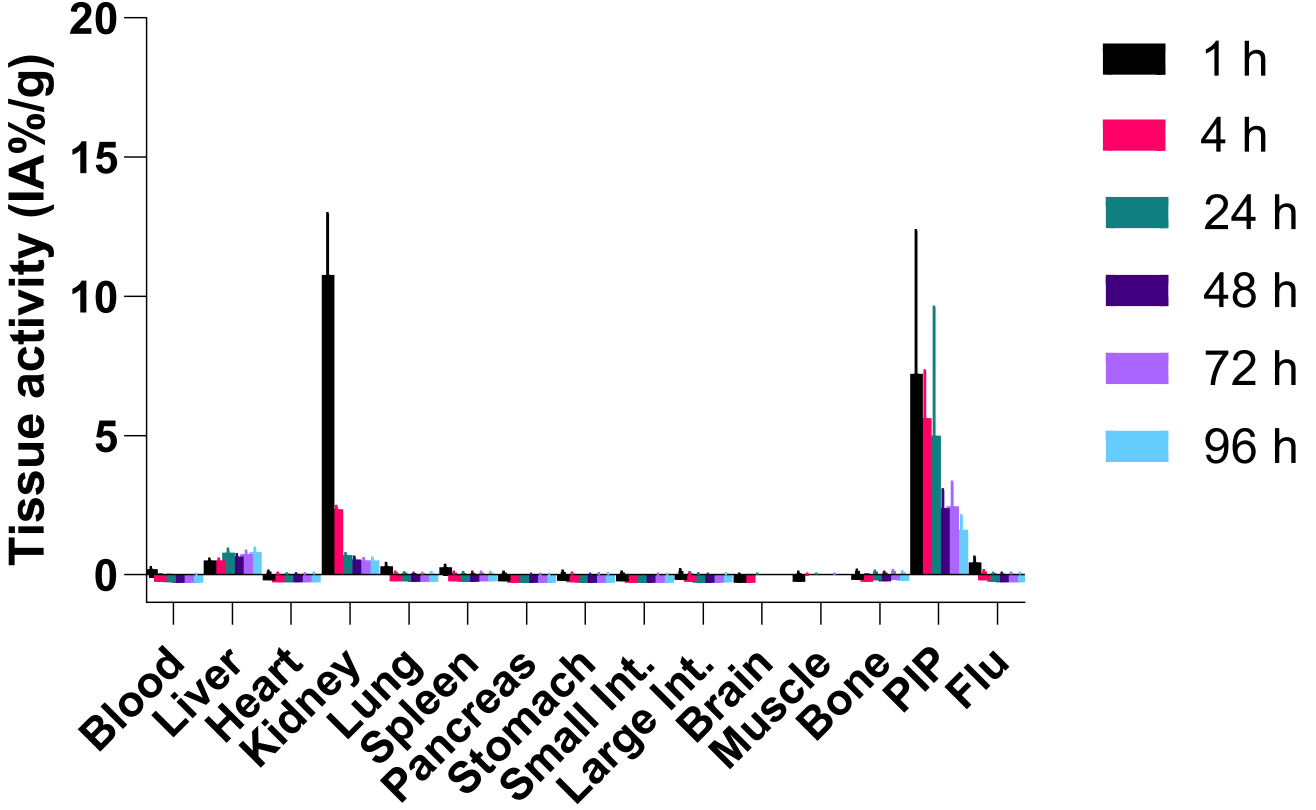


PET Imaging of ^{134}Ce-PSMA-617 in dual xenograft models

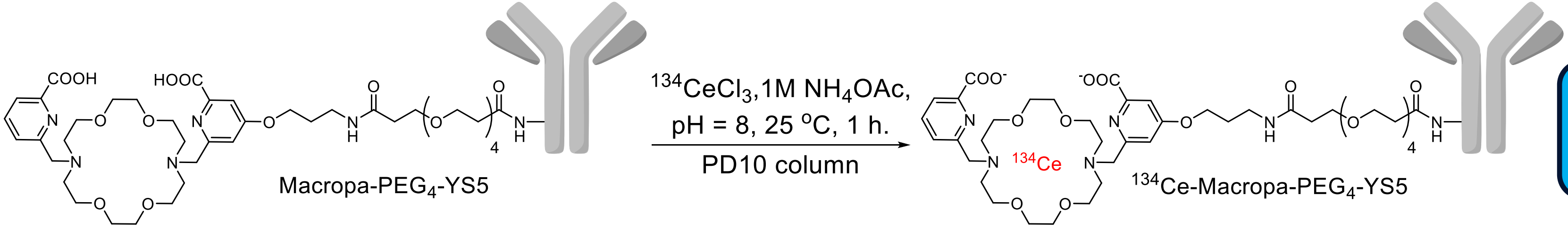


PC3 PiP = PSMA positive
PC3 Flu = PSMA negative

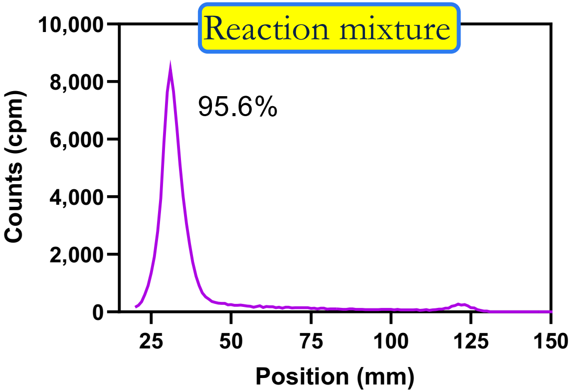
^{134}Ce-PSMA-617_BioD

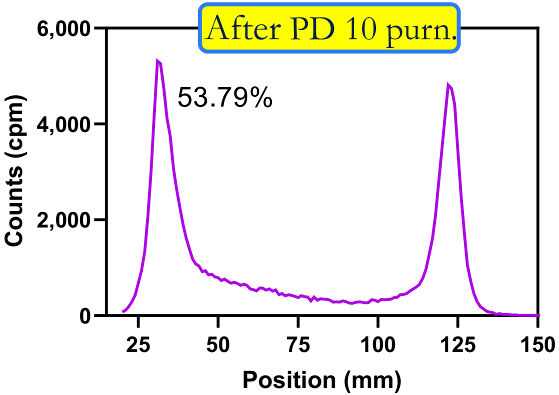


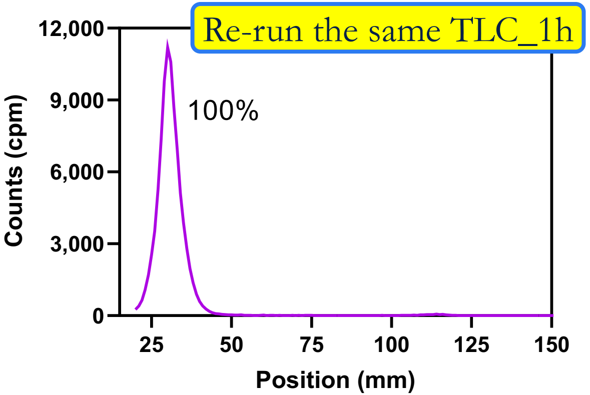
Radiolabeling of Macropa-PEG_4-YS5



RCY~95.6%
SA=4.1 mCi/mg
NDC







- ✓ Able to visualize the recoil emission of ^{134}La from the chelates by TLC
- ✓ Similar observations with ^{134}Ce-PSMA-617

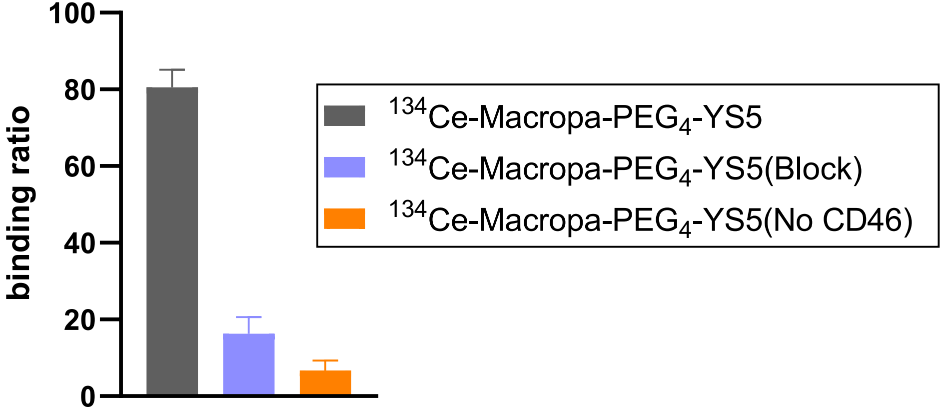
TLC: ITLC-SG, 10 mM EDTA, pH=5.5

❖ Bobba KN, et al., JNM, 2023, 00:1-7, DOI:10.2967/jnumed.122.265355

In vitro assay

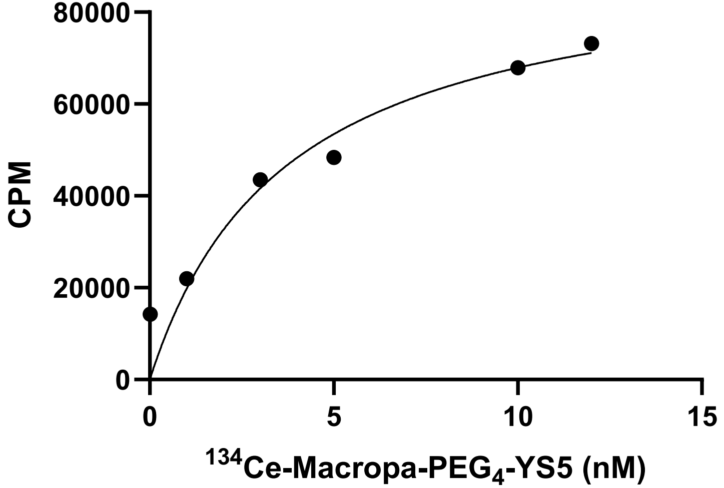
❖ Immunoreactivity assay

~80.54±4.55%



❖ Binding constant in 22Rv1 cells

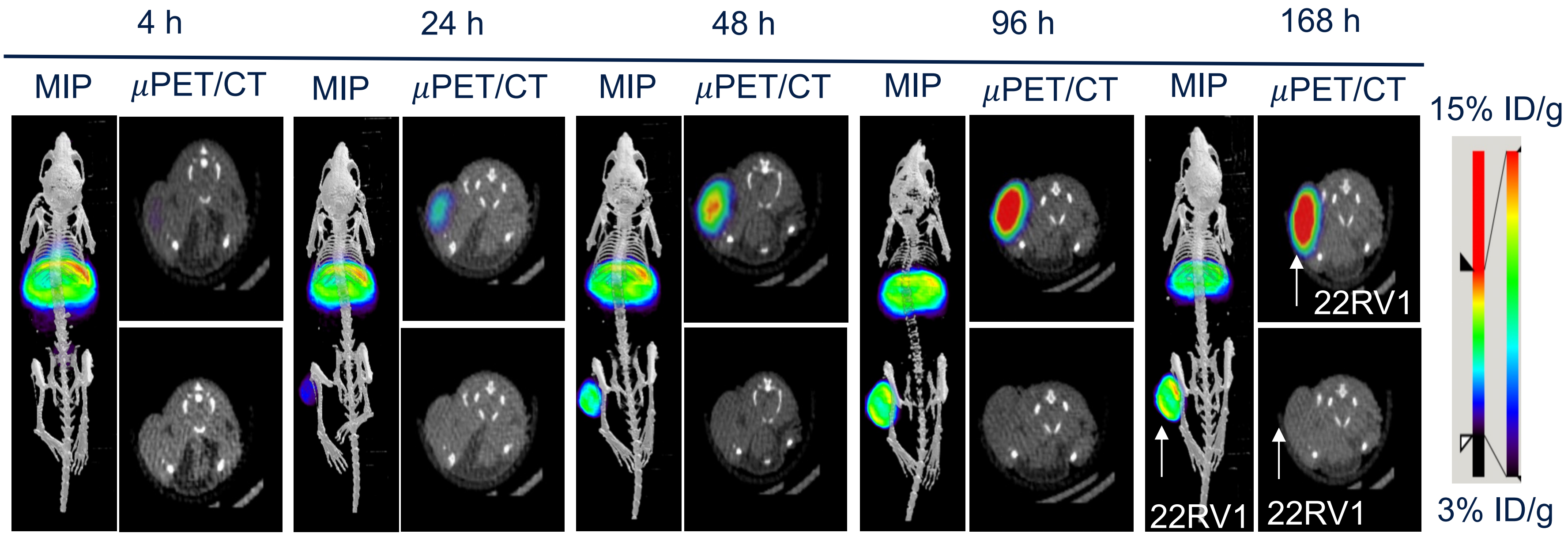
K_d = 3.7 nM



✓ It could be synthesized effectively with 1:1 ligand-to-metal ratios, with a little or no loss of CD46 binding affinity

❖ Bobba KN, et al., JNM, 2023, 00:1-7, DOI:10.2967/jnumed.122.265355

PET Imaging



- ✓ 22Rv1 xenografts at various time points 4 h to 7 days p.i.; n=4
- ✓ High tumor uptake, low in background tissues except for the Liver

❖ Bobba KN, et al., JNM, 2023, 00:1-7, DOI:10.2967/jnumed.122.265355

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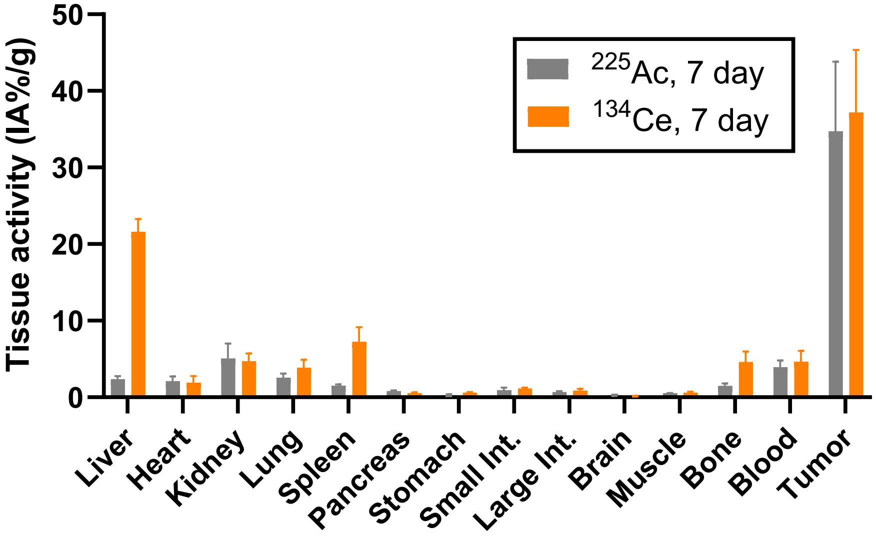
Biodistribution of $^{134}Ce/^{225}Ac$-Macropa-PEG$_4$-YS5



- ✓ Similar uptake in tumor and most of the visualized tissues for ^{225}Ac and ^{134}Ce
- ✓ Significant differences in the liver ($p<0.0001$) and spleen ($p=0.0109$) uptake were observed at 7 d p.i.
- ✓ 22Rv1 xenografts at 7 d (n=5) p.i.

❖ Bobba KN, et al., JNM, 2023, 00:1-7, DOI:10.2967/jnumed.122.265355

Summary

- ✓ Radiolabeling methodology for ^{134}Ce is suitable for small molecules using DOTA, biomolecules benefit from Macropa chelate
- ✓ In vivo PET imaging revealed high in vivo stability of ^{134}Ce-DOTA/Macropa.NH_2
- ✓ ^{134}Ce-PSMA-617 has similar *in vitro* cell binding to ^{225}Ac-PSMA-617
- ✓ PET imaging of ^{134}Ce-Macropa-PEG_4-YS5, showed a high tumor uptake at 7d p.i.
- ✓ The ex vivo biodistribution was consistent with the ^{225}Ac-Macropa-PEG_4-YS5 in tumor and most tissues, with the exception of liver and spleen
- ✓ Therefore, ^{134}Ce/^{225}Ac could serve as a theranostic pair for prostate cancer

❖ Bobba KN, et al., JNM, 2023, 00:1-7, DOI:10.2967/jnumed.122.265355

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DoD Translational science PCRP awards W81XWH-20-1-0292, W81XWH-21-1-0792

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UCSF Precision Imaging of Cancer and Therapy Award

Thank you for your attention!

Questions?

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