



Department of Radiology  
and Biomedical Imaging

# Development of $^{134}\text{Ce}/\text{La}$ pair imaging surrogate for $^{225}\text{Ac}$ rad in prostate cancer

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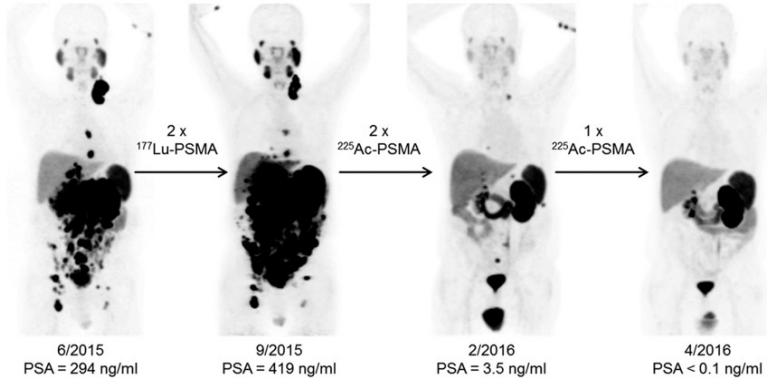
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Assistant Professional Researcher, UCSF

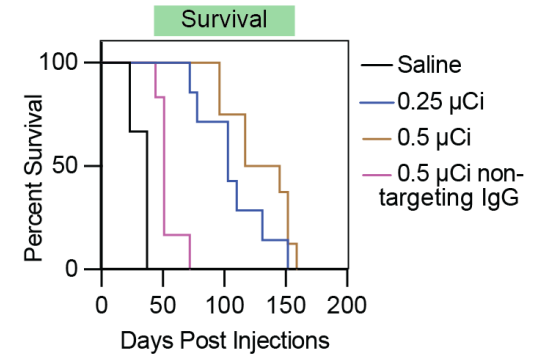
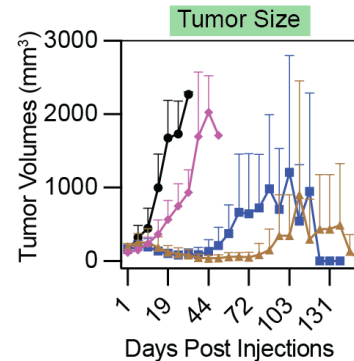
# $^{225}\text{Ac}$ radionuclide therapy

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

## [ $^{225}\text{Ac}$ ]PSMA-617

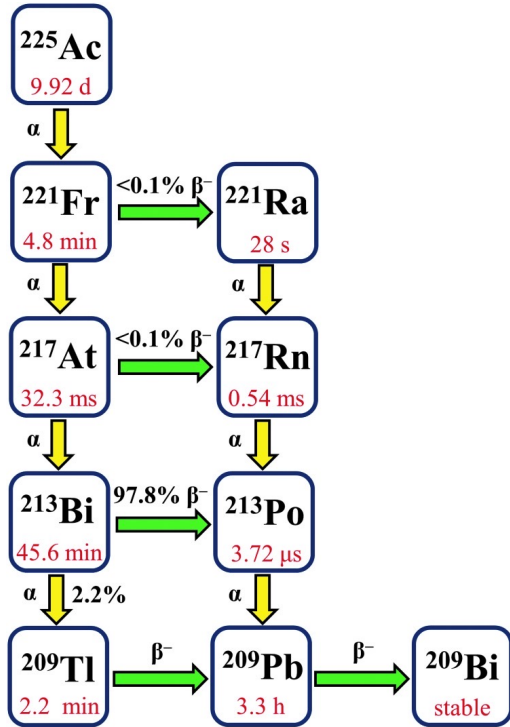


## [ $^{225}\text{Ac}$ ]DOTA-YS5: 22Rv1 tumors



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

# $^{225}\text{Ac}$ Imaging?



- ✓ Two “Imageable” daughters; emits low-energy  $\gamma$ -rays, which are challenging to image with SPECT

# Radio-lanthanides

1 1IA 1A																	18 VIIIA 8A
1 H Hydrogen 1.008	2 IIA 2A											13 IIIA 3A	14 IVA 4A	15 VA 5A	16 VIA 6A	17 VIIA 7A	2 He Helium 4.003
3 Li Lithium 6.941	4 Be Beryllium 9.012											5 B Boron 10.811	6 C Carbon 12.011	7 N Nitrogen 14.007	8 O Oxygen 15.999	9 F Fluorine 18.998	10 Ne Neon 20.180
11 Na Sodium 22.99	12 Mg Magnesium 24.305	3 IIIB 3B	4 IVB 4B	5 VB 5B	6 VIB 6B	7 VIIB 7B	8 VIII 8	9 VIII 8	10 VIII 8	11 IB 1B	12 IIB 2B	13 Al Aluminum 26.982	14 Si Silicon 28.086	15 P Phosphorus 30.974	16 S Sulfur 32.065	17 Cl Chlorine 35.453	18 Ar Argon 39.948
19 K Potassium 39.098	20 Ca Calcium 40.078	21 Sc Scandium 44.956	22 Ti Titanium 47.887	23 V Vanadium 50.942	24 Cr Chromium 51.996	25 Mn Manganese 54.938	26 Fe Iron 55.845	27 Co Cobalt 58.933	28 Ni Nickel 58.693	29 Cu Copper 63.546	30 Zn Zinc 65.38	31 Ga Gallium 69.723	32 Ge Germanium 72.631	33 As Arsenic 74.922	34 Se Selenium 78.971	35 Br Bromine 79.904	36 Kr Krypton 83.799
37 Rb Rubidium 85.468	38 Sr Strontium 87.62	39 Y Yttrium 88.906	40 Zr Zirconium 91.224	41 Nb Niobium 92.906	42 Mo Molybdenum 95.95	43 Tc Technetium 98.907	44 Ru Ruthenium 101.07	45 Rh Rhodium 102.906	46 Pd Palladium 106.42	47 Ag Silver 107.868	48 Cd Cadmium 112.414	49 In Indium 114.818	50 Sn Tin 118.711	51 Sb Antimony 121.760	52 Te Tellurium 127.6	53 I Iodine 126.904	54 Xe Xenon 131.294
55 Cs Cesium 132.905	56 Ba Barium 137.328	57-71 Lanthanide Series	72 Hf Hafnium 178.49	73 Ta Tantalum 180.948	74 W Tungsten 183.84	75 Re Rhenium 186.207	76 Os Osmium 190.23	77 Ir Iridium 192.217	78 Pt Platinum 195.085	79 Au Gold 196.967	80 Hg Mercury 200.592	81 Tl Thallium 204.383	82 Pb Lead 207.2	83 Bi Bismuth 208.980	84 Po Polonium 209 [84]	85 At Astatine 209 [85]	86 Rn Radon 222.018
87 Fr Francium 223.020	88 Ra Radium 226.025	89-103 Actinide Series	104 Rf Rutherfordium [261]	105 Db Dubnium [262]	106 Sg Seaborgium [263]	107 Bh Bohrium [264]	108 Hs Hassium [265]	109 Mt Meitnerium [266]	110 Ds Darmstadtium [267]	111 Rg Roentgenium [268]	112 Cn Copernicium [269]	113 Nh Nihonium [286]	114 Fl Flerovium [289]	115 Mc Moscovium [288]	116 Lv Livermorium [293]	117 Ts Tennessine [294]	118 Og Oganesson [294]
		57 La Lanthanum 138.905	58 Ce Cerium 140.116	59 Pr Praseodymium 140.908	60 Nd Neodymium 144.243	61 Pm Promethium 144.913	62 Sm Samarium 150.36	63 Eu Europium 151.964	64 Gd Gadolinium 157.25	65 Tb Terbium 158.925	66 Dy Dysprosium 162.500	67 Ho Holmium 164.930	68 Er Erbium 167.259	69 Tm Thulium 168.934	70 Yb Ytterbium 173.055	71 Lu Lutetium 174.967	
		89 Ac Actinium [227]	90 Th Thorium 232.038	91 Pa Protactinium 231.036	92 U Uranium 238.029	93 Np Neptunium 237.048	94 Pu Plutonium 244.064	95 Am Americium 243.061	96 Cm Curium 247.070	97 Bk Berkelium 247.070	98 Cf Californium 251.080	99 Es Einsteinium [254]	100 Fm Fermium 257.085	101 Md Mendelevium 258.1	102 No Nobelium 259.101	103 Lr Lawrencium [262]	

- ✓ 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 $^{225}\text{Ac}$

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

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

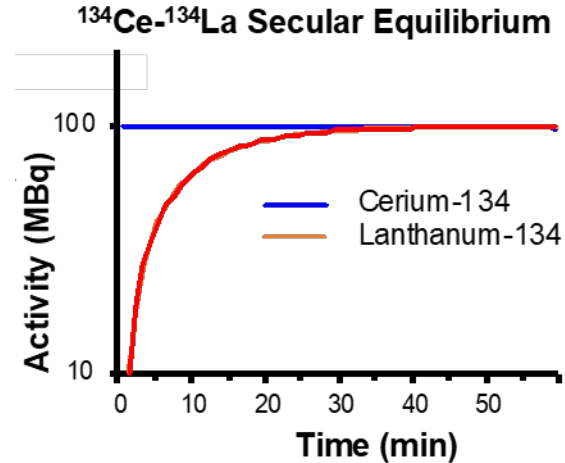
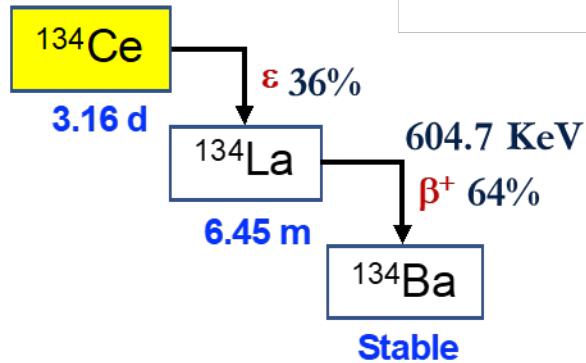
❖ Nelson BJB, et al., J Nuc Med. 2022, 63: 584-90

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

# $^{134}\text{Ce}/^{134}\text{La}$ pair

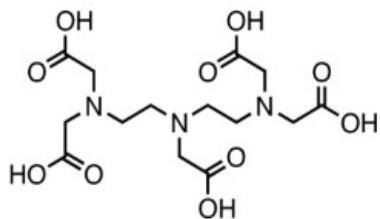
- ✓  $\text{natLa}$  (p, 6n) yielding  $^{134}\text{Ce}$

## Decay scheme

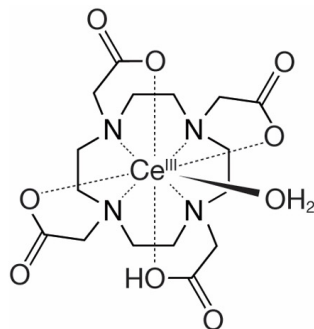


- ✓  $^{134}\text{Ce}/^{134}\text{La}$  is an in-situ generator

## ❖ $^{134}\text{Ce}/\text{La}$ pair (Abergel lab)



**DTPA**  
(+3 metal chelator)

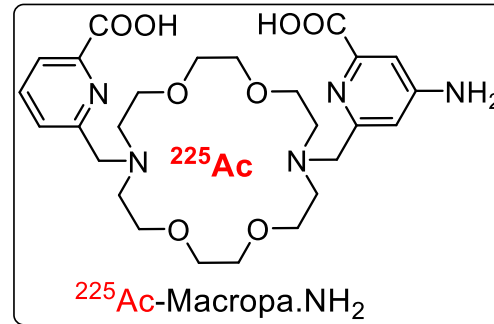
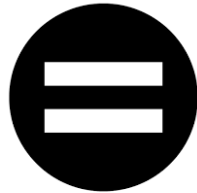
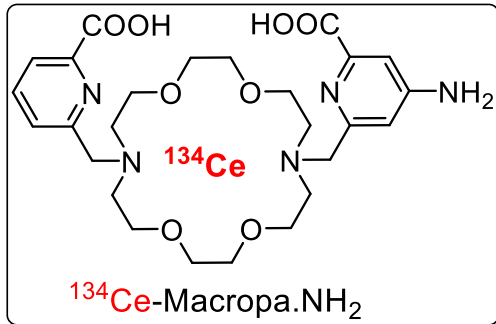


**DOTA**  
(+3 metal chelator)

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

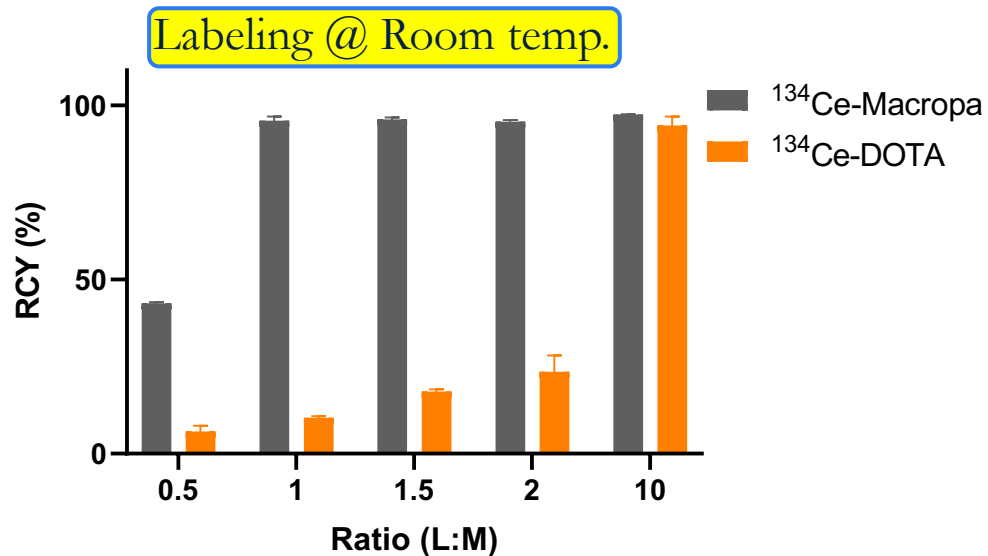
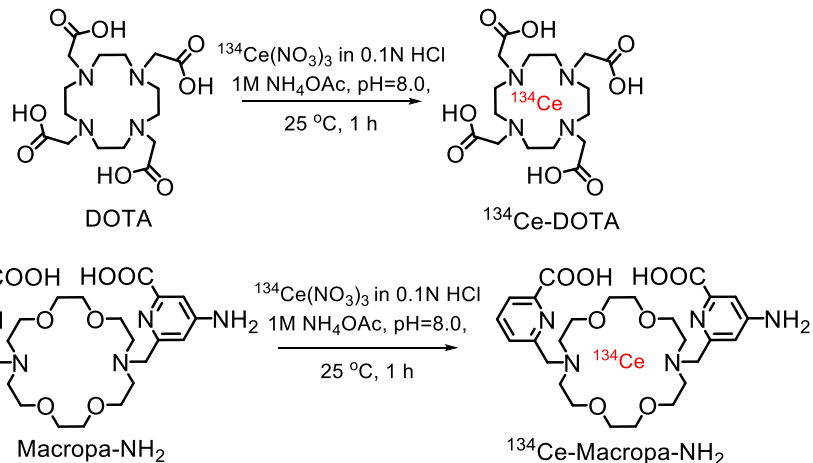
# Objective

- ✓ Develop a robust radiolabeling method for chelation with  $^{134}\text{Ce}$ , which can serve as a surrogate for  $^{134}\text{Ce}/^{225}\text{Ac}$  theranostic agents.
- ✓ Utilize the developed methods for prostate cancer imaging using the small molecule PSMA-617, and prostate cancer targeting antibody YS5





# Model chelator studies: Macropa.NH<sub>2</sub> & DOTA



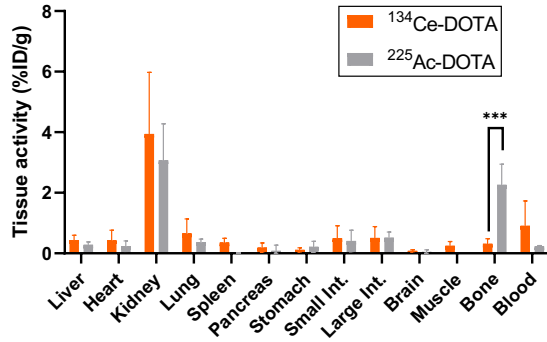
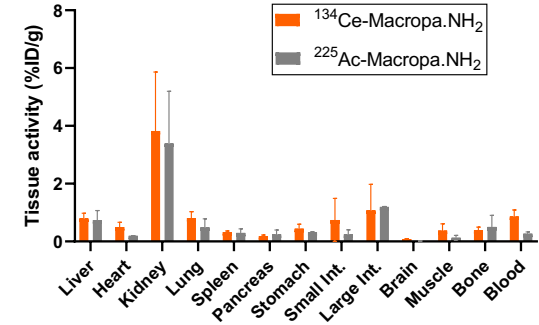
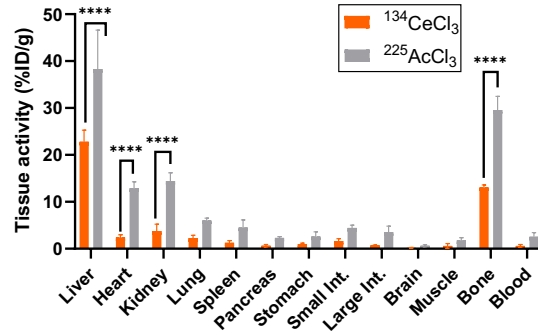
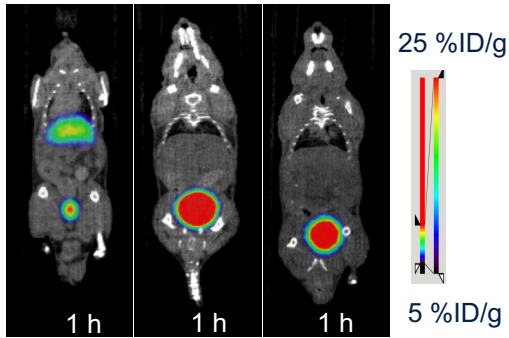
✓ Macropa.NH<sub>2</sub> is effective at a lower ligand-to-metal ratios than DOTA

TLC : C18, 10% NH<sub>4</sub>Cl:MeOH (1:1)

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

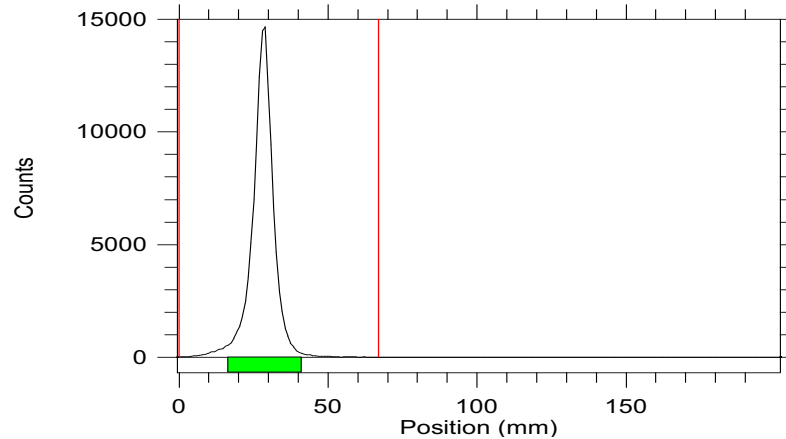
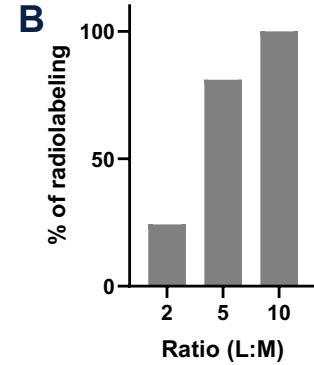
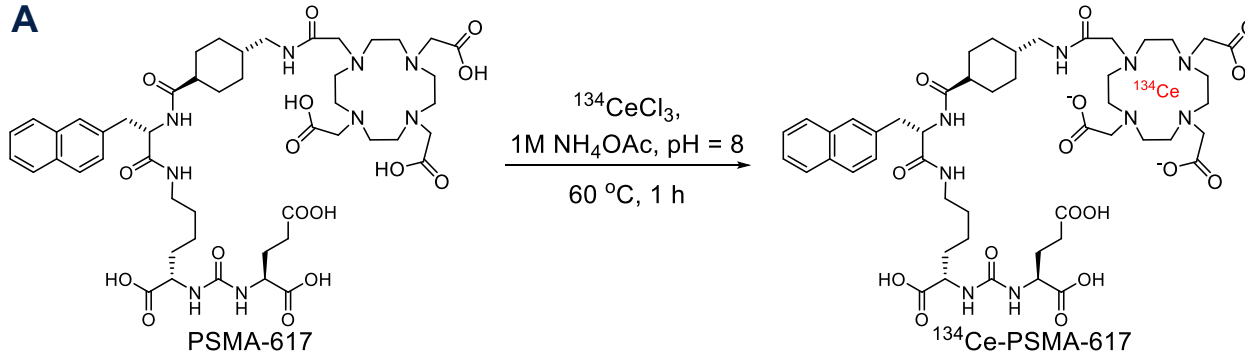
# $^{134}\text{Ce}$ -DOTA/Macropa.NH<sub>2</sub> in vivo

$^{134}\text{CeCl}_3$   $^{134}\text{Ce-Mac.NH}_2$   $^{134}\text{Ce-DOTA}$



- ✓ High in vivo stability of  $^{134}\text{Ce}$ -DOTA and Macropa.NH<sub>2</sub>
- ✓  $^{225}\text{Ac}$  &  $^{134}\text{Ce}$ -DOTA/Macropa ex-vivo biodistribution are largely similar

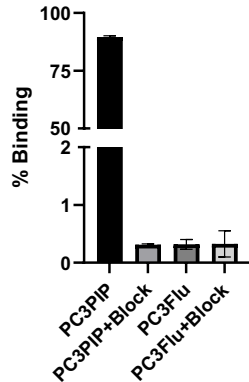
# Radiolabeling of $^{134}\text{Ce}$ -PSMA-617



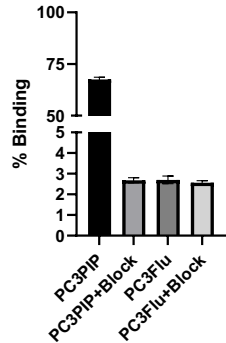
# In vitro studies in PCa cells with $^{134}\text{Ce}$ -PSMA-617

## ❖ Cell binding

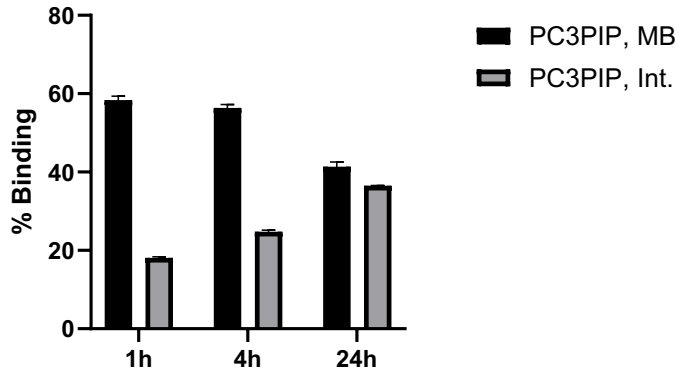
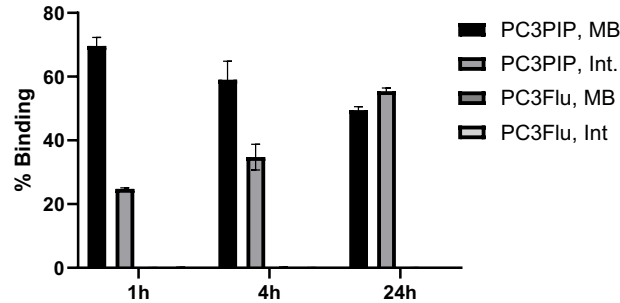
$^{134}\text{Ce}$ -  
PSMA-  
617



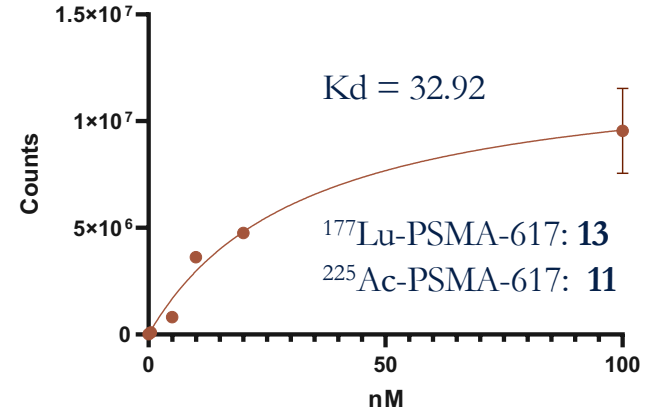
$^{225}\text{Ac}$ -  
PSMA-  
617



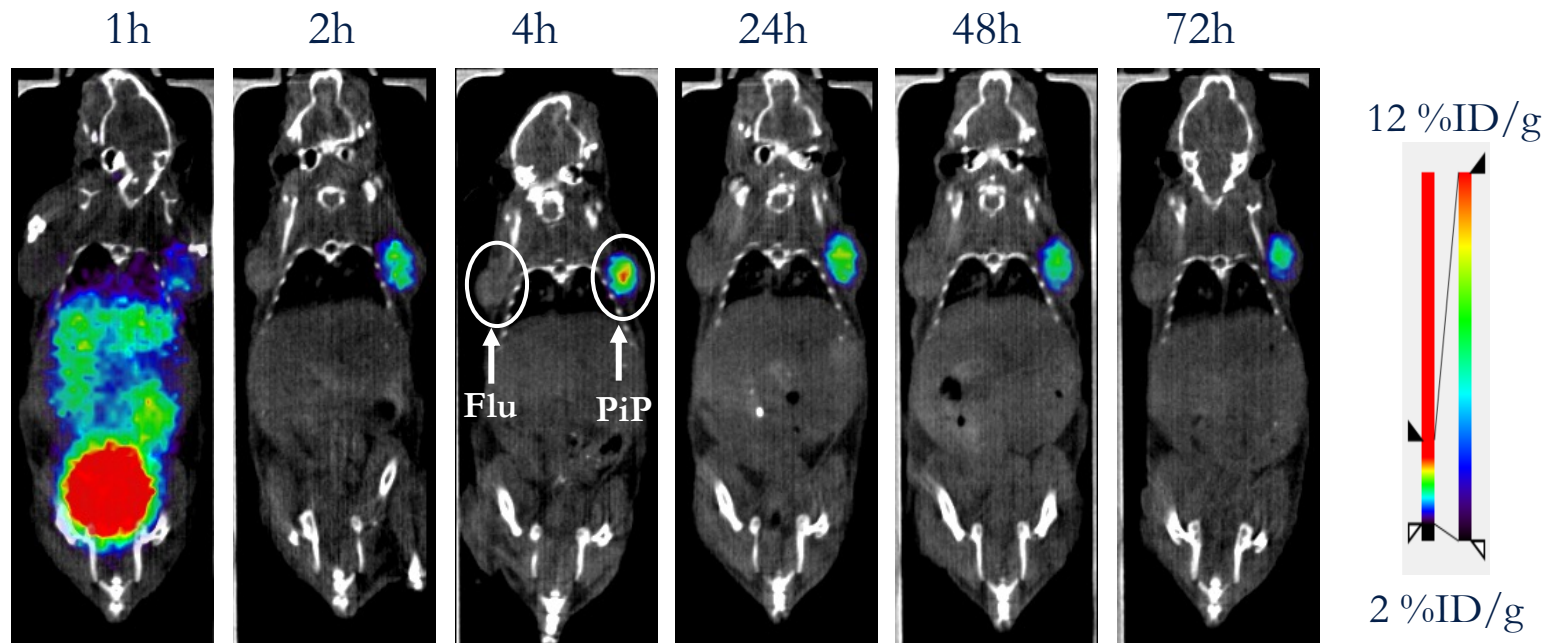
## ❖ Membrane bound and Internalization



## ❖ Saturation binding assay

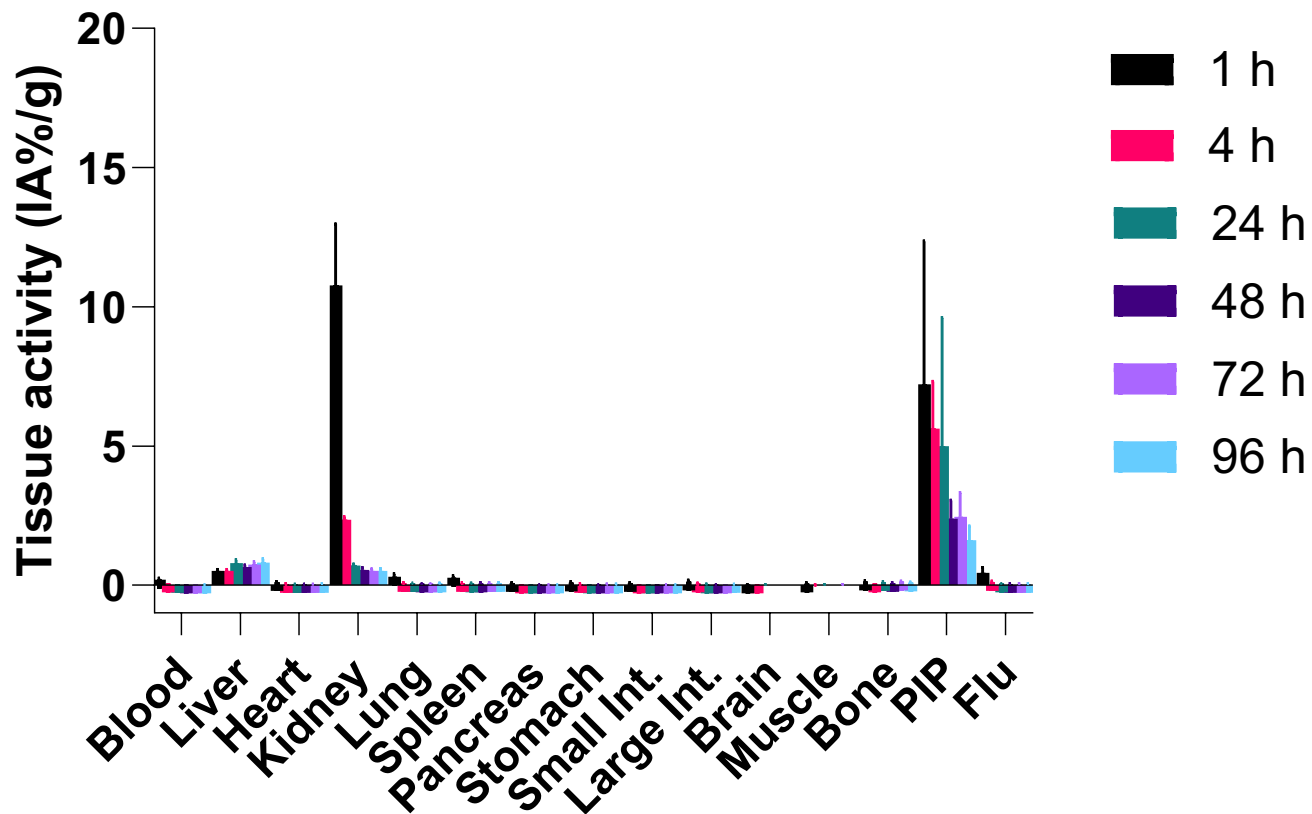


# PET Imaging of $^{134}\text{Ce}$ -PSMA-617 in dual xenograft models

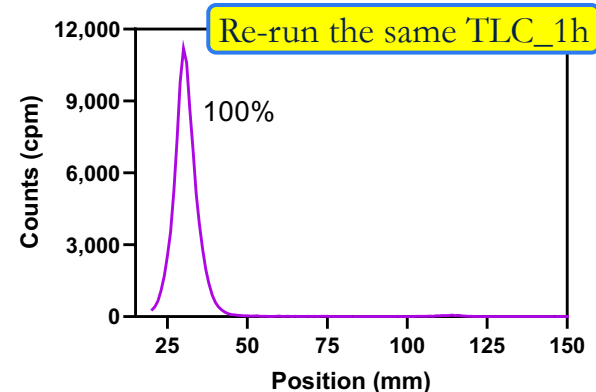
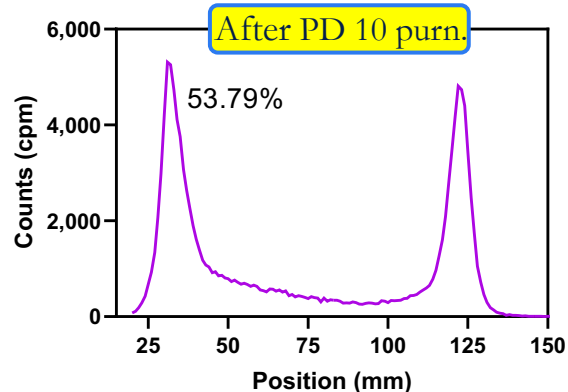
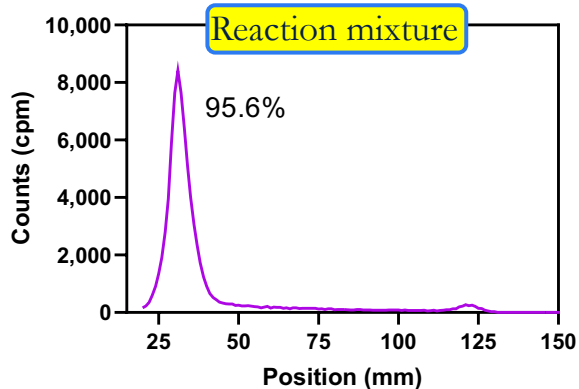
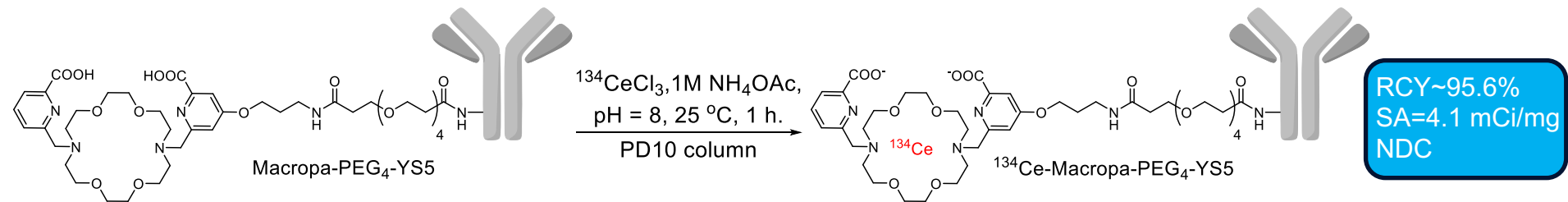


PC3 PiP = PSMA positive  
PC3 Flu = PSMA negative

# $^{134}\text{Ce}$ -PSMA-617\_BioD



# Radiolabeling of Macropa-PEG<sub>4</sub>-YS5



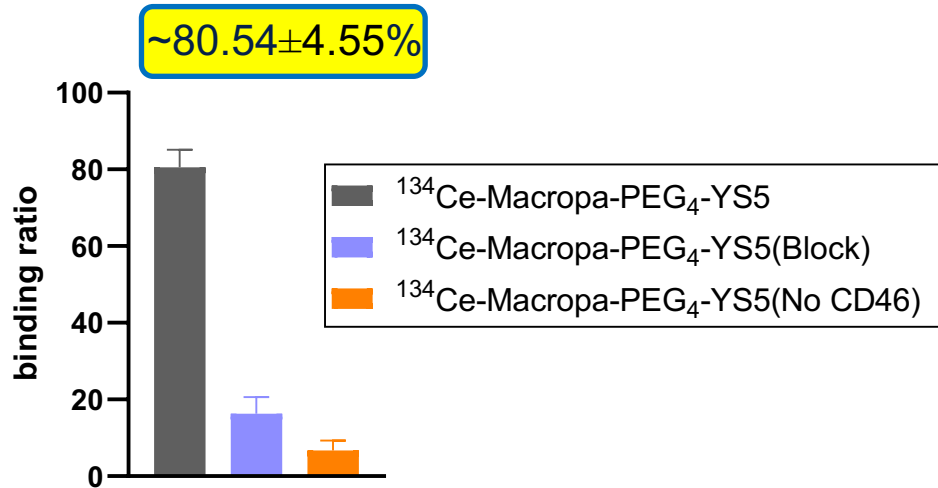
- ✓ Able to visualize the recoil emission of  $^{134}\text{La}$  from the chelates by TLC
- ✓ Similar observations with  $^{134}\text{Ce}$ -PSMA-617

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

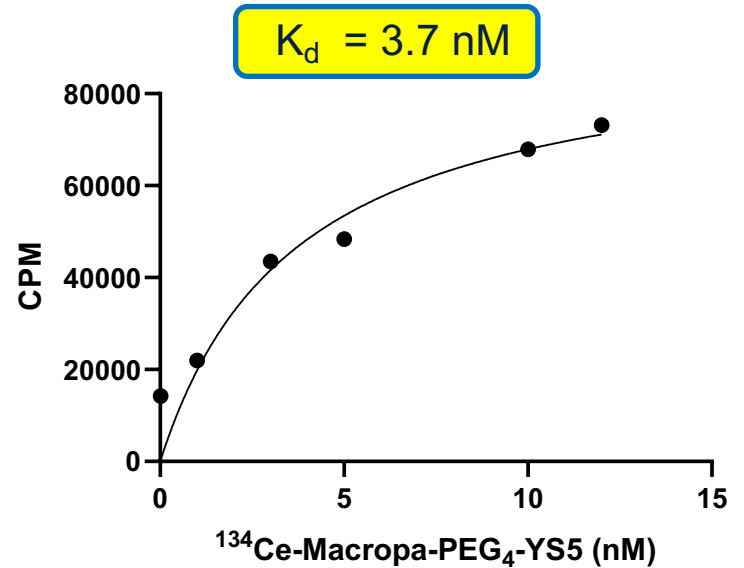
❖ Bobba KN, et al., JNM, 2023, 00:1-7, DOI:10.2967/jnumed.122.265355

# In vitro assay

## ❖ Immunoreactivity assay



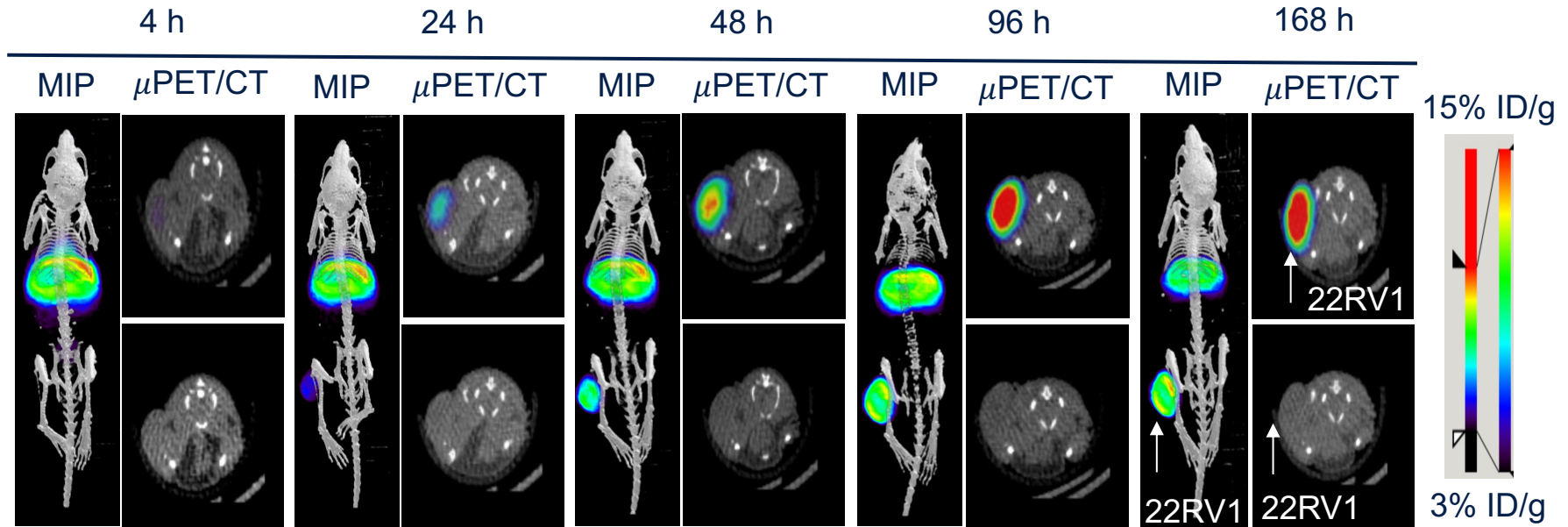
## ❖ Binding constant in 22Rv1 cells



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

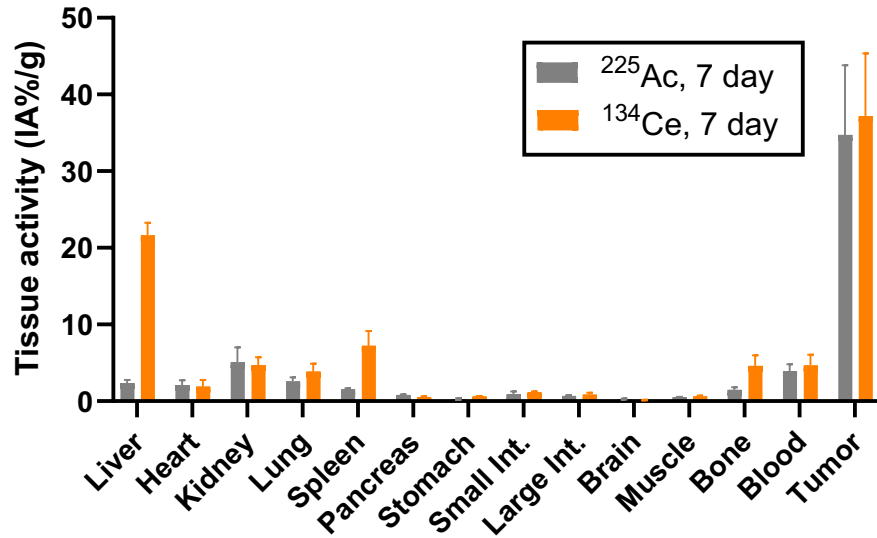


# PET Imaging



- ✓ 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

# Biodistribution of $^{134}\text{Ce}/^{225}\text{Ac}$ -Macropa-PEG<sub>4</sub>-YS5



✓ 22Rv1 xenografts at 7 d (n=5) p.i.

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

# Summary

- ✓ Radiolabeling methodology for  $^{134}\text{Ce}$  is suitable for small molecules using DOTA, biomolecules benefit from Macropa chelate
- ✓ In vivo PET imaging revealed high in vivo stability of  $^{134}\text{Ce}$ -DOTA/Macropa.NH<sub>2</sub>
- ✓  $^{134}\text{Ce}$ -PSMA-617 has similar *in vitro* cell binding to  $^{225}\text{Ac}$ -PSMA-617
- ✓ PET imaging of  $^{134}\text{Ce}$ -Macropa-PEG<sub>4</sub>-YS5, showed a high tumor uptake at 7d p.i.
- ✓ The ex vivo biodistribution was consistent with the  $^{225}\text{Ac}$ -Macropa-PEG<sub>4</sub>-YS5 in tumor and most tissues, with the exception of liver and spleen
- ✓ Therefore,  $^{134}\text{Ce}/^{225}\text{Ac}$  could serve as a theranostic pair for prostate cancer

# Acknowledgements

Flavell lab

**K. Naidu Bobba**

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Robin Peter

Becka Schuere

Bin Liu

Scott Bidlingmeier

Henry VanBrocklin

DOE Isotope Development Grant DE  
SC0023467

US DOE for  $^{225}\text{Ac}$  and  $^{134}\text{Ce}$

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

R01 CA271606, CA279203

UCSF Precision Imaging of Cancer and  
Therapy Award

Thank you for your attention!

Questions?

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