[$^{203/212}$Pb]VMT-α-NET Theranostic Pair Achieved Complete Response in SSTR2+ Preclinical Tumor Model

A Path from Bench → Bed

Dijie Liu, DVM, Ph.D

2022 Lead-212 User Group Meeting

10/04/2022

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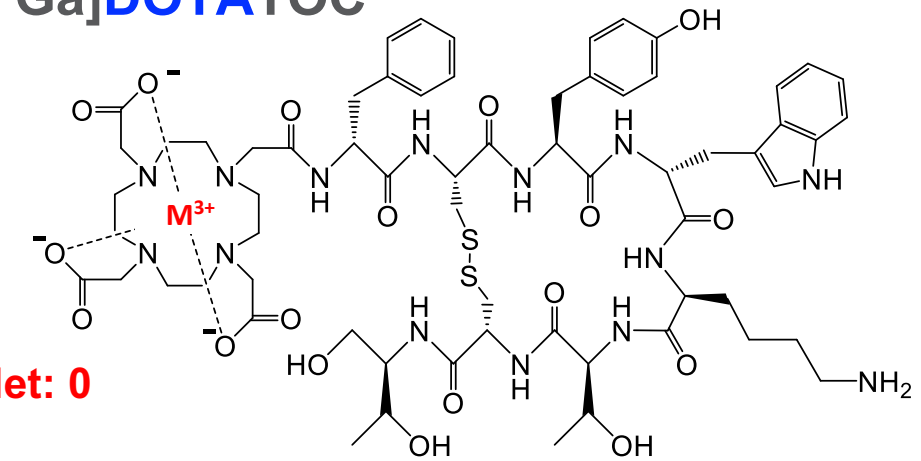
Disclosure

- Employed at Viewpoint Molecular Targeting Inc.

$^{203/212}$Pb-Based Theranostics Targeting SSTR2

[^{68}Ga]DOTATOC

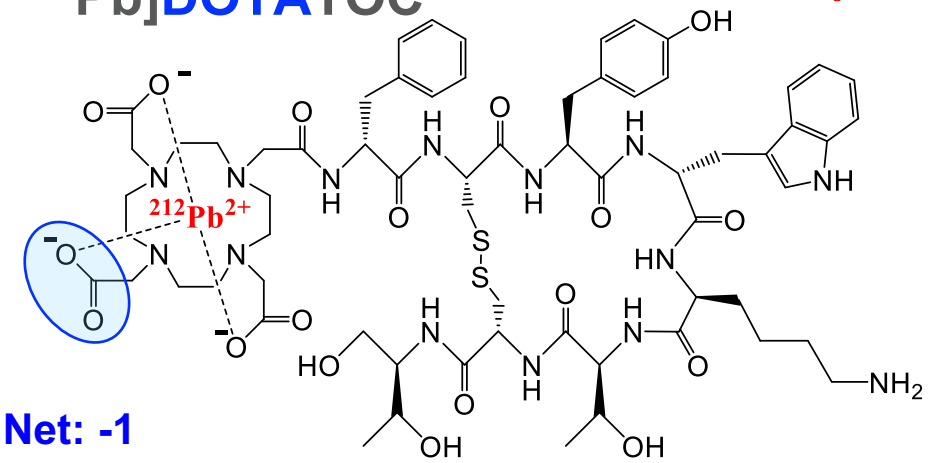


Radionuclides (M3+) : $^{67/68}$Ga, ^{90}Y, ^{177}Lu, ^{225}Ac

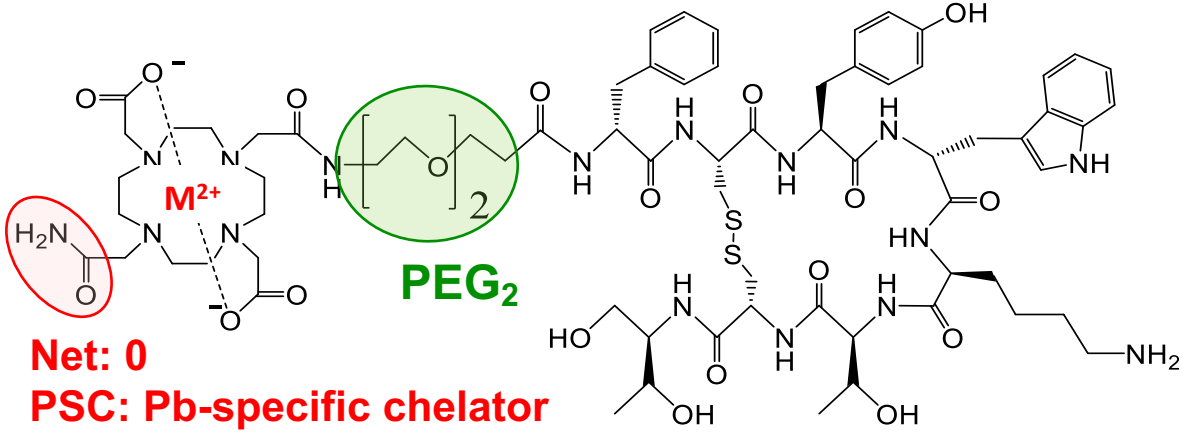
Targeted-alpha-emitter radiotherapy

"Lead Gospel"

[$^{203/212}$Pb]DOTATOC



[$^{203/212}$Pb]PSC-PEG$_2$-TOC (VMT-α-NET)



Radionuclides (M2+) : ^{64}Cu, ^{203}Pb, ^{212}Pb

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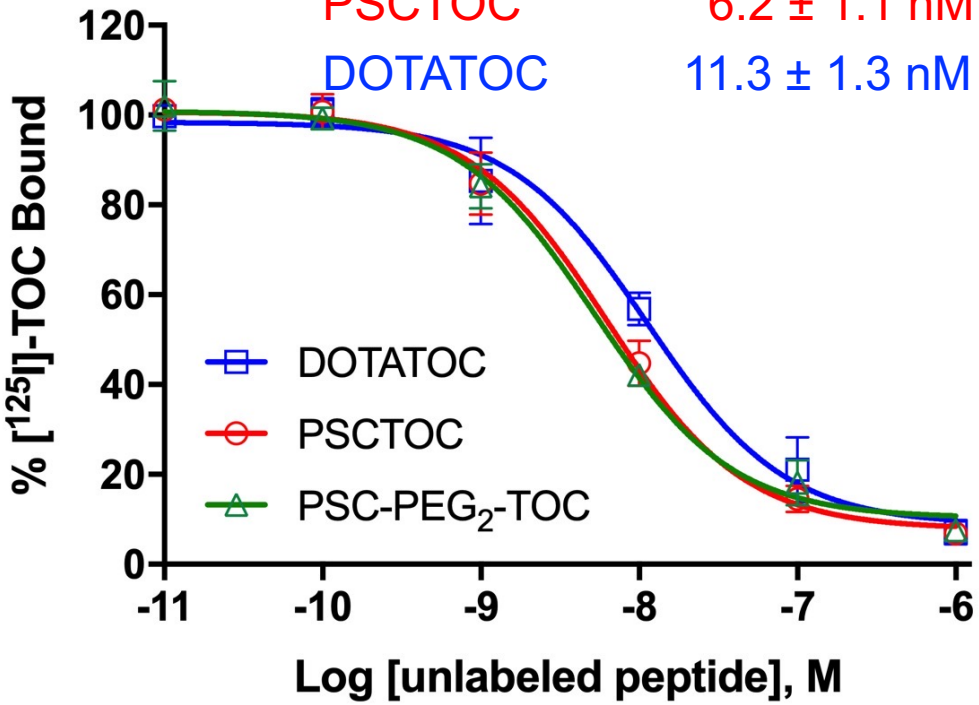
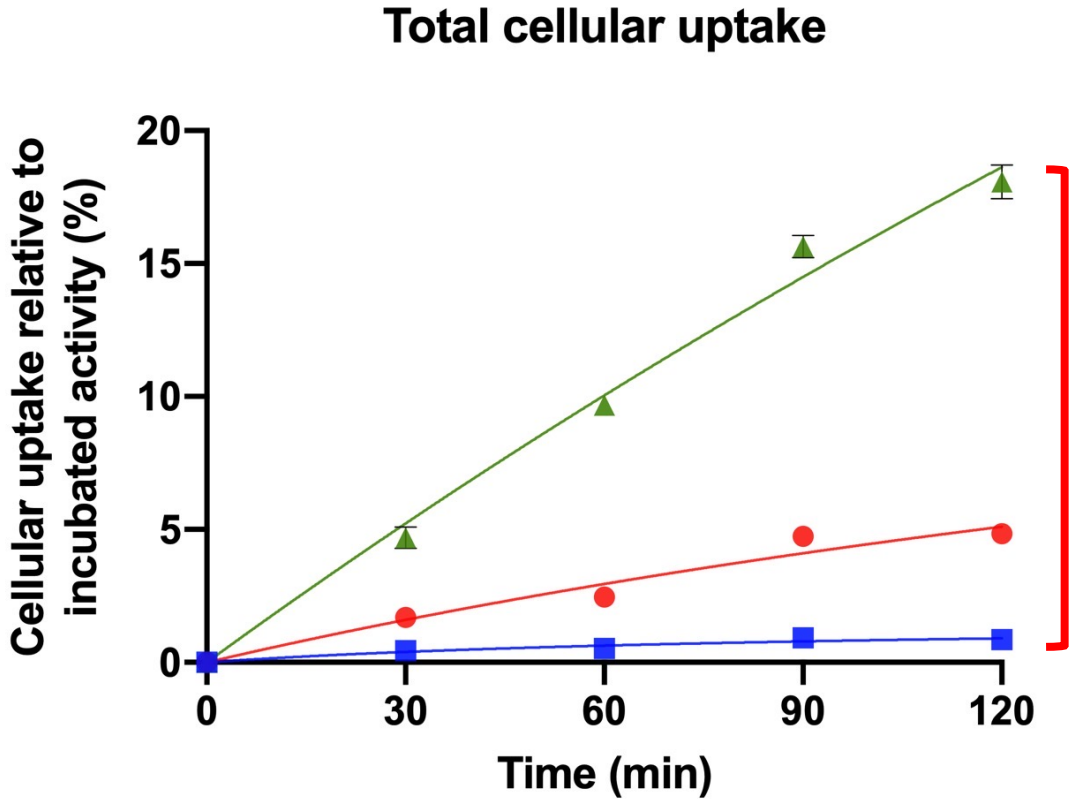
Binding Affinity & Cellular Uptake to SSTR2

Dongyoul Lee, PhD

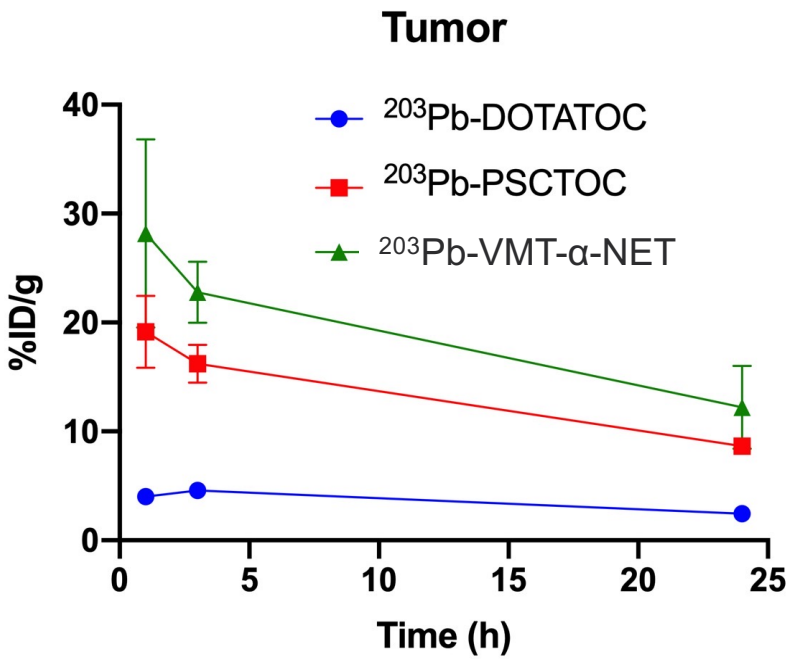
PSC-PEG$_2$-TOC 5.3 ± 1.2 nM
PSCTOC 6.2 ± 1.1 nM
DOTATOC 11.3 ± 1.3 nM

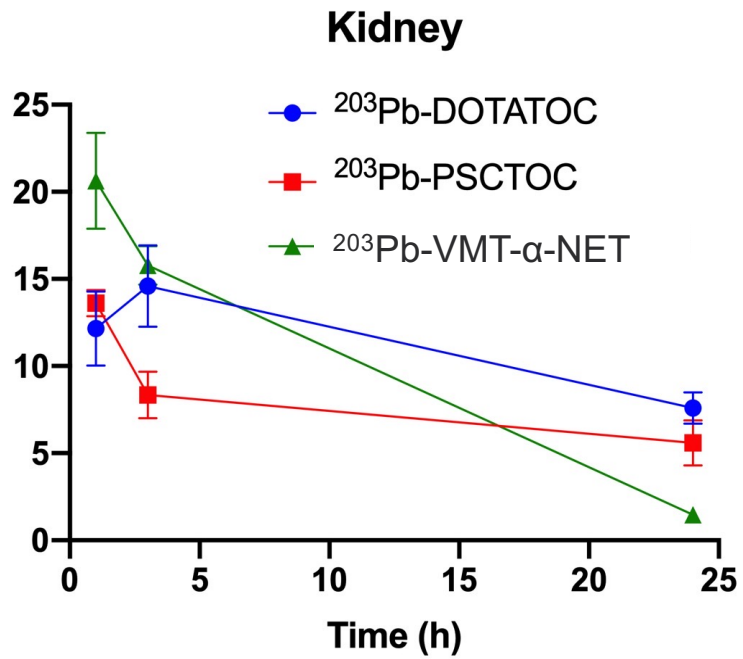


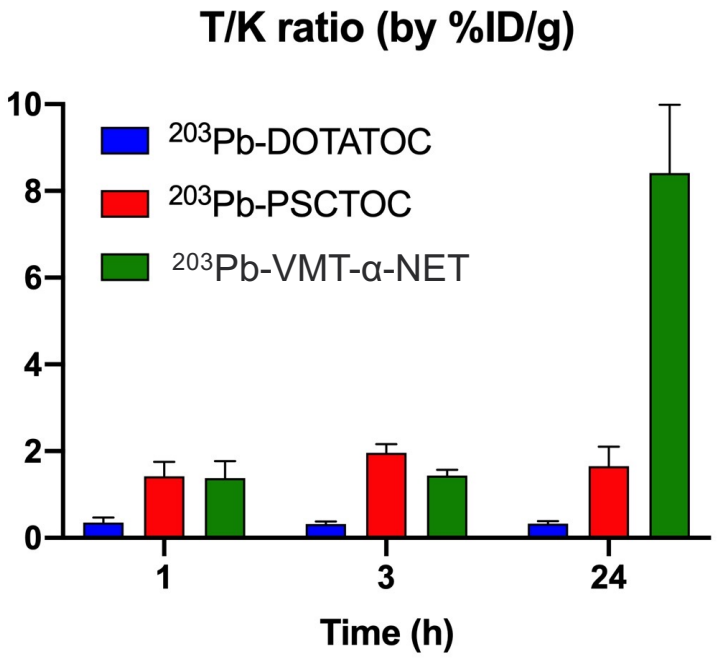


AR42J cells are SSTR2+ and used as the model cell line.

Higher Tumor Uptake and Faster Renal Clearance of ^{203}Pb-VMT-α-NET vs. ^{203}Pb-DOTATOC

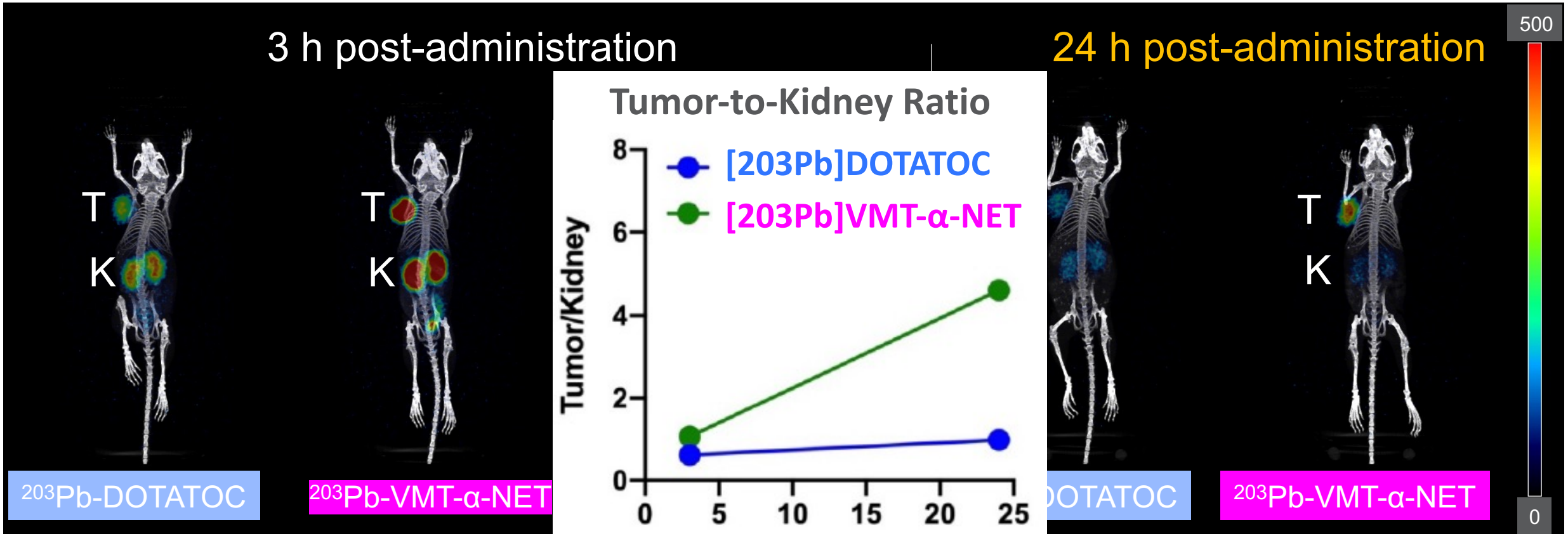






Tumor: SSTR2 positive AR42J

SPECT imaging Confirmed Specific SSTR2 Targeting



T, AR42J tumor; K, Kidneys

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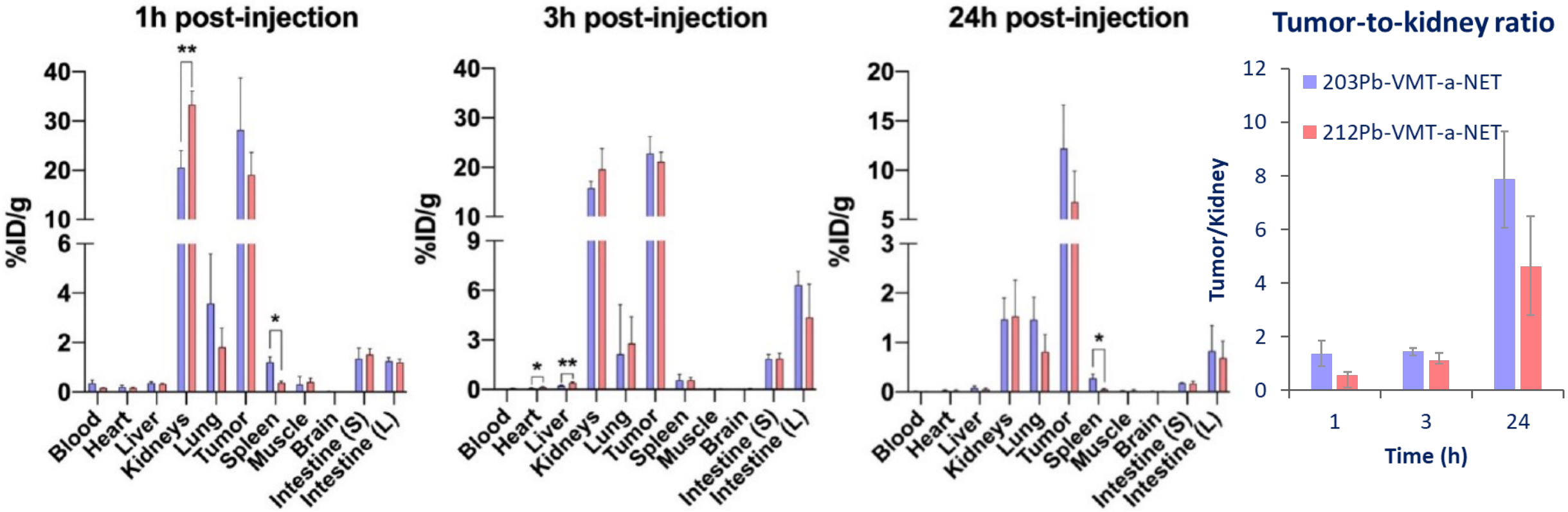
Comparable BioD profiles of [203Pb] vs. [212Pb]VMT-α-NET



[203Pb]VMT-α-NET [212Pb]VMT-α-NET

** P < 0.01; * P< 0.05

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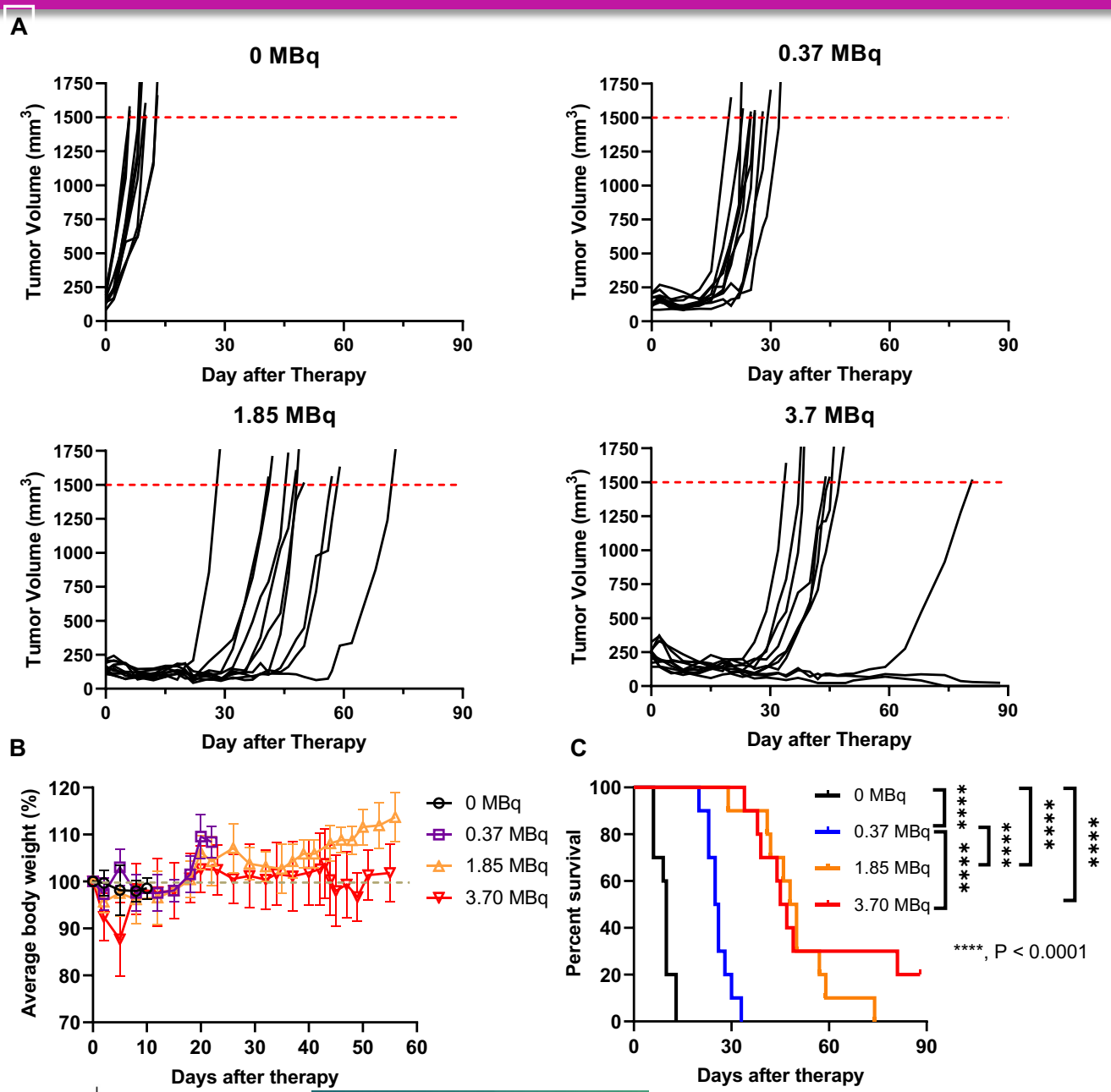
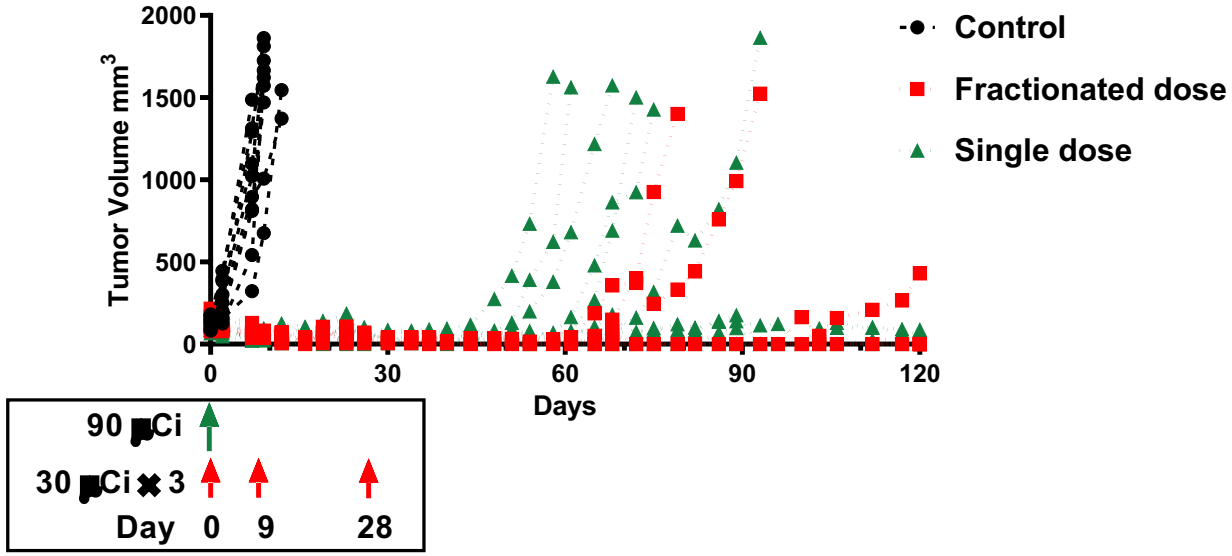
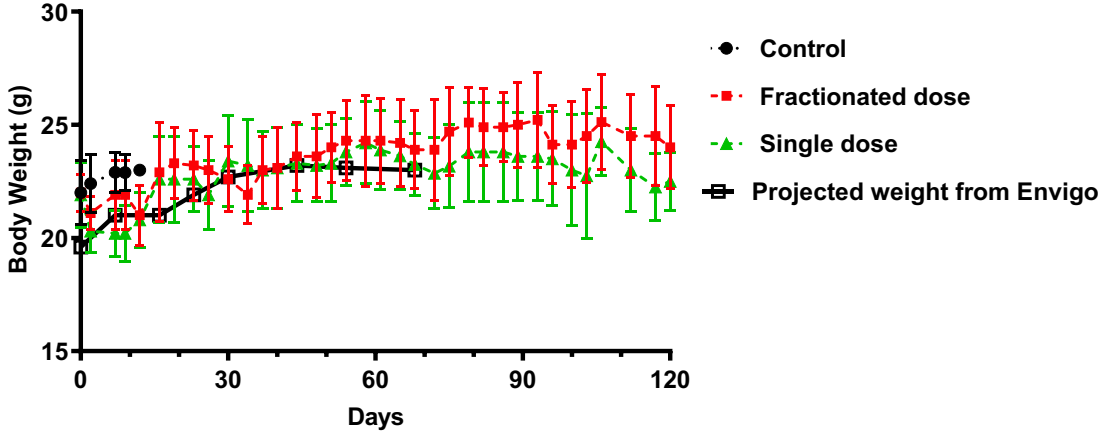
Efficacy Study 1- Dose Escalating

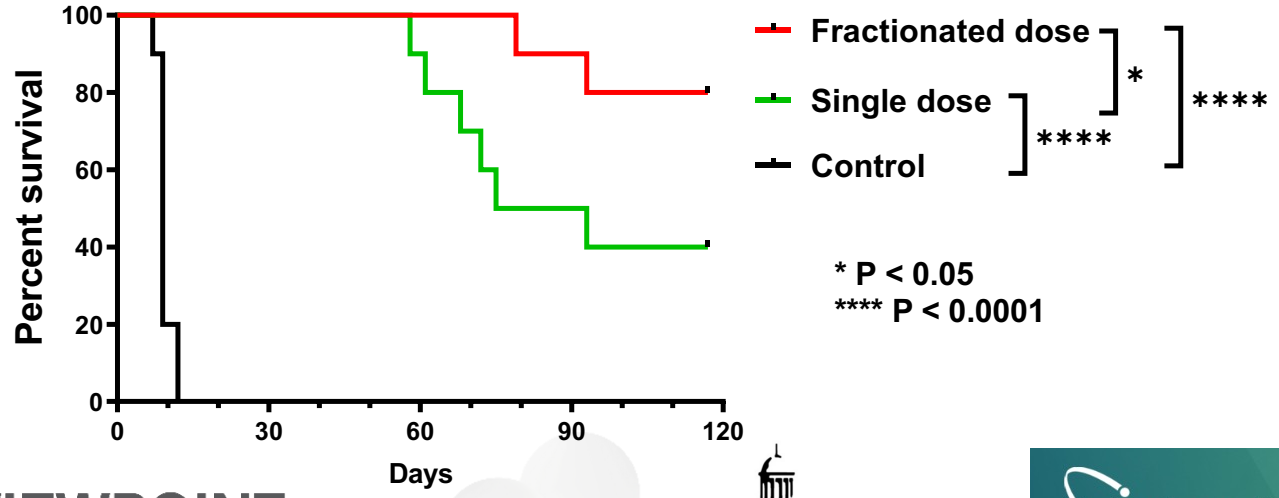
- Maximum Tolerate Dose (MTD) was determined at 3.70 MBq of [212Pb]VMT-α-NET.
- Dose-response efficacy was manifested.



Efficacy Study 2- Single vs. Fractionated Doses







Fractionated: CR 70%; OS 80%

Single dose: CR 40%; OS 40%

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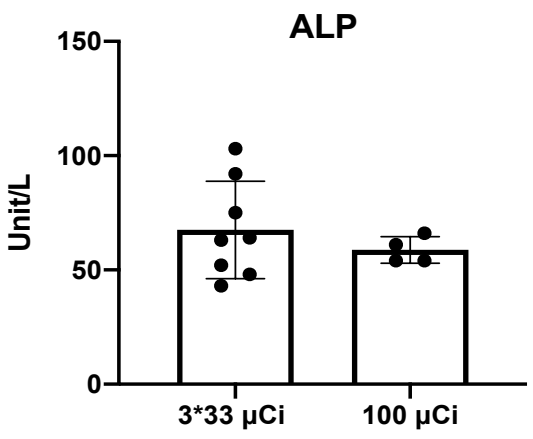
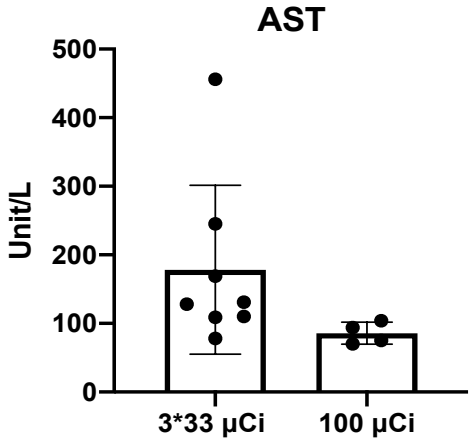
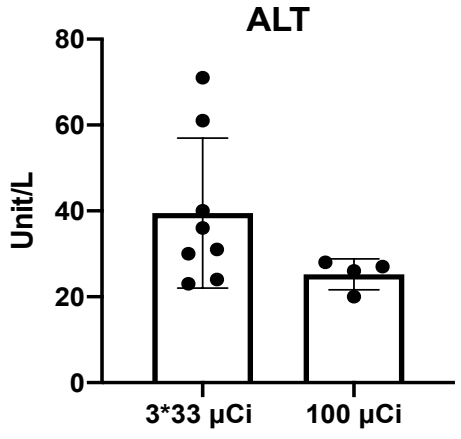
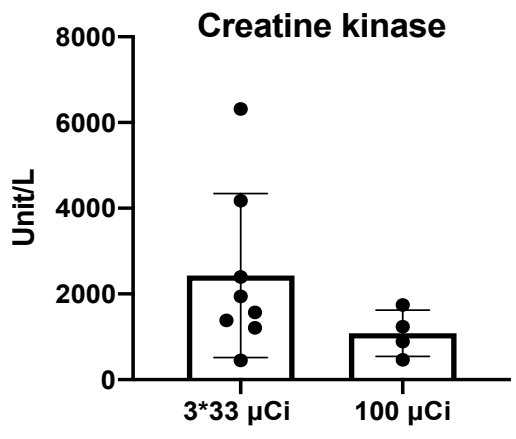
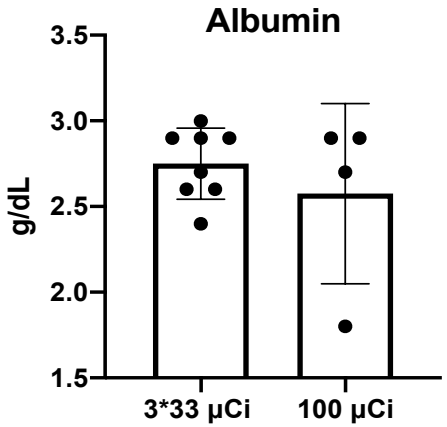
Serum Chemistry End of Study (Day 120)

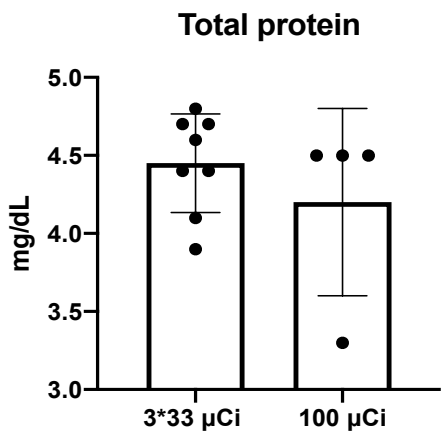


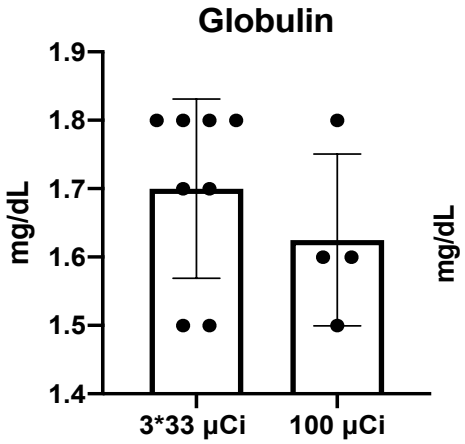


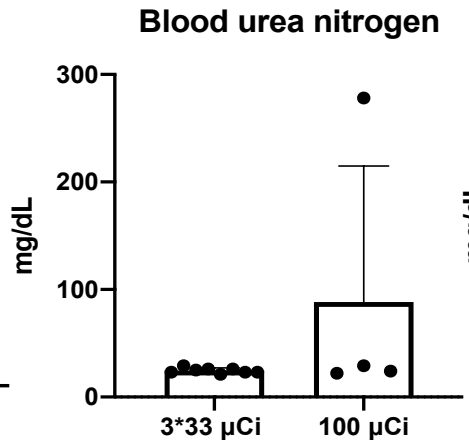


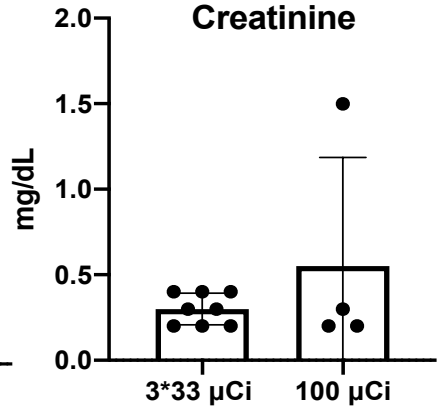












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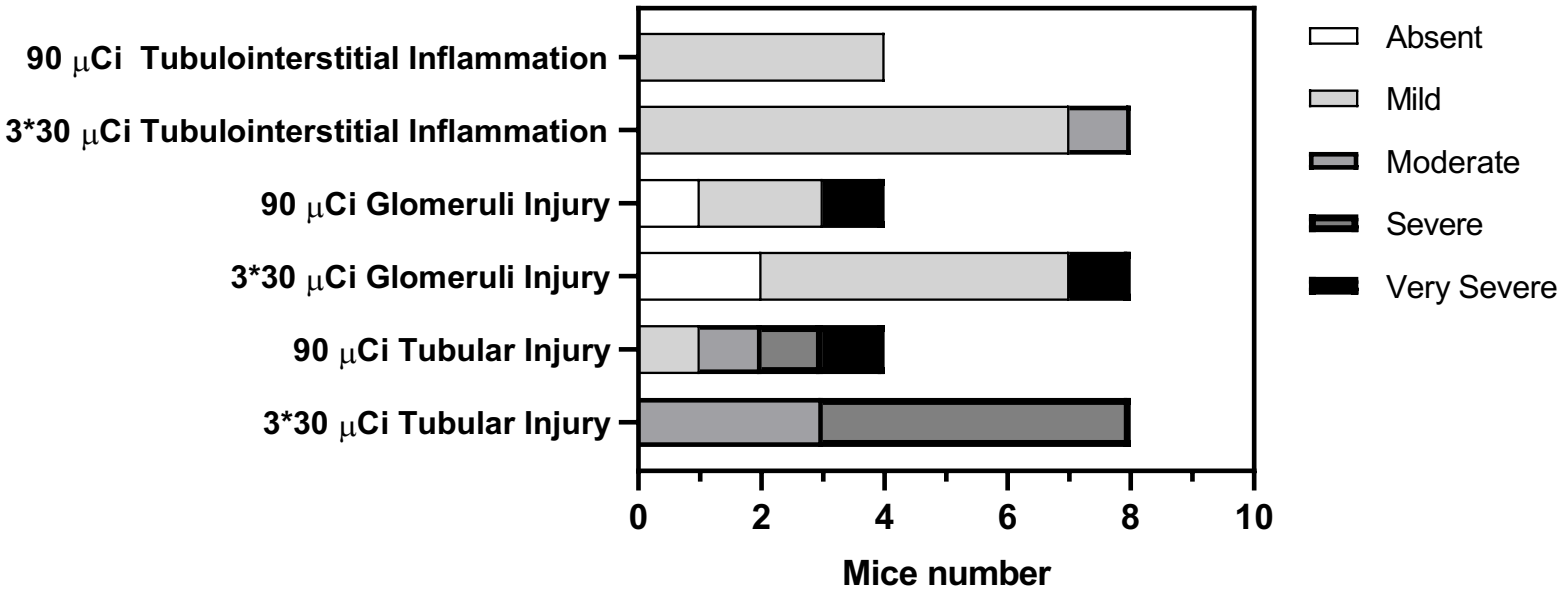
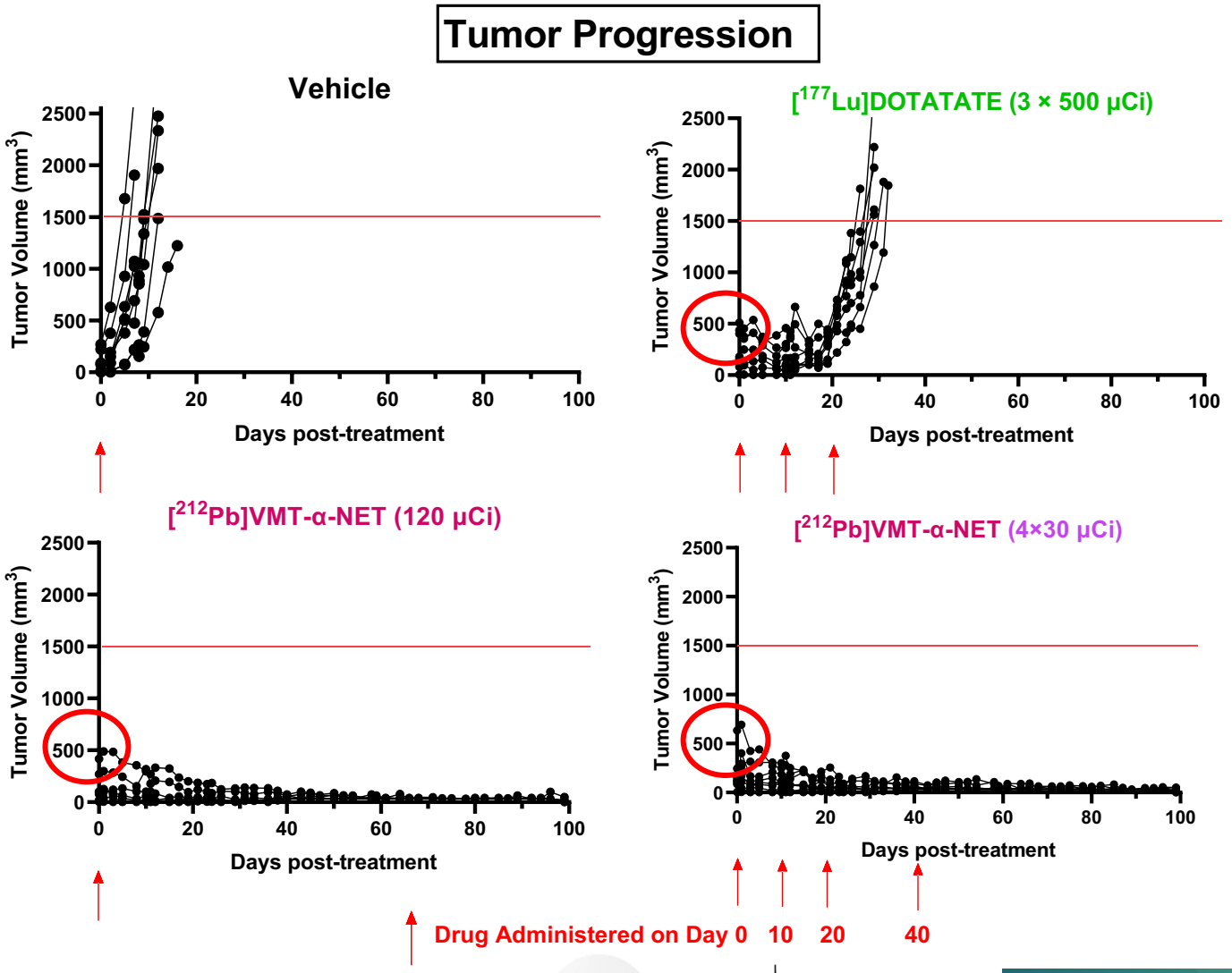
Renal Histopathological Observance



Scoring:	Tubulointerstitial Inflammation	Glomeruli Injury	Tubular Injury
0- Absent	0%	0%	0%
1- Mild	1-10%	1-10%	1-10%
2- Moderate	11-25%	11-20%	11-25%
3- Severe	26-50%	21-30%	26-50%
4- Very Severe	> 50%	> 31%	> 50%
	Tubular Changes: stained bodies of various sizes, vacuolization, loss of epithelial cells nuclei, dark acidophilic cytoplasm, loss of tubular epithelial cells into tubular lumen, and acellular sections of tubules.		
	Glomerular changes: glomeruli with any degree of sclerosis or collapse and thrombonecrotic lesions.		

Efficacy Study 3-Direct Comparison



- Both single and fractionated doses regimen of [212Pb]VMT-α-NET completely inhibit tumor progression for 100 days, even with initial big tumor.
- [177Lu]DOTATATE didn't finish the planned 4th dose.

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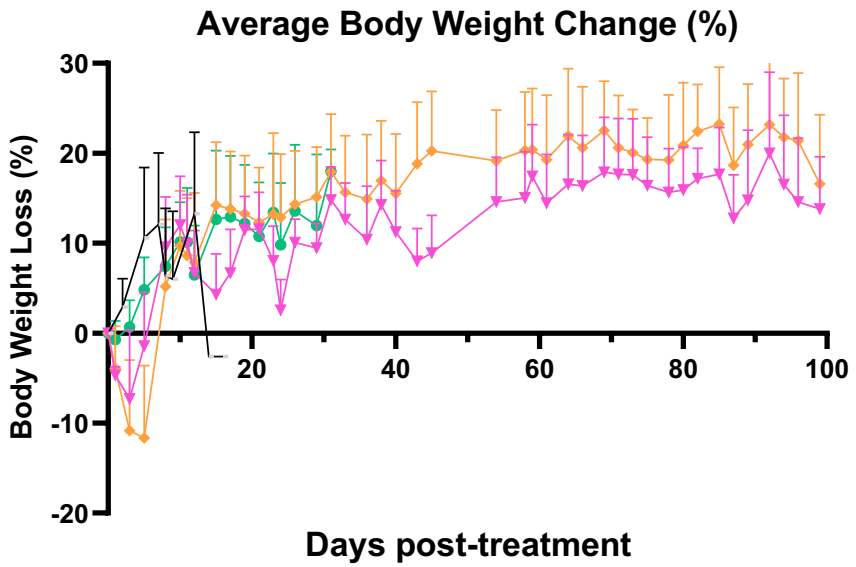
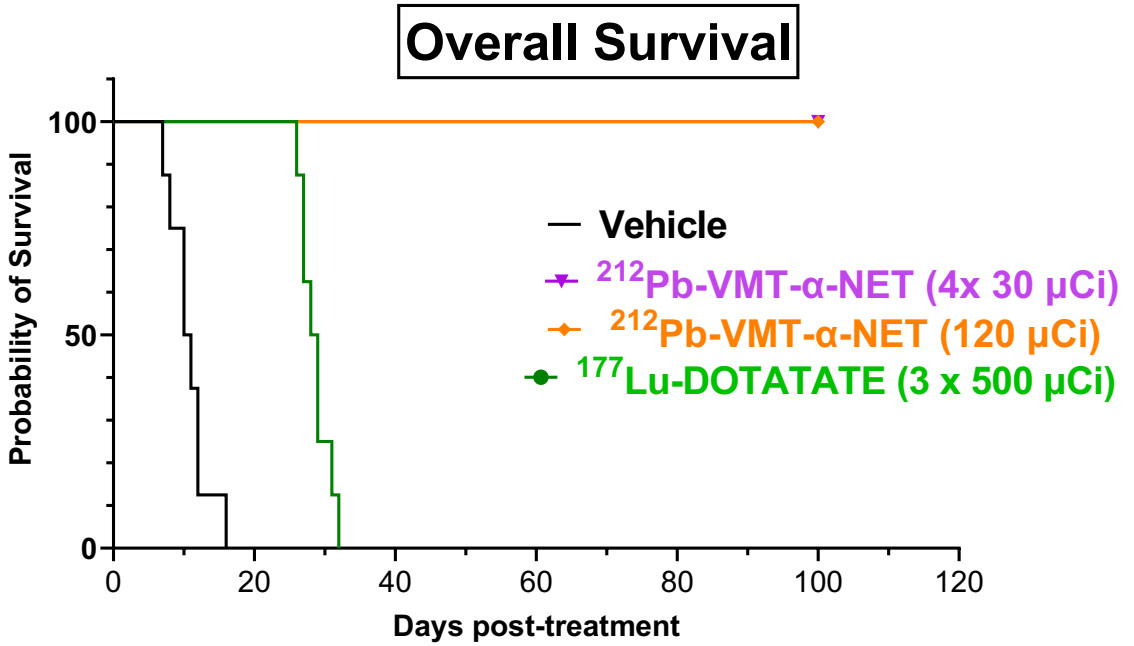
Efficacy Study 3-Direct Comparison





Both single and fractionated doses of [212Pb]VMT-α-NET demonstrated

- tolerable toxicity with continual body weight gain during the 100-day study
- 100% progression free survival

Median survival days for [177Lu]DOTATATE and vehicle were 28.5 and 10.5, respectively.

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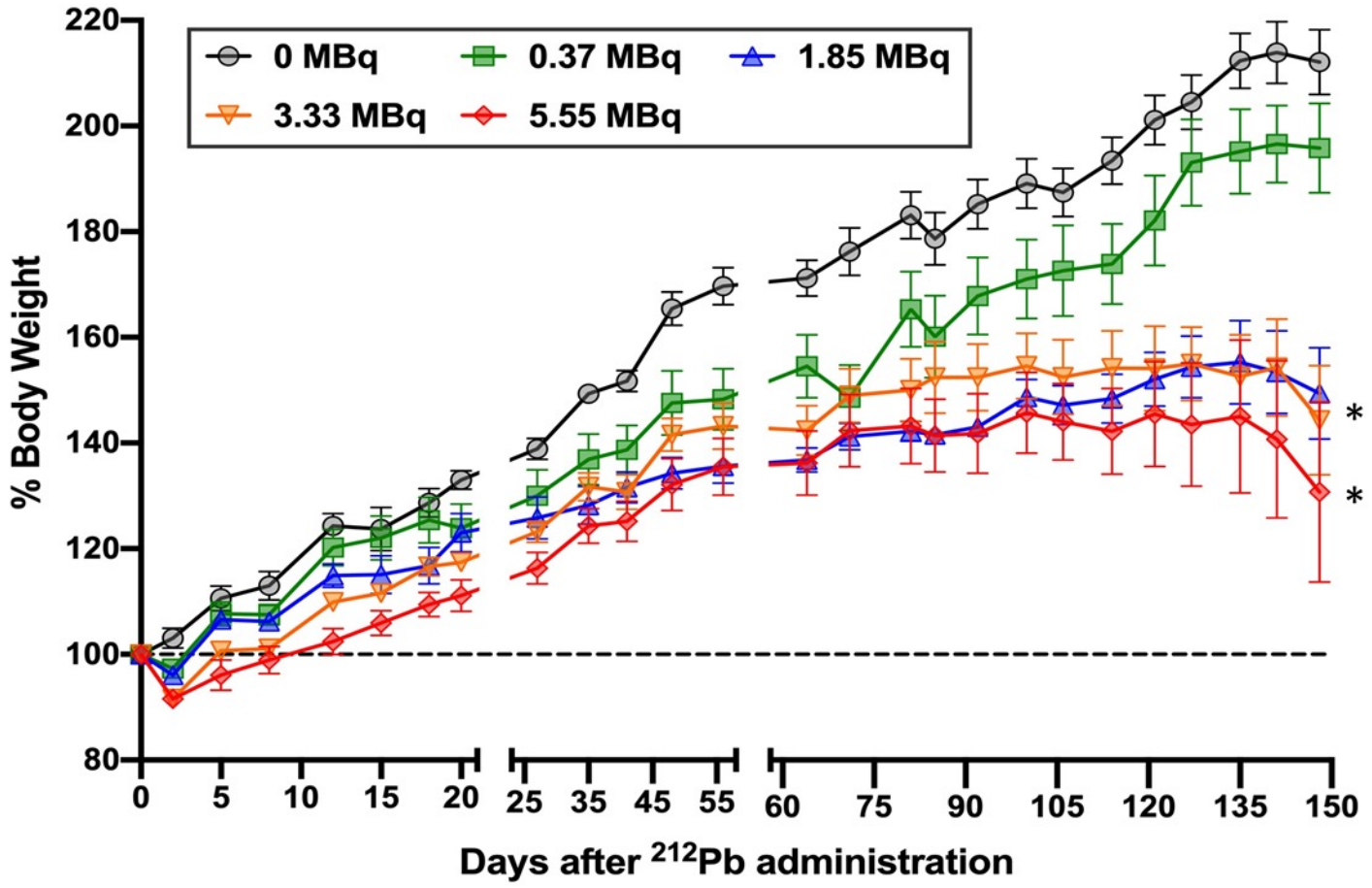
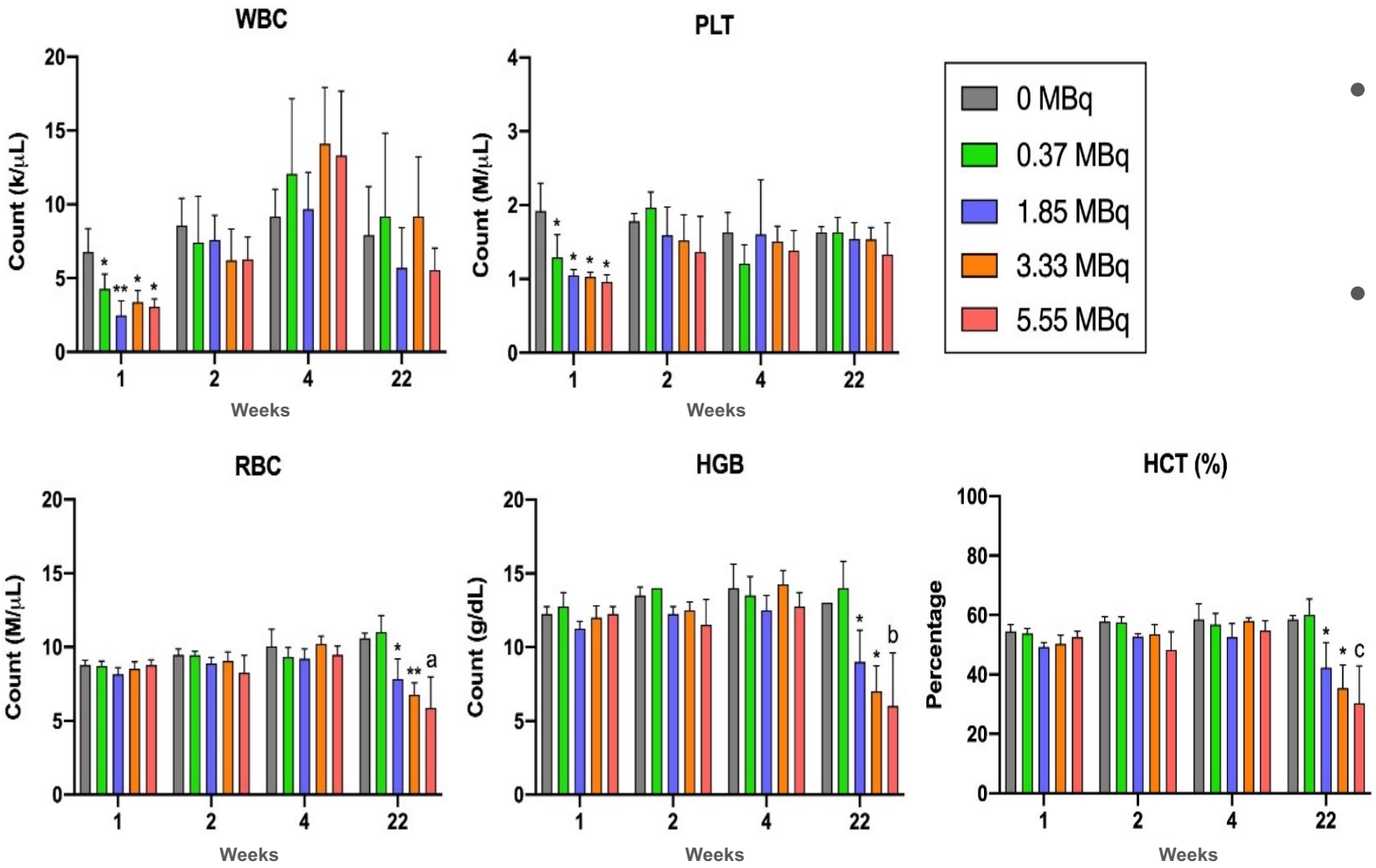
Hot Toxicity Study in male CD1-Elite



- **MTD was in the window of 3.33-5.55 MBq (90-150 µCi).**

Hot Toxicity Study in male CD1-Elite-Sequential CBC



- **Transit CBC difference occurred at 1 week pi.**
- **Trend of dose-dependent reduction of RBC and HGB in long-term**

Secured ^{212}Pb Source: VMT-α-Gen

- **VMT-α-Gen for CMC for IND of [212Pb]VMT-α-NET.**
- **For Preclinical Research at VMT.**

Summary & Updates

- **VMT-α-NET demonstrated outstanding *in vitro* and *in vivo* profile targeting SSTR2.**
- **[203Pb]VMT-α-NET can be a reliable surrogate for imaging diagnosis and dosimetry for targeted alpha-therapy using [212Pb]VMT-α-NET.**
- **[212Pb]VMT-α-NET fractionated doses or single high dose (120 µCi) achieved 100% complete response to SSTR2+ tumor with tolerable toxicity in mice.**
- **FDA has approved the IND of [203Pb]VMT-α-NET for Phase I clinical trial in patients with SSTR2 positive tumors.**
- **FDA has approved the IND of [212Pb]VMT-α-NET for Phase I clinical trial in patients with SSTR2 positive tumors.**
- **FDA has approved Fast Track Designation of [212Pb]VMT-α-NET at VMT.**

Acknowledgement

- Personnel

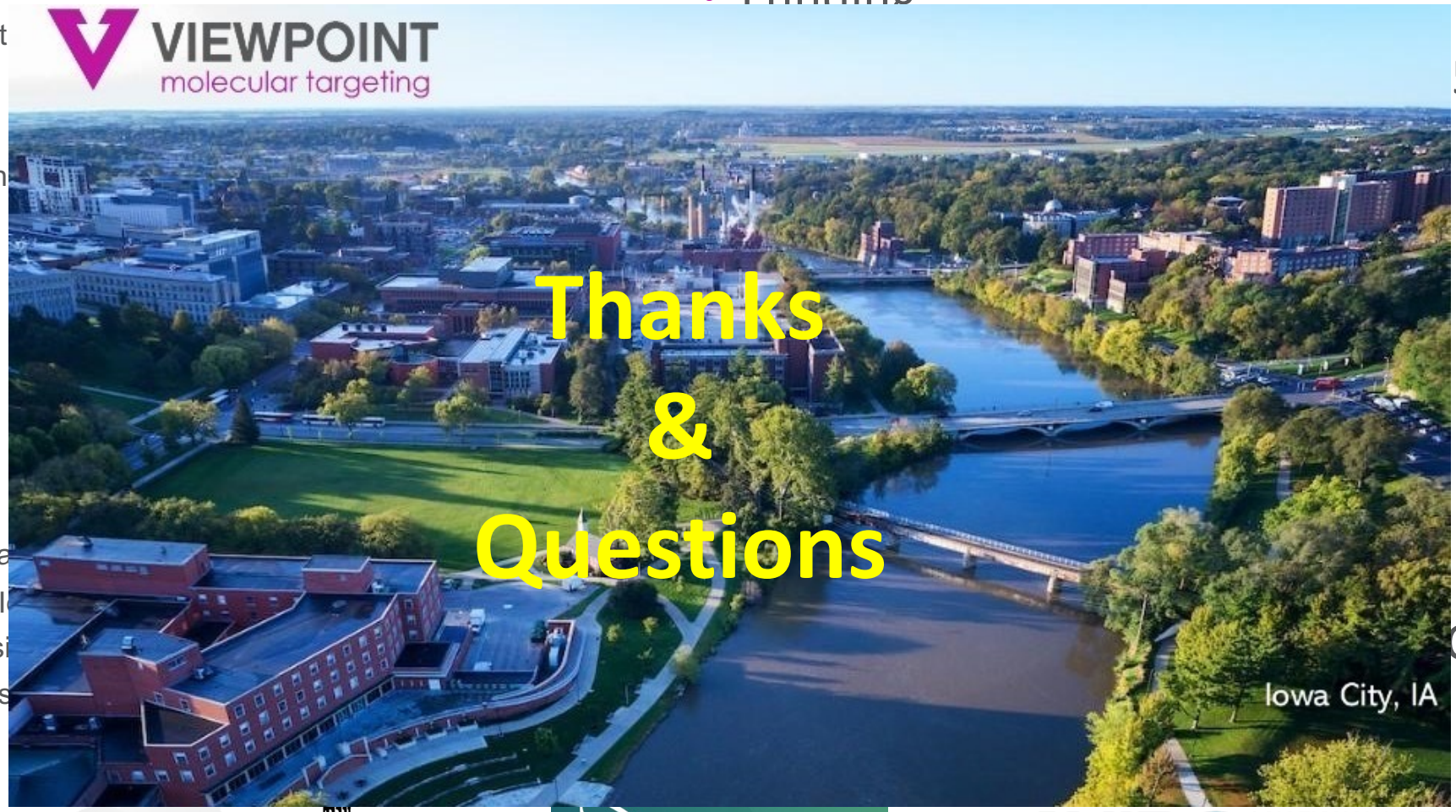
  Viewpoint Molecular Target
  Michael K Schultz, Ph.D
  Mengshi Li, Ph.D
  Nicholas J. Baumhover, Ph
  Brianna Cagle, Ph.D
  Brenna M. Marks, BS
  Edwin A. Sagastume, BS
  Sam Rodman, Ph.D
  Ephraim R. Obot, MS
  Frances L. Johnson, MD

  Dongyoul Lee, Ph.D, Korea
  Zhiming Dai, University of I
  Yusuf Menda, MD, Universi
  John Wilson, Ph.D, Univers

- Funding

  521

  Core



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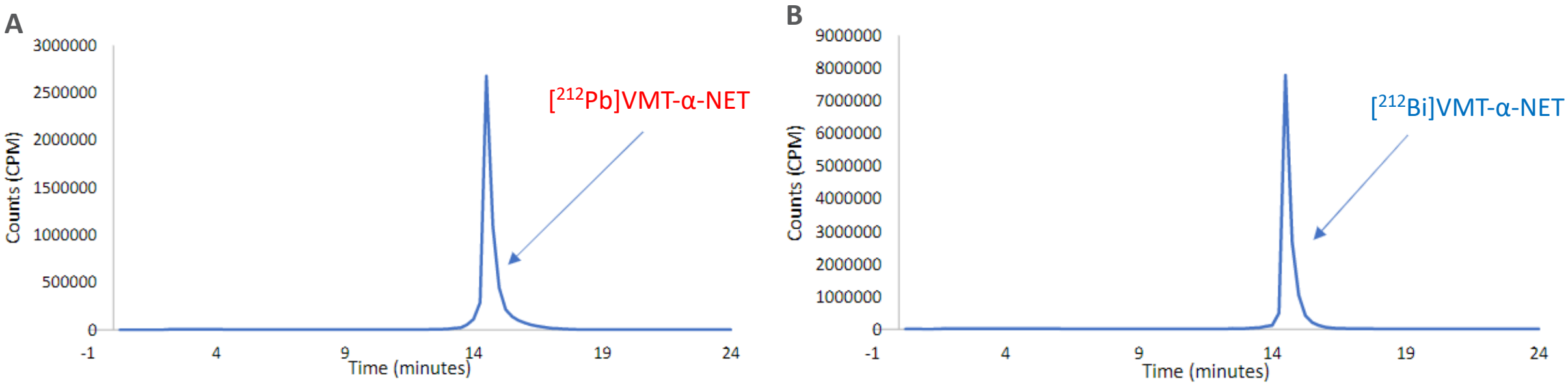
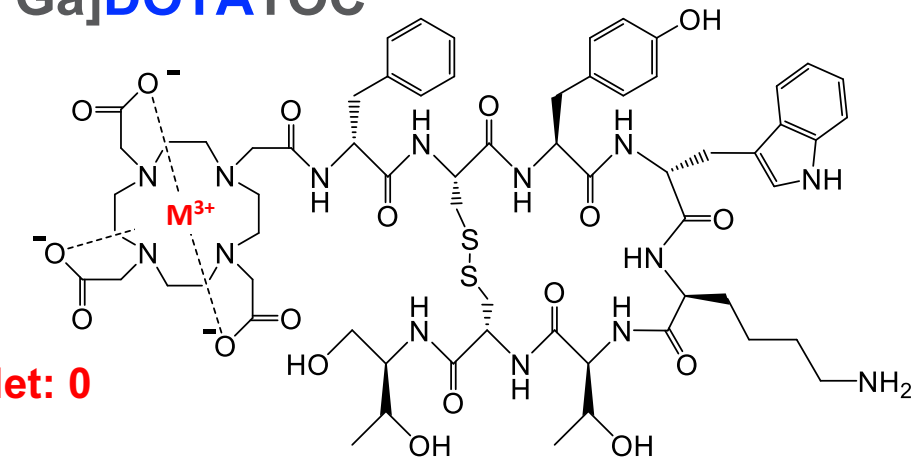
Stability of [^{212}Pb] and [^{212}Bi]VMT-α-NET



Representative chromatogram of fractionated HPLC collections of (A) [^{212}Pb]VMT-α-NET (B) [^{212}Bi]VMT-α-NET drug product measured via gamma counter.

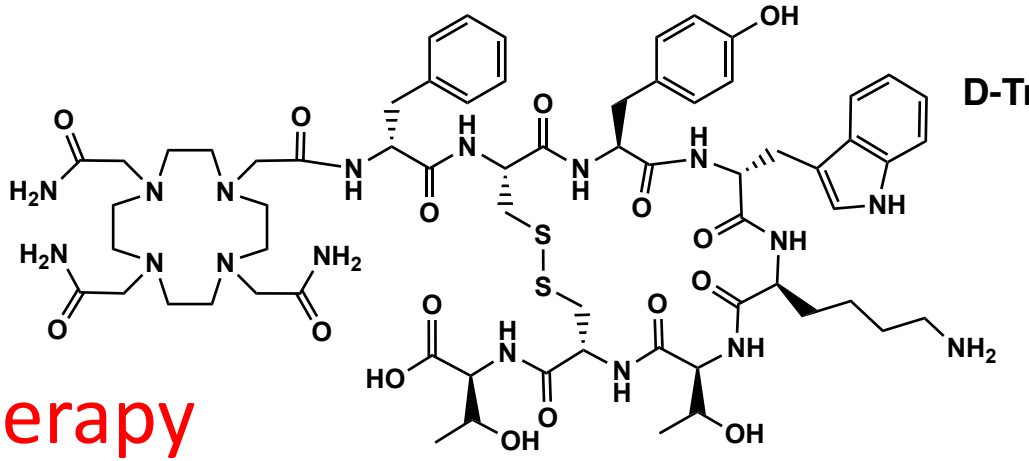
$^{203/212}$Pb-Based Theranostics Targeting SSTR2

[^{68}Ga]DOTATOC



Radionuclides (M3+) : $^{67/68}$Ga, ^{90}Y, ^{177}Lu, ^{225}Ac

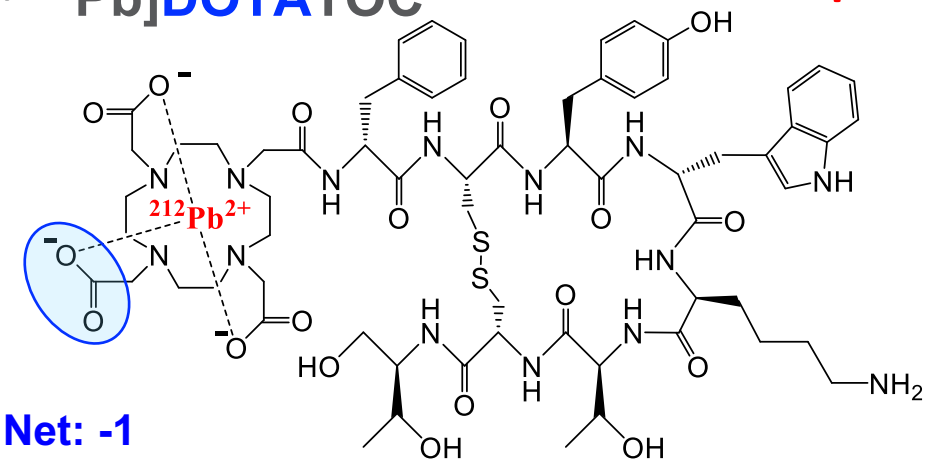
DOTAMTATE



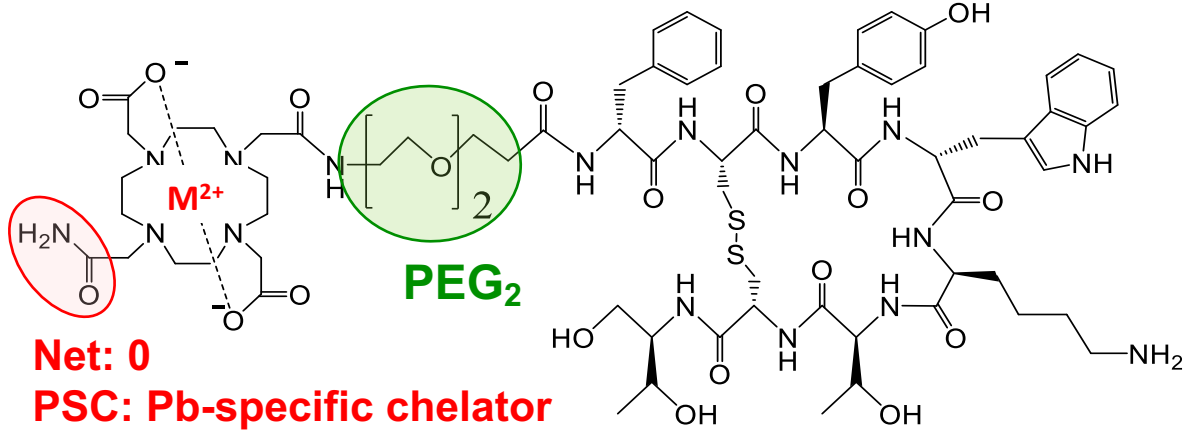
Targeted alpha-emitter radiotherapy

"Lead Gospel"

[$^{203/212}$Pb]DOTATOC



[$^{203/212}$Pb]PSC-PEG$_2$-TOC (VMT-α-NET)



Radionuclides (M2+) : ^{64}Cu, ^{203}Pb, ^{212}Pb

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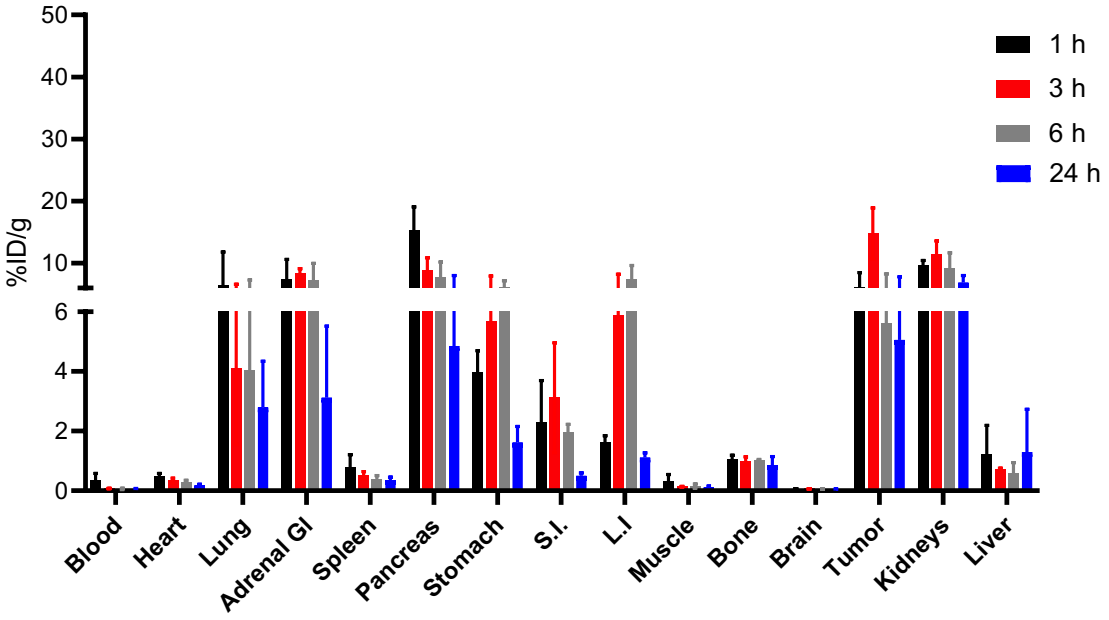
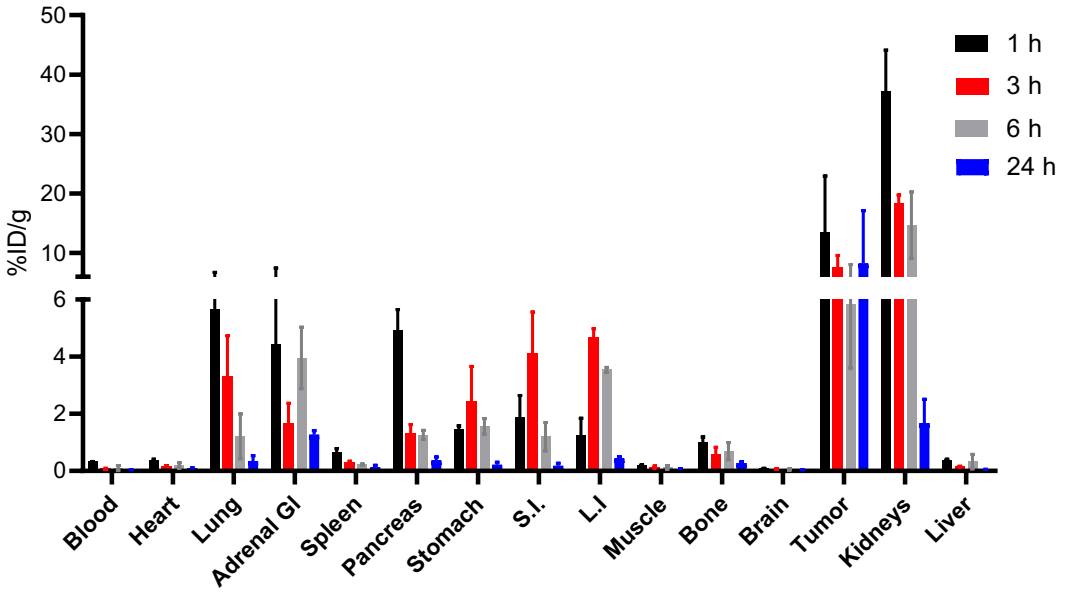
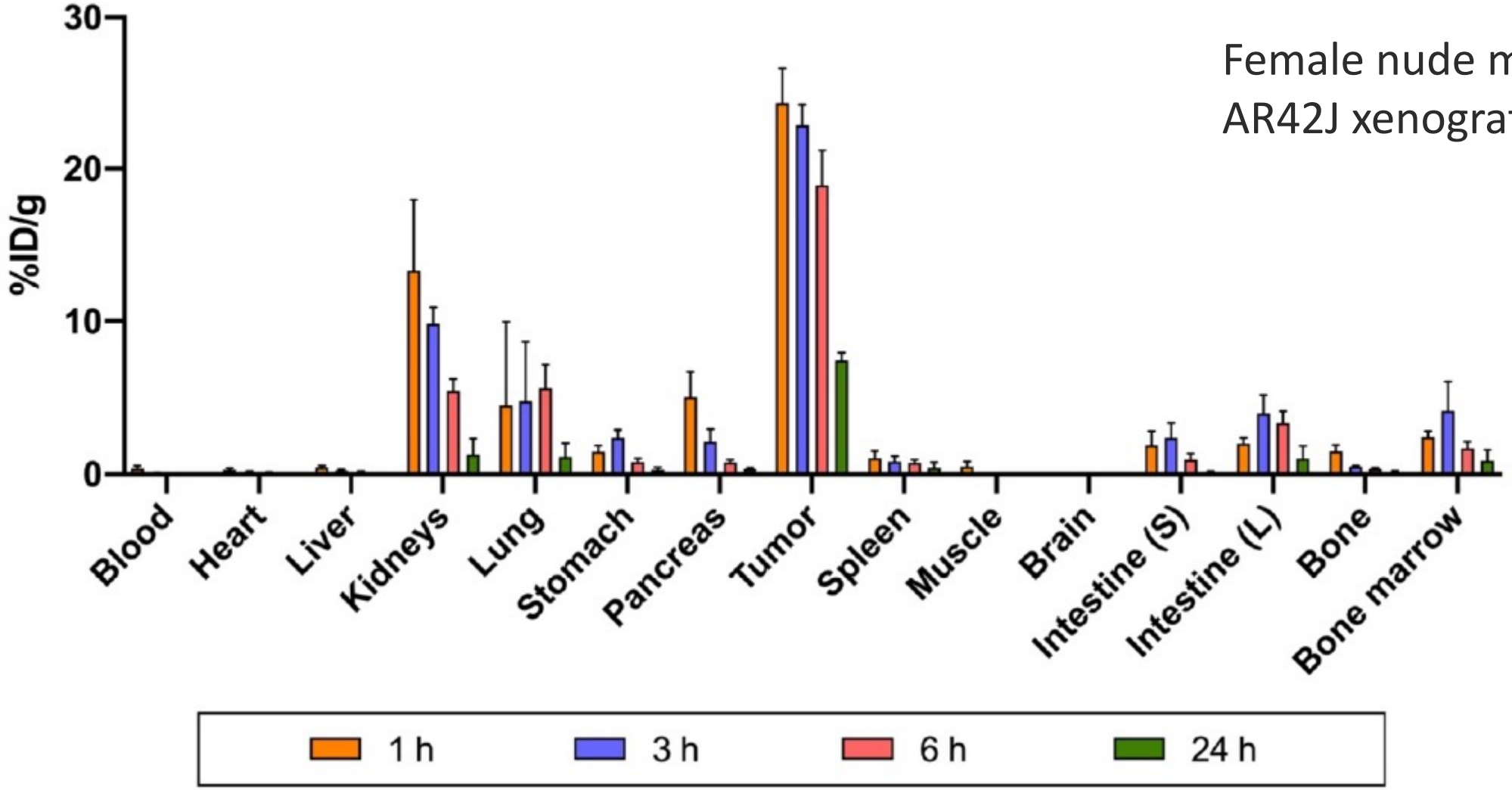
BioD of ^{203}Pb-DOTAMTATE in female nude mice bearing AR42J xenografts (n=3 /time point)



BioD of ^{203}Pb-PSC-PEG2-TOC in female nude mice bearing AR42J xenografts (n=3/time point)



BioD of [203Pb]VMT-α-NET co-injected with Lysine



Female nude mice
AR42J xenograft

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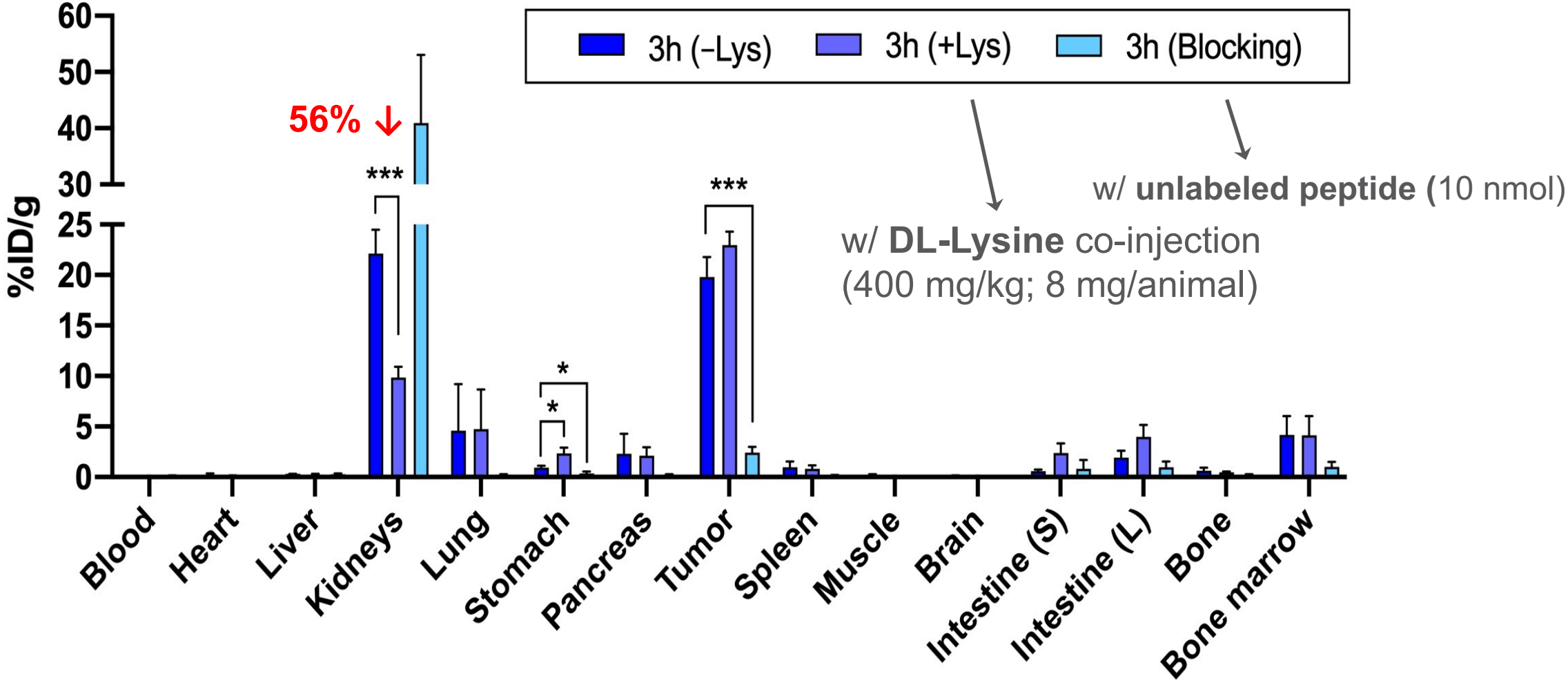
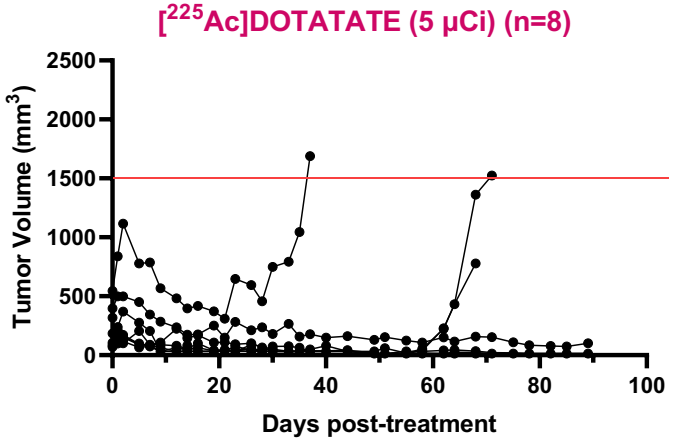
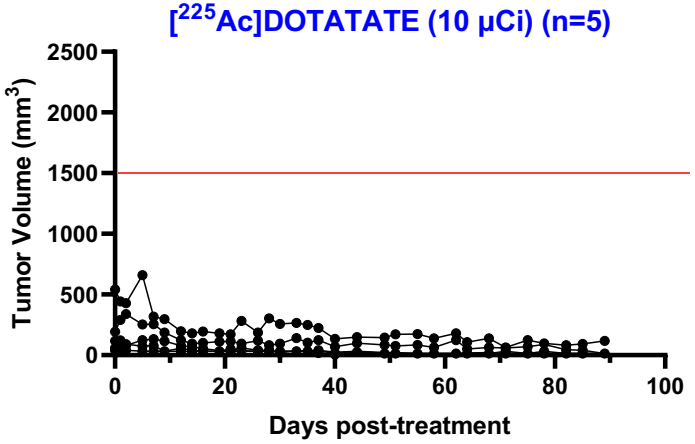
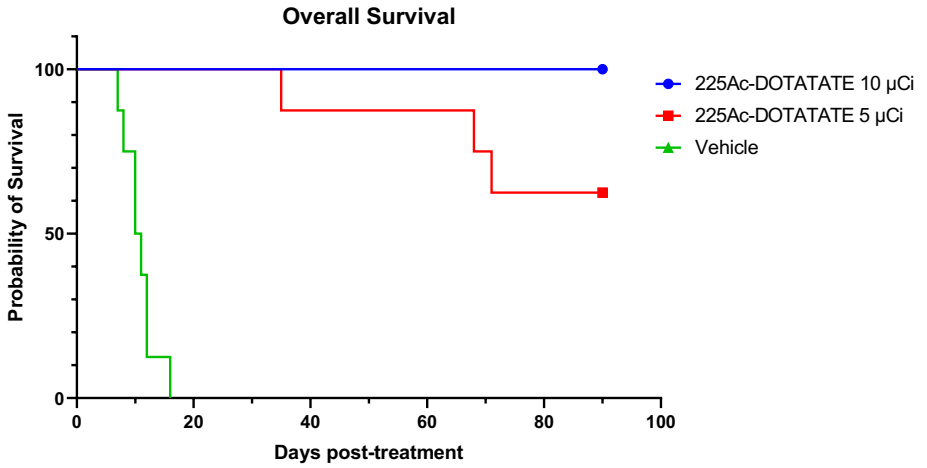
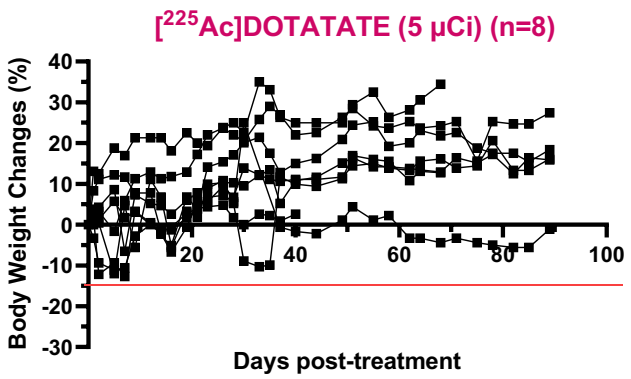
Lysine co-injection reduces the renal accumulation of [203Pb]VMT-α-NET

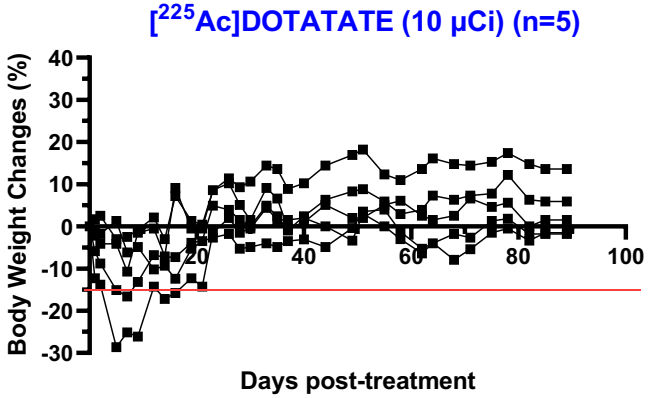



[225Ac]DOTATATE (5 µCi) (n=8)
Tumor Volume (mm3)
2500
2000
1500
1000
500
0
0
20
40
60
80
100
Days post-treatment

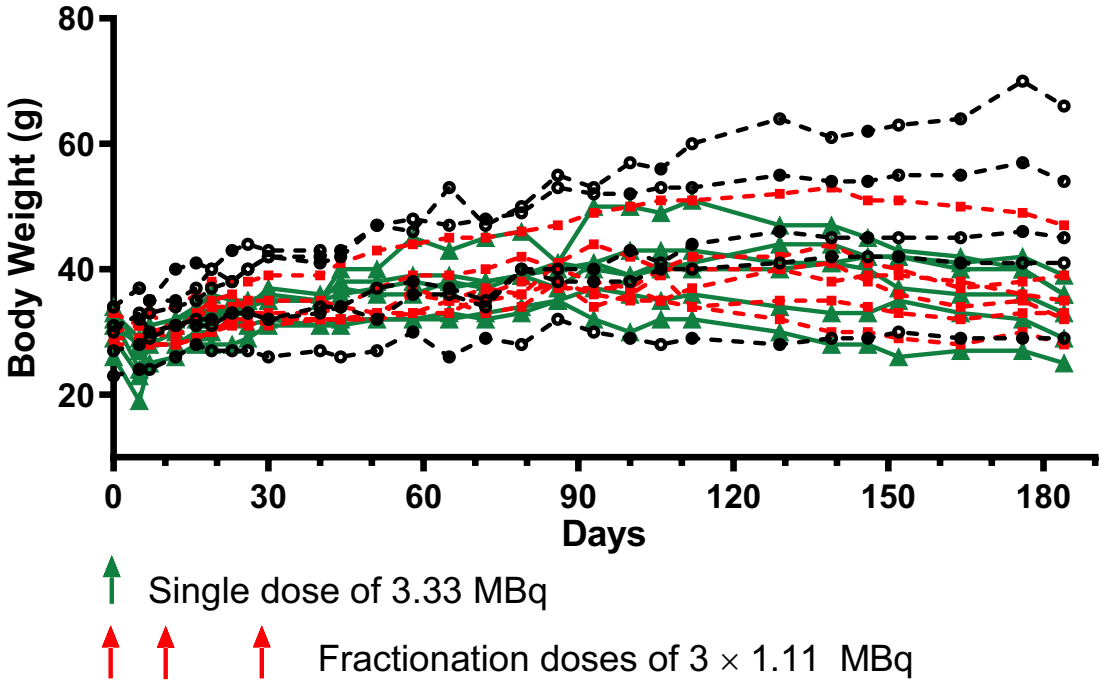

[225Ac]DOTATATE (10 µCi) (n=5)
Tumor Volume (mm3)
2500
2000
1500
1000
500
0
0
20
40
60
80
100
Days post-treatment

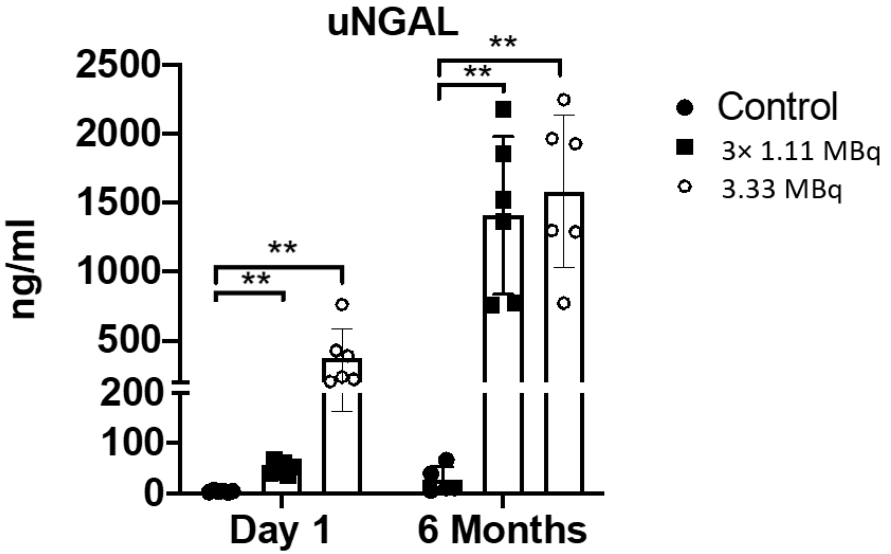

Overall Survival
Probability of Survival
100
50
0
0
20
40
60
80
100
Days post-treatment
225Ac-DOTATATE 10 µCi
225Ac-DOTATATE 5 µCi
Vehicle


[225Ac]DOTATATE (5 µCi) (n=8)
Body Weight Changes (%)
40
30
20
10
0
-10
-20
-30
20
40
60
80
100
Days post-treatment


[225Ac]DOTATATE (10 µCi) (n=5)
Body Weight Changes (%)
40
30
20
10
0
-10
-20
-30
20
40
60
80
100
Days post-treatment

Hot Toxicity Study 2 in male CD1-Elite





- **Transit CBC difference occurred at 1 week pi.**
- **Dose-dependent reduction of RBC and HGB in long-term**

VIEWPOINT molecular targeting

THE UNIVERSITY OF IOWA

Isotope Program U.S. Department of Energy

NIDC NATIONAL ISOTOPE DEVELOPMENT CENTER MANAGED BY THE U.S. DEPARTMENT OF ENERGY ISOTOPE PROGRAM

Acknowledgement

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  Nicholas J. Baumhover,
  Brianna Cagle, Ph.D
  Brenna M. Marks, BS
  Edwin A. Sagastume, B
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Core