Preclinical evaluation of $^{203/212}$Pb-based theranostics: dosimetry and renal toxicity

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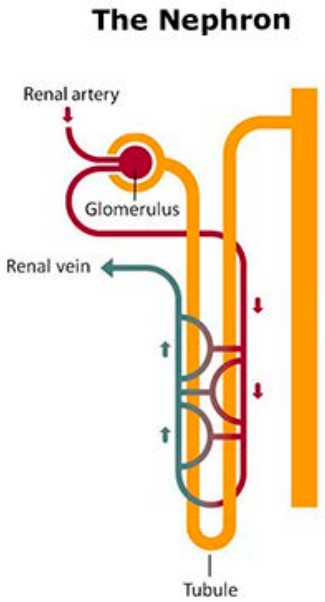
Disclosures

Viewpoint Molecular Targeting, Inc.

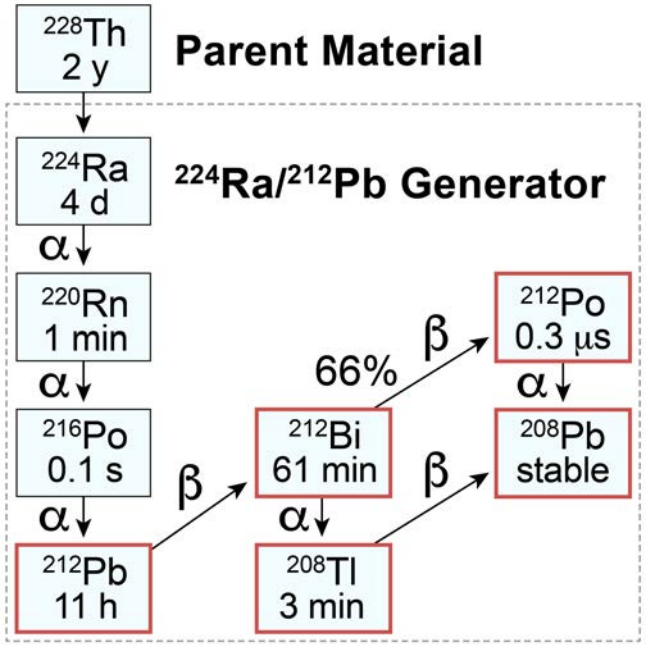
Key topics

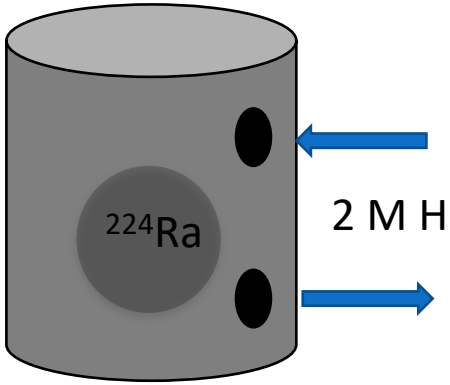
- **Radiolabeling of $^{212}Pb/^{212}Bi$**
- **Kidney dosimetry of ^{212}Pb radiopeptide in preclinical model**
- **Urine and blood biomarkers for acute kidney injury (AKI)**
  - **NGAL (Neutrophil gelatinase associated lipocalin);**
  - **TIMP-2 (Tissue inhibitor of metalloproteinases);**
  - **IGFBP7 (Insulin like growth factor binding protein 7)**

  } NEPHROCHECK®
  - **BUN (Blood urea nitrogen); Creatine**
- **Histopathology analysis of kidney sections**



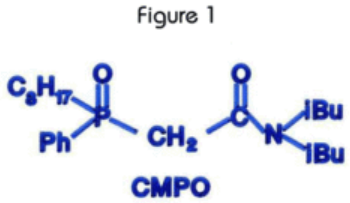
Purification of ^{212}Pb and ^{212}Bi from ^{224}Ra generator



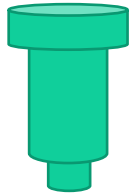


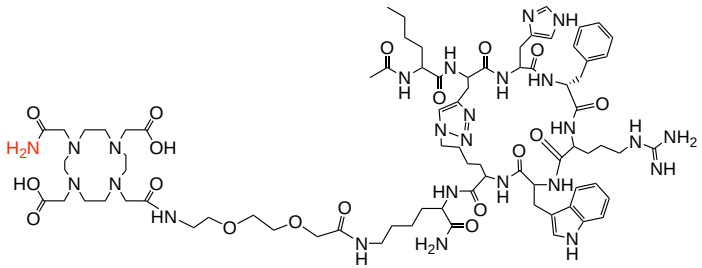
2 M HCl

Pb-Resin



TRU Resin





Top

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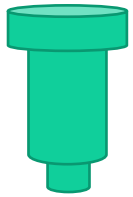
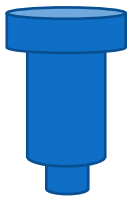
Bottom

TRU Resin

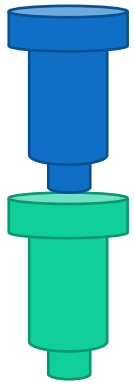


^{212}Bi

Pb-Resin



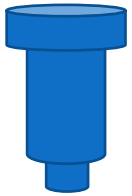
^{212}Pb



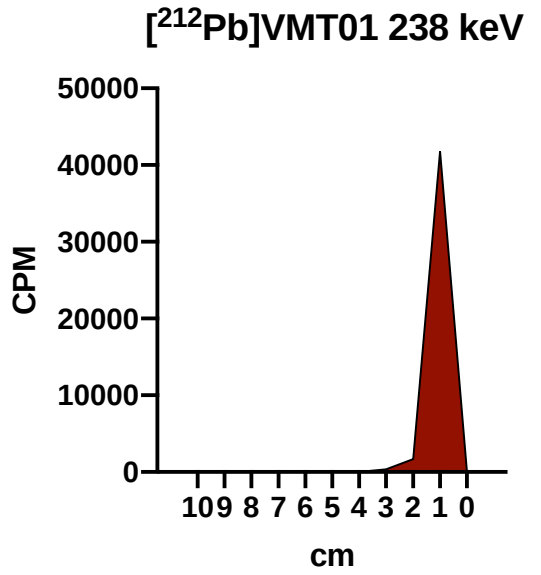
^{212}Pb

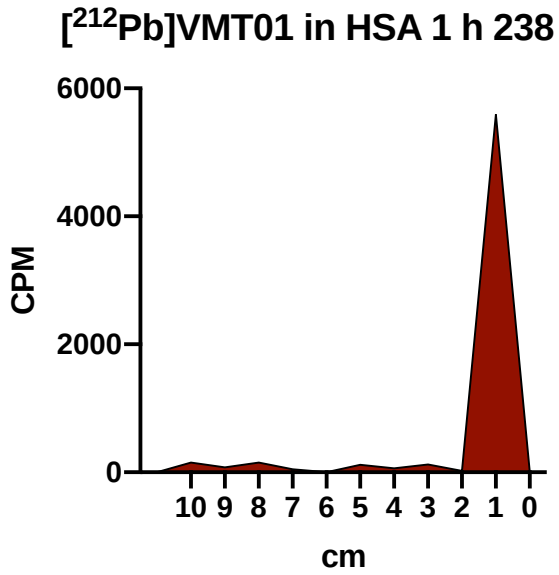
^{212}Bi

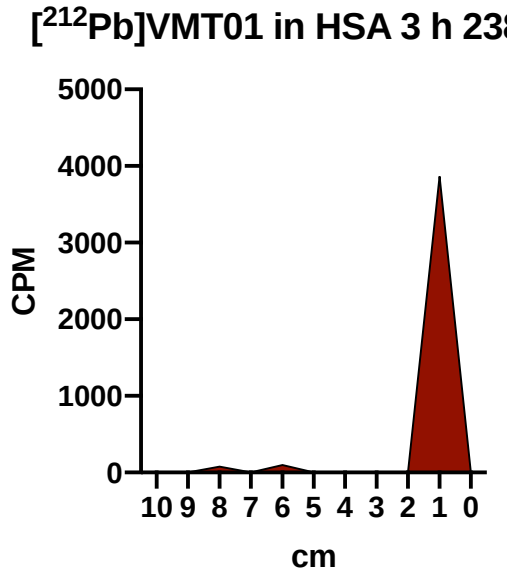
Radiolabeling of VMT01 with purified ^{212}Pb

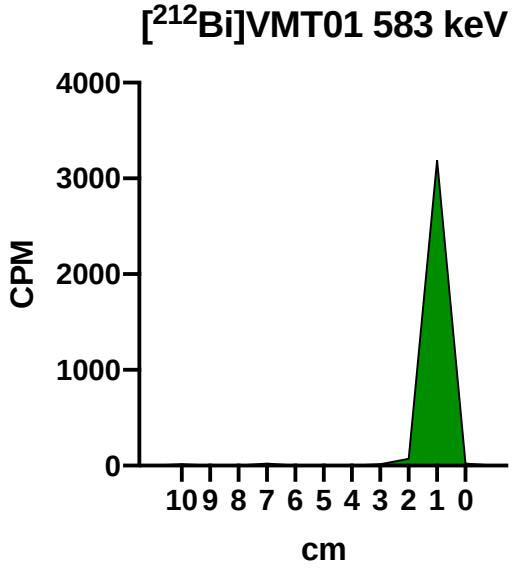


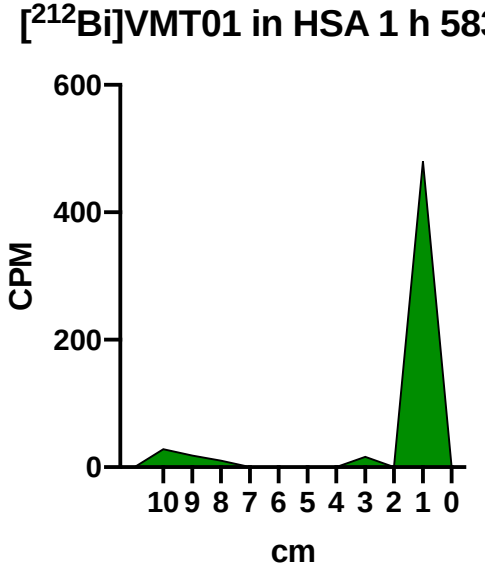
^{212}Pb

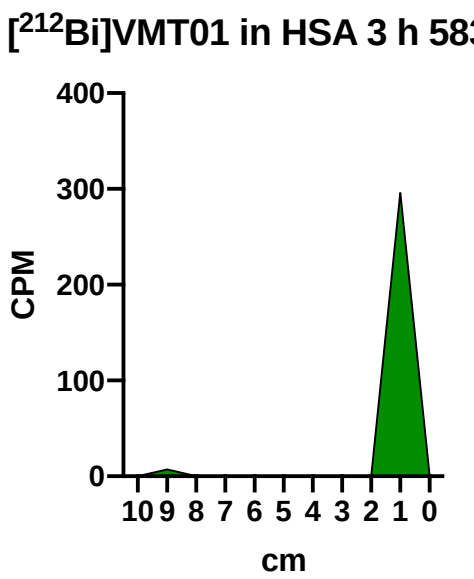




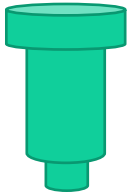




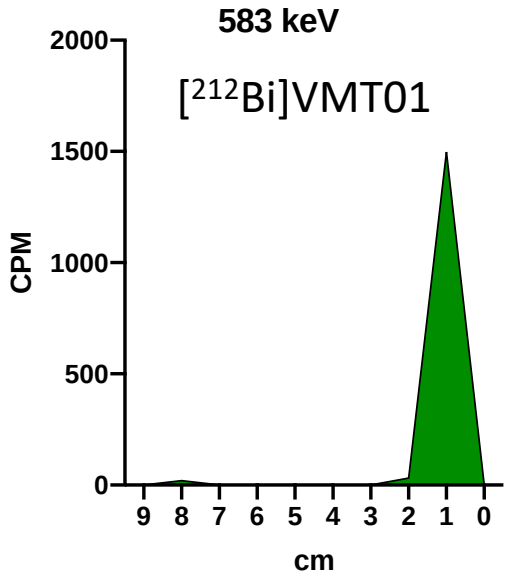


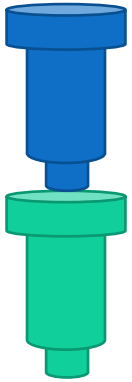


Radiolabeling of PSC-conjugated peptide with ^{212}Bi and ^{212}Pb + ^{212}Bi



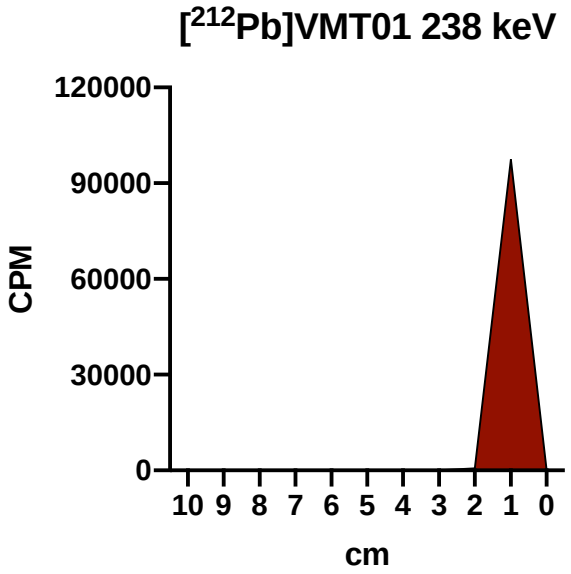
^{212}Bi

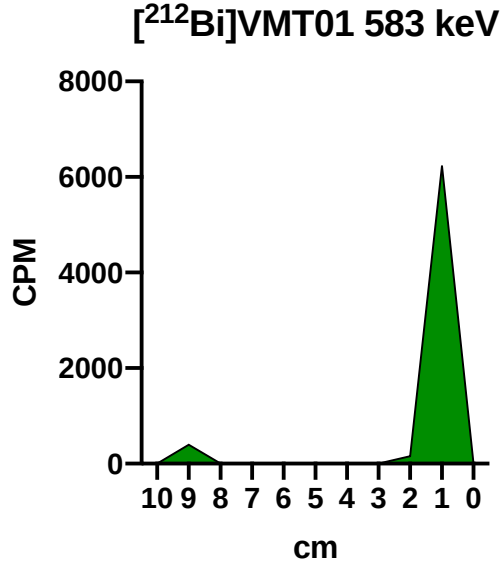




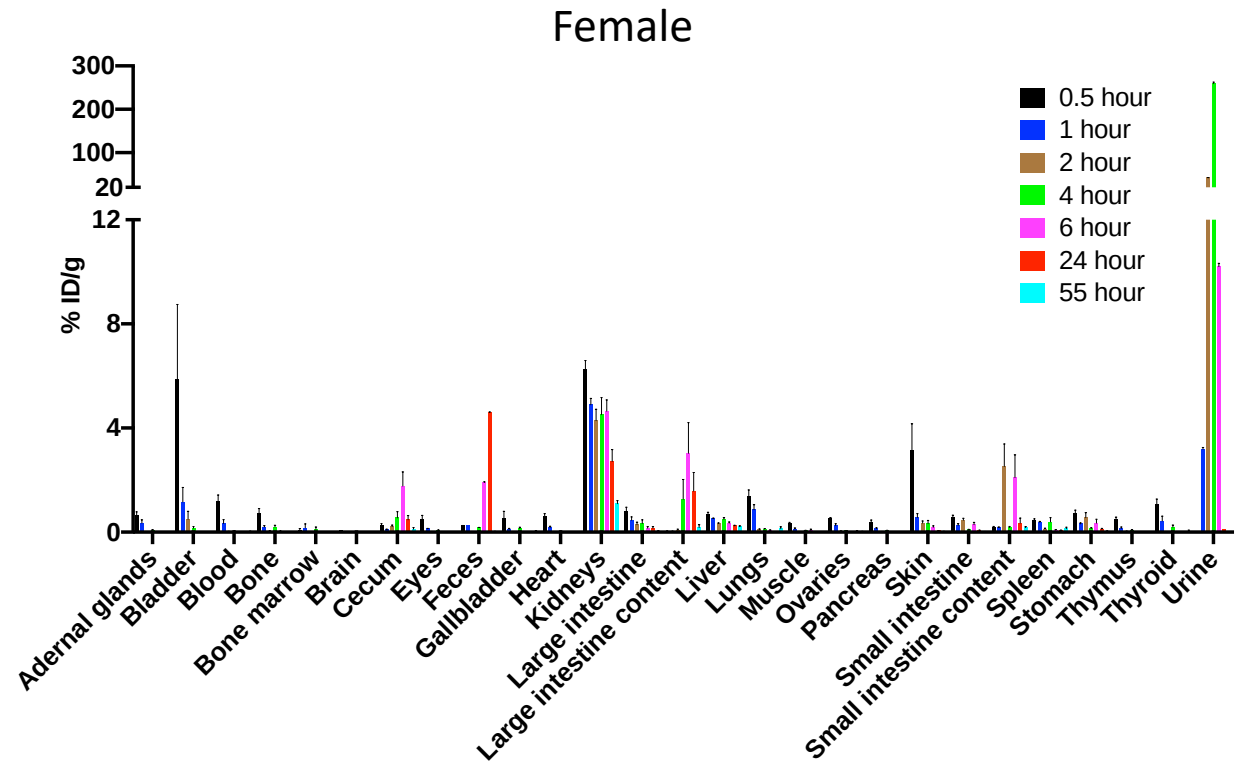
^{212}Pb

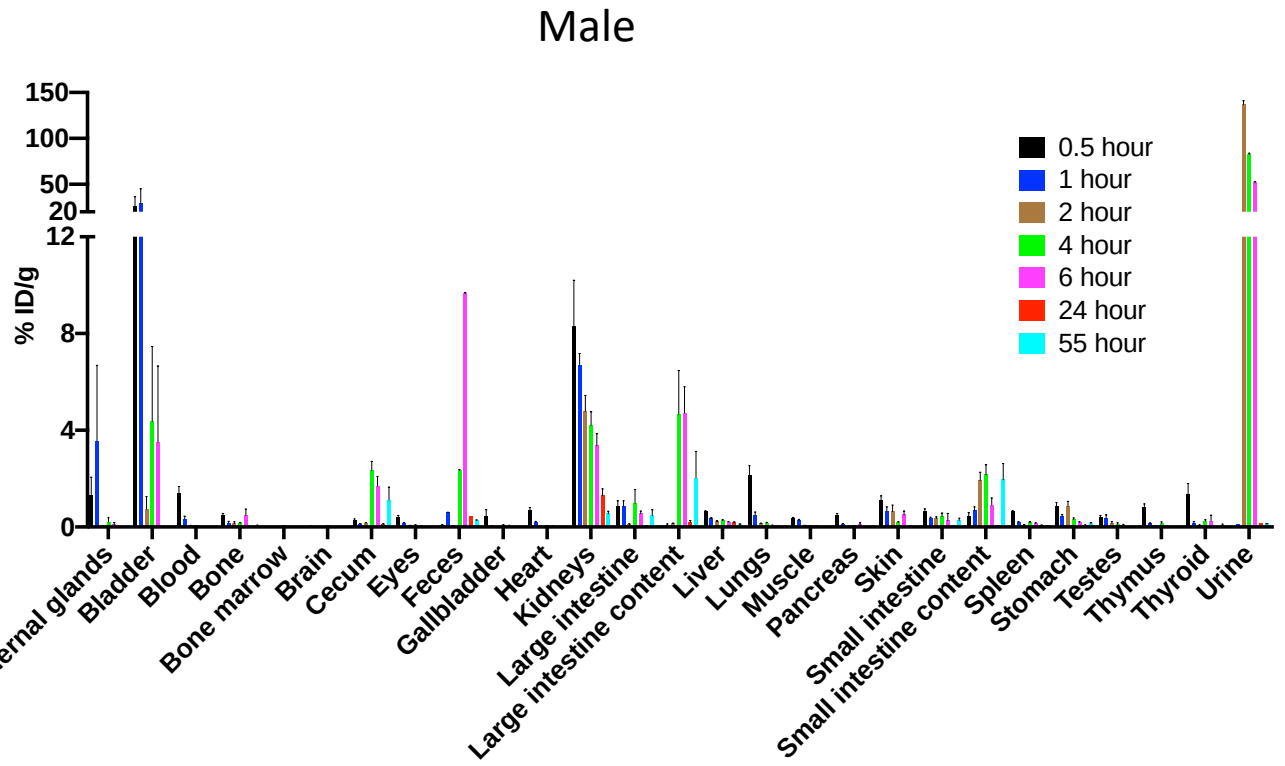
^{212}Bi



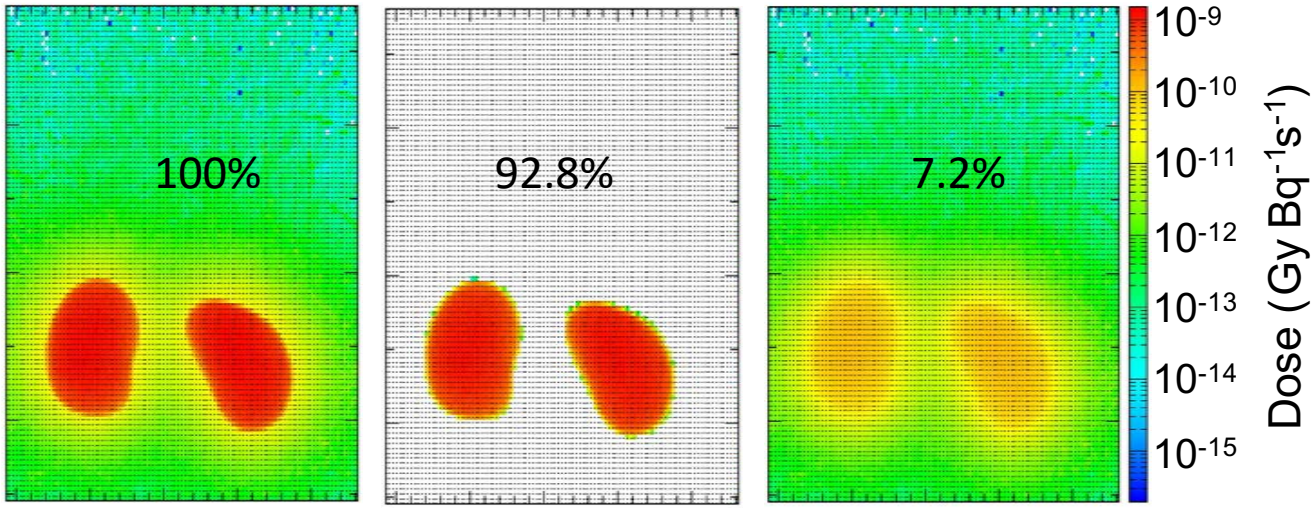


Biodistribution of [^{203}Pb]VMT01 in CD-1 IGS mice



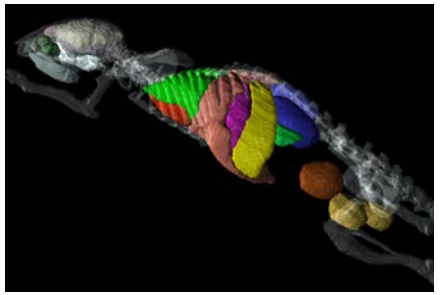


Dosimetry analysis of [^{212}Pb]VMT01 in the kidney of CD-1 mice



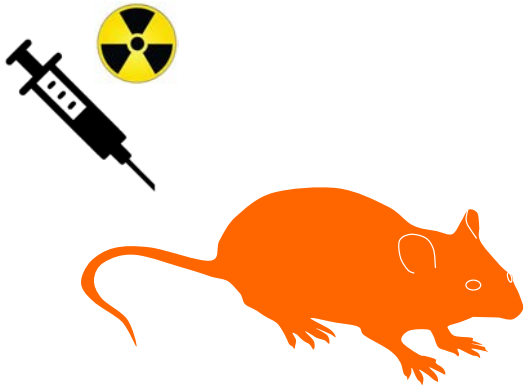
Dongyoul Lee PhD

Radiation source	Estimated dose from injected activity (Gy)		
	0.9 MBq	3.0 MBq	6.7 MBq
All	**1.93**	**6.18**	**13.89**
Alpha particles	1.79	5.73	12.89
Electrons	0.14	0.45	1.00

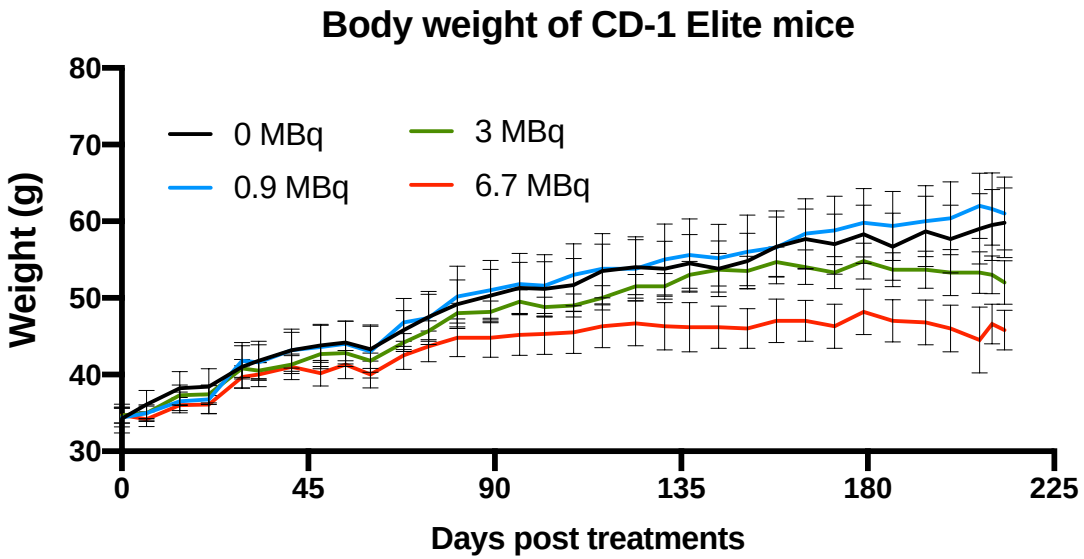


Lee, D.; Li, M.; Bednarz, B.; Schultz, M.K. Modeling Cell and Tumor-Metastasis Dosimetry with the Particle and Heavy Ion Transport Code System (PHITS) Software for Targeted Alpha-Particle Radionuclide Therapy. *Radiation research,* **2018,** *190* (3), 236-247.

Dose escalation of [^{212}Pb]peptide
Collect blood and urine sample



Male CD-1 mice



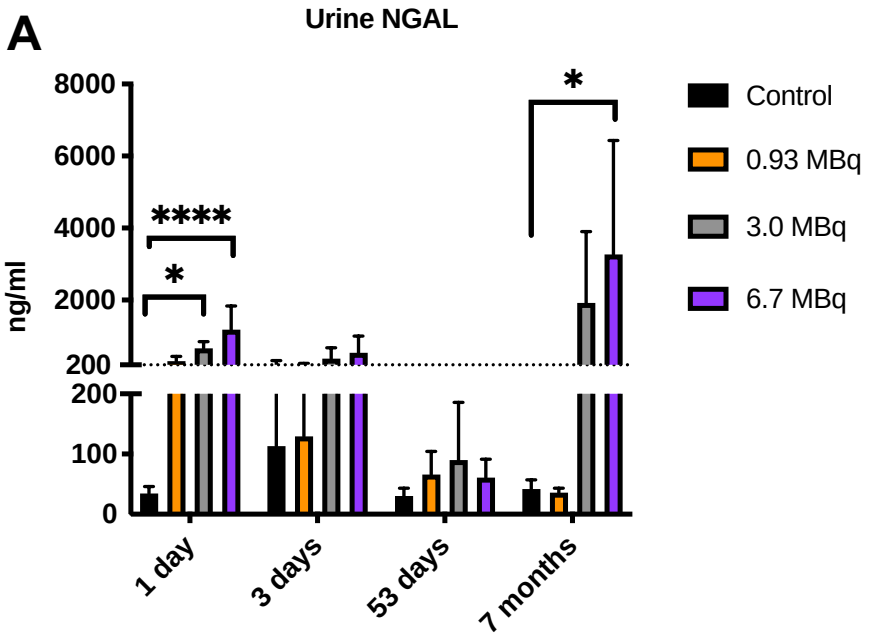
Urine analysis

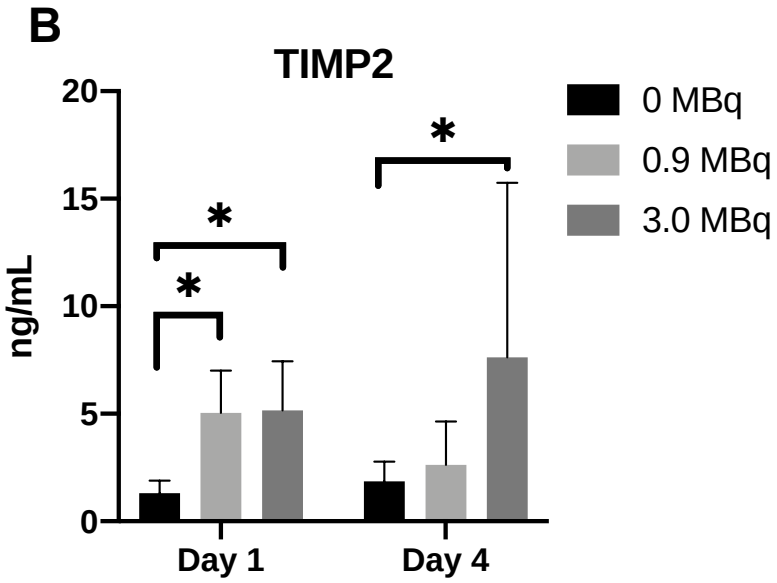
1 day	3-4 day	8 weeks	7 months
NGAL, TIMP-2, IGFBP7	NGAL, TIMP-2, IGFBP7	NGAL	NGAL

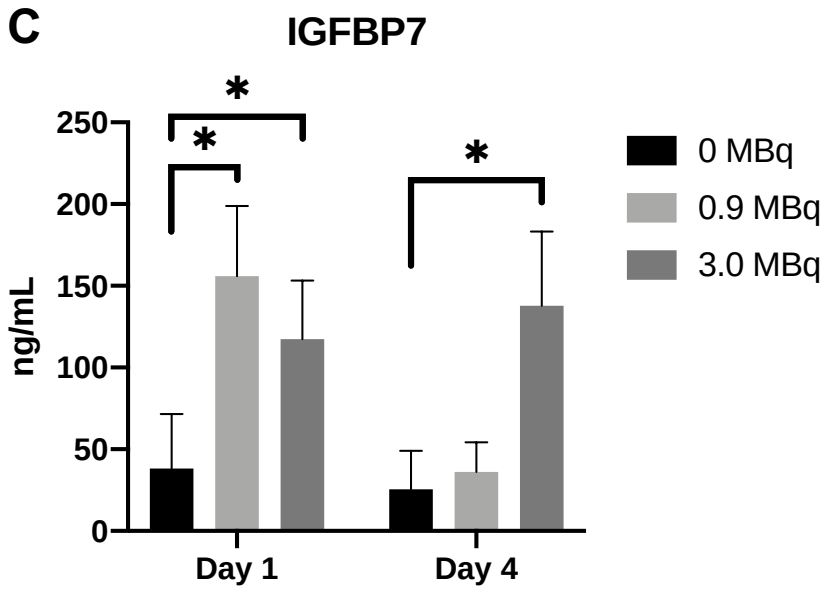
Blood analysis

1 week	3 weeks	5 weeks	8 weeks	7 months
Blood chem	CBC	Blood chem	Blood chem	Blood Chem, CBC

Dose-dependent response observed *via* urine biomarkers in male CD1-Elite mice after injection of [^{212}Pb]VMT01

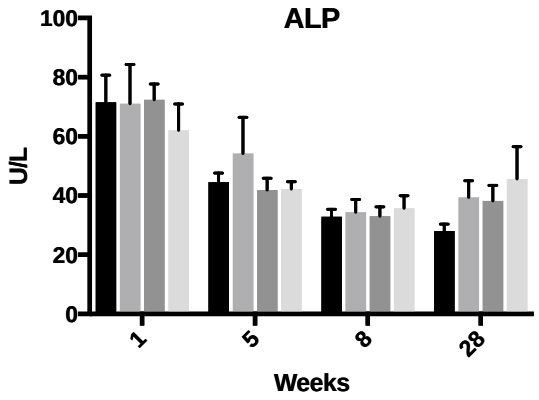


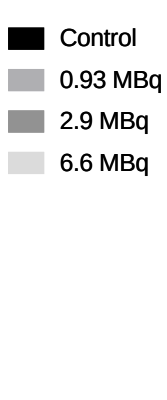


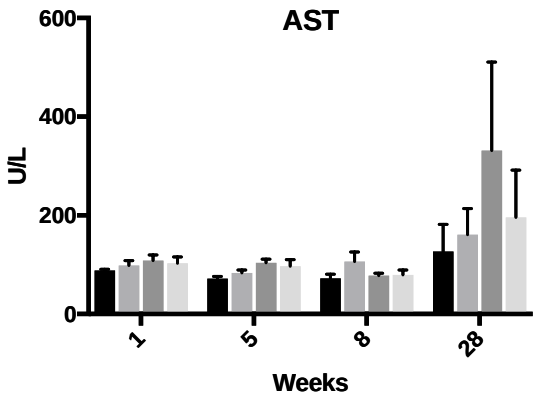


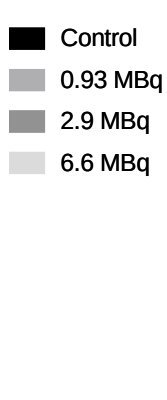
Statistical analysis by two-way ANOVA, *p<0.05, ****p<0.0001

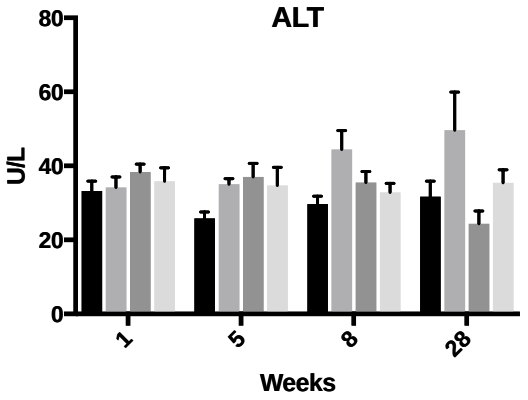
Blood chemistry analysis post-injection of [^{212}Pb]peptide

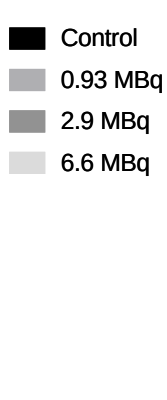


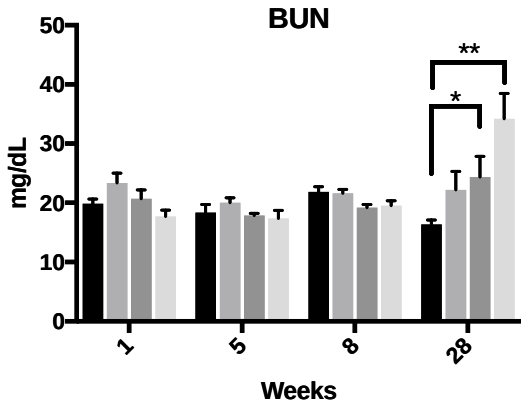


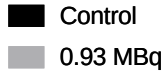


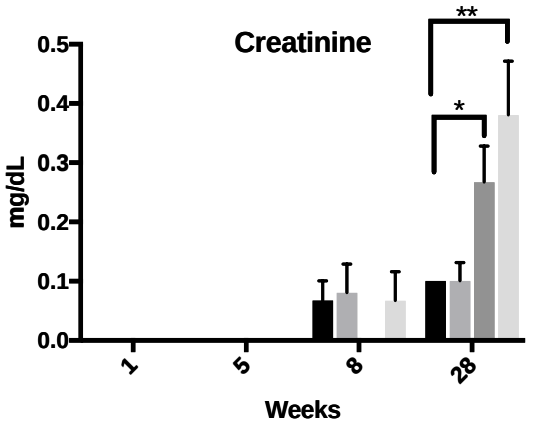


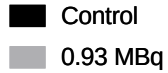








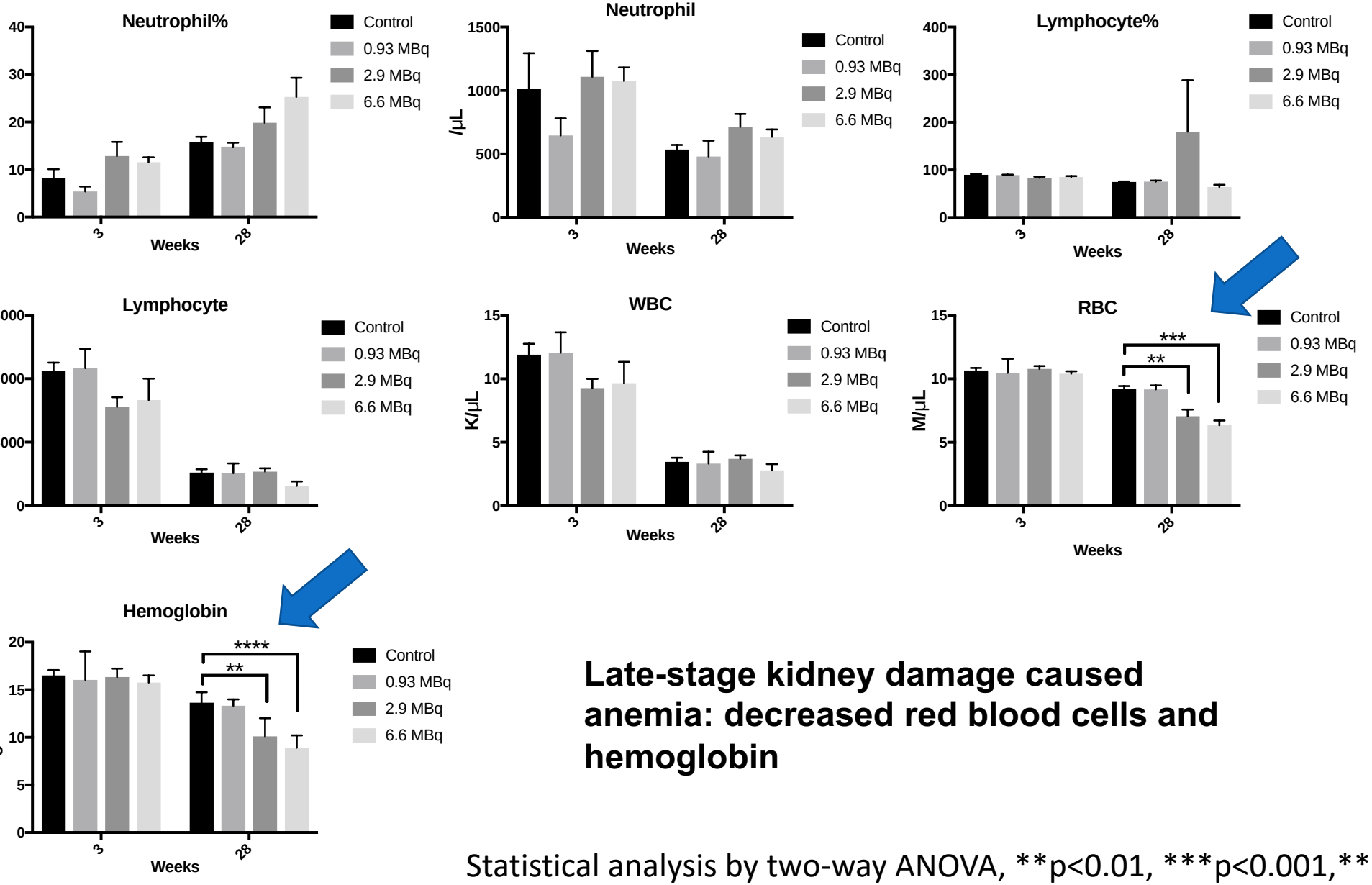




Dose-dependent elevation of blood urea nitrogen (BUN), creatinine, and cystatin C in late-stage kidney damage

Statistical analysis by two-way ANOVA, *p<0.05, **p<0.01

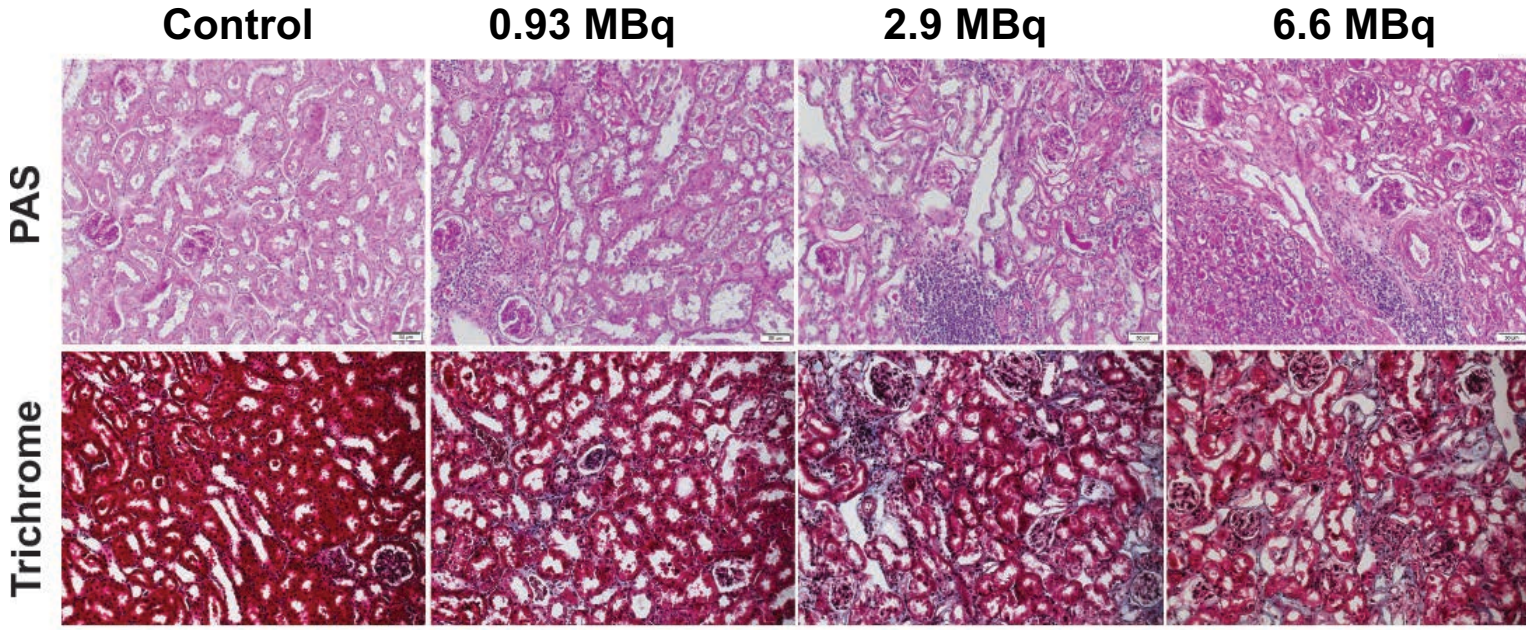
Complete blood count post-injection of [^{212}Pb]peptide



Late-stage kidney damage caused anemia: decreased red blood cells and hemoglobin

Statistical analysis by two-way ANOVA, **p<0.01, ***p<0.001,****p<0.0001

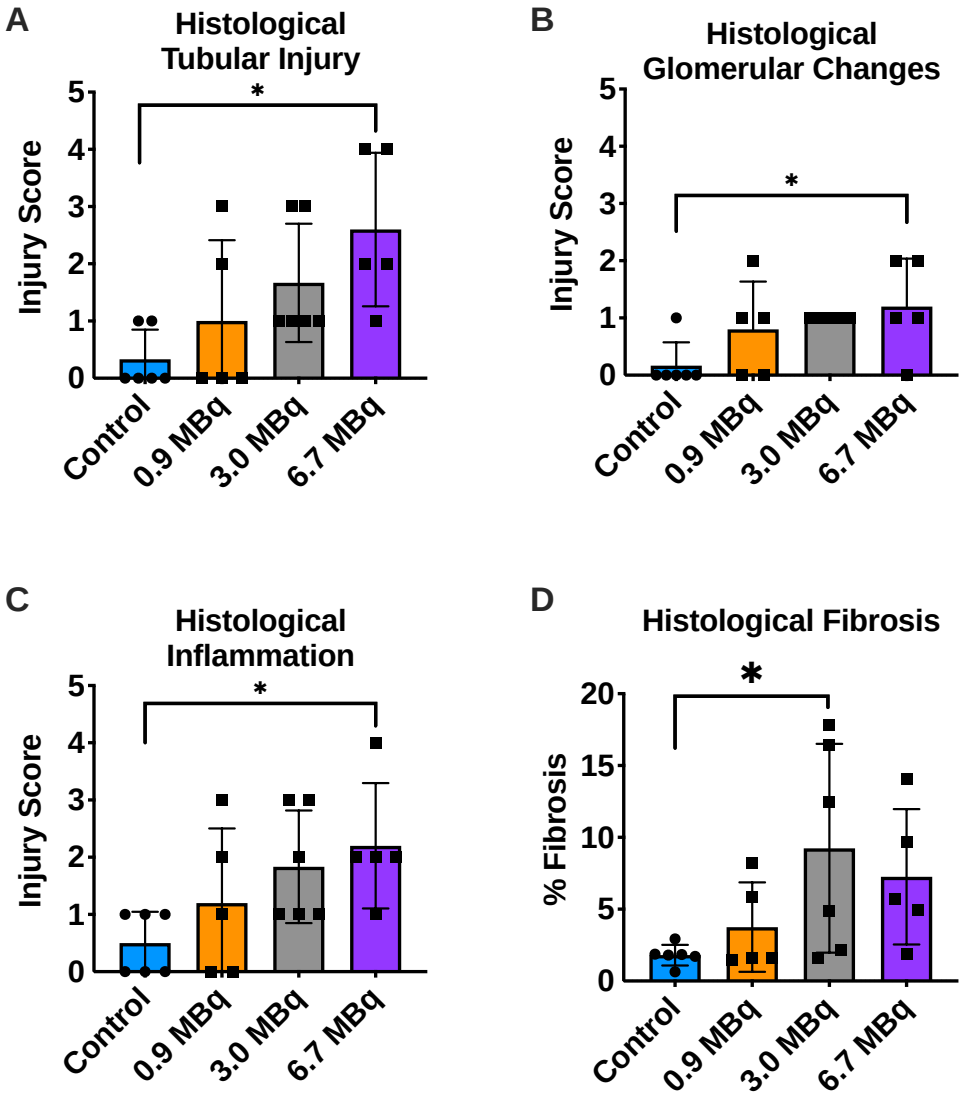
Prerna Rastogi, MD, PhD



Endpoint histological staining:

- 3-micron kidney sections were stained by periodic acid-schiff (PAS) and trichrome;
- Stained sections were scored by pathologist

Histology scoring of tubular/glomerular injury, fibrosis and inflammation



Tubular Injury Scoring			Glomerular Changes	
0	Absent		0	Absent
1	Mild (1-10%)		1	1-10%
2	Moderate (11-25%)		2	11-20%
3	Severe (26-50%)		3	21-30%
4	Very Severe > 50%		4	31% and greater
Tubulointerstitial Inflammation			Interstitial Fibrosis	
0	Absent		0	Absent
1	Mild (1-10%)		1	Mild (1-10%)
2	Moderate (11-25%)		2	Moderate (11-25%)
3	Severe (26-50%)		3	Severe (26-50%)
4	Very Severe > 50%		4	Very Severe > 50%

Statistical analysis by two-way ANOVA, *p<0.05, **p<0.01

Summary and Conclusions

- **Stable chelation of both ^{212}Pb and ^{212}Bi was observed**
- **Kidney dosimetry for [^{212}Pb]VMT01 was established using [^{203}]PbVMT01 surrogate**
- **Increased urine biomarkers (*i.e.* NGAL, TIMP-2, IGFBP7) were observed at early time points (1st week) post-injection**
- **Increased blood chemistry biomarkers (*i.e.* BUN, creatinine) were seen only at late time points (months)**
- **Histological staining identified tubular damage, glomerular damage, inflammation and fibrosis in kidney**
- **A detailed understanding of the potential toxicities is important for radiopharmaceutical development**

Acknowledgements

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