The Potential of Lead

A Preclinical Perspective

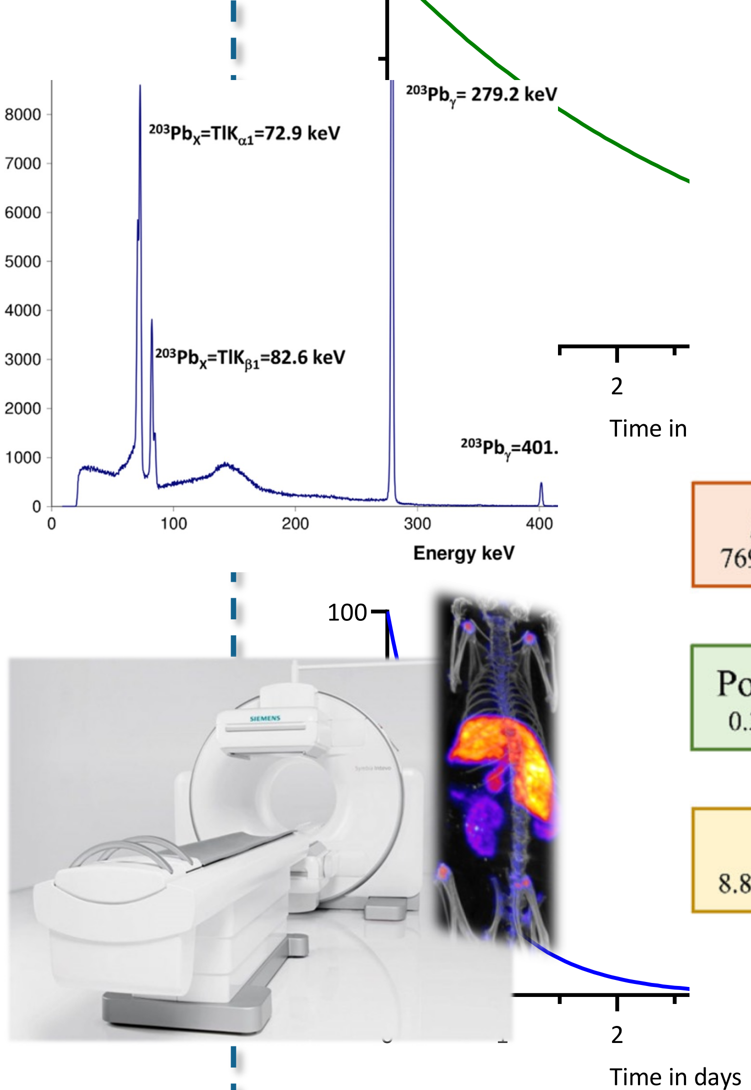
Memorial Sloan Kettering Cancer Center

David Bauer, Ph.D.

Jason Lewis Laboratory

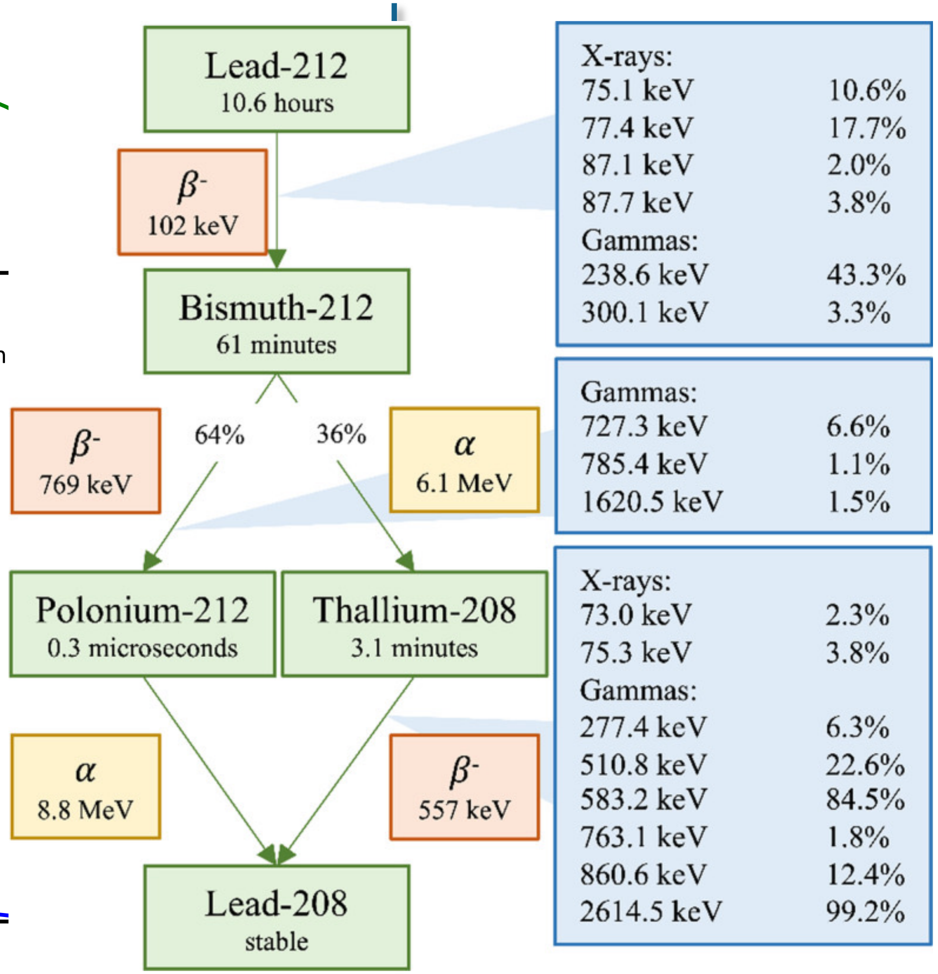
Physical Properties of Radiolead

^{203}Pb: SPECT Imaging



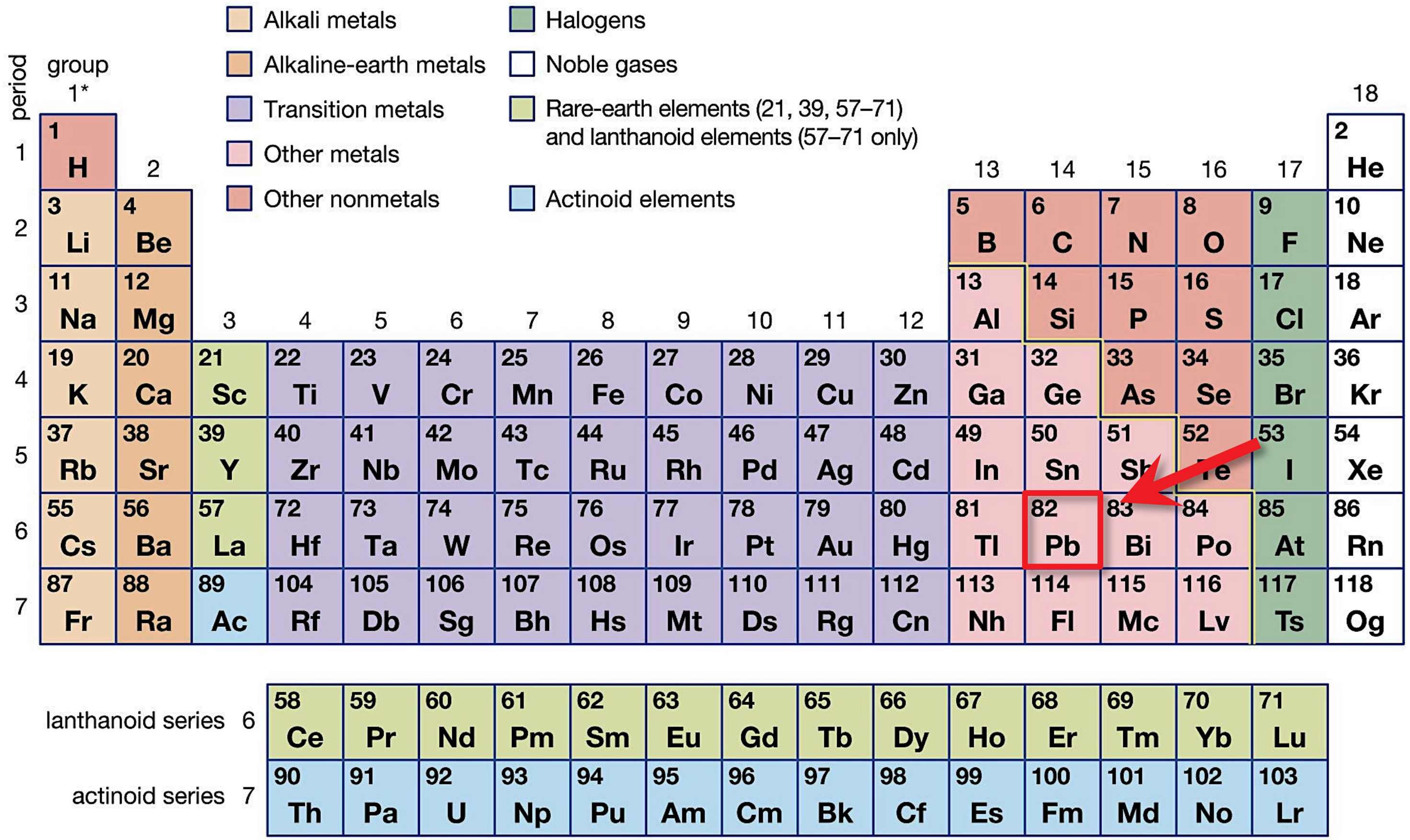
Máthé, et al. Appl Radiat Isot (2016), **PMID: 27156049**

^{203}Pb ^{212}Pb: In vivo Alpha-Generator



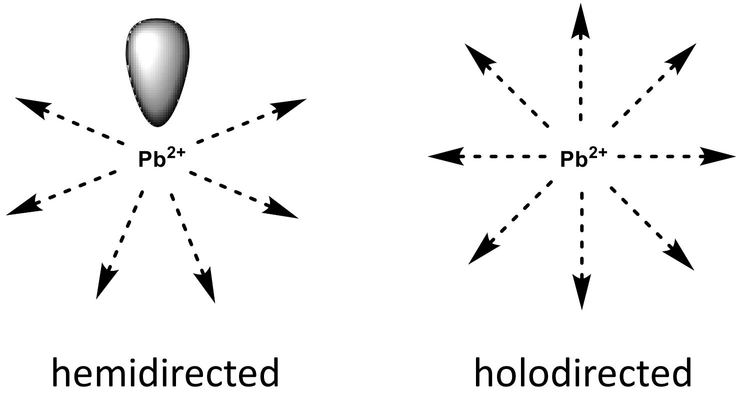
Kvassheim, et al. EJNMMI Phys (2022), **PMID: 35925521**
Kvassheim, et al. EJNMMI Phys (2023), **PMID: 37603123**

Chemical Properties of Lead



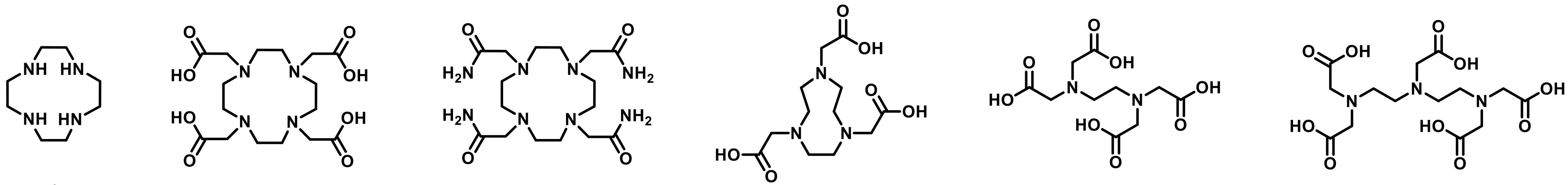
Encyclopedia Britannica

Electron config.:	$4f^{14}\ 5d^{10}\ 6s^{2}\ 6p^{2}$
Pb^{2+} (CN = 6):	1.19 Å
CN < 6	hemidirected
CN 8+	holodirected
HSAB behavior	borderline



Sacks, et al. Int J Stroke (2018), **PMID: 29786478**

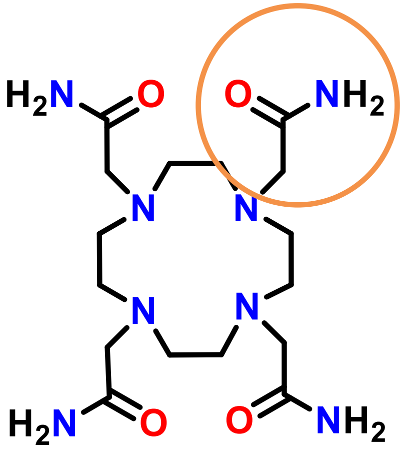
The Chelation of Lead



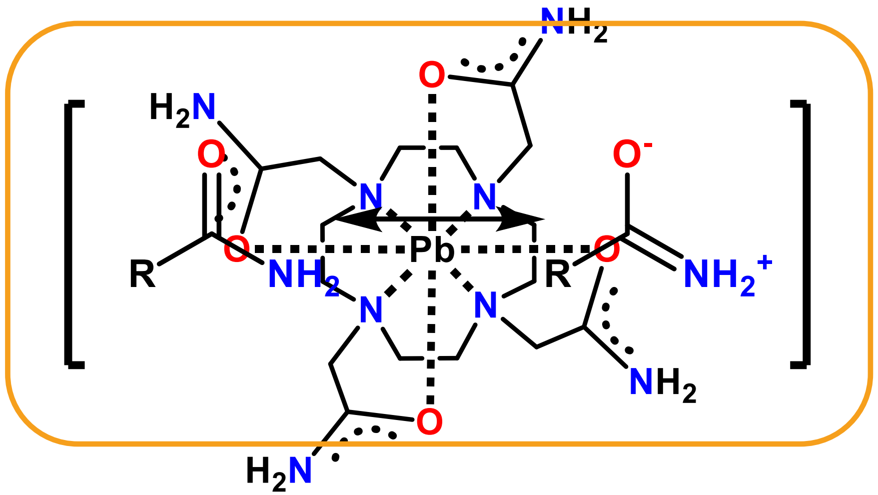
cyclen DOTA TCMC NOTA EDTA DTPA

Ligand	cyclen	DOTA	TCMC	NOTA	EDTA	DTPA
log β	15.9	22.7	>19	16.6	18.0	18.8

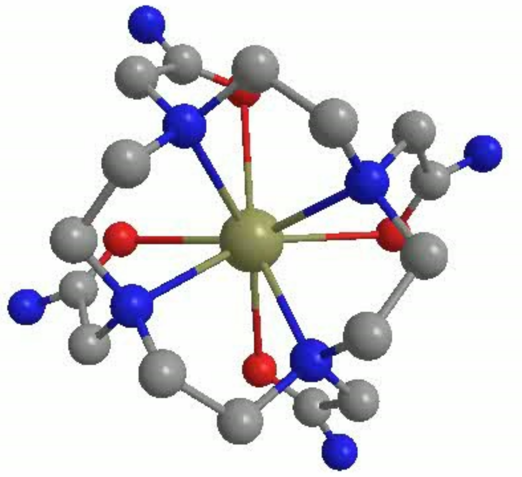
Kokov, et al. Pharmaceutics (2022), **PMID: 35057083**



TCMC

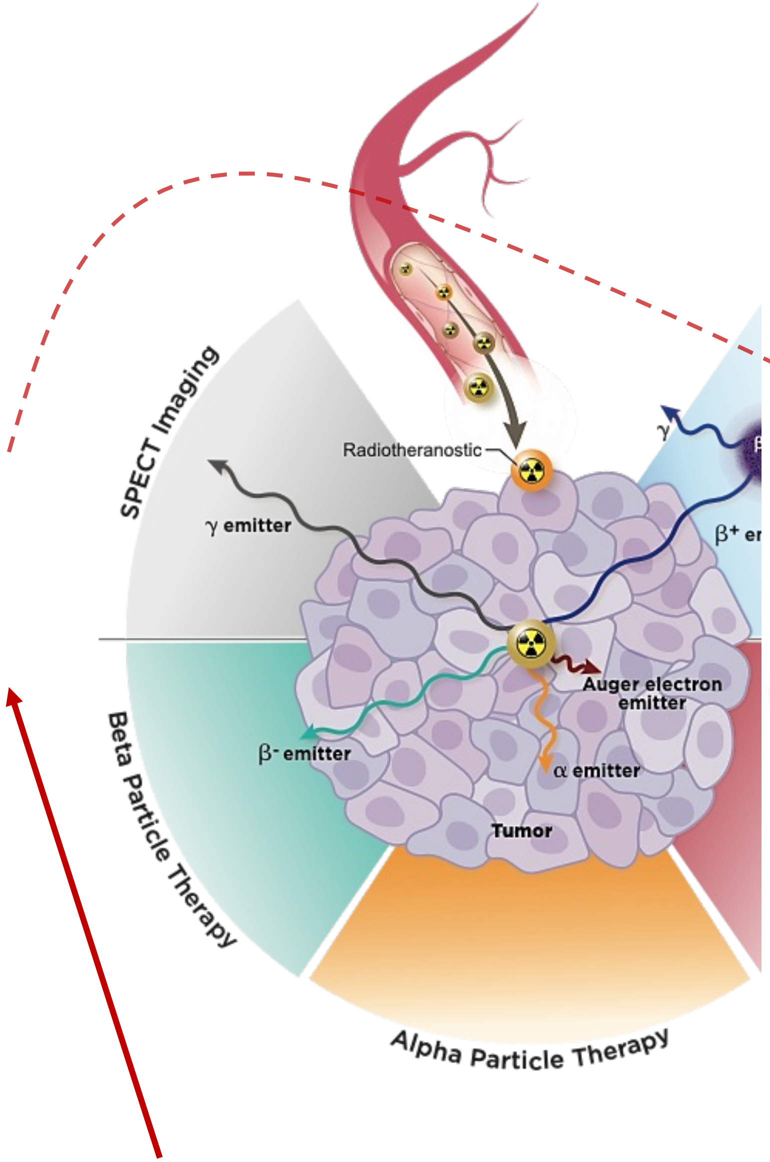


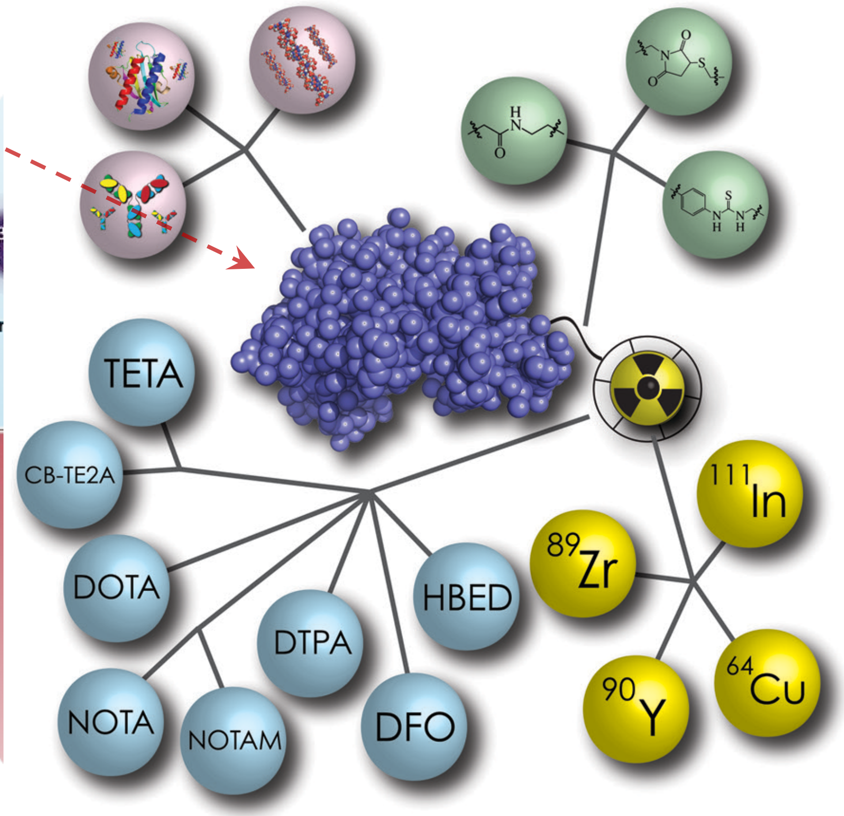
[Pb-TCMC]



Cuenot, et al. EurJIC (2007), **DOI: 10.1002/ejic.200700819**

Theranostics with Lead



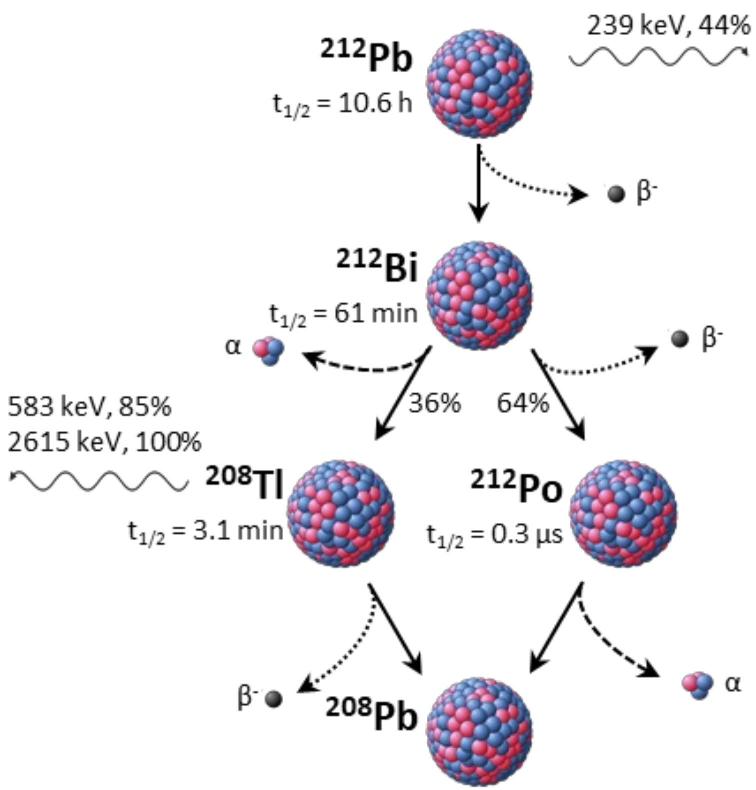


PSMA, SSTR2, CXCR4, GRPR, MC1R, HER2

Zeglis, et al. Dalton Transactions (2011), **PMID: 21442098**

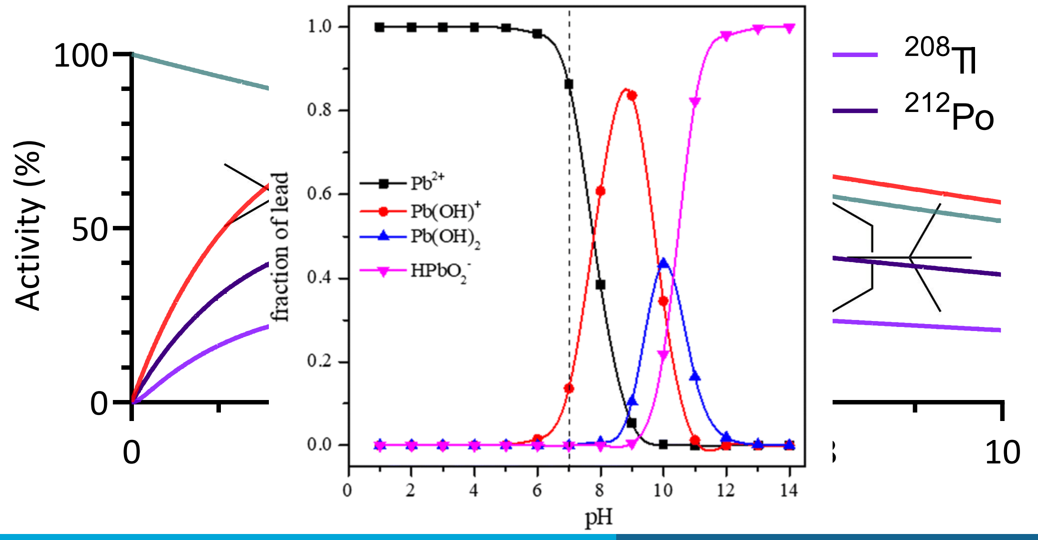
Herrero, et al. ChemMedChem (2021), **PMID: 33792195**

The Radiolabeling of Lead



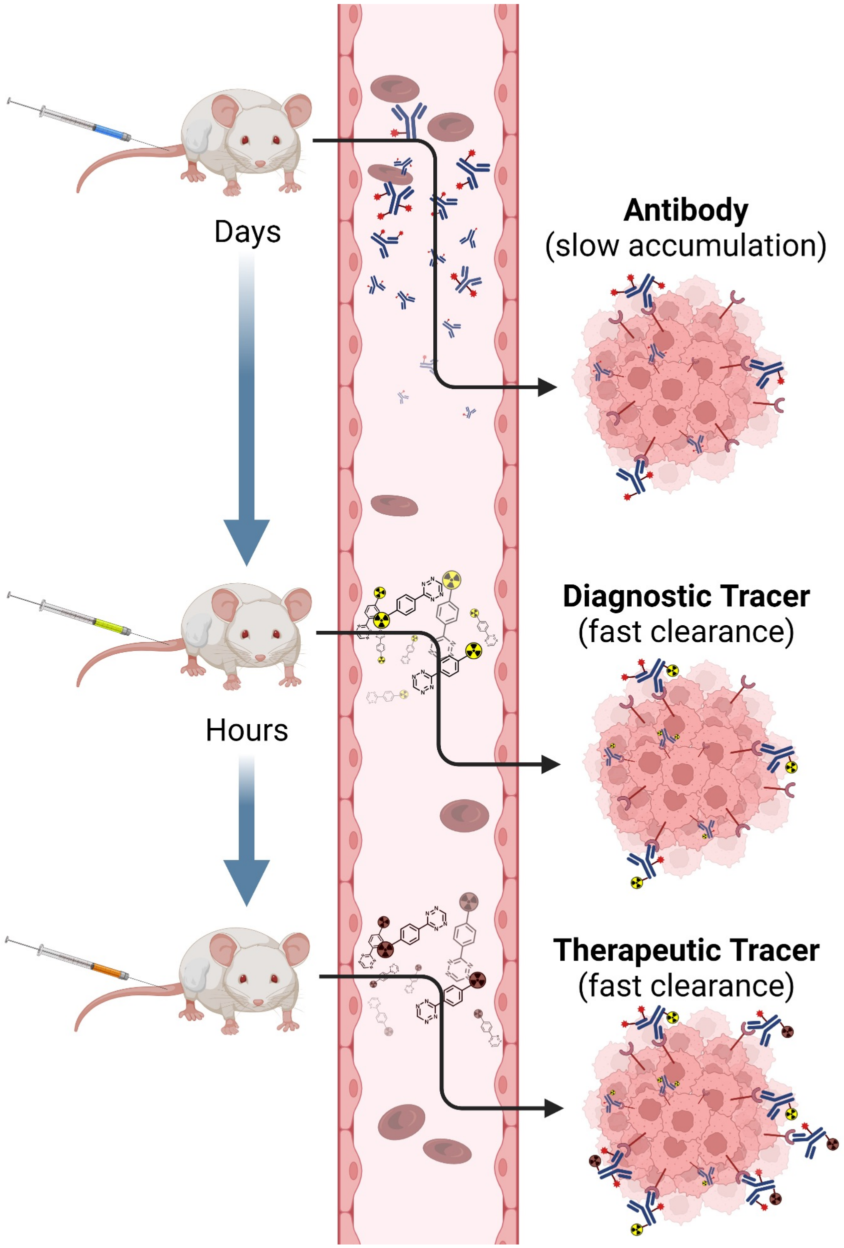
The “Kit” procedure:

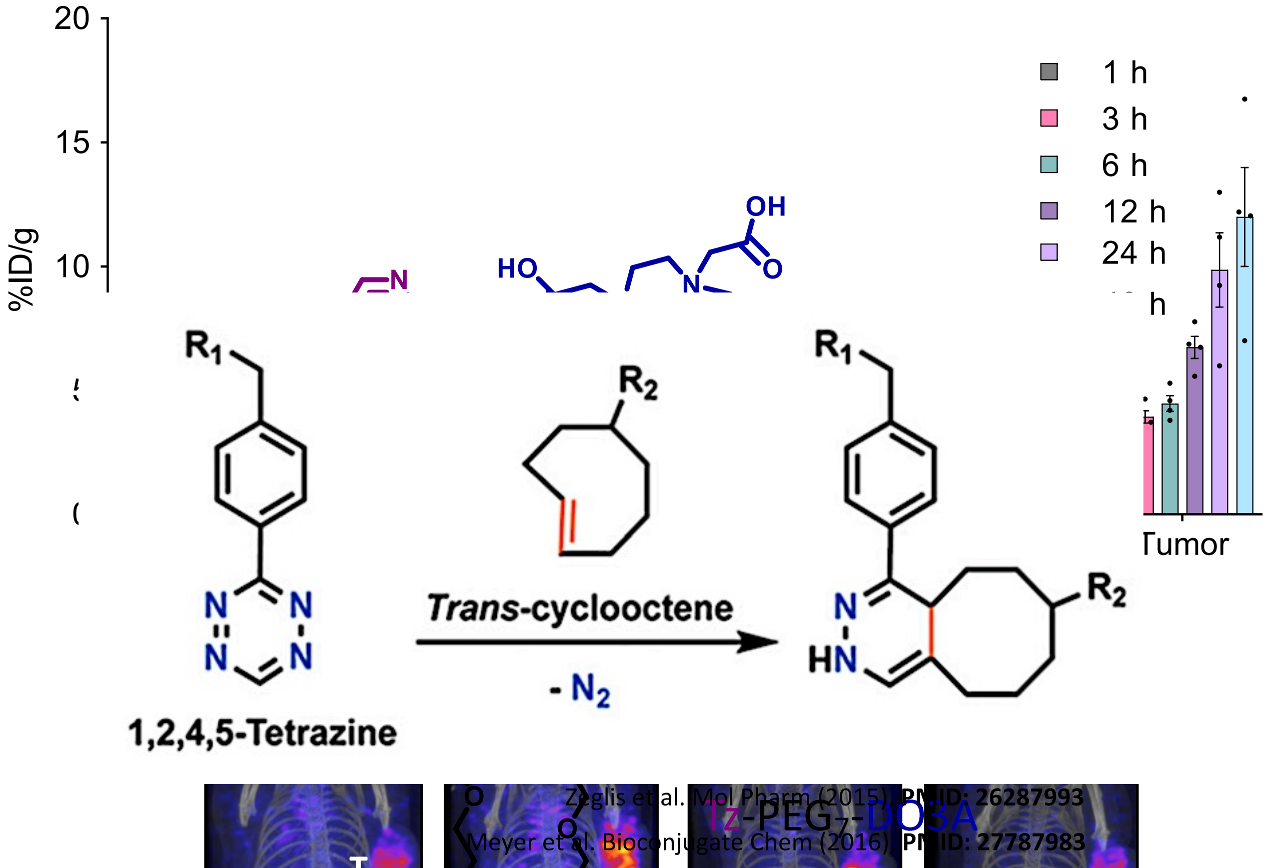
1) Reconstitute precursor in buffer	**pH 4.5–5.5**
2) Add radiolead	**Pb Resin purification**
3) Check pH	**!**
4) Incubation	**RT, 10-30 min**
5) Formulate for injection	**Purification, EQ !**
6) QC	**HPLC (+)**

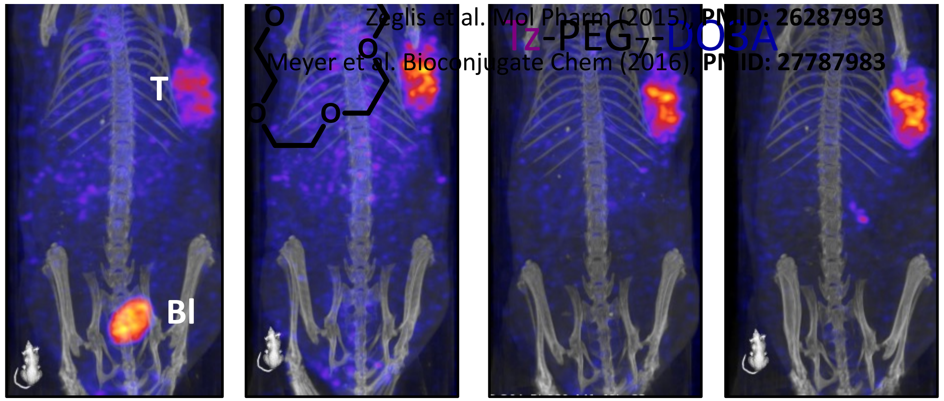


McNeil et al. EJNMMI (2021), **PMID: 33527221**
Li et al. Pharmaceutics (2023), **PMID: 36839736**
Oliveira et al. Water Air Soil Pollut (2019), **DOI: 10.1007/s11270-019-4240-8**
Baidoo et al. Nucl Med Biol (2013), **PMID: 23602604**
Chapeau et al. Pharmaceutics (2023), **PMID: 37513897**

Pretargeting with Lead-212

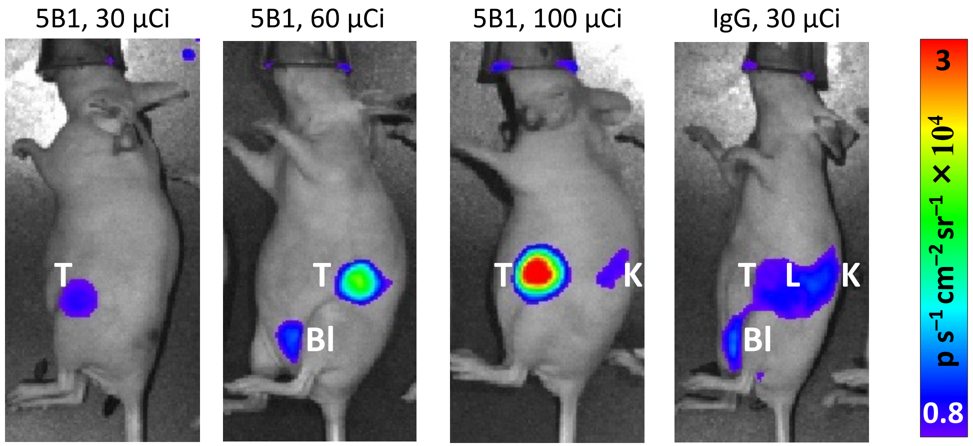


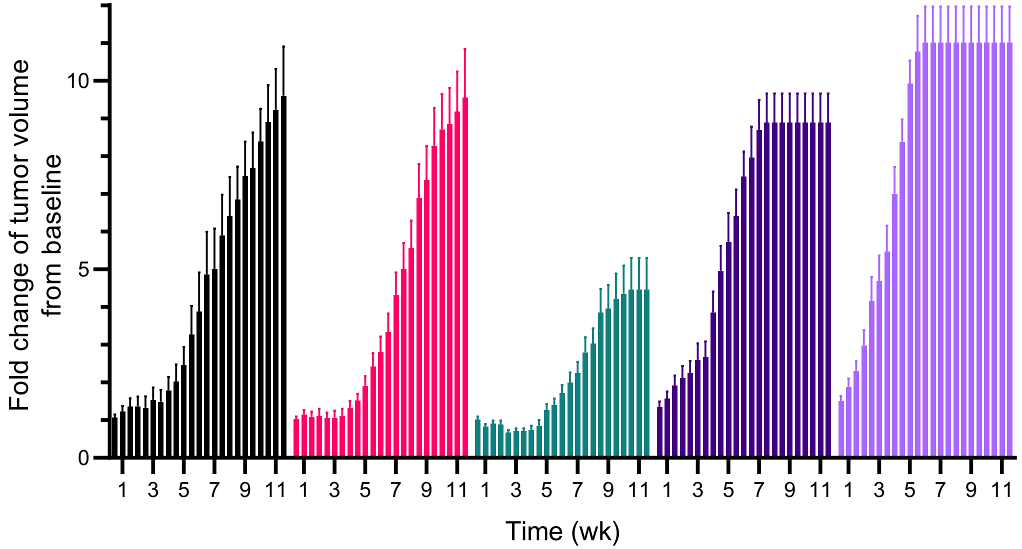




Bauer, et al. JNM (2023), accepted

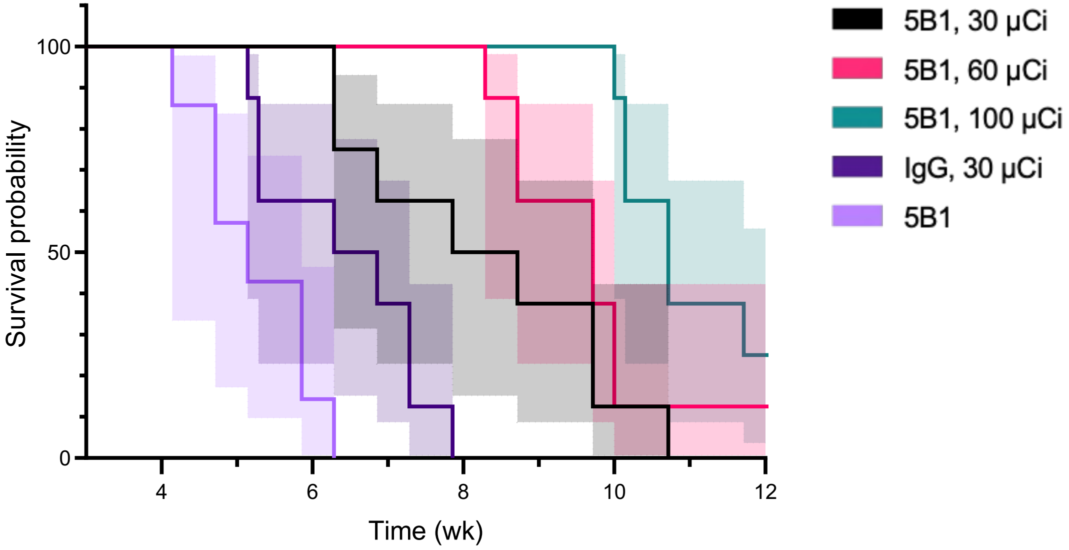
Therapy with Lead-212 is Effective!





Median Survival in Weeks

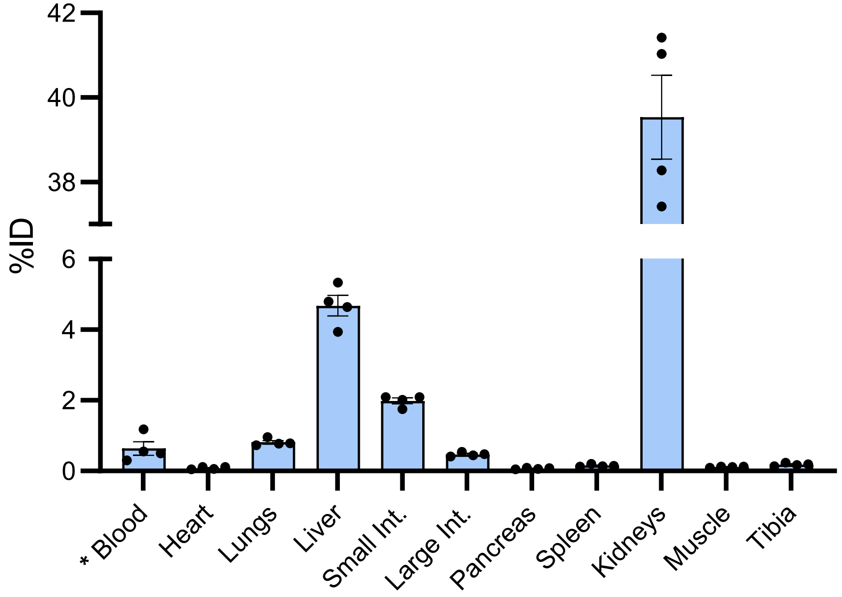
30 µCi DO3A	60 µCi DO3A	100 µCi DO3A	30 µCi IgG, DO3A	NaCl
8.3	**9.7**	**10.7**	**6.5**	**5.1**



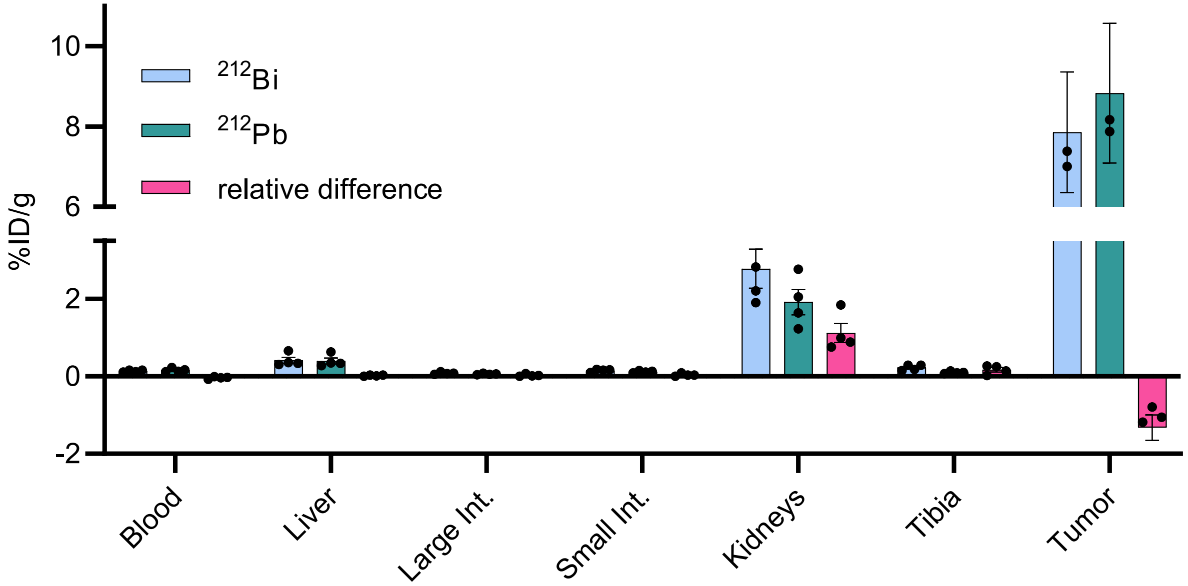
Bauer, et al. JNM (2023), accepted

Investigating Bismuth-212

Biodistribution of [^{212}Bi]$BiCl_3$ in healthy mice
(*n* = 4)

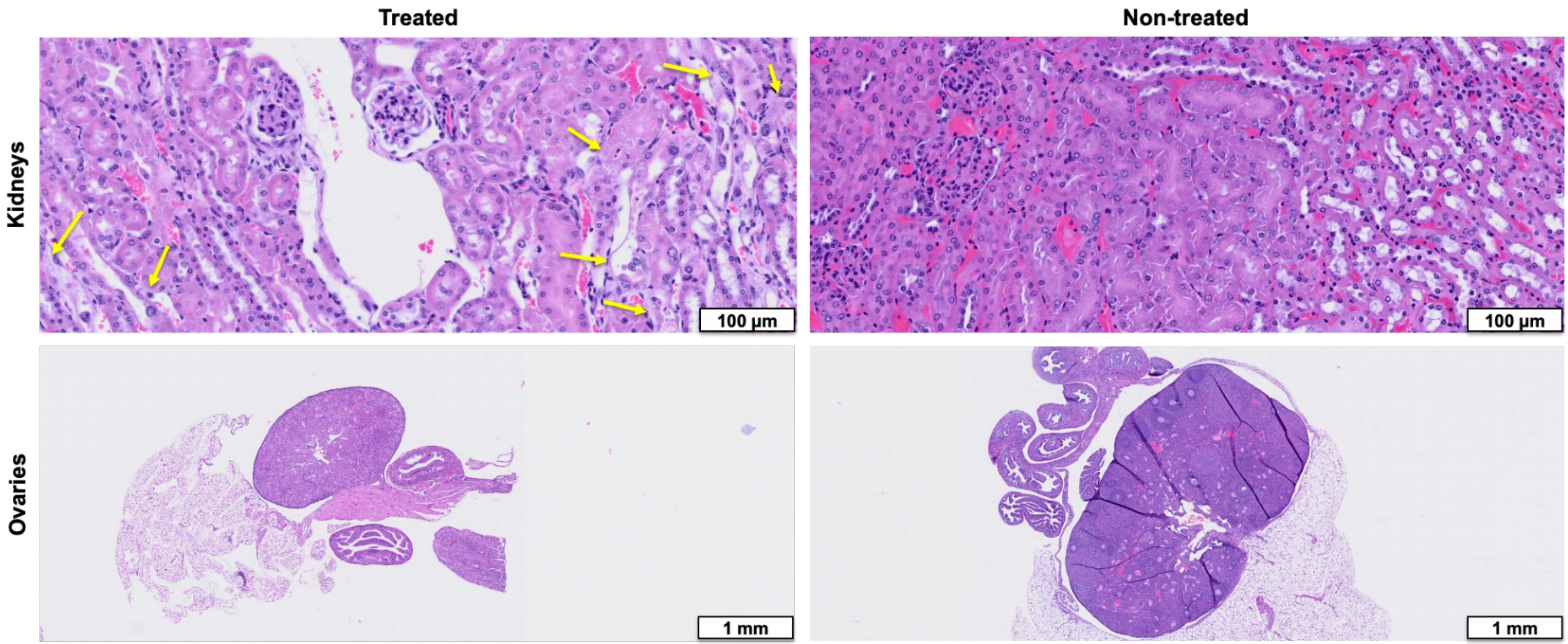


^{212}Bi redistribution study
(*n* = 4)



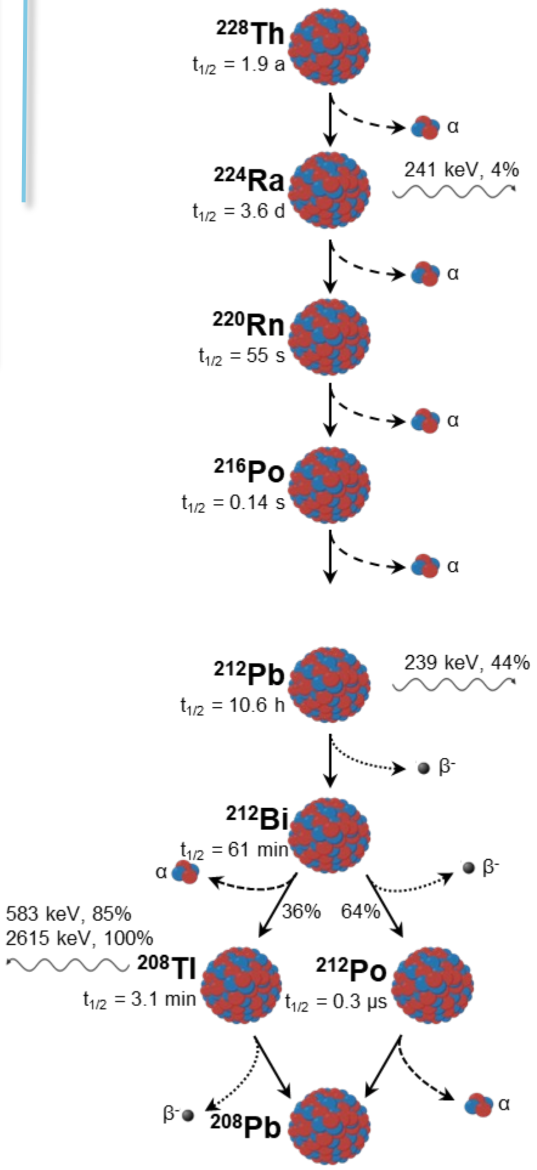
Bauer, et al. JNM (2023), accepted

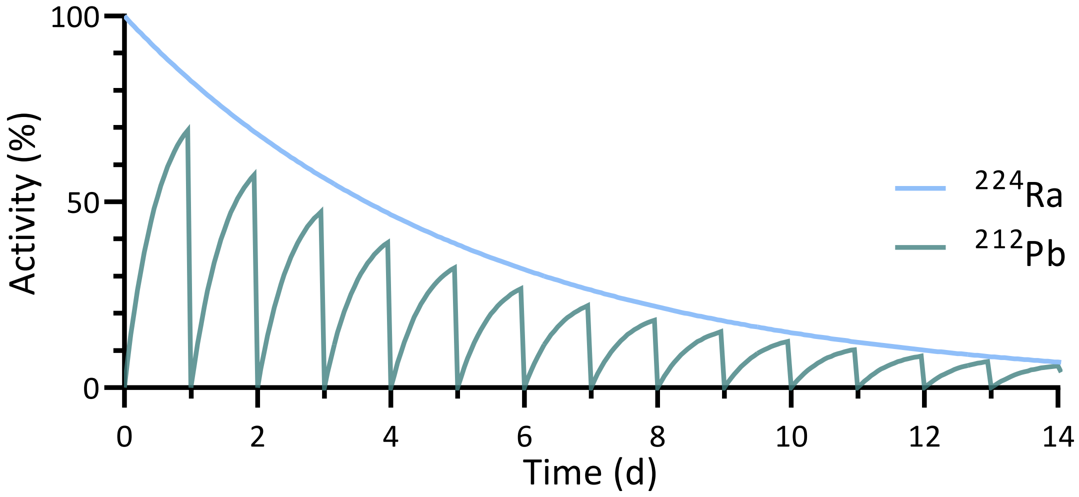
Histopathological Examination

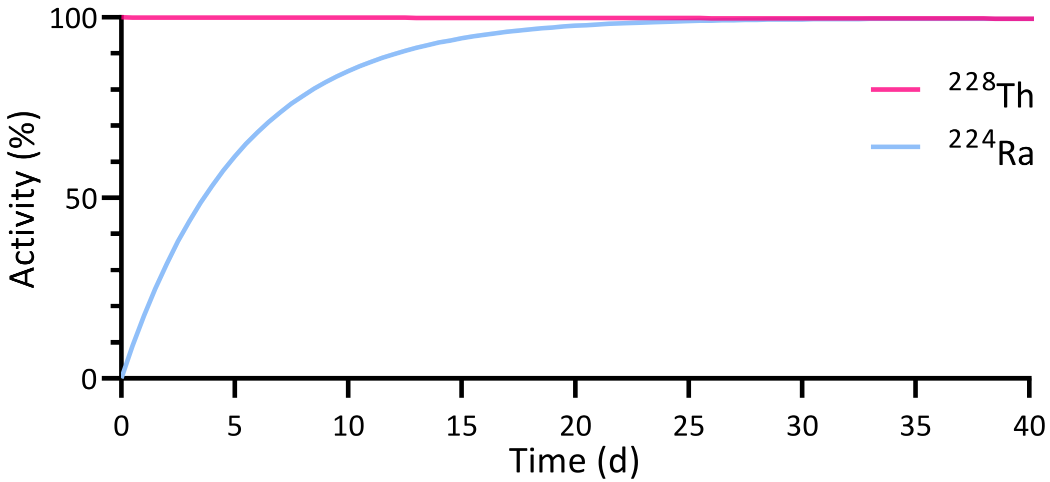


Bauer, et al. JNM (2023), accepted

Obtaining Lead-212

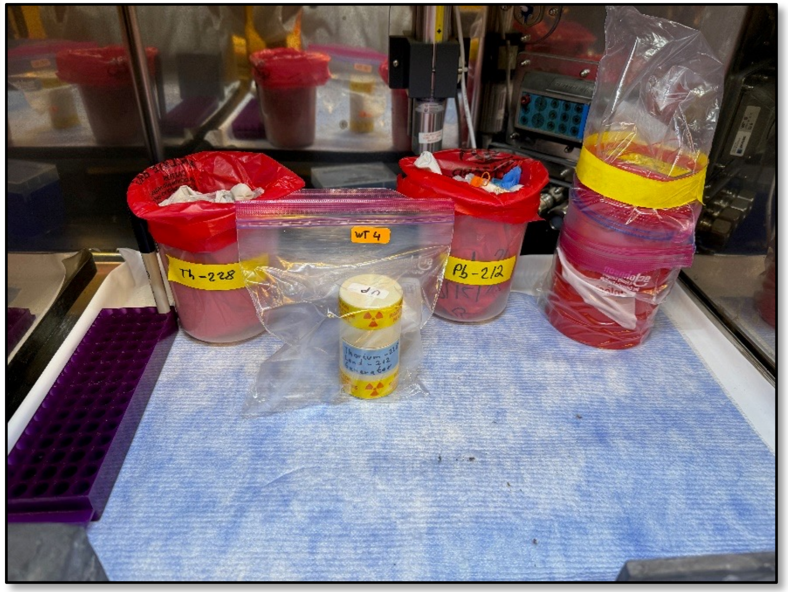


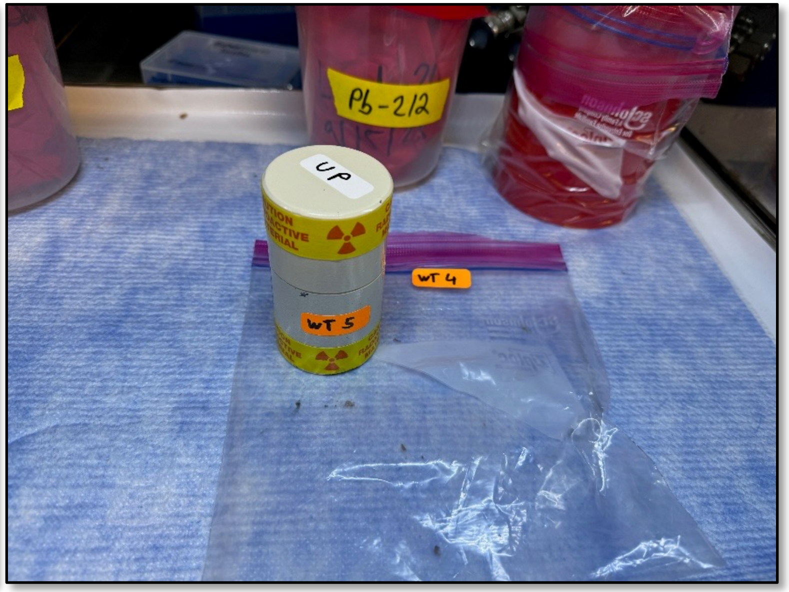


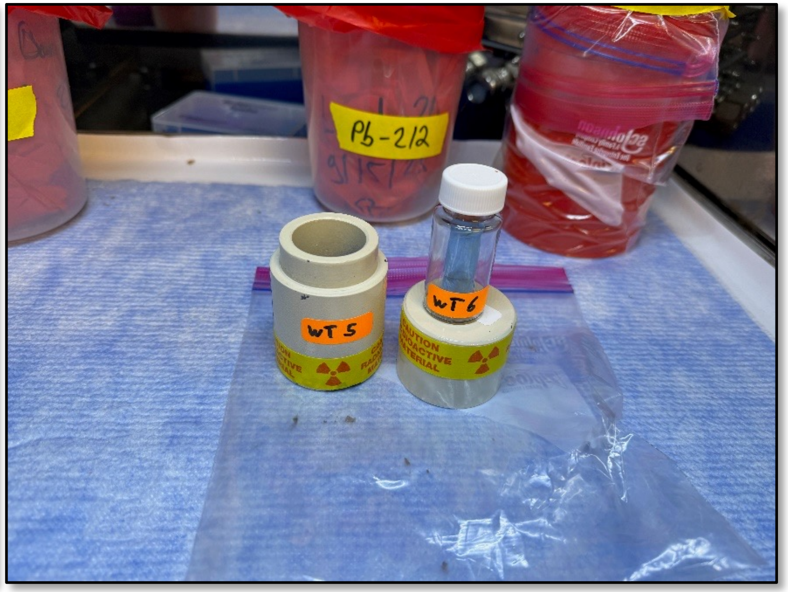


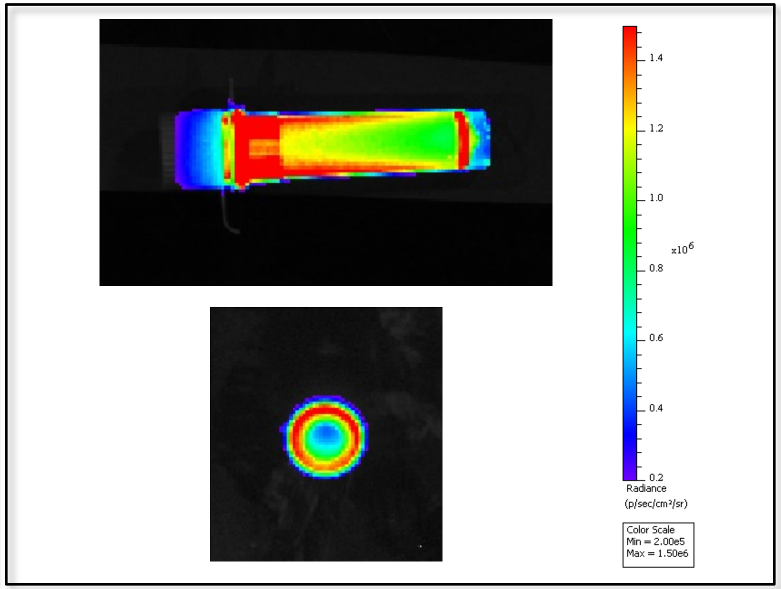
Li et al. JNM (2023), **PMID: 35798556**
Napoldi et al. Appl Radiat Isot (2020), **PMID: 32979756**

Radon-220 Emanation









Acknowledgments

Jason Lewis Laboratory

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Memorial Sloan Kettering Cancer Center

The Tow Foundation Fellowship Program

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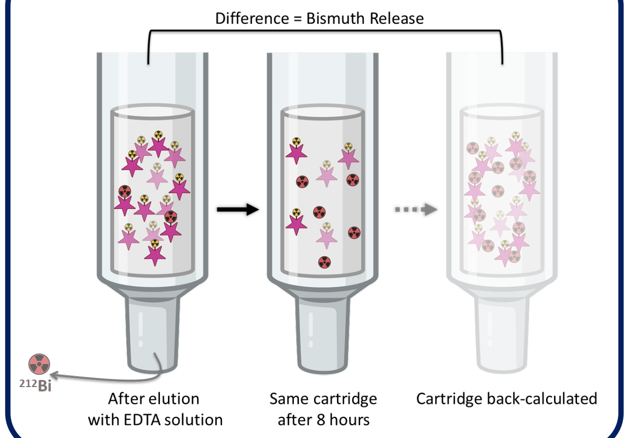
R35 CA232130
P30 CA008748
S10 RR02892-01
S10 OD016207-01
P30 CA008748

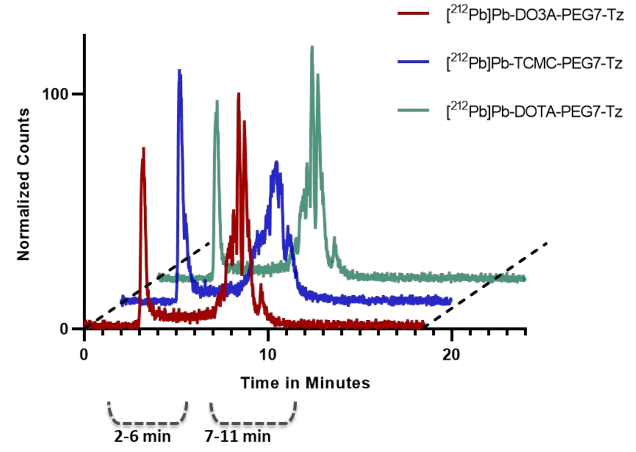
Thank you for your attention!

Bismuth-212 Release Studies – Results

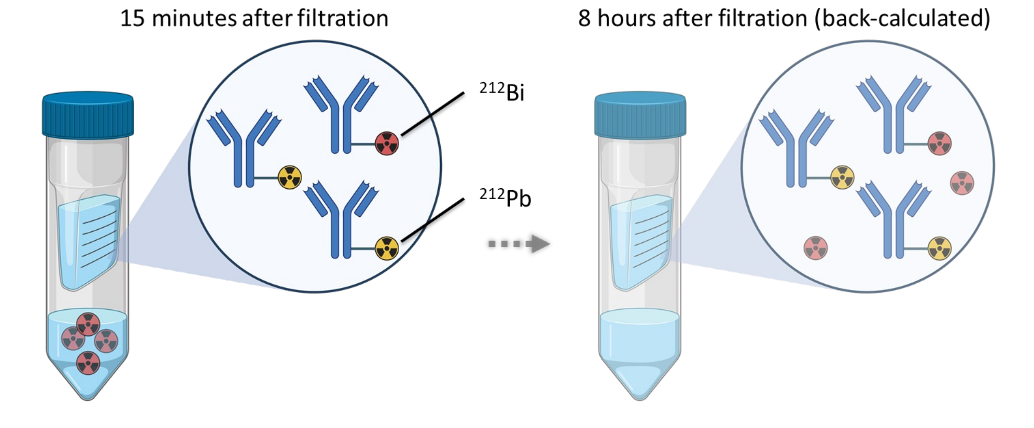
C18-based assay



HPLC-based assay

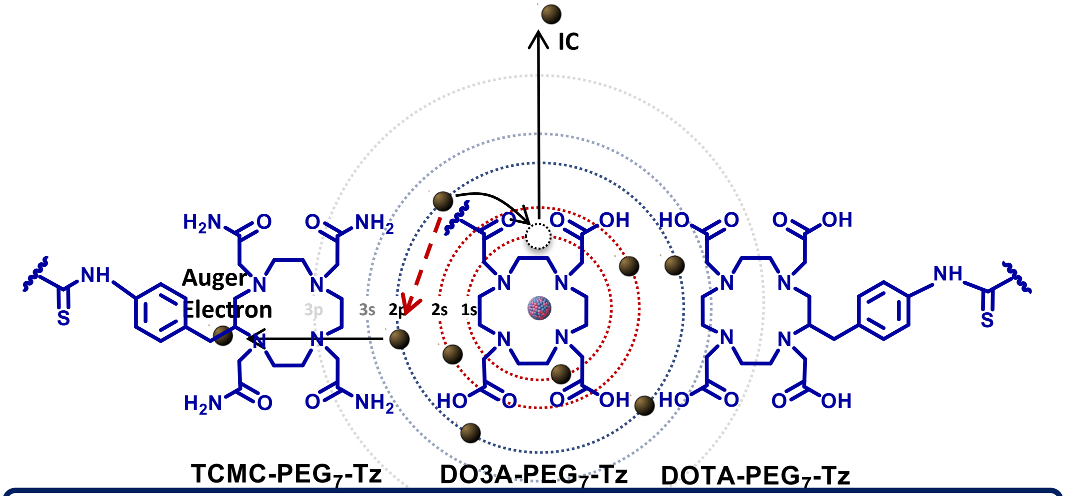


Ultrafiltration-based assay



Bismuth Release

	C18	HPLC	UF
TCMC-PEG$_7$-Tz	(42 ± 5) %	(39 ± 5) %	(44 ± 5) %
DO3A-PEG$_7$-Tz	(41 ± 5) %	(37 ± 5) %	(46 ± 5) %
DOTA-PEG$_7$-Tz	(43 ± 5) %	(37 ± 5) %	(43 ± 5) %



Ruble, et al. IJROBP(1996) 34:609-616
Su, et al. Nucl Med and Biol (2005) 32:741-747
Mirzadeh, et al. Radiochemica Acta (1993) 60:1-10
Bauer, et al. unpublished work

(40 ± 5) %

For ^{212}Pb: 37% Auger & conversion electrons from the K shell
30% Auger & conversion electrons from the L – O shells

Safety Concerns

```
9/28/2023   7:15:00 PM        QuantaSmart (TM) - 4.00 - Serial# 129347              Page # 1
Protocol# 1 - Wipe Test.lsa                                                User: Rad Safety
                                   Rad Safety LSC - ZRC-20
```

Assay Definition

```
Assay Description:
Generic Wipe Test for Lab users.
Assay Type: DPM (Dual)
Report Name: Report1
Output Data Path: C:\Packard\Tricarb\Results\Rad Safety\Wipe Test\20230928_1859
Raw Results Path: C:\Packard\Tricarb\Results\Rad Safety\Wipe Test\20230928_1859\20230928_
1859.results
Assay File Name: C:\Packard\TriCarb\Assays\Wipe Test.lsa
```

Count Conditions

```
Nuclide: Wipe Test
   Quench Indicator: tSIE/AEC
   External Std Terminator (sec): 0.5 2s%
   Pre-Count Delay (min): 0.00
Quench Sets:
   Low Energy: 3H-UG
   Mid Energy: 14C-UG
Count Time (min): 1.00
Count Mode: Normal
Assay Count Cycles: 1          Repeat Sample Count: 1
#Vials/Sample: 1               Calculate % Reference: Off
```

Background Subtract

```
Background Subtract: On - 1st Vial
Low CPM Threshold: Off
2 Sigma % Terminator: Off
```

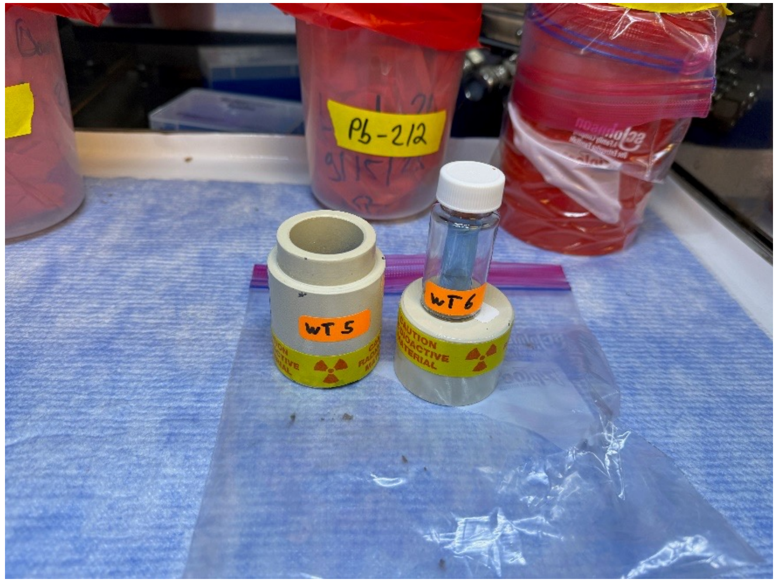
Regions	LL	UL	Bkg Subtract
A	0.0	18.6	1st Vial
B	18.6	156.0	1st Vial
C	156.0	2000.0	1st Vial

Count Corrections

```
Static Controller: On              Luminescence Correction: n/a
Colored Samples: Off               Heterogeneity Monitor: n/a
Coincidence Time (nsec): 18        Delay Before Burst (nsec): 75
```

Cycle 1 Results

S#	Count Time	CPM 1	DPM1	CPM 2	DPM2	CPM 3	DPM3	Total DPM	tSIE
Missing vial 1.									
2	1.00	32	49	5	6	11	12	67	982.99
3	1.00	29	65	7	9	8	9	83	509.61
4	1.00	73	167	12	16	17	19	202	504.43
5	1.00	51	117	10	13	12	13	143	503.47
6	1.00	57	126	13	18	16	18	162	507.44
7	1.00	75	176	7	9	21	23	208	504.31
8	1.00	54	113	24	33	73	81	227	503.81



Generator-Details:

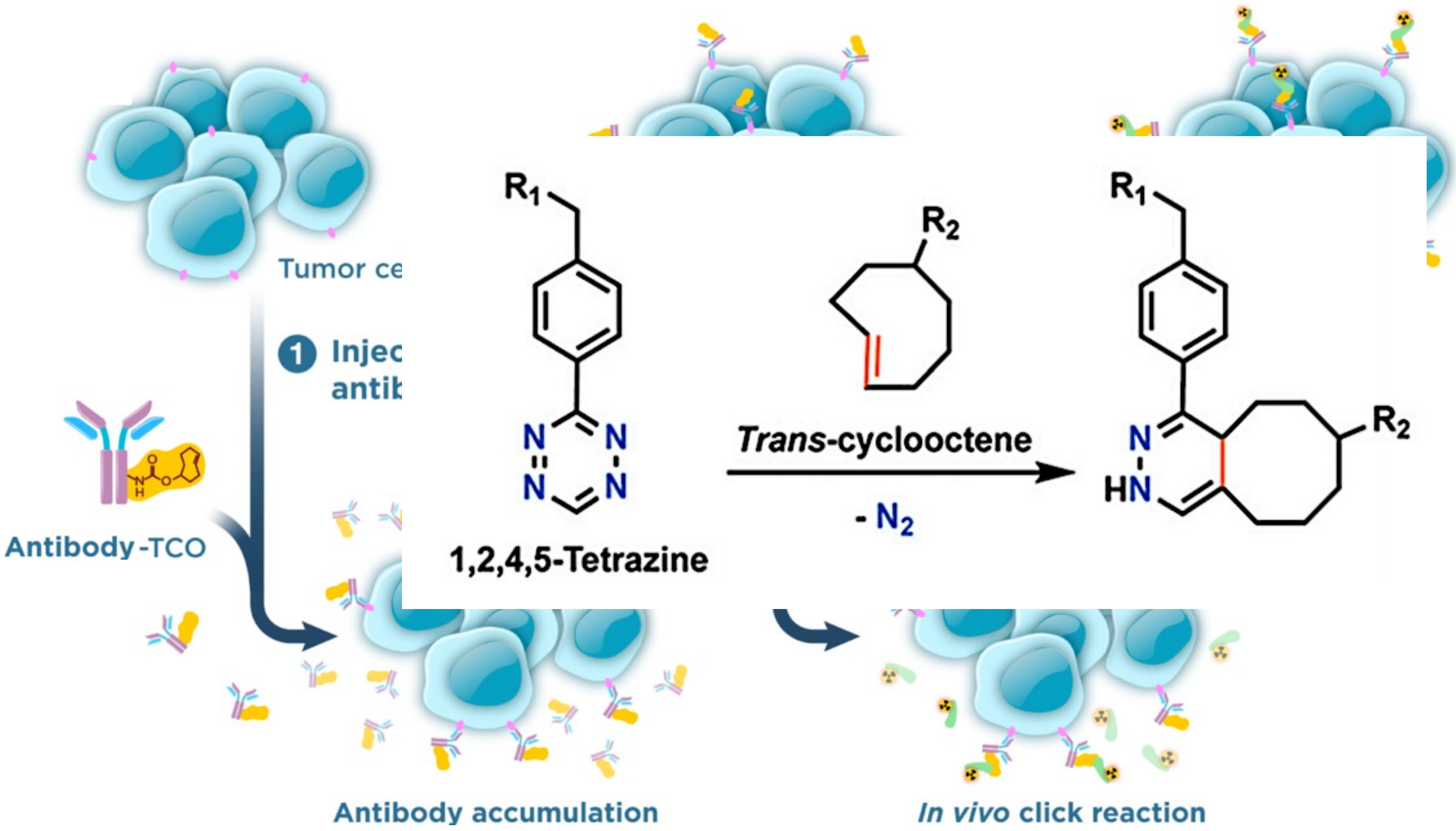
- 1.0 mCi thorium-228
- 400 µCi lead-212 deposit
- 300 µCi lead-212 transferred

Cycle 1 Results

S#	Count Time	CPM 1	DPM1	CPM 2	DPM2	CPM 3	DPM3	Total DPM	tSIE
Missing vial 1.									
2	1.00	32	49	5	6	11	12	Control	
3	1.00	29	65	7	9	8	9	Door	
4	1.00	73	167	12	16	17	19	Hood -Frame	
5	1.00	51	117	10	13	12	13	Hood-Wall	
6	1.00	57	126	13	18	16	18	Plastic Bag	
7	1.00	75	176	7	9	21	23	Lead Container	
8	1.00	54	113	24	33	73	81	Generator Vial	

David Bauer | Jason Lewis Laboratory

Pretargeting – The Concept



Zeglis et al. Mol Pharm (2015), **PMID: 26287993**

Meyer et al. Bioconjugate Chem (2016), **PMID: 27787983**