PERSPECTIVE THERAPEUTICS

Alpha Radiation Impacts on Chromatographic Separations

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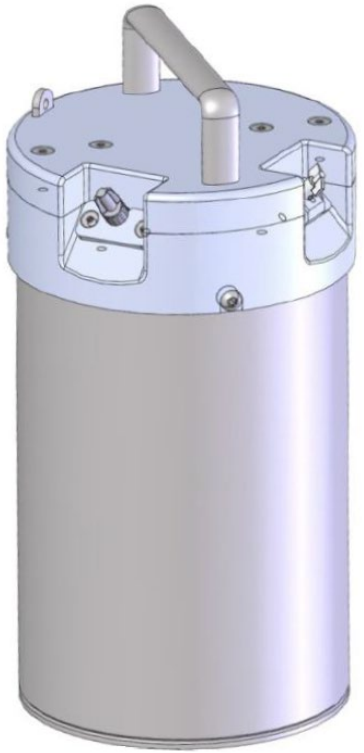
Eichrom Users Group Meeting

Perspective Therapeutics Isotope Generator

VMT-α-GEN

- Perspective Therapeutics has a proprietary ^{212}Pb isotope generator (patent pending) for the development of ^{212}Pb-bearing radiopharmaceuticals for targeted alpha therapies to treat various types of cancer
- The generator contains up to 35 mCi (~1.3 GBq) of ^{224}Ra bound to a substrate and allows for routine production of ^{212}Pb via radioactive ingrowth
- ^{224}Ra is purified from a ^{228}Th source on a routine basis to provide on demand ^{224}Ra/^{212}Pb generators for drug product manufacturing



VMT-α-GEN

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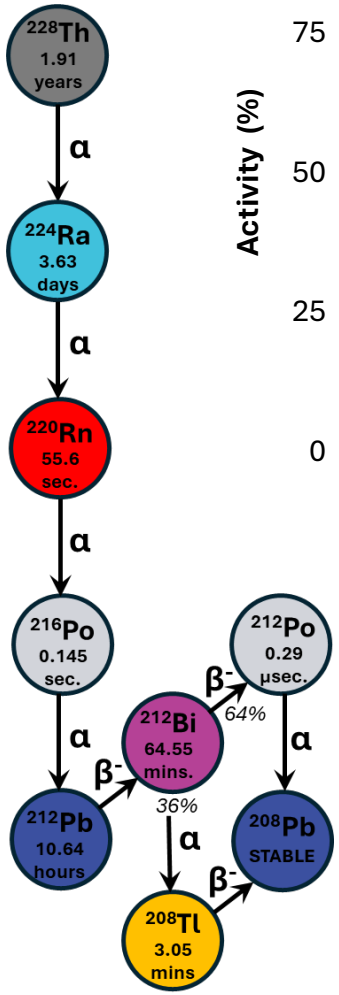
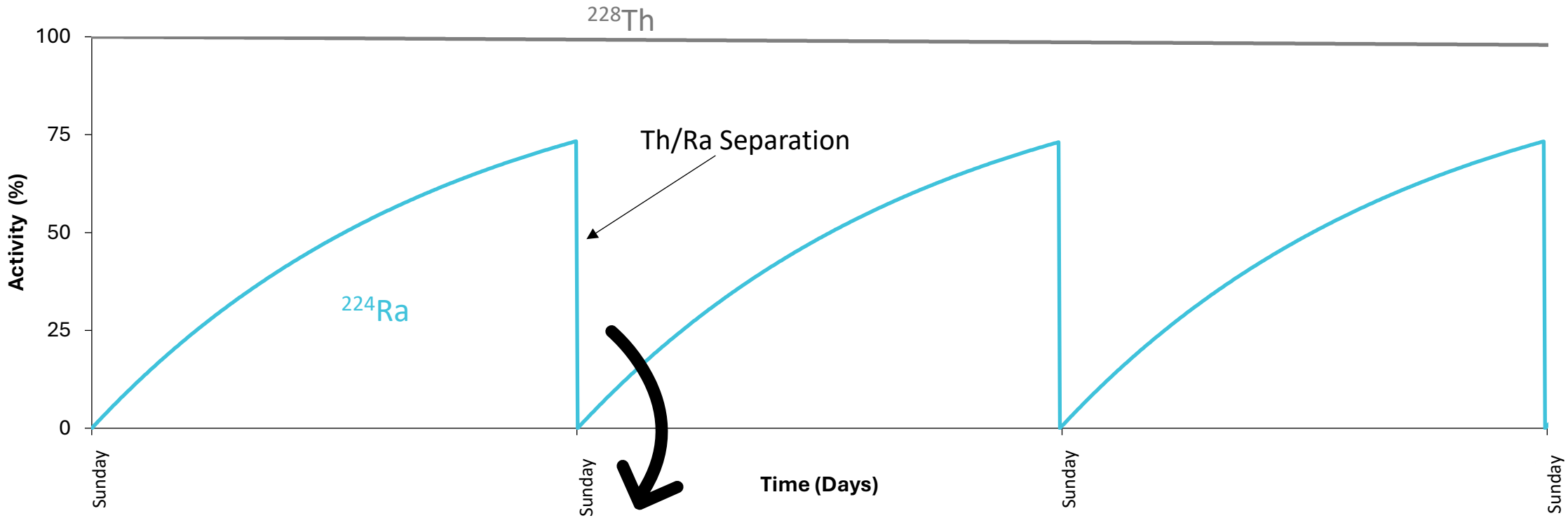
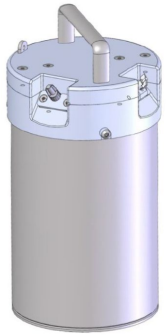
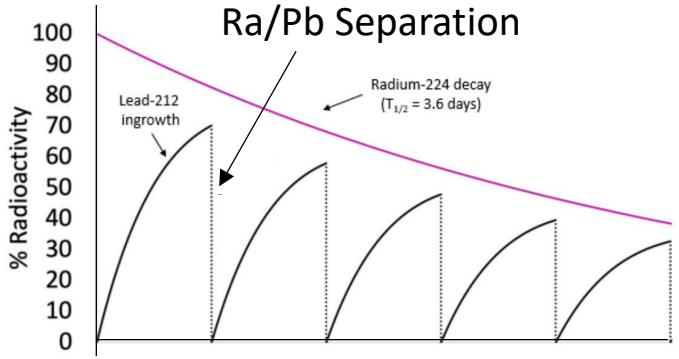
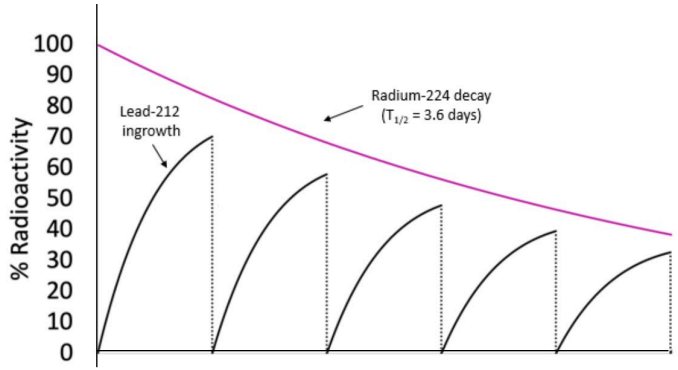
Utilizing the Th-228 Decay Chain







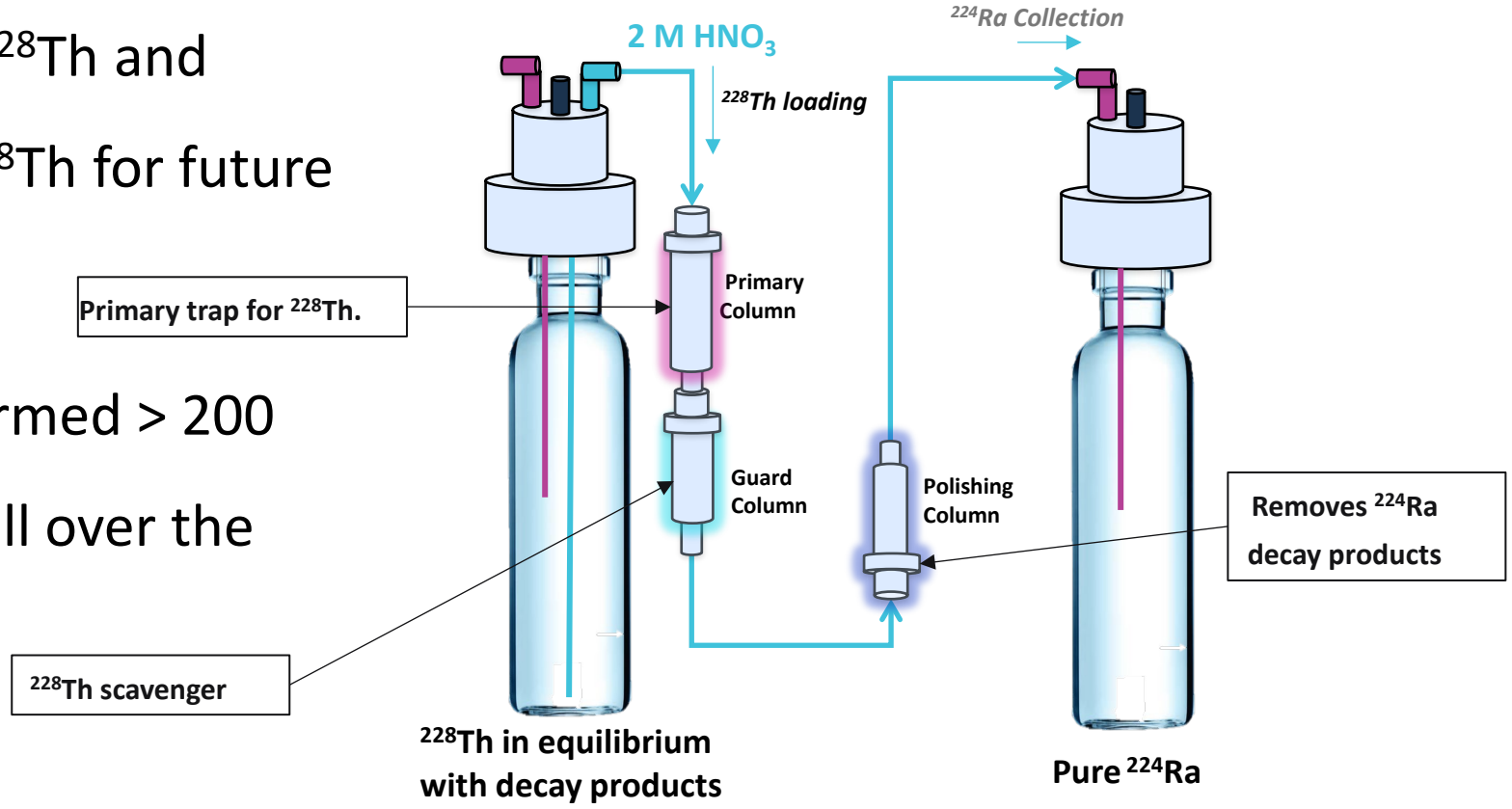




PERSPECTIVE THERAPEUTICS

Radium-224 Purification

- Process purifies ^{224}Ra from ^{228}Th and subsequently recycles the ^{228}Th for future use.
- This process has been performed > 200 times to supply generators all over the world.



PERSPECTIVE THERAPEUTICS

Radium-224 Purification

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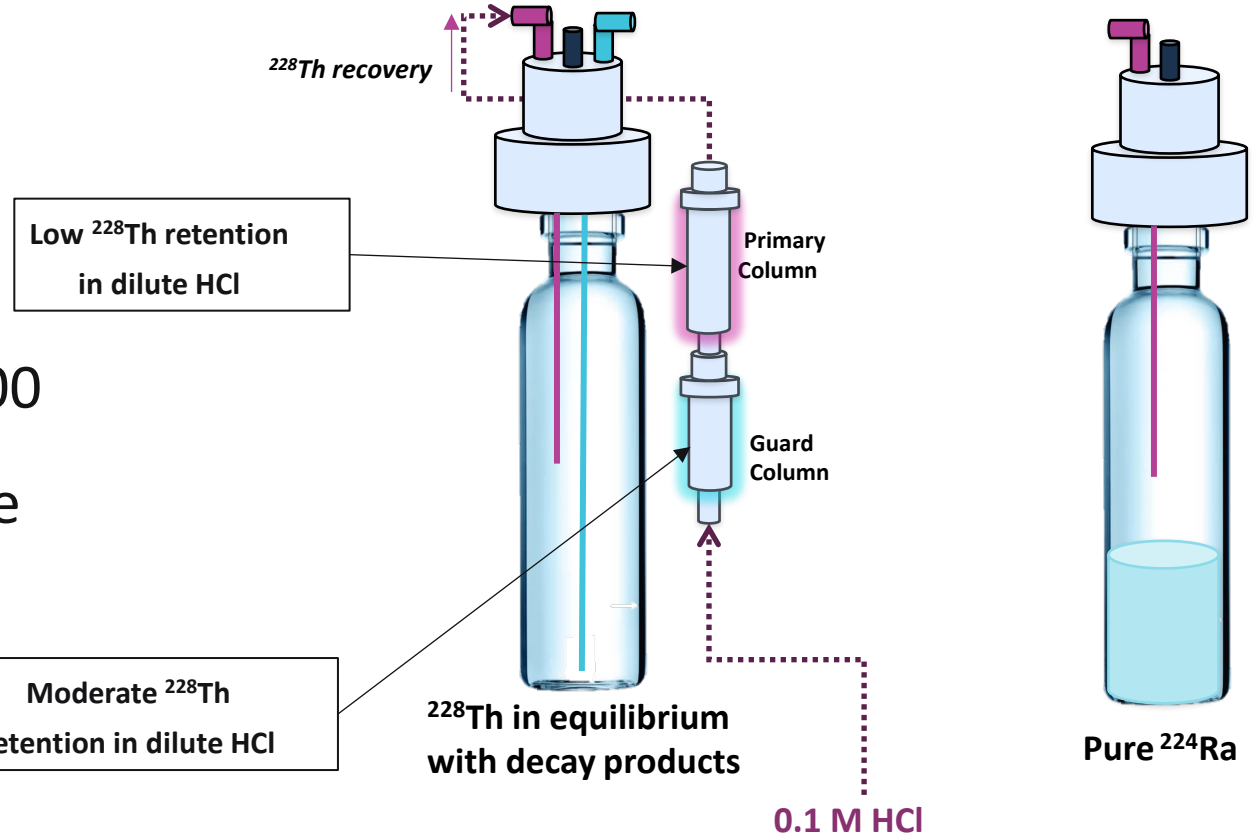
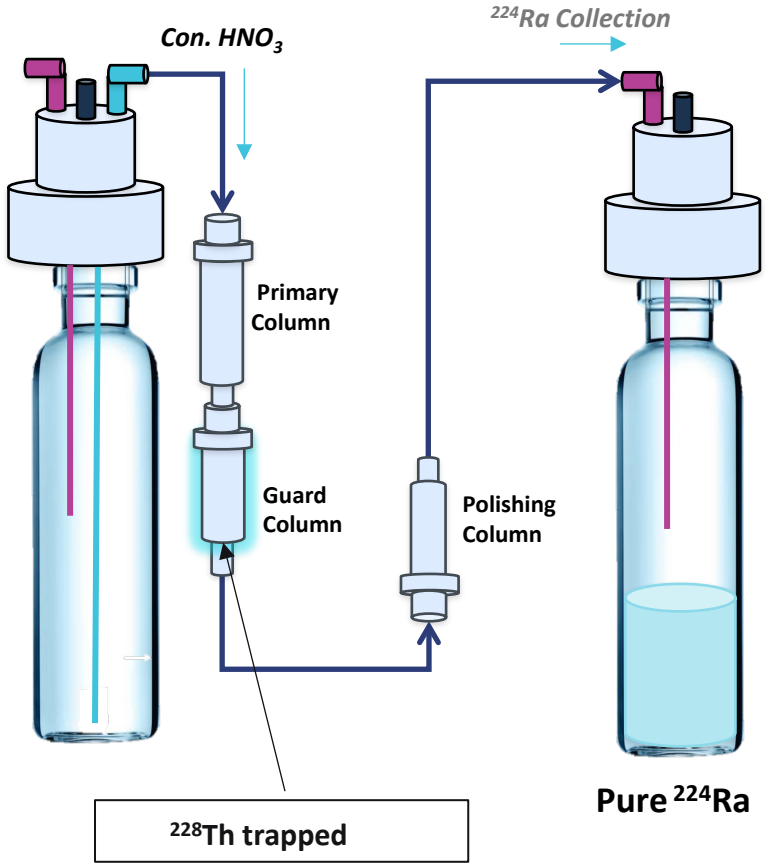


PERSPECTIVE THERAPEUTICS

Manufacturing Error

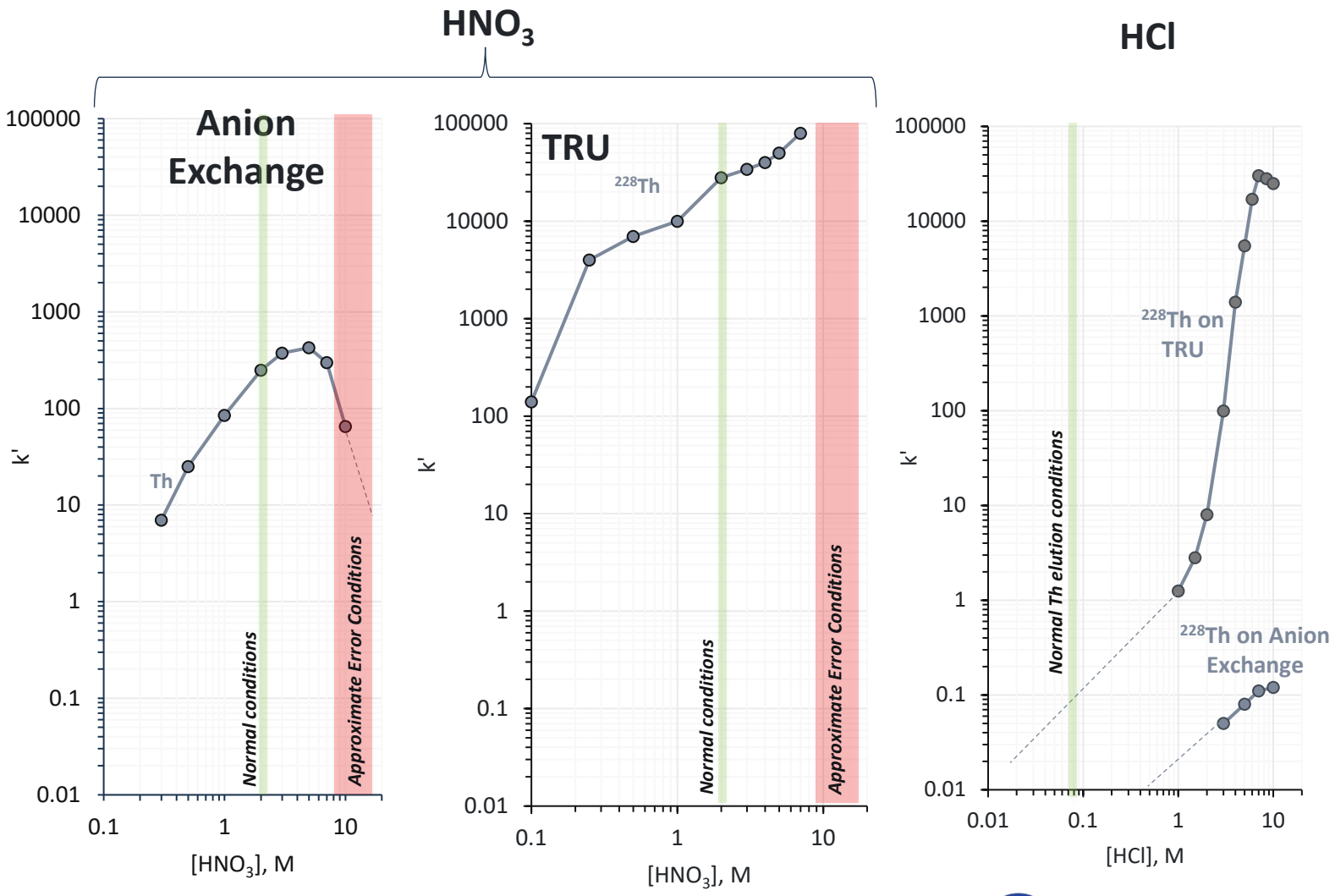
- One time, following loaded Th/Ra with ~12 mL of 2 M HNO_3 instead of rinsing the system with 3 mL of 2 M HNO_3, it was rinsed with 1.5 mL of concentrated HNO_3....
- Likely all the Th passed through the primary column and remained adsorbed onto the guard column
- Purified ^{224}Ra acid concentration needed to be adjusted prior to loading onto the generator
  - This was successful and the generator pass all QC checks.
- **But how do we get Th off and back into a useful form?**



PERSPECTIVE THERAPEUTICS

How will Th Behave?

- Usually, ^{228}Th primarily resides on the anion exchange column and can be recovered in ~10 mL of <0.1 M HCl
- Under the approximate conditions of the error, it is expected that ^{228}Th pass through the anion exchange column and remain tightly associated with TRU.



PERSPECTIVE THERAPEUTICS

Initial Attempt to Recover Th

- TRU and the anion exchange column were rinsed with 1.5 mL of water to try to displace and dilute some of the nitric acid
- Then 10 mL of 0.1 M HCl were added to try to recover ^{228}Th
- Each fraction and the column were set aside for ~3 weeks to wait for in-growth and then were analyzed with a dose calibrator

Fraction	Activity (mCi)	% Activity
1.5 mL water Rinse	0.10	0.3%
10 mL 0.1 M HCl Rinse	1.6	5.5%
Chromatographic Resins	26.8	94.2%
Total	**28.5**	**100%**

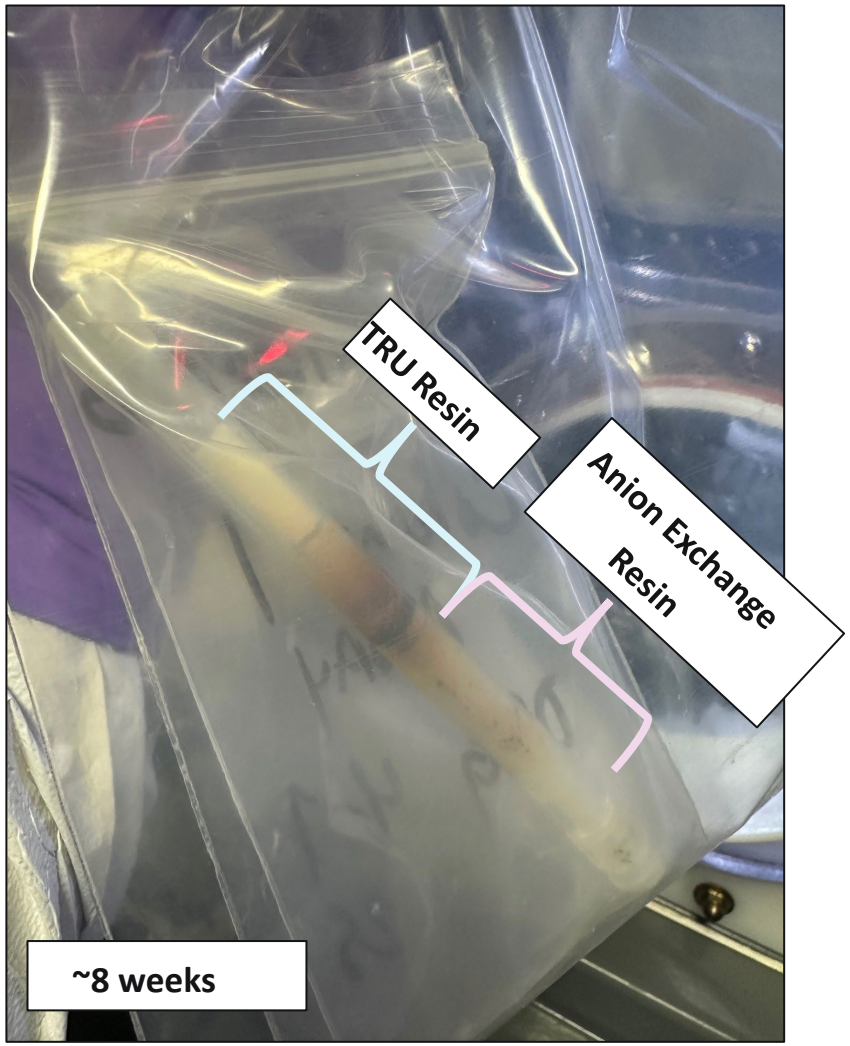
Needed to develop a more aggressive ^{228}Th recovery strategy

A Unique Opportunity

1. Under normal conditions 0.5 – 3% of ^{228}Th is lost during the separation and remains associated with the resin, therefore we have had a desire to explore enhanced recovery options
   - In scaled-up activities 0.5% - 3 % of Th-228 corresponds to a significant amount of money lost on the column
   - Work with Dan/Maddy at Eichrom to develop a more aggressive recovery method for Thorium.
2. With scale-up effort and eventual commercialization, we have a deep interest in how increased radiation will impact separations
   - Very challenging to test systematically with alpha particle emitters and limited data exists.

In the meantime…

~28 mCi (~1.0 GBq) of ^{228}Th remains on TRU Resin



- Very few studies exist evaluating resin performance versus alpha particle degradation
- Very few studies exist evaluating TRU resin and the impact of radiation on its behavior
- The amount of radioactivity, the type of radioactivity, and the resin type have led us to an unknown situation
- **Limitations:**
  - Eichrom has the capability to burn or chemically destroy the resin and recover the Th, but the activity is far too high
  - Manufacturing sites can handle the radioactivity, but limited in the strategies to recover ^{228}Th

PERSPECTIVE THERAPEUTICS

The Effects of Resin Degradation May Be Agnostic to Type of Radiation

- The type, the dose rate, nature of the media surrounding the resins, and other factors play a role in how resins degrade and the extent of the degradation [1,2]
- However, recent studies have shown that exposure of similar doses from different sources results in similar sorption behavior[1,2]
  - Alpha particles would likely cause more localize, direct damage[2]

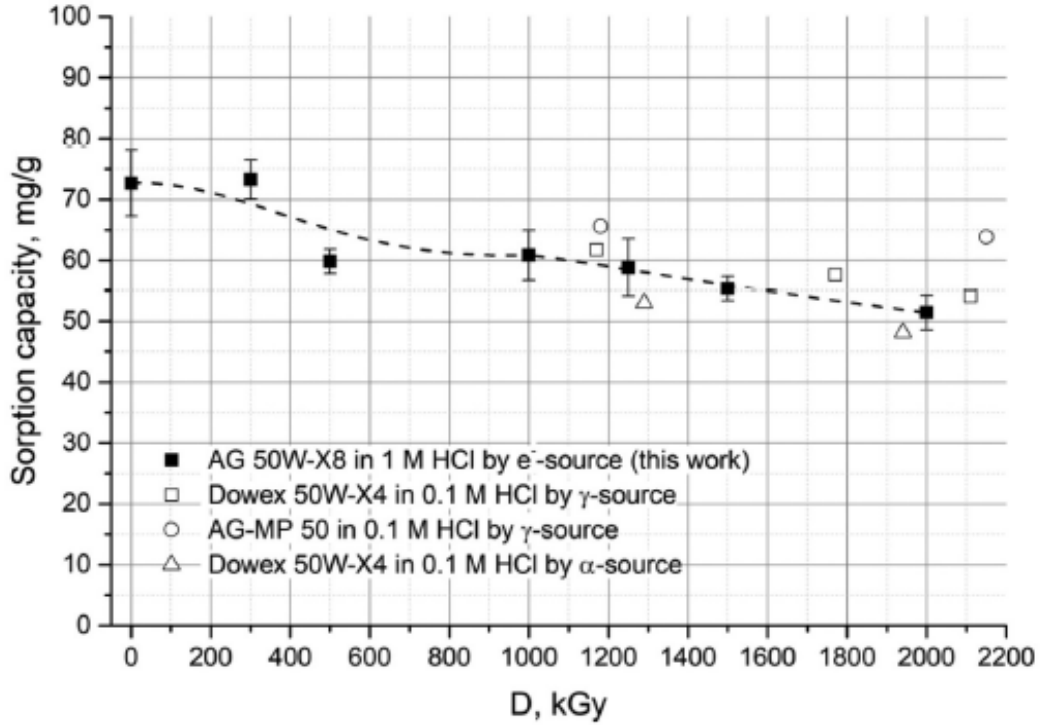


Figure 3. Sorption capacity of AG 50 W-X8 for yttrium as a function of absorbed dose under static conditions. *m* (AG 50 W-X8) = 0.05 g, *V* (1 M HCl) = 2 mL, shaking time = 24 h. Literature data recalculated for yttrium (no correction for weight changing): Dowex 50 W-X4 in 0.1 M HCl irradiated by external gamma-source[41]; AG-MP 50 in 0.1 M HCl irradiated by external gamma-source[40]; Dowex 50 W-X4 in 0.1 M HCl irradiated by internal alpha-source.[42]

[1]Vasiliev, A. et al (2021) Solvent Extraction and Ion Exchange, [2]Zhu, H. et al. (2023) RSC Advances

PERSPECTIVE THERAPEUTICS

Estimate How Much Radiation

Case study with 100 mCi of ^{225}Ac

$$D = 1.602x10^{-10}\ x\ A_0\ \frac{1-e^{-\lambda t}}{\lambda}\ x\ \frac{Q_\alpha}{m}$$

- Dose, Gy
- Constant
- Initial activity
- Time dependent radioactive decay
- Resin mass
- Total Alpha Particle Energy (MeV)

Fig. 3 Pictures of AG MP-50 (a) and SAC (b) before and after exposure to gamma radiation.

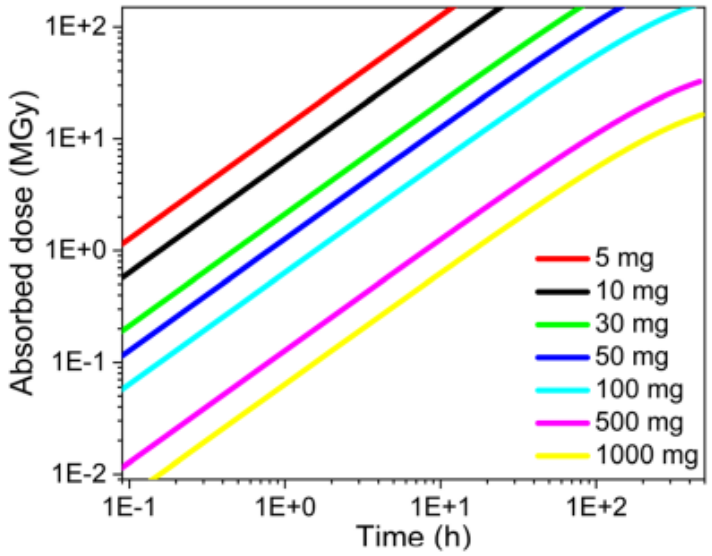
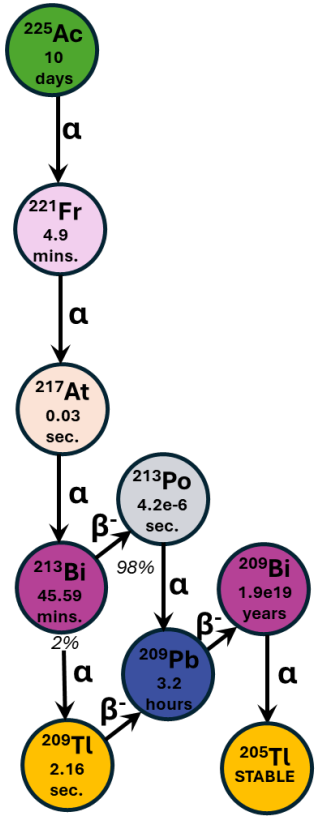


Fig. 10 Absorbed dose of the sorbent as a function of the contact time.

Q_α = 27.5 MeV



PERSPECTIVE THERAPEUTICS

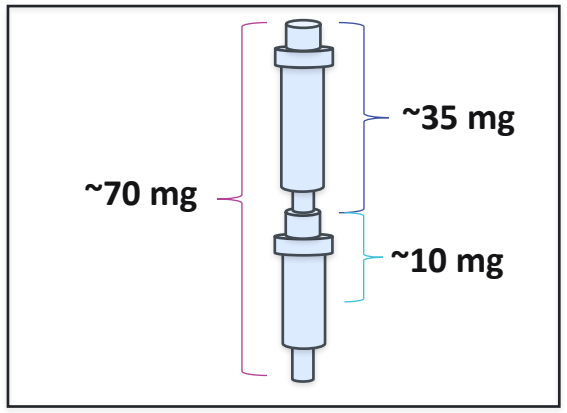
Estimate How Much Radiation

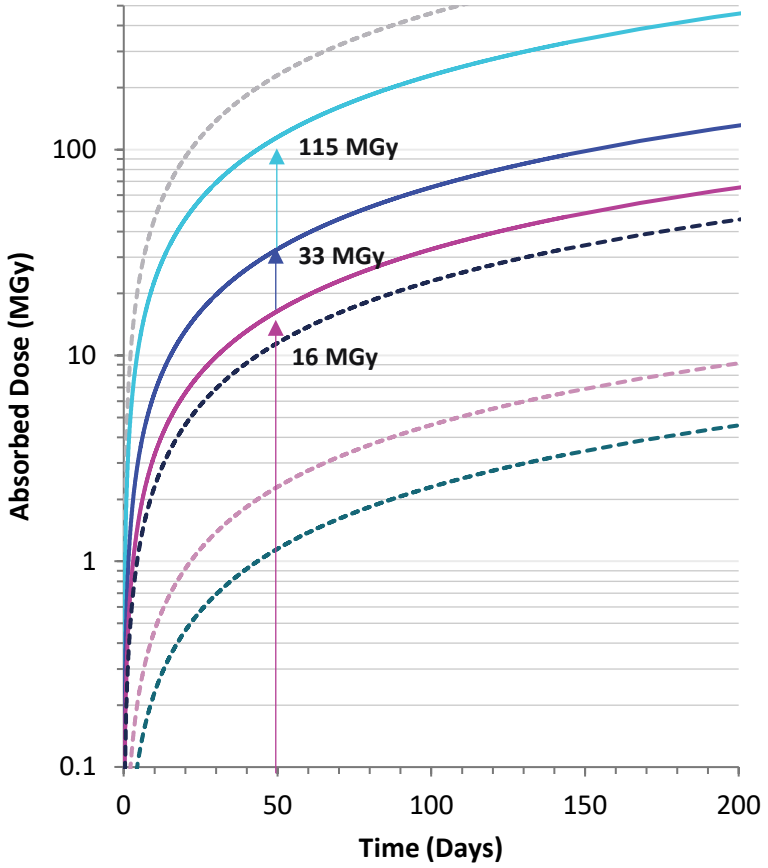
For 30 mCi of ^{228}Th

$$D = 1.602x10^{-10}\ x\ A_0\ \frac{1-e^{-\lambda t}}{\lambda}\ x\ \frac{Q_\alpha}{m}$$

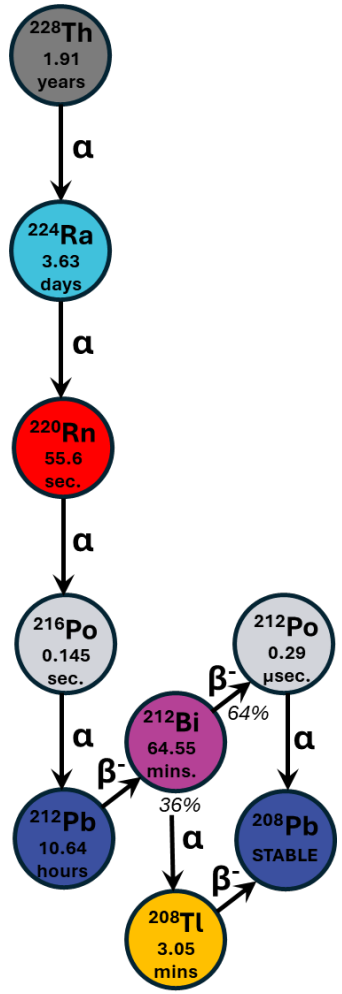
- D: Dose, Gy
- $1.602x10^{-10}$: Constant
- A_0: Initial ^{228}Th activity = 30 mCi
- $\frac{1-e^{-\lambda t}}{\lambda}$: Time dependent radioactive decay
- Q_α: Total Alpha Particle Energy (MeV)
- m: Resin mass

Where is ^{228}Th on the columns?





Q_α = 35.9 MeV



PERSPECTIVE THERAPEUTICS

Some Radionuclides used in Nuclear Medicine

How do the estimated Q values compare?

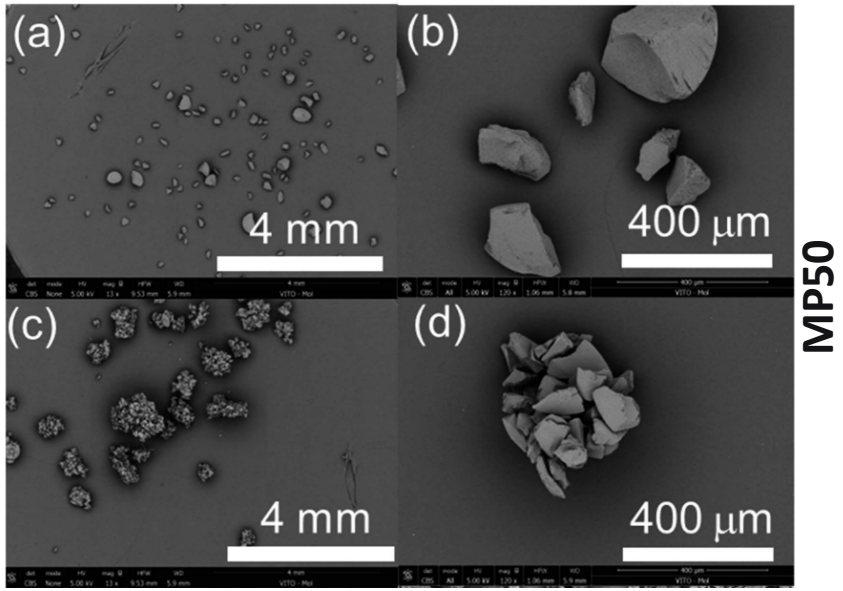
Radionuclide	Half-life	Estimated Q (MeV)*	Use in Nuclear Medicine
^{228}Th	1.91 Years	35.9	Precursor or parent in an isotope generator
^{225}Ac	9.91 Days	27.5	Isotope for Therapy
^{224}Ra	3.63 Days	29.6	Parent in Isotope Generator
^{223}Ra	11.43 Days	26.0	Isotope for Therapy
^{211}At	7.22 Hours	9.77	Isotope for Therapy
^{212}Pb	10.63 Hours	10.9	Isotope for Therapy
^{213}Bi	45.61 Mins	8.4	Isotope for Therapy
^{212}Bi	60.55 Mins	10.9	Isotope for Therapy
^{177}Lu	6.65 Days	0.4	Isotope for Therapy
^{131}I	8.02 Days	0.6	Isotope for Therapy
^{68}Ge	271.04 Days	1.7	Parent in Isotope Generator

*** Calculated in equilibrium with decay products. Primarily accounting for major emissions**

What Happens to Resins when Exposed to High Amounts of Radioactivity?

Particle Aggregation and Clogging

- A DOE ^{224}Ra generator loaded with ~27 mCi on MP50 had a 3-week travel delay
  - Upon Receipt, it was eluted 1 time to retrieve 0.5 mCi of ^{212}Pb. Subsequent elution attempts were unsuccessful as the column became clogged.

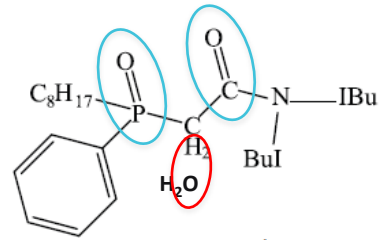


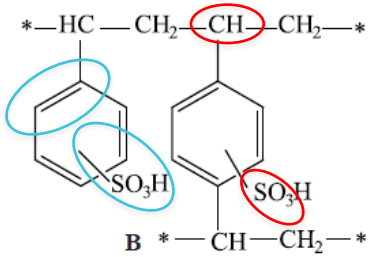
Chemical Changes

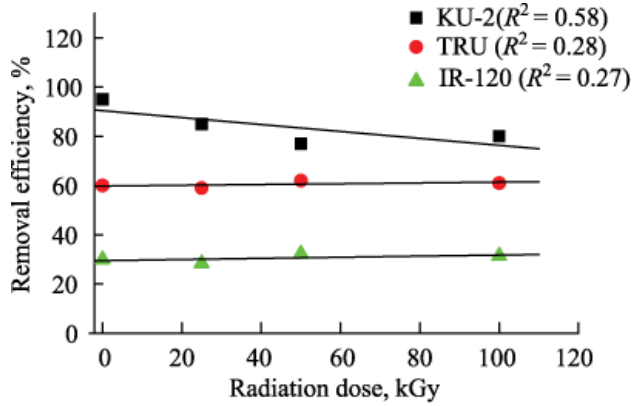
- Radiolytic degradation can cause decomposition and scission of functional groups, modification to the degree of cross linking, and possible resins interactions with degradation products. Which *may* lead to changes in resin behavior.

Dose, kGy	KU-2 and Amberlite® IR-120 resins				TRU resin		
	SO_2OH[a]	S=O[a]	C–H[b]	C=C[c]	H–OH[d]	P=O[e]	C=O[f]
	before irradiation						
0.0	3430	1123	2921	1630	3428	1149	1736
	after irradiation						
25	3429	1126	2925	1631	3430	1149	1735
50	3428	1124	2925	1628	3427	1146	1733
100	3428	1125	2926	1626	3428	1144	1732

[a] Sulfonic group, [b] alkane, [c] alkene, [d] lattice water, [e] phosphine oxide, and [f] carbonyl.





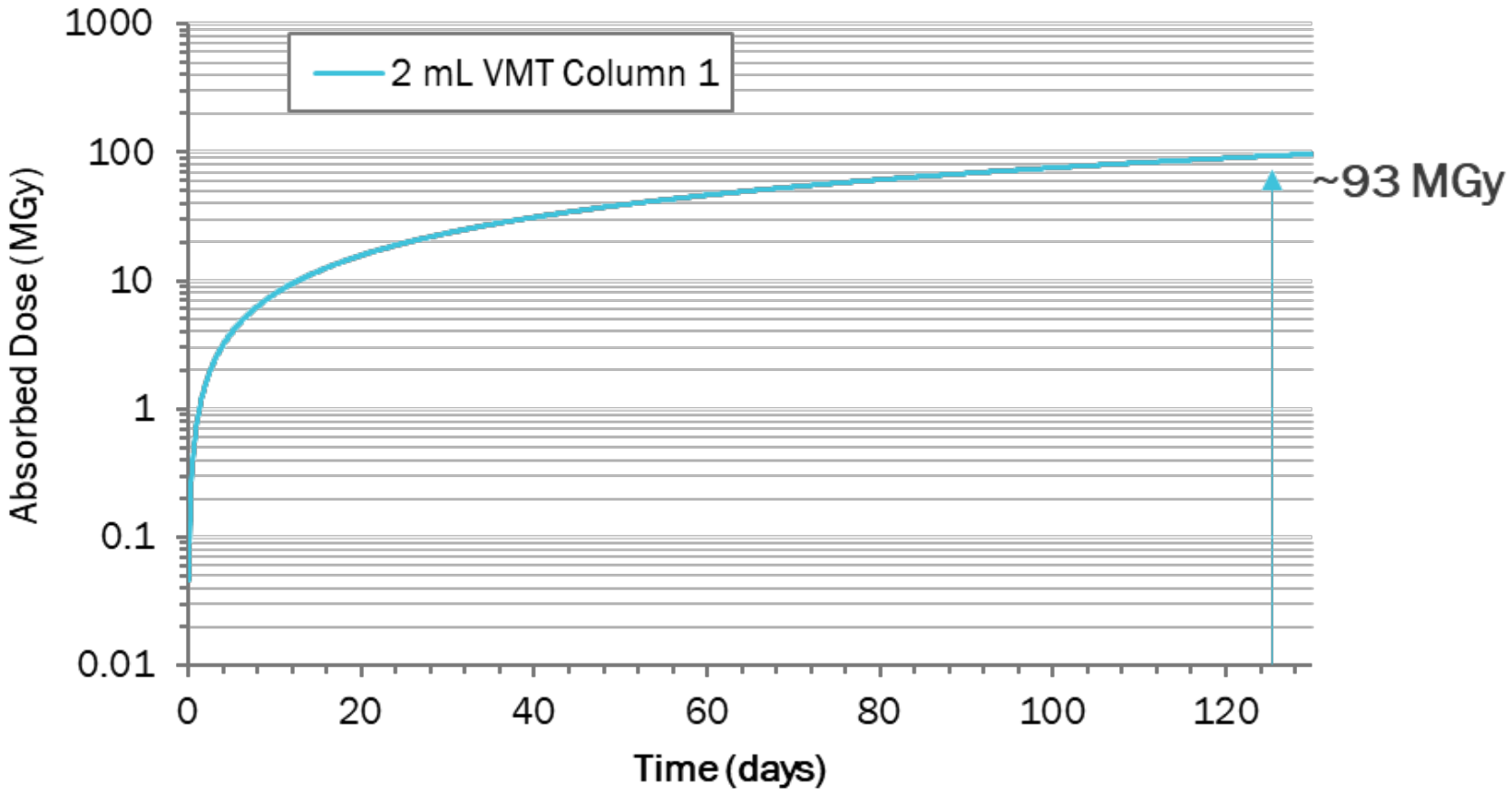


Fisher, D.R. (2012) PNNL Report. Zhu, H. et al. (2023) RSC Advances. Attallah, M. et al. (2020) Radiochemistry.

PERSPECTIVE THERAPEUTICS

The clock is ticking…

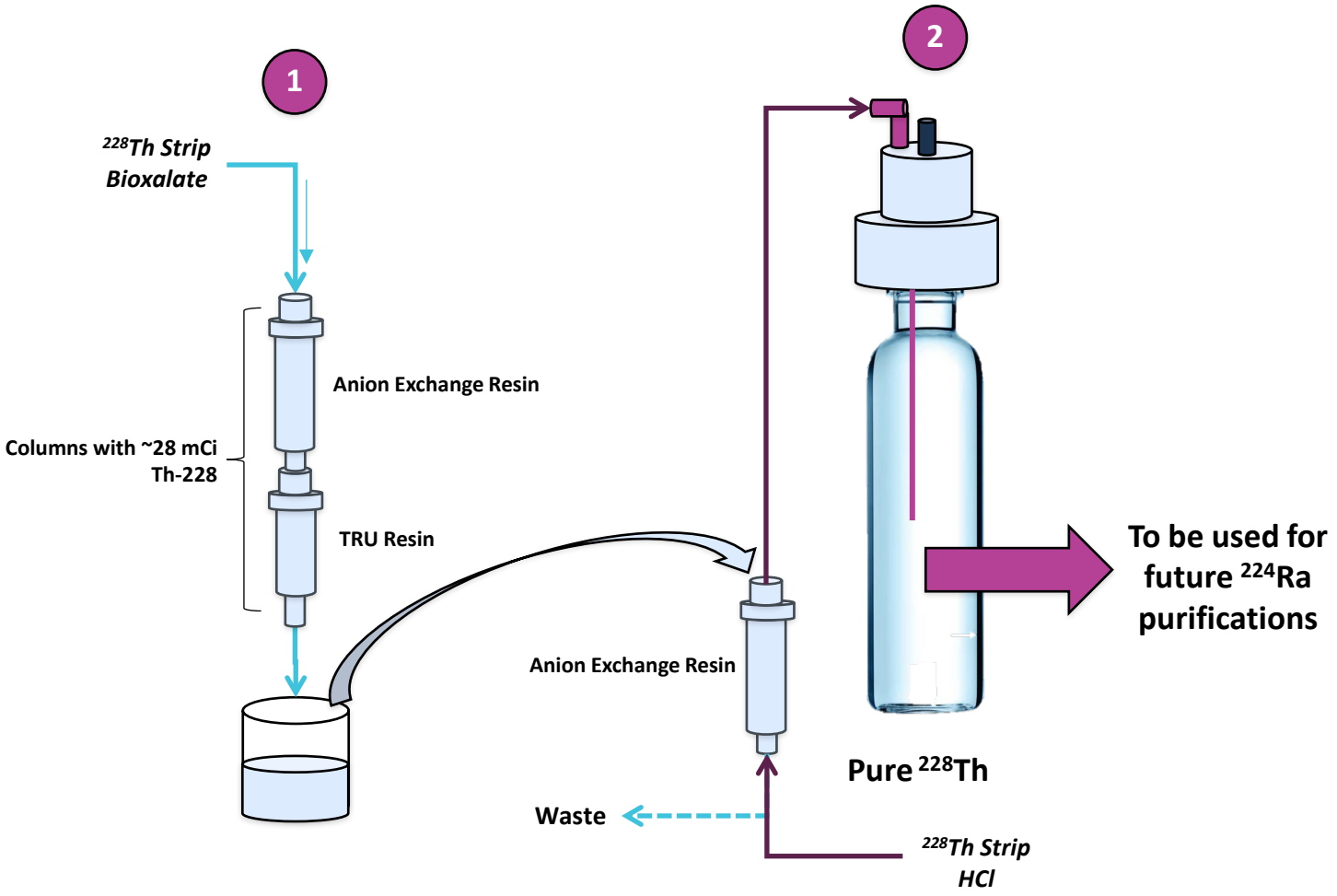
- After ~126 days, the recovery plan was finalized to retrieve the ^{228}Th that was stuck on the column
- Estimate > 93 MGy seen by the resin.



PERSPECTIVE THERAPEUTICS

Th-228 Recovery Plan

- Goals:
  1. Strip ^{228}Th from TRU Resin using a mild chelator
  2. Adsorb recovered ^{228}Th onto another column to return the ^{228}Th to a form consistent with existing ^{228}Th source for future ^{224}Ra purification



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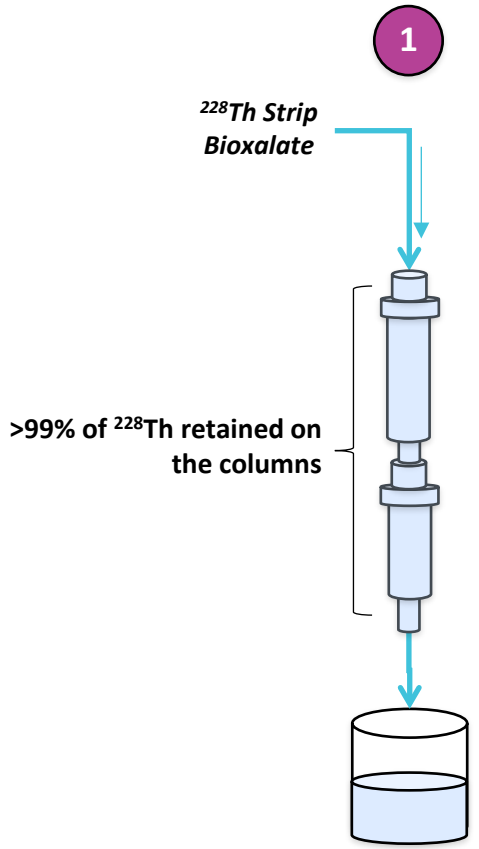
Recovery Attempt

- The strip with bioxalate did not work as 99% of the radioactivity remained adsorbed to the columns
  - Checked by dose calibrator after sufficient decay product in-growth.



Fraction	Activity (mCi)	% Activity
Aliquot from Bioxalate Strip	n.d.	0%
Effluent from Second Anion Exchange Resin	n.d.	0%
Initial Chromatographic Resins	25.6	>99%
Total	**25.6**	**99%**

PERSPECTIVE THERAPEUTICS

Other Possible Confounding Variables

- Mass Effects
  - The ^{228}Th mass is about 35 ug and Th is prone to precipitation with bioxalate.
    - Eichrom evaluated this with ^{232}Th and 35 ug is not sufficient mass to prevent elution due to precipitation
- Kinetic Effects
  - Since ^{228}Th was adsorbed onto the resin for several months, maybe it formed a very stable thermodynamic product
    - Eichrom evaluated this, on a limited time-scale over the course of several days, and saw no impact of time on Th elution
- Solvent/Media Effects
  - The method was developed using a resin preconditioned with 0.1 M ammonium bioxalate, the real situation was last eluted with 0.1 M HCl
    - Eichrom evaluated the impact of 0.1 M HCl on the bioxalate strip and did not impact the Th elution

Radiation effects are likely the sole culprit that led to the inability to recover Th

Next Steps

- Burn the resin to recover the ^{228}Th
  - This will likely work, however it is not something that can be done at the manufacturing facility and likely not at the commercial facility
  - Would ideally have an aqueous-based separation to recover residual ^{228}Th.
- Send off the material for Academic studies to evaluate what the extractant components in TRU resin look like

Conclusions

What We Learned

- Worked to develop an effective method to recover ^{228}Th from a TRU resin (when not damaged by radiation).
  - Could be implemented during initial separation and improve Th recoveries.
- ~100 MGy causes too much radiation damage and leads to possibly irreversible adsorption of ^{228}Th
  - Suggests a limit exists to the use of generator technologies due to the impacts of radiation

What Still Needs to Be Addressed

- What is the relationship between the extent of radiation damage on TRU resin and the ^{228}Th adsorption behavior?
  - Starting to be evaluated
    - What species form in-situ that led to the formation of a stable Th-extractant
- How much radiation can TRU resin (and other separation resins) endure before unanticipated analyte behavior occurs?
- Does radiation damage behavior depend on the type of radiation?

Questions