TRIUMF

# Recent developments in the production and application of actinoids and lanthanoids at TRIUMF

**Paul Schaffer, PhD**
Director, Life Sciences
TRIUMF

CERN
2024-10-17

# Disclosure



- I am a full-time employee of TRIUMF
- I am compensated by ARTMS as Chief Technology Officer
- I am a listed inventor on patents in technology licensed to ARTMS
- This presentation will include mention of solid target technology related to ARTMS' product line
- To avoid bias, the advantages and disadvantages of alternative isotope production approaches will be discussed, when appropriate

artms A Telix Company

- Topics for today's presentation:



Background: TRIUMF, Infrastructure, and Capabilities

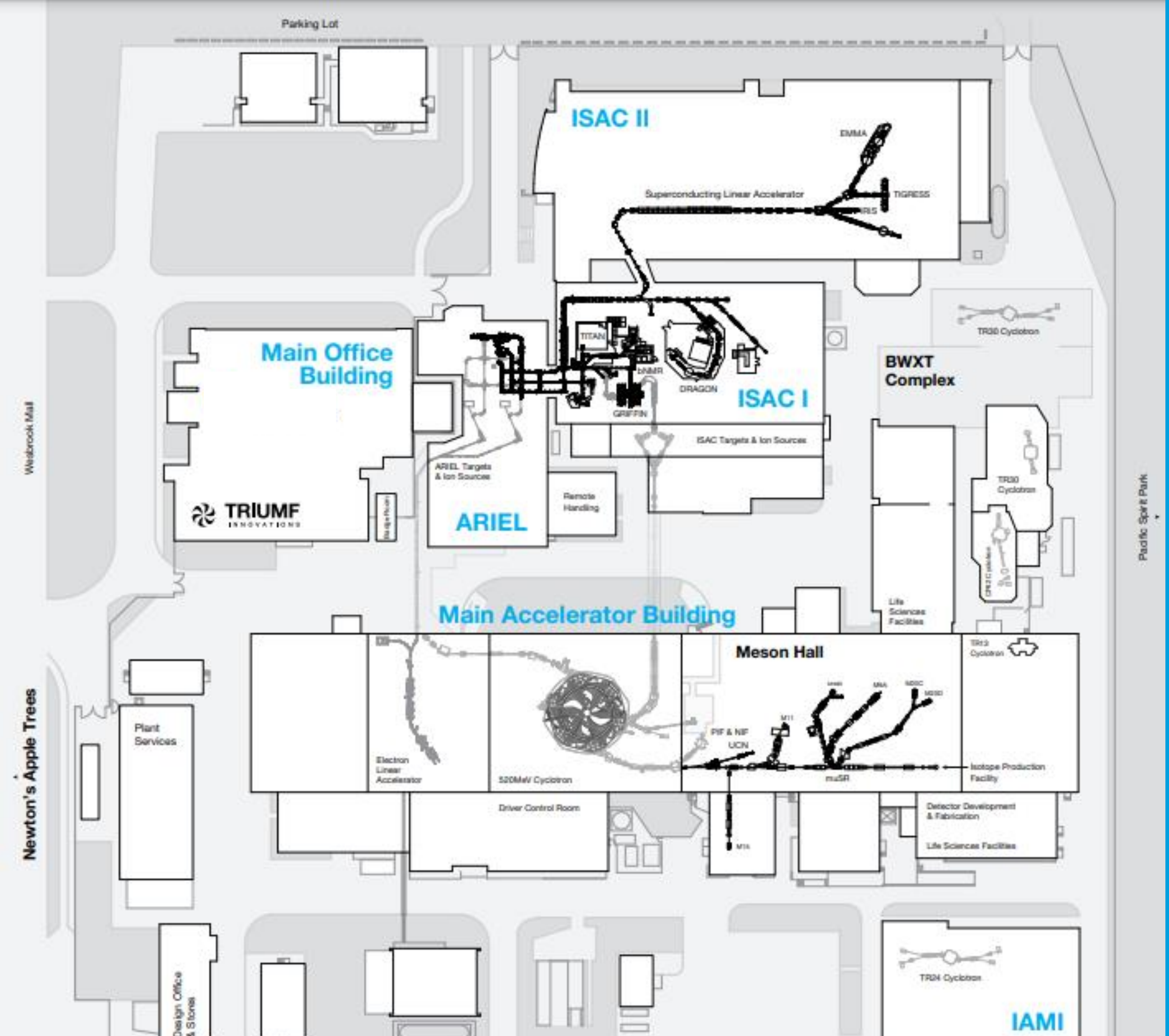
Discussion:
Isotope Production Research (A Cyclotron Perspective)
Radiopharmaceutical Design and Development

Summary, Conclusions

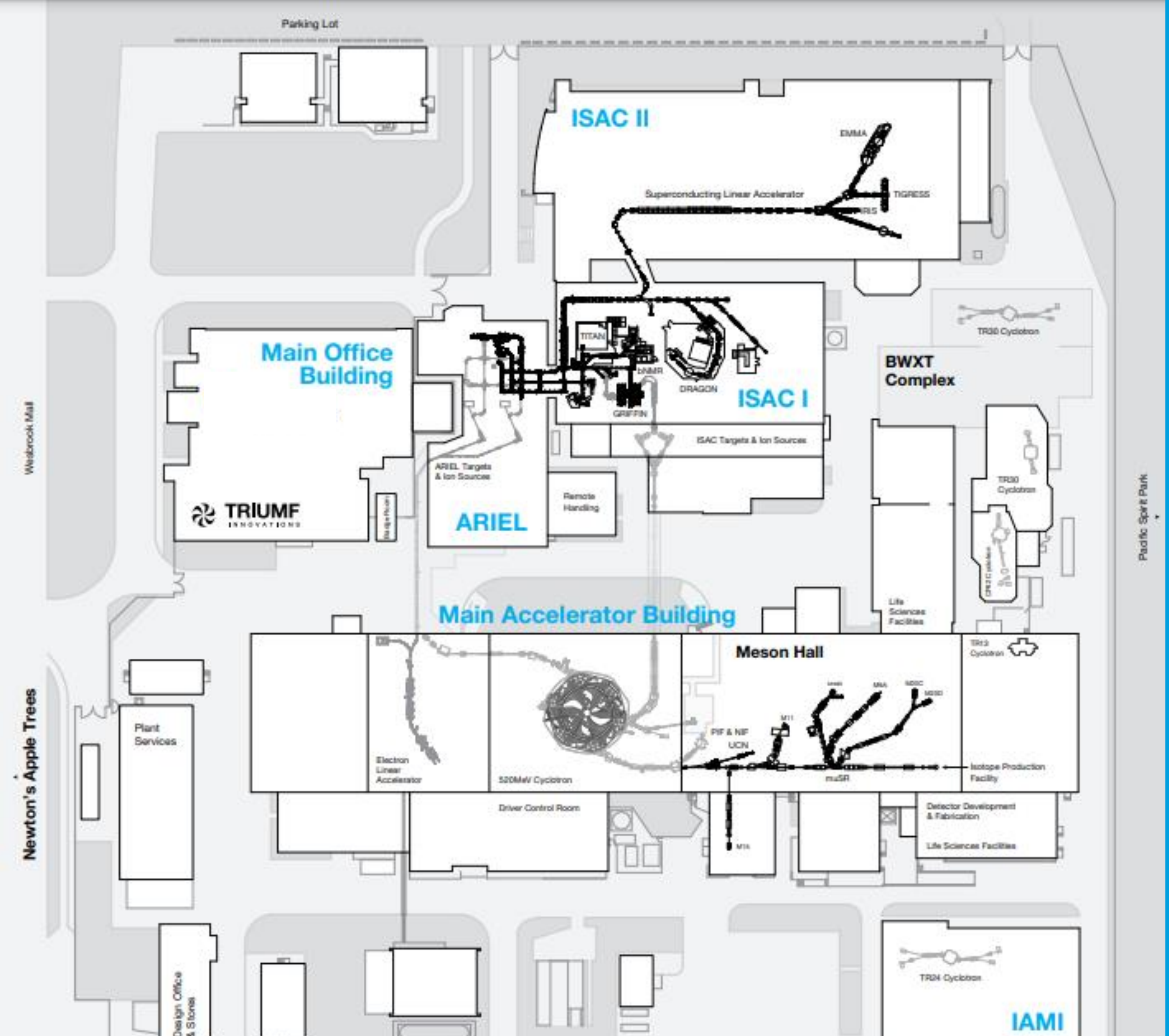
# What is TRIUMF?

TRIUMF is Canada's particle accelerator centre. **We are a world-class hub of research, education, and innovation that is home to ~600 staff and students**

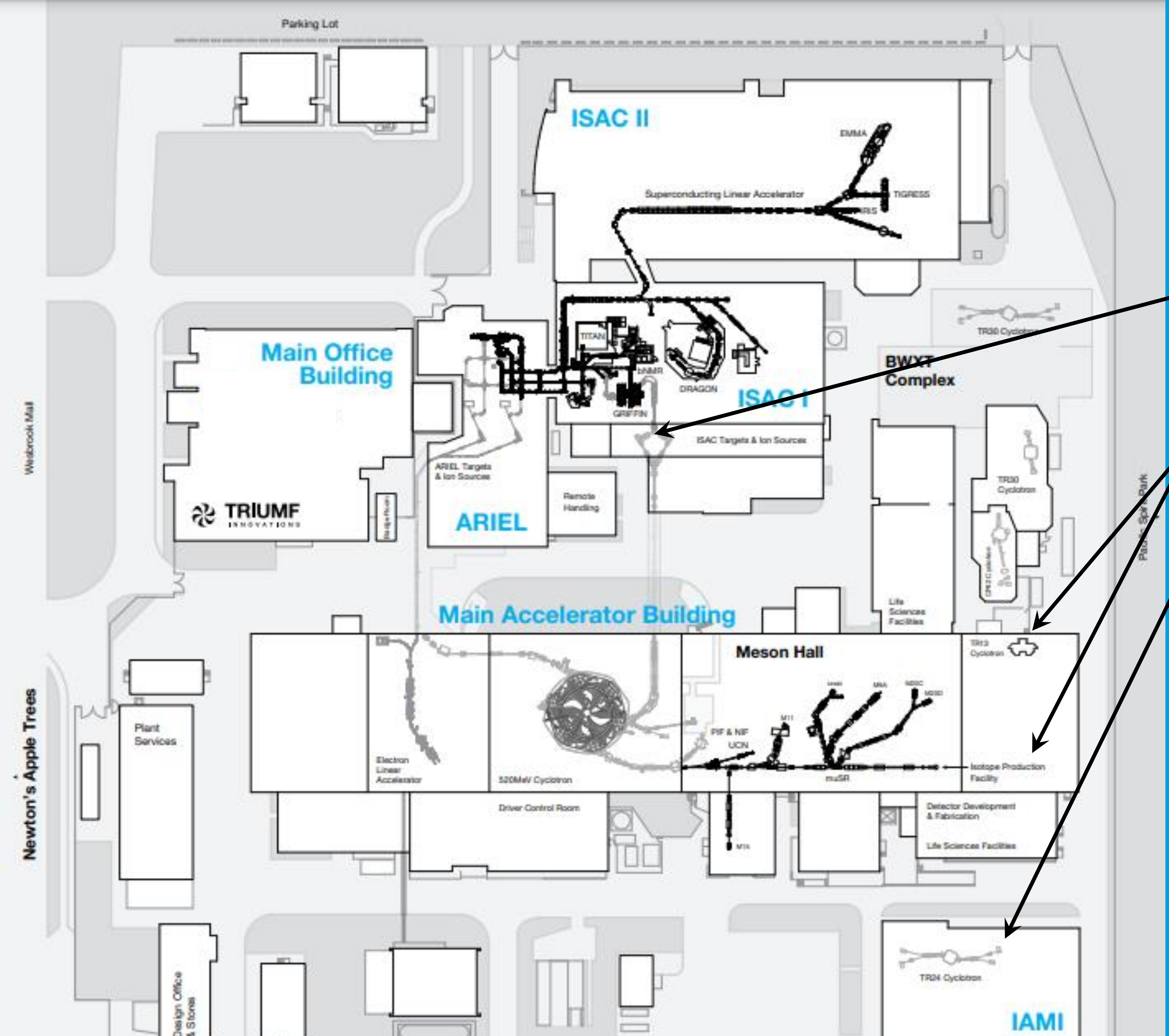
Founded in 1968 by the University of British Columbia, Simon Fraser University, and the University of Victoria, TRIUMF has evolved into a multidisciplinary facility owned and operated by a consortium of Canadian universities from coast to coast



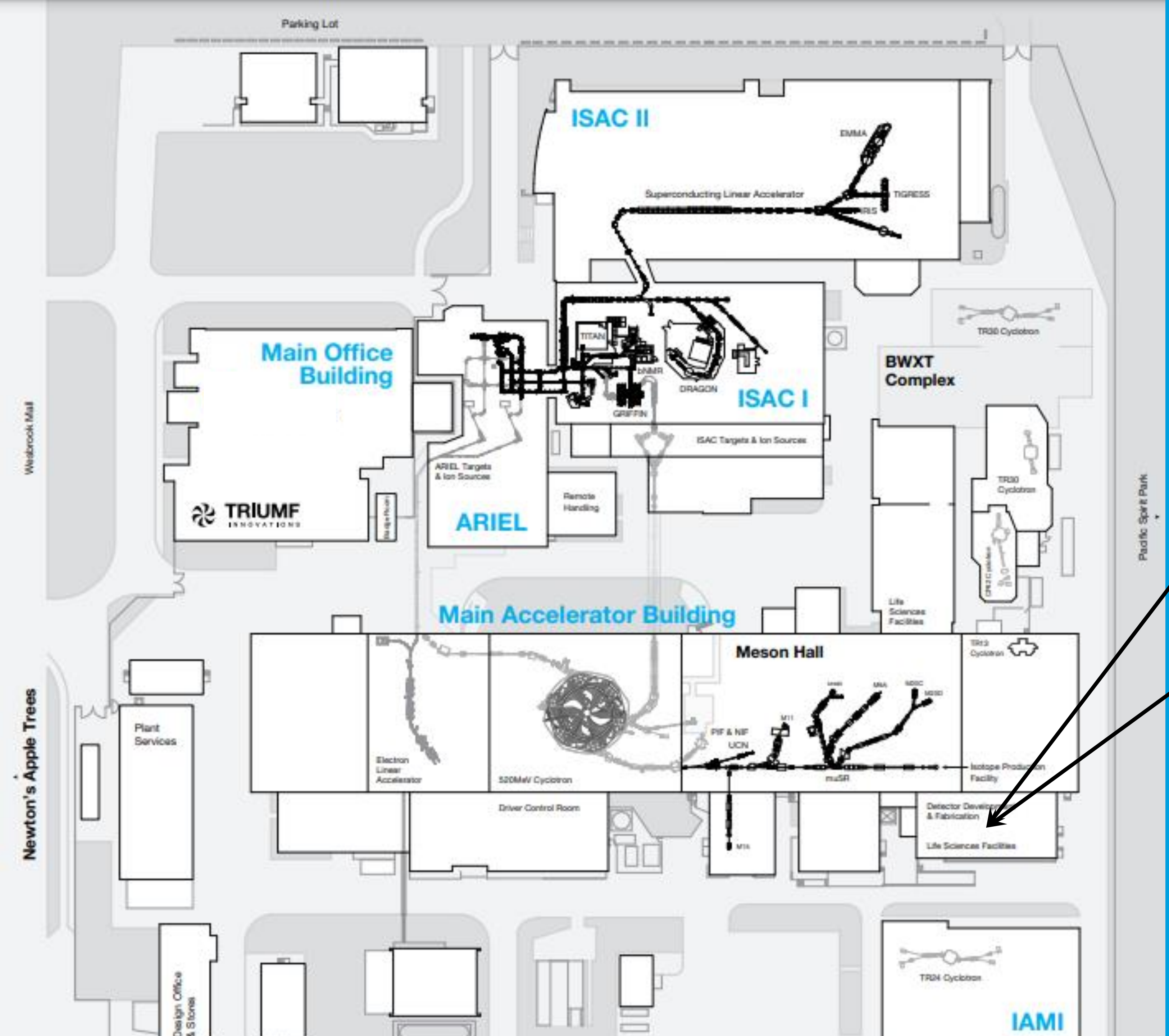

- Six (soon to be seven) cyclotrons & two linear accelerators on site
- Over 1-kilometer of beamlines; accelerating sub-atomic and rare-isotope beams
- Users and collaborators from over 40 countries
- Over 1000 visitors per year (2019)



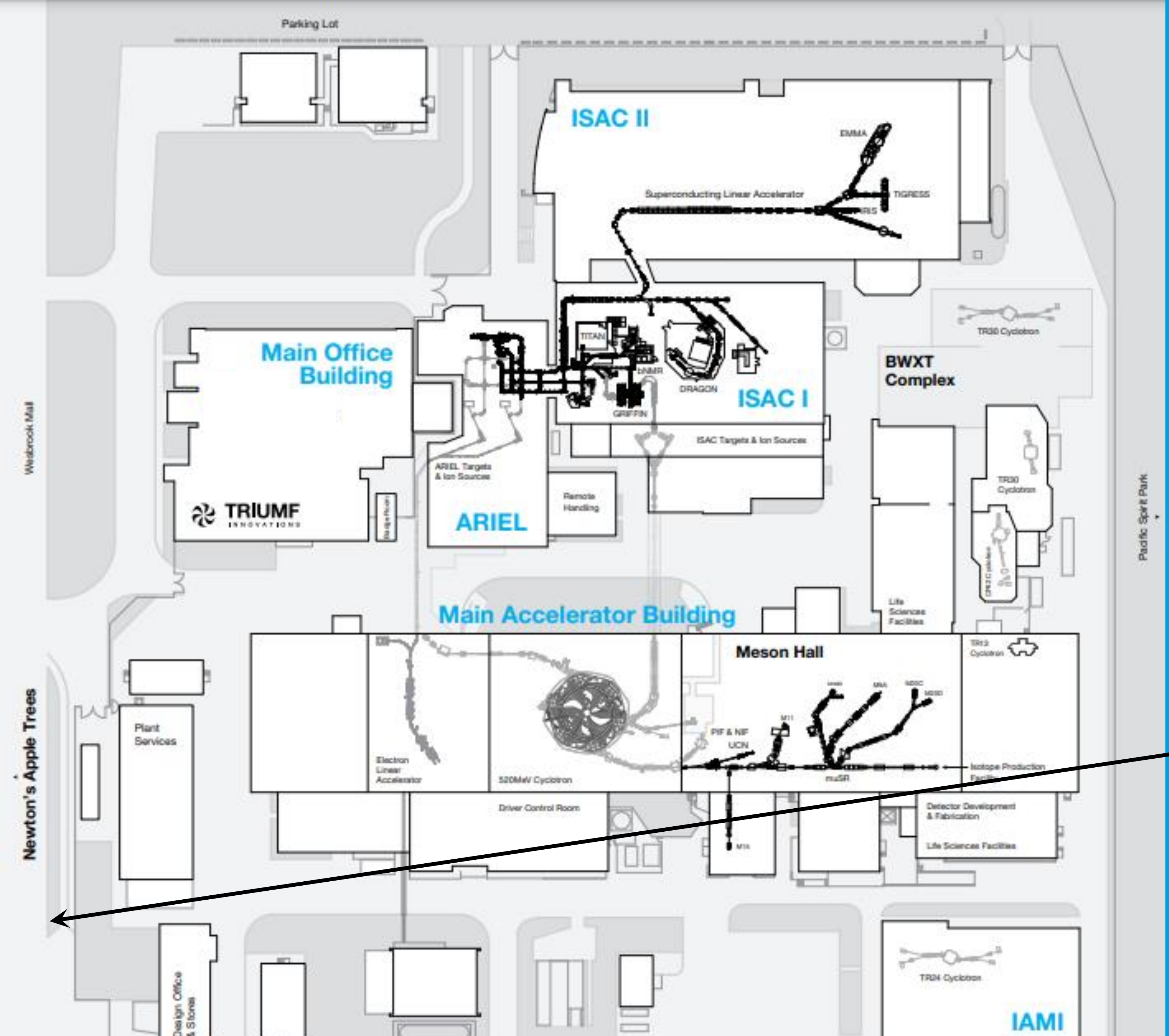

- Six (soon to be seven) $H^-$ medical cyclotrons:
  - Energy range: 13 to 520 MeV
  - Intensity:
    - 25 µA @ 13 MeV
    - ~1mA @ 30 MeV (BWXT)
    - 350 µA @ 520 MeV
  - Isotope production
  - Radiochemistry
  - Proton Therapy
  - Bio-βNMR
- Other drivers:
  - ARIEL, ISAC




- Radioisotope work:
  - ISAC ISOL
  - IPF
  - TR13
  - Future:TR24/PETTrace/ARII
  - Radiochemistry
    - Purification
    - Chelate development
  - *In vitro* testing
  - *In vivo* testing
    - UBC Centre for Comparative Medicine



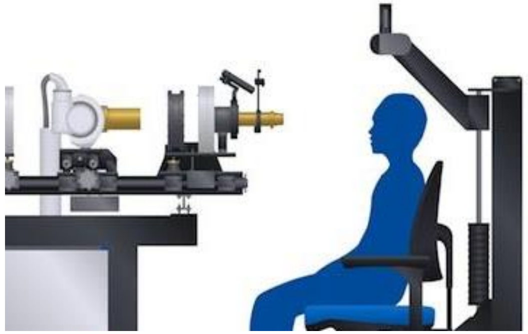

- Radioisotope work:
  - ISAC ISOL
  - IPF
  - TR13
  - Future:TR24/PETTrace/ARII
  - Radiochemistry
    - Purification
    - Chelate development
  - *In vitro* testing
  - *In vivo* testing
    - UBC Centre for Comparative Medicine

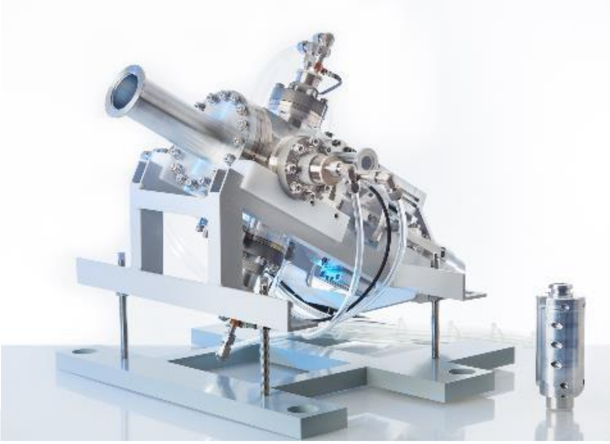


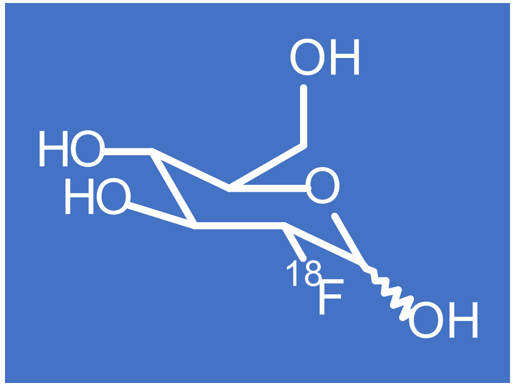

- Radioisotope work:
  - ISAC ISOL
  - IPF
  - TR13
  - Future:TR24/PETTrace/ARII
  - Radiochemistry
    - Purification
    - Chelate development
  - *In vitro* testing
  - *In vivo* testing
    - UBC Centre for Comparative Medicine

# Life Sciences at TRIUMF

- Applied Ion Beams
- Nuclear Chemistry
- Applied Isotopes





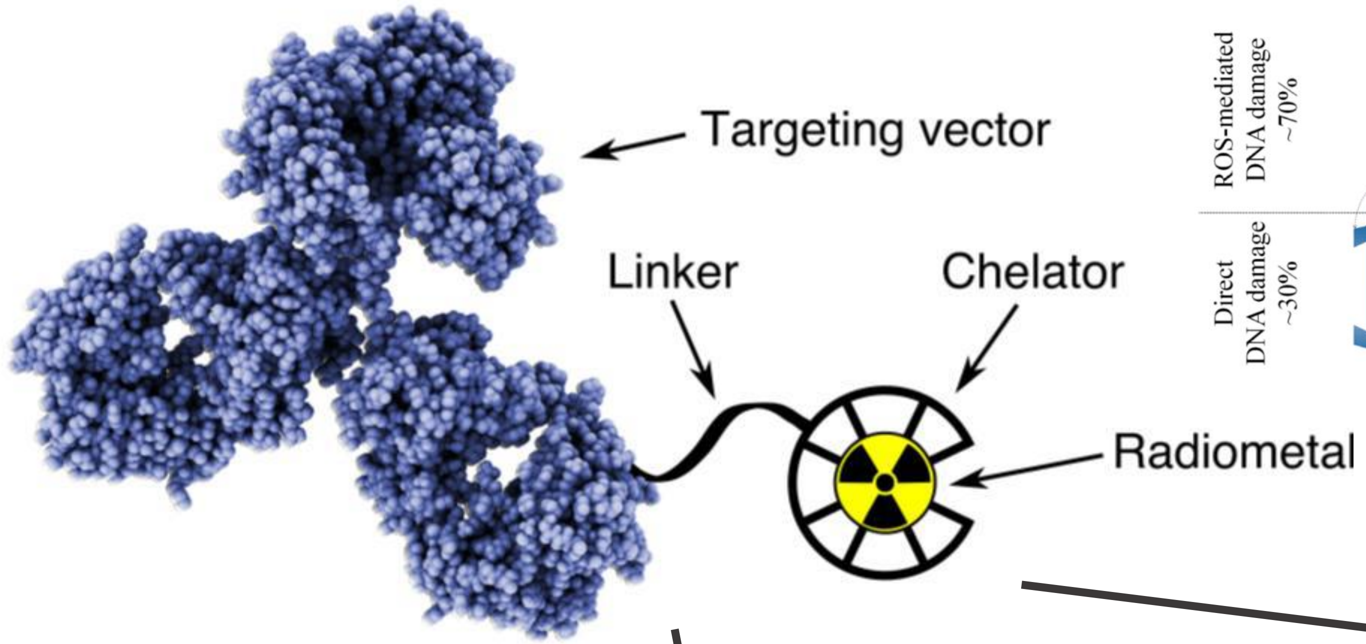


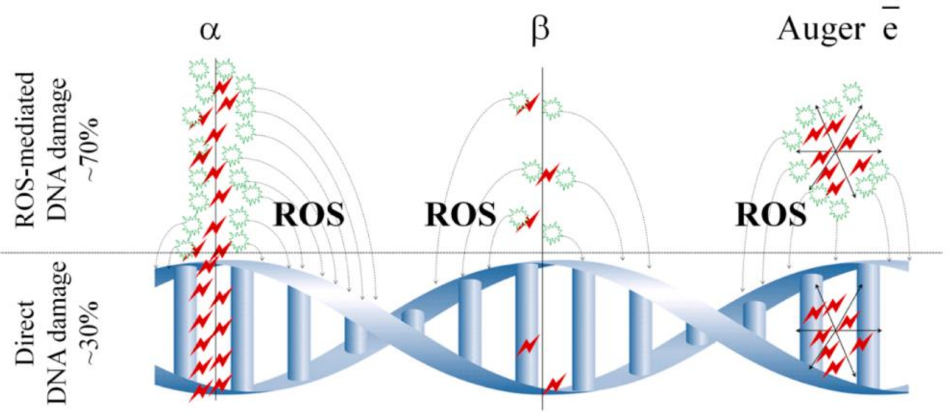

TRIUMF Life Sciences focuses on advancing accelerator-based technology for the development of isotopes that can improve life

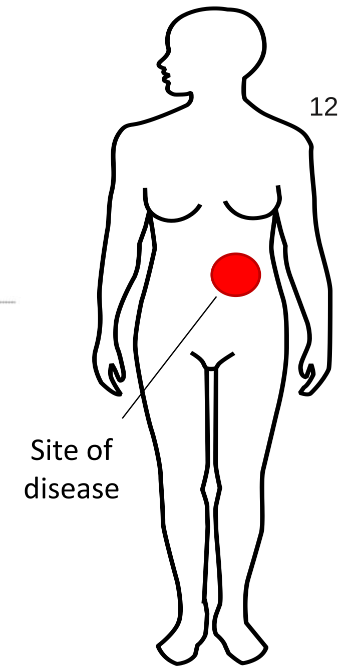
Discovery, accelerated

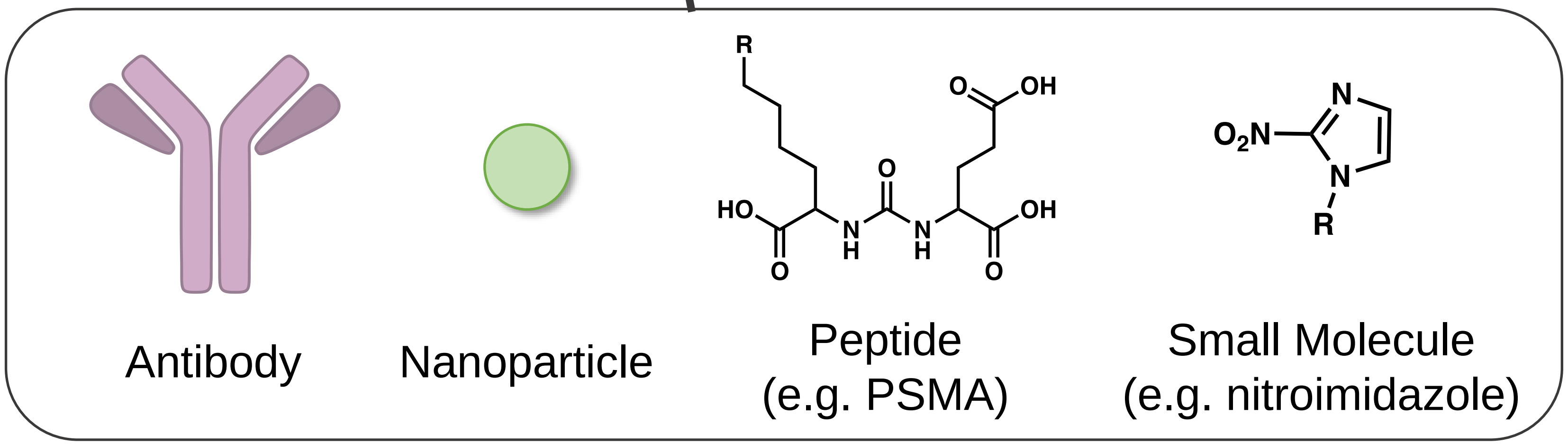
# Radiopharmaceuticals

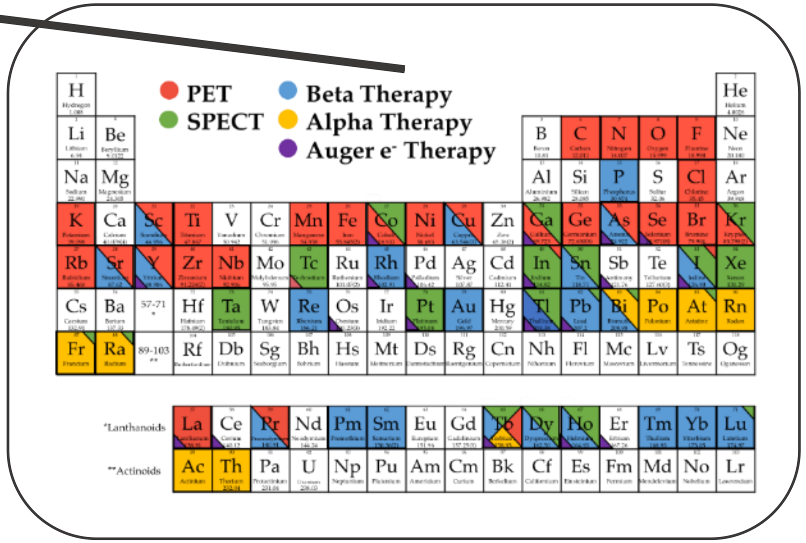




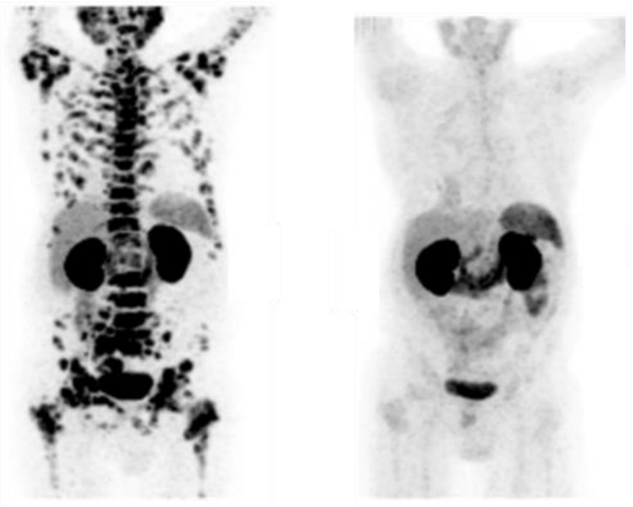



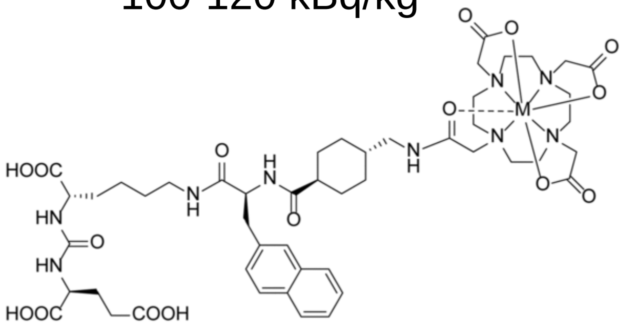



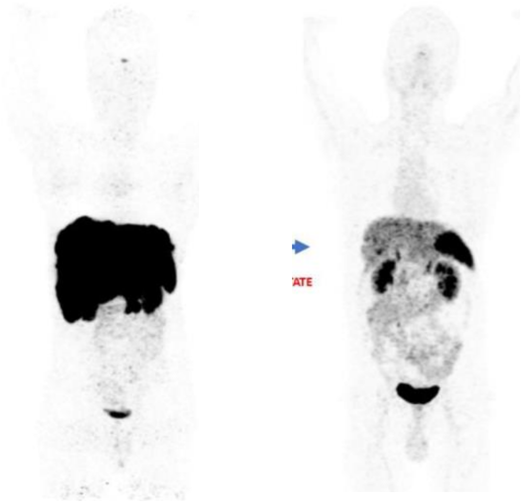
# Targeted Radionuclide Therapy – Intense Interest in Alphas



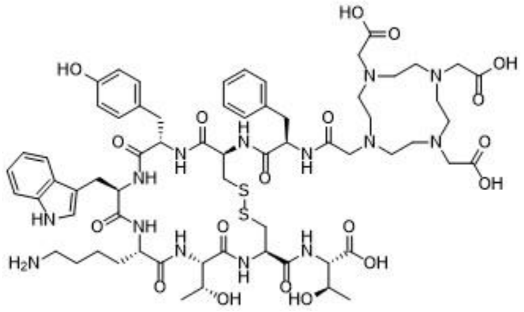
4 cycles [$^{225}$Ac]PSMA-617
100-120 kBq/kg



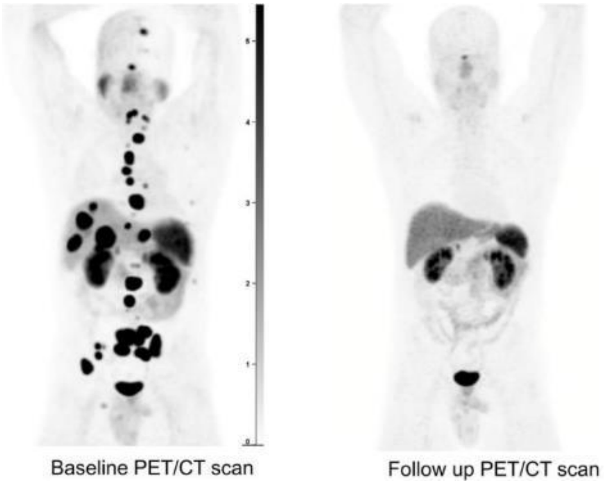
Kratochwil et al. J Nucl Med. 2016 57(12):1941.



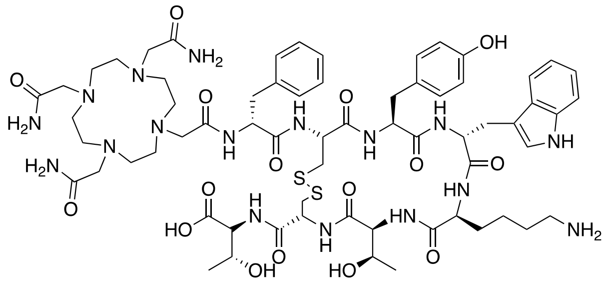
6 cycles [$^{225}$Ac]DOTATATE
100-120 kBq/kg



Ballal, S. *et al*. J. Nucl. Med. 2023,*64*,211.

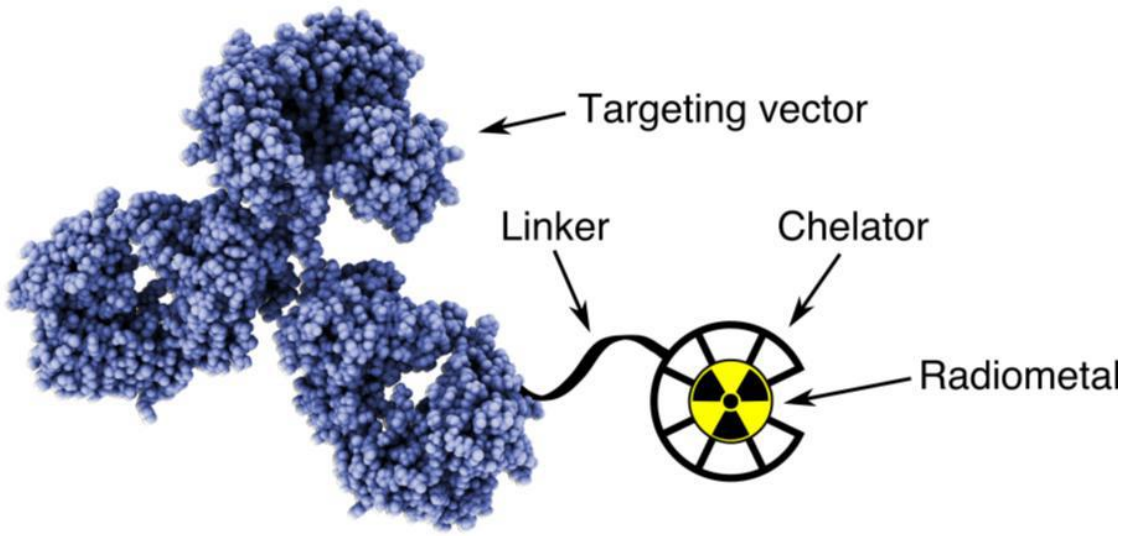



4 cycles [$^{212}$Pb]DOTAMTATE
2.50 MBq/kg



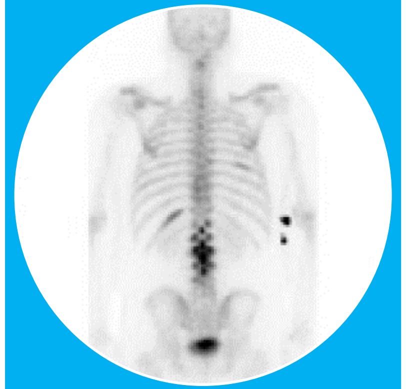
Delpassand, E. *et al*. J. Nucl. Med. 2022,*63*,1326.

# Targeted Alpha Therapy: Not all isotopes qualify




| Isotope | Half-life | Common ion | Ionic radius, Å | Common coordination number | Hard/soft | pKa (aq.) |
|---|---|---|---|---|---|---|
| $^{149}Tb$ | 4.1 h | $Tb^{3+}$ | 1.04 | 8-9 | Hard | 7.9 |
| $^{211}At$ | 7.2 h | $At^{+}$, $AtO^{+}$ | - | - | - | - |
| $^{212}Bi$, $^{213}Bi$ | 60.6 m, 45.6 m | $Bi^{3+}$ | 1.17 | 8 | Intermediate | 1.1 |
| $^{212}Pb$ (for $^{212}Bi$) | 10.6 h | $Pb^{2+}$ | 1.43 | 8 | Intermediate | 0.9 |
| $^{223}Ra$ | 11.4 d | $Ra^{2+}$ | 1.48 | 8-12 | Hard | 3.1 |
| $^{225}Ac$ | 9.9 d | $Ac^{3+}$ | 1.12 | 9-10 | Hard | 9.4 |
| $^{226}Th$,$^{227}Th$ | 30.7 m, 18.7 d | $Th^{4+}$ | 1.05 | >8 | Hard | 3.2 |
| $^{230}U$ | 20.8 d | $[UO_2]^{2+}$ | - | 6 | Hard | 4.2 |

# TRIUMF Life Sciences Core Competencies and Collaborations



TRIUMF capabilities

Accelerator Development and Operations

Accelerator Target Development

Isotope Production

Radio-pharmaceutical Production

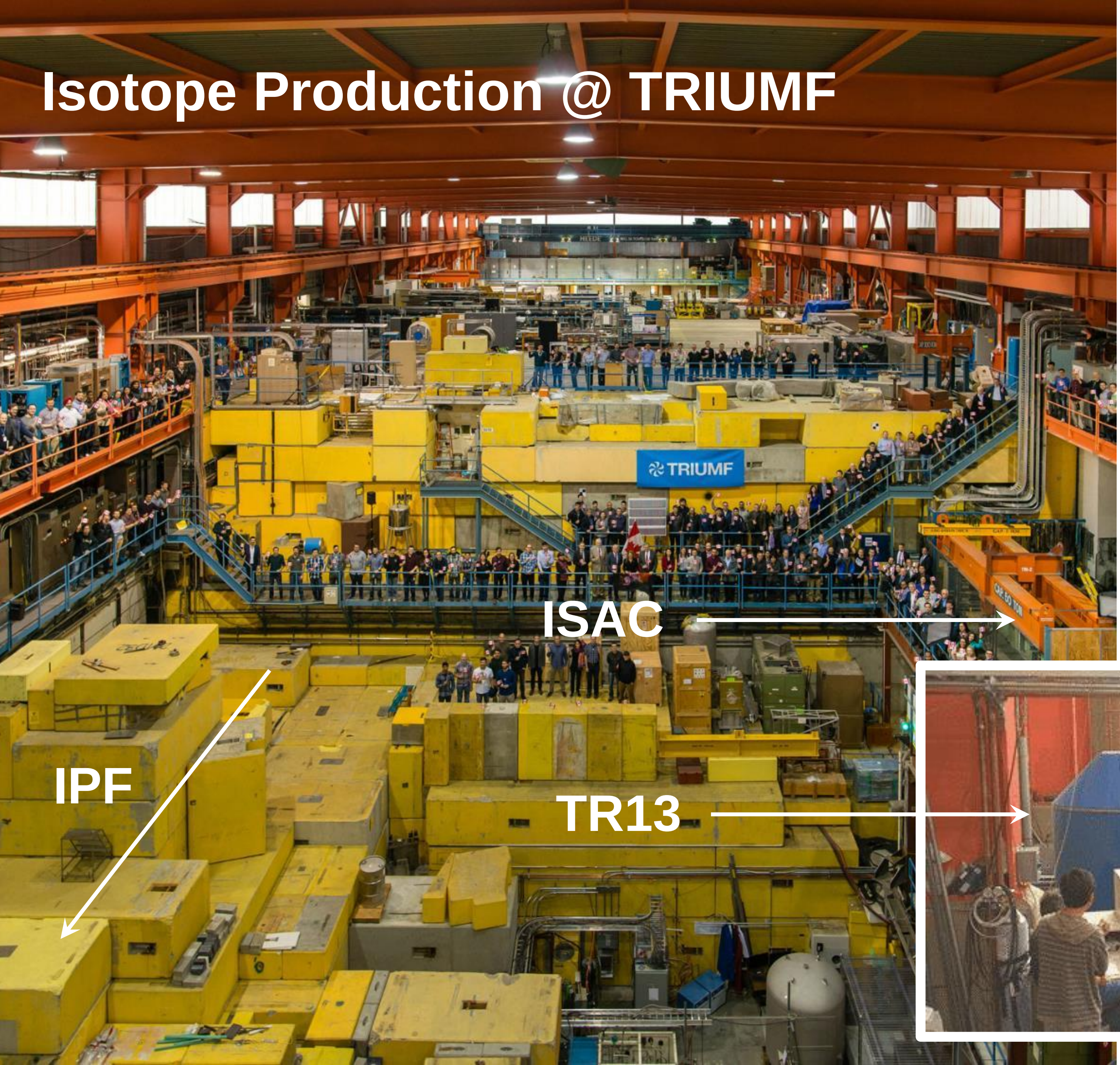
(Pre)Clinical Studies

Imaging and Detector Development

Partnerships

# 500 MeV Isotope Production (Isotope Production Facility)

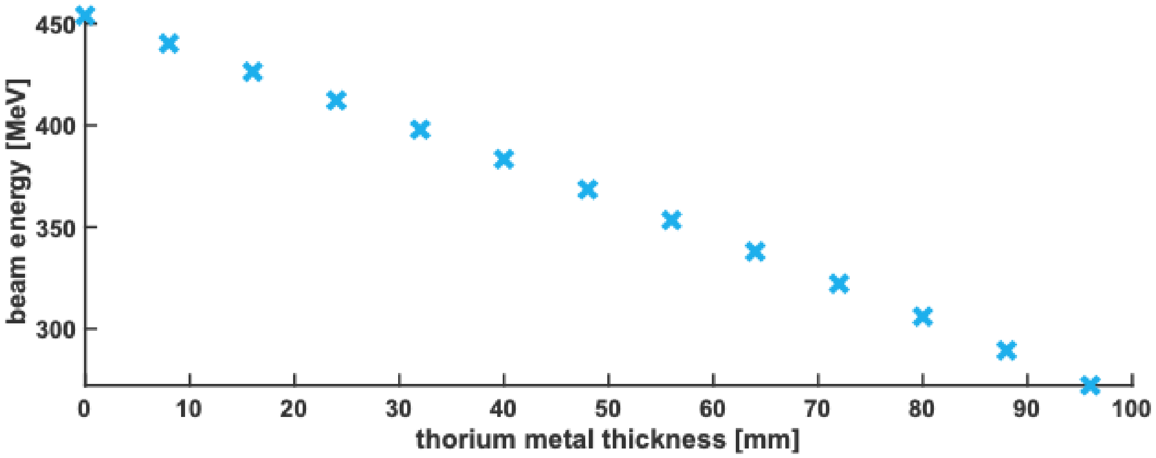
# Isotope Production @ TRIUMF

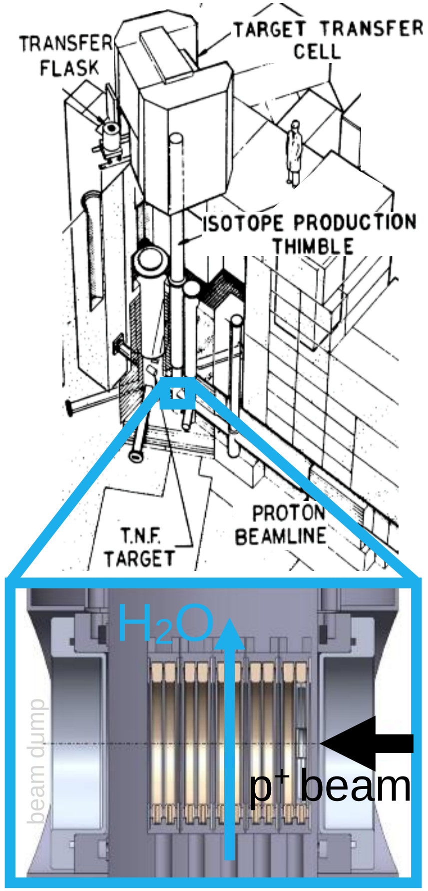


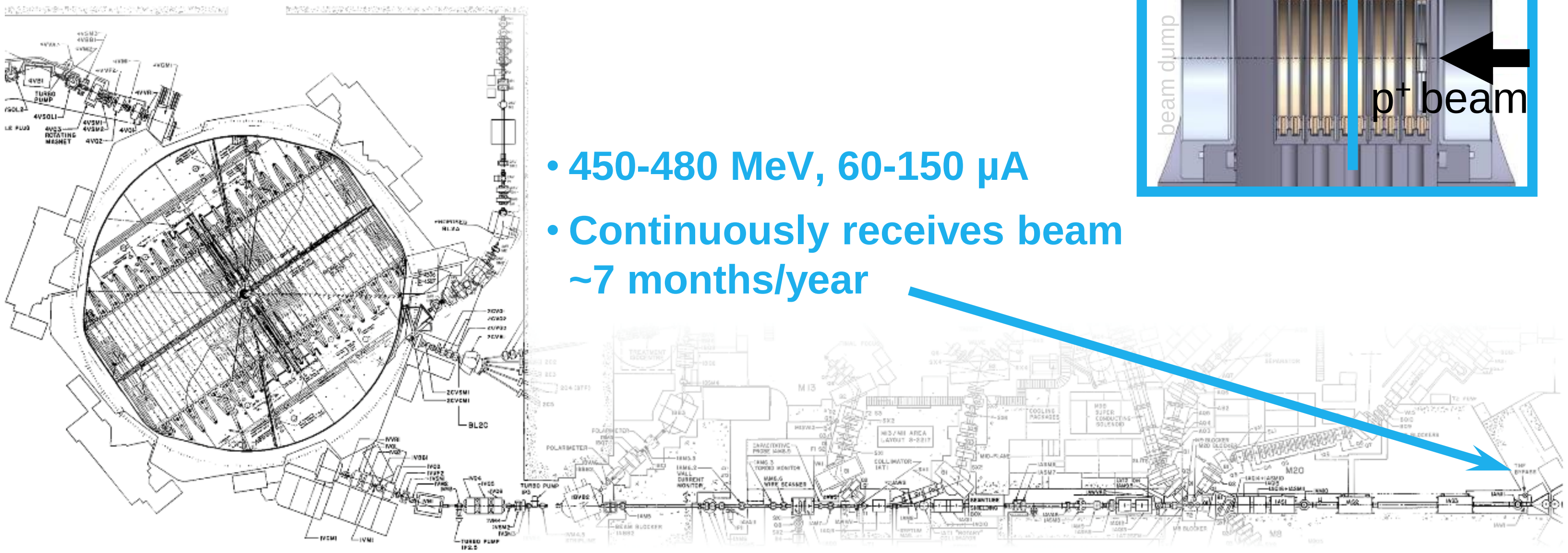

# TRIUMF's IPF

## 500 MeV Isotope Production: $^{232}Th(p,x)$

Simultaneous irradiation of 12 targets (max 8 mm each)



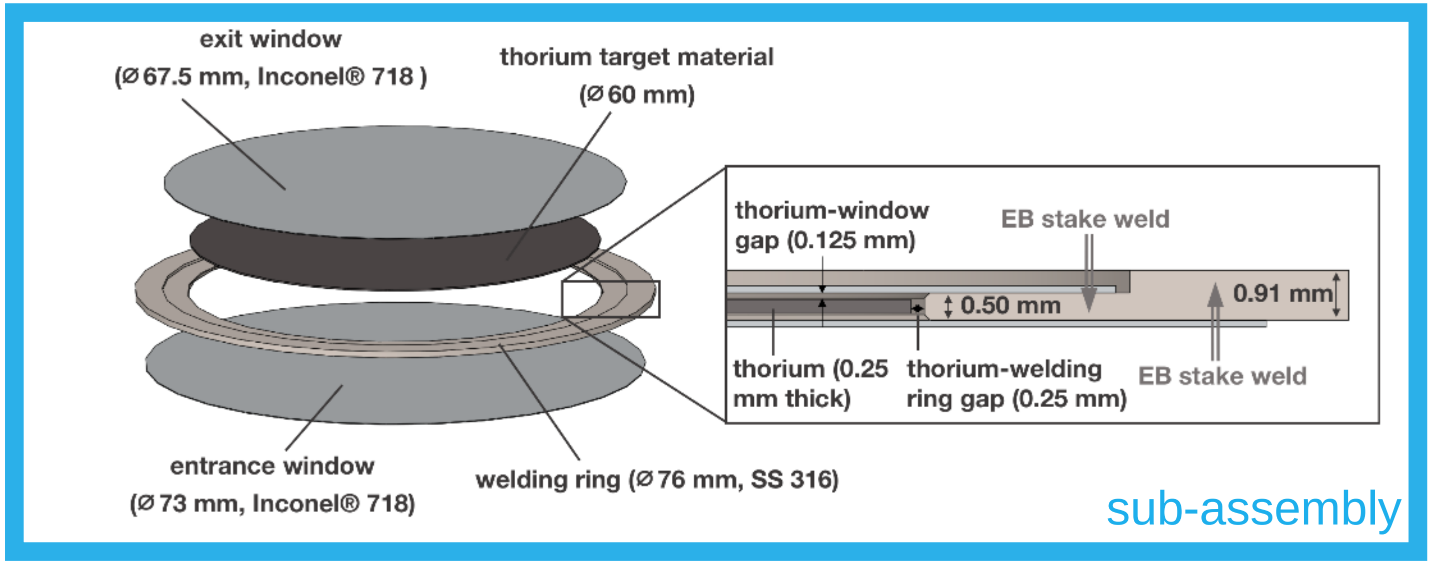



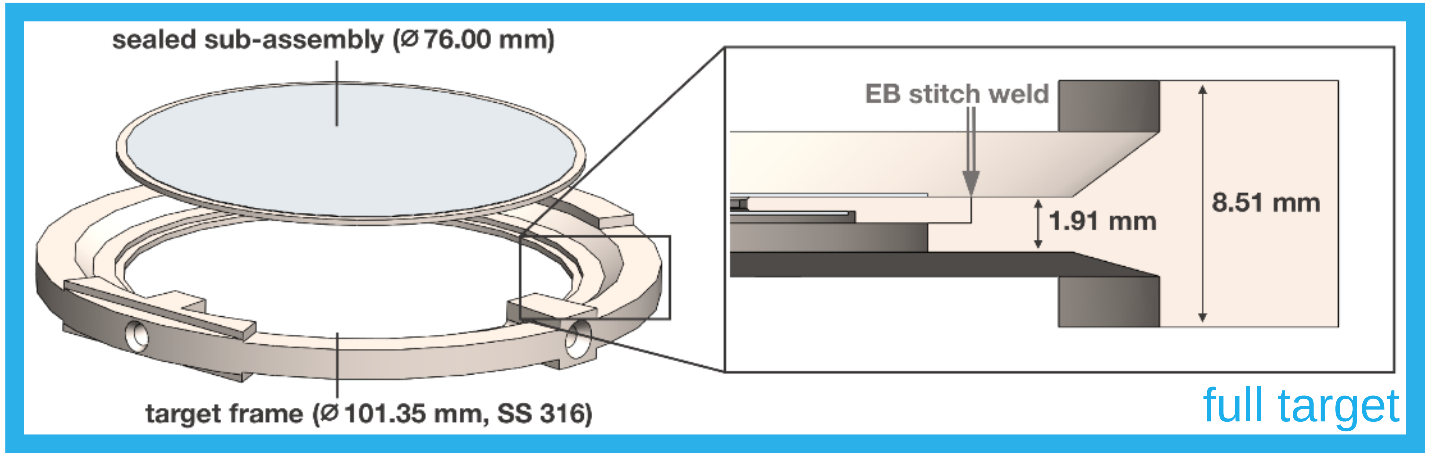



- 450-480 MeV, 60-150 μA
- Continuously receives beam ~7 months/year

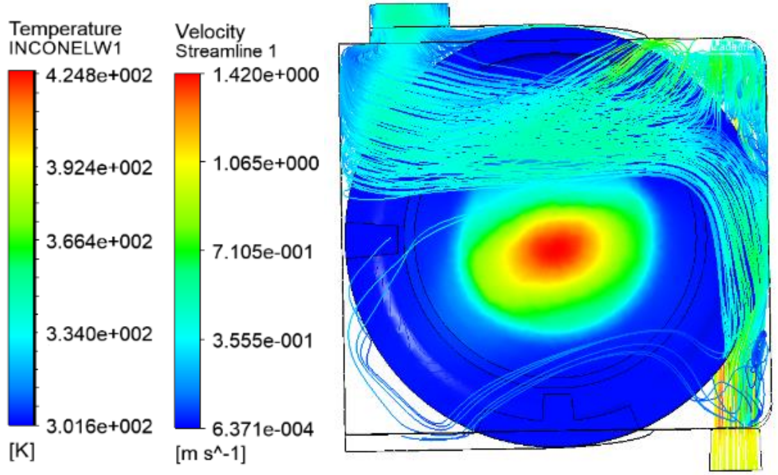
# Thorium target manufacture

## current design details

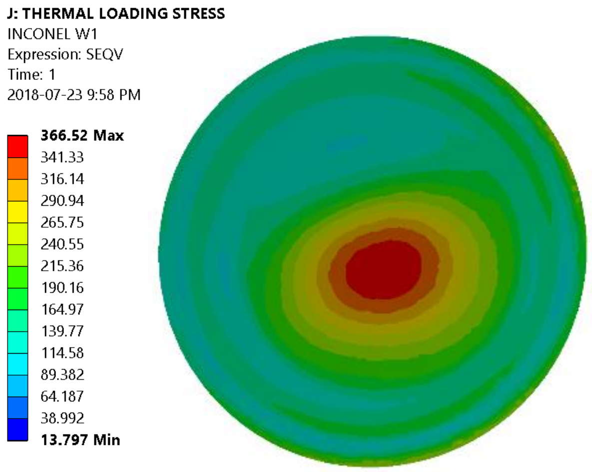


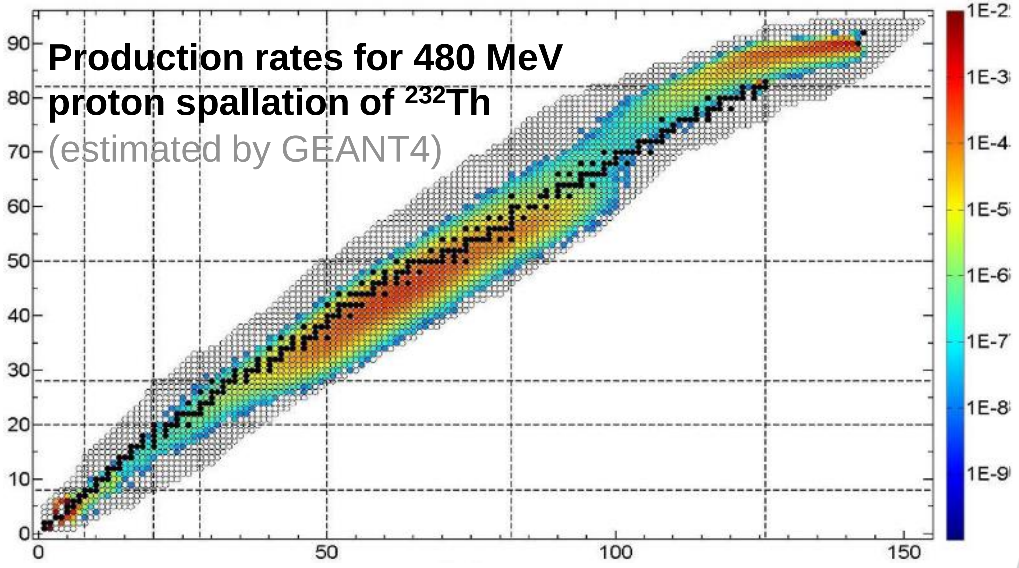

## sample thermal results




## sample mechanical results



# $^{232}$Th(p,x) produces two different $^{225}$Ac products




$^{227}$Ra + $^{225}$Ra + $^{228}$Ra + $^{224}$Ra + $^{226}$Ra

$t_{1/2}$ = 42 min | $t_{1/2}$ = 14.9 d | $t_{1/2}$ = 5.8 y | $t_{1/2}$ = 3.6 d | $t_{1/2}$ = 1600 y

rapid decay

$^{224}$Rn $^{222}$Rn

$^{225}$Ac + $^{224}$Ac + $^{226}$Ac + $^{227}$Ac

$t_{1/2}$ = 9.9 d | $t_{1/2}$ = 3 h | $t_{1/2}$ = 29 h | $t_{1/2}$ = 22 y

concerns (from some) about $^{227}$Ac content and impact on waste management — no consensus

**"directly-produced $^{227,225}$Ac†"**

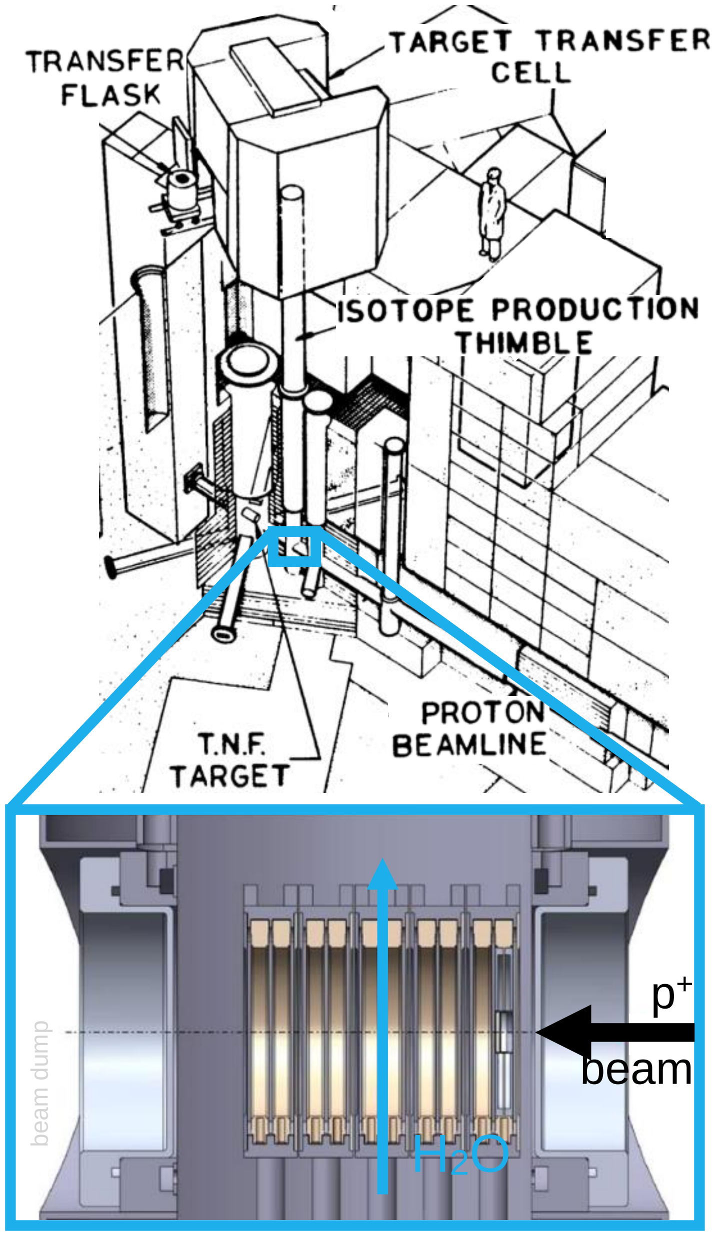
$^{225}$Ac + $^{228}$Ac

$t_{1/2}$ = 9.9 d | $t_{1/2}$ = 6 h

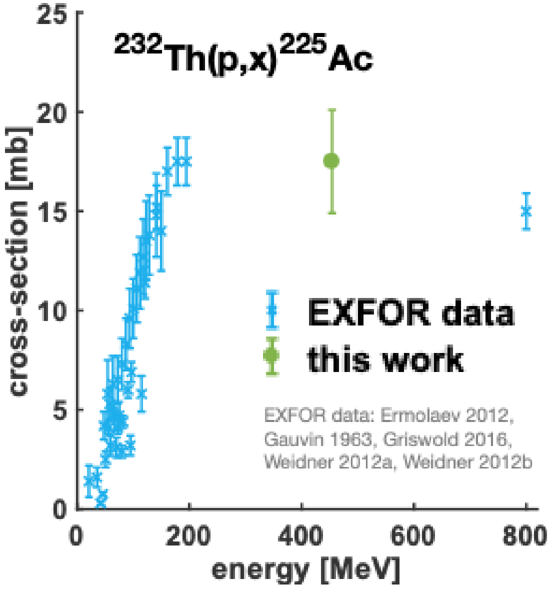
**"generator-produced $^{225}$Ac*"**

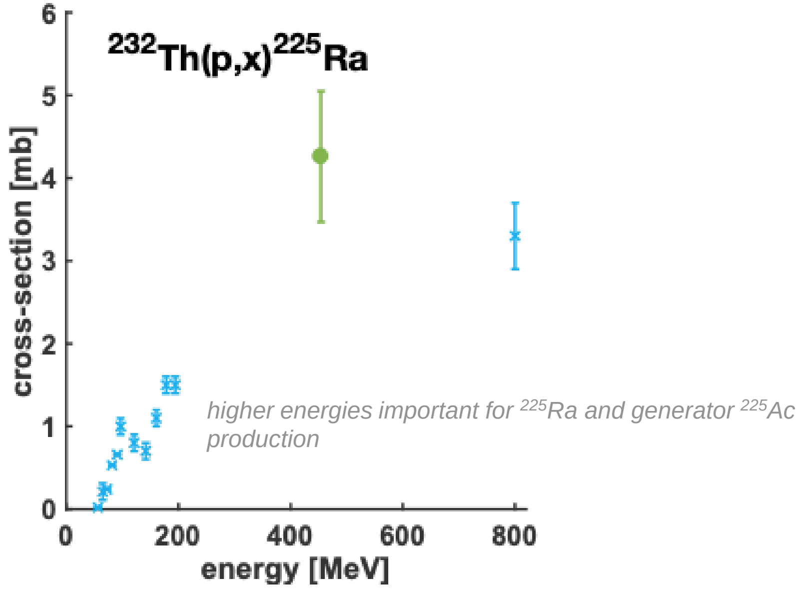
**AKH Robertson et al.**, *Inorganic Chemistry* 2020, 59, 12156

# TRIUMF's 500 MeV Isotope Production Facility (IPF)




Typical beam: 65-85 μA, 454 MeV

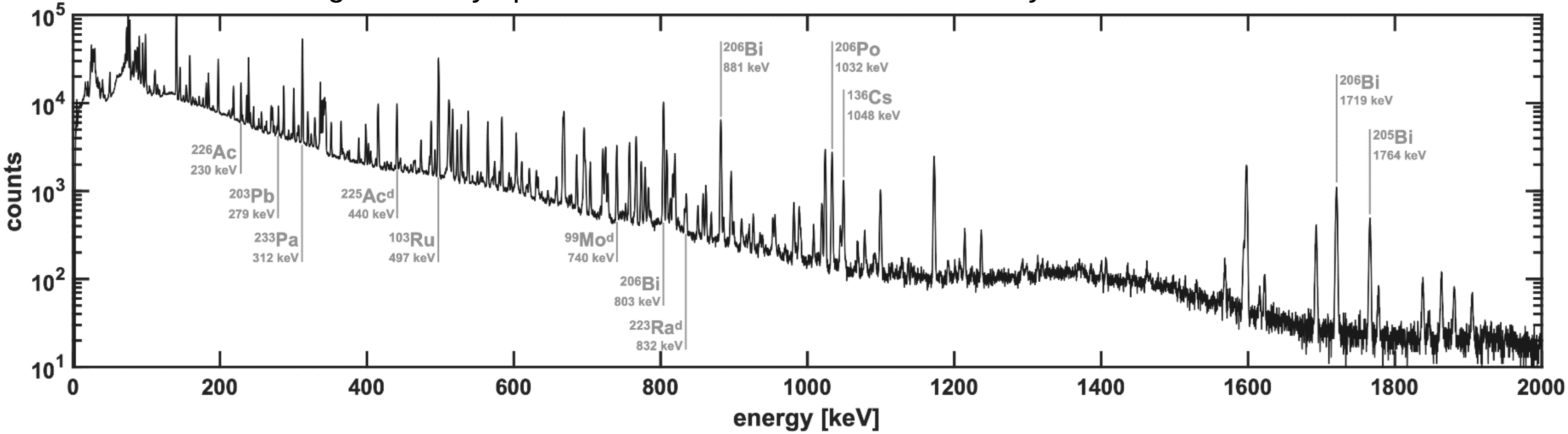



AKH Robertson et al., *Phys. Rev. C* 2020, 102, 044613

# Gamma spectroscopy was used to measure the target's radioactive inventory

gamma ray spectrum of irradiated thorium at 7 days after irradiation




**Acceptance criteria:**

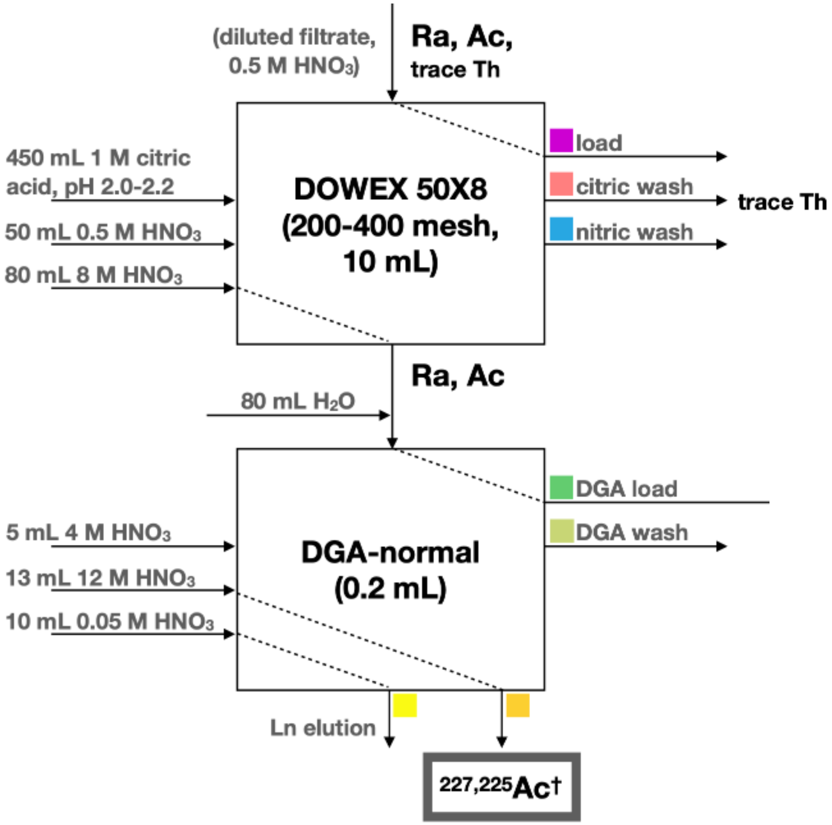
- Multiple gamma lines providing consistent activity measurement, or
- Gamma line decays with half-life of the nuclide

**47 nuclides quantified, resulting in 38 cross section measurements**

AKH Robertson et al., *Phys. Rev. C* 2020, 102, 044613

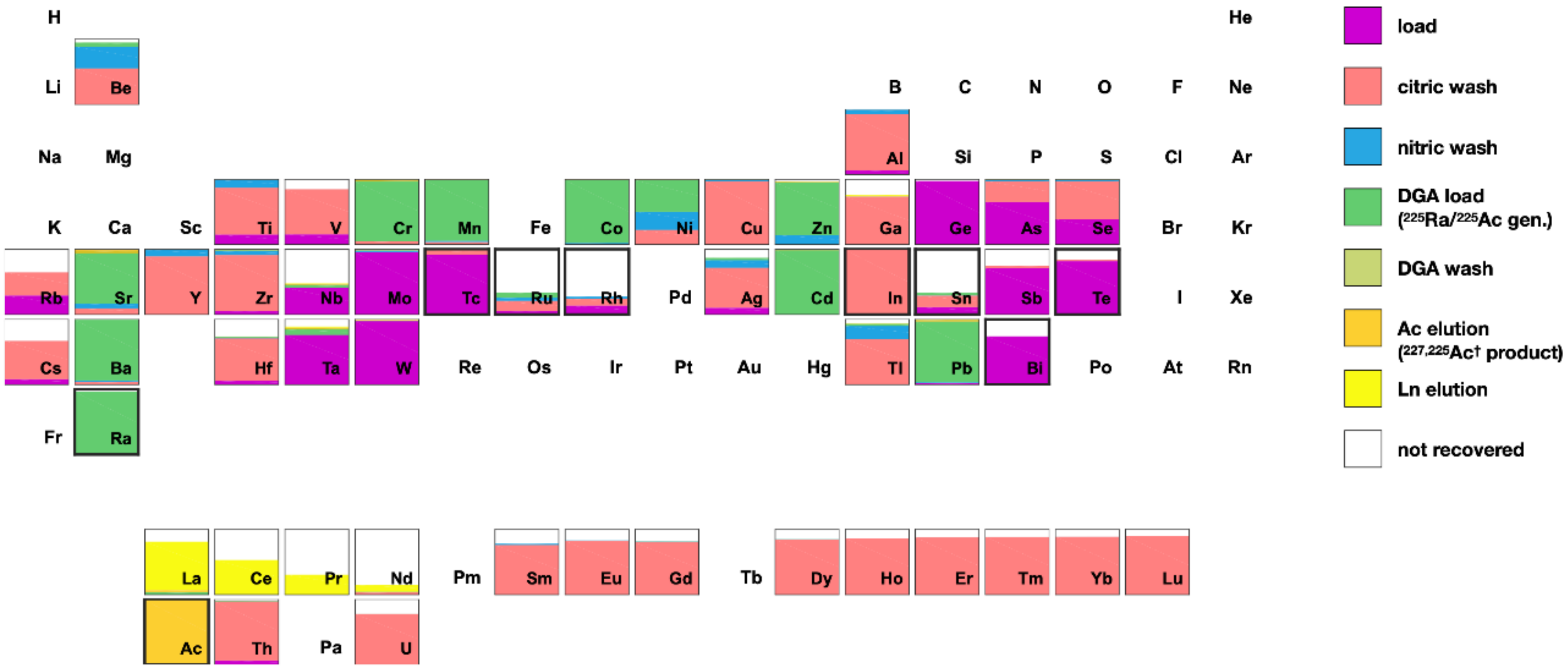
# Separation of $^{227,225}Ac^{\dagger}$ from remaining Th and spallation/fission products

**Ion exchange + extraction chromatography**




**Results from stable and radioactive tracers studies**

(area of each colour is proportional to % of elemental tracer found in the fraction)

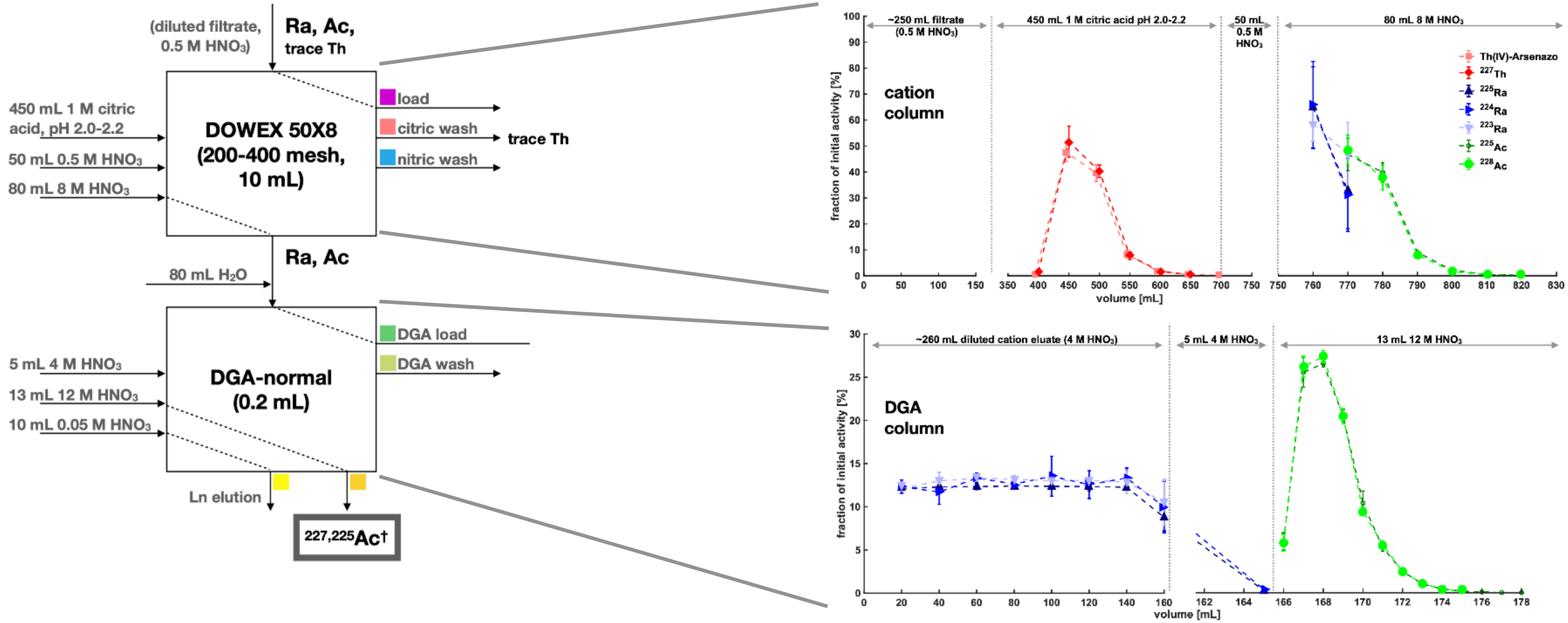



V Radchenko et al., Tantala, 2017, 175, 318

AKH Robertson et al., *Phys. Rev. C* 2020, 102, 044613

# Separation of $^{227,225}Ac^{\dagger}$ from remaining Th and spallation/fission products

**Ion exchange + extraction chromatography**

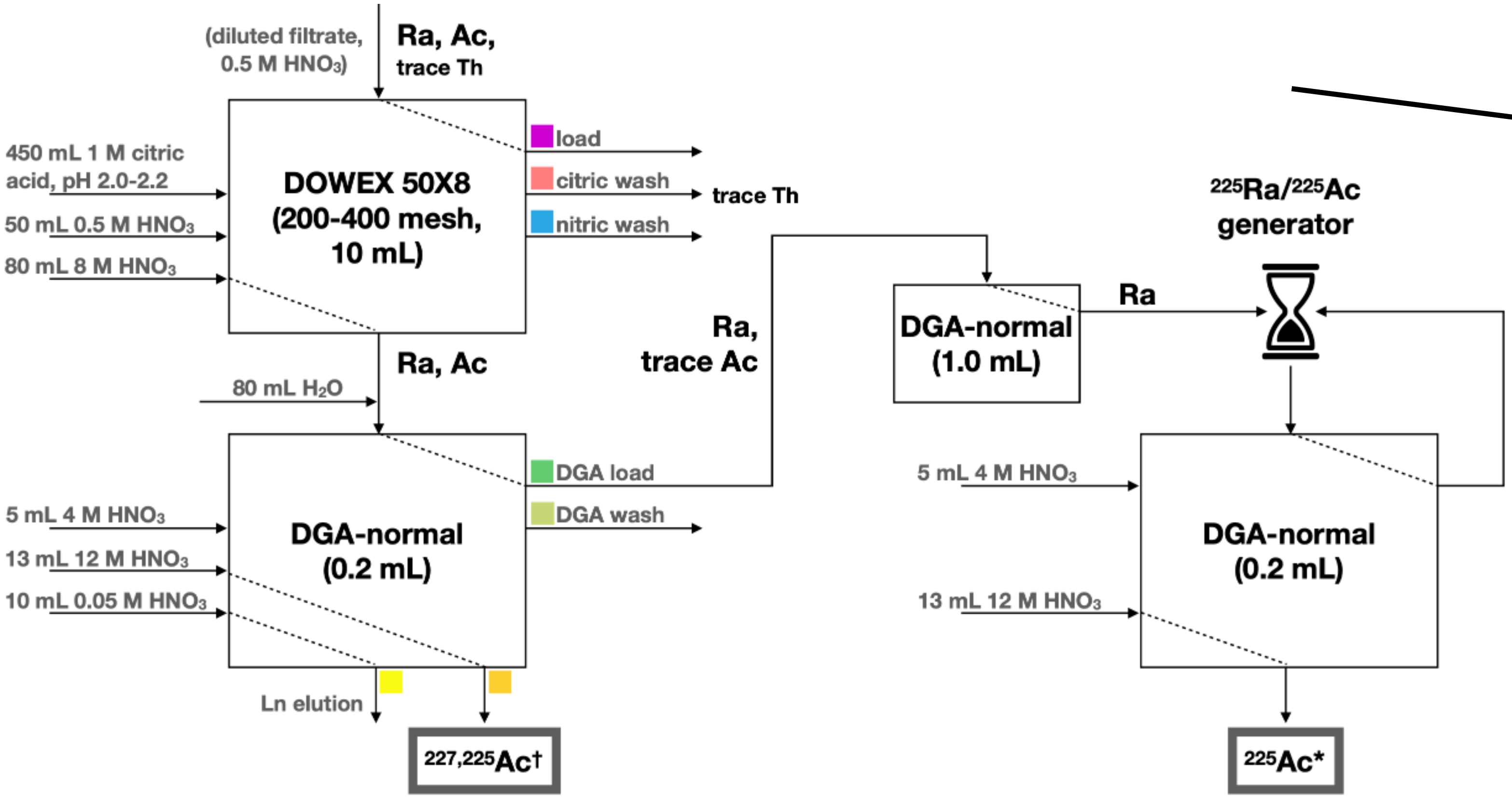


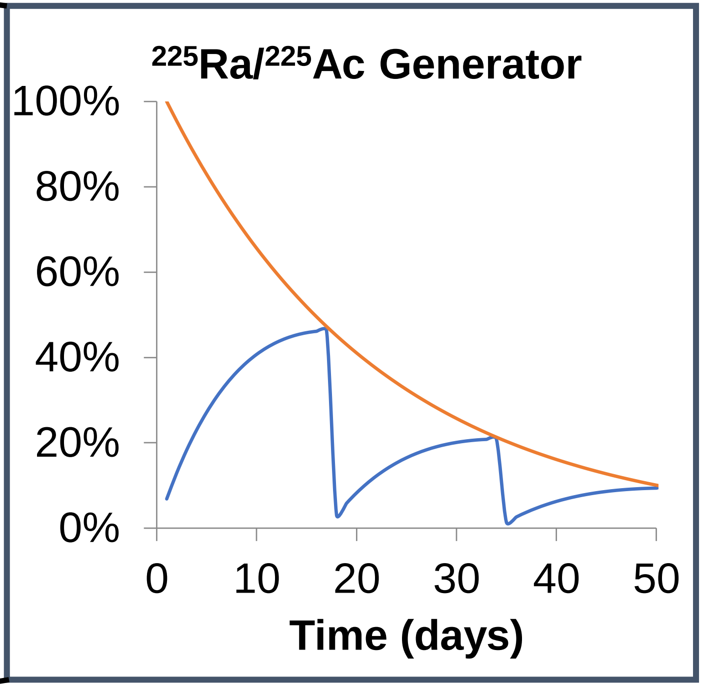

V Radchenko et al., Tantala, 2017, 175, 318

AKH Robertson et al., *Phys. Rev. C* 2020, 102, 044613

# Repeating final process step produces $^{225}Ac$*

$^{225}Ra/^{225}Ac$ generator operation




V Radchenko et al., Tantala, 2017, 175, 318

AKH Robertson et al., *Phys. Rev. C* 2020, 102, 044613

# Generator-produced $^{225}$Ac* has higher radionuclidic purity and reduced $^{227}$Ac content

reduced $^{227}$Ac →

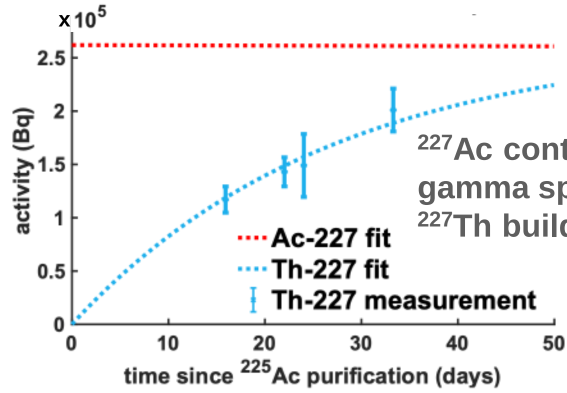
simple changes expected to reduce these →

| | percent radioactivity [%] | |
|---|---|---|
| | $^{227,225}$Ac† | $^{225}$Ac* |
| **Ac-225** | **93.04** | **98.82** |
| **Ac-227** | **0.17** | **<7.2E-5** |
| Ac-226 | 4.03 | <0.01 |
| La-140 | 2.29 | 0.01 |
| Ru-106 | <0.04 | 0.13 |
| Ru-103 | 0.25 | 0.72 |
| Sr-85 | 0.14 | 0.33 |
| Th-227 | <0.04 | <0.17 |
| Ra-226 | <0.01 | <0.06 |
| Ra-225 | <0.01 | <0.05 |
| Ra-224 | <0.07 | <0.02 |
| Ra-223 | <0.04 | <0.14 |
| Ce-141 | <0.01 | <0.03 |
| Ba-140 | <0.01 | <0.04 |

**Radionuclidic purity measured by gamma spectroscopy** at end of processing (n = 2)

$^{228}$Ac likely present but decays before measurement

***$^{227}$Ac measured by ICP-MS and gamma spec** (via $^{227}$Th build-up)




$^{227}$Ac content via gamma spec of $^{227}$Th build-up

**Robertson et al.**, *Inorganic Chemistry* 2020, 59, 12156

# How much Ac-225 can we produce?

TRIUMF's Actinium production focuses on supporting internal research and collaborations with external partners.

| | | |
|---|---|---|
| **Target:** | ~10g Thorium    Dose: 12,500 µAh    Cool-down time: 7 days | |
| First Pass | Ac-225/Ac-227: ~1.3 GBq (10 days after EOB) | |
| | Ra-225: ~0.3 GBq (10 days after EOB) | |
| Second Pass | First elution (after 14-day grow-in period): 80-90 MBq | Total actinium yield per target : up to 220 MBq |
| | Additional 5 elutions with 7-day grow-in periods in between | |

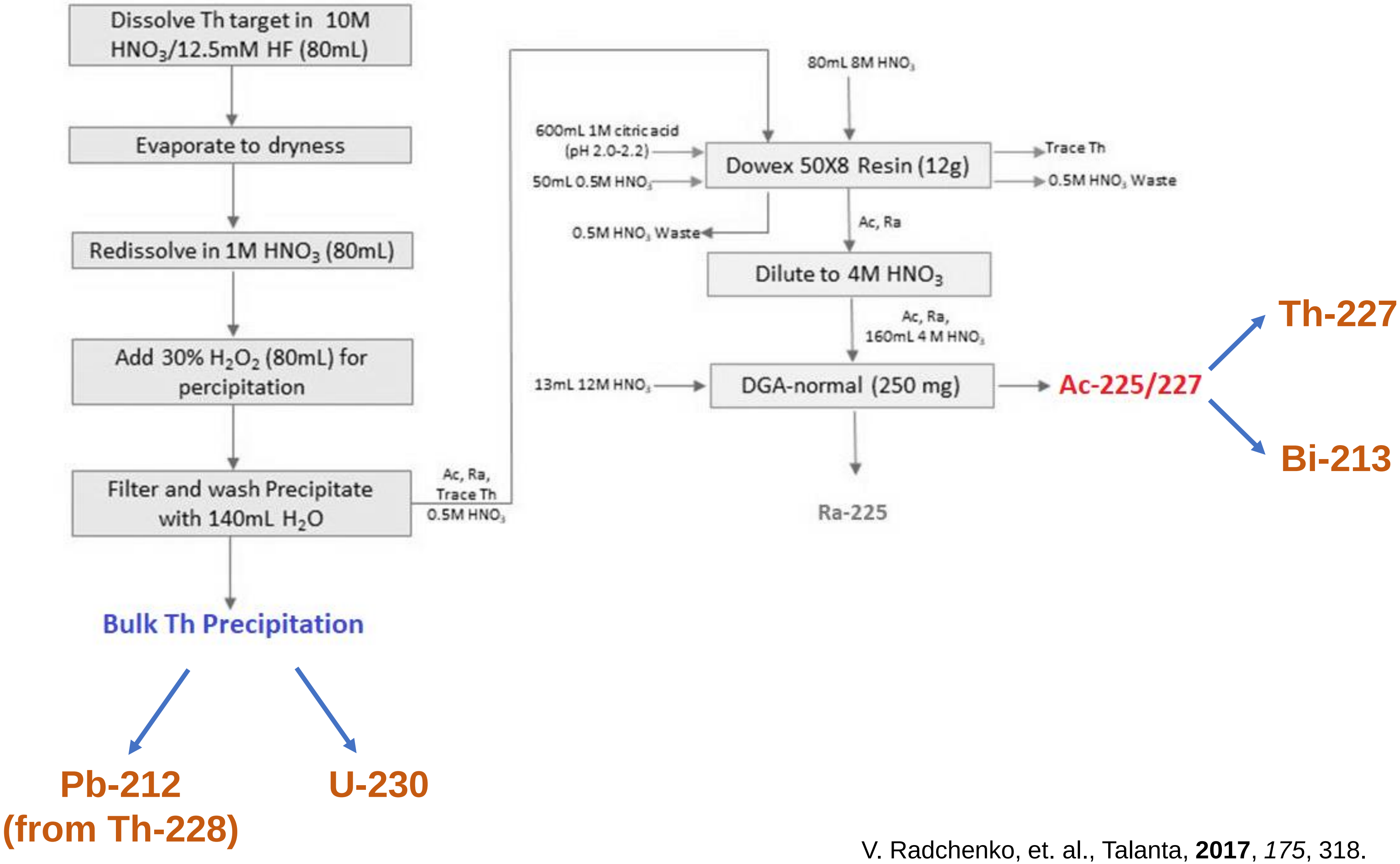
**To improve the Actinium Yield:**

- increase target material
- increase irradiation dose
- shorten the cool-down time

**Thorium-232 targets for BWXT Medical, Inc.**
**(producing higher yields of Ac-225 for clinical trial use)**

- Dose: 25,000 µAh
- Cool down time: 1 day,
- Thicker targets planned for the near future

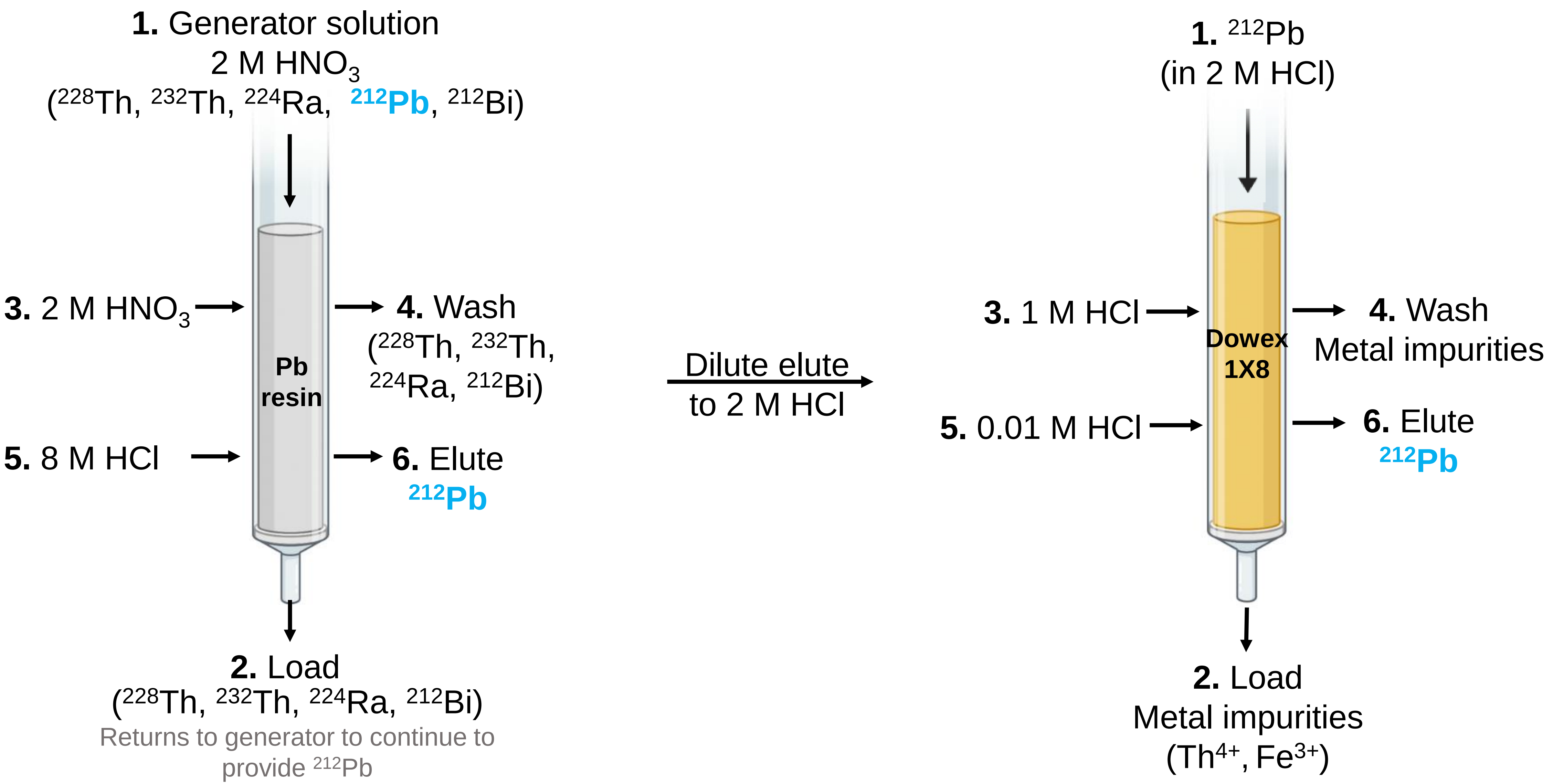
# After Thorium spallation, which other radiometals can we utilize?




V. Radchenko, et. al., Talanta, **2017**, *175*, 318.
AKH Robertson, et. al., Inorg. Chem., **2020**, *59*, 12156.

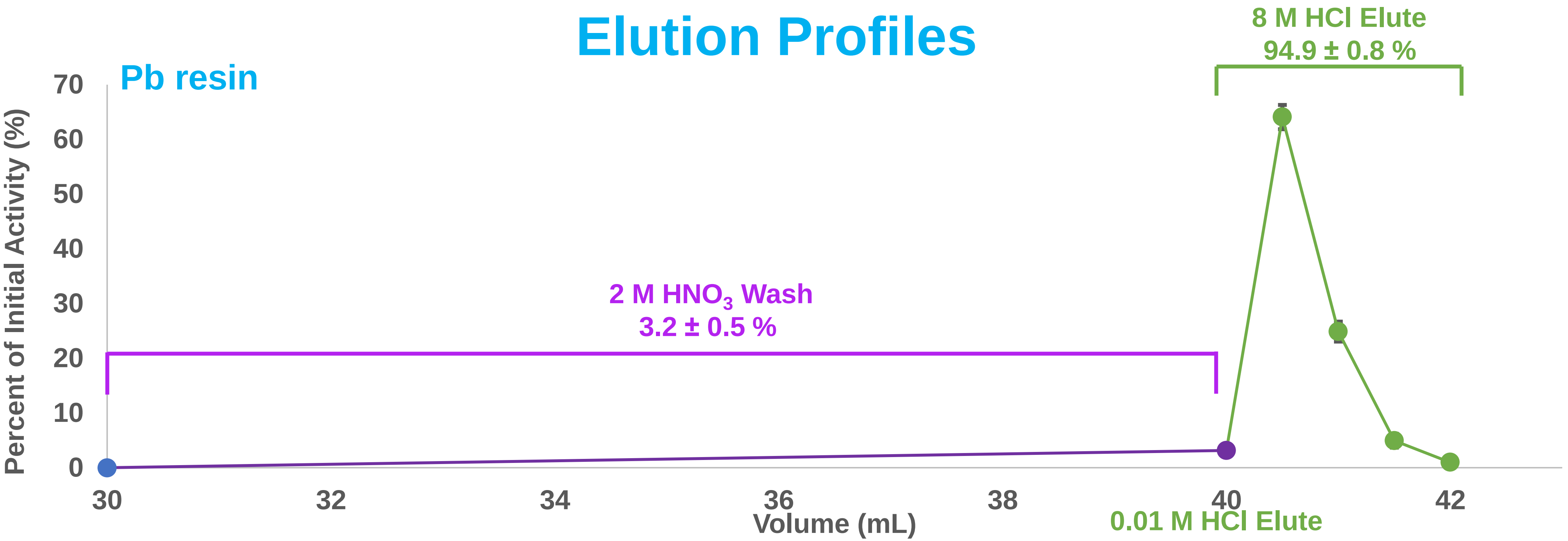
# $^{228}Th/^{212}Pb$ Generator

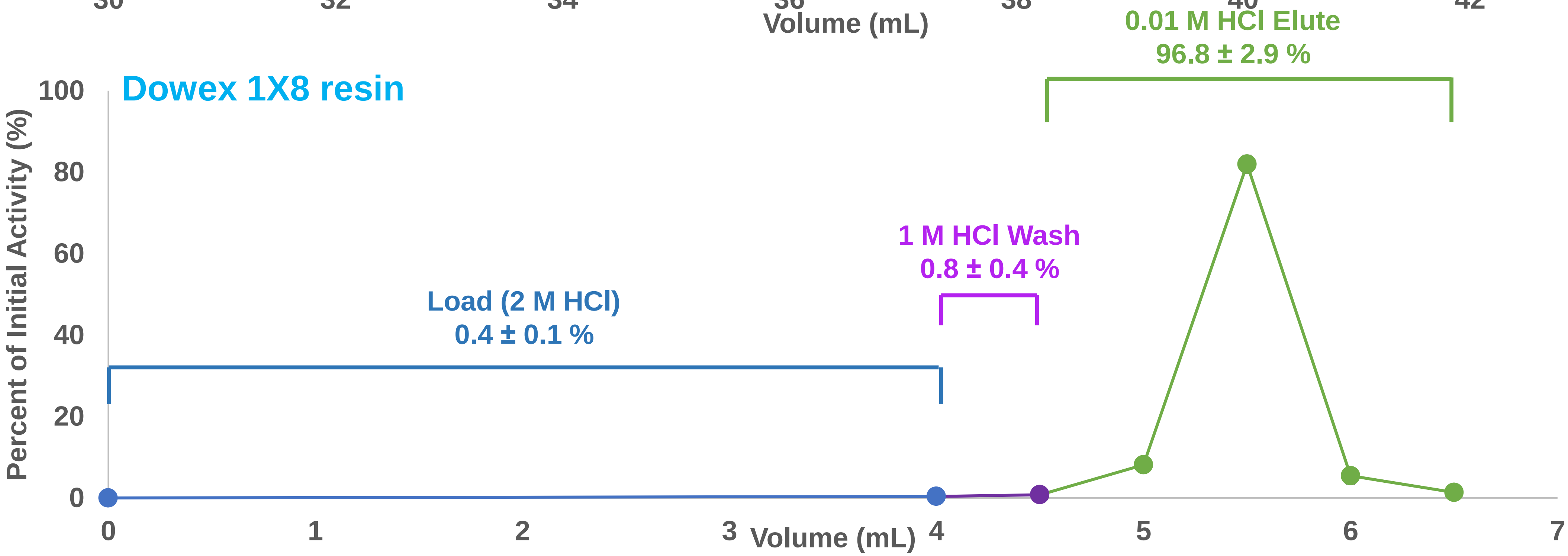
29




McNeil, B. *et al*. EJNMMI. 2021, *6*(6).

# Elution Profiles



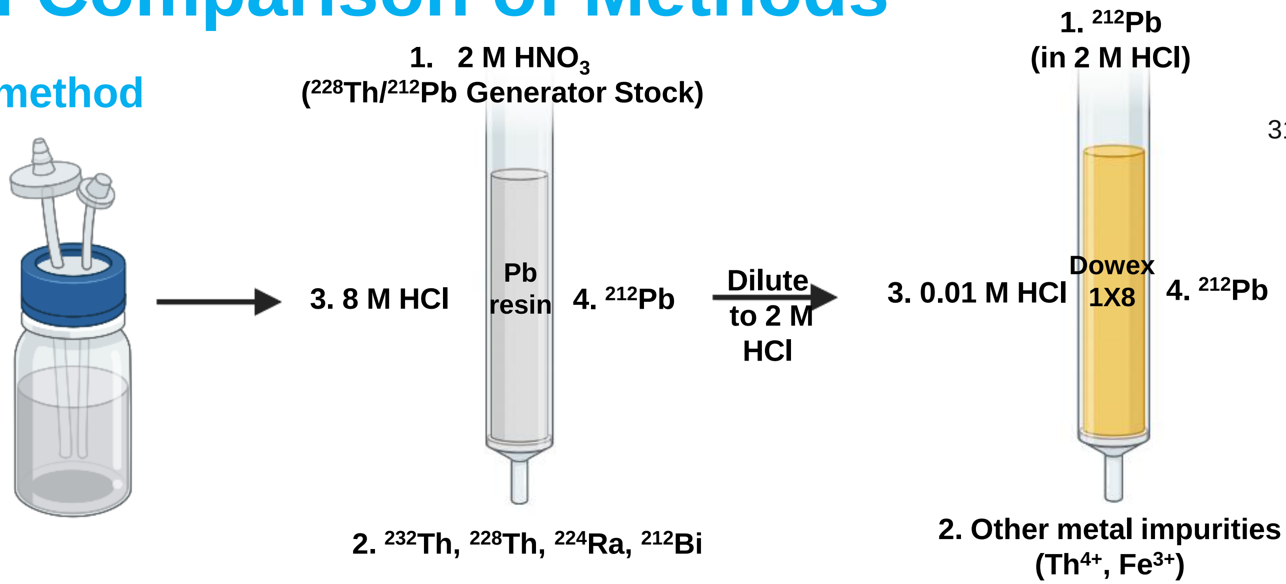

30

# ICP-MS Results and Comparison of Methods

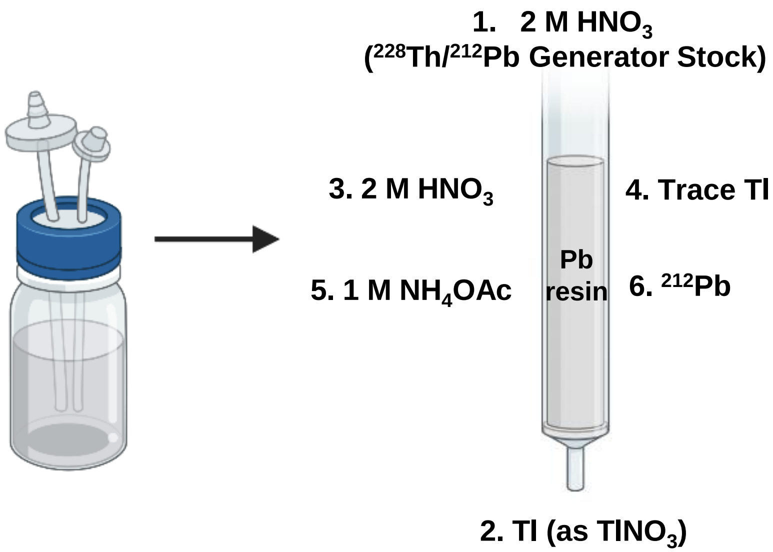


| Metal | Concentration with Old Method (ppb) (n = 3) | Concentration with New Method (ppb) (n = 3) |
|---|---|---|
| Al | 22 ± 9 | 2 ± 3 |
| Mg | 612 ± 226 | 15 ± 7 |
| Ca | N.S. | 15 ± 5 |
| Ti | 354 ± 168 | N.S. |
| Fe | N.S. | N.S. |
| Cu | 3 ± 2 | 4 ± 2 |
| Zn | N.S. | N.S. |
| Th | 24,352 ± 16,227 | 291 ± 56 (In 8 M HCl strip 37,650 ± 3,195) |
| Pb | 2 ± 2 | 4 ± 2 |

## New method



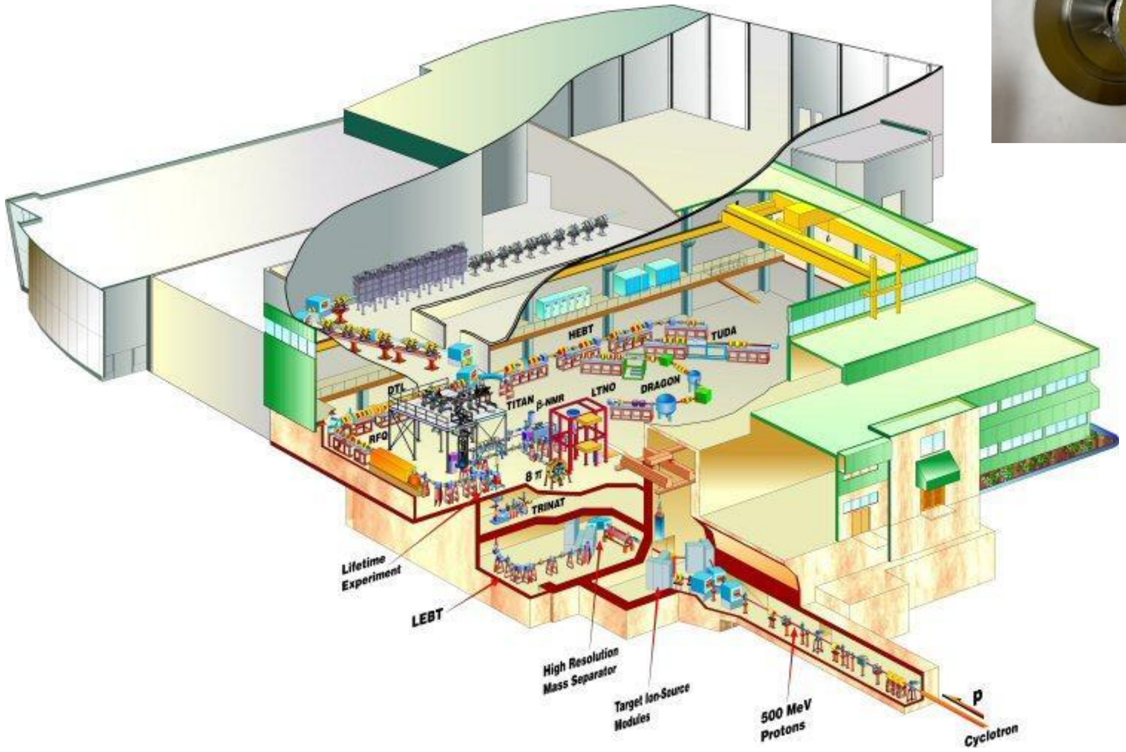

## Old method

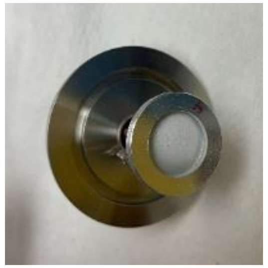


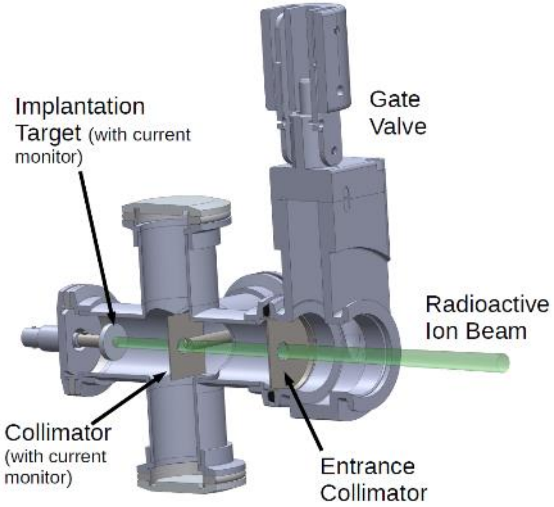

McNeil, B. *et al*. EJNMMI. 2021, *6*(6).

# Isotope Separation On-Line

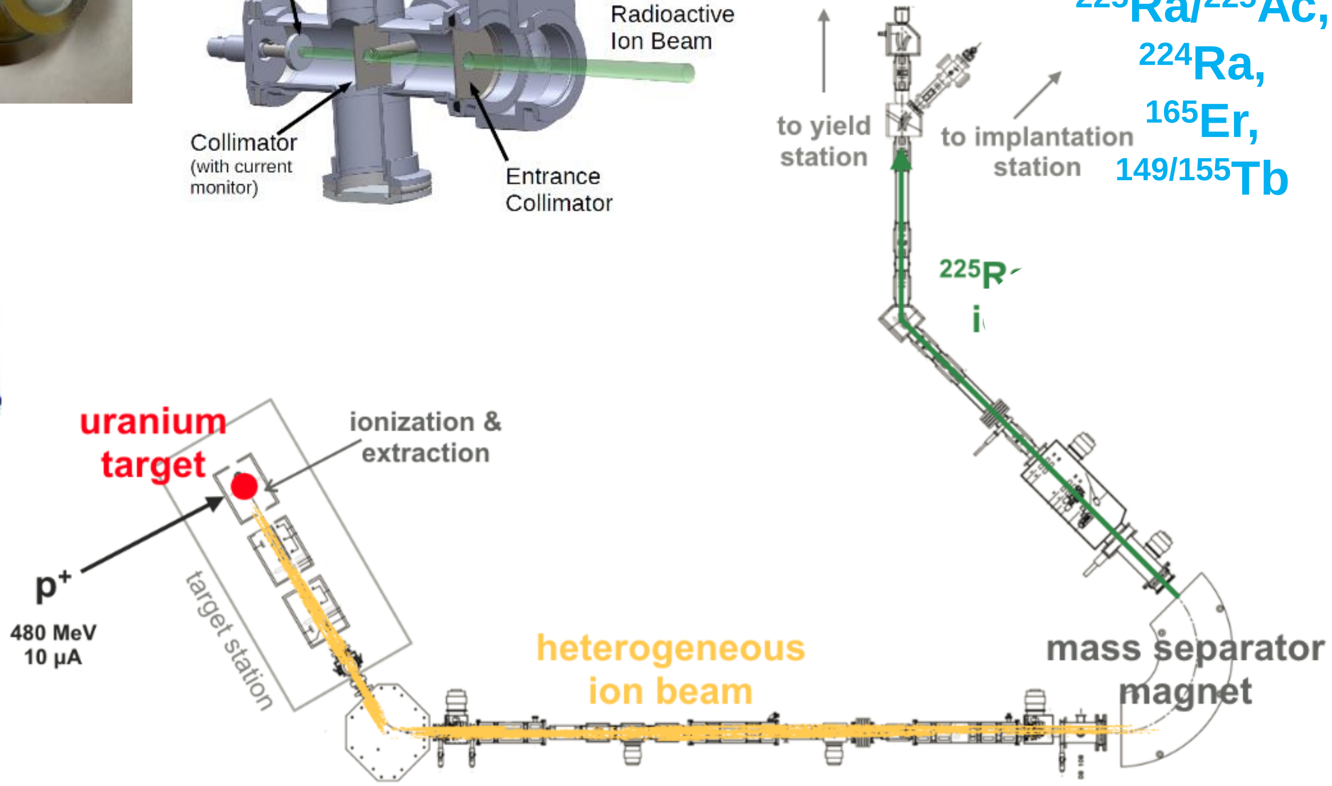







$^{211/209}$At,
$^{226}$Ra/$^{226}$Ac,
$^{225}$Ra/$^{225}$Ac,
$^{224}$Ra,
$^{165}$Er,
$^{149/155}$Tb

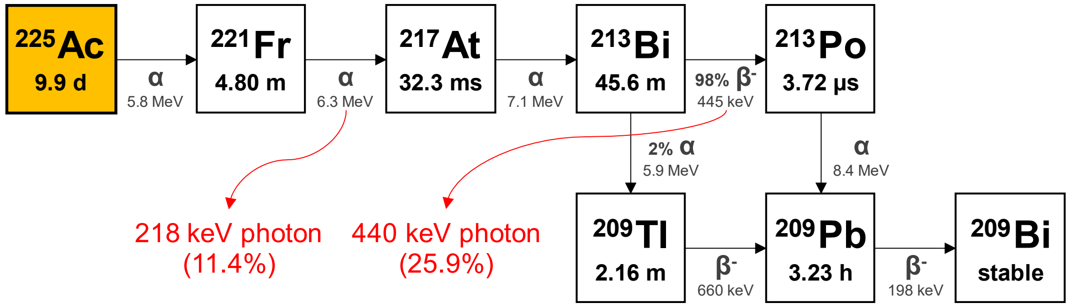


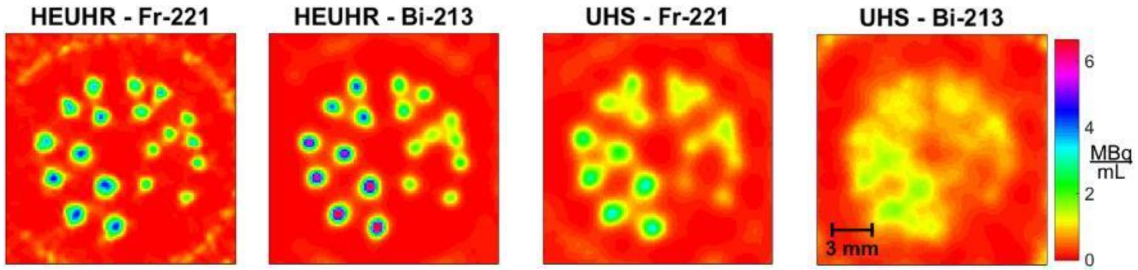

J. Dilling, R. Krüecken, et al. ISAC and Ariel: The TRIUMF Radioactive Beam Facilities and the Scientific Program, Springer Netherlands, **2014.;**
P. Kunz, C. Andreoiu, P. Bricault, M. Dombsky, J. Lassen, A. Teigelhöfer, et al. Nuclear and in-source laser spectroscopy with the ISAC yield station. Review of Scientific Instruments, **2014**, 85, 053305.
J. Crawford, P. Kunz, H. Yang, P Schaffer, T. Ruth *Appl. Radiat. Isotope*. 2017; 62:122-222

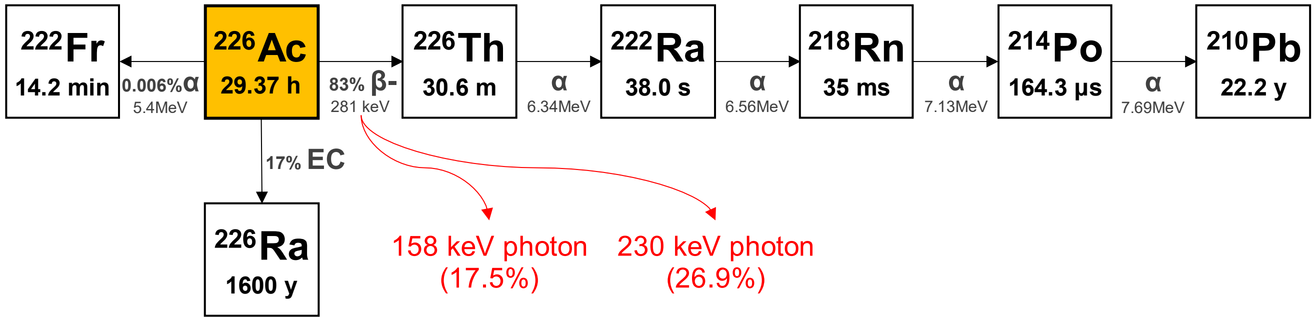
# Production and SPECT Imaging of $^{225}$Ac and $^{226}$Ac

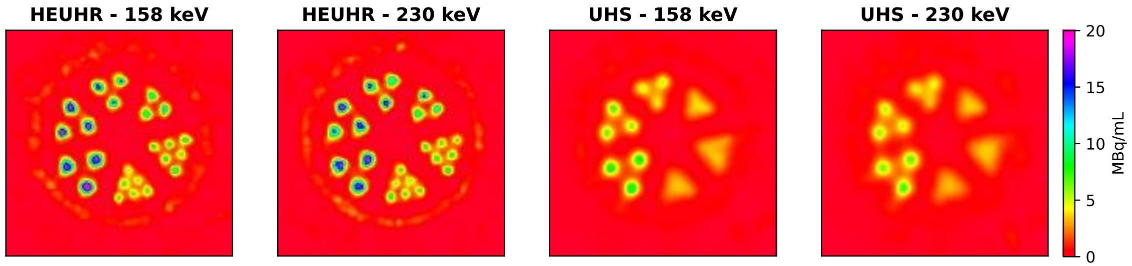
## Key Question: Where do Ac and daughters reside?





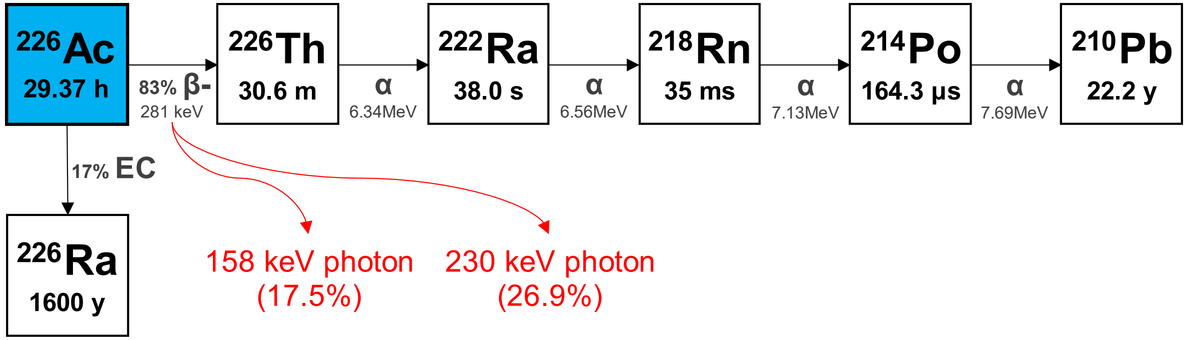



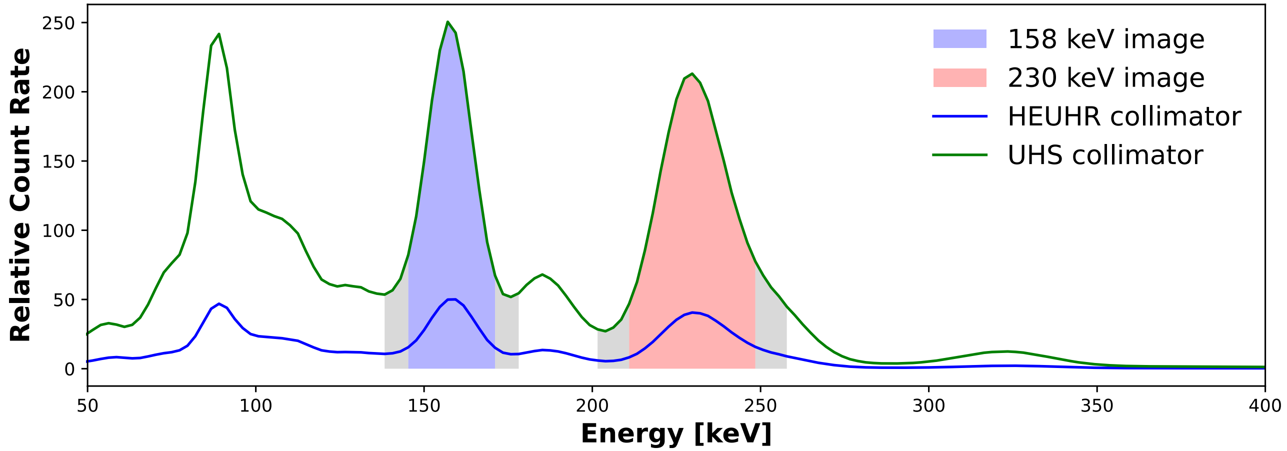




Robertson, et al. *Phys Med Biol*. 2017; 62:4406-4420. Fiaccabrino, et al. *Nucl Med Biol*. 2021; 94-95:81-91. Koniar, et al. *Phys Med. Biol. 2022*, 67, 185009

# $^{226}$Ac phantom SPECT Imaging

- Can the gamma emissions from $^{226}$Ac produce quantitative SPECT images with high accuracy and resolution?
- Goal: Quantify optimal protocols for our preclinical scanner to conduct $^{226}$Ac imaging




$^{226}$Ac energy spectra acquired by the VECTor scanner for both HEUHR (blue) and UHS (green) collimators, normalized by acquisition time and decay corrected activity

# Methods: $^{226}Ac$ Production Run Summary



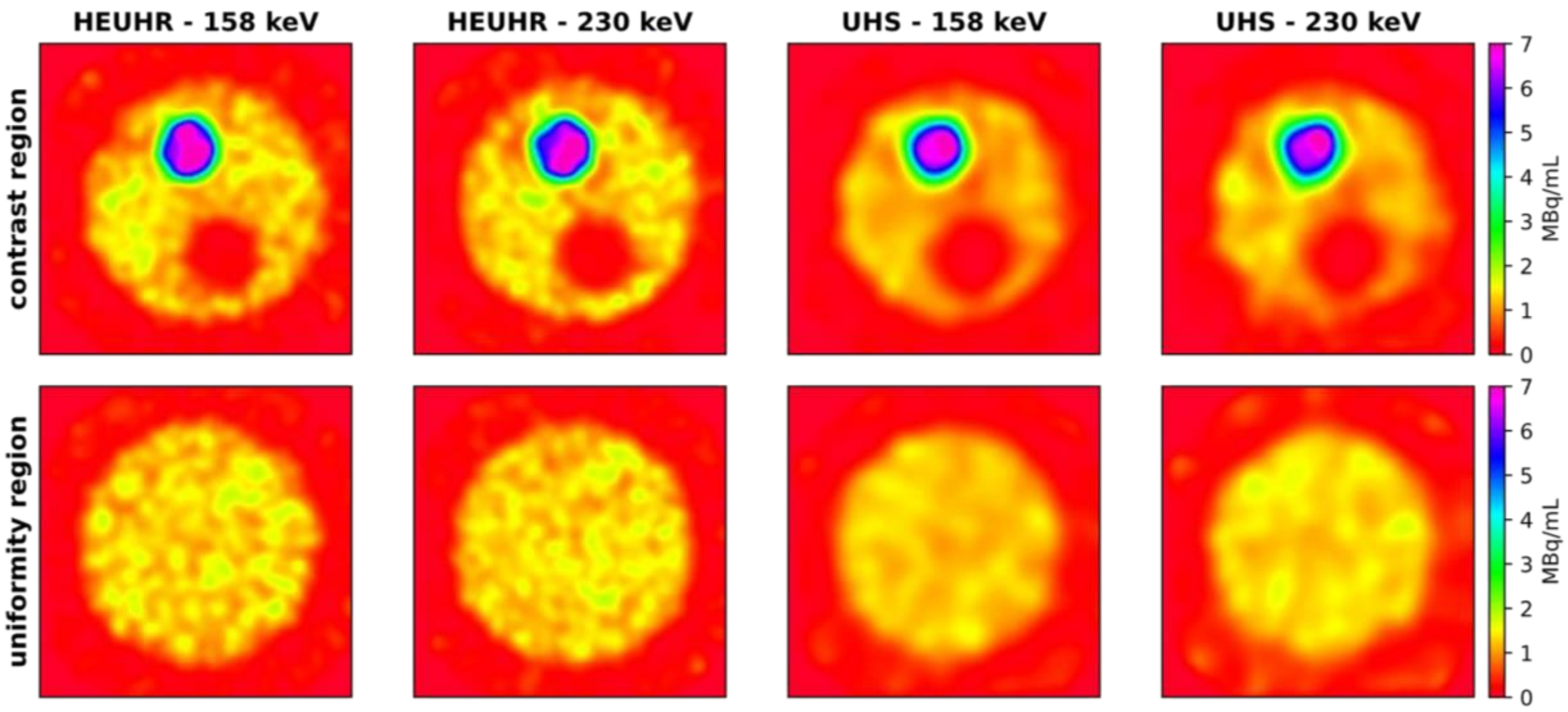
| Date | Run time | Yield [1/s] | Activity produced | Experiments enabled |
|---|---|---|---|---|
| 2020-09-16 | 24 h | 3.74e+7 | 22 MBq | Proof-of-concept production run, radiolabelling, stability |
| 2021-07-27 | 24 h | 8.14e+7 | 37 MBq | Phantom SPECT imaging with resolution, uniformity, and contrast phantoms |
| 2022-08-03 | 8 h | 4.98e+7 | 5 MBq | ***In vivo* SPECT imaging** |

https://yield.targets.triumf.ca/search/isotope/data

# Results: Contrast and uniformity phantom

## $^{226}$Ac phantom SPECT imaging






158 keV and 230 keV SPECT images acquired with both the HEUHR and UHS collimators of the SPECTIQ phantom's contrast region (*top*) and uniformity region (*bottom*). Images were filtered with a 1 mm FWHM Gaussian filter.

# Results: Contrast and uniformity phantom

## $^{226}$Ac phantom SPECT imaging

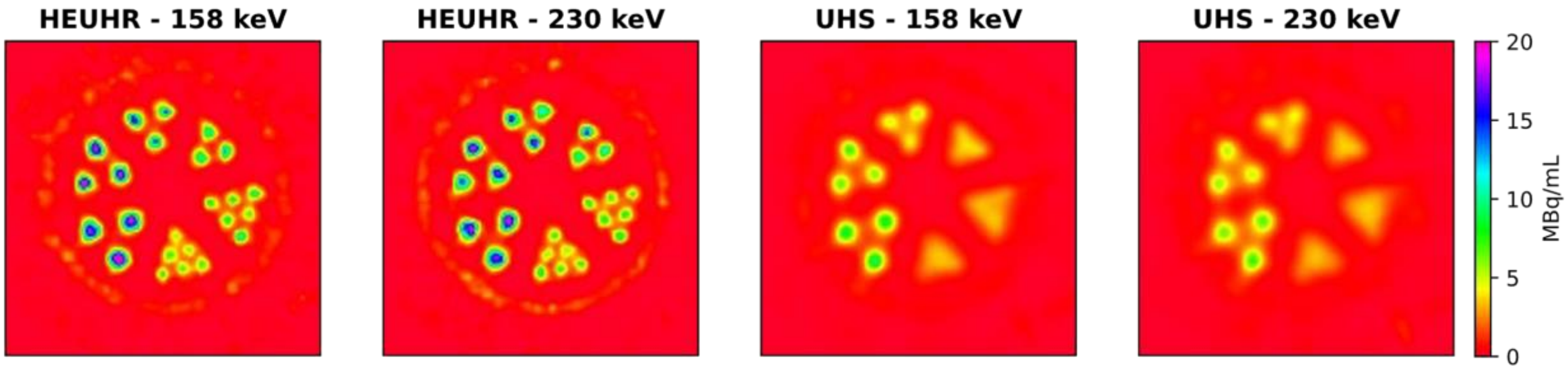


Table: Image contrast and uniformity results, with expected ideal values.

| Collimator | Photopeak energy | Quantitative accuracy | | Contrast recovery | | Uniformity | |
|---|---|---|---|---|---|---|---|
| | | Hot region mean (%) | Warm region mean (%) | Hot-Warm (%) | Warm-Cold (%) | Noise (%) | Background variability (%) |
| HEUHR | 158 keV | 91.7 | 91.6 | 100.1 | 86.5 | 1.7 | 7.1 |
| | 230 keV | 91.9 | 92.4 | 99.3 | 87.9 | 2.8 | 7.9 |
| UHS | 158 keV | 83.3 | 88.2 | 92.9 | 86.1 | 4.4 | 6.4 |
| | 230 keV | 84.5 | 94.4 | 86.6 | 83.7 | 2.5 | 6.3 |
| Ideal | | 100 | 100 | 100 | 100 | 0 | 0 |

# Results: Resolution phantom

## $^{226}Ac$ phantom SPECT imaging

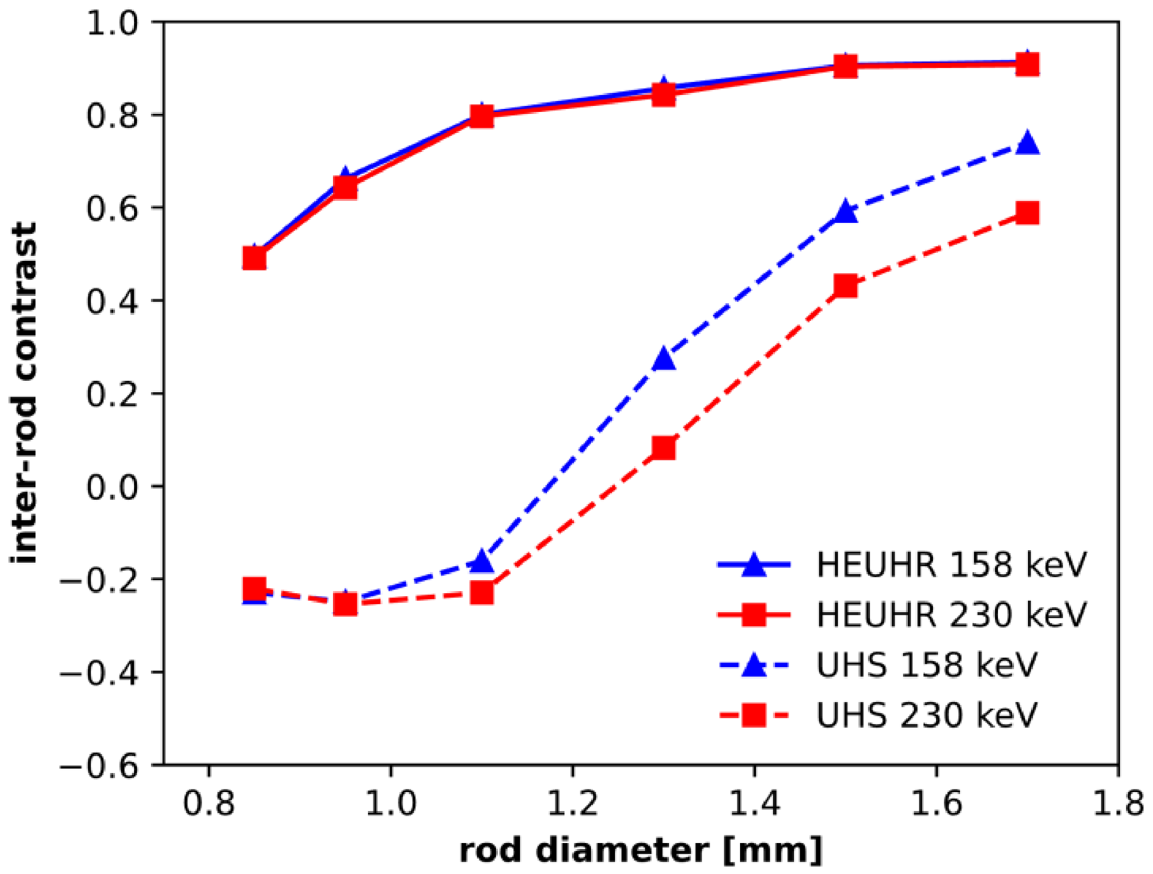



SPECT images of the resolution phantom reconstructed from the 158 keV and 230 keV photopeaks acquired with both the HEUHR and UHS collimators.

# Results: Resolution phantom

## $^{226}Ac$ phantom SPECT imaging






Inter-rod contrast measurements from the SPECT images of the resolution phantom.

Recovery coefficients from the resolution phantom.

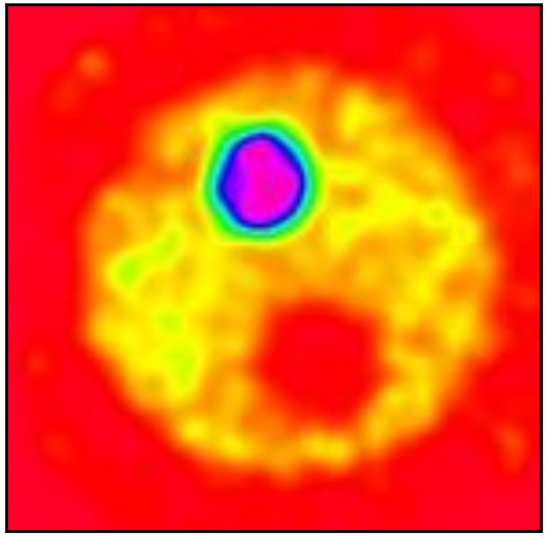
| Collimator | Photopeak energy | Rod diameter (mm) 0.85 | 0.95 | 1.10 | 1.30 | 1.50 | 1.70 |
|---|---|---|---|---|---|---|---|
| HEUHR | 158 keV | 0.34 | 0.43 | 0.56 | 0.64 | 0.80 | 0.82 |
| | 230 keV | 0.34 | 0.41 | 0.55 | 0.65 | 0.76 | 0.81 |
| UHS | 158 keV | – | – | – | 0.31 | 0.44 | 0.55 |
| | 230 keV | – | – | – | – | 0.36 | 0.44 |

# Summary

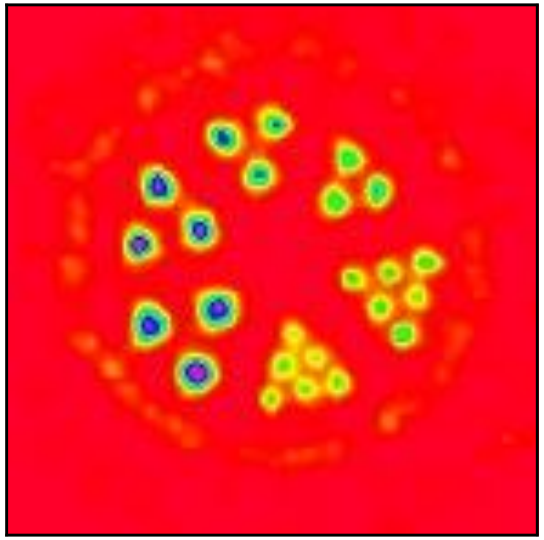
## $^{226}Ac$ phantom SPECT imaging

- HEUHR 158 keV images have the best quantitative accuracy and higher contrast recovery.
- For *in vivo* imaging, high resolvability and quantitative accuracy is important, so the HEUHR collimator is most appropriate.

HEUHR - 158 keV



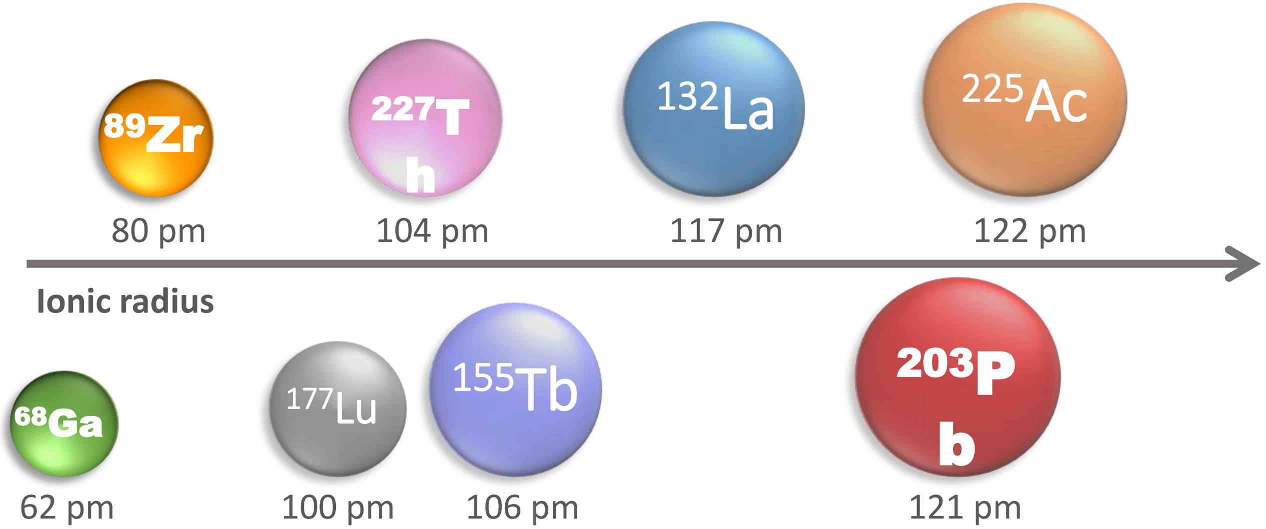
HEUHR - 158 keV

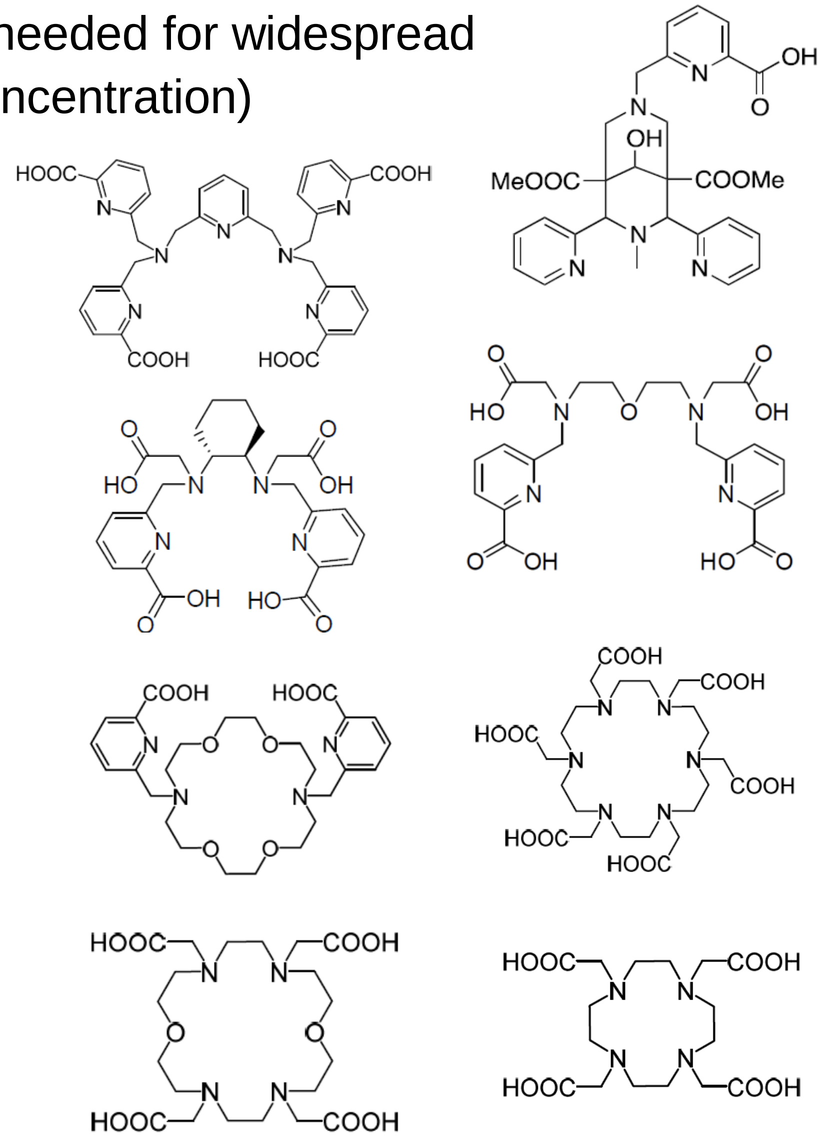


# Chelate and Radiopharmaceutical Development

# Designing chelators capable of binding emerging isotopes of clinical importance

- Commercially-available chelates may not exhibit chemical behaviour needed for widespread use, on-site formulation of radiopharmaceuticals (temperature, pH, concentration)
- High-denticity chelator for large metals
- Understand selectivity for various isotopes
- Enable kit-like formulation
- Enable multi-isotope incorporation (i.e. theranostic applications)

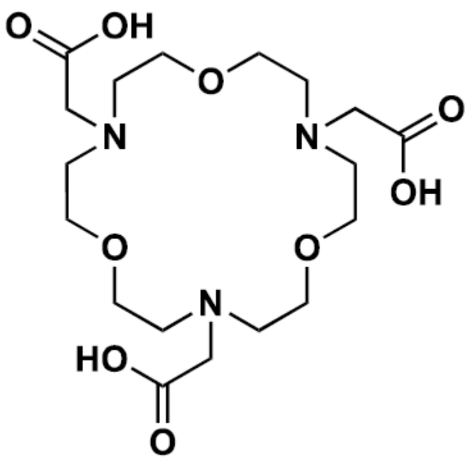


**Yang et al.**, *J. Nucl. Med.* 2022, 63, 5-13

# Designing chelators capable of binding emerging isotopes of clinical importance

**‘Trica’**

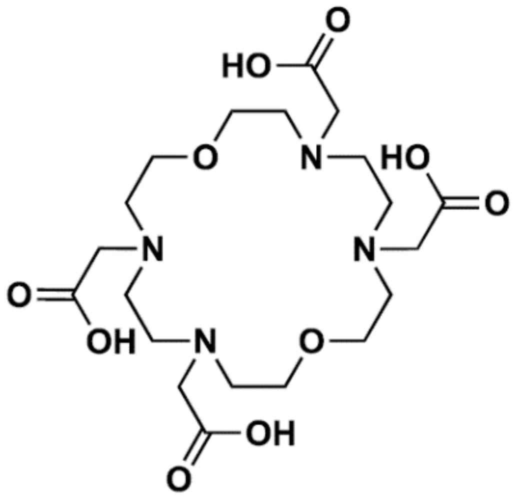



D Fiaccabrino et al. *Inorg. Chem.* **2024**, 63, 13911

**Ideal properties:**

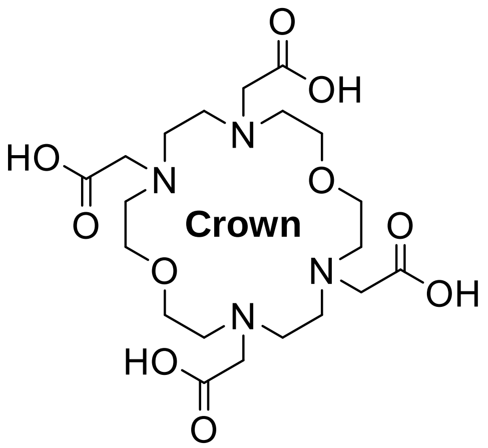
- Fast complexation
- Mild conditions
- Selectivity/versatility
- High thermodynamic stability
- High kinetic inertness
- High molar activity

**‘Crown’**



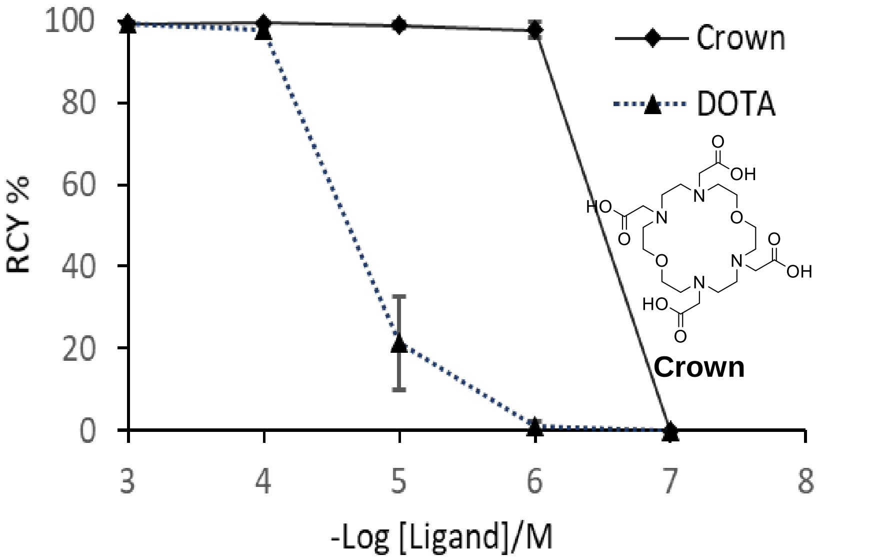

H Yang, et. al. *Chem. Eur. J.* **2020**, 26, 11435

# New chelators for therapeutical isotopes: 'Crown'



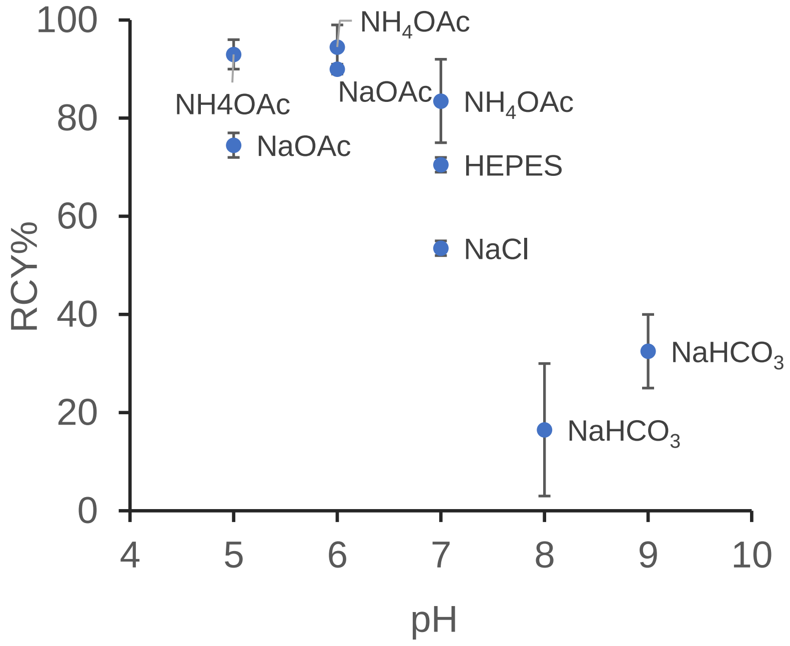

- Crown: a macrocyclic chelate for therapeutic isotopes: $Ac^{3+}$, $Bi^{3+}$, $Lu^{3+}$, $Tb^{3+}$
- Labeling: quantitative, fast, ambient temperature, physiological pH
- Simple, hydrophilic, comparable with DOTA chemistry

$^{225}Ac$ labeling at various ligand concentration
Crown: r.t.; DOTA: 85ºC, 15 min

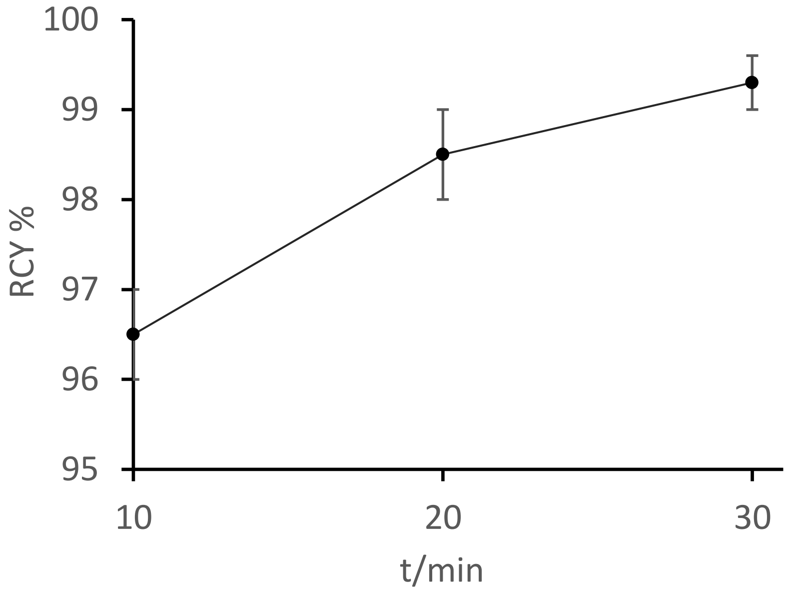



Labels $^{225}Ac$ 100 x more efficient than DOTA

$^{225}Ac$ labeling yield with various buffer and pH



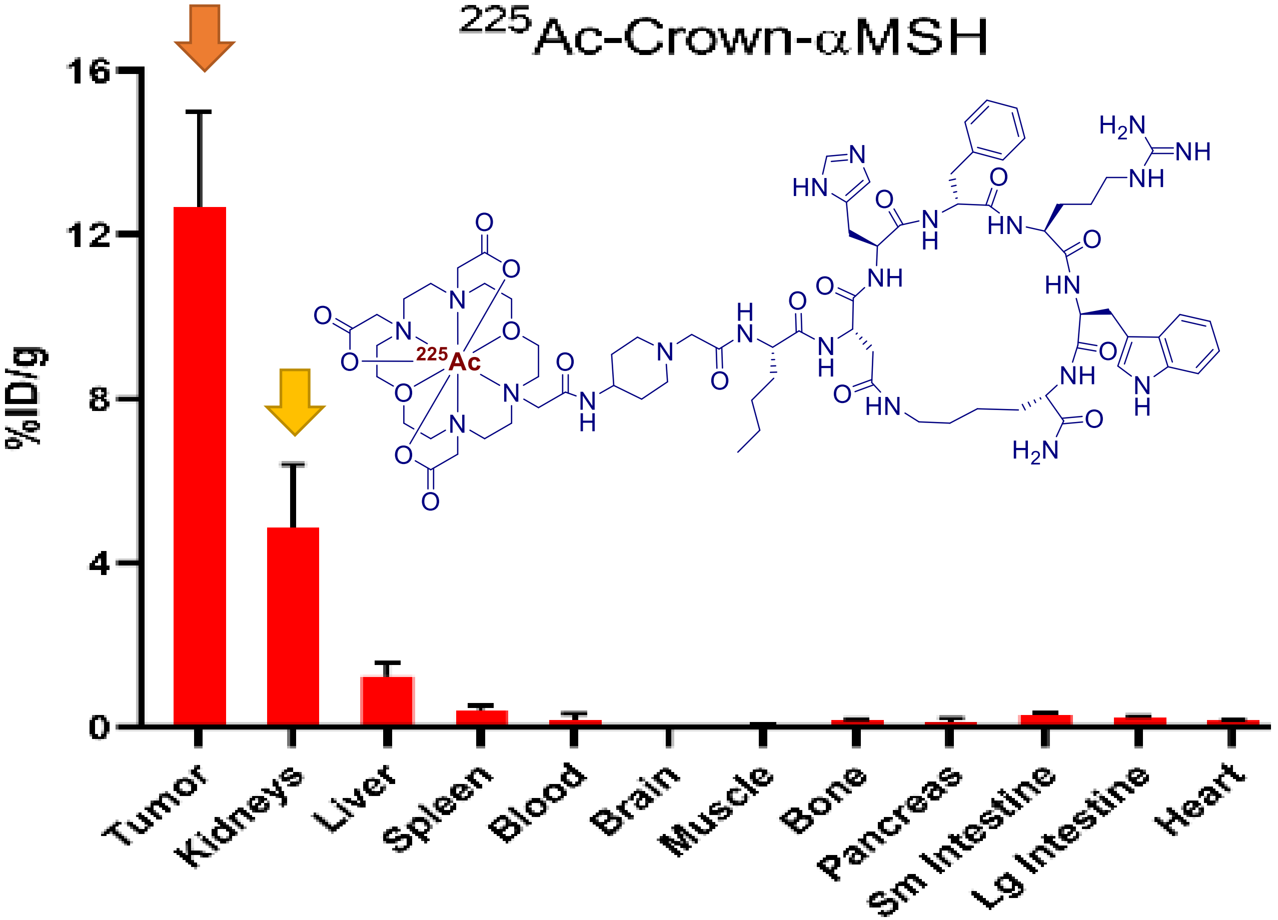

$^{225}Ac$ labeling yield over time



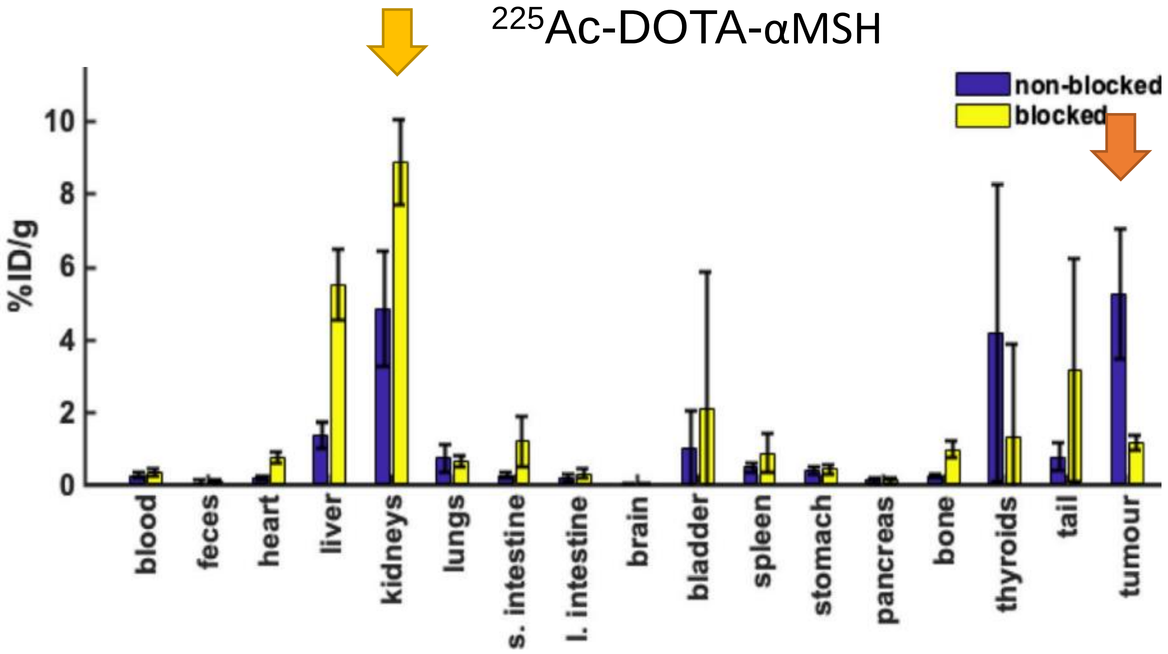

*Slide courtesy of Hua Yang*

Yang, et. al. *Chem. Eur. J.* **2020**, 26, 11435
Wharton, et. al, Molecules, **2023**, 28, 3155

# Radiopharmaceutical development [$^{225}$Ac]crown-αMSH




Crown: improves apparent molar activity
→ less peptide with the same amount of activity, less chance to saturate the receptor.

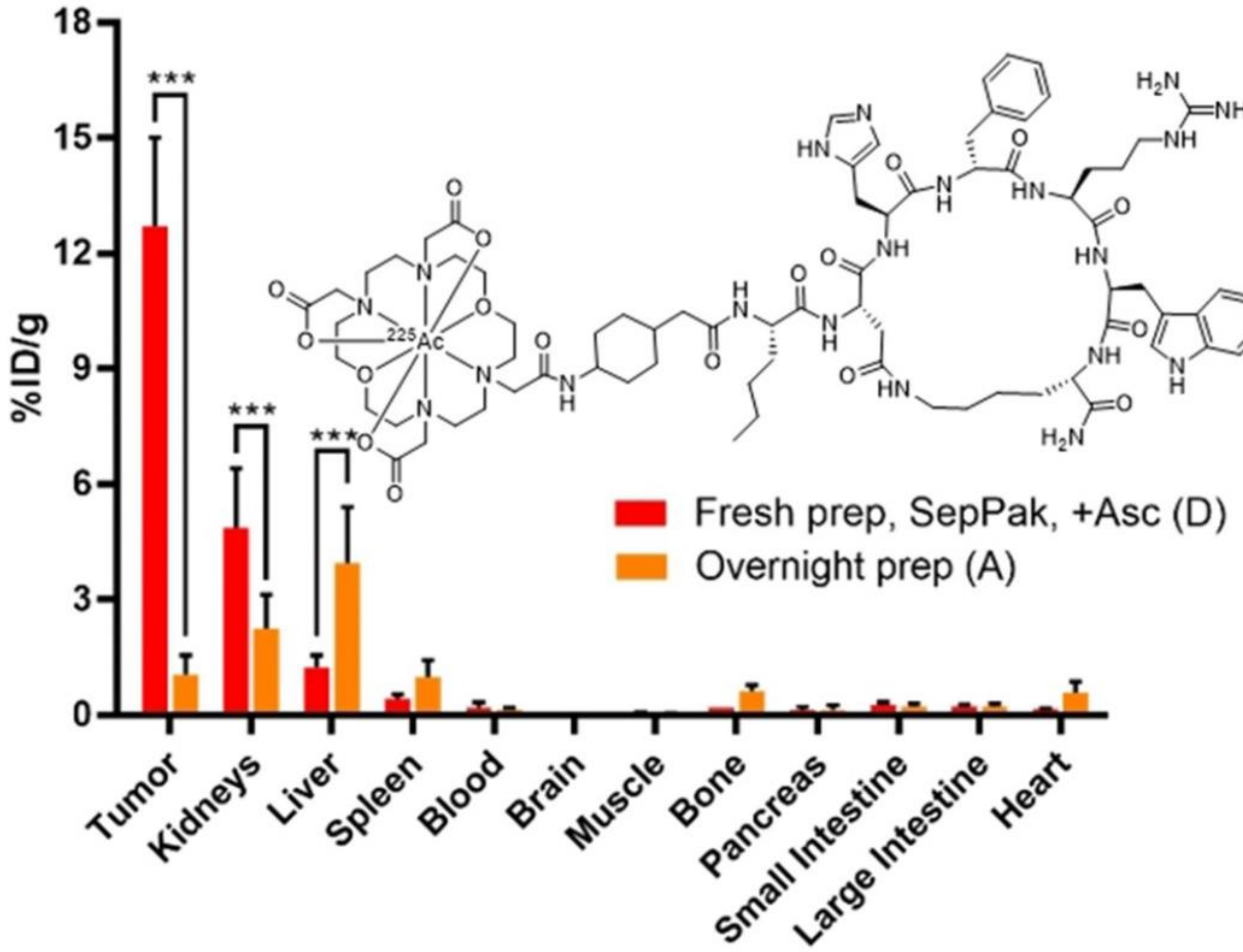


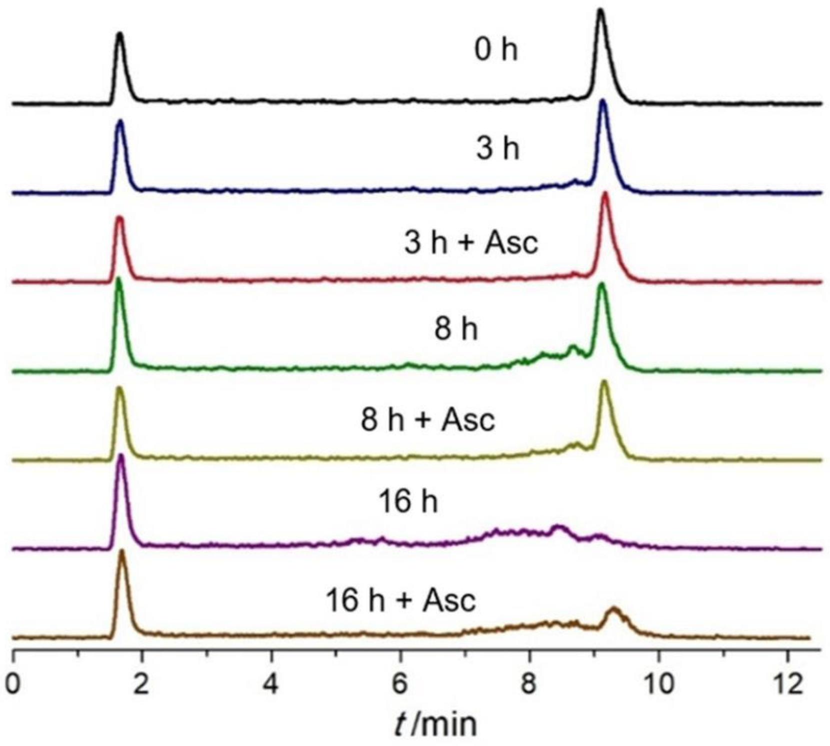

BioD in B16F10 (melanoma tumor bearing mice) at 2-hour post injection

- **MSH derivatives targeting MC1R are highly promising for therapy and imaging in melanoma**
- **$^{225}$Ac-crown-aMSH showed high tumor accumulation and low uptake in healthy organs and tissues (low toxicity)**

*Slide courtesy of Hua Yang*

# [$^{225}$Ac]crown-αMSH chelate and compound stability



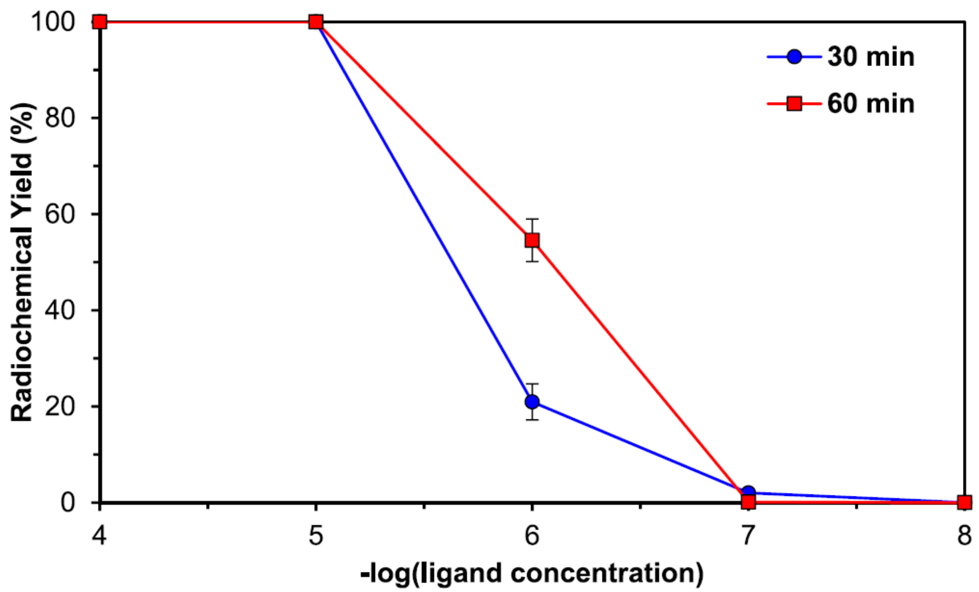

- Several targeted radiopharmaceutical preclinical studies underway

CF Ramogida et al. *EJNMMI Radiopharm. & Chem.*, 2019, 4, 21

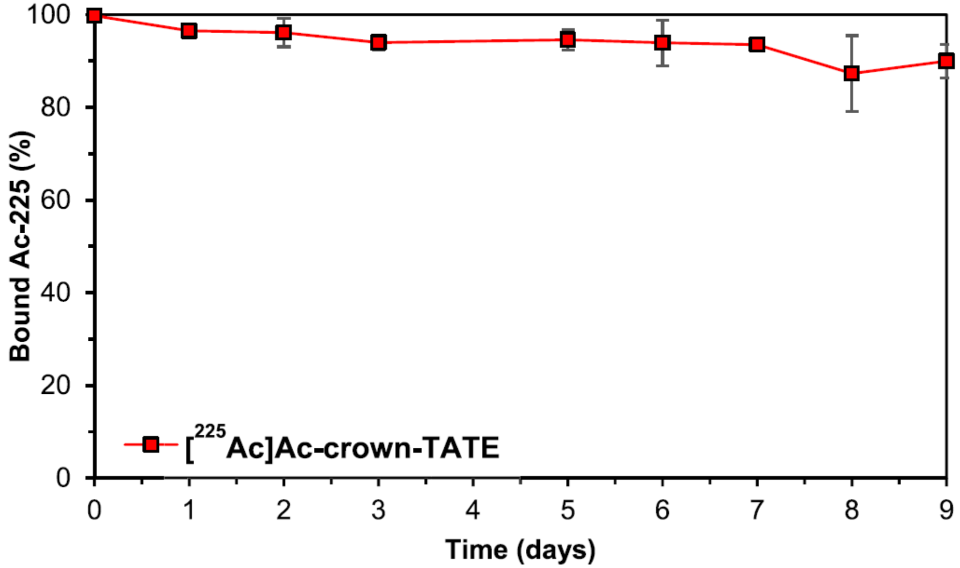
# [$^{225}$Ac]Ac-crown-TATE

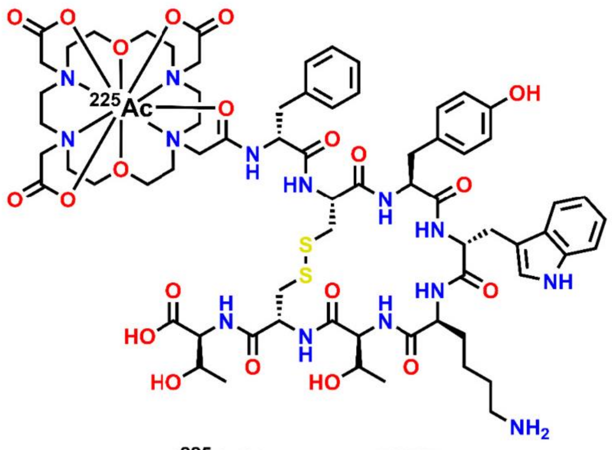


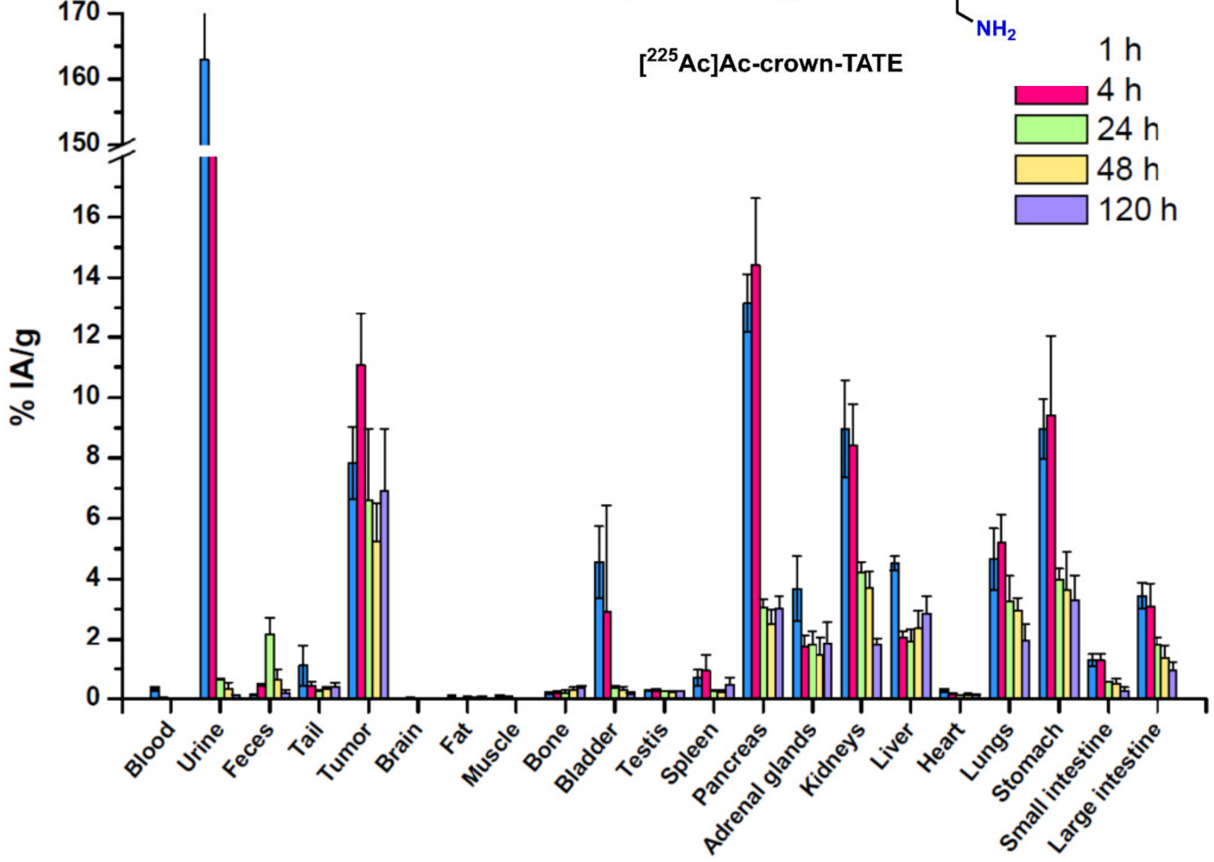
Radiolabeling of crown-TATE in $NH_4OAc$ buffer (pH 7), (23◦C)




Stability of crown-TATE in human serum, 37◦C (n = 2)



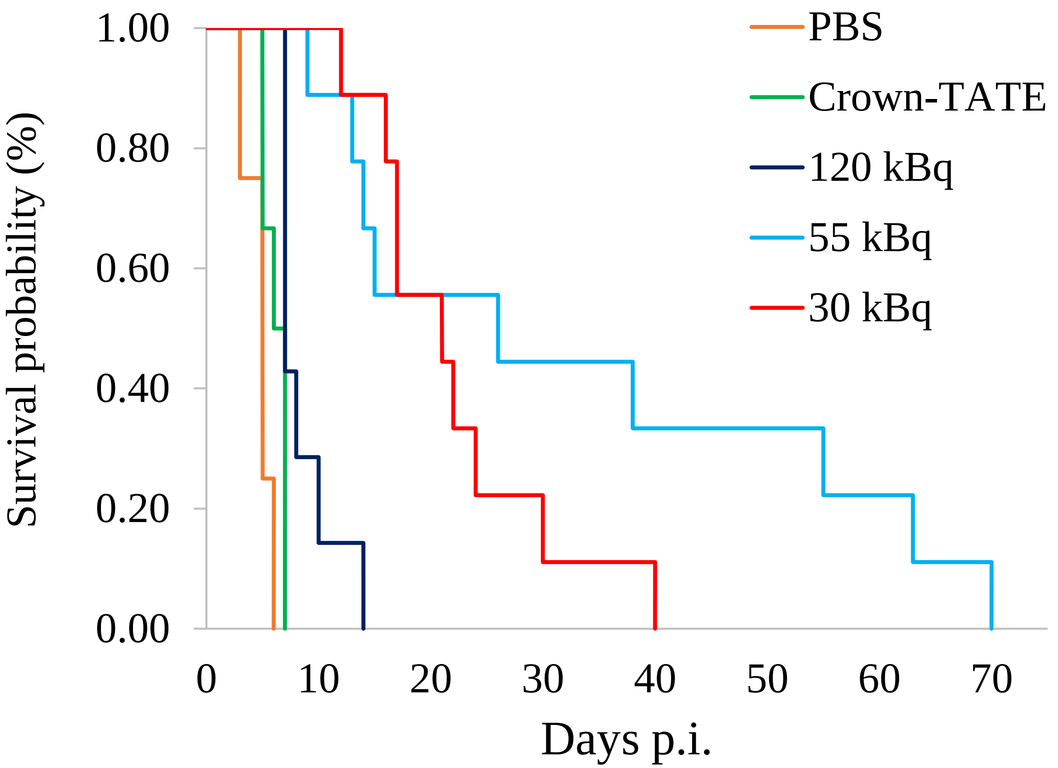




A Ingham et al. 2024 *Nuc. Med. Biol.* 2024, 138-139, 108944

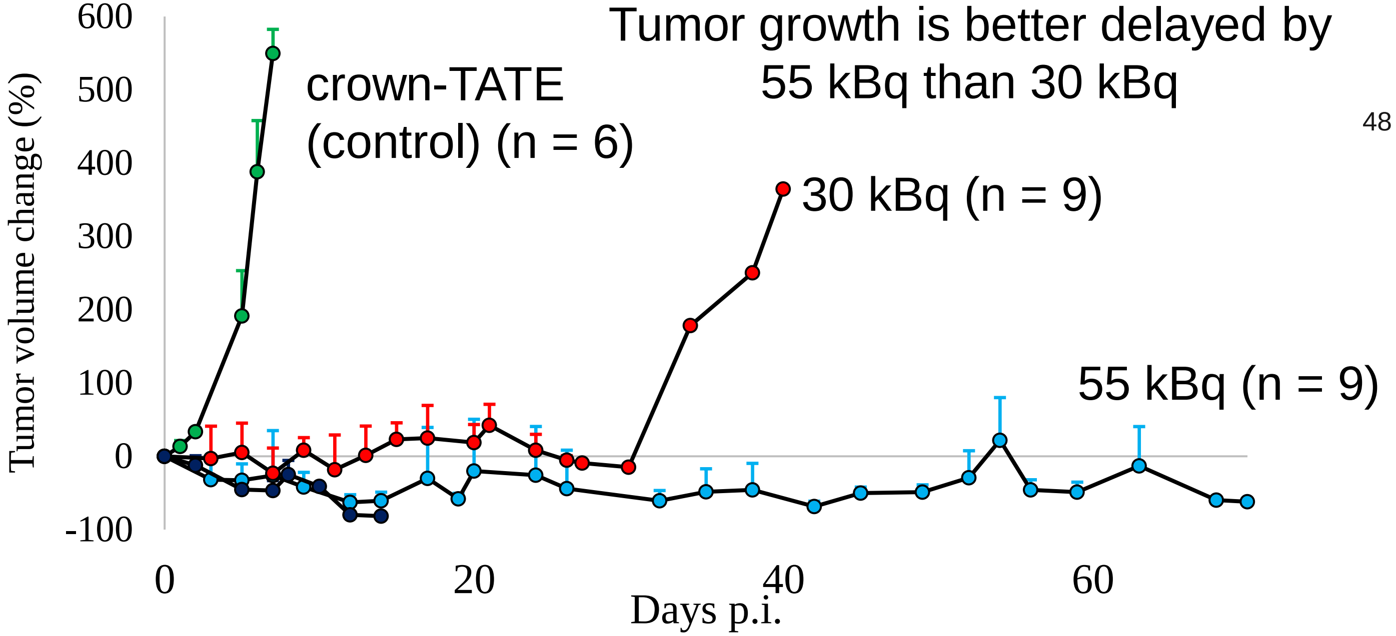
# [$^{225}$Ac]Ac-crown-TATE animal studies

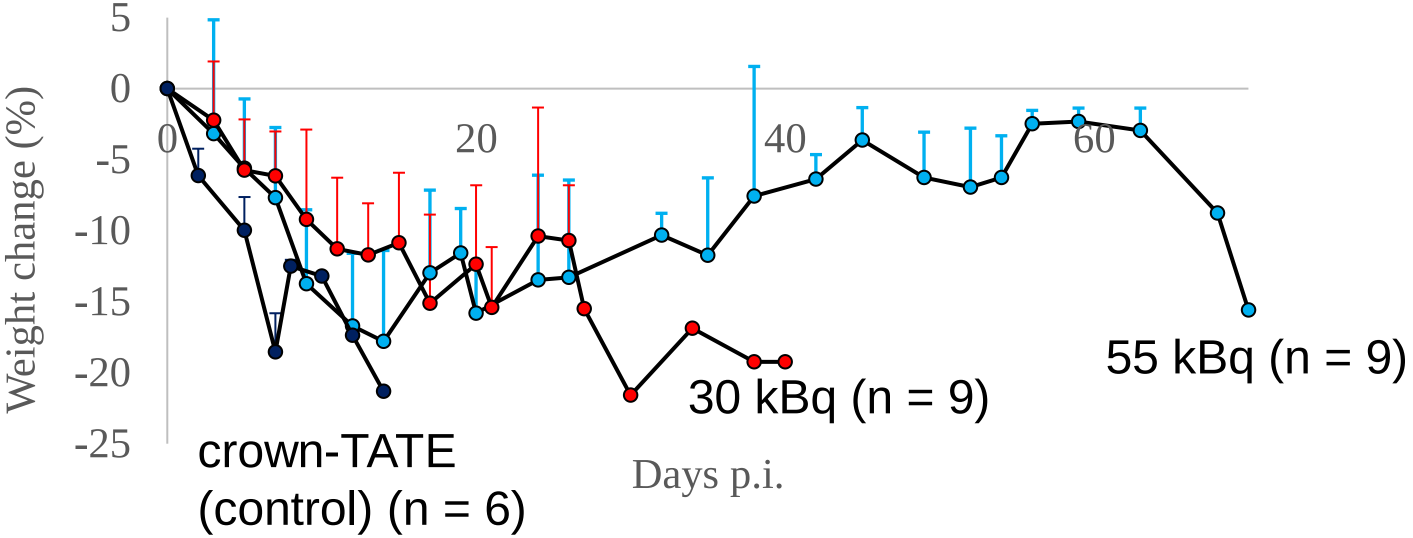





AR42J tumour bearing mice treated with 30 or 55 kBq of [$^{225}$Ac]Ac-crown-TATE survived longer

Tumor growth is better delayed by 55 kBq than 30 kBq

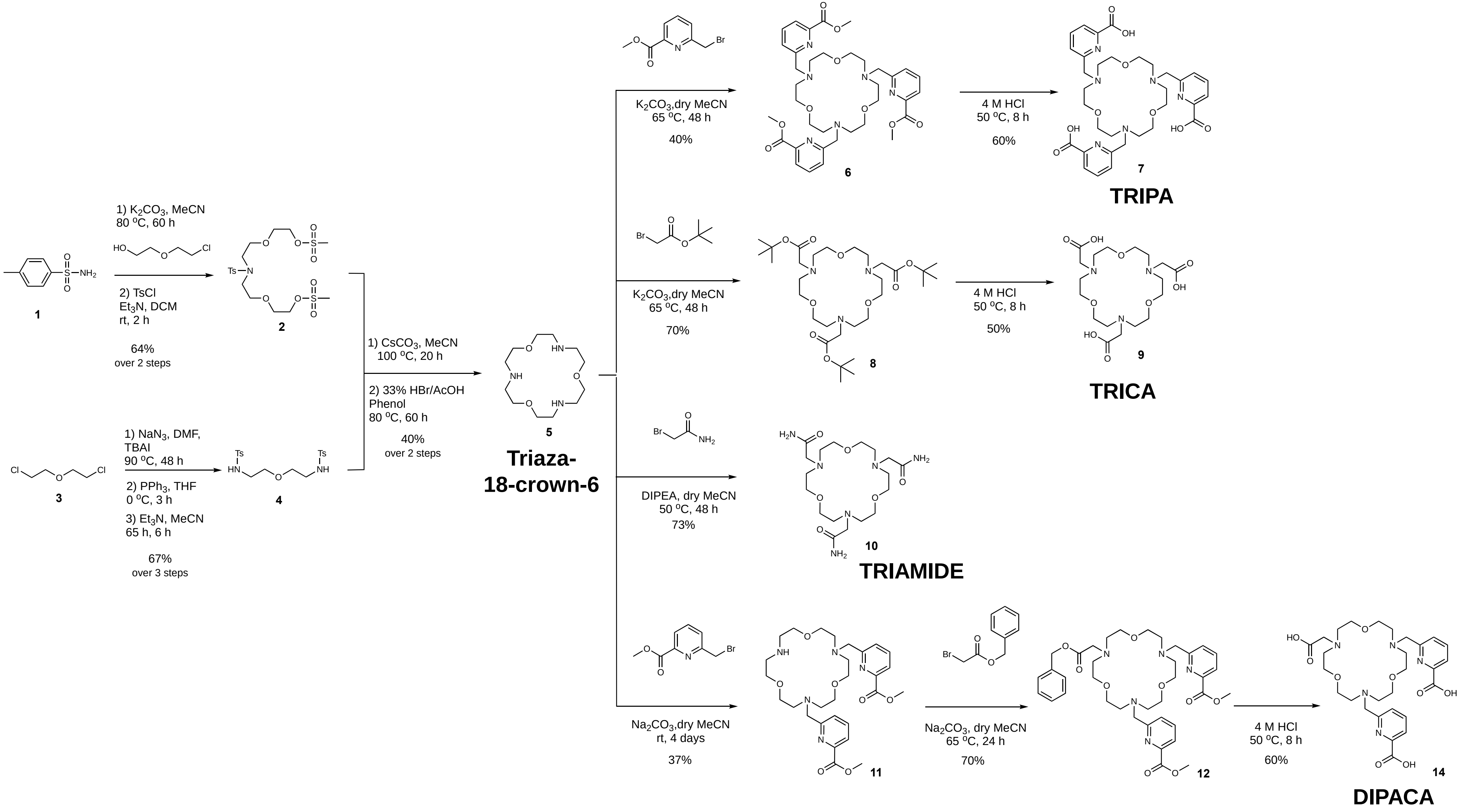



A Ingham et al. 2024 *Nuc. Med. Biol.* 2024, 138-139, 108944

# Synthesis: Triaza-18-crown-6 Based Chelators

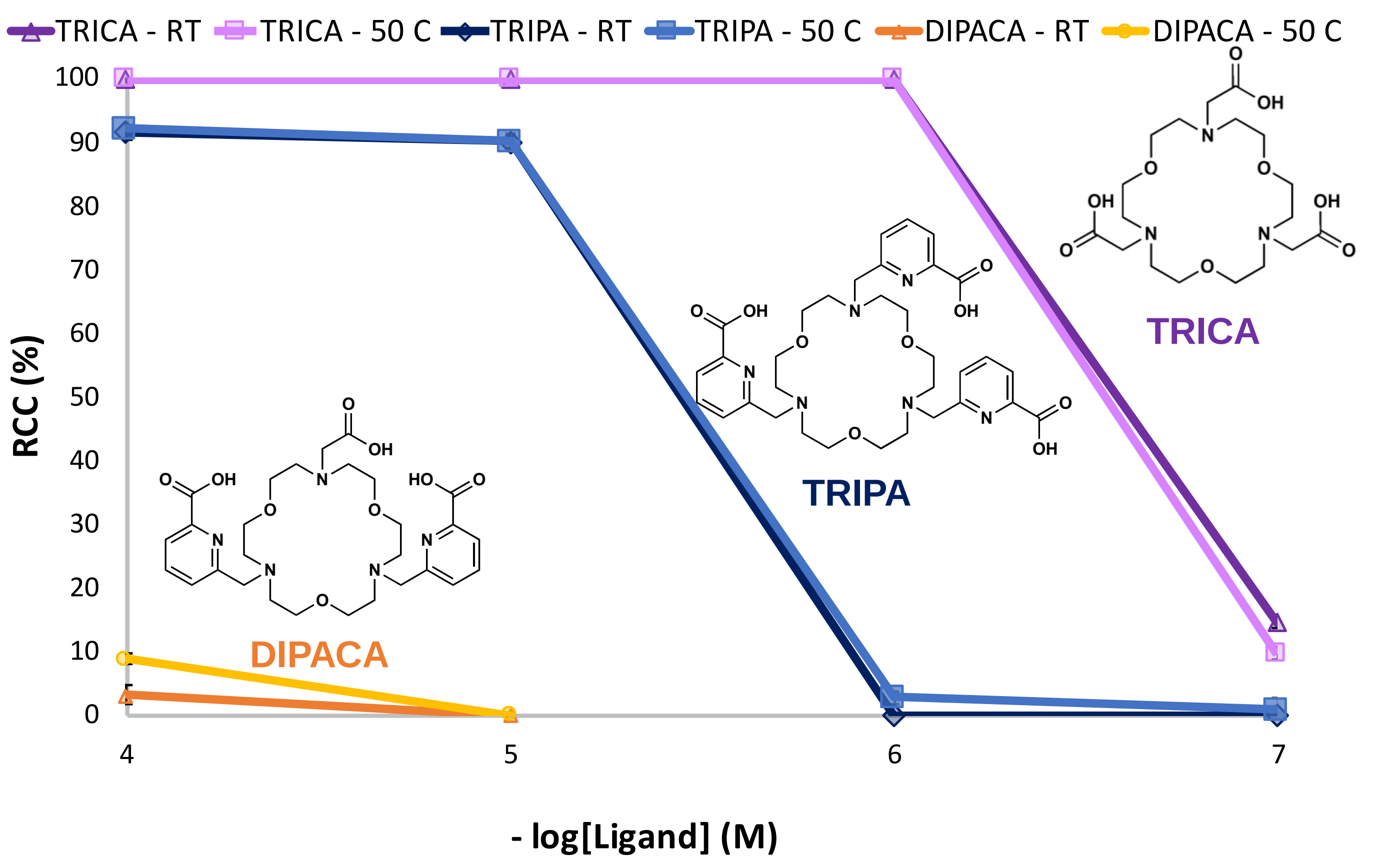




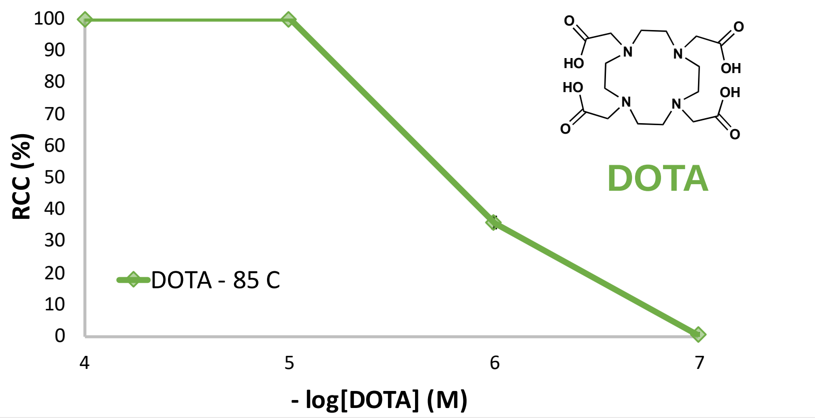

Griffin, J. L. W.*; et al. Inorg. Chem.* **1990**, *29*, 4366–4368
Wharton, L.; *et al. Inorg. Chem*. **2021**, *60*, 4076–4092

# Triaza-18-crown-6 chelators and $[^{225}Ac]Ac^{3+}$ (α therapy)

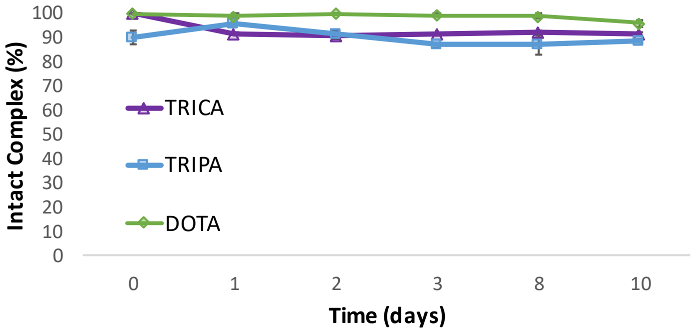
**A** **Concentration-dependent studies of TRICA, TRIPA and DIPACA at RT and 50 ºC**




**B** **$[^{225}Ac]$AcDOTA concentration-dependent at 85 ºC**




**C** **Human Serum Assay**




***Reaction conditions:***

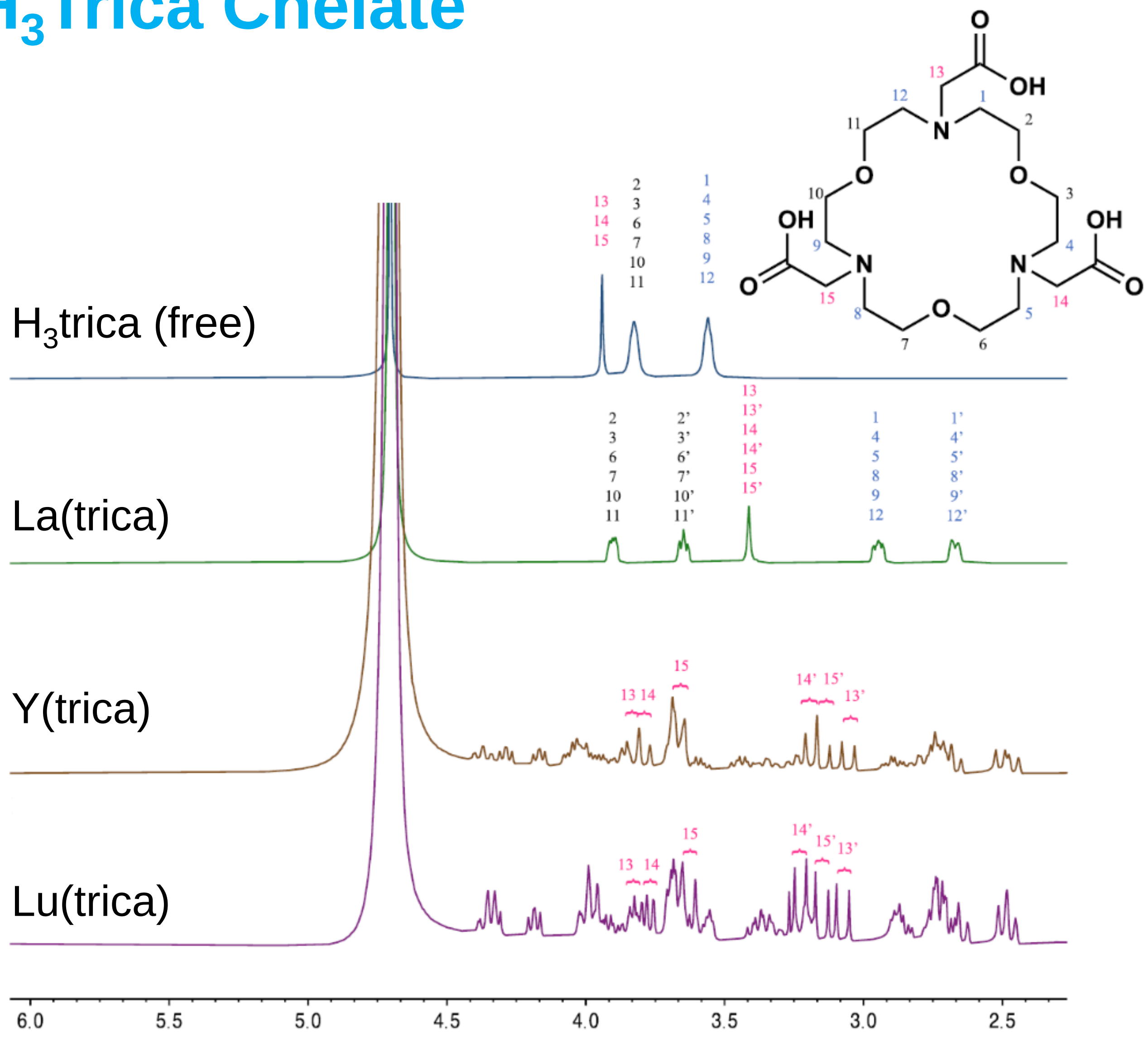
Concentration-dependent radiolabeling studies: $[^{225}Ac]Ac(NO_3)_3$ (50 kBq) in 0.5 $NH_4OAc$, pH 7, 30 minutes (n = 2).

Human serum stability studies: $[^{225}Ac]Ac(NO_3)_3$ (80 kBq) in 0.5 $NH_4OAc$, pH 7 (n = 2), incubation at 37 ºC for 10 days.

*TLC conditions:* instant thin-layer chromatography (iTLC) with silicic acid (SA)-impregnated paper TLC plates, using EDTA (50 mM, pH 5.5) as eluent.

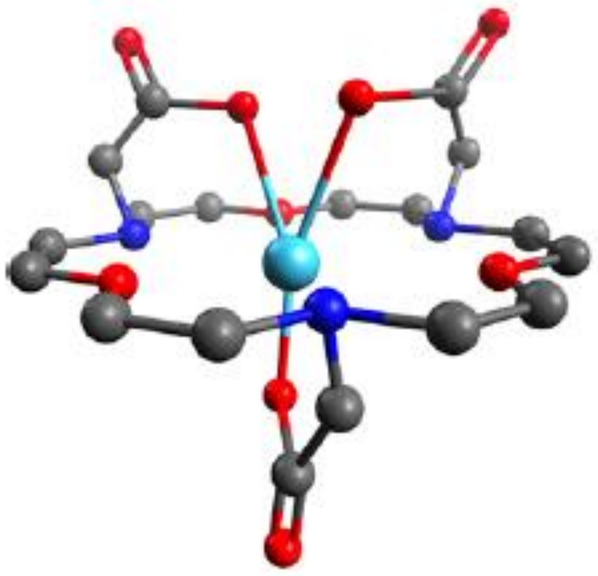
Discovery, accelerated

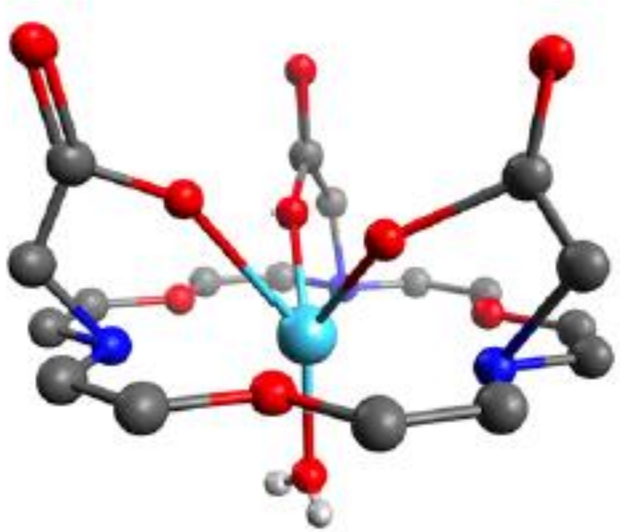
# $H_3$Trica Chelate




$^1$H NMR spectra (400 MHz, D2O, 298 K, pD 7)

## Conformation 'A'





## Conformation 'B'

D Fiaccabrino et al. Inorg. Chem. 2024; 63, 13911

# Shifting to $^{226}$Ac via ISOL



## $^{226}$Ac *in vivo* SPECT imaging

- 2 male NRG mice with AR42J tumour xenografts were injected with 2 MBq $^{226}$Ac-crown-TATE or 4 MBq of free $^{226}$Ac
- Assess the accuracy of activity quantifications from SPECT images with *ex vivo* biodistribution measurements
- Mice were sacrificed at 24 hpost injection for activity measurements

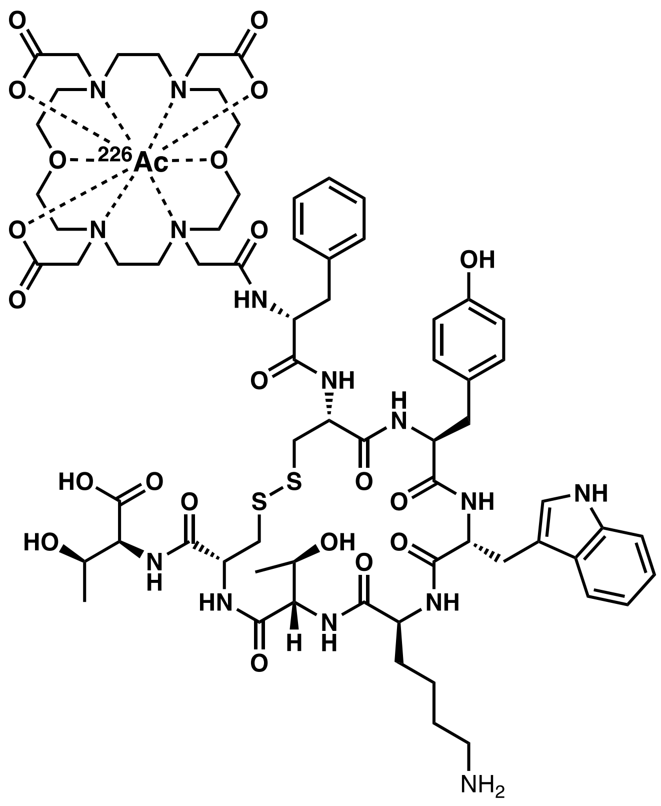


Figure 4.1: Chemical structure of [$^{226}$Ac]Ac-crown-TATE.

Koniar, et al. 2024 *J. Nucl. Med.* accepted

# Methods: Image reconstruction

## $^{226}$Ac *in vivo* SPECT imaging



- SPECT images were reconstructed from 158 keV, 230 keV, and dual photopeaks
- SPECT images made quantitative with scatter, background, and attenuation corrections
- Calibration factors determined with point source with known activity concentration

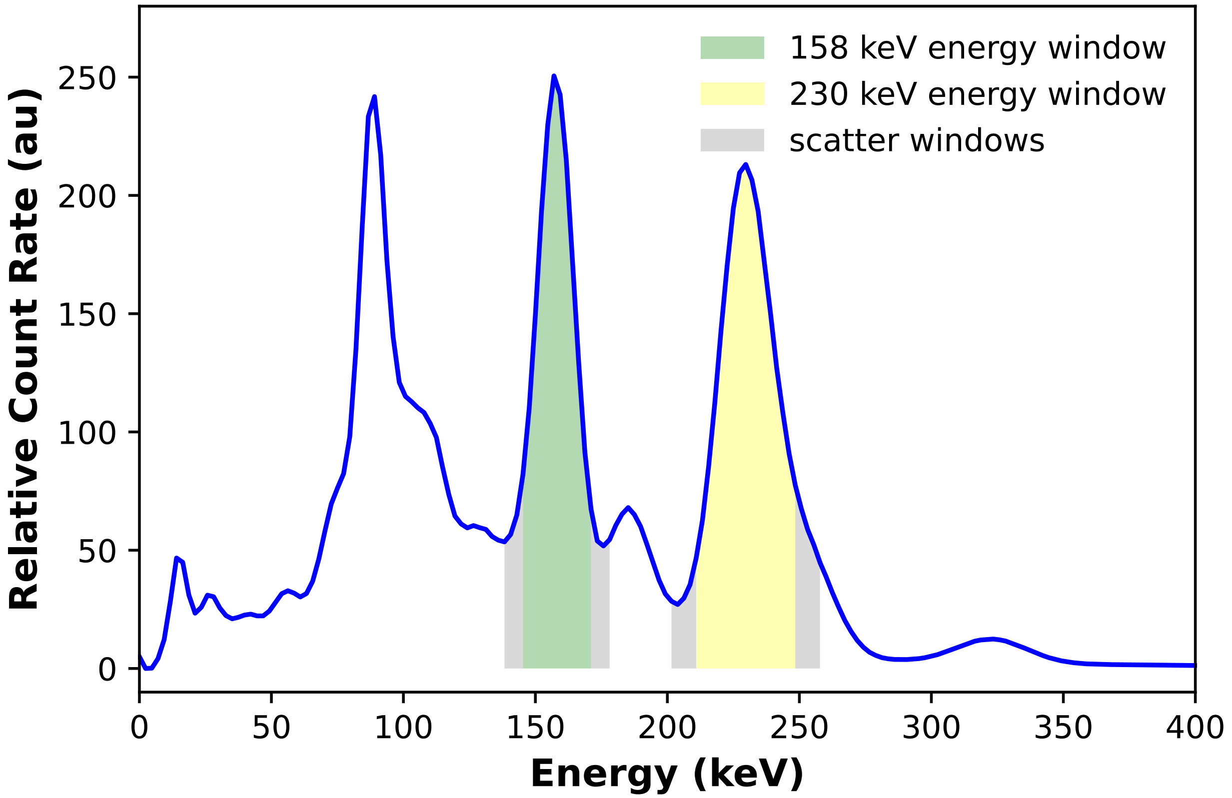


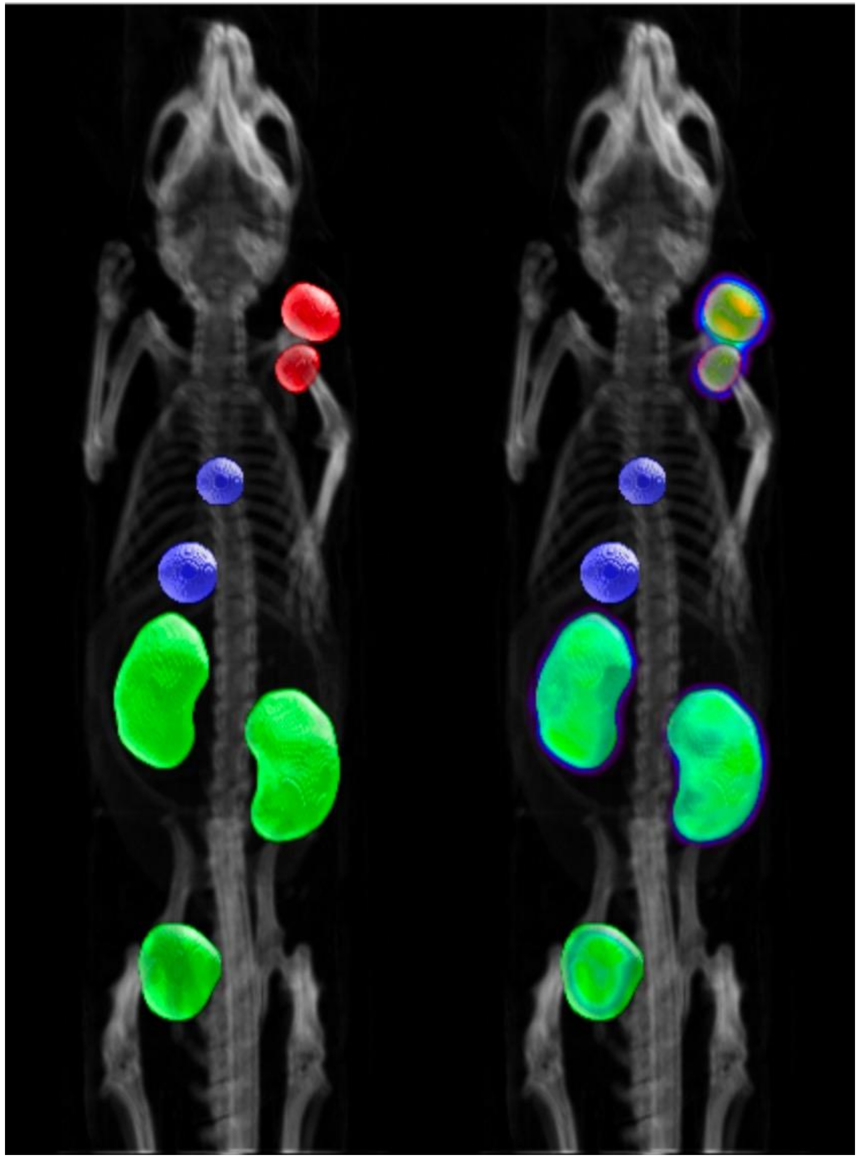

Figure 4.2: Energy spectrum from counts binned during $^{226}$Ac SPECT scan.

Koniar, et al. 2024 *J. Nucl. Med.* accepted

# **Methods:** Image analysis

## $^{226}$Ac *in vivo* SPECT imaging

- *In vivo* measurements of activity taken directly from quantitative SPECT images
- VOIs are defined in the tumour, kidneys, bladder, liver and heart
- Converted the mean VOI voxel value in quantitative SPECT images to activity concentration (MBq/mL) and %IA/g



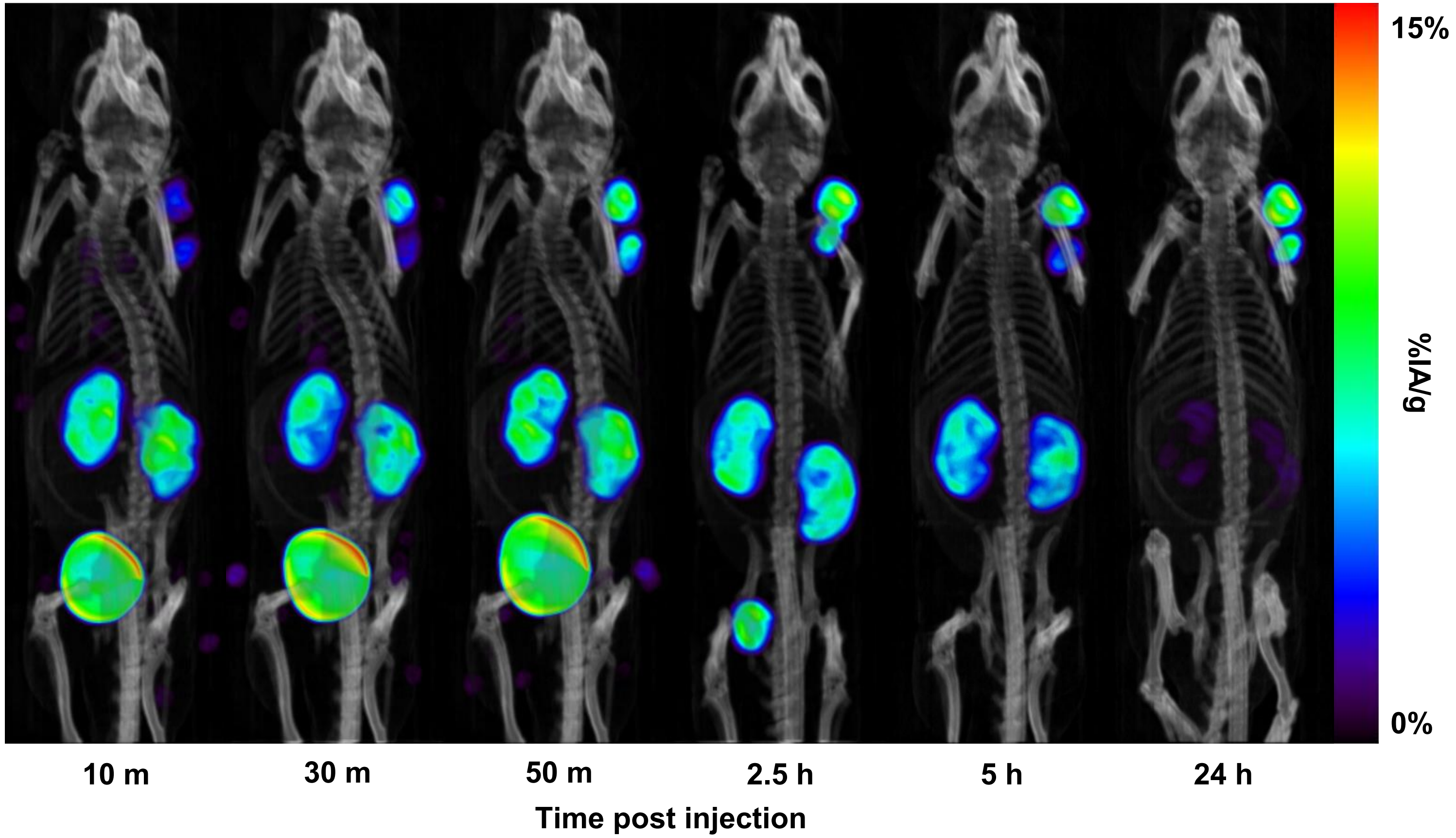
Examples of VOIs drawn on SPECT/CT scans of AR42J tumour bearing mice

Koniar, et al. 2024 *J. Nucl. Med.* accepted

# **Results:** *In vivo* quantitative SPECT imaging

## $^{226}$Ac *in vivo* SPECT imaging



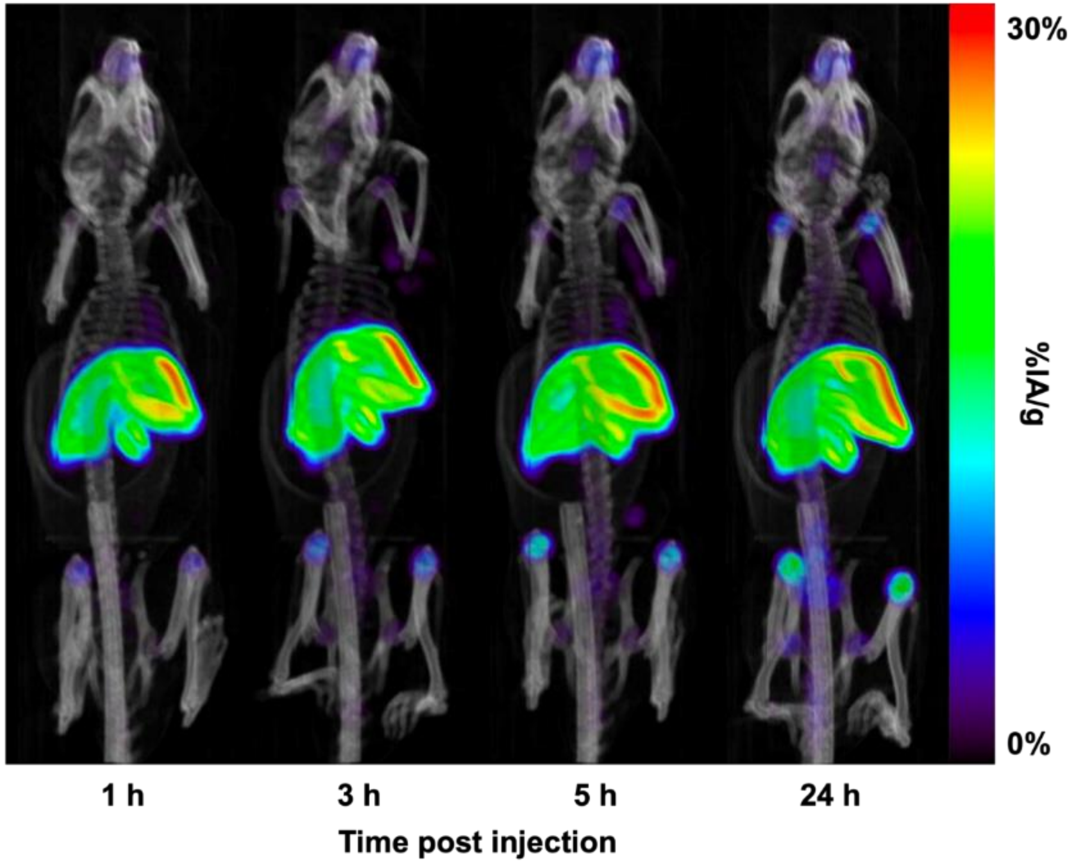



SPECT/CT MIP of NRG mice with AR42J tumour xenograft injected with 1.96 ± 0.15 MBq of [$^{226}$Ac]Ac-crown-TATE. SPECT images were reconstructed with dual energy photopeaks. A 2 mm FWHM gaussian filter was applied post-reconstruction.

# Results: *In vivo* quantitative SPECT imaging



## $^{226}$Ac *in vivo* SPECT imaging

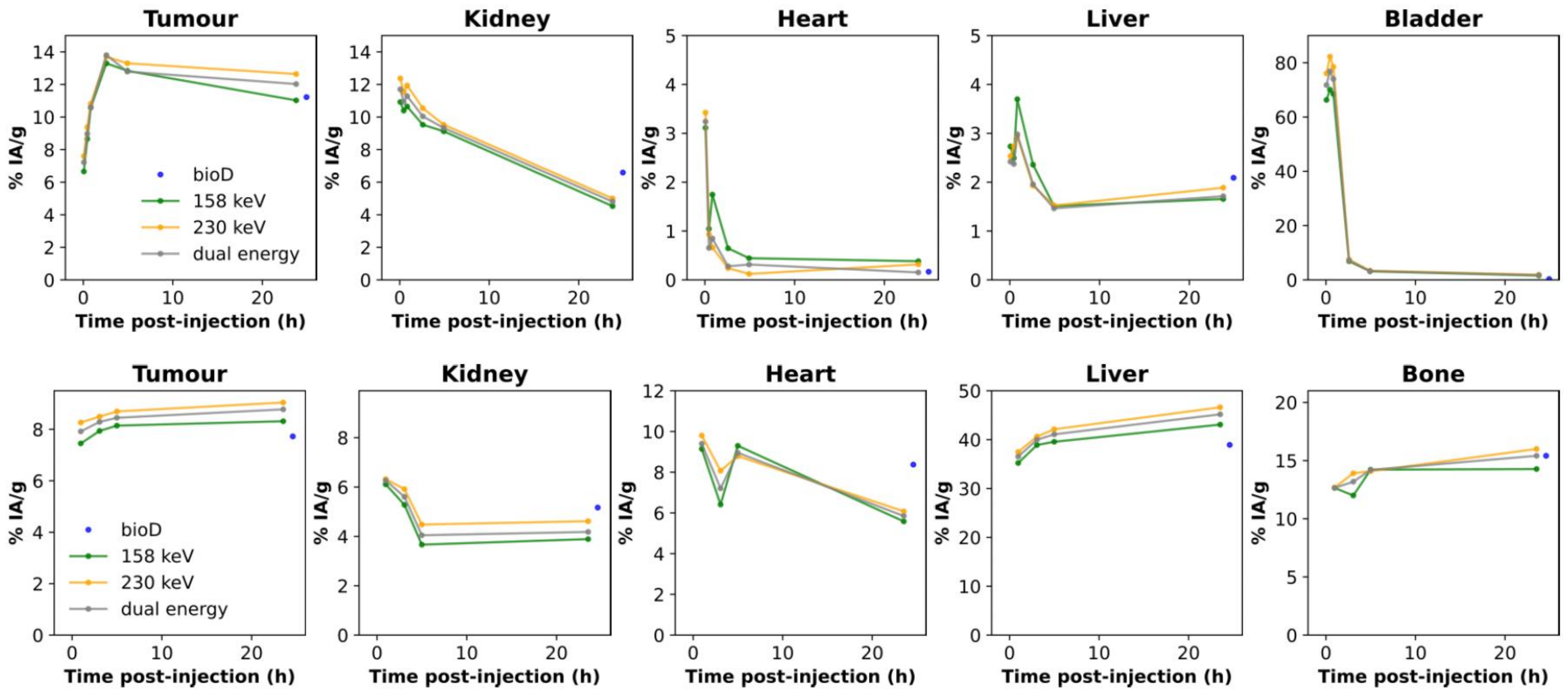



SPECT/CT MIP of NRG mice with AR42J tumour xenograft injected with 4.32 ± 0.35 MBq of free [$^{226}$Ac]$Ac^{3+}$. SPECT images were reconstructed with dual energy photopeaks. A 2 mm FWHM gaussian filter was applied post-reconstruction.

# **Results:** Time activity curves



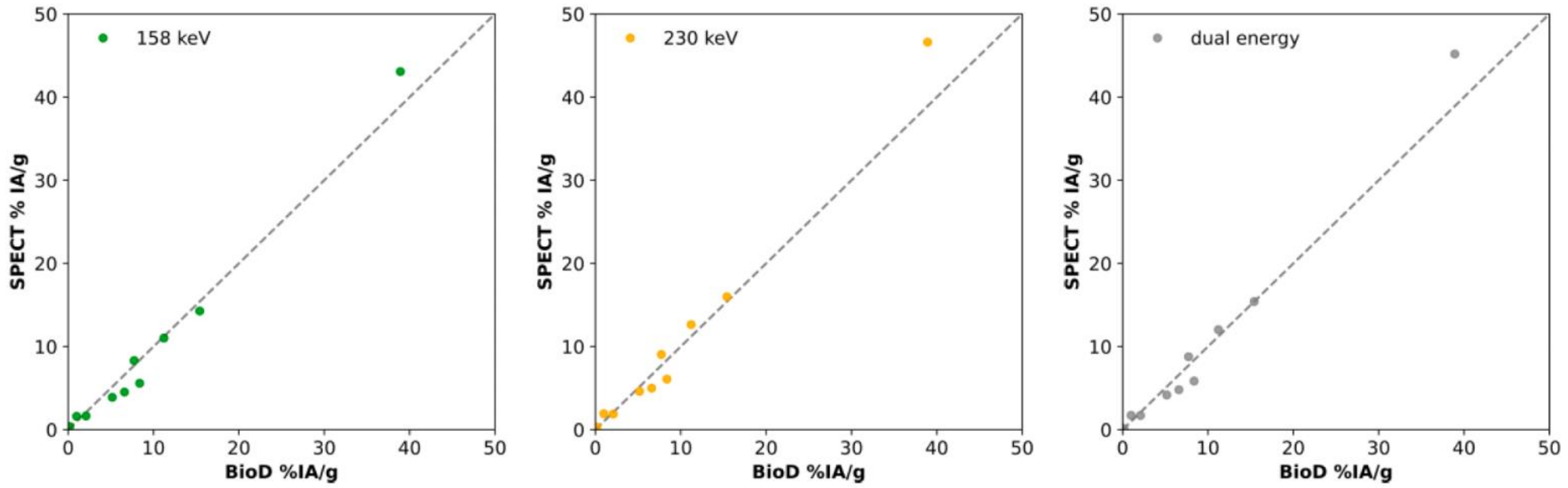
## $^{226}$Ac *in vivo* SPECT imaging




Decay-corrected time activity curves from in vivo SPECT images in select organs of interest in AR42J tumour bearing NRG mice injected with [$^{226}$Ac]Ac-crown-TATE (top) and free [$^{226}$Ac]$Ac^{3+}$ (bottom). *Ex vivo* biodistribution data are shown in blue.

# **Results:** Correlation between *in vivo* and *ex vivo*

## $^{226}$Ac *in vivo* SPECT imaging



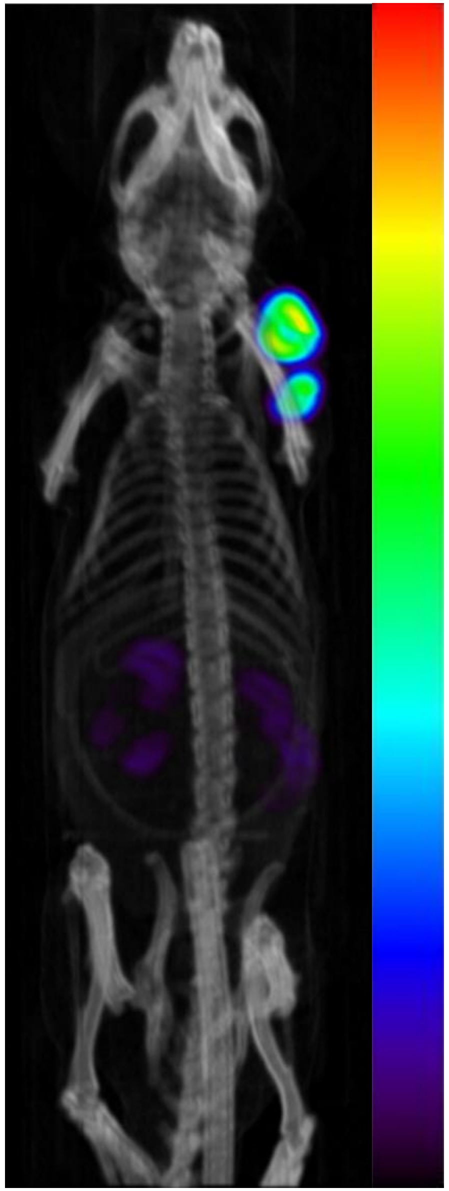

*In vivo* SPECT data at 24 h post injection plotted against *ex vivo* biodistribution data (BioD) collected immediately following scan. Dashed line represents the line of identity.

# Summary

## $^{226}Ac$ *in vivo* SPECT imaging



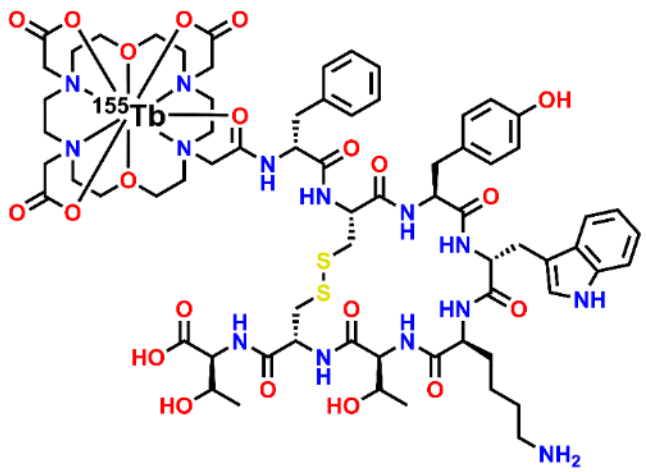
- First *in vivo* quantitative SPECT images of $^{226}Ac$
- Validates theranostic potential of $^{226}Ac$ SPECT imaging
- Future work will evaluate pharmacokinetics of matched $^{225}Ac/^{226}Ac$ preclinical radiopharmaceuticals
- Demonstrates personalized dosimetry can start at preclinical stages




Koniar, et al. 2024 *J. Nucl. Med.* accepted

# A Brief Mention: [$^{155}$Tb]Tb-crown-TATE animal studies

- [$^{155}$Tb]Tb-crown-TATE was prepared with high molar activity and radiochemical purity.




[$^{155}$Tb]Tb-crown-TATE

- Radiolabeling conditions:
  - 37 $^{o}$C, 30 min, $NH_4OAc$ (0.5 M, pH 6.0)
- Molar activity: 9.74 MBq/nmol
- Administered dose: 330 kBq/animal

- NRG mice bearing AR42J tumours were administered with [$^{155}$Tb]Tb-crown-TATE.

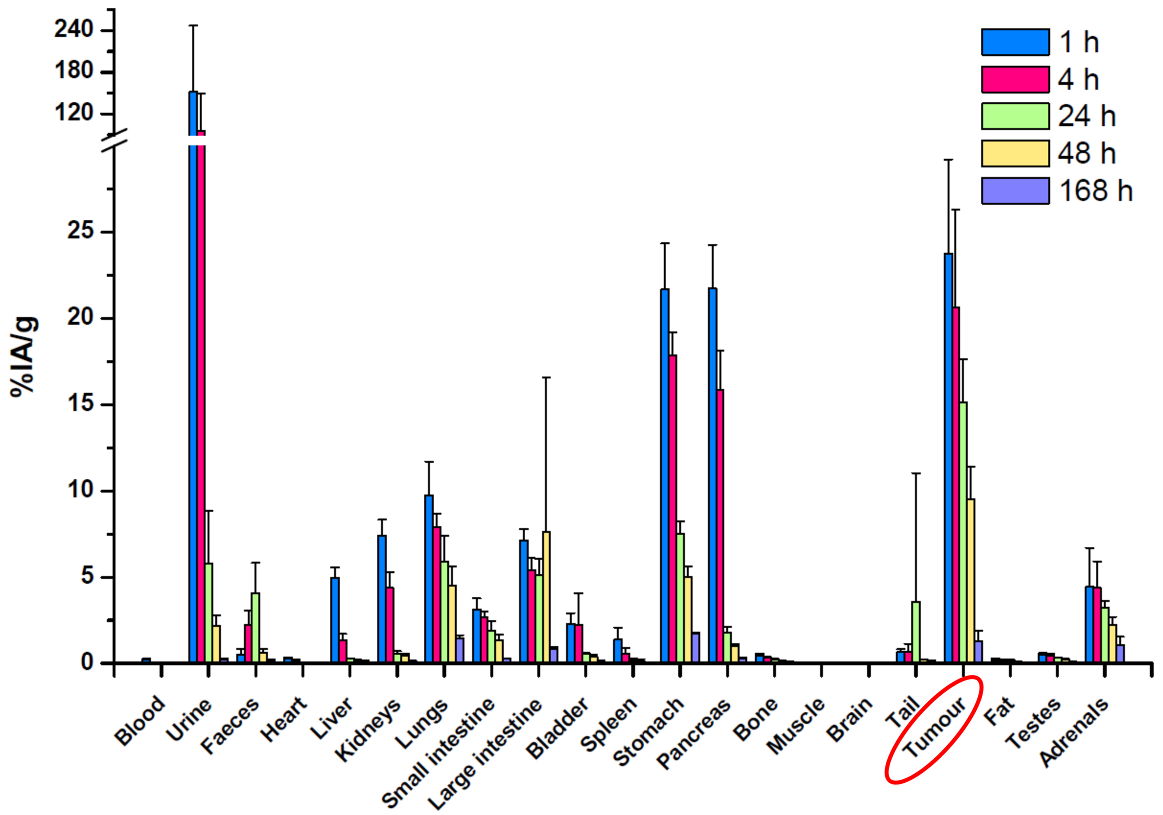
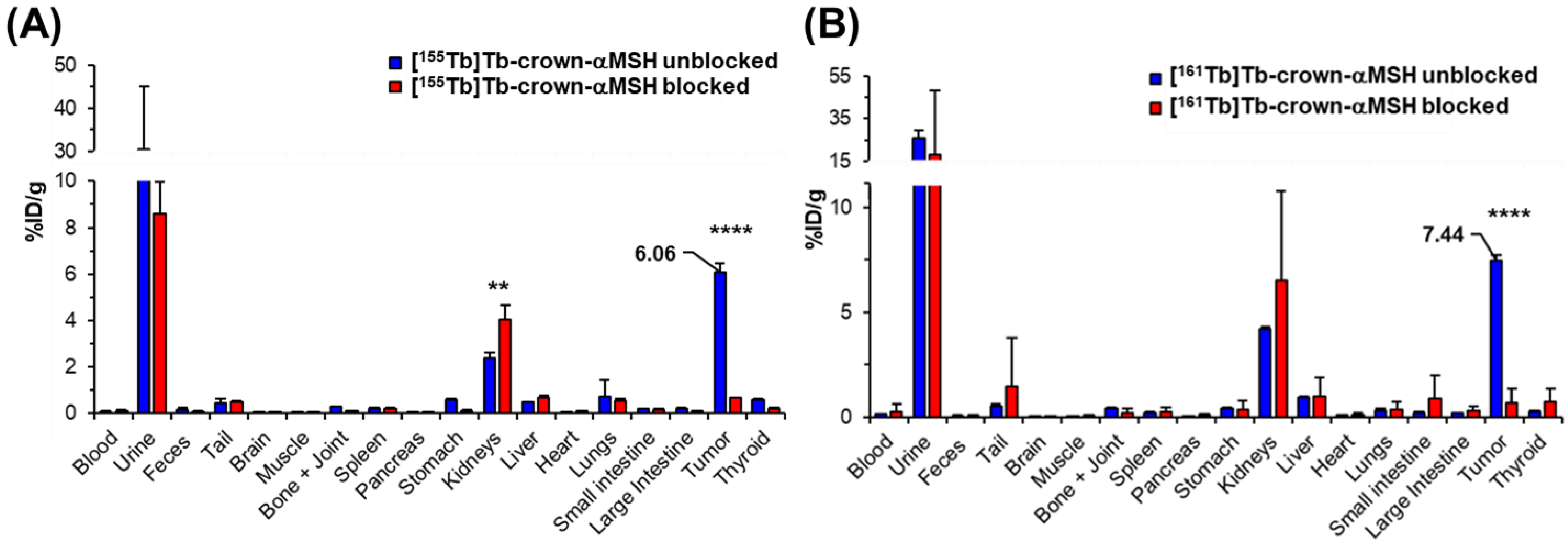



**Figure 1.** Biodistribution study of [$^{155}$Tb]Tb-crown-TATE (9.74 MBq/nmol) in male NRG mice bearing AR42J tumours, measured at 1, 4, 24, 48, and 168 h post-administration. Injected dose = 330.9±16.1 kBq/animal (34 pmol/animal), n=5 per group.

**Credits to: Hua Yang, Luke Wharton, Diduo Zhang. Maryam Osooly, Cristina Rodríguez-Rodríguez**

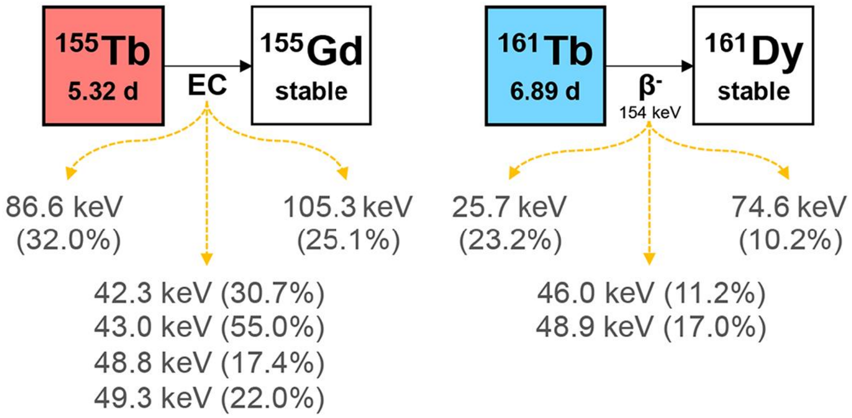
# Biodistribution of [$^{155/161}$Tb]Tb-crown-αMSH

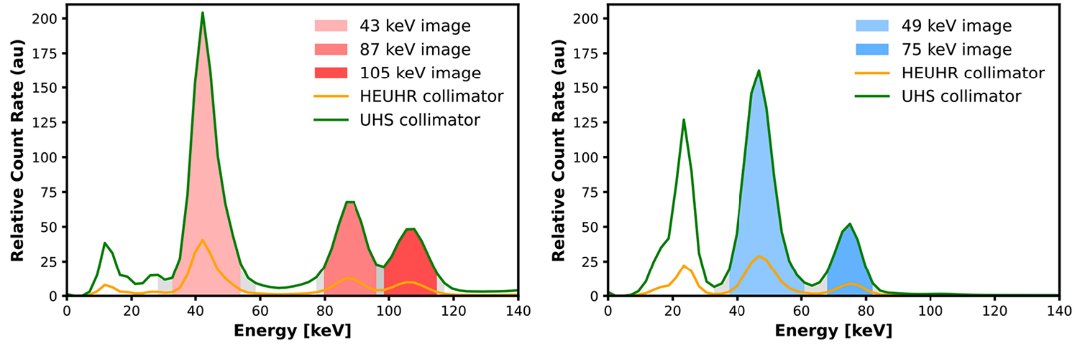



Biodistribution studies in male C57BL/6J mice bearing B16-F10 tumors performed at 2 h post administration

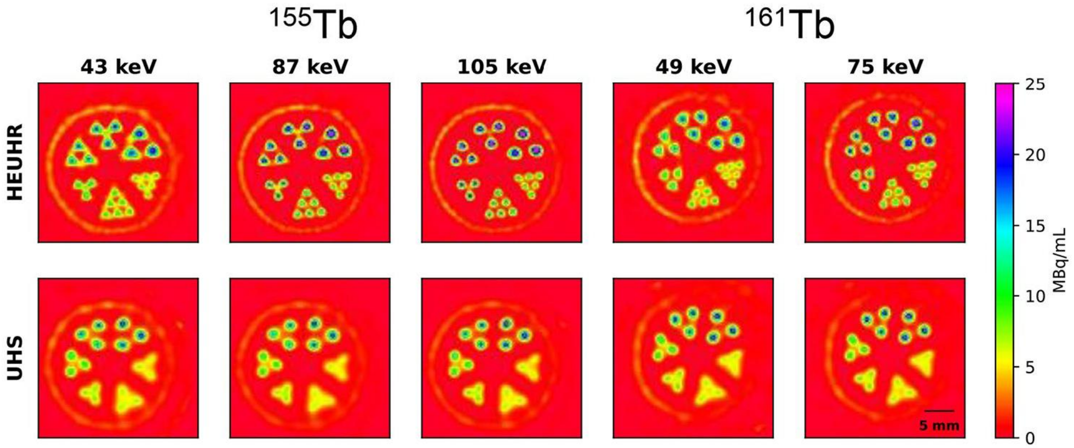
Credits to: Luke Wharton, Scott McNeil, Peter Kunz, Michiel Van de Voorde

# SPECT imaging with $^{155}$Tb and $^{161}$Tb




Energy spectra for point-sources of $^{155}$Tb (left) and $^{161}$Tb (right). Energy spectra were recorded using two collimators: ultra-high sensitivity (UHS) and high-energy ultra-high resolution (HEUHR).



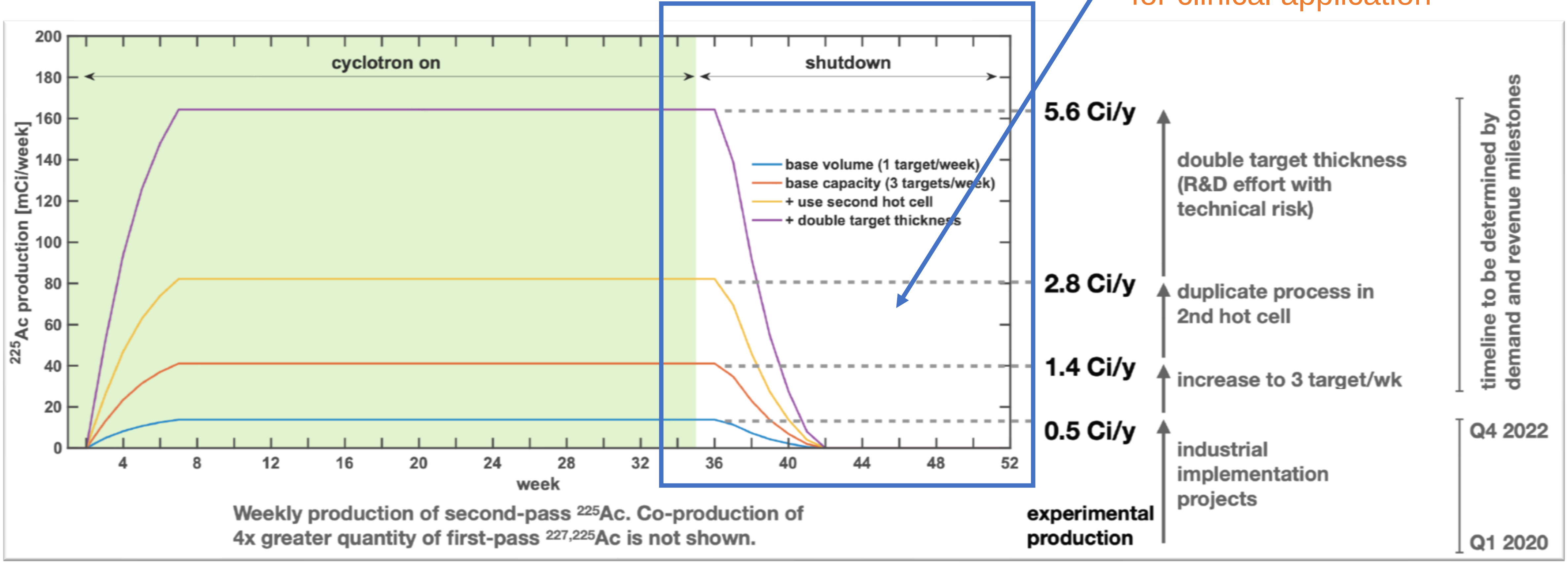

Quantitative SPECT image of $^{155}$Tb and $^{161}$Tb resolution phantom using HEUHR and UHS collimator(s).

H Koniar et al. *EJNMMI Physics* 2024, 11:77

# Key Challenges and Future Directions

# Key Challenges: Maintenance Shutdown(s)

Production gap
is emerging as a key risk
for clinical application




Weekly production of second-pass $^{225}Ac$. Co-production of 4x greater quantity of first-pass $^{227,225}Ac$ is not shown.

# Key Challenges: Old Infrastructure

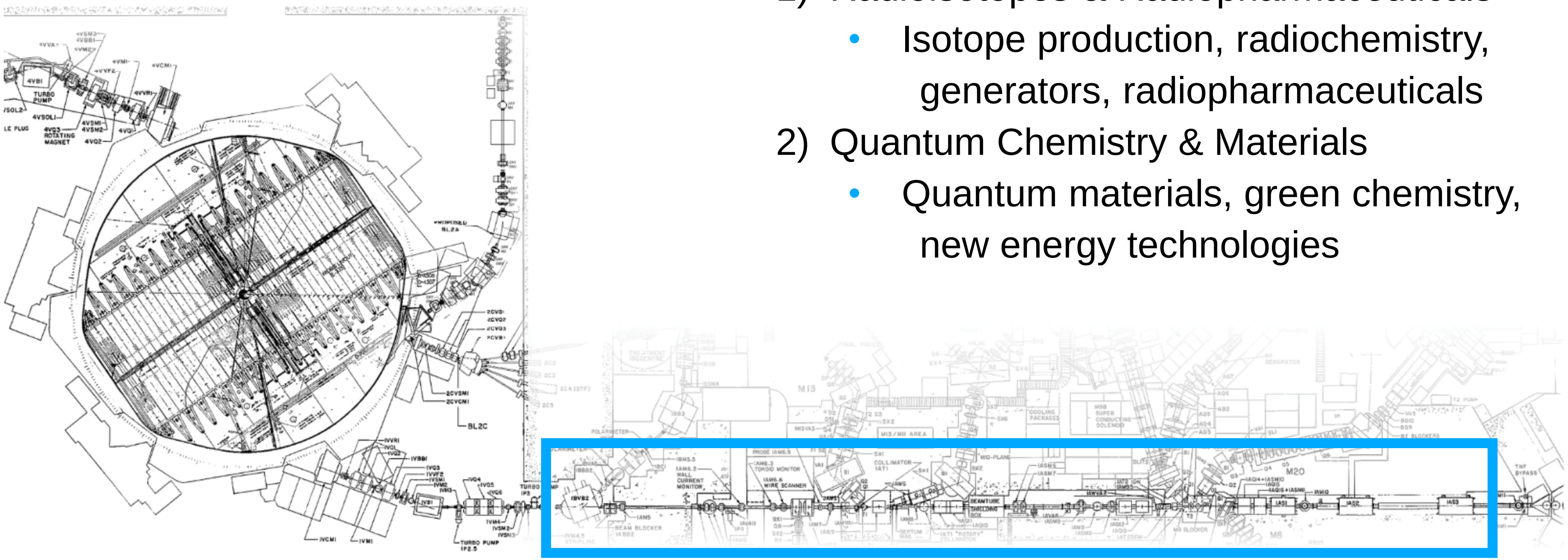
**Objective:** replace, enhance functionality of BL1A

**Next step:** 2025 CFI Infrastructure Fund; **application submitted for consideration**

- Under review
- $13M budget ($8M from CFI + provincial matching)

**Two Research Programs:**

1) Radioisotopes & Radiopharmaceuticals
   - Isotope production, radiochemistry, generators, radiopharmaceuticals
2) Quantum Chemistry & Materials
   - Quantum materials, green chemistry, new energy technologies



# NFRF-Transformation: Rare Isotopes to Transform Cancer Therapy

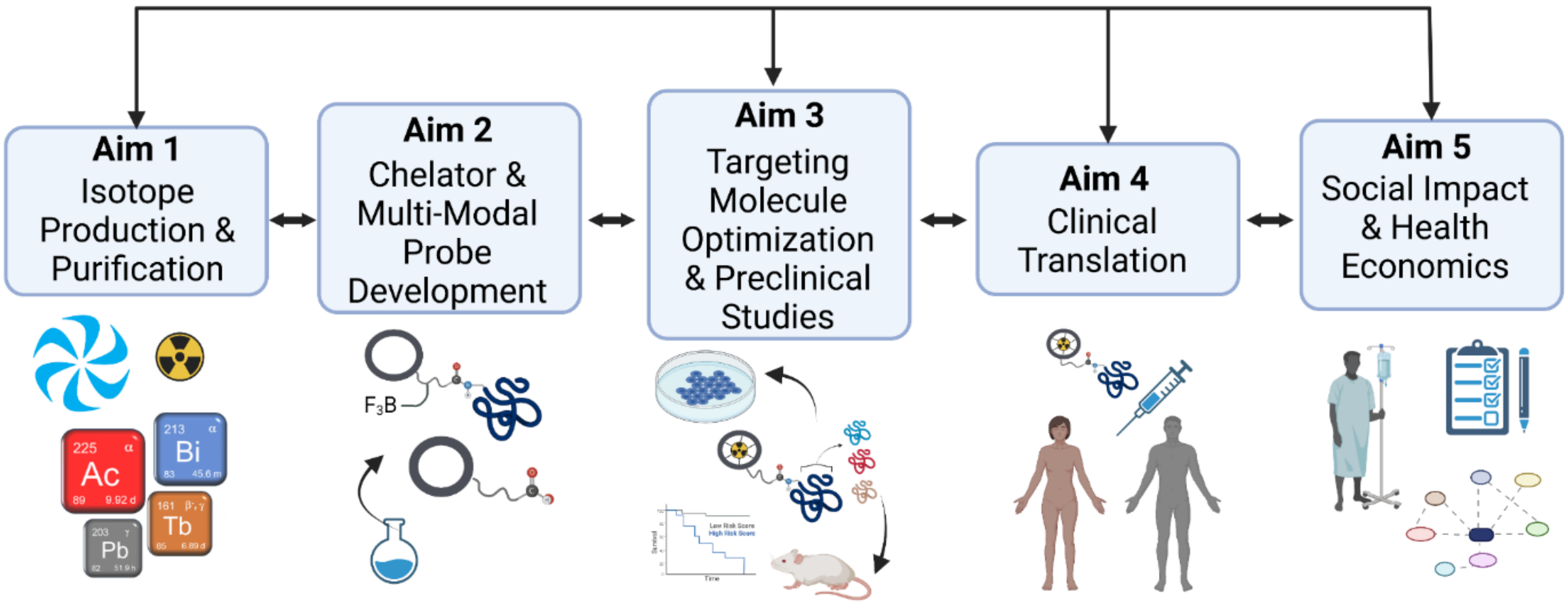
New Frontiers in Research Fund
Fonds Nouvelles frontières en recherche

$23.7 mil over 6 years

NPI: Bénard (UBC/BC Cancer)

Co-PI: Ramogida (SFU/TRIUMF)

TRIUMF Team: Hoehr, Radchenko, Schaffer, Yang

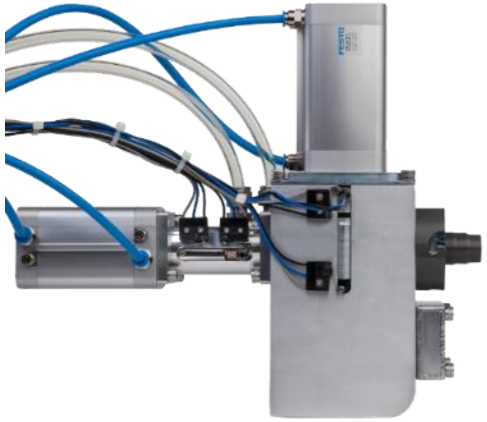



UBC · BC CANCER · Western · TRIUMF · SFU · UNIVERSITY OF ALBERTA · UNIVERSITÉ DE SHERBROOKE · BC Children's Hospital · UNIVERSITÉ LAVAL · UNIVERSITY OF TORONTO

# <24 MeV Isotope Production

# Emergence of radiometals assisted by technology advancements

TRIUMF-led consortium developed, tested and translated hardware and processes



**Target Irradiation**

**Automated Target Transfer**

**Target Dissolution**

**Isotope Purification**

**Radiopharmaceutical Production**

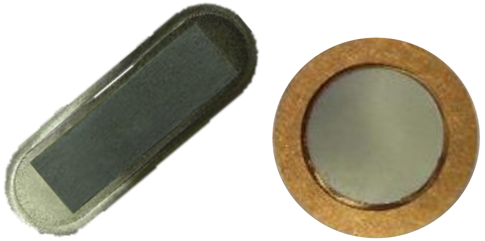
Results: Powerful hardware, advances in solid target automation, making radiometals easier to produce

- More complex local operations compared to generator approach
- Process outputs typically geared to match isotope generator formulation
- Decentralized/networked production reduces widespread supply outages; albeit enhances regulatory risks

# Radiometals by hospital-based cyclotron



Metallic isotopes are a growing component of isotope research, upcoming clinical applications

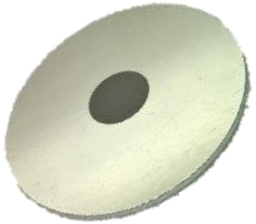


43 (97.9072)
**Tc**
**Technetium**
(Kr)$4d^5 5s^2$

($t_{1/2}$ = 6.02 hours)

31 69.723
**Ga**
**Gallium**
(Ar)$4s^2 3d^{10} 4p^1$

($t_{1/2}$ = 68 min)



29 63.546
**Cu**
**Copper**
(Ar)$3d^{10} 4s^1$

($t_{1/2}$ = 12.7 hours)

40 91.224
**Zr**
**Zirconium**
(Kr)$4d^2 5s^2$

($t_{1/2}$ = 3.3 days)

**Examples of large-scale production:**

$^{99m}$Tc ~ 1400 GBq (24 MeV, 500 µA, 6 hrs)
$^{68}$Ga ~ 370 GBq (13 MeV, 80 µA, 2 hrs)
$^{89}$Zr ~5.4 GBq (13 MeV, 80 µA, 3 hrs)*
$^{64}$Cu ~ 16.6 GBq (13 MeV, 65 µA, 1.5 hrs)*

**Development work underway for:**

$^{225}$Ac, $^{203}$Pb, $^{197}$Hg, $^{165}$Er, $^{155}$Tb, $^{13x}$La…

* To be finalized

# A Comparison of Approaches



$^{68}Ge/^{68}Ga$
(271 d, 68 min)


$^{68}Zn(p,n)^{68}Ga$

**Generators:**

- Centralized production, efficiency of scale
  - Risk: large-scale supply interruptions
- GMP compatible
- Simple operation, reduces local skills burden
- Limited isotope output (50, 100 mCi/elution)

**Cyclotron Production:**

- Decentralized production, supply redundancy
  - Risk: potential for site-to-site variability
- GMP compatible
- More complex local Radiopharmacy operation
- Increased local skills burden
- Significant isotope output (10,000 mCi/2 hr irradiation
- Relevant adjacencies apply ($^{99m}Tc$, $^{89}Zr$, $^{64}Cu$...)

H Thisgaard et al. EJNMMI Radiopharm & Chem 2021, 6:1

## New Infrastructure:
# Institute for Advanced Medical Isotopes (IAMI)

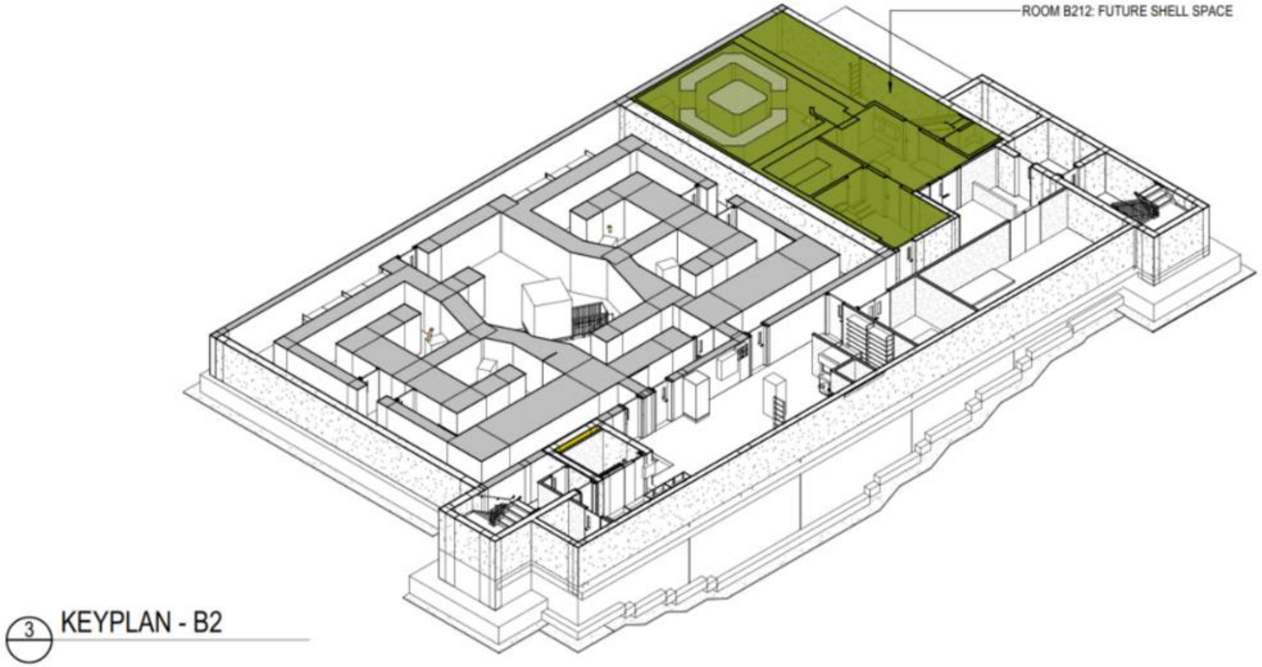
New >$70M facility
Building substantially complete
TR24 installed
PETTrace procurement underway
6 GMP-capable hot labs
1 standard chemistry lab
2 QC laboratories
Quarantined storage
2 floors of office space
Hot Commissioning 2025

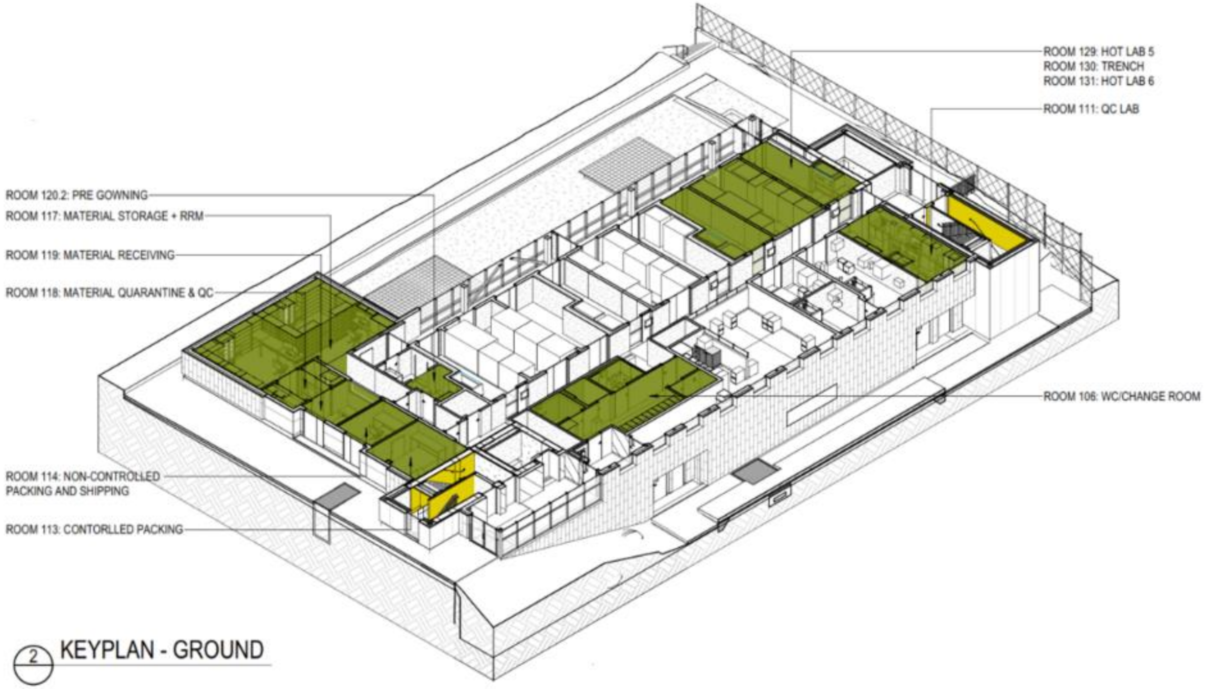
Canada BRITISH COLUMBIA TRIUMF BC CANCER UBC


71

# Completing IAMI





# Summary

**$\beta^+/\gamma$-emitters:**

$^{11}$C
$^{18}$F
$^{64}$Cu
$^{68}$Ga
$^{89}$Zr
$^{99m}$Tc
$^{111}$In
$^{155}$Tb

**α-emitters:**

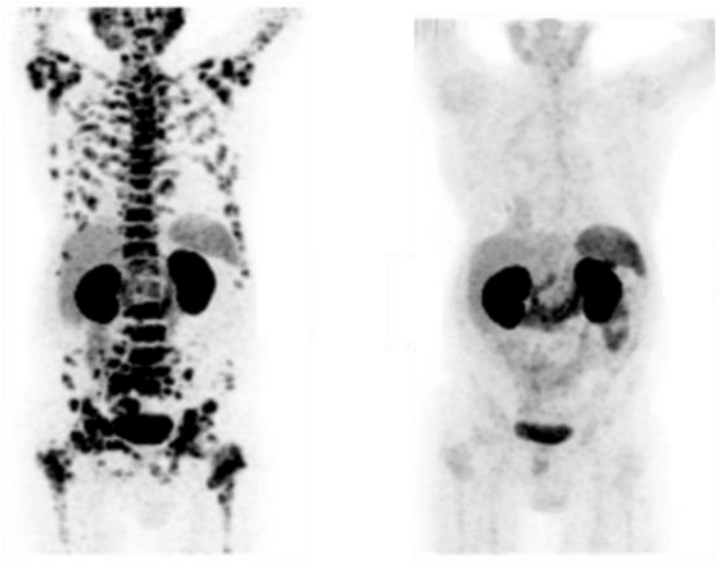
$^{211}$At
$^{225}$Ac
$^{212\text{-}213}$Bi
$^{212}$Pb
$^{223}$Ra
$^{227}$Th
$^{149}$Tb

**$\beta^-$-emitters:**

$^{89}$Sr
$^{90}$Y
$^{131}$I
$^{153}$Sm
$^{161}$Tb
$^{177}$Lu

**Auger-emitters:**

$^{58m}$Co
$^{71}$Ge
$^{103}$Pd
$^{103m}$Rh
$^{119}$Sb
$^{191}$Os



- Direct, cyclotron-production of many radiometals is paving the way for a robust, decentralized supply system for isotopes of emerging clinical importance
- Promising clinical results for treating late-stage cancers is driving demand for both beta- and alpha- emitting isotopes for use in TRT
- ISOL-produced isotopes can be used for preclinical TRT, as shown with [$^{225/226}$Ac]Tb-crown-TATE in neuroendocrine tumour-bearing mice
- Large accelerator facilities, such as TRIUMF (and PSI!) can serve to innovate new isotopes, and new technologies by applying their accelerator infrastructure, along with their **multidisciplinary expertise** to help understanding life at the molecular level

# Acknowledgements

## TRIUMF (Research)

Desiree Fiaccabrino
Cornelia Hoehr
Aidan Ingham
Helena Koniar
Peter Kunz
Jens Lassen
Brooke McNeil
Scott McNeil
Gokce Engudar
Zheliang Yuan
Valery Radchenko
Caterina Ramogida
Andrew Robertson
Luke Wharton
John Wong
Hua Yang
Diduo Zhang
Cheng Cheng Zhang

Life Sciences Ops team
TR13 Ops team
ISAC Ops team

## BC Cancer

Nadine Colpo
Helen Merkens
François Bénard

## UBC

Cristina Rodriguez-Rodriguez
Maryam Osooly
Chris Orvig

Thank you

Merci

www.triumf.ca

Follow us **@TRIUMFLab**

Discovery, accelerated

# Backup

Discovery, accelerated

LAWSON
HEALTH RESEARCH INSTITUTE

NOUS SOMMES PRÊTS

a place of mind
UBC

Canada Foundation for Innovation
Fondation canadienne pour l'innovation

BC CANCER

TRIUMF

BWXT

cpdc

NSERC
CRSNG

Fusion
Pharmaceuticals Inc.

CIHR IRSC
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Canadian Cancer Society

Natural Resources Canada
Ressources naturelles Canada
Canada

# Acknowledgements




**TRIUMF Team**
J Balatoni,
C Currie,
R Delpeache-Roomes
T Epp,
A Hampaul
V Hanemaayer,
**C Hoehr,**
J Huser,
E Khozeimeh,
P Kunz,
S McDiarmid,
B McNeil,
Q Miao,
D Prevost,
V Radchenko,
**C Ramogida,**
A Robertson,
V Radchenko,
TJ Ruth,
S Sharma
P Sokacz,
M Stachura,
L Tran,
**H Yang,**

**TRIUMF Team (cont'd)**
I Carbo Bague,
J Carson,
H Chen,
G Engudar,
D Fiaccabrino,
A Fong,
J Hanlon,
K Hayashi,
G Hodgson,
**H Koniar,**
E Kurakina,
K Ladouceur,
K McDuffie,
F Pau,
I Rodrigo,
**L Wharton,**
L Wang,
N Weatherall,

**BC Cancer Agency**
**F Bénard,**
A Celler,
H Corbett,
N Colpo,
G Dias,
W English,
K Frantzen,
X Hou,
KS Lin,
G Langlois,
H Merkens,
J Rousseau,
J Song,
J Schlosser,
M Vuckovic,
CC Zhang

**ARTMS**
D Gentilcore
S Borjian
J Kumlin
M Cross
ARTMS team

**Lawson Health Research**
M Kovacs,
F Prato,
S Foster,
J Corsault,
and team

**CPDC**
J Valliant,
T Besanger,
P Ruddock,
J McEwan,
A Goodbody,
and team