TRIUMF

Production and Application of Radiolanthanides at TRIUMF

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PRISMAP Workshop
2024-09-03

TRIUMF

Disclosure

- I am a full-time employee of TRIUMF
- I am compensated by ARTMS, Inc. as Chief Technology Officer
- I am a listed inventor on patents in technology licensed to ARTMS

TRIUMF

- Topics for today's presentation:

Background: TRIUMF, Infrastructure and Capabilities

Discussion:
Radiolanthanide work @ TRIUMF
(Production, Radiochemistry, Radiopharmaceutical Development)

Summary, Conclusions

Discovery, accelerated

TRIUMF’s Research Programme

TRIUMF’s work **addresses the most compelling challenges in contemporary science** and connects fundamental scientific research through to commercialisation.

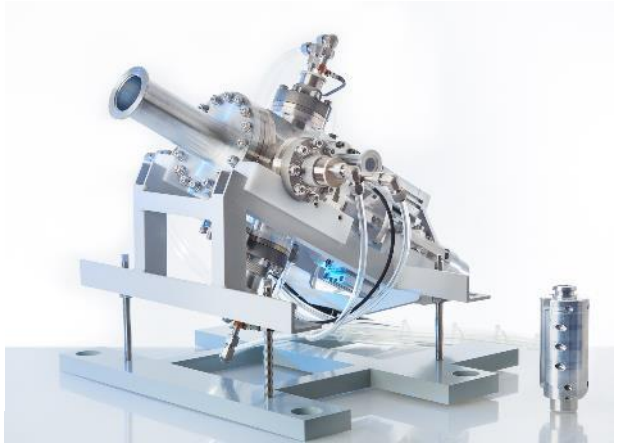
TRIUMF is a hub of excellence centred on a **core of expertise in accelerator technology, detector development and isotope research.**

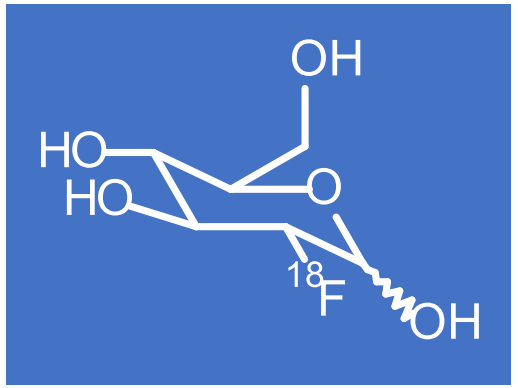
From supporting Nobel-prize winning research to delivering life-saving breakthroughs in health and technology, **TRIUMF is a major asset in Canada's high-tech landscape delivering economic and societal benefit to Canadians.**

TRIUMF

Life Sciences at TRIUMF

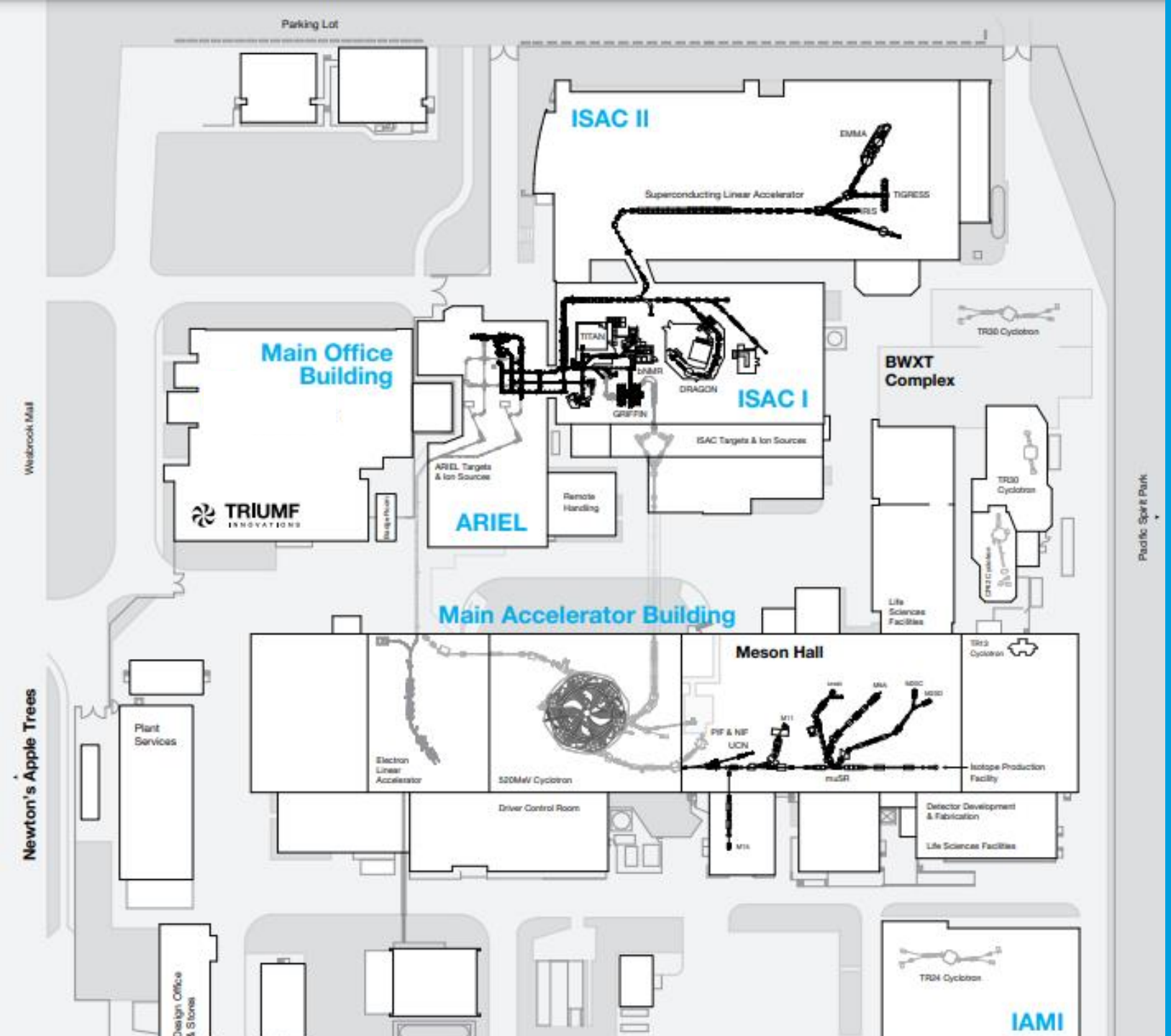
- Applied Ion Beams
- Nuclear Chemistry
- Applied Isotopes



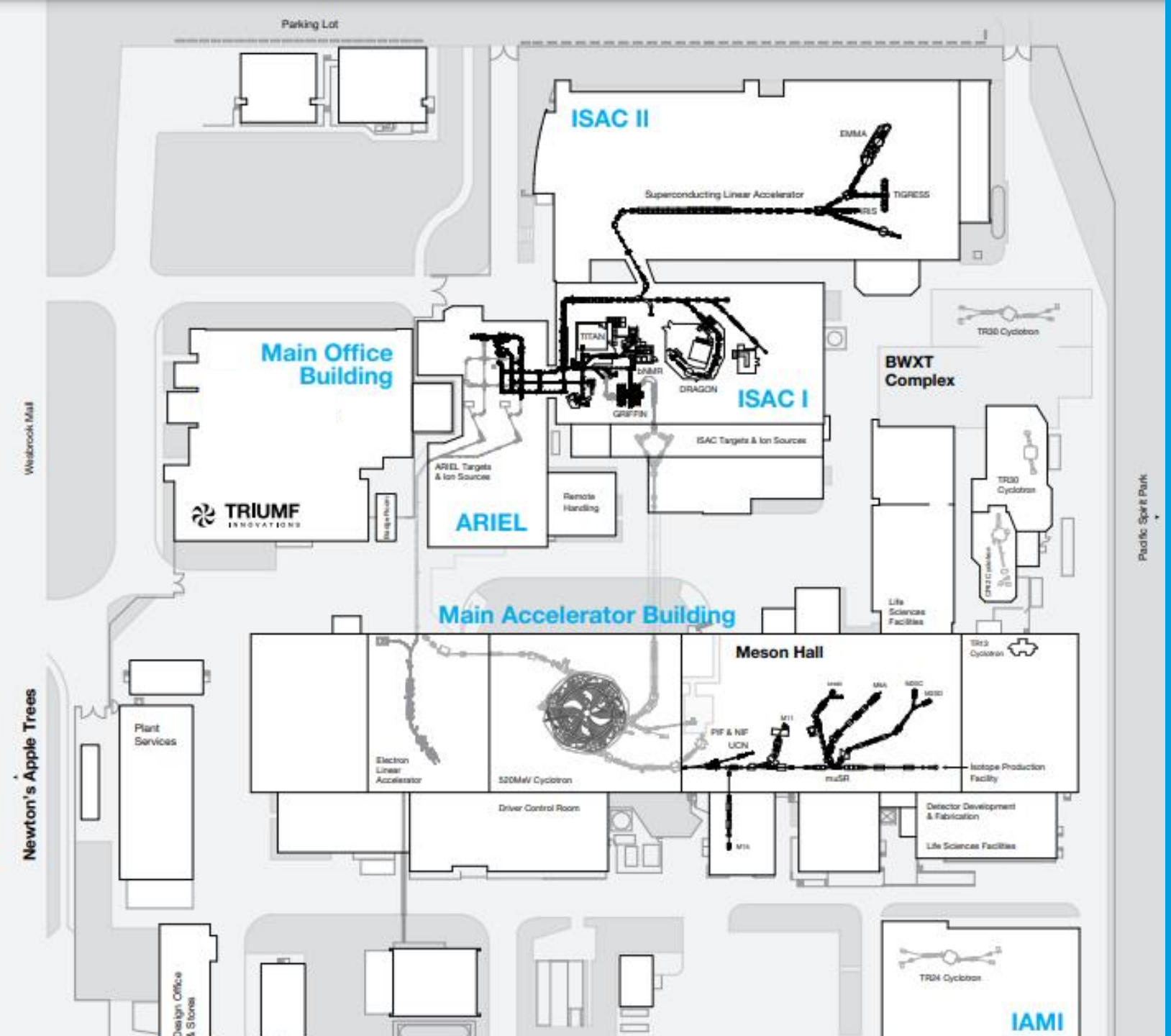


TRIUMF Life Sciences focuses on advancing accelerator-based technology for the development of isotopes that can improve life

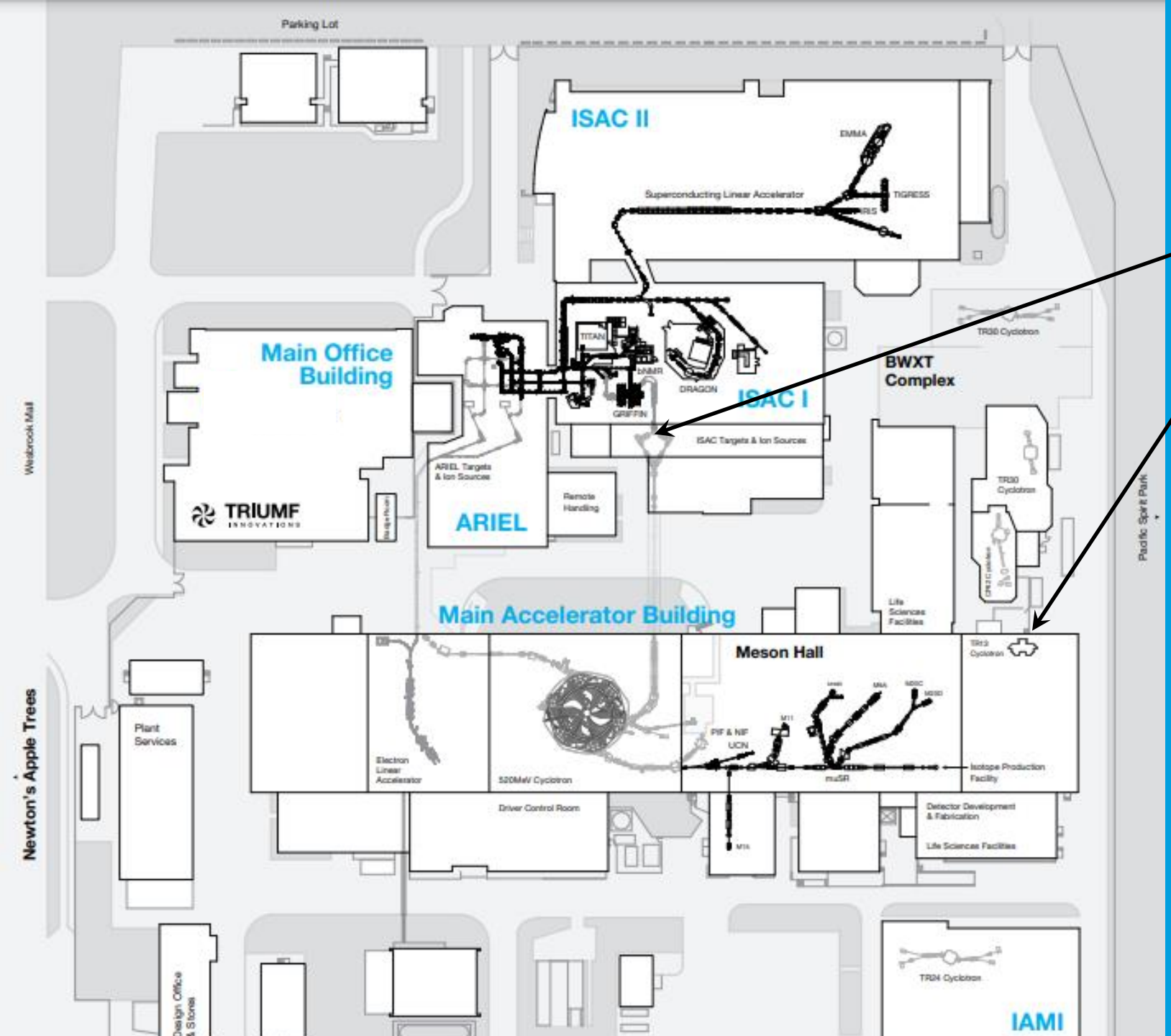
Discovery, accelerated



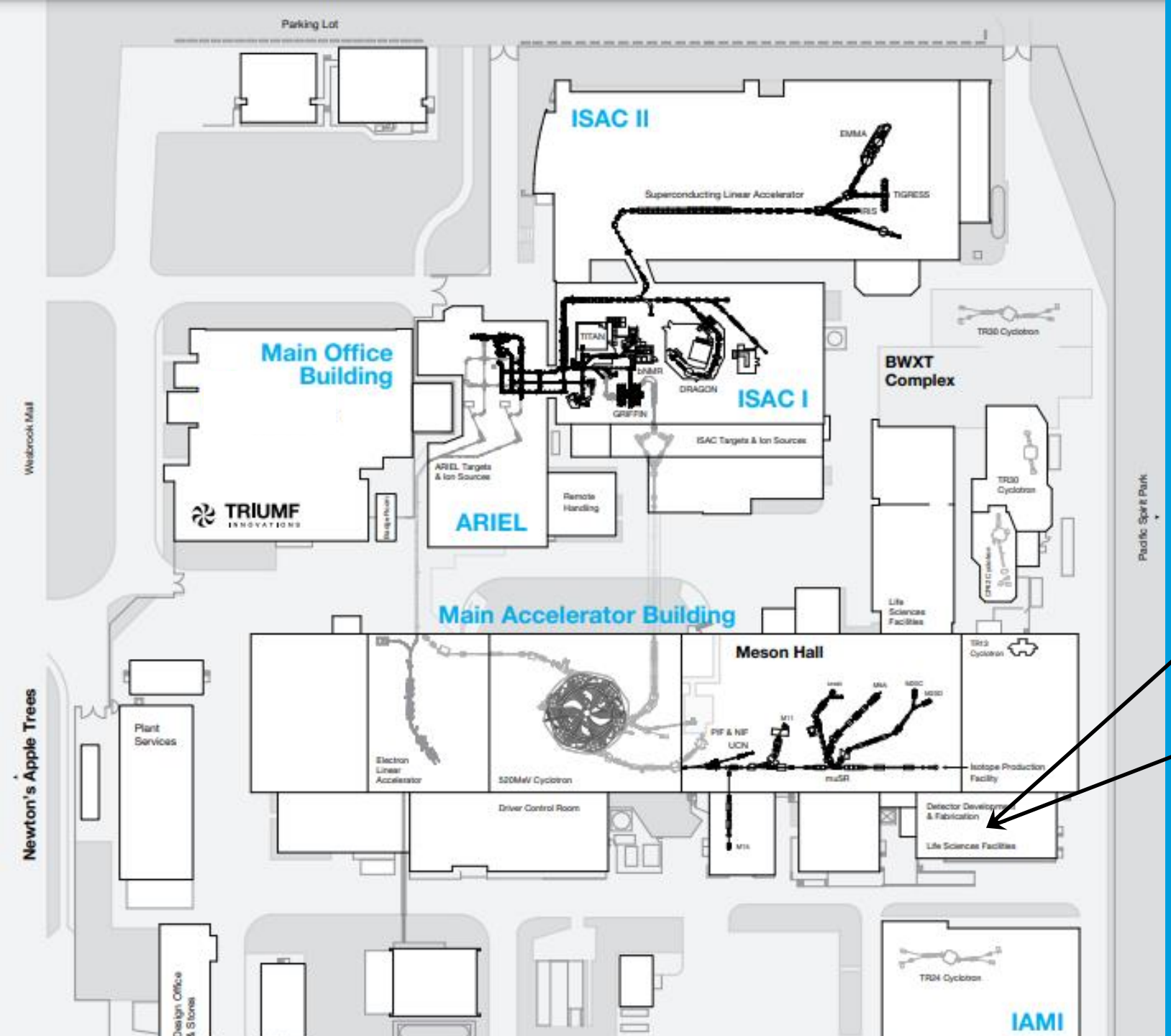
- Six (soon to be seven) cyclotrons & two linear accelerators on site
- Over 1-kilometer of beamlines; accelerating sub-atomic and rare-isotope beams
- Users and collaborators from over 40 countries
- Over 1000 visitors per year (2019)



- 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



- Radiolanthanide work:
  - ISAC: ^{149,155}Tb via ISOL
  - TR13:
    - ^{nat}Ba(p,x)^{132}La
    - ^{165}Ho(p,n)^{165}Er
    - ^{nat}Gd(p,x)^{155}Tb
  - outsource: ^{161}Tb (SCK)
  - TR24/PETTrace: future
  - Radiochemistry
    - Purification
    - Chelate development
  - *In vitro* testing
  - *In vivo* testing
    - UBC Centre for Comparative Medicine



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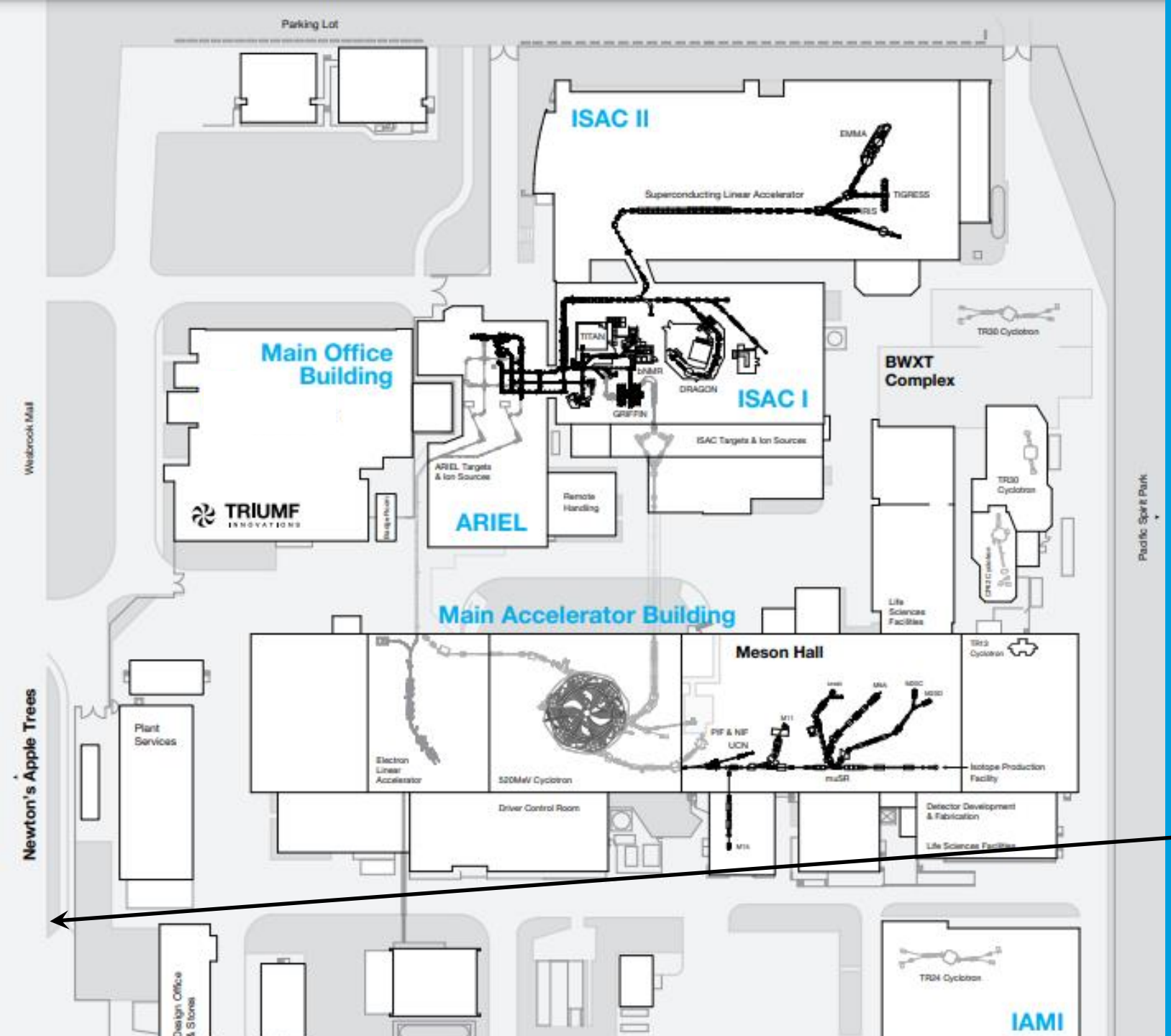

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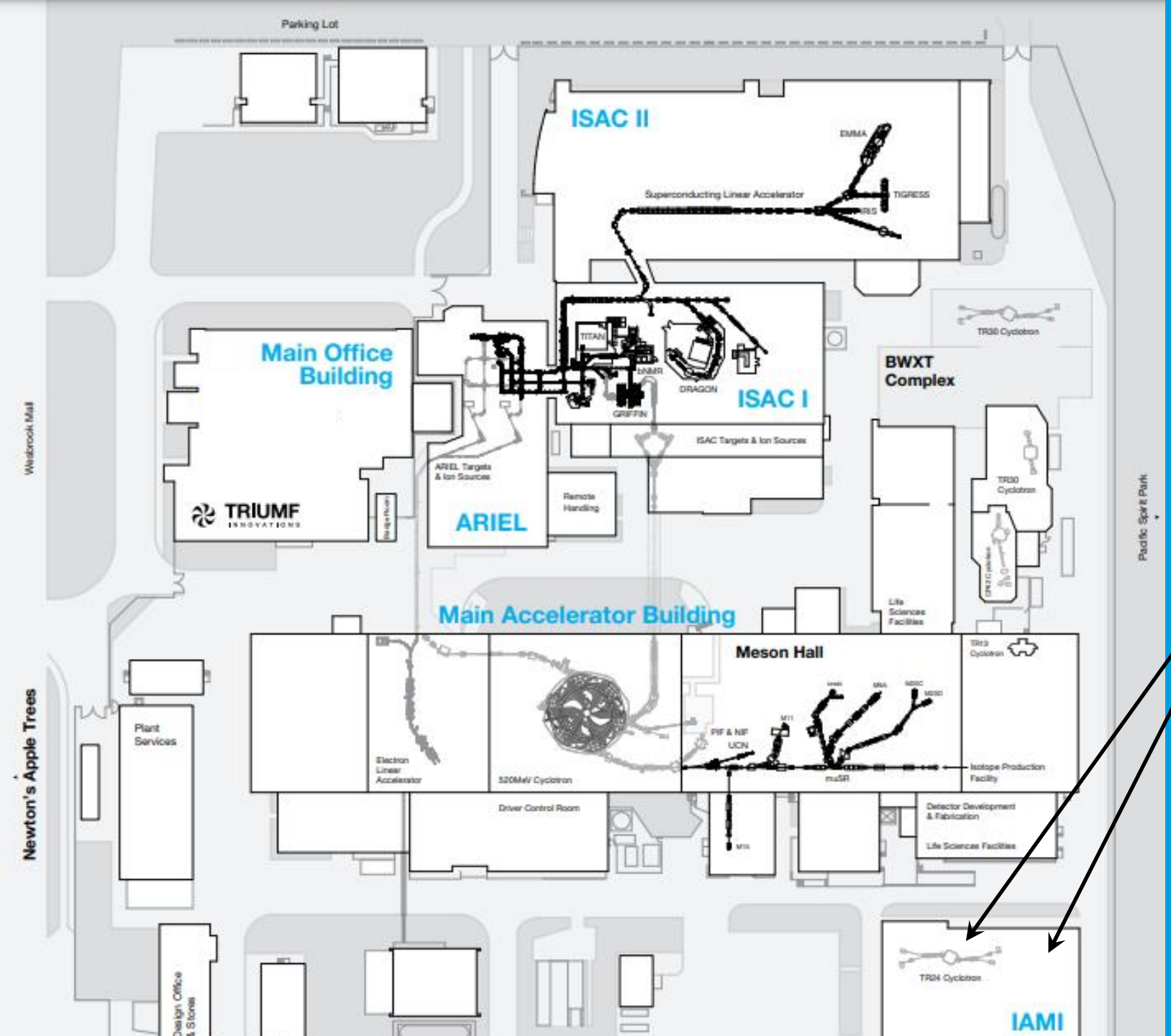

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Life Scientists at TRIUMF

Applied Ion Beams

Cornelia Hoehr

Nuclear Chemistry

Valery Radchenko

Paul Schaffer

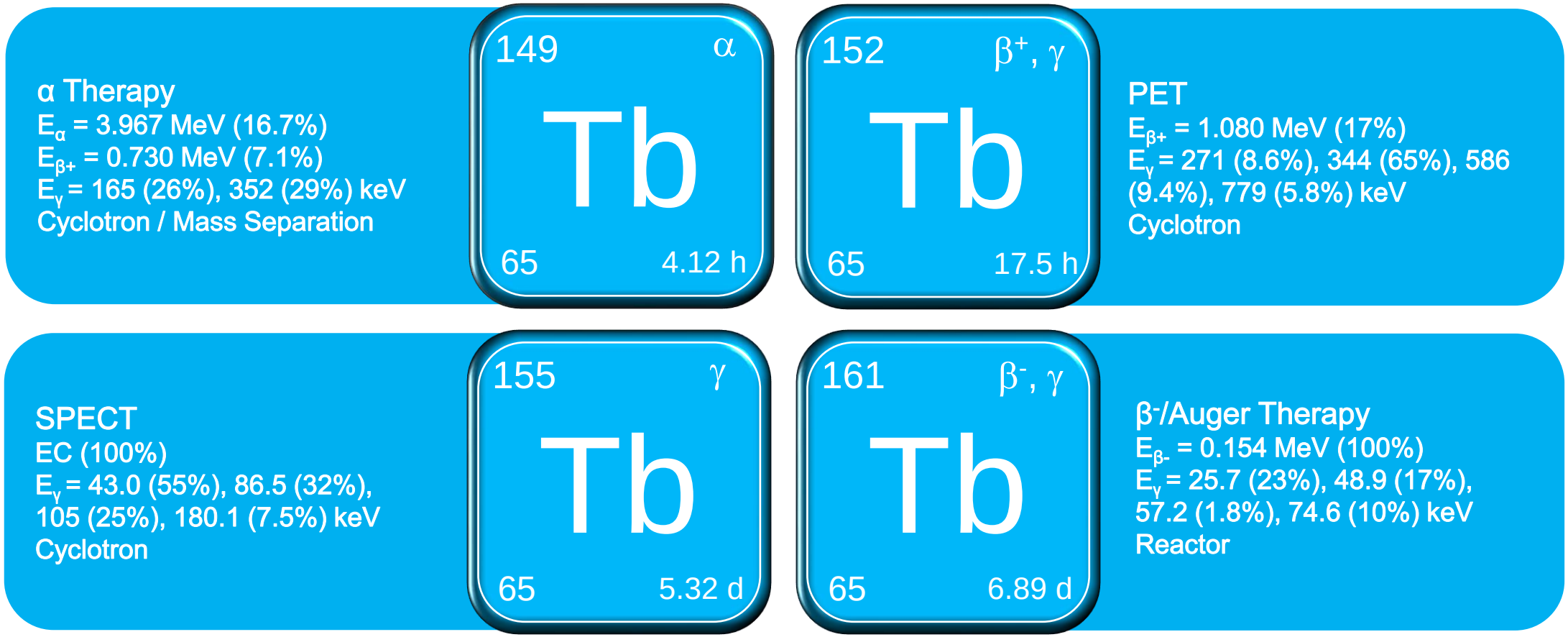
Applied Isotopes

Hua Yang

Caterina Ramogida
(joint SFU)

Production (at ISAC-ISOL)

Terbium radioisotopes

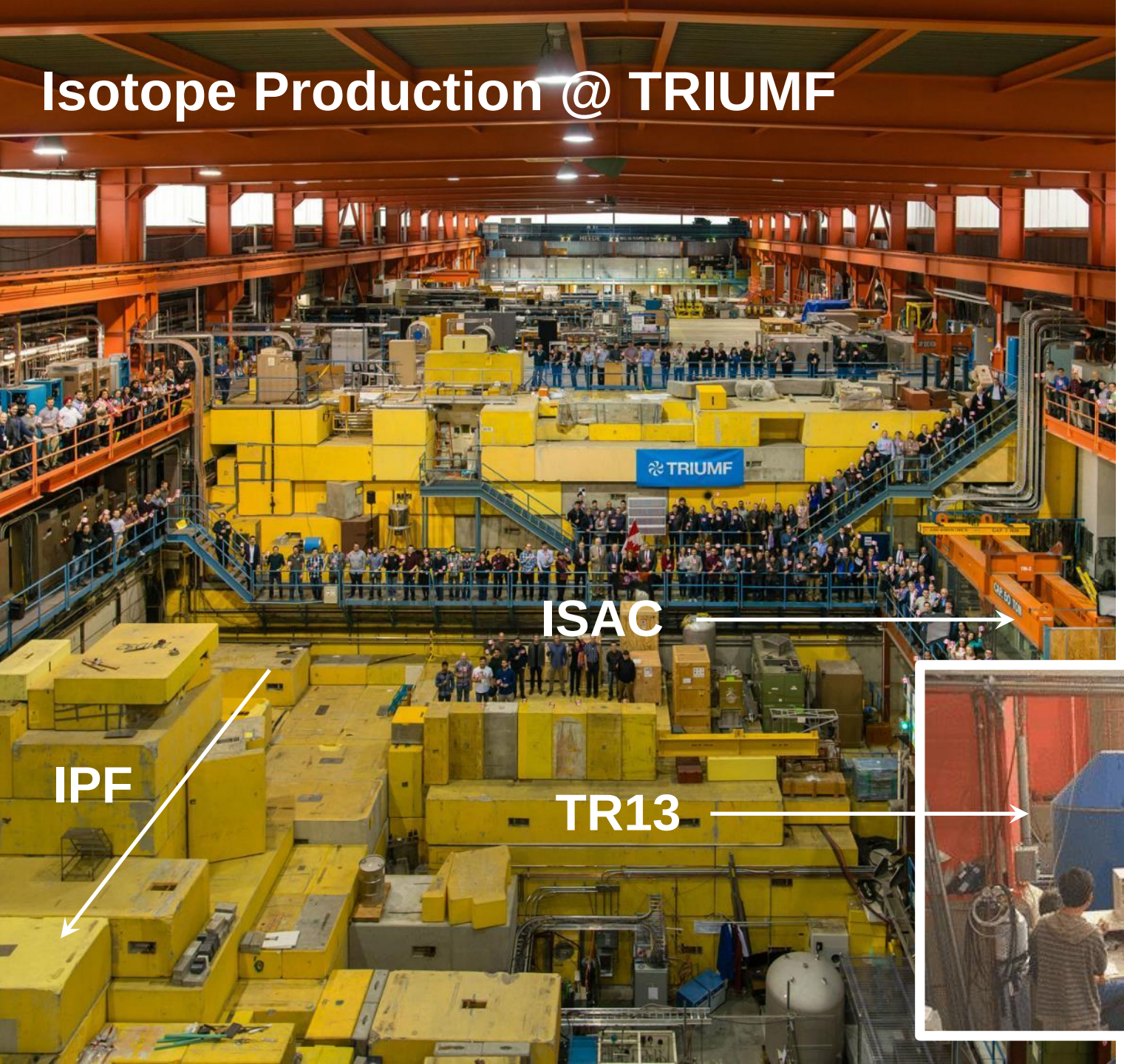


- Tb has four medically relevant isotopes, covering all major nuclear medicine modalities
- Enable theranostics with chemically identical radiopharmaceuticals
- For most, ^{155}Tb and ^{161}Tb are more available

Slide credit: H. Yang

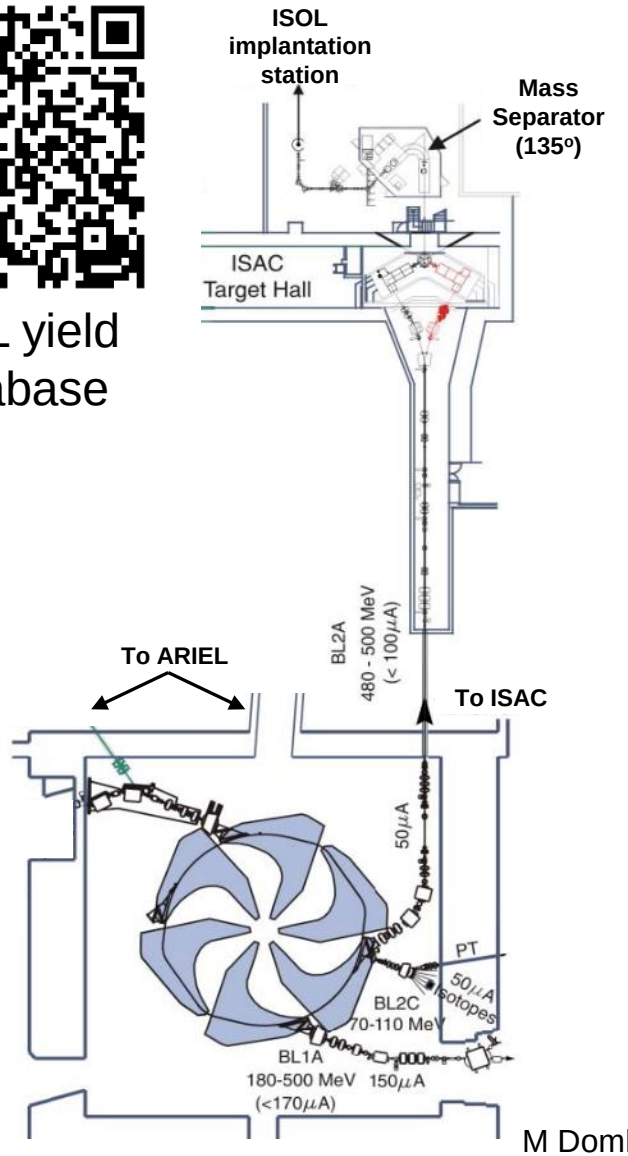
C Muller, et al., JNM, **2012**, 53 (12) 1951-1959

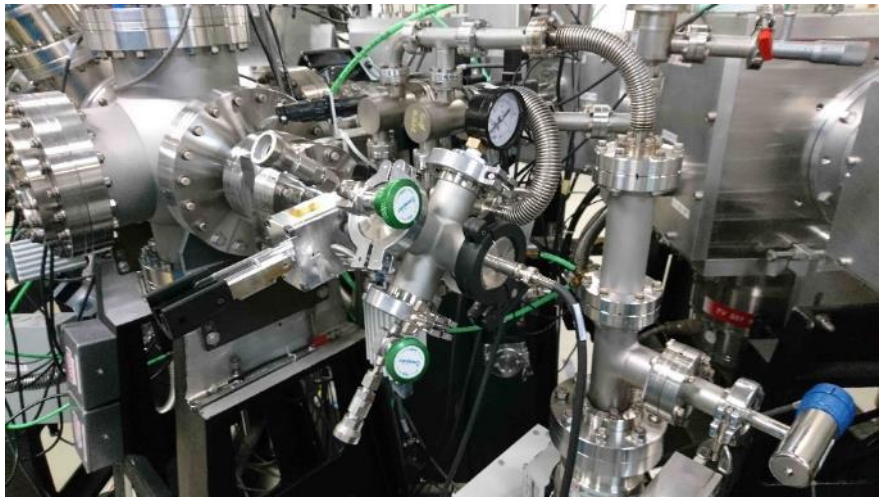
Isotope Production @ TRIUMF

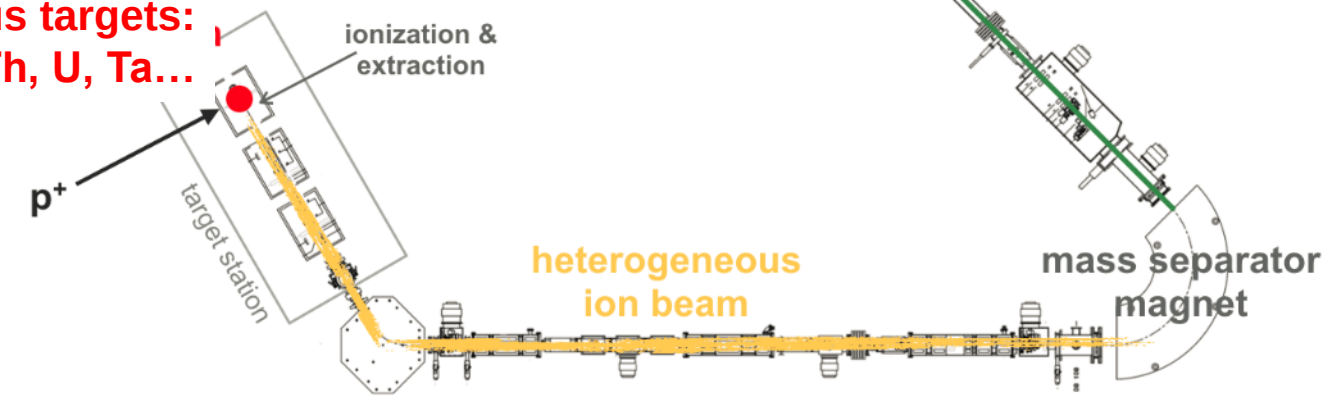


TRIUMF ISAC-ISOL

ISOL yield database







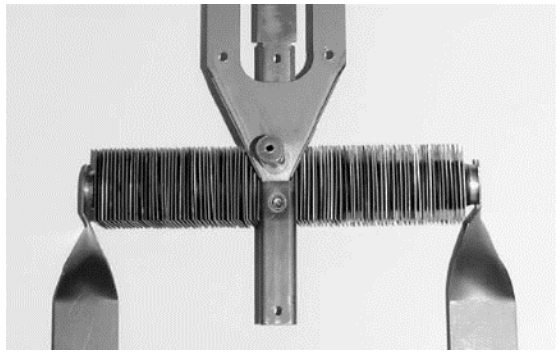
$^{211/209}$At,
^{226}Ra/^{226}Ac,
^{225}Ra/^{225}Ac,
^{224}Ra,
^{165}Er,
^{155}Tb

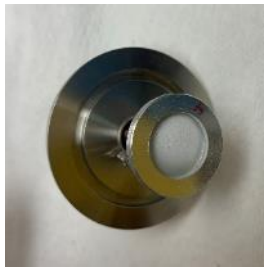
M Dombsky, P Bricault. Nucl. Instrum. Methods Phys. Res. B **2008**;266:4240–6.
P Kunz, C Andreoiu, P Bricault, et al. Review of Scientific Instruments, **2014**, 85, 053305.
P Kunz, C Andreoiu, V Brown, et al. EPJ Web Conf **2020**;229:06003.

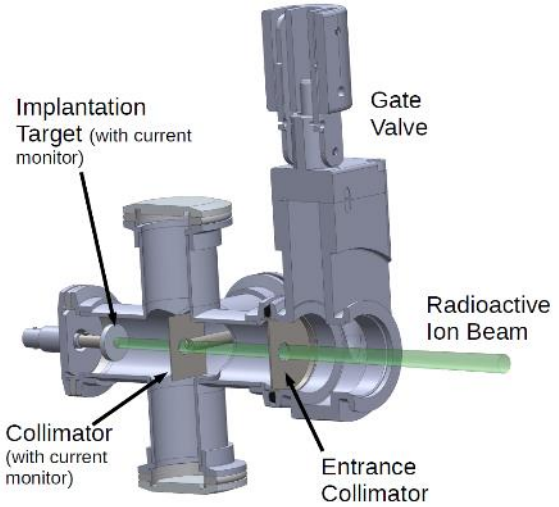
Isotope Separator and Accelerator (ISAC)

Isotope Separation On-line (ISOL)

Tantalum: 0.14 mol/cm²





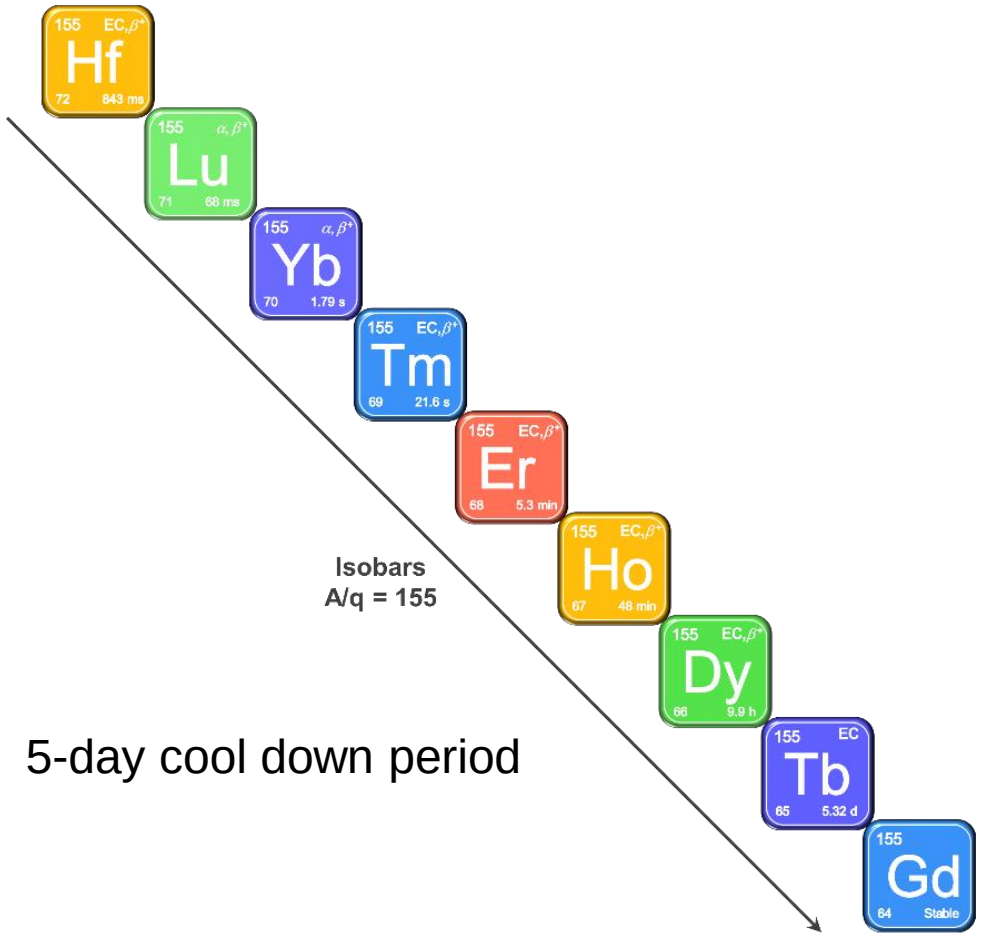


Credits to: P Kunz, J Lassen, V Radchenko, D Fiaccabrino

D Fiaccabrino et al. Nucl Med Biol 2021; 94–95:81–91.

Isotope Separator and Accelerator (ISAC)

Isotope Separation On-line (ISOL) of A/q = 155



5-day cool down period

Yield estimates based on GEANT4 simulations.

Produced Isotope	Half-life	Production Rate [isotopes/sec]	Yield (after 5 day cool down)
^{155g}Sm	22.18 min	3.49×10^{6}	n/a
^{155g}Eu	4.753 y	6.44×10^{7}	5.09×10^{11} atoms (2.35 kBq)
^{155g}Gd	Stable	1.11×10^{9}	~8.78×10^{12} atoms
^{155g}Tb	5.32 d	1.05×10^{10}	~2.45×10^{14} atoms (370 MBq)
^{155g}Dy	9.9 h	5.07×10^{10}	n/a
^{155g}Ho	48 min	1.33×10^{11}	n/a
^{155g}Er	5.3 min	1.77×10^{11}	n/a
^{155g}Tm	21.6 s	6.72×10^{10}	n/a
^{155g}Yb	1.79 s	4.46×10^{9}	n/a
^{155g}Lu	68 ms	1.55×10^{8}	n/a
^{155g}Hf	843 ms	7.00×10^{5}	n/a

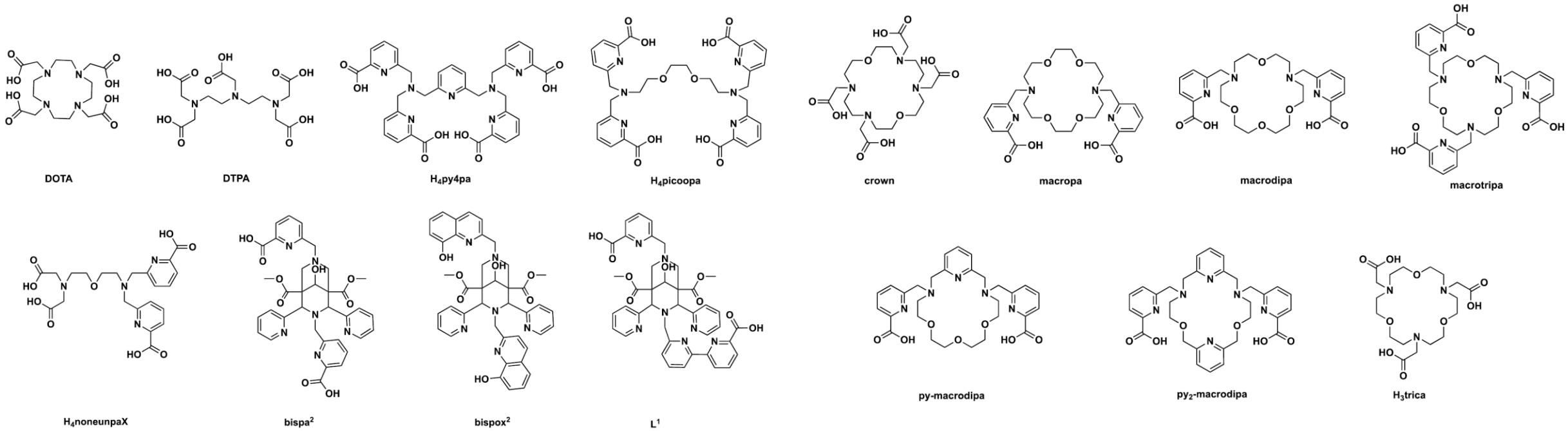
Slide credit: L Wharton, H Yang

Nuclear Inst. and Methods in Physics Research, B 541 (2023) 117–120

Radiochemistry

Designing chelators capable of binding emerging isotopes of clinical importance

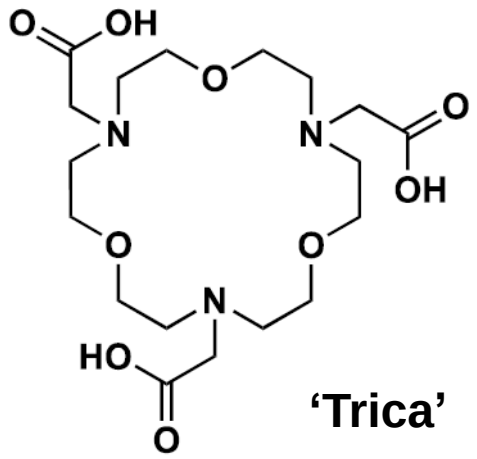
- Various chelates have been developed to enable radioactinide and radiolanthanide complexation for targeted radiopharmaceutical development
- High-denticity, acyclic and cyclic chelators



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

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)

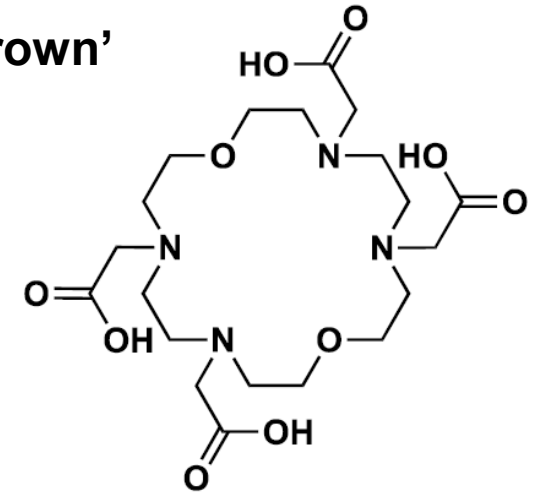


‘Trica’

Ideal properties:

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

‘Crown’

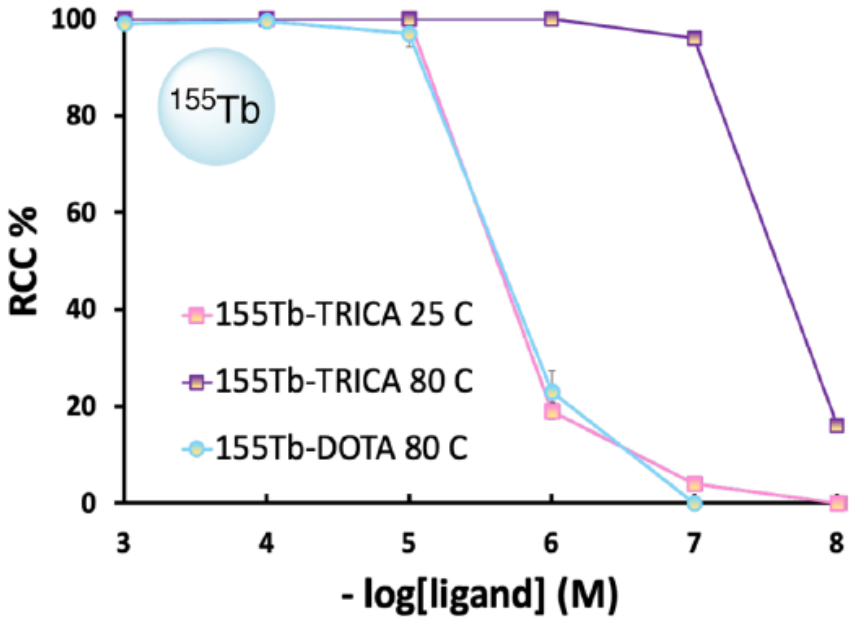


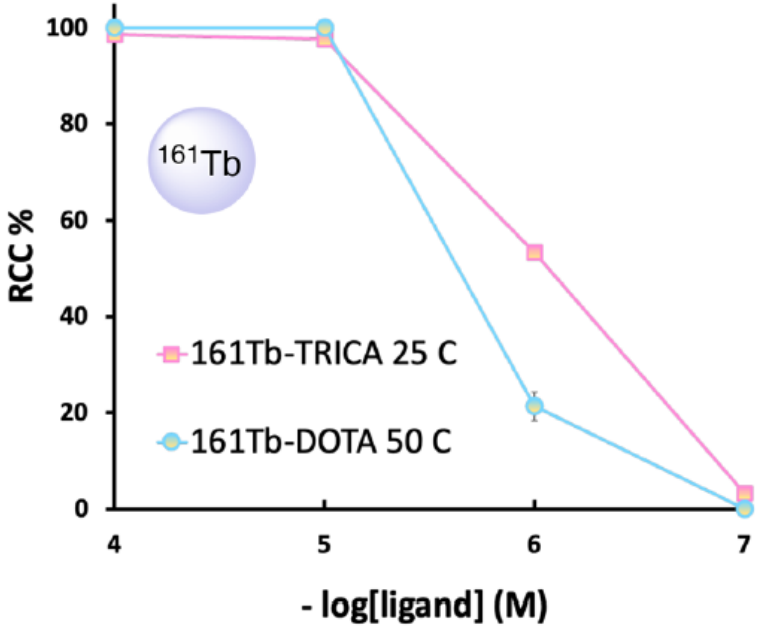
D Fiaccabrino et al. *Inorg. Chem.* **2024**, 63, 13911

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

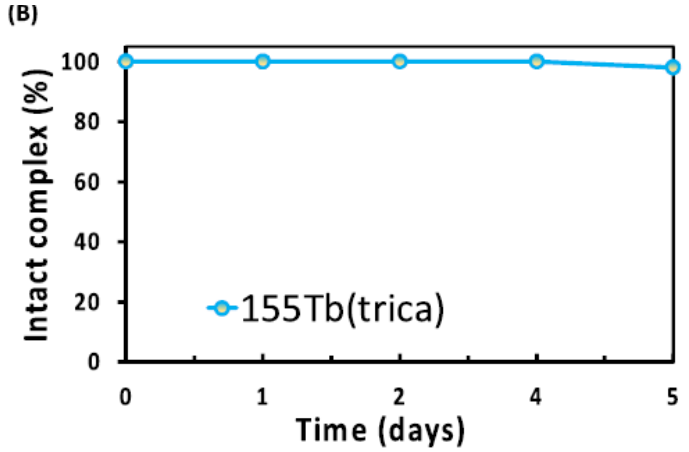
H_3Trica Chelate

Concentration-dependent radiolabeling studies of H_3trica and DOTA with $[^{155}Tb]Tb^{3+}$, and $[^{161}Tb]Tb^{3+}$, (100 kBq) in NH_4OAc (0.5 M, pH 6).**





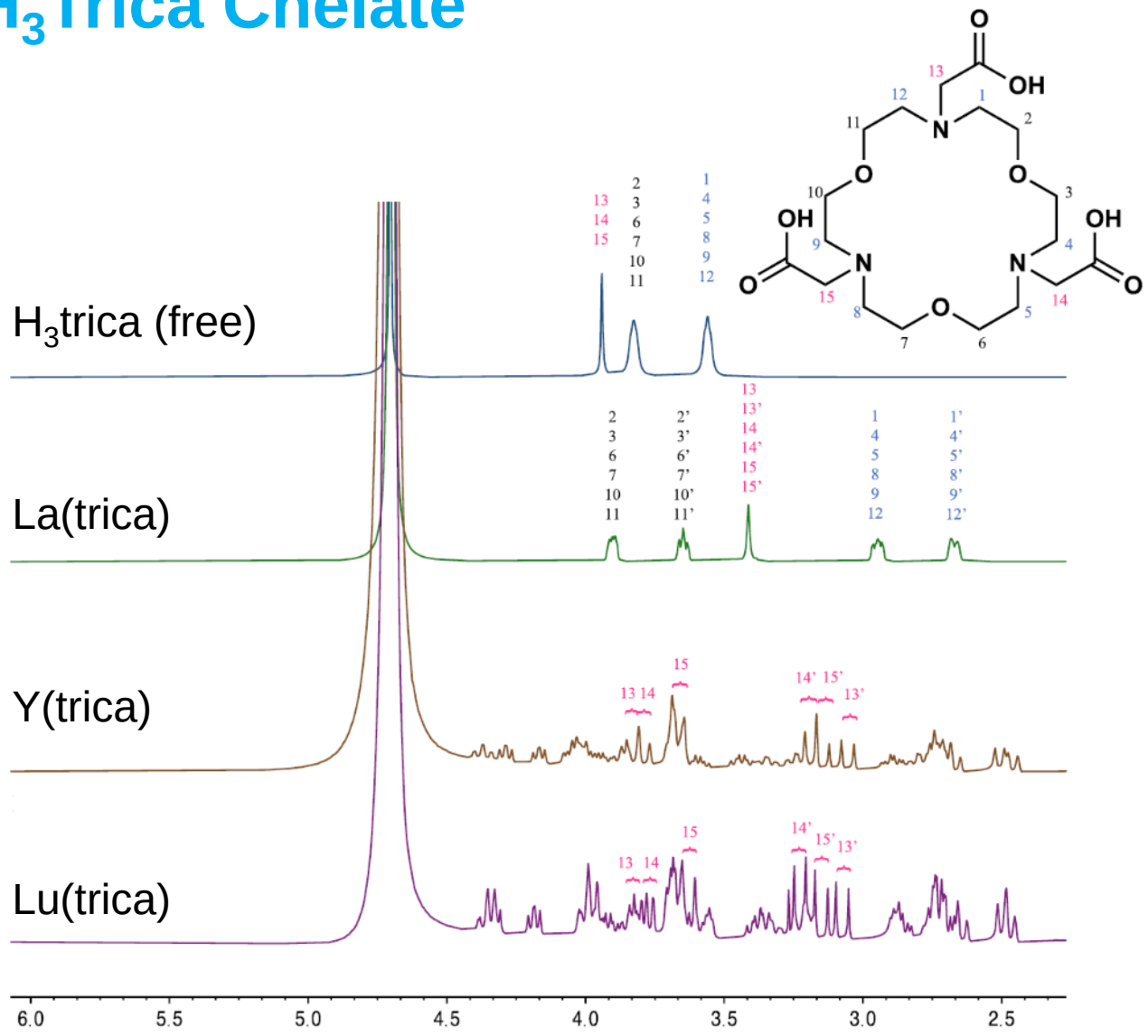
H_3Trica-TATE radiolabeling study just completed, data forthcoming



**Tb-161 obtained from SCK

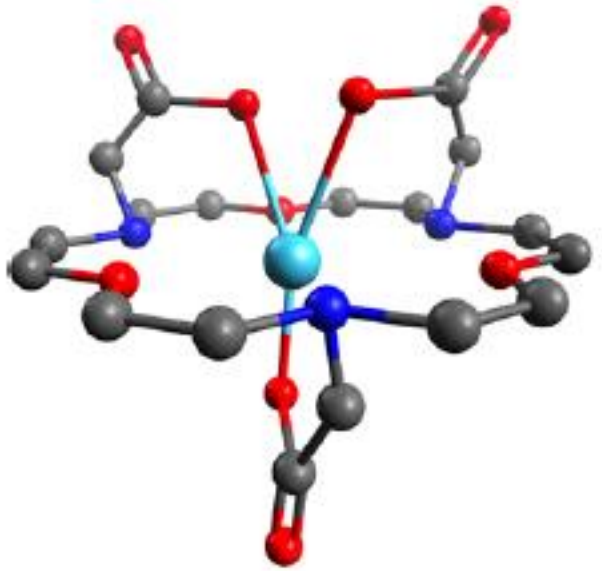
D Fiaccabrino et al. Inorg. Chem. 2024; 63, 13911

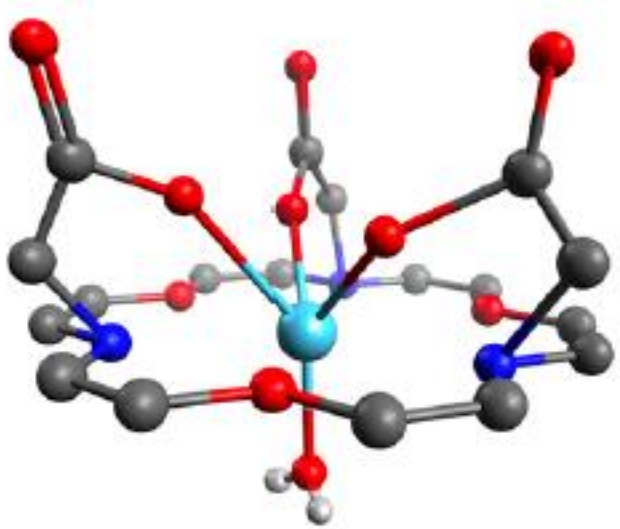
H_3Trica Chelate



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

Conformation ‘A’



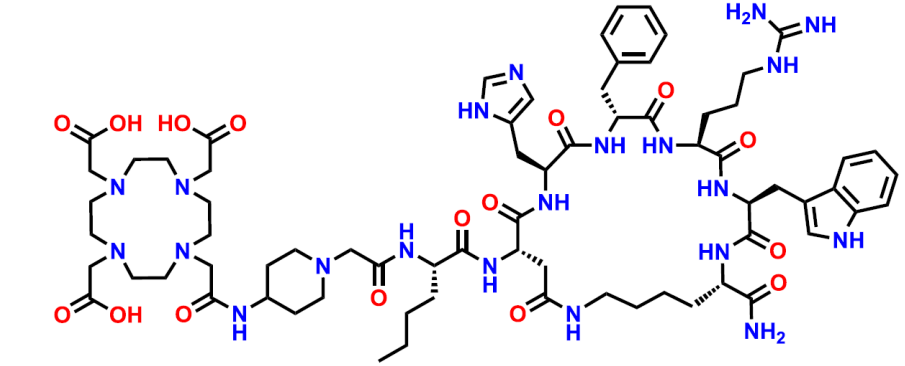


Conformation ‘B’

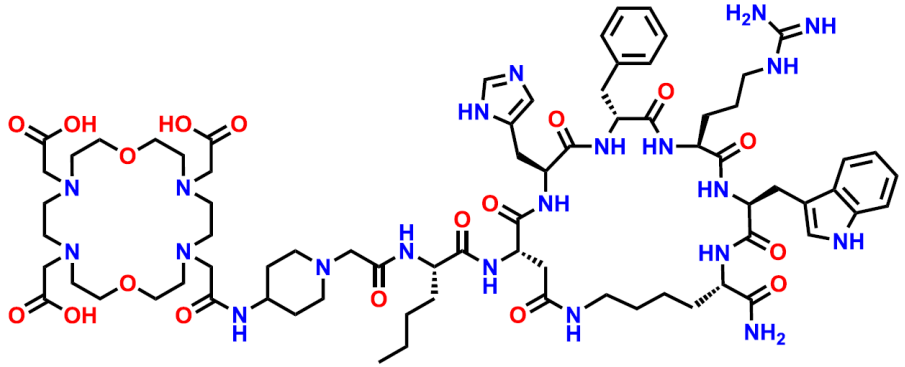
D Fiaccabrino et al. Inorg. Chem. 2024; 63, 13911

Radiopharmaceutical Development

[$^{155/161}$Tb]Tb-crown-αMSH



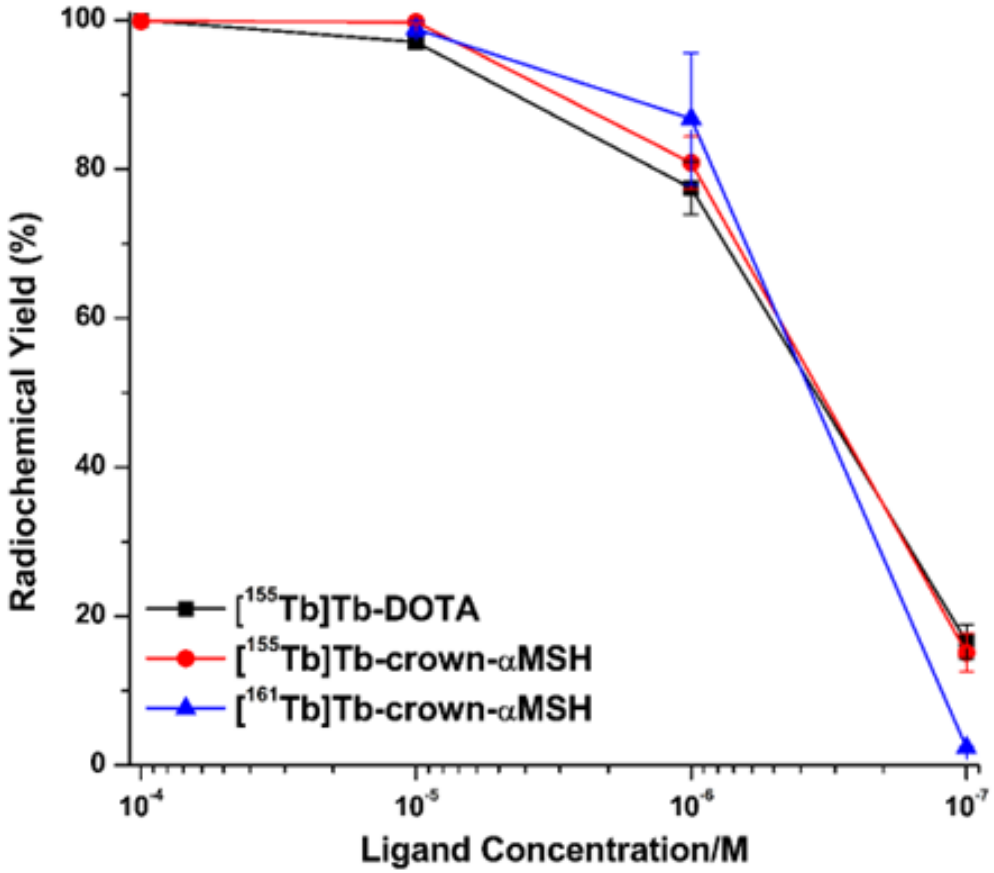
DOTA-αMSH



crown-αMSH

Concentration-dependent radiolabeling studies with:

- [^{155}Tb]Tb^{3+} (100 kBq) or [^{161}Tb]Tb^{3+} (100 kBq),
- DOTA (90 °C, 30 min) and crown-αMSH (RT, 15 min)
- NH_4OAc (0.5 M, pH 6.0)



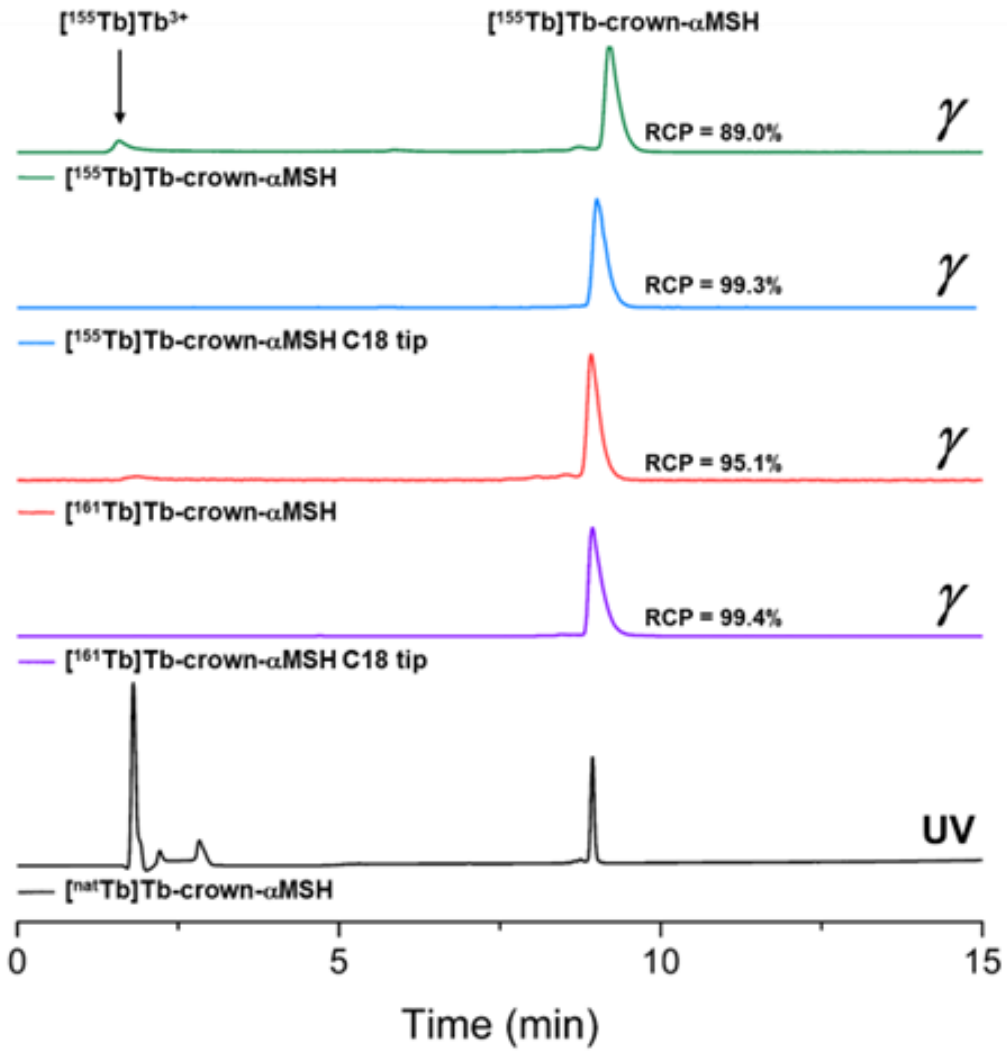
Credits to: Hua Yang, Luke Wharton, Peter Kunz, Michiel Van de Voorde

*[^{161}Tb] supplied by SCK CEN

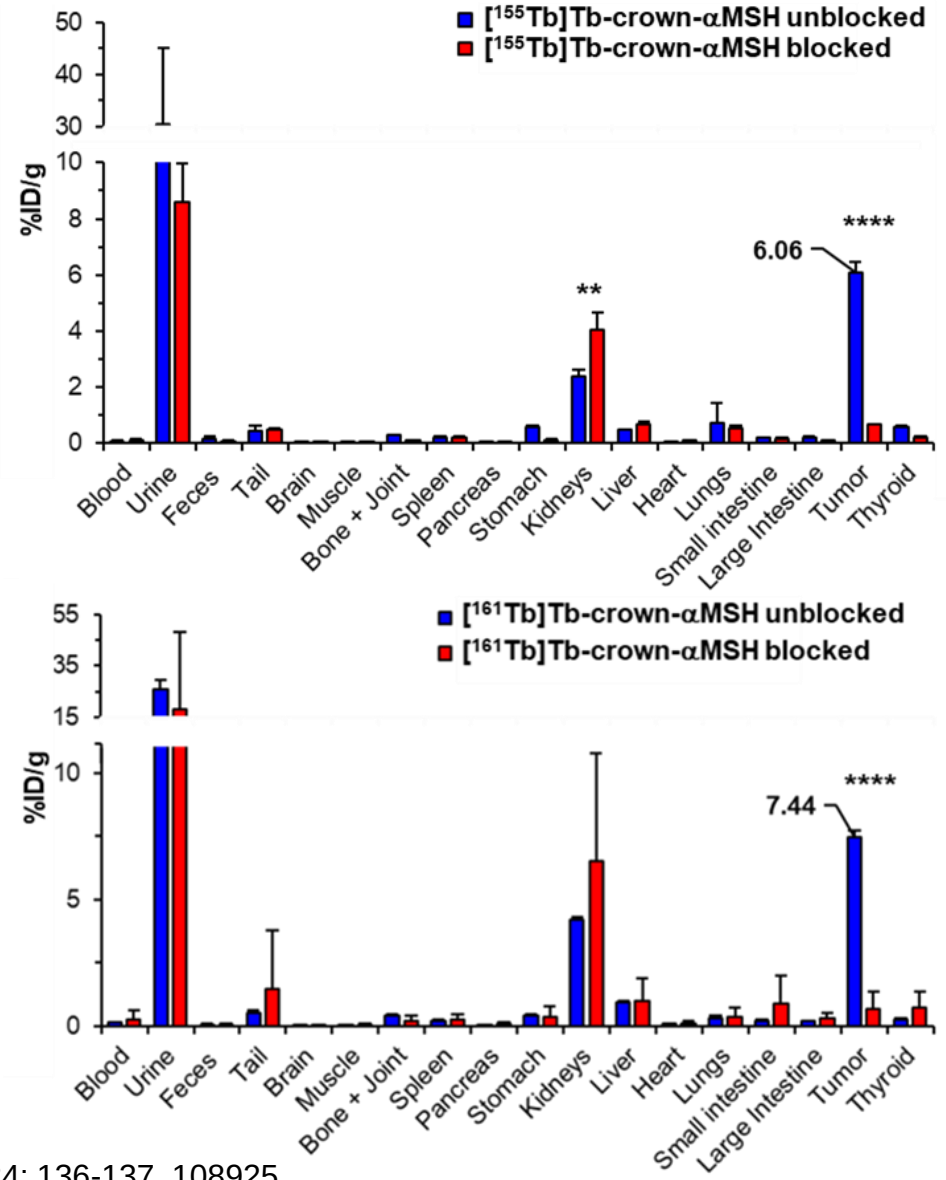
L Wharton et al. Nuc. Med. Biol 2024; 136-137, 108925

[$^{155/161}$Tb]Tb-crown-αMSH

HPLC chromatograms for [$^{155/161/nat}$Tb]Tb-crown-αMSH



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



Credits to: Hua Yang, Luke Wharton, Peter Kunz, Michiel Van de Voorde

*[^{161}Tb] supplied by SCK CEN

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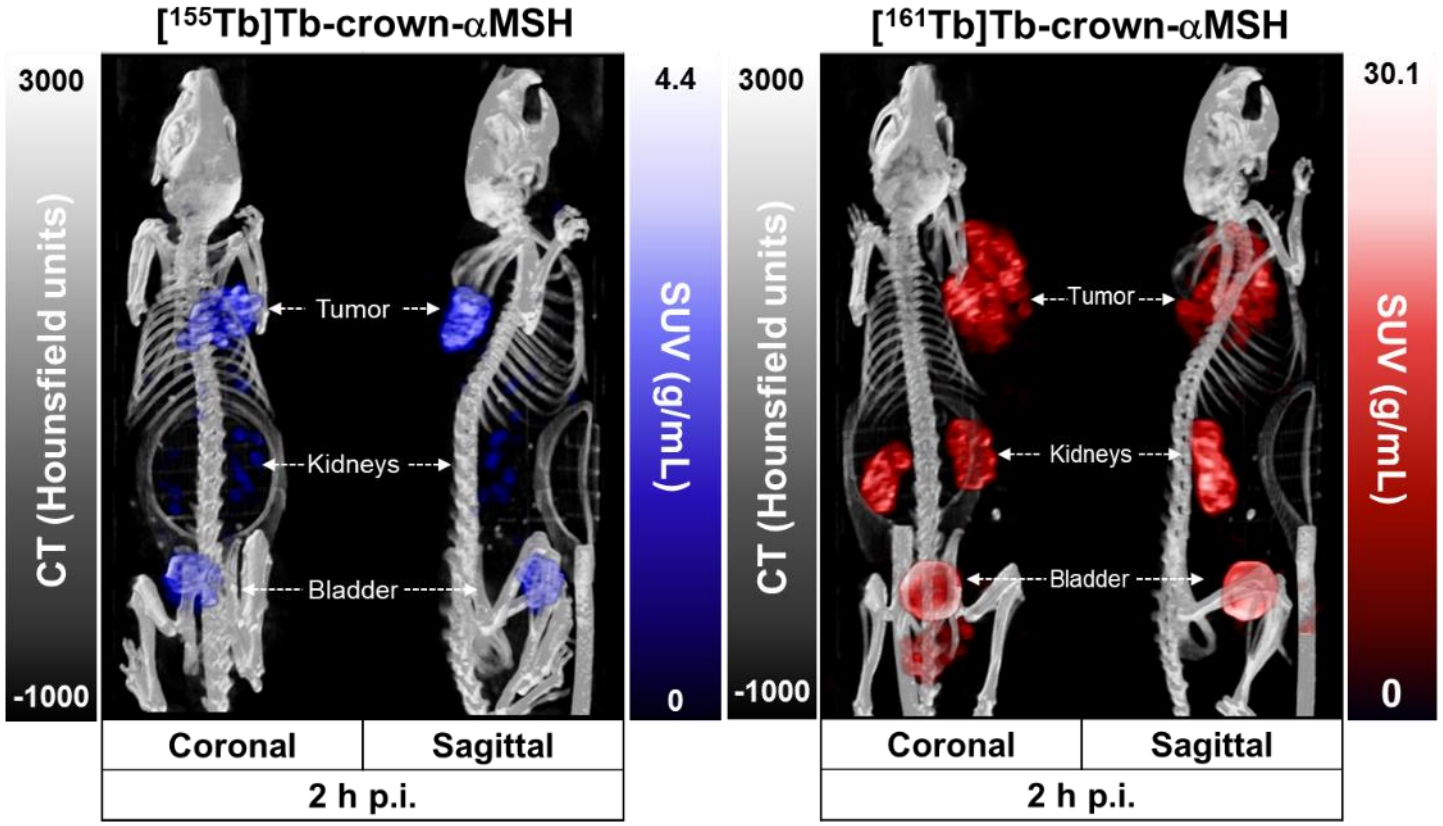
Quantitative SPECT with [$^{155/161}$Tb]Tb-crown-αMSH

SPECT imaging in C57BL/6J mice bearing B16-F10 melanoma tumors at 2 h post administration



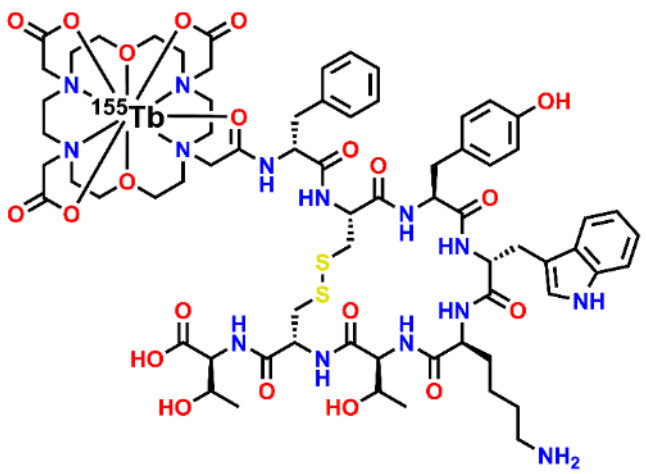
[^{155}Tb]Tb-crown-αMSH (~196 kBq/subject, 21.7 MBq/nmol)
[^{161}Tb]Tb-crown-αMSH (~3.30 MBq/subject, 39.6 MBq/nmol)

	[^{155}Tb]Tb-crown-αMSH		[^{161}Tb]Tb-crown-αMSH	
	SPECT %ID/g	BioD %ID/g	SPECT %ID/g	BioD %ID/g
Tumor	8.2	9.3	3.3	3.3
Kidney (L)	2.9	4.0	6.5	6.2
Kidney (R)	3.6		6.0	
Bladder	18.9	21.8	109.8	136.8

L Wharton et al. Nuc. Med. Biol 2024; 136-137, 108925

Biodistribution of [^{155}Tb]- and [^{161}Tb]Tb-crown-TATE

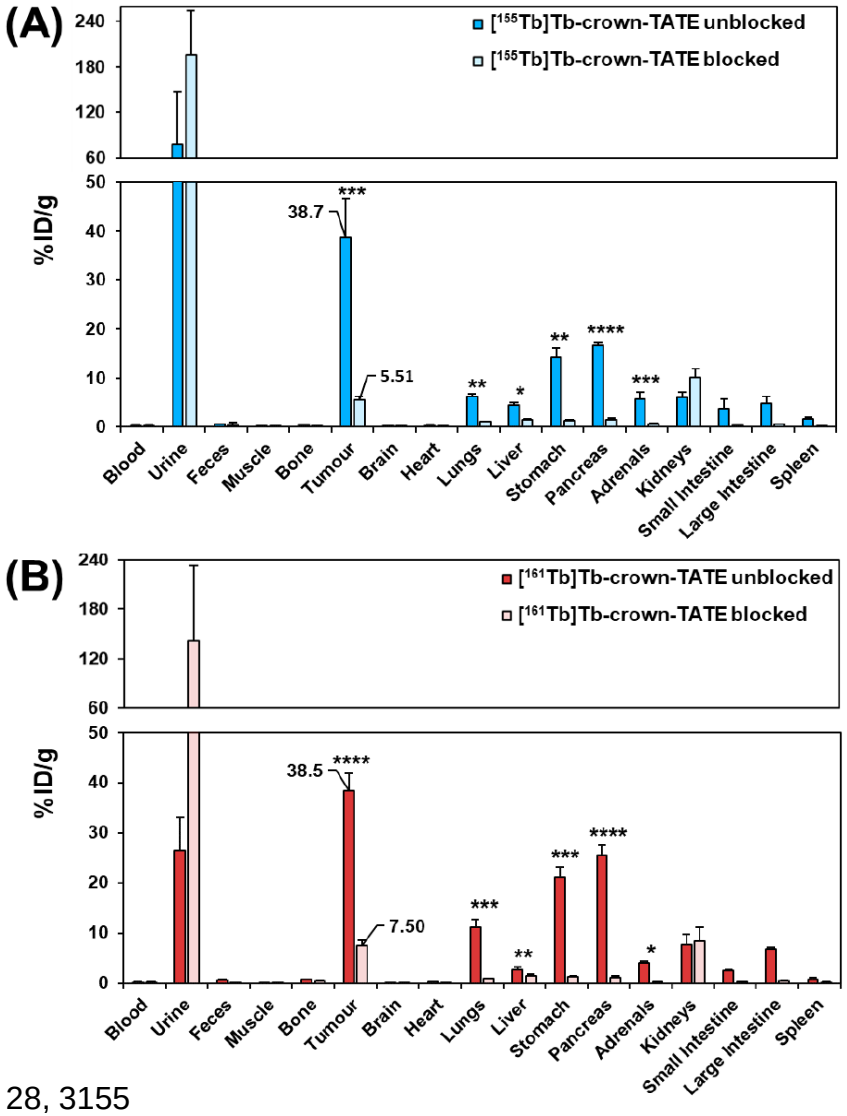
- [^{155}Tb]Tb-crown-TATE was prepared with high molar activity and radiochemical purity.



[^{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

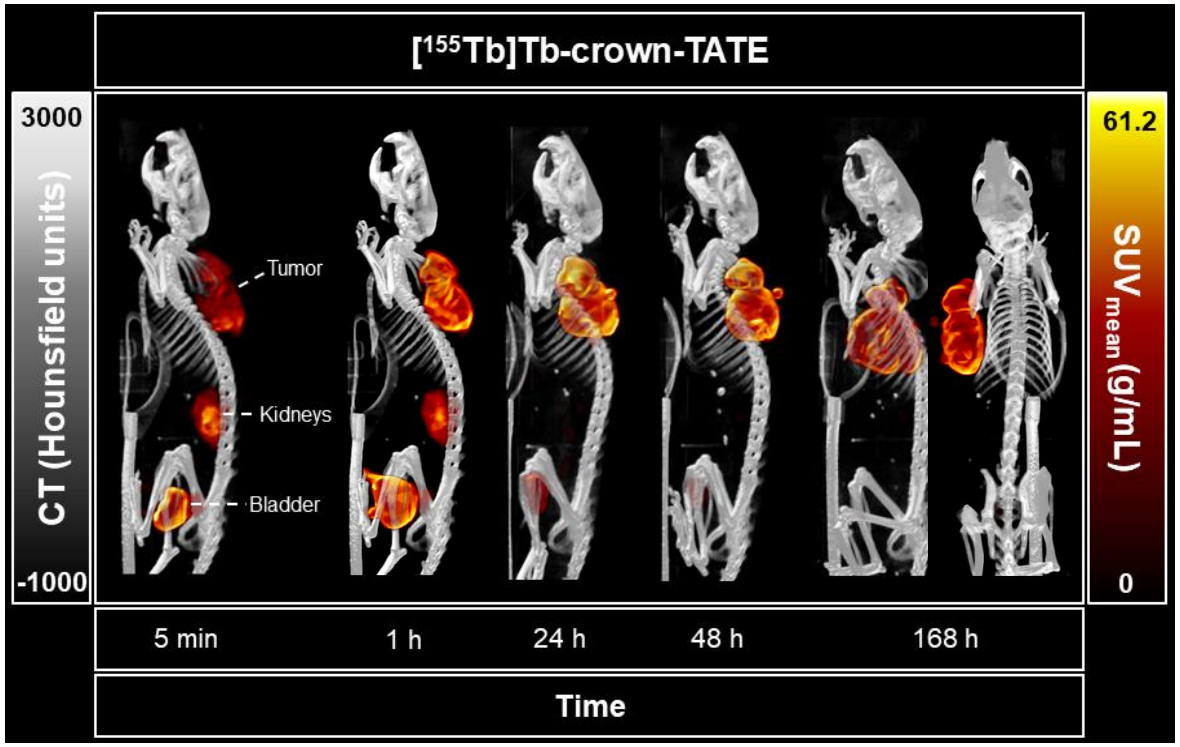
- Biodistribution in NRG mice bearing AR42J tumours; 2 hrs p.i. ~175kBq [^{155}Tb]- and ~850 kBq [^{161}Tb]Tb-crown-TATE.



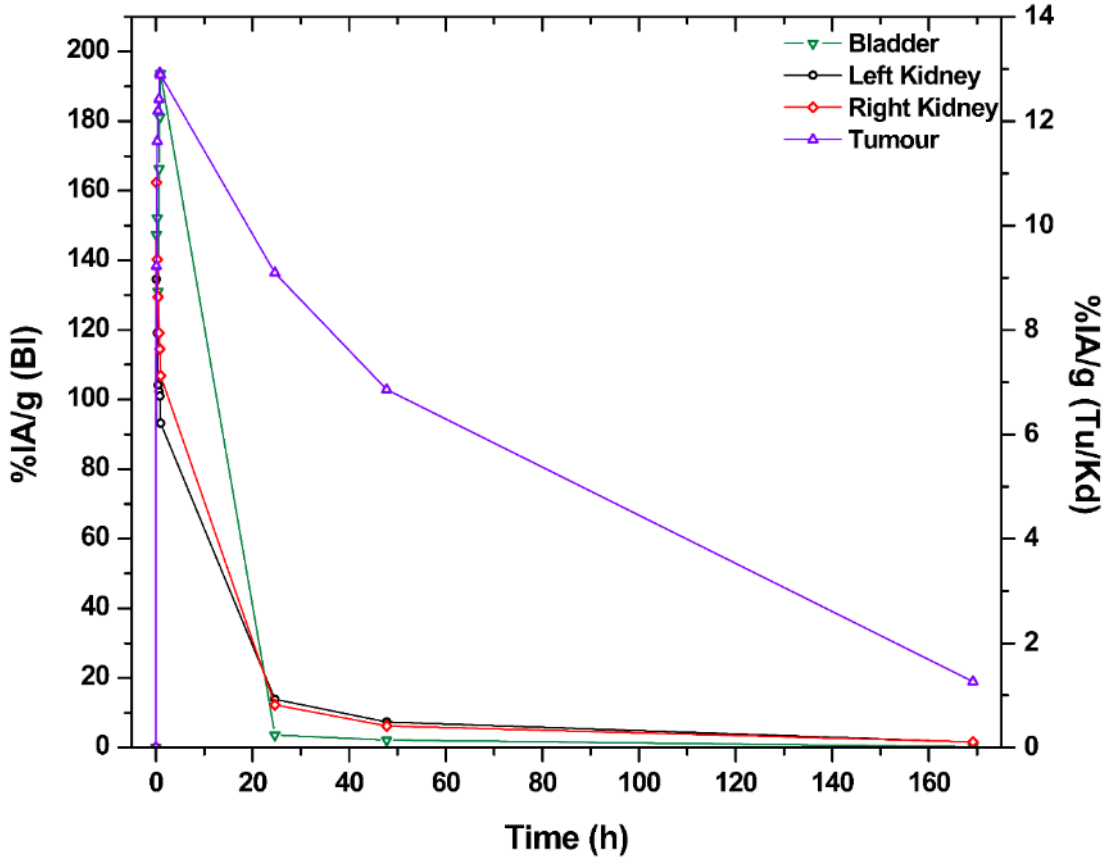
Credits to: H Yang, L Wharton, P Kunz, M Van de Voorde
*[^{161}Tb] supplied by SCK CEN

L Wharton et al. Molecules 2023; 28, 3155

Longitudinal [^{155}Tb] SPECT/CT Imaging



Maximum intensity projections from quantitative static SPECT/CT scans of [^{155}Tb]Tb-crown-TATE (11.1 MBq, 613 pmol) from 0-to-168 h post-administration in male NRG mice bearing AR42J tumour xenografts on left-shoulder.



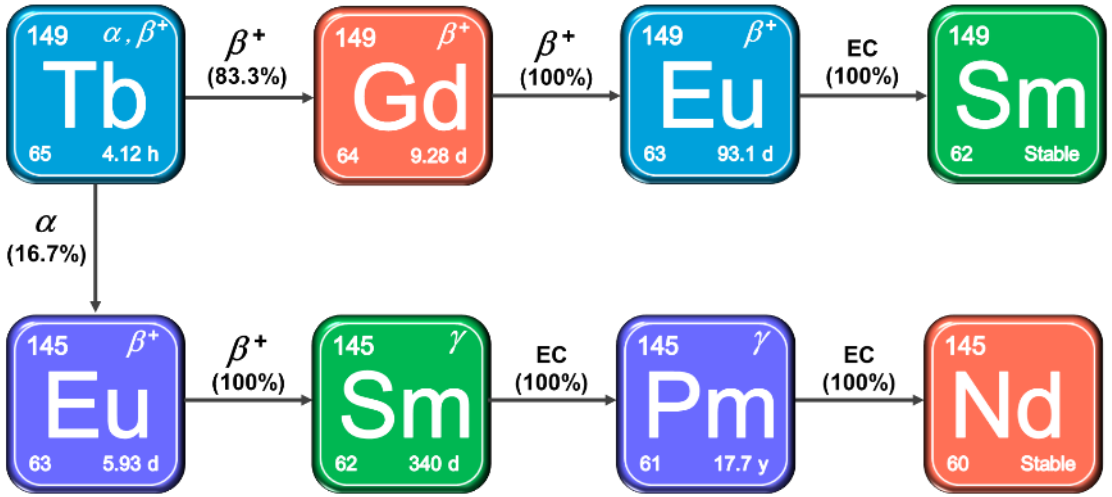
Credits to: H Yang, L Wharton, D Zhang. M Osooly, C Rodríguez-Rodríguez

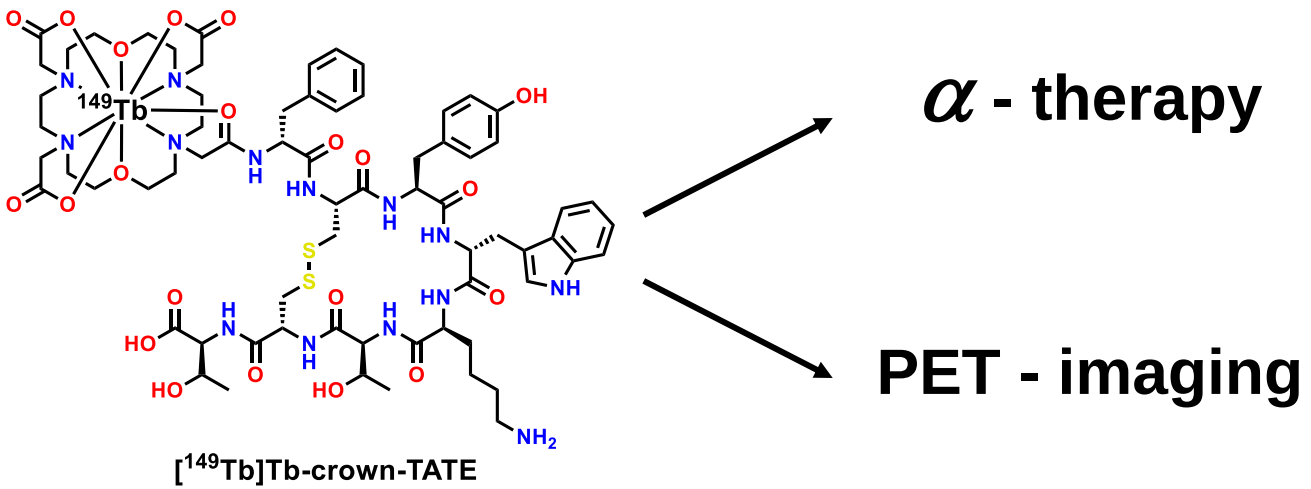
L Wharton et al. Molecules 2023; 28, 3155

Terbium-149

Unpublished results

- Overview:
  - ^{149}Tb ($t_{1/2}$ = 4.12 h) is a short-lived α and β^+-emitter; potential for theranostics involving alpha-therapy and PET imaging (dosimetry).
- Goals:
  - First-time production of ^{149}Tb at TRIUMF using ISAC/ISOL.
  - Isolate and quantify activity.
  - Perform radiolabelling studies with crown-TATE.
  - Undertake preliminary biodistribution and PET imaging at BCCA.



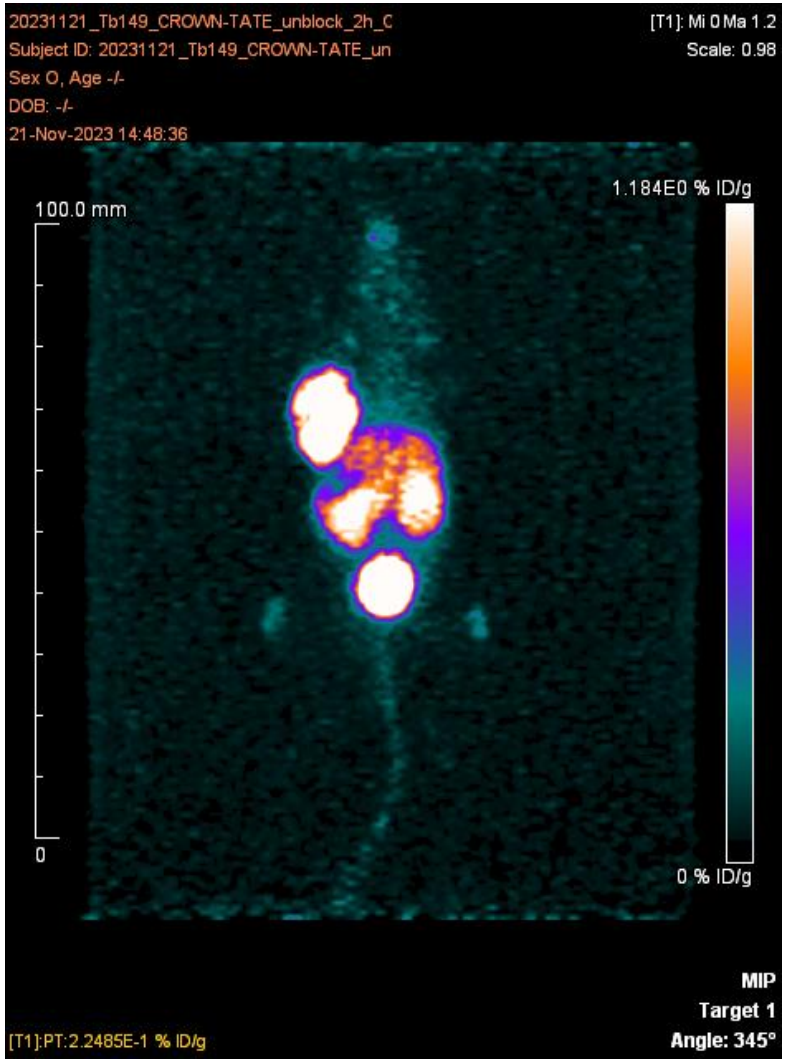


Credits to: H Yang, L Wharton, P Kunz, J Lassen, H Merkens, N Colpo

Terbium-149

Unpublished results

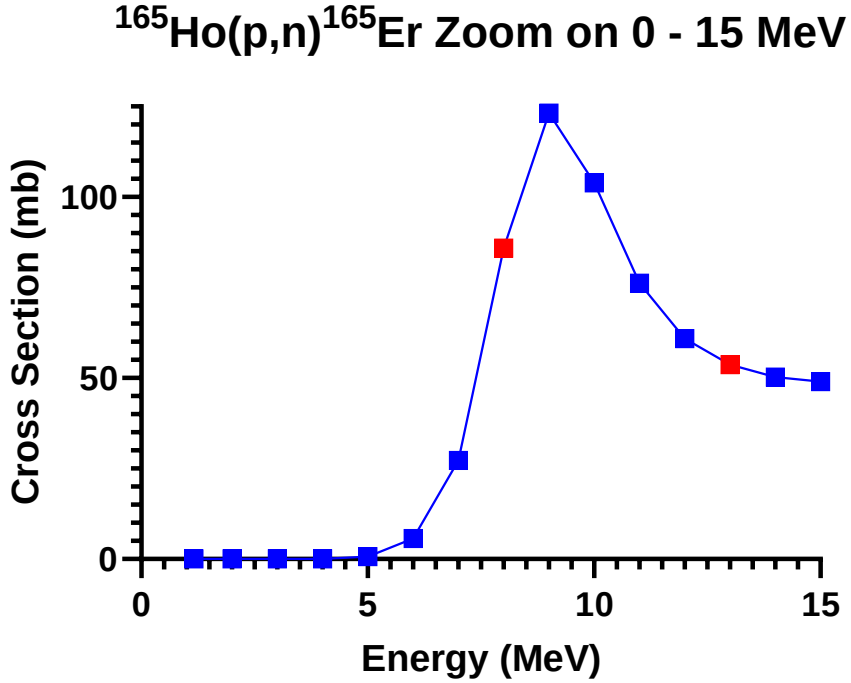
- Goals:
  - ~ First-time production of ^{149}Tb at TRIUMF using ISAC/ISOL.
    - 4 h implantation time, 30 min cool down.
    - 2 production runs.
    - 680 μSv/hr (shielded).
  - ✓ Isolate and quantify activity.
    - ~ 65 MBq ^{149}Tb in 87 μL water.
  - ✓ Perform radiolabelling studies with crown-TATE.
    - 100% RCY (RT, 30 min).
    - Molar activity: 53.6 MBq/nmol.
  - ✗ Undertake preliminary biodistribution and PET imaging at BCCA.
    - No prior calibration of PET scanner or gamma counter.
    - Too much activity injected per animal (10 MBq/animal).
    - Wrong energy windows for gamma counting.



Credits to: H Yang, L Wharton, P Kunz, J Lassen, H Merkens, N Colpo

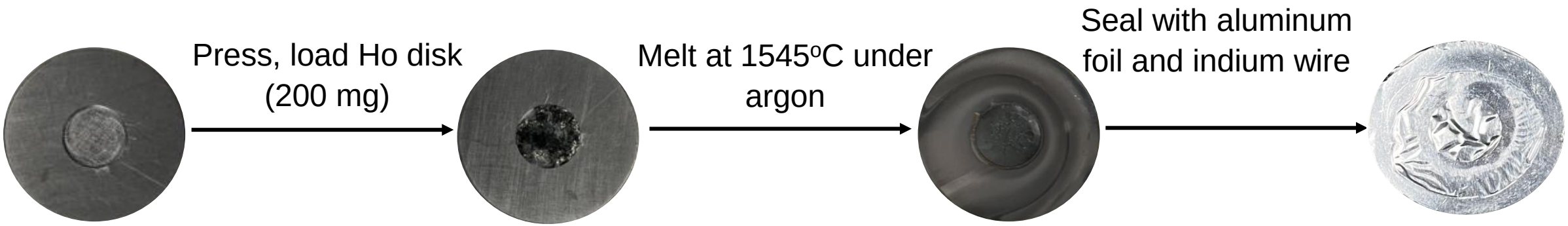
^{165}Ho(p,n)^{165}Er at 13 MeV Cyclotron

- Production via low-energy (13 MeV) cyclotron
- ^{165}Ho(p,n)^{165}Er; ^{165}Ho is monoisotopic, available
- Pure Auger e^- emitter
- Therapy potential: 7 Auger e^- per decay
- Preclinical SPECT imaging: 47.1 keV (59.4%) and 54.3 keV (14.3%)



^{165}Ho Target Production

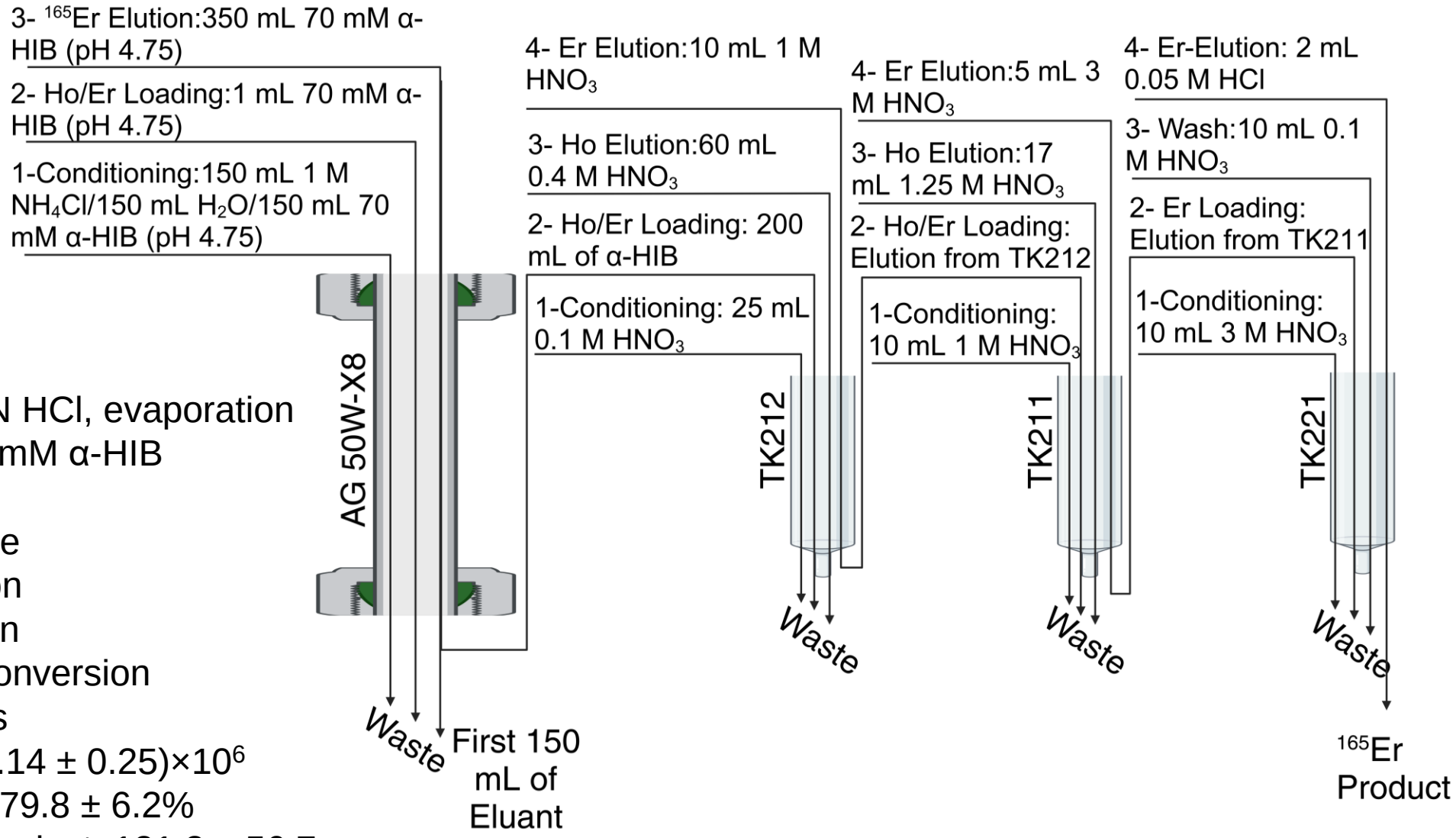
- 200 mg ^{165}Ho
- 250 mg.cm^{-2} or 0.29 mm of thickness
- 8 MeV exit energy
- 25 MBq·μA^{-1}h^{-1}



B. Saeedi Saghez, H. Yang, V Radchenko *Inorganic Chemistry*, 2024,*63*(12), 5330–5340.

^{165}Er Purification

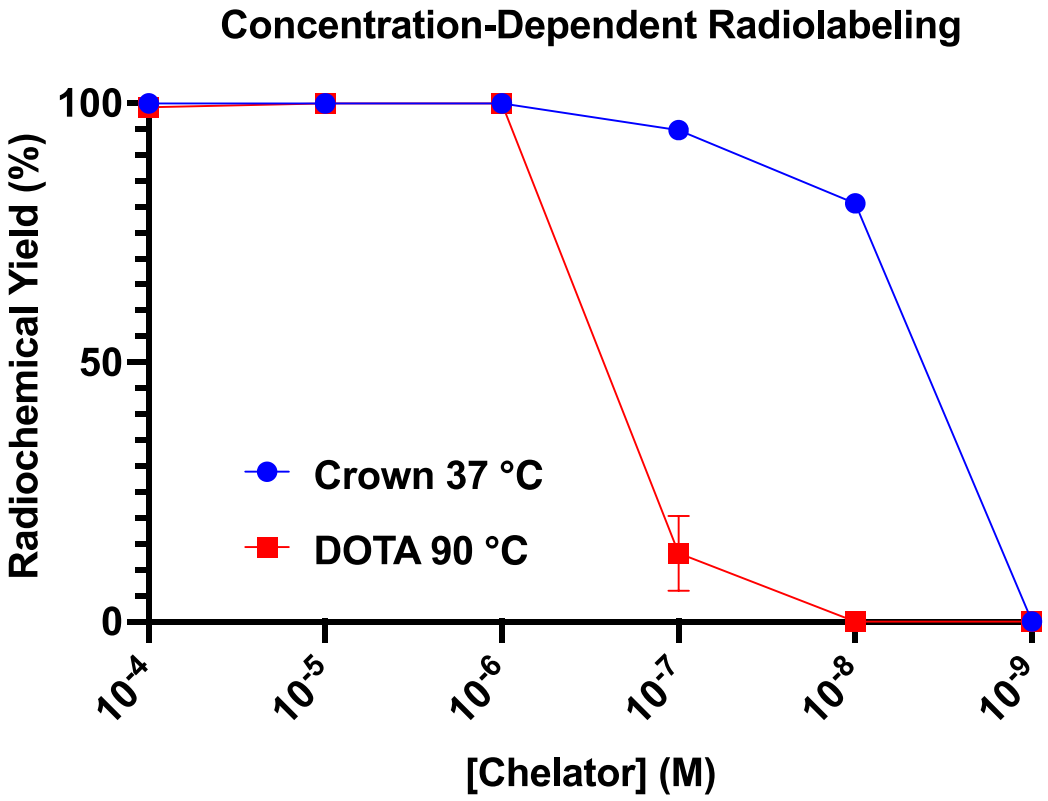
- Acid Dissolution: 12N HCl, evaporation
  - Redisolve in 70 mM α-HIB
- Four resin system:
  - Cation exchange
  - TK212 extraction
  - TK211 extraction
  - TK221 media conversion
- Time: 4.0 ± 0.5 hours
- Separation factor: (1.14 ± 0.25)×10^6
- ^{165}Er recovery (DC): 79.8 ± 6.2%
- ^{165}Ho remaining in product: 121.2 ± 56.7 ng

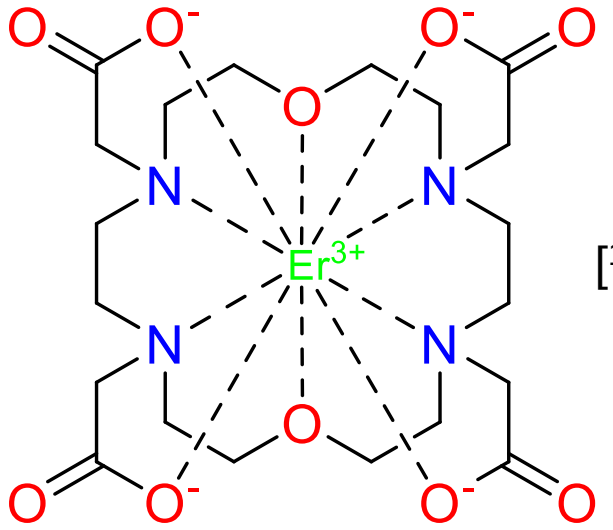


B. Saeedi Saghez, H. Yang, V Radchenko *Inorganic Chemistry*, 2024,*63*(12), 5330–5340.

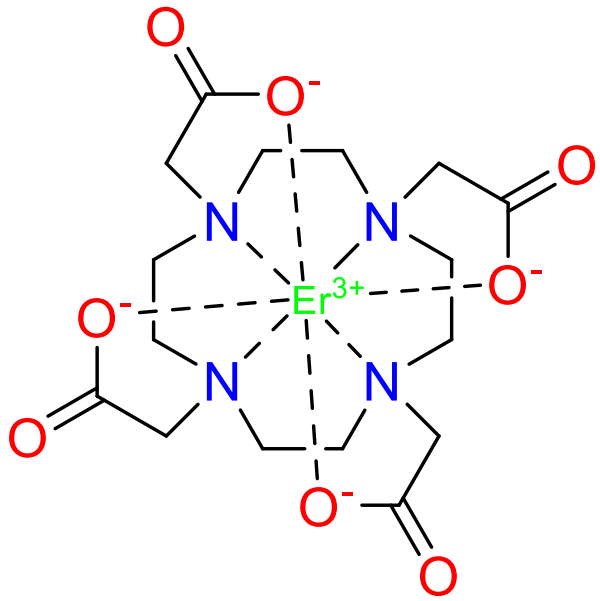
^{165}Er Radiolabeling

- 0.5 M NH_4OAc buffer (pH 5.5)
- 500 kBq ^{165}Er at EoS
- 50 µL total volume





[^{165}Er]Er-Crown

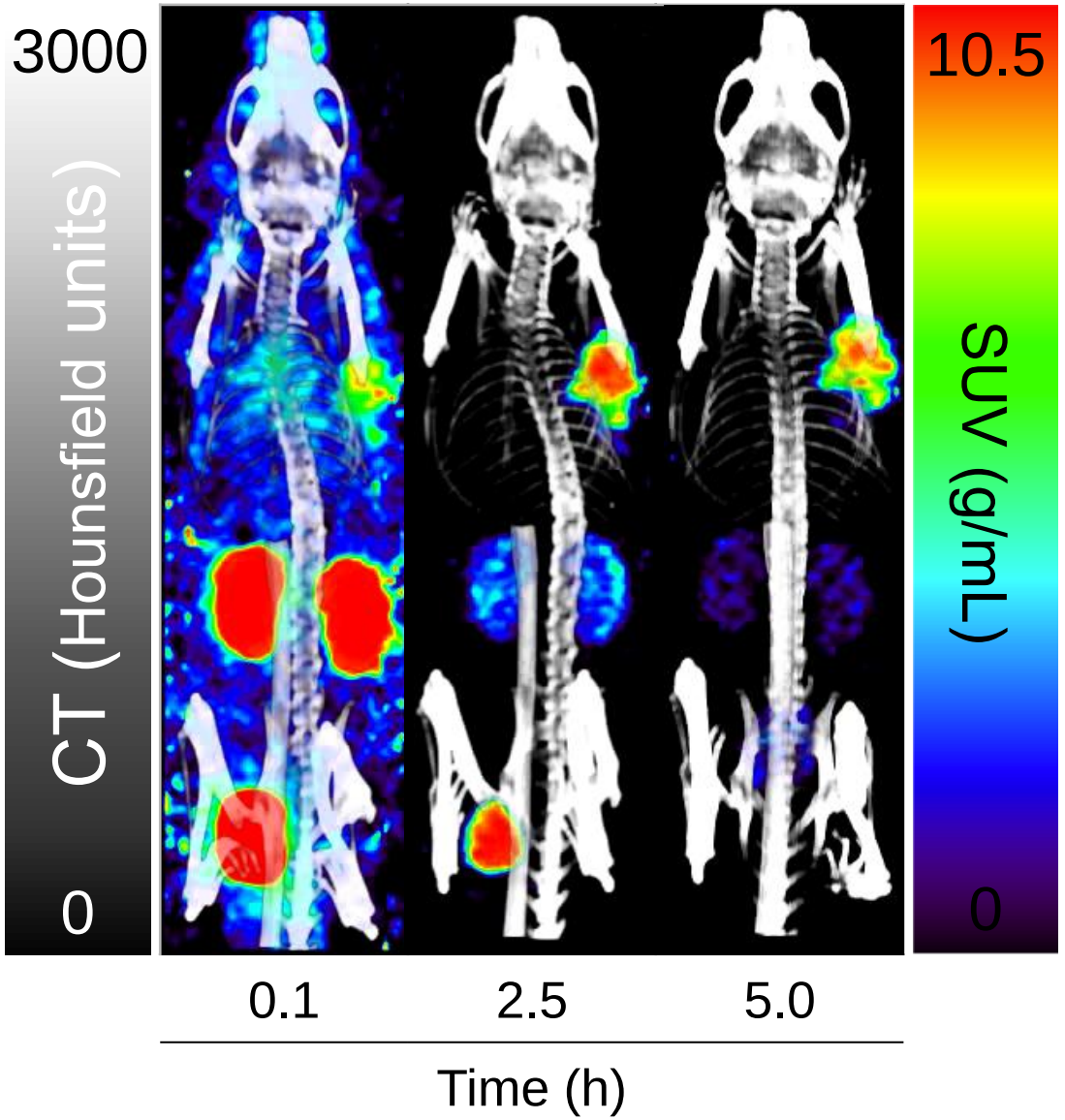


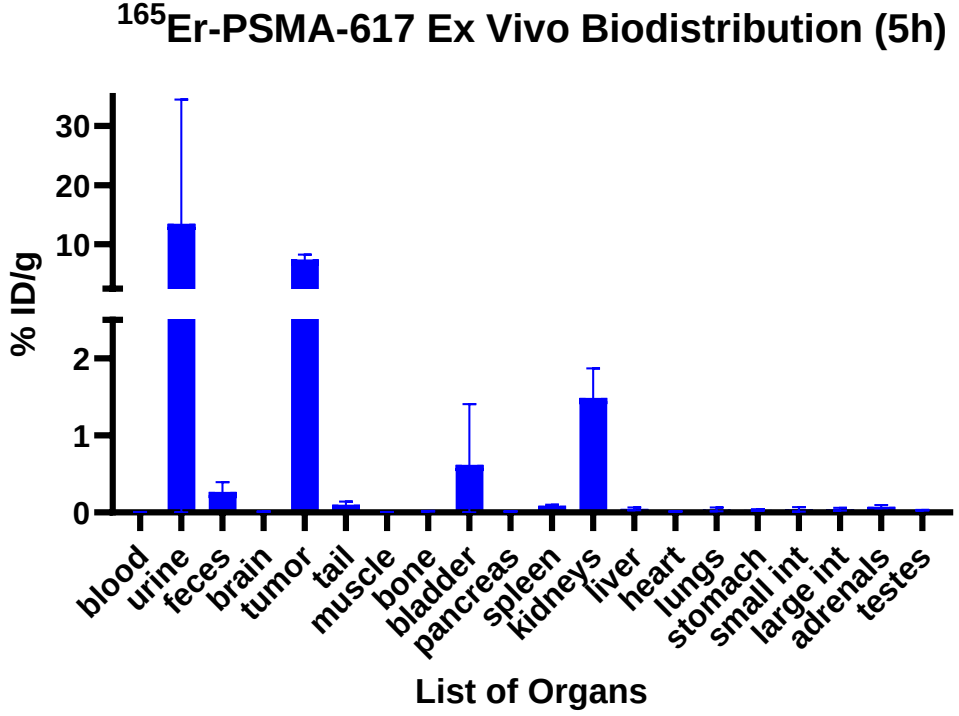
[^{165}Er]Er-DOTA

B. Saeedi Saghez, H. Yang, V Radchenko *Inorganic Chemistry*, 2024,*63*(12), 5330–5340.

^{165}Er-PSMA-617 SPECT and *ex vivo* Biodistribution

MIPs for LNCaP tumor bearing mice injected with ^{165}Er-PSMA-617 (21 MBq, 0.2 nmol)

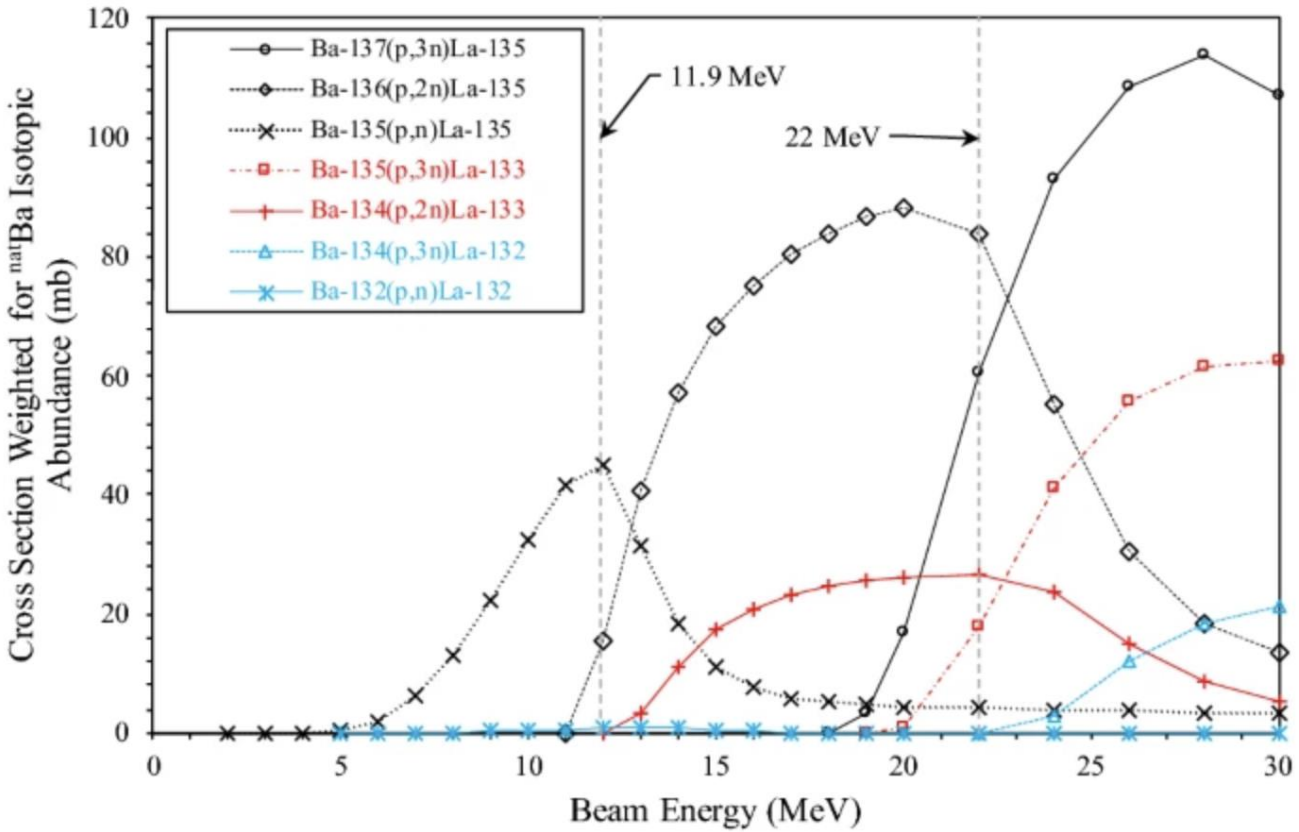




Organ	Density (g/mL)	5.0 h SPECT			5.0 h BioD
		SUV (g/mL)	%ID/mL	%ID/g	%ID/g
Tumor	1	3.86	9.14	9.14	8.14
Kidneys	1.06	0.28	0.92	0.88	1.25
Bladder + Urine	1.03	0.47	1.57	1.53	2.55

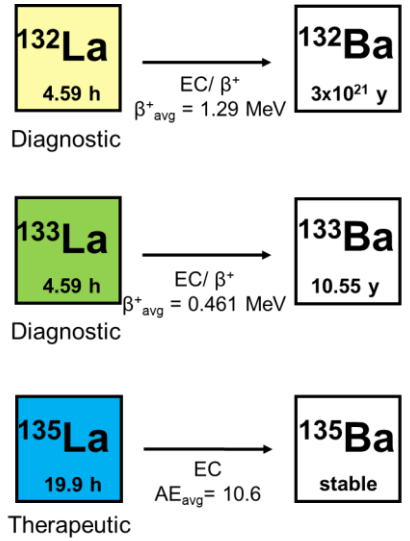
B. Saeedi Saghez, H. Yang, **Unpublished Data**

Radiolanthanum as an ^{225}Ac Surrogate



Nelson, B., *et al*. Sci. Rep. 2020, *10*, 22203.

^{132}Ba abundance = 0.1%
^{134}Ba abundance = 2.42%
^{135}Ba abundance = 6.59%
^{136}Ba abundance = 7.85%
^{137}Ba abundance = 11.2%
^{138}Ba abundance = 71.7%

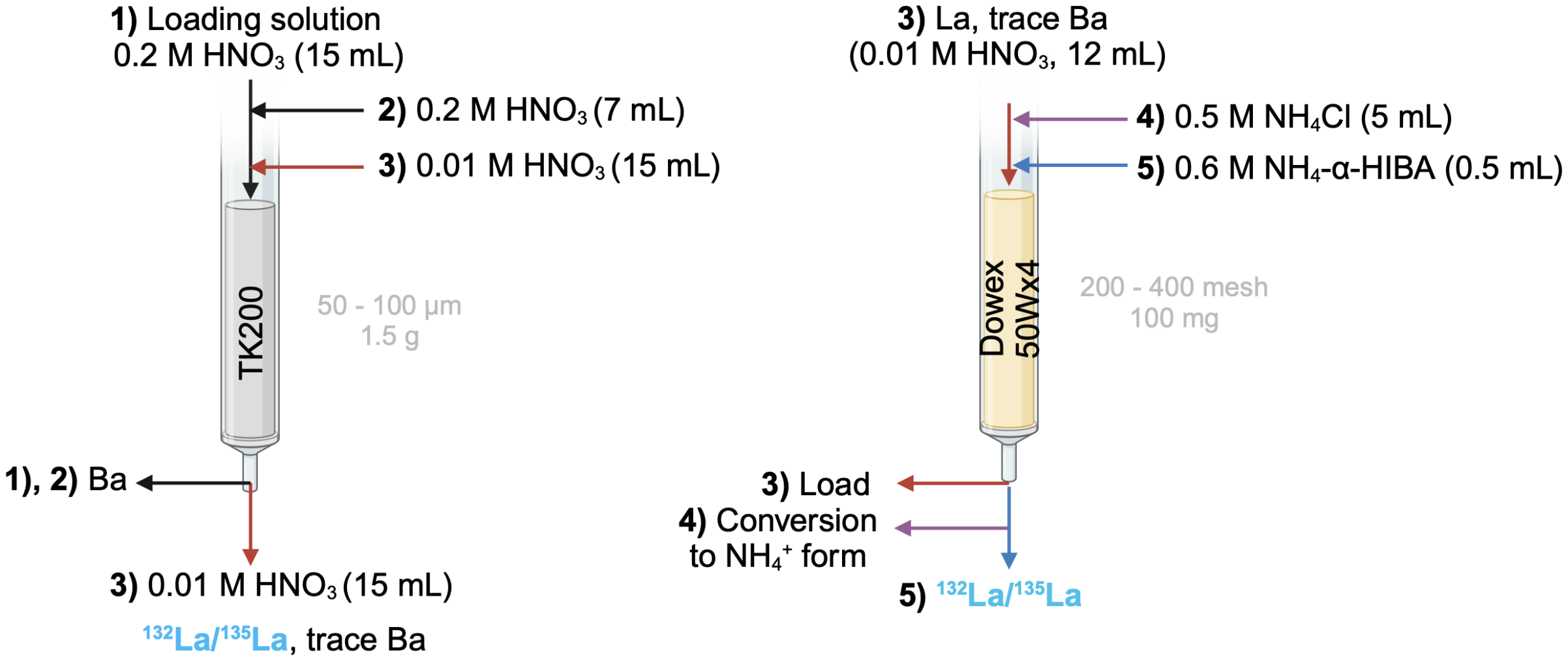


Sealed coin target (In wire) to prevent oxidation during transport, installation, removal

2-hour irradiation at 10 µA (n= 3):
^{132}La = 4.9 ± 0.8 MBq
^{135}La = 112.8 ± 18.3 MBq

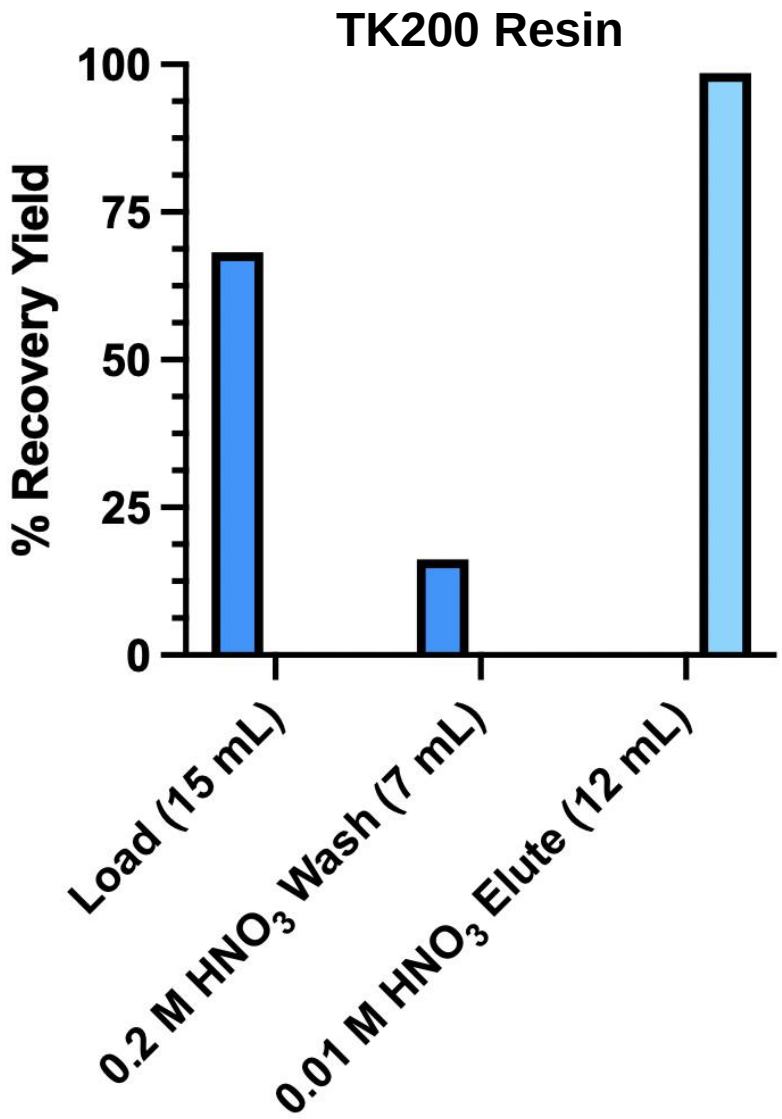
Credits to: B McNeil, C Ramogida

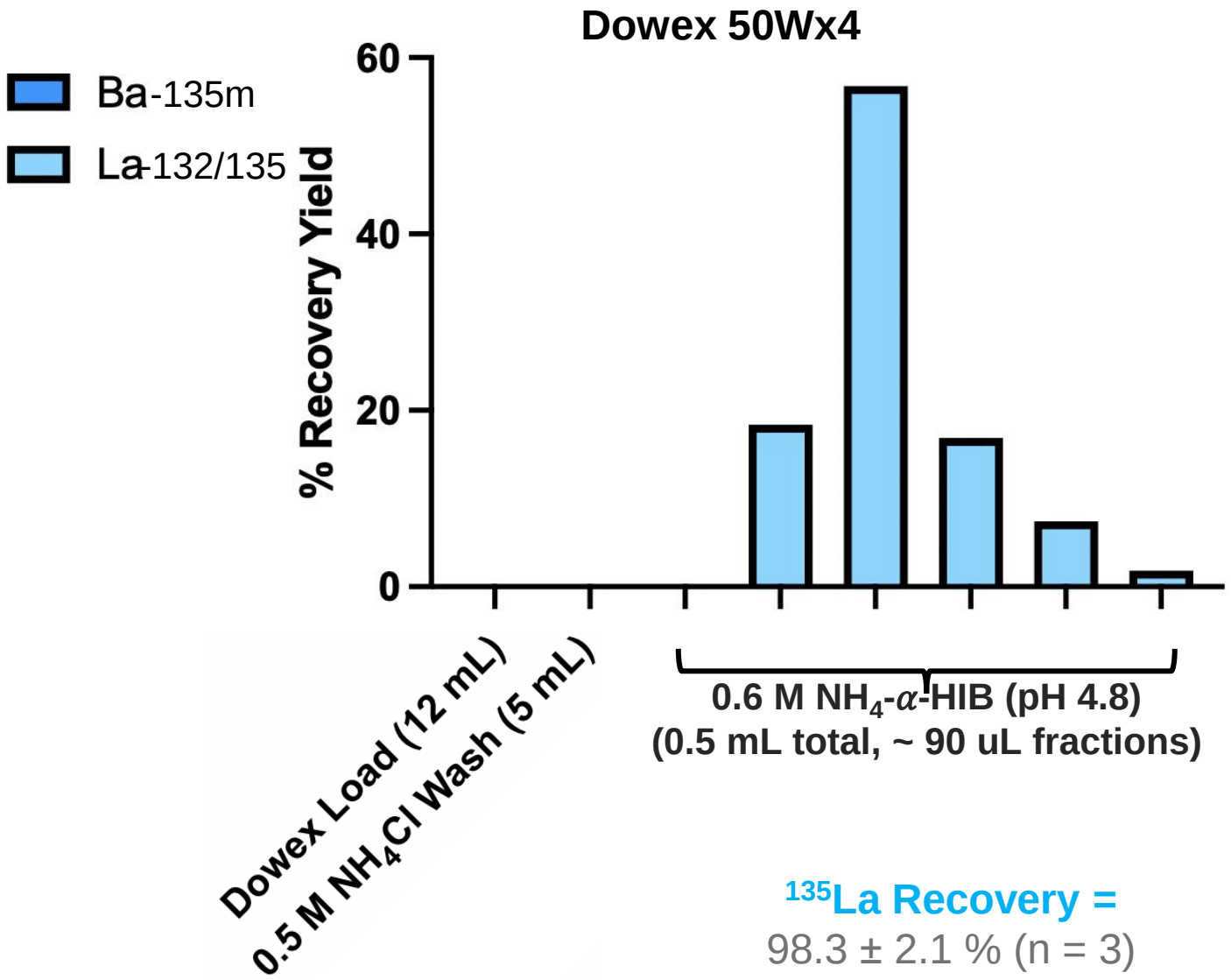
Proposed La Purification Method



Credits to: B McNeil, C Ramogida, E Kurakina, V Radchenko

La Elution Profile



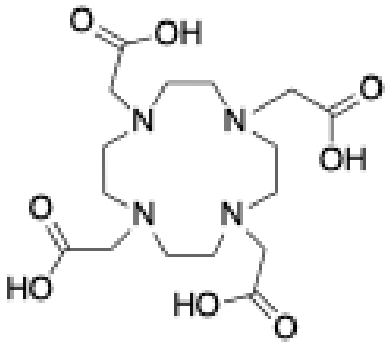


^{135}La Recovery =

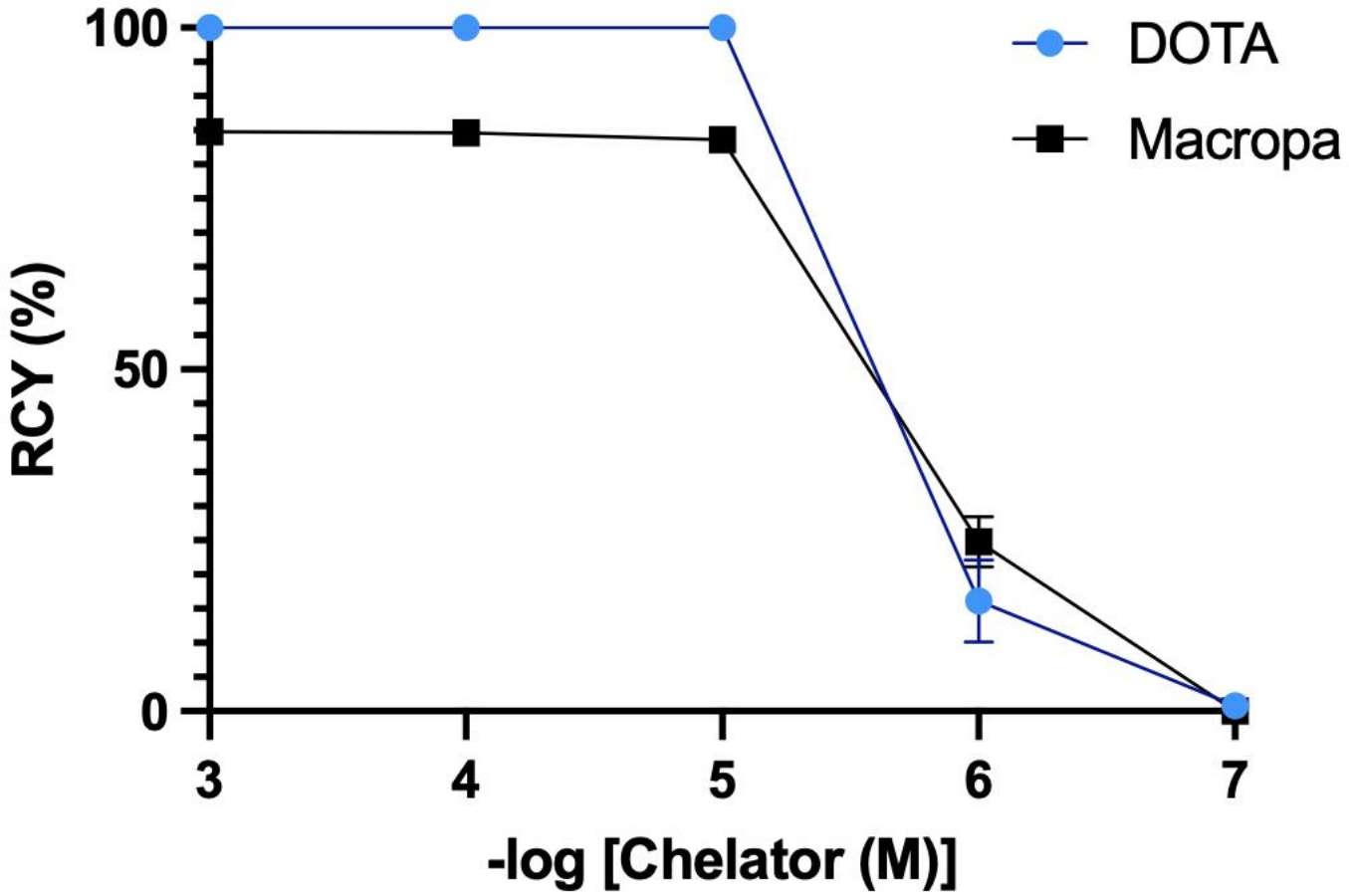
98.3 ± 2.1 % (n = 3)

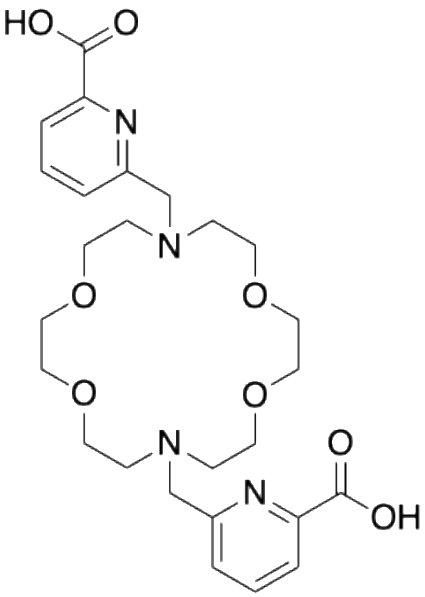
Credits to: B McNeil, C Ramogida, E Kurakina, V Radchenko

^{135}La Radiolabeling



DOTA





Macropa

(740 kBq ^{135}La, 0.2 M NH_4-α-HIB pH ~5, 80 ^{o}C, 30 minutes, n = 6)

Summary

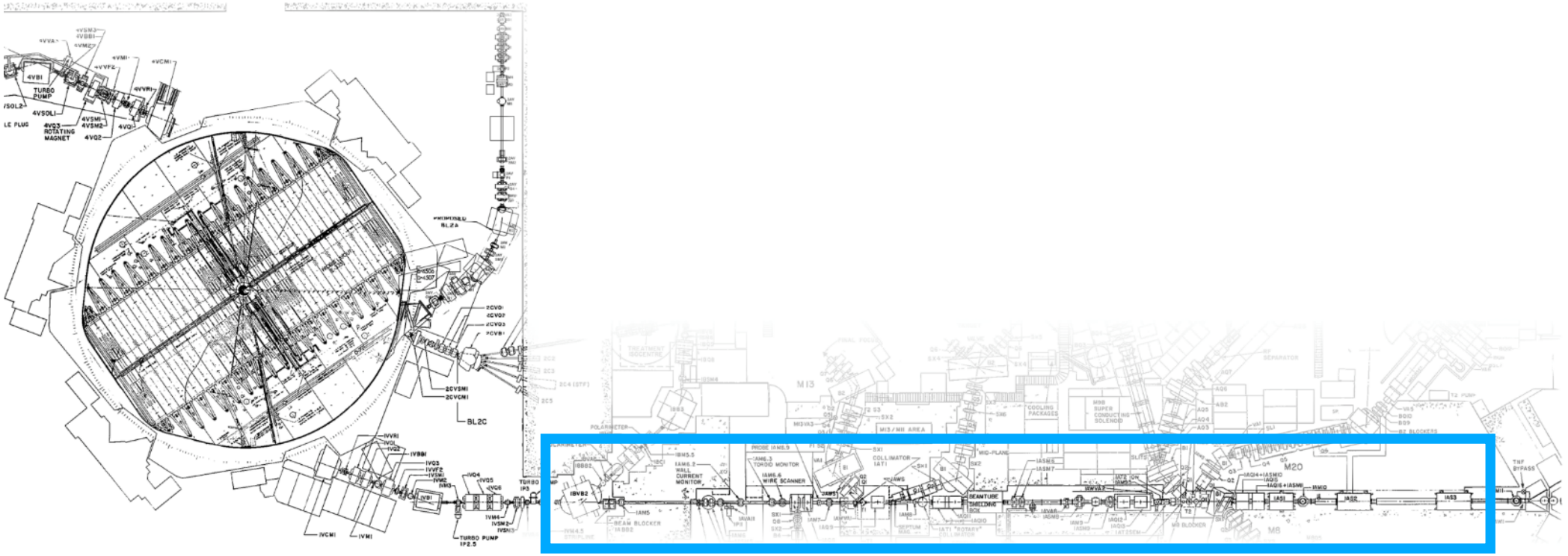
- ISAC-ISOL can produce certain isotopes in sufficient yield and purity to allow radiochemistry and radiopharmaceutical development
  - Important for development of isotopes such as ^{149}Tb
- With advancements in solid-target technology, low energy cyclotrons can produce an increasing repertoire of radiolanoids (and radioactinides)
- Macrocyclic chelates are proving to be powerful enablers of radiolanthanides (and radioactinides)
- Several radiolanthanide radiopharmaceuticals were produced and used as imaging- and/or therapy tools for melanoma and neuroendocrine tumor models.
- Applications in other tumour models, and therapy response studies are ongoing

Aging Infrastructure: Replacing TRIUMF's Main Beamline

Objective: replace, enhance functionality of BL1A

Funding: 2025 Cdn Foundation for Innovation - Infrastructure Fund

Next Step: Awaiting Decision



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 labs
2 QC laboratories
Quarantined storage
2 floors of office space
Hot Commissioning 2025

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NRC·CNRC Canada

NSERC CRSNG

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

Canadian Cancer Society

New Frontiers in Research Fund
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NET NEUROENDOCRINE TUMOR RESEARCH FOUNDATION
DEDICATED TO CURING NEUROENDOCRINE CANCER

Thank you
Merci

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