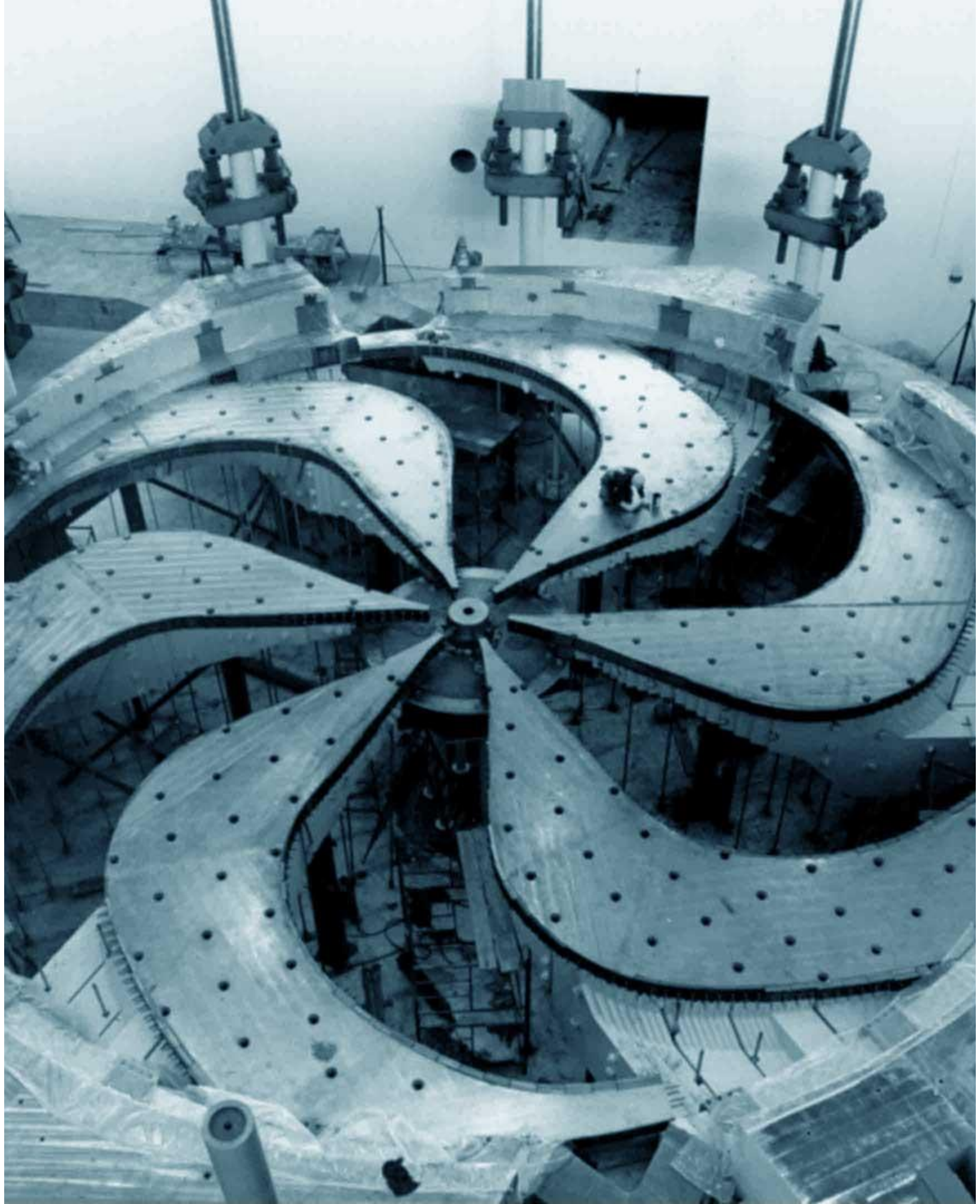
TRIUMF

Life Sciences

2025-2030 Five Year Plan



Aug 2nd, 2023
Paul Schaffer, PhD
Director, Life Sciences

Discovery, accelerated

Today's presentation:

The Backdrop: LS Vision, Mission; The Team; Our Pillars

A Summary of Achievements: Infrastructure and Research

IAMI Status and Ramp-up

What's coming: 2025-2030

Life Sciences Vision and Mission Statements

Vision Statement:

The Life Sciences Division will place TRIUMF as a global leader in the application of accelerator research toward the life sciences in a manner that derives maximum societal and economic benefit.

Mission Statement:

The Life Sciences Division at TRIUMF will innovate new accelerator technologies, isotopes and radiopharmaceuticals to better health, understand life and better the environment. The Division will leverage its core expertise to lead in our community as an interdisciplinary centre of excellence that enables ourselves, and our partners, with world-class people and state-of-the-art facilities.

Current Life Sciences Priorities

1) Build IAMI
2) Implement GMP capabilities – complete validation master plan
3) Grow/Enable Therapeutic Isotope Program
4) Deliver on our commitments (to our researchers and our partners)

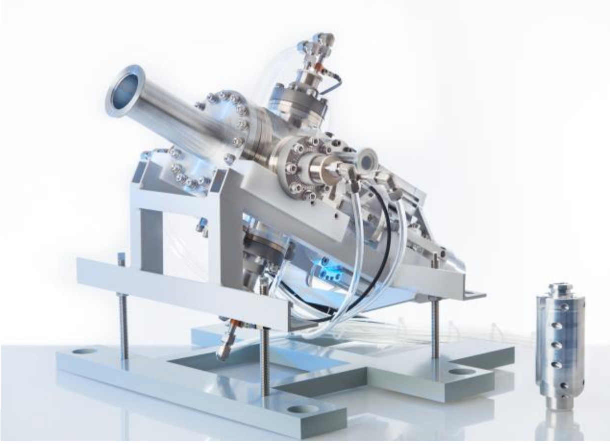
These priorities are set via internal reviews, coupled with external peer evaluation (LSPEC)

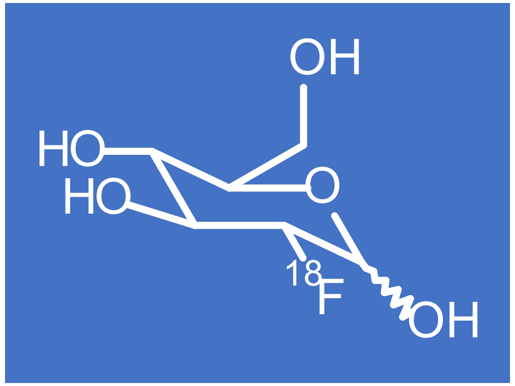
Align with TRIUMF's goals within:

- Science and Technology
    - Make ground-breaking discoveries across our multidisciplinary research portfolio
    - Strengthen our position as a world-leading particle accelerator centre
- People and Skills
    - Become a hub for interdisciplinary education and training
    - Inspire Canadians to discover and innovate
- Innovation and Collaboration
    - Translate science and technology into innovation
    - Drive national and international collaboration in research, technology and innovation

Life Sciences at TRIUMF

Applied Ion Beams | Nuclear Chemistry | Applied Isotopes

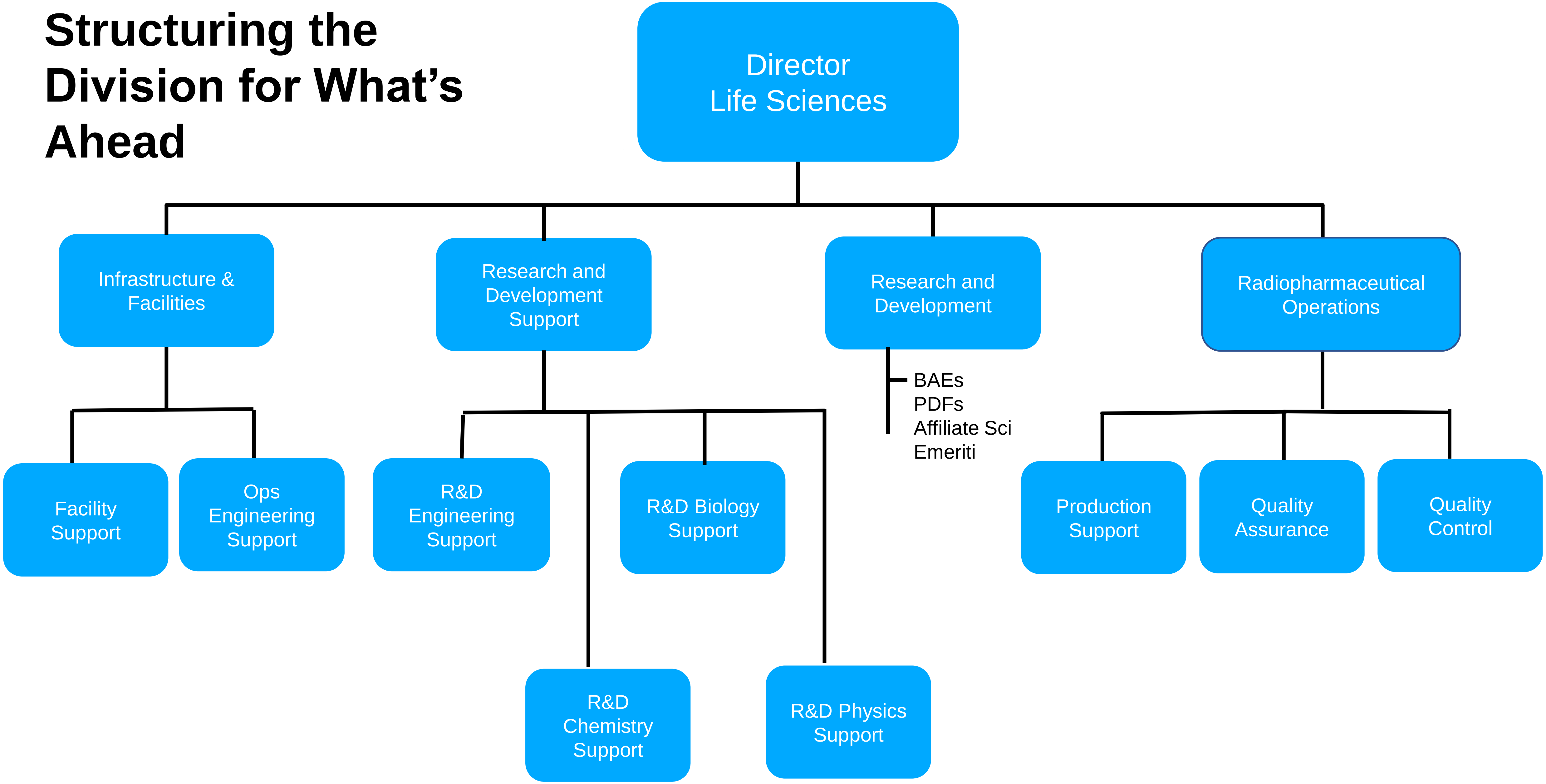


TRIUMF Life Sciences focuses on advancing accelerator-based technology for the development of isotopes that can improve life

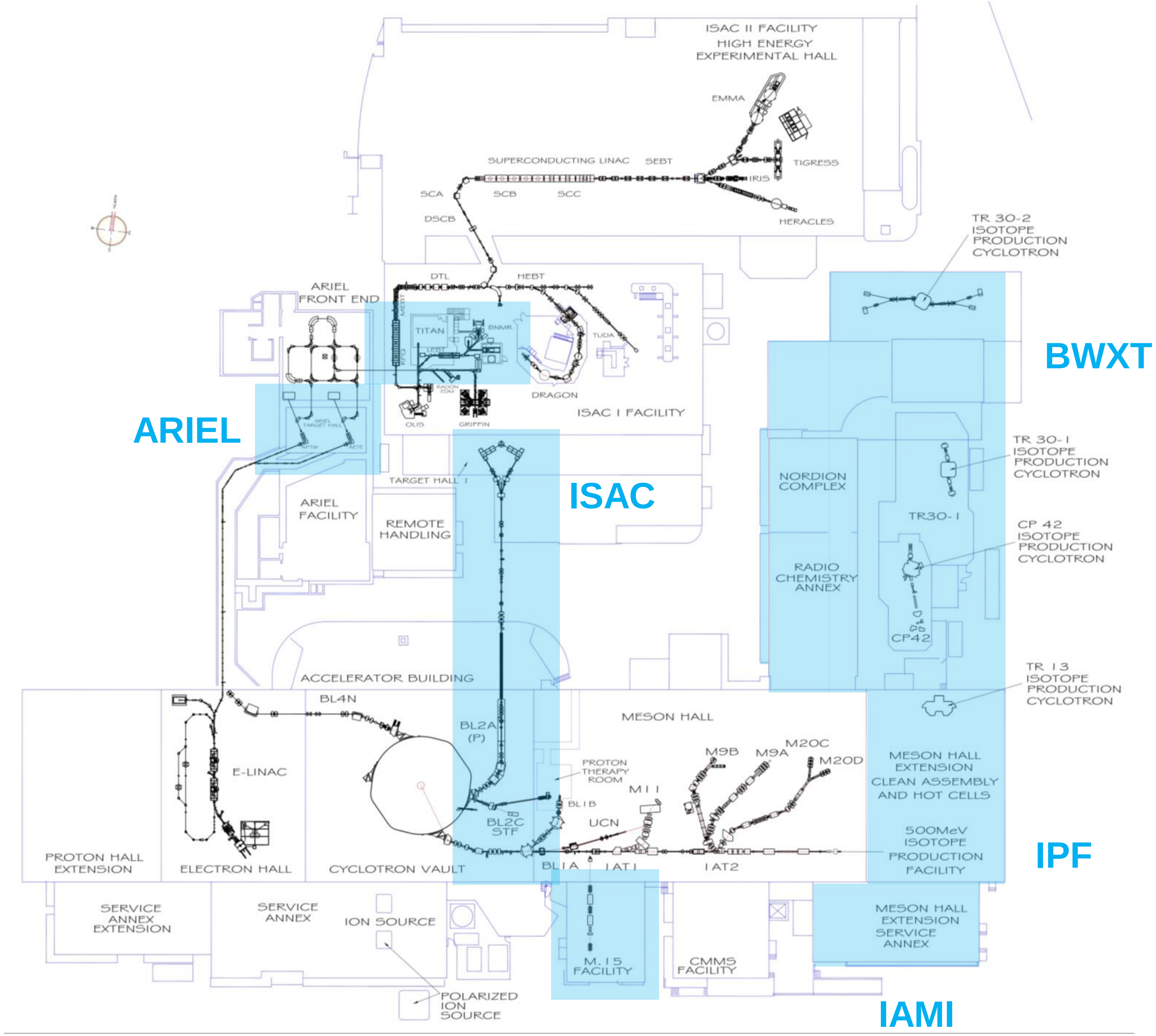
Life Sciences BAEs at TRIUMF

Applied Ion Beams		Nuclear Chemistry		Applied Isotopes	
					
Monika Stachura (2016)	Cornelia Hoehr (2013)	Valery Radchenko (2016)	Paul Schaffer (2009)	Hua Yang (2020)	Caterina Ramogida (2018) (joint SFU)

Structuring the Division for What's Ahead

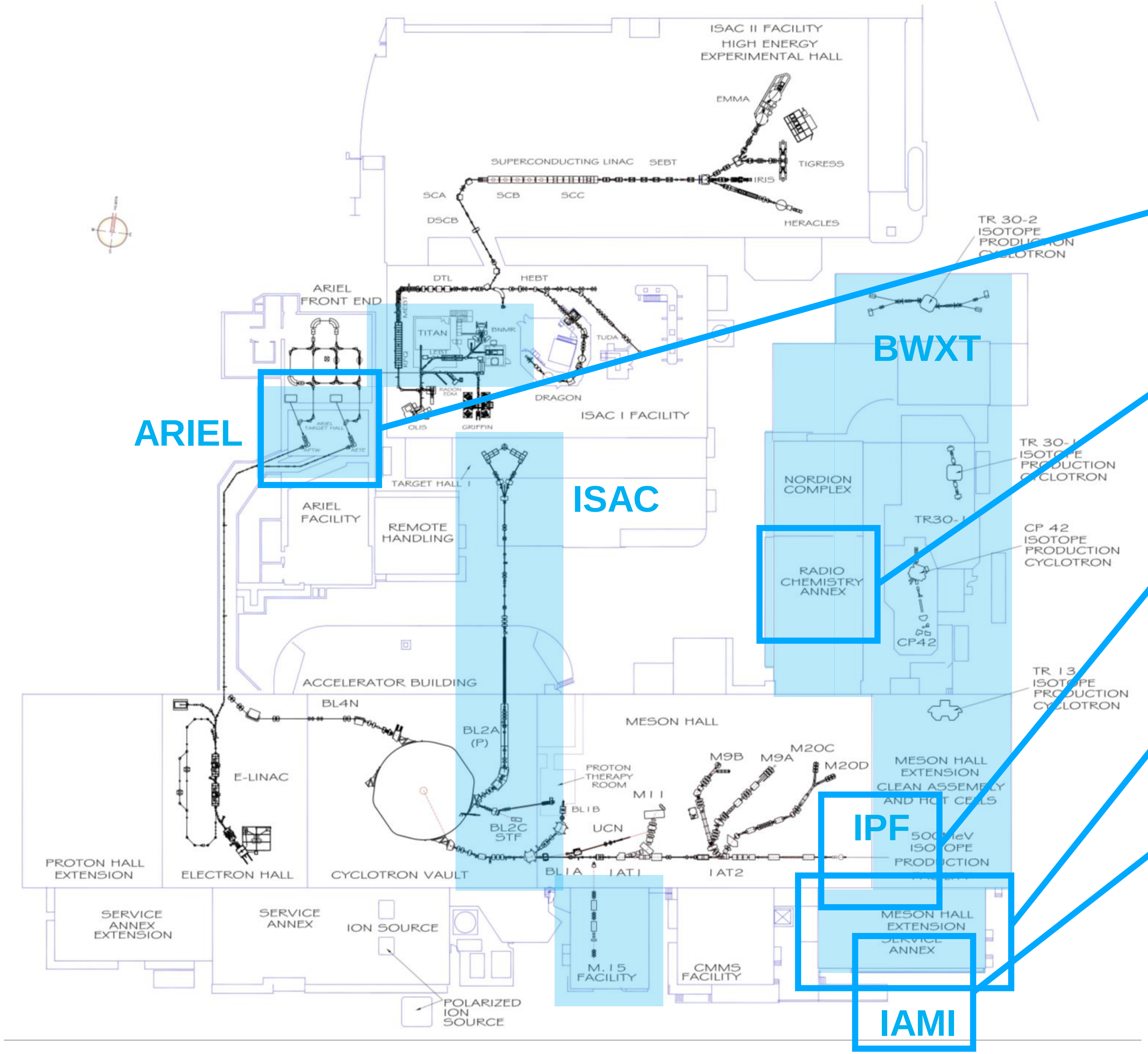


Life Sciences at TRIUMF



- Many applications derived from beams and isotopes obtained from 13 to 520 MeV machines
  - Isotope production
  - Radiochemistry
  - Proton Therapy
  - Bio-βNMR
- Other drivers: ARIEL, ISAC/ISOL
- Partnerships:
  - UBC: Science, Pharmacy, Medicine, Engineering
  - SFU: Science
  - BC Cancer
  - Fusion, BWXT
  - …

LS Facility Updates



P405: Symbiotic Medical Isotope Production

P412: GMP Radiopharmaceutical Upgrades

P457: Isotope Production Facility Nuclear Ventilation Upgrade

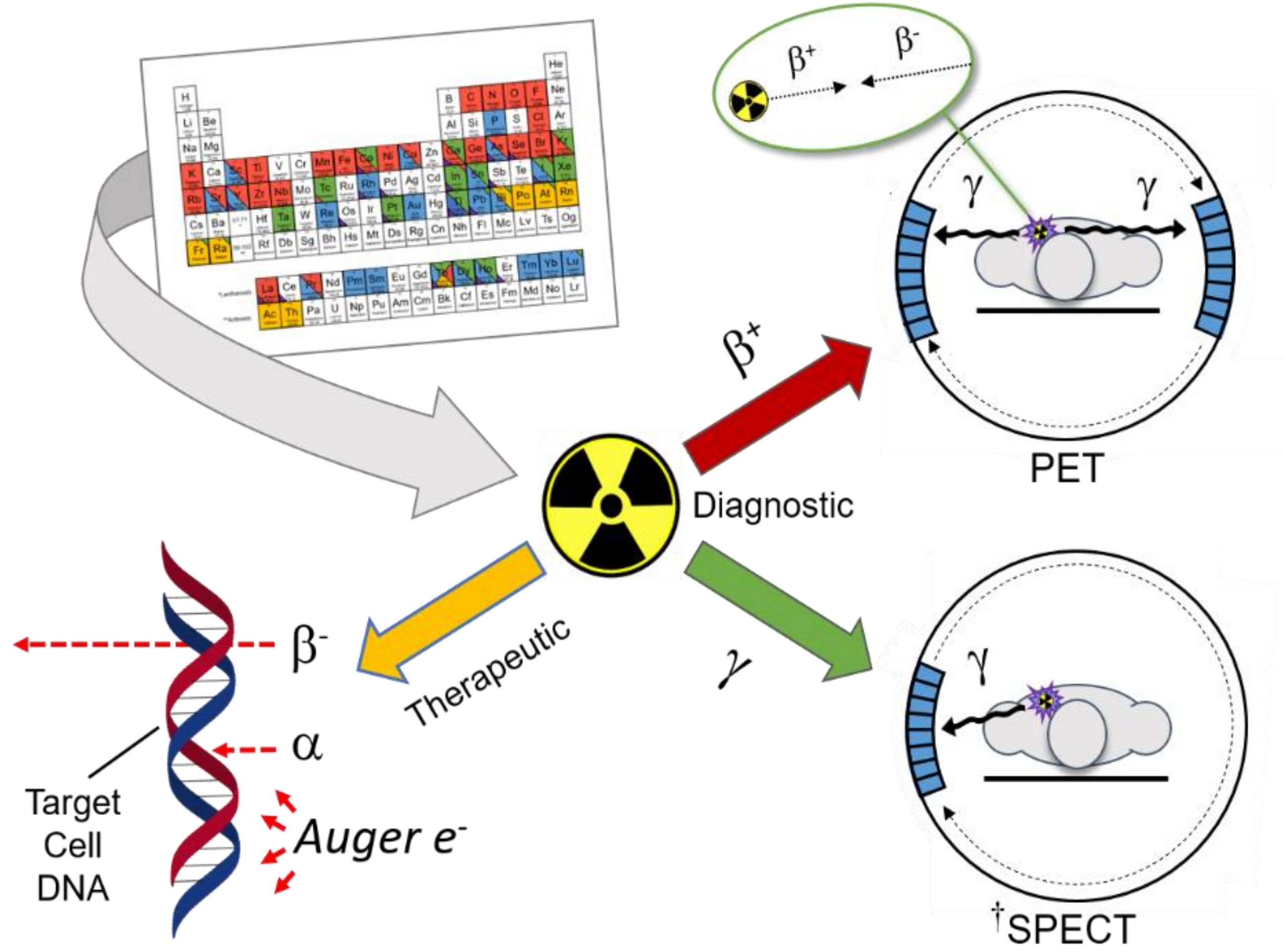
P468: Biohazard Facility

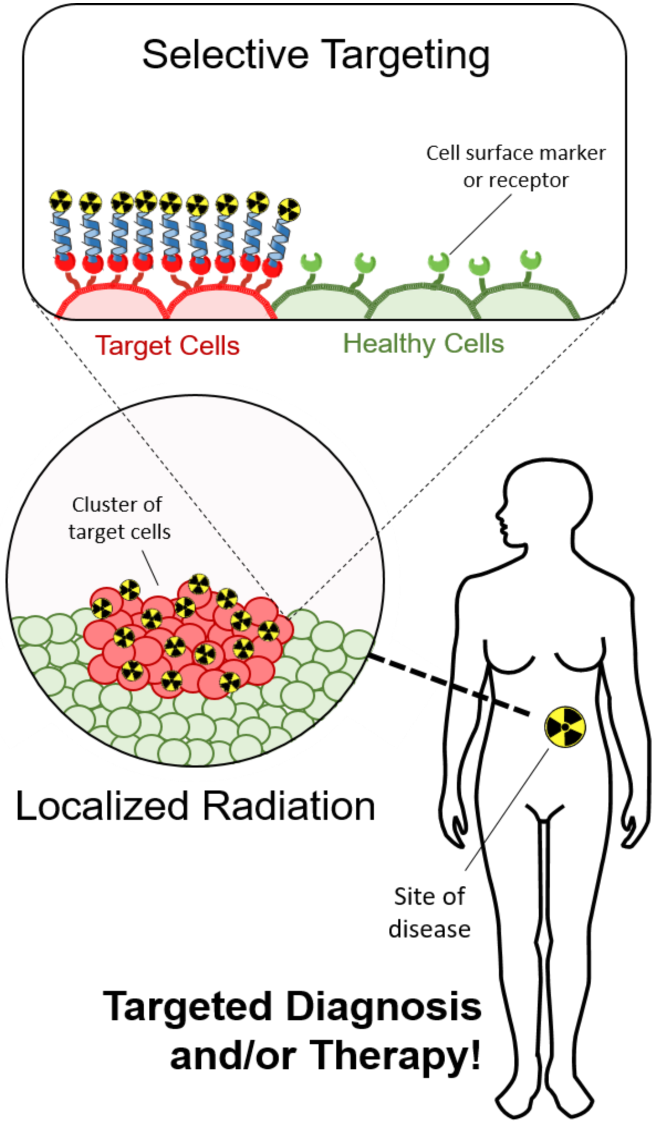
P442, 471, 527, 550:
IAMI Buildout

Discovery,
accelerated

Facility Upgrades, Research Space for the Future

2025-2030: Applying Physics to Life

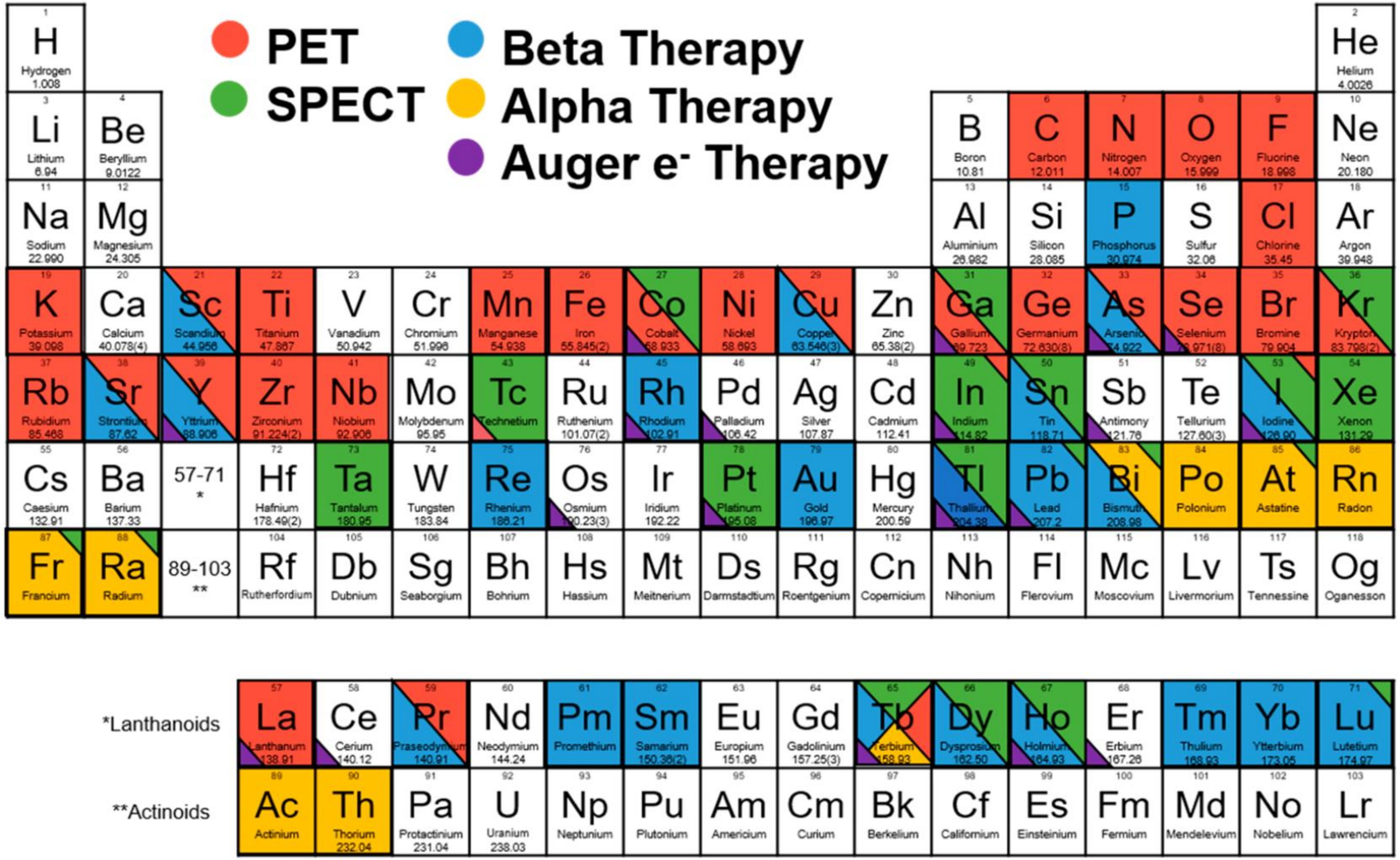




Targeted Diagnosis and/or Therapy!

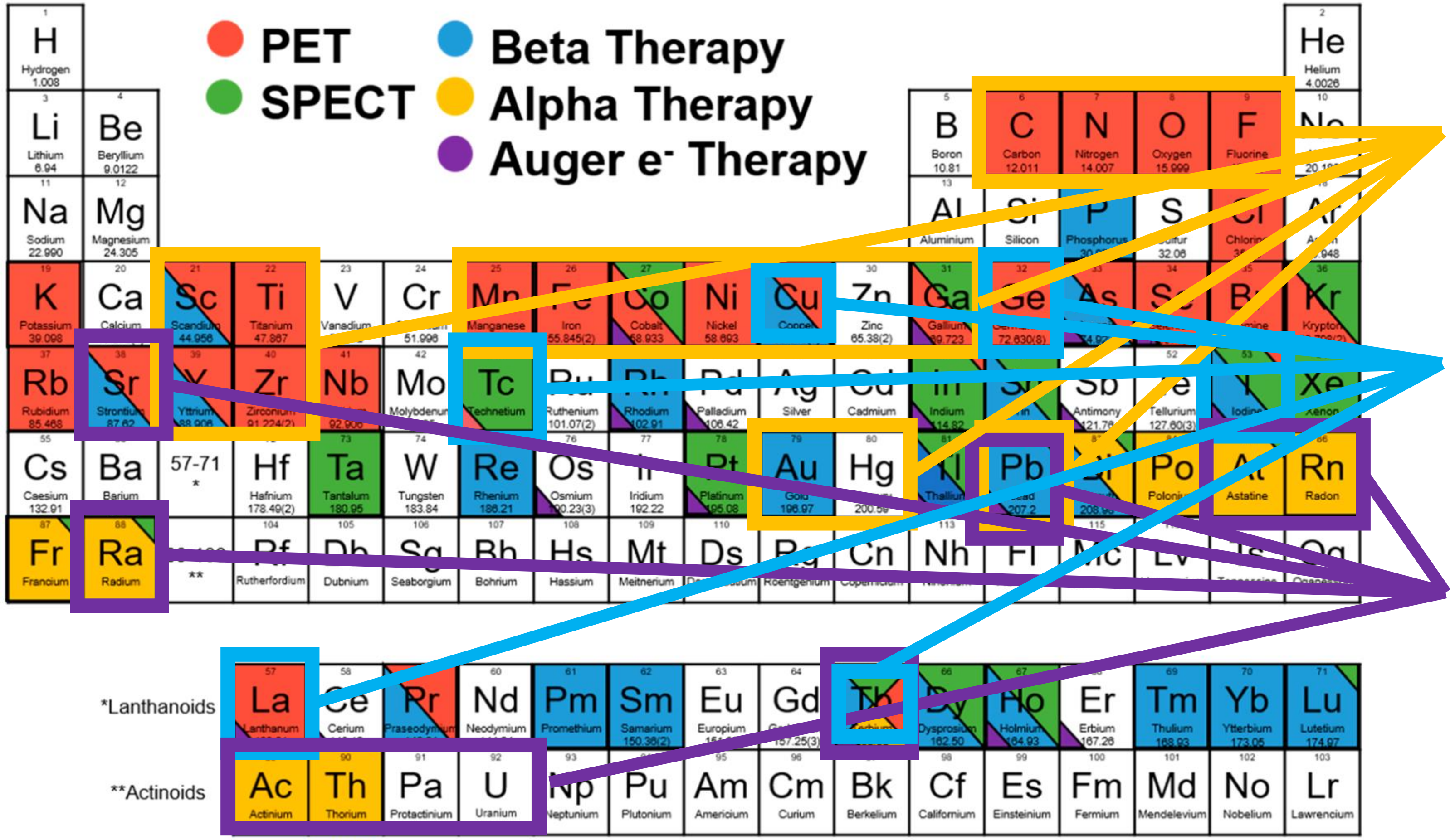
T. I. Kostelnik, C. Orvig *Chem. Rev.* **2019**, *119*, 902 invited for **Metals in Medicine** issue
JP Pouget et al. Nat. Rev. Clin. Oncol. 2011, 8, 720-734
SV Gudkov et al. Int. J. Mol. Sci. 2016, 17, 33

2025-2030: Focus on Radiometals **(Radchenko, Yang talks, Monday)**



T.I. Kostelnik and C. Orvig, Chem. Rev. 2019, 119, 902-956

2025-2030: Focus on Radiometals (Radchenko, Yang talks, Monday)



TR13 MeV
- Legacy machine operating at ideal energy for many isotopes

24 MeV
- Modern, high-intensity machine that expands on TRIUMF's isotope repertoire

520 MeV (IPF, ISAC)
- Globally unique machine that provides access to equally unique isotopes, applications

T.I. Kostelnik and C. Orvig, Chem. Rev. 2019, 119, 902-956

^{225}Ac Production at TRIUMF (P476)

Objective

Establish, commission and demonstrate the performance of infrastructure, equipment, processes, and procedures required for safe, weekly production and quality control of Ac-225 from BL1A

Top Level Deliverables:

- Robust equipment/processes for routine thorium target radiochemical processing
- Ac-225 product quality control program
- Waste management program
- Radiochemistry lab facilities to support routine Ac-225 production

Previous campaigns:

- 2020 Irradiations: 3 targets for a total of 6,320 µAh
- 2021 Irradiations: 5 targets for a total of 28,900 µAh
- 2022 Irradiations: 4 targets for a total of 42,500 µAh

  * Three additional targets planned for 2022 with a total of 37,500 µAh

  **isolated over 12 GBq of direct production Ac-225 (decay corrected to EOB); and 1.4 GBq Ra-225 for generators (decay corrected to EOB).

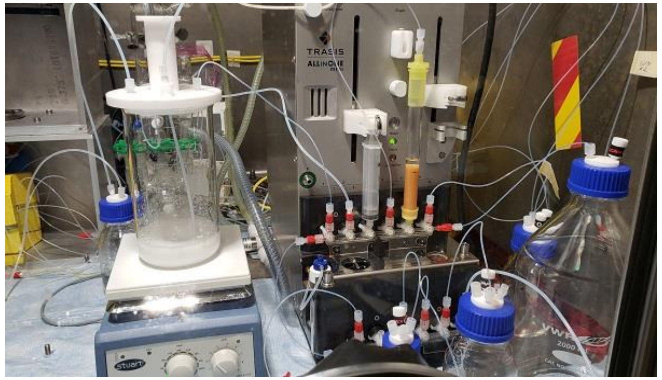
  *** generators were eluted 19 times for a total of 470 MBq of high purity Ac-225 for distribution to collaborators and TRIUMF researchers

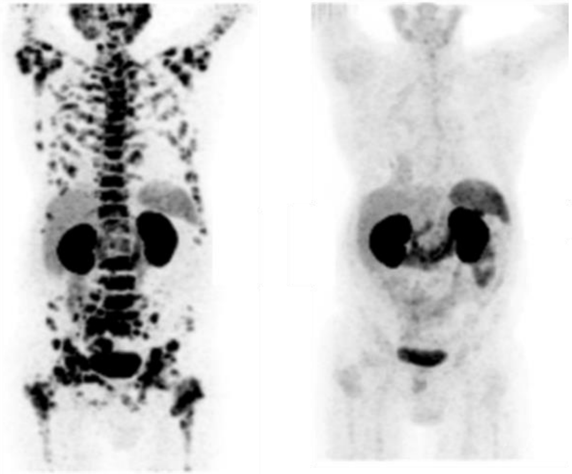
2023 Campaign

- Goal: Transition to regular/monthly ~100 MBq generator production
- Develop and validate a robust QC process
- Enable access to other radioisotopes produced as by-products from the spallation process. Examples include U-230, Pb-212, Th-227

Five-Year Plan

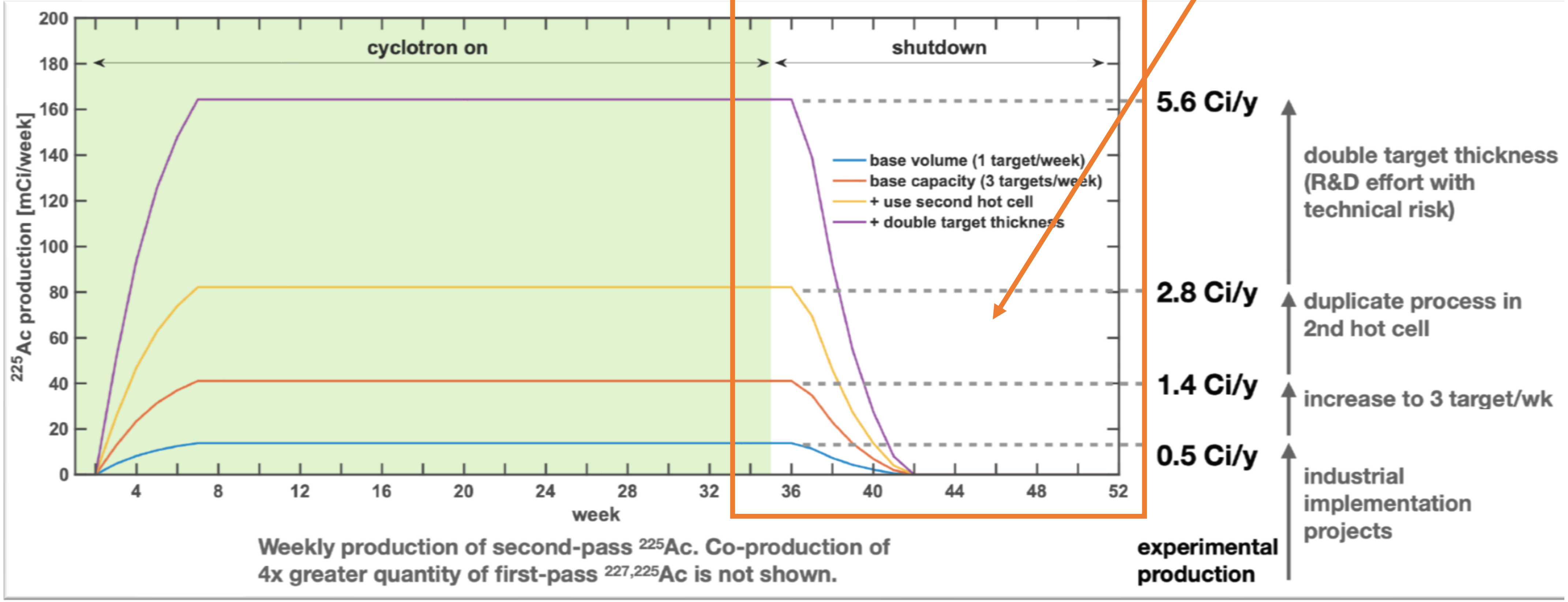
- **Prepare for NFRF-T effort (Caterina Ramogida – next talk)**





Current ^{232}Th-based ^{225}Ac Production Trajectory at TRIUMF

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.

Other methods for ^{225}Ac (P526)

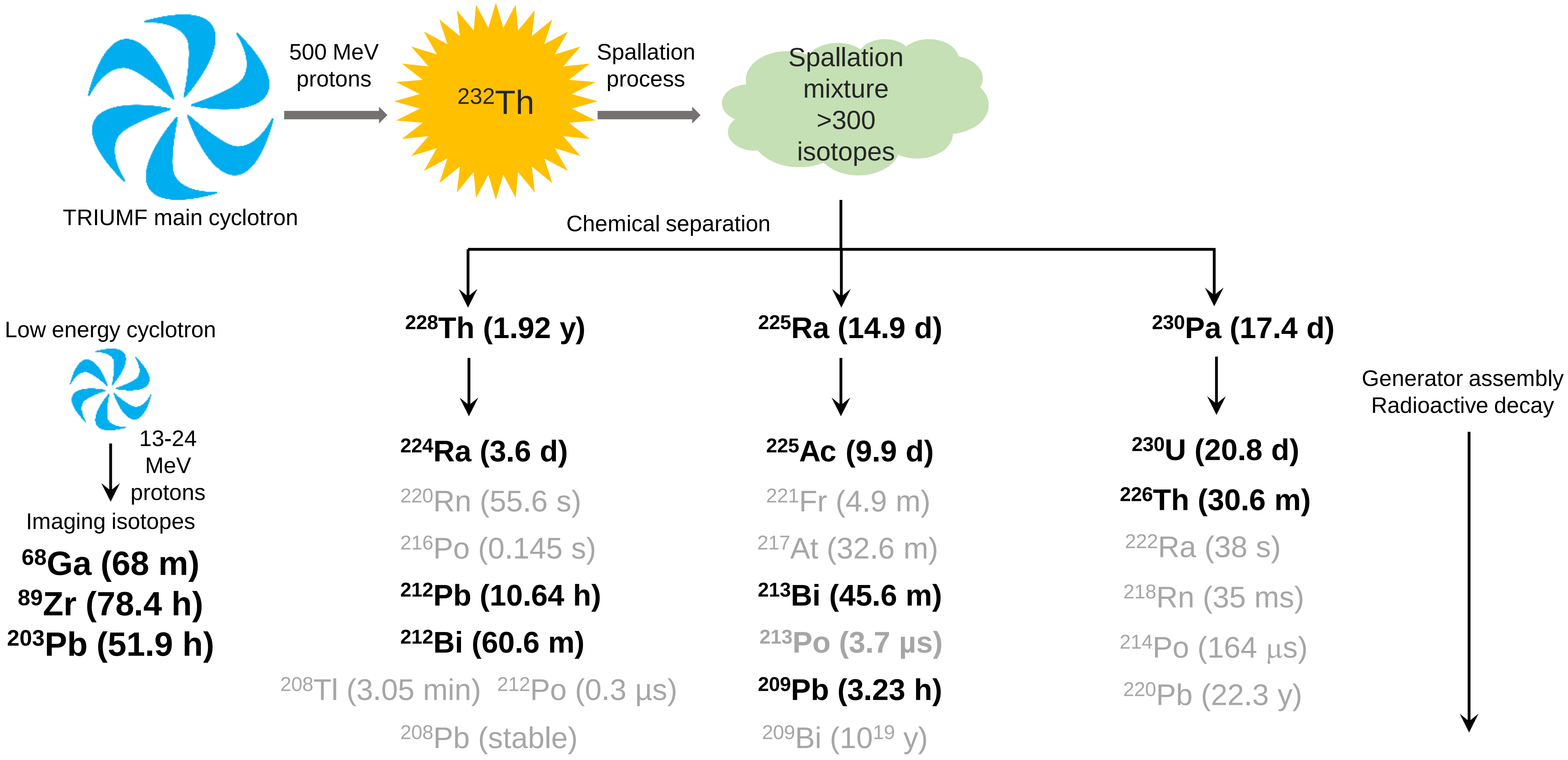
	Production Method	Facility	Capabilities	Monthly ^{225}Ac Production [GBq (Ci)]
Current Sources	^{229}Th generator	ORNL ITU IPPE	0.704 g (150 mCi) of ^{229}Th 0.215 g (46 mCi) of ^{229}Th 0.704 g (150 mCi) of ^{229}Th	2.2 (0.06) 1.1 (0.03) 2.2 (0.06)
Potential	^{232}Th(p, x)^{225}Ac	TRIUMF	500 MeV, 120 µA	11266.5 (304.05)
		BNL	200 MeV, 173 µA	2675.84 (72.32)
		INR Arronax	160 MeV, 120 µA 70 MeV, 2×375 µA	1002.0 (27.08) 462.1 (12.49)
		LANL	100 MeV, 250 µA	444.0 (12.00)
		iThemba LABS	66 MeV, 250 µA	127.7 (3.45)
Future	^{226}Ra(p, 2n)^{225}Ac	20 MeV, 500 µA cyclotron 15 MeV, 500 µA cyclotron		3983.1 (107.65) 1157.4 (31.28)
Sources	ISOL	TRIUMF (existing) TRIUMF (potential upgrades)		0.37 (0.01) 190.6 (5.15)
	^{226}Ra(γ, n)^{225}Ra	medical linac ALTO	18 MeV, 26 µA 50 MeV, 10 µA	48.1 (1.3) 55.5 (1.5)
	^{226}Ra(n, 2n)^{225}Ra	fast breeder reactor		~37 (1)

*values for potential sources list estimates of maximum possible production at facilities that have dedicated stations for large-scale medical isotope production.
**Values listed for ^{226}Ra targets assume a target mass of 1 g.

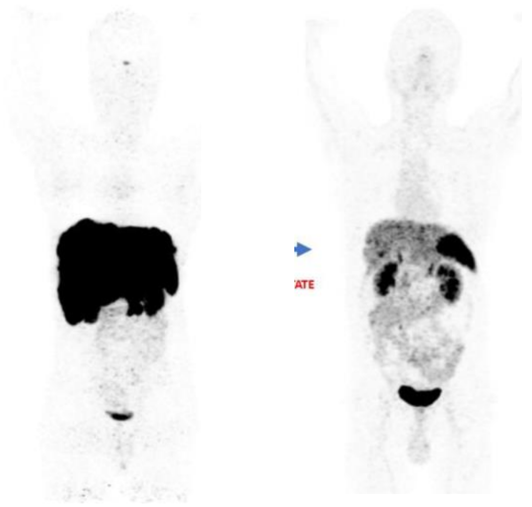
A Robertson et al. Curr Radiopharm. 2018, *11,* 156-172

Beyond Ac-225

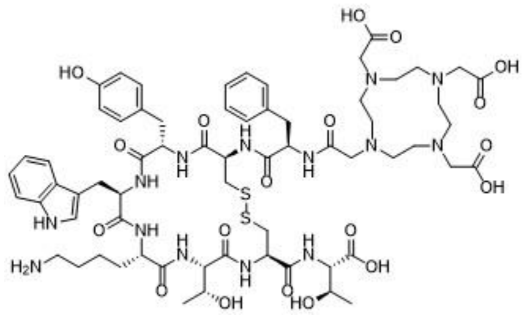
Diagnostic, Therapeutic and Theranostic Isotopes



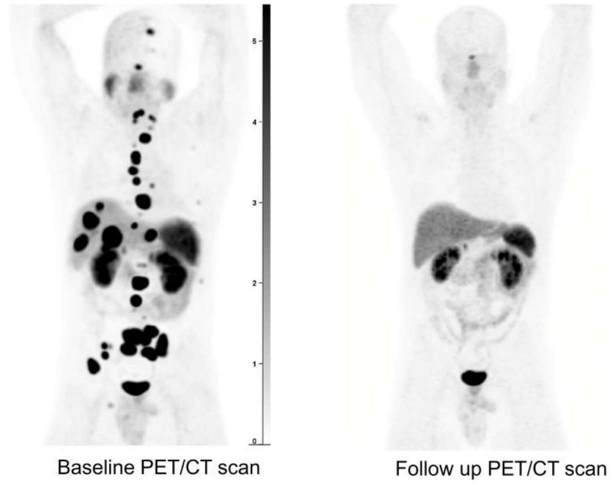
What’s next for Targeted Alpha Therapy?



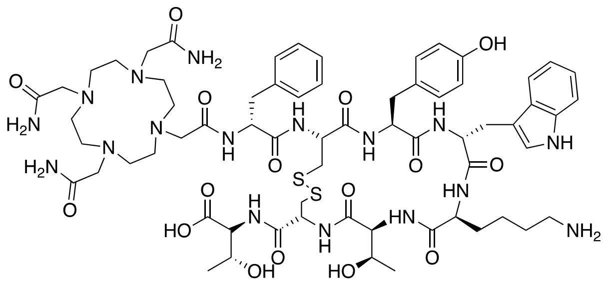
6 cycles [^{225}Ac]DOTATATE
100-120 kBq/kg



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



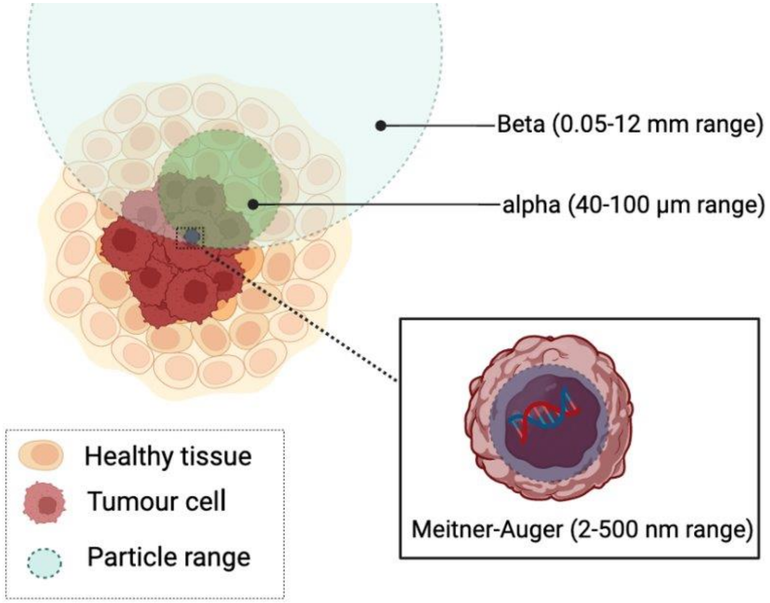
4 cycles [^{212}Pb]DOTAMTATE
2.50 MBq/kg



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

- Applications for cancers typically found late (metastatic)
  - Pancreatic, melanoma, ovarian, blood…
- Unmet need: establish patient dose based on target expression levels
- Leverage emerging tools, such as AI to:
  - molecular target selection
  - optimize drugs/pairings
  - calculate injection amounts and frequency to optimize therapeutic response
- Non-cancer applications
  - Bacterial/fungal infections,
  - immune-based diseases
  - …

Radionuclide Therapy is not limited to alpha-, beta- emitters



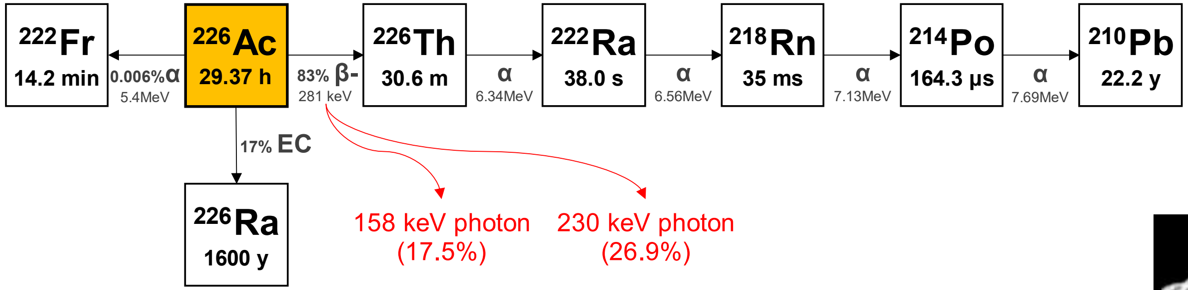
Auger-emitters:

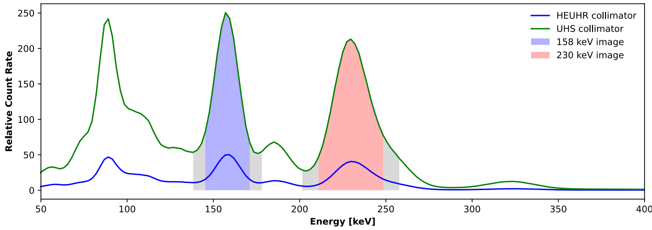
^{58m}Co
^{71}Ge
^{103}Pd
^{103m}Rh
^{161}Tb
^{165}Er
^{191}Os
^{239}Np
…

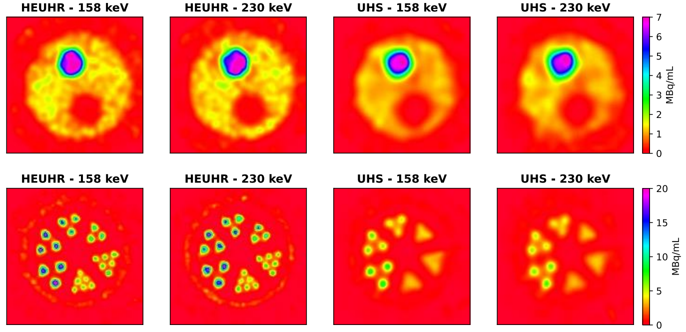
- Continued pursuit of:
  - Novel production methods
  - Separation chemistry
  - Chelate chemistry
  - Applications

Filosofov D, *et al*. Nuc. Med. Biol. 2021, 94-95, 1-19

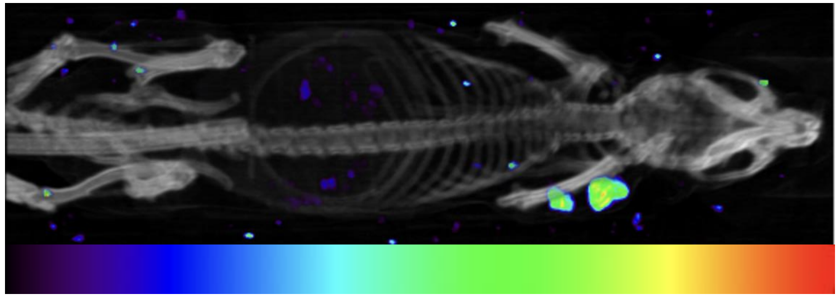
ISAC/ISOL for R&D into unconventional radionuclides



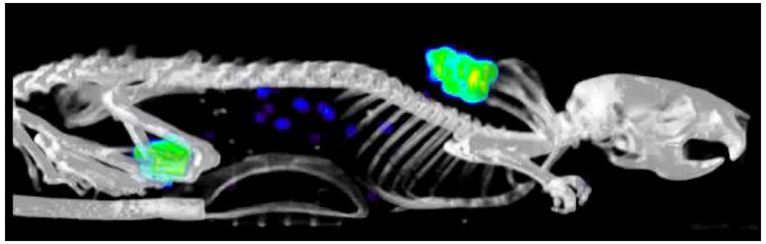




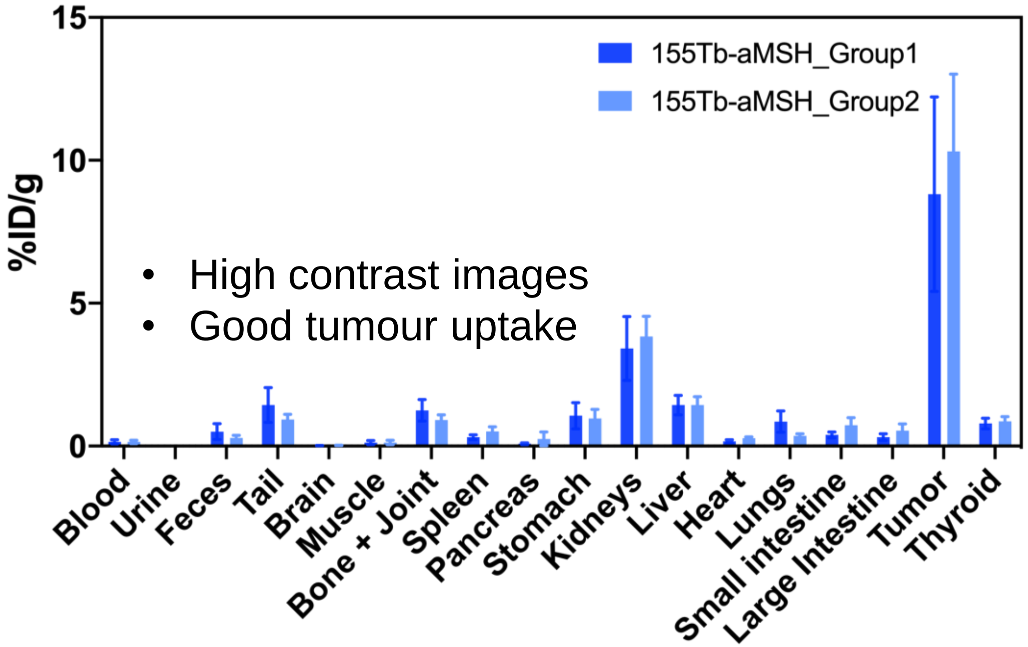
[^{226}Ac]-crown-TATE Biodistribution 24 h p.i.



[^{155}Tb]Tb-crown-αMSH SPECT , 2h p.i.,



[^{155}Tb]Tb-crown-αMSH Biodistribution 2 h p.i.

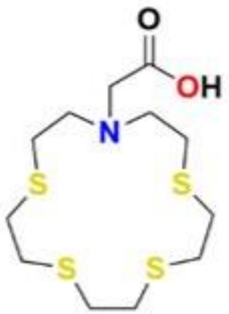


- High contrast images
- Good tumour uptake

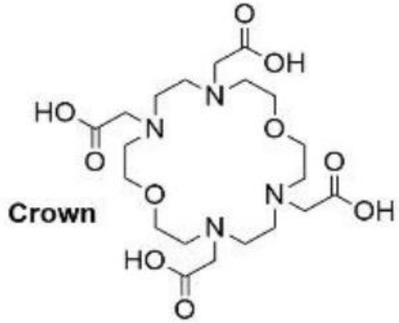


Radiopharmaceuticals Development

Macrocyclic chelates:

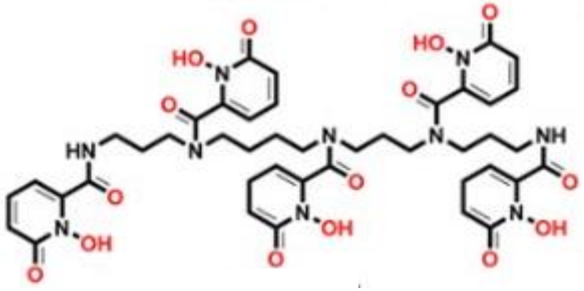


^{197}Hg

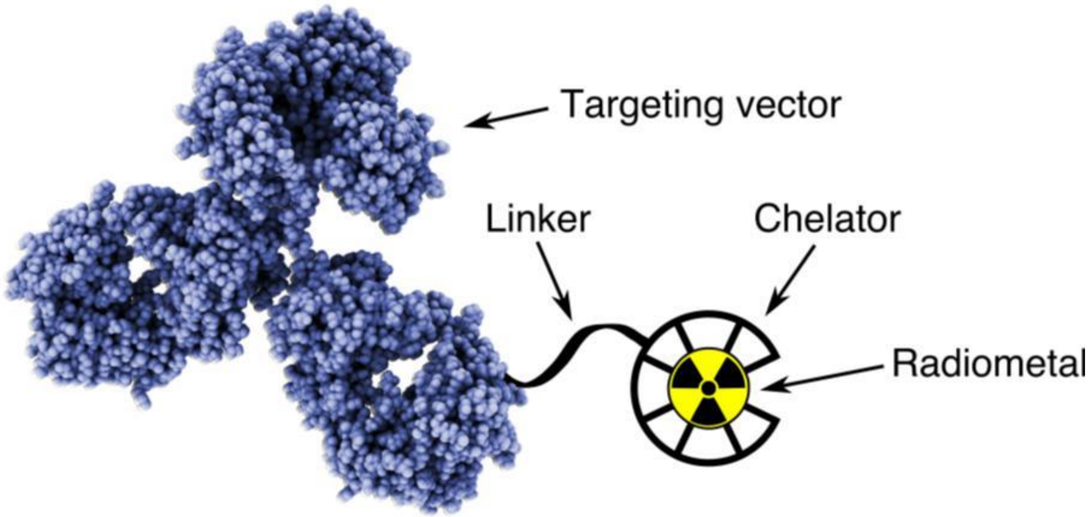


^{225}Ac, ^{213}Bi, ^{155}Tb, ^{177}Lu

Acyclic chelates:



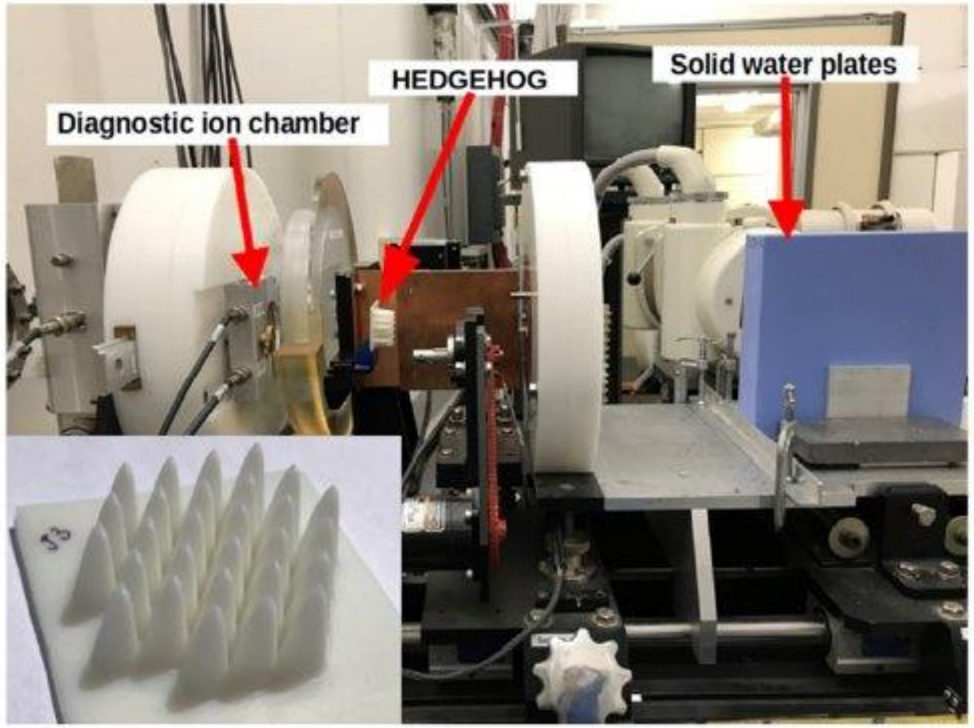
^{225}Ac, ^{213}Bi, ^{255}Tb, ^{177}Lu

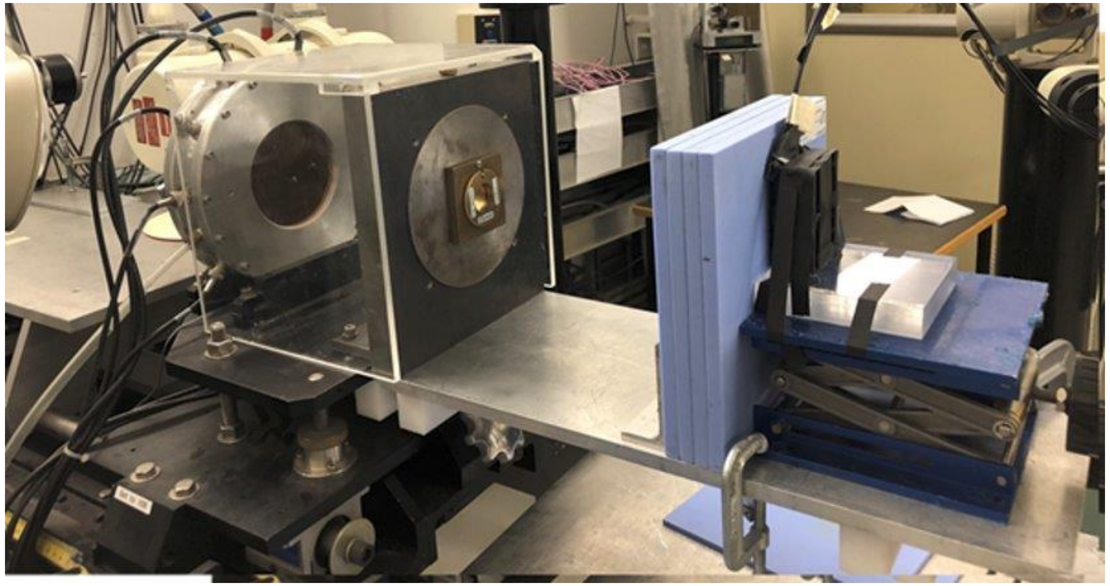


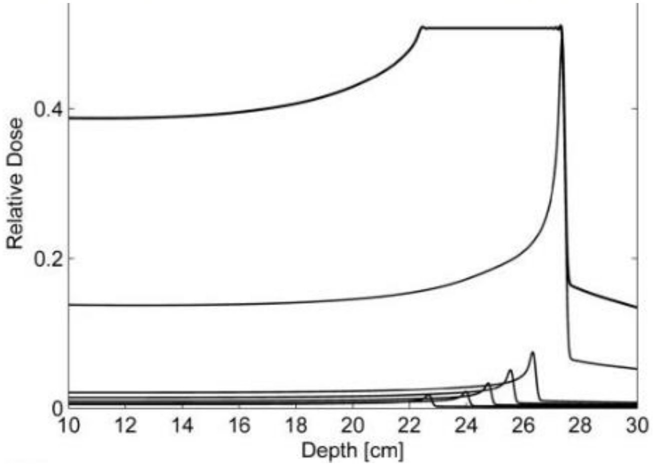
- Different metals have different bond requirements
- Continued pursuit of optimized chelates for Gen 4 radiopharmaceuticals:
  - Novel synthesis, labeling
  - Ideal conditions: low conc ($<10^{-6}$M), fast (minutes), neutral pH, ambient temp.
  - Bifunctional molecular 'handle' to enable controlled conjugation to targeting agents

Proton (and photon) FLASH at TRIUMF

Continue building on decades of PT experience at TRIUMF







- Goal: research ways to enhance therapeutic index for proton therapy
  - Use FLASH effect: deliver therapeutic dose to target tissue in minimal time; spare surrounding healthy tissue
- Measure irradiation effects on cell cultures
- Develop novel technologies that provide real time feedback on dose delivery (see fiber work C Hoehr talk Monday)
  - Apply to relevant adjacencies (i.e. isotope production tgts)
- Continue to nurture international collaborations inherent to the effort

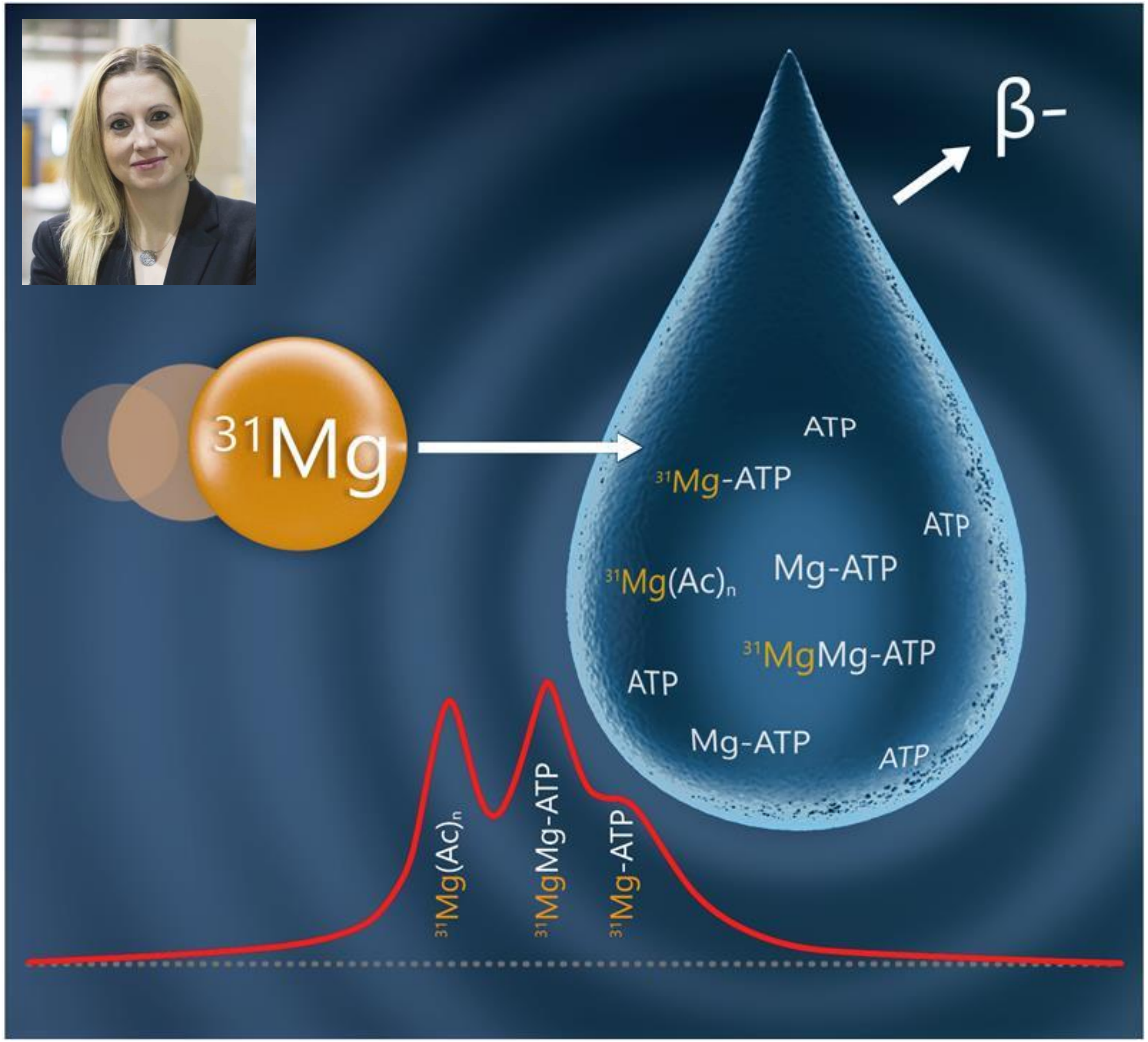
Bio-βNMR at TRIUMF

Current interests:

- ^{31}Mg + ^{8}Li (routine)
- $^{58/74}$Cu (under development)
- ^{226,230}Ac (under development)

Attributes:

- Unique, high-impact science;
- International collaboration;
- Private sector interest;
- Threats: beam availability



Complete ARIEL (P405 – Symbiotic Isotope Production)

Design efforts underway:

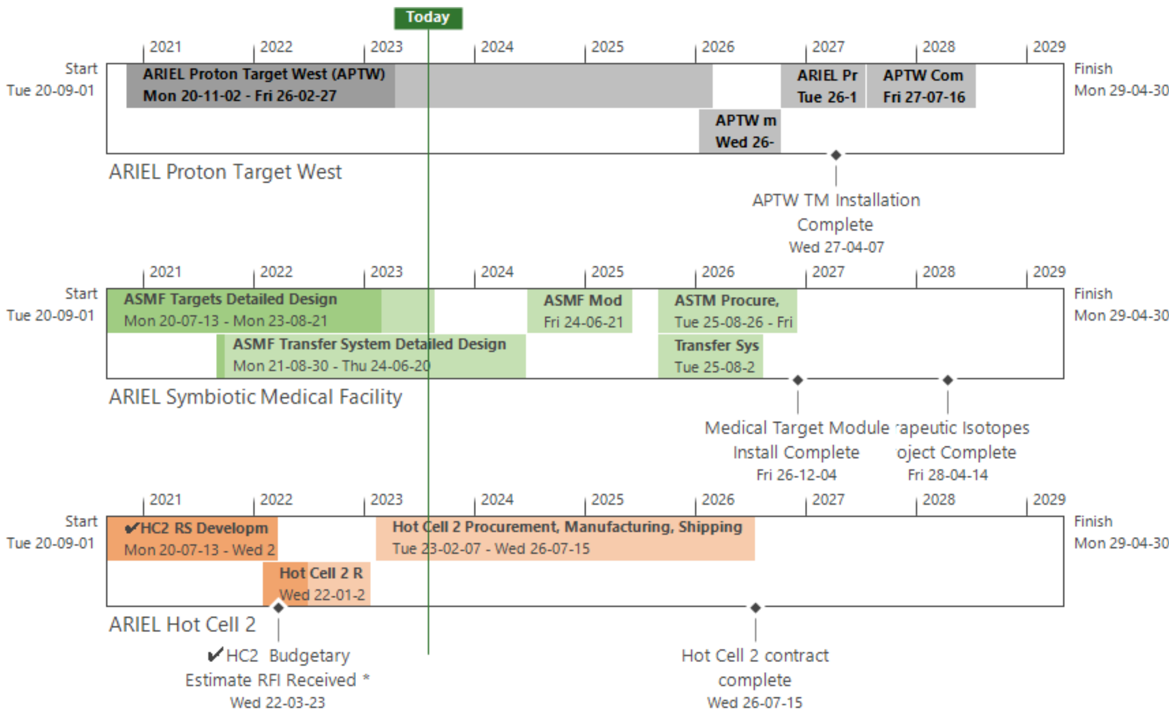
1. Development effort paced with APTW
   - RFI for Hot cell 2 completed
   - Re-baseline from updated cost estimates
2. ASMF Targets Design development
   - Medical Target testing complete
   - Feasibility testing of Target Module being underway

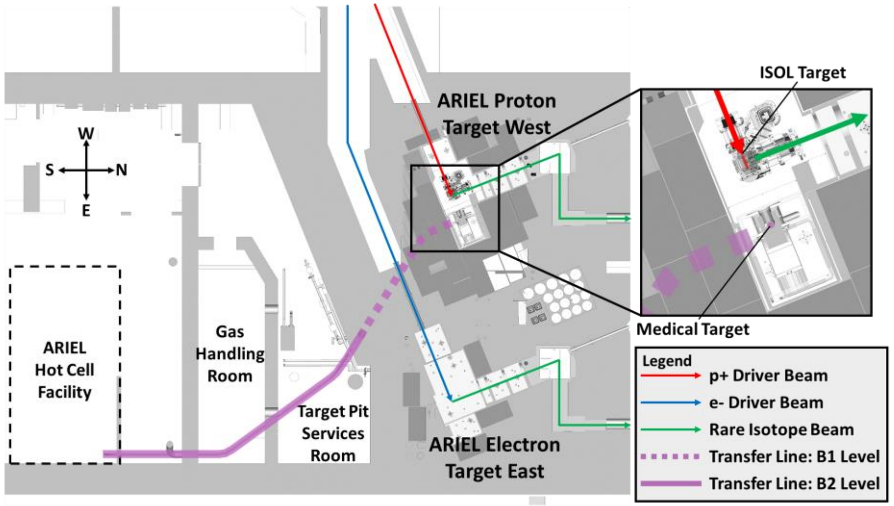
Team:

1. Hiring of Qualified personnel is proving to be challenging
2. AMSF scope being split into technical WBS leadership
   - Medical Module → P353 Target Stations
   - Transfer System → P424 Target Hall Infrastructure
   - Hot Cell Integration → P487 Hot Cell

5YR Outlook

- Implementation of promised scope in CFI to continue as planned
- Integration of processing of Medical targets inside Hot Cell 1
- Therapeutic Isotope Commissioning planned for October 2027
- Estimated project completion April 2028





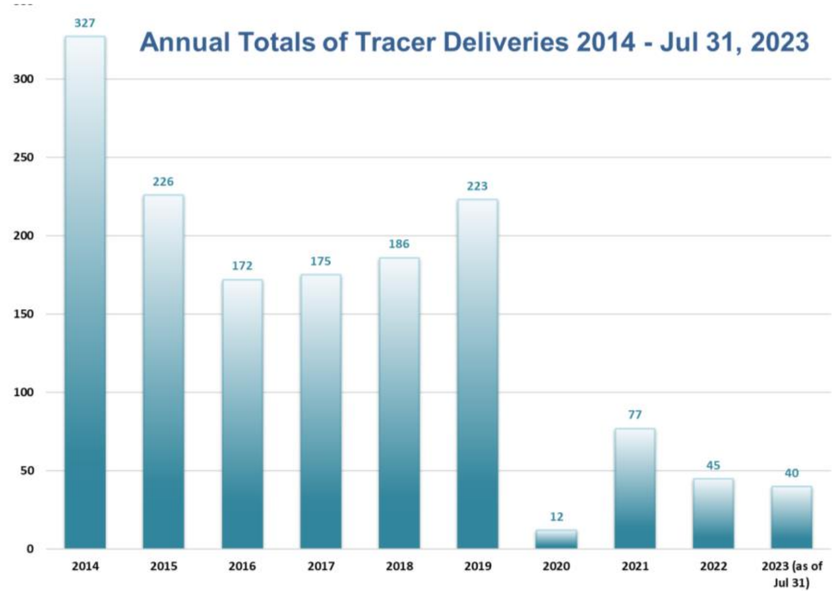
UBC

CFI | FCI

UBC; BC Cancer tracer supply

Status on Tracer deliveries:

- Deliveries of [^{11}C] tracers to UBC resumed in January 2021
- Low demand for tracers continues to be challenging
- TRIUMF has met production reliability targets that were mutually agreed upon
- BC Cancer no longer utilizing F-DOPA as a clinical tracer
    - Replaced with [^{68}Ga]DOTATOC



Status on advancing GMP compliance:

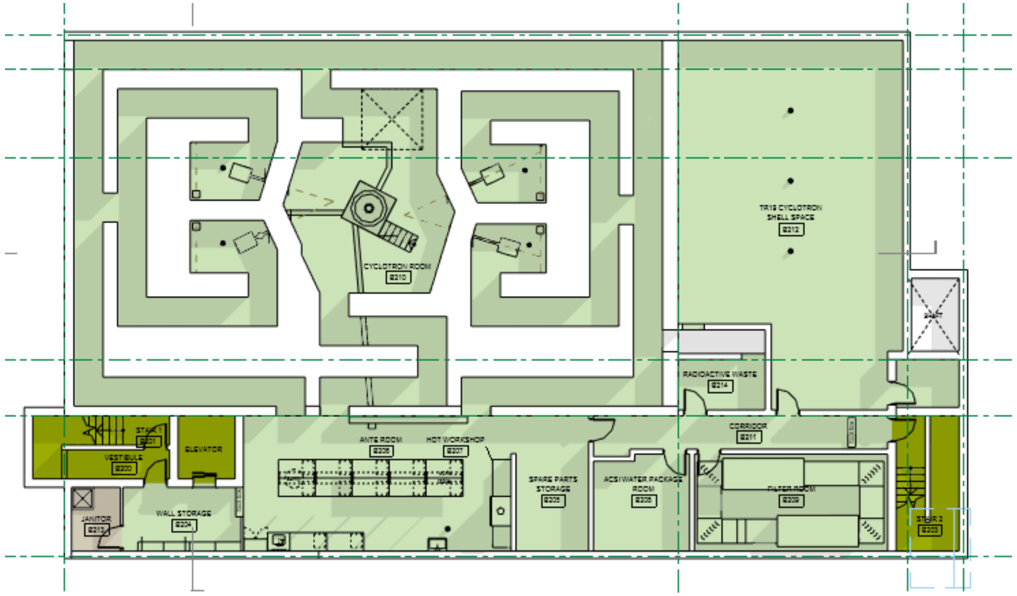
- 265 GMP documents released (over 80 documents have gone through multiple releases)
- All tracer production is now performed under GMP conditions
- Continuous improvements have been made on the implementation of GMP processes.
    - (100 Change Controls, 64 CAPAs have been filed and put into effect since 2021 Jan)
- New GMP Lab 007 coming online soon pending Engineering Services close-out

Getting ready for the IAMI era

- Clean lab for F-18 radiotracer production.
- Tc-99m production Implementation to support PHSA.
- Ac-225 production to collaborate with Fusion and other commercial partners.

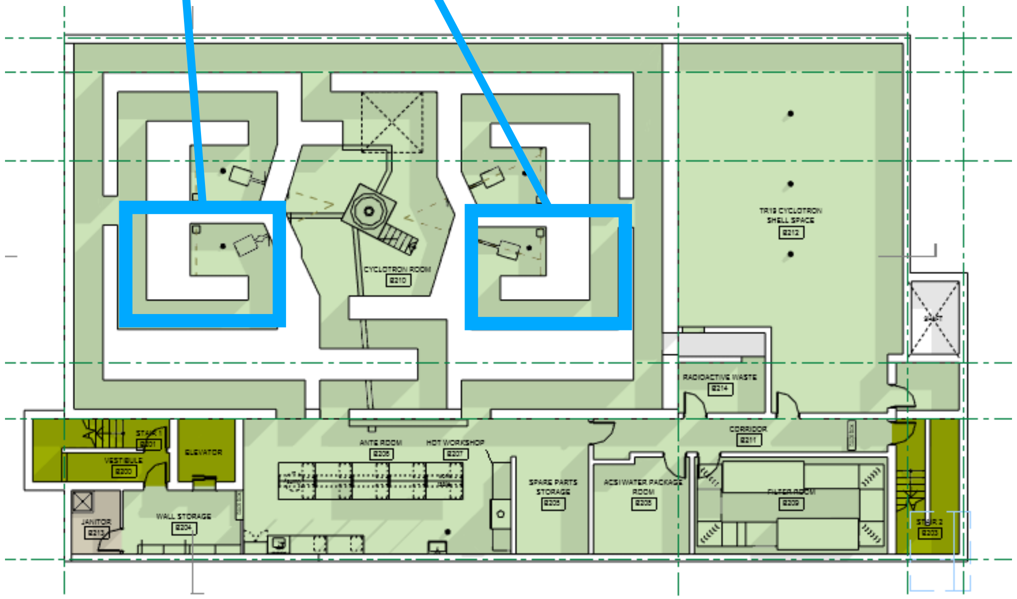
IAMI (P442)

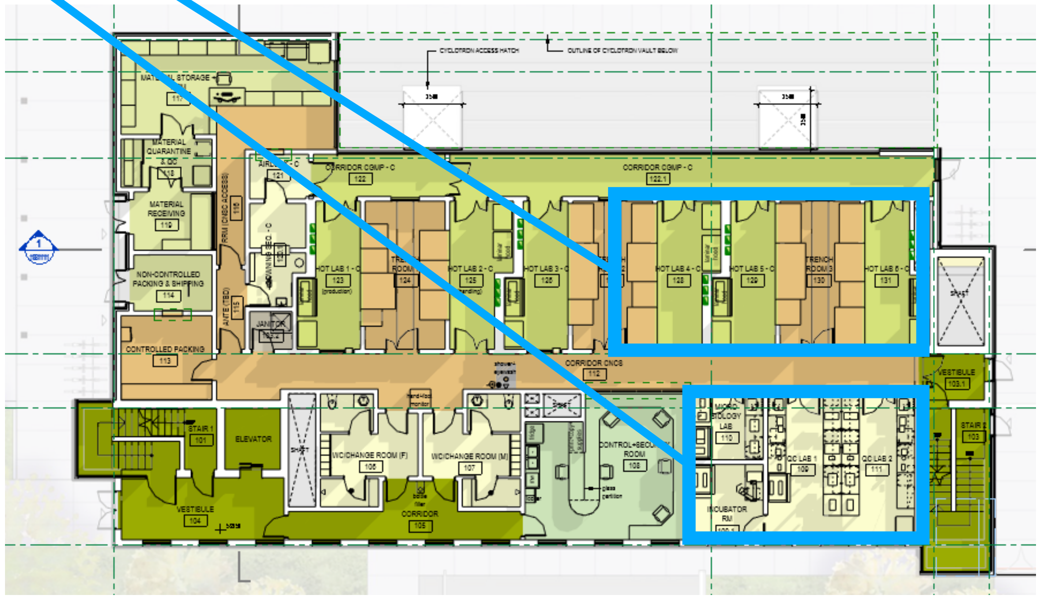
- includes P471, P550, P527
  - Construction substantially complete
  - BC Provincial Health Authority will be placing 2nd cyclotron in facility; additional lab space to support expanding provincial PET program
  - Additional funding requests continue in discussion with provincial funding ministries
  - If all remaining funding materializes, expect operations to commence in 2025



IAMI (P442)

- includes P471, P550, P527
  - Construction substantially complete
  - BC Provincial Health Authority will be placing 2nd cyclotron in facility; additional lab space to support expanding provincial PET program
  - Additional funding requests continue in discussion with provincial funding ministries





IAMI: Operations Model

Current proposal (pending full review, ratification by TRIUMF Board, Partners):
Operations and Governance will evolve through phases: Start-up through to Full Ops

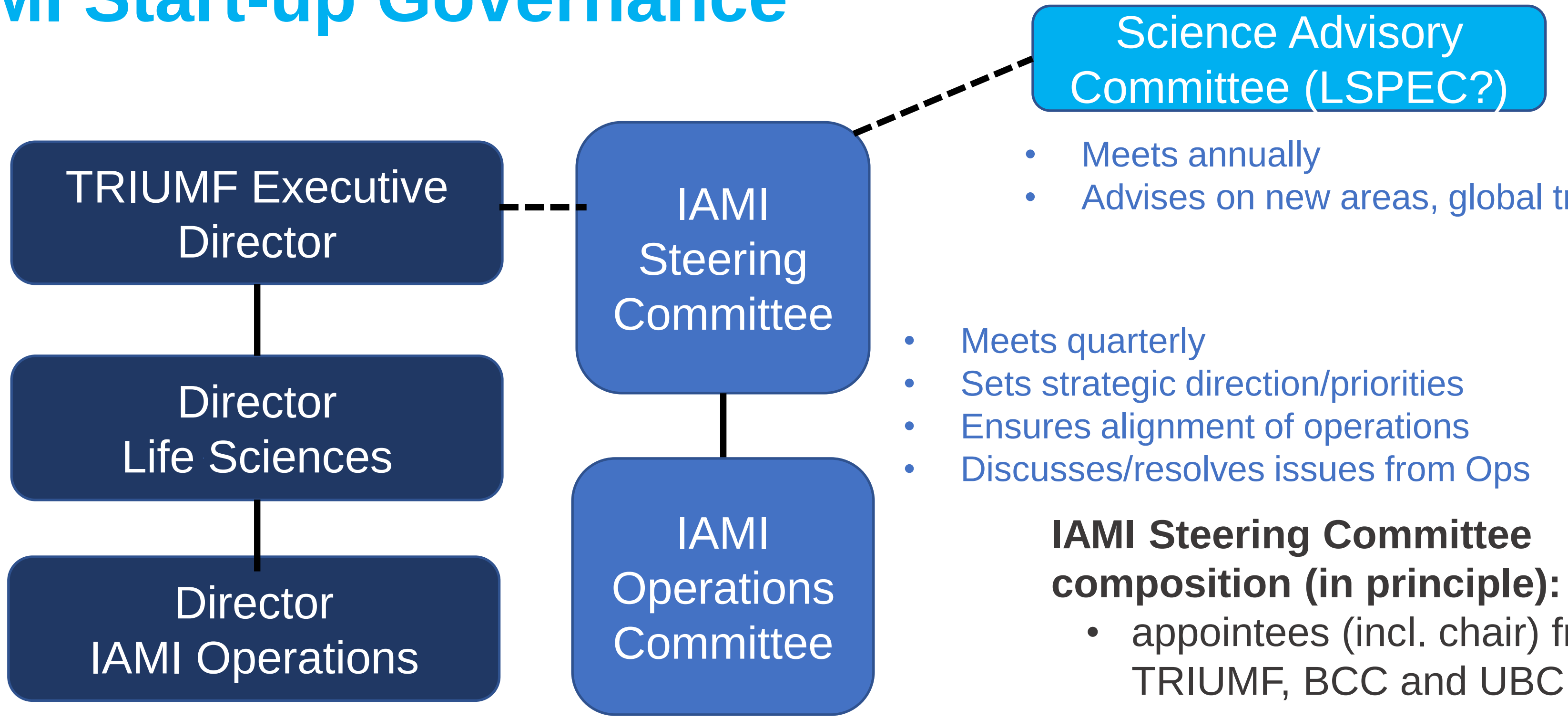
- Start-up operations occur in an integrated fashion within an existing, albeit modified Life Sciences organization. Operations supported by TRIUMF and partners;
- Full operations are initiated once IAMI crosses a legal, financial or administrative threshold that has yet to be determined

Governance will be achieved through a Steering Committee that will recommend resource allocation to meet IAMI program objectives, including balance between R&D and revenue-generating activities

Next steps:

- Ratification of Operating and Governance Models
- Finalization of Business Plan – collaborate with TRIUMF Innovations

Proposed IAMI Start-up Governance



- Meets annually
- Advises on new areas, global trends

- Meets quarterly
- Sets strategic direction/priorities
- Ensures alignment of operations
- Discusses/resolves issues from Ops

IAMI Steering Committee composition (in principle):

- appointees (incl. chair) from TRIUMF, BCC and UBC

- Meets monthly
- Manages/coordinates scheduling, operations
- Facilities communications
- Discusses and resolves issues

Status:

1) Phase 1 Lease and Operating Agreements are being finalized
2) LOU and LOI for expanded efforts are signed
3) Business and operating plans are being updated now that partner activities are becoming more well defined
4) Steering and Operating Committee Terms of References are finalized
5) Services Agreement for expanded effort has been drafted and is under review
6) Sublease for expanded effort is being drafted

NFRF-Transformation: Rare Isotopes to Transform Cancer

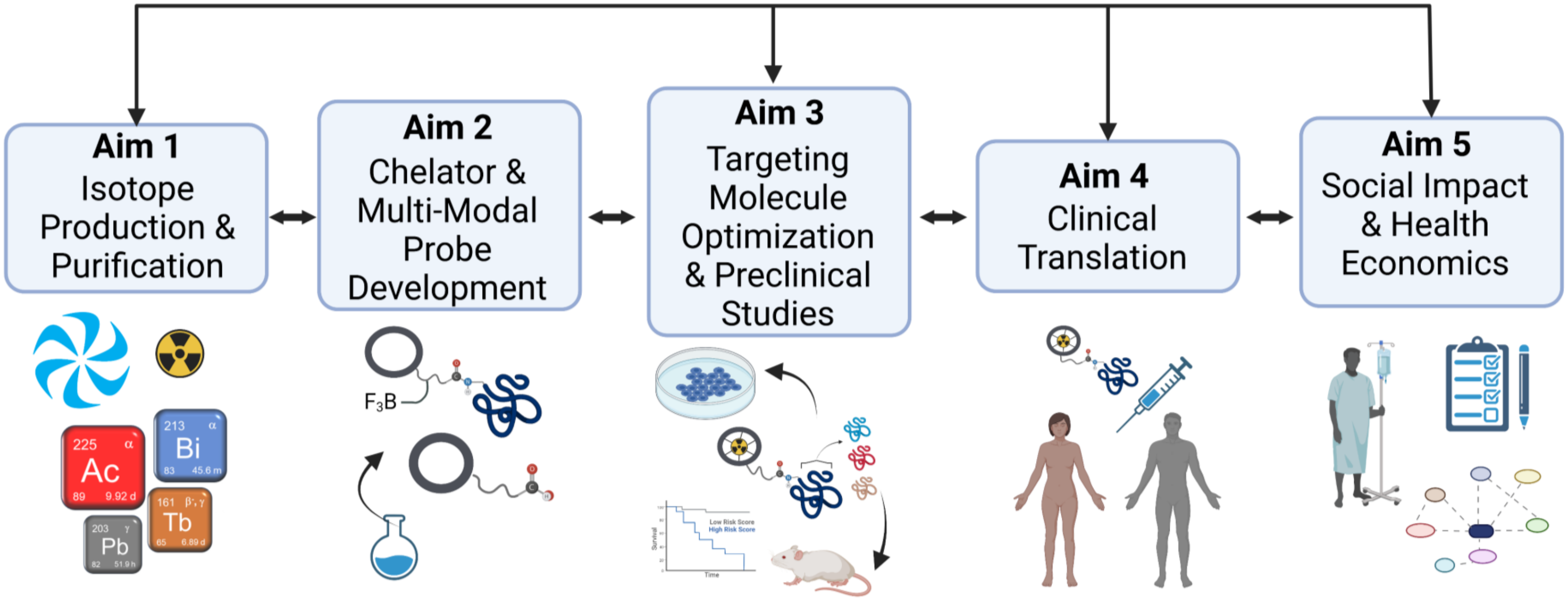
New Frontiers in Research Fund
Fonds Nouvelles frontières en recherche

$23.7 mil over 6 years

NPI: Bénard (UBC/BC Cancer)

Co-PI: Ramogida (SFU/TRIUMF)

TRIUMF Team: Hoehr, Radchenko, Schaffer, Yang



Summary

- The Life Sciences Division is nearing completion of several major facility buildouts and renovations
- Current strategic priorities remain as IAMI, ARIEL, therapeutic isotopes
- Future initiatives to continue focusing on building LS capabilities and infrastructure; leveraging both to foster strategic partnerships
  - Includes operating IAMI, ARIEL
  - investing in:
    - BL1A
    - Expansion of TRIUMF’s isotope, radiochemistry and radiopharmaceutical portfolio
    - Strategic directions re: FLASH, bio βNMR

Our 20 Year Vision for Life Sciences

Think Big

Pursue Creative, Impactful Science

TRIUMF is inherently multidisciplinary and translational, brining together science, creativity, innovation and novel infrastructure; encouraging and inviting collaborators from around the world to answer some of life's most difficult questions.

Be Different

Apply Physics to Life

TRIUMF Life Sciences will be an engine that applies accelerator science toward the study of life – in order to derive maximum societal benefit.

TRIUMF has globally unique infrastructure, rare talent, and an innovative mindset to better life for all.

Be Bold

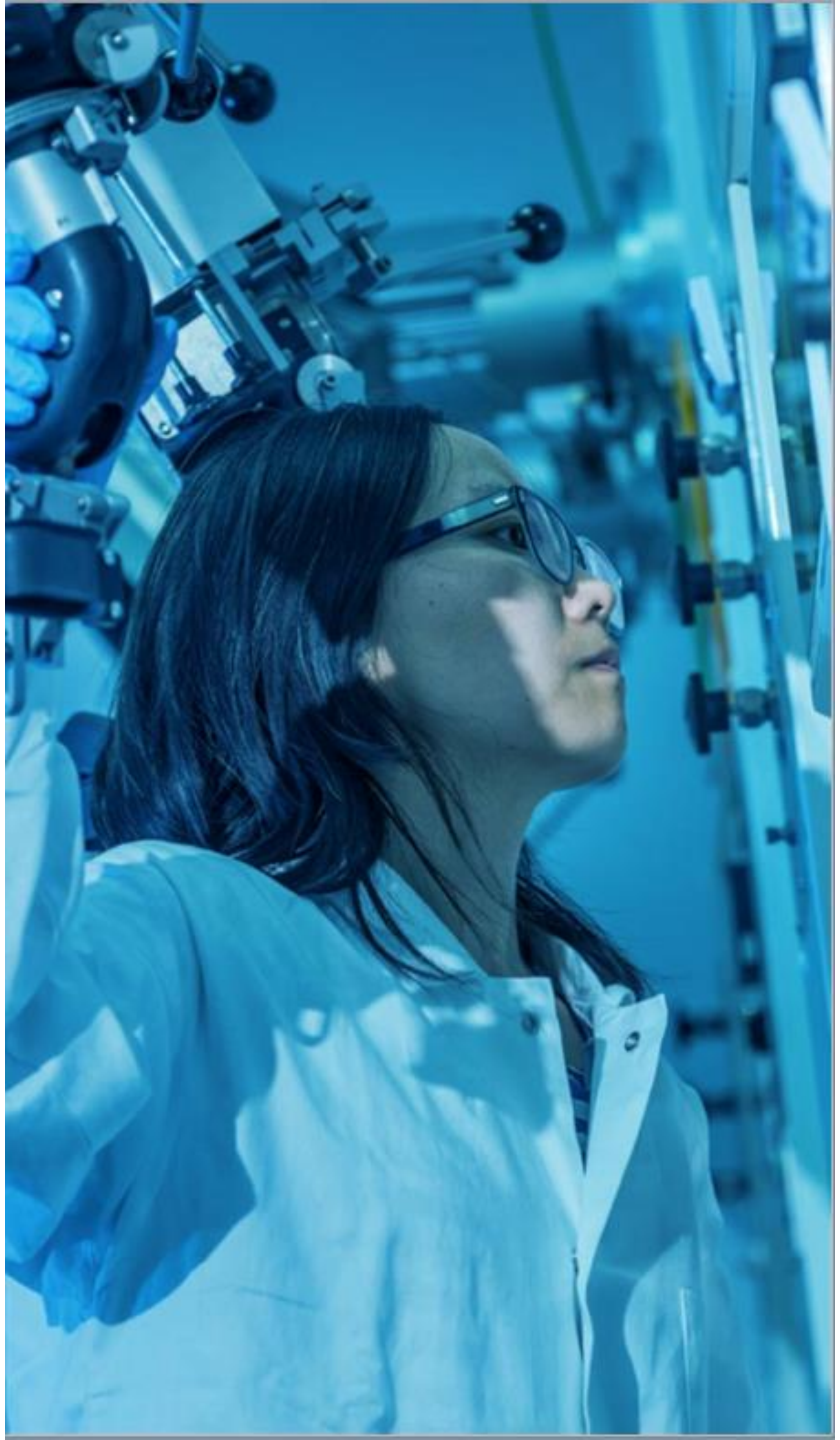
Train and Send Forth World-Class Talent

Creative, impactful research will be woven into the cultural fabric of TRIUMF Life Sciences; training a generation of innovative thought and technology leaders to work collaboratively across disciplines to ask tough questions and derive elegant answers.

Thank you

www.triumf.ca

Follow us **@TRIUMFLab**



Discovery,
accelerated

Replace BL1A

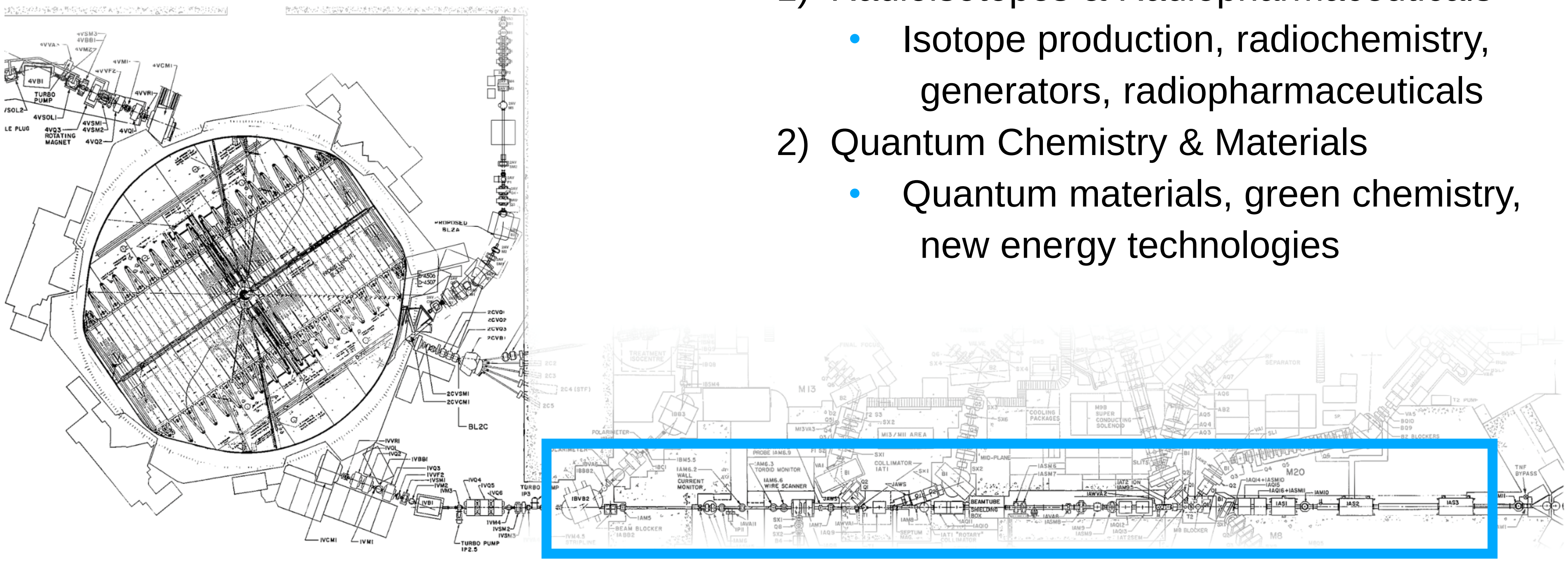
Objective: replace, enhance functionality of BL1A

Next step: 2023 CFI Infrastructure Fund application **not successful!**

- Title: TRIUMF High-Energy Accelerator Proton Irradiation Experiments (THErAPIE)
- $28+M budget ($9.7M from CFI) involving 9 institutions across 4 provinces

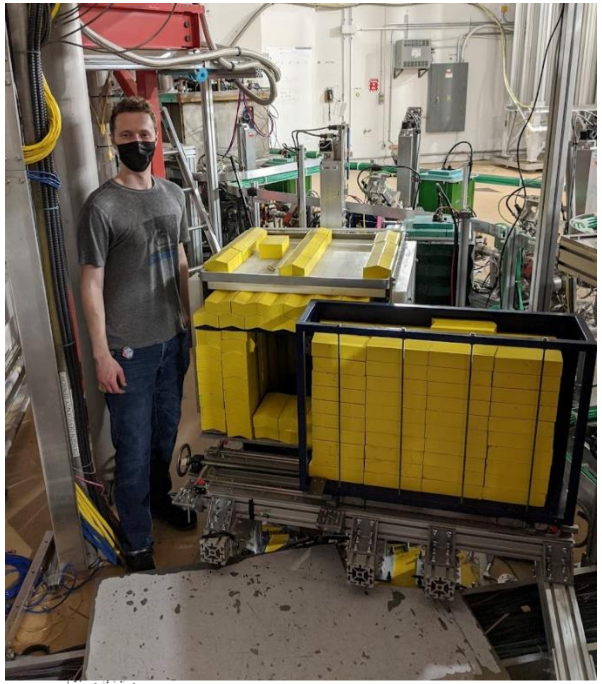
Two Research Programs:

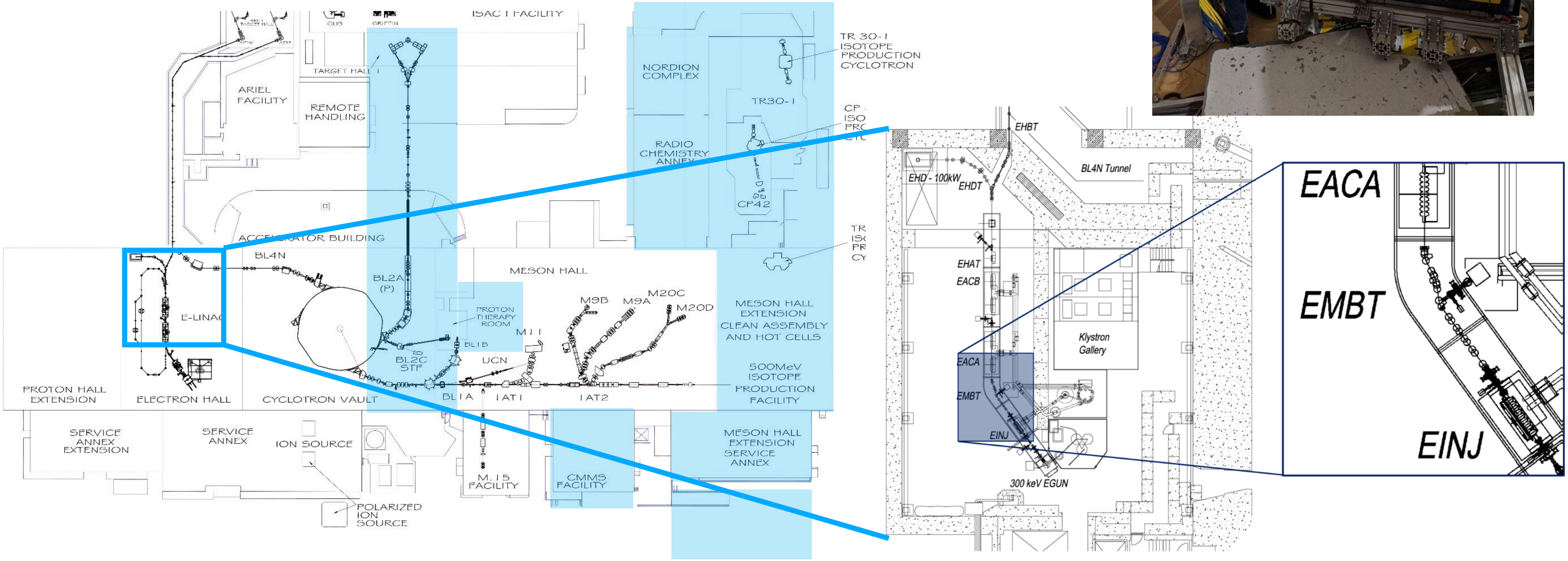
1) Radioisotopes & Radiopharmaceuticals
   - Isotope production, radiochemistry, generators, radiopharmaceuticals
2) Quantum Chemistry & Materials
   - Quantum materials, green chemistry, new energy technologies



FLASH Proton and X-ray Therapy (P490)

- **Objective:** establish go/no-go for larger-scale infrastructure investment at TRIUMF
- **Current Status:** Feasibility (NFRF-Exploration grant) with animal studies underway
- **Next steps:** prepare CFI application (2025)





Expand bio-β-NMR (P382, P464)

- **Objective:** enhance bio-βNMR infrastructure at TRIUMF
- **Next steps:** prepare CFI application (2025)