TRIUMF

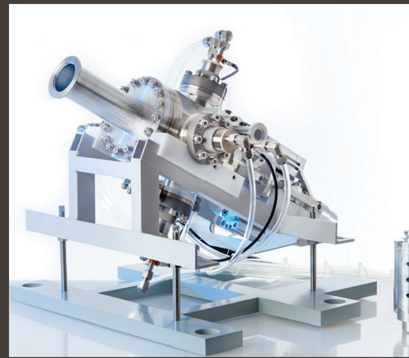
Canada's national laboratory for particle and nuclear physics
Laboratoire national canadien pour la recherche en physique nucléaire et en physique des particules

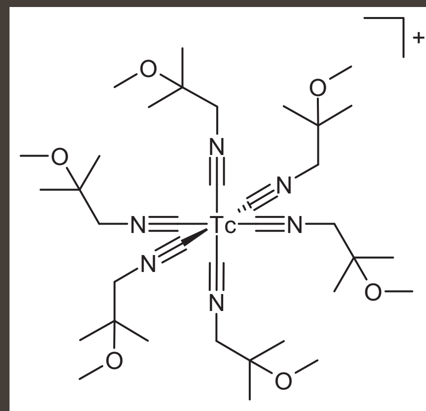
Isotopes for Science and Medicine: The Pursuit, Study and Application of Medical Isotopes at TRIUMF

HIAT 2015

September 7th, 2015

Paul Schaffer
Associate Laboratory Director, Life Sciences, TRIUMF

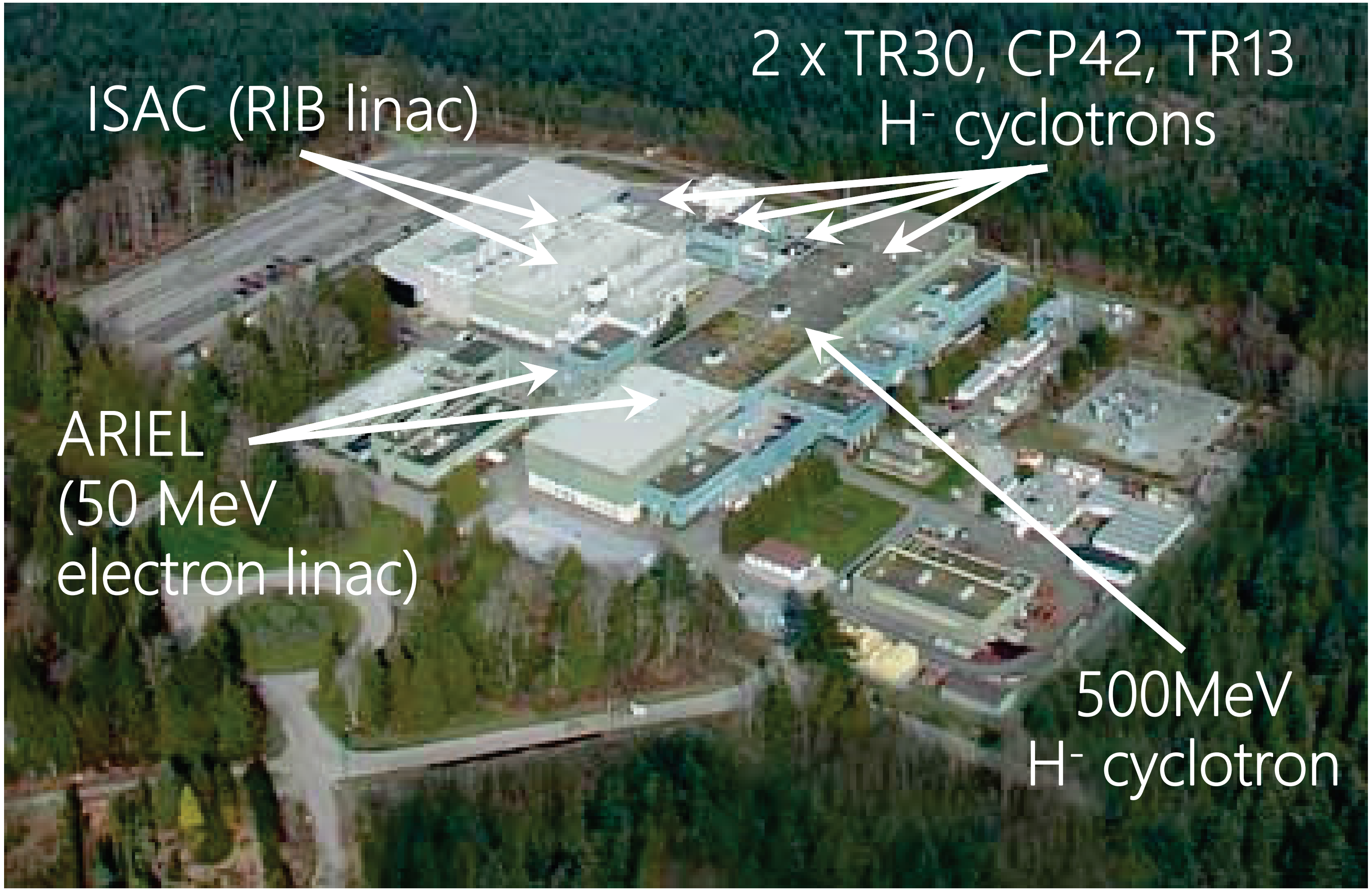




Accelerating Science for Canada
Un accélérateur de la démarche scientifique canadienne

Owned and operated as a joint venture by a consortium of Canadian universities via a contribution through the National Research Council Canada
Propriété d'un consortium d'universités canadiennes, géré en co-entreprise à partir d'une contribution administrée par le Conseil national de recherches Canada

Accelerators at TRIUMF



New addition: TR24; to be installed

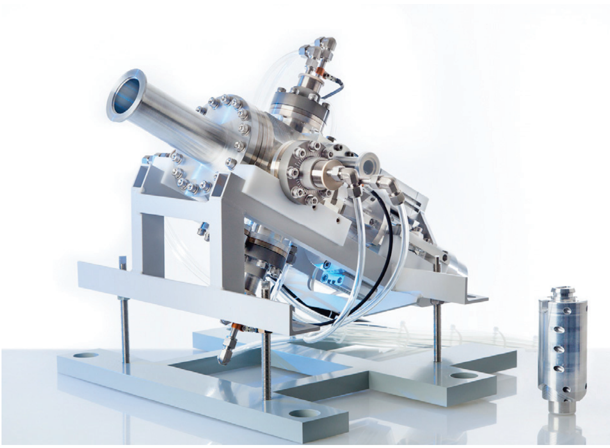
Three Pillars of Nuclear Medicine at TRIUMF

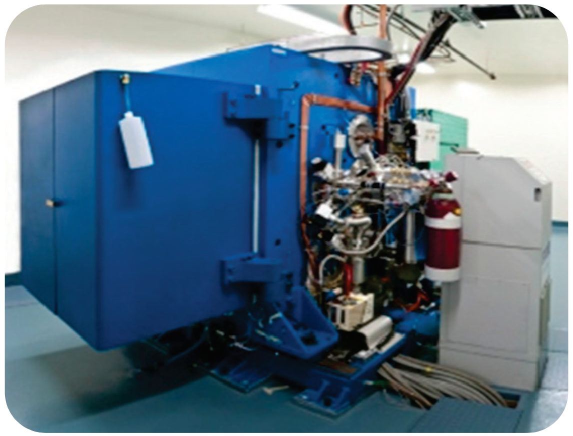
Nuclear Medicine

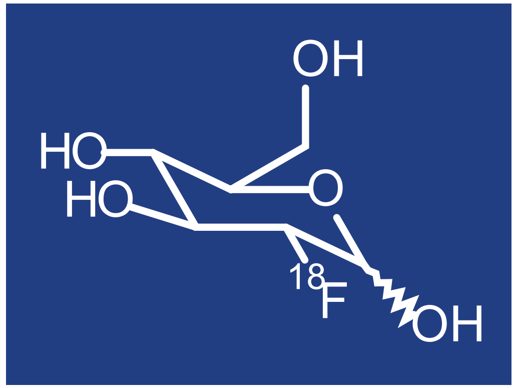
Accel. Targets

Isotope Production

Radiochemistry







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CP42, TR30, TR13 Operations

TRIUMF Capabilities:

- CP42: up to 42 MeV and 200 μA, installed 1980
- TR30-1: up to 30 MeV and 900 μA, installed 1990
  - first TR30 designed, assembled by TRIUMF, components manufactured by EBCO, commissioned by TRIUMF
- TR30-2: up to 30 MeV and 1000 μA, installed 2003
  - Manufactured, installed by EBCO, commissioned by TRIUMF
- TR13: 13 MeV, 25μA, installed 1986 (UBC Neurology)
  - Capable of ^{11}C, ^{18}F, ^{13}N, ^{68}Ga, ^{89}Zr, ^{64}Cu, ^{44}Sc, ^{86}Y, ^{55}Co, ^{52}Mn…solid, liquid, gas targets
- TR24: 24 MeV, >400 μA, to be installed

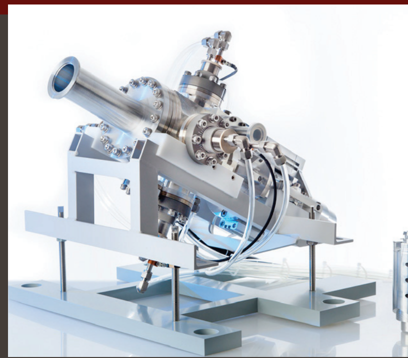
Overall

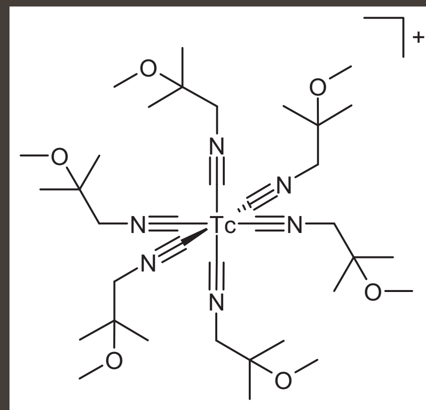
- 5 solid target, 3 gas stations operating at 30 MeV
  - Commercial production: ^{67}Ga, ^{111}In, ^{123}I, ^{103}Pd, ^{201}Tl
- Future commercial production: ^{99m}Tc

Direct, multi-Curie production of ^{99m}Tc on three different cyclotrons

K Buckley, F Bénard, M Kovacs, J Valliant, T Ruth, P Schaffer

1) TRIUMF
2) University of British Columbia;
3) BC Cancer Agency;
4) Lawson Health Research Institute;
5) Centre for Probe Development and Commercialization





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Tc-99m Alternatives: Many options

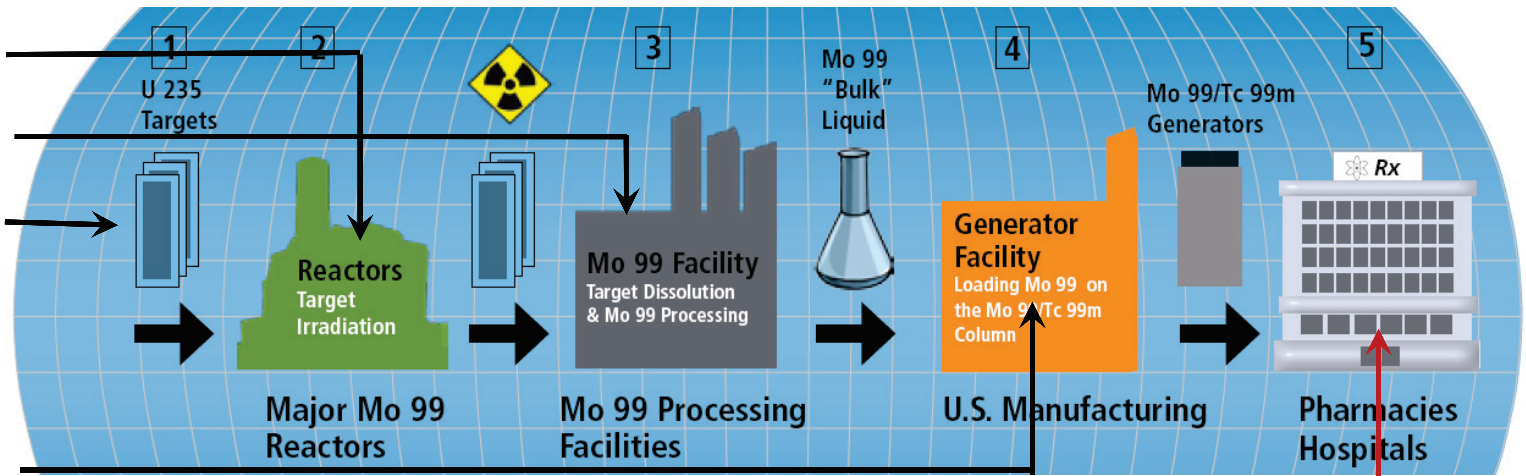
- ^{99}Mo/^{99m}Tc in high demand (~ 40M doses/yr)
- Gov't owned reactors produce majority of ^{99}Mo supply
- NRU going offline Oct. 2016 (~40% of global supply)
- Capacity emerging (existing reactors, new technology)
- Projections range from oversupply to shortages[1]
- Must move to full-cost recovery

Alternatives:

^{98}Mo(n,γ)^{99}Mo

^{238}U(γ,F)^{99}Mo

LEU ^{235}U(n,F)

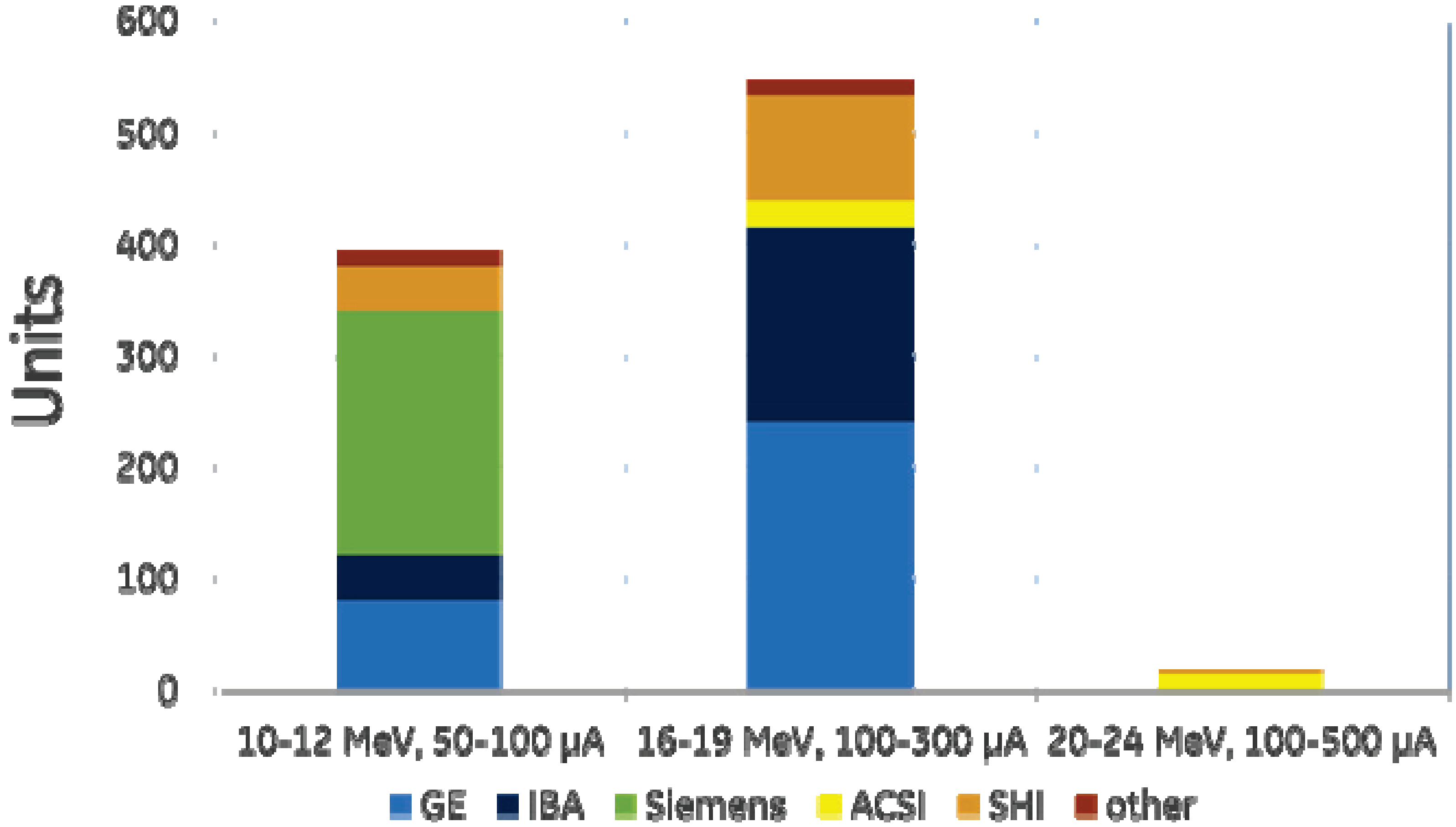


^{100}Mo(γ,n)^{99}Mo

^{100}Mo(p,2n)^{99m}Tc

1) OECD - NEA/SEN/HLGMR(2014)2
graphic from http://www.covidien.com/

Cyclotrons By the Numbers



Estimated global cyclotron numbers by various manufacturers
(with data from ACSI, GE, IBA and Siemens, Sumitomo data estimated)

P Schaffer et al. Physics Procedia 2015, 66, 383

Direct Production of ^{99m}Tc

^{100}Mo Target	Cyclotron Modificatio n	Optimize Irradiation	Purify $^{99m}TcO_4$	Regulatory QA/QC	^{100}Mo Recovery

Goals:

- Demonstrate routine, reliable, commercial-scale production of ^{99m}Tc via $^{100}Mo(p,2n)$ at multiple sites, multiple brands;
- Obtain regulatory approval for clinical use in humans;
- Establish a business plan;
- Disseminate, commercialize the technology

Hypothesis: Future production will be from variety of sources (neutron, proton, electron) and market driven

J. Beaver, H. Hupf, J Nucl Med 1971;12:739-741

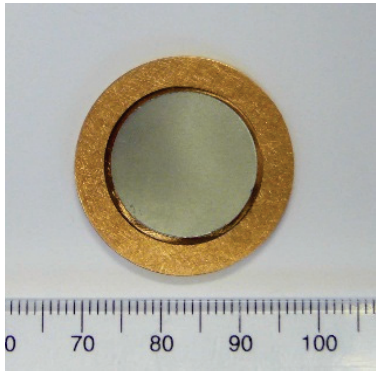
Target Manufacturing

^{100}Mo Target	Cyclotron Modification	Optimize Irradiation	Purify $^{99m}TcO_4$	Regulatory QA/QC	^{100}Mo Recovery

Goals:
- Maximize ^{99m}Tc production, minimize impurities
- Withstand up to 24 MeV, 500 μA, 6 hr irradiation
- Balance thermal conductivity with post irradiation dissolution
- Compatible with existing cyclotron infrastructure

Bénard et al., J. Nucl. Med. 2014, 55, 1017-1022

Results:
- Oblique ACSI 'TR19' (5.4 kW) and
- Oblique ACSI 'TR24' (10.8 kW) targets
- Orthogonal PETtrace (2.1 kW)
- Demonstrated yields:
  - >1110 GBq (>30 Ci) @ 24 MeV, 450 μA, 6 hrs
  - 420 GBq (11.3 Ci) @ 18 MeV, 300 μA, 6 hrs
  - 170 GBq (4.7 Ci) @ 16.5 MeV, 130 μA, 6 hrs,



Schaffer et al. Phys. Proc. 2015, 66, 383
Zeisler et al. WTTC 2014

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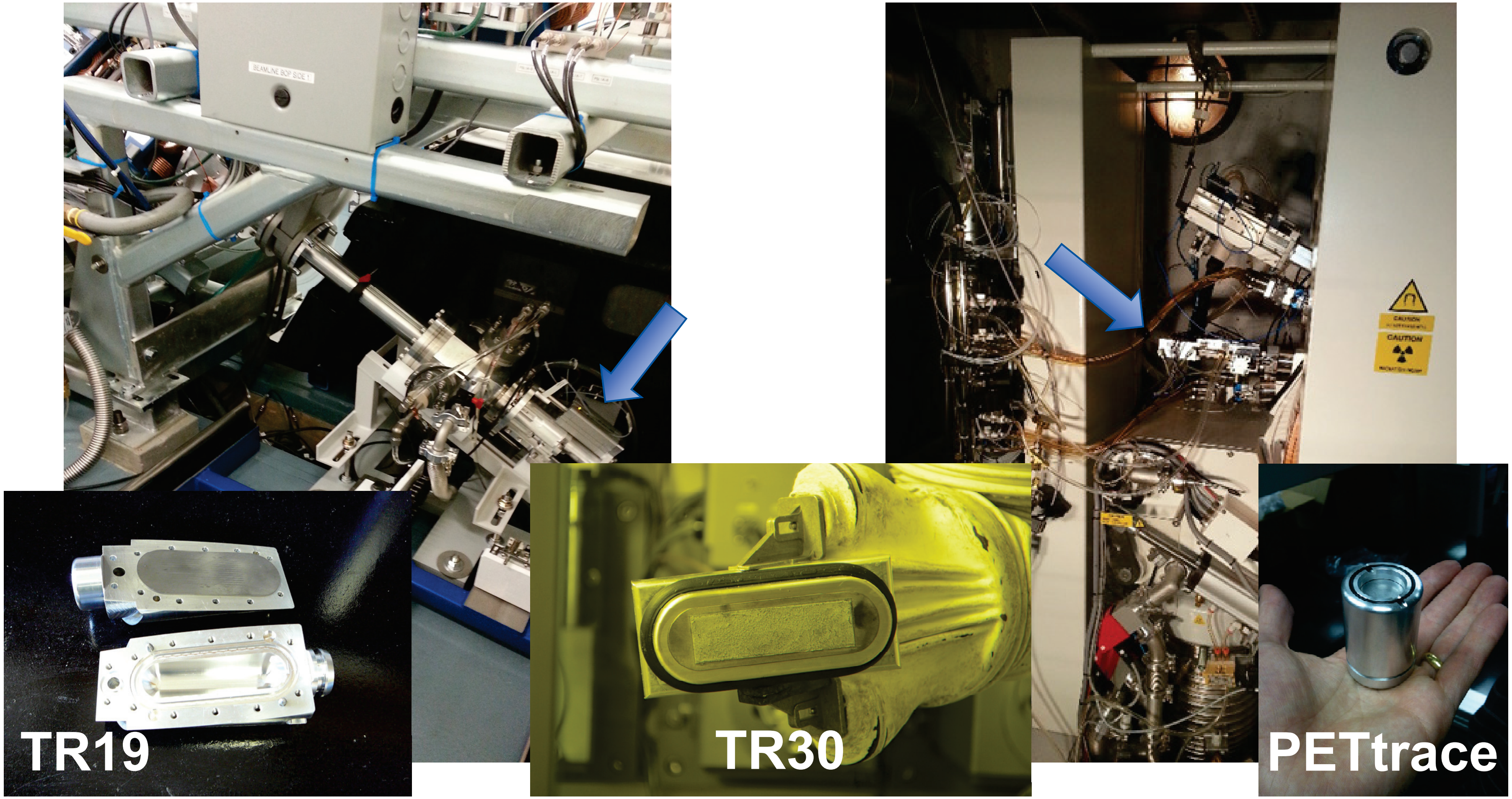
Retrofit Existing Infrastructure

^{100}Mo Target	Cyclotron Modificatio n	Optimize Irradiation	Purify $^{99m}TcO_4$	Regulatory QA/QC	^{100}Mo Recovery



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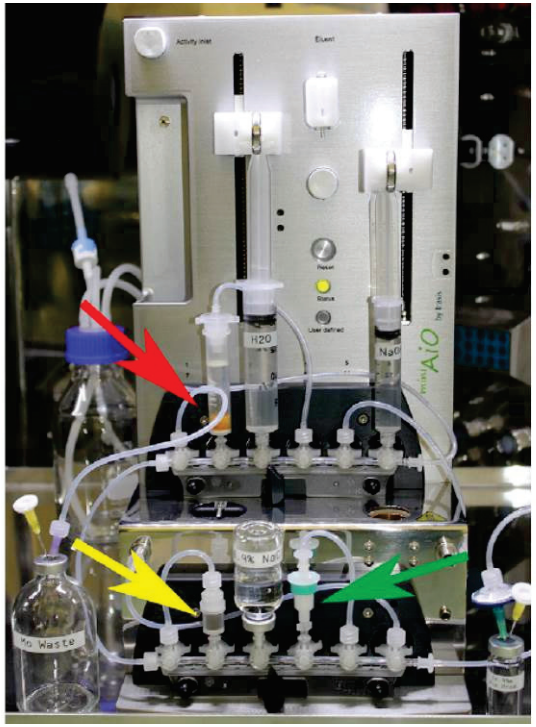
Purification of ^{99m}Tc

^{100}Mo Target	Cyclotron Modification	Optimize Irradiation	Purify $^{99m}TcO_4$	Regulatory QA/QC	^{100}Mo Recovery



- SPE-based method:
  - original work: Dowex™ vs ABEC
  - new alternative resin: ChemMatrix™
- Process Time: complete in <90 min.
- Efficiency Range: 92.7 ± 1.1%
- Radiochemical Purity: >99.99% TcO_4
- Trace analysis: <10 Bq Mo-99, <5 ppm Al^{3+}
- non-Tc impurities removed

Regulatory:

Disposable fluid path for GMP

Specifications and control tests

Morley et al. Nuc. Med. Biol. 2012, 551-559

Bénard et al., J. Nucl. Med. 2014, 55, 1017-1022

Regulatory Process: CTA nearly complete

^{100}Mo Target	Cyclotron Modification	Optimize Irradiation	Purify $^{99m}TcO_4$	**Regulatory QA/QC**	^{100}Mo Recovery

- Not currently approved by Health Canada, FDA, etc.
- CTA submitted, approved
- Shelf life (18 hrs), irradiation parameters are based on projected patient dose (objective <10% add'l vs. pure ^{99m}Tc)
  - Enrichment and irradiation parameters are interrelated and should not be considered independently
- Patient recruitment underway (60 patient trial)
- Fall - Winter 2015 – New Drug Submission (NDS) submission

^{100}Mo Raw Material/Irradiation Specifications

Isotope	Proposed max. isotopic impurity to maintain patient dose increase of ~10% compared to pure $^{99m}TcO_4$		
	≤ 20 MeV[1]	20 – ≤22 MeV[2]	22 - ≤24 MeV[3]
^{92}Mo	0.03	0.03	0.02
^{94}Mo	0.03	0.03	0.02
^{95}Mo	0.03	0.03	0.02
^{96}Mo	0.03	0.03	0.02
^{97}Mo	0.03	0.03	0.02
^{98}Mo	7	0.8	0.5

[1]Maximum increase in patient dose of 9.8 % at 20 MeV, 18 hours after EOB.
[2]Maximum increase in patient dose of 10.1% at 22 MeV, 18 hours after EOB.
[3]Maximum increase in patient dose of 10.6% at 24 MeV, 18 hours after EOB.

- *Based on theoretical yield calculations with ^{99m}Tc pertechnetate*
- *Mitigates the impact of dose due to ^{98}Mo(p,3n)^{96}Tc reaction at higher E*

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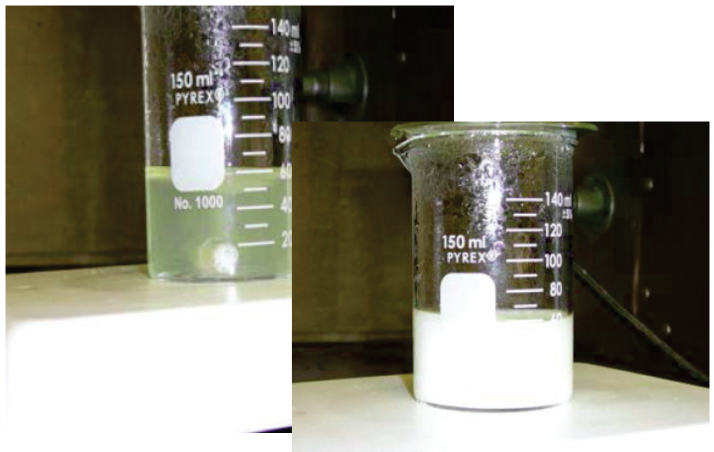
Mo-100 Recovery/Recycling

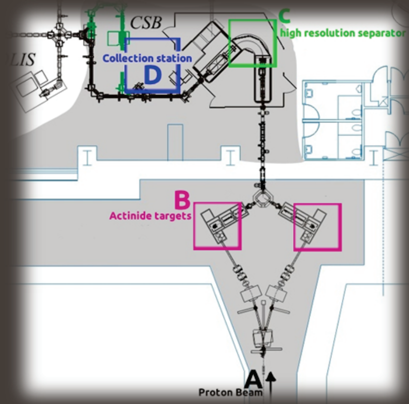
^{100}Mo Target	Cyclotron Modification	Optimize Irradiation	Purify $^{99m}TcO_4$	Regulatory QA/QC	**^{100}Mo Recovery**

- High efficiency recovery process for multi-gram quantities of $^{100}MoO_4^{2-}$ required
- Some trace long-lived radionuclidic impurities (Nb, W…)
- Target dissolution waste stream (liquid, 10’s of mL/batch)
- Currently finalizing acidic precipitation, thermal decomp. process
- Routine recovery yields >99%
- Analysis of recovered ^{100}Mo underway



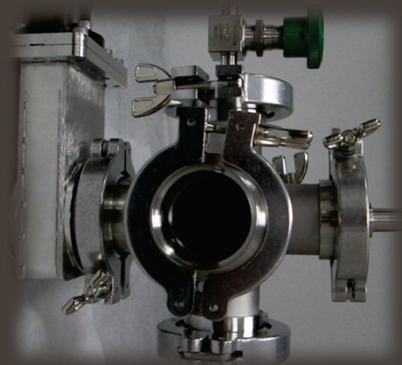
Remaining Challenges for Cyclotron Production of ^{99m}Tc

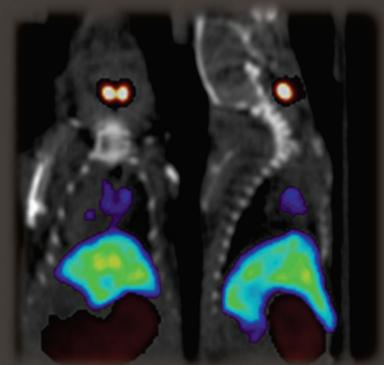
- Process: Determine long-term reliability (cyclotron and target)
- Quality Control: Decentralized production inherently leads to a greater likelihood of product variability, dose uncertainty
- Regulatory: Considerations need to include target isotopic enrichment, but also batch-to-batch target consistency, irradiation energy/duration, shelf-life (patient dose)
- Economic: Arguments in one region may not apply in others but Full Cost Recovery must apply to all
- Availability: A viable alternative/backup needs to be used regularly



Production and assessment of radiotherapeutic isotopes

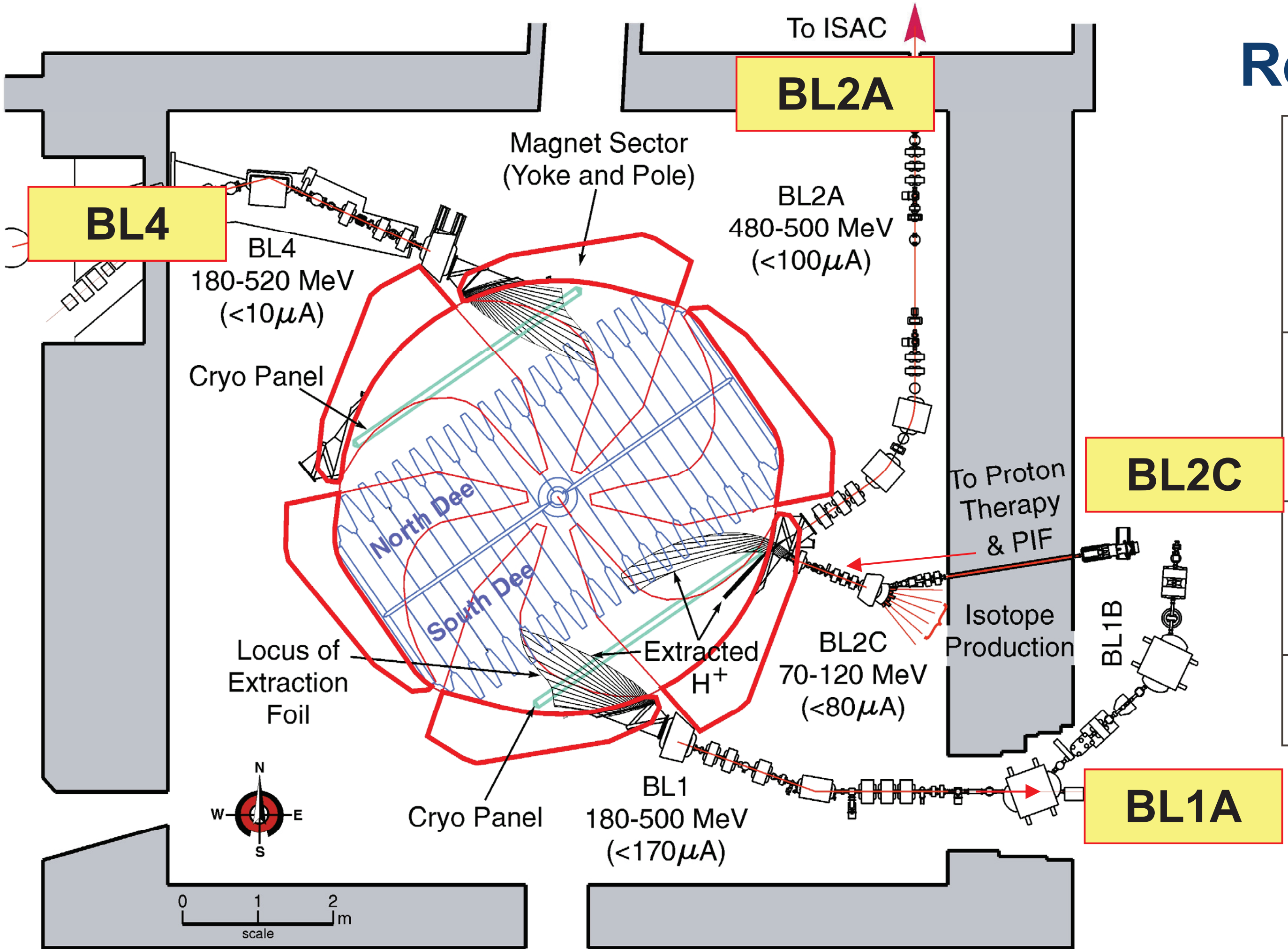
Thanks to: J Crawford, P Kunz, C Ramogida, K Ladouceur, A Robertson, H Yang, B Laxdal, T Ruth





500 MeV Cyclotron Capabilities

Previous decade: routine operation at 220-250µA

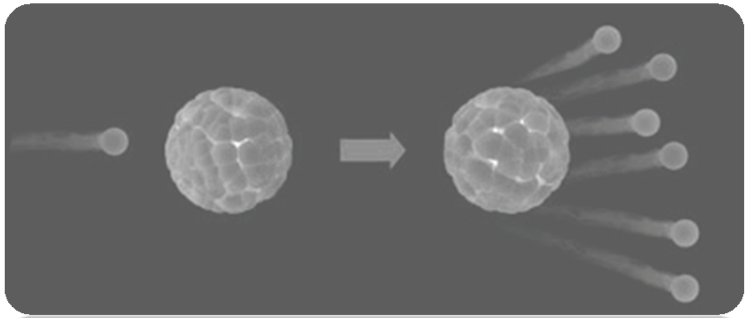


Recently achieved:

Materials science, **500 MeV isotopes:** • **BL1A (100µA)**
ISAC program: • BL2A (100µA)
Sr production: • **BL2C (100µA)**
• **Total (300µA)**

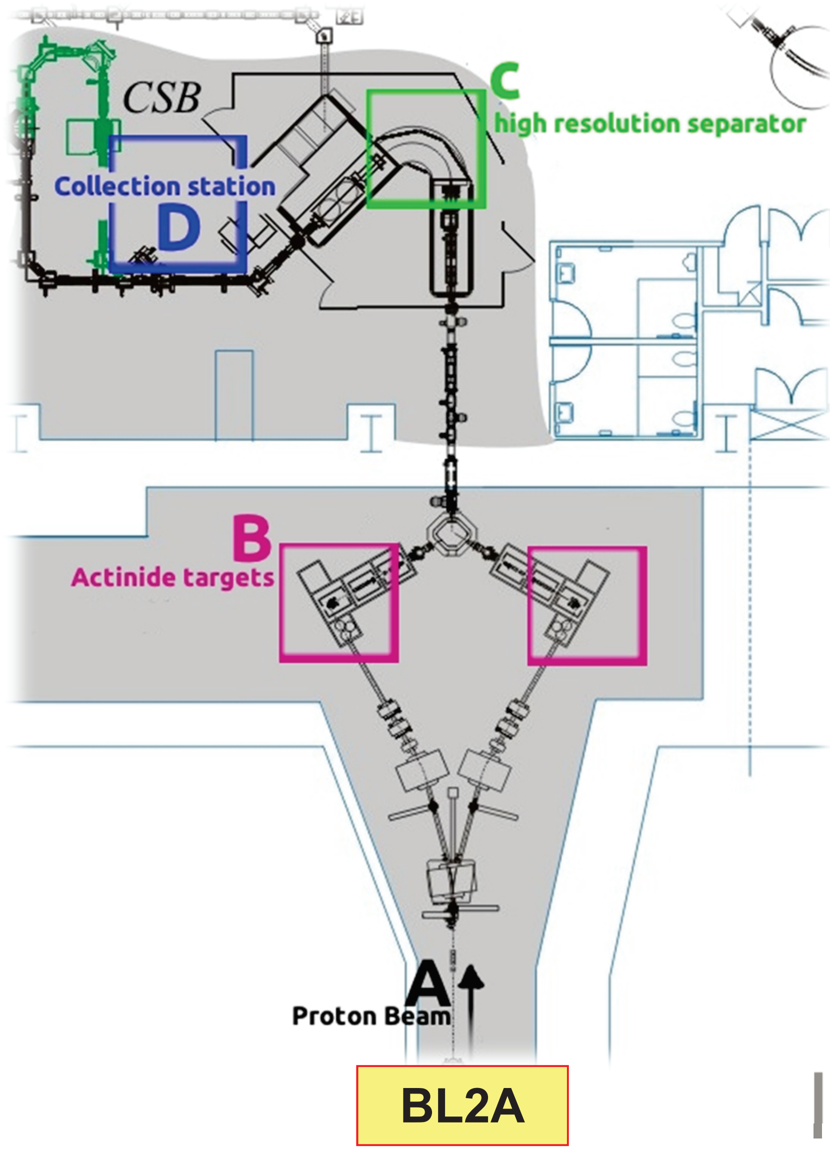
Isotope Accelerator Program (ISAC): 50 kW ISOL Facility

Isotope production via spallation of uranium:



Implementation of ISOL technique:

- Uranium carbide, thorium oxide
- 480 MeV protons, 10 μA
- Various available ion sources
- ~2500:1 mass separation resolution (~10^6–10^9 ions/s)
- Ion energy = ~20-60 keV



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Candidate α-emitters for therapy

Isotope	Half-life	Standard Production	1st Ion. E.	ISAC yield
^{149}Tb	4.2 h	Spallation, heavy-particle accelerator	5.86 eV	High
^{211}At	7.2 h	α-cyclotron	9.54 eV	Low
^{212}Bi	1.0 h	Generator (^{224}Ra/^{212}Bi)	7.29 eV	High for parent
^{213}Bi	0.76 h	Generator ^{225}Ac	7.29 eV	High for parent
^{223}Ra	11.4 d	Generator (^{227}Ac/^{223}Ra)	5.38 eV	High
^{224}Ra	3.7 d	Generator ^{232,228}Th	5.38 eV	High
^{225}Ac	10 d	Generator (^{229}Th/^{225}Ac)	5.38 eV	High

ISAC yields are high for Tb, Bi, Ra and Ac, but low for astatine isotopes

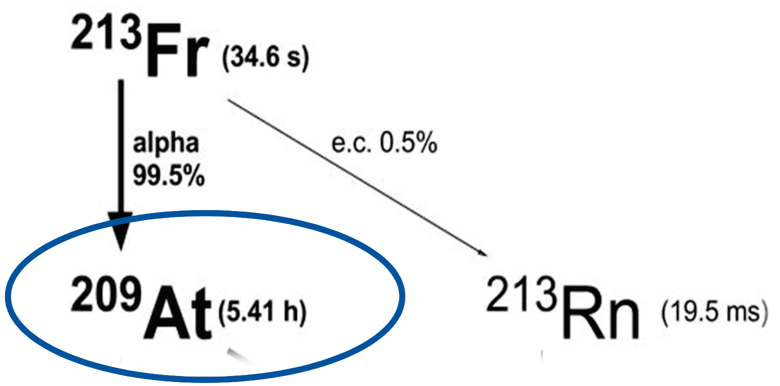
Astatine isotopes can be collected from the decay chains of high yield francium ion beams (ionization energy of Fr = 3.94 eV)

^{209}At-based imaging to establish ^{211}At α-therapy

^{209}At identified as novel SPECT isotope

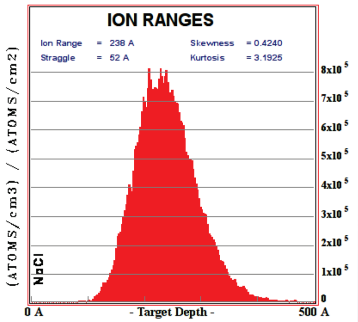
Therapy	Imaging
^{211}At $t_{1/2}$= 7.2 h	^{209}At $t_{1/2}$= 5.4 h
(α-emitter)	(γ-emitter)

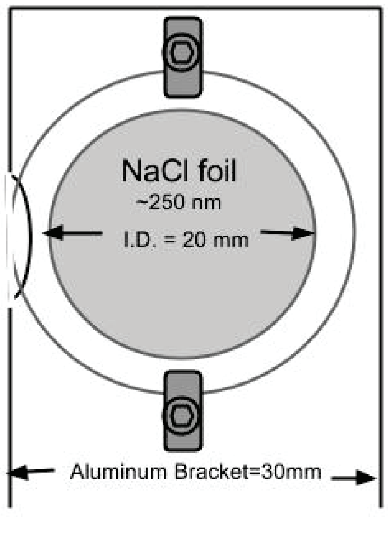
^{209}At collected from ^{213}Fr ion beams

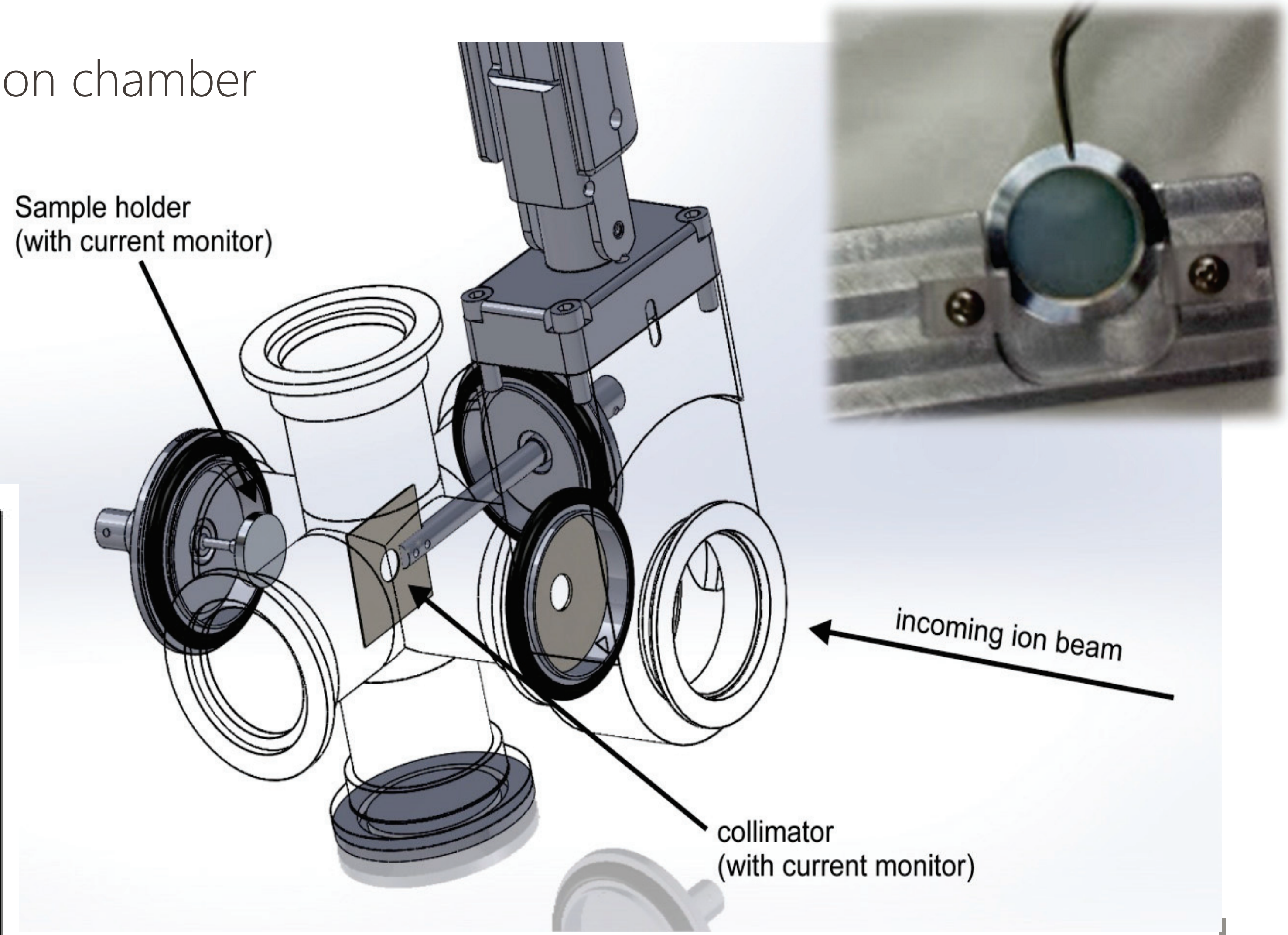


ISOL pilot study: ^{209}At

Implantation chamber







From bench to (pre-clinical) bedside

10^9 ions/s of ^{213}Fr collected for up to 9.5 h

↓

^{209}At recovered by dissolving NaCl targets in 0.1 N NaOH (< 300 μL)

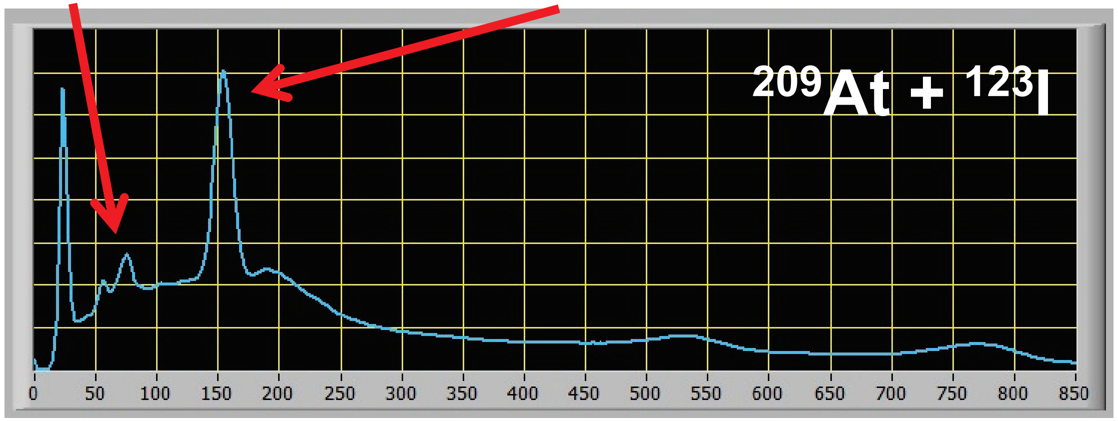
↓

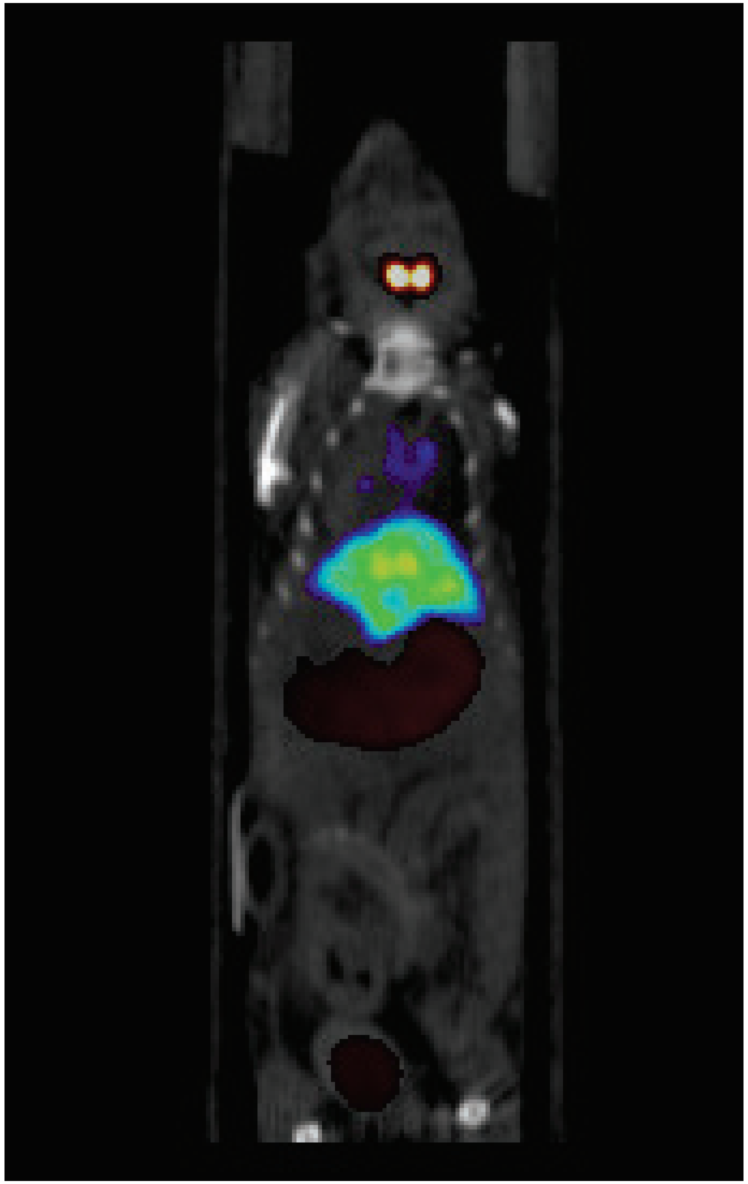
Up to 8.9 mCi ^{209}At (EOB)
(Measured by γ-ray spectroscopy)

↓

Labeling Chemistry

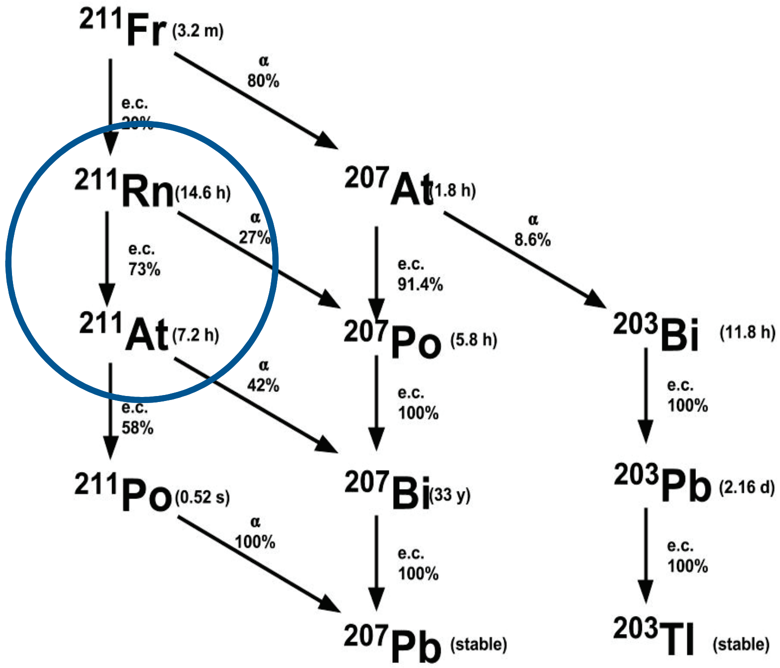
^{209}At: 80 keV peak **^{123}I: 159 keV peak**



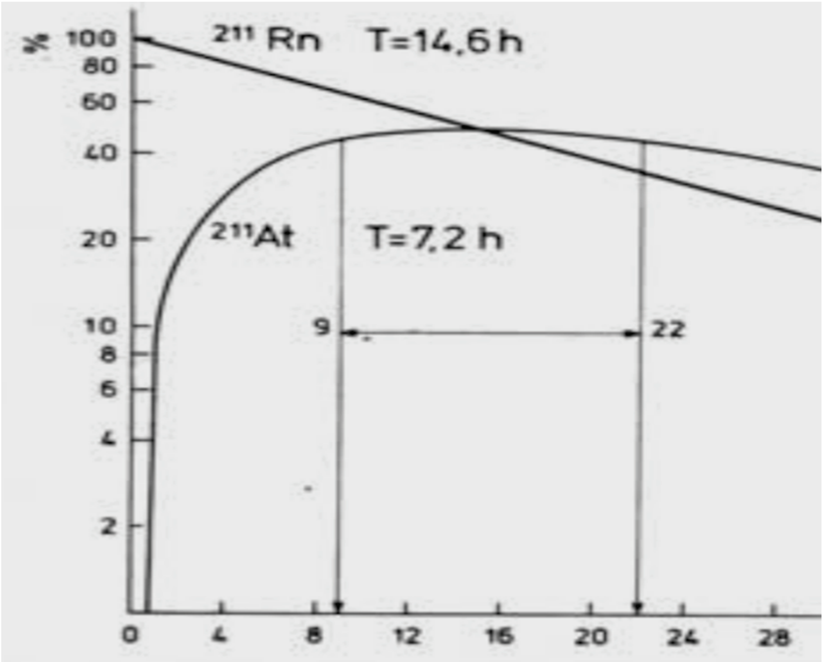


$^{211}Rn/^{211}At$ generator system from ^{211}Fr ion beams ($>10^9$ ions/s)

The ^{211}Fr decay chain provided a novel approach to ^{211}Rn production



$^{211}Rn/^{211}At$ generator could increase ^{211}At supply and opportunities for distribution

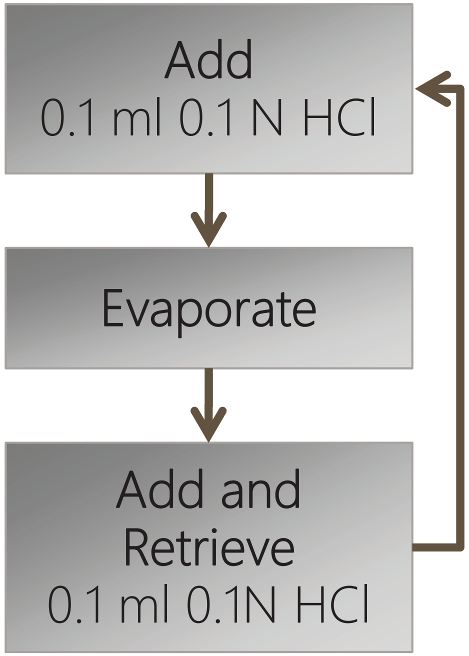


^{211}Rn was isolated in dodecane, other radioactive inventory was washed away with aqueous solution

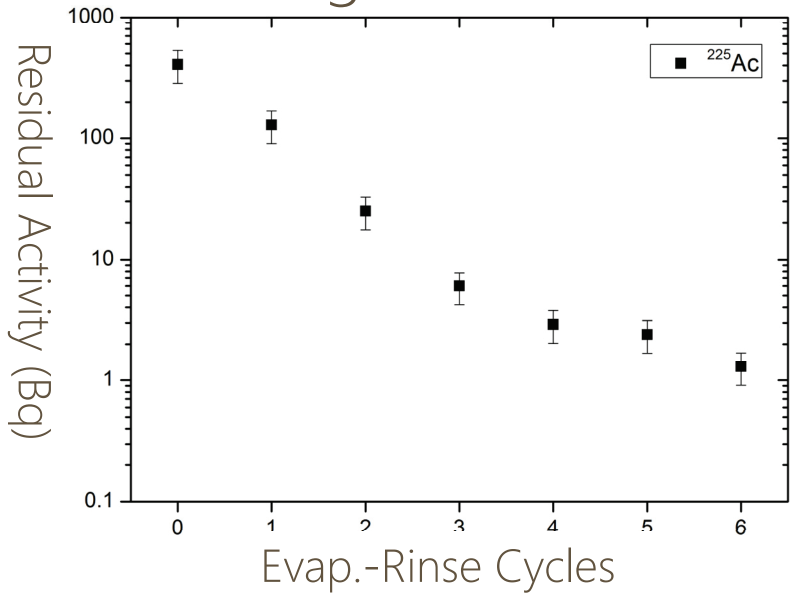
↓

^{211}At progeny recovered after several hours of grow-in

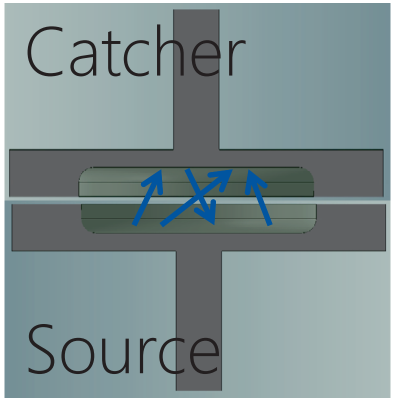
Moving on to feasibility of $^{225}Ra/^{225}Ac$

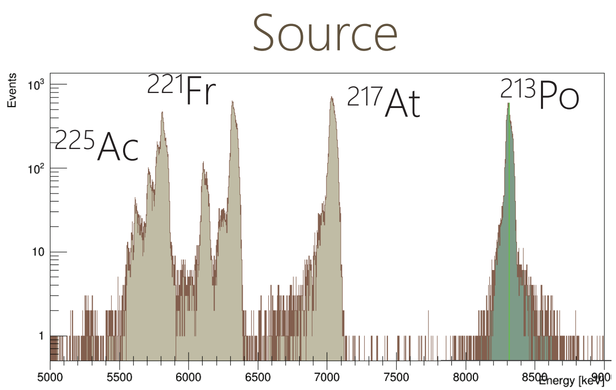


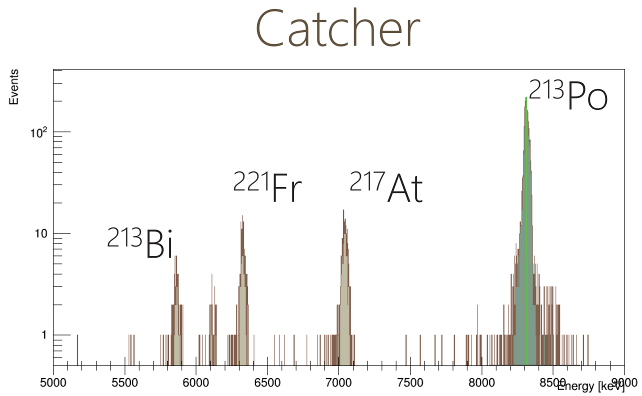
Extraction using 0.1N HCl solution



Recoil transfer in vacuum







Efficiency ~30%

Future Direction: $^{225}Ac/^{213}Bi$

- ISOL and Target Dissolution/Extraction

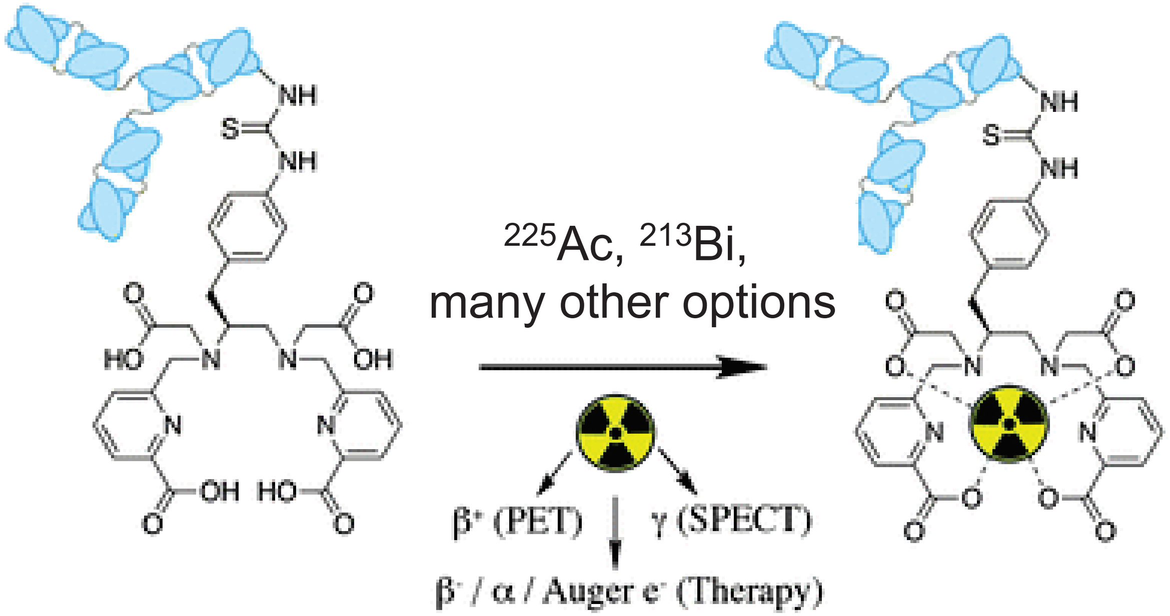
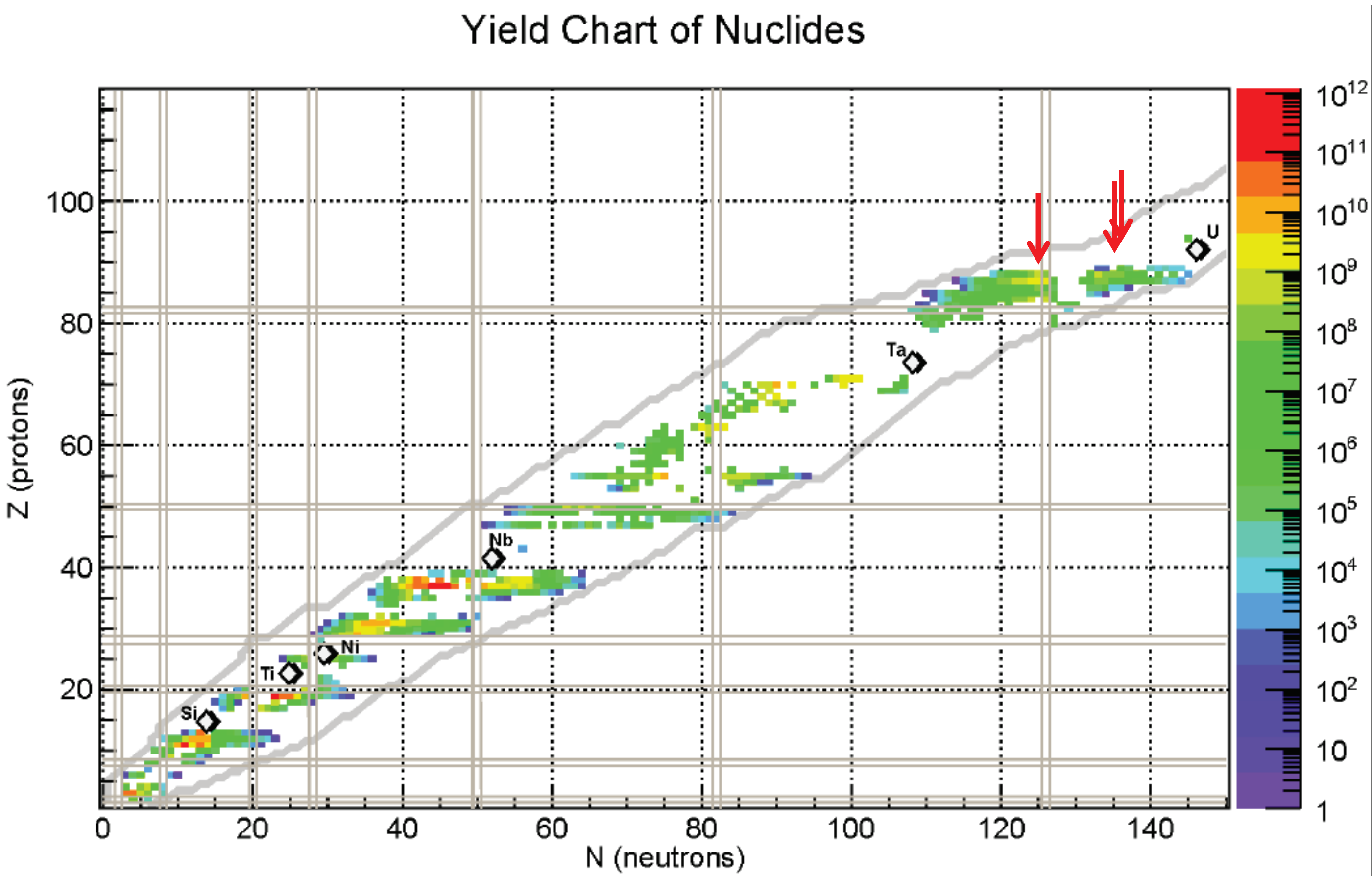


Image taken from: E Price, C Orvig, *Chem. Soc. Rev.*, 2014,43, 260-290

- TRIUMF capable of producing large (Ci) quantities of isotopes such as ^{225}Ac, $^{223,225}Ra$, ^{213}Bi, ^{211}Rn
- Possible to ship targets for off-site processing (short-term)
- Effort in early stages, infrastructure, regulatory capabilities being pursued/implemented (long-term)

Medical Isotopes from ISAC/ISOL

- Future Direction(s): From ISOL to full target harvest…



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- The Team:

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  Ken Buckley, Vicky Hanemaayer, Brian Hook, Stuart McDiarmid, Stefan Zeisler, Frank Prato, Anne Goodbody, Joe McCann, Conny Hoehr, Tom Morley, Julius Klug, Philip Tsao, Milan Vuckovic, Patrick Ruddock, Maurice Dodd, Guillaume Langlois, Wade English, Xinchi Hou, Jesse Tanguay, Jeff Corsault, Ross Harper, Frank Prato, Constantinos Economou

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Natural Resources Canada Ressources naturelles Canada

Canada

BC Cancer Agency CARE & RESEARCH An agency of the Provincial Health Services Authority

LAWSON HEALTH RESEARCH INSTITUTE

cpdc

a place of mind UBC

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Canadian Cancer Society Société canadienne du cancer

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Don Hamlin (UW)
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