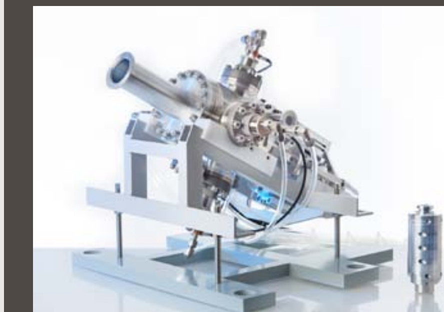
TRIUMF
Canada's national laboratory for particle and nuclear physics
Laboratoire national canadien pour la recherche en physique nucléaire et en physique des particules

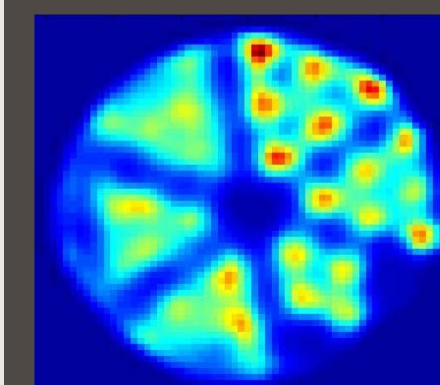
Medical radioisotopes made at TRIUMF

Accelerating medicine for Canada

Cornelia Hoehr | Research Scientist

- SPECT isotope: Tc-99m
- PET isotopes: radiometals
- α-emitters: At-209/211





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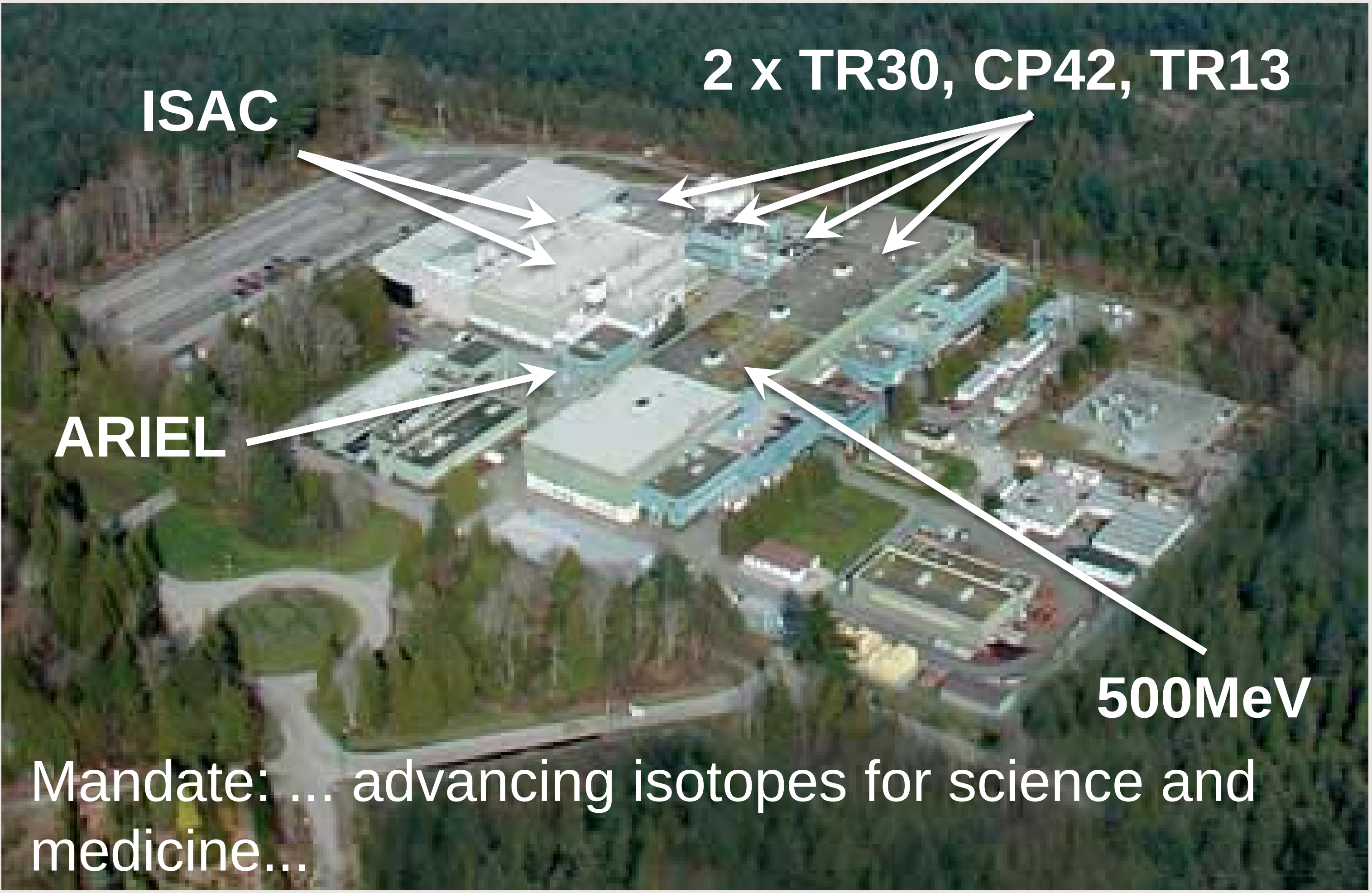


Mandate: ... advancing isotopes for science and medicine...

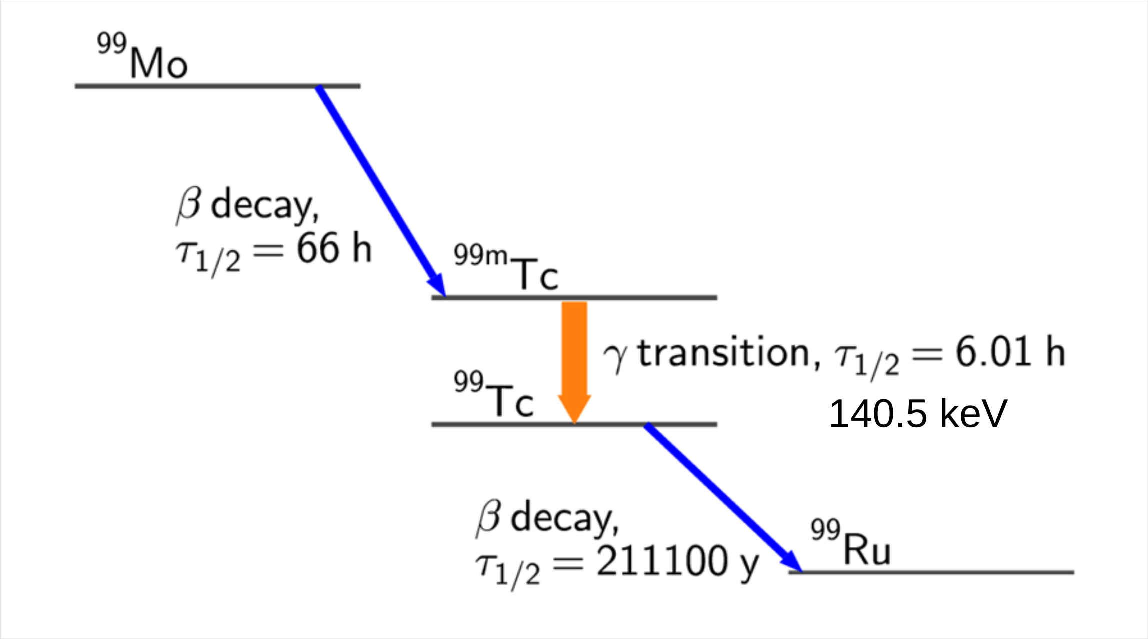
^{11}C, ^{13}N, ^{18}F, ^{44}Sc, ^{52}Mn, ^{55}Co, ^{56}Co, ^{68}Ga, ^{86}Y, ^{89}Zr, ^{61}Cu, ^{94m}Tc, ^{192}Ir

Also:
^{82}Rb, ^{103}Pd, ^{123}I, ^{201}Tl etc.

Owned and operated as an independent joint venture between 19 Canadian universities

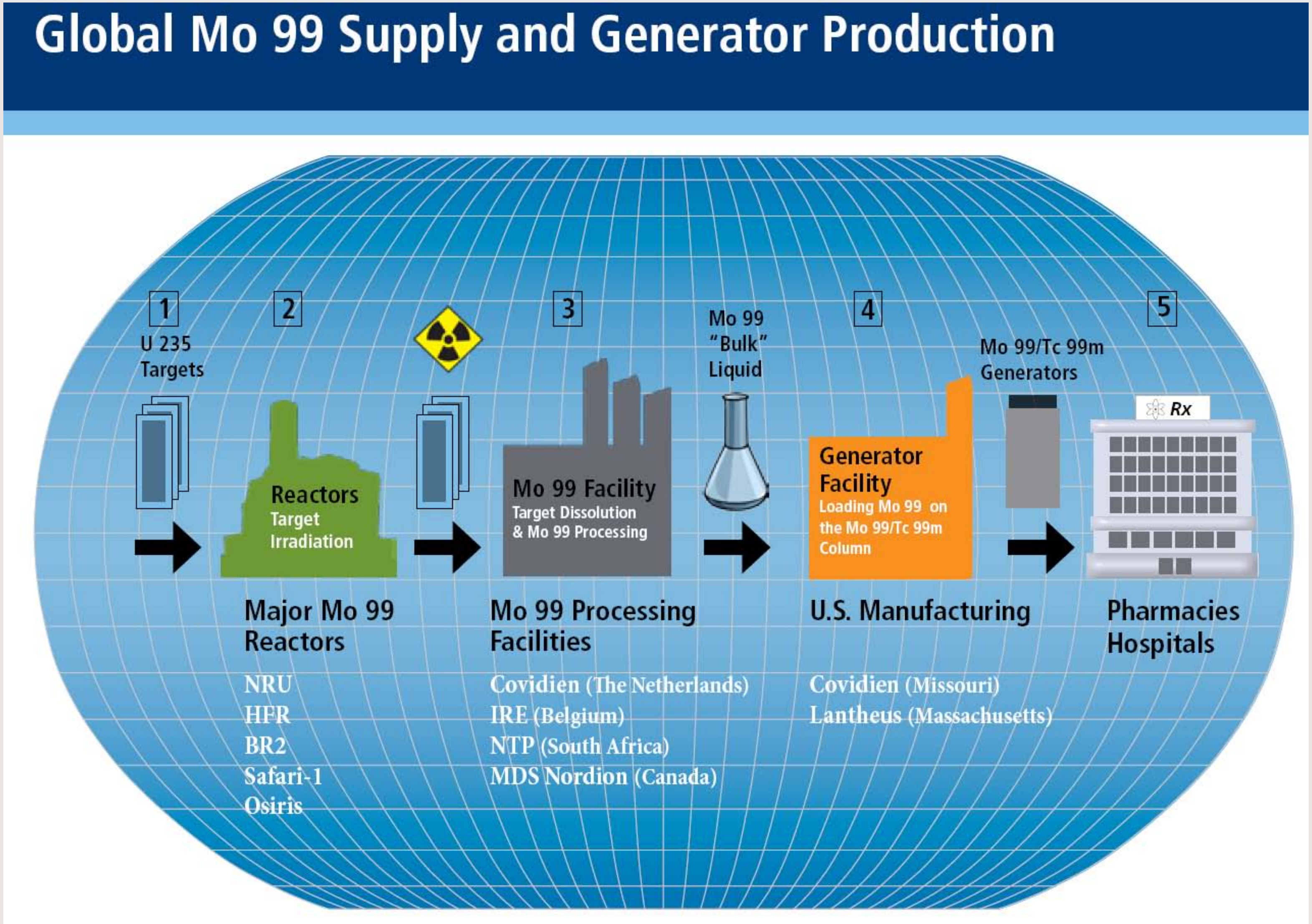
SPECT: Tc-99m

- SPECT: Single-photon emission computed tomography



- Simple distribution & use
- Global demand for ^{99}Mo/^{99m}Tc ~ 40 million doses/yr
  - >1 scan/second (brain, myocardium, thyroid, lungs, liver, gallbladder, kidneys, skeleton, blood, tumors)

Defining the Problem: Centralized Production of $^{99}Mo/^{99m}Tc$



graphic from http://www.covidien.com/

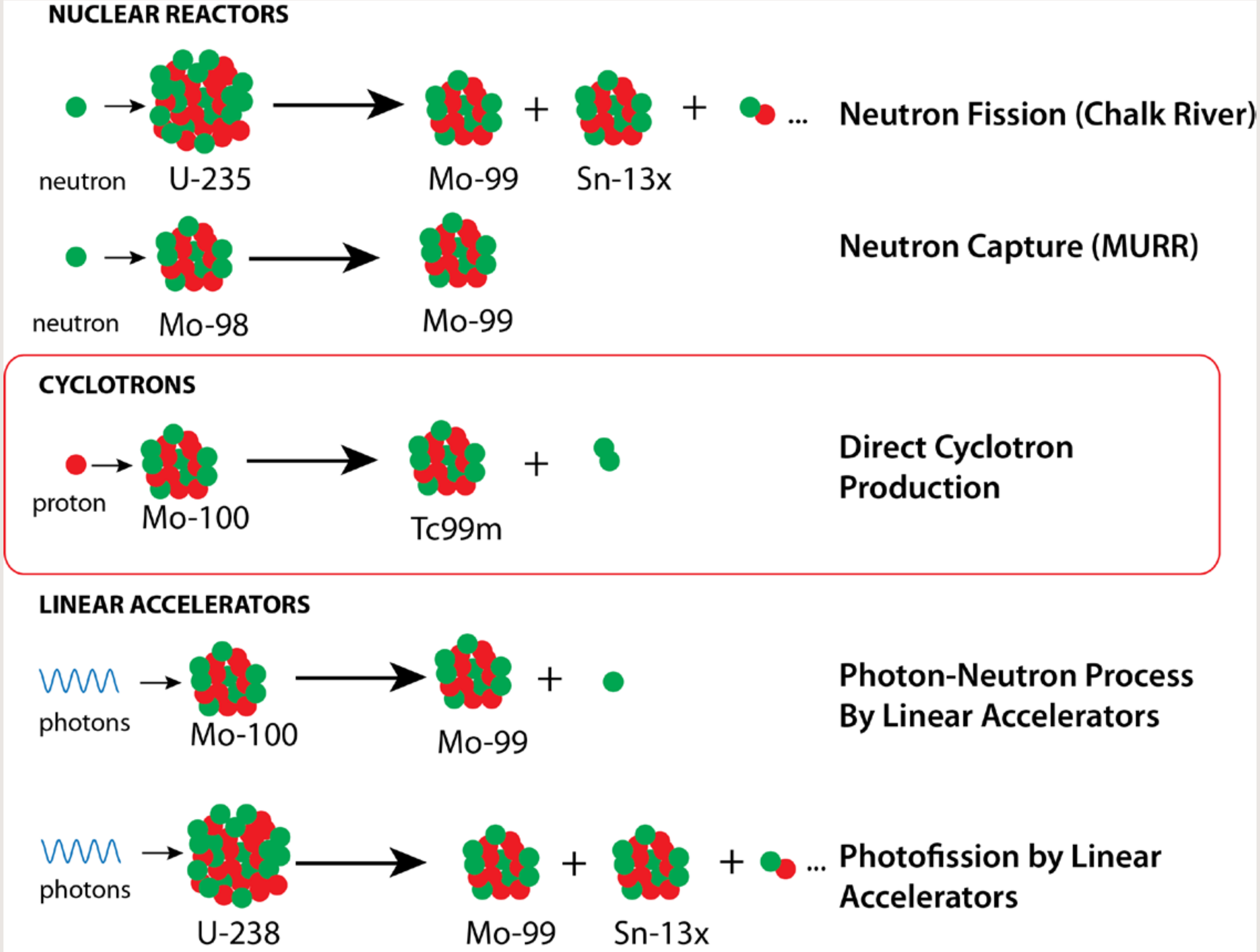
$^{99}Mo/^{99m}Tc$ Supply chain for North America

- The Mo-99 is mainly generated in five nuclear facilities,
  - the NRU reactor (Chalk River, Ontario, Canada; 40%),
  - HFR (Petten, The Netherlands; 30%),
  - BR-2 (Mol, Belgium; 12%),
  - Safari-1 (Palindaba, South Africa; 12%) and
  - OSIRIS (Saclay, France; 5%).

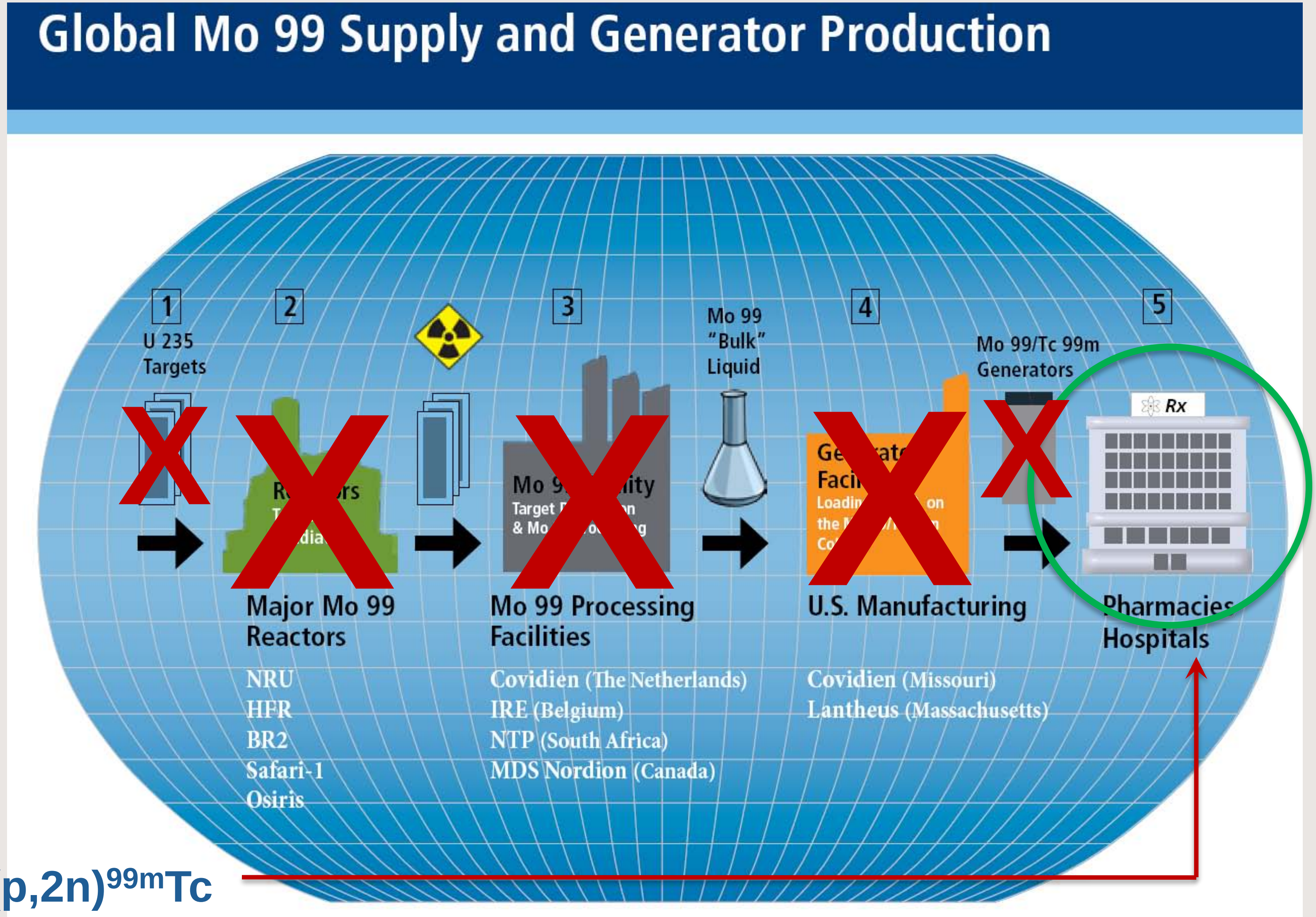
- All of these reactors are between 45 and 55 years old.

- Pressure to move away from HEU.

The Technology



Defining the Problem: Centralized Production of $^{99}Mo/^{99m}Tc$



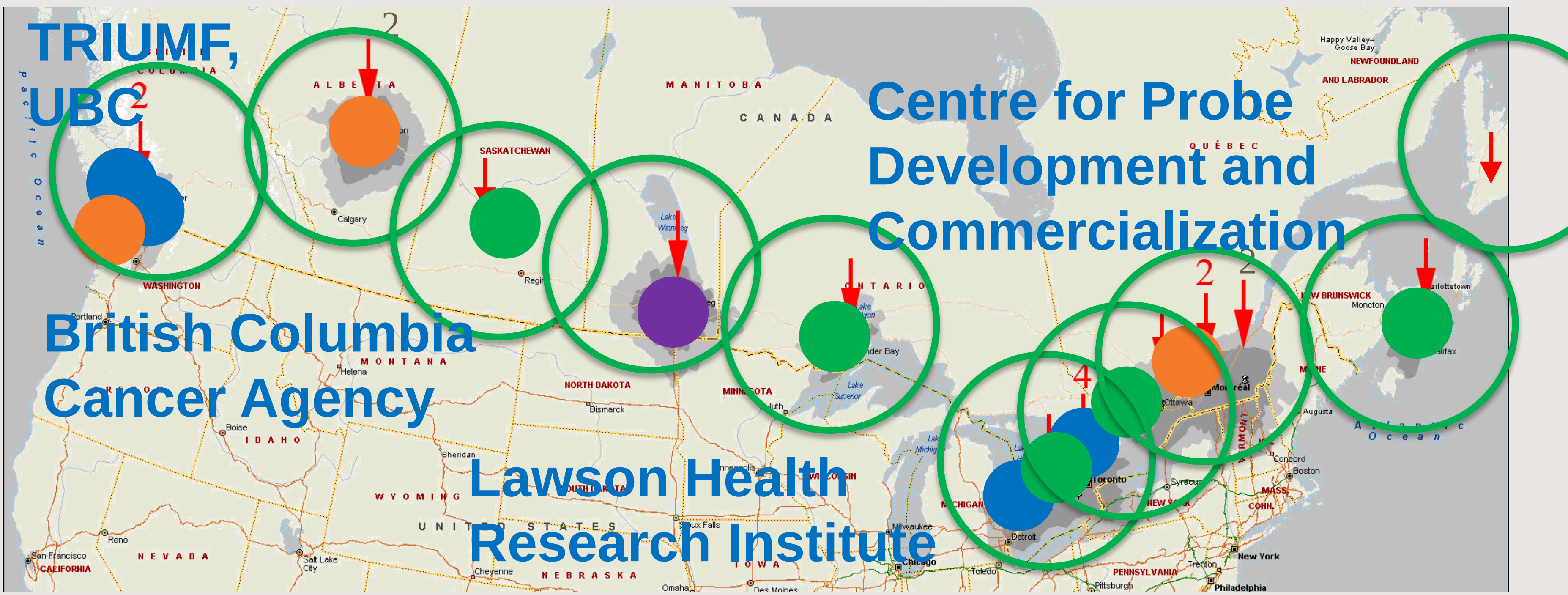
$^{100}Mo(p,2n)^{99m}Tc$

graphic from http://www.covidien.com/

Decentralized ^{99m}Tc Production in Canada

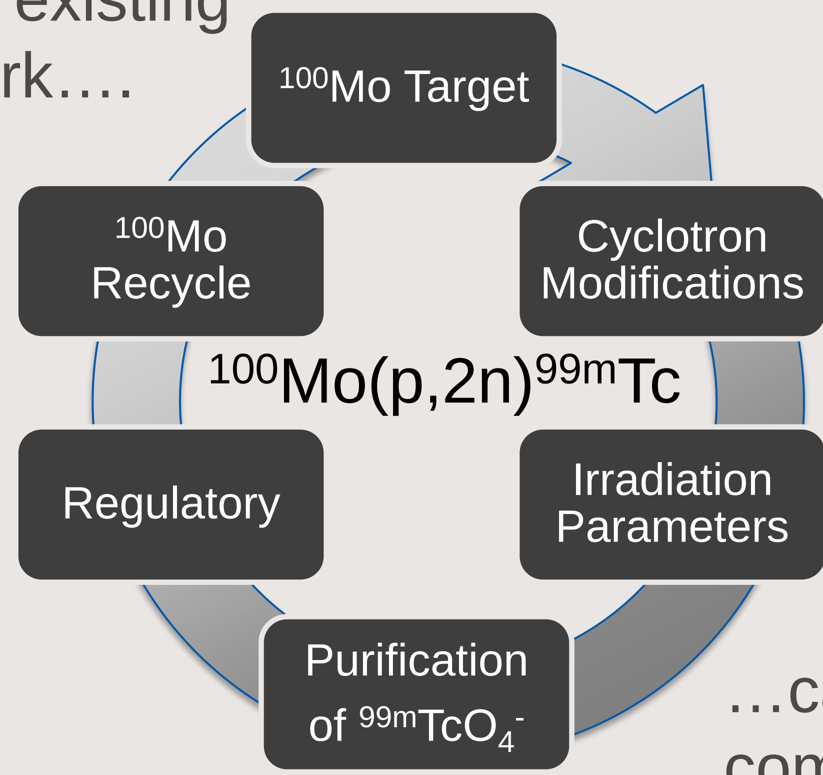
- NRCan-funded ITAP – 4 years (ending 2016), $25M, 3 proponents

● TRIUMF consortium,
● ERC consortium,
● CLS/PIPE effort
● Future/Prospective TRIUMF partner



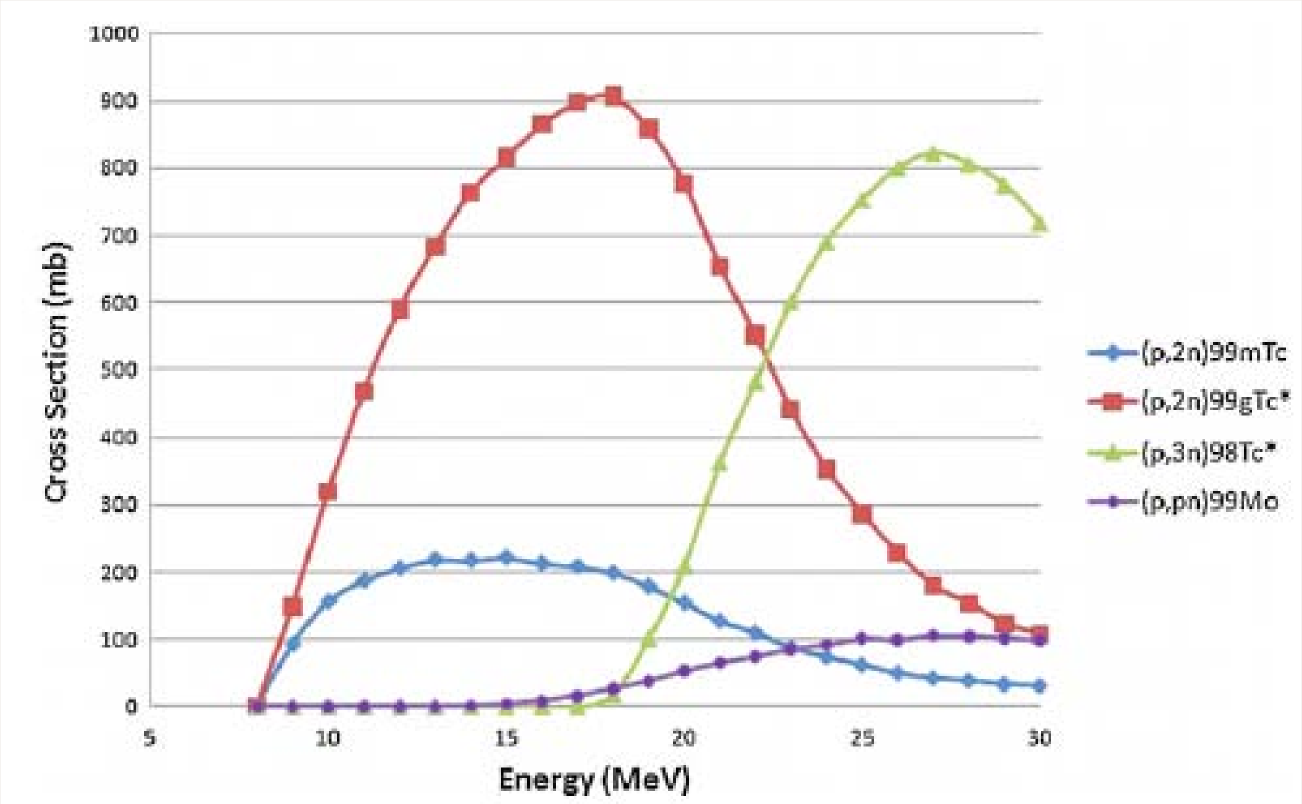
Making the Leap: From Lab Scale to Large Scale

To demonstrate existing cyclotron network….



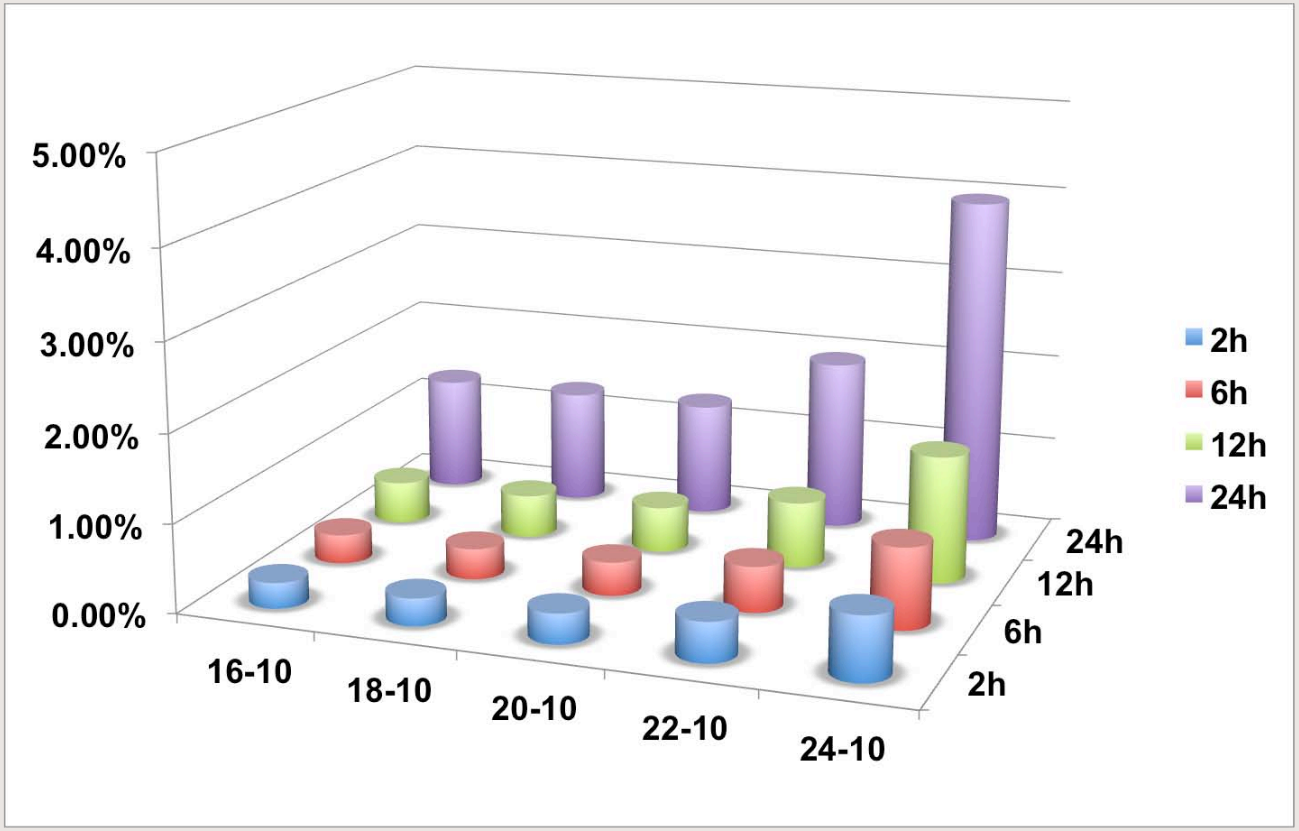
…can produce commercial quantities of ^{99m}Tc

Reactions on ^{100}Mo



Celler et al., Phys. Med. Biol. Vol. 56, pp 5469-5484, 2011.

High quality material allows longer shelf life and higher proton beam energy



99.815% enriched

% increase in patient radiation exposure vs. pure ^{99m}Tc-Sestamibi

- Critical Tc radionuclidic purity is determined by Mo-92-97 for energy 20 MeV or lower
- Mo-98 content important for energy 22-24 MeV (p,3n reactions)

Team Equipment/Capabilities

- TR19 (vaulted), PETtrace (self-shielded, vaulted)

TR19
13-19 MeV, ≤200µA
Upgraded to:
300 µA (single beam line)

GE PETtrace
16 MeV, ≤100 µA
Upgraded to: 130 µA (single beamline)

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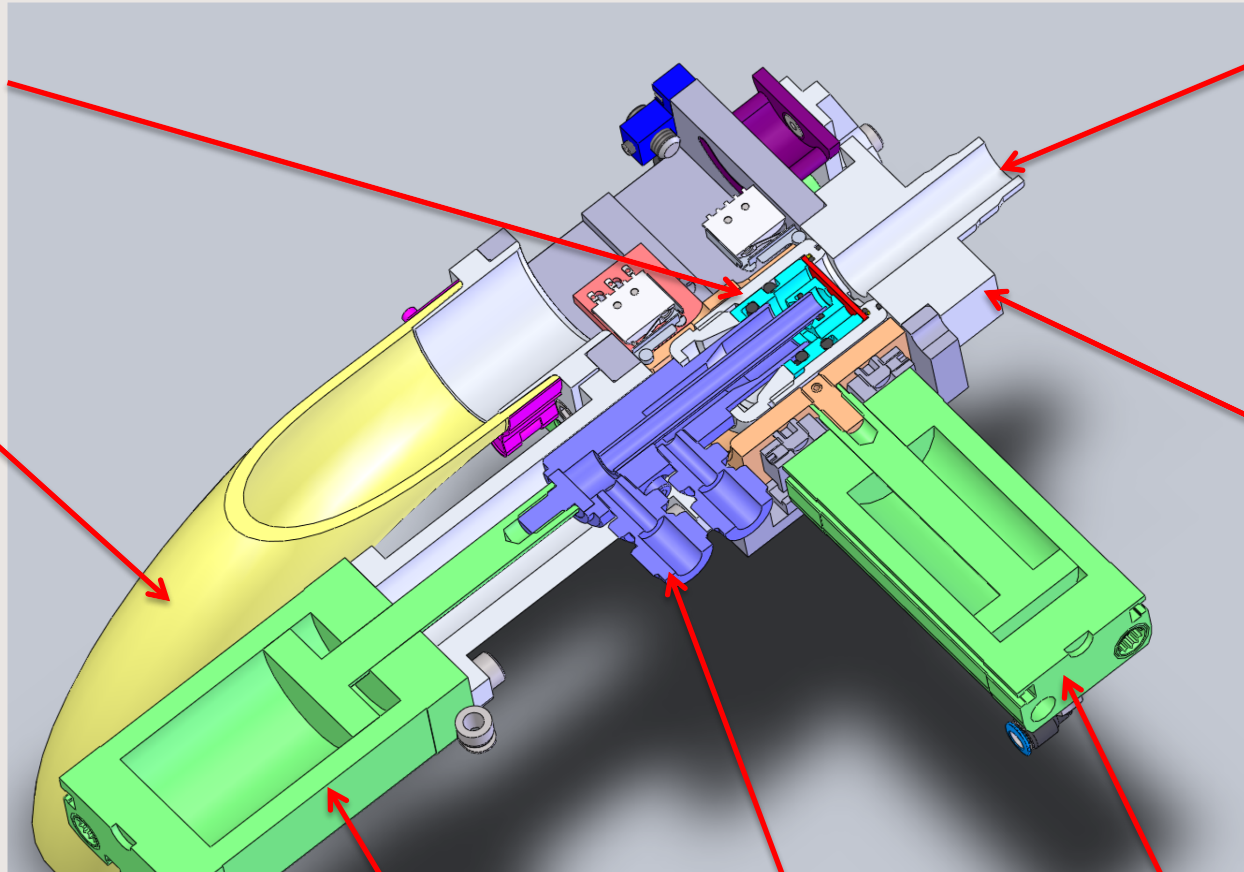
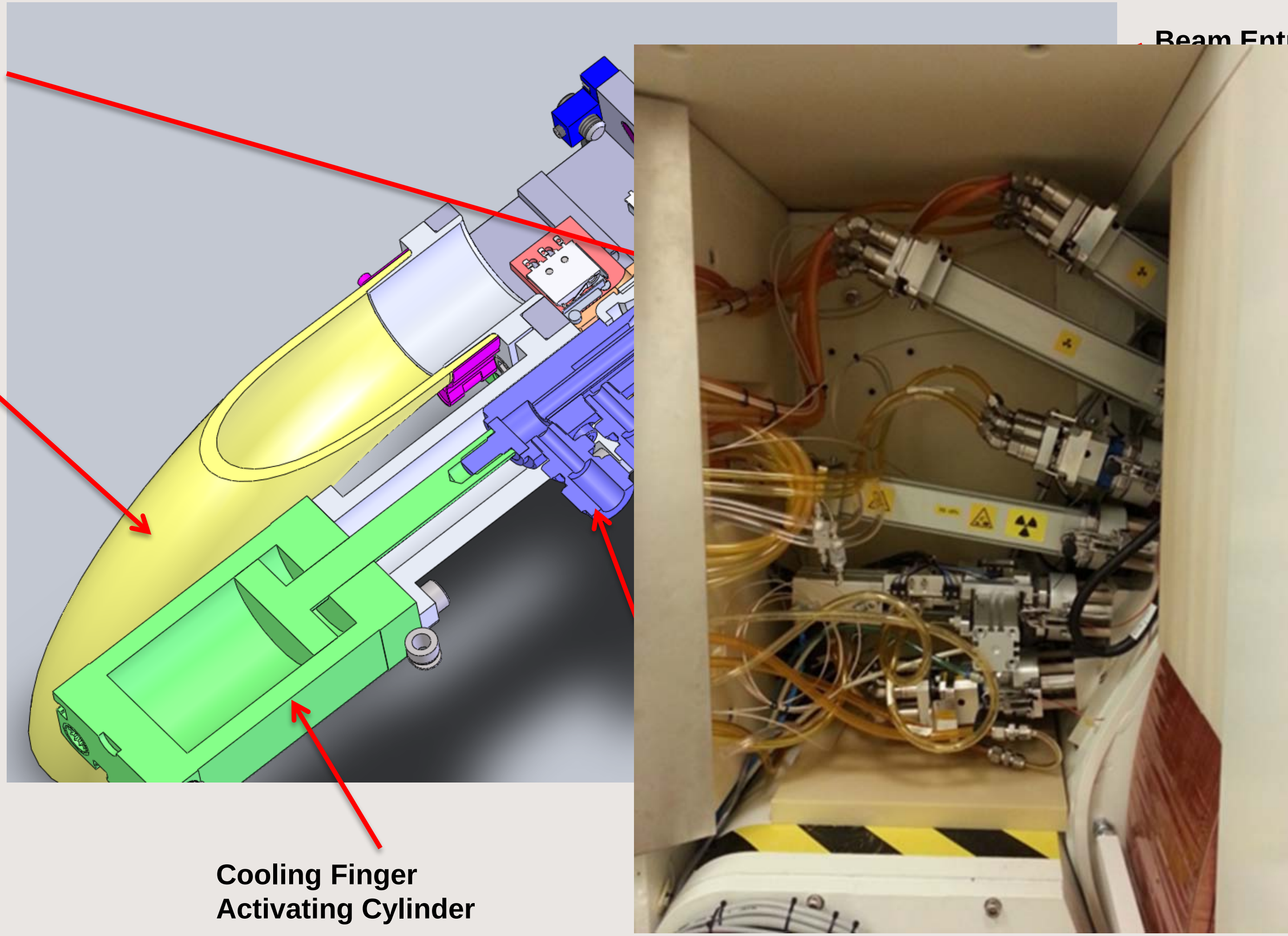
PETtrace target station



PETtrace target station

Target Capsule

Target Capsule Transfer Tube

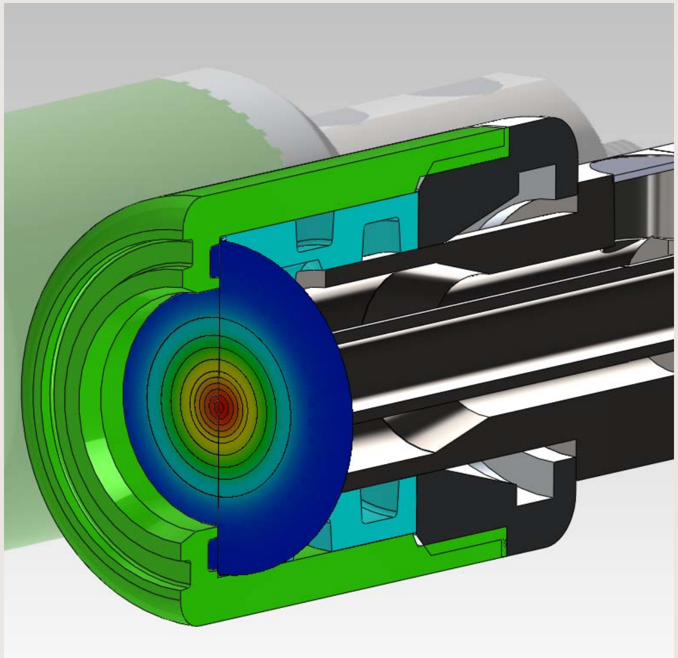


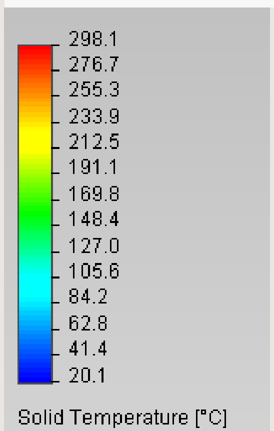
Beam Entry

ange

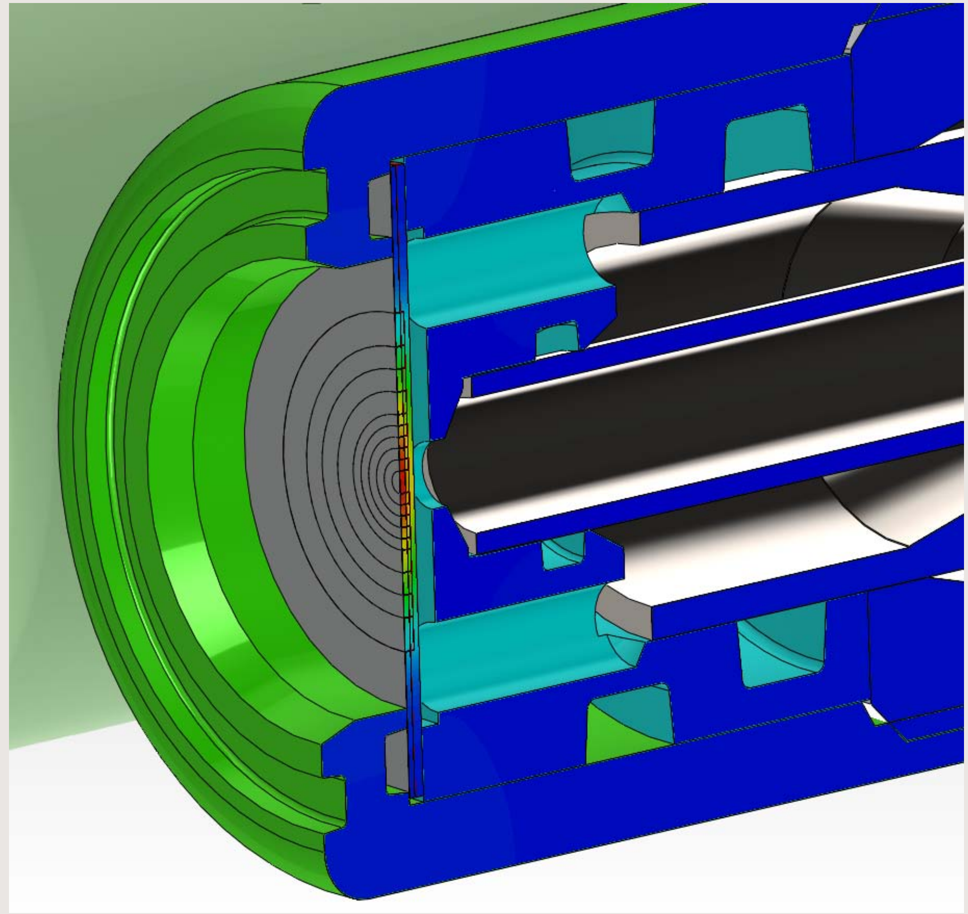
Cooling Finger Activating Cylinder

PETtrace thermal analysis





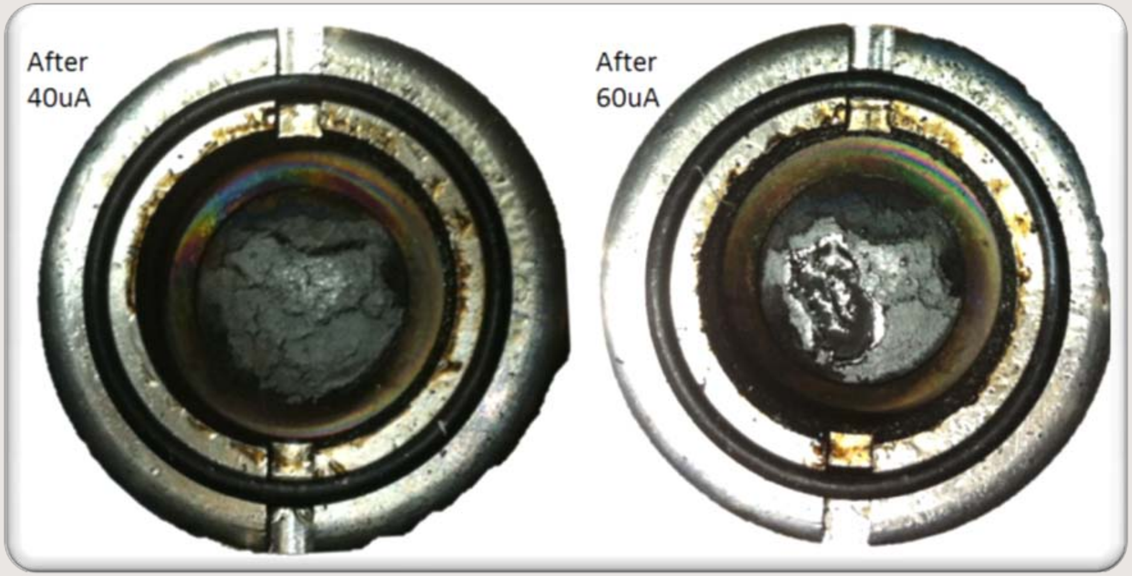
Temperature Distribution on Molybdenum Target against Rhodium Backing



Section View – Temperature distribution thru axial plane of ^{100}Mo GE Target Assembly

PETtrace thermal analysis

- PETtrace EPD targets failed
  - Inefficient heat transfer, orthogonal power density too high

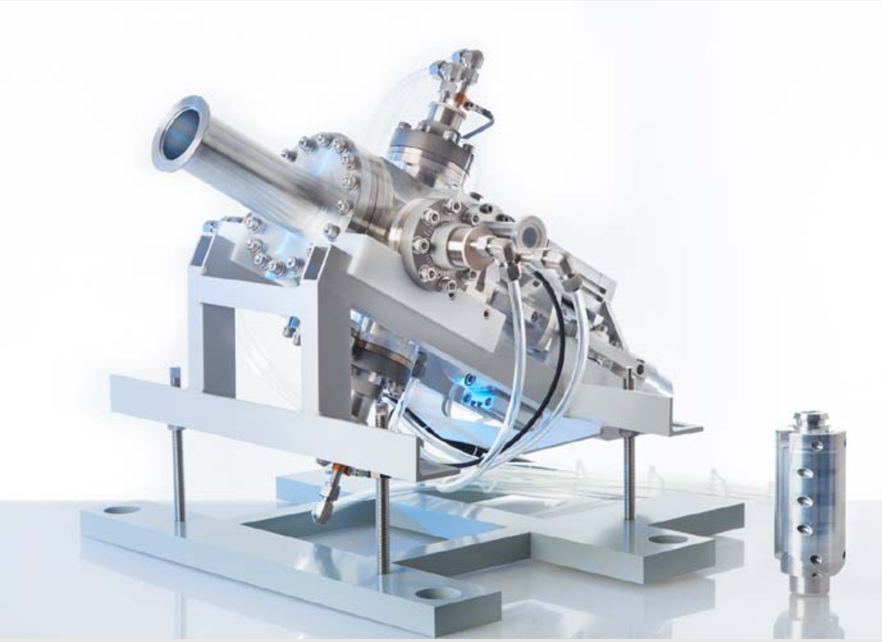


PETtrace thermal analysis

- Developed Pressed Sintered & Brazed ("PSB") targets

- After 130 μA operation for 1 hour
- Target has operated at the design goal of 2.1 kW for 6 hours, multiple times
- Yields up to 4.7 Ci

TR-19 Target Station



- Tested to 300 μA
- No target degradation
- 9.4 Ci for 6.9 h run at 220 μA

Bottom Line

- Technology successfully implemented for large scale production in BC and Ontario
- No long term radioactive waste, no enriched uranium, lower financial and environmental risk
- Cyclotron-produced ^{99m}Tc costs estimated to be competitive vs. current generator costs
- Offers redundancy and security of supply
- Funds spent locally to hire highly qualified personnel
- Synergy with positron emission tomography.

PET: Radiometals

- PET: Positron- Emission Tomography
- Most common PET isotopes: F-18 (FDG), C-11, but increasing interest in radiometals (oncology, neurology)

- Goals:
  - Allow broader access to a variety of radiometallic isotopes
  - Enable faster optimization of vector-isotope pairing
  - Radiometal production without generators, solid-target installation
  - Established cyclotron centers can obtain research, and possibly clinical quantities of various radiometals by irradiating salt solutions in modified liquid targets
- Accepted trade-off:
  - Lower production yields in exchange for isotope versatility

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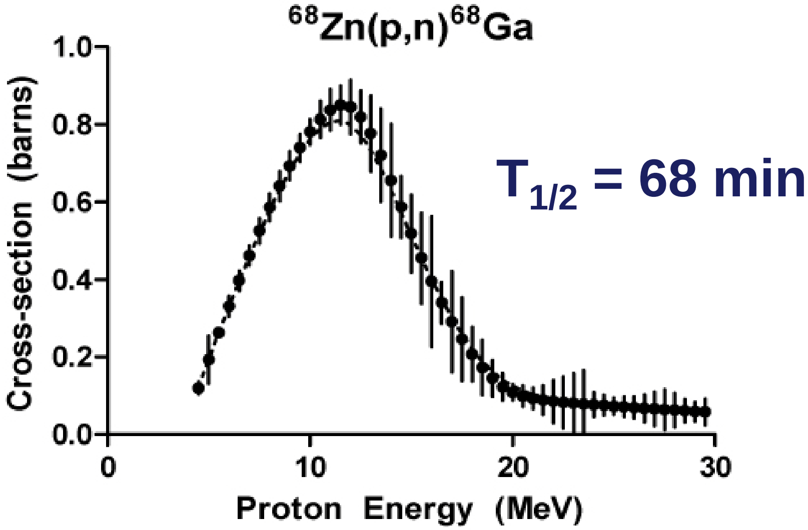
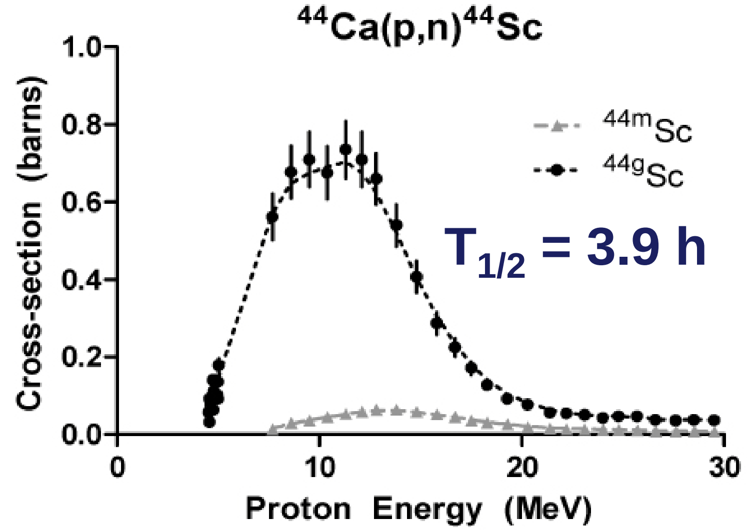
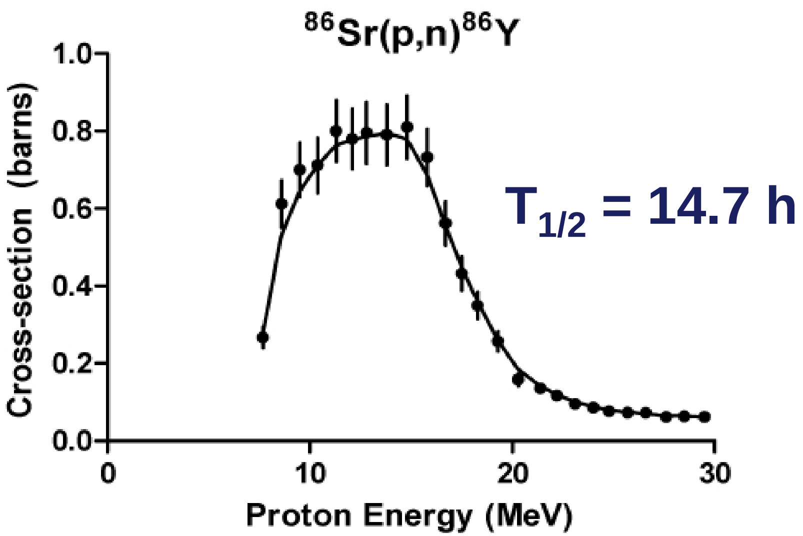
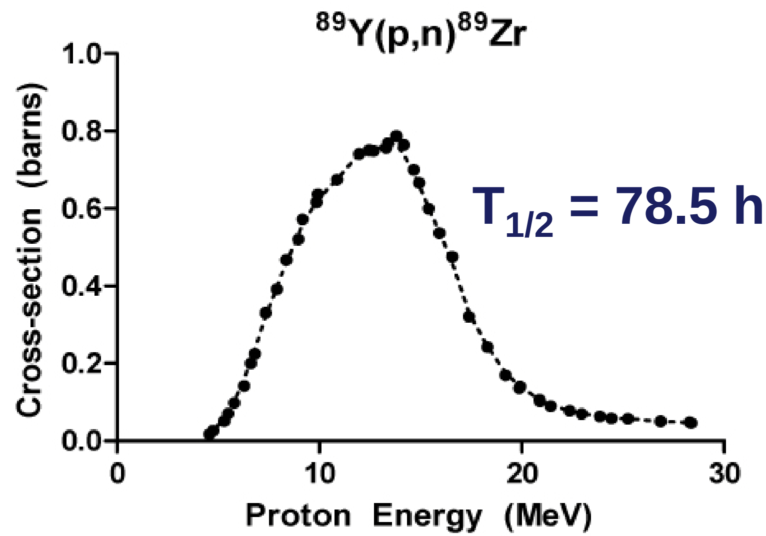
Assessing Feasibility: Cross-sectional Considerations









Preparation of Liquid Target Solutions

Isotope	Irradiated metal	Salt	Highest Metal conc. (g/cm^3)
^{44}Sc	Calcium	$Ca(NO_3)_2 \cdot 4H_2O$	0.180
^{68}Ga	Zinc	$Zn(NO_3)_2 \cdot 6H_2O$	0.307
^{86}Y	Strontium	$Sr(NO_3)_2$	0.196
^{89}Zr	Yttrium	$Y(NO_3)_3 \cdot 6H_2O$	0.204
^{94m}Tc	Molybdenum	$(NH_4)_6Mo_7O_{24} \cdot 4H_2O$	0.541

- Feasibility studies with non-enriched metal salts

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Preparation of Liquid Target Solutions

- Gas evolution during irradiation = high target pressures in a closed target body
  - Radiolysis of water, formation of O_2, H_2 gas.
  - Implemented 1M nitric acid for ^{nat}Zn and ^{nat}Sr salt irradiations*
- Compatibility between salt solutions and target components
  - Havar foil (Co-based, Cr, Ni, Fe, W, Mo, Mn)
    - Failed with Cl^- salts
    - Analysis by SEM shows heavy etching
  - Al vacuum foil (failed in boil tests)
  - Target body (Al) - corrodes easily
    - Changed to Nb target body
    - Use nitrates

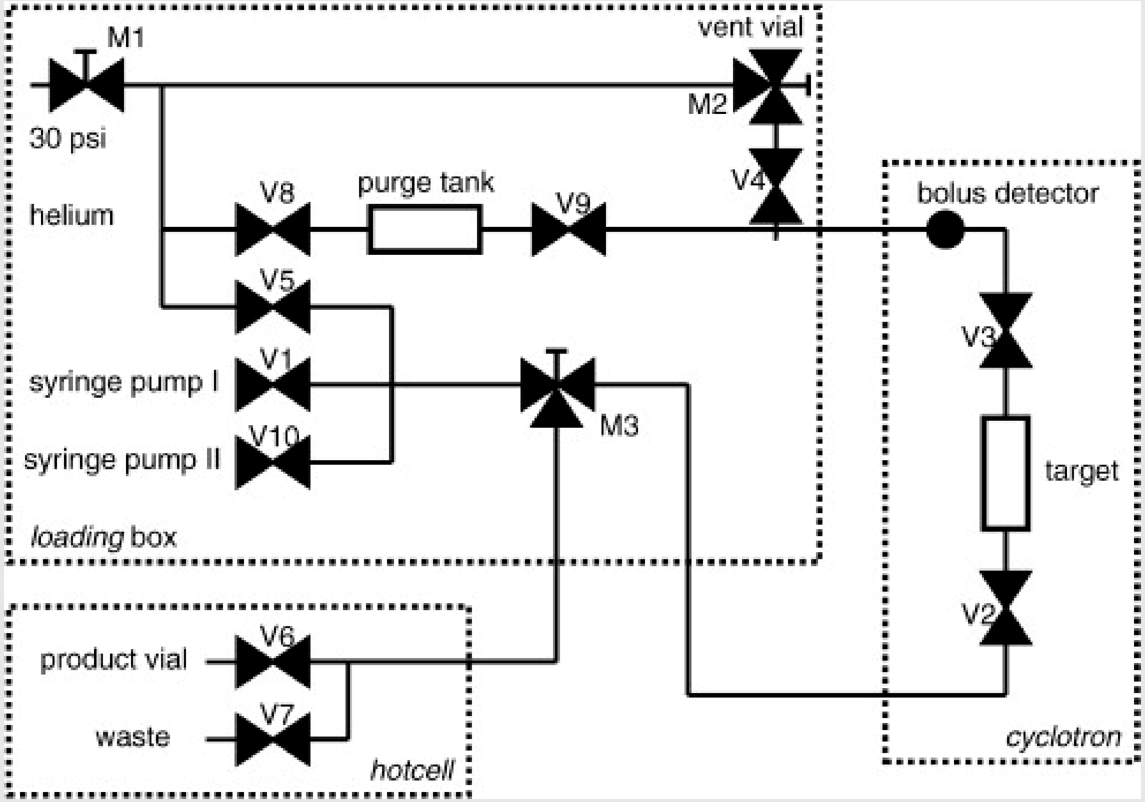
* Pandey MK, et al., Nucl. Med. Biol. 2014;41:309-16.

Preparation of Liquid Target Solutions

- Salt precipitation
  - Irradiation induces precipitation in some instances
  - Solution: automated loading system, adding nitric acid

Target Loading/Unloading

- Automated loading system imperative for consistency



- From twice a week to three times a day

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Production summary

Prod	Production route	Metal salt	Density (g/mL)	Beam current (μA)	Time (min)	Yield (MBq)	Sat. yield (MBq/ μA)
^{94m}Tc	$^{94}Mo(p,n)^{94m}Tc$	$(NH_4)_6Mo_7O_{24}$	1.66	5	60	110±20	40±6
^{44}Sc	$^{44}Ca(p,n)^{44}Sc$	$Ca(NO_3)_2$	1.55	7.6	60	5.55±0.22	4.58±0.25
^{68}Ga	$^{68}Zn(p,n)^{68}Ga$	$Zn(NO_3)_2$	1.65	6.8	60	212±14	68.2±6.7
			1.56	6.96	60	448±22	140.86±0.18
^{89}Zr	$^{89}Y(p,n)^{89}Zr$	$Y(NO_3)_3$ x HNO_3	1.49	8.1	60	17.6±1.1	244±22
^{86}Y	$^{86}Sr(p,n)^{86}Y$	$Sr(NO_3)_2$	1.43	1.55	60	0.186±0.005	2.54±0.08

Radiometals summary

- A simple method for the production of research quantities of various radiometals using a modified liquid-target system.

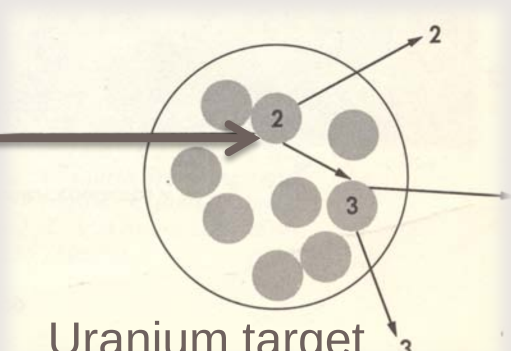
- Salt solutions of natural isotopic abundance were irradiated in a standard water target on our 13 MeV cyclotron for 60 min. After irradiation, all solutions were withdrawn from the target and purified using cation exchange or chelating resins. Labeling has been demonstrated.

- Several isotopes (^{68}Ga, ^{89}Zr, ^{44}Sc, ^{89}Y, ^{94m}Tc) were produced in a standard water target on our 13 MeV cyclotron.

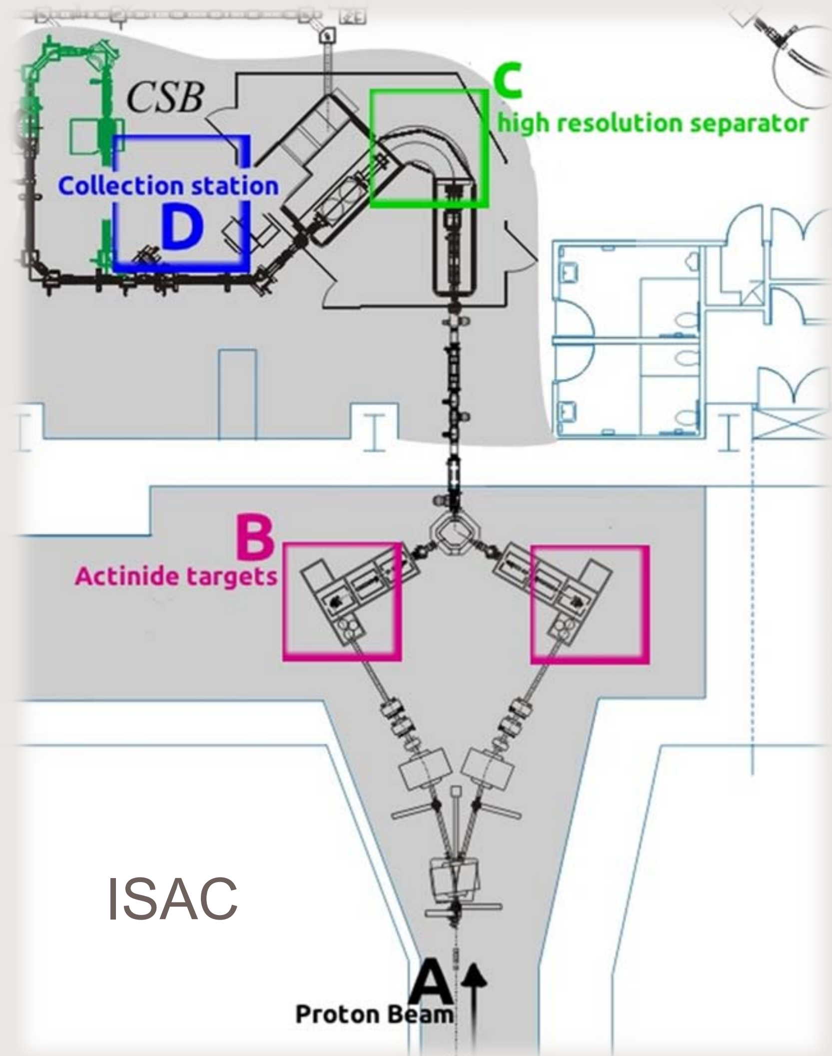
Treatment: At-209

High mass isotope production by spallation of ^{238}U:

480 MeV Protons



Variety of isotopes produced



^{213}Fr implantation for ^{209}At

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

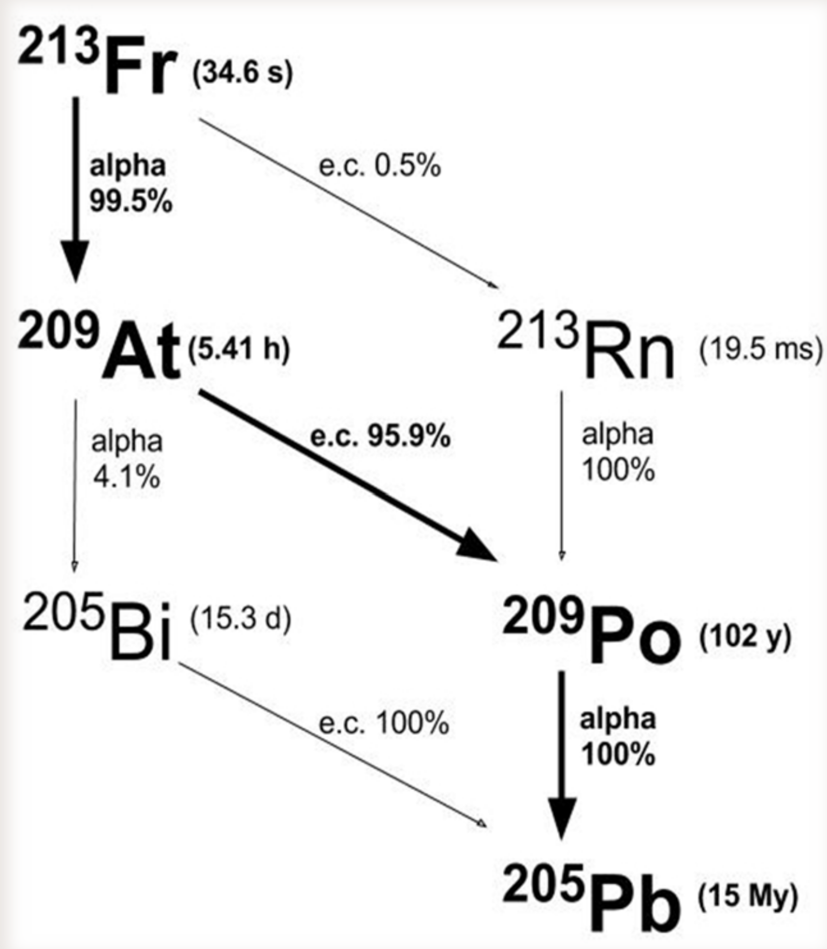
ISAC yield measurements:

^{213}Fr = 7.7x10^{8} ions/s,

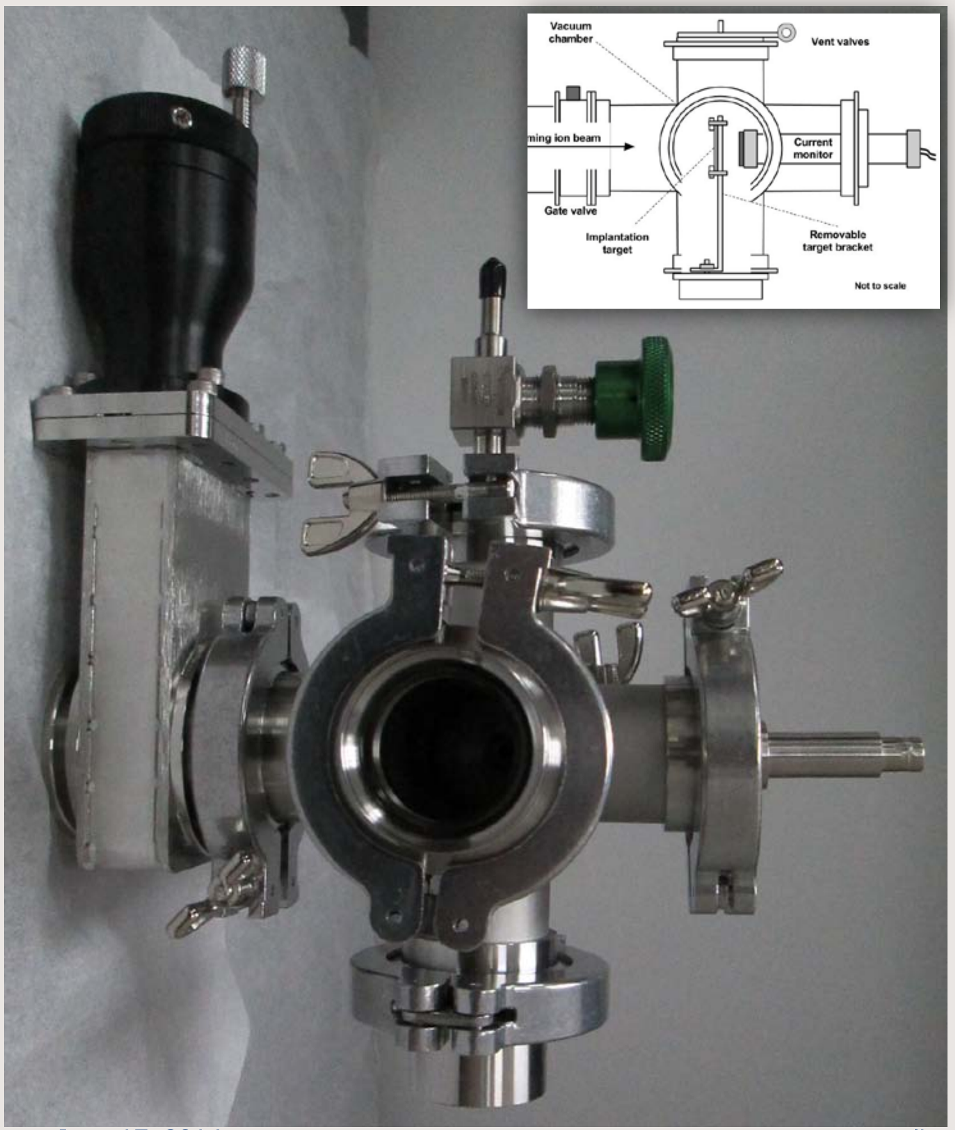
^{213}Ra = 1.6x10^{8} ions/s

Radium-213 is co-implanted (30%),

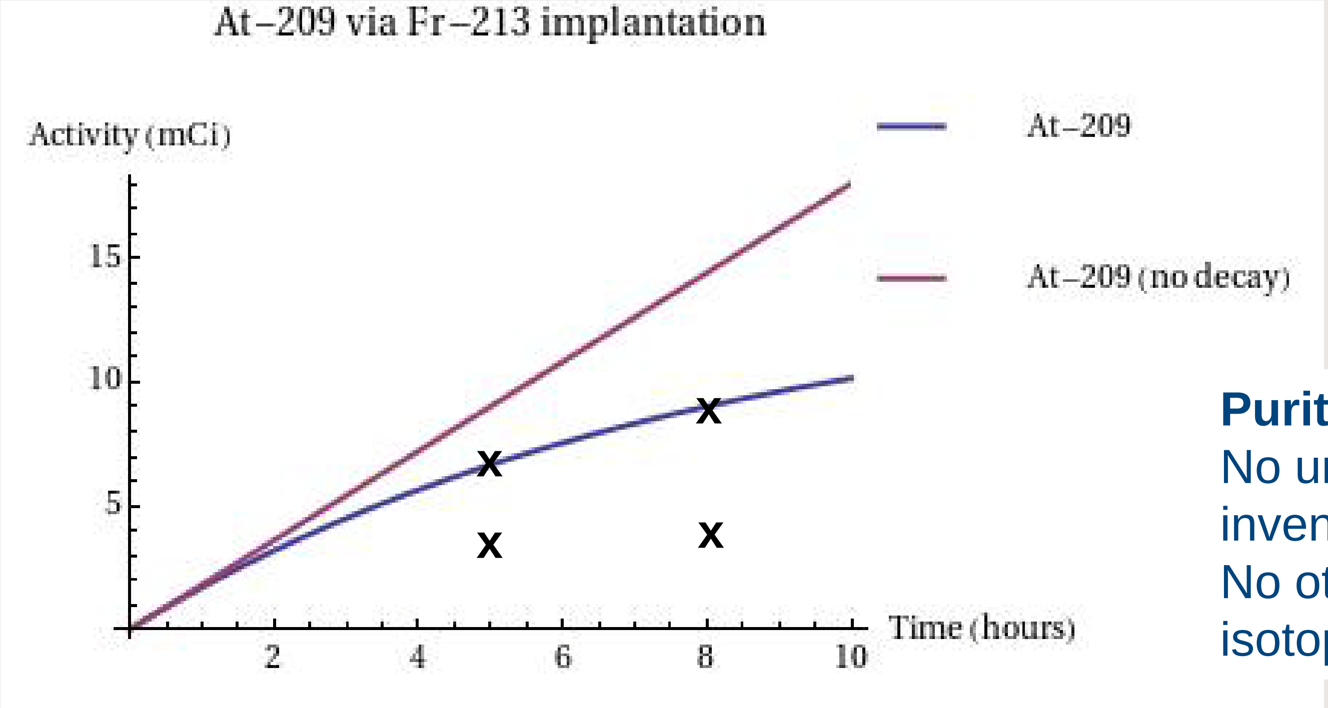
- 20% decays to ^{213}Fr → ^{209}At
- 80% decays to ^{209}Rn ($t_{1/2}$=29m)
- 83% of ^{209}Rn decays to ^{209}At



Apparatus for ^{213}Fr/^{209}At collection



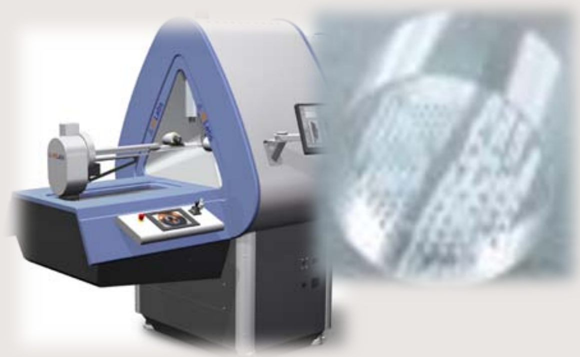
Theoretical ^{209}At build-up during ^{213}Fr implantation

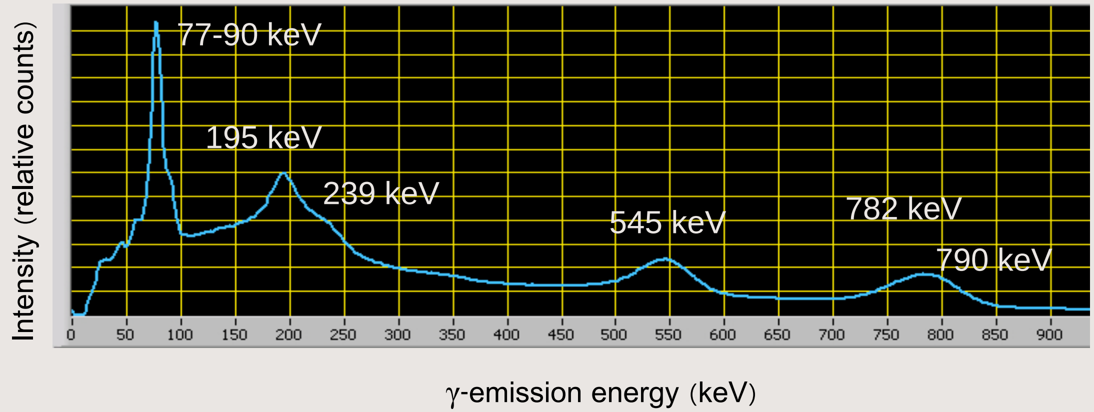


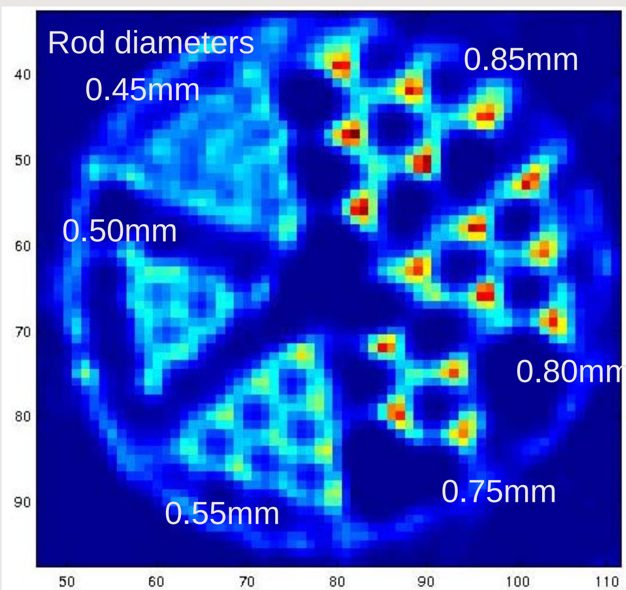
Purity of ^{209}At >99%
No unexpected inventory
No other astatine isotopes

8.2 hr implantation → 3.2 mCi @EOB
5.0 hr implantation → 3.0 mCi @EOB

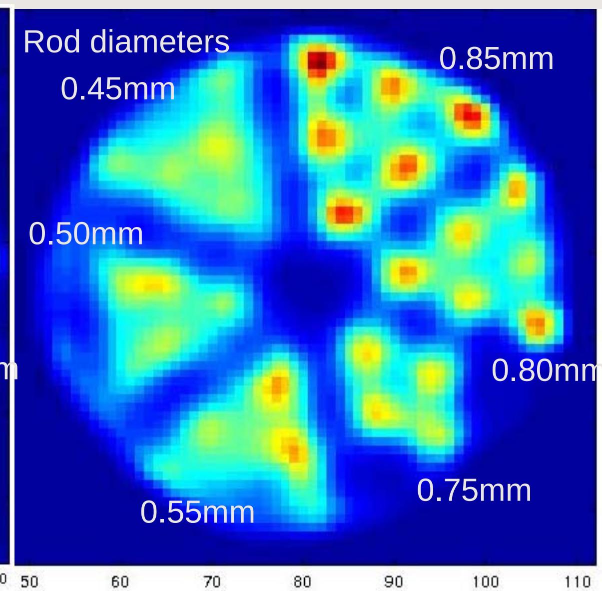
^{209}At-SPECT with hotrod phantom







70-90 keV Peak

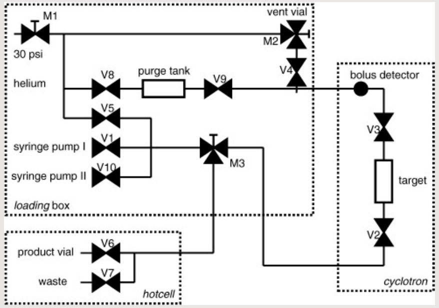


545 keV Peak

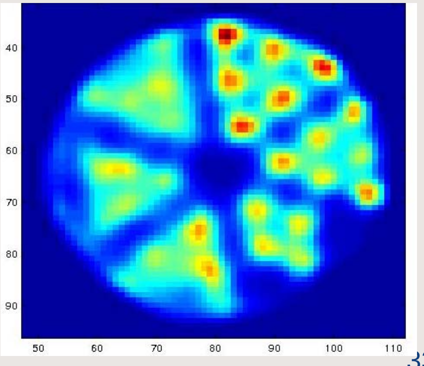
Summary

- Tc-99m: production on small medical cyclotrons feasible - avoiding centralized supply system, HEU

- Radiometals: demonstrated production in liquid targets – increasing availability of new and emerging isotopes for PET (and other)



- At-209: first SPECT image of At-209, tool for development of At-211



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Acknowledgement

- **Tc-99m:** K. Buckley, V. Hanemaayer, B. Hook, S. McDiarmid, S. Zeisler, F. Prato, C. Leon, A. Goodbody, J. McCann, T. Morley, J. Klug, P. Tsao, M. Vuckovic, J. P. Appiah, M. Dodd, G. Amouroux, W. English, X. Hou, J. Tanguay, J. Corsault, R. Harper, C. Economou, F. Bénard, T.J. Ruth, A. Celler, J. Valliant, M. Kovacs, P. Schaffer
- **Radiometals:** E. Oehlke, X. Hou, V. Hanemaayer, S. Zeisler, M. Adam, T.J. Ruth, A. Celler, K. Buckley, F. Benard, P. Schaffer
- **At-209:** J. Crawford, T.J. Ruth, H. Yang, J. Lassen, P. Kunz, P. Machule, S. Zeisler, S. Chan, G. Sheffer, J. Mildenberger, V. Sossi, D. S. Wilbur, D. Hamlin, M. Adam, F. Benard, K.-S. Lin, P. Schaffer

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