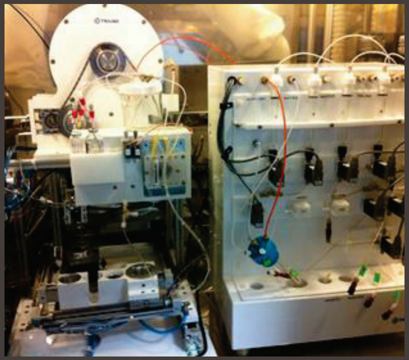
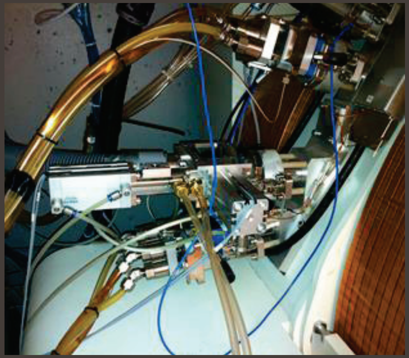
Cyclotron Production of Tc-99m

Cyclotrons 2013

Ken Buckley | TRIUMF





Representing…

- TRIUMF
  - Paul Schaffer (PI), Tom Ruth, Stefan Zeisler, Vicky Hanemaayer, Maurice Dodd, Stuart McDiarmid, Brian Hook, Tom Morley, Conny Hoehr, Mark Preddy, Juergen Kaefer, Mahendra Rathod
- British Columbia Cancer Agency
  - Francois Benard, Jean-Pierre Appiah, Milan Vuckovic, Julius Klug, Kuo-Shyan Lin, Guillaume Langlois, Wade English
- Centre for Probe Development and Commercialization
  - Chris Leon, Constantinos Economou, John Valliant, Bart Bycinzski, Joe McCann, Neil Cockburn, Anne Goodbody
- Lawson Health Research Institute
  - Mike Kovacs, Jeff Corsaut, Jean-Yves Kazock, Laura Close, Frank Prato
- University of British Columbia
  - Anna Celler, Xinchi Hou, Ed Asselin, Leah Penner

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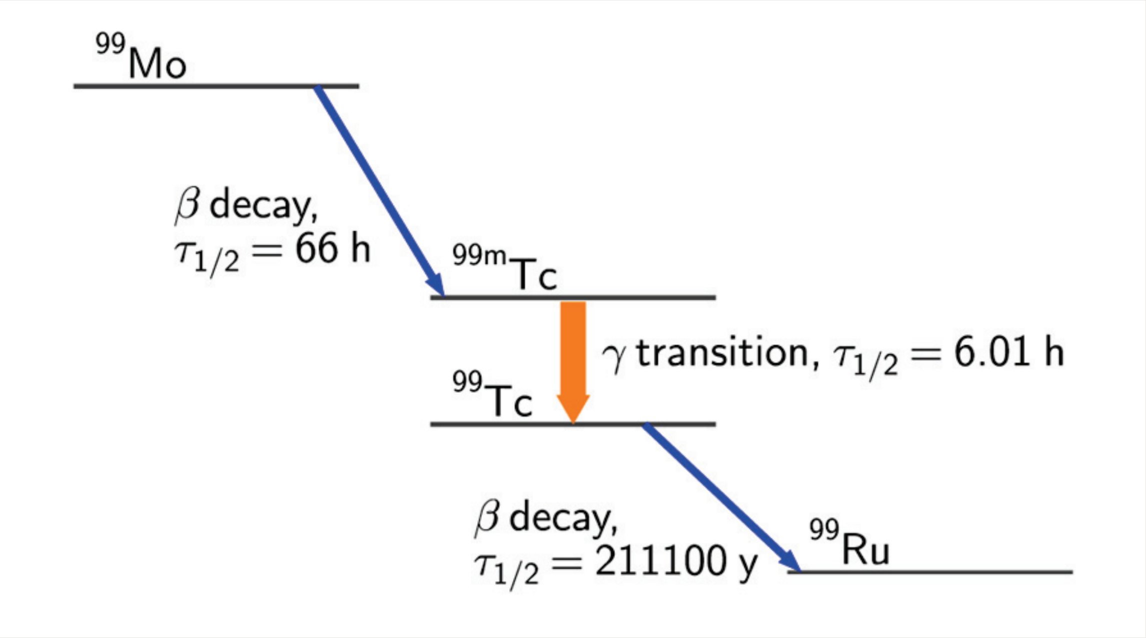
A brief history of ^{99m}Tc

- BNL, 1950s: found Tc-99m as a contaminant in Te-132/I-132 generator
- Tucker and Green developed the first 99Mo/99mTc generator (1958)
- BNL provided Mo-99/Tc-99m generators until 1966 when backed out of generator production in favour of commercial suppliers

From Technetium-99m: The Early Days, P. Richards BNL-43197

Isotope Generators have Enabled Molecular Imaging



- Simple distribution & use
- Global demand for ^{99}Mo/^{99m}Tc ~ 40 million doses/yr
  - >1 scan/second

$^{99}Mo/^{99m}Tc$ 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.

Canada's NRU

- Starting in late 2007, several independent reactor outages significantly disrupted global 99Mo supplies.

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Chalk River repairs have $70-million price tag: AECL

52-year-old reactor has been plagued by shutdowns in recent years

Article | Comments (16)

Steve Rennie
Ottawa — The Canadian Press
Published on Monday, Oct. 19, 2009 7:00PM EDT

Atomic Energy of Canada Ltd. has put a $70-million price tag on repairing its downed Chalk River reactor.

News Room

Unplanned shutdown of NRU reactor extended

Chalk River, 2009 May 18 — Atomic Energy of Canada Limited (AECL) reported on Friday, May 15th that the NRU reactor was safely shut down on Thursday, May 14th due to a loss of electrical power that occurred in parts of eastern Ontario and western Quebec.

During routine monitoring in the early morning hours of May 15th, a small leak of heavy water was detected within the NRU reactor facility. The leak rate is estimated to be at about 5 kg/hr. The heavy water is fully contained and is being stored in specially designed drums.

The location of the heavy water leak has been identified at the base of the reactor vessel in a location where there is corrosion on the outside wall of the vessel. Repair options are currently under consideration and activities are being planned. As a result, AECL anticipates that the NRU reactor will remain out of service for more than one month.

- 2009-2010 NRU & HFR both off-line
- Significant cancellations or delays in patient services

Canadian government response…

- Cease Mo-99 production on NRU in 2016
- Thru federal agency Natural Resources Canada fund two sequential programs to develop alternative production of Mo-99 and/or Tc-99m

Alternatives

- Neutron approaches
  - LEU $^{235}U(n,F)^{99}Mo$
  - $^{98}Mo(n,\gamma)^{99}Mo$
- Photon approaches
  - $^{238}U(\gamma,F)^{99}Mo$
  - $^{100}Mo(\gamma,n)^{99}Mo$
- Proton approach
  - $^{100}Mo(p,2n)^{99m}Tc$
  - Direct production
- Make use of existing small medical cyclotrons

PET paradigm

- Typically irradiate gas or liquid targets
- Target material is transferred in tubes by pressure differential
  - Never an “open source” of radioactivity
- Short half-life isotopes (i.e. gone tomorrow)
- Little need for “contamination barriers”
- Tc-99m production
  - Solid target (potential for particulate in vacuum and/or around target station)
  - 6 hr half-life -> several days to decay (+ longer lived contaminants)

Project scope

- Solid target irradiation systems
  - GE PETtrace cyclotron
  - ACSI TRPET cyclotron
- Mo-100 coated target plate
- Molybdenum dissolution system
- Purification of Tc-99m from moly solution
  - Recycling of Mo-100
- Regulatory approval for human use
- Commercialization of technology and/or production

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

- 1971 – Beaver and Hupf report $^{100}Mo(p,2n)^{99m}Tc$ in JNM Vol. 12 pp 739-741

PRODUCTION OF ^{99m}Tc ON A MEDICAL CYCLOTRON: A FEASIBILITY STUDY

J. E. Beaver and H. B. Hupf

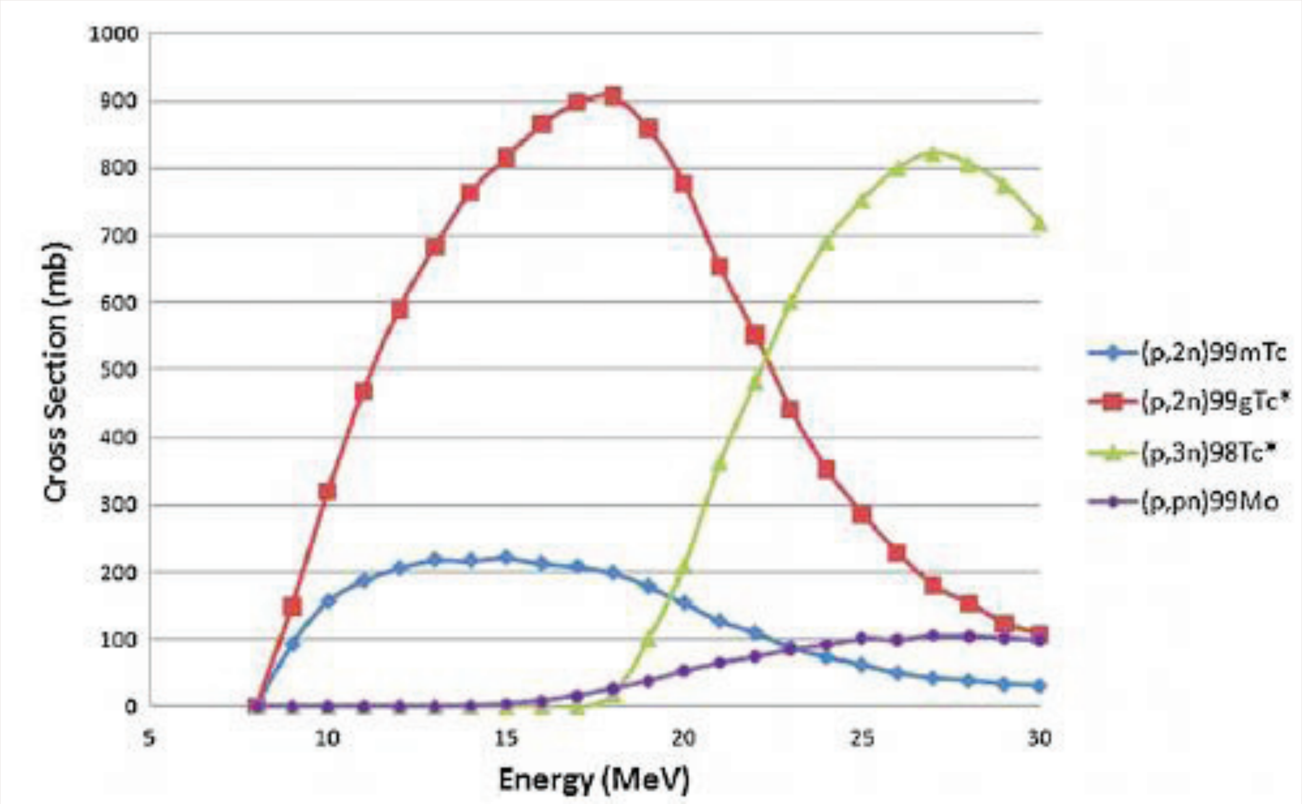
University of Miami School of Medicine, Mount Sinai Medical Center, Miami Beach, Florida

Experimental data indicate that yields of 15 Ci/hr of ^{99m}Tc and 500 mCi/hr of ^{99}Mo are possible with 22-MeV protons at a target power level of 10 kW

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

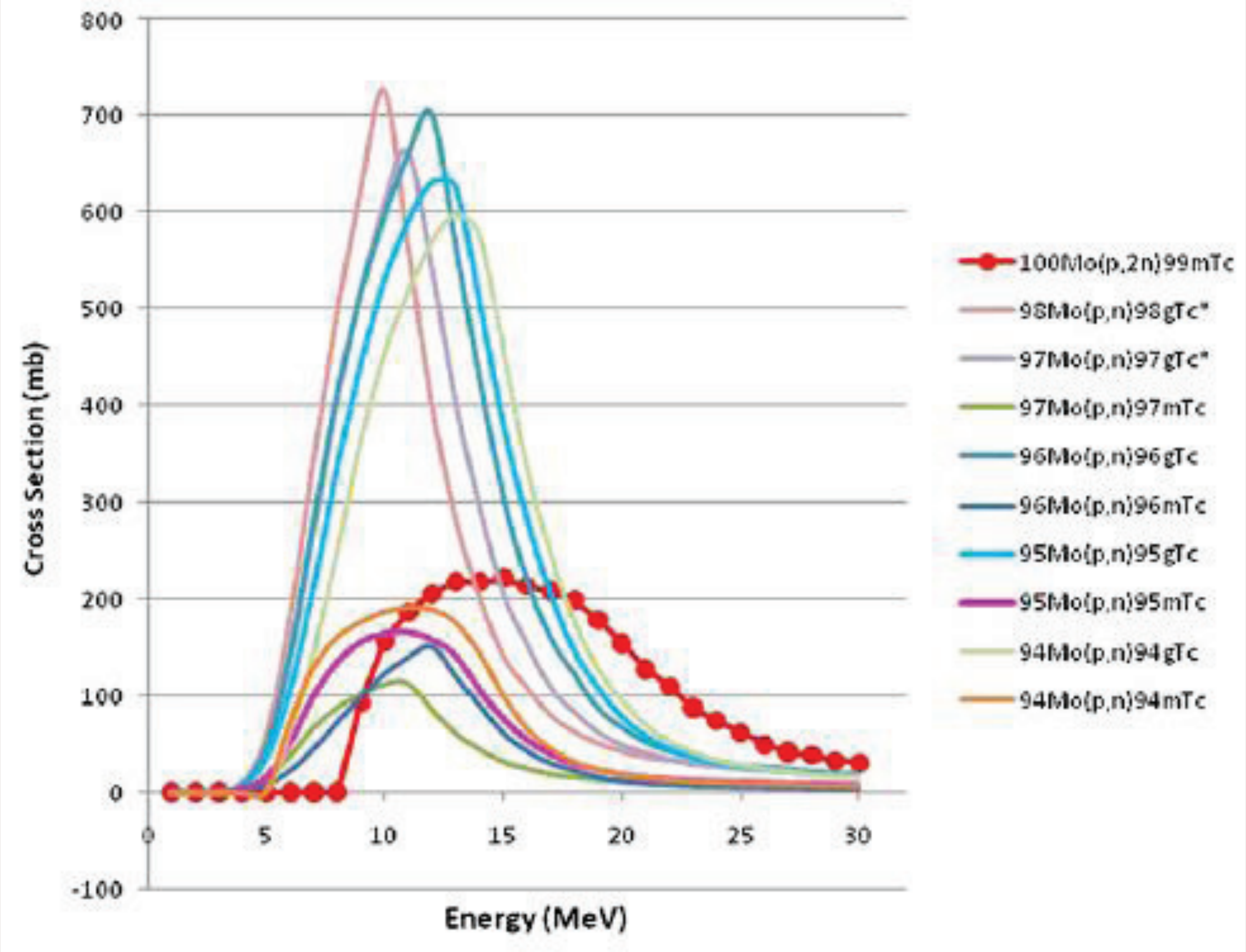
- 1999-2010 several reports on cross-section measurements
- 2010 – Targholizadeh et al. bombard natural moly 160 μA @ 25 MeV
  - Nukleonika Vol. 55 No. 1, pp 113-118, 2010.
- 2011 – Gagnon et al. re-measure ^{99m}Tc and determine ^{99g}Tc cross sections. Refined production yield to 8.8 Ci in 1hr @ 22 MeV with 99m/99g ratios of 25%
  - Nuclear Medicine & Biology, Vol.38, pp 907-916, 2011.

Reactions on ^{100}Mo



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

Reactions on other Mo isotopes



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

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Molybdenum purity

Mo-100 enrichment is not the whole story

Critical Tc radionuclidic purity is determined by masses < 98 due to patient dose

Cost $0.50/gram

Isotope	Natural	Batch 1	Batch 2	Batch 3
Mo-100	9.63	99.01	97.39	99.815
Mo-98	24.13	0.55	2.58	0.17
Mo-97	9.55	0.08	0.01	0.003
Mo-96	16.68	0.11	0.005	0.003
Mo-95	15.92	0.10	0.005	0.003
Mo-94	9.25	0.06	0.005	0.003
Mo-92	14.85	0.09	0.005	0.003

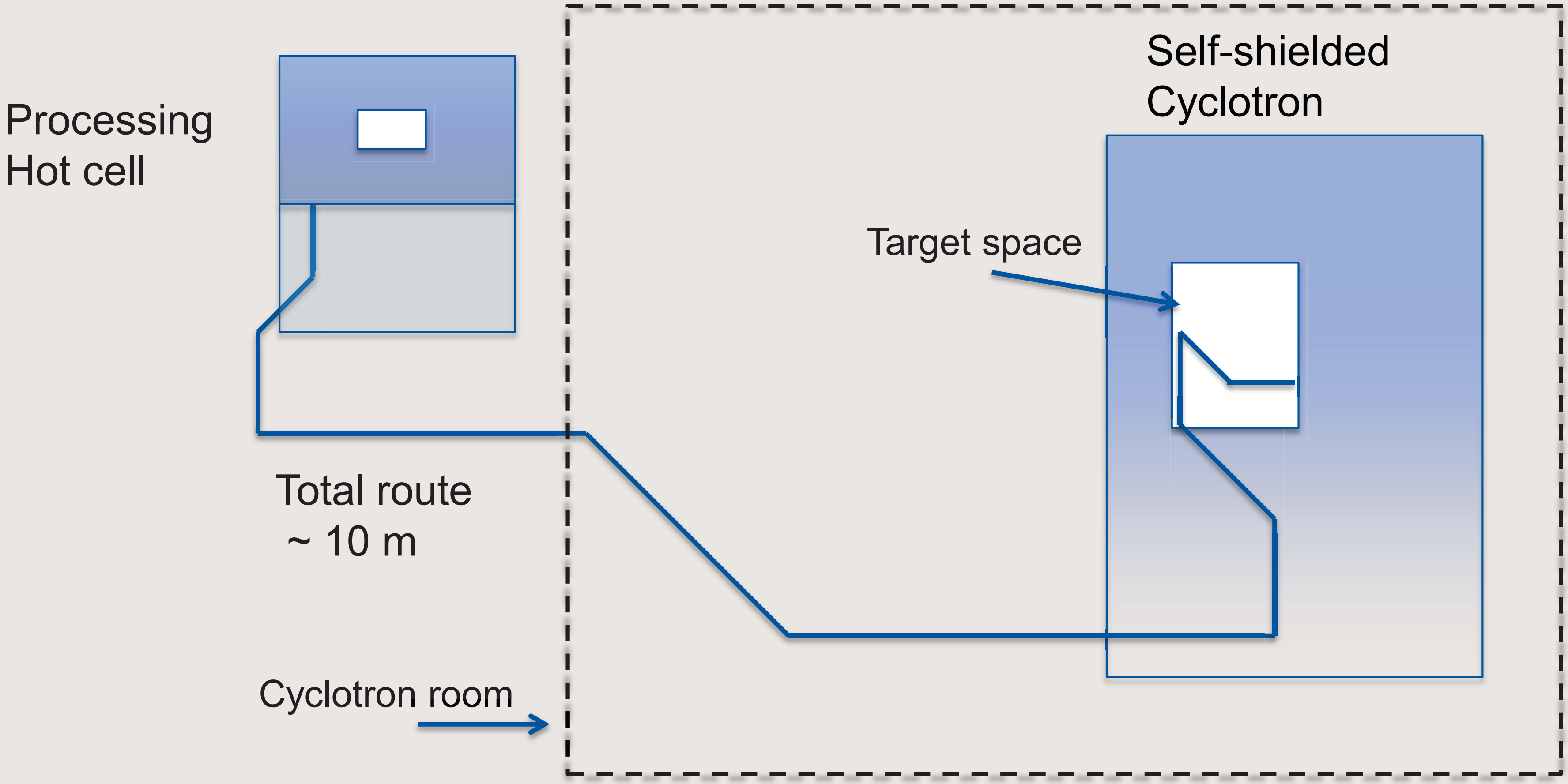
System Parameters

	PETtrace	TRPET
Beam energy	16.5 MeV	18 MeV
Beam current	130 μA	300 μA
Power	2.1 kW	5.4 kW
Beam spot	<15 Ø mm	20 mm x 10 mm
Target location	On cyclotron	On beamline

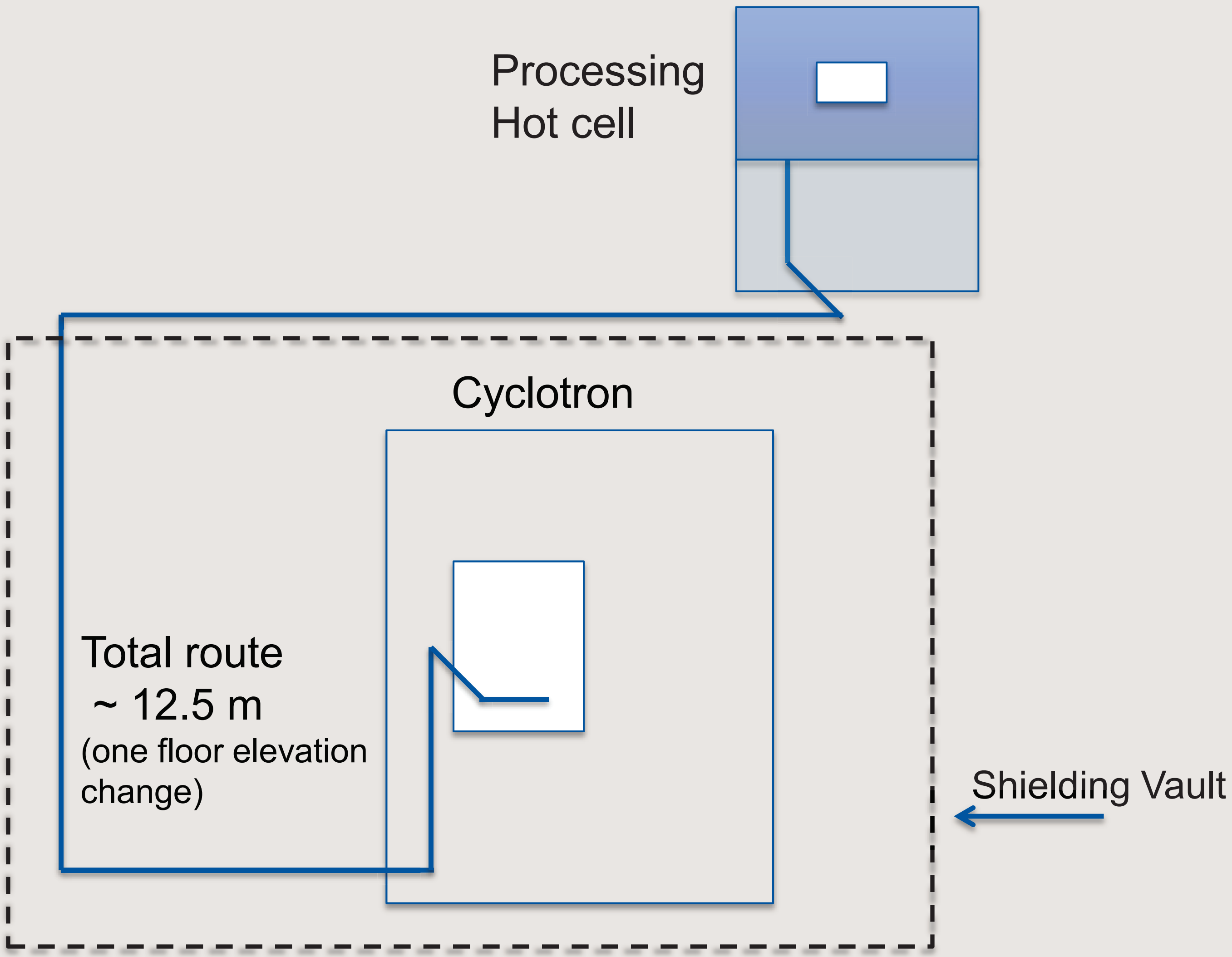
Self-shielded PETtrace

Vaulted PETtrace

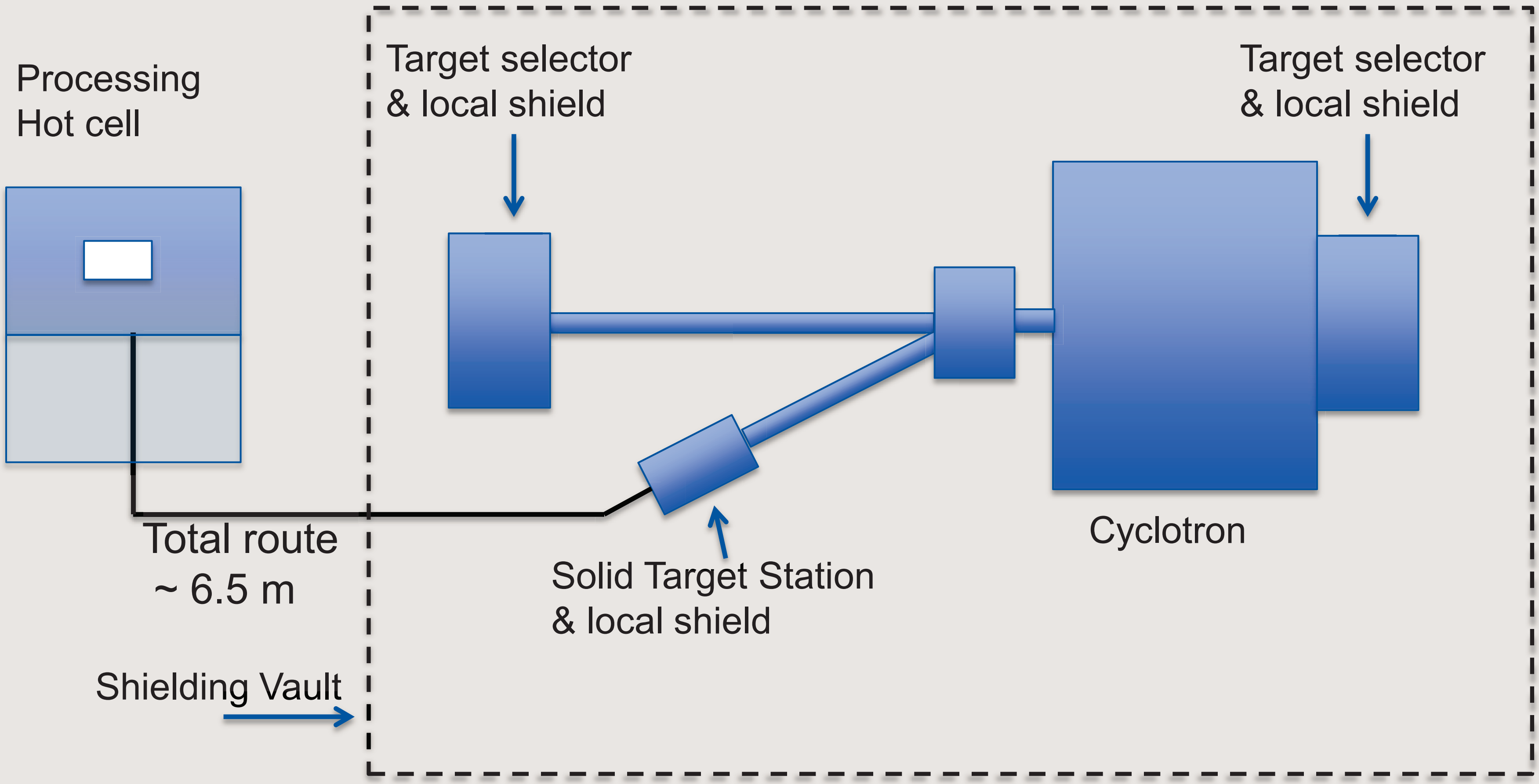
LHRI Site


Processing
Hot cell
Self-shielded
Cyclotron
Target space
Total route
~ 10 m
Cyclotron room

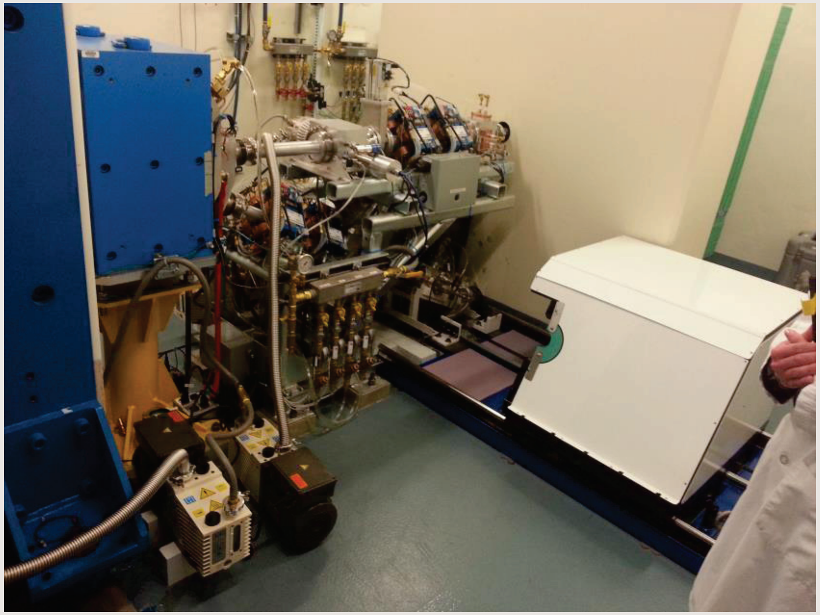
CPDC Site


Processing
Hot cell
Cyclotron
Total route
~ 12.5 m
(one floor elevation change)
Shielding Vault

BCCA


Processing
Hot cell
Target selector
& local shield
Target selector
& local shield
Total route
~ 6.5 m
Solid Target Station
& local shield
Cyclotron
Shielding Vault

ACSI TRPET cyclotron



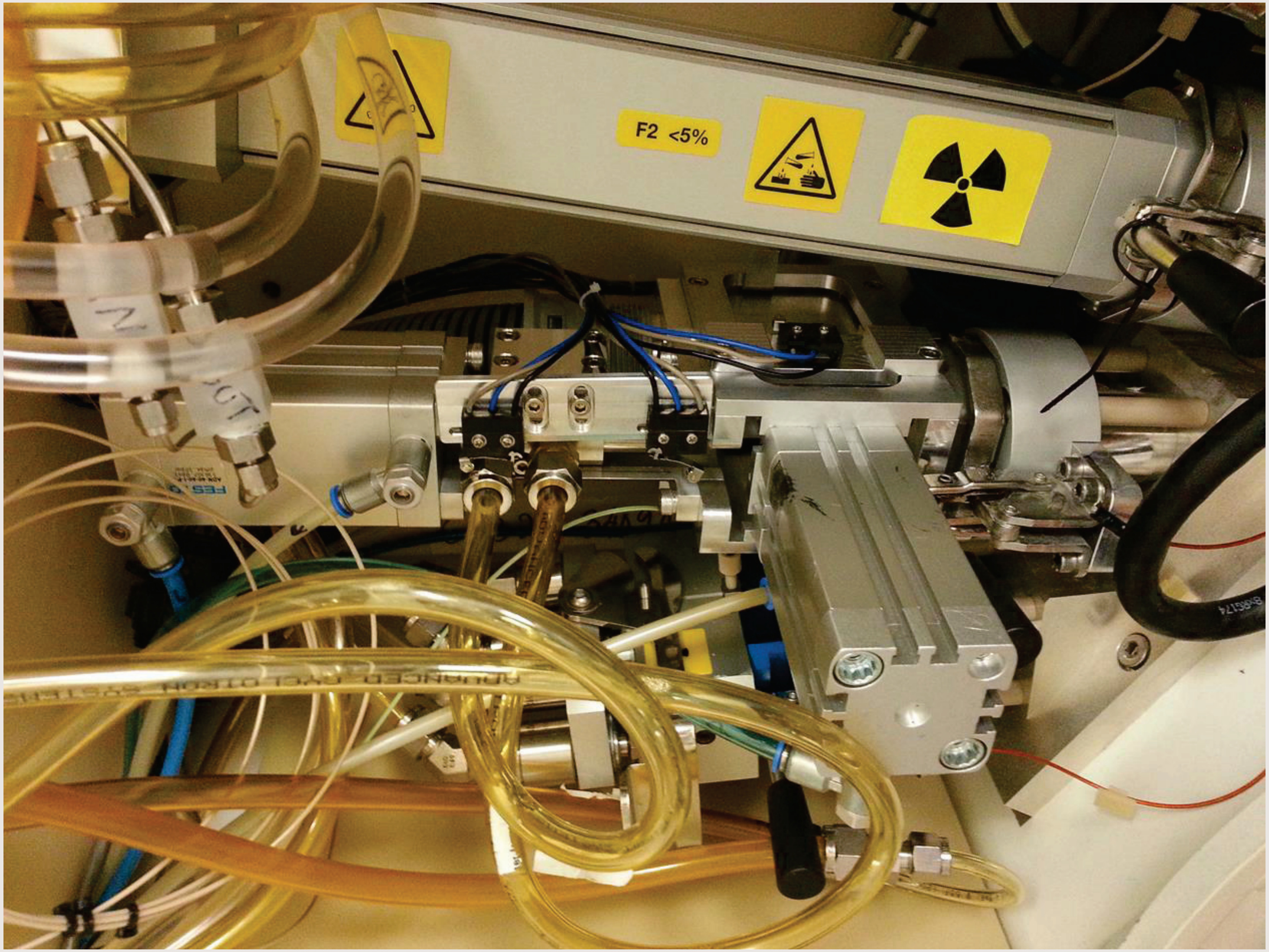
System Parameters

	PETtrace	TRPET
Beam energy	16.5 MeV	18 MeV
Beam current	130 μA	300 μA
Power	2.1 kW	5.4 kW
Beam spot	<15 Ø mm	20 mm x 10 mm
Target location	On cyclotron	On beamline
Target angle	90º	10º
Projected beam size	<15 Ø mm	20 x 60 mm
Target capsule size	36 Ø mm x 54 mm	63 Ø mm x 165 mm
Transfer route length	10 & 12.5 m	6.5 m
Route bends (90º)	9 & 6	1

PETtrace target station

- Limited space
  - ~ shoebox size
- Single penetration for transfer tube <50 mm diameter
- Mo-100 plate orthogonal to beam
- Open to cyclotron vacuum
- 300 μm thick to degrade to 10 MeV

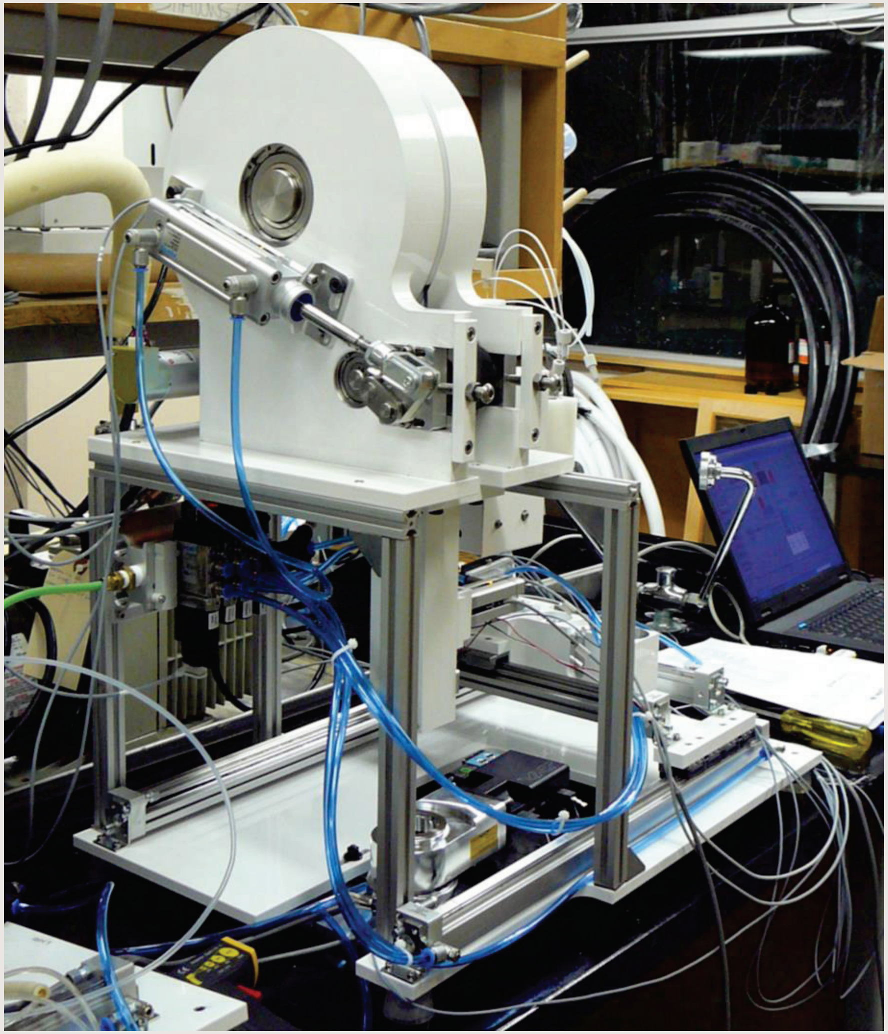
PETtrace target station

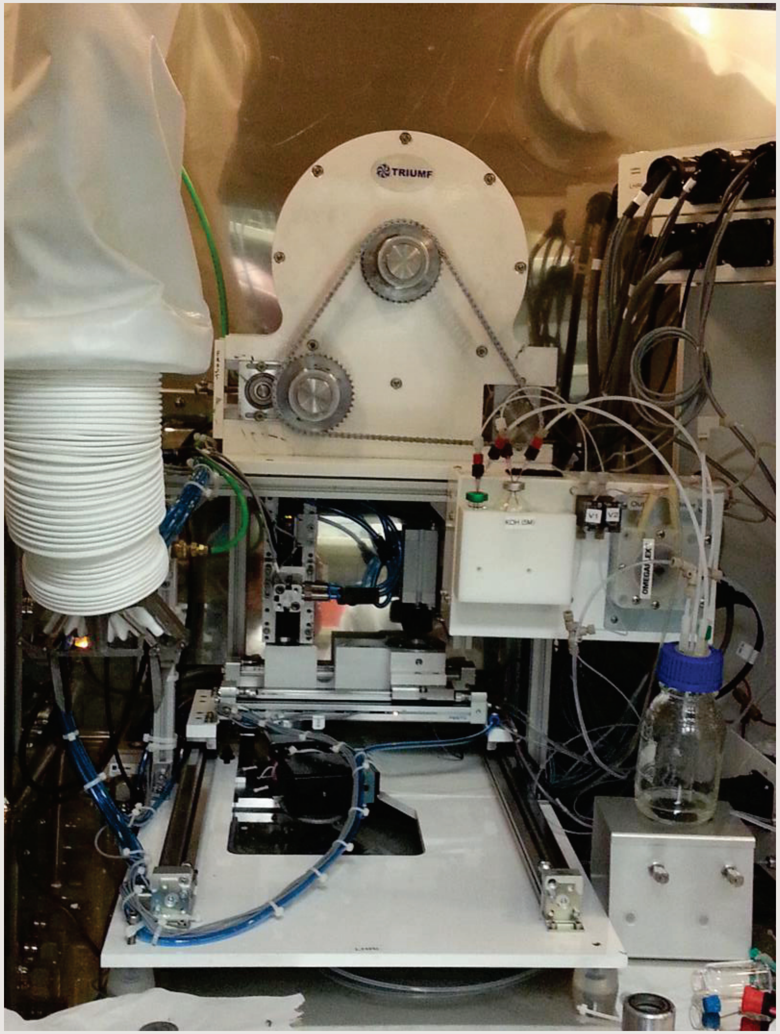


Transfer system

- Moves target between processing and irradiation stations
- Spring steel tape, pinch rollers to drive forward, wind on drum to retrieve
- Issues:
  - Buckling of spring steel tape in tube
  - Limit to distance & number of bends
- Booster stations provide additional drive at intermediate location

Tape Drive





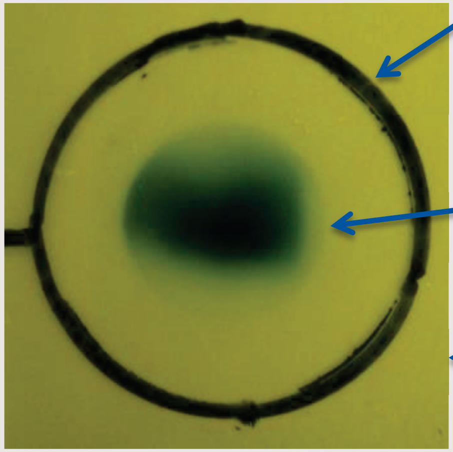
Radiographs

- Gafchromic film (www.gafchromic.com)
  - Use residual radioactivity
  - No developing required
  - Image is proportional to dose
    - Scan to image file for quantitative analysis
  - Exposure of seconds to hours

Avila-Rodriquez et al. "*A Simple Method for Measuring the Beam Profile of Charged Particle Accelerators*", WTTC12 (2008) proceedings at wttc.triumf.ca

Radiographs

- PETtrace beam profile
  - Collimated to 15 mm diameter
  - Assume FWHM such that 5% is lost on collimator

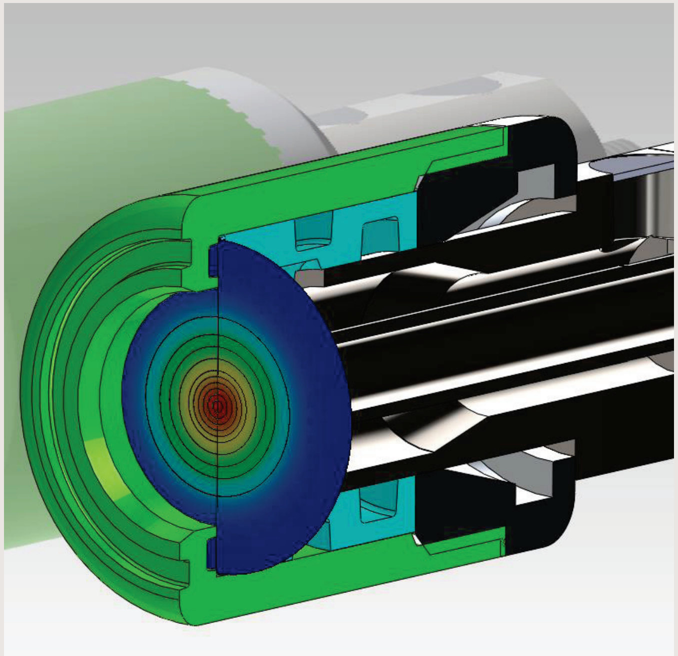


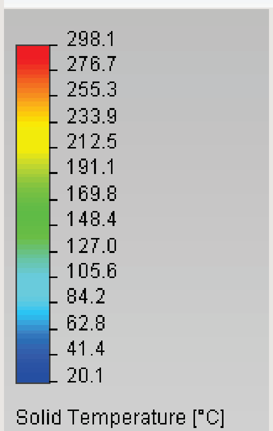
28mm diameter

15mm diameter

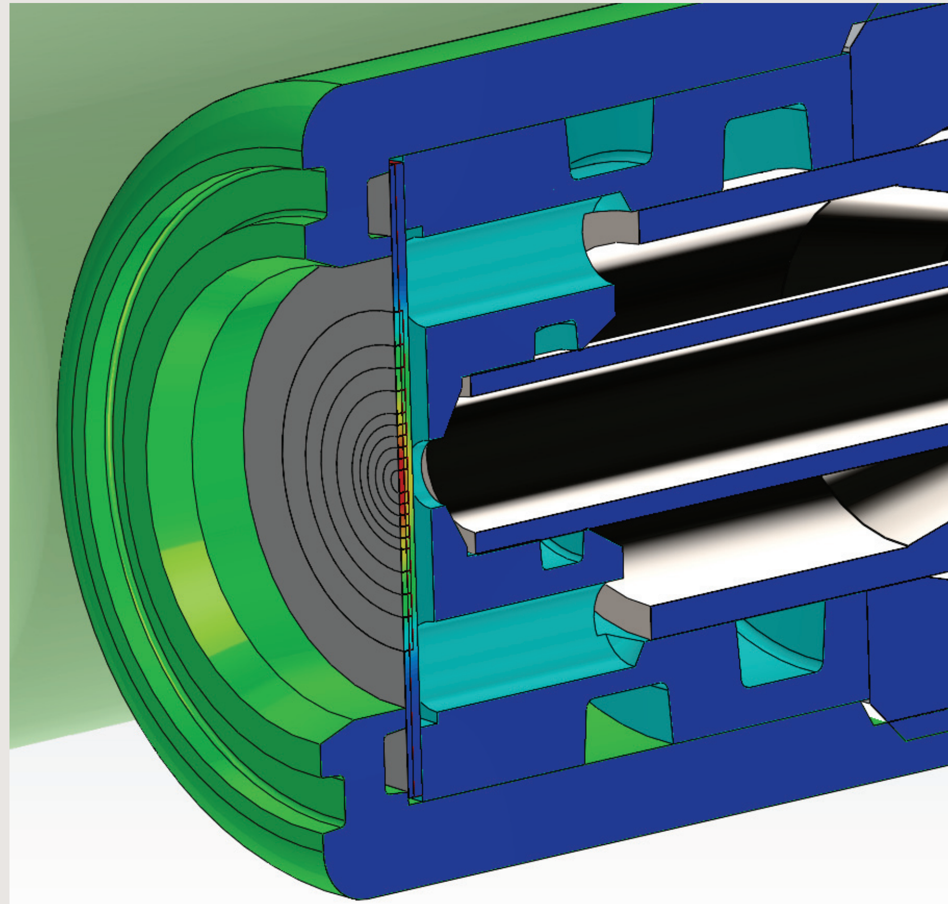
Gafchromic EBT2 film

PETtrace thermal analysis





Temperature Distribution on Molybdenum Target against Rhodium Backing



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

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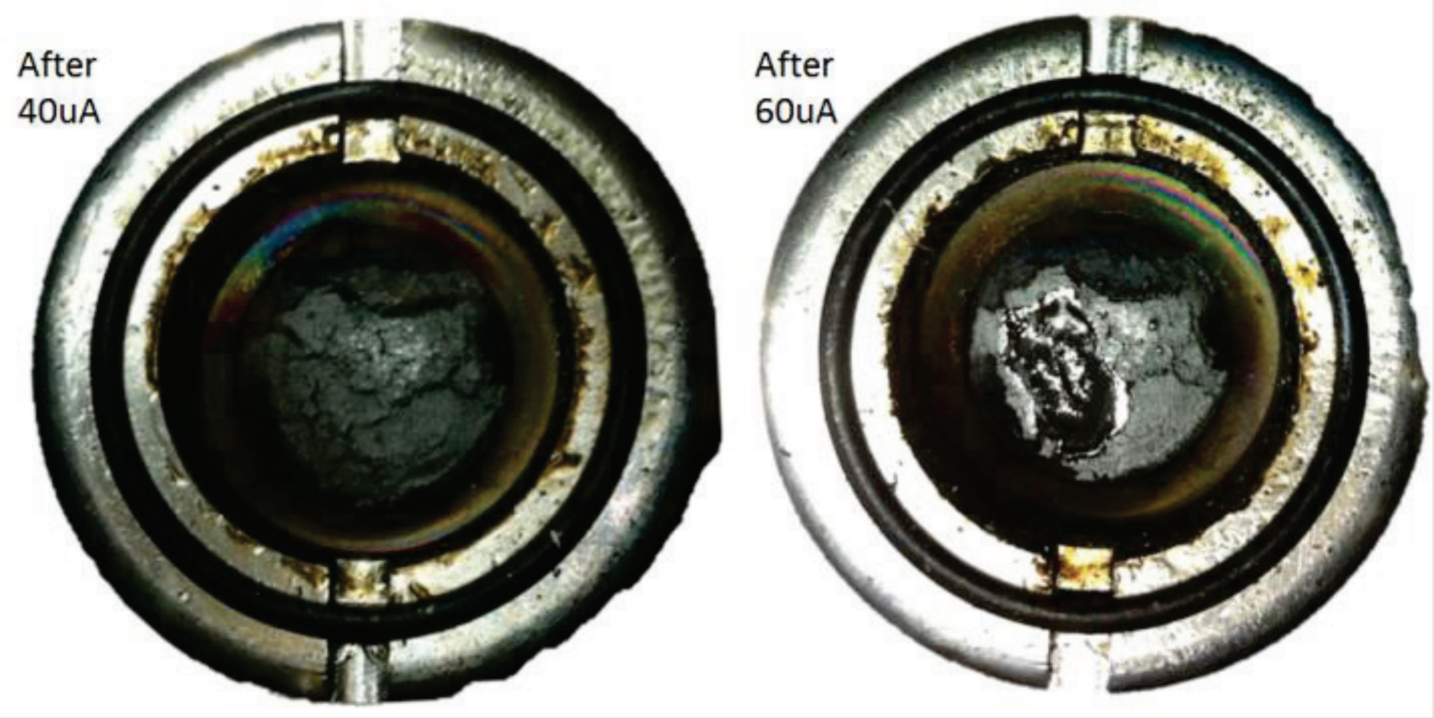
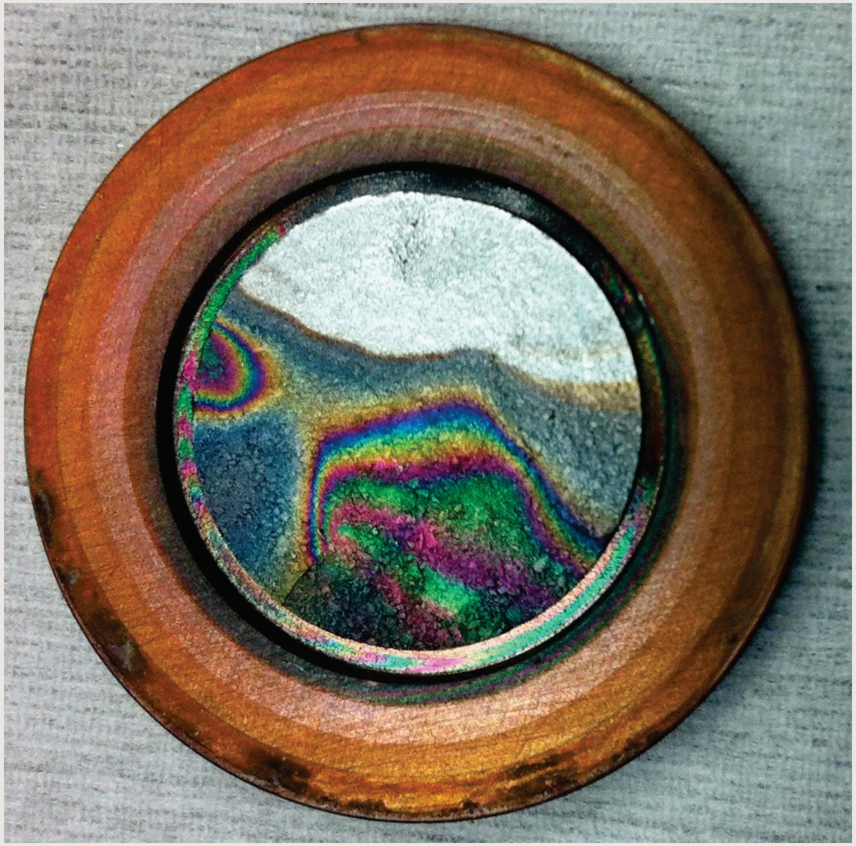
PETtrace thermal analysis

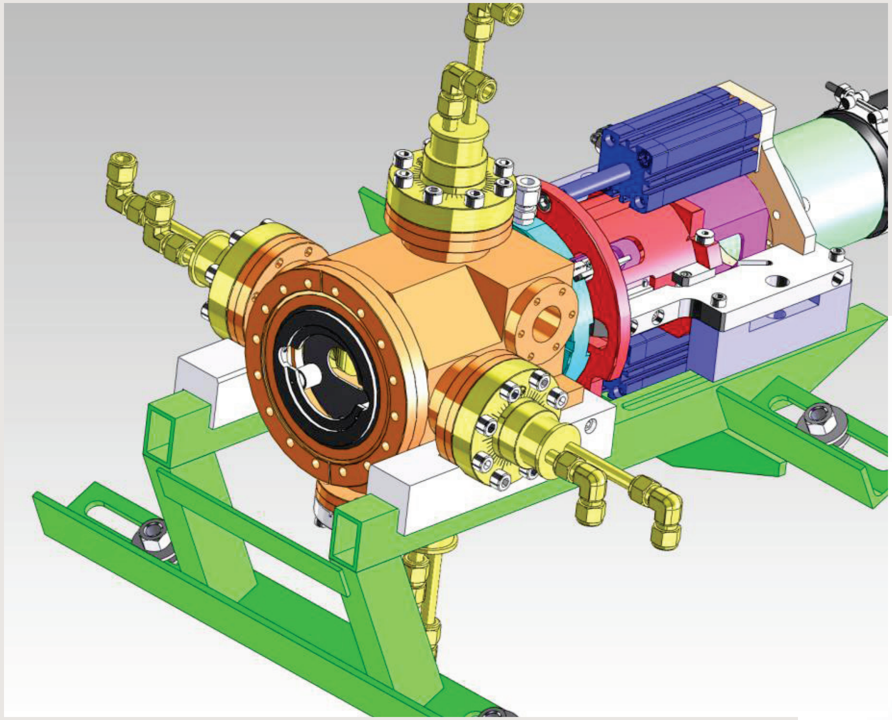


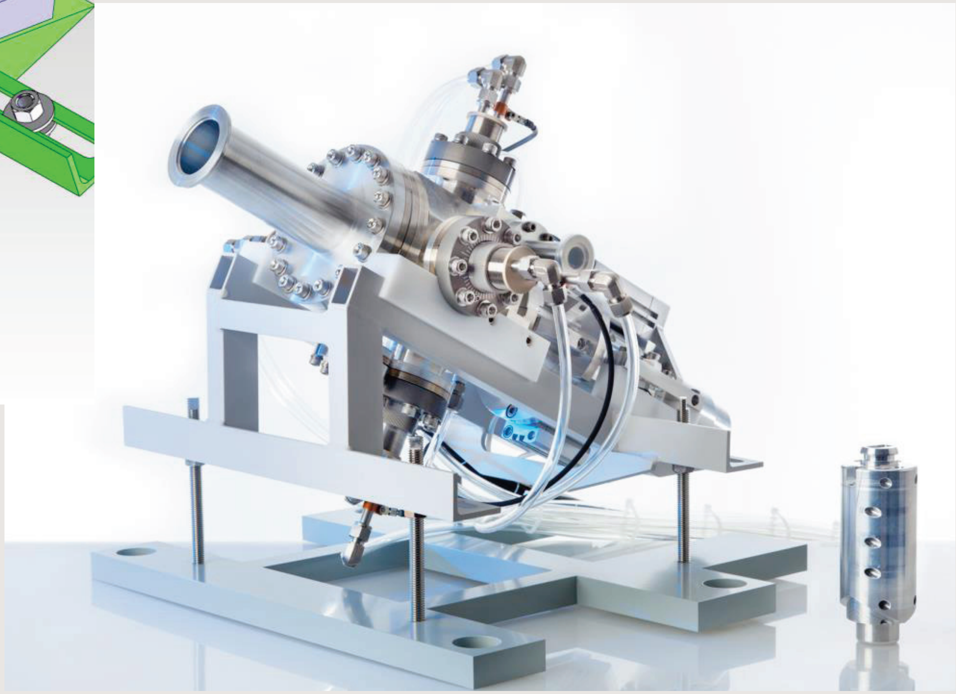
PETtrace thermal result!

- Now demonstrated 100 μA on target
  - Is that diffusion pump oil on target?
- Expect to test at 130 μA soon…



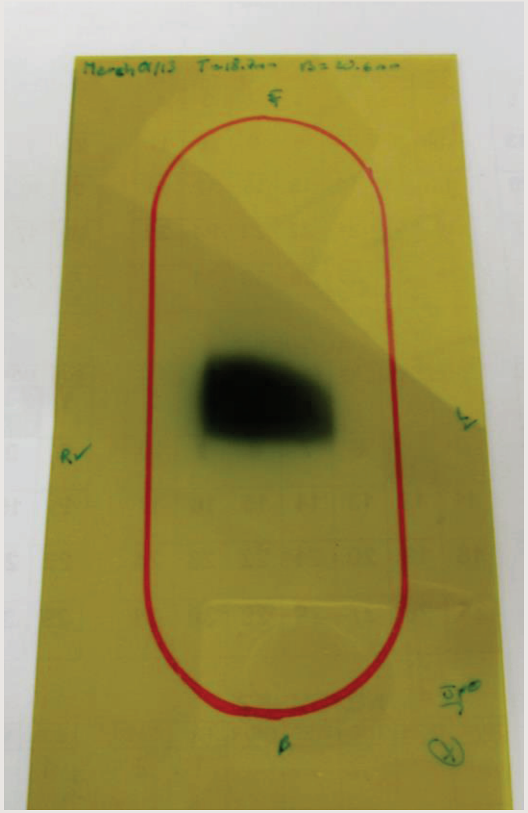
TRPET Target Station

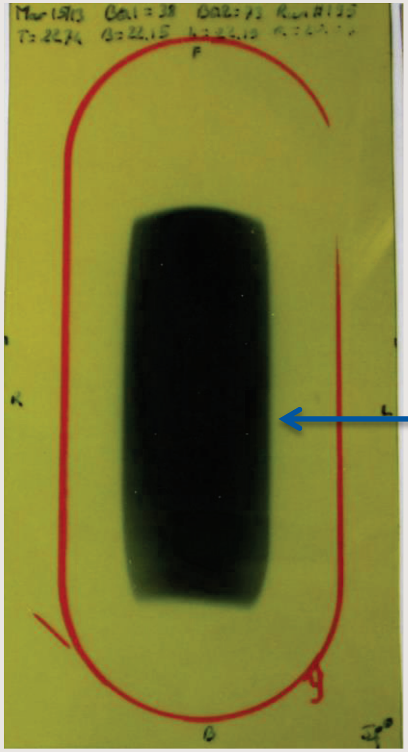




Radiographs

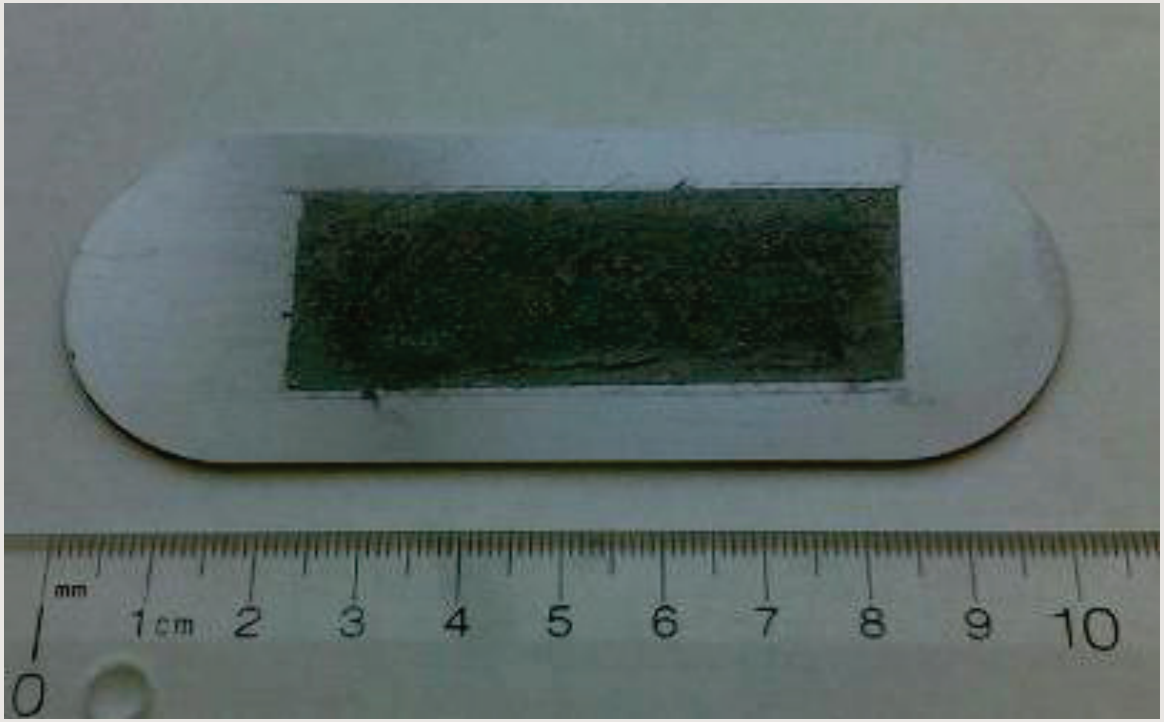
- Alignment of TRPET solid target station collimators





20mm wide x 60mm tall

TRPET Target plate



TRPET Target plate

- Irradiated at up to 230 μA to date
  - 348 GBq after ave. 220 μA for 7 hours
- Total power is higher
  - power density is lower
  - molybdenum layer is thinner

Recovery of Tc & Mo

- Dissolution of molybdenum
  - Hydrogen peroxide (30-60 mL)
    - Exothermic reaction – oxidation of molybdenum + decomposition of peroxide
- Subsequent separation of molybdate and pertechnetate by solid phase extraction
  - Molybdate (i.e. Mo-100) is retained for reprocessing into future targets

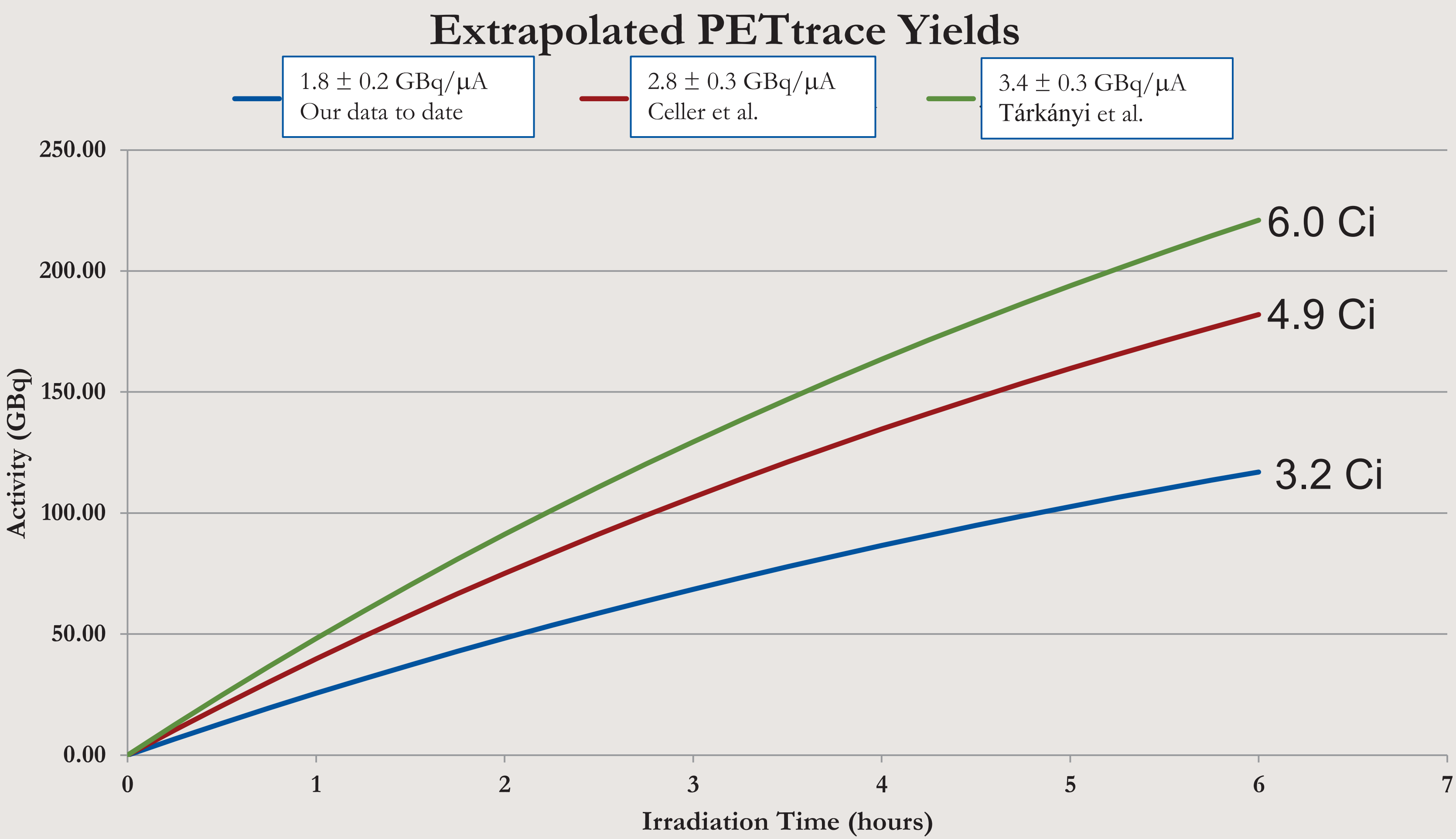
Production Metrics

	PETtrace (GBq/μA)	TRPET (GBq/μA)
Celler	2.8 ± 0.3	3.8 ± 0.4
Tárkányi	3.4 ± 0.3	4.4 ± 0.4
Our Data (to date)	1.8 ± 0.2	3.5 ± 0.4

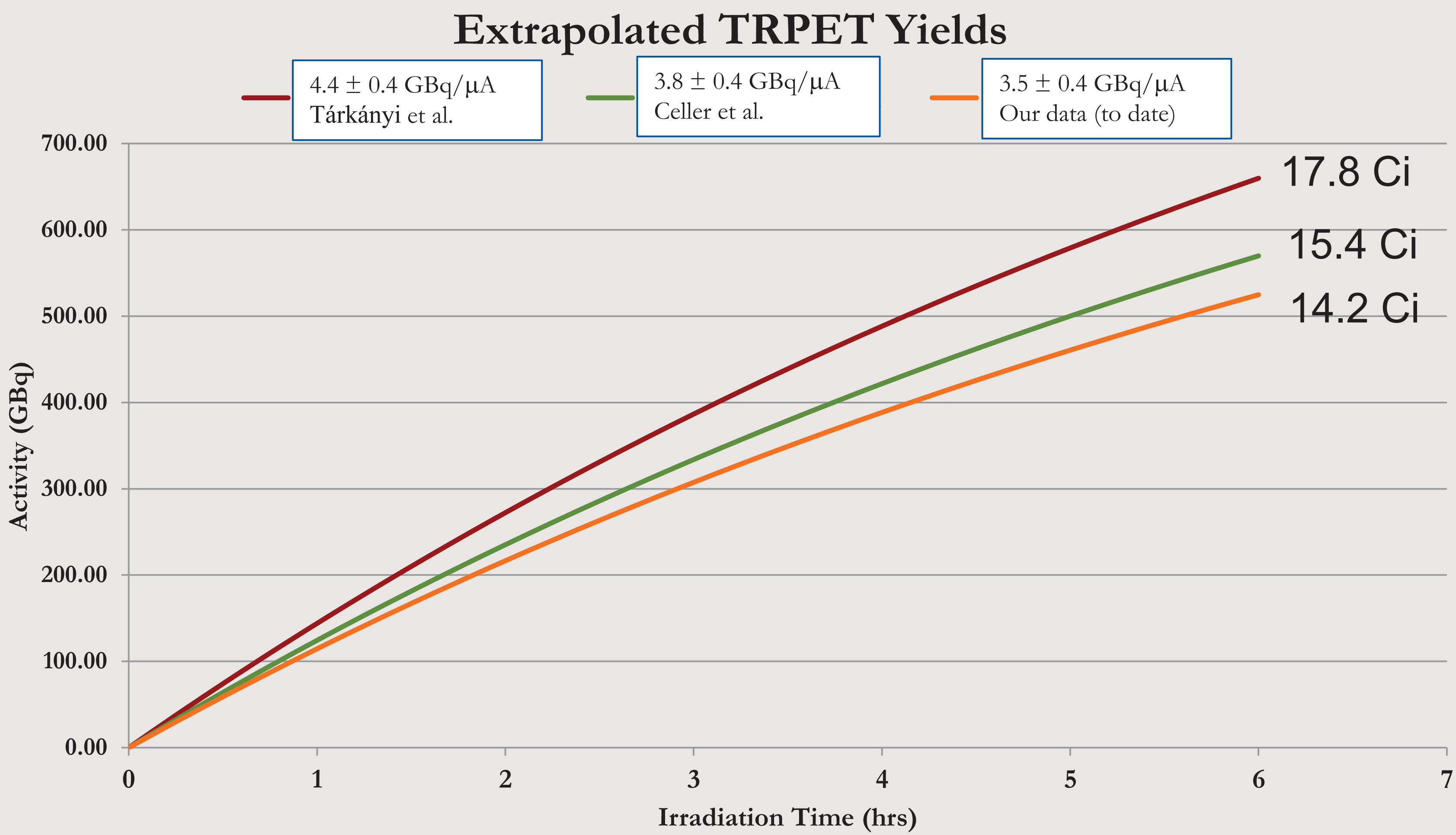
Celler et al., Phys. Med. Biol. Vol. 56, pp 5469-5484, 2011.

Tárkányi et al., Nucl. Instr. and Meth. in Phys. Res. B (2012), doi: 10.1016/j.nimb.2012.02.029

Production Metrics



Production Metrics



Remaining work…

- Confirmation of radionuclidic composition
- Demonstrate regular & routine production
- Perform clinical trial to demonstrate functional equivalence to generator derived Tc-99m
- Submit application to Health Canada for approval as a “new drug”

Thank you!
Merci!

Questions?