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

Technical Summary and Preliminary Cost Analysis for the Direct Production of ^{99m}Tc

NNSA Mo-99 Workshop, Washington, DC

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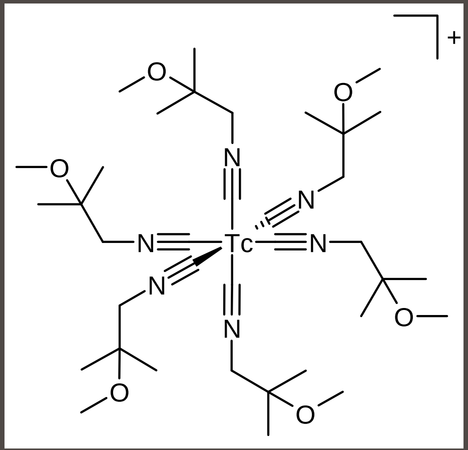


BC Cancer Agency CARE & RESEARCH An agency of the Provincial Health Services Authority

LAWSON HEALTH RESEARCH INSTITUTE

cpdc

a place of mind UBC

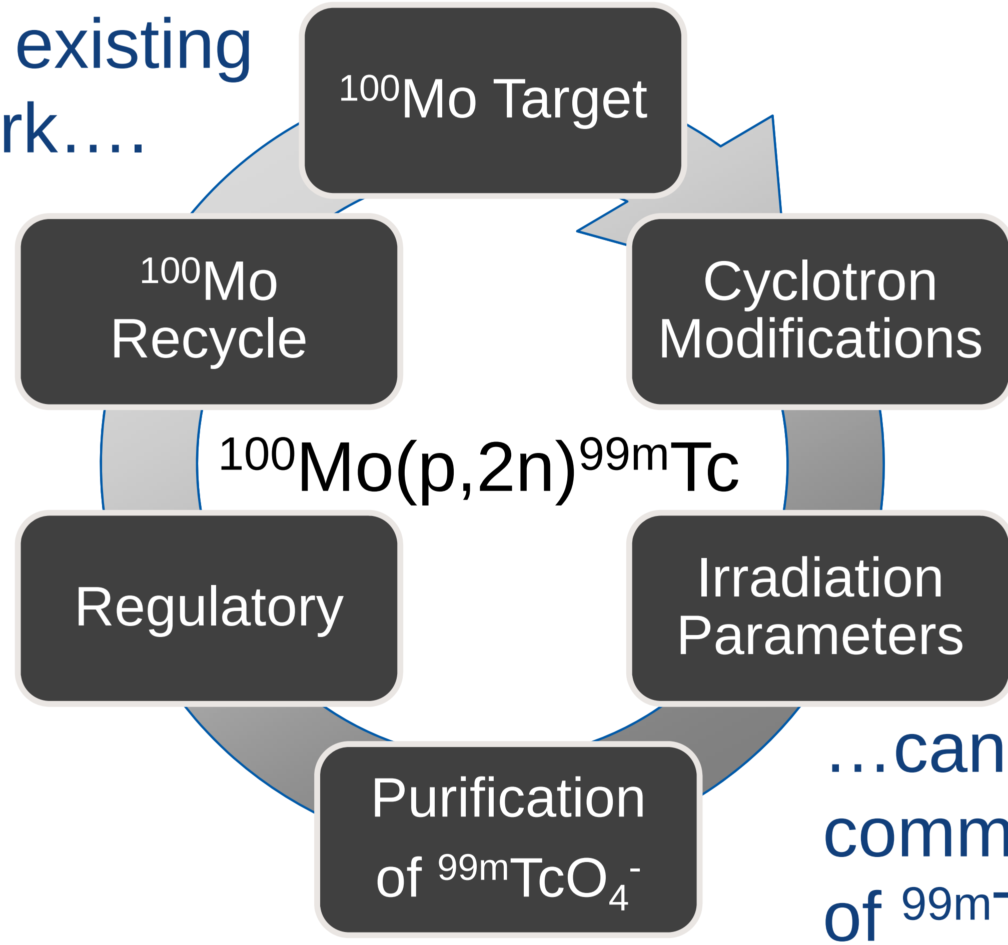
NRCan-funded Isotope Acceleration Technology Program (ITAP) - Project Goals

- Goals
  - Demonstrate routine, reliable, commercial-scale production of ^{99m}Tc in each city involved;
  - On multiple cyclotron brands found in Canada;
  - To obtain regulatory approval for such ^{99m}Tc to be used in humans;
  - Use the resulting production data to validate the business plan;
  - Disseminate production information and commercialize the technology

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

Project Goal: Commercial-Scale ^{99m}Tc

To demonstrate existing cyclotron network….



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

Team Equipment/Capabilities

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

TR19
13-19 MeV, ≤200µA
Upgrade to: 300 µA

GE PETtrace
16 MeV, ≤100 µA
Upgrade to: 130 µA (160 µA capable)

TRIUMF: CP42; 2 x TR30; Future: TR24

Direct Production of ^{99m}Tc in 1971

Background (Beaver and Hupf, U Miami):

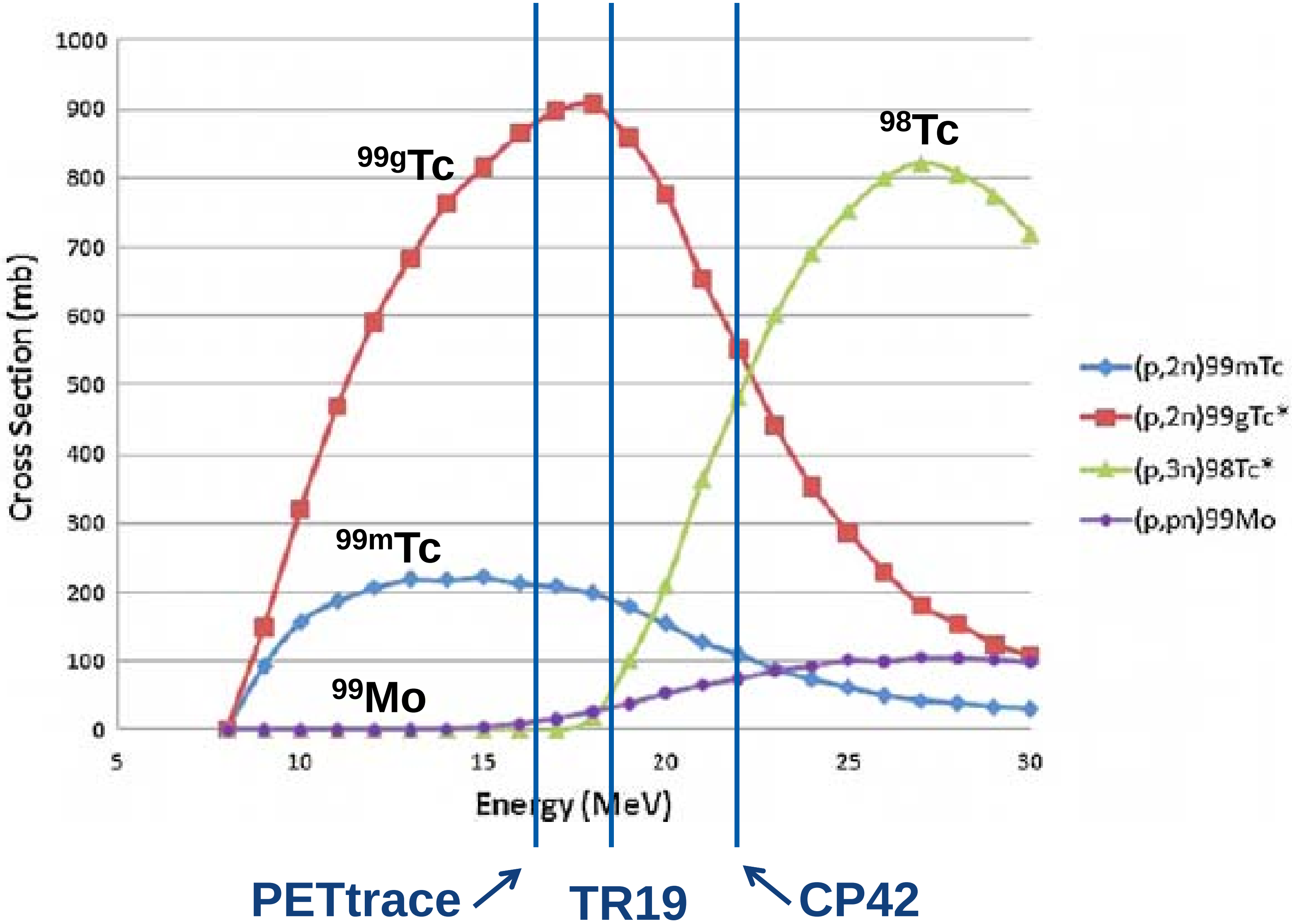
- **^{99m}Tc via cyclotron:**
  - Thin ^{nat}Mo foils, ^{100}Mo powder at 21.4, 20.2, 15.2 MeV,
  - integrated beam: <0.0296 μA·hr
- **Conclusions:**
  - ^{100}Mo (97.42%) at 22 MeV and 455 μA will produce **15 Ci/hr of ^{99m}Tc and 500 mCi/hr of ^{99}Mo**
  - Assuming an operating cost of $100/hr, cost of ^{99m}Tc production = $0.015/mCi !!!

No motivation to pursue given avail. of ^{235}U(n,F)^{99}Mo

J.E. Beaver and H.B. Hupf, J. Nucl. Med. 1971, 12, 739-741

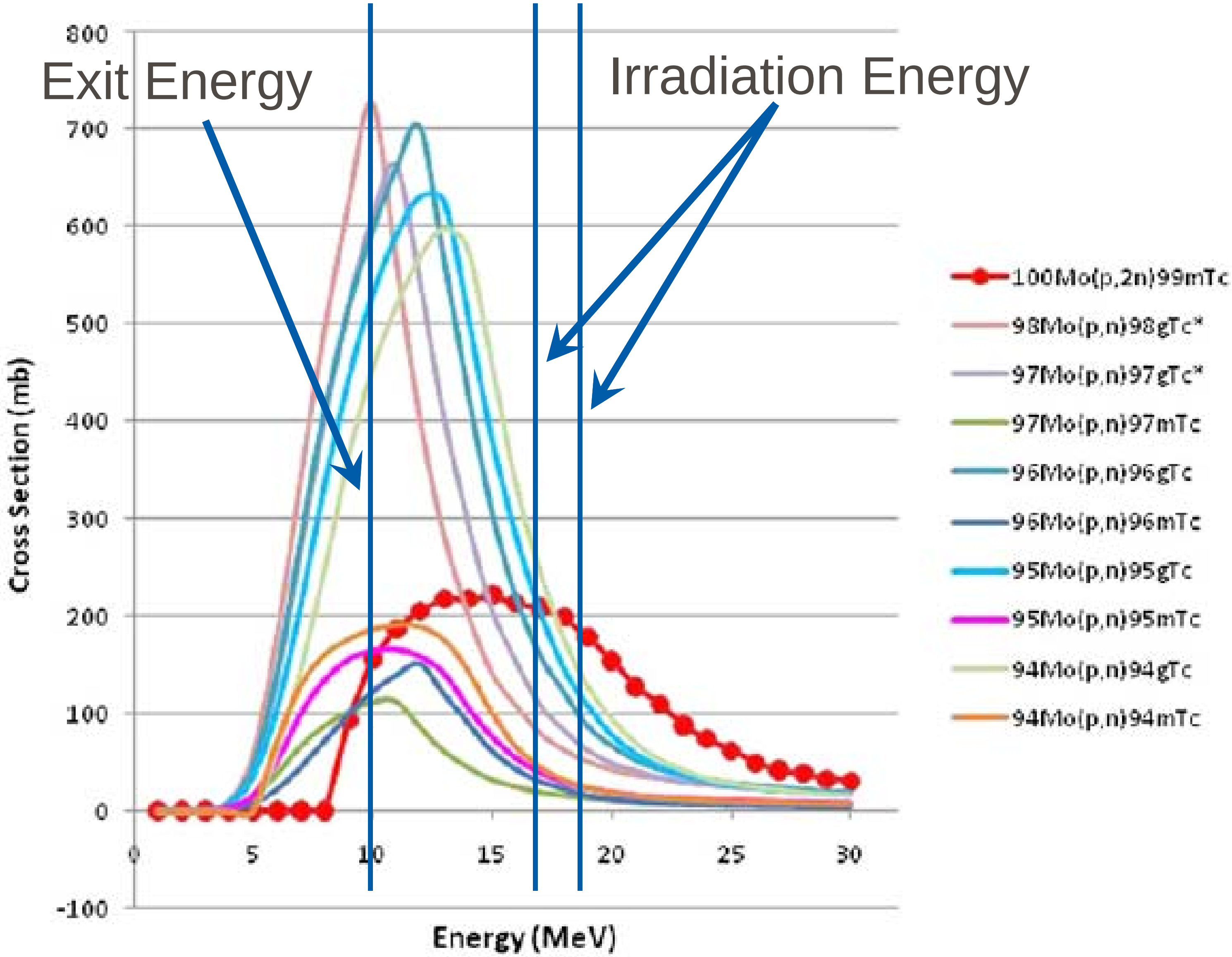
The Calculated Approach: Predicting Products/Yields

$^{100}Mo(p,x)$ reactions of highest probability



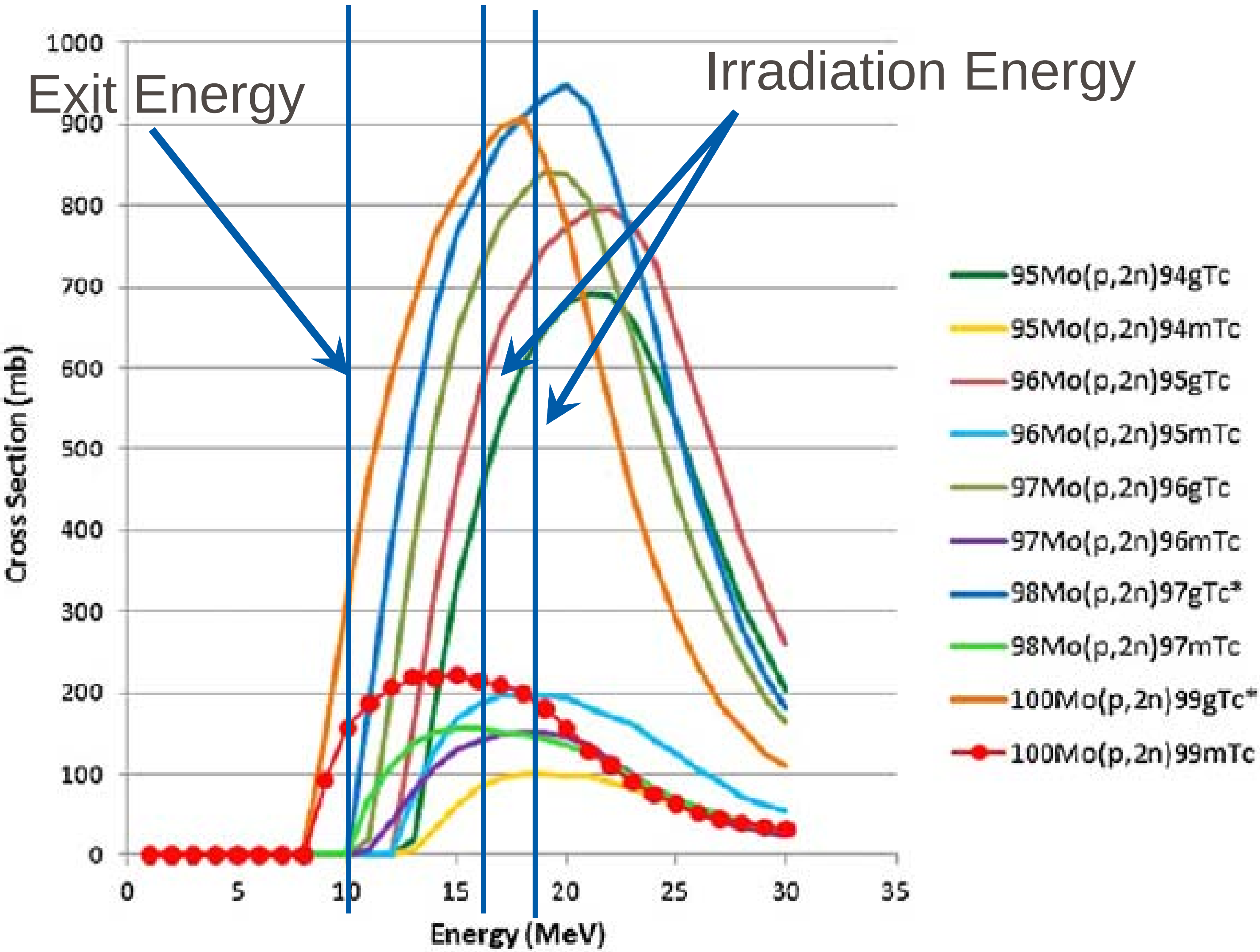
A. Celler, X. Hou, F. Bénard, T. Ruth, Phys. Med. Biol. 2011, 56, 5469

Side Reactions: $^{94-97}$Mo(p,n)



A. Celler, X. Hou, F. Bénard, T. Ruth, Phys. Med. Biol. 2011, 56, 5469

Side Reactions: $^{94-97}Mo(p,2n)$



Optimal energy range: 16-19 MeV

A. Celler, X. Hou, F. Bénard, T. Ruth, Phys. Med. Biol. 2011, 56, 5469

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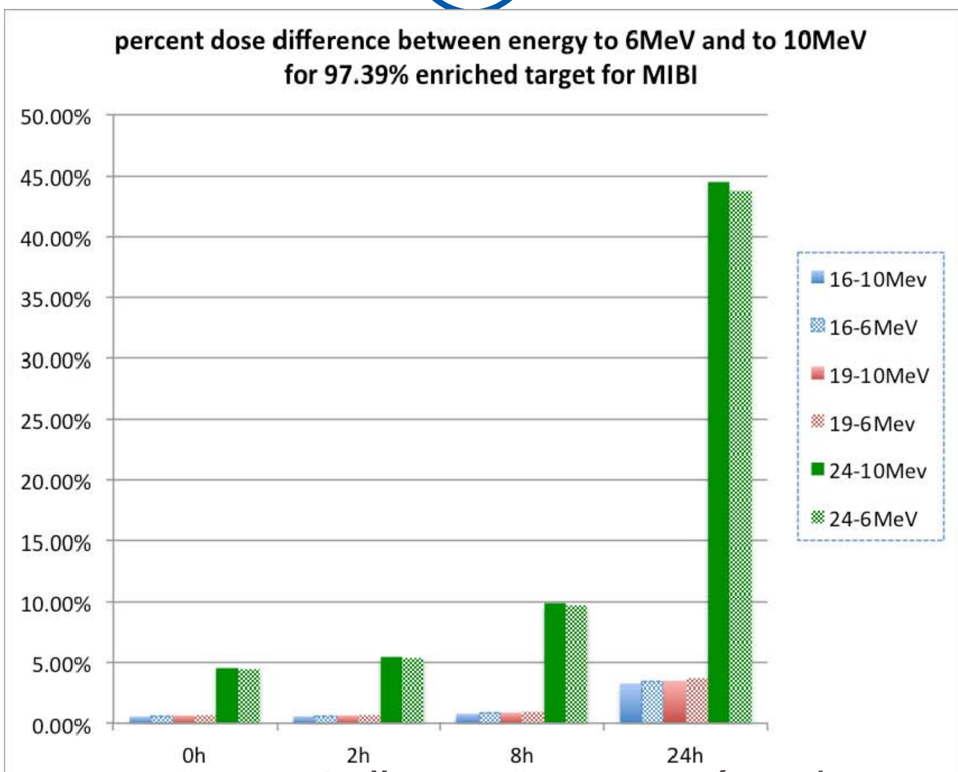
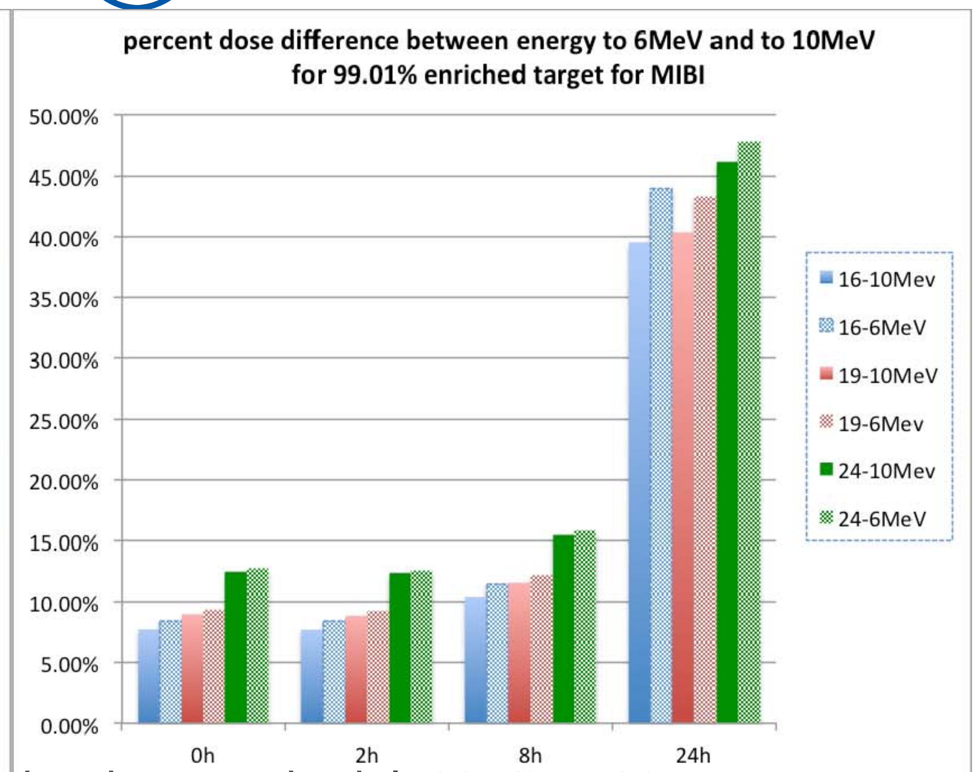
Target Enrichment: Issues with lighter Mo isotopes

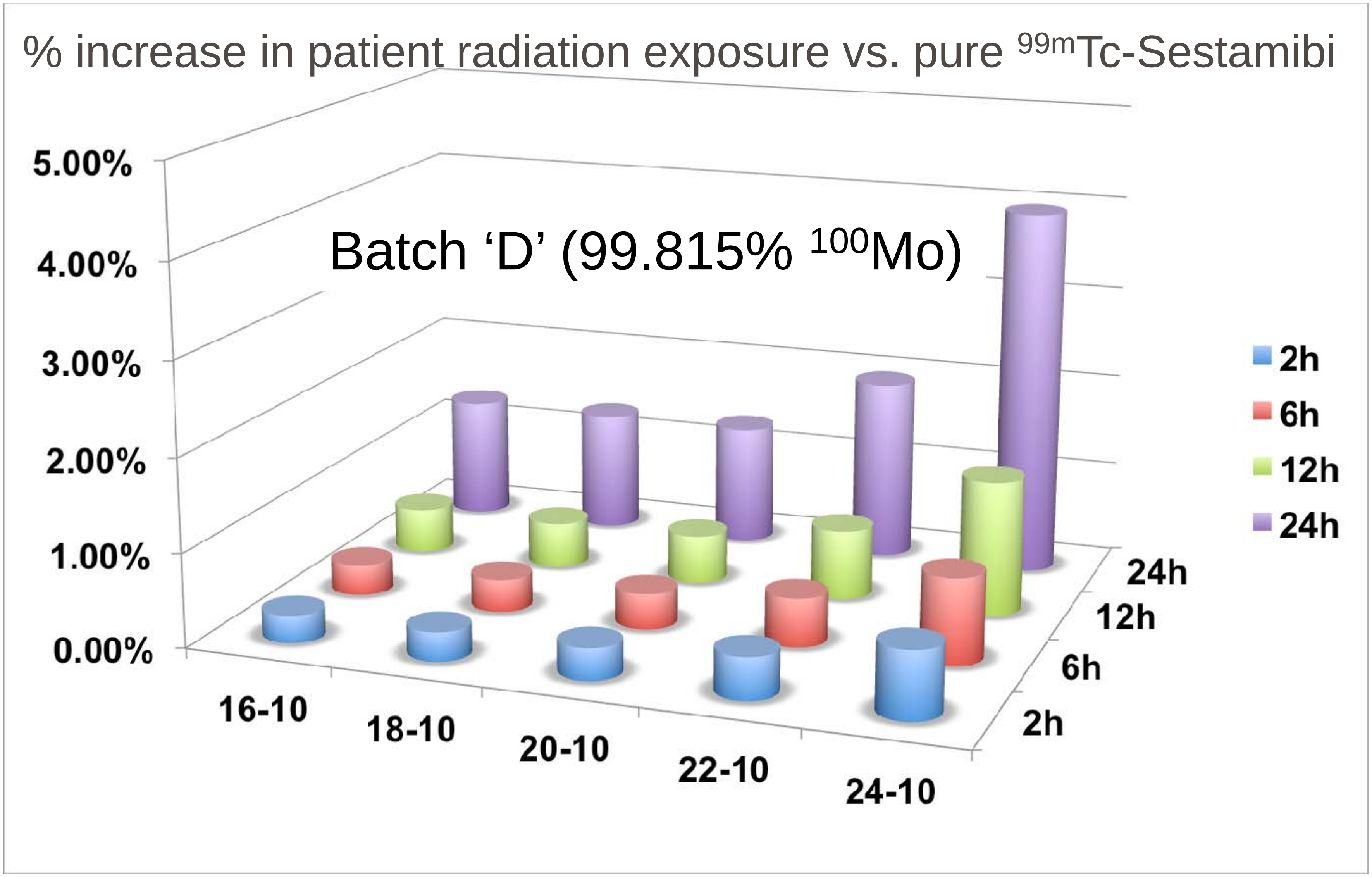
Isotope	Enriched				Natural
	A	B	C	D	
^{92}Mo	0.005	0.006	0.09	0.003	14.85
^{94}Mo	0.005	0.0051	0.06	0.003	9.25
^{95}Mo	0.005	0.0076	0.1	0.003	15.92
^{96}Mo	0.005	0.0012	0.11	0.003	16.68
^{97}Mo	0.01	0.0016	0.08	0.003	9.55
^{98}Mo	2.58	0.41	0.55	0.17	24.13
^{100}Mo	**97.39**	**99.54**	**99.01**	**99.815**	**9.63**





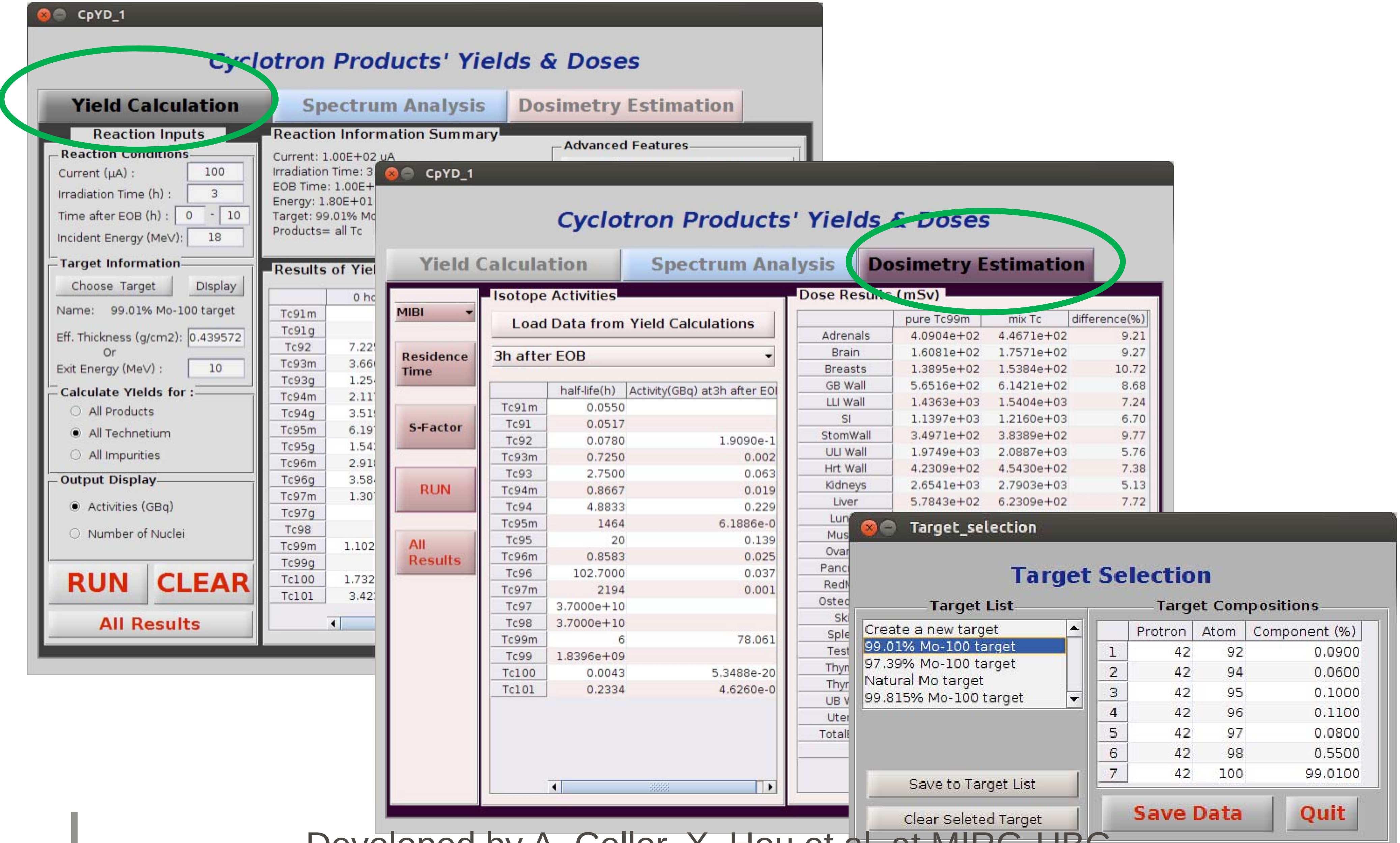
A. Celler, X. Hou, F. Bénard, T. Ruth, Phys. Med. Biol. 2012, 1499

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



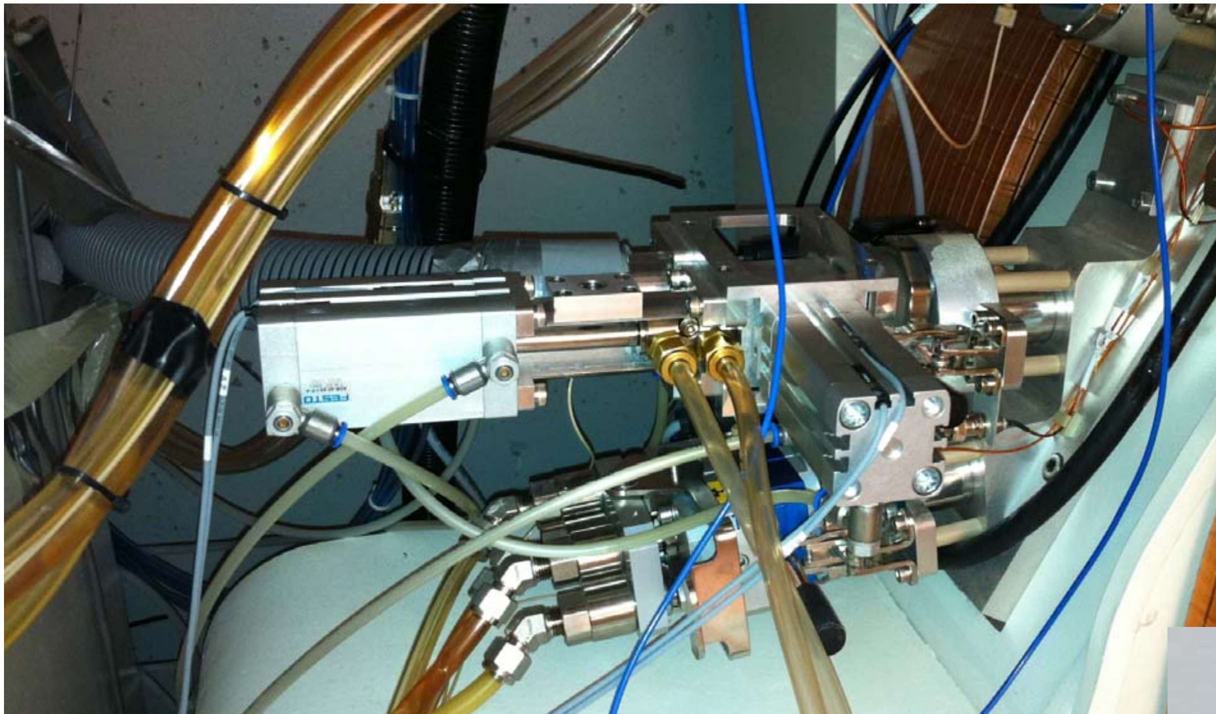
Pre-clinical trials underway to validate calculations

Graphical User Interface (GUI) for Yield and Dose Projections



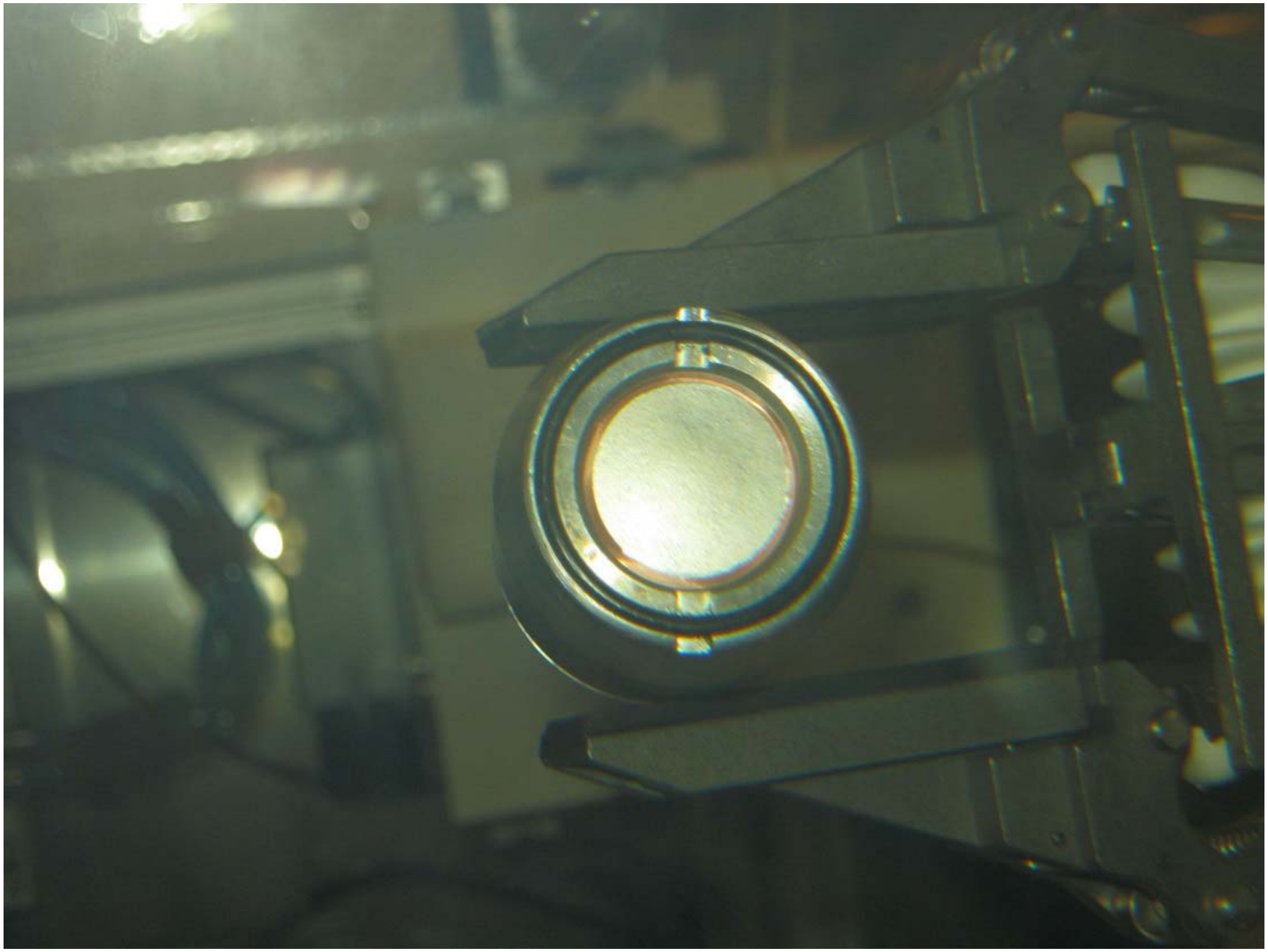
Developed by A. Celler, X. Hou et al. at MIRG-UBC

PETtrace Target Stations



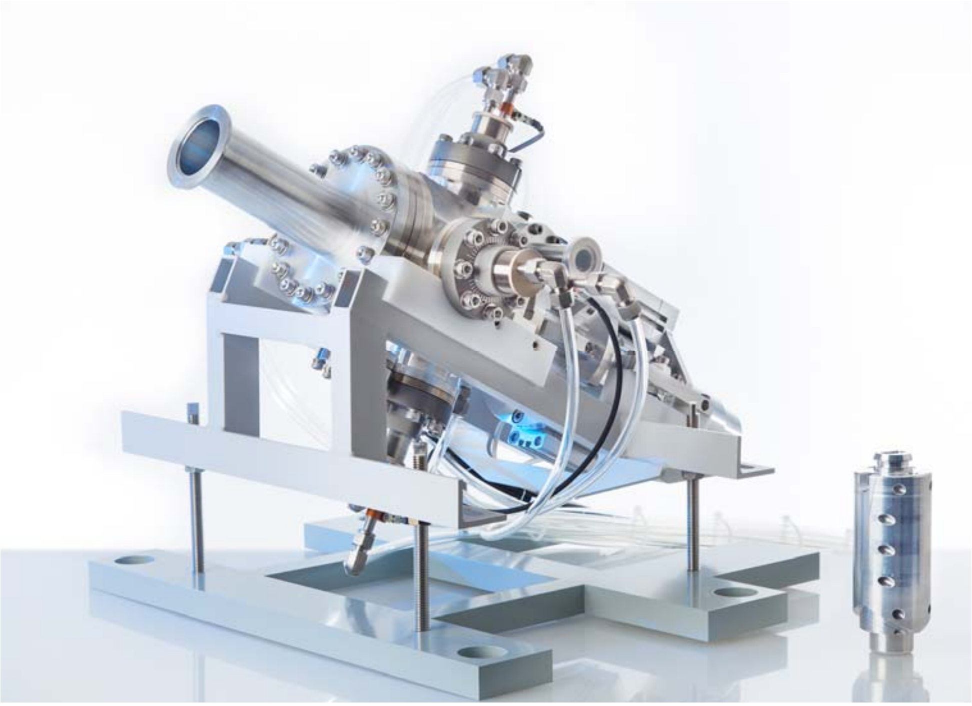
Tested to 130 μA
No target degradation
4.7 Ci achieved per 6 h run
Saturated yields: 2.8 GBq/μA
75.7 mCi/μA

Target Integrity Confirmed



GE PETtrace target, after irradiation at 130 µA

TR-19 Target Station

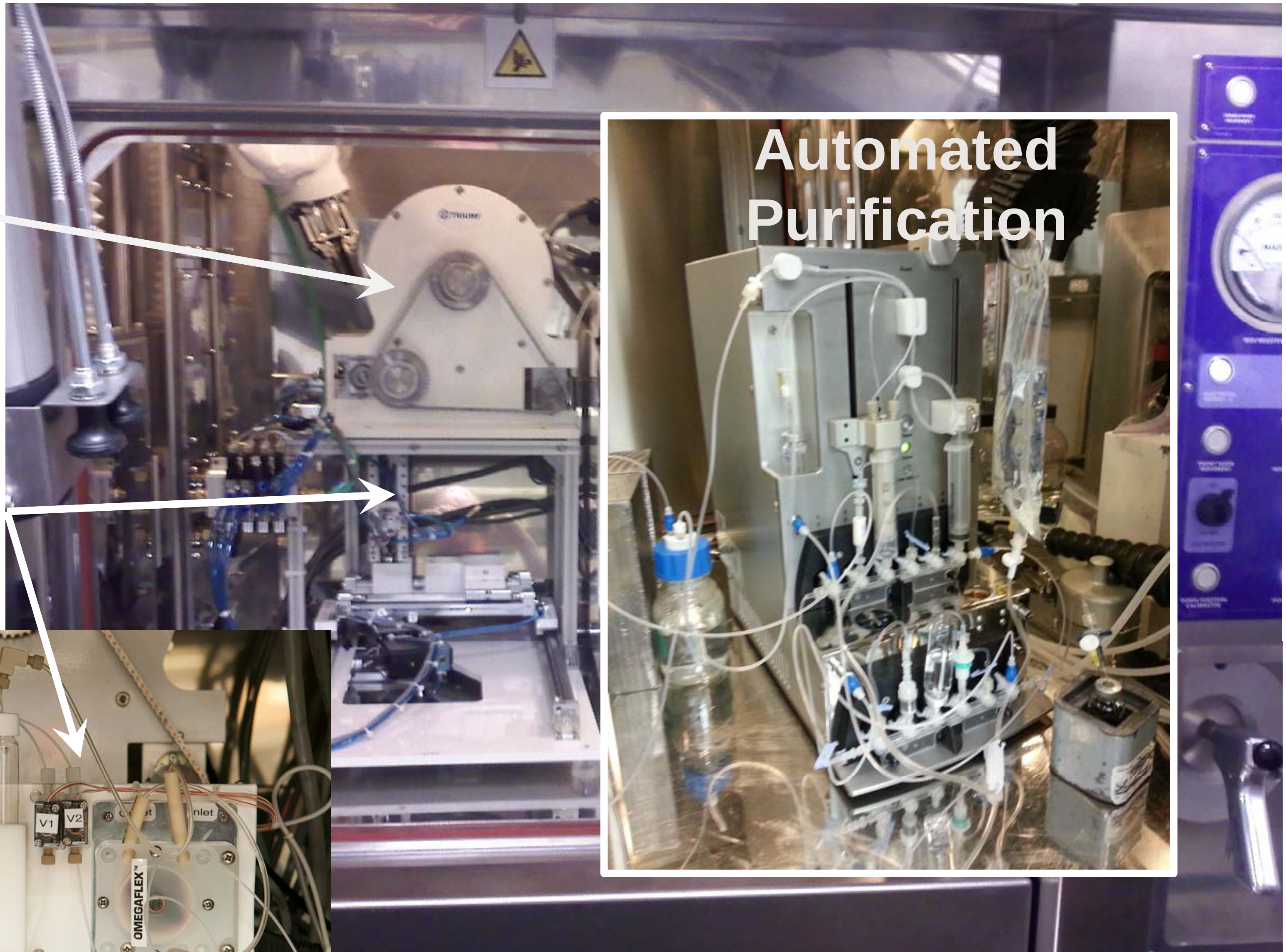


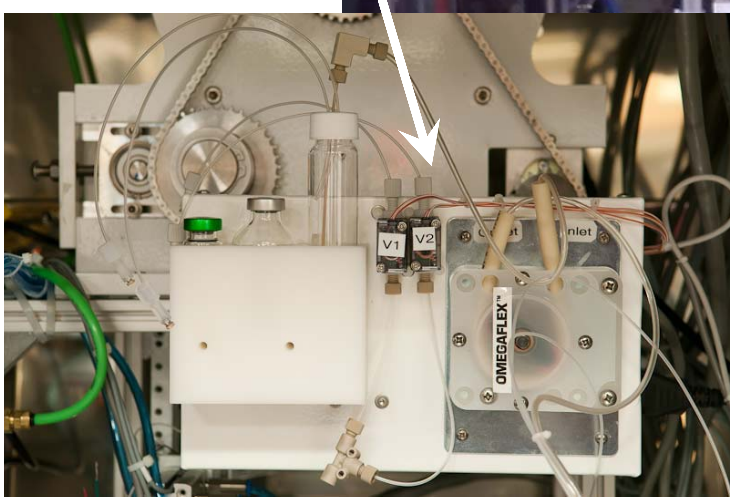
Tested to 300 µA
No target degradation
13 Ci capacity for 6 h run
10 Ci achieved to date
Saturated Yields: 3.8 GBq/µA
102.7 mCi/µA

2010-2014: Development and Installation of High-Power Solid Targets, Associated Hardware

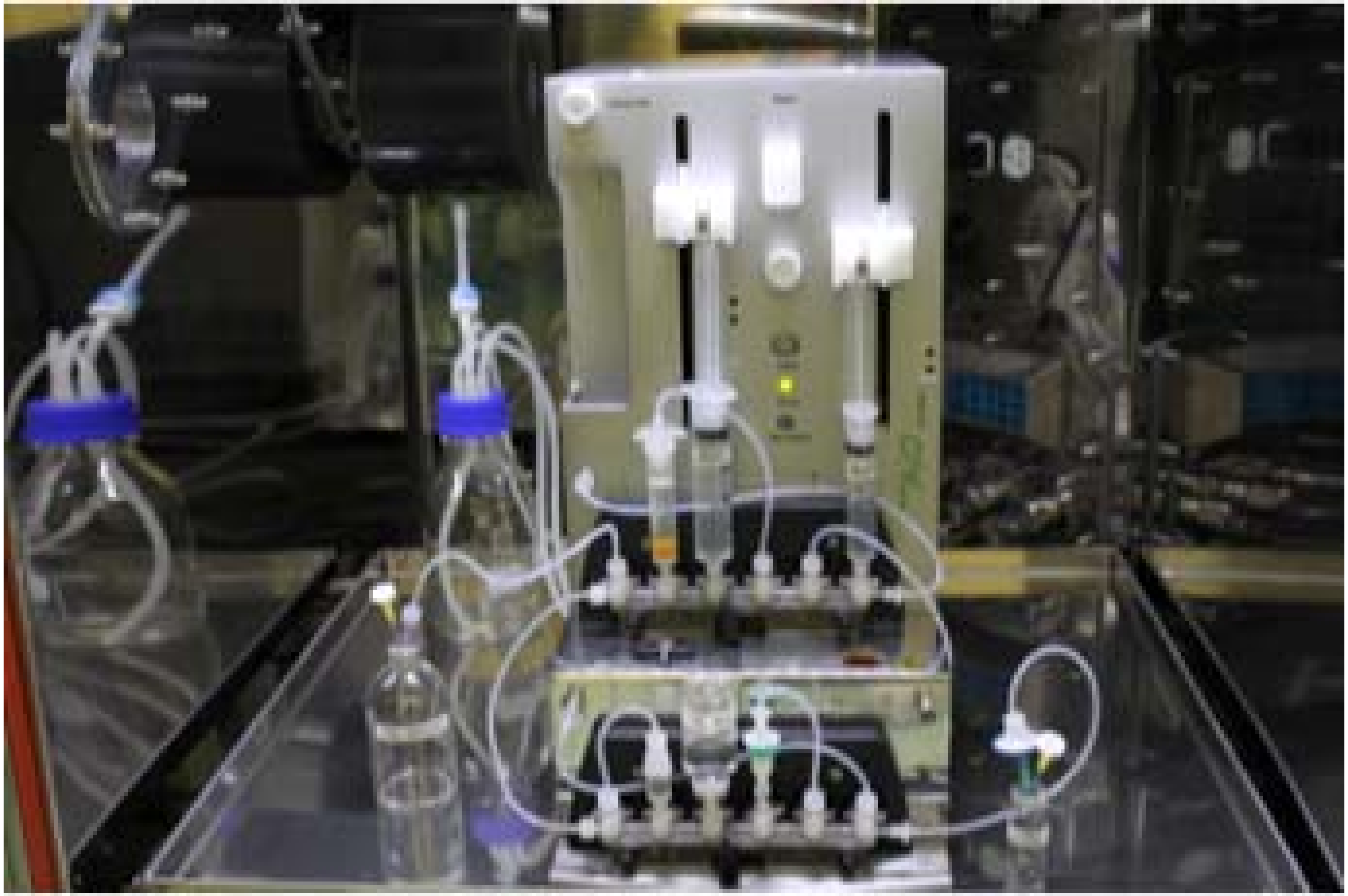
Transfer Drive

Receive and Dissolve



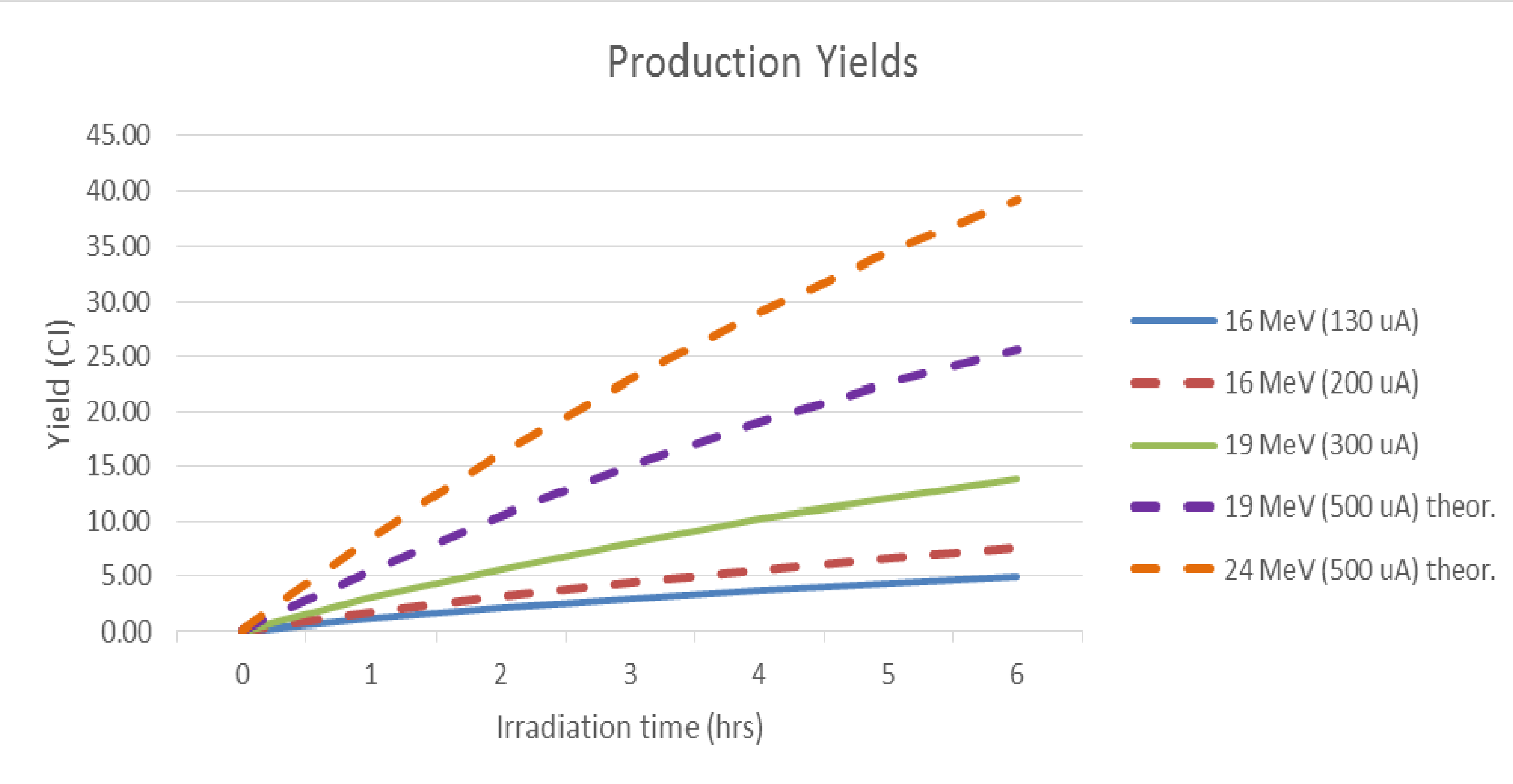


GMP Production with Disposable Fluid Path



Numerous commercially available resins avail.
Reproducible yields 92.7 ± 1.1% (range 91.5 – 93.5%) with actual production runs (up to 4.5 Ci processed)

Yield Comparison: Energy, Current Considerations



Technical Summary of Results

- ^{100}Mo Target irradiations at 19 MeV, 300 µA to date
- Yields: ~340 GBq (TR19), ~174 GBq (PETtrace)
- Recovery: ~93% as $Na^{99m}TcO_4$
- Radiopharmaceutical Production:
  - 3 types of kits (Sestamibi, HMPAO, MDP) radiolabeled
  - All passed standard QC (n = 3 each)
- Radiochemical Purity:
  - Small amounts of ^{93}Tc, ^{94m}Tc, ^{94}Tc, ^{95}Tc, ^{96}Tc impurities were observed – full quantitation underway
  - Non-Tc by-products (^{95}Nb, ^{99}Mo) collected in waste stream
  - ^{100}Mo recycled with 85% recovery yield (range 80 – 92%)

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

Results Interpretation (so far)

- Production capacity: energy, time, current
  - Energy – intrinsic to machine (16-19 MeV, <22MeV)
  - Time – defined by other commitments (3-6 hrs)
  - **Current – best option for increasing production**
- ^{100}Mo isotopic purity is important
  - ^{95,96,97}Mo content is important below 22 MeV
  - ^{98}Mo content is important between 22-24 MeV
  - ^{100}Mo (p,3n) above 20 MeV will invariably increase ^{98}Tc content
- ^{99m}Tc specific activity needs regulatory consideration
  - Presence of impurities and affect on chemistry, dosimetry
  - Dosimetry limits require regulatory input
    - Link to USP and EP

Canada vs. USA – Substantial ^{99m}Tc Production Capacity Currently in Place

(1 x 6hr runs/d, 240d/yr)

Canada

Population: ~35M (2012)

Annual ^{99m}Tc needs: 971 TBq

With losses: **1900 - 3000 TBq**

Cyclotrons: 22+6 (>16 MeV)

Existing Capacity: 2483 TBq

USA

Population: ~ 314M (2012)

Annual ^{99m}Tc needs: ~8700 TBq

With losses: **17,400 - 27,200 TBq**

Cyclotrons: ~110 of 261 (>16 MeV)

Existing Capacity: ~9160 TBq

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Estimated cost for direct production of ^{99m}Tc

- Assessments of 16, 19 and 24 MeV operations
- Key assumption: Maximum production of $Na^{99m}TcO_4$ with distribution (and sale) of everything to a centralized radiopharmacy
- Estimates:
  - Losses: 38% (process efficiency, time), 50% (shipping, scanning)
  - Demands (20 mCi doses, 5% usage rate vs. population)
- Costs considered:
  - Variable (salaries, power, consumables)
  - Admin (amortization, insurance, shipping, waste, maintenance, etc.)
  - Capital (Brownfield – cyclotron upgrade)
  - Start-up (training, materials, regulatory)

Preliminary Cost Estimates

	Current (uA)	Time (h)	Batch size (Ci)	Shipped (Ci)	Rec'd (Ci)
16 MeV	130	6	4.9	3	1.5
19 MeV	300	6	15.4	9.4	4.8
24 at 19 MeV	500	6	25.7	15.9	7.9
24 MeV	300	6	23.5	14.6	7.3
24 MeV	500	6	39.2	24.3	12.2

* Note that cyclotron costs are brownfield estimates, including upgrades, amortization of cyclotron, not structures

Current estimated price <$1.00/mCi

Regulatory Aspects of Cyclotron-Produced $^{99m}TcO_4$ – Ongoing Work

- Summer 2014 – GLP preclinical (rodent) data
- Implement GMP production
- Set acceptance for molybdenum enrichment and irradiation parameters
  - Shelf life, irradiation parameters are based on projected patient dose (objective <10% vs generator-sourced ^{99m}Tc)
  - Enrichment and irradiation parameters are interrelated and should not be considered independently
- Fall 2014 – Clinical trial application
- Jan. – April 2015 - Clinical trial (human) data
  - $Na^{99m}TcO_4$ and hyperthyroid patient trial
- Summer – Fall 2015 - NDS submission

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Regulatory Approach

Upstream:

- Target quality
- ^{100}Mo cert. of analysis
- ICP-MS – specific activity vs irradiation metrics
- Gamma spectroscopy – full radionuclidic analysis

Cyclotron facility:

- Filter Integrity Test (FIT)
- Quantity, Radionuclidic purity (dose calibrator): Δ Patient dose <10%

Radiopharmacy

- Assays: Mo, Al, PEG, H_2O_2 – colourimetric (ppb – ppm)
- pH: spot/strip test
- Visual inspection: particulate
- Radiochemicial identity: TLC (as per package insert)
- Radiochemical purity: TLC (as per package insert)

Outsourced/3rd Party

- Sterility, pyrogenicity (endotoxin)

Acknowledgements

- **The Team:**
  - Ken Buckley, Vicky Hanemaayer, Brian Hook, Stuart McDiarmid, , Stefan Zeisler, Frank Prato, Chris Leon, Anne Goodbody, Joe McCann, Conny Hoehr, Tom Morley, Julius Klug, Philip Tsao, Milan Vuckovic, Jean Pierre Appiah, Maurice Dodd, Guillaume Amouroux, Wade English, Xinchi Hou, Jesse Tanguay, Jeff Corsault, Ross Harper, Constantinos Economou
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Thank you!
Merci

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Canada

NSERC CRSNG

CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

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