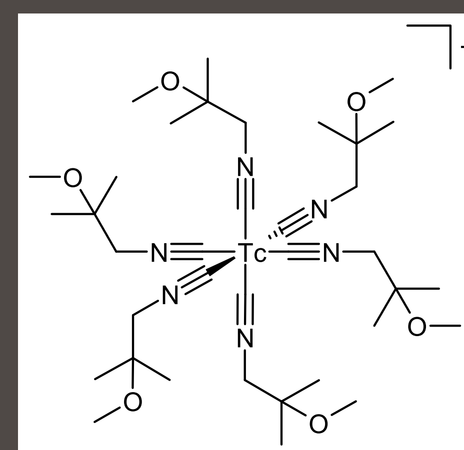
TRIUMF

^{99m}Tc Production Development at TRIUMF

Paul Schaffer | Head, Nuclear Medicine | TRIUMF

In Partnership with:

BC Cancer Agency;
University of British Columbia;
Lawson Health Research Institute;
Centre for Probe Development and Commercialization



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TRIUMF: A National Laboratory

Members

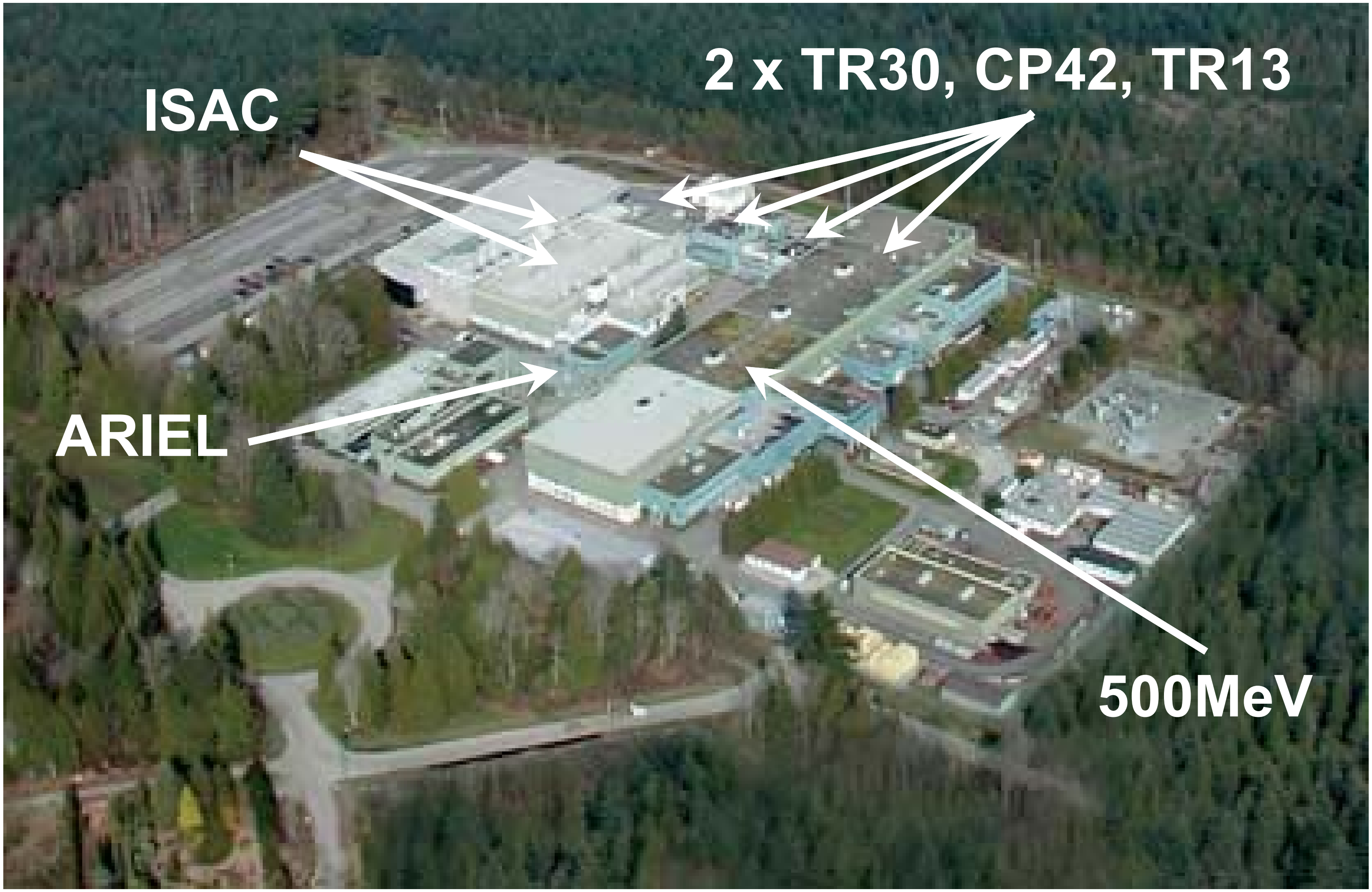
University of Alberta
University of BC
Carleton University
University of Guelph
University of Manitoba
Université de Montréal
Queen's University
Simon Fraser University
University of Toronto
University of Victoria
York University

Associate Members

University of Calgary
McGill University
McMaster University
University of Northern BC
University of Regina
Saint Mary's University
University of Winnipeg
Western University

TRIUMF is owned and operated by a consortium of 19 universities
Founded 47 years ago in Vancouver

TRIUMF accelerators



- Deep expertise in: cyclotrons, targetry, radiochemistry
- Knowledge of large-scale production: i.e. Nordion (^{82}Rb, ^{123}I, ^{201}Tl, ^{103}Pd…)
- Vision: To implement multi-site ^{99m}Tc production

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^{99m}Tc and the Recent Global Isotope Crisis

- Global demand for ^{99}Mo/^{99m}Tc ~ 40 million doses/yr
- 76,000 scans/day (>1 scan/second)
- $1-3B industry
- Overall, ~5 gov't owned reactors supply >95% of global demand
- **30-40% of global ^{99}Mo obtained from NRU in Canada**
- **Recent reactor outages:** widespread shortages, cost fluctuations
- Technical and regulatory challenges for new suppliers
- Perceived issues with production capacity issues ceding to greater likelihood of processing capacity issues (2017)
- Future demands to increase (difficult to quantify)

Ongoing Challenges with Reactor-Sourced $^{99}Mo/^{99m}Tc$

- Ageing fleet, high maintenance/replacement cost (OSIRIS, NRU shutdown), PALLAS timeline
- Single point of failure vulnerability – need reserve capacity
- Need to reduce reliance on HEU (downstream effects on yield, process and waste)
- Current economic model is insufficient for long-term sustainability
    - Requirement for full-cost recovery to allow market forces to exert themselves on supply chain

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Tc-99m Alternatives: Many options

Alternatives:

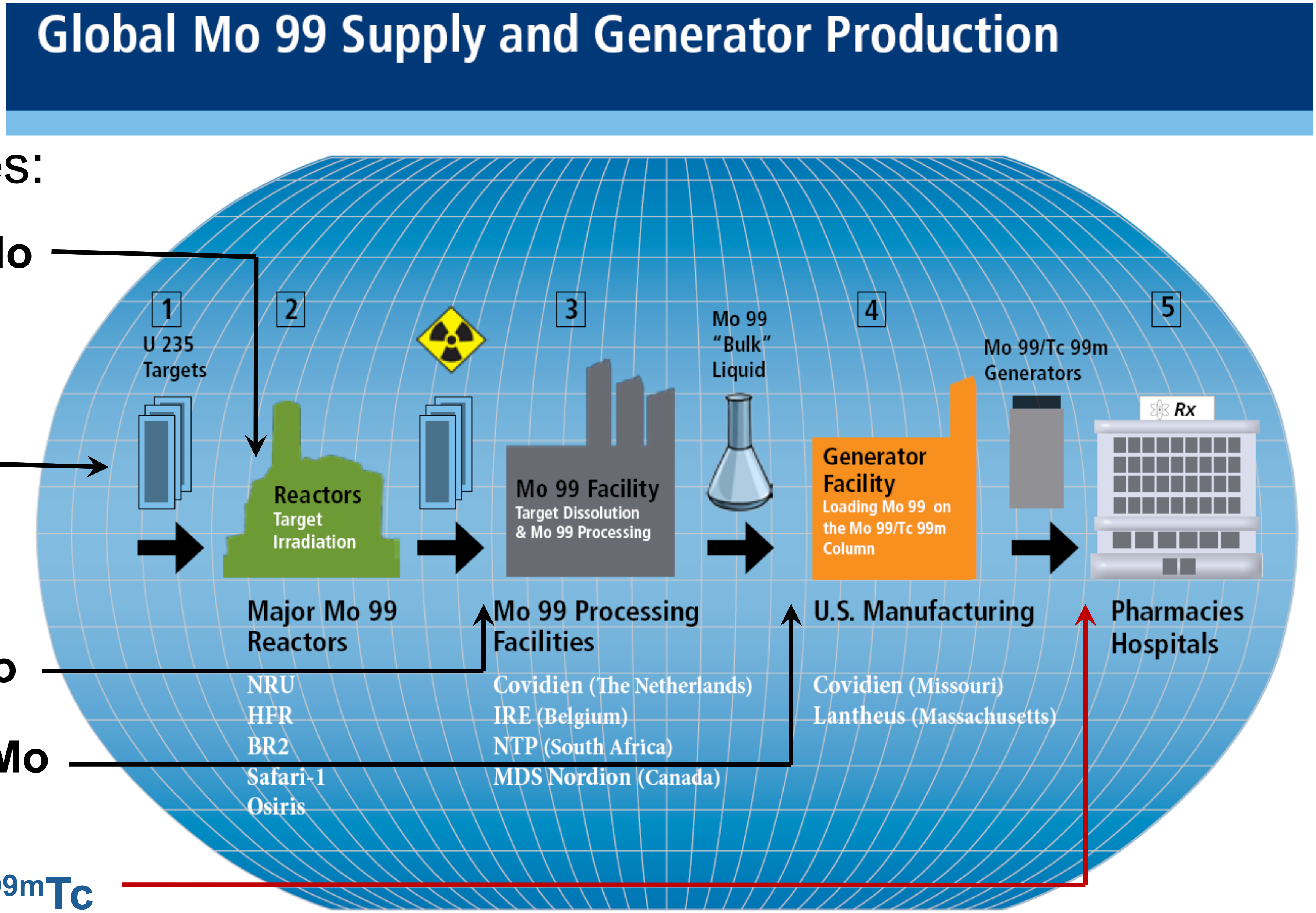
^{98}Mo(n,γ)^{99}Mo

LEU

^{238}U(γ,F)^{99}Mo

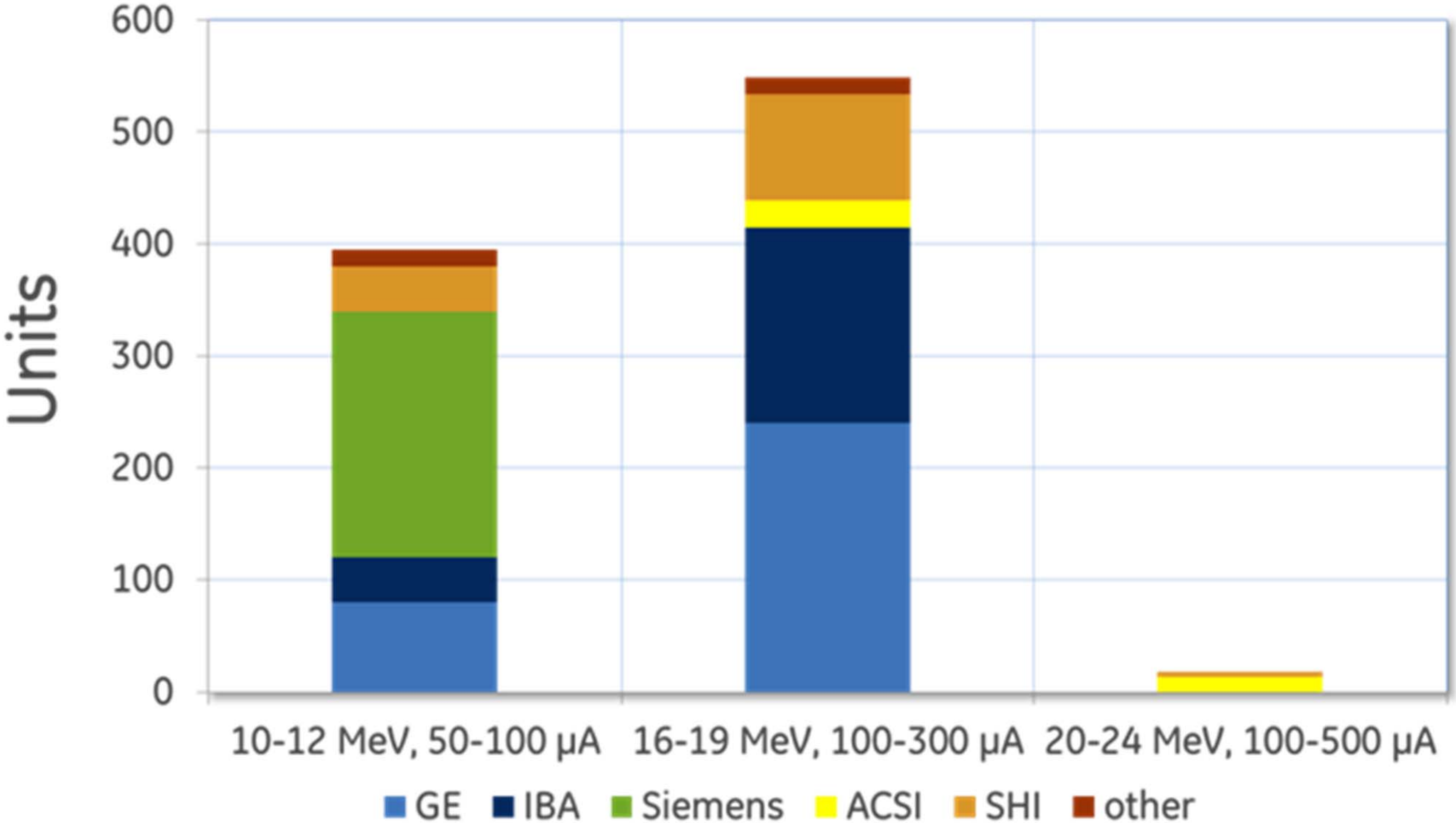
^{100}Mo(γ,n)^{99}Mo

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



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

Cyclotrons By the Numbers

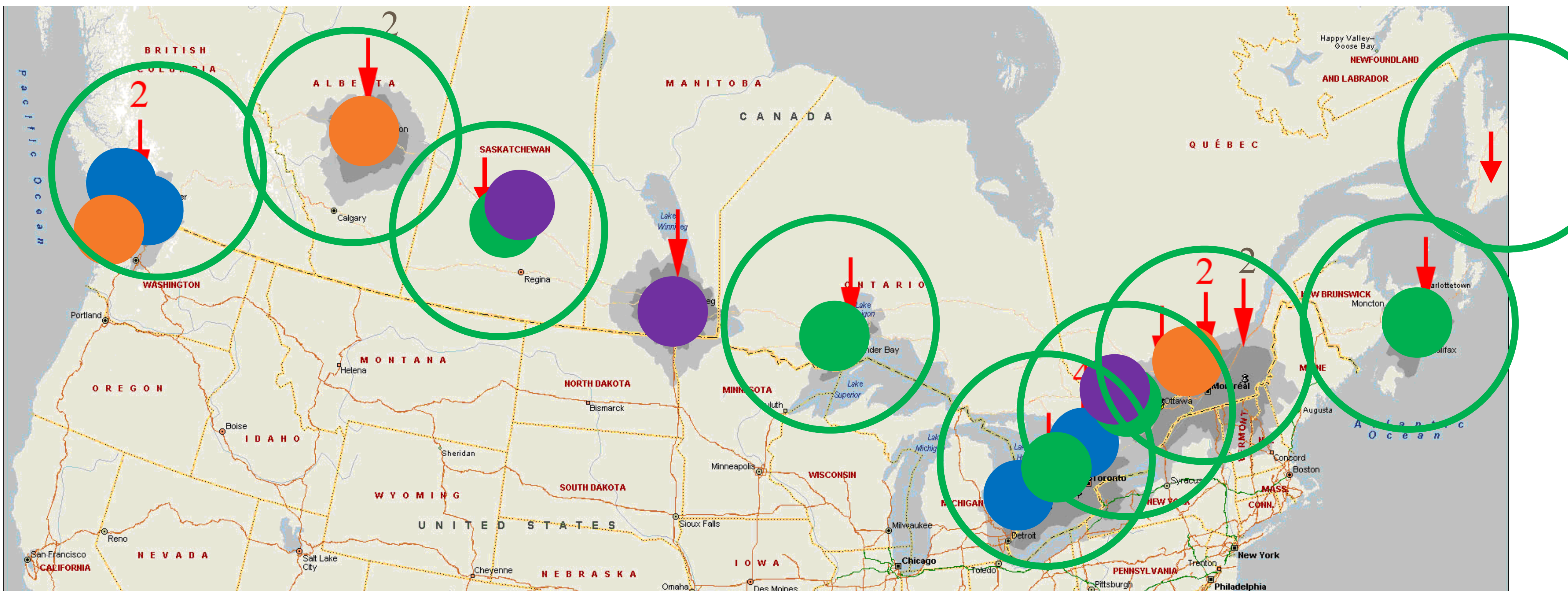


Estimated global cyclotron numbers by various manufacturers (with data from ACSI, GE, IBA and Siemens, Sumitomo data estimated)

Schaffer et al. Phys. Proc. in press (2014).

Decentralized ^{99m}Tc Production in Canada

- NRCan-funded ITAP* – 4 years (ending 2016), \$25M, 3 proponents
- TRIUMF consortium,
- ERC consortium,
- CLS/PIPE effort ($^{100}Mo(\gamma,n)^{99}Mo$)
- Future cyclotron-^{99m}Tc sites



* cont. of NRCan-funded NISP – 2 years (ending 2012), \$35M

Team Equipment/Capabilities

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

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

GE PETtrace
16 MeV, ≤100 μA
Upgraded to: 130 μA

2 x TR30
≤30 MeV, ≤1mA

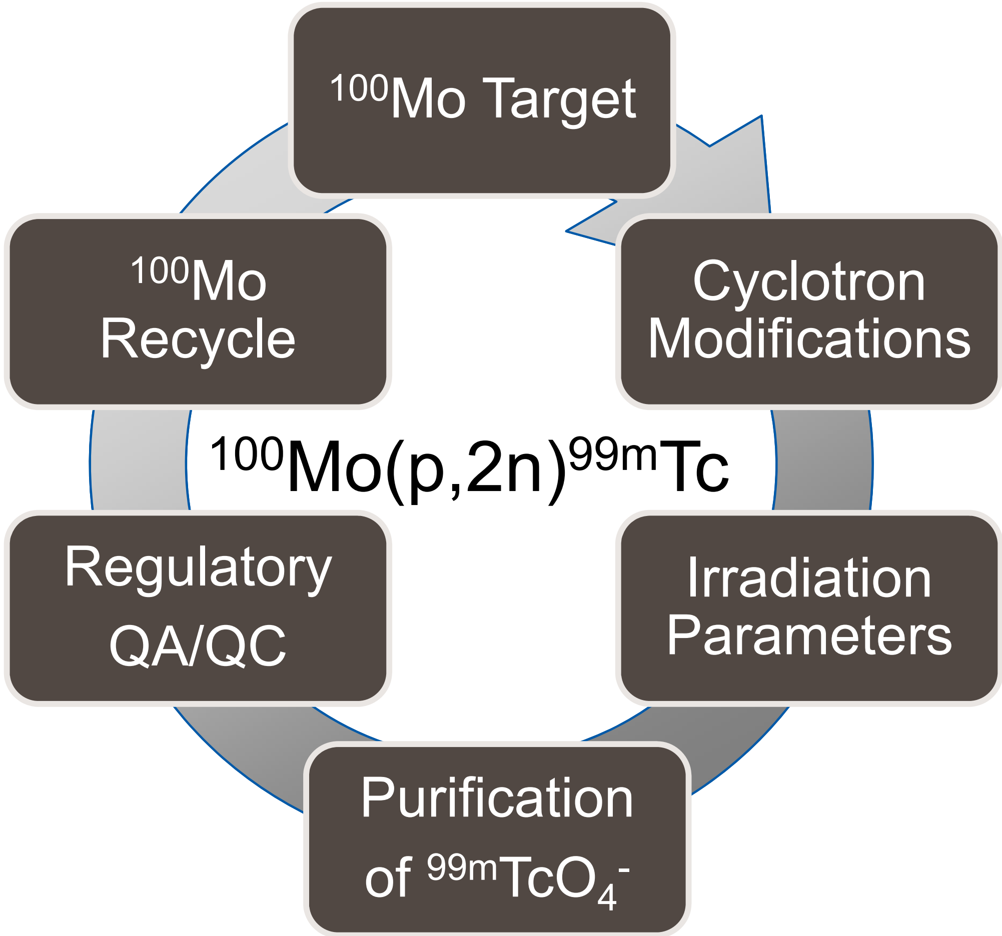
* Machines owned by Nordion, Inc., used under special agreement

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

- Goals
  - Demonstrate routine, reliable, commercial-scale production of ^{99m}Tc via $^{100}Mo(p,2n)$ at each site;
  - 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

Direct Production of ^{99m}Tc

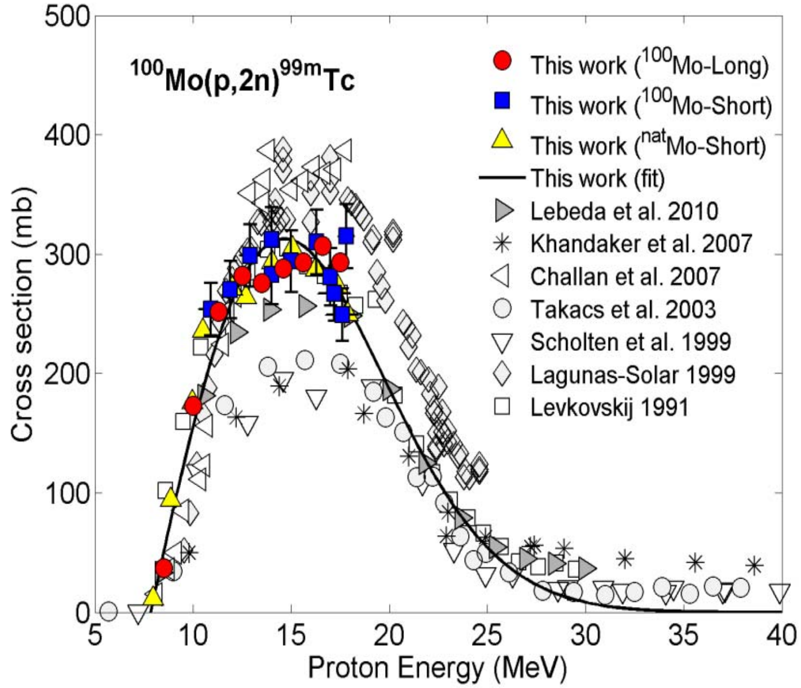


1971-2009 Focus: Development, Uncertainty in $^{100}Mo(p,2n)$

- First reported by Beaver and Hupf:
  - Foils, pressed powders at low current; natural and enriched Mo

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

- No motivation to pursue given avail. of $^{235}U(n,F)^{99}Mo$
- Progress limited to data refinement in subsequent years
  - Lagunas-Solar, Challan, Takács, Lebeda, Gagnon…



K. Gagnon et al., Nuc. Med. Biol. 2011, 38, 907-916

- Consider also contributions from (p,x) on ^{100}Mo and ^{9x}Mo, etc.

TRIUMF Consortium
Results Achieved to Date

- Production yields of ^{99m}Tc
  - GE **PETTrace** (16.5 MeV, 130 μA): **4.7 Ci** in 6 hours
  - ACSI **TR19** (18 MeV, 240 μA): **9.4 Ci** in 6 hours
  - ACSI **TR30** (24 MeV, 450 μA): **34** Ci in 6 hours
- Dual beam irradiation for concurrent ^{18}F production demonstrated successfully
- Targets for all cyclotrons withstand prolonged (6h) irradiations without degradation at stated beam current
- Purification efficiency: **93%**
- Molybdenum recycling efficiency: **>95%**

^{99m}Tc Production Targets for Multiple Cyclotrons

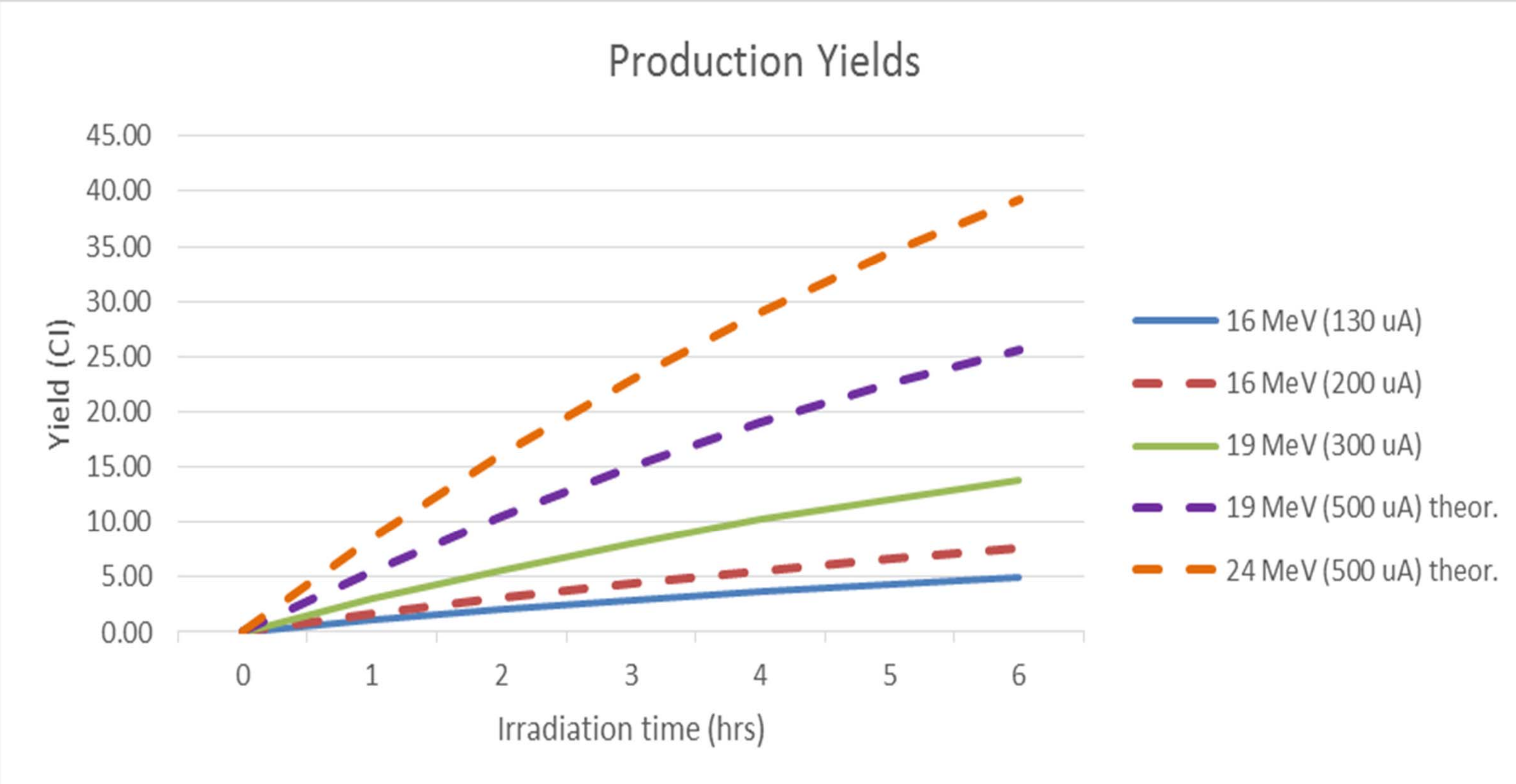
GE PETtrace
16.5 MeV, 130 μA
Theoretical 4.9 Ci (6h)
Achieved 4.7 Ci
Sat^n: 75.6 mCi/μA

TR19
18 MeV, 300 μA
Theoretical 15.4 Ci (6h)
Achieved 9.4 Ci (@ 240 μA)
Sat^n: 103 mCi/μA

TR30 (@24 MeV)
24 MeV, 500 μA
Theoretical 39 Ci (6h)
Achieved ~32 Ci (@ 450 μA)
Sat^n: TBD

Schaffer et al. Phys. Proc. in press (2015). Bénard et al., J. Nucl. Med. 2014, 55, 1017-1022

Yield Comparison: Energy, Current Considerations



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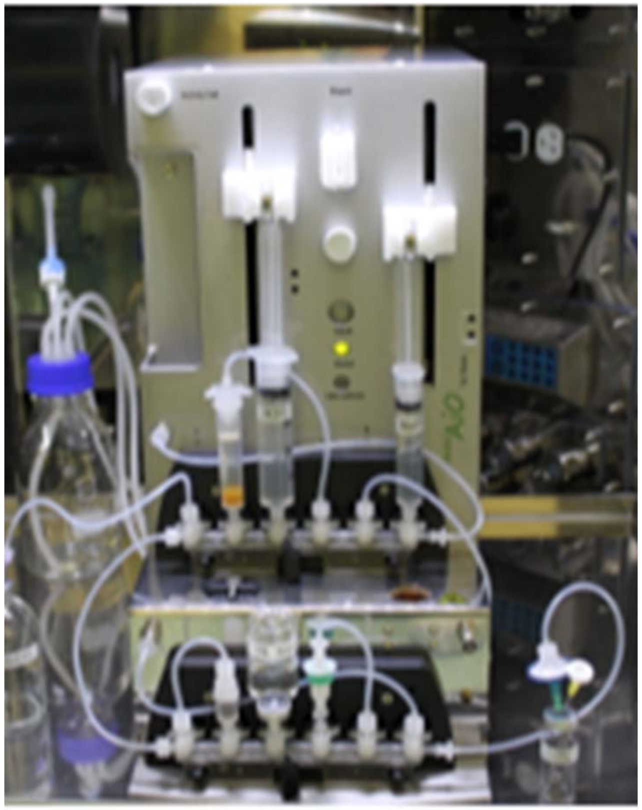
Automated Isotope Purification

Remote-operated separation system



- **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

Disposable fluid path for GMP

Inherent Resin Versatility: Vendor Agnostic

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

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

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

- GLP preclinical rodent data (complete)
- Finalize GMP production process (complete)
- Set acceptance for molybdenum enrichment and irradiation parameters (underway)
  - Shelf life, 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
- Fall 2014 – Clinical trial application (underway)
- June – Aug. 2015 – Collect clinical trial data
  - $Na^{99m}TcO_4$ - 60 patient trial
  - Recent guidance: look at two kit formulations
- Fall 2015 - NDS submission

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

- 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 FCR must apply
- Availability: A viable alternative/backup needs to be used regularly

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Regulatory Approach

- Path to CTA, NDS in Canada
  - Despite acknowledgement of GPP and CPP from toxicology standpoint, ANDS not possible due to lack of reference product
  - Downward pressure on patient dose limits
  - Supported CPP monograph statements regarding kit useage with appropriate data
  - Request by Health Canada for pre-CTA meetings
  - 3 meetings to date:
    - Approval of pre-clinical study approach (rodent) for CTA and commercial registration
    - Approval of clinical trial design – 60 patients
      - will examine consistency across sites
    - Agreement that toxicology study not necessary for CTA or commercial registration

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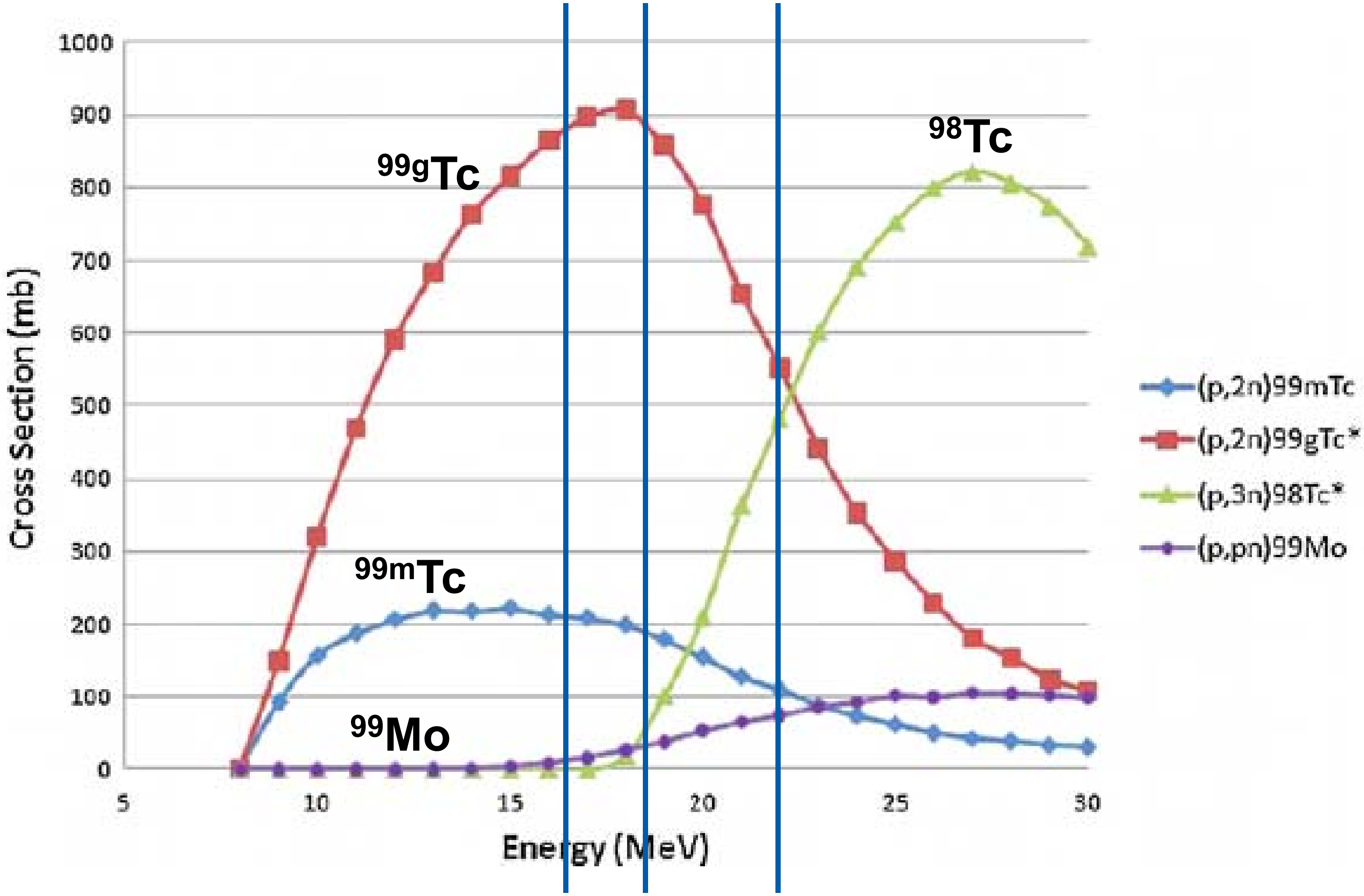
Consistent Products/Yields

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



A. Celler, X. Hou, F. Bénard, T. Ruth, Phys. Med. Biol. 2011, 56, 5469
K Gagnon et al. Nuc. Med. Biol. 2011, 38, 907

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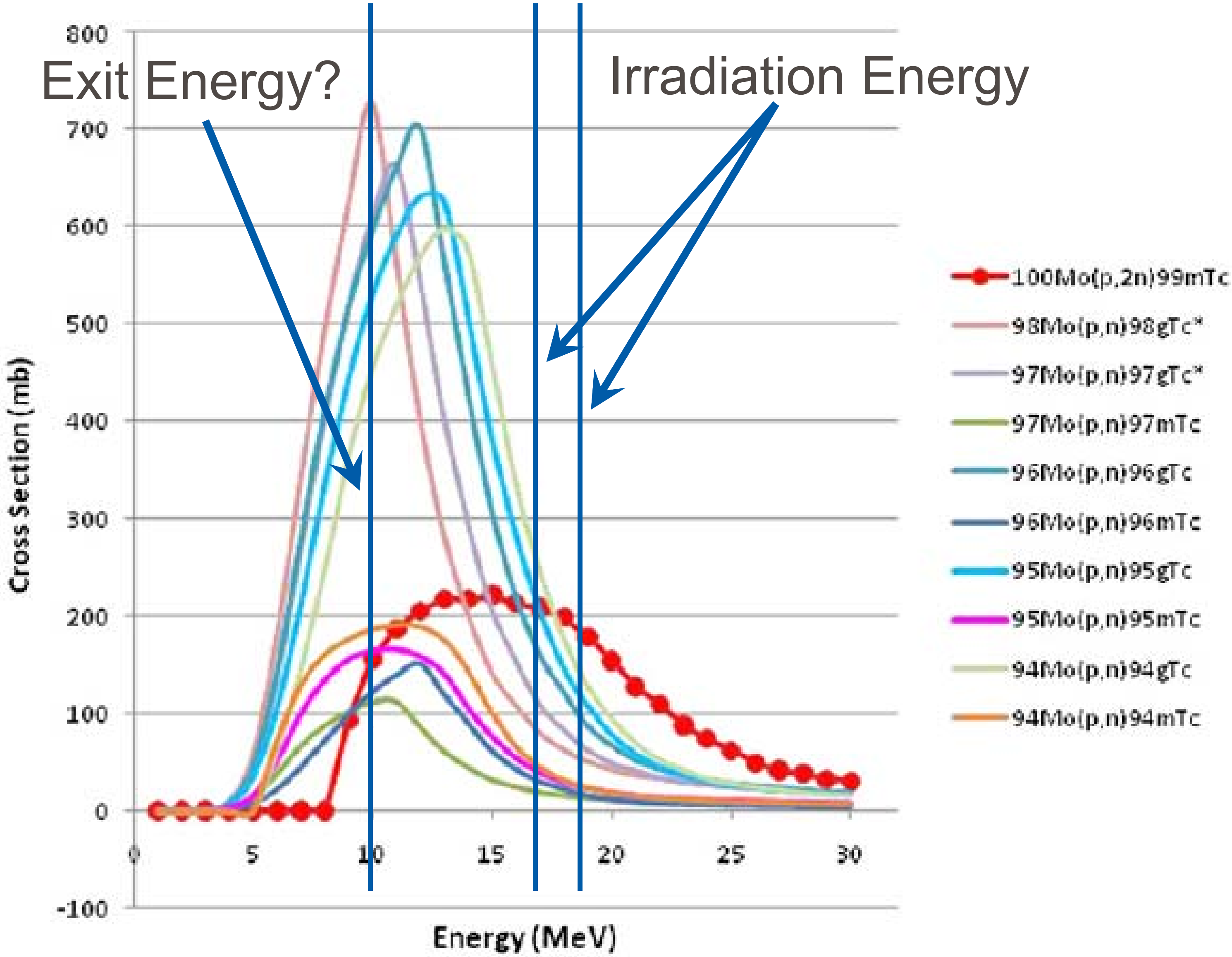
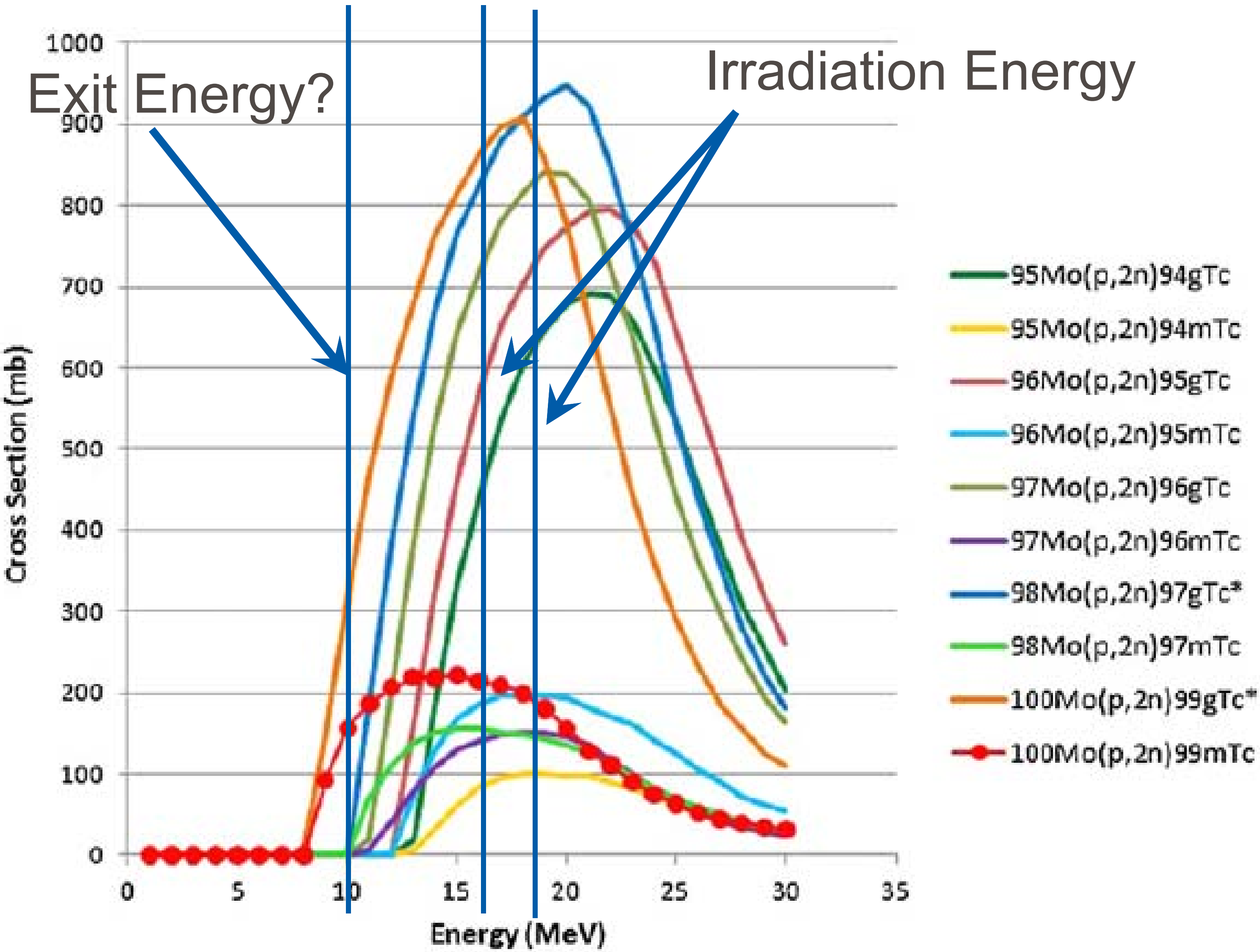
Side Reactions: $^{94-97}Mo(p,n)$



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

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



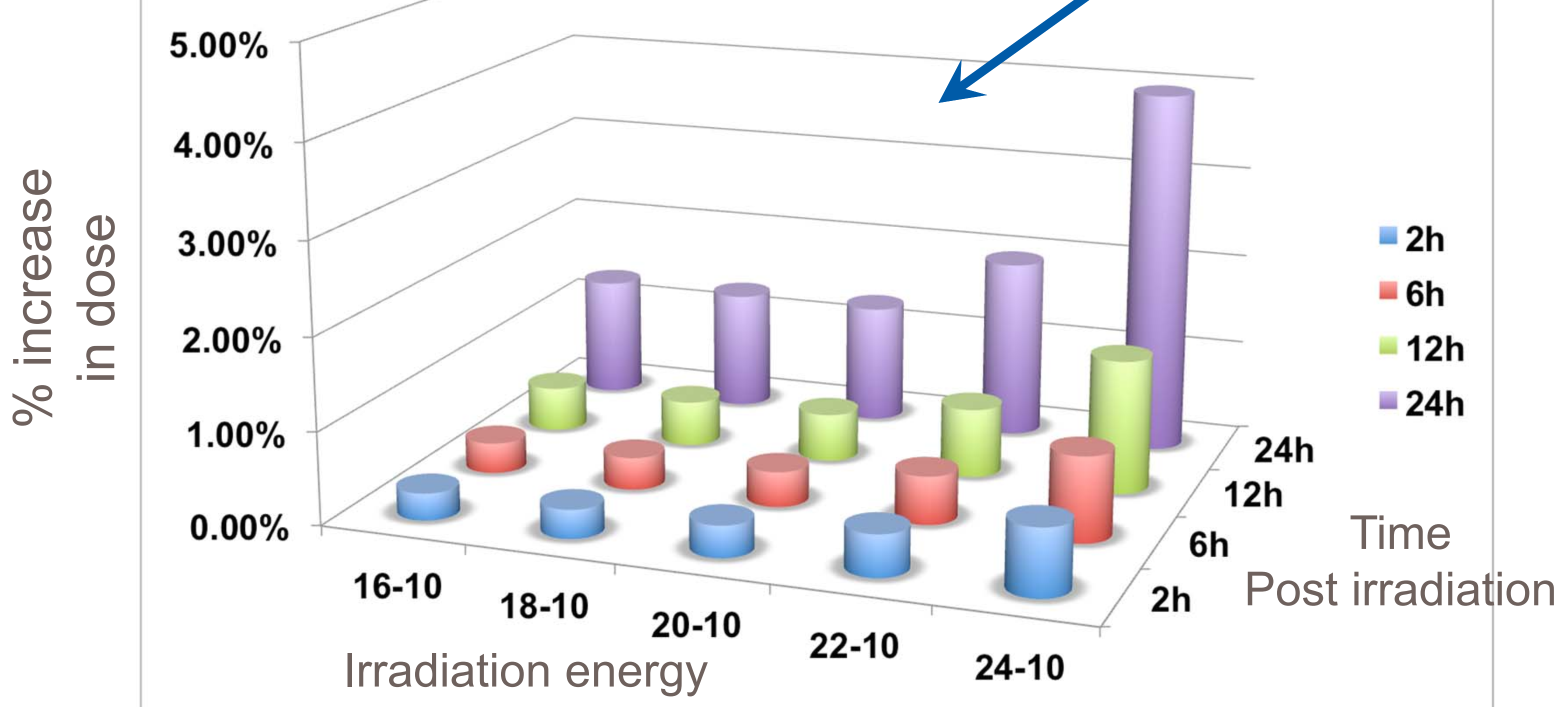
Optimal energy range: <20 MeV or <22 MeV?

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

Target Enrichment and issues with Mo isotopic contamination

Isotope	Enriched A	Enriched B	Enriched C	Enriched D	Natural
^{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**

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



Impurities and Effective Whole-Body Dose

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Measured radionuclidic content at EOB for ^{100}Mo after 1.5 hr, 100μA 18-10 MeV irradiation

final product		waste stream	
radionuclide	% activity	radionuclide	% activity
Tc-99m	99.940(4)	Mo-99	0.78(42)
Tc-97m	0.003(4)	Nb-96	0.06(3)
Tc-96g	0.002(1)	Nb-97	4.0(2.9)
Tc-95m	<0.0001		
Tc95g	0.009(5)		
Tc-94m	0.044(12)		
Tc-94g	0.012(4)		
Tc-93g	0.007(4)		

- Radionuclidic purity: HPGe gamma spectrometer
- 3, 24, 145 and >720 hrs EOB
- Waste vials were taken at 4-6 hours after EOB

Tc Isotope	Estimated effective dose mSv/MBq
^{93m}Tc	0.00873
^{93g}Tc	0.00782
^{94m}Tc	0.051
^{94g}Tc	0.0966
^{95m}Tc	0.187
^{95g}Tc	0.0777
^{96m}Tc	0.00179
^{96g}Tc	0.446
^{97m}Tc	0.0145
^{99m}Tc	0.00925

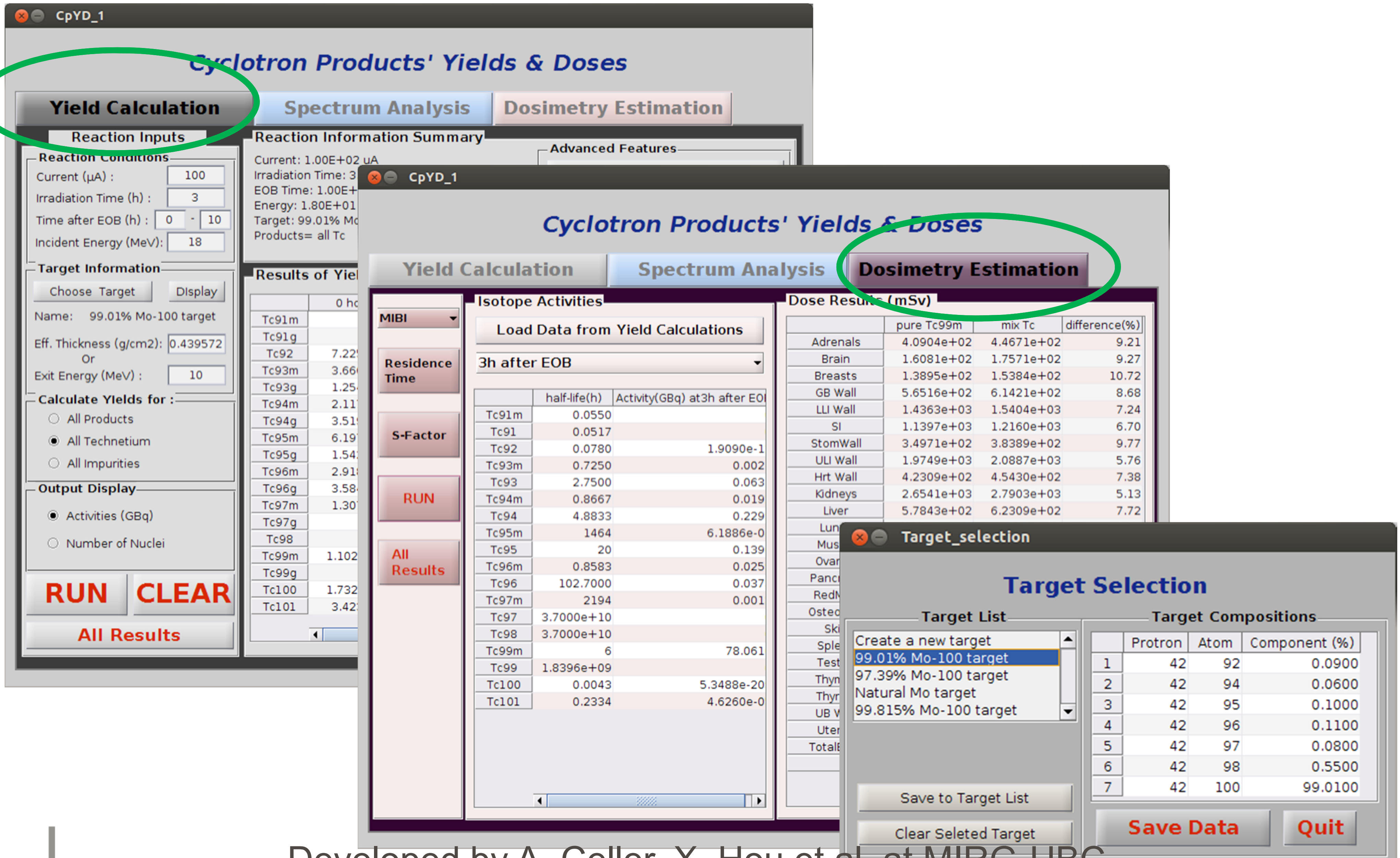
*Calculated with OLINDA/EXM for a 70-kg adult patient using bio-distribution data from ICRP publication 53.

Target /Cyclotron Consistency

- Method for quantifying relationships between random variations in production parameters, including ^{100}Mo target thicknesses and proton beam currents, and reproducibility of absolute ^{99m}Tc yields
- Achieving less than 20% variability in ^{99m}Tc yields will require highly-reproducible target thicknesses and cyclotron performance.
- achieving service rates of 84.0%, 97.5%, and 99.9% with 20% variations in target thicknesses requires producing on average 1.2, 1.5, and 1.9 times the minimum daily activity requirement

Tanguay et al. Phys. Med. Biol 2015, in press

Graphical User Interface (GUI) for Yield and Dose Projections



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

Economics

- Assessments of 16, 19 and 24 MeV operations
- Activitiy-based costing model with 3 phases:
  i) plate manufacturing and Mo-100 recycling
  ii) irradiation, dissolution and purification
  iii) target plate and Tc-99m distribution + indirect
- Activities: Materials, salaries/benefits, power/utilities, equipment, waste, process failure and training.
- Indirect costs: wages, admin(sales, general), regulatory and capital.
- Amortization for most lab equipment was 3 to 7 years (usually 7), except cyclotron (25 years) and building (40 years)
- Production rate: 2.8 GBq/uA at saturation
- Injected doses: 20 mCi;
- ^{100}Mo: $0.50/mg
- Activity losses: 65%, average wait time of 9hrs between EOB and injection

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Acknowledgements

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Canada

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

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a place of mind UBC

TRIUMF: Alberta | British Columbia | Calgary Carleton | Guelph | Manitoba | McMaster Montréal | Northern British Columbia | Queen's Regina | Saint Mary's | Simon Fraser | Toronto Victoria | Winnipeg | York

Thank you!
Merci

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NSERC CRSNG

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

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