Implementation of Cyclotron-Produced Tc-99m

P. Schaffer[1,2]

1) The ITAP Consortium, Associate Laboratory Director, TRIUMF
2) ARTMS Products, Inc. CEO

Sept. 13th, 2017

TRIUMF-led Consortium

Natural Resources Canada | Ressources naturelles Canada

NSERC CRSNG

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

- Funding from federal government to develop alternate supply methods for medical isotopes
- TRIUMF joined with four other institutions to implement direct production of ^{99m}Tc
  - British Columbia Cancer Agency
  - Centre for Probe Development and Commercialization
  - Lawson Health Research Institute

2009 to Present: Project Mandate

^{100}Mo Target	Cyclotron Modification	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 cyclotron OEMs;
- Obtain regulatory approval for clinical use in humans;
- Develop and execute a business plan;
- Disseminate and 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

Global OEMs: Different Machines, Different Capabilities

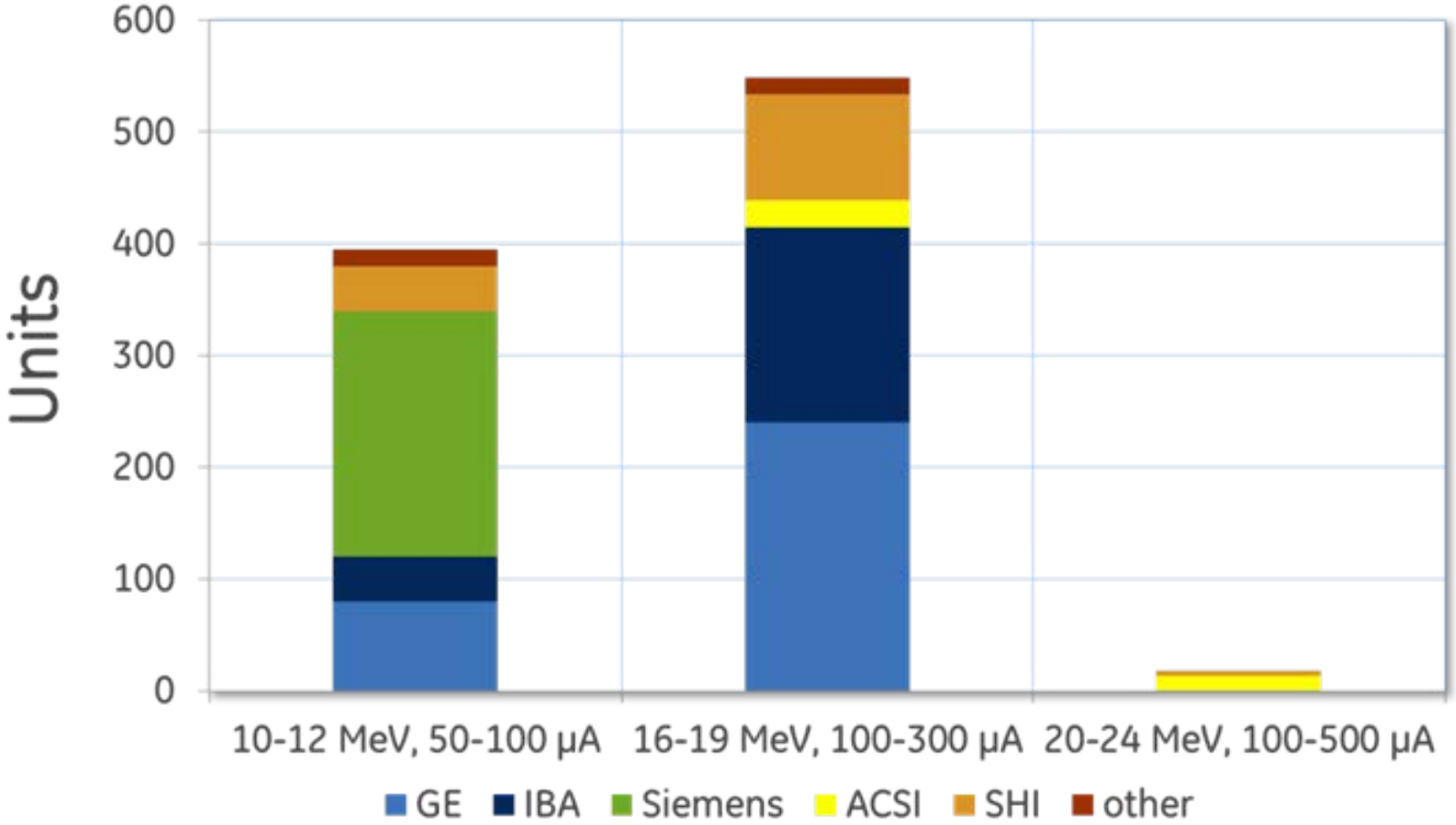
TRIUMF

LAWSON HEALTH RESEARCH INSTITUTE

cpdc

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

Cyclotrons by the Numbers



P Schaffer, F. Benard, A. Berstein et al. Phys Proc. 2015, 66, 383.

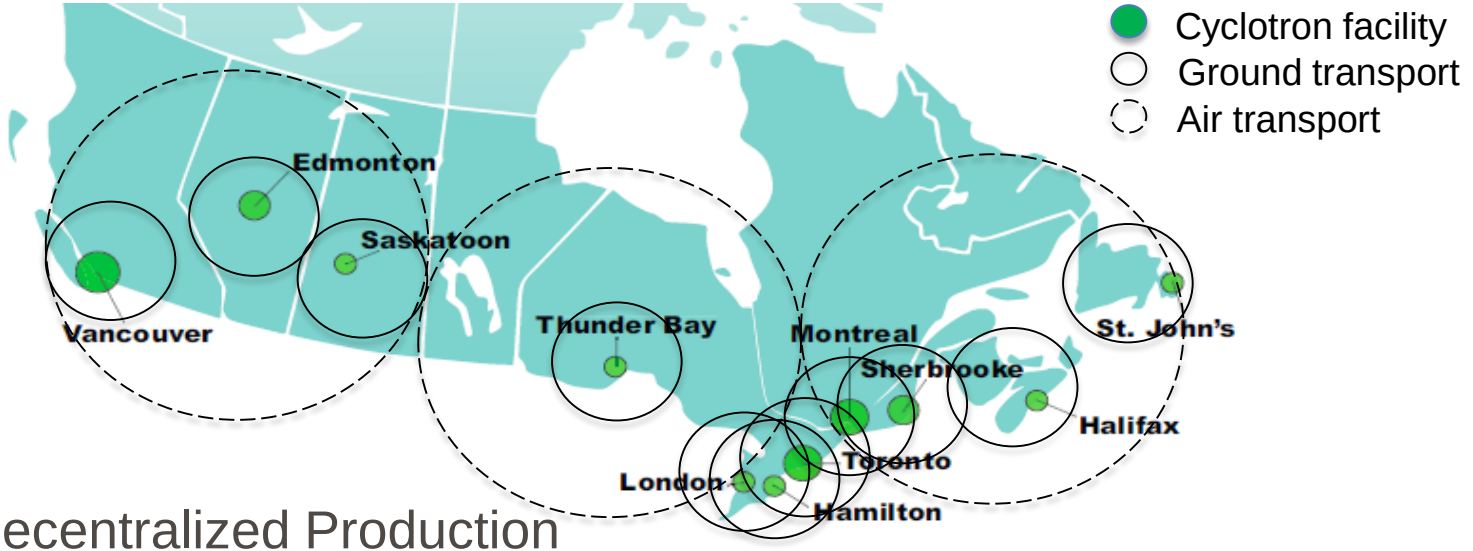
Our Approach

Cyclotron + ARTMS Technology

Radiopharmacy

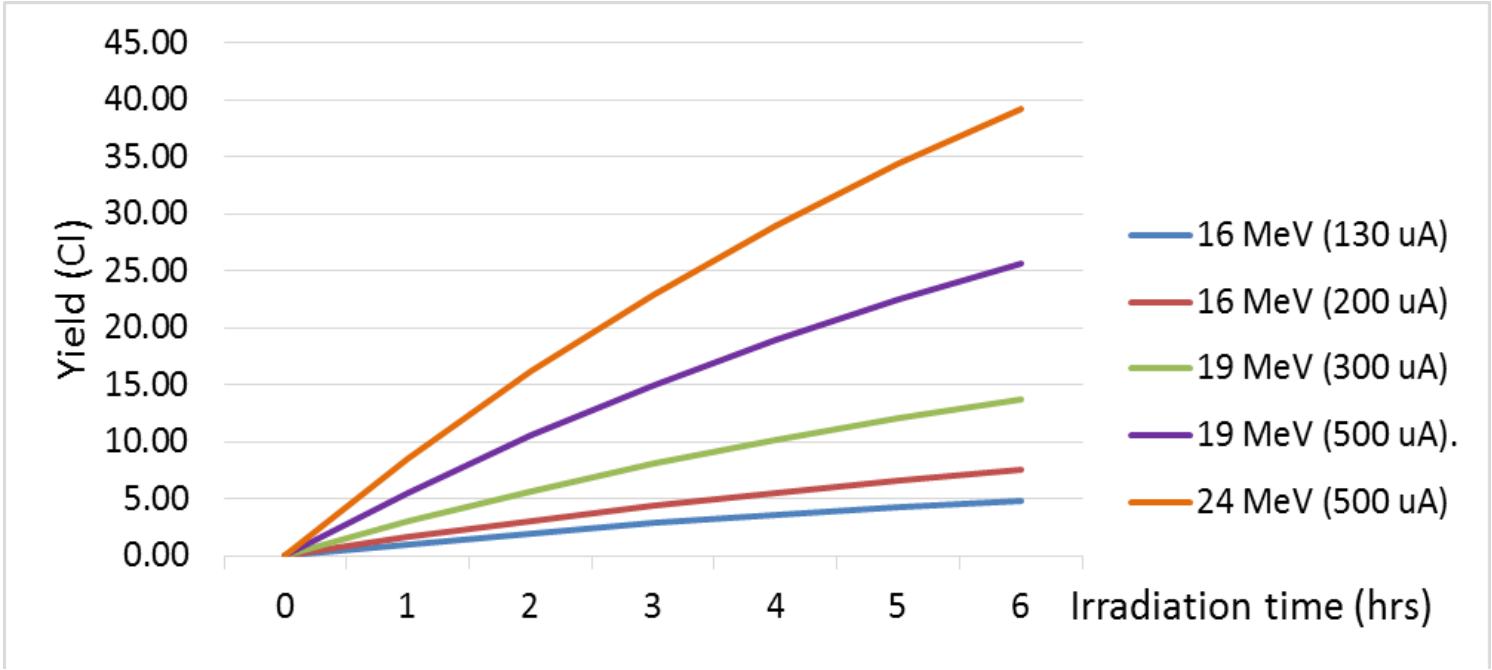
Clinic

Ubiquitous Distribution: Canadian Perspective



- Decentralized Production
  - ^{99m}Tc locally produced, locally used, competitively priced: CONTROL
  - Redundant supply to avoid widespread shortages
  - Fits with existing radiopharmacy distribution model
  - Complementary to:
    - other medical isotopes produced by cyclotrons (^{18}F)
    - other sources of ^{99m}Tc

Real and Projected Yields of ^{99m}Tc



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

TR19
18 MeV, 300 µA
Theoretical 15.4 Ci (6h)
Achieved 15.0 Ci (@ 300 µA)
Expected Sat^{n}: 103 mCi/µA

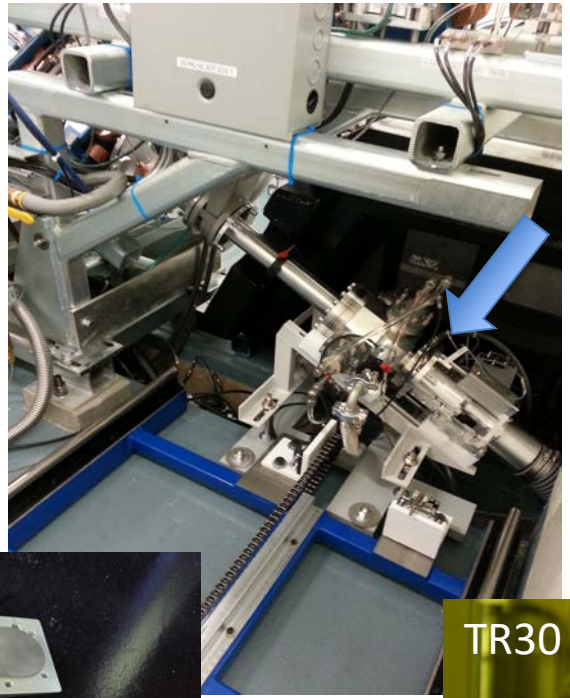
TR30 (@24 MeV)
24 MeV, 500 µA
Theoretical 39 Ci (6h)
Achieved ~32 Ci (@ 450 µA)
Expected Sat^{n}: 156.8 mCi/µA

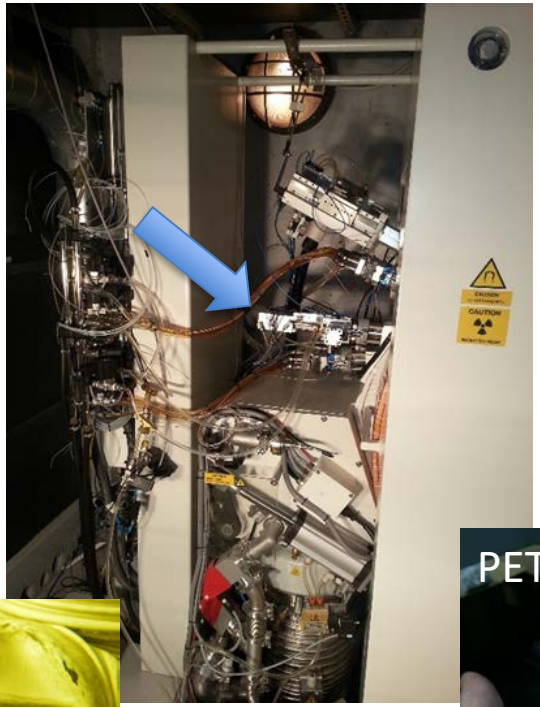
Capacity

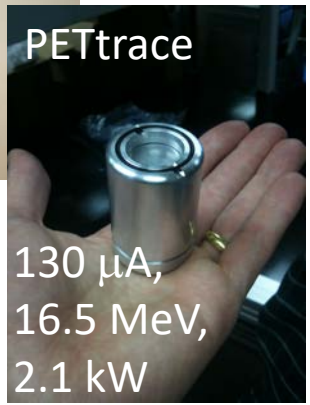
- Assumptions:
  - 1 × 6 hr run/day, 5 days/wk, 48 wks/yr
  - 555 MBq pertechnetate dose, require 4x dose (due to decay)
  - 3% of population require a scan each year

Machine	Pertechnetate Released Per run (GBq)	Annual Production (GBq)	# Available Today	Possible Annual Production (GBq)	Canadian Annual Demand (GBq)
TR24	874	210,000	4	840,000	2,331,000
TR19	334	80,000	3	240,000	
PETtrace	112	27,000	7	188,000	
Cyclone18	167	40,000	3	120,000	
Our Consortium only		134,000	Total Potential	1,388,000	

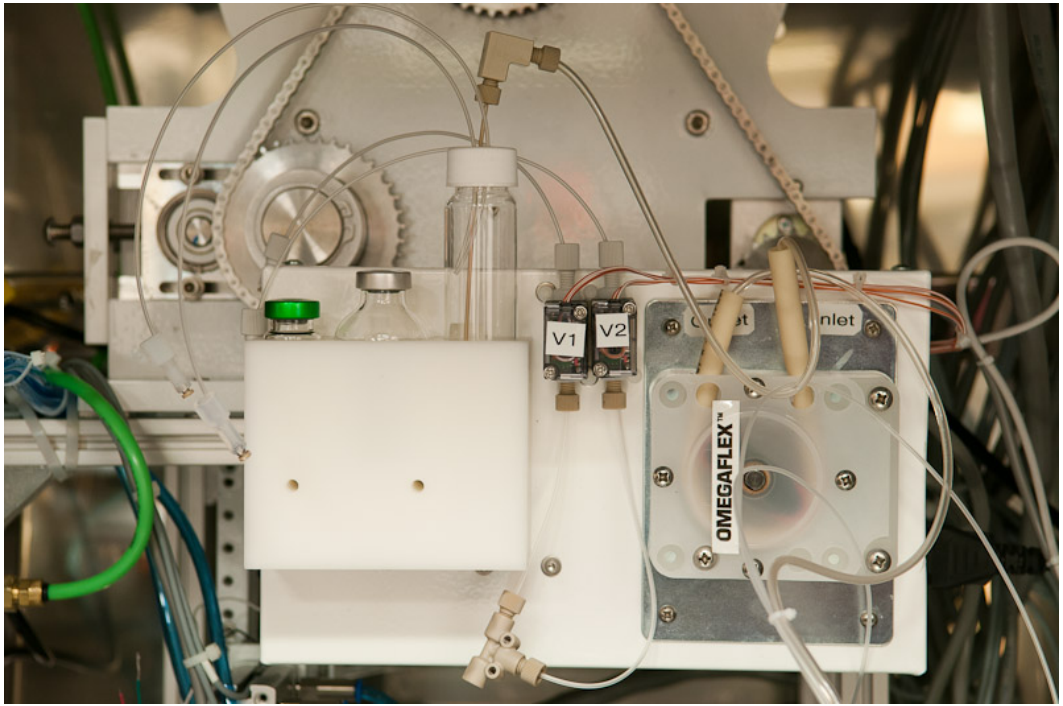
Available of New and Existing Hardware: Cyclotron Retrofit







Purification of ^{99m}Tc



- **Target Dissolution**
  - Target transfers pneumatically for dissolution
  - 30% H_2O_2 circulated with peristaltic pump
  - 5M NaOH added and circulated
  - 45 minutes
  - Transferred to processing module for MoO_4^{2-} / TcO_4^- separation

Morley et al. Nuc. Med. Biol. 2012, 551-559
Bénard et al., J. Nucl. Med. 2014, 55, 1017-1022

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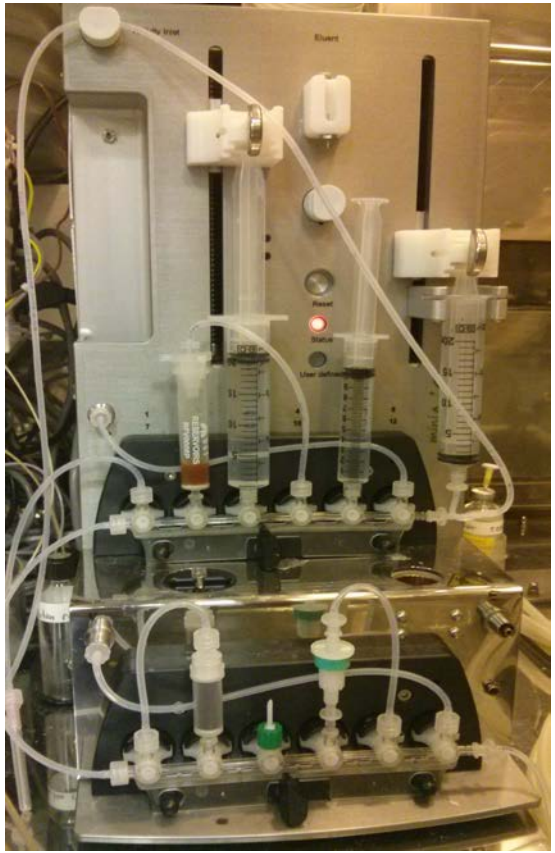

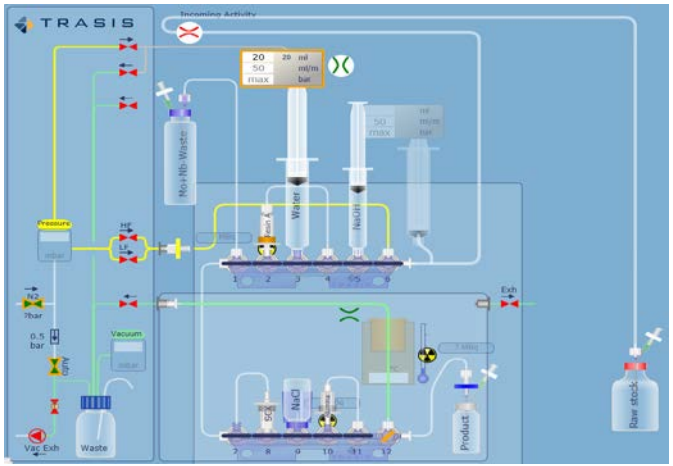

Purification:

- Solid-phase extraction
- Process Time: ~45 min.
- Efficiency: 92.7 ± 1.1%
- Final Product: $Na[^{99m}TcO_4]$
- GMP compliant

Morley et al. Nuc. Med. Biol. 2012, 551-559
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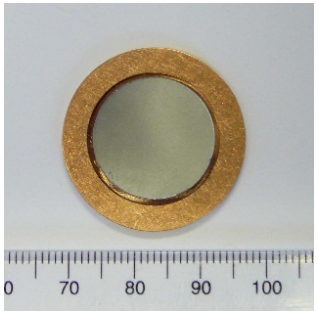
^{100}Mo Target Manufacturing

Electrophoretic deposition

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

Press-Sinter-Braze



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

Goals in Target Manufacturing Process and Final Target Design:

- Maximize ^{99m}Tc production, minimize impurities through ^{100}Mo purity, target thickness, irradiation energy/time
- Reduce density, balance thermal conductivity

Assessing Purity, Correlating Dose

^{99m}Tc purity relies on a non-linear interplay between:

- Irradiation energy and duration (max <24 MeV)
- ^{100}Mo isotopic purity (reduce ^{92,94,}**^{95,96}**^{,97}Mo)
- Contaminants in ^{100}Mo material (i.e. W)
- Target thickness & uniformity (H^+ exit energy)
- Purification process performance (breakthrough)

Findings to date:

- 'worst case scenario' irradiations (high energy, long duration) – radionuclidic purity >99.9%
- Average patient dose increase (from validation runs, relative to pure ^{99m}Tc) was 0.32 ± 0.07 % (calc'd: 1.7%)

Recycling method determined, recycled targets not yet implemented. *Recycling ^{100}Mo for direct production of ^{99m}Tc on medical cyclotrons.* Kumlin et al. Physics Proceedia 2017, in press.

Validation Batch Analysis

Process Validation Batch No.		1509011	1509025	1510005
Batch Size (EOS) (GBq)		35.3	51.7	37.0
Final Product Amount at EOB (GBq)		41.2	61.1	43.5
Estimated Yield (%) (decay-corrected)		100	135	89
Membrane filter integrity (≥ 50 psi)		62	61	65
Specification	**Acceptance Criteria**	**Results**		
Visual Appearance	Clear, colorless solution, free from visible particulates	Conforms	Conforms	Conforms
pH	4.5 to 7.5	7.5	7.0	7.5
Radionuclidic purity	Isotopes other than ^{99m}Tc contribute an emission rate < 6,000 emissions/ sec/MBq of ^{99m}Tc	34	52	53
Radionuclidic identity	Half-life between 5.72 and 6.32 hours	5.81	5.84	5.83
Radiochemical purity	≥ 95%	100	100	100
Radiochemical identity	Rf = 0.8 – 1.0	1.0	1.0	1.0
Aluminum content	≤ 10 µg/mL of solution (10 ppm)	<10	<10	<10
Hydrogen peroxide content	≤ 50 mg/L of solution (50 ppm)	0	0	0
Molybdenum content	≤ 30 µg/mL of solution (30 ppm)	0	0	0
Radioactivity concentration	(≤ 27.8 GBq/mL)	1.83	2.58	1.84
Bacterial endotoxins[2]	≤ 17.5 EU/mL	<2.5	<2.5	<2.5
Sterility[2]	No growth	No growth	No growth	No growth

J Tanguay et al. PhysMedBiol2015, 60, 8229

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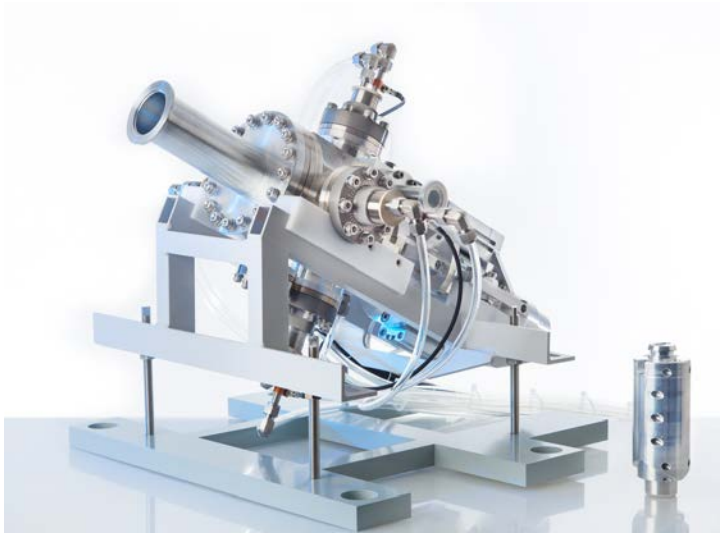
Regulatory Approvals

- Issue: Mo/Tc generator approved in Canada as a medical device
- ^{99m}Tc Pertechnetate requires Market Authorization
  - NDS submission required
  - Health Canada has been quite collaborative in allowing for reduced NDS requirements, but did not agree to an ANDS
  - Small clinical trial to demonstrate same performance as generator derived pertechnetate
  - Quality data for 3 different radiopharmaceutical kit formulations (cationic, anionic, neutral)
- Once submitted, team will request registry trial in the event of an isotope shortage (60 day approval time)

^{99m}Tc Path Forward: Clinic and Commercialization

Project Status:

- Recall: solutions developed for GE (16 MeV), ACSI 19 and 24 MeV machines
- **Clinical Trial Completed!**
  - 30/30 bone patients scanned (Vancouver)
  - 30/30 thyroid patients scanned (Vancouver, London, Hamilton)
  - ‘kit study’ underway
- NDS submission (bone + kit) Q4 2017
- Rollout into UK – Q2-3 2018 (TR24 systems)
- 1 order for GE hardware system completed
  - Additional orders being filled
- Discussions with Province of BC – ongoing



Moving Forward: Next Stage of Commercialization

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An agency of the Provincial Health Services Authority

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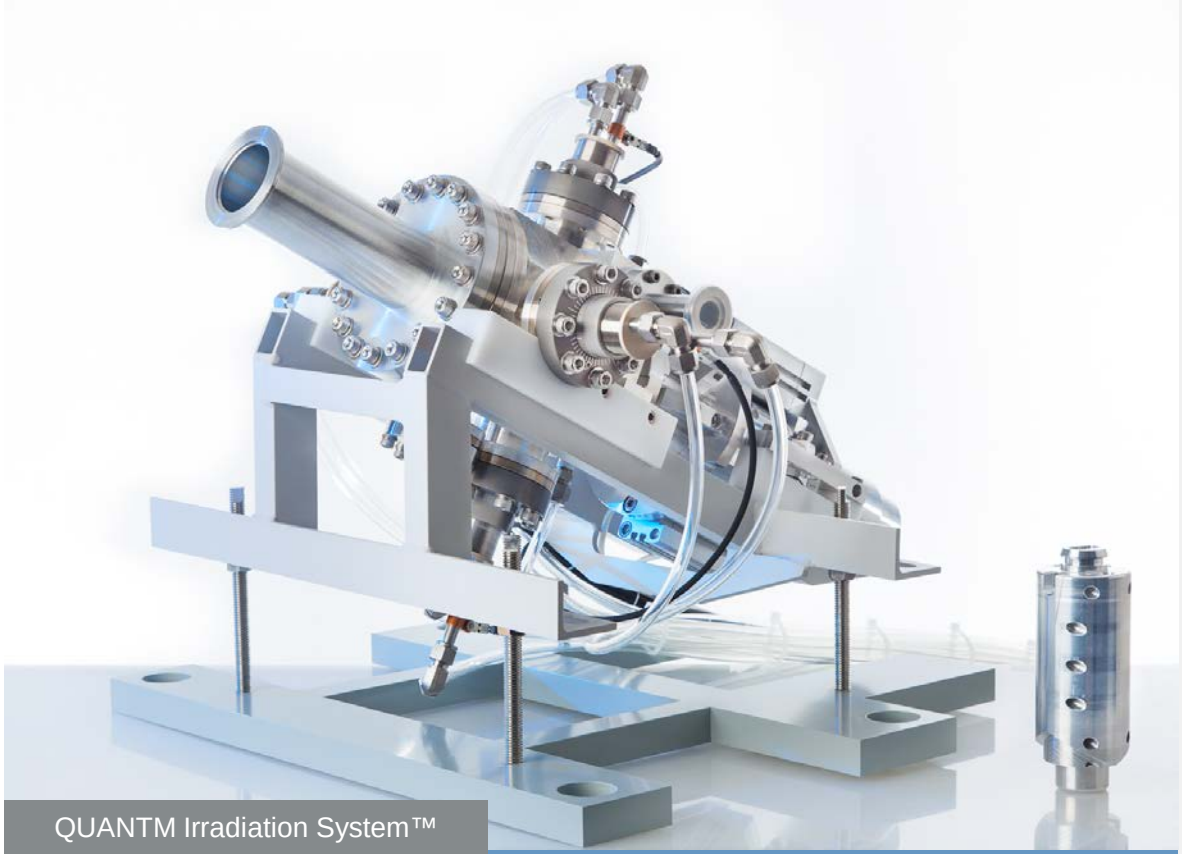
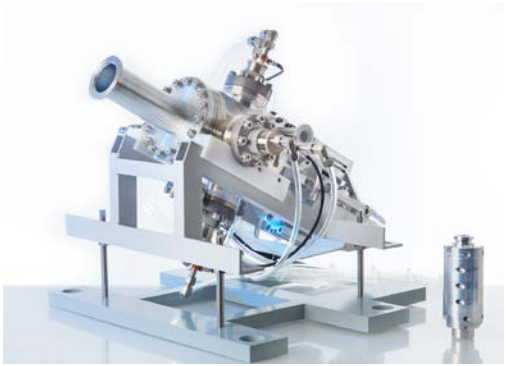


QUANTM Irradiation System™

artms

- ARTMS Products, Inc. tasked with translation of a game-changing technology that:
  - Leverages $40M in federal funding, protected by multiple patent applications
  - Has attracted initial global commercial relationships
  - Enables multiple market opportunities (other high value isotopes) with revenue potential
  - With founding institutional team, offers a unique competitive advantage

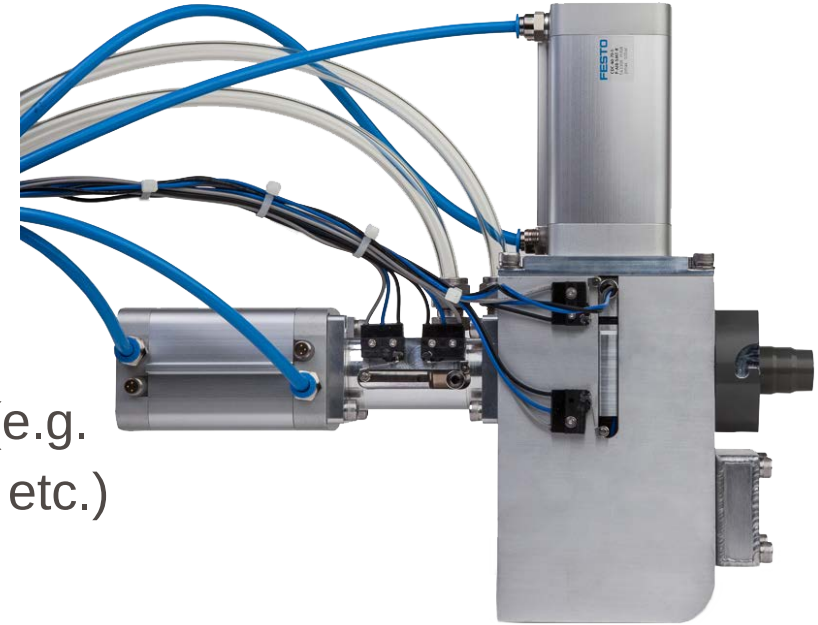


QUANTM Irradiation System™

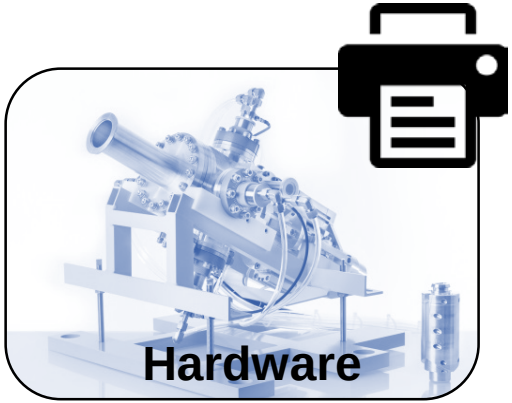
- ARTMS target station installed on cyclotron (retrofit or new)
  - Shuttles and houses the ARTMS target plate for irradiation
- IP foundation (target plate)
  - Unique, proven design and manufacturing techniques
- Established target processing method
  - Novel purification and formulation process
- Environmentally friendly
  - No long-lived, highly radioactive waste
  - Recycling of ^{100}Mo material established

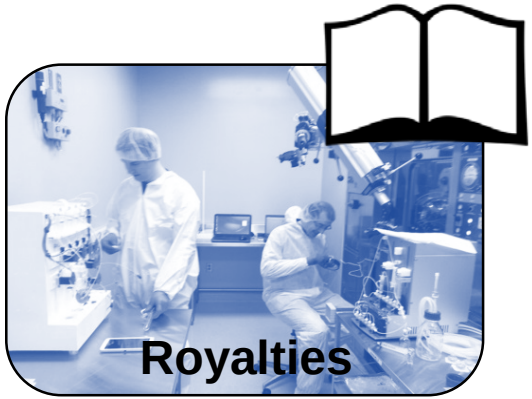
Value Proposition

- Reliable, ’green’ supply of medical isotopes
  - Avoids single point of failure supply chain
- Supply independence and logistical compatibility
  - Local control, responsive to market needs
  - Well-suited for geographically concentrated patient populations
- Multiple revenue sources enabled by multiple isotope production capabilities (e.g. ^{68}Ga, ^{64}Cu, ^{89}Zr, ^{44}Sc, ^{55}Co, ^{119}Sb, ^{165}Er, etc.)



ARTMS Business Model





- The QUANTM Irradiation System™ is a high-power solid target solution for multiple cyclotron brands and models
  - Similar production and distribution logistics to F-18
- IP foundation: Unique, proven design and manufacturing techniques
- Established target processing methods
  - Novel purification and formulation process
- ^{89}Zr, ^{68}Ga and ^{64}Cu processes under development

Key Achievements

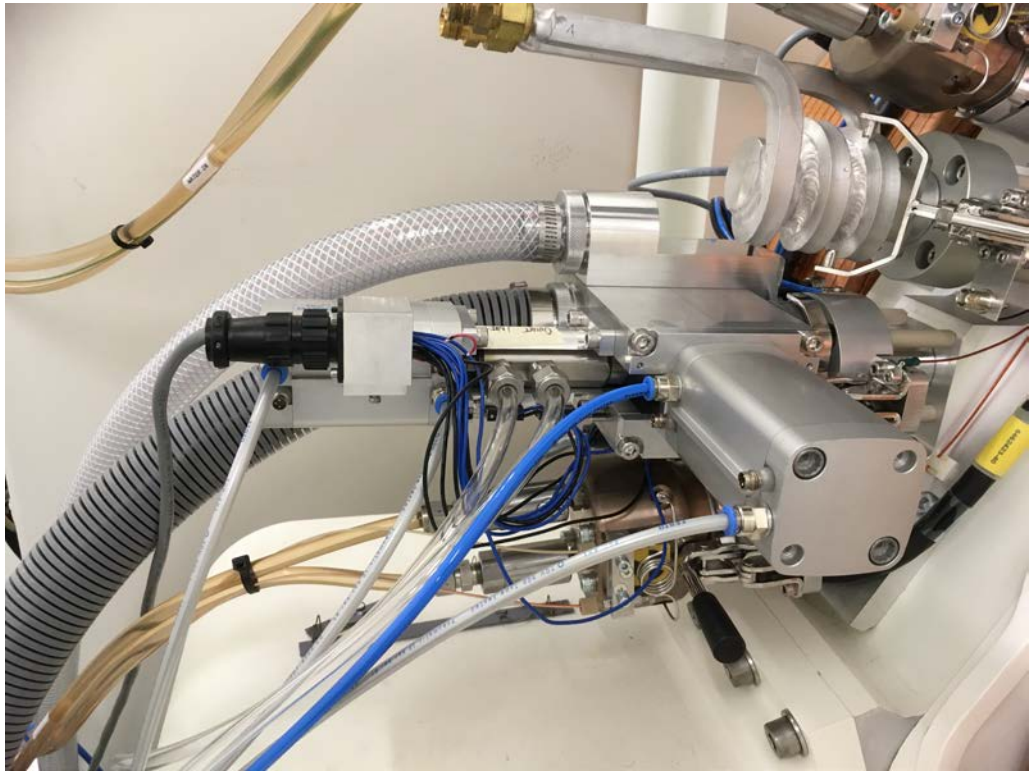
- Filing and completion of multi-centre clinical trial in two indications
- Negotiation and execution of first OEM agreement for supply of systems
- Multiple patent filings and responses to office actions
- Validation through execution of first international technology license (UK)
- Closing first seed investment
- Multiple term sheets received for Series A financing

First Installation

- ARTMS-GE collaboration
- Cu-64 production from Ni-64
- ARTMS Responsibilities
  - Solid Target Station and Transfer System
  - Dissolution System
  - Dissolution and Separation Processes
  - Electroplating Apparatus
- GE Responsibilities
  - Comecer Hotcell
  - GE FASTLab2 ASU
  - Beam Degrader 16.5-13 MeV

1 week from install to isotope production

First Installation



Award-Winning Technology

2017 BCTech TIA Most Promising Pre-Commercial Technology

LEGISLATIVE ASSEMBLY
of BRITISH COLUMBIA

John Horgan, MLA
109-501 Belleville St.
Victoria, BC
V8V 1X4

June 28th, 2017

Paul Schaffer
ARTMS Products
4004 Wesbrook Mall
Vancouver, BC V6T 2A3

Dear Paul:

On behalf of the New Democrat Caucus, I would like to extend my sincere congratulations for receiving the award for Most Promising Pre-Commercial Technology at the 2017 Technology Impact Awards.

My colleague and MLA for Vancouver-Fairview, George Heyman, had the pleasure of attending the awards ceremony in Vancouver on my behalf. I was intrigued to hear about the evening and the many innovations and talented entrepreneurs in our province's dynamic technology sector.

We value the importance of your work, and we are committed to growing BC's tech sector around the province. Our economy is shifting, and we believe that recent and continued growth across all of the facets of the technology sector will help build a better BC for everyone.

We look forward to working closely together to solidify British Columbia's position as a global leader in technology and innovation.

Once again, thank you for your work and congratulations on your achievement and recognition by your peers.

Sincerely,

John Horgan
Premier-designate

Economics

Because people always ask…

- Costs associated with cyclotron-produced pertechnetate:
  - Extensively modeled by ARTMS founding institutions
  - Independently verified by UK partner
- Different machines have different production capabilities
- General rule(s) of thumb:
  - 16.5 MeV – sufficient for catchment of ~1M ppl
  - 19 MeV – sufficient for catchment of 2 to 2.5M ppl
  - 24 MeV – sufficient for catchment of ~4.5M ppl
- Different regions have different distribution logistics
- FCR cost/dose is lower than current price @ 24 MeV, higher for 16.5 MeV

Acknowledgements

- **The Team:**

  PIs: F. Bénard, T. Ruth, A. Celler, J. Valliant, M. Kovacs,

  Ken Buckley, Vicky Hanemaayer, Brian Hook, Laurel Stothers
  Stuart McDiarmid, Stefan Zeisler, Frank Prato, Joe McCann
  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,
  Costas Economou, Joel Kumlin, Jason McEwan

- **TRIUMF and BCCA machine shops**
- **Finances/Admin**
  - Mike Cross, Travis Besanger, Henry Chen, Francis Pau, Jenny Song, Steven Foster, Frank Gleeson, James Schlosser, Jim Hanlon, Ann Fong, Neil McLean, Kevin McDuffie, Niki Martin, Karen Young, Anthony Lam

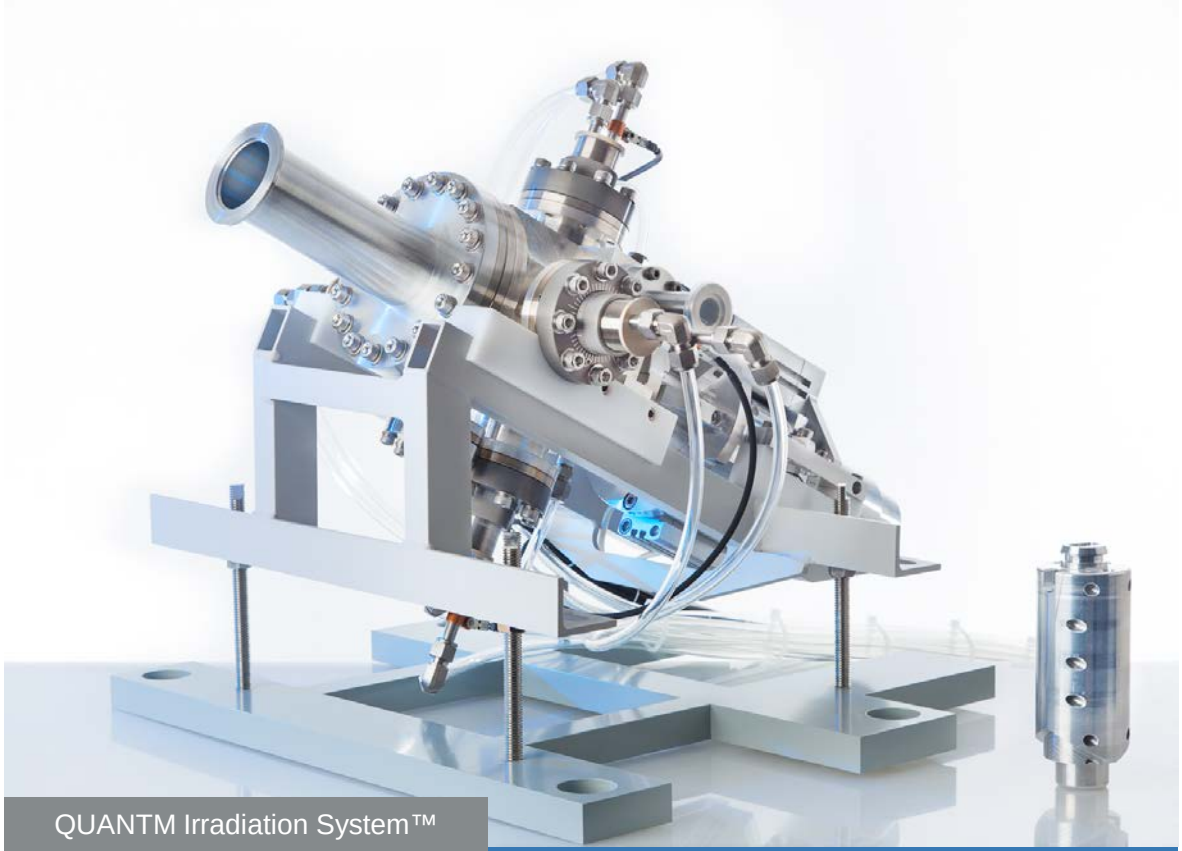
BC Cancer Agency
CARE & RESEARCH
An agency of the Provincial Health Services Authority

LAWSON HEALTH RESEARCH INSTITUTE

cpdc

a place of mind
UBC

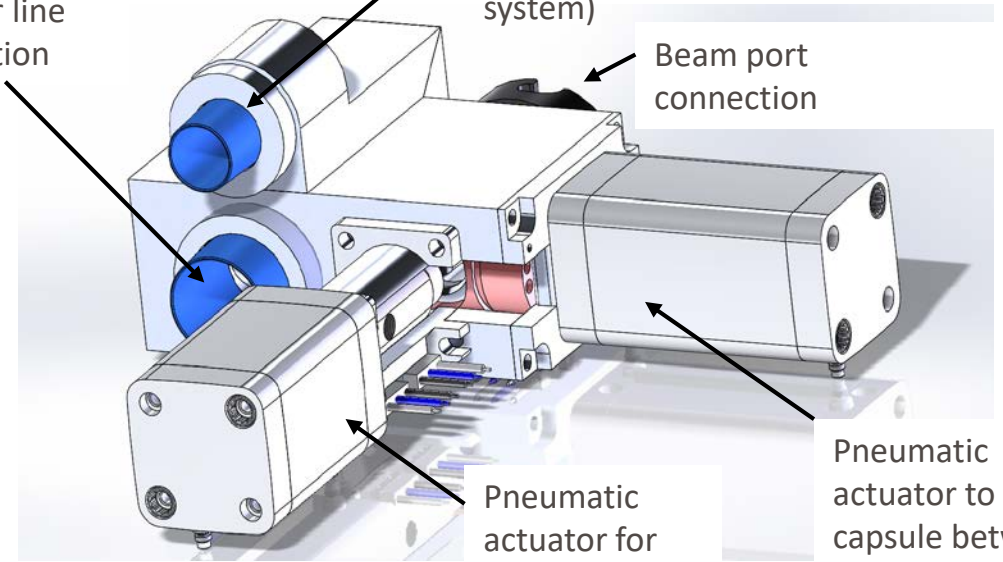
Natural Resources Canada | Ressources naturelles Canada
Canada



QUANTM Irradiation System™

Thank You

Contact: Paul Schaffer, CEO
pschaffer@artms.ca


Vent line connection (for sealed transfer system)
Transfer line connection
Beam port connection
Pneumatic actuator to move capsule between transfer tube and beam port
Pneumatic actuator for cooling services