Cyclotron Production of Tc-99m

Cyclotrons 2013

Ken Buckley | TRIUMF
Representing...

- **TRIUMF**
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- **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
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/$^{99m}$Tc 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
• Simple distribution & use
• Global demand for $^{99}$Mo/$^{99m}$Tc ~ 40 million doses/yr
  • >1 scan/second
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.
Starting in late 2007, several independent reactor outages significantly disrupted global 99Mo supplies.

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

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

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 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
  - $^{235}$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
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
1971 – Beaver and Hupf report $^{100}\text{Mo}(p,2n)^{99}\text{mTc}$ in JNM Vol. 12 pp 739-741

PRODUCTION OF $^{99}\text{mTc}$ 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 $^{99}\text{mTc}$ and 500 mCi/hr of $^{99}\text{Mo}$ are possible with 22-MeV protons at a target power level of 10 kW.
• 1999-2010 several reports on cross-section measurements

• 2010 – Targholizadeh et al. bombard natural moly 160 μA @ 25 MeV

• 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%
Reactions on $^{100}$Mo

Reactions on other Mo isotopes

## Molybdenum purity

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

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
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<thead>
<tr>
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<th>PETtrace</th>
<th>TRPET</th>
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<tbody>
<tr>
<td>Beam energy</td>
<td>16.5 MeV</td>
<td>18 MeV</td>
</tr>
<tr>
<td>Beam current</td>
<td>130 µA</td>
<td>300 µA</td>
</tr>
<tr>
<td>Power</td>
<td>2.1 kW</td>
<td>5.4 kW</td>
</tr>
<tr>
<td>Beam spot</td>
<td>&lt;15 Ø mm</td>
<td>20 mm x 10 mm</td>
</tr>
<tr>
<td>Target location</td>
<td>On cyclotron</td>
<td>On beamline</td>
</tr>
</tbody>
</table>
Self-shielded PETtrace
Vaulted PETtrace
LHRI Site

Processing
Hot cell

Total route
~ 10 m

Self-shielded
Cyclotron

Target space

Cyclotron room
Processing
Hot cell

Cyclotron

Total route
~ 12.5 m
(one floor elevation change)

Shielding Vault
Processing
Hot cell

Target selector
& local shield

Solid Target Station
& local shield

Cyclotron

Shielding Vault

Total route
~ 6.5 m
ACSI TRPET cyclotron
## System Parameters

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<tr>
<td>Target location</td>
<td>On cyclotron</td>
<td>On beamline</td>
</tr>
<tr>
<td>Target angle</td>
<td>90º</td>
<td>10º</td>
</tr>
<tr>
<td>Projected beam size</td>
<td>&lt;15 Ø mm</td>
<td>20 x 60 mm</td>
</tr>
<tr>
<td>Target capsule size</td>
<td>36 Ø mm x 54 mm</td>
<td>63 Ø mm x 165 mm</td>
</tr>
<tr>
<td>Transfer route length</td>
<td>10 &amp; 12.5 m</td>
<td>6.5 m</td>
</tr>
<tr>
<td>Route bends (90º)</td>
<td>9 &amp; 6</td>
<td>1</td>
</tr>
</tbody>
</table>
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
Radiographs

• **Gafchromic film** ([www.gafchromic.com](http://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

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

![Image](attachment:image.png)

20mm wide x 60mm tall
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
• **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

<table>
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<tr>
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<th>PETtrace  (GBq/µA)</th>
<th>TRPET (GBq/µA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celler</td>
<td>2.8 ± 0.3</td>
<td>3.8 ± 0.4</td>
</tr>
<tr>
<td>Tárkányi</td>
<td>3.4 ± 0.3</td>
<td>4.4 ± 0.4</td>
</tr>
<tr>
<td>Our Data (to date)</td>
<td>1.8 ± 0.2</td>
<td>3.5 ± 0.4</td>
</tr>
</tbody>
</table>


Extrapolated PETtrace Yields

- 1.8 ± 0.2 GBq/μA  
  Our data to date
- 2.8 ± 0.3 GBq/μA  
  Celler et al.
- 3.4 ± 0.3 GBq/μA  
  Tárkányi et al.

Activity (GBq) vs. Irradiation Time (hours)

- 6.0 Ci
- 4.9 Ci
- 3.2 Ci
Extrapolated TRPET Yields

4.4 ± 0.4 GBq/μA  
Tárkányi et al.

3.8 ± 0.4 GBq/μA  
Celler et al.

3.5 ± 0.4 GBq/μA  
Our data (to date)

Activity (GBq)

Irradiation Time (hrs)

17.8 Ci
15.4 Ci
14.2 Ci
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?