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

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• **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....

$^{100}$Mo Target

$^{100}$Mo Recycle

Cyclotron Modifications

Regulatory

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

Irradiation Parameters

Purification of $^{99m}$TcO$_4^-$

...can produce commercial quantities of $^{99m}$Tc
Team Equipment/Capabilities

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

  **BC Cancer Agency**
  
  TR19
  13-19 MeV, \( \leq 200 \mu A \)
  Upgrade to: 300 \( \mu A \)

  **Lawson**
  
  GE PETtrace
  16 MeV, \( \leq 100 \mu A \)
  Upgrade to: 130 \( \mu A \) (160 \( \mu A \) capable)

  **CPDC**
  
  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: $<0.0296 \, \mu A \cdot hr$

- Conclusions:
  - $^{100}$Mo (97.42%) at 22 MeV and 455 $\mu$A 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

The Calculated Approach: Predicting Products/Yields

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

$^{99}\text{gTc}$ $^{99}\text{mTc}$ $^{98}\text{Tc}$

PETtrace $\rightarrow$ TR19 $\rightarrow$ CP42

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

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

Optimal energy range: 16-19 MeV

Target Enrichment: Issues with lighter Mo isotopes

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Enriched A</th>
<th>Enriched B</th>
<th>Enriched C</th>
<th>Enriched D</th>
<th>Natural</th>
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</thead>
<tbody>
<tr>
<td>$^{92}\text{Mo}$</td>
<td>0.005</td>
<td>0.006</td>
<td>0.09</td>
<td>0.003</td>
<td>14.85</td>
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<tr>
<td>$^{94}\text{Mo}$</td>
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<td>0.0051</td>
<td>0.06</td>
<td>0.003</td>
<td>9.25</td>
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<tr>
<td>$^{95}\text{Mo}$</td>
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<td>0.0076</td>
<td>0.1</td>
<td>0.003</td>
<td>15.92</td>
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<tr>
<td>$^{96}\text{Mo}$</td>
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<td>0.0012</td>
<td>0.11</td>
<td>0.003</td>
<td>16.68</td>
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<tr>
<td>$^{97}\text{Mo}$</td>
<td>0.01</td>
<td>0.0016</td>
<td>0.08</td>
<td>0.003</td>
<td>9.55</td>
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<tr>
<td>$^{98}\text{Mo}$</td>
<td>2.58</td>
<td>0.41</td>
<td>0.55</td>
<td>0.17</td>
<td>24.13</td>
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<tr>
<td>$^{100}\text{Mo}$</td>
<td>97.39</td>
<td>99.54</td>
<td>99.01</td>
<td>99.815</td>
<td>9.63</td>
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</tbody>
</table>

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

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

Batch ‘D’ (99.815% $^{100}$Mo)

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

July 21, 2014
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

Automated Purification
Numerous commercially available resins avail.
Reproducible yields $92.7 \pm 1.1\%$ (range 91.5 – 93.5%) with actual production runs (up to 4.5 Ci processed)
Yield Comparison: Energy, Current Considerations

Production Yields

- 16 MeV (130 uA)
- 16 MeV (200 uA)
- 19 MeV (300 uA)
- 19 MeV (500 uA) theor.
- 24 MeV (500 uA) theor.

Yield (Cl) vs. Irradiation time (hrs)
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, <22 MeV)
  - 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

Canada
Annual $^{99m}$Tc needs: 971 TBq
With losses: 1900 - 3000 TBq
Cyclotrons: 22+6 (>16 MeV)
Existing Capacity: 2483 TBq

USA
Annual $^{99m}$Tc needs: ~8700 TBq
With losses: 17,400 - 27,200 TBq
Cyclotrons: ~110 of 261 (>16 MeV)
Existing Capacity: ~9160 TBq

(1 x 6hr runs/d, 240d/yr)
Estimated cost for direct production of $^{99mTc}$

- Assessments of 16, 19 and 24 MeV operations
- Key assumption: Maximum production of Na$^{99mTcO_4}$ 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

<table>
<thead>
<tr>
<th>Current (uA)</th>
<th>Time (h)</th>
<th>Batch size (Ci)</th>
<th>Shipped (Ci)</th>
<th>Rec'd (Ci)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 MeV</td>
<td>130</td>
<td>6</td>
<td>4.9</td>
<td>3</td>
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<tr>
<td>19 MeV</td>
<td>300</td>
<td>6</td>
<td>15.4</td>
<td>9.4</td>
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<tr>
<td>24 at 19 MeV</td>
<td>500</td>
<td>6</td>
<td>25.7</td>
<td>15.9</td>
</tr>
<tr>
<td>24 MeV</td>
<td>300</td>
<td>6</td>
<td>23.5</td>
<td>14.6</td>
</tr>
<tr>
<td>24 MeV</td>
<td>500</td>
<td>6</td>
<td>39.2</td>
<td>24.3</td>
</tr>
</tbody>
</table>

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

Current estimated price <$1.00/mCi
• 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 ⁹⁹ᵐTc)
  • Enrichment and irradiation parameters are interrelated and should not be considered independently
• Fall 2014 – Clinical trial application
• Jan. – April 2015 - Clinical trial (human) data
  • Na⁹⁹ᵐTcO₄ and hyperthyroid patient trial
• Summer – Fall 2015 - NDS submission
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): $\Delta$ Patient dose <10%

Radiopharmacy
• Assays: Mo, Al, PEG, $\text{H}_2\text{O}_2$ – colourimetric (ppb – ppm)
• pH: spot/strip test
• Visual inspection: particulate
• Radiochemical 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
  • François Bénard, Tom Ruth, Anna Celler, John Valliant, Mike Kovacs

• TRIUMF and BCCA machine shops

• Finances/Admin
  • Niki Chen, Nina Levi, Henry Chen, Jenny Song, Steven Foster, Neil McLean, Jim Hanlon, Ann Fong, Kevin McDuffie, Niki Martin
Thank you!

Merci

Canada’s national laboratory for particle and nuclear physics
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With support from: GE, Nordion, AAPS, others

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