The Critical Need for Nuclear Medicine Radioisotopes and Research

University of Missouri Research Reactor Center’s Radioisotope Production and BNCT Research

13 October 2009
University of Missouri –
A Unique Set of Resources
University of Missouri Research Reactor Center
The MURR Center — a Global Resource

- A 10 MW reactor that operates 24 hours a day, seven days a week, 52 weeks a year, 20 year NRC license extension submitted in 2006
- >150 full time & >30 part-time employees
- In 2008 produced 49 different isotopes with ~1000 shipments to 14 different countries
- Each and every week MURR supplies the active ingredients for FDA approved Quadramet® and TheraSpheres®
MURR Core Competencies include Strong Record of Regulatory Compliance
## Recent Infrastructure Upgrades

**R&R Grant, DOE, $6.6M, 9/29/00 - 12/31/08**

<table>
<thead>
<tr>
<th>Description</th>
<th>Expenditure</th>
</tr>
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<tbody>
<tr>
<td>New Fire Detection/Suppression System</td>
<td>713,919</td>
</tr>
<tr>
<td>New Primary and Pool Coolant Heat Exchangers (3)</td>
<td>578,780</td>
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<tr>
<td>2006 Beryllium Reflector</td>
<td>533,624</td>
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<tr>
<td>Engineering Assessments for relicensing</td>
<td>519,721</td>
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<tr>
<td>Radioactive Liquid Waste Disposal System Upgrades</td>
<td>430,810</td>
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<tr>
<td>Facility Electrical Distribution System Upgrades</td>
<td>424,566</td>
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<tr>
<td>Security &amp; Surveillance Enhancements</td>
<td>326,941</td>
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<tr>
<td>Revised/Updated Safety Analysis Report for relicensing</td>
<td>288,000</td>
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<tr>
<td>Hot cell Processing</td>
<td>160,665</td>
</tr>
<tr>
<td>New Reactor Plant Make-Up Water Storage Tanks (2)</td>
<td>149,423</td>
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<tr>
<td>New Stack Monitor</td>
<td>119,429</td>
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<tr>
<td>New Control Blades</td>
<td>115,647</td>
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<tr>
<td>Containment Building 15-Ton Overhead Crane Catwalk</td>
<td>95,436</td>
</tr>
<tr>
<td>New Graphite Reflector Elements</td>
<td>84,831</td>
</tr>
<tr>
<td>Reactor Instrumentation Upgrades</td>
<td>65,097</td>
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# MURR Radioisotopes

<table>
<thead>
<tr>
<th>Isotopes Shipped in 2008 (49)</th>
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<tbody>
<tr>
<td>As-76</td>
</tr>
<tr>
<td>Au-198; Au-199</td>
</tr>
<tr>
<td>Ba-135m</td>
</tr>
<tr>
<td>Ca-45; Ca-47</td>
</tr>
<tr>
<td>Ce-141</td>
</tr>
<tr>
<td>Co-60</td>
</tr>
<tr>
<td>Cr-51</td>
</tr>
<tr>
<td>Cs-134</td>
</tr>
<tr>
<td>Eu-154</td>
</tr>
<tr>
<td>Fe-55</td>
</tr>
<tr>
<td>Fe-59</td>
</tr>
<tr>
<td>Gd-159</td>
</tr>
<tr>
<td>Ge-71</td>
</tr>
<tr>
<td>Hg-197; Hg-203</td>
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</tbody>
</table>
Other Reactor Producers

• Domestic, Non-DOE
  – MIT (5 MW) - Gold, Yttrium, and Irridium – research quantities
  – UC Davis (2 MW) – Currently improving Iodine -125 production system, Argon-41 and Sodium-24 as tracers for the Oil industry
  – Oregon State (1 MW) - non-routine – Gold and Silver as biotracers, Sodium and Rubidium as environmental tracers, Argon and Sodium for industry
  – Texas A&M (1 MW) - Various as environmental tracers

• Foreign Sources
  – Petten – Netherlands, Mo-99, Lu-177
  – BR-2 – Belgium, Mo-99, I-131, Xe-133, Ir-192
  – Russian Institutes - P-32, P-33 Sr-90, W-188
  – South Africa - Mo-99, Lu-177
  – NRU – Canada – Mo-99
  – Poland - various
  – Australia - various, mostly for in-country use, Mo-99
A 25-year history of successful and innovative radiopharmaceutical R&D and collaborations with industry….

- **Ceretec™** (with Tc-99m), a diagnostic used to evaluate cerebral blood flow in patients & label white blood cells
- **Quadramet®** (with Sm-153), a therapeutic for treatment of pain associated with metastatic bone cancer
- **TheraSphere®** (with Y-90), a glass microsphere used to treat patients with inoperable liver cancer
- Cesium-131 brachytherapy seeds to treat prostate cancer
- Gd-159 and Ho-166 for research in skeletal targeted radiopharmaceuticals
- Iridium-192 brachytherapy seeds to treat solid tumors
- Lu-177 and Pm-149 for receptor-targeted radiopharmaceuticals (support 30 research and clinical trials)
- P-32 and P-33 biomedical radiotracers
- Se-75 biomedical radiotracers
MURR Core Competencies include Volume Radiochemical Processing

**Hot Cells**

*Designed with Versatility in Mind*

1st Application...
200 Ci batches of Ho-166
Designed for 500 Ci Batches

Lu-177
Weekly producing 40 Ci batches
Potentially capable of 1000’s Ci per week
MURR Competencies
FDA-approvable cGMP and GLP Programs
FDA Approvable
...cGMP Facilities
Currently developing a suite of *carrier free lanthanides* to work in conjunction with *selective targeting agents* to locate and treat cancer.

<table>
<thead>
<tr>
<th>Ln</th>
<th>$t_{1/2}$</th>
<th>$\beta_{max}$</th>
<th>$E_g (I_g)$</th>
<th>Avg Range (cell diameter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{177}$Lu</td>
<td>6.7 d</td>
<td>0.5 MeV</td>
<td>208 keV (11%)</td>
<td>20</td>
</tr>
<tr>
<td>$^{166}$Ho</td>
<td>1.1 d</td>
<td>1.8 MeV</td>
<td>286 keV (3%)</td>
<td>60</td>
</tr>
<tr>
<td>$^{149}$Pm</td>
<td>2.2d</td>
<td>1.1 MeV</td>
<td>81 keV (6%)</td>
<td>120</td>
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</tbody>
</table>

![Diagram showing Metal-Ligand Conjugate, Organic Linker, Receptor, and Tumor Cell]
Radiopharmaceutical Research

MURR $^{177}$Lu

- Currently being evaluated in over 30 clinical applications for radiotherapy of cancer
  - Metastatic prostrate cancer
  - Non-hodgkins lymphoma
  - Neuroendocrine tumors
  - Ovarian cancer
  - Metastatic bone cancer
  - Colon cancer
  - Lung cancer

- MURR upgrading process to meet FDA guidelines for Clinical grade production
Essential Isotopes, LLC
Cyclotron – GE 16.8 MeV PET Trace
Cyclotron Produced Isotopes

Essential Isotopes, LLC currently producing:

• Fluorine-18  FDG -Imaging agent
  – Multiple commercial customers
  – Phase Two clinical trials in Kansas City and St. Louis

• Copper-64
  – Collaboration with Washington University
  – Used to study genetic diseases such as Wilson’s and Menke’s

• More isotopes planned
• Have built-in facilities to support on-site imaging trailer.
Need for Mo-99/Tc-99m

- Tc-99m is used in over 80% of all medical isotope procedures worldwide.
- National need – used ~50,000/day in U.S.
- Use is expected to increase ~5% annually for the next ten years.
- More than 30 different radiopharmaceuticals use Tc-99m for disease detection & organ structure & function.
U.S. History of Mo-99 Production

- 1967 - MURR begins production of \((n, \gamma)\) Mo-99 for Mallinckrodt Nuclear Co.
- 1977 - MURR increases Mo-99 production for MediPhysics Inc.
- 1980 - Cintichem, Inc. begins production of HEU fission product Mo-99 and is the single U.S. supplier.
- 1984 - MURR ceases Mo-99 production.
- 1989 - Cintichem reactor develops leak and is closed.
- 1991 - DOE purchased Cintichem technology, equipment and DMFs for production of Mo-99, I-125, X3-133
- 1991 - DOE identified Omega West Reactor at LANL as proposed backup supply facility and constructs processing facility.
- December 1992 - Omega West Reactor at LANL develops leak and is closed.
- Until 1993, two Canadian reactors, operated by Atomic Energy of Canada Limited (AECL) at the Chalk River site (located about 100 miles from Ottawa, Canada), were available to produce Mo-99.
- 1996 - DOE selects Annular Core pulse reactor at Sandia National Lab. to become backup supply facility and constructs processing facilities. Project never completed.
- 1998 - Canadian MAPLE reactors were scheduled to open, but remain shutdown today due fundamental design flaw.
- 2006 - begins feasibility studies to produce LEU fission Mo-99
- 2008 - Decision made to discontinue work on MAPLE 1 & 2.
Mo-99 Production at MURR

- Overall objective is to develop the capability to produce Mo-99 from LEU targets.

- Production objective is ~50% of current U.S. weekly demand.
  - Current U.S. weekly demand is estimated to be 6000 six-day Curies (Ci) per week
    - 6000 six-day Ci equates to about 40,000 Ci (End-of-Irradiation), Synonymous with “Out-of-Reactor” Ci
    - Must irradiate / process 40 - 50 targets per week to satisfy ~50% weekly demand.
Reactor Plan View

Wedge (Typical of 12)

- Beryllium Reflector
- A, B, C - Flux Trap
- F1 - F8 - Fuel Elements
Proof of Concept - DU Cold Process

- 5.2 Depleted Uranium (DU) foil in 1.02 g Nickel envelope
- Dissolve under heat and pressure
- Evacuate dissolver to cold-trap to remove gasses
- Perform chemistry in glass-ware
- Collect final product and assay
- Two bench-top chemistry trials produced > 90% Molybdenum carrier recovery
- Full “cold” process in hot cell produced greater than 94% recovery
Proof of Concept - Hot Cell Modifications

- Identify Hot Cell
- Decontaminate cell interior
- Remove processing subfloor
- Add shielding for LN2 system
- Design and install LN2 system for cold finger gas trap
- Modify exhaust to include carbon filtration
- Design and install chemistry handling apparatus
Target Geometry
Annular vs. Plate
Proof of Concept
Sample Target Holder
Proof of Concept
Target Cutter Assembly
Target Loading Density
Effective Use of Irradiation Space

Total of 8 Dispersion Plate Targets Irradiated / Processed as a Batch

Photos Courtesy of NRG
Mo-99 CRP Workshop
Vienna, November 2006
Target Loading Density
Effective Use of Irradiation Space (Cont’d)

Batch of Eight (8) Targets in Transit to Irradiation Position
Why MURR?

• The largest university operated research reactor in the U.S.
  – MURR sets the example for safe and efficient operation for U.S research reactors.

• University of Missouri and MURR are leaders in the development and supply of radioisotopes for research and medical uses.

• Demonstrated experience
  – 24/7 operations 52 weeks a year
  – >150 Full-Time Employees
  – Radioisotopes shipped around the globe every week
  – FDA - cGMP and cGLP programs

• Only real need is a processing facility.

• Realistic timeline to reach large-scale production (2012-2013).

• Support of Missouri Congressional Delegation.
Reactor Parameters: HEU to LEU

MURR is a pressurized, reflected, heterogeneous, open pool-type, which is light-water moderated and cooled

- Maximum thermal power – 10→12 MW
- Peak flux in center test hole – 6.0 → 6.4E14 n/cm²-s
- Core – 8 fuel assemblies (775 → ~1410 grams of U-235 per assembly)
- Control blades – 5 total: 4 boral shim-safety, 1 SS regulating
- Reflectors – beryllium and graphite
- Forced primary coolant flow rate – 3,750 gpm (237 lps)
- Forced pool coolant flow rate – 1,200 gpm (76 lps)
- Primary coolant temps – 120 °F (49 °C) inlet, 136 → 139 °F (60 °C) outlet
- Primary coolant system pressure – >75 psia (586 kPa)
- Pool coolant temps – 100 °F (38 °C) inlet, 107 °F (42 °C) outlet
- Beamports – three 4-inch (10 cm), three 6-inch (15 cm)