Features of MURR

• Highest neutron flux of any U.S. university reactor
  – Compact Flux Trap [ca. 8 cm diam. X 1 m long cylinder]

• High reliability -- operates 105% of schedule [91% of clock time]
  – Produces more neutrons/year than all other U.S. University reactors combined
History of Medical Radioisotope Production at MURR

- 1966 Start up (5 MW)
- 1969 100 hr/wk operation - Mo-99 Production begins
- 1975 Power Upgrade (10 MW) - P-32 & S-35 Prod.
- 1977 155 hr/wk operation - Increased Mo-99 Production
- 1980 Y-90 Glass Microspheres R & D begins
- 1982 Sm-153-EDTMP & Re-186-HEDP R & D begins
- 1989 Irradiation of Au-198 and Ir-192 Seeds begins
  - (Cintichem Reactor decommissioned)
MURR Reactor
Radioisotopes for Medical Imaging

**Diagnostic**
- Emit gamma or X-rays which can penetrate out of the body so they can be detected/imaged by instruments external to body.

**Therapeutic**
- Emit particles (beta- or alpha-particles) so they can deliver a high LOCALIZED radiation dose to tissues (e.g., tumors) where they deposit. Particles deposit their energy at site (1-2 mm) of the decay of radioisotope.
Radioisotopes for Medical Applications
Physical Properties

A) Half-lives are relatively short

**Diagnostic**
- $^{99m}$Tc – 6 hours
- $^{18}$F – 110 minutes
- $^{201}$Tl – 3 days
- $^{11}$C – 20 min

**Therapeutics**
- $^{131}$I – 8 days
- $^{153}$Sm – 2 days
- $^{90}$Y – 2.7 days
- $^{177}$Lu – 6.7 days

B) Optimal Radioactive Decay Characteristics

1. Diagnostic/Imaging – Minimize radiation dose to tissues in patients
   Gamma-rays with $E = 50$-350 keV
   Positron generated photons with $E = 511$ keV
   Minimal Particles Emitted

2. Therapy – Maximize radiation dose to tumor
   Particle Emission required
   Gamma-ray emission – low level
Reactor Processes

- \( n, f \) (fission)
- \( n, \gamma \) (thermal neutrons, \( \sim 0.025 \) eV)
  - no change in \( Z \)
- \( n, \gamma \) (followed by decay)
  - generators?
- \( n, p \) (fast neutrons)
- \( n, \alpha \) (fast neutrons)
- Indirect Reactions
Reactor-Produced Radionuclides: Fission Products

- carrier-free radionuclides
- radionuclides generally have atomic numbers from 28-65
- must be separated by chemical separation methods
  - contamination with other non-desired radionuclides a problem
- fission products generally decay by $\beta^-$ because of excess neutrons
- special nuclear material, high level waste
  - not many are useful for gamma scintigraphy
Examples of Fission Separation Products Used in Nuclear Medicine

- $^{99}\text{Mo}$ (parent of $^{99m}\text{Tc}$)
- $^{131}\text{I}$ (uptake/therapy)
- $^{133}\text{Xe}$ (inhalation)
- $^{137}\text{Cs}$ (sealed source)
Issues

• Tc-99m is most widely used radionuclide for nuclear medicine procedures in the world and accounts for >80% of all procedures

• Major efforts in connecting to biological molecules to assess
  – Cardiac function
  – Blood flow
  – Bone metastases

• A generator is a device used to extract one nuclide from another
• Half life & chemical properties of Mo-99 and Tc-99m are exploited to separate them in generator
  – Mo-99/Tc-99m generator invented at Brookhaven National Laboratory
  – Mo-99 half life is 66 hours, Tc-99m has a half life of 6 hours
  – Process of separating Mo-99 and Tc-99m called “milking”

• Milking can be repeated over many times

• Generators sent around the world
Diagnostic Imaging

Gamma Camera Image Following Tc-99m Injection Indicates Malfunctioning Left Kidney

Tc-99m Breast Image Tumor Evaluation

Tc-99m Brain Image Seizure Evaluation
Supply Chain for $^{99}\text{Mo}$
Supply Chain for $^{99}$Mo generators in NA
Figure 2.2: Overview of the present production process for Mo-99.
Issues

- Currently AECL/MDS Nordion supply 40% of world’s demand and able to handle 80%

- AECL runs the (130 MW) NRU reactor with LEU fuel and HEU targets (HEU is highly enriched uranium & is weapons grade uranium)
  - Substantial radioactive waste is generated in processing
  - HEU (> 19.7% U-235) comes from the US and waste is also HEU
  - Fission of U-235 induced by thermal neutrons
  - Natural uranium is 99.284% U-238 and 0.711% U-235

- Chemistry is performed on targets by AECL resulting in a Mo-99 solution
- Solution shipped to MDS Nordion for purification and placement into column
- Mo-99 is eluted (extracted with a solvent) from the column
- Produced eluate is conditioned and $^{99}\text{Mo}$ re-extracted

- Demand is growing but slowly and may become flat as PET gains more use
- Meeting US demand requires about 34,000–46,000 Curies/week at the reactor
  - Accounts for processing losses and 30 hour processing and shipping time, the delivered supply is 5,000 6-day Ci
  - $1 \text{ Ci} = 3.7 \times 10^{10}$ decays per second
Other Issues

• US production was halted in 1989
  – Foreign subsidies were claimed to be the cause for lower costs abroad
  – Deemed “not worth it” to continue in US
• Low market price, risk of reactor business, and high cost of production facilities
• Half of US demand met by Canada
• HEU has significant security issues; future will likely require use of something else
Non-Proliferation Objective

- The major Mo-99 producers use high enriched uranium (HEU); ≥20% enriched in U-235
- Worldwide concerns regarding transport of weapons-grade material will eventually end its use
- Argonne National Lab has demonstrated that fission product Mo-99 can be produced using low enriched uranium (LEU); <20% enriched in U-235
- LEU-foil annular target designed by Argonne National Laboratory
Energy Policy Act of 2005

• Establishing a domestic supply of Mo-99 that is produced from LEU is paramount to the United States' nonproliferation mission and will significantly reduce dependence on foreign supplies.

• Section 630, Medical Isotope Production, of the "Energy Policy Act of 2005," states, in part, “The Secretary shall enter into an arrangement with the National Academy of Sciences to conduct a study to determine - - (i) the feasibility of procuring supplies of medical isotopes from commercial sources that do not use highly enriched uranium”

• The Act requires that the Secretary submit a report to Congress not later than 5 years after the date of enactment of the “Energy Policy Act of 2005” to document the results of the National Academy of Sciences study.
DOE Support

- Funding is provided by the National Nuclear Security Administration (NNSA) to support implementation of the Reduced Enrichment Research and Test Reactors (RERTR) Program managed by ANL.
- The use of LEU material to produce Mo-99 is promoted by the U.S. Global Threat Reduction Initiative (GTRI).
- The GTRI mission is to reduce and protect vulnerable nuclear and radiological materials located at civilian sites worldwide.
- GTRI is:
  - a vital part of the President’s March 2006 National Security Strategy of the U.S.
  - an important element of the President’s July 2006 Global Initiative to combat Nuclear Terrorism, and
  - directly addresses recommendations of the Bipartisan 9/11 Commission.
International Atomic Energy Agency

- Coordinated Research Project (CRP) on Developing Techniques for Small-Scale Indigenous Production of Mo-99 Using LEU or Neutron Activation (T.1.20.18) – ongoing 2005-2009

**Contract Holders:**
- LEU Foil: Chile (CCHEN), Libya (DRETC), Pakistan (PINSTECH), Romania (INR Pitesti)
- Neutron Activation/Gel Moly – Kazakhstan (INP), Romania (IFIN-HH Magurele)

**Agreement Holders:**
- Argentina (CNEA), India (BARC-BRIT), Indonesia (BATAN), Korea (KAERI), US (ANL), US (MURR)
- *NEW* - Poland (POLATOM)
- *RECEIVED* – Egypt (EAEA)
- *EXPECTED* – Russia (Institute of Nuclear Materials Zarechny)
MURR Mo-99 Projects

- MURR n-Gamma “Gel Moly” Generator
- LEU Fission Mo-99 Initial ANL/CRP
- Customer supported n-Gamma Gel Project
- Other n-Gamma (neutron Moly) Production
- MURR LEU Fission Mo-99 Production Model
- (Fuel Element Dissolution Fission Mo-99)
MURR Mo-99 Projects

- **Reflector, LEU Targets**
  - Foil Modified Cintichem (Acid Dissolution Organic Precipitation)
  - Dispersion Aluminum Base Dissolution with Filtration
  - Foil Acid Dissolution with Resin Separation

- **Flux Trap, n-Gamma Mo Metal Target**
  - 60 % Density Natural Metal (~24% $^{98}\text{Mo}$)
  - 100% Density Natural Metal (~24% $^{98}\text{Mo}$)
  - Metal powder enriched to >98% $^{98}\text{Mo}$ ($$$)

- **Fuel dissolution**
  - Conceptual not pursued
Selected Medical Radiosiotopes Currently Supplied by MURR

- Clinical Radioisotopes
  - Sm-153, Ho-166, Lu-177
- Research Radioisotopes
  - Rh-105, Re-186, Re-188, Au-198, Pd-109
- Brachytherapy
  - Ir-192, Au-198
- Biomedical Tracers
  - P-32, P-33, S-35, Se-75
Why Radiolanthanides?

- Chemistry
  - Similar for All
- Nuclear Properties
  - Variety of half-lives
  - Variety of $\beta^-$ energies
- Production
  - Many have large cross sections
## Nuclear Properties of Radionuclides

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life (days)</th>
<th>$\beta^-$ max (MeV)</th>
<th>$\gamma$ (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ho-166</td>
<td>1.12</td>
<td>1.8</td>
<td>80.6</td>
</tr>
<tr>
<td>Sm-153</td>
<td>1.93</td>
<td>0.8</td>
<td>103</td>
</tr>
<tr>
<td>Lu-177</td>
<td>6.65</td>
<td>0.49</td>
<td>208</td>
</tr>
<tr>
<td>Pm-149</td>
<td>2.21</td>
<td>1.0</td>
<td>286</td>
</tr>
<tr>
<td>Yb-175</td>
<td>4.19</td>
<td>0.47</td>
<td>396</td>
</tr>
<tr>
<td>Tb-161</td>
<td>6.91</td>
<td>0.59</td>
<td>80</td>
</tr>
<tr>
<td>Y-90</td>
<td>2.67</td>
<td>2.28</td>
<td></td>
</tr>
</tbody>
</table>
Average Range of the $\beta^-$ in Water for Selected Radiolanthanides

- Y-90
- Ho-166
- Pm-149
- Sm-153
- Lu-177

Note: $\sim 0.25 \text{ mm} = \sim 20 \text{ cell diameters}$
• Sm-153 identified as a useful nuclide for radiotherapy by MU researchers
• Development began in early 1980’s at MU in collaboration with the Dow Chemical Company [phosphonate ligands]
• Successful in palliative treatment of bone cancer in canine patients, with added bonus of ~15% cure rate [MU College of Veterinary Medicine program of Comparative Oncology]
## Comparative Oncology: Treated Dogs with Bone Cancer

<table>
<thead>
<tr>
<th>Response</th>
<th># of Dogs (%)</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Free</td>
<td>7 (18%)</td>
<td>11 - 60</td>
</tr>
<tr>
<td>Partial Response</td>
<td>25 (62%)</td>
<td>1 - 16</td>
</tr>
<tr>
<td>No Response</td>
<td>8 (20%)</td>
<td>0.5 - 1</td>
</tr>
</tbody>
</table>
Story of QuadraMet™ -- II

• Clinical trials began in late 1980’s, with doses supplied by MURR for Phase I and II studies
• ~ 80% efficacy, with ~ 25% obtaining full pain remission
• Approved in U.S. for pain palliation of metastatic bone cancer in March, 1997
Phase I Clinical Trials at MU and VA Hospitals
Ho-166 DOTMP Clinical Trial Support

- Skeletal Targeted Radiotherapy (STR) for Multiple Myeloma
- Phase I/II Clinical Trials (NeoRx)
- 23 of 57 Patients have Achieved Complete Remission (single doses as high as 4 Ci)
- Pivotal (Phase III) Trials Started in 2004
Clinical Trial Support at MURR

- Ho-166 DOTMP Clinical Trial Support
  - Multi-Curie production
  - Distribution challenges
Chelating Agents

- Bifunctional Chelating Agent
- Requires high specific activity
Current Radiopharmaceutical Research at MU

• Small Peptides for Diagnosing and Treating Cancer
  – Somatostatin analogs (neuroendocrine tumors)
  – Bombesin (prostate, pancreatic and other cancers)
  – Antibody Pretargeting
  – α-Melanocyte Stimulating Hormone (skin cancer)
## Typical Specific Activities

(Direct Neutron Capture)

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life (days)</th>
<th>Decay $\beta^-$ (MeV)</th>
<th>Achieved (% of atoms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ho-166</td>
<td>1.12</td>
<td>1.9</td>
<td>0.31%</td>
</tr>
<tr>
<td>Sm-153</td>
<td>1.93</td>
<td>0.69</td>
<td>1.4%</td>
</tr>
<tr>
<td>Lu-177</td>
<td>6.71</td>
<td>0.50</td>
<td>27.7%</td>
</tr>
</tbody>
</table>
## Lu-177 Production

<table>
<thead>
<tr>
<th>Neutron Activation Equation</th>
<th>Thermal Neutron Cross Section (barns)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{176}\text{Lu} + n \rightarrow ^{177}\text{Lu}$</td>
<td>2050</td>
</tr>
<tr>
<td>$^{176}\text{Lu} + n \rightarrow ^{177m}\text{Lu}$</td>
<td>7</td>
</tr>
<tr>
<td>$^{175}\text{Lu} + n \rightarrow ^{176m}\text{Lu}$</td>
<td>20</td>
</tr>
</tbody>
</table>
IAEA Co-Operative Research Project
‘Development of therapeutic radiopharmaceuticals based on \( ^{177}\text{Lu} \) for radionuclide therapy’ (2006-2009)

– Objective:
  • To generate know how and expertise in the production and radiochemical processing of \( ^{177}\text{Lu} \)
  • Preparation of therapeutic radiopharmaceuticals
  • \( ^{177}\text{Lu}\)-EDTMP
  • Development of \( ^{177}\text{Lu} \) peptides (Substance-P, minigastrin)
  • Antibodies (hR\(_3\), anti CD 20),
  • Particles for colon carcinoma

  – Argentina, Austria, Brazil, China, Chile, Cuba, Czech, Hungary, India, Italy, Mexico, Pakistan, Peru, Poland, Russian Federation, Uruguay, United States
Lu-177 Bone Uptake Study in Normal Mice
Lu-177 Clinical Trials

• 30 clinical applications
• Metastatic prostate cancer
• Non-hodgkins lymphoma
• Colon cancer
• Metastatic bone cancer
• Lung cancer
• Ovarian cancer
• Neuroendocrine tumors
Recent Reports Comparing Lu-177 to other radionuclides

- Lower side effects
- Use allows for repeat treatments
- More efficacious
“No Carrier Added Radioisotopes”

- Receptor/molecular targeting requires very high specific activities – i.e., ‘no carrier added’
- Isotopes like Lu-177 can be produced by direct bombardment of Lu-176 or indirectly by decay of Yb-177 produced by bombardment of Yb-176
- The latter approach requires a chemical separation, to produce higher specific activity Lu-177, approaching “carrier-free” levels
Indirect Production of NCA radioisotopes:

176\text{Yb} (n,\gamma) \rightarrow 177\text{Yb} \rightarrow ^{177}\text{Lu} \beta^- (1.9 \text{ hr})

164\text{Dy} (2n,\gamma) \rightarrow 166\text{Dy} \rightarrow ^{166}\text{Ho} \beta^- (81.6 \text{ hr})

148\text{Nd} (n,\gamma) \rightarrow 149\text{Nd} \rightarrow ^{149}\text{Pm} \beta^- (1.7 \text{ hr})
Lanthanides

$^{140}\text{La} \quad^{149}\text{Pm} \quad^{153}\text{Sm} \quad^{166}\text{Ho} \quad^{177}\text{Lu}$

La  Pm  Sm  Ho  Lu

large  small

ionic radii
Rhodium-105

- 35.4 hour half-life
- 0.566 (70%) and 0.248 (30%) MeV $\beta^-$ particles
- 319 keV (19%) $\gamma$ photon
- High specific activity
Rh-105 Production

$^{104}\text{Ru} + ^1\text{n} \rightarrow ^{105}\text{Ru} + \gamma \rightarrow ^{105}\text{Rh}$

$^{105}\text{Rh} \rightarrow ^{105}\text{Pd}$
Separation of High Specific Activity Rh-105

- 5 M NaOH used to trap excess Cl₂
- ¹⁰⁵Rh remains in reaction vial and is acidified with HCl
- Separation factor of 20,000 achieved

Before sep: 3 mg Ru (7 mM) vs. <10⁻⁹ M of Rh
After sep: 15 μg Ru (35 μM) vs. <10⁻⁹ M of Rh
Why Gold?

- Au-199, half-life of 3.14 days
- Beta max of 0.453 MeV
- Gamma emissions of 158.4 (40%) and 208 MeV (9.1%)

- Au-198, half-life of 2.7 days
- Beta max of 0.96 MeV
- Gamma emissions of 412 keV (95.6%)
Producing Au-198 and Au-199

**No Carrier-Added:**

\[ {^{198}\text{Pt}} + ^1\text{n} \rightarrow {^{199}\text{Pt}} \rightarrow \beta^- \rightarrow {^{199}\text{Au}} \]

\( t_{1/2} = 30 \text{ min} \)

**Carrier-Added:**

\[ {^{197}\text{Au}} + ^1\text{n} \rightarrow {^{198}\text{Au}} + ^1\text{n} \rightarrow {^{199}\text{Au}} \]
Wish List

- Mo-99
- Pt-195m
- Cu-67
- As-74, As-77
- Sc-44, Sc-47
- At-211, Ac-225
Conclusions

• Through collaborative research efforts, MURR has successfully developed and commercialized two radiopharmaceutical products for the treatment of cancer.

• MURR continues to identify, develop, and supply novel radioisotopes for radiopharmaceutical research and therapy.