SBIR/DOE Phase II Project

High Specific Activity $^{153}\text{Sm}$
by Post Irradiation Isotope Separation

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There is a pressing need for new and improved radiotherapeutic isotopes.

Radiative neutron capture at a nuclear reactor is optimal production method

Target isotope + neutron = Product ;
Target >>> Product

Difficult to separate isotopes of an element with a chemical approach for isotopes produced using radiative neutron capture.

Electromagnetic (EM) approach can be used for isotopic separation.
**MOTIVATION**

(for $^{153}\text{Sm}$)

$^{153}\text{Sm}$ is presently used in therapeutic bone agent, Quadramet, for pain palliation.

Excellent efficacy for pain palliation, but not as useful for cancer treatment due to low specific activity (LSA). LSA cannot be used with peptides and antibodies.

$^{153}\text{Sm}$ is produced by $^{152}\text{Sm}(n,\gamma)^{153}\text{Sm}$ reaction with a typical 2% yield (at MURR).

Need to produce higher specific activity (higher isotopic purity) material to test if HSA $^{153}\text{Sm}$ is compelling as a form of treatment.
Production and Separation of $^{153}\text{Sm}$

Production of $^{153}\text{Sm}$:

$^{152}\text{Sm}$ (neutron, gamma) $^{153}\text{Sm}$

Separation/Purification of $^{153}\text{Sm}$ from target material using magnetic mass separator.

Reactors → Transport → Ion Source → Isotope Mass Separator

High specific activity (radioactivity/weight)
Involves Four Separate Groups/Laboratories

**ITG (Isotherapeutics Group, Texas)**
- Recovery of HSA $^{153}$Sm from DLC Foil
- Labeling and biodistributions studies with HSA $^{153}$Sm

**ORNL (Oak Ridge National Laboratory)**
- Neutron Irradiation at HFIR Nuclear Reactor to make $^{153}$Sm
- Purification and preparation of HSA $^{153}$Sm using EM technique

**TRIUMF/AAPS (Advanced Applied Physics Solutions)**
- Development of Ion Source and Collection Systems

**MURR (Missouri University Research Reactor)**
- Chemistry Development and production of LSA $^{153}$Sm
ISOTherapeutic Group: Fully Equipped for Radiopharmaceutical R&D

Key R&D Equipment

ICP-OES

HPLC-MSD

GE GAMMA DETECTOR
TWO FULLY EQUIPPED LABORATORIES FOR cGMP MANUFACTURING

Phosphor Imaging System

NaI Well Detector
RADIOISOTOPE LABELING EXPERIENCE

Iodinating Proteins and Small Molecules (I-131, I-125)

Labeling Proteins with Bifunctional Chelating Agents (Ac-225, Ho-166, In-111, Lu-177, Sm-153, Sn-117m and Y-90)

Labeling Small Molecules with Short-Lived Alpha Emitters (Bi-213)

Preparing Chelates using Redox Chemistry (Tc-99m, Re-186, Re-188)

Labeling Nanoparticles with Isotopes for Biodistribution Determination (I-131, In-111)
**PROJECT OVERVIEW**

**YEAR ONE**  (Stable Sm Isotopes)

Developed new ion source for production of Sm$^+$ ion beam using samarium **metal** as feed material  
(using ISTF at TRIUMF/AAPS)  - COMPLETED

Developed appropriate collection approach following mass separator  - COMPLETED

Developed method for recovery of implanted samarium from DLC foil  
(at MURR)  - COMPLETED
PROJECT OVERVIEW

YEAR TWO (completed)

Full test of ion source and collector unit at ORNL isotope mass separator (IRIS2) with stable Sm metal - COMPLETED

Full test of entire procedure from irradiation to delivery to ITG with radioactive $^{153}$Sm. - COMPLETED

________________________________________________________

Deliverables to ITG for labeling studies

Produced 4 HSA samples of $^{153}$Sm at ORNL - COMPLETED
**YEAR 2: EXPERIMENTAL SPECIFICS**

**GOAL** – Delivered four samples of 10-16 mCi of HSA$^{153}$Sm to ITG

Irradiated $^{152}$Sm (>99%; 5 mg): flux = 3.5-4.5 x $10^{14}$ n/cm$^2$·s for 10 hours; HFIR

{$\sim$10 Ci $^{153}$Sm (0.4% $^{153}$Sm conversion) with 30 µCi $^{154}$Eu contamination}

Performed isotopic mass separation (IRIS2 at ORNL)

Implanted ~25 mCi $^{153}$Sm onto 10µm Diamond-Like Carbon (DLC) foils

{ Sm$^+$ ion beam for 10 h and ~200 nA}

Transported to ITG (Texas); (~1 Day) - ~15 mCi $^{153}$Sm

Sample radioactively pure using gamma spectrum

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<table>
<thead>
<tr>
<th>Nuclear Properties $^{153}$Sm</th>
<th>Nuclear Properties $^{154}$Eu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half life – 46.3 hours</td>
<td>Half life – 8.6y</td>
</tr>
<tr>
<td>Radiations</td>
<td>Radiation</td>
</tr>
<tr>
<td>Gamma – 69 and 103 keV (~30%)</td>
<td>Gamma – 82 and 184 keV</td>
</tr>
<tr>
<td>Beta – low energy (~0.5 MeV)</td>
<td>Beta – low energy (~0.2 MeV)</td>
</tr>
<tr>
<td>Decay Product – Stable</td>
<td>Decay Product – Stable</td>
</tr>
</tbody>
</table>
PHASE II (YEAR 2)

Electromagnetic mass separator, IRIS2, tested with samarium metal

Operation successful and implanted samarium beam for about 30 h
~37 µg of samarium deposited (includes sputtered amount)

Implanted foils tested for efficiency to remove Sm and
~90% of Sm recovered in aqueous solution

Full test runs with hot/irradiated material (4 runs).

Irradiation at HFIR for 10h in quartz ampule; 9-10 Ci $^{153}$Sm

Using IRIS2 EMIS, implanted ~30 mCi onto DLC foils
(primary and sputter) during 12-16 hour run

Delivered (10-16 mCi) to ITG for initial testing

Results indicate ~95% recovery of $^{153}$Sm
A Sm-152 enriched DLC foil from ORNL was pyrolyzed in a muffle furnace (see pics above). Samples, in 10 mL quartz crucibles, were heated to approximately 900°C over ~75 minutes then allowed to cool to ambient temperature.
<table>
<thead>
<tr>
<th>Date Received</th>
<th>Initial Activity In Foil (mCi)</th>
<th>Recovered Activity (mCi)</th>
<th>Activity left in crucible</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/1/13</td>
<td>10.0</td>
<td>9.5</td>
<td>0.3</td>
</tr>
<tr>
<td>1/30/14</td>
<td>10.9</td>
<td>11.6</td>
<td>0.6</td>
</tr>
<tr>
<td>3/19/14</td>
<td>16.0</td>
<td>14.7</td>
<td>2.0</td>
</tr>
<tr>
<td>5/21/14</td>
<td>13.7</td>
<td>13.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>
HPGe Analysis of HSA Sm-153

Gamma Peaks found in the Sample
41.29 keV
46.89 keV
69.60 keV
83.33 keV
97.35 keV
103.23 keV

All gamma energies are consistent with Sm-153
## ICP-MS Results Hot Runs

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>Natural Sm (ng/mL)</th>
<th>152Sm in excess of natural (ng/mL)</th>
<th>Natural Eu (ng/mL)</th>
<th>153Eu in excess of natural (ng/mL)</th>
<th>Species at mass 154 (assumed to be 154Eu), natural 154Sm subtracted</th>
</tr>
</thead>
<tbody>
<tr>
<td>2M HCl</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
</tr>
<tr>
<td>2M HCl J.S. 7-16-14 after heat, no foil</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
</tr>
<tr>
<td>2M HCl 4-16-14 after heating with foil</td>
<td>0.0080</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
</tr>
<tr>
<td>H.S.A. Sm-153, 1-31-14</td>
<td>0.547</td>
<td>0.267</td>
<td>&lt;LOD</td>
<td>5.74</td>
<td>0.0584</td>
</tr>
<tr>
<td>H.S.A. Sm-153 3-20-14</td>
<td>0.0756</td>
<td>0.148</td>
<td>&lt;LOD</td>
<td>7.14</td>
<td>0.0120</td>
</tr>
<tr>
<td>H.S.A. Sm-153 5-22-14</td>
<td>0.0513</td>
<td>0.126</td>
<td>&lt;LOD</td>
<td>7.44</td>
<td>0.0027</td>
</tr>
</tbody>
</table>
# Sm-153 Activity Recovered & Specific Activity

<table>
<thead>
<tr>
<th>Separation</th>
<th>mCi Sm-153</th>
<th>% Sm-153/total Sm &amp; Eu</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>@ Analysis</td>
<td>@ End of Separation</td>
</tr>
<tr>
<td>Separation 2</td>
<td>11.6</td>
<td>17.3</td>
</tr>
<tr>
<td>Separation 3</td>
<td>14.7</td>
<td>19.3</td>
</tr>
<tr>
<td>Separation 4</td>
<td>13.7</td>
<td>21.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Separation</th>
<th>mCi Sm-153</th>
<th>% Sm-153/total mass 153</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>@ Analysis</td>
<td>@ End of Separation</td>
</tr>
<tr>
<td>Separation 2</td>
<td>11.6</td>
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<tr>
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<td>19.3</td>
</tr>
<tr>
<td>Separation 4</td>
<td>13.7</td>
<td>21.6</td>
</tr>
</tbody>
</table>
Three Different Radiopharmaceutical Areas (labeling with small, medium, and large molecules)

Bone-seeking chelants (with HSA $^{153}\text{Sm}$)
- Quadramet (EDTMP) and Cyclosam (DOTMP)
  - Reduce the amount of chelant used due to high specific activity
  - Extend availability of radiopharmaceuticals since no contaminants
  - Waste disposal issues reduced due to removal of long-lived Eu-154/155
  - Evaluate biodistribution in laboratory rats

Labeling a small peptide
- DOTA-Octreotate (8 amino-acid analogue; diagnoses and cancer)
  - Presently used with $^{177}\text{Lu}$ but HSA $^{153}\text{Sm}$ could be used

Labeling of antibodies & proteins: HuM195 and human serum albumin
- Labeled HuM195 useful to diagnose and treat leukemia
- Human serum albumin most abundant blood protein
- Successful labeling is $>30\%$ labeling efficiency
RADIOLABELING WITH HSA Sm-153

Sm-153-DOTMP
>99% Complexed

DOTAAtate
>95% Labeling
Radiolabeling with HSA Sm-153

HuM-195 (150 kDa)  
>92% Pre-Complexation

Human Serum Albumin  
(67 kDa)  
>92% Pre-Complexation  
~99% Direct labeling

\[ \text{p-SCN-Bn-DOTA} \]
DOTMP chelate made with HSA $^{153}$Sm: and 99% chelation was achieved. This was then administered to 2 rats and the biodistribution below shows the specificity to the bone. This distribution is consistent with known bone agents in rodents.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Rat 1</th>
<th>Rat 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% ID</td>
<td>% ID/G</td>
</tr>
<tr>
<td>Blood*</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Heart</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Lung</td>
<td>1.3%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Skeletal*</td>
<td>1.7%</td>
<td>31.1%</td>
</tr>
<tr>
<td>Muscle*</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Liver</td>
<td>1.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.4%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Sm. Int.</td>
<td>0.3%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Lg. Int.</td>
<td>0.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Tail</td>
<td>1.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>U/F</td>
<td>35.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Total</td>
<td>41.8%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Biodistribution in Rats with HSA Sm-153 DOTMP
COMMERCIALIZATION PLANS
Therapeutic Isotope Separator

Glove Boxes
Magnet
Ion Collector
Robotic Handling
Ion Source
THERAPEUTIC ISOTOPE SEPARATOR FACILITY (TISF)
MURR FLOOR PLAN
CONCLUDING REMARKS

SBIR Phase II project demonstrated that an EMIS approach can be used to convert low SA materials to high SA and shows potential for use of high specific activity, $^{153}$Sm as a therapeutic agent.

Year one: developed new ion source and testing with stable isotopes;
Year two: produced high specific activity $^{153}$Sm for labeling and biodsitribution studies at ITG

This project, if successful, could be of great benefit for the future production and use of radionuclides as therapeutic agents.

Breakthrough project from perspective of demonstration of EM technique applied to isotopes made by neutron capture, i.e. many diagnostic and therapeutic isotopes.

The Long Term Goal is a commercial operation for the production of high specific activity, reactor produced, radiodiagnostic and radiotherapeutic isotopes.

But really need ORNL HRIBF facilities to perform R&D studies with radioactive materials.