SBIR/DOE Phase II Project

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

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Motivation

(for Electromagnetic approach)

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}Sm)

^{153}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.

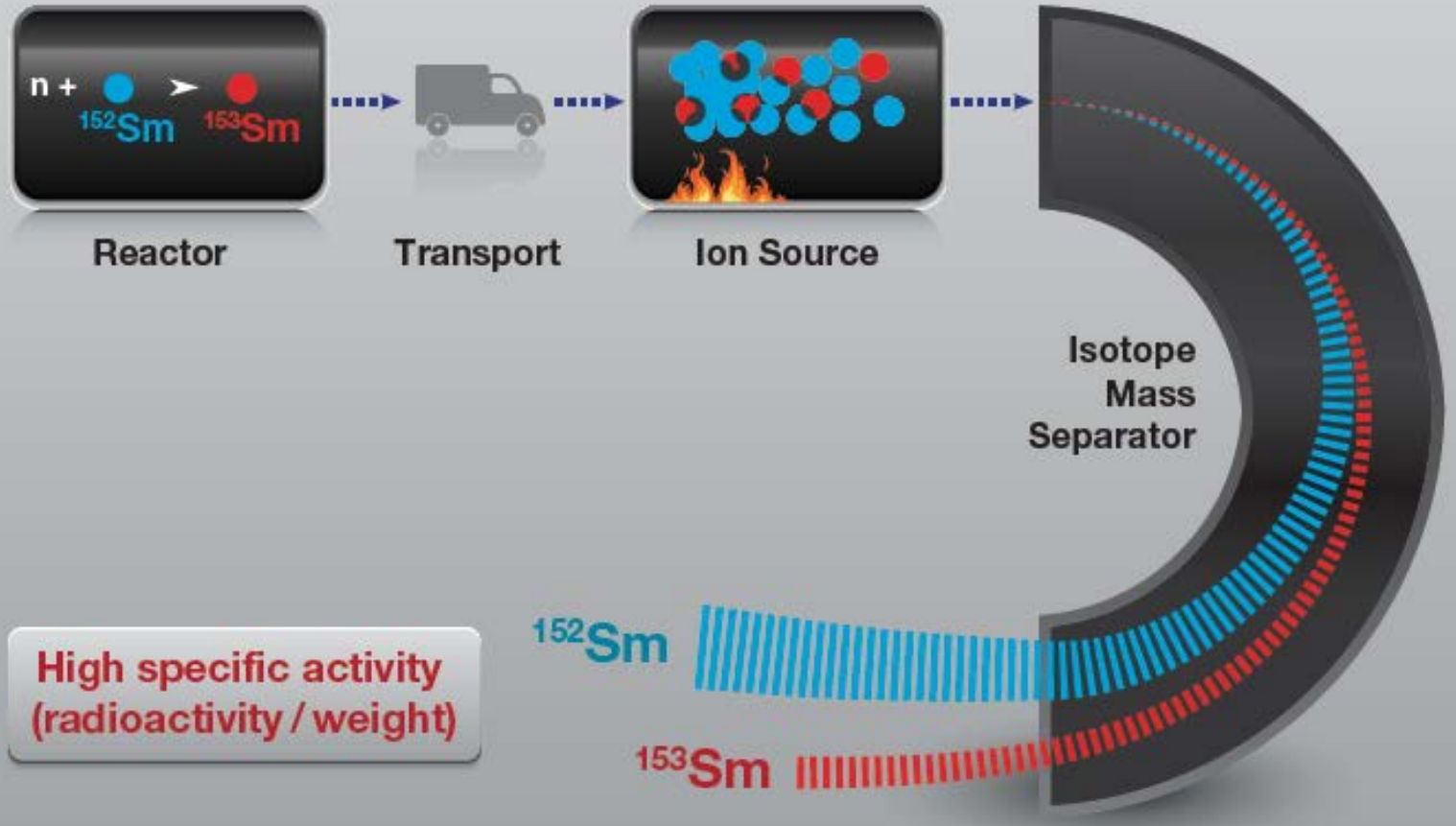
^{153}Sm is produced by ^{152}Sm(n,γ)^{153}Sm reaction with a typical 2% yield (at MURR)

Need to produce higher specific activity (higher isotopic purity) material to test if HSA ^{153}Sm is compelling as a form of treatment

Production and Separation of ^{153}Sm

Production of ^{153}Sm: ^{152}Sm (neutron, gamma) ^{153}Sm

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



High specific activity (radioactivity / weight)

Project Team

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

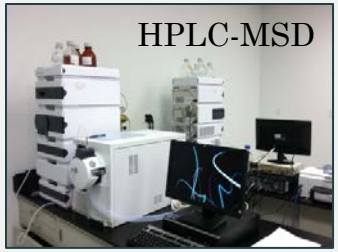
MURR (Missouri University Research Reactor)

- Chemistry Development and production of LSA ^{153}Sm

IsoTherapeutic Group: Fully Equipped for Radiopharmaceutical R&D


GE GAMMA DETECTOR


ICP-OES

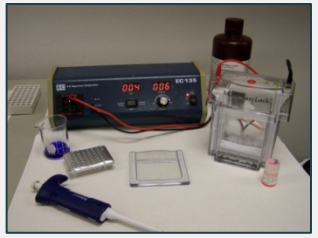

HPLC-MSD

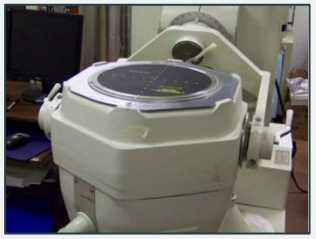
Key R&D Equipment

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)

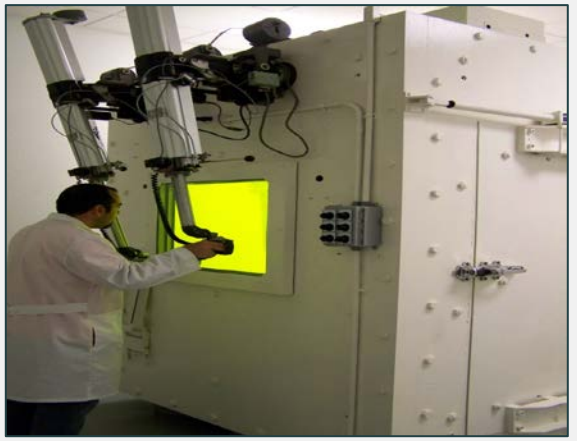
Labeling Proteins with Bifunctional Chelating Agents (Ac-225, Ho-166, In-111, Lu-177, Sm-153, Sn-117m and Y-90)

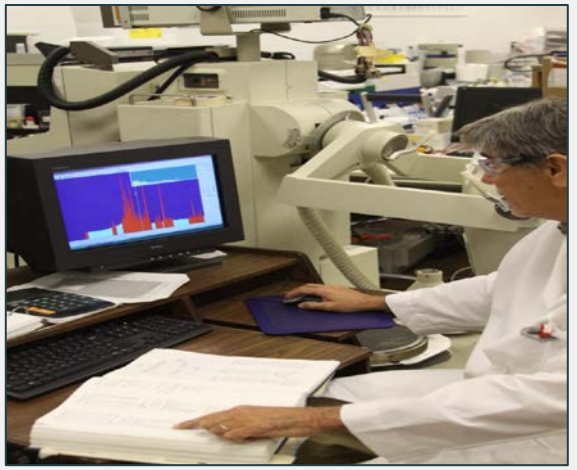
Labeling Small Molecules with Short-Lived Alpha Emitters (Bi-213)

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

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

Hot Cell





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

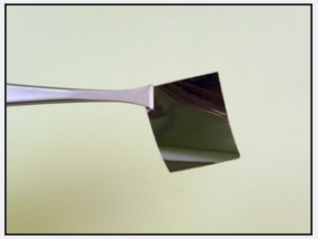
Irradiated ^{152}Sm (>99%; 5 mg): flux = 3.5-4.5 x 10^{14} n/cm^2·s for 10 hours; **HFIR**

{~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

Nuclear Properties ^{153}Sm
- **Half life – 46.3 hours**
- **Radiations**
  - **Gamma – 69 and 103 keV (~30%)**
  - **Beta – low energy (~0.5 MeV)**
- **Decay Product – Stable**

Nuclear Properties ^{154}Eu
- **Half life – 8.6y**
- **Radiation**
  - **Gamma – 82 and 184 keV**
  - **Beta – low energy (~0.2 MeV)**
- **Decay Product – Stable**

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

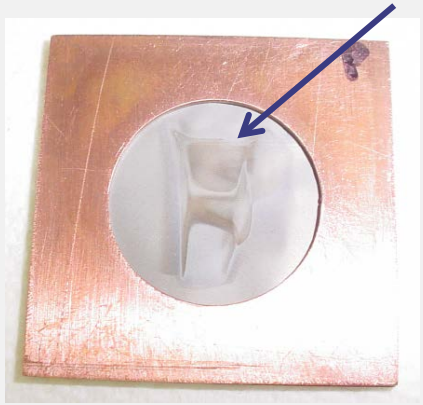
Full test runs with hot/irradiated material (4 runs).

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



^{152}Sm DCL Foil Pyrolysis

SmDLC: Labeled "Primary DLC Foil – Removed from IRIS2 09/27/13"

SmDLC: Labeled "Primary DLC Foil – Removed from IRIS2 09/27/13"

SmDLC side view

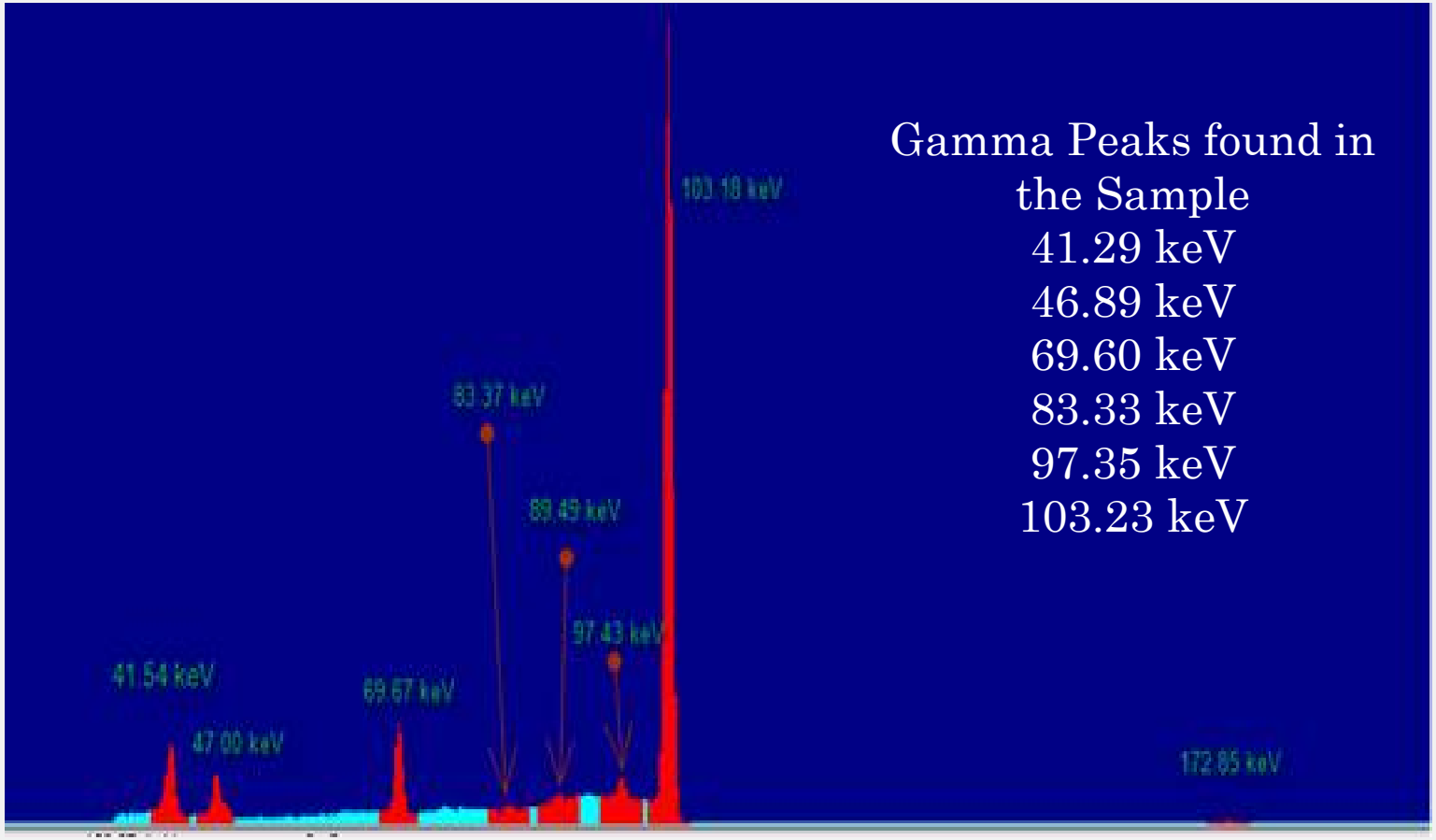
Samples (with crucible covers) in muffle furnace before heating

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.

Sm-153 Recovery

Date Received	Initial Activity In Foil (mCi)	Recovered Activity (mCi)	Activity left in crucible
11/1/13	10.0	9.5	0.3
1/30/14	10.9	11.6	0.6
3/19/14	16.0	14.7	2.0
5/21/14	13.7	13.7	0.6

HPGe Analysis of HSA Sm-153



All gamma energies are consistent with Sm-153

ICP-MS Results Hot Runs

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

Sm-153 Activity Recovered & Specific Activity

	mCi Sm-153		% Sm-153/total Sm & Eu	
	@ Analysis	@ End of Separation	@ Analysis	@ End of Separation
Separation 2	11.6	17.3	39%	59%
Separation 3	14.7	19.3	45%	59%
Separation 4	13.7	21.6	40%	64%

	mCi Sm-153		% Sm-153/ total mass 153	
	@ Analysis	@ End of Separation	@ Analysis	@ End of Separation
Separation 2	11.6	17.3	45%	68%
Separation 3	14.7	19.3	46%	61%
Separation 4	13.7	21.6	41%	65%

Radiolabeling Studies with HSA ^{153}Sm

Three Different Radiopharmaceutical Areas (labeling with small, medium, and large molecules)

Bone-seeking chelants (with HSA ^{153}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

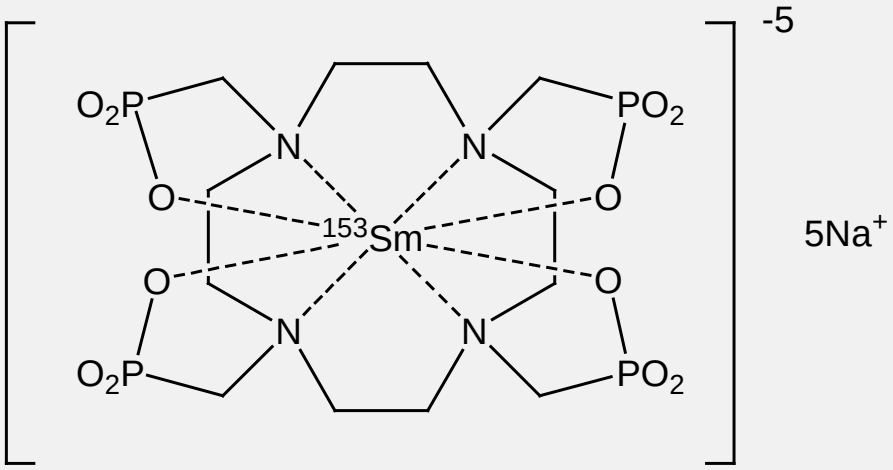
DOTA-Octreotate (8 amino-acid analogue; diagnoses and cancer)

- Presently used with ^{177}Lu but HSA ^{153}Sm could be used

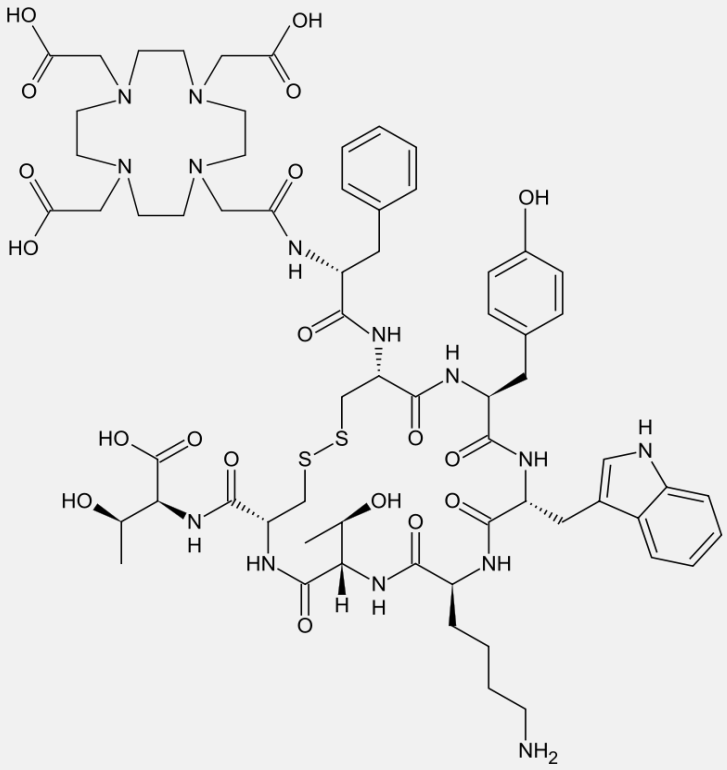
Labeling of antibodies & proteins: HuM195 and human serum albumin

- Labeled HuM195 useful to diagnose and treat luekemia
- Human serum albumin most abundant blood protein
- Successful labeling is >30% labeling efficiency

Radiolabeling with HSA Sm-153

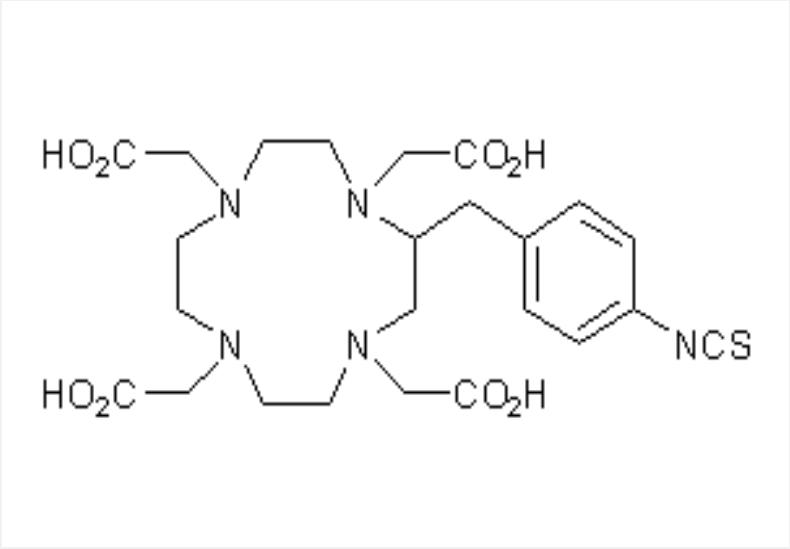


Sm-153-DOTMP
>99% Complexed



DOTAtate
>95% Labeling

Radiolabeling with HSA Sm-153



p-SCN-Bn-DOTA

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

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

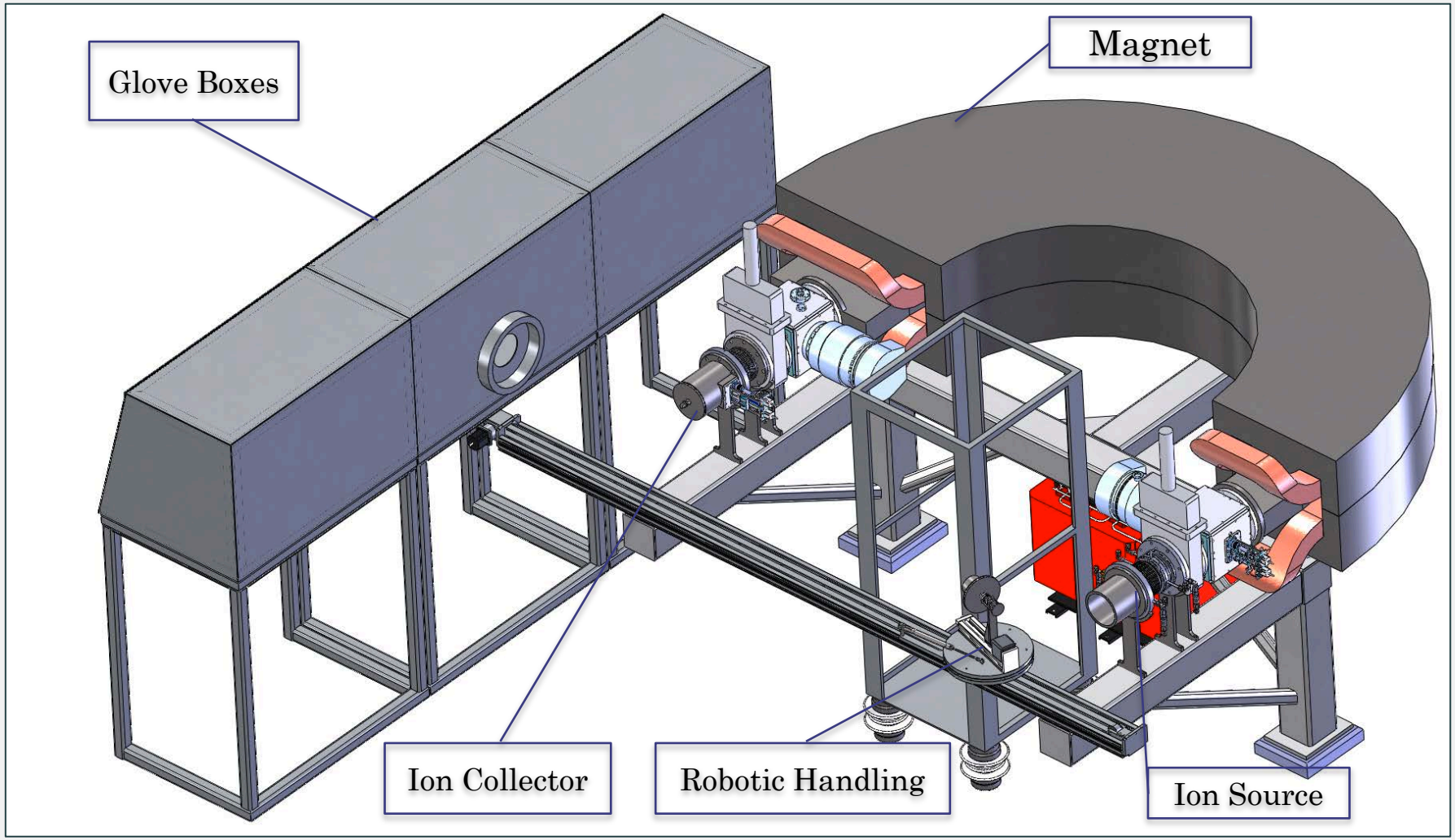
Biodistribution in Rats with HSA Sm-153 DOTMP

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.

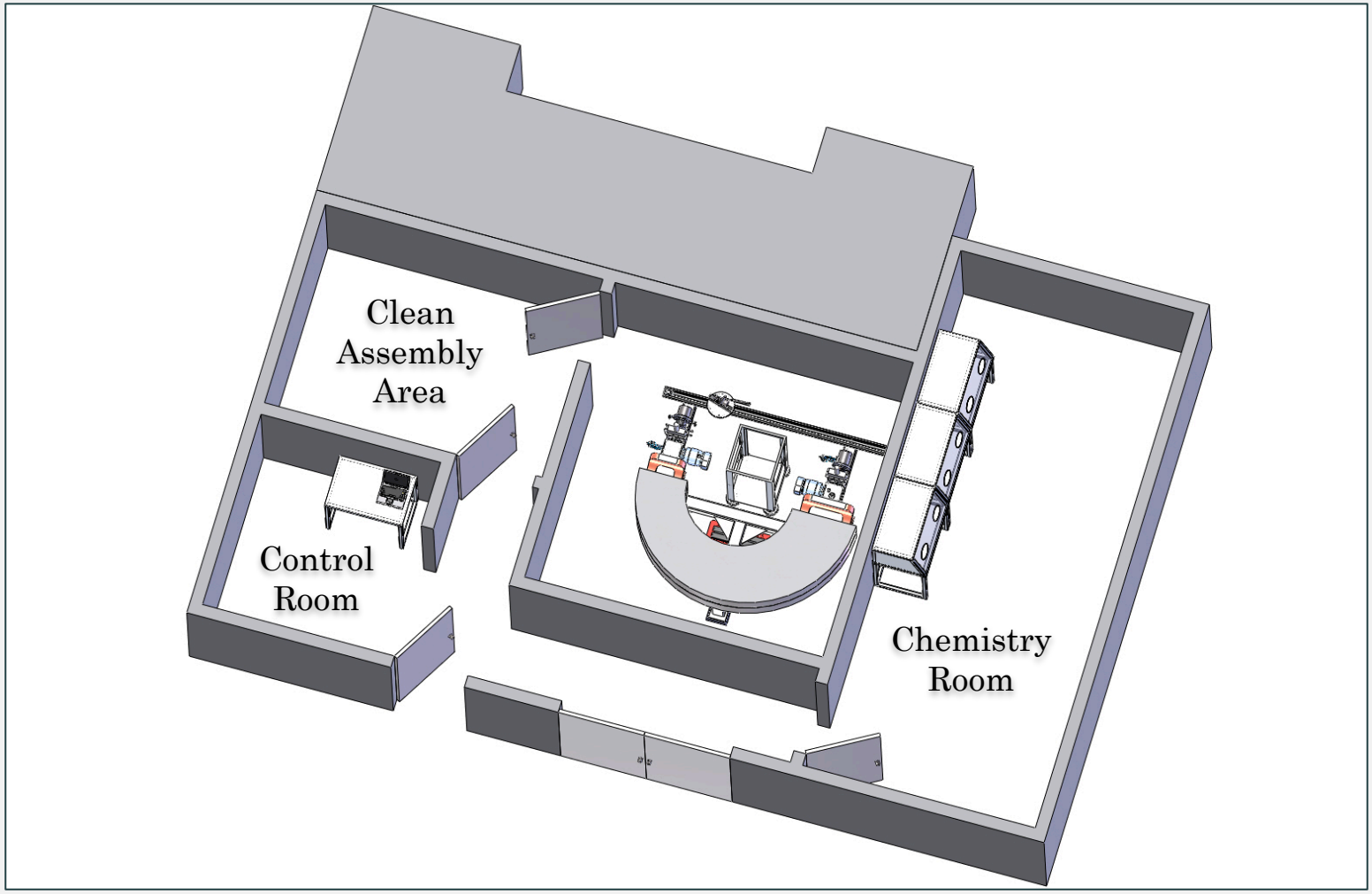
	Rat1					Rat 2			
Tissue	% ID	% ID/G	CPM	Normalized	Tissue	% ID	% ID/G	CPM	Normalized
Blood*	0.0%	0.0%	264.6	0.0%	Blood*	0.0%	0.0%	0	0.0%
Heart	0.0%	0.0%	0.0	0.0%	Heart	0.0%	0.0%	0	0.0%
Lung	1.3%	1.0%	36805.2	1.8%	Lung	0.9%	0.6%	22206.5	1.1%
Skeletal*	1.7%	31.1%	910178.9	**43.7%**	Skeletal*	2.0%	35.8%	916765.7	**45.2%**
Muscle*	0.0%	0.0%	0.0	0.0%	Muscle*	0.0%	0.0%	0	0.0%
Liver	1.2%	0.1%	34938.8	1.7%	Liver	0.6%	0.0%	15286.4	0.8%
Spleen	0.1%	0.1%	3091.2	0.1%	Spleen	0.1%	0.1%	2324.6	0.1%
Kidney	0.4%	0.2%	10724.2	0.5%	Kidney	0.4%	0.2%	10064.6	0.5%
Sm. Int.	0.3%	0.0%	9196.5	0.4%	Sm. Int.	0.1%	0.0%	1459.5	0.1%
Lg. Int.	0.4%	0.0%	10275.5	0.5%	Lg. Int.	0.2%	0.0%	5772.4	0.3%
Stomach	0.0%	0.0%	1208.2	0.1%	Stomach	0.0%	0.0%	471.3	0.0%
Tail	1.4%		41949.3	2.0%	Tail	1.4%		34743.5	1.7%
U/F	35.0%		1023817.3	49.2%	U/F	39.9%		1020973.2	50.3%
Total	41.8%			100.0%	Total	45.6%			100.0%
		Blood	11.9				Blood	0	
		Femur	50776.2				Femur	52137.8	
		Muscle	0				Muscle	0	

Commercialization Plans

THERAPEUTIC ISOTOPE SEPARATOR



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.