SBIR/DOE Phase II Project

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

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and Simon Fraser University

SBIR/STTR Exchange Meeting
November 7, 2013

Outline

- Goal and Objectives of Project
- Motivation and Rationale (Why?)
- The Team
- General description/Background (How?)
- Experimental Status
- Concluding Remarks

Goal

Demonstrate that high specific activity (HSA*) ^{153}Sm, can be produced by post irradiation, followed by isotope separation;

and that its use is compelling as a therapeutic agent (based on pre-clinical study results).

* Specific activity – Radioactivity of specific isotope/total mass

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**

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

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.

Radioisotopes for Therapy

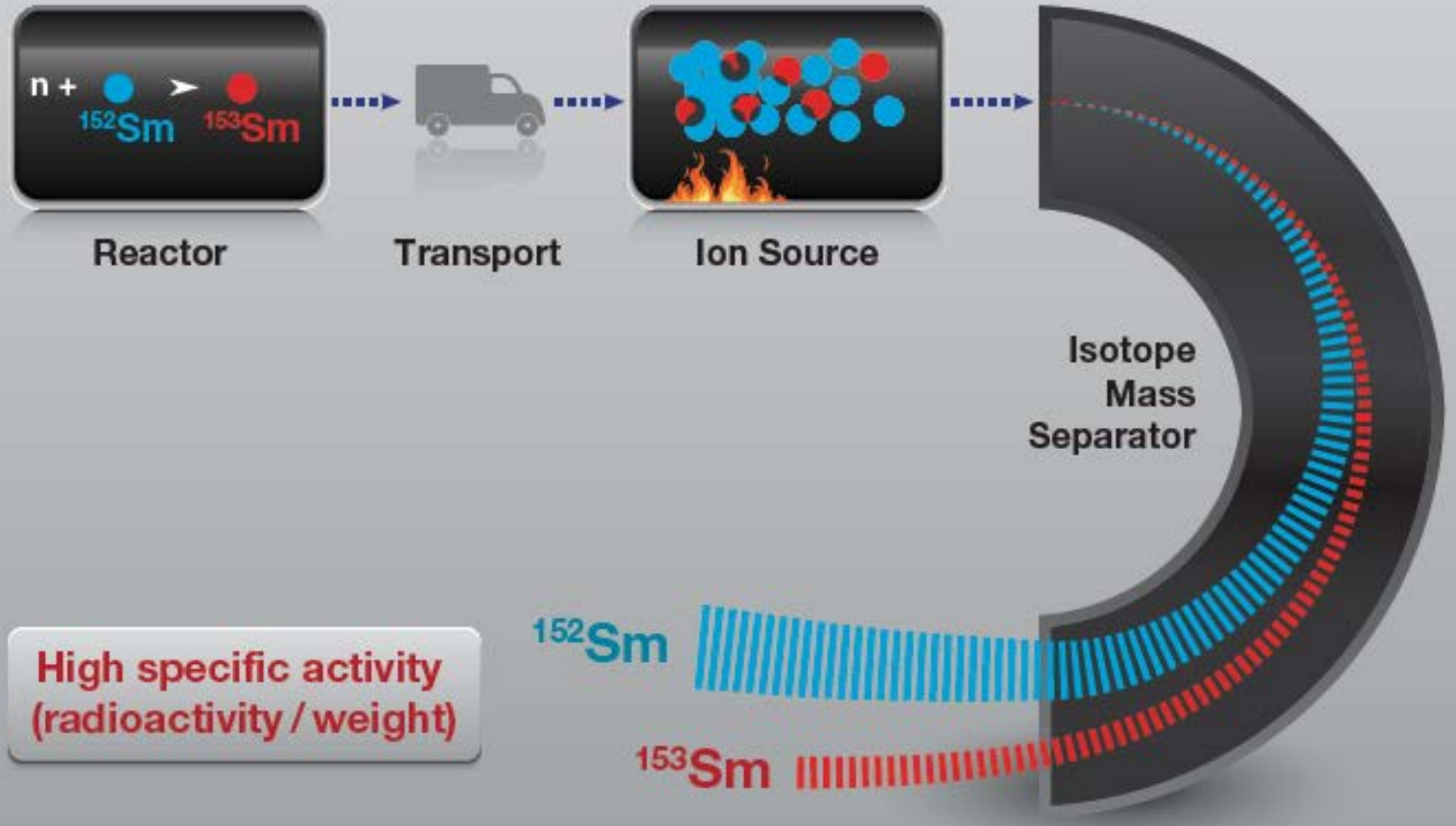
Isotope	$t_{1/2}$	Reaction	Possible Use
^{67}Cu**	62h	Accelerator	Ovarian cancer
^{90}Y	2.67 d	Fission $^{90}Sr(\beta^-)$ ^{90}Y	Various cancers
^{131}I	8.02 d	$^{130}Te(n,\gamma,\beta^-)^{131}I$	hyperthyroidism
^{153}Sm**	46.3 h	$^{152}Sm(n,\gamma)^{153}Sm$	Bone cancer
^{117m} Sn*	13.6 d	$^{116}Sn(n,\gamma)$ $^{117m,g}Sn$	theranostic
^{166}Ho**	27 h`	$^{165}Ho(n,\gamma)^{166}Ho$	Liver cancer
^{177}Lu**	6.85 d	$^{176}Lu(n,\gamma)^{177}Lu$	Various cancers
^{186}Re**	3.72 d	$^{185}Re(n,\gamma)^{186}Re$	Bone cancer
^{211}At**	7.2 h	$^{209}Bi(\alpha,2n)$ ^{211}At	Various cancers

** Not yet available in commercially usable amounts

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

MURR (Missouri University Research Reactor)

Chemistry Development and production of LSA ^{153}Sm

ITG (Isotherapeutics Group, Texas)

Preclinical studies of 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

Collaborators

Keith Frank, CEO	IsoTherapeutics Group, LLC-Texas
Jaime Simon	IsoTherapeutics Group, LLC-Texas
Alan Ketring	Missouri University Research Reactor
Dan Stracener	Oak Ridge National Laboratory
Keith Ladouceur	Advanced Applied Physics Solutions
Suzy Lapi	Washington University (St. Louis)
Tom Ruth	TRIUMF (Emeritus)
Paul Schmor	TRIUMF (Emeritus)/SPAC Inc.

IsoTherapeutics Group (ITG)

EXPERIENCED GROUP OF PEOPLE (14)
IN RADIOPHARMACEUTICAL R&D & MANUFACTURING

Radiopharmaceutical R&D Manufacturing

- R&D capabilities
  - Chelation
  - Conjugation
  - Kits
  - Analytical capabilities
- 4,000 sq. ft. cGMP facility
- 5' x 5' hot cell
- I-131, I-125, Lu-177, Y-90, Ac 225, Sm-153, Ho-166, Tc-99m, Sn-117m, Re-186, Re-188, In-111, Zr-89

Small Animal Studies

- Rodent facilities on site
- Experience with dogs
- Collaborations with cancer centers and veterinary medical schools
- Biodistribution studies and calculations (OLINDA/EXM)

Experienced People

- Over 120 patents by company scientists
  - QUADRAMET®
  - STR (166Ho-DOTMP)
- Lead ChelaMed℠ radiopharma services at The Dow Chemical Company
- Strong scientific advisory board
- Receipts of NIH and DOE SBIR Awards

Project Overview

PROJECT OVERVIEW

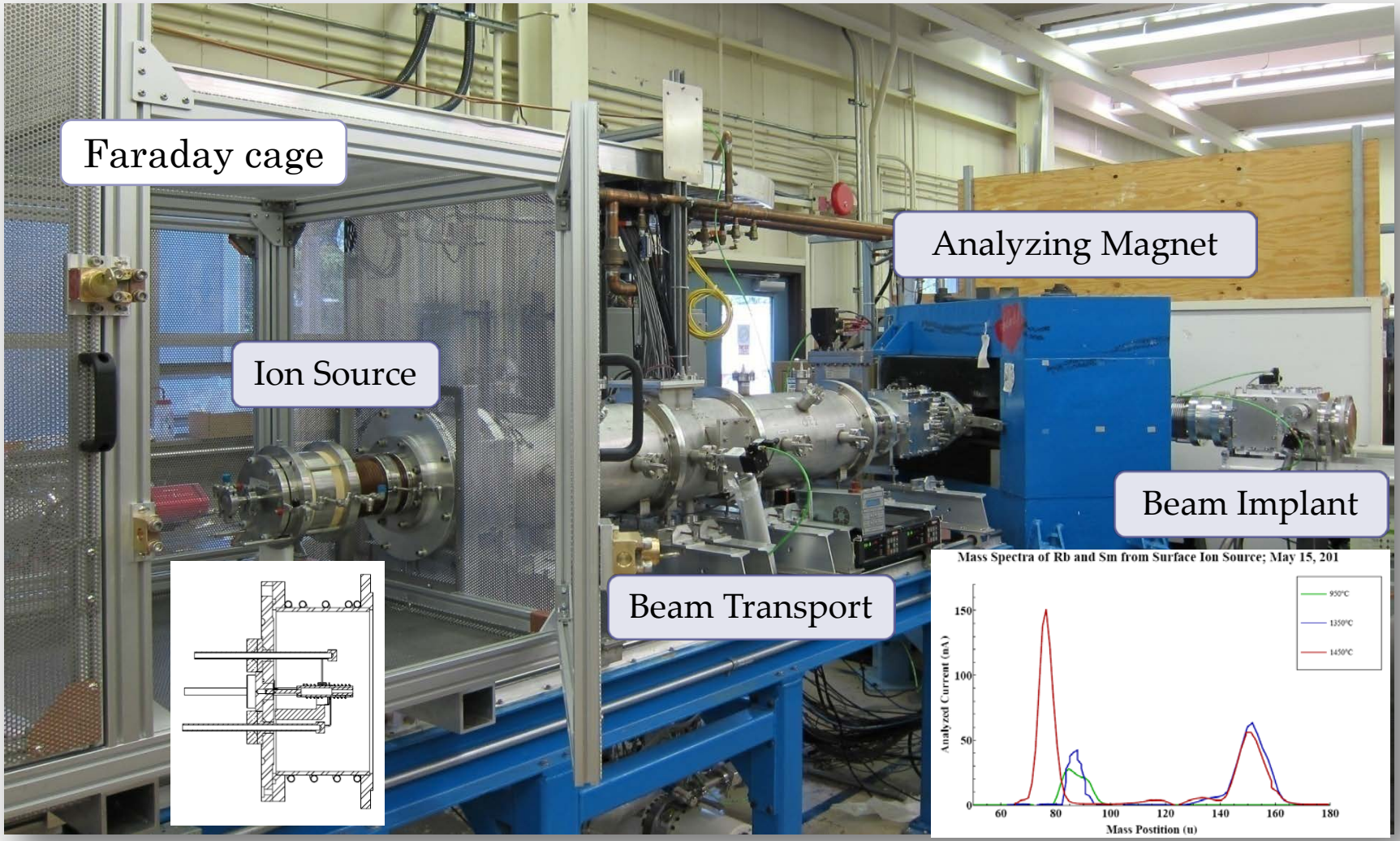
YEAR ONE (Stable Sm Isotopes)

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

Develop appropriate collection approach following mass separator
- COMPLETED

Study removal of implanted samarium for implanted foil
(at MURR) - COMPLETED

Ion Source Test Facility (ISTF)



Project Overview

YEAR TWO (in progress)

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

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

Deliverables to ITG for pre-clinical studies

Produce HSA samples of ^{153}Sm

(up to 5; one per 6 week interval) at ORNL

Experimental

YEAR 2: EXPERIMENTAL SPECIFICS

GOAL – Deliver five samples of 10 mCi of HSA^{153}Sm to ITG

The Plan

Irradiate ^{152}Sm (>95%; 5 mg): flux = 5 x 10^{14} n/cm^2·s for ONE day; **HFIR**

{~ 16 Ci ^{153}Sm (0.8% ^{153}Sm conversion) with 0.5 μCi ^{155} Eu contamination}

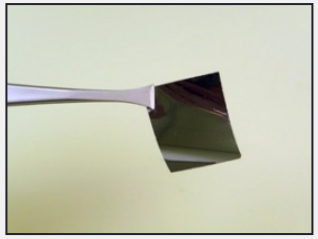
Perform isotopic mass separation (IRIS2 at ORNL)

Implant ~30 mCi ^{153}Sm onto 10μm Diamond-Like Carbon (DLC) foils

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

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

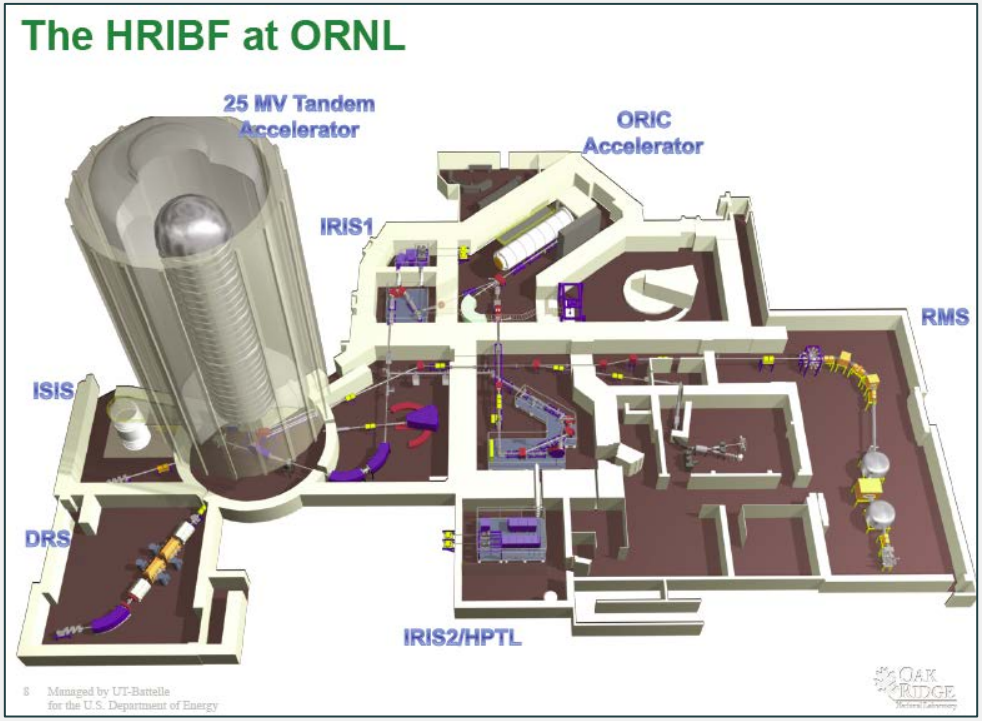
Sample radioactively pure using gamma spectrum

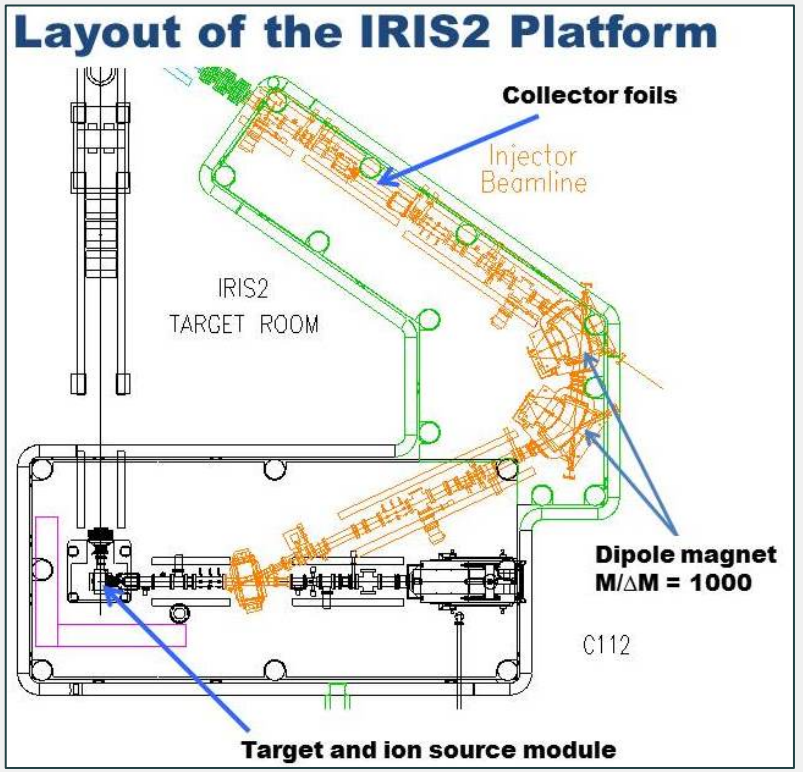


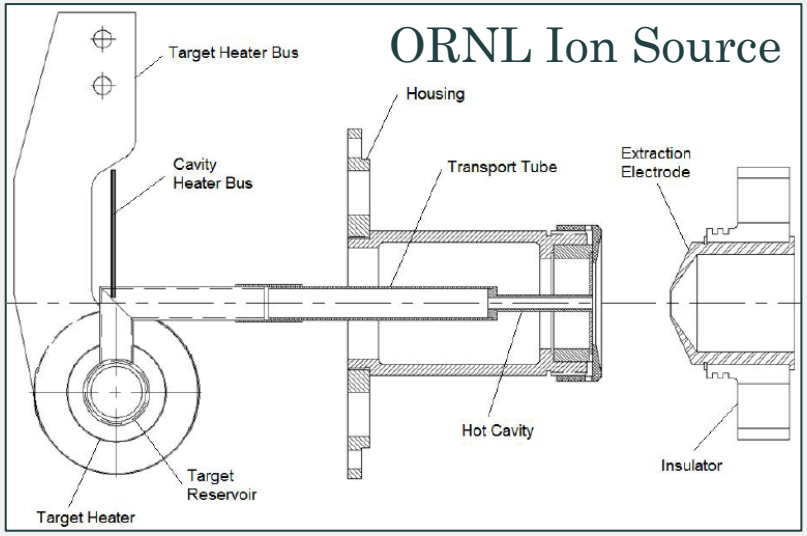
Nuclear Properties ^{153}Sm
- **Half life – 46.3 hours**
- **Radiations**
  - **Gamma – 69 and 103 keV (~30%)**
  - **Beta – low energy (~0.5 MeV)**
- **Decay Product – Stable**

Nuclear Properties ^{155}Eu
- **Half life – 4.76y**
- **Radiation**
  - **Gamma – 86 and 105 keV**
  - **Beta – low energy (~0.2 MeV)**
- **Decay Product – Stable**

ORNL



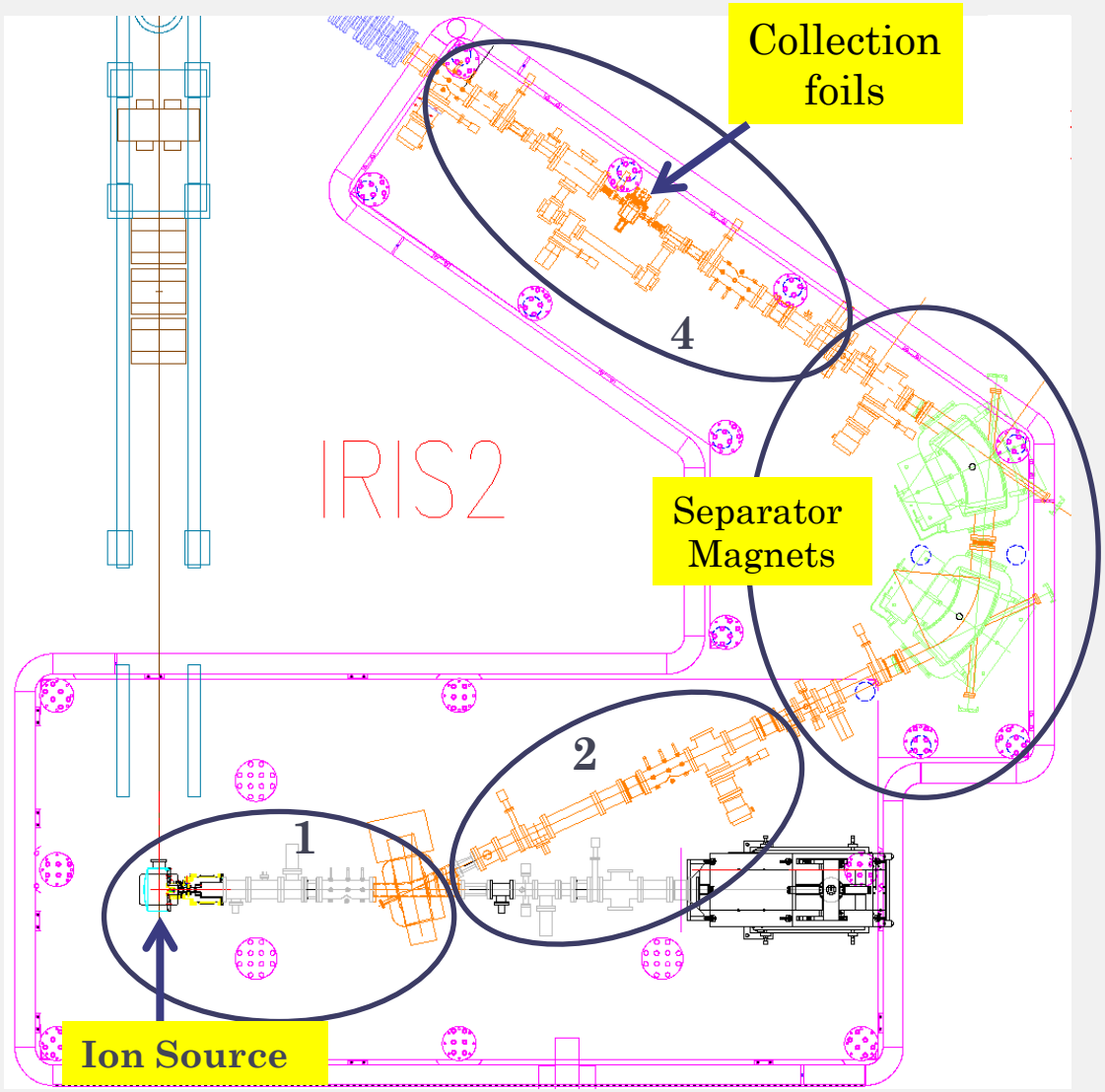




HFIR (High Flux Isotope Reactor)
for (n,γ) Reaction

And IRIS2 for EM Isotope Separator

Injector Beamline Overview



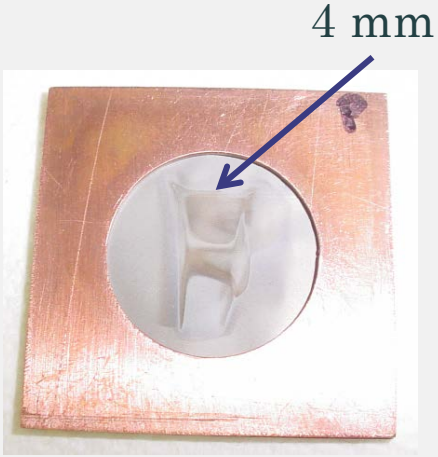
1. 1st leg – includes ion source, BPM/FC, x/y-steerer, EQT lens and 25° dipole magnet
2. 2nd leg – y-steerer, BPM, EQT lens
3. 1st-stage mass separator magnet system – BPM, x/y-slits & FC at object & image positions; two 60° double-focusing dipole magnets
4. 3rd leg – x/y-steerer, EQT lens, CEC w/FC's or Cooler, BPM, x/y-steerer and EQT lens

Status of 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 into aqueous solution



Full test run with hot/irradiated material; Oct. 28-31.

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

Using IRIS2 EMIS, implanted ~15 mCi onto DLC foils
(primary and sputter) during ~12 hour run

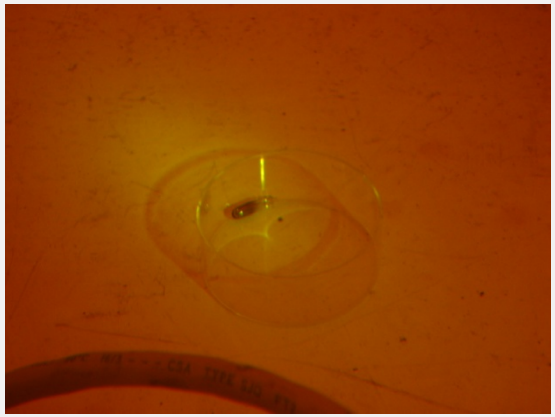
Delivered (~10 mCi) to ITG for initial testing of procedure

Initial results indicate ~95% recovery of ^{153}Sm

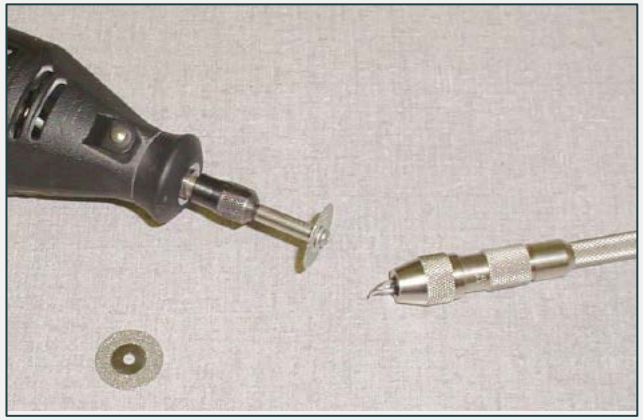
First official run with delivery set for **Dec. 9, 2013**

Experimental Handling Details

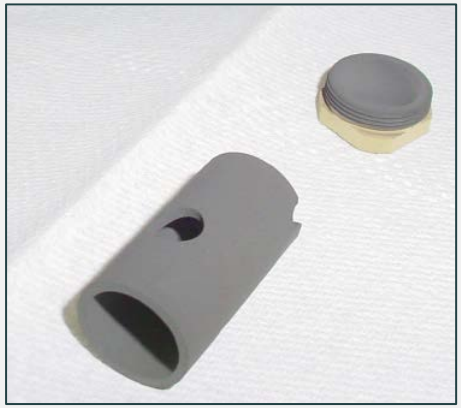
Ampules with Sm foil for HFIR



Quartz after irradiation

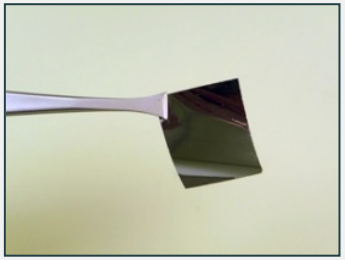


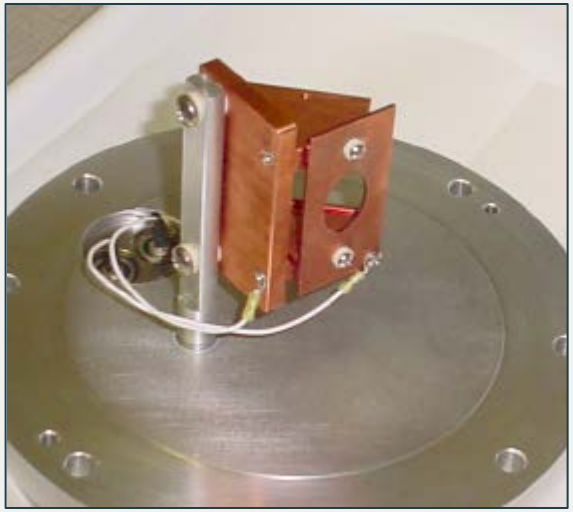
Method to Open Ampule in Hot Cell

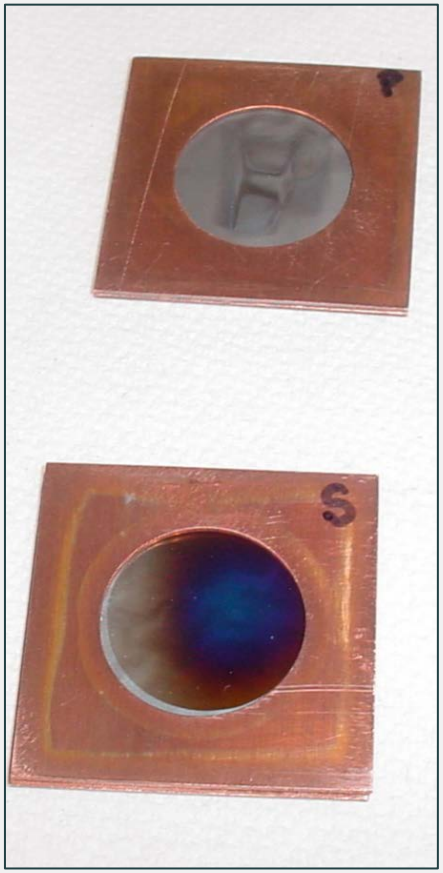


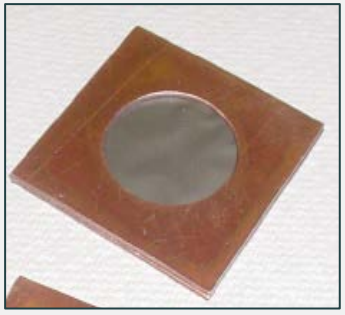
Graphite capsule to hold hot Sm foil for ion source

Collection System



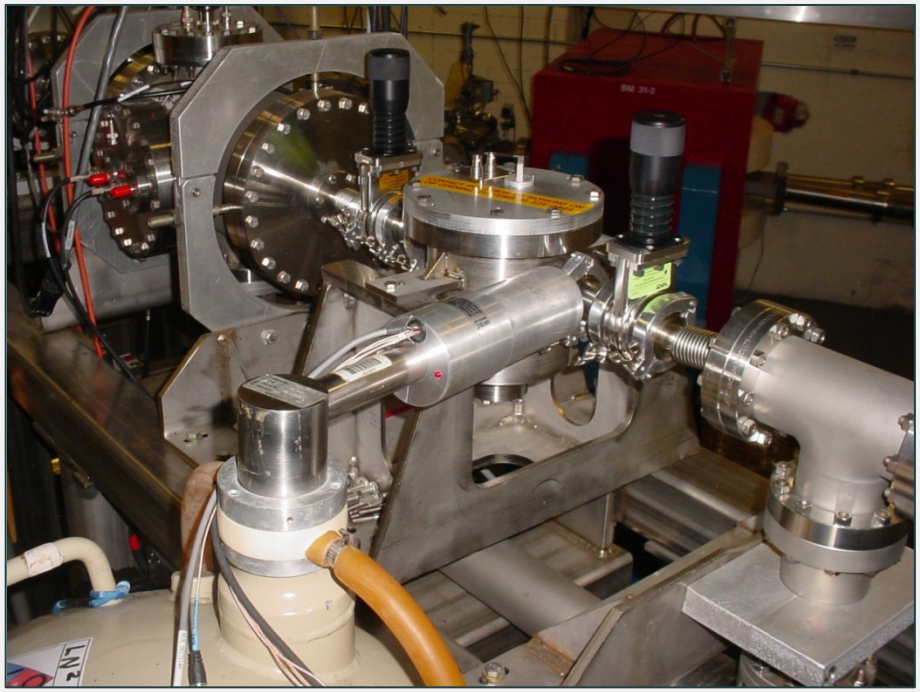




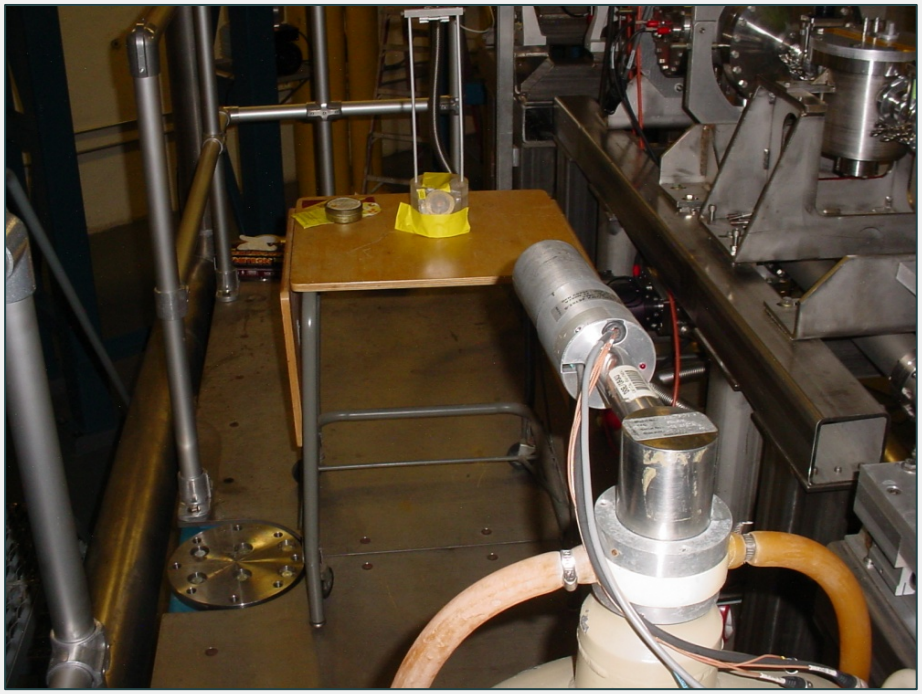


Activity collected was both monitored with Ge gamma detector and by monitoring the beam current

Ge Detector

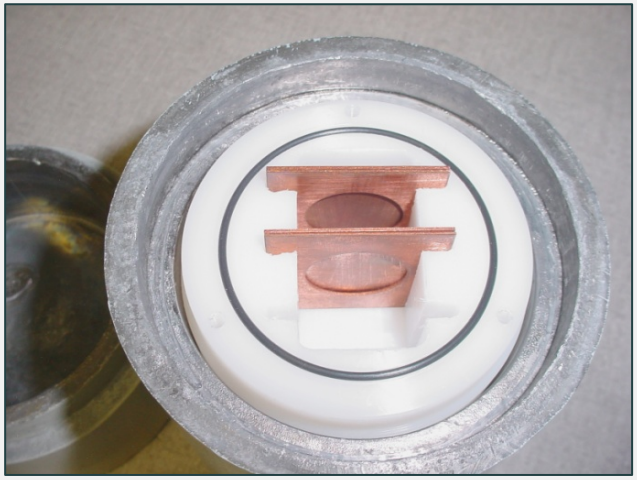


Measuring activity during implantation



Measuring activity after implantation

Shipment To ITG



Pyrolyze the DLC foil graphite at 900C, dissolve Sm residue in acid

Chemically convert to biochemical compound

Remember ^{153}Sm decays to ^{153}Eu which reduces specific activity.
i.e., after 2 days, SA ~ 50% of NCA (No Carrier Added), but better than 2% present for LSA (and stripped of radioactive Eu contaminants), and increased from a SA of 0.3% following the irradiation at HFIR.

Pre-Clinical 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 since less chelant
- Need to determine minimum amount of chelant needed for chelate
- Evaluate biodistribution in laboratory rats and confirm similar to present.

Labeling a small peptide

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

- Presently used with ^{177}Lu but ^{153}Sm better given HSA & purity
- Need to show can be used & determine lowest amount of protein needed

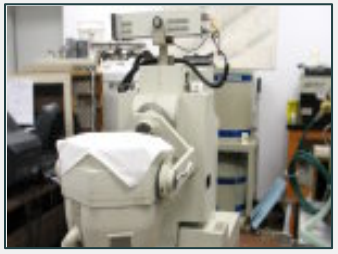
Studies with protein Annexin (36,000 Daltons)

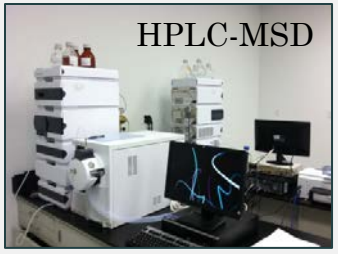
- Labeled Annexin useful to diagnose cardiovascular and cancer
- Need longer lived isotope such as ^{153}Sm
- Beta emission also useful for therapy
- Success is >30% labeling efficiency and retaining bio. activity

Fully Equipped to Help Advance Radiopharmaceuticals


GE GAMMA DETECTOR


ICP-OES



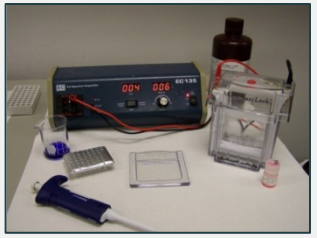

HPLC-MSD

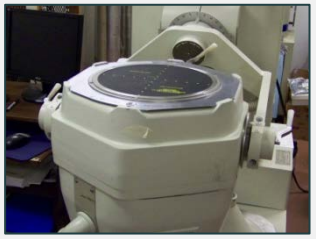
Key R&D Equipment

Two Fully Equipped Laboratories and cGMP Manufacturing

Phosphor Imaging System

NaI Well Detector





Radioisotope Labeling Experience

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

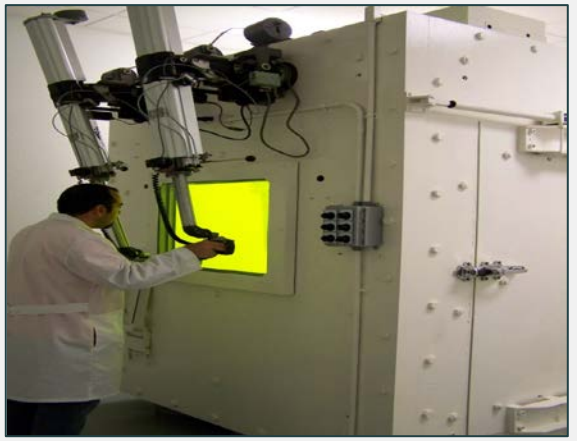
Labeling Proteins with Bifunctional Chelating Agents (Ac-225, Ho-166, In-111, Lu-177, Sm-153, Sn-117m and Y-90)

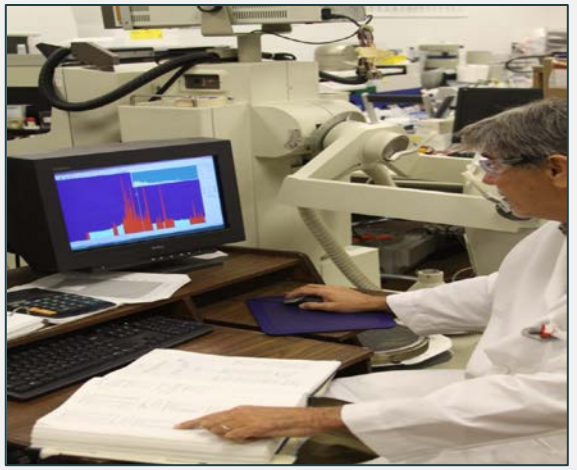
Labeling Small Molecules with Short-Lived Alpha Emitters (Bi-213)

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

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

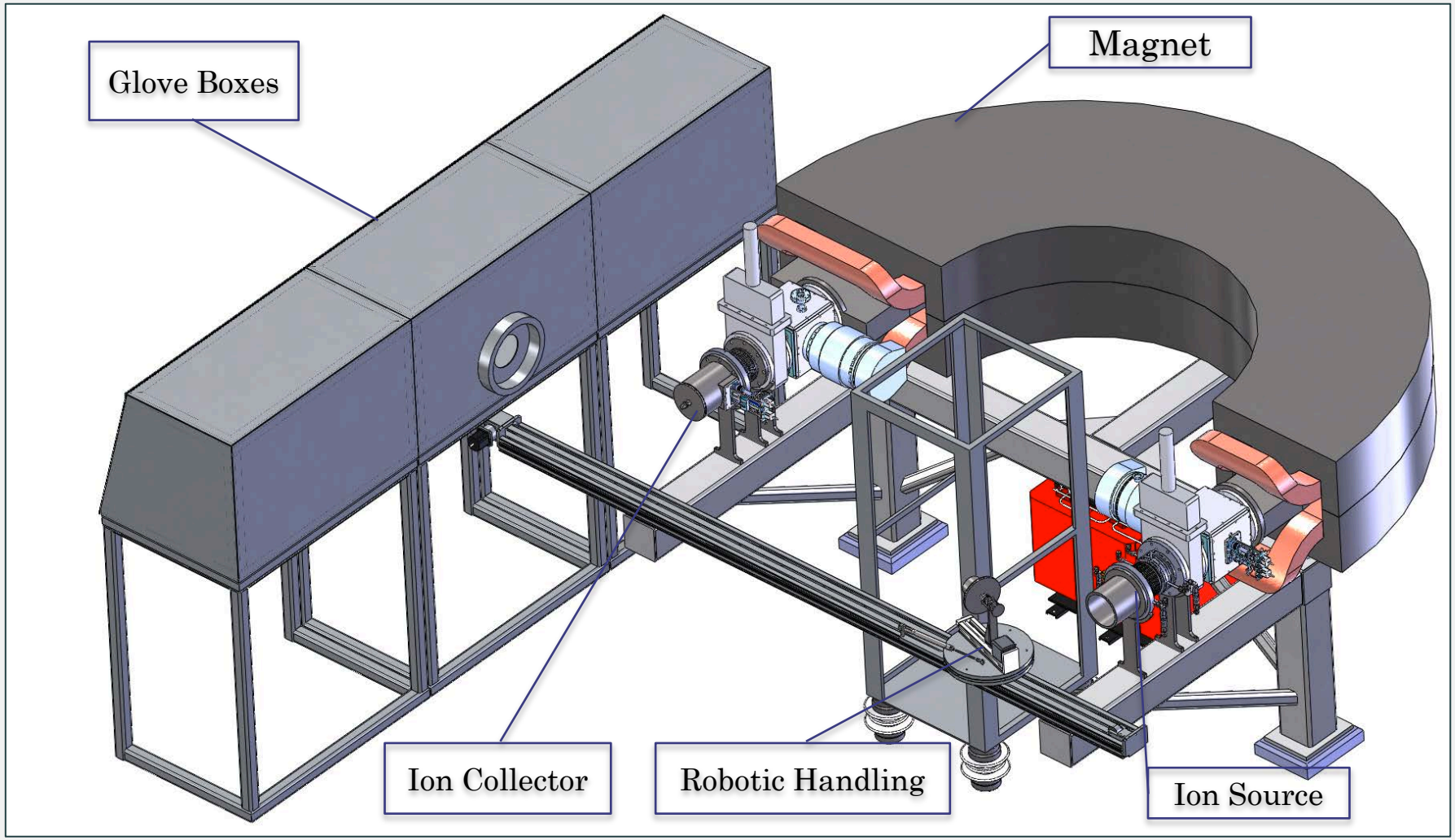
Hot Cell



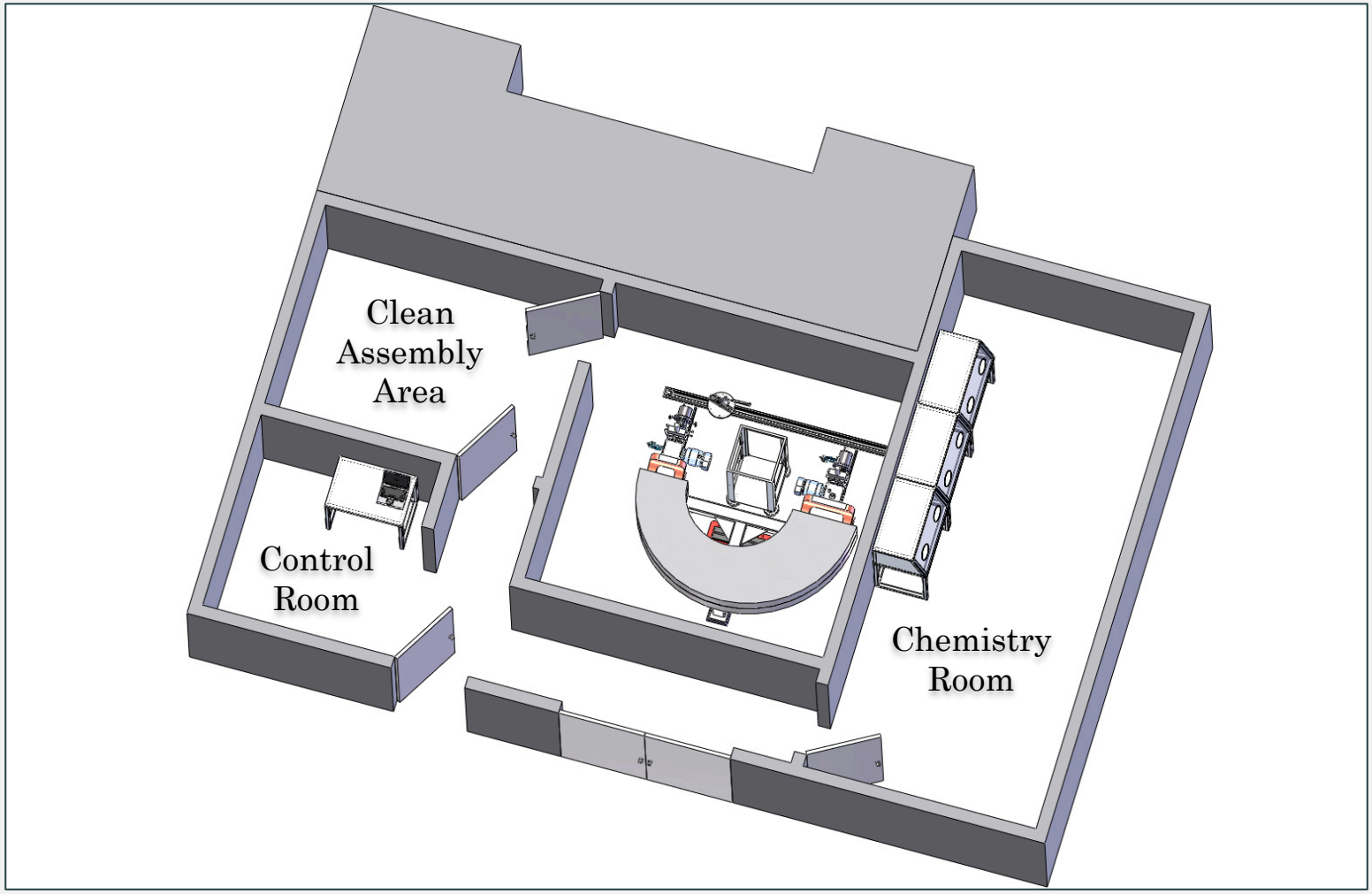


Commercialization Plans

THERAPEUTIC ISOTOPE SEPARATOR



Therapeutic Isotope Separator Facility (TISF) MURR Floor Plan



Concluding Remarks

SBIR Phase II project in progress to demonstrate that an EMIS approach can be used
to convert low SA materials to high SA and
to show use of high specific activity, ^{153}Sm,is compelling as a therapeutic agent.

Year one involved developing new ion source and stable isotopes;

Year two involves producing high specific activity ^{153}Sm for pre-clinical studies at ITG

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

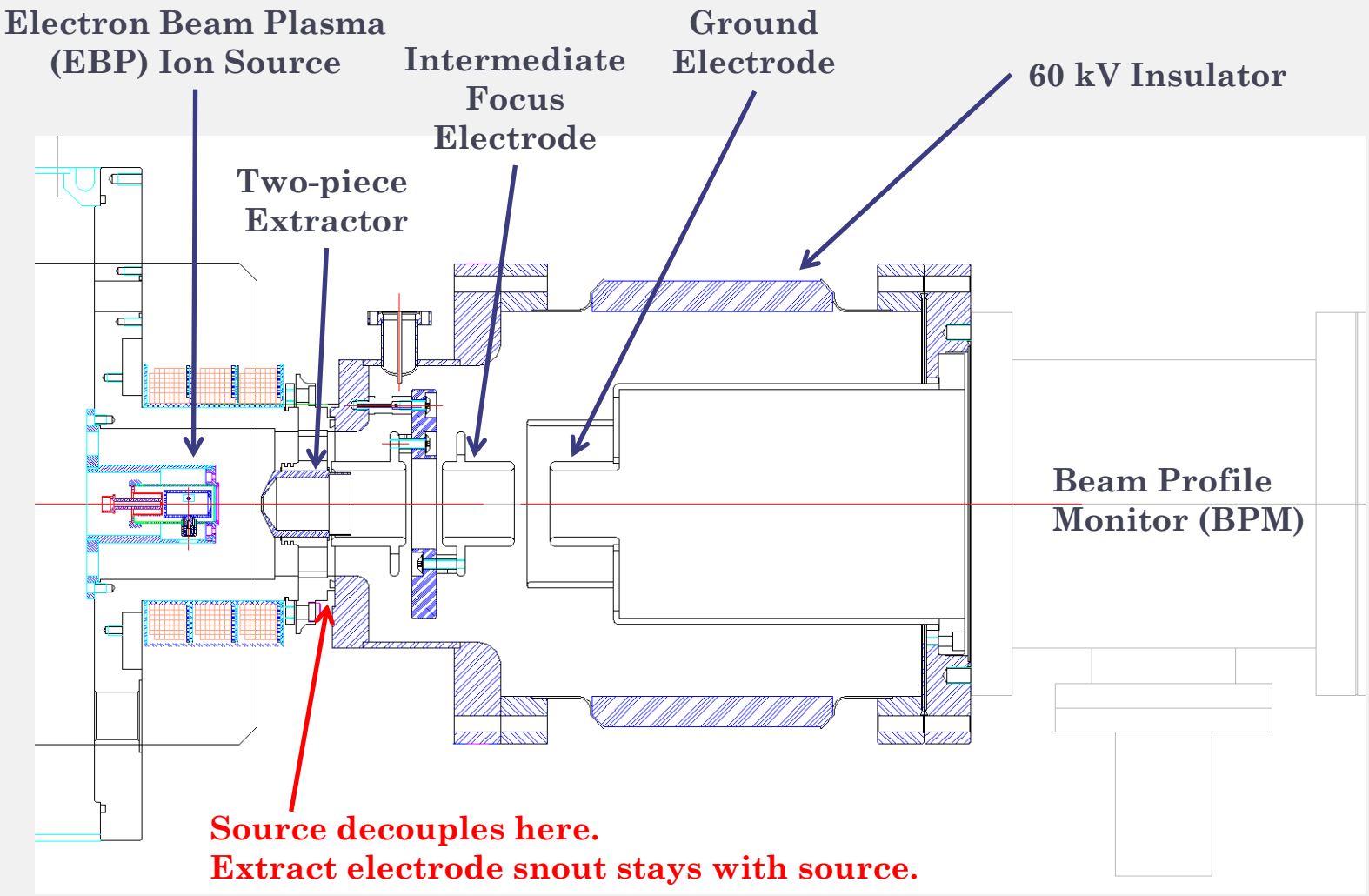
Breakthrough project from perspective of demonstration of EM technique applied to isotopes made by neutron capture, i.e. many diagnostic and therapeutic isotopes.

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.

End of Slides

Ion Source Extraction



Abstract

Title: High Specific Activities of Medical Isotopes using an Electromagnetic Separation Approach

There is a need in society for radioisotopes for diagnostic and therapeutic purposes but with higher specific activities (HSA, radioactivity per weight) than presently available. One technique to produce such isotopes is using an electromagnetic (EM)mass separation approach. Mass spectroscopy is a well-known technique for many years but never applied for commercial production of such desired isotopes. The project at hand is a first attempt to demonstrate both the usefulness of this approach and that the use of higher specific activity of the therapeutic isotope, ^{153}Sm, is compelling. IsoTherapeutics LLC has been using LSA for some years and will compare the use of HSA ^{153}Sm in their studies. In Phase I a new ion source for the ionization of samarium was developed and in Phase II, a series of reactor irradiations will be performed at ORNL (Oak Ridge National Laboratory) HFIR nuclear facility to produce desired activities of ^{153}Sm , approximately monthly, isotopically mass separated at an EM facility at ORNL, and delivered to ITG for this subsequent chemical and biochemical tests. Status of this project will be presented along with a vision for future commercial projects possibly involving a new EM facility at the MURR (Missouri University Research Reactor) facility.

Collected Foils