

Production of Commercial High Specific Activity Sn-117m Radiochemical and Chelates

PI: Nigel Stevenson, Clear Vascular, Inc.

DOE-NP SBIR/STTR Exchange Meeting
(August 6-7, 2015)



SBIR Funding

Funding Agency: U.S. Department of Energy

FY: 2013

Funding Opportunity Number: DE-FOA-0000782

CFDA Number: 81.049

Submission Date: December 11, 2012

Company Name: Clear Vascular, Inc.

Company Address: 21 Waterway Ave, Suite 225, The Woodlands, TX 77380

Project Title: Production of Commercial High Specific Activity Sn-117m Radiochemical and Chelates

Principal Investigator: Nigel Stevenson, Ph.D.

Topic Number / Subtopic Letter: 36 b (2012 Topics)

Phase I Grant Award No.: 99475S12-I



Unique Characteristics of Sn-117m

Major Emissions	Energy, KeV	Intensity, %
Auger-L	3	91.0
Auger-K	21	10.8
CE*-K1	126.8	66.3
CE-K2	129.4	11.9
CE-L1	151.6	27.3
CE-L2	154.1	1.5
CE-M1	155.1	5.6
Gamma	158.6	86.4

*C.E. = Conversion Electron

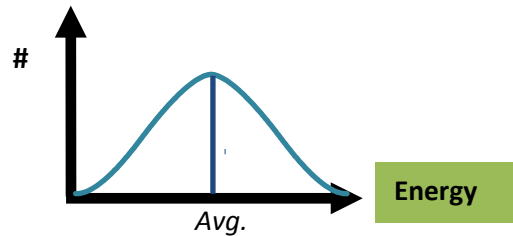
No High Energy Emissions

- ❖ **Mono-energetic conversion electrons** of ~140 KeV discrete energy for therapy have an average **range of ~300 μ m**
 - Lower external radiation
 - Easier handling and reduced hospitalization containment
 - C.E. have been proven to induce apoptosis
- ❖ **Half-life of 14 days** is consistent with treatment requirements
 - Logistic flexibility
 - Cell division cycles and therapy dosing
- ❖ **Gamma ray (159 KeV) similar to Tc-99m (140 KeV)** allowing for existing standard gamma camera imaging & techniques



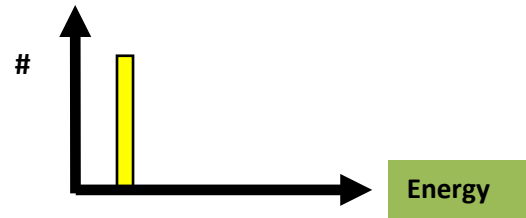
Comparing Energy Types for Radiopharmaceuticals

Beta

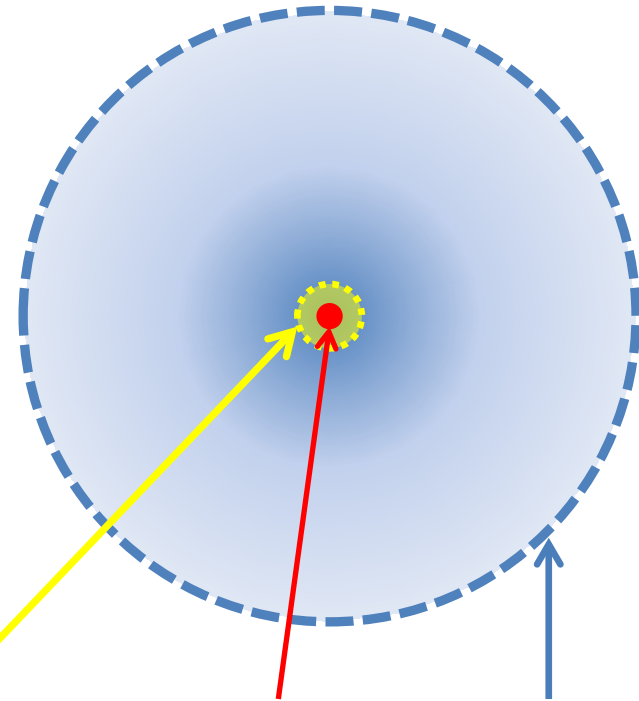


Produces a range of tissue penetration

Conversion
Electron



Penetrates to a set distance



	Tin-117m	Alpha Particles ¹	Beta Particles ²
Range in tissue (μm)	290	40-90	50-5000
Shielding needed during administration	No	No	Yes

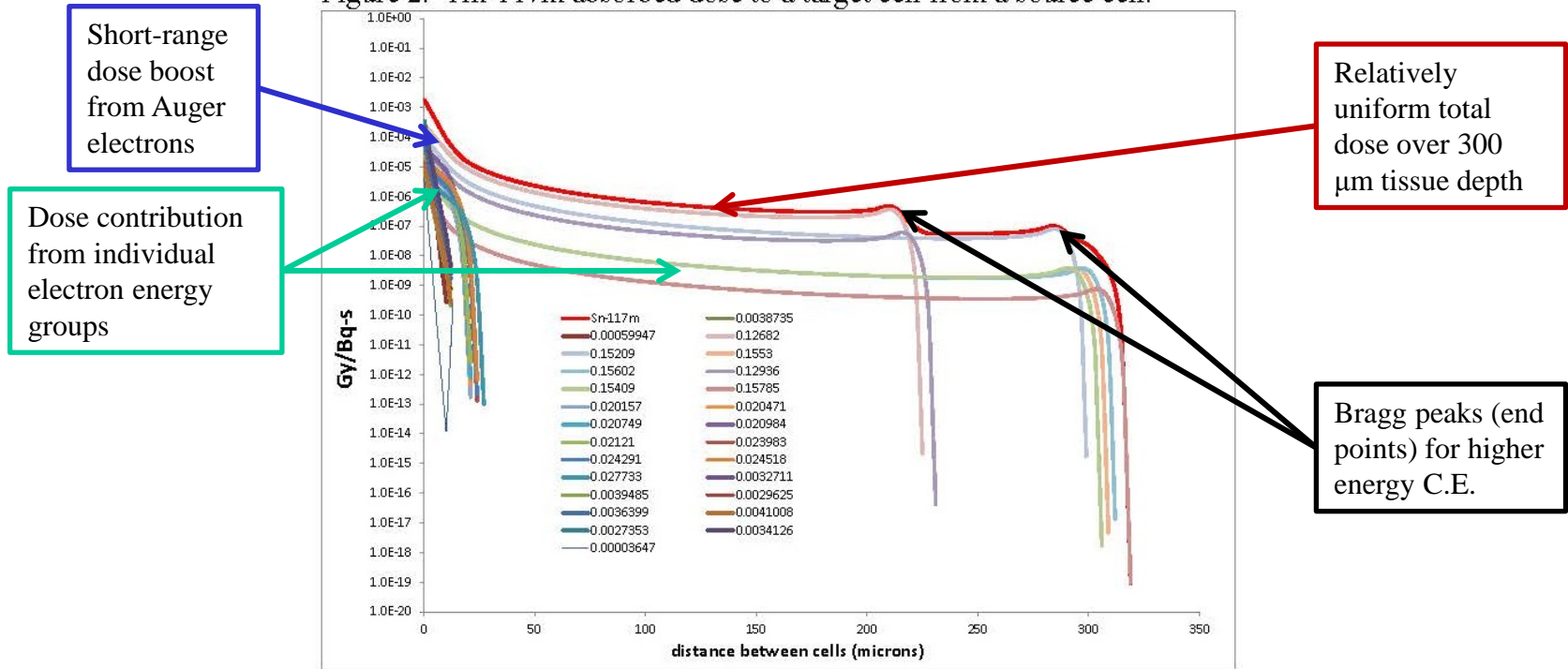
¹XOFIGO; ²METASTRON & QUADRAMET



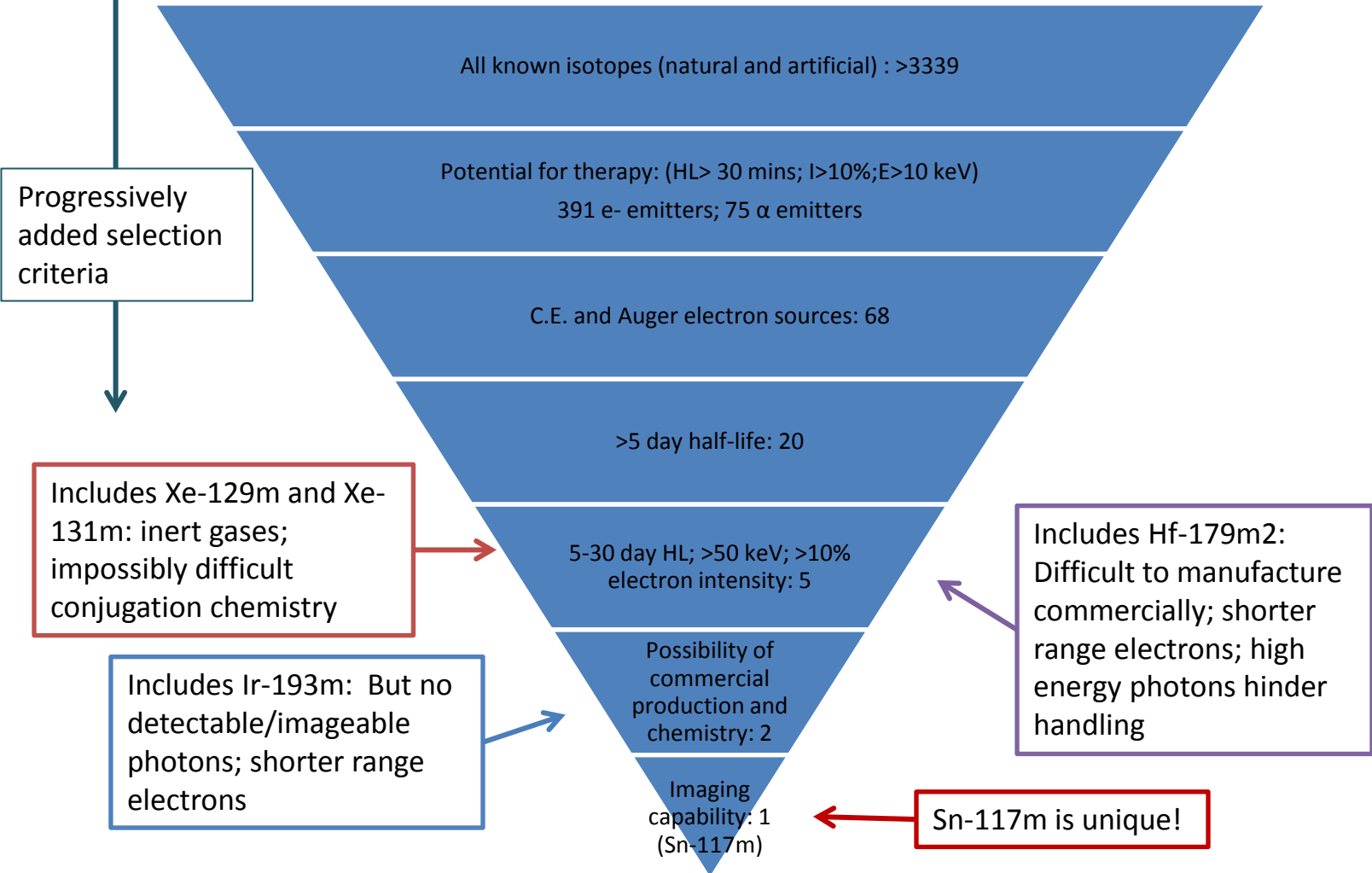
Well-Defined Range of Sn-117m in Tissue

- Confirmation by G. Sgouros (JHU) of **relatively uniform dose deposition** and 300 μm range of C.E. in tissue

Figure 2. Tin-117m absorbed dose to a target cell from a source cell.



Tin-117m is Unique



- No other isotope has the characteristics that are so ideally suited to our cardiovascular application



Tin-117m: Past Work & Development

- Suresh Srivastava, BNL, performed Bone **Pain Palliation** ([Sn-117m]-DTPA) studies and trials
 - 125+ subjects successfully treated
- **Cardiovascular** – Vulnerable/Unstable Plaque ([Sn-117m]-DOTA-Annexin)
 - Imaged in human clinical trials
 - Therapy in animals confirmed
- **Rheumatoid Arthritis** (Sn-117m colloid)
 - Animal models
- **Lymphoma and Leukemia**
 - Labeled molecules targeted conditions
- Linking to **Antibodies**
 - Excellent labeling efficiencies
- **Medical Devices: Colangiocarcinoma Stent**
 - IP for superior electroplating method



Scope of Project

- **Aim 1:** Reproducibly prepare high specific activity Sn-117m in large enough quantities to perform chelation and conjugation experiments that could be used in human clinical studies.

Successfully Completed

- **Aim 2:** Prepare at least two different chelates of high enough purity to evaluate *in-vivo* or *in-vitro* for biological activity.

Successfully Completed

- **Aim 3:** Show that it is possible to scale up the production of Sn-117m to commercially relevant quantities.

Successfully Completed



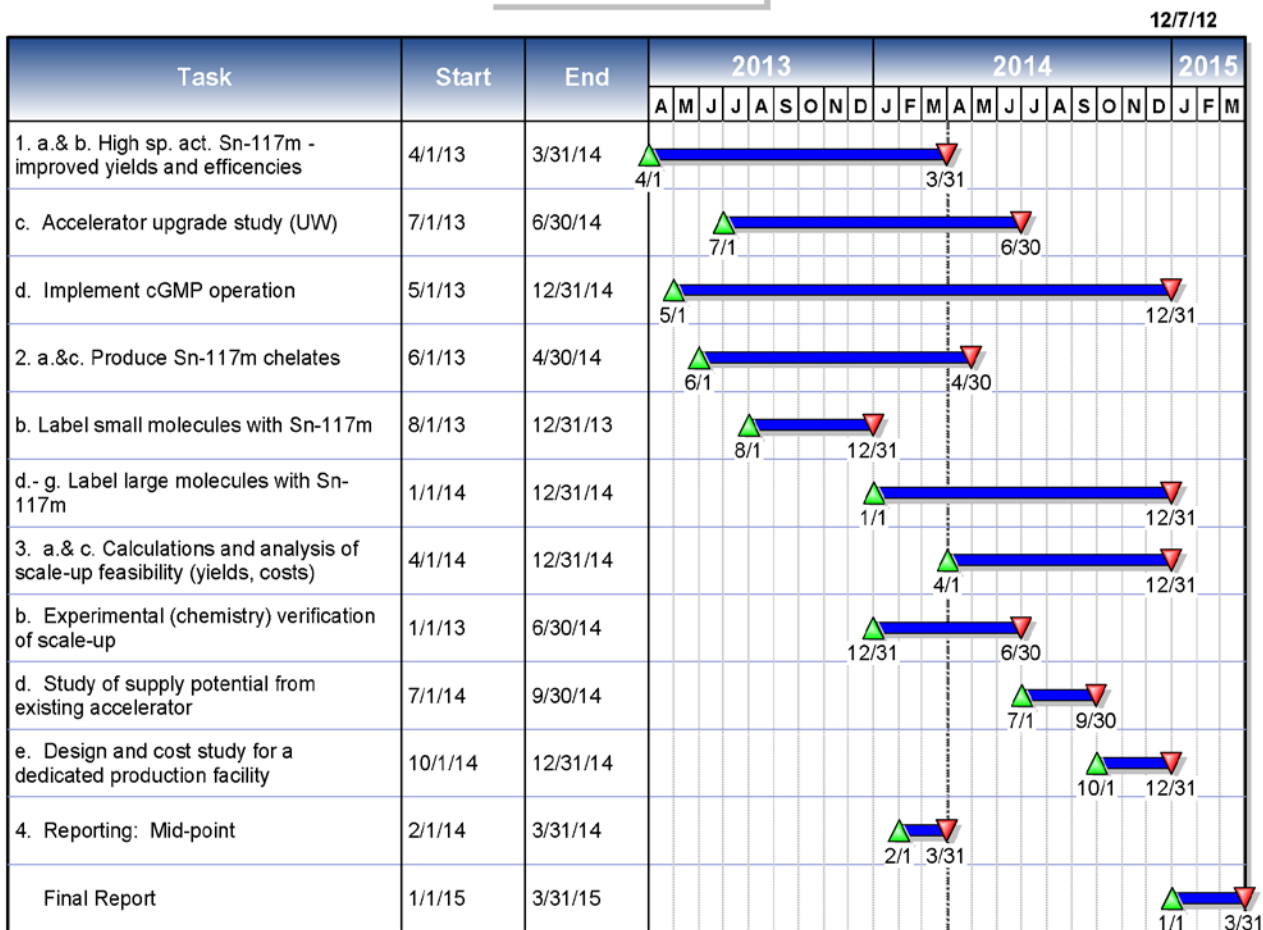
Examples of SBIR program achievements

- New separation method to extract Sn-117m from Cd-116
 - Complete in a few hours
 - Cd:Sn below 1:1
 - >99.7% Sn-117m
 - Scalable to multi-curie
 - Straightforward and reliable commercial cGMP method
- Labeled molecules and other products
 - Large biologics
 - Small targeting molecules
 - Long-term SPECT imaging agents
 - Radiocolloids
 - Electroplated stents
- Multiple production centers being assembled to form a network
 - Manufacturing security



Project Timeline

SBIR Phase II



Synergy with DOE-NP Interests

US DOE SBIR/STTR Topics 2015 (Phase I) section 26. NUCLEAR PHYSICS ISOTOPE SCIENCE AND TECHNOLOGY:

- “... new technologies must have the potential to ensure a cost-effective and stable supply and distribution of such isotopes. Examples of high priority isotopes include ... dual-purpose (‘theragnostic’) radioisotopes, such as high specific activity ... tin-117m...”
- “High-purity isotope products are essential for high-yield protein radiolabeling, for radiopharmaceutical use, or to replace materials with undesirable radioactive emissions. Improved product specifications and reduced production costs can be achieved through improvements in separation methods.”
- “Sn-117m has favorable nuclear properties for both imaging and therapy. Scaled up production for the supply of commercial quantities of high specific activity Sn-117m would be of high interest.”



Production of HSA Sn-117m

Alpha + Cd-116

Performed at the University of Washington Medical Center. Other sites in development.



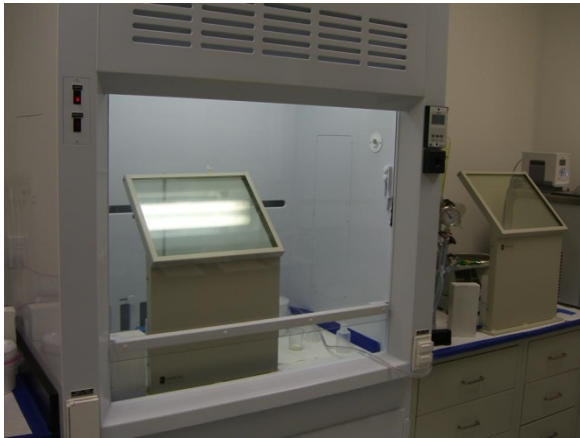
Electroplated target
and Irradiation
Room at UW



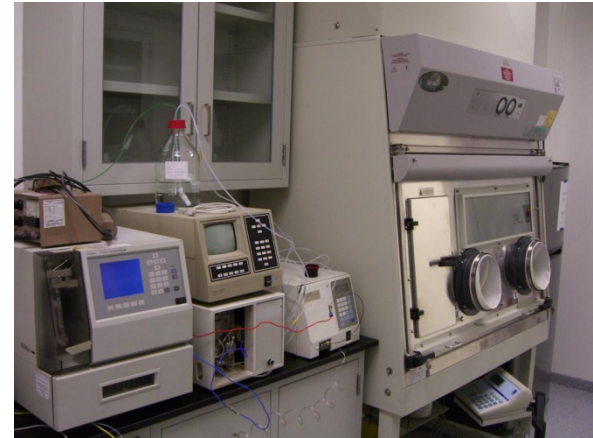
Clear Vascular, Inc.

Collaborators, Manufacturing and IP

- CVI has been actively involved with over 40 institutions worldwide
- CVI has a **cGMP** process and product (~90 manufacturing procedures with ~30 support procedures) used in the clinical trials:
 - CVI has two dedicated cGMP suites to manufacture the product
 - CVI has highly innovative radiochemistry collaborators
- **Over 50 patents** filed/licensed with 30 issued and additional extensive trade secrets



Radiochemical Preparation

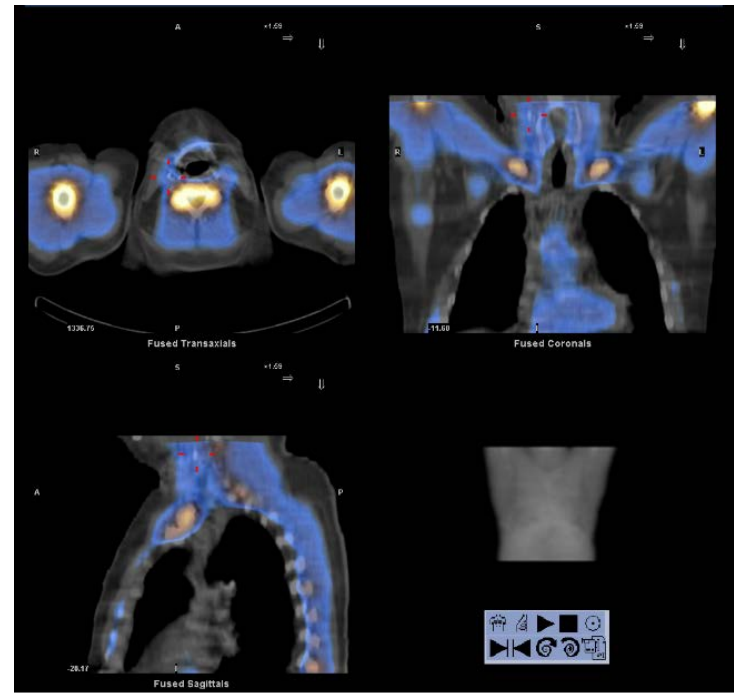
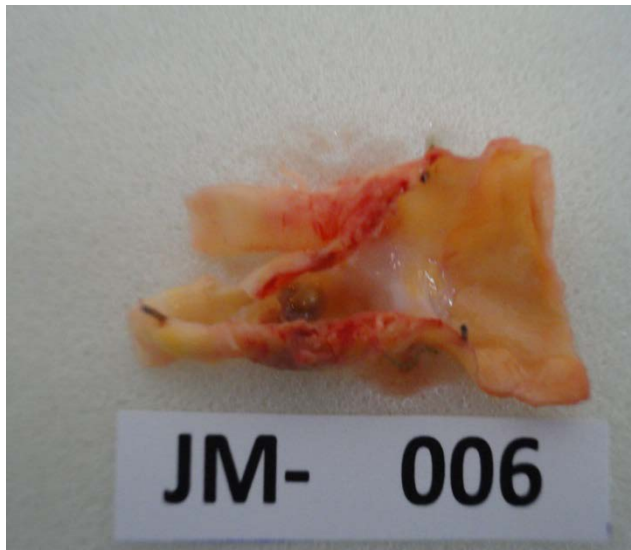


Final Product Manufacturing



Clear Vascular, Inc.

- ❑ Formed in 2005
- ❑ Virtual facilities; Based in TX
- ❑ First product: Radiopharmaceutical agent, Tin-Annexin, for imaging and therapy of vulnerable and unstable plaque
- ❑ Phase 2 imaging trials complete; preparing for therapeutic trials in US
- ❑ www.clearvascular.com



Clear Vascular, Inc.

Summary of Studies

ANIMAL PRE-CLINICAL STUDIES COMPLETED AND HUMAN CLINICAL STUDIES - COMPLETED AND ONGOING

- Normal mouse and rabbit bio-distribution (BD) and atherosclerotic rabbit BD, therapy and imaging studies
- Pig and rabbit stent therapy studies
- Normal mouse sterile abscess pK studies
- Preliminary and validating Apo-E mouse therapy studies
- Rat toxicity studies

ANIMAL Pre-clinical Studies

CAROTID #1 (Very Low Dose Study)

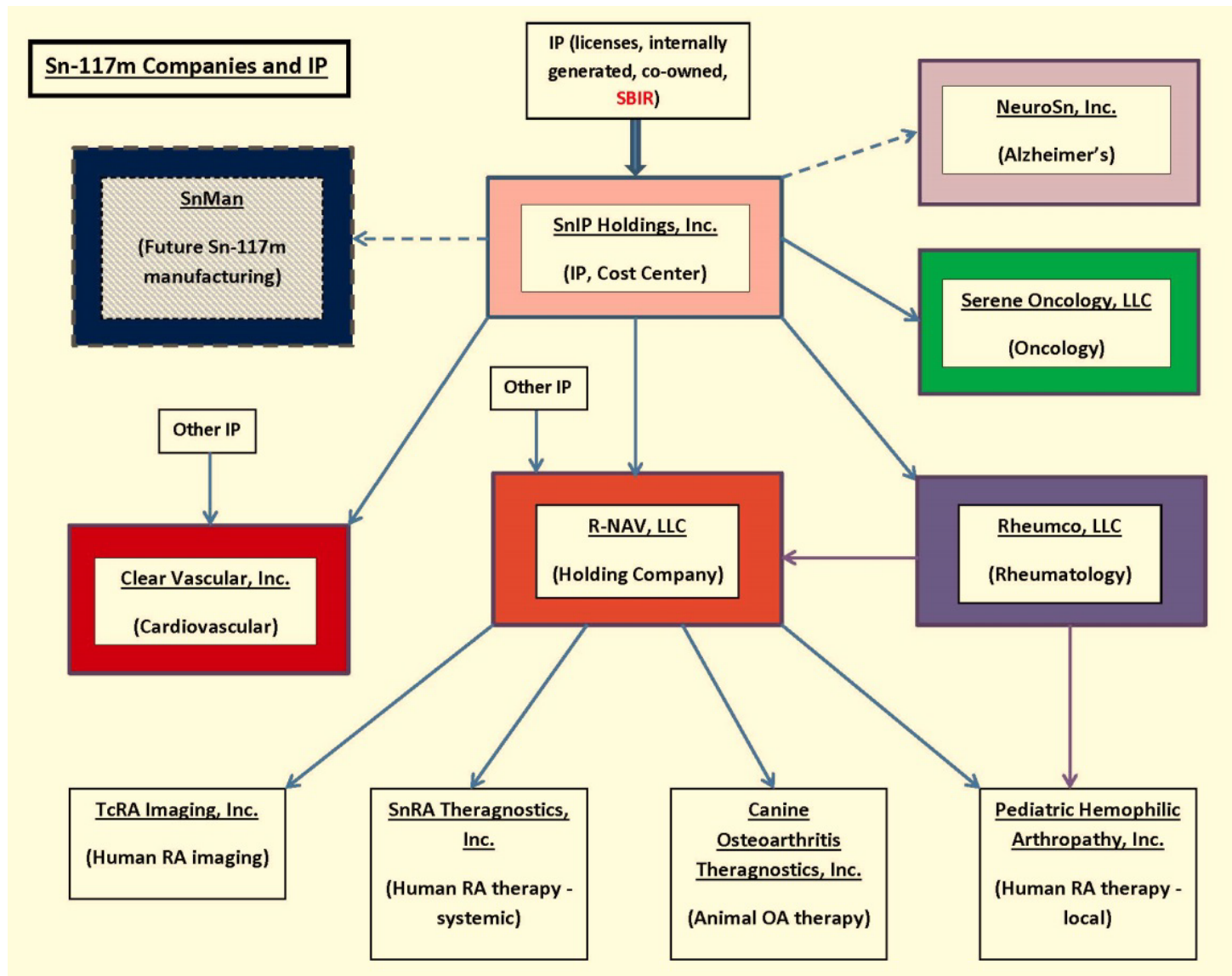
- Imaging and pathology on 6 CEA subjects
- 500 μ Ci cGMP dose to determine dosimetry for Carotid #2 study
- Identification by ultrasound (U/S) and histology of VP
- Binding to VP

- Imaging/pathology on 9 CEA subjects dose
- 3 mCi cGMP dose
- Identified VP by U/S and histology
- Identified VP by autoradiography co-registration
- Imaging of AAA
- Addition of therapeutic markers on 5 CEA subjects
- Plaque dosimetry

CAROTID #2 (Low Dose Study)



Sn-117m Companies and IP



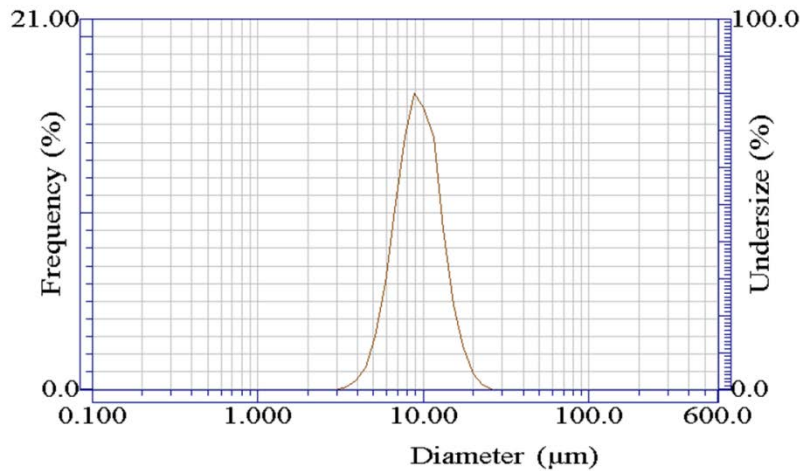
Sn-117m Colloid Studies

Retention of colloid in normal rat joint:

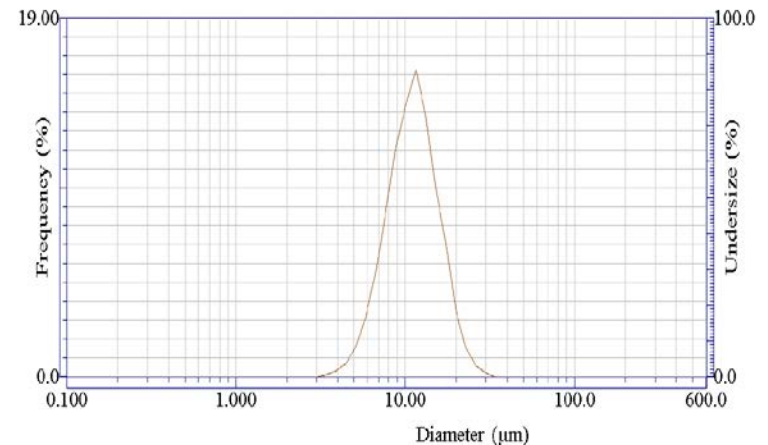
Time	7 days	2 weeks	6 weeks
Retention	>99.9%	>99.9%	99.8%

Ongoing studies:

- Controlling size and distribution
- Shelf-life studies
- Storage/Shipping temperature
- Retention/Biodistribution
- Scale-up



Sn-117m Colloidal Aggregate Particle Size at time of manufacturing



Stability studies - colloid size distribution after 7 days at room temp

Rat OA Trial – Sn-117m colloid

Figure 10a. Total Joint Score - 1 wk

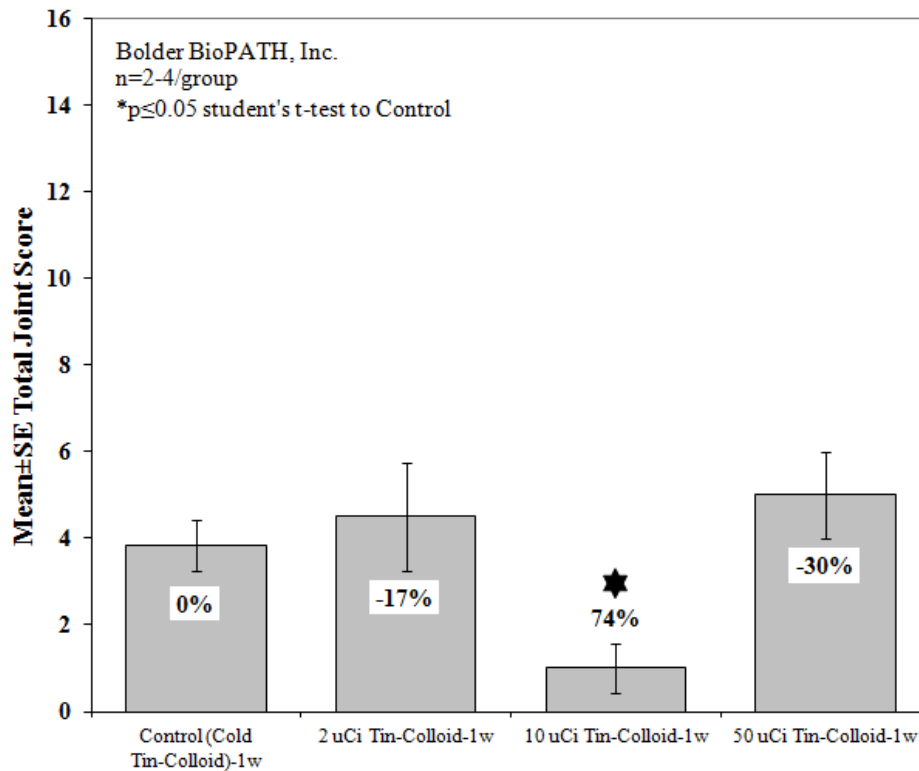
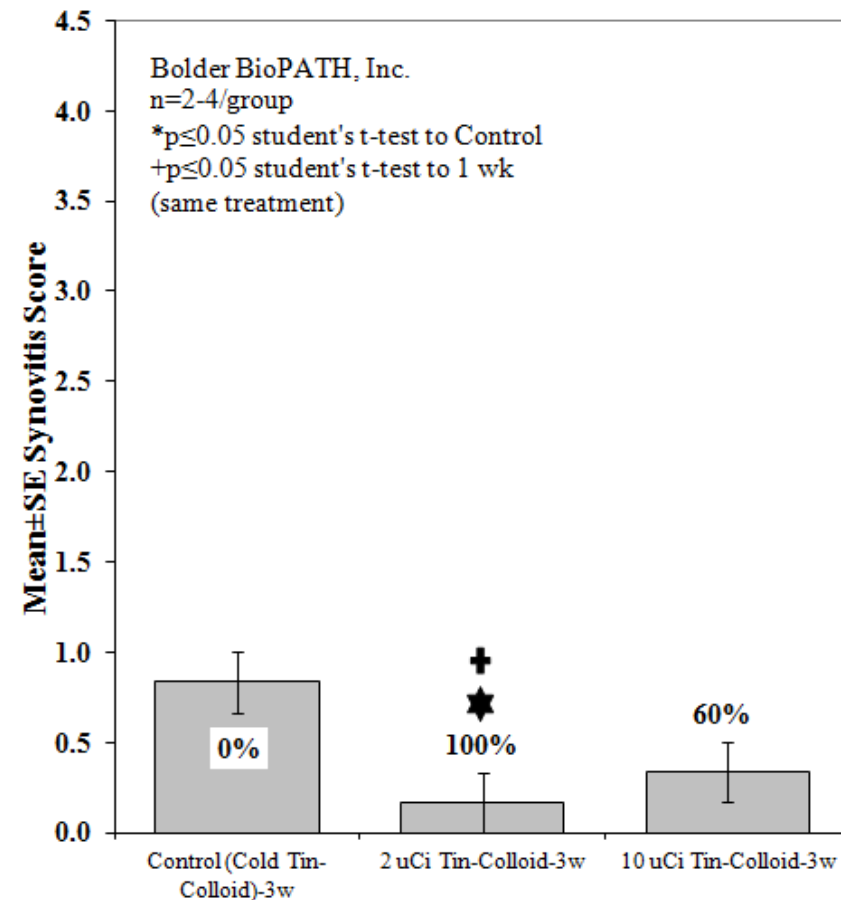


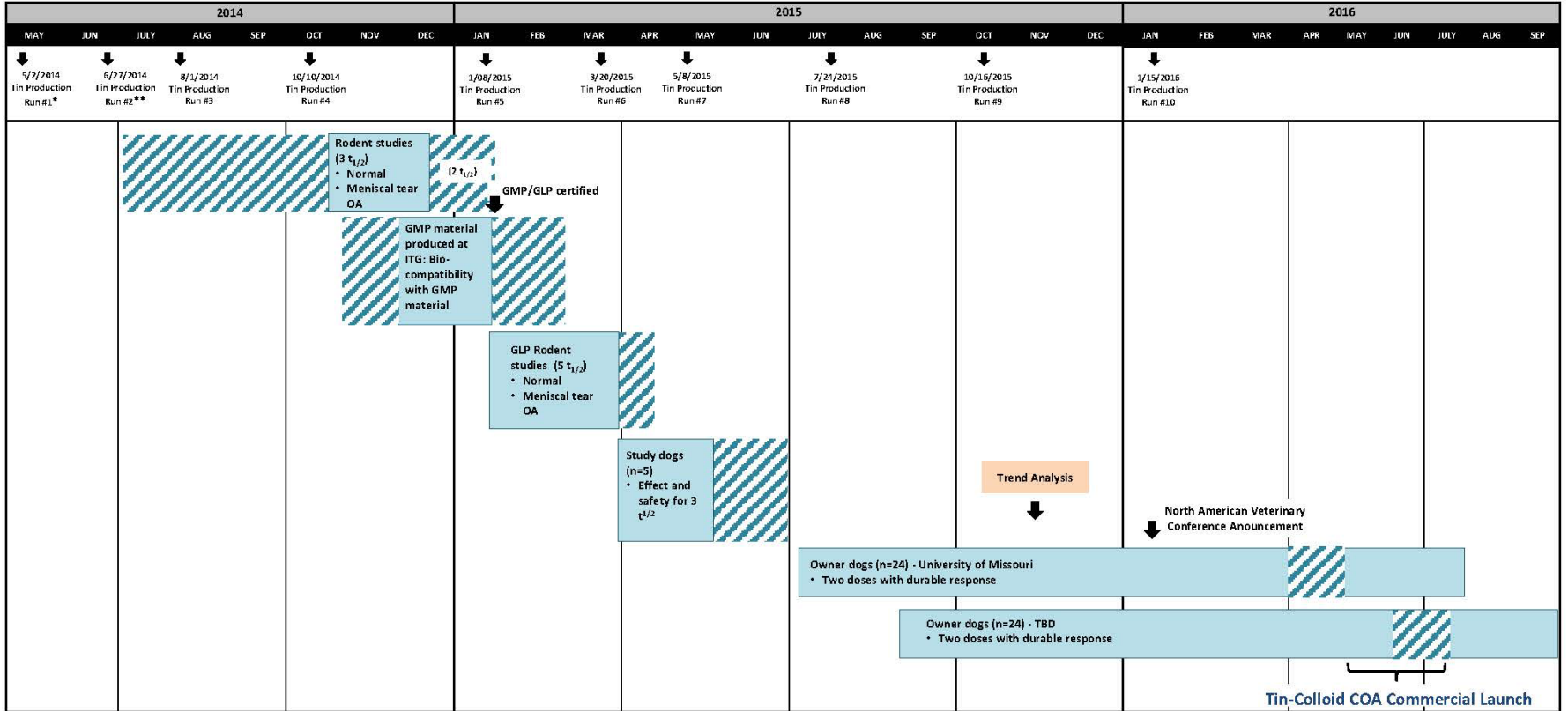
Figure 11c. Synovitis Score - 3 wk



Timeline

DATE: 7/13/2015

R-NAV Tin-Colloid Timeline - Updated July 13, 2015



* Tin production run used for colloid and radiochemical purification development work.

** Tin production run used for colloid work and early animal trials.

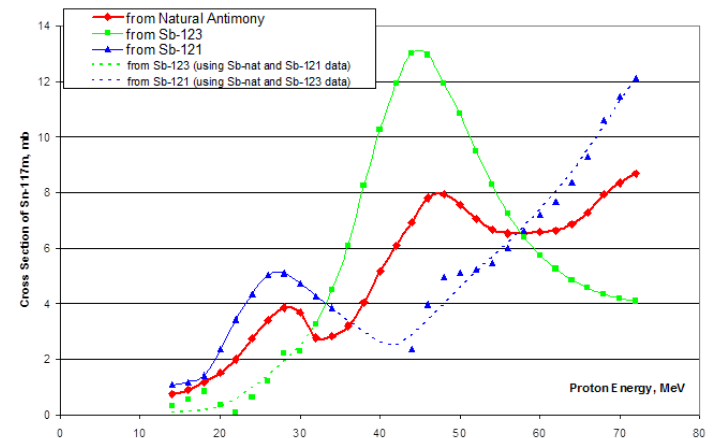
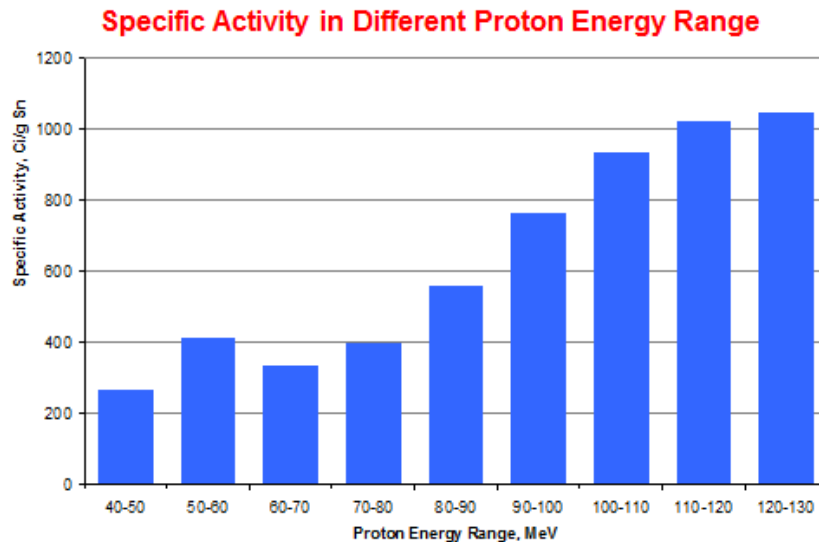
IPP Project: Sb(p,x)Sn-117m

- IPP Program, under Contract # DE-AC02-98CH10886 at Brookhaven National Laboratory
- CRADA with Clear Vascular
- Work carried out at RIAR and INR (Russia)
 - Increase reactor yield and spec. act. (LSA product)
 - Feasibility of accelerator production (NCA/HSA product)



IPP Project: Sb(p,x)Sn-117m

- Yields, spec. act., byproducts determined
- Method feasibility established
- Commercialization not yet achieved:
 - Electroplated targetry desirable/required
 - Chemistry needs to be simplified



Plans to Supply/Use HSA Sn-117m

- SnMan – production of radiochemical and labeled products
 - Reactor production optimized
 - Cd-116($\alpha,3n$) accelerator method optimized
 - Sb(p,x) accelerator method needs more work – further grant (SBIR) support needed

- First commercial company starts in 2016; others to follow
- Oncology, CV, RA, Neurology applications in development
 - Veterinary applications (OA, laminitis, oncology)**
- Academic and commercial institutions now testing Sn-117m

- Without DOE-NP SBIR and other support this would not have been possible**

