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, 2014)

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

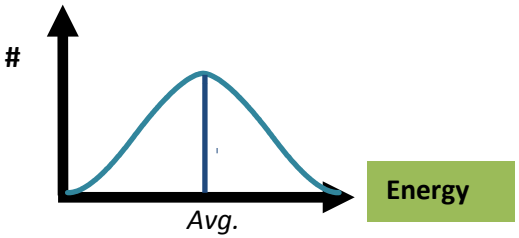
*C.E. = Conversion Electron

No High Energy Emissions

- **Mono-energetic conversion electrons of ~140 KeV discrete energy for therapy have an average range of ~300 µm**
  - 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 toTc-99m (140 KeV) allowing for existing standard gamma camera imaging & techniques**

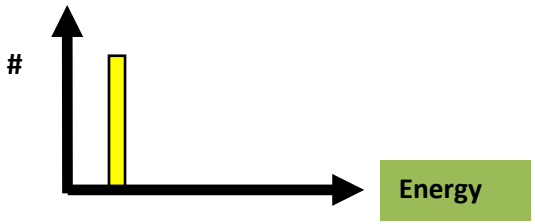
Comparing Energy Types for Radiopharmaceuticals

Beta

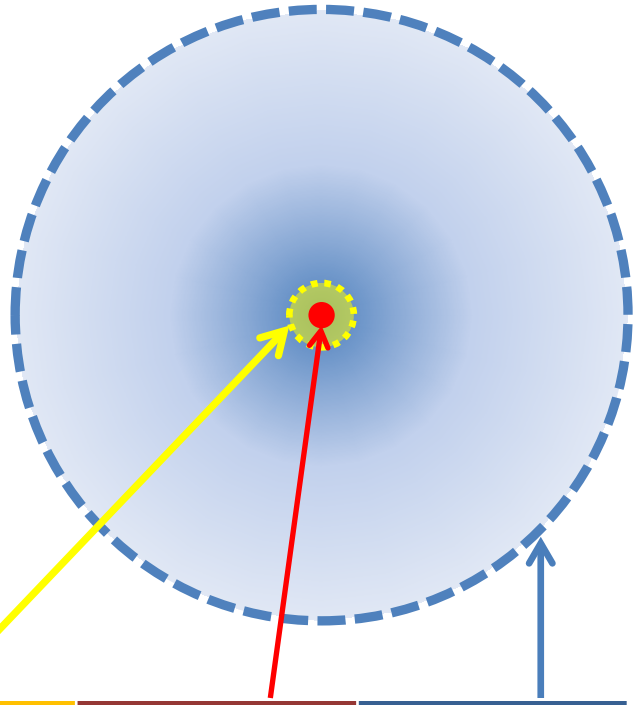


Produces a range of tissue penetration

Conversion Electron



Penetrates to a set distance



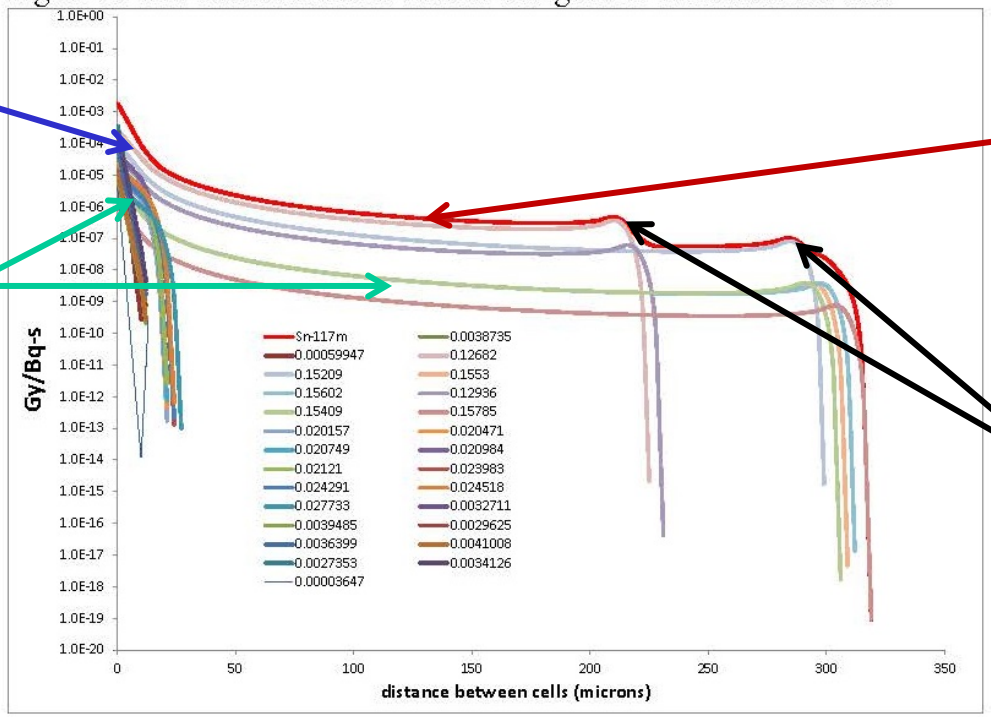
	Tin-117m	Alpha Particles[1]	Beta Particles[2]
Range in tissue (µm)	290	40-90	50-5000
Shielding needed during administration	No	No	Yes

[1]XOFIGO; [2]METASTRON & 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.



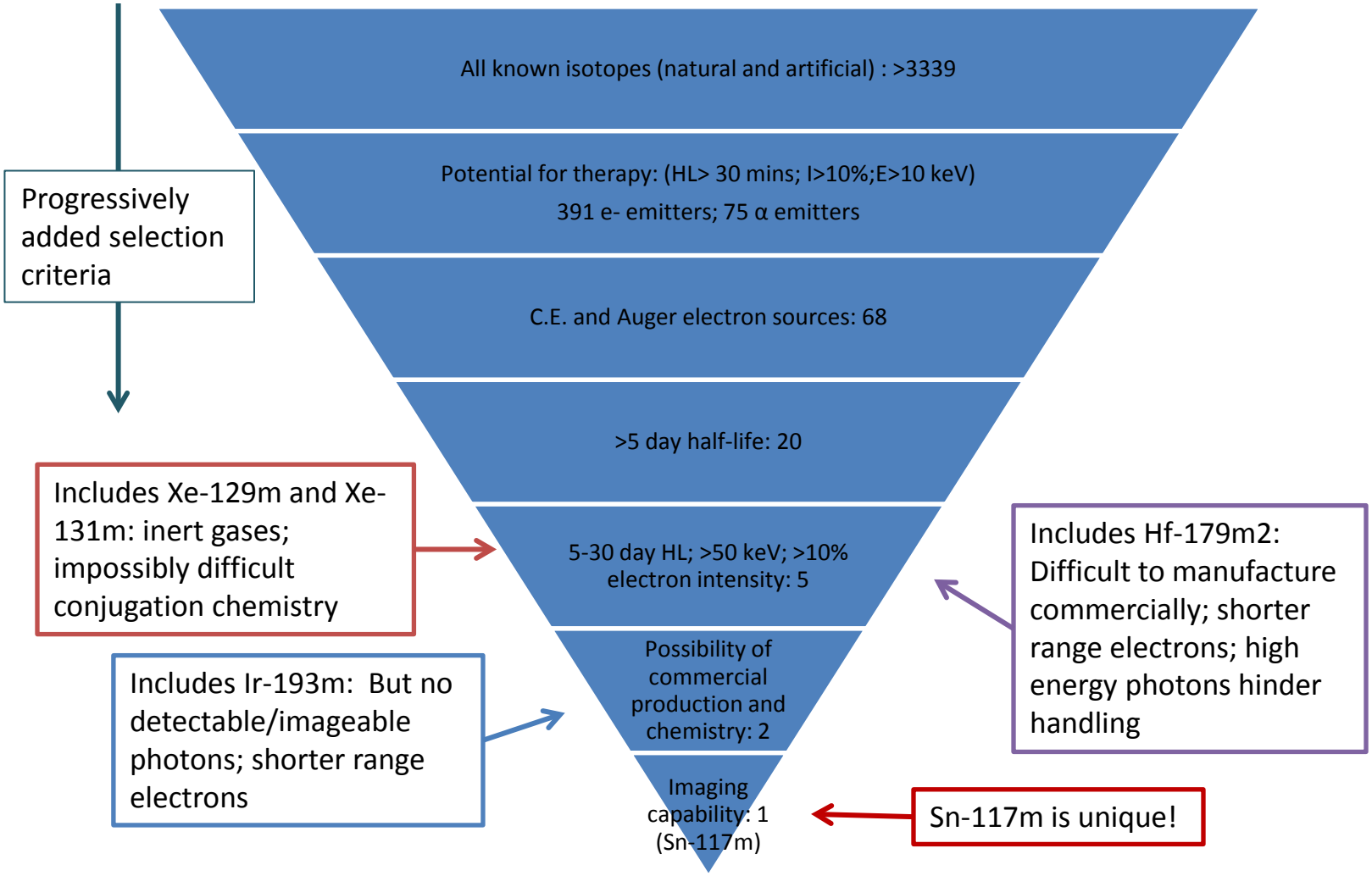
Short-range dose boost from Auger electrons

Dose contribution from individual electron energy groups

Relatively uniform total dose over 300 μm tissue depth

Bragg peaks (end points) for higher energy C.E.

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

Production of HSA Sn-117m Alpha + Cd-116

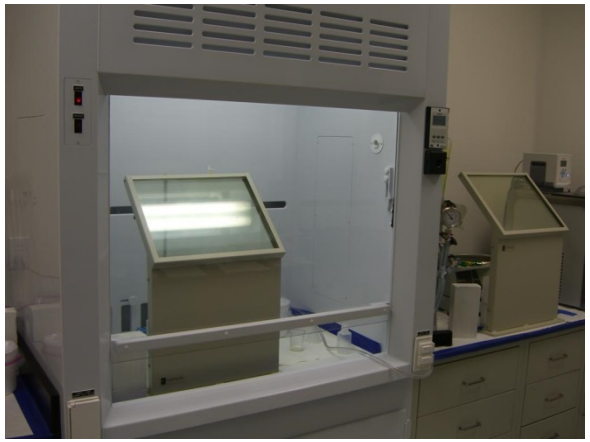
Performed at the University of Washington Medical Center

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
- **53 patents** filed/licensed with 30 issued and additional extensive trade secrets



Radiochemical Preparation

Final Product Manufacturing

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.

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

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

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."

SBIR Aim 1: Improved Production of HSA Sn-117m

1. The **first** technical objective is to adequately supply **HSA Sn-117m radiochemical** to ongoing R&D/Clinical Trial activities over next 2-3 years: Reproducibly prepare HSA Sn-117m in high enough quantities to perform chelation and conjugation experiments that could be used in human clinical studies.

   - A. Improved production yields and quality. *This aim will be successful by showing the production of at least 3 batches of Sn-117m that have the following characteristics:*
     - At least 75 mCi of final radiochemical per run
     - Specific activity of >10,000 Ci/g
     - No metal ion that will interfere with chelation > 1 µg/mCi
   - Results: These characteristics are routinely met e.g., Run 59
     - 110 mCi
     - 21,622 Ci/g
     - no metals above 0.9 µg/mCi

SBIR Aim 1: Improved Production of HSA Sn-117m (cont.)

- B. Improve processing efficiencies. *This aim will be successful if we achieve the following:*
  - Decrease the time taken to produce the purified radiochemical to < 2 days

	HCl Etch, HNO3 elution on Bromated Column	HNO3 Etch, HCl/H2O2 elution
Etch	10-20 hr	1-1.5 hr
Etch Strip	2 hr	1-2 hr
Column elution	6 hr	10 hr
Eluate Strip	3-4 hr	6-8 hr
Ashing	8-12 hr	0
Conversion to 4 M HCl solution	1-2 hr	0.5 hr
TOTAL	30-46 hr	18.5-22 hr

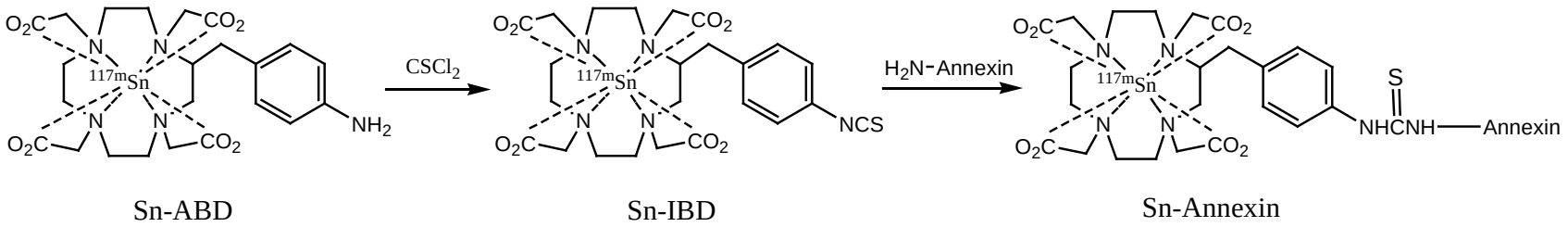
  - New liquid-liquid separation method reduces time further (12 hrs)

SBIR Aim 1: Improved Production of HSA Sn-117m (cont.)

- C. Cyclotron production. A feasibility analysis (including engineering details and production impact studies) for increasing the production capacity at the University of Washington MC50. *Success will be shown if it is possible and realistic to double the beam current (≥ 100 uA) and/or production capacity for Sn-117m thereby helping assure a supply of the radiochemical until a dedicated facility is built.*
  - **Underway**
  - The initial design study (by an external group) was commissioned as to the feasibility of an external ion source.
  - Evaluation of improved internal source and RF system underway
- D. cGMP manufacturing. *Success will be achieved if we can produce the radiochemical under cGMP conditions*.
  - **Achieved**
  - Several external audits - confirmed cGMP capabilities

SBIR Aim 2: Chelation of HSA Sn-117m for Pharmaceuticals

2. The **Second** technical objective of this proposal is to "show that HSA Sn-117m can be used to prepare **HSA Sn-117m based radiopharmaceuticals** and demonstrate that they perform adequately."
   - Sn-117m small chelates: Sn-117m-DTPA**.** **Complete**
   - Improved process for the preparation of Sn-117m-aminobenzyl-DOTA. **Underway**
   - Side effects of Sn-117m-annexin**.** **Complete**
   - Somatostatin analogues. **Underway**
   - Antibodies and Proteins. **Underway**



Sn-ABD Sn-IBD Sn-Annexin

SBIR Aim 3: Scale-Up Production of HSA Sn-117m

3. The **third** technical objective is "To define the pathway to a future large-scale **commercial HSA Sn-117m production facility** - show that it is possible to scale up the production of Sn-117m to commercially relevant quantities".

   - A. Modeling calculations. *This aim will be successful if it can be shown by theoretical calculations that it is possible to produce at least 5 Ci/week of Sn-117m using the method of aim 1 and employing new cyclotrons/accelerators.* ***Complete***
   - B. Experimental verification. *Success will be achieved if the separation methods used in aim 1 can be shown (using equivalent low specific activity Sn-117m) to be able to handle the separation of a batch of at least 1 Ci of Sn-117m.* **Future**
   - C. Cost of goods sold. *This aim will be successful if the cost of large-scale commercial production is calculated (modeled) to be less than $10/mCi for ≥5 Ci/week batches.* **Complete**

SBIR Aim 3: Scale-Up Production of HSA Sn-117m (cont.)

Cd-116(α,3n)Sn-117m

- The thick target yield over the energy range of 47→20 MeV is about 150 µCi/µAh
- Specific activity ~20,000 Ci/g
- The present limiting factor is the availability and power of existing alpha accelerators and targetry
- Commercial accelerators being developed that are capable of very high alpha beam powers could be available in 2-3 years; IBA cyclotrons are an available and existing technology

Accelerator:	IBA Cyclotron	Positive ion LINAC
Particle:	He-4 (alpha)	He-4 (alpha)
Energy:	>=50 MeV	>=50 MeV
Current:	>=200 µA; higher current cyclotron solution will be sought	>=1500 µA
Targetry:	Internal – standard electroplated target	External – standard electroplated target
Beamlines:	N/A	1 with pulsing switcher to split beam to 2 or 3 targets for simultaneous irradiation

- Yields/year **200-300 Ci** **1,500-3,000 Ci**

SBIR Aim 3: Scale-Up Production of HSA Sn-117m (cont.)

($ in USD, Production Unit in mCi)

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Supplies		$9,550,000	$9,550,000	$9,550,000	$9,550,000	$9,550,000	$11,550,000	$13,050,000	$13,050,000	$13,050,000
Salary and Benefits		2,457,180	2,506,324	2,556,450	2,607,579	2,659,731	3,134,110	3,626,401	3,698,929	3,772,907
Overhead		737,154	751,897	766,935	782,274	797,919	940,233	1,087,920	1,109,679	1,131,872
Depreciation		2,275,000	2,275,000	2,275,000	2,275,000	2,662,500	3,437,500	3,825,000	3,825,000	3,825,000
Total COGS	**$3,700,703**	**$15,019,334**	**$15,083,221**	**$15,148,385**	**$15,214,853**	**$15,670,150**	**$19,061,843**	**$21,589,321**	**$21,683,607**	**$21,779,779**
Unit (mCi) Produced	74,014	194,805	274,799	468,186	1,253,647	2,254,282	3,019,605	3,586,651	4,033,902	4,435,582
COGS per Unit	$50.00	$77.10	$54.89	$32.36	$12.14	$6.95	$6.31	$6.02	$5.38	$4.91
Operating Metrics:										
Total Headcount	30	30	30	30	30	30	35	40	40	40
Number of accelerators or cyclotrons	2	2	2	2	2	3	4	4	4	4
Production Capacity		2,295,000	2,295,000	2,295,000	2,295,000	2,295,000	3,442,500	4,590,000	4,590,000	4,590,000
Production as % of 150 hour per week		8%	12%	20%	55%	98%	88%	78%	88%	97%
Hours of operation per week		13	18	31	82	147	132	117	132	145
CapEx	45,500,000	0	0	0	0	15,500,000	15,500,000	0	0	0
COGS per Unit	$50.00	$77.10	$54.89	$32.36	$12.14	$6.95	$6.31	$6.02	$5.38	$4.91

SBIR Aim 3: Scale-Up Production of HSA Sn-117m (cont.)

3. The **third** technical objective is "To define the pathway to a future large-scale **commercial HSA Sn-117m production facility** - show that it is possible to scale up the production of Sn-117m to commercially relevant quantities".

   – D. Calculations and estimates of capacities and production capabilities in existing accelerators. *This aim will be successful if it can be demonstrated that there is sufficient capacity to service increasing projected Sn-117m demands until special purpose facilities can be brought into operation for commercial production.* ***Complete***

   – E. Manufacturing facility. *This aim will be successful if the detailed costs and feasibility study are consistent with the accepted commercialization plan.* ***Underway***

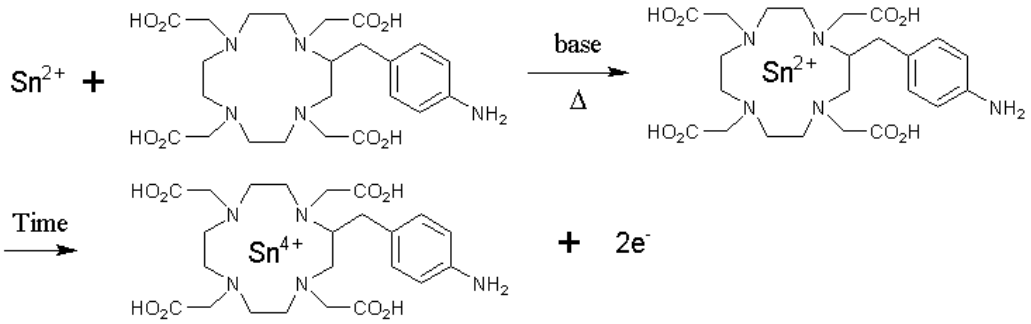
ALTERNATIVE PRODUCTION SOURCE SITES

SEVERAL SUITABLE ACCELERATORS ARE AVAILABLE

Location	Beam (p/α)	Energy (MeV)	Current (μA)	Max Avail (%)	Availability TBN (%)	Rate (μCi/μA.h)	Max Yield (mCi/week)	Yield (mCi/week)	Comments (Target)
UW (MC50) - USA	α	47.3	70	60	50	150	1,058	882	Cd-116
KIRAMS (MC50) - U	α	47.3	50	90	70	150	1,134	882	Cd-116
INR - Russia	p	55.0	140	60	40	29	409	273	Sb-nat
LANL - USA	p	55.0	300	50	30	15	378	227	Sb-nat-Ti
BNL - USA	p	55.0	115	50	30	29	280	168	Sb-nat
TRIUMF - Canada	p	55.0	80	50	20	29	195	78	Sb-nat
iThemba (S. Africa)	p	55.0	350	50	30	15	441	265	Sb-nat-Ti
ARRONAX (France)	p	55.0	700	50	20	15	882	353	Sb-nat-Ti
Buffalo	p	30.0	400	90	50	6	363	202	Sb-121 target
Nordion - Canada	p	42.0	250	90	50	12	454	252	Sb-121 target
30 MeV - other	p	30.0	2,000	90	50	6	1,814	1,008	Several machines (Sb-121)
42 MeV - other	p	42.0	450	90	50	12	816	454	Several machines (Sb-121)
					TOTAL		**8,225**	**5,042**	

SBIR: Latest Developments

- **New radiochemical processing method**
  - Replaced the more expensive, longer and laborious column method
  - Liquid-Liquid separation using HI to form iodides
  - Final Sn-117m shows complete removal of Cd (and Cu)
  - Completed within 1 day
- **Reduction of Sn-117m(IV) to Sn-117m(II)**
  - Uses $5Sn^{4+} + 2Sb(s) \xrightarrow[HCl]{Redox} 5Sn^{2+} + 2Sb^{5+}$
  - Sb falls out of solution and is removed; any residual Sb does not chelate
  - Sn(II) chelates into DOTA and oxidizes in-situ
  - Allows for adding the Sn-117m to DOTA-annexin V cold kit
  - Allows for labeling other molecules with Sn-117m, e.g., DOTATATE



Product Specification for L-L Method

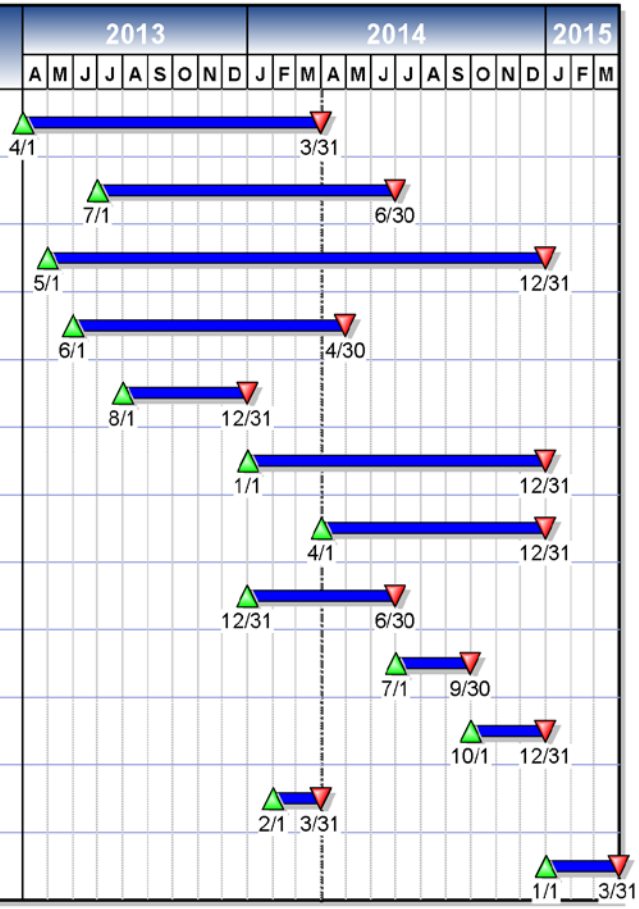
Lot Number:	62-3			Solution:		4 N HCl
Assay Date & Time:	5/16/14 1:30 PM			Total Mass (g):		0.76
Isotopic Analysis by Gamma Spectroscopy					(* = < det. Limit)	
Isotope	Activity Concentration (mCi/g)		Total Activity (mCi)			Radionuclidic Purity (%)
	1st Sample	2nd Sample	1st Sample	2nd Sample	Average	
Ag-112	*	*	0.00	0.00	0.00	0.00%
Cd-115	*	*	0.00	0.00	0.00	0.00%
Cd-115m	*	*	0.00	0.00	0.00	0.00%
Ga-66	*	*	0.00	0.00	0.00	0.00%
Ga-67	*	*	0.00	0.00	0.00	0.00%
In-111	*	*	0.00	0.00	0.00	0.00%
In-114m	*	*	0.00	0.00	0.00	0.00%
In-115m	*	*	0.00	0.00	0.00	0.00%
Sn-113/In-113m	*	*	0.00	0.00	0.00	0.00%
Sn-117m	5.02	5.32	3.81	4.04	3.93	100.00%
Zn-65	*	*	0.00	0.00	0.00	0.00%
Metals Analysis by ICP/AES					(nd = <LOD, * = <LOQ, x = > 110% high std)	
Element	Concentration (µg/g)			µg/mCi of Sn-117m		
	1st Sample	2nd Sample	Avg.			
Ca	11.3	10.8	11.1	2.15		
Cd	nd	nd	nd	nd		
Cu	nd	nd	nd	nd		
Fe	1.1	1.0	1.0	0.20		
Mg	0.2	0.2	0.2	0.03		
Ni	nd	nd	nd	nd		
Pb	nd	nd	nd	nd		
Sn	2.9	2.9	2.9	0.55		
Zn	nd	nd	nd	nd		

Plan to Completion

SBIR Phase II

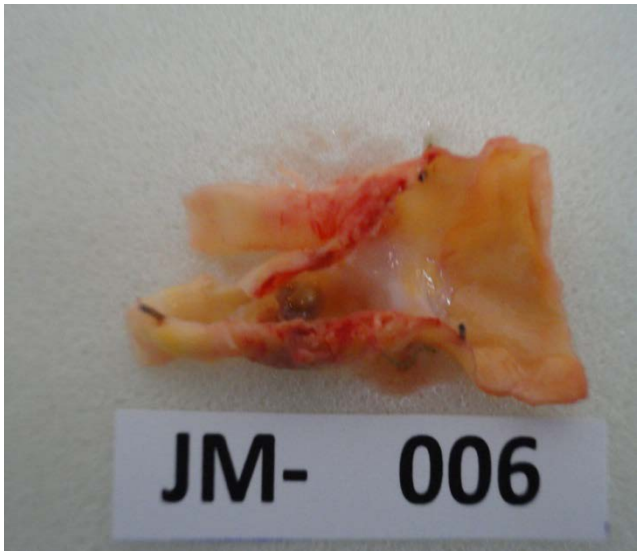
12/7/12

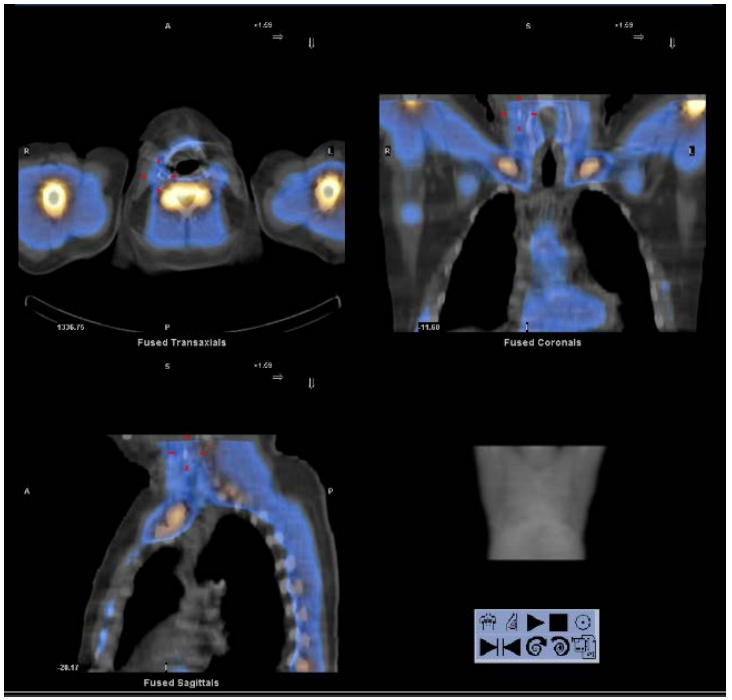
Task	Start	End
1. a.& b. High sp. act. Sn-117m - improved yields and efficencies	4/1/13	3/31/14
c. Accelerator upgrade study (UW)	7/1/13	6/30/14
d. Implement cGMP operation	5/1/13	12/31/14
2. a.&c. Produce Sn-117m chelates	6/1/13	4/30/14
b. Label small molecules with Sn-117m	8/1/13	12/31/13
d.- g. Label large molecules with Sn-117m	1/1/14	12/31/14
3. a.& c. Calculations and analysis of scale-up feasibility (yields, costs)	4/1/14	12/31/14
b. Experimental (chemistry) verification of scale-up	1/1/13	6/30/14
d. Study of supply potential from existing accelerator	7/1/14	9/30/14
e. Design and cost study for a dedicated production facility	10/1/14	12/31/14
4. Reporting: Mid-point	2/1/14	3/31/14
Final Report	1/1/15	3/31/15



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
- Over 50 patents filed
- www.clearvascular.com





Clear Vascular, Inc.

Summary of Studies

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

ANIMAL Pre-clinical Studies

- Normal mouse and rabbit bio-distribution (BD) and athero-sclerotic 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

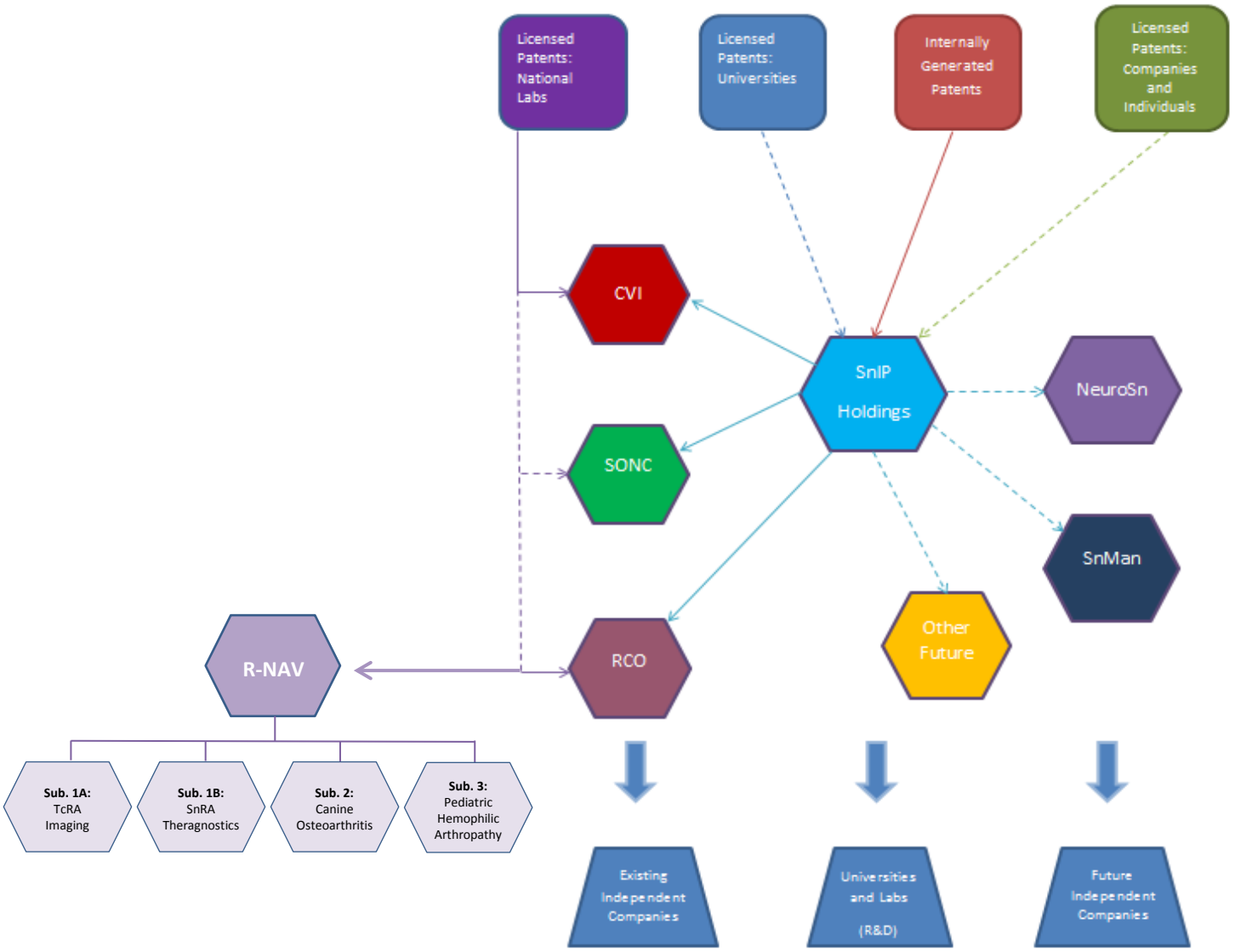
CAROTID #1 (Very Low Dose Study)

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

CAROTID #2 (Low Dose Study)

- 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

TIN-117M COMPANIES AND IP LICENSES



Future Use and Supply of HSA Sn-117m

- "R-NAV" - Wall Street Journal press release:
  - http://online.wsj.com/article/PR-CO-20140716-905524.html
  - Uses Sn-117m colloids and Sn-117m labeled biomolecules – RA & OA
- "NeuroSn" – Sn-117m labeled molecule for treatment of AD
- Other similar JV collaborations being considered
- Supplying other groups with Sn-117m
  - Academic institutions
  - International
  - Commercial companies
- "SnMan" – Sn-117m sourcing and in-house manufacturing
  - Coordinate production and supply demands
  - Source from reactors and accelerators
  - Eventually invest in in-house manufacturing facilities

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