

“Harnessing Sn-117m for Improved Quality of Life”

Nigel R. Stevenson, Ph.D.

President, WCI
Exubrion Therapeutics, Inc.

nstevenson@exubrion.com

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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

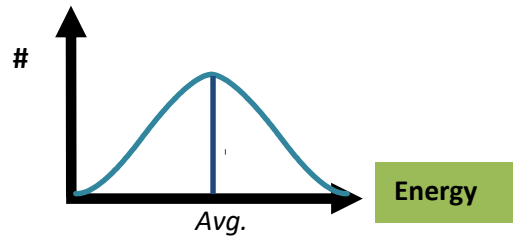
*CE = Conversion Electron

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
 - CE 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

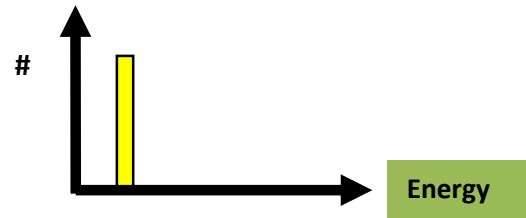
Comparing Energy Types for Radiopharmaceuticals

Beta

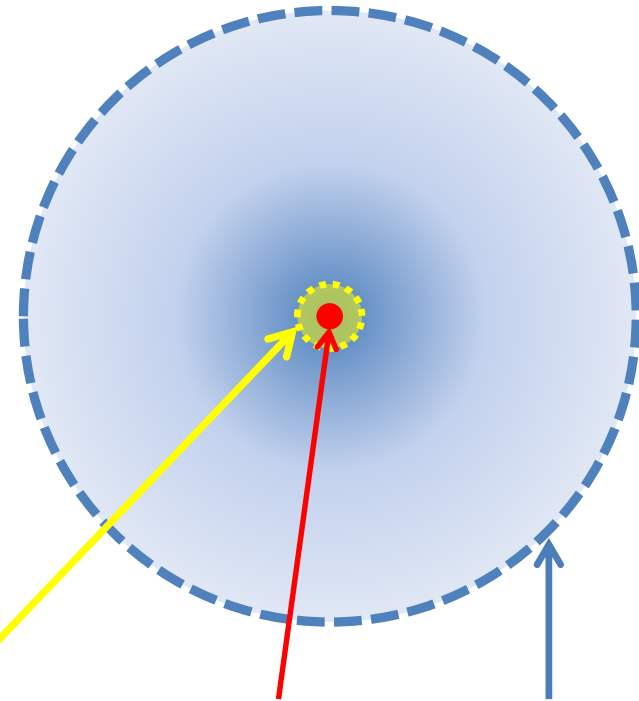


Produces a range of tissue penetration

Conversion
Electron



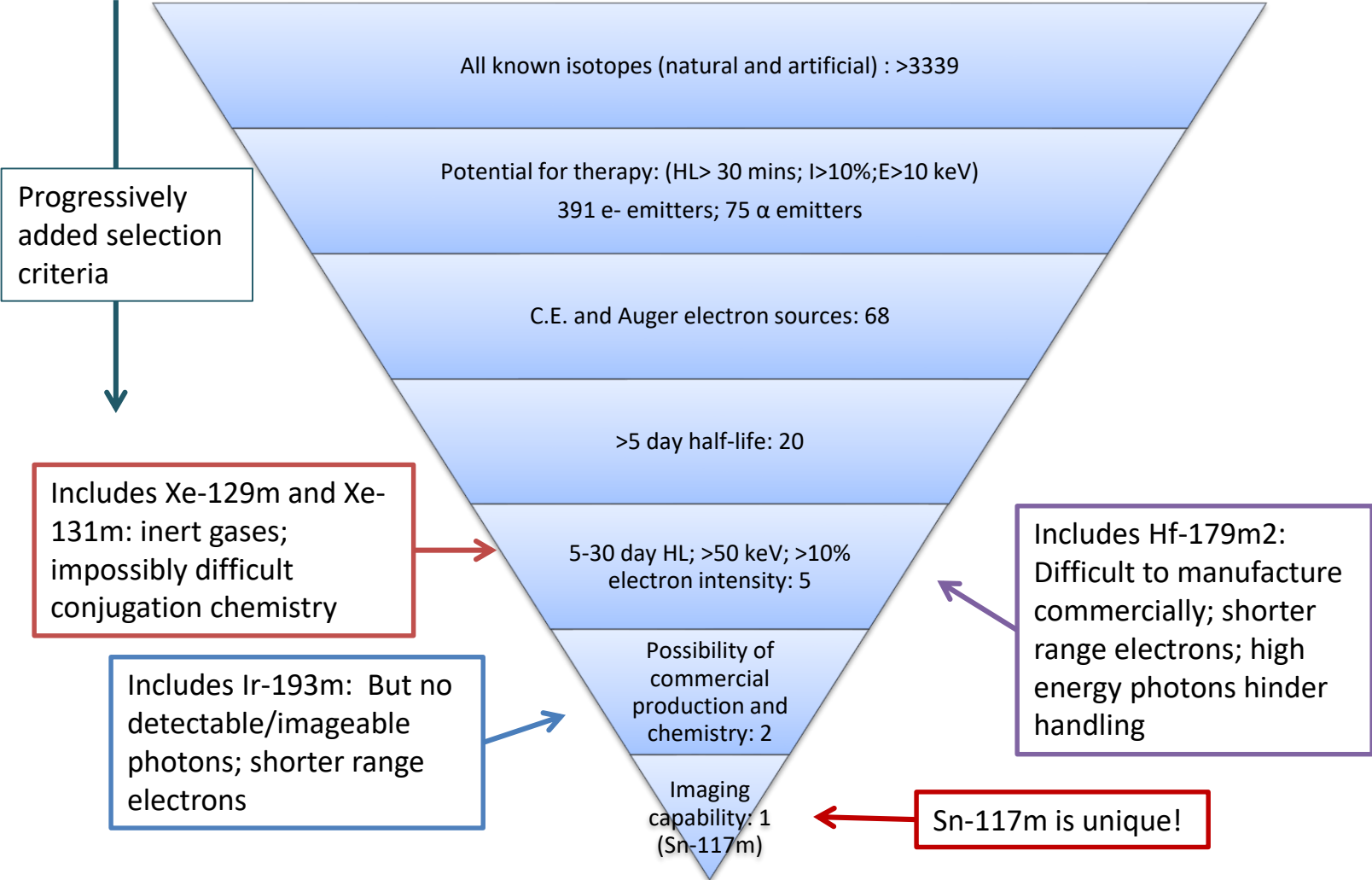
Penetrates up to a set distance



	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

Tin-117m is Unique



Production of Sn-117m

Reactors:



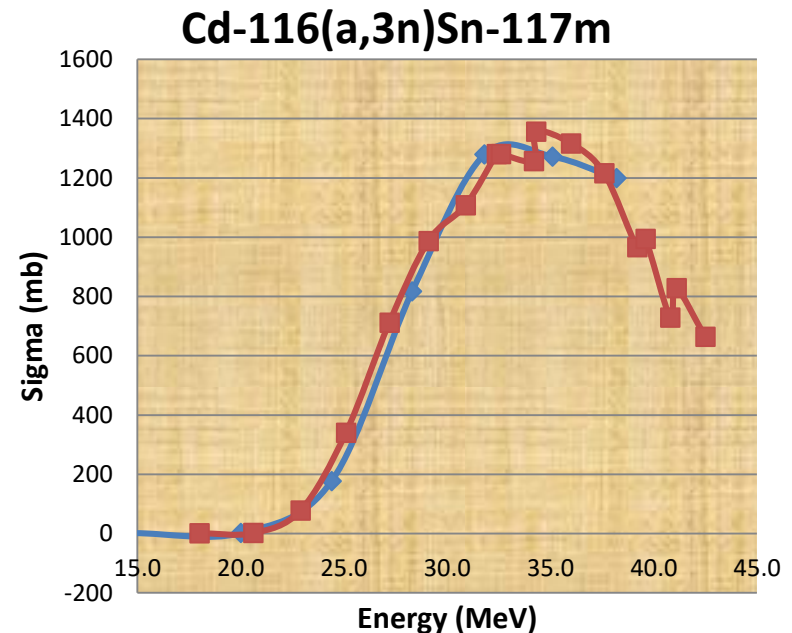
Accelerators:



Accelerator production of Sn-117m

Cd-116(α ,3n)Sn-117m

- ❑ Traditionally limited by availability of suitable accelerators and/or beam current ($< 70 \mu\text{A}$)
- ❑ New high-current accelerator (2mA+) coming on-line in 2 years
- ❑ Provides (commercially viable) possibility for labeling molecules, etc.



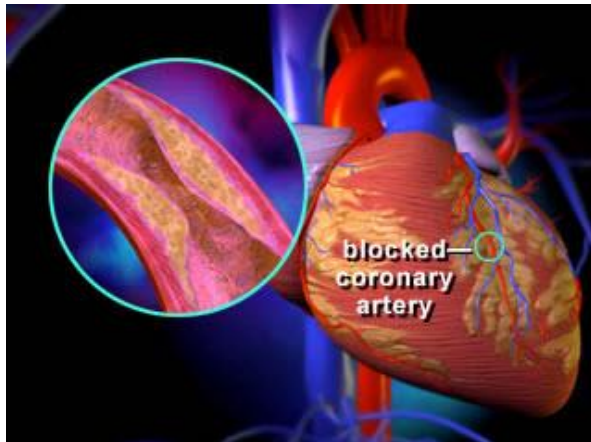
The thick target yield over the energy range of 47→20 MeV is about 150 $\mu\text{Ci}/\mu\text{Ah}$

Tin-117m: Past Work & Development

- Suresh Srivastava, BNL, performed **Bone Pain Palliation** ([Sn-117m]-DTPA) studies and trials
 - >120 subjects successfully treated
- **Cardiovascular** – Vulnerable/Unstable Plaque ([Sn-117m]-DOTA-Annexin)
 - Imaged in human clinical trials
 - Therapy in animals confirmed
- **Osteoarthritis and Rheumatoid Arthritis** (Sn-117m colloid)
 - Animal models
- **Lymphoma and Leukemia**
 - Labeled molecules targeted conditions
- Linking to **Antibodies**
 - Excellent labeling efficiencies – breast cancer targeting
- **Medical Devices: Cholangiocarcinoma Stent**
 - IP for superior electroplating method for other medical devices
- **Alzheimer's disease**
 - Targeting molecules linked to Sn-117m
 - Human brain dosimetry demonstrated

Cardiovascular - Vulnerable Plaque

- ❖ Vulnerable plaque forms outside of the lumen in coronary/carotid artery walls - inflammation is the main driver
- ❖ VP is usually covered by a thin cap on the lumen side [thus also called thin cap fibroatheroma (TCFA)]
- ❖ **Majority of all significant cardiac events (60-70%) leading to MI and sudden cardiac death are a result of VP, not calcified lumen atherosclerosis**
- ❖ Treatment of inoperable symptomatic high grade carotid stenosis
- ❖ Ruptured thin cap “releases” highly thrombogenic material activating clotting cascade and inducing thrombosis



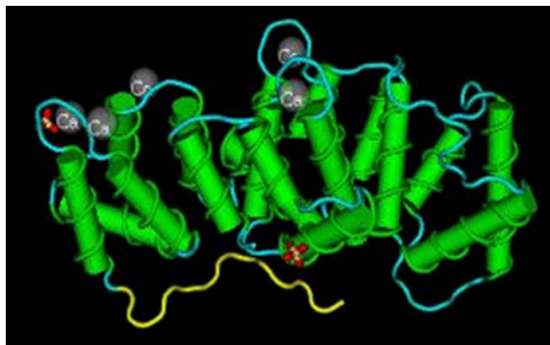
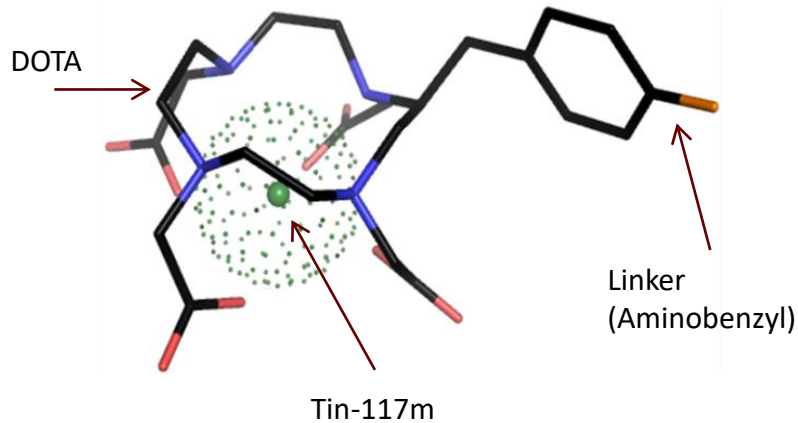
Luminal Calcified Plaque



Extra-Luminal Vulnerable Plaque

Cardiovascular Imaging and therapy

THE PRODUCT IS COMPRISED OF A RADIOISOTOPE, TIN-117M, THAT IS HELD WITHIN A DOTA MOLECULE WHICH IS LINKED TO A TARGETING MOLECULE, ANNEXIN V



Tin-117m

- Imaging gamma compatible with existing gamma cameras
- Therapeutic conversion electron has strong ionization effect over relevant biological range
- 14 day half-life

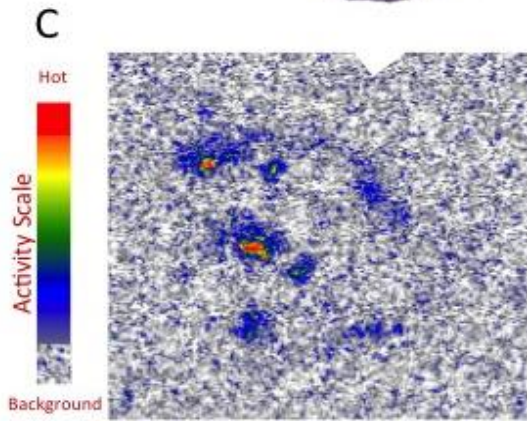
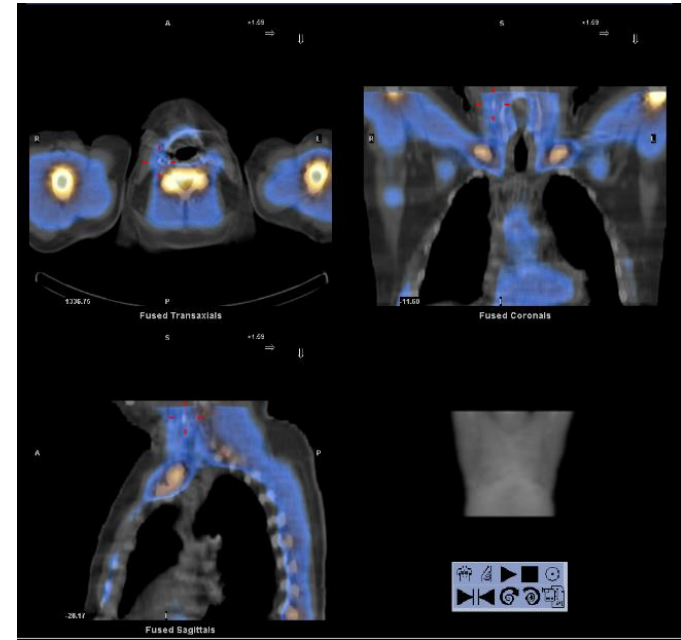
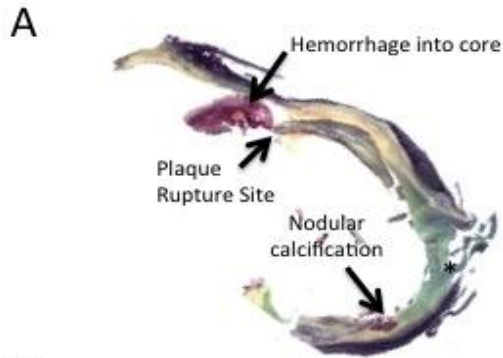
Aminobenzyl DOTA

- Securely holds the Tin-117m

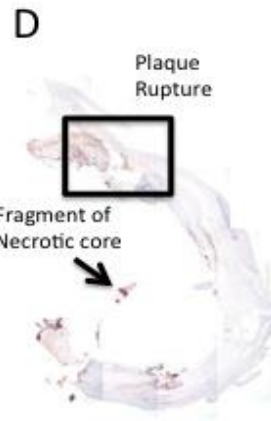
Annexin V

- Naturally occurring human protein
- Annexin V binds to specific cell membrane chemicals that are expressed in apoptotic inflammatory cells

Imaging, Autoradiograph and Histology

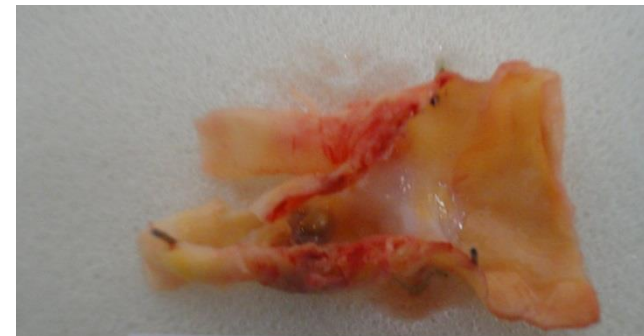


Autoradiograph
[5d Exposure]



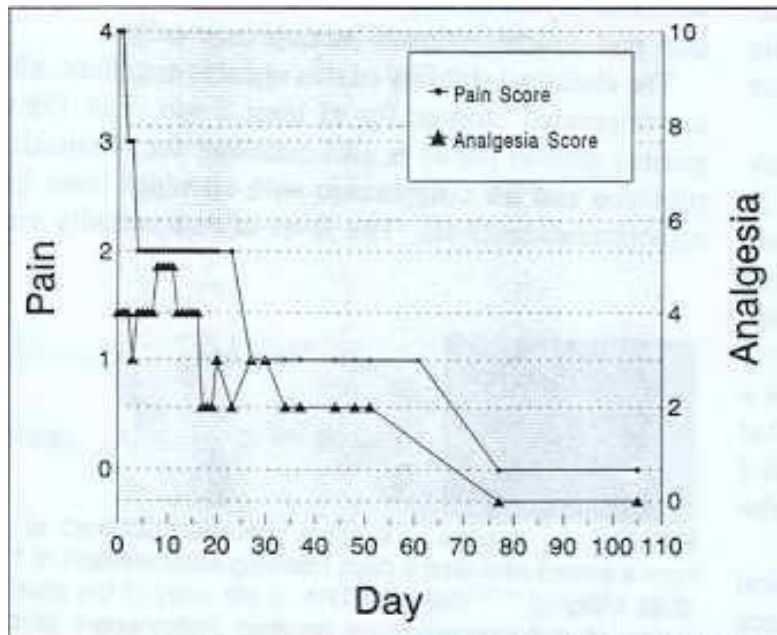
Lesional Macs
[CD68]

Hormetic Dose!



Oncology: Bone Pain Palliation and Therapy

- ❑ Metastatic bone pain where all other treatments failed
- ❑ [Sn-117m]-DTPA
- ❑ Phase I/II Trial with over 120 patients
- ❑ 2.64 to 10.58 MBq (71-286 μ Ci) per kg
- ❑ Relief of pain of 75% (60-83%)
- ❑ Minimal myelotoxicity



Response to $^{117}\text{Sn}(4+)\text{-DTPA}$ In a patient with prostate carcinoma metastatic to bone. Analgesia Score refers to number of doses required per day

Sn-117m DTPA: Planned Clinical Studies

- ❑ NCI collaborating with commercial company (Serene)
- ❑ Repeat of original formulation to establish standards
- ❑ Sn-117m DTPA with *possible* improved formulation:
 - ❑ Simpler production method
 - ❑ Less free DTPA
 - ❑ Higher specific activity
- ❑ Manufacturing development underway
- ❑ US Phase 1 trials planned to start later this year

Cholangiocarcinoma Stent

Stainless steel laser cut electroplated stents

Treat Symptoms

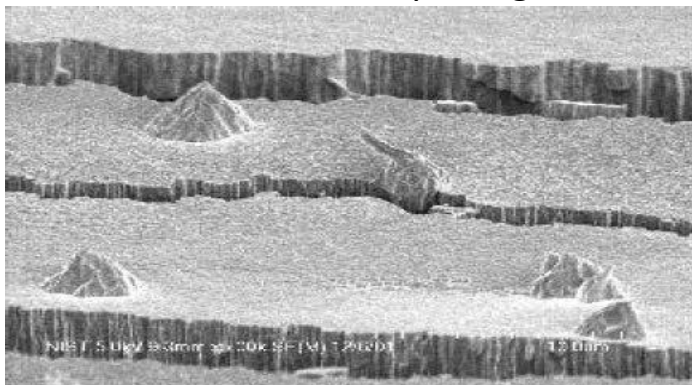
- stent expands to open the occluded duct – palliation of symptoms

Treat Cancer

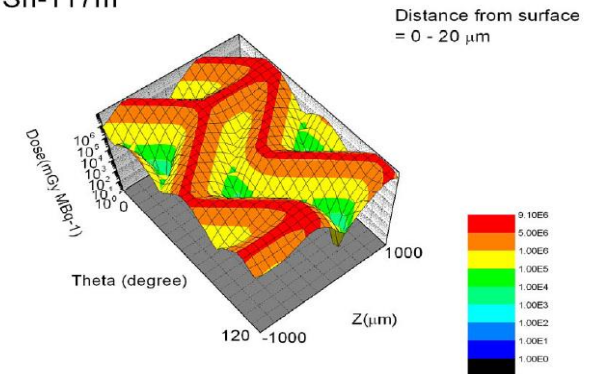
- conversion electron (C.E.) emitting metallic isotope – treat cancer, reduces tumor mass
- electroplating metallic dendrites increases dosimetry surface area

Resolves Issues with Existing Stents

- Prevents migration
- suppress microbial burden – organism-induced biofilm and fungal mass occlusion
- selective surface electroplating – enhance re-endothelialization



Sn-117m



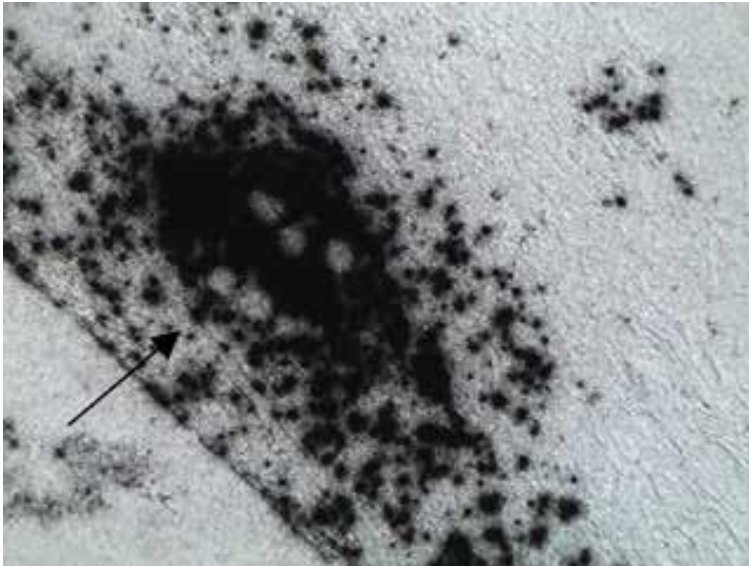
Radiosynoviorthesis Isotopes

Isotope	t1/2 (d)	Imaging Particle	Energy (keV)	Therapy Particle	Max Energy (keV)	Range (mean) in Tissue (mm)	Range (max) in Tissue (mm)	Typical Dose (mCi)	Joint Size
Sn-117m	13.6	γ	159	CE	151	0.27	0.29	0.5-1.0	Small/Med
Er-169	9.3	None	-	β^-	350	0.14	1.1	1	Small
Re-186	3.7	γ	137	β^-	1070	1.1	4.4	2.5	Medium
Y-90	2.7	None	-	β^-	2280	4.1	11	4	Large
P-32	14.3	None	-	β^-	1711	2.8	8.4	2	Large
Au-198	2.7	γ	412	β^-	960	0.9	4.2	7	Large/Med
Sm-153	1.9	γ	103	β^-	808	0.55	3.3	5	Medium
Re-188	0.7	γ	155	β^-	2120	3.1	10.4	10	Large
Ho-166	1.1	γ	81	β^-	1855	2.6	9.2	10	Large
Dy-165	0.1	γ	95	β^-	1289	1.3	5.9	270	Large
Tm-170	129	γ	84	β^-	968	0.9	4.2	1.6-4.8	Medium

Homogeneous Tin-117m Colloid for RSO

Test	Method	Specification
Appearance	Visual inspection	White turbid particles and white, cream or pale-red colored solution ¹
pH	microprobe	6.5 - 9.0
Median Particle Size (PS)	Horiba Model LA-300 Particle Size Analyzer	2.5 - 6 μm
Particle Size Range (D10 to D90)	Horiba Model LA-300 Particle Size Analyzer	$\geq 90\%$ above 1.5 μm $\geq 90\%$ below 20 μm
Endotoxin	Kinetic-chromogenic (Charles River Endosafe PTS)	< 58 EU/mL
Sterility	ISO 20857	SAL $\geq 10^{-6}$ Sterile based on visual assessment of BI colors
Free Sn	Radioactivity measurement	$\leq 0.2\%$

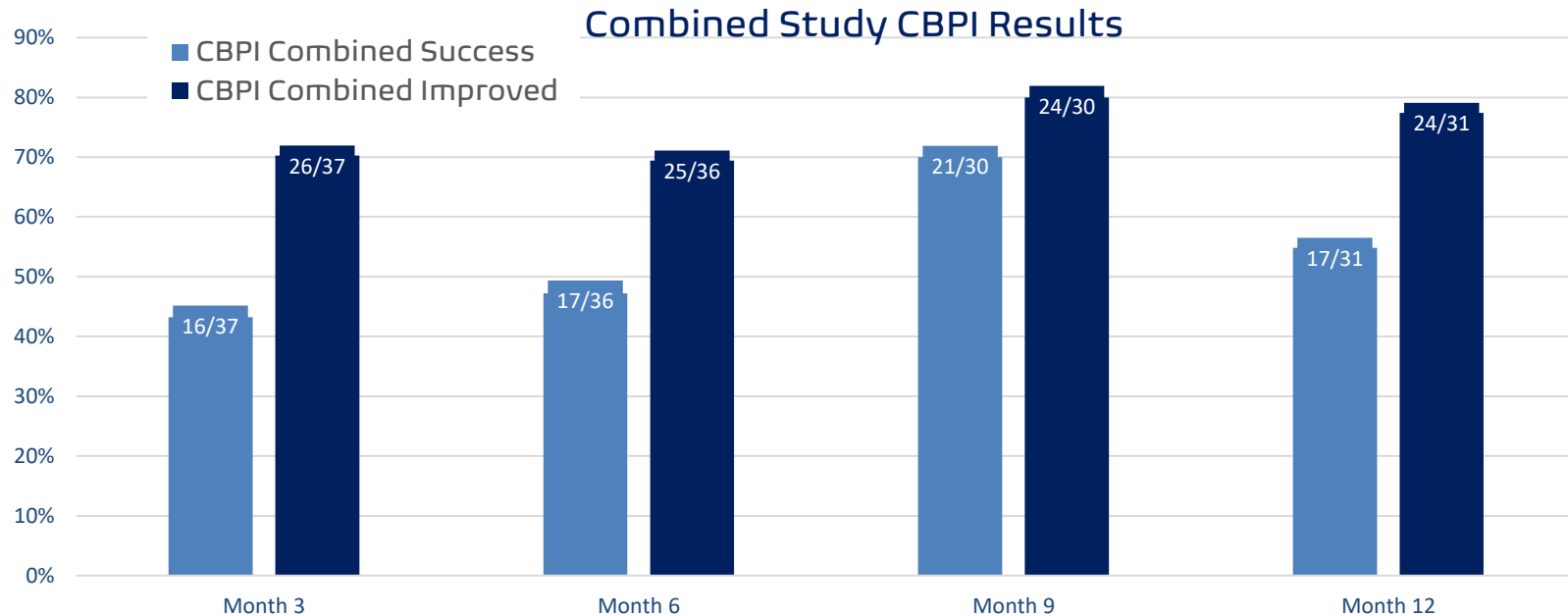
RSO - Tissue Autoradiography



Phagocytosed colloidal particles (unaltered) migrate deeper in tissues to areas of sub-synovial inflammation

Potential to treat larger joints, for a longer time and with a much lower dose

Overall Treatment Success (label dose) – Canine OA



- CBPI Success (successful reduction of pain AND successful increase in level of activity as compared to baseline values)
- CBPI Improved (successful reduction of pain OR successful increase in level of activity with no worsening from baseline values)

Canadian RSO Trial in Knee Arthritis Imaging Schedule

Dose	mCi	MBq
Low	1.0	37.0
Medium	2.4	88.8
High	6.0	222.0

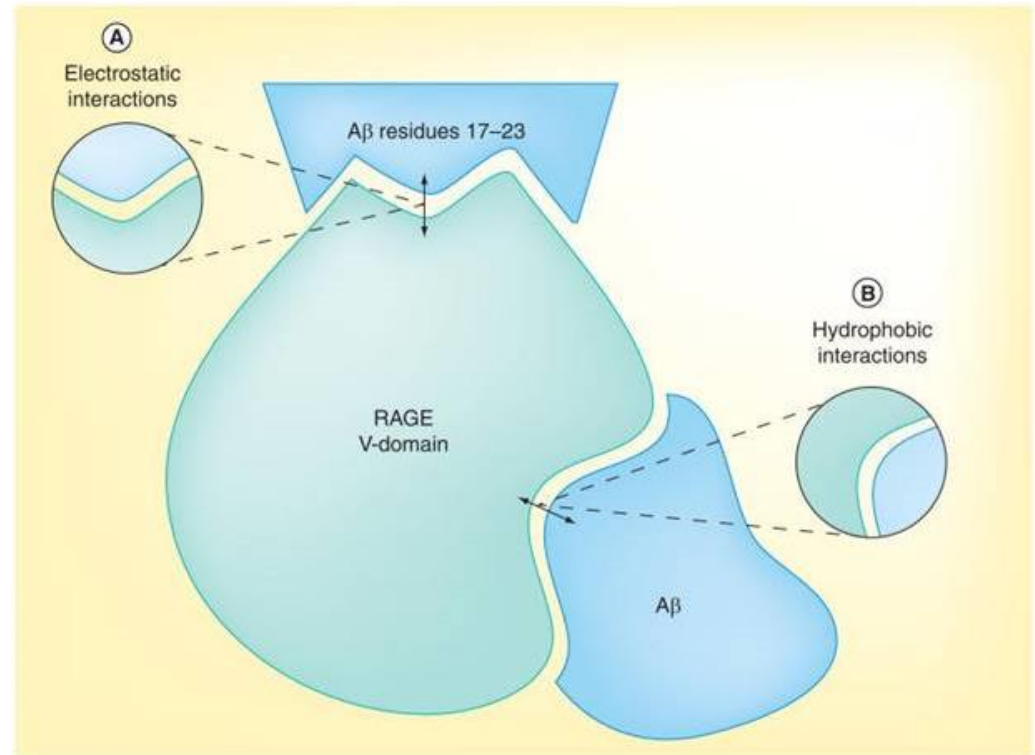
Procedure/ parameter	Screening	Study Week								EOS
		1	2	3	5	9	14	27	40	
^{117m} Sn scan (γ camera)		X	X		X					
Plain X-rays of both knees	X									
Ultrasound	X				X		X	X		X
Treatment (RSO)		X								

OA and RA Trial in Canada. Approved to proceed.

Neurology – Treatment of Alzheimer’s Disease

Microglia are Recognized as an Upstream Link in the Cascade to Amyloid Beta (A β) Plaque Formation

- ❑ **Microglia (MG)** are the “macrophages” of the brain and are **hyper-reactive in AD**
- ❑ **Tin-Annexin V** actively crosses the Blood Brain Barrier (BBB) and **induces apoptosis** in macrophages
- ❑ **Annexin A1** crosses and stabilizes/repairs the BBB, and is strongly expressed in AD



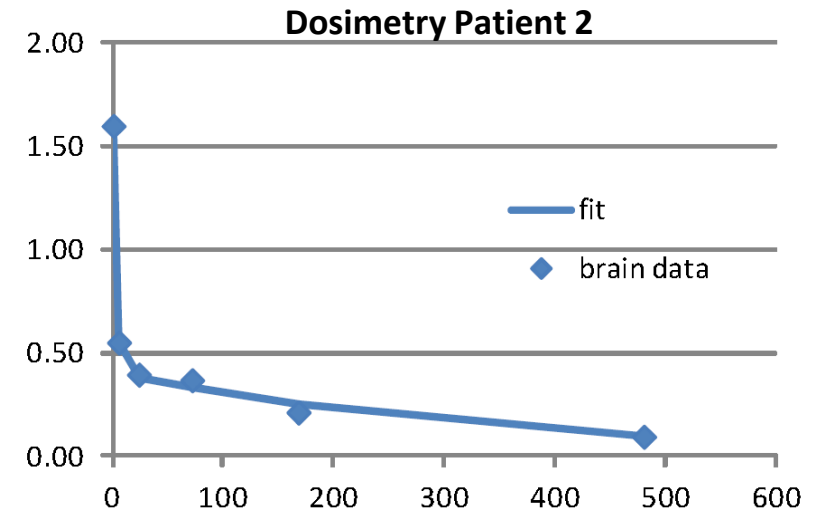
Sn-117m is linked to the 8AA that binds to RAGE V-domain

Neurology - NeuroSn Approach

Systemically delivered Tin-annexin V resides in subjects with injured BBB

Microglia as a Target for AD Treatment

- ❑ **Tin-Annexin V** must enter and reside in the brain in order to **induce apoptosis in aged microglia**
- ❑ Systemic (IV) delivery of Tin-Annexin V to human brain validated in human dosimetry study
- ❑ **Mouse trials** can determine in 3 to 9 months reduction in β amyloid plaque and τ neurofibrillary tangles

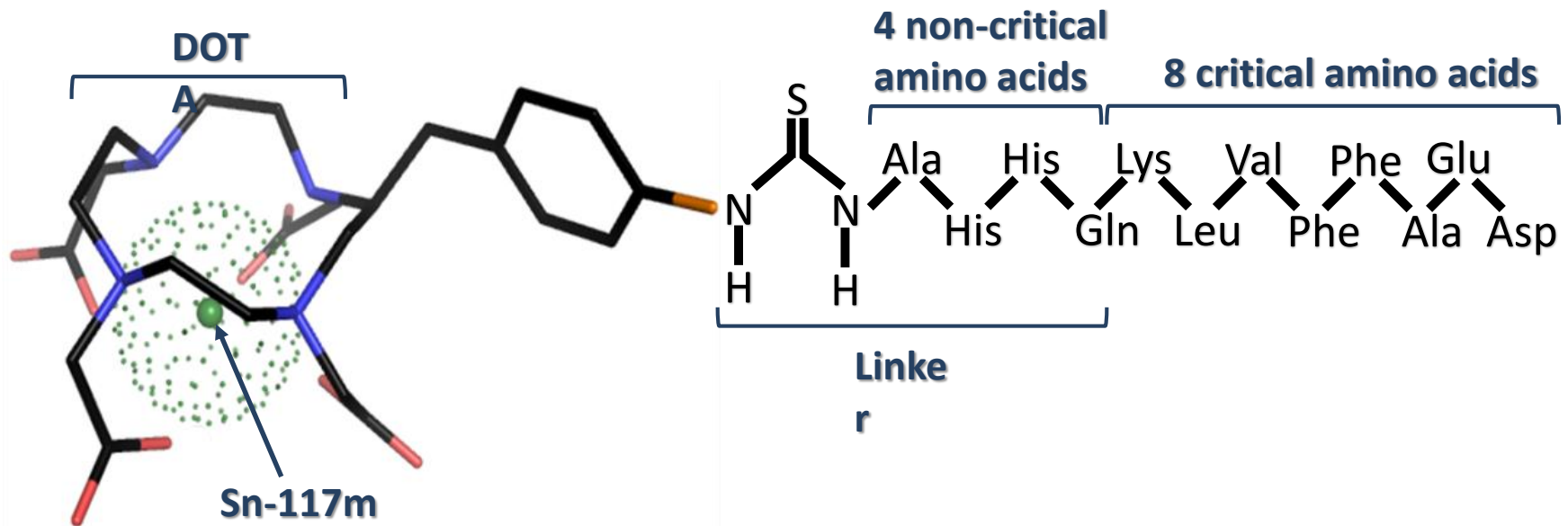


Neuroinflammatory Hypothesis: Microglia are in the pathway to $A\beta$ formation

RAGE Targeting

4-(DOTA-2-yl-methyl)-phenylcarbamothioyl- β -Ala-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-OH trifluoroacetate salt

A RAGE-targeting molecule containing a critical 8 amino acid (aa) portion plus Sn-117m linked DOTA has been constructed



Conclusion

- Sn-117m produced cGMP
- High (accelerator) and low (reactor) sp. act.
- Labeling to variety of molecules
- Electroplating and colloids
- Applications in:
 - Cardiology (vulnerable/unstable plaques)
 - Rheumatology (OA, RA)
 - Neurology (Alzheimer's)
 - Oncology
 - Veterinary and human
- Imaging and Therapy (High Dose and Hormetic)