

Manufacturing and Nuclear Medicine Applications of the Novel Isotope Sn-117m

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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

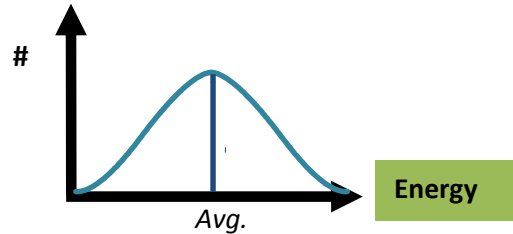
*C.E. = Conversion Electron

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 to Tc-99m (140 KeV)** allowing for existing standard gamma camera imaging & techniques

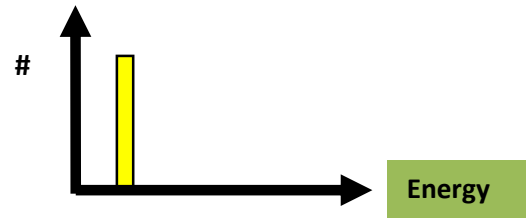
Comparing Energy Types for Radiopharmaceuticals

Beta

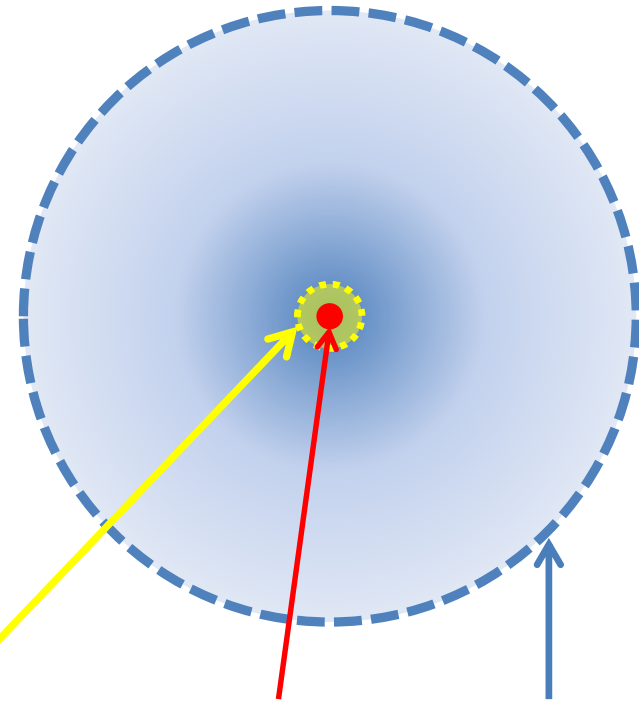


Produces a range of tissue penetration

Conversion
Electron



Penetrates up to a set distance



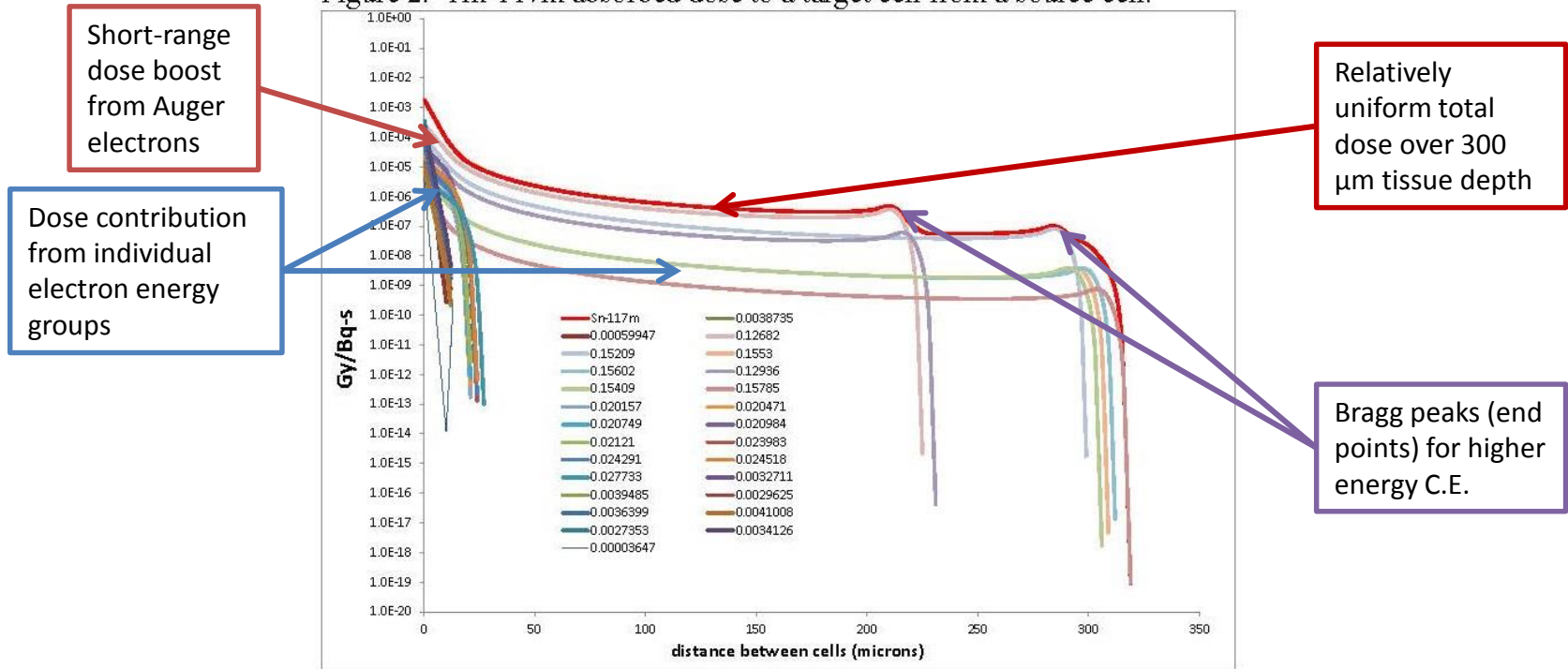
	Tin-117m	Alpha Particles ¹	Beta Particles ²
Range in tissue (µm)	290	40-90	50-5000
Shielding needed during administration	No	No	Yes

¹XOFIGO; ²METASTRON & QUADRAMET

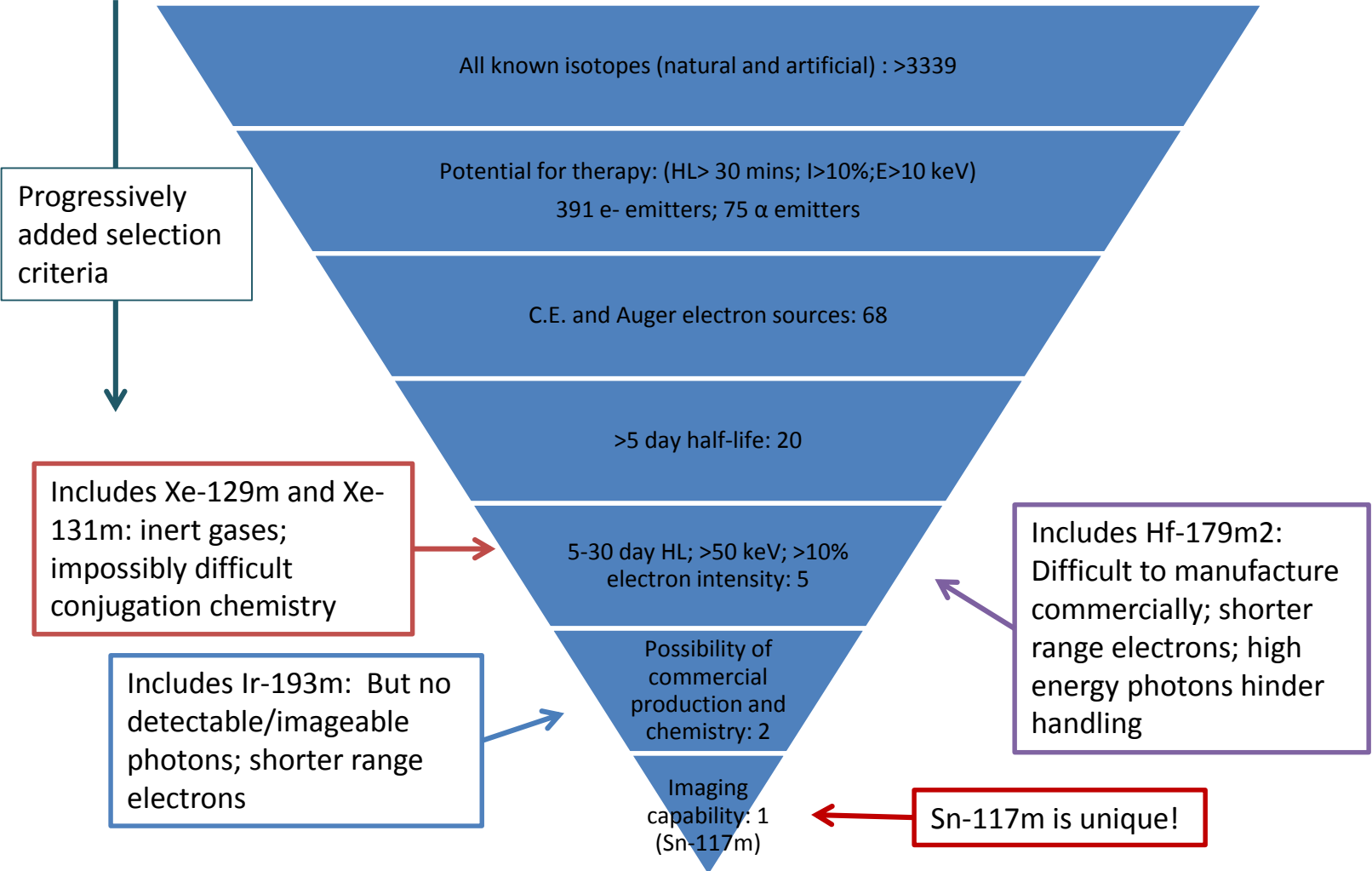
Well-Defined Range of Sn-117m in Tissue

- 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 medical applications

Reactor Production of Sn-117m

Sn-116(n, γ)Sn-117m

- Requires 2-3 week irradiation
- Low specific activity (typically ~ 1 Ci/g)
- Electromagnetic/laser separators to increase specific activity to 100-1000 Ci/g?
- Feasibility being evaluated

Sn-117(n,n' γ)Sn-117m

- Higher specific activities (typically 2-20 Ci/g)
- Higher yields but post e-m enhancement not possible

Accelerator Production of Sn-117m

Sb-nat(p,x)Sn-117m

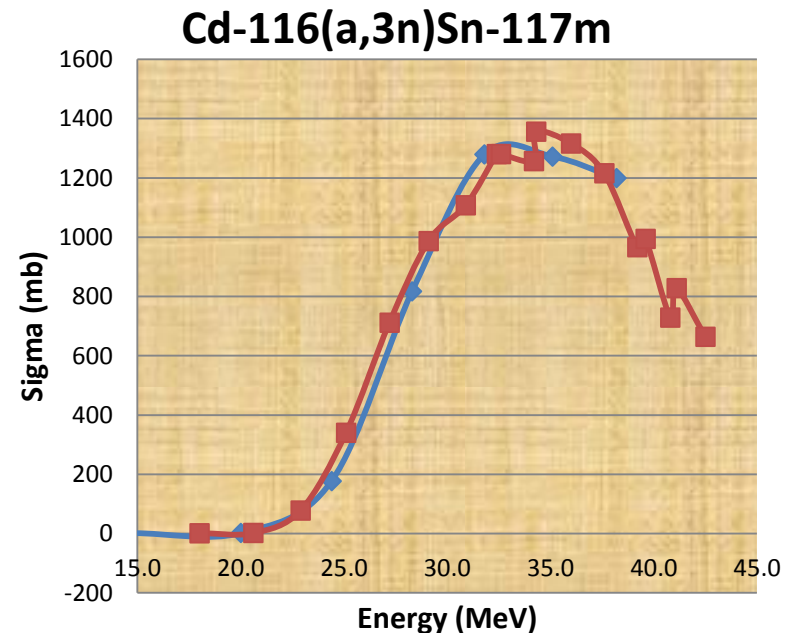
- ❑ Proven method developed in Russia under IPP; transferred to USA
- ❑ IP controlled by R-NAV, LLC
- ❑ Can be produced free of Sn-113 at <55 MeV
- ❑ High power 30 and 42 MeV cyclotrons can use standard electroplated targets and Sb-121
- ❑ High power targetry developed to capitalize on maximum available beam currents
- ❑ Several existing accelerators suitable for use worldwide

Accelerator production of Sn-117m

IRRADIATION AT UNIVERSITY OF WASHINGTON MC50 CYCLOTRON

Cd-116($\alpha,3n$)Sn-117m

- Target prepared (electroplating) in Texas
- Shipped (FedEx) to UW
- Irradiated (typically up to 20 hrs)
- 60-80 μA @ 47.3 MeV
- Produces about 10 mCi/hr
- Product allowed to cool for 1 day
- Shipped (by FedEx) to Texas for processing



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

Production of HSA Sn-117m

Alpha + Cd-116

Performed at the University of Washington Medical Center



Electroplated target
and Irradiation
Room at UW

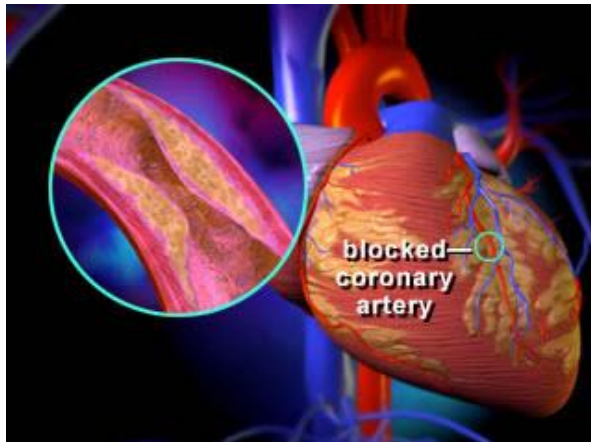


Tin-117m: Past Work & Development

- 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
- **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



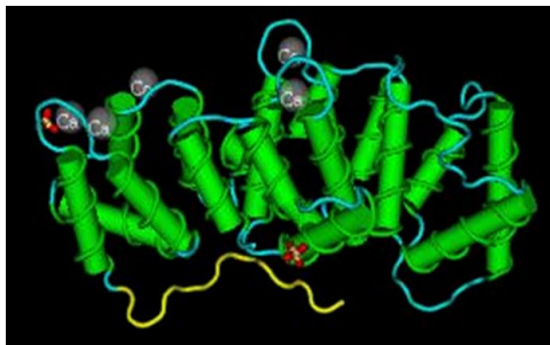
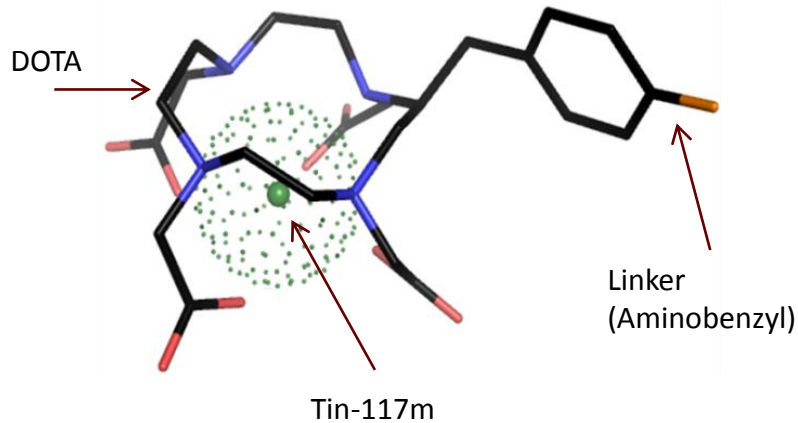
Luminal Calcified Plaque



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

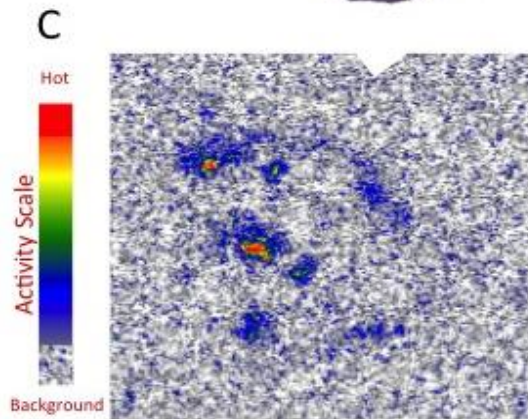
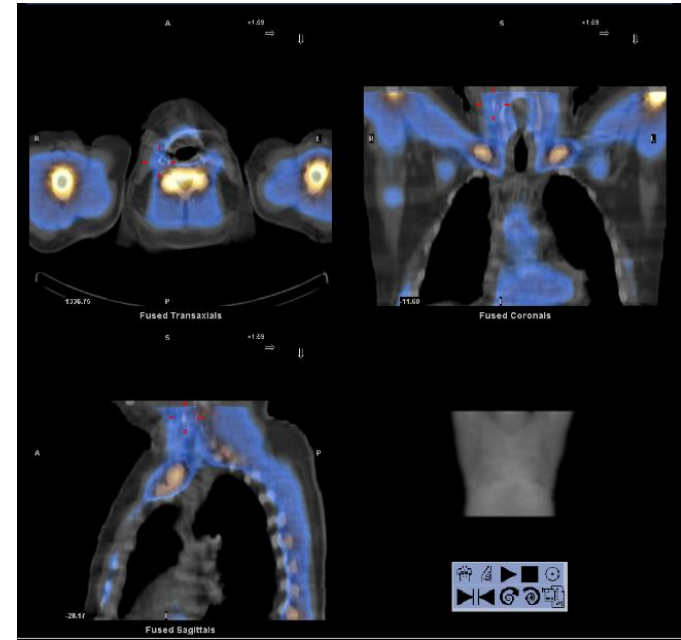
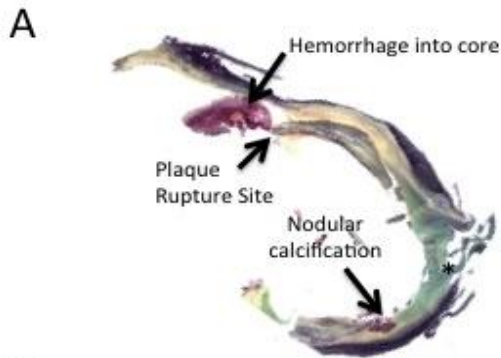
Aminobenzyl DOTA

- Securely holds the Tin-117m

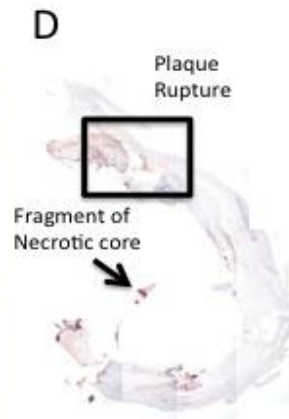
Annexin V

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

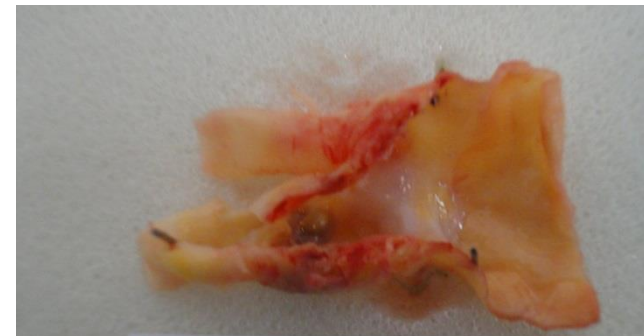
Imaging, Autoradiograph and Histology



Autoradiograph
[5d Exposure]

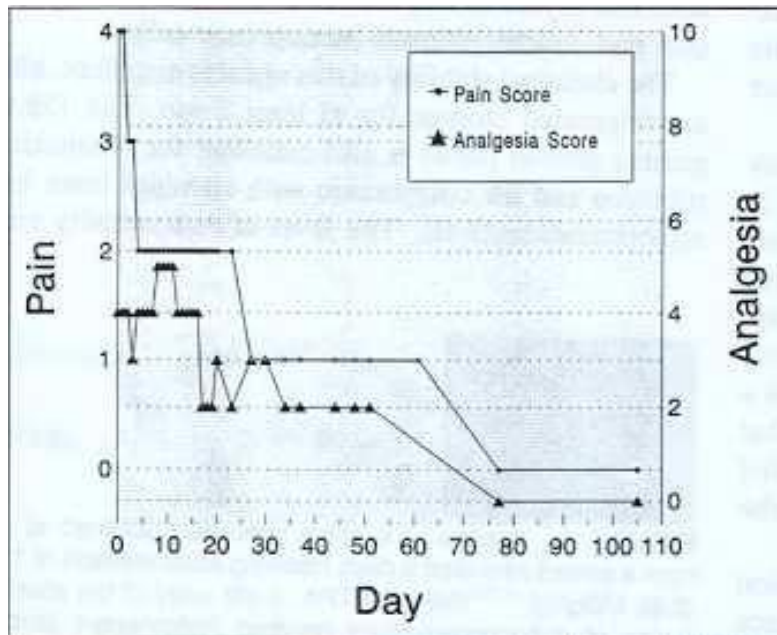


Lesional Macs
[CD68]



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

Cholangiocarcinoma Stent

Stainless steel laser cut electroplated stents

Treat Symptoms

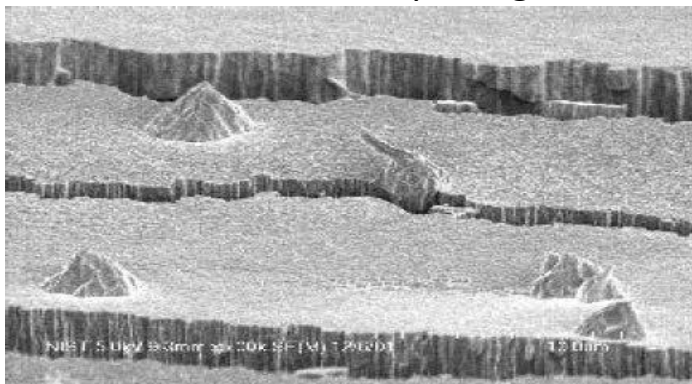
- stent expands to open the occluded duct – palliation of symptoms

Treat Cancer

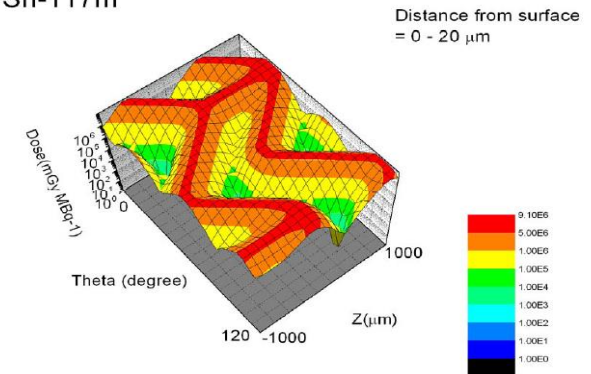
- conversion electron (C.E.) emitting metallic isotope – treat cancer, reduces tumor mass
- electroplating metallic dendrites increases dosimetry surface area

Resolves Issues with Existing Stents

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



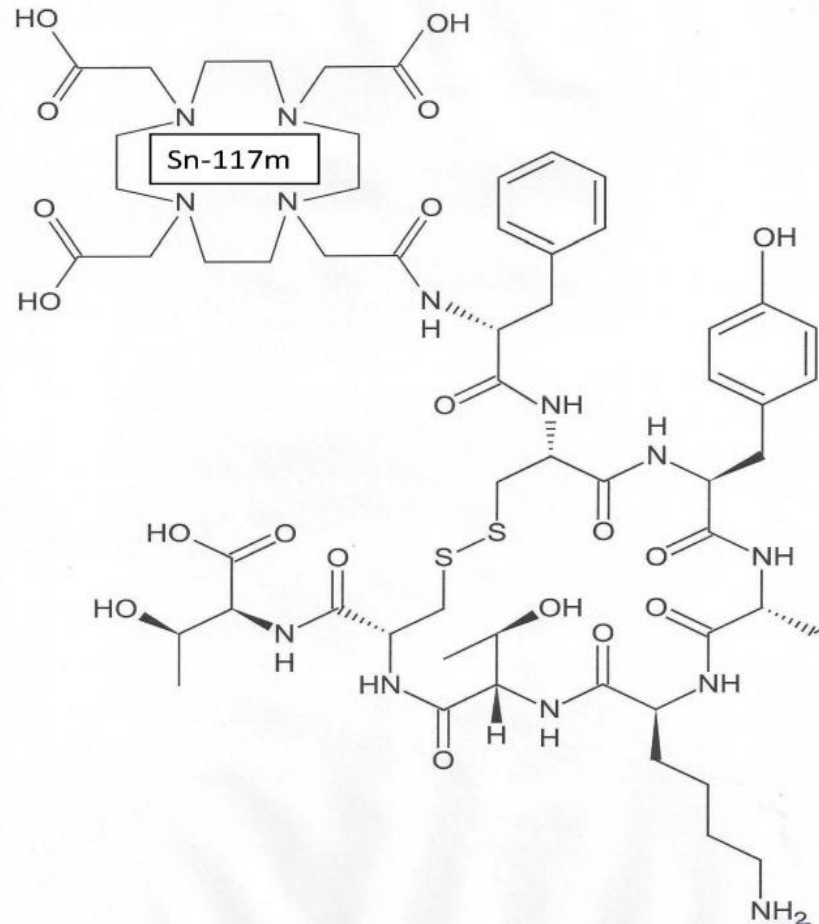
Sn-117m



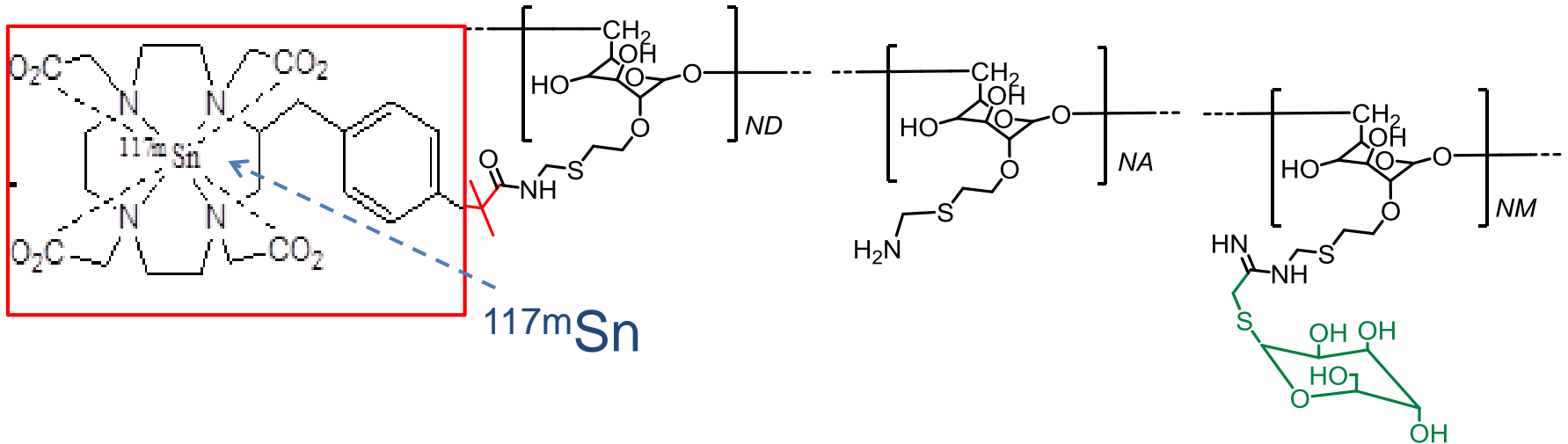
Labeled Molecules for Oncology

[Sn-117m] Dotatate for GEPNET

Sn-117m can be attached as a finished molecule during production i.e., ready to inject. Alternatively, it can be inserted immediately prior to treatment



Rheumatology - Systemic RA



- Dextran chain (structure)
- Mannose (targeting)
- Aminobenzyl-DOTA (chelation/linking)
- Sn-117m radioisotope (imaging & therapy)

Rheumatology – Local Administration

Comparison of all radiosynoviorthesis isotopes

Radiosynoviorthesis Isotopes																		
Isotope	T _{1/2} (d)	Imaging Particle	Energy (keV)	Intensity (%)	Image Quality†	Therapy Particle	Mean Energy (keV)	Maximum Energy (keV)	Intensity (%)	Range (mean) Tissue* (mm)	Range (max) Tissue* (mm)	Range (max) Bone** (mm)	Range (max) Air* (m)	Typical*** Particle Size (µm)	Typical Dose (mCi)	Joint Size	Colloidal Compound(s)	Comments
Sn-117m	13.6	γ	158.6	86	Good	C.E.	140	151	~112	0.27	0.29	0.17	0.3	5-10	~ 1	Small	hydroxide	new isotope colloid
Er-169	9.3	None	-	-	None	β ⁻	100	350	100	0.14	1.1	0.64	0.9	2-5	1	Small	citrate sulfide	Standard isotopes used throughout most of the world
Re-186	3.7	γ	137	9	Poor	β ⁻	347	1070	93	1.1	4.4	2.8	4.4	1-4	2.5	Medium		
Y-90	2.7	None	-	-	None	β ⁻	934	2280	100	4.1	11	6.6	10.3	10-20	4	Large	silicate, citrate	
P-32	14.3	None	-	-	None	β ⁻	695	1711	100	2.8	8.4	5	7.8	0.1-1.0, 6-20	2	Large	chromic phosphate	used off-label in US
Au-198	2.7	γ	412	97	Moderate	β ⁻	312	960	100	0.9	4.2	2.5	3.9	20-70	7	Large/Med	elemental	Discontinued
Sm-153	1.9	γ	103	29	Moderate	β ⁻	224	808	100	0.55	3.3	2	3.1	1-10	5	Medium	hydroxyapatite	R&D
Re-188	0.7	γ	155	16	Moderate	β ⁻	763	2120	100	3.1	10.4	6.2	9.7	1-4	10	Large	sulfide	R&D
Ho-166	1.1	γ	81	6	Poor	β ⁻	665	1855	100	2.6	9.2	5.2	8.3	5-10	10	Large	ferric hydroxide, chloride	R&D
Dy-165	0.1	γ	95	4	Poor	β ⁻	440	1289	100	1.3	5.9	3.5	5.4	3-5	270	Large	ferric hydroxide	R&D
Tm-170	129	γ	84	3	Poor	β ⁻	317	968	99	0.9	4.2	2.5	3.9	1-10	1.6-4.8	Medium	Labeled onto tin oxide	R&D
	[5]	[5]	[3],[5]	[5]		[5]	[3],[5]	[3],[5]	[5]	[2],[3]	[2]			[1], [4]	[4]	[4]	[2]	

* p=1.00 g/cc for tissue (= water); 0.0012 g/cc for air <http://physics.nist.gov/PhysRefData/Star/Text/ESTAR.html>

** p=1.85 g/cc for cortical bone <http://physics.nist.gov/cgi-bin/Star/compos.pl?refer=ap&matno=120>

*** Particle size varies depending on specific formulations. Typical numbers/ranges reflect the most commonly reported values.

† Based on primary photon emissions only. Bremsstrahlung radiation is not included.

[1] *Chronic hemophilic synovitis: the role of radiosynovectomy*, Mauricio Silva & James V. Luck Jr., World Federation of Hemophilia, 2004

[2] *Nuclear medicine therapy*, Eary & Brenner, Informa Healthcare USA, Inc., 2007

[3] *The Role of Electron-Emitting Radiopharmaceuticals in ... radiosynovectomy...*, S.C. Srivastava, Brazilian Arch. Biol & Tech, V50 (S) p49 (2007)

[4] *Radiosynoviorthesis in the Treatment of Disabling Arthritis*, Kumar et al, MJAFI 2005; 61: 367

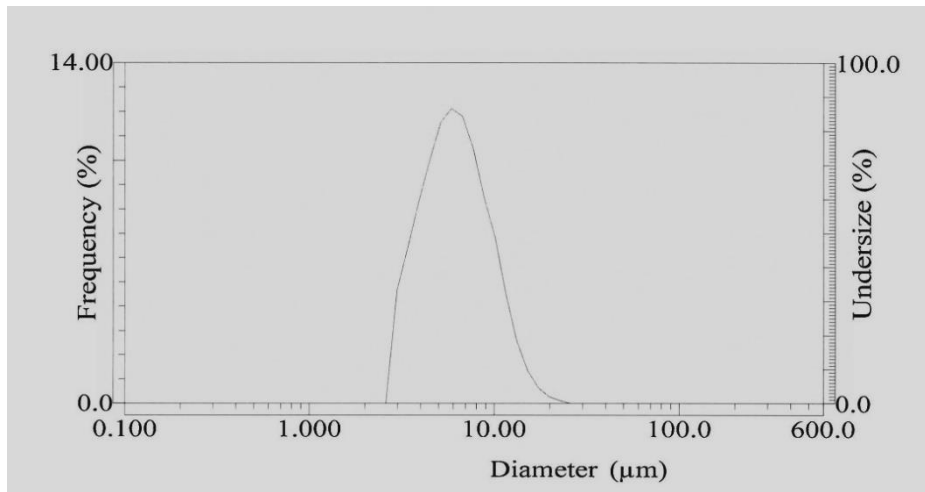
[5] NNDC Chart of Nuclides <http://www.nndc.bnl.gov/chart/reCenter.jsp?z=66&n=99>

NRS 12-19-2015

Colloid joint retention and stability studies

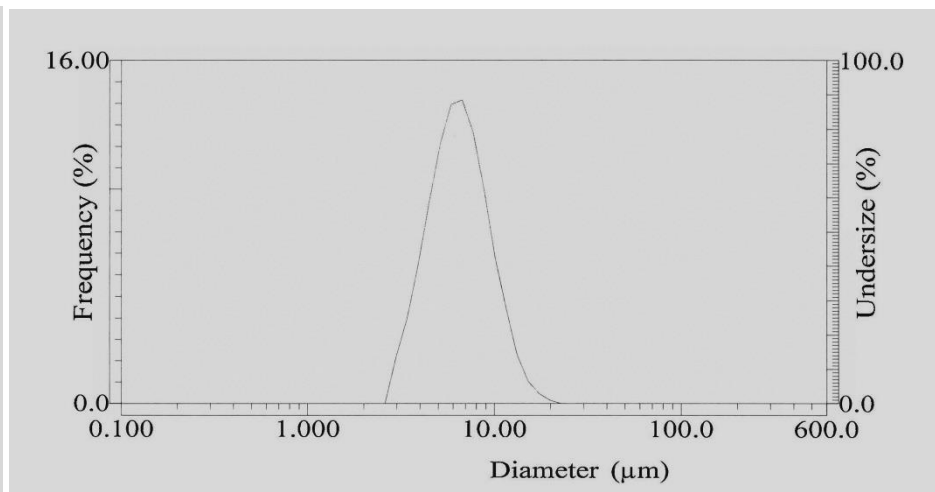
Retention of colloid in normal rat joint:

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



Stability studies – colloid size particle distribution at manufacture

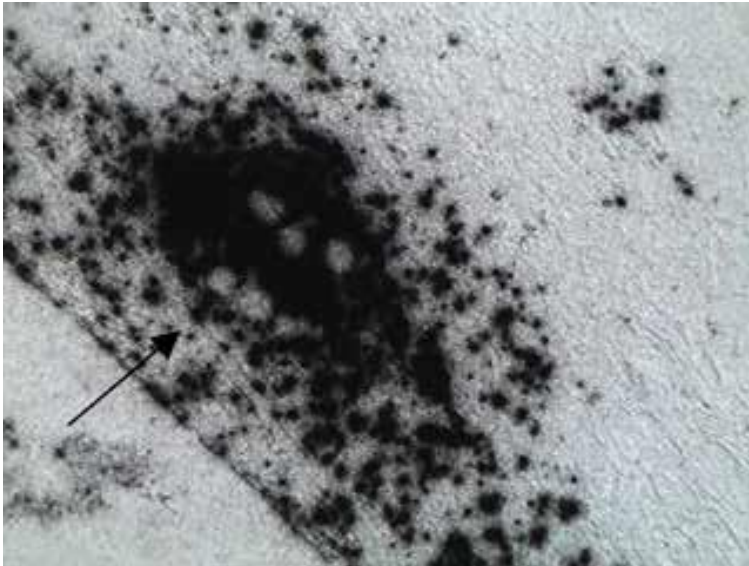
Mean = 6.28 µm SD=2.76 µm



Stability studies – colloid size particle distribution at 5 weeks in room temperature

Mean = 6.43 µm SD=2.47 µm

RSO - Tissue Autoradiography



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

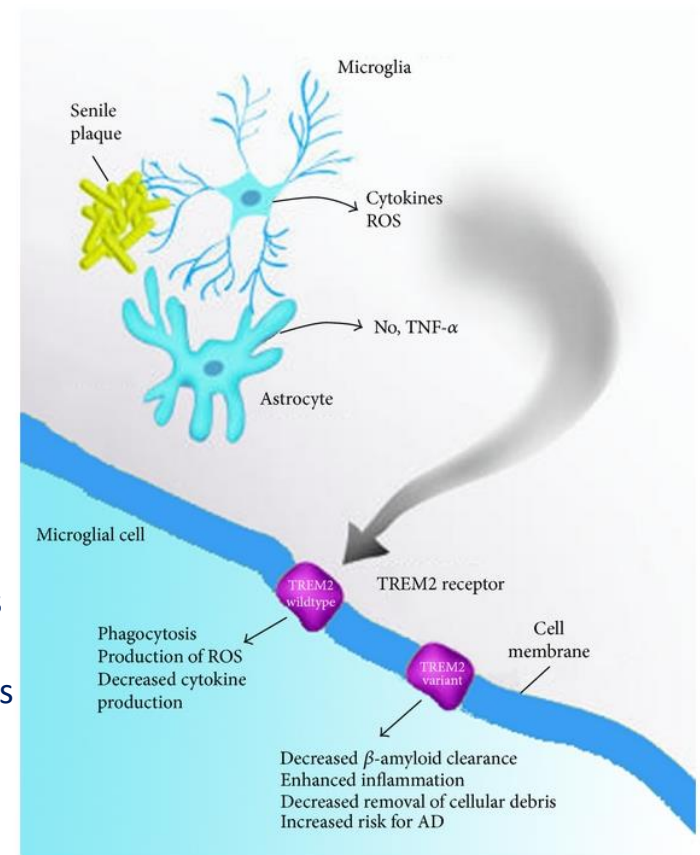
Potential to treat larger joints, for a longer time and with a much lower dose

Neurology – Treatment of Alzheimer’s Disease

Microglia are Recognized as an Upstream Link in the Cascade to Amyloid Beta (AB) 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
- ❑ Annexin A1 and annexin V are very similar in structure

Figure: A central role for MG in AD is dependent upon a functional TREM2 receptor. The important actions of MG appear to be mediated through activation of the TREM2 receptor whose few known roles include suppressing inflammation and stimulating phagocytosis. The loss of TREM2 function and altered immune responses by microglia may explain the increased risk for AD for individuals carrying the heterozygous mutations in TREM2.

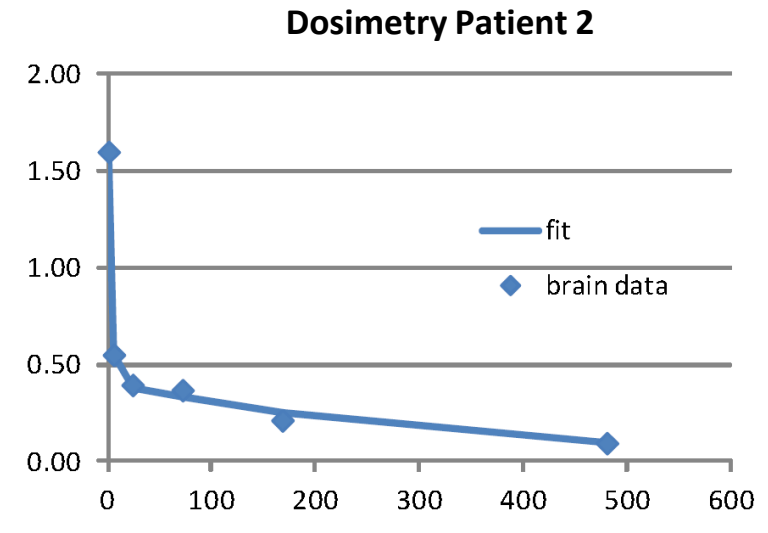


Neurology - NeuroSn Approach

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



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

**Sn-117m available to try with your
own R&D program/molecules**