Applications of Sn-117m and the Potential World Supply and Demand

Nigel R. Stevenson, Ph.D.

President, WCI
COO, Serene, LLC

KARA Radiation Promotion Conference (Busan)

(September 14, 2018)

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

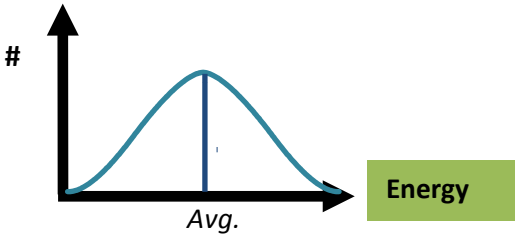
*CE = Conversion Electron

No High Energy Emissions

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

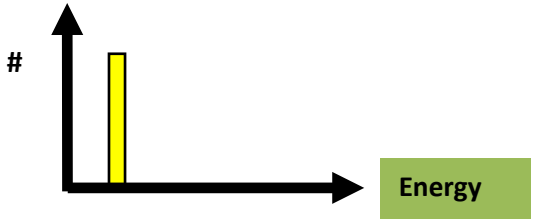
Comparing Energy Types for Radiopharmaceuticals

Beta

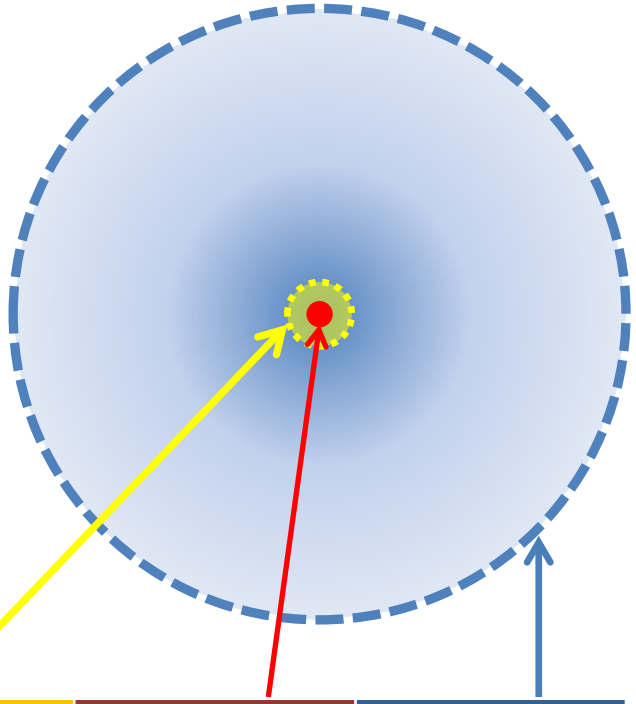


Produces a range of tissue penetration

Conversion Electron



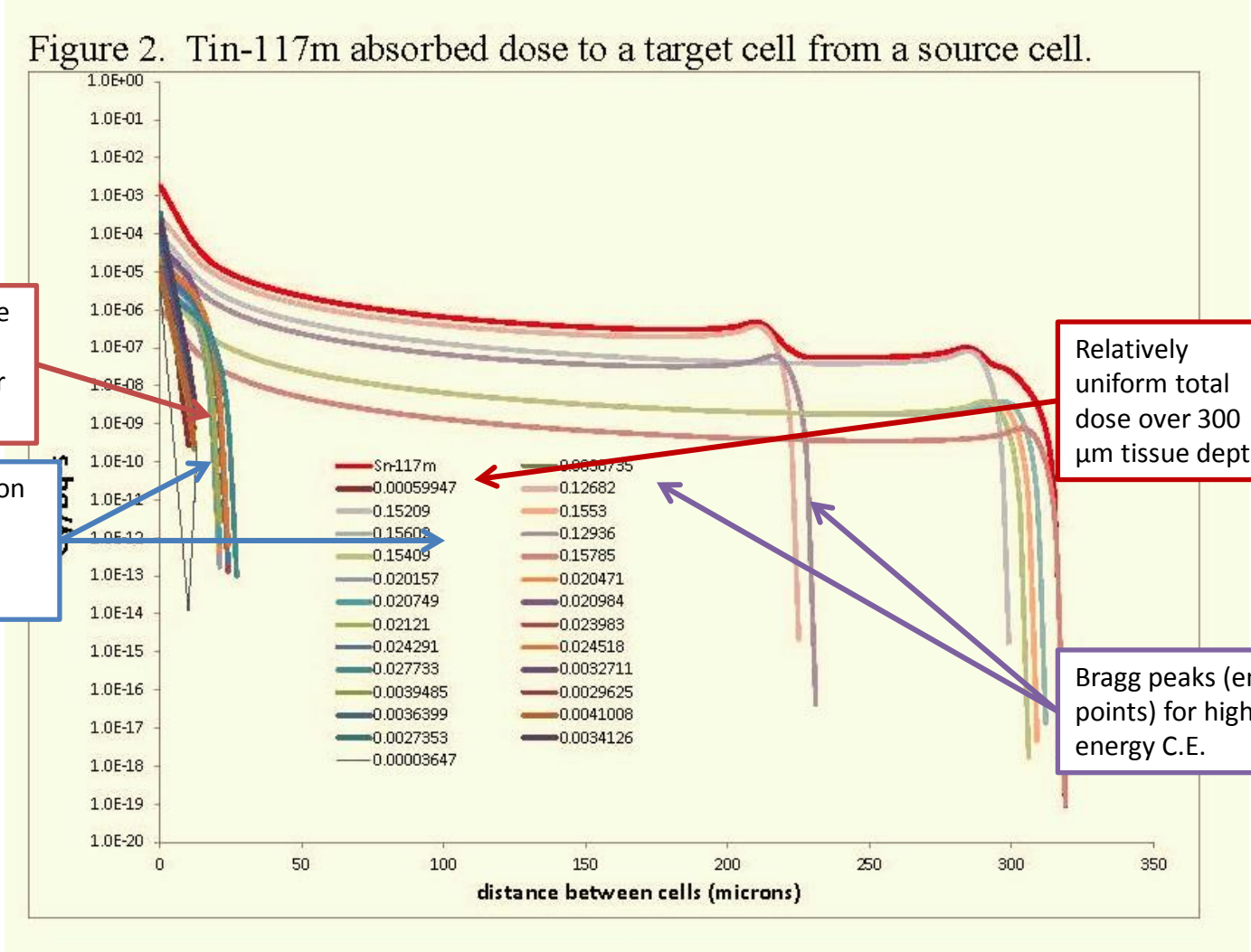
Penetrates up to a set distance



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

[1]XOFIGO; [2]METASTRON & QUADRAMET

Well-Defined Range of Sn-117m in Tissue



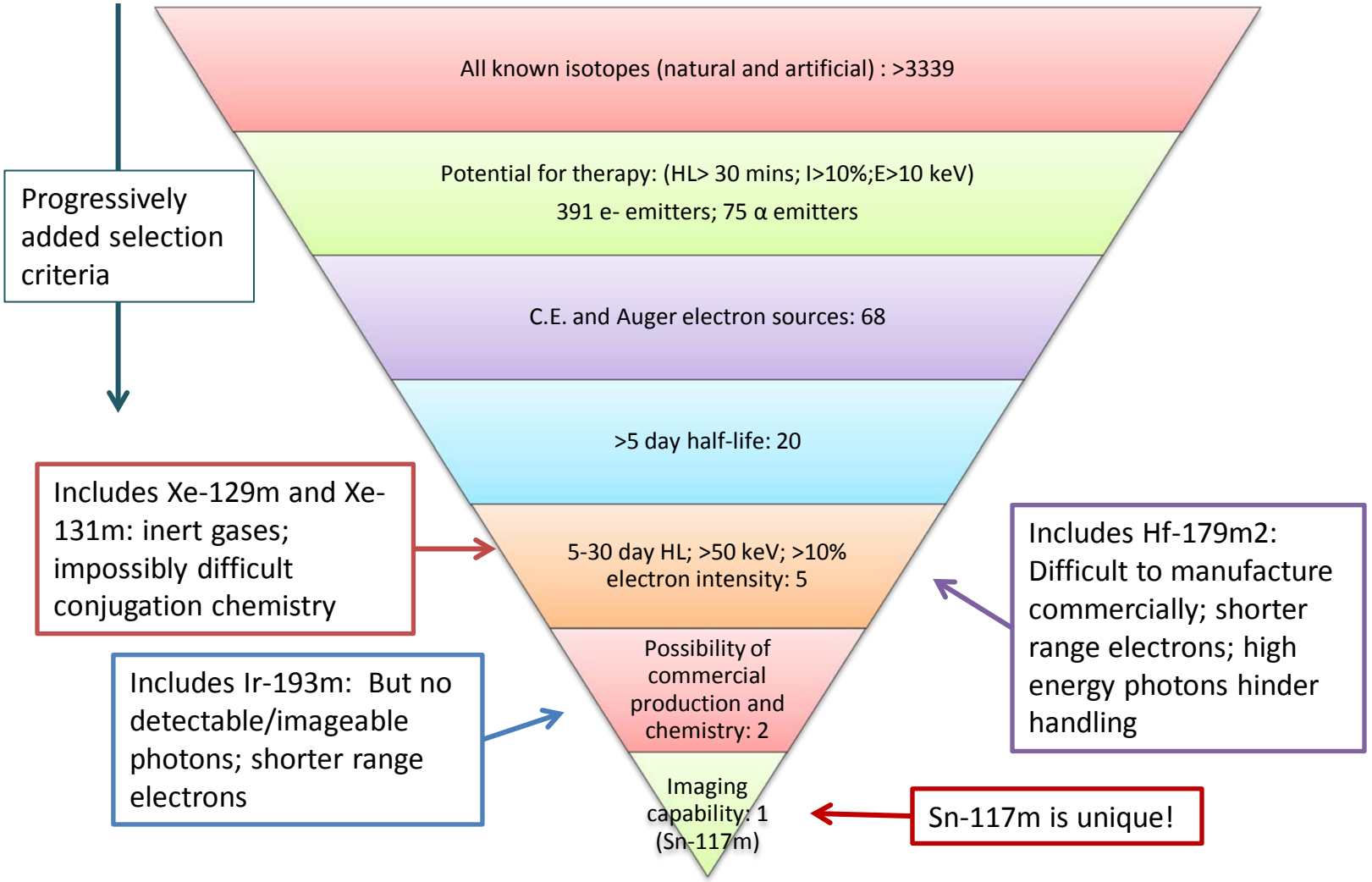
Short-range dose boost from Auger electrons

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 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

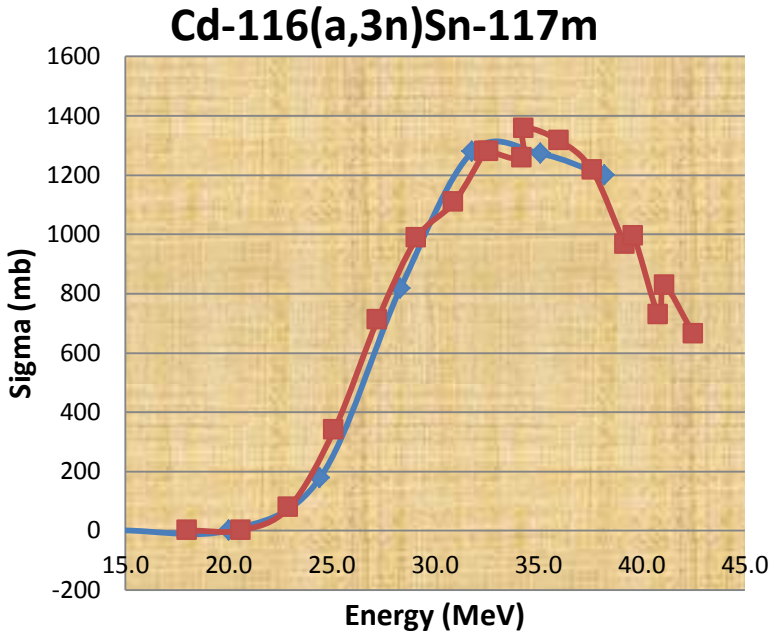
- Proven method developed in Russia under IPP; transferred to USA
- IP controlled by Serene, LLC
- Can be produced free of Sn-113 at <55 MeV
- High power 30 and 42 MeV cyclotrons can use standard electroplated targets and Sb-121
- High power targetry developed to capitalize on maximum available beam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

Accelerator production of Sn-117m

IRRADIATION AT UNIVERSITY OF WASHINGTON MC50 CYCLOTRON

Cd-116(α,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 µCi/µAh

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 at hormetic dose level
- **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

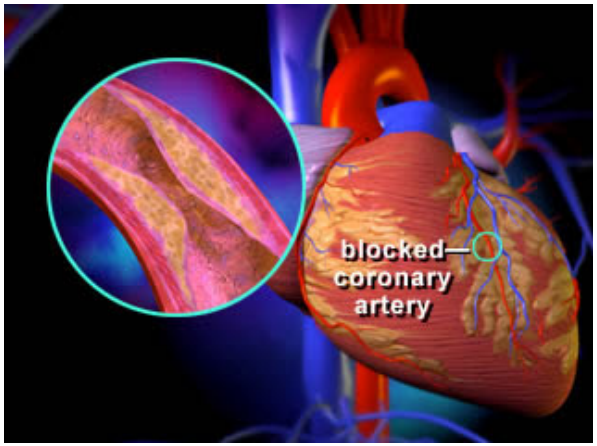
❖**Vulnerable plaque forms outside of the lumen in coronary/carotid artery walls - inflammation is the main driver**

❖**VP is usually covered by a thin cap on the lumen side [thus also called thin cap fibroatheroma (TCFA)]**

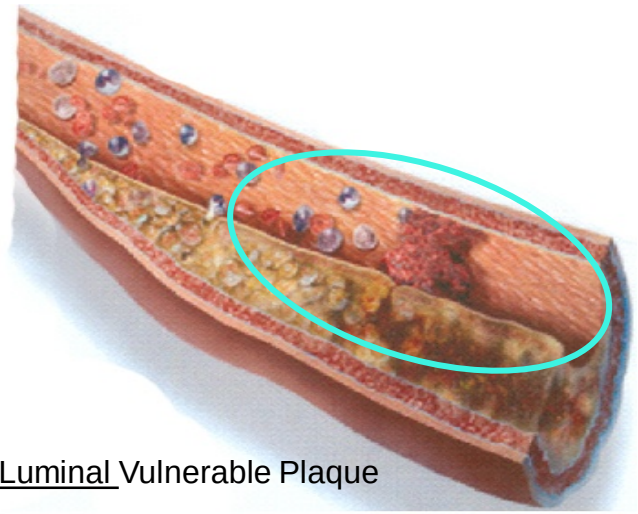
❖**Majority of all significant cardiac events (60-70%) leading to MI and sudden cardiac death are a result of VP, not calcified lumen atherosclerosis**

❖**Treatment of inoperable symptomatic high grade carotid stenosis**

❖**Ruptured thin cap "releases" highly thrombogenic material activating clotting cascade and inducing thrombosis**



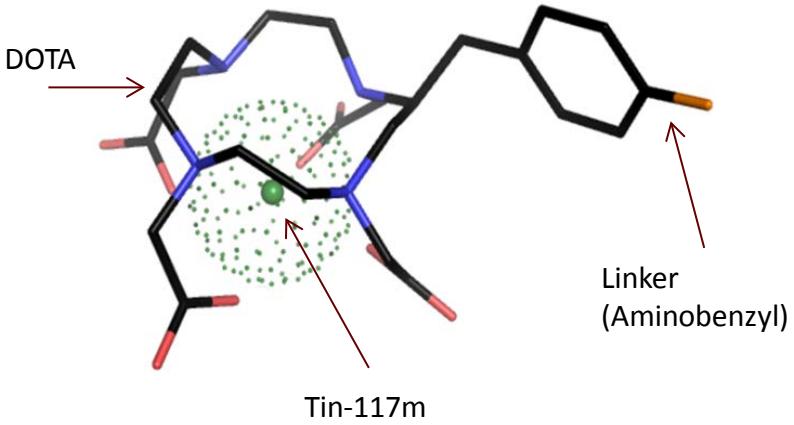
Luminal Calcified Plaque

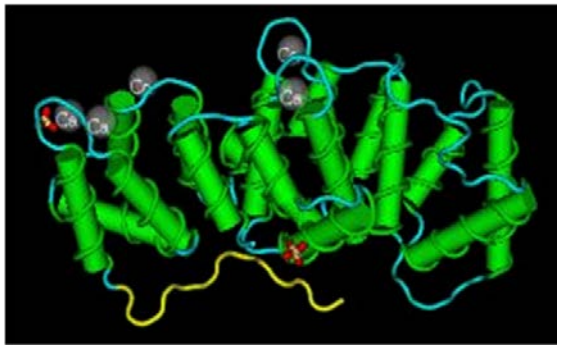


Extra-Luminal Vulnerable Plaque

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





Annexin

Tin-117m

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

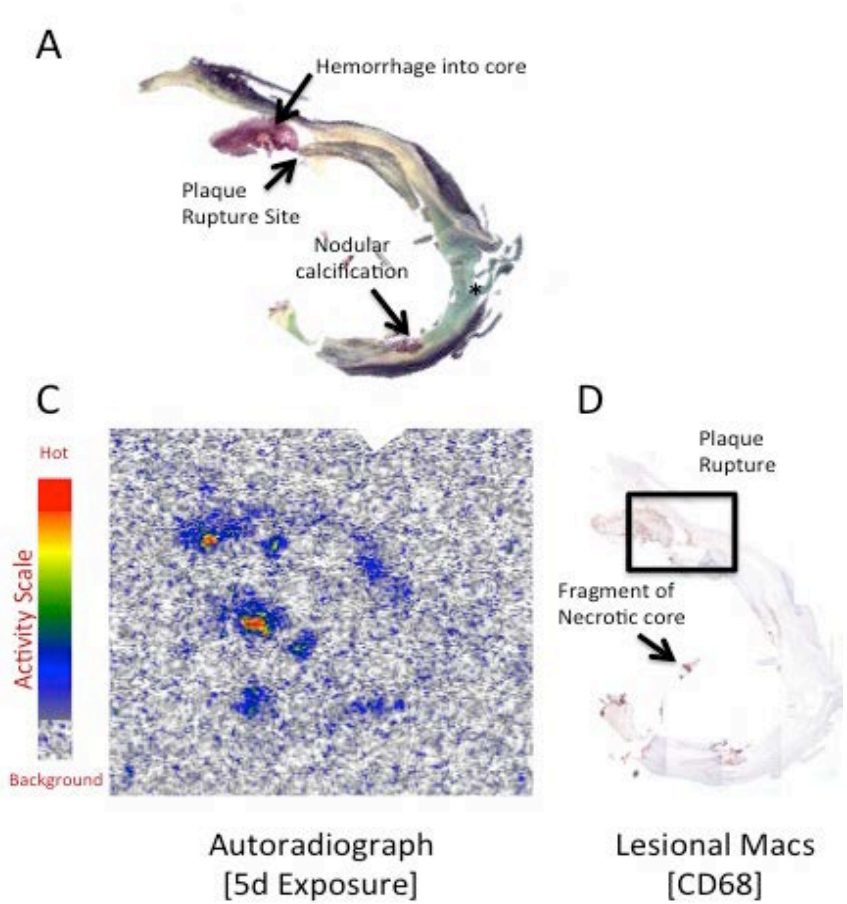
Aminobenzyl DOTA

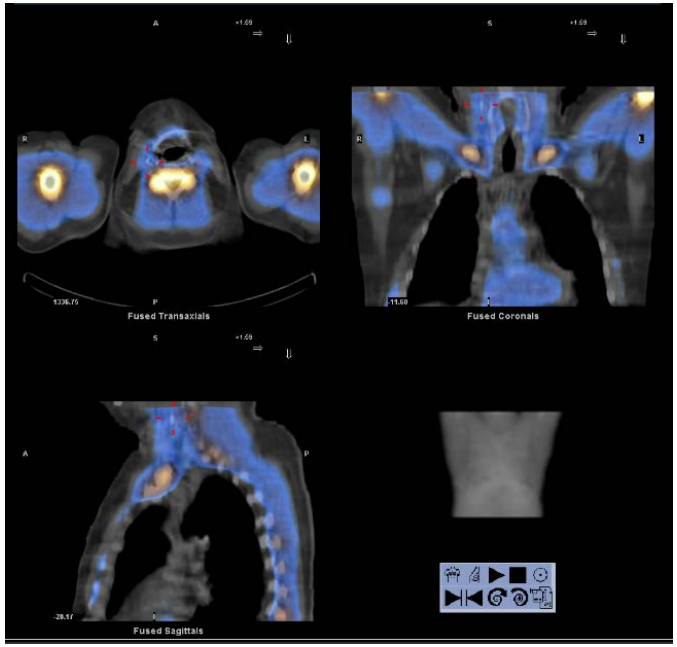
- Securely holds the Tin-117m

Annexin V

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

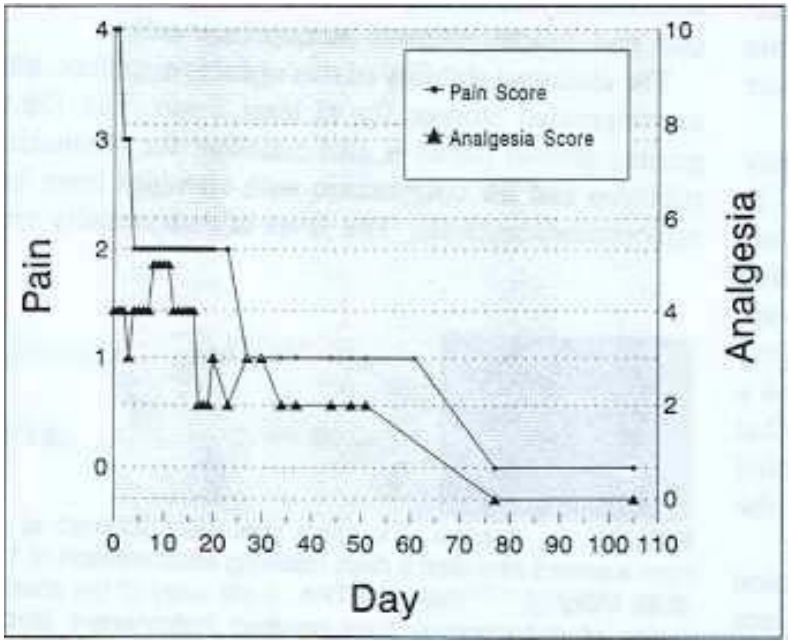
Imaging, Autoradiograph and Histology





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 µCi) per kg
- Relief of pain of 75% (60-83%)
- Minimal myelotoxicity



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

Cholangiocarcinoma Stent

Stainless steel laser cut electroplated stents

Treat Symptoms

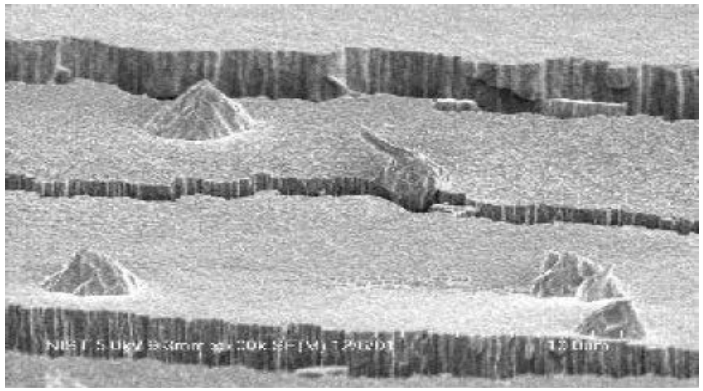
- stent expands to open the occluded duct – palliation of symptoms

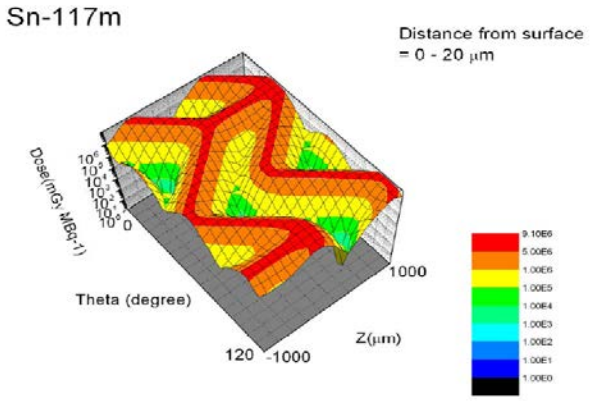
Treat Cancer

- 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

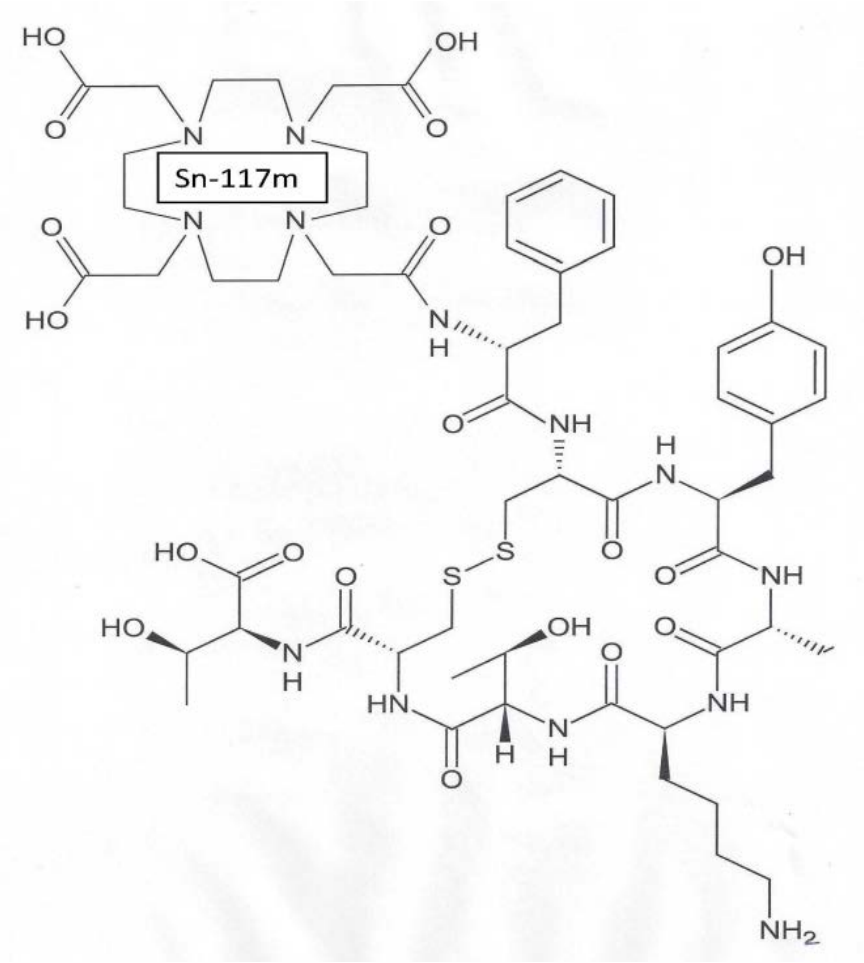




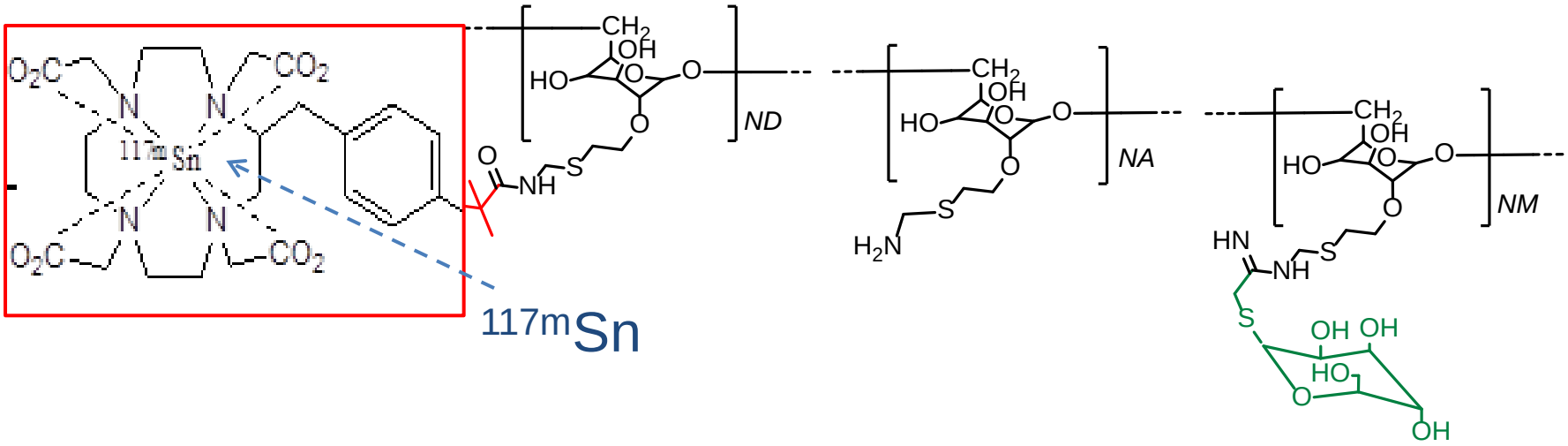
Labeled Molecules for Oncology

[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)

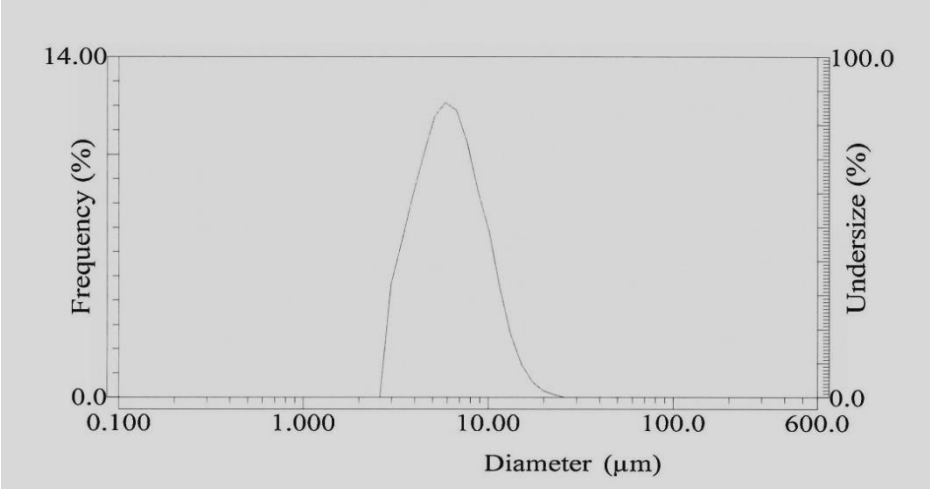
Radiosynoviorthesis Isotopes

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

Colloid joint retention and stability studies

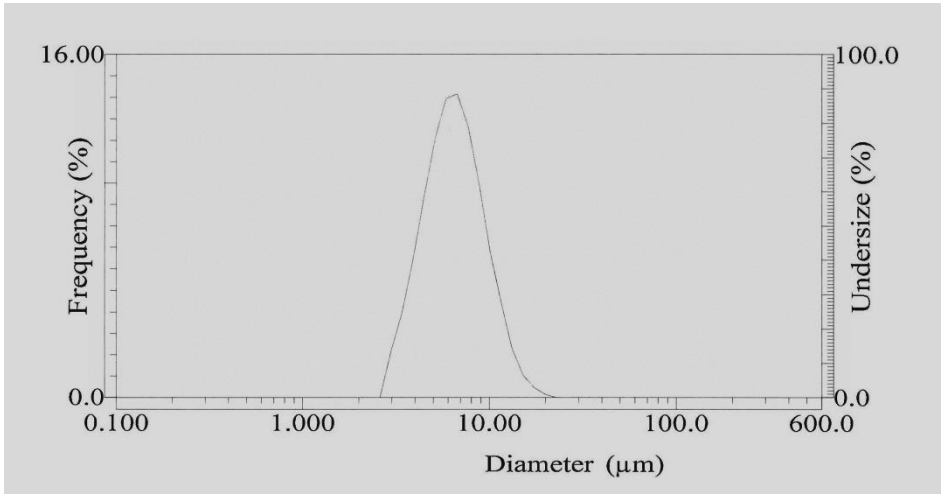
Retention of colloid in normal rat joint:

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



Stability studies – colloid size particle distribution at manufacture

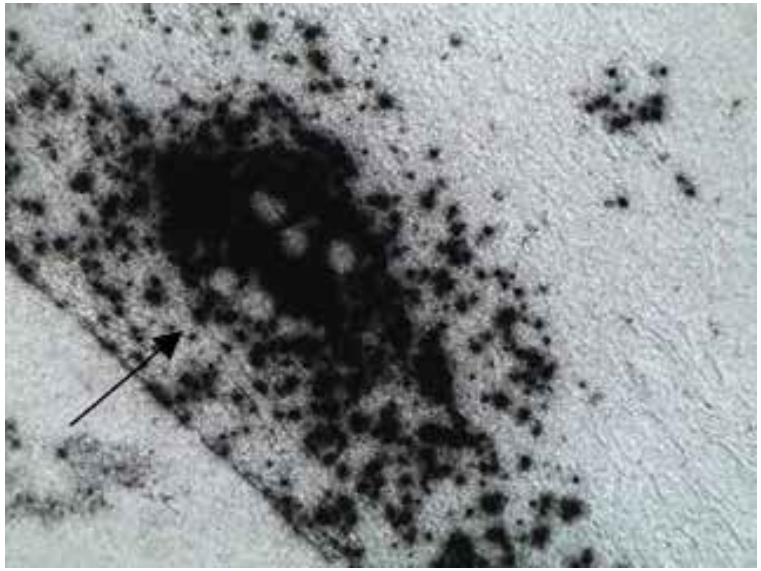
Mean =6.28 µm SD=2.76 µm



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

Mean =6.43 µm SD=2.47 µm

RSO - Tissue Autoradiography

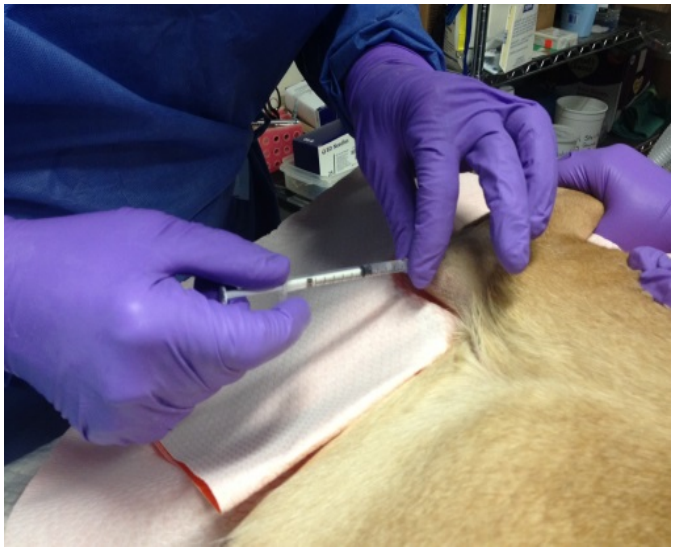


Phagocytosed colloidal particles (unaltered) migrate deeper in tissues to areas of sub-synovial inflammation

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

Arthritis Projects

- Serene, LLC (**HRA, Inc.)**
  - Canadian Human Phase 1/2 trials
  - 2019
- **Convetra, Inc.**
  - Veterinary applications
  - Canine OA
  - Other animals (e.g., horses)
  - Clinical studies complete
  - Launching start of 2019



RSO Procedure

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

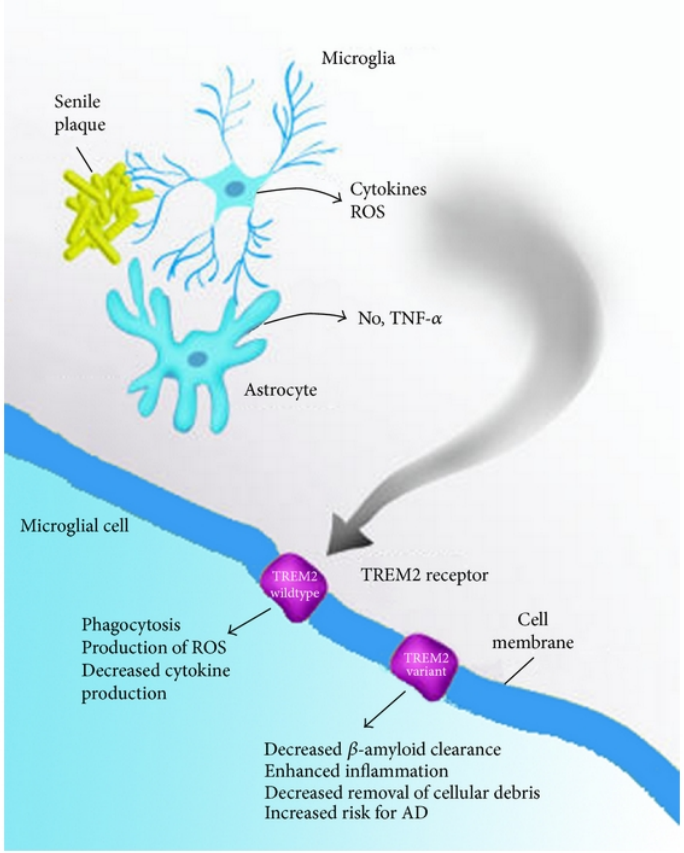


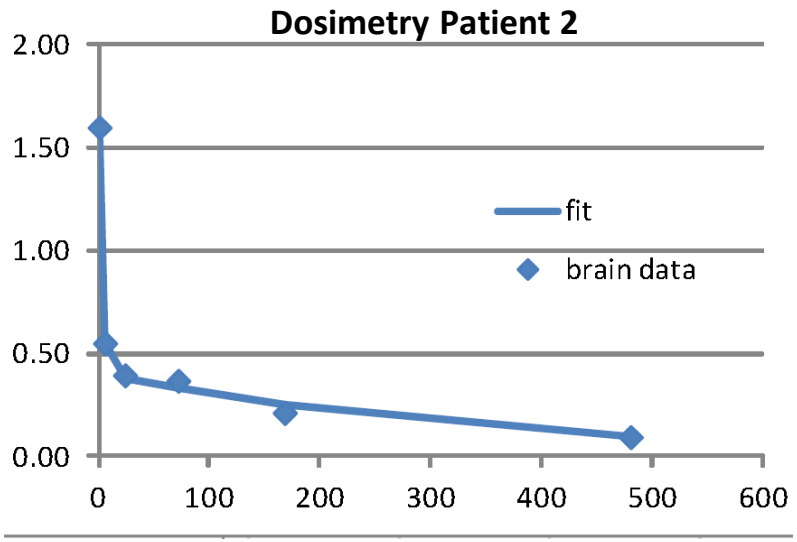
Figure: A central role for MG in AD is dependent upon a functional TREM2 receptor. The important actions of MG appear to be mediated through activation of the TREM2 receptor whose few known roles include suppressing inflammation and stimulating phagocytosis. The loss of TREM2 function and altered immune 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



Neuroinflammatory Hypothesis: Microglia are in the pathway to Aβ formation

Examples of Potential Demand for Sn-117m

- Canine OA: US - 250 Ci/y by year 6+
- Human OA and RA: 2,000 Ci/y US, Canada, EU5
- Cardiovascular: US (carotid VP) - 360 Ci/y
- Oncology: Bone pain/therapy – 1,200 Ci/y (5% of market)
- Neurology: Alzheimers - >5,000 Ci/y (10% of US market)

Supply of Sn-117m - HSA

- High Specific Activity:
  - Proton Accelerators (30-55 MeV; ~500 µA) - many
  - Alpha Accelerators (30-60 MeV)
    - U. Washington MC50 (Seattle, USA) - 70 µA
    - KIRAMS MC50 (Seoul, Korea) - 70 µA
    - ARRONAX CYCLONE 70 (Nantes, France) - 70 µA+
    - AlphaSource (Los Angeles, USA) – 2 mA+

Supply of Sn-117m - LSA

Requires high flux reactors:

- RIAR (Russia)
- BR2 (Belgium)
- Petten (Netherlands)
- ORNL (USA)
- China?

- Other reactors if post-irradiation separator used:
  - e.g., HANARO (Korea)

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