

# Novel treatments for arthritis in humans and animals using the theranostic isotope Sn-117m: Colloids and labeled molecules

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# Rheumatologic Conditions

- ▶ Inflammatory Arthritides e.g., **Rheumatoid Arthritis (RA)**
- ▶ Mechanically induced e.g., **Osteoarthritis (OA)** – affects humans and animals
  
- ▶ **Treatments:**
  - Steroids, hyaluronic acid, collagen, DMARDs, surgery, stem cell...
  - Systemic or local (intraarticular) injection
  - Often inadequately addressed
  - **Radiosynoviorthesis** (a.k.a. radiosynovectomy)
  
- ▶ **Extent of problem:**
  - 1.6–3.2M adults live with RA in the US alone
  - 16.6M dogs in the US have some degree of OA in at least one joint

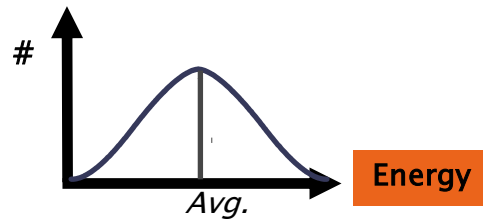
# Unique Characteristics of Tin-117m

Major Emissions	Energy (KeV)	Intensity (%)
Auger-L	3	91
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

- **Mono-energetic conversion electrons** of ~140 KeV discrete energy for therapy have an average range of ~300  $\mu\text{m}$  in tissue
  - 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 emission (159 KeV)** similar to Tc-99m (140 KeV) allowing for existing standard gamma camera imaging & techniques

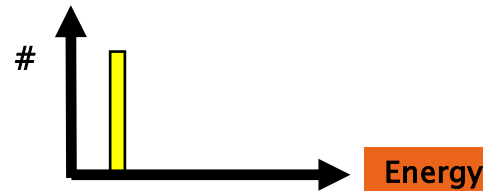
# Radiation Energy Types

## Beta

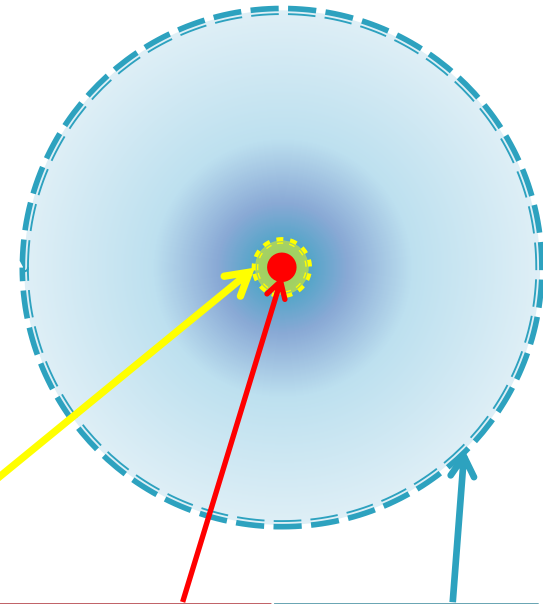


Produces a range of tissue penetration

## Conversion Electron



Penetrates to a set distance  
(discrete energy)

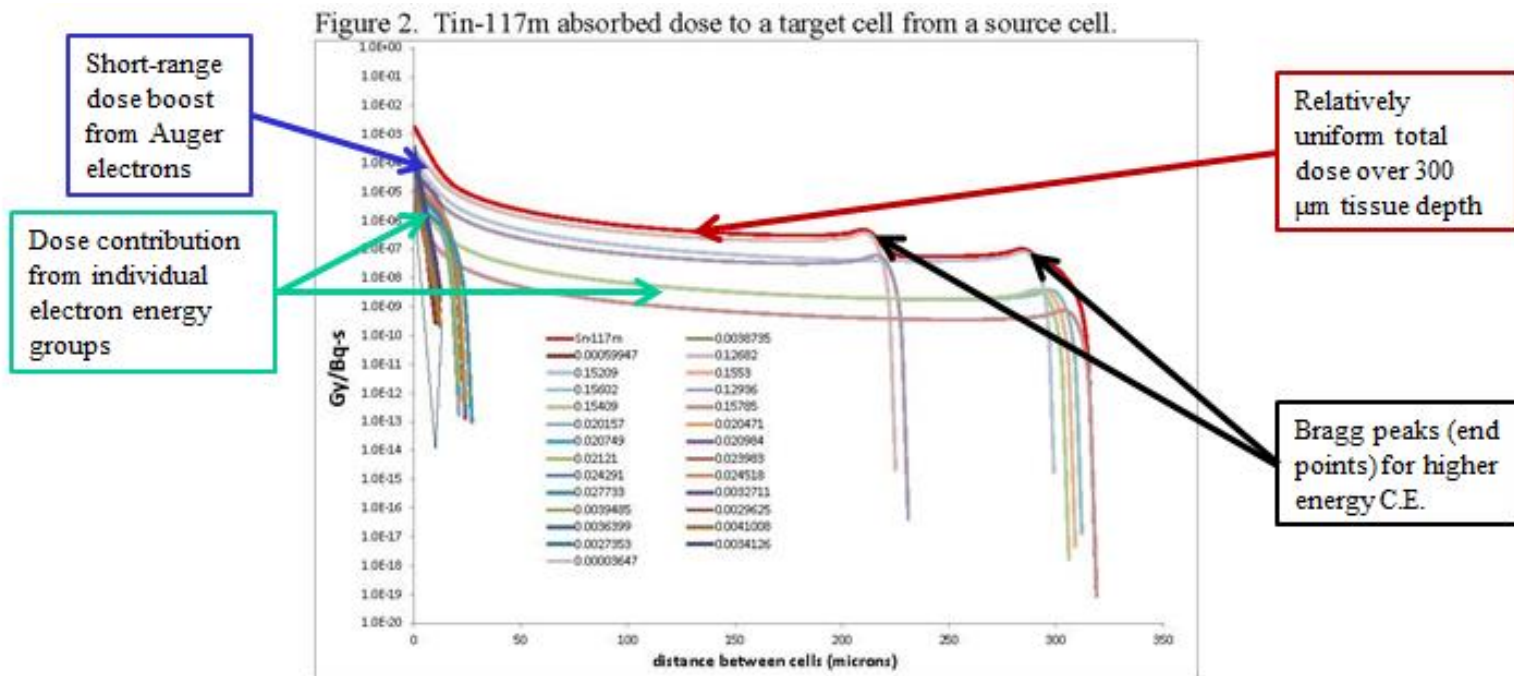


	Tin-117m	Alpha Particles <sup>1</sup>	Beta Particles <sup>2</sup>
Range in tissue (µm)	300	40-90	50-5000
Shielding needed during administration	No	No	Yes

<sup>1</sup>XOFIGO; <sup>2</sup>METASTRON & QUADRAMET

# Radiobiology

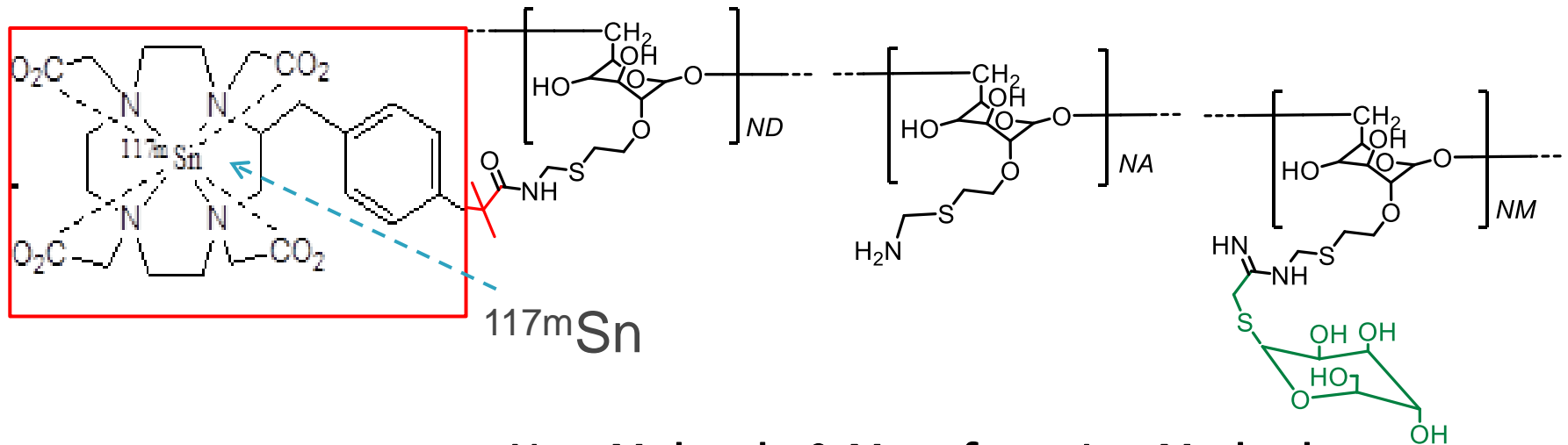
- Confirmation by KOLs that there is a “hormesis-like” therapeutic effect (L. Feinendegen, BNL)
- Plans to investigate radiobiological pathways and mechanisms responsible
- Confirmation by G. Sgouros (JHU) of relatively uniform dose deposition and ~300  $\mu\text{m}$  range of C.E. in tissue



# Systemic Treatment of RA

- ▶ No Cure; medications:
  - Reduce Inflammation
  - Control pain
  - Halt/slow down joint damage
  - E.g., NSAIDS, steroids, DMARDs–methotrexate, biologic response modifiers
- ▶ Occupational therapy and assistive devices
- ▶ Surgery
  
- ▶ Lymphoseek® (Tc-99m) shown to target CD206 for imaging
- ▶ Prevalent in RA (not normal or OA) joints
- ▶ Produce a systemic map of RA in joints
  
- ▶ Produce a similar Sn-117m labeled molecule to treat RA symptoms
  - Same biodistribution

# Systemic RA Composition

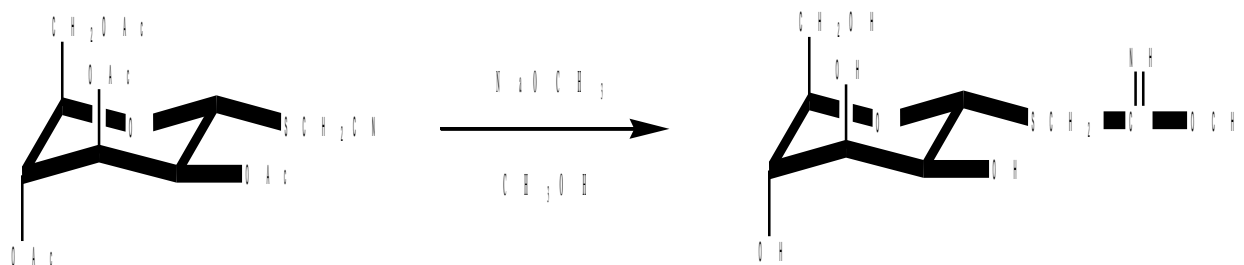


## New Molecule & Manufacturing Method

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

# Production of Sn-117m Labeled Molecule

## Step 1

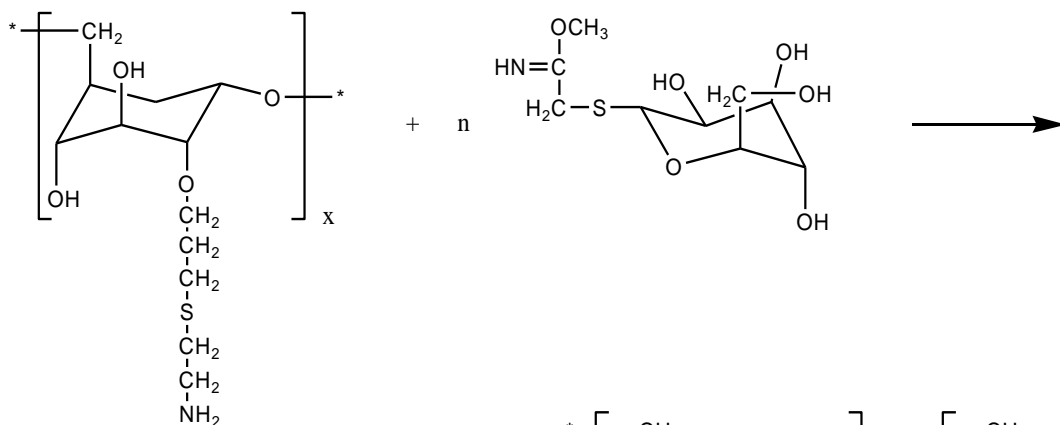


Deacetylation/Activate  
cyanomethylmannose to  
reactive methyl amidate:  
room temp, overnight



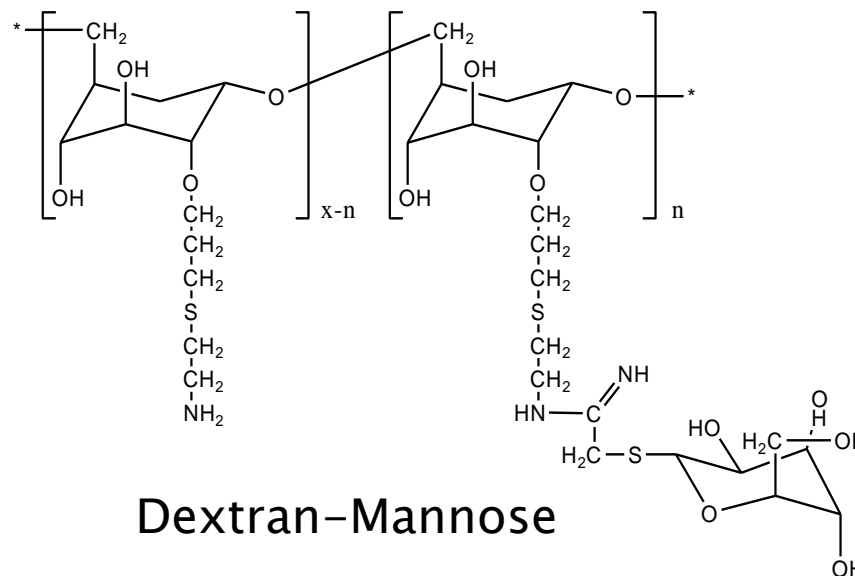
# Production of Sn-117m Labeled Molecule

## Step 2



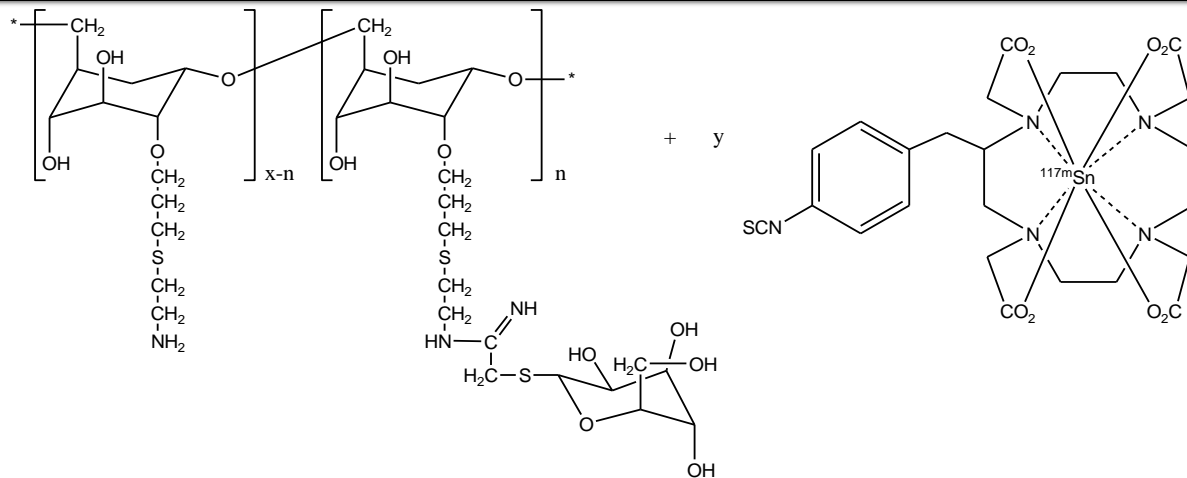
Attach mannose to dextran amine leaving some free amines, (room temp, sodium bicarbonate buffer, overnight)

Mannose occupancy ~ 48%

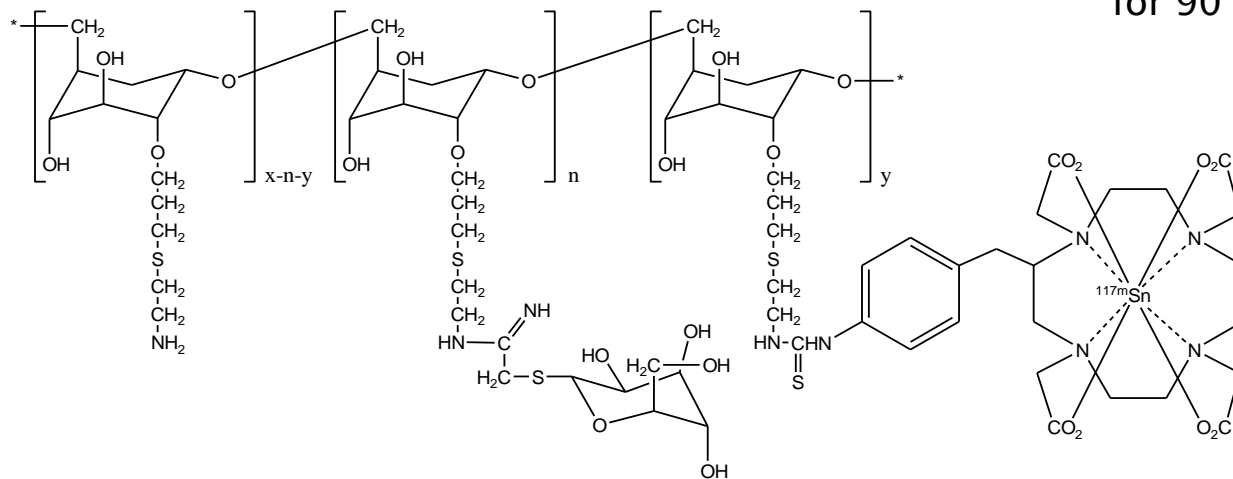


# Production of Sn-117m Labeled Molecule

## Step 3



Attach Sn-  
117m-DOTA to  
Polymer  
(pH = 9, 37C  
for 90 minutes)



# Biodistribution Studies

- ▶ Four groups (A–D) of 4 BALB/c male mice
- ▶ Sterile abscess (containing CD206) induced in R hind leg muscle (injected with 20  $\mu$ L of turpentine 24 hrs prior)
- ▶ Two groups (A,B) injected with (20  $\mu$ L;~20  $\mu$ Ci) Tc-99m Tilmanocept in tail vein
- ▶ Two groups (C,D) injected with (20  $\mu$ L;~20  $\mu$ Ci) new Sn-117m composition in tail vein
- ▶ Groups A and C sacrificed at 2 hr – biodistribution performed
- ▶ Groups B and D sacrificed at 24 hr – biodistribution performed

- ▶ Results:
  - Liver uptake higher for Sn-117m
  - Ratio of abscess/tissue similar:

	Tc-99m	Sn-117m
2 hrs	3.5	5.5
24 hrs	4.4	4.5

# Radiosynoviorthesis Isotopes

## Radiosynoviorthesis Isotopes

Isotope	t <sub>1/2</sub> (d)	Imaging Particle	Energy (keV)	Intensity (%)	Image Quality†	Therapy Particle	Mean Maximum		Intensity (%)	Range (mean)		Range (max)		Typical*** Particle Size (µm)	Typical Dose (mCi)	Joint Size	Colloidal Compound(s)	Comments
							Energy (keV)	Energy (keV)		Tissue* (mm)	Tissue* (mm)	Bone** (mm)	Air* (m)					
<b>Sn-117m</b>	14	γ	158.6	86	Good	C.E.	140	151	~112	0.27	0.29	0.17	0.3	6-20	1.5-1.0 (est)	Small	hydroxide	new isotope colloid
<b>Er-169</b>	9.3	None	-	-	None	β <sup>-</sup>	100	350	100	0.14	1.1	0.64	0.9	2-5	1	Small	citrate	Standard isotopes used throughout most of the world
<b>Re-186</b>	3.7	γ	137	9	Poor	β <sup>-</sup>	347	1070	93	1.1	4.4	2.8	4.4	1-4	2.5	Medium	sulfide	
<b>Y-90</b>	2.7	None	-	-	None	β <sup>-</sup>	934	2280	100	4.1	11	6.6	10.3	10-20	4	Large	silicate, citrate	
<b>P-32</b>	14.3	None	-	-	None	β <sup>-</sup>	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
<b>Au-198</b>	2.7	γ	412	29	Moderate	β <sup>-</sup>	312	960	100	0.9	4.2	2.5	3.9	20-70	7	Large/Med	elemental	Discontinued
<b>Sm-153</b>	1.9	γ	103	29	Moderate	β <sup>-</sup>	224	808	100	0.55	3.3	2	3.1	1-10	5	Medium	hydroxyapatite	R&D
<b>Re-188</b>	0.7	γ	155	16	Moderate	β <sup>-</sup>	763	2120	100	3.1	10.4	6.2	9.7	1-4	10	Large	sulfide	R&D
<b>Ho-166</b>	1.1	γ	81	6	Poor	β <sup>-</sup>	665	1855	100	2.6	9.2	5.2	8.3	5-10	10	Large	ferric hydroxide, chloride	R&D
<b>Dy-165</b>	0.1	γ	95	4	Poor	β <sup>-</sup>	440	1289	100	1.3	5.9	3.5	5.4	3-5	270	Large	ferric hydroxide	R&D
<b>Tm-170</b>	129	γ	84	3	Poor	β <sup>-</sup>	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

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

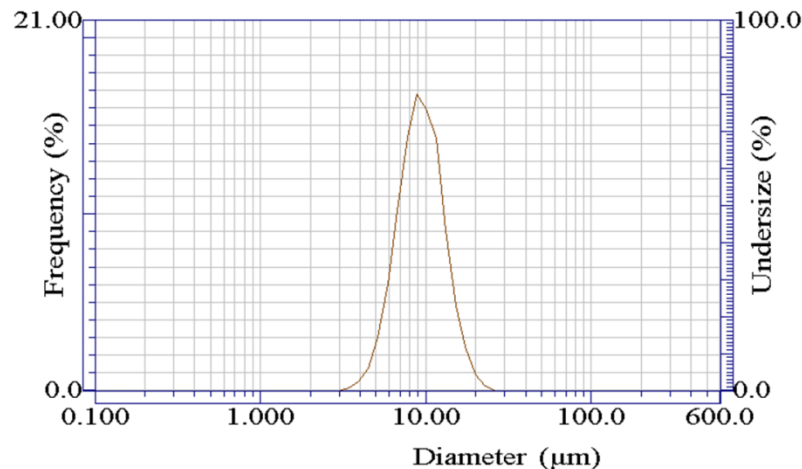
# Colloidal Sn-117m for intra-articular injection

- ▶ Homogeneous Precipitation of  $^{117m}\text{Sn}(\text{IV})$ 
  - Used sterile, pyrogen-free microwave vial equipped with a stir bar
  - Combined Sn-117m, with carrier Sn and urea
  - Heated at 90 °C for 4 hours
  - Continue to heat at 130 °C for 35 minutes to sterilize
  - Test for sterility, pyrogens and particle size
  - Package and ship
- ▶ Slow increase of pH globally in solution to prepare homogeneous  $^{117m}\text{Sn}$  hydrous oxide

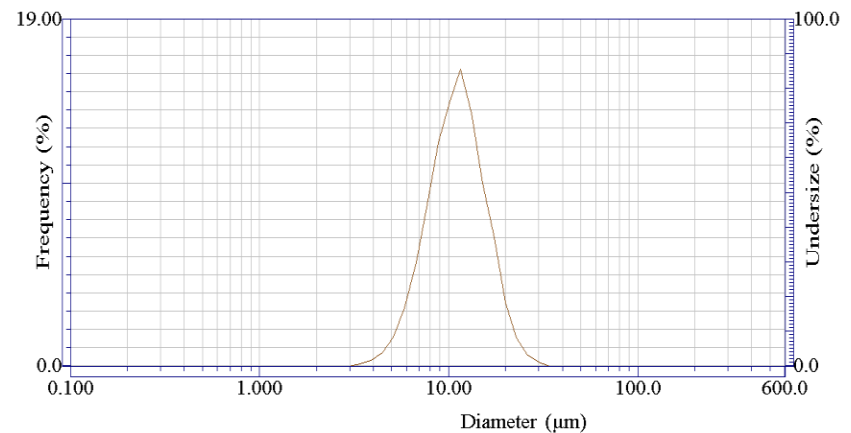
# Colloid Studies

## Retention of Sn-117m colloid in normal rat joint

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

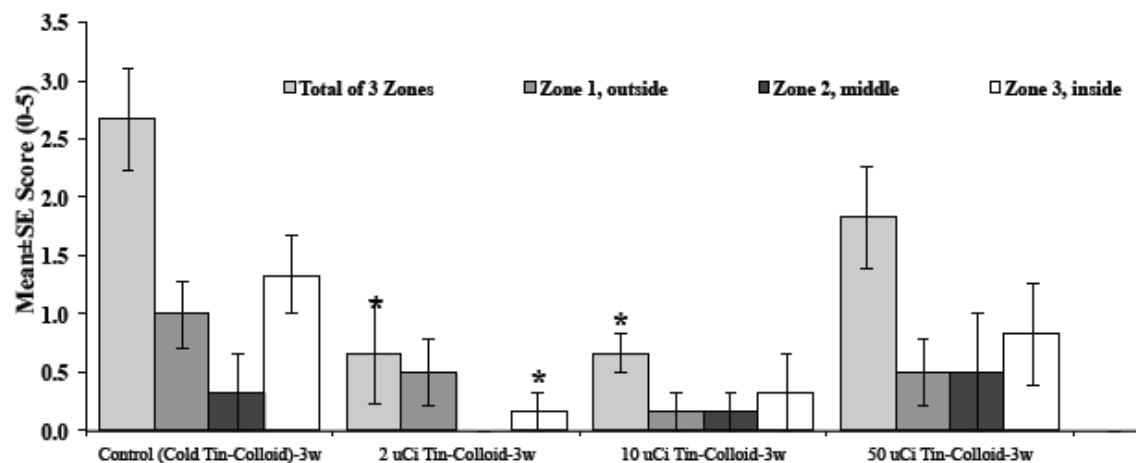


Sn-117m Colloidal Aggregate Particle Size at time of manufacturing



Stability studies - colloid size distribution after 5 weeks at room temp

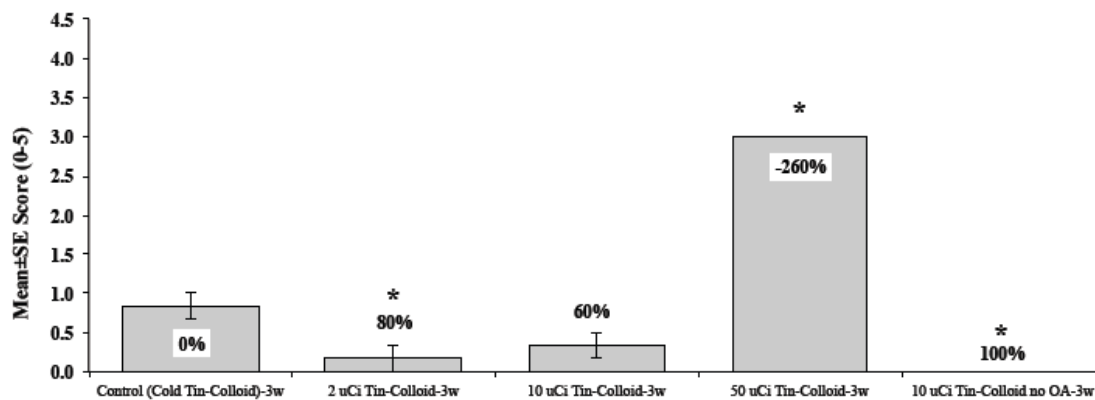
# Non-GLP Rat Osteoarthritis Study Results



**Figure 18. Total Joint Score (3 wk)**

*n*=2-3/group

\**p*≤0.050 Student's *t*-test to Control



**Figure 19. Synovitis Score (3 wk)**

*n*=2-3/group

\**p*≤0.050 Student's *t*-test to Control

# Safety Study

## MU Study Dog Summary

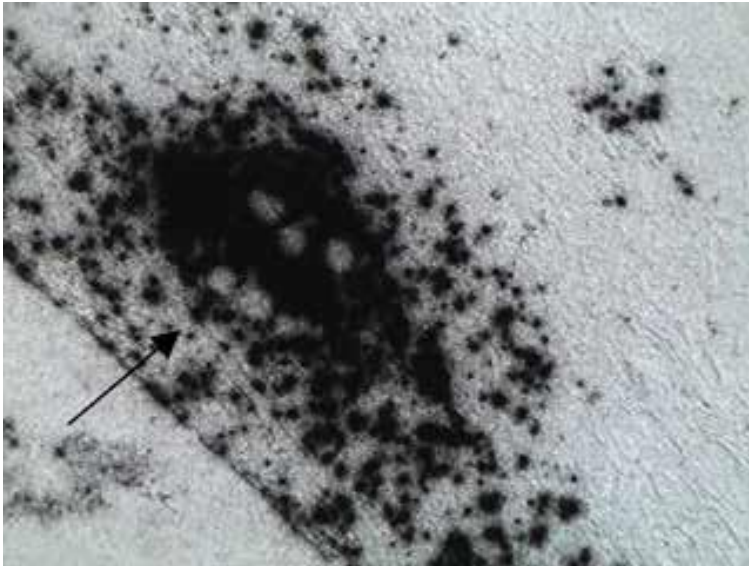
- **Study dogs (n=5)**
  - University of Missouri College of Veterinary Medicine
    - Jimmy Lattimer DVM and Kimberly Selting DVM
  - Followed to 3  $t_{1/2}$  safety with 2.5mCi
  - Data collected includes:
    - Histopathology (pending), PET/MRI, x-ray, excretion, distribution, autoradiography, dosimetry, synovial fluid analyses, physical examinations, radiation field

D15-57	3-Apr	6-Apr	7-Apr	8-Apr
Background	1353	1260	1238	1274
Blood	1294	1236	1240	1274
Background	1353	1260	1238	1274
Urine	1867		1849	1446
Background	1353	1260	1238	1274
Feces	1259	1205	1162	1252

Distance	8-Apr-15
1 Meter	155 $\mu$ R/hr
Surface (2 in/5cm)	15.3 mR/hr



# Autoradiography



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

Potential to treat larger joints

# Client Owned Dogs With Naturally Occurring Elbow OA–Summary

- **Client-owned elbow disease companion dogs (n=48), May 2015**
  - University of Missouri College of Veterinary Medicine and possible 2<sup>nd</sup> site
  - Randomized to 3 doses, option for a repeat dose
  - Long term safety in dog
  - Efficacy (follow-up to 12 months at 3 month intervals)
  - Data collected includes:
    - PET/MRI/x-ray
    - Blood chemistries
    - Lameness Locator Assessment
    - Joint fluid evaluation
    - Clinical evaluation for effusion, etc.
- **Results so far (at 1 month) are very promising**

# Rationale for Sn-117m Colloid Use in Human Rheumatoid Arthritis

- 1.6–3.2M adults with RA in the United States alone
- RA drugs account for 25% of all specialty drug costs in the US at \$20B
- Annual cost of biologics is \$20–30k/year
- Biologics fail in 20–30% of patients
- In first year up to 30% discontinue use, by 2<sup>nd</sup> year up to 50%
- Even patients ‘successfully treated’ with biologics have an average of 3–4 unresponsive painful/swollen joints

# Conclusions

- Extensive prior human clinical data with systemic Sn-117m demonstrating safety and efficacy
- Extensive prior and ongoing animal data showing safety and efficacy of Sn-117m
- [Sn-117m]-DOTA-mannosyl-dextran composition shows favorable biodistribution and promise to treat RA systemically
- Sn-117m homogeneous colloid developed at cGMP level
- Canine OA trials ongoing
- Potential to replace existing approved RSO isotopes in human RA (and OA)
- May be useful for larger RSO joint treatment