Tin-117m: A New Isotope and Approach to Radiosynoviorthesis and Other Therapies

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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

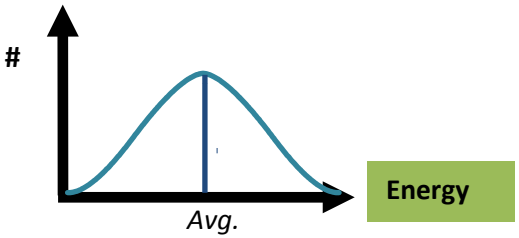
*CE = Conversion Electron

No High Energy Emissions

- **Mono-energetic conversion electrons of ~140 KeV discrete energy for therapy have an average range of ~300 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**

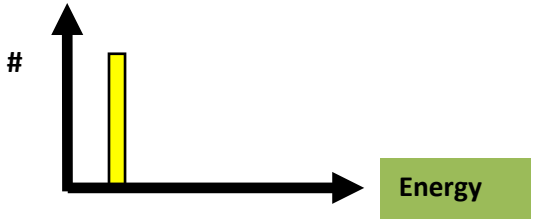
Comparing Energy Types for Radiopharmaceuticals

Beta

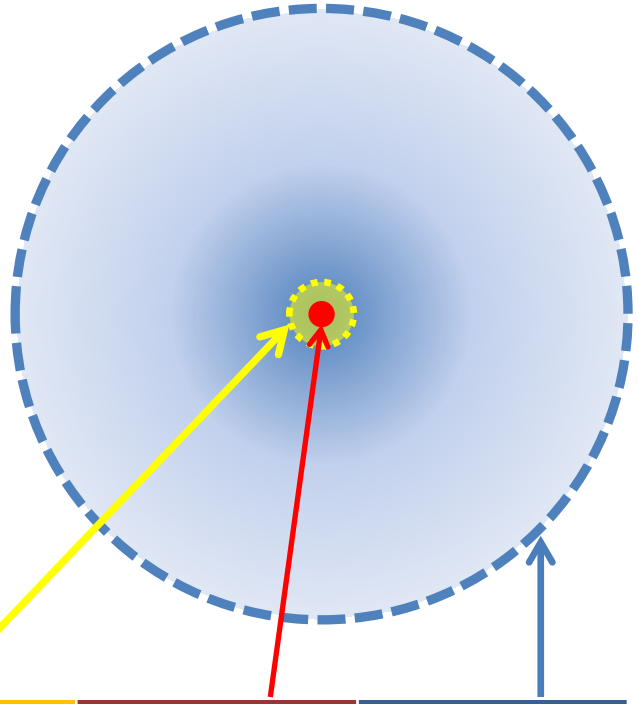


Produces a range of tissue penetration

Conversion Electron



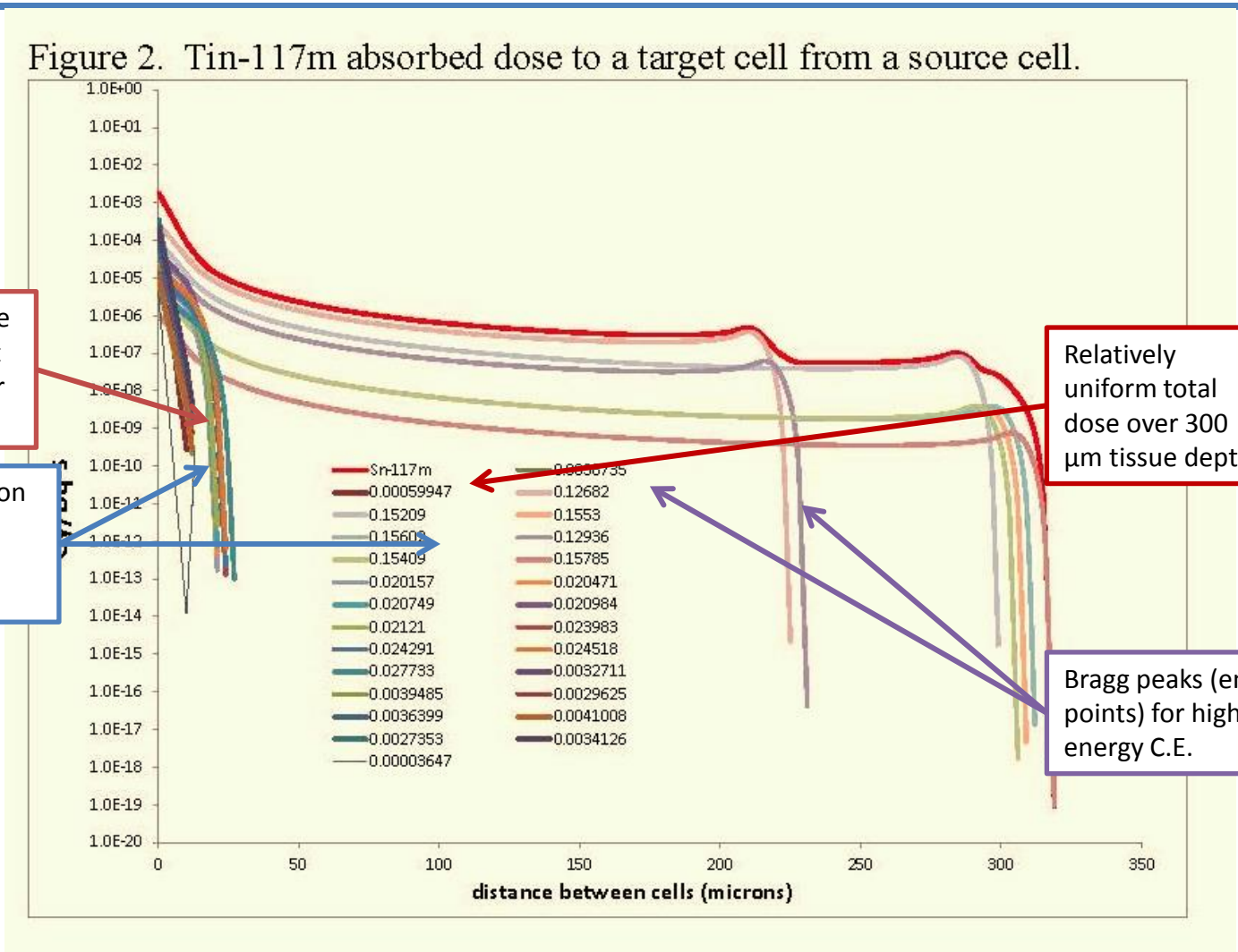
Penetrates up to a set distance



	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



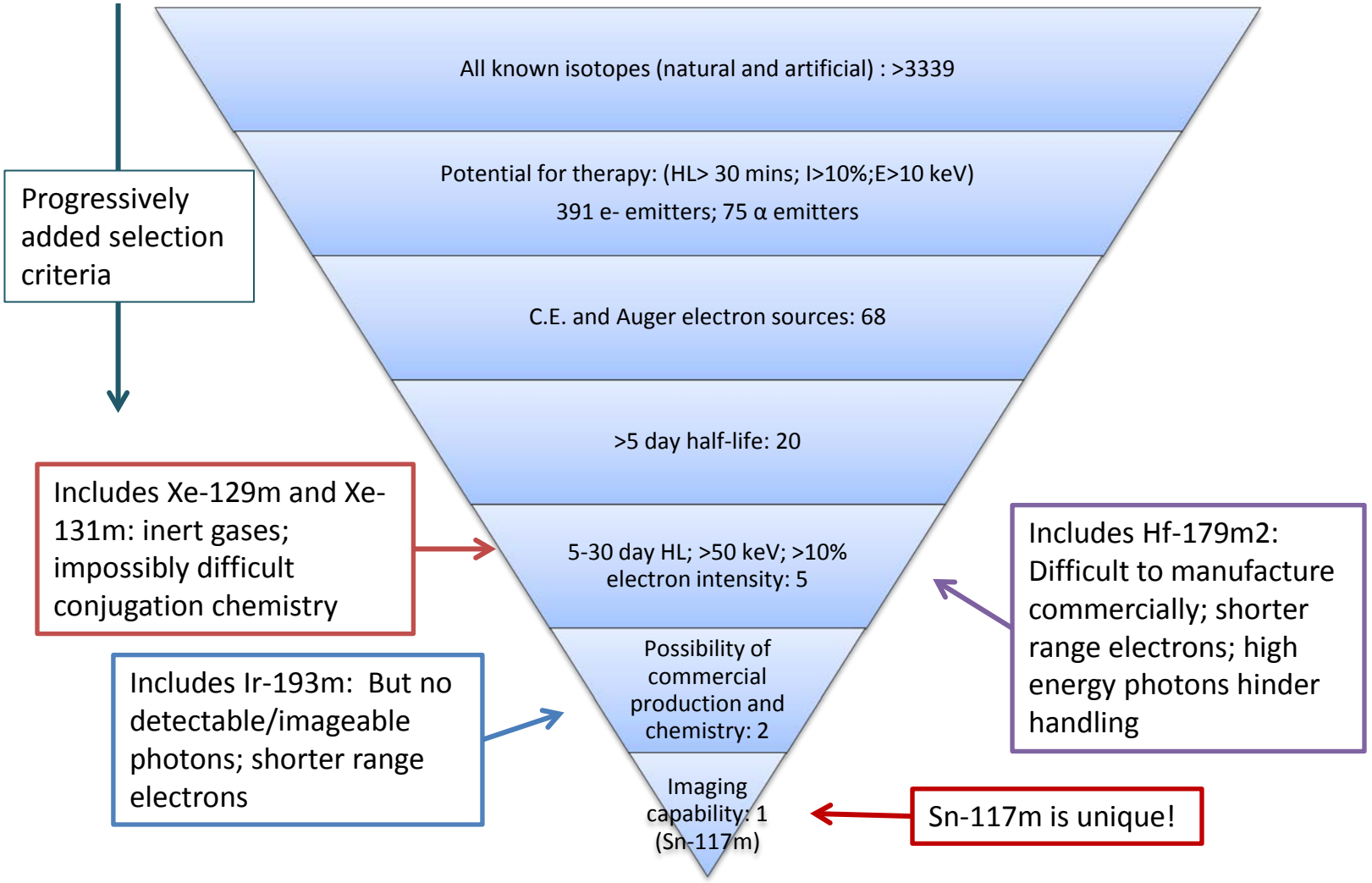
Short-range dose boost from Auger electrons

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



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

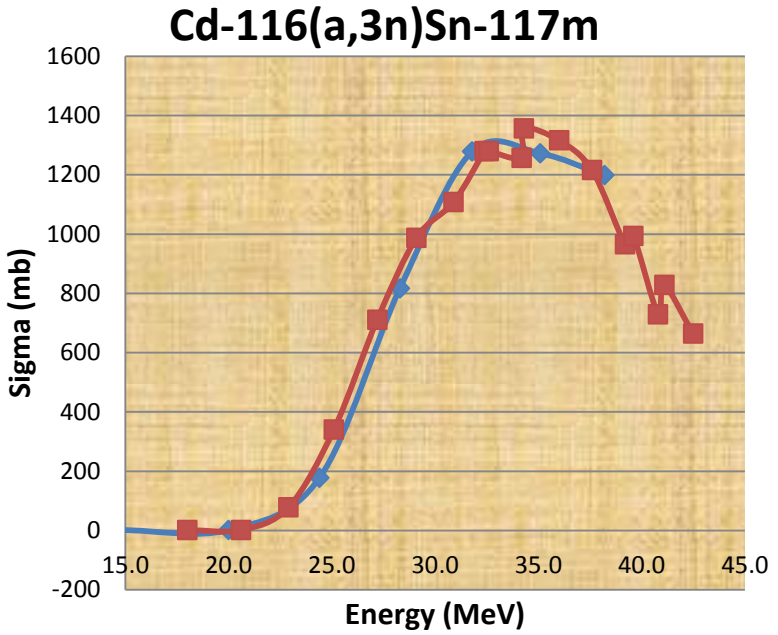
- Proven method developed in Russia under IPP; transferred to USA
- IP controlled by Serene, LLC
- Can be produced free of Sn-113 at <55 MeV
- High power 30 and 42 MeV cyclotrons can use standard electroplated targets and Sb-121
- High power targetry developed to capitalize on maximum available beam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

Tin-117m: Past Work & Development

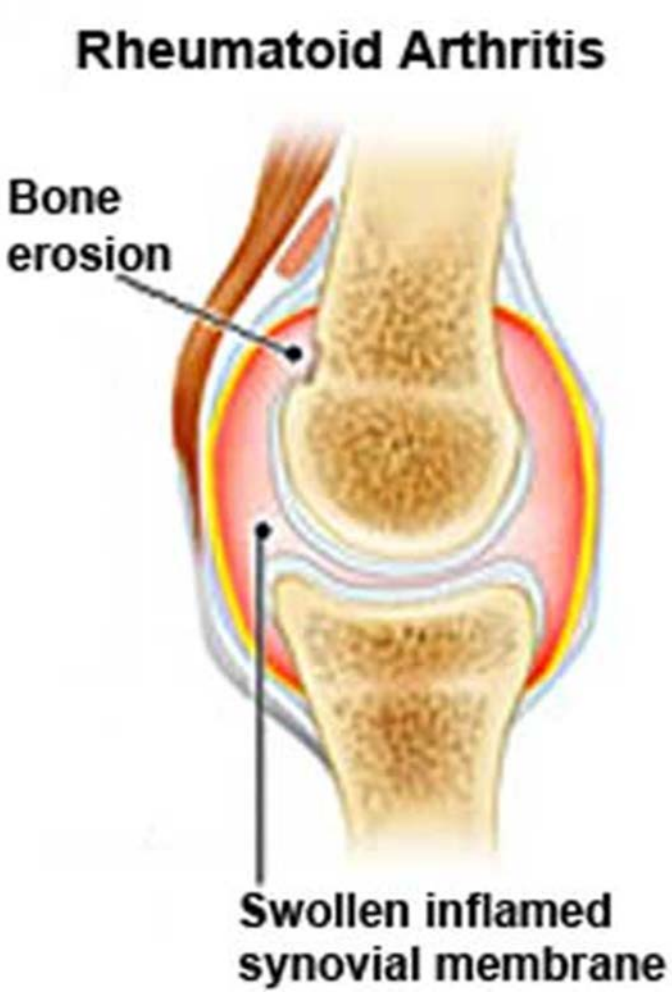
- Suresh Srivastava, BNL, performed Bone **Pain Palliation** ([Sn-117m]-DTPA) studies and trials
  - >120 subjects successfully treated
- **Cardiovascular** – Vulnerable/Unstable Plaque ([Sn-117m]-DOTA-Annexin)
  - Imaged in human clinical trials
  - Therapy in animals confirmed
- **Rheumatoid Arthritis** (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

Radiosynoviorthesis (RSO)

- A.k.a. Radiosynovectomy
- Treatment for arthritis
- Used worldwide for over 60 years
- Radioactive colloid injected directly into the synovial cavity
  - Intracavitary radiotherapy to reduce pain, effusion, perfusion and inflammation (synovitis)
- Commercial isotopes are Y-90, Re-186, Er-169, P-32
  - Y-90 for large joints (knee)
  - Re-186 for mid-size joints (elbow, wrist, ankle)
  - Er-169 for small joints (fingers)
  - P-32 Hemophilic arthropathy

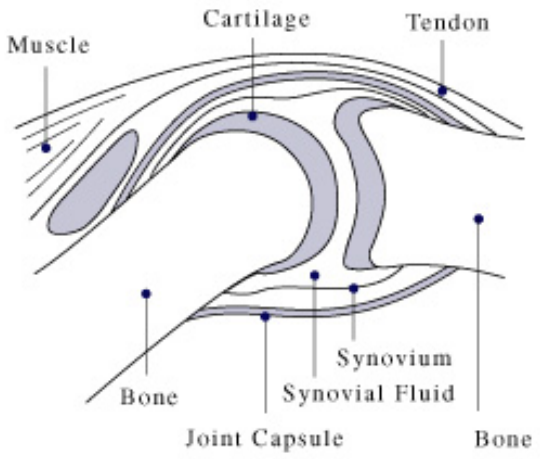
Rheumatoid Arthritis (RA)

- Rheumatoid arthritis is an autoimmune disease that causes chronic inflammation of the joints
- Systemic disease
- The body's tissues are mistakenly attacked by their own immune system
- Inflammation of the tissue around the joints and inflammatory arthritis
- Bone erosion, pain and tissue destruction
- Can also cause inflammation and injury in other organs in the body

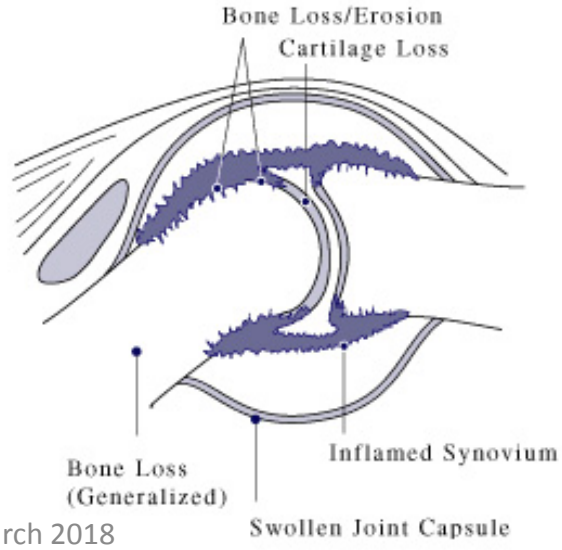


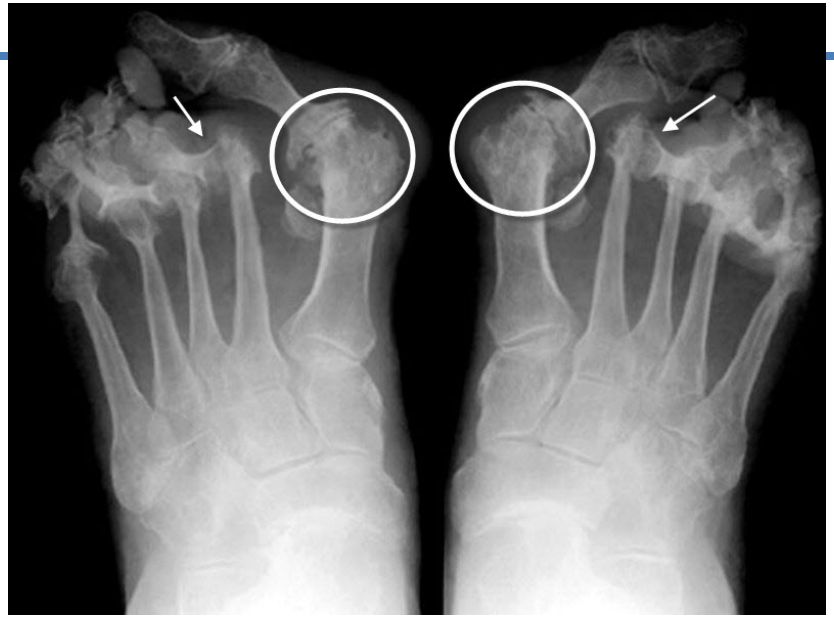
Rheumatoid Arthritis

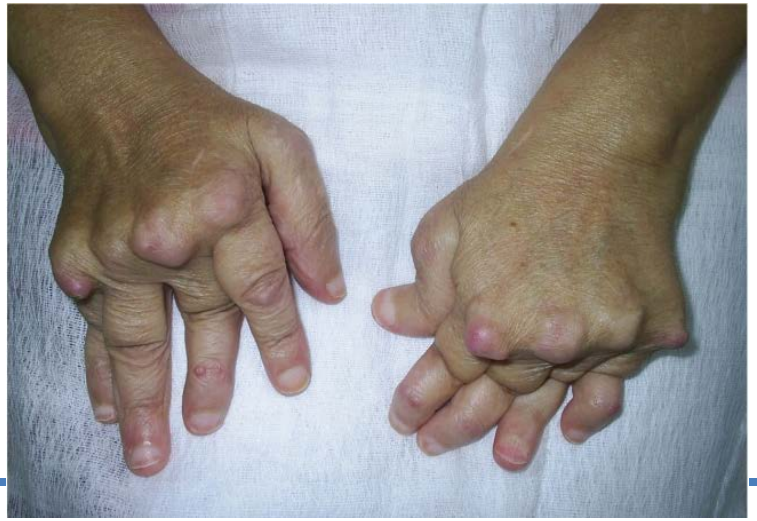
Normal Joint



Joint Affected by Rheumatoid Arthritis







Rheumatoid Arthritis

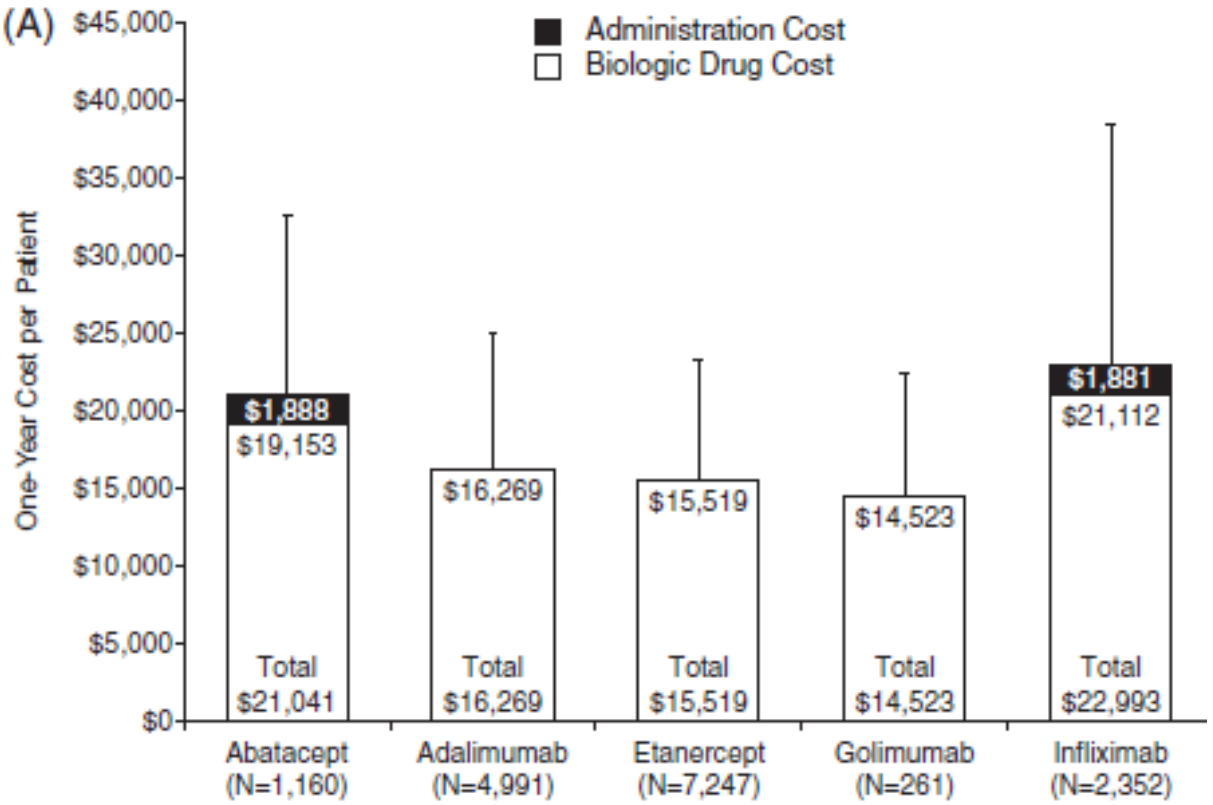
- Many RA patients have had "successful" treatment with biologics, but still have swollen painful joints
- Biologics are widely used to treat RA patients, but are incompletely effective in most patients
  - Biologics have been shown to reduce symptoms and Rx changes in up to 70-80% of patients (*i.e. failure in 20-30%)*[1]
  - Within 1 year of initial treatment up to *30% of RA patients discontinue treatment* (meaning they either stop or switch to something else), and within 2 years that increases to *50%*[2]
  - Patients who continue biologic treatment have an **average of 3-4 unresponsive, tender/swollen joints**[3]
- RA drugs account for ¼ of all specialty drug spend in the US[4], over $20B annually[5]
  - Annual spend on therapeutics that include biologics ranges from **$22,000-$25,000 per patient**[3]

1. Wu N, Clin Ther Aug 1;36,8,1231-41, Cost of biologics per treated patient across immune-mediated inflammatory diseases in a PBM; 2. Zhang et al, Arthritis Care Res, 2011 december;63(12):1672-9; 3. Wu N, Clin Ther Aug 1;36,8,1231-41, *Managed Care*, "Cost of biologics per treated patient across immune-mediated inflammatory diseases in a PBM"; [3] Zhang et al, Arthritis Care Res, 2011 december;63(12):1672-9; [4] American Health & Drug Benefits. Trends in Biologic Therapies for Rheumatoid Arthritis. March/April, 2012. [5] American Health & Drug Benefits. Trends in Biologic Therapies for Rheumatoid Arthritis. March/April 2012

Yearly costs of biologics in USA

Response rate

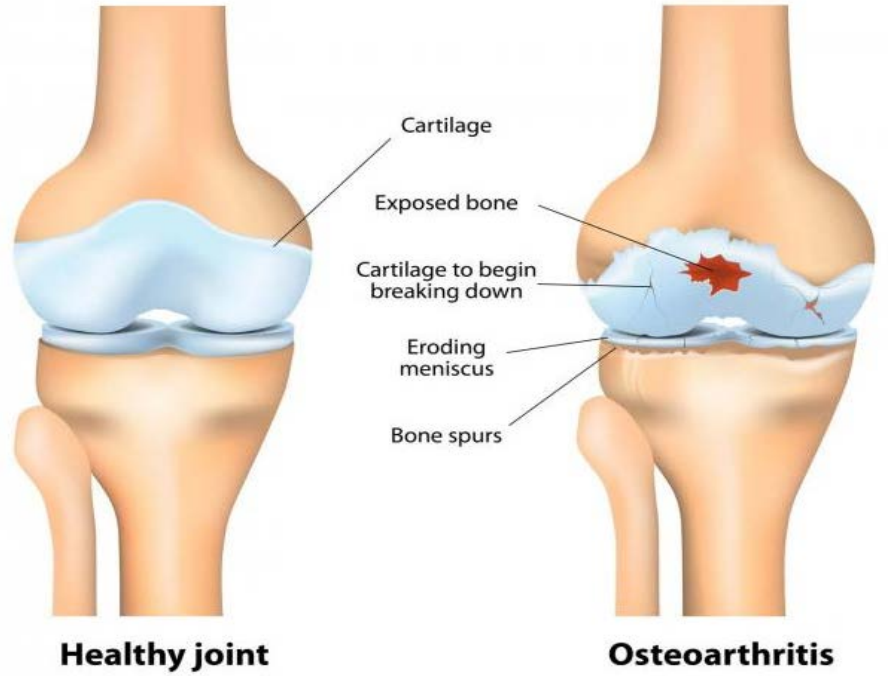
- Etanercept 31%
- Abatacept 29%
- Adalimumab 29%
- Golimumab 27%
- Infliximab 20%



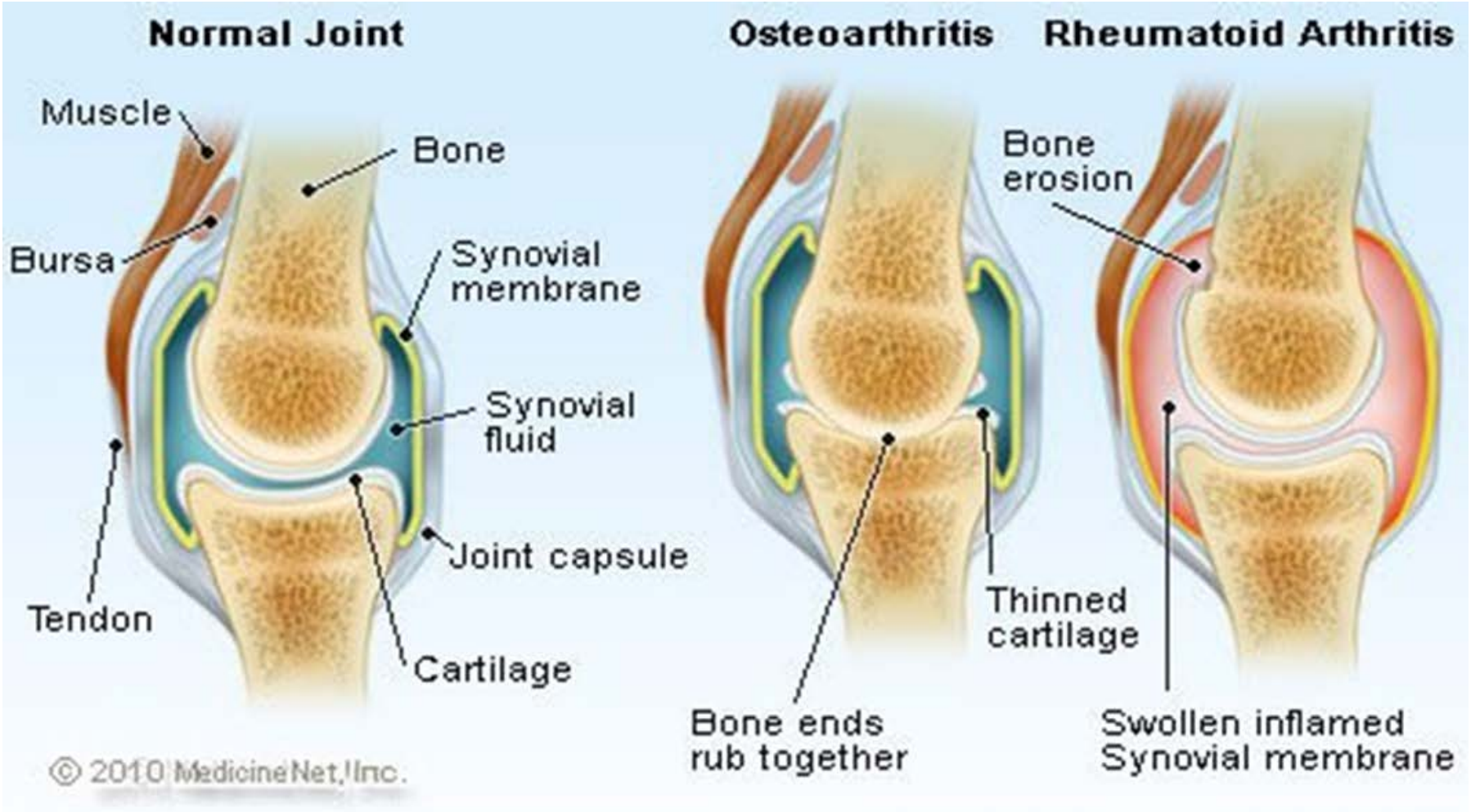
Curtis JR et al J Med Econ 2014

Osteoarthritis (OA)

- Progressive breakdown and loss of joint cartilage
- Most common type of arthritis, also known as degenerative joint disease
- Average age of diagnosis is 56
- Affects 14% of adults aged 25 and older, and 34% of those aged 65 and older
- Commonly treated with NSAIDS or steroids
- Many OA patients progress to intractable joint pain requiring invasive therapy (joint replacement)
- Accounts for >$186B in annual US healthcare expenditures



Normal and Arthritic Joints

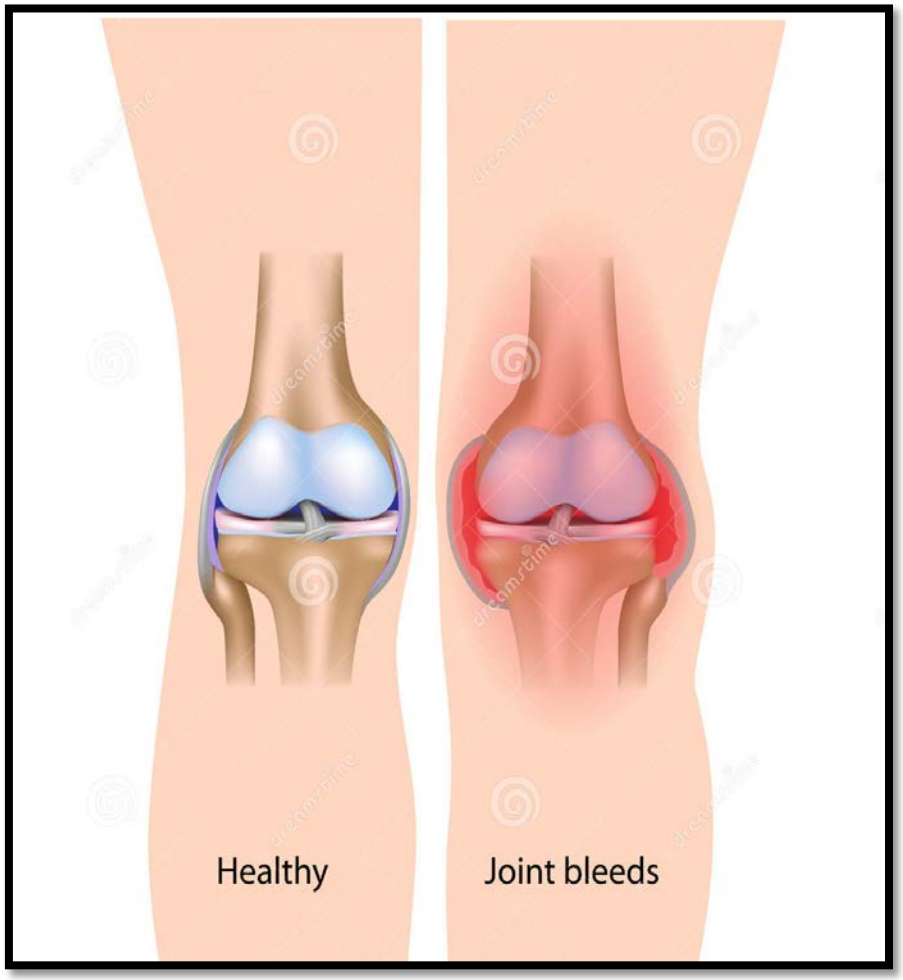


Other Diseases and Conditions Addressed by RSO

Ongoing Canadian human trial to treat refractory inflammatory articular disease includes the following:

- Rheumatoid Arthritis
- Osteoarthritis
- Spondyl-arthropathy:
  - i. Psoriatic arthritis
  - ii. Ankylosing spondylitis
  - iii. Reactive arthritis
  - iv. Enteropathic arthritis
- Other inflammatory joint disease:
  - i. Behçet
  - ii. Lyme disease
- Calcium pyrophosphate deposition arthritis
- Pigmented villonodular synovitis
- Hemophilic arthropathy
- Recurrent joint effusion after surgery or prosthesis

Hemophilic Arthropathy and Joint Replacement Issues



Polymeric inlays

Particles from abrasion leads to arthritis

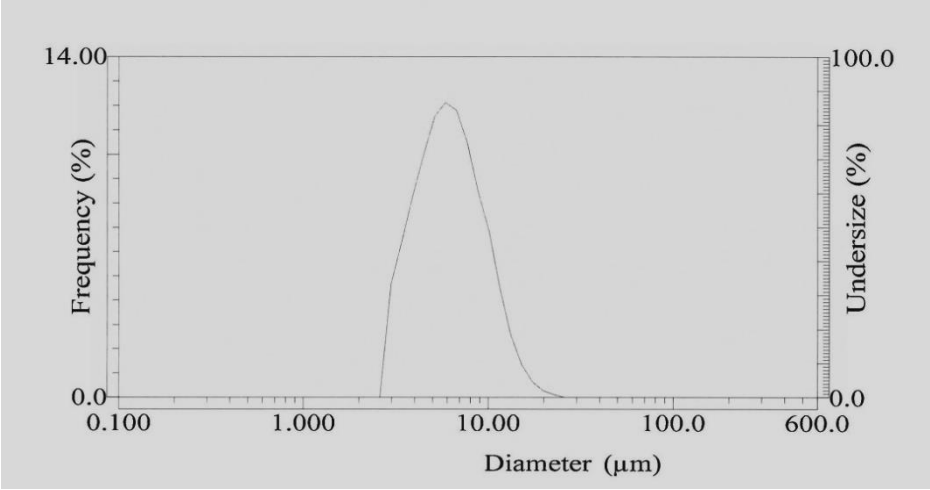
Radiosynoviorthesis Isotopes

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

Sn-117m Colloid joint retention and stability

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

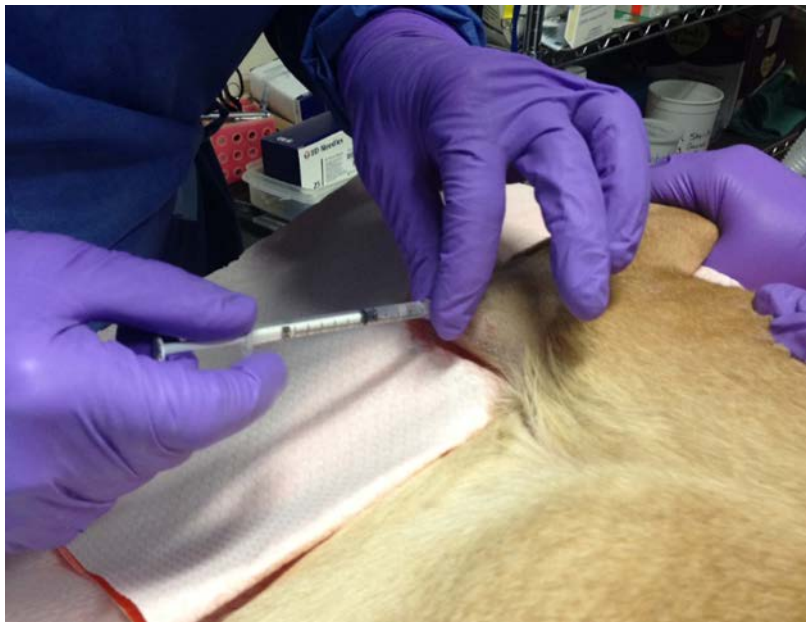
Mean =6.43 µm SD=2.47 µm

Veterinary Trials for Sn-117 RSO Colloid

Rats – to determine a suitable dose range

Normal Dogs – to determine safety profile

Dogs with OA – dose ranging, efficacy and safety



Dog being injected with Synovetin OA at the University of Missouri Veterinary Health Center

Human Trials Planned for Sn-117m RSO Colloid

- Initial human **clinical trials** using HTC RSO in **Canada 4Q18**
  - Pilot trial medium/large joints RA/OA
    - Dose ranging and safety (primary objectives at 6 months)
    - Efficacy (secondary objectives at 12 months)
  - Pivotal trial small/medium/large joints in RA/OA planned
- **IAEA**-sponsored clinical trial using HTC RSO in several **developing countries** enrolling in 2019

RSO Agent Doses

Meta-analysis

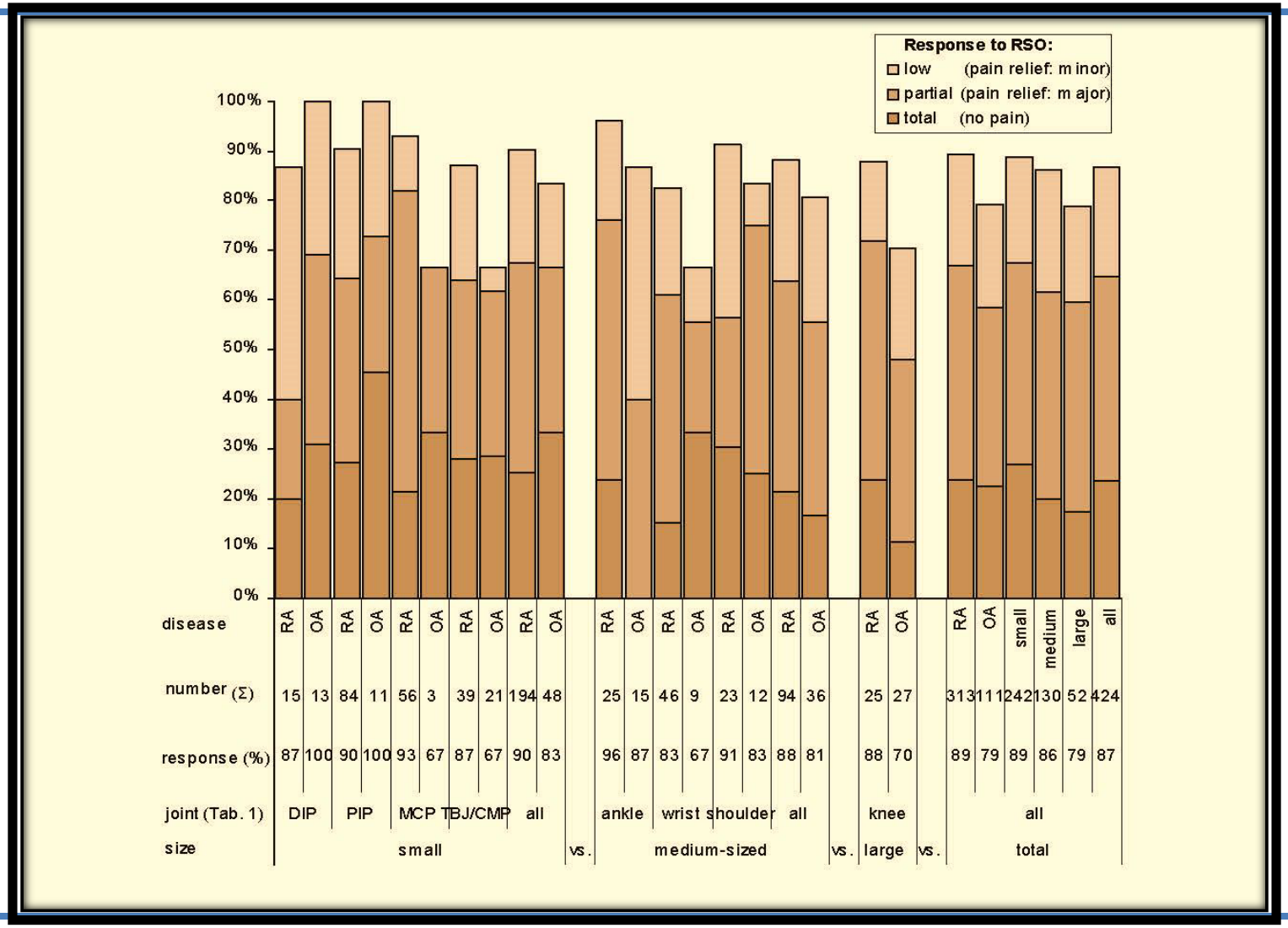
- 2190 joints in a period from 1971 to 1999 were evaluated
- overall response rate: 73 ± 17%
- response rate of rheumatoid arthritis: 67 ± 15%
- response rate osteoarthritis : 52 ± 24%
- response rate haemophilic arthritis: 91 ± 4%
- synovectomy by Steinbrocker stage I: 73 ± 12%
- synovectomy by Steinbrocker stage II: 64 ± 17%
- synovectomy by Steinbrocker stage III/ IV: 56 ± 11%

Kresnik et al.: Nucl Med Comm 2002; 23: 683-688

More recent meta-analyses are even higher

Meta-Analysis

Zuderman *et al*, Ann. Nucl. Med. (2008) 22, 735-741

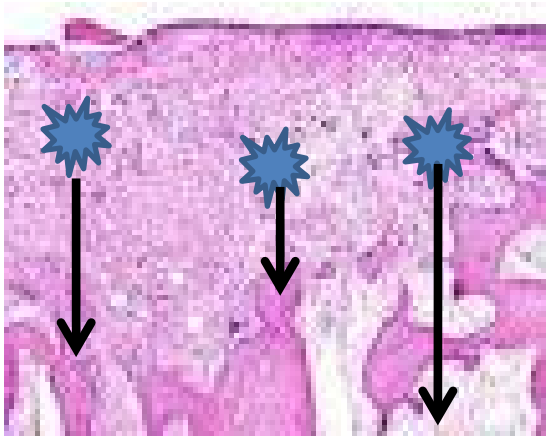


Procedure

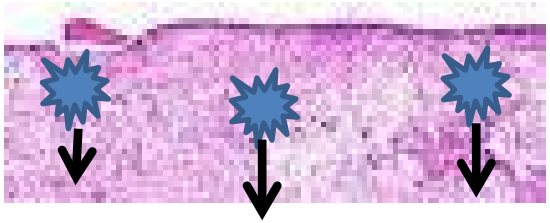
Selection of Isotope

Match thickness of tissue to range of therapeutic particle?

Knee



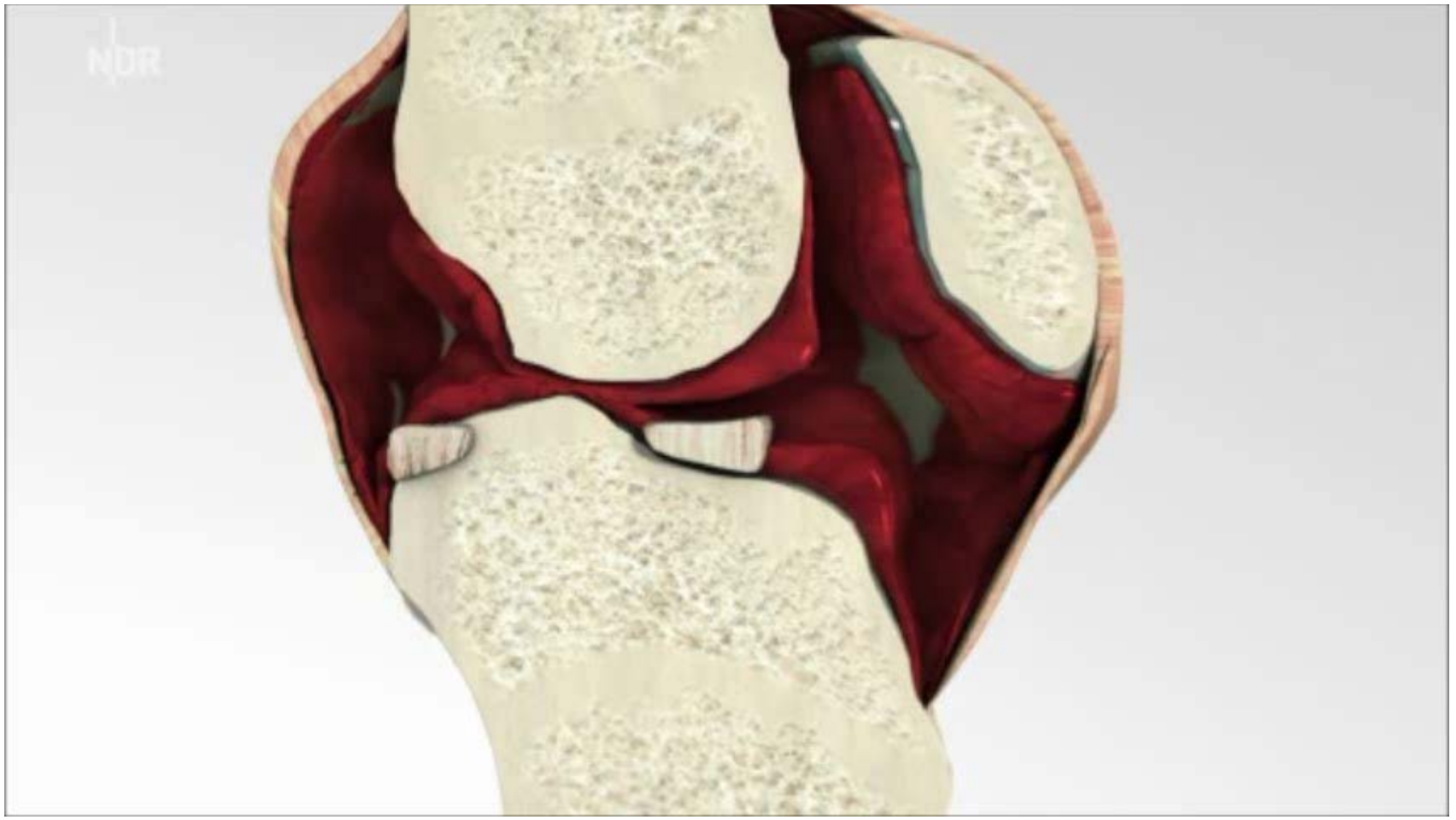
medium joints



small joints

	^{90}Y	^{186}Re	^{169}Er
Maximal tissue range	11.0 mm	3.7 mm	1.0 mm
Mean tissue range	3.6 mm	1.2 mm	0.3 mm

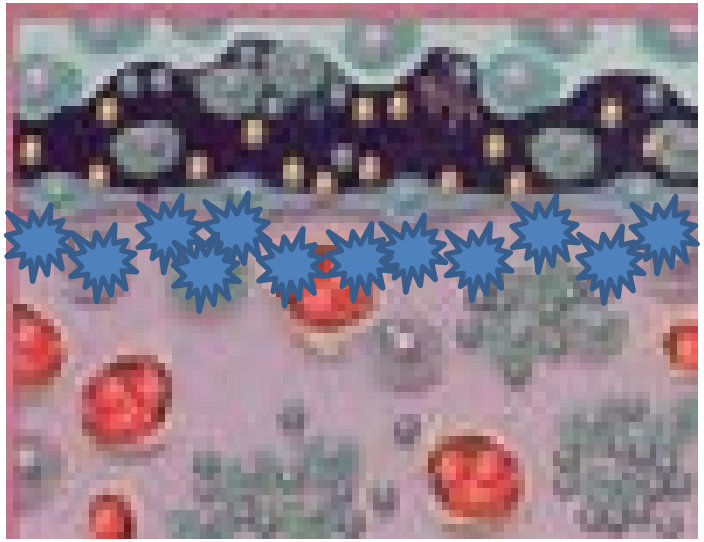
Phagocytosis



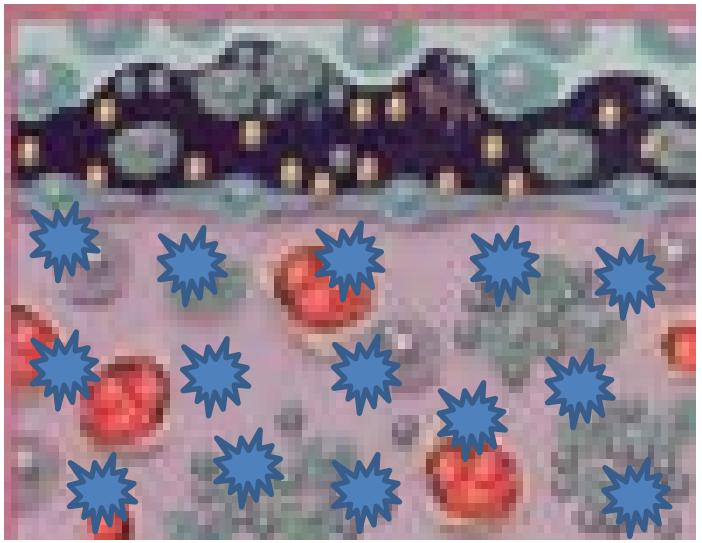
Effects of Phagocytosis

If colloid is correct **size** and **stable in-vivo** and radioisotope has a longer **half-life** then:

- Macrophages engulf colloid
- Transport colloid through synovial layers
- Colloid irradiates throughout the inflamed synovium

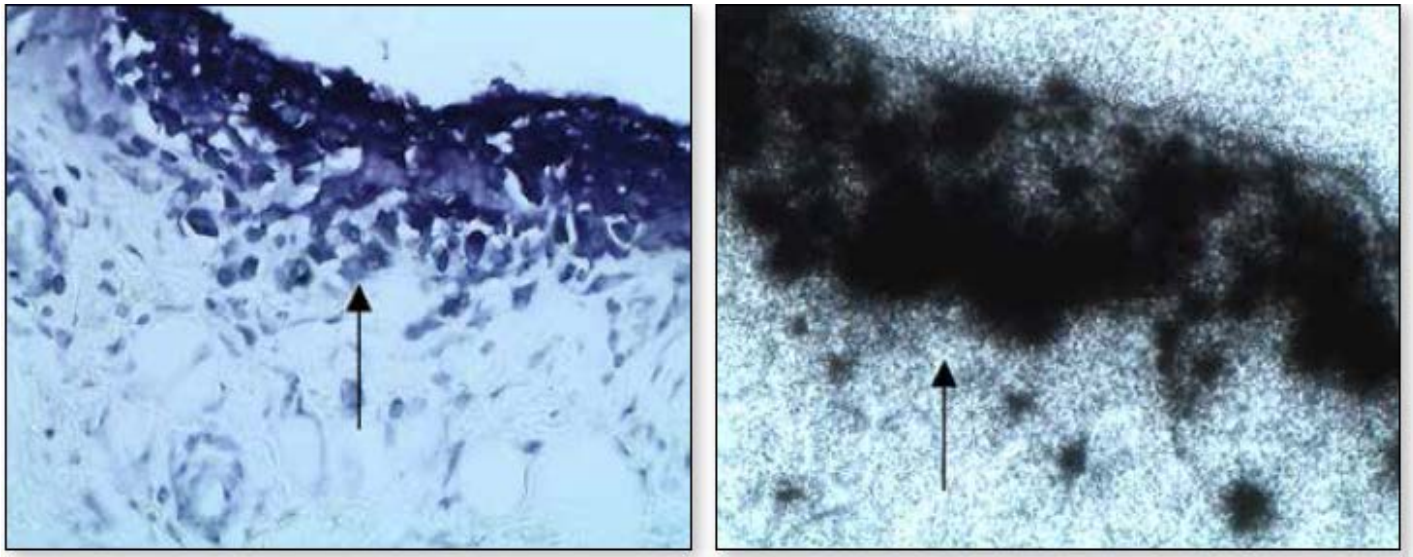


Match isotope to electron range



Range of radiation not important

Autoradiography



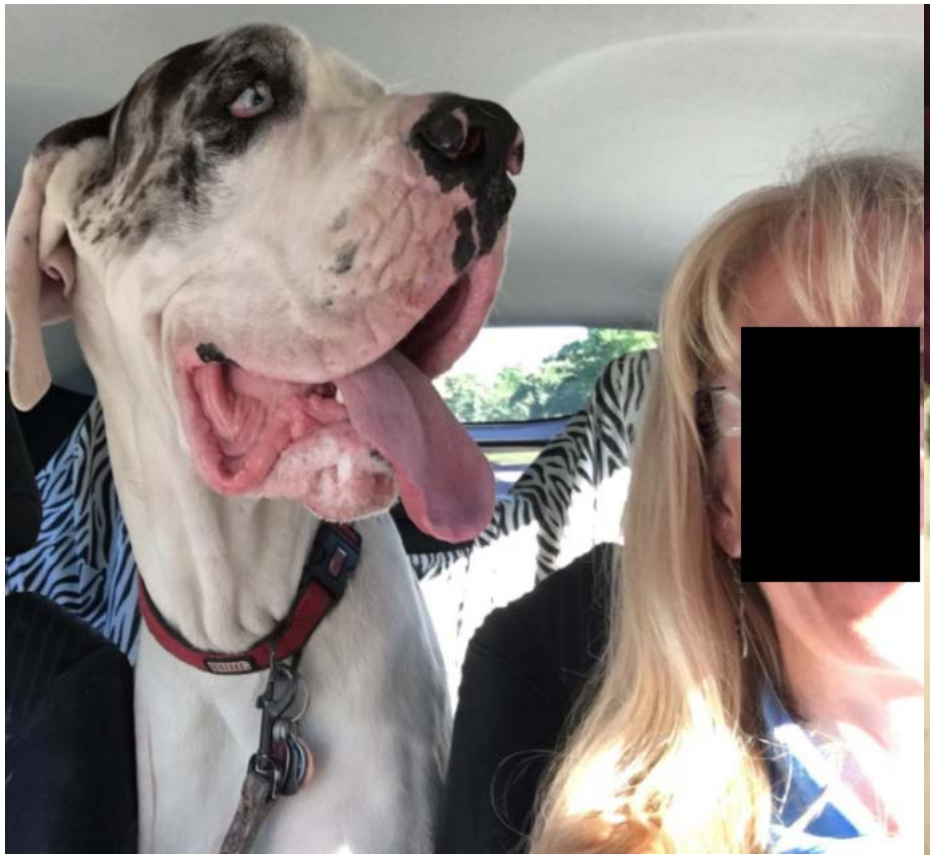
Arrowhead identifies articular cartilage. Arrow identifies area of inflammation. H identifies humerus. R identifies radius. AR sections show increased Sn-117m in the areas of inflammation below the synovial surface.

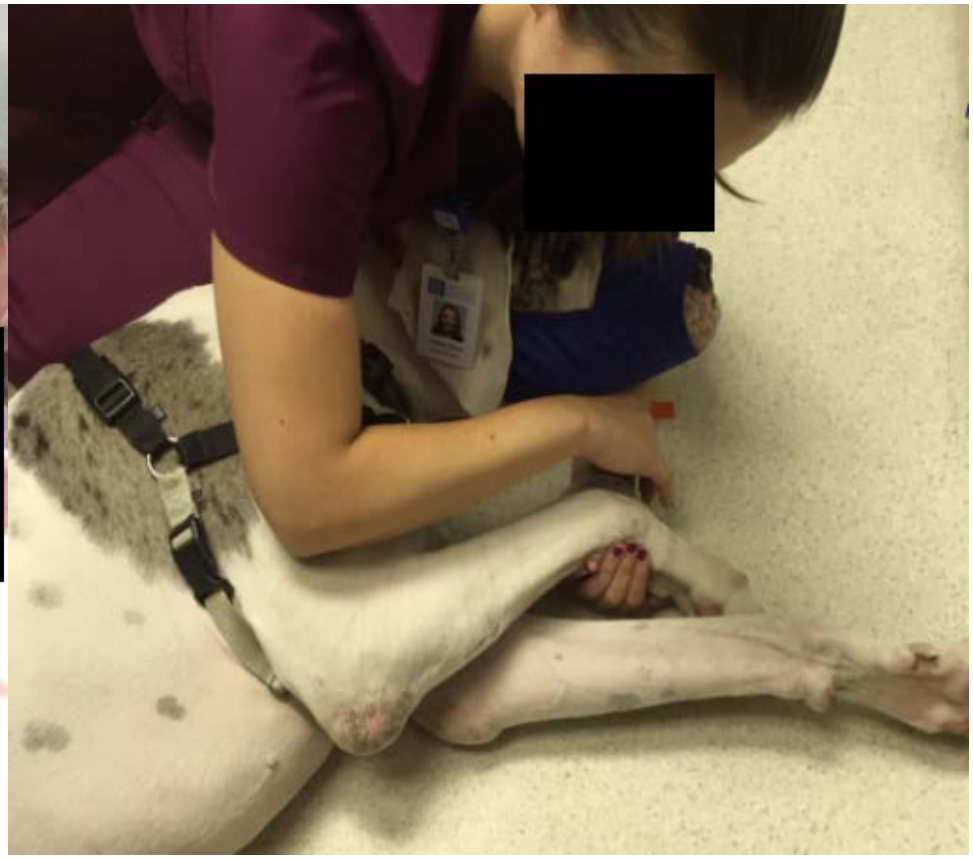
- Leads to the possibility of a single RSO agent for all size joints
- Reduced costs, delivery logistics

Use of Sn-117m in Larger Joints

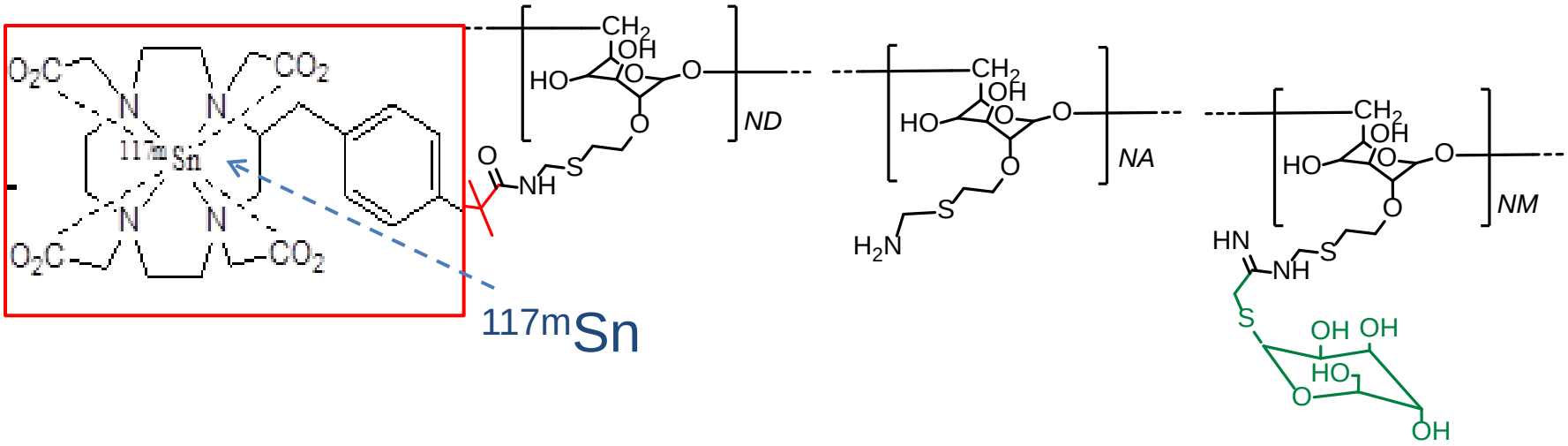
^{117m}Sn colloid used to effectively treat large dog joints

→ Comparable with medium joints in human





Rheumatology - Systemic RA



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

Cardiovascular - Vulnerable Plaque

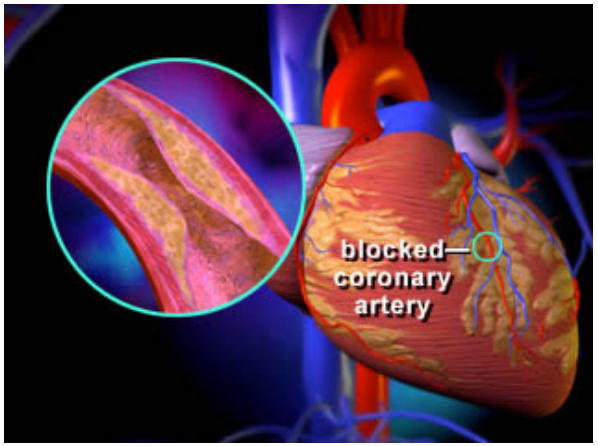
❖**Vulnerable plaque forms outside of the lumen in coronary/carotid artery walls - inflammation is the main driver**

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

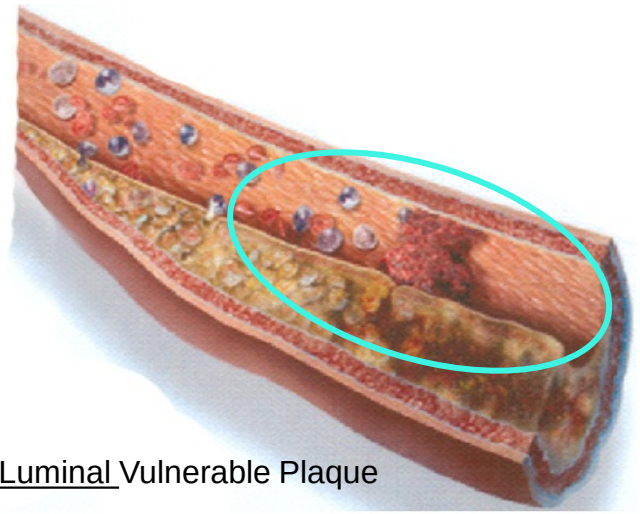
❖**Majority of all significant cardiac events (60-70%) leading to MI and sudden cardiac death are a result of VP, not calcified lumen atherosclerosis**

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

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



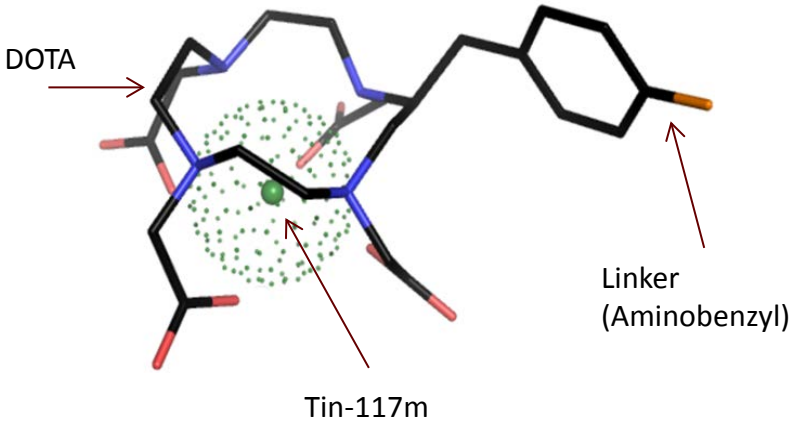
Luminal Calcified Plaque

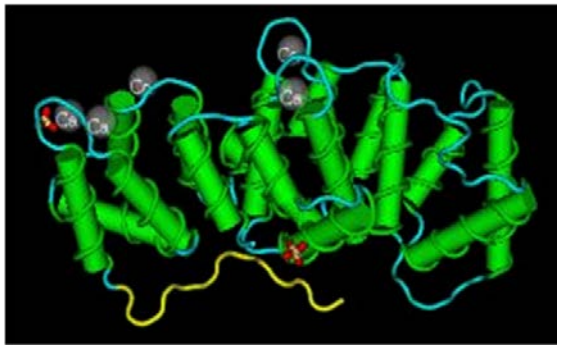


Extra-Luminal Vulnerable Plaque

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

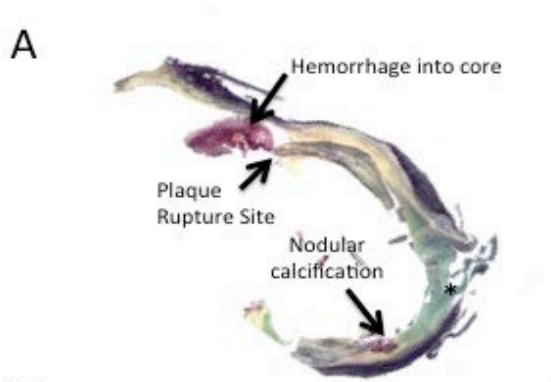
Aminobenzyl DOTA

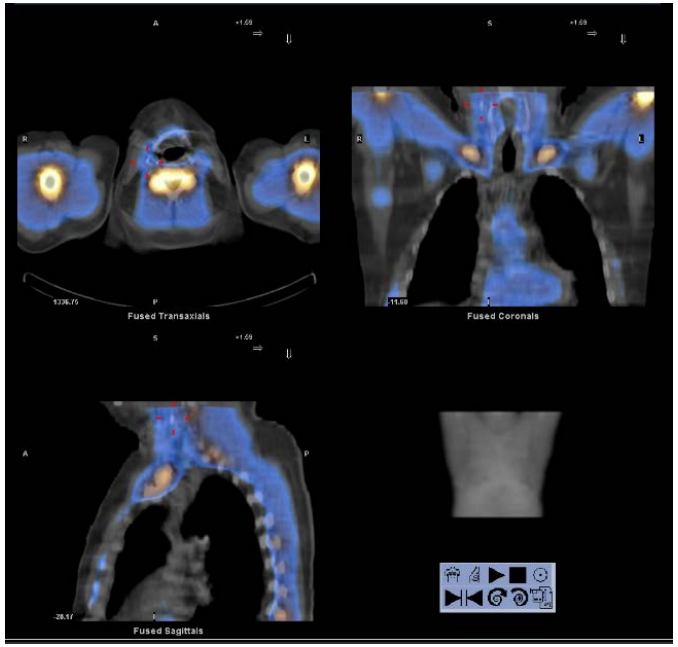
- Securely holds the Tin-117m

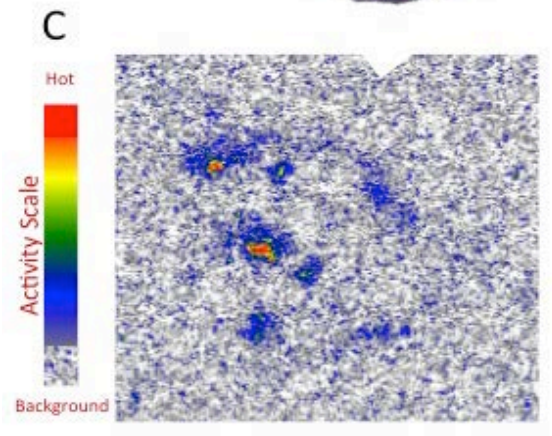
Annexin V

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

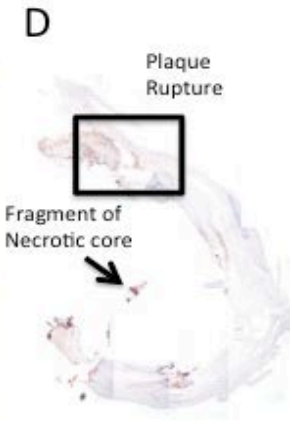
Imaging, Autoradiograph and Histology



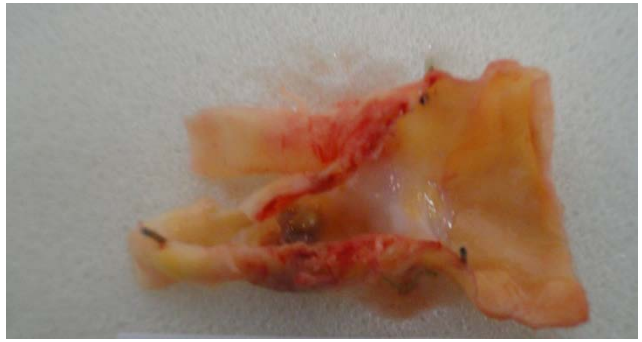




Autoradiograph
[5d Exposure]

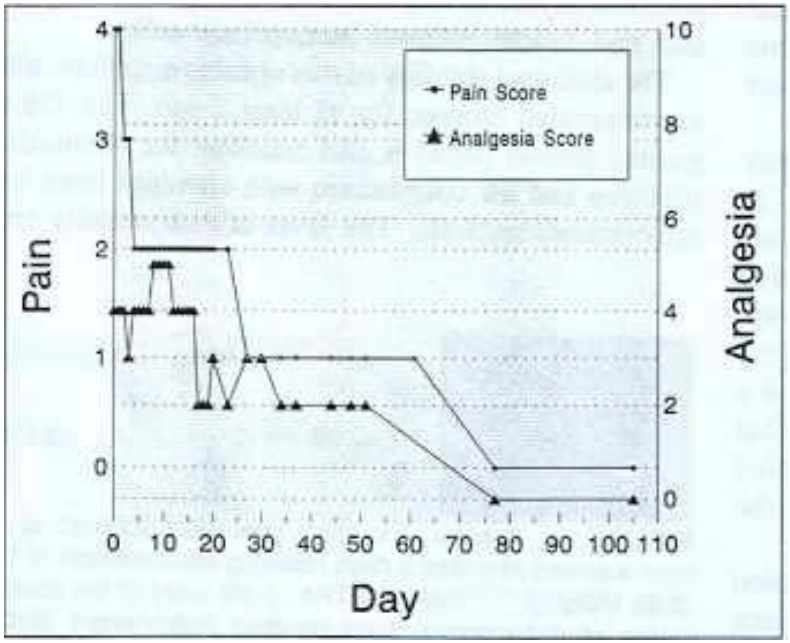


Lesional Macs
[CD68]



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

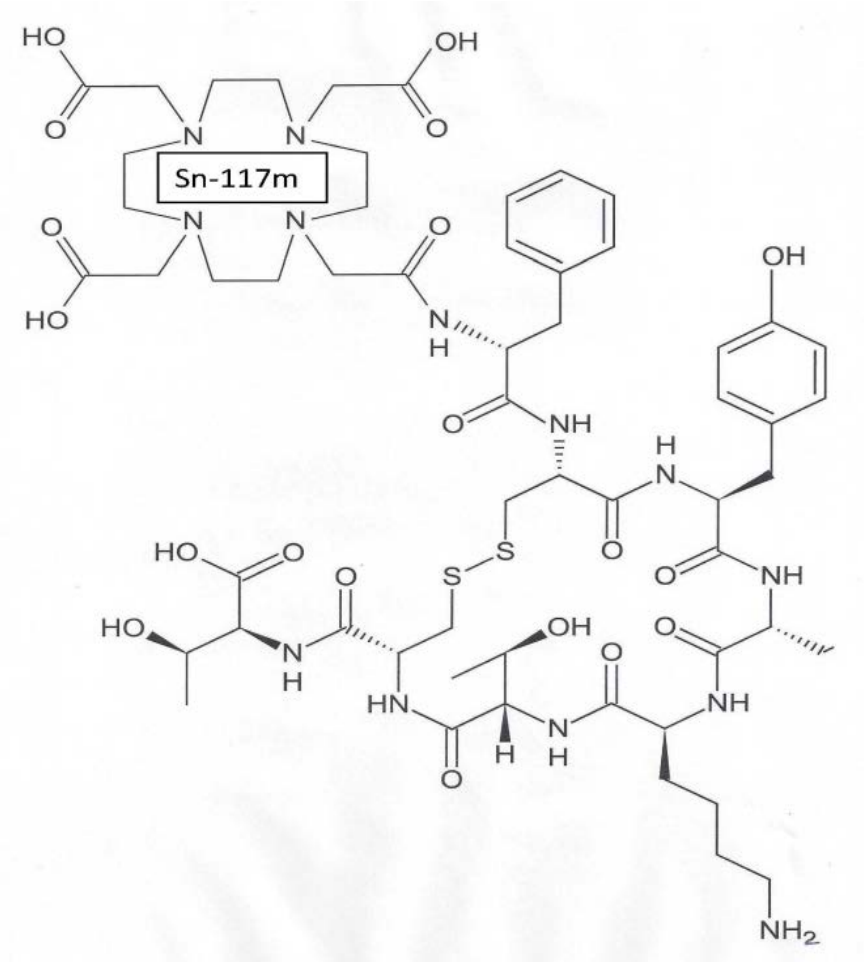


Response to $^{117}Sn(4+)$-DTPA In a patient with prostate carcinoma metastatict to bone. Analgesia Score refers to number of doses required per day

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



Cholangiocarcinoma Stent

Stainless steel laser cut electroplated stents

Treat Symptoms

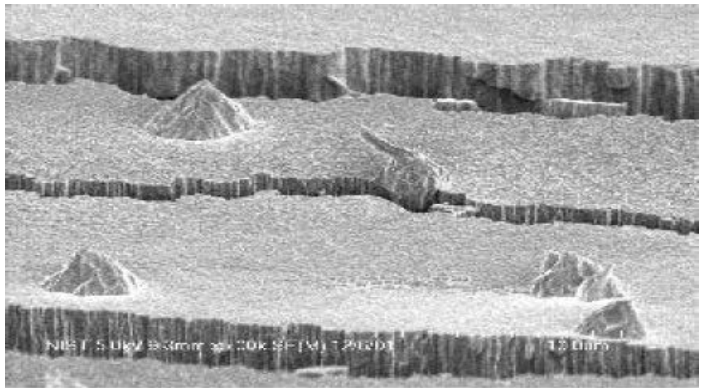
- stent expands to open the occluded duct – palliation of symptoms

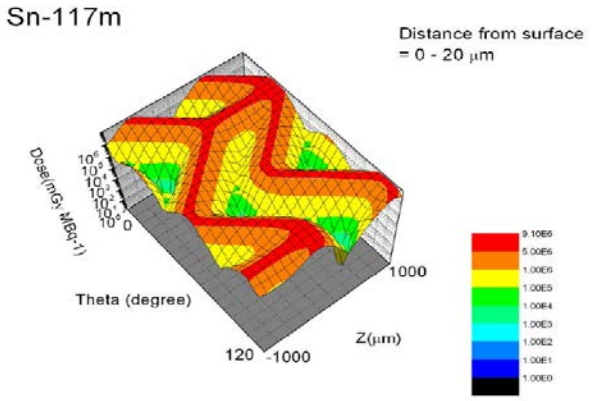
Treat Cancer

- 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





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

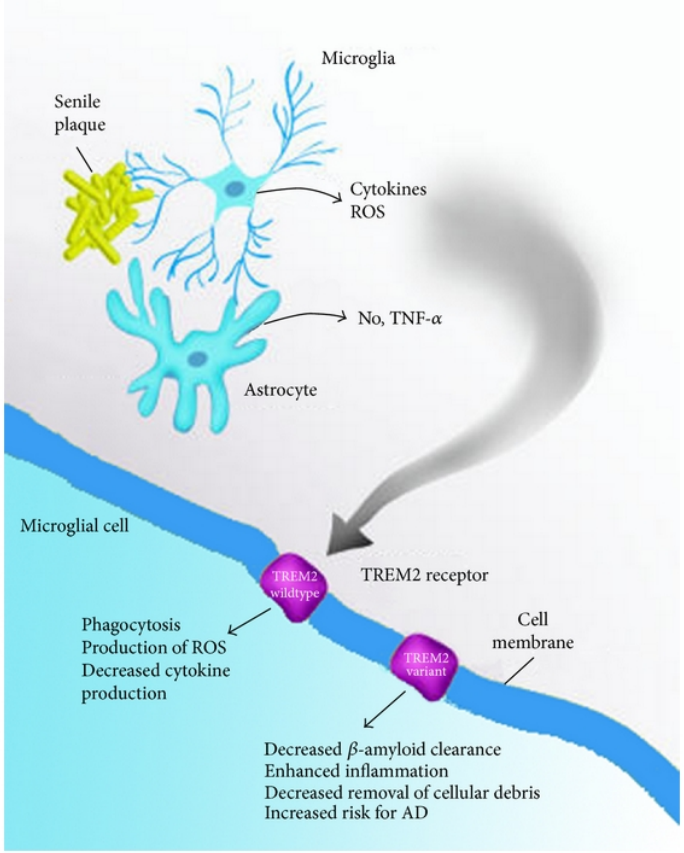


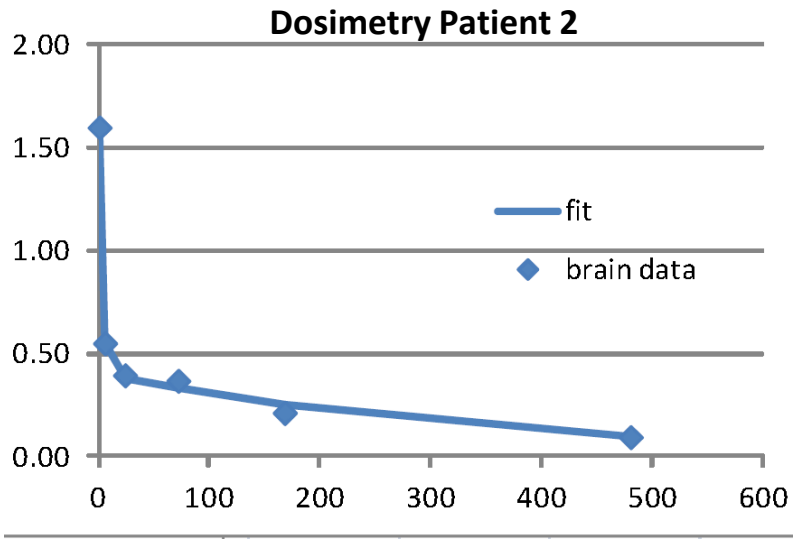
Figure: A central role for MG in AD is dependent upon a functional TREM2 receptor. The important actions of MG appear to be mediated through activation of the TREM2 receptor whose few known roles include suppressing inflammation and stimulating phagocytosis. The loss of TREM2 function and altered immune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

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