Serene

Canadian Association of Nuclear Medicine
February 7-9, 2019

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Homogeneous Sn-117m Colloid: A New Isotope for Use as a Radiosynoviorthesis (RSO) Agent in Canada

Disclosures

- Cynthia Doerr MD is an employee of Serene, LLC
- Nigel Stevenson PhD is an employee of Convetra, Inc., a subsidiary of Serene, LLC

RSO and Synovitis

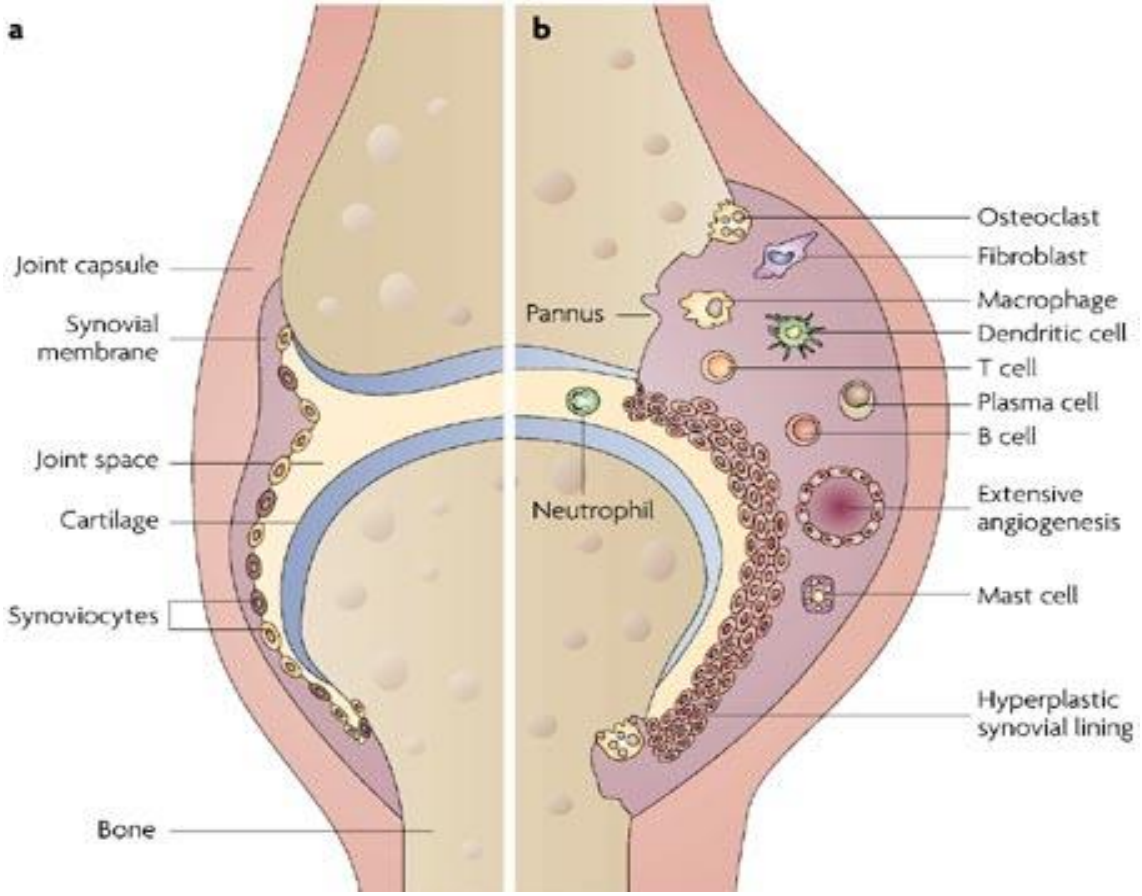
Radiosynoviorthesis (RSO) With Currently Available Agents

- A.k.a. Radiosynovectomy/RSV
- Treatment for *synovitis* (RA, OA, psoriatic arthritis etc.)
- Used worldwide since 1952[1]
- Radioisotope injected directly into the joint space
  - Phagocytosed by synovial macrophages
  - *Necrosis and fibrosis* of synovial membrane
  - Reduce pain, effusion, and inflammation
- The majority of recent randomized clinical trials of RSO have shown significant benefits as compared to controls in a variety of arthritides in various joints treated with one of the 3 commercially available nuclides[2-9]
- Global commercial isotopes (none approved in Canada):
  - Y-90 for large joints (knee)—limited availability in Canada
  - Re-186 for mid-size joints (elbow, wrist, ankle)—not available in Canada
  - Er-169 for small joints (fingers etc.)—not available in Canada

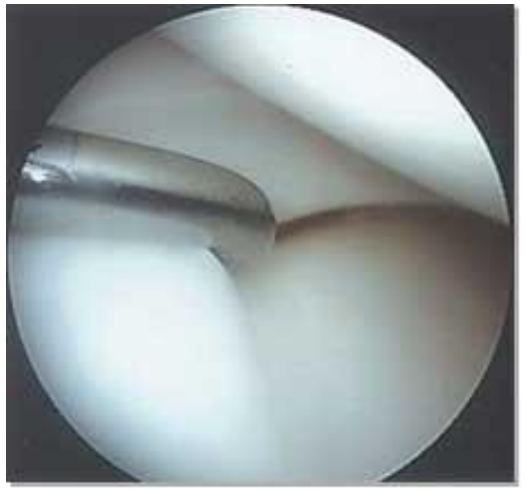
1. Fellinger, K and Schmid J, *Wien Z Inn Med*. 1952;33(9):351-63.
2. Zuderman L, Liepe K *et al, Ann Nucl Med.* 2008;22:735-41.
3. Dos Santos , MF et al, Clinics 2009;64:1187-93
4. Dos Santos, MR et al, Clin Rheumatol 2011;30:77-85
5. Jahangier, ZN et al, Arthritis Rheum 2005;52:3391-402
6. Kahan, A et al, Clin Exp Rheumatol 2004;22:722-6
7. Kampen, WU et al, Eur J Nucl Med Mol Imaging 2005;32:575-80
8. Liepe, K et al, Ann Nucl Med 2011;25:317-23
9. Van Der Zant, FM et al, Eur J Nucl Med Molec Imaging 2007;34:212-8

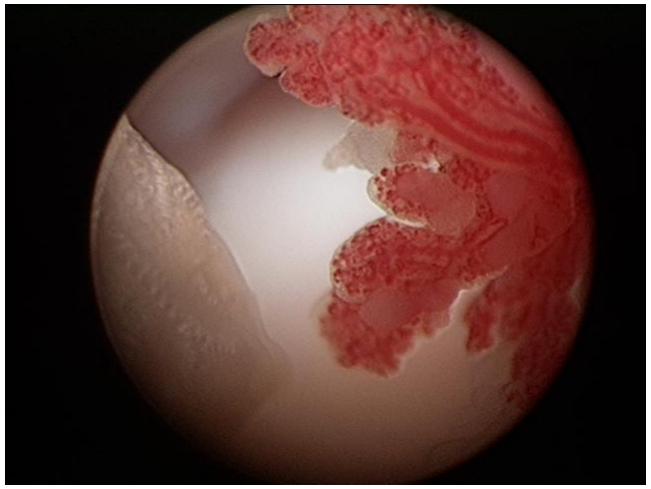
Role of Synovitis in Arthritis Conditions

Normal joint	Joint with synovitis



- Early synovitis initiates intra-articular inflammatory cascade
- Macrophages, other pro-inflammatory cells are activated
- Synovial angiogenesis → edema, inflammatory cell infiltration[1]





1. Mapp PI, Walsh DA. *Nat. Rev. Rheumatol*. 2012;8:390–398.

History of Global Use of RSO

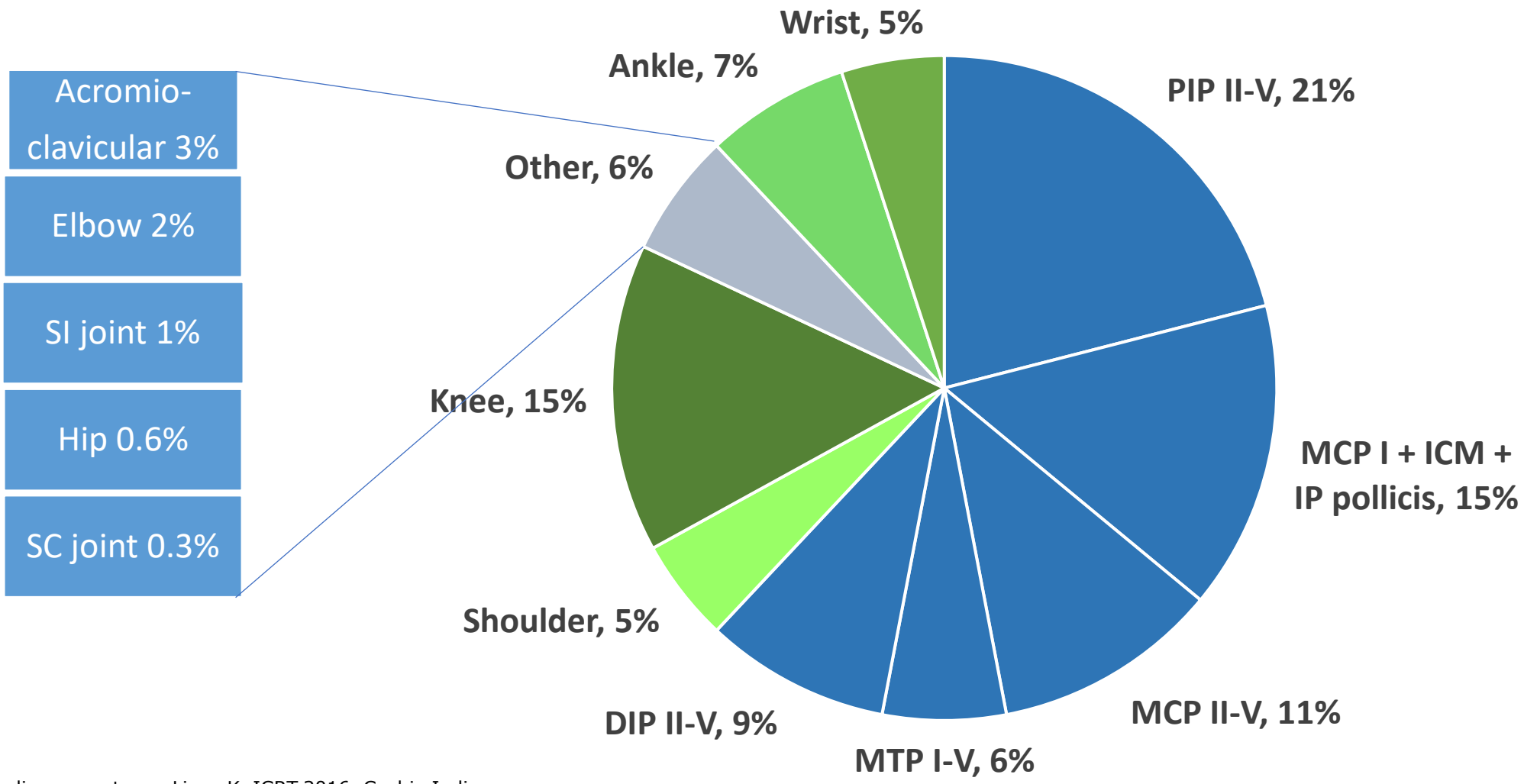
RSO Performed/Approved in Many Countries

German experience

- 5 large centers, >100 centers
- 40,000-60,000 joints treated annually
- Er-169, Re-186, Y-90 used

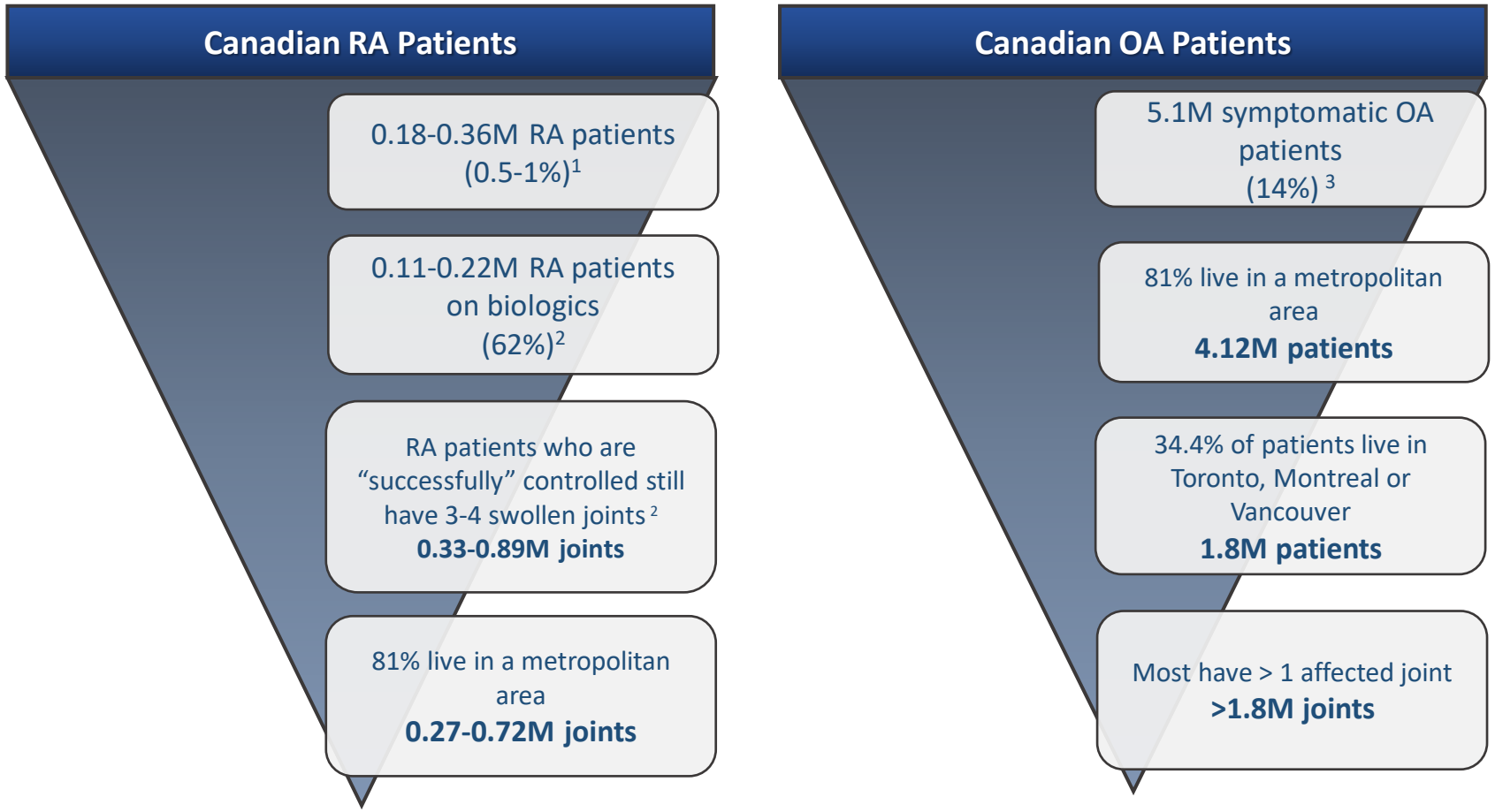
RSO Performed/Approved in Many Countries

Distribution of Treated Joints in Germany, Czech Rep, Poland Where Y-90, Re-86 and Er-69 are Available



117mSn Colloid in Radiosynovectomy, Liepe K, ICRT 2016, Cochin India

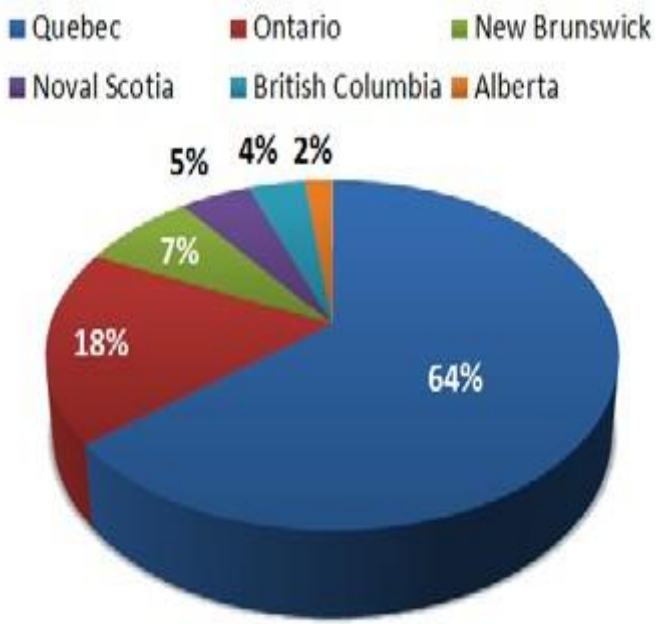
Synovitis-Related Conditions in Canada

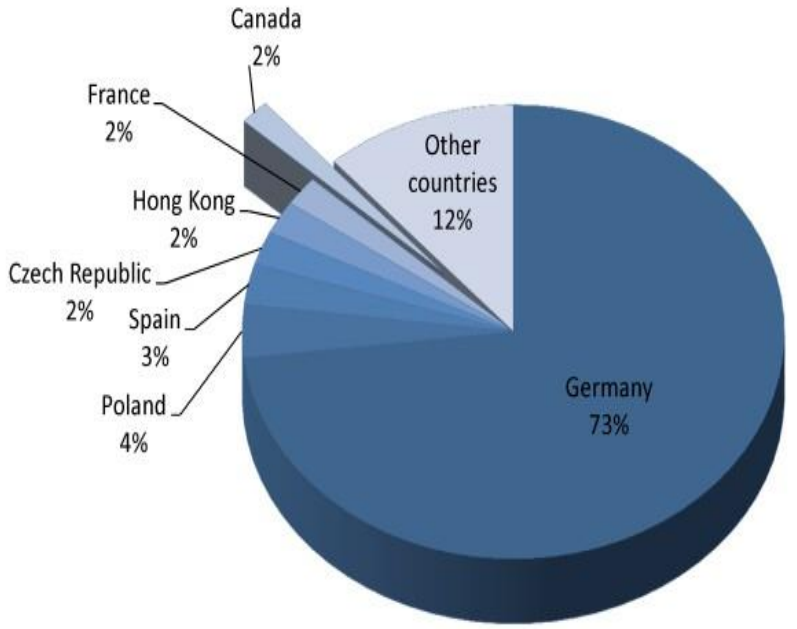


1. CDC
2. Zhang et al, Arthritis Care Res, 2011 December;63(12):1672-9
3. Cisternas et al, Arthritis Care Res, 2016 May; 68(5)

Historical Use of RSO in Canada

- 2009--398 knee RSO using Y-90
- 2009--74 Re-186 injections, all in Quebec
- No Er-169
- Montreal 1979-1992
  - 862 RSO
  - 77% RA
  - 7% psoriatic
  - 4% inflammatory arthrosis
  - 10% other
- Follow up >2 years
  - 83% pain relief at rest
  - 80% pain relief at walk
  - 93% a.m. stiffness relief
  - 80% increased ROM
  - ~1/3 no longer used support





Radiosynoviorthesis, CANM Guidelines, Official release March 8th, 2011

Characteristics of Sn-117m, Homogeneous Tin Colloid and RSO Modeling

Sn-117m Emissions

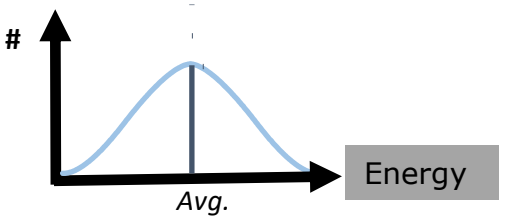
Major Emissions	Energy (KeV)	Intensity (%)
Auger-L	3	91
Auger-K	21	10.8
CE-K1	126.8	66.3
CE-K2	129.4	11.9
CE-L1	151.6	27.3
CE-L2	154.1	1.5
CE-M1	155.1	5.6
Gamma	158.6	86.4

No High Energy Emissions

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

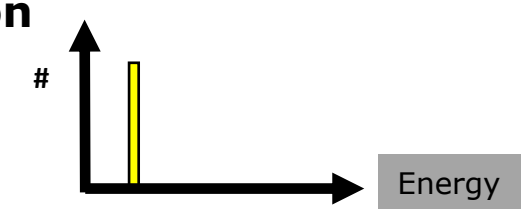
Characteristics of Sn-117m C.E.

Beta Particles

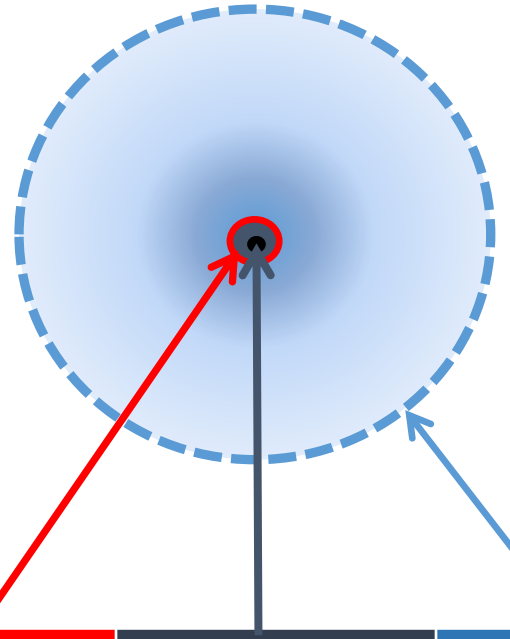


Produces a *range* of tissue penetration

Conversion Electron (CE)



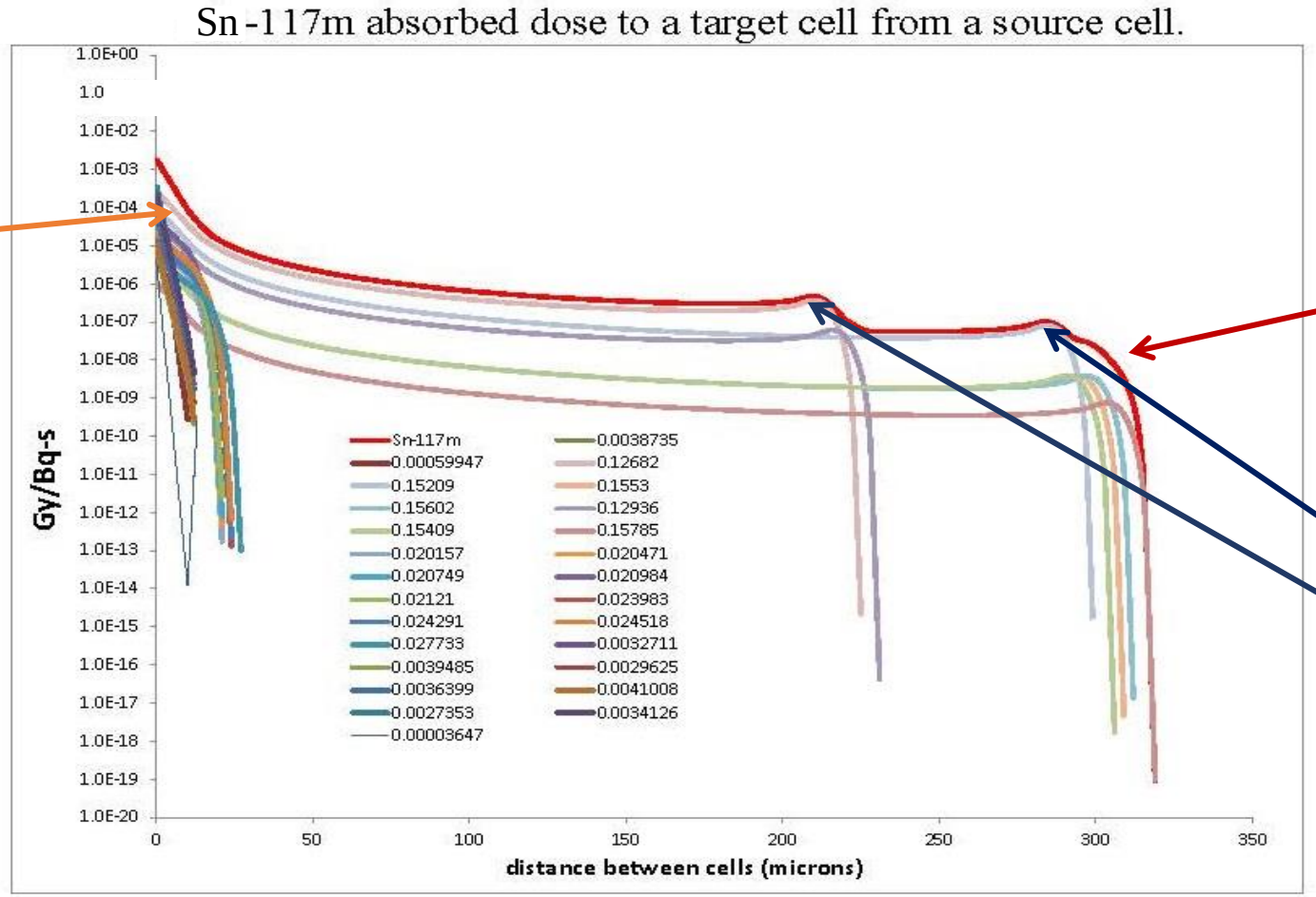
Penetrates up to a *set distance* (discrete energy)



	Sn-117m (CE)	Alpha Particles	Beta Particles
Range in tissue (µm)	**300**	**40-90**	**50-5000**
Shielding needed during administration	**No**	**No**	**Yes**

Well-defined Range of Sn-117m in Tissue

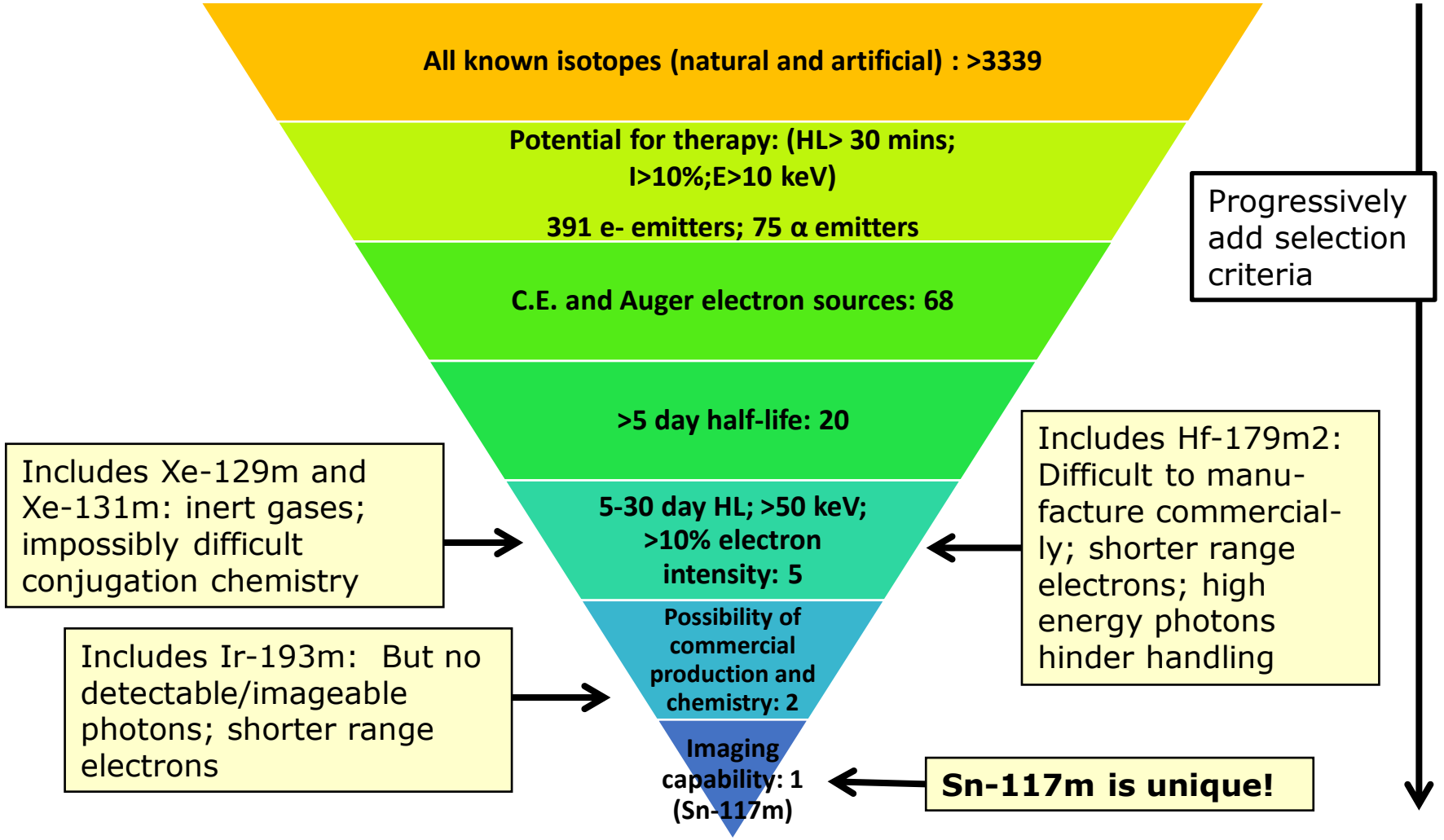
Short-range dose boost from Auger electrons



Relatively uniform total dose over 300 µm tissue depth

Bragg peaks (end points) for higher energy C.E.

Sn-117m is a Unique Isotope



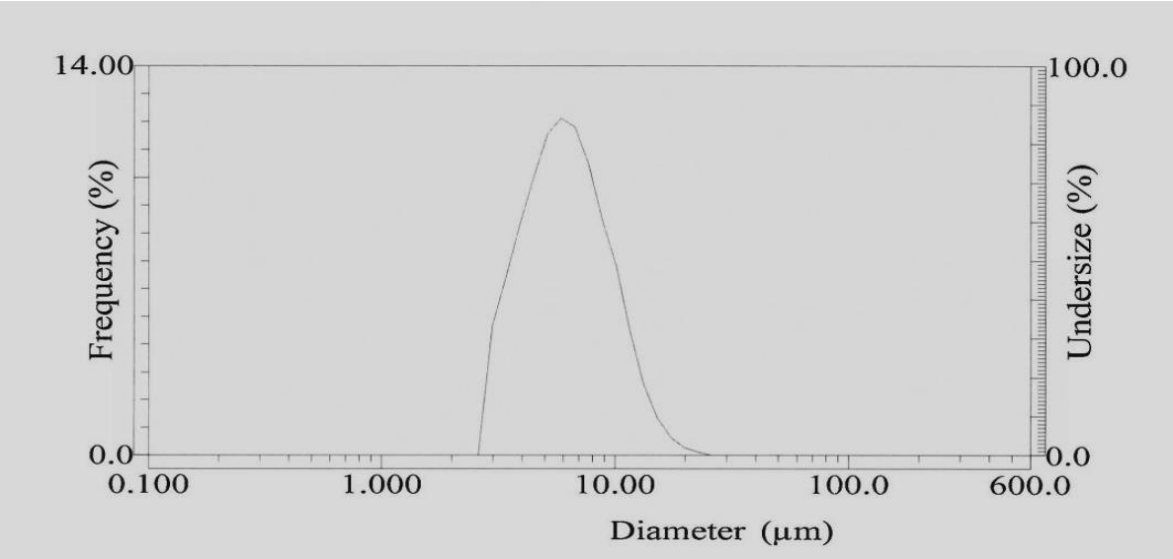
Radiosynoviorthesis Isotopes

Isotope	$t_{1/2}$ (d)	Imaging Particle	Energy (keV)	Therapy Particle	Maximum Energy (keV)	Range (mean) Tissue (mm)	Range (max) Tissue (mm)	Typical Dose (MBq)	Joint Size
Sn-117m	14	γ	158.6	C.E.	151	0.27	0.29	18.5-111+	S,M,L
Eb-169	9.3	None	-	β^-	350	0.14	1.1	18.5-37	S
Re-186	3.7	γ	137	β^-	1070	1.1	4.4	74-111	M
Y-90	2.7	None	-	β^-	2280	4.1	11	148-222	L
P-32	14.3	None	-	β^-	1711	2.8	8.4	18.5-74	L

Sn-117m Colloid Joint Retention and Stability

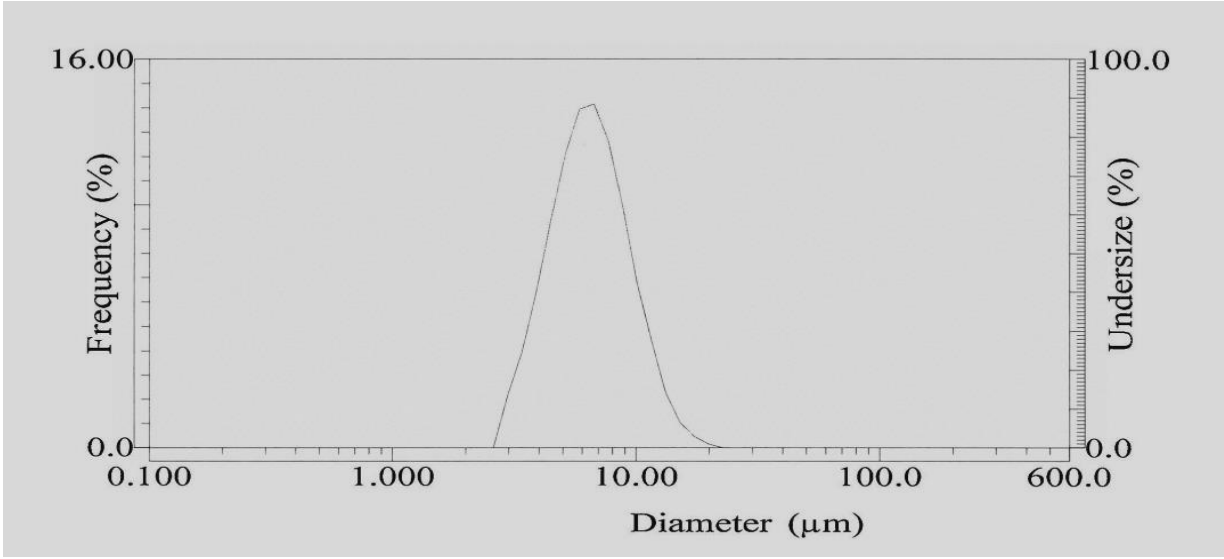
Retention of colloid in normal rat joint:

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

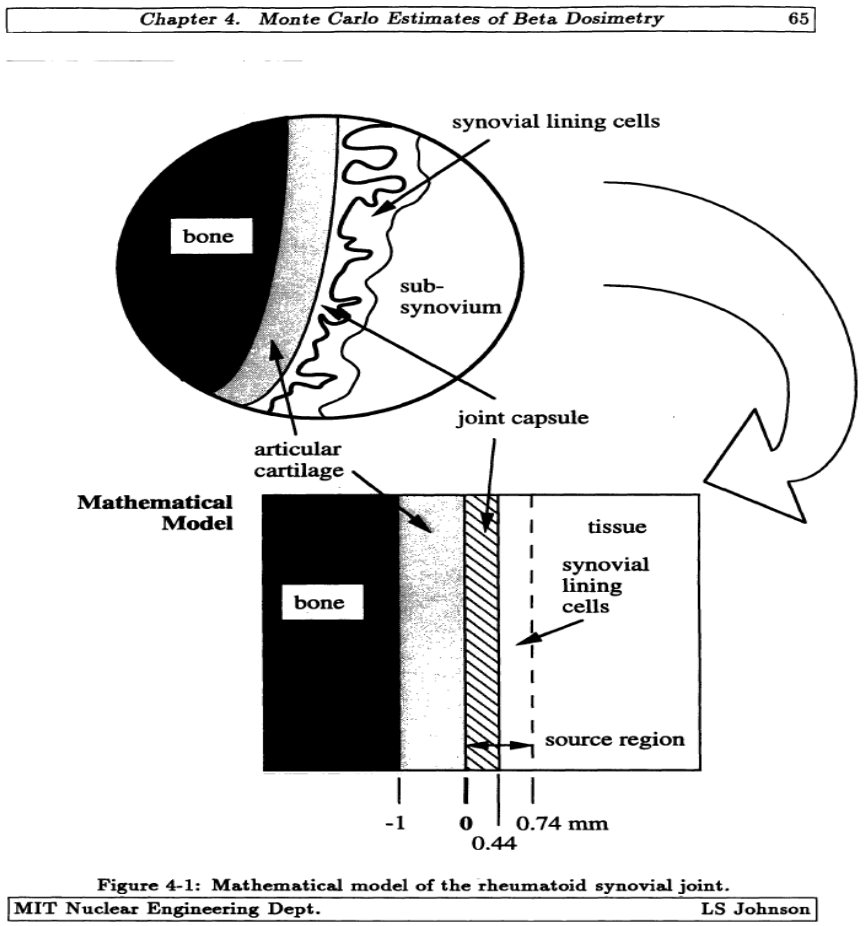
Mean =6.43 µm SD=2.47 µm

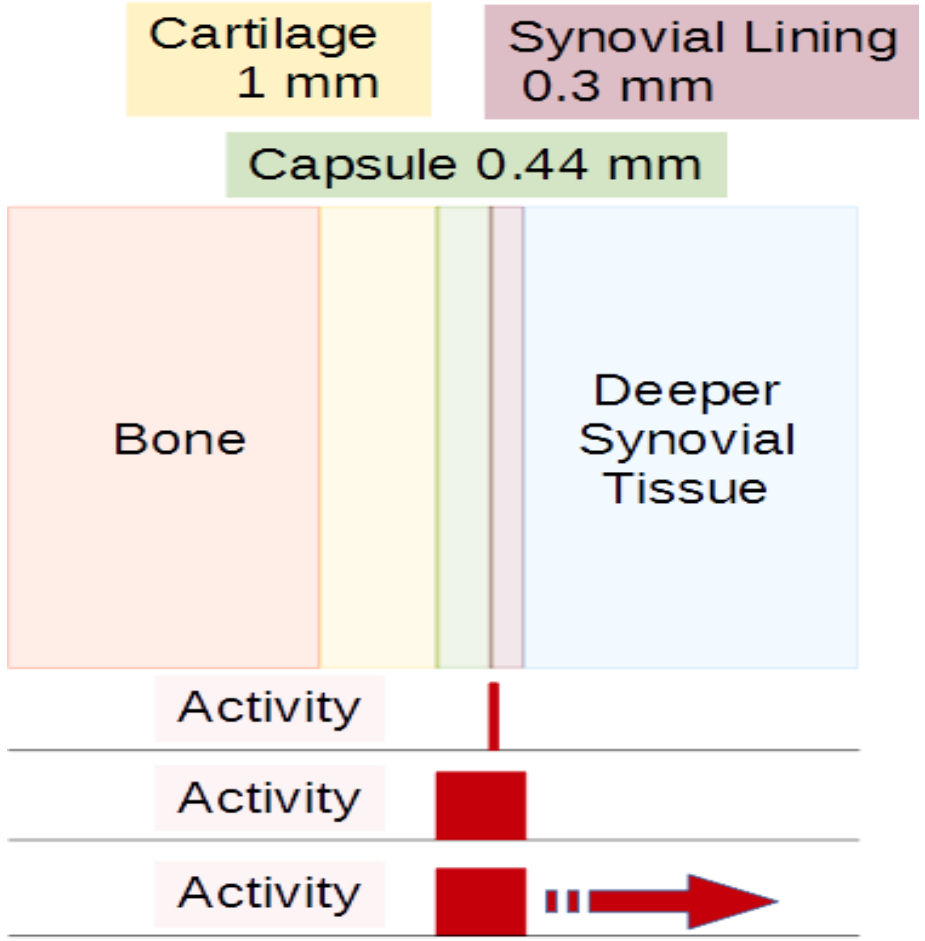
Homogeneous Sn-117m Colloid (HTC) for Human Applications

- Sn-117m Activity Concentration: 74-148 MBq/mL
- Shelf-Life: 2 weeks
- Visual: White turbid particles in clear solution
- pH: 6.5-9.0
- Median particle size: 2.5 to 6 µm
- Particle size range: D10 to D90 range = 1.5 > 20 µm
- Endotoxin: < 11 EU/mL
- Sterility: sterility assurance level of 10-6

Dose Range (for trial): Up to 222 MBq (3 mL) in knee

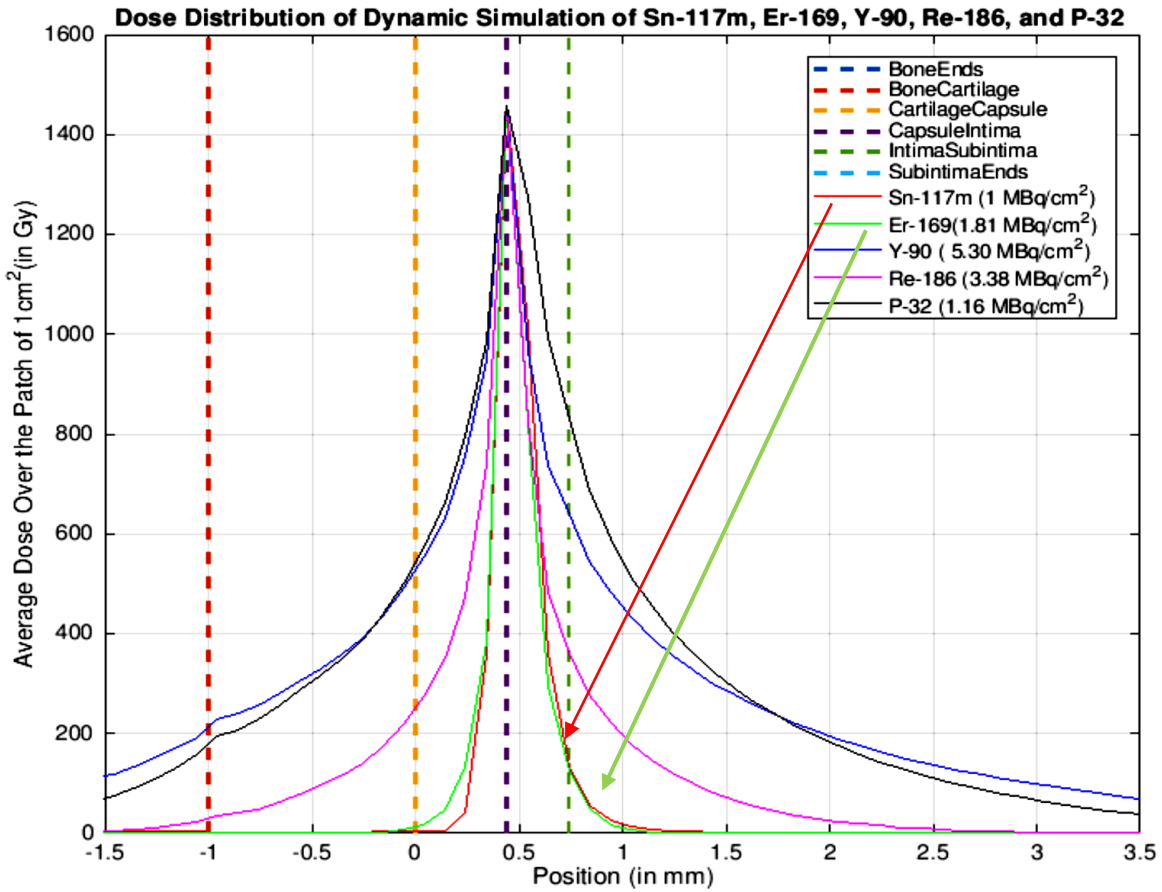
Model of the Synovial Joint





LS Johnson, *Beta-Particle Dosimetry in Radiation Synovectomy and Use of the $^{10}B(n,\alpha)$ Nuclear Reaction to Examine the Pathology of Rheumatoid Arthritis*, PhD, Massachusetts Institute of Technology, 1994, p. 65. Figure used with the permission of Dr. Johnson.

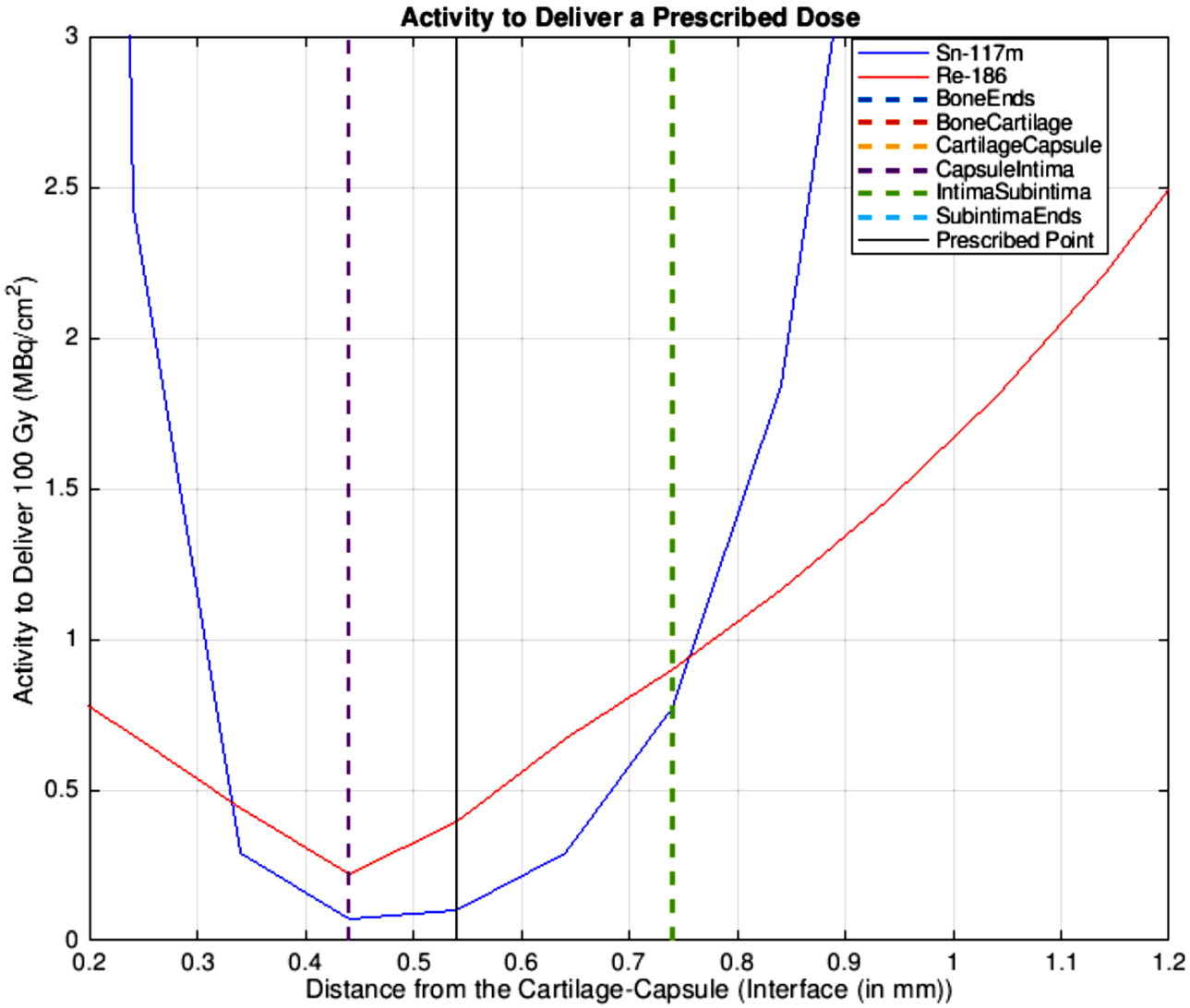
Dose Distribution of Dynamic Simulation Using Monte Carlo



- Relationship between the dose deposited by radionuclides at different distances from the Cartilage-Capsule interface
- Simulated for 20 half-lives with a uniform distribution of velocity from stationary to 8.58×10-8 mm/s
- The dose profile of Sn-117m is very close to that of Er-169
- Increasing the administered activity of Sn-117m results in a dose profile in the deeper synovium similar to Re-186

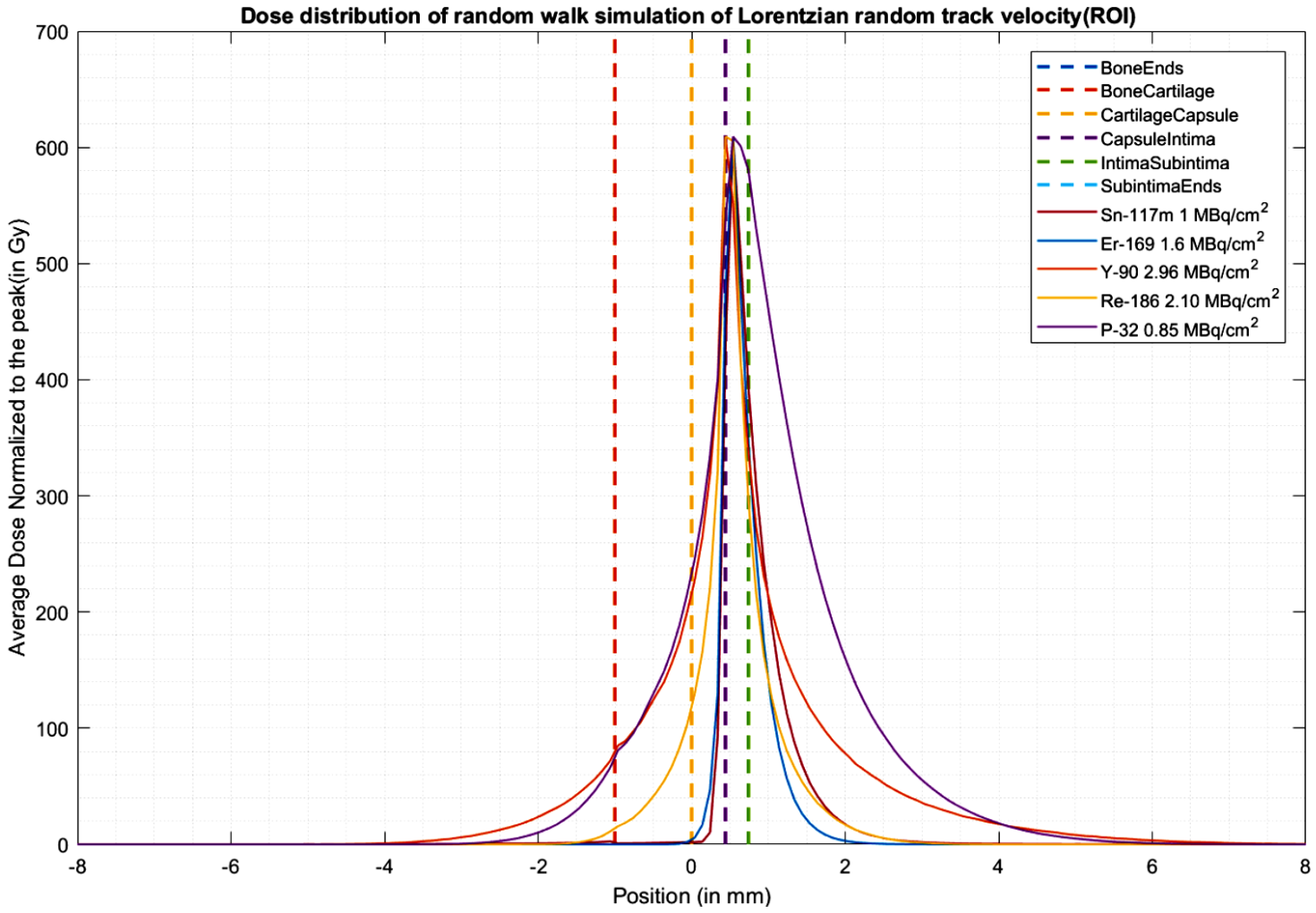
A Monte-Carlo study of Sn-117m radiosynoviorthesis to treat arthritic joints
Aashish C. Gupta[1], Richard E. Wendt III[2], and Nigel R. Stevenson, SNMMI, June 2018

Activity to Deliver a Prescribed Dose



- Relationship between the administered activity of Sn-117m and Re-186 to deliver 100 Gy at different distances from the Cartilage-Capsule interface
- **To deliver 100 Gy at 0.1 mm:**
  - **0.1026 MBq/cm2 of Sn-117m**
  - **0.3923 MBq/cm2 of Re-186**

Dose Distribution with a Velocity ~40×10-8 mm/s (Inflamed Tissue)



- Sn-117m penetrates into **deeper layers** of inflamed synovium
- Sn-117m does not irradiate the bone or cartilage
- Sn-117m provides a **low dose rate/longer-lasting** treatment
- Sn-117m reaches at least as deep as Re-186

Characteristics of Sn-117m

Solves the issues related to current commercial RSO isotopes

- **Mono-energetic conversion electrons** of ~140 KeV discrete energy for therapy have an average range of ~300 μm
- **On-demand production**—no need to "batch" patients
- **Easier handling and shipping**—easy to shield, and track
- **Readily imaged**—gamma ray (159 KeV) similar toTc-99m (140 KeV) proves you are in the joint space
- **Homogeneous colloid**—large enough to stay in joint, small enough for macrophage engulfment
- **Retained at injection site/no need for splinting**—remains in primarily in the joint
- **One product for all size joints**

Sn-117m Pre-Clinical Data

Prior Technical and Clinical Development of Sn-117m

- Brookhaven National Laboratory 1980s
- Decades of Sn-117m labeled compound characterization
- Preclinical work in numerous models
  - Tox Study: LD_{50} for Sn-117m DOTA annexin V is 50X therapeutic dose
  - Locally delivered on electroplated **stents** in vascular lumen in animals
  - Exploratory development for use in **Alzheimer's Disease**
- Human clinical trials
  - >120 human subjects safely and effectively treated with Sn-117m DTPA in **bone metastases**
  - 15 human subjects safely treated with Sn-117m DOTA annexin V in **carotid artery disease**
- ***No local or systemic adverse events in animals or humans***
- Launching HTC for canine RSO in the US veterinary market 2019

Pre-Clinical RSO Rat Studies Summary

- Normal rats POC to demonstrate colloid joint retention at 5 $t_{1/2}$ (10 wks)
- Non-GLP OA
  - Dose escalation, toxicology, histopathology, metabolic, organ distribution, excretion, autoradiography, dosimetry, radiation field
- GLP OA
  - Same data collection as non-GLP study
- Non-GLP intentional mis-administration
  - Full dose deposited orally, cutaneously, injected subcutaneously and IV
- GLP radiotoxicology
  - 1X, 4X, 10X dose

Conclusions:

- HTC is safe (even in intentionally mis-administered high dose)
- HTC is retained in knee > 99% in properly administered injections
- Efficacy demonstrated in OA models
- No evidence of fibrosis on histopathology using proposed analogous human doses

Disease Modifying Agent

"Multiple histopathology meniscal tear model studies of osteoarthritis in male Lewis rats treated using radiosynoviorthesis (intra-articular injection) with homogeneous Sn-117m colloid (HTC) have been performed at Bolder BioPATH, Inc. We conclude that certain doses of HTC appear to show a ***disease modifying effect***."

Alison Bendele, DVM, PhD, DACVP
President/CEO, Bolder BioPATH

Dog RSO Studies

- Normal dogs—(n=5)
  - Data collected included: blood chemistry, PET/MRI, scintigraphy, histopathology, autoradiography, radiation excretion and radiation field
- Grade 1-2 elbow OA—(n=42 dogs, 43 elbows)
  - Testing: similar to above
- Grade 3 elbow OA—(n=15 dogs, 27 elbows)
  - Testing: similar to above
- Grade 1-3 elbow OA re-injection—(n=10 dogs, 20 elbows)
  - Testing: similar to above

Conclusions From Dog Trials

Safe (even in unintentionally mis-administered high dose) with no incidence of radio-necrosis in all dogs

Efficacious: significant improvement v. baseline

- **Canine Brief Pain Inventory:** response rates
  - 3mos—41%
  - 6mos—40%
  - 9mos—62%
  - 12mos—50%
- **Force Plate**
  - Significant improvement in >80% of treated dogs in at least one time point

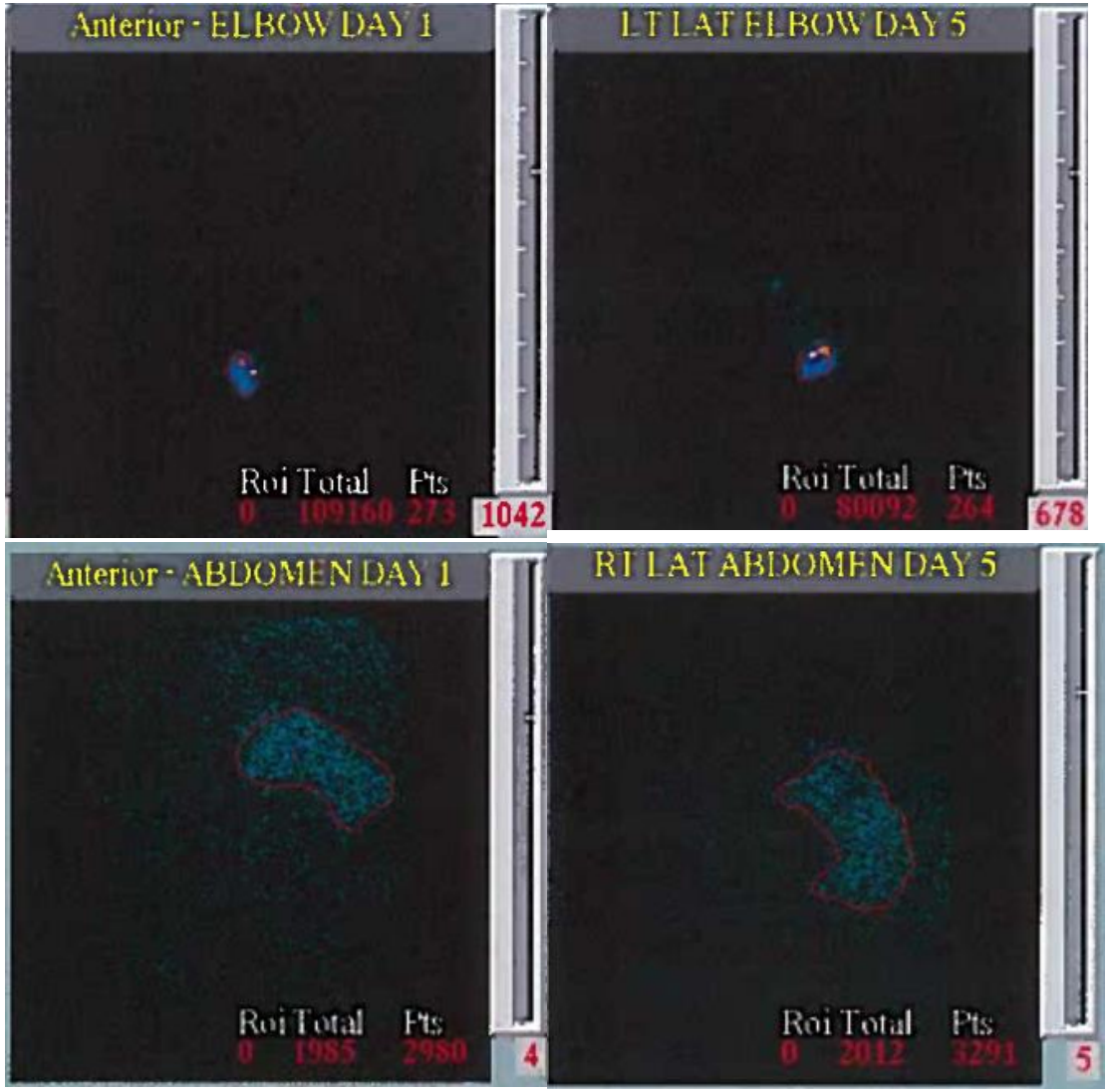
Conclusions From Dog Trials Cont.

- HTC is **retained in elbow > 99%**
- ***No evidence of fibrosis*** on histopathology of normal elbow at 6 weeks (3 half-lives) with high dose
- HTC is **completely phagocytosed by 2 weeks** (1 half-life) and distributed throughout synovium with no distribution to adjacent tissue
- **Radiation field is below NRC release criteria** immediately after administration
- Product preparing for **US veterinary launch 2019** using the medium dose

Example of Clinical Improvement After Injection--Baseline

Example of Clinical Improvement After Injection—6 Months

Example of HTC Distribution, Excretion and Radiation Field Data

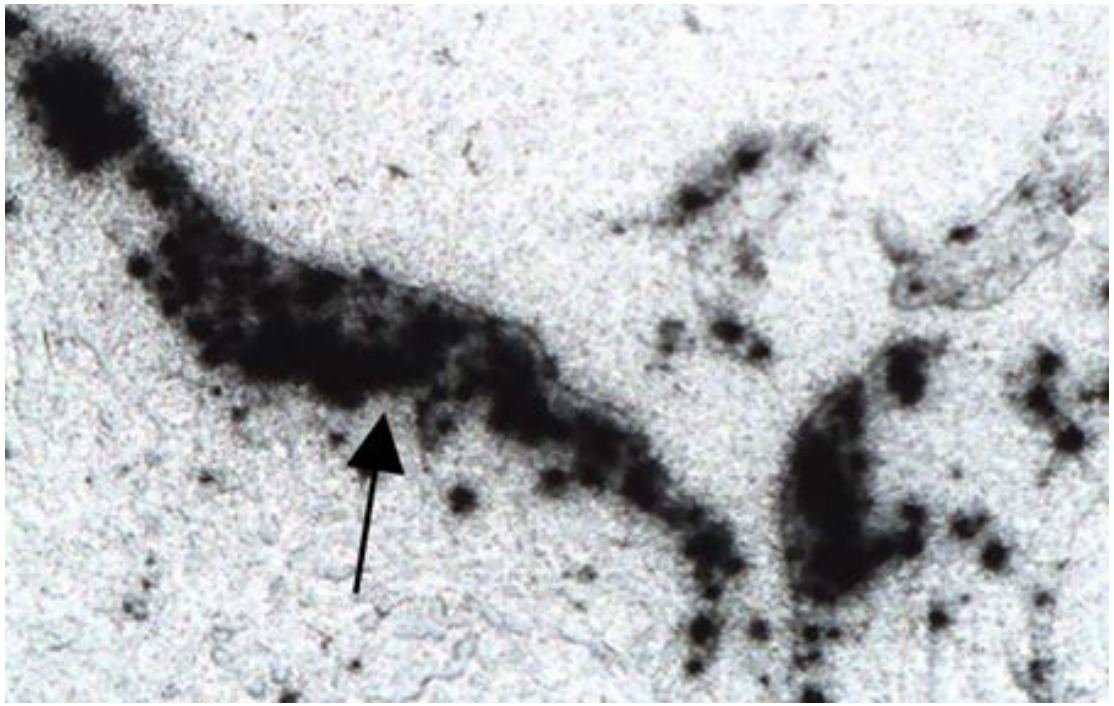


D15-57	3-Apr-	6-Apr-	7-Apr	8-Apr
Background	**1353**	**1260**	**1238**	**1274**
Blood	1294	1236	1240	1274
Background	**1353**	**1260**	**1238**	**1274**
Urine	1867		1849	1446
Background	**1353**	**1260**	**1238**	**1274**
Feces	1259	1205	1162	1252

Distance	8-Apr-15
1 Meter	155 µR/hr
Surface (2 in/5cm)	15.3 mR/hr

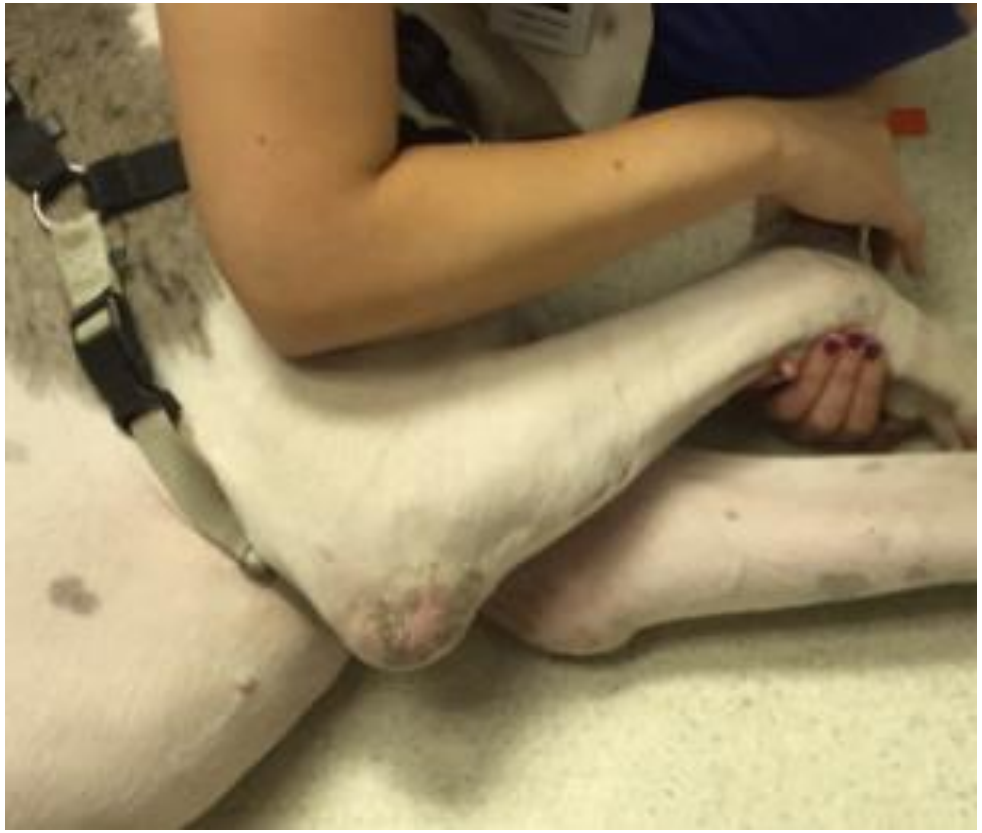
Gamma radiation field is well below typical release criteria of 500 µR/hr at 1m

Autoradiography Shows Migration Into Synovium



Autoradiography of normal canine elbow at ~ 3 half-lives shows macrophage distribution of the HTC throughout the synovium (arrow).

Examples of Larger Joints Treated



Positive response through 12 months

126 pound/57kg Newfoundland 2.04 mCi/75.5 MBq

Positive response through 3 months (died of volvulus)

148 pound/67kg Great Dane
3.7 mCi/137 MBq

Sn-117m Canadian Human Clinical Trial
Pilot Study of ^{117m}Sn Hydroxide Colloid for Radiosynoviorthesis in Refractory Arthritis of the Knee

Multicenter, Canada

Philip Cohen, MD

Lead Principal Investigator, Vancouver

RSO in a Knee

Study Objectives

Primary:

- Determination of which of the doses tested has an acceptable safety profile for randomized, controlled efficacy trials

Secondary:

- Assessment of safety of the HTC injected into the knee in patients with persistent or recurrent inflammatory arthritis or osteoarthritis

Exploratory:

- Efficacy assessments
- Determination of distribution of HTC within the joint

Pilot HTC RSO Trial in Knee Arthritis: Study Design
Initiate 3Q of 2019

- Stratified by type of arthritis (minimum of 12 and maximum of 24 OA)
- No concomitant corticosteroids
- No immobilization
- 3 at low (if no problems)→ 3 at medium (if no problems)→ 3 at high (if no problems)→ 1:1:1
- Endpoints:
  - Safety (evaluated at 26 weeks/13 half-lives follow up)
    - Retention of HTC in joint
    - No issues with laboratory, physical exam, concerning AE or toxicity
  - Efficacy (primary)
    - Decrease in mean 11-point Likert pain score over 1 week at evaluations
    - 2-point change in average pain compared to baseline
  - Efficacy (secondary)
    - Joint swelling
    - Pain index assessment
    - Changes in pain medication usage

Pilot HTC RSO Trial in Knee Arthritis: Inclusion

36 patients with at least one knee poorly controlled despite ≥6 months' adequate Rx.

Key Inclusion Criteria

- Knee RA, OA, or seronegative spondyloarthritis
- One knee > pain
- 1 week average Likert pain score ≥6 (on a basis of 0-10)
- Weight 50-120kg
- Patients with inflammatory arthritis must have synovitis on US

Pilot HTC RSO Trial in Knee Arthritis: Exclusion

Key Exclusion Criteria

- < 18 years of age
- Pregnancy or lactation
- Prior RSO, fracture, infection, Baker's Cyst
- Complete loss of joint space
- Other painful joints likely requiring change in medications within 3 months
- Current or recent infection or joint puncture
- 3 year prior history of cancer
- Major organ dysfunction, as defined in protocol, or major concomitant illness which may confound study results

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	53
^{117m}Sn scan (γ camera)		X	X		X					
Plain X-rays of both knees	X									
Ultrasound	X				X		X	X		X
Treatment (RSO)		X								

Fully funded trial: Sites and investigators paid, no cost to patient

Backup Slides

Canadian RSO Trial in Knee Arthritis Study Design (n=36)
Initiate 3Q of 2019