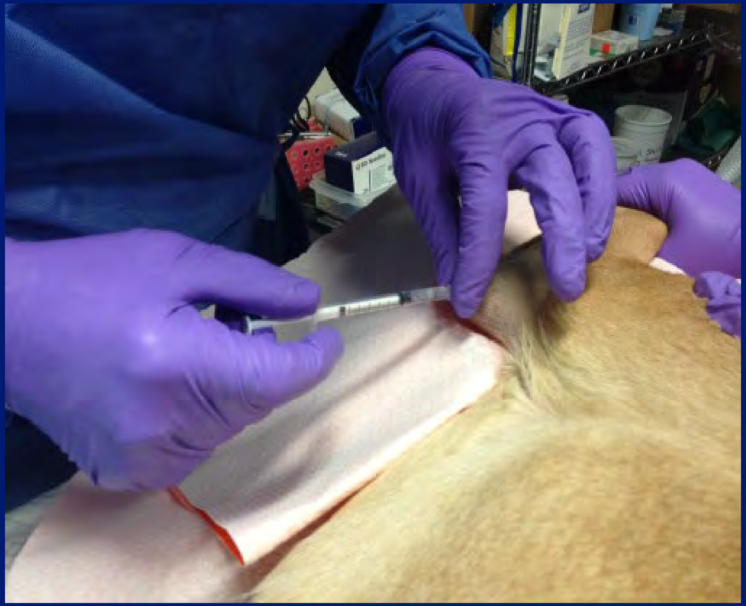
Synovitis and Radiosynoviorthesis

John M. Donecker, VMD, MS
Chief Veterinary Officer
Convetra, Inc.



Disclosures and Acknowledgements

Disclosures

Dr. J. Donecker is an employee of Convetra, Inc.
Dr. S. Fox is a consultant for Convetra, Inc.

Acknowledgements

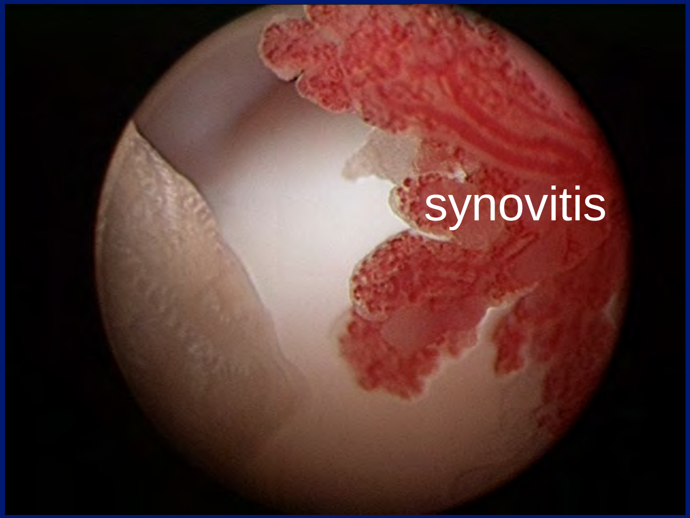
This presentation is based on 2 technical bulletins in which Drs. N. Stevenson, S. Fox and J. Donecker have contributed in association with Mark Dana of Scientific Communication Services, LLC

Usual approach to diagnosis and treatment of canine DJD*

- Clinical exam
- Radiographic assessment
- Conservative treatment with NSAIDs, corticosteroids, piprants
- Weight control
- Surgery, as required

Degenerative joint disease: Inclusive term for end-stage arthritides, including osteoarthritis (OA)

Synovitis – the initial, pre-radiographic event in DJD



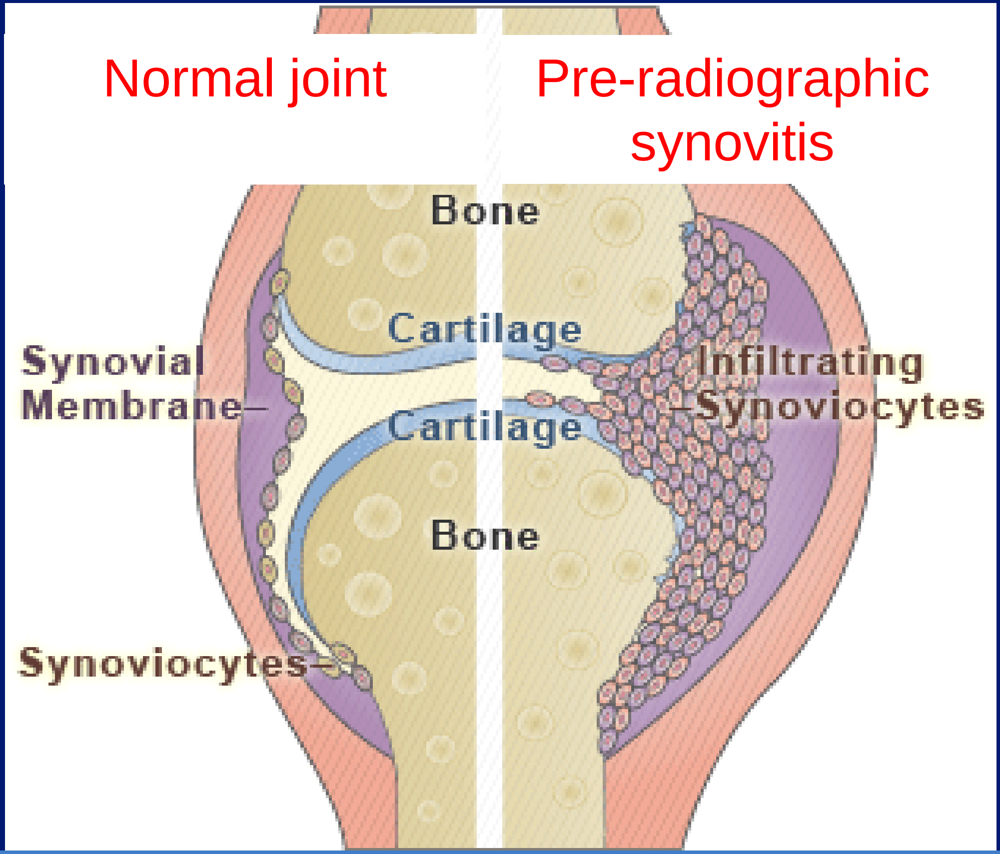
Arthroscopic view of a canine diarthroidial joint with early-onset DJD reveals robust synovitis and synovial hyperplasia, the initial event in the histopathology of DJD. (Photo, S. M. Fox, *Chronic Pain in Small Animal Medicine*, used with permission.)

- Clinical signs: synovial hyperplasia, joint swelling, pain, "morning stiffness"
- Present from earliest stages of DJD[1]
- Precedes development of OA[1-3]
- Early intervention can prevent, delay, or limit arthritic changes

1. Wenham CY, Conaghan PG. *Ther Adv Musculoskel Dis*. 2010;2:349-359.
2. Roemer FW, Guermazi A, Felson DT, et al. *Ann Rheum Dis*. 2011;70:1804-1809.
3. Atukorala I, Kwoh CK, Guermazi A, et al. *Ann Rheum Dis*. 2016;75:390-395.

The role of synovitis in DJD progression – effusion and hyperplasia

- *Left:* Normal joint synovium is 1-3 cells thick
- *Right:* Following joint injury, synovial effusion and hyperplasia precede arthritic changes



The role of synovitis in DJD progression – effusion and hyperplasia

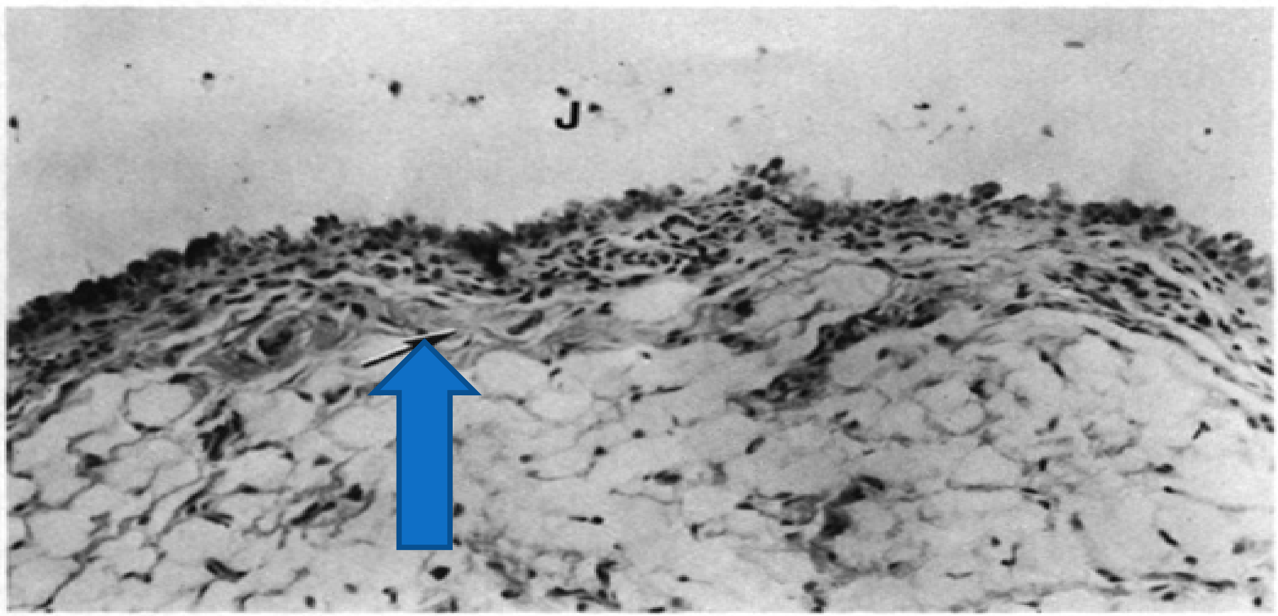
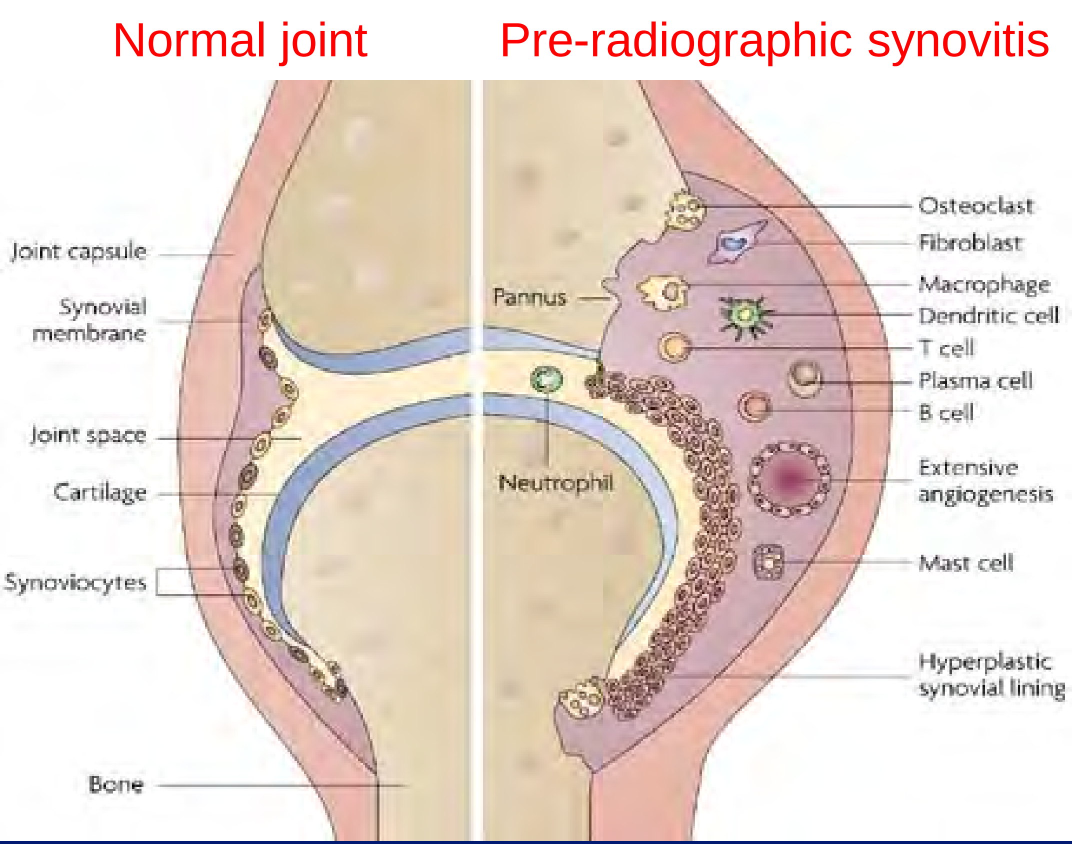


FIG. 87-4 Synovial membrane from the stifle of a dog in whom the cranial cruciate ligament was experimentally transected 8 weeks previously. The synoviocytic layer is 5 to 7 cells thick. Superficial cells are perpendicular rather than parallel with the joint space (*J*). Beginning fibrosis of the normal adipose sub-synovial tissues is apparent (*arrow*). (H & E × 60)

Slide courtesy of upenn

The role of synovitis in DJD progression – inflammatory cascade, angiogenesis

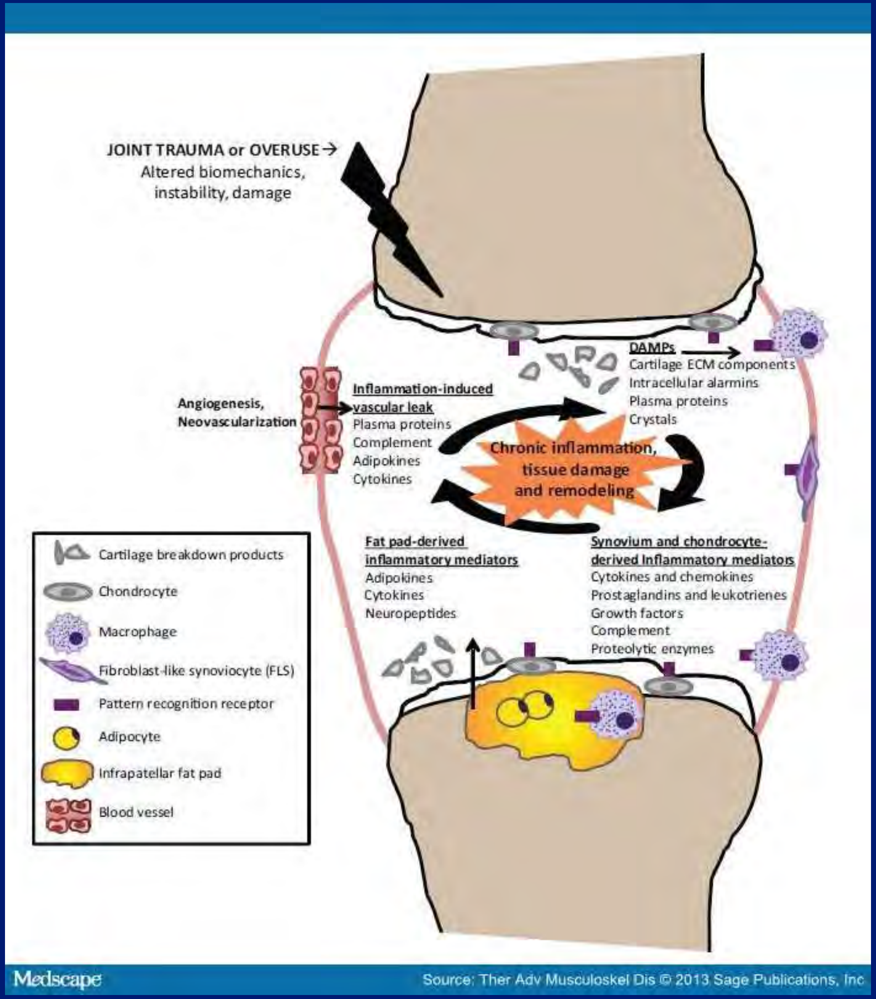
- *Right:* Early synovitis initiates intra-articular inflammatory cascade
- Macrophages, other pro-inflammatory cells are activated
- Synovial angiogenesis → edema, inflammatory cell infiltration



What is the role of angiogenesis? [4]

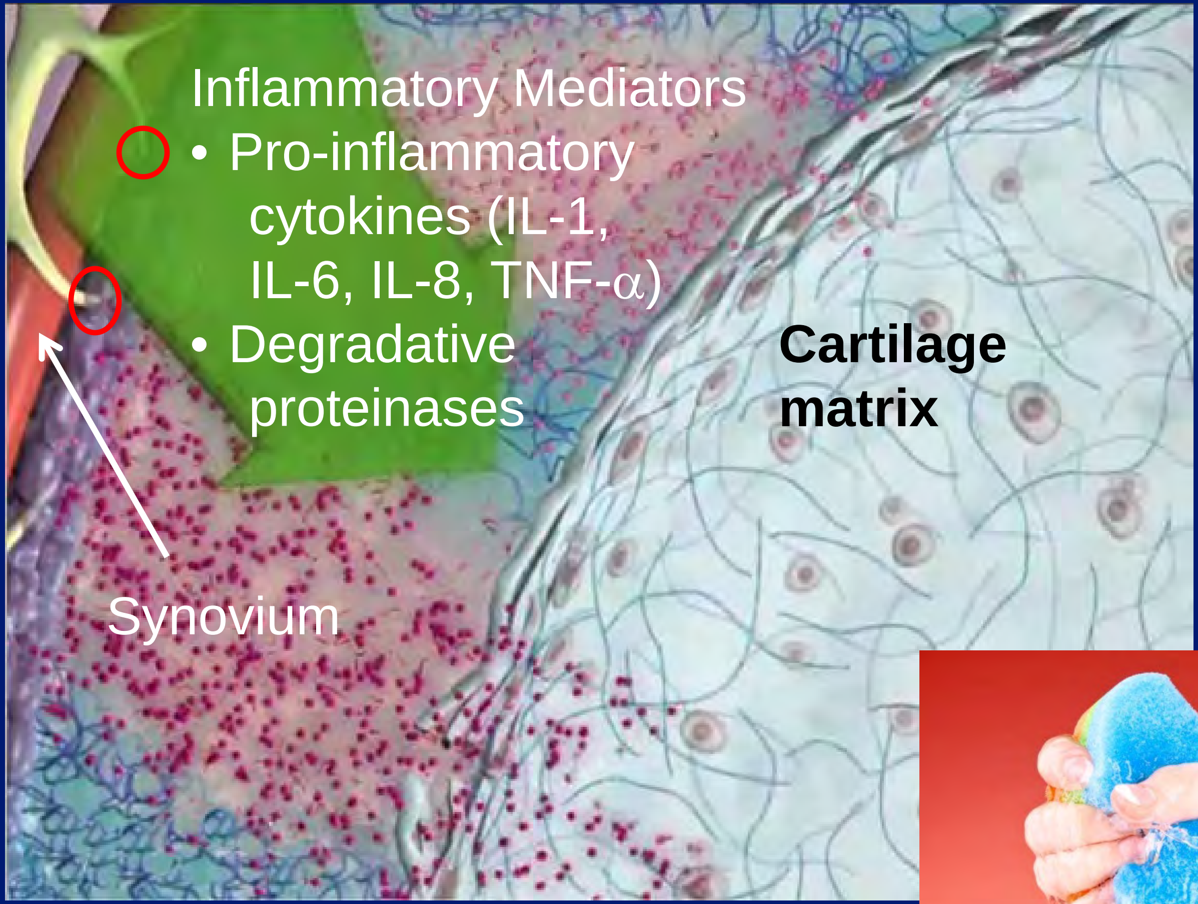
- May contribute to the progression of OA similar to the "angiogenic switch" in solid tumors including possible involvement of macrophage polarization

- ***HOWEVER***: precise mechanisms by which inhibition of angio-genesis reduces pain in animal models of OA are unknown, as is whether blocking the nerve growth associated with angio-genesis could provide sustained analgesia



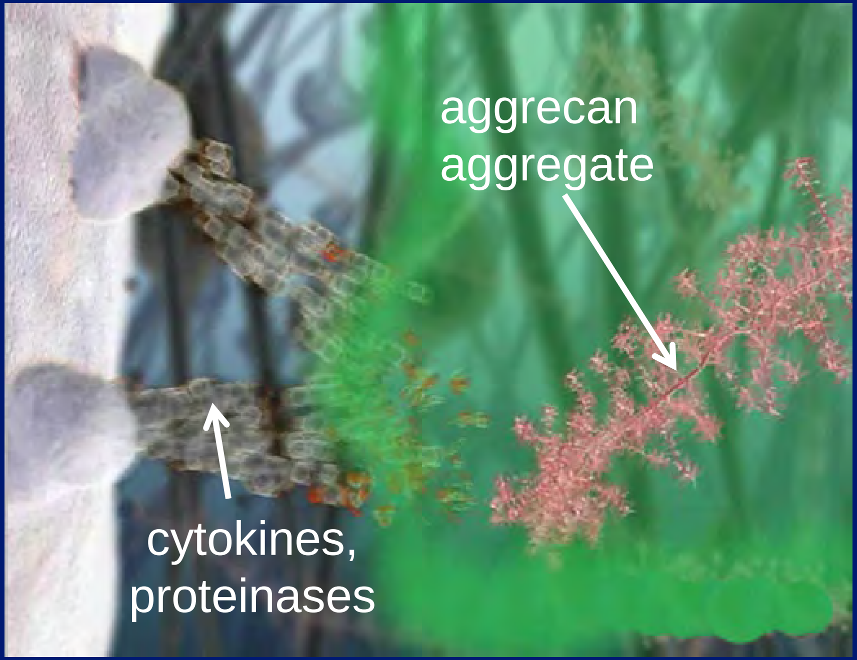
4. Paul I. Mapp and David A. Walsh; *Nat. Rev. Rheumatol*. 8, 390–398 (2012)

The sponge effect: Inflammatory mediators diffuse into cartilage matrix



Acting like a sponge, cartilage matrix assimilates and releases inflammatory mediators with normal joint loading and unloading

Effects of inflammatory cascade on cartilage



Pro-inflammatory cytokines and proteinases seek out and destroy cartilaginous aggrecan aggregates

Arthritic changes occur over time

Radiosynoviorthesis (RSO): A new therapy for veterinary use

What is it? Intra-articular injection of radioisotope (radionuclide) to treat joint inflammation

Medical history: Extensively used in human medicine since the 1960s
670,000 patients treated in EU 1990 - 2011[5]

Mode of action: Radionuclide is absorbed by synoviocytes and phagocytized by macrophages in synovium resulting in apoptosis and ablation of inflammatory cells

5. Kampen WU, EANM meeting presentation, Hamburg 2015

Radiosynoviorthesis: A long history of clinical use

- First used in Europe where European Assn of Nuclear Medicine (EANM) guidelines apply
- Accepted outpatient therapy for early stage RA, OA, and psoriatic arthritis[6-8]
- Effective in small as well as larger joints[7]
- Favorable cost-benefit ratio, low rate of adverse effects
- Often used in patients who have side effects to traditional first-line therapies (NSAIDs, corticosteroids, hyaluronate injections) or as part of multimodal approach

6. Kampen WU, Voth M, Pinkert J, et al. *Rheumatology*. 2007;46:16-24.
7. Karavida N, Notopoulos A. *Hippokratia.* 2010;14:22-27.
8. Klett R, Lange U, Haas H, et al. *Rheumatology*. 2007;46:1531-1537.

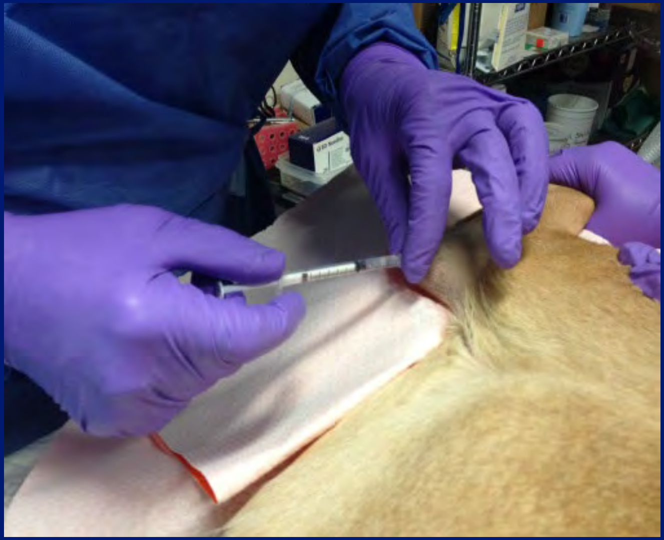
Radiosynoviorthesis (RSO): a long history of clinical use

- Three radionuclides widely used for RSO in human medicine:
  - yttrium-90 (^{90}Y)
  - erbium-169 (^{169}Er)
  - rhenium-186 (^{186}Re)
- Radionuclide absorbed by innermost layer of synovial membrane
- Radiation destroys inflamed cells
- Efficacious radionuclide must have:
  - Adequate half-life
  - Sufficient tissue penetration energy

Radiosynoviorthesis (RSO): a new therapy for veterinary use

Advantages:

- Minimally invasive
- Extended therapeutic benefit ensuring compliance
- Interrupts synovitis inflammatory cycle
- Potentially disease modifying therapy
- Inexpensive vs. surgery (e.g., joint replacement or repositioning)
- Avoids NSAIDs toxicity and corticosteroid side effects
- Suitable for multi-modal therapy
- Applicable for multiple joints



Disadvantages:

- Radioisotope handling training of personnel
- Facility radioactive material license (RAML)

Radionuclides used for radiosynoviorthesis[9]

Radionuclide	Half-life (days)	Max. energy (keV)	Max. tissue penetration (mm)	Therapeutic emission
yttrium-90	2.7	2,280	11.0	beta
rhenium-186	3.7	1,070	4.4	beta
erbium-169	9.4	350	1.1	beta
tin-117m	13.6	152	0.3	conversion electrons

Advantages of novel radionuclide tin-117m:

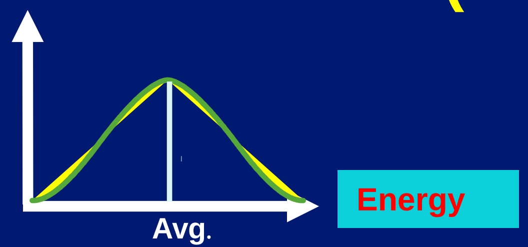
- *14-day half-life:* Long enough for therapeutic effect
- *Low-energy emissions:* Minimizes inadvertent tissue injury
- *Short, non-diminishing penetration in tissue:* Precise dosing, no effect on non-target tissues
- *Emits abundant conversion electrons:* vs. high-energy beta emissions with wide range of soft-tissue penetration

9. Brenner W. Radionuclide joint therapy. In: Eary JF, Brenner W, eds. *Nuclear Medicine Therapy*

Radiation energy comparison: conversion electrons vs. beta particles

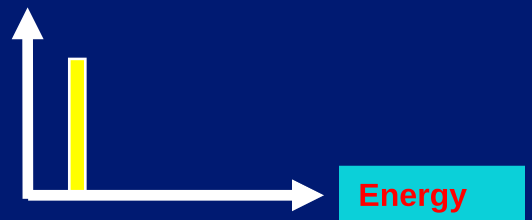
Emissions range in tissue (mm)

Beta Particles

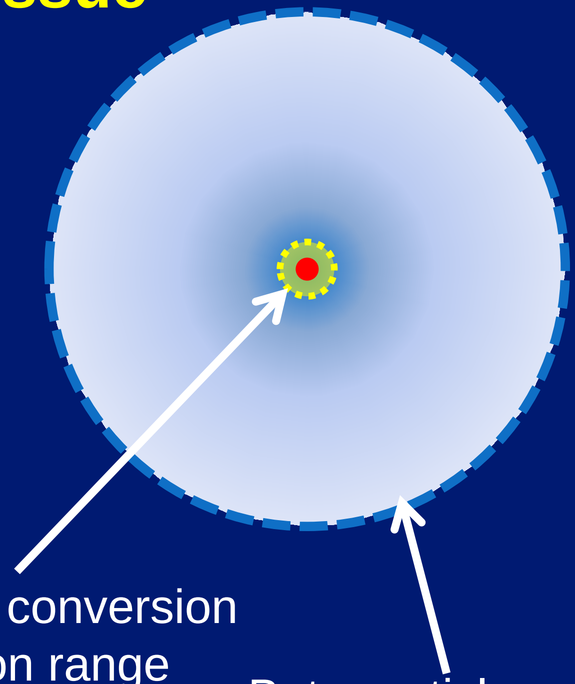


Produces a range of tissue penetration

Conversion Electrons



Penetrates to a set distance (discrete energy)

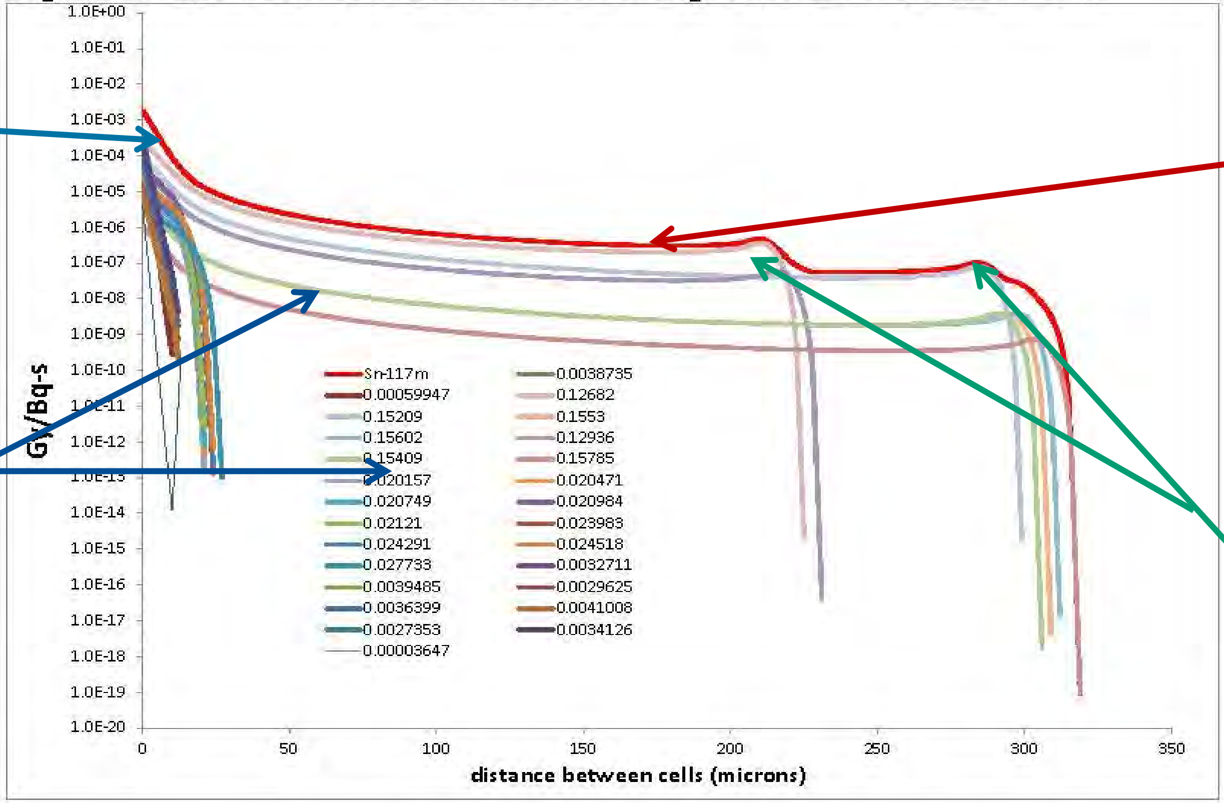


Tin-117m conversion electron range (0.3 mm)

Beta particle range (up to 11.0 mm)

Well-defined range of tin-117m in tissue

Figure 2. Tin-117m absorbed dose to a target cell from a source cell.



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.

Unique characteristics of tin-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

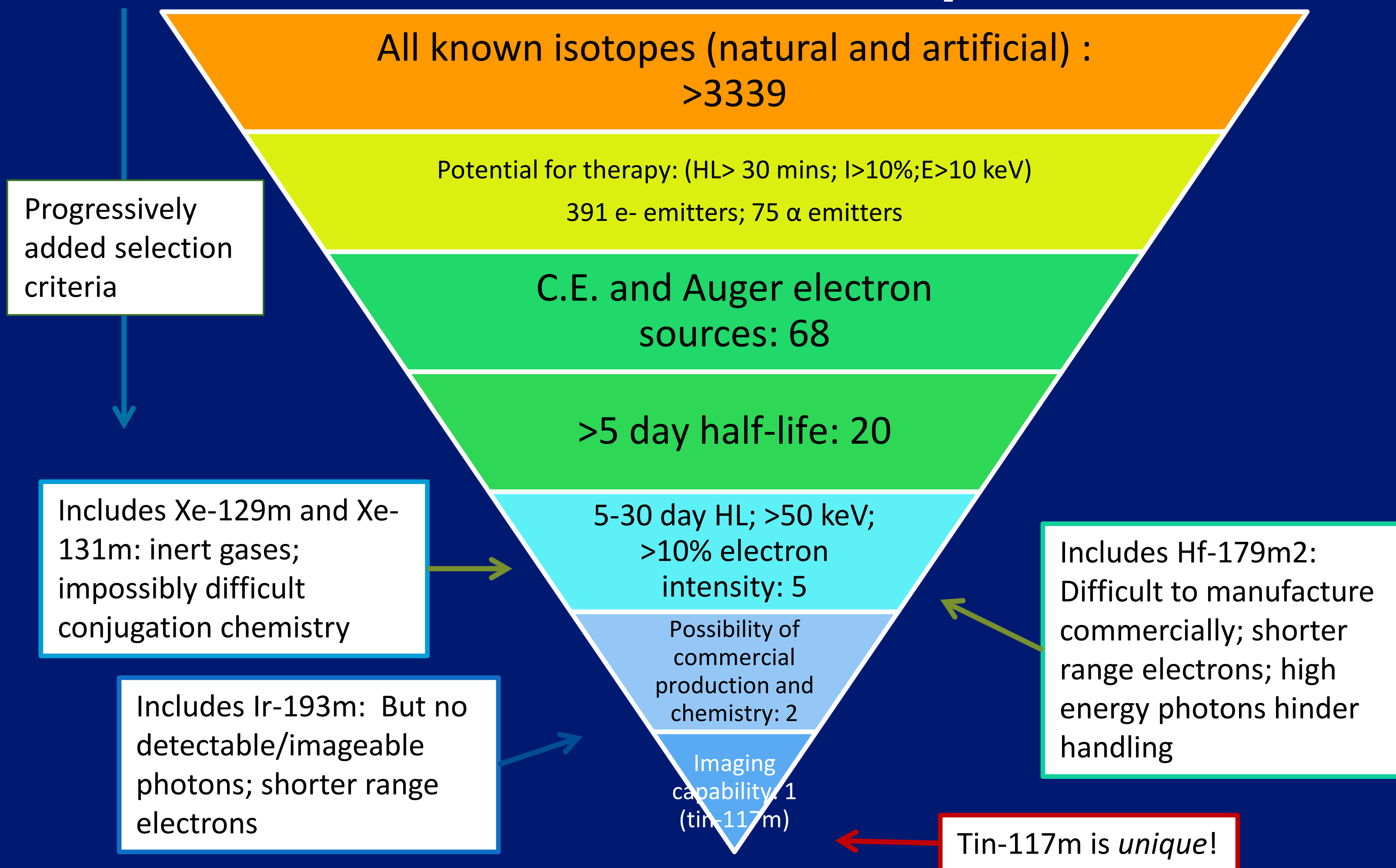
No High Energy Emissions

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

Radiation energy comparison: conversion electrons vs. beta particles

Conversion electrons	Beta particles
Therapeutic radionuclide: tin-117m (^{117m}Sn)	Therapeutic radionuclides: ^{90}Y, ^{169}Er, ^{186}Re
Low-energy	High energy
Short, discrete tissue penetration (0.3 mm)	Wide, variable tissue penetration (up to 11.0 mm)
Non-diminishing penetration range	Diminishing tissue penetration range
Relatively long half-life (13.6 days)	Relatively short half-life (2.7-9.4 days)
Enables precise dosimetry	Imprecise dose control
Ensures adequate duration of effect	Variable duration of effect

Tin-117m is *Unique*



No other isotope has the characteristics that are so ideally suited to our application

Production of tin-117m

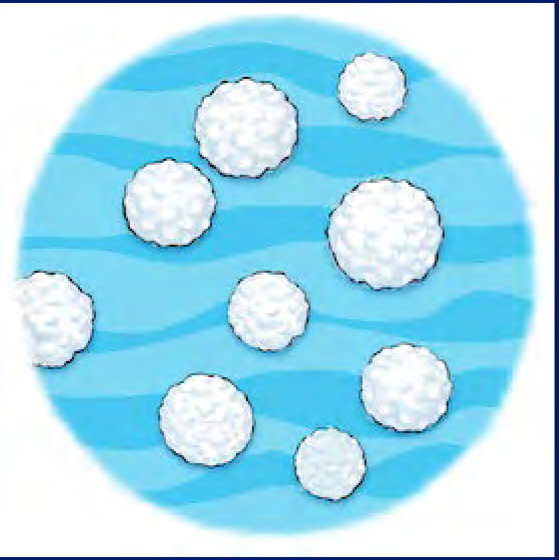
- Reactors
  - Large quantities
  - Low specific activity
  - Low Impurities
  - Suitable for colloids, electroplating, etc.

- Accelerators
  - Modest quantities
  - High specific activity
  - Low Impurities
  - Suitable for labeling molecules

What is a colloid?

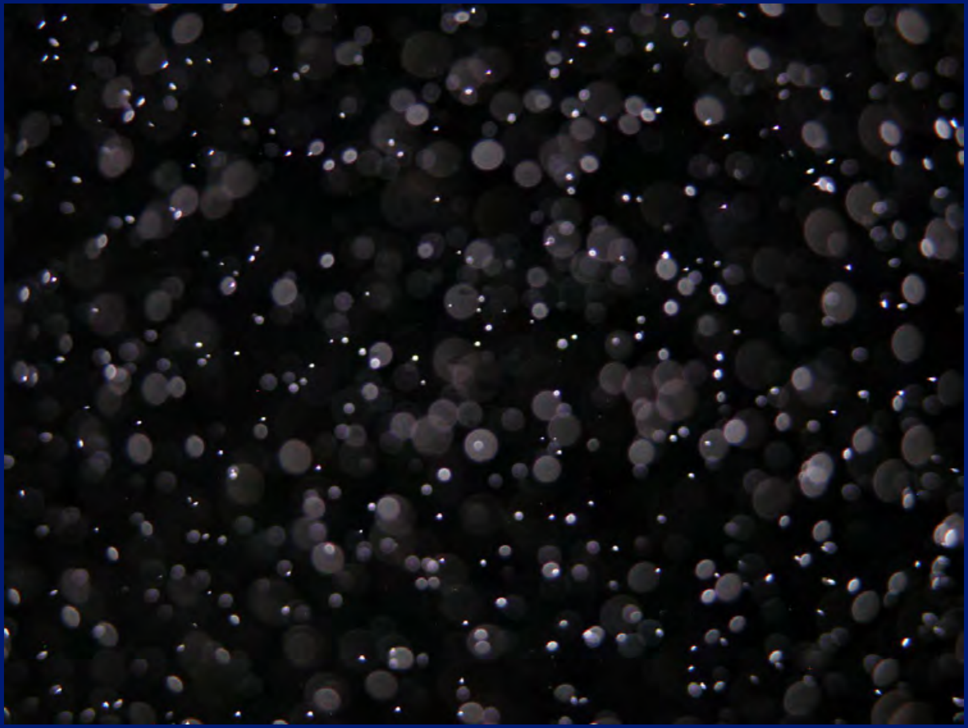
A colloid is a substance in which microscopically dispersed insoluble particles are suspended throughout another substance

Examples: milk, fog, butter, smoke, paint



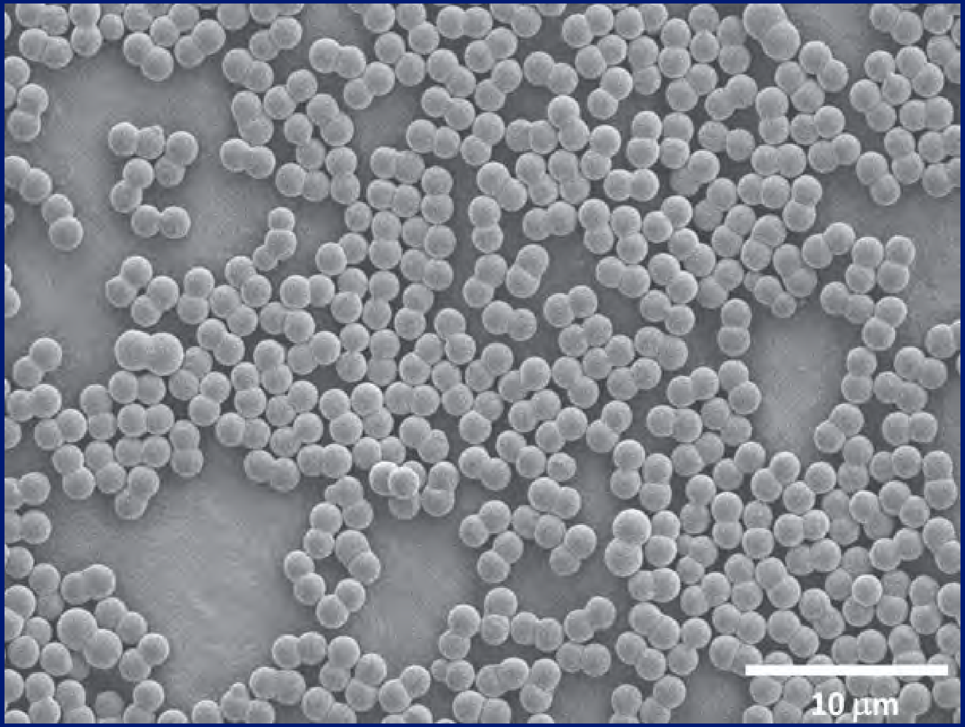
What is a heterogeneous colloid?

A colloid with a non-uniform distribution of particles
e.g. Fog



What is a homogenous colloid?

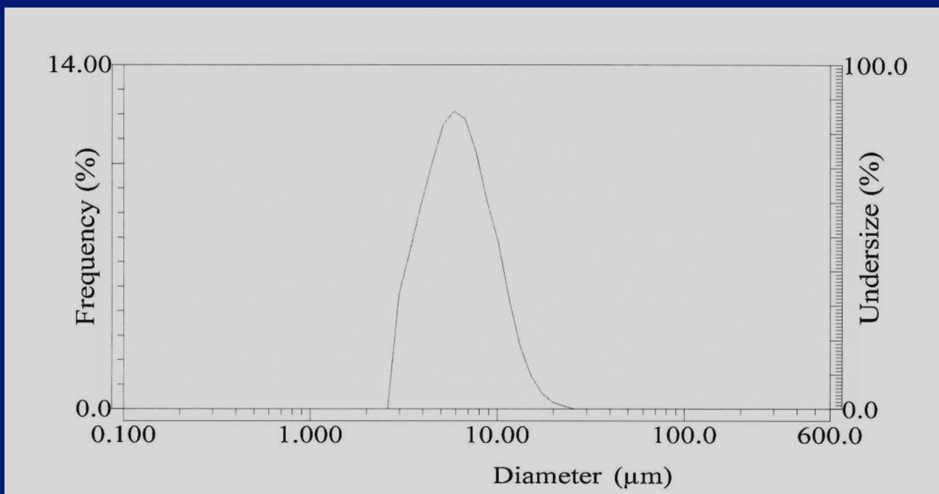
When a colloid forms under identical conditions (homogeneously) throughout a medium it has a very narrow range of sizes



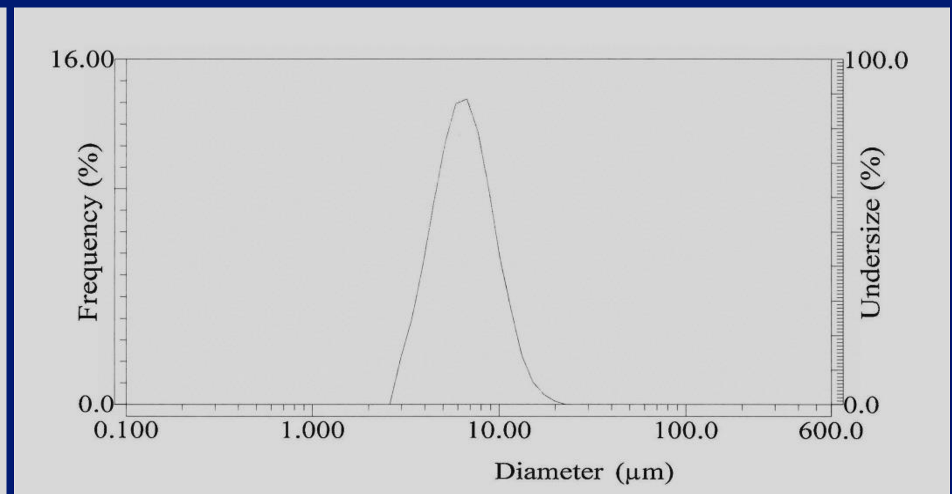
Tin-117m colloid

Retention of colloid in normal rat joint:

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



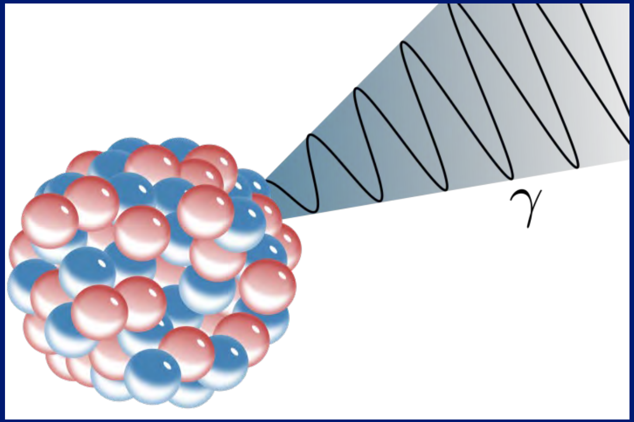
Stability studies – colloid size particle distribution at manufacture
Mean =6.28 μm SD=2.76 μm



Stability studies – colloid size particle distribution at 5 weeks in room temperature
Mean =6.43 μm SD=2.47 μm

Tin-117m diagnostic emission: gamma radiation

- Zero-mass quantum of light
- Emitted by *some* radionuclides, including tin-117m, technetium-99m
- Results from nuclear decay
- Non-therapeutic
- Readily detectable in tissue by imaging
- Relevance: Enables diagnostic monitoring of response to RSO, disease staging
- Comparable to diagnostic radionuclide technetium-99m



Tin-117m and technetium-99m are both gamma-emitting diagnostic radionuclides. Post-treatment scintigraphy can confirm location of injection material

Synovetin OA™: a homogenous colloid suspension of tin-117m (HTC)

Mode of action:

- Emits discrete (0.3 mm radiation range), low-energy conversion electron radiation

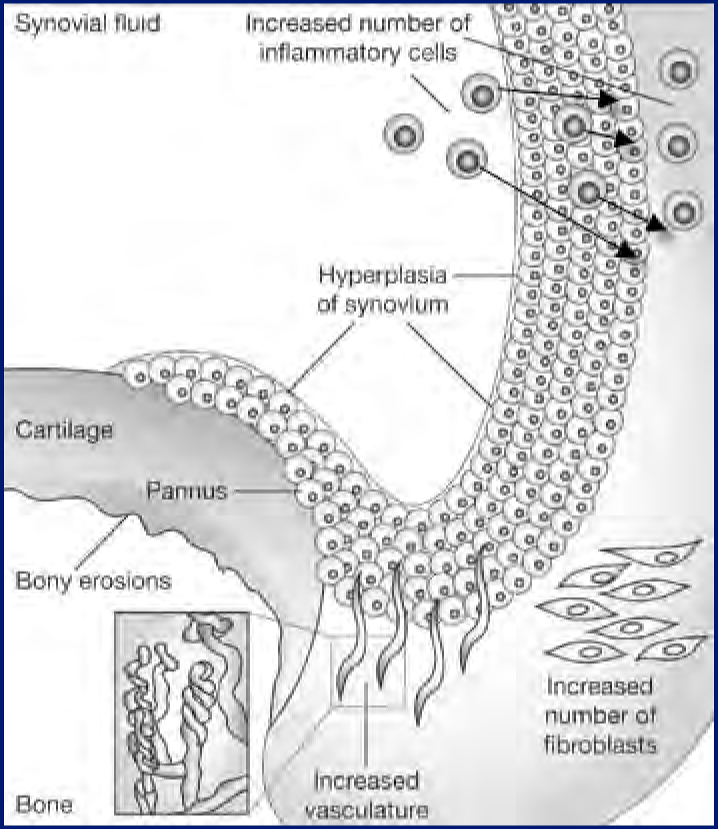
- Colloid containing micro particles retained in joint space for at least 42 days (3 half-lives)

- Particles absorbed by synoviocytes and macrophages reducing pain and swelling

Scintigraphy of an HTC injected canine elbow shows >99% retention in synovial tissue, indicating a continuous therapeutic effect consistent with the 14-day half-life of tin-117m. (Image courtesy of Jimmy Lattimer, DVM.)

Proposed disease modifying effects of homogenous tin colloid (Synovetin OA™)

- Pro-inflammatory macrophages recruited during synovial hyperplasia engulf colloid embedded tin-117m particles
- Phagocytized tin-117m is transported to synovium and held *in situ*
- Conversion electrons destroy macrophages responsible for inflammation
- Synovium more closely resembles the pre-inflammatory state post treatment



Proof of concept: University of Missouri canine elbow safety study

Objectives:

- Assess distribution of HTC in the normal canine elbow joint synovium
- Assess treatment-related histopathology in synovium or non-synovial tissue

Investigators:

- Dr. Jimmy Lattimer DVM, MS
  Diplomate ACVR
- Dr. Kim Selting DVM, MS
  Diplomate ACVIM

Trial design

- Prior GLP OA rat trials determined approximate dosage (1.0-2.5 mCi) for canine elbows
- GLP Safety trial in 5 normal purpose bred hounds (50 lb.)
- Highest anticipated dosage (2.5 mCi)
- Followed to 3 $t_{1/2}$ (March-May, 2015)
- Data collected included:
  - Histopathology, PET/MRI, x-ray, excretion, distribution, autoradiography, dosimetry, synovial fluid analyses, physical examinations, radiation field

Normal canine elbow study: results

Top autoradiograph (dog 1):

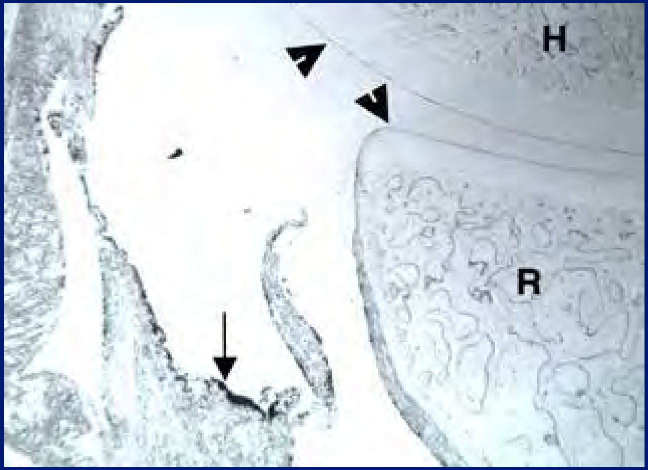
- Normal cartilage (arrowheads) of humerus (H) and proximal radius (R)
- Uptake of HTC by macrophages in inflamed area of synovium (arrow), 16x

Bottom autoradiograph (dog 1):

- Synovium and sub-synovium showing uptake of HTC by macrophages (arrow), 100x

Interpretations:

- Synovitis precedes radiographic arthritic changes (top)
- Inflammatory synovial macrophages phagocytize and distribute HTC evenly throughout the synovium (bottom)



Normal canine elbow study: results

Top histopathology slide (dog 2):

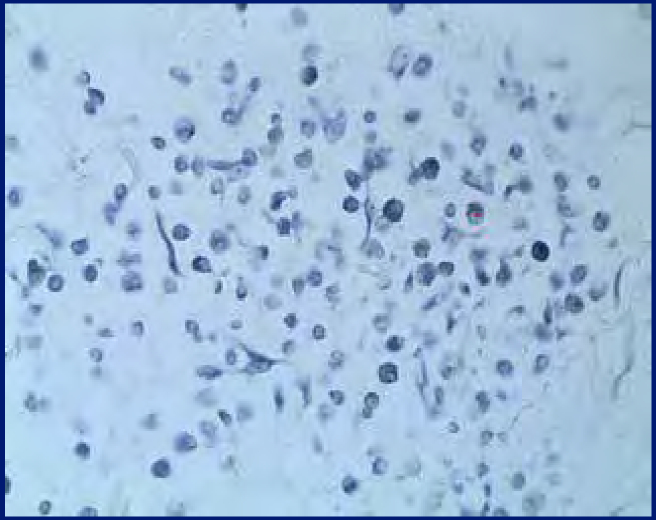
- Inflammatory cells from synovium

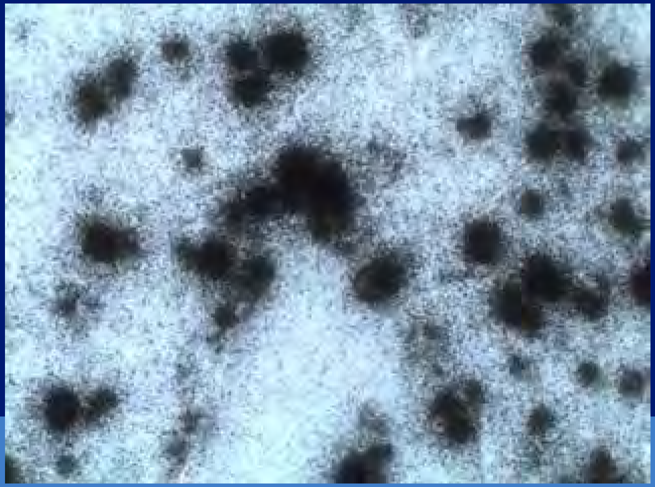
Bottom autoradiograph (dog 2):

- HTC particles phagocytized by macrophages below synovial surface, 400x

Interpretation:

- Pro-inflammatory macrophages were recruited to site of synovial inflammation (top)
- Intra-articular injection results in uptake of HTC by inflammatory cells at target site (bottom)





Normal canine elbow study: results

Top histopathology slide (dog 1):

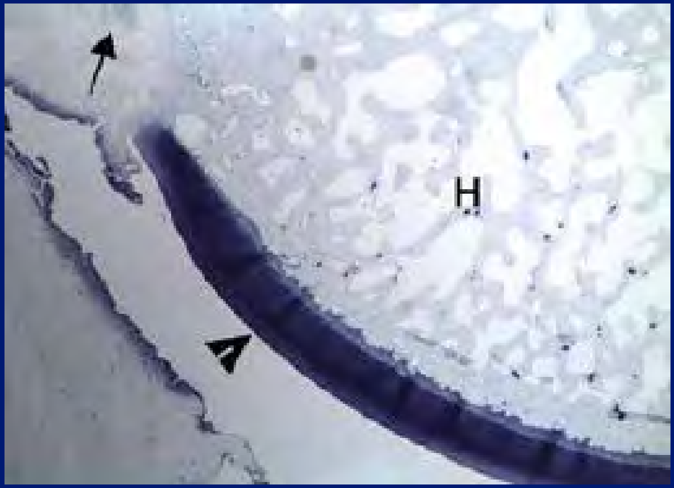
- inflammatory cells (arrow) below synovial surface
- normal articular cartilage (arrowhead) of humerus (H), 16x

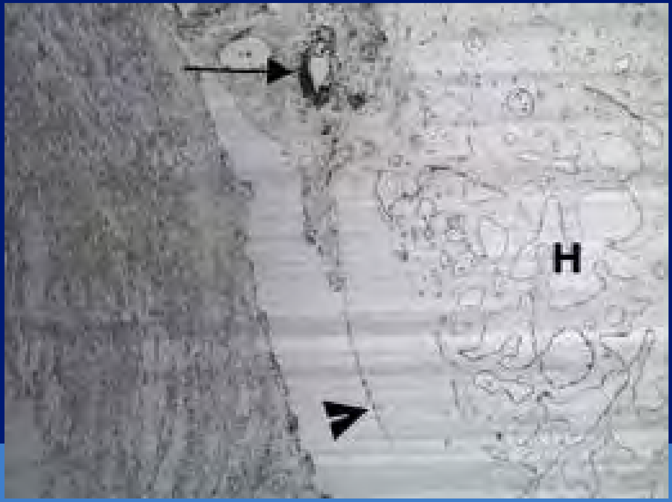
Bottom autoradiograph (dog 1):

- HTC particles phagocytized by sub-synovial macrophages (arrow)
- normal articular cartilage of humerus (arrowhead), 400x

Interpretation:

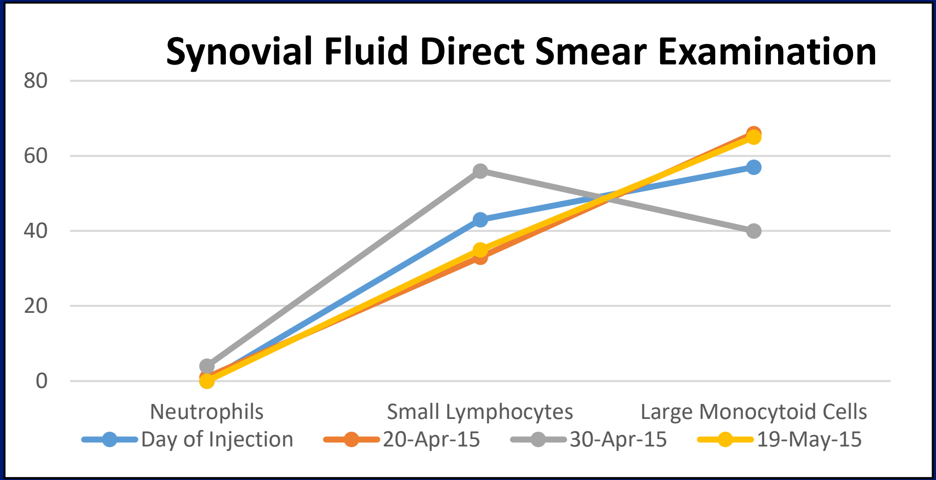
- no histopathology in non-target tissue (top)
- intra-articular injection of HTC results in uptake of tin-117m by inflammatory cells at target site (bottom)

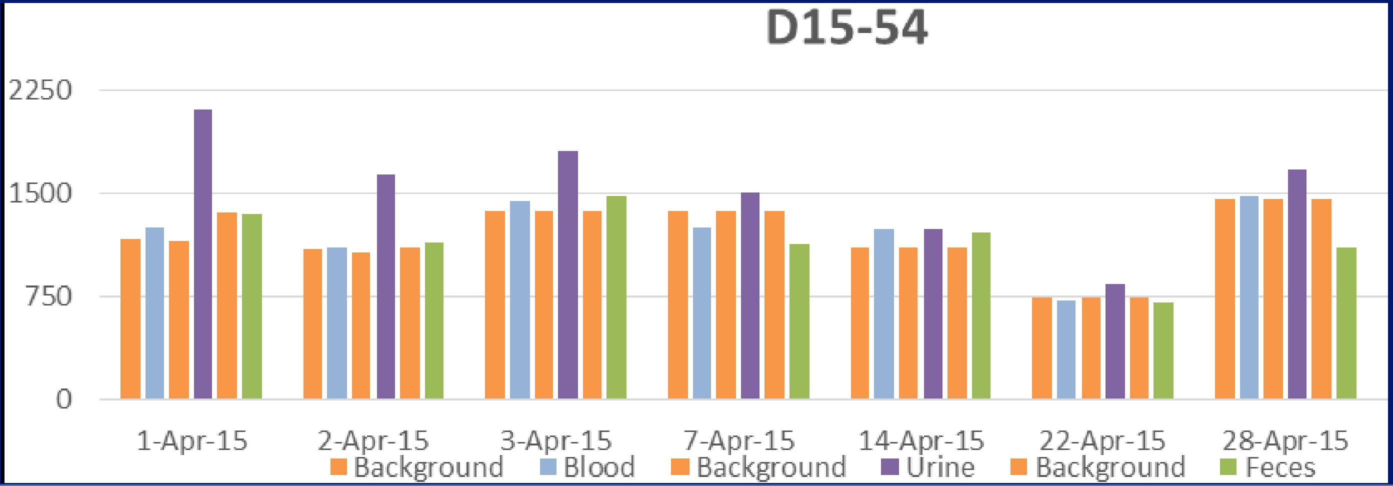




Bio distribution – fluids/excreta

- Urine, blood and fecal samples were taken from each dog for several weeks after injection
- Radioactivity in the samples was measured using a solid NaI detector. Background and back-decay corrections
- Efficiency and sample size corrections applied

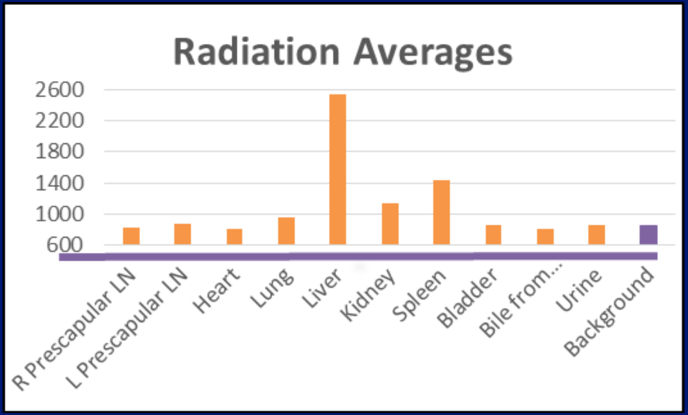




- Synovial fluid @ 6 weeks had < 1% of initial colloid content - majority had been incorporated into the synovial membrane

Bio distribution - organs

- Tissue/fluid samples were counted on a NaI crystal attached to a multichannel analyzer for 20 seconds. Background subtracted and back-decayed
- Detector efficiency and sample size corrections applied

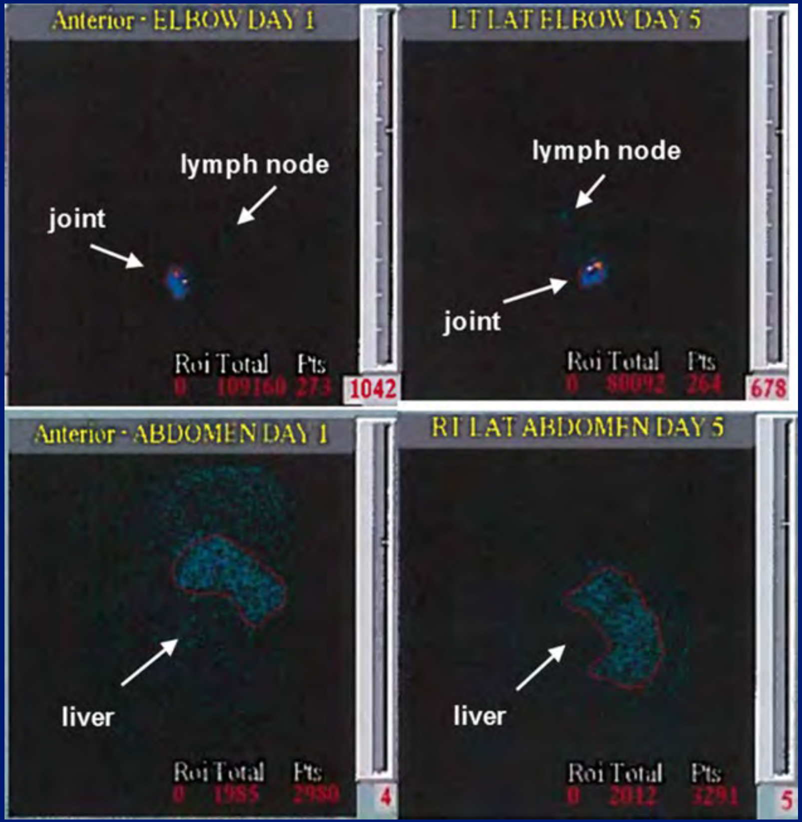


Dog Number	% in Organs	% in blood, urine and feces	% Left at site of injection
971227	0.40	0.10	99.50
973246	1.13	0.05	98.82
972916	1.39	0.05	98.56
968676	0.50	0.07	99.43
970824	0.75	0.06	99.19

- Injected elbow joint retained almost all of the activity (**99.1%**) (confirmed by direct measurements)

Retention

- Retention = 99.1%
  (Despite multiple synovial punctures during the 42 days of the study)
- External radiation fields immediately after 2.5 mCi inj.
  - Surface˜20 mR/hr*
  - @1 m˜330 µR/hr
- Agrees with Monte Carlo modeling (R. Wendt)
- Typical animal release criteria:
  - Field @ 1m < 500 µR/hr
  - Excreta low (exempt = 27 µCi)



* Use of a shielded syringe recommended to reduce hand dose during procedure

Post-treatment tin-117m radiation exposure risk

M. D. Anderson Cancer Center dosimetry modeling:

- Evaluated external radiation exposure following normal canine elbow joint administration
- Confirmed no post-procedure risk of tin-117m contamination of premises, clinic personnel or pet owner[9]

No post-procedure confinement:

- No post-treatment confinement indicated
- Dogs safely released as outpatients or returned to general clinic population

9. Wendt RE, *MD Anderson Cancer Center Report*, Oct. 1, 2015

48 client owned dog 12 month efficacy study

- *3 clinical sites*
  - University of Missouri CVM
    (principal investigator: Dr. Lattimer)
  - Louisiana State University SVM
    (Drs. Aulakh and Gaschen)
  - Gulf Coast Veterinary Specialists (Drs. Fabiani, Hudson and Beale)

- *Facility requirements*
  - Radioactive material license to include Sn 117m (State or NRC)
  - Dose calibrator
  - Ludlum dosimeter
  - Magnetic stirrer

- *Inclusion criteria*
  - Radiographic grade 1 or 2 elbow OA with documentable lameness
  - dogs > 8 kg and 1 yo
  - No comorbid condition that may preclude survival for 1 year

48 client owned dog 12 month efficacy study sampling

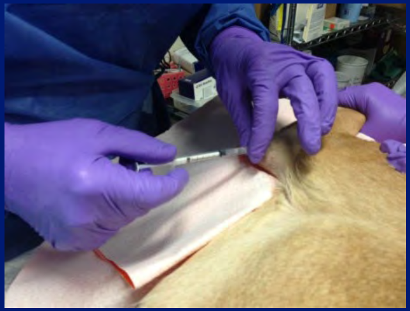
Client-owned dogs schedule

	Prior to Tx	Day of Tx	Day 1 post	Days 2/3/4/5 if in rad. iso.	1mo	3mo	4mo phone call	5mo phone call	6mo	7mo phone call	8mo phone call	9mo	10mo phone call	11mo phone call	12mo
blood															
CBC	x				x	x			x			x			x
radiation dosimetry sample(s)			x	x/x/x/x											
chemistry	x				x	x			x			x			x
Urine															
radiation dosimetry sample(s)			x	x/x/x/x											
UA	x				x	x			x			x			x
feces															
radiation dosimetry sample(s)			x	x/x/x/x											
Elbow															
radiation dosimetry			x	x/x/x/x											
Joint fluid															
analysis		x			x	x			x			x			x
Imaging															
x-ray (orthogonal both)	x	x			x	x			x			x			x
CT scan		x			x	x			x			x			x
MRI		x			x	x			x			x			x
scintigraphy (lat elb/thx/abd)			x last day in iso.												
Lameness evaluation															
force plate analysis	x				x	x			x			x			x
owner CBPI	x				x	x	x	x	x	x	x	x	x	x	x
clinician CPS	x				x	x			x			x			x
elbow ROM	x				x	x			x			x			x
limb circumference	x				x	x			x			x			x
video w&tr	x				x	x			x			x			x
medication / lameness log	Throughout the study as indicated														

Synovetin OA™: a safe and effective RSO radionuclide

- Low-energy conversion electrons have limited, discrete emission depth corresponding to synovium thickness
- Half-life long enough to provide reasonable shelf life and therapeutic effect
- Homogenous colloid binds tin-117m so it cannot escape the joint
- Suitable colloid particle size for synovial phagocytosis and *in situ* retention
- Gamma emissions for diagnostic imaging
- Clinical profile demonstrating high degree of safety, efficacy

Comparing Synovetin OA™ with iodine-131



Comparison	Tin-117m	Iodine-131
Indication	OA	Feline hyperthyroidism
Administration	Local device	Systemic drug
Radionuclide distribution	Intra-articular	Systemic
Isolation	Not required	Required

Key points

- DJD is not a single entity but a series of events resulting in joint pain
- Synovitis is the initial, pre-radiographic event leading to OA
- Early intervention to treat synovitis may prevent, delay or limit the extent of arthritic changes
- Synovetin OA™, a homogenous colloid of the novel radionuclide tin-117m, is a device designed for intra-articular administration of dogs to treat synovial pain and inflammation
- Synovetin OA™ is phagocytized by macrophages in the synovial membrane, resulting in apoptosis and ablation of inflammatory cells

Key points

- Synovetin OA™ potentially has a disease-modifying effect (already shown in laboratory rats) by reversing the inflammatory, hyperplastic effect of synovitis
- A University of Missouri study confirmed that Synovetin OA™ injected into normal canine elbow joints is phagocytized by inflammatory macrophages in the synovium without affecting adjacent tissues
- The targeted effect of Synovetin OA™ differs from NSAIDs and corticosteroids, avoiding the toxicities and side effects of these traditional, first-line therapies
- Synovetin OA™ has a different MOA than NSAIDs and piprants, allowing it to be used as co-therapy with these drug classes, sodium hyaluronate and with corticosteroids as part of a multimodal approach to treat DJD

Question:
How will this option impact your practice?

J Donecker contact information:
jdonecker@r-nav.com
1(336) 552 - 6027