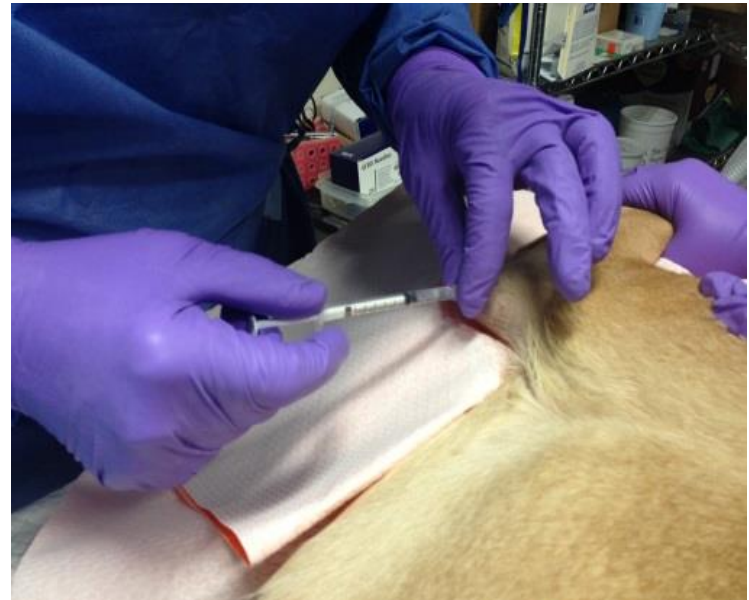


Synovetin OA™

Results of Clinical Trials Using a Homogeneous Tin Colloid for Treatment of Elbow Osteoarthritis

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Chief Veterinary Officer
Convetra, Inc.



Disclosures and Acknowledgements

Disclosures:

Dr. J. Donecker is an employee of Convetra, Inc.

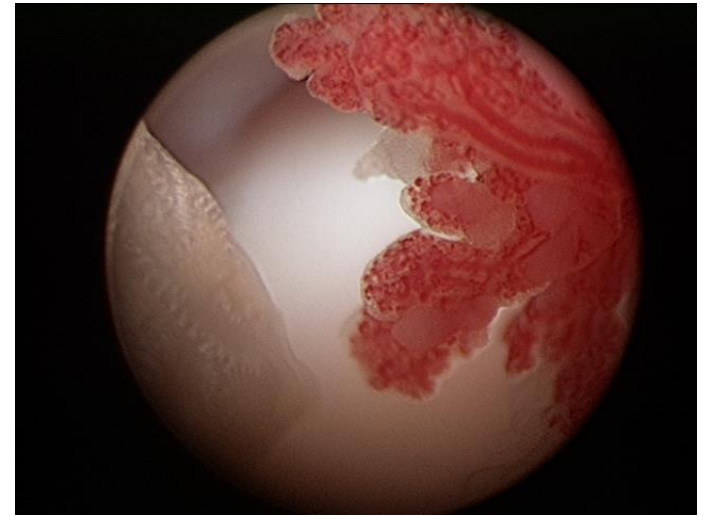
Dr. S. Fox is a consultant for Convetra, Inc.

Acknowledgements:

This presentation is a compilation of clinical research conducted at the University of Missouri College of Veterinary Medicine, Louisiana State University School of Veterinary Medicine, Gulf Coast Veterinary Specialists (Houston, TX) and by consultants at the University of Texas MD Anderson Cancer Center (Houston, TX) and Isotherapeutics Inc. (Angleton, TX)

Synovitis – The Initial, Pre-Radiographic Event in DJD

- Clinical signs: synovial hyperplasia, joint swelling, pain, “morning stiffness”
- Present from earliest stages of DJD¹
- Precedes development of OA¹⁻³
- Early intervention can prevent, delay, or limit arthritic changes (DJD modifier)

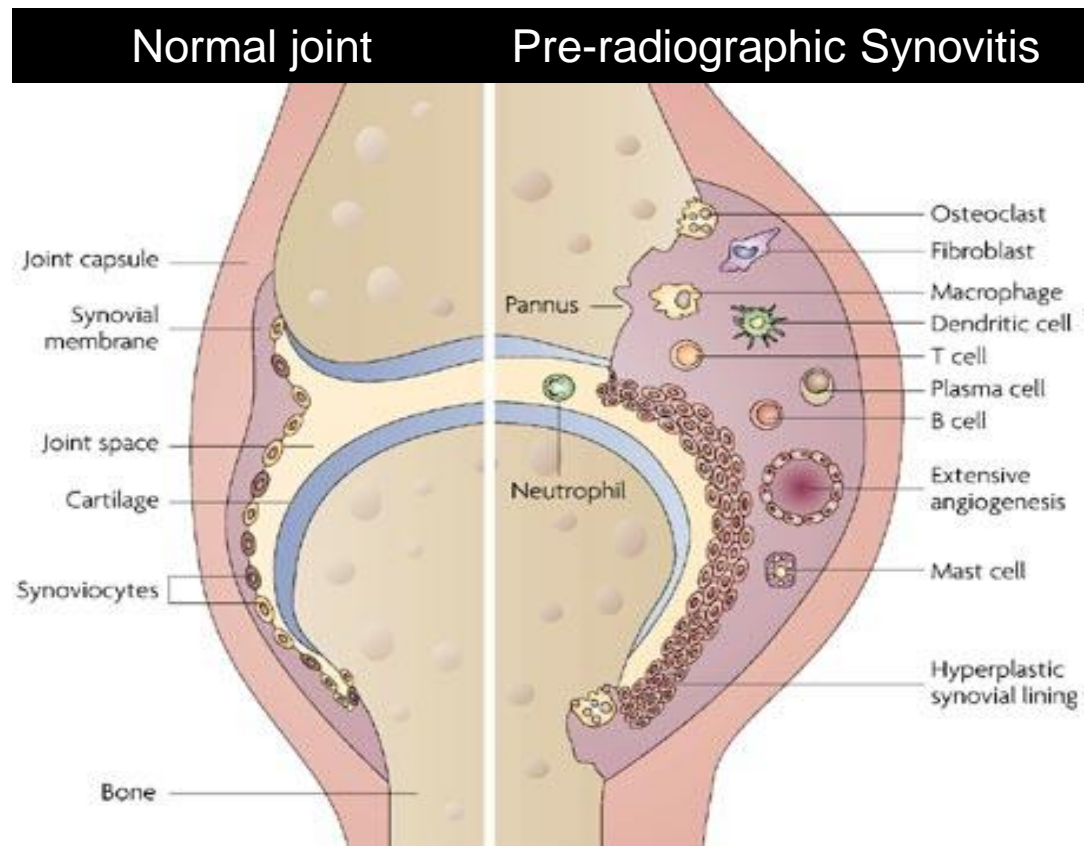


Arthroscopic view of a canine diarthroidal joint with early-onset DJD reveals robust synovitis and synovial hyperplasia, the initial event in the histopathology of DJD. (Photo, S. M. Fox, *Chronic Pain in Small Animal Medicine*, used with permission.)

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, Kwok CK, Guermazi A, et al. *Ann Rheum Dis.* 2016;75:390-395.

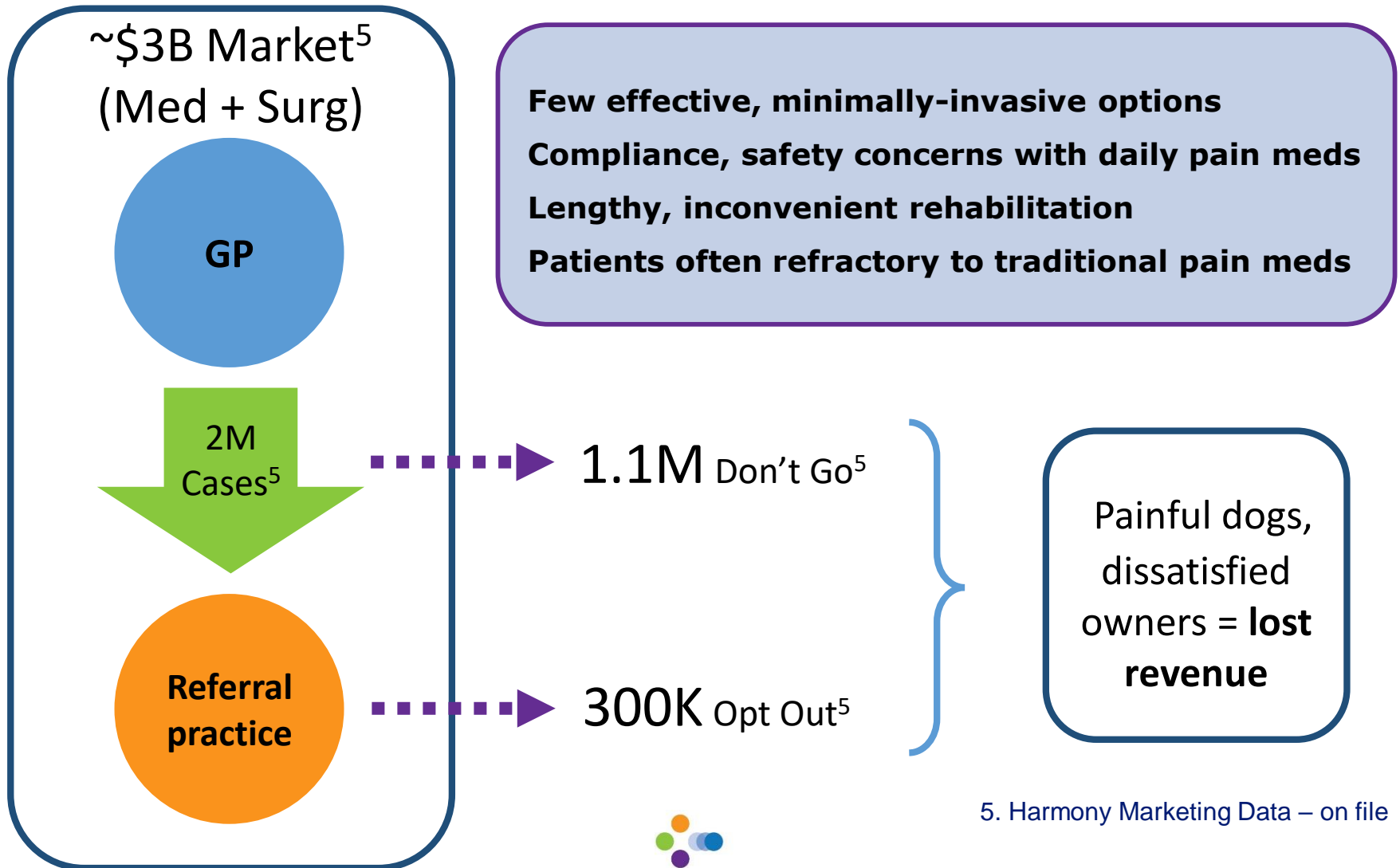
The Role of Synovitis in DJD Progression – Inflammatory Cascade, Angiogenesis

- Right: Early synovitis initiates intra-articular inflammatory cascade
- Macrophages, other pro-inflammatory cells are activated
- Synovial angiogenesis → edema, inflammatory cell infiltration⁴



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

Canine Pain Management



5. Harmony Marketing Data – on file

Synovetin OA™: A Device Containing HTC

- 6+ month duration of action
- Device designation
- Intra-articular (IA) mode of administration
- Low energy conversion electron radiation



Scintigraphy of an HTC injected canine elbow shows >99% retention in synovial tissue (Image courtesy of Jimmy Lattimer, DVM.)

Synovetin OA™: A Homogenous Colloid Suspension of Tin-177m

Mode of action (MOA):

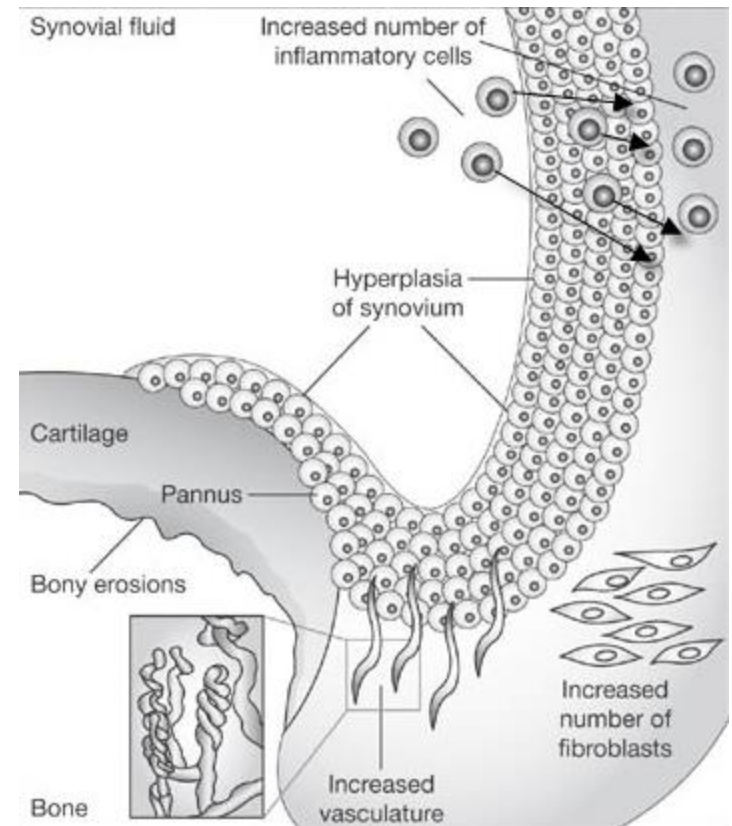
- Emits discrete low-energy conversion electron emission (0.3 mm radiation range),
- Colloid containing micro particles retained in joint space for at least 42 days (3 half-lives)
- Particles absorbed by synoviocytes and macrophages reducing pain and swelling



Scintigraphy of an HTC injected canine elbow shows >99% retention in synovial tissue (Image courtesy of Jimmy Lattimer, DVM.)

OA Disease Modifying Effects of 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 electron emissions destroy macrophages responsible for inflammation (apoptosis)
- Synovium more closely resembles the pre-inflammatory state post treatment



Preclinical Studies Trialing Synovetin OA™

Tin-117m clinical trials					
Rodents					
Study Name	Study Number	Experiment Date	Number Evaluated	Site / PI	Notes
Effects of tin-117m colloid on developing type II collagen arthritis in rats	databook # 0202-03	December 11, 2012 - December 26, 2012	6	IsoTherapeutics Group, LLC Jaime Simon, PhD	POC
Effects of tin-117m-annexin and Sm153 colloid on developing type II collagen arthritis in rats	databook # 0202-09	January 15, 2013-January 29, 2013	6	IsoTherapeutics Group, LLC Jaime Simon, PhD	POC
Meniscal tear model of osteoarthritis in rat (ROA)	ITG # 2014-02	October 28, 2014 - January 6, 2015	79	IsoTherapeutics Group, LLC Jaime Simon, PhD	non-GLP OA
Meniscus tear model of OA in rats 2	ITG # 2015-01	January 29, 2015 - April 16, 2015	110	IsoTherapeutics Group, LLC Jaime Simon, PhD	GLP OA
Collagen model of RA in rats	ITG # 2015-02	February 17, 2015 - May 8, 2015	42	IsoTherapeutics Group, LLC Jaime Simon, PhD	GLP RA
Tin-117m radiosynoviorthesis missed injection and topical exposure study	ITG # 2015-08	August 13, 2015 - September 10, 2015	12	IsoTherapeutics Group, LLC Jaime Simon, PhD	non-GLP topical exposure
Mis-administration of IV dose	ITG # 2017-07	December 19, 2017 – January 2, 2018	20	IsoTherapeutics Group, LLC Jaime Simon, PhD	Non-GLP IV exposure
Long term toxicity	ITG # 2017-04	October 5, 2017 – February 28, 2018	89	IsoTherapeutics Group, LLC Jaime Simon, PhD	GLP LTT

- These studies validated homogeneous tin colloid (HTC) to be a therapeutic device for radiosynoviorthesis (RSO).
- Bolder BioPATH, Inc. validated HTC to be an OA disease modifying device with beneficial cartilage effects seen in rats at 1, 4 and 6 weeks.

Synovetin OA™ Five Normal Dog Safety Study

- No dog exhibited any lameness after injection during 6 week study
- Gamma camera confirmed retention in joint at 24 hours
- Urine and feces collection indicated > 99% average joint retention
- Imaging studies were normal and static between studies
- Post mortem studies
 - Organ and elbow activity indicated > 99% retention in elbow
 - No histologic abnormalities were found in organs or joints
 - Micro autoradiography confirmed synovial localization

Normal Dog Safety Study: Results

Top Histopathology Slide (Dog 1):

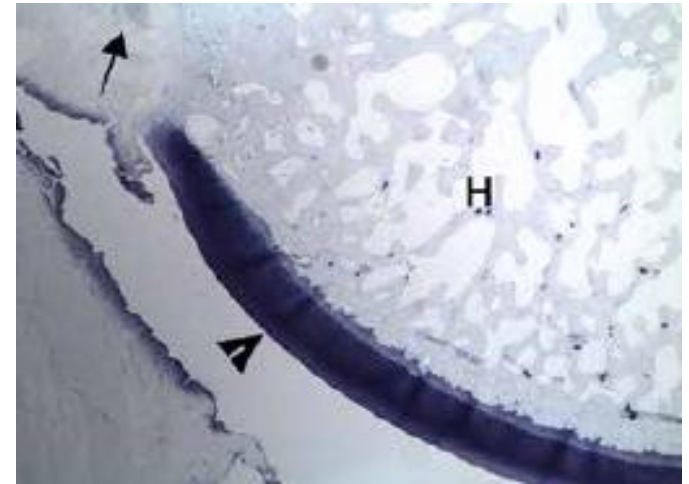
- Inflammatory cells (arrow) below synovial surface
- Normal articular cartilage (arrowhead) of humerus (H), 16x

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)



Synovetin OA™ Canine Clinical Studies

Canine				
Study Name	Study Number	Date Completed	Number Evaluated	Site/PI
5 normal dog safety study	None assigned by University of Missouri	May 2015	5 (5 elbows)	University of Missouri College of Veterinary Medicine, (Jimmy Lattimer DVM)
Safety and efficacy of tin-117m colloid for treatment of canine osteoarthritis	None assigned by University of Missouri	February 2018	43 (44 elbows)	Gulf Coast Veterinary Specialists (Michelle Fabiani DVM) Louisiana State University School of Veterinary Medicine (Karanvir Aulakh DVM) University of Missouri College of Veterinary Medicine (Jimmy Lattimer DVM)
The use of tin-117m colloid (Synovetin OA™) for treatment of naturally occurring grade 3 osteoarthritis of the elbow in client owned dogs	C-22017	July 2018	15 (27 elbows)	Gulf Coast Veterinary Specialists (Michelle Fabiani DVM) Louisiana State University School of Veterinary Medicine (Karanvir Aulakh DVM)
Re-injection of tin-117m colloid (Synovetin OA) in naturally occurring grade 1 or 2 osteoarthritis of the elbow in client owned dogs	C - 80817	June 2018	10 (20 elbows)	Louisiana State University School of Veterinary Medicine (Karanvir Aulakh DVM) University of Missouri College of Veterinary Medicine (Jimmy Lattimer DVM)

- Studies C-22017 and C-80817 are GMP, GLP, GCP and GDP studies validating commercially produced Synovetin OA™ and the commercial manufacturing process utilizing the Belgium reactor (BR2) and Theragenics, Inc. a human medical radioisotope manufacturer based in Buford, GA (NE of Atlanta)

Client Owned Dog Naturally Occurring Grade 1 & 2, 3 Elbow OA and Reinjection Studies



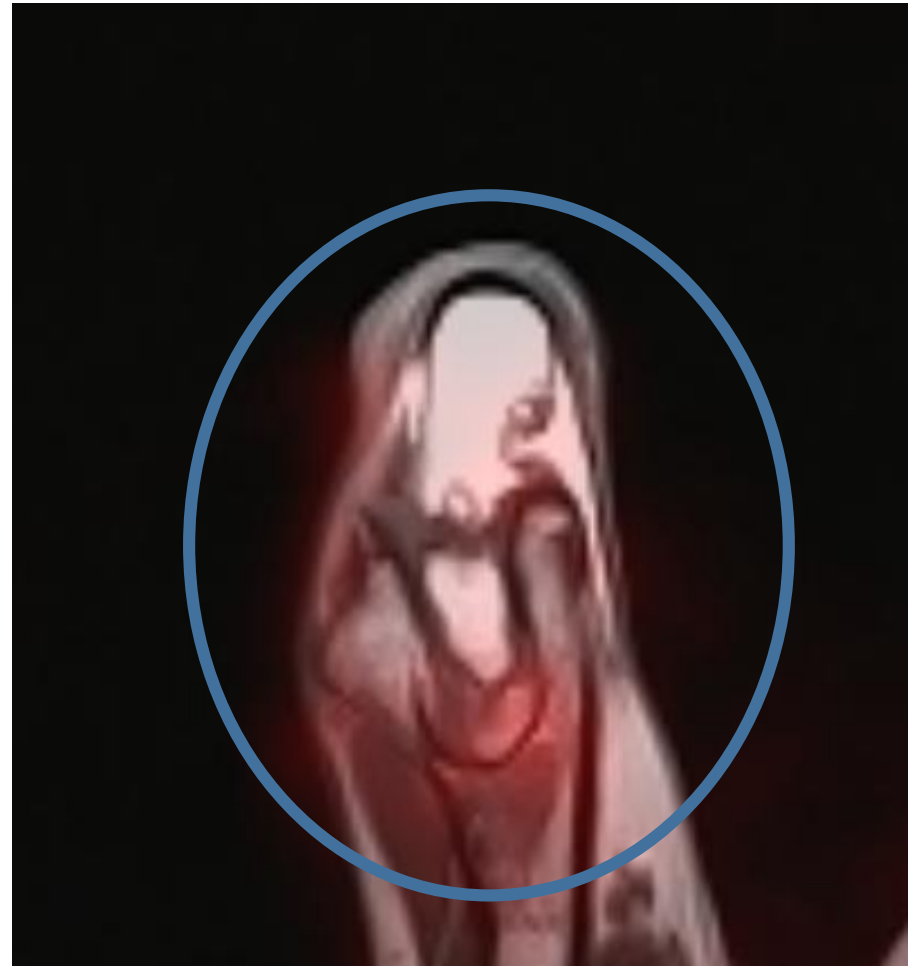
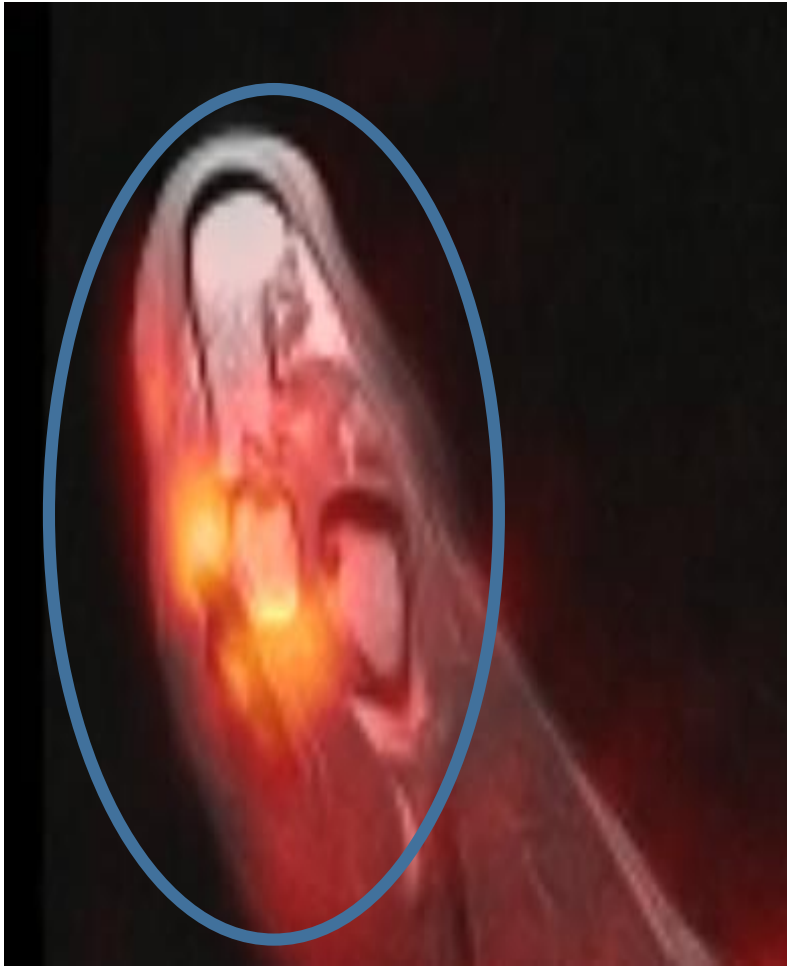
- **3 Clinical Sites**
 - University of Missouri CVM - Principal Investigator: Dr. Lattimer
 - Louisiana State University SVM - Drs. Aulakh and Gaschen
 - Gulf Coast Veterinary Specialists - Drs. Fabiani, Hudson and Beale
- **Facility Requirements**
 - Radioactive material license to include tin-117m (State or NRC)
 - Dose calibrator
 - Ludlum dosimeter
 - MRI
- **Inclusion Criteria**
 - Radiographic grade 1-3 elbow OA with documentable lameness
 - dogs > 8 kg and 1 yo
 - No co-morbid condition that may preclude survival for 1 year



Client Owned Dog 12 Month 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	5mo phone	6mo	7mo phone	8mo phone	9mo	10mo phone	11mo phone	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														

Synovitis Pre and 9 mos. Post Treatment with Synovetin OA™



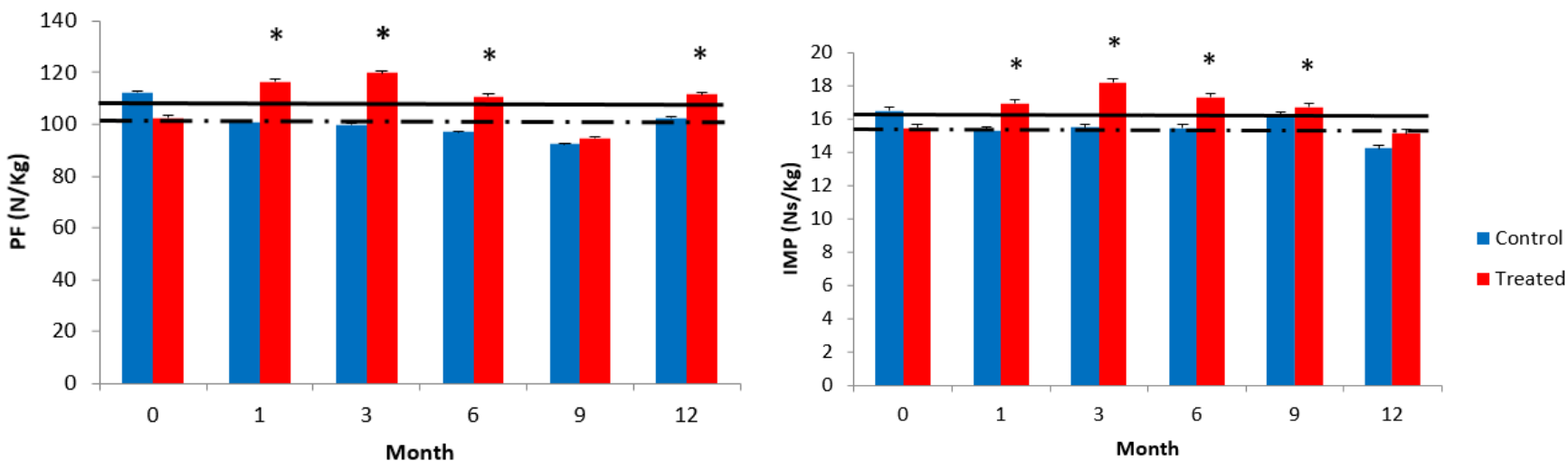
(Fused PET/MRI images courtesy of Jimmy Lattimer DVM, MS, DACVR)

Synovetin OA™

Study Force Plate Data Examples

Determination of Treatment Success

Treatment Success (TS) was defined as an improvement (>5%) and/or a significant ($P < 0.05$) increase in mean PF and/or IMP at Months 1, 3, 6, 9, and/or 12, compared to baseline (0 Month) for that individual dog evaluated on the force plate.



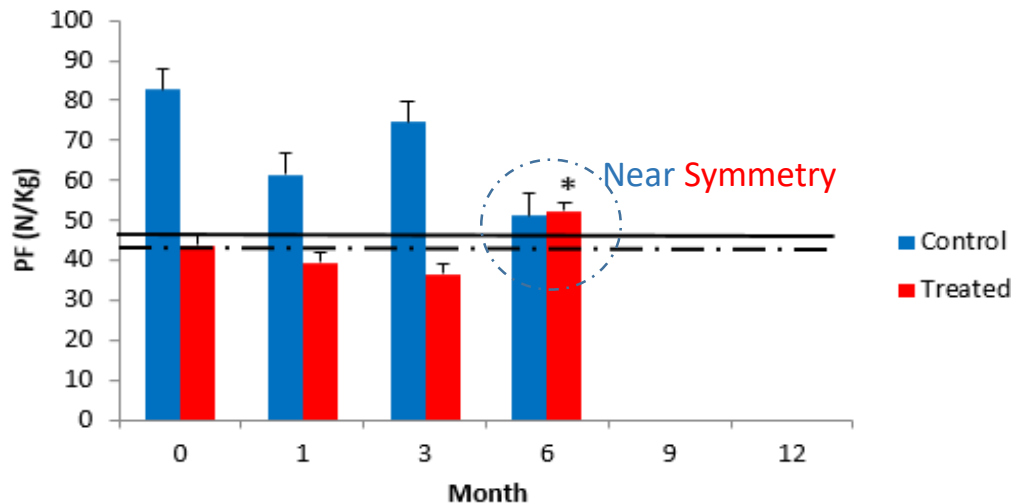
Example Figure: Treatment success (TS) shown here and defined as a 5% increase or significant ($P < 0.05$) increase in the mean PF (5 trials) for each month. The dashed line denotes baseline values and solid line denotes a 5% increase from baseline.

Synovetin OA™

Study Force Plate Data Examples

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Example Figure: Treatment success (TS) shown here and defined as a 5% increase or significant ($P < 0.05$) increase in the mean PF (5 trials) for each month. The dashed line denotes baseline values and solid line denotes a 5% increase from baseline.

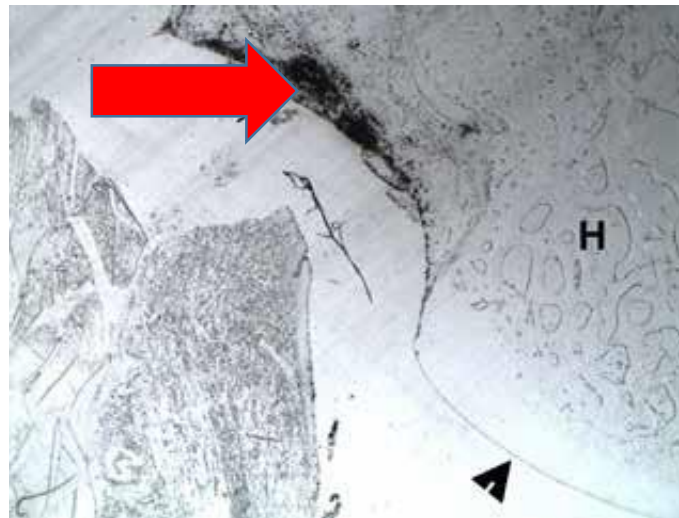
Client Owned Dog Elbow OA Trials Status

- Data validation and source documentation followed by statistical analysis underway for all 3 studies
- Currently 69 dogs and 93 elbows treated with no clinically significant adverse reactions
 - 1 missed IA injection with no complications other than ineffective
- Final Force Plate conclusions – significant treatment effect in > 80% of dogs treated
- INTERIM PET analysis – reduction in synovitis seen in > 70%
- INTERIM Canine Brief Pain Inventory scores analysis – reduction of pain, increased level of activity and/or Quality of Life scores were improved at 6 months and beyond for 80% or more for the 3 study populations

Synovetin OA™: A Safe and Effective Radiosynoviorthesis (RSO) Radionuclide

Synovetin OA™ treatment can be used as part of a multi-modal approach

Device with disease modifying mode of action



Autoradiography, distal humerus & synovium, 16x.
(Image courtesy of Allison Bendele DVM, PhD, DACVP)

Release of Dogs Following Synovetin OA™ Intra-Articular Injections⁶

M. D. Anderson Cancer Center Dosimetry Modeling:

- Measured external radiation exposure following unilateral or bilateral canine elbow joint intra-articular (IA) joint administration
- Measurements of gamma radiation obtained from 12 dogs treated for grade 3 elbow OA using label dose

Conclusions:

- Dogs may safely be released immediately after treatment
- People should avoid more than momentary touching of the treated joint (e.g., they should not sleep with the dog) for at least a month after the treatment.



6. Wendt RE et al, "Release of Dogs Following Sn-117m Colloid Intra-articular Injections", June 26, 2018 presentation SNMMI, Philadelphia, PA

Q & A

How many of you are already associated with a practice which has a radioactive materials license or would like to obtain one?

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

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 (sc/po)
Isolation	Not required	Required