

Disclosure Slide

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Serial imaging of inflammation and therapeutic response with clinically translational ^{19}F MRI

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Fluorine-19 Magnetic Resonance Imaging (^{19}F MRI)

- Non-invasive, non-radioactive method of cellular imaging
- ^{19}F perfluorocarbon (PFC) contrast agent used to label cells
- Highly specific due to the absence of endogenous ^{19}F in biological tissues
- Signal is independent of tissue depth
- Quantitative measurements of ^{19}F accumulation (linear correlation with ^{19}F present and signal detected)
- The proprietary PFC used in these studies has a short T1, long T2, and essentially a single major peak at -91 ppm, and is optimized for ^{19}F MRI over prior art
- ^1H MRI taken in the same imaging session provides the anatomical context for colocalization of the ^{19}F signal

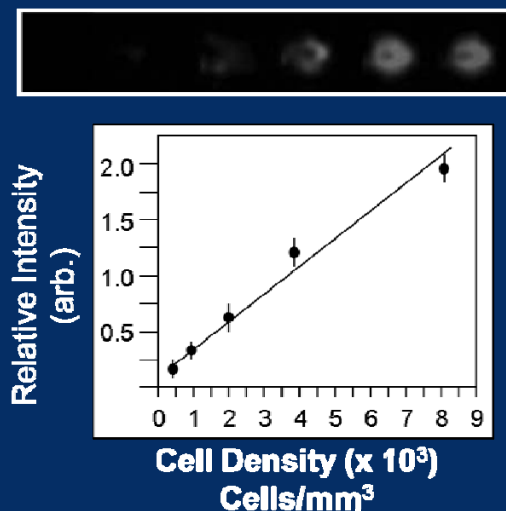
Contrast Agents for Cellular Imaging by ^{19}F MRI

1. Tracers for cell tracking
2. Contrast agents for *in situ* uptake by phagocytes

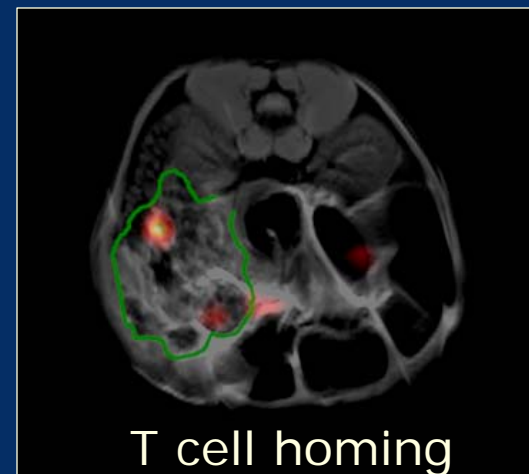
^{19}F MRI Contrast Agents for Cell Tracking

(see poster #45)

- Therapeutic cells are labeled *ex vivo* prior to administration, and accumulations of cells are imaged *in vivo* by ^{19}F MRI
- **Cell Sense** (CS-1000) is a perfluorocarbon (PFC) emulsion designed for uptake by nearly any cell type without transfectants (dual mode version for fluorescent detection)
- Measuring the labeling efficiency (^{19}F uptake/cell) enables quantification of cells in a given region of interest (ROI)

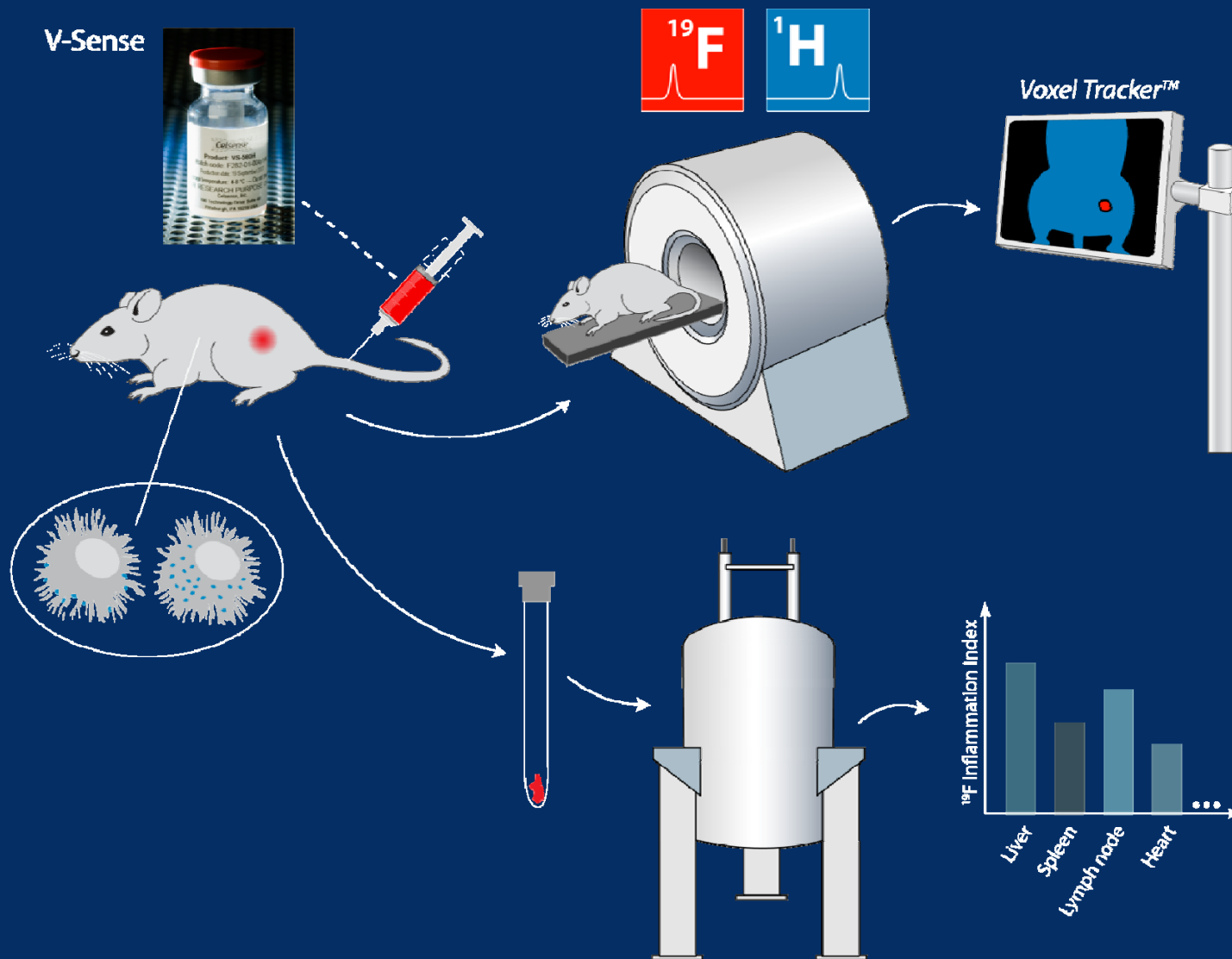


Bonetto et al, *Int. J. Cancer* 2010



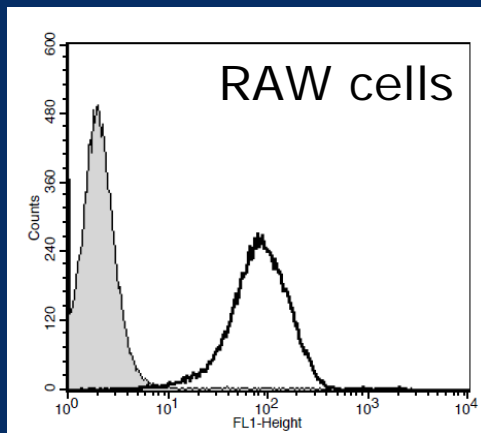
Kadayakkara et al, *Pancreas*. 2010

Contrast Agents for inflammation

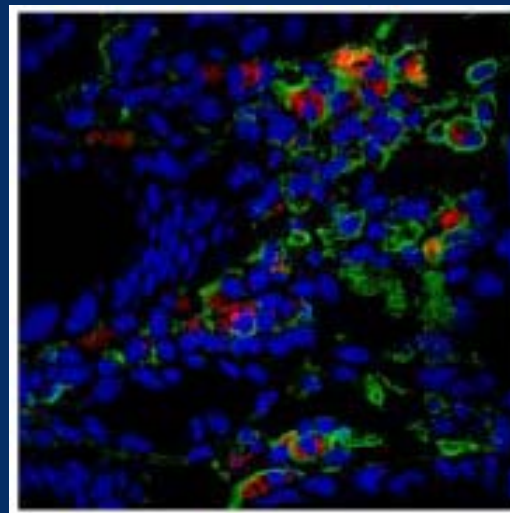


Labeling of macrophages:

In vitro:



V-Sense-DM-Green
Unlabeled

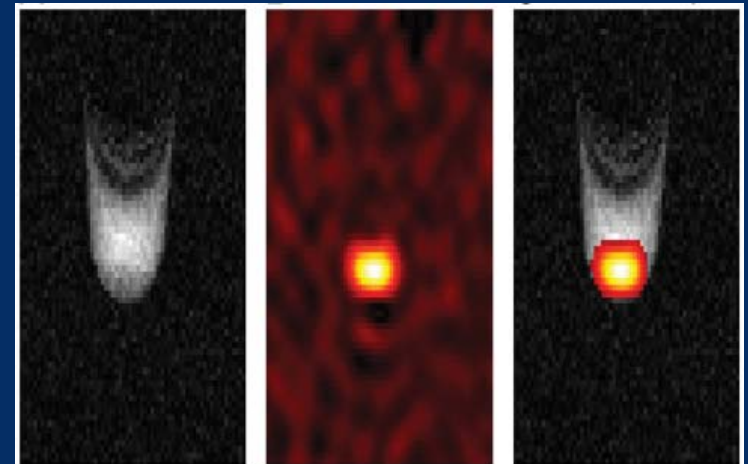


DiI-labeled V-Sense
F4/80
DAPI

Courtesy Kadayakkara et al
Carnegie Mellon University

In vivo:

PBMC after 24 hrs V-Sense



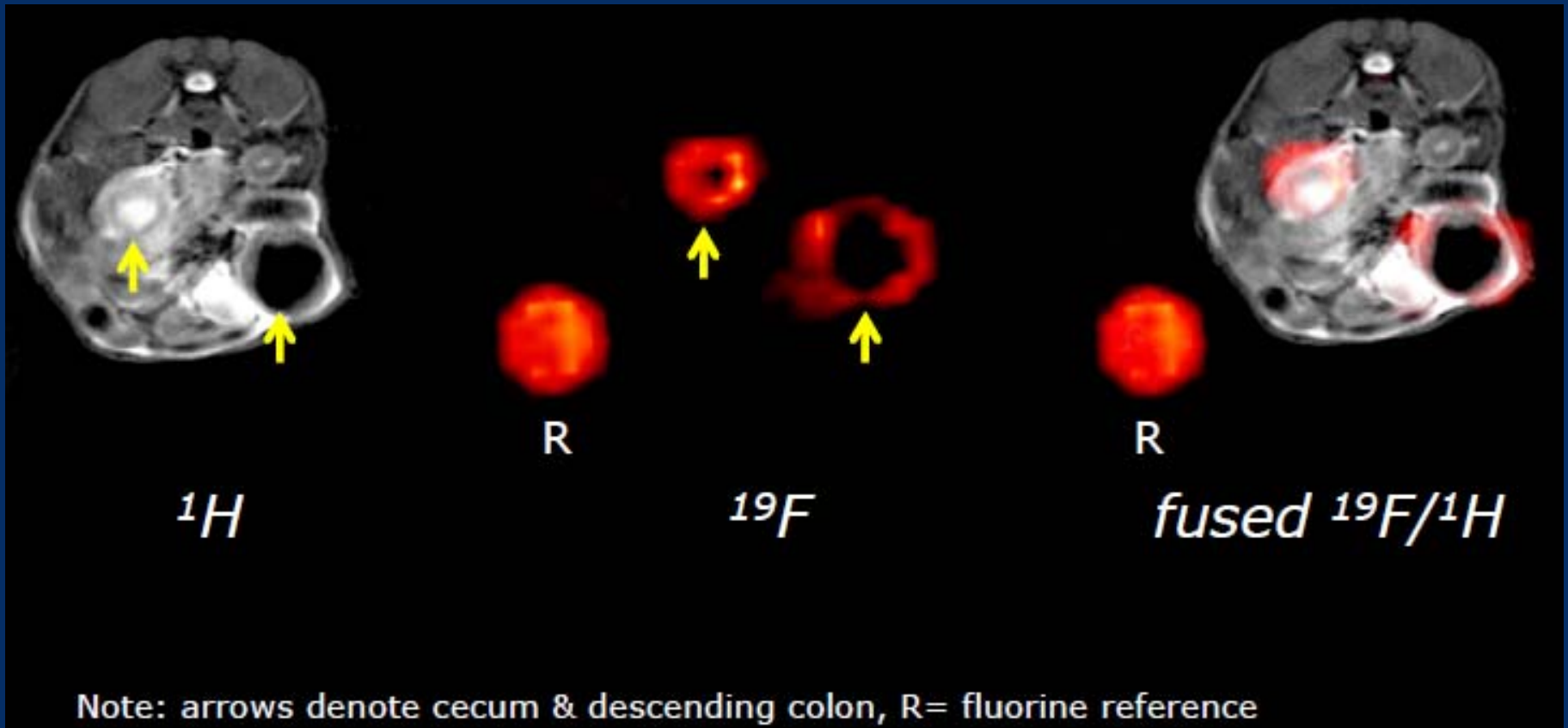
^1H

^{19}F

Overlay

Weise et al, *Exp. Neurol.* 2011

Inflammatory Bowel Disease



IBD mouse model: IL-10^{-/-} + piroxicam diet

(Kadayakkara et al, in press)

^{19}F MRI to visualize inflammatory disease

- Transplant rejection (acute and chronic)
 - Hitchens et al Magn Reson Med 2011;65:1144
- Cardiac and cerebral ischemia induced inflammation
 - Flogel et al, Circulation 2008;118(2):140-148
- Neuroinflammation
 - Weise et al, Exp Neurol 2011doi:10.1016/j.expneurol.2011.03.020
- Bacterial infection
 - Hertlein et al, PLoS ONE 2011;6:e18246.
- Inflammatory bowel disease
 - Kadayakkara et al, Pancreas 2010;39(4):510-515.
- Multiple sclerosis (EAE)
 - Ahrens et al BioTechniques 2011;50:229

Hypothesis:

Serial ^{19}F MRI can be used to measure:

- 1. The extend of inflammatory disease*
- 2. Progression or response to therapy*

Methodology:

Rheumatoid arthritis model: collagen-induced arthritis

- Female Lewis rats immunized twice with Type II collagen in incomplete Freund's adjuvant, 1 week apart
- Disease onset by day 15 in hind limbs, >90% prevalence
- Characterized by clinical swelling, mononuclear inflammatory cell infiltration, followed by bone destruction in late disease.

Imaging

- PFC emulsion (V-Sense, VS-1000): 1.5 mL by IV, 48 hours prior to imaging session.
- Varian 7 Tesla DirectDrive MRI spectrometer (Agilent Technologies, Santa Clara, CA)
- 35 mm i.d. transmit/receive volume coil, tunable for ^1H or ^{19}F imaging (m2m Imaging Corp., Cleveland, OH)
- Voxel Tracker image analysis software (Celsense, Inc.)

Detection of inflammatory lesions in rat hind limbs with V-Sense

Naïve

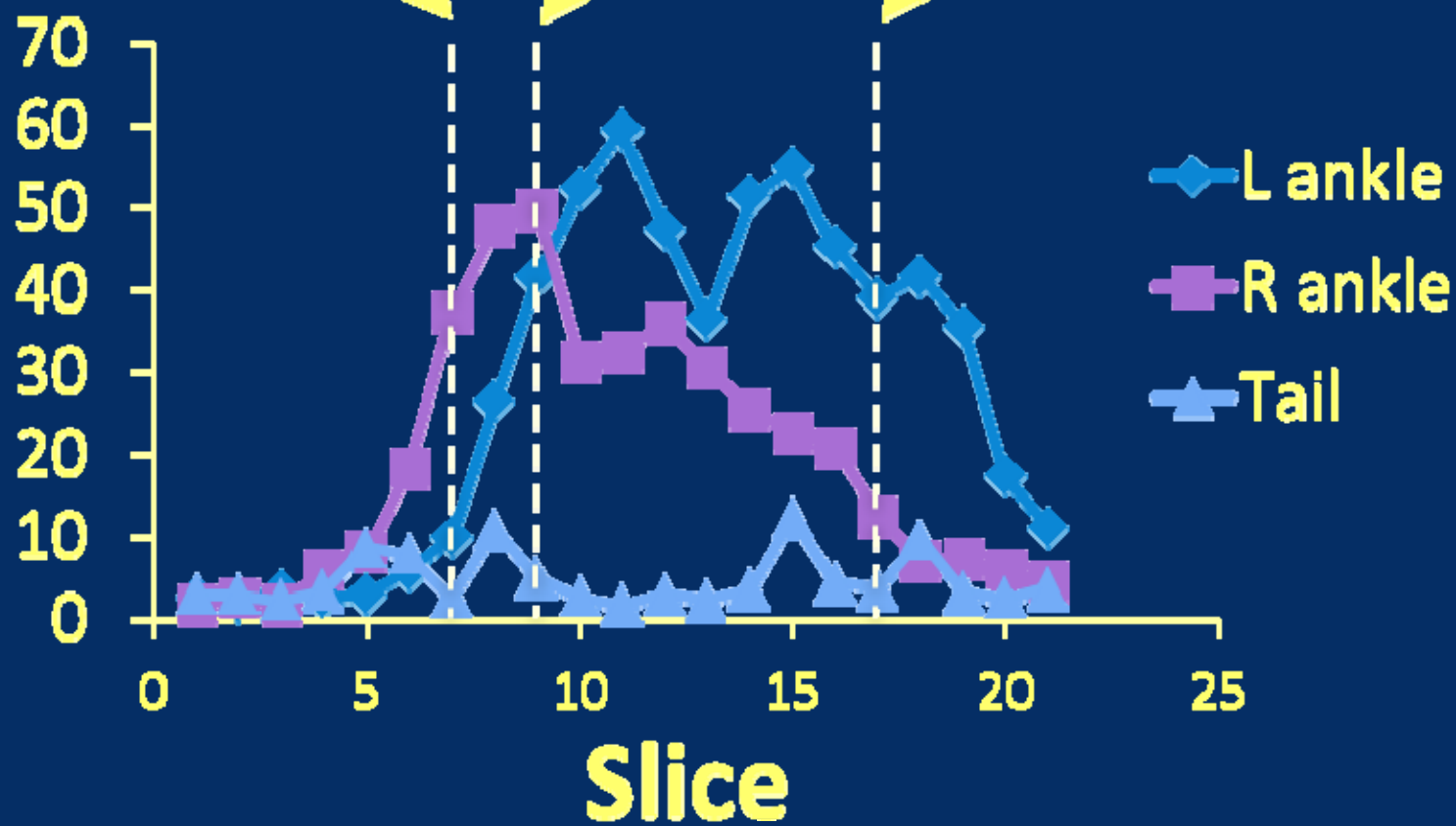


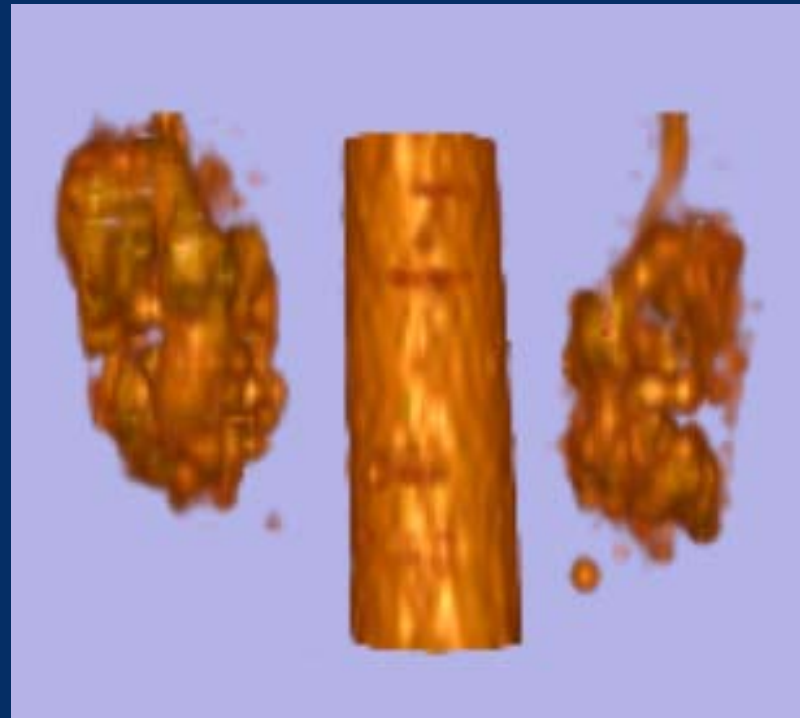
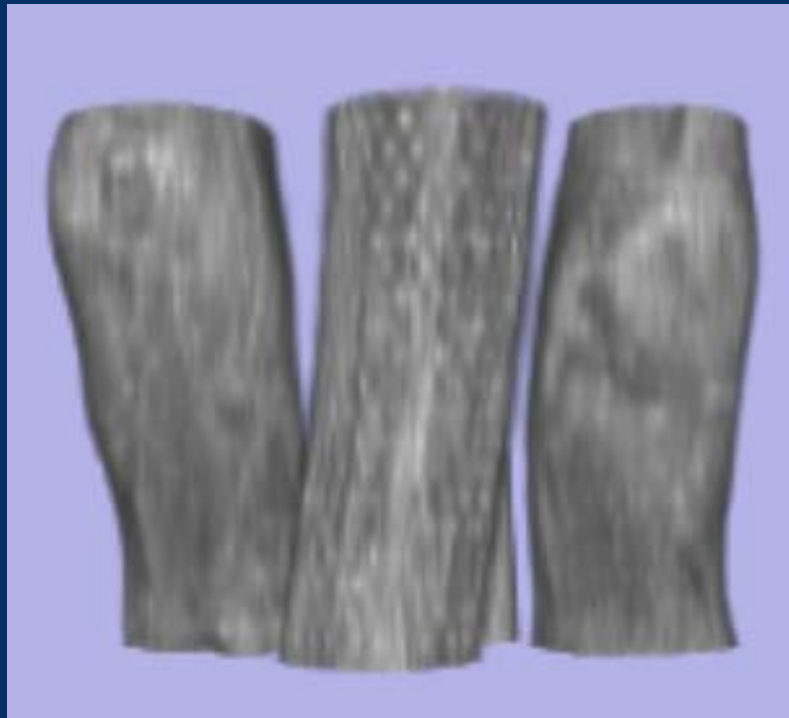
Arthritic



Day 15

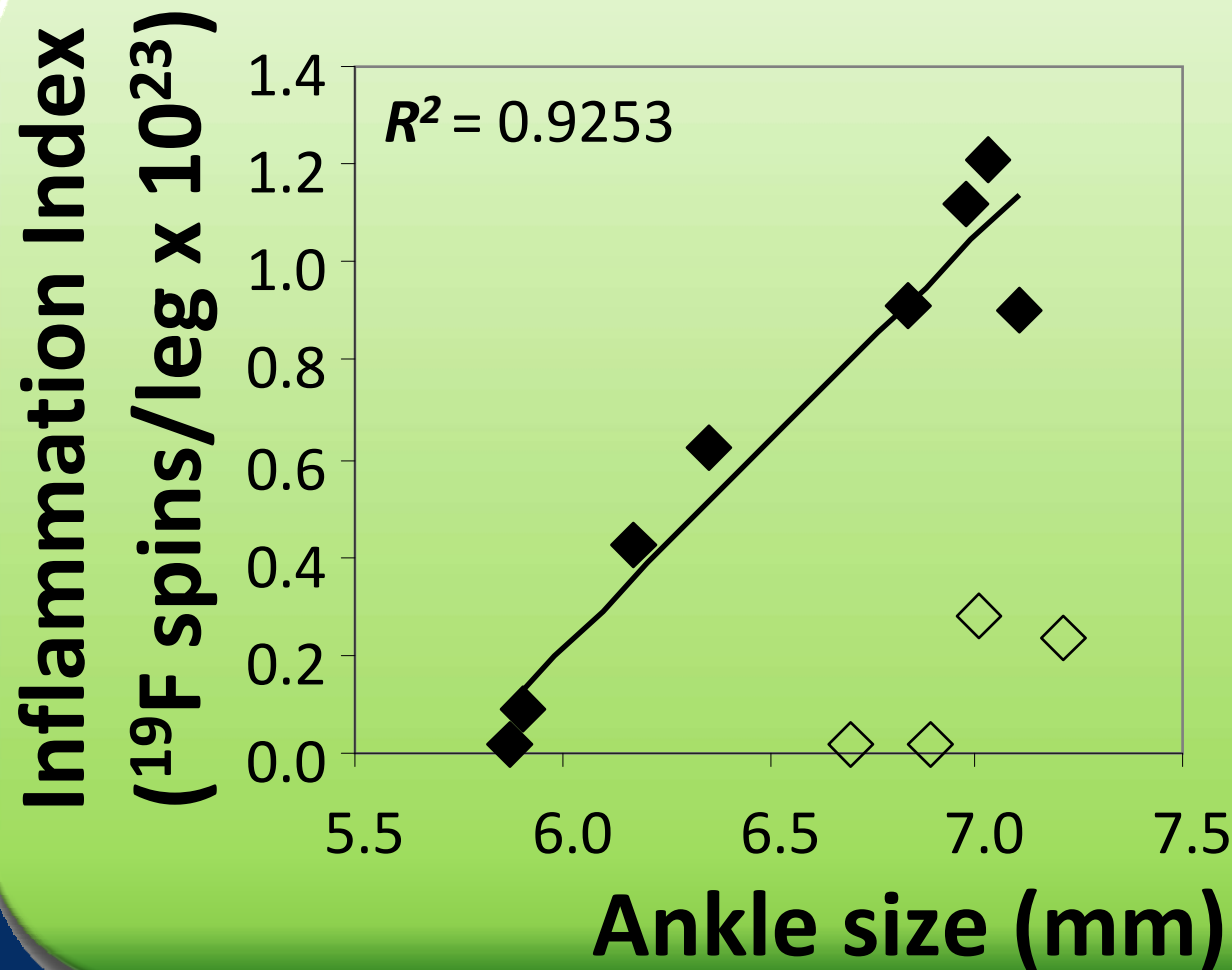
^{19}F Detected $\times 10^{20}$



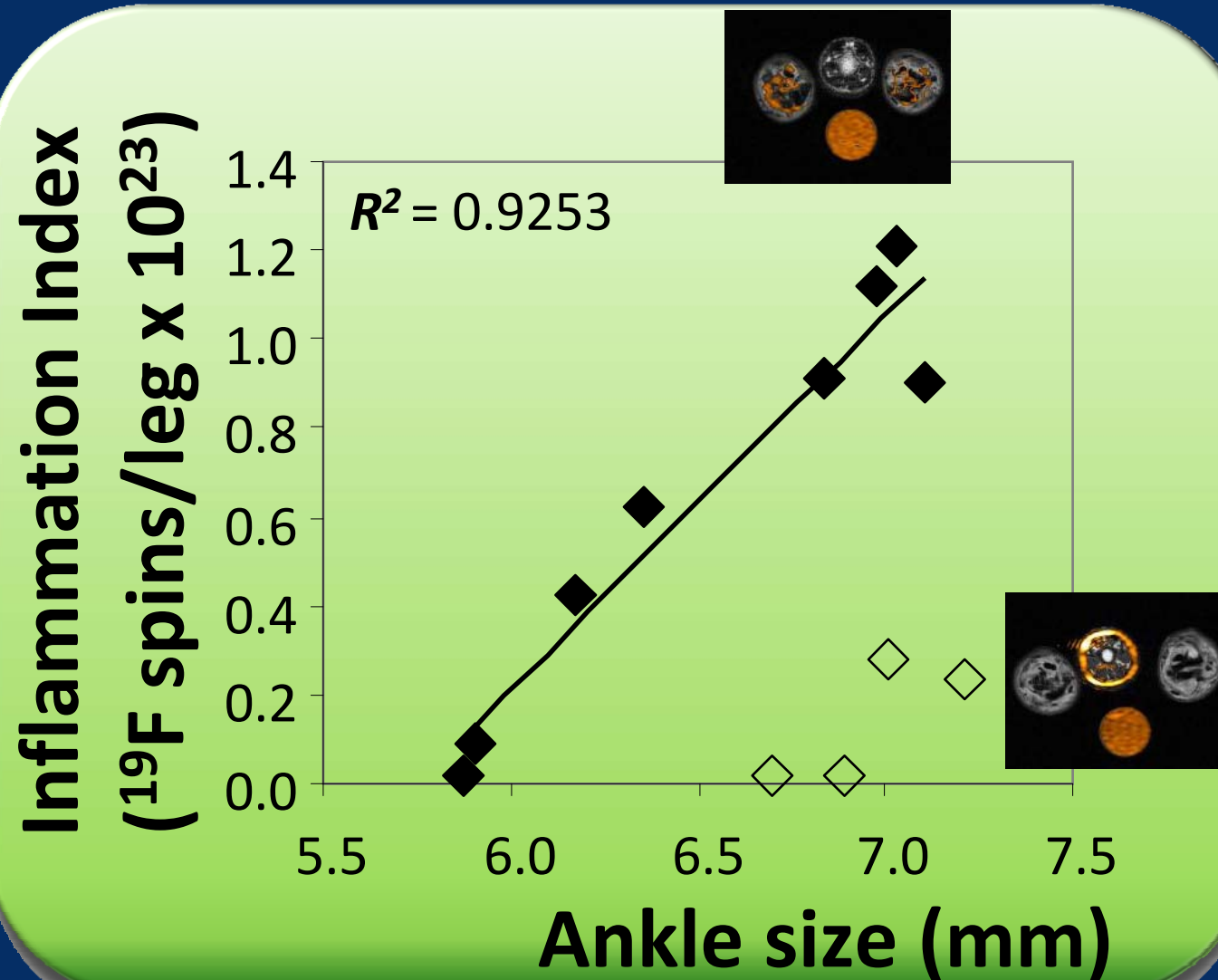


3D reconstruction of $^1\text{H}/^{19}\text{F}$

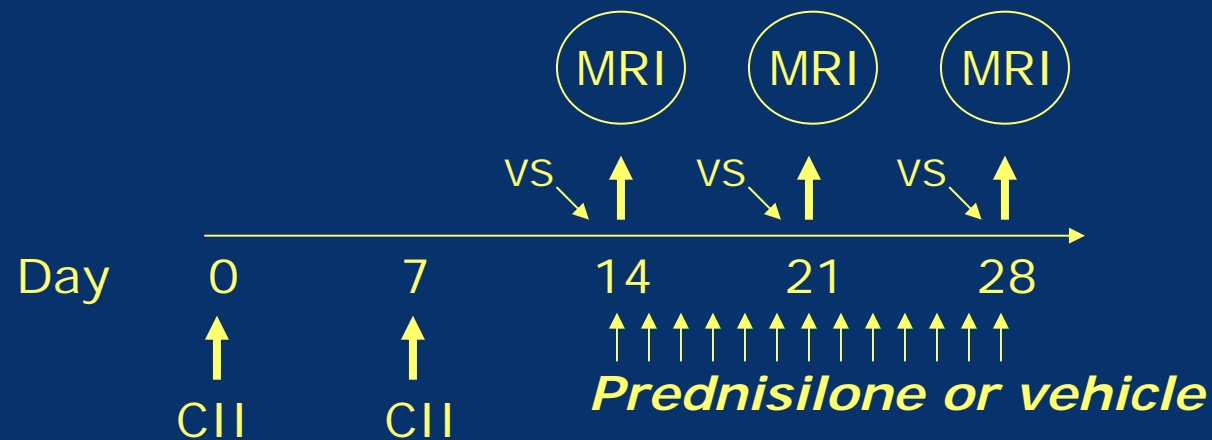
Correlation of ^{19}F accumulation with clinical measurements



Correlation of ^{19}F accumulation with clinical measurements



V-Sense serial monitoring of arthritis

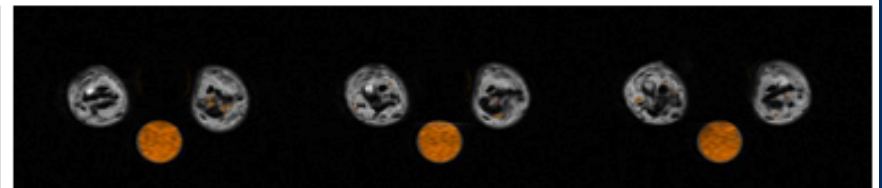
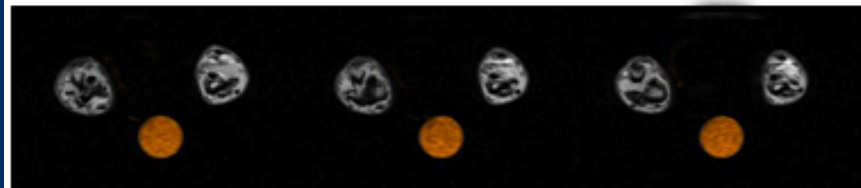


Rat collagen induced arthritis model of RA

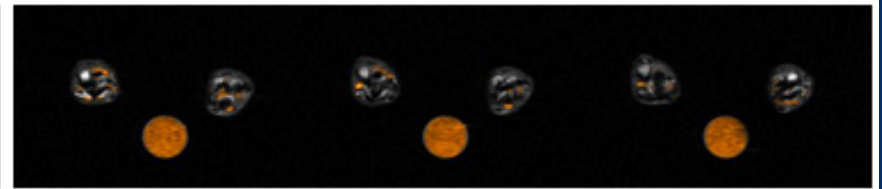
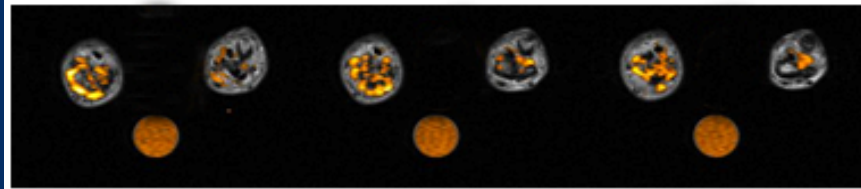
V-Sense serial monitoring of arthritis

DAY

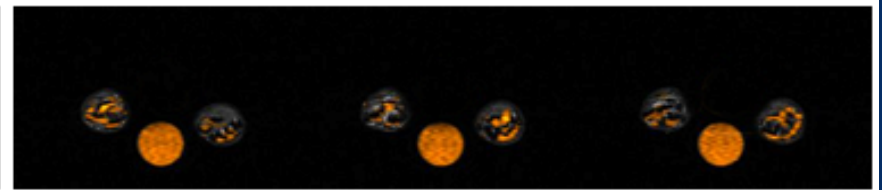
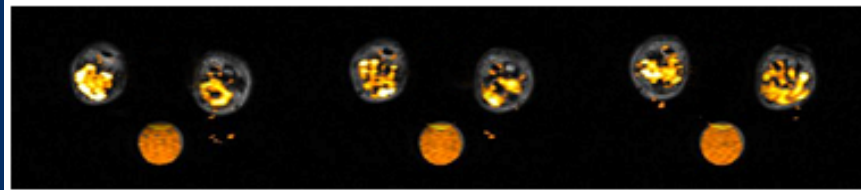
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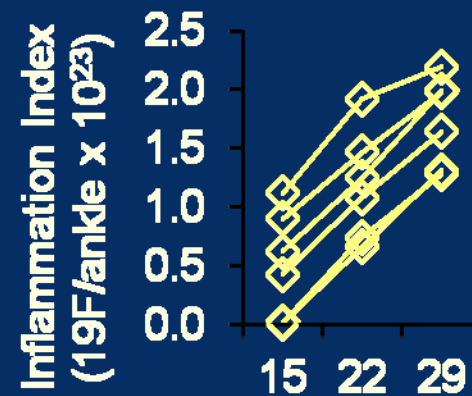
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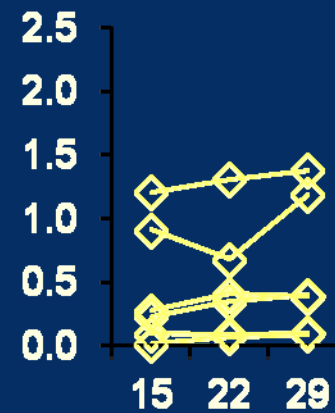
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Vehicle

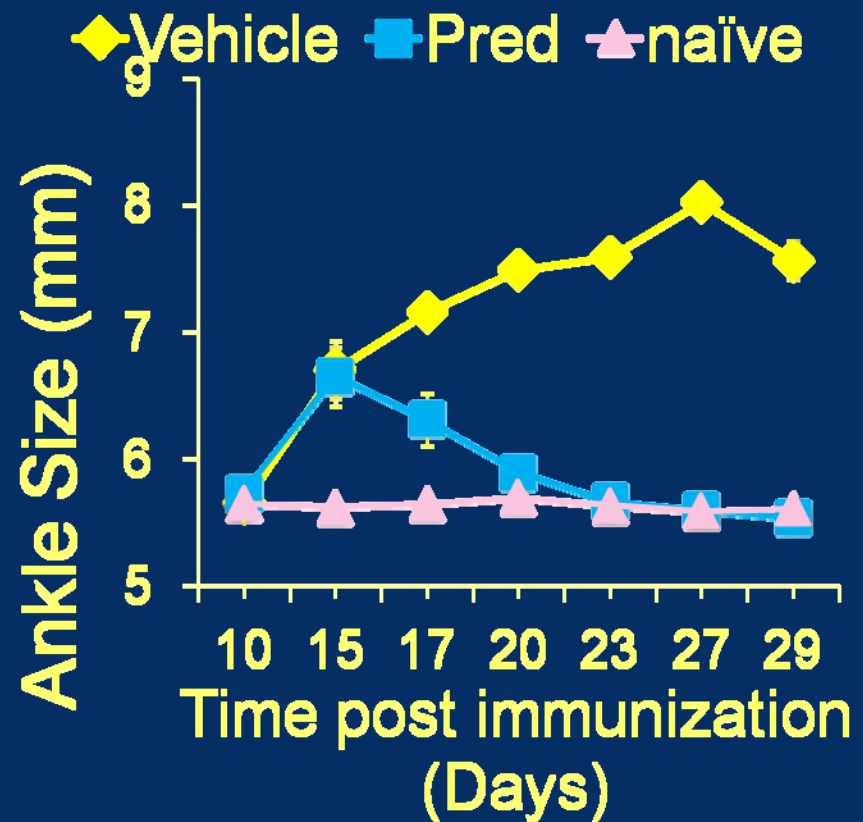
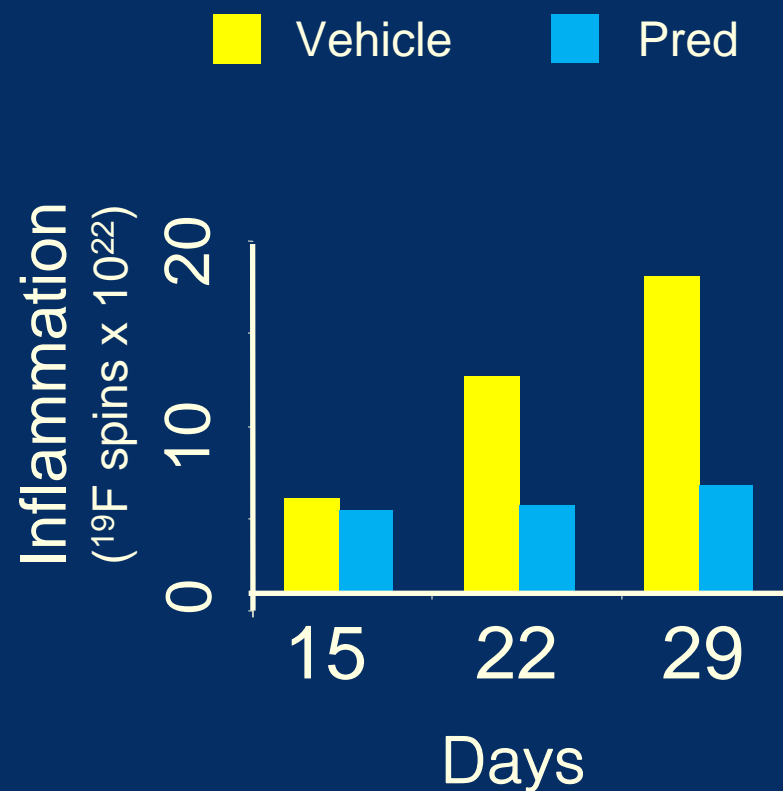


Prednisilone



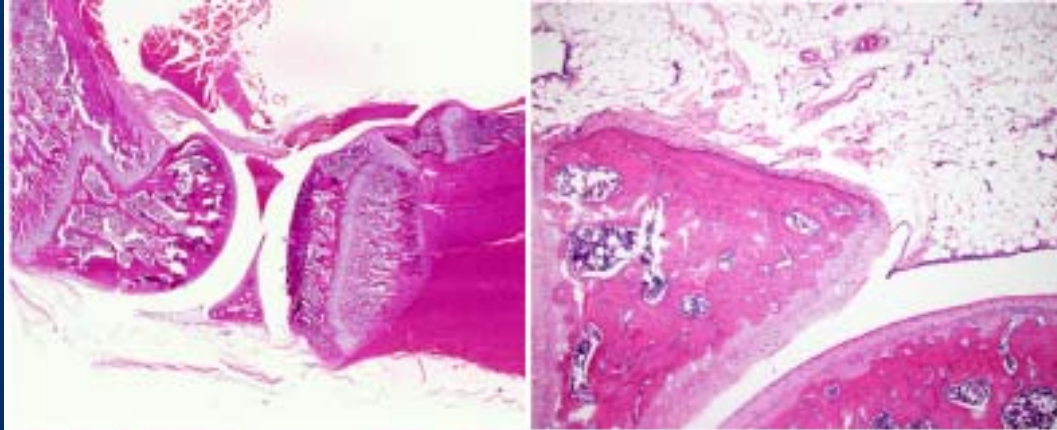
Time (days)

V-Sense quantification of response to therapy

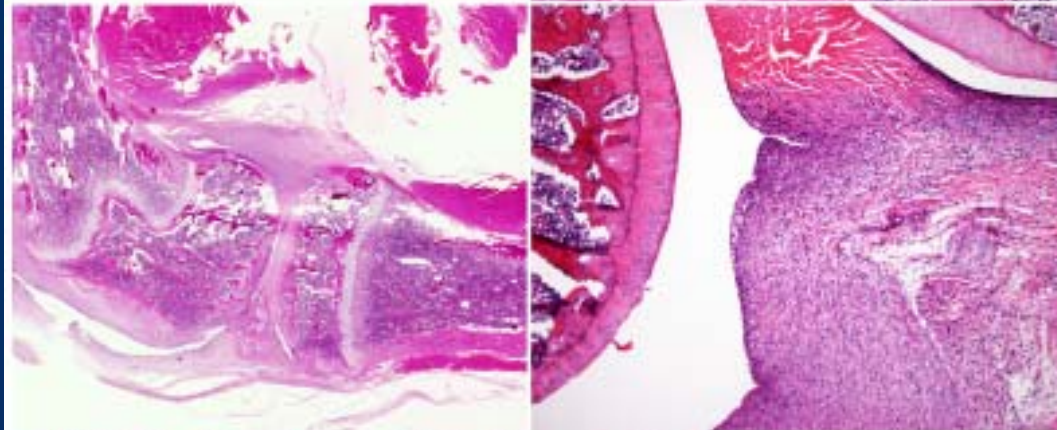


Whole mount knee 20X objective

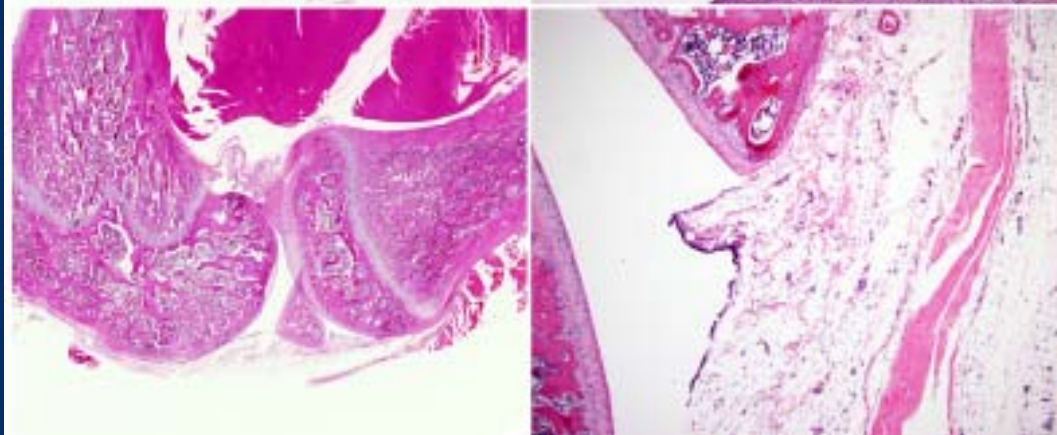
Naive



Arthritis
+
vehicle



Arthritis
+
Prednisilone



Summary

- Specific accumulation of ^{19}F in affected tissues reveals inflammatory infiltrates in arthritis by MRI
- Absence of signal in normal, healthy control joints
- ^{19}F MRI signal (inflammation index) correlates with disease severity in CIA model
- Enables serial monitoring of disease progression or response to therapy *in vivo*
- Correlates with histological assessment of affected tissues

Cancer relevance of ^{19}F MRI

- Chronic inflammation is associated with:
 - the development of cancer
 - progression of cancer to metastatic disease
- Inflammatory infiltrates can modulate response to immunotherapy
 - M1/M2 macrophages
 - Myeloid suppressor cells
 - Dendritic cells
- Biofunctional imaging of inflammation by ^{19}F MRI may enable detection of disease, progression or responses to anti-cancer treatment regimens

Key features of PFC cell tracking

- High specificity for labeled cells
- Imaging without 'pre'-scans
- Quantification *in vivo*
- Low toxicity
 - *Cellular functions preserved in vitro and in vivo*
- Potential for clinical translation

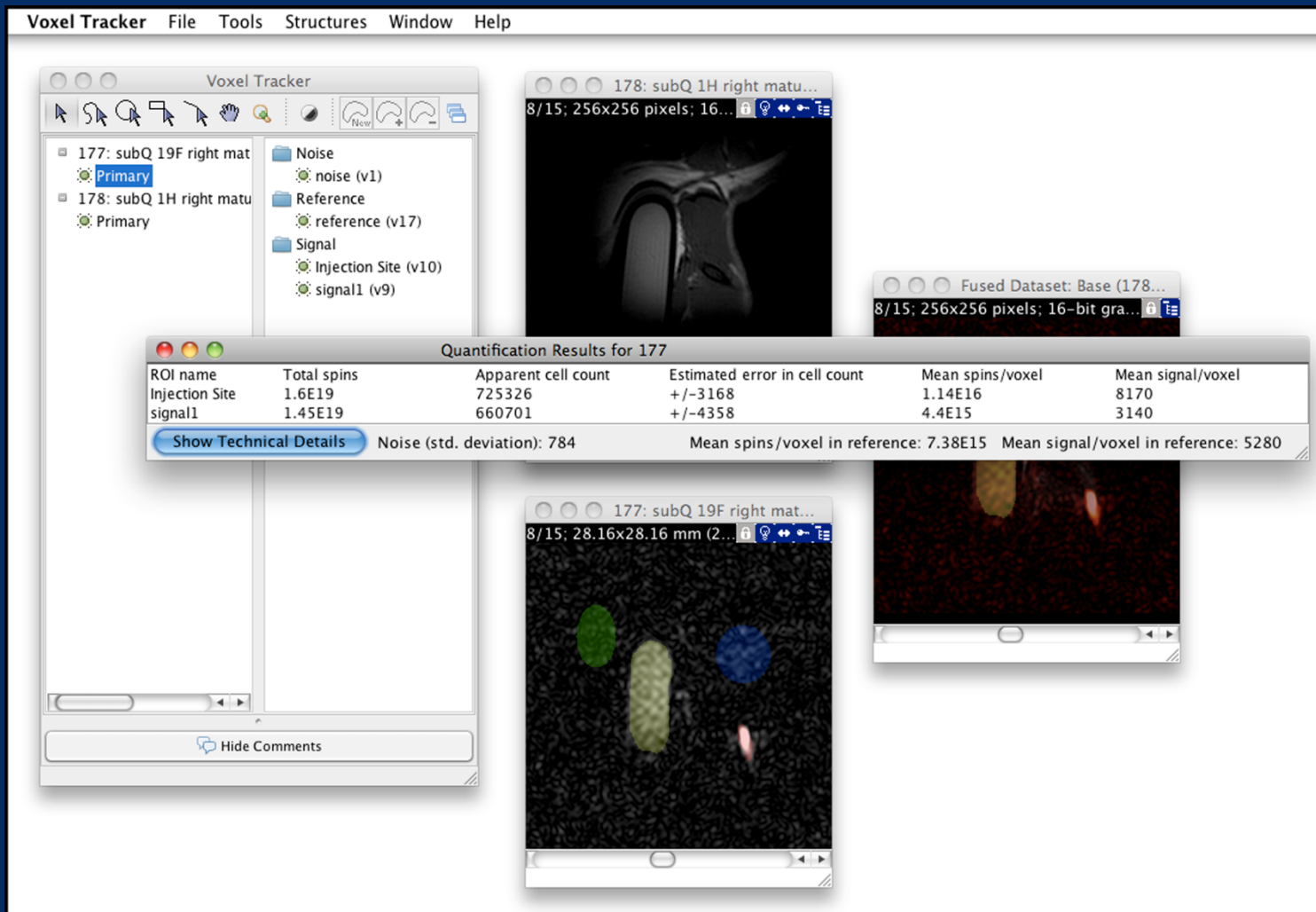
Acknowledgements

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www.celsense.com

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Celsense, Inc.



Voxel Tracker™: Visualize, quantify, manage



Voxel Tracker™: Visualize, quantify, manage

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http://voxeltracker.com/voxbase/view_datasets.php?studyid=2

List Datasets

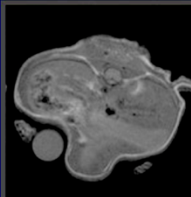



Celsense **Voxel Tracker** Powered by Voxport v1.9.3

All Studies
Current Study
Demo

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	<u>Thumbnail</u> <small>settings</small>	<u>Name</u> <small>settings</small>	<u>Description</u> <small>settings</small>	<u>Stacks</u> <small>settings</small>	<u>ID</u> <small>settings</small>	<u>Scan Date</u> <small>settings</small>	<u>Parent ID</u> <small>settings</small>	<u>Extra Data</u> <small>settings</small>	<u>Date Added</u> <small>(desc) settings</small>
▶		V-Sense - Proton (1H)	Anatomical proton image of PVS sponge disk subcutaneously implanted in a mouse. V-Sense was injected intravenously to systemically label phagocytic immune cells. The mouse was imaged 5 days post-injection at 7 Tesla. Dimensions: 256 X 256 X 15	3	333			no data	2010-01-20 21:17:29
▶		V-Sense - Fluorine (19F)	Corresponding 19F dataset with identical field-of-view. Dimensions: 64 X 64 X 15. Reference, signal, and noise structures have been created for demonstration of signal quantification.	3	332			no data	2010-01-20 21:15:53
▶		Cell Sense - Proton (1H)	Anatomical proton image of 3 million human dendritic cells labeled with Cell Sense, injected into mouse quadriceps, and imaged at 7 Tesla. Dimensions: 128 X 128 X 15	3	189			no data	2009-11-25 17:55:54
▶		Cell Sense - Fluorine (19F)	Corresponding 19F dataset with identical field-of-view. Dimensions: 64 X 64 X 15.	3	188			no data	2009-11-25 17:55:54

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