Disclosure Slide

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Salary,

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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 (¹⁹F MRI)

- Non-invasive, non-radioactive method of cellular imaging
- ¹⁹F perfluorocarbon (PFC) contrast agent used to label cells
- Highly specific due to the absence of endogenous ¹⁹F in biological tissues
- Signal is independent of tissue depth
- Quantitative measurements of ¹⁹F accumulation (linear correlation with ¹⁹F 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 ¹⁹F MRI over prior art
- ¹H MRI taken in the same imaging session provides the anatomical context for colocalization of the ¹⁹F signal
1. Tracers for cell tracking

2. Contrast agents for *in situ* uptake by phagocytes
19F MRI Contrast Agents for Cell Tracking

(see poster #45)

- Therapeutic cells are labeled \textit{ex vivo} prior to administration, and accumulations of cells are imaged \textit{in vivo} by 19 F MRI

- \textbf{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 (19F uptake/cell) enables quantification of cells in a given region of interest (ROI)

Bonetto et al, \textit{Int. J. Cancer} 2010

Kadayakkara et al, \textit{Pancreas}. 2010
Contrast Agents for inflammation
Labeling of macrophages:

**In vitro:**
- RAW cells
- V-Sense-DM-Green
- Unlabeled

**DiI-labeled V-Sense**
- F4/80
- DAPI

**In vivo:**
- PBMC after 24 hrs V-Sense

1H  19F  Overlay

Courtesy Kadayakkara et al, Carnegie Mellon University

Inflammatory Bowel Disease

IBD mouse model: IL-10−/− + piroxicam diet

(Kadayakkara et al, in press)
19F MRI to visualize inflammatory disease

- Transplant rejection (acute and chronic)
- Cardiac and cerebral ischemia induced inflammation
  - Flogel et al, Circulation 2008;118(2):140-148
- Neuroinflammation
- Bacterial infection
- Inflammatory bowel disease
- 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 $^1$H 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
3D reconstruction of $^{1}\text{H}/^{19}\text{F}$
Correlation of $^{19}$F accumulation with clinical measurements

$R^2 = 0.9253$

**Inflammation Index** ($^{19}$F spins/leg x $10^{23}$)

**Ankle size (mm)**
Correlation of $^{19}$F accumulation with clinical measurements

$R^2 = 0.9253$
V-Sense serial monitoring of arthritis

Rat collagen induced arthritis model of RA

Day 0, 7, 14, 21, 28

CII CII

MRI MRI MRI

Prednisilone or vehicle
V-Sense serial monitoring of arthritis

DAY

15

22

29

Vehicle

Prednisilone

Inflammation Index (19F/ankle x 10^23)

Time (days)
V-Sense quantification of response to therapy

Inflammation ($^{19}$F spins x $10^{22}$)

Days

Ankle Size (mm)

Time post immunization (Days)

- Vehicle
- Pred
- naïve
Naive

Arthritis + vehicle

Arthritis + Prednisilone

Whole mount knee 20X objective
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 \textit{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
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