Department of Radiology

Hospital of the University of Pennsylvania
In Memoriam

John S. "Jack" Leigh
1939-2008
Metabolic Magnetic Resonance Research and Computing Center
Regional Resource

Development of MR and Optical Imaging based biomarkers for

- tissue function,
- early diagnosis, and
- evaluation of therapeutic efficacy

in a host of pathologies.
Overview

Additions and Changes since the award:

1. Optical imaging core
2. Proposed new center for optical imaging
3. 7T project
4. Resources for hyperpolarized gas and $^{13}$C
5. Clinical Translation
Cores

- **Multinuclear MR**
  - P.Is: Ravinder Reddy and Mitchell D. Schnall

- **Functional Imaging**
  - P.Is: John Detre and J.J. Wang

- **Hyperpolarized Gas MRI**
  - P.Is: Rahim R. Rizi and Masaro Ishii

- **Optical Imaging**
  - P.Is: Arjun Yodh and Turgut Durduran

- 16 collaborative projects...
CORE I: Multinuclear MR

P.Is.:
Ravinder Reddy
Mitchell D. Schnall
Subprojects

Core I.1: 3D & multi-slice $T_{1\rho}$ imaging techniques for high fields

Core I.2: Temporal radial filters for k-space weighted imaging
Collaborative Projects

COLL.I.1. **Quantitative MR Imaging in Arthritis**
NIH R01 AR45242 (RR), NIH R01 AR45404 (RR), NIH R21 EB00480 (RR)

COLL.I.2. **Measurement of Oxygen Consumption Rates in Hearts and Tumors**
NIH 5R01 CA51935-12 (JDG), 5R24CA083105-05 (JDG), 5R01 CA44982-16 (JB), P01 CA56690-09A20002 (Dennis Leeper)

COLL.I.3. **Traumatic Brain Injury and Alzheimer’s Disease**
NIH P01 AG 09215-13 (JQT), NIH P30 AG 10124 (JQT), NIH PO1 AG 17586-03 (VYL)

COLL.I.4. **Transgenic Mouse Models of Tau Pathologies**
NIH P01 AG 11542-09 (VYL ), NIH P01 AG 09215-13 (JQT), NIH P30 AG 10124 (JQT), NIH PO1 AG 17586-03 (VYL)

COLL.I.5. **Dynamic Contrast enhanced Studies of Tumor Response to Anti-Angiogenesis Therapy**
5R01CA049820, grants from: Oxigene Inc., Bayer Corporation, AstraZeneca
Publications

Peer reviewed journal articles: 17
Abstracts in international conferences: 42
Core Research

- Fast 3D $T_{1\rho}$ mapping sequence, TrueFi
  - Enables a 3D $T_{1\rho}$ map in about 10 min
- $T_{1\rho}$ and Alzheimer’s disease (AD)
- Role of sodium imaging as a biomarker
  - in AD and diffuse axonal injury
- $T_{1\rho}$ as a biomarker in OA and IVD
  - Interleaved sodium and $T_{1\rho}$
- KWIC update
$T_{1\rho}$ and Sodium MR as Biomarkers

$T_{1\rho}$ as a surrogate biomarker in pathologies:

- Alzheimer’s disease
- Arthritis
- Disc degeneration
SLIPS pulse sequence

Enables Rapid $T_{1\rho}$ mapping

3D $T_{1\rho}$ mapping (30 slices) in about 10 min

Figure 1: The SLIPS pulse sequence for acquiring $T_{1\rho}$-weighted images. The steady-state magnetization is stored in the z-direction by the last $\alpha/2$ pulse of the TRUF1 sequence and then recalled by the $T_{1\rho}$ preparatory cluster and then returned to the z-axis by the second hard $\pi/2$ pulse.
Male, 77 years with AD

Slice corresponding to $T_{1\rho}$ map
1. Elevated $T_{1\rho}$ in Medial Temporal Lobe
2. Increased sulci volume
$T_{1\rho}$ results from AD subjects

$T_{1\rho}$ (mean ± std. error) in GM of MTL:

AD = 90.3 ± 1.2ms (N=14)
Control = 85.4 ± 1.0ms (N=16)
MCI = 87.6 ± 1.4ms (N=11)

Differences are statistically significant (p<0.05).
$T_{1\rho}$ and FDG PET

PET

F-65 AD

F-67 control

$T_{1\rho}$

rCMRGlc (Norm to Pons)

1.5

150ms

10
Sodium MRI and AD

Rationale:

1. Loss of neurons $\rightarrow$ increase in the volume of extra-cellular space $\rightarrow$ increase in MRI-detectable sodium (due to the longer $T_2$).

2. Positively charged sodium ions are attracted by the negatively charged side-chains on proteoglycan (PG) macromolecules resulting in an increase in sodium content.
[Na] was 99.6mM and 83.6mM in the AD and control brains, respectively, in the circular ROI located in the hippocampus. This 19% increase [Na] may be due to:

1. An increase in extra-cellular volume of sodium.
2. AD-related pathology resulting in an increase in [Na].

Neuroimage (submitted)
$T_{1\rho}$ in OA and IVD degeneration
GAG and $T_{1\rho}$

Relationship between GAG and $T_{1\rho}$ relaxation rate in articular cartilage.

\[
\frac{1}{T_{1\rho}} = \frac{1}{T_{1\rho}^0} + f[R_{1\rho}]
\]
### Subject 22

**Date**: 09/12/07  
**MRI Date**: 12/13/07  

**Cartilage**
- Diffuse grade 1 chondromalacia throughout the entire knee joint  
- Superficial increased T1\(\rho\) lateral portion of MFC relative to contralateral side.  
- Diffuse elevated T1\(\rho\) of the LPF corresponds with abnormality on T2W.

**Other Tissues**
- Complex tear of medial meniscus  
- Partial medial meniscectomy was performed by debridement and contouring.

### Subject 27

**Date**: 08/01/07  
**MRI Date**: 11/19/07  

**Cartilage**
- Grade 3 chondromalacia of the patella with unstable chondral edges.  
- Grade 4 chondromalacia of the medial femoral condyle with several unstable flaps.  
- Grade 2 diffuse chondromalacia of the lateral compartment, but focal grade 4 chondromalacia of the LFC.

**Other Tissues**
- Partial lateral meniscectomy.  
- Chondroplasty of patella and MFC to stabilize cartilage.
Integrated Na and $T_{1\rho}$
Sodium and $T_{1\rho}$
Patellar Cartilage - healthy

Sodium map

$T_{1\rho}$ map
IVD and $T_{1\rho}$
$T_{1\rho}$ and Sodium image comparison between healthy 26yo male (left) and non healthy 24 yo male (right). Scale bar in milliseconds.
KWIC
Need for High Spatial and Temporal Resolutions

High spatial resolution
- Rim enhancement
- Spiculated/smooth
- Focal/lobular

High temporal resolution

Graph showing intensity over time (min): 0 to 45, Time (min): 0 to 9
PCA can be used to analyze the dynamic time series of the undersampled radial data series. Components that primarily contribute to image streaking and noise are rejected, while those that contain information of the tumor are maintained.
Figure 1 Results from PCA processing of undersampled radial data set
(a) Full dataset image: 512 points x 384 views (2 min acquisition).
(b) Magnified and cropped image of (a).
(c) Image from a single pass: 512 points x 48 views (15 sec).
(d) PCA processed: 512 points x 48 views (15 sec).
(e) Parametric map: RED = Signal wash-out, BLUE = Plateau.
Self Navigated Projection Reconstruction

RL: No Nav

PR: Nav
New Collaborations

1. $T_{1\rho}$ imaging in pediatric population
   Diago Jarmilio and Harish Hosalker, CHOP
2. $T_{1\rho}$ and CERND (Neurology)
3. AO Spine (Orthopedic Surgery, Pennsy)
4. MCRC (Orthopedic Surgery and Bioengineering)
5. TBIC and ITMAT
Collaborations with industry

1. Wyeth
   a) $T_{1\rho}$ Imaging of cartilage in a cross sectional study
   b) In vitro evaluation of drug efficacy with $T_{1\rho}$

2. GSK
   a) $T_{1\rho}$ evaluation in an animal model of OA

3. Histogenics
   a) $T_{1\rho}$ evaluation of cartilage implants

4. Zimmer/ NYU
   1. $T_{1\rho}$ Imaging of Disc in a cross sectional study

5. ACRIN trial
   Collaboration with,
   a) Jefferson University,
   b) University of Pittsburgh
   c) Fox Chase Cancer Center
   d) Hershey Medical Center
Patents

Patents on $T_{1\rho}$ technology

- **Pulse imaging sequences and methods for $T_{1\rho}$-weighted MRI**, Ravinder Reddy, Arijitt Borthakur and E. M. Shapiro, Sridhar R. Charagundla (USP6836114), December 2004

- **Reduced Specific Absorption Rate $T_{1\rho}$-weighted MRI**, Ravinder Reddy, Arijitt Borthakur and Andrew Wheaton, S. R. Charagundla (USPA20050151537), July 2005

- **A method for the simultaneous $T_{1\rho}$ and sodium MRI mapping of macromolecules and structure of tissues**, Ravinder Reddy, Arijitt Borthakur and Walter Witschey (Provisional Filed), 2007

- **SLIPS: A pulse sequence for fast 3D $T_{1\rho}$ MRI**, Ravinder Reddy, Arijitt Borthakur and Walter Witschey (Provisional Filed), 2007

- **Artifacts in $T_{1\rho}$-Weighted Imaging: Compensation for B1 and B0 Field Imperfections**, Ravinder Reddy, Arijitt Borthakur and Walter Witschey (Provisional Filed), 2007

Ongoing and Future Directions

1. $T_{1\rho}$ and sodium MRI in AD and its correlation with PET
2. Diffuse axonal injury and sodium MRI
3. MRI correlates of OA pain and fMRI
4. Built in $T_{1\rho}$ contrast in SSFP
Service

- RR also plays a major role in CAMRIS and SAIF which deal with
  - magnet time allocation
  - regulatory issues (IRB and IACUC)
  - safety and monitoring
  - data processing and analysis
  - hands on training on the MR scanners
  - custom built RF coils
- CAMRIS and SAIF both serve over 100 service projects from within and outside the institution
- 7T user group
Service/Dissemination of $T_{1\rho}$ Technology

Institutions that received the $T_{1\rho}$ pulse sequence

1) Jeff Dunn, Ph.D., Department of Radiology, University of Calgary, Calgary, Alberta Canada

2) Diego Jaramillo, M.D., Department of Radiology, CHOP, Philadelphia, PA

3) Daniel R. Thedens, Ph.D., Department of Radiology, U. of Iowa, Iowa City, IA

4) Gilles Beaudoin, Ph.D., Department of Radiology, U. of Montreal, Montréal QC, Canada

5) Ian Cameron, Ph.D., Department of Physics, U. of Ottawa, Ottawa, Ontario Canada

6) J. Bruce Kneeland, M.D., Department of Radiology, Pennsylvania Hospital, Philadelphia, PA

7) Mark Wagshul, Ph.D., Department of Radiology, SUNY, Stony Brook, NY

8) Bart Milestone, M.D., Department of Radiology, Fox Chase Cancer Center, Philadelphia, PA

9) C. Kent Kwoh, M.D., Division of Rheumatology and Clinical Immunology, Univ. of Pittsburgh, Pittsburgh, PA

10) Alex Dresner, Ph.D., Department of Radiology, Thomas Jefferson Univ., Philadelphia, PA

11) Tim Mosher, M.D., Department of Radiology, Penn State Univ., Hershey Medical Center, Hershey, PA

12) , Department of Radiology, UCSF, San Francisco, CA

13) Susanta Sarkar, M.D., Department of Radiology, GSK, Collegeville, PA

14) Department of Radiology, Boston Children’s, Boston, MA
ASL Tech transfer and service

- Technology was transferred to a total of 51 sites including 12 new sites in the past year.
- In the near future, Siemens is going to make it available as a standard tool on its platform.
Dissemination

CfN High Field Workshop.
Organized by: John Detre,
Sponsored by: RR and CfN
Venue: University of Pennsylvania
Date: April 9, 2008
Dissemination

2nd International Workshop on Hyperpolarized Carbon-13 and its Applications in Metabolic Imaging.
Organized by: Rahim Rizi
Sponsored by: RR and Dept of Radiology
Venue: University of Pennsylvania
Date: July 28-30, 2008
Dissemination

The 2008 International Workshop on Functional Pulmonary Imaging.

Organized by: Rahim Rizi
Sponsored by: RR and Dept of Radiology
Venue: University of Pennsylvania
Date: August 1-3, 2008
Dissemination

Workshop on “Recent Advances in Musculoskeletal Imaging”

Organized by: Ravinder Reddy and Felix Wehrli
Sponsored by: RR and ISMRM
Venue: Lake Louise
Date: February 20-24, 2009
Seminar series

- Seminars organized during the past year:
  - MMRRCC Journal club (weekly) --> 45
  - MR research and MMRRCC (bi-weekly) --> 12
  - Translational Neuroimaging (weekly) --> 40
  - Functional Pulmonary Imaging series (weekly) --> 40
  - Advances in Biomedical Optics (new-monthly) --> 8
Training

- BMB 603: Advanced topics in Magnetic Resonance, (Reddy, Leigh)
- BMB 581: Techniques of Magnetic Resonance Imaging (Felix Wehrli and Hee Kwon Song)
- BMB 620: Molecular Beacons, (Britton Chance)
- BE 480: Introduction to Biomedical Imaging, (Vadim Markel)
- Phys 421, 530: Modern Optics (Arjun Yodh)
Training

- Howard Hughes Medical Imaging Program
- Graduate students
- Undergraduates
- Post doctoral fellows
- Summer Students
- Minority students
- Visiting Fellows and faculty
- Radiology Residents and Fellows
- Hands on training on MR Optical Imaging equipment
Acknowledgements

H. Ralph Schumacher
J. Bruce Kneeland
George R. Dodge
Jess H. Lonner
Jay Udupa
Matthew Sochor
Matthew Fenty

Ari Borthakur
Walter Witschey
Eric Mellon
Mark Elliott
Michael Wang
John Q. Trojanowski
Virginia M-Y, Lee