"From Molecules to Man: The Importance of Molecular Imaging in Clinical Medicine"

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ADVANCED IMAGING
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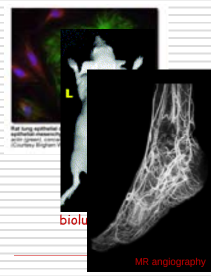
Frontiers in Biomedical Imaging symposium for STARS, Oct. 12, 2013

What is Molecular Imaging?



"Anatomy Lesson of Dr. Nicolaes Tulp" by Rembrandt
(slightly modified by Lewis Culver, UTSW)

Topics covered today

- Responsive molecular imaging agents
  - Optical agents
  - MRI agents
- Imaging physiology & metabolism
  - H^+, Zn^{2+} and metabolic fluxes
  - Hyperpolarized ^{13}C

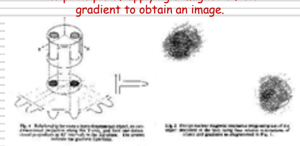
First, a little history

- The oldest "molecular imaging" technique (optical) has been around for centuries.
  - Romans were familiar with the ability of a prism to generate a rainbow of colors
  - Newton published on the dispersion of light & eventually the concept of wave theory
  - 1859 - Atomic emission studied by German physicists, Kirchhoff & Fraunhofer.
  - First synthetic dye – William Henry Perkin – 1856
  - Substantial dye industry after WWI - Germany
- MRI has been around for ~33 years!

Discovery of MRI

Paul Lauterbur

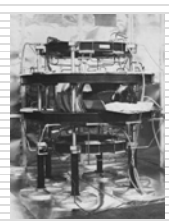
In 1971, Paul Lauterbur, a physical chemist from SUNY-Stony Brook sketched in his notebook the principle of applying a magnetic field gradient to obtain an image.



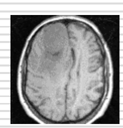
Lauterbur PC. Nature 1973; 242: 190-191.

1973- Peter Mansfield published the first cross-section image of a human finger
1975 – First cross-sectional image through a human abdomen.

The quick evolution of MRI scanners



1974 – first prototype MRI scanner at Aberdeen



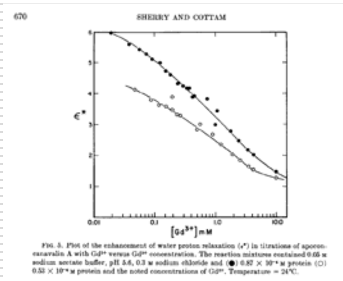
Circa 1980 MRI of human brain

2005 - 3T Philips clinical MRI scanner

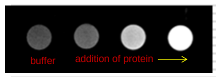
My first publication as a faculty member at UT Dallas

"Proton Relaxation Rate and Fluorometric Studies of Manganese and Rare Earth Binding to Concanavalin A"

AD Sherry & GL Cottam, Arch. Biochem. Biophys., **156**, 665-672 (1973).

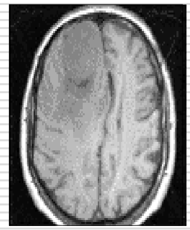


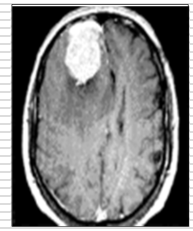
Little did we know how important this observation was to become and the role Gd^{3+} would one day play in medicine!



GdDTPA (Magnevist) was the first MR contrast agent approved for brain imaging -1987

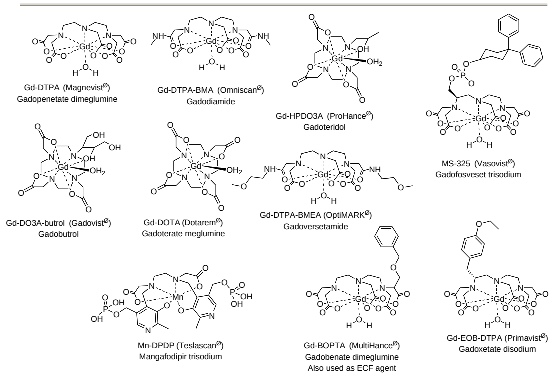
0.1 mmol/kg dose ⇒ 0.5M x 0.2 mL/kg x 65 kg = 13 mL



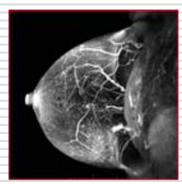


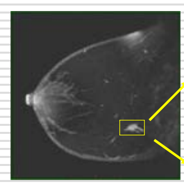
pre-Gadolinium post-Gadolinium

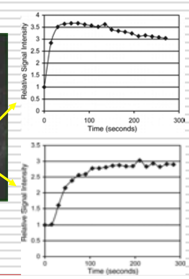
Clinical paramagnetic MRI contrast agents



Gd^{3+} MRI contrast agents commonly used for dynamic contrast enhancement (DCE) studies to diagnose tumors

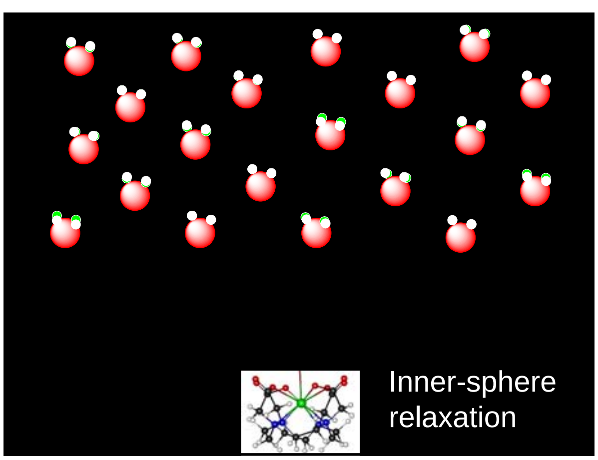




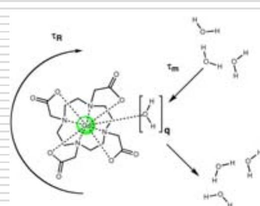


3D data set Single slice

Schnall, M. D. et al. Radiology 2006;238:42-53



Factors to consider in the design of a responsive probe for MRI



One of three parameters can be modified:

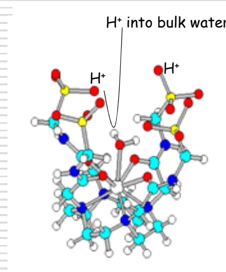
1. Rotational motion (τ_R)
2. number of inner-sphere water molecules (q)
3. Water exchange lifetime (τ_M)

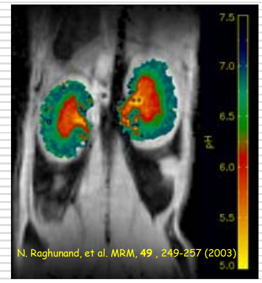
Why image H^+ and Zn^{2+}?

Inorganic ions are often overlooked in molecular imaging because……

1. There is no simple direct way to image the distribution of these ions in tissues
2. The tissue distribution of these ions can change dramatically with physiology
3. Ions are not easily manipulated using biology

Gd^{3+} complexes with slower water exchange rates can be an advantage for imaging pH

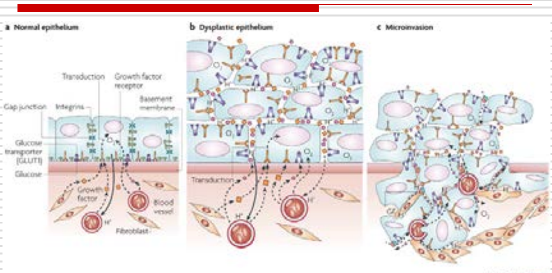




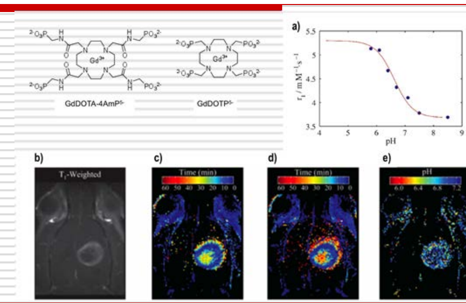
Nice, but unsatisfactory because an independent measure of agent concentration is necessary

A microenvironmental model of carcinogenesis

Gatenby & Gillies, Nature Reviews Cancer, 8, 56-61 (2008)



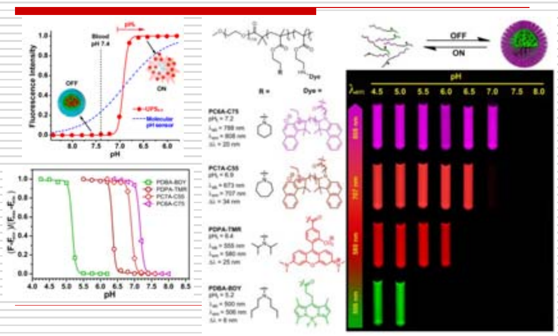
Imaging pH *in vivo*



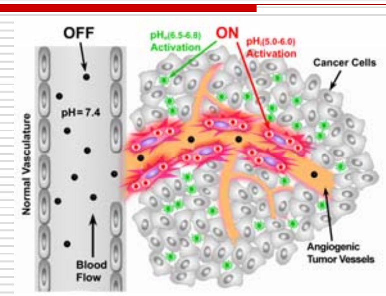
Garcia-Martin, et al., Magn. Reson. Med., **55**, 309-315 (2006)

Multicolored pH-Tunable and Activatable Fluorescence Nanoplatform Responsive to Physiologic pH Stimuli,

K Zhou, J Gao et al., JACS, 134, 7803-11 (2012)

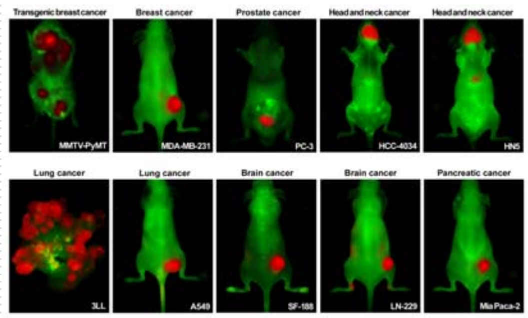


Targeting the Tumor Microenvironment



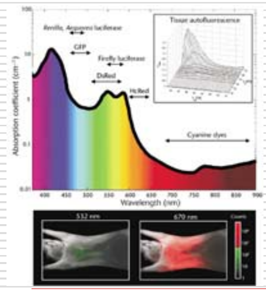
Yiguang Wang, Jinming Gao

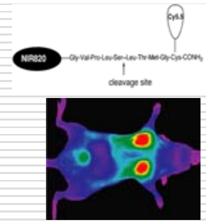
cRGD-coated micelles (PC7A-C55) show broad specificity in 10 tumors



Yiguang Wang, Jinming Gao

Optical imaging: The key for optical imaging applications in humans will be to find safe new reporter molecules for the NIR region





NIRF imaging of Breast cancer
(cathepsin-sensitive probe)

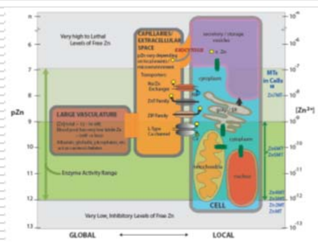
Intra-operative optical imaging guided surgery: Simple removal of light emitting tumors

Seeing is Curing:
A revolution in surgical Oncology !!

Mouse has been injected with a tumor specific NIRF probe

Jean-luc Coll, Grenoble

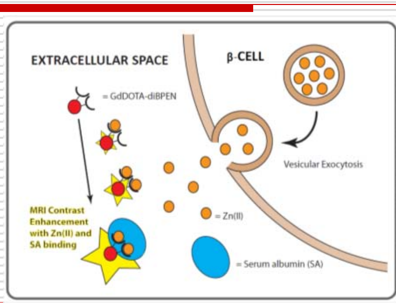
Why image free Zn^{2+}?



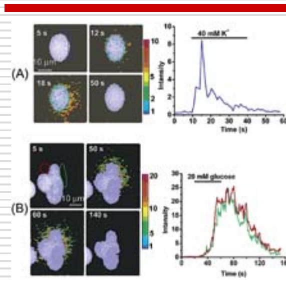
Zn^{2+} is an essential element used as a cofactor for many enzymes and transcription factors. Free Zn^{2+} is heavily regulated; too much is toxic and too little is detrimental for many biological processes.

Tissues with the most total Zn^{2+}:
- Brain
- Prostate
- Pancreas

Can we use release of free Zn^{2+} as an measure of β-cell function in the pancreas?



Fluorescence imaging of Zn^{2+} release from β-cells using FluoZin-3 (K_D= 15 nM)



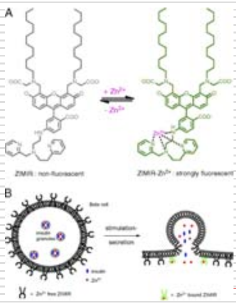
(A) Zn^{2+} release from a single cell induced by 40 mM K^+ stimulation.

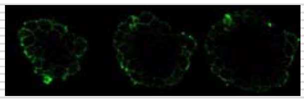
(B) Zn^{2+} release from a cluster of four cells induced by 20 mM glucose stimulation.

The total Zn^{2+} concentration near the cells reached 600 nM, and Zn^{2+} was detectable at least 15 μm away from secreting cells.

From: Qian, Gee & Kennedy, *Anal. Chem.*, 2003, 75 (14), pp 3468–3475

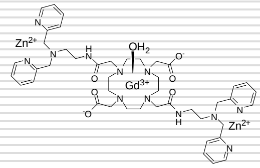
Imaging dynamic insulin release using a fluorescent zinc indicator for monitoring induced exocytotic release (ZIMIR)
Wen-hong Li, *et al.*, PNAS, **108**, 21063-68 (2011)

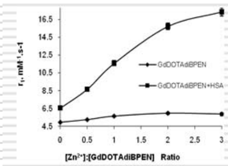




Confocal images of a single islet pre-loaded with ZIMIR (three different slices) after exposure of 20 mM glucose

A novel MRI Zn^{2+} sensor





In the absence of albumin, r_1 increases from 5 to 6 $mM^{-1}s^{-1}$ upon addition of Zn^{2+}

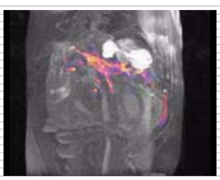
In the presence of albumin, r_1 increases from 6.6 to 17.5 $mM^{-1}s^{-1}$ upon addition of Zn^{2+}

K_d = 5 nM Positive contrast!

Esqueda, et al., JACS, 131: 11387-11391 (2009)

Imaging β-cell function in vivo

A new Gd-based Zn^{2+} sensor shows MR imaging enhancement of the pancreas only after a bolus injection of glucose



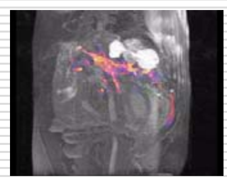
control

after STZ

Lubag, et al., PNAS 108: 18400-18405 (2011)

Imaging β-cell function in vivo

A new Gd-based Zn^{2+} sensor shows MR imaging enhancement of the pancreas only after a bolus injection of glucose



control

Photograph of the abdomen of an adult mouse (strain B6.Cg-Tg(ACTB-DsRed*MST) 1Nagy/J). Compliments of Sven Gottschalk, Ph.D., Max Planck Institute, Tuebingen.

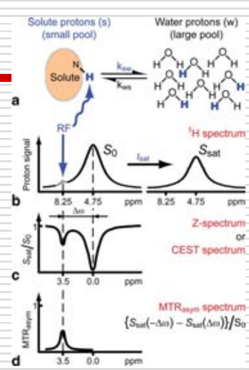
Lubag, et al., PNAS 108: 18400-18405 (2011)

CEST and paraCEST agents

projects for clinical translation

There are many chemical types of exchanging protons in tissue:

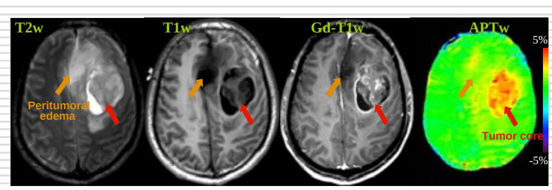
- N-H from proteins & amino acids, nucleic acids
- O-H from sugars, polysaccharides
- S-H from cysteine & glutathione
- many others



From "Chemical Exchange Saturation Transfer (CEST): What is in a Name and What Isn't?" P. van Zijl & N. N. Yadav, Magn. Reson. Med. 65: 927-948 (2011)

Amide Proton Transfer (APT) signal of tumors reflects enhanced –NH proton exchange

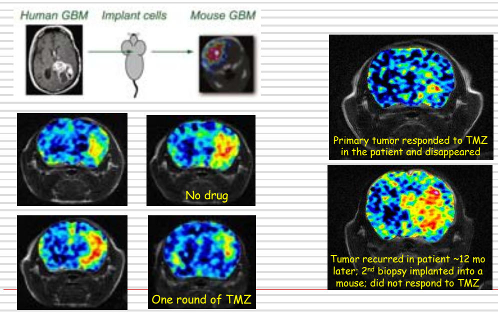
Wen, et al., NeuroImage, 51: 616-622 (2010)



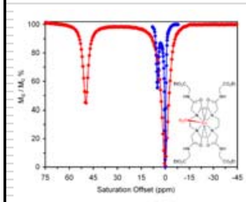
Note: limited contrast in edema region (orange arrow); high APT contrast in tumor

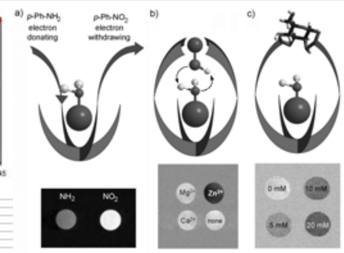
APT imaging detects early response in glioblastoma (GBM) to temozolomide

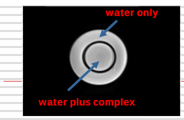
M. Takahashi, et al., PNAS, in preparaton



PARACEST agents can be turned "on" and "off" using frequency-selective RF pulses







The CEST intensity is highly sensitive to water exchange rates ⇒ relatively easy to design responsive agents

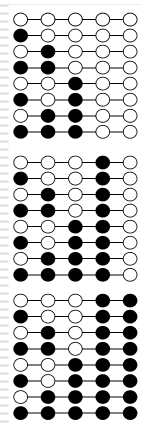
Other MR active nuclei for probing physiology and metabolism

^{13}C is important as a tracer of metabolism but its NMR properties are not favorable (0.016 to ^{1}H)

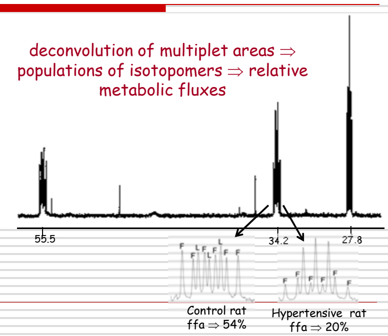
- Steady-state ^{13}C isotopomer methods
- Hyperpolarized ^{13}C tracers of metabolism

^{13}C isotopomer analysis of tissue metabolites

FEBS Lett, 212: 58-62 (1987); J Biol Chem, 263: 6964-71 (1988); Biochem J, 254: 593-8 (1988).

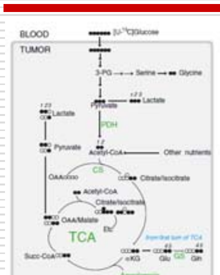


deconvolution of multiplet areas ⇒ populations of isotopomers ⇒ relative metabolic fluxes

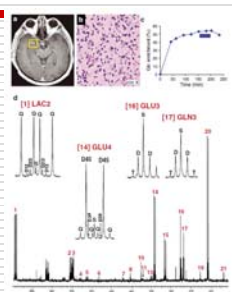


Metabolism of [U-$^{13}C_6$]glucose in human brain tumors *in vivo*

EA Maher, et al., NMR in Biomed. 25: 1234-1244 (2012)

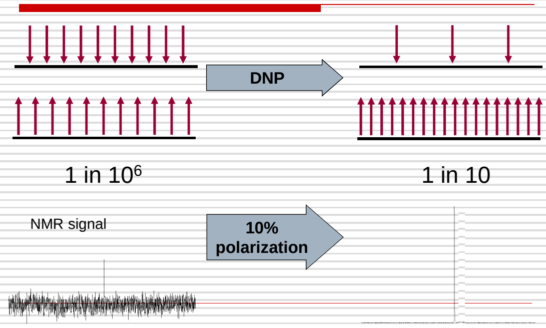


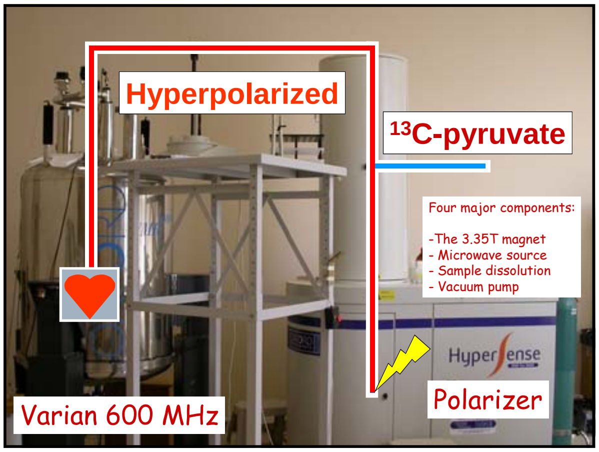
Summary of glucose metabolism in tumors. Filled circles represent a carbon with enriched ^{13}C; open circles reflect ^{12}C



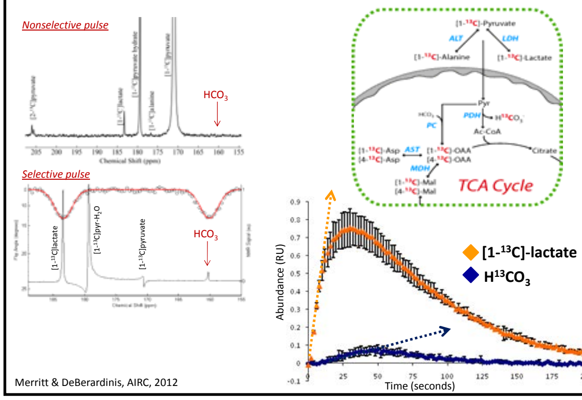
^{13}C NMR spectrum of tumor tissue removed from a patient with a WHO grade II astrocytoma after infusion of [U-^{13}C]glucose for 2 hr prior to surgical resection and during removal (8 g/h)

Dynamic nuclear polarization



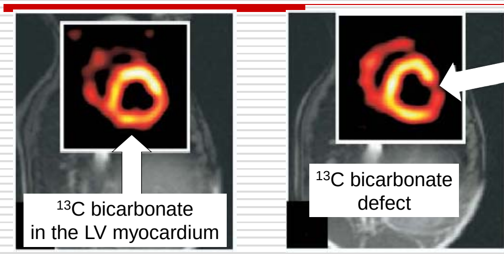


Metabolism of Hyperpolarized Pyruvate in Cancer Cells



Merritt & DeBerardinis, AIRC, 2012

^{13}C imaging of metabolism through PDH

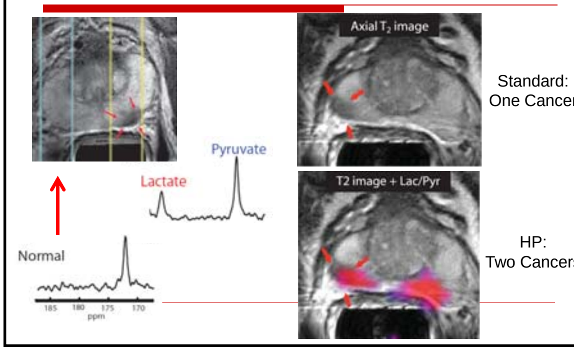


Pre Ischemia | Post Ischemia

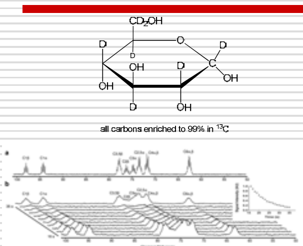
Golman, et. al. *Academic Radiology* 3: 932-942 (2006)

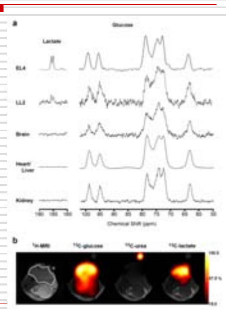
Metabolic Imaging of Patients with Prostate Cancer Using Hyperpolarized [1-^{13}C]Pyruvate

S. Nelson, et al., Sci Transl Med, 5: (2013)



Imaging glycolysis using HP-[U-$^{13}C_6$-$^2H_{12}$]-glucose?





Perdeuterated glucose has a long (enough) polarization lifetime, ave $T_1 \sim 9$ s

Rodrigues, T, et al., *Nature Med.* In press

Summary

- Optical imaging is great for studying biology & for surgical procedures but otherwise limited in humans.
- Magnetic resonance is less sensitive than optical by far but one can obtain high resolution images of deep tissues.

- Responsive MR agents will provide important diagnostic information if………..they approved by the FDA.
- Zn^{2+} sensitive agents may prove useful for monitoring β-cell function in implanted islets (type I) and during development of type II diabetes.
- Hyperpolarized ^{13}C imaging is moving quickly toward clinical applications.

The biggest joy in science is having the opportunity to work with so many smart and talented people

Thanks to my many students, postdocs & collaborators

- Grad & UG students, postdoctoral fellows: approaching 100
- Former Postdocs: Mark Woods (Portland State & OHSU), Jurriaan Huskens (Twente), Gyula Tirsco (Hungary), Ravi Ramasamy (NYU), John Jones (Coimbra), Navin Bansal (IUPUI), Zoltan Kovacs, Jimen Ren, Eunsook Jin, Shanrong Zhang, Yunkou Wu and Shawn Burgess (UTSW).
- Collaborators: Garry Kiefer (CEO, Macrocyclics), Carlos Geraldes (Portugal), Chris Newgard (Duke), Bob Gillies (Moffitt), Peter Caravan (MGH), Erno Brücher (Hungary), Silvio Aime (Torino), Peter van Zijl (Hopkins), Bob Lenkinski, Jinming Gao, Mark Jeffrey, Matthew Merritt, and Craig Malloy (UTSW).

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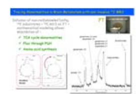
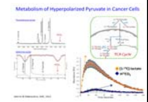
Earn a PhD from UT Southwestern in Biomedical & Molecular Imaging (BMI)

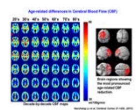
Chemistry, physics, biochemistry and other physical science majors. Come join an exciting group of basic science and clinical investigators develop and apply new cutting edge imaging technologies, molecular imaging probes, and image processing techniques. The BMI track offers many new opportunities to apply your knowledge and skills in helping translate new discoveries from bench-to-bedside.



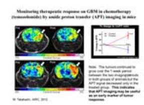
7 Tesla MRI and MRS



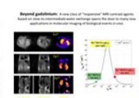
Imaging cancer metabolism



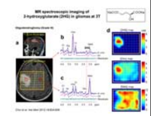
Clinical & basic science brain imaging



Small animal imaging



The chemistry of new PET and MRI probes



Translating spin physics to cancer patients