

**Strategies for synergizing pre-clinical and clinical acquisition for future co-clinical trials**

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**Why co-clinical trials?**

- Goal to develop a synergistic approach, imaging pre-clinically and clinically that is compatible
  - Introduce you to HP MRI – probably the hardest example
- First need the same hardware
- Need the same molecules
  - HP preparation, design and enhancements
- Need the same acquisition sequences
  - Dynamics?
- Reconstruction/data processing



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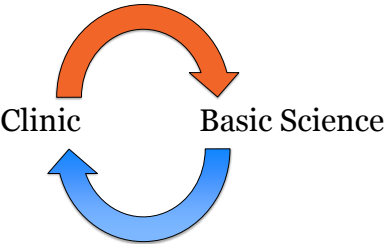
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**Why co-clinical trials?**



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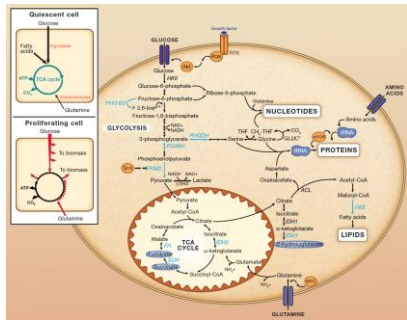
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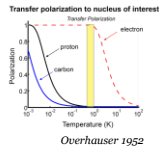
## Why co-clinical trials with HP MRI



Finley et al. Cell Metab 2013

Memorial Sloan-Kettering  
Cancer Center

## Hyperpolarized Magnetic Resonance (HP MR)

Clever  
Physical Chemistry

Which leads to Hyperpolarization!

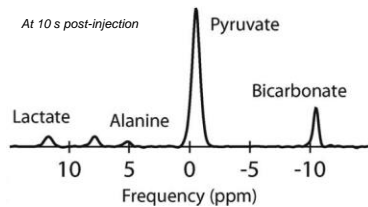
+ HP

Present

Memorial Sloan-Kettering  
Cancer Center

## Using HP MR to image Metabolic Dynamics

- How do we use HP MR to image metabolism using this non-radioactive probe?
- We utilize an endogenous substrate, pyruvate
- Follow the conversion of HP pyruvate through many pathways in seconds!
  - Reduction to HP Lactate
  - Transamination to HP Alanine
  - Decarboxylation to HP carbon dioxide and later bicarbonate (pH)



Lui et al. Magn Reson Med 2011

Memorial Sloan-Kettering  
Cancer Center

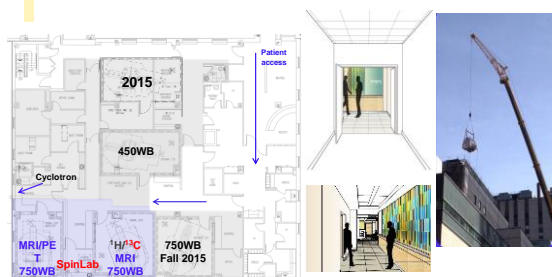
## Hyperpolarized Probes for Cancer Metabolism

Potential Probes	Structure	Cancer Role/ Metabolic Target
Pyruvate		Lower glycolysis (LDH, ALT, TCA)
Fructose		Higher glycolysis (including PPP)
Bicarbonate		Extracellular pH
Fumarate		Necrosis
Urea		Perfusion
Dehydroascorbate		Redox/oxidative stress
Glutamine		Glutaminolysis

Koshari and Wilson Chem Soc Rev 2014



## Center for Integrated Metabolic Imaging (CIMI)

11<sup>th</sup> floor of the Bobst Building – Department of Radiology

## Hyperpolarized MR Metabolic Imaging at MSKCC

2<sup>nd</sup> hyperpolarizer installed in New York!Installed in Memorial Hospital (11<sup>th</sup> floor of Bobst) - "Highest" in the world, approximately 173ft above sea level

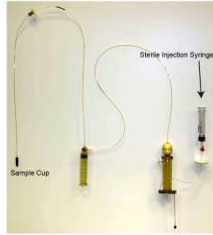
## Center for Integrated Metabolic Imaging (CIMI)

5T SpinLab Hyperpolarizer



Quality Control System

Sterile Fluid-path Assembly



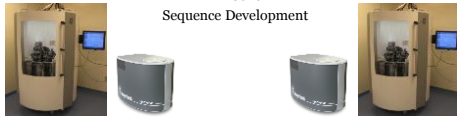
## Multi-modality Metabolic Imaging Hardware

Memorial Hospital (CIMI)

E. 68<sup>th</sup> St.

Cancer Metabolism  
Probe Development  
RF Coils  
Sequence Development

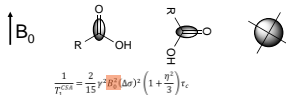
Sloan Kettering Institute (Keshari Lab)



## Why does field strength matter for MRI?

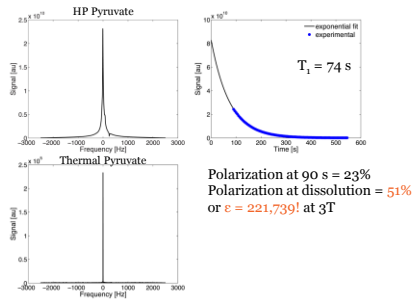
- Relaxation ( $T_1$ ,  $T_2$ , etc.) properties of both tissue and molecules
- For anatomic imaging, contrast is dependent on field strength
  - E.g. the effect of Gd based contrast agents is dramatically different at high field as compared to typical clinical field strengths (1.5-3T)
- For HP, molecular  $T_1$ s are a function of field strength
  - Chemical Shift Anisotropy (CSA)  $\Rightarrow$  shorter  $T_1$ s at high field, can change the biomarkers we observe

“Wobbling” induced relaxation

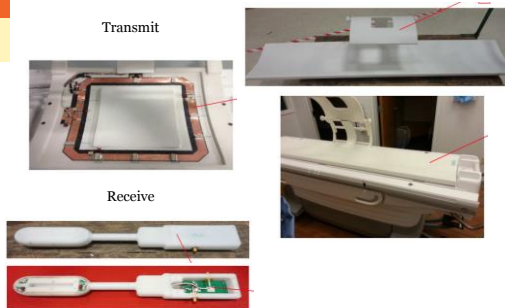


Center for Integrated Metabolic Imaging  
(CIMI)

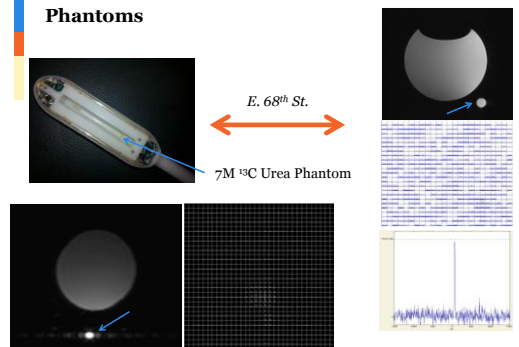
- First polarization on a clinical 3T at MSKCC from the full system (patient size dose)



Detection – RF Coils

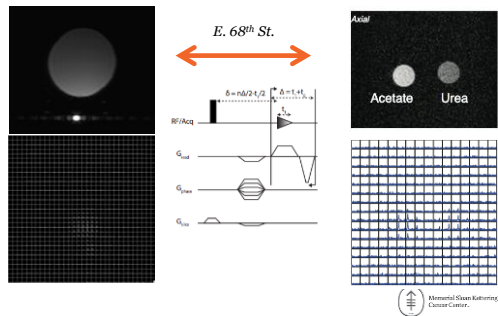


Phantoms

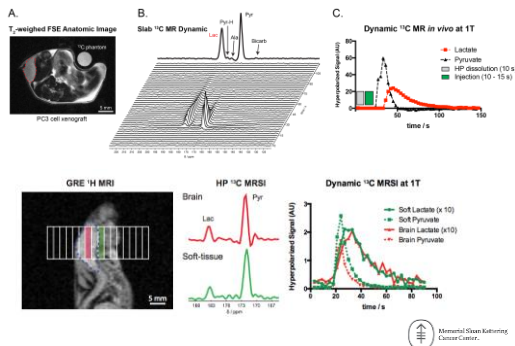


## Sequences

### 2D/3D Echo-planar Spectroscopic Imaging (EPSI)

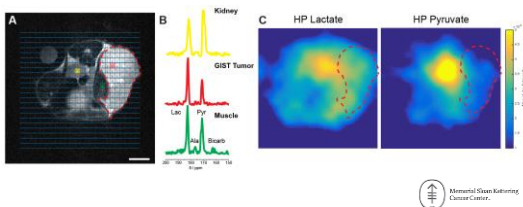


## Animal dynamic data



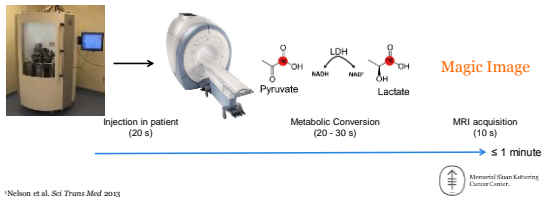
## Reconstruction and analysis

- Once the data is acquired, we need uniform reconstruction methods
  - For HP MRI this becomes simple, FT
- More importantly, we need to develop translational biomarkers that go back and forth (bench to clinic and back)
  - The challenge of quantitation
  - Benefit of HP MRI derived ratios (e.g. Lac/Total Carbon maps)

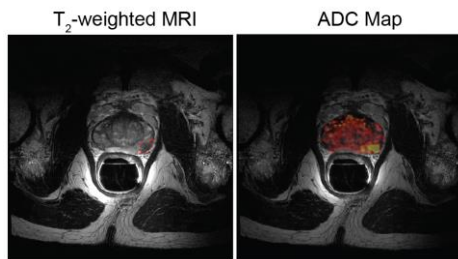


## Clinical Translation of *HP* MR

- Phase 1 of HP pyruvate demonstrates safety<sup>1</sup>
- IRB protocol for HP pyruvate **approved** (#14-205 PI: Keshari, CoPI: Hricak)
- IND **acknowledged** for sterile compounding of pyruvate onsite (#11259470, PI: Keshari, Co-PI: Hricak)



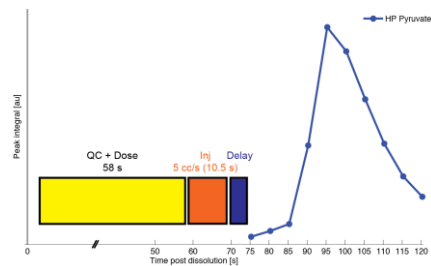
Identify a suitable prostate cancer patient (Patient 1)



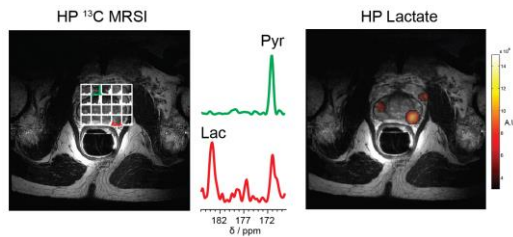
- Left base, midgland and apex had biopsy proven G4+4, PSA = 11.06ng/ml



Infuse the Patient 1 with HP pyruvate



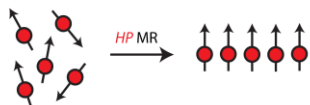
## HP pyruvate in our first patient



- Left base, midgland and apex had biopsy proven G4+4, PSA = 11.06ng/ml



## Now and the Future...



- Hyper**polarized Magnetic Resonance (HP MR) can work...believe it or not
- At MSKCC we have begun patient trials to build a foundation for imaging of patients
- Dynamics of delivery are important and this will allow us to go between mice and man
- Synergy with other anatomic/functional imaging, including PET!
- Will propose co-clinical trials where patient and mice receive the same therapy and receive the same imaging at the same field



## Acknowledgements

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Keshari Lab

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### Colleagues/Collaborators

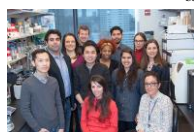
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Donna Pechl

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James Tropp  
Rui Chen  
James Trigger



<http://www.mskcc.org/research/lab/kayvan-keshari>



Experimental Therapeutics Center  
Cycle for Survival  
Translational Kidney Cancer Research Program  
Center for Molecular Imaging and Nanotechnology  
Mary Ralph Fund  
Geoffrey Beene Cancer Center

