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San Francisco

Co-Clinical Quantitative Imaging of Small Cell Neuroendocrine Prostate Cancer Using Hyperpolarized ^{13}C MRI

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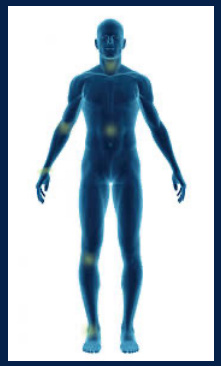
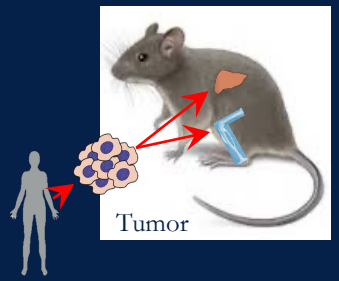
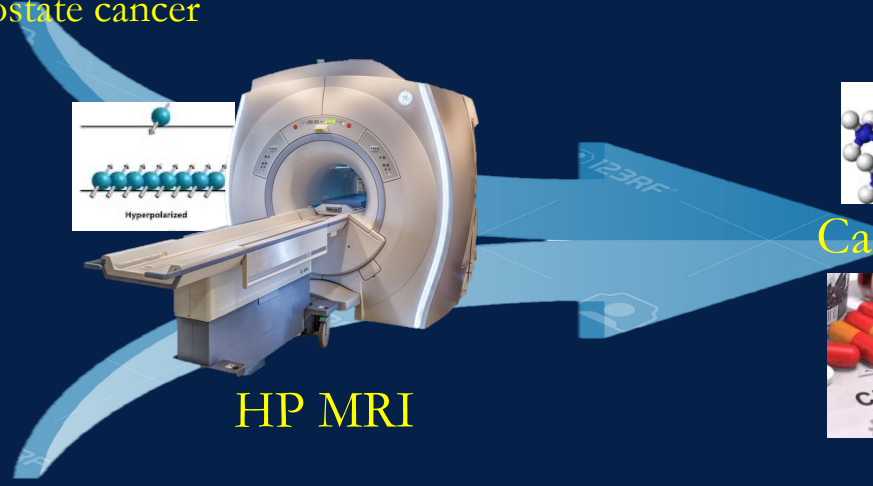
U24 - Oncology Co-Clinical Imaging Research Resources to Encourage Consensus on Quantitative Imaging Methods and Precision Medicine

This co-clinical study is aimed at developing comparable optimal murine HP ^{13}C MRI protocols in realistic and representative models of small cell neuroendocrine prostate cancer bone and liver metastases to inform on therapeutic response using quantitative metrics to populate an online resource.

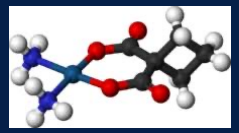


Biopsy proven neuroendocrine prostate cancer

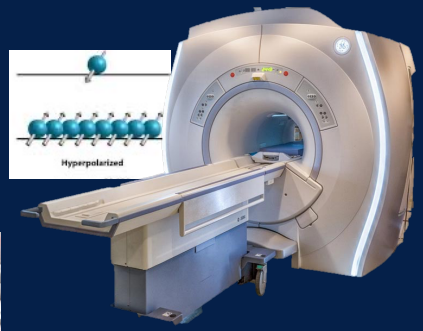




HP MRI



Carboplatin



Repeat - HP MRI

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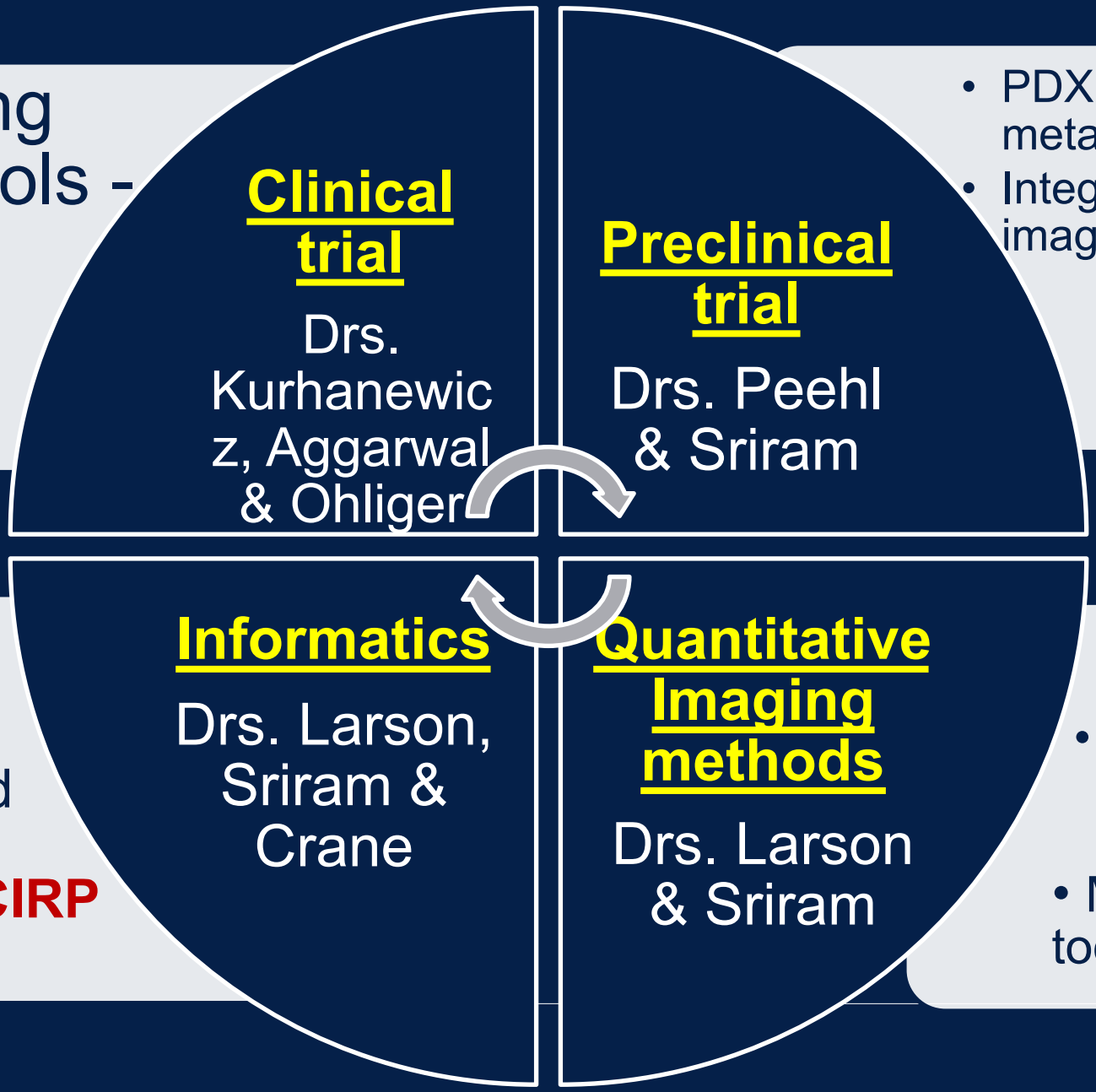
UCSF Team



- Imaging protocols - **TCIA**

- PDX models of metastases
- Integration of imaging & biological data - **OMF**

- Online data and analysis portal - **CIRP**

- Optimized imaging routines
- Modeling toolbox - **QIN**

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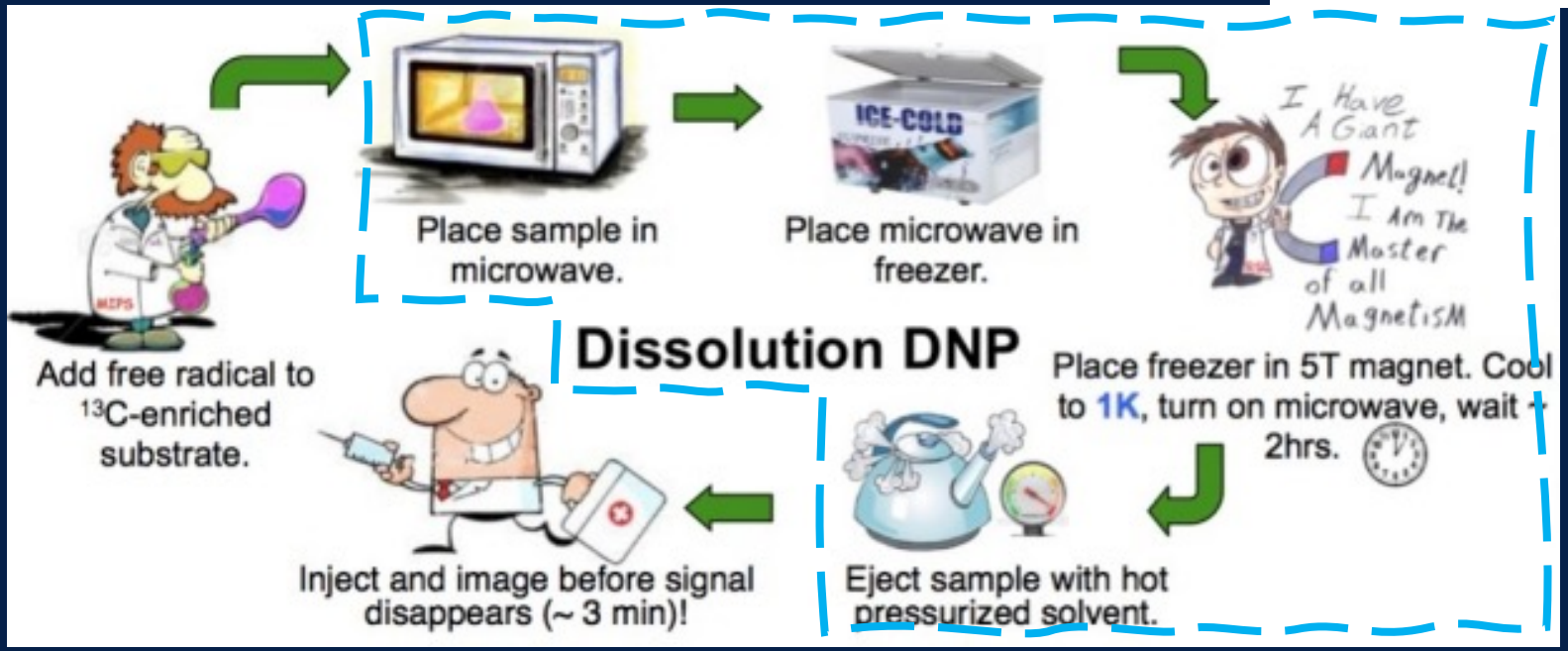
What is hyperpolarized 13C MRI?

Clinical

Preclinical

Polarizer



Credits: Stanford.edu

Ardenkjaer-Larsen et al. *PNAS* 2003.

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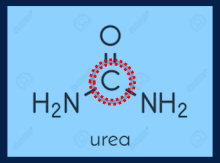
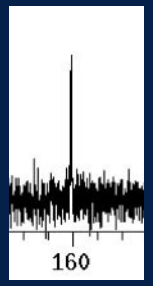
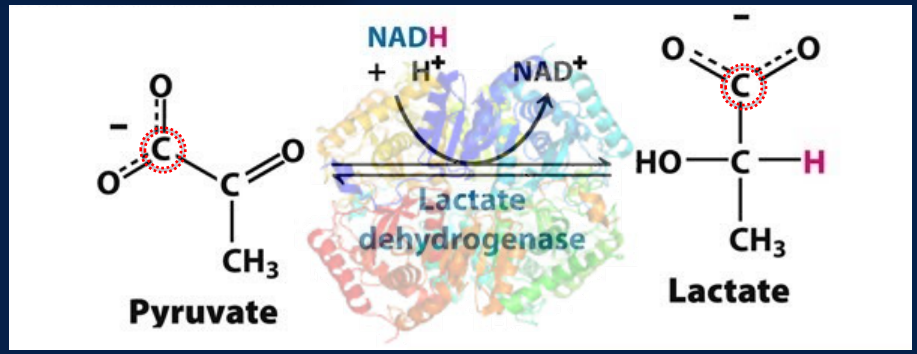
What is hyperpolarized 13C MRI?





$>10^4$



- Rapid dissolution methods
- Over 50,000- fold enhancement
- T_1 – dependent signal decay
- Enables observation of dynamic enzymatic conversion

Credits: Stanford.edu

Ardenkjaer-Larsen et al. *PNAS* 2003.

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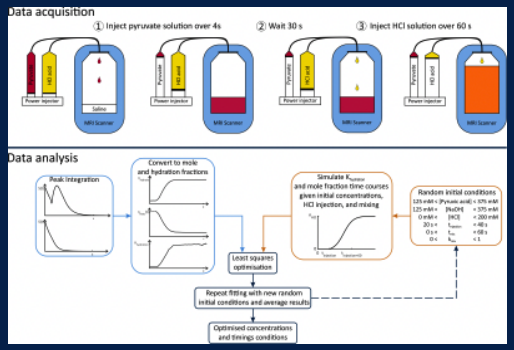
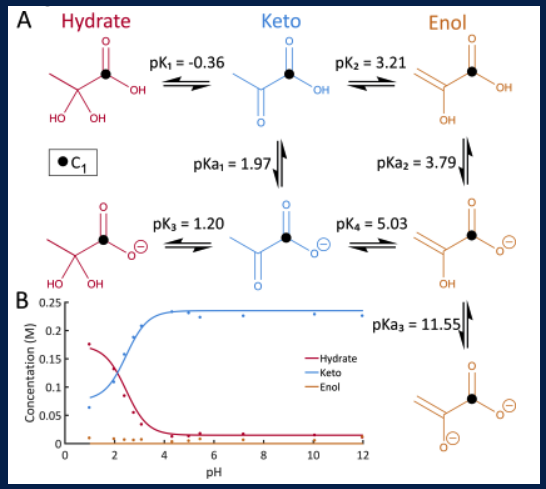
Project 1: Development of phantoms for testing rigor and reproducibility of hyperpolarized signal and kinetic modeling

Chemistry based





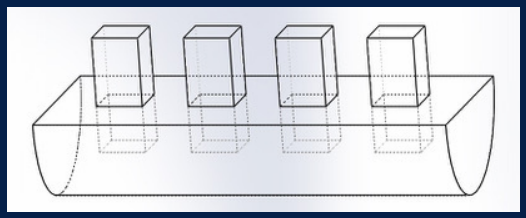
3028

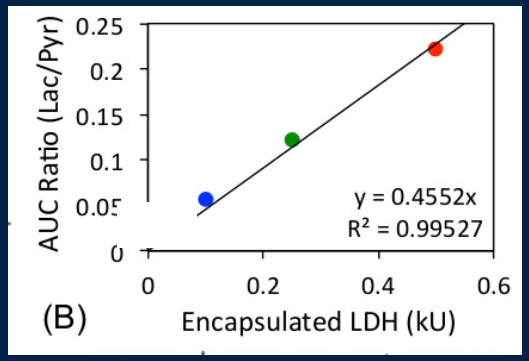
ROKET: a Robust Keto Enol Tautomerisation phantom for multi-site, multi-vendor hyperpolarized ^{13}C studies

Liam A J Young[1,2], Jack JJJ Miller[1,3], Ladislav Valkovic[1,4], Esben SS Hansen[5], Mary A McLean[6,7], Ferdia A Gallagher[7], Christoffer Laustsen[5], Damian J Tyler[1,3], Christopher T Rodgers[1,2], and Justin YC Lau[1,3]

[1]Oxford Centre for Clinical Magnetic Resonance Research (OCMR), University of Oxford, Oxford, United Kingdom, [2]Wolfson Brain Imaging Centre, Department of Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom, [3]Department of Anatomy and Physiology, University of Oxford, Oxford, United Kingdom, [4]Department of Imaging Methods, Institute of Measurement Science, Slovak Academy of Sciences, Bratislava, Slovakia, [5]Department of Clinical Medicine, the MR Research Centre, Aarhus University, Aarhus N, Denmark, [6]CRUK Cambridge Institute, University of Cambridge, Cambridge, United Kingdom, [7]Department of Radiology, University of Cambridge, Cambridge, United Kingdom

Enzyme based





Phantom layout with varying concentrations of enzyme, B) Measurement of hyperpolarized signal in LDH trapped alginate microspheres with 0.1 (blue), 0.25 (green) and 0.5 (red) kUnits.

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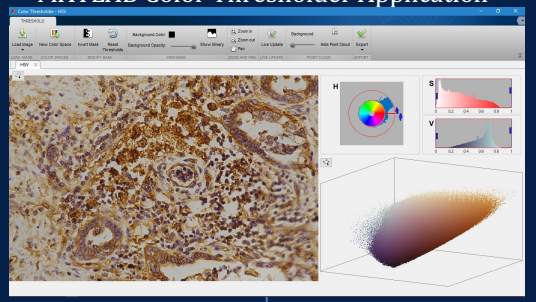
Project 1: Development of phantoms for testing rigor and reproducibility of hyperpolarized signal and kinetic modeling

- Goal : Develop and test phantoms in clinical and preclinical polarizers for repetability
- Encompasses:
  - 3D printing
  - Basic biochemistry – enzyme kinetics isoforms, keto-enol tautomerization
  - Hyperpolarized ^{13}C MRI
  - Kinetic Modeling

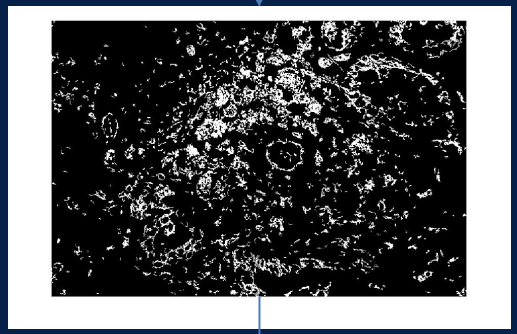
Project 2: Quantification of immunohistochemical stains

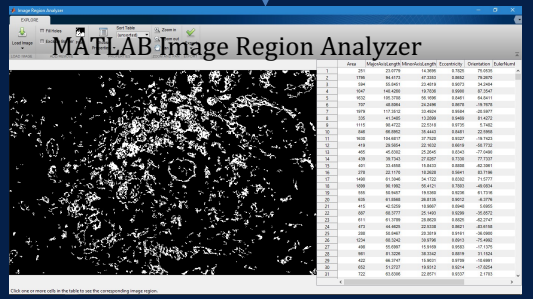
- Need: Correlate quantitative imaging metrics to molecular pathological markers
- Goal : Develop image processing algorithms to quantify expression of specific proteins form immune histochemical stains
- Encompasses:
  - Immunohistochemical stains
  - Clinical Pathology
  - Microscopy
  - Image Processing

MATLAB Color Thresholder Application



Threshold





% MCT4 calculated using sum of pixels detected

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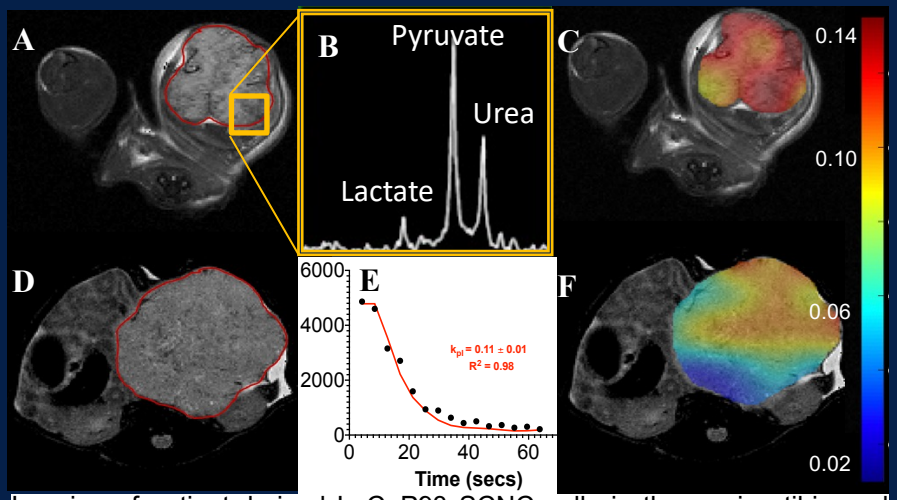
Data Analysis

- Inputless unidirectional model to calculate k_{PL} the apparent rate of conversion of pyruvate to lactate. Optimization of model and its parameters
  - Multi-compartment model
  - Inclusion of vascular input function
  - Impact of T1 values used for modeling
- Reproducibility
  - Robustness of model parameters using phantom
  - Evaluate intra and inter tumor variability



Imaging of patient-derived LuCaP93 SCNC cells in the murine tibia and liver. (A,D) T_2-wt MRI shows the tumor in the left limb and liver (outlined in red). B) HP spectroscopic imaging shows the injected HP pyruvate and urea signal and the HP lactate produced from pyruvate in tumor voxel (orange square). E) Lactate signal dynamics observed in the liver tumor over time (black dots) was fitted using inputless model (red line) to yield a k_{PL} of 0.11 s^{-1} in the liver. (C,F) Calculated k_{PL} map overlaid on the tumor.