

Specialty area: Session: Imaging Metabolism with Hyperpolarized Nuclei
Talk title: Preclinical Metabolic Imaging (Cancer, Cardiac, Kinetic Analysis)
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Highlights

- Indicative of increased tumor glycolysis, multiple pre-clinical models show elevated lactate labeling using hyperpolarized ^{13}C -pyruvate, with lactate signals characteristic of cancerous tissue, reflective of tumor grade, and indicative of early treatment response.
- ^{13}C -pyruvate (Pyr) is a particularly promising cardiac imaging agent with the relative conversion to acetyl-coA compared to lactate potentially serving as an assessable in vivo signal of myocardium viability.
- Kinetic analysis techniques are used to better establish the quantitative linkage between the observed MR signal changes and the underlying physiology.

Background. The development of MRS of hyperpolarized substrates has enabled for the first time the real-time investigation of *in vivo* metabolism with more than a 10,000-fold signal increase over conventional methods, with studies of ^{13}C -labeled compounds polarized using Dynamic Nuclear Polarization (DNP), to date, finding the most applications [1]. In vivo studies of pre-clinical animal models using this technology has provided and continues to provide important new insights into metabolic processes within healthy and diseased tissue. Here we highlight findings from two important applications, cancer and heart disease, followed by a discussion of the ongoing efforts to better quantify the findings in order to establishment of a stronger linkage between the observed MR signal changes and the underlying physiology.

Cancer. In addition to their abnormally high proliferative rates, cancer cells universally demonstrate an abnormal phenotype characterized by an overutilization of glycolysis (GLY) relative to the more energy efficient mitochondrial oxidative phosphorylation (OXPHOS). It is thus not surprising that one of the most successful applications of hyperpolarized MRS has been following the *in vivo* fate of ^{13}C -labeled Pyr as a substrate occupying a key nodal point in the metabolic pathway in which glucose is either converted to lactate (reflecting GLY) or converted to acetyl CoA, the first step towards OXPHOS. Multiple pre-clinical models show lactate-labeling characteristic of cancerous tissue, reflective of tumor grade, and indicative of early treatment response [2].

Cardiac Applications. Cardiac metabolism is highly regulated by physiological conditions and energetic needs, with the heart able to rapidly switch between fatty acids, ketones, and glucose. Altered substrate utilization is strongly interlinked with diseases such as cardiomyopathy, hypertension, and ischemia, with multiple large and small animal models showing the utility of ^{13}C MRS of hyperpolarized substrates to measure these changes in normal and diseased hearts [3].

Kinetic Analysis Tools. Interpretation of MR findings are complicated by multiple processes, including metabolic flux versus isotopic exchange, nonlinear saturation and inhibition effects, and intrinsic pool size limitations. A variety of analysis approaches including metabolite ratios, apparent exchange rates, saturation kinetics, and filtering of non-locally produced metabolites have been proposed to tease apart these effects with varying degrees of success.

Conclusion. MR metabolic imaging of hyperpolarized ^{13}C -labeled compounds in preclinical models have revealed both new insights into health and disease and, often for the first time, provided non-invasive *in vivo* measures of key metabolic pathways. Such animal studies are critical for improved diagnosis, outcome prediction, and therapy monitoring, ultimately leading to the development of new drugs and/or direct clinical trials of hyperpolarized ^{13}C -MRS.

References

1. Mansson, S., et al., *^{13}C imaging—a new diagnostic platform*. Eur Radiol, 2006. **16**(1): p. 57-67.
2. Brindle, K.M., et al., *Tumor imaging using hyperpolarized ^{13}C magnetic resonance spectroscopy*. Magn Reson Med. **66**(2): p. 505-19.
3. Malloy, C.R., M.E. Merritt, and A.D. Sherry, *Could ^{13}C MRI assist clinical decision-making for patients with heart disease?* NMR Biomed. **24**(8): p. 973-9.