Towards Real-time Metabolic And Molecular Imaging Of Cancer By Three Different Modalities Of Hyperpolarization

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Purpose: Hyperpolarized magnetic resonance is a non-toxic, non-radioactive method for assessing tissue metabolism and other physiologic properties. Hyperpolarization allows for over 10,000-fold signal enhancement relative to conventional magnetic resonance imaging (MRI) or spectroscopy (MRS). After hyperpolarization, the signal enhancement can be retained on the metabolites of the hyperpolarized molecules for several minutes prior to relaxing. Several laboratories are working on techniques to extend this relaxation time so that more detailed imaging studies over longer time scales can be considered.

Methods: My laboratory has worked on three different modalities of hyperpolarization, both on technique development as well as advancing novel *in vivo* applications. The research described is focused on the different *in vivo* applications of Parahydrogen Induced Polarization (PHIP) (and subsequent transfer to ^{13}C), continuous flow Dynamic Nuclear Polarization (DNP) of water (^{1}H), and long lived DNP hyperpolarized signal of Silicon nanoparticles (^{29}Si) as molecular imaging agents.

Results: a) By PHIP, we have hyperpolarized diethyl succinate and used this endogenous compound to image the downstream metabolites of the Krebs cycle in real time in rodents within one minute (1). Efforts are underway to fingerprint the ^{13}C resonances of the TCA cycle metabolome in different cancer models *in vivo* and to correlate that with the gene expressions (Fig 1). b) Employing continuous flow DNP of hyperpolarized water, we were able to obtain perfusion contrast for (^{1}H) MR imaging, thereby providing localized angiography *in vivo* in rat models (Fig 2) (2). This sensitivity gain of water rivals that of gadolinium-based contrast agents. c) We have extended the hyperpolarized applications in nanoparticles by demonstrating direct *in vivo* imaging of hyperpolarized ^{29}Si nuclei in silicon particles using MRI (3). ^{29}Si hyperpolarization was generated by low-temperature DNP using naturally occurring defects at the particle surface, and showed a characteristic decay time of over 40 min, unaffected by particle tumbling in solution, surface functionalization, or the local *in vivo* environment. Applications in gastrointestinal, intraperitoneal, intravascular and perfusion imaging at sub-picomolar concentrations have been shown (Fig 3). Efforts are underway to develop this technique for non-invasive colonoscopy to detect colon polyps and tumors at an early stage as well as functionalize the nanoparticle surface for targeted receptor imaging in pancreatic and ovarian cancers *in vivo*.

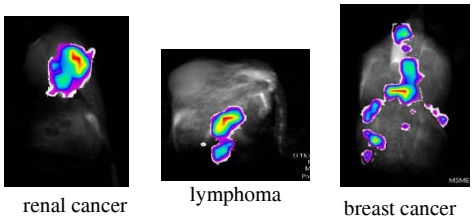

Fig 1. PHIP ^{13}C hyperpolarized imaging on three sub-cutaneous animal models in a 4.7T animal scanner. The ^{13}C-images (false color) illustrate the difference in the biodistribution of hyperpolarized Diethylsuccinate after intravenous injection of 20 µmol of hyperpolarized agent in three types of allograft tumor animal models. The signal persists for ~1.5 mins.

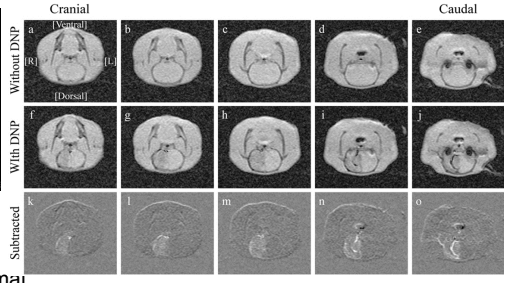

Fig 2. *In Vivo* brain imaging in a rat employing hyperpolarized water MR in a clinical 1.5T MR scanner. The signal from the right hemisphere of the brain was attenuated and arteries in the brain were visualized when injecting water into the right carotid artery.

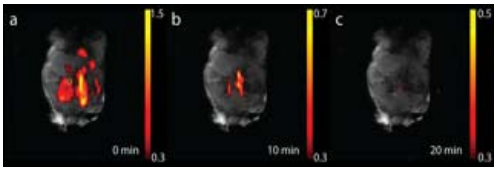

Fig 3. ^{29}Si MRI of hyperpolarized silicon particles injected into the tumor of a prostate cancer (TRAMP) animal in a 4.7T animal scanner. At 10 and 20 minutes, the silicon particles are more concentrated in the upper right side of the tumor indicating the area of blood flow from the tumor.

Conclusion: The three different hyperpolarized imaging modalities have opened up the possibilities for visualizing metabolism and other molecular events in real time wherein the local status of cancer can be interrogated on the time scale of seconds to tens of minutes with unprecedented chemical specificity and MR sensitivity, where both early detection as well as the efficacy of cancer therapy can be imaged.

References: (1) Zacharias, *et al.* J Am Chem Soc 2012;134(2):934-43. (2) Lingwood, et al. Radiology 2012;265:418-425. (3) Cassidy, *et al.* 2012.

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