Next-Generation Enabling Clinical MRI Technologies

WAYNE STATE UNIVERSITY

Ed Chekmenev

September 13, 2023
Wayne State University
Academy of Scholars

BARBARA ANN Karmanos CANCER INSTITUTE
Wayne State University

SUPPORT UKRAINE

Biography & Disclosures

1994-1998	B.S., Department of Chemistry, Perm State University, Perm, Russia
1998-2003	Ph.D., Department of Chemistry, University of Louisville, Louisville, KY Physical Chemistry, solid-state Nuclear Magnetic Resonance (NMR) with Richard J. Wittebort
2003-2005	Postdoctoral Fellow, National High Magnetic Field Laboratory, Tallahassee, FL Solid-state NMR spectroscopy of transmembrane proteins (Influenza A) with Tim Cross
2006-2009	Postdoctoral Fellow (James G. Boswell fellowship and NCI K99 award), California Institute of Technology & Huntington Medical Research Institutes (HMRI), Pasadena, CA with Dan Weitekamp (Caltech) and Brian D. Ross, MD, Oxon (HMRI) Hyperpolarized NMR and MRI
2009-2015	Assistant Professor of Radiology and Radiological Sciences at Vanderbilt University Institute of Imaging Science (VUIIS), VUMC, Vanderbilt University
2016-2018	Associate Professor of Radiology and Radiological Sciences at Vanderbilt University Institute of Imaging Science (VUIIS), VUMC~~, Vanderbilt University~~
2017	Co-founded XeUS Technologies, LTD, Nicosia, Cyprus Instrumentation for MRI contrast agents production
2018-now	Associate Professor (promoted to full in 2021) of Chemistry and Oncology Department of Chemistry, Karmanos Cancer Institute (KCI), Integrative Biosciences (Ibio) Wayne State University, Detroit, MI
2022-now	Scientific Advisory Board (SAB) of Vizma Life Sciences, Durham, NC Instrumentation for MRI contrast agents production

Acknowledgements

Wayne State University

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- Mohammad Kabir
- Clementinah Oladun
- Md Firoz Ahmed
- Anna Samoilenko, Pharm D
- Prof. Juri G. Gelovani
- Dr. Ayman Soubani
- Prof. Anthony Shields
- Dr. Michael Bradley
- Prof. Safwan Badr

External Collaborators & Contributors

- Prof. Boyd Goodson & team: (SIUC, Carbondale, IL)
- Dr. Kirill V. Kovtunov, Prof. Igor V. Koptyug, Dr. Nikita Chukanov, Dr. Larisa Kovtunova & Dr. Oleg Salnikov from International Tomography Center, Novosibirsk/Russia
- Prof. Matthew S. Rosen (MGH, Harvard)
- Prof. Yi-Fen Yen (MGH, Harvard)
- Prof. Thomas Theis & team (NCSU, Raleigh, NC)
- Prof. Warren S. Warren & team (Duke University, Durham, NC)
- Prof. Stephan Appelt (RWTH Aachen University, Germany)
- Prof. Chunqi Qian (Michigan State University, Lasning, MI)
- Prof. Rahim Rizi and Prof. Stephen Kadlecek (Upenn)
- Dr. Jessica Ettedgui (NHLBI)
- Dr. Rolf Swenson & team (NHLBI)
- Dr. Murali Cherukuki & team (NCI)
- Prof. Roman V. Shchepin (South Dakota School of Mines and Technology)
- Dr. Michael J. Barlow (University of Nottingham, UK)
- Prof. W. Michael Snow (Indiana University Bloomington, IN)
- Prof. Wellington Pham (Vanderbilt University Institute of Imaging Science)
- Dr. Andreas Schmidt & team (University of Freiburg, Germany)

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- NHLBI 1F32HL160108 (Ariyasingha)
- Wayne State University, Department of Chemistry Rumble PhD Fellowship (Nantogma & Adelabu)

Motivation

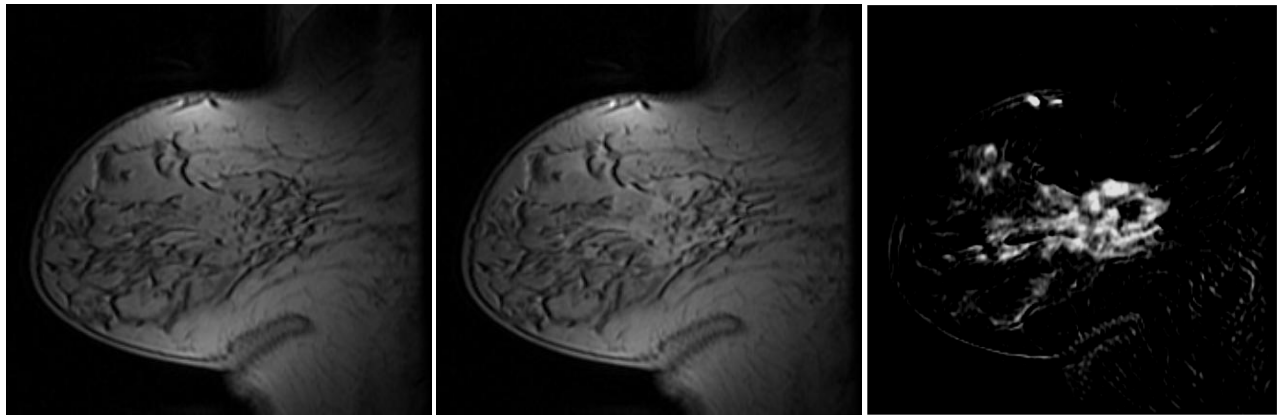
- ✓ Develop new ways to image organ function and disease
- ✓ Current focus areas: cancer and lung diseases

Ways to Get There

- ✓ Develop new *hyperpolarized* molecular imaging MRI probes
- ✓ Develop cheap, disposable, small (ideally handheld) technologies for production of *hyperpolarized* molecular imaging MRI probes
- ✓ Develop new sensing approaches

MR Imaging (MRI) and Spectroscopy (MRS) of Cancer

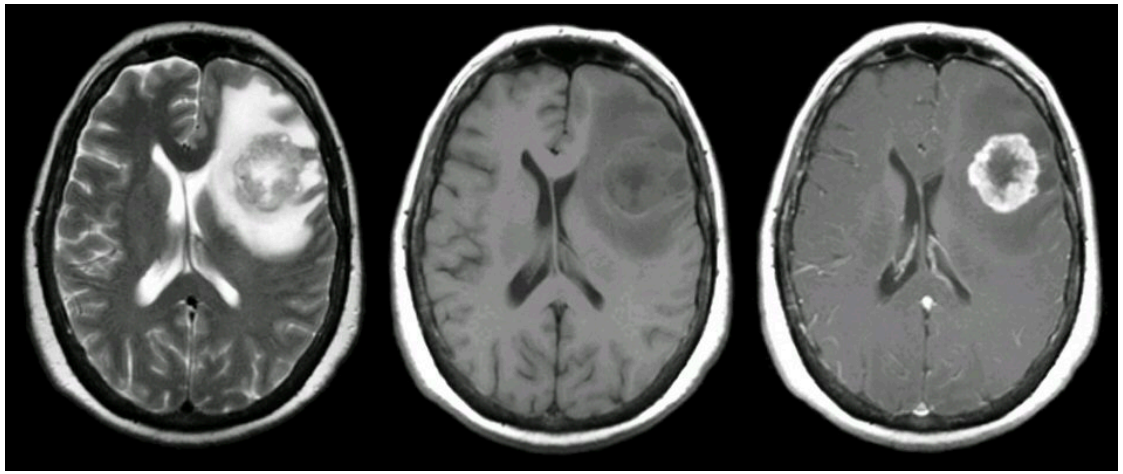
DCE MRI of Breast Cancer with Contrast Agent



Pre-contrast Post-contrast Subtraction

DCE Images Courtesy of Prof. Yankeelov (UT Austin)

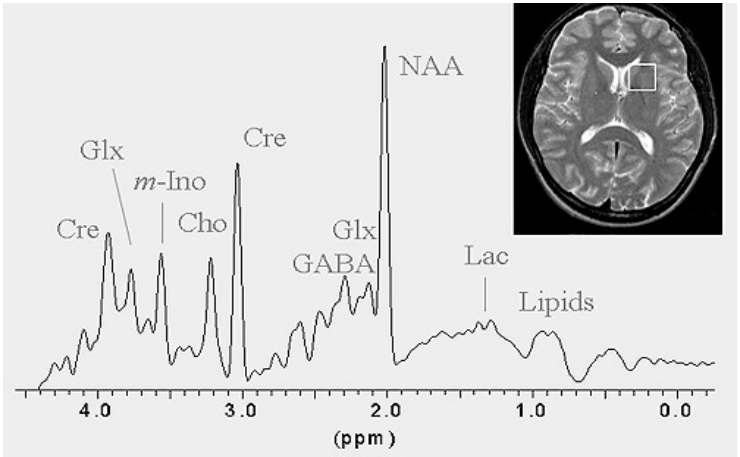
MRI of Metastatic Disease - Breast Cancer



T_2 MRI T_1 MRI T_1 with Gd contrast

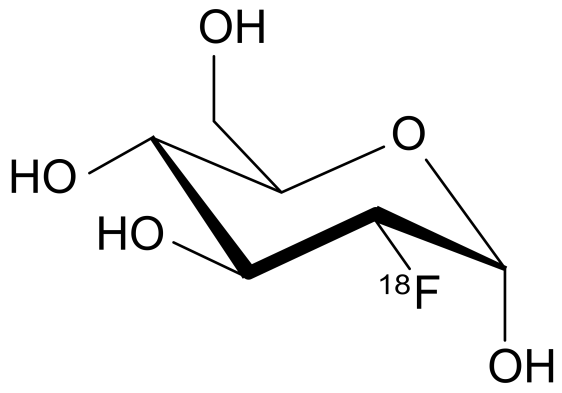
https://case.edu/med/neurology/NR/breast%20ca4.htm

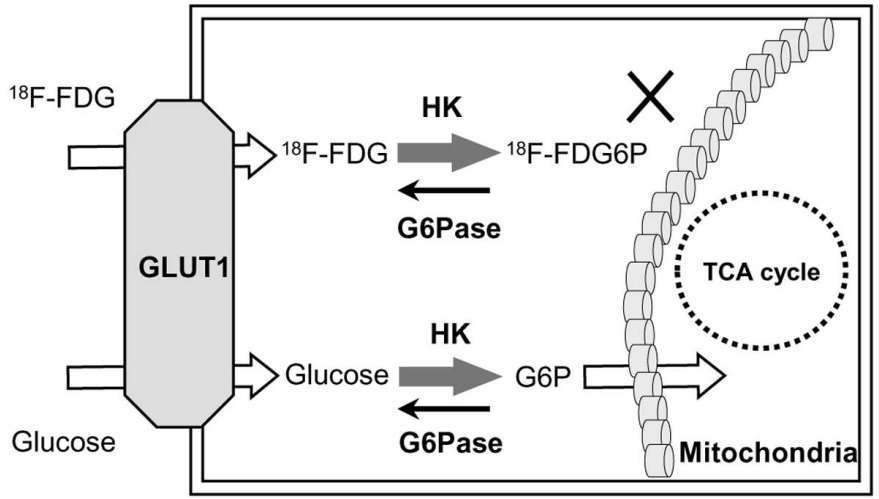
MRS of Brain Cancer

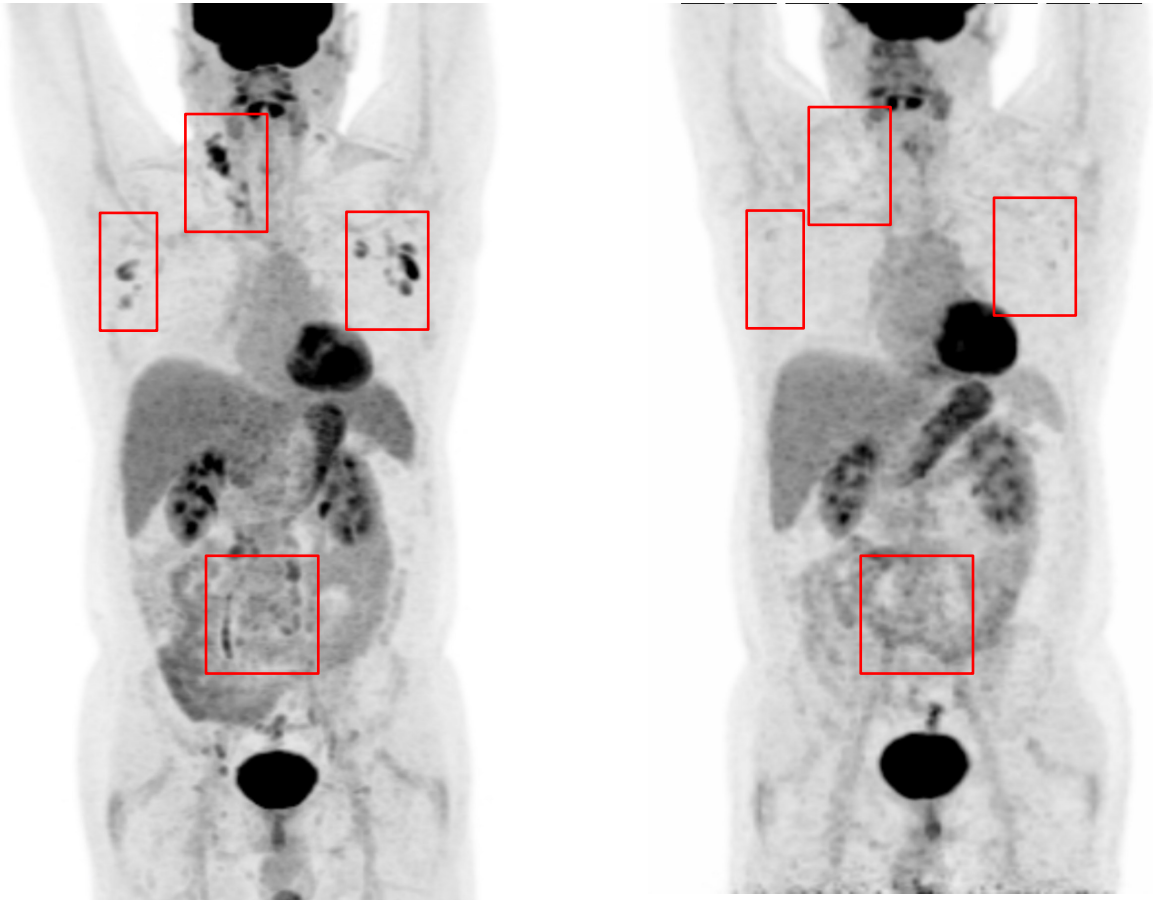


Croall ID, et al, (2014) 83, 494–501.

Modern Clinical Molecular Imaging: ^{18}F-FDG-PET

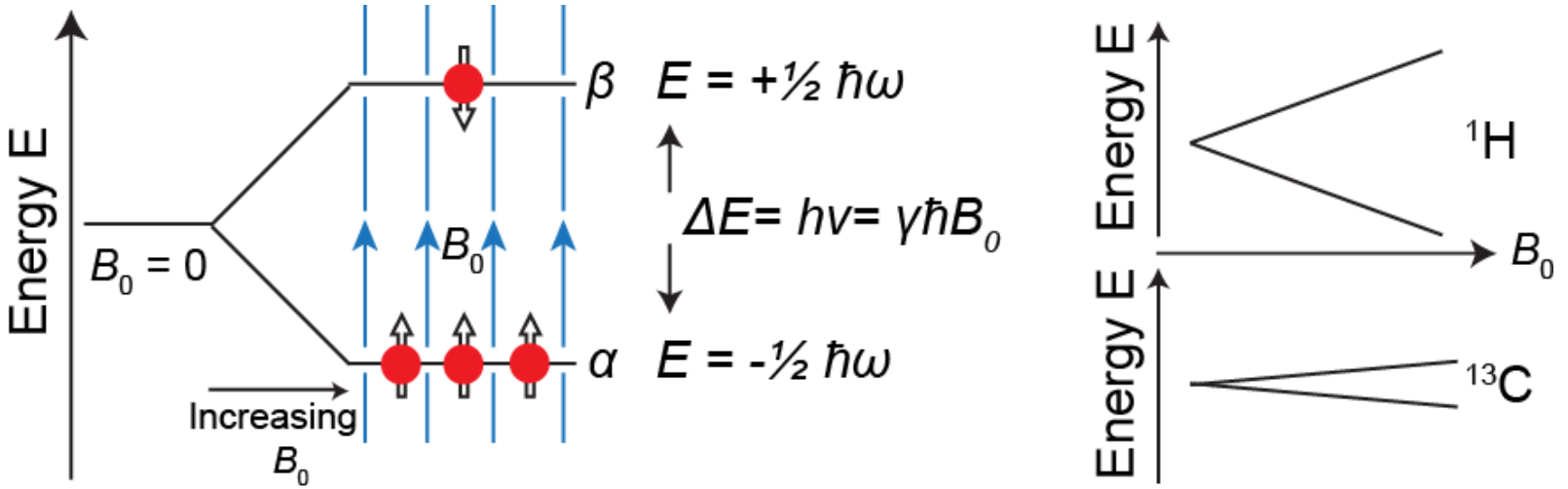






Clinical whole-body FDG-PET scan of 43-y.o. male patient with stage-3 low-grade Follicular lymphoma.
(left) FDF-PET scan at the time of the diagnosis showing the presence of metastatic disease;
(right) FDG-PET scan performed 3 months later after completion of targeted therapy with monoclonal antibody, showing complete metabolic remission, which manifests as the disappearance of FDG metabolic activity in the metastases. Note the physiological background signal in the brain, heart, bowel, liver and prostate.

Nuclear Spin Polarization



Zeeman splitting of nuclear spin states (spin I = ½ nuclei) in a magnetic field

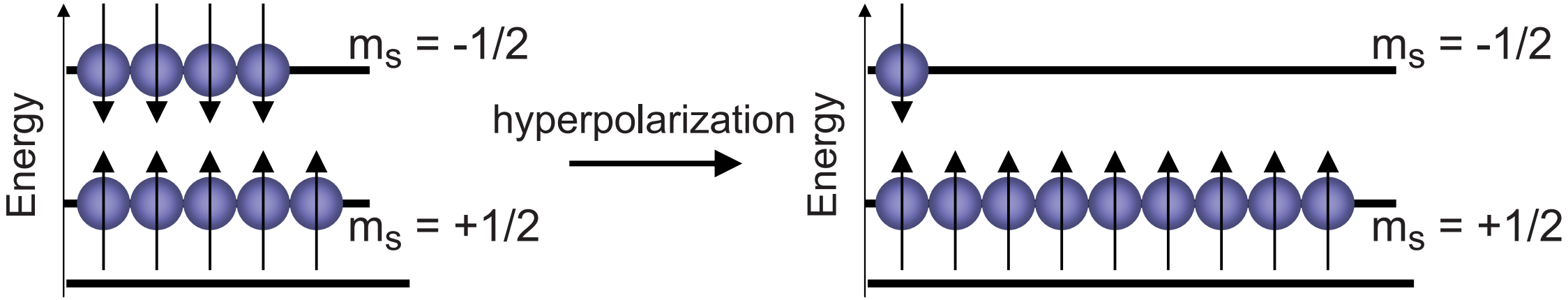
Boltzmann population statistics for thermal equilibrium state yields the nuclear spin polarization *P*:

$$P \equiv \frac{N_{1/2} - N_{-1/2}}{N_{1/2} + N_{-1/2}} \approx \frac{\gamma\hbar B_0}{2kT}$$

NMR Hyperpolarization

Definition

Hyperpolarization , *noun*. Temporarily increased nuclear spin polarization of nuclei (far) beyond the Boltzmann thermal equilibrium conditions

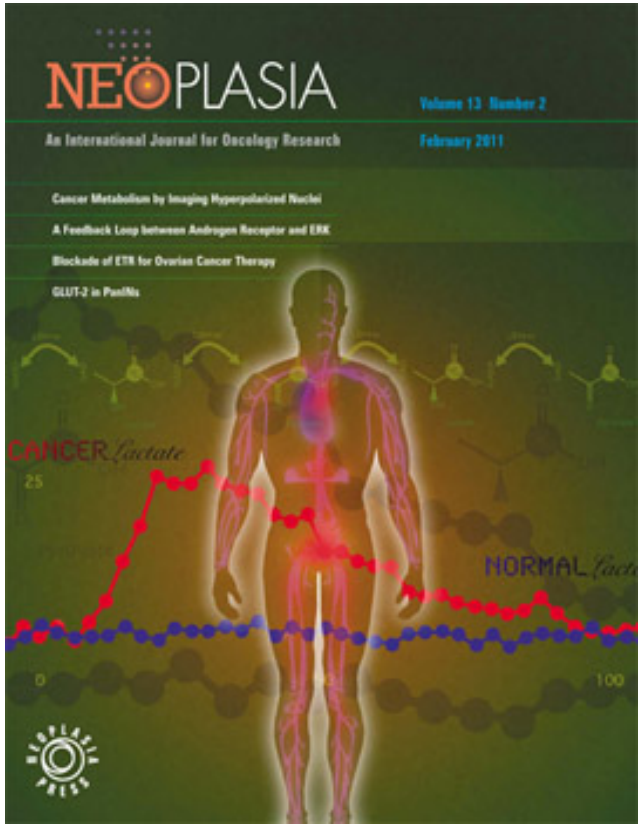


$$P \equiv \frac{N_{1/2} - N_{-1/2}}{N_{1/2} + N_{-1/2}} \approx \frac{\gamma \hbar B_0}{2kT}$$

- For example, ^{13}C polarization = 2.5×10^{-6} or 2.5 ppm at 3 T
- P ≈ 1 or 100% can be achieved by several methods
- Enhancement Factor, $\varepsilon = P_{HP}/P_{Thermal}$

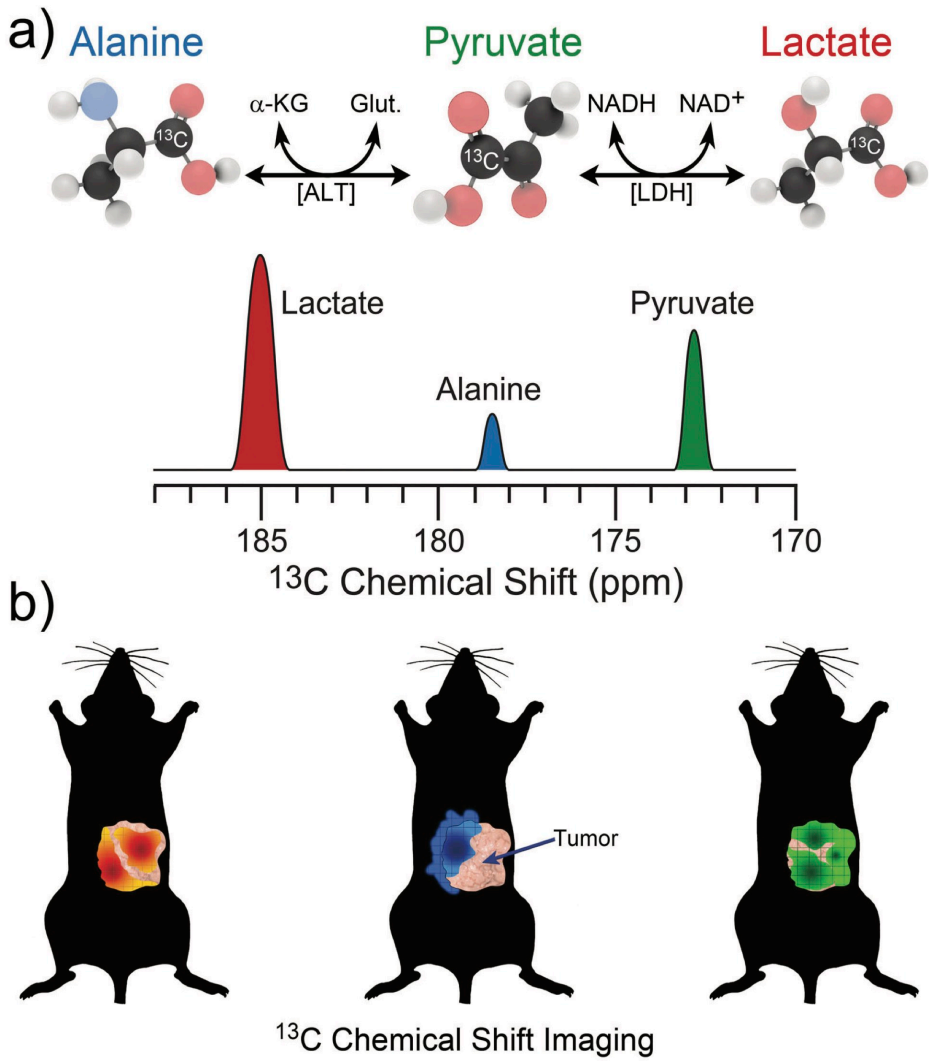
Benefits of Hyperpolarization

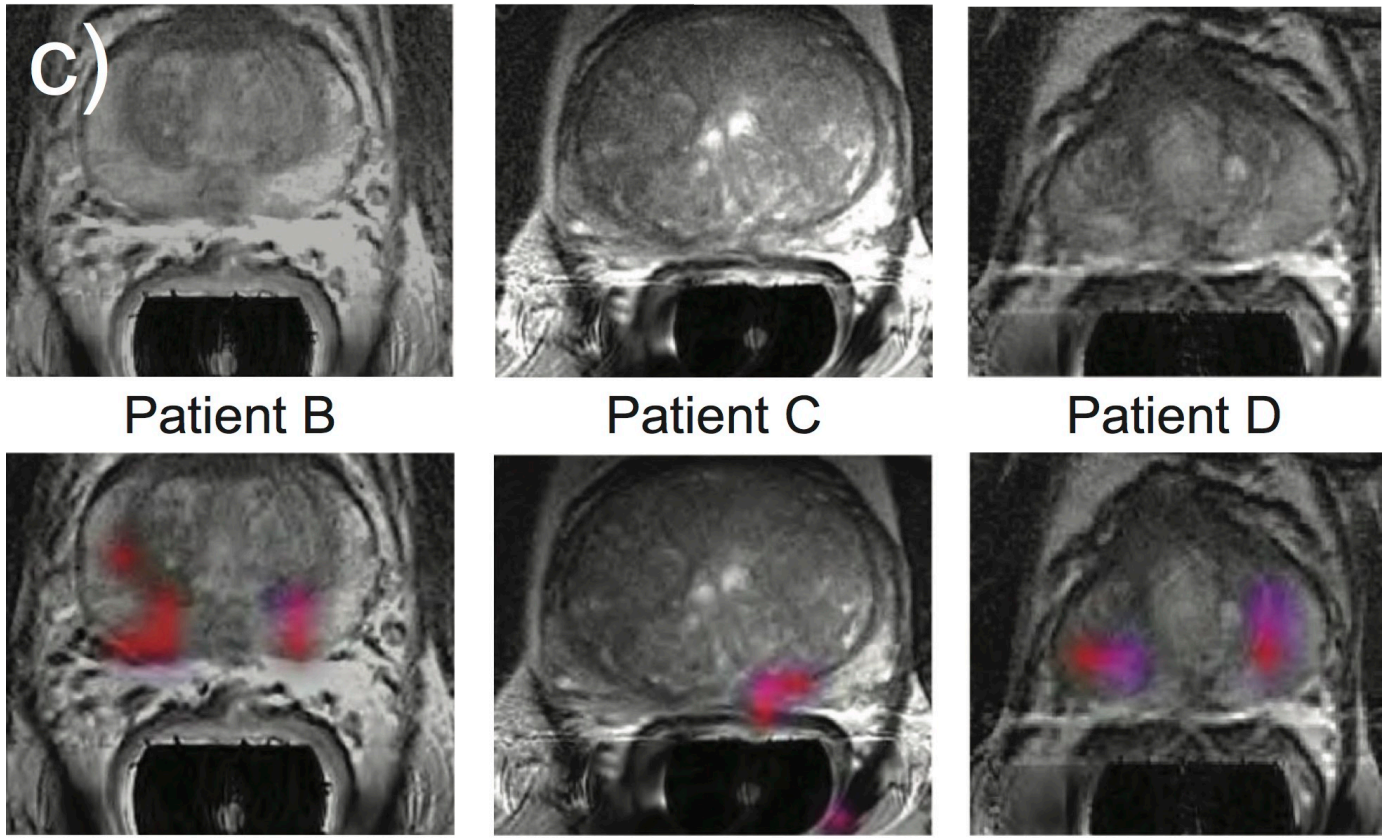
- Enhanced MR Sensitivity (by orders of magnitude)
- Improved Spatial and Temporal Resolution: scan time – few seconds to 1 min
- Detection Sensitivity (SNR) No Longer Depends on the Main Magnetic Field $\boldsymbol{B_0}$



Kurhanewicz, J.; Vigneron, D. B.; Brindle, K.; Chekmenev, E. Y.; Comment, A.; Cunningham, C. H.; DeBerardinis, R. J.; Green, G. G.; Leach, M. O.; Rajan, S. S.; Rizi, R. R.; Ross, B. D.; Warren, W. S.; Malloy, C. R. *Neoplasia* **2011**, *13*, 81.

Metabolic Imaging Using Hyperpolarized [1-^{13}C]Pyruvate





c) Representative examples of 3D single-time-point magnetic resonance spectroscopic imaging (MRSI) data of three prostate cancer subjects after IV injection of HP [1-^{13}C]pyruvate. The axial T_2-weighted images and false-color overlays of hyperpolarized [1-^{13}C]lactate/[1-^{13}C]pyruvate ratio are from the three patients labeled as B, C, and D.

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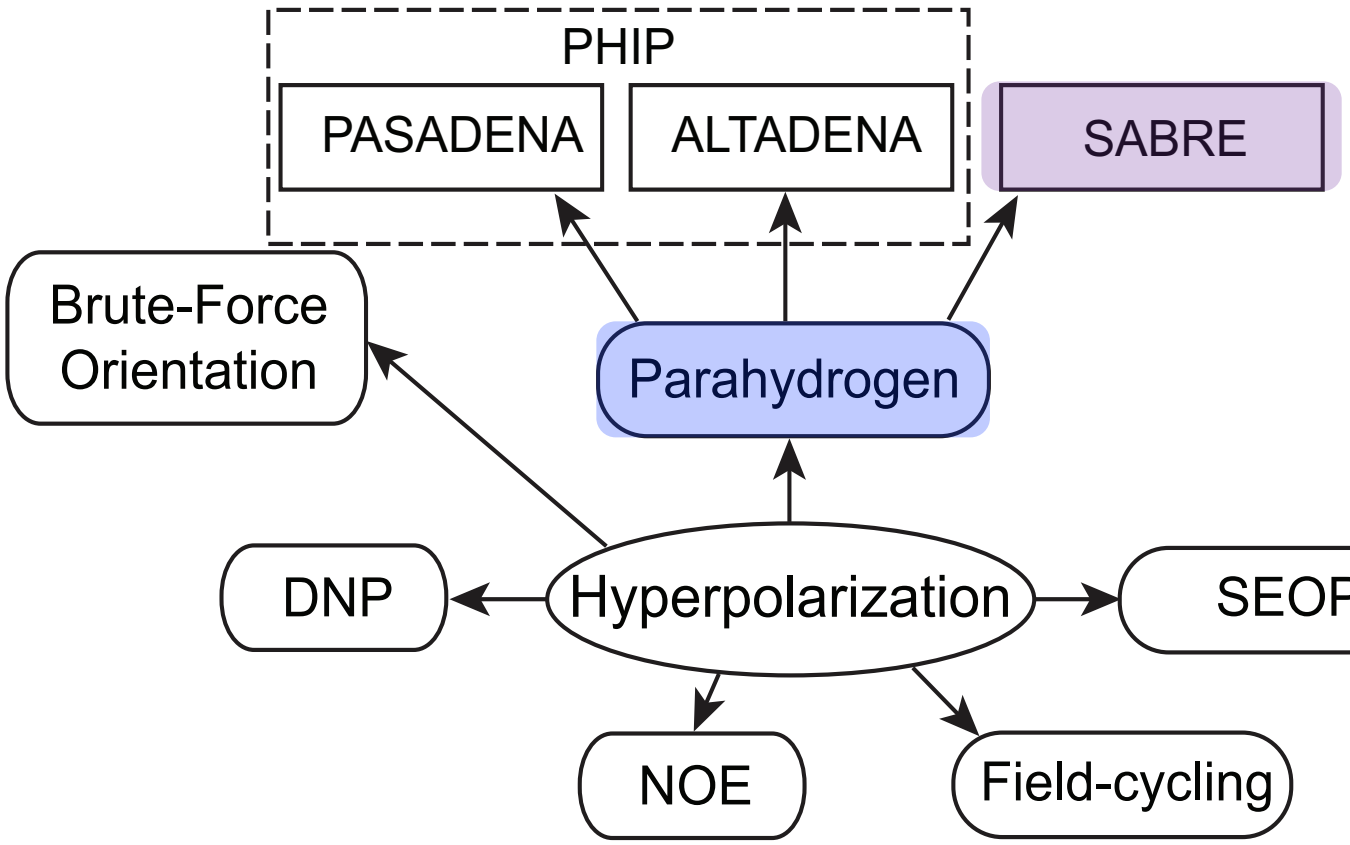
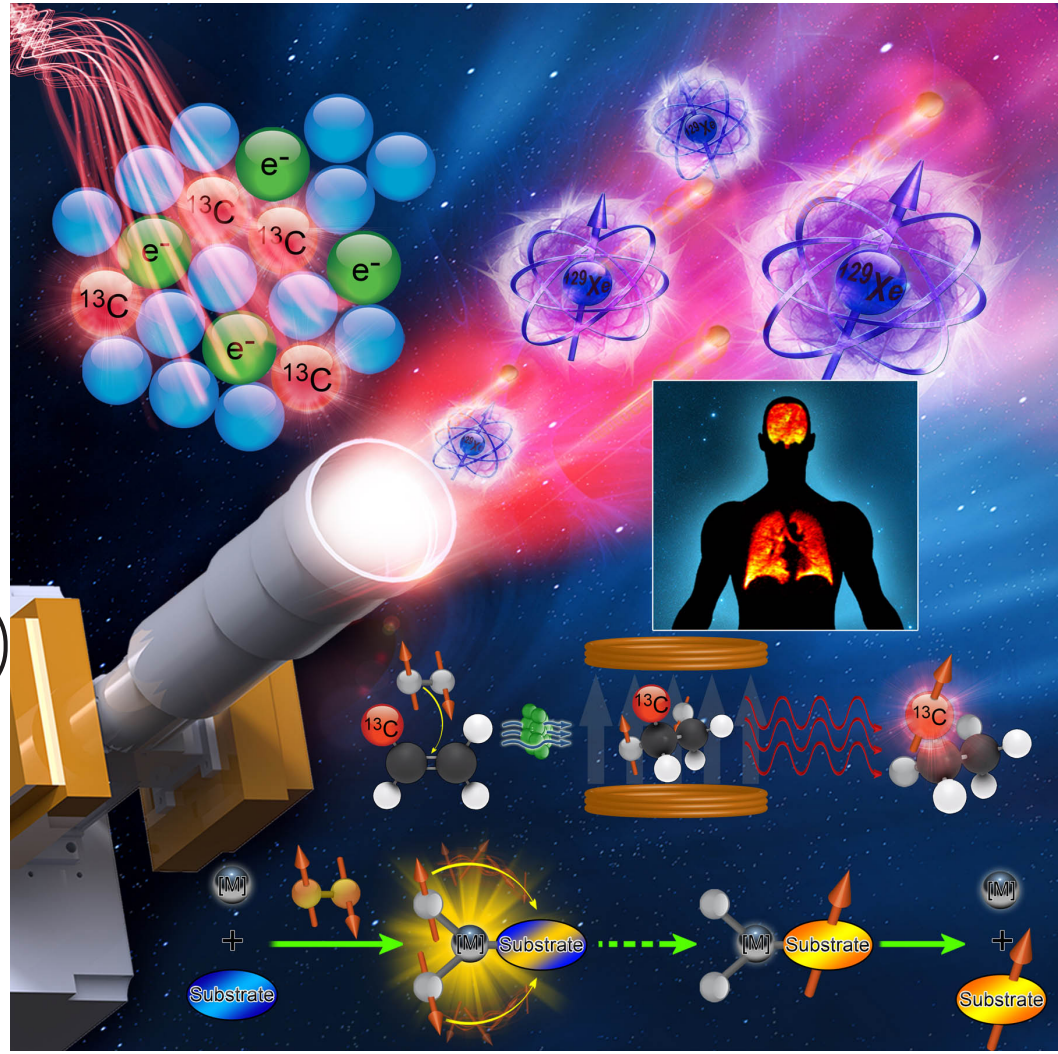
2. Nelson, S. J.; Kurhanewicz, J.; Vigneron, D. B.; Larson, P. E. Z.; et al. *Sci. Transl. Med.* **2013,** *5*, 198ra108.

Methods of Hyperpolarization





DNP: Dynamic Induced Polarization;
PHIP: Parahydrogen Induced Polarization;
PASADENA: Para-Hydrogen and Synthesis Allow Dramatically Enhanced Nuclear Alignment;
ALTADENA: Adiabatic Longitudinal Transport After Dissociation Engenders Net Alignment;
SABRE: Signal Amplification by Reversible Exchange;
SEOP: Spin-Exchange Optical Pumping;
NOE: Nuclear Overhauser Enhancement.

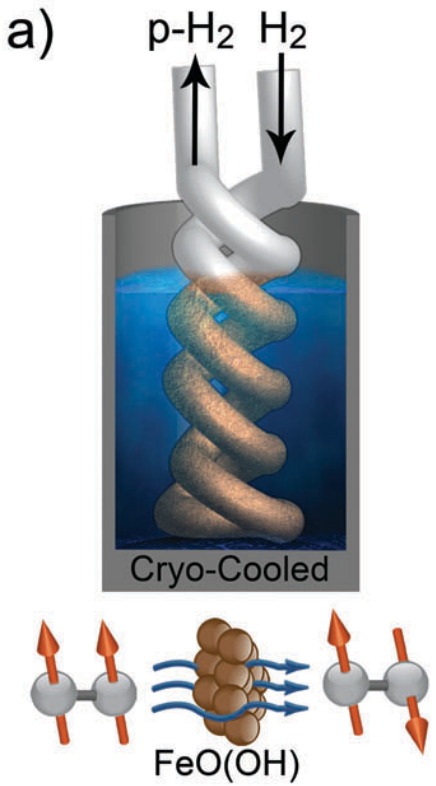
Nikolaou, P.; Goodson, B. M.; Chekmenev, E. Y. *Chem. Eur. J.* **2015,** *21*, 3156-3166.

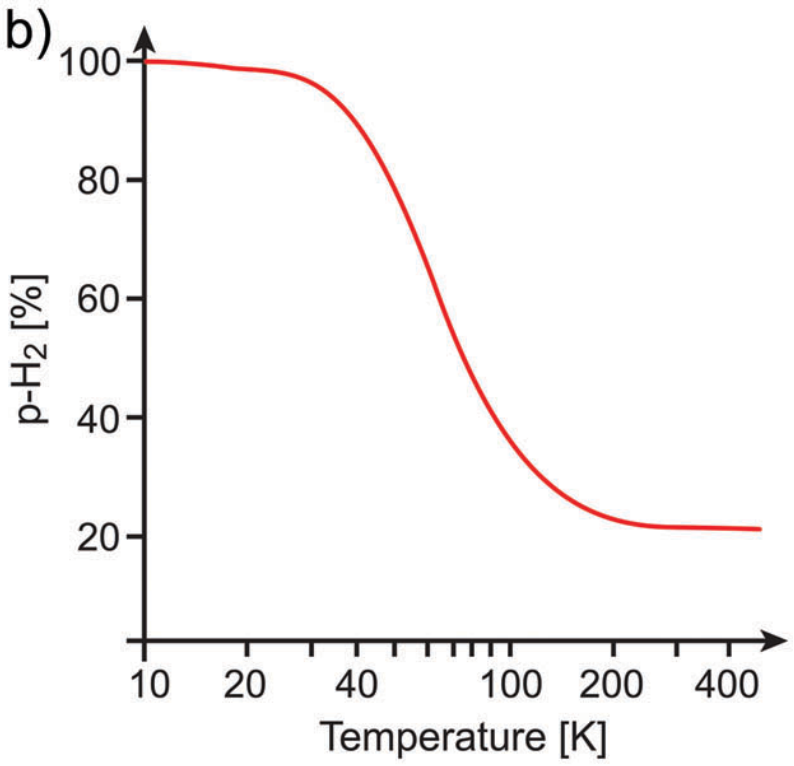
How HP [1-^{13}C]Pyruvate Is Produced Today In >30 Clinical Trials

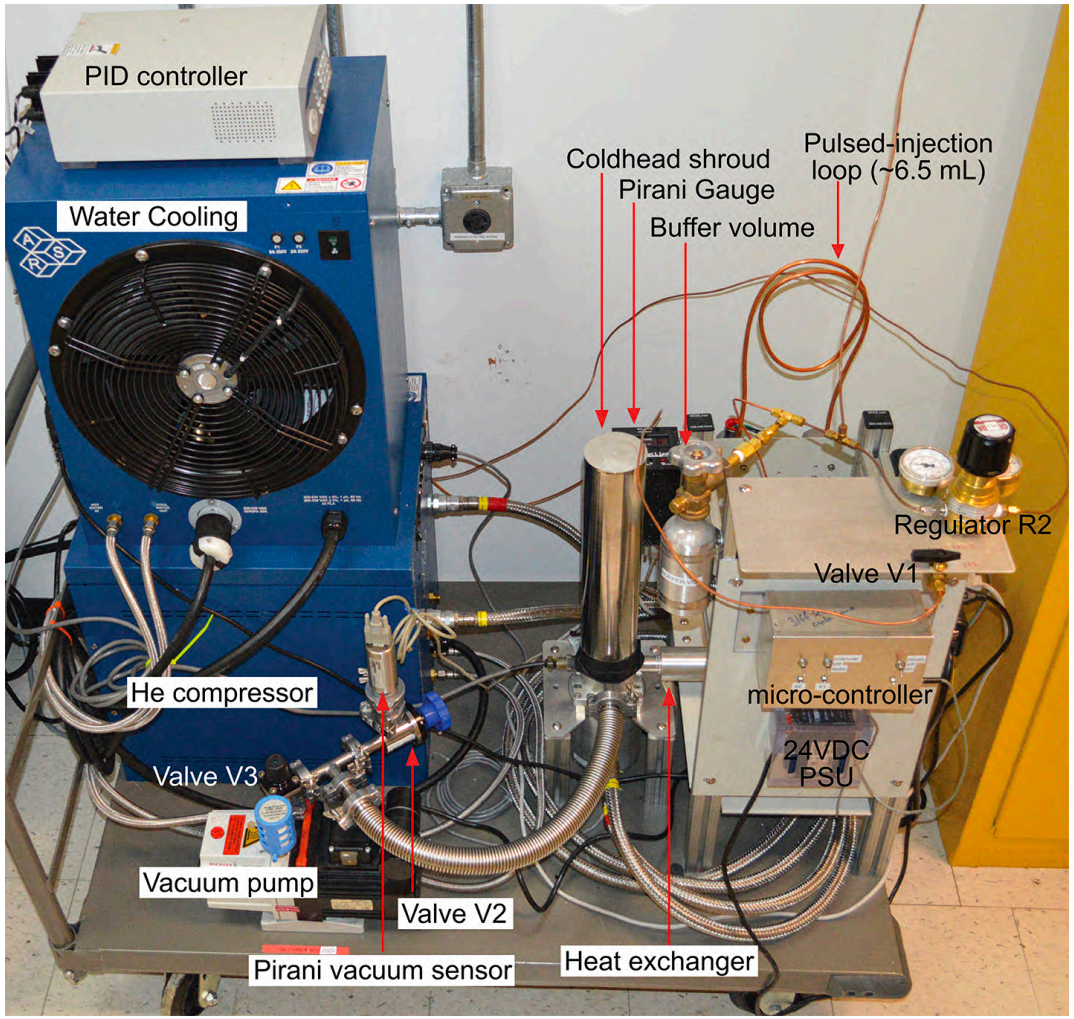
- HP [1-^{13}C]pyruvate is prepared via dissolution Dynamic Nuclear Polarization (d-DNP)
- HP [1-^{13}C]pyruvate and its metabolites are detected using Research MRI scanner equipped with ^{13}C capability (fewer than 100 installed globally)

Parahydrogen Induced Polarization

…of any sort requires parahydrogen that acts as a source of nuclear spin polarization

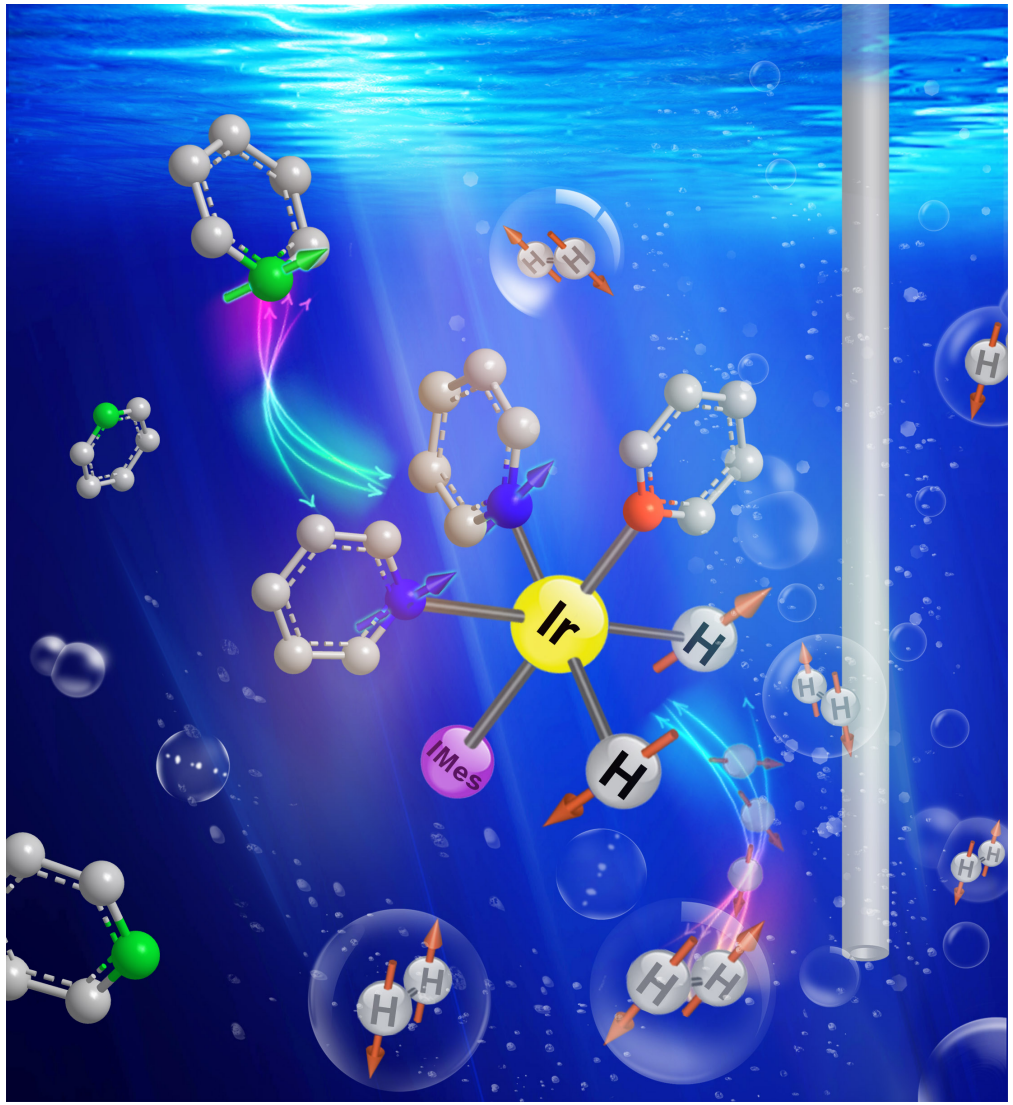


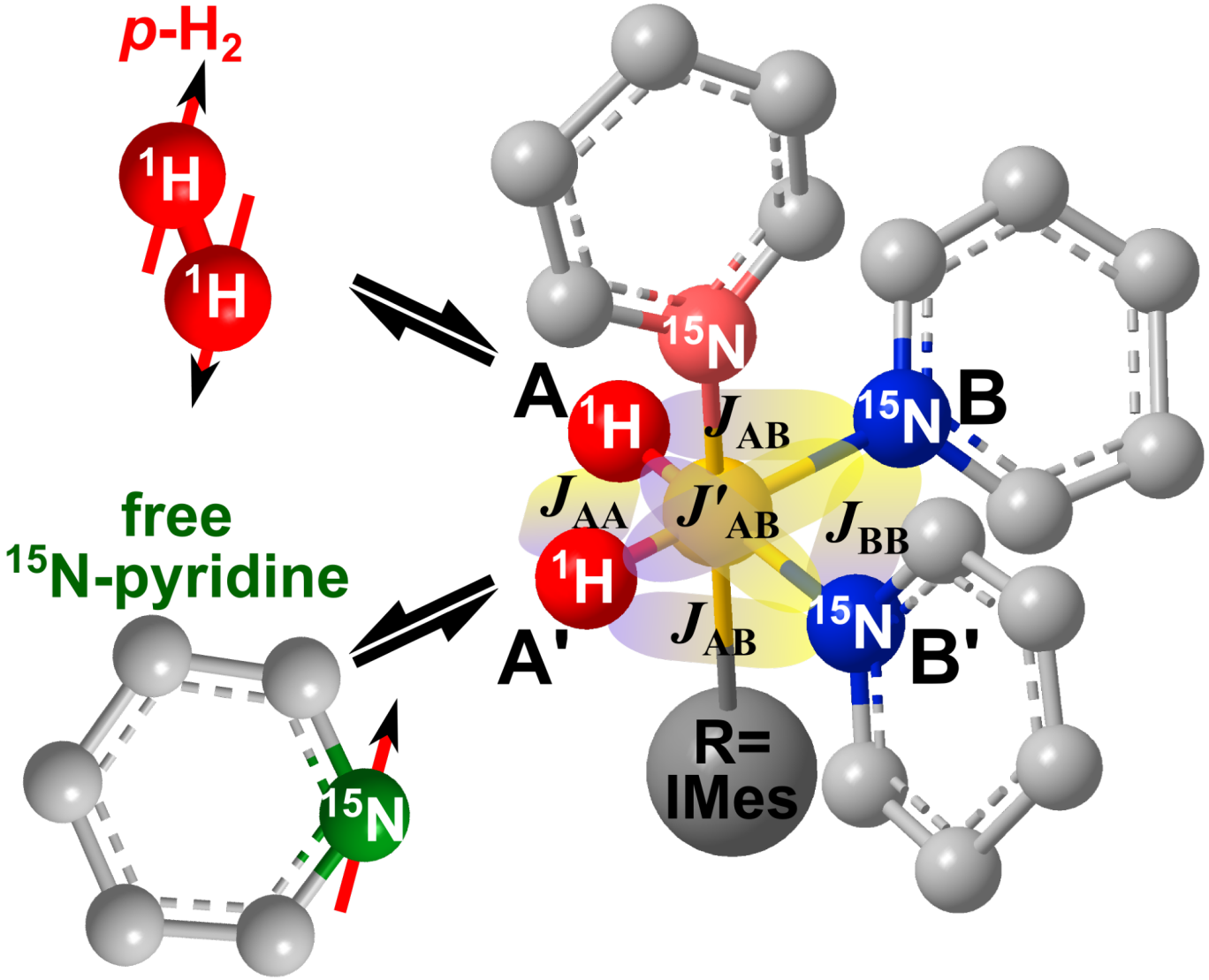




Nantogma, S.; Joalland, B.; Wilkens, K.; Chekmenev , E. Y. Clinical-Scale Production of Nearly Pure (>98.5%) Parahydrogen and Quantification by Benchtop NMR Spectroscopy. *Anal. Chem.* **2021,** *93*, 3594–3601.

^{15}N and ^{13}C Signal Amplification By Reversible Exchange (SABRE)





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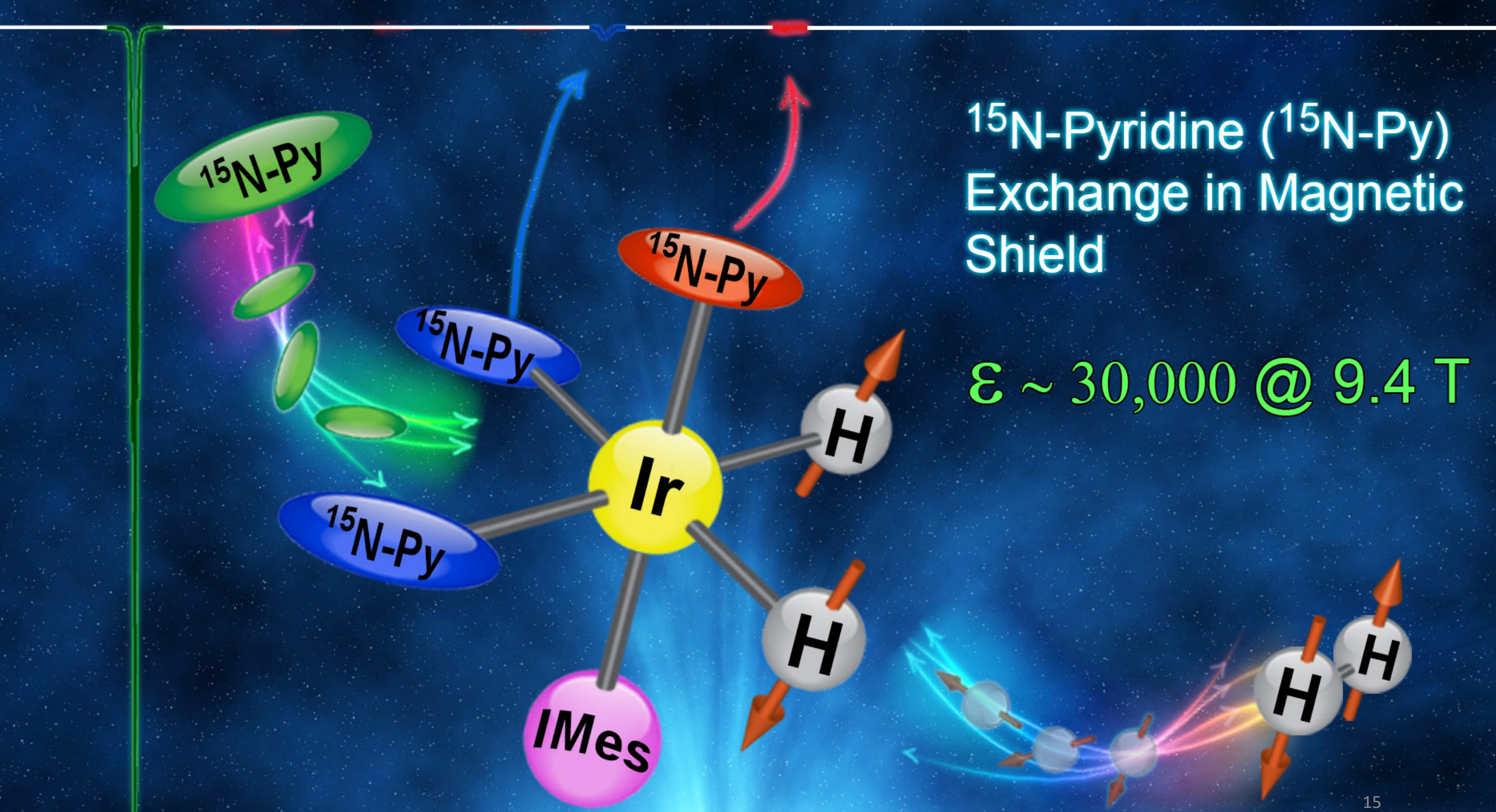
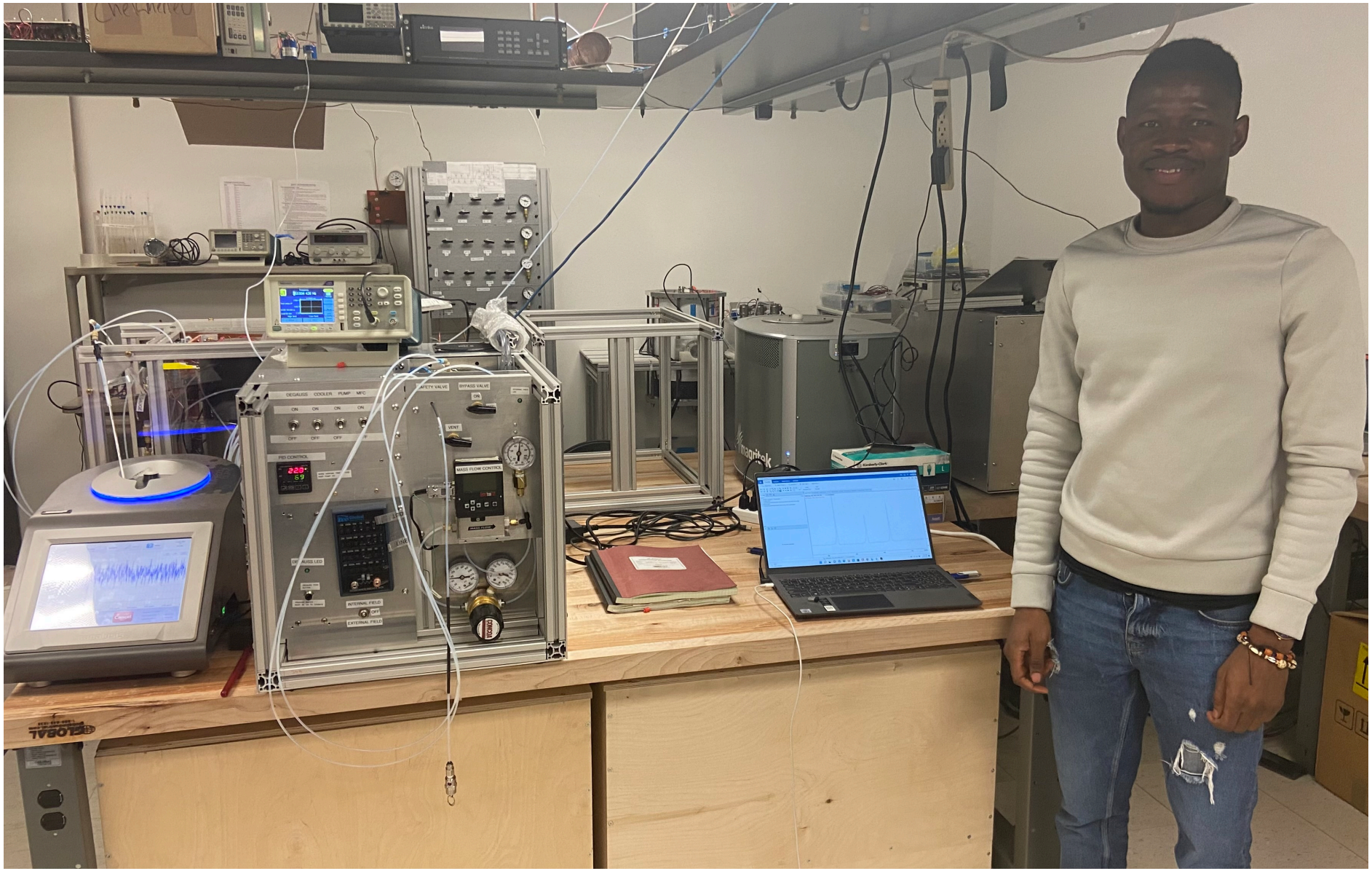
2. Truong, M. L.; Theis, T.; Coffey, A. M.; Shchepin, R. V.; Waddell, K. W.; Shi, F.; Goodson, B. M.; Warren, W. S.; Chekmenev, E. Y. ^{15}N Hyperpolarization By Reversible Exchange Using SABRE-SHEATH. *J. Phys. Chem. C* **2015,** *119*, 8786–8797.



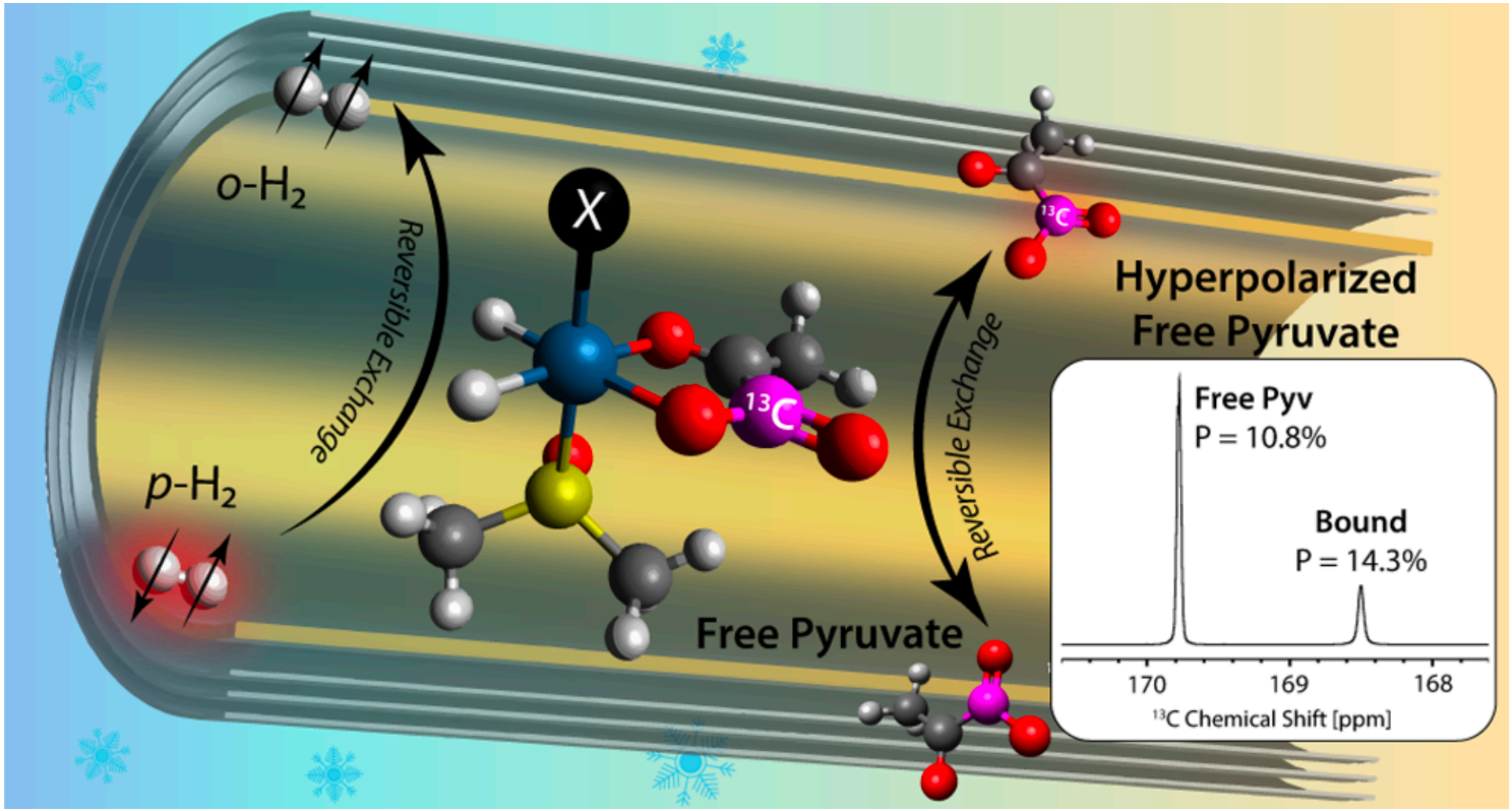
is, T.; Truong, M. L.; Coffey, A. M.; Shchepin, R. V.; Waddell, K. W.; Shi, F.; Goodson, B. M.; Warren, W. S.; Chekmenev, E. Y. *J. Am. Chem. Soc.* **2015,** *137*, 1404.

Bench-Top Polarizer for Liquid-State SABRE



Shiraz Nantogma (Chemistry Dept. Rumble fellowship)

SABRE Hyperpolarization of [1-^{13}C]Pyruvate



Isaiah Adelabu (Chemistry Dept. Rumble fellowship)

1. TomHon, P.; Abdulmojeed, M.; Adelabu, I.; Nantogma, S.; Kabir, M. S. H.; Lehmkuhl, S.; Chekmenev, E. Y.; Theis, T. *J. Am. Chem. Soc.* **2022,** *144*, 282–287.
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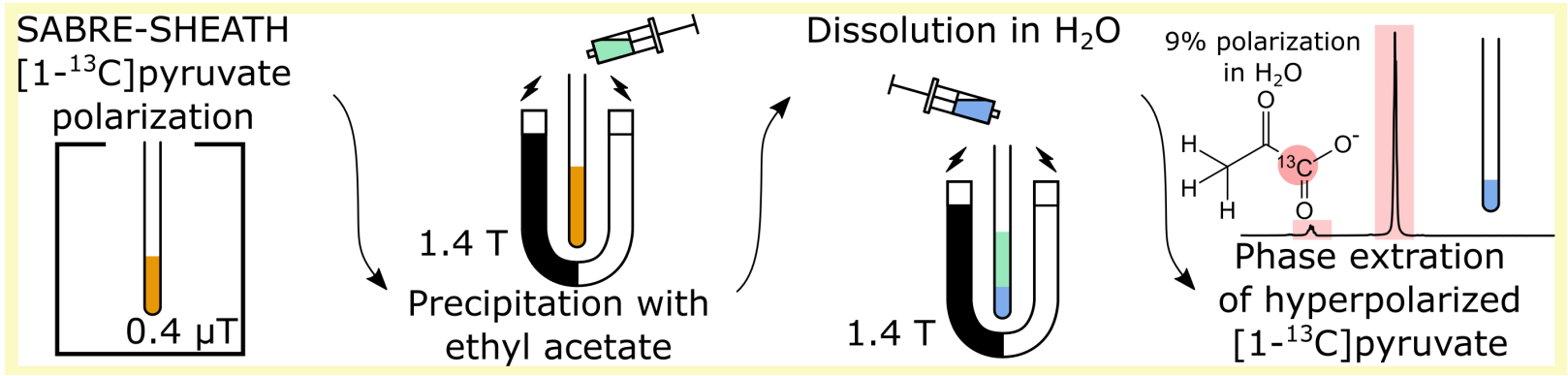
3. Adelabu, I.; TomHon, P.; Kabir, M. S. H.; Nantogma, S.; Abdulmojeed, M.; et al. *ChemPhysChem* **2022**, 23, 131–136.

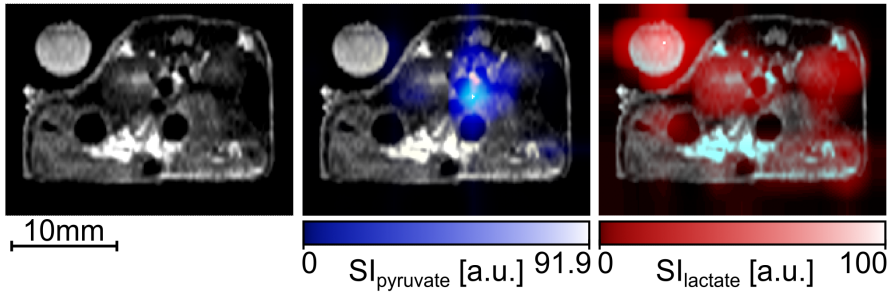
Preparing Biocompatible Solutions via Re-Dissolution SABRE

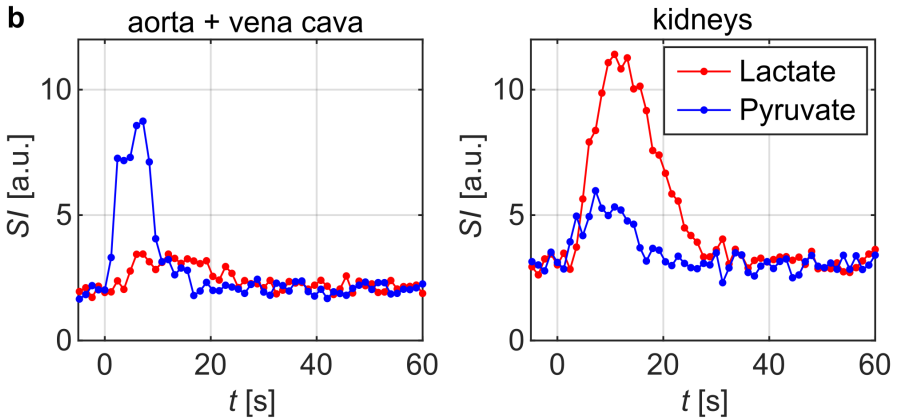


Schmidt, A. B.; de Maissin, H.; Adelabu, I.; Nantogma, S.; Ettedgui, J.; TomHon, P.; Goodson, B. M.; Theis, T.; Chekmenev, E. Y. Catalyst-free aqueous hyperpolarized [1-^{13}C]pyruvate obtained by re-dissolution signal amplification by reversible exchange. *ACS Sensors* **2022,** *7*, 3430-3439.

Andreas Schmidt, PhD

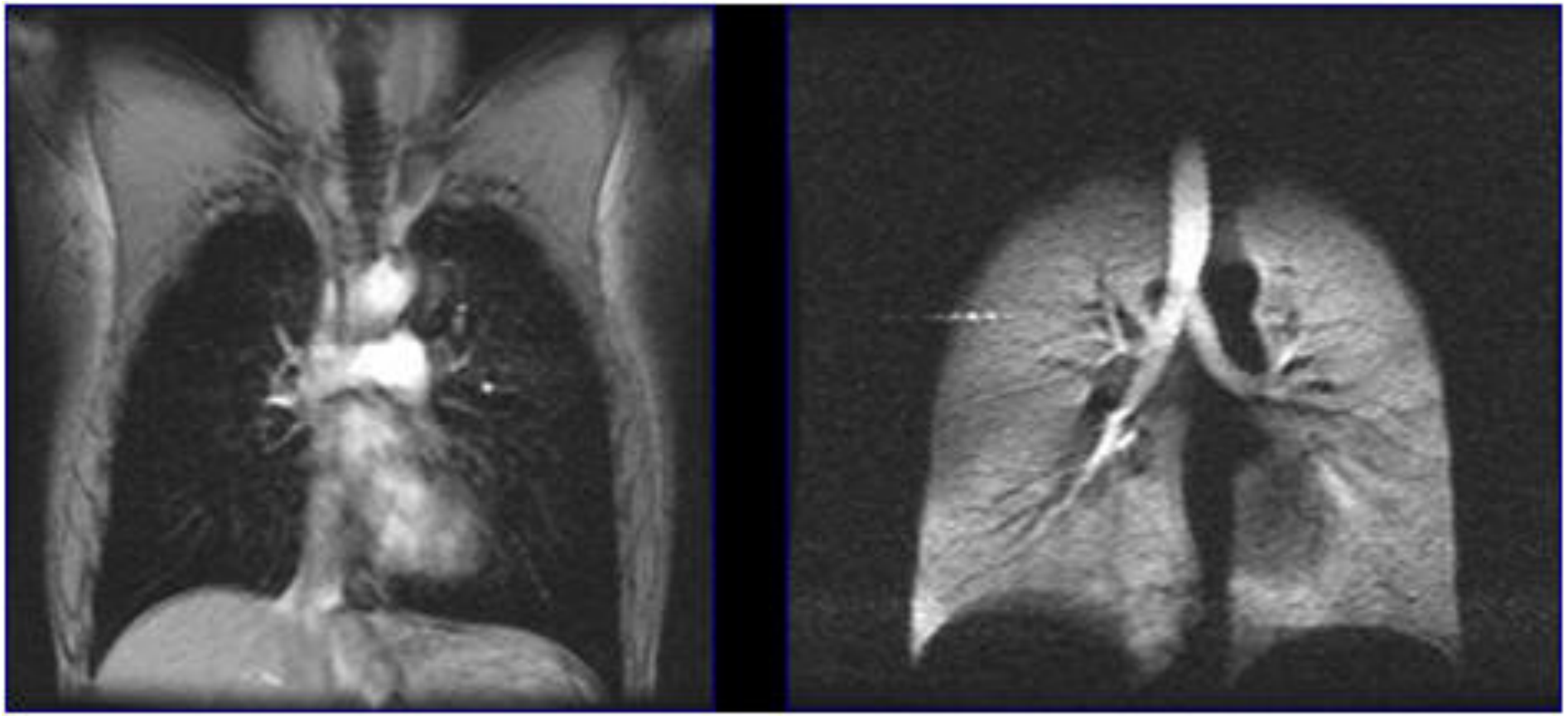
WSU PD Fellow ➡ Group Leader, University of Freiburg, Germany)





de Maissin, H.; Groß, P. R.; Mohiuddin, O.; Weigt, M.; Nagel, L.; Herzog, M.; Wang, Z.; Willing, R.; Reichardt, W.; Pichotka, M., et al. In Vivo Metabolic Imaging of [1-^{13}C]Pyruvate-d3 Hyperpolarized By Reversible Exchange With Parahydrogen. *Angew. Chem. Int. Ed.* **2023**, e202306654.

Pulmonary Imaging of Inhaled Hyperpolarized Gas

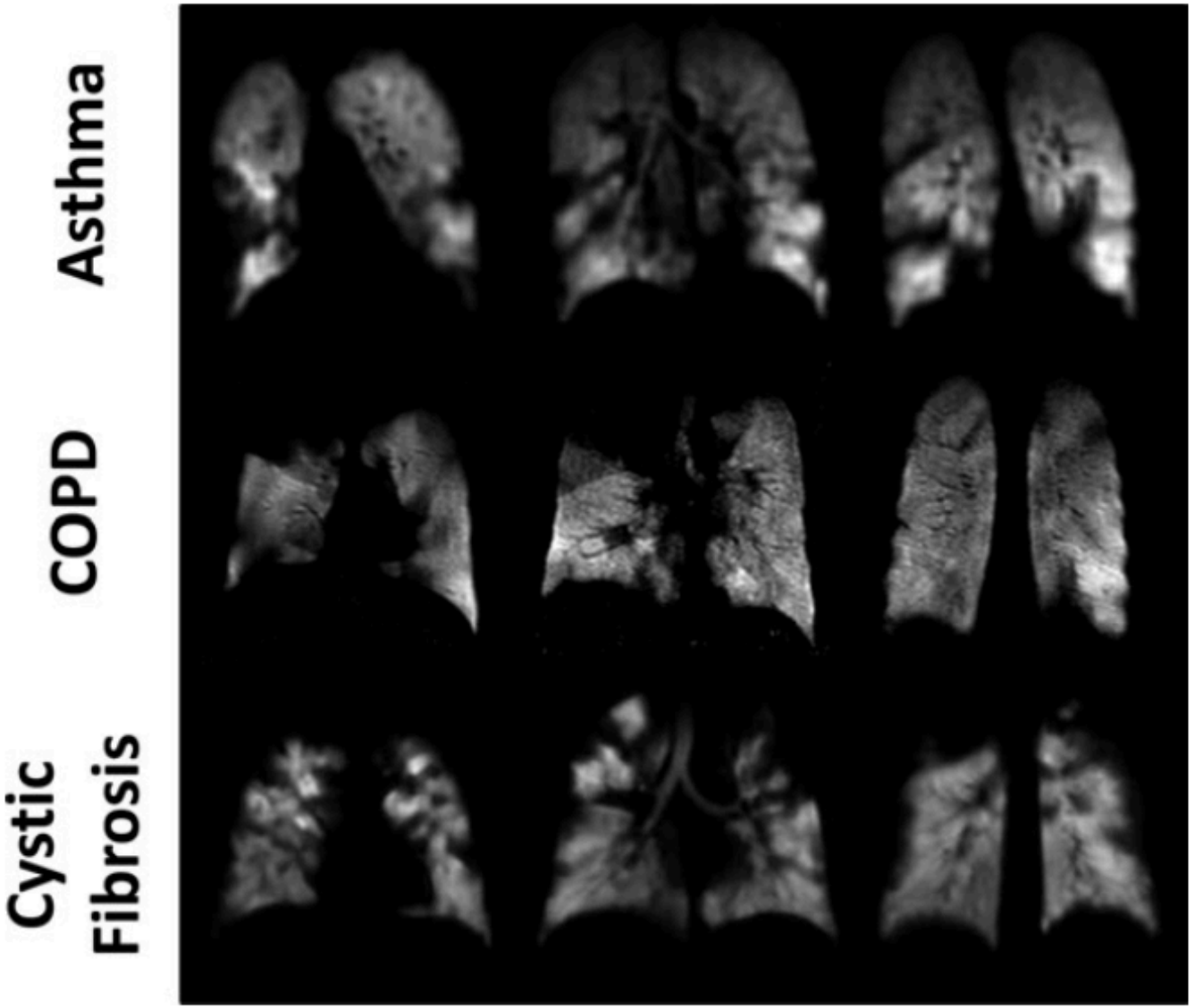


Conventional (Proton)
MRI

Hyperpolarized Gas
MRI

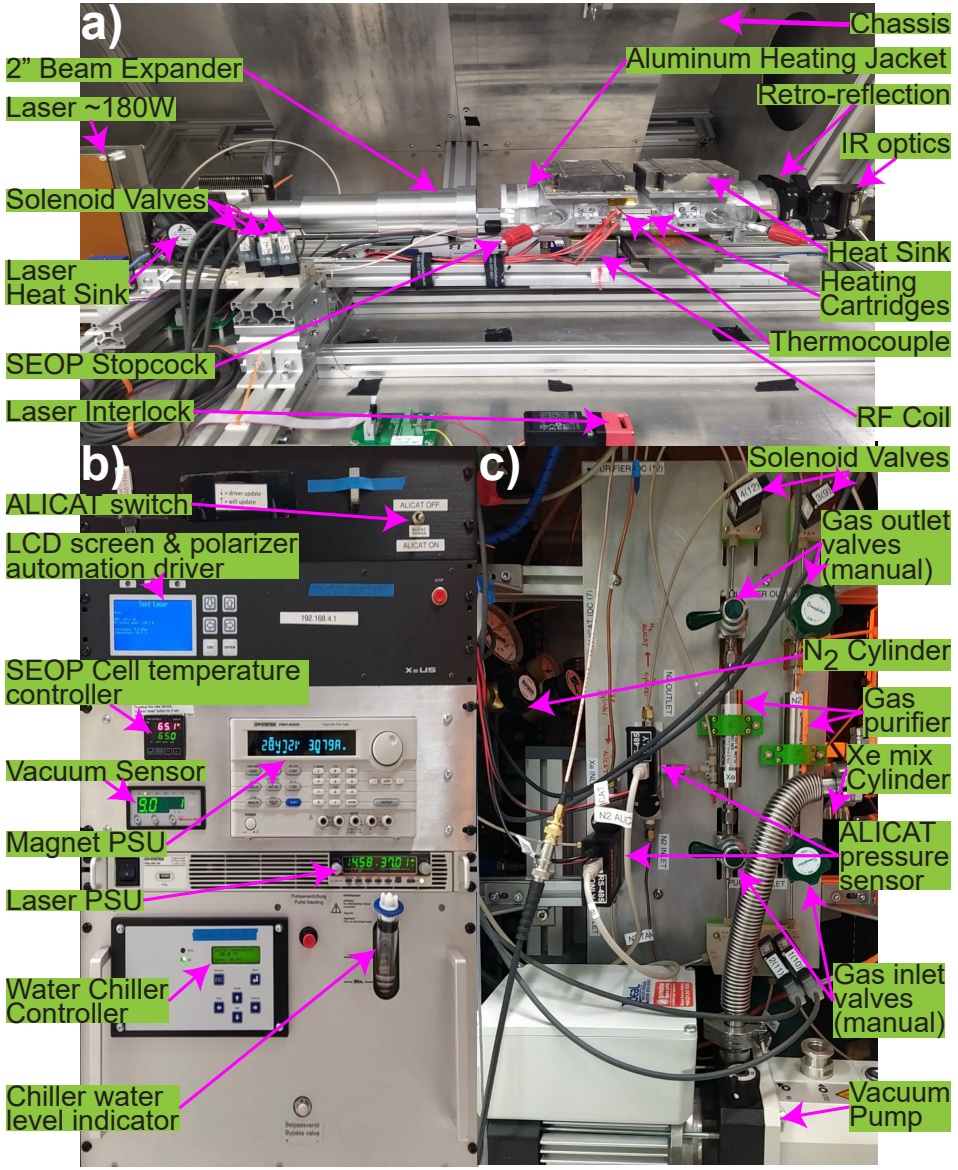
Mugler, J. P.; Altes, T. A. Hyperpolarized ^{129}Xe MRI of the human lung. *J. Magn. Reson. Imaging* **2013,** *37*, 313-331.

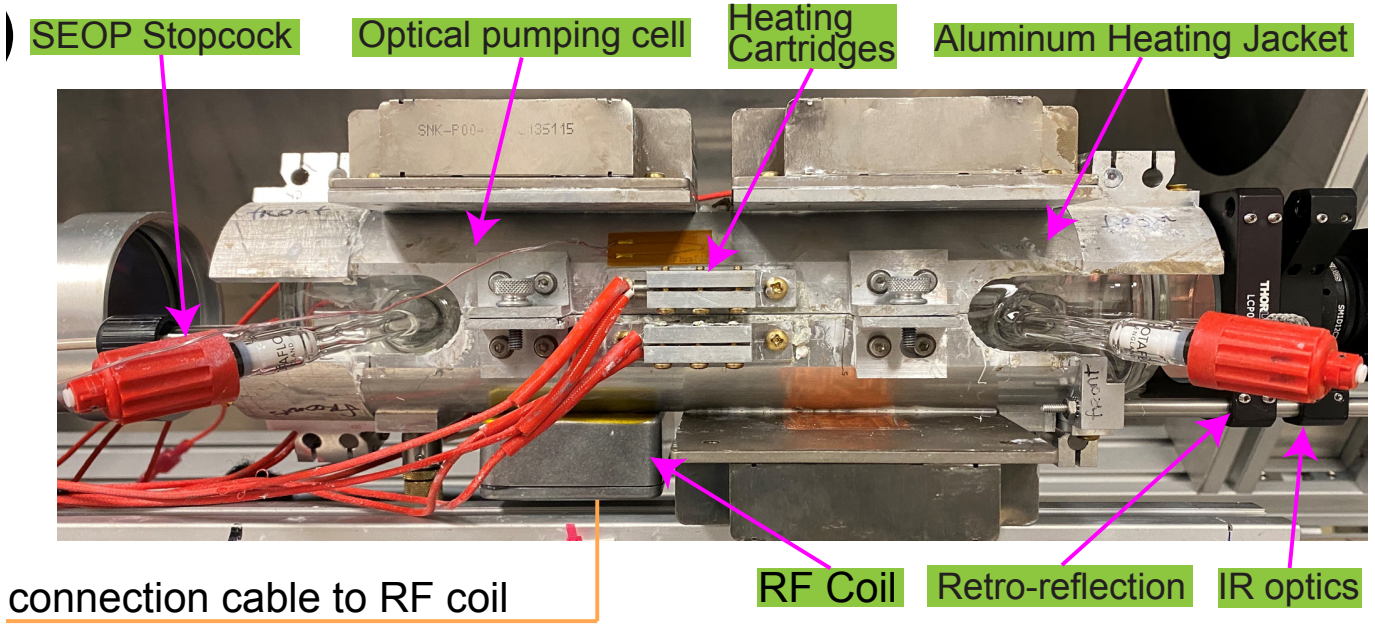
Functional Lung Imaging of Disease



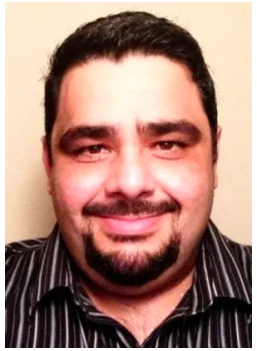
Mugler, J. P.; Altes, T. A. *J. Magn. Reson. Imaging* **2013**, *37*, 313.

Spin-Exchange Optical Pumping: Batch-Mode Clinical-Scale XeUS (XE Ultimate Spin-Exchange)





Jonathan Birchall, PhD
PD fellow (now University of Cambridge)



Peter Nikolaou, PhD
PD fellow (now in XeUS Techologies)

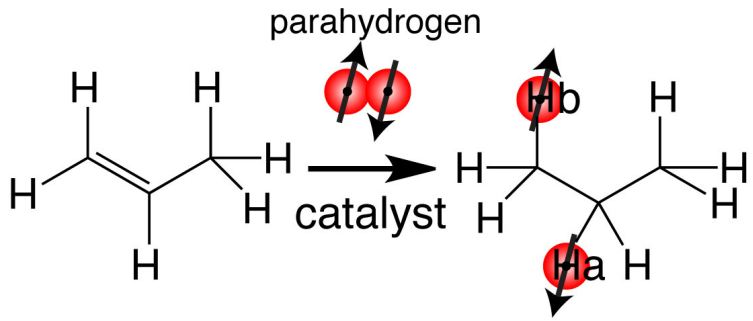
1) Birchall, J. R.; et al. *Anal. Chem.* **2020,** *92*, 4309-4316.
2) Birchall, J. R.; et al. *Molecules* **2022,** *27*, 1327.

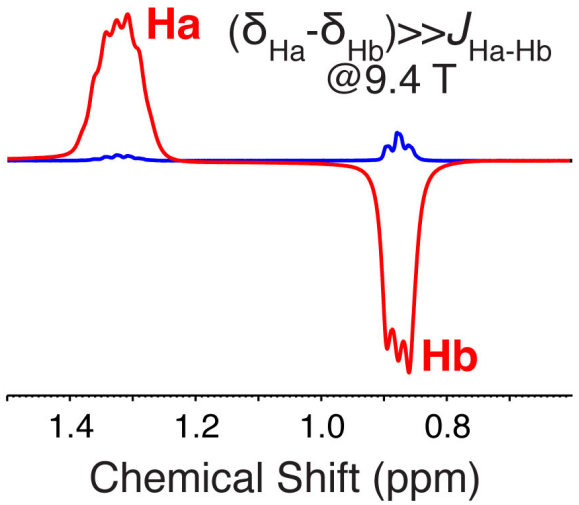
Heterogeneous Parahydrogen Induced Polarization (HET PHIP)

$(\delta_{Ha}-\delta_{Hb}) \sim 0.45$ ppm

$J_{Ha-Hb} \sim 7.3$ Hz

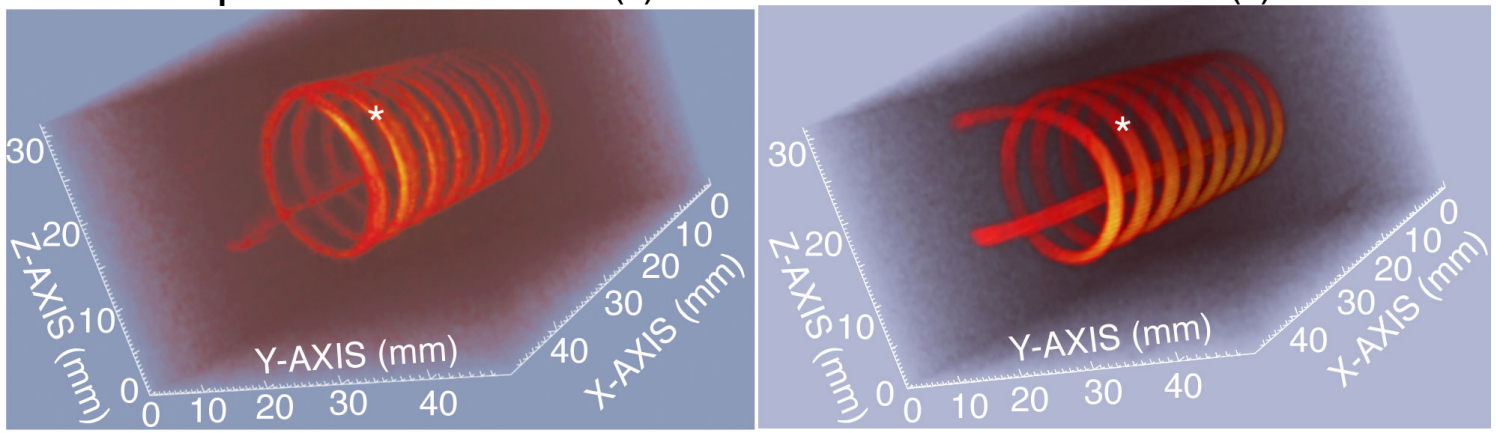
$(\delta_{Ha}-\delta_{Hb}) \sim J_{Ha-Hb}$ @ 0.4 T





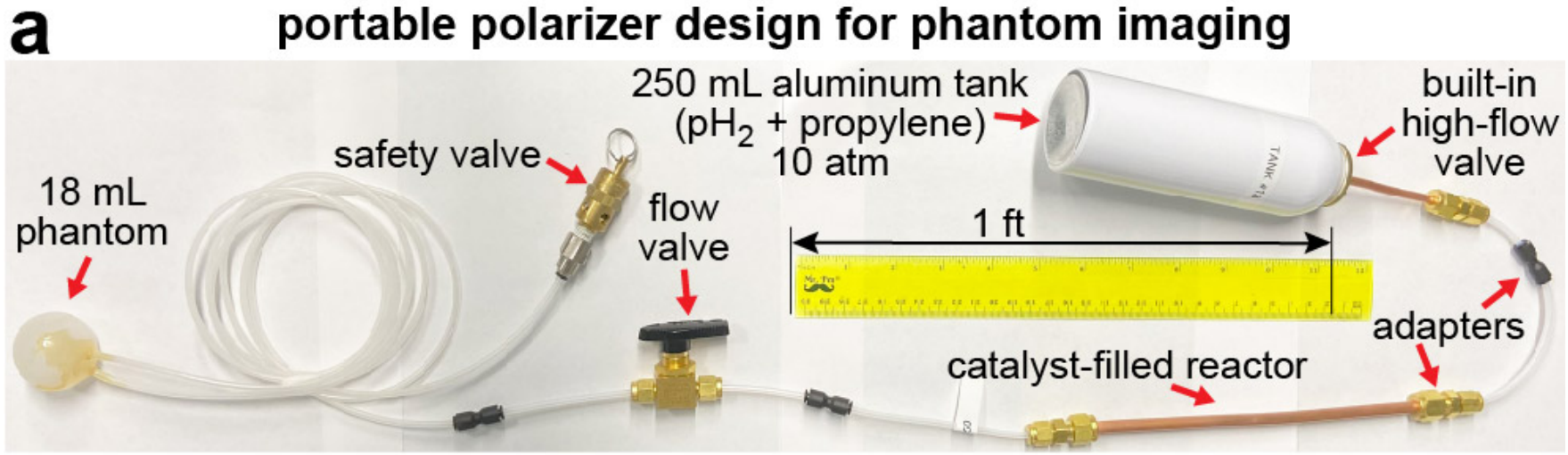
3D MRI at 4.7 T of ***flowing propane gas*** ($\%P_H \sim 1\%$): 0.5×0.5×0.5 mm^3 spatial resolution in 21 s

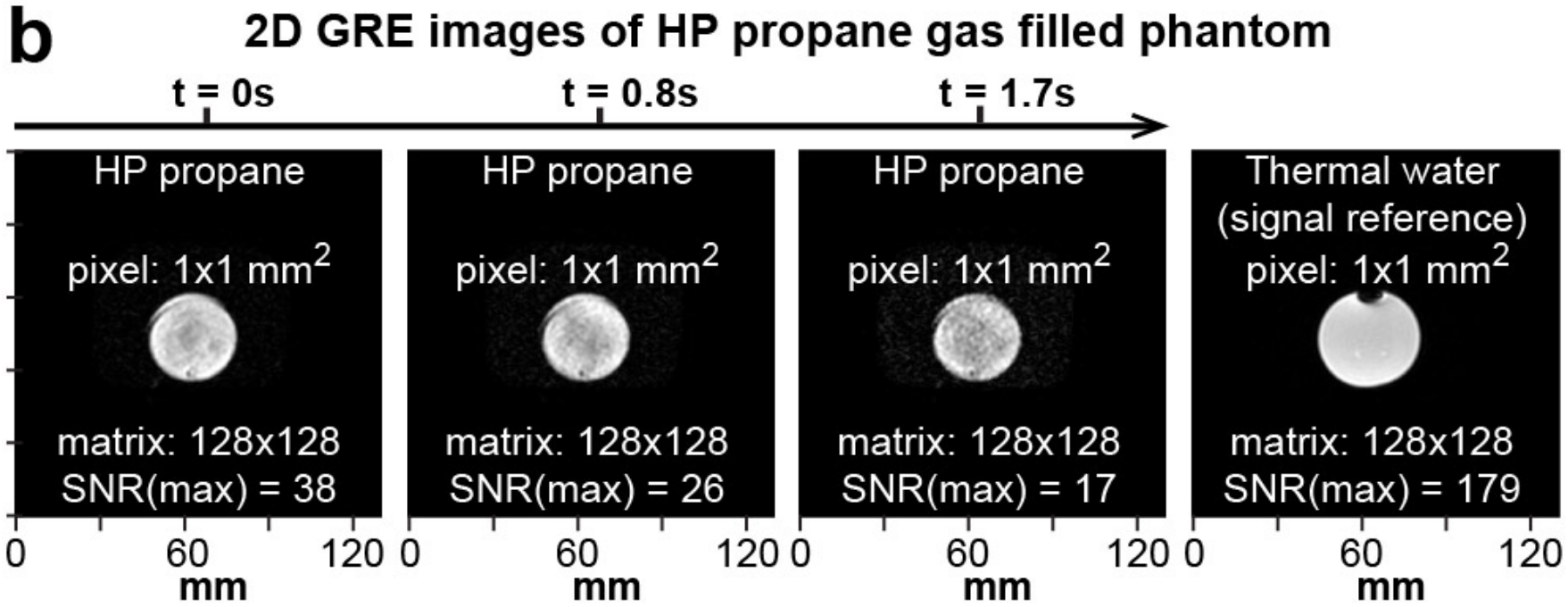
HP Propane: 20 mM SNR(*)=15 Water: 55 M SNR(*)=30



Kovtunov, K. V., et al. *Chem. Eur. J.* **2014**, *20*, 11636–11639.

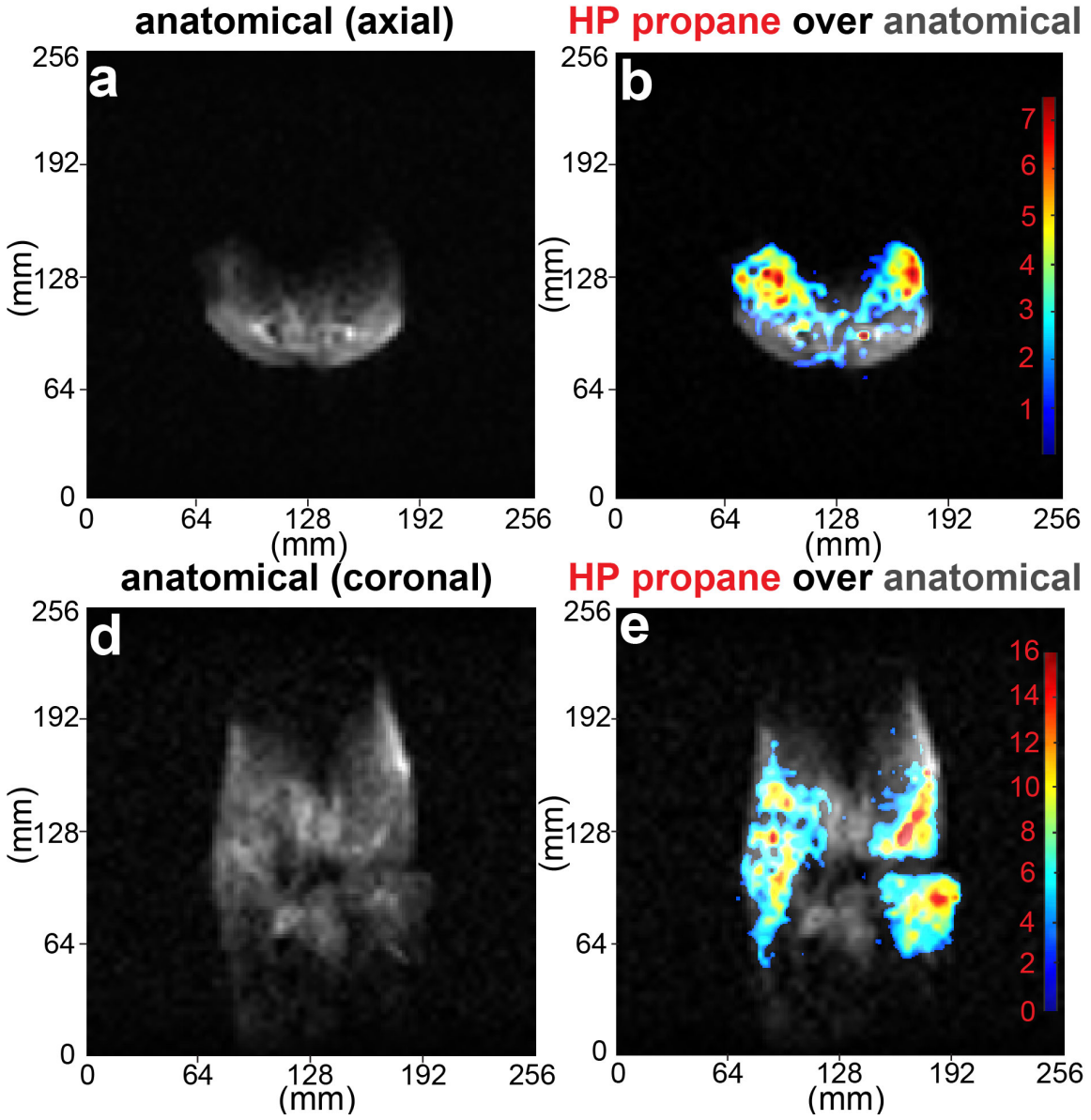
Hand-Held Disposable Clinical-Scale Propane Hyperpolarizer





Ariyasingha, et al. *ACS Sensors*, **2023**, accepted.

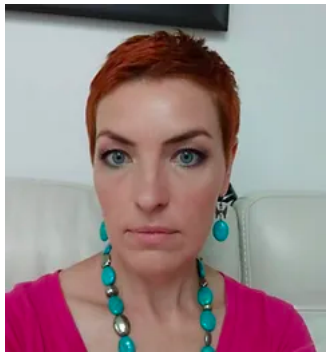
Pilot Imaging in Excised Pig Lungs



Ariyasingha, et al. *ACS Sensors*, **2023**, accepted.

Nuwandi Ariayasingha PhD
F32 NHLBI fellowship

Raduan Chowdhury



Anna Samoilenko, Pharm D

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CURRENT:

DOD CDMRP PRMRP W81XWH-20-10576
NSF CHE-1904780
NHLBI F32 HL160108
NHLBI R21 HL154032
NIBIB R21 EB033872

PENDING:

NIH OFFICE OF DIRECTORS R01 OD035097
NIBIB R01 EB034197-01A1
NHLBI R01 HL172946
DOD CDMRP BRP BC230221
DOD CDMRP PRMRP PR231743

COMPLETED:

DOD CDMRP PRMRP W81XWH-15-1-0271
NCI 1 R21 CA220137-01
NCI 1U01CA202229
DOD CDMRP BRP BC112431 (career award)
NSF CHE-1416268
NIBIB 1R21EB020323
NIBIB 1R21EB018014-01A1
NCI K99/R00CA134749 & 3R00CA134749-02S1
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PREVENT CANCER FOUNDATION
NHLBI 1R01HL096471-01A1
NINDS 1R01NS072497-01A1
NIBIB F32EB021840
EXXON MOBIL KNOWLEDGE BUILD
UNIVERSITY OF NOTTINGHAM CONTRACT
NIBIB 1 R01 EB029829