Development of MR Molecular Imaging Agents

A second objective of our research program is the development of new molecular imaging agents for detection via hyperpolarized xenon-129 magnetic resonance imaging (HP-Xe MRI). Our research team has already synthesized dozens of cyclotriveratrylene and cryptophane compounds that are capable of reversibly binding xenon and, with the help of our collaborator, Mitchell Albert at the Thunder Bay Regional Research Center, have acquired HyperCEST ^{129}Xe spectra and images of these compounds in organic solvents, saline and blood (Figure 1).

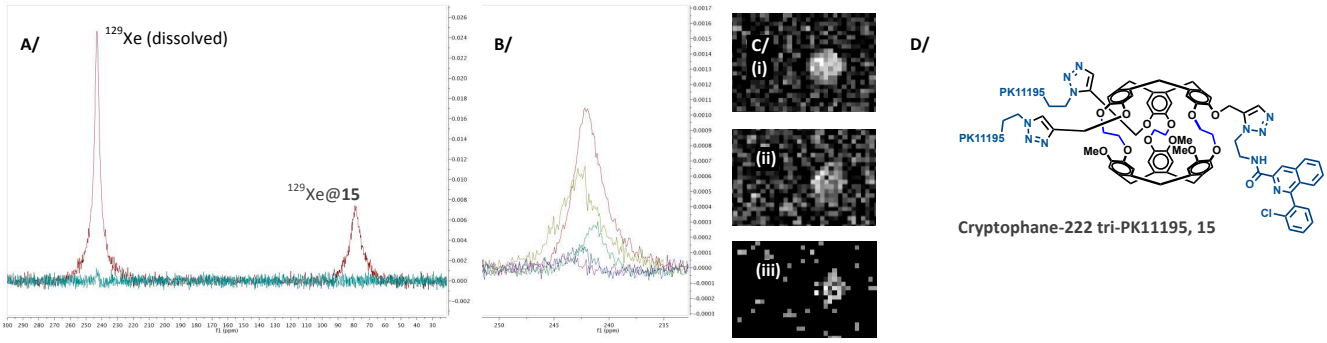

Figure 1. A/ ^{129}Xe HyperCEST NMR spectrum of a 30 mM solution of **15** in DMSO without presaturation pulses (red) and with 10 presaturation pulses (blue-green). ^{29}Xe gas is at δ = 0 (not shown). **B/** Signal decrease as a function of multiple 6 ms, 3-lobe sinc HyperCEST prepulses (0 pulses = red, 3 pulses = yellow, 5 pulses = blue-green, 7 pulses = blue, 10 pulses = purple). **C/** ^{129}Xe HyperCEST imaging of **15** using a gradient echo pulse sequence: **(i)** no prepulse, **(ii)** with HyperCEST prepulses and **(iii)** difference image showing the HyperCEST effect, which should be sufficient for in vivo molecular imaging. (These images are poor quality compared to the ones that we have acquired recently. See the attached manuscript for higher quality images.) **D/** Structure of **15**, a potential HyperCEST molecular probe for sensing inflammation by selectively binding the peripheral benzodiazepine receptor (unpublished results).

Recently, our collaborative team published the first HyperCEST images in whole blood,[12] and we have preliminary evidence indicating that this method can be extended to *in vivo* imaging in live animals. We are currently working to synthesize targeted biosensors that can be used to detect tumors and the plaques associated with Alzheimer's disease via HP-Xe MRI. The synthesis of these probes is not easy, but we have recently developed two novel methods for attaching ligands to xenon host molecules.

While this field is relatively new to us, we have generated encouraging preliminary data, and have forged a fruitful collaboration with Prof. Albert, one of the founders of the HP-Xe MRI technology.[13] Overall, this collaborative project leverages our synthetic abilities with Prof. Albert's preclinical and clinical imaging prowess, thus creating an exciting environment for performing transformative research.

(12) Hane, F. T.; Smylie, P. S.; Li, T.; Ruberto, J.; Dowhos, K.; Ball, I.; Tomanek, B.; DeBoef, B.; Albert, M. S. HyperCEST Detection of Cucurbit[6]uril in Whole Blood Using an Ultrashort Saturation Pre-Pulse Train. *Contrast Media Mol. Imaging* **2016**, *11*, 285.

(13) Albert, M. S.; Cates, G. D.; Driehuys, B.; Happer, W.; Saam, B.; Springer, C. S.; Wishnia, A. Biological Magnetic Resonance Imaging Using Laser-Polarized ^{129}Xe. *Nature* **1994**, *370*, 199.