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Using Hyperpolarized ¹²⁹Xe Magnetic Resonance Imaging to Identify Potential Supramolecular Scaffolds for Xenon Biosensor Molecular Imaging Agents

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Disclosure

Braedan R.J. Prete

- Relationships with commercial interests: NONE
- Potential for conflict(s) of interest: NONE



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¹²⁹Xe Biosensor Imaging Agents

- ¹²⁹Xe biosensors are composed of a supramolecular cage structure, which can efficiently encapsulate ¹²⁹Xe [1].
- The sensitivity of ¹²⁹Xe biosensors in molecular magnetic resonance imaging (MRI) is similar to that of radio-tracers in position emission tomography (PET).
- ¹²⁹Xe biosensors utilize the advantageous submillimeter spatial resolution of MRI and they operate without exposure to ionizing
 Science 314: A46-449.

Schröder L et al., (2006), Science, 214: 446-449.
 Witte C et al., (2009) Any Grand Community Int'l Ed. 54: 2806-2810.
 Rowe C et al., (2008) The Lancet Neurology. 7: 129-135.



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¹²⁹Xe Biosensor Imaging Agents



Image source: Hane FT et al., (2017) Bioconjugate. Chem. Manuscript Submitted.

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Hyperpolarized ¹²⁹Xe MRI

- Polarization of the nuclear spin of ¹²⁹Xe is achieved through spin-exchange optical pumping (SEOP), using a circularly polarized light laser [4].
- This process enhances the magnetization of ¹²⁹Xe nuclei by up to 100,000 times over thermally polarized gas [5, 6].
- Used predominantly for lung and brain imaging [6].





[4] Happer W et al., (1984) *Phys. Rev.* 29(6), 3092. *Image sources*: [5] Walker TG et al., (1997) *Rev. Mod. Phys.* 69(2), 629. (top)
[6] Albert MS et al., (1994) *Nature.* 370, 6486. (bottom)

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Hyperpolarized Chemical Exchange Saturation Transfer (HyperCEST)

- There is a constant exchange of HP ¹²⁹Xe in to, and out of, the supramolecular host [1].
- A radiofrequency (RF) saturation pulse is applied at the chemical shift offset of ¹²⁹Xe nuclei interacting with the cage, subsequently depolarizing these nuclei.
- The exchange of ¹²⁹Xe via HyperCEST reduces HP ¹²⁹Xe in the dissolved pool, thereby reducing the NMR signal of xenon in the dissolved phase [1].
 [1] Schröder L et al., (2006) Science. 314: 446-449.

Image source: Hane FT et al., (2016) Contrast Media Mol. Imaging. 11.



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Molecular Imaging via HyperCEST



Image source: Hane FT et al., (2016) Contrast Media Mol. Imaging. 11.

Saturation Map

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Molecular Imaging via HyperCEST



Image source: Hane FT et al., (2017) Sci. Rep. 7, 41027.

Hane FT, et al. 9:00 AM Saturday, Oct. 14. Faculty Lounge.

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Molecular Imaging via HyperCEST





[18F]2FA BP_{RI} in NC



[¹⁸F]2FA BP_{RI} in AD

Image sources: Hane FT et al., (2017) Sci. Rep. 7, 41027. (left) Okada H et al., (2013) Brain. 136: 3004-3017. (right)

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Functionalized ¹²⁹Xe Biosensor Imaging Agents



- Functionalized ¹²⁹Xe biosensors have the potential to accumulate in high concentrations and target many disease pathology markers at exceptional specificity.
- The ultra-high sensitivity of novel ¹²⁹Xe biosensors facilitates their use as selective contrast agents in biomedical molecular imaging [1].
- Some ¹²⁹Xe biosensors are notably difficult to functionalize [7], while others perform poorly once conjugated to an antibody.

Schröder L et al., (2006) Science. **314**: 446-449.
 Khan et al., (2015) Bioconjugate Chem. **26**, 101.
 Image source: Hane FT et al., (2017) Bioconjugate Chem. Manuscript Submitted.

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Functionalized ¹²⁹Xe Biosensor Imaging Agents





- We've identified two potential scaffolds for HP ¹²⁹Xe biosensor molecular imaging agents:
 - A. Monofunctionalized cucurbit[6]uril derivatives
 - B. Cyclodextrin-based pseudorotaxanes [8]

[8] Hane FT et al., (2017) Bioconjugate. Chem. Manuscript Submitted.

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Functionalized ¹²⁹Xe Biosensor Imaging Agents







= Antibody/ affinity tag

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Experimental Method



- Spectral data was acquired in vitro with the use of a custom-made glass frit phantom placed inside an NMR RF coil inside the bore of the MRI.
- A 2.5 mL sample of a solution containing a functionalized xenon biosensor scaffold was drawn into the fritted vessel with a syringe.
- HP ¹²⁹Xe was continuously introduced to the solution via a glass frit which produced microbubbles that dissolved
 Note into solution spectroscopy was conducted in a 3.0 T whole body Philips Achieva MRI.





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Experimental Results



[8] Hane FT et al., (2017) Bioconjugate. Chem. Manuscript Submitted.

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Experimental Results



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What's Next?







- We plan to apply a similar methodology using one of these biosensor scaffolds with a biologically-active linkage, such as an antibody or affinity tag, using a living mammalian model (*in vivo*).
- Ultimately, following the *in vivo* step, we hope to apply our methods in a preclinical setting with human participants to investigate the feasibility of our scaffolds as potential biosensors for various neurodegenerative diseases.

Image sources: Hane FT et al., (2017) Sci. Rep. 7, 41027. (left) Okada H et al., (2013) Brain. 136: 3004-3017. (right)

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Conclusions

- These results demonstrate that monofunctionalized CB6 derivatives and cyclodextrin-based pseudorotaxanes can successfully perform as a HP ¹²⁹Xe molecular MR imaging agent *in vitro*.
- We have shown that these biosensor scaffolds can be used in MRI with comparable sensitivity to PET, but with enhanced spatial resolution and without to exposure to potentially harmful ionizing radiation.
- Ultimately, we believe that the future of molecular imaging and, in fact, the future of detecting early disease onset lies within this technology.





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