Molecular Imaging with Hyperpolarized 129Xe

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Molecular imaging is a rapidly developing field of visualization, characterization, and measurement of biological processes at the molecular and cellular levels [1], which became a stepping stone for active implementation and further development of personalized medicine paradigms [2]. Conventional magnetic resonance imaging (MRI) does not perform well in molecular imaging settings due to the overall high background signal and general lack of sensitivity. To overcome these challenges, a hyperpolarized chemical exchange saturation transfer (HyperCEST) imaging approach has been developed [3]. It relies on the utilization of hyperpolarized (HP) xenon-129 (^{129}Xe) MRI, which provides up to five orders of magnitude signal boost due to metastable HP nuclear state, in conjunction with supramolecular macrocycles capable of reversible encapsulation of HP 129Xe. By irradiating the encapsulated ^{129}Xe with an external radiofrequency (RF) pulse(s), it is possible to destroy the HP state which in conjunction with a constant chemical exchange with a much larger dissolved HP ^{129}Xe pool will result in an overall signal reduction on MRI image.

HyperCEST contrast mechanism allows for up to eight orders of magnitude MRI sensitivity enhancement making this a suitable approach for molecular imaging. While the practical application of this technique has proven its feasibility for molecular imaging in living organisms, there are two major limitations that restrain HyperCEST molecular MRI imaging from rapid growth and implementations for disease detection. Firstly, there are no fully designed HyperCEST active molecular imaging biosensors due to the challenges of functionalization of various supramolecular cages. Secondly, for more than a decade, there was no MRI pulse sequence optimization performed to maximize the sensitivity of the developed HyperCEST molecular agents. Overcoming these two limitations became a focus of our work.

In our group, we performed the first HyperCEST molecular imaging pulse sequence optimization resulting in up to 4 times sensitivity increase for the imaging of cucurbit[6]uril [4] – the only HyperCEST agent previously used for in vivo imaging. This increased sensitivity allowed us, for the first time, to observe HyperCEST contrast not just from blood plasma, but also from red blood cells. The same pulse sequence was utilized next to detect, for the first time, a HyperCEST effect from novel resorcinarene trimer (R3) methanesulfonate (R3- Noria-$MeSO_3H$) [5]. This novel supramolecular cage demonstrated a strong HyperCEST contrast, extreme solubility in aqueous solutions, and additional strong negative effective spin-spin relaxation contrast. This novel R3- Noria-$MeSO_3H$ macrocycle is also easy to functionalize

due to the presence of the 12 sulfonic acid groups. Overall, the implementation of the novel R3- Noria-$MeSO_3H$ with optimized HyperCEST MRI pulse sequence has the potential to bring us much closer to clinical applications of HyperCEST molecular imaging.

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