Development of Blood Pool Mn-based Magnetic Imaging Resonance (MRI) agents

Tarek El Sayed, Karna Terpstra, Jennifer Whetter, Kerui Xu Lingyang Zhu, Sagnik Chakrabati Shreyan Majumdar, Eszter Boros, Liviu M. Mirica

Magnetic Resonance Imaging (MRI) is an imaging modality widely used to diagnose various diseases due to its high resolution. However, due to sensitivity issues, contrast agents are administered intravenously to enhance the relaxivity of water protons in tissues, hence providing higher-quality images. Gd-based agents have dominated the field, but concerns due to toxicity and retention of Gd in the brain have accelerated the development of Mn2+ and Fe3+ alternatives. Usually, MRI agents are hydrophilic; hence, they do not bind to proteins and are rapidly excreted from the body, making them non-specific. Blood pool MRI agents that bind albumin increase the circulation time of the agent in the body, which is beneficial for tumor uptake and imaging. Making a more lipophilic chelator and controlling the overall charge of the complex is expected to modulate the affinity of the Mn chelators towards albumin. Herein, we report a series of chelators based on the pyridinophane ligand with different donor arms that enhance Mn complexes' thermodynamic stability and kinetic inertness. The coordination chemistry of the chelators was studied by spectrophotometric titrations, cyclic voltammetry, and X-ray crystallography. Their MRI potential was evaluated using a 1.4 T tabletop and 9.4 T MRI scanner. Extensive relaxation and 17O measurements were performed to understand the underlying physical properties that make them effective MRI agents. Extensive MRI animal studies and 52Mn PET experiments have shown that our lead compound grants further clinical development.