

Specialty area: Molecular Imaging

Speaker's name: Zheng-Rong Lu, Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH, USA. zhengrong.lu@case.edu

Highlights:

- Delivery strategies of Gd(III) based contrast agents for molecular imaging
- Safety considerations for the design of targeted Gd(III) based contrast agents for molecular imaging
- Selection of molecular targets for effective molecular MRI

Title: Targeted Delivery of Gd-Based Contrast Agents for MR Molecular Imaging

Target audience: Researchers in the area of MRI contrast agents and molecular imaging and radiologists and clinicians specialized in cancer and cardiovascular diseases.

Objectives: To be familiar with the challenges for molecular MRI, the delivery strategies of contrast agents for molecular MRI, stability, biodistribution and safety considerations of targeted MRI contrast agents, methods for determining the stability of Gd(III) based contrast agents.

MRI is a powerful medical imaging modality and provides high-resolution three-dimensional visualization of anatomical structures of soft tissues in the body. However, contrast enhanced MRI has not been effective for clinical molecular imaging because of its low sensitivity and lack of safe and effective targeted MRI contrast agents. Molecular MRI requires the delivery of a sufficient amount contrast agents to molecular targets to generate detectable signal enhancement. This presentation will discuss different strategies of delivering Gd(III) based MRI contrast agents for molecular imaging, including small molecular and nanosized targeted contrast agents.

Safety is a major concern for design and development of Gd(III) based MRI contrast agents. Stability, biodistribution and elimination of Gd(III) chelates are the essential parameters for the safety of the Gd(III) based MRI contrast agents. Chelation structure determines the stability of Gd(III) based contrast agents. Generally, macrocyclic chelates have much higher chelation stability than linear chelates. Some of commonly used methods for evaluating the stability of Gd(III) based MRI contrast agents will be discussed. Size of contrast agents has a crucial impact on the pharmacokinetics, biodistribution and elimination of MRI contrast agents. Complete excretion of the contrast agents should be achieved in order to minimize any potential toxic side effects. Examples of different Gd(III) based contrast agents will be used to discuss the safety issues in the delivery of Gd(III) based contrast agents for molecular imaging.

Selection of molecular targets is another key for delivery of targeted contrast agents for effective molecular imaging. Solid biology of the molecular targets is the necessity of selecting targets for molecular imaging. Selection of molecular targets should be supported by strong biological and clinical evidence and associate with certain diseases. They should also be abundant and accessible for binding of contrast agents. An example of designing of small molecular MRI contrast agents specific to an abundant biomarker of malignant tumors will be used to discuss the significance of target selecting for molecular MRI.

Reference:

1. Zhou Z, Lu ZR. Gadolinium-based contrast agents for magnetic resonance cancer imaging. *Wiley Interdiscip Rev Nanomed Nanobiotechnol.* 2013, 5, 1-18.
2. Wu X, Zong Y, Ye Z, Lu ZR. Stability and biodistribution of a biodegradable macromolecular MRI contrast agent Gd-DTPA cystamine copolymers (GDCC) in rats. *Pharm Res.* 2010, 27, 1390-7
3. Ye Z, Wu X, Tan M, Jesberger J, Griswold M, Lu ZR. Synthesis and evaluation of a polydisulfide with Gd-DOTA monoamide side chains as a biodegradable macromolecular contrast agent for MR blood pool imaging. *Contrast Media Mol Imaging.* 2013, 8, 220-8.
4. Tan M, Wu X, Jeong EK, Chen Q, Lu ZR. Peptide-targeted Nanoglobular Gd-DOTA monoamide conjugates for magnetic resonance cancer molecular imaging. *Biomacromolecules.* 2010, 11, 754-61.
5. Wu X, Burden-Gulley SM, Yu G, Tan M, Lindner D, Brady-Kalnay SM, et al. Synthesis and evaluation of a peptide targeted small molecular Gd-DOTA monoamide conjugate for MR molecular imaging of prostate cancer. *Bioconjugate Chem.* 2012;23:1548-56.
6. Tan M, Burden-Gulley SM, Li W, Wu X, Lindner D, Brady-Kalnay SM, et al. MR molecular imaging of prostate cancer with a peptide-targeted contrast agent in a mouse orthotopic prostate cancer model. *Pharm Res.* 2011;20:953-60.
7. Zhou, Z.-X., Wu, X.-M., Kresak, A., Griswold, M., Lu, Z.-R., Peptide Targeted Tripod Macrocyclic Gd(III) Chelates for Cancer Molecular MRI. *Biomaterials.* **2013**, 34, 7683-7693.
8. Xueming Wu, Niranjana Balu, Wen Li, Yong Chen, Xiaoyue Shi, China Kummitha, Xin Yu, Chun Yuan, and Lu, Z.-R., Molecular MRI of Atherosclerotic Plaque Progression in an ApoE^{-/-} Mouse Model with a CLT1 Peptide Targeted Macrocyclic Gd(III) Chelate. *Am. J. Nucl. Med. Mol. Imaging.* 2013, 3, 446-455.