Targeted Agents

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Molecular MR imaging is an expanding field with applications in cancer, cardiovascular disease, diabetes and other disease states. Molecular MRI combines the molecular/cellular specificity of molecular imaging with the strengths of MRI: high spatial resolution, no ionizing radiation, excellent soft tissue contrast and exquisite anatomical detail, and functional, physiological readouts such as perfusion and permeability. While some review articles on molecular imaging state that MR lacks the sensitivity for molecular imaging, this is far from the reality. While it is true that MR requires micromolar concentrations to achieve detection, there are many paths to achieve robust image contrast. High concentration targets, targets that accumulate and internalize probe, multimeric or nanoparticle probes to deliver high signal payload, and activatable probes are examples of approaches that enable molecular MRI.

This overview will focus on "targeted agents". These are probes that contain a targeting vector to direct the probe to its biological target. The targeting vector can be a small molecule, peptide, antibody or antibody fragment, oligonucleotide (e.g. aptamers), or polysaccharide. Sometimes the probe can be incorporated into a naturally occurring macromolecule which has its own innate targeting mechanism, e.g. high density lipoprotein (HDL) – based probes. There are different imaging reporters that can be used to generate MR contrast. These include T2 agents like iron oxide nanoparticles that make the target dark, T1 agents like gadolinium-based probes that make the target appear bright, chemical exchange saturation transfer (CEST) based agents whose contrast is pulse sequence selective, and chemical shift and heteronuclear probes based on fluorine-19 or hyperpolarized C-13. Probes can also combine more than one imaging reporter (e.g. MR-PET).

Imaging probes can also be classified in terms of their physical properties. There are small molecules that can rapidly extravasate from the vascular system into the extravascular, extracellular space, and in some cases into cells. There are probes based on nanoparticles that deliver a large payload imaging reporter, but which have different pharmacokinetics and biodistributions compared to small molecules. Probes can also undergo chemical transformations in vivo to alter their distribution properties.

This presentation will review the state of the art in targeted agents and list examples of targeted agents that have been validated in animal models. Using examples from the literature it will cover the questions of molecular probe design by comparing Gd vs FeO vs other contrast generating moieties, and by discussing the benefits/weaknesses of small molecule vs macromolecule approaches. Using specific cases, we will explore how to validate the mechanism of action of a targeted probe.

For additional information on this topic, the following can be consulted
Reviews:

1. Caravan P, Zhang Z, Targeted MRI contrast agents. In: Helm L, Toth E, and Merbach AE, editors. The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging, 2nd edition. Chichester : Wiley ; 2013, pp 311-42.
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Fibrin targeted probe and applications as an example:

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Collagen targeted probe and applications as an example:

6. Caravan P, Das B, Dumas S, Epstein FH, Helm PA, Jacques V, Kolodziej A, Shen L, Zhang Z, Collagen targeted MRI contrast agent for molecular imaging of fibrosis. Angew. Chem. Int. Ed. 2007; 46:8171-3.
7. Fuchs BC, Wang H, Yang Y, Wei L, Polasek M, Schühle DT, Lauwers GY, Parkar A, Sinskey AJ, Tanabe KK, Caravan P. Molecular MRI of Collagen to Diagnose and Stage Liver Fibrosis. J Hepatol. 2013; 59:992-8.
8. Caravan P, Yang Y, Zachariah R, Schmitt A, Mino-Kenudson M, Chen HH, Sosnovik DE, Dai G, Fuchs BC, Lanuti M. Molecular MR imaging of pulmonary fibrosis in mice. Am J Resp Cell Mol Biol. 2013; 49:1120-6.