Speciality Area: Molecular Imaging, Cancer Course Educational Weekend Session

Speaker Name: Angelique Louie, Professor, Department of Biomedical Engineering, University of California, Davis, CA 95616 aylouie@ucdavis.edu

Highlights:

- MRI agents can be designed to sense specific biomarkers
- Two major approaches to sensing are 1) Targeting and 2) Switching
- While targeting methods are straightforward in principle and almost uniformly similar in approach, agents that can switch assume a variety of forms. We will provide several examples to illustrate mechanisms for switching that have been explored in the literature.

Talk Title: Switching and Sensing

Target Audience: Researchers and clinicians interested in noninvasive methods to identify molecules in living systems.

Outcome/Objectives:

- Describe mechanisms by which an MRI contrast agent can be made into a sensor
    - T1 agents
    - T2 agents
- List examples of biomarkers and molecular function that can be detected by MRI sensors
- Discuss the benefit of multimodal approaches to improve the utility of MRI sensors
- Spur creative ideation to speculate on untapped potential for sensors in cancer

Brief Overview:

This is a brief tutorial on the design of MRI contrast agents that facilitate noninvasive "sensing". "Sensing" refers to the identification of a target of interest by its location or function and MRI sensors are key components for molecular imaging. Historical examples are given to provide a context of evolution of the field, with a focus on agents with a potential for utility in cancer applications.

Sensing by targeting is a simple concept—contrast agents are designed to bind to a molecule of interest and detection is afforded by increased concentration of agent at sites where the molecule localizes. The success of this method for detection of disease is dependent upon the uniqueness of the molecule of interest to the abnormal cells or tissues, and the sensitivity of the agent in context of the abundance of the molecule of interest.

Sensing by switching is a more complex construct. It depends on the molecule of interest acting upon the contrast agent in some way that changes its ability to affect image intensity. The mechanism for modulating contrast depends upon the type of MRI agent under consideration.

T2 agents affect nearby water protons through a local magnetic field effect. To alter a T2 agent's ability to affect nearby protons, one needs to modify the strength of the local field it produces. The most comment method for achieving this is a controllable aggregation of the agents, such as iron oxide nanoparticles. Another approach is to genetically program cells or interest to produce "natural" contrast agents, such as iron carrying molecules and magnetosomes, in response to specific cues. We will discuss a few of the most recent examples of agents that utilize these mechanisms and their biological efficiency.

T1 agents, on the contrary, require direct interaction with water protons. There are a number of routes to affect a T1 agent's ability to interact with water protons, these include modulating the degree of hydration,

the rate of water exchange, and the tumbling rate for the agent. An additional challenge compared to targeted agents is that one must be able to distinguish a difference in concentration of the agents from a difference in activation of the agents. We will look at examples in the recent literature that use different mechanisms to achieve switching.

Targeting and switching methods both rely on identification of an appropriate biological marker whose location or function can be used to identify or stage disease. This is one of the major challenges for the success of sensing and switching agents as tools for research and clinic practice.

There is a very rich library of review articles dealing with activatable agents available in journals ranging from the perspective of chemical synthesis or biological application. A partial list is provided here for the student's reference.

Reviews on activatable agents:

Aime, S., A. Barge, et al. (2002). "Controlling the variation of axial water exchange rates in macrocyclic lanthanide(III) complexes." Chem Comm: 1120-1121.

Aime, S., C. Cabella, et al. (2002). "Insights into the use of paramagnetic Gd(III) complexes in MR-molecular imaging investigations." Journal of Magnetic Resonance Imaging **16**(4): 394-406.

Aime, S., S. G. Crich, et al. (2006). "High sensitivity lanthanide(III) based probes for MR-medical imaging." Coordination Chemistry Reviews **250**(11-12): 1562-1579.

Bogdanov, A. and R. Weissleder (1998). "The development of in vivo imaging systems to study gene expression." TIBTECH **16**: 5-10.

Bonnet, C. S. and E. Toth (2010). "MRI probes for sensing biologically relevant metal ions." Future Medicinal Chemistry **2**(3): 367-384.

De Leon-Rodriguez, L. M., A. J. M. Lubag, et al. (2009). "Responsive MRI Agents for Sensing Metabolism in Vivo." Accounts of Chemical Research **42**(7): 948-957.

Elias, D. R., D. L. J. Thorek, et al. (2008). "In vivo imaging of cancer biomarkers using activatable molecular probes." Cancer Biomarkers **4**(6): 287-305.

Hanaoka, K. (2010). "Development of Responsive Lanthanide-Based Magnetic Resonance Imaging and Luminescent Probes for Biological Applications." Chemical & Pharmaceutical Bulletin **58**(10): 1283-1294.

Jacques, V. and J. F. Desreux (2002). New classes of MRI contrast agents. Contrast Agents I. **221:** 123-164.

Louie AY (2013) "MRI Biosensors: A Short Primer". Journal of Magnetic Resonance Imaging, 38(3):530-9. doi: 10.1002/jmri.24298

Louie AY, (2010) "Multimodal Imaging Probes". Chemical Reviews 110(5): 3146–3195.

Louie AY: "MRI Contrast Agents in the Study of Development", Current Topics in Developmental Biology (2005) 70:35-56.

Louie AY: "Design and Characterization of Magnetic Resonance Imaging Gene Reporters", invited book chapter, invited book chapter MRI: Methods and Biological Applications, Methods in Molecular Medicine, ed. Pottumarthi PV (2005) 124:401-417.

Neeman, M., A. A. Gilad, et al. (2007). "Molecular imaging of angiogenesis." Journal of Magnetic Resonance Imaging **25**(1): 1-12.

Que, E. L. and C. J. Chang (2010). "Responsive magnetic resonance imaging contrast agents as chemical sensors for metals in biology and medicine." Chemical Society Reviews **39**(1): 51-60.

Schellenberger, E. (2010). "Bioresponsive nanosensors in medical imaging." Journal of the Royal Society Interface **7**: S83-S91.

Shapiro, M. G., T. Atanasijevic, et al. (2006). "Dynamic imaging with MRI contrast agents: quantitative considerations". Magnetic Resonance Imaging **24**(4): 449-462.

Tu C, Louie AY (2012) "Strategies for the development of Gd-based activatable, "q activatable" MRI

contrast agents". NMR in Biomedicine 6 APR 201 DOI: 10.1002/wnan.1170
Tu C, Osborne E, Louie AY (2011) "Activatable Magnetic Resonance Imaging Contrast Agents". Annals Biomedical Engineering 39(4) 1335-1348.