Visualizing cell fate: Bioactivated-multimodal probes for imaging stem cells, b-islets and cancer

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Fundamental biological and clinical questions have driven technological advances in an area of research known as biological molecular imaging. One technique that has been a powerful tool in both settings is magnetic resonance imaging (MRI). MRI offers a non-invasive means to map structure and function by sampling the amount, flow or environment of water protons in vivo. Such intrinsic contrast can be augmented by the use of paramagnetic contrast agents in both clinical and experimental settings. It is non-invasive and yields a true volume rendering of the subject with cellular resolution (~10 microns).

Currently, the direct observation of ongoing developmental events in living embryos and the descendants of individual precursors in an intact embryo are labeled by microinjection of a stable, nontoxic, membrane impermeable MRI lineage tracers. Since a complete time-series of high-resolution three-dimensional MR images can be analyzed forward or backward in time, it is possible to reconstruct the cell divisions and cell movements responsible for any particular descendant(s). Unlike previous methods, where labeled cells are identified at the termination of the experiment, this technique allows the entire kinship relationships of a clone to be determined. In order to realize the potential of this technique a systematic means of delivering the charged MR contrast agents must be developed. We have been investigating the development of molecular MR probes that are capable of crossing cell membranes and the blood brain barrier.

In order to understand signal transduction mechanisms of gene expression in whole animals we have developed a library of molecular MR probes that are biochemically activated in-vivo. The lanthanide chelates modulate fast water exchange with the paramagnetic center, yielding distinct "strong" and "weak" relaxivity states. The modualtion is triggered by two types of biological events: i. enzymatic processing of the contrast agent and, ii. the reversible binding of an intracelluar messenger. In order to direct the intracellular uptake of these agents, we have prepared a number of small molecule “chaperones” that are covalently attached to the marcorcyclic skeleton of the agent. The chaperones are capable of transporting the agent inside a cell in relatively high yield and to not interfere with the activation of the agent by an enzyme or the binding of Ca^{2+}.