Probe Development: Fundamentals/Chemistry

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Molecular and cellular imaging is a relatively young field that is rapidly changing our approach towards understanding and solving problems in *in vivo* diagnoses with innovative solutions.

The development of high sensitive, targeting and responsive agents is a major challenge to enhance the role of MRI in the field of Molecular Imaging applications.
Understanding the relationships between structure and dynamics of Lanthanide(III) chelates has been fundamental for the development of high sensitive Gd(III) based agents.
From targeting Human Serum Albumin for the development of angiographic agents, our research efforts are now addressing the visualization of molecules (characterizing diseased states) that are present at much lower concentration(1).
The need of targeting molecules that are present at very low concentration requires the development of a novel class of contrast agents characterized by higher contrasting ability and improved targeting capabilities. Efficient targeting procedures for cellular labeling and recognition of epitopes characterizing important pathologies have been set up (2).
Furthermore, interesting insights on nano-sized structure containing paramagnetic ions have been gained to suggest that innovative approaches to high relaxivity agents may also be possible. As far as the delivery of a large number of Gd-complexes at the targeting sites is concerned, several systems are currently under intense scrutiny, including dendrimers, liposomes and other types of lipophilic aggregates.

Currently, much attention is also devoted to CEST agents that represent an emerging class of MRI contrast media of huge potential. They act as negative agents by reducing the signal intensity of water protons through saturation transfer mediated by chemical exchange. The great potential of CEST agents lies on the possibility of switching on and off the contrast at will, making possible the detection of more agents, each uniquely characterized by specific frequency of their mobile protons. Marked sensitivity improvements have been obtained by using as source of mobile protons the water molecules contained in the inner cavity of liposomes, properly shifted by the addition of a shift reagent(3).

Finally, paramagnetic metal complexes and their formulation may be designed in order to act as "smart" agents, i.e. to make their effect on the water signal responsive to specific parameters of the microenvironment in which they distribute. Several paramagnetic metal complexes responsive to pH, pO_2, enzymatic activity, metabolites' concentration have been reported. An important issue that limits the *in vivo* applications of responsive agents deals with the need of accessing to an independent measure of their local concentrations. Efforts to tackle this issue in the field of paramagnetic Lanthanide(III) complexes will be presented.

1) S. Aime, et al., Design of Contrast Agents for Molecular Imaging *In Vivo*. in "In Vivo MR Techniques in Drug Discovery and Development" (Ed. N. Beckmann), Taylor & Francis, New York, 2006, chap. 4, pp. 47-72.
2)Geninatti Crich S, et al.,Cancer Res. 2006, 66 (18), 9196-201.
3) Terreno e., et al, Angew. Chem. Int. Ed. 2007, 46,966