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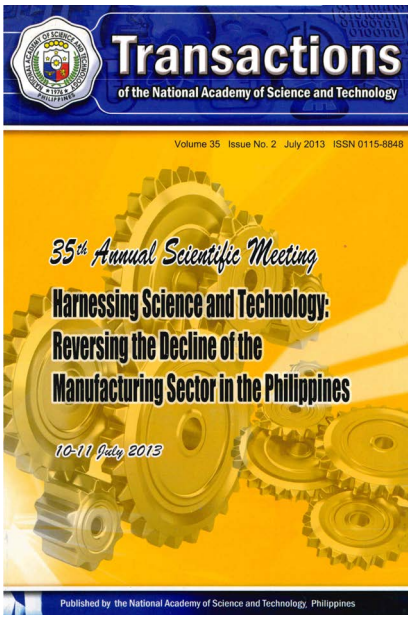

Lanthanide-Based Diagnostic Medical Contrast Agent Development

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LANTHANIDE-BASED DIAGNOSTIC MEDICAL CONTRAST AGENT DEVELOPMENT

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The early diagnosis of disease is important for effective therapy. Lanthanide-based medical contrast agents have found widespread application in both *in vivo* diagnostic imaging and *in vitro* biochemical assays. For instance, several Gd^{3+}-based complexes, proven to be stable and non-toxic *in vivo*, have received FDA approval and are routinely used in the clinic for Magnetic Resonance Imaging (MRI) of the blood pool to detect vascular occlusion and other physiological phenomena associated with vascular disease. The strong, unparalleled paramagnetic character of the Gd^{3+} ion makes it ideal for the generation of MRI images with enhanced contrast, permitting the visualization of circulatory vasculature up to millimetre resolution. On the other hand, lanthanides such as Eu^{3+}, Tb^{3+} and Yb^{3+} have been found to exhibit strong photon emission lines of red, green, and near infrared, respectively, which are long-lived, ranging from micro- to millisecond lifetimes, in comparison with conventional organic fluorophores, which exhibit broad emission lines with only nanosecond lifetimes. Hence, emissive lanthanide complexes are quickly gaining application in *in vitro* assays for the detection of biochemical analytes associated with particular disease states, such as the over-expression of transmembrane receptors characteristic of particular cancers.

As a young faculty member of the UP Diliman Institute of Chemistry, I am currently establishing a laboratory whose primary activities are directed towards lanthanide-based contrast agent development. Current projects include:

1. **The development and optimization of simple colorimetric assays for the detection of free lanthanide ions in solution.** Lanthanide ions are small, hard cations, which when present in plasma, may substitute endogenous ions in their natural physiological roles, such as in signal transduction cascades or in structural roles (e.g.. bone). In lanthanide-based contrast agent development, simple colorimetric

assays involving classical uv-vis absorption spectroscopy are useful in monitoring the successful formation of stable complexes.

2. **Ligand synthesis, structure elucidation, thermodynamic, and kinetic stability studies.** Macrocyclic ligands have been found to form more stable lanthanide complexes than acyclic ligands due to the rigidity of the resulting complex. We have synthesized a variety of macrocyclic ligands based on a cyclen backbone, elucidated their structures using 1-D and 2-D $^{1}H/^{13}C$ NMR techniques, used them to form complexes with different lanthanide ions, and employed the colorimetric assays described above to determine thermodynamic and kinetic complex stability under a variety of experimental conditions.

3. **Synthesis of lanthanide-labelled neuroactive bacterial peptides as potential optical probes in neurophysiology.** Recently, a family of bacterial peptides isolated as secondary metabolites from mollusc-associated symbiotic bacteria were found to inhibit the action of capsaicin on neuroreceptors implicated in the sensation of heat and pain. We have successfully undertaken the total synthesis of the most active of these peptides, and labelled it with lanthanides towards the development of a targeted molecule probe which will permit the direct optical visualization of the peptide-neuroreceptor binding event.

4. **Synthesis of macromolecular MRI contrast agents with enhanced water solubility.** Enhanced MRI contrast is achieved by increasing the molecular weight of the contrast agent, thereby increasing its rotational correlation time in plasma. To this effect, we are investigating the use of a polyamidoamine (PAMAM) dendrimer co-labeled with polyethylene glycol (PEG) as a platform for the synthesis of a multi-metallic Gd^{3+}-based MRI contrast agent which will potentially exhibit even further MR contrast enhancement, in addition to improved pharmacokinetic properties.