Editorial: Lanthanide compounds for therapeutic and diagnostic applications

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The medical applications of lanthanides are diverse: MRI contrast agents, hypophosphatemic agents for kidney dialysis patients, luminescent probes in cell studies, and for palliation of bone pain in osteosarcoma.

The diverse nature of medical applications of lanthanides may come as a surprise to many readers. Only recently have lanthanides achieved a measure of fame and increasingly intense research interest, primarily as a result of the phenomenal success of gadolinium-based MRI contrast agents. But there are many other medically relevant applications of lanthanides, for example, as hypophosphatemic agents for kidney dialysis patients, as luminescent probes in cell studies, and for palliation of bone pain in osteosarcoma. Lanthanides, known originally as rare earth metals, are now recognized as being neither rare, nor truly earths. They are inner transition elements, defined as the 4f-orbital-filling elements, but also generally including La itself, with electron shell $[Xe]4d^16s^2$. A singular characteristic of the lanthanide series is that the ionic radii contract across the series.[1] Lanthanide ions are usually most stable in solution as trivalent ions, with the exception of cerium, which can exist as a quadrivalent species, and europium, also found as a bivalent species. All lanthanides show a marked bioinorganic similarity to Ca^{2+}, with near equivalence of ionic radii, but with a higher charge density. This combination makes displacement of calcium in a physiological milieu a driving concern for many therapeutic and diagnostic applications.

Uses of lanthanide ions in medical applications before the invention of gadolinium-based contrast agents such as Magnevist™ are few and far between. Isolation of lanthanum and individual lanthanides was incomplete before the early part of the twentieth century. Their very chemical similarity precluded accurate identification before then. Earliest biologically relevant uses for lanthanides were as spectroscopic and magnetic probes, since they tend to have clear spectroscopic and magnetic signatures, unlike calcium. Most exhibit strong fluorescence in aqueous solutions. More recently, the strong resemblance of lanthanides to their heavier, and frequently radioactive, cousins, the actinides, has been exploited to good effect. Incorporation of lanthanides into coordination compounds as potential medicinal agents, both therapeutic and diagnostic, is the most recent development that is yielding rich rewards.

Lanthanides are not inherently incorporated in biological systems, and their toxic potential has never been in question. For this reason, most lanthanum and lanthanide compounds used in medicinal settings are required to be thermodynamically very stable. Rapid and complete excretion of the lanthanides is generally desirable (lanthanide carbonate for hyperphosphatemia is a good counter-example, discussed herein).

The intentional introduction of a lanthanide ion into a biological system for either therapeutic or diagnostic purpose requires that safety considerations be kept paramount. The quality of improved imaging in MRI with lanthanide-based contrast agents assures that this application for lanthanides will continue to grow exponentially. Of the six magnetic resonance imaging contrast agents now available clinically, four are Gd^{3+}-based, and all are in heavy clinical use.[2] These therapeutic and diagnostic applications of lanthanides, as well as two additional reviews that include ligand design issues of relevance to lanthanides in medical use, are the subject of this dedicated issue of *Chem. Soc. Rev.*

References

1 J.-C. G. Bünzli and C. Piguet, *Chem. Soc. Rev.*, 2005, **34**, 1048.
2 M. Bottrill, L. Kwok and N. J. Long, *Chem. Soc. Rev.*, 2006, **35**, 557.

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