Applications of lanthanides for medicine

Lanthanides have been used for medicinal applications since the 1980s but the development of technology has led to a demand for new developments. 1 Lanthanides, known as rare-earth elements, have a wide range of photophysical properties that are amenable to spectroscopic and crystallographic studies. 1 This, along with the absence of lanthanides in biological systems, makes them ideal for studying protein structure and interactions. The chemistry of lanthanides arises from the shielded electrons in the 4f orbitals, located within the outermost filled 5s/5p orbitals2. This shielding means the luminescent f-f transitionsehibited by lanthanides are almost ligand-dependent. Despite their chemical similarities each lanthanide gives its own distinctive colour, luminescence emission spectra and nuclear magnetic properties. 2 They are electropositive, very reactive and favour the Ln3+ oxidation state. It is these properties that make them useful as medicinal agents. 1

Figure – The f block lanthanidesLn3+ ions have similar ionic radii, donor atom preferences and coordination numbers in binding sites as Ca2+ ions which means that to some extent Ln3+ can mimic Ca2+ behaviour. 3 For drugs molecules to reach their target they first need to be absorbed across the cell membrane – a calcium dependent process. Calcium concentrations of mM are needed for efficient drug uptake, but these are rarely achieved under cellular conditions and even when it is the cell is likely to become damaged. 3 It has recently been found that Ln3+ can perforate the membrane at concentrations as low as 10-5 M. It is therefore no surprise that co-administration of drugs with Ln3+ has led to an increased intracellular

accumulation. 3 This property has allowed lanthanides to be used as a co-administer to drugs, as a drug itself and imaging agents. 3

Medicinal applications

Anti cancer agents

Lanthanides have been known to be anti cancer agents since the early 1990’s primarily through the induction of apoptosis. 3 Lanthanides, particularly Tb3+, increase the infux of Ca2+ into cells thus increasing the intracellular levels. This increases the endonuclease activity, leading to DNA cleavage and therefore apoptosis. 4 The same result is achieved by the inhibition of phosphodiesterase, the molecule responsible for the degradation of cyclic adenosine 3′, 5′-monophosphate (cAMP). 4, 5 The molecule cAMP has an important role in DNA replication and an increase in its levels leads to a corresponding increase in the protein kinase (PKA) levels. This has two effects both of which lead to apoptosis; the increase of endonuclease activity and the expression of apoptosis genes. 3, 5 However, these methods were not selective and influenced healthy tissues as well as cancerous ones. 4

New developments have targeted this drawback in an attempt to limit the side effects of treatment. Titania nanoparticles (NPs) have the potential to target tumours in a non-invasive manner. 4 Titania, a wide band gap semiconductor, produces reactive oxygen species (ROS) following excitation of valence band electrons to the conductance band upon stimulation. 4 These photoelectrochemical reactions can be promoted by x-ray irradiation which allows non-invasive penetration of the human body. Two papers,

published by H. Townley et al. and A. Gnach et al., reported the discovery that the interaction of titania-NPs with x-rays can be optimised by using lanthanides as dopants. 4, 5 Normal cells can tolerate a certain level of exogenous ROS due to a reserve of antioxidants which counteract the ROS activity. 3 Cancerous cells have metabolic abnormalities which increase the intracellular ROS levels. This makes them more dependent on the intracellular antioxidant system and vulnerable to exogenous ROS levels. 4, 5 Lanthanide doped NPs generate higher levels of ROS, due to the lanthanides allowing increased x-ray absorption, than general NPs thus playing on this vulnerability. The increased levels cause DNA and mitochondrial damage, causing apoptosis. 4, 5 NPs have the capability to accumulate in tumours as a result of the defective tumour vasculature. This gives them the potential to be selective to cancer cells thus reducing side effects. The NPs can also be coated with moieties for specific targeting and activation further limiting the damage to healthy tissues. 5 These properties of the NPs are enhanced by lanthanide doping thus giving a new application for lanthanides. The best results have been seen for TiO2@GdNd and TiO2@GdEuEr. 5

Imaging

Figure – The traditional contrasting agent with Gd3+ bound to the chelate ligand and the water molecule under observation. Magnetic Resonance Imaging (MRI) has been vastly improved due to the use of contrasting agents (CA) since 1988. 6 These act to improve the contrast between healthy and pathological tissue by influencing the relaxation rate of protons of bound water molecules, T2. 7 The faster the relaxation rate, the higher the intensity

and the sharper the image achieved. Relaxation rates are increased when the water molecule is close to a paramagnetic centre. Gd3+ has 7 unpaired electrons and is used as contrasting agents in MRI due to its highly paramagnetic centre. 6 The traditional contrasting agents used Gd3+ bound to a chelate ligand through eight donor atoms (figure 2). This gives the complex the stability and strong binding needed to ensure that Gd3 is not released into the blood. 6 However, Gd3+ is unselective and distributes over a wide region of extracellular space. Developments have been made to make the distribution more selective by linking Gd3+ chelates to moieties that cause accumulation in areas of interest. 7 However, the increase of the magnetic strength from 64 MHz to the present 125 MHz has led to the decrease in the efficiency of Gd3+ based CAs. Therefore developments have had to be made to meet the technological demands.

Current commercial contrasting agents are based on Gd-DPTA, Gd-DOTA and their derivatives but utilizing the magnetic and luminescent properties of other lanthanides has allowed the developments of new CA. 8 A paper recently published by C. Andolinia et al. described how the near infrared (NIR) luminescence of the lanthanides Dy3+ and Yb3+ has been combined with the traditional MRI-CA to create new multimodal imaging agents. 6 These complexes act as light harvesting antenna due to the bifunctional chelators/chromophores present. They surround the reaction centre, in this case the tissues, and funnel absorbed energy to the reaction centre. 8 It is through this method that more of the incoming radiation is absorbed and the contrast is improved. Optical probes absorb photons from the excitation source within the visible region as well as absorbing the photons caused by

biomolecules. 6 Therefore the absorption and luminescent emission of optical probes are both in the visible region which leads to a decrease in the limit of detection as well as the depths that the photons can reach. The NIR probes have the advantage that the depth of light penetration is increased due to their excitation wavelengths being outside of the ‘ biological window’. 6 Evaluation of all of the lanthanides has shown Yb3+ to be the most efficient NIR and MRI bimodal imaging agent. 7

Osteoporotic treatment

Bones are involved in a very precise cycle of the resorption and desorption of the bone tissue, see figure 3. Osteoporosis is a skeletal disease in which the bone density is decreased through higher levels of resorption than desorption. It is most commonly treated with biphosphonates which inhibit resorption thus preventing bone degradation. 9 However, this class of drugs is poorly lipophilic and thus have a low oral bioavailability. To counteract this, the drug must be administered in high concentrations which causes GI tract problems, low patient tolerability and suspected osteoporotic issues in the jaw. 9

Figure – The continuous cycle of bone degradation and rebuildingIt is well known that lanthanide ions preferentially accumulate within the bone3 where they have an inhibitory effect on osteroclasts (bone degradation) and a stimulatory effect on osteoblasts (bone making). Due to the chemical similarities of Ln3+ and Ca2+ mentioned before, Ln3+ can potentially replace Ca2+ ions within the bone and affect the bone turnover cycle. 3 Y. Mawani et al. discovered that heavier lanthanide ions show a 50-70%

accumulation in the bones compared to lighter ions which have a > 25% accumulation. 9 The half life for a lanthanide ion in the bone is 2. 5 years compared to an elimination time from soft tissues, such as the liver, of 15 days. These properties have led to heavier lanthanide ions being used for osteoporotic therapy. 9 Furthermore, adjustment of the ligand structure has allowed the improvement of oral availability leading to an increased uptake and reduced side effects. Previous lanthanide complexes were found to be poorly soluble in aqueous phases therefore reducing the absorption across the GI tract. 9 This led to small levels of lanthanide ions accumulating in the bones therefore making the treatment inefficient. The development of an orally active drug that can pass through the GI tract has allowed efficient delivery of lanthanides to the bone.

Conclusion

Despite the initial disregarding of lanthanides due to suspected toxicity they have shown to have excellent properties for use as medicinal agents. The similarity of Ln3+ and Ca2+ has allowed lanthanides ions to be used as anti-osteoporotic agents as well as for increasing the permeability of cells to other drugs. New developments have seen lanthanide ions being used as cancer agents, by causing increased levels of ROS, as well as improving the already existing imaging techniques.