Chem Soc Rev

Harnessing the Bone-seeking Ability of Ca(II)-like Metal Ions in the Treatment of Metastatic Cancer and Resorption Disorders

SCHOLARONE™
Manuscripts

Key learning points:

(1) Diseases of the bone primarily occur due to a decoupling in the remodelling cycle.
(2) The skeleton is a target organ for several metal ions.
(3) Radioactive metal ions play a very important role in the diagnosis and therapy of metastatic bone cancer.
(4) Trivalent lanthanum compounds have the potential to treat osteoporosis.

Journal Name

ARTICLE

Harnessing the Bone-seeking Ability of Ca(II)-like Metal Ions in the Treatment of Metastatic Cancer and Resorption Disorders

D. M. Weekes[a] and C. Orvig*[a]

Metal ions are naturally retained by skeletal tissues in living systems because of their high affinity for the hydroxyapatite-like mineral matrix that makes up cortical bone. This is particularly true for metal ions that bear a close resemblance to calcium(II) (such as the lanthanides or alkaline earth metals), and in a few key cases this targeting ability has been exploited in order to develop medicinal agents that are intended to treat bones which have become diseased. In this review, we focus on two areas where this has been particularly effective: first is in the diagnosis and therapy of metastatic bone cancer, in which radioactive metal ions including ^{99m}Tc, ^{153}Sm, and ^{223}Ra are used to image, alleviate, and ablate harmful cancerous legions with good specificity versus healthy tissues; second is the use of trivalent lanthanides to treat osteoporosis, an emerging concept which has gathered significance over the last 15 years, and is now entering preclinical trials with carefully designed systems.

1. Introduction

1.1 Bone structure, function, and disease

The human skeleton, comprising over 200 individual bones, is responsible for a number of vital functions in the body, including the protection of underlying soft tissues and organs, storage and regulation of hormones and minerals, and providing the framework which supports and maintains the shape of our bodies. The most evident property of bone that enables it to carry out these functions is hardness, which can be attributed to the densely packed mineral matrix in cortical bone that makes up around 80% of all bone tissue.[1]

Contrary to intuition, bone is a highly dynamic living tissue. It is constantly undergoing a remodelling cycle of resorption and formation, tightly controlled by a number of systemic and local pathways, and kept in balance through a homeostatic equilibrium. In a simplified schematic, the primary cell groups involved in this turnover cycle are osteoblasts – responsible for bone building, and osteoclasts – responsible for bone resorption (Fig. 1). During periods of growth and development, bone formation is dominant until adulthood is reached and the two processes occur more or less consistently across the skeleton. Bone turnover may be upregulated at sites of high stress such as the joints, or act as a repair mechanism for damaged bone.[2]

When the bone turnover cycle becomes uncoupled and therefore imbalanced, skeletal diseases occur. A common example is osteoporosis – a disease impacting millions of

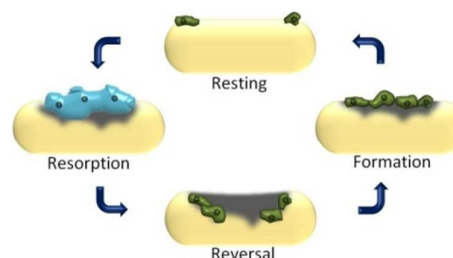people worldwide – in which the rate of resorption outweighs that of

Fig. 1 The four main stages of the bone remodelling cycle. Osteoblasts are shown in green, osteoclasts in blue.

formation leading to bones with decreased mineral density, increased brittleness, and a heightened susceptibility towards damage and fracture. Osteoporosis predominantly impacts women who have reached menopause; however, osteoporotic type symptoms can arise from a number of factors such as malnutrition, hormonal imbalance, or adverse drug reactions.[3] Another skeletal disorder is Paget's disease of the bone, in which both resorption and formation rates are augmented and new bone is deposited in a highly disordered fashion leading to abnormal growth, localized pain, and weakened bone.[4] As well as these specific conditions, perturbations to the bone cycle often arise in cancer patients when metastatic tumour cells migrate to osseous tissues. In these cases, disruptions can come about in a number of ways including uncontrolled proliferation of pre-differentiated osteoblasts, inhibition of cell apoptosis, and blocking of various signal pathways leading to deregulated and chaotic growth or mineral depletion.[5]

a. Medicinal Inorganic Chemistry Group, Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC, V6T 1Z1, Canada. E-mail: orvig@chem.ubc.ca.

In spite of these numerous causes of skeletal disorders, they all share a few unifying aspects: they are challenging to diagnose, particularly at early stages; they are painful and debilitating; and there are a very limited number of safe and effective pharmaceutical agents available to treat them. Metal based drugs play a crucial role in this sense, and herein we will discuss medicinal chemists' attempts to exploit a special relationship between metal ions and osseous tissues for various therapeutic and diagnostic tools.

1.2 Bone as a target for metal ions

Metal ions play a vital role in medicinal chemistry. A few metals are considered essential, such as copper, iron, and zinc, and are actively incorporated into our diet in order to maintain a good state of health. The remaining "non-essential" metals have historically been considered exclusively toxic; however, that notion has been increasingly confronted as the field of medicinal inorganic chemistry has grown. The unique electronic properties, variable oxidation states, flexible coordination numbers, and in some cases radiochemical properties of metal ions present both challenges and opportunities in drug design, with emphasis often placed on developing reliable dose-response data, and rational chelator design in order to improve target specificity and drug efficacy.[6] The skeleton is a natural sink for metal ions which are absorbed by the body. Those which are not excreted eventually accumulate in the bone matrix, where retention times can be in excess of several years. Often, a key aspect to any metallodrug design paradigm is preventing the natural tendency for metal ions to gravitate towards bone, since the fixing of metals in skeletal tissue limits their bioavailability, and therefore hinders activity towards an intended target. The retention of metals in hard tissues has also proven crucial in an archaeological sense, where trace metal analysis of bones from various eras has unearthed information about environment, pollution, and human health and behaviour from multiple generations.[7]

Biological bone mineral bears a close resemblance to hydroxyapatite (HAP), a naturally occurring calcium phosphate with the formula $[Ca_5(PO_4)_3OH]_n$, crystallised in a hexagonal lattice and stacked in a plate-like fashion with two distinct calcium(II) environments, one seven coordinate and one nine coordinate (Fig. 2).[8] The skeleton's propensity to attract and retain metal ions is often attributed to the vast number of potential binding interactions present within the HAP-like matrix, as well as its ability to undergo both cationic and anionic substitution without incurring significant structural alterations.[9] Multiple studies have therefore used HAP as a model for trying to predict the mechanistic intricacies of metal ion substitution in bone tissue, and the physiological impact this has.[10,11]
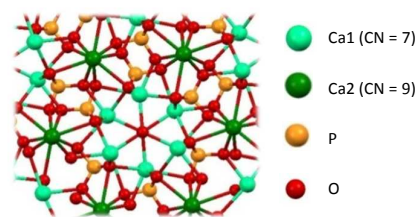

Fig. 2 The structure of hydroxyapatite viewed along the *c*-axis.[8]

This relationship between metals and bones is particularly important in the case of the 4f transition metals – referred to as the lanthanide (Ln) series – which include the 15 elements from lanthanum to lutetium. These elements have a wide number of applications, and in a medicinal context alone they have found uses as antimicrobials, treatments for burn wounds, cancer imaging and therapy agents, and renal disease treatments.[12] In aqueous solution the lanthanides tend to form stable 3+ ion complexes and differ only slightly in their chemical behaviour across the series, with ionic radii ranging from approximately 1.06 Å for La(III) to 0.85 Å for Lu(III), similar to Ca(II) which has a radius 0.99 Å.[13] Their exceptionally high affinity for bone tissue is easily explained by their preference for hard donor ligands and coordination numbers ranging from 7 to 10, which render them highly suited for substitution into HAP's phosphate-rich matrix.[11]

In synthetic HAP, the predicted mechanism for isomorphous trivalent lanthanide incorporation into the mineral matrix includes surface sorption followed by diffusion into the crystal lattice, with cationic Ln(III)-Ca(II) substitution preferentially taking place at nine coordinate Ca2 sites, and the degree of substitution directly dependant on the similarity in ionic radius between Ca(II) and the guest ion;[14] however, in living systems there is added complexity from glycoproteins, collagen, and other amorphous calcium phosphate phases, rendering *in vivo* mechanistic predictions at the molecular level extremely challenging.[15] As a result the interaction between the f-elements and bone tissue is an ongoing subject of interest and relevance, in order that their biochemistry and toxicology can be better understood.[16]

In some situations, medicinal chemists have attempted to take advantage of the skeleton's natural tendency for metal ion uptake by designing drugs in which diseased or damaged bone tissue is the intended target organ, and the properties of the metal ion (lanthanide or otherwise) are such that a desirable therapeutic or diagnostic effect could be invoked. Rarely is this a trivial task, and the considerations required and challenges involved go far beyond the basic interaction between the metal and bone mineral. For the remainder of this tutorial review we will highlight the cases that have led either to approved pharmaceutical agents which fall into this category, or to breakthrough results which have significantly advanced this field of research.

2. Radiometals for metastatic bone cancer

2.1 Bone metastases

Metastatic bone tumours occur by the migration of cancerous cells from an existing legion to skeletal tissues. For patients with malignant forms of cancer, it is an alarmingly common and disheartening occurrence, affecting more than 2 in 3 sufferers of prostate and breast cancer, and more than 1 in 3 sufferers of lung, thyroid, and kidney cancer.[17] Lesions resulting from bone metastases can cause spinal-cord compressions, disruptions to musculoskeletal function, atypical fractures, and deregulated bone turnover. From a patient perspective the result is often pain and discomfort, loss of mobility, a reduced quality of life, and in many cases diminished life expectancy.[18]

Metal-based radiopharmaceuticals play a vital role in the treatment of bone metastases. Depending on the chemical and radioactive properties of the element selected, they have found applications in imaging and diagnosis of skeletal tumours, management and palliation of bone pain, and as therapeutic tools for the ablation of bone-based legions. In all cases, it is the metal ion's affinity for bone tissue – particularly in areas of augmented turnover – that enable site specific treatment to take place.[19-26]

2.2 Samarium-153

Under the trademark name Quadramet®, the samarium-153 complex of ethylenediamine-N,N,N',N'-tetrakis(methylene phosphonic acid) (^{153}Sm-EDTMP or ^{153}Sm-lexidronam, Fig. 3) is one of the most well-known clinically approved drugs for treating bone metastases. Samarium is a relatively cheap and abundant lanthanide element, and it accordingly forms stable 3+ cations with a high affinity for bone mineral.[11] The clinical relevance of the ^{153}Sm isotope is due to a number a reasons: it has a short half-life of 47 h, which allows for fractional dosing and limits undesirable exposure times; it decays primarily by β-emission; however, also produces a γ signal enabling facile *in vivo* detection by conventional imaging techniques; it clears rapidly from the blood after injection, allowing efficient uptake in the target tissue; and it is relatively easy to produce by irradiation of enriched ^{152}Sm$_2$O$_3$.[19]
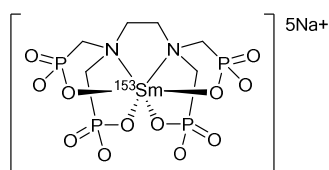

Fig. 3 Postulated structure of samarium-153-ethylenediamine-N,N,N',N'-tetrakis(methylene phosphonic acid) (^{153}Sm-EDTMP).

Nitrate and citrate salts of ^{153}Sm have been briefly studied as more general tumour imaging agents; however, their biodistribution was inconsistent and unpredictable.[20] It was noted that chelation with EDTA led to increased skeletal uptake, which prompted investigation by Goeckeler *et al.* into a series of phosphonate-containing ligands with ^{153}Sm, with the aim of producing a single-species complex in which the ligand would contribute to both complex stability and bone targeting properties.[20] The afore-mentioned 1:1 ^{153}Sm-EDTMP compound successfully met these criteria, and progressed to animal studies where it was shown that the radionuclide accumulated preferentially in bone tumours as opposed to healthy bone, rationalized by the augmented rates of tissue turnover in skeletal legions.[19] These uptake results were emulated in human trials, along with rapid clearance from non-osseous tissues.[21] This eventually led to drug approval by the FDA in the late 1990s, and since then ^{153}Sm-EDTMP has been continually scrutinized in various studies and reviews for its toxicity and efficacy. Most crucially – and from a clinical perspective – it appears that in most patients with bone metastases a partial-to-excellent degree of pain palliation results from samarium-153 β-emission particles.[22] Alleviation occurs rapidly (within a few days) and can last up to 6 weeks after injection, leading to increased mobility, better sleep, and improved quality of life.

Interestingly, in spite of the vast amount of clinical and biochemical research that has been performed on ^{153}Sm-EDTMP, an X-ray crystal structure of the complex with the stable Sm(III) isotope has never been obtained. It was only in 2015 that Yang, Pushie *et al.* were able to use a variety of spectroscopic and computational methods, including extended X-ray absorption fine structure (EXAFS), DFT, FTIR, and NMR, to give the first characterization of Sm-EDTMP at atomic resolution.[23] The coordinating environment observed for Sm(III) was in good agreement with the atomic arrangement that has long been hypothesized (Fig. 3), and this refinement in structural resolution allows a better understanding of the drug's *in vivo* behaviour, and enables well-guided modifications that could lead to an improvement in efficacy.

2.3 Radium-223

In May 2013 the drug Xofigo® (Radium-223 dichloride, ^{223}RaCl$_2$) was approved by the FDA in the United States for the treatment of metastatic bone cancer originating from prostate cancer. Similar to Quadramet, an injected dose clears efficiently from the blood and accumulates preferentially in areas with metastatic bone legions or osteosarcomas due to high bone turnover in these regions.[24] Unlike samarium, radium is an alkaline earth metal – the same group as calcium – and as the 2+ ion it targets bone tissue *in vivo* almost exclusively and without a carefully designed ligand system.[24]

The most significant differences between the two drugs can be inferred by their radioactive properties (summarized in Table 1). The ^{223}Ra isotope decays via emission of α-particles, which are heavier, of higher energy, and inherently more damaging than β-particles. This is advantageous as it induces a greater cytotoxic effect towards bone tumour cells, effectively enabling site-specific radioactive ablation of cancerous tissue from inside a patient. Moreover, since α-particles can only penetrate a fraction of the distance from their origin compared to β-particles, the amount of unwanted damage to neighbouring bone marrow is minimized, and the localization of the radiation that is delivered is improved.[25] This results not

only with fast and effective pain palliation, but a marked improvement in life expectancy for sufferers of metastatic bone cancer.[26]

Table 1 General comparison of two approved drugs, Quadramet and Xofigo, for the treatment of metastatic bone cancer.[27]

Trademark name	Quadramet	Xofigo
Radionuclide	^{153}Sm	^{223}Ra
Ligand environment	EDTMP	Chloride
Emitted particle	β	α
Half-life (days)	1.9	11.4
Particle range (μm)	>500	50-100
Gamma imaging	Yes	Yes
Pain Palliation	Yes	Yes
Prolonged survival	None evidenced	Yes

This is not the first time that researchers have attempted to exploit the ablative properties of α emitters in radiotherapy. In fact, in the early twentieth century a different radium isotope, radium-226, was also used for the treatment of bone cancer, but it was eventually declared unsuitable as its decay pathway leads to the gaseous α-emitting daughter nuclide radon-222 which can diffuse away from its origin over a long half-life ($t_{1/2}$ = 3.8 days) and impose severe unwanted damage on neighbouring tissues.[25] Conversely, the decay cascade of ^{223}Ra (Fig. 4) leads initially to radon-219 which decays much more rapidly ($t_{1/2}$ = 4.0 seconds), preventing the undesirable dispersion of radiation. It is this "safe" decay pathway associated with ^{223}Ra that makes it one of the few α-emitters considered suitable for internal therapy.[25,26]
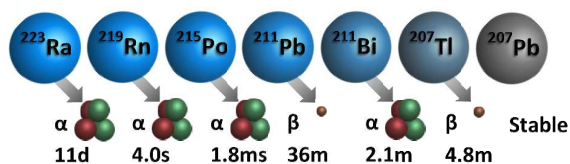
Fig. 4 The radioactive decay cascade of radium-223; the safe use of Xofigo has been attributed to the short-lived half-lives of its α-emitting daughter nuclides.

2.4 Other radiometals

Radium and samarium are two elements radioisotopes of which have been applied in the successful development of drugs for treating bone metastases due to their exceptionally high affinity for bone mineral, and in particular their high uptake in cancerous regions where turnover rates are high in preference to healthy bone. As mentioned previously, several other metals in the periodic table also have a strong tendency to be retained by osseous tissues, and considering the chemical tuning that can be achieved with ligand design the scope for drug development is vast. An example of another radiometal – which has proved vital in a diagnostic sense – is technetium-99m, which when combined with the ligand methylenediphosphonate (MDP) is routinely used in the clinic as an agent for the detection of bone metastases.[27] MDP

enhances the specific uptake of ^{99m}Tc in bone legions, where the metal is retained and its emitting properties allow for SPECT imaging. Other radiometals investigated to varying degrees of success in the treatment or diagnosis of cancerous bone include strontium-89, yttrium-90, tin-117m, holmium-166, thulium-170, lutetium-177, rhenium-186 and rhenium-188.[28]

It should be noted that, in spite of the benefits discussed thus far of applying radioactive metals as medicinal agents, they come with the invariable drawback of exposing healthy tissues to harmful radiation. This is especially true when dosing is elevated to invoke a therapeutic response, as is the case for both Quadramet and Xofigo. Common side-effects associated with radioactive therapies include nausea, vomiting, diarrhoea, and, in particular for drugs intended for targeting bone, aching of the joints and a reduced white blood cell count. The use of such drugs is only justifiable in the case of bone metastases due to the poor prognosis associated with malignant cancers that are resistant to other types of non-radioactive therapy. That being said, such is the strong relationship between metals and the skeleton, that inorganic drugs are continually being explored as therapies for metastatic bone cancer.

3. Lanthanum compounds for osteoporosis

3.1 Lanthanum carbonate

The relationship between lanthanum and osteoporosis is a curious one; it begins with a metallodrug that was intended for a different purpose. Lanthanum carbonate ($La_2(CO_3)_3$), trademarked as Fosrenol®, is commonly prescribed to prevent the build-up of phosphates (hyperphosphatemia) in people suffering from end-stage renal disease. When taken orally, lanthanum acts as a scavenger for excess phosphates (in the GI tract) that cannot be processed by the kidneys, safely excreting as stable La(III) compounds.

Fosrenol takes advantage of the extremely low intestinal absorption of lanthanum carbonate, with the absolute oral bioavailability of La(III) estimated to be as low as 0.0012%.[29] Because Fosrenol is intended for long-term use, and lanthanum is a non-essential element, much of the concern surrounding the drug's preliminary investigations focused on determining the fate of the absorbed lanthanum, and the physiological effect that its bioaccumulation would have on a patient. Not surprisingly, given the aforementioned similarity in biophysical and biochemical characteristics between Ca(II) and La(III), uptake and retention in bone tissue was observed, with evidence that lanthanum readily exchanged with calcium in the HAP-like mineral matrix.[30] What was surprising though was the effect that lanthanum had on the bone remodelling cycle, with various studies suggesting that at certain lanthanum concentrations, the proliferation of bone-building osteoblasts was promoted, leading to an increase in the rate of mineralization and bone formation.[31] Since osteoporosis is a condition in which the rate of bone resorption outweighs that of bone formation, it was hypothesized that a compound

containing lanthanum could be used in the treatment and/or therapy for such diseases.[32]

3.2 Available treatments for osteoporosis

Currently, the most commonly prescribed treatments for bone resorption disorders such as osteoporosis are the orally delivered bisphosphonates (Fig. 5a), which target bone mineral with very high specificity by mimicking the pyrophosphate network in HAP, and act by supressing osteoclastic activity to restore balance to a disrupted bone turnover cycle.[33] Since their initial release, there have been an ever-increasing number of negative side-effects associated with bisphosphonate use, including atypical femur fractures, oesophageal cancer, and osteonecrosis of the jaw. In addition, long term efficacy and safety have been called into question, with studies suggesting that bisphosphonate usage for more than three years may be more detrimental than beneficial to bone health.[34]

Also approved for treating osteoporosis is the inorganic drug Protelos®, the active component of which is the strontium(II) salt of ranelic acid (Fig. 5b). As one would expect for a divalent group II metal, strontium is readily incorporated into bone mineral where, through various pathways, it has been shown to simultaneously repress bone resorption and promote bone formation, which both work to minimize mineral depletion and fracture risk in osteoporosis sufferers.[35] Since its approval, substantial evidence has suggested that the use of Protelos leads to serious adverse cardiovascular events and increased threat of heart failure.[36] Consequently, prescription of strontium ranelate is now limited only to patients with severe and established osteoporosis with an extremely high risk of fracture.

As the average age of the population increases (particularly in the developed world), the number of people suffering from bone resorption disorders will continue to increase. Given the apparent limitations and negative side effects of currently approved drugs, the link between lanthanum and osteoporosis has drawn attention from both researchers and drug companies.
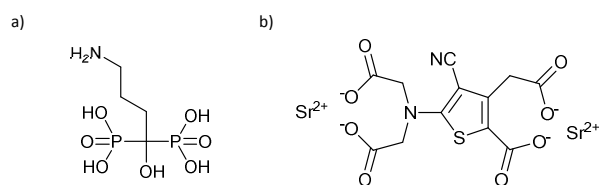
Although the initial discovery dates back to 2001,[32] the evidence that lanthanum invokes a positive response in sufferers of bone resorption disorders is, at present, far from conclusive. A 2004 study from Behets et al. reported no observed toxicity towards osteoblasts in rats with either chronic renal failure or normal renal function after multiple oral dosing with $La_2(CO_3)_3$, but did note abnormal mineralization in the group administered with the highest dose (1000 mg/kg/day).[37] In 2008, Wang et al. published findings from an in vitro study which suggested that osteoblast differentiation was enhanced due to the presence of $LaCl_3$;[38] however, one year later a report from the same group demonstrated a suppressive effect in vivo from the same La(III) source via a different pathway.[39] Various other in vitro studies suggest that osteoblastic response to trivalent lanthanide ions is dose-dependent, but out of the context of a living system it is difficult to draw definitive conclusions.[40]

In 2012, a study from von Rosenberg and Wehr presented evidence for an improvement in bone composition and formation due to the oral administration of lanthanum carbonate in small animal models with induced post-menopausal osteoporotic-type symptoms (OVX rats).[31] This corroborated the initial hypothesis that intestinally absorbed lanthanum could give a positive therapeutic effect; however, it did not address the issue of the extremely low bioavailability of La(III) as the carbonate salt. Fosrenol is already known to have adverse effects towards the GI tract, so presumably elevating the dose in order to target osteoporosis would be met with extremely poor patient compliance.

In this light, the progression towards a lanthanum compound that is orally active has been made through the design of ligand systems which bind La(III) and improve bioavailability via tuneable functionalities. The first iteration of this by Barta et al. investigated a series of bidentate 3-hydroxy-4-pyrones and -pyridinones – molecules known for their synthetic accessibility and low toxicity – as tris-metal complexes with various trivalent lanthanide ions.[41] The most significant testing parameter was apparent cell permeability, as this gave an indication of bioavailability in vivo. It was found that the lanthanum complex $La(dpp)_3$ (Fig. 6) gave the best results, with over 10-fold greater transport of La(III) across a cell membrane model compared to lanthanum carbonate, as measured by ICP-MS.
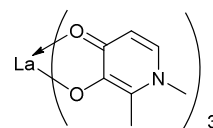

Fig. 5 Two approved of drugs for the treatment of osteoporosis: a) the bisphosphonate alendronate, marketed as Fosamax, and b) strontium(II) ranelate, marketed as Protelos. Both drugs have drawbacks which have prompted the search for alternative types of treatment.

3.3 Towards rational drug design

Fig. 6 The structure of the lead compound, $La(dpp)_3$, from Barta et al. intended as an orally active lanthanum(III) compound for treating osteoporosis.[41]

A later study by Mawani et al. included the same type of pyridinone ligand motif, but diversified the design paradigm by including functionalities with bone mineral binding properties

such as phosphonates and bisphosphonates. The aim of this study was to enhance bone seeking ability already intrinsic to the lanthanides and improve overall specificity toward skeletal tissue *in vivo*.[42] Also included in this study was the 1:1 lanthanum complex of a phosphinate-containing EDTA-type chelator bis[[bis(carboxymethyl)amino]methyl]phosphinate (H$_5$XT) – a ligand with higher inherent denticity and complex stability than the pyridinones – as the potassium salt (K$_2$[La(XT)], Fig. 7).[43] In a similar cell permeability assay to the one performed by Barta *et al.*, it was found that La(XT) enabled the greatest transport of La(III) across a cell membrane, whilst also exhibiting a favourably low cytotoxicity profile.[42]
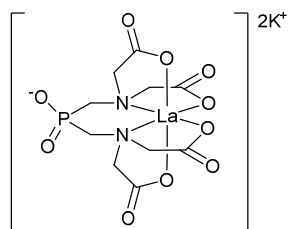
Fig. 7 The hypothesized structure of La(XT), a 1:1 lanthanum chelator with a "bone-seeking" moiety in the form of a phosphinate group, the lead compound from Mawani et al. in the search for new drugs for osteoporosis.[42]

With these results in hand, the *in vivo* plasma clearance and biodistribution of the two complexes La(dpp)$_3$ and La(XT) from single and multiple dose intravenous administration in healthy rats were examined.[44] For both compounds lanthanum(III) cleared rapidly from plasma and was redistributed to various tissues, including bone, as measured by ICP-MS. Crucially, a greater lanthanum uptake was observed in regions of the bone with higher turnover versus those with normal turnover in healthy bone tissue (Fig. 8). Although these results do not assess the oral activity of either complex, they do show that lanthanum is actively incorporated into bone mineral via the turnover mechanism, and that the inclusion of a ligand system, whether 1:1 or 3:1, does not hinder this uptake.[44]
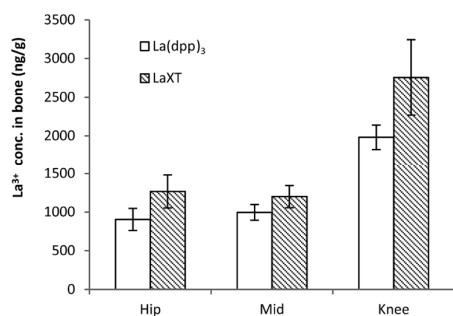
Fig. 8 Femur distribution of La(III) as measured by ICP-MS from multiple dose IV injections (1 mg/kg/day) for 5 days of either La(dpp)$_3$ or La(XT) from 6 trials. Results show consistently higher uptake in the knee region of the bone, where bone turnover is greater, versus the hip or mid regions.[44]

In order to truly assess the viability of either of these systems as potential drugs for osteoporosis, a chronic oral study examining the cumulative uptake and biodistribution *in vivo* versus lanthanum carbonate should be performed to assess healthy and osteoporotic bone compared to currently available pharmaceutical agents. While it is the authors' belief that lanthanide complexes do have the potential to act as antiresorptive agents, it is clear that the true extent of that potential is yet to be fully realized.

4. Conclusions

The tendency for metal ions to be absorbed and retained by bone tissue has been exploited by medicinal chemists in the strategic design of pharmaceutical agents for treating skeletal disorders. The area that has witnessed the most success (in terms of clinically approved agents) has been in the treatment of metastatic bone cancer, where several radioactive metals in combination with particular ligand systems have been used to image, diagnose, treat, and ablate painful and debilitating bone legions. Much of the success of these drugs can be attributed to their ability to specifically target areas with elevated rates of bone turnover, as this is what distinguishes cancerous bone from healthy bone. The most recent advance in this area has been the identification and approval of a bone-targeting α-emitter (Radium-223) that decays via a safe pathway and has been shown to improve the life expectancy of patients suffering from advanced forms of prostate cancer. Despite this success, radiometal based therapies will always be limited to the treatment of late-stage cancers because of the side-effects associated with exposing healthy tissues to harmful radiation.

In terms of non-radioactive metal-based therapies, the lanthanides have gained attention because of their potential to suppress the debilitating effects of augmented bone resorption in sufferers of osteoporosis. This potential was first realised by examining the physiological impact of orally dosed lanthanum carbonate – a drug approved for treating hyperphosphatemia; however, the low bioavailability of La(III) in this form prevents its usefulness as an antiresorptive agent. Currently, two complexes of La(III) with ligand scaffolds designed to improve oral bioavailability are undergoing preclinical trials.[44]

In this review we have shown that metals undoubtedly have the ability to invoke a positive therapeutic effect on sufferers of skeletal disorders. It is only through judicious selection of the metal ion and strategic ligand design that this ability can be truly harnessed, and safe and effective treatments can be developed.

Acknowledgements

References

1 M. J. Glimcher, in *Metabolic Bone Disease and Clinically Related Disorders*, ed. L. V. Avioli and S. M. Krane, Academic Press, San Diego, 3rd edn, 1998, ch. 2, pp. 26-50.

2 D. J. Hadjidakis and I. I. Androulakis, *Women's Health and Disease: Gynaecologic, Endocrine, and Reproductive Issues*, Annals of the New York Academy of Science, 2006, **1092**, pp. 385-396.

3 National Osteoporosis Foundation, http://nof.org/articles/5, (accessed October 2015).

4 M. Vallet and S. H. Ralston, *J. Cell. Biochem.*, 2016, **117**, 289.

5 P. J. Marie, O. Fromigué and D. Modrowski, *Bone Cancer: Primary Bone Cancers and Bone Metastases*, ed. D. Heymann, Elsevier, Amsterdam, 2nd edn., 2015, ch. 4, pp. 39-54.

6 K. H. Thompson and C. Orvig, *Science*, 2003, **300**, 936 and references therein.

7 C. Güner, V. Aliyev, D. Atamtürk, I. Duyar and T. Soylemezoglu, *Euras. J. Antropol.*, 2011, **2**, 27.

8 M. I. Kay, R. A. Young and A. S. Posner, *Nature*, 1964, **204**, 1050. E. D. Eanes and A. S. Posner, *Biological Calcification: Cellular and Molecular Aspects*, ed. H. Schraer, Springer US, New York, 1970, ch. 1, pp. 1-26.

9 C. C. Ribeiro, I. Gibson and M. A. Barbosa, *Biomaterials*, 2006, **27**, 1749.

10 T. J. Webster, E. A. Massa-Schlueter, J. L. Smith and E. B. Slamovich, *Biomaterials*, 2004, **25**, 2111.

11 J. F. Cawthray, A. L. Creagh, C. A. Haynes and C. Orvig, *Inorg. Chem.*, 2015, **54**, 1440.

12 S. P. Fricker, *Chem. Soc. Rev.*, 2006, **35**, 524 and references therein.

13 D. G. Karraker, *J. Chem. Educ.*, 1970, **47**, 424.

14 L. I. Ardanova, E. I. Get'man, S. N. Loboda, V. V. Prisedsky, T. V. Tkachenko, V. I. Marchenko, V. P. Antonovich, N. A. Chivireva, K. A. Chebishev and A. S. Lyashenko, *Inorg. Chem.*, 2010, **49**, 10687.

15 G. J. Behets, S. C. Verberckmoes, L. Oste, A. R. Bervoets, M. Salomé, A. G. Cox, J. Denton, M. E. De Broe and P. C. D'Haese, *Kidney Int.*, 2005, **67**, 1830.

16 C. Vidaud, D. Bourgeois and D. Meyer, *Chem. Res. Toxiciol.*, 2012, **25**, 1161 and references therein.

17 H. L. Abrams, R. Spiro and N. Goldstein, *Cancer*, 1950, **3**, 74.

18 R. E. Coleman, *Cancer Treat. Rev.*, 2001, **27**, 165.

19 W. F. Goeckeler, B. Edwards, W. A. Volkert, R. A. Holmes, J. Simon and D. Wilson, *J. Nucl. Med.*, 1987, **28**, 495.

20 W. F. Goeckeler, D. E. Trouter, W. A. Volkert, B. Edwards, J. Simon and D. Wilson, *Nucl. Med. Biol.*, 1986, **13**, 479.

21 J. F. Eary, C. Collins, M. Stabin, C. Vernon, S. Petersdorf, M. Baker, S. Hartnett, S. Ferency, S. J. Addison, F. Applebaum and E. E. Gordon, *J. Nucl. Med.*, 1993, **34**, 1031.

22 I. G. Finlay, M. D. Mason and M. Shelley, *Lancet Oncol.*, 2005, **6**, 392.

23 Y. Yang, M. J. Pushie, D. L. Cooper and M. R. Doschak, *Mol. Pharmaceutics*, 2015, **12**, 4108.

24 S. Nilsson, R. H. Larsen, S. D. Fosså, L. Balteskard, K. W. Borch, J.-E. Westlin, G. Salberg and Ø. S. Bruland, *Clin. Cancer Res.*, 2005, 11, 4451.

25 P. M. Anderson, V. Subbiah and E. Rohren, in Current Advances in Osteosarcoma, ed. E. S. Kleinerman, Spinger International, Switzerland, 2014, vol. 804, part IV ch. 3, pp. 291-304.

26 C. Parker, S. Nilsson, D. Heinrich, S. I. Helle, J. M. O'Sullivan, S. D. Fosså, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A.

Widmark, D. C. Johannessen, P. Hoskin, D. Bottomley, N. D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N. J. Vogelzang, C. G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø. S. Bruland and O. Sartor, *N. Engl. J. Med.*, 2013, **369**, 213.

27 O. K. Hjelstuen, *Analyst.*, 1995, **120**, 863.

28 F. D. C. Guerra, A. A. S. Tavares and J. M. R. S. Tavares, *Med. Phys.*, 2014, **41**, 114101.

29 M. Pennick, K. Dennis and S. J. P. Damment, *J. Clin. Pharmacol.*, 2006, **47**, 738.

30 F. Fernandez-Gavarron, T. Huque, J. L. Rabinowitz and J. G. Brand, *Bone Miner.*, 1988, **3**, 283.

31 S. J. von Rosenberg and U. A. Wehr, *J. Anim. Physiol. Anim. Nutr.*, 2012, **96**, 855.

32 N. D. Atherton, J. W. Totten, M. D. Gaitonde, Patent WO2002000227 A2, January 3, 2002.

33 S. Zhang, G. Gangal and H. Uludağ, *Chem. Soc. Rev.*, 2007, **36**, 507.

34 M. Whitaker, J. Guo, T. Kehoe and G. Benson, *N. Engl. J. Med.*, 2012, **366**, 2048.

35 J. Y. Reginster, *Curr. Pharm. Des.*, 2002, **8**, 1907.

36 B. Abrahamsen, E. L. Grove and P. Vestergaard, *Osteoporos. Int.*, 2014, **25**, 757.

37 G. J. Behets, G. Dams, S. R. Varcauteren, S. J. Damment, R. Bouillon, M. E. De Broe and P. C. D'Haese, *J. Am. Soc. Nephrol.*, 2004, **15**, 2219.

38 X. Wang, L. Yuan, J. Huang, T. L. Zhang and K. Wang, *J. Cell. Biochem.*, 2008, **105**, 1307.

39 Y. L. Shi, L. W. Wang, J. Huang, B. D. Gou, T. L. Zhang and K. Wang, *J. Cell. Biochem.*, 2009, **108**, 1184.

40 Z. Dawei, Z. Jinchao, C. Yao, Y. Mengsu and Y. Xinsheng, *Prog. Nat. Sci.*, 2007, **17**, 618.

41 C. A. Barta, K. Sachs-Barrable, J. Jia, K. H. Thompson, K. M. Wasan and C. Orvig, *Dalton Trans.*, 2007, 5019.

42 Y. Mawani, J. F. Cawthray, S. Chang, K. Sachs-Barrable, D. M. Weekes, K. M. Wasan and C. Orvig, *Dalton Trans.*, 2013, **42**, 5999.

43 L. Xu, S. J. Rettig and C. Orvig, *Inorg. Chem.*, 2001, **40**, 3734.

44 J. F. Cawthray, D. M. Weekes, O. Sivak, A. L. Creagh, F. Ibrahim, M. Iafrate, C. A. Haynes, K. M. Wasan and C. Orvig, *Chem. Sci.*, 2015, **6**, 6439.