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Grand challenges in bioinorganic chemistry

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Introduction

In this combined grand challenge article, the specialty co-chief editors have attempted to pull-out the promising and burgeoning areas of bioinorganic chemistry both from a general and a personal perspective. Emphasising how these are dependent on inorganic syntheses, they seek to highlight the strengths and opportunities of these research directions and to suggest where aspects of these fields might be heading and why.

Why is bioinorganic chemistry so important?

Bioinorganic chemistry sits at the interface of Chemistry and Biology and deals with metal ions in biological systems. It is a young and evolving field although its inception lies in the 19th century when metal ions bound to proteins and enzymes were first discovered. The unambiguous proof of the presence of Zn in enzymes was established in the 1930's and elements such as Ni and Se were only known as components of important enzymes in the 1970's. Today, compounds comprising 76 elements are either approved or under clinical trial for use in diagnostic and therapy (Imberti and Sadler, 2020).

The human body has trace amounts of many metal ions, whose concentrations are tightly regulated through homeostasis. Transition metals are generally found bound to proteins, or in cofactors, for example in porphyrins and cobalamins, or in clusters. Na, K, Mg, Ca, Mn, Fe, Co, Cu, Zn, and Mo account for 2.5% of the human body mass. Their roles are so important that without them red blood cells could not be produced (Co in vitamin B_{12}), and metabolism would not function properly (*p.e.* the role of Fe, Cu and Zn). It is believed that at least one-third of human proteins and one-half of enzymes require a metal ion to function. Understanding how metals bind to proteins, act as co-factors, or as inhibitors and modify processes *via* changes in structure and/or function are of utmost importance to our understanding of disease.

The unique diagnostic and therapeutic opportunities that metal complexes present while rapidly expanding, are still highly underdeveloped. In this challenge article the specialty chief editors highlight at a high-level some important directions of enquiry and provide an in-depth critique of one of them.

The complexity of the biological environment

The speciation transition metal elements undergo in biological environments presents vast challenges. The biological activity exerted by coordination and organometallic compounds is determined by the metal centre and its ligands, and the underlying

thermodynamics and kinetics. Transition metal ions in aqueous solution are subject to hydrolysis and substitution reactions and can form many different species in several oxidation states. Biomolecules, such as proteins, nucleic acids, carbohydrates, lipids and metabolites can bind metal ions and compete with the original ligands. This highlights the complexity of developing a metal compound for any biological application and the importance speciation studies in biological environments present in the Chemical Biology field (Kiss et al., 2017; Wenzel and Casini, 2017; Nunes et al., 2020). Moreover, the full understanding of the reactions metal complexes experience in physiological conditions can help to improve the specificity of their interactions and to control their potential toxicity. Targeting is key to selectivity and decreased side-effects. Unless targeting strategies take advantage of cell specificity, for instance, overexpression of target proteins, lower cytosolic pH, and altered metal homeostasis, the aim of attaining selectivity (lower toxicity to healthy cells) will be unsuccessful.

The brain

An important challenge is understanding the complicated bioinorganic chemistry of the brain. Here the aims are to elucidate how metal ions contribute to brain function at the molecular level and to gather knowledge on the pathways controlling metal ion homeostasis (Goldberg and Lippard, 2017). It is crucial to determine the speciation and distribution of metal species in neuronal tissues and to identify the metal ions involved in the physiology and pathology of the nervous system, such as Ca, Mg, Na, K, Cu, and Zn. It is equally important to make the connection between toxic metals, such as Cr and Hg, with diseases, such as Alzheimer's and Parkinson's, but all these studies require the development of new tools. Such tools must detect and locate metal ions with high sensitivity and provide concentration data with high spatial and temporal resolution (*p.e.* time-resolved microscopy and spectroscopy). Very recently nanoscale deposits of metallic Cu and Fe were found within the amyloid plaques of the brain tissue of deceased Alzheimer's patients, by using synchrotron-based scanning transmission X-ray microscopy (Everett et al., 2021). This finding raises several questions since it is the first time that elemental metallic species are found in a human body. It also highlights the extreme redox changes occurring in the brain of Alzheimer's patients. Therapeutic approaches to fight metal-mediated neurodegeneration are a fertile ground for exploration and they would benefit from a better understanding of metal ion dynamics in the brain and result in improvements in the life quality of millions of people.

Imaging and contrast agents

A continuing challenge in bioinorganic chemistry is the design of new molecular imaging agents to investigate non-invasively, biological and biochemical processes and gather information on both anatomy and disease (Wahsner et al., 2019). Most of the clinically available imaging techniques, that include magnetic resonance imaging (MRI), radionuclide imaging, computed tomography, fluorescence/phosphorescence optical imaging, and image-guided surgery, make use of metal complexes. Gd(III) complexes are widely used as MRI contrast agents and tens of millions of MRI scans are performed annually. However, concerns regarding their toxicity are arising due to *in vivo* demetallation, and the relatively large concentration of compound required for a successful scan, which after repeated MRI examinations results in long-term accumulation of Gd in patients. Efforts towards enhancing relaxivity without sacrificing stability are being developed (Clough et al., 2019), as well as moving to Gd(III)-free alternatives (Gale and Caravan, 2018). Other innovative imaging methods combine different modalities in single probes, such as linking nuclear and optical probes, as there is great potential to move from passive distribution to contrast agents that are biochemically targeted, increasing specificity to diseased tissues (Hernandez Vargas et al., 2019). Contrast agents, whose signal is responsive to stimuli such as pH, ion flux or temperature, embody a stimulating and growing area of research (Fu et al., 2021).

Application of nanoparticles

The emergence and development of nanotechnology has generated unprecedented prospects for addressing numerous unmet clinical needs. In many medicinal fields nanoparticles are becoming increasingly prominent, and nanodelivery is being explored as a strategy to incorporate metal centres in materials as different as carbon and metal nanoparticles, carbon nanotubes, quantum dots, metal-organic frameworks, coordination polymers and polymeric micelles. This is becoming the next step in the development of new diagnostic, imaging and therapeutic drugs (Poon et al., 2020), and tackling the growing threat of antibiotic resistance (Hajipour et al., 2021). Sensors for bacteria based on metal nanoparticles (NPs) are the subject of a wide research effort (Li et al., 2019). For instance, nanomaterials such as Au NPs, having surface plasmon resonance (SPR) properties, are being used for bacterial detection, after modification with target recognition elements (Bhandari et al., 2022). A key issue is the biodegradability and biocompatibility of the nanodevice, which needs to be finely tuned, and evaluated, since it may cause serious health and environmental problems (Su and Kang, 2020).

Cancer therapeutics

The importance of mechanistic elucidation is perhaps best exemplified in the development of chemotherapy treatments. Cisplatin has been involved in more clinical trials than any other anticancer agent and an understanding of how it exerts its antiproliferative effect was a cornerstone in the development of second- and third-generation Pt-drugs (Zhang et al., 2022). It was mechanistic insight that helped to develop non-classical Pt-complexes with modes of action distinct from those of previous clinical drugs. Among these are multi-modal metallodrugs, that take advantage of releasable bioactive ligands (Štarha and Trávníček, 2019) and Pt (IV) prodrugs (Gibson, 2021). Mechanistic discovery has also led us to understand metallodrugs containing other metal species (Tchounwou et al., 2021) including Au, Ru, Os, Ir, and 1st

row transition metals (Zhang and Sadler, 2017; Yousuf et al., 2021). These are promising alternatives that can help to overcome the drawbacks of platinum-based chemotherapy (e.g., nephrotoxicity and resistance).

New cancer hallmarks (Hanahan, 2022) and new targets, such as epigenetic reprogramming (Arakelyan et al., 2023) and anticancer immunotherapy (Englinger et al., 2019), are at the forefront of modern cancer therapeutics. The 2018 Nobel Prize in Physiology or Medicine, awarded jointly to James P. Allison and Tasuku Honjo, was for the discovery of the inhibition of negative immune regulation. It opened-up many new strategies for cancer therapies: immune checkpoint inhibitors that block regulators of T cell activation; adoptive T cell therapy, in which lab-grown immune cells are administered to cancer patients; and therapeutic cancer vaccines that prompt the immune system to eliminate neoplastic cells (Waldman et al., 2020). At the heart of many innovations in cancer treatment is a deep mechanistic evaluation, however a systematic and wide evaluation of the multiple interactions occurring between the metal species and different steps of the anticancer immune cycle are widely missing. The assumption that metallodrugs are immunosuppressive is being challenged as both pro- and anti-inflammatory effects have been identified. It is clearly necessary to clarify their role as immunomodulators (Sun et al., 2018).

Other therapeutic approaches are being developed to overcome off-target toxicity, e.g., the intratumoral administration of anticancer drugs has proven particularly suitable for skin malignancies that are physically accessible (Huppert and Daud, 2022), for inoperable cancers and for the management of unstable metallodrugs that cannot be administered by the IV route (Levina et al., 2022). Such concepts have led to our chosen hot topic for deeper discussion, the emergence of Photodynamic Therapies, in which accumulating evidence suggests that anticancer effects are also mediated by indirect stimulations of immune responses (Falk-Mahapatra and Gollnick, 2020).

Photodynamic therapies

The interaction of light with biological materials is important for life, for photosynthesis and for human health, e.g., as a means of vitamin D generation. Over-exposure to light in any of its forms is problematic, but particularly to UVA and UVB, as a large number of biological structures absorb light below wavelengths of 500 nm. Skin is a protective barrier but provides a therapeutic window (630–960 nm) that is an opportunity for non-invasive photodynamic treatments. In this region light can be used to trigger wanted rather than unwanted biological reactions.

Photodynamic Therapy (PDT) is a widely accepted but comparatively new technique in cancer treatment. It involves the use of a non-toxic agent (photosensitiser, PS) which on excitation, using light of a specific wavelength, produces cytotoxic species (usually singlet oxygen or radicals) that damage the irradiated cancer cells and lead to cell death. PDT allows discreet areas of tissue to be targeted (e.g., skin or exposed tumour site) and compared to other treatments (chemo-, radio-, immuno-therapies/surgery) leaves healthy tissue (non-irradiated) undamaged.

In this in-depth exposé the co-chief speciality editors take a deeper dive into current thinking in terms of improving the efficacy and application of photodynamic treatments and consider how future investigations might seek to exploit new mechanisms, materials, and modes of action. There are many excellent and current review articles which give testament to the description of this area of research as a hot topic. Readers are recommended to revert to these [e.g., (Algorri et al., 2021; Pham et al., 2021; Karges, 2022; Wu et al., 2022; Xiong et al., 2022)] and to those covering materials that for brevity are excluded here (nanoparticles, carbon nanotubes, aggregation-induced-emission-PS) (Villemin et al., 2019; Dai et al., 2020; Liu et al., 2022).

The molar absorbance and excitation wavelength of the photosensitiser are important considerations because biological materials can have competing optical properties. An ideal PDT agent will operate within the therapeutic window, possess a high singlet oxygen quantum yield (>30%), have low dark toxicity, good bio- and photo-stability (minimal photobleaching), target specific tumour cells rapidly and at low concentrations (high potency) and be excreted quickly after use. The search for molecular designs that optimise these characteristics are active lines of synthetic enquiry with the metal center(s) and the ligand(s) or organic scaffolds being separate foci.

Many non-topical photosensitisers involve Ru(II), Os(II), Ir(III) and Pt (II). These heavy-metal centres mediate strong spin-orbit coupling and fast intersystem crossing rate constants. Recent research is beginning to expose the opportunities arising from the use of other attractive (non-precious) and first row metals (Gourdon et al., 2022) or other electron-dense inorganic elements trapped within twisted or highly conjugated conformations (e.g., involving I, S or P).

Although the topology of metal-based excited state electronic configurations differ they are readily tuned (in comparison to nanoscale metal organic framework or metallic composites). In addition, the oxidation state of the metal centre contributes to the overall charge of the complex and therefore its solubility, lipophilicity, subcellular uptake and pharmo-kinetics/dynamics. Often the biodistribution, subcellular uptake and location of the PS can be visualised using confocal microscopy, Single-Photon Emission Computed Tomography (SPECT) or other common techniques such as Inductively Coupled Plasma–Mass Spectrometry (ICP-MS).

Polymetallic complexes are to date rare in the field, however the learnings from other non-biological fields (triplet-triplet annihilation upconversion, photopolymerisation) suggest that they might exhibit higher molar absorptivities and singlet oxygen quantum yields, than their monometallic counterparts. As a research direction poly- or heterometallic PS might be expected to impart additional opportunities for dual therapeutic systems.

Through ligand design, existing research directions seek.

- to develop PS that operate *via* long-wavelength near-infrared (NIR), or two-photon excitation (TPE) (the later offering higher spatial and temporal resolution) so as to increase the depth of tissue penetration;

- to overcome the resistance of solid or hypoxic tumours by promoting less oxygen-dependent mechanisms (e.g., T_1 and S_1 activation, Photoactivated Chemotherapy (PACT));
- to advance selectivity *via* the addition of biological tags or conjugated antibodies (Gomez et al., 2020) that target tumour tissue or certain subcellular organelles (e.g., mitochondria which are associated with tumorigenesis and tumour progression and susceptible to oxidative stress);
- to reduce dark toxicity e.g., *via* encapsulation (Villemin et al., 2019);
- to advance the development of theranostic agents (Vaidya et al., 2022) and sonodynamic therapies (Mandal et al., 2022).

The first generation PS (reaching clinical trials) mainly incorporated porphyrin, chlorin, cyanine and other dyes. Second generation species containing metal centres have phthalocyanine, texaphyrin, bacteriocholorphyll and very recently polypyridyl ligand scaffolds. The majority of these materials operate *via* an oxygen dependent mechanism.

Three types of photosensitisers are known (classified on the basis of the reactive oxygen species generated). In type I the photosensitiser in its lowest energy singlet (S_1*) or triplet (T_1*) excited state generates superoxide or hydroxide radicals by proton or electron transfer with oxygen, water or biological substrates. Type II photosensitisers undergo triplet-triplet annihilation to give singlet oxygen and are the most dependent on intracellular oxygen concentrations. In the much rarer Type III mechanism, the photosensitiser itself targets and binds the biomolecules in the cell and through excited state energy transfer, causes cell death (Grin et al., 2022).

These modes of action are not mutually exclusive. A deeper understanding of their co-existence or interconnectedness is an active area of study requiring advanced investigations and the application of non-invasive or time-resolved techniques which might involve synchrotron sources. Potentially one compound could exhibit PDT *via* different modes of action when excited at different energies and/or be anticipated to advance cell death *via* non-apoptotic processes. Excited states might be accessed by a combination of one and two-photon excitation processes invoking dark or non-emissive states to elicit singlet oxygen production (Condon et al., 2021). Treatments that are effective in both normoxic and hypoxic tumour environments are desirable and might operate by catalytic interference of the cellular redox balance.

Multimodal therapies seek to supress the recovery of tumour cells after exposure to PDT or to accentuate their susceptibility to PDT. There are many recent examples in which existing or even approved chemotherapy agents are used in tandem with a photosensitiser, to enhance the therapeutic effect. A plethora of combinations remain to be explored (Fan et al., 2017).

The future development of optimised PS for PDT should draw inspiration from the designs of PS generated with other applications in mind (solar cells, photocatalysis, upconversion). Currently the laboratory-specific nature of the published data is both a strength and a weakness. Avenues for exploration remain open but cross-comparisons which would emerge in a standardised research setting are obscured, e.g., when the light dose (intensity and duration time) and cell lines are different, and the solvent dependent nature of the accessible excited states are not reported.

Conclusion

There are opportunities and challenges, and directions of travel to take in Bioinorganic Chemistry, and while these exist there will be researchers willing to participate in the journey to understand the intricate and complex role of metal centres in biology. They will use this knowledge to develop treatments and diagnoses with improved efficacy and wide-reaching applications but also to consider biological, environmental and industrial processes more holistically, in a world in which human health and planetary health are so intimately connected.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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