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PERSPECTIVE

Bioinorganic chemistry: where from and where to?

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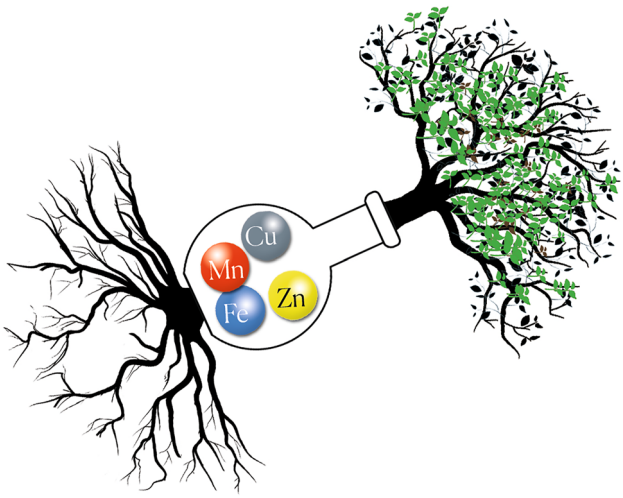
Abstract
Bioinorganic chemistry is a multidisciplinary field that bridges the apparent divide between inorganic chemistry and biology. The very name "bioinorganic" is an intriguing oxymoron, as "inorganic" chemistry traditionally refers to the study of the inanimate world, while the "bio" prefix refers to living systems. Bioinorganic chemistry focuses on metallic systems within biological environments, with the dual aims of better understanding these natural systems and leveraging the solutions developed through evolution to design new industrial or therapeutic applications. As a close cousin of the field of metallomics, bioinorganic chemistry shares the fundamental principles that underpin metallomics' systemic analyses of metal-containing biomolecules. In this article, we trace the historical development of bioinorganic chemistry, highlighting its recent advancements and outlining future research challenges in this dynamic interdisciplinary area.

Graphical abstract



Keywords Bioinorganic chemistry · Inorganic chemical biology · Metallomics · Metal ions essentialities · Metal ions cellular economy

Introduction

The aim of bioinorganic chemistry is to identify, understand and control inorganic metal-based molecules within living organisms, whether they are endogenous (e.g., metalloproteins) or exogenous (e.g., metallodrugs). The purpose is, on the one hand, to characterize these molecules and explain how they work in the biological environments, and, on the

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other hand, to prepare synthetic compounds with biological activity. These metallic compounds may be systems with no endogenous equivalent but likely to play a role in a biological environment (such as cisPt or contrast agents, for example). Alternately, they may be inspired by biological molecules (in which case they are called bio-inspired [1]) and reproduce an activity of potential therapeutic or industrial interest, to be used in biological systems (therapeutic agents) or as biomimetic or bio-inspired catalysts (industrial catalysts).

But what is a metal? In vernacular language, metal refers to broken stones for use in making roads: to metal a road means to make or mend it. Historically, metals all come from the mines as ores: *μέταλλον* in Greek or *metallum* in Latin means *mine*. For astrophysicists, a metal is anything but H and He and the metallicity of a star is an indication of its age: the older, the more elevated are the abundance of the elements heavier than H and He. In this article, we will use the more conventional definition from physics, chemistry, geochemistry, biology, etc.: a metal element is characterized in its 0 oxidation-state by good electrical and thermal conductivities —in the terrestrial conditions; note that H can become a liquid metal at elevated pressions found in Jupiter for instance! This metallic state M(0) is also fusible, malleable, ductile, and shines a special metallic luster. It readily loses electrons to form metal cations M^{n+} that show specific properties used by Nature, notably at the active site of metalloproteins.

Metal compounds in medicine or as biocides

Various metals and metal ions such as those of zinc, iron, magnesium, mercury or gold were used in pharmacopeia very early in the human history. We can take the example of khôl (or kohl) used in Ancient Egypt as make-up for men and women alike. Analyzed by modern techniques (X-fluorescence), ancient khôl showed the presence of lead compounds that were clearly manufactured and not of natural origin [2]. Khôl was used explicitly to heal wounds and to protect eye against infection, probably associated with the lead present that is able to activate macrophages [2, 3]. Lead-based paintings, such as natural or man-made lead acetate called cerusite, were used for their toxicity as biocides not only to prevent the development of algae or infestation of shipworms on the hull and floors of Royal navy ships [4] but also in flats to prevent mold on walls. Children in rundown housing are prone to eat the crumbling "white lead" paint because cerusite tastes sweet, inducing potentially lead-poisoning. For that reason, the White Lead Convention was established in 1921 to advance the prohibition of using lead paints [5].

But toxicity also carries therapeutic properties and, if one thinks, most drugs are characterized by a targeted toxicity: antibacterial, antifungal and anti-cancerous are meant to kill or limit the growth of bacteria, fungi or cancerous cells, respectively. Few drugs, among which antioxidants for instance, are meant to restore normal life in a biological system that has been driven to imbalance.

In the early twentieth century, Paul Ehrlich, from the Royal Institute of Experimental Therapy in Frankfurt, founded chemotherapy by developing the metal-based antibacterial arsphenamine (or salvarsan: 'the arsenic that saves') and its more water-soluble analog, neosalvarsan (see Fig. 1), against syphilis, a disease caused by *Treponema pallidum*, a spirochete. These metallodrugs replaced the deadly treatment with mercury that had been used for centuries, in different chemical forms and administration modes [6]. Very early in his career, Paul Ehrlich, like many others in the XIX^{th} century, was interested in the use of newly developed artificial synthetic dyes to stain bacteria. The fact some dyes, such as azo dyes (see Fig. 1), caused bacteria to stop swimming under the microscope led to the idea that such chemicals could kill them [7]. With the microbiologist Sahachiro Hata, who joined his group from Japan, Paul Ehrlich tested a number of dyes against spirilla and spirochetes and then came to an As-based compound synthesized in 1863 by Antoine Béchamp (Atoxyl) [8]. Together with his colleague Alfred Bertheim, they derivatized this compound, which led to salvarsan. As Ehrlich analyzed himself in the preface of [8] "The difficulty of my work is due especially to the fact it extends over three different territories which touch and complete each other: chemistry, biology and experimental therapy". This makes this collaboration, involving several disciplines in a horizontal manner (as opposed to vertical monodisciplinary collaboration, between a master and their student for instance), one of the first highly productive interdisciplinary work in science history. Thought by Ehrlich, Bertheim and Hata to have an As = As double bond, by analogy with azo-dyes (see Fig. 1), it was demonstrated in 2005 to be a mixture of As-based metallacycles [9]. Penicillin was used as of the end of World War II and salvarsan derivatives were then retrieved due to side effects. The reborn of inorganic medicinal chemistry had to wait the late 1960 with the serendipitous discovery (*see* "*INSERT*") of cis-diamminedichloroplatinum(II) (cisPt) by Barnett Rosenberg and Loretta Van Camp et al.. In the course of a program against cancer, they wanted to evaluate how electric fields could impact the growth of tumors. They started by investigating the effect of electric field on the growing of *E. coli*. To do so, they used Pt electrodes to generate the electric field, but that could have been any other type of electrodes. It happens that electrolysis at the Pt-electrode, within a culture medium rich in amino-acids and chloride, produced Pt-derivatives, including cisPt. This particular derivative was found to modify the growth of *E. coli* leading to long spaghetti-like bacteria [10, 11]. Its antiproliferative

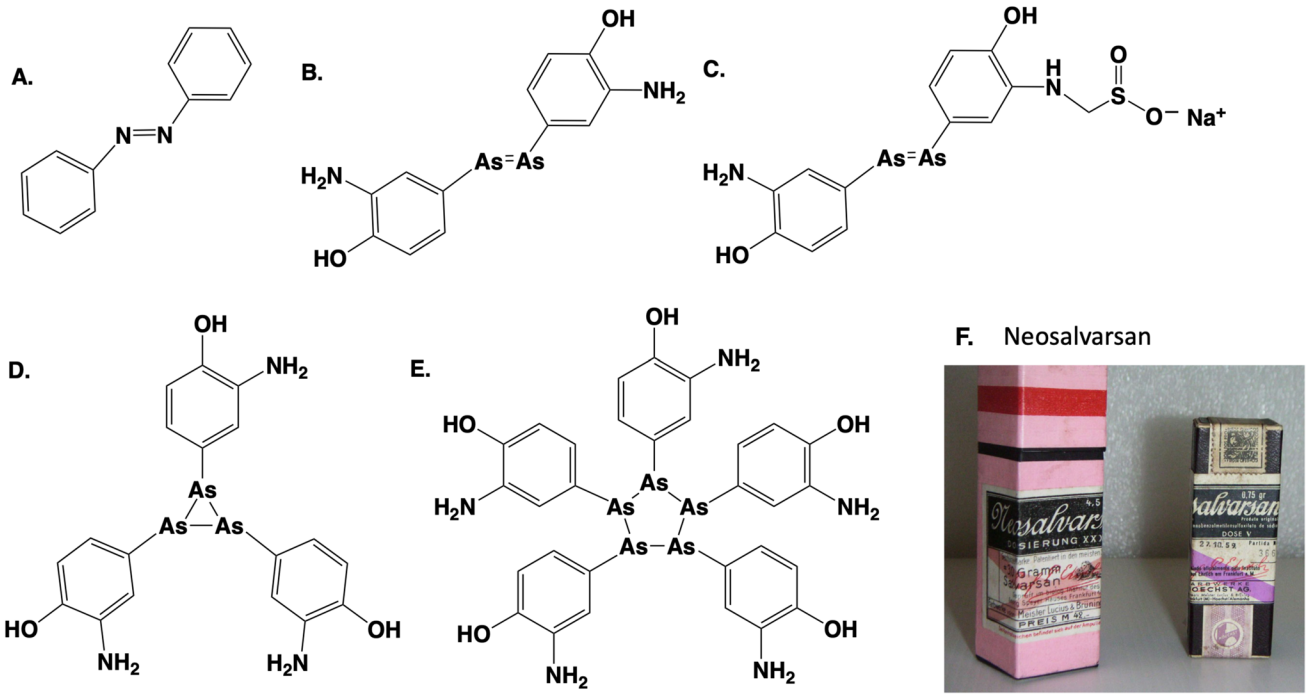

Fig. 1 Salvarsan and neosalvarsan: the first molecules developed for chemotherapy. A: Structure of an azo-compound, shown to kill some bacteria by observation under the microscope. B and C. Structure of the molecules Paul Ehrlich et al. thought they had synthesized as salvarsan (B) and neosalvarsan, its water-soluble analog (C). D and E. Salvarsan was in fact a mixture of two As-metallacycles D and E, as shown in 2005 [9]. F. Photograph of a commercial neosalvarsan dosages, with the curtesy of the Museu de farmacia, Lisboa, https://www.museudafarmacia.pt/

effect on eukaryotic cells was soon after demonstrated [12]. This initiated an intense program of research on the use of heavy metal complexes in medicine [13].

Despite the fact that the first chemotherapeutic agent was a metal-based complex, the medicinal industry built up during the XXth century and until now relies mainly on organic molecules. So far, only few metal-based drugs have been approved clinically and found their way to the market [14]. This is difficult to draw reason for that, and that may confine at "science history fiction". However, let us try. One key feature of the first-row transition-metal complexes is their intrinsic lability and dynamic nature. As fast ligand-exchangers [15], they are efficient catalytic centers, able to cycle: to welcome a substrate in their coordination sphere, to modify its electronic distribution and thus its reactivity, leading to the product that can be released from the coordination sphere, freeing the catalytic center for a next cycle. However, as exemplified in the case of salvarsan, it makes the structure of transition-metal-based derivatives not easy to characterize. Because biological media abound with metal ions and Lewis bases, metal complexes characterization is all the more difficult in any biological environment. The idea that a mixture, as salvarsan was, can be active and used as a medicine goes against the 'holy' Grail of the chemists, who, since the XIXth century, long for the separation, isolation, purification and characterization of the so-called "molecular active principle". This might be the reason why there is still so few metallic systems developed as medicine by the pharmaceutical industry. To that extent, this is worth noting that the only clinically approved metallodrugs involve heavier metal compounds from the second row or below in the periodic table, as cisPt and its analogs or a Pd-porphyrin*, more inert than those from the first row. One aluminum complex is also in the list, with a porphyrin as a ligand. In clinical trials, we can count at this time Ru complexes, notably Nami-A in Phase II, and two first-row transition-metal complexes, Mn with a macrocycle or a porphyrin* as a ligand and ferroquine** [14, 16].

However, in the context of the threat of antibiotic resistance, the clear role of metal ions on the virulence of bacteria and on fight between the host and bacteria [17–19], may put metal systems or ligands more to the forefront. Indeed, bacteria require metal ions in a way that may be more fundamental than other pathways, and difficult or even impossible to bypass. The emergence of bacterial resistance is due to the ability of bacteria to mutate in order to bypass pathways that are impaired by a drug. The pathways involving metal economy could be more difficult to bypass paving the way for the development of metal- or ligand-based antibacterial

agents for which bacterial resistance would be less to fear [20].

Note that the development of inorganic medicinal chemistry has also led bioinorganic chemists to ask questions on more integrated scales. The pharmacological properties of a molecule are closely linked to its ability to reach a biological target, possibly deeply buried in cellular compartments. This has raised the question of the cellular penetration of complexes and complexing agents, as well as their targeting to a given receptor, cell type or tissue, of their bioavailability, of their distribution and of their speciation (nature). In these matters, there is a strong overlapping with the field of metallomics, as discussed below (see the section **Bioinorganic chemistry and metallomics**).

Endogenous metal ions and essentiality

Even if metallic derivatives have been used as medicine for centuries, the recognition of their endogenous physiological role is much more recent. The conception that metals or metal ions were endogenous constituents of the living world was not taken for granted. As a matter of fact, ***in***organic (or mineral) chemistry is etymologically that of the inanimate. ***Organ***ic chemistry, a term that was coined at the end of the XIXth for "*chemistry of **organi**zed bodies*" [21–23], was considered as that of matter derived from the living. The essentiality of metal cations in living organisms in general, and in humans in particular, was considered to be a relevant question only at the beginning of the XXth century. These elements have been called trace or ultratrace (see below for a comment on that term). The essentiality of trace elements was gradually established for different cations and different species (see Table 1).

Iron

Iron, one of the most abundant among the metallic elements in the universe and in living systems (see Table 1 and Fig. 2), was one of the first to be identified as a natural component of living systems, through a rather long pathway. Iron was discovered in the human body by Louis Lemery [24], the son of Nicolas Lemery. However, he considered that iron was adsorbed and carried by blood but not that it was a natural constituent for it [25, 26]. Vincenzo Menghini established in 1746 that iron accumulates in the red vesicles previously discovered in blood fluids by Antoni van Leeuwenhoeke in 1674 [27]. In the mid XIXth century, iron was identified by Louis René Canu (1830) [26] as a component of the red blood pigment called then *globuline* or *hematosine*, soon after identified as the

Table 1 Elements and date of the discovery of their essentiality for mammals. Concentration of the elements in human blood plasma and sea water

"Trace" elements essential to mammals	Symbol	Date of the discovery of essentiality in mammals[a]	Sea water concentration (µg/L)[b]	Blood plasma concentration (µg/L)[b]
Iron	Fe	End of XIXth century (see references in the text)	0.000 03	1.2
Iodine	I	1850	0.058	0.000007
Magnesium	Mg	1932 (rat) [38]	1280	17.5
Copper	Cu	1928 (rat) [39], 1931-2 (infants) [40]	0.00015	0.75
Manganese	Mn	1931 (mouse) [41]	0.00002	0.00057
Zinc	Zn	1934 (rat) [42]	0.00035	0.651
Cobalt	Co	1935 (merino sheep) [43]	0.000001 2	0.00011
Molybdene	Mo	1956 (rat) [44]	0.010	0.00095
Selenium[c]	Se	1957 [45] — Se as a component of GSH peroxidase 1973 [46]	0.00016	0.16
Chromium	Cr	1959 [47]	0.00021	0.000069
Tin	Sn	1970 [48, 49]	0.000000 5	0.00051
Vanadium	V	1970 [49]	0.002	0.000031
Fluorine	F	1972 [50]	1.3	0.019
Silicon	Si	1972 [51]	2.8	0.14
Nickel	Ni	1972 [52]	0.00048	0.00023
Arsenic	As	1976 [53]	0.0012	0.00045

[a] Dates from [33] and references indicated in the table

[b] Data from [55]

[c] We have indicated here Se although it is a non-metal element

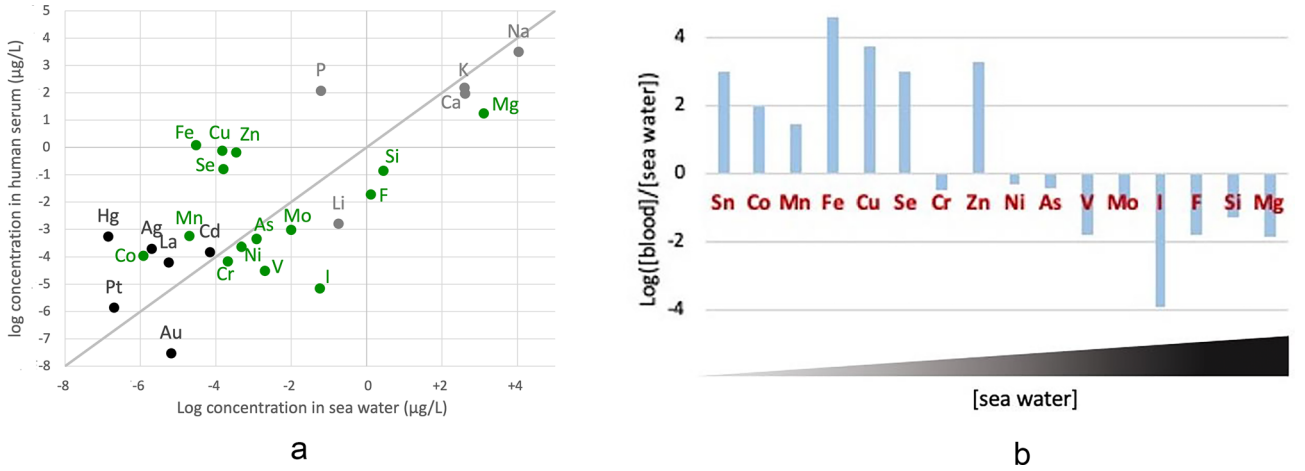

Fig. 2 **a** Concentration of the elements in human blood serum and sea water. Data from [33]. : In green: the "trace" elements listed in Table 1; in gray: some other essentials elements; in black: other elements. **b** Plot of the ratio [blood serum]/[sea water] showing those of the elements that accumulate in biology (blood) in comparison with the environment (sea water)

dioxygen carrier by Friedrich Ludwig Hünefeld (1840) [28] and to reversibly bind dioxygen by Felix Hoppe-Seyler [29].

Zinc

Zinc being one of the next more abundant metal ions in living systems (see Table 1 and Fig. 2), this is not surprising that it was also identified very early. Jules Raulin, a collaborator of Louis Pasteur at the *Ecole Normale Supérieure* in Paris and working on Louis Pasteur's minimal media for bacteria, showed in 1869 that zinc salts were required to the growing of a fungus, namely *Aspergillus niger* [30–32]. The idea that a metal ion was not replaceable in a living system, and in other term, essential, was thus born. This point was immediately recognized as important by plant physiologists and bacteriologists of the XIXth century, but overlooked by animal nutritionists, including human nutritionists. Because of that, iron remained the only metal "trace" element considered as essential for animals including humans until the end of first quarter of the XXth century [33].

The amount of iron in a human being is only about twice that of zinc (see Table 1, data for blood plasma). However, there is a difference of about half a century for the date of the discovery of their respective essentiality. Two possibilities can be suggested to explain this difference. Firstly, iron complexes are colored (Fe(II) being d^6 and Fe(III) d^5) whereas Zn(II) complexes are not (d^{10}). But also Zn is distributed in more different proteins than Fe (about 2800 for Zn [34] versus 400 for Fe [35] in the human genome, with 60 to 80 % of iron being in hemoglobin [36]): a similar amount distributed in a larger number of different proteins makes each of them less abundant in the case of Zn, and thus less easy to identify or purify.

Endogenous metal ions and essentiality

During the XXth century, there were two major periods in the history of the establishment of essentiality of metal ions in animals [33, 37]. From 1925 to 1955, most of the discovery were at random, by accident or in response to outbreak of unexplained diseases in livestock. As often when a new scientific area is being explored, serendipity presided over the initial advances of a science in the making (*see* "*INSERT*"). This led to the discovery of essentiality of copper, zinc, cobalt, manganese and molybdenum in animals (see Table 1 for the date of discovery for mammals [33]).

From 1955 to 1980, under the aegis of Klaus Schwarz who was based at the Laboratory of Experimental Metabolic Diseases, Medical Research Program, Veterans Hospital, Long Beach, systematic programs were set up based on the experimental induction of trace-element deficiencies in animal models. In a world where metals were already everywhere, as of the industrial revolution, learning how to strictly induce nutritional deficiencies of metal ions and study them in animal models had to be associated with technical developments: designed synthetic and semisynthetic diets, specific metal-free environments (plastic cage, filtration of the air…) [54]. The increased in sensitivity of analytical techniques dedicated to metal ions [55–59] also favored these discoveries. Selenium, chromium, tin, vanadium, fluorine, silicon, nickel, and lithium but also surprisingly lead, cadmium and arsenic were then suggested as elements essential to mammals by Klaus Schwarz at the end of his life [33, 37].

As pointed out by Robert Goyer in [60] and earlier by Klaus Schwarz as reported by Gerhard Schrauzer [33], toxicity and essentiality are not related: a toxic element can be essential and have a biological function. Indeed, toxicity is

a matter of dose, as expressed by Paracelsus [61, 62]. For some metal ions, essentiality may be in a concentration window so weak that it makes experimentation difficult, due to environmental contamination. For both lead and arsenic, a biological role has been suggested and their deficiency has been shown to cause adverse effects (Pb [60, 63, 64] and As [65–67]). However, the evidence presented for Pb has not led to an official declaration of Pb as a dietary requirement for rats [60]. In contrast, As has been suggested to be an essential element even for humans with 7 mg/human 70 kg for As to be compared to 43 kg O, 16 kg C, 7 kg H, 1.8 kg N, 4.2 g Fe and 2.3 g Zn [65] and is proposed to have a link with methionine metabolism [66] and to interact with Se and Zn-fingers [67].

Cadmium has been found to be essential for *Thalassiosira weissflogii* [68], but there is currently no evidence of its essentiality to mammals.

Note that the list may be not closed yet. Indeed, as of 2010, early lanthanides (La, Ce, Pr, Nd, Pm, Sm, Eu) were found essential, if not to human beings, to bacteria living in volcano muds where these elements are in rather high concentration [69].

Concept of essentiality

The concept of essentiality was defined during this second period, notably by George Cotzias, from the Rockefeller Institute for Medical Research and Brookhaven national Laboratory, with four criteria [33, 37, 70, 71].

(1) the element's tissue concentration is comparable from one individual to another within a species, which means it is genetically controlled;
(2) its elimination through strict dietary deficiency induces a physiologic or structural deficiency;
(3) a normal physiology is restored by a return to usual doses of this element;
(4) a specific biochemical function is associated with this element. This fourth point is the center of bioinorganic chemistry as a field.

Advent of bioinorganic chemistry as a field

Once the involvement of exogenous and endogenous inorganic entities in biological systems had been demonstrated, the focus shifted to the understanding of how these entities function: a new field of knowledge emerged, bioinorganic chemistry, born at the confluence of inorganic chemistry, physical chemistry, biochemistry, biology, and biophysics in the late 1970s, early 1980s. Prior to this period, there had been works on the characterization of metallobiomolecules, and more particularly metalloproteins, and their function, with for instance the seminal work of Linus Pauling and Charles Coryell on hemoglobin [72]. Works on complexes of biological interest were also conducted, such as those of James Collman mimicking the reversible binding of dioxygen by globins using metalloporphyrins [73]. But after 1980's these approaches were systematized and gradually organized into an independent research field.

Bioinorganic chemistry unquestionably became a discipline in its own right in 1983, when the first session of the International Conference in Bio-Inorganic Chemistry (ICBIC) was held, and in 1995 the Society of Bio-Inorganic Chemistry (SBIC, https://www.sbichem.org) was founded. Note that other local societies have emerged at the same period, such as SAMBAS (standing for *Sites actifs métalliques en biologie et analogues synthétiques* or Metallic active sites in biology and synthetic analogues), a French network dealing with synthetic analogs of metalloproteins that first met in 1987 in France, then in 1989 with the German community, and led to the congress EUROBIC that was first held in Newcastle in 1992. SAMBAS evolved into FrenchBIC (https://frenchbic.cnrs.fr/) in 2024. AsBIC (Asian BioInorganic Chemistry) conference was first held in 2002 and LABIC (Latin America Bioinorganic Chemistry) congress in 2008.

A multidisciplinary corpus for an inventive fundamental chemistry to understand metal-based biological mechanisms

The study of metallobiomolecules and metal complexes in a biological context, or for biological applications, requires expertise shared between organic and inorganic chemists, biochemists, biophysicists, physical chemists, and, more recently, cell biologists and theoretical chemists. With the development of new, highly demanding techniques, in imaging, mass spectrometry (MS), metallomics, or directed evolution, not to mention artificial intelligence, dense and dynamic networks of collaborations have favorably developed all over the world.

Chemistry, with its formalisms and tools for studying structure–property relationships and dynamic phenomena, with fundamental concepts in thermodynamics and kinetics, is essential to the understanding of the mechanisms of these metallobiomolecules or to the design and study of metal-based compounds in a biological context or as biomimetic catalysts. In return, chemistry has much to gain from the study of these systems, Nature being, in a way, an endless reservoir of challenges and ideas [74].

One of the contributions of chemistry involves the synthesis and study of transition-metal complexes with biological activity and of bio-inspired catalysts. There are two types of approach here, not mutually exclusive: informative or functional perspective (see Fig. 3).

In the **informative perspective**, the aim is to better describe and understand metallobiomolecules. The study of low-molecular-weight complexes is of interest here because they are more

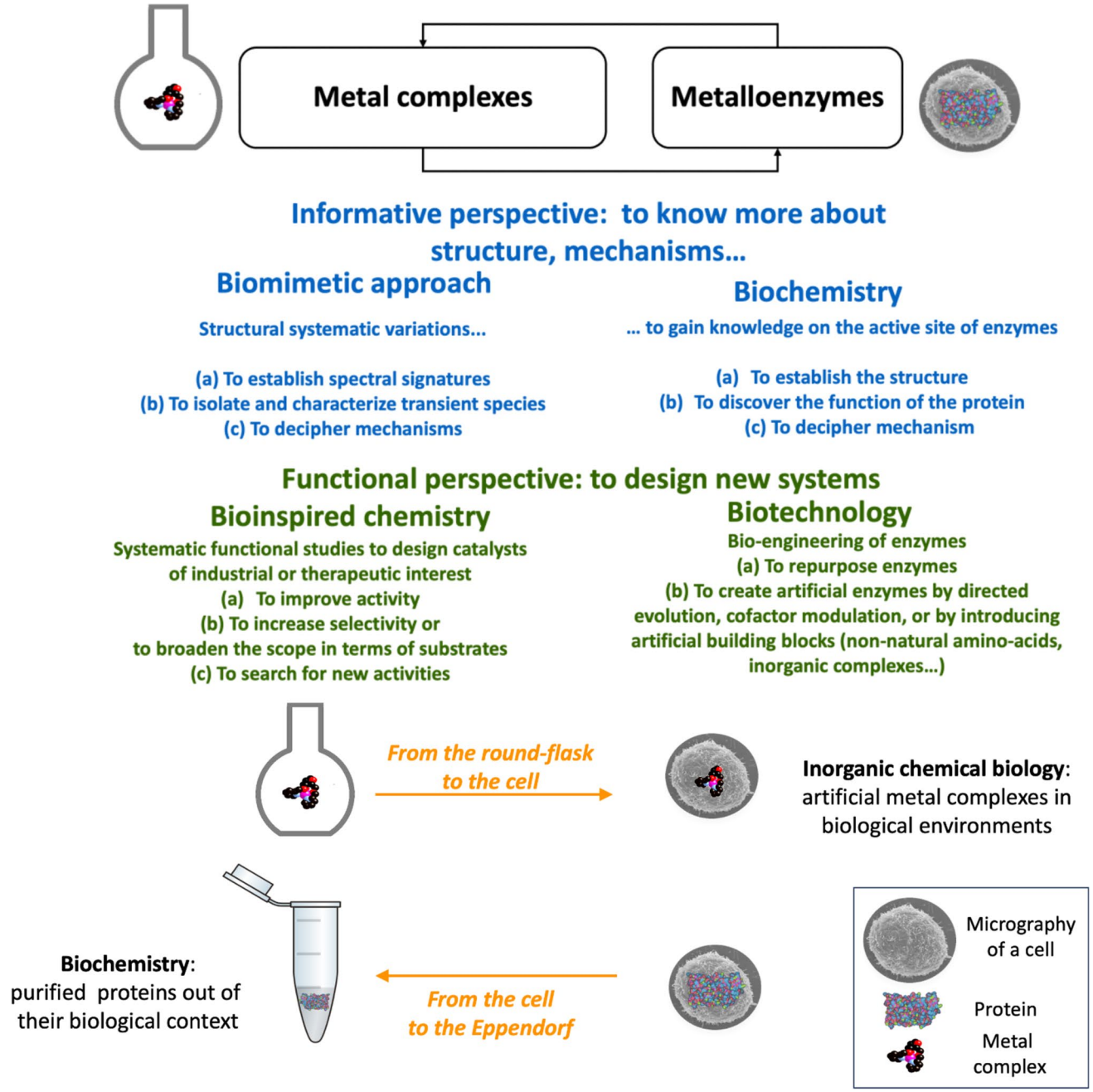

Fig. 3 Research in bioinorganic chemistry, delineating the informative and functional perspectives. In the field of inorganic chemical biology, metal complexes are now reintroduced in biological environments, when the field of biochemistry is proceeding by extraction of proteins from their biological environment, for crystallization and physico-chemical studies (see arrows in orange, opposite movement) Adapted from [1]. Copyright 2024 American Chemical Society

amenable to systematic variations than metallobiomolecules. The synthetic modeling helped greatly in identifying (i) repertoires of spectral signatures in a range of spectroscopies (electronic absorption, vibrational, Mössbauer, electron paramagnetic resonance, etc.), and (ii) structural and functional properties of metallobiomolecules [74]. In addition, these low-molecular-weight complexes can be manipulated in organic solvents, i.e., at low temperatures in a solvent remaining liquid, enabling the study of reactivity and the characterization of fugitive species at low temperature (metal-oxo called in the IUPAC nomenclature [75] metal-oxido M = O, or metal-peroxido M-OO for example) [76–79]. With regard to catalysts inspired by metalloproteins, reactivities have been finely rationalized with regard to the chemical nature of the catalyst (control of the redox potential

for instance), to the bulkiness of the environment, but also at the spin state level [80]. This enables chemists to design catalysts with a tuned reactivity but it also provides the understanding of how exquisite the control of reactivity of metalloenzymes can be.

In metalloenzymes, metal cations can be found in an unusual environment imposed by the protein matrix. "Unusual" may mean a low coordination number, which is difficult to maintain in small, unconstrained systems in solution, as "being soluble" rhymes with "interacting with the solvent", this solvent being able most of time to act as an additional ligand that fills in the coordination sphere.

Unusual may also involve a coordination geometry distorted from that preferred by the metal ion, this distorted geometry being not controlled by the configuration (d^n) of the metal ion. This can induce unusual properties (spectral signatures, redox potential shift, substitutional inertia/lability…). This is the case for instance for the spectral signature of blue copper proteins [81]. This is also the case in the distorted environment of Mn-based superoxide dismutases: low coordination number to keep room for the substrate superoxide to enter the coordination sphere of the metal ion and a distorted axial geometry in bipyramidal trigonal geometry to stabilize the Mn(III) d^4 (Jahn–Teller stabilisation) and therefore tuning the redox potential of the Mn(II/III) couple [82, 83].

Indeed, deviations from the ideal geometry —ideal meaning controlled by the electronic configuration d^n— of these structures are accompanied by a destabilization that is responsible for the reactivity of the site: this is known as the entatic state [84–88]. Reproducing such distorted and activated environments by designing constrained ligands is a challenge for the chemists [84, 85].

The activities of metalloenzymes, like those of enzymes in general, are often of high added value (functionalization of alkanes, dihydrogen and dioxygen production, carbon dioxide reduction, electron flow, energy conversions, control of oxidative stress, etc.) and the chemist can find in them a source of inspiration for designing metallic entities, or more broadly molecules, with controlled properties of industrial or pharmaceutical interest. This is the second type of approach, with a **functional perspective**, targeting activity (see Fig. 3). The aim is then not to chemically copy the structure or spectroscopic features of an active site, but rather to forge new intuitions by studying and understanding the mechanisms selected in the course of the slow process of Darwinian evolution. Armed with this new dimension of reflection, the bioinorganic chemist can then, in the words of S. Diekmann [89], open their toolbox (organic, inorganic, biochemical and theoretical) to build entities with controlled reactivity, be they efficient catalysts or modified proteins with hijacked activity.

In this design, there has been a gradual change in scale, at several levels, over the years. Low-molecular-weight metal complexes have been encapsulated into large matrices designed to modulate their activity, possibly mimicking the second coordination sphere and beyond (H-bond network, electrostatic interactions, etc.) [90]. These matrices include materials such as clays or zeolites [91], or macrobiomolecules such as antibodies [92], polypeptides [93] and protein scaffolds [94]. These artificial enzymes design, notably to perform abiotic reactions [95], has gained significant attention in the last two decades, involving rational design, aided by computation, artificial intelligence, or directed evolution [96].

The status or role of cells has also evolved. They are used as nano-plants to produce material catalysts, such as metallic nanoparticles [97]. They are also increasingly considered as non-conventional nanoreactors to perform catalysis [98], either for therapeutic applications [99] or to benefit from the cell economy. Indeed, the cell can provide catalysis partners (reducing agents, cofactors, etc.), and enable a continual renewal of the metal complex's ligands or matrix through biosynthesis.

In a sense, there is here an opposite, "antiparallel", movement between (i) inorganic chemical biology, that can be considered as a subfield of both bioinorganic chemistry and chemical biology, with this introduction of artificial metallic structures into biological systems, and (ii) biochemistry that purifies (metallo)proteins to study them out of any cellular contexts (see Fig. 3, bottom). But more and more, proteins are studied in their native biological environment as the specific nature of the biological media (viscosity, overcrowding, see below [100]) is now recognized as key to their mechanism.

Bioinorganic chemistry and metallomics

Organization of cells at mesoscopic scales is increasingly studied and this knowledge is important to the understanding of the cellular metal ions economy [101]: compartmentalization within organelles, organization of enzymatic (or metalloenzymatic) complexes in membranes, flow of protons or electrons across membranes from one cellular compartment to another (with the question of their coupling and of the role of metal ions in this matter), flow of metal ions in and out cells and between compartments, etc. With these questions, central to bioinorganic chemistry, there is a strong overlap with metallomics, a field defined in 2004 by Hiroki Haraguchi [55], after the term metallome was coined by Robert Williams in 2001 [102]. Metallomics integrates with other "omics" to emphasize the importance of inorganic elements, including metal ions, in biology and refers to the characterization of metal species within biological systems [103]. But we believe that metallomics can be extended to the tracking

Table 2 Concentration of some ions in sea water and blood plasma, from [110]

Ion	Concentration in sea water (mM)	Concentration in blood plasma (mM)
Cl^-	570	100
Na^+	470	140
Mg^{2+}	50	2
K^+	10	10
Ca^{2+}	10	3
MoO_4^{2-}	0.2 µM	2–20 µM
First row transition-metal ions	1–10 nM	2–20 µM

and characterization of metallic species in the environment (mines for instance) or in art (paintings for instance [104]). In a way, bioinorganic chemistry, as defined at the beginning of this article, provides many of the fundamental principles and understanding that metallomics builds upon for its system-wide analyses.

As shown in Tables 1 and 2, there is a rough homothetic relationship between the composition of seawater and human plasma, revealing our marine origin. But the metal ions fall out that trend and accumulate in living organisms. These metal ions have been referred to as "trace" elements, but this is clearly a misnomer [101]. Firstly, qualitatively, because of the key importance of metal-based bio-catalysts for physiology, even at low concentrations. Secondly, quantitatively: even if they are globally low in amount, because they are not homogeneously distributed in biological systems between sub-compartments as organelles, intracellular metal ions can actually not be in so weak concentrations in subcellular compartments of low volume where they are present. Indeed, they are maintained at levels from a few ten of micromolar (Cu, Mo, Mn, Ni, Se, Cr, V…) to levels as high as the millimolar (Fe-Zn) in *E. coli*, as shown by the pioneering work of Thomas O'Halloran and Caryn Outten [105]. Over the past 30 years, it has become increasingly clear that metal ions play an important role in cellular regulation and metabolic pathways, participating in the control the chemical and biological states of cells. This is why there is such a tight control of metal homeostasis. This involves an intricate network of sensing, importing, exporting, and storage. Transient/short storage involve intermediate proteins to shuttle metal ions where they are needed (metallochaperones known for Cu [106] and Zn [107]). Longer storage can also exist, as for iron in an internal "cellular attic", in the solid oxide form into ferritin, with a fast mobilization when needed through simple triggers (pH [108] or reduction [109] for instance).

Thorough studies applying concepts of thermodynamics and kinetics in the new context of cell interior led to a better picture of these processes, initiating new innovative ways to look at them [111–114]. These studies brought evidence for the important role of the very specific physico-chemical characteristics of biological media. Beside the reductive nature of the cell interior, its high viscosity, molecular overcrowding, compartmented environment, or high content in Lewis bases and metal ions [100], can impact kinetics and thermodynamics (see also [115] for a film simulating of the cell interior). As delineated by Nigel Robinson and Kevin Waldron, cells are definitely not ideal solutions and kinetics factors may be at stake with regard to inertia of multiprotein complexes or metal ions availability/distribution and protein metalation status [112]. For instance, for a given complex LM with a given dissociation constant K_d, the actual position in the association equilibrium (L + M = LM), that can be reported by the percentage of metal within the LM species, is dependent on the concentration: upon dilution, a complex dissociates, whatever its K_d. This is similar to a weak acid becoming strong when diluted: no change of the absolute pKa of course, but a behavior of complete dissociation when diluted [116]. The reverse is true: for a given system, association can be favored by an increase in concentration. For these reasons, studies performed using spectroscopies directly in whole cells are essential.

Compartmentalisation of biological media is a key feature. The localization into small-volume compartments, organelles like mitochondria or vesicles like zincosomes [117–119] or ferrosomes [120–122], explains how minute amounts of a metal ion correspond locally to not so weak concentrations. Fragile and crucial multiprotein complexes from the respiratory chain or photosynthesis, the basis for the energy production and storage in cells***, are embedded into a membrane, a very small volume "compartment". Intramembrane embedment of proteins or other molecules increases their effective concentration and limits their diffusion to 2D, entropically favoring interactions. This embedment probably also impacts vibrational structure, which has been suggested to be optimized for charge separation [123]: limiting vibrational desexcitation favors other pathways. Compartmentalization of metal ions (Mn/Cu) was also shown to prevent competitive metal ions such as Cu from coordinating to proteins meant to work with Mn [124]: this is a challenge considering that Mn(II), for a same ligand, has a lower association constant than Cu(II), as identified by the Irving and Williams series (see also below) [125].

Detection and imaging: which pool?

The increasing occurrence of the usage of metal-based artificial systems in biology leads to the question of their detection and of their mapping within cells [83], as well as their in vivo or in-cells speciation. To that extent, the techniques developed not only in metallomics but also in geochemistry,

with the aim notably to characterize the speciation of metal ions in the environment, can cross-fertilize bioinorganic chemistry.

Because of the dynamic nature of the ligand to metal bond, there is always the question of the speciation of metal ions, already stressed above in the case of metal-based drugs: what is the nature of a metal ion of interest in cells or in bacteria? To address this question, techniques able to assess the molecular structure, such as MS possibly hyphenated to another technique, are essential. One very efficient technique consists to couple MS with ion mobility meant to separate ions depending on their mass and shape. This technique, very efficient to address protein folding for instance [126], involves the movement of ions under an applied electric field, with a gas flow that either push or retain molecules depending on their rotationally averaged collision cross-section (CCS in $Å^2$). It has been shown to be powerful enough to discriminate between low-molecular weight divalent metal complexes from the same ligand across the first-row transition elements [127]. In order to have as little effect as possible on speciation, more and more experiments are being designed to reduce sample preparation to a minimum.

John Lisher and David Giedroc have proposed a very enlightening classification of metal ions, as competitive or bioavailable [128]. When exploring metals ions in cells, one should carefully distinguish (a) the total cell-associated metal ions, (b) the pool of metal ions that is not labile, typically tightly bound to proteins or other biomolecules, and (c) the pool that is loosely bound, more often to low-molecular weight biological non proteinaceous Lewis bases, such as non-proteic amino acids, nucleosides, nucleotides, orthophosphate, citrate, or carbonate [128, 129] (with a = b + c). Note that metal ions in a solid form mainly belong to (b) as the interior of solids is not very accessible but surfaces or small particles may be fastly mobilized, as for iron in ferritine: they may then belong to (c). The solid form is not considered below (for a discussion see [130]).

As the cell interior is reductive, we only consider here the reduced form of the metal ions. Cu(I) and Zn(II) d^{10} metal ions show an association constants, for a given unconstrained ligand, higher than Mn(II) and Fe(II) do, as known from the Irving and Williams series [125, 131]. Interestingly, the bacterial sensors association constants for metal ions follow this series [113]. The homeostasis machinery identifying metal overload activates for Cu and Zn at much lower thresholds than for Mn and Fe. This means that import is cut off and export activated at lower concentration for Cu/Zn than for Mn, which contributes to maintaining the availability of the metal ions to the inverse of the Irving and Williams series [113]. Cu and Zn are tightly controlled by proteins: as soon as they get inside cells, they are taken up by metallochaperones that deliver the metal to the protein of interest to which it tightly binds. The Cu and Zn pool of cell-associated metal ion is similar to the protein-associated pool, with less than one ion of Cu or Zn per bacteria for the loosely bound pool (see in bacteria: [132] and [105]). In contrast, there is dynamic and richer exchangeable pool for Mn(II), available to protein/ligand metalation and which has been described to play a role in the control of oxidative stress notably in diverse microorganisms [133]. We wish to stress here two implications.

(a) The first one is a paradox, but can be understood in terms of thermodynamic competition: for a Mn(II)-complex to be stable in a biological environment, the requirement in terms of association constant is less drastic than with Cu(II) or Zn(II), because of this exchangeable bio-available Mn-pool that contributes to shift the L + Mn = LMn equilibrium toward LMn [83, 134].

(b) When performing quantification or imaging, it is very important to assess the type of pool that is probed. Many reviews have delineated the main features of metal-quantification and imaging techniques, their limits and applicabilities and we encourage the reader interested to refer to them [56, 57, 135–142]. Here, we just wish to stress the intrinsic difference with regard to the pool detected between techniques probing the metal ion based on its elemental properties and those based on its coordination properties as a Lewis acid.

In the first category fall mass-based techniques such as inductive-coupled-plasma mass spectrometry (ICP-MS) (for detection, and associated to laser ablation for imaging, LA-ICP-MS) and secondary ion mass spectrometry (nanoSIMS) or micro-X-fluorescence. They can be used for imaging by focalization of the beams (laser for LA-ICP-MS, ion beam for nanoSIMS, X-ray light for μXRF). These techniques, called also *elemental imaging*, probe the total element content. In X-fluorescence, there is a potential access to information about the redox state using XANES and on the coordination sphere using EXAFS, however, this is not easy to combine with imaging performed on cell layer or tissue sections due to the small voxel probed.

In the second category, are the reporters interacting with the metal ions [143]. Due to the widespread of fluorescent microscopes, most of these reporters are fluorescent. They can be synthetic or genetically-encoded. Recently, probes able to report metal content by vibrational detection have also been developed [144]. In all cases, the detection relies on a change of the spectroscopic properties of the sensor upon metal ion coordination and depends on the competition between association to the biological ligand(s) and to the sensor. These techniques probe, not the whole pool, but the metal ion pool available to the sensor: that means the pool in the same compartment, kinetically and thermodynamically available, with a threshold that is determined by the association constant (K_a) of the probe itself.

Clearly, the imaging of metal ions has brought the understanding of their roles in biological systems a step further and this will probably even advance faster with the capacity

Table 3 Information to retrieve the unconventional or old references that do not have an available doi. NB: In the list of references below, the doi or link to the reference is systematically indicated. For the references that are older or non-conventional in a scientific paper (letter, simulation for instance), the doi is not always available. The reader will find the way to retrieve them in Table 3 with an open url and, for books, the ISBN is indicated

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of treatment, analyses and comparison of images now available with artificial intelligence.

Conclusion: bio-inorganic chemistry: a fertile chimera

The field of bioinorganic chemistry really shows how the intricate, dynamic, and highly regulated environments of living systems can challenge our traditional understanding of physico-chemical concepts and principles. For that reason, the bioinorganic perspective is invaluable for teaching chemistry. By looking from a new angle, it gets students to think beyond textbook models and develop a deeper understanding of chemical principles. By grappling with the intricacies of metalloenzymes, or metal trafficking, the next generation of chemists will be better equipped to tackle complex, real-world challenges at the interface of chemistry and biology.

In turn, these insights gleaned from natural systems can spark innovative solutions in areas like catalysis, medicine, and materials science amenable to solve societal key issues. In a way, it is almost like the tension between "bio" and "inorganic", etymologically embedded in its very name, is precisely what makes this field so rewarding to explore. The lessons of bioinorganic chemistry are not just academic. As we confront pressing societal issues like sustainable energy, environmental remediation, and improved human health, this perspective is essential. By taking inspiration from biological systems, chemists can devise transformative technologies or therapies that address global needs. Embracing the bioinorganic worldview is thus crucial not only for advancing fundamental science, but for developing practical solutions that improve our world.

INSERT: Serendipity *is a term coined by Horace Walpole in 1754 [145] from the Persian tale « Three Princes of Serendip » in which three princes are sent by their father king to explore the world. During their journey, they solve many questions they were not asked to look at by mere observation.*
It describes a process of discovery where research leads to something that was neither programmed nor anticipated and that can be much more valuable than the initial prospect. Serendipity also refers to the ability to set aside an initial goal for a greater one, not anticipated. Note that this is not "discovery by luck" or "at random", but "discovery closeby".
In the case of the discovery of cisPt, this applies perfectly. Barnett Rosenberg and Loretta Van Camp et al. were looking for a way to disrupt cell growth in a cancer research program and their idea was to use an electric field, for which they chose Pt electrodes. This choice was the lucky part. The important aspect here is that they did not just throw away an electric field experiment that did not work, but they took a step back and thought about it, which led eventually to identify cisPt and its potentialities.
As a researcher, we need a goal, but it is not essen tial as such. It is there to set us in motion, but it does not matter if we reach it or not, as long as we make other discoveries along the way, and sometimes these unplanned discoveries are more important than the initial goal: that's the magic of research!

References and notes

*Porphyrins and macrocycles are ligands that provide a high association constant. **Ferroquine is also quite inert in biological media.

*** We suggest to prefer the expression "in cells" or "in-cells" to "in cellulo". If one wants to use Latin, it should be "in cellulam" or "in cellam" (from *cella, ae*, room, attic and *cellula, ae*, small room), "in cellulo" not being an existing expression in Latin.

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Author contributions CP wrote and revised the manuscript.

Data Availability No datasets were generated or analysed during the current study.

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