

Edited by Yu-Feng Li and Hongzhe Sun

Applied Metallomics

From Life Sciences to Environmental Sciences



medimetallomics

agrometallomics

environmentallomics

nanometallomics

Targeted/
non-targeted metallomics
spatial metallomics
metalloproteomics

Synchrotron

Neutron

Proton

Other tech.

Applied Metallomics

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Edited by Yu-Feng Li and Hongzhe Sun

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Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <<http://dnb.d-nb.de>>.

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Print ISBN: 978-3-527-35144-2

ePDF ISBN: 978-3-527-84037-3

ePub ISBN: 978-3-527-84038-0

oBook ISBN: 978-3-527-84039-7

Cover Design and Image: Schulz Grafik-Design, Fußgönheim, Germany

Typesetting Straive, Chennai, India

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Foreword

Metallomics is the systematic study of the interactions and functional connections of metallome with genes, proteins, metabolites, and other biomolecules within organisms. It aims to provide a global understanding of metal uptake, trafficking, role, and excretion in biological systems, and potentially to be able to predict all of these in silico using bioinformatics and even artificial intelligence.

With the development for over two decades, metallomics has converged with different research fields to form diverse branches of metallomics, such as nanometallomics, environmentalomics, agrometallomics, clinimetallomics, and metrometallomics, to name a few. Besides, with the development of high throughput analytical techniques, methodologies in metallomics were also formed, such as targeted/non-targeted metallomics, spatial metallomics, temporal metallomics, spatiotemporal metallomics, metalloproteomics, and metametallomics.

In 2010, Prof. Zhifang Chai, Prof. Yuxi Gao, and I co-edited a book entitled *Nuclear Analytical Techniques for Metallomics and Metalloproteomics*, which is the first monographic book to address the key aspects of the application of nuclear analytical techniques to metallomics study. After that, several books on metallomics edited by distinguished scientists were published, such as *Metallomics and the Cell*; *Metallomics: A Primer of Integrated Biometal Science*; *Metallomics: Recent Analytical Techniques and Applications*; and *Metallomics: The Science of Biometals*, which greatly enhanced the development of metallomics.

It my pleasure to introduce this new book of *Applied Metallomics*. This book is a collection of 16 chapters contributed by eminent experts in China. In Chapters 2–12, different branches of metallomics were introduced, while in Chapters 13–15, dedicated methodology and tools were presented. Specifically in Chapter 16, data mining with machine learning and even artificial intelligence for metallomics was introduced, which is highly desired for metallomics studies.

The co-editors of this book, Prof. Yu-Feng Li and Prof. Hongzhe Sun, are co-founders of the “CAS-HKU Joint Laboratory of Metallomics on Health and Environment,” who have been dedicated to metallomics and metalloproteomics

studies for over 20 years. With their hard work and close collaboration, I am happy to see this book being published, which is suitable for not only scientists already involved in metallomics research but also for young scientists, graduate students, and others who are interested in understanding the vital roles of metals/metalloids in life and many other fields.

Chunying Chen

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Preface

Since its coinage by Haraguchi and Williams in early 2002 as “integrated biometal science” and the following definition by International Union of Pure and Applied Chemistry (IUPAC) in 2010, metallomics has seen great development not only in methodology but also in its application in different research fields. Considering the important role of metallome, it is regarded as one of the five pillars of life along with genome, proteome, lipidome, and glycome. With the development of high throughput analytical methods, it is believed that metallomics will evolve to elementomics, which will cover all the elements in the periodic table. However, here in this book, we will pay our attention mainly on metal/metalloids rather than all the elements.

Over the last two decades, metallomics has converged with nanoscience, environmental science, agricultural science, medical science, toxicological science, metrological science, radiological science, archaeology, and materials science to form different branches of metallomics, such as nanometallomics, environmentalomics, agrometallomics, clinimetallomics, metrometallomics, radiometallomics, archaeometallomics, and matermetallomics. These developments show the diversity and prosperity of metallomics in different research fields.

High throughput analytical techniques are commercially available, such as inductively coupled plasma optical emission spectroscopy (ICP-OES) and inductively coupled plasma optical mass spectrometry (ICP-MS). Besides, large research infrastructures, such as synchrotron radiation facilities, free electron lasers, spallation neutron sources, proton sources, and heavy ion sources, can provide cutting-edge techniques as superb tools for metallomics. Based on these high throughput analytical techniques, targeted/non-targeted metallomics, spatial metallomics, temporal metallomics, spatiotemporal metallomics, metalloproteomics, and metametallomics are formed as dedicated tools for studying the quantification, distribution, speciation, and function of metallomes.

The aim of this book is to present the latest development of metallomics in both its application in different research fields and its methodology development. There are 16 chapters in this book. Chapter 1 gives a brief introduction to metallomics and presents the key issues and challenges in metallomics. From Chapters 2 to 12, different branches of metallomics, such as nanometallomics, environmentalomics, agrometallomics, metrometallomics, medimetallomics, clinimetallomics, matermetallomics, archaeometallomics, metallomics in toxicology,

pathometallomics, oncometallomics, and bio-elementomics, are presented, which cover both the analytical techniques and their applications in the specific research field. This is also why we give the name of this book *Applied Metallomics*, since we want to show that metallomics is very useful in many fields. From Chapters 13 to 15, the methodology and tools in metallomics, especially ICP-MS, are presented. Last but not least, Chapter 16 presents machine learning in metallomics for data mining. We would like to thank all the contributing authors for their hard work and efforts in forming this book, since we are hoping to present the latest development and application of metallomics in diverse research fields. Besides, through the publication of this book, we are also hoping to attract more and more distinguished researchers, young scientists, graduate students, and other people who are interested in understanding the vital roles of metals/metalloids in life sciences and many other fields to join the metallomics family.

Both Chinese Academy of Sciences (CAS) and the University of Hong Kong (HKU) pay high attention to metallomics study, and a “CAS-HKU Joint Laboratory of Metallomics on Health and Environment” was established in 2019. Besides, the “Beijing Metallomics Facility” was established in 2020, which includes 12 universities, institutes and even hospitals resides in Beijing area. Furthermore, the “National Consortium for Excellence in Metallomics” was also initiated in 2020 to cover all the interested parties around China. We would like to thank all the scientists and colleagues with whom we worked together on metallomics these years.

We would like to acknowledge the financial support from the National Natural Science Foundation of China (NSFC, Nos. 11975247, 11475496, 11205168), Research Grants Council of Hong Kong (SRFS2122-7S04) and the Ministry of Science and Technology (2022YFA1207300, 2020YFA0710700, 2016YFA0201600). We also thank the support of the joint research scheme from RGC and NSFC (No. 20931160430).

We would like to express our sincere appreciation to Felix Bloeck, Kelly Labrum, Shwathi Srinivasan, Tanya Domeier, Farhath Fathima, and Elizabeth Rose Amaladoss from Wiley. Without their patience and kind help, the publication of this book would be impossible.

March 1, 2024

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1

Introduction

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1.1 A Brief Introduction to Metallomics

Metals and metalloids play vital role in life and even death, acting as catalysis, structural components, signal transmitters or electron donors [1–3], etc. However, metals or metalloids do not work alone; they may interact with each other through synergism or antagonism in biological systems. The systematic understanding on the roles of all the metals and metalloids in biological systems is called “metallomics,” which was proposed by Haraguchi in 2002 as “integrated biometal science,” [4, 5] while the term “metallome” was first used by Williams in 2001, referring to “an element distribution or a free element content in a cellular compartment, cell or organism.”[6] In 2010, metallomics was defined by the International Union of Pure and Applied Chemistry (IUPAC) as a research field focusing on the systematic study of the interactions and functional connections of metallome with genes, proteins, metabolites, and other biomolecules within organisms [7]. Metallomics aims to provide a global understanding of the metal uptake, trafficking, role, and excretion in biological systems, and potentially to be able to predict all of these *in silico* using bioinformatics [8, 9].

Metallomics aims to understand the biological systems and life process at the atomic level [10], which is similar to ionomics in this regard [11–13]. However, metallomics also works at molecular levels like the study on metalloproteins [14] and speciation study [15, 16]. Therefore, it covers both the atomic and molecular levels of metallome. The metallome has been proposed as a fifth pillar of elemental – vis-à-vis molecular-building blocks alongside the genome, proteome, lipidome, and glycome in life [17] as illustrated in Figure 1.1. With the technical advances, it is expected that metallomics will be evolved to elementomics [18–21], which will cover all the elements in the periodic table.

Applied Metallomics: From Life Sciences to Environmental Sciences, First Edition.

Edited by Yu-Feng Li and Hongzhe Sun.

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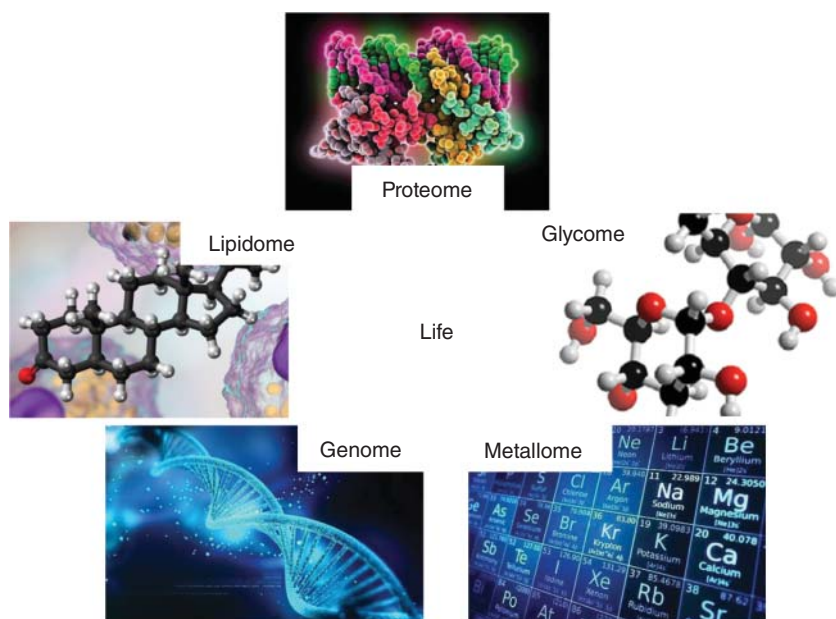


Figure 1.1 Metallome as one of the five pillars in life alongside the genome, proteome, lipidome, and glycome. Source: abhijith3747/Adobe Stock; Yu-Feng Li (Author).

Metallomics is considered both a basic science to understand the chemical structures and biological functions of metallome and an applied science in convergence with many research fields [5, 17]. Metallomics has gained increasing attention among scientists working outside the biological science, such as nanoscience, environmental science, agricultural science, medical science, food science, geoscience, toxicological science, materials science, and metrological science [8–10, 15, 22–28]. The convergence of metallomics with these research field has led to new branches of metallomics such as nanometallomics [22, 29–31], environmentalomics [32–34], agrometallomics [35], metrometallomics [36], clinimetallomics [37], radiometallomics [38], archaeometallomics [39], and matermetallomics [40]. A special issue called “Atomic spectroscopy for metallomics” published in *Atomic Spectroscopy* covered some of these topics [10].

Dedicated analytical techniques are required for the characterization of metallome and their interactions with genome, proteome, metabolome, and other biomolecules in the biological systems. Commercially available instruments like inductively coupled plasma optical emission spectroscopy (ICP-OES) and inductively coupled plasma optical mass spectrometry (ICP-MS) have been widely applied in metallomics for the quantification of metallome [15, 24–26]. On the other hand, there are scientific instruments which are commercially less available but accessible to scientists, i.e. large research infrastructures (LRIs). LRIs are built to solve the strategic, basic, and forward-looking scientific and technological problems in economic and social development [41].

Particle accelerators are such kinds of LRIs, which produce beams of fast-moving, electrically charged atomic or subatomic particles, such as electrons, positrons, protons, or ions [42]. They are used for particle physics and nuclear physics like the structure of nuclei, the nature of nuclear forces, and the properties of nuclei not found in nature [43]. They are also used for radioisotope production, industrial radiography, radiation therapy, sterilization of biological materials, and radiocarbon dating [44, 45], etc. Furthermore, the particle accelerator-derived electrons, positrons, protons, or ions beams have many advantages compared to the commercially available ones, which make them superb tools in many research fields including metallomics.

1.2 Key Issues and Challenges in Metallomics

It is desired to know which and how many elements are there in a biological system, and this includes the high-throughput quantification of elements, their species, and also the metal/metalloid-binding molecules like metalloproteins.

For the quantification of metallome, it is required to know first which metallome is to be quantified. There are over 20 elements like C, N, O, F, Na, Mg, Si, P, S, Ca, Fe, Cu, Zn, and I that have been proved to be essential elements for humans [46]. Plants also require B, while some bacteria need W, La, and Ce instead of Ca [47]. In some marine diatoms, Cd-containing carbonic anhydrase was found [48]. It is also desired to quantify the presence of non-essential elements in the biological system since new technologies and manufacturing practices lead to new industrial emissions, releases, or discharges to the environment. For example, the electronic industry uses rare-earth elements and many transition elements in the periodic table. With nearly 60 million tonnes of electronic waste generated in 2021 alone, it is also desired to know to which extent that humans, plants, animals, and microorganisms are exposed to these elements [49]. Another example is the increased production and application of nanomaterials these years, which inevitably lead to the environmental burden of nanomaterials themselves or their degraded products [31, 50]. Therefore, it is desired to quantify as many elements as possible or even the whole elements in the periodic table in a high-throughput way; however, this indeed is one of the big challenges for the quantification of metallome since huge concentration difference of elements exists in the biological systems [21].

The speciation of elements is also required since different species of the same element may have different biological effects. One example is Cr. Cr^{3+} is positive on glucose on lipid metabolism, while Cr^{6+} in the form of chromate is a carcinogen [46]. Another example is Hg. It is known that mercury selenide (HgSe) is stable and generally not bioavailable, while methylmercury (MeHg) is highly toxic and bioaccumulative in biological systems [51]. For the speciation in metallomics, the challenge is to identify the species in situ. This is also required for the quantification of metalloproteins and other non-protein complexes of metal ions in metallomics study.

Besides knowing the concentration and speciation of metallome in a whole biological system, it is also desired to know how many of them exist in a particular location, i.e. the distribution of metallome. Seeing is believing. This includes knowing the two-dimensional (2D) and three-dimensional (3D) distribution of metallome in a biological system, which is called spatial metallomics [52–54]. Spatial metallomics is the study on the distribution of metallome at the subcellular, cellular, tissue, and whole-body levels including human-sized objects or even larger ones [55], requiring the spatial resolution at the nanometer, micrometer, millimeter, centimeter, and even larger ones [56].

The challenge for mapping the metallome in 2D and 3D is to have a tunable spatial resolution, which will greatly facilitate the study on the distribution of metallome in a biological system through a coarse scan first, following by a fine scan of the samples [57]. For 3D mapping, high-speed data acquisition is highly desired, while non-destructive analysis is highly preferred.

The 2D and 3D spatial distribution of chemical species is also required in the metallomics study. This includes the *ex situ* and *in situ* study, while the *in situ* chemical speciation is always desired. The study on the distribution of metals/metalloids in metalloproteins and other non-proteins complexes, i.e. their 3D structure can also be included in spatial metallomics.

The temporal change of metallome in a biological system forms series of live pictures of metallome in a biological system, i.e. the movie of metallome. The study on this can be called temporal metallomics. Furthermore, the study on the spatial distribution of metallome with a temporal resolution in a biological system can be called the spatiotemporal metallomics [52]. This shows the dynamic changes of metallome in a biological system.

For both the temporal and spatiotemporal metallomics, a challenge lies in the *in situ* monitoring of the dynamic changes of metallome in the biological system, especially at the single-cell level, which is called single-cell metallomics [17, 52]. Besides, considering the individual variations in mixed communities of organisms like cells, metametallomics was proposed to cover this [17, 26]. Temporal and spatiotemporal metallomics also include the study on the dynamic changes of metals in metalloproteins and other biomolecules.

1.3 About the Structure of this Book

As abovementioned, with the fast development in the last 20 years, metallomics has been converging with different research fields such as nanoscience, environmental science, agricultural science, biomedical science, toxicological science, materials science, archaeology, and analytical science to form new metallomics branches like nanometallomics, environmetallomics, agrometallomics, and medimetallomics. Dedicated tools through synchrotron radiation, neutrons, protons and other commercially available techniques can be applied in metallomics study. Besides, the methodology of metallomics including targeted or non-targeted metallomics, spatial metallomics (including single-particle/single-cell metallomics), temporal

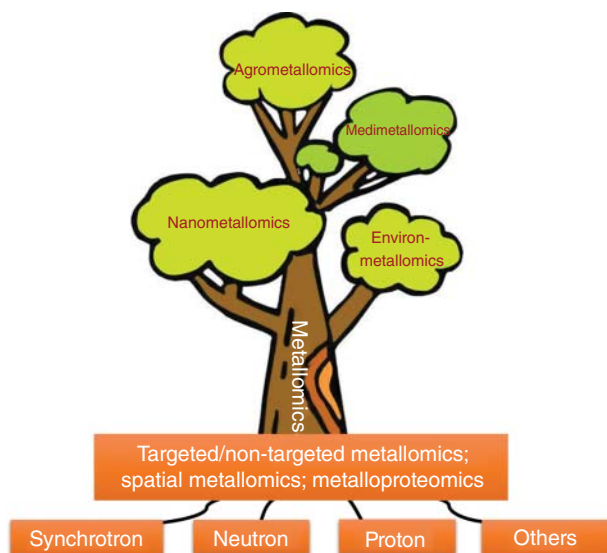


Figure 1.2 The different branches of metallomics and the methodologies and tools. Source: Yu-Feng Li.

metallomics, spatiotemporal metallomics, and metalloproteomics is also formed (Figure 1.2).

Therefore, from Chapters 2–11, these metallomics branches will be introduced: Chapter 2, Nanometallomics (coordinated by Yu-Feng Li); Chapter 3, Environmetallomics (coordinated by Ligang Hu); Chapter 4, Agrometallomics (coordinated by Xuefei Mao); Chapter 5, Metrometallomics (coordinated by Liuxing Feng); Chapter 6, Medimetallomics and clinimetallomics (coordinated by Qun Xu and Huiling Li); Chapter 7, Matermetallomics (coordinated by Zheng Wang); Chapter 8, Archaeometallomics (coordinated by Xiangqian Feng); Chapter 9, Metallomics in toxicology (coordinated by Ming Xu); Chapter 10, Pathometallomics: Taking neurodegenerative disease as an example (coordinated by Qiong Liu); and Chapter 11, Oncometallomics: Metallomics in cancer studies (coordinated by Xin Wang and Chao Li). Each chapter covers both the analytical techniques and the application of metallomics in a definite discipline or more. This is also why we call this book *Applied Metallomics*. Since metallomics is expected to be evolved to elementomics, an introduction and application of bio-elementomics is presented in Chapter 12, Bio-elementomics (coordinated by Jingyu Wang).

In addressing the key issues and challenges of metallomics, methodologies and tools, especially ICP-MS, machining learning and data mining are introduced in Chapter 13, Methodology and tools for metallomics (coordinated by Qiuquan Wang); Chapter 14, ICP-MS for single-cell analysis in metallomics (coordinated by Bin Hu); Chapter 15, Novel ICP-MS-based techniques for metallomics (coordinated by Meng Wang); and Chapter 16, Machine learning for data mining in metallomics (coordinated by Wei Wang).

Through all these efforts, this book is intended to reflect the latest development and application of metallomics in different research fields.

References

- 1 Fraústo da Silva, J.J.R. and Williams, R.J.P. (2001). *The Biological Chemistry of the Elements: The Inorganic Chemistry of Life*. New York: Oxford University Press.
- 2 Olwin, J.H. (1977). Metals in the life of man. *J. Anal. Toxicol.* 1: 245–251.
- 3 Han, N., Li, L.-G., Peng, X.-C. et al. (2022). Ferroptosis triggered by dihydroartemisinin facilitates chlorin e6 induced photodynamic therapy against lung cancer through inhibiting GPX4 and enhancing ROS. *Eur. J. Pharmacol.* 919: 174797.
- 4 Haraguchi, H. and Matsuura, H. (2003). Chemical speciation for metallomics. Presented at *Proceedings of International Symposium on Bio-Trace Elements 2002 (BITRE 2002)* Wako.
- 5 Haraguchi, H. (2004). Metallomics as integrated biometal science. *J. Anal. At. Spectrom.* 19: 5–14.
- 6 Williams, R.J.P. (2001). Chemical selection of elements by cells. *Coord. Chem. Rev.* 216–217: 583–595.
- 7 Lobinski, R., Becker, J.S., Haraguchi, H., and Sarkar, B. (2010). Metallomics: guidelines for terminology and critical evaluation of analytical chemistry approaches (IUPAC technical report). *Pure Appl. Chem.* 82: 493–504.
- 8 Li, Y.-F., Sun, H., Chen, C., and Chai, Z. (2016). *Metallomics*. Beijing: Science Press.
- 9 Mounicou, S., Szpunar, J., and Lobinski, R. (2009). Metallomics: the concept and methodology. *Chem. Soc. Rev.* 38: 1119–1138.
- 10 Li, Y.-F. and Sun, H. (2021). Metallomics in multidisciplinary research and the analytical advances. *At. Spectrosc.* 42: 227–230.
- 11 Baxter, I.R., Vitek, O., Lahner, B. et al. (2008). The leaf ionome as a multivariable system to detect a plant's physiological status. *Proc. Natl. Acad. Sci.* 105: 12081–12086.
- 12 Salt, D.E., Baxter, I., and Lahner, B. (2008). Ionomics and the study of the plant ionome. *Annu. Rev. Plant Biol.* 59: 709–733.
- 13 Zhang, Y., Xu, Y., and Zheng, L. (2020). Disease ionomics: understanding the role of ions in complex disease. *Int. J. Mol. Sci.* 21: 8646.
- 14 Zhou, Y., Li, H., and Sun, H. (2022). Metalloproteomics for biomedical research: methodology and applications. *Annu. Rev. Biochem.* 91: <https://doi.org/10.1146/annurev-biochem-040320-104628>.
- 15 Michalke, B. (2016). *Metallomics: Analytical Techniques and Speciation Methods*. Berlin: Wiley.
- 16 Chai, Z., Mao, X., Hu, Z. et al. (2002). Overview of the methodology of nuclear analytical techniques for speciation studies of trace elements in the biological and environmental sciences. *Anal. Bioanal. Chem.* 372: 407–411.

- 17 Maret, W. (2022). The quintessence of metallomics: a harbinger of a different life science based on the periodic table of the bioelements. *Metallomics*.
- 18 Li, Y.-F., Chen, C., Qu, Y. et al. (2008). Metallomics, elementomics, and analytical techniques. *Pure Appl. Chem.* 80: 2577–2594.
- 19 Xiong, Y., Ouyang, L., Liu, Y. et al. (2006). One of the most important parts for bio-elementomics: specific correlation study of bio-elements in a given tissue. *J. Chin. Mass Spectrom. Soc.* 27: 35–36.
- 20 Jakubowski, N. and Hieftje, G.M. (2008). The broadening scope of JAAS. *J. Anal. At. Spectrom.* 23: 13–14.
- 21 Liu, J., Peng, L., Wang, Q. et al. (2022). Simultaneous quantification of 70 elements in biofluids within 5 min using inductively coupled plasma mass spectrometry to reveal elementomic phenotypes of healthy Chinese adults. *Talanta* 250: 123720.
- 22 Chen, C., Chai, Z., and Gao, Y. (2010). *Nuclear Analytical Techniques for Metallomics and Metalloproteomics*. Cambridge: RSC publishing.
- 23 Banci, L. (2013). *Metallomics and the Cell*. Amsterdam: Springer Netherlands.
- 24 Maret, W. (2016). *Metallomics: A Primer of Integrated Biometal Science*. London: Imperial College Press.
- 25 Ogra, Y. and Hirata, T. (2017). *Metallomics: Recent Analytical Techniques and Applications*. Tokyo: Springer Japan.
- 26 Arruda, M.A.Z. (2018). *Metallomics: The Science of Biometals*. Cham: Springer.
- 27 Sablok, G. (2020). *Plant Metallomics and Functional Omics: A System-wide Perspective*. Berlin: Springer.
- 28 Sun, H. and Chai, Z.-F. (2010). Metallomics: An integrated science for metals in biology and medicine. *Annu. Rep. "A" (Inorg. Chem.)* 106: 20–38.
- 29 Benetti, F., Bregoli, L., Olivato, I., and Sabbioni, E. (2014). Effects of metal(loid)-based nanomaterials on essential element homeostasis: the central role of nanometallomics for nanotoxicology. *Metallomics* 6: 729–747.
- 30 Li, Y.-F., Gao, Y., Chai, Z., and Chen, C. (2014). Nanometallomics: an emerging field studying the biological effects of metal-related nanomaterials. *Metallomics* 6: 220–232.
- 31 Wang, L., Zhao, J., Cui, L. et al. (2021). Comparative nanometallomics as a new tool for nanosafety evaluation. *Metallomics* 13: mfab013.
- 32 López-Barea, J. and Gómez-Ariza, J.L. (2006). Environmental proteomics and metallomics. *Proteomics* 6: S51–S62.
- 33 Hu, L., He, B., and Jiang, G. (2016). *Metallomics* (ed. Y.-F. Li, H. Sun, C. Chen, and Z. Chai). Beijing: Science Press.
- 34 Chen, B., Hu, L., He, B. et al. (2020). Environmetallomics: systematically investigating metals in environmentally relevant media. *Trends Anal. Chem.* 126: 115875.
- 35 Li, X., Liu, T., Chang, C. et al. (2021). Analytical methodologies for agrometallomics: a critical review. *J. Agric. Food. Chem.* 69: 6100–6118.
- 36 Pan, M., Zang, Y., Zhou, X. et al. (2021). Inductively coupled plasma mass spectrometry for metrometallomics: the study of quantitative metalloproteins. *At. Spectrosc.* 42: 262–270.

- 37 Song, X., Li, H., Ma, C. et al. (2021). Clinimetallomics: arsenic speciation in urine of arsenism patients by HPLC-ICP-MS. *At. Spectrosc.* 42: 278–281.
- 38 Liang, Y., Liu, Y., Li, H. et al. (2021). Advances of synchrotron radiation-based radiometallomics for the study of uranium. *At. Spectrosc.* 42: 254–261.
- 39 Li, L., Yan, L., Sun, H. et al. (2021). Archaeometallomics as a tool for studying ancient ceramics. *At. Spectrosc.* 42: 247–253.
- 40 Li, Q., Cai, Z., Fang, Y., and Wang, Z. (2021). Matermetallomics: concept and analytical methodology. *At. Spectrosc.* 42: 238–246.
- 41 Chen, H. (2011). *Large Research Infrastructures Development in China: A Roadmap to 2050*. Berlin, Heidelberg: Springer.
- 42 Gao, J. (2021). *Physics and Design for Accelerators of High Energy Particle Colliders*. Shanghai: Shanghai Jiao Tong University Press.
- 43 Yuan, C.-Z. and Karliner, M. (2021). Cornucopia of antineutrons and hyperons from a super j/ψ factory for next-generation nuclear and particle physics high-precision experiments. *Phys. Rev. Lett.* 127: 012003.
- 44 Oda, H., Akiyama, M., Masuda, T., and Nakamura, T. (2007). Radiocarbon dating of an ancient Japanese document “minamoto no yoritomo sodehan migyosho” by accelerator mass spectrometry. *J. Radioanal. Nucl. Chem.* 272: 439–442.
- 45 Housley, R.A. (1990). Radiocarbon dating by accelerator mass spectrometry (AMS): an introduction. *Geol. Today* 6: 60–62.
- 46 Chai, Z. and Zhu, H. (ed.) (1994). *Introduction to Trace Element Chemistry*. Beijing: Atomic Energy Press.
- 47 Pol, A., Barends, T.R.M., Dietl, A. et al. (2014). Rare earth metals are essential for methanotrophic life in volcanic mudpots. *Environ. Microbiol.* 16: 255–264.
- 48 Lane, T.W. and Morel, F.M.M. (2000). A biological function for cadmium in marine diatoms. *Proc. Natl. Acad. Sci. U.S.A.* 97: 4627–4631.
- 49 King, A.H. (2019). Our elemental footprint. *Nat. Mater.* 18: 408–409.
- 50 Chen, C., Li, Y.-F., Qu, Y. et al. (2013). Advanced nuclear analytical and related techniques for the growing challenges in nanotoxicology. *Chem. Soc. Rev.* 42: 8266–8303.
- 51 Lin, X., Zhao, J., Zhang, W. et al. (2021). Towards screening the neurotoxicity of chemicals through feces after exposure to methylmercury or inorganic mercury in rats: a combined study using microbiome, metabolomics and metallomics. *J. Hazard Mater.* 409: 124923.
- 52 Fan, Y., Cui, L., Wang, L. et al. (2022). Large research infrastructure based spatial metallomics and single-cell/single-particle metallomics. *Chin. J. Inorg. Anal. Chem.* 12: <https://doi.org/10.3969/j.issn.2095-1035.2022.3904.3021>.
- 53 Zhao, Y., Chen, C., Feng, W. et al. (2022). Professor Zhifang Chai: scientific contributions and achievements. *Chin. Chem. Lett.* 33: 3297–3302.
- 54 Chang, P.-P., Zheng, L.-N., Wang, B. et al. (2022). ICP-MS-based methodology in metallomics: towards single particle analysis, single cell analysis, and spatial metallomics. *At. Spectrosc.* 43: <https://doi.org/10.46770/as.42022.46108>.
- 55 Grüner, F., Blumendorf, F., Schmutzler, O. et al. (2018). Localising functionalised gold-nanoparticles in murine spinal cords by X-ray fluorescence imaging and

- background-reduction through spatial filtering for human-sized objects. *Sci. Rep.* 8: 16561.
- 56** Wang, L., Yan, L., Liu, J. et al. (2018). Quantification of nanomaterial/nanomedicine trafficking in vivo. *Anal. Chem.* 90: 589–614.
- 57** Chaurand, P., Liu, W., Borschneck, D. et al. (2018). Multi-scale x-ray computed tomography to detect and localize metal-based nanomaterials in lung tissues of in vivo exposed mice. *Sci. Rep.* 8: 4408.

