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Metallomics Research — Good Luck on New Publication

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Abstract

The Japan Society for Biomedical Research on Trace Elements decided to publish the new journal "Metallomics Research" from October, 2021, instead of their previous journal "Biomedical Research on Trace Elements" (BRTE). On this occasion, the history of trace element study in Japan and the progress of metallomics as integrated biometal science proposed about 20 years ago are reviewed. In the latter part of this review, basic concepts of metallomics research are discussed in relation to homeostasis and all-present theory, and finally it is considered that metallomics research has a mission to contribute to our humans and nature through the SDGs (Sustainable Development Goals), mainly with focusing on health science and environmental/green science as multidisciplinary science.

Key words: metallomics, metals in biology, health science, homeostasis, multidisciplinary science, all-elements present theory

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1. Metals in biology

In 1969, the present author was employed as an assistant professor in the laboratory of Prof. Keiichiro Fuwa in the Department of Agricultural Chemistry, Faculty of Agriculture, the University of Tokyo. Prof. Fuwa had spent in the Medical School of Harvard University for 14 years, where he worked as the research staff with Prof. BL Vallee. Prof. Vallee was famous in the pioneer work of zinc physiology. In 1968, Prof. Fuwa came back to Japan, and he was responsible for the laboratory of Analytical Chemistry. There, he proposed to the laboratory members that "metals in biology" was the main research theme of his laboratory. "Metals in biology" was really new aspect to us, and gave great influences in our research life after that.

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2. Progress of analytical atomic spectrometry

In 1974, Prof. Fuwa also held his position as the Division Head of Chemistry and Physics in the National Institute for Environmental Studies which was just newly established, and I moved to the same institute. As well known, those days our country had serious environmental pollution problems such as Minamata disease and Itai-Itai (Auch-Auch) disease caused by toxic metals such as mercury and cadmium. However, it was not so easy to analyze mercury, cadmium and other toxic metals sensitively and precisely, and we had to start to develop sensitive analytical instruments. Those days, atomic absorption spectrometry (AAS) was the popular method for environmental analysis, but AAS was a tedious method for analyses of many elements in many samples, because AAS was the instrument for single element analysis. Then we tried to develop new analytical methods which allowed simultaneous multielement analysis using an inductively coupled argon plasma (ICP), "so-called" inductively coupled plasma atomic emission spectrometry (ICP-AES) and inductively coupled plasma mass spectrometry (ICP-MS). Both methods can analyze 40-50 elements simultaneously with the analytical sensitivity (detection limit) of ppb (10^{-9} g/ml) level for the former and ppt (10^{-12} g/l) level for the latter [1,2].

3. Japan Society for Biomedical Research on Trace Elements and Journal of "Biomedical Research on Trace Elements (BRTE)"

In 1984, the 1st Conference of International Society for Trace Element Research in Humans (ISTERH) was held by the effort of Dr. Prasad, Dr. Abdulla, Dr. Brewer, Dr. Fell, Dr. Parr, and Dr. Solomons in Palm Spring, California, USA. Prof. Issei Nomiyama (Jichi Medical University), who was one of participants from Japan in the 1st conference, invited the 2nd conference to Japan. Then, in 1989, the 2nd Conference (ISTERH) was held in Tokyo, under the chairmanship of Prof. Hiroshi Tomita (Nihon University). More than 1000 participants who were interested in trace element research related to medical and environmental sciences got-together in Tokyo from the world. After the conference the excellent proceedings over 500 pages was published by the edition of Prof. Tomita [3]. According to the proceedings, Prof. Prasado delivered the invited lecture entitled "Discovery of Human Zinc Deficiency and Marginal Deficiency of Zinc", and Prof. Tomita did "Zinc in Taste and Smell Disorders" [3]. In response to success of 2nd ISTERH, the Japanese scientists who participated the 2nd conference, decided to establish the Japan Society for Biomedical Research on Trace Elements in 1990. At the same time, the quarterly journal entitled "Biomedical Research on Trace Elements" (BRTE) was also launched by the Japan Society. The annual meetings of the society have been held every year around many places, and 31 volumes of BRTE have been published, where the original research papers and notes, reviews and other related information have been presented in each volume. As the result, the society has been playing important roles as the platform for scientific information and mutual exchange of biomedical research concerned with trace elements in Japan until now. Many medical doctors joined as the members of the society, and they had hot discussion in the meetings. Then we could learn many practical matter and knowledge concerned with medical and clinical fields. All articles in BRTE can be seen in the J-STAGE, and so the activities of the society are not commented any more.

Here I would like to introduce unforgettable memory that I got in the society meeting. I could not remember when, but I could not forget Prof. Nomiyama's report provided in the executive board meeting. One day he reported the results of application of scientific grant in the executive board meeting. He was enthusiastic to organize the big research group of trace element research as the national project under the support of big scientific grant from the government in the early 1990s, but he failed after application several times. Most clear reason why he could not succeed in getting such a grant, he said, was that the definition of trace elements and their biological significance were incomprehensible in comparison to vitamins and hormones. In the Evaluation Committee for Grant, he got many comments that the function of each vitamin or hormone was known clearly, while the biological functions of trace elements were not elucidated clearly. "What are trace elements and how much are they useful for life?" This Nomiyama's report shocked to me, but it became the origin to explore some understandable and clear term instead of trace element.

About 10 years later, I got the Grant-in-Aid for Specially Promotion Research with the program of "Creation of New Science "Metallomics" for 2004-2006 (3 years term). This was the kind of national research project. In this project, terminology of metallomics was approved in the Evaluation Committee for Grant. At this moment, the Prof. Nomiyama's report described above was remembered, although he already died.

4. Proposal of "Metallomics" and after that

In January, 2004, at last, the first paper entitled with "Metallomics as Integrated Biometal Science" was published in JAAS (Journal of Analytical Atomic Spectrometry) from the Royal Society of Chemistry [4]. Thus the year 2004 was a memorial year for "metallomics" in science. Since many papers in various journals have been published and the international or domestic meetings have been often held, we can get easily the information about progress of metallomics from many sources nowadays. Also, I published the review articles about metallomics in the journals [5.6], and Ogra and Hirata published an excellent book

[7]. Thus I hesitated to write the review which was asked from the editorial office. After significant consideration, however, I made up my mind to write the present review, by adding the brief explanation about the Japan Society of Biomedical Research on Trace Elements and their journal BRTE in Section 3.

In late1990s, proteomics was emphasized on an emerging scientific field after genomics. Omics-science such as genomics and proteomics were interested in interdisciplinary science to cell biology. Those days I was thinking the idea to take the position for metals in biology as a part of omics-science. One evening with drinking, I got inspiration of "metallomics" as the "metal-assisted biological function science" in early 2002. In 2002, fortunately, I had the chances to convey the idea "metallomics" in domestic seminar and international symposium. Then, actually the year of 2002 was the milestone for "metallomics".

In June, 2002, the present author gave the invited lecture in the Tokushima Seminar on Chemical Engineering held in Tokushima, Japan [8]. The title of the lecture in the seminar was "A Challenge to Pico-World and Metallomics: A New Frontier of Trace Element Chemistry" (in Japanese). In this seminar, I proposed the scientific term of "metallomics" for the first time. Since the Tokushima seminar was a memorial talk, the abstract of the presentation is cited below (translated). [8]

> *In recent years, the analytical detection sensitivities have been increasingly improved to pico (10^{-12}) gram in the absolute amount or sub-ppt (10^{-12} g/ml) level in the concentration, according to the development of ICP-MS. As a result, now we have a good chance to challenge the research on the pico-technology or pico-science, which may be called "Pico-World Science".*
>
> *Such a progress of analytical atomic spectrometry will lead to another interesting and important research on bio-trace elements in the biological systems including our "human beings" because all-elements including ultratrace elements might be contained in the biological systems. This concept is referred to as "Extended All Present Theory of the Elements". Furthermore, various trace elements play important roles in the biological systems, as metalloproteins and/or metalloenzymes. Then, now is the good time to challenge to trace element biochemistry to open our new scientific world "**metallomics**".*

The second chance was the International Symposium on Bio-Trace Elements 2002 (BITREL 2002) in autumn of the same year [9]. This symposium was held as the joint symposium of RIKEN and Yamanashi Institute of Environmental Sciences (YIES), for October 28-November 2, which was co-organized by Dr. Shuichi Enomoto in RIKEN and Dr. Yoshiyuki Seko in YIES. The present author delivered the invited lecture, entitled on "Trace Element Speciation for Metallomics". "Metallomics" was proposed as a new scientific term in English for the first time. As can be seen from the abstract in the Tokushima seminar [8], my first idea for metallomics came as the result of progress of analytical atomic spectrometry as well as the concept of the All Present Theory of the Elements derived from the idea for all elements analysis of all materials on earth. However, my idea was still under consideration at this moment. The followings are the abstract in the proceedings in BITREL 2002 [9].

> *In this paper, "metallomics" is newly proposed as a new scientific field in order to integrate the research fields related to bio-trace metals. Metallomics might be the scientific field of post-genomics and post-proteomics, where metal-containing compounds are defined as metallome, in a similar manner to genome in genomics and proteome in proteomics. Since the elucidation of the biological or physiological functions of metal-containing species in the biological systems is the main research target of metallomics, elemental speciation is important as one of analytical technologies to promote metallomics.*

In BITREL 2002, the distinguished scientists in the field of trace metal science were invited; they were Prof. Ryszard Lobinski (Warsaw University of Technology, Warsaw, Poland), Prof. Zhifang Chai (Institute of High Energy Physics, Chinese Academy of Science, Beijing, China), Prof. Wolfgang Maret (Harvard Medical School, USA; now Imperial College, London, UK), Prof. Bibudhendra Sarkar (University of Toronto, Ontario, Canada) and so forth.

The importance of speciation analysis (species analysis) of trace elements in the biological samples and biological systems was emphasized in the lecture, because trace elements (metals actually exist as the ionic forms in the biological systems) are contained in metalloproteins and/or metalloenzymes, and in particular trace elements play essential roles mostly as the active centers of metalloenzymes for biological and physiological functions. On the other hand, it is also known that metals and metalloids often cause seriously toxic or hazardous problems to humans and living organisms due to environmental pollution. These scientific fields including the functions of both essential and toxic trace metals have been generally called "trace element science", as will be discussed in Section 10. The new scientific term of "metallomics" proposed in two symposiums achieved great response as the hot topics on the science community of trace metal science.

During BITREL 2002, Prof. Lobinski recommended me to submit a paper about metallomics to Journal of Analytical Atomic Spectrometry (JAAS), published from the Royal Society of Chemistry, UK, because the journal was just planning to publish the special issue on "Metals in Biology". Then, in 2004, my paper entitled on "Metallomics as integrated biometal science" was published in JAAS, which was analytical chemistry- or atomic spectrometry-oriented journal. Since the following abstract of the paper in JAAS [4] was the first proposal of metallomics in the scientific journal and gave significant suggestion for future direction of metallomics research, the abstract of the article is cited below [4].

> *In this paper, "metallomics"is proposed as a new scientific field in order to integrate the research fields related to biometal. Metallomics should be a scientific field in symbiosis with genomics and proteomics, because syntheses and metabolic functions of genes, (DNA and RNA) and proteins cannot be performed without the aid of various metal ions and metalloenzymes. In metallomics, metalloproteins, metalloenzymes and other metal-containing biomolecules are defined as"metallomes", in a similar manner to genomes in genomics as well as proteomes in proteomics. Since the identification of metallomes and the elucidation of their biological or physiological functions in the biological systems are main research targets of metallomics, chemical speciation for specific identification of bioactive metallomes is one of the most important analytical technologies to establish as the integrated bio-metal science.*

(Note: In this abstract [4], "*metallomes*" was used as common noun, but it might be my mistake. It is better to use metallome as collective noun because a scientific term of "metallome" is now used for an entirety of bioactive metal and metalloid species.)

5. International Symposium on Metallomics (ISM)

Metallomics had been receiving great attention as the newly emerging scientific field after publication of the above paper in 2004. According to the recommendation of many scientists, the International Symposium on Metallomics 2007 (ISM 2007) was held in Nagoya for November 28-December 1, 2007, as the first symposium on metallomics, which was organized by Haraguchi, chairman as well as by Profs. Kazuo Suzuki, Hiromu Sakurai and Naoki Furuta, vice-chairmen. This symposium was supported by IUPAC (International Union of Pure and Applied Chemistry), Chemical Society of Japan, Nagoya City and other academic societies and companies. In this symposium, about 350 scientists participated and more than 250 lectures and posters were presented [10]. The Proceedings of ISM 2007 was also published as the special issue of Pure and Applied Chemistry from IUPAC in 2008 [11].

In the International Advisory Board meeting of ISM 2007, Haraguchi summarized that ISM 2007 was a successful symposium, and proposed that the symposium would be held regularly in every 2 years around the world, to promote metallomics as an emerging science field in future. This proposal was approved unanimously in the advisory board meeting.

After Nagoya, ISMs have been held at Cincinnati, USA, Munster, Germany, Oviedo, Spain, Beijing, China, Vienna, Austria,

Table 1. | The years, conference place and organizers of the International Symposium on Metallomics (ISM)

	Year	Place	Organizers
1	2007	Nagoya, Japan	H. Haraguchi
2	2009	Cincinnati, USA	J. Caruso, G. Hiefje
3	2011	Munster, Germany	U. Karst, M. Sperling
4	2013	Oviedo, Spain	A. Sanz-Medel
5	2015	Beijing, China	Z. Chai. X. Zhang
6	2017	Vienna, Austria	G. Köllensperger
7	2019	Warsaw, Poland	R. Lobinski. L. Ruzik
8	2021*	Kanazawa, Japan (*scheduled*)	Y. Ogra

* The 8th ISM is scheduled during July 11-14, 2022 in Kanazawa, Japan.

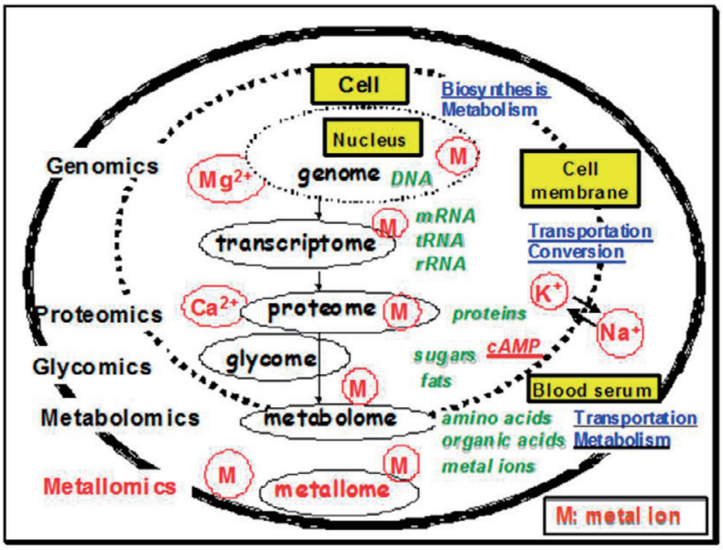

Fig. 1. Simplified model of biological system, showing the relationship of *omics*-science [4,18]. The continuous line outside indicates biological organ and/or whole body, while the dotted line inside does each biological cell.

and Warsaw, Poland. The 8th ISM is scheduled at Kanazawa, Japan, in 2022. All the past International Seminars are listed in **Table 1**. By the way, the summary reports of the ISMs held above have been presented on Metallomics [12-14]. It was sad that Prof. JA Caruso who organized the second ISM and the first editor-in-chief of Metallomics journal passed away in November, 2015.

In addition, in Japan the Metallomics Research Forum has been held every even-number year since 2008 as the domestic meeting. Some selected papers presented in the Metallomics Research Forum were reported as the themed issue in journal Metallomics [15,16].

6. Publication of the journal "METALLOMICS" from RCS

It was a surprising and great news that the academic journal of "Metallomics-Integrated Bimetal Science (now "**Metallomics**") was launched in January, 2009, from RSC [17]. Until now 13 volumes of Metallomics have been distributed, in which many excellent research and review papers have been presented. It should be highly evaluated that the publication of Metallomics has prompted progress of metallomics researches as multidisciplinary science.

In 2021, the publisher of Metallomics was transferred to the Oxford University Press from RCS.

7. "Metallomics Research"; New journal from the Japan Society for Biomedical Research on Trace Elements

The Japan Society for Biomedical Research on Trace Elements decided to change the old journal of "Biomedical Research on Trace Elements (BRTE)" to a new journal "**Metallomics Research**". Old journal was of a mixed-language (Japanese and English) style, including the information of society events. New journal, which is an international, open access, peer-reviewed journal including research papers, notes and reviews written only in English, will be launched from October, 2021. Prof. Yasumitsu Ogra (Chiba University), the present president of the society, and Prof. Masahiro Kawahara (Musashino University), the present Journal Editor-in-Chief, have made up their mind to accelerate research activities in biometals not only in Japan as well as in the world. Then, they asked me to write a review article about the history, activities, international symposium, and the perspectives of metallomics, maybe, because I coined the concept of "metallomics", as mentioned before. First of all, it is hoped that **Metallomics Research** will play a role of the platform to promote biomedical science developed by the Japan Society for Biomedical Research on Trace Elements since 1990.

8. A simplified model of the biological system

Fig. 1 is a schematic diagram of simplified model of the biological system [4,18], which is illustrated in order to get an insight into the scientific aspects of metallomics. In the figure, the dotted line (inside) and continuous line (outside) indicate a biological cell unit and an organ/whole body, respectively. Biological fluids (e.g., blood serum) are circulating between cell membrane and organ. Some biological species and their functions in the biological system are also indicated in **Fig. 1**. As is known, biological cells containing various microorgans (organelles) are composed of numerous internal structures, so that the cell structures in

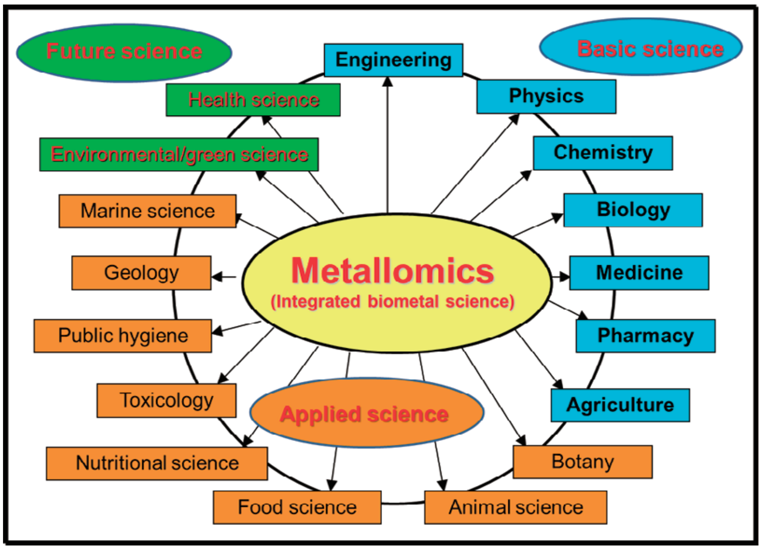

Fig. 2. Correlation map of metallomics as multidisciplinary science consisted of various scientific fields [23].

the biological system (either in prokaryotes or in eukaryotes) are complicated assemblies, but their functions are well organized.

On the left hand side of the simplified model shown in **Fig. 1**, the omics-science such as genomics, proteomics and metabollomics are depicted along with metallomics to indicate their research areas in the biological system. Such a simplified model also helps to understand the relationship of metallomics with genomics, proteomics and other omics-sciences (for example, metabolomics and glycomics). As is well known, genomics deals with the genetic information of DNAs and RNAs encoded as the sequences of nucleic bases. The entirety of DNAs and RNAs are generally called "genome", which preserve the information to synthesize proteins, to control protein structures and to regulate the protein functions. A large number of proteins are distributed inside and outside the cells as well as in membranes, and they work as enzymes for synthesis and metabolism of various biological substances inside the cells. It is well known, for example, that DNAs and RNAs are synthesized by DNA polymerase and RNA polymerase, which are zinc enzymes. Since various proteins play essential roles to regulate and maintain the life system through biosyntheses and metabolisms, proteomics as protein science has been also receiving great attention as post-genome science linked with genomics.

In addition, many biological substances as well as metal ions are transported inside and outside the cells through membranes. In general, since material conversion is actively occurring inside cells and also in cell membranes, such scientific field for material conversion and transportation/exclusion processes through the cells are now called "metabolomics" [19]. Biological substances such as amino acids, organic acids and metal-binding biomaterials produced in metabolism are defined "metabolome" in a similar manner to genome in genomics.

As can be seen from **Fig. 1**, metal ions are ubiquitously distributed inside and outside cells to assist the physiological/biological functions of genome, transcriptome, proteome, glycome and metabolome, maybe, with strong interactions and/or weak interactions. Here, strong interactions mean covalent bond formations between metal ions and biomaterials such as metalloproteins, while weak interactions do labile bond formations or ion-pair formations like in the case of Mg ion and phosphate groups in DNA or in the case of Ca ion and carboxyl groups in proteins. It is desirable to refer to the excellent literatures [4,20-22] in order to understand the functions of metal ions in the biological systems.

9. Multidisciplinary science for metallomics research

Metallomics is integrated biometal science, and so a variety of science fields are concerned with each other. In another words, metallomics is really multidisciplinary and/or interdisciplinary science. These situations are illustrated in **Fig.2**, where metallomics is illustrated in the center. Health science and environmental/green science should be performed as the main research purposes in metallomics, and so they are shown as future science in **Fig. 2**. Many individual academic fields as basic science and applied science are arranged around metallomics, as can be seen in **Fig. 2**. Although the academic fields in **Fig. 2** are conveniently arranged, biometal research is carried out based on biochemical and/or biological/physiological science. Then it should be stressed here that all these science fields are cooperated as multidisciplinary research.

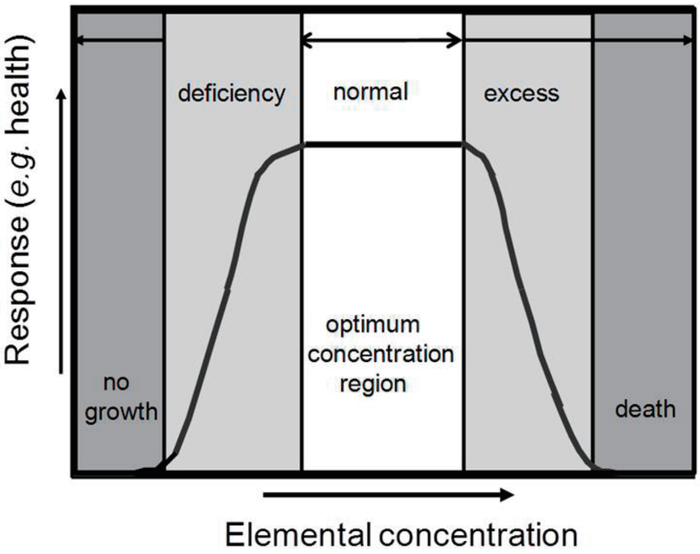

Fig. 3. The dose response curve of biological system [24].
The figure is illustrated as the response curve of elemental concentration *versus* response (*e.g.*, health condition). The optimum concentration corresponds to the homeostasis level.

10. Essentiality and toxicity of the elements

In analytical chemistry, the elements in the concentration ranges of 100-1%, 1-0.01%, 0.01-0.0001% and below 0.0001% are defined as major, minor, trace and ultratrace elements, respectively. Since 0.0001% is equal to 1 ppm (part per million), trace elements are corresponding to those in the concentration range of 1-100 ppm. It is noted here that, in medical and biological sciences, ultratrace elements are usually not distinguished from trace elements, and thus, the elements whose concentrations less than 100 ppm are called trace elements hereafter.

In trace element chemistry, the terms of essential elements and toxic (or hazardous) elements are often used, when the biological effects of the elements are discussed. In such cases, the biological effects of the elements on the biological systems (humans, animals, plants and microorganisms) are generally explained as the response of biological systems to the dose of the elements (generally through nutrients, foods, chemicals and so forth). The dose response curve is schematically shown in **Fig. 3**, where the concentration of the element as a dose is taken on the horizontal axis and the biological response is taken on the vertical axis. In the figure, the health condition is taken as the marker of the dose response of the element. As the biological response except for health, body height or weight, growth rate of microorganisms, plant growth, other medical indices and so forth are considered in the response curve, where the upper position of the curve indicates the better health condition (more normal). It is well known that the response curve in the biological systems generally shows a trapezoid-shaped curve, as is seen in **Fig. 3**.

In such a biological response curve in the trapezoid-shape, three regions such as deficiency region, normal region and excess region are usually observed, when the element concentration is increased from the lower to the higher (from the left to the right in **Fig. 3**). The normal region (the central region) is called the optimum concentration region, where our health is physiologically or functionally maintained to be normal or optimum, without any disease or allergic symptoms. This region is corresponding to the homeostasis level in biology. In the future research in health science, it is desirable that the homeostasis levels of various metals are evaluated in the biological systems (body, organ, cell, blood, and microorgan) for optimum regulation.

The deficiency region is lower in the concentration than the normal region, where some diseases due to deficiency are often caused because of the lack of specific nutrient supply, for example, like iron deficiency and vitamin deficiency. That is, when the nutrient supply becomes too smaller, various diseases or less growth are caused seriously. In the extreme case, for example, microorganism such as Escherichia coli (*E.coli*) does not grow, if the zinc concentration is below 1 ppb.

On other hand, the higher dose than the homeostasis level is called the excess region. In this region the excess amounts of the elements cause serious damages or dysfunctions to the biological systems, and such effects become fatal in the extreme cases. The typical examples are the environmental issues where serious adverse effects are caused by the environmental pollution due to toxic elements or hazardous chemicals. It should be carefully noticed that any element causes some toxic effects on the biological systems due to over-dose of nutrients (elements), as in the right-hand side of **Fig. 3**. If an element causes some adverse effect or disease due to the smaller amount of dose, that element is called highly toxic element. It should be also noticed that acute toxicity or chronic toxicity are often observed, depending on the elements or chemicals.

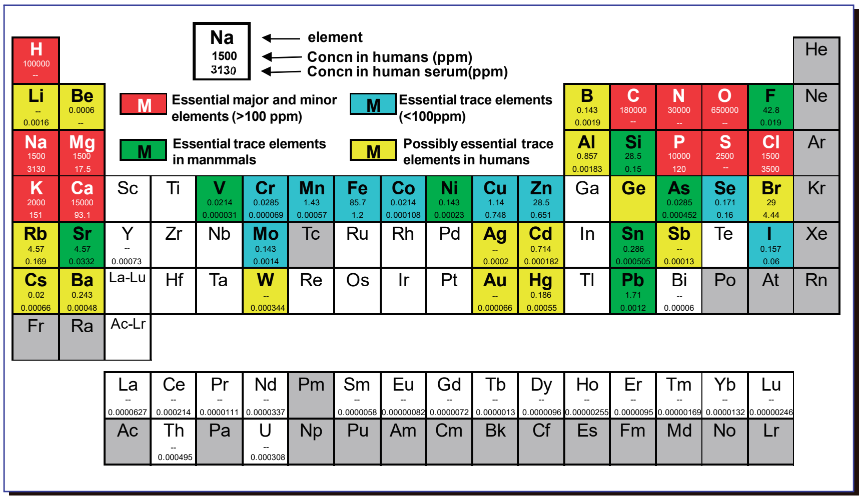

Fig. 4. Periodic table, which shows essential major and minor elements, essential trace elements and possibly essential trace elements in humans and animals.

According to definition of essential element, there are two types of essential elements. First, when the element is found in bioactive molecules such as Fe in hemoglobin, Zn in carboxypeptidase, and Se in glutathione peroxidase, Fe, Zn and Se are of course essential elements. Second, when the deficiency observed as physiological dysfunctions or abnormal diseases is recovered to the normal condition by adding dietary supplement containing a specific element, the element contained in supplement is considered as essential element.

Essential elements known in humans and mammals are summarized in the periodic table shown in **Fig. 4**. It can be seen in **Fig.4** that not only trace elements but also major and minor elements recognize as essential element in the biological systems. Essential trace elements should be elucidated by examining the response curves shown in **Fig. 3**. On the other hand, major and minor elements mainly consist of body structures of humans and mammals. In this sense, major and minor elements are indispensable, i.e., essential, in humans and animals. The situations are the same as plants and other biological systems.

According to **Fig. 4**, 11 elements (H, C, N, O, Na, Mg, P, S, Cl, K, Ca) are essential major and minor elements, which consist of whole body structures of the living organisms (biological systems) on earth. It is known that 8 elements (Cr, Mn, Fe, Co, Cu, Zn, Se, Mo, I) are essential trace elements known for humans, and 7 elements (F, Si, V, Ni, As, Sr, Sn, Pb) are essential trace elements proved for experimental mammals. It is interesting that the elements shown in yellow color boxes in **Fig. 4** are appreciated as possibly essential trace elements, among which Cd and Hg usually known as toxic or hazardous elements are included. One possibility is that their deficiencies or homeostasis levels have not been examined yet. Therefore, since possible essentialities of such elements have not been elucidated so far, further extensive research on their essentiality and physiological functions as biological trace elements may be required in the future.

As for the interpretation of essential and non-essential elements, Maret published the interesting article considering essential and non-essential elements in the biological periodic table [23]. His consideration is very similar to that discussed in this Section 10. The abstract in his article is cited below, as reference.

> *A significant number of chemical elements are either essential for life with known functions, or present in organisms with poorly defined functional outcomes. We do not know all the essential elements with certainty and we know even less about the functions of apparently non-essential elements. In this article, I discuss a basis for a biological periodic system of the elements and that biochemistry should include the elements that are traditionally part of inorganic chemistry and not only those that are in the purview of organic chemistry. A biological periodic system of the elements needs to specify what "essential" means and to which biological species it refers. It represents a snapshot of our present knowledge and is expected to undergo further modifications in the future. An integrated approach of biometal sciences called metallomics is required to understand the interactions of metal ions, the biological functions that their chemical structures acquire in the biological system, and how their usage is fine-tuned in biological species and in populations of species with genetic variations.*

11. Extended All-Elements Present Theory

In 1936, I. Noddack published the article entitled "Concerning the ubiquitous nature of the chemical elements" (the original title in Germany was "Über die Allgegenwart der chemischen Elemente") in ANGEWANDTE CHEMIE and suggested that "all elements in the periodic table supposed to be present in all rocks and minerals on earth" [24]. Prof. P. Kuroda supported the Noddack's idea (hypothesis) of ubiquitous presence of all elements in geological samples in his book "The Origin of the Chemical Elements and the Okhlo Phenomenon", published in 1982 [25], and he named the Noddack's concept "the All-Present Theory of the Elements".

In 1930s, the number of the elements detected in minerals were limited because the analytical methods available in those days, such as flame emission spectrometry, arc/spark emission spectrometry, electrochemical methods and so forth, were not sensitive enough to detect the low-abundant elements. Therefore, many scientists thought that the elements whose concentrations were unknown were not contained in the samples of interest. Nevertheless, Noddack believed that the existence of all elements in all geochemical samples might be proved, when the sensitive analytical techniques for trace analysis would be advanced in the future.

These days, according to great progress in analytical methodology, as mentioned earlier, almost all elements are able to be determined or detected not only in geochemical samples, but also in the biological and environmental samples. Since 1990, thus, the Haraguchi's research group in Nagoya University challenged all-elements analyses of various samples collected from the atmosphere, lithosphere, hydrosphere, biosphere, and urbanosphere (urban area); for example, they were airborne particulate matter, rocks, seawater and lake/river water, biological samples from humans and plants, and bottom/fly ashes collected from the waste incinerators [1,4,8,22]. Based on the experimental results, Haraguchi proposed a new concept of "the Extended All-Present Theory of the Elements" [1], as summarized below;

> *The elements contained in rocks and minerals are dissolved into water because of the weathering processes on earth, and plants growing in soil absorb the elements dissolved in water for nutrition, and then animals ingest plants for food, and humans drink water and ingest plants and animals as food because humans are at the top of food chain. Consequently, it is obvious to consider that plants and animals, even their organs and blood, contain all elements through the elemental cycles on earth. In another words, the All-Present Theory of the Element is true not only for rocks and minerals, but also for all materials including all biological systems on earth. This concept indicates that all elements in the periodic table are ubiquitously present even in all biological systems, such as animals, plants, and microorganisms as well as humans.*

Haraguchi is further thinking that the final goal of the All-Elements Present Theory is to prove the existence of all elements in single biological cells. This concept, that is, "the presence of all elements in single biological cell" is called "cell microcosm" [4]. If cell microcosm is scientifically elucidated for the living biological cells, such knowledge may provide great influence to the study on chemical revolution in whole universe including earth. This is the dream of the present author.

All elements analysis of salmon egg cells was challenged in order to examine the concept of cell microcosm, *i.e.*, all-elements presence in single biological cell. The analytical results are not shown in this article, but they can be seen in the references [22]. In the experiment, natural/artificial radioactive elements and rare gas elements were not measured because the specific experimental facilities for protection from harmful radioactivity were required for analyses of radioactive elements and the specific gas sampling systems as well as the skillful gas treatment techniques were necessary in rare gas analysis. As a result, 78 elements in the periodic table were the target of all-elements analysis in the standard laboratory.

The analytical results for 72 elements were experimentally obtained, where the metallic and metalloid elements were measured by ICP-AES and low resolution- ICP-QMS, and nonmetallic elements such as H, C, N, and O were determined by the conventional elemental analysis method. Finally, 65 elements among 78 could be determined and other 7 elements (Li, F, Zr, Nb, Hf, Ir, Bi) were just detected because of their low abundances in salmon egg cell [22]. Rhodium, Te, Ta and Re were not able to be determined or detected at this moment, maybe because of their extremely low concentrations in salmon egg cells. However, these elements except for F were detected by HR (high resolution)-ICP-MS in the recent experiments.

Many interesting facts can be found from the analytical results. For example, Fe, Zn, Cu, Co, Mn, Se and P provided the bio-accumulation factors larger than 10,000 [22], which indicate that these elements in salmon egg cell were enriched by 10,000-fold compared to those in seawater.

12. Research trends and subjects of metallomics

Finally research trends, research subjects and perspective of metallomics should be reviewed in this manuscript. However, such works are beyond the limit of capacity and ability of the present author. Then, the following two tables are shown with small comments here.

Table 2 is the top-20 ranked articles in the literatures, in which metallomics is used as the keyword. This table is summarized by referring to "current contents connect" in the Web of Science from Thomson Reuters. The original article of metallomics published in 2004 is still ranked at No.6. This year is the beginning of metallomics. As a whole, it seems that the researches listed in the ranking in **Table 2** reflect the present research trends. The largest interest is drug design and chemotherapy, where the compounds of ruthenium, platinum, copper and other metals are the targets in anti-cancer drugs. The research concerned with the role of metal dyshomeostasis in Alzheimer's disease may be interesting, but difficult research problems must be solved. The work in terms of zinc transporters by Fukada and Kambe is ranked at No.18, which is highly appreciated, and it is expected to be developed furthermore in the future. Anyway, it is recommended to read all the articles listed in **Table 2**, which are at the forefront of metallomics research.

Table 3 is the research subjects considered for metallomics research. Although the different research subjects were listed in the original paper [4], the list shown **Table 3** is corrected this time, because a variety of advanced research works/results have been achieved along with progress of analytical technologies after about 20 years since 2002. However, this list was made for personal use. It is desired to develop a list of research subjects especially for biomedical science as the recommended or approved version by the society for innovation in metallomics research.

Finally, the books published so far are listed as reference [7,27-29].

13. Summary

On the occasion of publication of a new journal Metallomics Research, the history of the Japan Society of for Biomedical Research on Trace Elements and its journal Biomedical Research on Trace Elements (BRTE) were looked back in order to consider publication program in the society. Since metallomics is relatively new science field, the background of proposal, international symposiums, journal publication Metallomics from RSC (presently Oxford University Press), and achievement as science were also reviewed as reference. In the future, it is hoped that metallomics will be developed as the multidiciplinary science focusing around health science and environmental science, and it is expected that new journal Metallomics Research will play an important role as the international version.

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Table 2. | The Top-20 ranked articles in the literatures, in which *metallomics* is used as a key word.

	Authors and titles of articles	Times of citation[a)]
1	Levina A, Mitra A, Lay, PA: Recent developments in ruthenium anticancer drugs. METALLOMICS 1: 458-470, 2009.	464
2	Todd RC, Lippard SJ: Inhibition of transcription by platinum antitumor compounds. METALLOMICS 1: 280-291, 2009.	366
3	Szpunar J: Advances in analytical methodology for bioinorganic speciation analysis: metallomics, metalloproteomics and heteroatom-tagged proteomics and metabolomics. Analyst 130: 442-465, 2005.	331
4	Roman M, Jitaru P, Barbante C: Selenium biochemistry and its role for human health. METALLOMICS 6: 25-54, 2014.	321
5	Berners-Price SJ, Filipovska A: Gold compounds as therapeutic agents for human diseases. METALLOMICS 3: 863-873, 2011.	312
6	Haraguchi H: Metallomics as integrated biometal science. Journal of Analytical Atomic Spectrometry 19: 5-14, 2004.	299
7	Colvin RA, Holmes WR, Fontaine CP, Maret W: Cytosolic zinc buffering and muffling: Their role in intracellular zinc homeostasis. METALLOMICS 2: 306-317, 2010.	282
8	Khan MAK, Wang FY: MERCURY-SELENIUM COMPOUNDS AND THEIR TOXICOLOGICAL SIGNIFICANCE: TOWARD A MOLECULAR UNDERSTANDING OF THE MERCURY-SELENIUM ANTAGONISM. EMVIRONMENTAL TOXICOGY AND CHEMISRY 28: 1567-1577, 2009.	276
9	Denoyer D, Masaldan S, Fontaine SL, Cater MA: Targeting copper in cancer therapy: 'Copper That Cancer'. METALLOMICS 7: 1459-1476, 2015.	272
10	Arita A. Costa M: Epigenetics in metal carcinogenesis: nickel, arsenic, chromium and cadmium. METALLOMICS 1: 222-228, 2009.	252
11	Kell DB, Pretorius E: Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. METALLOMICS 6: 748-773, 2014.	248
12	Mounicou S, Szpunar J, Lobinski R: Metallomics: the concept and methodology. CHEMICAL SOCIETY REVIER 38: 1119-1138, 2009.	243
13	Gautier A, Cisnetti F: Advances in metal-carbene complexes as potent anti-cancer agents. METALLOMICS 4: 23-32, 2012.	228
14	Bonda DJ, Lee HG, Jeffrey A Blair JA, Zhu XW, Perry G, Smith MA: Role of metal dyshomeostasis in Alzheimer's disease. METALLOMICS 3: 267-270, 2011.	220
15	Lobinski R, Moulin C, Ortega R: Imaging and speciation of trace elements in biological environment. BIOCHEMIE 88: 1591-1604, 2006.	199
16	Dupont CL, Grass G, Rensing C: Copper toxicity and the origin of bacterial resistance-new insights and applications. METALLOMICS 3: 1109-1118, 2011.	183
17	Raliya R, Nair R, Chavalmane S, Wanga WN, Biswas P: Mechanistic evaluation of translocation and physiological impact of titanium dioxide and zinc oxide nanoparticles on the tomato (Solanum lycopersicum L.) plant. METALLOMICS 7: 1584-1594, 2015.	180
18	Fukada T, Kambe T: Molecular and genetic features of zinc transporters in physiology and pathogenesis. METALLOMICS 3: 662-674, 2011.	177
19	Duncan C, White AR: Copper complexes as therapeutic agents. METALLOMICS 4:127-138, 2012.	177
20	Darrah TH, Prutsman-Pfeiffer JJ, Poreda RJ, Campbell ME, Hauschka PV, Hannigan RE: Incorporation of excess gadolinium into human bone from medical contrast agents. METALLOMICS 1: 479-488, 2009.	171

a) Times of citation were referred to “current contents connect” in the Web of Science of Thomson Reuters on August 25, 2021.

Table 3. | Research subjects in metallomics.

1)	Homeostasis study of the elements in the biological fluids, cell, organs etc.
2)	Search and identification of metalloproteins and metalloenzymes
3)	Bioimaging research for spatial distributions of metals
4)	Correlation of structures and functions of metallome (metal-binding molecules)
5)	Elucidation of reaction mechanisms of metalloenzymes
6)	Metabolisms of metal-containing biomolecules (metabolome and metabolites)
7)	Medical diagnosis of health and disease related to metallome
8)	Design of inorganic drugs for chemotherapy
9)	Toxicology and environmental science
10)	Chemical evolution of the living systems and organisms on earth (universe)

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