Brazilian Journal of Analytical Chemistry
2023, Volume 10, Issue 41, pp 9-11
doi: 10.30744/brjac.2179-3425.letter-imachado.N41

BrJAC

LETTER

Metallomics as an Essential Analytical Tool for the Development of Potential Metallodrugs

Ignacio Machado

Associate Professor, BIOESP Group, Analytical Chemistry, Faculty of Chemistry, Universidad de la República, Montevideo, Uruguay

Metallomics is an emerging area of the omics disciplines that has grown enormously since its conception as an academic discipline in 2004. This discipline integrates research related to biometals, along with other disciplines such as genomics, proteomics, metabolomics, and bioinorganic chemistry. It is defined as the study of the metallome, the interactions and functional connections of metal ions or species with genes, proteins, metabolites, and other biomolecules in biological systems. The study of the metallome of a species can provide information on the distribution of an element between cellular compartments, on the coordination environment in which a biomolecule is incorporated, or on the concentration of individual metal species present. In this regard, it plays a very important role in providing integrated information that connects metallomics with other omics disciplines.[1,2]

The term 'metallomics' was pronounced for the first time in June 2002 during the Tokushima Seminar on Chemical Engineering held in Tokushima, Japan, where the development of this new omics discipline was suggested, which was closely influenced by the progress of Analytical Atomic Spectrometry, in particular by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) and Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES). Since the mid-1970s, ICP-MS and ICP-AES techniques have been positioned as highly sensitive analytical tools with excellent possibilities for simultaneous quantification of multiple elements. Nowadays, it is possible to carry out analyses of basically all the elements in any type of sample using one of these two techniques. Likewise, the use of several other techniques for metallomic studies has been reported, such as Electrothermal Atomic Absorption Spectrometry (ETAAS), Microwave Plasma Atomic Emission Spectrometry (MP-AES), Laser Induced Plasma Spectroscopy (LIBS), and Energy Dispersive X-Ray Fluorescence Spectrometry (EDXRF), among others.[2]

A very useful bioanalytical study, within the field of metallomics, is the cellular uptake assay of potential metallodrugs. Using an adequate analytical technique, the metallic center of a given metallodrug can be monitored, and thus the fraction capable of entering a certain type of cell can be evaluated. Likewise, the distribution at the subcellular level and the association of the studied metallodrug with biomacromolecules of interest may be studied. In this context, our research group has been working on the optimization and validation of different bioanalytical methods for monitoring potential metallodrugs with activity against *Trypanosoma cruzi*, a protozoan parasite that causes Chagas disease, which is a pressing health problem in high-poverty areas of Latin America.[3]

A large number of metallic compounds with anti-*Trypanosoma cruzi* activity have been synthesized by our group, using as a strategy the coordination of metal ions or organometallic centers of pharmacological importance with bioactive organic ligands that have proven activity against *Trypanosoma cruzi*. Binding to metal can modify properties such as the solubility, lipophilicity, stability, and electronic and transport properties of the organic ligand, generating compounds that may be more active and/or less toxic. These metallic compounds can act by affecting two or more targets in the parasite: the ligand itself and others

Cite: Machado, I. Metallomics as an Essential Analytical Tool for the Development of Potential Metallodrugs. *Braz. J. Anal. Chem.* 2023, *10* (41), pp 9-11. http://dx.doi.org/10.30744/brjac.2179-3425.letter-imachado.N41

resulting from the presence of the metal. The biological properties of the metal–bioactive ligand compound will depend on the nature of the metallic center and the bioactive ligand, the presence of other ligands, and, fundamentally, its physicochemical-structural properties. In this regard, our group has focused its attention on the rational design of antiparasitic metallic compounds based on the relationships between chemical structure, physicochemical properties, and biological activity. This research line has led to important contributions that have been transferred to the scientific field, showing the vital importance of cellular uptake metallomic studies to understand the fate of potential metallodrugs and elucidate targets and mechanisms of action.

In this context, the potential as an antitrypanosomal agent of a new rhenium(I) tricarbonyl compound with the formula *fac*-[Re(I)$(CO)_3$(tmp)(CTZ)](PF_6), where CTZ = clotrimazole and tmp = 3,4,7,8-tetramethyl-1,10-phenanthroline, was recently evaluated. It showed very good activity against the epimastigote form of *Trypanosoma cruzi*, with IC_{50} values (half maximal inhibitory concentration) in the low micromolar range. For this task, a new bioanalytical method based on the MP-AES technique was developed and validated.[3] This technique has reemerged in the last few years with several improvements and can be considered as a good strategy for the determination of highly refractory elements such as rhenium. The method was applied to the determination of the percentage of rhenium taken up by the parasites and the association of the compound with the main biomacromolecules: soluble proteins, insoluble fraction, DNA, and RNA. The results of the metallomic study showed a low percentage of total rhenium taken up by the parasites, around 1%, and a preferential accumulation in the soluble protein fraction, around 83%. Also, the low localization of the compound in the DNA and RNA fractions, less than 1%, made it possible to discard these biomolecules as the main targets of action. The developed method turned out to be an economical and efficient alternative for metallomic studies of potential rhenium metallodrugs, applied for the first time for the analysis of this particular element.[3] In order to deepen in the localization of the compound taken up in the whole parasite, confocal Raman microscopy was performed.[4] However, the main bands of the rhenium(I) tricarbonyl compound showed a strong overlap with signals coming from lipids, proteins, and DNA from the parasite, and due to the low concentration assayed, signals associated with ν(CO) could not be detected. Notwithstanding that, the overlap found by confocal Raman spectroscopy gave us a clue to the actual location of the compound inside the parasite, constituting an interesting indirect metallomic tool.[4]

Similar bulk studies were previously carried out by our research group using the ETAAS technique. For this task, novel bioanalytical methods were developed and validated, which were successfully applied to study the cellular uptake of potential palladium, platinum, and vanadium metallodrugs against *Trypanosoma cruzi*.[5,6]

This example of interdisciplinary work highlights the importance of developing and validating bioanalytical methods such as metallomic strategies to carry out cellular uptake studies, in order to assess the fate and possible targets and mechanisms of action of potential metallodrugs. Likewise, they promote the key role of Bioanalytical Chemistry in supporting Medicinal Inorganic Chemistry during the development of new potential metallodrugs, in the search for answers to important Public Health issues.

REFERENCES

(1) Haraguchi, H. Metallomics as integrated biometal science. *J. Anal. At. Spectrom*. **2004**, *19*, 5–14. https://doi.org/10.1039/B308213J

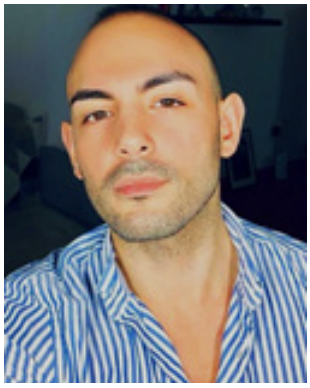
(2) Arruda, M. A. Z. (Ed). *Metallomics. The Science of Biometals*. Springer, Cham, 2018. https://doi.org/10.1007/978-3-319-90143-5

(3) Soba, M.; Scalese, G.; Pérez-Díaz, L.; Gambino, D.; Machado, I. Application of microwave plasma atomic emission spectrometry in bioanalytical chemistry of bioactive rhenium compounds. *Talanta* **2022**, *244*, 123413. https://doi.org/10.1016/j.talanta.2022.123413

(4) Soba, M.; Scalese, G.; Casuriaga, F.; Pérez, N.; Veiga, N.; Echeverría, G. A.; Piro, O. E.; Faccio, R.; Pérez-Díaz, L.; Gasser, G.; Machado, I.; Gambino, D. *Dalton Trans*. **2023**, *52*, 1623–1641. https://doi.org/10.1039/d2dt03869b

(5) Mosquillo, F.; Bilbao, L.; Hernández, F.; Machado, I.; Gambino, D.; Garat, B.; Pérez-Díaz, L. Effect of a new anti-*T. cruzi* metallic compound based on palladium. *Biometals* **2018**, *31*, 961–974. https://doi.org/10.1007/s10534-018-0140-4

(6) Scalese, G.; Machado, I.; Salinas, G.; Pérez-Díaz, L.; Gambino, D. Heteroleptic oxidovanadium(V) complexes with activity against infective and non-infective stages of *Trypanosoma cruzi*. *Molecules* **2021**, *26*, 5375. https://doi.org/10.3390/molecules26175375



Ignacio Machado is Associate Professor of Analytical Chemistry at the Faculty of Chemistry, Universidad de la República, Montevideo, Uruguay. He works mainly on Atomic Spectrometry and Mass Spectrometry, focused on Bioanalytical Chemistry. He was a postdoc researcher at the Department of Trace Element Analysis, Institute of Analytical Chemistry of the ASCR, Prague, Czech Republic in 2017. He has been a member of the Academic Assembly of Faculty of Chemistry, Universidad de la República since 2018 and the International Medical Geology Association (IMGA) since 2019. He has been researcher of the National System of Researchers (SNI, Uruguay) since 2016 and of the Basic Sciences Development Program – Chemistry Area (PEDECIBA - Química, Uruguay) since 2017. He is responsible for the BIOESP Group.