

Twenty Years of Metallomics and Metalloproteomics: From Inorganic Chemical Biology to Drug Development against Emerging Infectious Diseases

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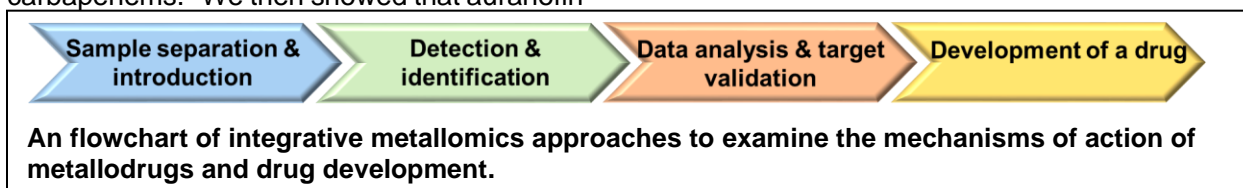
Metal-(metallo)drug-protein interactions play a crucial role for metals in life processes. It is important to identify metal-protein interactions at a proteome-wide scale which are difficult due to diversity of metal-protein interactions.^{1,2} We have integrated metallomics with metabolomics, trans-cryptomics and deep learning (DL) to examine multiple cellular changes to the numerous intracellular process affected³ and to quantify the metals for rapid metallome/ proteome-wide profiling of metal-binding proteins.

Based on our integrative metallomic/metalloproteomic approach, we have found that metallo-agents (e.g., Bi(III) and Au(I)) interfere with Zn(II) biochemistry in microbials, and propose to use Bi(III) complexes to inhibit Zn(II) enzymes in superbugs (metallo- β -lactamases (MBLs)) and coronaviruses.⁴ We show that colloidal bismuth subcitrate (CBS), and related Bi(III) complexes irreversibly inhibit different types of MBLs and have demonstrated a high potential of Bi(III) compounds as the first broad-spectrum MBL inhibitors to treat MBL producing bacterial infection in combined use with existing carbapenems.⁵ We then showed that auranofin

serves as a dual inhibitor to resensitize carbapenem- and colistin-resistant bacteria to antibiotics.⁶ We further expand repurposing metallodrugs in combination with different families of antibiotics can synergistically eliminate multidrug-resistant *P. aeruginosa* by targeting iron homeostasis.

We recently have demonstrated that Bi(III) drugs effectively suppress SARS-CoV-2 replication and relieves virus-associated pneumonia in Syrian hamsters. The metallodrug may inhibit multiple viral Zn(II) enzymes including helicase (nsp13) and ExoN/MTase (nsp14).⁷ Our integrative metallomic approach can be readily extended to other essential metals and metallodrugs, opening a new horizon for metallobiology and inorganic chemical biology for drug development and precision medicine.

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