The role of metal-dependent enzymes (a.k.a., metalloenzymes) in biological systems is quite ubiquitous and as such, metalloenzymes play widespread and varied roles in human disease. More than one-third of all enzymes are metalloenzymes, but less than 7% of all FDA-approved drugs engage these valuable therapeutic targets. To advance the development of small molecule therapeutics against metalloenzymes, our laboratory has spent nearly two decades bringing together concepts in inorganic and medicinal chemistry. These efforts have culminated in the utilization of fragment-based drug discovery (FBDD) for metalloenzymes, the development of metal-binding pharmacophores (MBPs), and the introduction of metal-binding isosteres (MBIs), among other discoveries. This presentation will highlight our journey blending inorganic and medicinal chemistry and our latest efforts to see these concepts have a clinical impact on human disease.

2:30 p.m.  Redox Control of the Immune Response by Indoleamine 2,3-Dioxygenase

Professor John T. Groves, Hugh Stott Taylor Chair of Chemistry, Princeton University

Indoleamine 2,3-dioxygenase (IDO1) is a heme protein that accounts for ~95% of tryptophan metabolism. The first intermediate in this signaling pathway is N-formylkynurenine, which is subsequently transformed into kynurenine and eventually into niacin and NAD. IDO1 is highly upregulated in response to the aryl hydrocarbon receptor and cytokine-induced inflammation. Significantly, many types of cancer cells over-express IDO1 to deplete tryptophan, which inactivates surrounding immune cells through the combined effects of low tryptophan and higher concentrations of kynurenine. T-cells are especially sensitive to low tryptophan concentrations, causing them to decrease proliferation and to differentiate into immunosuppressive regulatory states. Inhibitors of human IDO1 have been widely explored as a potential means to defeat the ability of cancer cells to avoid immune detection. This kynurenine pathway also affects a wide variety of other processes including autoimmune disorders, response to infection, tolerance in transplantation, HIV infection and blood pressure regulation. In this lecture, I will discuss recent results aimed at elucidating modes of IDO activation and inhibition. In particular, we will discuss IDO1 reaction pathways and reactive intermediates, redox-triggered inactivation, heme loss and the surprising activation of IDO1 by physiological levels of polysulfides.

3:15 p.m.  Biosynthesis of a Copper-Chelating Natural Product

Professor Amy Rosenzweig, Weinberg Family Distinguished Professor of Life Sciences, Departments of Molecular Biosciences and Chemistry, Northwestern University

Methanobactins (Mbnbs) are copper-binding natural products currently under investigation as therapeutics for diseases of copper metabolism. Mbnbs are ribosomally produced, post-translationally modified peptide (RiPP) natural products generated from a precursor peptide, MbnA. The known and predicted Mbn structures are diverse, but all Mbnbs characterized thus far bind copper with two nitrogen-containing heterocycles and two neighboring thioamide groups. These moieties are generated from cysteine residues in MbnA by an iron-containing heterodimer of the MbnB and MbnC proteins (MbnBC). Progress toward elucidating the oxidation state and nuclearity of the MbnBC iron active species as well as the molecular details of how MbnB and MbnC interact with one another and bind the MbnA precursor peptide substrate will be presented.

4:00 p.m.  From Microbes to Mussels: Bioinorganic Chemistry in the Marine Environment

Alison Butler, Distinguished Professor, Nichols Medalist, Department of Chemistry & Biochemistry, University of California-Santa Barbara

The bioinorganic chemistry of the marine environment reflects the chemical composition in which organisms have evolved. The transition metal ion composition of the surface ocean differs remarkably from terrestrial environments, with molybdenum being the most abundant transition metal in surface seawater followed by vanadium. By contrast, iron is particularly low, yet despite its paucity, iron is essential to marine organisms. Many marine microbes have evolved siderophores to sequester Fe(III) with intriguing properties, including photoreactive and surface-adhesive groups. This talk will cover the progression of our work in marine bioinorganic chemistry, from vanadium haloperoxidases to our recent work on the biosynthesis of siderophores, and to applications of siderophore analogs in wet adhesion as mimics of the mussel foot proteins mussels use to adhere to rocks in the intertidal zone of the ocean.

4:45 p.m.  Break

5:30 p.m.  Medal Award Ceremony

Presiding: Dr. Kathleen Kristian, 2022 Chair, ACS New York Section