Published in final edited form as:

Curr Opin Chem Biol. 2008 April ; 12(2): 194–196. doi:10.1016/j.cbpa.2008.03.008.

Inorganic Chemical Biology: From small metal complexes in biological systems to metallo-proteins

Sheila S. David^{1,*} and Eric Meggers²

¹ Department of Chemistry, University of California Davis, One Shields Avenue, Davis CA 95616, USA

² Philipps-Universität Marburg, Fachbereich Chemie, Hans-Meerwein-Straße, 35043 Marburg, Germany, Email: meggers@chemie.uni-marburg.de

What defines Chemical Biology is often different depending on the vantage point of the scientist offering up the definition. Indeed, to some, chemical biology is a broad term relating to the use of chemical approaches and techniques to study biology and the harnessing of biological techniques to make new molecules and study chemistry (1). Chemical biology is also often defined in terms of the use of small molecules to reveal the intricacies of biology (2). Where does inorganic chemistry intersect with chemical biology?? The interface between inorganic chemistry and biology has been a rich one dating back several centuries (3,4). In more recent times, this field has been referred to as bioinorganic chemistry. The core of bioinorganic chemistry has focused on the study of metal sites in metalloproteins and metalloenzymes (3). Synthetic chemistry, an important component of chemical biology, has been used by bioinorganic chemists to make small molecule spectroscopic and functional models of metal sites in proteins. In addition, the use of small molecules to study biology also applies to inorganic complexes. Indeed, inorganic complexes have and continue to be used to investigate and influence biological processes, and such approaches trace back to the early times of mixing of chemistry and biology (4). Clearly, regardless of the label used, research at the interface between inorganic chemistry and biology continues to thrive. In this issue of *Current Opinions in Chemical Biology* focusing on “Bioinorganic Chemistry” or “Inorganic Chemical Biology” a diverse set of topics are reviewed that provides a snapshot of some of the interesting new findings in this broad research area. Specifically, an emphasis has been placed on small molecule inorganic complexes, as probes and that may occur naturally.

Bruijninx and Sadler give an overview of new innovative developments for the use of metal complexes and organometallic agents with anticancer activities. DNA remains the most important target for metal-based anticancer drugs. Stimulated by the clinical success of cisplatin, targeted delivery and prodrug activation strategies of platinum complexes have been developed. A family of ruthenium and osmium half-sandwich complexes show promising anticancer properties and allow more ligand tuning than platinum complexes. Non-coordinative interactions with DNA duplexes, quadruplex structures and other secondary structures are being exploited by mono- and polynuclear metal complexes. Proteins are gaining importance as nontraditional targets for metal complexes either by using the metal as a

*Corresponding author: Email: david@chem.ucdavis.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

structural scaffold or by exploiting the reactivity of coordination compounds towards protein anticancer targets.

Suh and Chei discuss metal-based compounds which serve as artificial proteases and hold promise for future catalytic drugs in which the target protein is getting destroyed in a catalytic fashion. This emerging strategy is highly desirable because it reduces the required drug dose and irreversibly eradicates the protein target. Typically, in such a design strategy, hydrolytically active metal complexes are brought into close proximity to a target protein by linking it to a protein binder or enzyme inhibitor.

The concentration of metal ions in cells is closely monitored and regulated. Chen and He review the advances that have been made regarding an understanding of the remarkable selective recognition of metal ions by metalloregulatory proteins in bacteria and yeast. For example, the MerR family of proteins is an important group of bacterial metalloregulatory proteins and members of this family have been demonstrated to sense and control levels of cadmium(II), zinc(II), cobalt(II), silver(I), gold(I), mercury(II) and lead(II).

There is a growing interest in the participation of metals in neurological processes. Barnham and Bush review the involvement of metals in Alzheimer's and Parkinson's diseases, which are characterized by elevated tissue iron and miscompartmentalization of copper and zinc. Important in this context has been the elucidation of copper and zinc release and flux at the cortical glutamatergic synapse where amyloid is first deposited at the onset of Alzheimer's disease.

Designed polypyridyl transition metal complexes have been established as powerful tools to bind DNA and reveal factors influencing DNA recognition by small molecules and proteins. These complexes have also been used to illustrate the remarkable property of charge transport (CT) within DNA. Merino, Boal and Barton review recent work using metal complex probes to demonstrate DNA charge transport in biologically relevant contexts such as within the mitochondria and nuclei of HeLa cells and in isolated nucleosomes. Intriguingly these studies reveal that DNA damage resulting from CT is funneled into regulatory sites in mitochondria suggesting this may serve as a mechanism to protect the genomes of mitochondria. In addition, the use of these metal complexes has allowed for observation of long range CT in DNA mediated by DNA binding proteins that contain redox sites (iron sulfur cluster or disulfide linkages). These experiments provide compelling evidence that such charge-transfer processes between proteins mediated by DNA may be used in biology.

Nitric oxide (NO) plays an important role in cellular signaling and is involved in a myriad of biological processes. One important role of NO is in inducing apoptosis when present at high concentrations, and therefore the use of NO as a therapeutic has received much recent interest. The use of metal complexes as delivery vehicles for NO is the topic of the review by Rose and Mascharak. Metal-NO complexes serve as unique NO-containing drugs in which the delivery of NO to a cancer cell can be controlled by light. Much progress in recent years has been made in the synthesis of stable metal-based NO carriers and tuning of the properties for the rapid release of NO upon treatment with the appropriate source of light. New chromophore conjugation strategies show great promise in making M-NO complexes where the NO may be released by exposure with infrared light. The combination of light, metals and NO offers an exciting new approach for treatment of cancer and for studying NO signaling pathways in biology.

The role of siderophores in the uptake of iron by bacteria is well understood. However, the mechanism by which copper is assimilated by bacteria is less clear. In an insightful review by Balasubramanian and Rosenzweig, the properties of high-affinity copper binding ligands called methanobactins is reviewed and compared to those of iron siderophores. Many properties of

the methanobactins are reminiscent of siderophores, and recent work in yeast have identified copper binding ligands as well. This indicates that mechanisms for copper uptake are similar to iron uptake, and suggest that there may be unrecognized roles for copper binding ligands in biology.

Much effort has been directed at understanding the role of metal ions in catalyzing the hydrolysis of phosphodiester bonds of nucleic acids. Restriction enzymes are metallonucleases that have a wide variety of active site motifs and contain a variety of different metal ions. This property has made it difficult to propose a simple streamlined mechanism for these enzymes. In this issue, Dupureur reviews the structural, mechanistic and computational properties of restriction enzymes with a focus on the role of the metal ions and the metal coordination sphere. This comparison illustrates unifying themes in the catalysis of the phosphodiester linkage by different restriction enzymes. Indeed, there are features that converge about the chemistry that provide insight into how changes in active sites and metals may lead to the same overall outcome of phosphodiester backbone cleavage. Of note, many computational studies suggest that mechanisms may involve metal ion movement, a new idea in catalysis that provides inspiration for future directions.

Acknowledgments

We would like to thank all of the authors who contributed to this issue and provided their insight and opinions. Though it was only possible to highlight a fraction of the amazing work of scientists in this area, we hope that when thinking of Chemical Biology, the potential roles of metals and the potential power of inorganic complexes will not be forgotten.

References

1. Borman S. Chemistry, Biology Cross-Fertilization 2007;85:31–32.
2. Schreiber SL. Small molecules: this missing link in the central dogma. *Nature Chem Biol* 2005;1:64–66. [PubMed: 16407997]
3. Lippard SJ. The Inorganic side of Chemical Biology. *Nature Chem Biol* 2007;3
4. Morrison KL, Weiss GA. The Origins of Chemical Biology. *Nature Chemical Biology* 2007;3

Biographies

Sheila S. David, Department of Chemistry, University of California Davis, One Shields Avenue, Davis CA 95616, Email: david@chem.ucdavis.edu, URL: <http://www.chem.ucdavis.edu>

Sheila S. David received her BA degree with distinction in Chemistry in 1984 from Saint Olaf College in Northfield, Minnesota. She did her graduate work at the University of Minnesota in bioinorganic chemistry in the laboratory of Professor Lawrence Que, Jr. and received her Ph.D. in 1989. She was an NIH postdoctoral fellow in the laboratory of Professor Jacqueline K. Barton at the California Institute of Technology (1990–1992). She joined the faculty at the University of California, Santa Cruz in the Department of Chemistry and Biochemistry as an Assistant Professor in 1992. During 1996, she moved her laboratory to Salt Lake City to join the faculty in the Department of Chemistry at the University of Utah where she rose to the rank of Full Professor. She recently moved (2007) her laboratory to the University of California, Davis where she is a Professor of Chemistry. Her laboratory integrates inorganic and organic chemistry with biology to study the fascinating and important process of DNA repair.

Eric Meggers, Philipps-Universität Marburg, Fachbereich Chemie, Hans-Meerwein-Straße, 35043 Marburg, Email: meggers@chemie.uni-marburg.de

Eric Meggers received his Diploma and Ph.D. in chemistry from the University of Bonn (Germany) and University of Basel (Switzerland), respectively. After postdoctoral research at the Scripps Research Institute (USA), he started in 2002 his independent career at the University of Pennsylvania. In 2007, Eric Meggers moved back to Germany and is holding now a Professorship in the Department of Chemistry at the Philipps-University Marburg. His research interests revolve around the combination of synthetic organic and inorganic chemistry to create compounds with novel biological, physicochemical, and materials properties.