de Novo Designed Protein Catalysis

V. L. Pecoraro, W. Pitts and V. Borghessi
Department of Chemistry, University of Michigan, Ann Arbor, MI USA
vlpec@umich.edu

One of the greatest unanswered questions of metalloprotein chemistry is how protein structure influences the active site to afford a desired activity. The protein may influence both the first coordination sphere (ligand type, number, and relative geometry) as well as the outer coordination environment. While native metalloenzyme studies provide valuable insights, interpretations of these systems are often complicated because of the intricacy of the scaffold or the presence of multiple metal centers. Similarly, small molecules can afford insight on reactions but are often limited by the solvent or the synthetic complexity required to append functional groups. For this reason, we utilize an intermediate approach, *de novo* designed □-helical proteins, which are easily synthesized, water soluble and recapitulate native metalloprotein active sites well. These designed systems provide native-like folds that can be manipulated simply in order to limit the variables that are probed during our studies. In this presentation we will present well-defined scaffolds, employing both canonical and non-canonical sequences, as well as non-coded amino acids to expand the chemical landscape that may be explored beyond that which is available in native systems. Studies focused on enhancing copper catalyzed nitrite reductase and superoxide dismutase activities will be discussed. We will show how systematic modifications to first coordination sphere ligands, the immediate outer sphere environment as well as the helical pitch can lead to significant variations in the observed activity.