World Academy of Science, Engineering and Technology
International Journal of Biomedical and Biological Engineering
Vol:13, No:11, 2019

De Novo Design of Functional Metalloproteins for Biocatalytic Reactions

Authors : Ketaki D. Belsare, Nicholas F. Polizzi, Lior Shtayer, William F. DeGrado

Abstract : Nature utilizes metalloproteins to perform chemical transformations with activities and selectivities that have long been the inspiration for design principles in synthetic and biological systems. The chemical reactivities of metalloproteins are directly linked to local environment effects produced by the protein matrix around the metal cofactor. A complete understanding of how the protein matrix provides these interactions would allow for the design of functional metalloproteins. The de novo computational design of proteins have been successfully used in design of active sites that bind metals like di-iron, zinc, copper containing cofactors; however, precisely designing active sites that can bind small molecule ligands (e.g., substrates) along with metal cofactors is still a challenge in the field. The de novo computational design of a functional metalloprotein that contains a purposefully designed substrate binding site would allow for precise control of chemical function and reactivity. Our research strategy seeks to elucidate the design features necessary to bind the cofactor protoporphyrin IX (hemin) in close proximity to a substrate binding pocket in a four helix bundle. First- and second-shell interactions are computationally designed to control orientation, electronic structure, and reaction pathway of the cofactor and substrate. The design began with a parameterized helical backbone that positioned a single histidine residue (as an axial ligand) to receive a second-shell H-bond from a Threonine on the neighboring helix. The metallo-cofactor, hemin was then manually placed in the binding site. A structural feature, pi-bulge was introduced to give substrate access to the protoporphyrin IX. These de novo metalloproteins are currently being tested for their activity towards hydroxylation and epoxidation. The de novo designed protein shows hydroxylation of aniline to 4-aminophenol. This study will help provide structural information of utmost importance in understanding de novo computational design variables impacting the functional activities of a protein.

Keywords : metalloproteins, protein design, de novo protein, biocatalysis
Conference Title : ICPED 2019 : International Conference on Protein Engineering and Design
Conference Location : San Francisco, United States
Conference Dates : November 05-06, 2019