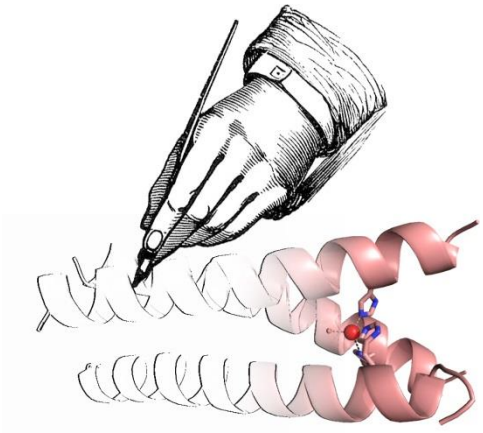
PhD in Chemical Sciences

Advanced Course 2019

Protein Design and Metalloprotein Design



Metalloproteins promote some of the most complex molecular processes in Nature, and approximately 40% of proteins has a metal cofactor (either structural or catalytic) in their active site. Although confined for a long time within the fences of structural biology, recent advances demonstrate how protein design is now accessible to chemists. The course will illustrate how the structural and functional features of metalloproteins and metalloenzymes were deciphered using few chemical principles. More, during the course it will be described how the same chemical principles were used to design new active sites into proteins. Special focus will be given to those constructs that can be prepared through standard peptide synthesis. Finally, the design and isolation of proteins with completely artificial (even metallorganic) catalytic sites will be discussed.

Along with examples form the literature and from the real Nature's world, during the course the Protein Data Bank and the software PyMol (proteins and nucleic acids analysis and visualization) will be presented by means of a practical lecture in the computer's room.

Bibliographic material and references for further study of these subjects will be provided.

The course is composed by four 2-hours lectures, distributed over two weeks, for a total of 8 hours, corresponding to 1 CFU. Students will get credits according to their attendance to the lectures and a score based on a final exam.

The lectures titles and contents are:

1- ***Metalloproteins: from chemical principles to active site analysis***

The binding of metal ions to protein constructs and their structural or functional behavior obey to a few but still fundamental chemical principles: ligand field effects, hard-soft properties of metals and ligands, coordination (un)saturation, ligand substitution kinetics. Also, several metal sites exist in different oxidation states, which are relevant for redox enzymatic catalysis. These principles are a guideline for the design of metal sites in protein constructs. They will be presented along with information on the principal spectroscopic and electrochemical techniques for the characterization of metal sites in proteins.

2- ***Protein structural information: Protein Data Bank and Pymol***

The structural knowledge of proteins and metalloproteins is essential for the design of new constructs. In this lecture the Protein Data Bank website will be presented. The lecture will be held at the Computer Room, where the software PyMol (structural analysis and protein graphic representation) will be presented to the students with practical examples.

3- Metalloproteins: what they are and what they do

In this lecture the most representative active sites of metalloproteins (structural, transport and catalytic sites) will be presented. The sites will be discussed in terms of representative structural features and catalytic aspects. Focus will be given to paradigmatic or challenging active sites in relationship to metalloprotein design.

4- *Protein Redesign and De Novo Design*

A brief highlight will be given on Directed Evolution as an approach for protein design. The principles of protein redesign and of de novo design will be introduced, with focus on rational protein design. As for protein redesign, examples from the literature with increasing complexity will be discussed (from the substitution of the metal ion in the active site to the redesign of first and second shell interactions). As for de novo design, α-helical constructs will be discussed. During the lecture the use of the educational software FoldIt (https://fold.it/portal/) for the design of proteins will be presented.

The lectures will be held by Prof. Matteo Tegoni.

MT does his research in the field of thermodynamics of metal complexes, with expertise in the study of self-assembly of metal-based supramolecules, interaction of metal ions with peptides and proteins, and metal-based drugs. He has been coordinator of several international projects (EU Marie Curie, Italy-USA) and participant to national and local research projects. MT has published over 50 articles on peer-reviewed journals, including two reviews on protein design.

General reviews

Yu, F.; Cangelosi, V. M.; Zastrow, M. L.; Tegoni, M.; Plegaria, J. S.; Tebo, A. G.; Mocny, C. S.; Ruckthong, L.; Qayyum, H.; Pecoraro, V. L. ***Protein Design: Toward Functional Metalloenzymes***. Chem. Rev. 2014, 114, 3495–3578.

Tegoni, M. ***De Novo Designed Copper α-Helical Peptides: From Design to Function***. Eur. J. Inorg. Chem. 2014, 2014, 2177–2193.

Research Papers

Tegoni, M.; Yu, F.; Bersellini, M.; Penner-Hahn, J. E.; Pecoraro, V. L. ***Designing a functional type 2 copper center that has nitrite reductase activity within α-helical coiled coils***. Proc. Natl. Acad. Sci. U. S. A. 2012, 109, 21234–21239.

Ferretti, L.; Elviri, L.; Pellinghelli, M. A.; Predieri, G.; Tegoni, M. ***Glutathione and N-acetylcysteinylglycine: Protonation and Zn^{2+} complexation***. J. Inorg. Biochem. 2007, 101, 1442–1456.