PhD position on ultrafast structural dynamics of therapeutic enzymes in XFELs at IQF-CSIC, Madrid

Dr. Martín García's research group at the Institute of Physical Chemistry Blas Cabrera (IQF-CSIC) focuses on uncovering the ultrafast dynamics and reaction mechanisms of enzymes through the application of the cutting-edge technique of time-resolved serial femtosecond crystallography (TR-SFX). The group's work aims to provide deep insights into how enzymes function at the atomic level, with an emphasis on studying their fast reactions and conformational changes. The ability to track these rapid structural shifts allows researchers to map out the entire catalytic cycle of enzymes and identify key intermediate states that are often invisible to conventional structural biology techniques. These discoveries have significant implications for advancing the field of biochemistry, specifically in the understanding of enzyme mechanisms that are essential for designing novel therapeutics.

Duration: 4 years

Estimated incorporation date: January-March 2025

Center: Department of Crystallography and Structural Biology, Institute of Physical Chemistry Blas Cabrera (IQF-CSIC), Madrid

Eligibility requirements: Candidates should hold a master's degree in biotechnology, biology, biochemistry, or a related discipline. While not required, experience in protein expression and purification, along with structural biology techniques, will be viewed positively valued.

Funding: Ayuda para la formación de personal investigador predoctoral, Convocatoria PID2023 (Proyectos de Generación de Conocimiento) de la Agencia Estatal de Investigación.

Project title: New approaches in time-resoled crystallography at the millisecond scale for 3D structural and dynamic studies of enzymes of therapeutic interest. (TREX-3D)

Project reference: PID2023-151100NB-I00

Principal Investigator: José Manuel Martín García

Contact: Please send your CV and a motivation letter to jmmartin@iqf.csic.es

More about the research group:

- ORCID: 0000-0002-4558-3858
- Group website: https://jmmartin46.wixsite.com/josemartin-group

Project summary:

Enzymes drive life by catalyzing nearly all biochemical reactions, including metabolic processes, energy transfer, genetic information processing, and signaling. Despite extensive research, a key question remains: how do structural fluctuations in enzymes enhance their ability to catalyze complex reactions? Understanding this could revolutionize biology and biotechnology, leading to insights into enzyme efficiency, novel enzyme activities, and the design of artificial biocatalysts for therapeutic and industrial use. While X-ray crystallography has traditionally been static, advances in time-resolved serial crystallography now allow us to observe biomolecular reactions and structural changes with near-atomic resolution. In this project we will use time-resolved serial femtosecond crystallography at X-ray free-electron lasers and synchrotrons to determine 3D structures of transient intermediates with ultrafast (100 fs) time resolution with the aim at establishing the timescales of structural changes in enzyme crystals compared to those in solution. Our novel approach involves initiating a chemical reaction in protein nanocrystals and tracking its progress with time-resolved serial crystallography. We will identify key time points to determine the 3D structures of intermediates and use hybrid quantum mechanics/molecular mechanics and molecular dynamics simulations to validate our data. This will provide unprecedented insights into the reaction mechanisms of enzymes such as Anmk, AGT, CYPE2D6, and RFK-PNPOx. Ultimately, we aim to create molecular "flipbook" movies, providing a detailed view of reaction processes and identifying principles applicable to other proteins. Our approach could fundamentally enhance our understanding of cellular processes and lead to improved drug and treatment designs.