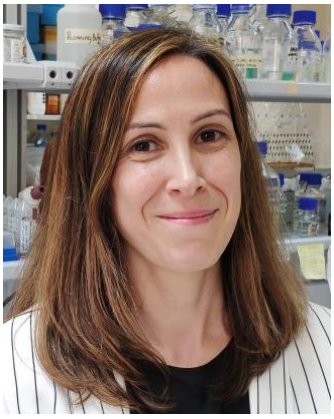
Host-pathogen interactions in pathogenic mycobacteria
Underlying molecular mechanisms and new ways for antimicrobial development



J. Inmaculada Pérez Dorado

Department of Chrystallography & Structural Biology, Blas Cabrera Institute for Physical Chemistry

jiperez@iqf.csic.es

The *Mycobacterium* genus contains over 150 recognized species, many of which produce infectious diseases in human such as tuberculosis or leprosy, caused by *Mycobacterium tuberculosis* (Mtb) and *Mycobacterium leprae*, respectively. Human tuberculosis is one of the world's most devastating human ID responsible of ~1.5 million deaths every year; while leprosy is an IDs associated with permanent deformation, disability and stigma, with > 200.000 new cases every year. Our group aims at using structural biology approaches to acquire a deep understanding of biological systems involved in host-pathogen interactions in pathogenic mycobacteria, as well as finding new ways for antimicrobial development. Our work mainly focuses on the study of the ESX5 secretion system and LysA mycobacteriophage-encoded endolysins. The ESX5 secretion system is a complex molecular machine, and key virulence factor essential for the viability of pathogenic mycobacteria, including Mtb. $EccC_5$ is a large ATPase, and pivotal ESX5 component, providing the secretion driving force via ATP hydrolysis. Our structural studies reveal the lack of ATPase activity proposed for the N-terminal DUF domain of $EccC_5$, which is likely conserved in other ESX systems from mycobacterial and non-mycobacterial species. These results uncover key features of the ESX-dependent secretion mechanism, and it may open new ways for inhibitor development targeting the $EccC_5$-DUF domain. Bacteriophage endolysins are peptidoglycan hydrolases targeting the bacterial surface that, when exogenously applied, can produce a rapid and specific elimination of pathogenic bacteria. In this line, DS6A-LysA and D29-LysA are complex multidomain endolysins with potential antimicrobial application against pathogenic mycobacteria. Our crystallographic studies of DS6A-LysA and D29-LysA catalytic domains uncovers important aspects of the mechanism of cell-wall binding and hydrolysis by these endolysins, knowledge that is key for their potential application as specific antimicrobials.