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Faculty of Science

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SEMINAR

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Hosted by Assistant Prof Luo Min

Structural and Mechanistic Bases of β-Lactam Resistance in MRSA: From PBP2a Allostery to BlaR Signaling

By Juan Hermoso

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About the Speaker

Juan A. Hermoso is Full Professor at the Spanish National Research Council (CSIC) in the Department of Crystallography and Structural Biology at the Institute of Physical Chemistry "Blas Cabrera" (IQF-CSIC). He served as Director of the Institute from 2021 to 2025. He received his PhD in Physics from the Complutense University of Madrid and completed postdoctoral training at CNRS laboratories in Grenoble, including the Institut de Biologie Structurale (CEA-CNRS).

His research program focuses on the structural and mechanistic analysis of bacterial cell-wall remodeling, division machinery, virulence factors, and antibiotic resistance. By integrating X-ray crystallography, cryo-electron microscopy, and advanced biophysical methods, his work has provided key insights into peptidoglycan dynamics and resistance mechanisms in major bacterial pathogens.

Professor Hermoso has authored more than 219 peer-reviewed publications (h-index 54) and deposited over 270 macromolecular structures in the Protein Data Bank. He has led over 40 competitive research projects and supervised numerous PhD students and postdoctoral researchers. He is actively involved in scientific evaluation and governance, serving on national and international advisory boards, editorial boards, and review committees of major research infrastructures. His work has had a significant impact on structural microbiology and the development of innovative strategies to combat antimicrobial resistance.

Methicillin-resistant Staphylococcus aureus (MRSA) represents one of the most persistent challenges in antibacterial chemotherapy, largely due to its ability to evade β-lactam antibiotics while maintaining essential cell-wall biosynthesis. This lecture will present a structural and mechanistic framework explaining how MRSA achieves resistance and how this process can be therapeutically reversed.

Our work has revealed that penicillin-binding protein 2a (PBP2a), the central determinant of methicillin resistance, is not a rigid, intrinsically resistant enzyme but a highly regulated molecular machine. Structural, biochemical, and dynamic studies uncovered an allosteric network that couples ligand binding at a remote regulatory site to activation of the transpeptidase active site, enabling catalysis under antibiotic pressure. Disruption or hijacking of this allosteric communication provides a powerful strategy to restore β-lactam susceptibility.

Building on these insights, we will discuss recent findings demonstrating that resistance in MRSA can also be overcome by targeting the β-lactam sensor BlaR. Structural and mechanistic analysis shows how small-molecule interference with BlaR signaling prevents induction of resistance, thereby resensitizing MRSA to clinically relevant β-lactams.

Together, these studies establish allostery and signal transduction as central, druggable vulnerabilities in MRSA. By integrating structural biology with chemical biology and microbiology, this work illustrates how mechanistic understanding can inform novel strategies to counteract antibiotic resistance and revive the clinical utility of existing antibiotics.