COMPUTER SIMULATION AND THEORY OF MACROMOLECULES

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Section 1:

List of Oral Contributions, sorted by Number

Poster #158 **online**

Molecular Basis for FOF1-ATP Synthase Allosteric Drug Development: Aurovertin Binding Site

Presenting author: **Luis Fernando Cofas-Vargas**

National Autonomous University, Institute of Chemistry, Biomacromolecular Chemistry, Mexico City, Mexico

Co-author/s: Paola Mendoza-Espinosa, Enrique García-Hernández

FOF1-ATP synthase performs diverse key regulatory functions in the cell membrane in addition to its central role in the mitochondria as the primary producer of ATP. A growing number of human pathologies, including hypertension, atherosclerosis, cancer, and some neurodegenerative, autoimmune, and aging diseases, have been linked to its dysfunction. Furthermore, the inhibition of this enzyme jeopardizes the survival of several bacterial pathogens that pose a threat to public health. FOF1-ATP synthase has emerged as a novel drug target for treating human diseases and combating antibiotic resistance. The rotary mechanism that drives FOF1-ATP synthase catalysis is based on multiple intra- and intersubunit communication events that generate transient pockets that provide the opportunity to develop new types of enzyme inhibitors. Significantly, numerous natural exogenous inhibitors bind to a number of these pockets outside of the catalytic sites, which can be considered "validated" inhibitor allosteric sites. To pave the way for the structure-based development of new allosteric drugs targeting FOF1-ATP synthase, we characterized the binding sites of the fungal antibiotic aurovertin computationally. Significantly, numerous natural exogenous inhibitors bind to a number of these pockets outside of the catalytic sites, which can be considered "validated" inhibitor allosteric sites. To facilitate the structure-based development of new allosteric drugs targeting FOF1-ATP synthase, we computationally characterized the binding sites of the fungal antibiotic aurovertin. Using molecular dynamics simulations and end-point binding free energy calculations, novel aspects of the aurovertin binding sites were revealed in terms of intra- and intersubunit communications, conformational trends, hot spot binding residues, and solvent sites, which could be utilized as pharmacophoric guides in virtual screening campaigns.

* For Abstract, see Section 1: List of Oral Contributions