Molecular picture of the mechanochemical coupling in ATP synthase as a conceptual framework for the development of novel antimicrobial drugs

ATP synthase, also known as F-ATPase, is a protein that plays a fundamental role in functioning of all living organisms. It is involved in cellular respiration processes in which energy stored in chemical bonds of various nutrients is converted into its biologically available form. More specifically, a primary function of F-ATPase in most cells is to produce ATP, a universal biological energy currency, used to power all cellular processes. Regardless of its pivotal biological importance, ATP synthase exhibits a unique, complex and as of yet not fully understood mechanism of action, ensuring a very high efficiency of energy conversion.

Due to this complexity and multiple inhibition mechanisms, ATP synthase has also recently emerged as an attractive target for the development of novel therapeutics. Therefore, the main goal of the current project is to advance our understanding of the ATP synthase mechanism of action to a degree that would allow for rational design of small organic compounds that selectively block the enzyme in microbial cells and thus could serve as anti-infectious drugs. To achieve this goal, we will use a state-of-the-art computational approach providing a detailed insight into mechanisms of biomolecules at the atomic level that is hardly accessible by experiment. High resolution research techniques, that allow for identifying often subtle differences in cellular targets between human host and microbial cells, are in fact necessary for rational design of therapeutics.

With steady development of a methodological framework and ever-increasing computational power, the predictive power of computer simulations of biomolecules and their biological funcion at the atomic level has been constantly progessing over time. Accordingly, our previous research experience with ATP synthase suggests that the current project provides a unique and genuine opportunity to understand the mechanism of action of the important protein nanomachine with the aim of opening a new avenue for rational design of novel antimicrobial drugs. This will be possible by deriving the first all-atom model of the ATP synthase complex through including into the simulation recently reported cryo-electron microscopy data by the use of the new refinement procedure developed by one of our collaborators. Thus obtained model of ATP synthase will allow us to identify any differences in the mechanism of action of F-ATPase between human mitochondria and pathogenic bacteria or fungi. In particular, we will analyze how the structural disparities between these forms of the enzyme, previously determined in our simulations, affect the energy conversion mechanism. Additionally, employing a recently solved crystal structure of ATP synthase with bedaquiline (i.e., the first novel anti-tuberculosis drug in 40 years), we will elucidate how this compound and related antibiotics inhibit the activity of the enzyme in multidrug resistant mycobacteria. Using thus acquired knowledge, we will next examine whether the structure of ATP synthase gives the opportunity to extend the antimirobial spectrum of these inhibitors to other pathogenic bacteria.

Results to be obtained within the current research project will provide a detailed knowledge on the mechanism of energy transfer and conversion in ATP synthase, accounting for extremely high efficiency of this process, crucial for energy metabolism of all living cells. Furthermore, the obtained high-resolution data might encourage and facilitate the development of novel antibacterial and antimycotic drugs exhibiting new mechanisms of action, needed to address the emergence of pathogens resistant to currently available therapeutics. Since ATP synthase is also considered as a potential target of drugs for non-infectious diseases, such as autoimmune disorderes and cancer, molecular-level understanding of the enzyme mechanism of action is also expected to support research on these molecules. Finally, thorough explanation of the mechanochemical properties of ATP synthase, as a prototype of a highly efficient rotary motor, will also provide a new paradigm for the design of synthetic protein machines in bionanotechnology.