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Integrating advanced molecular dynamics simulations and AI to investigate and modulate ABC transporters involved in cancer multidrug resistance

ATP Binding Cassette (ABC) transporters are crucial for cellular detoxification and the transport of a diverse range of substrates, including drugs. Their roles in multidrug resistance (MDR), drug-drug interactions (DDIs), and severe genetic diseases make them key targets for therapeutic intervention. Structurally, they are organized into two halves, each consisting of a transmembrane domain (TMD) responsible for substrate transport and a nucleotide-binding domain (NBD) that binds and hydrolyzes ATP controlling the transport cycle. To ensure their function, these transporters switch between inward-facing- (IF, with separated NBDs) and outward-facing- (OF, with paired NBDs), open and occluded states.

We developed enhanced sampling methods to investigate these conformational transitions at molecular level. For ABCG2/BCRP (Breast Cancer Resistance Protein), involved in MDR and DDIs, our kinetically excited targeted MD (ketMD) simulations revealed key intermediates in the transport cycle, including a novel substrate-binding pocket between the two established cavities that regulates substrate progression. Furthermore, we demonstrated that substrate presence in the first cavity is essential for synchronizing the NDB-TMD movements, facilitating efficient substrate transport (Dudas et al. CSBJ 2022). For ABCB1/P-gp (P-glycoprotein), another MDR- and DDI-associated transporter, we implemented an adiabatic biased MD (ABMD) protocol to elucidate the ligand entry, translocation, and inhibition mechanisms. Our results demonstrated that the conformational transitions between IF-open, IF-occluded, and OF states are controlled by specific structural events,notably the kinkingand unkinking of particular TM helices. Inhibition of P-glycoprotein was suggested to occur by disrupting the communication between the TMDs and NBD2, preventing the conformational transitions necessary for substrate efflux (Elbahnsi et al. CSBJ 2024).

Building on these MD simulations, we are integrating the enhanced sampling data into machine learning and deep learning frameworks to develop predictive models for identifying potent inhibitors of BCRP and P-gp, aiming to address therapeutic challenges associated with MDR and transporter-related diseases.

Keywords
ABC transporters, Cancermultidrug resistance, moleculardynamics simulations, artificial intelligence

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Biography

Ahmad Elbahnsi is a postdoctoral researcher at Inserm (Université Paris Cité).

His research focuses on structural bioinformatics, molecular modeling and artificial intelligence applied to drug discovery. He develops integrative computational approaches combining molecular dynamics simulations, enhanced sampling techniques and machine learning to study the functions and modulation of membrane transporters, with a particular emphasis on membrane transporters. Ahmad actively collaborates with experimental teams to identify and optimize small-molecule modulators, aiming to improve therapeutic strategies targeting challenging biomedical targets.

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