Structural Insights into CYP3A4–P-gp Interactions and Their Role in Personalized Autoimmune Drug Therapy

Cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) are critical regulators of drug metabolism and disposition, with significant implications for inter-individual variability in pharmacokinetics and therapeutic outcomes. CYP3A4 is a major hepatic enzyme responsible for the oxidative biotransformation of a wide range of drugs, while P-gp functions as an efflux transporter, actively exporting drugs out of cells and limiting intracellular drug accumulation.. Alterations in P-gp and CYP3A4 activity—whether due to genetic variation, co-administered inhibitors or inducers—can significantly affect drug pharmacokinetics (absorption, distribution, metabolism, and excretion - ADME), posing challenges in dose optimization and drug safety. Notably, previous studies demonstrated a functional interplay between CYP3A4 and P-gp, particularly in tissues where they are co-expressed, such as the intestinal epithelium. This interaction has been shown to influence the metabolism and transport of their shared substrates.

In this study, we investigated the structural-functional crosstalk between CYP3A4 and P-gp through protein–protein interaction (PPI) modeling using three different tools: Rosetta protein–protein docking, Schrödinger pipeline for protein-protein docking, and AlphaFold 3. Resulting complexes were refined and validated via molecular dynamics simulations. We further examined the impact of CYP3A4–P-gp interactions on the metabolism and transport of three Janus kinase (JAK) inhibitors—tofacitinib, baricitinib, and ruxolitinib —which are widely used in autoimmune disease therapy. Molecular docking and simulation analyses revealed how the CYP3A4–P-gp interaction may influence the binding behavior and metabolic handling of these drugs. Preliminary results suggest that physical association between the two proteins may alter substrate accessibility and retention, potentially modulating drug bioavailability and clearance profile. Finally, we constructed an *in silico* pharmacokinetic compartment model to simulate drug disposition under varying enzymatic and transporter activity.

Our findings highlight the importance of integrating PPI, molecular pharmacology, and pharmacokinetics modeling to advance personalized medicine approaches in immunology.