Contribution ID: **17** Type: **Poster**

Allosteric Modulation of Plasmodium falciparum Isoleucyl tRNA Synthetase by South African Natural Compounds

Targeting *Plasmodium falciparum* aminoacyl tRNA synthetases (PfaaRSs) is one of the viable strategies to overcome multidrug-resistance in malaria parasites. In this study, we focused on *Plasmodium falciparum* isoleucyl tRNA synthetase (PfIleRS) by combining multiple *in silico* approaches and tools to identify potential modulators specific for PfIleRS from diverse South Africa Natural Compounds (SANCDB, https://sancdb.rubi.ru.ac.za/). The 3D structures of the Pf protein and its human homolog were modelled, and potential allosteric pockets were identified that could accommodate the binding of small-molecule compounds. Eleven potential hit compounds were selected based on their binding affinity, which were lower in the plasmodial protein compared to the human IleRS. These compounds targeted pockets located at key functional sites in PfIleRS other than the orthosteric site; including the N- and C-terminal Rossmann fold, zinc-finger hinge, connective peptide 1, and the anticodon binding domains. MD simulations revealed that the hit compounds induced changes in the global conformation of the PfIleRS protein, especially SANC456, suggesting they might have allosteric modulatory effects. Importantly, SANC ligand binding disrupted the stability of the AMP molecule and increased AMP binding energy, indicating possible allosteric impact of the hits on the protein's aminoacylation activity. Dynamic residue network analysis revealed possible information-flow pathways of high averaged *betweenness centrality* (*BC*) residues traversing the editing, catalytic Rossmann fold, anticodon binding, and junctional domains of PfIleRS in the holo protein system. Some ligand-bound systems (SANC382, SANC456, SANC1095, and SANC522) revealed potential allosteric pathways, induced by the ligands, going from their respective pockets towards the active site. Averaged *eigenvector centrality* (*EC*) uncovered important residue clusters on both sides of the holo active site which became altered in the ligand-bound systems, indicating possible allosteric activity. We believe these compounds can serve as reliable starting points to develop new and effective antimalarials against multi-drug-resistant plasmodium parasites.

Keywords: Multi-drug resistance malaria, *Plasmodium falciparum*, Isoleucyl tRNA synthetase, South African Natural Compounds, Structure-based drug discovery, Aminoacylation.

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Session Classification: Poster