Integrative Validation of a Conserved BPGM Allosteric Dimer Pocket for Drug Repurposing in Sickle Cell Disease

Harasani, Jana (School: Jeddah World Academy)

Sickle cell disease (SCD) remains a major global health challenge, with no widely accessible targeted cure and most existing therapies focused on symptom management or partial disease modification. Elevated levels of 2,3-bisphosphoglycerate (2,3-BPG) reduce hemoglobin oxygen affinity, promoting hemoglobin S polymerization and red blood cell sickling. Bisphosphoglycerate mutase (BPGM), the key enzyme regulating 2,3-BPG levels in erythrocytes, represents a promising yet underexplored therapeutic target. This study aimed to validate a conserved allosteric pocket at the BPGM dimer interface and evaluate its potential for ligand binding. Structural characterization using computational analysis confirmed that the interface pocket exhibits favorable druggability features. A library of 1,600 FDA-approved drugs was screened using a hierarchical molecular docking workflow followed by MM-GBSA rescoring. Top candidates, including ketorolac, amlodipine, and avatrombopag, demonstrated stable binding at the interface during molecular dynamics simulations. However, their pharmacological profiles may limit suitability for chronic use in SCD. To identify more suitable candidates, a natural compound library was subsequently screened. The natural compound acarbose, an FDA-approved drug with a favorable safety profile, demonstrated stable binding and consistent interactions at the interface site in molecular dynamics simulations. Post-simulation analyses suggest that ligand binding at this region may influence protein dynamics consistent with an allosteric mechanism. These findings validate the BPGM dimer interface as a druggable allosteric site and identify clinically relevant scaffolds for further optimization and experimental evaluation as a potential antisickling strategy in SCD.

Awards Won:
King Abdulaziz &amp
his Companions Foundation for Giftedness and Creativity: NOT TO BE READ -- $200 cash prize for each Enrichment award recipient
King Abdulaziz &amp
his Companions Foundation for Giftedness and Creativity: Mawhiba Universal Enrichment Program awards (and a $200 cash prize)