Contribution ID: **9** Type: **Poster (Chemistry SIG)**

Microbes, not humans: Exploring the molecular basis of Pseudouridimycin selectivity towards bacterial and not human RNA polymerase

The ability of a drug molecule to selectively bind to and inhibit a biological target is an important attribute that account for high efficiency and reduced toxicity. More recently, drug selectivity has been highly considered in the discovery and developmental processes of antimicrobial compounds with broad spectrum activities. Although bacterial RNA polymerase (bRNAP) was reported as a crucial therapeutic target for curtailing microbial activity, structural and sequence similarities with human RNA polymerase (hRNAP) makes it difficult to target. Recently, Pseudouridimycin (PUM), a novel nucleoside analogue was reported to selectively inhibit bRNAP as against the human form, even though the molecular mechanisms of selectivity remains a question yet to be answered. This serves as the core of this study, wherein we seek to provide molecular insights. Using ClustalW sequence alignment method, we observed that the ’ subunits of both bRNAP and hRNAP were highly conserved while the subunits of both protein forms were characterized by high sequence variations. Furthermore, the impact of these variations on the differential binding of PUM was evaluated using MMPB/SA binding free energy and per-residue decomposition analyses. These revealed that PUM binds better to bRNAP than hRNAP while binding site residues of bRNAP had higher energy contributions to the binding and stabilization of PUM as compared to hRNAP. Also, the binding of PUM to hRNAP was characterized by the formation of unfavorable interactions. In addition, PUM exhibited unpredicted orientations in bRNAP that could possibly enhance its mobility towards the hydrophobic core region. On the contrary, unfavorable intramolecular interactions characterize PUM orientations at the binding site of hRNAP, which could restrict its movement due to electrostatic repulsions. Therefore, these findings would enhance the design of potent and selective drugs for broad-spectrum antimicrobial activity

Presenter Biography

Ph student

Primary authors: Mr RABBAD, ALI (aMolecular Modeling and Drug Design Research Group, School of Health Sciences, University of KwaZulu Natal, Westville Campus, Durban 4001, South Africa); Prof. SOLIMAN, MAHMOUD (aMolecular Modeling and Drug Design Research Group, School of Health Sciences, University of KwaZulu Natal, Westville Campus, Durban 4001, South Africa)

Presenter: Mr RABBAD, ALI (aMolecular Modeling and Drug Design Research Group, School of Health Sciences, University of KwaZulu Natal, Westville Campus, Durban 4001, South Africa)

Session Classification: Chemistry and Material Science SIG Seminar

Track Classification: Chemistry and Material Science SIG Seminar