Contribution ID: **13** Type: **Student Micro-talk**

Comparison of irreversible drugs inhibition targeting HSP72 protein (first generation TCI8 and third generation TCI2); The resurgence of covalent drugs developments

The covalent inhibition mechanism of action, which overcomes competition with high-affinity, high-abundance substrates of challenging protein targets, can deliver effective chemical probes and drugs. Heat shock protein 72 (HSP72) expressed in cancer cells may be responsible for tumorigenesis and tumor progression by providing resistance to chemotherapy. In this study, we explore the most optimal binding mechanism in the inhibition of the HSP72 by two different covalent generation, TCI2 and TCI8. However, the structural basis and conformational changes associated with this preferential covalent inhibition to HSP72-TCI2 over HSP72-TCI8 remain unclear. Our results revealed that HSP72-TCI2 covalent complex was more able to stabilize and induce better interaction with high correlated dynamic motion of HSP72-NBD at ATP binding site throughout the simulation in comparison to the HSP72-TCI8 covalent complex. This is supported by the dynamic cross-correlation and principal component analysis that was more dominant in the HSP72-TCI2 inhibited complex. The insights demonstrating the above binding mechanism of HSP72 establish TCI2 covalent inhibition as the preferred method of inhibiting the HSP72 protein. This investigation aids in the understanding of the structural mechanism of HSP72 inhibition and would assist in the design of more potent covalent inhibitors of HSP72.

Student?

Yes

Supervisor name

Mahmoud Soliman

Supervisor email

soliman@ukzn.ac.za

Primary authors: Dr AIMEN, Aljoundi (UKZN); Prof. SOLIMAN, Mahmoud (Ukzn)

Presenter: Dr AIMEN, Aljoundi (UKZN)

Session Classification: Micro-talks

Track Classification: Computational Chemistry