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Allosteric Inhibition Induces an Open WPD-Loop: A New Avenue Towards Glioblastoma Therapy

Background: The mobility of loops around the catalytic site of a protein is crucial to the catalytic activity of many proteins upon substrate binding. The proximity of these loops to the catalytic site suggests their functional mobility could influence ligand binding and catalytic activity. Dynamics of the WPD-loop is an essential determinant of the catalytic activity of tyrosine-protein phosphatase zeta, an implicated protein in glioblastoma cells. WPD-loop assumes a closed conformation upon substrate binding in order to position its catalytic aspartate to participate in catalysis.
Results/methods: Herein, we explore the impact of the inhibitory activity of NAZ2329, a recently identified allosteric inhibitor of PTPRZ on the atomic flexibility of the WPD-loop using molecular dynamics simulations. A structural investigation revealed that NAZ2329 induced an open conformation of the crucial WPD-loop, consequently impeding PTPRZ activity even upon substrate binding. A generated pharmacophore model exhibits important functional moieties of NAZ2329 upon interaction with PTPRZ.
Conclusion: These findings provide an insightful molecular and structural mechanism in targeting PTPRZ as a therapeutic intervention for glioblastoma. We believe that this optimized pharmacophoric model will aid in the design of improved anti- tyrosine phosphatase agents, thus allowing for increased patient adherence as well as a decline in cross-resistance.

HPC Content

The lengau cluster CHPC was employed to perform the molecular dynamics (MD) simulations for this study. The openMPI 1.8.8 GNU compilers, the GCC 5.1.0, amber modules and the /apps/chpc/chem/amber/14 application code were integrated to access the Amber14 suite. For system parameterization, the ANTECHAMBERand LEAP modules were incorporated.In analyzing generated MD trajectories, the CPPTRAJ and PTRJ mod-ules were used. Running on 2 nodes and 48 cores, the GPU accelerated PMEMD engine was used

Presenter Biography

Clement Agoni is currently a Ph.D. candidate in Pharmaceutical Chemistry at UKZN and affiliated to the Molecular Bio-Computation and Drug Design Research Group. He recently graduated with a master degree summa cum laude from UKZN with a couple publications to his credit. His research focused on the application of advanced computational tools in exploring the co-inhibitory activity of a novel anti-TB agent to suppress Rifampin resistance. His current research seeks to provide atomistic and structural perspectives into the inhibitory activity of several novel anticancer agents.

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