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Checking the checkpoint: Unraveling the mechanisms of immune checkpoint blockade by novel BMS antagonists; BMS-1001 and BMS-1166 in cancer immunotherapy

Background: The use of small molecule antagonists in cancer immunotherapy represents a paradigm shift towards the achievement of novel treatment modalities with improved efficacies. This strategy was potentiated with the recent identification of novel inhibitors; BMS-1001 and BMS-1166, which specifically target PDL-1, induced dimerization and prevent association with PD-1, its naturally occurring target. However, these molecular occurrences, which could be essential to the future design of novel antagonists have remained unresolved till date.
Methodology: Therefore, in this study, we investigated the antagonistic mechanisms of these compounds towards PDL-1, using advanced computational methods. The lengau cluster CHPC was used 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 ANTECHAMBER and LEAP modules were employed. In analyzing generated MD trajectories, the CPPTRAJ and PTRJ modules were used. Running on 2 nodes and 48 cores, the GPU accelerated PMEMD engine was used.
Result: MM/PBSA estimations revealed that both compounds were bound to PDL-1 with considerably high-affinities as evidenced by high ΔG values. Moreover, while these compounds traversed the tunnel-like binding cleft formed by two PDL-1 monomers, they concurrently maintained high-affinity hydrogen and ionic interactions with crucial residues located within and outside the tunnel. Furthermore, BMS-1001 and BMS-1166 induced distinctive high structural motions, flexibility and activity in each monomer as compared to the unbound model, which demonstrated structural compactness and rigidity over the MD simulation period. Comparatively, BMS-1001 had higher ΔG value as well as structural impact on PDL-1 than BMS-1166, indicative of a superior antagonistic activity. Taken together, BMS-1001 and BMS-1166 bind specifically and strongly to PDL-1 due to high-affinity interactions with crucial residues at the tunnel-like binding cleft and induced high structural flexibility favorable for protein-protein interaction (dimer formation).
Conclusion: We believe these findings would enhance the future design of novel highly-affinity small molecule immune checkpoint inhibitors in cancer immunotherapy.

Presenter Biography

I have a master degree in Biochemistry specializing in cancer research and Molecular Biology. I am currently a PhD student in Computational Biology studying the use of some novel compounds as potential target in cancer. I have strong unflinching passion for cancer research and this has informed my choice of career path.

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