Molecular Dynamics Investigation of Poly [ADP-Ribose] Polymerase 1 Inhibitors as Treatment for V762A Single-Nucleotide Polymorphism Correlated with Ovarian Cancer, Lung Cancer, and Follicular Lymphoma

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Ovarian cancer, lung cancer, and follicular lymphoma are collectively attributed to 2.8 million deaths annually with an average treatment cost of $212,000. A prevalent mutation in the human enzyme Poly [ADP-Ribose] Polymerase 1 (PARP-1), resulting in the PARP-1 V762A variant, has been correlated with all of these diseases. Inhibitors that limit PARP-1 functionality are used to treat adverse effects of this mutation but have varying success. Chemical interactions of PARP-1 with three FDA-approved benzimidazole-based inhibitors were analyzed to better understand the inhibition process and thus help create better inhibitors. Molecular dynamics (MD), a computational method that uses classical physics and approximate parametric functions to simulate the time evolution of molecular systems, was applied to dynamically view protein-inhibitor interactions in a supercomputing environment. MD simulations were run for three trials on each combination of mutated and wild-type PARP-1 bound to three inhibitors: Rucaparib, Niraparib, and Talazoparib. Despite having similar structures and binding to the same active site, these inhibitors had drastically different chemical interactions with PARP-1. Niraparib was the most stable with twice the number of hydrogen bond interactions. Rucaparib had the greatest influence on energy with the highest van der Waals energies and Coulomb interactions between the inhibitor and mutated site. Talazoparib had the greatest impact on movement with a significant RMSF and distinct movement around residue 810. The discovered insights about the uniqueness of PARP-1 inhibitors will enable drug makers to create more effective and personalized inhibitors that reduce the prevalence of these diseases and save lives.

Awards Won:

Fourth Award of $500

Embark China: Third Award

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