From Computational Screening to Biological Validation: Targeting TNIK in Triple-Negative Breast Cancer

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Triple-negative breast cancer (TNBC) remains a clinical challenge due to its aggressive nature and the lack of targeted therapies. Traf2 and NCK-interacting kinase (TNIK), a key regulator of the canonical Wnt signaling pathway, is strongly implicated in the proliferation and metastasis of TNBCs. Despite its clinical relevance, there are no TNIK inhibitors approved yet. This study aimed to identify and characterize potential TNIK inhibitors using an integrated in silico and in vitro approach. A structure-based computational screening of 24,000 compounds from the Enamine Hinge Binders Library was conducted on the TNIK protein (PDB ID: 5D7A). The top ten compounds were selected based on sequential molecular docking, protein-ligand interactions, binding free energy calculations, and ADMET profiling. The best three compounds (T1, T2, and T3) were then subjected to 100 ns Molecular Dynamics simulations to understand the stability of TNIK-ligand complexes. ADMET analyses revealed that the selected compounds did not show the cardiotoxicity and hepatotoxicity risks that were associated with the standard TNIK preclinical drug, NCB-0846. In silico data indicated that all three identified compounds exhibited strong hinge-binding affinities, showed stable protein-ligand interaction profiles, and possessed favorable drug-like properties. In vitro assays using the selected compounds demonstrated significant dose-dependent cell death (~40%, $p < 0.005$) against the TNBC cell line MDA-MB-231, similar to the reference NCB-0846, validating the effectiveness of the screening pipeline. Overall, this work identifies three promising new molecular scaffolds with strong TNIK inhibitory potential and provides a foundation for further optimization and development of TNIK-targeted therapies in TNBC.

Awards Won:
Second Award of $2,400