Targeting TP53 Methylation Inhibition With RG108 for Cancer Prevention

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Cancer has remained the leading cause of death globally, with the mutation of the Tumor Suppressor Gene TP53 via DNMT1 methylation occurring in 50% of cases. Current epigenetic therapies miss the mark as they exhibit poor specificity, low potency, and high toxicity (often causing secondary cancers). This project investigates the efficacy of RG-108, a novel DNMT1 inhibitor, in maintaining TP53's integrity to block the initiation of Cancer. Through in-silico modeling, we analyzed the interactions between RG-108 and DNMT1 to evaluate its binding affinity, potency, specificity, and feasibility. Subsequently, we compared methylation patterns in the promoter regions of TP53 when it interacted with DNMT1 with and without RG-108 inhibition. Lastly, using TCGA genomic data from over 1,200 cancer samples, we correlated methylation rates to clinical outcomes. We concluded that RG-108 exhibited strong binding affinity (-10.37kcal/mol) and potency (25nM) at a rate 40-400x better than current therapies. Moreover, it displayed high specificity for DNMT1 when compared to proto-oncogenes and other proteins (target specificity >2) with significantly reduced toxicity. Additionally, with a half life of over 48 hours when delivered orally, RG-108 has high feasibility. When administered with regular dosage (250 nM), RG-108 reduced methylation by 86.5% while increasing cell viability by 75% at lower doses (25nM). TCGA analysis found a statistically significant correlation ($p<0.001$) between reduced methylation and preserved TP53 function and ergo Cancer prevention. RG-108 is the first true preventive epigenetic therapy that maintains TP53 function with high potency, low toxicity, and high feasibility to prevent cancer initiation.

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