Protein Assassins: Screening for Improved Degraders to Reverse Tumor Immortality

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Glioblastoma (GBM) is the most common malignant brain cancer in adults, and patient survival still remains low. However, 83% of GBM cases have Telomerase Reverse Transcriptase promoter (TERTp) mutations, enabling the GA-binding protein (GABP) transcription factor complex to bind and reactivate TERT expression. While directly targeting telomerase has systemic toxicity, targeting GABP may allow tumor-specific TERT silencing. Last year, I designed a GABPA dominant negative fused to an E3 ubiquitin ligase to create a biological Proteolysis-Targeting Chimera (bioPROTAC) targeting GABP, reducing TERT expression in glioma cells. To improve the degrader's potency, I took a two-pronged approach: 1) degrader stability could be improved by removing external lysines that may serve as ubiquitination sites, and 2) degrader efficiency could be improved by enhancing the binding affinity to GABPA. First, candidate lysine residues were identified and substituted to prevent potential self-ubiquitination and auto-degradation of the bioPROTAC. Second, protein structure modeling algorithms, like AlphaFold2 and Structural-Evolution, were used to assess the in silico affinity maturation of the GABPA binding domain, narrowing thousands of candidates to 116. Following in vitro experimental validation, the best-performing variant was identified, showing a 73-95% decrease in TERT expression across different cancer cell lines. This study demonstrates that integrating machine learning models into therapeutic design dramatically accelerates screening, not only for brain tumors but also for other tumor types. Validation of these results serves as a proof-of-concept, providing a powerful example for the potential applications in other transcription factor-regulated diseases.

Awards Won:
Third Award of $1,200