***Strategic Design and Synthesis of Dual-Protein Degraders to Unveil Novel Targeted Prostate Cancer Therapies***

Prostate cancer (PCa) is the most prevalent cancer diagnosed in American men, eventually culminating in its deadliest form, metastatic Castration-Resistant Prostate Cancer (mCRPC). Current therapies for mCRPC involve Enzalutamide, an Androgen Receptor-targeted therapy, however resistance occurs in almost all patient cases. Diseases with high mutation rates, such as mCRPC, require constant innovation for the discovery of therapies with novel modes of action. While traditional occupancy-driven pharmacology is a known and established approach to inhibition; mutations, resistance, and undruggable targets have urged scientists to devise strategies beyond small molecule design. Proteolyzing Targeting Chimeras (PROTACs) are heterobifunctional molecules that simultaneously bind to a biological protein of interest (POI) and components of the ubiquitin-proteasome system to enable ubiquitination and inducing degradation of the biological target via the cell’s proteasome. This type of event-driven pharmacology may overcome various limitations of small molecule inhibition by their unique degrading mechanism, lower dose requirements in therapeutic applications, and unconventional binding modes making targeted degraders a focal point for modern drug discovery programs. Despite numerous advantages, their advancement onto FDA approved targeted degraders for cancer therapy has remained limited, presumably due to the lack of novel chemical approaches to PROTACs. Since the Glucocorticoid Receptor (GR) signaling has been identified as a crucial driver of AR-therapy resistance in mCRPC, various small molecule inhibitor-type GR antagonists have been developed to target the resistant mCRPC, such as mifepristone, Relacorilant and ORIC-101 but so far have been unsuccessful due to the sole inhibition of GR signaling reverses the dependency of mCRPC tumor cells back to AR signaling. Indeed, it is well documented that mifepristone treatment induces the activation of AR signaling and promotes mCRPC tumor growth. Those results suggest that the simultaneous inhibition of both GR and AR signaling is necessary to effectively overcome the AR therapy resistant mCRPC growth. Currently, our strategy focuses on the development of a novel dual-targeting PROTAC-based protein degrader platform and how this novel GR/AR degrader will aid in overcoming mCRPC therapy resistance. Herein, we demonstrate the synthesis of targeted degraders through chemical innovation. We have synthesized effective “mono-PROTACs” whose GR targeting/degrading abilities have been demonstrated via Western Blot analysis. Currently, we are in the process of building our dual degrader scaffold to assess the possibility of a simultaneous dual degradation of both targets of interest. Moreover, the rapid access to diverse PROTACs by adding a different E3 recruiting ligase ligand such as the Cereblon (CRBN) E3 ligase ligand or the inhibitor of apoptosis protein (IAP) E3 recruiter will be pursued. With our GR and AR targeting Chimeras, our collaborators will examine whether the dual-targets PROTAC-based GR/AR degrader can prevent or reverse the AR therapy resistance in mCRPC tumors *in vitro*, *in vivo* and in patient derived models, utilizing single cell transcriptomics to evaluate its efficacy in heterogenous subclones. These studies will demonstrate the efficacy of a first-in-class GR/AR dual-degrader in overcoming AR therapy resistance in mCRPC. The dual-targeting PROTAC-based degrader platform developed from this study would also provide an innovative tool for simultaneously targeting a wide spectrum of oncogenic drivers in other cancers. The results obtained from this study may also lay the foundation for a following clinical trial designed to combat AR therapy resistance with this novel dual-degrader in mCRPC and other GR-high cancers, such as breast cancer.