Development of PROTAC degraders of SMARCA proteins for the treatment of cancer

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Epigenetic dysregulation is a common and prominent feature in many diseases, including cancer, autoimmune diseases and mental health disorders. Over the past decade, epigenetic regulators have been recognized increasingly as attractive therapeutic targets in human cancers and other types of human diseases. For example, the SWI/SNF chromatin remodeling complex regulates gene expression by altering the histone-DNA contact landscape through an ATP-dependent manner. In the SWI/SNF chromatin remodeling complex, mutations are present in approximately 20% of human cancers. The SWI/SNF chromatin remodeling complex contains two mutually exclusive catalytic ATPase subunits, SMARCA2 and SMARCA4. Mutations of SMARCA4 occur in various types of cancers including ovarian cancer, melanoma and non-small-cell lung cancer. This gene has a mutation frequency of 11%, making it one of the most frequently mutated genes. In three independent studies, an exquisite dependence of SMARCA2 in SMARCA4-deficient cells for their growth and proliferation by RNAi-mediated silence of SMARCA2 in vitro and in vivo has been demonstrated, indicating a synthetic-lethal relationship between SMARCA2 and SMARCA4. These findings suggest that SMARCA2 is a promising therapeutic target in SMARCA4-deficient cancers.

Both SMARCA2 and SMARCA4 contain a bromodomain which recognizes acetylated lysine residues in histones, and a catalytic ATPase domain which drives the chromatin-remodeling activity of the SWI/SNF complex. Based upon the success of BET bromodomain inhibitors entering clinical trials, efforts have been made to discover SMARCA bromodomain inhibitors. Unfortunately, SMARCA bromodomain inhibitors fail to display antiproliferative activity against SMARCA4-deficient cancer cells. Subsequent genetic studies indicated that the ATPase but not the bromodomain drives cancer dependence, suggesting that inhibition of the SMARCA bromodomain is not an effective therapeutic strategy.

An alternative approach to targeting SMARCA proteins is development of small-molecule degraders based upon the proteolysis targeting chimera (PROTAC) strategy. PROTAC degraders are heterobifunctional small molecules that induce targeted protein degradation through the ubiquitin-proteasome mechanism. The most advanced PROTAC therapy is now in phase 2 clinical trials, validating it as potential therapeutics for the treatment of human diseases. Based on this strategy, we have developed several highly potent SMARCA2/4 degraders. Our lead compound achieves $DC_{50} < 10$ nM and $D_{max} > 95\%$ for SMARCA2/4 proteins in the H1792 NSCLC cell line. It potently inhibits cell growth in a panel of cancer cell lines.

The future study will focus on the optimization of the pharmacokinetics/pharmacodynamics properties of our lead SMARCA degrader to achieve oral availability. The ultimate goal is to develop orally available, selective SMARCA2 degrader to avoid potential toxicity issues resulted from degradation of SMARCA4.