Design of Selective BRM Bromodomain Inhibitors and Bivalent Small-Molecule Degraders of BRM for the Treatment of BRG1-Deficient Cancer

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Epigenetic dys-regulation is known to play an important role in the development of cancer. A very common mechanism of epigenetic dys-regulation is mutations in chromatin regulators, which change chromatin states and alteration of gene expression in cancer cells. One of the frequently mutated chromatin regulators is the mammalian SWI/SNF chromatin remodeling complex. The catalytic subunit of SWI/SNF complex can be either BRG1 or BRM. Approximately 25% of 59 lung cancer cell lines have inactivated BRG1. Studies have also shown that BRM is essential for tumor growth in BRG1-deficient cancer cell lines, and depletion of BRM in these cell lines leads to cell growth arrest, induction of senescence and globally increased levels of H3K9Me3. Designing and developing BRM bromodomain inhibitors and bivalent small molecules inducing degradation of BRM will be promising for the treatment of BRG1-deficient cancer based upon the concept of “synthetic lethality”.

BRM has two potentially “druggable domains”, the ATPase domain and the bromodomain. Bromodomains are conserved protein-protein interaction modules that bind to acetyl lysine on proteins and histone tails. Scientists from Pfizer have recently reported the discovery of a small-molecule probe of BRM (PFI-3) with nano-molar affinity, demonstrating that designing a high-affinity, cell-permeable, non-peptide small-molecule probe of the BRM bromodomain is achievable. A new class of non-peptide, small-molecule inhibitors of the BRM bromodomain has been developed in this research and the best of these compounds have K_d values of 200 nM.

Recently, it has conclusively shown that the ATPase domain of BRM, but not its bromodomain is the relevant therapeutic target. Therefore, small-molecule inhibitors of the BRM bromodomain are expected to not affect the function of BRM, rendering them ineffective to target BRM. To overcome this major deficiency, bivalent small molecules, conjugating our BRM bromodomain inhibitors to phthalimide, to induce BRM degradation have been designed and synthesized. Phthalimide conjugation strategy is a small molecule Proteolysis Target Chimera (PROTAC) technology which has successfully induced BRD4, BCR-ABL degradation. Although our bivalent molecules could maintain the binding affinity to BRM bromodomain, they failed to cause BRM degradation and growth inhibition in BRG1-deficient cells.

Our future study will focus on the further chemical modification to improve the binding affinity of our ligands to BRM bromodomain and exploration other PROTAC technologies with our ligands to cause BRM degradation.