Cancer Cell Vulnerability to SMARCA2/4 Degradation by PROTACs

INTRODUCTION

Vulnerability of SMARCA4 mutated cancer cells to loss of SMARCA2

RESULTS

Construction of the First SMARCAD2 - PROTAC

ACBI1 Causes Fast and Complete Degradation of SMARCA2, -4 and PBRM1

ACBI1 Induces Apoptosis in SMARCA4-Deficient Cells

ACBI1 is Selective towards SMARCA2, -4 and PBRM1

SUMMARY

CONCLUSIONS

Abstract # 3849

Targeting subsets of BAF (SWI/SNF) chromatin-remodeling complexes has been proposed as an approach to exploit cancer vulnerabilities. Here we describe PROTAC degraders of the BAF ATPase subunits SMARCA2 and SMARCA4 using a bromodomain ligand and recruitment of the E3 ubiquitin ligase VHL. High-resolution ternary complex crystal structures and biophysical investigation guided rational and efficient optimization towards ACBI1, a potent and cooperative degrader of SMARCA2, SMARCA4 and PBRM1. ACBI1 induced antiproliferative effects and cell death caused by SMARCA4 depletion in SMARCA4-mutant cancer cells. These findings exemplify a successful biophysics- and structure-based PROTAC design approach to degrade high profile drug targets and pave the way towards new therapeutics for the treatment of tumors sensitive to the loss of BAF complex ATPases.

• Selective degradation of BAF complex subunits offers novel opportunities for the development of cancer therapeutics.

TEAM

• Structure-guided drug design leads to potent and efficient PROTACs targeting SMARCA2, -4 and PBRM1.
• PROTAC mediated degradation of SMARCA2 and 4 can induce apoptosis in cancer cells.

ACBI1-mediated degradation of SMARCA2 and 4 can induce apoptosis in cancer cells. Selective degradation of BAF complex subunits offers novel opportunities for the development of cancer therapeutics.