Potential SMARCA2 targeted protein degraders induce genetic synthetic lethality in SMARCA4 deleted cancer

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INTRODUCTION

- SWI/SNF complexes play an important role in controlling gene expression by remodelling chromatin.
- SMARCA (BRM) and SMARCB (Brg) are the core subunits of the SWI/SNF complexes that mediate catalytic ATPase activity.
- SMARCA protein expression is lost in some cancers due to damaging mutations (e.g. nonsense, frameshift deletion, splice site mutations) and SMARCA-deflated cancer cells are highly dependent on their paralog gene SMARCB for their survival.
- Patients with homozygously deleted SMARCA cancer show worse prognosis, compared to patients with SMARCB WT expression cancer, and are not likely to benefit from currently available targeted therapy/immunotherapy.
- We demonstrate that targeting SMARCA using SMARCA-selective degraders induce strong synthetic lethality in SMARCB-deleted cancer cells.

RESULTS

SMARCA DELETED CANCERS DEPEND ON ITS PARALOG GENE SMARCA FOR SURVIVAL

IDENTIFICATION OF POTENT AND SELECTIVE SMARCA2 DEGRADERS

SELECTIVE SMARCA2 DEGRADERS FORM BINARY/TERTIARY COMPLEX WITH BOTH SMARCA2 AND SMARCA4

SMARCA DEGRADERS SELECTIVELY INHIBIT PROLIFERATION OF SMARCA4-DEL NSCLC CANCER CELL LINES AND PATIENT-DERIVED LUNG CANCERS

GLOBAL CELLULAR PROTEOMICS PROFILE WITH SMARCA2 SELECTIVE DEGRADERS

CONCLUSIONS

- Our validation studies confirmed the concept of strong synthetic lethality of targeting SMARCA2 in SMARCA4 deleted cancer, consistent with previous reports by other groups.
- Both the SMARCA deletion mutation and SMARCA expression could be essential biomarkers for patient selection strategy of targeting SMARCA2.
- Selective SMARCA2 degrader over SMARCA4 does not require high selectivity of binary/tertiary complex formation for SMARCA2 monobound degraders to SMARCA4 selective tertiary conformation that are competent for ubiquitination and subsequent degradation.
- Our SMARCA2 degraders selectively targeting SMARCA2 protein levels significantly inhibits growth of SMARCA4-DEL NSCLC and PDX cells.
- Selective degrader of SMARCA2 over SMARCA4 was confirmed in vivo as xenograft model.
- In vivo efficacy studies with SMARCA2 selective degraders in SMARCA4-DEL NSCLC xenograft/PDX models are on going.