Discovery of oral SMARCA2 degraders for the treatment of SMARCA4 mutant tumors

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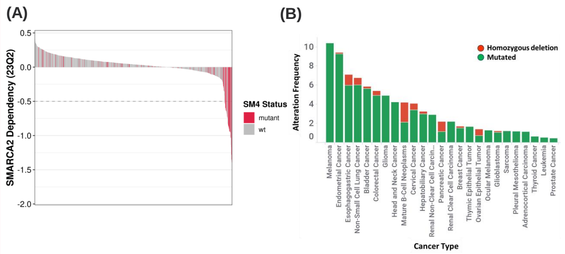
Background

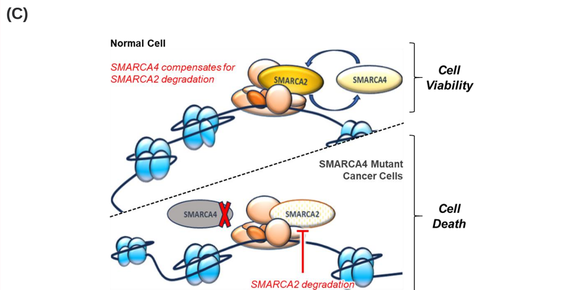
- SWI/SNF complex is a key ATP dependent regulator of chromatin remodeling with significant influence on gene expression[1,2]
- SMARCA2 and SMARCA4 are the subunits in the SWI/SNF complex able to hydrolyze ATP
- SMARCA4 has been found to be mutated in multiple solid tumors[1,2]
- The loss of SMARCA4 function renders the cell entirely reliant on SMARCA2 for survival[3,4]

Key Findings

- Potent and selective SMARCA2-targeted degraders demonstrate favorable pharmacokinetic properties after oral delivery
- Selective degraders show potent anti-proliferative activity in SMARCA4 Loss of Function (LoF) cancer models in vitro and in vivo with minimal impact on wild-type cells

Introduction





(**A**) Depmap data highlights that cell lines with SMARCA4 mutations exhibit dependency on SMARCA2[5]. (**B**) SMARCA4 mutations and deletions are common across multiple tumors. Data shown are from TCGA PanCancer Atlas Studies. (**C**) Synthetic lethality model of SMARCA2 degradation in SMARCA4 mutant tumors.

Figure 1. 3rd Gen SMARCA2 lead series degraders are potent, selective with good oral bioavailability

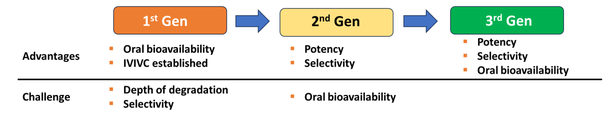


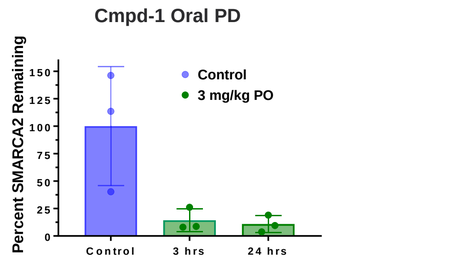
Figure 2. 1st Gen degraders exhibited good oral bioavailability and potent in vivo SMARCA2 degradation after oral administration

(A)

Cmpd-1 Mouse PK

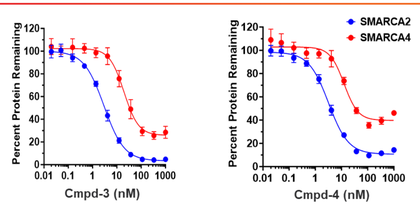
	Dose mg/kg	AUC (hr*ng/ml)	$T_{1/2}$ (hr)	CL (ml/min/kg)	F (%)
IV	1	6630	10	2	NA
PO	3	5325	8	NA	25

(B)



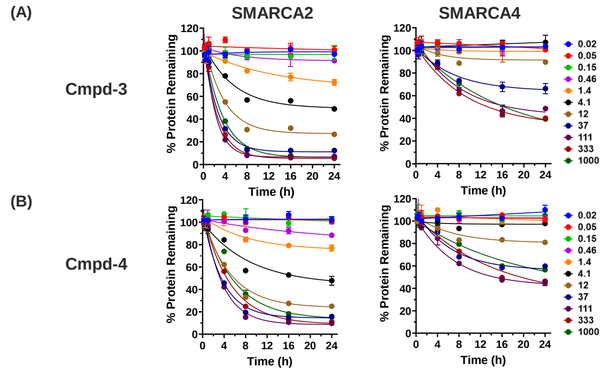
(**A**) Gen-1 degrader Cmpd-1 exhibited low clearance with good oral bioavailability. (**B**) Mice bearing NCIH838 tumors were treated orally with a single 3 mg/kg dose of Cmpd-1. SMARCA2 degradation was evaluated at 3 and 24 hrs and compared to vehicle treated animals. Robust SMARCA2 degradation was observed after 3 hrs and persisted through 24 hrs.

Figure 3. 3rd Gen SMARCA2 degraders exhibit potent and selective degradation of SMARCA2



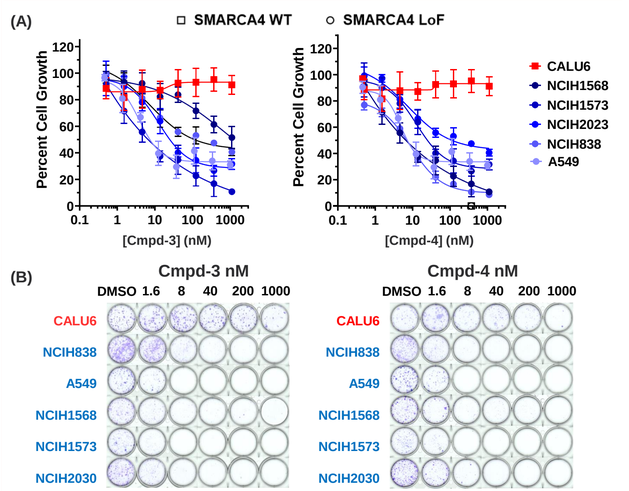
Representative degradation dose response curves demonstrating our lead series degraders Cmpd-3 and Cmpd-4 exhibiting potent and selective SMARCA2 degradation in HT1080 HiBit cell lines.

Figure 4. 3rd Gen SMARCA2 degraders exhibit rapid degradation kinetics



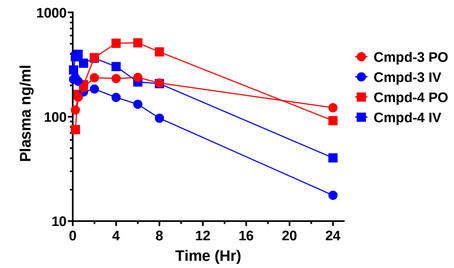
Degradation over time was measured using Hibit assay for degraders Cmpd-3 (**A**) and Cmpd-4 (**B**). Both degraders exhibit rapid degradation of SMARCA2 with only partial degradation of SMARCA4 even at highest concentrations tested. Degradation kinetic curves were fit to single exponential decay to calculate the maximal Dmax independent of time. The maximum degradation that can be achieved for SMARCA2 for Cmpd-3 and Cmpd-4 is 92 and 89%, respectively, and SMARCA4 69 and 55%, respectively, Data not shown.

Figure 5. 3rd Gen degraders Cmpd-3 and Cmpd-4 exhibit selective anti-proliferative activity in a panel of SMARCA4 LoF cells



(**A**) CTG based antiproliferative assay demonstrate 3rd Gen molecules to have selective anti-proliferative activity on a panel of SMARCA4 LoF cell lines with no effect on growth of wild-type CALU6 cells. (**B**) Colony formation assays confirm potent and selective anti-proliferative activity only on SMARCA4 LoF cell lines.

Figure 6. 3rd Gen degraders exhibit excellent oral bioavailability



Degrader	Dose (mg/kg)	CL (mL/min/kg)	Vdss (L/kg)	T1/2 (h)	F (%)
Cmpd-3	0.5 (IV) 1.0 (PO)	3.9	2.2	6.3	96
Cmpd-4		2.0	1.2	7.1	88

Mouse PK studies demonstrate that 3rd Gen degraders exhibit low clearance < 4 ml/min/kg and excellent oral bioavailability with >80 %F.

Conclusions

- First generation oral SMARCA2 degrader, Cmpd-1, demonstrates that in vitro degradation potency and in vivo oral bioavailability translates to potent in vivo SMARCA2 degradation
- Lead series degraders (Gen-3) exhibit:
  - Potent and selective degradation of SMARCA2 versus SMARCA4
  - Potent antiproliferative activity on SMARCA4 LoF cells compared to WT cells
  - Excellent oral bioavailability

References

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