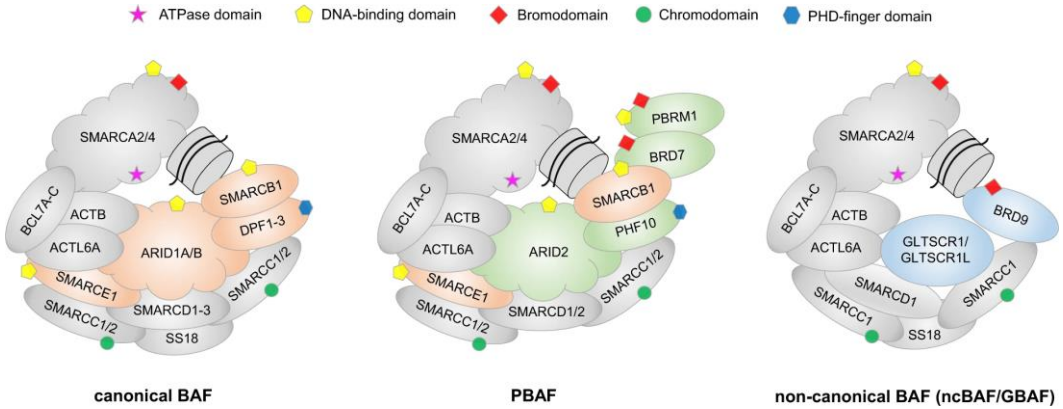
Discovery of Oral SMARCA2 Degraders for the Treatment of SMARCA4 Loss of Function Tumors

SK life science labs (SKLSL)
Formerly Proteovant Therapeutics

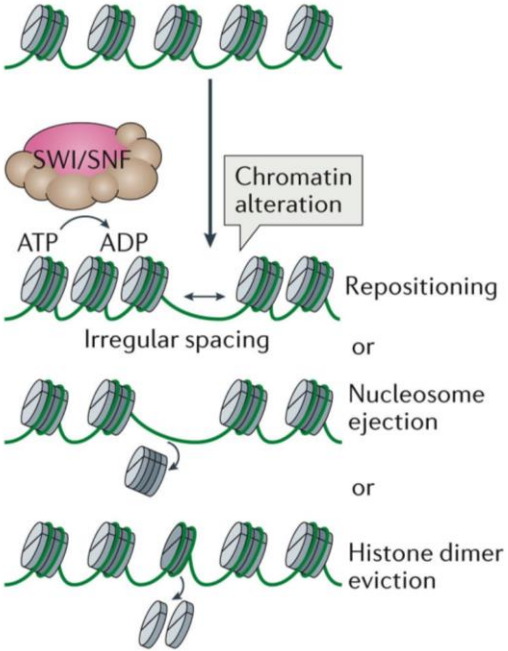
Jose C. Clemente .
Sr. Director of Biology
Oct 30th, 2023

SK life science labs
a subsidiary of SK biopharmaceuticals

SWI/SNF ATP-dependent chromatin remodeling is critical for nucleosome positioning



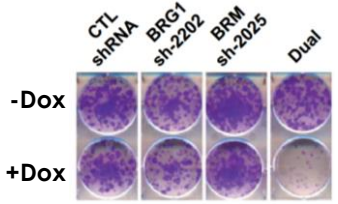
ATPase function within the SWI/SNF complex is only provided by the mutually exclusive SMARCA2/4 paralogous subunits



ATPase role of SMARCA is indispensable for the function of the SWI/SNF complex

Non-essential role of SMARCA2 and SMARCA4 BRD provide opportunity for driving selectivity through degradation

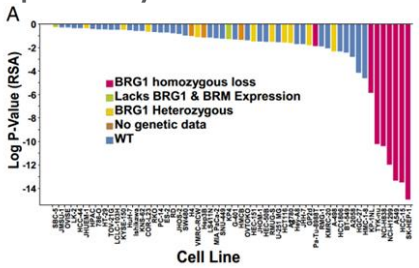
Simultaneous depletion of SMARCA2/4 is not tolerated



BRG1 = SMARCA4
BRM = SMARCA2

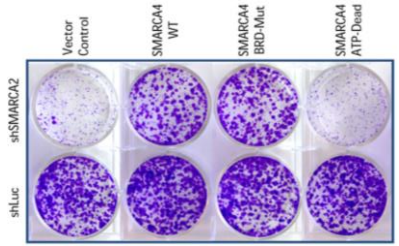
BEAS2B Cells (SM4/BRG1 Wild-type)

SMARCA2 depletion is synthetic lethal in SMARCA4 deficient cells

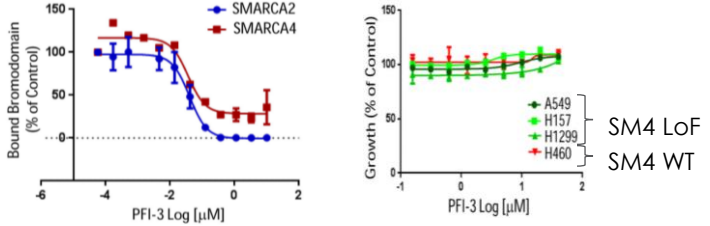


Hoffman Gregory R et al *PNAS* vol. 1118 (2014)

ATPase domain is vital to cell viability



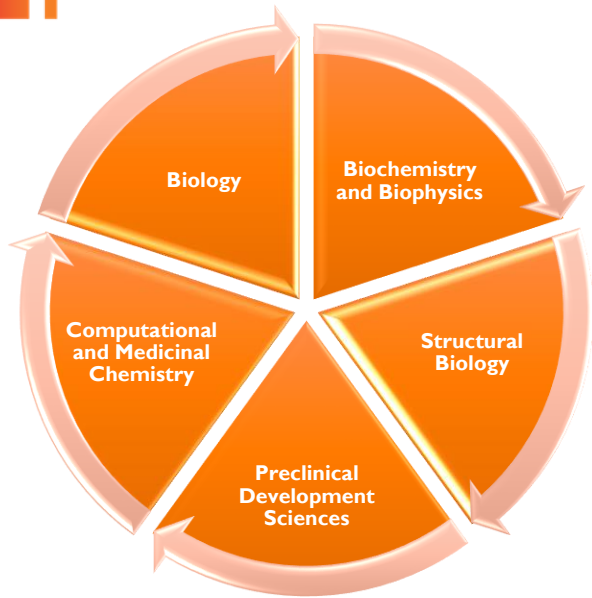
The bromodomain is not essential for cellular growth inhibition

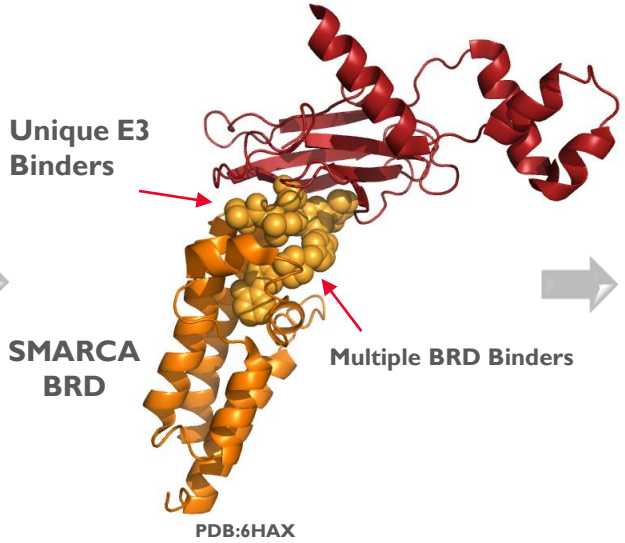


Vangamudi Bhavatarini et al. *Cancer research* vol. 7518 (2015): 3865-3878

- The essential role of SMARCA2/4 provides a clear mechanistic basis for the synthetic lethal relationship between the paralogs
- ATPase domain is druggable however inhibitors have faced selectivity challenges
- SMARCA2 bifunctional degraders can leverage BRD binding to retain cellular selectivity and minimize systemic toxicity

SKLSL strategy for the discovery of orally bioavailable potent and selective SMARCA2 heterobifunctional degraders

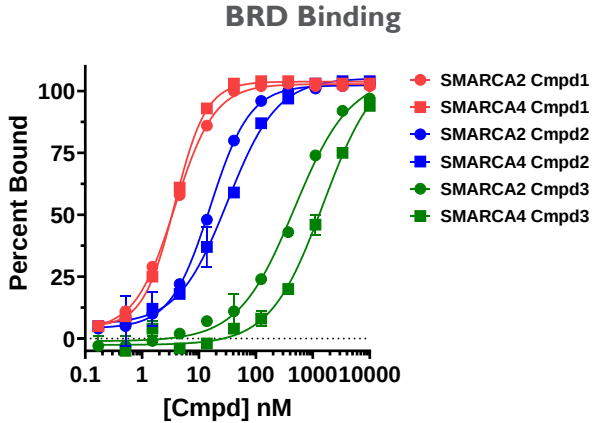




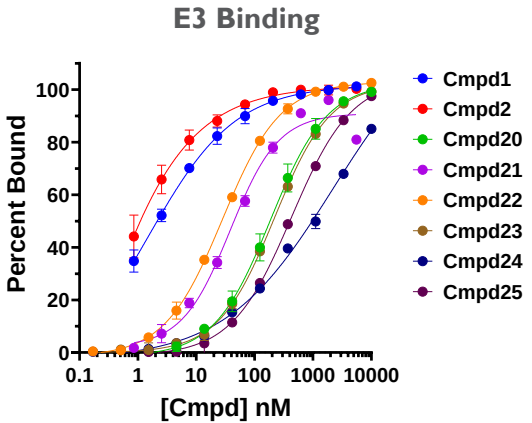
Orally bioavailable potent and selective SMARCA2 degraders

- SK life science labs (SKLSL) applies a multi-disciplinary approach to drug discovery
- Fully integrated discovery teams incorporate structure-based drug design
- SMARCA2 program series cover multiple E3s and BRD warheads

Initial warhead characterization determines binary binding to the target and E3

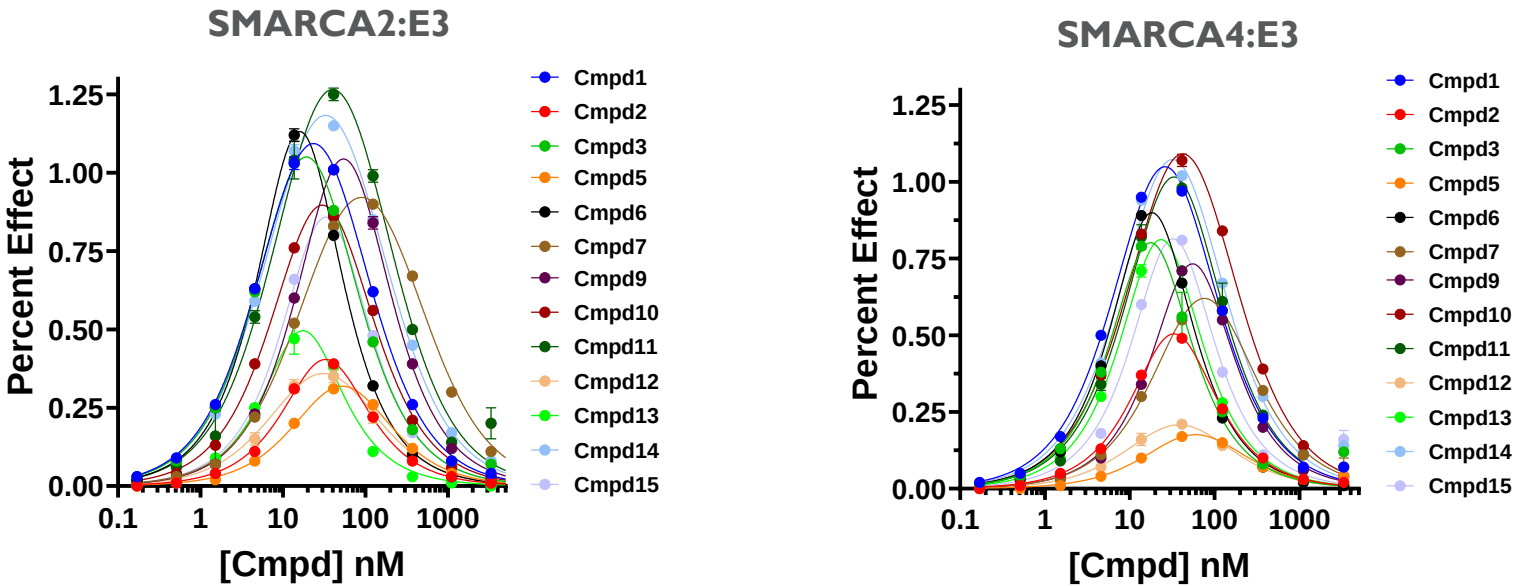


- HTRF assay utilized for evaluation of SMARCA2 and 4 BRD binding
- Chemical diversity in BRD binding molecules is evident through a range of potencies
- BRD binders exhibit similar potencies for SMARCA2 and 4



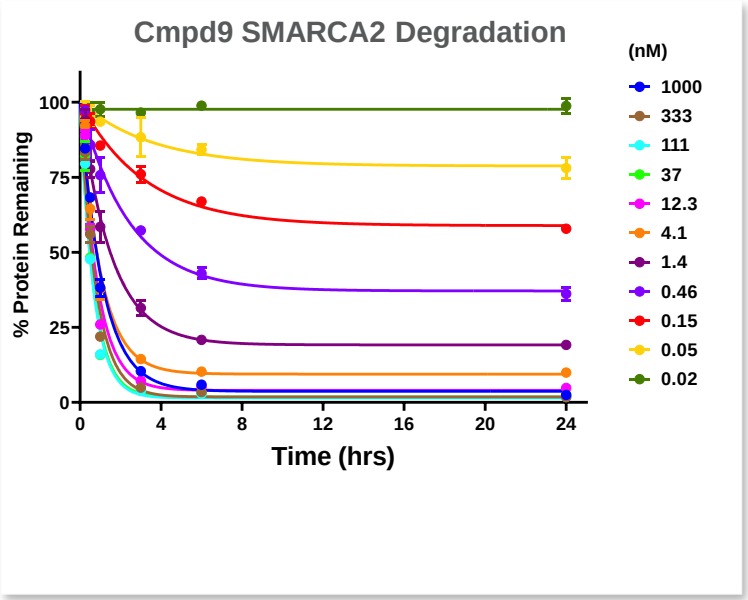
- HTRF assay utilized for evaluation of E3 warheads
- Chemical diversity in E3 binders exhibit a range of binding potencies
- Both high and low affinity binders can lead to potent degraders

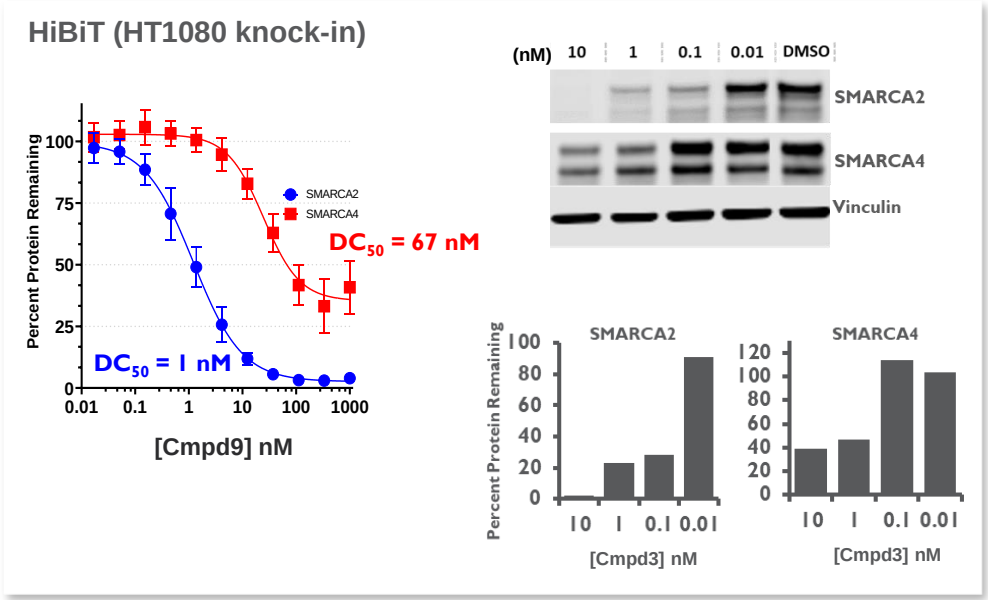
Compounds that represent an array of BRD and E3 binding potencies lead to a range of efficacy in ternary complex assays



- HTRF based ternary complex assay established to evaluate SMARCA2 or SMARCA4 with E3
- Chemically diverse and novel compounds with a range of BRD and E3 binding utilized to design heterobifunctional molecules with varied ternary complex potencies

Discovery of potent selective and rapid degraders of SMARCA2

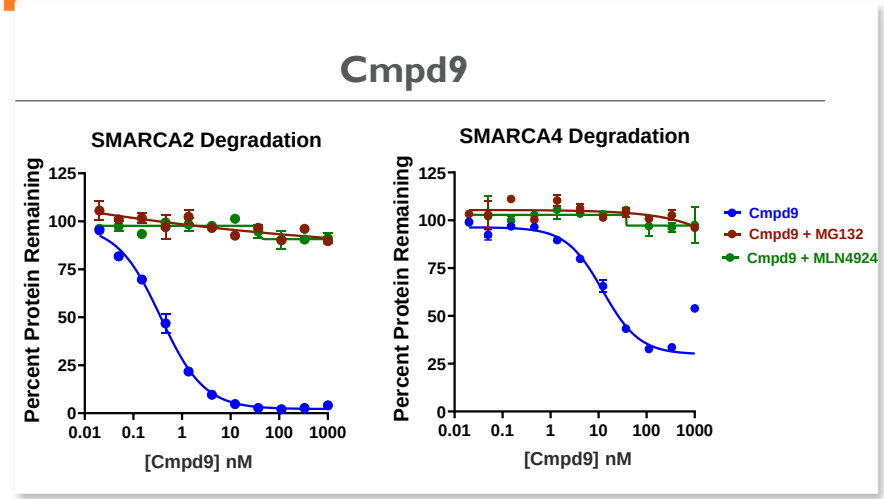


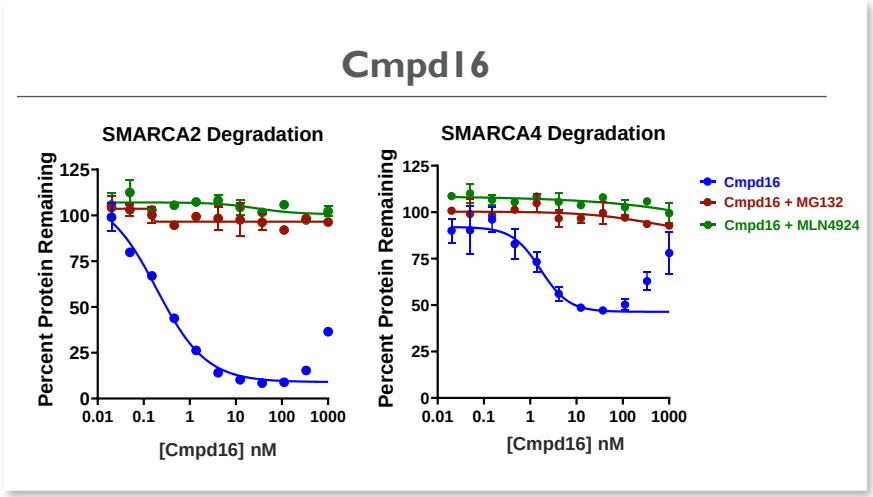


- SKLSL heterobifunctional degraders exhibit rapid kinetics
- Maximal degradation is achieved by 6 hours in HiBiT assay (HT1080 cells)

- HiBiT knock-in cell line utilized to determine degradation potency and selectivity
- Parental cell line exhibits similar response as HiBit degrader profiling cell line to confirm

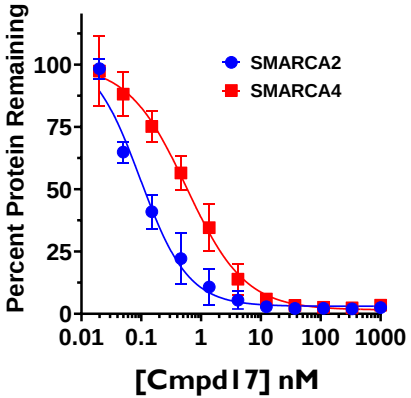
Structurally diverse molecules demonstrate proteasome dependent degradation of SMARCA2 and 4

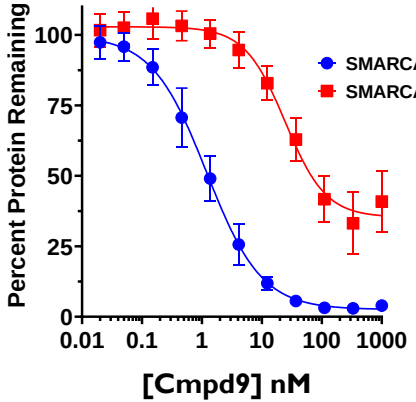




- Cmpd9 and Cmpd16 are two chemically diverse degraders
- Preincubation with neddylation inhibitor MLN4924 or proteosome inhibitor MG132 prevents degradation of SMARCA2 and 4
- Cmpd9 and Cmpd16 degradation of SMARCA2 and 4 exhibit cullin ring E3 ubiquitin ligase and proteasome dependence

SMARCA2 selective or dual degrader molecules allow for investigation of biology *in vitro* and *in vivo* correlation

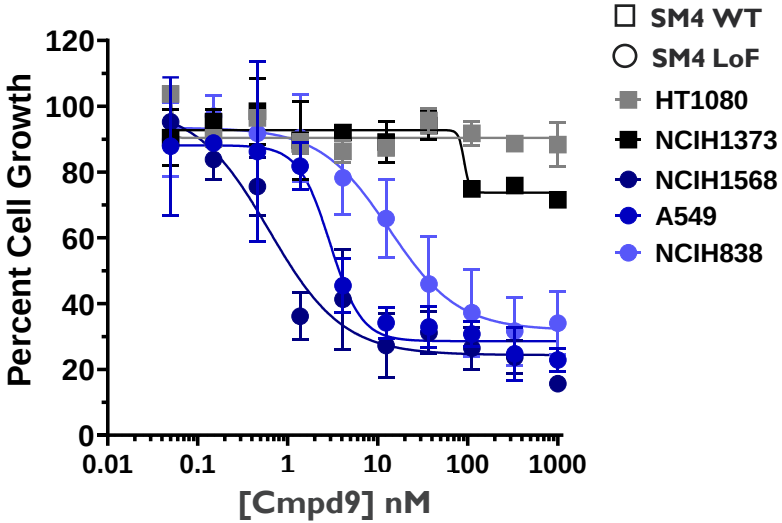


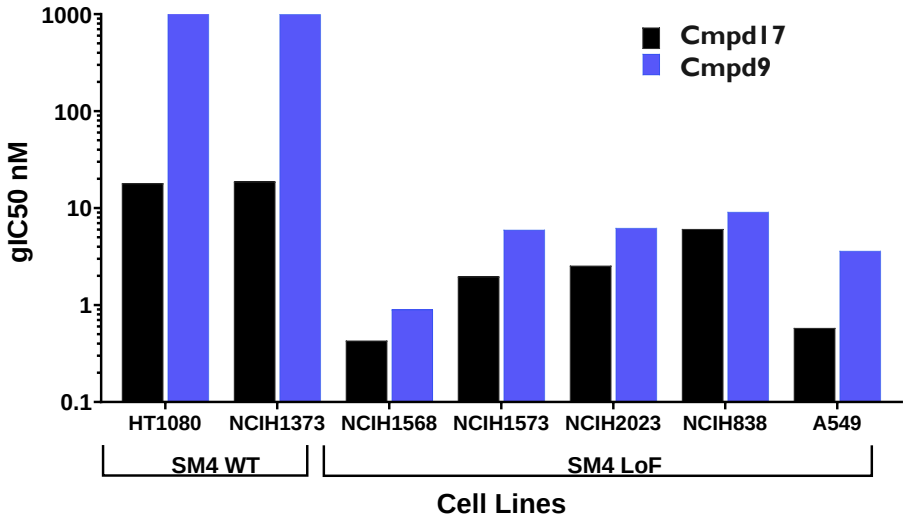


	SMARCA2		SMARCA4	
	DC_{50} (nM)	DMax (%)	DC_{50} (nM)	DMax (%)
Cmpd17	0.1	97	0.6	98
Cmpd9	1	97	67	65

- HT1080 HiBit assay utilized to evaluate degradation
- Cmpd17 and 9 exhibit differences in degradation potency and selectivity
- Cmpd9 is a potent and selective SMARCA2 degrader
- Cmpd17 and Cmpd9 exhibit equivalent plasma clearance and tumor exposure.

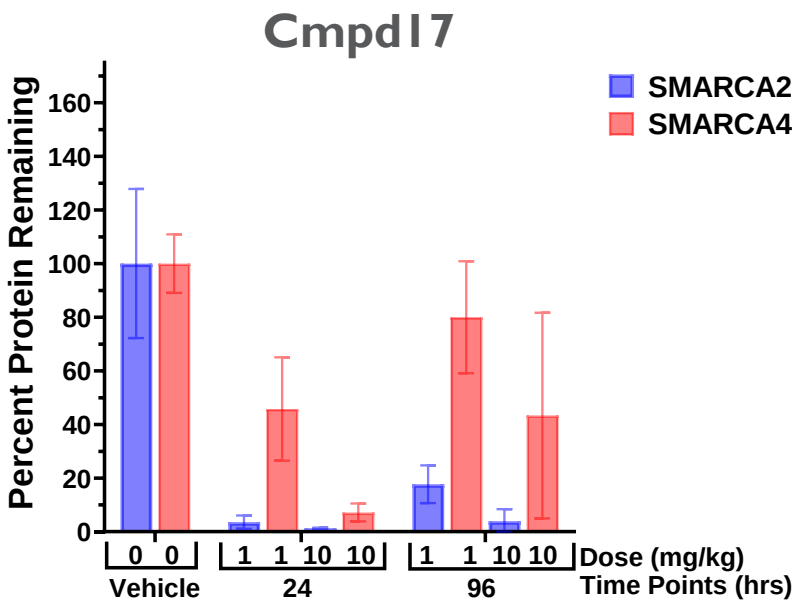
SMARCA2 degradation selectivity leads to selective *in vitro* anti-proliferative activity in SMARCA4 LoF cells

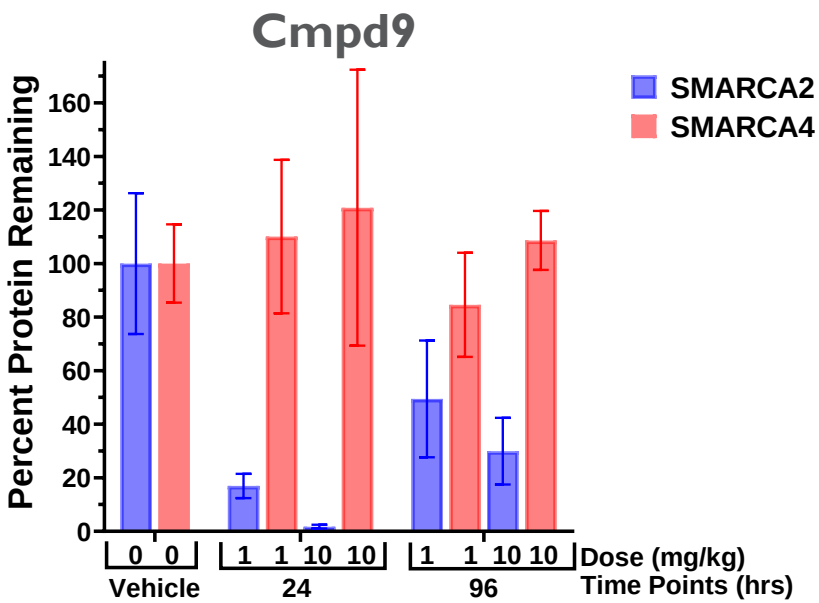




- 6-day proliferation assay used to investigate biological impact of SMARCA degradation
- Cmpd9 is a selective SMARCA2 degrader while Cmpd17 degrades SMARCA4 with similar potency
- Selective SMARCA2 degraders exhibit selective antiproliferative activity on SMARCA4 LoF cells

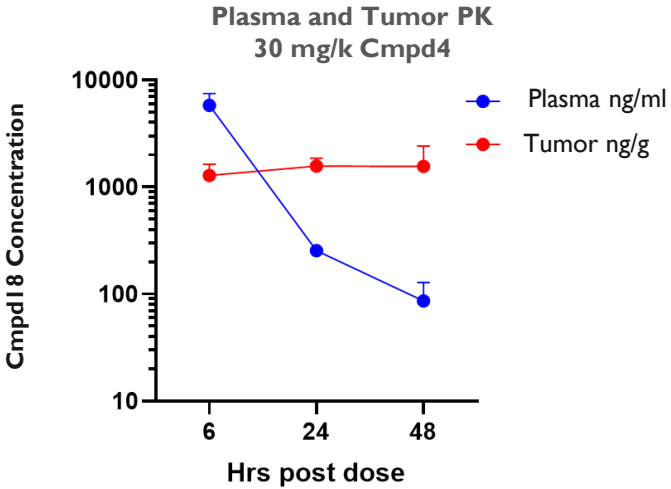
In vitro SMARCA2 degradation potency and selectivity translates to *in vivo* xenograft tumor model

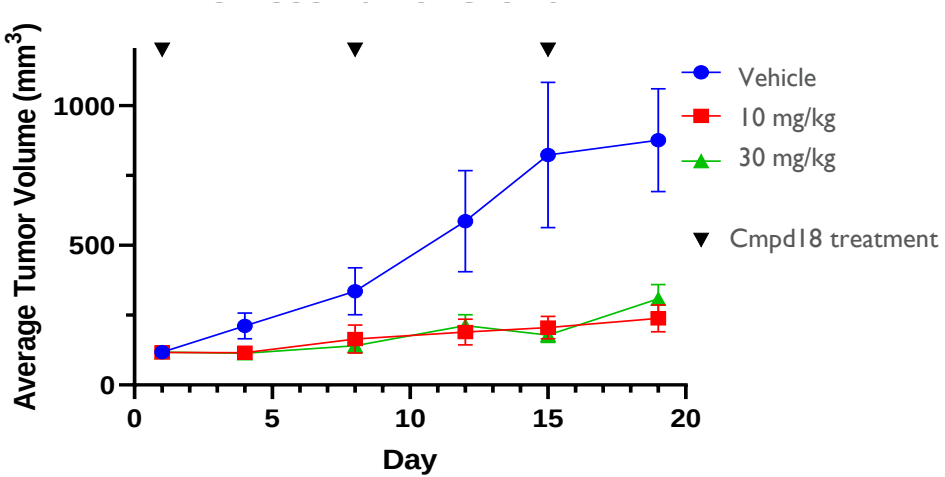




- HT1080 xenograft model established for *in vivo* assessment of degradation
- SMARCA2 and SMARCA4 degradation in tumors was assessed after single administration of Cmpd17 or Cmpd9
- Cmpd17 is more potent while Cmpd9 shows greater selectivity than Cmpd17 *in vivo* thereby correlating with *in vitro* results

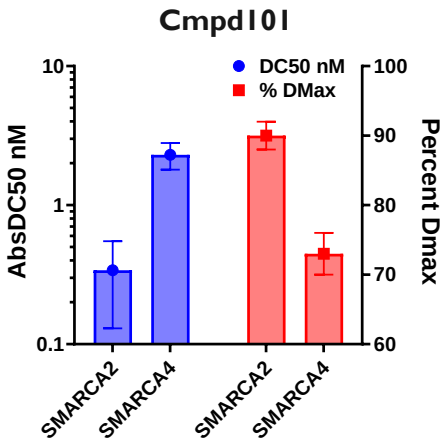
Cmpd18 showed sustained tumor exposure leading to anti-tumor efficacy in NCIH838 SMARCA4 LoF NSCLC tumor model

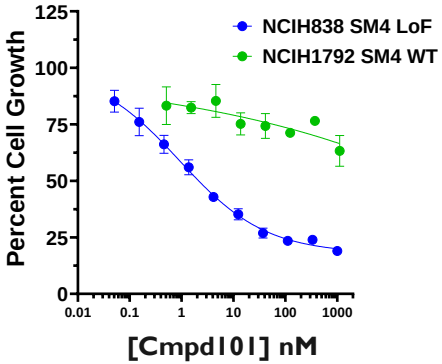




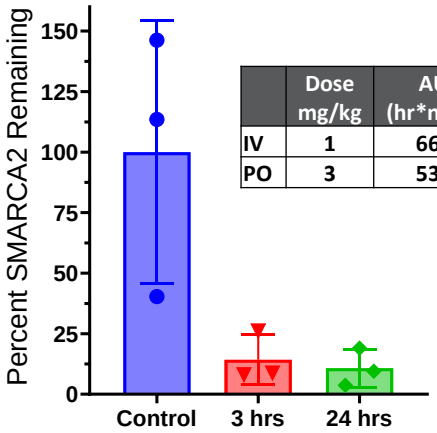
- Cmpd18 selectively degrades SMARCA2 over SMARCA4 *in vitro* and *in vivo*
- NCIH838 SMARCA4 LoF xenograft model was established for *in vivo* evaluation of SMARCA2 degrader efficacy
- Cmpd18 demonstrates sustained tumor exposure in NCIH838 xenograft model
- Cmpd18 treatment leads to potent anti-tumor efficacy effect in SMARCA4 LoF tumor model

Orally bioavailable Cmpd101 demonstrates potent and selective SMARCA2 activity *in vitro* and *in vivo*





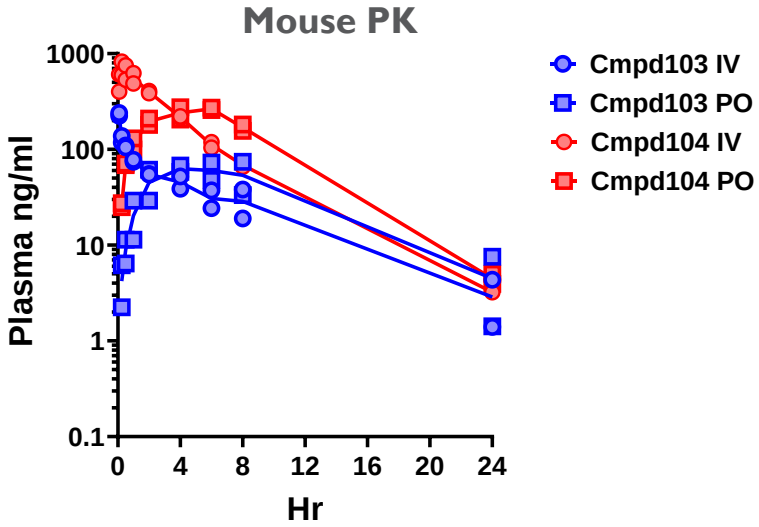
- Selective degradation evident in Hela HiBit assay
- Potent and selective antiproliferative activity on SMARCA4 LoF cells



	Dose mg/kg	AUC (hr*ng/ml)	T1/2 (hr)	CL (ml/min/kg)	F (%)
IV	1	6630	10	2	
PO	3	5325	8		25

- High circulating exposure and low clearance after Cmpd101 IV (1 mg/kg) and PO (3 mg/kg) administration
- Robust SMARCA2 degradation after single 3 mg/kg oral administration by 3 hours that persists through 24 hours

Two structurally unique series of SMARCA2 degraders demonstrate oral bioavailability



	Dose mg/kg	Vdss (L/kg)	T1/2 (hr)	CL (ml/min/kg)	F (%)
Cmpd 103	0.5 (IV) 1.0 (PO)	5.3	5.0	14	58
Cmpd 104		3.4	6.6	6.7	18

- SKLSL series of degraders exhibit oral bioavailability in mice ranging from 7-58 %F
- Rat oral bioavailability ranges from 9-31 %F
- Orally bioavailable degraders exhibit selective degradation of SMARCA2 and growth inhibition of SMARCA4 LoF cells

SKLSL rapidly advances selective SMARCA2 oral degraders through discovery

Degrader profile	• Multiple structurally diverse series • Rapid potent and selective degradation of SMARCA2 • Proteasome dependent degradation
Biology	• Potent and selective anti-proliferative activity on panel of SMARCA4 LoF cell lines with no impact on growth of WT cells • *In vivo* efficacy in SMARCA4 LoF xenograft model (IV delivery complete oral planned)

PK profile	• Potent degraders with demonstrated oral bioavailability
	  ◦ Mouse %F range 7 - 45% and low clearance
	  ◦ Rat %F range 9 - 31% and low clearance
	• Excellent *in vivo* exposure after oral administration that leads to >90% SMARCA2 degradation at 24 hrs

Acknowledgements

SK life science labs
a subsidiary of SK biopharmaceuticals

Biology & Computational Biology
Jose C. Clemente
Debangshu Samanta
Timothy Dougherty
Clemente Aguilar
Nathan Kendsersky
Shreyas Joshi

Chemistry & Computational Chemistry
Lal Harikrishnan
Zhenwu Li
Steve Knight
Matt Tudor
Qiaolin Deng

Biochemistry & Structural Biology
Elham Behshad
Peter Orth

DMPK
Rakesh Nagilla

Project Management
Christine Stuhlmiller

Discovery Leadership
Corey Strickland
Helai Mohammad
Larry Jolivette
Scott Priestley
Winston Wu
Zhihua Sui

University of Michigan

Prof. Shaomeng Wang

Chemistry
Lin Yang
Lingying Leng
Wenbin Tu
Rohan Rej
Srinivasa Rao Allu

Biochemistry/Cell Biology
Liyue Huang
Mi Wang
Wenbin Tu

In vivo Pharmacology
Wei Jiang
Yu Wang
Wen Bo
Duxin Sun

Computational design
Jelena Tosovic
Paul Kirchoff

Structural Biology
Jeanne Stuckey

partnering@proteovant.com