SK Life Science Labs:

Discovering Better Medicines through Target-Centric TPD Powered by MOPED™ Glue Platform

June 5, 2024

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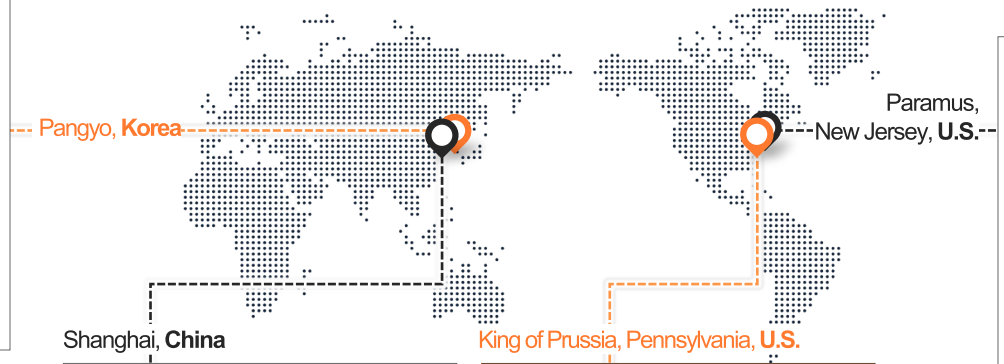
SK Life Science Labs is a U.S. Subsidiary of SK Biopharmaceuticals

HEADQUARTERS

SK biopharmaceuticals

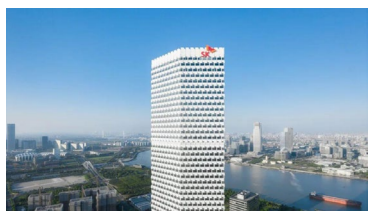
Discovery / R&D Center (CNS & Oncology)
Corporate Strategy & Business Development

SUBSIDIARIES



SK bio-pharm tech

Regulatory and Clinical Support
China Business Development



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Discovery R&D Center (TPD)

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Global Clinical Development
Quality Assurance & Regulatory Affairs
Sales & Marketing

Why targeted protein degradation?

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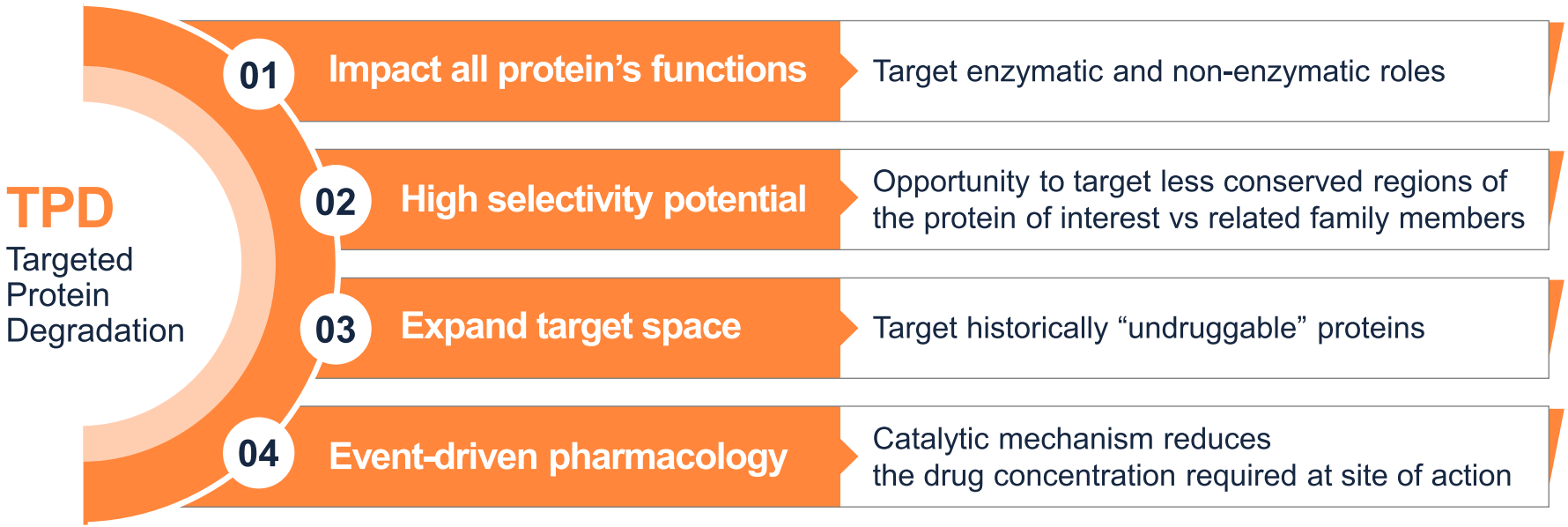
Protein degradation offers advantages to improve clinical outcomes



SK Life Science Labs TPD capabilities powered by innovative platform

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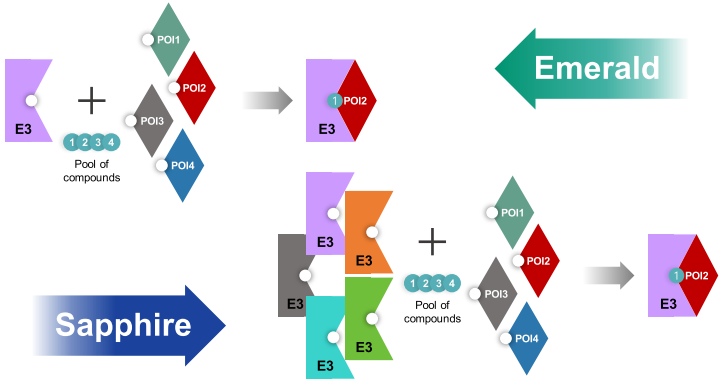
Proprietary drug discovery & preclinical development engine

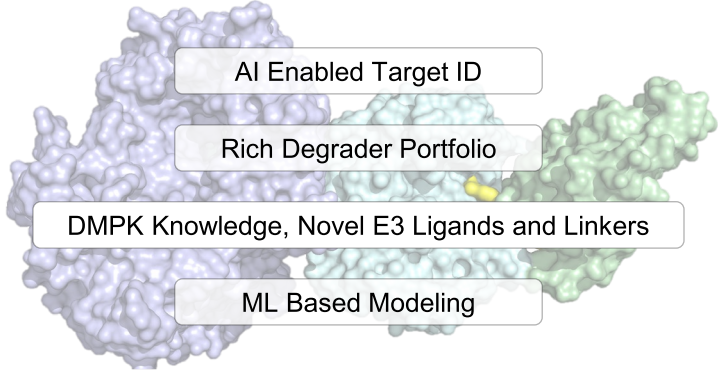
MOPED™ Glue Platform

Induced proximity platform
to find molecular glues that degrade
difficult targets or perturb function



Core TPD Capabilities

Fully integrated cross-functional expertise
from target identification
through preclinical development



MOPED™ Glue Platform

SK Life Science Labs Differentiated Approach Breaks Through Limits Of TPD

MOPED™ enables SK Life Science Labs to discover novel molecular glues utilizing an expanded set of E3s

Majority of TPD Companies

Most TPD companies primarily use CRBN and VHL, limiting target access

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SK Life Science Labs leverages a wider range of E3s to expand target access

MOPED™ Leverages Induced Proximity To Discover Glues

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MOlecular Proximity Enabled Detection (MOPED™)

Emerald
A highly sensitive biochemical workflow to discover glues against defined POIs

Sapphire
A cellular context-based workflow to discover glues against defined POIs

Molecular Glue Discovery

INCREASE ACCESS TO TARGETS
Targeting structured and unstructured regions

INCREASE NUMBER OF LEADS
Multiplexing compounds, targets, and/or E3s

EXPAND E3 OPPORTUNITIES
Known E3s, target matched E3s, and/or E3 agnostic

BROADEN BIOLOGICAL IMPACT
Exploring potential biological functions beyond TPD

Emerald: Biochemistry Designed For Molecular Glue Discovery

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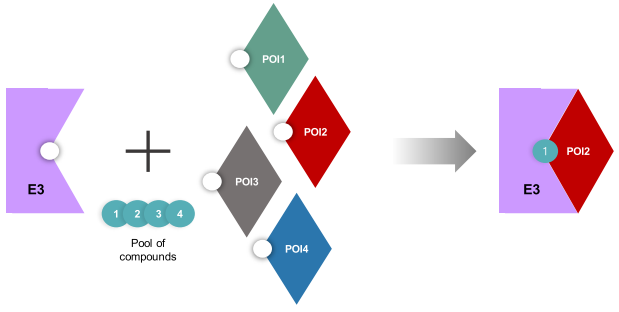
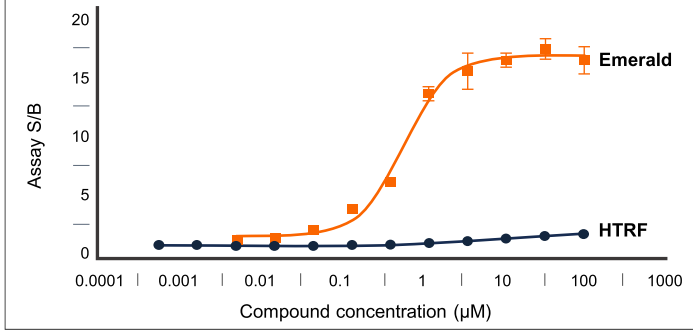
Highly sensitive assay to find leads for chemical optimization

MOPED™ Glue Platform



Highly Sensitive Format



Glue screen to measure ternary complex formation

- Biochemical assay format with sensitivity to detect < 2 nM of ternary complex
- ~20 E3s are tested individually with the library of E3s continually expanding
- Pools of compounds and POIs are tested for efficient 1536-well screening of a > 500,000 compound library

Hits discovered for 3 of 4 targets

- Degradation observed for target A
- Hits elaborated to <100 nM for target B
- Early stage of hit elaboration for target C
- Glues for 5 E3s across 4 targets discovered

Pipeline

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SK Life Science Labs Current Focus: Oncology & Immunology

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SK Life Science Labs programs and platforms are well positioned for partnering with significant market potentials

Program	Disease Area	Discovery	Preclinical
IKZF2	Solid Tumors	PVTX-405	
ER	HR+ Breast Cancer	PVTX-321	
p300	Oncology		
STAT3	Immunology, Oncology		
SMARCA2	Oncology		
Heterobifunctional Target	Oncology		
Molecular Glue Target	Oncology		

Packaging The Genome And Positioning Genes For Transcriptional Outcomes Requires Tightly Controlled Interplay Of Epigenetics

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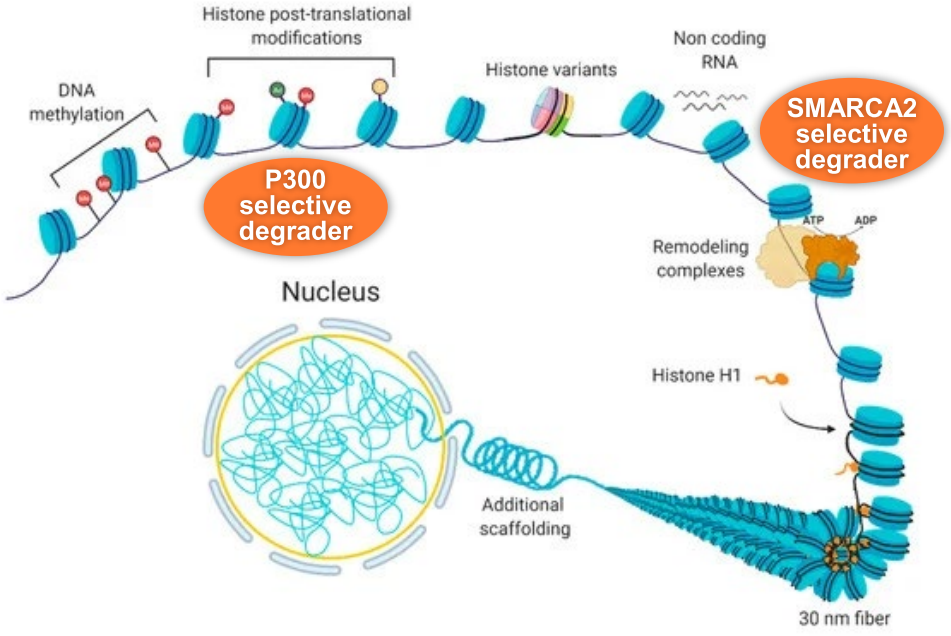
Machinery can read, write, erase, and remodel

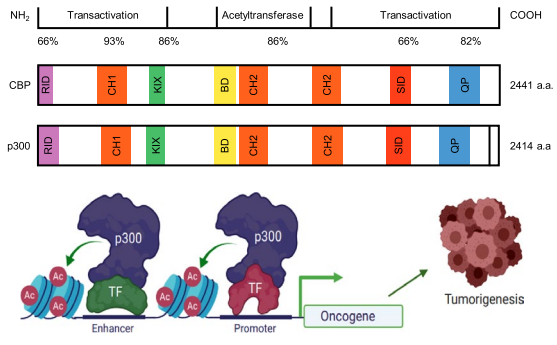


- **DNMTs** methylate CpG dinucleotides, frequently in the context of CpG rich regions
- **Histone modifying enzymes** catalyze the addition or removal of a variety of post-translational modifications (PTMs) including acetylation, phosphorylation, methylation, and many more
  - Epigenetic readers, including proteins that contain bromodomains or chromodomains, interpret the histone PTMs
- **Chromatin access** requires the activity of SWI/SNF ATP dependent remodeling complexes

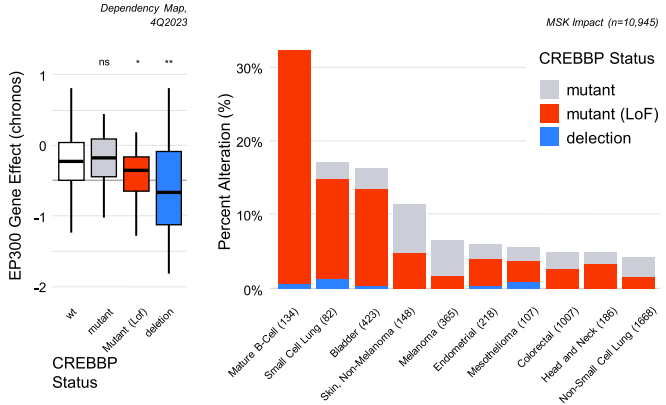
A Alpsoy et al., Biology (Basel) 2021

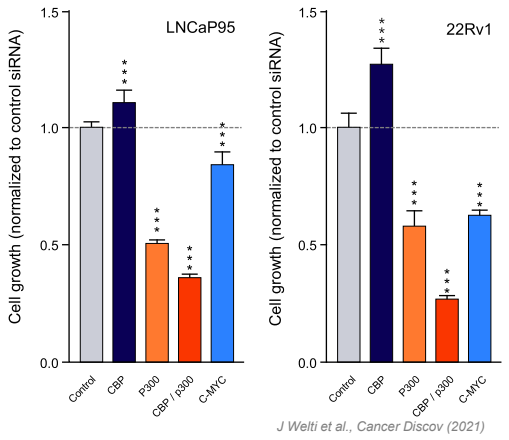
p300 is Required for the Growth of CBP Mutant or AR+ Cancer Cells

Selectivity over CBP offers tumor-specific improved tolerability in wild-type or normal cells



MV Karamouzis et al., Cell Research (2007), AR Waddell et al., Cancers (2021)



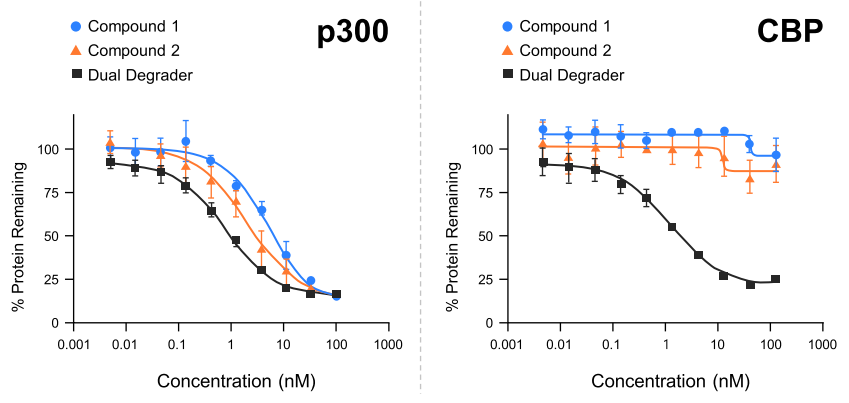


J Welti et al., Cancer Discov (2021)

- p300 and CBP are HAT (histone acetyl transferase) enzymes that mark proteins with an acetyl group to activate expression of genes that are important in normal and cancer cell biology
- p300 and CBP share high sequence similarity across functional domains posing an an unresolved challenge in discovery of selective inhibitors
- Dual inhibitors have entered the clinic despite narrow therapeutic margins
- p300 knock-down is synthetically lethal in presence of CBP mutations allowing for selective growth inhibition in this tumor-specific context
- p300 is required for the growth of AR+ prostate cancer cells while CBP is dispensable

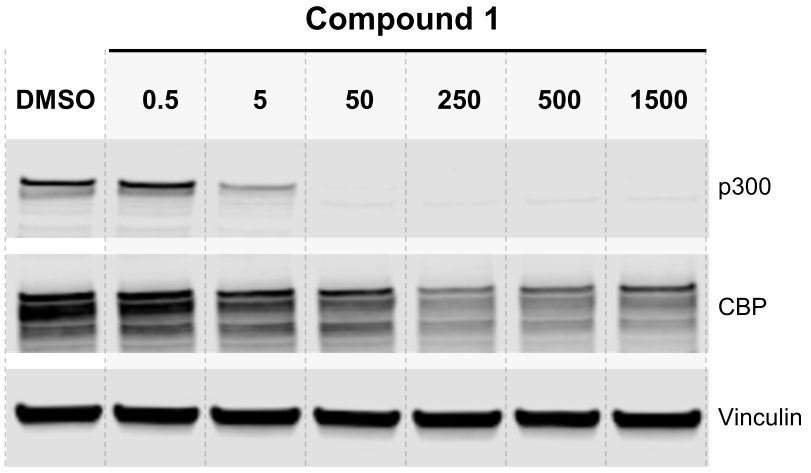
p300 Degraders Show Potent and Selective Degradation

p300 selective degraders show low nM potency with minimal impact on CBP



	P300		CBP	
	D_{max}(%)	DC_{50}(nM)	D_{max}(%)	DC_{50}(nM)
Compound 1	85	6.5	13	> max
Compound 2	85	2.0	27	> max
Dual Degrader	84	1.0	79	1.5

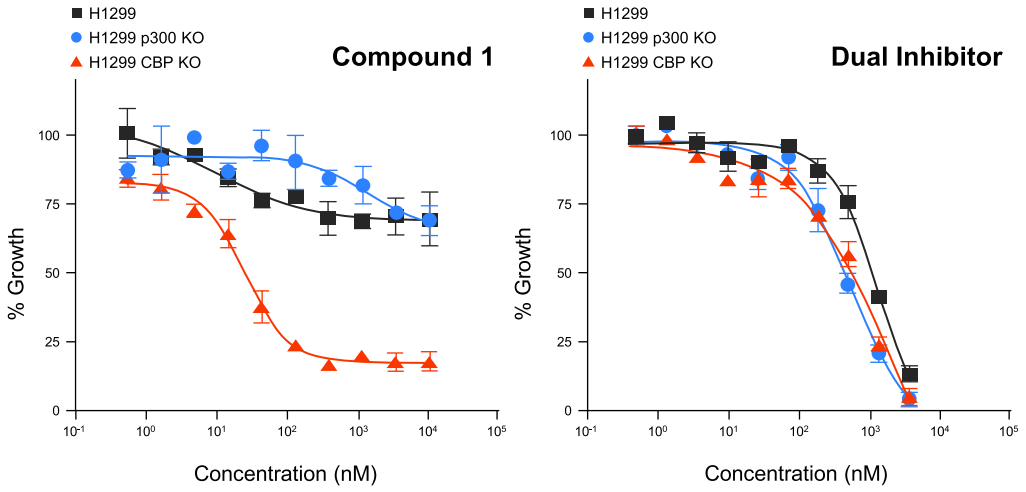
- Selectivity of degradation measured by HiBiT knock-in of either p300 (left) or CBP (right) in A549 cells

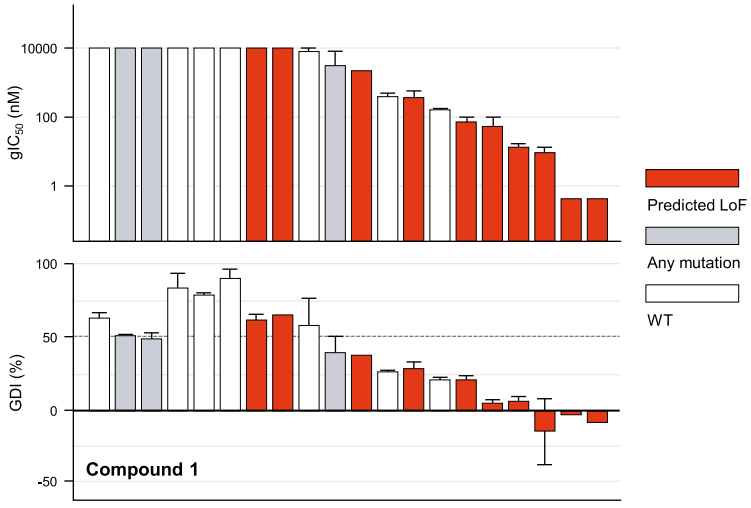


- Dose response by western blot confirms selectivity for p300 in H1299 cells expressing endogenous and untagged proteins

p300 Degraders Result in Selective Growth Inhibition in Synthetic Lethal Context

Potent growth inhibition is observed in CBP impaired cells

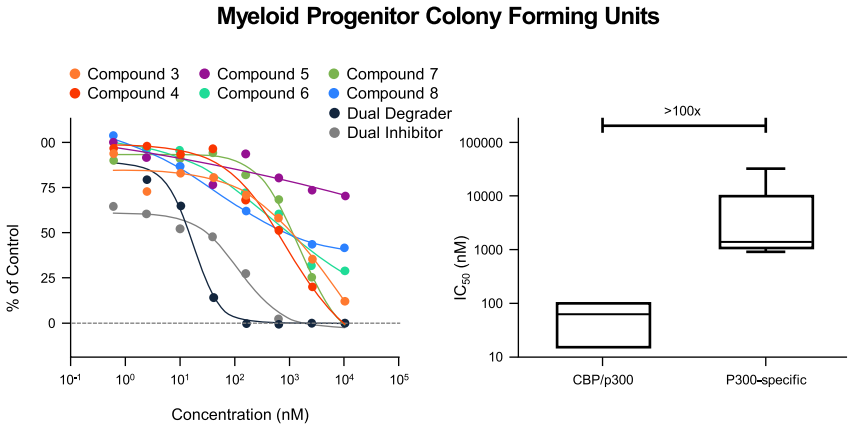


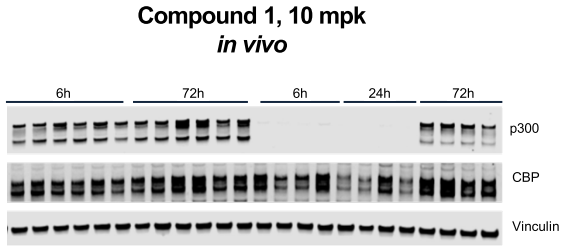


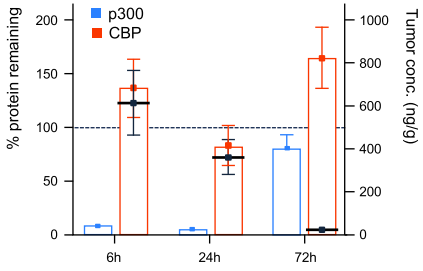
- Engineered cell lines and a cancer cell line panel were utilized to investigate effects on cell growth in 6-day proliferation assay
- A clinical stage dual p300/CBP inhibitor inhibits growth in all contexts while p300 degraders lead to growth inhibition in CBP knock-out of loss-of-function (LoF)
- Selective degraders show minimal impact to growth of p300 knock-out or wild-type cancer cells

p300 Degrader is Efficacious in AR+ Prostate Cancer Models

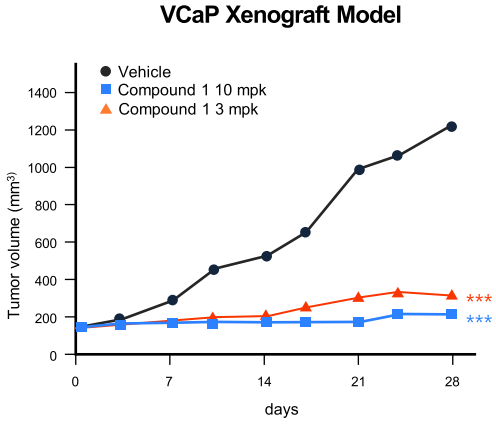
Toxicity to bone marrow derived progenitor cells is minimized through selectivity for p300

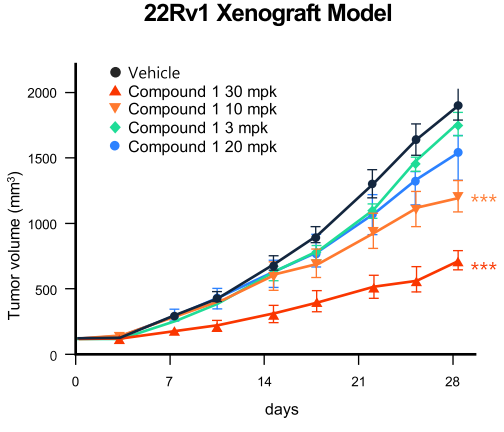






- Dual degrader and dual inhibitor inhibit the growth of bone marrow derived myeloid progenitor cells
- p300 selective degraders show markedly less potency in bone marrow toxicity assay suggesting a better therapeutic index
- Oral administration (once daily) of Compound 1 to mice with prostate cancer xenografts demonstrates substantial tumor growth inhibition at pharmacologically relevant doses





p300 Degrader With First-in-class Potential

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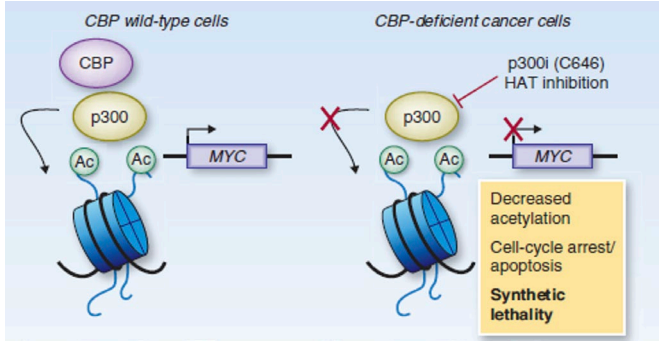
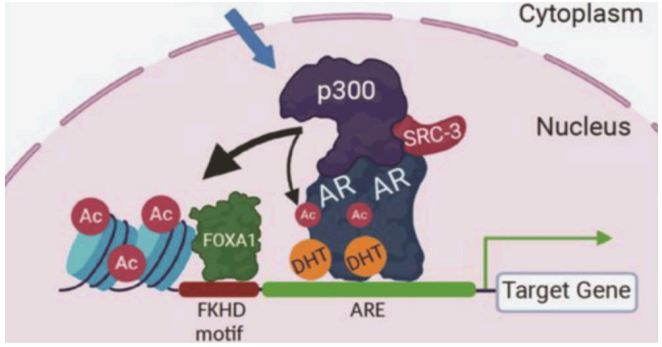
Orally available p300 selective heterobifunctional degrader for CBP mutant cancer and mCRPC



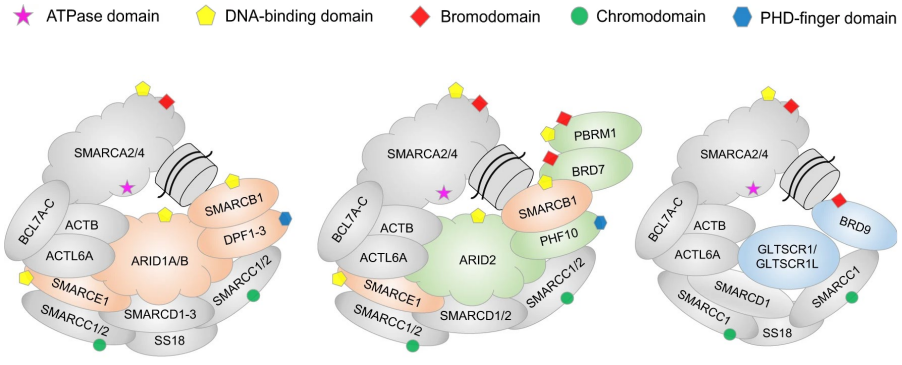


C Kadoch et al., Cancer Discovery (2016), AR Waddell et al., Cancers (2021)

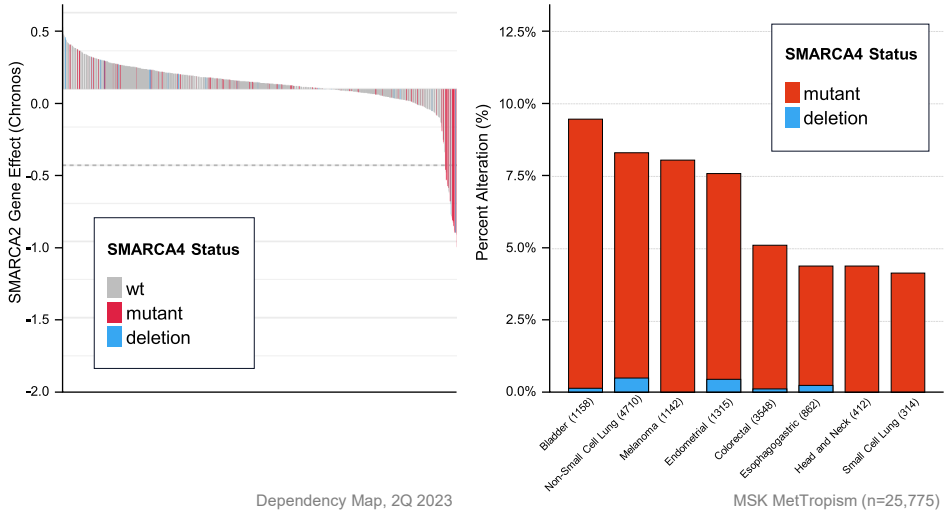
p300/CBP Regulate Histone Acetylation & Gene Expression	**Selective Growth Inhibition of CBP mutant Cancer Cells**
Tumor Regression in Prostate Cancer CDX Model	**Orally Bioavailable & Low Clearance**
Over 100X Improved Margin in HemeTox Assay (vs Clinical Compound)	**Potential to treat >20,000 AR+ mCRPC as well as >20,000 CBP mutant liquid and solid tumors** (U.S. incidence per year)

SMARCA2 Is A Synthetic Lethal Target In SMARCA4 Mutant Cancer Cells

SMARCA2/4 are essential components of the SWI/SNF chromatin remodeling complex



Wanior et al, Oncogene 2021



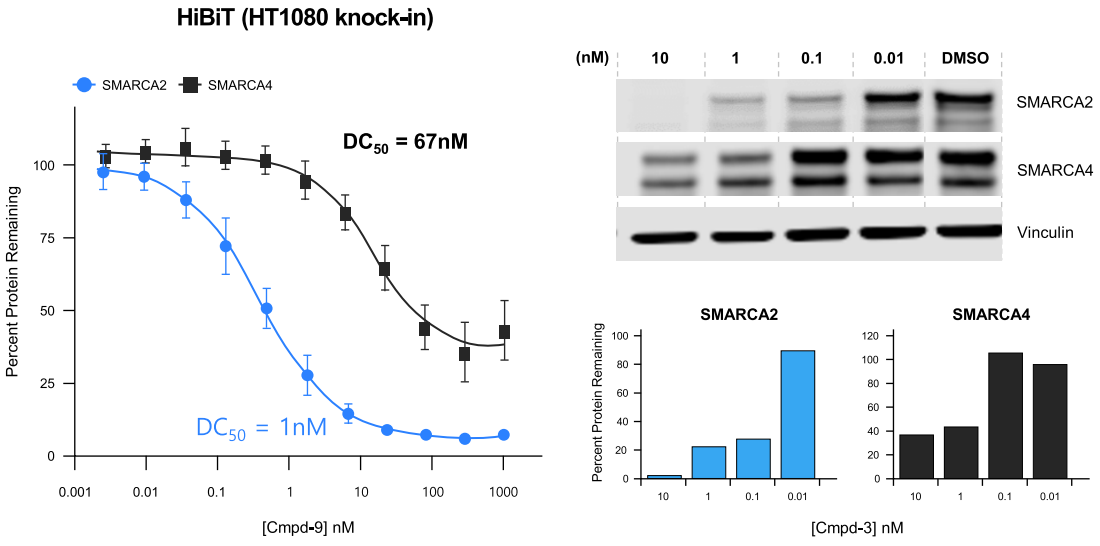
Dependency Map, 2Q 2023

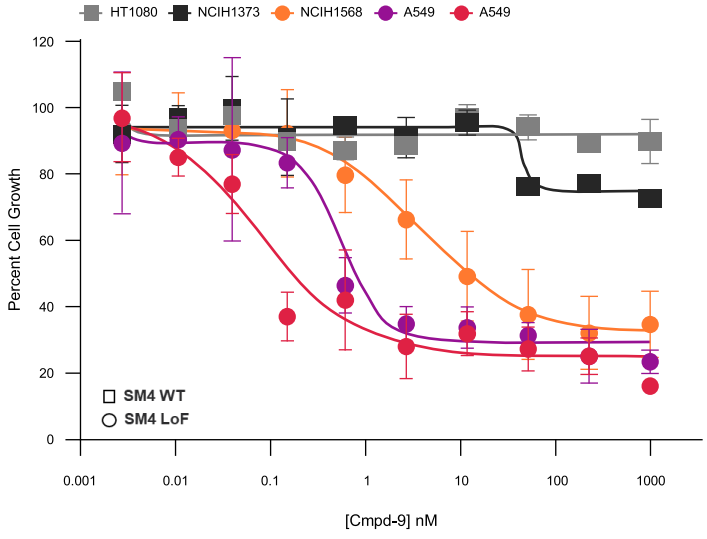
MSK MetTropism (n=25,775)

- ATPase function within the SWI/SNF complex is only provided by the mutually exclusive SMARCA2/4 paralogous subunits
- 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 binding to a non-essential domain, retain selectivity, and minimize systemic toxicity

Discovery of Potent, Selective, and Rapid Degraders of SMARCA2

SMARCA2 degradation selectivity leads to selective in vitro anti-proliferative activity





- SKLSL heterobifunctional degraders are potent and selective for SMARCA2 with minimal impact on SMARCA4
- Parental cell line exhibits similar response as HiBiT knock-in cells

- 6-day proliferation assay utilized to investigate biological impact of SMARCA degradation
- Selective SMARCA2 degraders exhibit selective anti-proliferative activity on SMARCA4 LoF cells

Advanced Series Degraders Cmpd-105 And 106 Exhibit High Oral Bioavailability

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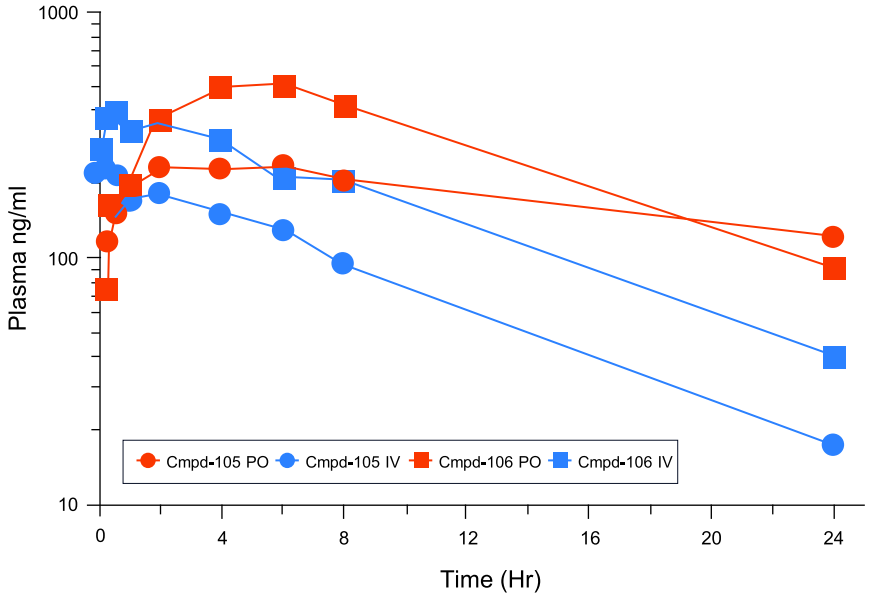
Cmpd-105 and -106 represent exemplars from most advanced series

Degrader	Dose (mg/kg)	CL (mL/min/kg)	Vdss (L/kg)	T1/2 (h)	F (%)
Cmpd-105	0.5 (IV) 1.0 (PO)	3.9	2.2	6.3	96
Cmpd-106		2.0	1.2	7.1	88

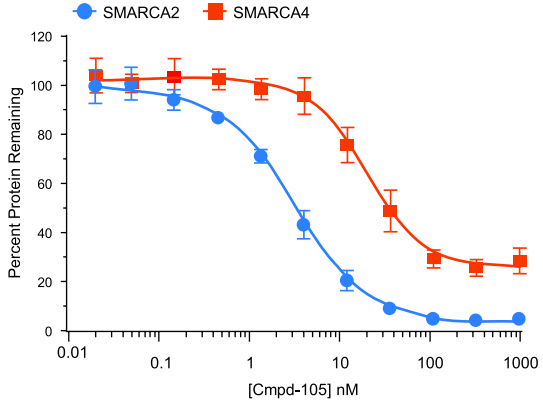


- SK Life Science Labs lead series of degraders exhibit oral bioavailability in mice >80 %F
- Degraders are well suited for *in vivo* degradation and efficacy studies

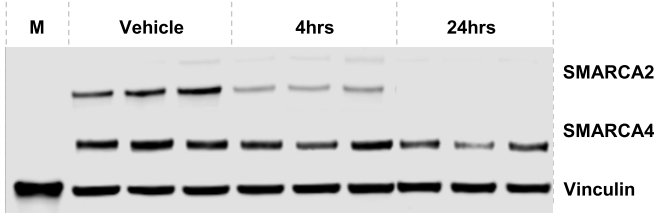
SKT-16737 *In Vitro* Potency And Selectivity Translates To *In Vivo* Degradation

Degradation in wild-type Calu6 xenograft tumor model confirms *in vitro* results

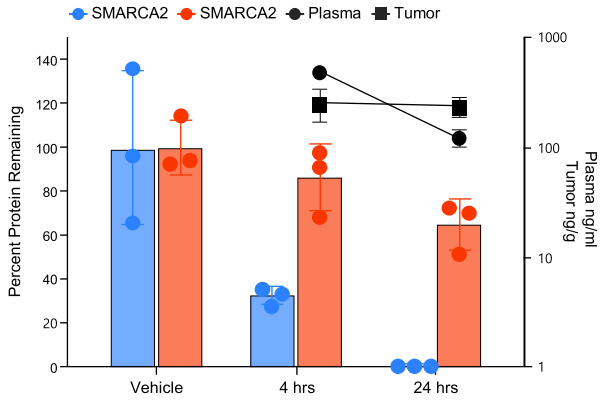
In vitro Degradation Assay



Degradation in Calu6 xenograft SMARCA2 and 4 western blot



Western blot quantification



- Calu6 xenograft model established for *in vivo* assessment of degradation
- SMARCA2 and SMARCA4 degradation in tumors was assessed after single administration of SKT-16737 at 3 mg/Kg
- Tumor exposure of Cmpd-105 is constant over 24 hrs
- **Cmpd-105 leads to 100% degradation of SMARCA2 and only 35% degradation of SMARCA4 at 24 hrs**
- Efficacy study is ongoing

Orally available SMARCA2 degrader has best-in-class potential

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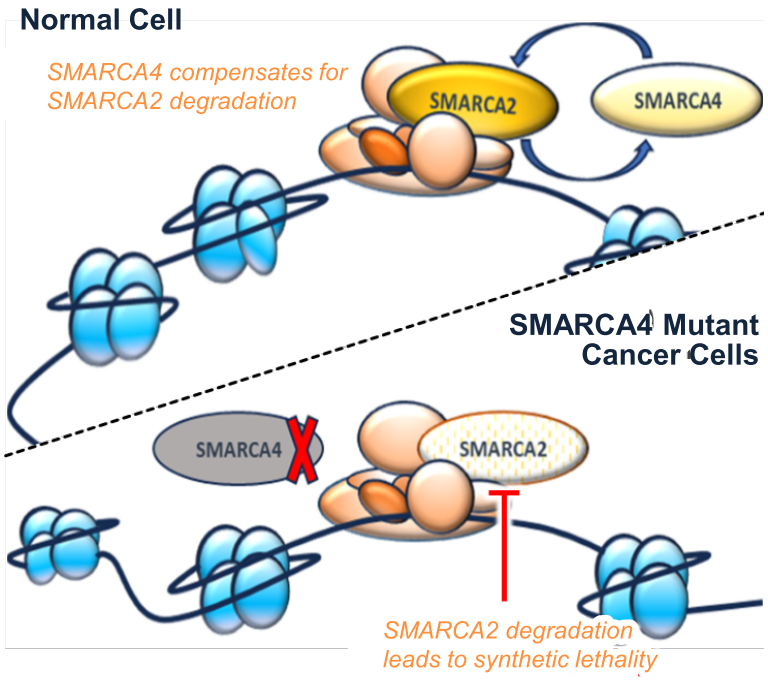
SMARCA2 selective heterobifunctional degrader for SMARCA4 mutant cancer



- SMARCA2/4 Regulate Chromatin Accessibility & Gene Expression
- Rapid, Potent & Selective SMARCA2 Heterobifunctional Degrader
- Selective Growth Inhibition of SMARCA4 Mutant Tumors Representing up to 65,000 cases per year (U.S.)
- Orally Bioavailable & Low Clearance
- Over 90% SMARCA2 Selective Degradation in Mice (P.O.)
- Three Structurally Diverse Series of Heterobifunctional Degraders

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