FOGHORN® THERAPEUTICS

Identification of First-in-Class Selective ARID1B Degraders

Targeted Protein Degradation Summit

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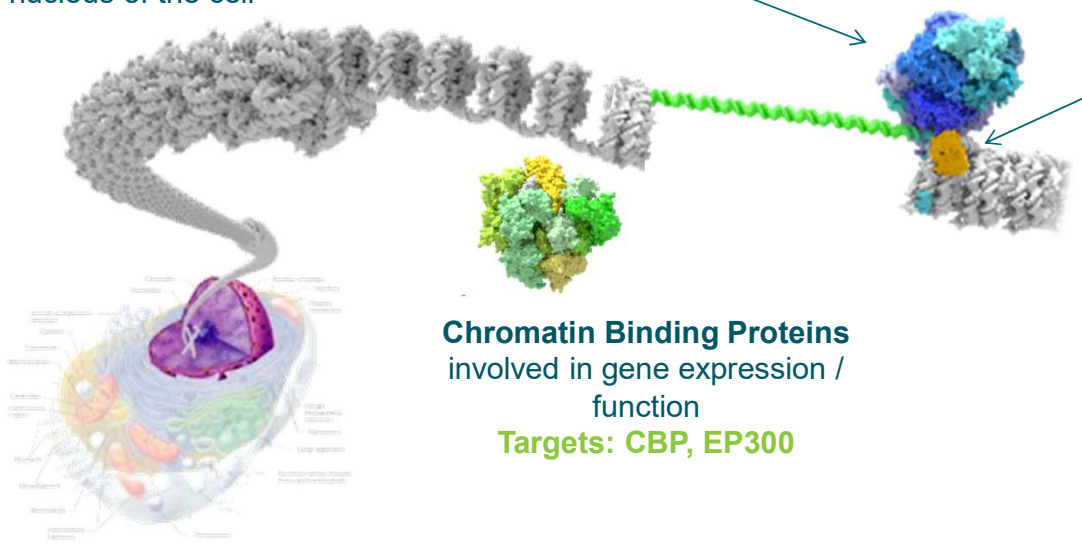
Chromatin Regulatory System Orchestrates Gene Expression: Multiple Opportunities for Targets and Therapeutics

Chromatin Regulatory System genes are **implicated** across a **wide range of cancers**

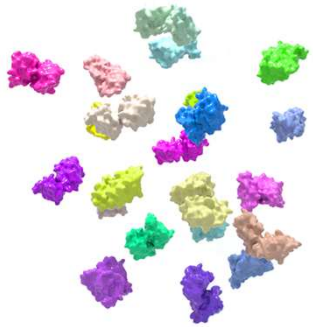
Chromatin – compacted form of DNA inside the nucleus of the cell

Chromatin Remodeling Complexes – specialized multiprotein machines that allow access to DNA
Targets: SMARCA2, ARID1B

Transcription Factors – proteins that help turn specific genes "on" or "off" by working in concert with the chromatin remodeling complex to bind to DNA
Targets: Multiple TFs

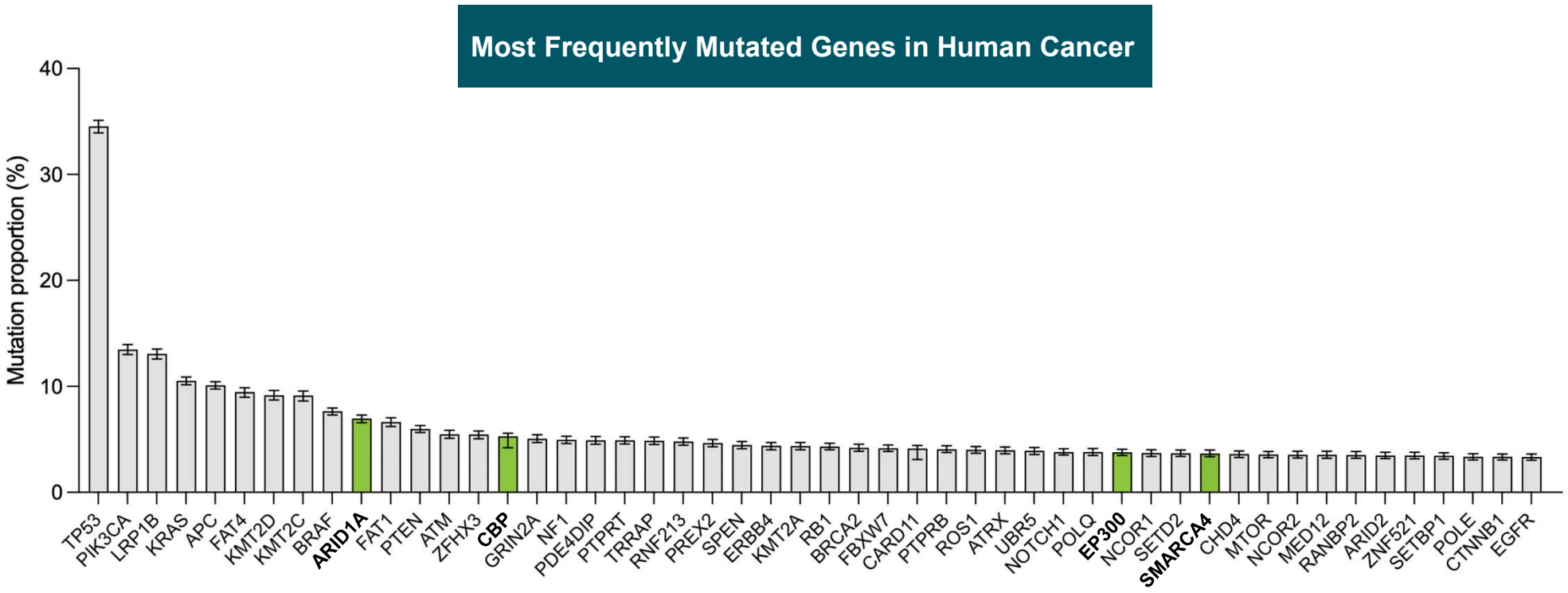


Chromatin Binding Proteins involved in gene expression / function
Targets: CBP, EP300



Leveraging **synthetic lethality** and **lineage dependencies**

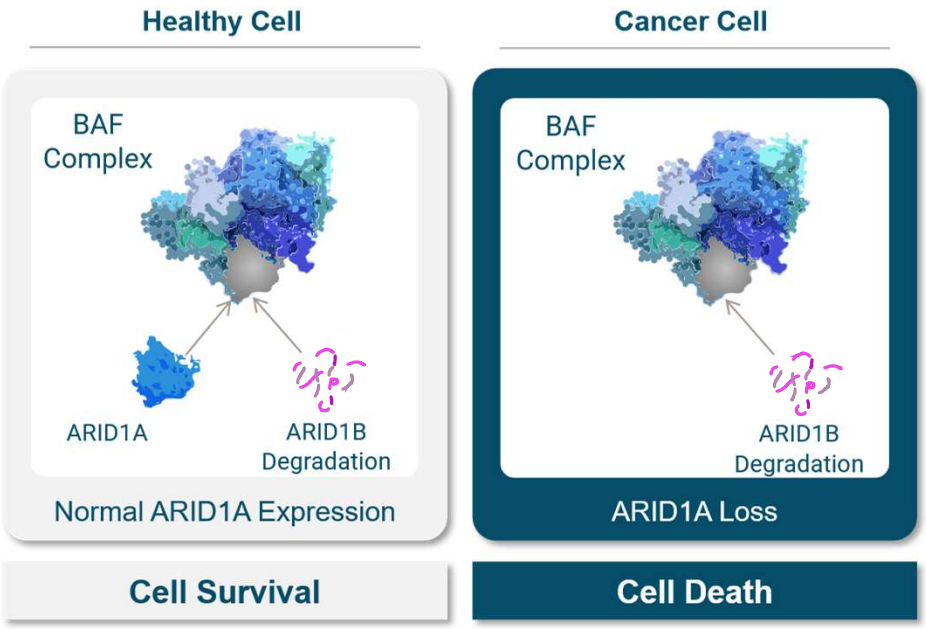
Foghorn is Focused on Some of the Most Relevant Genes in Cancer



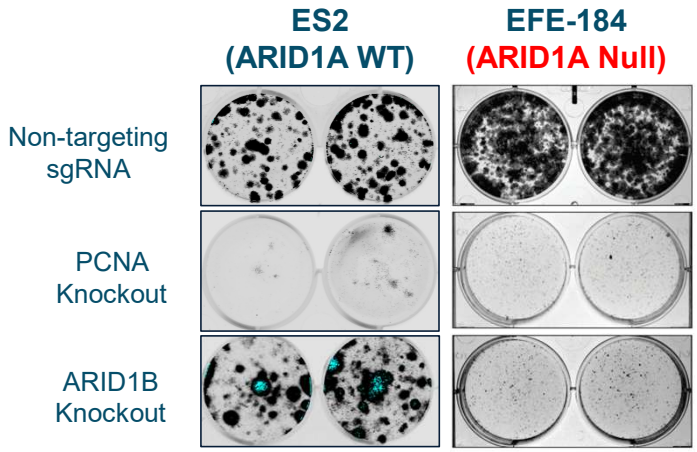
Mendiratta G, *et al. Nature Communications* (2021)

Selective ARID1B Targeting Unlocks Synthetic Lethal Strategy for the Treatment of ARID1A Mutant Cancers

Synthetic Lethal Relationship Between ARID1A and ARID1B



ARID1B Knockout Inhibits Cell Growth in ARID1A Mutant Cancer Cells



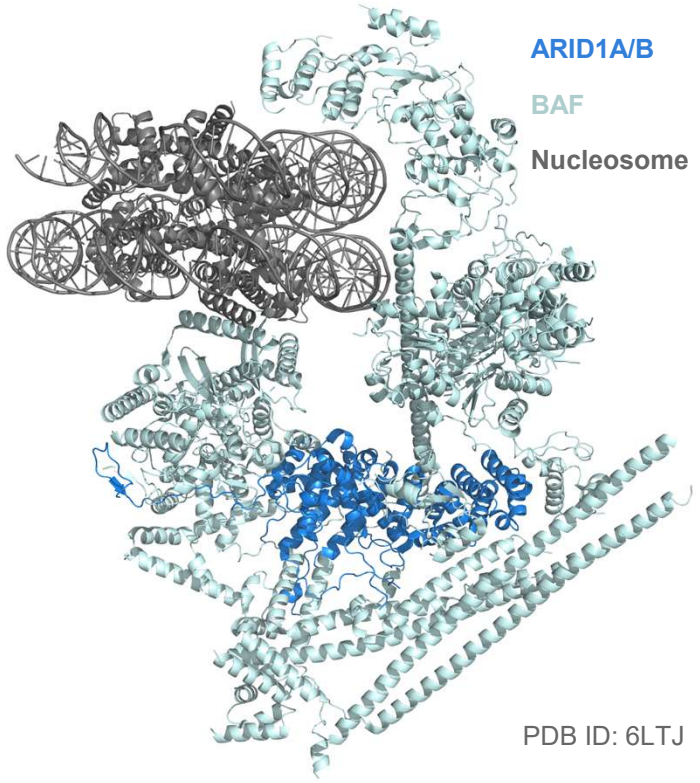
ARID1B: Drugging A Previously Undruggable Target

Drug Targeting Considerations

- Large and highly unstructured protein ~ 240 kDa
- No known enzymatic function
- Member of large, multi-subunit complex
- High sequence homology (~60%) to ARID1A

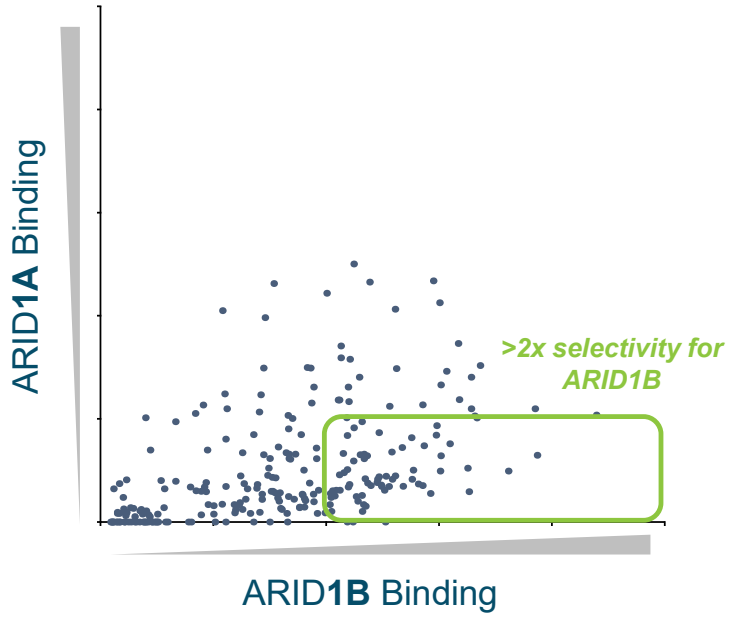
Approach

- Discover binders to ARID1B
- Use binders to develop bifunctional degraders

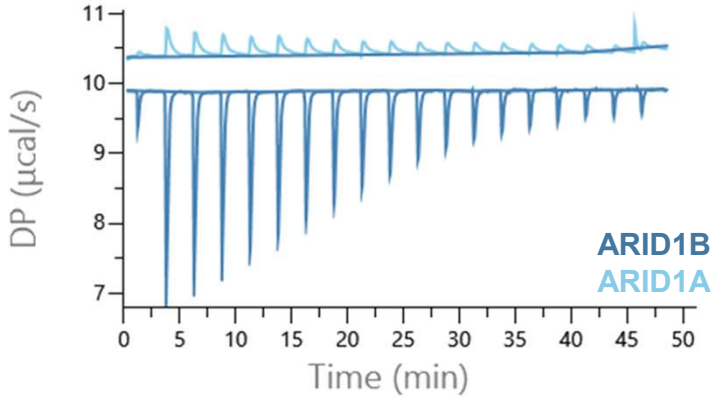


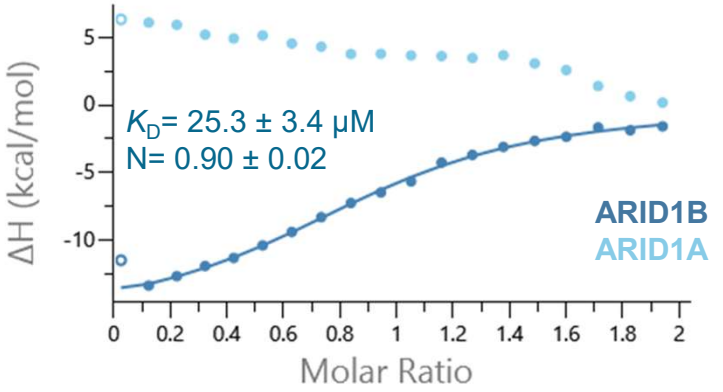
Foghorn Platform Yields Several Selective ARID1B Binder Series

SERIES A



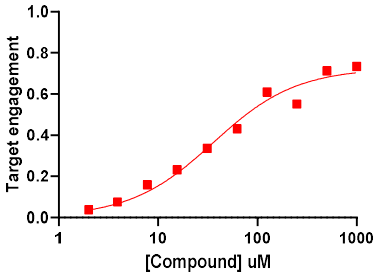
SERIES B

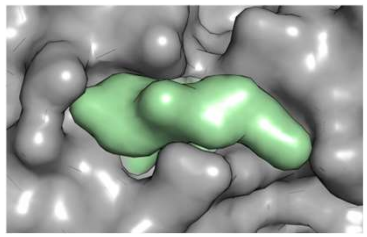




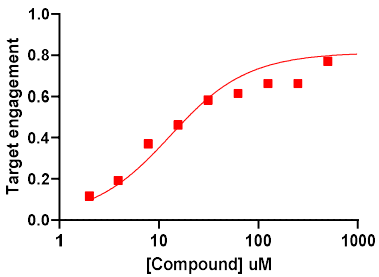
Structure-Based Optimization Drives Improved ARID1B Binding Affinity From 100 uM to Less Than 200 nM

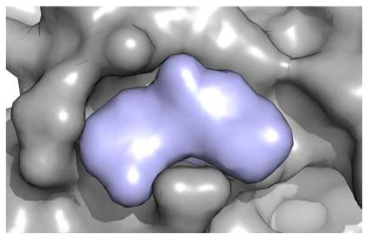
Screening Hit	Early Optimization	Sub-uM Affinity	
ARID1B K_d: **100 uM**	ARID1B K_d: **15 uM**	ARID1B K_d: **0.5 uM**	ARID1B K_d: **0.2 uM**



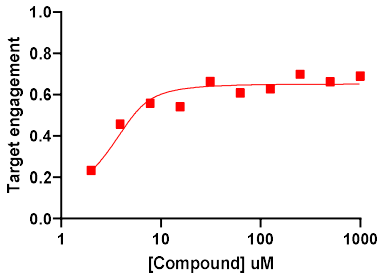


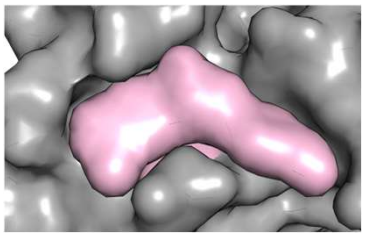
1.4 Å co-xtal structure



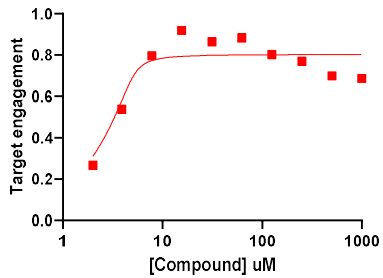


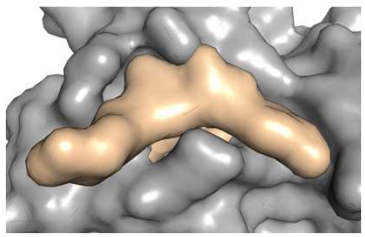
2.0 Å soak structure





1.9 Å co-xtal structure



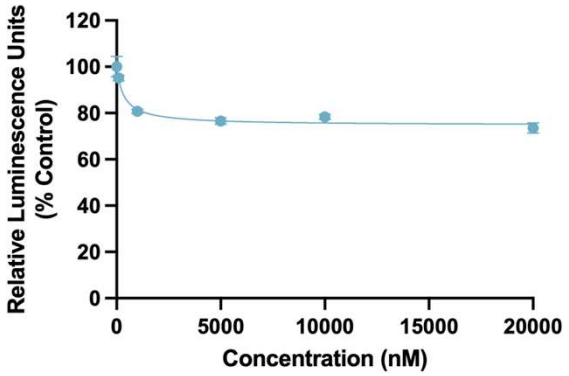


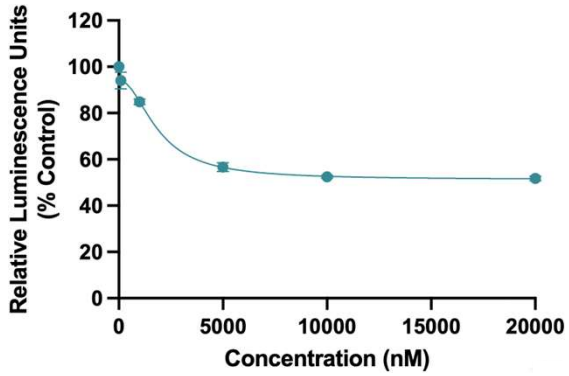
1.7 Å soak structure

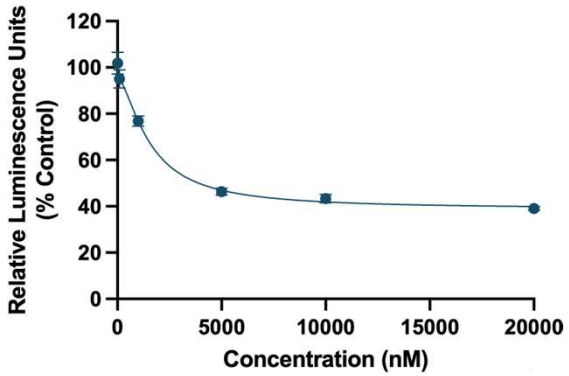
Solubility, **Media Stability**, and **Selectivity** among other optimized parameters

Maximum Optionality Achieved Through Progression of Both Cereblon and VHL Based Degraders in Parallel

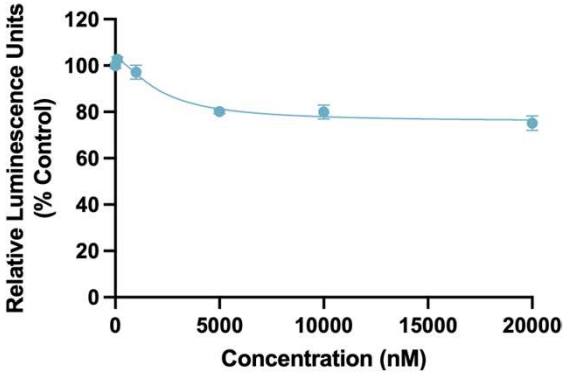
CEREBLON

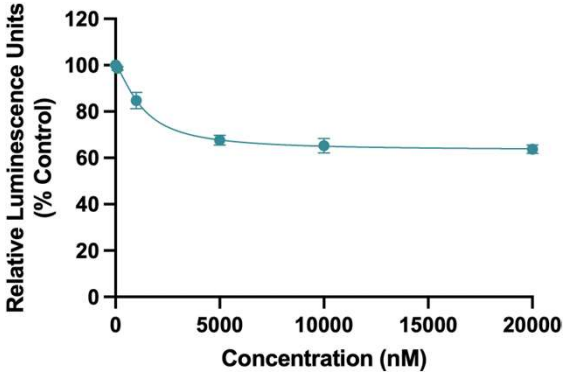


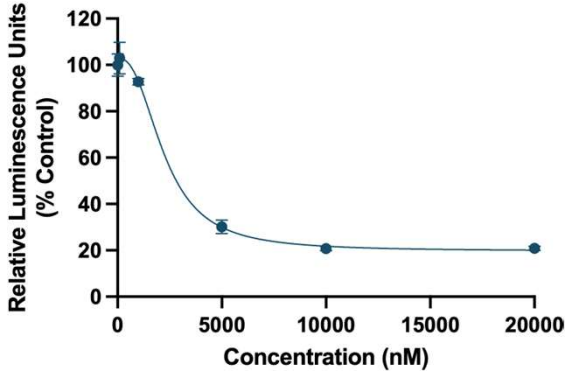




VHL







Lead ARID1B Degrader Demonstrates Robust Degradation Across Multiple Cell Lines

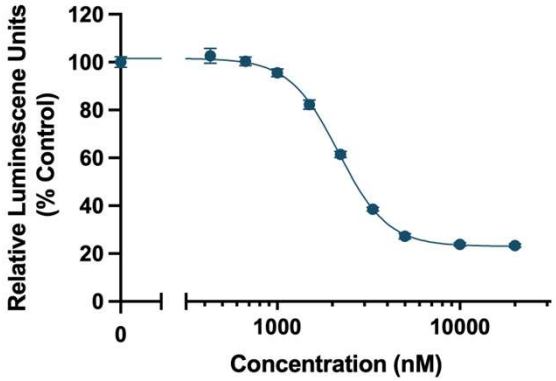
IMMUNOBLOT

HT-1376 (Bladder)

24 hours

HiBiT - ENDPOINT

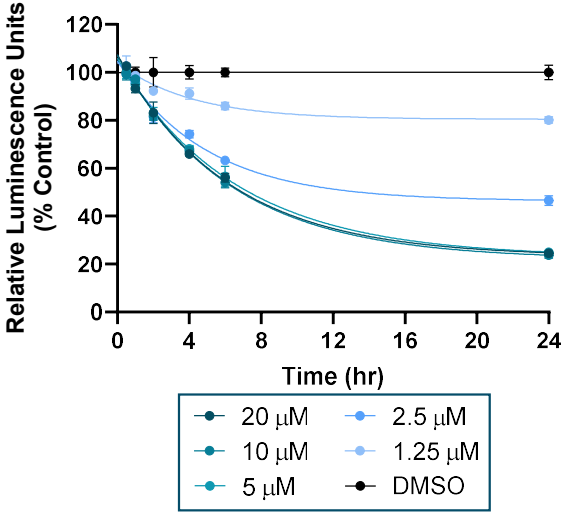
HCT116 (Colorectal)



24 hours

HiBiT – KINETICS

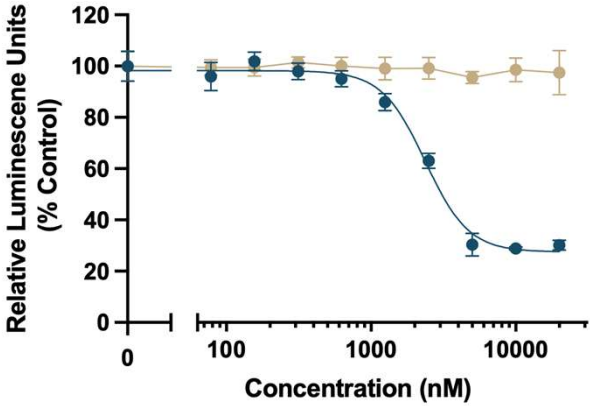
HCT116 (Colorectal)



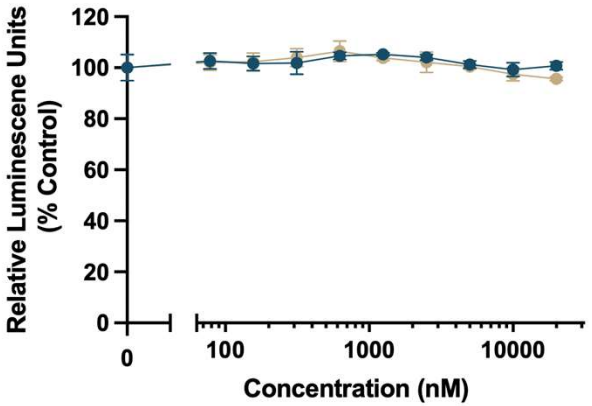
ARID1B Degradation is On-Mechanism Via Ubiquitin-Proteasome System

VHL-Inactive Degrader Does Not Affect ARID1B Levels

Degradation



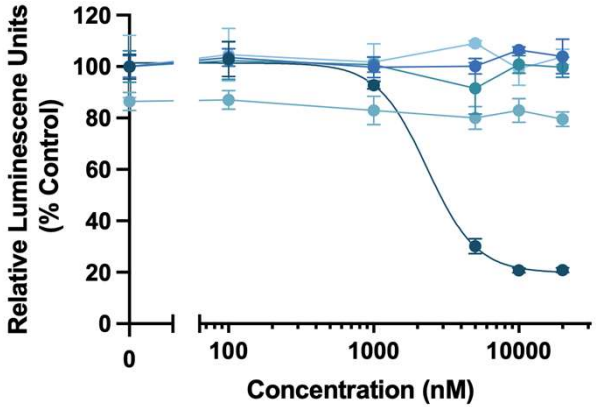
Cell Viability



Active Degrader Inactive Degrader

Inhibitors of the UPS Pathway Rescue Degradation

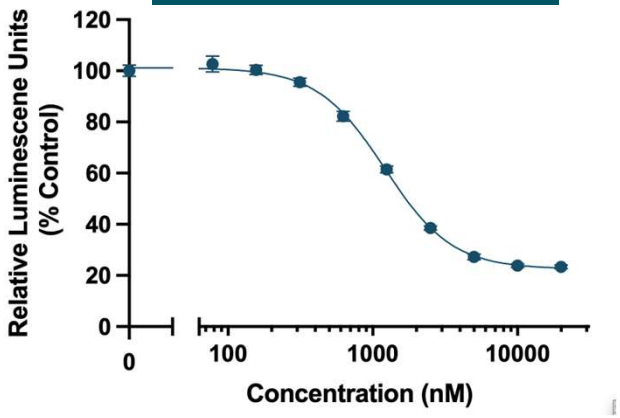
Degradation



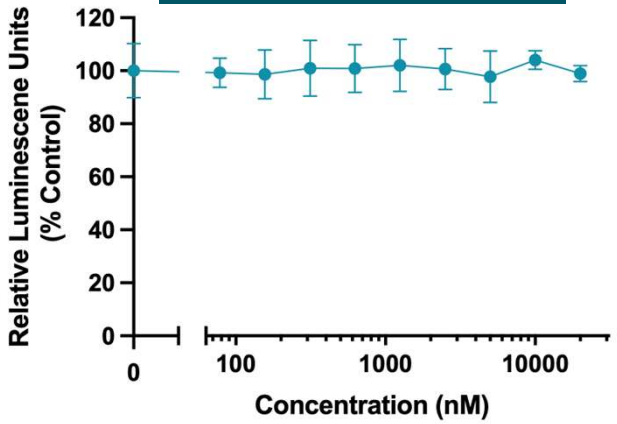
- ARID1B degrader
- + 750 nM MG132 (Proteosome inhibitor)
- + 250 nM Bortezomib (Velcade, Proteosome inhibitor)
- + 750 nM MLN4924 (Neddylation inhibitor)
- + 750 nM TAK-243 (Ub activating enzyme inhibitor)

ARID1B Degrader Exhibits High Target Selectivity

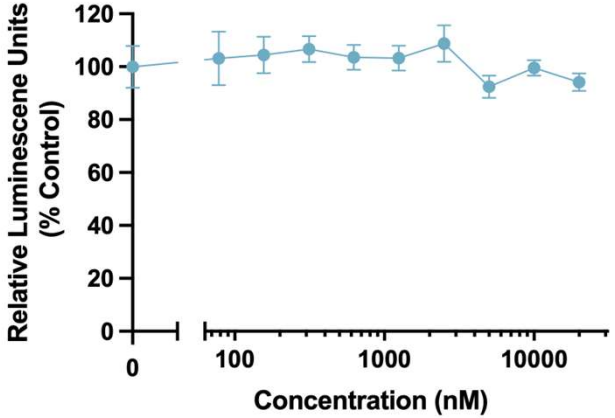
ARID1B-HiBiT HCT116



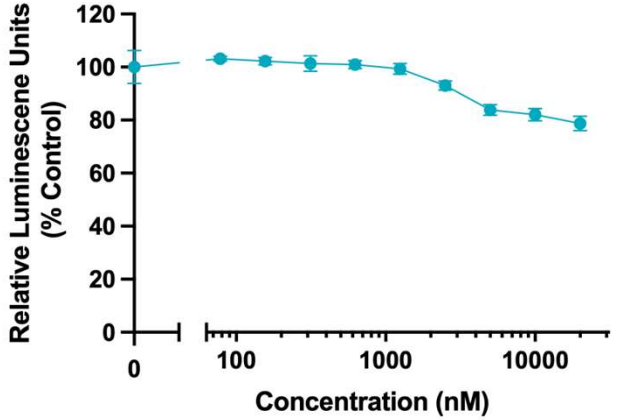
SMARCA2-HiBiT HeLa



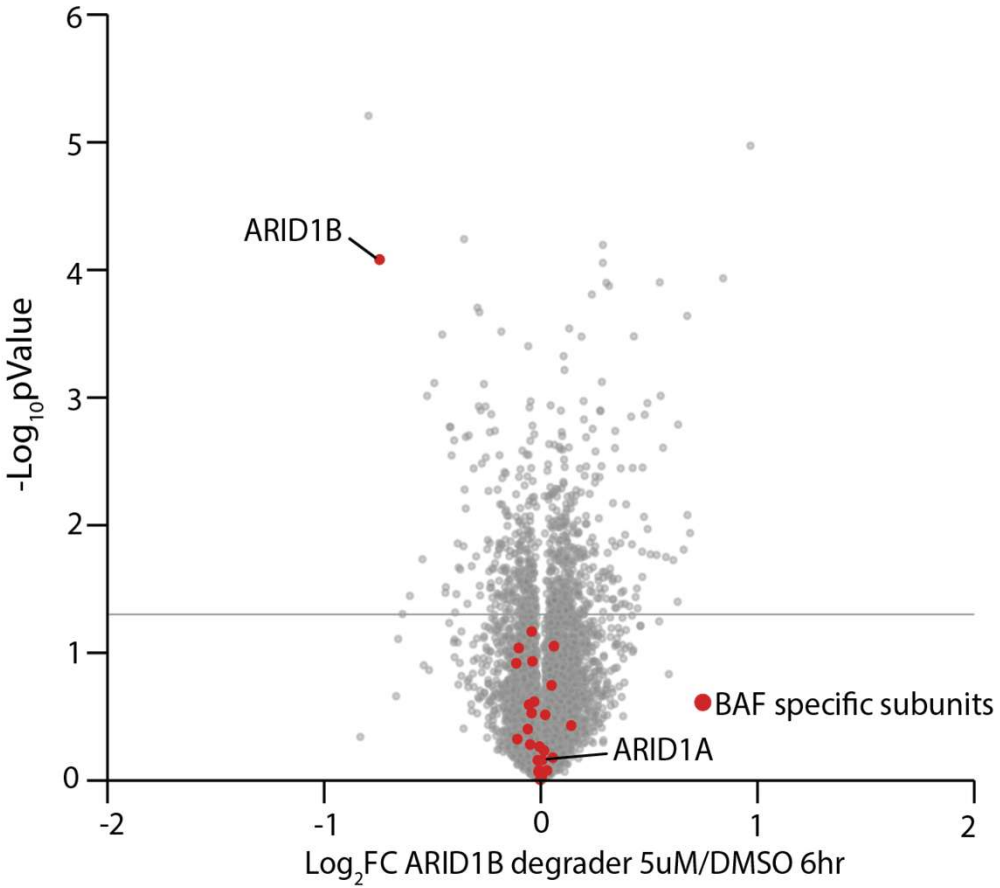
ARID1A-HiBiT HCT116



SMARCA4-HiBiT HeLa

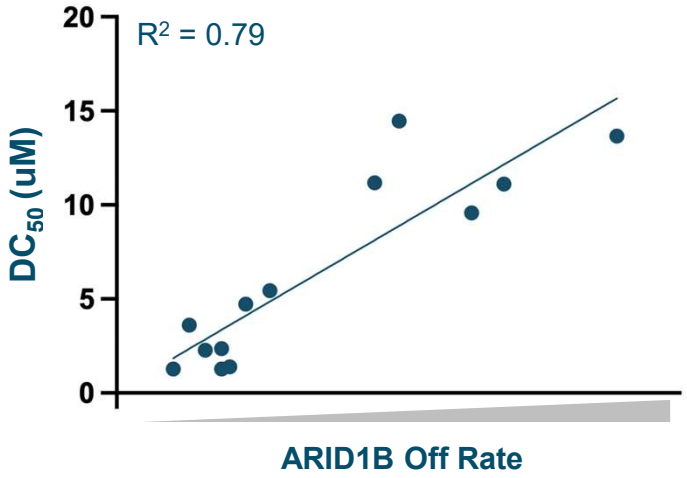


Selective ARID1B Degradation Demonstrated by Global Proteomics

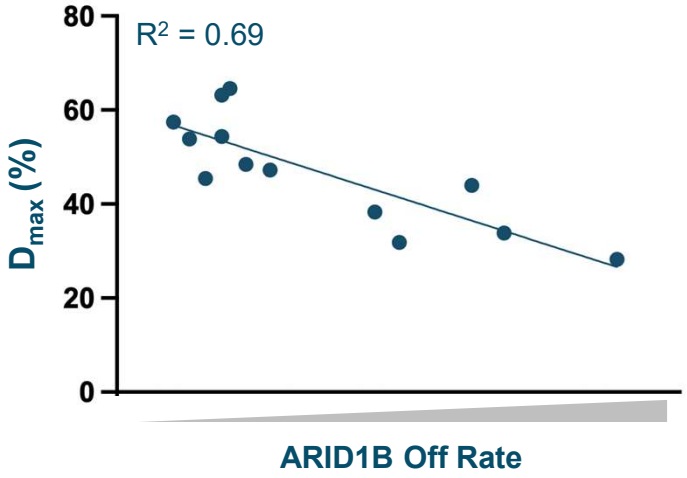


Biochemical Measurements of ARID1B Residence Time Correlate with Cellular Potency of Degraders Within a Series

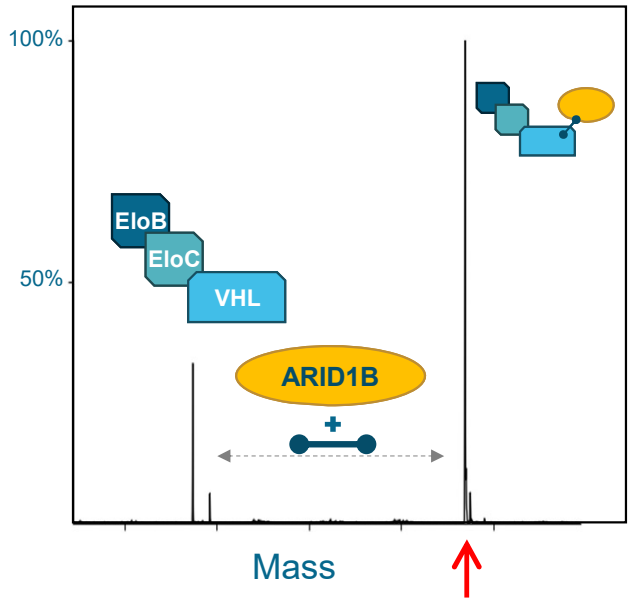
DC_{50} vs Off Rate



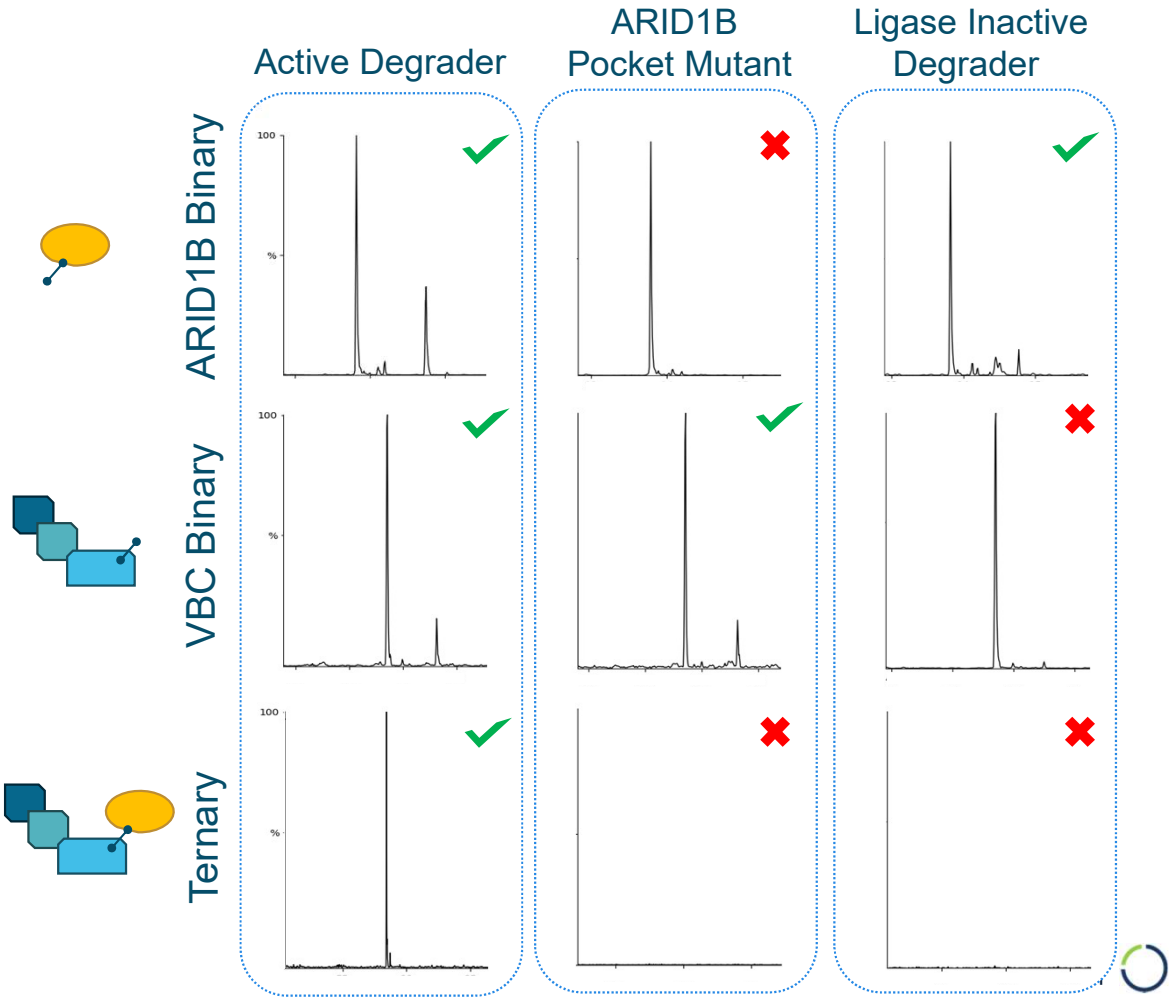
D_{max} vs Off Rate



Native Mass Spectrometry Demonstrates Ternary Complex Formation

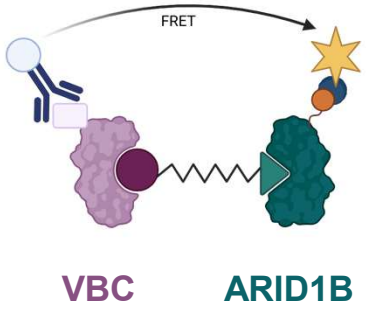


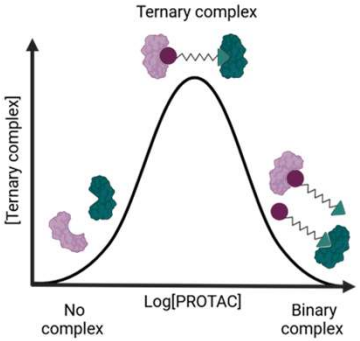
nMS allows for monitoring of binary and ternary complex formation

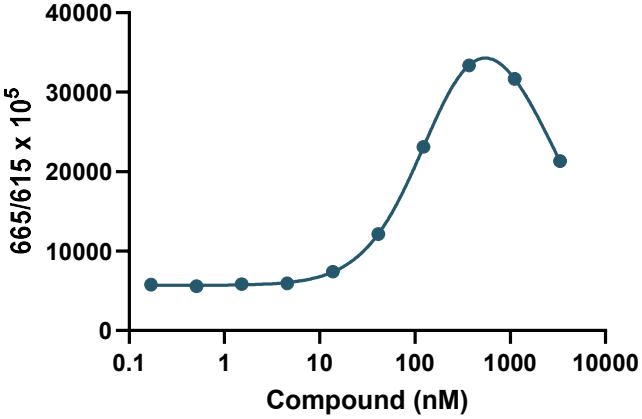


Ternary Complex Formation Confirmed in Biochemical and Cellular Proximity Assays

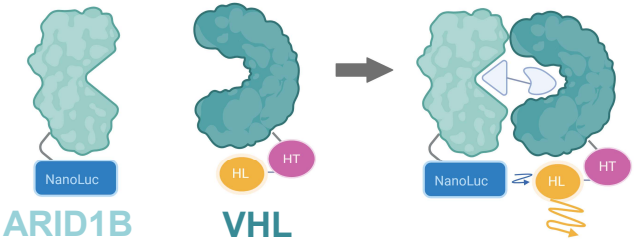
TR-FRET

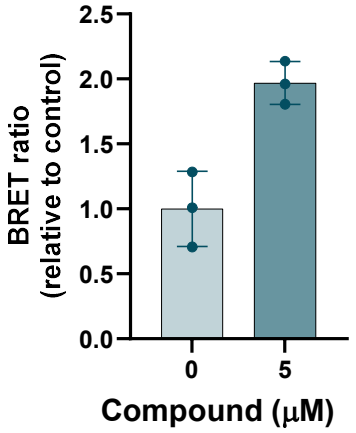




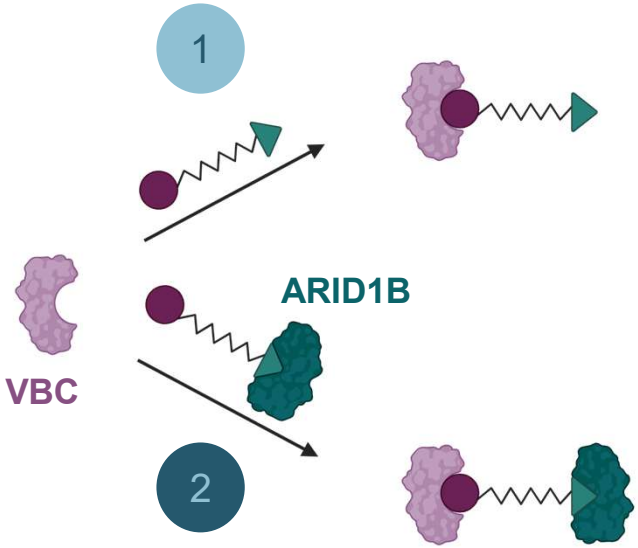


NanoBRET





Biochemical Cooperativity Assays Provide Quantitative Understanding of Ternary Complex Formation



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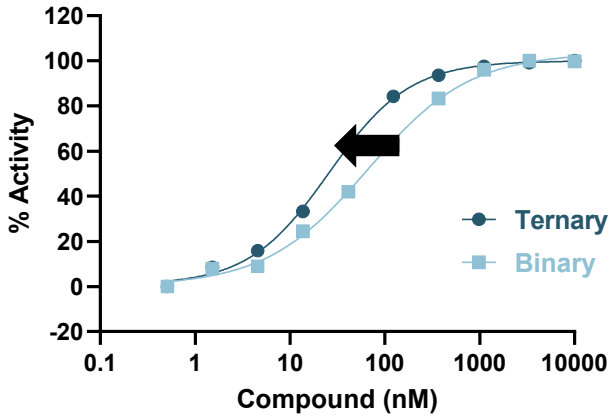
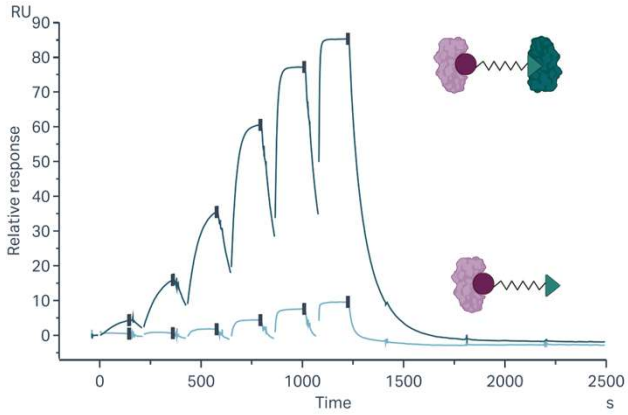


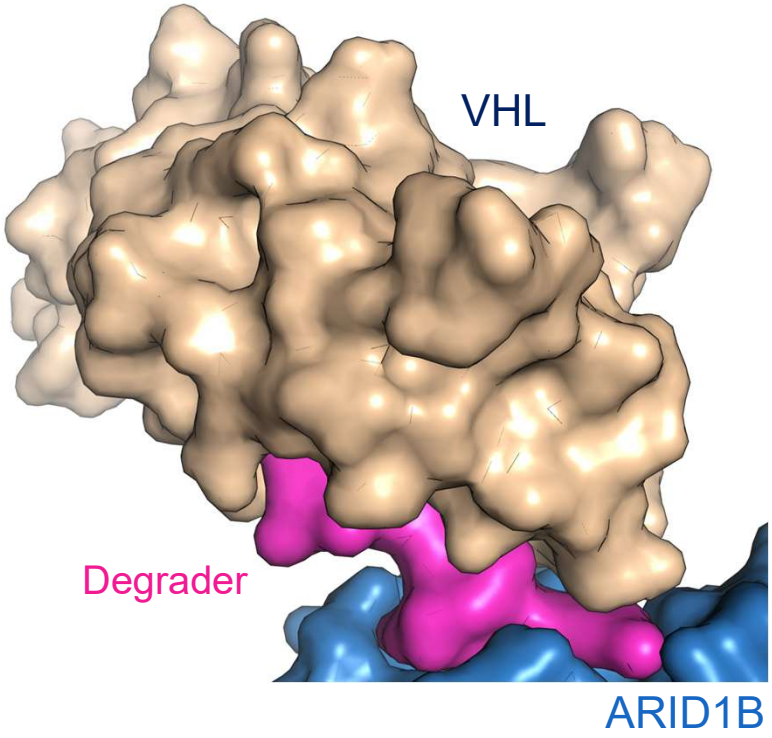
SPR



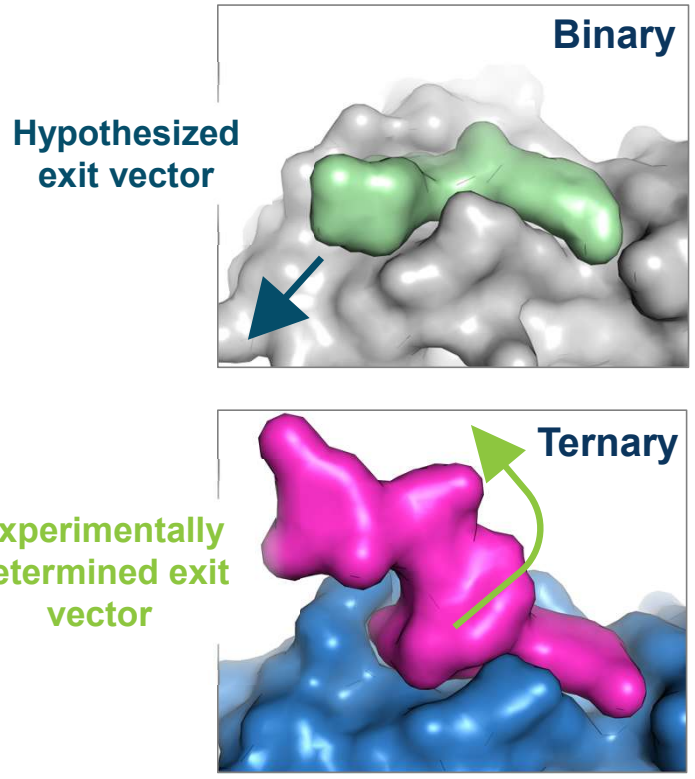
Ternary K_D: 15 nM

VBC Binary K_D: 115 nM

First Ternary Complex X-ray Structure Reveals Unexpected Degrader Geometry Paving Way to Improved Degrader Molecules



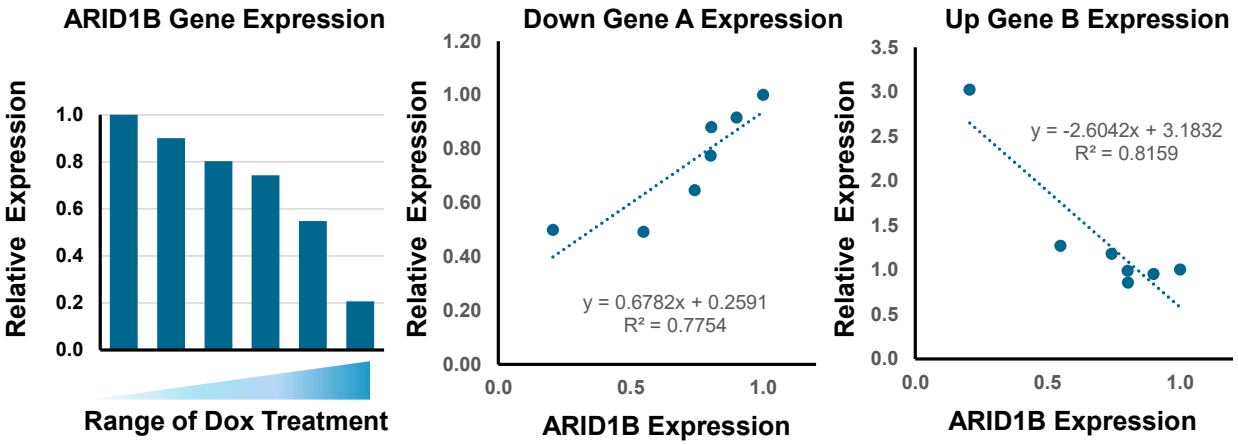
Determined to 2.1 Å resolution



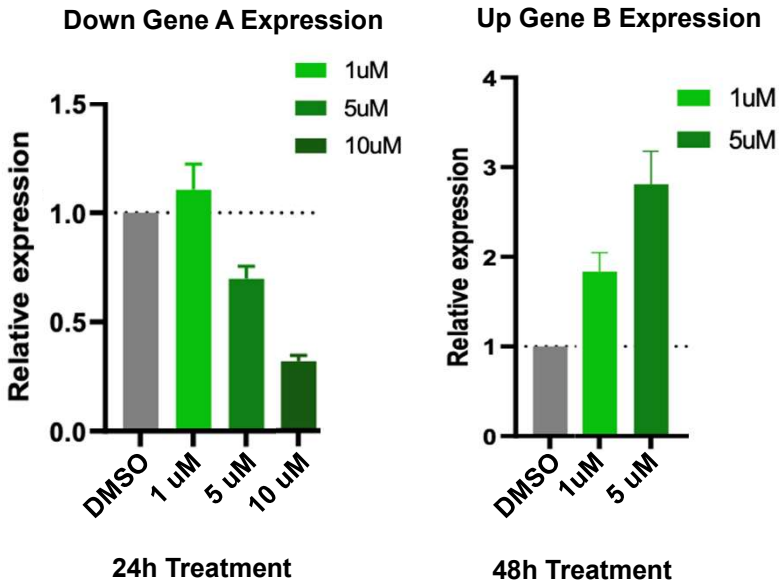
Selective ARID1B Degradation has Demonstrated Effects on Downstream Target Genes - Progressing Towards Proof of Concept

3 Day ARID1B shRNA Treatment

HCT-116 ARID1A^{mut} Cells



ARID1B Degrader Treatment



Putative target genes identified from literature and confirmed via internal shRNA efforts

Acknowledgements

Thank you!