# Identification of First-In-Class Selective ARID1B Degraders

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## 1. Abstract

ARID1B, a core component of the SWI/SNF chromatin remodeling complex, has long been considered undruggable due to the absence of known binders and lack of ligandable pockets. Striking dependency on ARID1B is observed across multiple cancer indications harboring ARID1A mutations, including endometrial, ovarian, and gastric cancers. This highlights the synthetic lethal relationship between the two paralogs and establishes ARID1B as a high-value target for precision oncology. We report the discovery and optimization of first-in-class selective ARID1B degraders for the treatment of ARID1A mutant cancers. Using our platform and structure-based design, we first identified several selective ARID1B binder series, which were then used to develop VHL- and CRBN-based molecules that induce robust ARID1B degradation via the ubiquitin-proteasome system. These compounds exhibit on-mechanism activity, high selectivity, and downstream transcriptional modulation. This work establishes ARID1B degradation as a promising therapeutic strategy and provides a blueprint for targeting previously intractable chromatin remodelers.

## 2. Targeting ARID1A Mutant Cancers by Selectively Degrading ARID1B

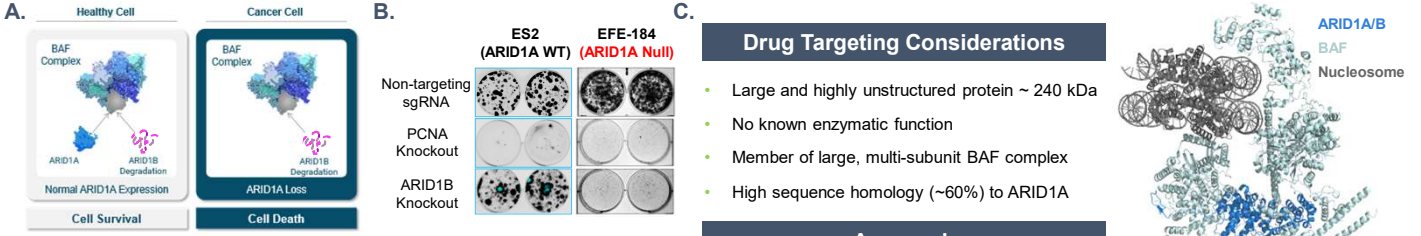


**Fig 2.** (A) Diagram illustrating the synthetic lethal relationship between ARID1A and ARID1B, highlighting the strength of a degradation approach for selective targeting of ARID1A mutant cancers. (B) CRISPR/Cas9 knockouts of ARID1B in ARID1A WT (ES2) and ARID1A Null cells (EFE-184) demonstrate selective toxicity in cells lacking ARID1A. (C) Foghorn's approach to targeting ARID1A mutant cancers. On the right is the Cryo-EM structure of the mammalian BAF complex bound to a nucleosome.

## 3. Discovery and Development of Potent ARID1B Ligands

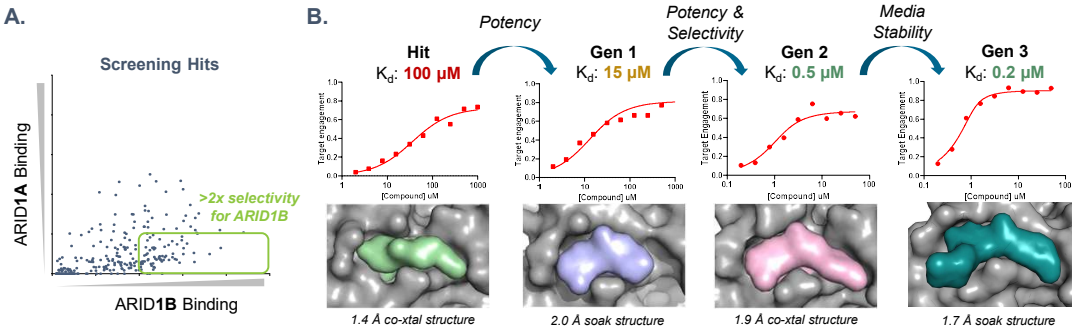


**Fig 3.** (A) Selectivity comparison of hits from high-throughput screen of ARID1B. (B) Progression of potency for ARID1B ligands in a biochemical target engagement assay, along with X-ray crystal structures of each ligand bound to ARID1B (gray).

## 4. Development of ARID1B Degraders

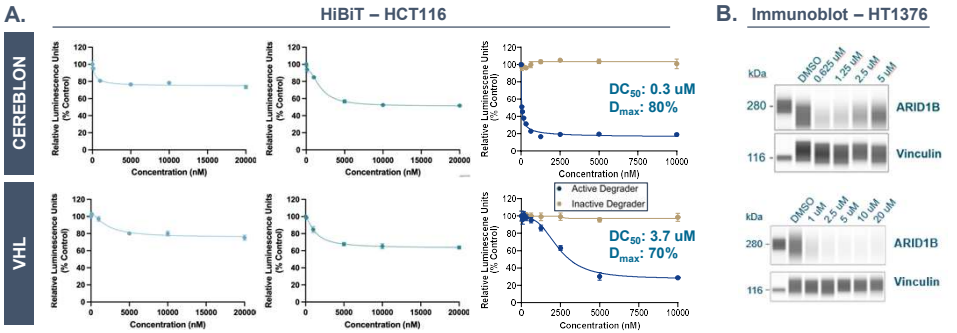


**Fig 4.** (A) Progression of potency and degradation for Cereblon and VHL series, measured by HiBiT luminescence in HCT116 cells. (B) Jess Immunoblots showing degradation of ARID1B in HT1376 cells by lead degraders.

## 5. ARID1B Degrader Validation

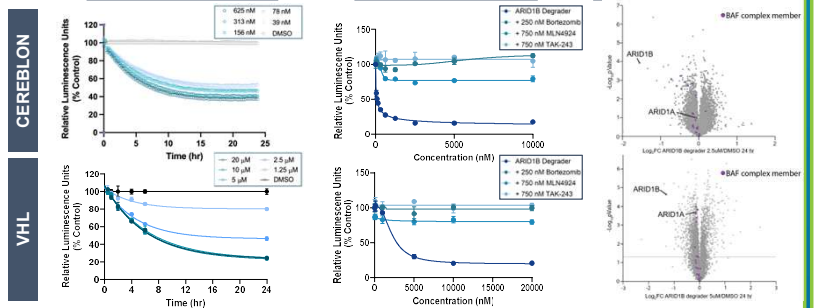


**Fig 5.** (A) HiBiT kinetics assay showing time-dependent degradation of ARID1B in HCT116 cells. (B) Control experiments showing ARID1B degraders function via the Ubiquitin-Proteasome System. (C) Proteomics showing selectivity of ARID1B degraders in HCT116 cells.

## 6. ARID1B Degraders Form Cooperative Ternary Complexes with Target E3 Ligases

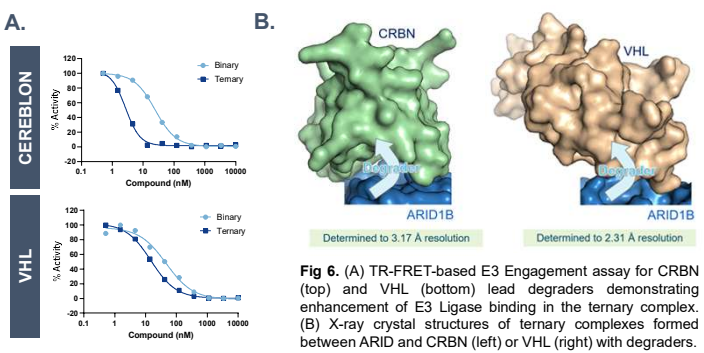


**Fig 6.** (A) TR-FRET-based E3 Engagement assay for CRBN (top) and VHL (bottom) lead degraders demonstrating enhancement of E3 Ligase binding in the ternary complex. (B) X-ray crystal structures of ternary complexes formed between ARID and CRBN (left) or VHL (right) with degraders.

## 7. Degradation Correlates with ARID1B Residence Time

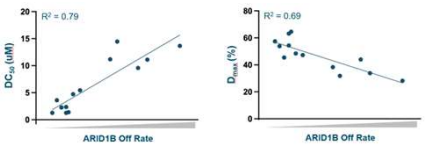


**Fig 7.** Correlation plots of biochemical ARID1B off rates with degradation parameters $DC_{50}$ and $D_{max}$ for ARID ligand variations in VHL series.

## 8. Conclusions

- We have developed novel potent and selective ARID1B binders, and converted them into two validated degrader series targeting Cereblon and VHL E3 Ligases
- Ternary Complex structures and in-depth biochemical analysis enable rational design of improved degraders
- On track for *in vivo* POC by end of 2026