Discovery Deep Dive: Prelude's Oral SMARCA2 Degrader (PRT7732)

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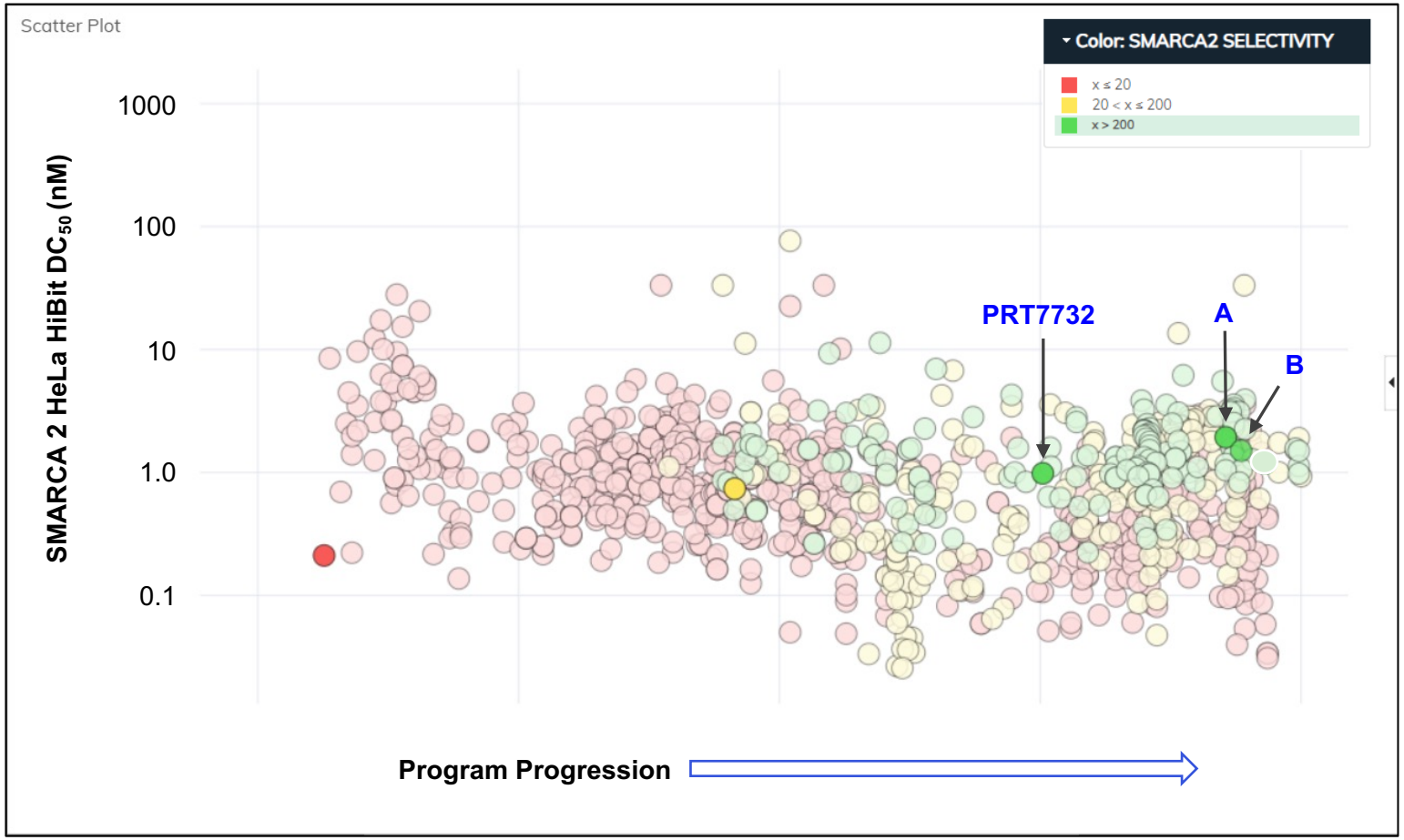
Learning Objectives

- What is the status of our oral SMARCA2 degrader program, and lead oral candidate PRT7732?
- Where is the science leading us next to further expand the reach of our SMARCA portfolio for patients?

Our SMARCA2 oral degrader program has progressed rapidly and systematically

SMARCA2 HiBit DC_{50} & SMARCA4 Selectivity



*Inactive & weakly potent compounds removed for clarity

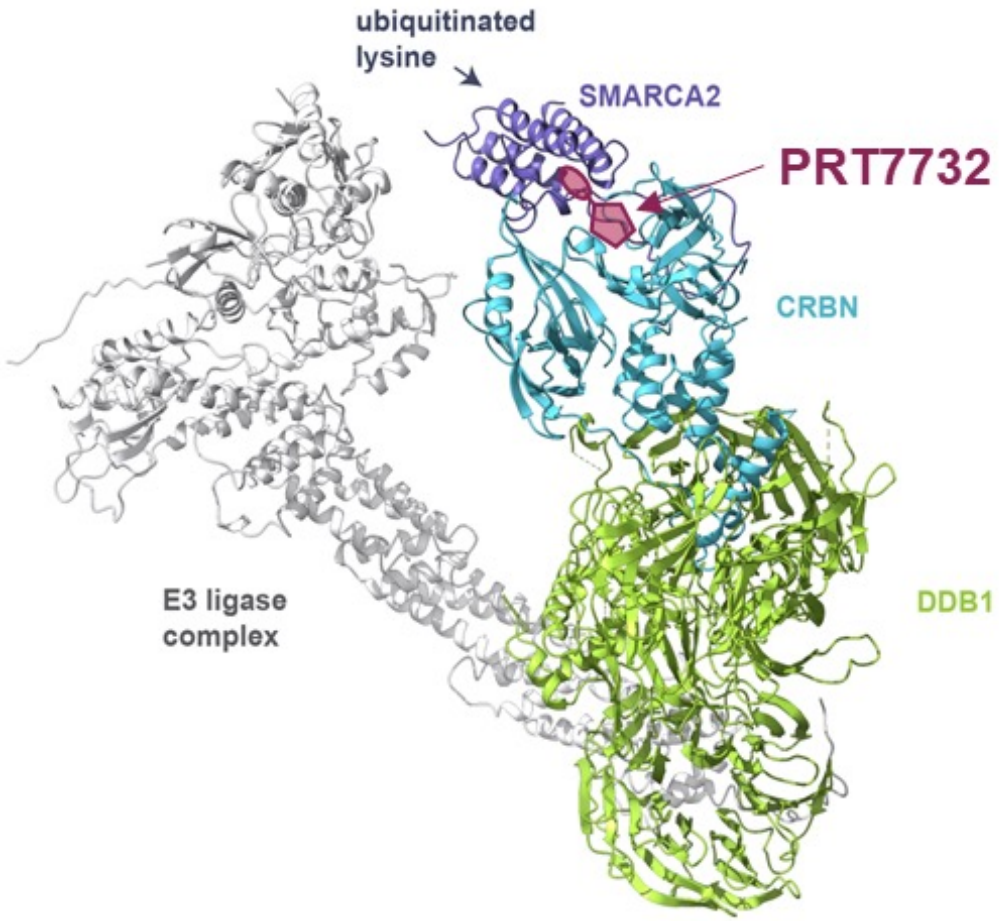
Solving for potency, selectivity and oral bioavailability was a challenge

PRT7732: Lead Oral Candidate with >3000-fold Selectivity

A and B: Two additional structurally distinct oral back-up candidates

PRT7732: Our Lead Oral SMARCA2 Degrader

Tertiary Complex of SMARCA2/ PRT7732/CRBN-DDB1 E3 Ligase



Source: Shvartsbart, K. Ito et al., AACR Poster, April 2024. Available here: Preclinical Characterization Of PRT7732: A Highly Potent, Selective, And Orally Bioavailable Targeted Protein Degrader Of SMARCA2

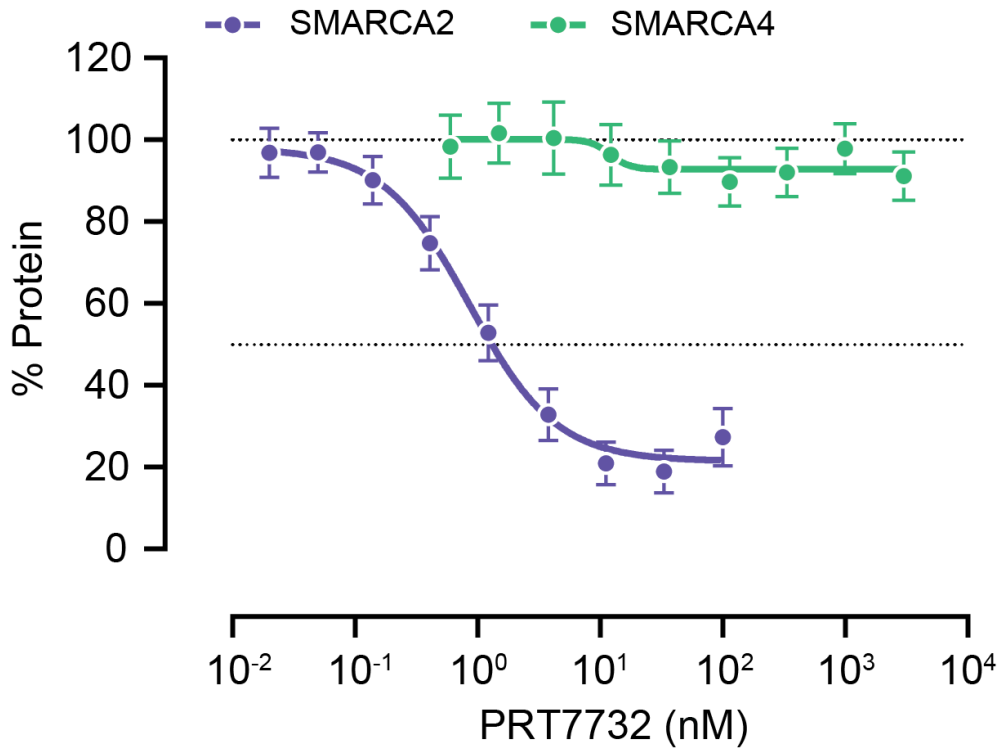
PRT7732 binds to the SMARCA2 bromodomain and CRBN-DDB1 E3 ligase complex

PRT7732 has been shown to catalyze the polyubiquitination of unique lysine residues expressed only in SMARCA2 and not SMARCA4

Unique conformational bias promotes selective ubiquitination and degradation of SMARCA2

PRT7732 is highly potent and orally bioavailable with near-absolute selectivity for SMARCA2

Assay	PRT7732
SMARCA2 Degradation (nM)	0.98
Selectivity: Degradation (SMARCA4 / SMARCA2)	>3000 fold
Selectivity: Cell Proliferation (SMARCA4 / SMARCA2)	>1000 fold*



Sub-nanomolar SMARCA2 degradation potency

Near-absolute cellular selectivity for SMARCA2 vs SMARCA4 (>3000 fold) in HiBit cell lines and >1000-fold in cell proliferation assays

Good oral bioavailability across species

* Based on highest concentration tested

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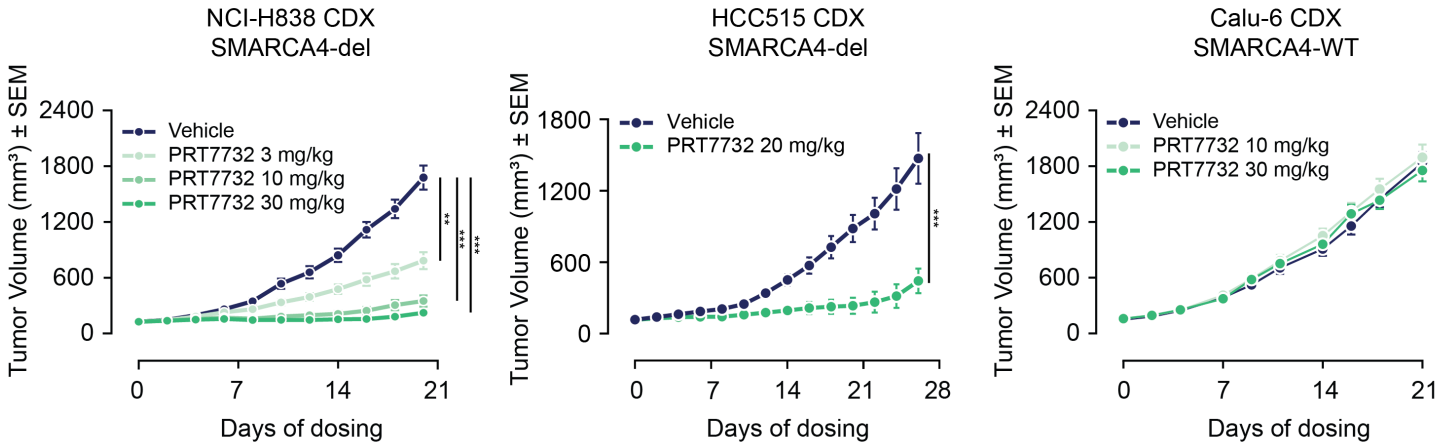
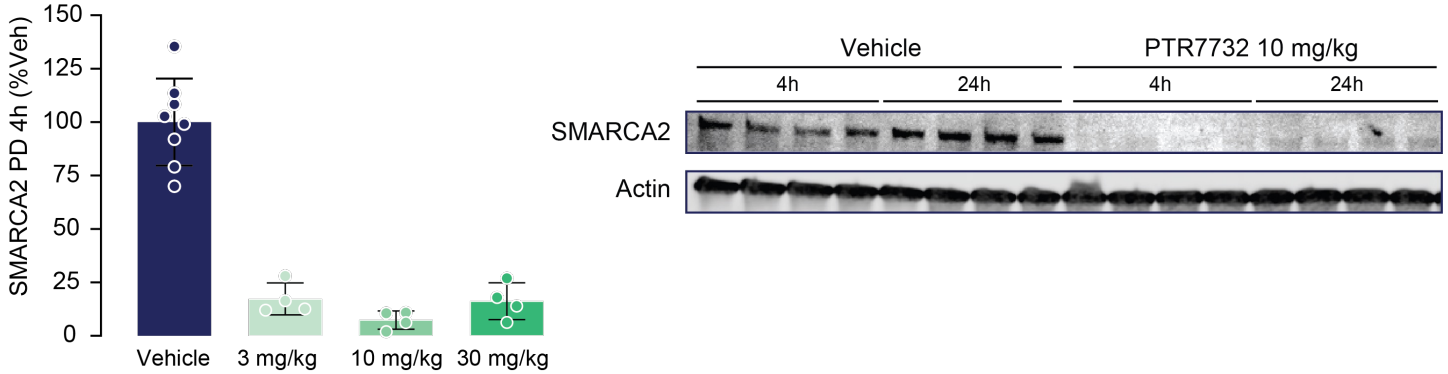
PRT7732 has significant anti-tumor activity in SMARCA4-deficient cancer xenograft models





Daily oral administration of PRT7732 inhibits growth of SMARCA4-deficient tumors but not SMARCA4 WT tumors

PRT7732 decreases SMARCA2 protein levels in NCI-H838 tumor tissues

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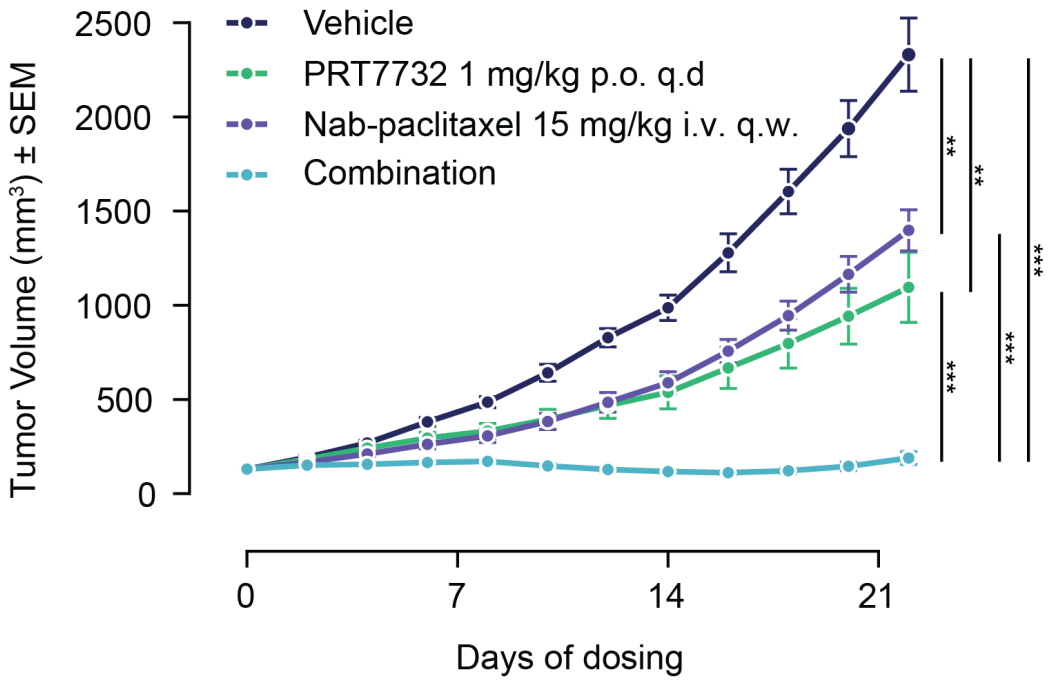
PRT7732 also shows high potential for synergy with other common anti-cancer agents



Oral daily administration of PRT7732 1 mg/kg in combination with nab-paclitaxel (Abraxane®) induces tumor regression in the NCI-H838 tumor model in mice

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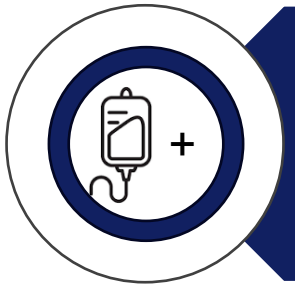
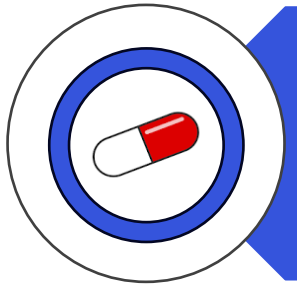
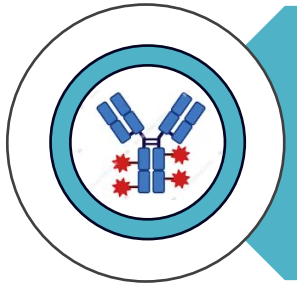
Expanding our portfolio of SMARCA-targeted therapeutics



Lead SMARCA2 Degrader (PRT3789)



Oral SMARCA2 Degraders (PRT7732)



SMARCA Degrader-Antibody Conjugates (“DACs”)

Prelude is continuing to lead the field

- Our lead oral SMARCA2 degrader PRT7732 shows >3000-fold selectivity and a PK/PD profile supporting a low-mg once daily projected human dose
- PRT7732 is advancing to Phase I in 2H 2024
- SMARCA Degrader-Antibody-Conjugates (“DACs”) have potential to dramatically expand the reach of this platform, including patients without SMARCA4 mutations

Key Takeaways