Discovery Deep Dive: Prelude's Lead SMARCA2 Degrader (PRT3789)

Andrew Combs, Ph.D.
Chief Chemistry Officer
Prelude Therapeutics

Peggy Scherle, Ph.D.
Chief Scientific Officer
Prelude Therapeutics

Forward Looking Statements

This presentation contains “forward-looking” statements within the meaning of the “safe harbor” provisions of the Private Securities Litigation Reform Act of 1995, including, but not limited to, anticipated discovery, preclinical and clinical development activities for Prelude’s product candidates, the potential safety, efficacy, benefits and addressable market for Prelude’s product candidates, the expected timeline for proof-of-concept data and clinical trial results for Prelude’s product candidates including its SMARCA2 degrader molecules.

Any statements contained herein or provided orally that are not statements of historical fact may be deemed to be forward-looking statements. In some cases, you can identify forward-looking statements by such terminology as ‘‘believe,’’ ‘‘may,’’ ‘‘will,’’ ‘‘potentially,’’ ‘‘estimate,’’ ‘‘continue,’’ ‘‘anticipate,’’ ‘‘intend,’’ ‘‘could,’’ ‘‘would,’’ ‘‘project,’’ ‘‘plan,’’ ‘‘expect’’ and similar expressions that convey uncertainty of future events or outcomes, although not all forward-looking statements contain these words. Statements, including forward-looking statements, speak only to the date they are provided (unless an earlier date is indicated).

Certain data in this presentation are based on cross-study comparisons and are not based on any head-to-head clinical trials. Cross-study comparisons are inherently limited and may suggest misleading similarities or differences. This presentation shall not constitute an offer to sell or the solicitation of an offer to buy, nor shall there be any sale of these securities in any state or other jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state or other jurisdiction.

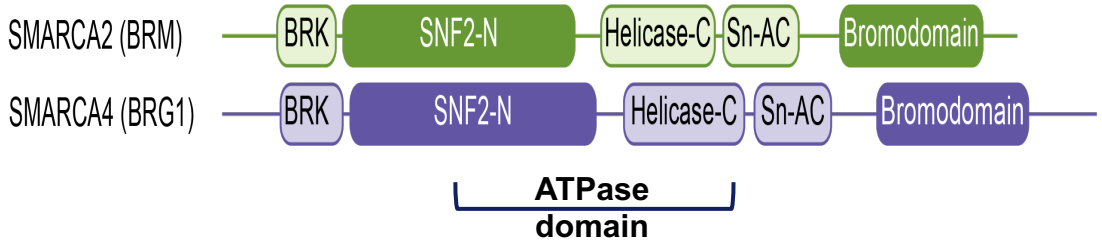
These forward-looking statements are based on the beliefs of our management as well as assumptions made by and information currently available to us. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. If such assumptions do not fully materialize or prove incorrect, the events or circumstances referred to in the forward-looking statements may not occur. We undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation to conform these statements to actual results or to changes in our expectations, except as required by law. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements. Additional risks and uncertainties that could affect our business are included under the caption “Risk Factors” in our filings with the Securities and Exchange Commission, including our Annual Report on Form 10-K for the year ended December 31, 2023.

Learning Objectives

- Why has SMARCA2 selectivity been so hard to achieve? How did Prelude succeed?
- Why are we so excited about the profile and potency of our lead program, PRT3789?

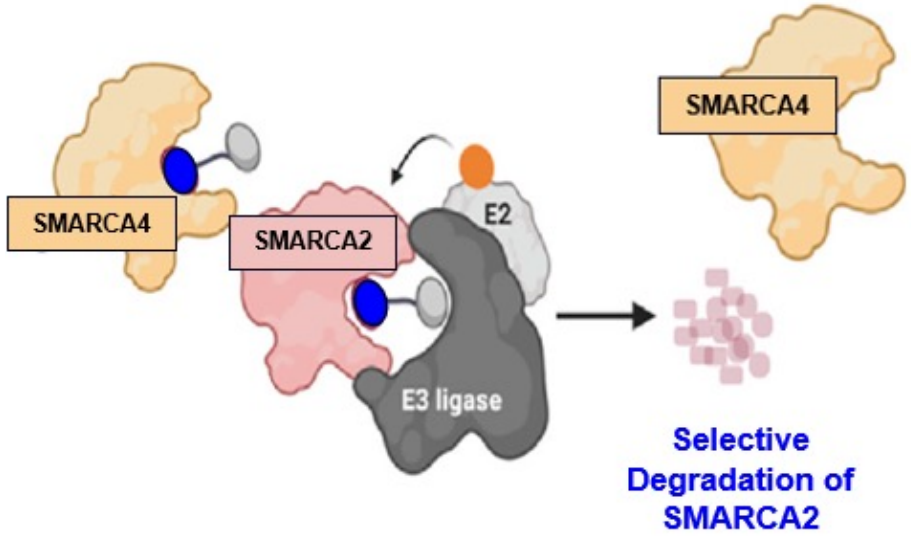
Selectively targeting SMARCA2 has been a significant challenge for industry

Selective SMARCA2 Inhibition is an Unmet Medicinal Chemistry Challenge



- **Bromodomain Binders**
  - Non-selective and inactive in SMARCA4 mutated cancer cells[1]
- **ATPase Inhibitors**
  - Inhibitors show low selectivity for SMARCA2 in cell proliferation assays (<10 fold[2] and ~33 fold[3])

Prelude's Targeted Protein Degradation (TPD) Approach



- **SMARCA2 Selective Degradation** is possible through differences in ternary complexes and subsequent ubiquitination of unique lysine residues

[1] Vangamudi et al, Cancer Res. **2015** (Pfizer); Taylor et al J. Med. Chem **2022** (Genentech)
[2] Papillon et al, J. Med. Chem **2018** (Novartis) [3] AACR **2024** (Foghorn/Lilly)

When it comes to targeting SMARCA2, degraders offer distinct advantages

	Inhibitors	Degraders
Potency	☑	☑
High Selectivity	X	☑
Extended PD	X	☑
Oral Bioavailability	☑	☑

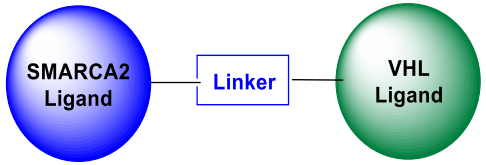
Early attempts at achieving both potency and selectivity with inhibitor approaches had challenges

Inhibitors do not degrade the target and need to be dosed at levels that retain IC_{90} coverage continuously

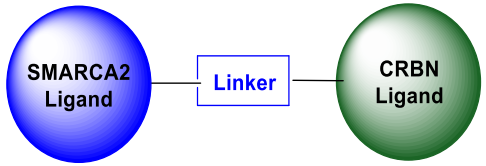
Degraders demonstrate sustained PD effect as it takes ~72h for SMARCA2 to resynthesize

Prelude scientists solved the SMARCA2 selectivity enigma

Parallel VHL- and CRBN-based SMARCA2 Degrader Programs



PRT3789
(IV or SC formulation)



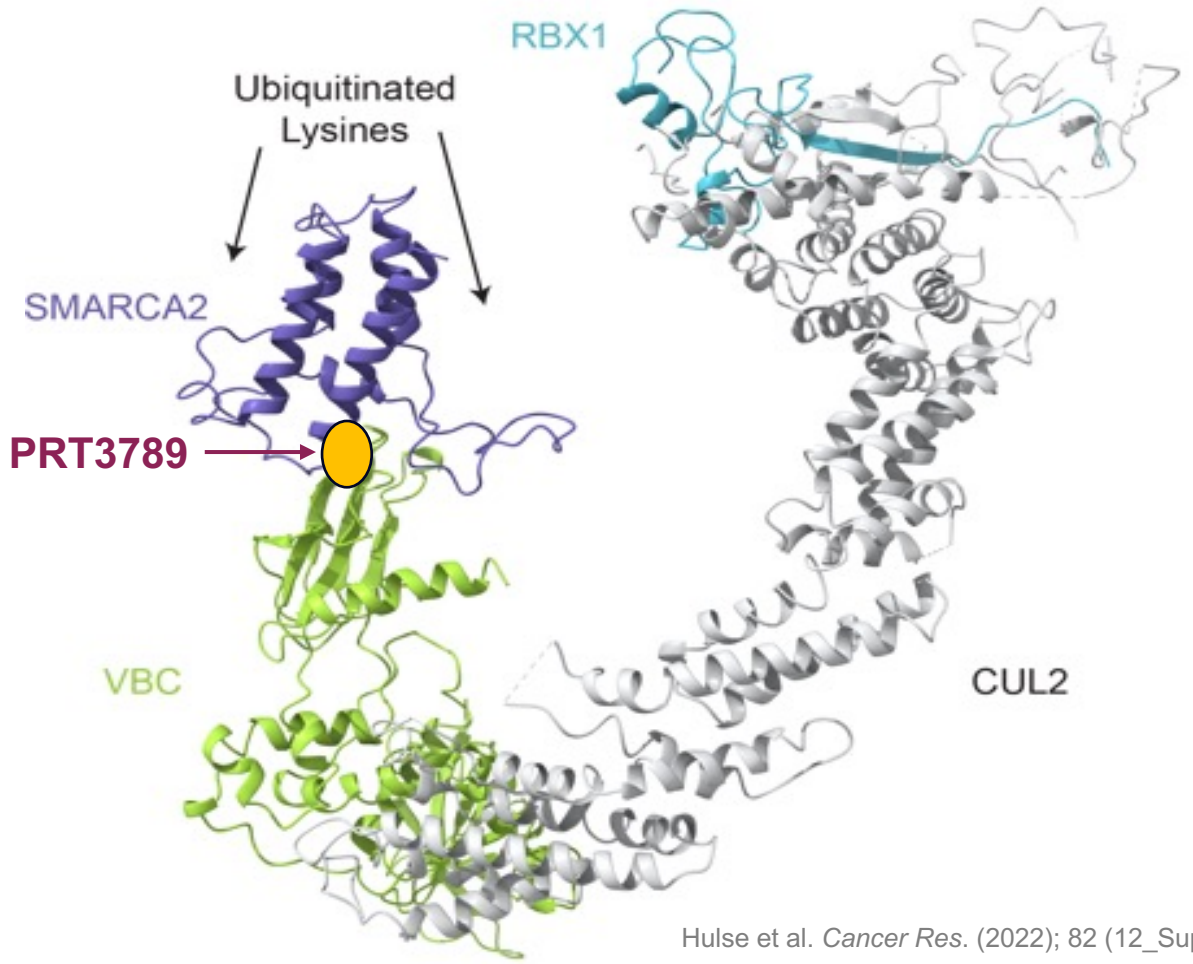
PRT7732
(Oral Candidate)

- **IV or SC Candidate** - **VHL-TPD**s provided an expedited path to potential clinical development with QW dosing
- **Oral Candidate** - **CRBN-TPD**s provided oral candidates, but required extensive lead optimization with balancing of potency, selectivity and oral PK properties

Our lead IV and oral clinical candidates both have sub-nanomolar degradation potencies and very high selectivity (>1000 fold) for SMARCA2 over SMARCA4

PRT3789: Our Lead SMARCA2 Degrader

Tertiary Complex of SMARCA2/ PRT3789/VHL E3 Ligase



Hulse et al. *Cancer Res*. (2022); 82 (12_Suppl) :3263.

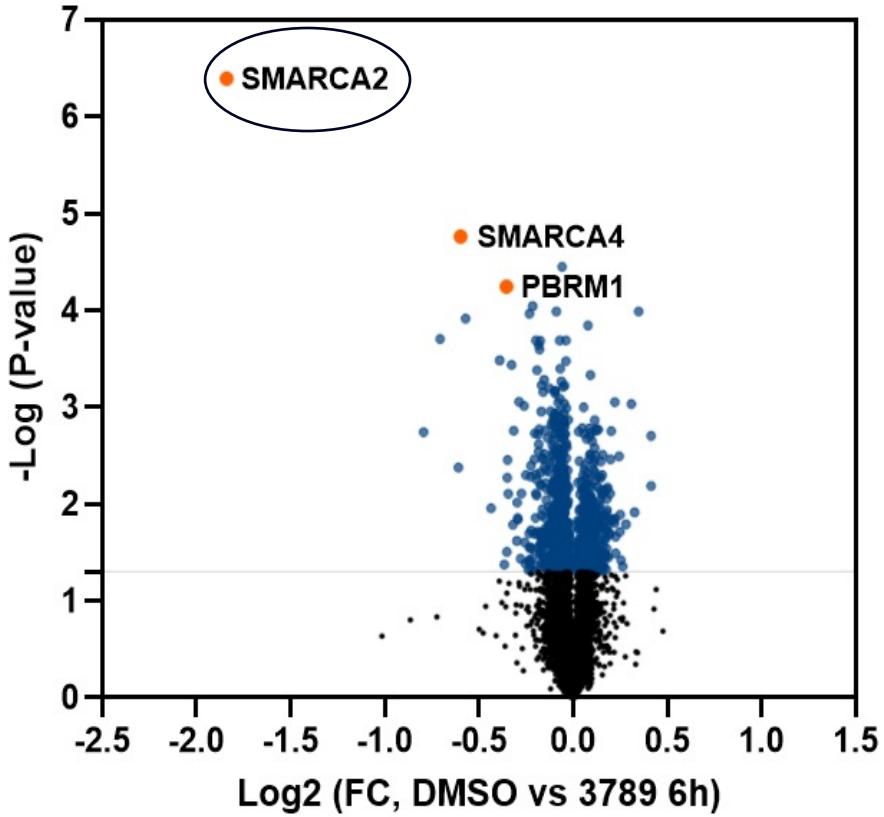
PRT3789 has been shown to catalyze the polyubiquitination of unique lysine residues expressed only in SMARCA2 and not SMARCA4

Unique conformational bias promotes selective ubiquitination and degradation of only SMARCA2

Presented at AACR 2023; https://preludetx.com/wp-content/uploads/2023/05/Ito_SMARCA2_AACR-2023_Poster_6277_01MAY23_CORRECTION.pdf

PRT3789 is highly potent and highly selective

Assay	PRT3789
SMARCA2 Degradation (nM)	0.73
Selectivity: Cell Proliferation (SMARCA4 / SMARCA2)	>1000 fold



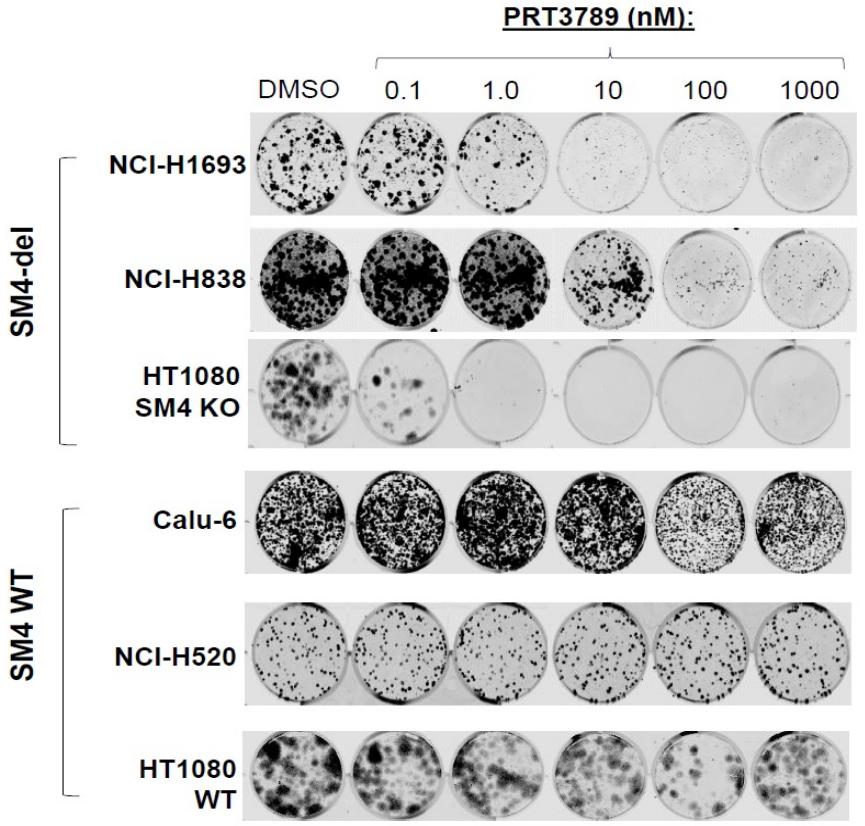
Sub-nanomolar SMARCA2 degradation potency

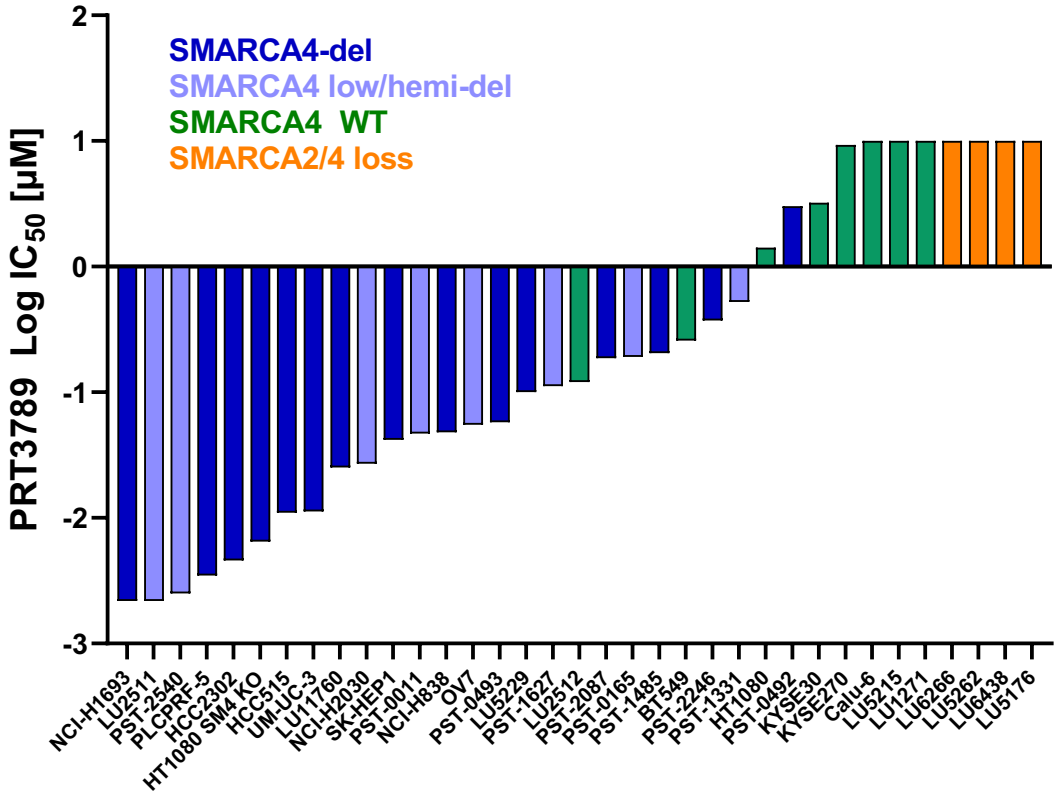
Highly selective for SMARCA2 vs SMARCA4 (>1000 fold)

High selectivity across the proteome

Presented at AACR 2022; https://preludetx.com/wp-content/uploads/2022/05/Prelude_AACR_Hulse-SMARCA2-FINAL-21Mar2022.pdf

PRT3789 induces synthetic lethality in SMARCA4-deficient cancer cells *in vitro*





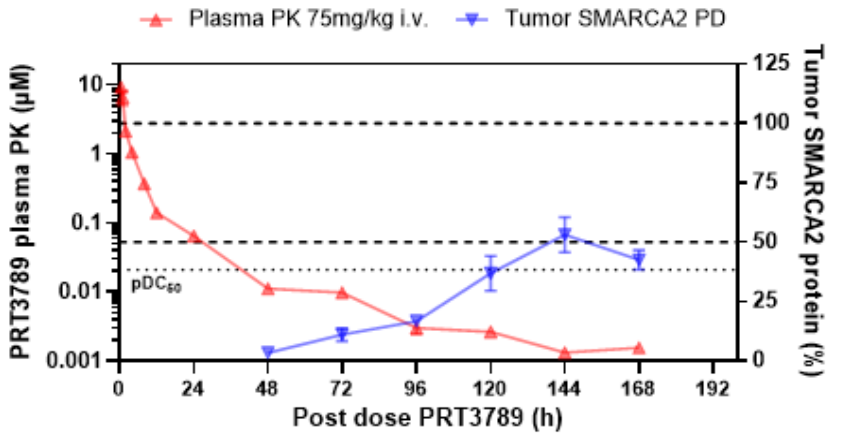
- PRT3789 selectively inhibits SMARCA4 deficient cancer cell proliferation *in vitro*
- None or limited response in SMARCA4 WT and SMARCA2/4 dual loss cancer cells
- >1000x selectivity in cell proliferation assays

1. Data on file. 2. Hulse et al. *Cancer Res.* (2022); 82 (12_Suppl) :3263.

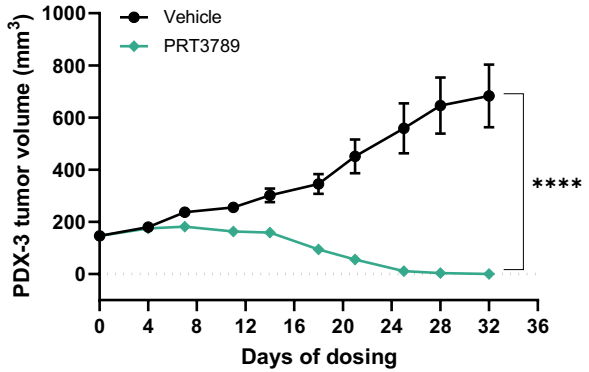
Prelude THERAPEUTICS

PRT3789 demonstrates selective tumor regression *in vivo*

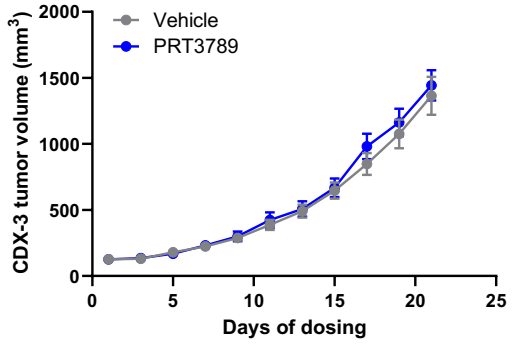
PK/PD - Highly Selective for SMARCA2 Degradation



Robust Tumor Growth Inhibition of SMARCA4 mutated but not WT Xenograft



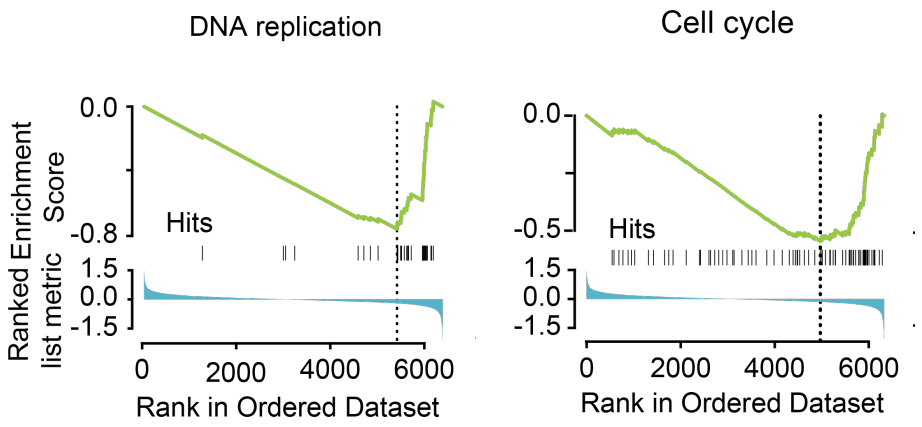
SMARCA4 mutant



SMARCA4 WT

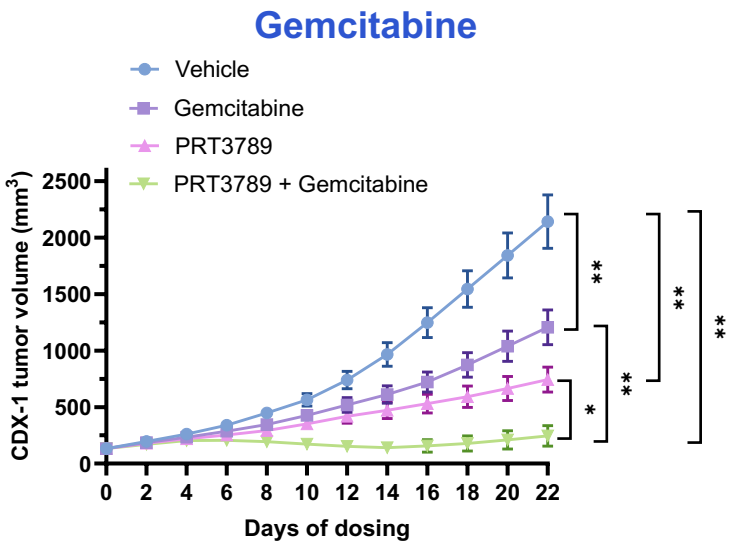
Presented at AACR 2023; https://preludetx.com/wp-content/uploads/2023/04/Hulse_SMARCA2_AACR-2023_Poster-6270_04APR23.pdf
Presented at AACR 2022; https://preludetx.com/wp-content/uploads/2022/05/Prelude_AACR_Hulse-SMARCA2-FINAL-21Mar2022.pdf

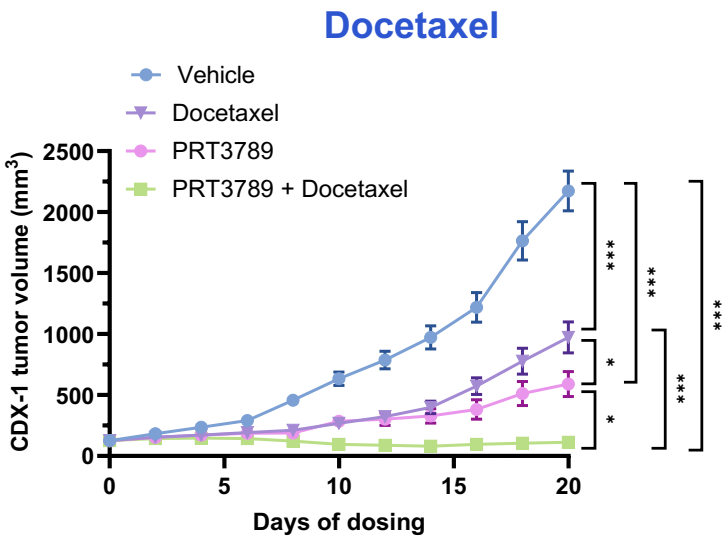
PRT3789 demonstrates potential for synergy with chemotherapy and apoptosis-inducing agents



FEN1, LIG1, MCM, PCNA, POLA1/2, POLD1/2/3, POLE/2/3

BUB1B, CCNA2/B2, CDC25C, CDK1/2, CHEK1/2





AACR 2022, 2023

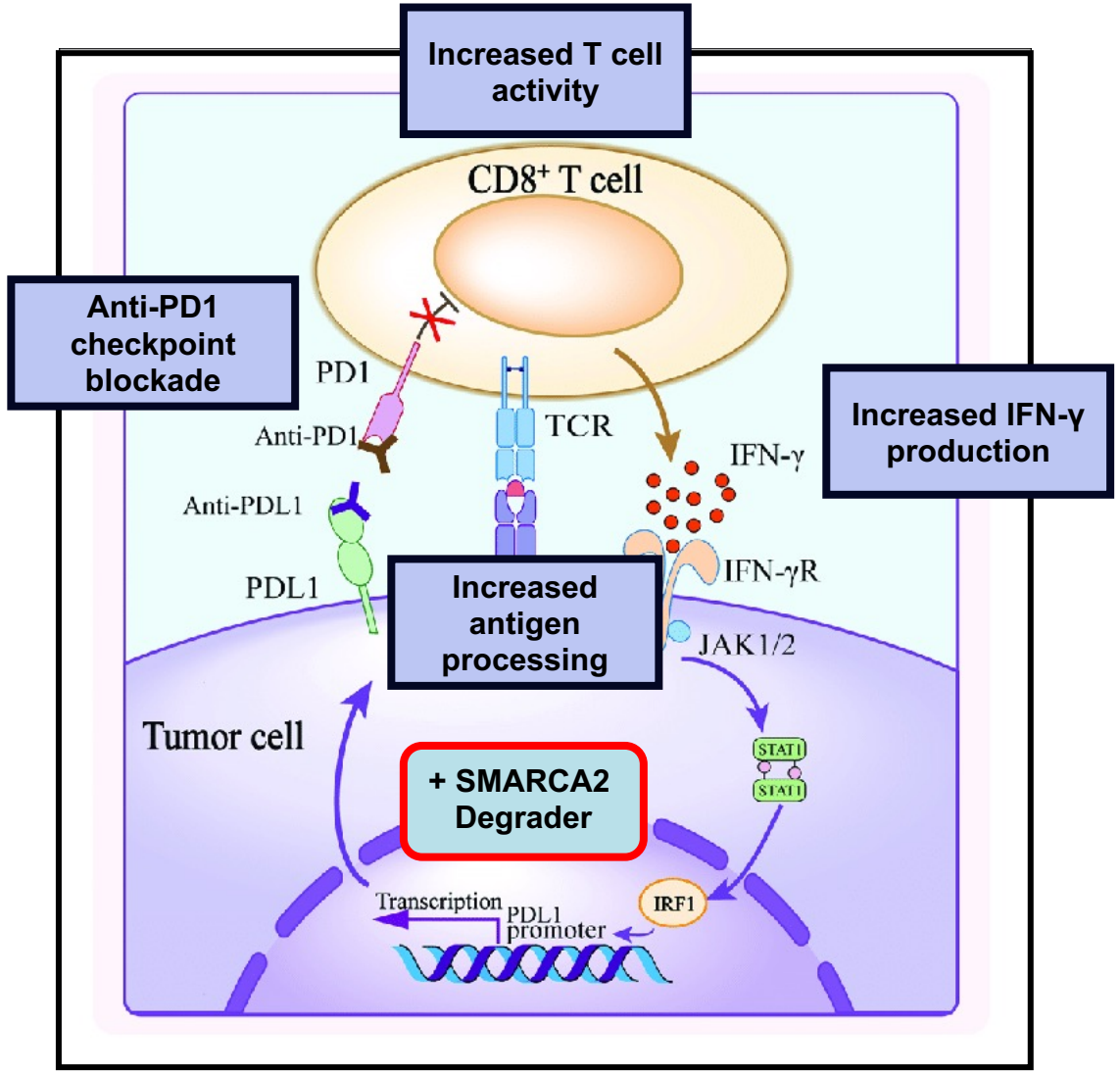
Several oncogenic gene sets regulated by PRT3789

Supports combination strategies with both cytotoxic and apoptosis-inducing agents (*e.g.*, RAS)

***In vivo* CDX models show strong tumor regression in combination with gemcitabine or docetaxel**

SMARCA degraders may also have synergy with and help to potentiate PD1/PDL1 immunotherapy

"Turning Cold Tumors Hot"



In SMARCA4-deficient cancer cell lines, SMARCA2 degradation…

Induces presentation of unique MHC-I peptide

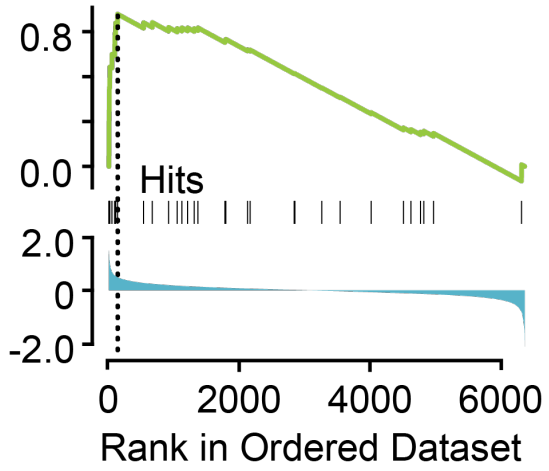
Upregulates antigen processing and presentation machinery

Increases cytokine production

Promotes T-cell activity and accelerates tumor cell killing

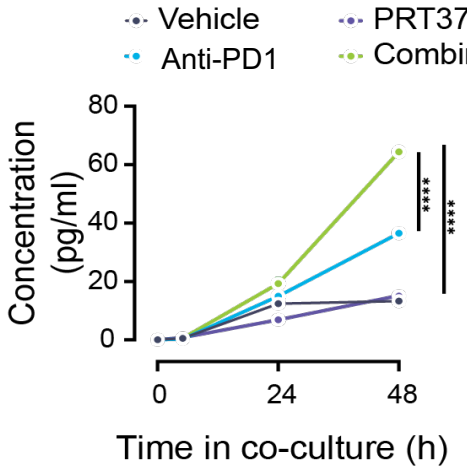
Preclinical data for PRT3789 support rationale for anti-PD1 combination

PRT3789 Upregulates Genes for Antigen Processing and Presentation

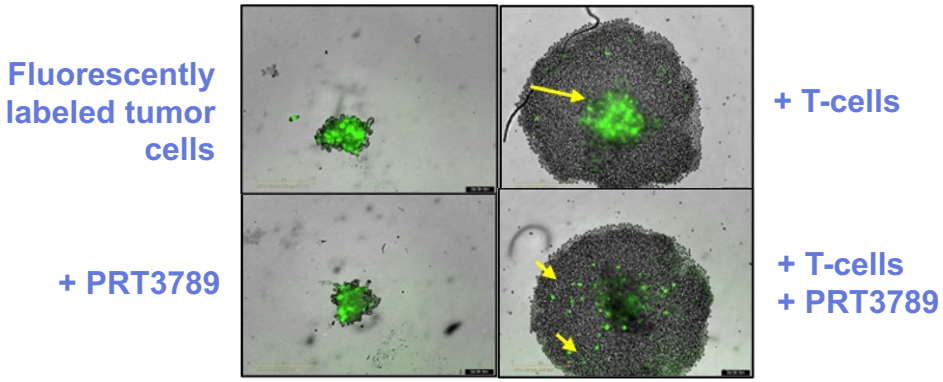


TAP1/2, HLA-A/C/G/F, B2M

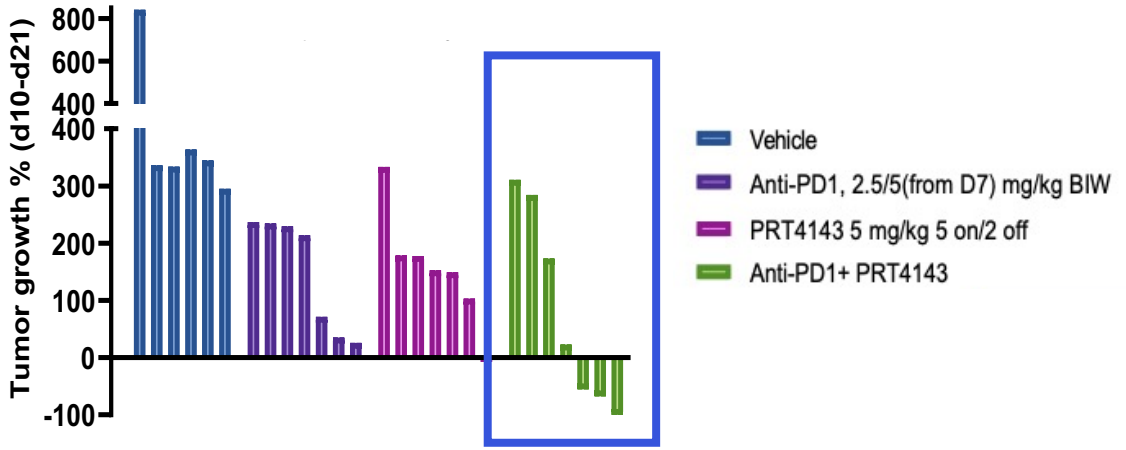
PRT3789 Increases IFN-g Levels in Combination with anti-PD1 *In Vitro*



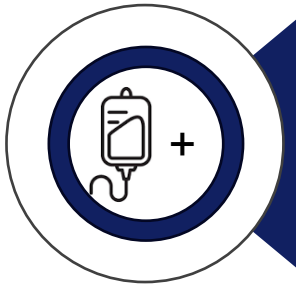
PRT3789 Promotes T-cell mediated Tumor Cell Killing *In Vitro*



SMARCA2 Degrader + Anti-PD1 Demonstrates Tumor Regression *In Vivo*

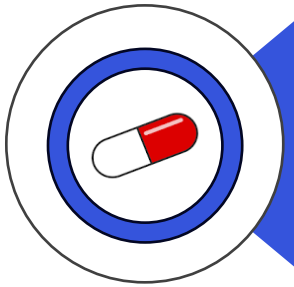


PRT3789 was the industry's first selective SMARCA2 degrader to enter the clinic



Lead SMARCA2 Degrader (PRT3789)

- ✓ Highly potent, selective degrader with once-weekly IV dosing
- ✓ Phase 1 trial underway, advancing well in clinic
- ✓ Generally well tolerated with no dose limiting toxicities observed to date
- ✓ Synergy with chemotherapy and immunotherapy



Oral SMARCA2 Degrader (PRT7732)

We solved SMARCA2 selectivity challenge >1000 fold

- Targeting SMARCA2 has been challenging due to the high homology between SMARCA2 and SMARCA4
- We have identified both IV and oral candidates with sub-nanomolar degradation potencies and high selectivity for SMARCA2 over SMARCA4
- Our lead program, PRT3789, is the first selective SMARCA2 degrader to enter clinical development
- Preclinical data for ‘3789 shows significant tumor regression in animal models, favorable safety, and high potential for chemoimmunotherapy synergy

Key Takeaways