Beyond Conventional Payloads: Unlocking New Therapeutic Landscapes With Precision Degrader-Antibody Conjugates (DACs)

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Disclosure Information

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Koichi Ito

I have the following relevant financial relationships to disclose:

Employee of: Prelude Therapeutics Incorporated

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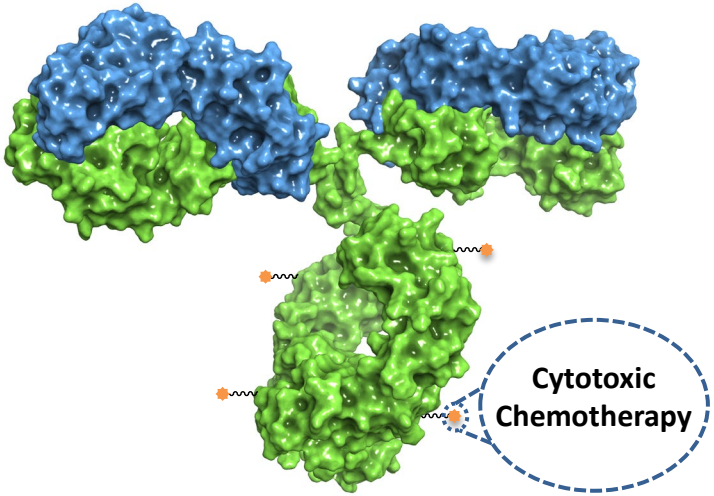
Traditional ADCs



"Why have traditional ADCs NOT fulfilled their promise of *The Silver Bullet?*"

"How selectively do ADCs actually deliver broadly cytotoxic payloads to cancer cells?"

Precision Degrader Antibody Conjugates (pDACs) Represent the Next Generation of ADCs

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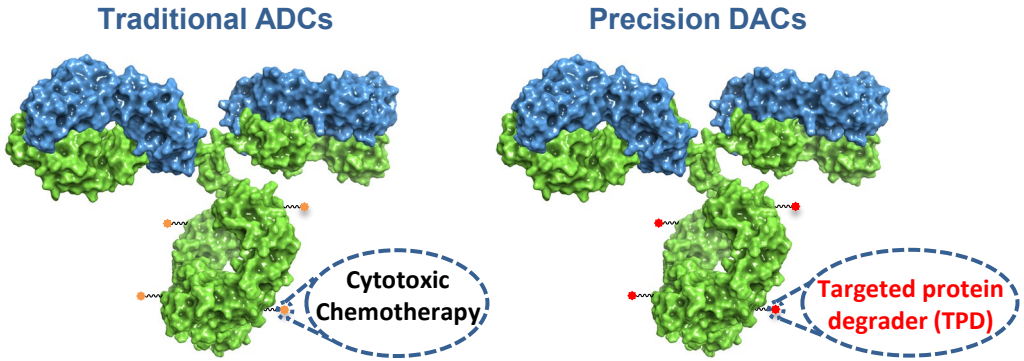

Property	Traditional ADC	pDAC
Potency	✓	✓
Antibody Selectivity	✓	✓
Payload Selectivity	X	✓
PD Marker - Payload	X	✓
Non-Genotoxic	X	✓

- **Dual Targeting with pDACs**
  - ✓ **Antibodies** to tumor-specific cell surface antigens, and
  - ✓ **Targeted Protein Degraders (TPDs)** of critical proteins in validated biological function
- **Potential to deliver both improved efficacy and improved tolerability**

For a review of ADCs, see Fu, Z., Li, S., Han, S. *et al. Sig Transduct Target Ther* **7**, 93 (2022).

Targeted Protein Degraders (TPDs) Represent An Emerging Therapeutic Class With Unique Advantages as Payloads

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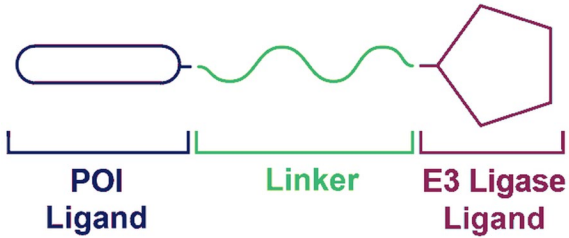
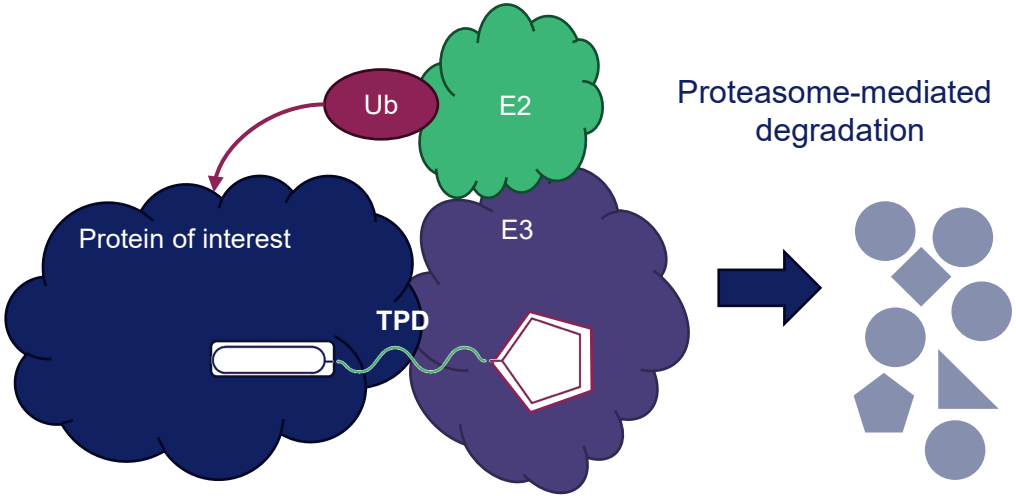
Components of heterobifunctional degrader



Mechanism of ubiquitin-proteasome degradation



Advantages of Targeted Protein Degrader (TPD) Technology

- Excellent potency and catalytic activity (event-driven pharmacology)
- Prolonged pharmacodynamic effects resulting from protein resynthesis
- Possibility for enhanced pharmacology beyond enzymatic function including targeting protein-protein interactions and disrupting protein complex assembly

For select, recent reviews, see 1) Zhang, C. et al. *Sci. Bulletin* **2024**, *69*, 1776. 2) Hong, K. B.; An, H. *J. Med. Chem.* **2023**, *66*, 140.

Among Clinical, "Next Gen" ADCs, Degraders Remain an Under-Represented Payload Class

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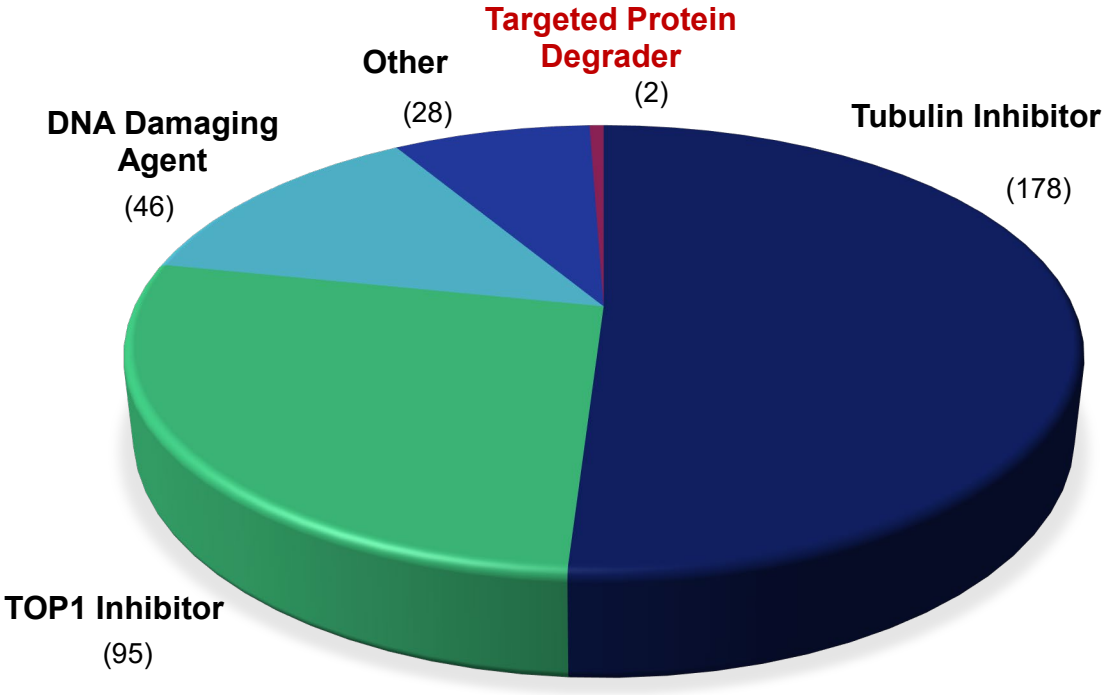

- Most clinical ADCs use three cytotoxic payload classes with limited diversification and similar liabilities
- TPDs uniquely suited as payloads with excellent potencies and added benefit of precision to cancer specific MoA

Data source: Morris, J. Beacon ADC by HansonWade. "Analyzing the ADC Boom: Landscape Review." World ADC (San Diego). November 2024. Denotes Payload MOA for clinical stage assets currently in development.

Degrader Payloads: Designed and Engineered to Improve Efficacy, Tolerability Compared to Traditional Cytotoxic Payloads

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Degrader Payload	pDAC	Rationale
Exceptional Potency	☑	Low DAR Improved developability
Permeable	☑	Bystander effect intact Improved efficacy
High Clearance	☑	Lower systemic toxicity
Prodrug	☑	Lower systemic toxicity Improved developability
Highly stable E3 Ligase binder	☑	Long pDAC half-life Improved efficacy
Non-Genotoxic	☑	Suitable for therapeutics beyond cancer

- **Exceptionally potent** and **cell line selective** targeted protein degraders
- Payload **permeability** is maintained to provide bystander effect
- Payloads are engineered to have **high clearance** to help reduce systemic toxicity
- **Prodrugs** of the degrader payloads can be engineered to limit systemic toxicity
- **Highly stable degraders** have the potential to provide improved efficacy

Medicinal Chemistry Approach Delivers Highly Optimized pDACs

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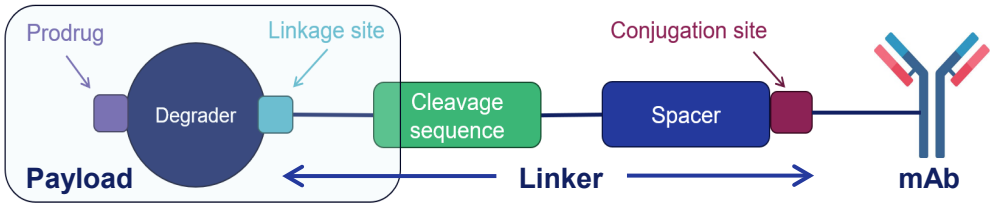

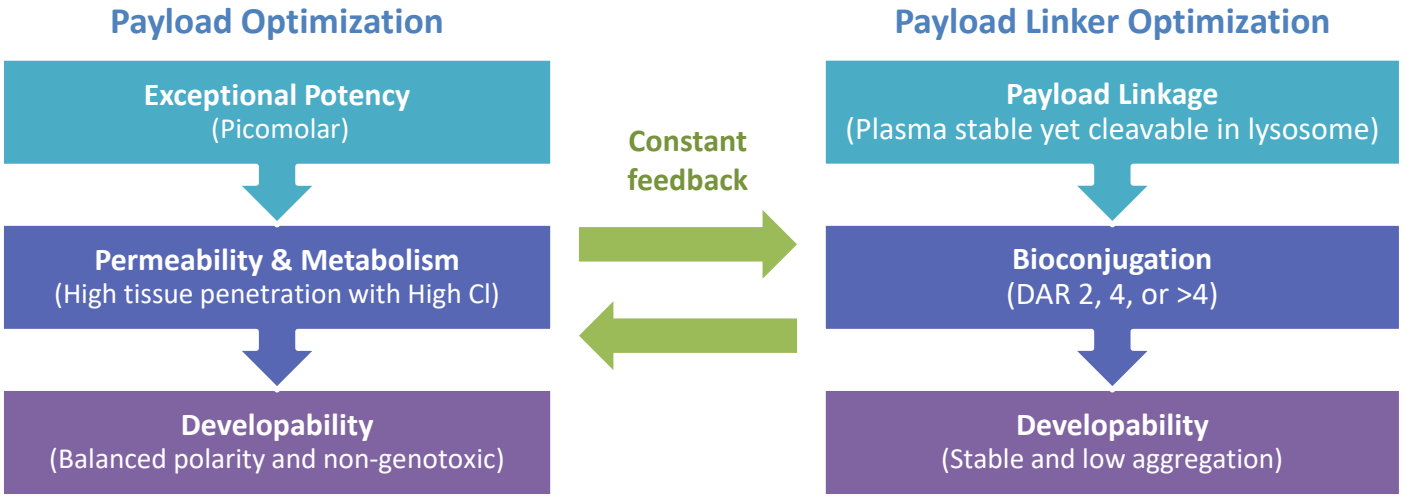

- An iterative medicinal chemistry approach accelerates discovery of novel DACs with innovative payload degraders and linkers

SMARCA2 and SMARCA4 in SWI/SNF chromatin remodeling complex in cancer

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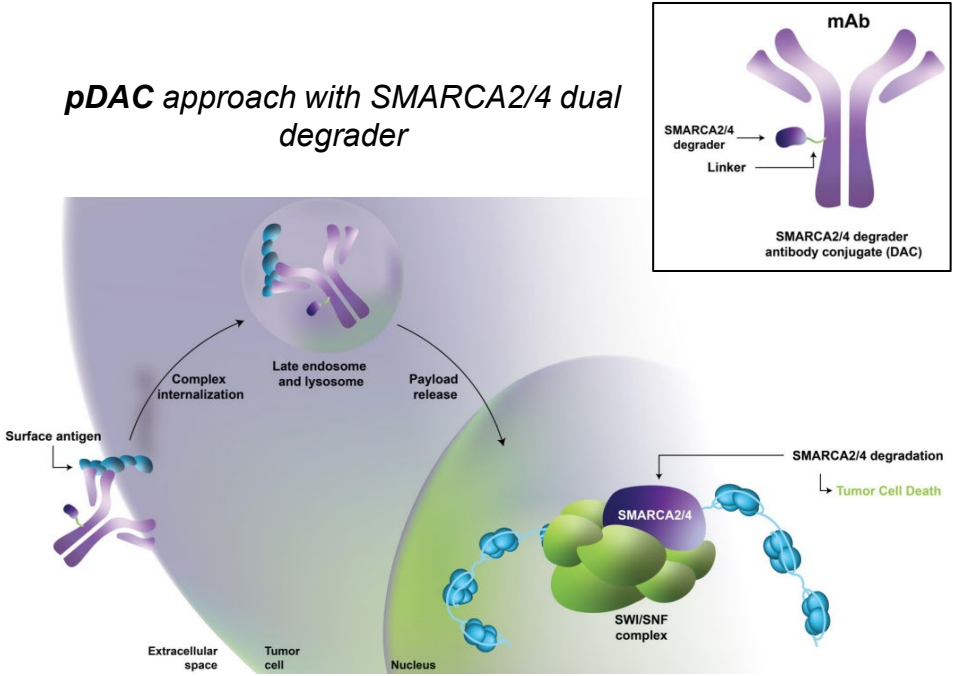
- **The SWI/SNF complex** is a major chromatin remodeling complex (1)
- It contains one ATPase catalytic subunit, either SMARCA2 (BRM) or SMARCA4 (BRG1) (1)
- Certain cancer types are highly sensitive to SWI/SNF complex inhibition (4)
  - Dual inhibition of SMARCA2/4 suppresses **specific cancer types** with poor tolerability
  - Antibody-drug conjugates (ADCs) represent a promising therapeutic approach

***pDAC** approach with SMARCA2/4 dual degrader*



(1) Gourisankar S et al. Nat Rev Genet. (2024) May;25(5):340-361.
(2) Hulse M et al. Cancer Res (2022) 82 (12_Supplement): 3263.
(3) Alessi JV et al. J Thorac Oncol. 2023;18(6):731-743
(4) Xiao L et al. Nature. 601, 434-439 (2022)

Tricyclic SMARCA2/4 binder enables early lead degrader identification

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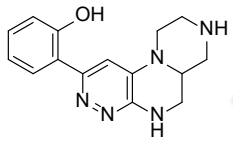
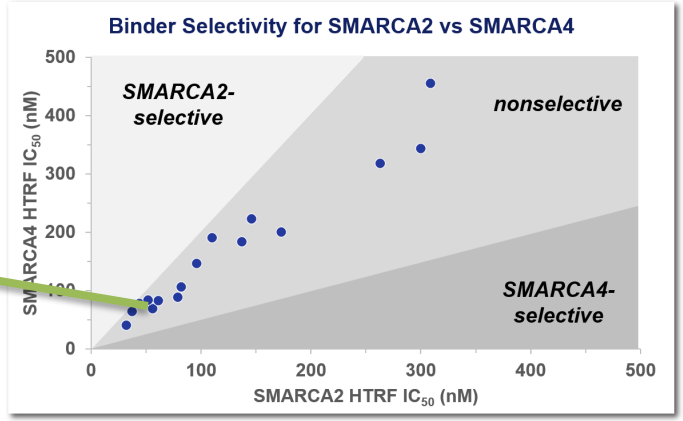
Binder identification

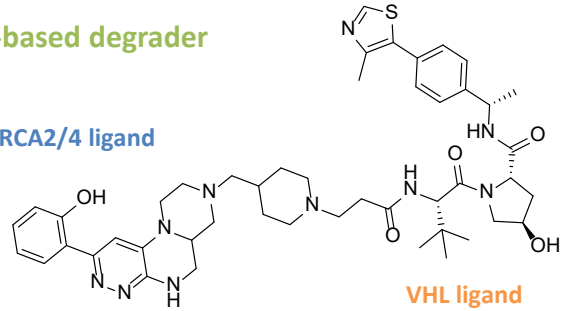




HTRF	SMARCA2/4 BD binder 01
SM2 IC_{50} (nM)	51
SM4 IC_{50} (nM)	80
Selectivity	1.6

VHL-based degrader

SMARCA2/4 ligand



VHL ligand

HiBiT	Degrader 02
SM2 DC_{50} (nM) (D_{max})	304 (88%)

- Medicinal chemistry campaign identified non-selective, **tricyclic binder 01** of SMARCA BRD domain
- Linking to VHL ligand provided promising **degrader 02**

Hulse, M. et al. Cancer Research, 2026

SMARCA2/4 Degrader 04 Demonstrates Potent Activity Across Various Tumor Types

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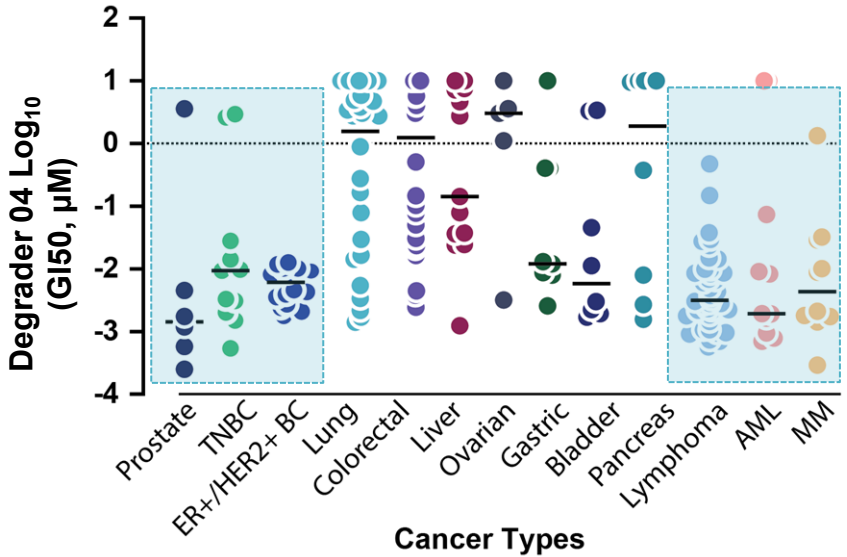
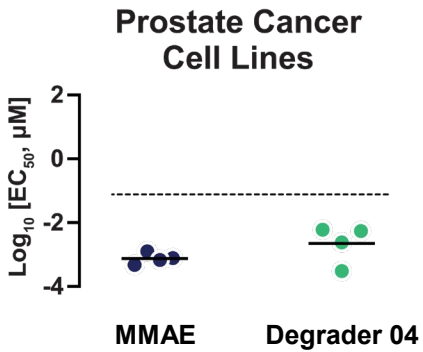
GI_{50} of cancer cell line panel treated with degrader 04



EC_{50} of prostate cell panel treated with degrader 04



- Several tumor types demonstrate notable sensitivity to SMARCA2/4 degradation
- SMARCA2/4 degrader payload **degrader 04** demonstrates comparable potency to MMAE in prostate cancer cell lines

Degrader 04 Administered Systemically Demonstrates Tumor Regressions but is Limited by Narrow Therapeutic Index

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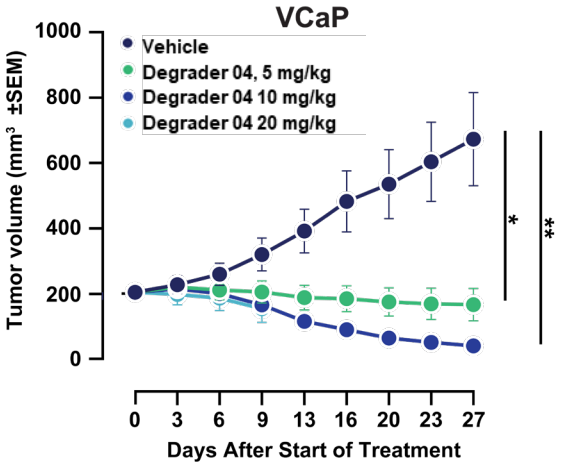

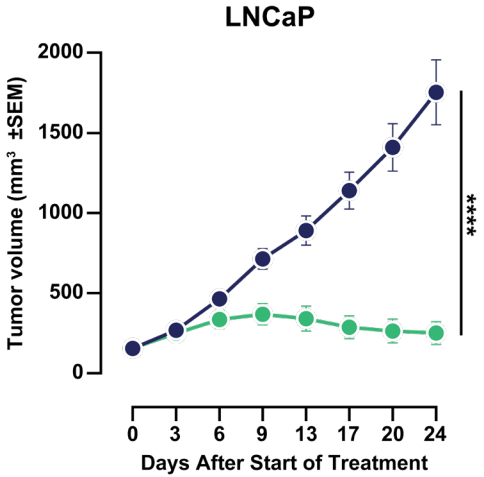

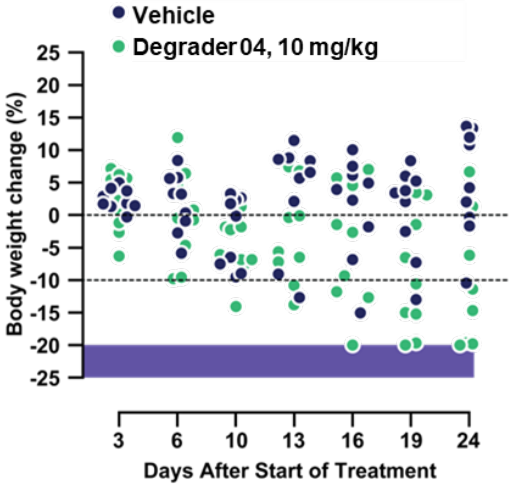

*P<0.05 **P<0.01 ****P<0.0001 versus vehicle (T-test)

- Tumor regression observed in multiple prostate cancer xenograft models
- However, time- and dose-dependent body weight loss and animal deaths were observed

→ ADC approach was warranted

Platform Validation of SMARCA2/4 pDAC Across Multiple Targets

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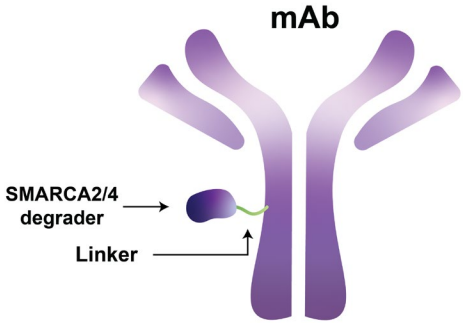
Tumor-specific Antigens

- PSMA (Prostate Cancer)
- Mutant CALR (MPN)
- TROP2 (Breast Cancer)
- CD123 (Acute Myeloid Leukemia)
- CEACAM5 (Colorectal Cancer)
- MET (Non-Small Cell Lung Cancer)

Novel Degrader Payloads

SMARCA2/4 dual degrader

SMARCA2/4 pDAC



- Established a versatile pDAC platform demonstrating activity across diverse tumor-specific antigens
- Utilized state-of-the-art linker and conjugation technologies to produce pDACs

Design of SMARCA2/4 payload-linker utilizes *N*-linkage and state-of-art linker

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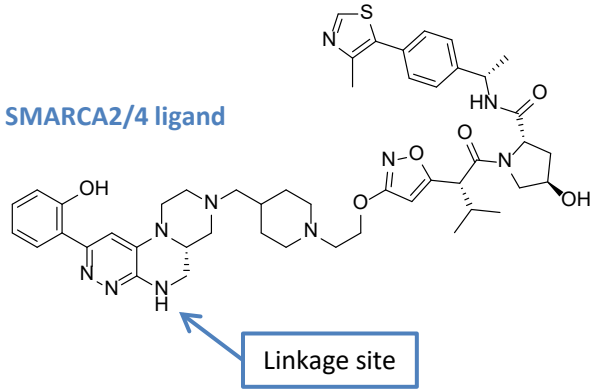

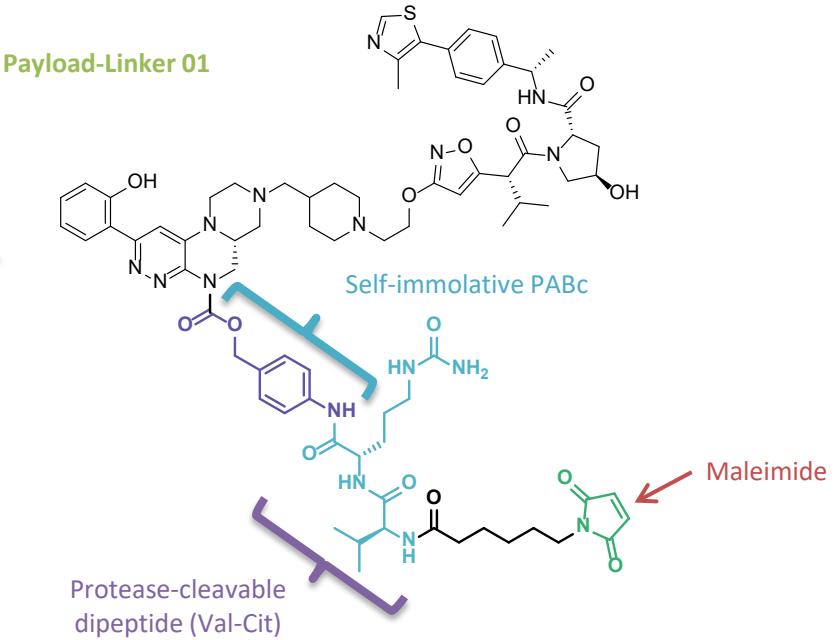

Potency & selectivity assays	Degrader 04
HeLa HiBit SM2 DC_{50} (pM) (D_{max})	370 (97%)
HeLa HiBit SM4 DC_{50} (pM) (D_{max})	2,700 (96%)
LNCaP prolif EC_{50} (pM) (E_{max})	210 (96%)

- SMARCA2/4 binder **N–H** selected as facile site of linker attachment
- Initially selected protease-cleavable, dipeptide linker with self-immolative PABc

PSMA x SMARCA pDAC Demonstrates Potent and Selective Degradation of SMARCA in PSMA-expressing Cells

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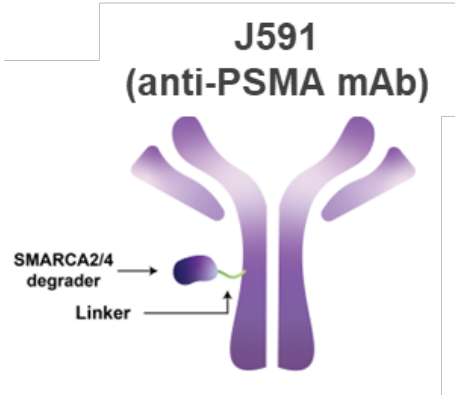
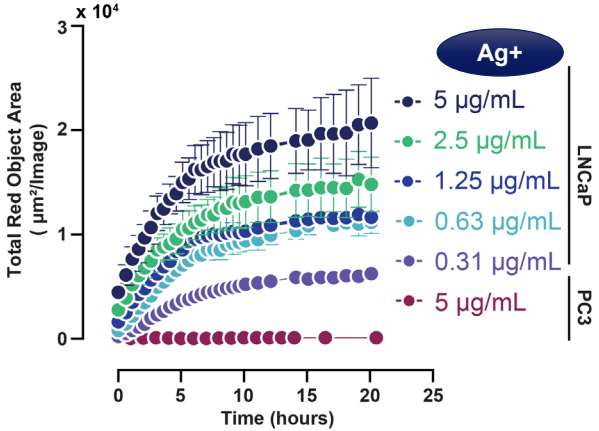
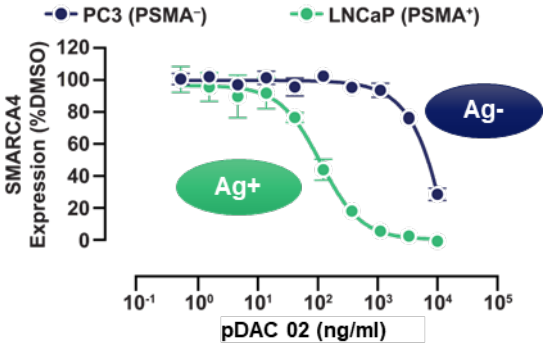
pDAC 02



Dose-dependent, selective, internalization



Antigen-selective SMARCA4 degradation



- pDAC 02 is selectively internalized in PSMA+ cells (LNCaP) and potently degrades SMARCA4 with no activity in PSMA- cells (PC3)

pDAC 02 Demonstrates Selective Efficacy in Antigen-Expressing CDX Model

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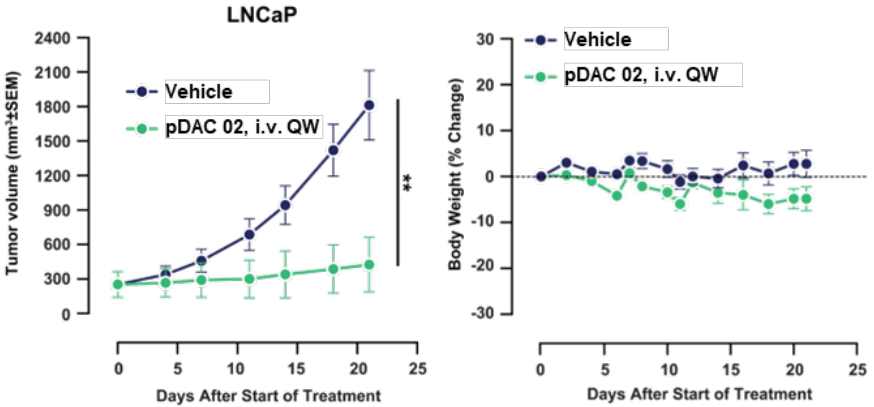
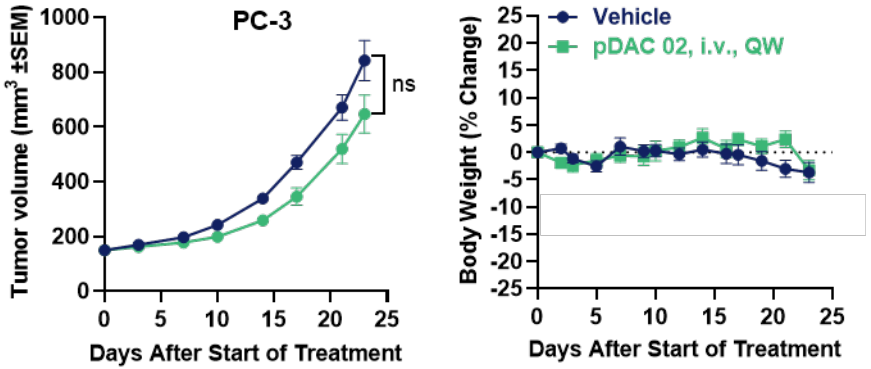
Robust efficacy in PSMA+ xenograft



No in vivo activity in PSMA- xenograft



- pDAC 02 demonstrated clear in vivo efficacy in PSMA-high LNCaP CDX model, but not in PSMA-low PC3 CDX model, demonstrating antigen selective anti-tumor activity
- pDAC 02 was well tolerated as measured by body weight change

CRBN-based degrader payload more potent than VHL-based payload

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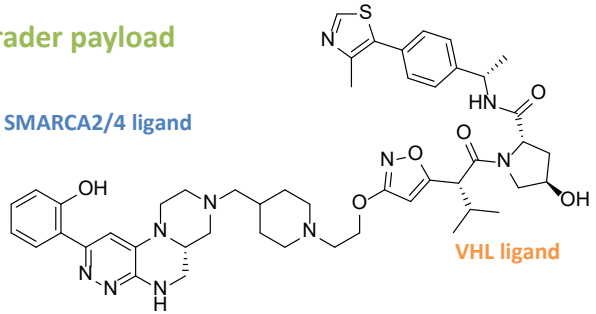
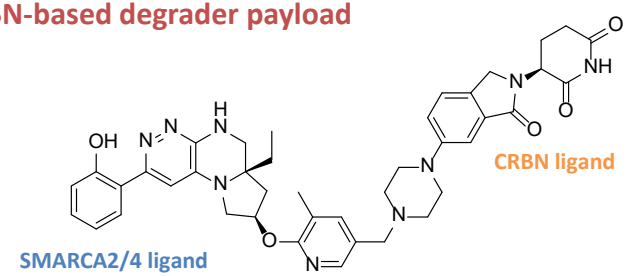
VHL-based degrader payload



CRBN-based degrader payload



Potency assays	Degrader 04	Degrader 06
HeLa HiBit SM2 DC_{50} (pM) (D_{max})	370 (97%)	40 (97%)
HeLa HiBit SM4 DC_{50} (pM) (D_{max})	2,700 (96%)	90 (97%)
Fold Selectivity SM4/SM2	7.3x	2.3x
LNCaP prolif EC_{50} (pM) (E_{max})	210 (96%)	74 (93%)
hIntCl HLM mL/min/kg (%HBF)	16 (77%)	19 (90%)

- CRBN-based **degrader 06** provided additional potency over degrader VHL-based **degrader 04**
- Maintained high clearance to minimize free payload exposures

Degrader 06 demonstrates on-antibody hydrolysis in human plasma

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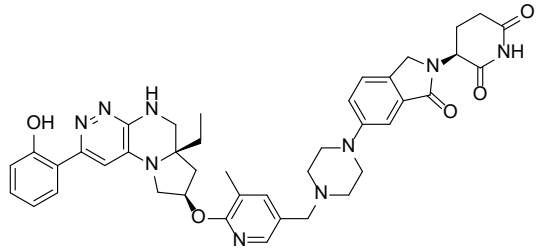
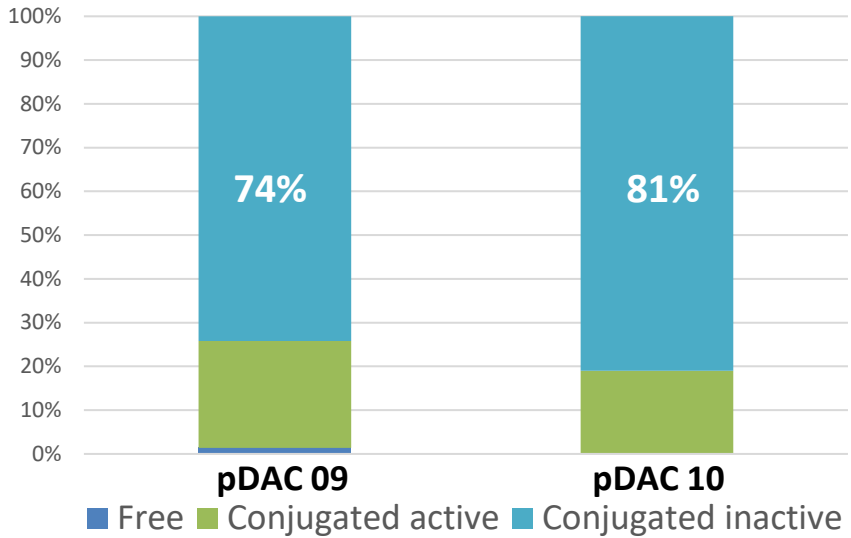
Payload stability upon aging in plasma



	Degrader 06
hPlasma stability, $t_{1/2}$ (h)	34
mPlasma stability, $t_{1/2}$ (h)	34

Payload species upon aging pDAC in plasma (2 d)



- In plasma, **degrader 06** hydrolyzes both alone as free drug and on-antibody as a conjugate
- Hydrolysis produces inactivated payload, which represents major conjugated species after just 2 day
- To advance more potent pDACs improved plasma stability proved essential

Medicinal chemistry approach extended payload stability in plasma

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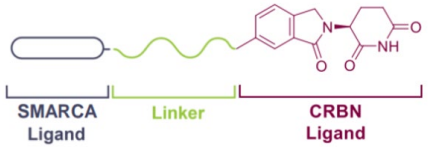
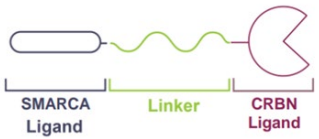
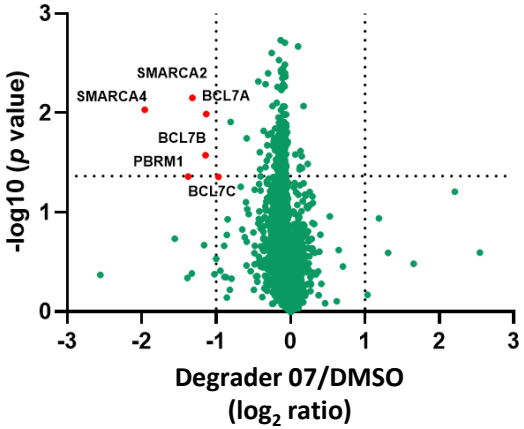


Improved stability



Potency & selectivity assays	Degrader 06	Degrader 07
HeLa HiBit SM2 DC_{50} (pM) (D_{max})	40 (97%)	31 (99%)
HeLa HiBit SM4 DC_{50} (pM) (D_{max})	90 (96%)	29 (99%)
Fold Selectivity SM4/SM2	2x	1x
In vitro ADME		
hPlasma stability, $t_{1/2}$ (h)	34	>200

Global proteomics in LNCaP cells



- **Degrader 07** improved human plasma stability
- **Degrader 07** rapidly disrupts SWI/SNF complex
- Bioconjugation of **degrader 07** with various antibodies for proof-of-concept studies are ongoing

Mutant CALR pDACs Demonstrate Robust and Selective SMARCA2/4 Degradation and Cytotoxicity in CALR Mutant Cells

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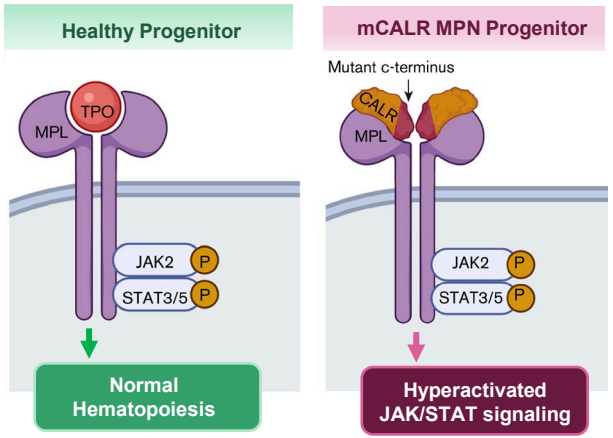

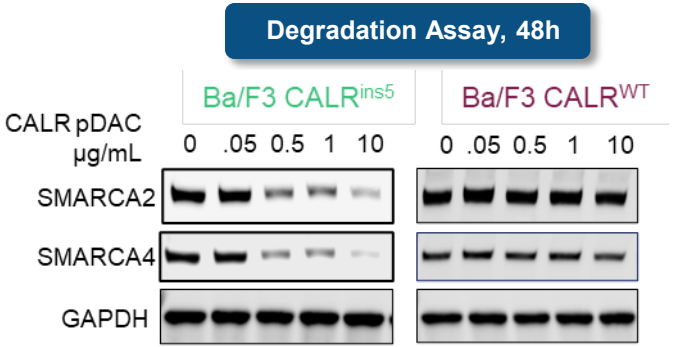

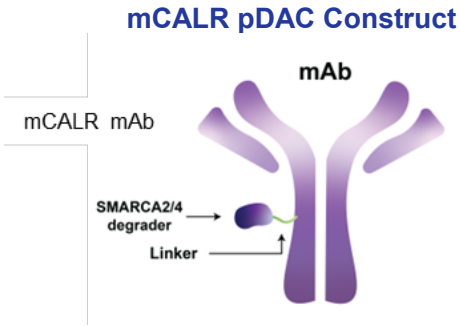

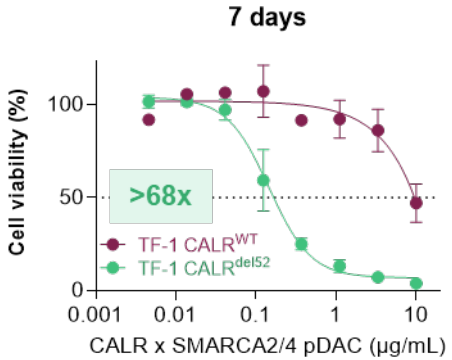

Heaton, W.L., 2026. Blood Neoplasia, p.100193.

mCALR pDACs Demonstrate Robust and Selective SMARCA2/4 Degradation and Cytotoxicity in CALR Mutant Cells

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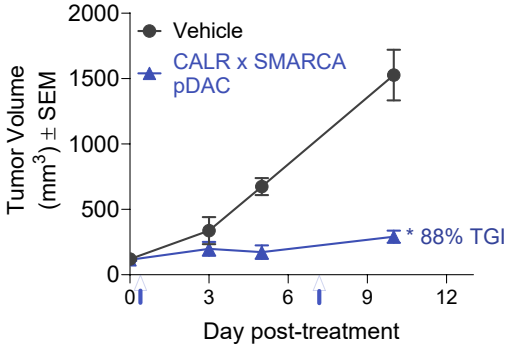
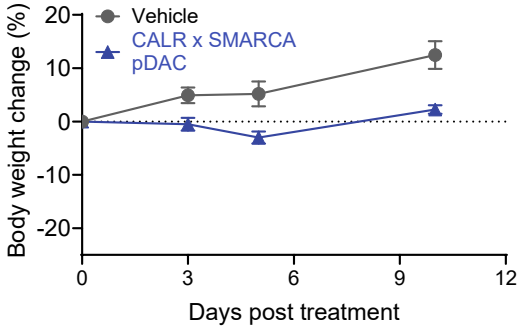
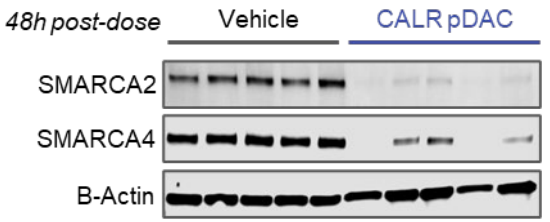
Robust tumor growth inhibition



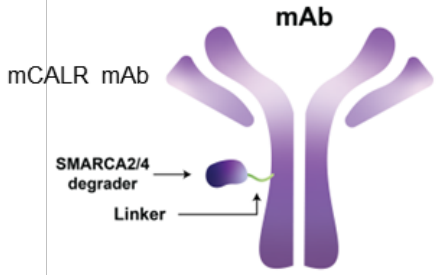
Well tolerated



Target degradation in tumor tissue



- **mCALR pDAC** demonstrate anti-tumor activity in TF1 CALR^{del52} CDX model at well tolerated doses
- **Target engagement** is confirmed in tumor tissue, supporting in vivo mechanism of action



TPDs Represent the Next Generation of Precision DAC Payloads

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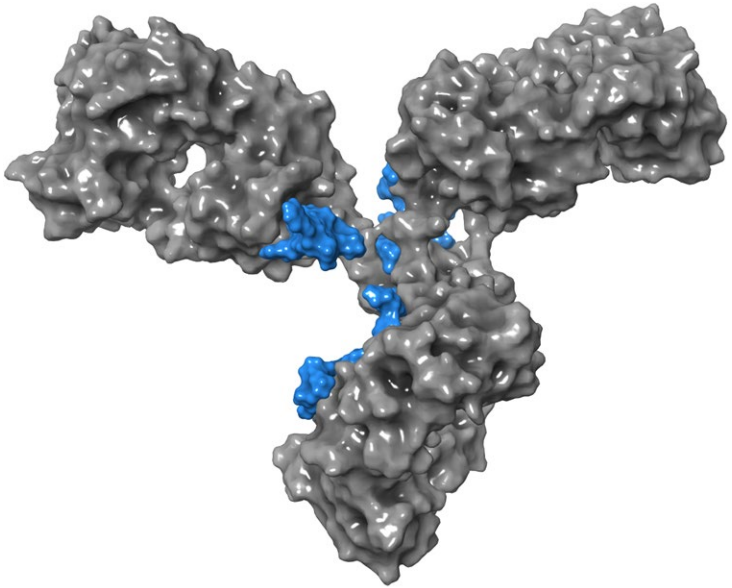
- **Exceptionally Potent and Stable TPD payloads** identified through focused medchem campaigns
- Precision DACs with highly potent TPDs exhibit antigen-selective *in vitro* potency and robust *in vivo* efficacy, improving therapeutic index

Novel TPD payloads hold potential to unlock new era of precision medicine

Model of Precision DAC With Novel Degrader Payload (DAR 4)



Acknowledging the Prelude Research Team

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Synthetic Chemistry, Analytical, and Bioconjugation

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Screening, Preclinical Biology, and DMPK

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