

Precision Degradable Antibody Conjugates (DACs): An Emerging Modality in Targeted Therapeutics

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Novel Drug Modalities: Tackling Difficult-to-Drug Targets with
Glues, Chimeras, Condensates, Conjugates, Peptides
24th Discovery on Target 2026 (Boston)



Disclosures & Financial Relationships

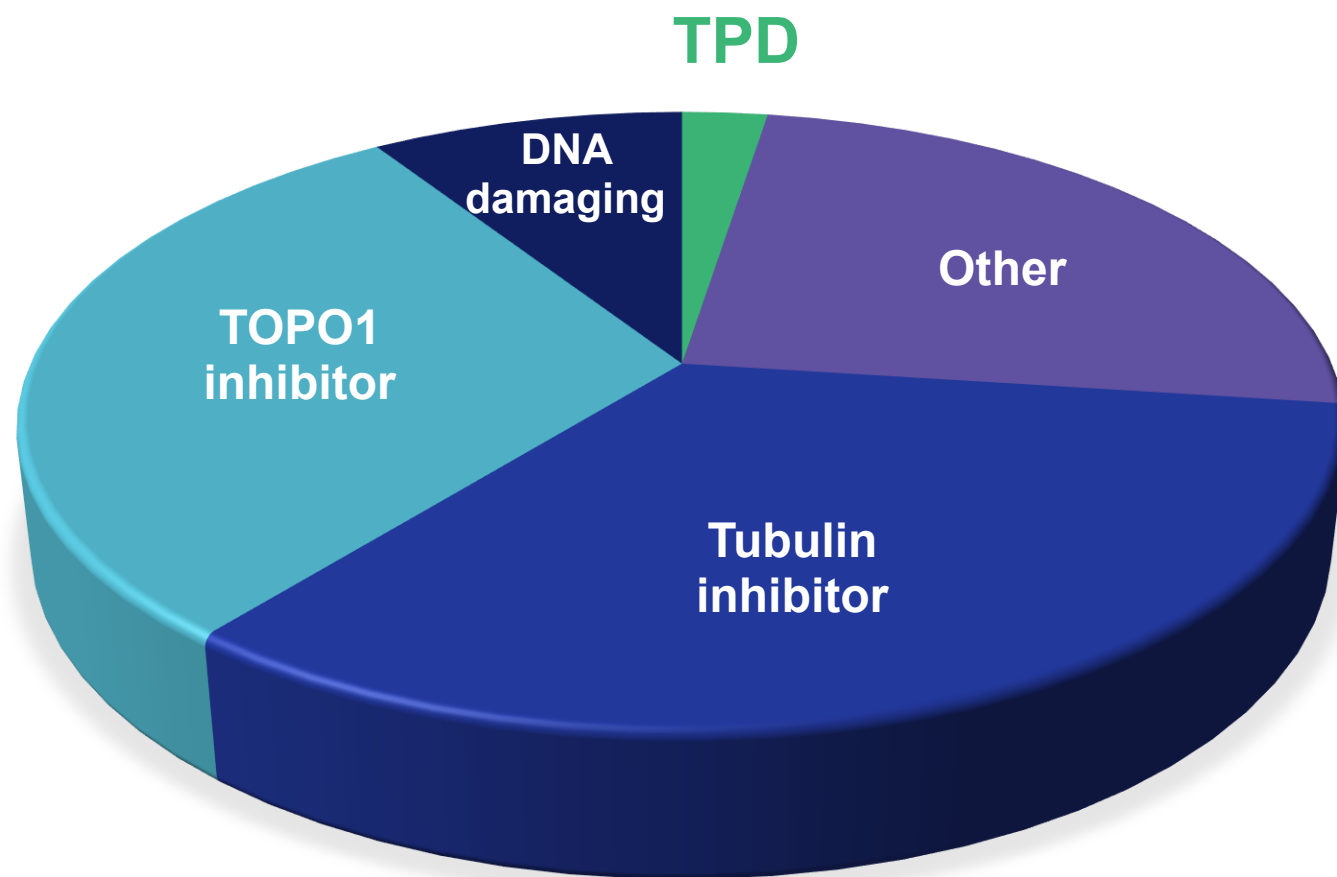
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Financial Relationships

Ryan Holmes is an employee and shareholder of Prelude Therapeutics Incorporated.

Degraders remain under-represented payload class



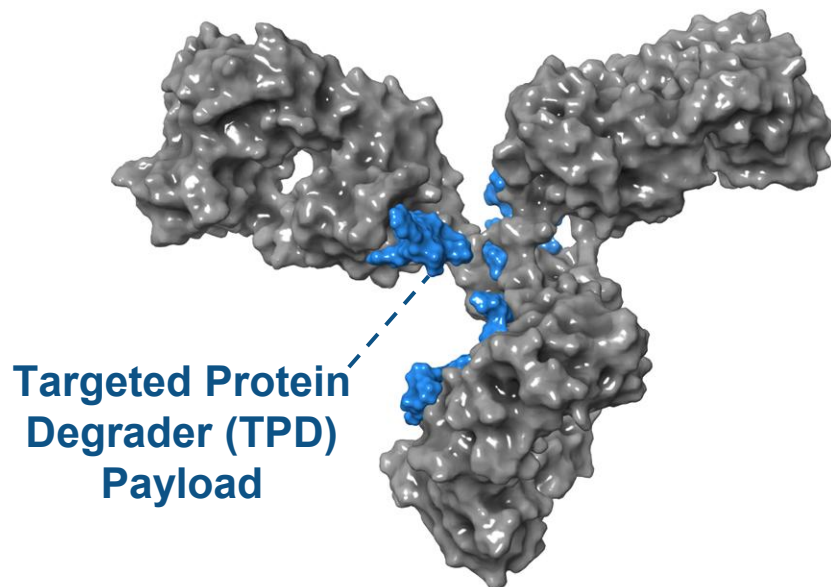
Why degrader payloads?

- ✓ Exceptional potency
 - Catalytic activity
 - Prolonged PD effects
 - Pharmacology beyond enzymatic function
- ✓ Precision by targeting validated pathways
- ✓ Design to minimize non-tumor tissue exposure
- ✓ Avoid genotoxicity liabilities

1) Graph of disclosed programs across all stages of development. Data source: *Recent Advances in ADCs*. NJ Bio, Inc., 2025. <https://njbio.com/antibody-drug-conjugates/> 2) For recent reviews, see: a) Zhang, C. et al. *Sci. Bulletin* **2024**, 69, 1776. b) Hong, K. B.; An, H. *J. Med. Chem.* **2023**, 66, 140. c) Fu, Z., Li, S., Han, S. et al. *Sig Transduct Target Ther* **7**, 93 (2022).

Degrader antibody conjugates represent next generation of precision ADCs

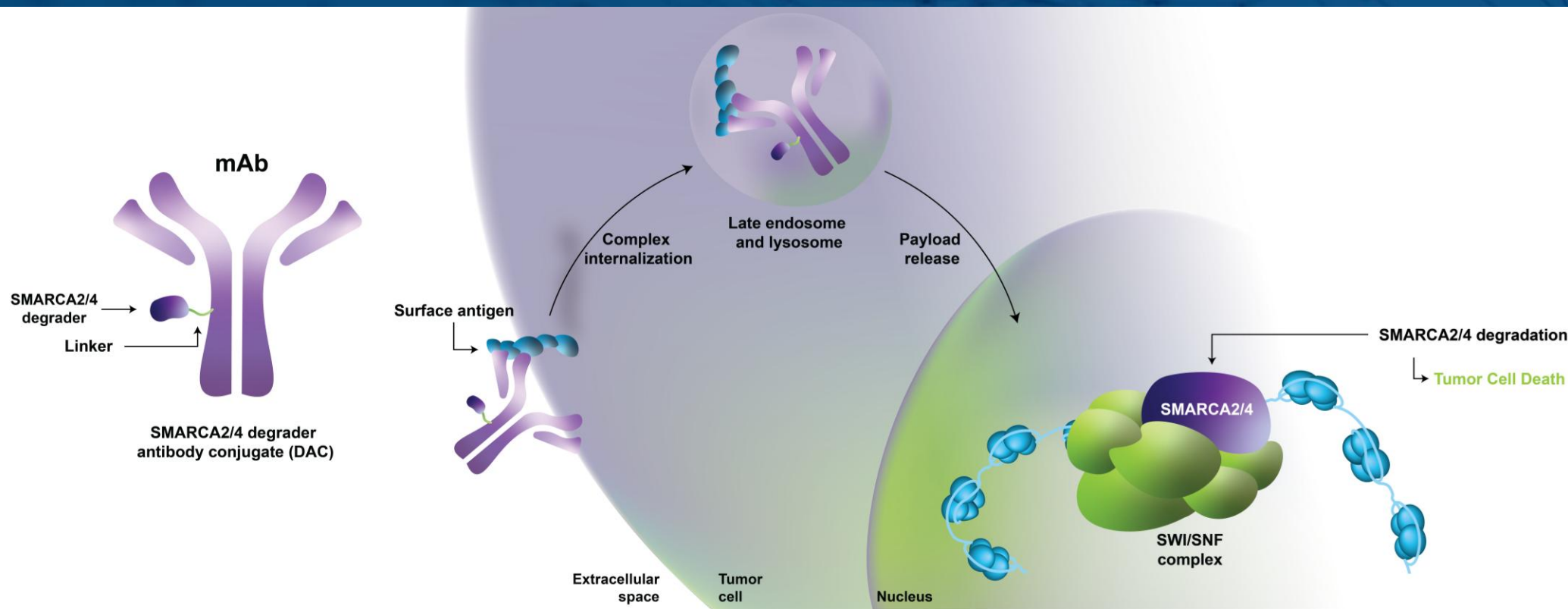
Model of Precision DAC
(DAR 4 example)



Property	Traditional ADC	Precision DAC
Potency	✓	✓
Antibody selectivity	✓	✓
Payload selectivity	✗	✓
PD Marker – payload	✗	✓
Non-genotoxic	✗	✓

- **Precision DACs enable improved selectivity in two ways**
 - ✓ **Antibodies** target tumor-specific cell surface antigens sparing healthy cells
 - ✓ **Targeted Protein Degraders** address critical proteins in validated biological pathways
- **Potential to deliver both improved efficacy and tolerability**

Leveraging SWI/SNF-dependence in transcription factor/enhancer-driver cancers



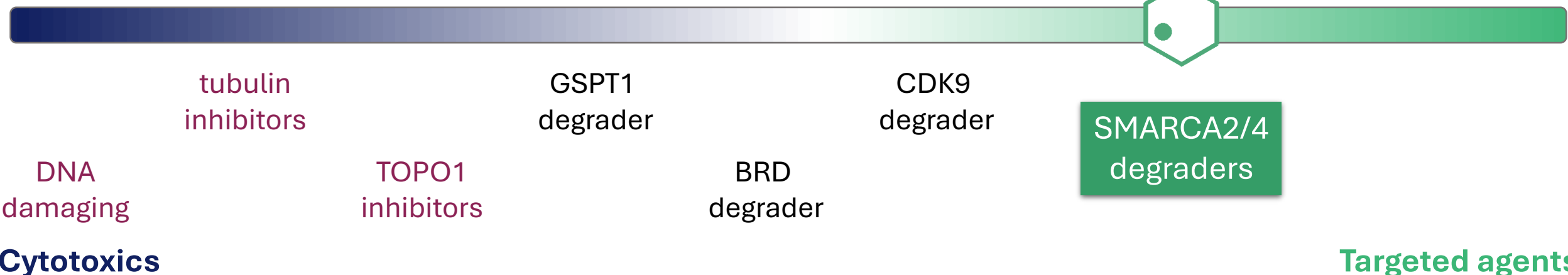
- Transcription factor (TF)/enhancer-driven cancers including prostate cancer are highly dependent on SWI/SNF complex and sensitive to SMARCA2/4 dual inhibitors and degraders
- SWI/SNF chromatin remodeling complex contains either SMARCA2 (BRM) or SMARCA4 (BRG1) as the ATPase catalytic subunit
- Dual inhibitors/degraders are not well tolerated as systemic agents due to dependence of normal cells on SMARCA2/4

Dialing in payload precision influences downstream ADC design and properties

General

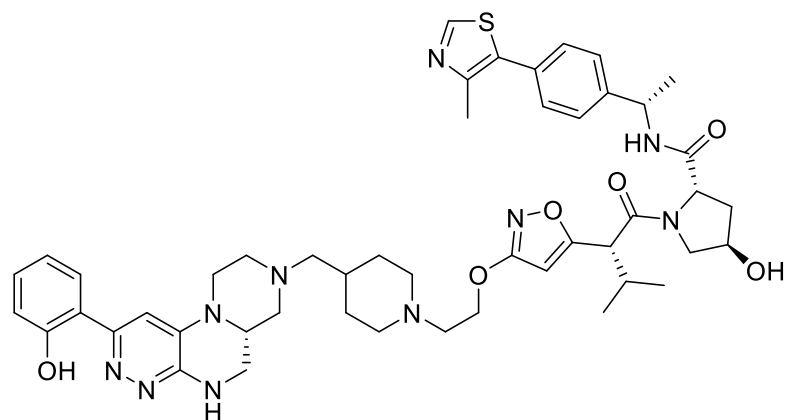


Precise

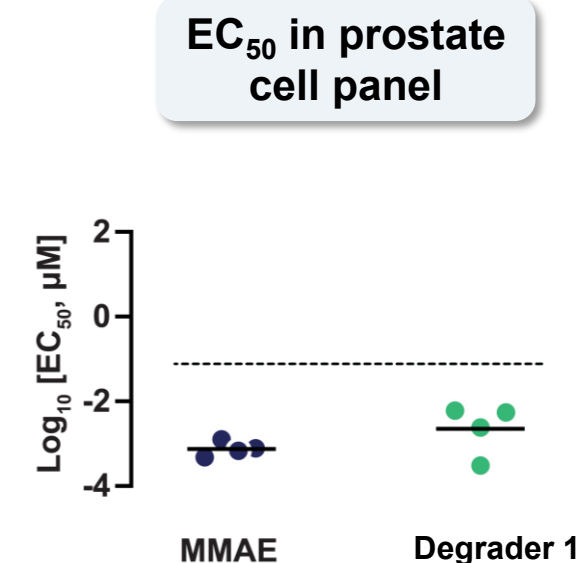
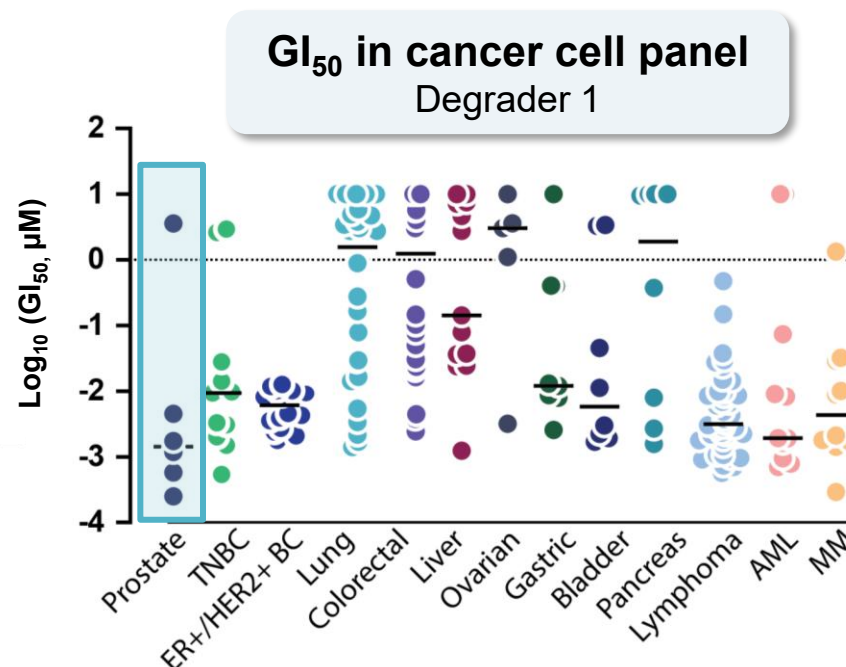


- Precision exists along spectrum from broad cytotoxics to highly indication-specific targeted agents
- Precision narrows application (generality) but offers potentially improved safety (therapeutic index)

Novel SMARCA2/4 dual degrader payload demonstrates potency and precision

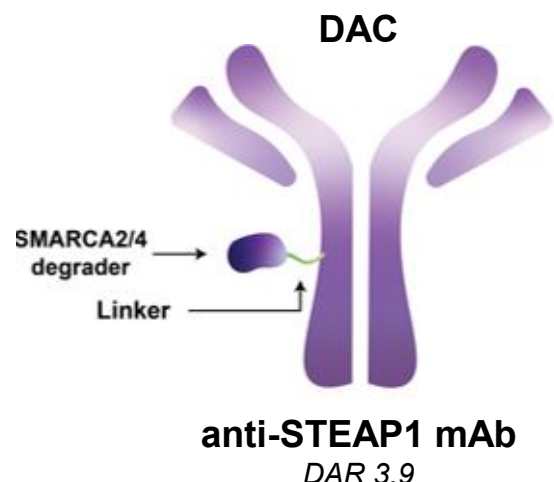


Degrader (pM)	1
E3 Ligase binder	VHL
HeLa HiBit SM2 DC ₅₀ (D _{max})	370 (97%)
HeLa HiBit SM4 DC ₅₀ (D _{max})	2,700 (96%)
Fold Selectivity, SM4/SM2	7x
LNCaP prolifer EC ₅₀ (E _{max})	210 (96%)



- Identified potent, dual SMARCA2/4 **degrader 1** with exceptional potency in prostate cancer cells
- Consistent with targeted approach, range of activity in other cancer types (even >1 μM in some cases)
- Potency comparable to MMAE in prostate cancer cells

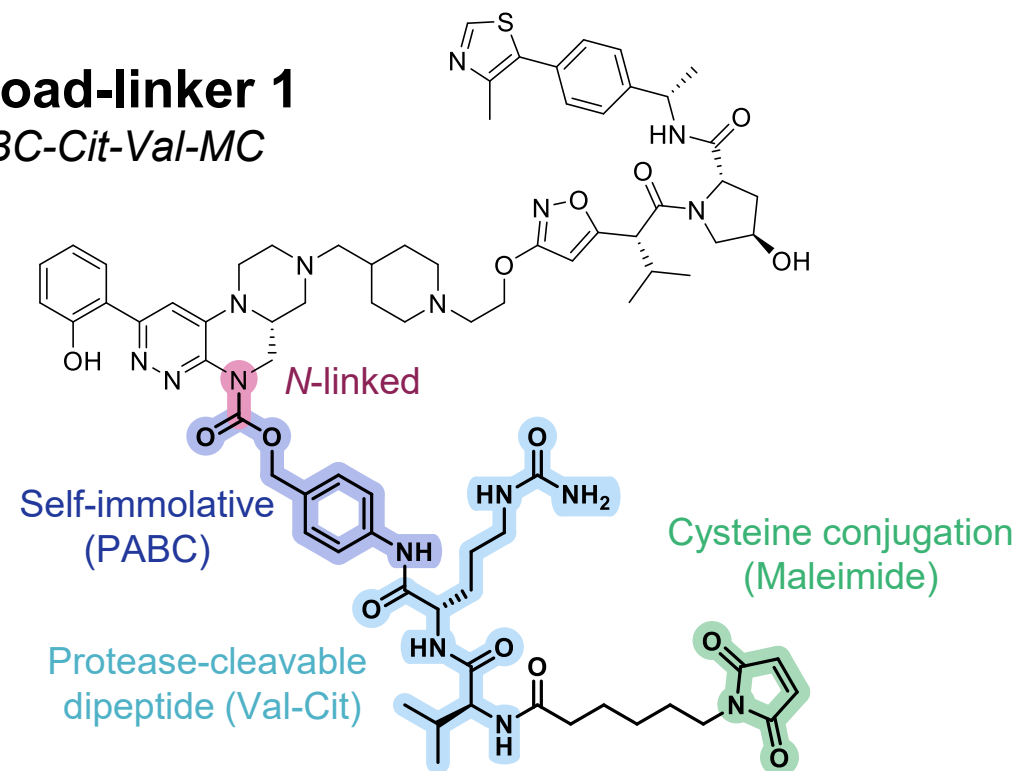
Exploring diverse architectures for SMARCA2/4 degrader payload-linkers



Cellular activity (ng/mL)	DAC 01
LNCaP SM2 DC ₅₀ (D _{max})	75 (88%)
LNCaP SM4 DC ₅₀ (D _{max})	2,700 (50%)
PC3 SM4 selectivity	1.5x
LNCaP CTG EC ₅₀ (E _{max})	460 (86%)

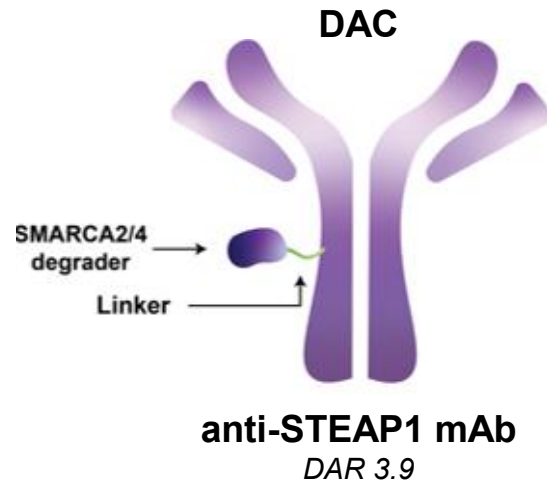
LNCaP STEAP1+. PC3 STEAP-.

Payload-linker 1 PABC-Cit-Val-MC



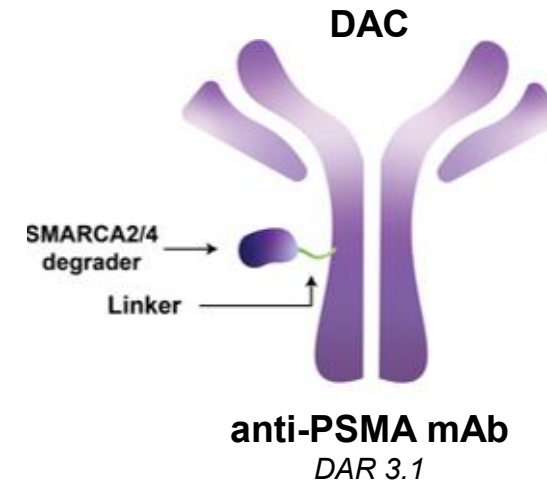
- **PL 01** conjugated via stochastic, native-cysteine conjugation to anti-STEAP1 antibody, vandortuzumab
- Acceptable SMARCA2 degradation and modest SMARCA4 degradation observed for **DAC 01**

Pairing the right antigen target for desired indication is essential



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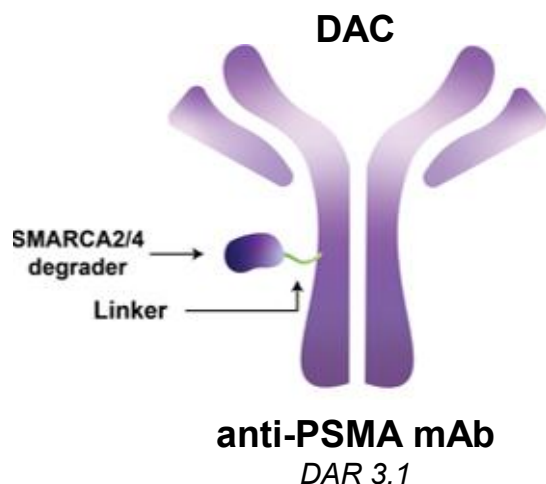
LNCaP STEAP1+; PSMA+. **PC3** STEAP-; PSMA-.



DAC 02
6.9 (87%)
26 (90%)
57x
57 (92%)

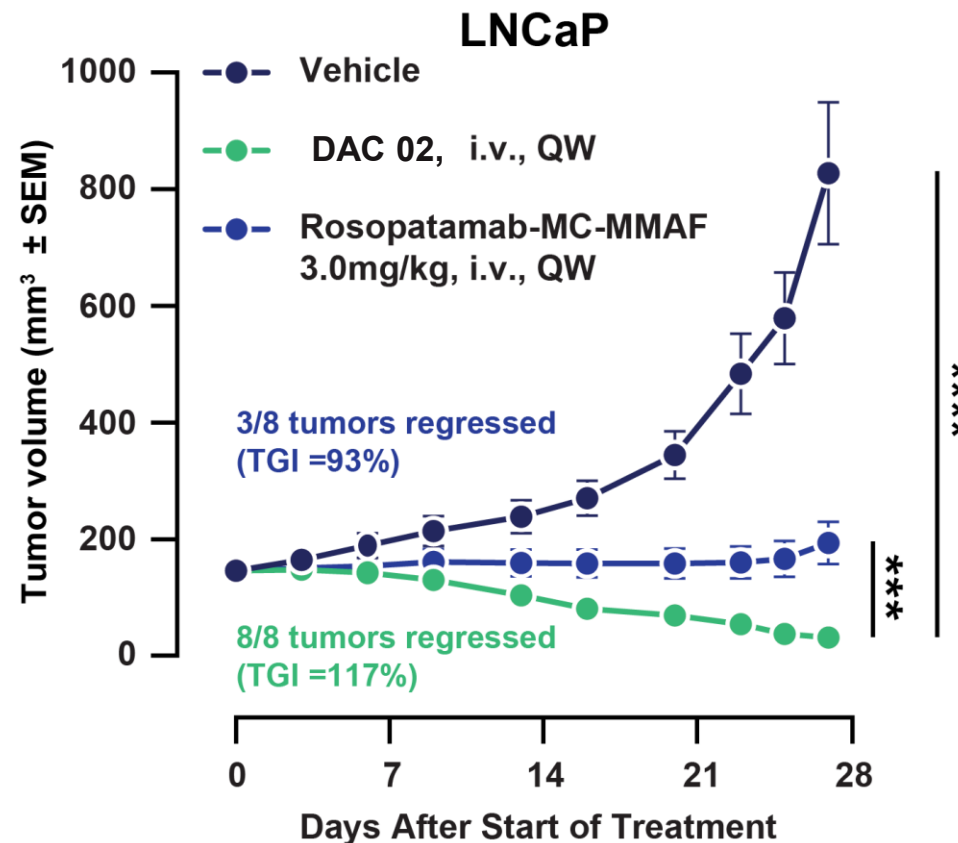
- SMARCA2/4 DACs demonstrate antigen-dependent activity in prostate cell lines
- Degradation **payload 1** shows greater cellular activity when conjugated to anti-PSMA antibody (rosopatamab)

PSMA SMARCA2/4 DAC induces regressions *in vivo*, exceeding MMAF benchmark



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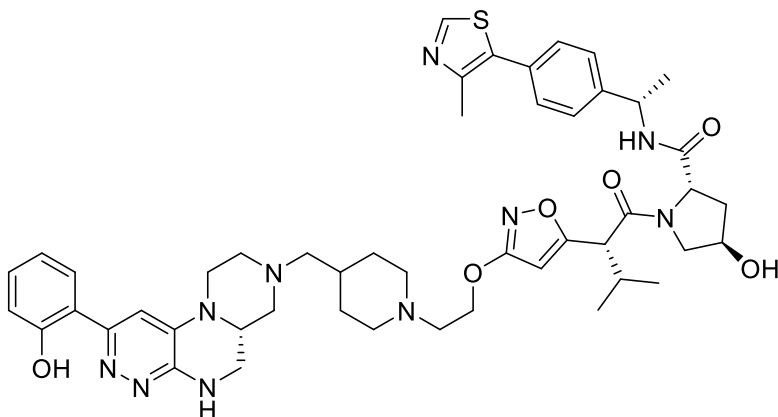
LNCaP PSMA+. PC3 PSMA-.



- Anti-proliferative activity of **DAC 02** comparable to MMAF benchmark ADCs
- In vivo, **DAC 02** induces regressions and exceeds efficacy of MMAF benchmark ADC

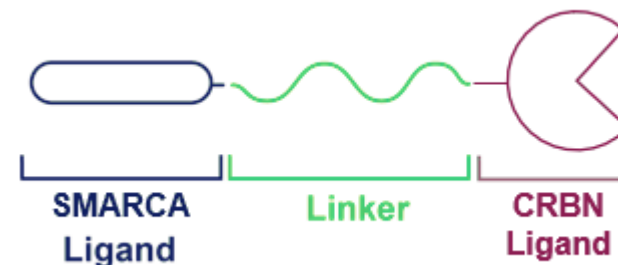
CRBN-based degrader payload more potent than VHL-based payload

VHL-based degrader payload



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E3 Ligase binder	VHL
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Fold Selectivity, SM4/SM2	7x
LNCaP prolifer EC ₅₀ (E _{max})	210 (96%)

CRBN-based degrader payload



2
CRBN
26 (93%)
35 (96%)
1x
49 (94%)

- CRBN-based **degrader 2** provided additional potency over VHL-based **degrader 1**
- Difference most notable in SMARCA4 with 77-fold increase in degradation potency

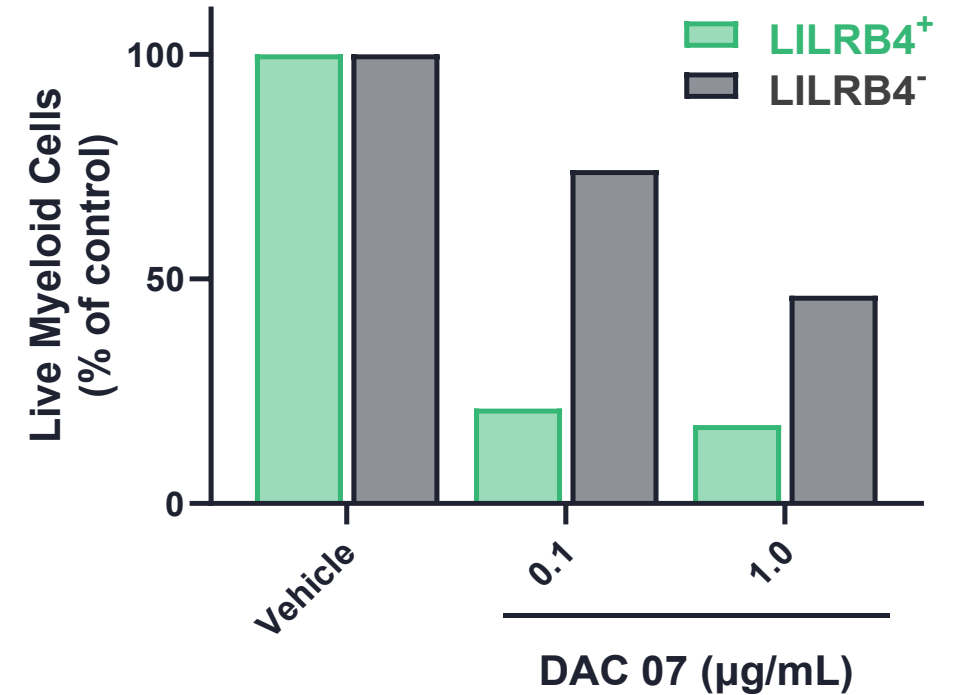
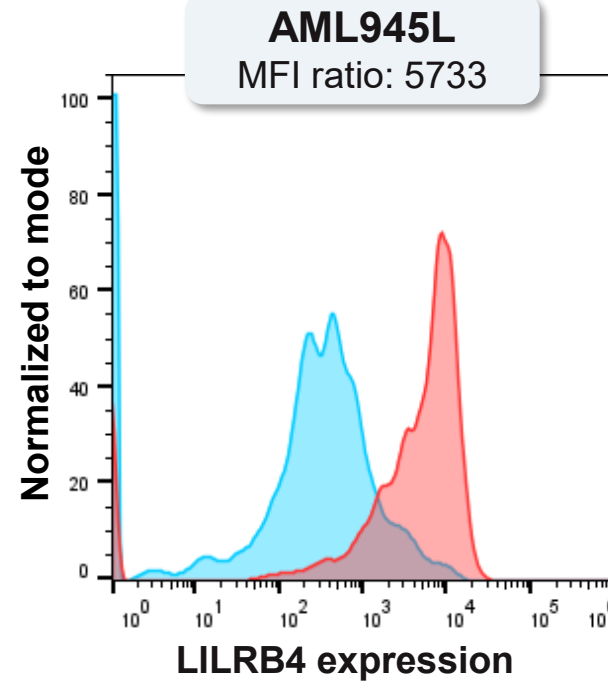
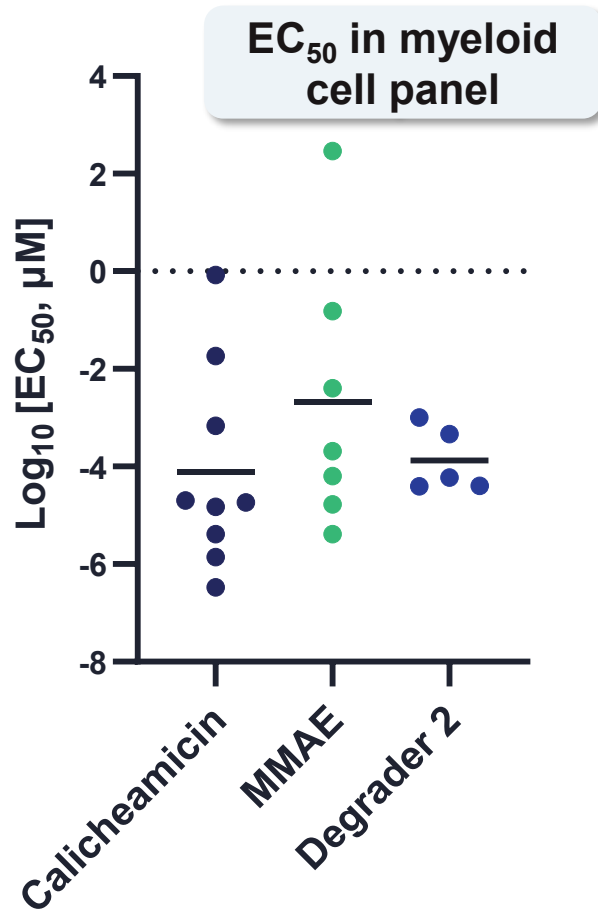
Potent CRBN-based payload expands DAC activity

DAC descriptors	DAC 03	DAC 04	DAC 05	DAC 06	DAC 07
Antigen	STEAP1	CEACAM5	cMET	Claudin18.2	LILRB4
Antibody	vandortuzumab	tusamitamab	telisotuzumab	osemitamab	anti-LILRB4
DAR	3.7	6.4	4.1	4.3	3.9
Cellular activity (ng/mL)					
Ag ⁺ SM2 DC ₅₀ (D _{max})	36 (89%)	58 (77%)	23 (80%)	15 (99%)	<100 (>99%)
Ag ⁺ SM4 DC ₅₀ (D _{max})	53 (80%)	44 (74%)	37 (73%)	--	<100 (>99%)
Ag ⁻ SM4 selectivity	>160x	230x	400x	>330x ^a	>100x
Ag ⁺ prolifer EC ₅₀ (E _{max})	210 (82%)	>10,000	>10,000	>1,000	92 (52%)

Ag⁺: THP-1 LILRB4⁺; TF-1 CALR⁺; MNK4 CEACAM5⁺; H2291 cMET⁺; SNU601 Claudin18.2⁺; LNCaP STEAP1⁺. Ag⁻: KG-1 LILRB4⁻; TF-1 CALR⁻; LNCaP CEACAM5⁻; LNCaP cMET⁻; LNCaP Claudin18.2⁻; PC3 STEAP1⁻. ^aSelectivity measure from SMARCA2.

- More potent CRBN-based **degrader 2** enables DACs across multiple antigens and indications
- Potent, antigen dependent degradation activity was observed with all DACs

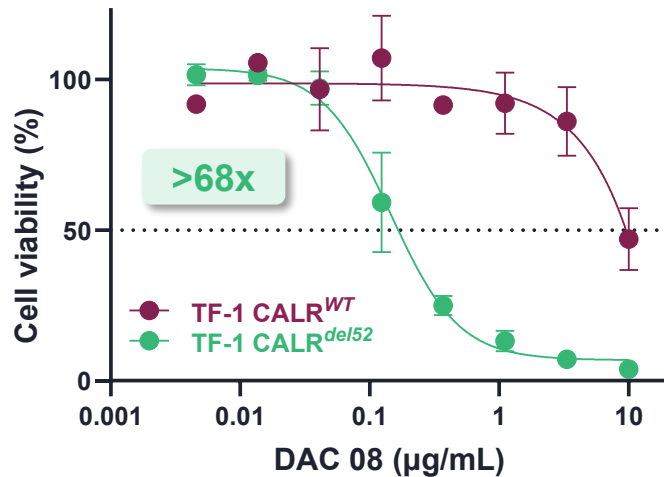
Case study #1: DAC 07 selectively targets LILRB⁺ myeloid cells



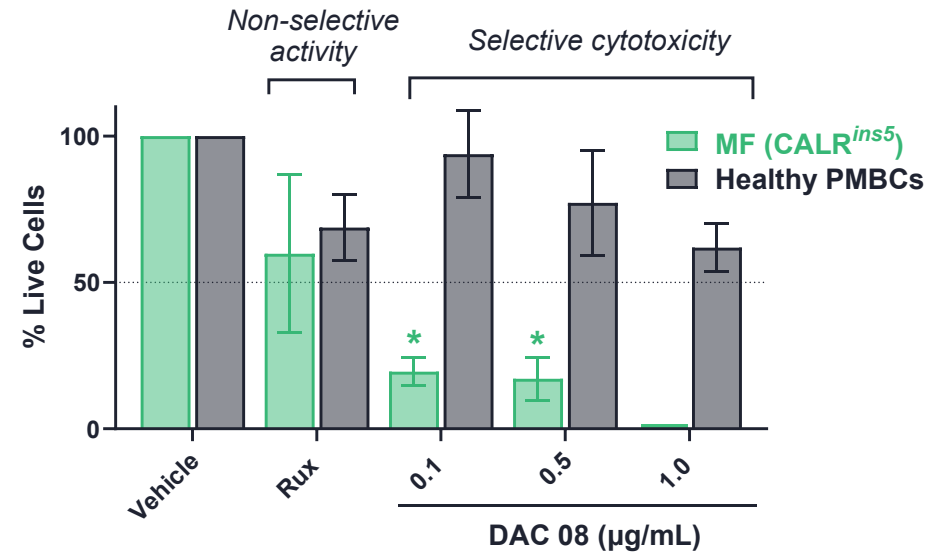
- **Degradar 2** maintains activity comparable to MMAE and calicheamicin in myeloid cancer cells
- In PBMCs isolated from a donor with AML (M4-staging; expressing LILRB4), **DAC 07** demonstrated selective antiproliferation activity in LILRB⁺ cells

Case study #2: DAC 08 targets and eliminates diseased CALR-mutant cells

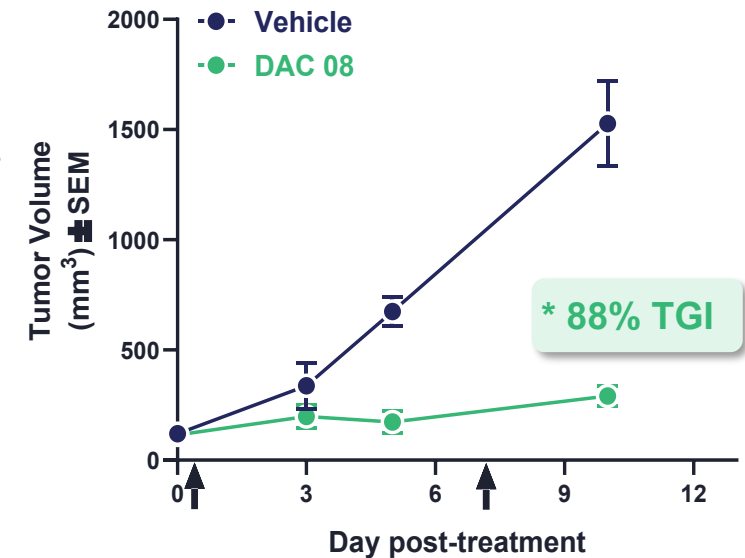
Antigen-dependent cytotoxicity



Ex vivo efficacy *m*CALR PMBCs



Robust TGI TF-1 CALR^{del52} CDX

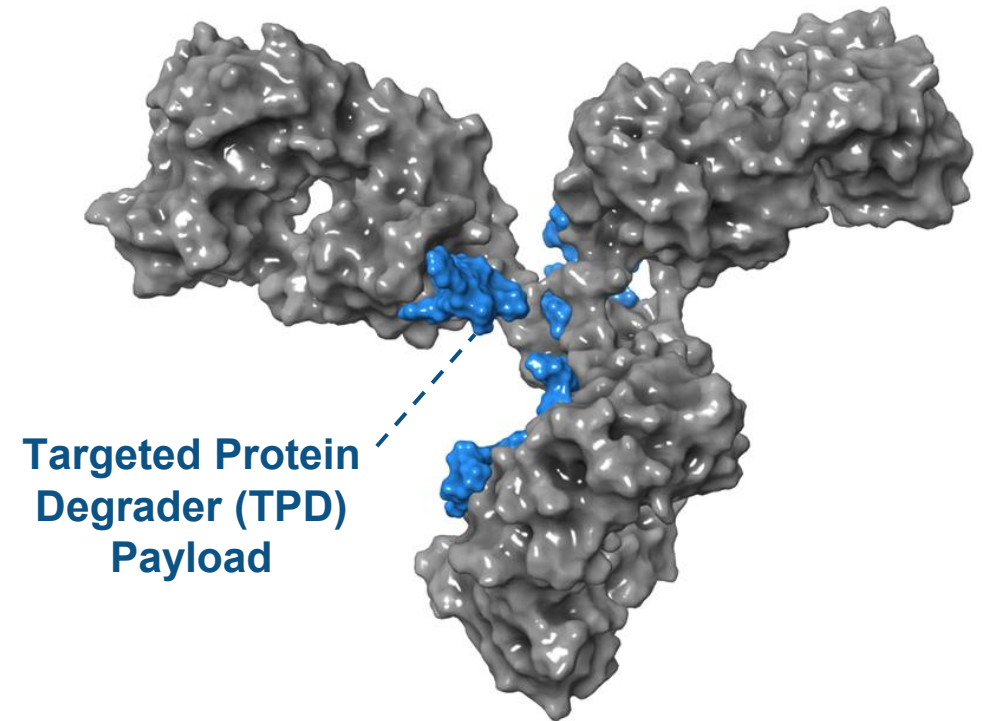


- **DAC 08** demonstrates antiproliferative activity *in vitro* and in peripheral blood mononuclear cells (PBMCs) isolated from a donor with myelofibrosis (expressing CALR^{ins5})
- Weekly i.v. administration of **DAC 08** was well tolerated and demonstrated robust tumor growth inhibition in TF-1 (CALR^{del52}) tumors

Precision degrader antibody conjugates, a new frontier in precision oncology

- SMARCA2/4 dual degraders demonstrate a new opportunity in ADC payloads
- Identifying DACs requires criteria that embrace the modality's complexities
- Degradar payloads must be highly potent to achieve ADC activity
- Pairing the right antigen target for the desired indication is essential

Model of Precision DAC
(DAR 4 example)



Acknowledging the Prelude Team

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