

Precision degrader antibody conjugates (pDACs): A novel platform for dual SMARCA2/4 degradation across diverse tumor antigens

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Precision degrader antibody conjugates (pDACs)

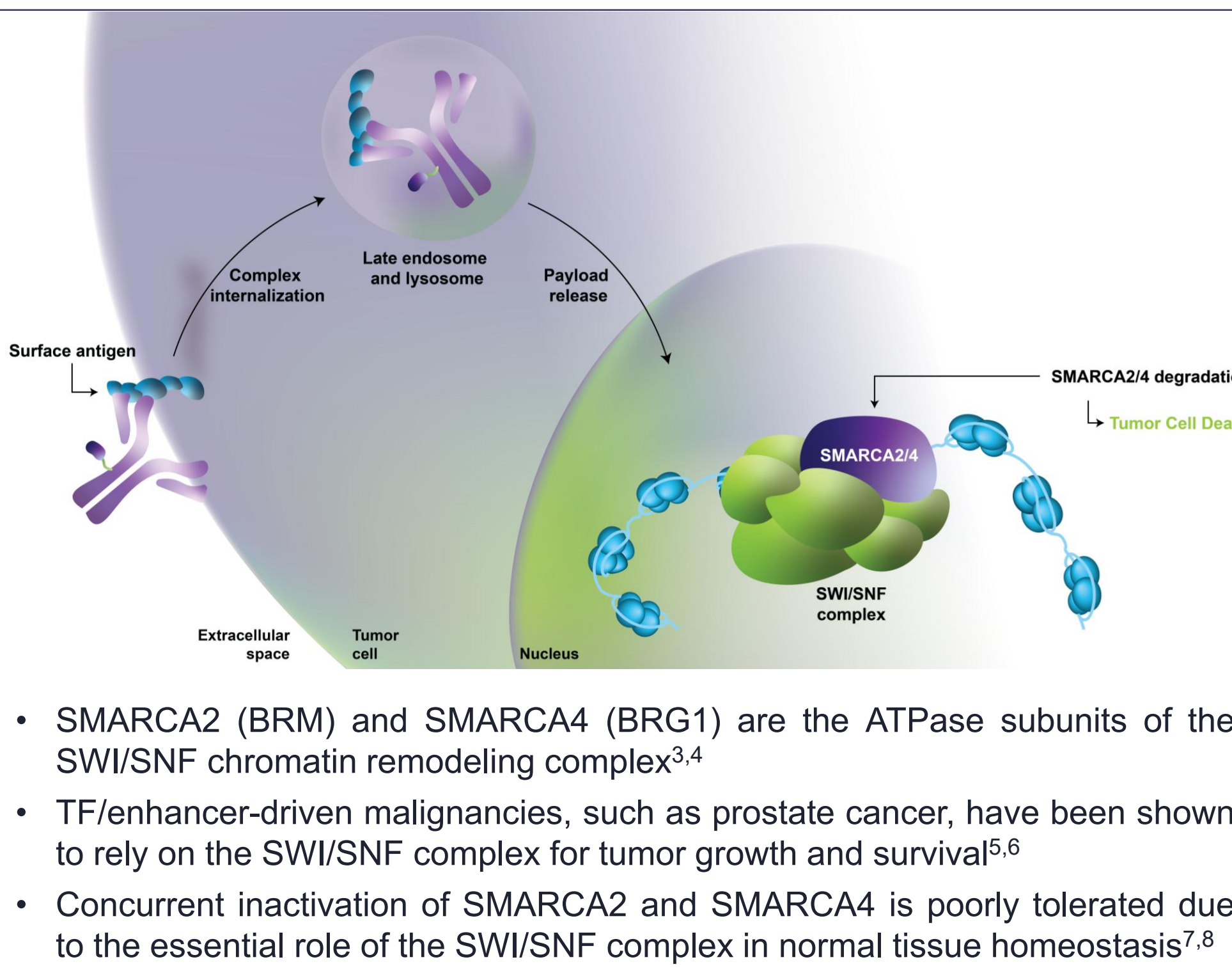
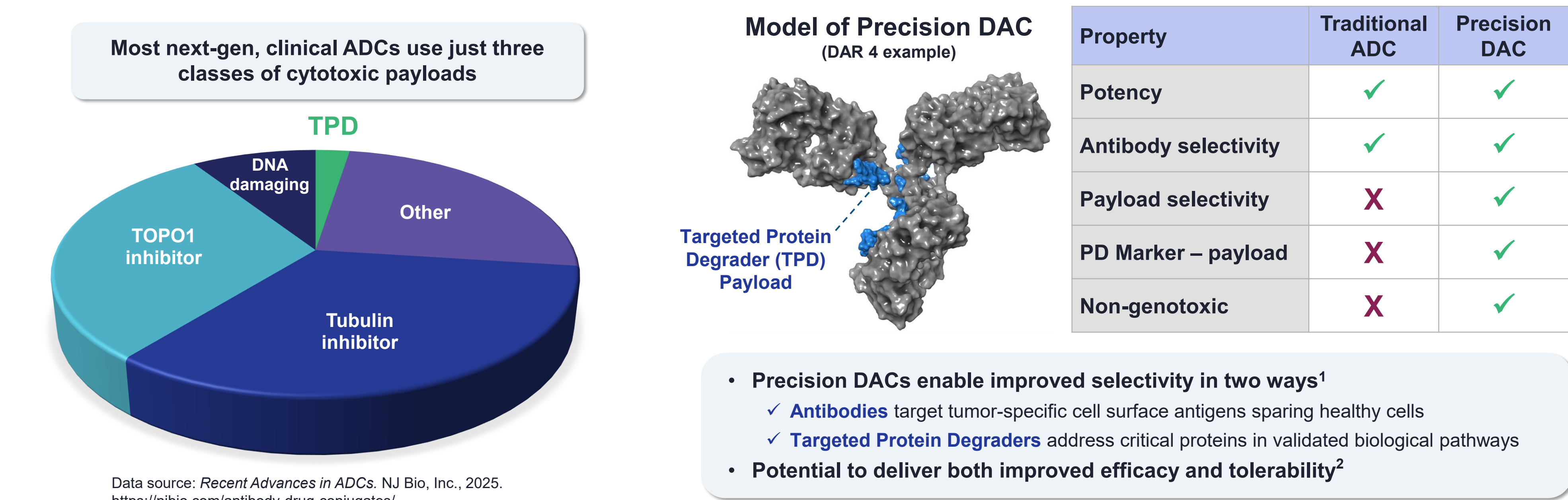


Figure 1. Identification of SMARCA2/4 dual degraders payloads

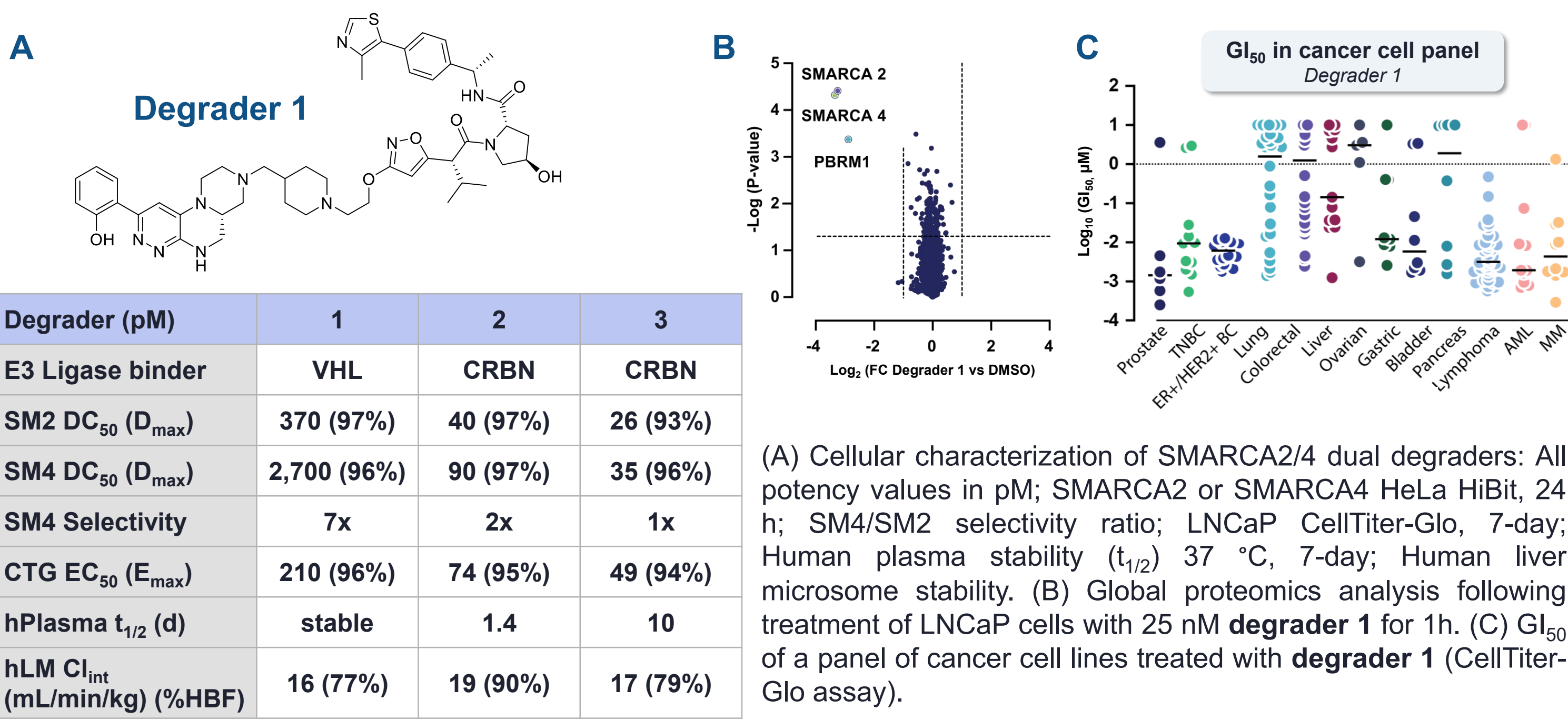


Figure 2. Exploring diverse architectures for SMARCA2/4 degrader payload-linkers

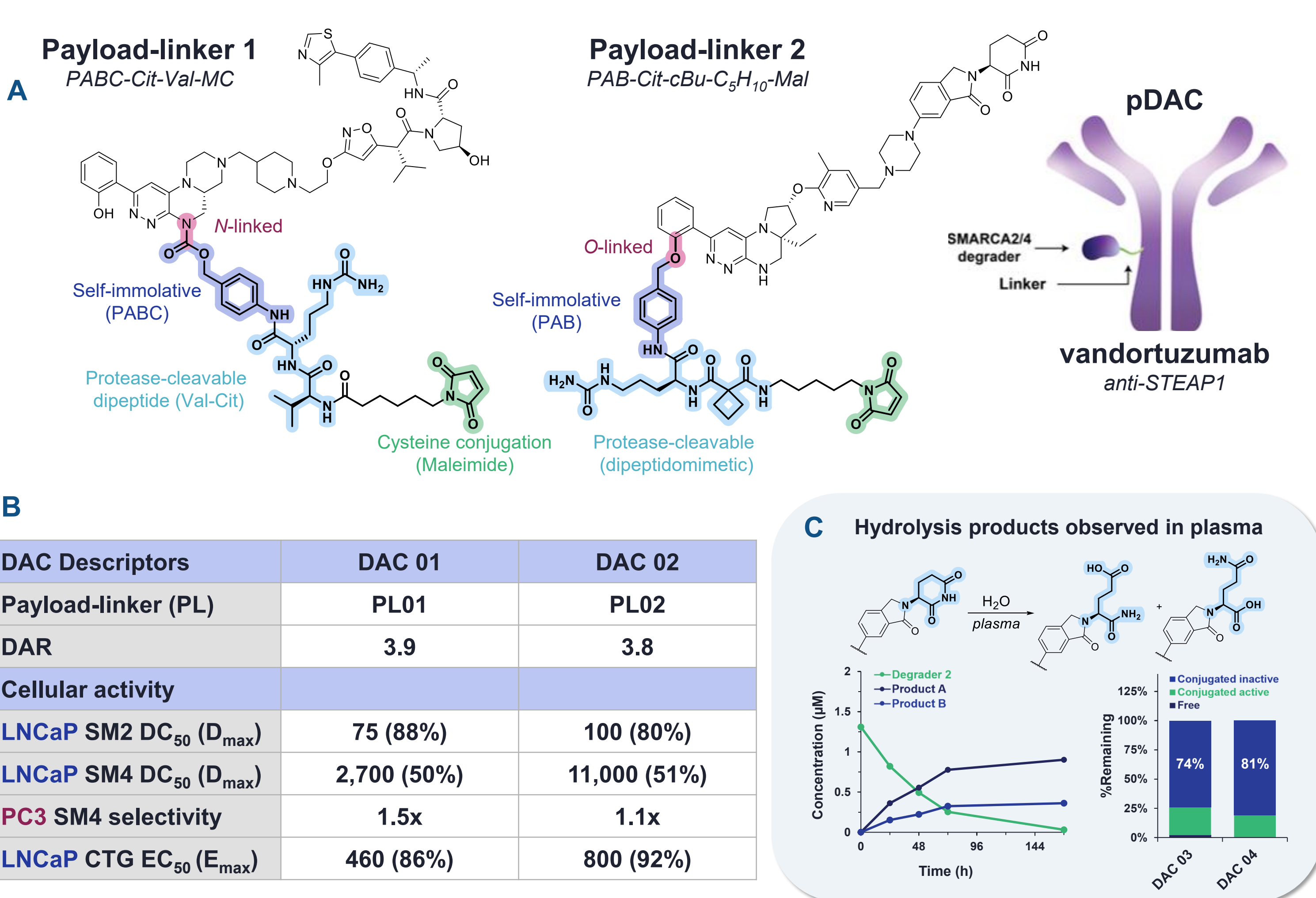


Figure 3. Stable CRBN-based payload expands pDAC activity

pDAC descriptors	DAC 05	DAC 06	DAC 07	DAC 08	DAC 09
Antigen	LILRB4	CEACAM5	cMET	Claudin18.2	STEAP1
Antibody	anti-LILRB4	tusamitamab	telisotuzumab	osemitamab	vandortuzumab
Payload	Degrader 3	Degrader 3	Degrader 3	Degrader 3	Degrader 3
DAR	3.9	6.4	4.1	4.3	3.7
Cellular activity (ng/mL)					
Ag ⁺ SM2 DC ₅₀ (D _{max})	<100 (>99%)	58 (77%)	23 (80%)	15 (99%)	36 (89%)
Ag ⁺ SM4 DC ₅₀ (D _{max})	<100 (>99%)	44 (74%)	37 (73%)	--	53 (80%)
Ag ⁺ SM4 selectivity	>100x	230x	400x	>330x ^a	>160x
Ag ⁺ prolifer EC ₅₀ (E _{max})	92 (52%)	>10000	>10000	>1,000	210 (82%)

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⁻.

Figure 4. DAC 05 selectively targets LILRB4⁺ myeloid cells

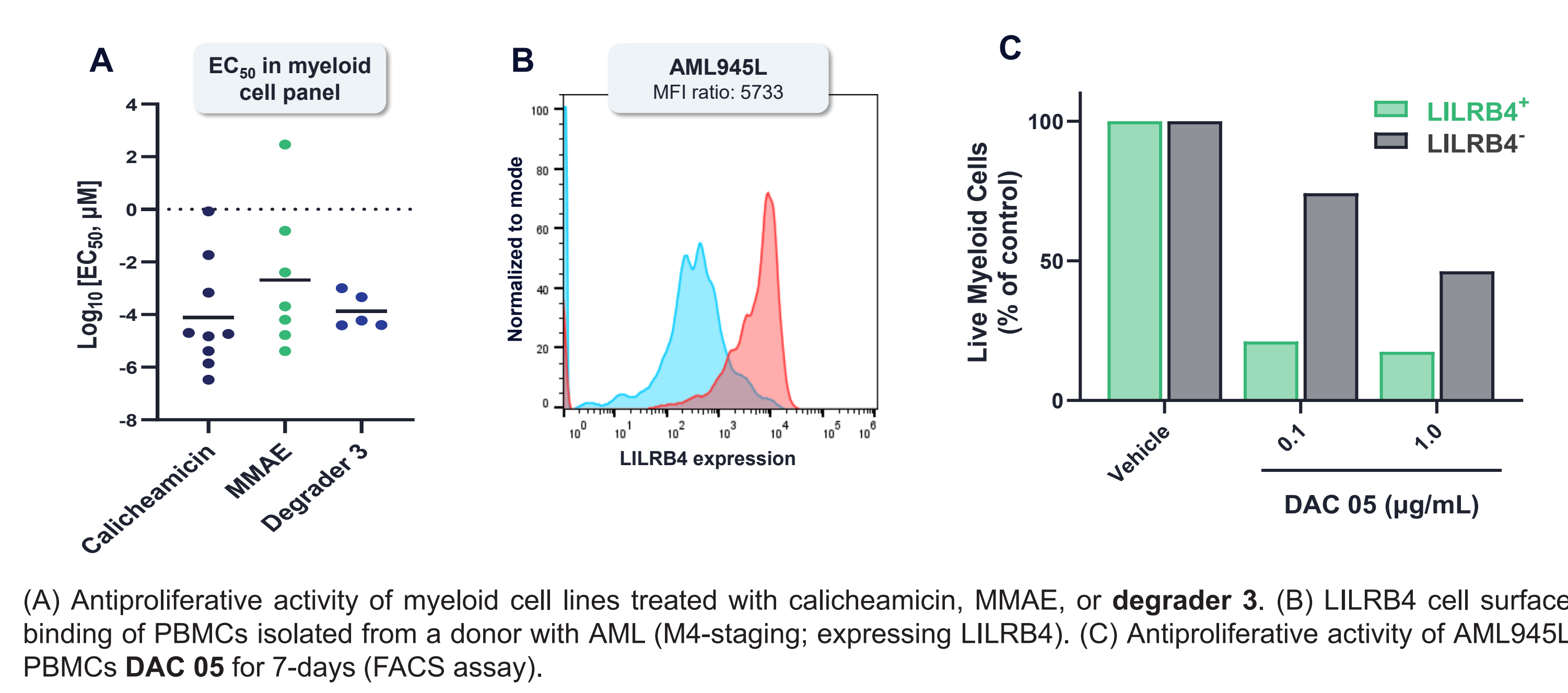


Figure 5. DAC 10 targets and eliminates diseased CALR-mutant cells

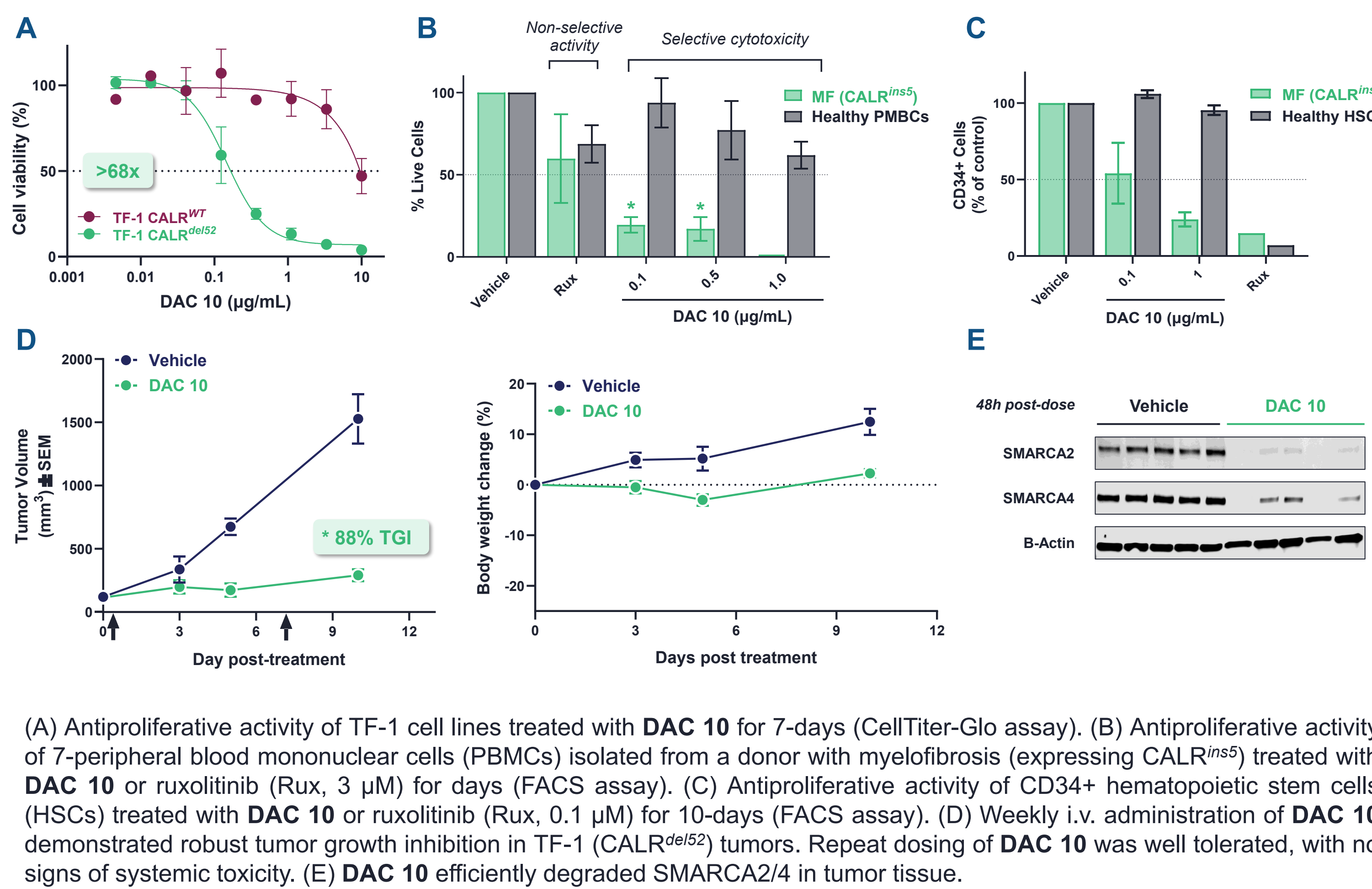
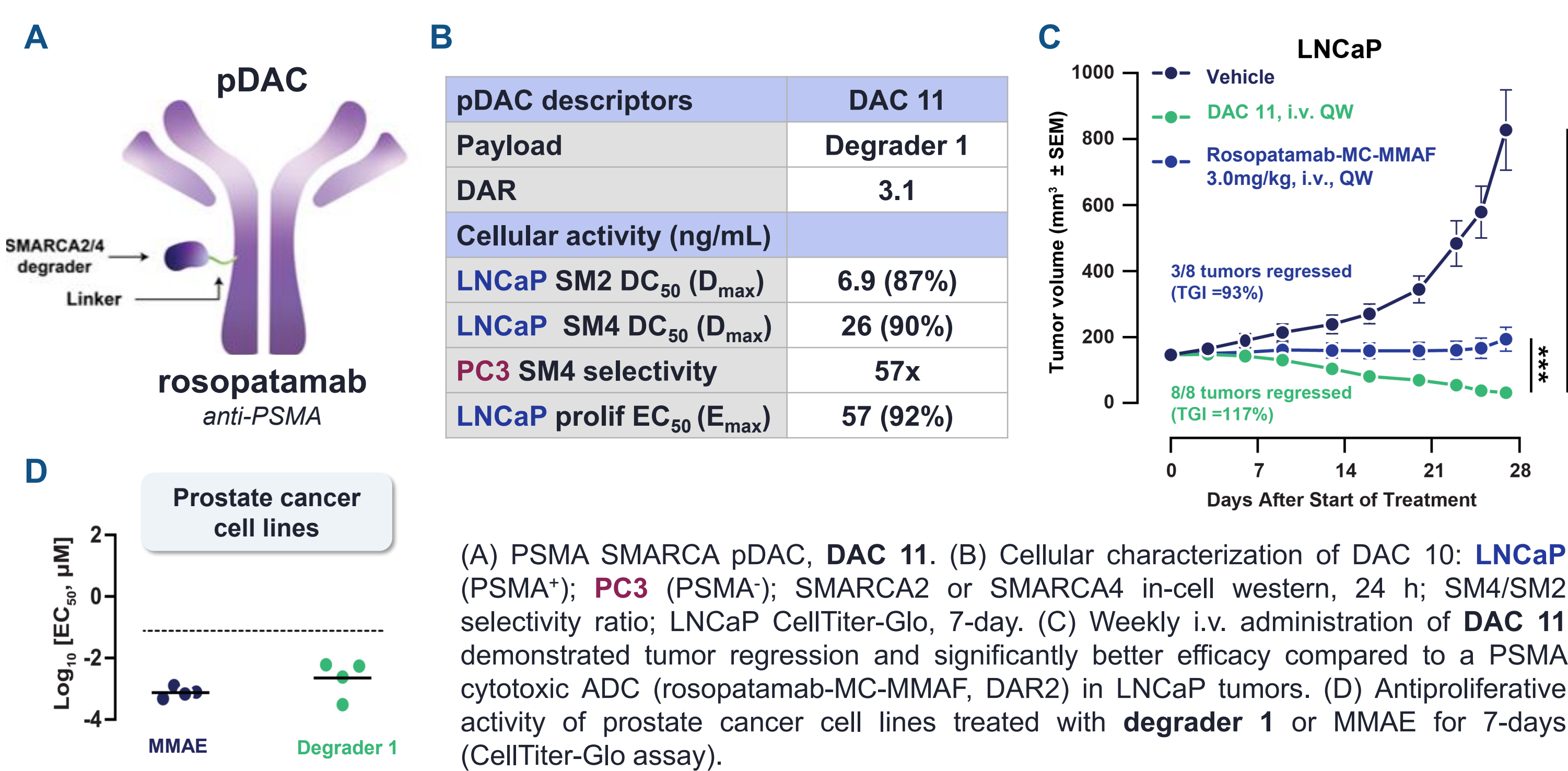


Figure 6. DAC 11 induces regressions *in vivo*, exceeding MMAF benchmark



Conclusions

- Successful pDAC design relies on the coordination of highly potent, stable degrader payloads with thoughtful antigen selection to address the unique demands of the modality
- SMARCA2/4 dual degrader payloads demonstrated robust antiproliferative activity across multiple cell lines, highlighting their potential as next-generation ADC payloads
- SMARCA pDACs targeting diverse tumor antigens demonstrated potent antigen-dependent activity *in vitro* and selective antitumor activity *in vivo*, supporting their potential as next-generation ADCs

Disclosures

All authors are or were employees of Prelude Therapeutics Incorporated at the time of research and may own equity in the Company.

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