

# Preclinical Characterization of PRT7732: A Highly Potent, Selective, and Orally Bioavailable Targeted Protein Degradator of SMARCA2

Artem Shvartsbart\*, Koichi Ito\*, Joseph Rager, Liang Lu, Michael Hulse, Anjana Agarwal, Komali Vykuntam, Jessica Burtell, Min Wang, Justin Kurian, Miles Cowart, Joy Cote, Nick Stahl, Monisha Sivakumar, Anthony Reichelderfer, Jack Carter, Alex Grego, Carly Bachner, Andrew Moore, Neha Bhagwat, Ross Kuskovsky, Shanthy Ganesan, Stefan Ruepp, Tom Emm, Philip Pitis, Corey Basch, Klare Bersch, Yongchun Pan, Song Mei, Raul Leal, John Rose, Danielle Roth, Chaoyi Xu, Karl Blom, Ganfeng Cao, Kris Vaddi, Sang Hyun Lee, Sandy Geeganage, Andrew Combs, Peggy Scherle

\*These authors contributed equally to the work. Prelude Therapeutics Incorporated, Wilmington, DE; contact: [ashvartsbart@preludetx.com](mailto:ashvartsbart@preludetx.com); [kito@preludetx.com](mailto:kito@preludetx.com)

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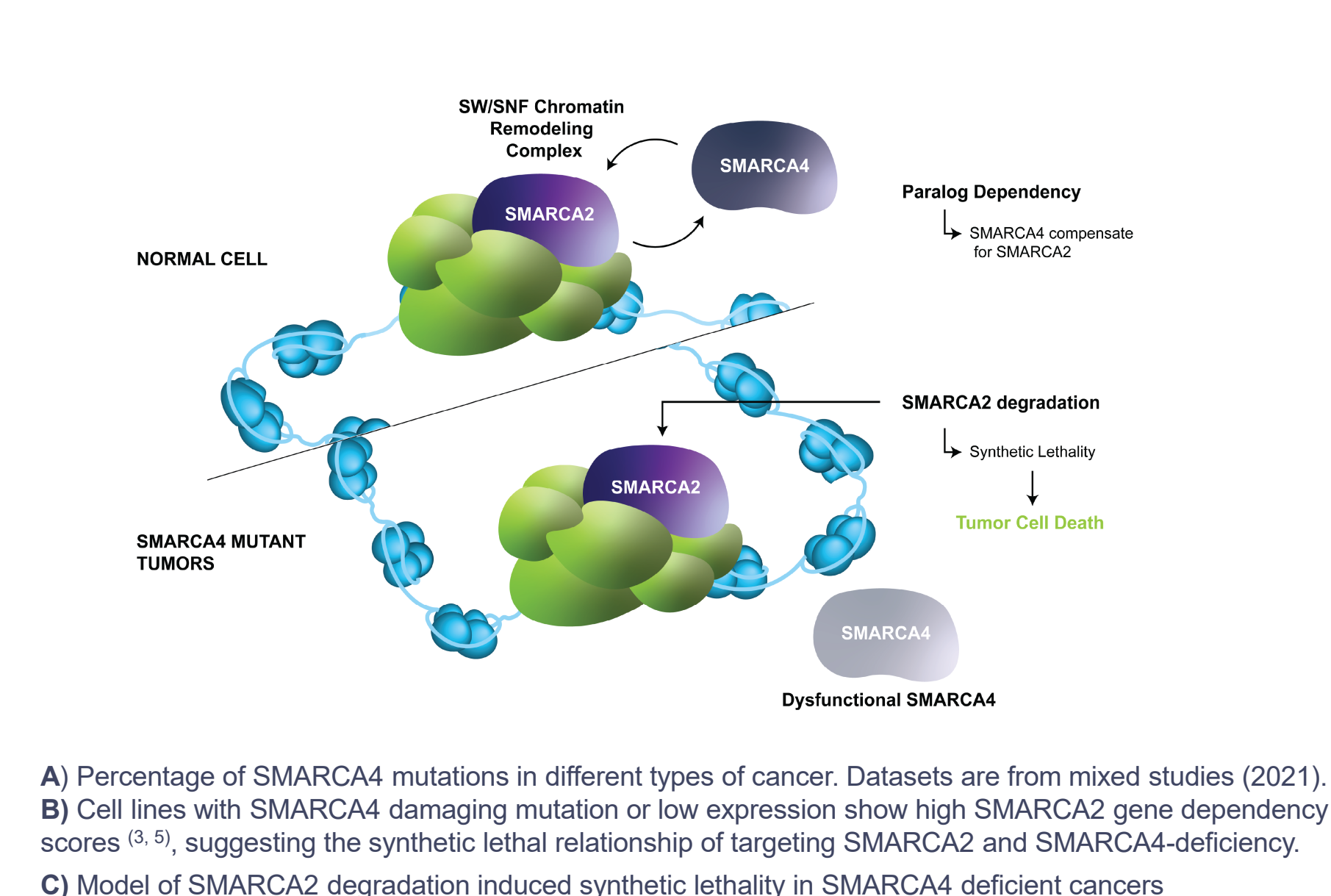
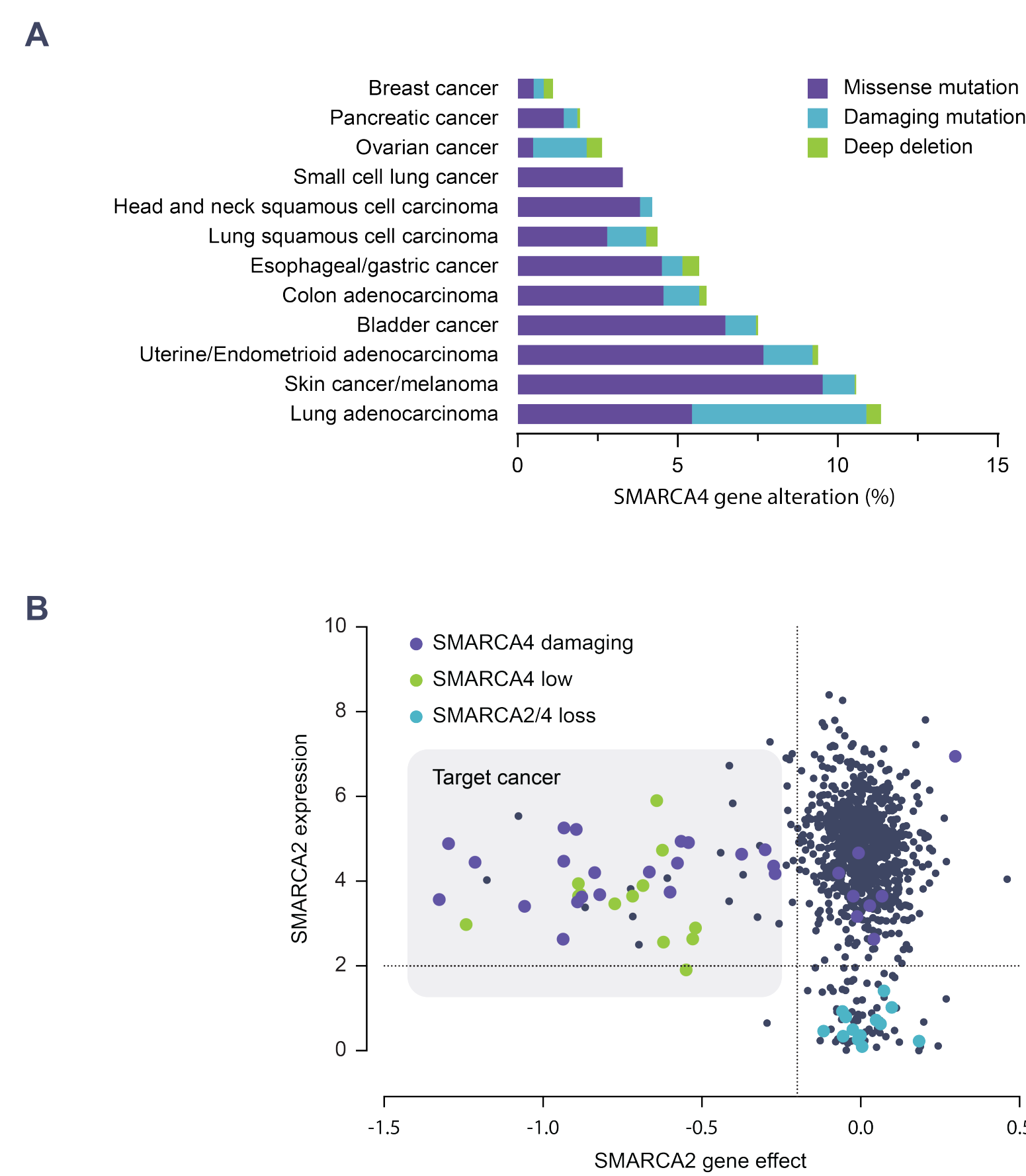


## Background

- SMARCA2 (BRM) and SMARCA4 (BRG1) are the two mutually exclusive catalytic core subunits of SWI/SNF complexes that play an important role in controlling gene expression by remodeling chromatin (1).
- SMARCA4 has been shown to be mutated in multiple cancers, including up to 10-12% of non-small cell lung cancer (2).
- The SMARCA4-deficient cancer cells are highly dependent on the paralog gene SMARCA2 for their survival (3,4,5).
- We have identified PRT7732: A highly potent, selective, and orally bioavailable targeted protein degrader of SMARCA2 that induces synthetic lethality in SMARCA4-deficient cancers.

## Introduction

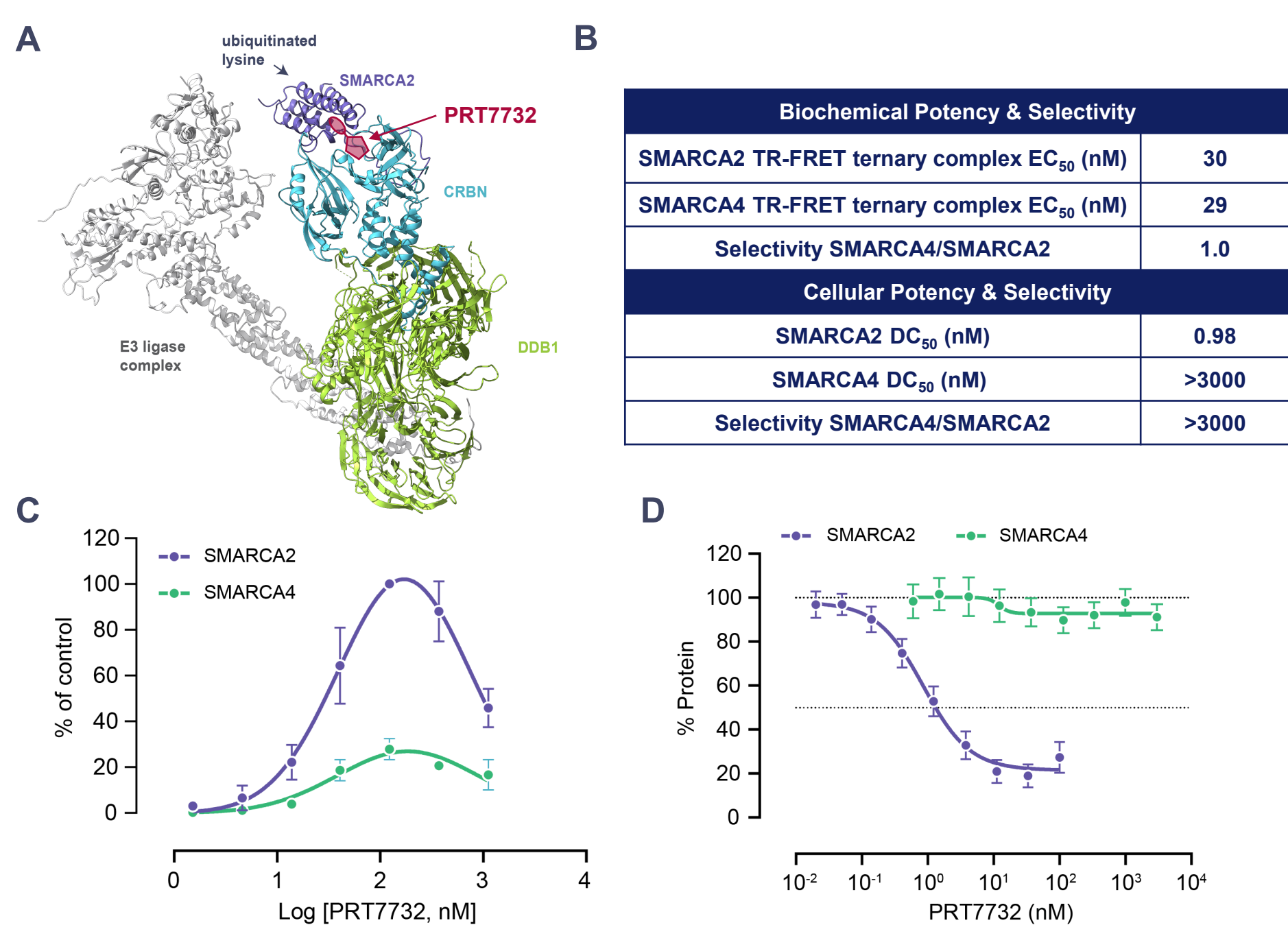
### Synthetic lethal relationship between targeting SMARCA2 and SMARCA4-deficiency in cancer



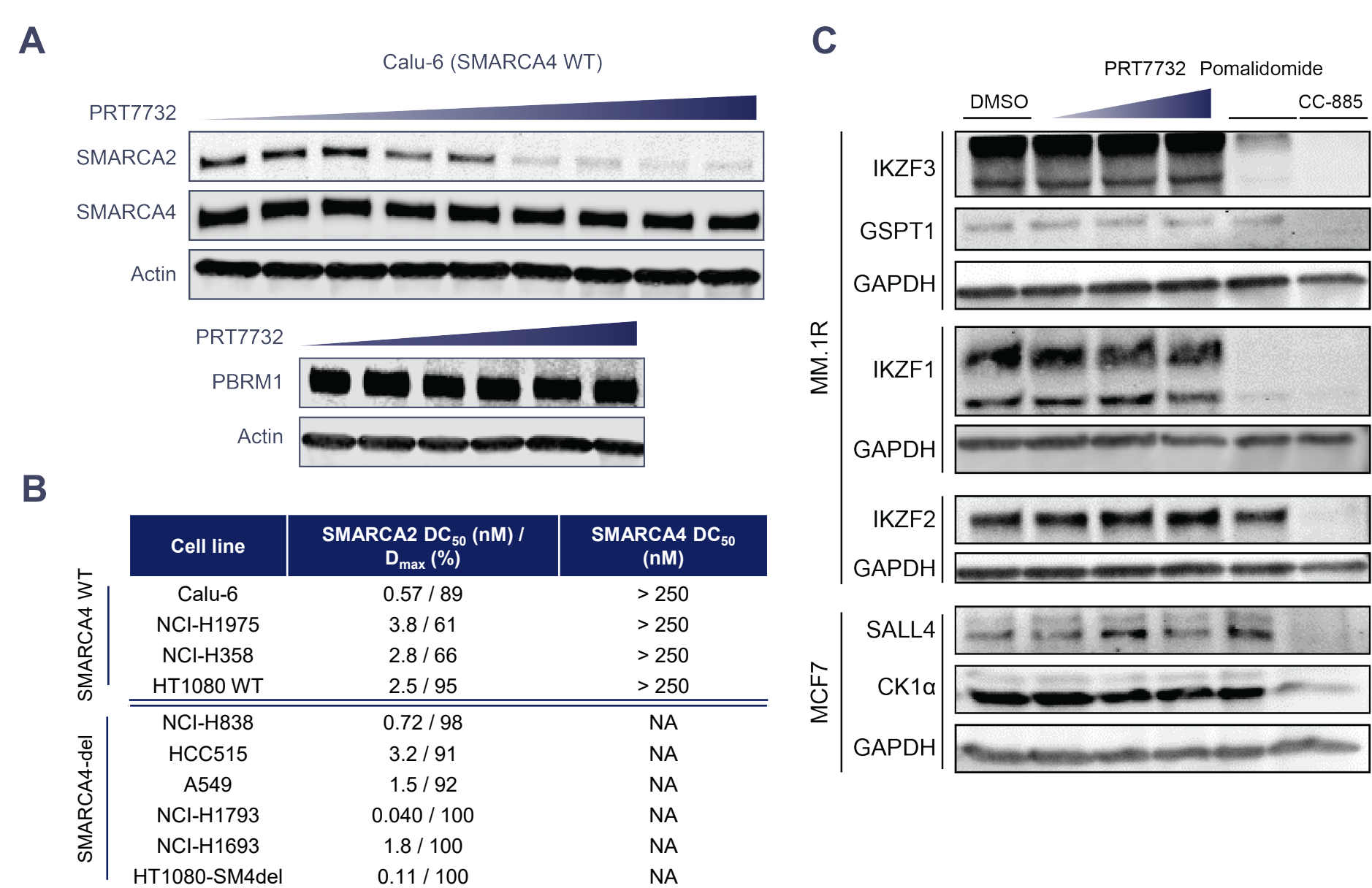
## Key Findings

- Identified potent, selective and orally bioavailable SMARCA2 degrader PRT7732
- PRT7732 exhibits >3000-fold selectivity for SMARCA2 over SMARCA4 in cell-based assays, with DC<sub>50</sub> values in cancer cell lines in the low nanomolar range
- PRT7732 shows favorable pharmacokinetic properties and safety profiles
- Oral administration of PRT7732 demonstrates robust efficacy in human SMARCA4-deficient lung cancer models in mice
- Oral administration of PRT7732 resulted in near-total degradation of SMARCA2 protein levels with complete selectivity over SMARCA4 protein *in vivo*

### Figure 2. Identification of PRT7732, a potent and selective orally bioavailable SMARCA2 degrader candidate



### Figure 3. PRT7732 shows excellent degradation potency and selectivity for SMARCA2 in human cancer cell lines

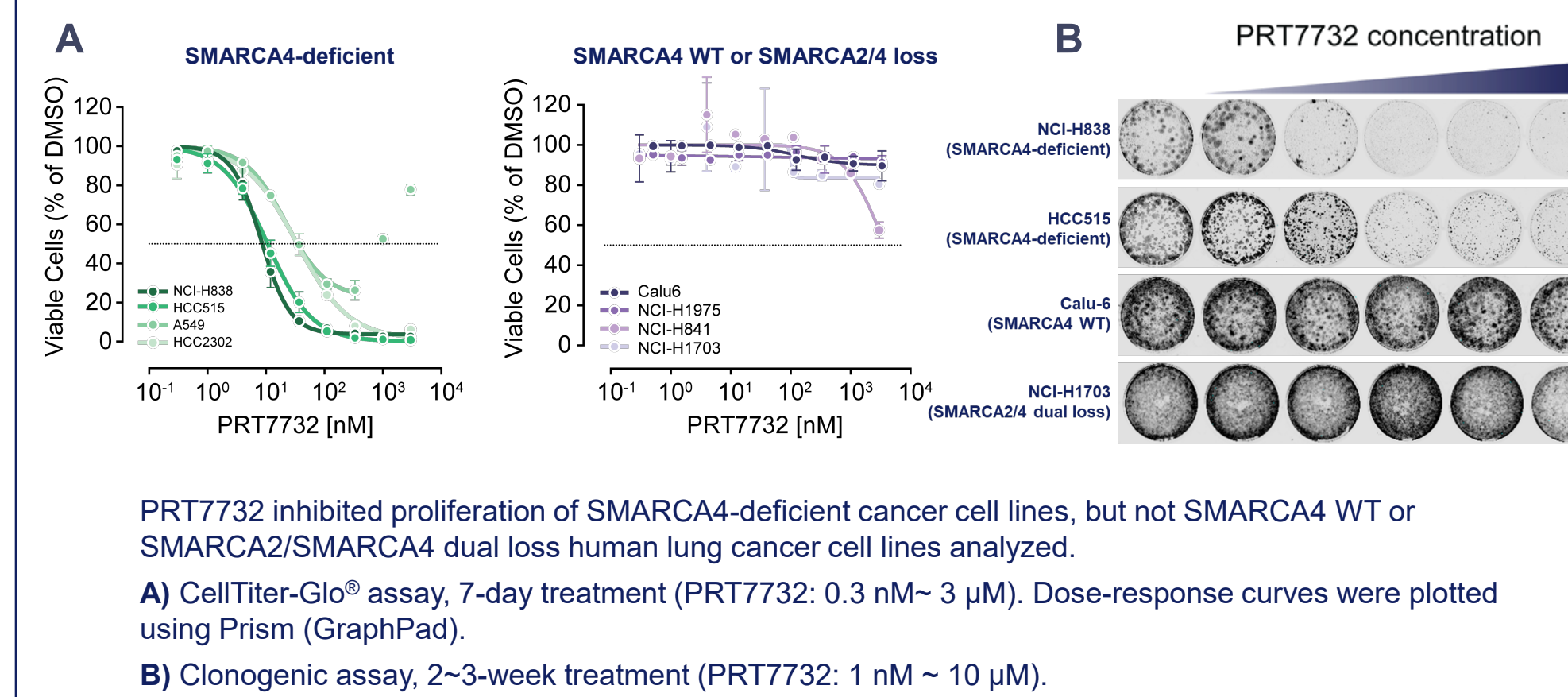


**A**) Western blot for SMARCA2, SMARCA4 and PBRM1 was performed using Calu-6 human lung cancer cell line. The cells were treated with PRT7732 (3.2 pM ~ 250 nM) for 24h.

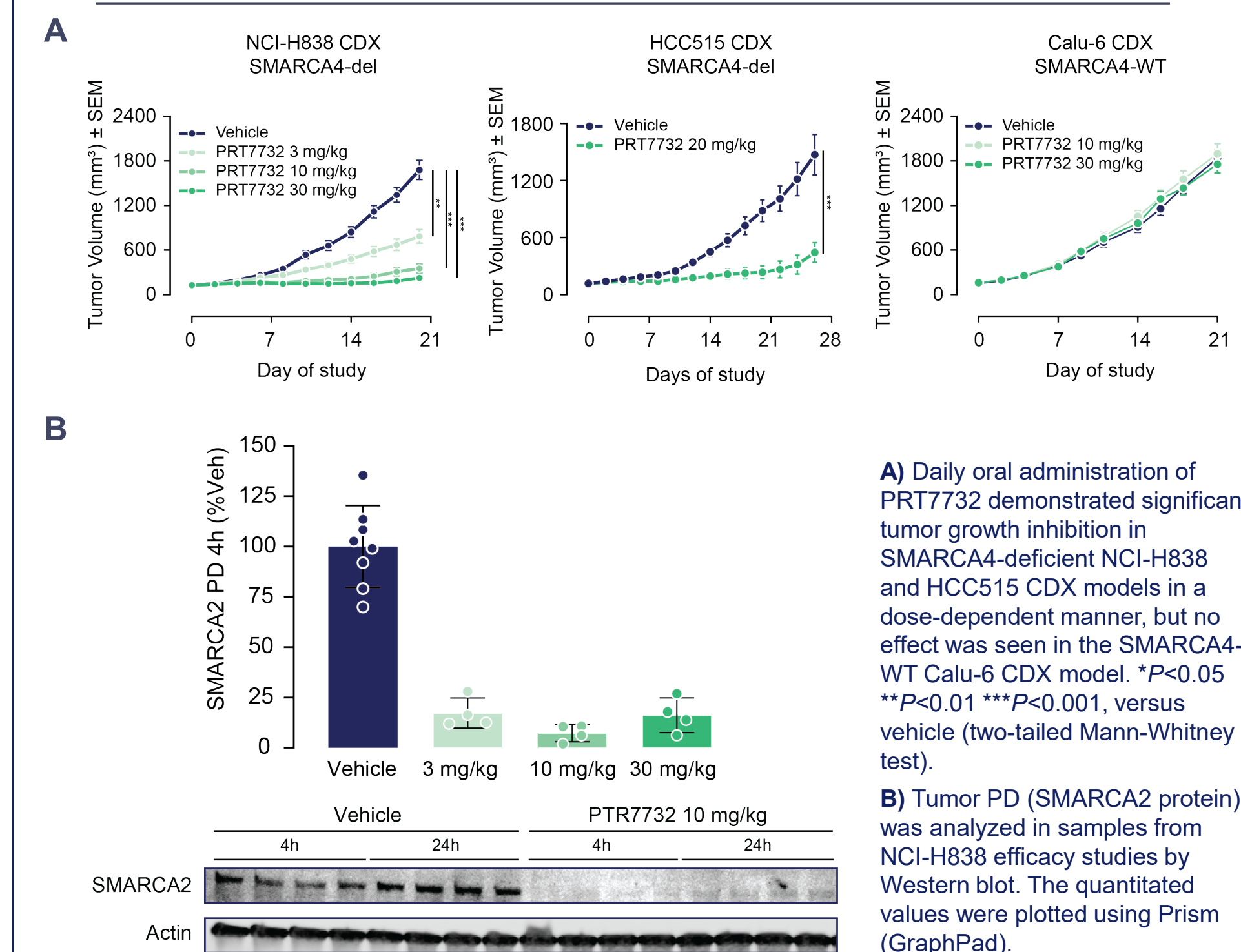
**B**) Western blot for SMARCA2 and SMARCA4 was performed in 10 human cancer cell lines. The SMARCA2 signals were normalized by GAPDH or actin control and DC<sub>50</sub> and D<sub>max</sub> were determined by Prism (GraphPad).

**C**) No off-target effects of PRT7732 (10 nM ~ 1.0 μM) on known IMiD neosubstrates were detected by western blot.

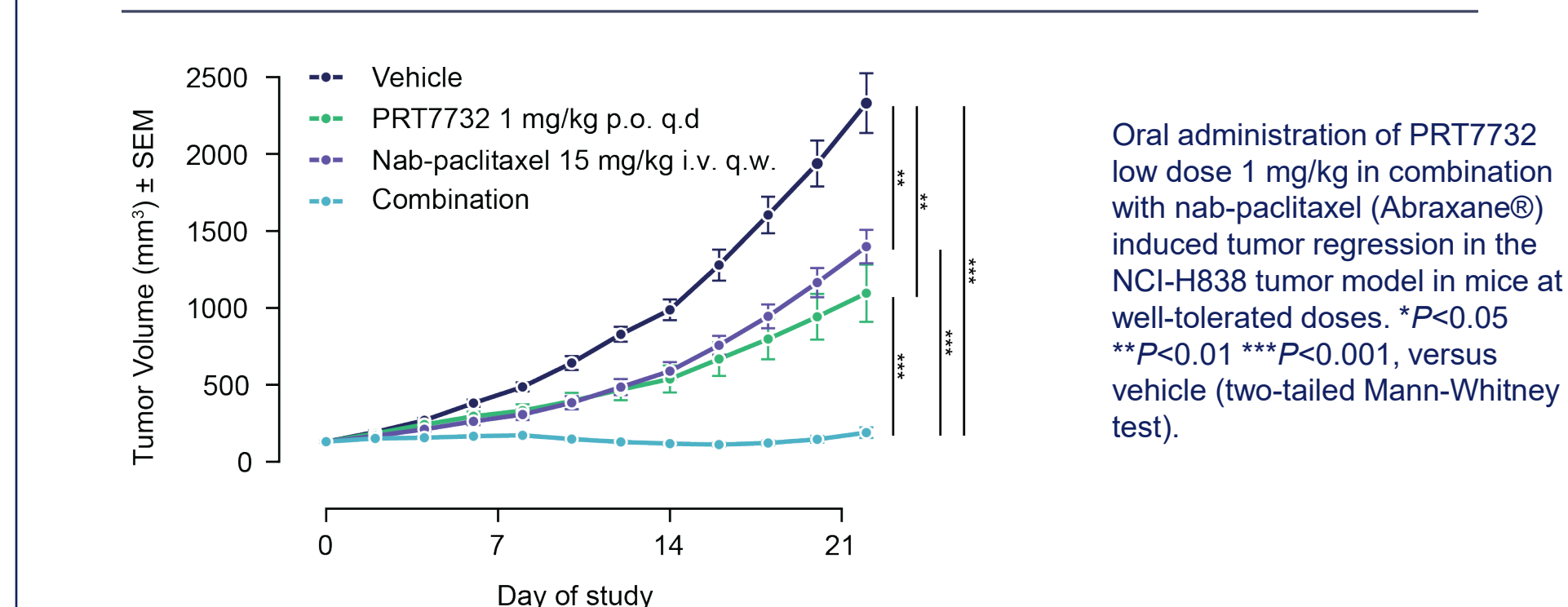
### Figure 4. PRT7732 demonstrates synthetic lethality in SMARCA4-deficient human cancer cells *in vitro*



### Figure 5. Daily oral administration of PRT7732 demonstrates significant anti-tumor activity in SMARCA4-deficient cancer xenograft models and had no effect in SMARCA4-WT model



### Figure 6. Low dose oral administration of PRT7732 in combination with nab-paclitaxel induces tumor regression in NCI-H838 SMARCA4-deficient lung cancer xenograft model

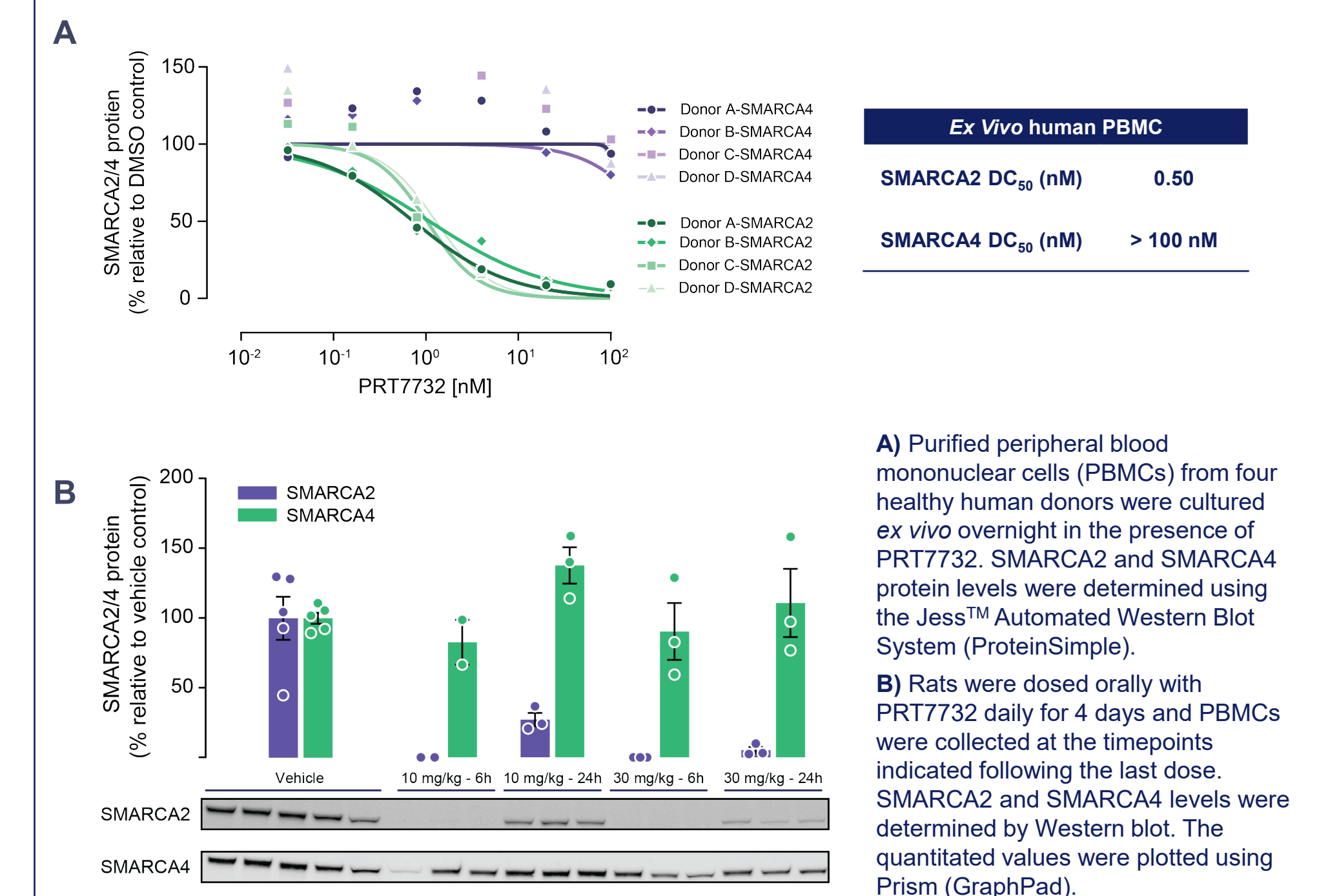


### Table 1. PRT7732 demonstrates good oral PK profile across preclinical species with clean safety pharmacology

Safety Pharmacology	
hERG IC <sub>50</sub> (μM)	> 30
CYP1A2, 2C9, 2C8, 2B6, 2D6, 3A4 IC <sub>50</sub> (μM)	> 10, no TDI
PK binding assay	Clean
Safety 47 panel	Clean
Pharmacokinetics	
F%	35 / 18 / 36 / 30

Safety pharmacology studies show no significant findings. Single dose PK studies show good oral bioavailability.

### Figure 7. Ex Vivo and in vivo PRT7732 treatment demonstrates near absolute selectivity for SMARCA2 degradation in human and rat PBMCs



## Conclusions

- We have identified development candidate PRT7732 that selectively degrades SMARCA2 over SMARCA4 by >3000-fold
- PRT7732 shows excellent potency and selectivity for SMARCA2 degradation both *in vitro* and *in vivo*
- PRT7732 shows strong anti-proliferation activity in SMARCA4-deficient cells, while sparing SMARCA4 WT cells, demonstrating synthetic lethality in SMARCA4-deficient cancers
- Oral administration of PRT7732 demonstrates robust anti-tumor activity in SMARCA4-deficient human lung cancer models *in vivo*
- Low dose oral administration of PRT7732 in combination with NSCLC SOC chemotherapy induces tumor regression in a SMARCA4-deficient human lung cancer model *in vivo*
- In vivo* PD studies in mouse xenograft models and rats indicate daily dosing of PRT7732 leads to complete SMARCA2 degradation, while sparing SMARCA4
- PRT7732 has completed IND-enabling studies and is on track to enter Phase 1 clinical trials in the second half of 2024

## References

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## Disclosures

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