Advancing our Understanding of SMARCA Science

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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.

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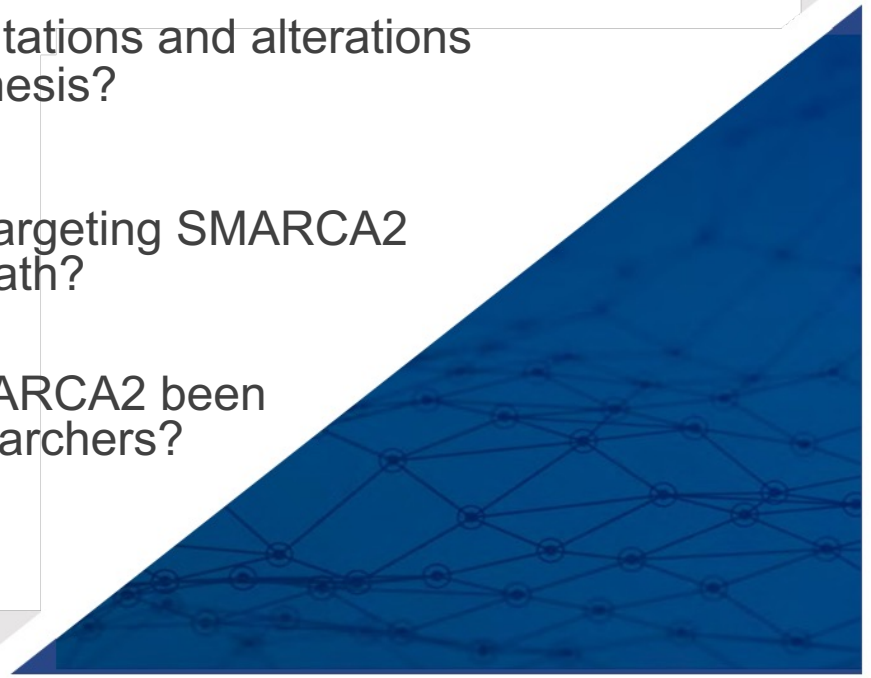
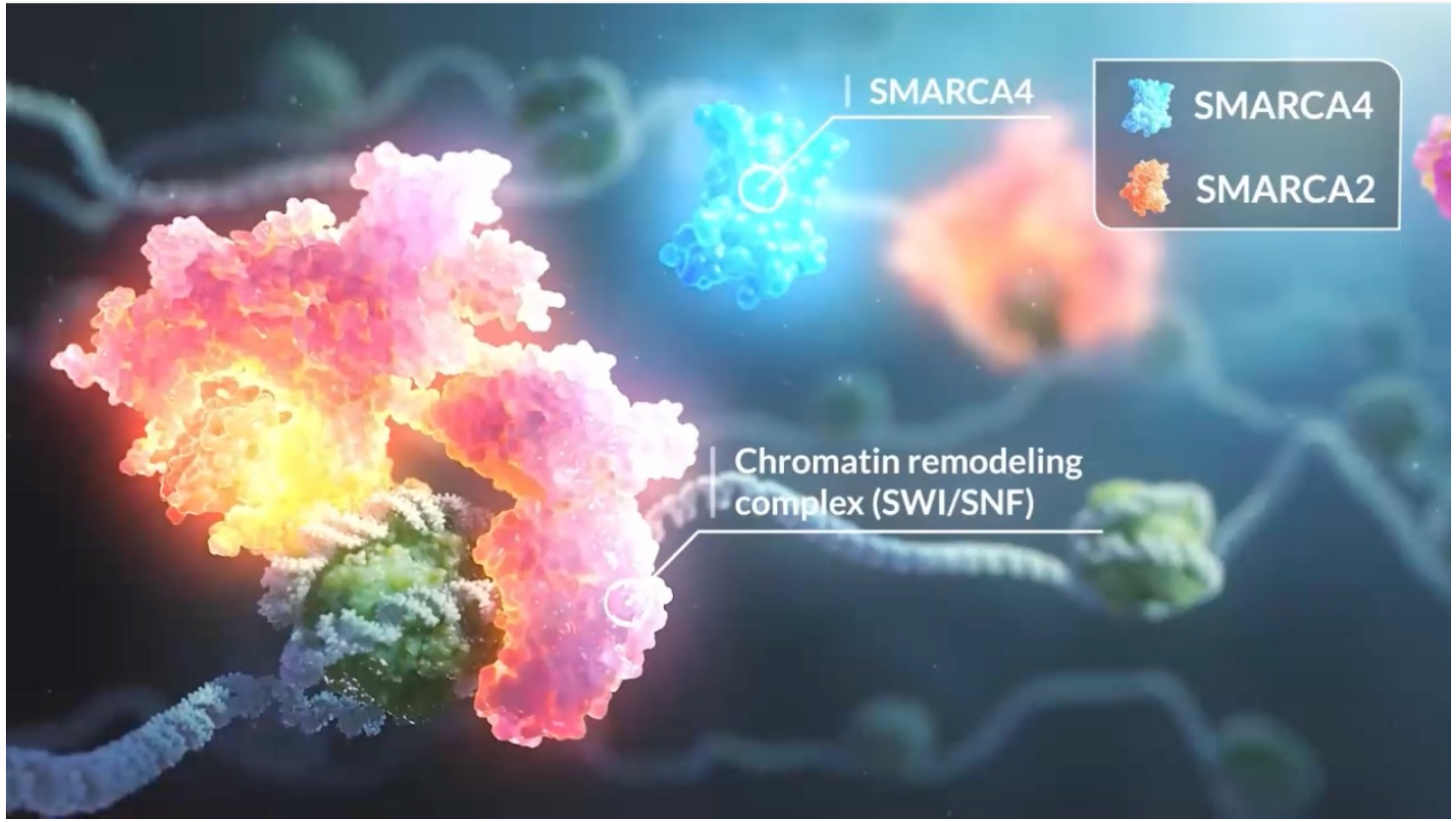
Learning Objectives

- Why has SMARCA garnered such interest as a target for cancer research?
- What is the function of SMARCA2 and SMARCA4 in healthy cells?
- How do SMARCA4 mutations and alterations contribute to tumorigenesis?
- How does selectively targeting SMARCA2 result in cancer cell death?
- Why has targeting SMARCA2 been so challenging for researchers?



Chromatin Remodeling (CR) is an essential step in DNA replication, repair and gene expression



SMARCA: SWI/SNF-related, Matrix-associated, Actin-dependent Regulator of Chromatin, subfamily A.

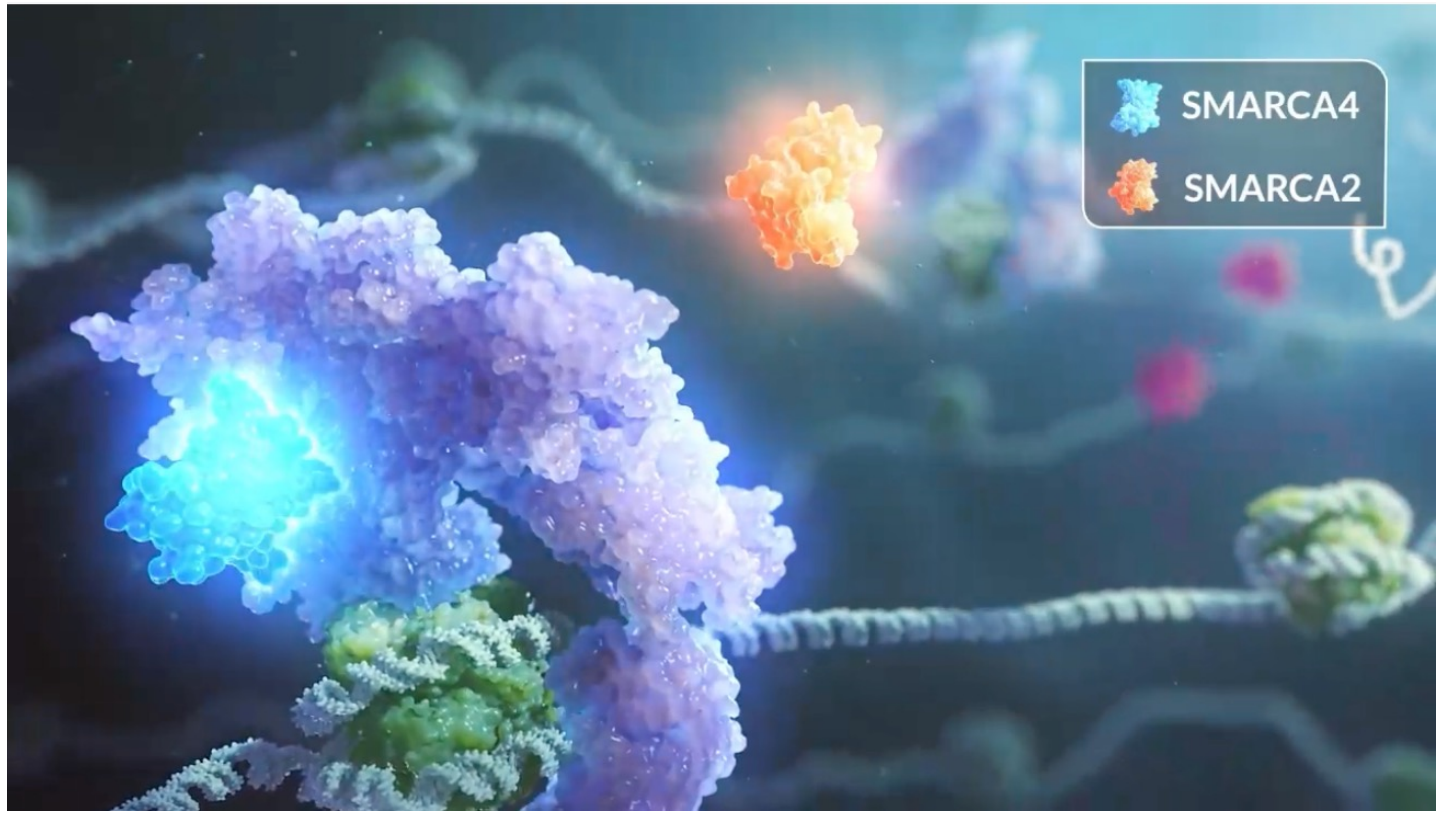
Chromatin Remodeling (CR) Complex (aka SWI/SNF)

Unwinds Chromatin

ATP-Dependent

> 20 Subunits

SMARCA2 and SMARCA4 are highly related, interchangeable ATPase subunits



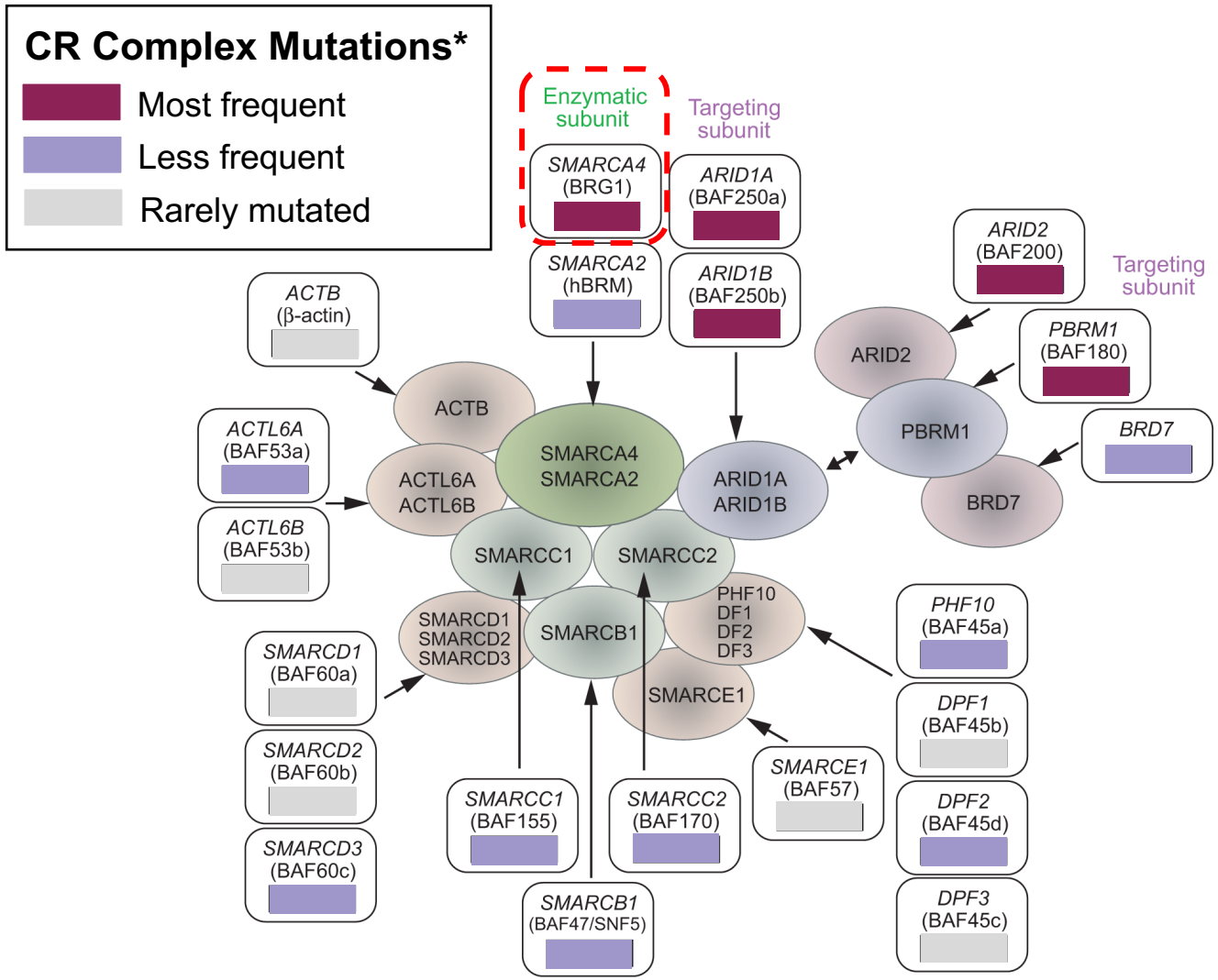
SMARCA2 is also known as “BRM”
SMARCA4 is also known as “BRG1”

SMARCA2 and SMARCA4 work in a complementary manner

Regulate gene expression and cell proliferation

Only one or the other is engaged at any given time

More than 20% of all human cancers harbor mutation(s) in at least one of the CR subunits



* Average frequency of subunit mutation across 18 distinct neoplasms tested

Shain AH, Pollack JR (2013) The Spectrum of SWI/SNF Mutations, Ubiquitous in Human Cancers. PLoS ONE 8(1): e55119

Mutations in the CR complex lead to cancer growth, resistance and poor prognosis

Implicated across a wide range of cancers

Challenging proteins to target for drug discovery

SMARCA4 mutations occur in ~10% of all NSCLC and to varying degrees across other cancers

NSCLC: 10%

Squamous cell lung: 8%

Esophageal: 8%

Colorectal: 6%

Gastric: 8%

Pancreatic: 3%

Endometrial: 13%

Urinary: 9%

Mostly non-overlapping with other "druggable" mutations

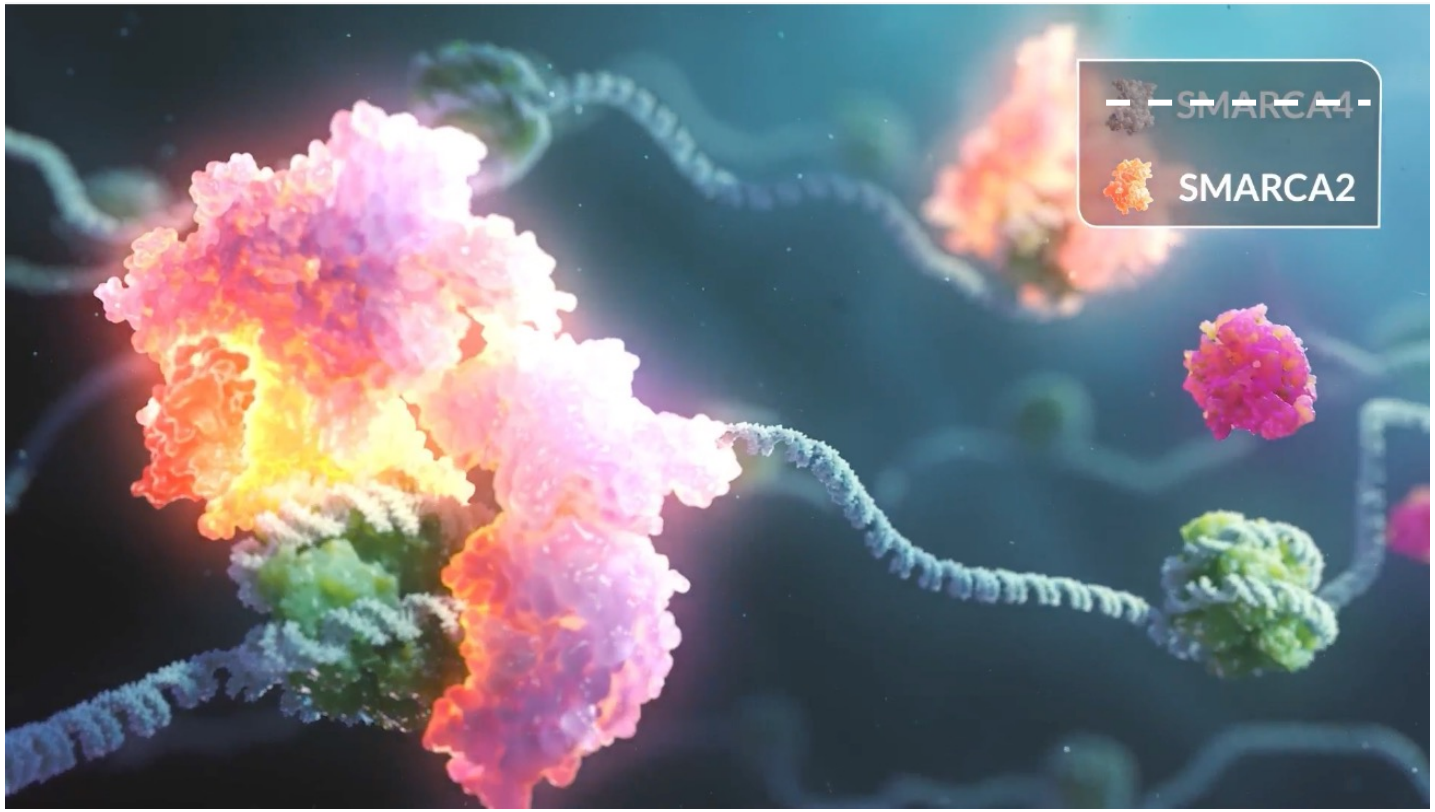
Types of mutations:

Class I (Loss-of-function)

Class II (Missense, other)

[1] Dagogo-Jack et al. Journal of Thoracic Oncology. 2020 Foundation Medicine dataset

When SMARCA4 is mutated, tumors become reliant on SMARCA2 for growth and survival



SMARCA4-*mutated* cancers become reliant on SMARCA2

In these cancers, when SMARCA2 is depleted, the CR complex no longer functions

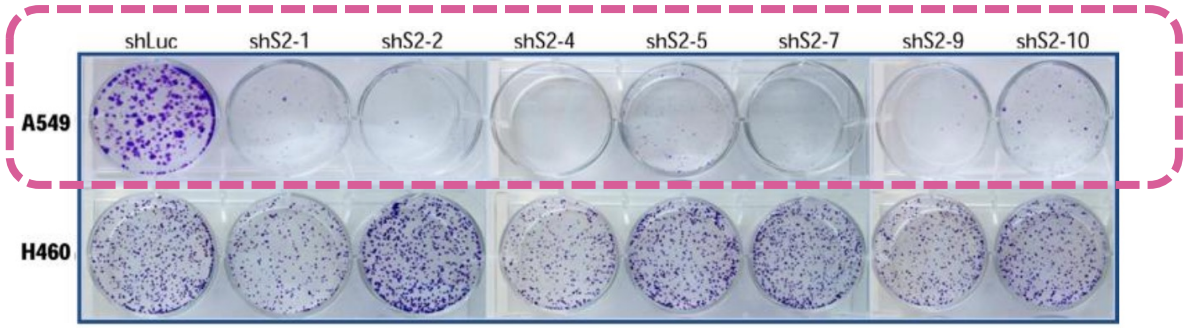
Cells can no longer survive and tumors regress

“Synthetic Lethality”

Selectively knocking out SMARCA2 induces synthetic lethality in SMARCA4-*mutated* cancers

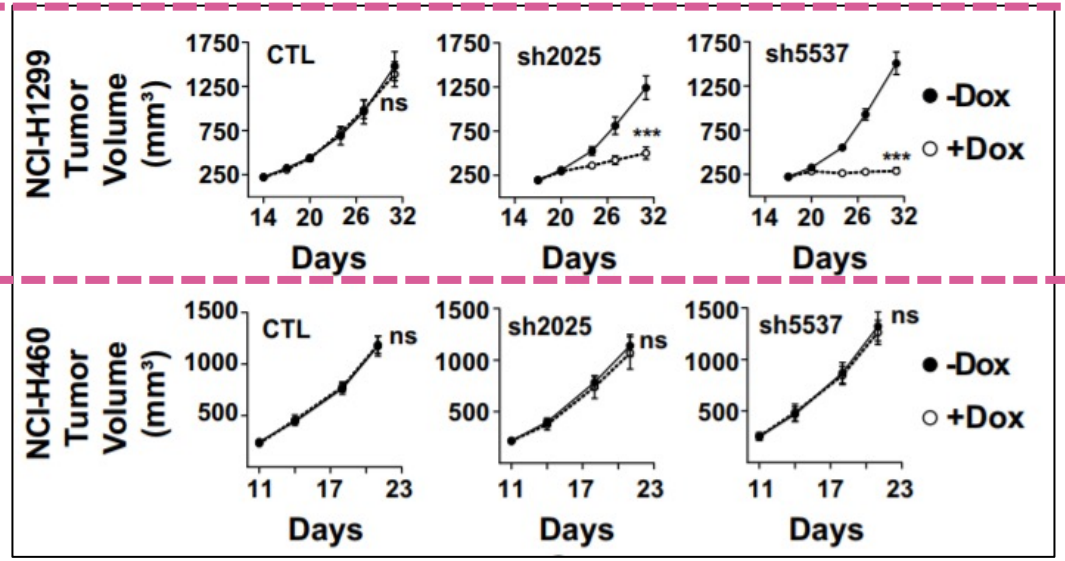
SMARCA4-*mut* cancer cells

SMARCA4 WT cancer cells



SMARCA4-*mut* cancer model

SMARCA4 WT cancer model

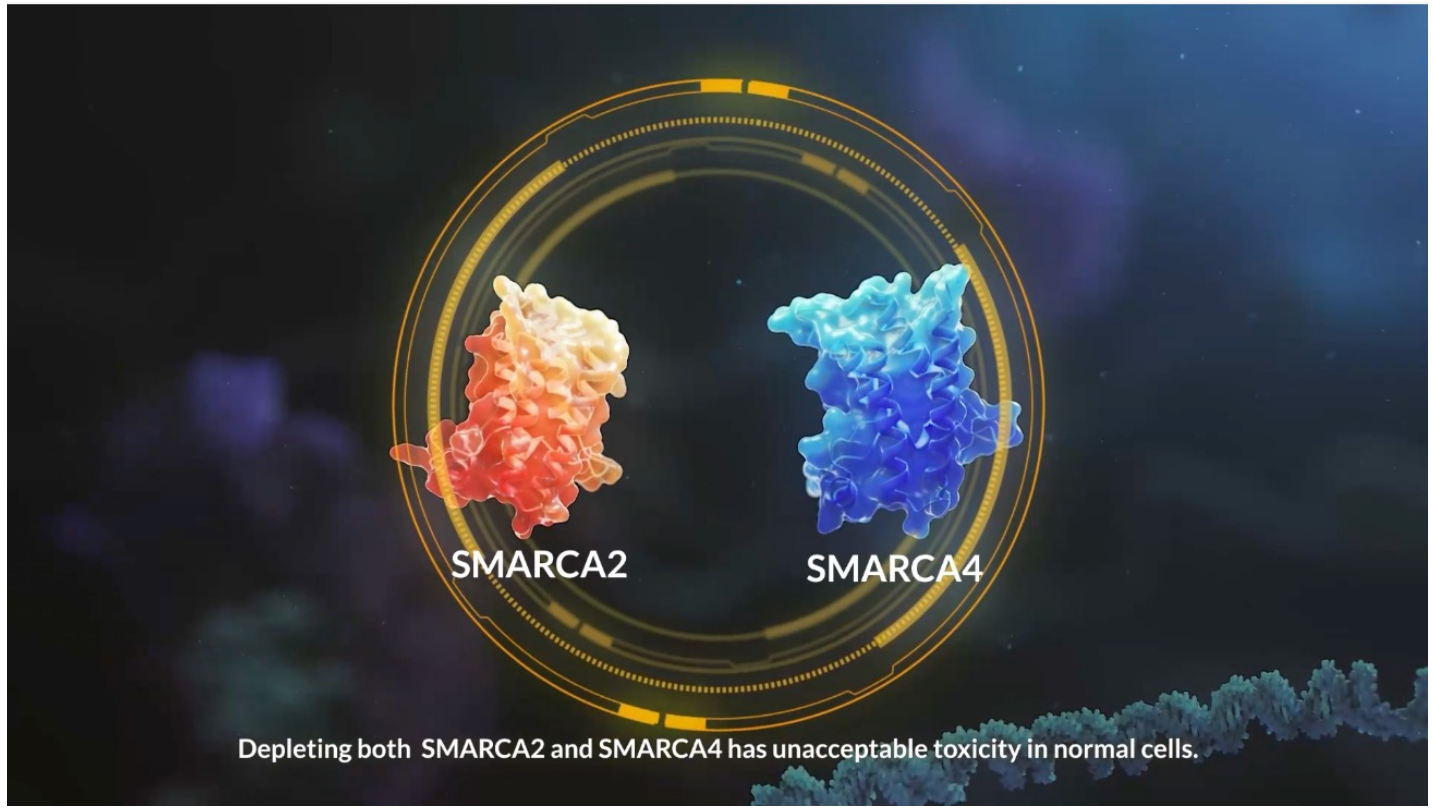


Hoffman GR et al. PNAS (2014); 111 (8): 3128-3133
Vangamudi et al. Cancer Res (2015); 75 (18): 3865-3878.

SMARCA2 gene knockdown shows tumor growth inhibition in SMARCA4-mutated cancers

… but NOT in SMARCA4 wild-type cancers

Selective SMARCA2 targeted treatments could have utility treating SMARCA4-mutated cancers



Selectively targeting SMARCA2 should induce tumor regression in SMARCA4-mutated cancers

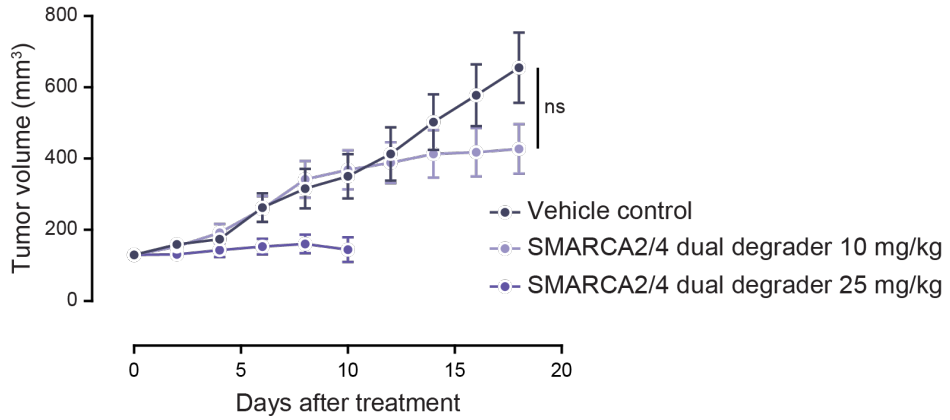
In healthy tissue, SMARCA4 should compensate for selectively depleted SMARCA2

If both are depleted, there would likely be adverse effects

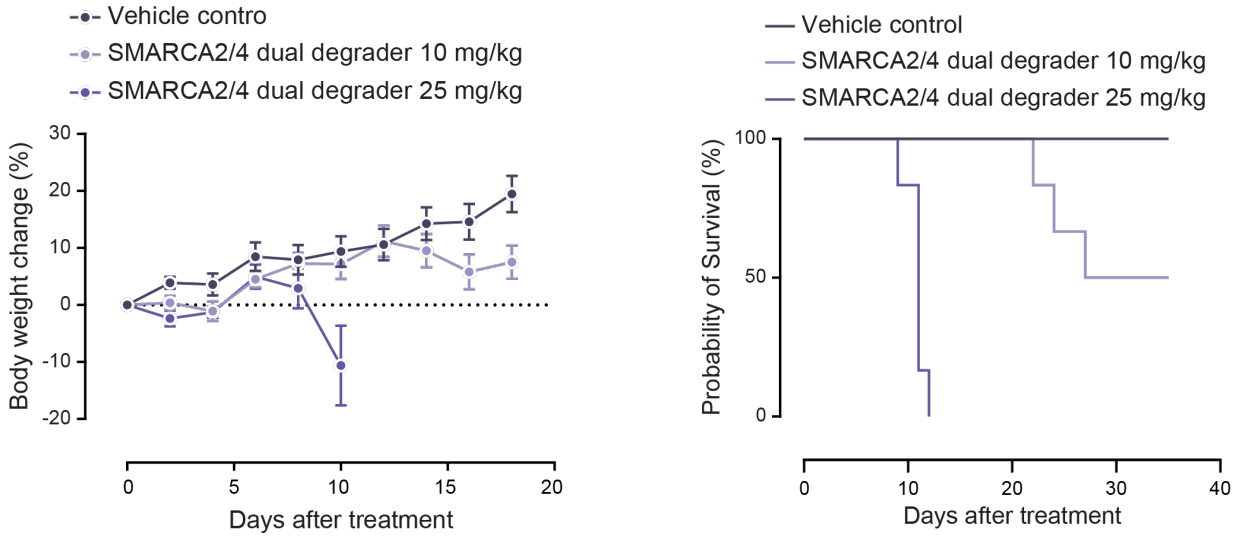
Selectivity is critical

SMARCA2/4 dual degraders show rapid tumor regressions, but may cause unacceptable toxicity

Rapid cell death and tumor regression



… but with unacceptable toxicity in animal models



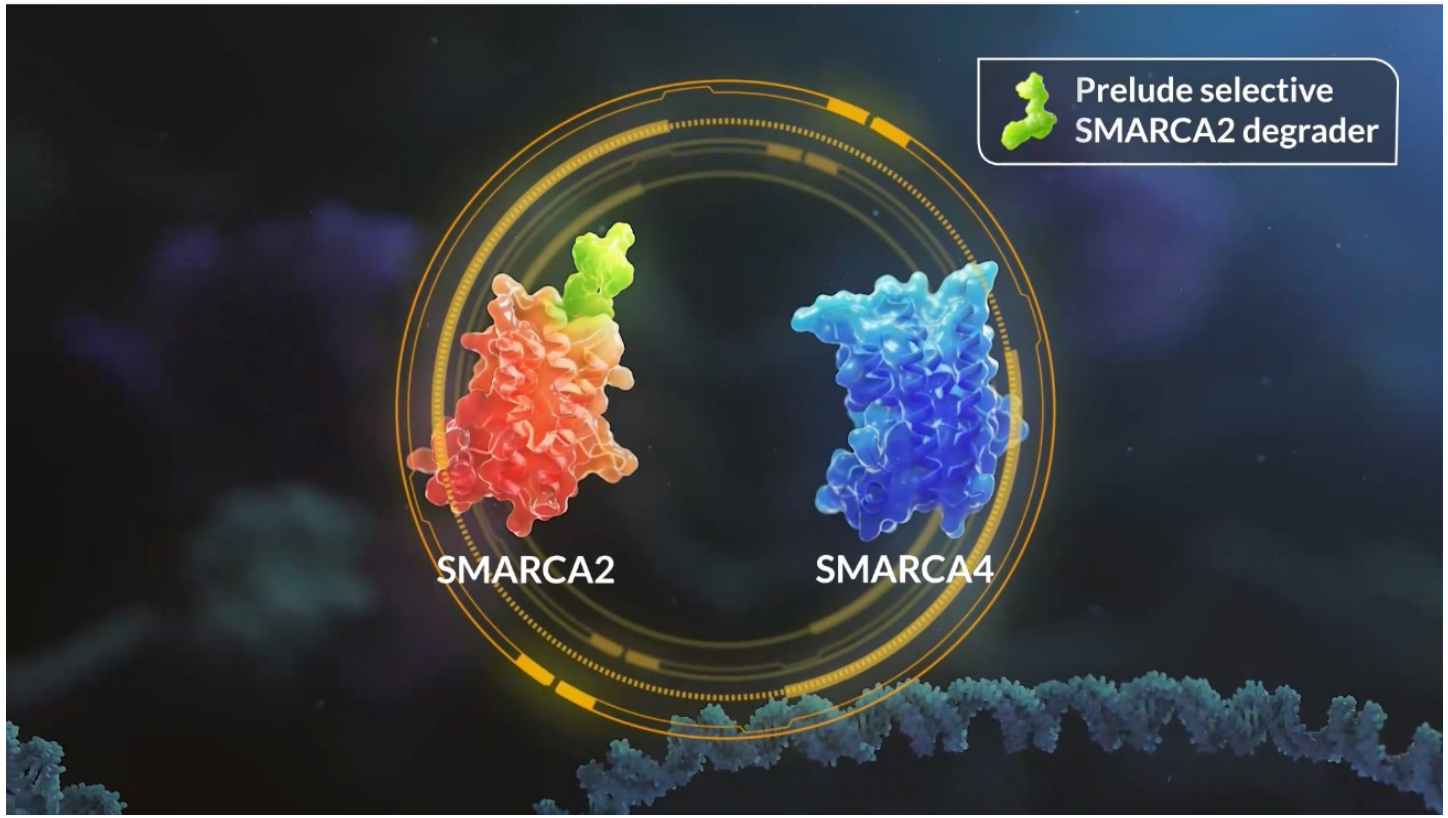
Prelude Data on File. Presented at 6th TPD Summit, 2023

SMARCA2/4 dual degraders showed rapid cell death and tumor regression

However, dual degraders also showed toxicity, body weight changes and shorter survival

Selectivity is key for a better therapeutic window

Achieving SMARCA2 selectivity has been a challenge for industry, until recently



Hard to achieve selectivity with inhibitors to the ATPase active site

Recent advances in targeted protein degrader technology allows for both potency and selectivity

Once “undruggable” target → now in human clinical trials

Targeting SMARCA2 represents an important new field of cancer research

- Mutations in the Chromatin Remodeling (CR) complex drive cancer growth and resistance
- SMARCA4 mutations are present in up to 10% of all NSCLC and across other cancers
- Cancer cells with loss of SMARCA4 expression through mutations or alteration are highly dependent on SMARCA2 for survival
- Selective SMARCA2 degraders have the potential to induce "synthetic lethality" in SMARCA4-*mutated* cancers
- Discovering new agents with high selectivity for SMARCA2 is critical

Key Takeaways