Discovery of First-in-Class Precision Antibody Drug Conjugates Targeting Mutant Calreticulin For the Treatment of Myeloproliferative Neoplasms.

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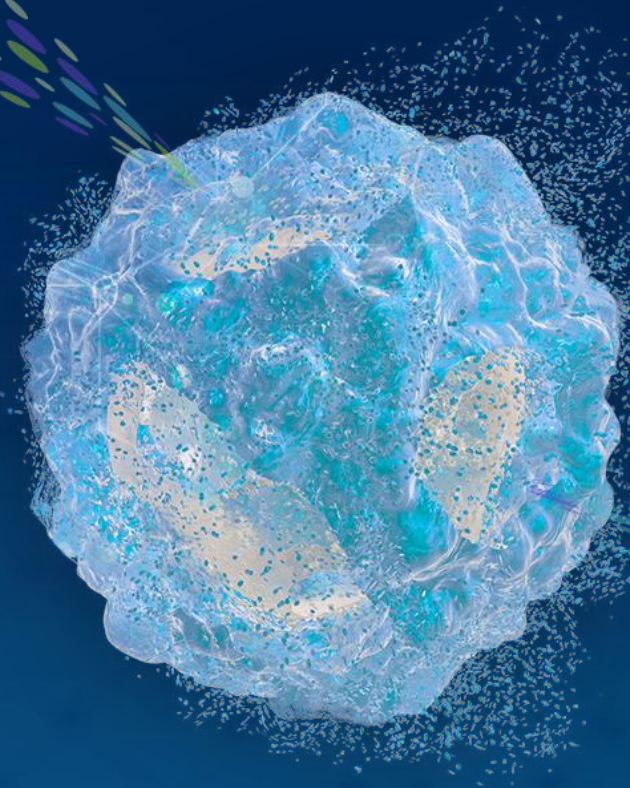

Disclosures and Financial Relationships

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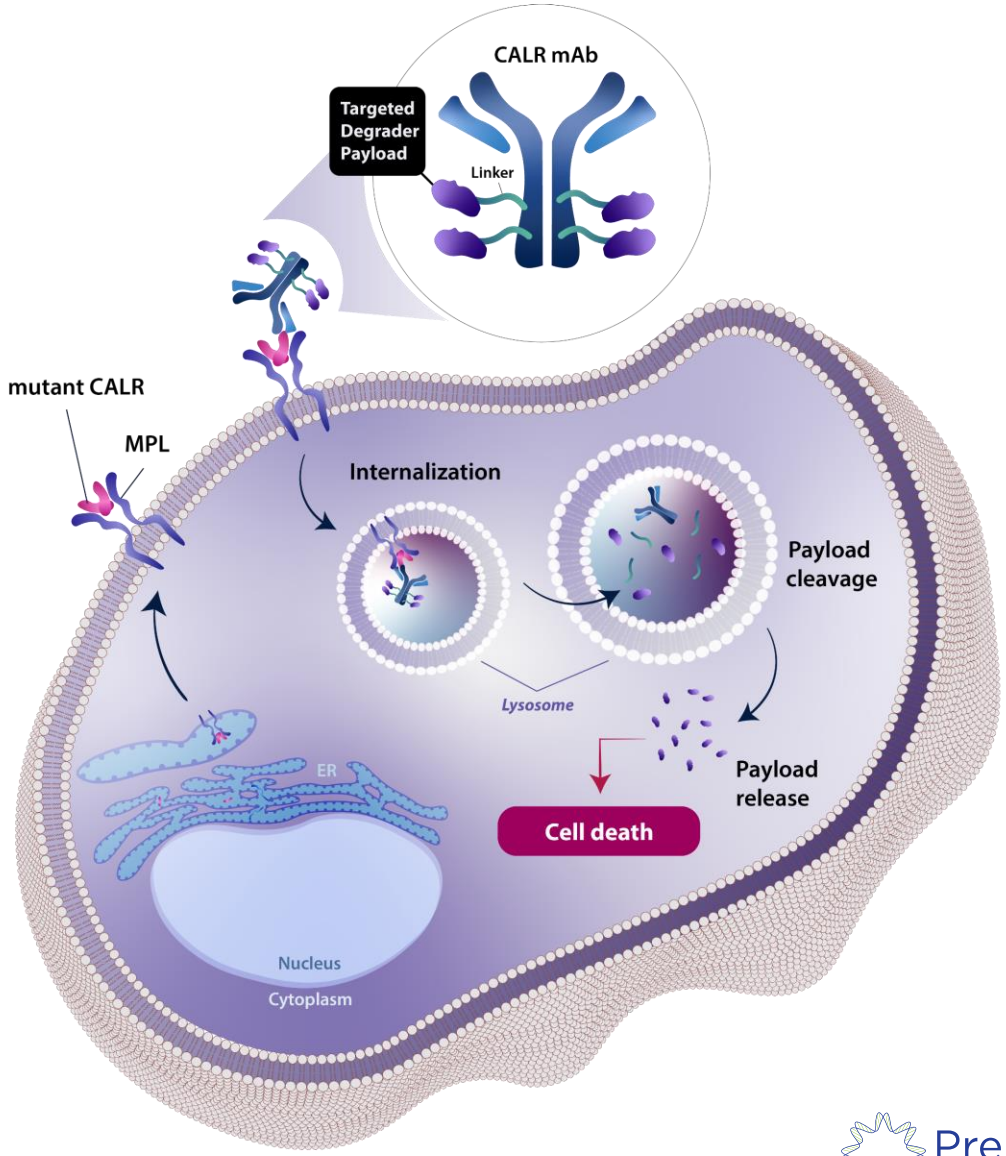
Financial Relationships

Norman Fultang is an employee and shareholder of Prelude Therapeutics Incorporated.

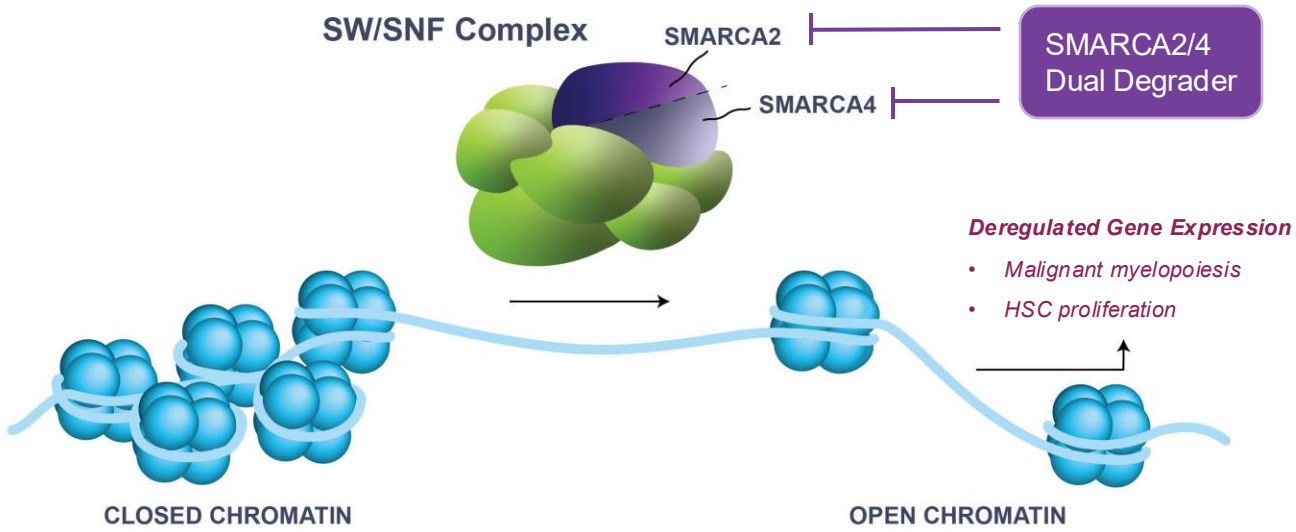
Mutated Calreticulin (mutCALR) Represents a Promising ADC Target and Pathway to Potential Molecular Remission in MPNs

- Mutant CALR is a neoantigen presented on the cell surface of malignant cells but not normal cells and is found in 25-35% of patients with MF and ET
- Current therapies for MPNs provide symptom relief but do not reduce allele burden, and are not curative
- The identification of therapeutic approaches that can selectively eliminate mutant CALR disease-initiating progenitors is an unmet medical need.



SWI/SNF ATPases SMARCA2 and SMARCA4 are Key Therapeutic Targets in MPN

- SWI/SNF nucleosome remodeling complexes regulate chromatin accessibility and are essential for hematopoietic stem cell maintenance.[1]
- Deregulated SWI/SNF activity has been linked to the pathogenesis of several myeloid disorders including AML, MDS and **MPN**.[2,3]
- In MPN, aberrant SWI/SNF activity in progenitor cells has been associated with malignant myelopoiesis, clonal proliferation and disease progression.[3,4,5]
- Mammalian SWI/SNF complexes contain two essential, mutually exclusive, ATPase subunits, **SMARCA2** and **SMARCA4**.[1]
- Degradation of SMARCA2 and SMARCA4 disrupts malignant SWI/SNF activity inducing cytotoxicity in diseased progenitors, restoring normal hematopoiesis.



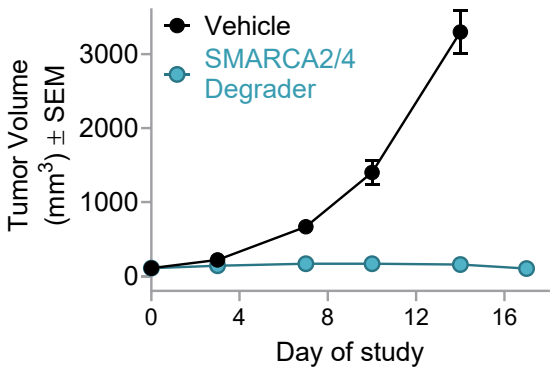
1.Centore, R.C., 2020. Trends in Genetics, 36(12), pp.936-950.
2.Andrades, A., 2023. Molecular cancer, 22(1), p.39.
3.Sharma, M., 2021. Onco. Letters, 21(3), p.204.
4.최진욱, 2012. Doctoral dissertation, 서울대학교 대학원
5.Sakai, H., 2014. Blood, 124(21), p.4610.

Prelude's SMARCA2/4 Degrader Payloads Demonstrate Robust Efficacy in MPN Preclinical Models With Limited Tolerability

- SMARCA2/4 dual degraders demonstrate robust efficacy including regressions in *in vivo* models of myeloid disease.
- Treatment with SMARCA2/4 degrader significantly reduces splenomegaly.
- Systemic SMARCA2/4 degradation is limited by on-target toxicity, reflecting the essentiality of the SWI/SNF complex in normal tissue homeostasis.
- An ADC strategy is warranted to enhance therapeutic index through selective targeting of diseased myeloid cells.

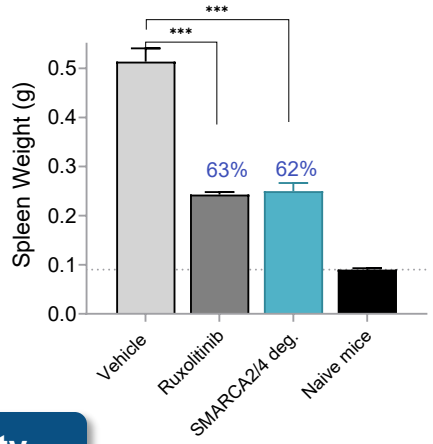
Robust Inhibition of tumor growth and splenomegaly

OCI-AML3, AML



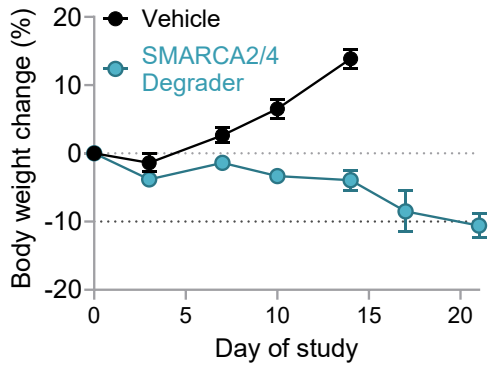
Ba/F3-MPL-CALR^{ins5}

% Reduction of Splenomegaly

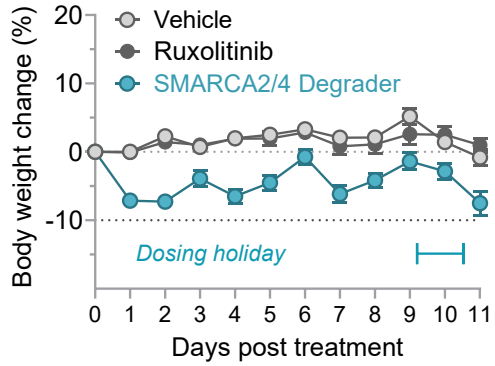


Limited Tolerability

OCI-AML3, AML

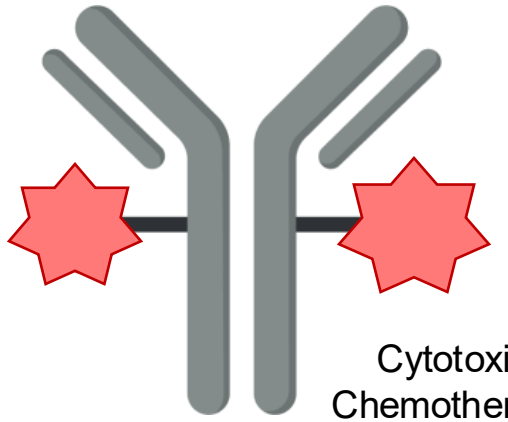


Ba/F3-MPL-CALR^{ins5}



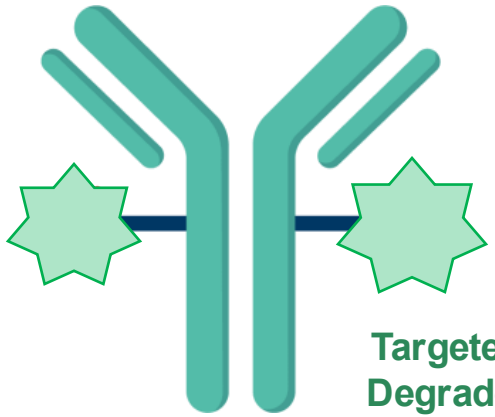
Precision ADCs (or "pADCs") Represent the Next Generation of ADCs

Current ADCs

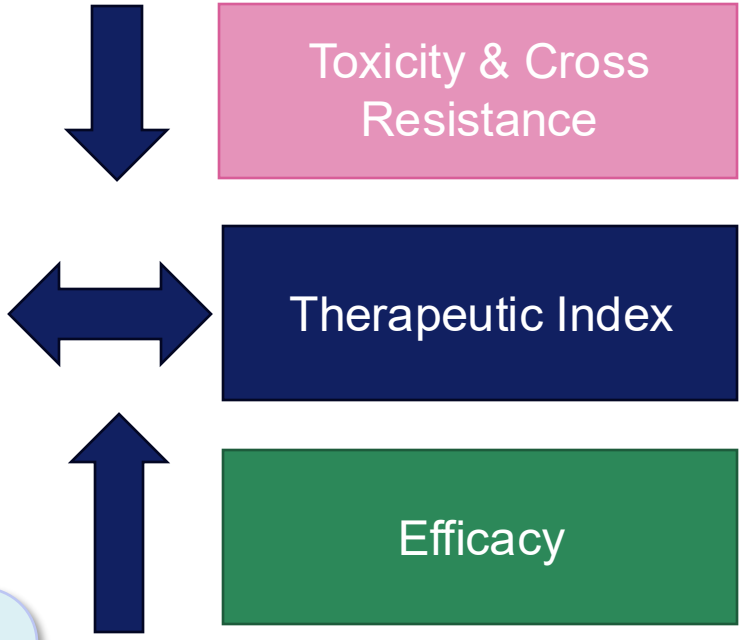


Cytotoxic Chemotherapy

Precision ADCs



Targeted Degrader Payloads



- Non-selective Genotoxic Payloads
- Limited Payload Diversity
- Broad Chemotherapy Liabilities
- Resistance Emerging to Common Cytotoxic Payloads

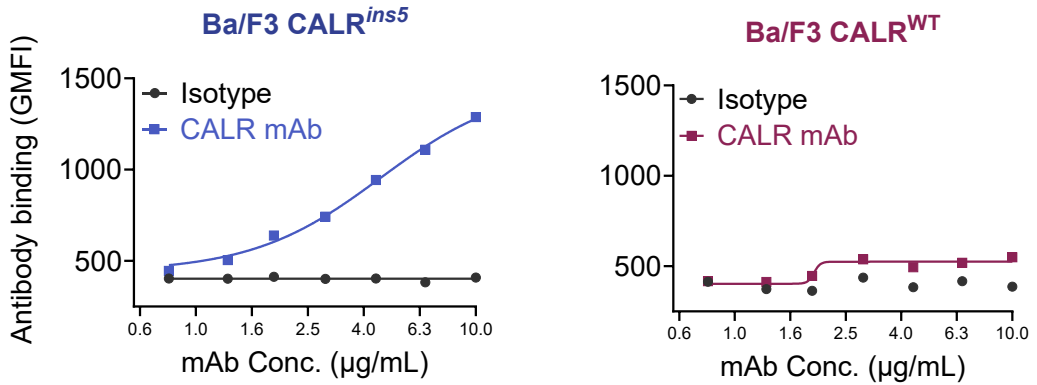
- Dual Targeting with Precision ADCs
  - Tumor-Specific Cell Surface Antigen, and
  - Targeted Degradation of Critical Proteins in Validated Cancer Pathways
- Dual Targeting Expands Therapeutic Index
- Overcomes Cytotoxic Payload Resistance

DACs, Degrader Antibody Conjugates

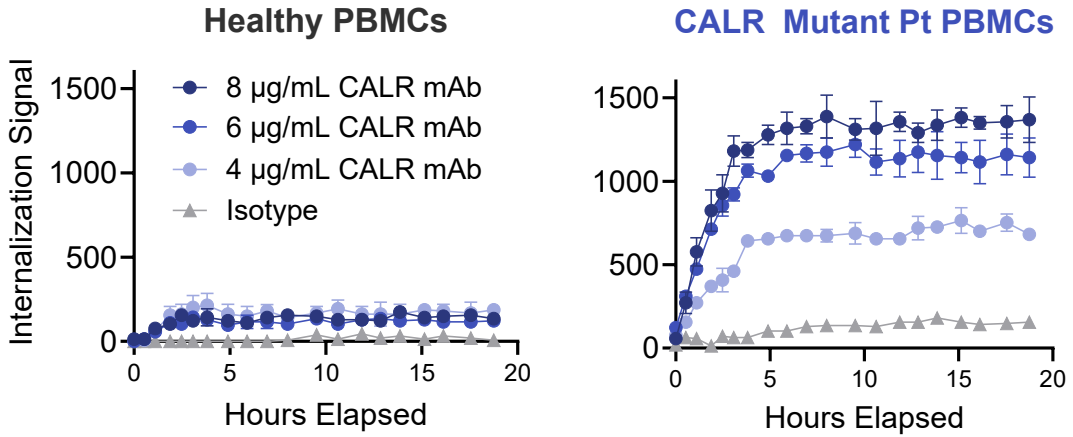
Fu, Z., Li, S., Han, S. *et al. Sig Transduct Target Ther* **7**, 93 (2022).

Identification of an Internalizing CALR Antibody To Enable Selective Delivery of SMARCA2/4 Degraders to CALR Mutant Cells

CALR antibody preferentially binds mutant CALR Ba/F3 cells over WT

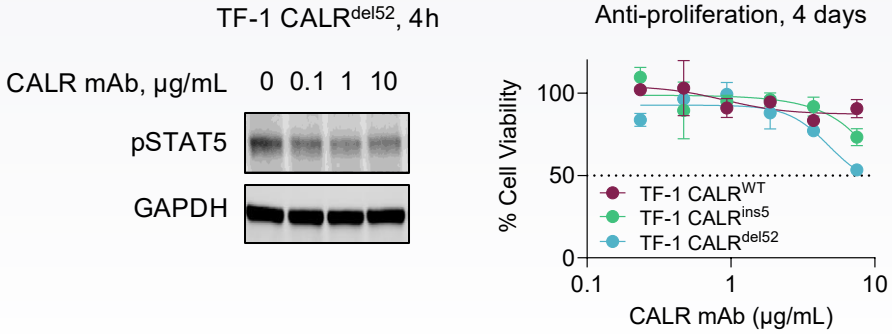


CALR antibody is selectively internalized in CALR mutant Pt cells



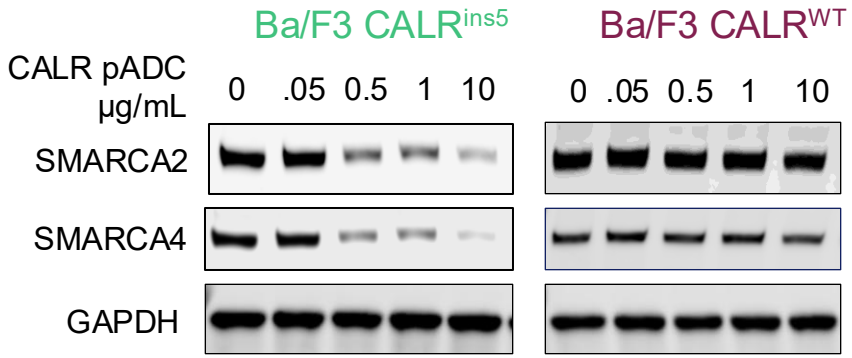
- Non-antagonizing, internalizing CALR antibody identified from a screen of monoclonal CALR antibodies
- CALR mAb is selectively internalized in CALR mutant patient cells but not healthy CALR WT cells

CALR mAb does not inhibit CALR-driven JAK/STAT signaling

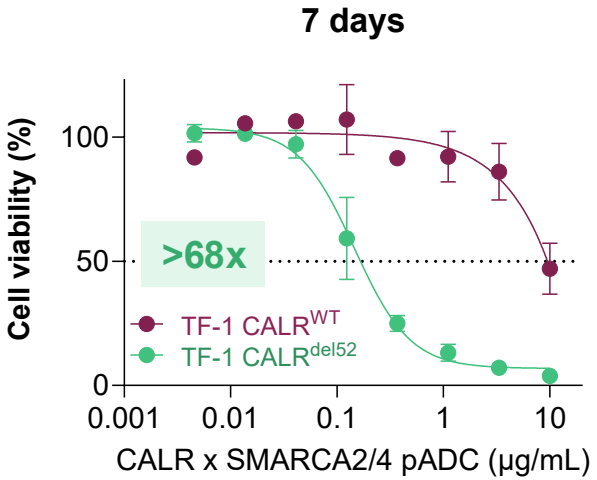


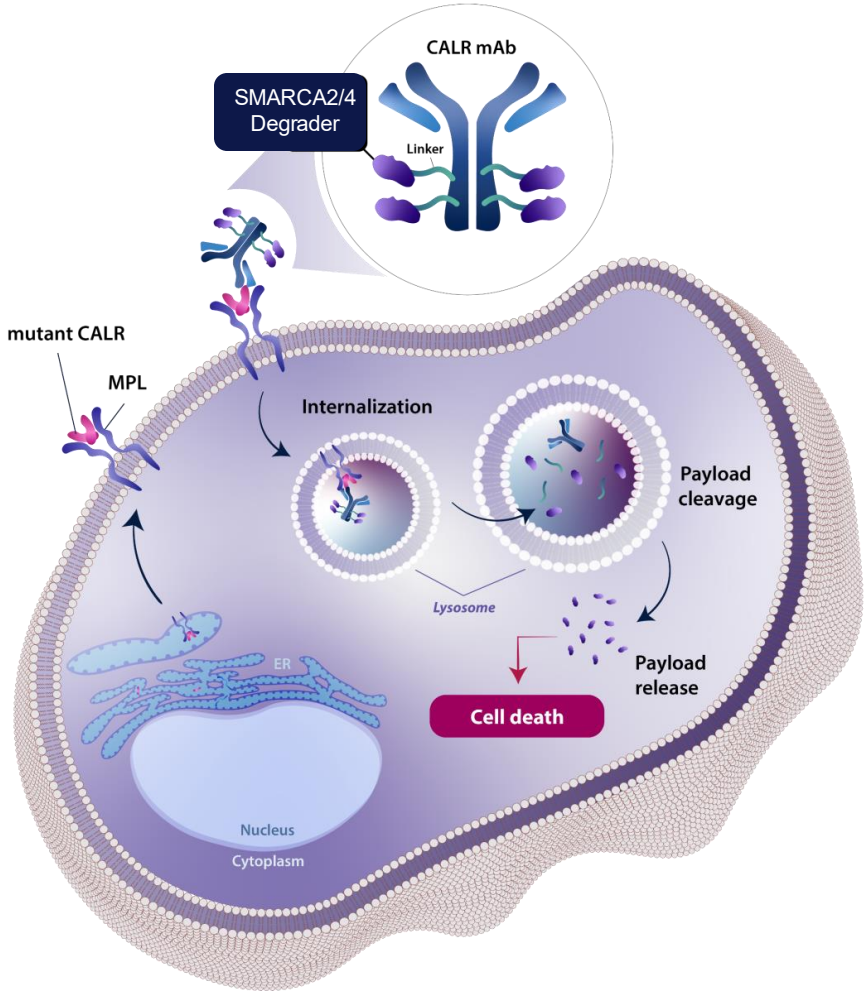
CALR pADCs Demonstrate Robust and Selective SMARCA2/4 Degradation and Cytotoxicity in CALR Mutant Cells

Degradation Assay, 48h



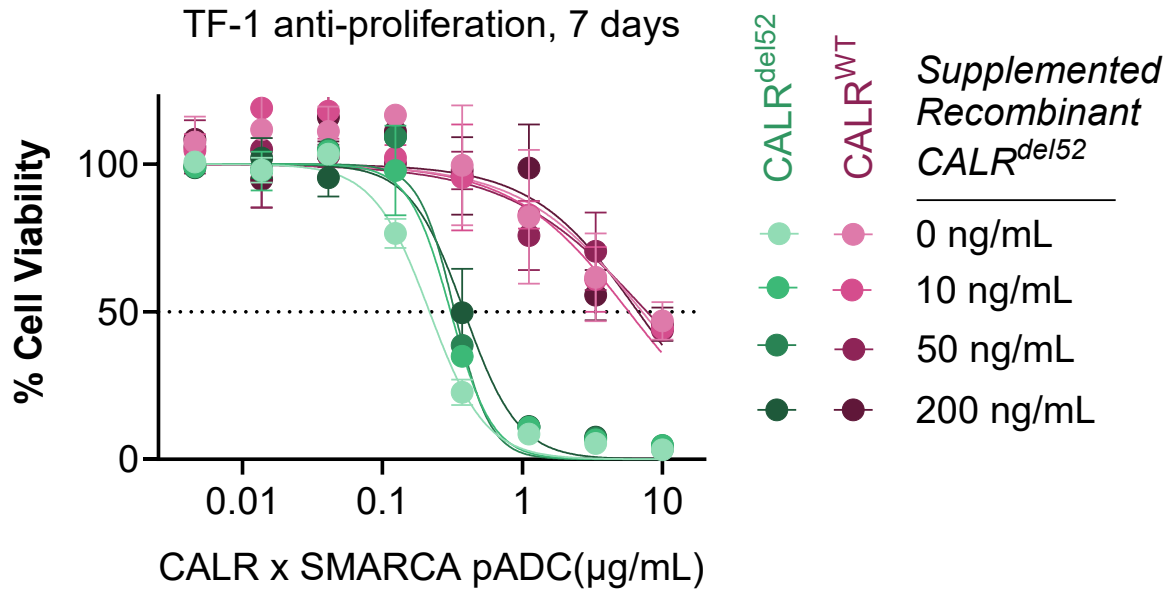
Anti-proliferation Assay





CALR x SMARCA pADC selectively degrades SMARCA2/4 in CALR mutant cells resulting in potent and selective killing of mutant cells

Presence of Soluble Mutant CALR Protein Does Not Affect CALR pADC Cytotoxicity



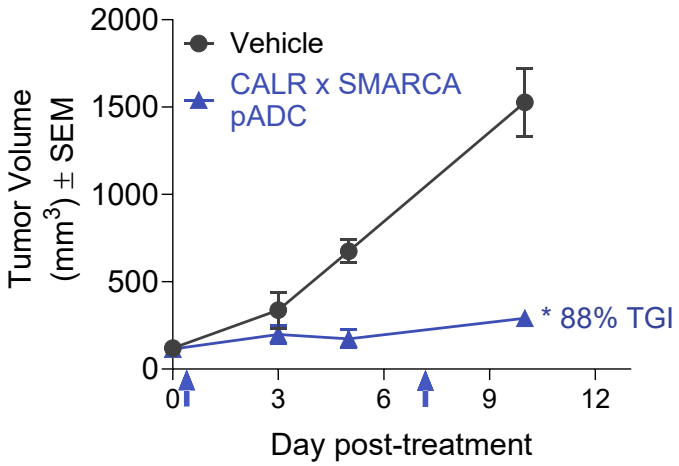
- Mutant CALR is secreted by mutant cells and detected in MPN patient plasma (mean: 25.6 ng/mL; range: 0–160 ng/mL).[1]
- Soluble mutant CALR does not impair CALR pADC potency in mutant cells (no "sink effect") and does not induce off-target binding or toxicity in healthy/CALR WT cells.

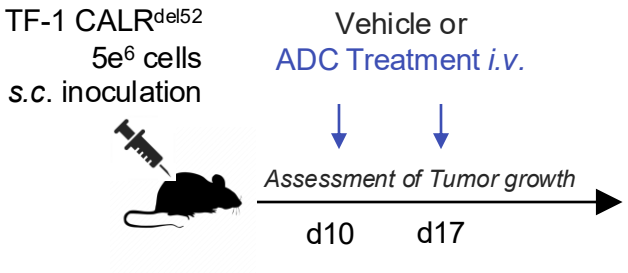
Soluble mutant CALR poses no risk to CALR pADC efficacy or safety

Pecquet, C., 2023. *Blood*, *141*(8), pp.917-929.

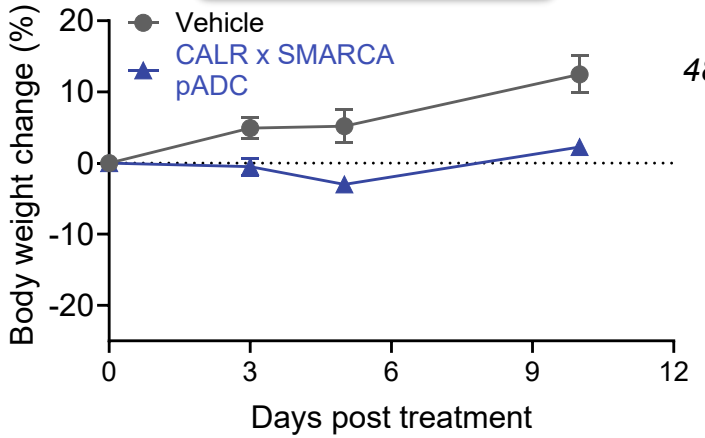
CALR pADCs Demonstrate Robust Anti-Tumor Activity In Vivo and Are Well-Tolerated

Robust tumor growth inhibition

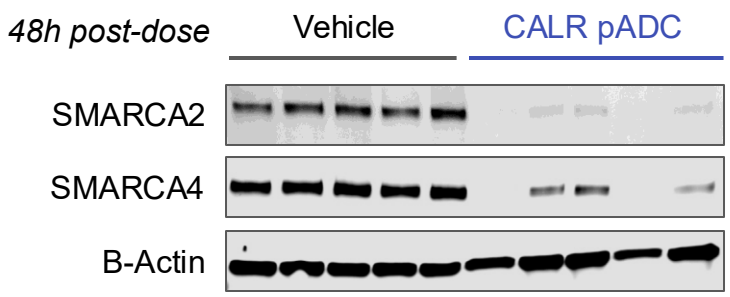




Well tolerated



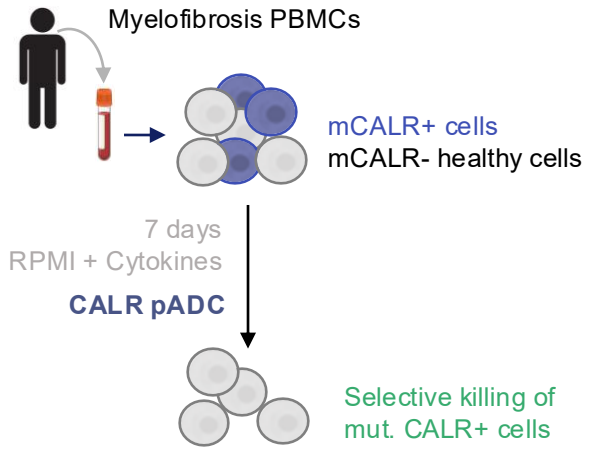
Target degradation in tumor tissue



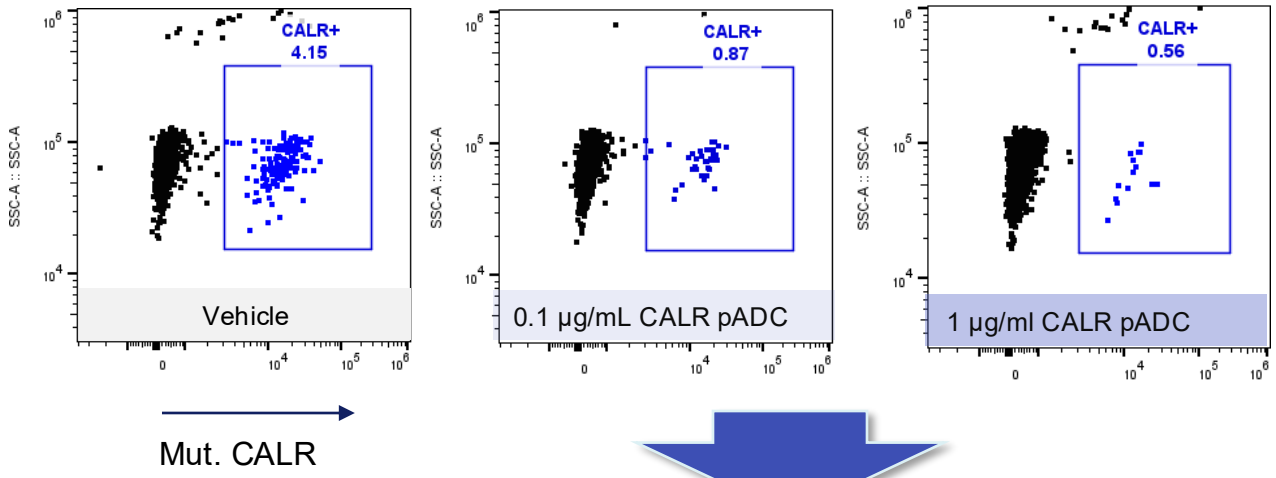
- ✓ CALR x SMARCA pADCs drive robust inhibition of growth in a TF-1 CALR^{del52} subcutaneous xenograft model highlighting their potent *in vivo* anti-tumor activity
- ✓ CALR x SMARCA pADCs efficiently degrade SMARCA2/4 in tumor tissue confirming effective payload delivery and on-target engagement
- ✓ Repeat dosing of CALR x SMARCA pADCs is well tolerated, with no signs of systemic toxicity, underscoring a favorable therapeutic index.

CALR pADCs Selectively Target and Eliminate Diseased CALR Mutant Cells from MPN Primary Cultures

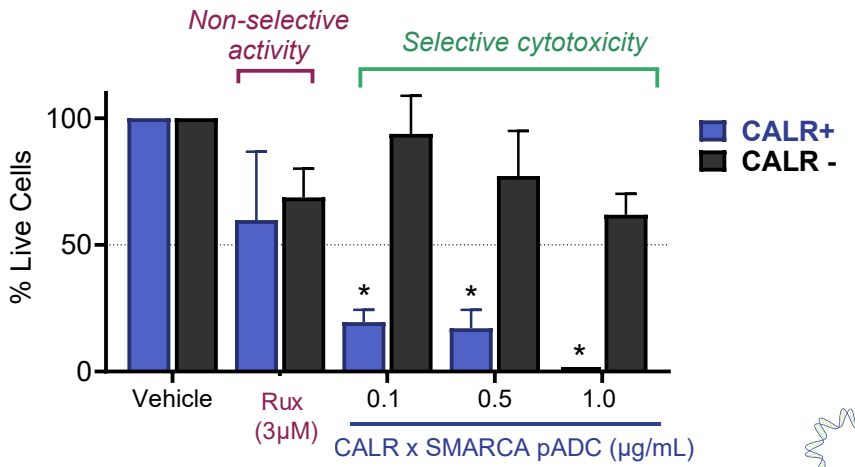
Liquid Culture Growth Assay



MF (CALR^{ins5}) PBMCs, Day 7



MF (CALR^{ins5}) PBMCs, Day 7

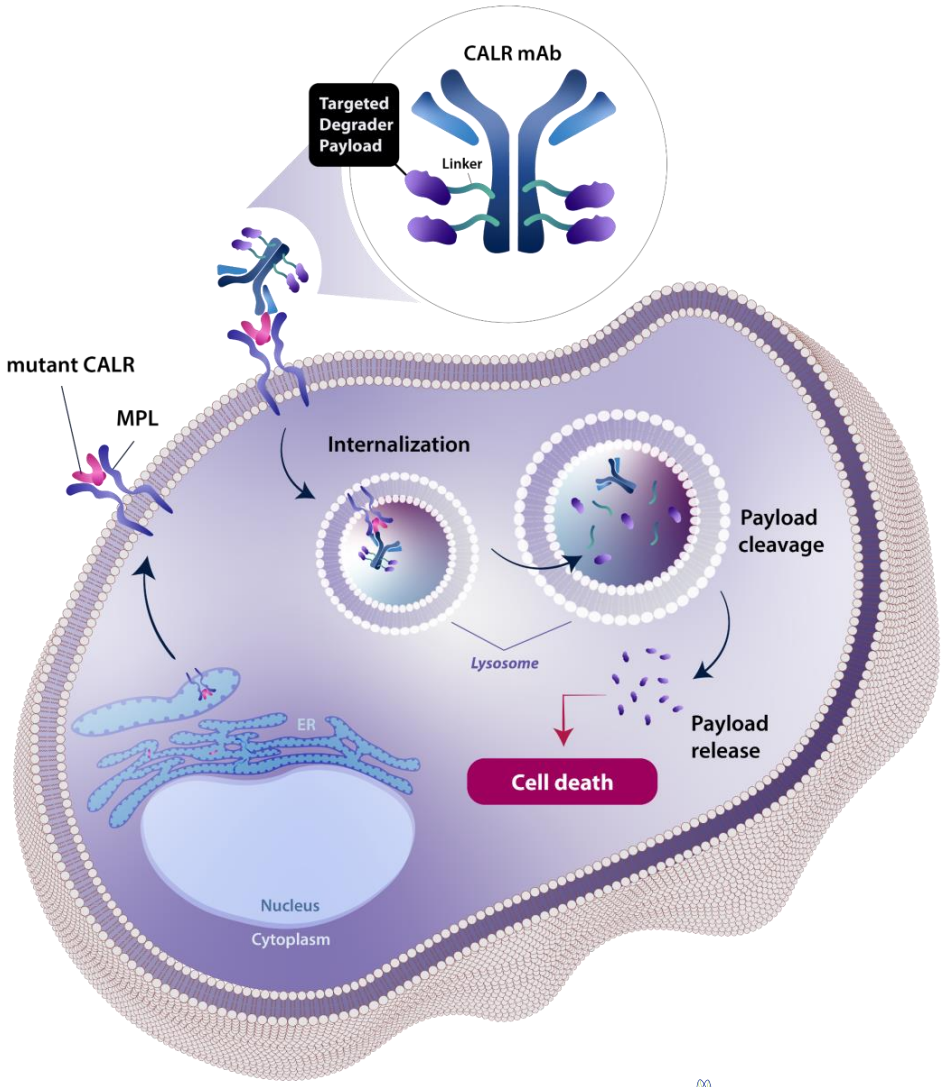


CALR pADCs selectively target and eliminate CALR mutant peripheral disease cells, while sparing healthy cells.

* P <0.05

Summary: Prelude's CALR pADCs: A Selective and Efficacious Approach for Targeting CALR-Mutant Disease

- ✓ Prelude's CALR pADCs selectively degrade SMARCA2/4 in CALR mutant cells and robustly inhibit CALR-mutant cell growth *in vitro* and *in vivo*
- ✓ In MPN models, CALR pADCs target and eliminate diseased CALR-mutant cells highlighting their potential as disease-modifying agents for CALR-mutant MPN
- ✓ CALR pADCs spare healthy hematopoietic cells, indicating a favorable therapeutic index
- ✓ Similar findings were observed with a CDK9-degrading CALR pADC, demonstrating the broader potential of this modality across multiple payloads for selectively targeting CALR-mutant cells



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