Discovery of First-in-Class Calreticulin-targeted Degrader Antibody Conjugates Delivering a CDK9 Degrader Payload for the Treatment of CALR-mutated MPNs

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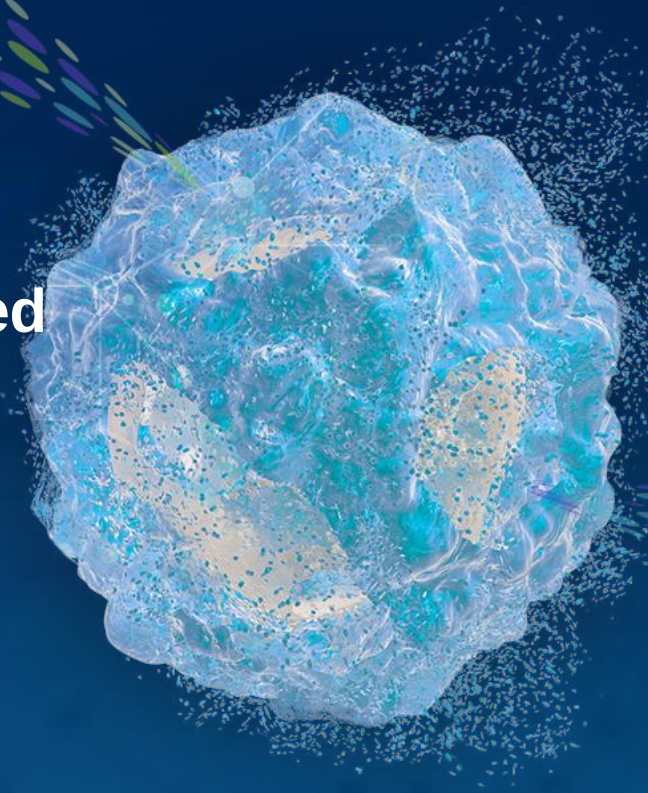
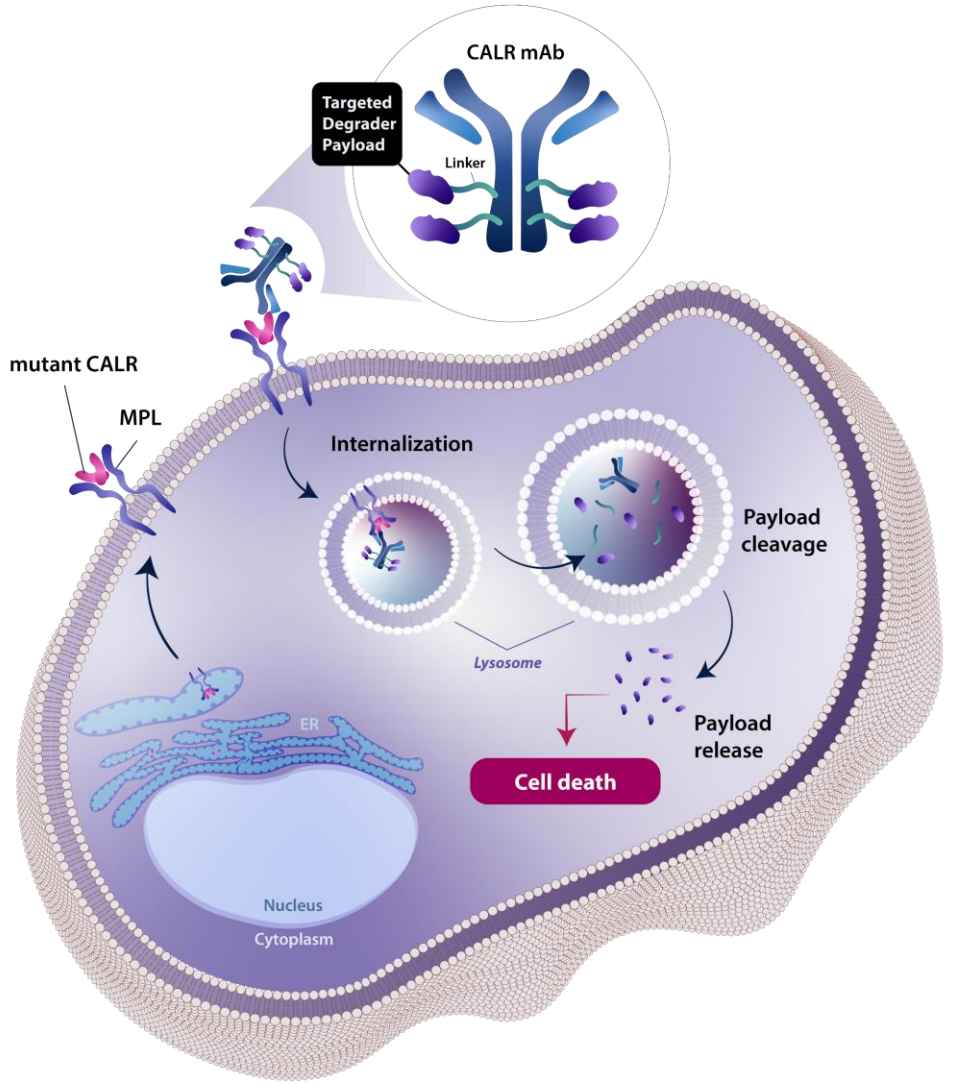


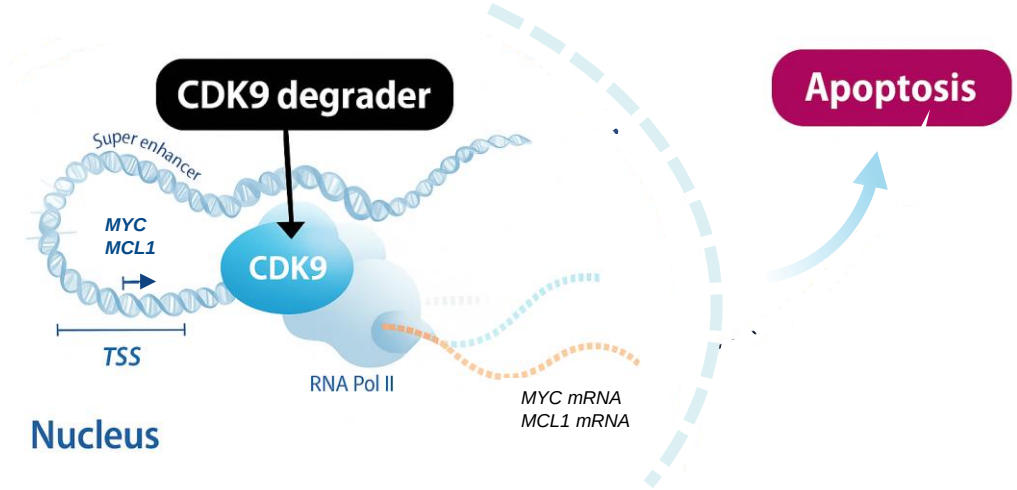
Mutated Calreticulin (mCALR) Represents a Promising ADC Target and Pathway to Potential Molecular Remission in Myeloproliferative Neoplasms (MPNs)

- Mutant CALR is a neoantigen presented on the 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
- Identification of therapeutic approaches that can selectively eliminate mutant CALR disease-initiating progenitors is an unmet medical need

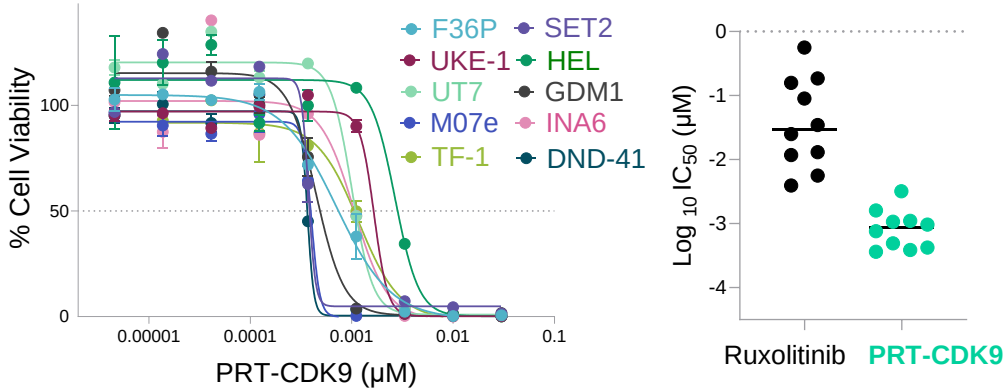


CDK9 is a Key Vulnerability in MPNs

- Aberrant activity of master transcription elongation factor, **CDK9**, contributes to malignant myeloproliferation in several myeloid neoplasms including AML, MDS and MPN. [1,2]
- CALR mutant MPNs exhibit transcriptional addiction making them vulnerable to CDK9-targeted degradation.[3]
- CDK9 drives MYC/MYB dependency in JAK2-WT / mCALR MPN. [4, 5, 6]
- CDK9 inhibition has the potential to demonstrate strong clinical efficacy in myeloid malignancies. [7]
- PRT-CDK9, a novel CDK9 degrader, demonstrates robust anti-proliferation in JAK/STAT-driven cell lines



CDK9 degradation is efficacious in JAK/STAT-driven lines

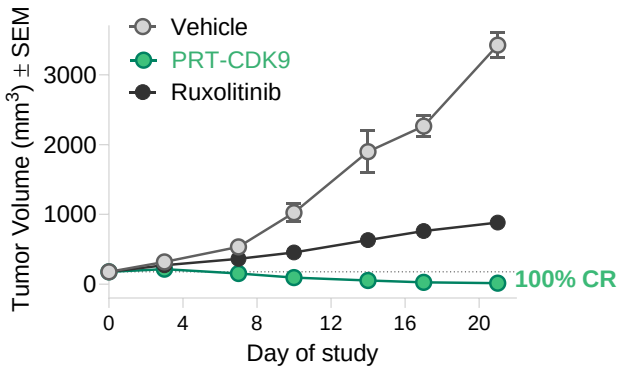


(1) Franco, L.C., 2018. *Journal of Cellular Biochemistry*, *119*(2), pp.1273-1284. (2) Fiskus, W., 2022. *Blood cancer journal*, *12*(1), p.23. (3) Pronier, E., 2018. *JCI insight*, *3*(22), p.e122703. (4) Bıçak, İ.U., 2023. *Turkish Journal of Hematology*, *40*(1), p.28. (5) Theophile, K 2008. Annals of Hematology, 87, pp.263-268. (6) Tapper 2015. Nature communications, 6(1), p.6691. (7) Sellas Life Sciences, 2025. *Press Release: July 15th*

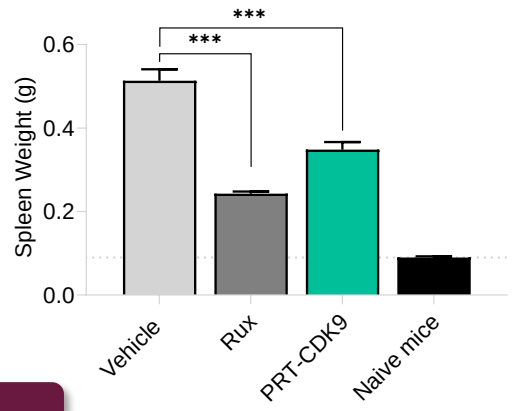
Prelude's CDK9 Degrader Payload (Unconjugated) Demonstrates Robust Efficacy in MPN Preclinical Models, Albeit With Limited Tolerability

Robust regression of tumor growth and splenomegaly

SET-2 (JAK2V617F)

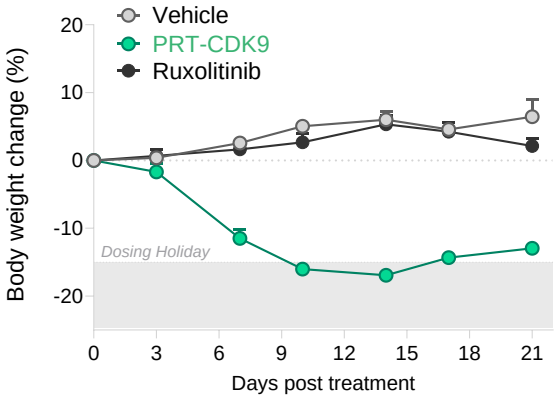


Ba/F3-MPL-CALR^{ins5}

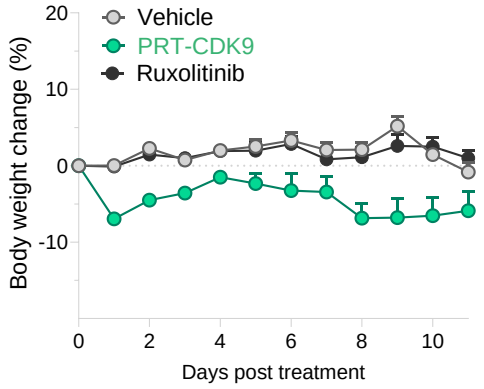


Limited tolerability

SET-2 (JAK2V617F)



Ba/F3-MPL-CALR^{ins5}

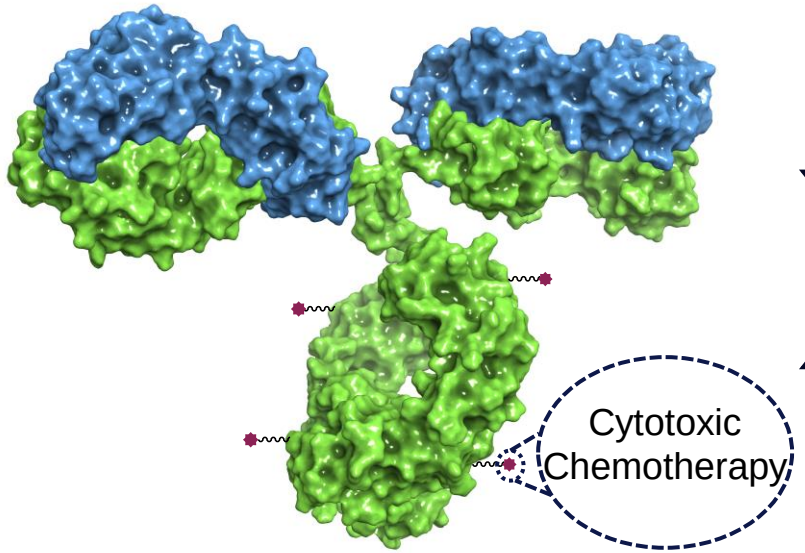


*** p<0.001 by Mann-Whitney test

- Prelude's CDK9 degrader achieves complete tumor regressions in JAK/STAT-driven xenograft models
- Significantly reduces splenomegaly in mCALR MPN models
- However, systemic CDK9 degradation has limited tolerability
- An ADC strategy is a promising approach for selectively targeting diseased progenitors

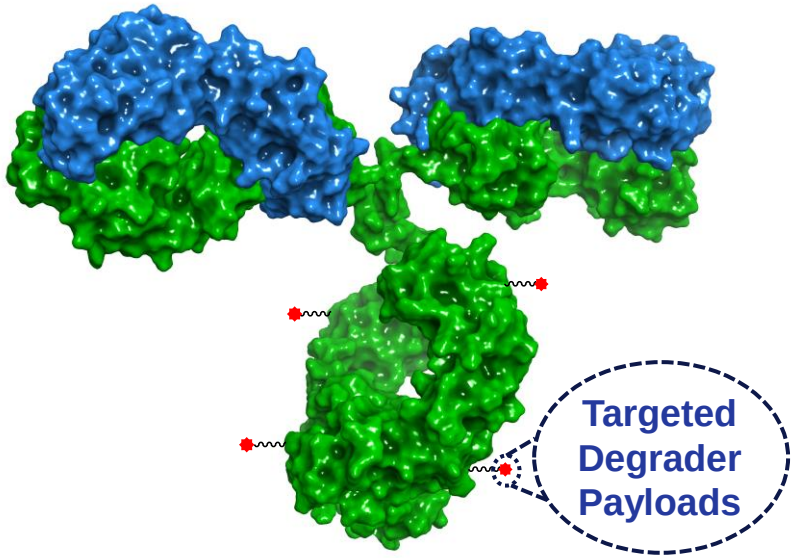
Degrader Antibody Conjugates (DACs) Represent The Next Generation of ADCs

Current ADCs



- Non-selective genotoxic payloads
- Resistance emerging to common cytotoxic payloads

DACs



- ✓ Dual targeting expands therapeutic index
  - Tumor-specific antigen, and
  - Targeted degradation of oncoprotein
- ✓ Overcomes cytotoxic payload resistance

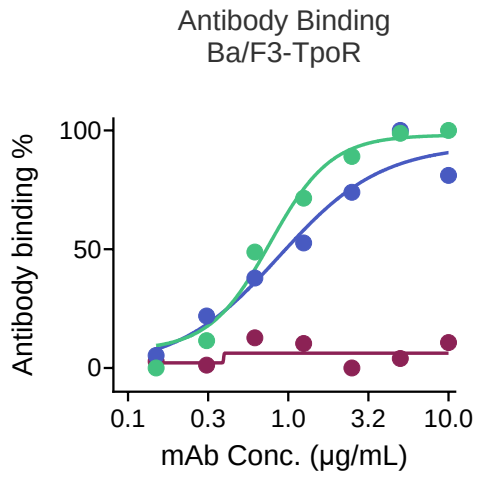
Reduced Toxicity and Resistance

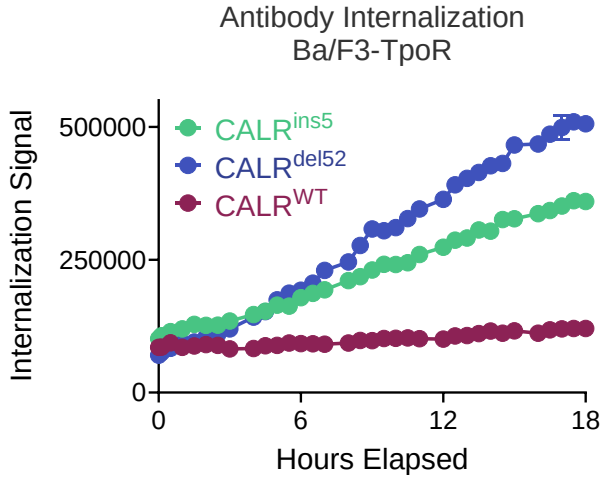
Improved Therapeutic Index

Improved Efficacy

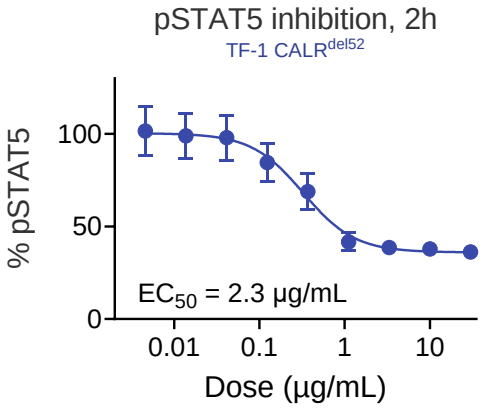
mCALR mAb Selectively Binds and Internalizes in CALR Mutant Cells But not WT

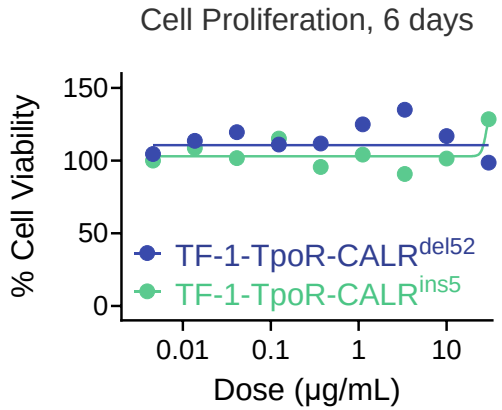
mCALR mAb selectively binds and internalizes in mutCALR cells but not WT





mCALR mAb modestly inhibits JAK/STAT signaling but not cell growth

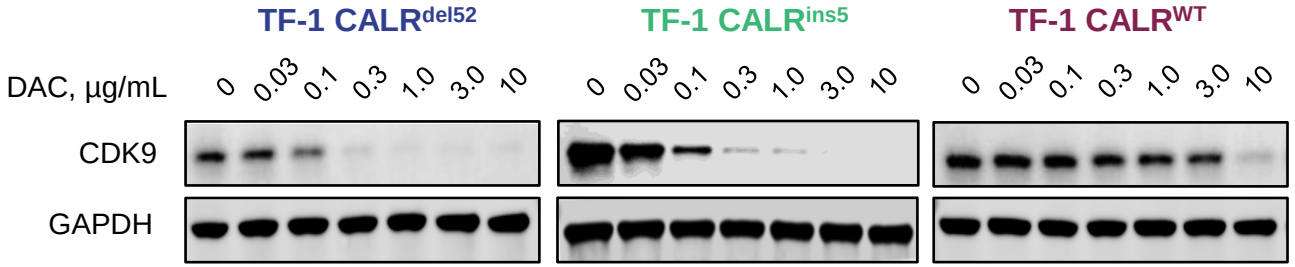




- mCALR mAb selectively binds and is internalized in CALR mutant Ba/F3 cells but not WT cells
- mCALR mAb demonstrates limited inhibition of JAK/STAT signaling at high doses (E_{max} 63%) but does not inhibit mutant cell growth

mCALR x CDK9d DACs Demonstrate Robust and Selective CDK9 Degradation and Cytotoxicity in mCALR Cells

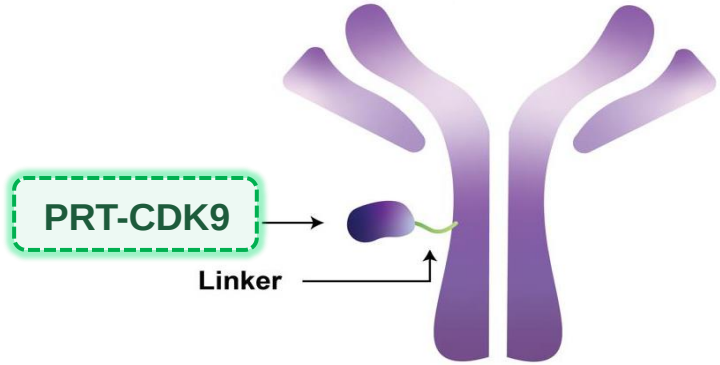
Selective CDK9 Degradation



107x *DC_{50} selectivity*

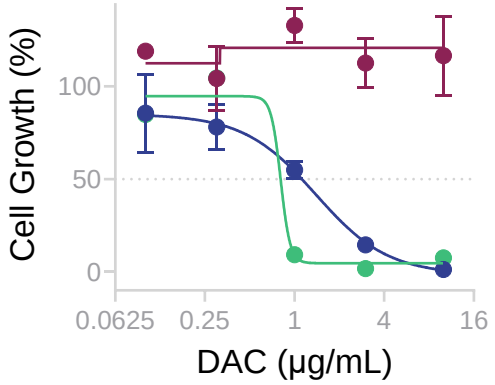
mCALR x CDK9d DAC

"mutCALR x CDK9-degrader Degrader Antibody Conjugate"

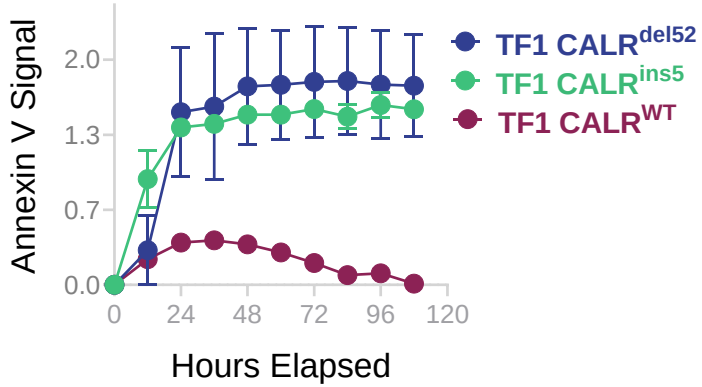


Mutant-selective Growth Inhibition and Apoptosis

Anti-proliferation, 5 days

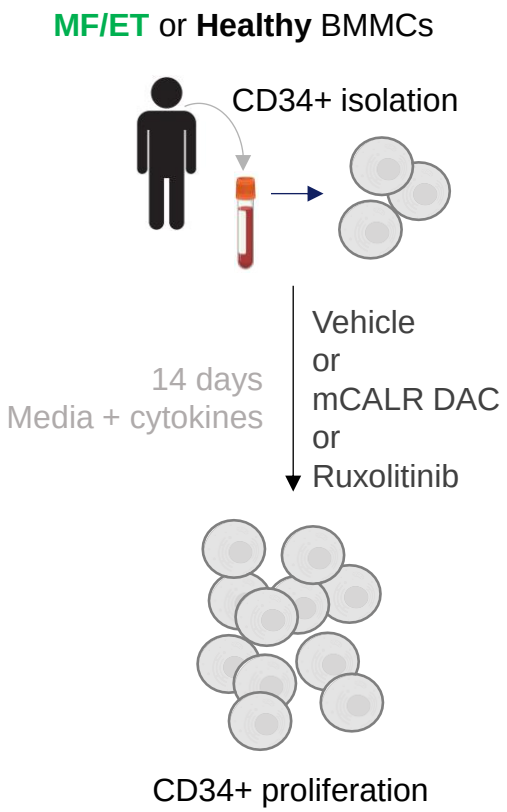


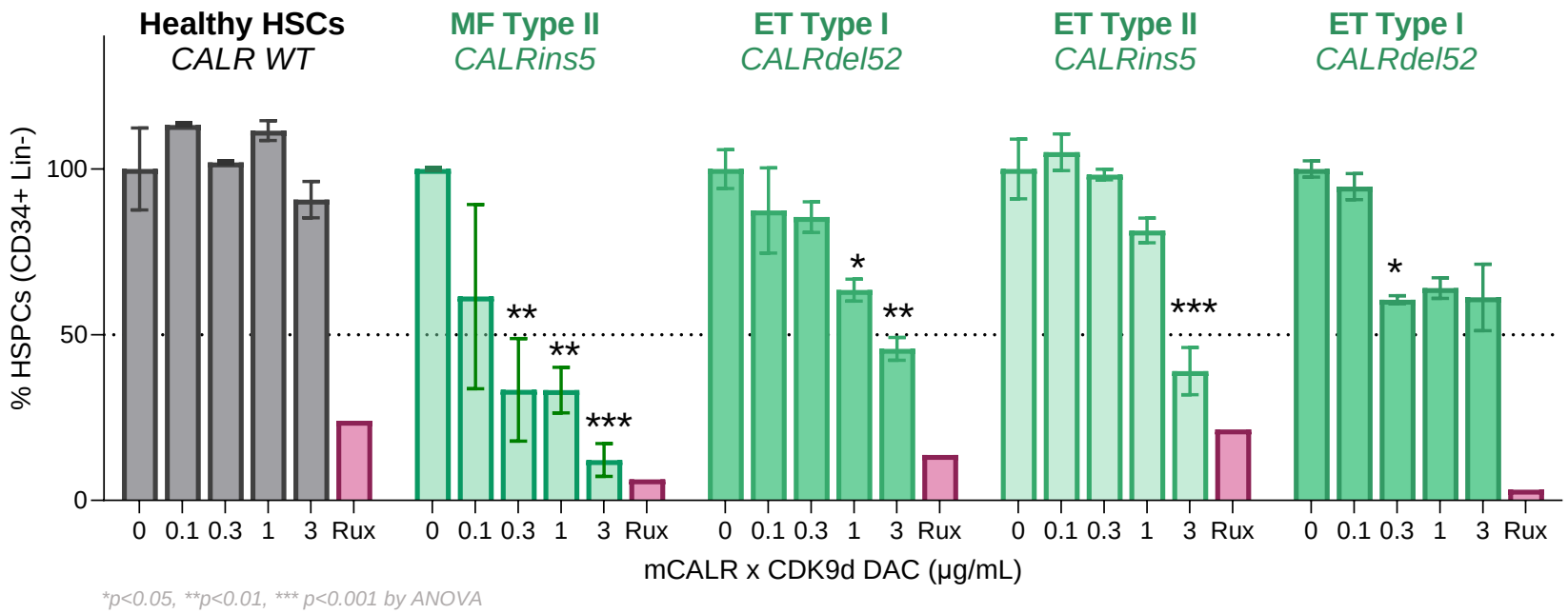
Apoptosis



mCALR x CDK9d DAC selectively degrades CDK9 in mCALR cells resulting in selective and equipotent killing of type I/II mutant cells

mCALR x CDK9d DACs Selectively Inhibit the Proliferation of mCALR Progenitors





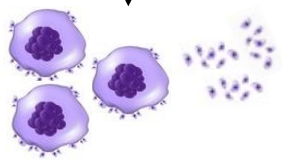
- mCALR x CDK9d DACs selectively inhibit CALR mutant HSC proliferation, sparing healthy HSCs
- Ruxolitinib non-selectively targets healthy and diseased progenitors alike

mCALR x CDK9d DACs Selectively Inhibit Mutant Megakaryopoiesis While Sparing Normal Megakaryopoiesis

Healthy or Myelofibrosis CD34+ HSCs

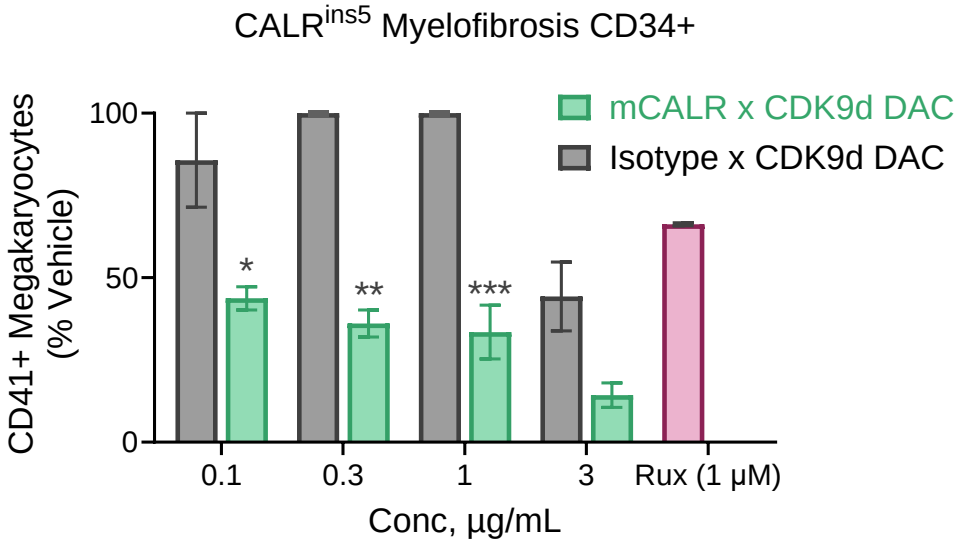
6-9 days SFEMII + Cytokines +/- *TPO*

mCALR DAC

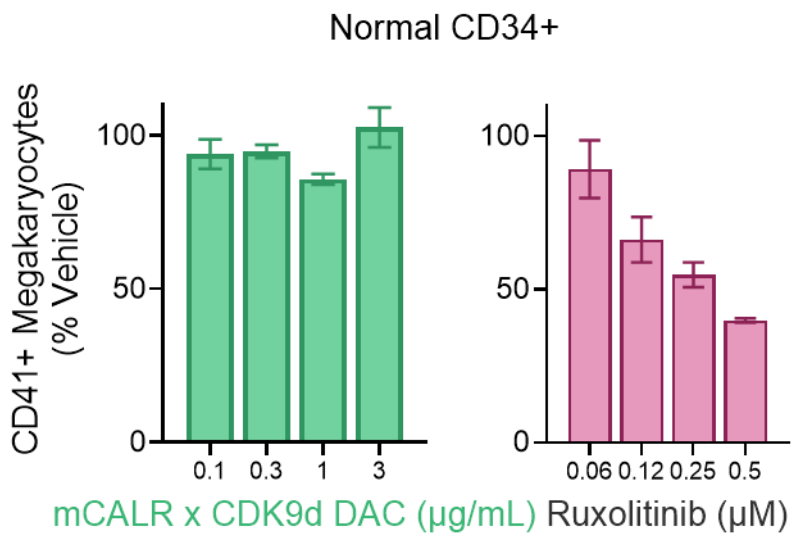


CD41+ CD42b+ megakaryocytes and platelets

Diseased megakaryocyte differentiation in mCALR HSCs



Normal megakaryocyte differentiation in healthy HSCs

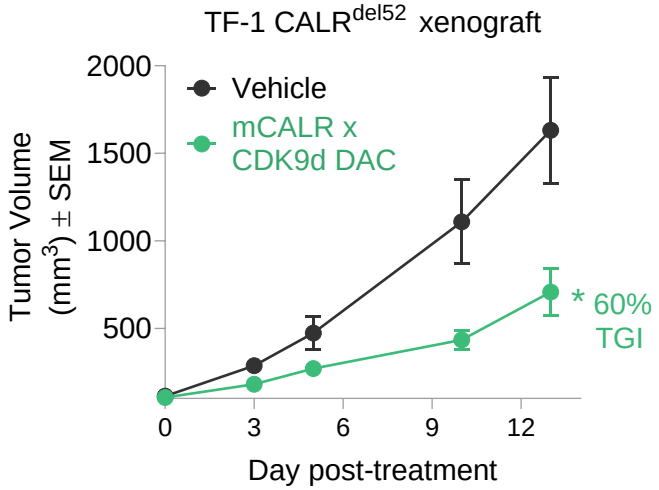


- mCALR x CDK9d DACs inhibit megakaryocyte proliferation and differentiation of CD34+ cells from CALR-mutant patients in a dose-dependent manner.
- Unlike JAK inhibitors, CALR DACs spare normal megakaryocyte differentiation, indicating potential for an improved therapeutic index

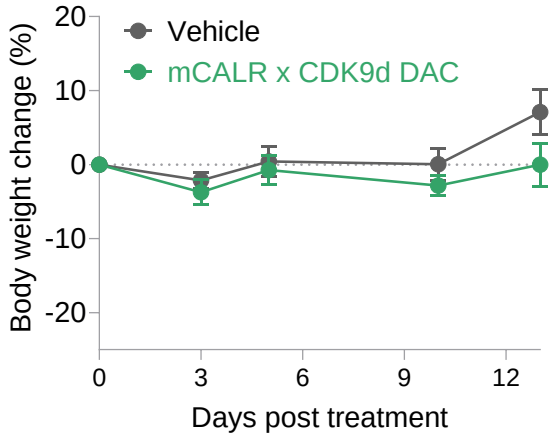
*P ≤0.05, ** ≤0.01, *** ≤0.001 by ANOVA

mCALR x CDK9d DACs Inhibit mCALR Tumor Growth In Vivo and Are Well-Tolerated

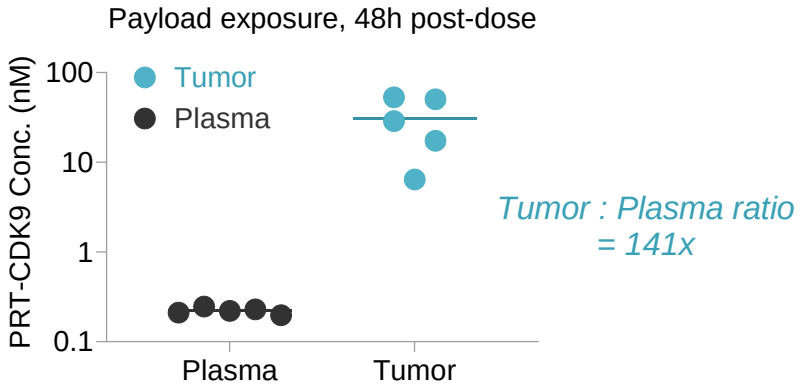
Robust tumor growth inhibition



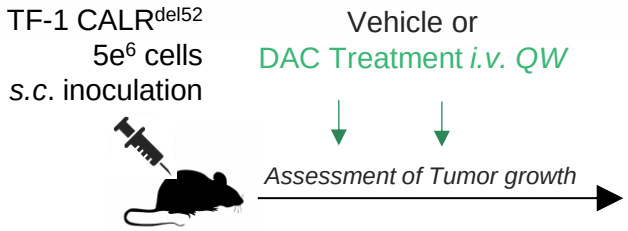
Well tolerated



Efficient payload delivery to mCALR tumors



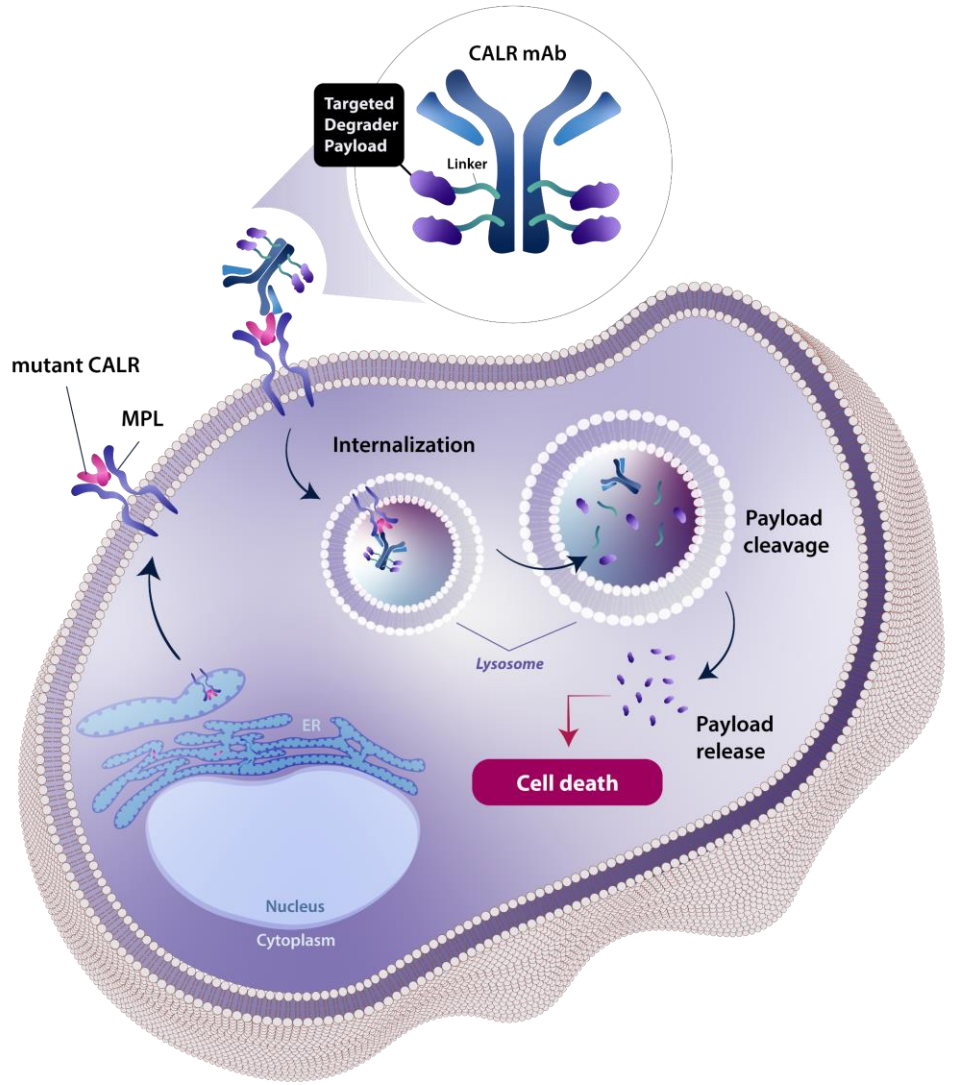
- mCALR × CDK9d DACs significantly inhibit TF-1 CALRdel52 xenograft growth *in vivo*
- Repeat dosing is well tolerated, with no signs of systemic toxicity, underscoring a favorable therapeutic index
- Efficient delivery of PRT-CDK9 to mCALR+ expressing tumors with minimal systemic release



** p<0.05 by Mann-Whitney test*

Summary: Prelude's mCALR DACs Represent a First-in-Class, Selective and Efficacious New Modality for Targeting CALR-Mutant Disease

- ✓ mCALR x CDK9d DAC delivers a CDK9 degrader selectively to the malignant clone
- ✓ Deep mutant-selective killing across cell lines, HSPCs, and primary cultures, highlighting disease-modifying potential
- ✓ mCALR DACs spare healthy hematopoietic cells, indicating a favorable therapeutic index
- ✓ Similar findings were recently highlighted with a SMARCA2/4-degrading mCALR DAC, demonstrating the broader potential of this modality across multiple payloads for selectively targeting CALR-mutant cells[1]
- ✓ Further optimization of payload potency and degrader-antibody-ratio (DAR) is underway



Fultang N., et al., EHA2025 Oral Abstract, 12 June 25; Discovery Of First-in-class Precision ADCs Targeting Mutant Calreticulin For The Treatment Of MPNs. (Link)