UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of The Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): May 12, 2026

Prelude Therapeutics Incorporated

(Exact Name of Registrant as Specified in its Charter)

Delaware	**001-39527**	**81-1384762**
(State or other jurisdiction of incorporation or organization)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

175 Innovation Boulevard **Wilmington, Delaware**	**19805**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (302) 467-1280

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	PRLD	Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 2.02 Results of Operations and Financial Condition.

On May 12, 2026, Prelude Therapeutics Incorporated (the "Company") issued a press release announcing its financial results for the three months ended March 31, 2026. A copy of the press release is attached as Exhibit 99.1 to this Current Report on Form 8-K.

Item 7.01 Regulation FD Disclosure.

The Company has prepared investor presentation materials with information about the Company, which it intends to use as part of investor presentations. A copy of the investor presentation materials to be used by management for presentations is attached as Exhibit 99.2 to this Current Report on Form 8-K and is incorporated herein by reference.

The information in this Current Report on Form 8-K and in Exhibits 99.1 and 99.2 attached hereto is being furnished, but shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended ("Exchange Act"), and is not incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Exchange Act, whether made before or after the date hereof, regardless of any general incorporation language in such filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit Number	Description
99.1	Press Release dated May 12, 2026
99.2	Presentation
104	Cover Page Interactive Data File (embedded within the Inline XBRL Document)

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

PRELUDE THERAPEUTICS INCORPORATED

Date: May 12, 2026

By: /s/ *Bryant Lim*
Bryant Lim
Chief Financial Officer and Chief Legal Officer

Prelude Therapeutics Reports First Quarter 2026 Financial Results and Provides Corporate Update

Initiated enrollment of Phase 1 Study of PRT12396, mutant-selective JAK2V617F inhibitor in patients with polycythemia vera (PV) and myelofibrosis (MF)

The Company expects to file the IND for PRT13722, first-in-class highly-selective oral KAT6A degrader, by mid-2026 with Phase 1 study initiation in ER+ breast cancer anticipated in the 2H 2026

Presented preclinical data demonstrating differentiated profile of PRT13722, at the American Association for Cancer Research (AACR) Annual Meeting 2026

Appointed Charles Morris, M.D. as Chief Medical Officer

Current cash runway expected into second quarter of 2028 based on preliminary estimates, driven by previously announced underwritten offering with gross proceeds of $90 million

WILMINGTON, Del., May 12, 2026 (GLOBE NEWSWIRE) – Prelude Therapeutics Incorporated (Nasdaq: PRLD), a clinical-stage precision oncology company, today reported its financial results for the first quarter ended March 31, 2026 and provided an update on its R&D pipeline and other corporate developments.

“Through this first quarter of 2026, our company has continued to demonstrate focused execution of the strategic priorities we set forth late last year.” stated Kris Vaddi, Ph.D., Chief Executive Officer of Prelude. “Since the beginning of this year, we’ve advanced PRT12396 into first-in-human studies, presented promising preclinical data from our highly selective KAT6A degrader development candidate, continued to progress towards a development candidate from our mCALR program and importantly, extended our cash runway into the second quarter of 2028.”

Program Updates and Upcoming Milestones

Mutant selective JAK2V617F JH2 inhibitor program
JAK2V617F is the primary driver mutation responsible for disease progression in the majority of patients living with myeloproliferative neoplasms (MPNs). The mutation impacts approximately 95% of patients with polycythemia vera (PV), 60% of patients with essential thrombocythemia (ET) and 55% of patients with myelofibrosis (MF). Identifying JAK2 JH2 inhibitors that selectively target V617F+ cells has long been the goal for advancing the treatment of MPNs.

Prelude has designed and identified novel allosteric inhibitors that bind into the JAK2 JH2 “deep pocket” where the V617F mutation resides. These candidates demonstrate mutant specific inhibition in multiple preclinical models of MPNs. Prelude believes this approach may have the potential to reduce mutant allele burden, slow or even reverse disease progression, and transform treatment outcomes for MPN patients.

PRT12396, Prelude’s lead, mutant-selective JAK2V617F inhibitor received IND clearance from the U.S. Food and Drug Administration, as previously announced in February 2026 and recently initiated and commenced enrollment into a Phase 1 study of PRT12396 in patients with PV and MF.

The JAK2V617F inhibitor program is subject to an exclusive option agreement with Incyte announced in November 2025.

Highly selective KAT6A oral degrader program
KAT6 is an emerging and recently validated target in the treatment of ER+ breast cancer. Prelude discovered and is developing first-in-class, highly potent, highly selective and orally bioavailable KAT6A selective degraders. The Company has selected a development candidate, PRT13722 and remains on track to file an IND application in mid-2026, and pending clearance, phase 1 study initiation expected in the 2nd half of 2026. Prelude believes that selectively degrading KAT6A has the potential for improved efficacy, tolerability and combinability with other agents relative to non-selective inhibitors of KAT6A/B.

The Company presented preclinical data supporting this hypothesis at the AACR Annual Meeting 2026. The presentation can be found at Publications - Prelude Therapeutics.

Degrader payloads for next generation DACs
Prelude is leveraging our expertise in targeted protein degradation to discover and develop novel degrader payloads for use with next generation DACs. We have developed highly potent SMARCA2/4 and CDK9 degrader payloads optimized for efficacy, tolerability and developability when coupled to a wide range of different antibodies. Building on our existing DAC partnership with AbCellera, the Company’s payloads and corresponding payload-linkers are available for licensing to additional partners to expand the reach of this new technology.

We have recently published preclinical data demonstrating that next generation DACs using Prelude degrader payloads have potential for significantly better *in vivo* efficacy and tolerability compared to traditional cytotoxic ADCs when tested head-to-head in xenograft models. These data can be found at: Publications – Prelude Therapeutics

Mutated calreticulin (mCALR) DAC discovery program
Mutant CALR is a neoantigen presented on the cell surface of malignant myeloid cells but not normal cells and is found in approximately 25-35% of patients with MF and essential thrombocythemia (ET). Recently, a mCALR-targeted monoclonal antibody demonstrated robust clinical activity in high-risk ET patients. Prelude is exploring mCALR-targeted DACs using the Company’s proprietary degrader payloads as a differentiated approach for patients with CALR mutations. This early discovery program is wholly owned and controlled by Prelude.

The Company presented the preclinical data from the program at the European Hematology Association 2025 Congress in June and the American Society of Hematology (ASH) 67th Annual Meeting in December 2025. The presentations can be found at Publications – Prelude Therapeutics.

Corporate Updates
In April 2026, the Company announced the appointment of Charles Morris, M.D. as Chief Medical Officer.

Upcoming Investor Conferences
The Company will participate in the 2026 Jefferies Global Healthcare Conference taking place in New York City. On Wednesday, June 3, 2026 at 12:15 PM ET, Kris Vaddi, Ph.D., Chief Executive Officer, Peggy Scherle, Ph.D., Chief Scientific Officer and Bryant Lim, Chief Financial Officer will participate in a fireside chat.

The Company will also participate in the Goldman Sachs 47th Annual Global Healthcare Conference taking place in Miami, FL. On Wednesday, June 10, 2026 at 11:20 AM ET, Kris Vaddi, Ph.D., Chief Executive Officer, Peggy Scherle, Ph.D., Chief Scientific Officer and Bryant Lim, Chief Financial Officer will participate in a fireside chat.

First Quarter 2026 Financial Results

Cash, Cash Equivalents, Restricted cash and Marketable securities:
Cash, cash equivalents, restricted cash and marketable securities as of March 31, 2026 were $84.8 million. Subsequent to March 31, 2026, the Company completed an underwritten offering with gross proceeds of approximately $90 million. Based on preliminary estimates, the Company anticipates that its existing cash, cash equivalents, restricted cash and marketable securities will fund Prelude's operations into the second quarter of 2028.

Research and Development (R&D) Expenses:
For the three months ended March 31, 2026, R&D expense decreased to $13.6 from $28.8 million for the prior year period. Included in the R&D expense for the three months ended March 31, 2026 was $1.1 million of non-cash expense related to stock-based compensation expense, including employee stock options, compared to $2.3 million for the three months ended March 31, 2025. Along with the decrease in stock-based compensation expense, the decrease was primarily related to lower expense incurred for our SMARCA2 clinical trials which we paused in 2025. Research and development expenses may fluctuate from period to period depending upon the stage of certain projects and the level of preclinical and clinical trial-related activities.

General and Administrative (G&A) Expenses:
For the three months ended March 31, 2026, G&A expenses decreased to $5.2 million from $5.8 million for the prior year period. Included in general and administrative expenses for the three

months ended March 31, 2026, was $0.9 million of non-cash expense related to stock-based compensation expense, including employee stock options, compared to $1.6 million for the three months ended March 31, 2025. The decrease in general and administrative expenses was primarily due to a decrease in stock-based compensation along with a decrease in employee-related expenses.

Net Loss:
For the three months ended March 31, 2026, net loss was $10.4 million, or $0.13 per share compared to $32.1 million, or $0.42 per share, for the prior year period. Included in the net loss for the three months ended March 31, 2026, was $2.0 million of non-cash expenses related to the impact of expensing share-based payments, including employee stock options due in part to fewer employees, as compared to $3.8 million for the same period in 2025.

About Prelude Therapeutics
Prelude Therapeutics is a leading precision oncology company developing innovative medicines in areas of high unmet need for cancer patients. Our pipeline features highly selective KAT6A degraders and JAK2V617F mutant selective inhibitors -- new approaches to clinically validated targets with transformative potential for patients. We are leveraging our expertise in targeted protein degradation to create and develop next generation degrader antibody conjugates (DACs) with novel payloads. We are on a mission to extend the promise of precision medicine to every cancer patient in need. For more information, visit preludetx.com.

Cautionary Note Regarding Forward-Looking Statements
This press release 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 clinical trial results for Prelude’s product candidates, and the sufficiency of Prelude’s cash runway into the second quarter of 2028. All statements other than statements of historical fact are statements that could be deemed forward-looking statements. The words “believes,” “anticipates,” “estimates,” “plans,” “expects,” “intends,” “may,” “could,” “should,” “potential,” “likely,” “projects,” “continue,” “will,” “schedule,” and “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements are predictions based on the Company’s current expectations and projections about future events and various assumptions. Although Prelude believes that the expectations reflected in such forward-looking statements are reasonable, Prelude cannot guarantee future events, results, actions, levels of activity, performance or achievements, and the timing and results of biotechnology development and potential regulatory approval is inherently uncertain. Forward-looking statements are subject to risks and uncertainties that may cause Prelude's actual activities or results to differ significantly from those expressed in any forward-looking statement, including risks and uncertainties related to Prelude's ability to advance its product candidates, the

receipt and timing of potential regulatory designations, approvals and commercialization of product candidates, clinical trial sites and our ability to enroll eligible patients, supply chain and manufacturing facilities, Prelude’s ability to maintain and recognize the benefits of certain designations received by product candidates, the timing and results of preclinical and clinical trials, Prelude's ability to fund development activities and achieve development goals, Prelude's ability to protect intellectual property, and other risks and uncertainties described under the heading "Risk Factors" in Prelude’s Annual Report on Form 10-K for the year ended December 31, 2025, its Quarterly Reports on Form 10-Q and other documents that Prelude files from time to time with the Securities and Exchange Commission. These forward-looking statements speak only as of the date of this press release, and Prelude undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date hereof, except as may be required by law.

PRELUDE THERAPEUTICS INCORPORATED

STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

(UNAUDITED)

(in thousands, except share and per share data)	Three Months Ended March 31, 2026	2025
Revenue	$ 4,580	$ —
Operating expenses		
Research and development	13,601	28,816
General and administrative	5,156	5,790
Total operating expenses	18,757	34,606
Loss from operations	(14,177)	(34,606)
Other income, net	3,792	2,521
Net loss	$ (10,385)	$ (32,085)
Per share information:		
Net loss per share of common stock, basic and diluted	$ (0.13)	$ (0.42)
Weighted average common shares outstanding, basic and diluted	82,519,981	75,986,281
Comprehensive loss:		
Net loss	$ (10,385)	$ (32,085)
Unrealized loss on marketable securities, net of tax	(49)	(23)
Comprehensive loss	$ (10,434)	$ (32,108)

BALANCE SHEETS

(in thousands, except share data)	March 31, 2026	December 31, 2025
Assets	(unaudited)	
Current assets:		
Cash and cash equivalents	$ 21,756	$ 35,256
Marketable securities	59,798	67,958
Prepaid expenses and other current assets	3,039	2,478
Total current assets	84,593	105,692
Restricted cash	3,235	3,235
Property and equipment, net	4,722	5,113
Right-of-use asset	26,778	27,165
Prepaid expenses and other non-current assets	314	110
Total assets	$ 119,642	$ 141,315
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 2,069	$ 3,983
Accrued expenses and other current liabilities	5,938	12,533
Deferred revenue	30,952	33,734
Operating lease liability	2,761	2,744
Total current liabilities	41,720	52,994
Deferred revenue, net of current portion	—	1,798
Other liabilities	2,779	2,841
Operating lease liability	14,960	15,045
Total liabilities	59,459	72,678
Commitments (Note 8)		
Stockholders' equity:		
Voting common stock, $0.0001 par value: 487,149,741 shares authorized; 48,290,087 and 48,225,493 shares issued and outstanding at March 31, 2026 and December 31, 2025, respectively	5	5
Non-voting common stock, $0.0001 par value: 112,850,259 shares authorized; 14,728,135 shares issued and outstanding at both March 31, 2026 and December 31, 2025	1	1
Additional paid-in capital	753,664	751,684
Accumulated other comprehensive (loss) income	(41)	8
Accumulated deficit	(693,446)	(683,061)
Total stockholders' equity	60,183	68,637
Total liabilities and stockholders' equity	$ 119,642	$ 141,315

Investor Contact:
Robert A. Doody, Jr.
Senior Vice President, Investor Relations
Prelude Therapeutics Incorporated
484.639.7235
rdoody@preludetx.com

Exhibit 99.2

Corporate Presentation

May 2026

Forward Looking Statements & Disclaimers

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 and milestones, the potential safety, efficacy, benefits and addressable market for Prelude Therapeutic Incorporated's (the "Company") product candidates.

Any statements contained herein or provided orally that are not statements of historical fact may be deemed to be forward-looking statements. In some cases, you can identify forward-looking statements by such terminology as ‘‘believe,’’ ‘‘may,’’ ‘‘will,’’ ‘‘potentially,’’ ‘‘estimate,’’ ‘‘continue,’’ ‘‘anticipate,’’ “aim,” ‘‘intend,’’ ‘‘could,’’ ‘‘would,’’ ‘‘project,’’ ‘‘plan,’’ ‘‘expect’’ and similar expressions that convey uncertainty of future events or outcomes, although not all forward-looking statements contain these words. Statements, including forward-looking statements, speak only to the date they are provided (unless an earlier date is indicated).

These forward-looking statements are based on the beliefs of our management as well as assumptions made by and information currently available to us. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. If such assumptions do not fully materialize or prove incorrect, the events or circumstances referred to in the forward-looking statements may not occur. We undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation to conform these statements to actual results or to changes in our expectations, except as required by law. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements. Additional risks and uncertainties that could affect our business are included under the caption “Risk Factors” in our filings with the Securities and Exchange Commission, including our Annual Report on Form 10-K for the year ended December 31, 2025.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to product growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

This presentation concerns drugs that are under clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration (the "FDA"). They are currently limited by Federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated.

Prelude THERAPEUTICS

Experienced Leadership Team With Proven Track Record

Kris Vaddi, PhD

Chief Executive Officer

Charles Morris, MD

Chief Medical Officer

Peggy Scherle, PhD

Chief Scientific Officer

Andrew Combs, PhD

Chief Chemistry Officer

Sean Brusky, MBA

Chief Business & Strategy Officer

Bryant Lim, J.D.

Chief Financial Officer, Chief Legal Officer, Secretary

Prelude's Pipeline & Discovery Engine

PROGRAM	POTENTIAL INDICATIONS	DISCOVERY	IND-ENABLING	PHASE 1	PROGRAM INTEREST	ANTICIPATED MILESTONES
JAK2V617F Mutant Selective JH2 Inhibitors	VF+ myeloproliferative neoplasms (MPNs) (MF, PV, ET)		PRT12396		Incyte [1]	Phase 1 now enrolling
KAT6A Selective Degraders	ER+ breast cancer, other malignancies		PRT13722		Prelude wholly owned	IND filing mid-2026
mCALR DAC	CALR-mutated MPNs (ET, MF)				Prelude wholly owned	Oral abstract presented at ASH 2025
Degrader Payloads for DACs	Broad utility across multiple indications		*Proprietary degrader payloads available for licensing to partners developing next generation DACs*		AbCellera [2] . . .	Additional Partnerships

JAK2, janus kinase 2; JH2, JAK2 homology domain 2 (pseudokinase regulatory domain); VF+, V617F mutated; MPNs, myeloproliferative neoplasms; MF, myelofibrosis; PV, polycythemia vera; ET, essential thrombocythemia; ER+, estrogen receptor positive; DAC, degrader antibody conjugate; mCALR = mutated calreticulin
1 - Exclusive option agreement with Incyte (Nov. 2025)
2 - DAC Discovery Collaboration with AbCellera (Nov. 2023, amended and expanded 2H 2025)

Our Investment Thesis Centers on Advancing Highly Differentiated Approaches to Clinically Validated Targets

JAK2V617F (PRT12396)

Mutant Selective Inhibitors

Potentially transformative JAK2V617F allosteric JH2 inhibitor with potential to reduce mutant allele burden and modify the course of disease progression in patients with myeloproliferative neoplasms (MPNs)

KAT6A (PRT13722)

Highly Selective Oral Degrader

Potentially first-in-class KAT6A degrader with absolute selectivity over KAT6B – a differentiated modality and profile with potential to become a backbone therapy in the treatment of ER+ breast cancer

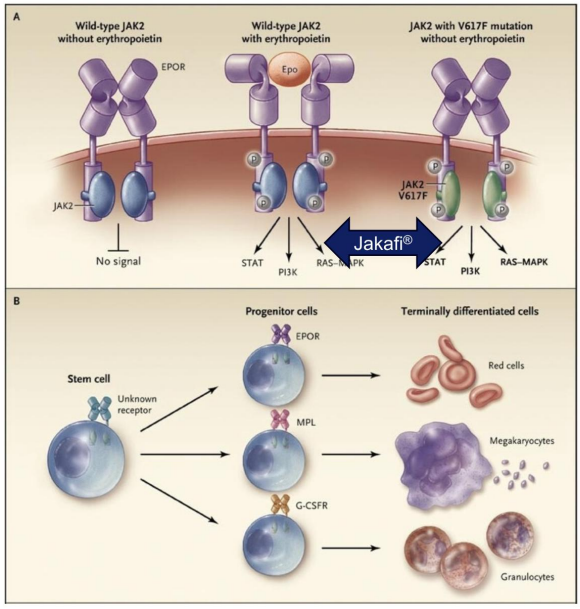
mCALR DAC

Next Generation Precision DAC

Potentially first-in-class mutated Calreticulin (mCALR) DAC (Degrader Antibody Conjugate) that is equipotent on all CALR mutations and >100x more potent compared to current lead clinical stage CALR antibody

JAK2V617F is the Primary Driver Mutation Leading to Activated JAK-STAT Signaling, Uncontrolled Proliferation, and Disease Progression in MPNs

- The JAK-STAT pathway mediates growth factor signaling, most notably:
  - Thrombopoietin receptor for platelet production
  - Erythropoietin receptor for red blood cell production
- The JAK2V617F mutation leads to **growth factor-independent hyperactivation of JAK-STAT pathway** and uncontrolled myeloid and erythroid proliferation
- Currently approved JAK inhibitors, like ruxolitinib (Jakafi®), while effective, equally inhibit both WT and V617F-mutated (VF+) JAK2, leading to dose limiting thrombocytopenia and anemia and do not alter disease progression
- JAK2V617F selective inhibitors target VF+ progenitor cells while sparing normal bone marrow function and offer the potential for disease modification and to transform treatment outcomes for MPN patients

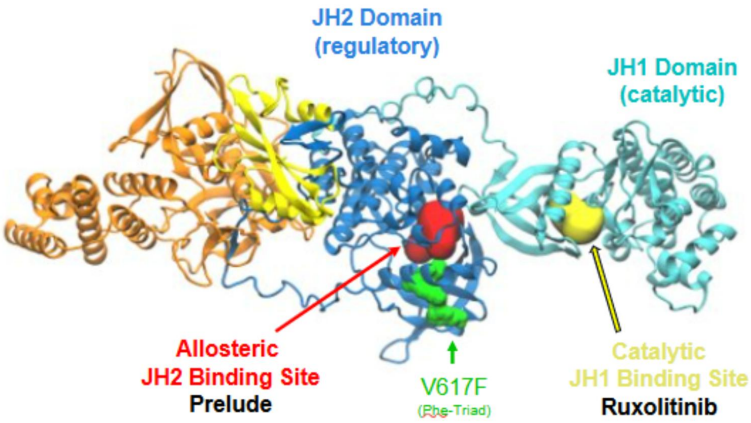


Campbell P.J. and Green A.R. N Engl J Med 2006;355:2452-2466

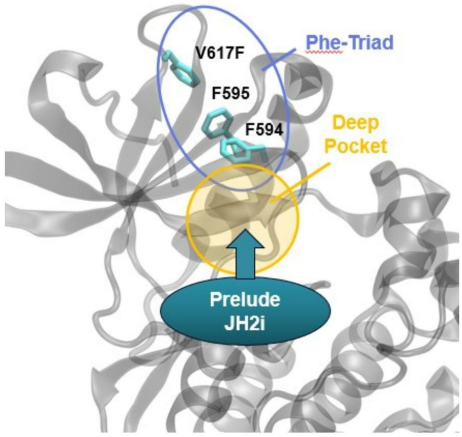
Jakafi® is a registered trademark of Incyte Corporation

Prelude Scientists Recently Discovered the First Known JAK2 Inhibitors that Bind in the JAK2 JH2 "Deep Pocket" Where the V617F Mutation Resides

Allosteric JH2 Regulatory Domain vs JH1 Catalytic Domain

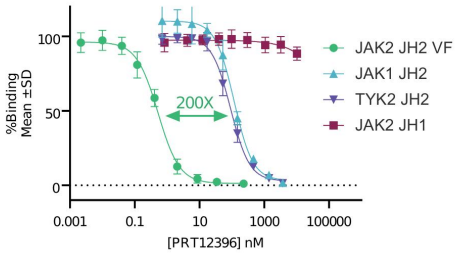


Prelude JAK2 JH2 Inhibitors Bind into the "Deep Pocket" Adjacent to V617F Mutation

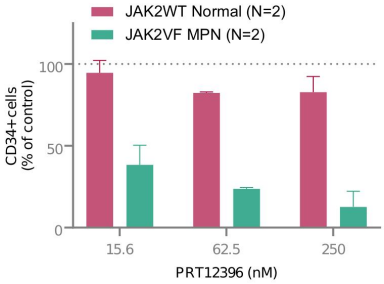


PRT12396 is a JAK2V617F Mutant Selective JH2 Inhibitor with Disease Modifying Potential in MPNs

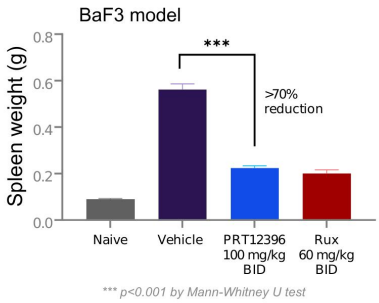
Isoform selectivity over JAK1/TYK2



Selective inhibition mutant cells in vitro



Efficacy in MPN models in vivo



**** p<0.001 by Mann-Whitney U test*

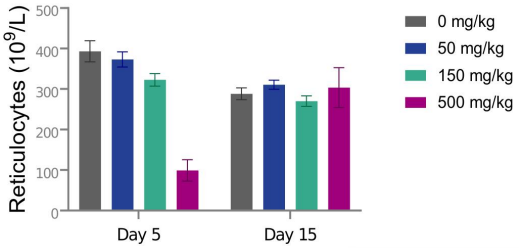
- >200X selectivity over JAK1 and TYK2 and clean profile in KinomeSCAN™ panel of >450 kinases
- Selective anti-proliferative effects in JAK2VF MPN cells with minimal impact on JAK2WT cells
- Significant reduction in splenomegaly and normalization of pathogenic cytokines in vivo, equivalent to or better than ruxolitinib in MPN models at well-tolerated doses

ASH Annual Meeting 2025 oral presentation (access here)

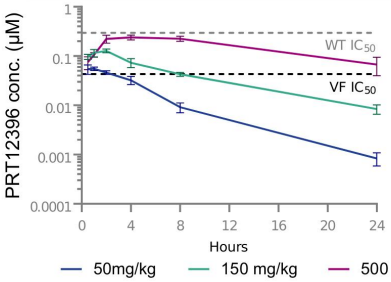
PRT12396 Demonstrates ~10X Therapeutic Window In Vivo – Potential to Overcome the Limitations of First Generation JAK2 Inhibitors

- No evidence of WT JAK2 inhibition in 2-week rat toxicology study at low and mid doses that provide efficacious exposures
  - Reduction in neutrophils and reticulocytes observed *only at high dose*, consistent with plasma exposure approaching WT JAK2 IC_{50}
- AUC exposures required for efficacy are *10X lower* than those associated with bone marrow suppression (reticulocyte inhibition)

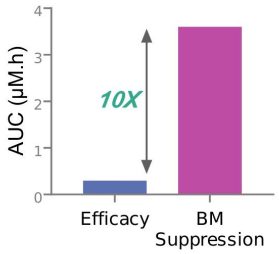
Reticulocyte Inhibition Only at High Dose, with Full Recovery by Day 15



Plasma Exposures at Low/Mid Doses Remain Below WT JAK2 IC_{50}



Efficacy AUC is 10X Lower Than Toxicity AUC



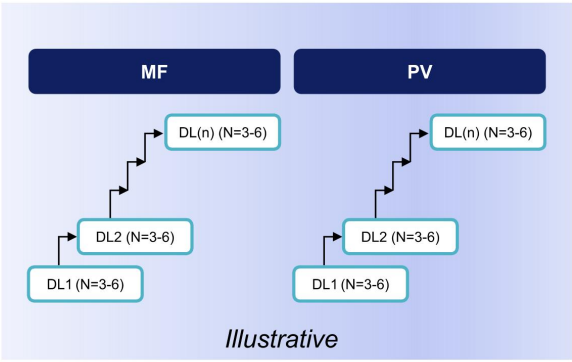
Dotted lines represent proliferation IC_{50} values from SET2 (VF) and UT-7 (WT) 7-day proliferation assay

ASH Annual Meeting 2025 oral presentation (access here)

PRT12396 – Phase 1 Study in MF and PV Cohorts in Parallel – Now Enrolling

IND Cleared in January 2026

Phase 1a Dose Escalation



Expansion Cohorts

Expansion in MF & PV at Dose

OBJECTIVE

- CHR rate, durability (24 week) and molecular response rate (allele burden reduction)
- Spleen and symptom benefit
- Data generation in preparation for first registrational trial(s)

First Look at Spleen/Symptoms/CHR
Mutant Allele Burden

MPNs, myeloproliferative neoplasms; MF, myelofibrosis; PV, high risk polycythemia vera; CHR, complete hematologic response; DL, dose level

Option Agreement With Incyte Provides Significant Capital to Further Advance Our JAK2V617F and KAT6A Programs

Prelude Therapeutics Announces Exclusive Option Agreement with Incyte to Advance Mutant Selective JAK2V617F JH2 Inhibitors

Incyte secures an exclusive option to acquire Prelude's mutant selective JAK2V617F JH2 inhibitor program

Mutant selective JAK2V617F JH2 inhibitors have disease-modifying potential in treating patients living with myeloproliferative neoplasms (MPNs)

Prelude to receive a $35 million upfront payment and $25 million strategic equity investment at closing, $100 million if Incyte were to exercise the option to acquire the program, and up to $775 million in additional potential milestones plus royalties on net sales

Prelude will continue to develop all JAK2V617F program assets during the option period; if optioned, Incyte would lead development and commercialization globally

Exclusive option agreement with Incyte (announced November 2025)

Our Investment Thesis Centers on Advancing Highly Differentiated Approaches to Clinically Validated Targets

JAK2V617F (PRT12396)

Mutant Selective Inhibitors

Potentially transformative JAK2V617F allosteric JH2 inhibitor with potential to reduce mutant allele burden and modify the course of disease progression in patients with myeloproliferative neoplasms (MPNs)

KAT6A (PRT13722)

Highly Selective Oral Degrader

Potentially first-in-class KAT6A degrader with absolute selectivity over KAT6B – a differentiated modality and profile with potential to become a backbone therapy in the treatment of ER+ breast cancer

mCALR DAC

Next Generation Precision DAC

Potentially first-in-class mutated Calreticulin (mCALR) DAC (Degrader Antibody Conjugate) that is equipotent on all CALR mutations and >100x more potent compared to current lead clinical stage CALR antibody

Selective KAT6A Degradation Could Represent a Differentiated Approach Versus KAT6A/B/(7) Inhibition With Potential for Broader Application

	2L/3L+ ER+/HER2- mBC	1L ER+/HER2- mBC	Early-stage ER+ BC (adjuvant, neo-adjuvant)
Current SoC[1]	• ET +/- CDK4/6 inhibitors • ADCs, Targeted Tx	• ET +/- CDK4/6 inhibitors • ET + PI3Kα inhibitors +/- CDK4/6i (*PIK3CAm*)	• ET +/- CDK4/6 inhibitors
Future SoC[2]	Oral SERDs, CDK2/4 inhibitors, pan-mutant PI3Kα inhibitors, ADCs, and other targeted therapies in development		
KAT6A/B/(7) Inhibitors	Pfizer, BeOne, Olema, Ideaya, Menarini, Others	• Monotherapy efficacy reported to date with KAT6A/B inhibitors (11% ORR) • KAT6B-mediated neutropenia may limit combinability with SoC agents used in the frontline and early-stage settings (*e.g.*, CDK4/6i, PI3Kαi, etc.)	
KAT6A Selective Degrader	Prelude THERAPEUTICS	• Only KAT6A degrader nearing the clinic • Potential for best-in-class monotherapy and combination efficacy • KAT6A selectivity may lower neutropenia and enable broad combinability	

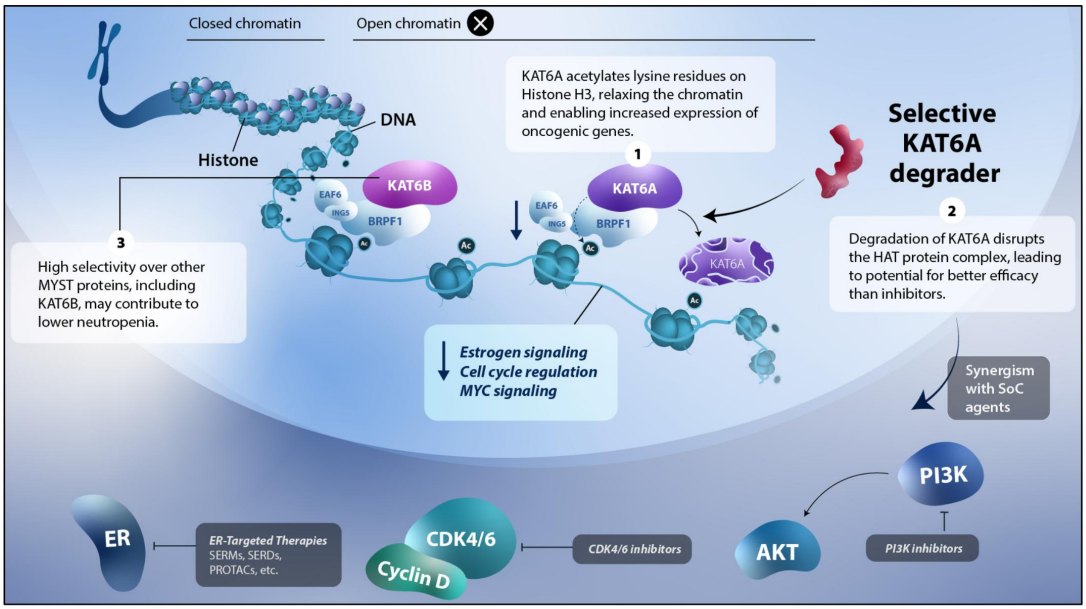
1 - NCCN Treatment Guidelines for Invasive Metastatic and Early Stage Breast Cancer (v5.2025); 2 - clinicaltrials.gov, investor presentations (multiple)
ET: Endocrine Therapy, inclusive of SERMs (e.g., tamoxifen), SERDs (e.g., fulvestrant), and aromatase inhibitors (e.g., letrozole, anastrozole, exemestane)

Prelude's First-In-Class Oral KAT6A Selective Degraders

- KAT6 is a clinically validated mechanism in ER+ breast cancer
  - A KAT6A/B dual inhibitor, prifetrastat is now in pivotal phase 3 trials in combination with fulvestrant, after progression on a CDK4/6 inhibitor[1]
  - Demonstrated compelling efficacy in post CDK4/6 inhibitor setting in a broad population of ER+ BC[1]
  - Clinically relevant safety observations including dysgeusia and grade 3/4 neutropenia are challenging and may limit dosing to maximal benefit in combination with SoC treatments (*e.g.,* CDK4/6 inhibitors)[1]
- Our KAT6A program aims to demonstrate a superior clinical profile
  - Optimal efficacy
  - Lower hematological toxicity
  - Improved combinability profile with other agents (*e.g.,* oral SERDs, AIs, CDK4/6is, PI3Kαis)
- ER+ breast cancer treatment market is projected to reach $42B by 2033[2]
  - Most common type of breast cancer, representing 70% of all cases

1 - P LoRusso, et. al,, Dose optimization of PF-07248144, a first-in-class KAT6 inhibitor, in patients (pts) with ER+/HER2− metastatic breast cancer (mBC): Results from phase 1 study to support the recommended phase 3 dose (RP3D) ASCO 2025 Annual Meeting, J *Clin Oncol* **43**, 1020(2025)
2 - Vision Research Reports; "Estrogen Receptor Positive Breast Cancer Treatment Market Forecast 2024-2033. ER+ Breast Cancer Treatment Market Size | Companies

KAT6A: An Emerging Target in the Treatment of ER+/HER2- Breast Cancer



- *KAT6* is a histone acetyltransferase that epigenetically regulates chromatin accessibility[1-2]
- The *KAT6A* complex regulates estrogenic, cell cycle, MYC, and other oncogenic pathways[1-2]
- *KAT6A* and *KAT6B* are mutually exclusive paralogs, with KAT6A being the primary driver of oncogenesis[1-2]
- *KAT6A* (8p11) is frequently amplified in breast, lung, and other cancers[1-2]

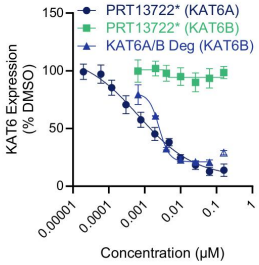
1 - White J, et al. Histone lysine acetyltransferase inhibitors: an emerging class of drugs for cancer therapy. Trends Pharmacol Sci 45 (3): 243-254 (2024).

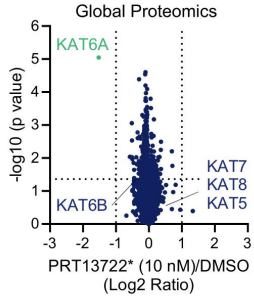
2 - Sharma S, et al. Discovery of a highly potent, selective, orally bioavailable inhibitor of KAT6A/B histone acetyltransferases with efficacy against KAT6A-high ER+ breast cancer. Cell Chem Biol 30 (10):1191-1210 (2023).

PRT13722: Our KAT6A Selective Degrader Development Candidate

- Absolute selectivity for KAT6A over KAT6B (>1000-fold) based on both degrader kinetics and proteomics
- Excellent oral PK across species enabling once-daily oral dosing
- Compelling *in vivo* efficacy as monotherapy in ER+ BC models, both KAT6A amplified/non-amplified
- Compelling *in vivo* efficacy in combo with SoC ET, CDK4/6, PI3Kα agents
- Reduced effect on neutrophils in multiple preclinical models
- IND filing on track for mid-2026

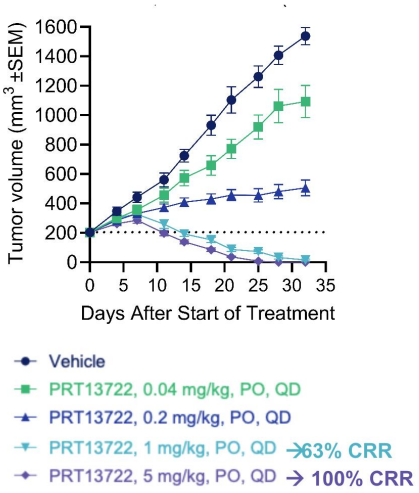
Absolute Degradation Selectivity (KAT6A vs KAT6B) *In Vitro*[1]





Compelling Monotherapy Efficacy Including Complete Regressions *In Vivo*[1]

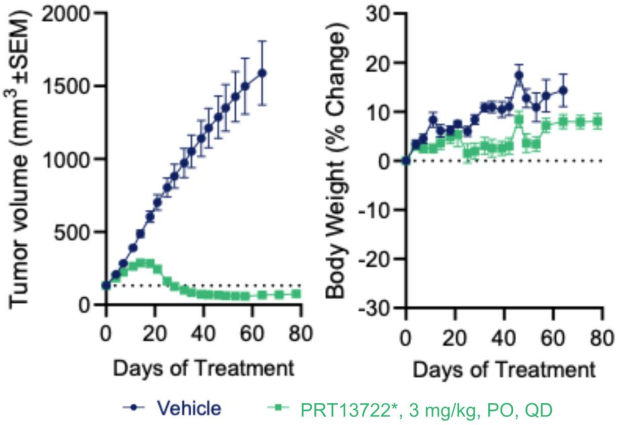
KAT6A Amplified ER+/HER2- Breast Cancer CDX Model (ZR-75-1) Dosed with PRT13722*



1 - AACR 2026 poster presentation (access here); CRR = Complete Response Rate;
**When denoted with an asterisk, PRT13722* indicates data shown is with the racemic mixture of PRT13722.*

PRT13722 Monotherapy Drives Durable Tumor Regressions in the More Challenging T47-D Model with Improved Efficacy Over prifetrastat + fulvestrant in Combination

Durable Tumor Regressions Observed at Low Doses (Tumors Below Baseline >2.5 months)[1]



Better Efficacy as Monotherapy vs. prifetrastat + fulvestrant in Combination[1]

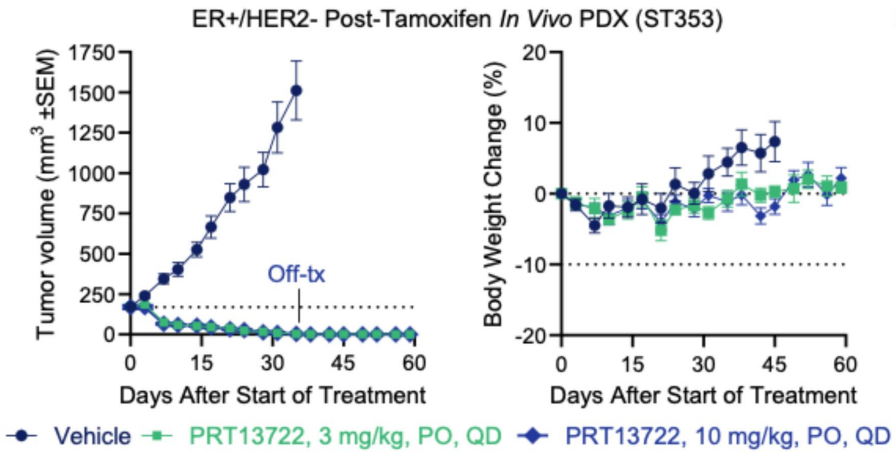
Class	Treatment	% Tumors Regressed
Mono-Tx	prifetrastat, 1 mg/kg	0%
	PRT13722, 1 mg/kg	50%
	PRT13722*, 3 mg/kg	75%
+ ET	prifetrastat, 1 mg/kg + fulvestrant	13%
	PRT13722, 1 mg/kg + fulvestrant	88%

Fulvestrant (25 mg/kg, SC, QW+LD)

- Well-tolerated over treatment duration of 80 days with no observed body weight loss in animals
- PRT13722 compared to prifetrastat with >50-fold lower AUC at efficacious doses

AACR 2026 poster presentation (access here)
1 - Mice harboring T47-D xenografts were treated with the racemic mixture of PRT13722*; effects on tumor growth are shown.

PRT13722 Monotherapy Eradicates Tumors in Post-Tamoxifen Patient-Derived Xenografts (PDX)



PRT13722 Achieved Complete Responses in ST353 PDX Model

Treatment	Mouse % CRR
PRT13722 3 mg/kg, PO, QD	100% (8/8)
PRT13722 10 mg/kg, PO, QD	100% (8/8)

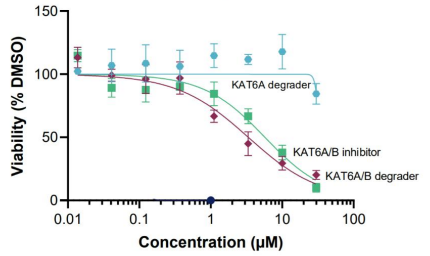
Tumors at endpoint;
CRR = complete response rate (no detectable tumor)

- PRT13722 achieved 100% complete response as a monotherapy in ER+/HER2- xenografts derived from a patient with recurrent disease following treatment with chemotherapy and tamoxifen
- Responses persisted following cessation of treatment
- No significant body weight loss observed in animals at either dose level

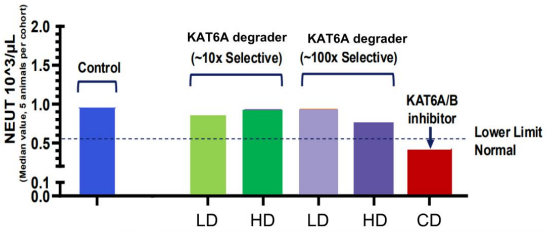
AACR 2026 poster presentation (access here); Off-tx indicates treatment cessation

PRT13722 Demonstrates Potential for Lower Bone Marrow Toxicity in Preclinical Models Compared to KAT6A/B Dual Inhibitors

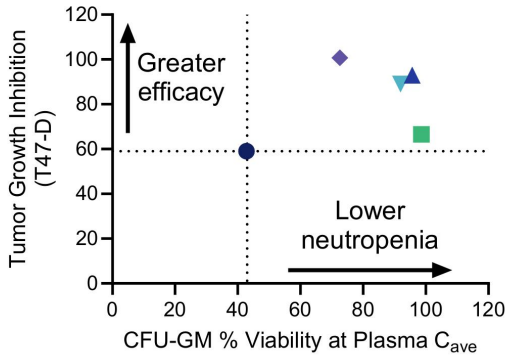
Ex Vivo Dose Response of CFU-GM



In Vivo Neutrophil Assessment (Day 5)



Plot of *In Vivo* Efficacy vs. Impact on CFU-GM Viability (PRT13722 vs. prifetrastat)

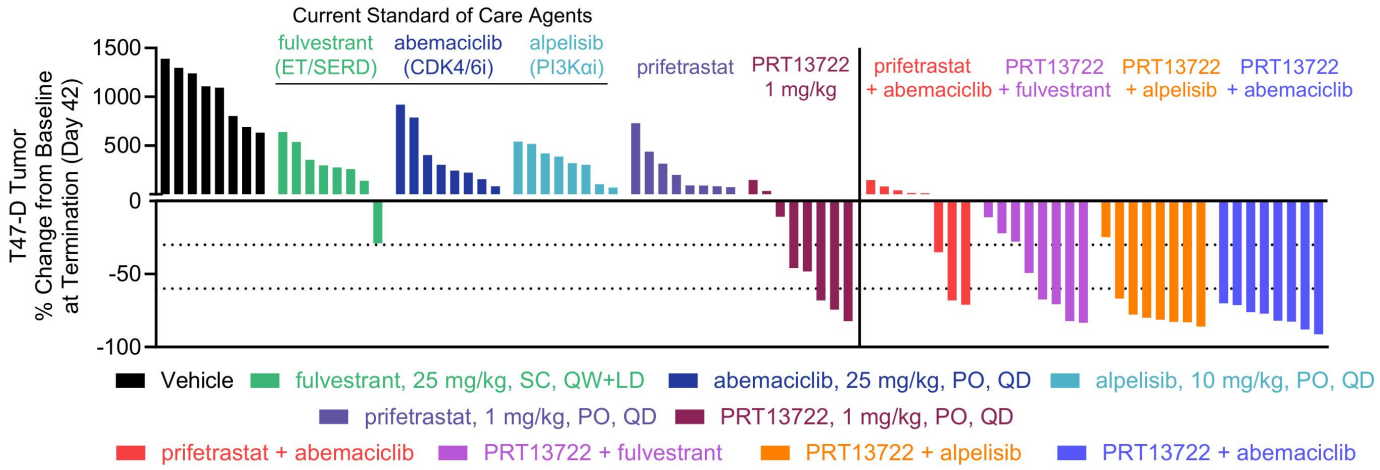


- prifetrastat, 1 mg/kg, QD
- PRT13722*, 0.3 mg/kg, QD
- PRT13722, 1 mg/kg, QD
- PRT13722*, 0.3 mg/kg, BID
- PRT13722*, 3 mg/kg, QD

KAT6A selective degraders show limited effects on neutrophils in contrast to dual KAT6A/B inhibitors, supporting potential for improved safety profile and combinability

Prelude Data on File; CFU-GM, Colony-Forming Unit-Granulocyte/Macrophage, myeloid progenitor cells found in bone marrow; LD, low dose; HD, high dose; CD, clinical dose
*Study conducted with racemic mixture of PRT13722; AACR 2026 poster presentation (access here)

PRT13722 Demonstrates Synergistic Potential in Combination with Current SoC Agents (ET, CDK4/6i, PI3Kαi) *In Vivo*



- Deeper monotherapy and combination efficacy H2H vs. prifetrastat at clinical doses
- Excellent *in vivo* efficacy in combination with fulvestrant (ET), alpelisib (PI3Kαi) and abemaciclib (CDK4/6i)
- No dosing holidays, body weight loss, mortality, or adverse clinical signs, alone or in combination

AACR 2026 poster presentation (access here)

KAT6A Selective Degrader Program Summary

- Prelude is advancing a potenial first-in-class, highly selective oral KAT6A degrader (PRT13722) with potential to become a new backbone therapy in the treatment of ER+/HER2- breast cancer
- PRT13722 has potential to achieve more robust efficacy relative to KAT6A/B/(7) inhibitors
- PRT13722 was well-tolerated, supporting potential to differentiate further based on overall safety and combinability with other agents
- On track for IND filing in mid-2026 with Phase 1 study start expected in 2H 2026

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JAK2V617F (PRT12396)

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Next Generation Precision DAC

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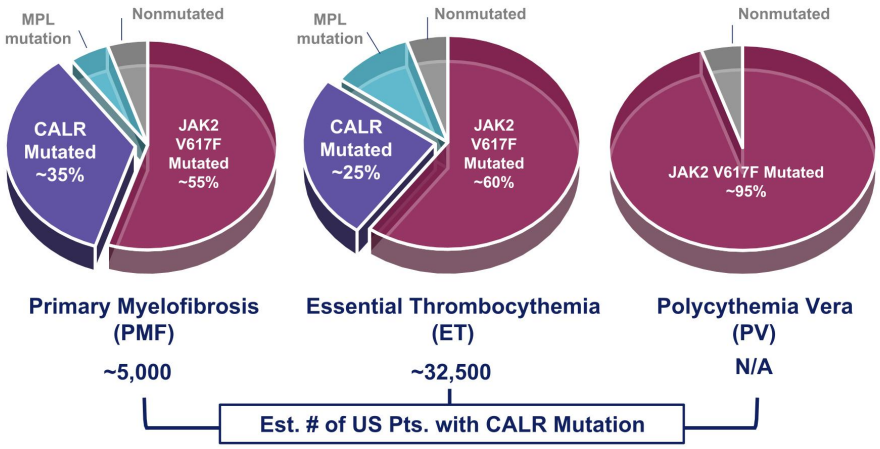
Mutated Calreticulin (mCALR) Represents a Promising Target for Next Generation DACs



Primary Myelofibrosis (PMF)	Essential Thrombocythemia (ET)	Polycythemia Vera (PV)
~5,000	~32,500	N/A

Est. # of US Pts. with CALR Mutation

mCALR is emerging as a clinically validated target in MPNs with disease modifying potential

Sources: NCI SEER Database (accessed Dec 2024), Leukemia & Lymphoma Society Facts & Figures; J.How et. al., Mutant calreticulin in myeloproliferative neoplasms, *Blood* (2019) 134 (25): 2242–2248

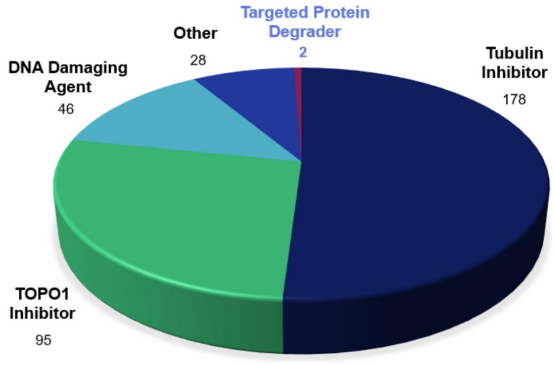
Mutant CALR is a neoantigen presented on the cell surface of malignant cells but not normal cells and is found in 25-35% of patients with Myelofibrosis (MF) and ET

SMARCA2/4 degraders are highly active in CALR mutated MPN cell lines and can be used as payloads for mCALR-targeted DACs

mCALR-targeted DACs, delivering Prelude's degrader payloads to disease-initiating clones have the potential for a differentiated approach for mCALR+ MPNs

Precision Degrader Antibody Conjugates (pDACs) Represent Next Generation ADCs

TPDs Remain an Under-represented Payload Class*



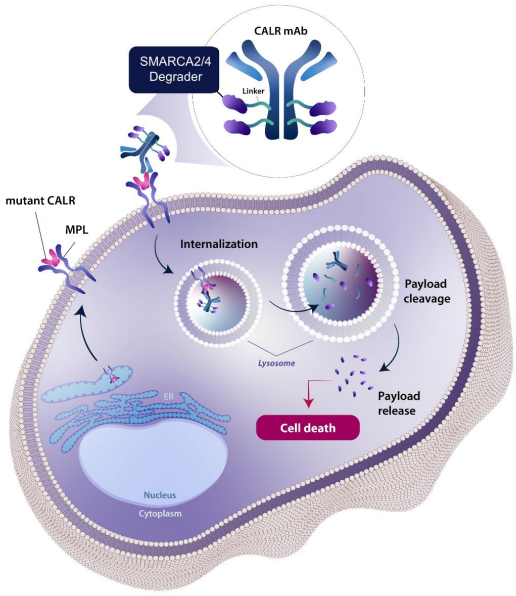
Property	Traditional ADC	Precision DAC
Potency	☑	☑
Antibody Selectivity	☑	☑
Payload Selectivity	☒	☑
PD Marker - Payload	☒	☑
Non-Genotoxic	☒	☑

- **Precision DACs enable improved selectivity in two ways**
  - ✓ **Antibodies** target tumor-specific cell surface antigens sparing healthy cells, and
  - ✓ **Targeted Protein Degraders** address critical proteins in validated biological pathways
- **Potential to deliver both improved efficacy and improved tolerability**

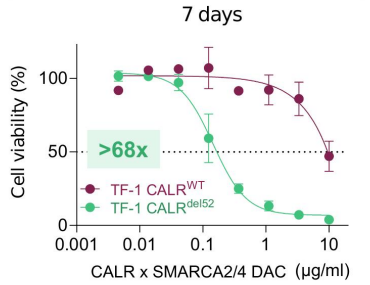
For a review of ADCs, see Fu, Z., Li, S., Han, S. *et al. Sig Transduct Target Ther* **7**, 93 (2022).

*Data source: Morris, J. Beacon ADC by HansonWade. "Analyzing the ADC Boom: Landscape Review." World ADC (San Diego). November 2024. Denotes Payload MOA for clinical stage assets currently in development at time of analysis.

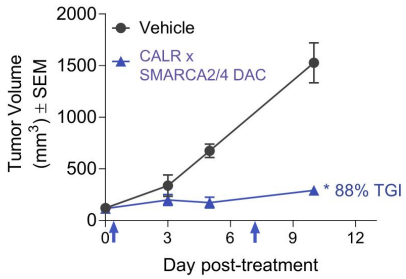
Prelude Discovered mCALR x SMARCA2/4 DACs With Robust and Selective *in vitro* and *in vivo* Activity and ~100x Improved Potency in CALR Mutant Cells



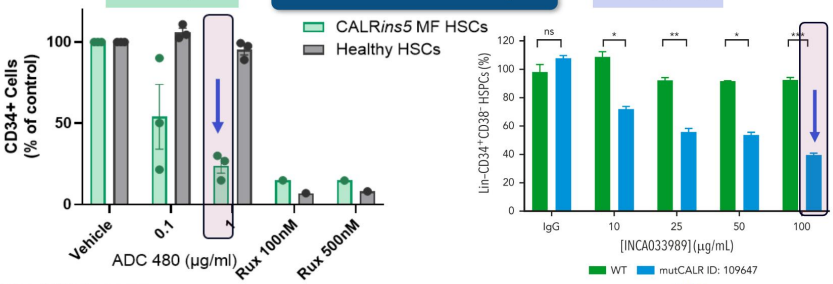
Selective Cytotoxicity *in vitro*



Robust Tumor Growth Inhibition *in vivo*



DAC ← **~100x Better Potency** → **Naked Ab**



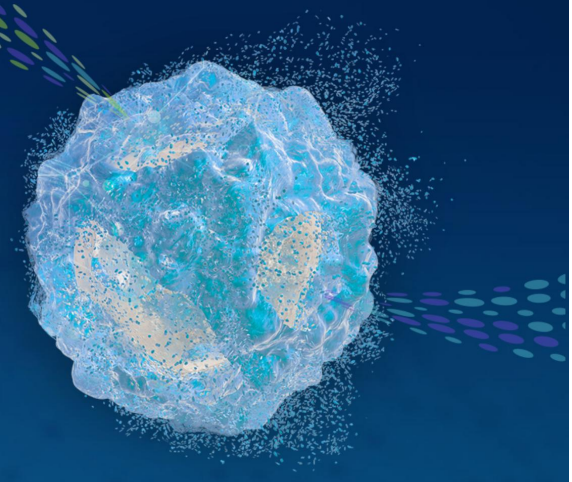
Fultang N., *et al.*, EHA2025 Oral Abstract, 12 June 25; Discovery Of First-in-class Precision ADCs Targeting Mutant Calreticulin For The Treatment Of MPNs. (access here); Reis, et al. Blood. 2024;144(22):2336

Prelude THERAPEUTICS

Executive Summary

- Lead JAK2V617F mutant selective inhibitor (PRT12396) IND cleared and Phase 1 study enrollment underway[1]
- Potentially first-in-class KAT6A selective degrader (PRT13722) on track to enter the clinic in 2026 with a path to differentiation in ER+/HER2- breast cancer market
- Novel approaches to clinically-validated targets (*e.g.*, mCALR) poised to deliver differentiated pipeline candidates beyond JAK2 and KAT6A
- Current cash runway expected into second quarter of 2028 based on preliminary estimates, driven by previously announced underwritten offering with gross proceeds of $90 million

1 - Subject of exclusive option agreement with Incyte (announced November 2025)



Thank You

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