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): November 3, 2025

Prelude Therapeutics Incorporated

(Exact name of registrant as specified in its charter)

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

175 Innovation Boulevard Wilminton, 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 (see General Instruction A.2. below):

☐ 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 Securities Exchange Act of 1934:

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

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 1.01 Entry into a Material Definitive Agreement.

Exclusive Option Agreement

On November 3, 2025, Prelude Therapeutics Incorporated (the "Company") entered into an Exclusive Option Agreement (the "Option Agreement") with Incyte Corporation ("Incyte") to acquire the Company's mutative selective JAK2V617F JH2 inhibitor program (the "Program") for patients with myeloproliferative neoplasms ("MPNs"). The Program has the potential to reduce mutant allele burden, modify disease progression, and transform treatment outcomes for MPN patients.

Under the Option Agreement, Incyte will receive an exclusive option to acquire the Company's entire right, title, and interest in and to certain assets, properties, and rights related to the Program, including the Company's library of preclinical candidates (collectively, the "Transferred Assets").

The Company will receive $60 million in capital, comprised of an initial payment of $35 million in cash, plus a $25 million equity investment by Incyte.

The Option Agreement includes, as an exhibit, the form of an Asset Purchase Agreement (the "APA"), which contemplates the sale, transfer, assignment, and conveyance by the Company to Incyte, and the purchase, acquisition, and assumption by Incyte from the Company, of the Company's entire right, title, and interest in and to the Transferred Assets in the event Incyte exercises its option under the Option Agreement.

The Company expects to continue to advance the Program with the goal of preparing an IND-ready data package. At any time commencing on the effective date of the Option Agreement until the later of (a) 30 days after the Company's delivery of the IND-ready data package or (b) 15 months after the effective date of the Option Agreement (which 15 month period shall automatically toll for the Company to deliver the IND-ready package but such tolling will not exceed 3 months unless otherwise agreed by the parties) (the "Option Period"), Incyte may elect to exercise its exclusive option to acquire the Program and associated assets from the Company pursuant to the APA for $100 million. Under the APA, the Company would be eligible to receive up to $775 million in additional clinical and regulatory milestones, and single digit royalties on global net sales. Combined, total potential cash payments from the transaction could reach up to $910 million.

The Company will continue to own and develop all Transferred Assets. If the option is exercised during the Option Period and the parties enter into and close the transaction set forth in the APA, Incyte will own all Transferred Assets subject to the Company's right, in its sole discretion and cost, to continue to conduct development activities during the Option Period to nominate and select development candidate(s) for the Program. If Incyte elects to not exercise its option to acquire the Program, all Transferred Assets would remain in the sole ownership and control of the Company.

Securities Purchase Agreement

Concurrently with the Option Agreement, on November 3, 2025, the Company entered into a securities purchase agreement with Incyte (the "Securities Purchase Agreement"), pursuant to which Incyte has agreed to purchase 6,250,000 shares (the "Shares") of the Company's non-voting common stock (the "Non-Voting Common Stock") at a price of $4.00 per share for a total of $25 million. Pursuant to the Company's Amended and Restated Certificate of Incorporation and subject to the Beneficial Ownership Limitation as set forth therein, Incyte may elect to convert the Shares into voting shares of the Company's common stock at any time. The closing of the purchase of the Shares (the "Closing") is expected to occur within five business days of the satisfaction of the Closing conditions set forth in the Securities Purchase Agreement.

The Securities Purchase Agreement includes, as an exhibit, the form of a registration rights agreement (the "Registration Rights Agreement") which the Company will enter into with Incyte upon Closing pursuant to which the Company will agree to prepare and file a registration statement on Form S-3 with the Securities and Exchange Commission (the "SEC") registering the resale of the Shares by Incyte (the "Resale Registration Shelf"), (i) as promptly as reasonably practicable following the request of Incyte, and in any event within sixty (60) days of such request, (ii) or no later than thirty (30) days after the Closing of the sale of the Non-Voting Common Stock. The Company will also agree to use reasonable best efforts to cause such registration statement to become effective as promptly as practicable after filing the Resale Registration Shelf.

The Company intends to apply the initial payment from the Option Agreement and net proceeds from the sale of the Shares pursuant to the Securities Purchase Agreement to advance its pipeline, including the KAT6A program, the JAK2V617F program, and for working capital and general corporate purposes.

The foregoing descriptions of the terms of each of the Option Agreement, Securities Purchase Agreement, and Registration Rights Agreement do not purport to be complete and are qualified in their entirety by the full text of each agreement, copies of which will be filed as exhibits to the Company's Annual Report on Form 10-K for the fiscal year ending December 31, 2025.

Item 3.02 Unregistered Sales of Equity Securities.

The information contained above in Item 1.01 is hereby incorporated by reference into this Item 3.02. Based in part upon the representations of Incyte in the Securities Purchase Agreement, the offering and sale of the Shares will be exempt from registration under Section 4(a)(2) of the Securities Act of 1933, as amended (the "Securities Act"). The Shares will not be registered under the Securities Act or any state securities laws and may not be offered or sold in the United States absent registration with the SEC or an applicable exemption from the registration requirements. The sale of the securities will not involve a public offering. Incyte represented that it is an accredited investor, as such term is defined in Rule 501(a) of Regulation D under the Securities Act, and that it is acquiring the Shares for investment purposes only and not with a view to any distribution of the Shares in violation of the United States federal securities laws.

Item 5.02 Departure of Directors or Certain Officers; Election of Directors; Appointment of Certain Officers; Compensatory Arrangements of Certain Officers

On November 4, 2025, the Company announced that Jane Huang, M.D. resigned as the President and Chief Medical Officer of the Company, effective on November 3, 2025 (the "Separation Date"). Dr. Huang's resignation was not due to any disagreement with the Company on any matter relating to the Company's operations, policies or practices. Effective as of November 4, 2025, the Company and Dr. Huang entered into a Consulting Agreement, pursuant to which Dr. Huang will provide consulting services regarding matters relating to the Company's clinical programs at an hourly rate of $750, as may be requested from time to time by the Company, until September 15, 2026 (the "Consulting Period"). During the Consulting Period, Dr. Huang's outstanding equity awards will continue to vest pursuant to the terms of the applicable equity award.

On November 4, 2025, the Company also announced that until September 15, 2026, Dr. Victor Sandor, M.D.C.M., former Chief Medical Officer of Array Biopharma and current board member of the Company and chair of the Science and Technology Committee, will provide strategic and operational oversight of clinical development.

Item 7.01 Regulation FD Disclosure.

On November 4, 2025, the Company and Incyte issued a press release relating to the Option Agreement and Securities Purchase Agreement. A copy of such press release is furnished herewith as Exhibit 99.1. The Company also issued a press release announcing its decision to pause the clinical development of its first-in-class SMARCA2 degrader program relating to its strategic portfolio shift. A copy of such press release is furnished herewith as Exhibit 99.2. In connection with the foregoing, the Company has updated its corporate presentation. A copy of the updated corporate presentation release is furnished herewith as Exhibit 99.3.

The information in Item 7.01 of this Current Report on Form 8-K and Exhibits 99.1, 99.2, and 99.3 attached hereto shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to liability under that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Cautionary Note Regarding Forward-Looking Statements.

This Current Report on Form 8-K 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 the Company's product candidates, the potential safety, efficacy, benefits and addressable market for the

Company's product candidates, the expected timeline for clinical trial results for the Company's product candidates, and the sufficiency of the Company's cash runway. 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 the Company believes that the expectations reflected in such forward-looking statements are reasonable, the Company 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 the Company's actual activities or results to differ significantly from those expressed in any forward-looking statement, including risks and uncertainties related to the Company'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, the Company's ability to maintain and recognize the benefits of certain designations received by product candidates, the timing and results of preclinical and clinical trials, the Company's ability to fund development activities and achieve development goals, the Company's ability to protect intellectual property, and other risks and uncertainties described under the heading "Risk Factors" in the Company's Annual Report on Form 10-K for the year ended December 31, 2024, its Quarterly Reports on Form 10-Q and other documents that the Company files from time to time with the SEC. These forward-looking statements speak only as of the date of this Form 8-K, and the Company 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.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press release announcing Exclusive Option Agreement with Incyte, dated November 4, 2025.
99.2	Press release announcing Strategic Business Update, dated November 4, 2025.
99.3	Corporate presentation, dated November 4, 2025.
104	Cover Page Interactive Data File (embedded within the Inline XBRL Document).

SIGNATURE

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

PRELUDE THERAPEUTICS INCORPORATED

Date: November 4, 2025

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

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, $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

WILMINGTON, Del., - Nov. 4, 2025 - Prelude Therapeutics Incorporated (Nasdaq:PRLD), a clinical-stage precision oncology company, today announced an exclusive option agreement with Incyte (Nasdaq:INCY) focused on Prelude's previously undisclosed mutant selective JAK2V617F JH2 inhibitor program in development for patients with myeloproliferative neoplasms (MPNs). Per the agreement, Incyte secures an exclusive option to acquire the JAK2V617F program in exchange for an upfront payment and a strategic equity investment in Prelude, plus potential downstream milestones and royalties.

Kris Vaddi, Ph.D., Chief Executive Officer of Prelude stated, "We're pleased to put this agreement in place with Incyte, recognized global leaders in the MPN field. Prelude and Incyte both aim to deliver transformational treatments to improve upon the standard of care established with first generation JAK2 JH1 inhibitors like Jakafi® (ruxolitinib). Our research team made significant progress discovering the first known inhibitors that bind into the JAK2 JH2 'deep pocket' where the V617F mutation resides. These potent and orally bioavailable compounds demonstrate mutant specific inhibition and the potential for disease modification in multiple preclinical models of MPNs. Today's agreement with Incyte provides us with the capital needed to advance further our JAK2V617F program, while also allowing us to advance the development of our other pipeline programs."

"The agreement with Prelude provides an opportunity to enhance our robust portfolio of clinical and preclinical JAK2V617F candidates for patients with MPNs," said Bill Meury, President and Chief Executive Officer of Incyte. "This transaction aligns with our strategy to develop new and innovative therapies poised to make a meaningful difference for patients."

Terms of the Agreement
Under the terms of the Transaction Agreement, Incyte secures an exclusive option to acquire Prelude's mutant selective JAK2V617F JH2 inhibitor program, including Prelude's library of preclinical candidates. Prelude will receive $60 million in capital, comprised of an upfront payment of $35 million, plus a $25 million equity investment by Incyte in Prelude. Incyte will purchase 6.25 million shares of Prelude non-voting common stock at a price of $4.00 per share at deal close. Prelude intends to apply the upfront payment and net proceeds from the sale of the purchased shares to advance the JAK2V617F program and other pipeline assets, and for working capital and general corporate purposes.

Prelude expects to advance the JAK2V617F program to pre-defined milestones. Incyte may elect to exercise its exclusive option during the option period to acquire the program and associated assets from Prelude for $100 million. As the JAK2V617F program candidates advance in the clinic, Prelude would be eligible to receive up to $775 million in additional clinical and regulatory milestones, and single digit royalties on global net sales. Combined, total potential cash payments from the transaction, excluding royalties, could reach up to $910 million.

If Incyte elects to not exercise its option to acquire the program, all JAK2V617F global program rights and interests would remain in the sole ownership and control of Prelude.

Prelude Therapeutics was advised on the transaction by Morgan Lewis & Bockius LLP as legal counsel.

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 a shared goal and challenge for industry. If successful, this approach has potential to reduce mutant allele burden, modify disease progression, and transform treatment outcomes for MPN patients. Prelude has discovered 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. The first disclosure of program data was accepted for oral presentation at the American Society of Hematology (ASH) 67th Annual Meeting taking place in Orlando, FL December 6-9, 2025. The abstract can be found on the ASH 2025 website ASH Annual Meeting & Exposition - Hematology.org.

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 mutant selective JAK2V617F JH2 inhibitors - new approaches to clinically validated targets with transformative potential for patients. We are also leveraging our expertise in targeted protein degradation to discover 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. Our corporate presentation can be found at Events & Presentations - Prelude Therapeutics. For more information, visit preludetx.com.

Prelude 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. 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, 2024, 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.

# # #

Contacts:

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Prelude Therapeutics Incorporated
484.639.7235
rdoody@preludetx.com

Prelude Therapeutics Announces Strategic Business Update

Prelude to prioritize development of mutant selective JAK2V617F JH2 inhibitor and KAT6A selective degrader programs

Pausing further clinical development of SMARCA2 selective degrader programs

JAK2V617F option agreement with Incyte, as previously announced, includes upfront payment of $35 million, a $25 million equity investment and $100 million if option is exercised

Cumulative capital expected to fund planned operations into 2027 based on the Company's preliminary estimates, and potentially into the third quarter of 2028 if Incyte exercises option on JAK2 program

Company to release third quarter 2025 financial results and conduct an investor conference call on November 12, 2025

WILMINGTON, Del., Nov. 4, 2025 (GLOBE NEWSWIRE) – Prelude Therapeutics Incorporated (Nasdaq: PRLD), a precision oncology company, today is providing a number of strategic updates, including its recently executed option agreement with Incyte Corporation centered on its previously undisclosed JAK2V617F mutant selective inhibitor program, prioritizing development of its first-in-class KAT6A selective degrader program and pausing of its SMARCA2 programs.

Earlier today, Prelude announced an exclusive option agreement with Incyte to advance its mutant selective JAK2V617F JH2 inhibitor program for patients with myeloproliferative neoplasms (MPNs). With this transaction, Incyte secures an exclusive option to acquire the JAK2V617F program in exchange for an upfront payment and an equity investment in Prelude, plus downstream milestones and royalties. Prelude will continue to own and develop all JAK2V617F program assets until point of option exercise, after which Incyte will lead development and commercialization globally.

Prelude is prioritizing the development of its highly selective KAT6A degrader for ER+ breast cancer. Selectively degrading KAT6A is a novel approach to a clinically validated target with transformative potential for patients. The Company expects to advance the program into clinical development in 2026 and generate initial proof-of-concept clinical data, including a potentially differentiated efficacy and safety profile compared to non-selective KAT6A/B inhibitors currently in clinical development.

Prelude also announced it has decided to pause the clinical development of its SMARCA2 degrader program. The decision to pause was based on a comprehensive review of clinical data generated to date and the Company's assessment of the capital and resource allocation required to advance the SMARCA2 program, versus the JAK2 and KAT6A programs, to key points of value inflection.

Based on these announcements, the Company's cash runway is now expected to extend into 2027 based on the Company's preliminary estimates. The cash runway could potentially be expected to extend into the third quarter of 2028 if Incyte exercises its option on the JAK2 program subject to customary closing conditions and based on the Company's preliminary estimates. As of October 31, 2025, the Company had approximately $52 million of cash, cash equivalents and marketable securities and will receive $60 million following the closing of the option and securities purchase from Incyte's upfront payment and equity investment.

"This morning, we announced important strategic decisions that we believe provide the most compelling set of opportunities to address important unmet needs for patients and value creation for our investors," stated Kris Vaddi, Ph.D. Chief Executive Officer of Prelude. "Our research team made significant breakthroughs in discovering highly differentiated molecules targeting clinically validated mechanisms that are positioned to enter the clinic in 2026. These molecules present potential proof of concept and differentiation opportunities early in clinical development with well understood development paths."

Vaddi continued, "Having actively pursued the clinical development of our SMARCA2 selective degraders, we determined that complex biology and aggressiveness of disease in patients with SMARCA4 deletions will likely require early intervention and combination strategies to make a meaningful impact for patients. We are not resourced to explore the mechanism fully in the timeframe needed to deliver a concrete and viable path forward. In addition, we believe that optimally resourcing the JAK2V617F mutant selective inhibitor and KAT6A degrader programs are of paramount importance and as noted in this morning's previous announcement, the agreement with Incyte brings in significant capital enabling us to advance both programs."

Prelude also announced the departure of President and Chief Medical Officer Jane Huang, M.D. to pursue other opportunities. Victor Sandor, M.D.C.M., former Chief Medical Officer of Array BioPharma and current Prelude board member and chair of the Science and Technology Committee, will provide strategic and operational oversight of clinical development as the Company advances KAT6A towards first-in-human studies, and its JAK2 program. Dr. Sandor brings extensive oncology development leadership experience, notably through his successful tenures at Incyte Corporation, Biogen Idec and AstraZeneca. The Company will seek to augment the clinical development leadership in a timeframe that fits with the maturation of the programs.

Added Vaddi, "Lastly, we would like to thank Dr. Huang for her many contributions to Prelude and wish her continued success in her future endeavors. We are honored and gratified that Dr. Sandor is stepping in to provide strategic leadership and oversight of our clinical development programs, as we prepare for IND filing and first in human studies for the mutant selective JAK2V617F and KAT6A programs."

Key Pipeline Programs

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 and remains on track to file an IND in mid-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 recently presented preclinical data supporting this hypothesis at the AACR Annual Meeting 2025. The presentation can be found at Publications - Prelude Therapeutics.

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 a shared goal and challenge for industry. Prelude has discovered 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.

Mutated Calreticulin (mCALR) degrader antibody conjugates (DACs)

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 myelofibrosis (MF) and essential thrombocythemia (ET). Recently, a mCALR-targeted monoclonal antibody demonstrated robust clinical activity in high-risk ET patients. Prelude is seeking to further optimize this modality by developing mCALR-targeted DACs using the Company’s proprietary degrader payloads. The Company presented the first preclinical data from this discovery effort at the European Hematology Association 2025 Congress in June. The presentation can be found at Publications - Prelude Therapeutics.

Precision ADCs with SMARCA2/4 dual degrader payload

Prelude is developing potent SMARCA2/4 dual degraders that robustly inhibit cancer cell growth and induce cell death across multiple cancer types as payloads for precision ADCs. The Company presented the first preclinical data from its precision ADC platform at the 36th EORTC-NCI-AACR Symposium in October. These data demonstrated that SMARCA2/4 degrader antibody conjugates have potential for significantly better *in vivo* efficacy and tolerability when compared to traditional cytotoxic ADCs when tested head-to-head in xenograft models. The presentation can be found at Publications - Prelude Therapeutics.

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 discover 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. Our corporate presentation can be found at Events & Presentations - Prelude Therapeutics. For more information, visit preludetx.com.

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Investor Contact:
Robert A. Doody, Jr.
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Prelude
THERAPEUTICS
Corporate Presentation
November 2025

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 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,’’ ‘‘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).

This presentation shall not constitute an offer to sell or the solicitation of an offer to buy, nor shall there be any sale of securities of the Company in any state or other jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state or other jurisdiction, or pursuant to an exemption from, or in a transaction not subject to, the registration requirements of the Securities Act of 1933, as amended, and any other applicable securities laws.

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, 2024.

Prelude THERAPEUTICS

Prelude THERAPEUTICS

We are on a mission to extend the promise of precision medicine to every cancer patient in need

- *Strive for first- or best-in-class and anchor to patient unmet need*
- *Select the best modality to precisely target oncogenic mechanisms*
- *Draw on decades of experience and proven leadership to drive innovation*

Experienced Leadership Team With Proven Track Records

Kris Vaddi, PhD

Chief Executive Officer

Peggy Scherle, PhD

Chief Scientific Officer

Andrew Combs, PhD

Chief Chemistry Officer

Sean Brusky, MBA

Chief Business Officer

Bryant Lim, J.D.

Chief Financial Officer, Chief Legal Officer, Secretary

Dr. Victor Sandor, former CMO at Array BioPharma and current member of our Board of Directors, will serve as a senior medical advisor, providing strategic and operational leadership for our clinical development programs

Prelude THERAPEUTICS

Prelude's Pipeline & Discovery Engine

	PROGRAM	POTENTIAL INDICATIONS	DISCOVERY/ LEAD OPT.	IND-ENABLING	PHASE 1	PROGRAM INTEREST	UPCOMING MILESTONES
IND Enabling	**JAK2V617F Mutant Selective JH2 Inhibitors**	VF+ myeloproliferative neoplasms (MPNs) (MF, PV, ET)				Incyte [1]	Oral abstract at ASH 2025
IND Enabling	**KAT6A Selective Degraders**	ER+ breast cancer, other malignancies				Prelude wholly owned	IND filing mid-2026
Discovery	**Degrader Antibody Conjugates ("DACs")**	Internal mCALR DAC program for ET, MF		*Proprietary degrader payloads available for licensing to develop DACs for other antigen targets*		AbCellera [2]	Oral abstract at ASH 2025 (mCALR)
Discovery	**New Discovery Programs**	Hard-to-treat cancers, "Undruggable" targets, High unmet need		*Established track record of delivering potentially first-in-class new programs into the clinic every 12-18 months*			

VF+ = V617F mutated, MF = myelofibrosis, PV = polycythemia vera, ET = essential thrombocythemia, mCALR = mutated calreticulin, ER+ = estrogen receptor positive
1 - Exclusive option agreement with Incyte announced November 2025
2 - Strategic partnership with AbCellera announced November 2023 (Press Release)

Our Investment Thesis Centers on Advancing Two Programs – Both Representing Highly Differentiated Approaches to Clinically Validated Targets

JAK2V617F

Mutant Selective Inhibitors

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

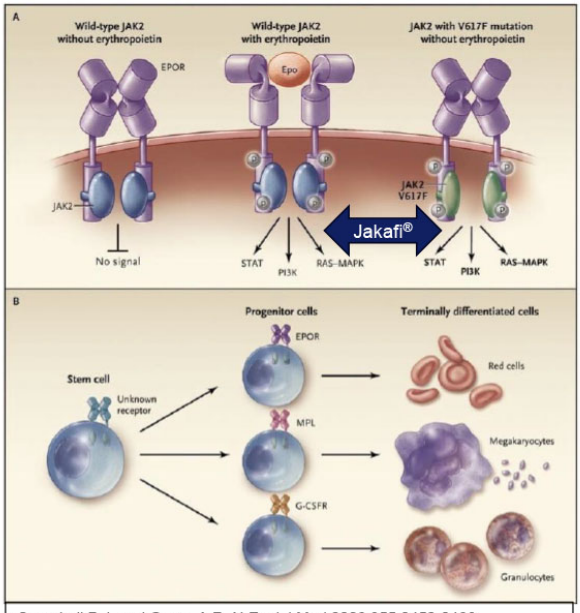
KAT6A

Highly Selective Oral Degraders

First-in-class KAT6A degraders, with absolute selectivity over KAT6B – a differentiated approach against a clinically validated target in ER+ breast cancer with pan-tumor potential in other malignancies

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

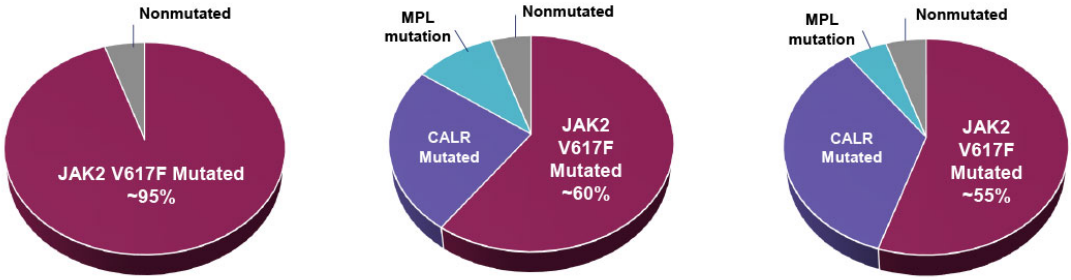
- The JAK-STAT pathway mediates growth factor signaling, most notably:
  - Thrombopoietin receptor for platelet production
  - Erythropoietin receptor for red blood cell production
- The JAK2V617F mutation leads to growth factor-independent hyperactivation of JAK-STAT pathway and uncontrolled myeloid and erythroid proliferation
- Inhibition of wildtype JAK2 causes anemia and thrombocytopenia and current JAK inhibitors, like ruxolitinib (Jakafi®), while effective, equally inhibit both WT and V617F-mutated (VF+) JAK2
- JAK2 JH2 inhibitors that selectively target VF+ progenitor cells have potential to reduce mutant allele burden, modify disease progression, and 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

A JAK2V617F Mutant Selective Inhibitor Could Become a Disease Modifying Option for the Majority of MPN Patients and Represents an Expansive Opportunity



Polycythemia Vera (PV)

~142,000

Essential Thrombocythemia (ET)

~78,500

Primary Myelofibrosis (PMF)

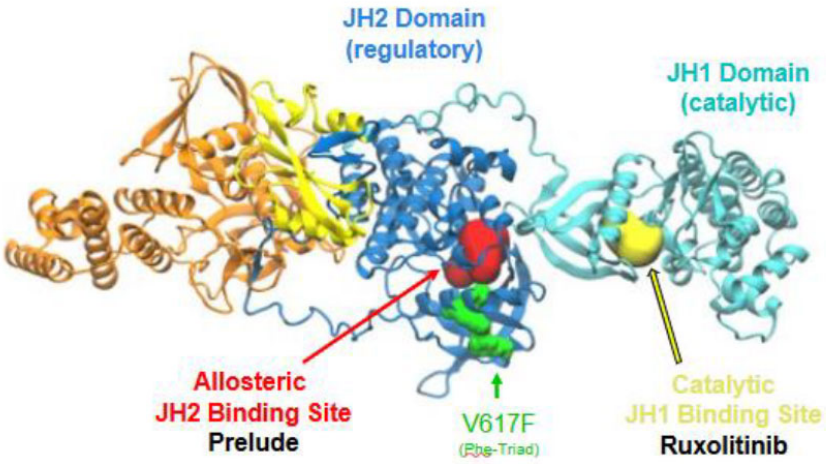
~8,000

Est. # of U.S. Patients with JAK2V617F Mutation
~228,500

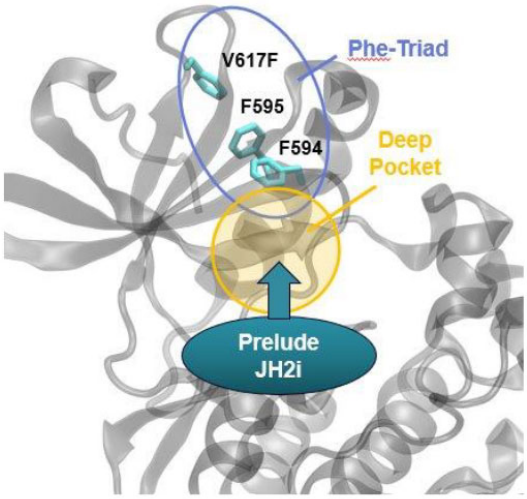
Sources: NCI SEER Database (accessed Dec 2024), Leukemia & Lymphoma Society Facts & Figures; F. Passamonte et.al., "Clinical Significance of JAK2 V617F Mutant Allele Burden"; Haematologica 2009 Jan;94(1):7–10

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 Catalytic Domain



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



JAK2V617F Mutant Selective Inhibitors Are Highly Differentiated From 1st Generation JAK Inhibitors in a Large and Growing Market

- Global sales of ruxolitinib (Jakafi® /Jakavi®) in MPNs grew to over $4.5B in 2024[1,2]
  - Continuing strong sales growth for ruxolitinib in PV
- First generation JAK inhibitors have delivered transformative efficacy for MF patients
  - Highly effective at reducing symptoms and spleen size
  - However, toxicities from wild-type activity limit ability to reach maximal efficacy
- Ruxolitinib is the only JAK inhibitor approved in PV (2L) and none are approved in ET
- Prelude's JAK2V617F mutant selective inhibitors demonstrate:
  - Potent and selective reduction in JAK2V617F cells *in vitro* compared to WT cells
  - Improved efficacy, reduced toxicity, and rapid reduction of mutant alleles *in vivo*
  - Potential for transformative efficacy and disease modification in PV, ET and MF

First Public Disclosure of Preclinical Data on Prelude's JAK2V617F Program Accepted for Oral Presentation at ASH 2025[3]

1 - Incyte Pharmaceuticals (Q4 2024 Financial Results and Corporate Update Presentation, February 10, 2025); JAKAFI is a registered trademark of Incyte
2 - Novartis Pharmaceuticals (Full Year 2024 Product Sales, Accessed August 2025; JAKAVI is a registered trademark of Novartis
3 - Abstract can be found on the ASH 2025 website ASH Annual Meeting & Exposition - Hematology.org.

Option Agreement With Incyte Provides Significant Capital to Further Advance the JAK2V617F and KAT6A Degrader 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 Two Programs – Both Representing Highly Differentiated Approaches to Clinically Validated Targets

JAK2V617F

Mutant Selective Inhibitors

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Highly Selective Oral Degraders

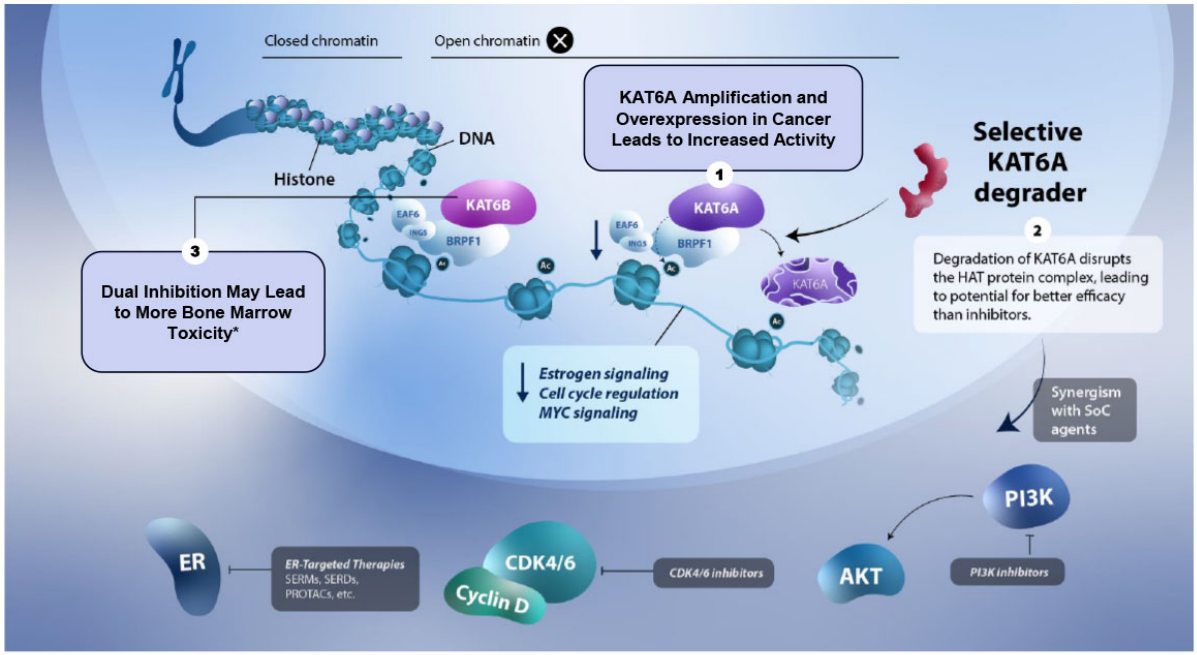
First-in-class KAT6A degraders, with absolute selectivity over KAT6B – a differentiated approach against a clinically validated target in ER+ breast cancer with pan-tumor potential in other malignancies

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

- A KAT6A/B dual inhibitor is now in pivotal phase 3 trials in combination with fulvestrant, after progression on a CDK4/6 inhibitor
  - Demonstrated efficacy in post CDK4/6 inhibitor setting in a broad population of ER+ BC including PIK3CA-, ESR1-mutated patients, providing clinical validation for target
  - Clinically relevant safety observations including dysgeusia and grade 3/4 neutropenia
  - Combinations with other agents, particularly CDK4/6 inhibitors could prove challenging with potential for overlapping toxicities and required dose modifications
- Our KAT6A program aims to demonstrate a superior clinical profile
  - Optimal efficacy
  - Lower neutropenia and dysgeusia
  - Improved combinability profile with other agents (*e.g.* oral SERDs, AIs, CDK4/6s, PI3Kis)
- ER+ breast cancer treatment market is projected to reach $42B by 2033[1]
  - Most common type of breast cancer, representing 70% of all cases

1. Vision Research Reports; "Estrogen Receptor Positive Breast Cancer Treatment Market Forecast 2024-2033. Estrogen Receptor Positive Breast Cancer Treatment Market Size | Companies

Selectively Degrading KAT6A is a Novel Approach with Potential to Deliver Differentiated Safety and Efficacy Over Non-Selective KAT6A/B Inhibitors

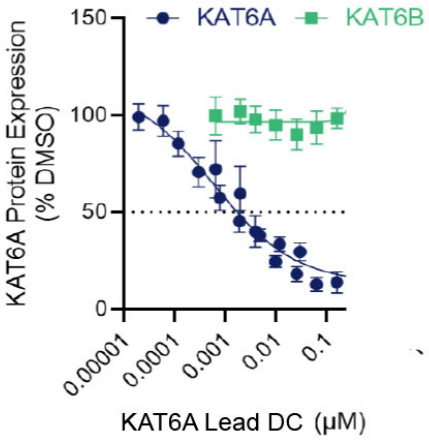


Our Lead KAT6A Selective Degrader Development Candidate

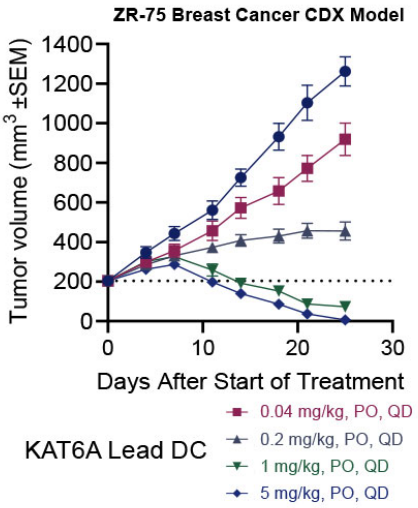
Lead DC is a Potent KAT6A Degrader in Preclinical Models

- Absolute kinetic selectivity for 6A/6B (>1000-fold)
- Global proteomics demonstrates selective KAT6A degradation
- Excellent oral PK across species
- Compelling *in vivo* efficacy as monotherapy in multiple models
- Reduced effect on neutrophils in preclinical models
- Non-GLP DRF studies complete
- IND-enabling studies initiated

Absolute Degradation Selectivity (KAT6A vs KAT6B)



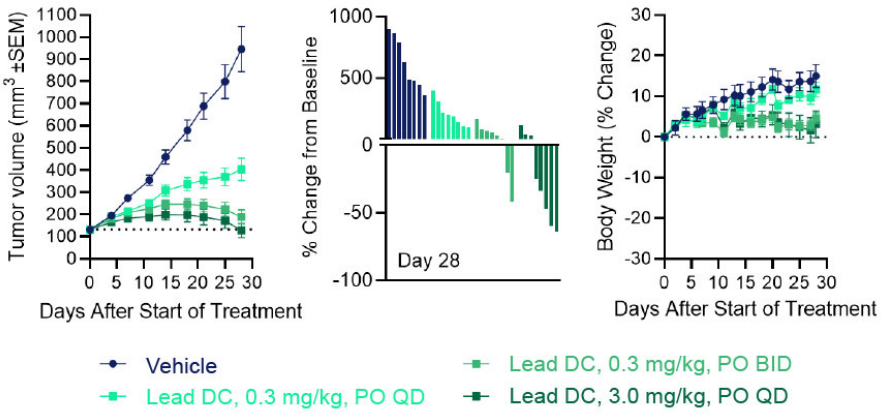
In Vivo Efficacy



Prelude Data on File

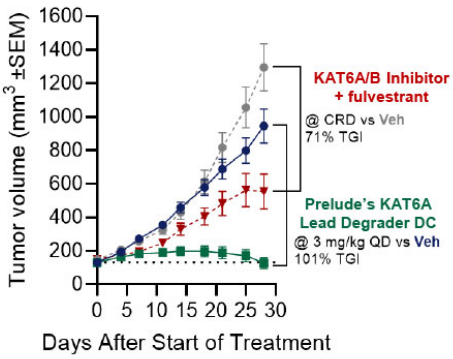
Our Lead DC Drives Tumor Regressions in T47-D Model with Significantly Greater Monotherapy Activity than KAT6A/B Inhibitor + Fulvestrant Combination

Tumor Regressions Observed at Low Doses



Vehicle
Lead DC, 0.3 mg/kg, PO QD
Lead DC, 0.3 mg/kg, PO BID
Lead DC, 3.0 mg/kg, PO QD

Significant TGI as Monotherapy vs. KAT6A/Bi + fulvestrant

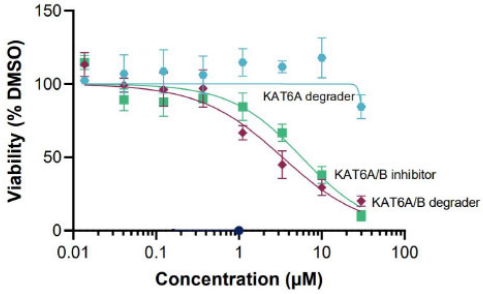


- Lead DC demonstrates dose-dependent efficacy, driving tumor regressions at low daily oral doses in preclinical models
- Human equivalent dose projection of 5-10 mg QD
- Well-tolerated with no observed body weight loss in preclinical models

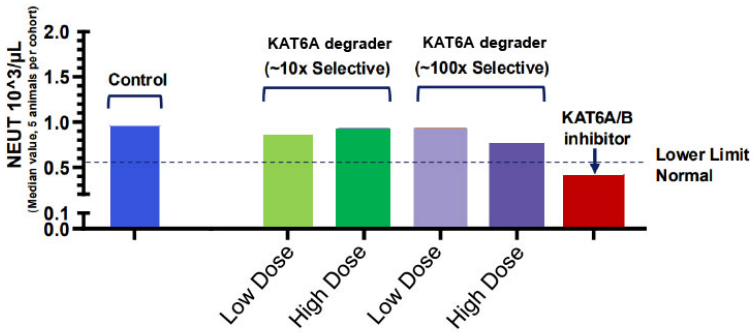
Prelude Data on File

KAT6A Selective Degraders Show Potential for Lower Bone Marrow Toxicity in Preclinical Models Compared to KAT6A/B Dual Inhibitors

Dose Response of CFU-GM



Neutrophils Day 5



Ex vivo and *in vivo* studies with KAT6A selective degraders show limited effects on neutrophils in contrast to dual KAT6A/B inhibitors and degraders

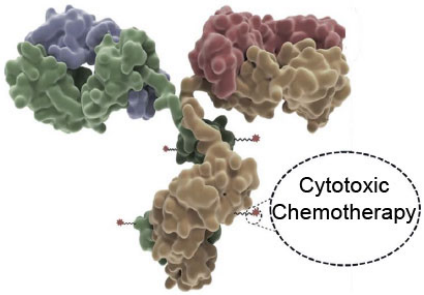
Prelude Data on File

KAT6A Selective Degrader Program Summary

- Prelude invented multiple first-in-class, highly selective KAT6A degraders which demonstrate favorable preclinical results
- KAT6A degraders show potential to achieve best-in-class efficacy and ability to differentiate on safety and combinability early in clinical development
- Lead DC has completed dosing in non-GLP studies in rats and dogs
- On-track to advance to IND filing in mid-2026
- Phase 1 start expected 2H 2026

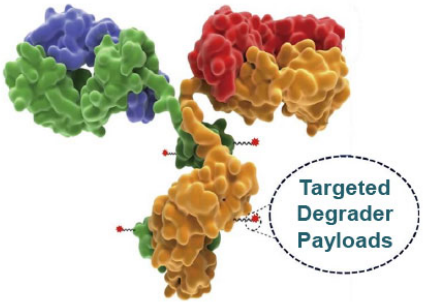
Prelude is Applying Our Expertise in Targeted Protein Degradation to Advance The Next Generation of Degrader Antibody Conjugates (DACs)

Traditional ADCs

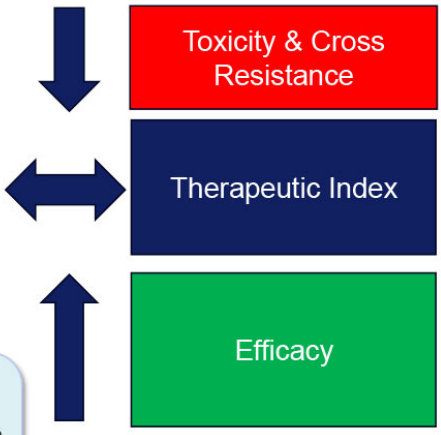


- Non-selective Genotoxic Payloads
- Limited Payload Diversity
- Broad Chemotherapy Liabilities
- Resistance Emerging to Common Cytotoxic Payloads

Next Gen DACs



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



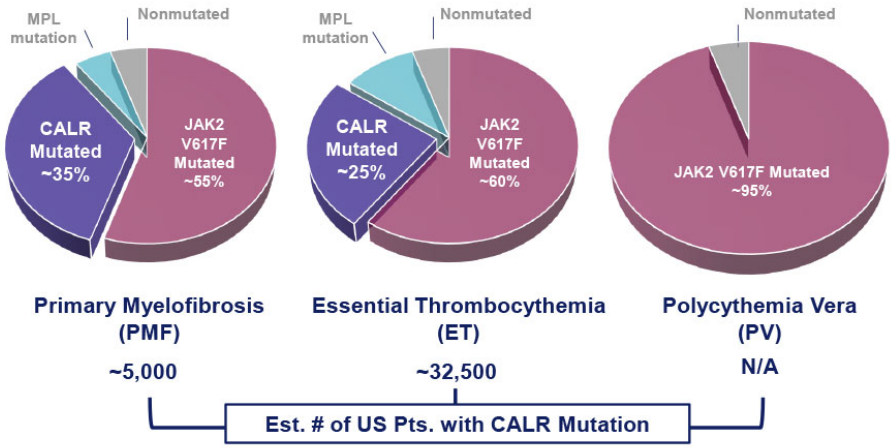
Fu, Z., Li, S., Han, S. *et al. Sig Transduct Target Ther* **7**, 93 (2022).

Prelude's Degrader Payloads: Engineered to Improve Efficacy, Tolerability and Developability Compared to Traditional Cytotoxic Payloads

Payload	Rationale	DAC Properties			Prelude Degrader Payload-Linkers
		Efficacy	Tolerability	Developability	
Exceptional Potency (pM)	Allows low DAR; Low aggregation	+		+	SMARCA2/4 Dual Degraders (VHL- and CRBN- based) CDK9 Degraders
Permeable or Non-Permeable	Enable localized bystander effect Limit off-target toxicity from payload diffusion	+ 	 +	 	
Highly stable E3 Ligase binder	Long $t_{1/2}$ in vivo; Stable drug substance	+		+	
Prodrug	Lower risk of cleavage in plasma		+	+	
High Clearance	Rapid clearance in plasma		+		
Non-Genotoxic	Indications beyond cancer		+		

Prelude's Degrader Payloads Have the Potential to Deliver Novel DACs with Improved Efficacy and Therapeutic Index

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

CALR mutations are important in MPNs, associated with poor clinical prognosis and disease progression

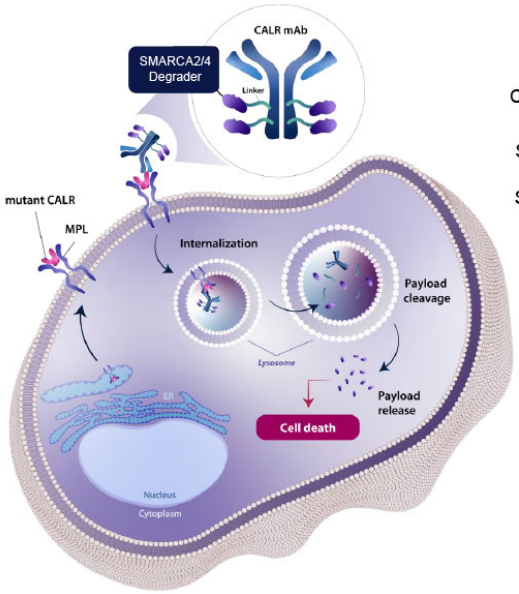
Sources: NCI SEER Database (accessed Dec 2024), Leukemia & Lymphoma Society Facts & Figures; J.How et. al., Mutant calreticulin in myeloproliferative neoplasms, *Blood* (2019) 134 (25): 2242–2248

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

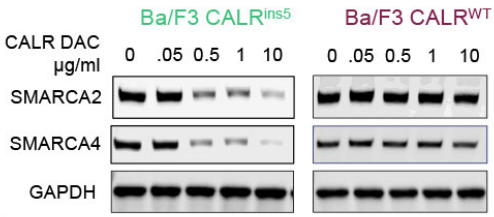
SMARCA2/4 and CDK9 degraders are both highly active in CALR mutated MPN cell lines and can be used as payloads for mCALR-targeted DACs

mCALR-targeted DACs, delivering Prelude's degrader payloads to disease-initiating clones have the potential to be first-in-class, disease modifying therapies

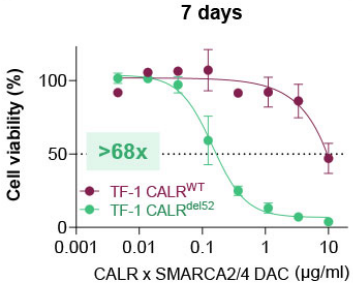
CALR x SMARCA2/4 DACs Demonstrate Robust and Selective Target Degradation and Cytotoxicity in CALR Mutant Cells and Robust Tumor Growth Inhibition In Vivo



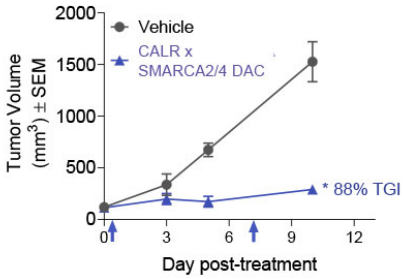
Degradation Assay, 48h



Anti-proliferation Assay



Robust Tumor Growth Inhibition *in vivo*



CALR x CDK9 DAC Abstract Accepted for Oral Presentation at ASH2025[1]

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)
1 - Abstract now available: ASH Annual Meeting & Exposition - Hematology.org

Executive Summary

- Newly disclosed JAK2V617F mutant selective inhibitor program subject of a strategic option agreement with Incyte, with first disclosure at ASH 2025
- First-in-class KAT6A selective degrader program poised to enter the clinic in 2026 with clear path to differentiation in ER+ breast cancer market
- On-going discovery effort focused on small molecules and DACs addressing areas of high unmet medical need
- Cash runway expected into 2027, based on the Company's preliminary estimates

Thank You

Contact Us:

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SVP, Investor Relations
rdoody@preludetx.com