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): March 16, 2023

MONTE ROSA THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**001-40522**	**84-3766197**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

645 Summer Street, Suite 102
Boston, MA 02210
(Address of principal executive offices, including zip code)

(617) 949-2643
(Registrant's telephone number, including area code)

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	**GLUE**	**The 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 March 16, 2023, Monte Rosa Therapeutics, Inc. (the "Company") announced its financial results for the quarter and year ended December 31, 2022. The full text of the press release issued in connection with the announcement is furnished as Exhibit 99.1 to this Current Report on Form 8-K.

Item 7.01. Regulation FD Disclosure

On March 16, 2023, the Company issued a corporate presentation that it intends to utilize in various meetings with securities analysts, investors and others. A copy of the corporate presentation is furnished as Exhibit 99.2 to this Current Report on Form 8-K.

The information under Item 2.02 and Item 7.01 in this Current Report on Form 8-K (including Exhibit 99.1 and Exhibit 99.2) 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 the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 9.01. Financial Statements and Exhibits

(d) Exhibits

99.1	Press Release issued by Monte Rosa Therapeutics, Inc. dated March 16, 2023.
99.2	Corporate Presentation furnished by Monte Rosa, Inc. on March 16, 2023.
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.

Monte Rosa Therapeutics, Inc.

Date: March 16, 2023

By: /s/ Markus Warmuth
Markus Warmuth
President and Chief Executive Officer

Monte Rosa Therapeutics Announces Fourth Quarter and Full Year 2022 Financial Results and Provides Corporate Update

- Phase 1/2 clinical trial evaluating MRT-2359 for treatment of MYC-driven solid tumors ongoing
- Disclosure of initial data from Phase 1 arm of study expected in second half of 2023
- MRT-2359 received Fast Track designation from FDA for treatment of patients with previously treated, metastatic non-small cell lung cancer (NSCLC) with L-MYC or N-MYC expression
- Nomination of multiple development candidates anticipated in 2023
- Year-end 2022 cash balance of approximately $268 million, with cash runway into 2025

BOSTON, March 16, 2023 – Monte Rosa Therapeutics, Inc. (NASDAQ: GLUE), a clinical stage biotechnology company developing novel molecular glue degrader (MGD)-based medicines, today reported financial results for the fourth quarter and full year ended December 31, 2022, and provided corporate updates.

"Last year was transformational for Monte Rosa, as we initiated a Phase 1/2 clinical trial with MRT-2359 for the treatment of MYC-driven solid tumors, and advanced our VAV1 program into lead optimization. We have now shown repeatedly that our QuEEN platform has the ability to generate selective molecular glue degraders for therapeutically relevant protein targets, and our pipeline of unique and differentiated MGDs serves as strong validation of QuEEN," said Markus Warmuth, M.D., CEO of Monte Rosa. "We look forward to presenting the first clinical data for MRT-2359 later this year, as well as nominating multiple development candidates from our pipeline programs. Backed by a strong cash runway, we are well positioned to continue showcasing the unique capabilities of our drug discovery engine and developing new treatment options for patients with serious diseases of high unmet medical need."

Monte Rosa's current programs are focused on delivering therapies to targets generally considered undruggable or inadequately drugged in well-characterized biological pathways across clinical indications in oncology, inflammation, immunology, and other diseases with high unmet needs. The Company's lead program, MRT-2359, is in Phase 1/2 clinical trials. Additional programs focused on the degradation of CDK2 for oncology, VAV1 for autoimmunity and NEK7 for inflammation are at the lead optimization stage, with multiple development candidates expected to be announced in 2023. Further discovery programs are focused on sickle cell disease-related proteins, as well as multiple currently undisclosed targets.

Business Highlights and Recent Developments

- **Initiated patient dosing in October of its Phase 1/2 clinical trial evaluating MRT-2359 for the treatment of MYC-driven solid tumors, including lung cancer.** MRT-2359 is a potent, selective, and orally bioavailable GSPT1-directed MGD, designed to disrupt protein synthesis in MYC-driven tumors and lead to anti-tumor activity. The Phase 1/2 open-label, multicenter study will primarily assess the safety, tolerability, pharmacokinetic (PK), pharmacodynamic (PD) and preliminary clinical activity of MRT-2359 in patients with previously treated selected solid tumors, including non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), high-grade neuroendocrine cancer of any primary site, diffuse large B-cell lymphoma (DLBCL) and solid tumors with L-MYC or N-MYC amplification. In the Phase 1 portion of the study, patients are receiving escalating doses of MRT-2359 to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D). Once the RP2D is determined, the anti-tumor activity of MRT-2359 will be assessed as part of the

Phase 2 portion of the study, which includes molecular biomarkers for patient stratification and selection.

- **U.S. Food and Drug Administration (FDA) granted Fast Track designation to MRT-2359 in January for the treatment of patients with previously treated, metastatic NSCLC with L-MYC or N-MYC expression.** Fast Track designation is designed to facilitate the development and expedite the review of drug candidates to treat serious conditions and fulfill an unmet medical need. Clinical programs with Fast Track designation may be eligible for more frequent interactions with the FDA throughout the regulatory review process and may be eligible for Accelerated Approval and Priority Review if relevant criteria are met.

- **Advanced immunology-focused VAV1 degrader program into Lead Optimization.** VAV1 is a pivotal signal transduction protein in the adaptive immune system. When activated, VAV1 relays a signal cascade that results in immune cell activation and the secretion of several pro-inflammatory cytokines. Prior to Monte Rosa's research, VAV1 had been considered undruggable. Through analysis and screening by QuEEN™, the Company developed highly potent and selective degraders that have been observed to induce rapid and deep VAV1 degradation, elicit expected on-target downstream functional effects and compelling *in vivo* activity. VAV1 has rapidly advanced into Lead Optimization and is one of three programs that may advance to IND-enabling studies in 2023.

- **Strengthened executive leadership team** with the promotion of Jennifer Champoux to Chief People & Operations Officer and the appointment of Magnus Walter, Ph.D., to Senior Vice President, Chemical Sciences and Process Development

- **Presented at recent scientific and medical conferences including:**
  - 5th Annual Targeted Protein Degradation Summit in Boston, October 25-28, 2022
  - 34th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Barcelona, October 26-28, 2022
  - Molecular Glue Drug Development Summit in Boston, January 25, 2023
  - 4th Swiss Industrial Chemistry Symposium in Basel, January 27, 2023

2023 Objectives and Upcoming Milestones

- Disclosure of initial clinical data including PK, PD, safety and available initial efficacy data from the Phase 1 arm of the ongoing Phase 1/2 clinical trial evaluating MRT-2359 is expected in the second half of 2023
- Nomination of multiple development candidates from Lead Optimization programs in immunology, inflammation and/or oncology and initiation of IND-enabling studies in 2023
- Disclosure of multiple new discovery programs
- Expand molecular glue degrader platform beyond CRBN

Upcoming Data Presentations

- Additional preclinical data from the MRT-2359 program will be presented at the upcoming American Association for Cancer Research (AACR) Annual Meeting, April 14-19, 2023, in Orlando, FL; presentation details, as follows:
  - **Oral Presentation**

Title: New Drugs on the Horizon - Discovery of MRT-2359, an orally bioavailable GSPT1 molecular glue degrader, for MYC-driven cancers
Session: New Drugs on the Horizon: Part 3
Presenter: Owen Wallace, Ph.D., Chief Scientific Officer of Monte Rosa
Date and Time: Monday, April 17; 10:15 - 11:45 a.m. ET

- **Oral Presentation**
  Title: Development of MRT-2359, an orally bioavailable GSPT1 molecular glue degrader, for the treatment of lung cancers with MYC-induced translational addiction
  Session: Mini Symposium
  Abstract: 3449
  Presenter: Gerald Gavory, Ph.D., Senior Director of Drug Discovery and Translational Research at Monte Rosa
  Date and Time: Monday, April 17; 2:30 - 4:30 p.m. ET

FOURTH QUARTER AND FULL YEAR 2022 FINANCIAL RESULTS

Research and Development (R&D) Expenses: R&D expenses for the fourth quarter of 2022 were $24.9 million compared to $18.1 million for the fourth quarter of 2021, and $85.1 million for the year ended December 31, 2022, compared to $57.2 million for the year ended December 31, 2021. The increase in R&D expense was primarily due to the expansion of research and development activities, including the advancement of MRT-2359 into the clinic, pipeline advancement of the VAV1, NEK7 and CDK2 programs, increased headcount and facilities in the United States and Switzerland, and corresponding increases in laboratory-related expenses. R&D expense included non-cash lease expense and non-cash stock compensation expense of $1.6 million and $1.8 million, respectively, for the quarter ended December 31, 2022, and $4.8 million and $6.1 million for the year ended December 31, 2022, respectively. Non-cash stock compensation expense was $1.0 million and $2.6 million for the same periods in 2021.

General and Administrative (G&A) Expenses: G&A expenses for the fourth quarter of 2022 were $7.6 million compared to $5.3 million for the fourth quarter of 2021, and $27.3 million for the year ended December 31, 2022, compared to $15.7 million for the year ended December 31, 2021. The increase in G&A expenses were a result of increased headcount and expenses in support of the company's growth and operations as a public company. G&A expenses included non-cash stock-based compensation of $1.6 million for the fourth quarter of 2022 and $5.6 million for the year ended December 31, 2022, compared to $1.0 million and $2.6 million, respectively, for the same periods in 2021.

Net Loss: Net loss for the fourth quarter of 2022 was $30.8 million compared to $23.4 million for the fourth quarter of 2021, and $108.5 million for the year ended December 31, 2022, compared to $74.0 million for the year ended December 31, 2021.

Cash Position and Financial Guidance: Cash, cash equivalents, restricted cash, and marketable securities as of December 31, 2022, were $268.1 million, compared to $351.4 million as of December 31, 2021. The company expects its cash, cash equivalents, restricted cash and marketable securities will be sufficient to fund planned operations and capital expenditures into 2025.

About Monte Rosa

Monte Rosa Therapeutics is a biotechnology company developing novel molecular glue degrader (MGD) medicines for patients living with serious diseases such as oncology, autoimmune and inflammatory diseases. MGDs are small molecule protein degraders designed to employ the body's natural mechanisms to selectively eliminate therapeutically relevant proteins. The Company's QuEEN™ (Quantitative and Engineered Elimination of Neosubstrates) platform enables it to rapidly identify protein targets and design highly selective degraders by combining diverse libraries of proprietary MGDs with in-house proteomics, structural biology, AI/machine learning, and computational chemistry capabilities. For more information, visit www.monterosatx.com

Forward-Looking Statements

This communication includes express and implied "forward-looking statements," including forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward looking statements include all statements that are not historical facts, and in some cases, can be identified by terms such as "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "potential," "continue," "ongoing," or the negative of these terms, or other comparable terminology intended to identify statements about the future. Forward-looking statements contained in herein include, but are not limited to, statements about our product development activities, including our expectations around MRT-2359 and the potential significance of obtaining Fast Track Designation from the FDA, the ongoing development of our QuEEN™ platform and the advancement of our pipeline and the various products therein, including the timing for initiation of IND-enabling studies for VAV1 and other programs, our expectations regarding and the timing of our clinical trial for MRT-2359, our ability to initiate and the timing of initiation of additional lead optimization programs, and our expectations regarding our ability to nominate and the timing of our nominations of additional development candidates, as well as our expectations of success for our programs and the strength of our financial position, among others. By their nature, these statements are subject to numerous risks and uncertainties, including the impact that the COVID-19 pandemic may have on our development activities and operations, as well as those risks and uncertainties set forth in our most recent Quarterly Report on Form 10-Q and Annual Report on Form 10-K for the year ended December 31, 2021 filed with the US Securities and Exchange Commission, and any subsequent filings, that could cause actual results, performance or achievement to differ materially and adversely from those anticipated or implied in the statements. You should not rely upon forward looking statements as predictions of future events. Although our management believes that the expectations reflected in our statements are reasonable, we cannot guarantee that the future results, performance or events and circumstances described in the forward-looking statements will be achieved or occur. Recipients are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date such statements are made and should not be construed as statements of fact. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, any future presentations or otherwise, except as required by applicable law. Certain information contained in these materials and any statements made orally during any presentation of these materials that relate to the materials or are based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party studies, publications, surveys and other data to be reliable as of the date of these materials, we have not independently verified, and make no representations as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, no independent source has evaluated the reasonableness or accuracy of our internal estimates

or research and no reliance should be made on any information or statements made in these materials relating to or based on such internal estimates and research.

Consolidated Balance Sheets
(in thousands, except share amounts)

	December 31,	
	2022	**2021**
Assets		
Current assets:		
Cash and cash equivalents	$ 54,912	$ 346,071
Marketable securities	207,914	—
Other receivables	7,656	—
Prepaid expenses and other current assets	4,444	2,595
Current restricted cash	960	—
Total current assets	275,886	348,666
Property and equipment, net	27,075	12,325
Operating lease right-of-use assets	34,832	—
Restricted cash, net of current	4,318	5,338
Other long-term assets	278	—
Total assets	$ 342,389	$ 366,329
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 7,862	$ 6,558
Accrued expenses and other current liabilities	14,580	10,080
Current portion of operating lease liability	3,127	—
Total current liabilities	25,569	16,638
Defined benefit plan liability	1,533	2,176
Operating lease liability	43,874	—
Total liabilities	70,976	18,814
Commitments and contingencies		
Stockholders' equity		
Common stock, $0.0001 par value; 500,000,000 shares authorized, 49,445,802 shares issued and 49,323,531 shares outstanding as of December 31, 2022; and 500,000,000 shares authorized, 46,794,295 shares issued and 46,535,966 shares outstanding as of December 31, 2021	5	5
Additional paid-in capital	503,696	471,566
Accumulated other comprehensive loss	(1,752)	(2,021)
Accumulated deficit	(230,536)	(122,035)
Total stockholders' equity	271,413	347,515
Total liabilities and stockholders' equity	$ 342,389	$ 366,329

Consolidated Statements of Operations and Comprehensive Income (Loss)
(In thousands, except share and per share amounts)

	Three months ended December 31,		Year ended December 31,	
	2022	2021	2022	2021
Operating expenses:				
Research and development	$ 24,868	$ 18,130	$ 85,061	$ 57,155
General and administrative	7,621	5,257	27,323	15,727
Total operating expenses	32,489	23,387	112,384	72,882
Loss from operations	(32,489)	(23,387)	(112,384)	(72,882)
Other income (expense):				
Interest income, net	1,990	13	3,764	46
Foreign currency exchange gain (loss), net	(283)	(66)	10	(162)
Gain on disposal of fixed assets	—	—	109	—
Changes in fair value of preferred stock tranche obligations, net	—	—	—	(960)
Total other income (expense)	1,707	(53)	3,883	(1,076)
Net loss	$ (30,782)	$ (23,440)	$ (108,501)	$ (73,958)
Net loss per share attributable to common stockholders—basic and diluted	$ (0.63)	$ (0.50)	$ (2.30)	$ (2.96)
Weighted-average number of shares outstanding used in computing net loss per common share—basic and diluted	48,893,160	46,509,897	47,227,370	25,000,124
Net loss	$ (30,782)	$ (23,440)	$ (108,501)	$ (73,958)
Other comprehensive income (loss):				
Provision for pension benefit obligation	619	(71)	718	(965)
Unrealized gain (loss) on available-for-sale securities	231	—	(449)	—
Comprehensive loss	$ (29,932)	$ (23,511)	$ (108,232)	$ (74,923)

Investors
Shai Biran, Monte Rosa Therapeutics
ir@monterosatx.com

Media
Dan Budwick, 1AB
dan@1abmedia.com


From Serendipity to Rational Design
Taking Molecular Glue Degraders to New Heights | March 2023
Monte Rosa
Therapeutics

Forward-Looking Statements

These materials include express and implied "forward-looking statements," including forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward looking statements include all statements that are not historical facts, and in some cases, can be identified by terms such as "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "potential," "continue," "ongoing," or the negative of these terms, or other comparable terminology intended to identify statements about the future. Forward-looking statements contained in herein include, but are not limited to, statements about our product development activities, including our expectations around the potential of molecular glue degraders and MRT-2359, such as for our ongoing clinical trial for MRT-2359 and the timing thereof, the ongoing development of our QuEEN™ platform and its potential for the discovery of additional product candidates, the advancement, and timing thereof, of our pipeline and the various products therein, our ability to initiate and the timing of initiation of additional lead optimization programs, and our expectations regarding our ability to nominate and the timing of our nominations of additional development candidates, as well as our expectations of success for our programs and the strength of our financial position, among others. By their nature, these statements are subject to numerous risks and uncertainties, including the impact that the ongoing COVID-19 pandemic will have on our development activities and operations, as well as those risks and uncertainties set forth in our Annual Report on Form 10-K for the fourth quarter and full year ended December 31, 2021 filed, with the US Securities and Exchange Commission on March 29, 2022, and any subsequent filings, including our most recently filed Quarterly Report on Form 10-Q, that could cause actual results, performance or achievement to differ materially and adversely from those anticipated or implied in the statements. You should not rely upon forward looking statements as predictions of future events. Although our management believes that the expectations reflected in our statements are reasonable, we cannot guarantee that the future results, performance or events and circumstances described in the forward-looking statements will be achieved or occur. Recipients are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date such statements are made and should not be construed as statements of fact. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, any future presentations or otherwise, except as required by applicable law. Certain information contained in these materials and any statements made orally during any presentation of these materials that relate to the materials or are based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party studies, publications, surveys and other data to be reliable as of the date of these materials, we have not independently verified, and make no representations as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, no independent source has evaluated the reasonableness or accuracy of our internal estimates or research and no reliance should be made on any information or statements made in these materials relating to or based on such internal estimates and research.

Monte Rosa Therapeutics - Highlights

Taking molecular glue degraders (MGDs) to new heights

Developing breakthrough drugs that **selectively degrade therapeutically-relevant proteins** previously considered undruggable

Five disclosed programs targeting high unmet medical needs in oncology, autoimmune disease, inflammation and other indications

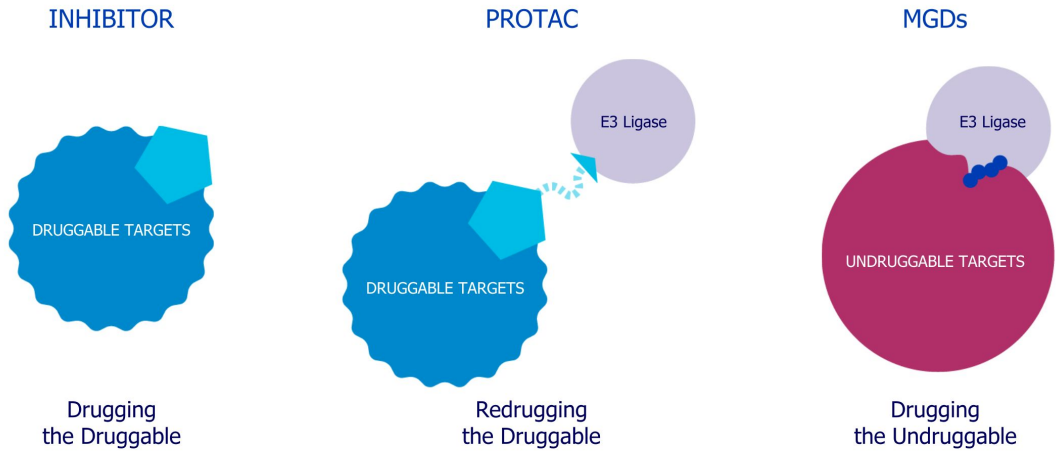
PhI/II initiated for MRT-2359 with clinical development in MYC-driven tumors

AI-based degron prediction & rational design of highly selective MGDs enable a next-generation molecular glue-based targeted protein degradation platform

Strong financial position with $268M cash as of December 31, 2022, providing runway into 2025

Molecular Glue Degraders (MGDs) – Drugging The Undruggable

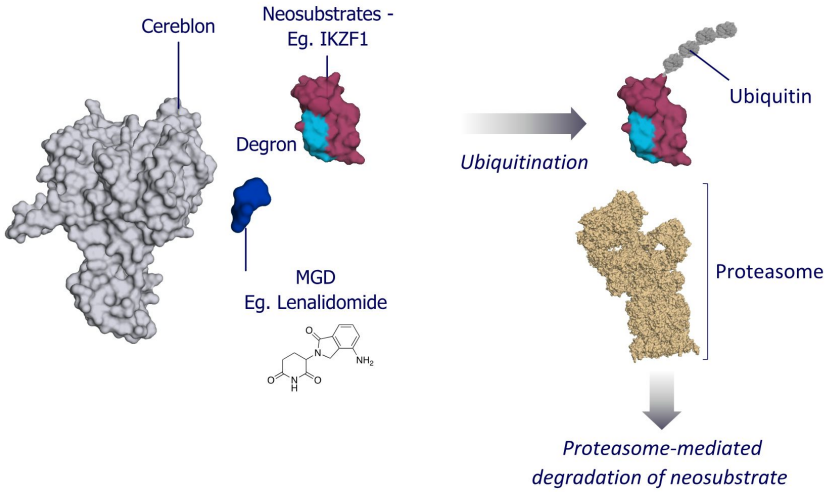
Expanding target space, fostering a new generation of drugs



Expanding the Degradable Proteome

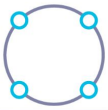
Target Space

Molecular Glue Degraders are a Clinically Validated Modality



- **Differentiated** target space
- Favorable **drug-like** properties
- Broad **tissue distribution**
- **No "hook effect"** (seen with PROTACS)
- Clinically **validated**

QuEEN™ is Redefining the Rules of MGD Discovery

Traditional thinking		Monte Rosa Therapeutics approach
'Target space is limited'		**QuEEN™ has vastly expanded the degradable target space across a broad range of undruggable protein classes**
'MGDs are identifed by serendipity'		**QuEEN™ enables target centric and systematic discovery of MGDs**
'Med Chem rules don't apply to MGDs'		**AI-driven and/or structure-based design allow rational Med Chem optimization of MGDs**
'MGDs are not selective'		**High specificity achievable even within same protein class, families and isoforms**

Monte Rosa Therapeutics

Portfolio

Leveraging a Leading Drug Discovery Platform

Purpose-built to discover and develop a wide landscape of therapeutically-relevant MGDs

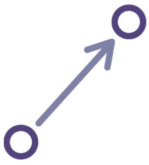
Monte Rosa's High-Value Proprietary Pipeline

Targets

Undruggable and inadequately drugged degron-containing proteins

Target non-catalytic and scaffolding functions

High level of target validation, preclinically and clinically



Clinical Path

Programs with a biomarker-based patient selection strategy and a clear path to the clinic

Opportunity for a rapid clinical PoC showing MOA and efficacy

Patient Benefit

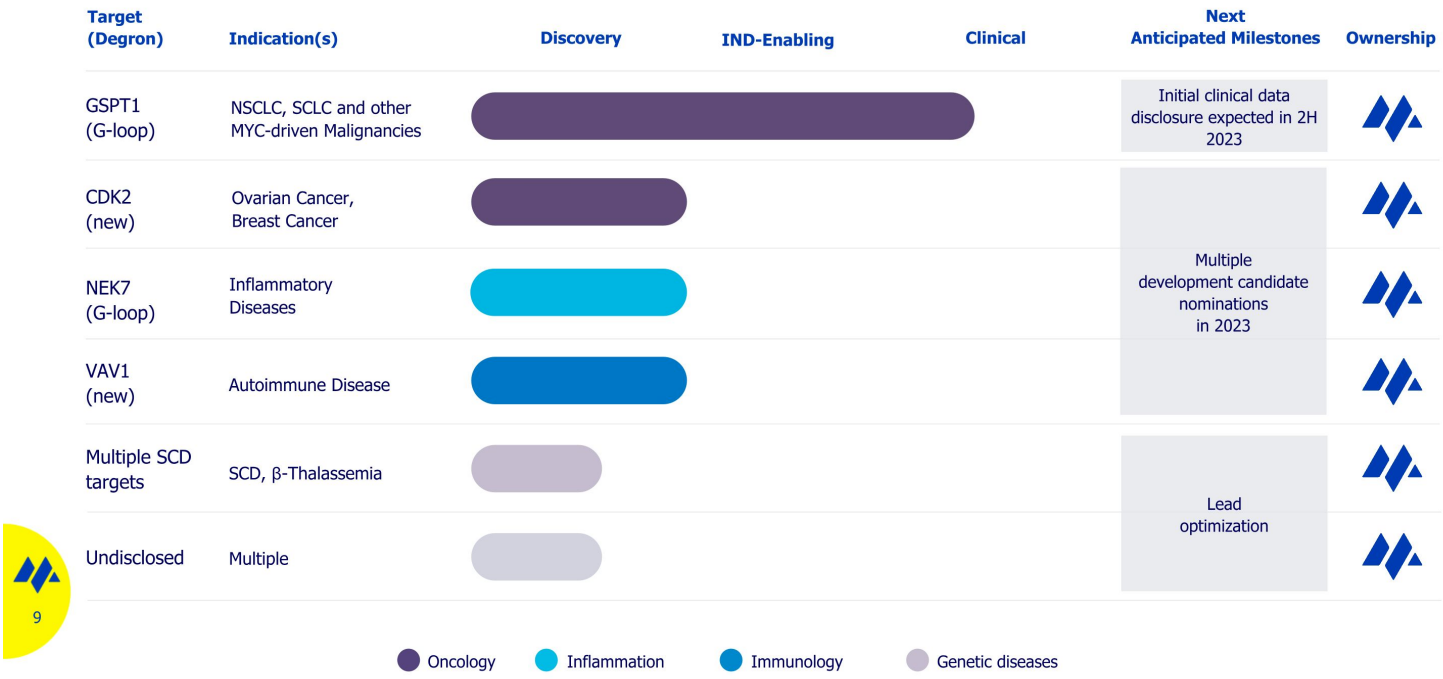
Address high unmet needs

Drug a wide range of therapeutically-relevant proteins in oncology and beyond

Create synergies within therapeutic areas

Monte Rosa Pipeline

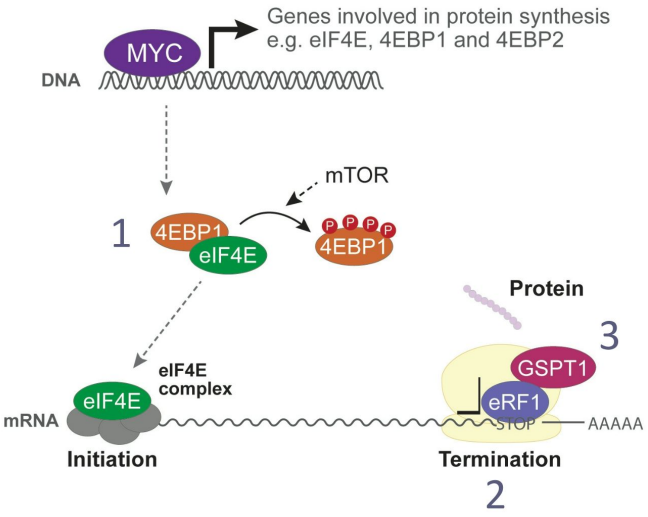
Rapidly advancing wholly owned MGD programs targeting undruggable proteins



Monte Rosa Therapeutics

GSPT1 Program

Targeting MYC-driven Tumors and Their Addiction to Protein Translation



1 Addiction

To sustain growth, MYC-driven tumors are **addicted to protein translation**

2 Dependency

This addiction creates a dependency on the **translation termination factor GSPT1**

3 Therapeutic vulnerability

GSPT1 is a therapeutic vulnerability of MYC-driven tumors which can be targeted using molecular glue degrader (MGD)

Discovery of MRT-2359

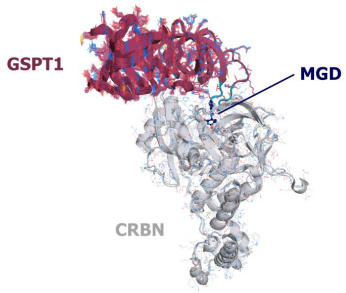
MRT-2359 – our GSPT1-directed MGD in Clinical Development for MYC-Driven Tumors

- MRT-2359 is a highly selective GSPT1-directed MGD designed through our QuEEN™ platform
- Has favorable drug like properties and is orally bioavailable
- Has optimal degradation kinetics to achieve preferential activity in MYC-driven cancer cells
- Shows preferential activity in MYC-driven cancer cells of various solid tumor lineages, including non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)
- Displays preferential in vivo activity across >70 primary human xenograft (PDX) models stratified for MYC expression levels as well as in NE lung cancer PDX models
- IND cleared for Phase 1/2 trial in September 2022 and patient dosing initiated in October 2022
- First clinical data disclosure including PK, PD, safety and available initial efficacy data expected in 2H 2023

QuEEN™ Discovery Engine Facilitates the Discovery of MRT-2359

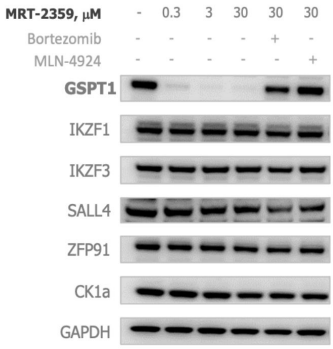
MRT-2359 is a potent GSPT1 degrader

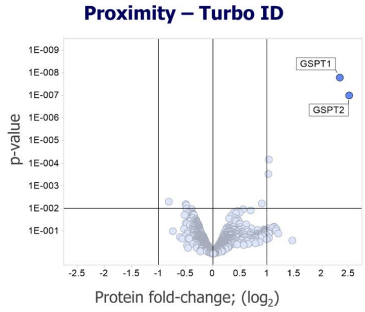
Ternary complex modelling



***in vitro* data**	
CRBN binding, K_i	113 nM
Ternary complex, EC_{50}	< 7 nM
Degradation, DC_{50} /D_{max} (in disease relevant cell lines)	1 - 20 nM / 100%

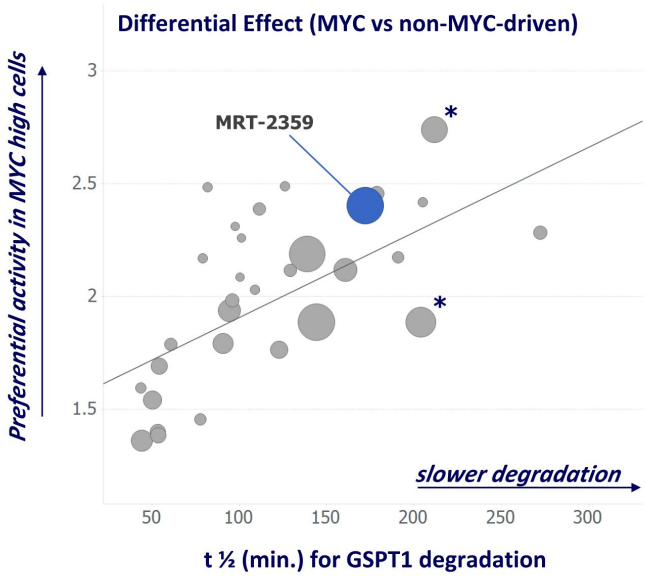
MRT-2359 induces selective GSPT1 degradation and has a favorable ADME/DMPK profile





ADMET profile	
CYP DDIs	> 30 µM
hERG inhibition patch clamp	EC_{50} > 30 µM
Oral bioavailability all species	~50%

MRT-2359 Has Optimized Degradation Kinetics, Selectivity and Bioavailability

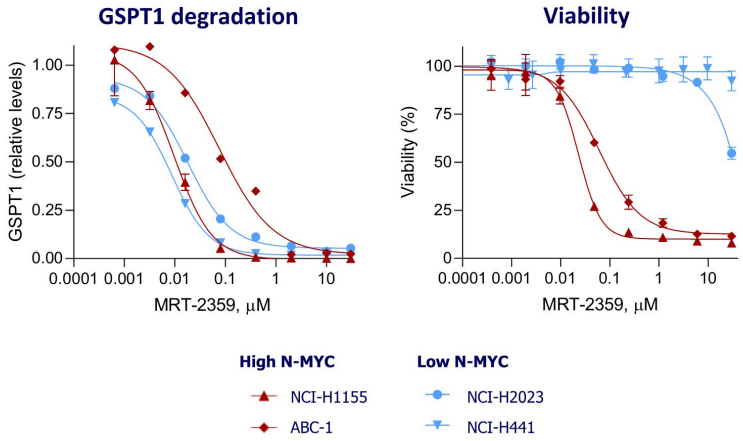


- Kinetic measurements of degradation reveal **novel parameter for optimization**
- GSPT1 degradation **kinetics are linked to its MoA**
- MRT-2359 achieves **a high preferential effect** (2.4 U) in high-MYC NSCLC
- MRT-2359 has been rationally designed to be in the ADMET sweet-spot
- Several compounds with good oral bioavailability discovered (large circles = >40% bioavailability PO)

*** Compounds with reactive metabolite flag**

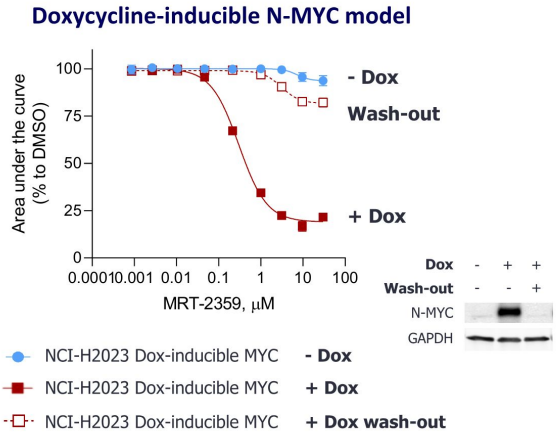
MRT-2359 Shows Preferential Activity in MYC-Driven NSCLC Lines

MRT-2359 induces GSPT1 degradation and shows preferential activity in N-MYC high cell lines



GSPT1 western blot at 6 hr (N-MYC high) and 24 hr (low). 72 hr viability assay (CTG)

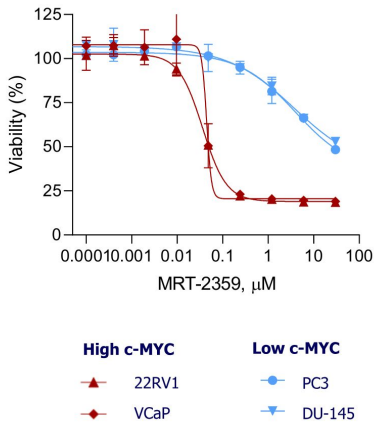
N-MYC overexpression sensitizes NCI-H2023 resistant cells to MRT-2359



Incucyte, 96 hr post treatment

MRT-2359 Shows Preferential Activity in MYC High or Neuroendocrine (NE) Cancer Cell Lines

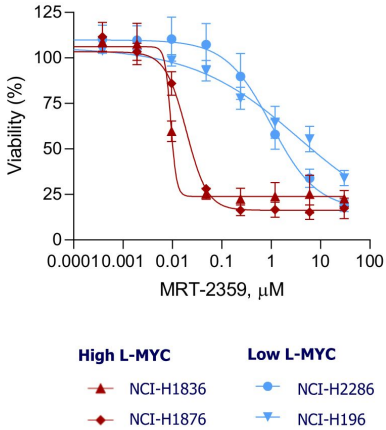
Prostate cell lines (c-MYC)



High c-MYC
- 22RV1
- VCaP

Low c-MYC
- PC3
- DU-145

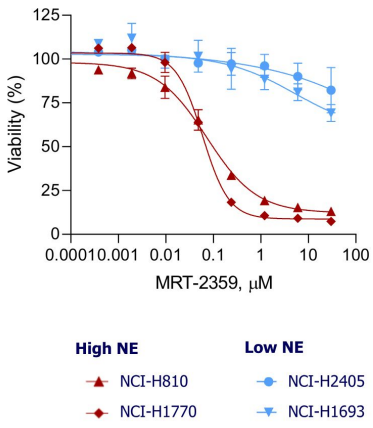
SCLC cell lines (L-MYC)



High L-MYC
- NCI-H1836
- NCI-H1876

Low L-MYC
- NCI-H2286
- NCI-H196

Lung cancer cell lines (NE)



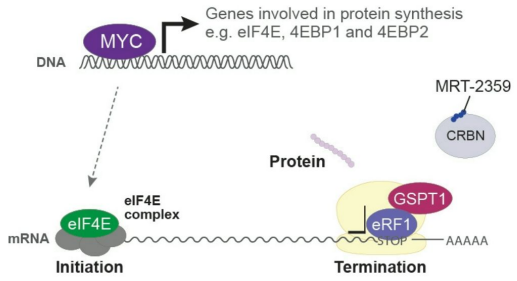
High NE
- NCI-H810
- NCI-H1770

Low NE
- NCI-H2405
- NCI-H1693

72 hr viability assay (CTG)

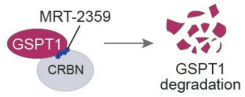
Mechanism of Action of MRT-2359

Three Mechanisms Driving Preferential Activity in MYC High Cancer Lines



Preferential GSPT1 degradation

MRT-2359 leads to rapid and deeper degradation of GSPT1 in cancer cells with high MYC expression

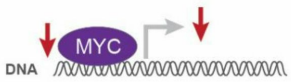


Preferential inhibition of translation

MRT-2359 preferentially impairs protein synthesis in tumor cells with high MYC expression

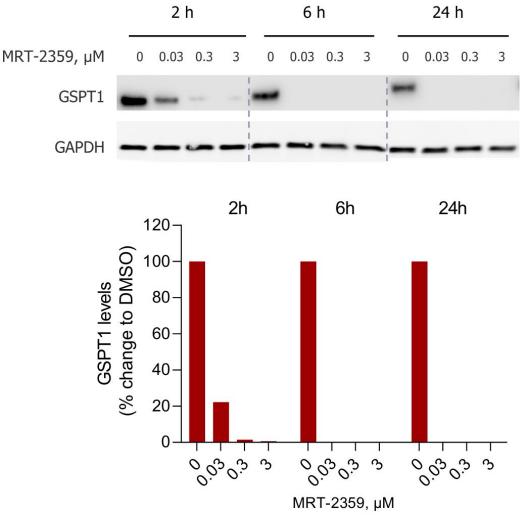
MYC down modulation

MRT-2359 indirectly affects MYC expression and transcriptional activity

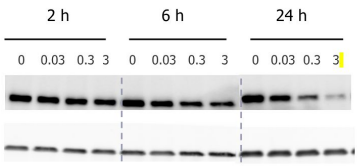


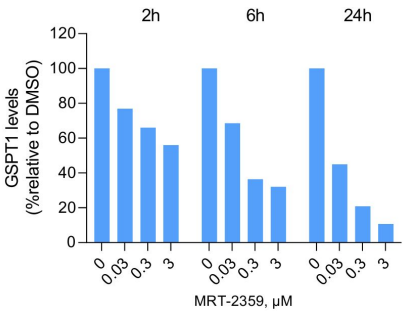
MRT-2359 Degrades GSPT1 More Rapidly in MYC-Driven Tumor Cells

High N-MYC
NCI-H1155



Low N-MYC
NCI-H2023





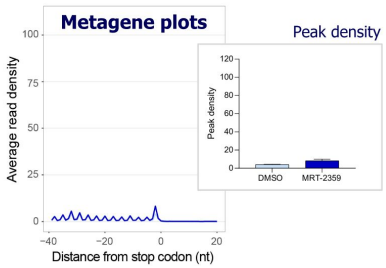
Similar effects shown in additional cancer cell lines

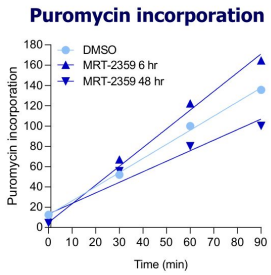
MRT-2359 Preferentially Impairs Protein Synthesis in Tumor Cells with High MYC Expression

MRT-2359 induces ribosome stalling at stop codon only in N-MYC high cell line

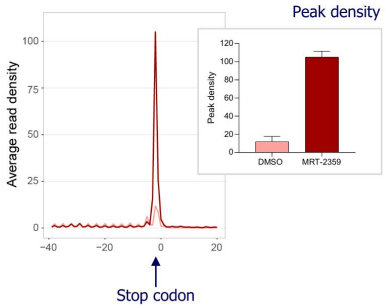
MRT-2359 completely abrogates protein synthesis only in N-MYC high cell line

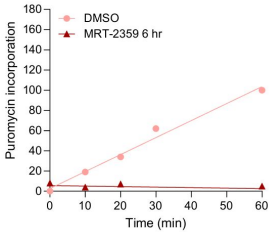
Low N-MYC
NCI-H2023





High N-MYC
NCI-H1155



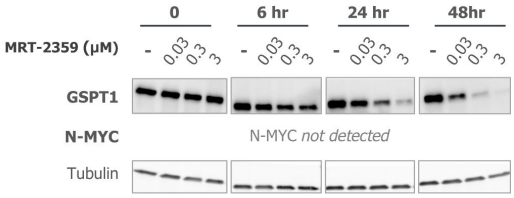


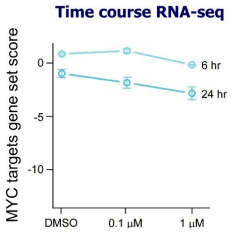
MRT-2359 Affects the MYC Pathway in N-MYC High NSCLC Cell Lines

MRT-2359 induce GSPT1 degradation leading to N-MYC protein downregulation in NCI-H1155

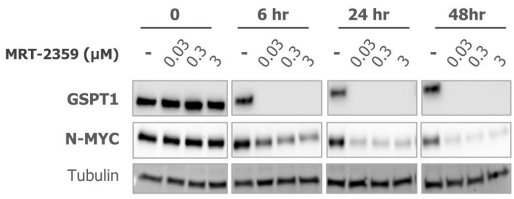
Degradation of GSPT1 leads to downregulation of N-MYC transcriptional output in NCI-H1155

Low N-MYC
NCI-H2023





High N-MYC
NCI-H1155



Transcriptional modulation of >200 MYC target genes

Benchmarking of MRT-2359

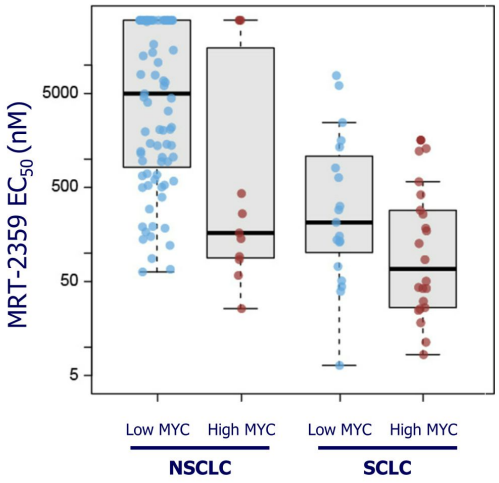
MRT-2359 Shows Superior Characteristics Compared to CC-90009

	Assay	MRT-2359	CC-90009
in vitro	Selectivity (TMT Px, WB)	GSPT1, GSPT2	GSPT1, GSPT2, SALL4, FIZ1, RNF166, ODC1
	CYP DDI (2B6, 1A2, 2D6,3A4, 2C8,2C9, 2C19)	> 30 uM	CYP2C19 @ 1.5 uM
	hERG (patch clamp)	> 30 uM	5.3 uM
	CEREP	a1A > 50% @ 10 uM	M1/M2 > 50% @ 10 uM
	Caco2 (Efflux Ratio)	9	>100
Clinical	Route of Administration	**PO**	**IV**
	Schedule	**5 days on / 9 days off cycles**	**5 days on / 23 days off**
	Stratification	**MYC high, neuroendocrine**	**None reported**
	Development status	Phase I/II	Phase I/II

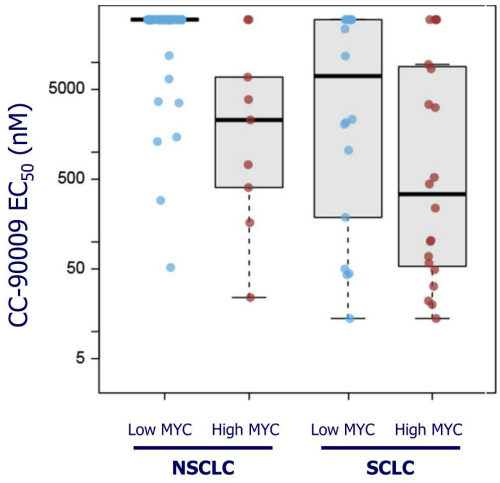
* Comparison based on internal profiling. Selectivity based on internal data as well as data from DFCI Proteomic data base https://proteomics.fischerlab.org

Superior Activity of MRT-2359 in MYC-driven Lung Cancer Cell Lines Compared to CC-90009

MRT-2359



CC-90009



* Comparison based on internal profiling

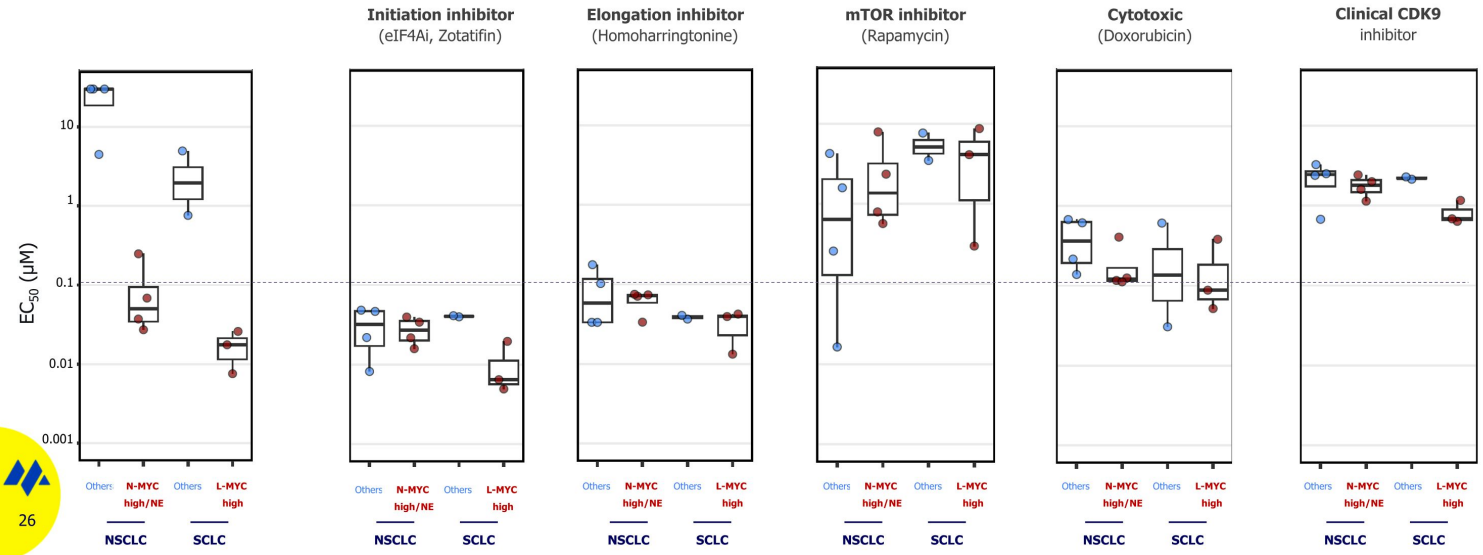
72 hr viability assay (CTG).

MRT-2359 - Unique Preferential Activity in MYC High Lung Cancer Lines

MRT-2359

Other therapeutic agents targeting protein translation process or machinery lack preferential activity in the MYC high lung lines

Similarly for agent targeting Myc transcriptional reprogramming



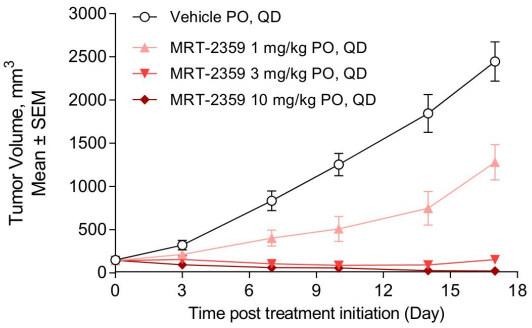
72 hr viability assay (CTG).

in vivo activity of MRT-2359

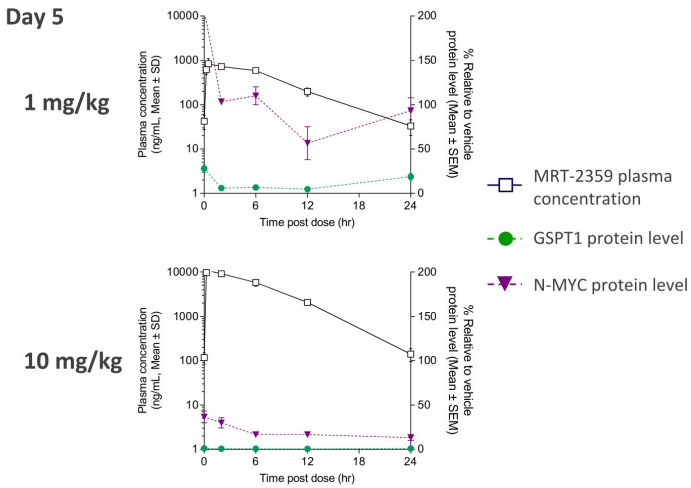
MRT-2359 Induces Tumor Regressions in N-MYC-driven Xenograft Models

Oral dosing of MRT-2359 shows anti-tumor activity and regressions in NCI-H1155

Similar observations in other high N-MYC expression models (ABC-1, NCI-H1770)



Dose- and time-dependent degradation of GSPT1 is associated with N-MYC downregulation

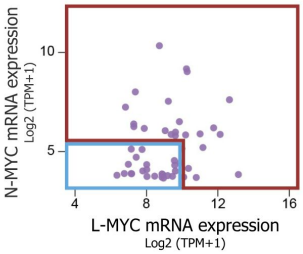


MRT-2359 Mouse-trial in NSCLC, SCLC and Lung NE Patient-derived Xenografts

Collection of PDX models

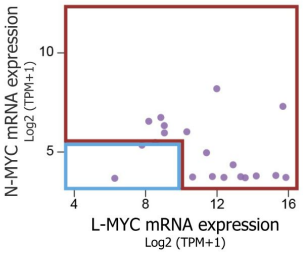
All models have been characterized by DNA and RNA-seq

NSCLC



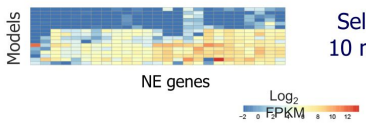
Selected 48 models

SCLC



Selected 20 models

Large cell NE carcinoma or NE lung cancer



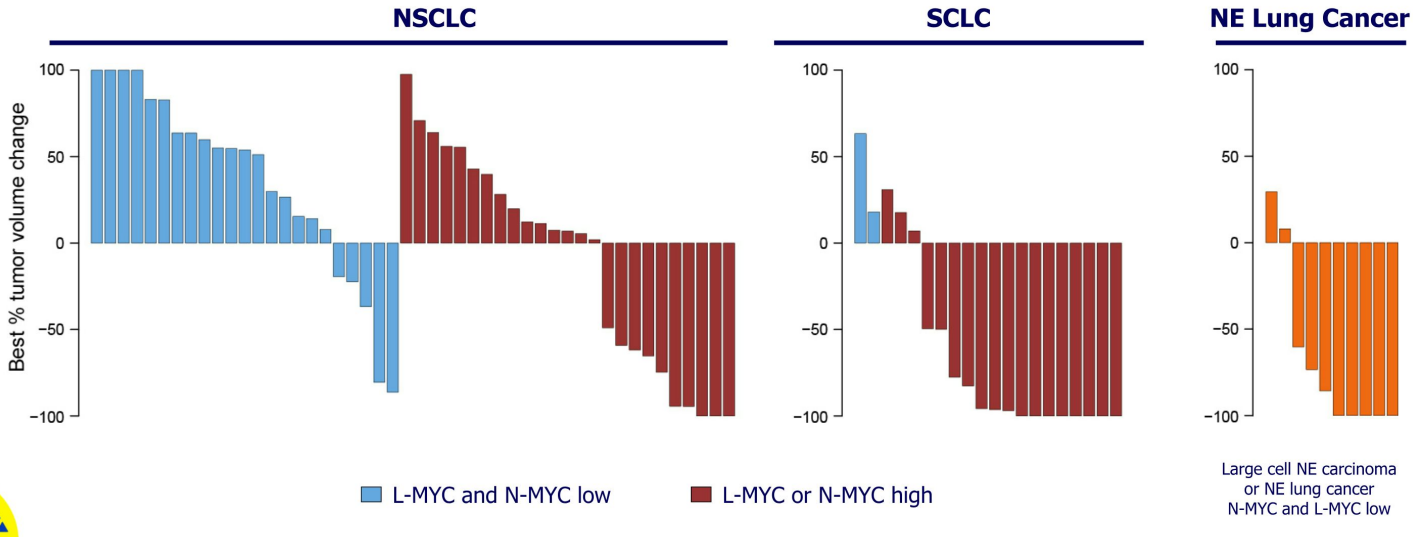
Selected 10 models

Models selected across a range of N-MYC and L-MYC mRNA expression levels or NE status were treated with

- Vehicle
- MRT-2359 10 mg/kg PO QD

3 mice for each treatment group

MRT-2359 Demonstrates Preferential Anti-tumor Activity in MYC High or Neuroendocrine (NE) Lung Cancer Patient-derived Xenografts



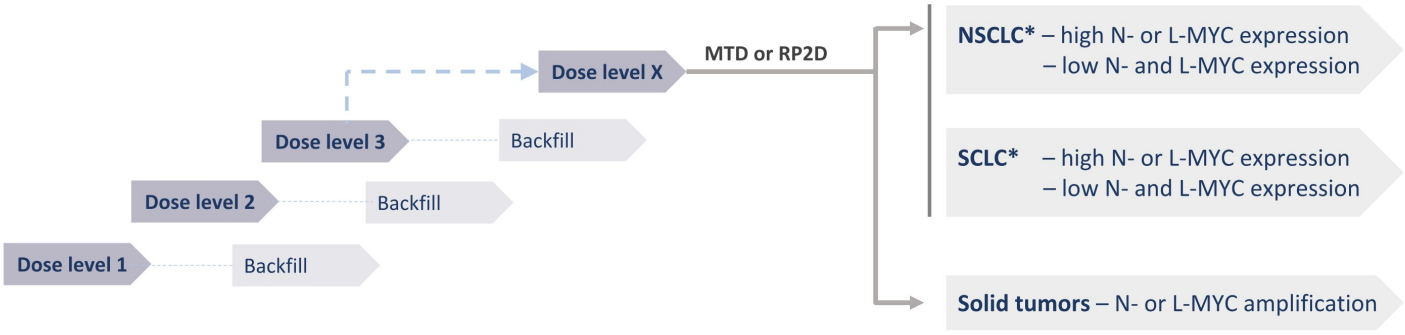
MRT-2359 10 mg/kg, PO, QD

MRT-2359 Clinical Development

MRT-2359-001 Phase 1/2 - Clinical Study Design

Phase 1: Dose Escalation

Lung cancer (NSCLC & SCLC), DLBCL, high-grade neuroendocrine tumors, and N-/L-MYC amplified solid tumors



Backfill slots for additional patients for each dose level

Phase 2: Expansion Cohorts

NSCLC* – high N- or L-MYC expression
– low N- and L-MYC expression

SCLC* – high N- or L-MYC expression
– low N- and L-MYC expression

Solid tumors – N- or L-MYC amplification

* Efficacy guided stratification per N-/L-MYC expression

Patient dosing initiated in October 2022

Targeting L-/N-MYC Positive and Neuroendocrine Tumors with MRT-2359

Current focus	Future options
Small cell lung cancer **67K patients** – 70% MYC high	**Triple-negative breast cancer**
Non-small cell lung cancer **394K patients** – 15% MYC high	**Ovarian cancer**
Neuroendocrine lung cancer	**Endometrial cancer**
Neuroendocrine prostate cancer	**Bladder cancer**

c-MYC driven indications being further explored in preclinical translational studies

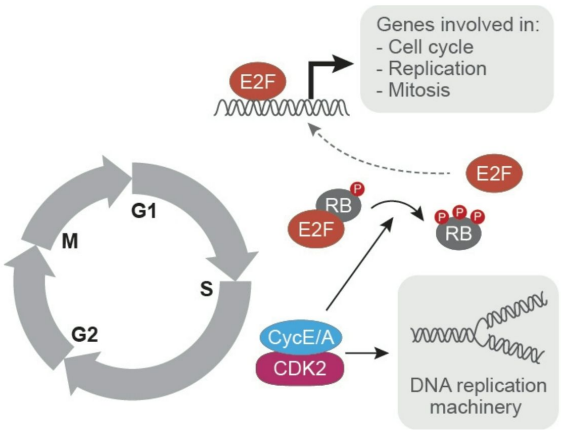
Patient diagnosed incidence #s, major markets (US, EU and JP): Decision Resources Group (DRG)
% population based on preliminary internal cut offs for high vs low expression applied to real world data provided by Tempus

Monte Rosa Therapeutics

CDK2 Program

CDK2 as a Target for Selected Solid Tumors

CDK2 is one of the key regulators of the cell cycle



Therapeutic hypothesis: Tumors with CDK2 pathway activation by:

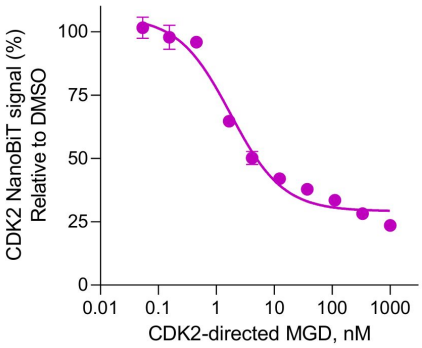
- High CyclinE1/E2 expression
- Loss of RB

Clinical Opportunity: CDK2 driven cancers: ER positive breast cancer pre and post treatment with CDK4/6 inhibitors (474K patients), ovarian cancer (64K patients), and endometrial cancer (124K patients)

Patient diagnosed incidence #s, major markets (US, EU and JP): Decision Resources Group (DRG)

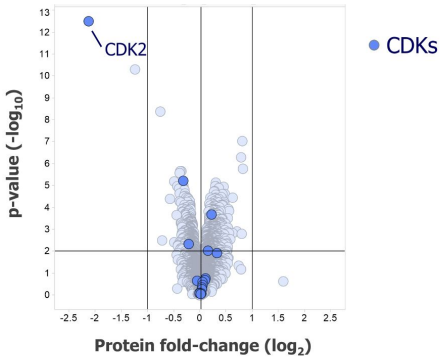
CDK2-directed MGD Shows Selective Degradation Over the Other CDKs

CDK2-directed MGD induces CDK2 degradation



NanoBiT assay (24hr) - HEK293

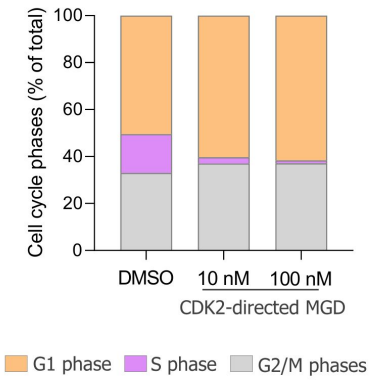
CDK2-directed MGDs are selective over other CDKs



TMT Proteomics (24hr) – HEK293

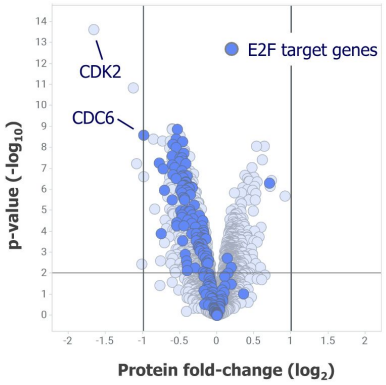
CDK2-directed MGD Shows Biological Activity in a CDK2-dependent Cell Line

CDK2 degradation arrests CDK2-dependent cells in G1 phase



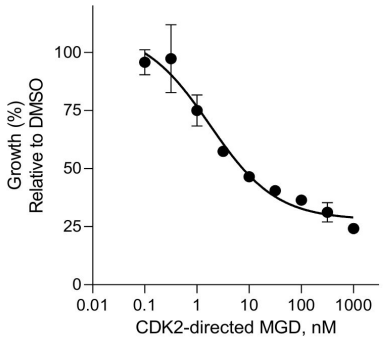
Cell cycle profile (48hr) – MDA-MB-157

CDK2 degradation results in reduction of E2F pathway proteins



TMT Proteomics (24 hr) – MDA-MB-157

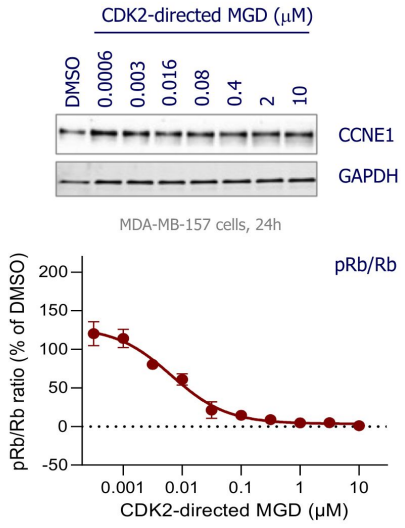
CDK2-directed MGD inhibits proliferation of CDK2 dependent cells



CyQuant assay (7d) – MDA-MB-157

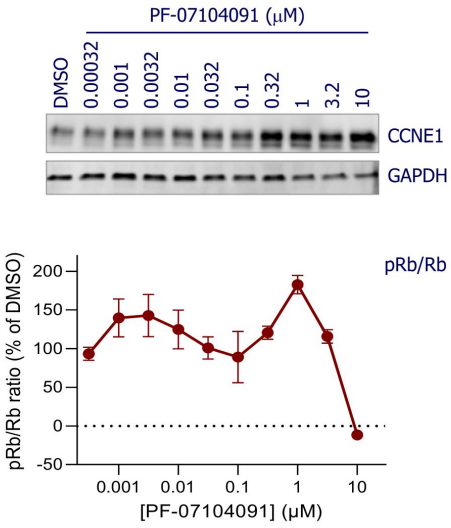
CDK2-directed MGDs Have a Differentiated MoA Compared to CDK2 Inhibitors

No CCNE1 upregulation or pRb rebound in CDK2-directed MGD treated cells



MDA-MB-157 cells, pRb (S780)/total Rb multiplex AlphaLISA, 24h

CDK2 Inhibitor, PF-07104091, upregulates CCNE1 and causes pRb rebound



MDA-MB-157 cells, pRb (S780) / total Rb multiplex AlphaLISA, 24h

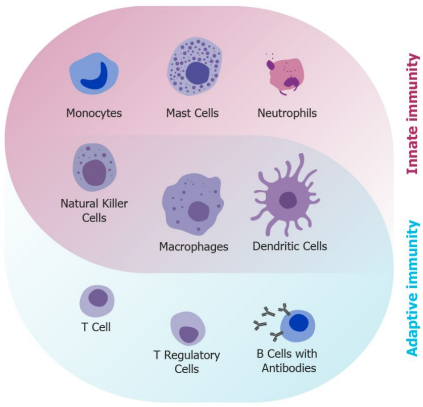
Monte Rosa Therapeutics

Inflammation and Immunology (I&I) Programs

QuEEN™ Enables Access to Undruggable Targets in Immune Pathways

Targets	Biology	Medical Need

- Multiple highly validated, undruggable targets amenable to our platform identified
- QuEEN™ platform enables exquisite selectivity required for non-oncology diseases
- CRBN shown to allow tunable elimination of immune target proteins
- VAV1 and NEK7 programs lead the way with multiple additional targets being explored



Systemic Lupus Erythematosus

Rheumatoid Arthritis

Gout

Systemic Sclerosis

Multiple Sclerosis

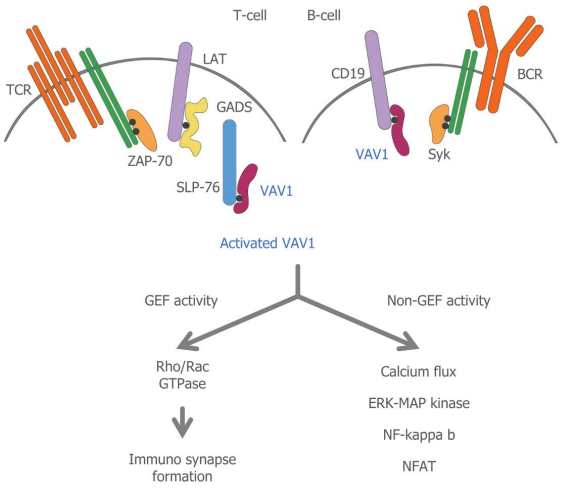
Additional indications

Monte Rosa Therapeutics

VAV1 Program

VAV1 as a Target for Autoimmune Disease

VAV1 plays a key role in T-cell and B-cell development and activation



Therapeutic hypothesis:

- VAV1 relays signals from both the T and B cell receptor
- VAV1 knockout/mutant mice have dysfunctional T cells and are resistant to immunopathologies such as autoimmune disease or graft-versus-host disease

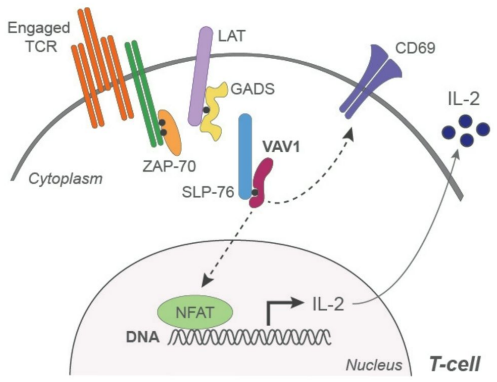
Clinical Opportunity:

- Autoimmune disorders including rheumatoid arthritis (6.2M patients), multiple sclerosis (1.3M patients), myasthenia gravis (36K – 60K patients in US), and acute graft-versus-host disease (10K patients)

Patient diagnosed prevalence and incidence #s, major markets (US, EU and JP): DRG; Facts about Myasthenia Gravis | MGFA accessed March 15, 2023

VAV1 is a Highly Validated Target for Attenuating T-cell Activity

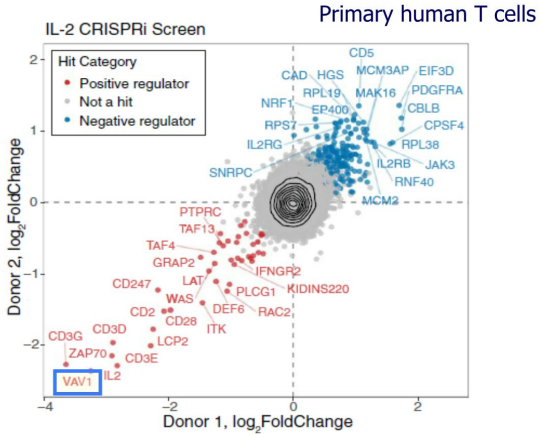
VAV1 controls several aspects of T-cell activity



TCR = T-cell receptor

Multiple CRISPR screens identified VAV1 as key player in T-cell function

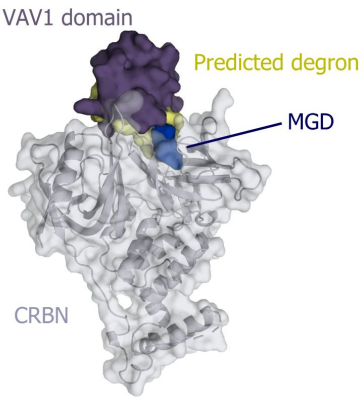
Primary human T cells



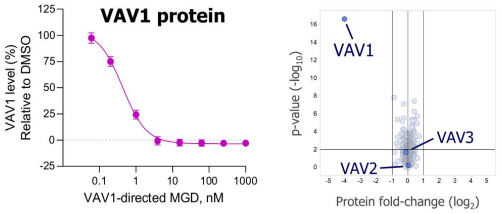
Schmidt et al., Science 2022

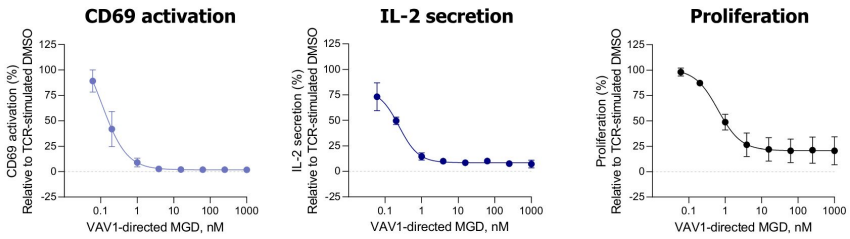
Discovery of Highly Selective VAV1-directed MGDs

Degron predicted and confirmed



MGD-induced degradation of VAV1 results in inhibition of TCR-mediated CD69 activation, IL-2 secretion, and proliferation

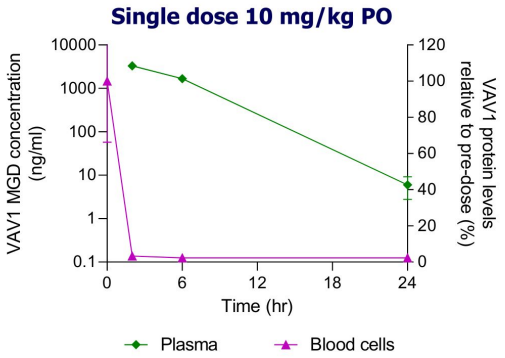




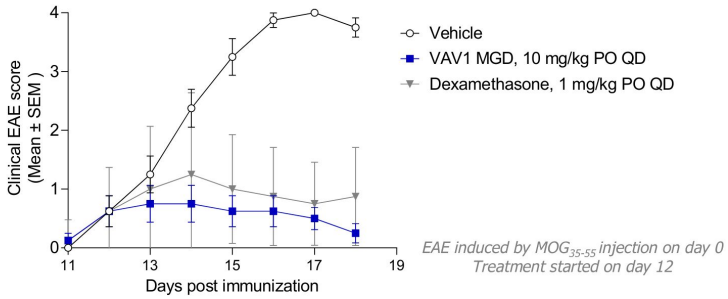
Human primary pan-T cells TCR stimulation = α-CD3/CD28

VAV1-directed MGD Inhibits Disease Progression in an EAE Mouse Model

MGD induces VAV1 degradation in PBMCs after a single oral dose in mice



MGD inhibits disease progression in experimental autoimmune encephalomyelitis (EAE) mouse model of multiple sclerosis



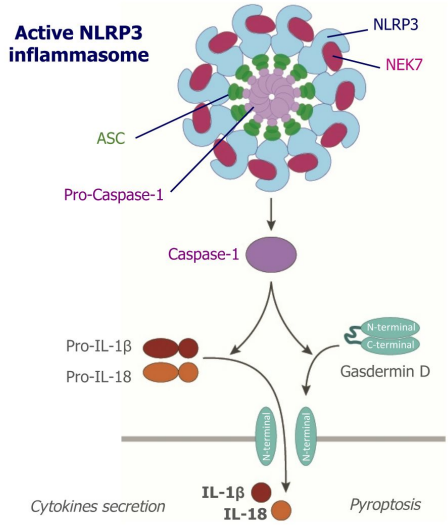
Additional autoimmune and immunology disease models are currently under evaluation

Monte Rosa Therapeutics

NEK7 Program

NEK7 (NIMA-Related Kinase 7) as a Target for Inflammatory Disease

NEK7 is an essential regulator of the inflammasome



Therapeutic hypothesis: Diseases with over-activated or mutated NLRP3 inflammasome

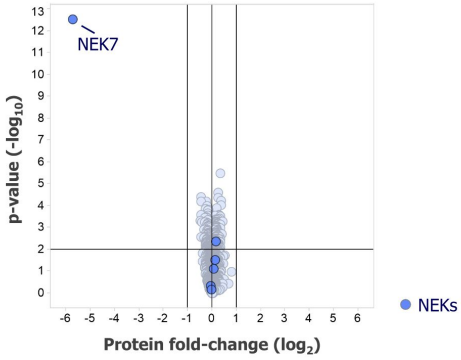
- NEK7 licenses NLRP3 assembly in a kinase independent manner
- NEK7-deficient macrophages are severely impaired in IL-1β and IL-18 secretion

Clinical opportunity: First-in-class NEK7 degraders for

- Over-activated NLRP3 inflammasome: metabolic pathologies, cardiovascular diseases, inflammatory issues and neurologic disorders
- NLRP3 activating mutations: Cryopyrin-associated periodic syndromes (CAPS)

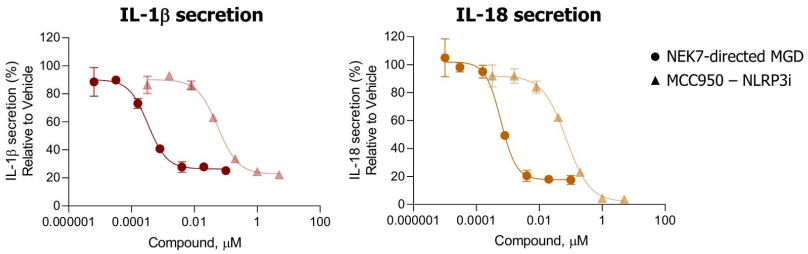
NEK7-directed MGDs Modulate NLRP3 Pathway in Human Macrophages

NEK7-directed MGD shows high selectivity



TMT Proteomics (24hr) – U937

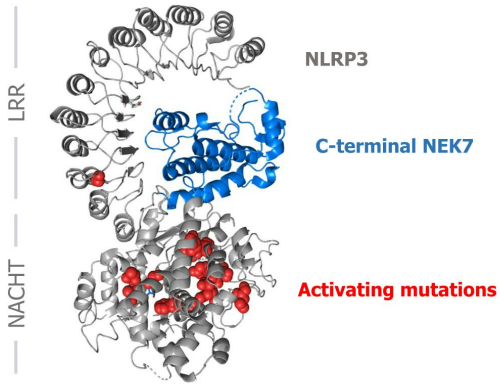
NEK7-directed MGD compared to NLRP3 inhibitor



IL-1β and IL-18 release (24hr) - human macrophages LPS/MSU stimulated

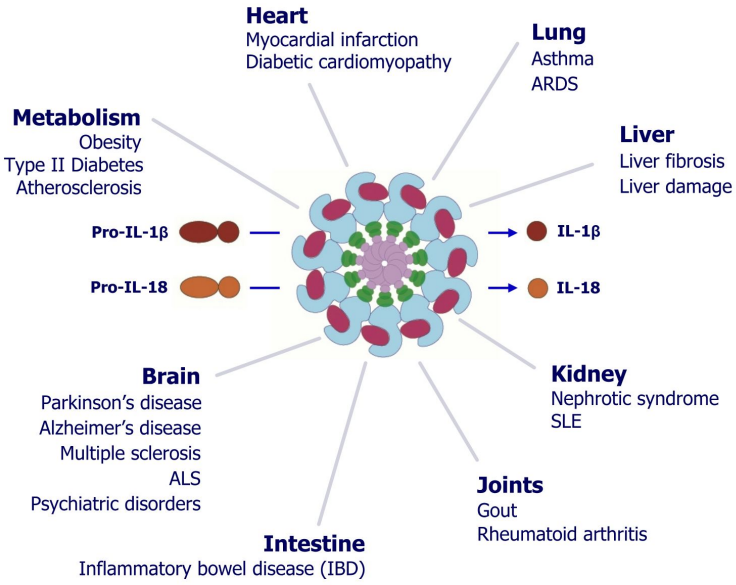
Overactivation of the NLRP3 Inflammasome in Disease

NLRP3 activating mutations



NLRP3 mutations found in CAPS (Cryopyrin-associated periodic syndromes – MWS*, FCAS**, CINCA/NOMID# Syndrome) might stabilize the active form of NLRP3

Over-activated NLRP3 inflammasome



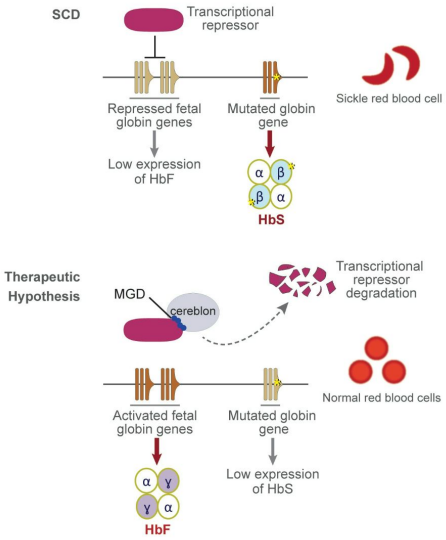
*Muckle-Wells Syndrome
**familial cold autoinflammatory syndrome, #Chronic infantile neurological cutaneous and articular/neonatal onset multisystem inflammatory disease

Monte Rosa Therapeutics

Sickle Cell Disease Program

Transcriptional Repressors as Targets for Hemoglobinopathies (SCD and β-Thalassemia)

Zinc finger domain-containing transcriptional repressors of the fetal globin genes



Therapeutic hypothesis: To reactivate expression of fetal hemoglobin (HbF) to compensate for mutated adult globin

Clinical Opportunity: First-in-class degraders for

- Sickle cell disease (SCD)
  - 180,000 patients (US and EU)
  - >6M patients (ROW)
- β-thalassemia
  - 17,000 patients (US and EU)

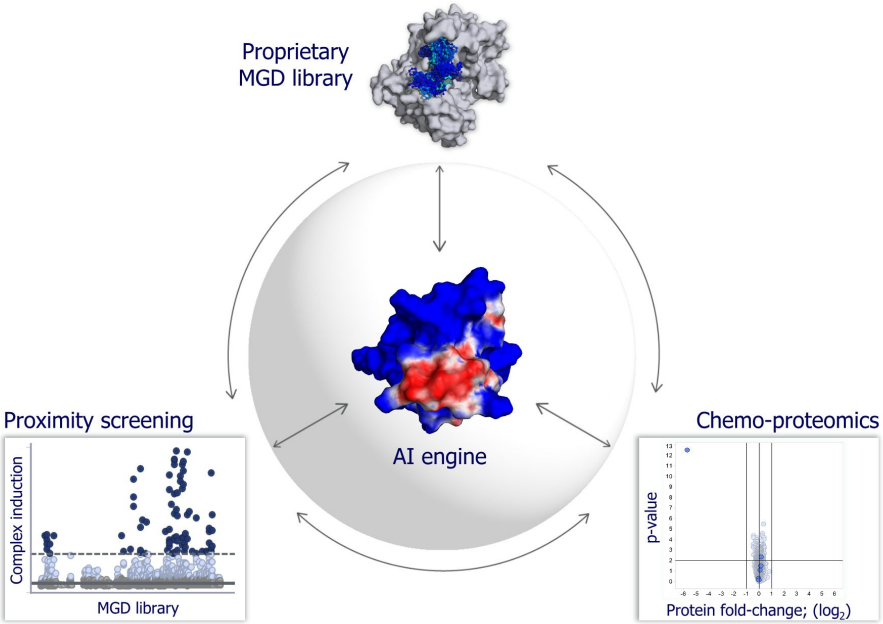
Patient diagnosed prevalence #s: DRG; https://www.notaloneinsicklecell.com/Global-Impact-Of-SCD/#s21 accessed March 15, 2023

Monte Rosa Therapeutics

QuEEN™ Discovery Engine

Quantitative and Engineered Elimination of Neosubstrates

QuEEN™ Discovery Engine: Unique Capabilities Enable Our Rational and Target-Centric Approach to MGDs



Proprietary AI/ML engine

In silico degron & ternary complex discovery using proprietary AI-powered algorithms

Proprietary MGD library

Diverse and growing MGD library (~35K), rationally designed using structural insights to engage diverse degrons

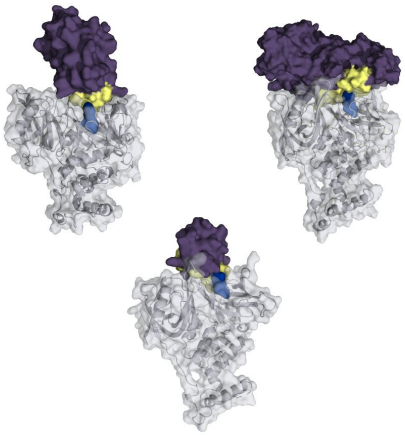
Chemo-proteomics engine

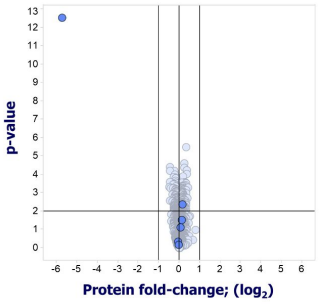
Scaled chemo-proteomics engine to explore cellular complex formation and protein degradation in high throughput

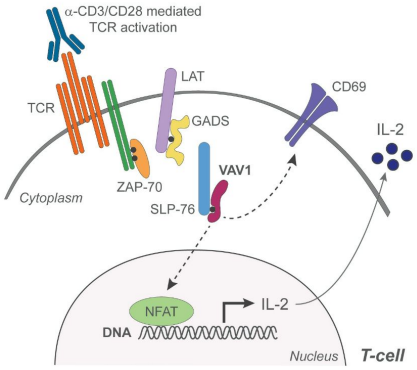
Proximity screening platform

Specialized suite of *in vitro* assays to assess proximity and degradation in high throughput

A Rich, Differentiated Target Space Across Protein Domains and Diseases







Degrons

QuEEN has enabled the discovery of diverse degrons across various protein domains and classes

Selectivity

Degrons have unique sequences enabling design of MGDs with unprecedented level of selectivity

Targets

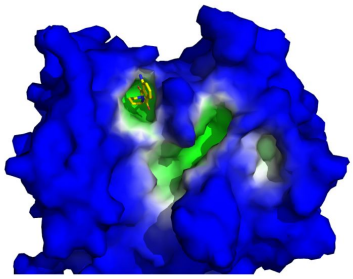
Our Degron Encyclopedia contains many highly credentialed, undruggable targets

Proprietary AI/ML Engines

Proprietary AI/ML Engines Enable the Discovery of Reprogrammable Ligases, Neosubstrates, and Selective MGDs

Reprogrammable E3 ligase prioritization

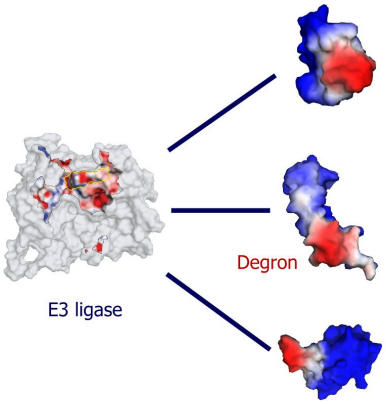
Surface evaluation for E3 ligase PPI propensity & reprogrammability



E3 ligase

Proteome-wide neosubstrate identification

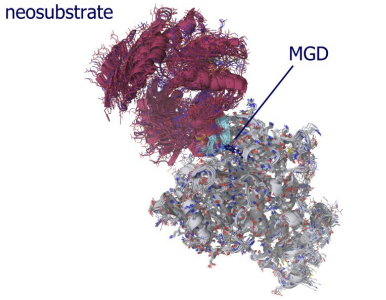
fAIceit™ surface complementarity connects E3 ligases to degron-containing neosubstrates



Candidate neosubstrates

in-silico MGD discovery

Rhapsody™ models ternary complexes and performs virtual screens for the discovery and design of selective MGDs

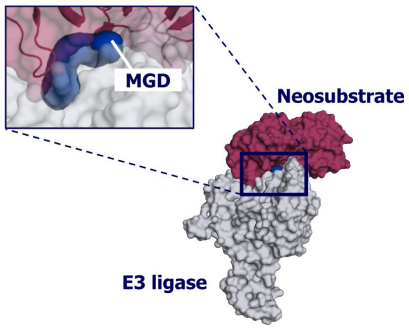


Creating a Highly Diverse CRBN-directed Library

MGDs Reprogram the Ligase Surface

Remodeled MGD-CRBN surface enables selective engagement of neosubstrates

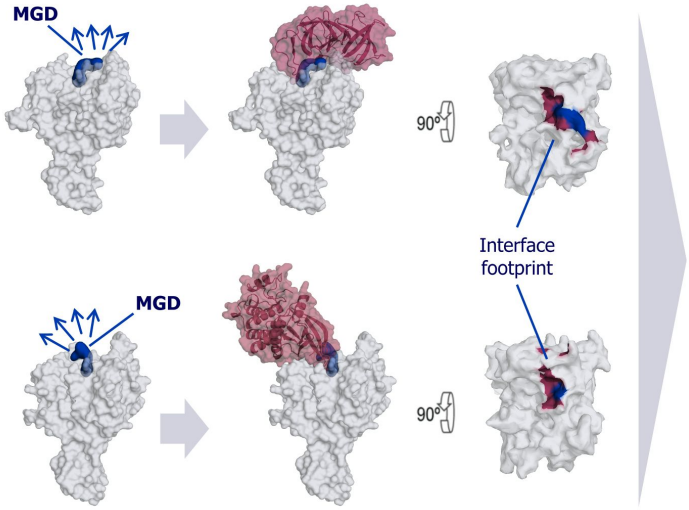
Multiple points of contact mediate formation of ternary complex



Effective ternary complex formation involves:

- MGD-cereblon interactions
- MGD-neosubstrate interactions
- CRBN-neosubstrate interactions

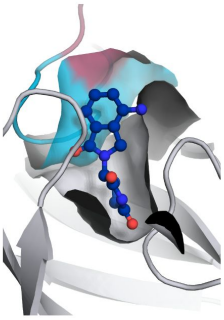
Known MGDs mediate vastly different binding modes despite representing limited chemical space



Create library diversity to multiply binding modes

Increasing Novelty and Structural Diversity to Match the Degron Space

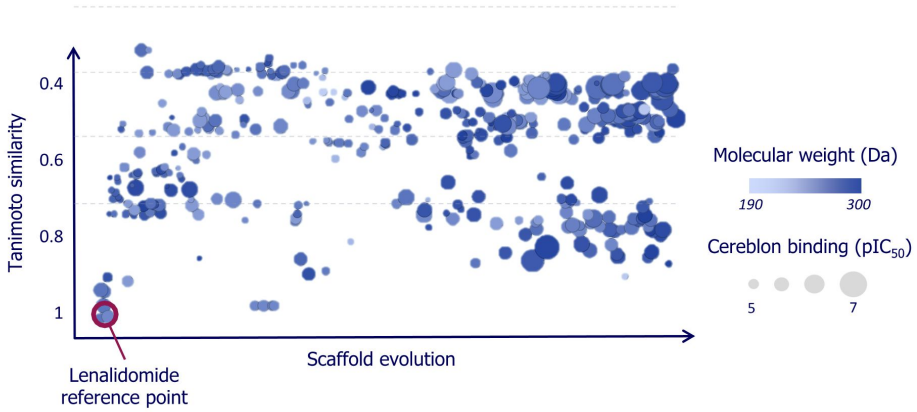
MGD scaffold anatomy



Core
CRBN binding, degron domain

Warhead
CRBN binding domain

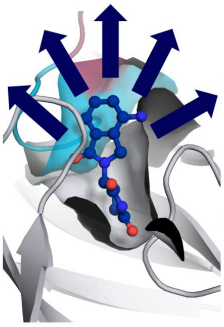
Increasing MGD scaffold diversity



MGD library is derived from **> 400 unique low molecular weight scaffolds** with **favorable CRBN binding** affinities

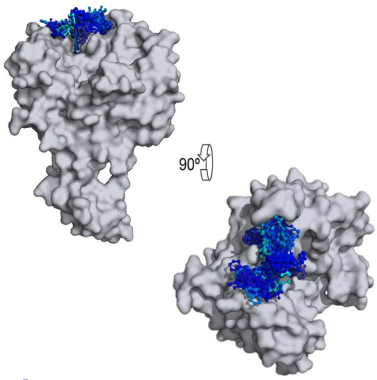
Expanding MGD Exit Vectorology Engages Novel Degron Classes

MGD diversification



Side-chains
PPI domain

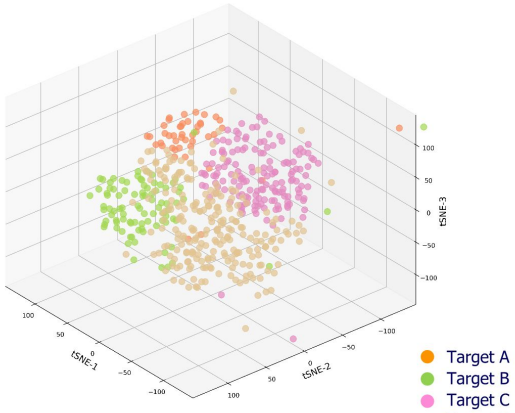
400+ Scaffolds



Library characteristics

- Current library size ~35K MGDs, continuing to expand
- High structural diversity and novelty
- Design focused on optimal drug-like properties

Expanded MGD diversity engages more degron classes



Chemical fingerprints of MGD hits

Monte Rosa Therapeutics

Summary

World-Class Leadership

Deep expertise in molecular glue discovery, drug development and Precision Medicine

Markus Warmuth, M.D.
Chief Executive Officer

H3 Biomedicine
NOVARTIS

Ajim Tamboli, CFA
Chief Financial Officer

COLUMBIA THREADNEEDLE INVESTMENTS
LEHMAN BROTHERS

Owen Wallace, Ph.D.
Chief Scientific Officer

Fulcrum Therapeutics
NOVARTIS

Sharon Townson, Ph.D.
Chief Technology Officer

KYMERA
Warp Drive Bio

John Castle, Ph.D.
Chief Data Scientist

agenus
BIONTECH

Filip Janku, M.D., Ph.D.
Chief Medical Officer

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Jullian Jones, Ph.D., J.D., MBA
Chief Business Officer

Lilly
Boehringer Ingelheim

Silvia Buonamici, Ph.D.
SVP, Drug Discovery Biology

H3 Biomedicine
NOVARTIS

Phil Nickson, Ph.D., J.D.
Head, Legal Operations

Momenta
FISH & RICHARDSON

Magnus Walter
SVP, Chemical Sciences and Process Development

abbvie
Lilly

Jennifer Champoux,
Chief People & Operations Officer

H3 Biomedicine
NOVARTIS

Monte Rosa Therapeutics

From serendipity to rational design of MGDs

Molecular glue-based targeted protein degradation platform developing breakthrough therapeutics that selectively degrade disease-causing proteins

Proprietary, **target-centric** drug discovery platform enabling **rational design**, and anticipated rapid development, of molecular glue-based degraders targeting the **undruggable proteome in oncology** and **non-oncology diseases**

Initial platform focus on **cereblon-mediated protein degradation** with **hundreds of potential targets** to address; potential to reprogram other E3 ligases to access more of the undruggable proteome through other degrons

Extensive and compelling pre-clinical *in vivo* data for **GSPT1 program**, demonstrating **potent anti-tumor activity** in MYC-driven tumor models with development candidate MRT-2359

Ongoing Phase 1/2 trial with MRT-2359 for the treatment of MYC-driven tumors including lung cancer patients

CDK2, NEK7, and VAV1 programs in lead optimization with **additional programs** at various stages of discovery


Thank You
Monte Rosa
Therapeutics