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): January 8, 2024

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.)**

321 Harrison Avenue, Suite 900
Boston, MA 02118
(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 7.01. Regulation FD Disclosure

On January 8, 2024 Monte Rosa Therapeutics, Inc. issued a press release titled "Monte Rosa Therapeutics Provides Corporate Update and Key Anticipated Milestones for 2024" and provided a corporate update in conjunction with its participation at the 42nd Annual J.P. Morgan Healthcare Conference in San Francisco, CA. The press release and presentation are furnished as Exhibits 99.1 and 99.2, respectively, to this Current Report on Form 8-K.

The information in this Form 8-K (including Exhibits 99.1 and 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 January 8, 2024.
99.2	J.P. Morgan Healthcare Conference presentation furnished by Monte Rosa Therapeutics, Inc. on January 8, 2024.
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: January 8, 2024

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

Monte Rosa Therapeutics Provides Corporate Update and Key Anticipated Milestones for 2024

Phase 1/2 clinical trial of MRT-2359 in MYC-driven solid tumors on track; recommended Phase 2 dose (RP2D) expected in Q2 2024

Received US FDA Fast Track Designation for MRT-2359 for previously treated, metastatic small cell lung cancer with L- or N-MYC expression

MRT-6160, a VAV1-directed MGD, anticipated to initiate Phase 1 study in mid-2024, supporting potential future Phase 2 proof-of-concept studies in multiple autoimmune diseases

Strong cash position expected to fund operations into H1 2026 and enable advancement of pipeline programs through significant early clinical milestones

Company to present at J.P. Morgan Healthcare Conference on Wednesday, January 10, 2024, at 3:00 p.m. PT

BOSTON, Mass., January 8, 2024 - Monte Rosa Therapeutics (Nasdaq: GLUE), a clinical-stage biotechnology company developing novel molecular glue degrader (MGD)-based medicines, today outlined anticipated 2024 milestones ahead of its participation in the 42nd Annual J.P. Morgan Healthcare Conference. The company's presentation, taking place on Wednesday, January 10, 2024, at 3:00 p.m. PT, will focus on strategic priorities for 2024, including anticipated progress with the ongoing Phase 1/2 clinical trial of MRT-2359 in MYC-driven solid tumors as well as future development plans for MRT-2359 and MRT-6160, its VAV1-directed MGD for autoimmune diseases.

"2023 was an exciting and highlight-filled year for Monte Rosa Therapeutics, including encouraging interim Phase 1/2 MRT-2359 clinical results, advancement of our VAV1-targeted MGD into IND enabling studies, and initiation of a strategic collaboration with Roche," said Markus Warmuth, M.D., Chief Executive Officer of Monte Rosa Therapeutics. "Building on last year's successes, this year we look forward to announcing the RP2D for our MRT-2359 program and initiating multiple Phase 2 expansion cohorts in tumors characterized by high L- and N-MYC expression, with the potential to consider indication expansion into c-MYC-driven tumor types such as ER+ breast cancer and castration-resistant prostate cancer. Our highly selective VAV1-directed MGD MRT-6160 is anticipated to enter a Phase 1 healthy volunteer study this year with the aim to move efficiently into early proof-of-concept studies in patients across multiple autoimmune indications. Lastly, we also expect to nominate additional development candidates in 2024 for programs in both oncology and inflammation/immunology. Our strong balance sheet and cash runway into 1H 2026 positions us to advance our programs through important clinical milestones."

Recap of 2023 Achievements

- Presented interim data from the Phase 1/2 clinical trial of MRT-2359 demonstrating tumor reductions in patients with biomarker-positive cancers and favorable pharmacokinetic (PK), pharmacodynamic (PD), and tolerability profiles.
- Announced development candidate MRT-6160, a VAV1-directed MGD, for the treatment of autoimmune diseases, and presented preclinical data demonstrating that MRT-6160 attenuates autoimmune disease progression.
- Entered into a strategic collaboration and licensing agreement with Roche to discover and develop novel molecular glue degraders targeting cancer and neurological diseases, with a $50 million upfront payment and eligibility to receive future preclinical, clinical, commercial and sales milestone payments exceeding $2 billion, as well as tiered royalties.

Corporate Updates and Key Anticipated Milestones

- Monte Rosa announced today that it has received U.S. Food & Drug Administration Fast Track Designation for MRT-2359 for the treatment of patients with previously treated, metastatic small cell lung cancer (SCLC) with L-MYC or N-MYC expression.
- Monte Rosa expects to announce the RP2D for the MRT-2359 Phase 1/2 clinical trial in MYC-driven solid tumors in Q2 2024. Enrollment is ongoing in backfill cohorts at clinically active doses using a 5 days on drug, 9 days off drug schedule. The Company has simultaneously started dose escalation of higher dose density cohorts using a 21 days on, 7 days off schedule.
- The Company expects to submit an IND for MRT-6160, a VAV1-targeted MGD, in the first half of 2024 and to initiate a Phase 1 single ascending dose / multiple ascending dose study in healthy volunteers in mid-2024.
- The Company expects to nominate a development candidate for the NEK7 preclinical program in Q1 2024.
- The Company expects to nominate a development candidate for the CDK2 preclinical program in 2024.

J.P. Morgan Healthcare Conference Presentation

Dr. Warmuth will present Monte Rosa's pipeline and business updates during a presentation at the 42nd Annual J.P. Morgan Healthcare Conference on Wednesday, January 10, 2024, at 3:00 p.m. PT. A webcast of the presentation will be accessible via the "Events & Presentations" section of Monte Rosa's website at ir.monterosatx.com, and an archived version will be made available following the presentation.

About MRT-2359

MRT-2359 is a potent, highly selective and orally bioavailable investigational molecular glue degrader (MGD) that induces the interaction between the E3 ubiquitin ligase component cereblon and the translation termination factor GSPT1, leading to the targeted degradation of GSPT1 protein. The MYC transcription factors (c-MYC, L-MYC and N-MYC) are well-established drivers of human cancers that maintain high levels of protein translation, which is critical for uncontrolled cell proliferation and tumor growth. Preclinical studies have shown this addiction to MYC-induced protein translation creates a dependency on GSPT1. By inducing degradation of GSPT1, MRT-2359 is designed to exploit this vulnerability, disrupting the protein synthesis machinery, leading to anti-tumor activity in MYC-driven tumors.

About MRT-6160

MRT-6160 is a potent, highly selective, and orally bioavailable investigational molecular glue degrader of VAV1, which in our *in vitro* studies has shown deep degradation of its target with no detectable effects on other proteins. VAV1, a Rho-family guanine nucleotide exchange factor, is a key signaling protein downstream of both the T-and B-cell receptors. VAV1 expression is restricted to blood and immune cells, including T and B cells. Preclinical studies have shown that targeted degradation of VAV1 protein via an MGD modulates both T- and B-cell receptor-mediated activity. This modulation is evident both *in vitro* and *in vivo*, demonstrated by a significant decrease in cytokine secretion, proteins vital for maintaining autoimmune diseases. Moreover, VAV1-directed MGDs have shown promising activity in preclinical models of autoimmune diseases and thus have the potential to provide therapeutic benefits in multiple autoimmune indications, such as multiple sclerosis, rheumatoid arthritis, and dermatological disorders. Preclinical studies demonstrate MRT-6160 inhibits disease progression in *in vivo* autoimmunity models.

About Monte Rosa

Monte Rosa Therapeutics is a clinical-stage biotechnology company developing highly selective molecular glue degrader (MGD) medicines for patients living with serious diseases in the areas of oncology, autoimmune and inflammatory diseases, and more. MGDs are small molecule protein degraders that have the potential to treat many diseases that other modalities, including other degraders, cannot. Monta Rosa's QuEEN™ (Quantitative and Engineered Elimination of Neosubstrates) discovery engine combines AI-guided chemistry, diverse chemical libraries, structural biology and proteomics to identify degradable protein targets and rationally design MGDs with unprecedented selectivity. The QuEEN discovery engine enables access to a wide-ranging and differentiated target space of well-validated biology across multiple therapeutic areas. Monte Rosa has developed the industry's leading pipeline of MGDs, which spans oncology, autoimmune and inflammatory disease and beyond, and has a strategic collaboration with Roche to discover and develop MGDs against targets in cancer and neurological diseases previously considered impossible to drug. 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 herein include, but are not limited to, statements about our product development activities, our ongoing clinical development of our GSPT1 degrader referred to as MRT-2359, including our expectations for the nature, significance, and timing for our disclosure of any data from our Phase 1/2 clinical trial of MRT-2359 in MYC-driven solid tumors, timing for our identification and any disclosure of a recommended phase 2 dose for MRT-2359, statements about the advancement of our preclinical programs, pipeline and the various products therein, including the ongoing development of our VAV1-directed degrader, referred to as MRT-6160, and the planned submission of an IND to the FDA for MRT-6160 in the first half of 2024, and the timing of our planned phase 1 healthy volunteer study and early proof-of-concept studies in patients across multiple autoimmune indications, our expectations regarding the potential clinical benefit for this program and our expectations of timings for the program, statements around the advancement and application of our pipeline, including identification and the timing thereof of a development candidate for NEK7 and a development candidate for CDK2, statements around the advancement and application of our platform, and statements concerning our expectations regarding our ability to nominate and the timing of our nominations of additional targets, product candidates, and 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 those risks and uncertainties set forth in our most recent Annual Report on Form 10-K for the year ended December 31, 2023, filed with the U.S. Securities and Exchange Commission on March 16, 2023, 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.

Investors
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Media
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From Serendipity to Rational Design
Taking Molecular Glue Degraders to New Heights | January 2024
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 ("MGDs"), the potential of our herein detailed pipeline of MGDs, including for GSPT1, VAV1, NEK7, CDK2, and our early stage undisclosed MGDs, our expectations regarding the advancement, and timing thereof, of our pipeline, including our ability to advance our candidates through lead optimization to development candidates, our expectations regarding the potential therapeutic opportunities for our pipeline of MGDs, our expectations for the ongoing clinical development of our MGD for GSPT1, referred to as MRT-2359, including regarding the potential relevance of certain interim clinical data and our expectations for the nature and timing of any future clinical data releases, our expectations for the nature and timing of our future clinical development of MRT-2359, including our plans for any potential Phase 2 study, our expectations for the ongoing pre-clinical and potential clinical development of our MGD for VAV1, referred to as MRT-6160, including our use of our pre-clinical data to predict MRT-6160's potential clinical usefulness across multiple autoimmune indications including indications associated with gastroenterology, dermatology, rheumatology, and neurology, our expectations of timing for filing an investigational new drug application for MRT-6160 and for MRT-6160 to enter the clinic, our expectations for the nature and timing of our future clinical development of MRT-6160, the potential for MRT-6160 to benefit patients across multiple autoimmune diseases, and our ability to obtain proof of concept for VAV1 as a target using such indications, including the timing thereof, our expectations for our ongoing pre-clinical development of our MGDs for NEK7, including any announcement and timing thereof of a development candidate for NEK7 and our use of our pre-clinical data to predict therapeutic opportunities for application of an MGD for NEK7, our expectations for our ongoing pre-clinical development of our MGDs for CDK2, including any announcement and timing thereof of a development candidate for CDK2 and our use of our pre-clinical data to predict therapeutic opportunities for application of an MGD for CDK2, our predictions of the size of potential patient populations for various indications for our various MGDs, including for GSPT1, VAV1, NEK7, CDK2, and our expectations regarding our the strength of our financial position, including our estimates of cash runway, among others. By their nature, these statements are subject to numerous risks and uncertainties, 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, 2022, filed, with the US Securities and Exchange Commission on March 16, 2023, 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.

Monte Rosa Therapeutics – Company Overview

Taking molecular glue degraders (MGDs) to new heights

Arsenal of rationally designed MGDs with potential to solve many of the limitations of other modalities by degrading therapeutically relevant proteins with unprecedented precision

Highly productive**, industry-leading discovery engine** combining experimentation **with AI to enable rational design of novel MGDs**

Multiple disclosed, wholly-owned programs spanning oncology, autoimmune and inflammation

Phase 1/2 clinical study ongoing with MRT-2359 in MYC-driven cancers; interim data demonstrated optimal pharmacodynamic modulation and **early signs of clinical activity; RP2D expected in Q2 2024**

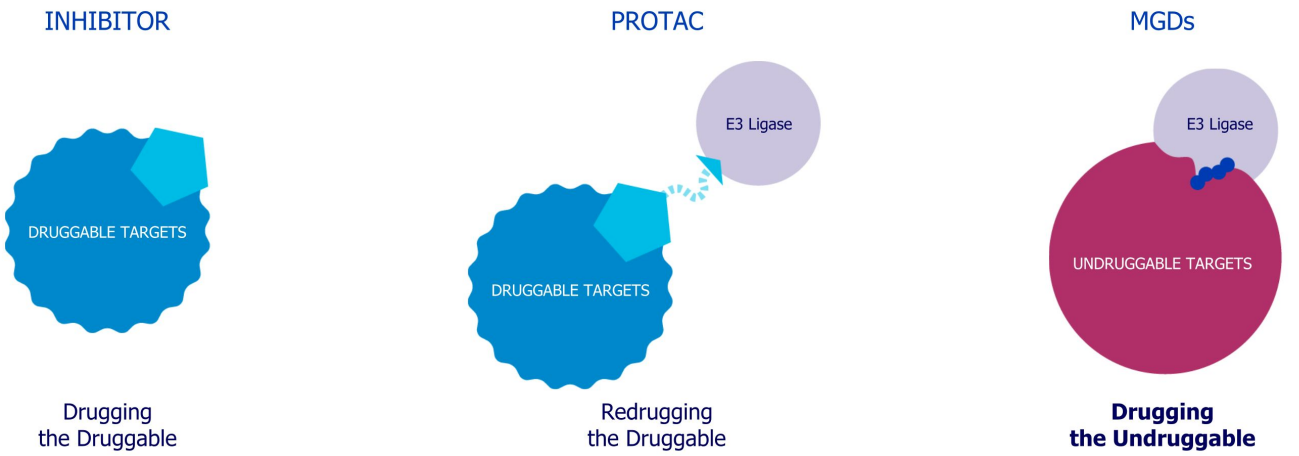
MRT-6160, highly selective VAV1-directed MGD, being rapidly advanced with IND expected in mid-2024; broad potential applications across autoimmune diseases

Partnership with Roche to develop MGDs for oncology and neurological conditions **– expands platform reach into neurology**

Strong financial position providing cash runway into H1 2026 and through multiple anticipated clinical readouts, including MRT-2359 Phase 1/2 and SAD/MAD for VAV1 and NEK7

Molecular Glue Degraders (MGDs) - Drugging The Undruggable

Expanding target space, fostering a new generation of drugs

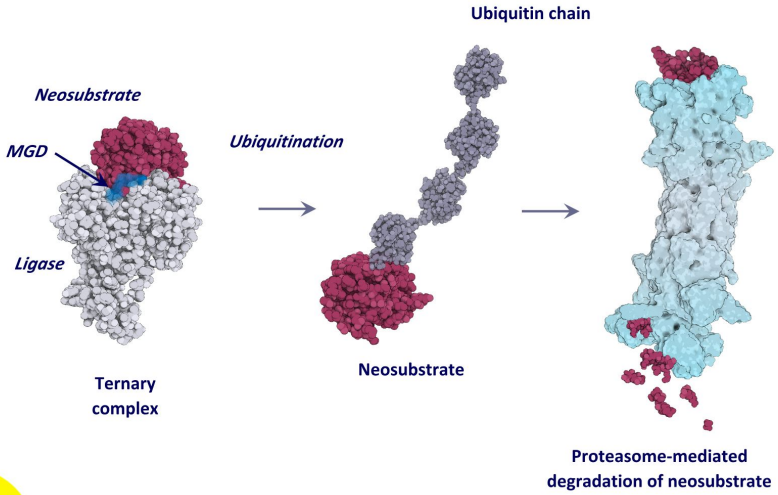


Expanding the Degradable Proteome

Target Space

Molecular Glue Degraders (MGDs) – A Highly Differentiated Modality

Potency and selectivity of large molecule modalities with orally bioavailable small molecules

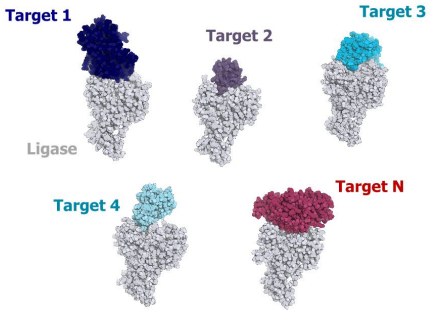


- Access to undruggable space
- Exquisite selectivity
- High potency
- Oral bioavailability
- Cellular permeability
- Systemic distribution
- CNS penetration
- Long lasting pharmacodynamic effects

Monte Rosa's rationally designed MGDs address key limitations of first-generation protein degraders and expand potential applications into Immunology, Neuroscience and other therapeutic areas

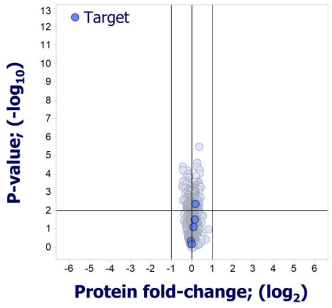
Key Advantageous of Our Rationally Designed MGDs

Unique Target Space



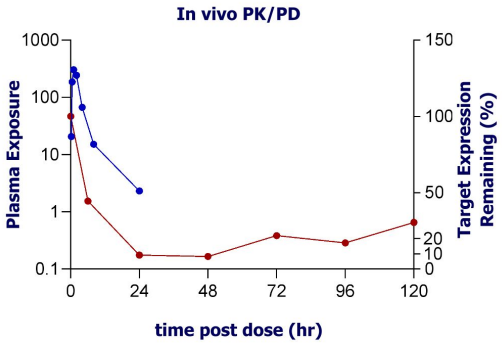
Disease-agnostic platform with initial focus on highly credentialed oncology and I&I targets

Unprecedented Selectivity



Unique insights into anatomy of ternary complexes allows unprecedented MGD selectivity

Non-occupancy Driven, Catalytic Mechanism of Action



Long lasting pharmacodynamic effect creates differentiated target product profiles

Monte Rosa Therapeutics – Key Firsts and Accomplishments

From serendipity to rational design of MGDs

Built **a proprietary molecular glue-based targeted protein degradation platform** developing breakthrough therapeutics that selectively degrade disease-causing proteins

Established **a target-centric** drug discovery approach combining experimentation with AI enabling **rational design** of highly potent and selective MGDs

Presented interim data from **Phase 1/2 trial of GSPT1-directed MGD MRT-2359 for the treatment of MYC-driven tumors; optimal pharmacodynamics*, favorable safety profile and initial clinical activity observed**

Progressed VAV1 MGD MRT-6160 into IND enabling studies; MRT-6160 is the *first* known MGD specifically developed for a non-oncology indication

Advanced several additional **highly credentialed targets** as amenable to degradation through our platform including CDK2, NEK7 and multiple discovery targets; began expanding approach **to E3 ligases** beyond Cereblon

Established **validating discovery collaboration with Roche** in oncology and neurological diseases

* Based on optimal PD modulation in preclinical studies

Monte Rosa Therapeutics

Portfolio

Monte Rosa Pipeline and Upcoming Milestones

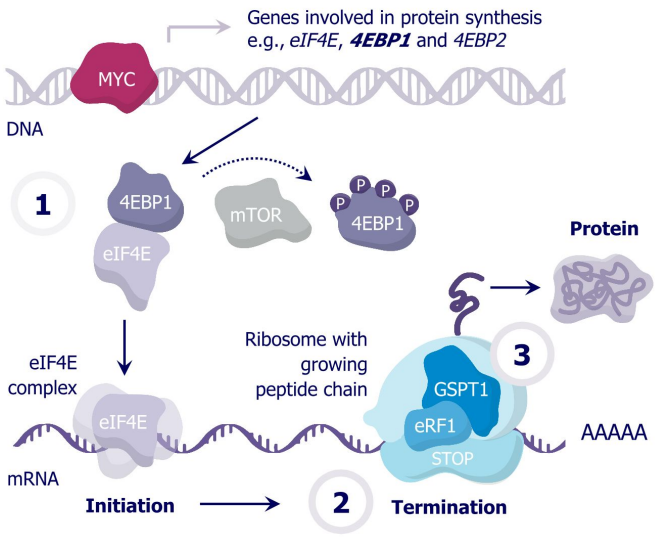
Program/ Target	Indication(s)	Discovery	IND-Enabling	Clinical	Next Anticipated Milestone	Ownership
MRT-2359 (GSPT1)	NSCLC, SCLC and other MYC-driven Malignancies				RP2D in Q2 2024	
MRT-6160 (VAV1)	Autoimmune Disease				IND in 1H 2024	
NEK7	Inflammatory Diseases				Development candidate in Q1 2024	
CDK2	Ovarian Cancer, Breast Cancer				Development candidate in 2024	
Discovery Targets	Multiple				Lead optimization	
Discovery Targets	Oncology and Neurological Diseases				Undisclosed	Roche

Oncology Immunology Inflammation Various

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

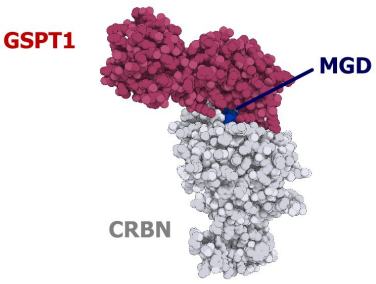
Therapeutic vulnerability

GSPT1 is a therapeutic vulnerability of MYC-driven tumors
leading to preferential activity of GSPT1 MGDs

MRT-2359 is a Potent and Highly Selective GSPT1-directed MGD

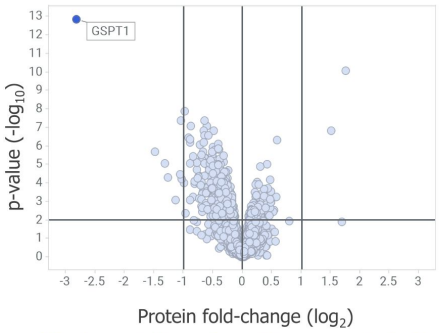
MRT-2359 is a potent GSPT1-directed MGD

Ternary complex modelling



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

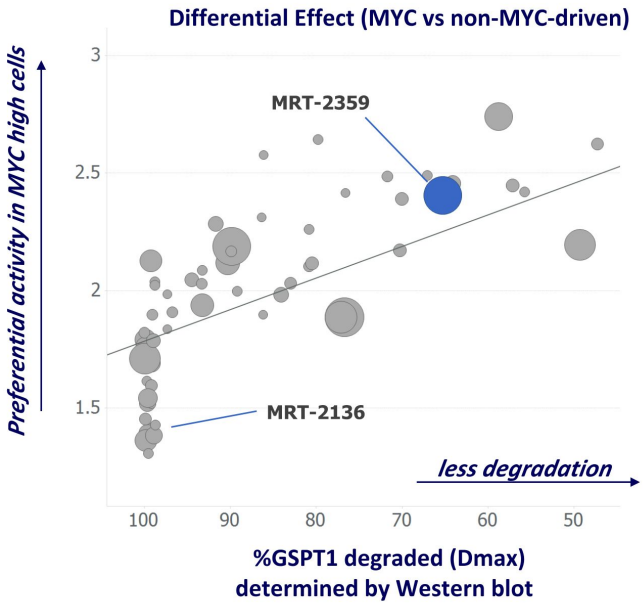
MRT-2359 induces selective GSPT1 degradation and shows favorable ADME/DMPK profile



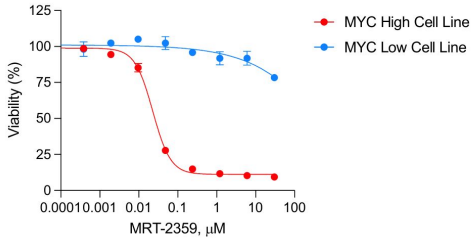
No degradation of cereblon neosubstrates

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

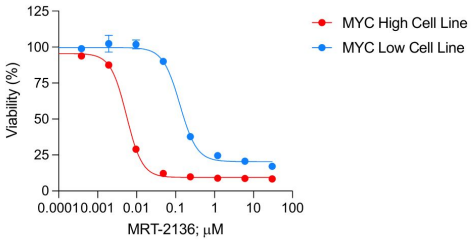
MRT-2359 Has Optimized Depth of Degradation To Achieve Preferential Activity in MYC High Cancer Cells



MRT-2359 displays preferential activity in MYC driven NSCLC cells



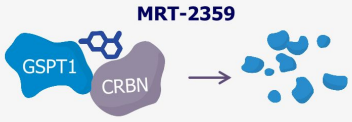
Non-optimal GSPT1 MGD (MRT-2136) shows limited preferential activity



Three Mechanisms Driving Preferential Activity in MYC High Tumor Cells

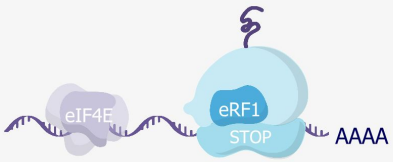
Preferential GSPT1 degradation

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



Inhibition of translation

MRT-2359-induced reduction of GSPT1 preferentially impairs protein synthesis in tumor cells with high MYC expression



MYC down-modulation

In a feedback loop, MRT-2359 decreases MYC expression and transcriptional activity

Large Potential Opportunities in MYC-Driven Tumors

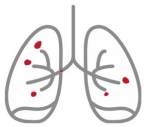
High unmet need with no currently approved therapies specifically for MYC high tumors

N-MYC High
and/or
L-MYC High

SCLC (70-80% L/N-MYC high)

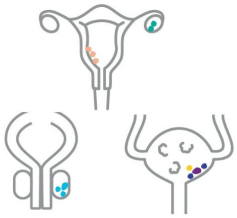
NSCLC
N-MYC high (5-10%)
SCLC/NE transformation

Neuroendocrine lung cancer



Neuroendocrine tumors

L-/N-MYC amplified tumors

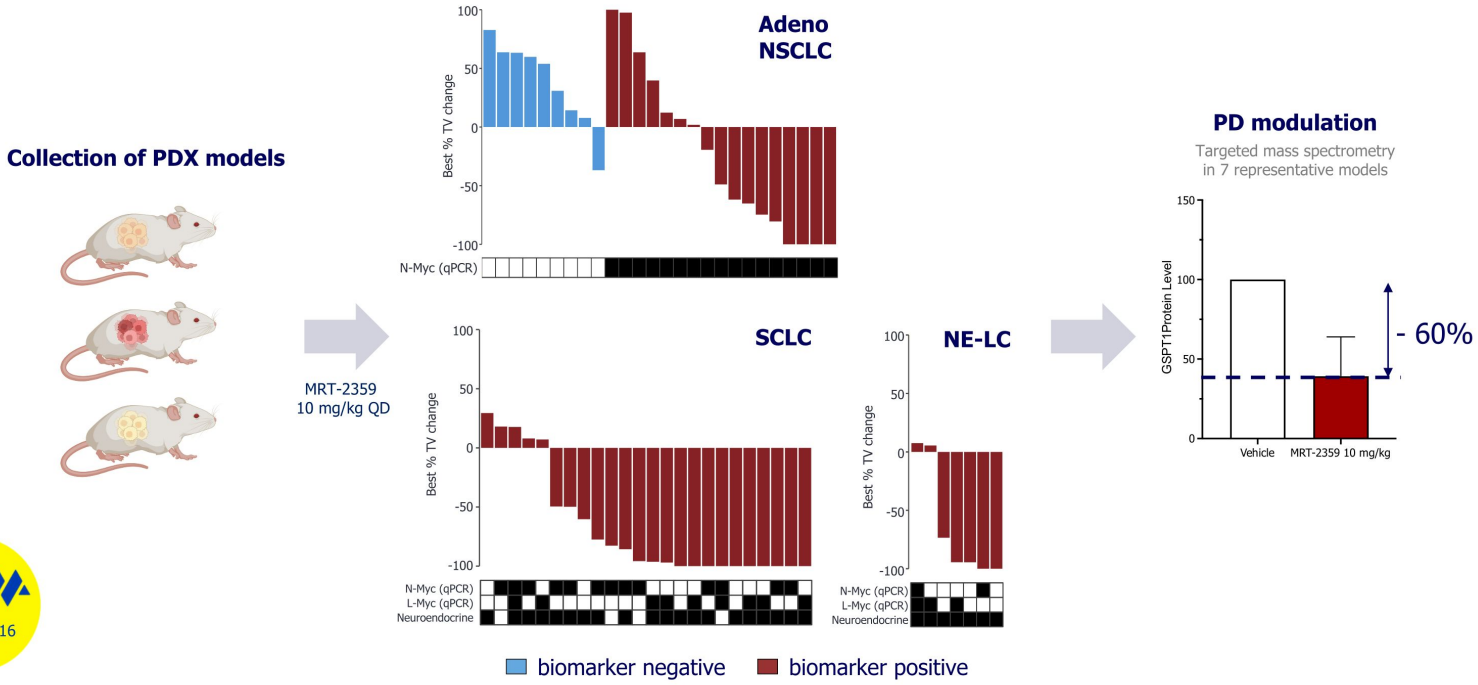


c-MYC High

Prostate cancer
AR and/or ARV7 positive
castration resistant

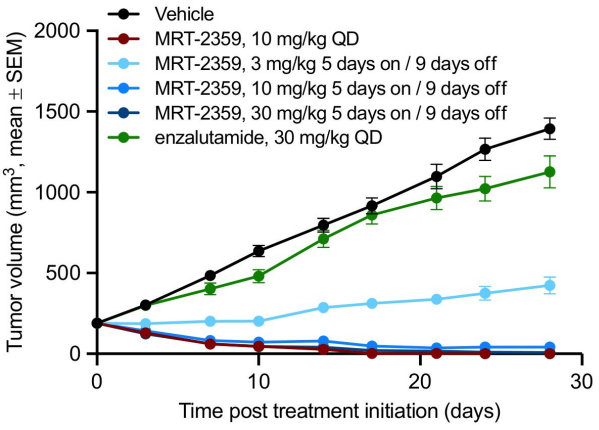
Breast cancer
ER positive metastatic

Preclinical Validation of Activity of MRT-2359 in Lung Cancer PDX Models

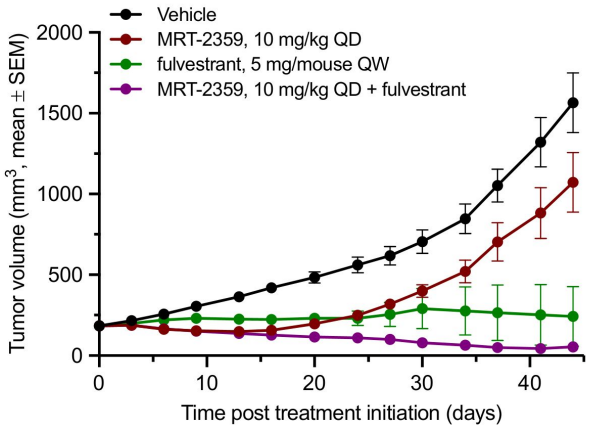


MRT-2359 is Active as Single Agent and in Combination with SOC Against AR-V7/MYC- and ER/MYC-Positive Tumor Xenografts

22RV1 - ARV7/MYC-positive Prostate Cancer



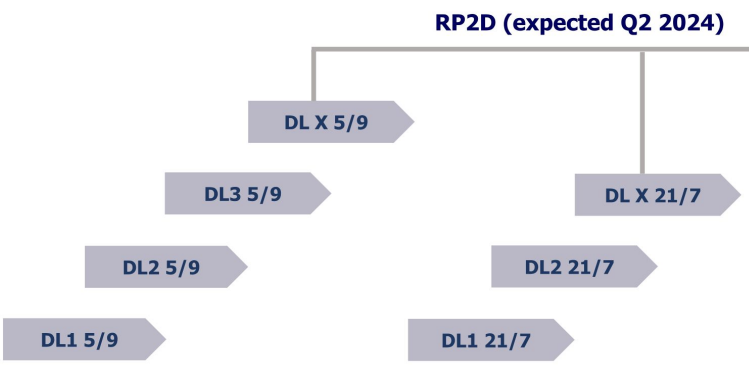
MCF7 – ER/MYC-positive Breast Cancer



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

Phase 1: Dose Escalation

Lung cancer, DLBCL, high-grade neuroendocrine tumors and solid tumors with N-/L-MYC amplification



Backfill: Up to 6 additional pts for each dose level

5/9 = 5 days on drug, 9 days off drug.
21/7 = 21 days on drug, 7 days off drug.

Phase 2: Expansion Cohorts

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

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

Solid tumors – N- or L-MYC amplification

Indication expansion under consideration:
- **Breast cancer**
- **Prostate cancer**
- **High-grade neuroendocrine tumors**

* Prospective stratification per N-/L-MYC expression
** Retrospective stratification per N-/L-MYC expression

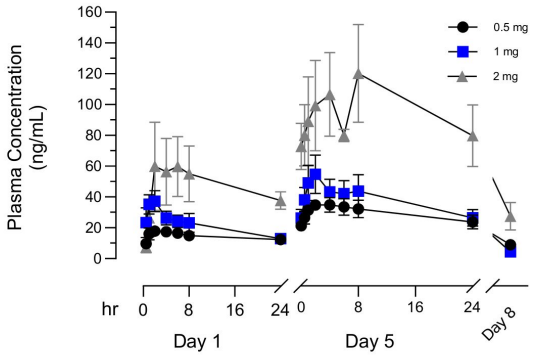
MRT-2359 Phase I Interim Data - October 2023

Objectives of Phase I interim analysis

- ✓ Demonstrate dose dependent PK
- ✓ Demonstrate significant GSPT1 degradation at safe dose levels in PBMCs and tissue biopsies (60% based on preclinical data)
- ✓ Share potential preliminary efficacy signals in biomarker positive patients

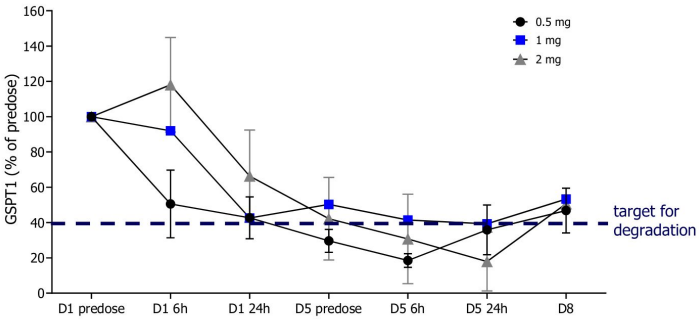
MRT-2359 Induces Optimal GSPT1 Degradation in PBMCs*

MRT-2359 displayed dose dependent plasma exposure



- Dose dependent exposure in line with preclinical PK models
- No food effect observed

MRT-2359 displayed deep GSPT1 degradation in PBMCs at all dose levels

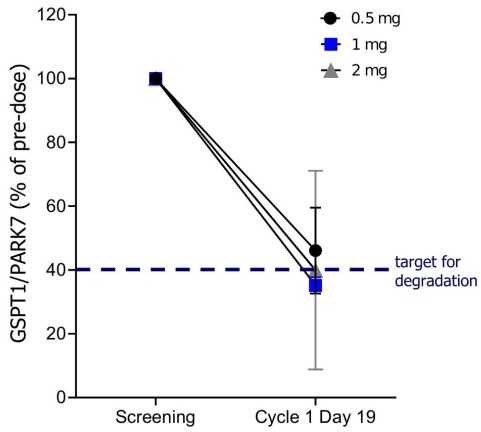


- GSPT1 expression assessed using targeted mass spectrometry
- PD modulation in PBMCs observed across all dose levels; level of degradation (~ 60%) in line with maximal degradation observed in preclinical studies using the same method
- Level of degradation equivalent across all dose levels, suggesting saturated PD response from 0.5 to 2 mg

* as presented on 10/17/23

MRT-2359 Induces Optimal GSPT1 Degradation in Tissue Biopsies*

MRT-2359 reduced GSPT1 protein expression in human tissue biopsies



- GSPT1 degradation assessed from pre-treatment screening biopsies and biopsies taken at day 19
- Matched biopsies obtained from 11 patients across the 3 cohorts analyzed
- GSPT1 expression assessed using targeted mass spectrometry
- PD modulation seen in tissue biopsies in line with PD modulation seen preclinically at efficacious dose levels using same assay (targeted mass spectrometry)

* Based on optimal PD modulation in preclinical studies as presented on 10/17/23

Summary of Treatment-Related Adverse Events (AEs) in ≥ 2 patients[#]

No observed clinically significant hypocalcemia or hypotension/cytokine release syndrome

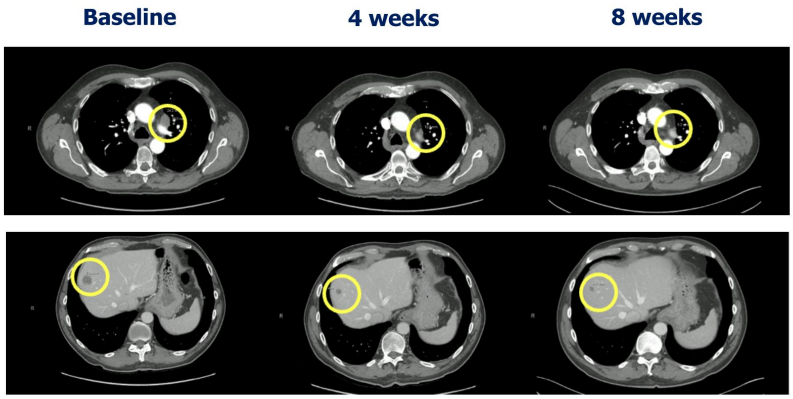
AE Preferred Term	0.5 mg (N=9)[##]		1 mg (N=7)[##]		2 mg (N=5) [##]		Overall (N=21)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Thrombocytopenia[###]	0	0	0	0	4 (80%)	3 (60%)[***]	4 (19%)	3 (14%)
Neutropenia[*]	0	0	0	0	2 (40%)	1 (20%)	2 (10%)	1 (5%)
Leukopenia	0	0	0	0	2 (40%)	2 (40%)	2 (10%)	2 (10%)
Nausea	3 (33%)	0	2 (29%)	0	1 (20%)	0	6 (33%)	0
Vomiting	1 (11%)	0	2 (29%)	0	1 (20%)	0	4 (19%)	0
Diarrhea[**]	1 (11%)	0	3 (43%)	0	1 (20%)	0	5 (24%)	0
Hypokalemia	0	0	1 (14%)	0	1 (20%)	0	2 (10%)	0
Fatigue	0	0	2 (29%)	0	0	0	2 (10%)	0
Decreased appetite	0	0	2 (29%)	0	0	0	2 (10%)	0
Rash	2 (22%)	0	0	0	0	0	2 (10%)	0

Note: As presented on 10/17/23

[#] Data cut-off: 7 SEP 2023
[##] MRT-2359 was given orally daily on the 5 days on and 9 days off schedule
[###] Data combined for 'thrombocytopenia' and 'platelet count decreased'
[*] Data combined for 'neutropenia' and 'neutrophil count decreased'
[**] Data combined for 'diarrhea' and 'feces soft'
[***] Dose limiting toxicity: Grade 4 thrombocytopenia in 2 patients

Confirmed Partial Response in High Grade Neuroendocrine Bladder Cancer*

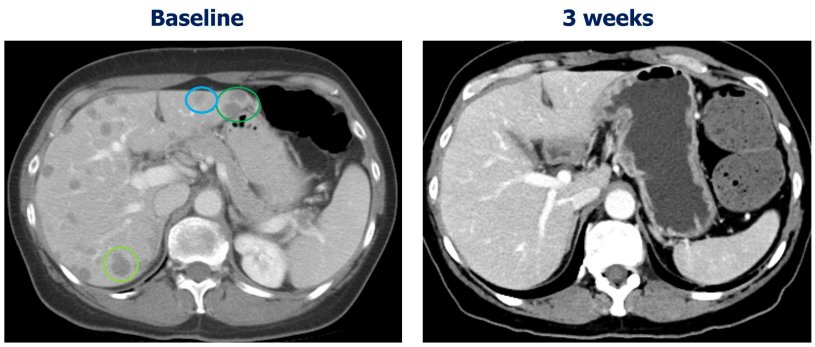
- High Grade (HG) neuroendocrine bladder cancer
- Baseline tumor biopsy demonstrated high N-MYC expression
- 4 prior lines of therapy including chemotherapy and pembrolizumab
- Patient initiated on 2 mg for first 5/9 regimen, then lowered to 1 mg and 0.5 mg and remains on therapy (> 3 month)
- CT scan after 4 weeks demonstrated PR (-34% per RECIST 1.1) that continued to improve at week 8 (-59% per RECIST 1.1)



* as presented on 10/17/23

Unconfirmed Partial Response in NSCLC with SCLC/NE Transformation*

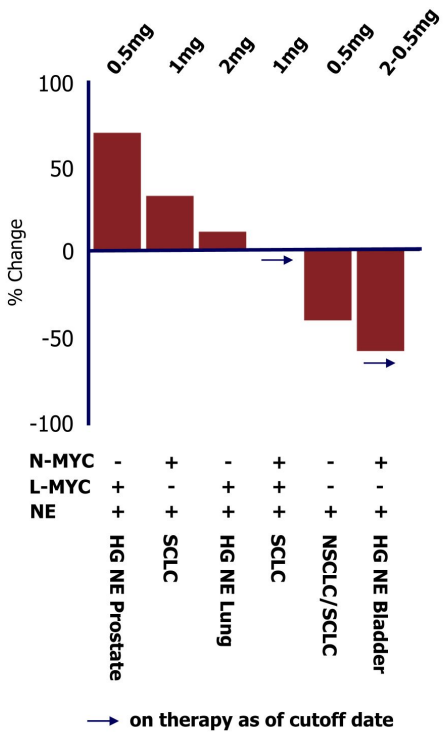
- NSCLC (adenocarcinoma)
- Baseline tumor biopsy demonstrated SCLC/NE transformation, low N- and L-MYC expression
- Multiple lines of prior therapy including chemotherapy, pembrolizumab and atezolizumab
- Patient initiated on 0.5 mg
- CT on C1D22 demonstrated resolution of liver metastases (-41% per RECIST 1.1)
- Patient experienced frequent dose interruptions due to bowel obstruction unrelated to MRT-2359



* as presented on 10/17/23

MRT-2359-001 – Preliminary Efficacy Data*

- As of September 7th, 2023, of 15 evaluable patients treated across 3 cohorts, tumors from 6 patients were identified as biomarker positive
- Of these 6 biomarker positive patients, 2 have experienced a PR (1 confirmed, 1 unconfirmed) and 1 patient has SD
  - PR (-59%) – HG NE bladder carcinoma
  - uPR (-41%) – NSCLC with SCLC/NE transformation
  - SD (0%) – SCLC (remains on therapy for > 4 months)
- In addition, one patient with NSCLC and unclear biomarker status remains on therapy for > 7 months with stable disease
- No clinical activity seen in biomarker negative patients
- All un-evaluable patients with early progression were BM negative



* as presented on 10/17/23

Favorable Safety at Clinically Active Doses*

Safety profile supports further development

- Preferential and more rapid degradation of GSPT1 in MYC high tumor cells enables favorable adverse event (AE) profile at clinically active doses of 0.5 and 1 mg – no Grade ≥3 AEs
  - Grade 1-2 AEs primarily GI-related and manageable
- No observations of previously reported limitations of other GSPT1-targeted agents
  - No observed clinically significant hypocalcemia or hypotension/cytokine release syndrome at any dose level
- Grade 4 thrombocytopenia identified as dose limiting toxicity (DLT) at 2 mg
- Favorable safety profile with lack of hypocalcemia has enabled exploration of 21/7 schedule, starting at 0.5 mg
- RP2D expected in Q2 of 2024

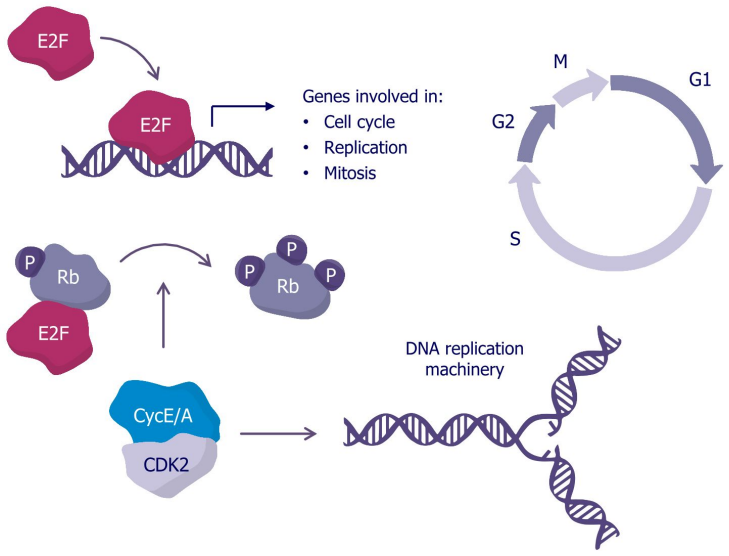
* as presented on 10/17/23

Monte Rosa Therapeutics

CDK2 Program

CDK2 as a Target for Selected Solid Tumors

CDK2 a key cell cycle regulator



Therapeutic hypothesis:

- CDK2 is a key driver of cancers with cyclin dependent kinase pathway alterations
- MGDs will achieve greater selectivity against other CDKs and kinases in general, as well as more sustained pathway inhibition compared to inhibitors

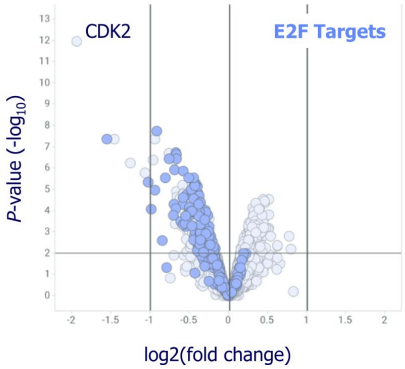
Clinical Opportunity:

- ER positive breast cancer pre and post treatment with CDK4/6 inhibitors (474K patients)
- Ovarian cancer (64K patients), endometrial cancer (124K patients) and other tumors with CCNE1 amplification

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

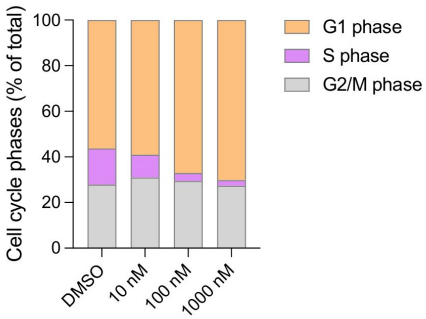
CDK2-directed MGDs are Selective and Inhibit Proliferation of CDK2-dependent Cancer Cells

CDK2 degradation results in reduction of E2F pathway proteins



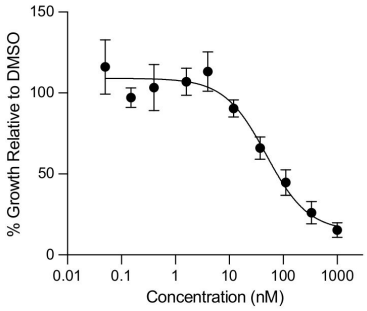
TMT Proteomics - MDA-MB-157 (1 uM/24 hr)

CDK2 degradation arrests CDK2-dependent cells in G1 phase



Cell cycle analysis (DAPI and EdU) - MDA-MB-157 (24 hr)

CDK2 degradation blocks proliferation

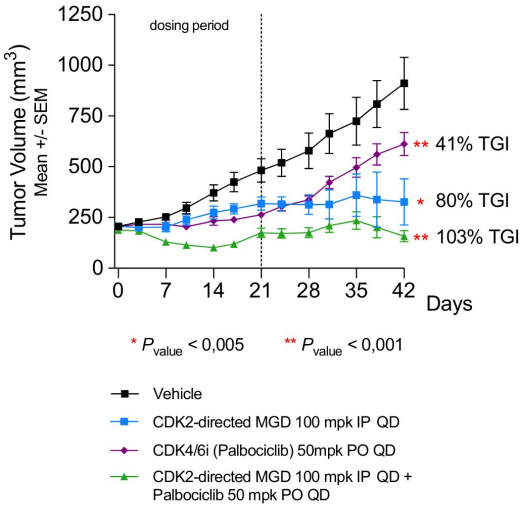


CRBN K_i = 129 nM
SPR half-life = 994 s
NanoBiT DC_{50} = 130 nM
CyQuant MDA-MB-157 EC_{50} = 46 nM

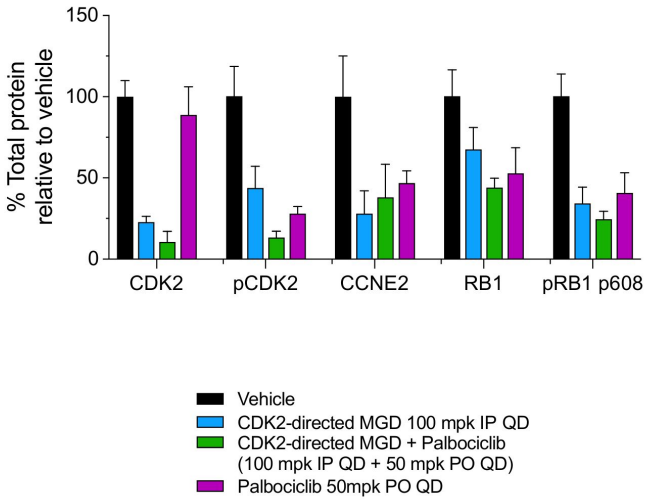
Proliferation (CyQuant) - MDA-MB-157 (7dr)

CDK2-directed MGD Demonstrates Activity as Single Agent and in Combination with CDK4/6i in ER+ Breast Cancer

CDK2directed MGD induces strong tumor growth inhibition ER-positive MCF7 *in vivo*



CDK2-directed MGD demonstrates significant PD modulation *in vivo*



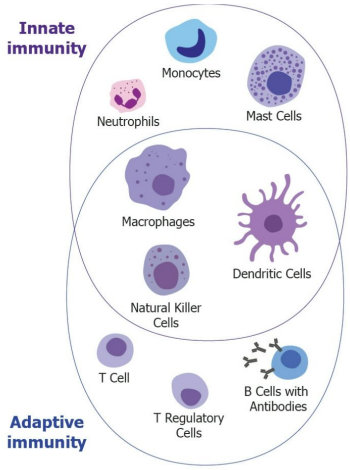
Monte Rosa Therapeutics

Inflammation and Immunology (I&I) Programs

QuEEN™: Accessing 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 are our most advanced Immunology & Inflammation programs, with multiple additional targets being explored



Rheumatoid Arthritis

Inflammatory Bowel Disease

Gout

Multiple Sclerosis

Systemic Sclerosis

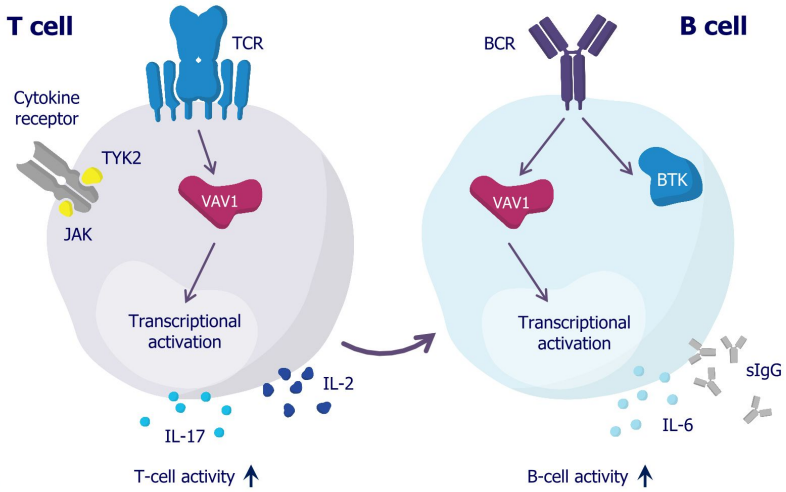
Additional indications

Monte Rosa Therapeutics

VAV1 Program

VAV1-directed MGDs: Unique MOA Targeting Both T and B Cells

VAV1-directed MGDs have the potential to modulate T- and B-cell function



VAV1 signaling increases cytokine production, proliferation, and differentiation

Therapeutic hypothesis:

- VAV1 is a pivotal scaffolding protein and signaling molecule downstream of both the T-cell and B-cell receptors – confirmed by multiple CRISPR screens VAV1 KO mice
- VAV1 degradation is predicted to impact both T- & B-cell function and has the potential to treat a broad set of autoimmune diseases

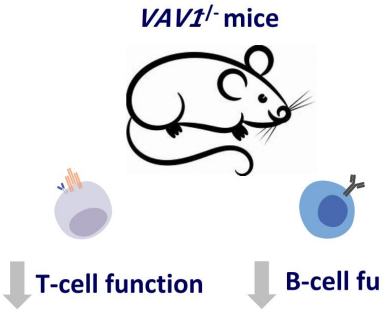
Clinical Opportunity:

Autoimmune disorders including rheumatoid arthritis (6.2M patients), multiple sclerosis (1.3M patients), and myasthenia gravis (36K – 60K patients in US)

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

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

VAV1-/- mice are viable, fertile, and display loss-of-function T- and B-cell phenotypes

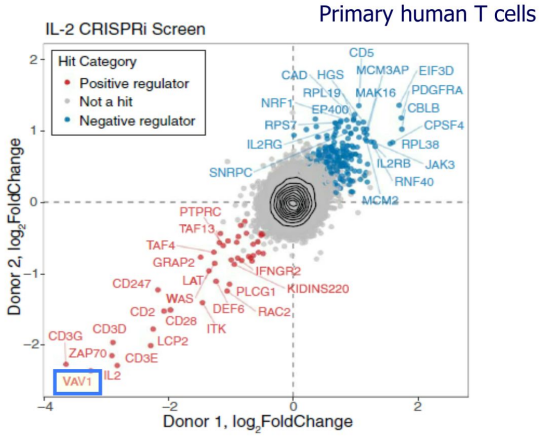


- Impaired T-cell proliferation and cytokine production
- Impaired B-cell proliferation and immunoglobulin production
- Evidence of impaired T-cell dependent B-cell response

Betzler et al., Front Cell & Dev Bio 2022
Turner et al., Nat Rev Immun 2002
Bachman et al., J. Immun 1999
Fischer et al., Curr Biol 1998

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

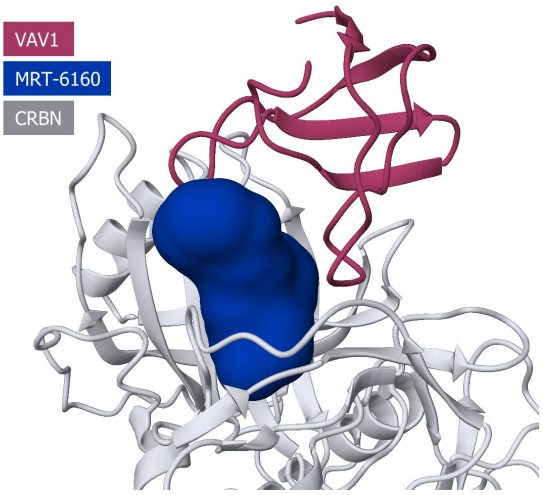
Primary human T cells



Schmidt et al., Science 2022

MRT-6160 is a Potent, Selective VAV1 MGD with a Favorable Drug-like Profile

VAV1 ternary complex (Cryo-EM)

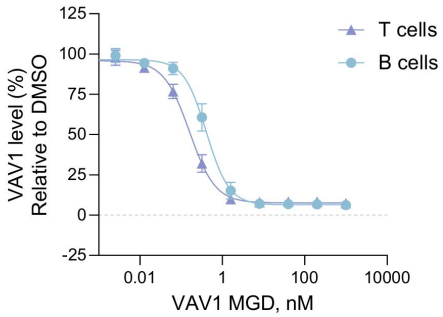


Cryo-EM structure of MRT-6160 in ternary complex with CRBN and VAV1

MGD Activity Profile	
CRBN Binding (HTRF, IC_{50})	0.67 µM
VAV1 Ternary Complex (HTRF, EC_{50})	11 nM
VAV1 Degradation (Jurkat, DC_{50}/Dmax)	7 nM / 97%
Selectivity (TMT proteomics)	Large VAV1 selectivity window
Physicochemical Properties	
LogD	1.5
MW	<400
Thermodynamic Solubility	7 µM
ADMET Profile	
Oral bioavailability (all species)	> 50 %
Metabolite Profile (*in vitro*)	No unique human metabolites or GSH adducts (mics)
CYP DDI (9 isoforms)	IC_{50} > 30 µM
Safety Pharmacology	
Mini-Ames	Negative
hERG inhibition (patch clamp)	No inhibition (EC_{50} > 30 µM)
CEREP (panel with 44 proteins)	No inhibition

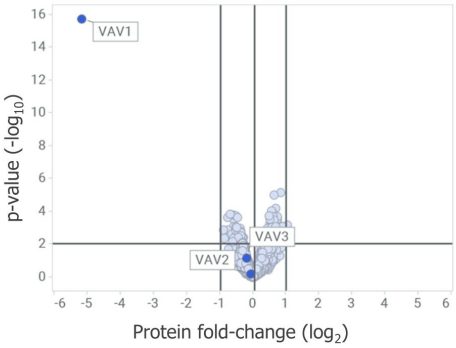
MRT-6160 is a Potent and Selective VAV1-directed MGD

MRT-6160 is a potent VAV1-directed MGD



in vitro data	
CRBN binding, IC_{50}	670 nM
Ternary complex, EC_{50}	11 nM
Degradation, DC_{50} /D_{max} (Jurkat)	7 nM / 97 %

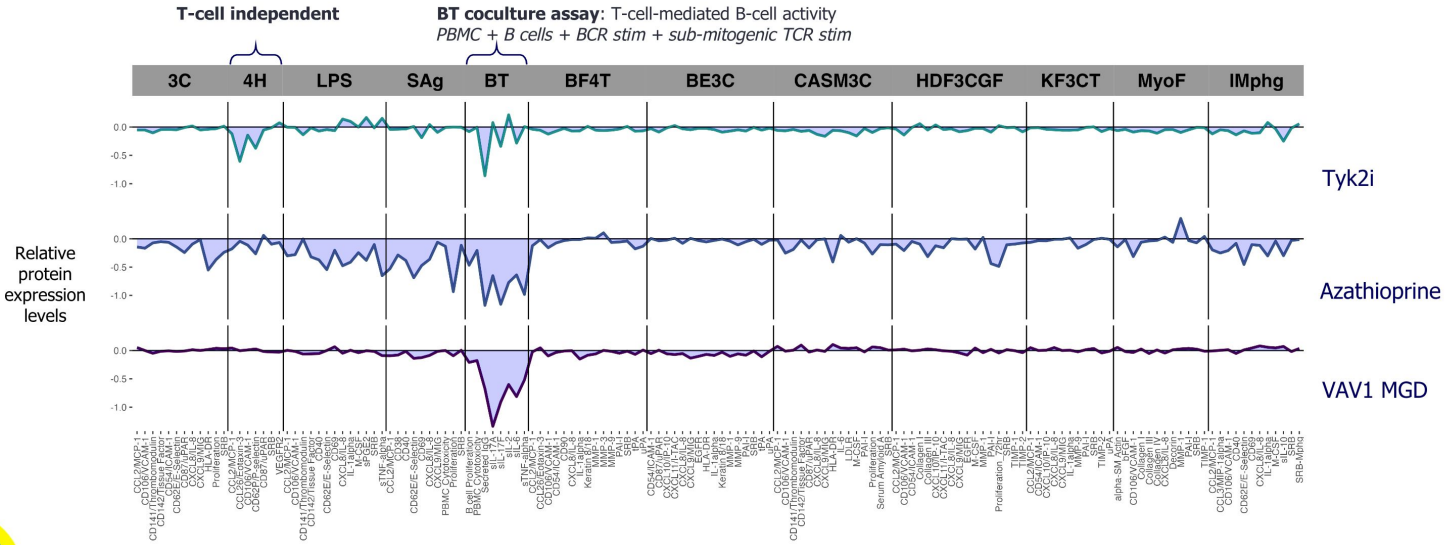
MRT-6160 induces highly selective VAV1 degradation and has a favorable ADME/DMPK profile



No degradation of cereblon neosubstrates

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

MRT-6160 Demonstrates Differentiated Activity (BioMAP) Profile



Tyk2i, Deucravacitinib, 400 nM

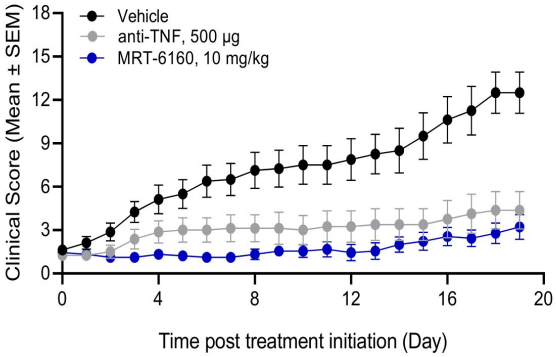
Azathioprine, 100 uM

VAV1 MGD, MRT-6160, 1000 nM

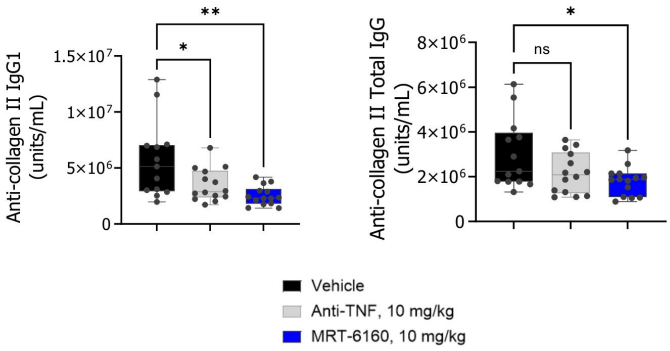
** Experiment performed by Eurofins*

MRT-6160 Inhibits Disease Progression, Joint Inflammation & Auto-Antibody Production in the Collagen-Induced Arthritis Disease Model

MRT-6160 inhibits disease progression



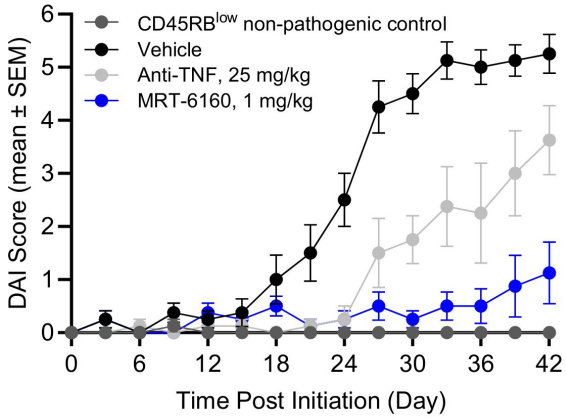
MRT-6160 inhibits anti-collagen II auto-antibodies



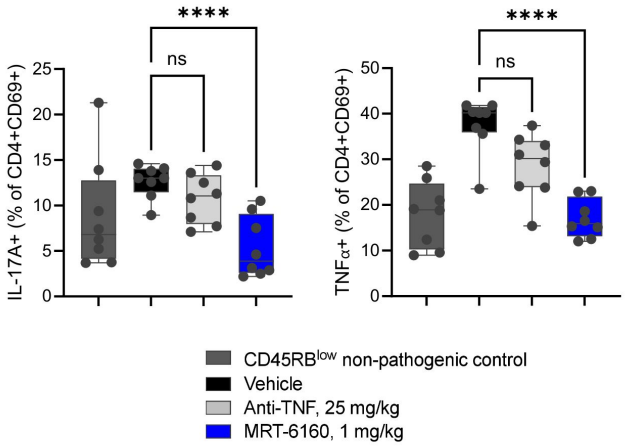
Collagen-induced arthritis T/B-cell (auto-antibody) driven model

MRT-6160 Inhibits Disease Progression and Cytokine Production in a Model of Inflammatory Bowel Disease

MRT-6160 inhibits disease progression in a model of colitis



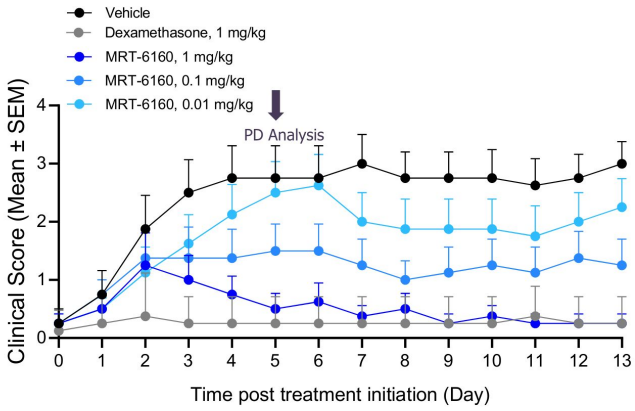
MRT-6160 reduces pro-inflammatory cytokine production by CD4+ T cells



CD4+ T cell transfer-induced colitis model

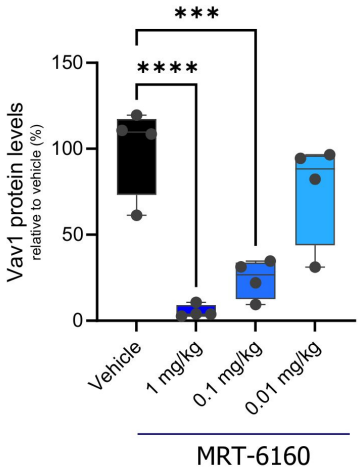
MRT-6160 Elicits Dose-Dependent Activity in T-cell-mediated Multiple Sclerosis Autoimmune Disease Model

MRT-6160 inhibits disease progression in a mouse model of multiple sclerosis



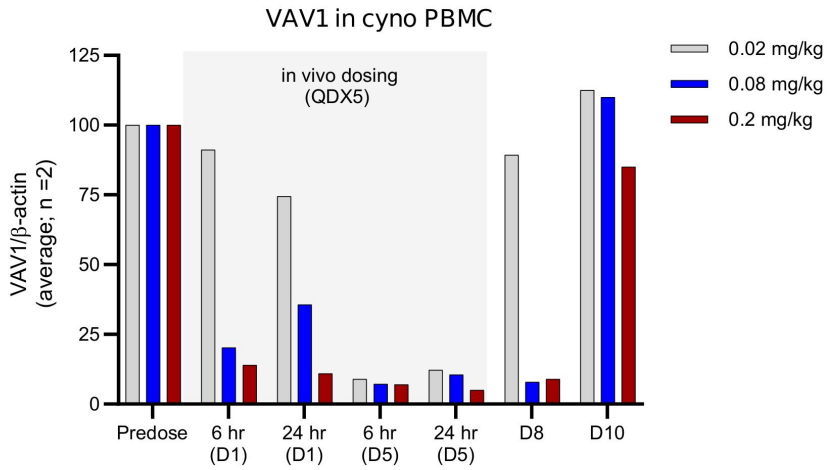
T-cell mediated model
EAE = MOG_{35-55} peptide-induced experimental autoimmune encephalitis
Dosing: QD (oral) for 14 days starting at disease onset; PD analysis on d6

MRT-6160-mediated activity correlates with VAV1 levels



Tissue PD; QD oral dosing of MRT-6160 for 6 days following disease onset

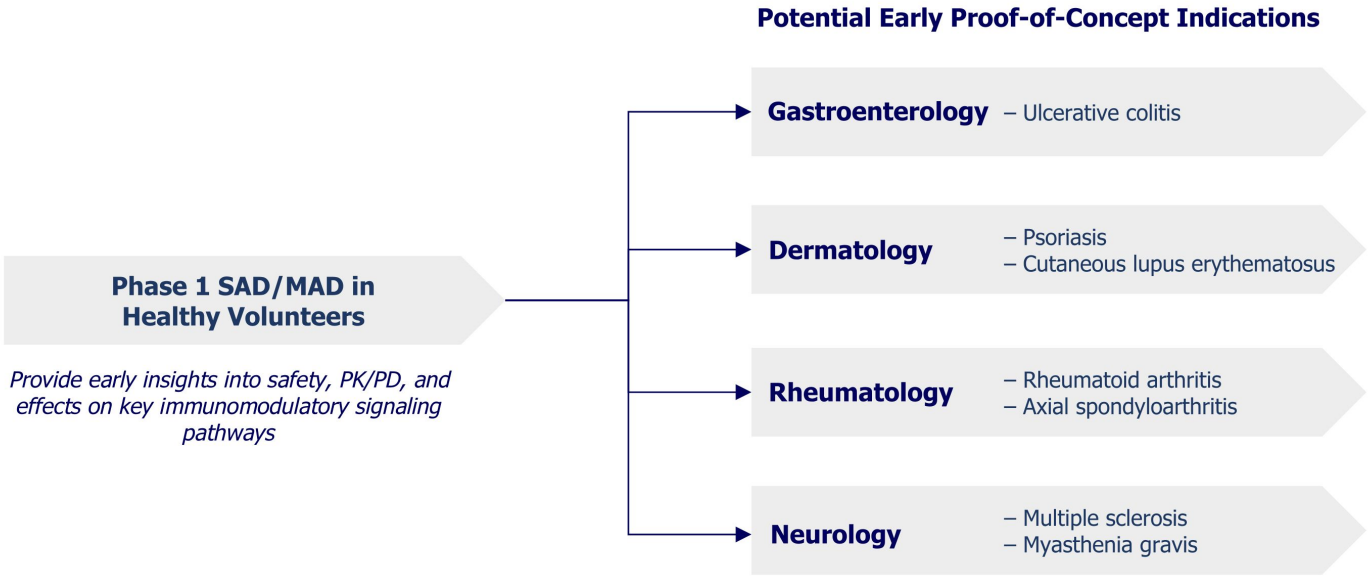
MRT-6160 Induces Significant VAV1 Degradation in Non-human Primates



- Increased degradation with repeat dosing
- Maximal VAV1 degradation at very low doses
- VAV1 levels return to baseline within 5 days of last dose

Preliminary MRT-6160 Development Plan through Early POC

Potential in multiple I&I indications with T cell and T/B cell-mediated pathophysiology



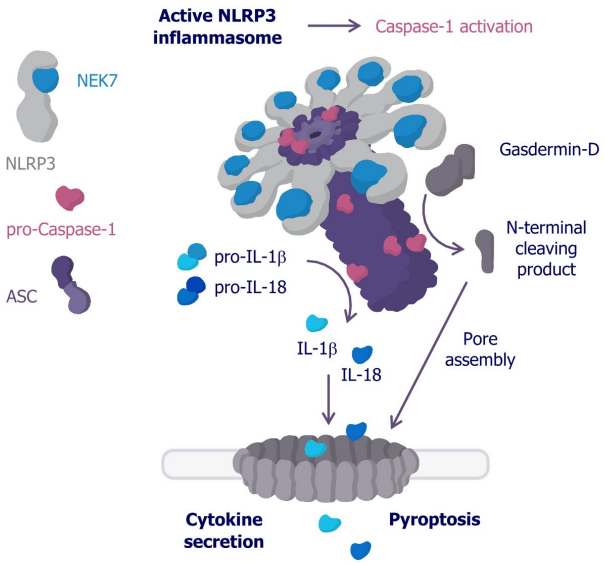
SAD/MAD study expected to initiate mid-2024

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:

Activation of the NLRP3 inflammasome critically depends on NEK7

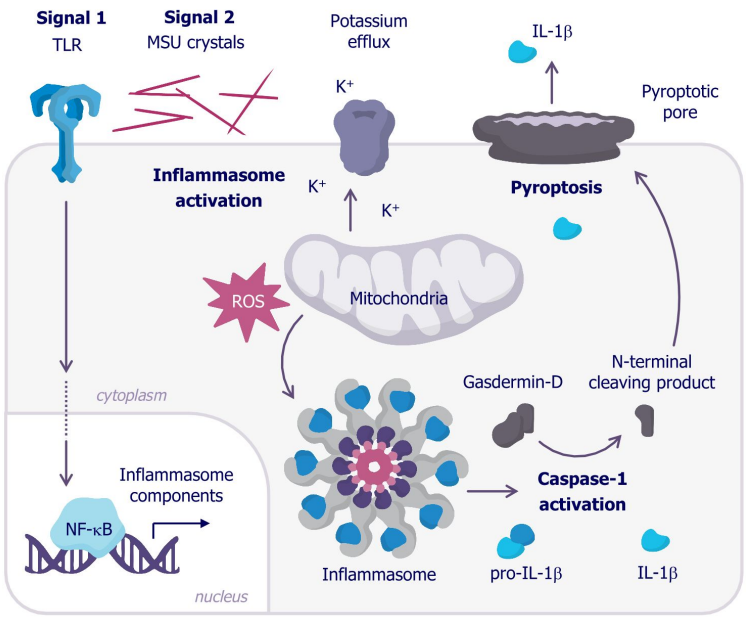
- NEK7 licenses NLRP3 assembly in a kinase-independent manner
- NEK7-deficient macrophages are severely impaired in IL-1β and IL-18 secretion

Consequently, NEK7 degradation has the potential to become an important treatment modality for a variety of inflammatory diseases

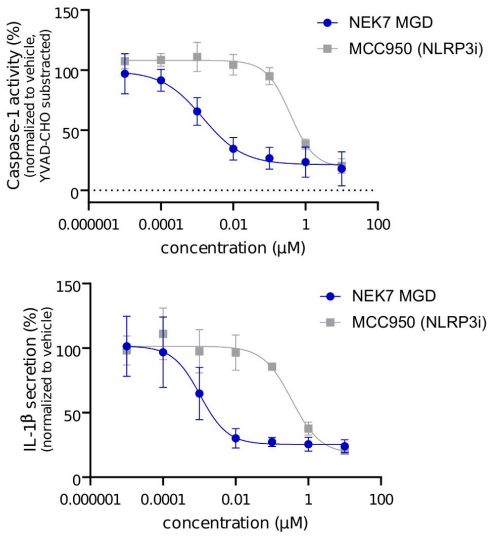
Clinical Opportunity:

Diseases with over-activated NLRP3 inflammasome: metabolic pathologies (e.g. gout), cardiovascular diseases, inflammatory diseases and neurologic disorders

NEK7 MGDs Inhibit NLRP3 Activation by Monosodium Urate



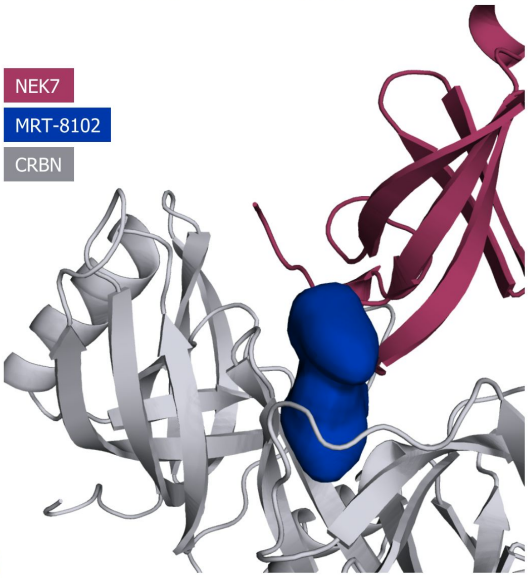
NEK7 MGDs reduce MSU induced NLRP3 Inflammasome activation



Human monocyte-derived macrophages LPS + MSU stimulation
Pretreatment with molecular glue degrader (MGD) or NLRP3 inhibitor (NLRP3i)

MRT-8102 is a NEK7-Directed MGD With Favorable Drug-like Properties

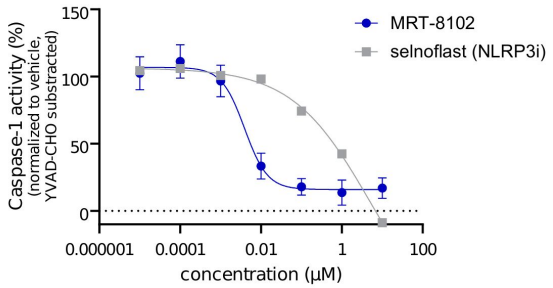
NEK7 Ternary Complex (Crystal Structure)



MGD Activity Profile	
CRBN Binding (HTRF, IC_{50})	0.2 µM
NEK7 Degradation (CAL51, DC_{50}/Dmax)	10 nM / 89%
Selectivity (TMT proteomics)	Excellent selectivity profile in different cell lines
Physicochemical Properties	
LogD	1.47
MW	<450
Thermodynamic Solubility	166 µM
ADMET Profile	
Oral Bioavailability	Yes
Metabolite Profile (*in vitro*)	No unique human metabolites or GSH adducts (mics)
Safety Pharmacology	
Mini-Ames	Negative
hERG (patch clamp)	No inhibition (EC50> 30 µM)
CEREP (panel with 44 proteins)	No inhibition

MRT-8102 is a Potent and Selective NEK7-directed MGD

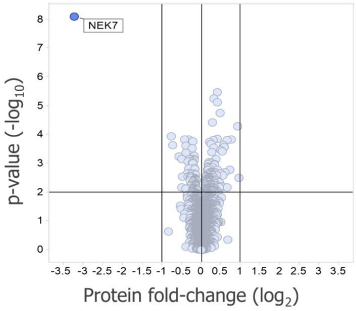
MRT-8102 potently suppresses inflammasome activation in primary human macrophages



in vitro data	
CRBN binding, IC_{50}	200 nM
Degradation, DC_{50} /D_{max} (Jurkat)	10 nM / 97 %

Human monocyte-derived macrophage (hMDM) assay
LPS + MSU stimulation; pre-treatment with MGD/NLRP3i
Similar reduction in IL-1β

MRT-8102 induces highly selective NEK7 degradation



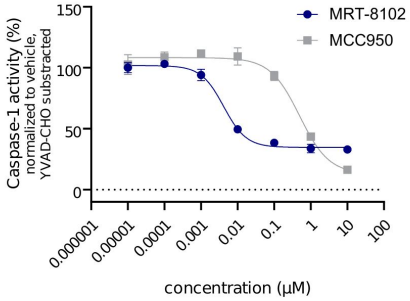
No degradation of cereblon neosubstrates

ADMET profile	
CYP DDIs	IC_{50} > 30 µM
Oral bioavailability (m/r)	>50%

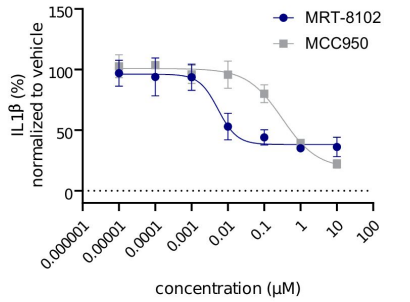
MRT-8102 at 10 µM in hPBMC, 24h
Additional cell lines screened:
U937, Kelly and MM1S

MRT-8102 Potently Inhibits NLRP3 Inflammasome-mediated Activation in Human Monocyte-derived Macrophages

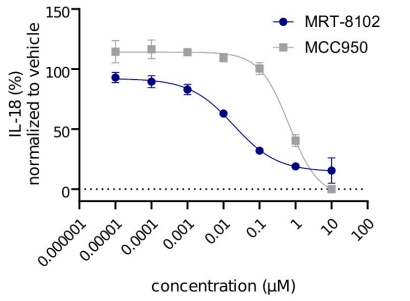
MRT-8102 inhibits caspase-1 activity in hMDMs after stimulation



MRT-8102 inhibits IL-1β secretion by hMDMs after stimulation



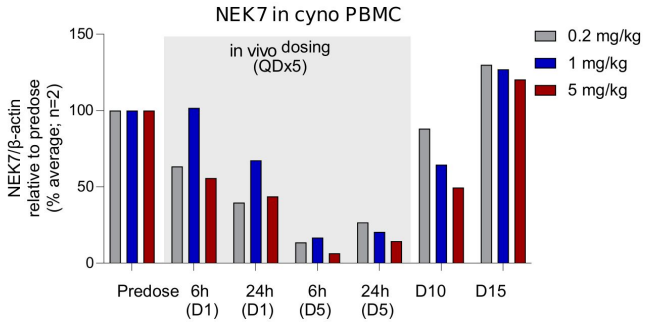
MRT-8102 inhibits IL-18 secretion by hMDMs after stimulation



Human monocyte-derived macrophage (hMDM) assay
Pre-incubation with MGD/NLRP3i; stimulated with LPS + MSU
Supernatants analyzed post-stimulation

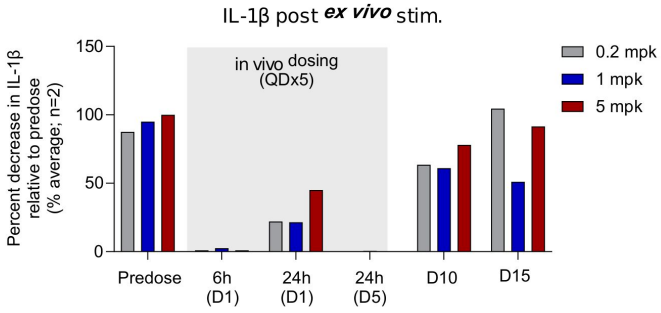
Suppression of *ex vivo* Inflammasome Activation Following Degradation of NEK7 in Non-human Primates

MRT-8102 leads to NEK7 degradation *in vivo*



No clinical observations reported

***In vivo* NEK7 degradation leads to inhibition of NLRP3 inflammasome in *ex vivo* stimulation assay**



IL-1β in plasma after *ex vivo* stimulation with LPS + nigericin

Monte Rosa Therapeutics

Team

World-Class Leadership

Deep expertise in molecular glue discovery, drug development and precision medicine

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Thank You
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