UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

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

Date of Report (Date of earliest event reported): May 9, 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 2.02. Results of Operations and Financial Condition

On May 9, 2024, Monte Rosa Therapeutics, Inc. (the "Company") announced its financial results for the quarter ended March 31, 2024. 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 May 9, 2024, 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 May 9, 2024.
99.2	Corporate Presentation furnished by Monte Rosa Therapeutics, Inc. on May 9, 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: May 9, 2024

By: /s/ Markus Warmuth

Markus Warmuth

President and Chief Executive Officer

Monte Rosa Therapeutics Announces First Quarter 2024 Financial Results and Provides Corporate Update

MRT-2359, a molecular glue degrader (MGD) being developed for MYC-driven solid tumors, advancing in ongoing Phase 1/2 clinical trial; determination of recommended Phase 2 dose expected in Q2 2024; Phase 1 clinical data anticipated in H2 2024

MRT-6160, a VAV1-directed MGD in development for systemic and neurological autoimmune diseases, on track toward expected IND submission in Q2 2024 and initiation of Phase 1 SAD/MAD study mid-year; Phase 1 clinical data expected in Q1 2025

MRT-8102, a first-in-class NEK7-directed MGD and NLRP3/IL-1β pathway inhibitor, demonstrated efficient blood-brain barrier penetration and CNS activity in non-human primates (NHPs); IND submission on track for Q1 2025

New discovery program unveiled for CCNE1-directed MGDs; first to directly drug important, previously undruggable solid tumor oncology target

Strong cash position expected to fund operations into H1 2026, enabling advancement of MRT-2359, MRT-6160, and MRT-8102 programs through clinical milestones

BOSTON, Mass., May 9, 2024 – Monte Rosa Therapeutics, Inc. (Nasdaq: GLUE), a clinical-stage biotechnology company developing novel molecular glue degrader (MGD)-based medicines, today reported business highlights and financial results for the first quarter ending March 31, 2024.

“We’re excited by the significant advances made across our entire portfolio, including both our oncology and immunology/inflammation programs,” said Markus Warmuth, M.D., Chief Executive Officer of Monte Rosa Therapeutics. “Our Phase 1/2 clinical trial evaluating MRT-2359 for MYC-driven solid tumors is on track and we plan to announce the recommended Phase 2 dose later this quarter and to report clinical data from this program in the second half of the year. We eagerly anticipate the initiation of a Phase 1 study of MRT-6160, the first of our MGD drug candidates for immune-related diseases, in mid-2024, with results from the study expected in Q1 2025. Preclinical GLP toxicology data we’ve announced today, along with data in multiple disease models, suggest the potential for a highly differentiated profile across multiple autoimmune diseases. Additionally, MRT-8102, our NEK7-directed MGD targeting diseases driven by IL-1β and the NLRP3 inflammasome, is rapidly progressing toward clinical studies. We’ve recently demonstrated strong CNS exposure and NEK7 degradation in non-human primates, supporting the potential development of MRT-8102 in neurologic indications and obesity amongst others, in addition to its potential use in gout, pericarditis, and other peripheral inflammatory conditions. We’re also very pleased to announce our discovery program for CCNE1 (Cyclin E1), a well-validated oncology target generally considered undruggable by conventional modalities. We believe our ability to degrade CCNE1 potently and selectively and to elicit anti-tumor activity in *in vivo* models provides further validation for the differentiation of our QuEEN™ discovery engine and the potential of our MGDs against a broad spectrum of targets.”

Dr. Warmuth concluded, “The rapid and efficient progression of our pipeline clearly illustrates the power of our AI/ML-driven QuEEN™ discovery engine. Through our ongoing internal efforts as well as our research collaboration with Roche, we look forward to continuing this strong progress.”

RECENT HIGHLIGHTS

MRT-2359, GSPT1-directed MGD for MYC-driven solid tumors

- Monte Rosa continues to evaluate MRT-2359 in a Phase 1/2 clinical trial in MYC-driven solid tumors (NCT05546268). Enrollment is ongoing in backfill cohorts at clinically active doses using a 5-days-on, 9-days-off drug schedule and in dose escalation cohorts using a 21-days-on, 7-days-off drug schedule. The Company is on track to determine the recommended Phase 2 dose (RP2D) in Q2 2024 and report Phase 1 study results in H2 2024. Monte Rosa expects to initiate the Phase 2 portion of the study before year-end.
- The Company presented preclinical data at the American Association for Cancer Research (AACR) Annual Meeting demonstrating that treatment with MRT-2359 resulted in marked tumor regressions in the AR-V7- and c-MYC-expressing 22RV1 xenograft mouse model of prostate cancer associated with resistance to anti-androgen agents.

MRT-6160, VAV1-directed MGD for systemic and neurological autoimmune/inflammatory diseases

- The MRT-6160 program is on track for an anticipated Investigational New Drug (IND) submission to the U.S. Food and Drug Administration (FDA) in Q2 2024, and initiation of a Phase 1 single ascending dose/multiple ascending dose (SAD/MAD) study in mid-2024. Phase 1 results are anticipated in Q1 2025.
- The Company today announced additional results from completed preclinical GLP toxicology studies of MRT-6160 in rats and non-human primates (NHPs). The data demonstrate a highly favorable safety profile with no significant changes in peripheral immune cell compartments.
- Monte Rosa expects to present additional preclinical data for MRT-6160 in models of autoimmune and inflammatory diseases at the upcoming Digestive Disease Week (DDW) and European Alliance of Associations for Rheumatology (EULAR) medical meetings.

MRT-8102, NEK7-directed MGD for inflammatory diseases driven by IL-1β and the NLRP3 inflammasome

- In March 2024, Monte Rosa announced the initiation of IND-enabling studies for MRT-8102, a first-in-class NEK7-directed MGD for the treatment of inflammatory diseases driven by interleukin-1β (IL-1β) and the NLRP3 inflammasome, critical elements of the inflammatory process. This is the first development candidate to be declared from the Company's NEK7 development program.
- Monte Rosa today announced that MRT-8102 has demonstrated highly favorable CNS exposure and degradation in a study in cynomolgus monkeys. The data support the potential for development of MRT-8102 in diseases including Parkinson's disease, Alzheimer's disease, and obesity. The Company is evaluating applications across multiple inflammatory disorders.
- Monte Rosa expects to submit an IND application for MRT-8102 in Q1 2025.

CCNE1-directed MGD program for CCNE1-amplified tumors

- Monte Rosa today announced a new discovery program for CCNE1 (Cyclin E1)-directed MGDs for the treatment of CCNE1-amplified tumors. CCNE1, a key component of the cell cycle and a known driver of many cancers, is generally considered an undruggable target by conventional modalities.

Additional corporate updates

- In October 2023, Monte Rosa entered into a strategic collaboration and licensing agreement with Roche, a global healthcare leader, to discover and develop MGDs against targets in cancer and neurological diseases. The collaboration continues to advance research activities according to plan.

ANTICIPATED MILESTONES

- Announce the recommended Phase 2 dose for the MRT-2359 Phase 1/2 study in Q2 2024 and report Phase 1 clinical results in H2 2024. Initiate the Phase 2 portion of the study before year-end. The Company is evaluating Phase 2 expansion cohorts in high-prevalence c-MYC-driven tumors including hormone receptor-positive breast cancer and prostate cancer, as well as tumor types and patient populations driven by L- and N-MYC including non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and solid tumors with amplifications of L- and N-MYC.
- Submit an IND application for MRT-6160 in Q2 2024 and initiate a Phase 1 SAD/MAD study in healthy volunteers in mid-2024; report results from the Phase 1 study in Q1 2025. Monte Rosa expects to subsequently initiate proof-of-concept (POC) studies in autoimmune/inflammatory diseases including ulcerative colitis and rheumatoid arthritis, with additional potential POC studies in dermatology, rheumatology, and neurology indications.
- Submit an IND application for MRT-8102 in Q1 2025.
- Nominate a development candidate for the CDK2 preclinical program in 2024.

UPCOMING PRESENTATIONS

- Monte Rosa plans to present a poster at the Digestive Disease Week (DDW) Conference on May 21, 2024, in Washington, DC, titled, “MRT-6160, a VAV1-Directed Molecular Glue Degrader, Inhibits Disease Progression in a T-cell Transfer Mediated Murine Colitis Model Concomitant with Reduced Calprotectin Expression.”
- Monte Rosa plans to present a poster at the European Alliance of Associations for Rheumatology (EULAR) Conference on June 14, 2024, in Vienna, Austria, titled, “MRT-6160, a VAV1-Directed Molecular Glue Degrader, Reduces Joint Inflammation, Cytokine Production, and Autoantibody Levels in a Collagen-Induced Arthritis Disease Model.”

FIRST QUARTER 2024 FINANCIAL RESULTS

Collaboration Revenue: Collaboration revenue for the first quarter of 2024 was $1.1 million, compared with $0 during the same period in 2023. Collaboration revenue represents revenue recorded under the Roche License and Collaboration agreement.

Research and Development (R&D) Expenses: R&D expenses for the first quarter of 2024 were $27.0 million, compared to $26.8 million during the same period in 2023. R&D expenses were driven by the successful achievement of key milestones in our R&D organization, including the continuation of the MRT-2359 clinical study, the progression and growth of our preclinical pipeline, the preparation of MRT-6160 to enter the clinic, and the continued development of the Company’s QuEEN™ discovery engine. Non-cash stock-based compensation constituted $2.7 million of R&D expenses for Q1 2024, compared to $2.1 million in the same period in 2023.

General and Administrative (G&A) Expenses: G&A expenses for the first quarter of 2024 were $9.0 million compared to $7.5 million during the same period in 2023. The increase in G&A expenses was a result of increased headcount, stock-based compensation expense, and fees paid to consultants in order to support our growth and operations. G&A expenses included non-cash stock-based compensation of $2.2 million for the first quarter of 2024, compared to $1.8 million for the same period in 2022.

Net Loss: Net loss for the first quarter of 2024 was $32.0 million, compared to $33.3 million for the fourth quarter of 2023.

Cash Position and Financial Guidance: Cash, cash equivalents, restricted cash, and marketable securities as of March 31, 2024, were $197.8 million, compared to cash, cash equivalents, restricted cash, and marketable securities of $237.0 million as of December 31, 2023. The decrease of $39.2 million was primarily due to operational use of cash.

The Company expects its cash and cash equivalents to be sufficient to fund planned operations and capital expenditures into the first half of 2026.

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 systemic and neurological autoimmune indications, such as multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, and dermatological disorders. Preclinical studies have demonstrated that MRT-6160 can inhibit disease progression in *in vivo* autoimmunity models.

About MRT-8102
MRT-8102 is a potent, highly selective, and orally bioavailable investigational molecular glue degrader (MGD) that targets NEK7 for the treatment of inflammatory diseases driven by IL-1β and the NLRP3 inflammasome. NEK7 has been shown to be required for NLRP3 inflammasome assembly, activation and IL-1β release both *in vitro* and *in vivo*. Aberrant NLRP3 inflammasome activation and the subsequent release of active IL-1β and interleukin-18 (IL-18) has been implicated in multiple inflammatory disorders, including gout, cardiovascular disease, neurologic disorders including Parkinson's disease and Alzheimer's disease, ocular disease, diabetes, obesity, and liver disease. In a non-human primate model, MRT-8102 was shown to potently, selectively, and durably degrade NEK7, and resulted in near-complete reductions of IL-1β

models following *ex vivo* stimulation of whole blood. MRT-8102 has shown a favorable profile in non-GLP toxicology studies.

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. Monte 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 ability to grow our product pipeline, statements around the Company's QuEEN™ discovery engine and the Company's view of its potential to identify degradable protein targets and rationally design MGDs with unprecedented selectivity, statements around the power and differentiation of the QuEEN discovery engine and the potential of the Company's MGDs against a broad spectrum of targets, statements about the advancement and timeline of our preclinical and clinical programs, pipeline and the various products therein, including (i) our product development activities, our ongoing clinical development of MRT-2359, our expectations to announce the recommended Phase 2 dose later in the second quarter of 2024, the timing for our disclosure of any initial data from our Phase 1 clinical trial of MRT-2359 in the second half of 2024, and our plans to initiate the Phase 2 portion of the study before year-end, (ii) the ongoing development of MRT-6160, and the planned submission of an IND to the FDA for MRT-6160 in the second quarter of 2024, our expectations of timing for initiation of a Phase 1 SAD/MAD study mid-2024 and the timing for our disclosure of Phase 1 clinical data of MRT-6160 in the first quarter of 2025, as well as our expectation to present additional preclinical data in models of autoimmune and inflammatory diseases at the upcoming DDW and EULAR medical meetings and our expectation to initiate POC studies for MRT-6160 in autoimmune/inflammatory diseases including ulcerative colitis and rheumatoid arthritis, with additional potential POC studies, dermatology, rheumatology, and neurology indications in mid-2024, (iii) our ongoing development of MRT-8102 and our expectations around its potential across neurologic indications and obesity amongst others, as well as potential use in gout, pericarditis, and other peripheral inflammatory conditions, including our expectations to submit an IND to the FDA in the first quarter of 2025, and (iv) our expectations to nominate a development candidate for the CDK2 preclinical program in 2024, 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, statements regarding regulatory filings for our development programs, including the planned timing of such regulatory filings, such as IND applications, and potential review by regulatory authorities as well as our expectations of success for our programs and the strength of our financial position, our use of capital, expenses and other financial results in the future, availability of funding for existing programs, ability to fund operations into the first half of 2026, 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 14, 2024, 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)
(Unaudited)

	March 31, 2024	December 31, 2023
Assets		
Current assets:		
Cash and cash equivalents	$ 99,752	$ 128,101
Marketable securities	93,140	104,312
Other receivables	601	505
Prepaid expenses and other current assets	5,543	3,294
Total current assets	199,036	236,212
Property and equipment, net	34,036	33,803
Operating lease right-of-use assets	28,422	28,808
Restricted cash	4,863	4,580
Other long-term assets	389	352
Total assets	$ 266,746	$ 303,755
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 6,828	$ 11,152
Accrued expenses and other current liabilities	10,713	14,600
Current deferred revenue	20,407	17,678
Current portion of operating lease liability	3,345	3,162
Total current liabilities	41,293	46,592
Deferred revenue, net of current	28,529	32,323
Defined benefit plan liability	2,568	2,713
Operating lease liability	41,837	42,877
Total liabilities	114,227	124,505
Commitments and contingencies		
Stockholders' equity		
Common stock, $0.0001 par value; 500,000,000 shares authorized, 50,210,309 shares issued and 50,200,304 shares outstanding as of March 31, 2024; and 50,154,929 shares issued and 50,140,233 shares outstanding as of December 31, 2023	5	5
Additional paid-in capital	553,063	547,857
Accumulated other comprehensive loss	(2,693)	(2,724)
Accumulated deficit	(397,856)	(365,888)
Total stockholders' equity	152,519	179,250
Total liabilities and stockholders' equity	$ 266,746	$ 303,755

Consolidated Statement of Operations and Comprehensive Loss
(in thousands, except share and per share amounts)
(unaudited)

	Three months ended March 31,	
	2024	2023
Collaboration revenue	$ 1,064	$ —
Operating expenses:		
Research and development	27,026	26,755
General and administrative	8,985	7,504
Total operating expenses	36,011	34,259
Loss from operations	(34,947)	(34,259)
Other income (expense):		
Interest income, net	2,442	2,437
Foreign currency exchange (loss) gain, net	620	(85)
Loss on sale of marketable securities	—	(131)
Total other income	3,062	2,221
Net loss before income taxes	(31,885)	(32,038)
Provision for income taxes	(83)	—
Net loss	$ (31,968)	$ (32,038)
Net loss per share—basic and diluted	$ (0.53)	$ (0.65)
Weighted-average number of shares outstanding used in computing net loss per common share—basic and diluted	60,156,187	49,347,473
Comprehensive loss:		
Net loss	$ (31,968)	$ (32,038)
Other comprehensive loss:		
Provision for pension benefit obligation	35	14
Unrealized gain (loss) on available-for-sale securities	(4)	345
Comprehensive loss	$ (31,937)	$ (31,679)

Investors
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From Serendipity to Rational Design
Taking Molecular Glue Degraders to New Heights | May 2024
Monte Rosa
Therapeutics

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 ability to grow our product pipeline, 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 initial data from our Phase 1/2 clinical trial of MRT-2359 in MYC-driven solid tumors, statements the Company's QuEEN™ discovery engine and the Company's view of its potential to identify degradable protein targets and rationally design MGDs with unprecedented selectivity, statements about the potential applications of our rationally designed MGDs in oncology, immunology, neuroscience and other therapeutic areas, statements about our collaboration with Roche, statements about the advancement and timeline of our preclinical and clinical programs, pipeline and the various products therein, including (i) our product development activities and our ongoing clinical development of MRT-2359, including our expectations to announce the recommended Phase 2 dose later in the second quarter of 2024, the timing for our disclosure of any initial data from our Phase 1 clinical trial of MRT-2359 in the second half of 2024, and our plans to initiate the Phase 2 portion of the study, (ii) the ongoing development of MRT-6160, including its rapid advancement with Phase 1 initiation expected in mid-2024, planned submission of an IND to the FDA for MRT-6160 in the second quarter of 2024, our expectations of timing for initiation of a Phase 1 single ascending dose / multiple ascending dose (SAD/MAD) study in mid-2024 and the timing for our disclosure of Phase 1 clinical data of MRT-6160 in the first quarter of 2025 and our expectation to initiate POC studies for MRT-6160 in autoimmune/inflammatory diseases, (iii) our ongoing development of MRT-8102, including our expectations to submit an IND to the FDA in the first quarter of 2025, statements about the timing for a clinical readout of data from a Phase 1 SAD/MAD study for MRT-8102 and our expectations of timing for clinical advancement for MRT-8102, and (iv) our expectations to nominate a development candidate for the CDK2 preclinical program in 2024, , 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, our use of capital, expenses and other financial results in the future, availability of funding for existing programs, ability to fund operations into the first half of 2026, 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 14, 2024, 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**

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

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, Phase 1 data in H2 2024**

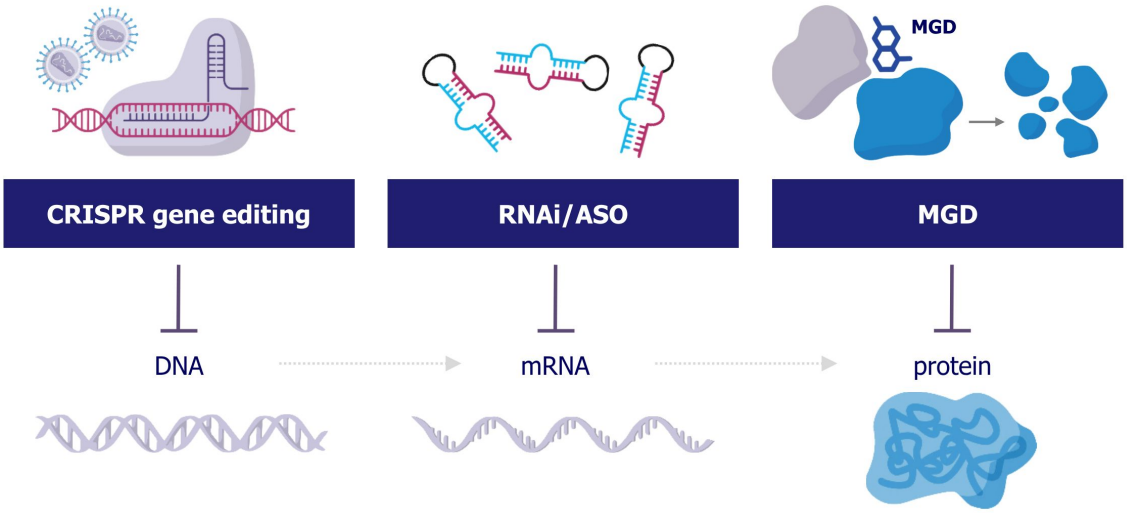
MRT-6160, highly selective VAV1-directed MGD, being rapidly advanced with Phase 1 initiation expected in mid-2024, data in Q1 2025; broad potential applications across autoimmune diseases

MRT-8102, highly selective NEK7-directed MGD for IL-1β/NLRP3-driven inflammatory diseases with IND submission anticipated Q1 2025

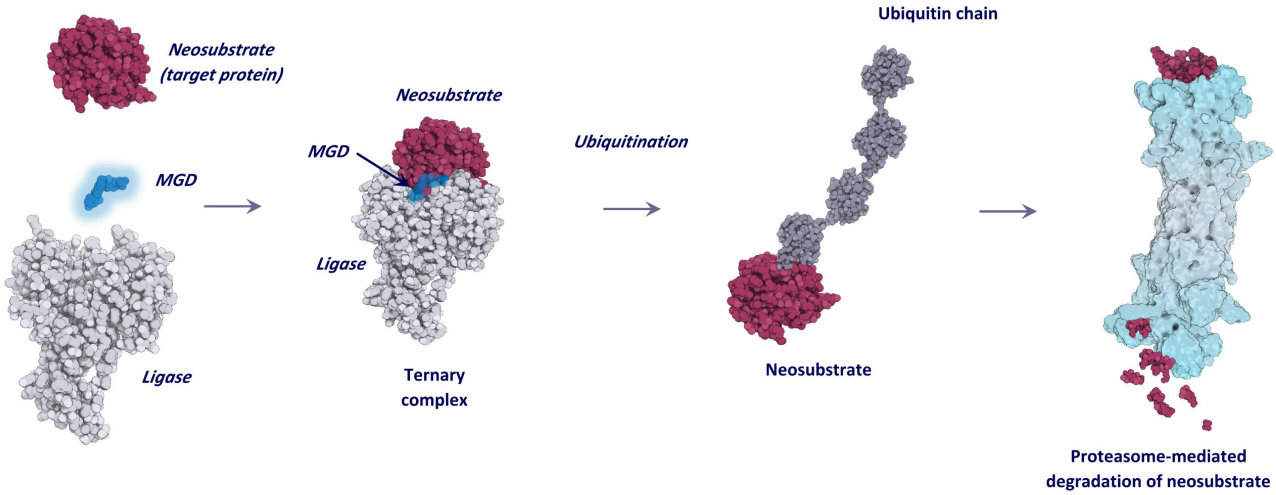
Strong financial position providing cash runway into H1 2026 and through multiple anticipated clinical readouts, including MRT-2359 Phase 1/2 and SAD/MAD for VAV1 and NEK7

Three Ways to Eliminate a Disease-Causing Protein

MGDs can directly and precisely target proteins that cause disease



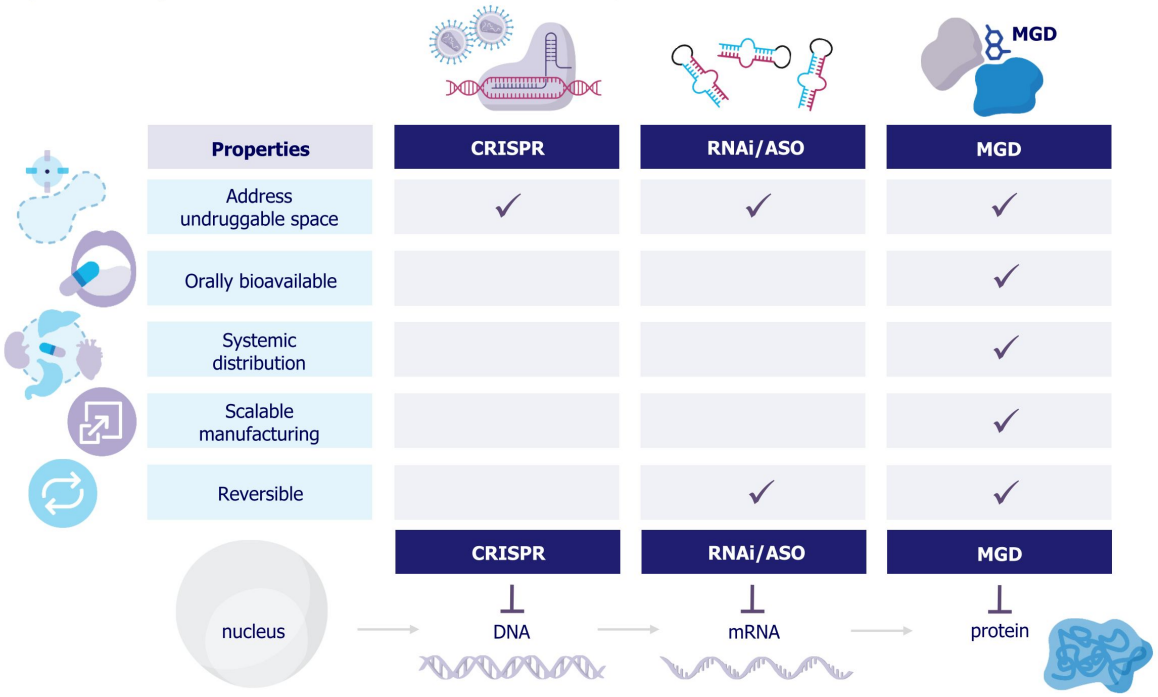
Our Molecular Glue Degraders (MGDs) Edit the Proteome



Monte Rosa's rationally designed MGDs have potential applications in Oncology, Immunology, Neuroscience and other therapeutic areas

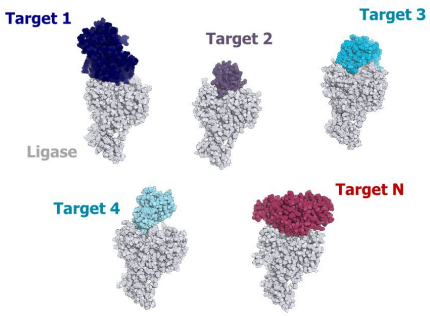
Molecular Glue Degraders (MGDs) – A Highly Differentiated Modality

Advantages of large molecule modalities with orally dosed small molecules



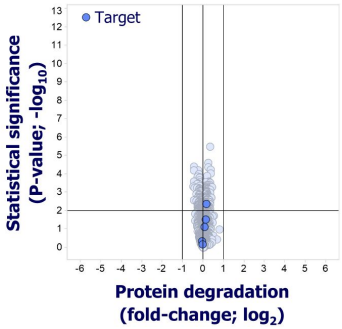
Key Advantages of Our Rationally Designed MGDs

Unique Target Space



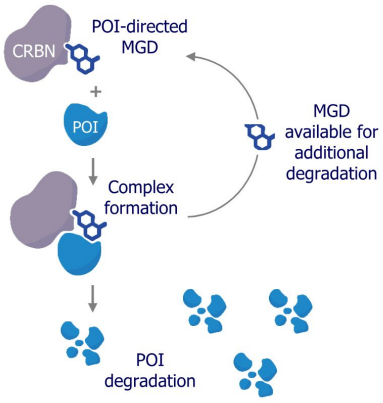
Disease-agnostic platform with initial focus on highly credentialed, undruggable oncology and immunology/inflammation targets

Unprecedented Selectivity



Unique insights into anatomy of protein-protein-MGD interaction allows unprecedented MGD selectivity

Catalytic Mechanism of Action



Long lasting, catalytic protein degradation effect creates differentiated target product profiles

POI = protein of interest

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 and NEK7 MGD MRT-8102 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 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

Target	Compound	Indication(s)	Discovery	IND-Enabling	Clinical	Next Anticipated Milestone	Ownership
GSPT1	MRT-2359	NSCLC, SCLC and other MYC-driven Malignancies				RP2D in Q2 2024	
VAV1	MRT-6160	Autoimmune Disease – Systemic and CNS				IND submission in Q2 2024	
NEK7	MRT-8102	IL-1β/NLRP3 driven Inflammatory Diseases				IND submission in Q1 2025	
	LO (2nd generation)					Development candidate	
CDK2	LO	Breast Cancer				Development candidate in 2024	
CCNE1 (Cyclin E1)	LO	CCNE1 amplified tumors				Development Candidate	
Discovery Targets	-	Multiple				Lead optimization	
Discovery Targets	-	Oncology and Neurological Diseases				Undisclosed	Roche

Oncology Immunology Inflammation Various

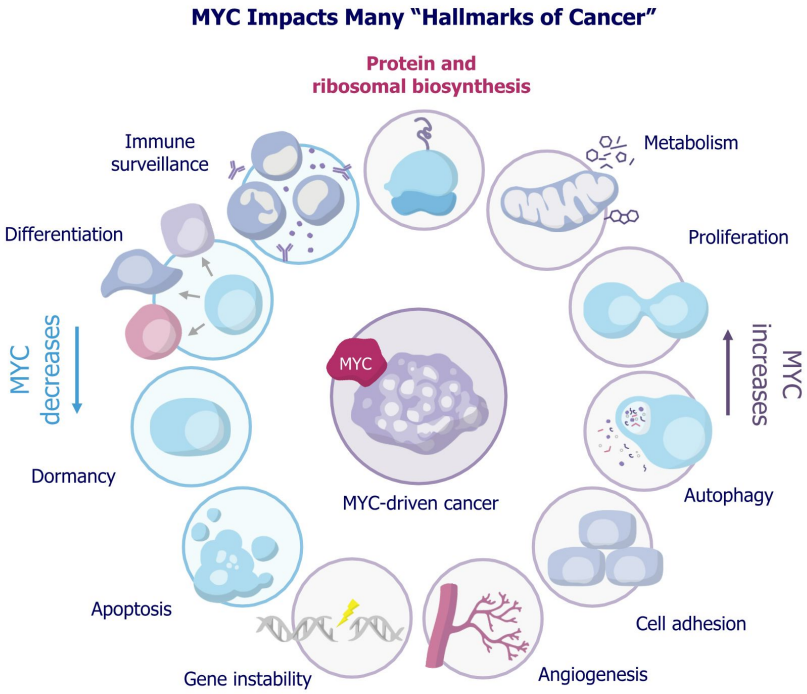
Monte Rosa Therapeutics

GSPT1 program (MRT-2359)

MYC is a Key Regulator of Cancer Growth and Immune Evasion

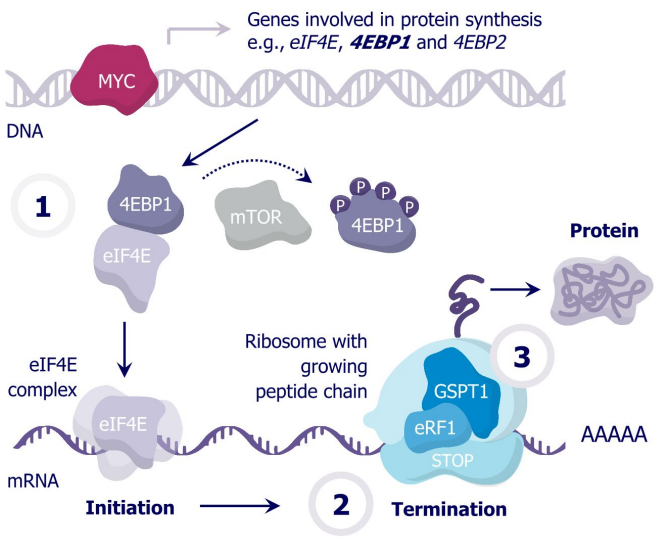
- Frequently activated across many cancers including some of the most common (e.g. lung, prostate, breast)
- Drives cancer progression through effects on both cancer cells and tumor microenvironment
- MYC signaling can enable tumor cells to evade immune response
- Very challenging to drug with conventional approaches; no approved MYC-targeted therapies

- MRT-2359 is designed to specifically target MYC-driven tumors



Source: Dhanesekaran R et al. Nat Rev Clin Oncol 2022

Targeting MYC-driven Tumors and Their Addiction to Protein Translation Through GSPT1 degradation



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

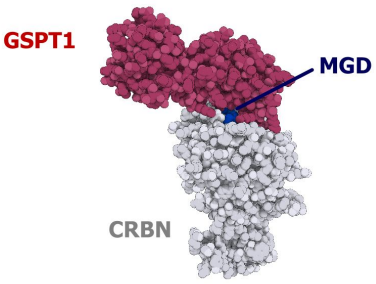
Therapeutic vulnerability

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

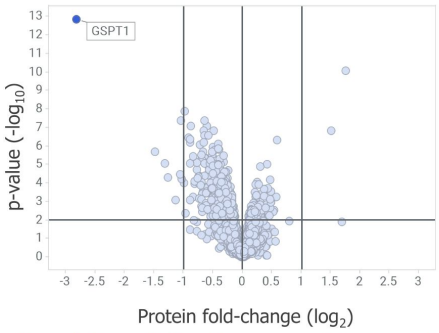
MRT-2359 is a potent GSPT1-directed MGD

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

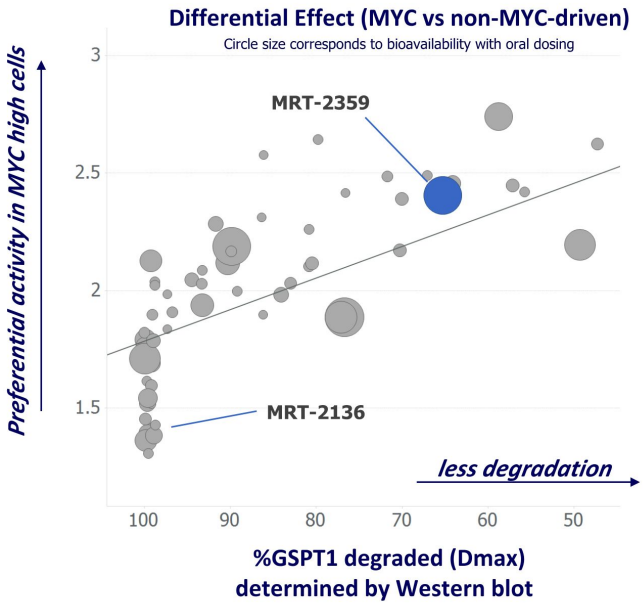
MRT-2359 induces selective GSPT1 degradation and shows favorable ADME/DMPK profile



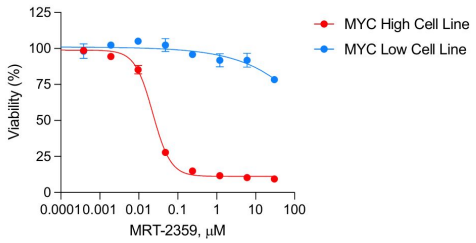
No degradation of other known cereblon neosubstrates

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

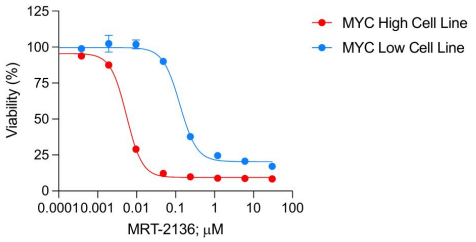
MRT-2359 Has Optimized Depth of Degradation To Achieve Preferential Activity in MYC High Cancer Cells



MRT-2359 displays preferential activity in MYC driven NSCLC cells



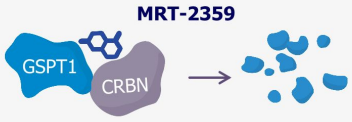
Non-optimal GSPT1 MGD (MRT-2136) shows limited preferential activity



Three Mechanisms Driving Preferential Activity in MYC High Tumor Cells

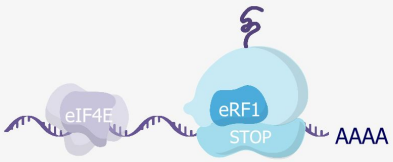
Preferential GSPT1 degradation

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

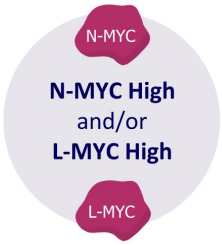


MYC down-modulation

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

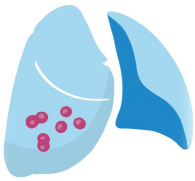


N-MYC High
and/or
L-MYC High

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

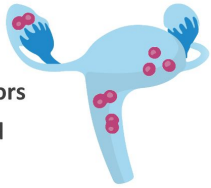
NSCLC
N-MYC high (5-10%)
SCLC/NE transformation

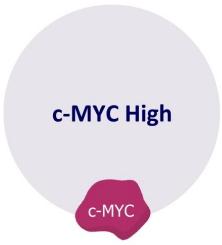
Neuroendocrine lung cancer



Neuroendocrine tumors

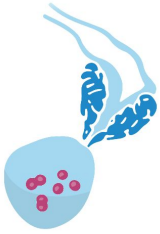
L-/N-MYC amplified tumors



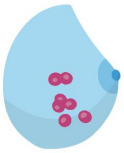


c-MYC High

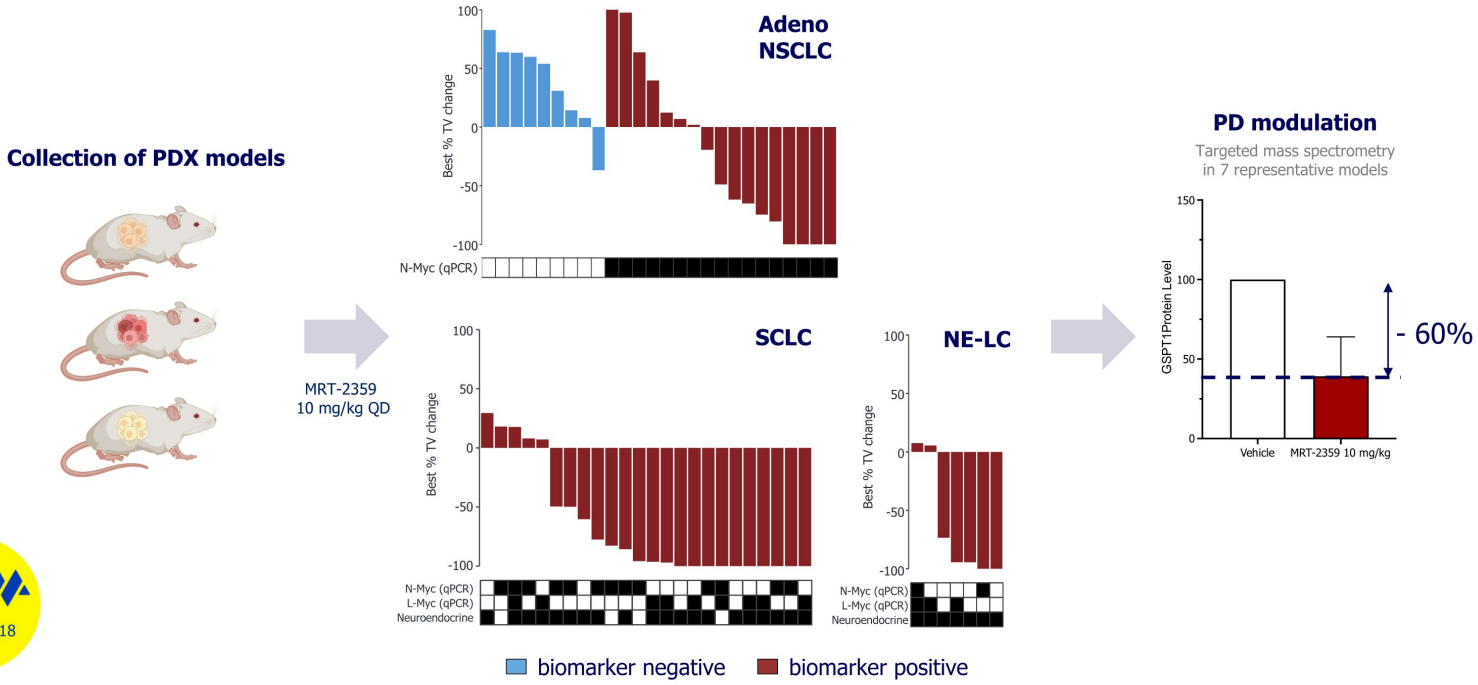
Prostate cancer
Including ARV7 positive



Breast cancer
ER positive metastatic

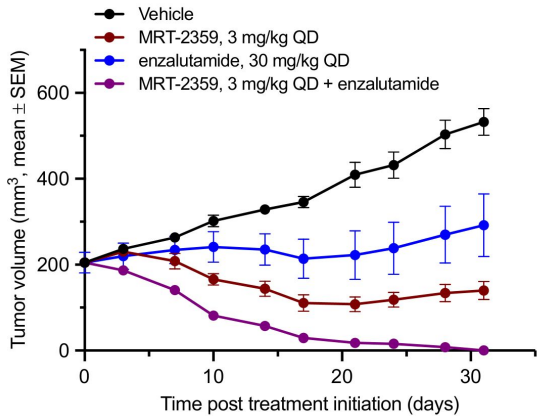


Preclinical Validation of Activity of MRT-2359 in Lung Cancer PDX Models

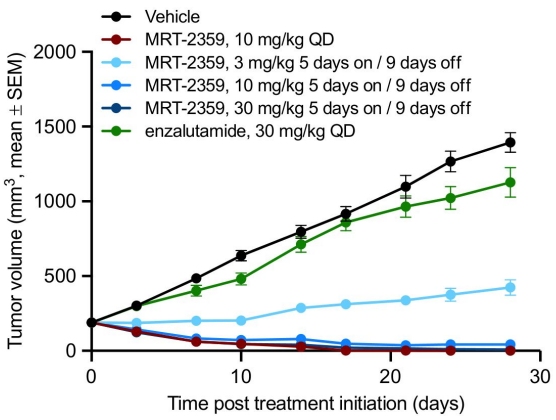


MRT-2359 Leads to Tumor Regressions in Preclinical Models of Castration Resistant Prostate Cancer and ARV7-driven Prostate Cancer

MRT-2359 displays activity in castrate resistant VCAP model

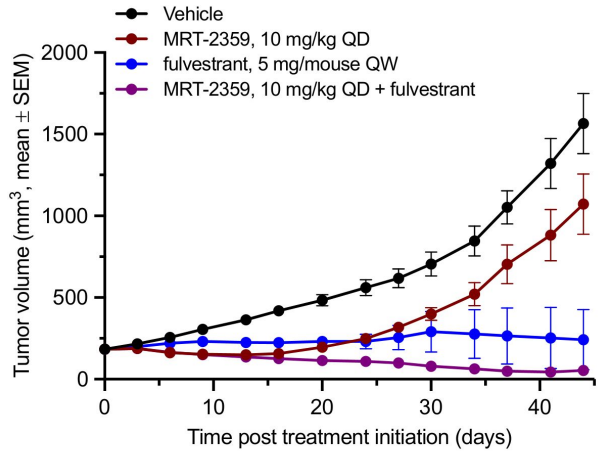


MRT-2359 displays activity in ARV7 driven 22RV1 model



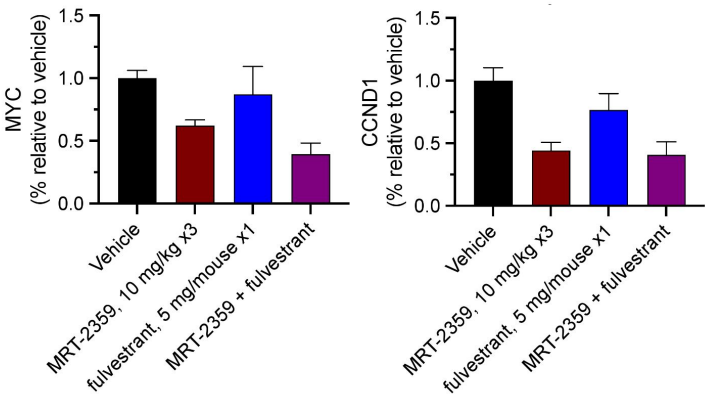
MRT-2359 Leads to Tumor Regressions in Preclinical Model of ER-positive Breast Cancer

MRT-2359 displays activity in MCF7 model of ER-positive breast cancer



MCF7 Breast CDX (ER+, HER2-)

MRT-2359 reduces MYC and CCND1 *in vivo*



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

Phase 1: Dose Escalation

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

RP2D (expected Q2 2024)

- 2mg 5/9
- 1.5mg 5/9
- 1mg 5/9
- 0.5mg 5/9
- DL 3 21/7
- DL2 21/7
- 0.5mg 21/7

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*
- SCLC**
- N-MYC/L-MYC amplified tumors
- HR+/Her2- Breast Cancer (+Fulv)
- Prostate cancer (+Enza)

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

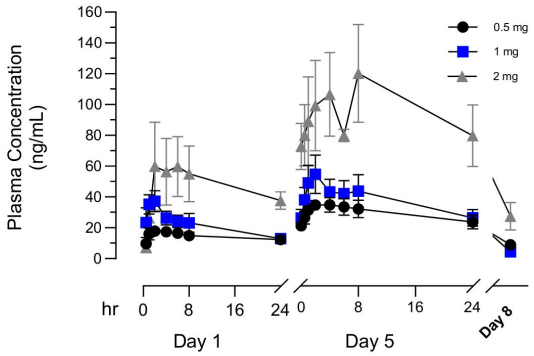
MRT-2359 Phase I Interim Data – October 2023

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

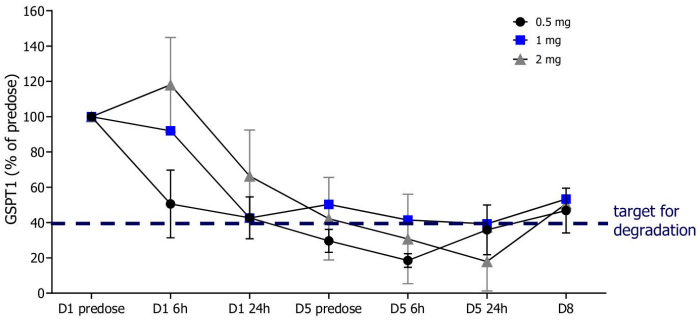
MRT-2359 Induces Optimal GSPT1 Degradation in PBMCs*

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

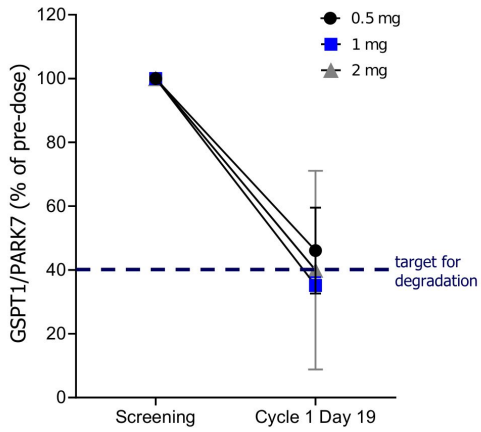


- GSPT1 expression assessed using targeted mass spectrometry
- PD modulation in PBMCs observed across all dose levels; level of degradation (~ 60%) in line with maximal degradation observed in preclinical studies using the same method
- Level of degradation equivalent across all dose levels, suggesting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

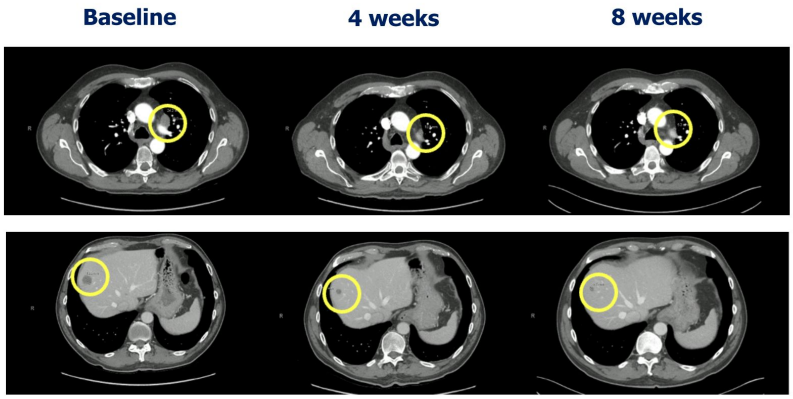
AE Preferred Term	0.5 mg (N=9)[##]		1 mg (N=7)[##]		2 mg (N=5) [##]		Overall (N=21)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Thrombocytopenia[###]	0	0	0	0	4 (80%)	3 (60%)[***]	4 (19%)	3 (14%)
Neutropenia[*]	0	0	0	0	2 (40%)	1 (20%)	2 (10%)	1 (5%)
Leukopenia	0	0	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*

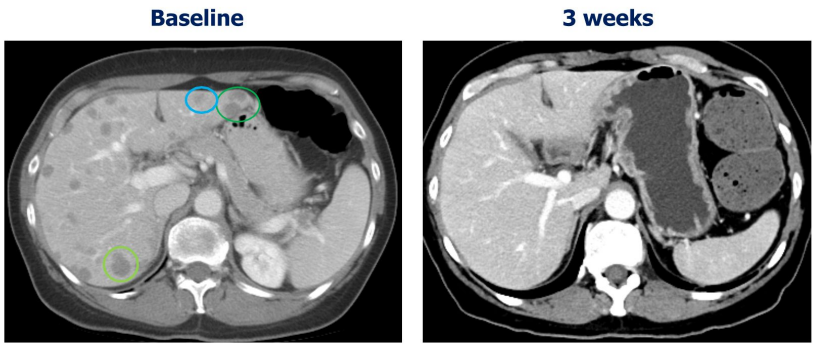
- High Grade (HG) neuroendocrine bladder cancer
- Baseline tumor biopsy demonstrated high N-MYC expression
- 4 prior lines of therapy including chemotherapy and pembrolizumab
- Patient initiated on 2 mg for first 5/9 regimen, then lowered to 1 mg and 0.5 mg and remains on therapy (> 3 month)
- CT scan 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*

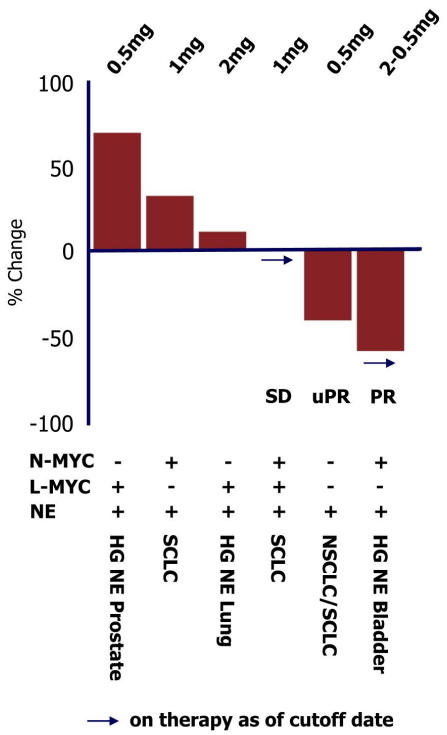
- NSCLC (adenocarcinoma)
- Baseline tumor biopsy demonstrated SCLC/NE transformation, low N- and L-MYC expression
- Multiple lines of prior therapy including chemotherapy, pembrolizumab and atezolizumab
- Patient initiated on 0.5 mg
- CT on C1D22 demonstrated resolution of liver metastases (-41% per 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



* as presented on 10/17/23

Favorable Safety Profile 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

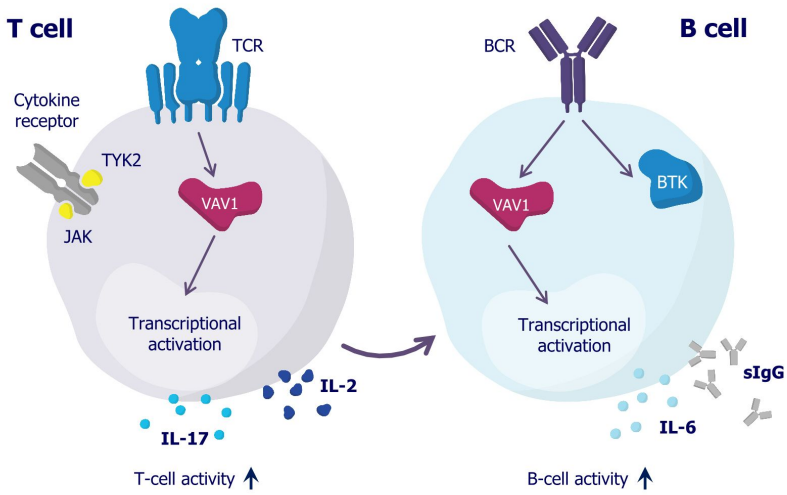
* as presented on 10/17/23

Monte Rosa Therapeutics

VAV1 Program (MRT-6160)

VAV1 is a Key Regulator of T- and B-cell Receptor Activity

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 knockout (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:

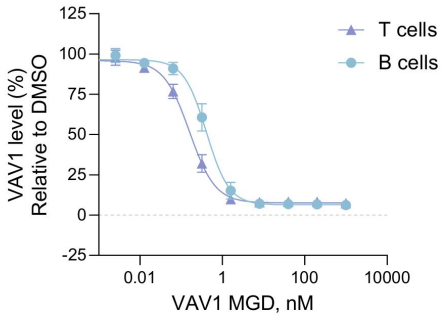
Autoimmune/inflammatory disorders including inflammatory bowel disease (4.1M patients), rheumatoid arthritis (6.2M patients), multiple sclerosis (1.3M patients), and myasthenia gravis (~300K patients)

TCR = T-cell receptor. BCR = B-cell receptor. IL-2, IL-17 and IL-6 are cell signaling molecules (cytokines) that promote immune response. sIgG is the most common circulating antibody.

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

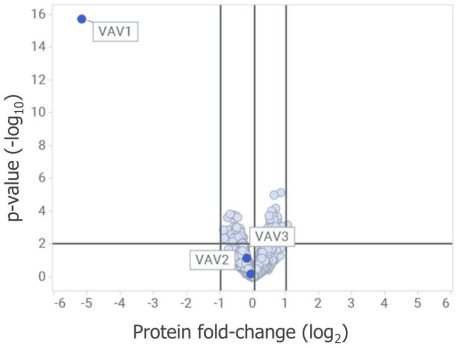
MRT-6160 is a Potent and Highly Selective VAV1-directed MGD

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

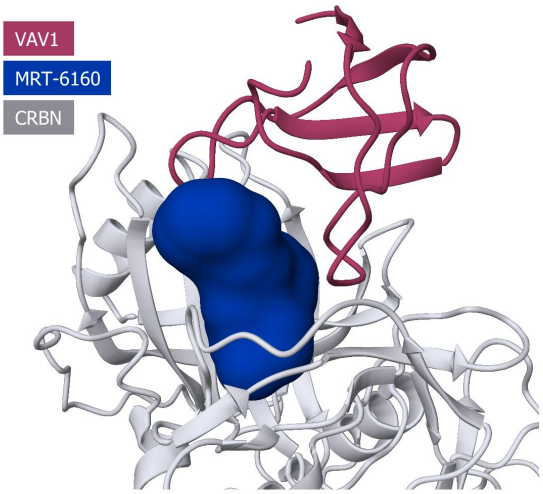


No degradation of other known cereblon neosubstrates

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

MRT-6160 is a Potent, Highly 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

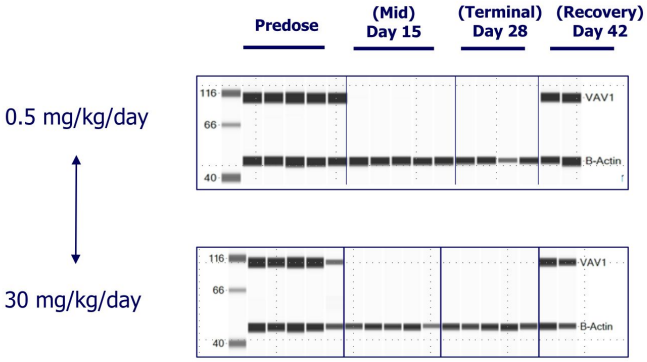
MGD Activity Profile	
CRBN Binding (HTRF, IC_{50})	0.67 µM
VAV1 Ternary Complex (HTRF, EC_{50})	11 nM
VAV1 Degradation (Jurkat, DC_{50} /Dmax)	7 nM / 97%
Selectivity (TMT proteomics)	Large VAV1 selectivity window
Physicochemical Properties	
LogD	1.5
MW	<400
Thermodynamic Solubility	7 µM
ADMET Profile	
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)
Counterscreens (panel with 98 targets)	No inhibition

28-day GLP Toxicology Studies Establish Highly Favorable Safety Margins

28-day GLP Toxicology Summary

- 28-day GLP Rat and Cyno studies completed with NOAEL set at the highest doses in both species
  - Rats: NOAEL is ~1000-fold over the projected human efficacious exposure
  - Cyno: NOAEL is ~600-fold over the projected human efficacious exposure
- No adverse immunotoxicity or impact on peripheral immune compartments in healthy cynomolgus monkeys
- No impact on bone marrow, peripheral hematopoietic cells counts, GI tract
- No off-targets identified in *in-vitro* safety profiling, no genotoxicity, phototoxicity, or hERG activity

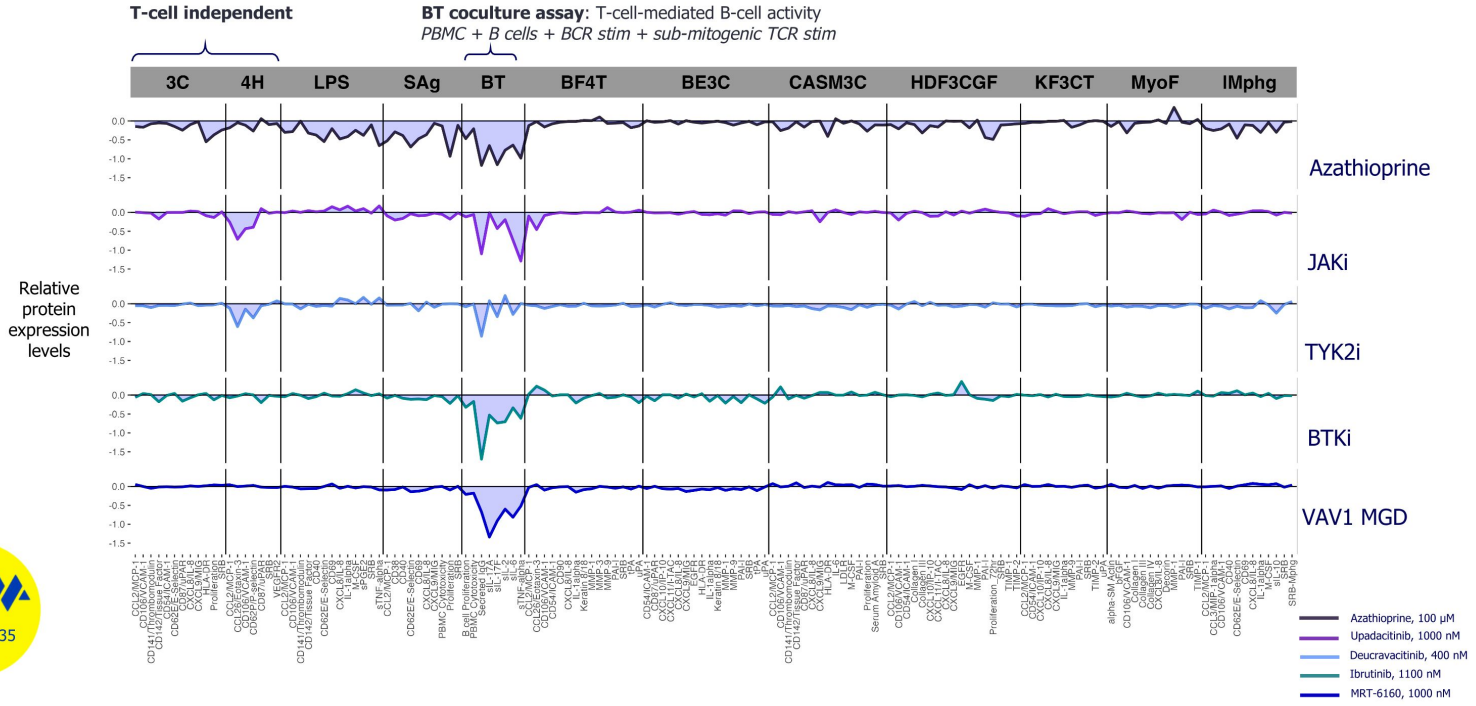
Robust VAV1 degradation and recovery observed in both low and high dose groups in cyno GLP tox study



**data shown from female cyno PBMCs, similar data obtained in males*

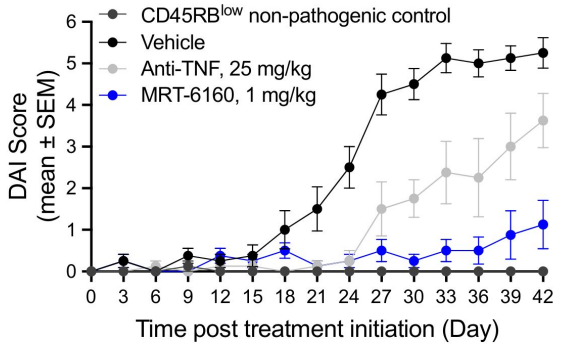
NOAEL = no observed adverse effect level

MRT-6160's Activity Profile in Immune Cell Assays (BioMAP) Supports a Role for VAV1 MGDs in Blocking T Cell-Mediated B Cell Activation

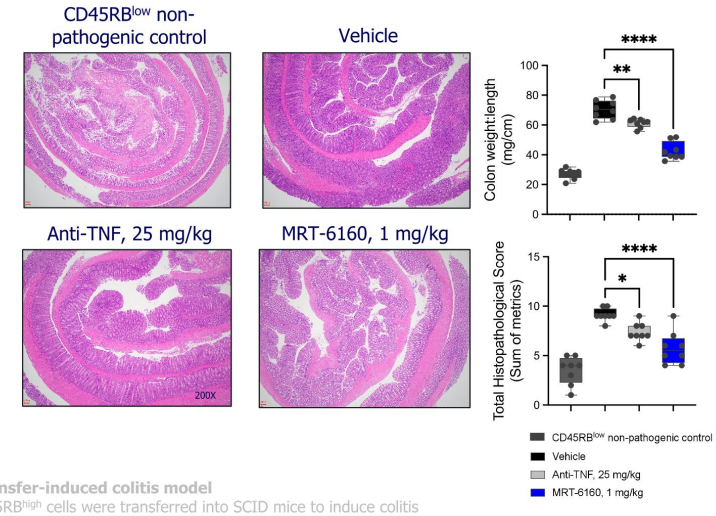


MRT-6160 Inhibits Disease Progression and Pro-Inflammatory Cytokine Production in the Colon in a Model of Inflammatory Bowel Disease

MRT-6160 inhibits disease progression in a model of colitis



MRT-6160 reduces swelling and tissue damage in the colon and reduces pro-inflammatory cytokine production



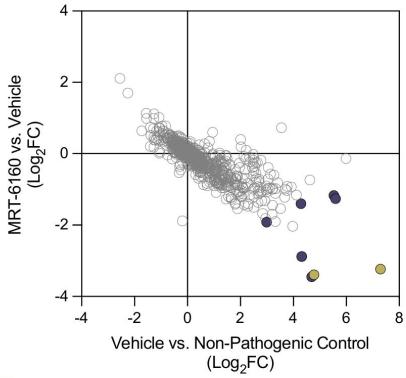
CD4+ T cell transfer-induced colitis model

Non-pathogenic CD45RB^{low} or pathogenic CD45RB^{high} cells were transferred into SCID mice to induce colitis

Mice were treated with vehicle or MRT-6160 (PO QD) or anti-TNF (IP Q3D) from Day 0 to Day 42 and assessed for disease every 3 days

MRT-6160 Reduces Expression of Pro-Inflammatory and Disease-Associated Genes in a Model of Inflammatory Bowel Disease

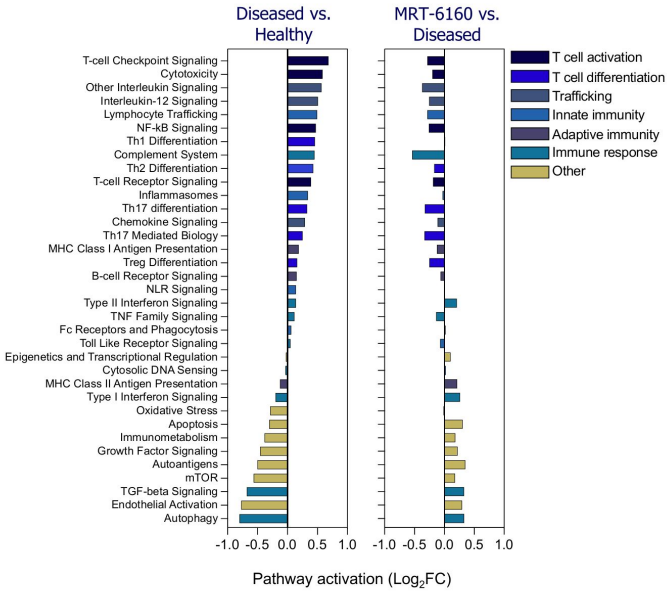
MRT-6160 reduces expression of colitis-associated genes and calprotectin subunits



Gene	Function
Clec4e	Augments IL-6, TNF, and IL-1β production
Mmp3	Degrades collagen and biologically activates IL-1β
Il1b	Induces Th17 differentiation
Cxcl10	Induces chemotaxis of monocytes and CD4+ T cells
Cxcl9	TNF-induced chemotaxis of monocytes and T cells
Ccl5	Induces MMP expression and leukocyte chemotaxis
S100a9	Calprotectin subunit
S100a8	Calprotectin subunit

NanoString analysis of colon transcripts
At study termination, RNA was extracted from colon tissues and assessed using the nCounter Mouse Autoimmune Profiling Panel

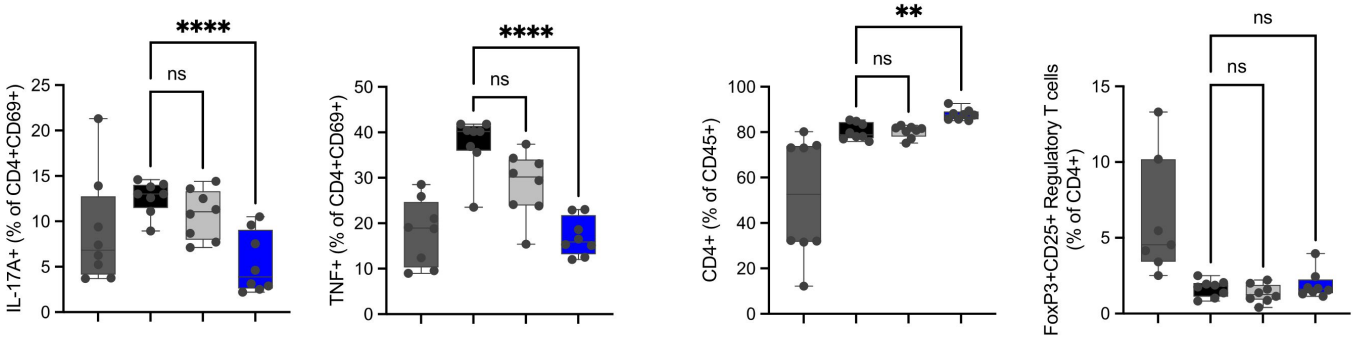
MRT-6160 attenuates expression of a pro-inflammatory disease gene signature



MRT-6160 Reduces Activation and Priming of Pathogenic CD4+ T cells in a Model of Inflammatory Bowel Disease

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

MRT-6160 does not reduce CD4+ T cell frequency or regulatory T cell frequency

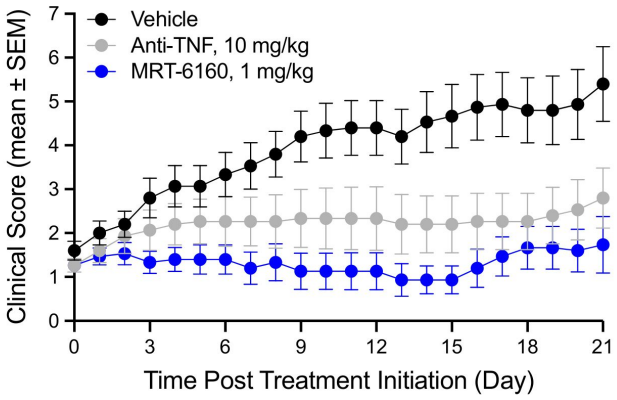


Flow cytometric immuno-profiling of mesenteric lymph node

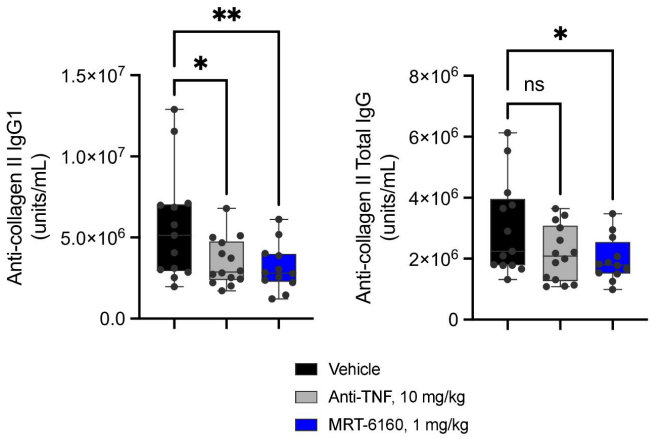
At the end of the CD4+ T cell transfer-induced colitis model, mesenteric lymph nodes were excised, and single cell suspensions were stimulated with PMA/ionomycin + protein transport inhibitors for 6 hours After stimulation, cells were stained with surface and intracellular markers and assessed by flow cytometry

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

MRT-6160 inhibits disease progression



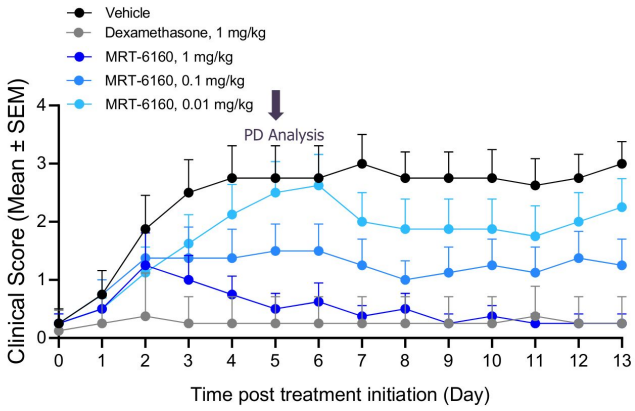
MRT-6160 inhibits anti-collagen II auto-antibodies



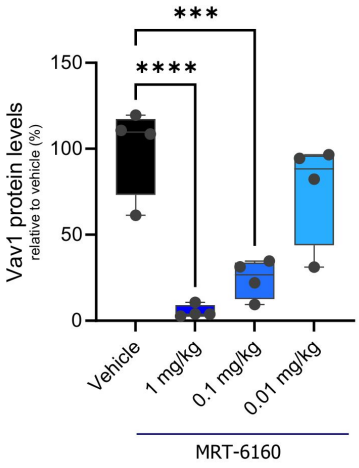
Collagen-induced arthritis T/B-cell (auto-antibody) driven model

MRT-6160 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



MRT-6160-mediated activity correlates with VAV1 levels



T-cell mediated experimental autoimmune encephalitis (EAE) model

Phase 1 Biomarker Strategy to Demonstrate MRT-6160 Pharmacodynamic Effects

Phase 1 SAD/MAD in Healthy Volunteers

Provide early insights into safety, PK/PD, and effects on key immunomodulatory signaling pathways

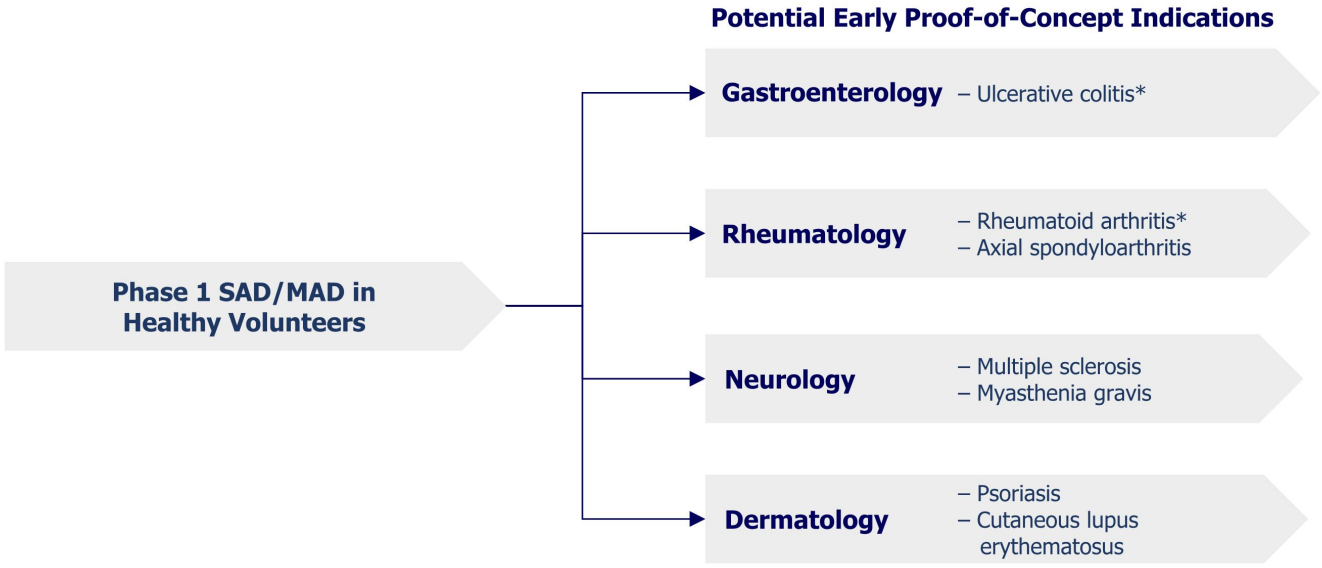
VAV1 protein degradation
- Flow cytometry on T and B cells: whole blood (WB)
- Targeted Mass Spec: PBMCs
- Potential: Mature B cell typing in MAD

Key downstream PD
- Flow cytometry for CD69 protein on T & B cells: WB
- Immunoassay for IL-2, IL-6, BAFF, CCL3/4
- hs C-reactive protein

Phase 1 SAD/MAD study expected to initiate mid-2024, clinical data anticipated Q1 2025

Preliminary MRT-6160 Development Plan through Early POC

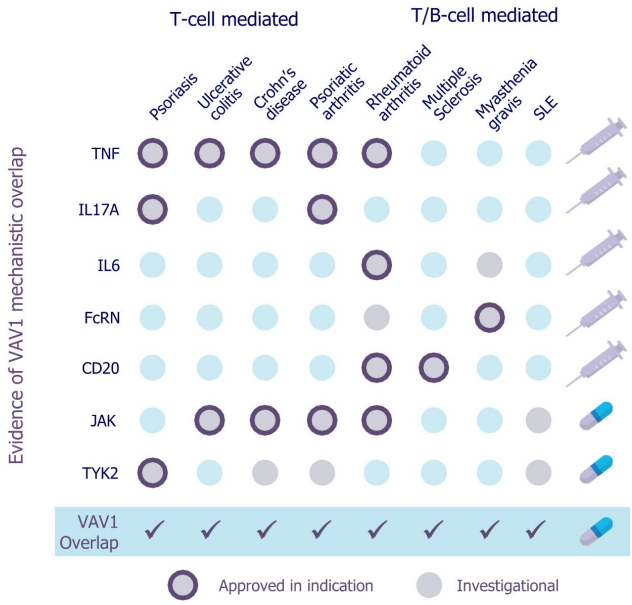
Potential in multiple I&I indications with T cell and T/B cell-mediated pathophysiology

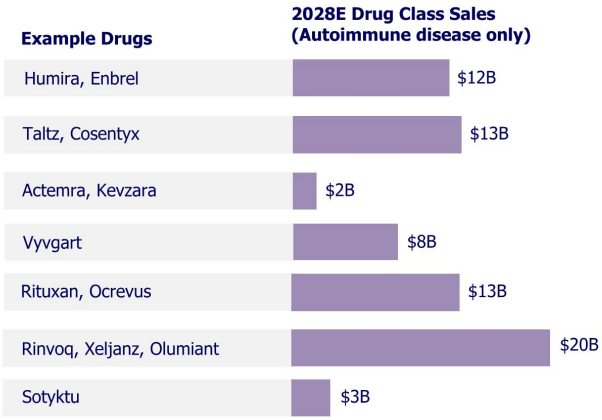


* Priority POC indications

VAV1: Unique Mechanism with Broad Potential Applications

Potential to address multiple autoimmune diseases with safe, oral therapy



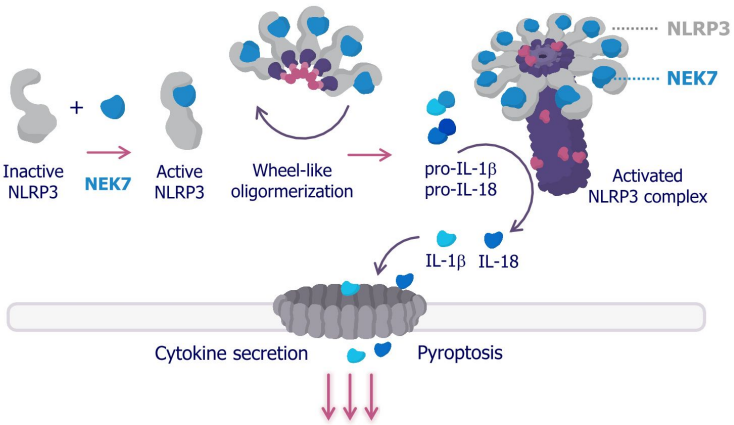


Note: Chart adapted from Hosack et al., Nat Rev Immunol 2023. Drug class sales from Evaluate Pharma. 2028E sales may include sales from anticipated future approvals.

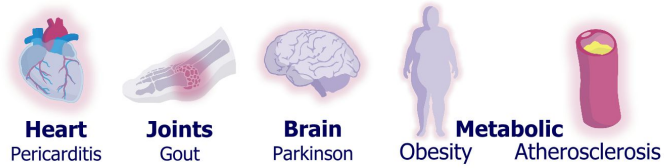
Monte Rosa Therapeutics

NEK7 Program (MRT-8102)

NEK7 is a Key Regulator of NLRP3 Inflammasomes and IL-1β and IL-18



Inflammation-driven diseases (selected examples)



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

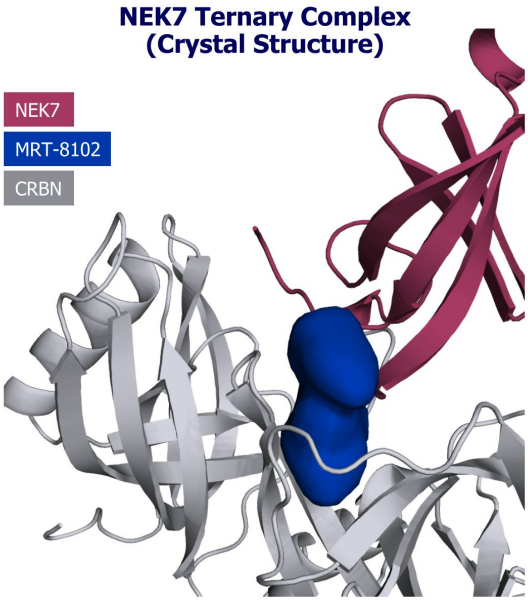
Consequently, NEK7 degradation has the potential to become an important treatment modality for a variety of inflammatory diseases

Clinical Opportunity:

Diseases driven by IL-1β and the NLRP3 inflammasome including gout, cardiovascular disease, neurologic disorders including Parkinson's disease and Alzheimer's disease, ocular disease, diabetes, obesity, and liver disease

MRT-8102 is a Potent, Selective NEK7-Directed MGD With a Favorable Drug-like Profile

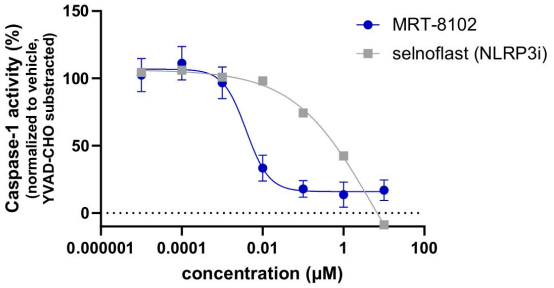
NEK7 Ternary Complex (Crystal Structure)



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)
Counterscreens (panel with 44 proteins)	No inhibition

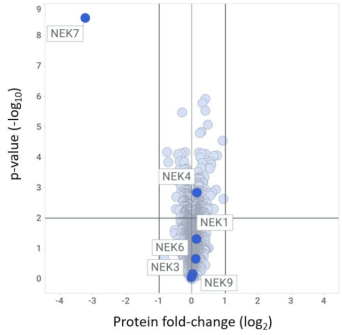
MRT-8102 is a Potent and Highly Selective NEK7-directed MGD

MRT-8102 potently suppresses inflammasome activation in primary human macrophages



in vitro data	
CRBN binding, IC_{50}	200 nM
Degradation, DC_{50} /D_{max} (CAL51)	10 nM / 89 %

MRT-8102 induces highly selective NEK7 degradation

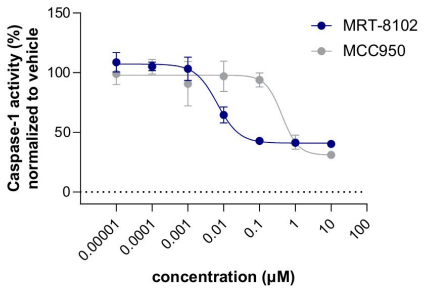


No degradation of other known cereblon neosubstrates

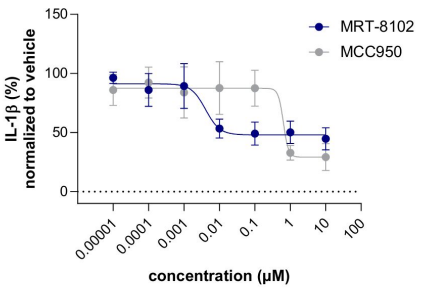
ADMET profile	
hERG	No inhibition
Oral bioavailability	Yes

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

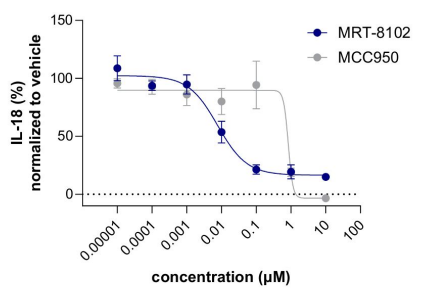
MRT-8102 inhibits caspase-1 activity in hMDMs after stimulation



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

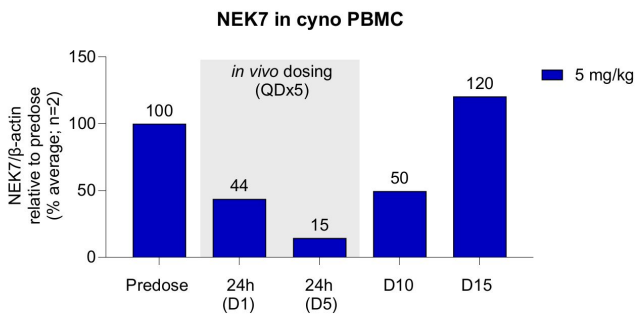


MRT-8102 inhibits IL-18 secretion by hMDMs after stimulation



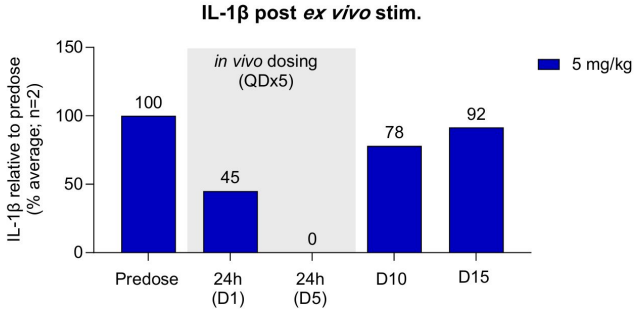
Suppression of *Ex Vivo* Inflammasome Activation Following Degradation of NEK7 After Single and Multi-dose Study in Non-human Primates

MRT-8102 induces degradation of NEK7 *in vivo* over several days



No clinical observations reported

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

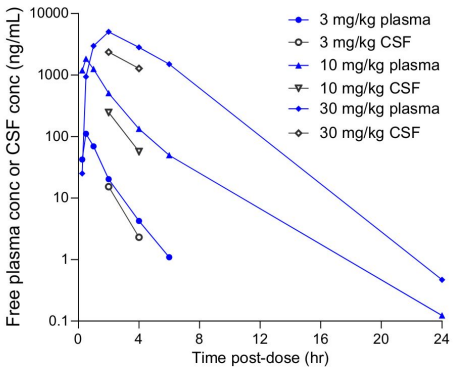


- IL-1β in plasma after *ex vivo* stimulation with LPS + nigericin
- Similar results for Caspase-1 activity from same study
- Follow-up study with 1 mg/kg MRT-8102, *i.v.* at 4 hr showed similar results

MRT-8102 Displays Significant Blood Brain Barrier Penetration

MRT-8102 displays CNS-penetrance

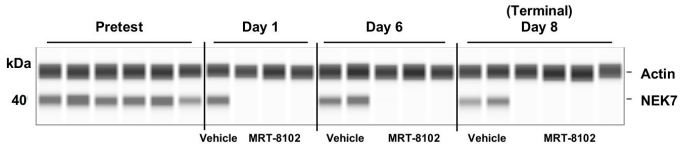
Single dose p.o.



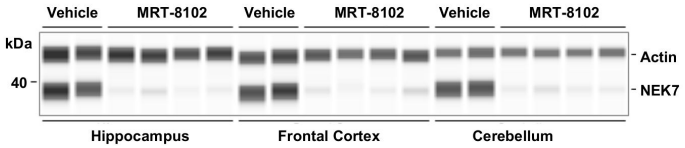
single-dose MRT-8102 p.o.
n=2 cynomolgus monkey (one male and one female)

Significant NEK7 degradation in various brain regions 24h post treatment

PBMCs



Brain



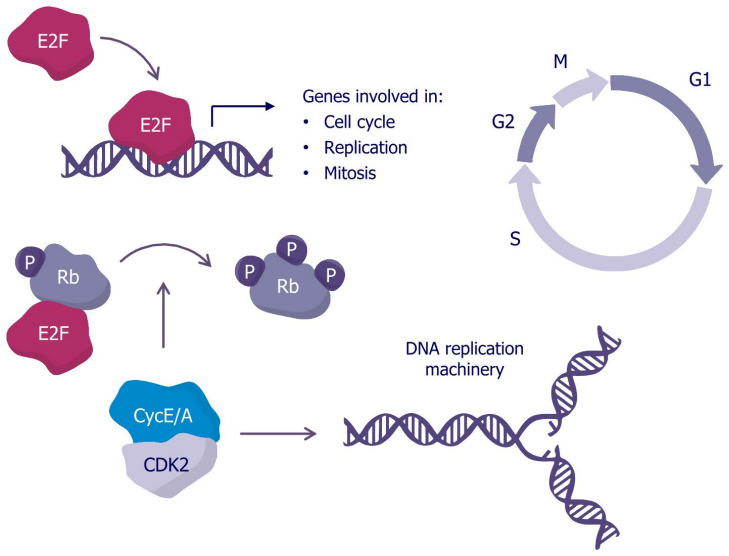
Daily dose of 30 mg/kg MRT-8102 for 7 days
Analysis on day 8 (24 hr post-final dose) by JESS Simple Western

Monte Rosa Therapeutics

CDK2 Program

CDK2 is a Key Driver of Cell Cycle Progression in Cancer

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

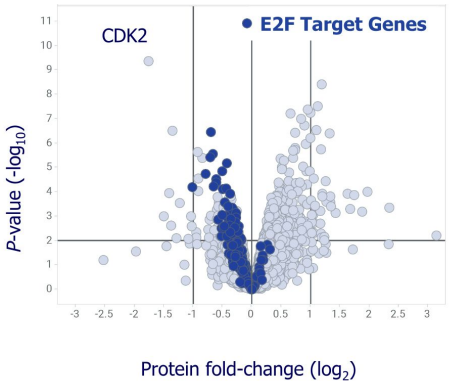
Clinical Opportunity:

- 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)

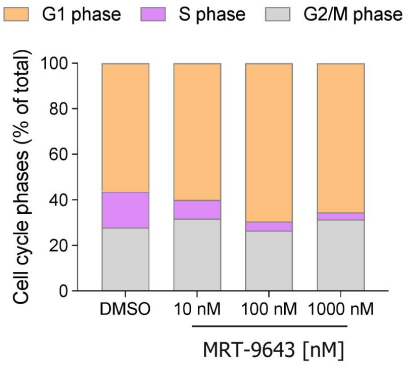
Orally Bioavailable MGD MRT-9643 is Selective and Shows Biological Activity in a CDK2 Dependent Cell Line

Selective CDK2 degradation reduces E2F pathway genes



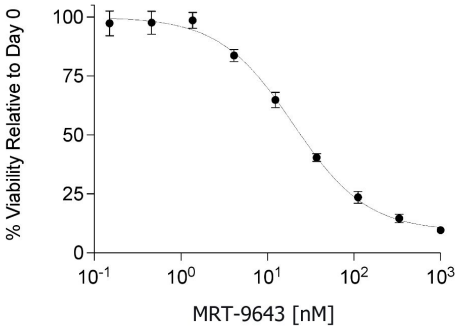
TMT Proteomics (24 hr/1 µM)
MDA-MB-157

CDK2 degradation arrest CDK2-dependent cells in G1 phase



Cell cycle profile (24 hr)
MDA-MB-157

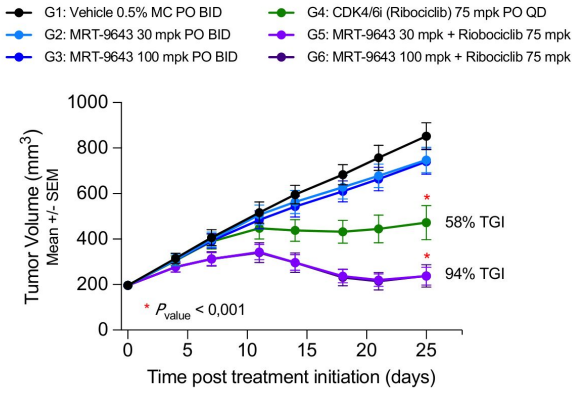
CDK2-directed MGD inhibits proliferation of CDK2 dependent cells



CyQuant Assay (7 d)
MDA-MB-157

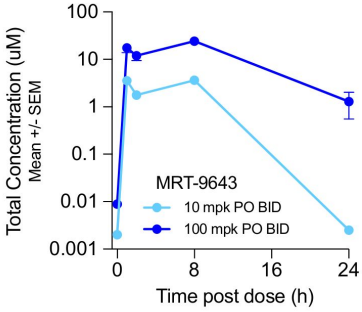
Orally Bioavailable MGD MRT-9643 Demonstrates Activity as Single Agent and in Combination with CDK4/6i in ER+ Breast Cancer

MRT-9643 induces strong TGI in combination with a CDK4/6i *in vivo*

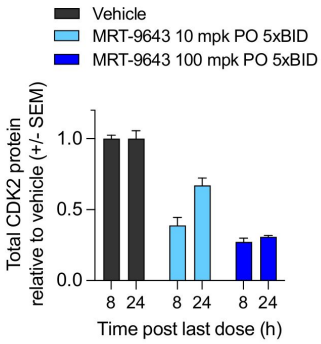


Efficacy evaluation, 25-day treatment
MCF7 ER+ BC CDX Model

MRT-9643 is orally bioavailable and degrades CDK2 *in vivo*



Plasma PK exposure
MCF7 ER+ BC CDX



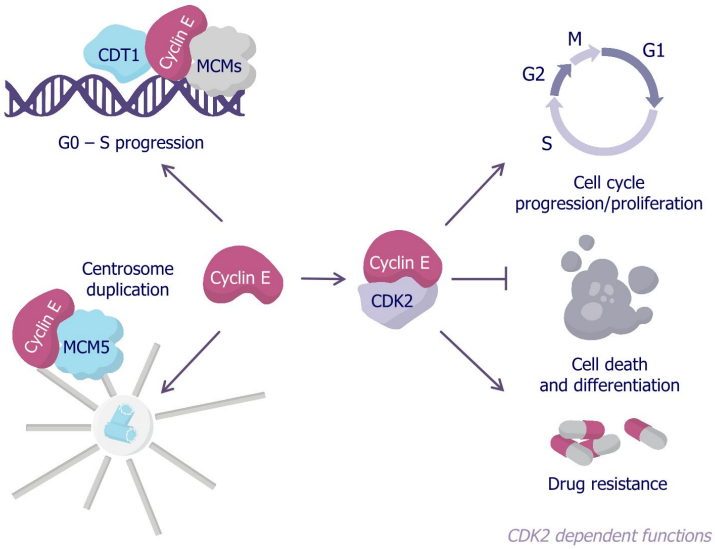
Oral PK/PD study
HCC1159 BC CDX

Monte Rosa Therapeutics

CCNE1 Program

CCNE1 (Cyclin E1) is a Target for Solid Tumors with Deregulated Cyclin E1

Cyclin E drives multiple hallmark cancer mechanisms



CDK2 dependent functions

Therapeutic hypothesis:

CCNE1 (Cyclin E1) is a well-recognized human oncogene that drives multiple hallmarks of cancer, and has been considered undruggable

Selective degradation of cyclin E1 can target tumors with deregulated cyclin E1 (amplification or overexpression)

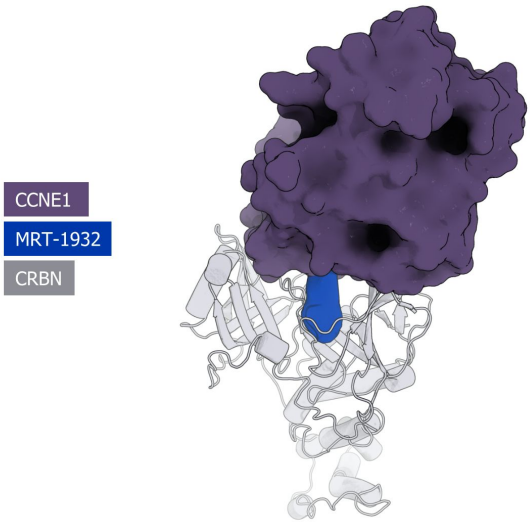
Clinical opportunity:

First-in-class Cyclin E1 degraders for Cyclin E1 amplified cancers

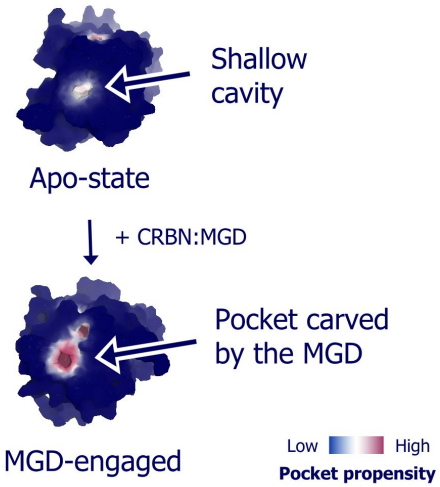
- Ovarian (19%) and endometrial (6%)
- Breast cancer and others

CCNE1-directed MGDs Engage a Cryptic Pocket at the Target Interface

CCNE1 binds CRBN through a novel binding mode

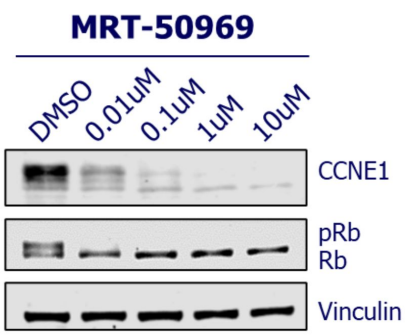


MGD induces a cryptic pocket on the CCNE1 surface



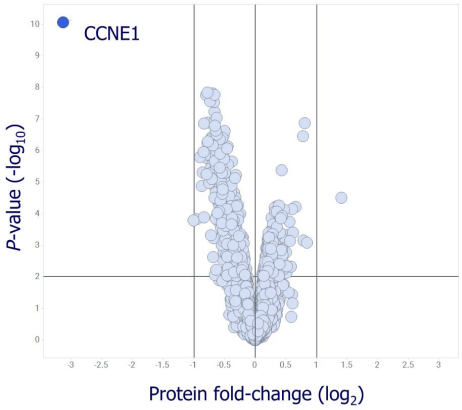
MRT-50969 is a Potent and Highly Selective CCNE1-directed MGD

CCNE1 degradation leads to downstream pathway suppression



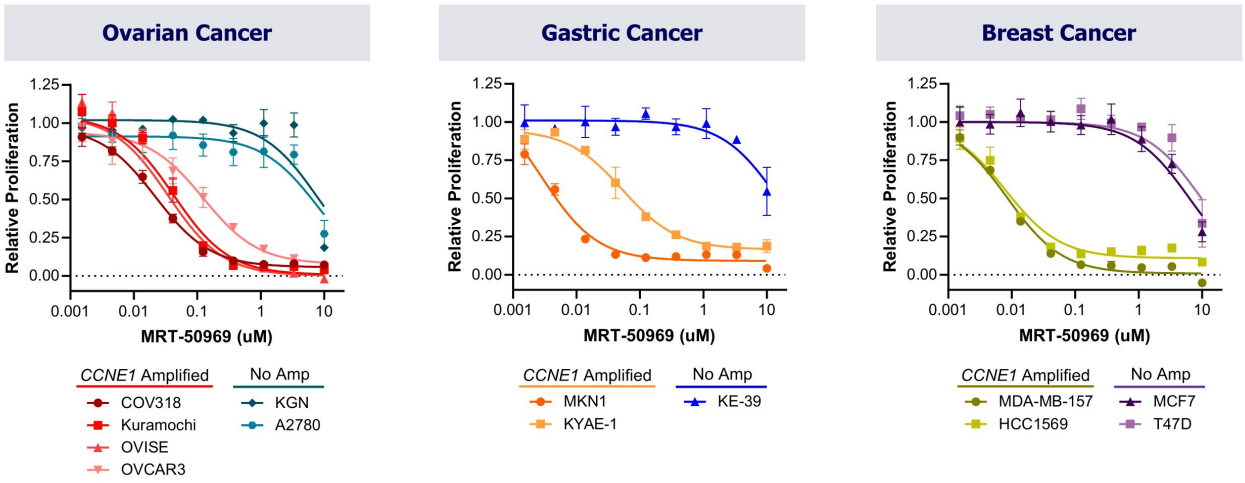
Western blot, OVISE, 24h

MRT-50969 is highly selective for CCNE1



TMT Proteomics, MDA-MB-157 Rb K/O
1µM MRT-50969, 24h

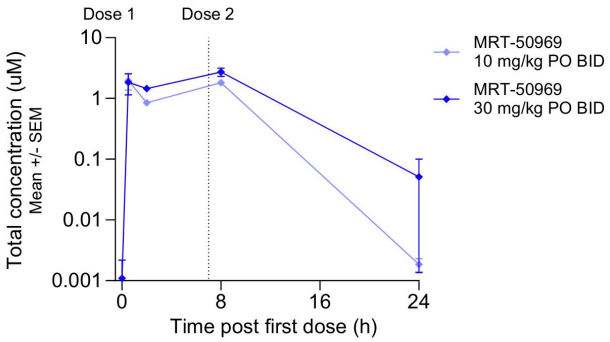
MRT-50969 Exhibits Preferential Growth Suppression in *CCNE1* Amplified Cell Lines of Multiple Lineages



CyQuant, 5 days

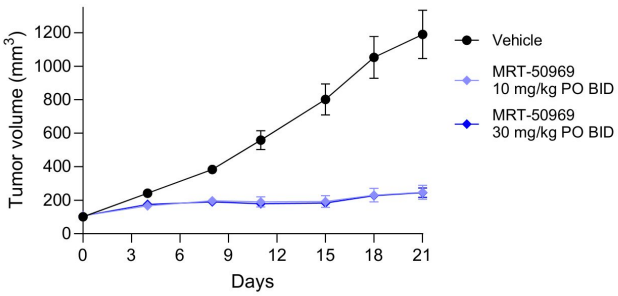
MRT-50969 is Orally Bioavailable and Inhibits MKN1 Tumor Growth *In Vivo*

MRT-50969 achieves oral exposure



Mouse plasma PK after initial day 1 dosing

MRT-50969 inhibits *in vivo* tumor growth in *CCNE1* amplified CDX model MKN1

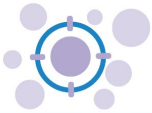


21-day efficacy study in MKN1 CDX model

Monte Rosa Therapeutics

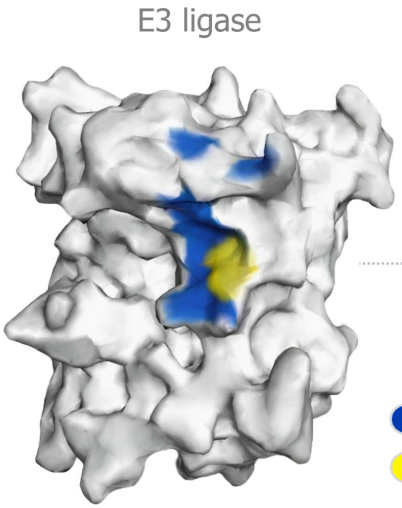
QuEEN™ Discovery Engine

Overcoming Past Limitations of Molecular Glue Degraders

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
'MGDs are not selective'		AI-driven and structure-based design enable rational Med Chem optimization of MGDs
'Med Chem rules don't apply to MGDs'		High selectivity achievable even within the same protein class, family and isoforms

Our Critical Insight: Surfaces are Critical for MGD Discovery

Surfaces, not structures, mediate PPIs and targeted protein degradation



E3 ligase neosurface

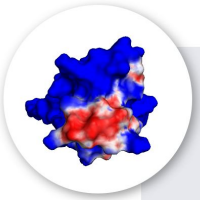
Neosubstrate footprint

MGD footprint

- Rationally-designed MGDs create diverse E3 ligase neosurfaces, enabling recruitment of new targets
- Our geometric deep learning algorithms use surfaces to **predict** targets.
- Our surface-based algorithms **design** MGDs to recruit targets.
- Our platforms generate **actionable data-at-scale** to test & train ("data moat")

QuEEN™ Unique Capabilities

Breakthroughs enabling rapid discovery of potent, selective, and oral MGDs



AI/ML

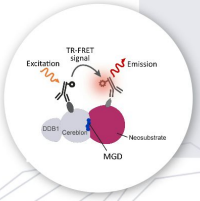
In silico discovery using proprietary AI-powered algorithms

Structure-based Design

Proprietary database of protein structures to enable rapid optimization of MGD chemistry

Proximity Screening

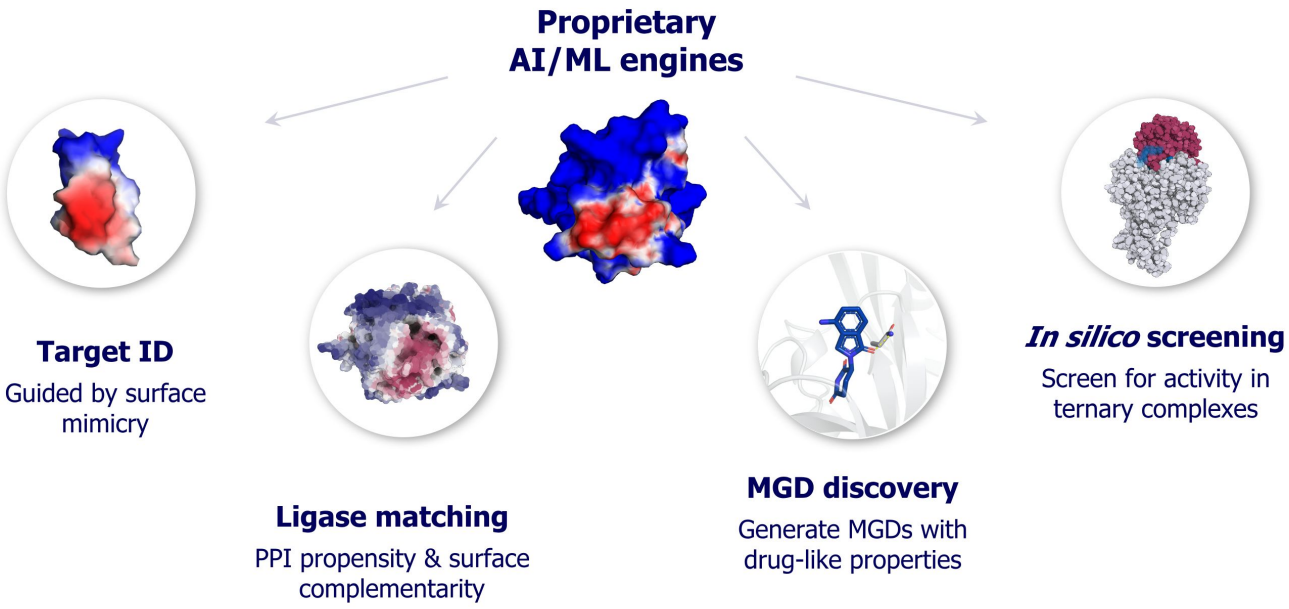
Specialized suite of biochemical, cellular and proteomics assays to assess proximity and degradation in high throughput



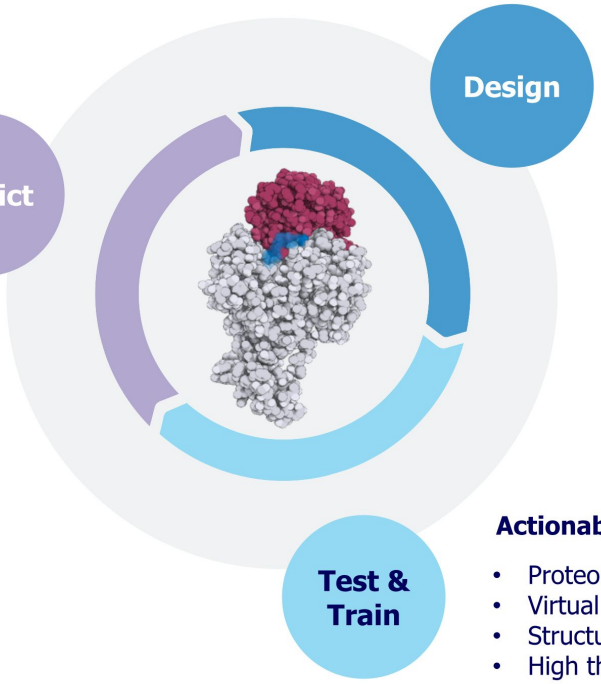
Proteomics

Integrated proteomics engine and database to identify novel targets and explore cellular complex formation and protein degradation

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



QuEEN™: How it Works



Target and ligase ID

- Surface-centric discovery process

AI-powered chemistry

- Surface-aware MGD generation & optimization

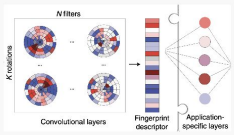
Actionable data-at-scale

- Proteomics
- Virtual screens
- Structural biology
- High throughput screens

Queen™ Toolbox to Rapid Discovery of Oral MGDs

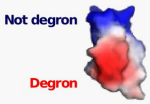
Predict
Target & ligase ID

fAIceit™ Ultra-fast fingerprint search for surface-based matchmaking



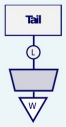
E3 ligase reprogrammability

fAIceit mimicry target ID

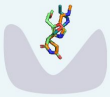


Design
AI-powered chemistry

FLASH™ virtual library

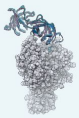


HitMan™ diverse library



GlueAID™ ADMET & synthesis

Rhapsody™ ternary complexes

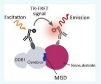


Test & Train
Actionable data-at-scale

Headlong™ virtual screens

Proteomics mass-spec farm

HT library screening



Structural biology X-ray & cryo-EM

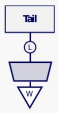
Algorithms Use MGD-focused, Moated Data to Identify Targets and Design MGDs

in silico experimentation

fAIceit mimicry
target ID

250
BILLION
Protein surface matchings

FLASH™
virtual library



37
BILLION
Virtual MGDs

Headlong™
virtual screens

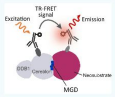
651
MILLION
Compounds screened

Lab experimentation

Proteomics
mass-spec farm

34
MILLION
protein measurements

HT library screening



6
MILLION
MGD activity measurements

Structural biology
X-ray & cryo-EM

>100
Structures

Cloud First and Cloud Native

Scalable Data Lake with purpose-built data services for seamless data movement and unified governance

Monte Rosa Therapeutics

Team

World-Class Leadership

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

Markus Warmuth, M.D.
Chief Executive Officer

H3 BIOMEDICINE
NOVARTIS

Sharon Townson, Ph.D.
Chief Technology Officer

KYMERA
Warp Drive Bio

John Castle, Ph.D.
Chief Data Scientist & Information Officer

agenus
BIONTECH

Magnus Walter, Ph.D.
SVP, Chemical Sciences and Process Development

abbvie
Lilly

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

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Phil Nickson, Ph.D., J.D.
General Counsel

Momenta
FISH & RICHARDSON

Jennifer Champoux
Chief People & Operations Officer

H3 BIOMEDICINE
NOVARTIS

Andrew Funderburk
SVP, Investor Relations and Strategic Finance

Kendall Investor Relations
Health Advances


Thank You
Monte Rosa
Therapeutics