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): October 16, 2023

MONTE ROSA THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

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

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 1.01 Entry into a Material Definitive Agreement.

On October 16, 2023, Monte Rosa Therapeutics AG ("Monte Rosa AG," hereinafter the "Company"), a wholly-owned subsidiary of Monte Rosa Therapeutics, Inc., F. Hoffmann-La Roche Ltd ("Roche Basel") and Hoffmann-La Roche Inc. ("Roche US" and together with Roche Basel, "Roche") entered into a Collaboration and License Agreement (the "Agreement"). Pursuant to the Agreement, the parties will seek to identify and develop molecular glue degraders ("MGDs") against cancer or neurological disease targets using the Company's proprietary drug discovery platform for an initial set of targets in oncology and neuroscience selected by Roche, with Roche having an option to expand the collaboration with an additional set of targets under certain conditions, each target being subject to certain substitution rights owned by Roche. The Company will lead pre-clinical discovery and research activities until a defined point. Upon such point, Roche gains the right to exclusively pursue further pre-clinical and clinical development activities.

Under the Agreement, Roche will have a worldwide, exclusive license under patents and know-how controlled by the Company to develop and commercialize products directed to applicable targets. The research collaboration activities governed by the Agreement will be overseen by a joint research committee.

Pursuant to the Agreement, the Company is entitled to receive from Roche: (1) for the initial multiple targets an upfront payment of $50 million, and potential pre-clinical, clinical, commercial, and sales milestones exceeding $2 billion, including up to $172 million for achieving pre-clinical milestones, and (2) for the optional additional targets, an upfront payment of up to $28 million, and potential pre-clinical, clinical, commercial, and sales milestones exceeding $1 billion. The Company is also eligible to receive tiered royalties ranging from high-single-digits to low- teens on any products that are commercialized by Roche as a result of the collaboration.

Unless earlier terminated, the Agreement will remain in effect for each product licensed under the Agreement until expiration of the royalty term for the applicable product. The parties have included customary termination provisions in the agreement, allowing termination of the Agreement in its entirety, on a country-by-country or a target-by-target basis.

Item 7.01 Regulation FD Disclosure.

On October 17, 2023, the Company issued a press release announcing its entry into the Agreement. A copy of the press release is furnished hereto as Exhibit 99.1.

In addition, on October 17, 2023, the Company issued a press release announcing interim PK/PD and clinical data for MRT-2359 in the Phase 1/2 trial for MYC-driven solid tumors and issued a related presentation that it intends to utilize in various meetings with security analysts, investors and others. The press release and presentation are furnished as Exhibits 99.2 and 99.3, respectively, to this Current Report on Form 8-K.

Additionally, on October 17, 2023, the Company issued a corporate presentation that it intends to utilize on a conference call with securities analysts, investors and others. A copy of the corporate presentation is furnished as Exhibit 99.4 to this Current Report on Form 8-K.

The information in Item 7.01 of this Form 8-K (including Exhibits 99.1, 99.2, 99.3 and 99.4) 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 8.01 Other Events.

On October 17, 2023, the Company announced interim data from the Phase 1 dose escalation part of its ongoing Phase 1/2 open-label, multi-center study of MRT-2359 in patients with MYC-driven solid tumors, including lung cancers and high-grade neuroendocrine cancer. MRT-2359 is an investigational, orally bioavailable, GSPT1-directed MGD discovered by the Company. Cancers driven by MYC overexpression have been demonstrated to be dependent on GSPT1, creating a therapeutic opportunity.

Interim clinical data from the MRT-2359 study have demonstrated favorable tolerability, pharmacokinetic ("PK"), and pharmacodynamic ("PD") profiles in heavily pre-treated patients with lung cancers and high-grade neuroendocrine cancer. In addition, MRT-2359 has been observed to significantly reduce GSPT1 protein levels in patient tumors and has shown evidence of tumor size reductions, including partial responses, in heavily pretreated patients with biomarker-positive tumors. The Company is continuing with dose level and schedule optimization in this ongoing study.

Summary of available study results:

- As of the analysis cutoff date of September 7, 2023, 21 patients had been dosed, with 15 of the 21 patients evaluable for efficacy.
- Optimal PD modulation of GSPT1 by MRT-2359 was observed at all dose levels, consistent with its designed activity based on preclinical studies. Following MRT-2359 dosing, approximately 60% reduction in GSPT1 protein expression was observed in peripheral blood mononuclear cells and tumor tissue biopsies. Similar levels of degradation were observed across all dose levels, suggesting saturated PD responses from 0.5 mg to 2 mg and supporting that pharmacodynamically, 0.5 mg is a fully active dose. The level of GSPT1 degradation observed was in line with the levels seen in preclinical studies that were associated with anti-tumor activity.

- Of the 15 evaluable patients that have been administered MRT-2359 across three dose cohorts (0.5 mg, 1 mg, and 2 mg in a 5 days on-drug, 9 days off-drug dosing schedule), six were identified as biomarker-positive in indicated tumor types, specifically N-MYC high non-small cell lung cancer ("NSCLC") adenocarcinoma, L-/N-MYC high small cell lung cancer ("SCLC"), L-/N-MYC high-grade neuroendocrine tumors (prostate, bladder, and others) and neuroendocrine tumors of the lung,
- Clinical activity was seen across all dose levels. Of the six biomarker-positive patients, two achieved a partial response ("PR"), one confirmed and one unconfirmed, and one patient experienced durable stable disease ("SD"). Additionally, one patient who had an unevaluable biomarker status also experienced durable SD.
- The MRT-2359 safety profile supports further clinical development, with no signs of hypotension, cytokine release syndrome ("CRS") or clinically significant hypocalcemia observed at any dose level, all of which have been reported as safety limitations of other GSPT1 degraders. The 0.5 mg and 1 mg dose levels resulted in Grade 1 or 2 treatment-related adverse events ("AEs") only. At the 2 mg dose level, Grade 4 thrombocytopenia (dose-limiting toxicity ("DLT"), n=2) and Grade 4 neutropenia (non-DLT, n=1) were observed, findings consistent with preclinical toxicology studies. No patients discontinued treatment due to AEs at any dose level, and the Grade 4 AEs observed at the 2 mg dose were transient and resolved with dose reductions.

The Company is continuing with dose and schedule optimization as well as enrollment of biomarker-positive patients into various backfill cohorts of the Phase 1 part of the study. The Company is currently dosing MRT-2359 at 1.5 mg in a 5 days on-drug, 9 days off-drug dosing schedule and, based on the observed safety profile, is considering a 21 days on-drug, 7 days off-drug dosing regimen.

Forward-Looking Statements

This Current Report on Form 8-K 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 the Company's ongoing pre-clinical and clinical development of the Company's GSPT1 degrader referred to as MRT-2359, including the Company's expectations regarding the potential relevance of certain interim clinical data, and the Company's expectations for the nature and timing of the Company's clinical development of MRT-2359, the potential for MRT-2359 to benefit patients living with a variety of difficult-to-treat cancers and MYC-driven solid tumors, the Company's plans to continue the Phase 1/2 Study of MRT-2359, including its anticipated progress, clinical trial design and the Company's ability to enroll the requisite number of patients and dose each dosing cohort in the intended manner, 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, and the Company's pipeline of MGDs being the industry leader, spanning oncology, autoimmune and inflammatory diseases and beyond, 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 the Company's most recent Annual Report on Form 10-K for the year ended December 31, 2022, 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 the Company's management believes that the expectations reflected in these statements are reasonable, the Company cannot guarantee that the future results, performance, or events and circumstances described in the forward-looking statements will be achieved or occur. These forward-looking statements speak only as of the date such statements are made and should not be construed as statements of fact. The Company undertakes 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.

Item 9.01. Financial Statements and Exhibits

(d) Exhibits

99.1	Press Release issued by Monte Rosa Therapeutics, Inc. dated October 17, 2023.
99.2	Press Release issued by Monte Rosa Therapeutics, Inc. dated October 17, 2023.
99.3	Data Presentation of Monte Rosa Therapeutics, Inc.
99.4	Corporate Presentation of Monte Rosa Therapeutics, Inc.
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: October 17, 2023

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

Monte Rosa Therapeutics Announces Strategic Collaboration with Roche to Discover Novel Molecular Glue Degraders Targeting Cancer and Neurological Diseases

Collaboration combines Monte Rosa Therapeutics' highly differentiated QuEEN™ discovery engine with Roche's strong expertise in delivering transformative therapies to patients

Monte Rosa to receive an upfront payment of $50 million and potential future payments exceeding $2 billion

BOSTON, Mass., October 17, 2023 – Monte Rosa Therapeutics, Inc. (Nasdaq: GLUE), a clinical-stage biotechnology company developing novel molecular glue degrader (MGD)-based medicines, today announced it has entered into a strategic collaboration and licensing agreement with global healthcare leader Roche to discover and develop MGDs against targets in cancer and neurological diseases previously considered impossible to drug.

"We are excited to partner with Roche, a leading healthcare and one of the world's top oncology companies. Our QuEEN™ discovery engine, a highly validated and industry-leading molecular glue degrader platform, has been the cornerstone for Monte Rosa's success, driving the discovery and development of our exquisitely selective MGDs successfully into the clinic. This collaboration will enable and accelerate expansion of our platform into neuroscience and additional areas of oncology. We believe our decision to partner with Roche, a company that shares our vision and drive, will amplify our collective strengths and capabilities to accelerate the development of transformative treatments for patients across several indications," said Markus Warmuth, M.D., CEO of Monte Rosa Therapeutics.

James Sabry, M.D., Ph.D., Global Head of Pharma Partnering at Roche, added: "We believe that molecular glue degraders are a powerful new class of small molecules that target disease-related proteins that traditional approaches have been unable to address. Together with Monte Rosa, we look forward to tackling high-value targets in both oncology and neuroscience with the goal of unlocking new therapeutic possibilities."

Under the terms of the agreement, Monte Rosa Therapeutics will receive an upfront payment of $50 million, and is eligible to receive future preclinical, clinical, commercial and sales milestone payments that could exceed $2 billion, as well as tiered royalties. The parties also agreed on a mechanism to expand the collaboration on multiple targets within the first two years. In that case, additional payments for nomination, preclinical, clinical, commercial and sales milestones are due, as well as tiered royalties on the resulting products. Monte Rosa Therapeutics will lead discovery and preclinical activities against multiple select cancer and neurological disease targets to a defined point. Roche gains the right to exclusively pursue further preclinical and clinical development of the compounds. Monte Rosa retains full ownership of its pipeline programs.

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. 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 QuEEN™ discovery engine and our view of its potential for the ongoing discovery and development of MGDs, including highly selective MGDs, our beliefs regarding the potential of MGDs to target previously unaddressable disease-related proteins, our expectations for our collaboration with Roche, including the discovery and development of MGDs therefrom, the acceleration of the expansion of our platform and the development of treatments across several indications, our expectations and estimates of potential future payments available under the collaboration, the advancement of our preclinical programs, pipeline and the various products therein, statements around the advancement and application of our pipeline and platform, including our lead program, MRT-2359, 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, 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, 2022, 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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Monte Rosa Therapeutics Announces Interim PK/PD and Clinical Data for MRT-2359 in Phase 1/2 Trial for MYC-Driven Solid Tumors

Optimal levels of degradation of GSPT1 in peripheral blood mononuclear cells and tumors observed at all doses, consistent with preclinical studies

Tumor size reductions observed in patients with biomarker-positive tumors

Safety profile supports further clinical development of MRT-2359

Conference call and webcast at 8:00 a.m. ET today

BOSTON, Mass., October 17, 2023 - Monte Rosa Therapeutics, a clinical-stage biotechnology company developing novel molecular glue degrader (MGD)-based medicines, today announced interim data from the Phase 1 dose escalation part of its ongoing Phase 1/2 open-label, multicenter study of MRT-2359 in patients with MYC-driven solid tumors, including lung cancers and high-grade neuroendocrine cancer. MRT-2359 is an investigational, orally bioavailable, GSPT1-directed MGD discovered by Monte Rosa Therapeutics. Cancers driven by MYC overexpression have been demonstrated to be dependent on GSPT1, creating a therapeutic opportunity.

Interim clinical data from the MRT-2359 study have demonstrated favorable tolerability, pharmacokinetic (PK), and pharmacodynamic (PD) profiles in heavily pre-treated patients with lung cancers and high-grade neuroendocrine cancer. In addition, MRT-2359 has been observed to significantly reduce GSPT1 protein levels in patient tumors and has shown evidence of tumor size reductions, including partial responses, in heavily pretreated patients with biomarker-positive tumors. Monte Rosa is continuing with dose level and schedule optimization in this ongoing study.

“We’re highly encouraged by the safety profile, the depth of pharmacodynamic modulation of GSPT1 in tumors, and even more so by the early evidence of anti-tumor activity of MRT-2359 in patients with biomarker-positive cancers,” said Markus Warmuth, M.D., Chief Executive Officer of Monte Rosa Therapeutics. “We believe these results, the first ever to show clinical activity of a rationally designed molecular glue degrader in solid tumors, represent an important advance for the field and underscore the potential for MRT-2359 to benefit patients living with a variety of difficult-to-treat cancers. We are excited to learn more about the clinical profile of MRT-2359 in our ongoing Phase 1/2 clinical study, and early next year we plan to provide further clarity on the expected timing for the full Phase 1 data disclosure in 2024.”

Summary of available study results:

- As of the analysis cutoff date of September 7, 2023, 21 patients had been dosed, with 15 of the 21 patients evaluable for efficacy.
- Optimal PD modulation of GSPT1 by MRT-2359 was observed at all dose levels, consistent with its designed activity based on preclinical studies. Following MRT-2359 dosing, approximately 60% reduction in GSPT1 protein expression was observed in peripheral blood mononuclear cells and tumor tissue biopsies. Similar levels of degradation were observed across all dose levels, suggesting saturated PD responses from 0.5 mg to 2 mg and supporting that pharmacodynamically, 0.5 mg is a fully active dose. The level of GSPT1 degradation observed was in line with the levels seen in preclinical studies that were associated with anti-tumor activity.
- Of the 15 evaluable patients that have been administered MRT-2359 across three dose cohorts (0.5 mg, 1 mg, and 2 mg in a 5 days on-drug, 9 days off-drug dosing schedule), six were identified as biomarker-positive in indicated tumor types, specifically N-MYC high non-small cell lung cancer (NSCLC) adenocarcinoma, L-/N-MYC high small cell lung cancer (SCLC), L-/N-MYC high-grade neuroendocrine tumors (prostate, bladder, and others) and neuroendocrine tumors of the lung.
- Clinical activity was seen across all dose levels. Of the six biomarker-positive patients, two achieved a partial response (PR), one confirmed and one unconfirmed, and one patient experienced durable stable disease (SD). Additionally, one patient who had an unevaluable biomarker status also experienced durable SD.
- The MRT-2359 safety profile supports further clinical development, with no signs of hypotension, cytokine release syndrome (CRS) or clinically significant hypocalcemia observed at any dose level, all of which have been reported as safety limitations of other GSPT1 degraders. The 0.5 mg and 1 mg dose levels resulted in Grade 1 or 2 treatment-related adverse events (AEs) only. At the 2 mg dose level, Grade 4 thrombocytopenia (dose-limiting toxicity (DLT), n=2) and Grade 4 neutropenia (non-DLT, n=1) were observed, findings consistent with preclinical toxicology studies. No patients discontinued treatment due to AEs at any dose level, and the Grade 4 AEs observed at the 2 mg dose were transient and resolved with dose reductions.

"Observing clinical activity in multiple patients who have exhausted all other treatment options strengthens our optimism about the potential of MRT-2359 for patients with MYC-driven solid tumors. This represents a sizable patient group, encompassing many cancer types, that currently experience significant unmet need. We continue to explore optimal doses and dosing schedules as we collect clinical data from this ongoing Phase 1/2 study," said Filip Janku, M.D., Ph.D., Chief Medical Officer of Monte Rosa Therapeutics.

Jordi Rodon Ahnert, M.D., Ph.D., Associate Professor, The University of Texas MD Anderson Cancer Center and Principal Investigator on the study, commented: “While the molecular role of MYC as a common driver of numerous cancers has been well appreciated for decades, the

development of an effective therapeutic targeting this pathway has remained elusive. An effective drug for MYC-driven cancers could represent an important new therapeutic approach with applicability against many cancers. These early MRT-2359 data suggest that this highly specific MGD is clinically active in a treatment-refractory population and strongly support continued development."

Monte Rosa Therapeutics is continuing with dose and schedule optimization as well as enrollment of biomarker-positive patients into various backfill cohorts of the Phase I part of the study. The company is currently dosing MRT-2359 at 1.5 mg in a 5 days on-drug, 9 days off-drug dosing schedule and, based on the observed safety profile, is considering a 21 days on-drug, 7 days off-drug dosing regimen.

Conference Call

Monte Rosa Therapeutics will host a conference call and webcast today at 8:00 a.m. ET to discuss the interim PK/PD and clinical data for MRT-2359. To participate via telephone and join the call live, please register in advance here. Upon registration, telephone participants will receive a confirmation email detailing how to join the conference call, including the dial-in number and a unique passcode. A live webcast of the call will also be available on the Investors section of the Monte Rosa website at ir.monterosatx.com, and a replay of the call will be available at the same link approximately two hours after its completion. The replay will be available for at least 30 days following the conclusion of the call.

About MRT-2359

MRT-2359 is a potent, 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 that 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 and leading to anti-tumor activity in MYC-driven tumors.

About the Phase1/2 Study of MRT-2359

The Phase 1/2, open-label, multicenter study is designed to assess the safety, tolerability, PK, PD and preliminary clinical activity of MRT-2359 in patients with previously treated selected solid tumors, including non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), high-grade neuroendocrine cancer of any primary site, diffuse large B-cell lymphoma (DLBCL) and solid tumors with L-MYC or N-MYC amplification. In the Phase 1 portion of the study, patients receive escalating doses of MRT-2359 to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D). Once the RP2D is determined, the anti-tumor activity of

MRT-2359 will be assessed as part of the Phase 2 portion of the study, which includes molecular biomarkers for stratification and selection.

For more information visit clinicaltrials.gov (Study Identifier: NCT05546268).

About Monte Rosa

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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
Andrew Funderburk, Kendall IR
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Media
Cory Tromblee, Scient PR
media@monterosatx.com


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

Forward-Looking Statements

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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, our expectations for our collaboration with Roche, including the discovery and development of MGDs therefrom, and our expectations and estimates of potential future payments available under the collaboration, our ongoing pre-clinical and clinical development of our GSPT1 degrader referred to as MRT-2359, including our expectations regarding the potential relevance of certain interim clinical data, our expectations for the nature and timing of any additional clinical data releases for MRT-2359, including any full phase 1 clinical data release, and our expectations for the nature and timing of our ongoing and future clinical development of MRT-2359, including our plan to continue the Phase 1/2 study of MRT-2359 and its anticipated timing and progress, and our ability to enroll the requisite number of patients and dose each dosing cohort in the intended manner, the potential for MRT-2359 to benefit patients living with a variety of difficult-to-treat cancers, our expectations regarding the advancement, and timing thereof, of our pipeline and the various products therein, our ability to advance our development candidates, including MRT-6160 and our expectations for MRT-6160 to enter the clinic in 2024 and its potential applications across multiple autoimmune diseases, our expectations regarding potential therapeutic opportunities for our MGDs, and our clinical development expectations therefor, our expectations regarding patient populations and medical needs for any potential therapeutic opportunities for our MGDs, our expectations regarding our proprietary QuEEN™ platform and its potential to be highly productive and an industry-leading platform for designing MGDs to address hard-to-drug disease targets via degradation, combining experimentation with AI to push the boundaries of what is possible with MGDs, and the strength of our financial position, including our estimates of cash runway, among others. 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Monte Rosa Therapeutics – Call Highlights

Interim analysis of data from our Phase I dose escalation study of MRT-2359, providing evidence of optimal PD modulation, clinical activity and a favorable tolerability profile

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

Updated cash runway into Q3 2025

Monte Rosa Therapeutics

Monte Rosa Therapeutics – Roche Partnership

Monte Rosa Tx – Roche Partnership: Summary

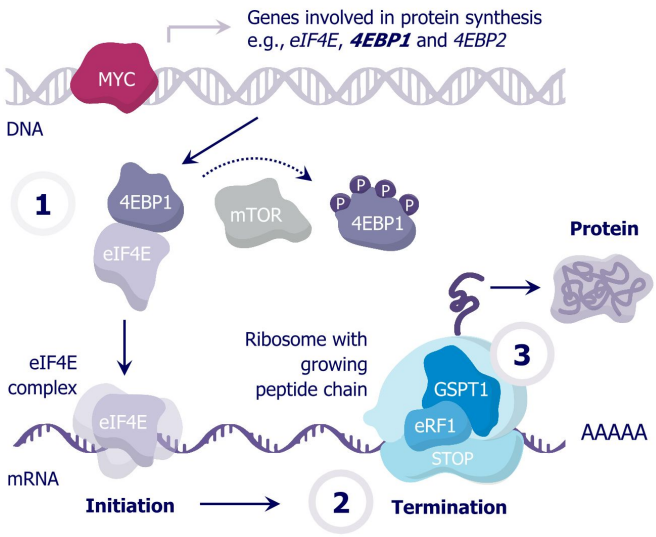
- Discovery partnership on targets in oncology and neurological disease
- Leverages synergies between Monte Rosa Tx – a leading molecular glue degrader company – and Roche – a leading global health care company
- Monte Rosa Tx performs preclinical drug discovery with Roche leading late preclinical discovery and clinical development
- Monte Rosa Tx to receive $50M upfront payment and potential preclinical, clinical, regulatory and sales milestones that could exceed $2B*
- Potential to expand collaboration to additional targets, which triggers potential additional payments including nomination, preclinical, clinical, regulatory and sales milestones
- Partnership provides additional validation of Monte Rosa Tx's QuEEN™ discovery engine and its opportunity to go beyond Oncology
- Monte Rosa Tx's publicly disclosed pipeline remains unencumbered*

* as disclosed in company 8K

Monte Rosa Therapeutics

GSPT1 Program – Phase I Interim Update

Targeting MYC-driven Tumors and Their Addiction to Protein Translation



1 **Addiction**

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

2 **Dependency**

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

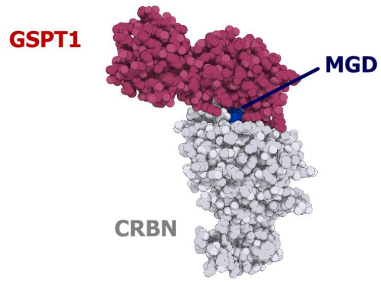
3 **Therapeutic vulnerability**

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

MRT-2359 is a Potent and Selective GSPT1 Degrader

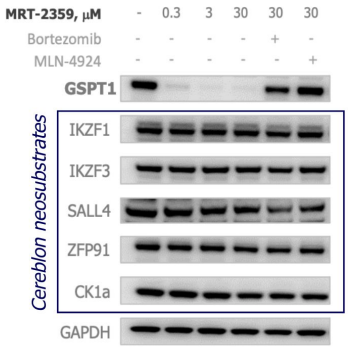
MRT-2359 is a potent GSPT1 degrader

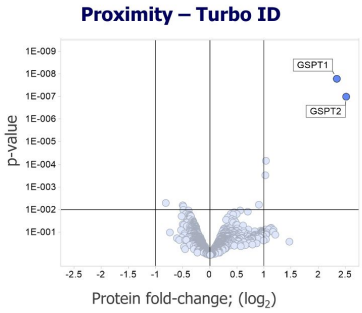
Ternary complex modelling



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

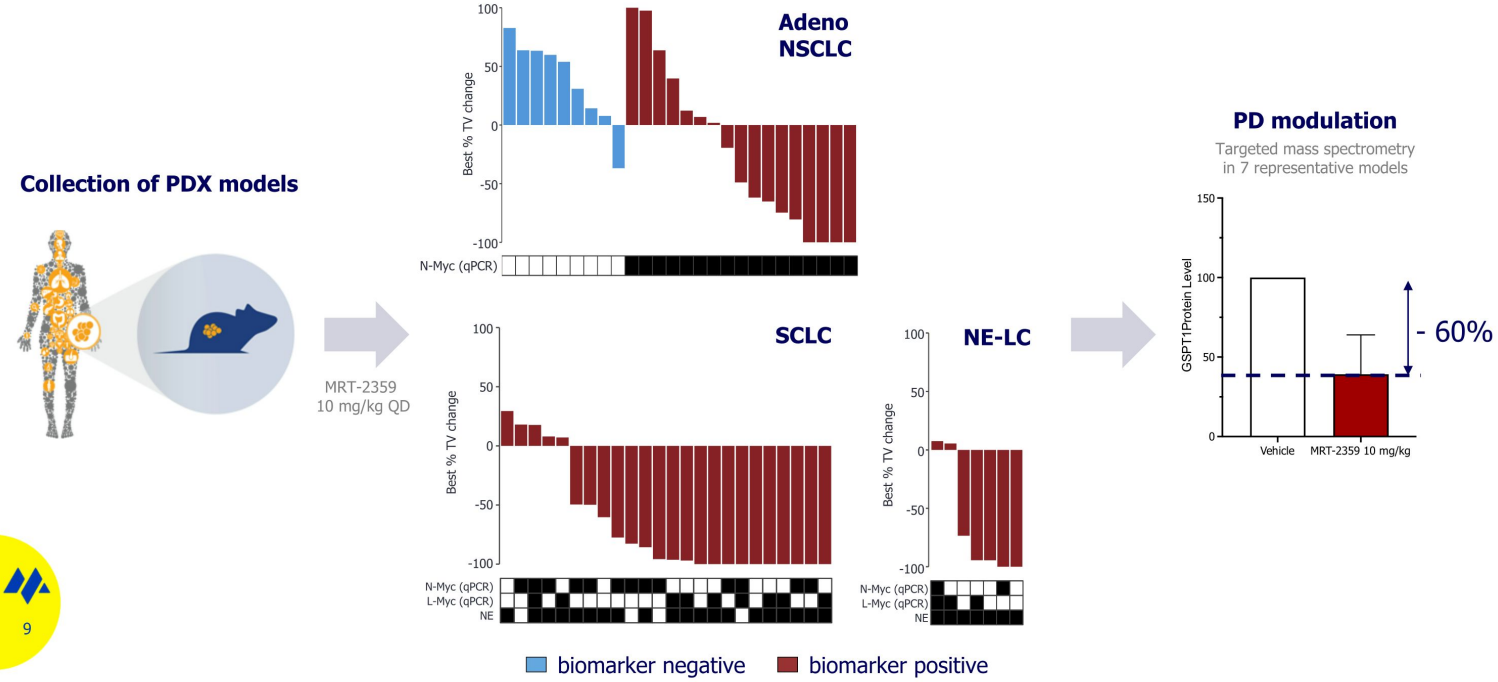
MRT-2359 induced selective GSPT1 degradation and showed favorable ADME/DMPK profile





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

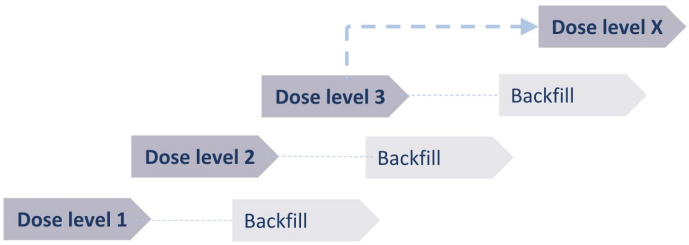
Activity of MRT-2359 in NSCLC, SCLC and Lung NE Patient-derived Xenograft Models



MRT-2359-001 Phase 1/2 – Phase 1 Interim Update

Phase 1: Dose Escalation

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



Backfill slots for additional patients for each dose level

Objectives of Phase I interim analysis

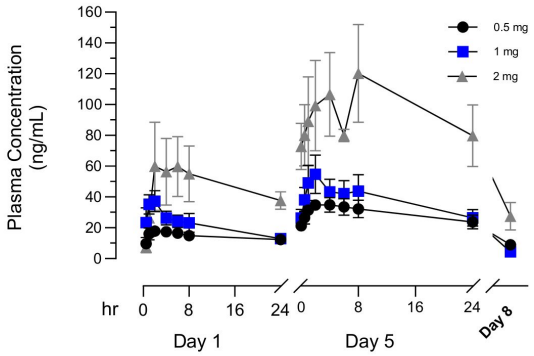
- ✓ Demonstrate dose dependent PK
- ✓ Demonstrate significant GSPT1 degradation at safe dose levels in PBMCs and tissue biopsies (60% based on preclinical data)
- ✓ Share potential preliminary efficacy signals in biomarker positive patients

Executive Summary

- As of September 7th, 2023, 3 dose levels (0.5 mg, 1 mg, 2 mg) have been completed with 21 patients enrolled (including backfill patients)
- Observed dose dependent PK after oral dosing
- Clinical data support that 0.5 mg starting dose was fully active based on pharmacodynamic (PD) assessment of peripheral blood mononuclear cells (PBMC) and tissue samples from patients, with optimal PD modulation across dose levels tested
- Encouraging initial clinical activity at all dose levels: 2 partial responses (PRs) (1 confirmed, 1 unconfirmed) and 1 stable disease (SD) in 6 evaluable, heavily pretreated patients identified with biomarker positive tumors; 1 SD in non-small cell lung cancer (NSCLC) with un-evaluable biomarker status
- Safety profile supports continued development:
  - Favorable adverse event (AE) profile at 0.5 and 1 mg
  - Grade 4 thrombocytopenia identified as dose limiting toxicity (DLT) at 2 mg
- Previously reported limitations of CC-90009 not observed:
  - No hypotension/cytokine release syndrome or clinically significant hypocalcemia observed at any dose level

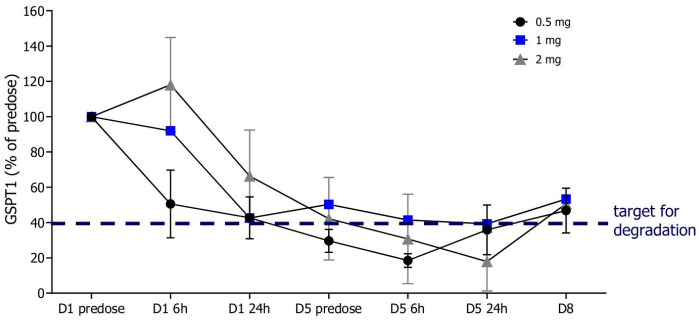
Summary of Pharmacokinetics and Pharmacodynamics

MRT-2359 displayed dose dependent plasma exposure



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

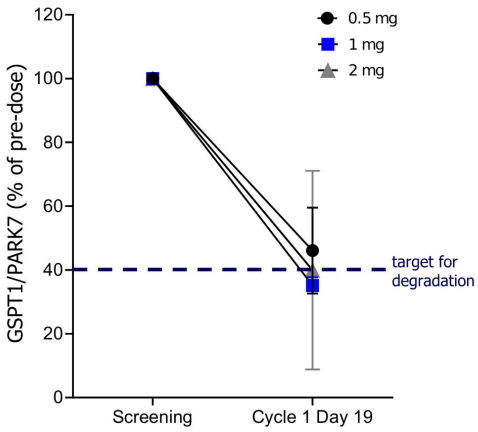
MRT-2359 displayed deep GSPT1 degradation in PBMCs at all dose levels



- 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

GSPT1 Degradation by Targeted Mass Spectrometry in Tissue Biopsies

MRT-2359 reduced GSPT1 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)

MRT-2359: Treatment-Related AEs Occurring in ≥ 2 patients[#]

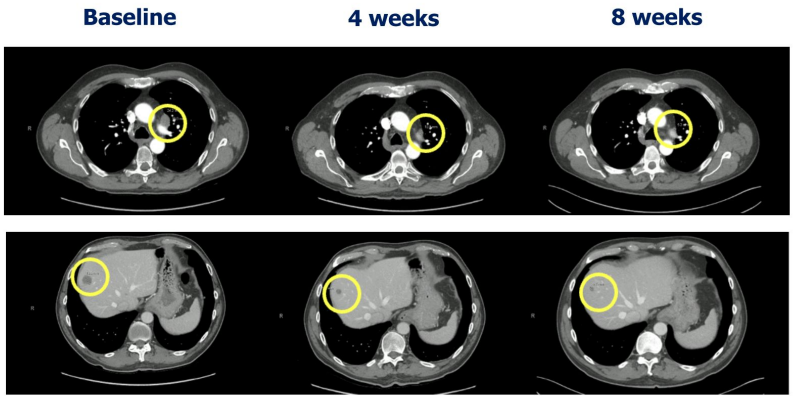
No observed clinically significant hypocalcemia or hypotension/cytokine release syndrome

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

[#] 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 PR in High Grade Neuroendocrine Bladder Cancer

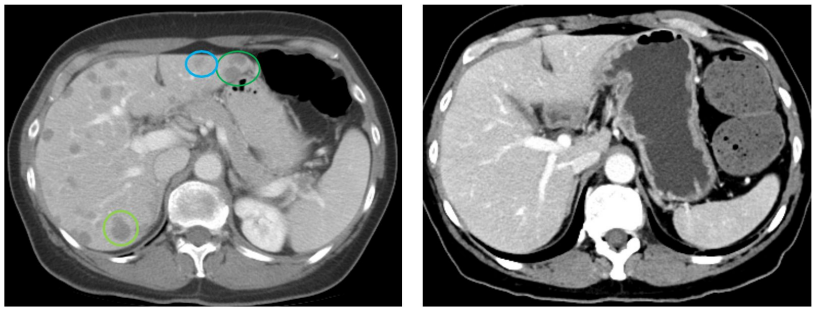
- High Grade (HG) neuroendocrine bladder cancer
- Baseline tumor biopsy demonstrated high N-MYC expression
- 4 prior lines of therapy including chemotherapy and pembrolizumab
- Patient initiated on 2 mg for first 5/9 regimen, then lowered to 1 mg and 0.5 mg and remains on therapy (> 3 month)
- CT scan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



Unconfirmed PR in NSCLC with SCLC/NE Transformation

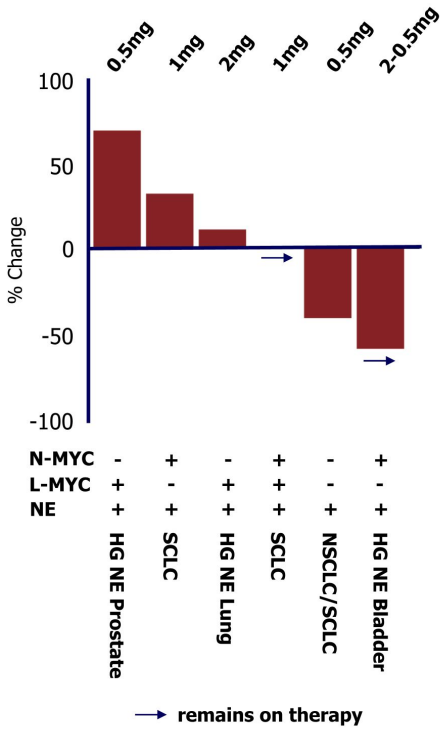
- NSCLC (adenocarcinoma)
- Baseline tumor biopsy demonstrated SCLC/NE transformation, low N- and L-MYC expression
- Multiple lines of prior therapy including chemotherapy, pembrolizumab and atezolizumab
- Patient initiated on 0.5 mg
- CT on C1D22 demonstrated resolution of liver metastases (-41% per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

Baseline **3 weeks**



MRT-2359-001 – Preliminary Efficacy Data

- As of September 7th, 2023, 15/21 evaluable patients treated across 3 cohorts, 6/15 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



Summary and Next Steps

- Clinical data support that 0.5 mg starting dose was active based on PD assessment (PBMC and tissue), with optimal PD modulation across dose levels tested
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  - Grade 4 thrombocytopenia identified as dose limiting toxicity (DLT) at 2 mg
- Previously reported limitations of CC-90009 not observed:
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Next Steps

- Currently dosing 1.5 mg, expected to complete DLT observation period by end of October
- Based on favorable tox profile, Company initiating intermittent dosing regimen of 21 days on and 7 days off drug (21/7)

Monte Rosa Therapeutics

Portfolio

Monte Rosa Pipeline

Program/ Target	Indication(s)	Discovery	IND-Enabling	Clinical	Next Anticipated Milestones	Ownership
MRT-2359 (GSPT1)	NSCLC, SCLC and other MYC-driven Malignancies				Full Phase 1 data (update on timing in early 2024)	
MRT-6160 (VAV1)	Autoimmune Disease				IND expected in 1H 2024	
NEK7	Inflammatory Diseases				Additional development candidate nomination expected in 2023	
CDK2	Ovarian Cancer, Breast Cancer					
Multiple SCD targets	SCD, β-Thalassemia				Lead optimization	
Undisclosed	Multiple					
Discovery Targets	Oncology and Neurological Diseases				Undisclosed	Roche

Oncology Immunology Inflammation Genetic diseases

Monte Rosa Therapeutics - Highlights

Taking molecular glue degraders (MGDs) to new heights

Rationally designed MGDs with potential to solve many of the limitations of other modalities by selectively degrading therapeutically relevant proteins considered undruggable or inadequately drugged

Highly productive, industry-leading platform for designing MGDs to address hard-to-drug disease targets via degradation, **combining experimentation with AI** to push the boundaries of what is possible with MGDs

Five promising, wholly-owned programs spanning oncology, autoimmune, inflammation and other TAs

Phase 1/2 clinical study ongoing with MRT-2359, with potential to treat difficult-to-drug MYC-driven cancers; optimal pharmacodynamic modulation and **early signs of clinical activity observed**

MRT-6160, highly selective VAV1-directed MGD, expected to enter clinic in mid-2024, with wide 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 Q3 2025


Thank You
Monte Rosa
Therapeutics


From Serendipity to Rational Design
Taking Molecular Glue Degraders to New Heights | October 2023
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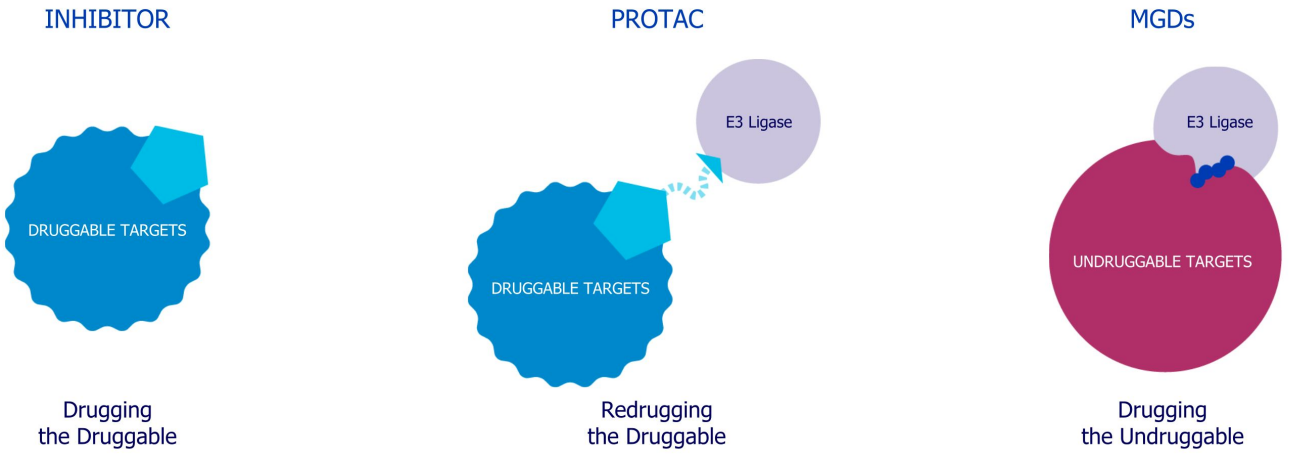
Five promising, wholly-owned programs spanning oncology, autoimmune, inflammation and other TAs

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

Strong financial position providing cash runway into Q3 2025

Molecular Glue Degraders (MGDs) - Drugging The Undruggable

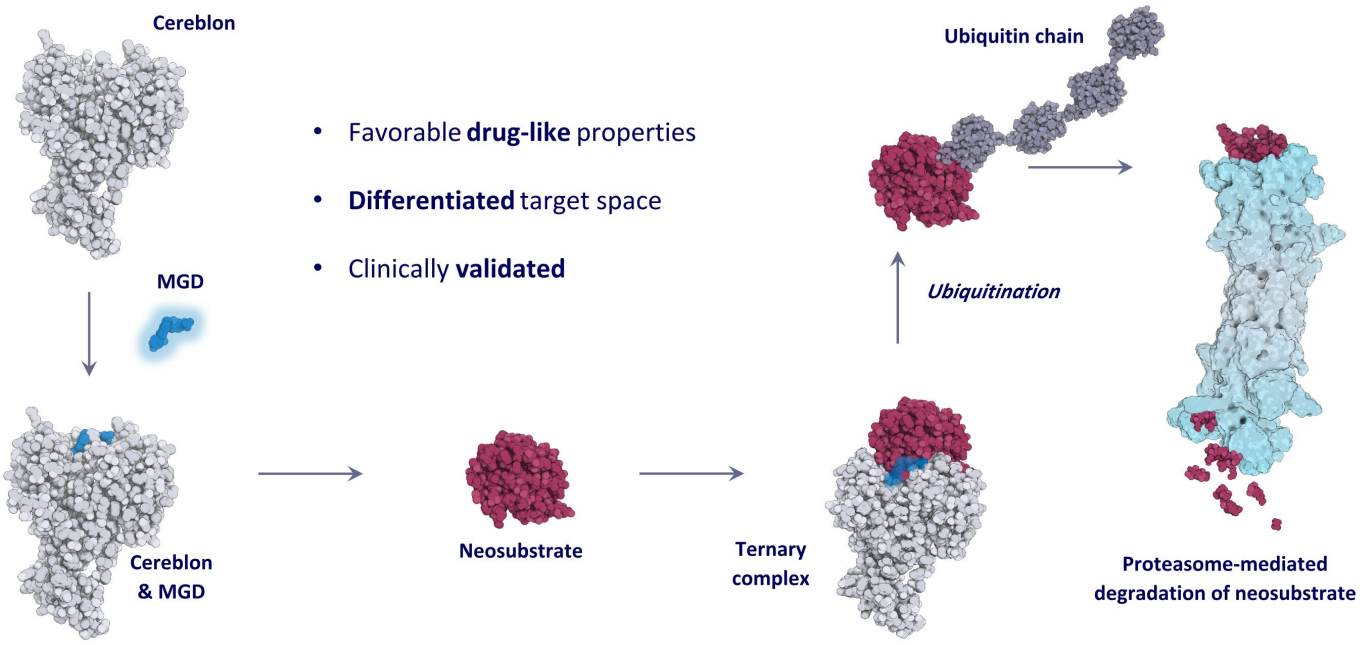
Expanding target space, fostering a new generation of drugs



Expanding the Degradable Proteome

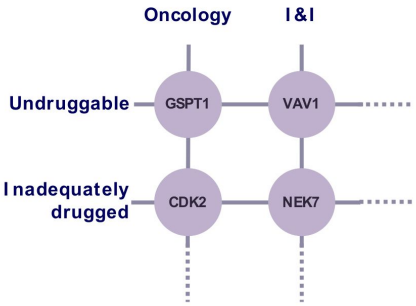
Target Space

Molecular Glue Degraders are a Clinically Validated Modality



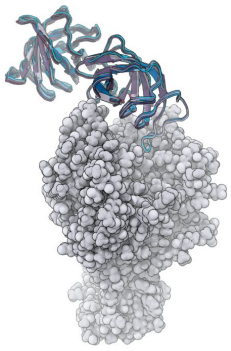
- Favorable **drug-like** properties
- **Differentiated** target space
- Clinically **validated**

Our Rationally Designed MGDs Selectively Target a Differentiated Target Space Across Protein Domains and Diseases



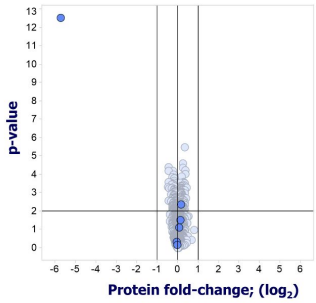
Targets

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



Rational Design

AI-guided chemistry drives target-centric, rationale MGD discovery



Selectivity

Unique insights into anatomy of ternary complexes allows unprecedented MGD selectivity

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; favorable safety profile and initial clinical signals observed – a first in solid tumors**

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

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

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

Monte Rosa Therapeutics

Portfolio

Leveraging a Leading Drug Discovery Platform

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

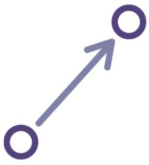
Monte Rosa's High-Value Proprietary Pipeline

Targets

Undruggable and inadequately drugged proteins

Proteins with non-catalytic and scaffolding functions

High level of target validation, preclinically and clinically



Clinical Path

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

Opportunity for a rapid clinical PoC showing MOA and efficacy

Patient Benefit

Address high unmet needs

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

Create synergies within therapeutic areas

Monte Rosa Pipeline

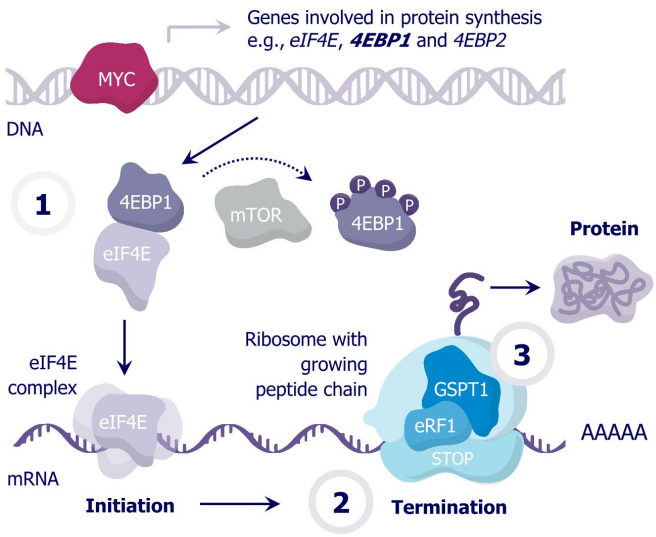
Program/ Target	Indication(s)	Discovery	IND-Enabling	Clinical	Next Anticipated Milestones	Ownership
MRT-2359 (GSPT1)	NSCLC, SCLC and other MYC-driven Malignancies				Full Phase 1 data (update on timing in early 2024)	
MRT-6160 (VAV1)	Autoimmune Disease				IND expected in 1H 2024	
NEK7	Inflammatory Diseases				Additional development candidate nomination expected in 2023	
CDK2	Ovarian Cancer, Breast Cancer					
Multiple SCD targets	SCD, β-Thalassemia				Lead optimization	
Undisclosed	Multiple					
Discovery Targets	Oncology and Neurological Diseases				Undisclosed	Roche

Oncology Immunology Inflammation Genetic diseases

Monte Rosa Therapeutics

GSPT1 program

Targeting MYC-driven Tumors and Their Addiction to Protein Translation



1 **Addiction**

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

2 **Dependency**

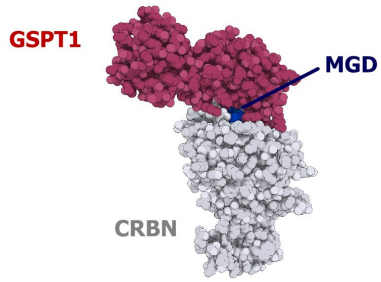
This addiction creates a dependency on the **translation termination factor GSPT1**

3 **Therapeutic vulnerability**

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

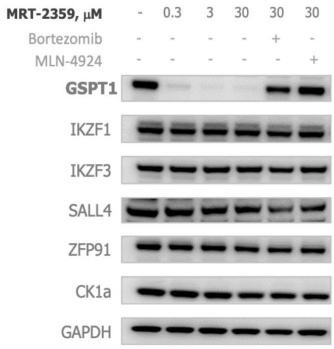
MRT-2359 is a Potent and Selective GSPT1 Degrader

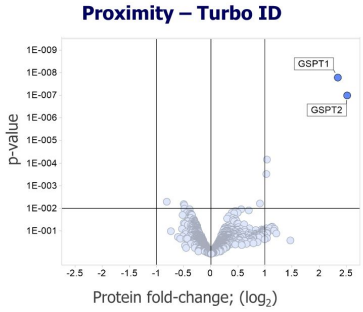
MRT-2359 is a potent GSPT1 degrader



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

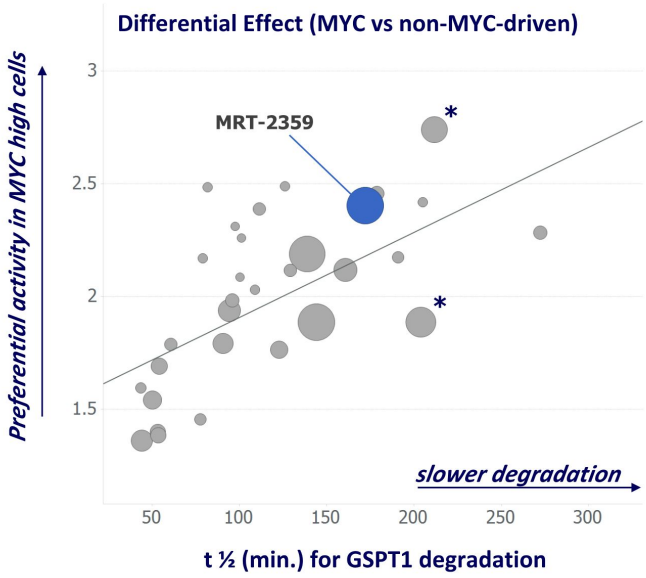
MRT-2359 induces selective GSPT1 degradation and has a favorable ADME/DMPK profile





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

MRT-2359 Has Optimized Degradation Kinetics, Selectivity and Bioavailability

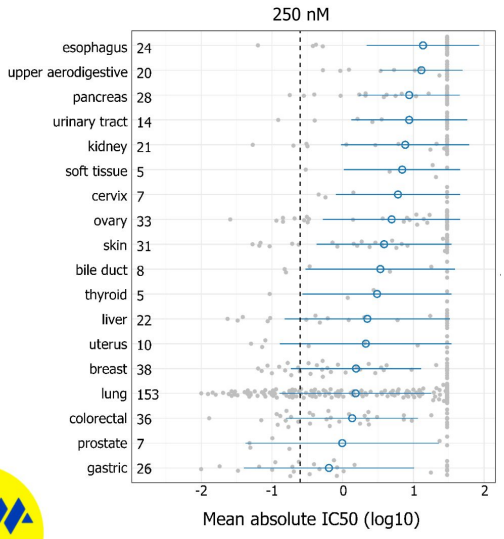


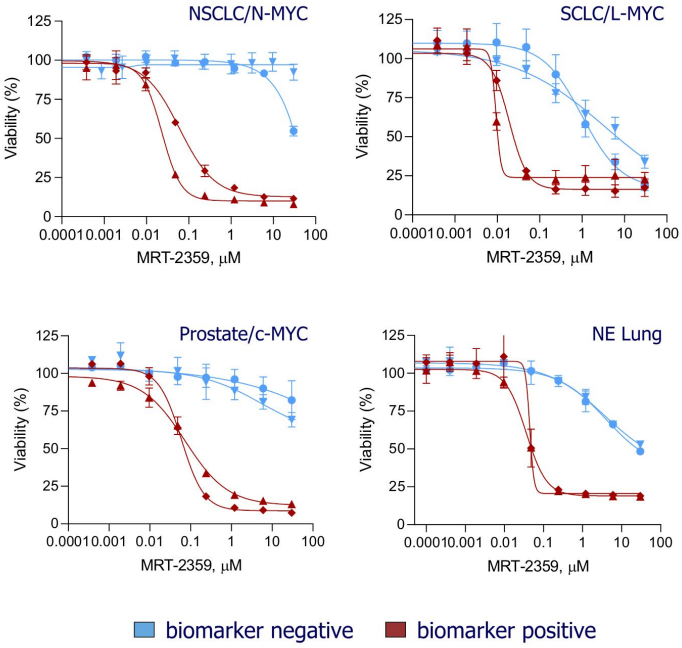
* Compounds with reactive metabolite flag

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

Preferential Activity of MRT-2359 Observed in Lung Cancer Cell Lines

Correlation to L- and N-MYC Expression

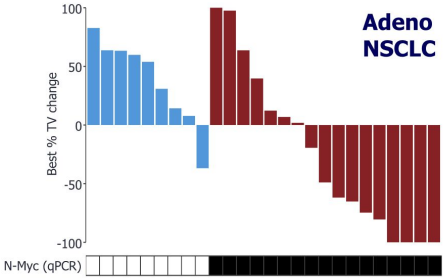


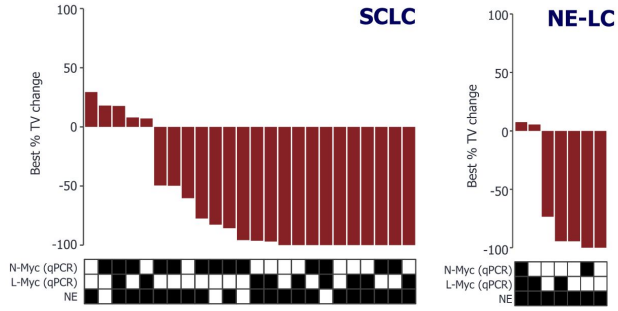


Activity of MRT-2359 in NSCLC, SCLC and Lung NE Patient-derived Xenograft Models

Collection of PDX models

MRT-2359
10 mg/kg QD

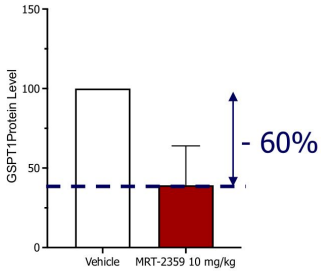




biomarker negative biomarker positive

PD modulation

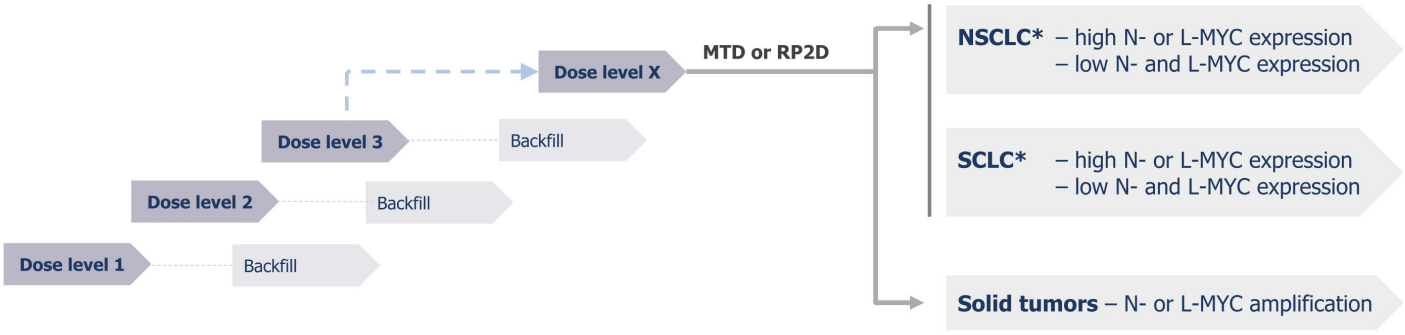
Targeted mass spectrometry
in 7 representative models



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

Phase 1: Dose Escalation

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



Backfill slots for additional patients for each dose level

Phase 2: Expansion Cohorts

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

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

Solid tumors – N- or L-MYC amplification

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

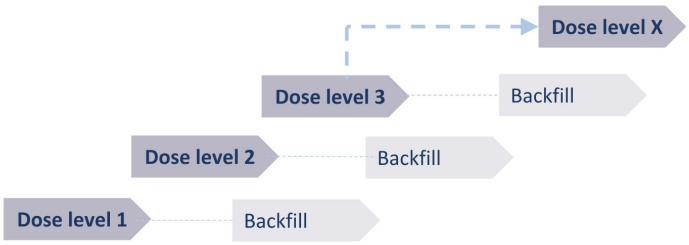
Patient dosing initiated in October 2022

MRT-2359 Phase I Interim Data - October 2023

MRT-2359-001 Phase 1/2 – Phase 1 Interim Update

Phase 1: Dose Escalation

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



Backfill slots for additional patients for each dose level

Objectives of Phase I interim analysis

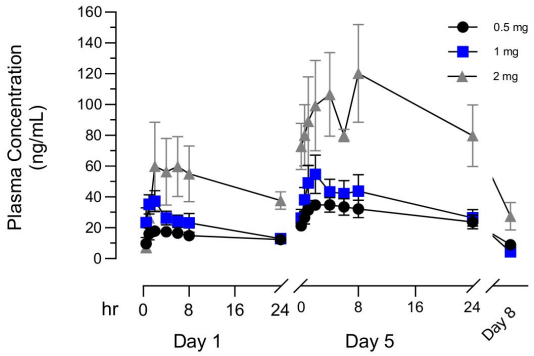
- ✓ Demonstrate dose dependent PK
- ✓ Demonstrate significant GSPT1 degradation at safe dose levels in PBMCs and tissue biopsies (60% based on preclinical data)
- ✓ Share potential preliminary efficacy signals in biomarker positive patients

Executive Summary

- As of September 7th, 2023, 3 dose levels (0.5 mg, 1 mg, 2 mg) have been completed with 21 patients enrolled (including backfill patients)
- Observed dose dependent PK after oral dosing
- Clinical data support that 0.5 mg starting dose was fully active based on pharmacodynamic (PD) assessment of peripheral blood mononuclear cells (PBMC) and tissue samples from patients, with optimal PD modulation across dose levels tested
- Encouraging initial clinical activity at all dose levels: 2 partial responses (PRs) (1 confirmed, 1 unconfirmed) and 1 stable disease (SD) in 6 evaluable, heavily pretreated patients identified with biomarker positive tumors; 1 SD in non-small cell lung cancer (NSCLC) with un-evaluable biomarker status
- Safety profile supports continued development:
  - Favorable adverse event (AE) profile at 0.5 and 1 mg
  - Grade 4 thrombocytopenia identified as dose limiting toxicity (DLT) at 2 mg
- Previously reported limitations of CC-90009 not observed:
  - No hypotension/cytokine release syndrome or clinically significant hypocalcemia observed at any dose level

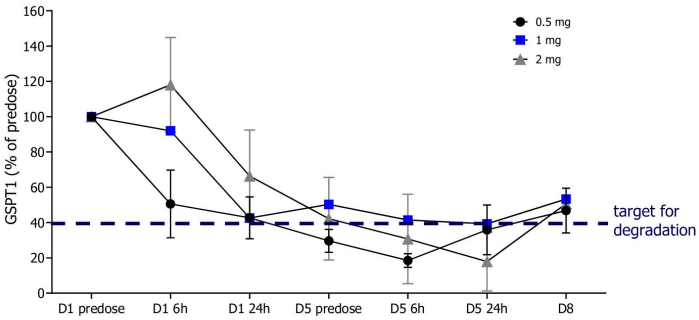
Summary of Pharmacokinetics and Pharmacodynamics

MRT-2359 displayed dose dependent plasma exposure



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

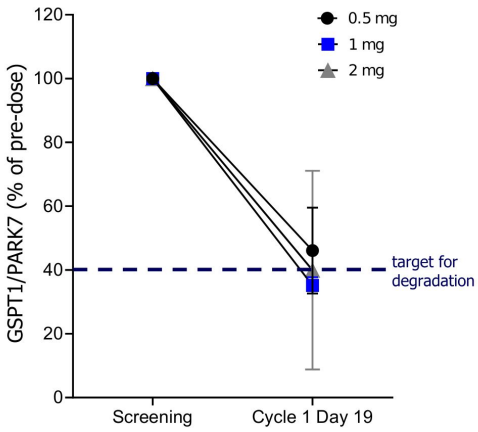
MRT-2359 displayed deep GSPT1 degradation in PBMCs at all dose levels



- 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

GSPT1 Degradation by Targeted Mass Spectrometry in Tissue Biopsies

MRT-2359 reduced GSPT1 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)

MRT-2359: Treatment-Related AEs Occurring in ≥ 2 patients[#]

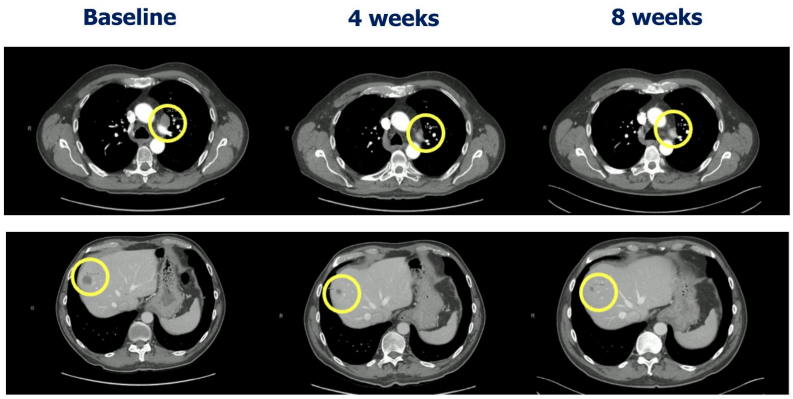
No observed clinically significant hypocalcemia or hypotension/cytokine release syndrome

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

[#] 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

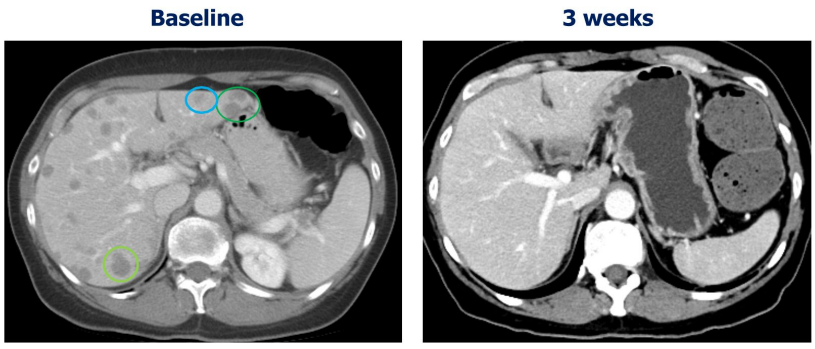
Confirmed PR in High Grade Neuroendocrine Bladder Cancer

- 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)



Unconfirmed PR 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



Summary and Next Steps

- Clinical data support that 0.5 mg starting dose was active based on PD assessment (PBMC and tissue), with optimal PD modulation across dose levels tested
- Encouraging initial clinical activity at all dose levels: 2 PRs (1 confirmed, 1 unconfirmed) and 1 SD in 6 evaluable, heavily pretreated patients identified with biomarker positive tumors; 1 SD in non-small cell lung cancer (NSCLC) with un-evaluable biomarker status
- Safety profile support further development:
  - Favorable AE profile at 0.5 and 1 mg
  - Grade 4 thrombocytopenia identified as dose limiting toxicity (DLT) at 2 mg
- Previously reported limitations of CC-90009 not observed:
  - No hypotension/cytokine release syndrome or clinically significant hypocalcemia observed at any dose level

Next Steps

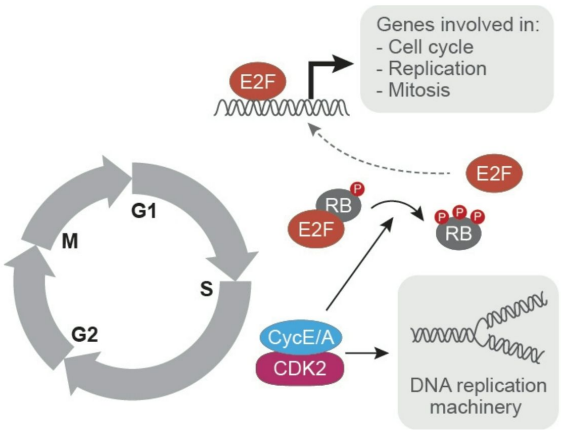
- Currently dosing 1.5 mg, expected to complete DLT observation period by end of October
- Based on favorable tox profile, Company initiating intermittent dosing regimen of 21 days on and 7 days off drug (21/7)

Monte Rosa Therapeutics

CDK2 Program

CDK2 as a Target for Selected Solid Tumors

CDK2 is one of the key regulators of the cell cycle



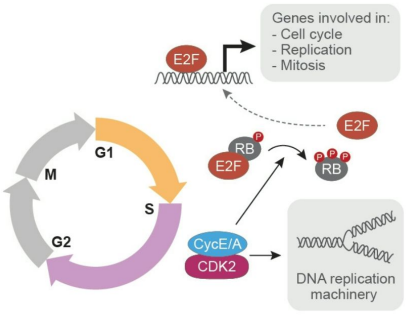
Therapeutic hypothesis: Tumors with CDK2 pathway activation by high CyclinE1/E2 expression

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

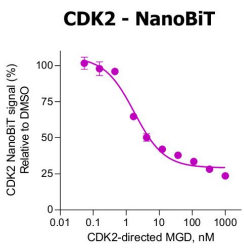
Patient diagnosed incidence #s, major markets (US, EU and JP): Decision Resources Group (DRG)

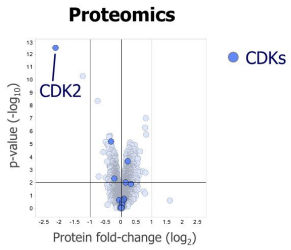
CDK2 Degradation Affects E2F Downstream Proteins and Inhibits Proliferation of CDK2-dependent Cancer Cells

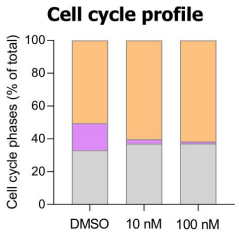
CDK2 is one of the key regulators of the cell cycle

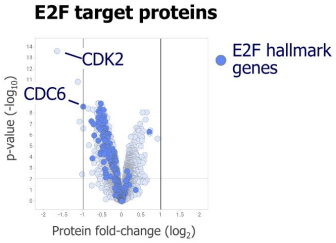


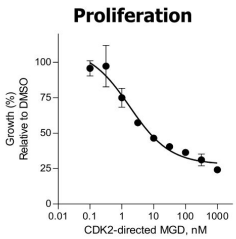
MGD-induced selective degradation of CDK2 results in reduction of E2F downstream proteins and inhibition of proliferation







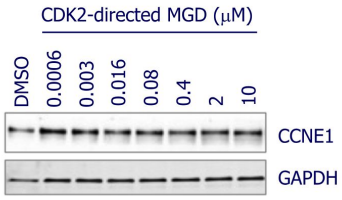




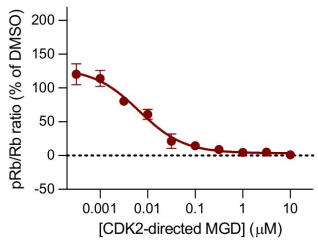
MDA-MB-157 - Cell cycle (48 hr), TMT Proteomics (24hr) and CyQuant (7d)

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

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



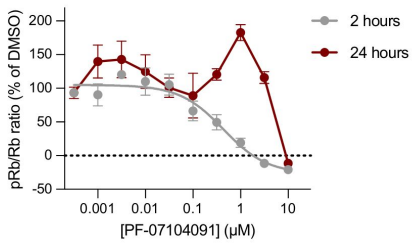
MDA-MB-157 cells, 24h



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

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

MDA-MB-157 cells, 24h



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

Monte Rosa Therapeutics

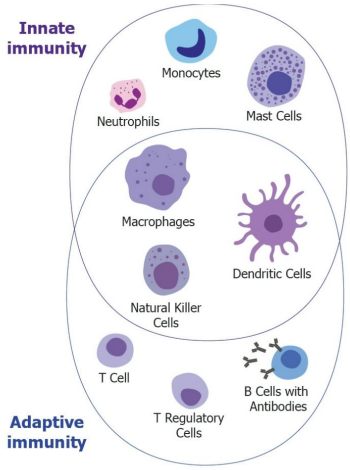
Inflammation and Immunology (I&I) Programs

QuEEN™ Enables Access to Undruggable Targets in Immune Pathways

Targets

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

Biology



Medical Need

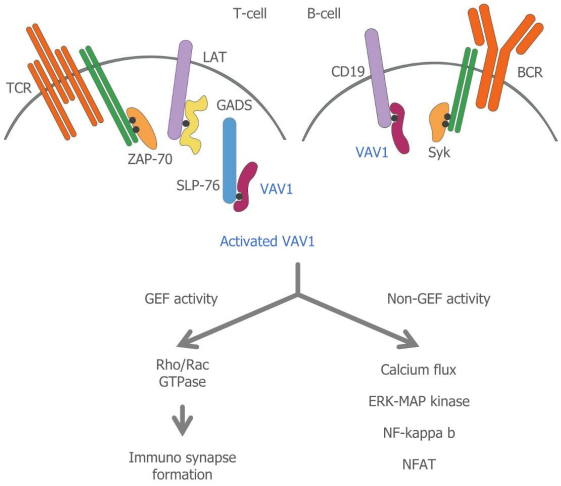
- Rheumatoid Arthritis
- Systemic Lupus Erythematosus
- Gout
- Multiple Sclerosis
- Systemic Sclerosis
- Additional indications

Monte Rosa Therapeutics

VAV1 Program

VAV1 as a Target for Autoimmune Disease

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



Therapeutic hypothesis:

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

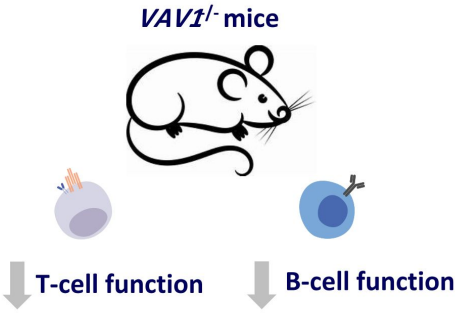
Clinical Opportunity:

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

Patient diagnosed prevalence and incidence #s, major markets (US, EU and JP): DRG; myasthenia.org

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

$VAV1^{-/-}$ mice are viable and display loss-of-function T- and B-cell phenotypes

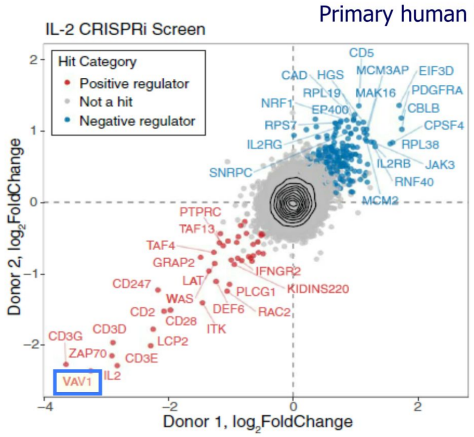


- Impaired T-cell proliferation and cytokine production
- Impaired B-cell proliferation and immunoglobulin production
- Evidence of impaired T-cell dependent B-cell response

Betzler et al., Front Cell & Dev Bio 2022
Turner et al., Nat Rev Immun 2002
Bachman et al., J. Immun 1999
Zhang et al., Nature 1995

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

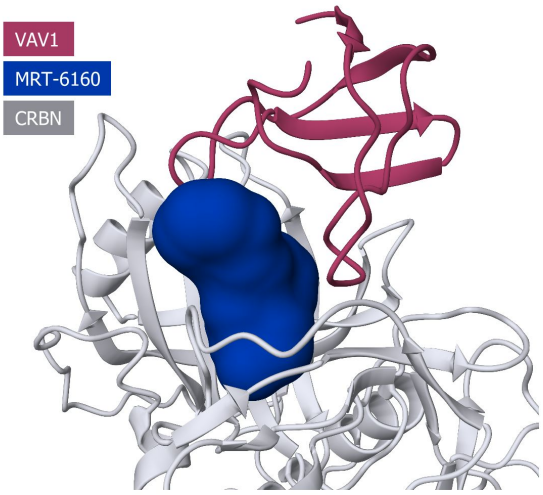
Primary human T cells



Schmidt et al., Science 2022

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

VAV1 ternary complex (Cryo-EM)

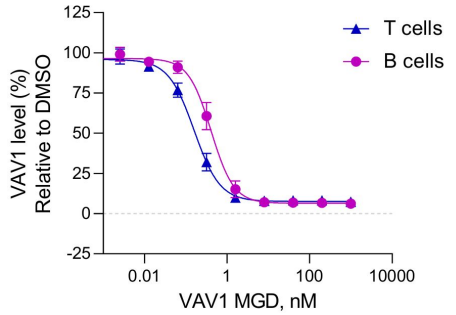


Cryo-EM structure of MRT-6160 in ternary complex with CRBN and VAV1

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

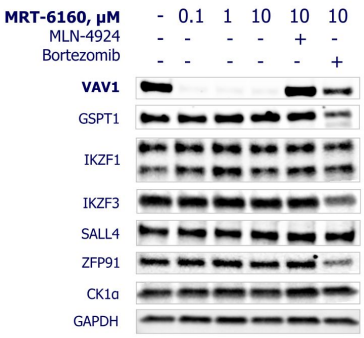
MRT-6160 is a Potent and Selective VAV1-directed MGD

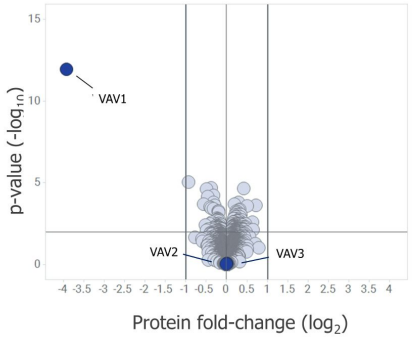
MRT-6160 is a potent VAV1-directed MGD



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

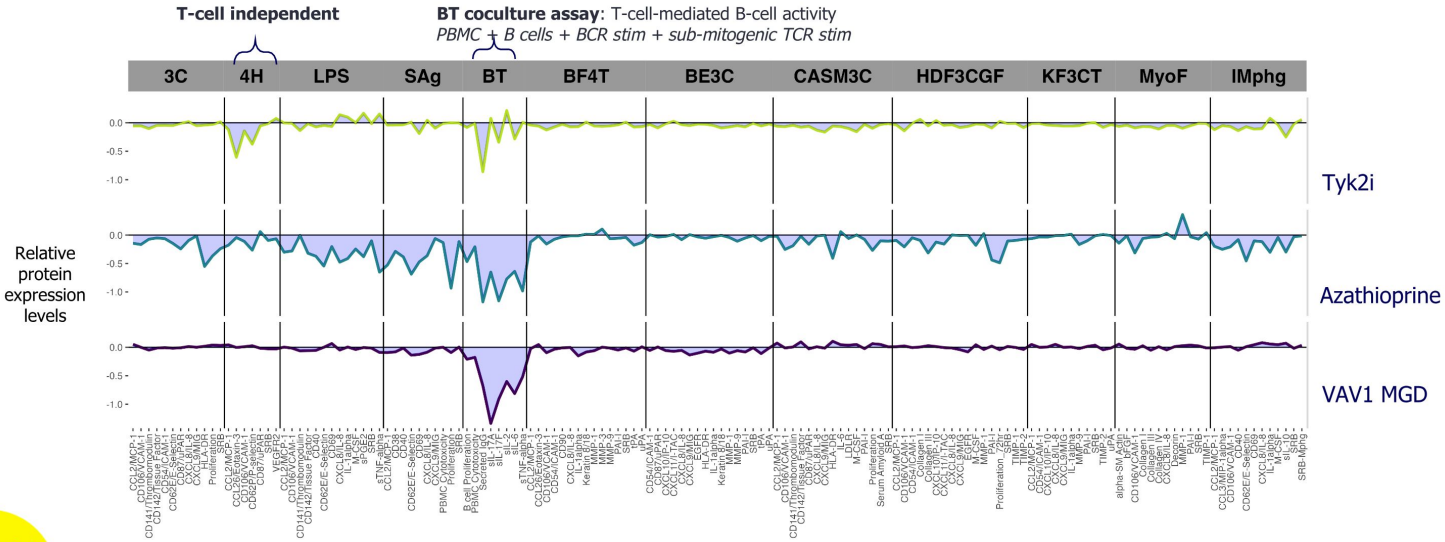
MRT-6160 induces selective VAV1 degradation and has a favorable ADME/DMPK profile





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 BioMAP Profile



Tyk2i, Deucravacitinib, 400 nM

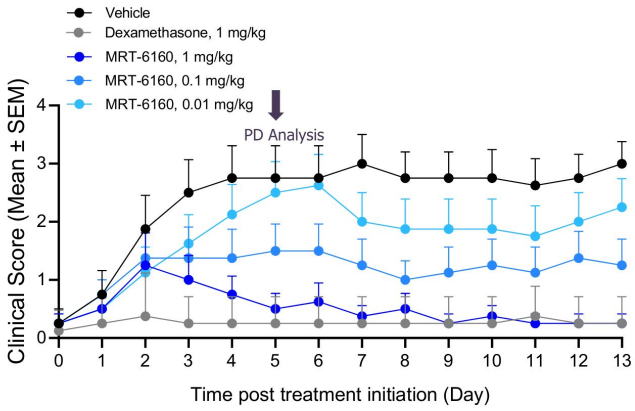
Azathioprine, 100 uM

VAV1 MGD, MRT-6160, 1000 nM

** Experiment performed by Eurofins*

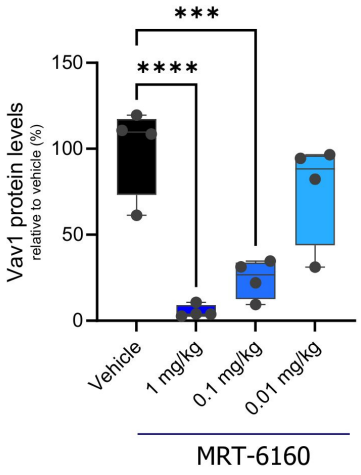
MRT-6160 Elicits Dose-Dependent Efficacy in T-cell-mediated Multiple Sclerosis Autoimmune Disease Model

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

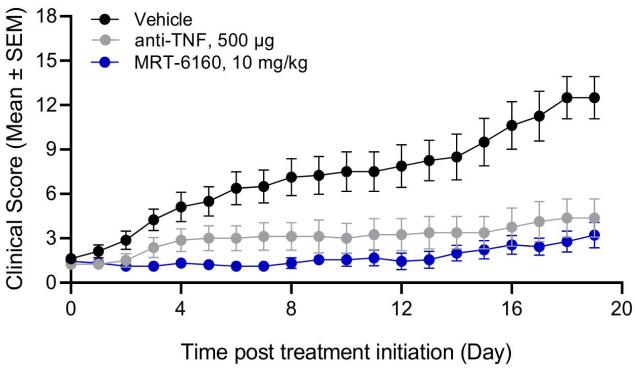
MRT-6160-mediated activity correlates with VAV1 levels



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

MRT-6160 Inhibits Disease Progression and Joint Inflammation/Damage in a T/B-cell-mediated Rheumatoid Arthritis Disease Model

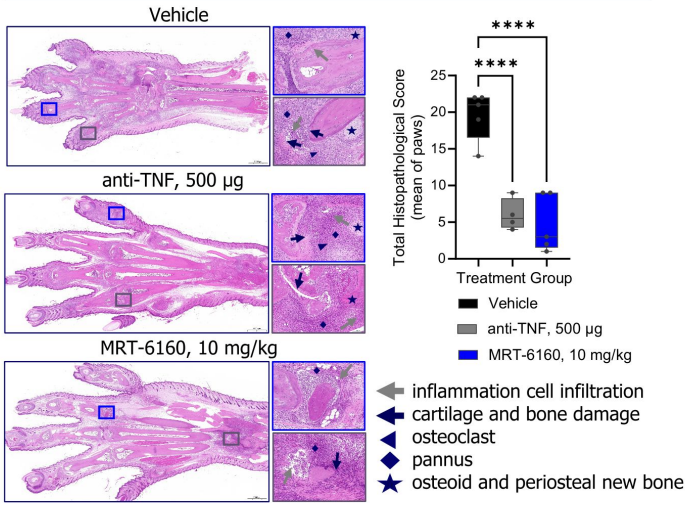
MRT-6160 inhibits disease progression in a rheumatoid arthritis model



T/B-cell (auto-antibody) driven model

CIA = collagen-induced arthritis
Dosing: Vehicle and MRT-6160, QD (oral); anti-TNF, TIW (IP) for 20 days starting at disease onset

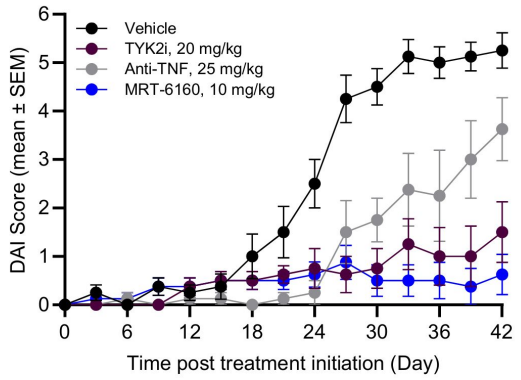
MRT-6160 inhibits joint inflammation and damage



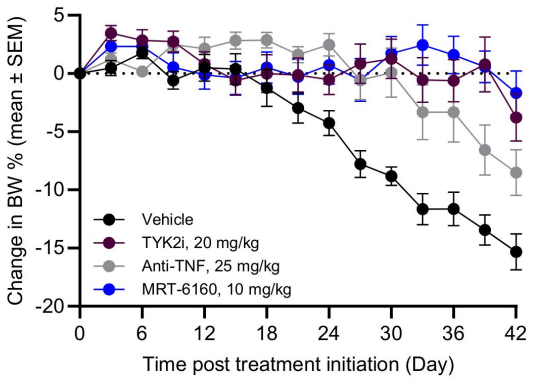
Histopathology performed on paws at end of study, total score is mean of parameters indicated, and representative images shown

MRT-6160 Inhibits Disease Progression and Incidence in a CD4 T-cell Transfer-induced Colitis Model

MRT-6160 inhibits disease progression in a colitis model



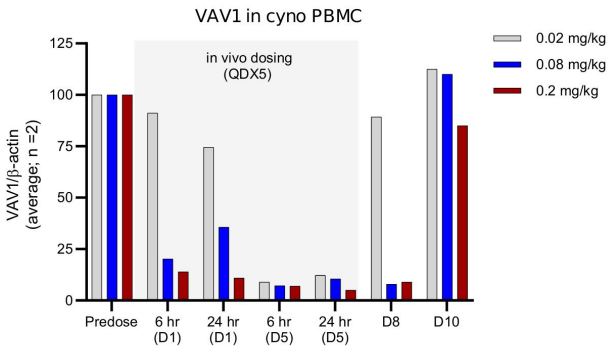
MRT-6160 reduces colitis-associated body weight loss



CD4+ T cell transfer-induced colitis model
Naïve CD4+ (CD45Rb high) T cells were transferred (IP) into SCID mice on day 0
Dosing: QD PO (vehicle, MRT-6160), BID PO (TYK2i, Deucravacitinib), or Q3D IP (anti-TNF) from day of adoptive cell transfer (day 0)

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

Degradation of VAV1 in non-human primates



Plasma exposure

Plasma Concentrations (ng/mL) @ 6hr			
mg/kg	**0.02**	**0.08**	**0.2**
D1	8	27	62
D5	15	41	104

MRT-6160 – Our VAV1-directed MGD for Autoimmune Disease

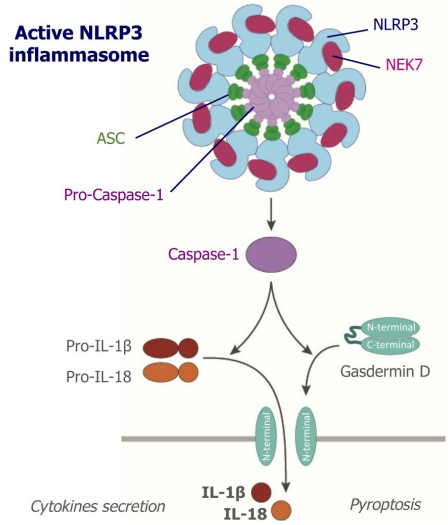
- MRT-6160 is a highly selective VAV1-directed MGD designed through our QuEEN™ platform and the first MGD being developed specifically for a non-oncology indication
- Attenuates multiple aspects of T- and B-cell receptor signaling in relevant preclinical models
- Engages VAV1 through a novel binding mode and non-canonical degron
- *In vivo* inhibition of disease progression shown in EAE, CIA and IBD mouse models
- IND filing expected in 1H 2024
- Current clinical plan developed with the goal of providing early insights into safety, PK and PD, and proof-of-concept (POC) regarding differentiated effects on key immunomodulatory signaling pathways
- Potential to address significant unmet opportunities in multiple autoimmune disorders including dermatology, IBD, multiple sclerosis and rheumatology

Monte Rosa Therapeutics

NEK7 Program

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

NEK7 is an essential regulator of the inflammasome



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

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

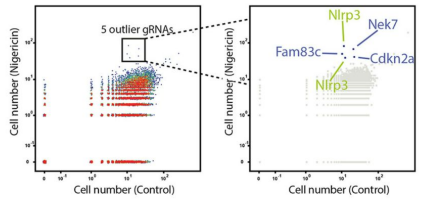
Clinical opportunity: First-in-class NEK7 degraders for

- Over-activated NLRP3 inflammasome: metabolic pathologies, cardiovascular diseases, inflammatory diseases and neurologic disorders

NEK7 as a Target to Attenuate NLRP3 Inflammasome Disease Activity

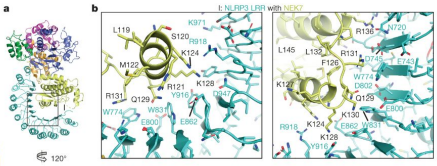
NEK7 is essential for NLRP3 inflammasome activation

Functional role for NEK7 in NLRP3 inflammasome



Schmid-Burgk, JBC 2016
He et al., Nature 2016

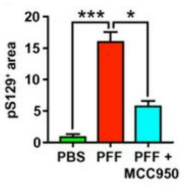
Structural licensing of NLRP3 by NEK7 binding



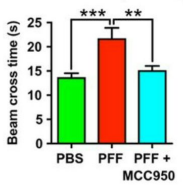
Sharif et al., Nature 2019

Inflammasome modulation reduces neuroinflammation in PD models

pS129 α-synuclein in the substantia nigra



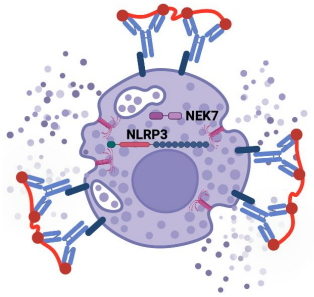
Balance beam (8 months)



Gordon et al., Sci Transl Med 2019

- Misfolded α-synuclein activates the inflammasome *in vitro*
- Inflammasome inhibition with MCC950 reduces misfolded α-synuclein, neuronal loss and protects against motor deficits in the Parkinson PFF disease model

NLRP3 and NEK7 facilitate mast cell degranulation



Adapted from Abraham et al. Research Square 2023

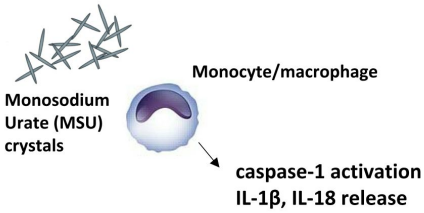
Ca^{2+}-triggered and NEK7-mediated dimerization of NLRP3 is an early regulatory signal leading to granulosome formation and mast cell degranulation

NEK7 MGDs Inhibit NLRP3 Activation by Monosodium Urate

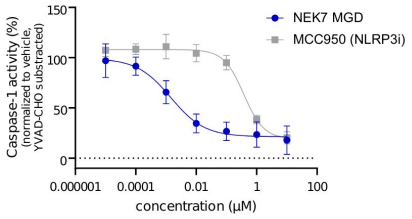
Gout is a high priority indication

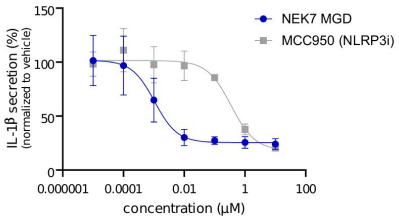
US prevalence
~**9.2 M** and increasing

- Strong link to NLRP3 biology
- Unwanted side effects and contra-indications with SOC agents (e.g. NSAIDs, colchicine)
- Large numbers of patients with poorly controlled disease
- Need for rapid relief (acute) and fewer flares (chronic)



NEK7 degradation leads to potent inhibition of NLRP3 inflammasome activation by gout-relevant stimulus MSU

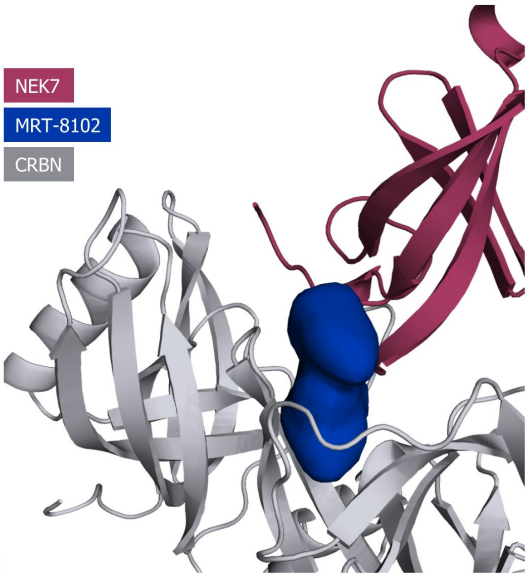




Human monocyte-derived macrophages
LPS + MSU stimulation
Pretreatment with molecular glue degrader (MGD) or NLRP3 inhibitor (NLRP3i)

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

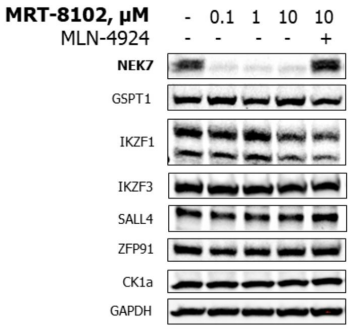
NEK7 Ternary Complex (Crystal Structure)



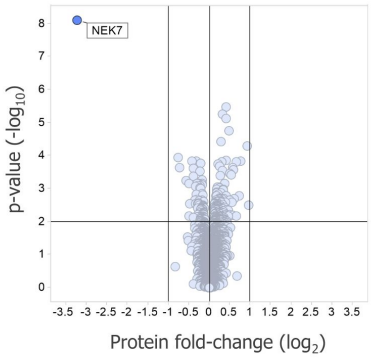
MGD Activity Profile	
CRBN Binding (HTRF, IC_{50})	0.2 µM
NEK7 Degradation (CAL51, DC_{50}/Dmax)	10 nM / 89%
Selectivity (TMT proteomics)	Excellent selectivity profile in different cell lines
Physicochemical Properties	
LogD	1.47
MW	<450
Thermodynamic Solubility	166 µM
ADMET Profile	
Oral Bioavailability	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 induces selective NEK7 degradation



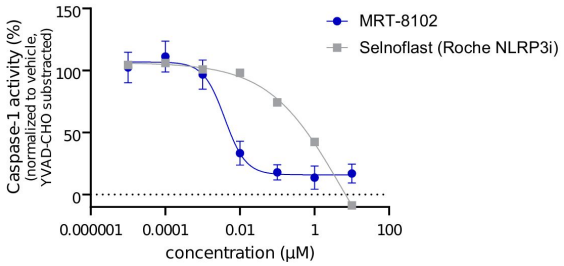
6 hr treatment in Kelly (SALL4) or MM.1S
2 µM MLN-4924, 30 min pre-treatment



MRT-8102 at 10 µM in hPBMC, 24h

Additional cell lines screened:
U937, Kelly and MM1S

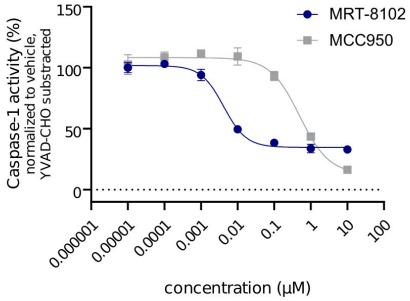
MRT-8102 potently suppresses inflammasome activation in primary human macrophages



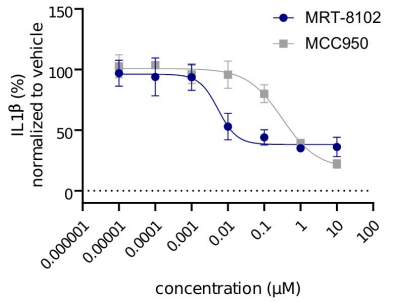
Human monocyte-derived macrophage (hMDM) assay
LPS + MSU stimulation; pre-treatment with MGD/NLRP3i
Similar reduction in IL-1β

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

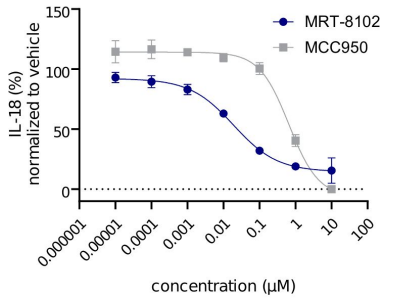
MRT-8102 inhibits caspase-1 activity in hMDMs after stimulation



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



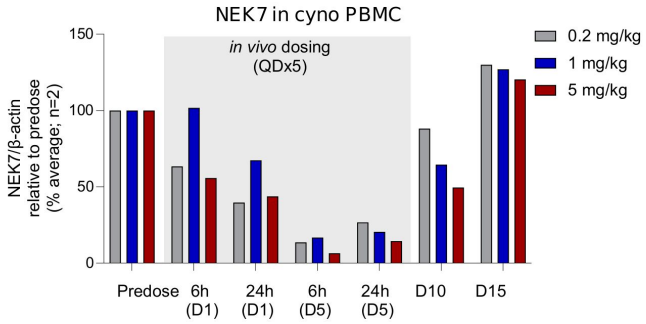
MRT-8102 inhibits IL-18 secretion by hMDMs after stimulation



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

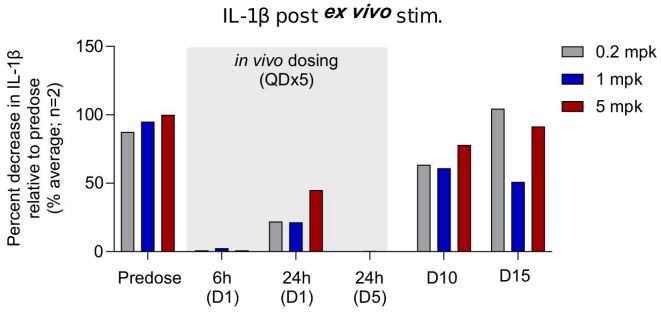
Suppression of *Ex Vivo* Inflammasome Activation Following Degradation of NEK7 in Non-human Primates

MRT-8102 induces NEK7 degradation *in vivo*



No clinical observations reported

Lack of *ex vivo* activation of NLRP3 inflammasome following degradation of NEK7



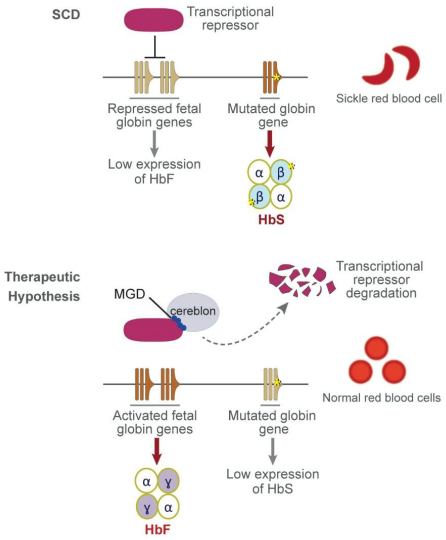
IL-1β in plasma after *ex vivo* stimulation with LPS+nigericin

Monte Rosa Therapeutics

Sickle Cell Disease Program

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

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



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

Clinical Opportunity: First-in-class degraders for

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

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

Monte Rosa Therapeutics

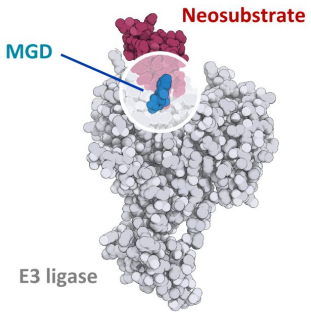
Our MGD Library

A rationally designed library as a starting point to tackle unprecedented neosubstrates

MGDs Reprogram the Ligase Surface

Remodeled MGD-CRBN surface enables selective engagement of neosubstrates

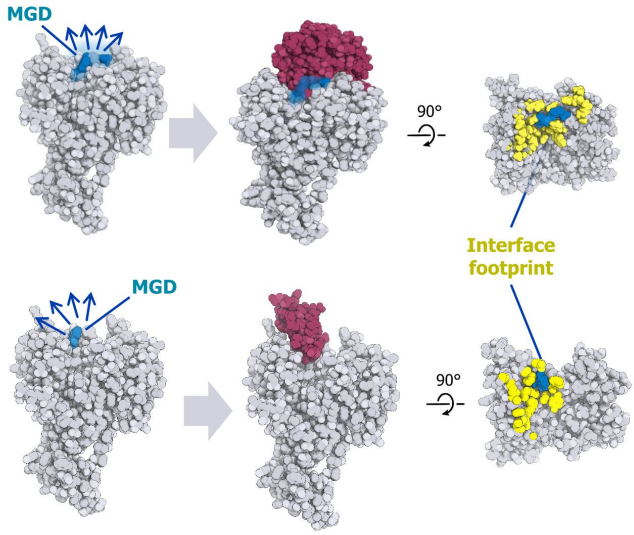
Multiple points of contact mediate formation of ternary complex



Effective ternary complex formation involves:

- MGD-ligase interactions
- MGD-neosubstrate interactions
- Ligase-neosubstrate interactions

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

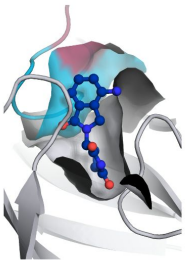


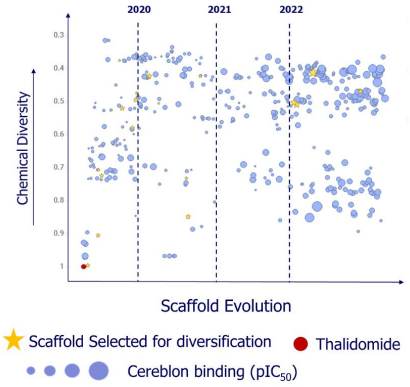
Create library diversity to multiply binding modes

Library Expansion Unlocks Novel Degron and Target Space

Ligase binding

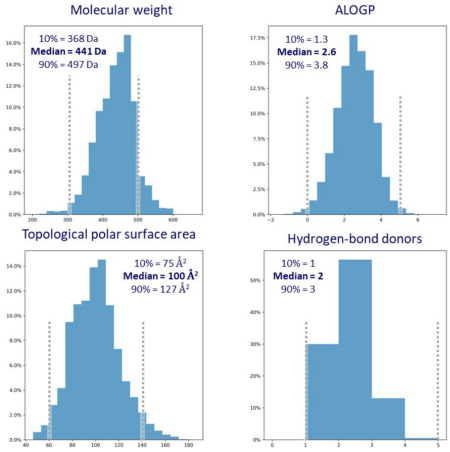
Structurally diverse scaffolds retain potent CRBN binding





Properties

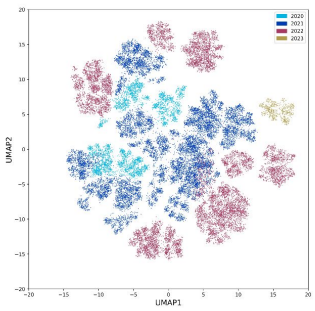
Well within drug-like property space



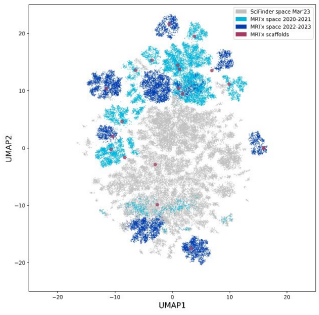
Teaching Cereblon New Tricks

Expanding the degradable proteome by AI-driven rational design of chemical space

Creating diverse and proprietary chemical space …



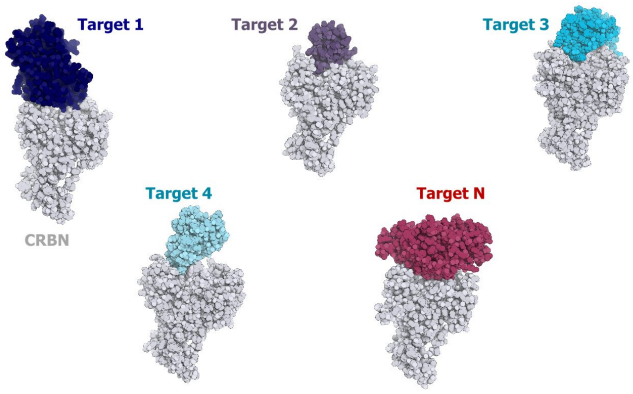
Clearly differentiated sub-libraries



that are clearly distinct from other's libraries

External space = SciFinder search based on published compounds (40K) containing glutarimide and MW < 500. The external space may contain PROTAC-like compounds, intermediates, and MolGlue-like compounds, among others. Internal space comprises Diversity Library, containing glutarimide and MW < 500.

… unlocks a large and unique targetable space



G-loop plus nine novel and unique binding modes increase degradable target space

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
NOVARTIS

Owen Wallace, Ph.D.
President of Research and Preclinical Development

Fulcrum Therapeutics
NOVARTIS

Sharon Townson, Ph.D.
Chief Technology Officer

KYMERA
Warp Drive Bio

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

agenus
BIONTECH

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

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

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

Lilly
Boehringer Ingelheim

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

Momenta
FISH

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

abbvie
Lilly

Jennifer Champoux
Chief People & Operations Officer

H3
NOVARTIS


Thank You
Monte Rosa
Therapeutics