From Serendipity to Rational Design

Taking Molecular Glue Degraders to New Heights | October 2023

Monte Rosa Therapeutics

Forward-Looking Statements

These materials include express and implied "forward-looking statements," including forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward looking statements include all statements that are not historical facts, and in some cases, can be identified by terms such as "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "potential," "continue," "ongoing," or the negative of these terms, or other comparable terminology intended to identify statements about the future. Forward-looking statements contained in herein include, but are not limited to, statements about our product development activities, including our expectations around the potential of molecular glue degraders ("MGDs"), the potential of our herein detailed pipeline and library of MGDs, including our MGDs for NEK7, CDK2, SCD targets, and our early stage undisclosed MGDs, our expectations for our collaboration with Roche, including the discovery and development of MGDs therefrom, 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, the nature and our expectations for our rationally-designed library of MGDs, including our ability to continue its expansion, and its ability to reprogram ligases surfaces, unlock novel degrons and target space, and the strength of our financial position, including our estimates of cash runway, among others. By their nature, these statements are subject to numerous risks and uncertainties, as well as those risks and uncertainties set forth in our Annual Report on Form 10-K for the fourth quarter and full year ended December 31, 2022, filed, with the US Securities and Exchange Commission on March 16, 2023, and any subsequent filings, that could cause actual results, performance or achievement to differ materially and adversely from those anticipated or implied in the statements. You should not rely upon forward looking statements as predictions of future events. Although our management believes that the expectations reflected in our statements are reasonable, we cannot guarantee that the future results, performance or events and circumstances described in the forward-looking statements will be achieved or occur. Recipients are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date such statements are made and should not be construed as statements of fact. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, any future presentations or otherwise, except as required by applicable law. Certain information contained in these materials and any statements made orally during any presentation of these materials that relate to the materials or are based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party studies, publications, surveys and other data to be reliable as of the date of these materials, we have not independently verified, and make no representations as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. 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Monte Rosa Therapeutics - Highlights

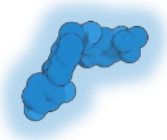
Taking molecular glue degraders (MGDs) to new heights

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

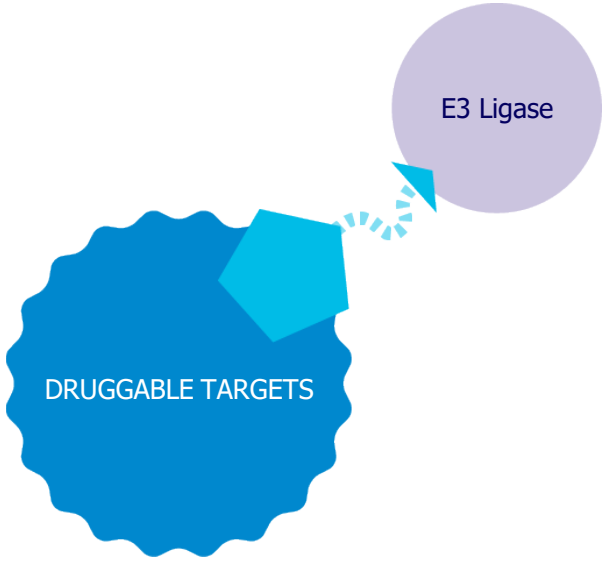
Molecular Glue Degraders (MGDs) - Drugging The Undruggable

Expanding target space, fostering a new generation of drugs

INHIBITOR

Drugging
the Druggable

PROTAC



Redrugging
the Druggable

MGDs

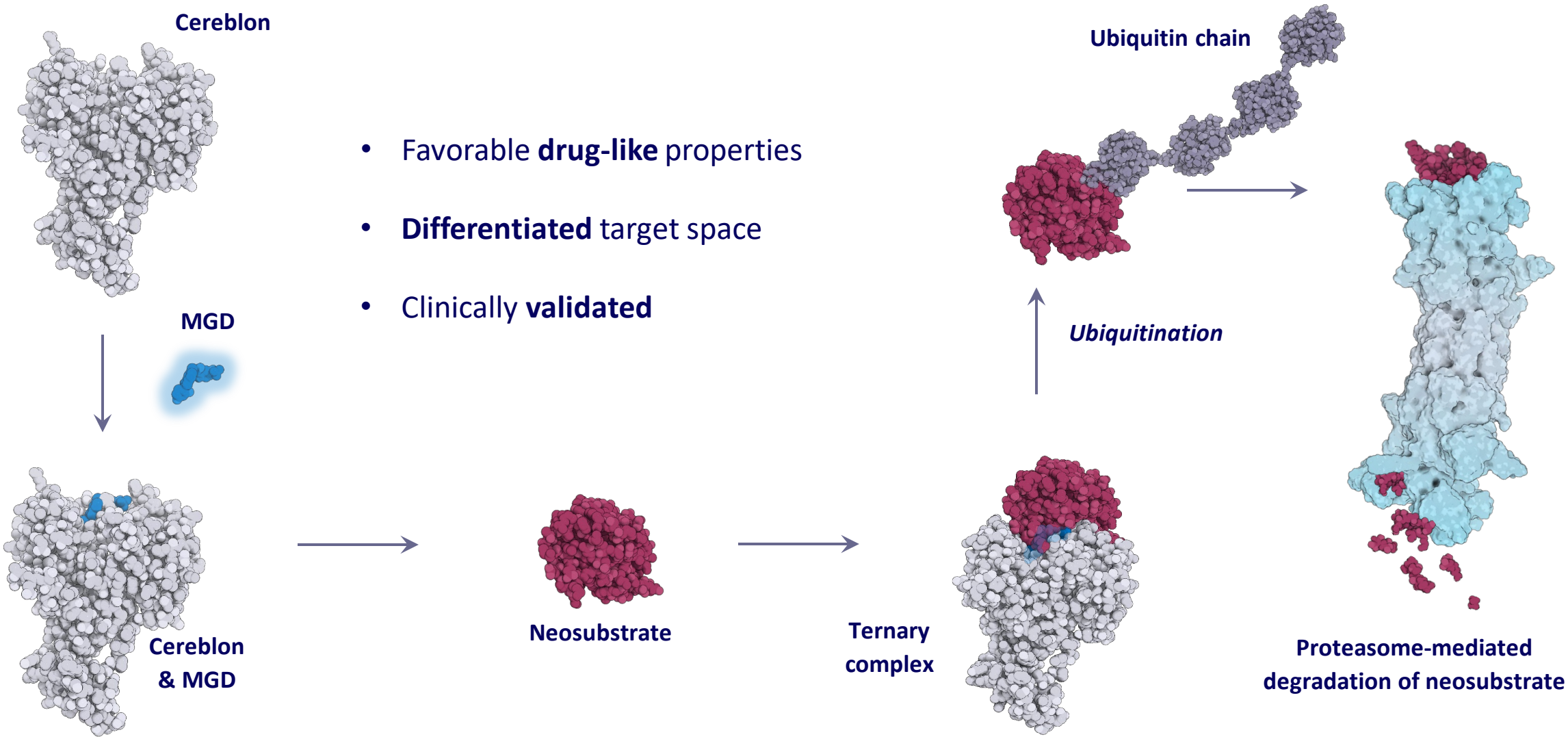
Drugging
the Undruggable

Expanding the Degradable Proteome

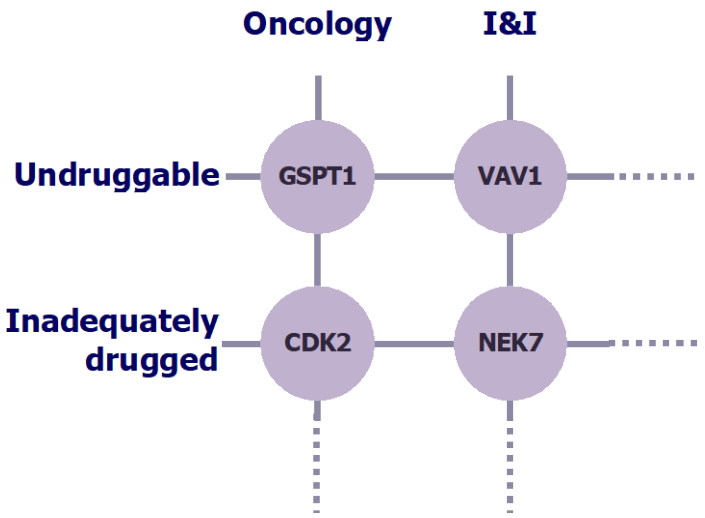
Target Space

Molecular Glue Degraders are a Clinically Validated Modality

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

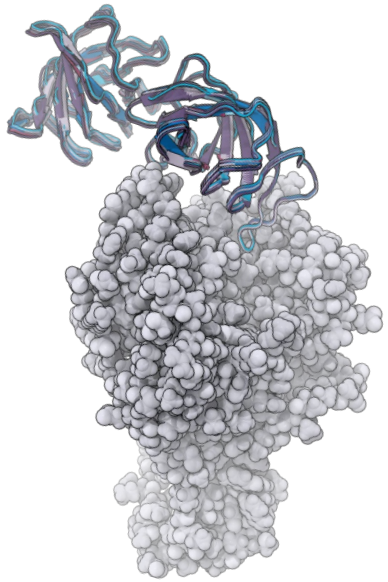


Our Rationally Designed MGDs Selectively Target a Differentiated Target Space Across Protein Domains and Diseases



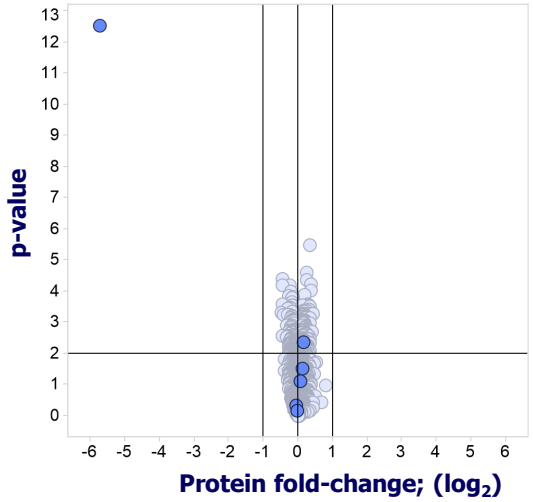
Targets

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

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Portfolio

Leveraging a Leading Drug Discovery Platform

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

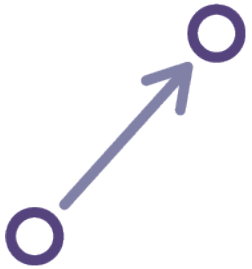
Monte Rosa's High-Value Proprietary Pipeline

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

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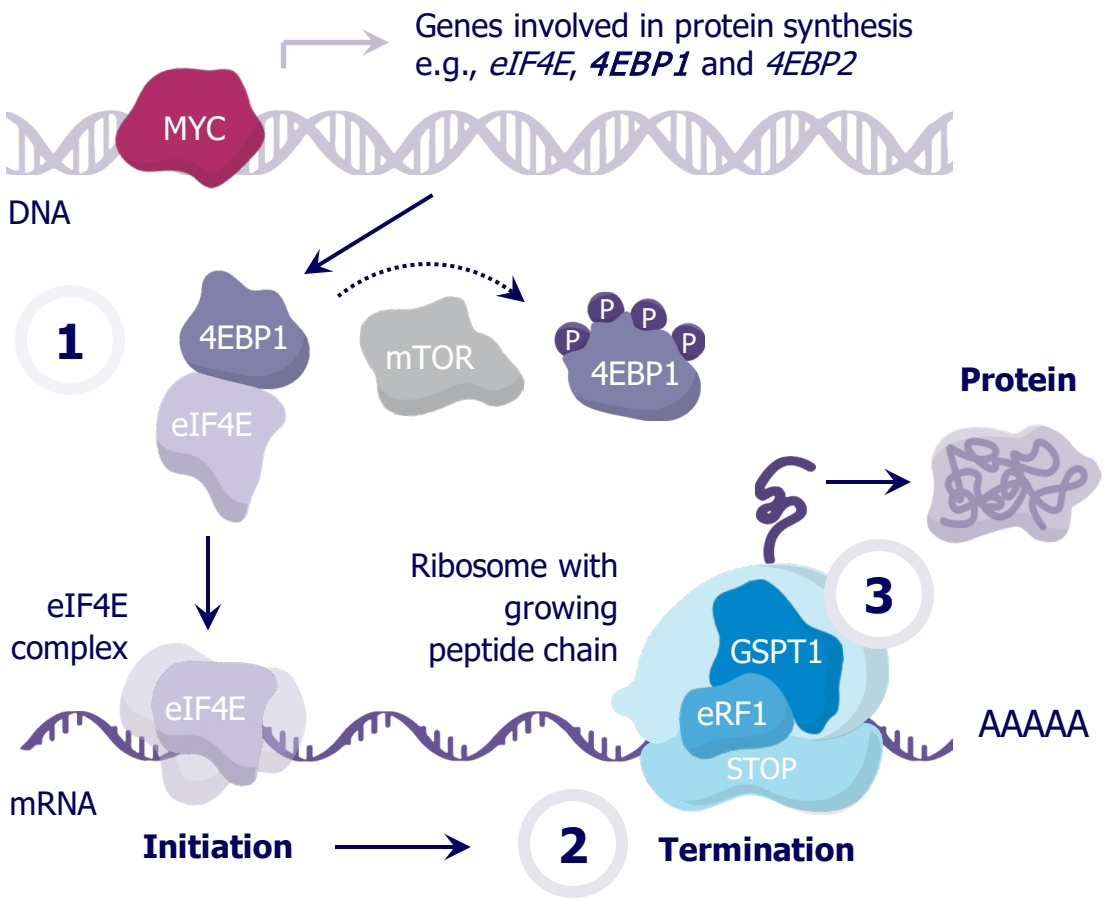
GSPT1 program

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**

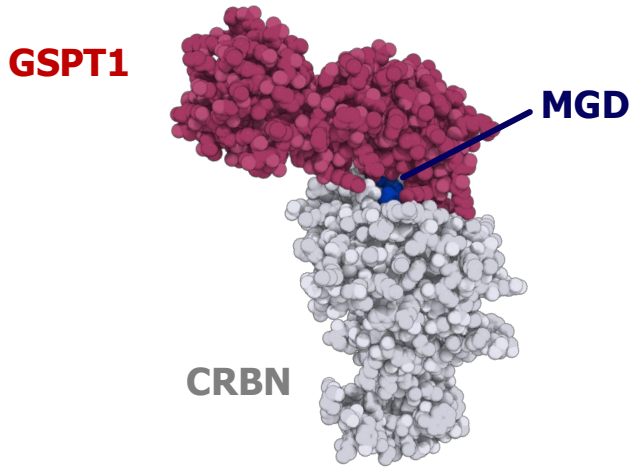
3

Therapeutic vulnerability

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

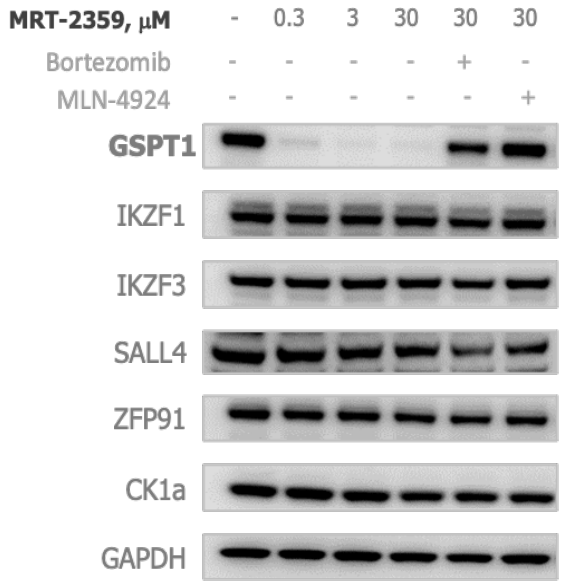
MRT-2359 is a Potent and Selective GSPT1 Degrader

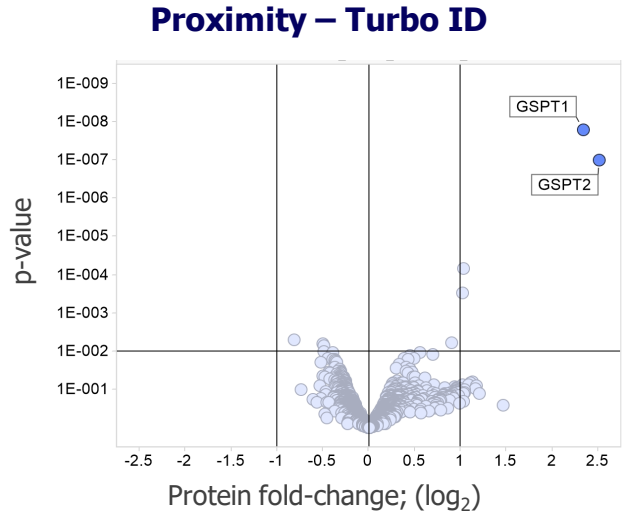
MRT-2359 is a potent GSPT1 degrader



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

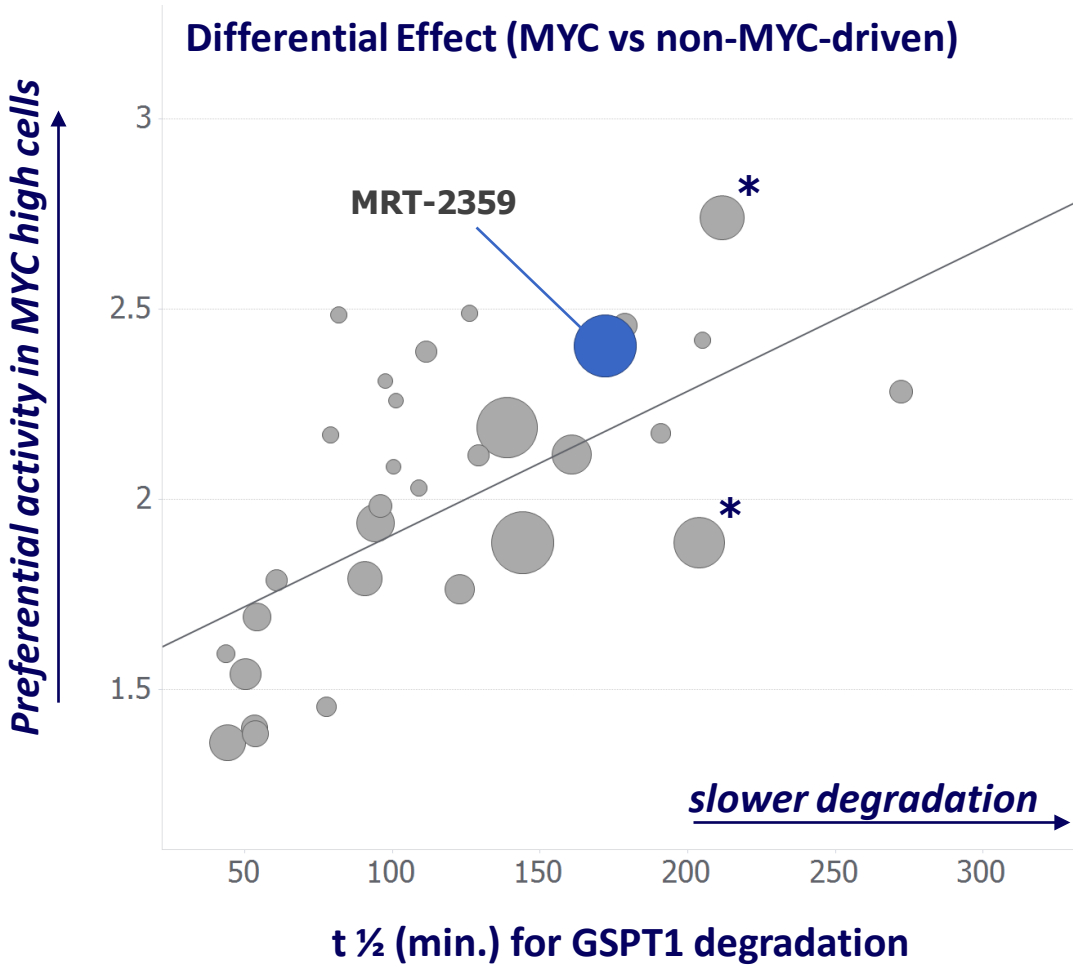
MRT-2359 induces selective GSPT1 degradation and has a favorable ADME/DMPK profile





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

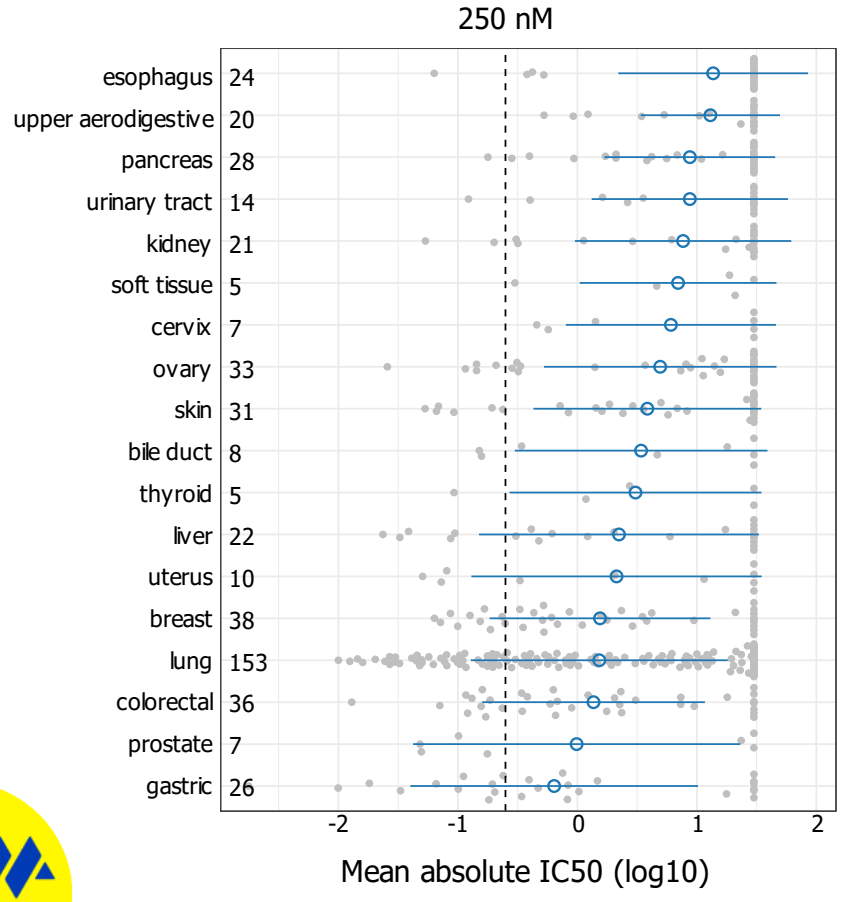


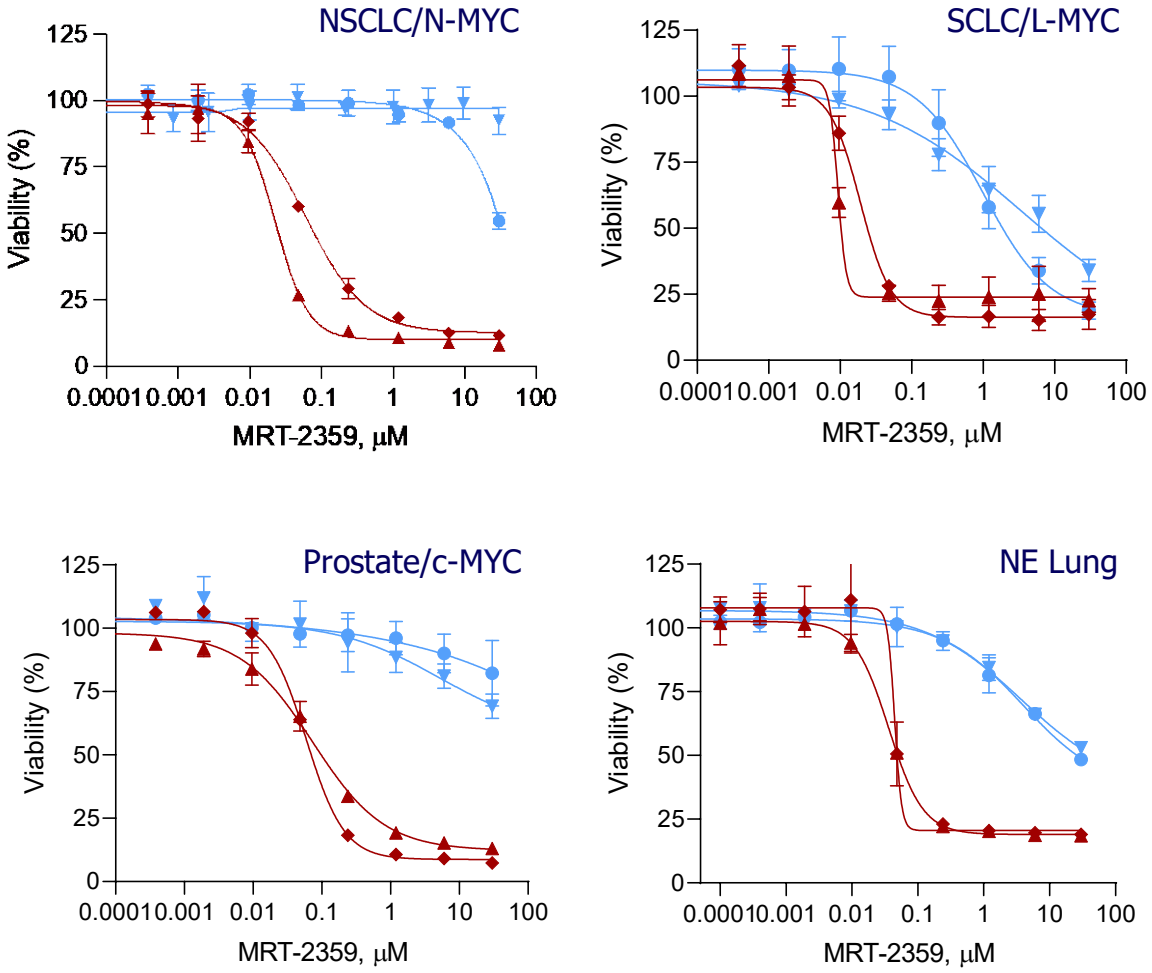
- Kinetic measurements of degradation reveal **novel parameter for optimization**
- GSPT1 degradation **kinetics are linked to its MoA**
- MRT-2359 achieves **a high preferential effect** (2.4 U) in high-MYC NSCLC
- MRT-2359 has been rationally designed to be in the ADMET sweet-spot
- Several compounds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

*** Compounds with reactive metabolite flag**

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

Correlation to L- and N-MYC Expression

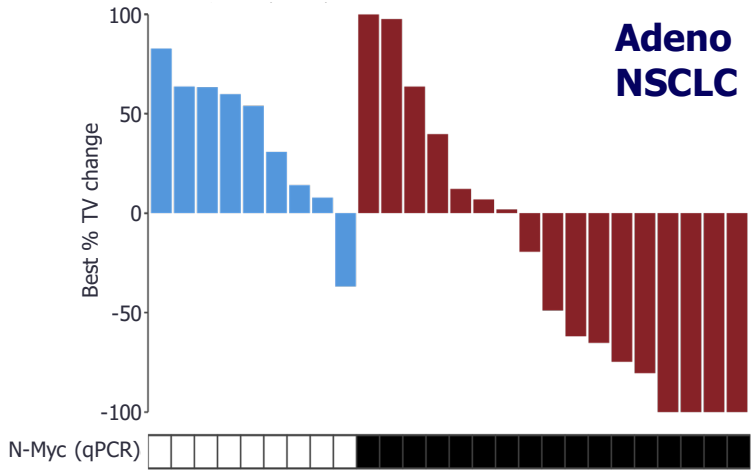


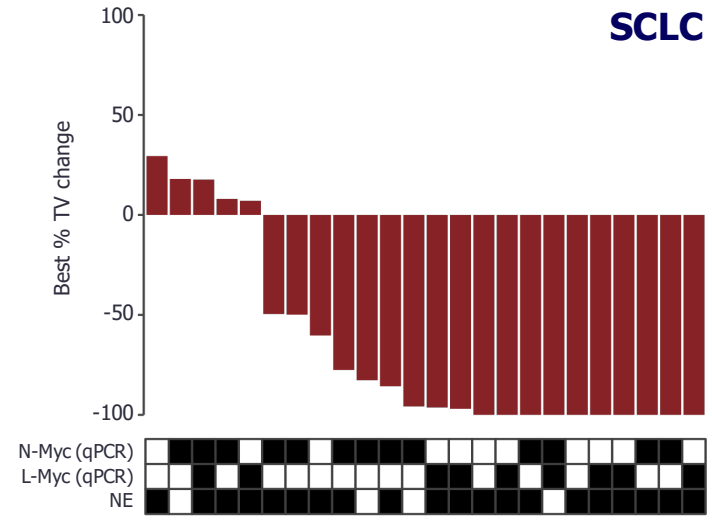


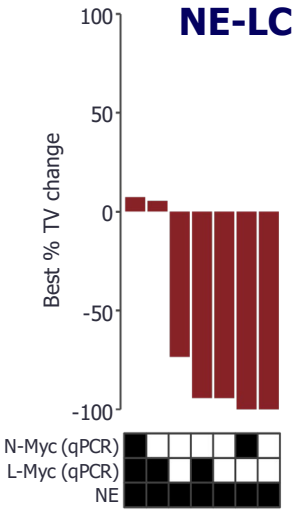
Activity of MRT-2359 in NSCLC, SCLC and Lung NE Patient-derived Xenograft Models

Collection of PDX models

MRT-2359
10 mg/kg QD

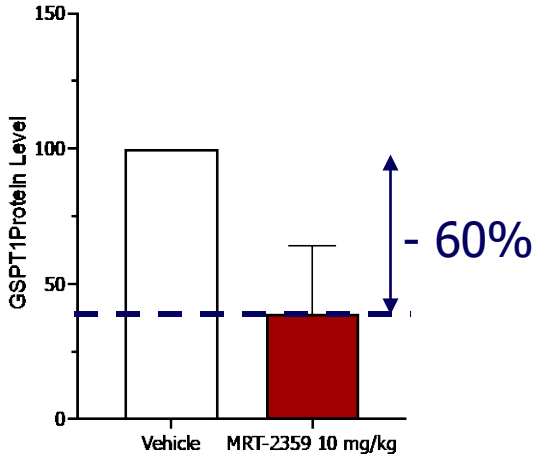






PD modulation

Targeted mass spectrometry
in 7 representative models

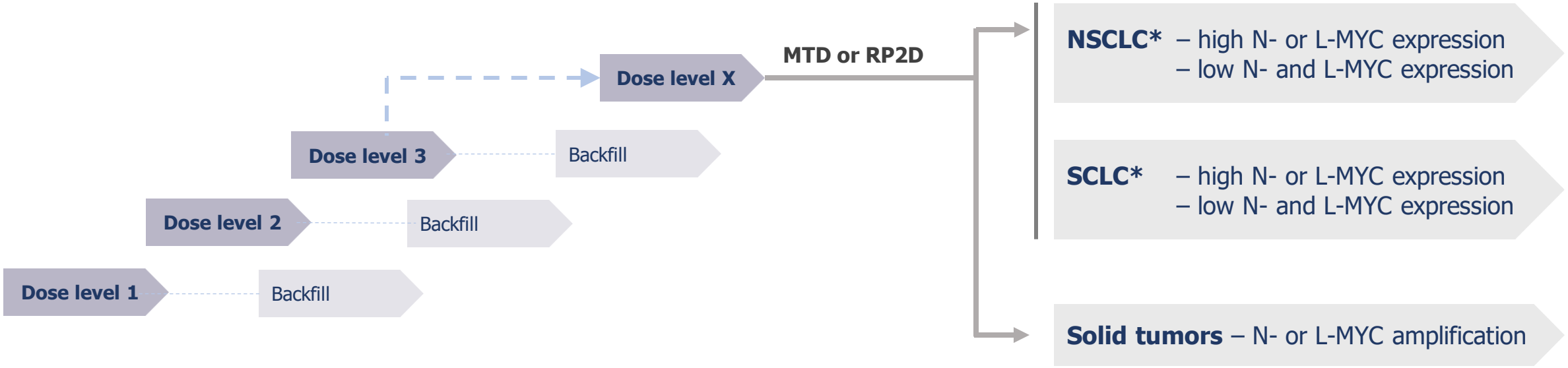


biomarker negative biomarker positive

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

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

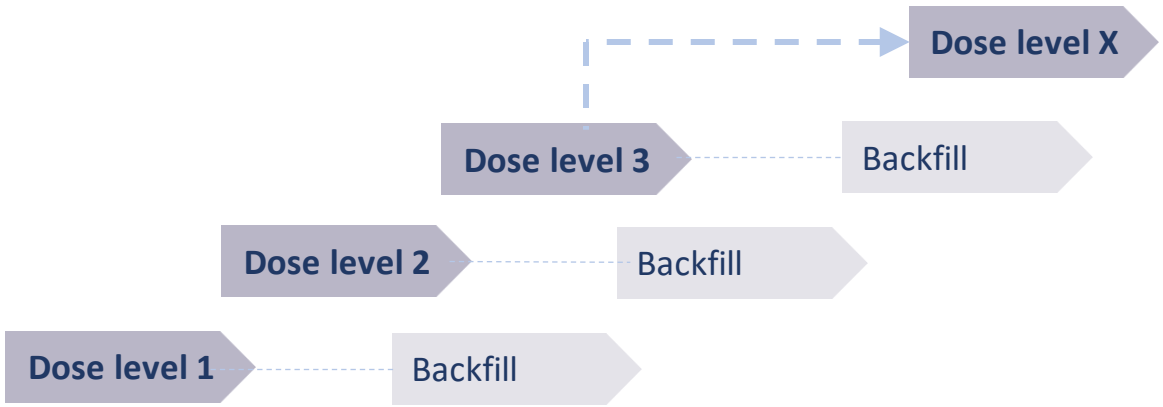
Patient dosing initiated in October 2022

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

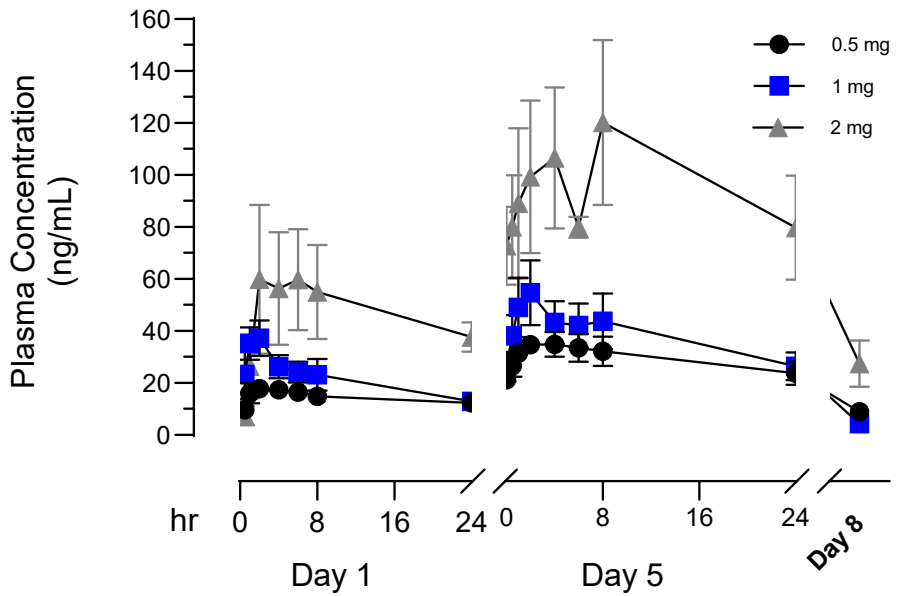
- ✓ Demonstrate dose dependent PK
- ✓ Demonstrate significant GSPT1 degradation at safe dose levels in PBMCs and tissue biopsies (60% based on preclinical data)
- ✓ Share potential preliminary efficacy signals in biomarker positive patients

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

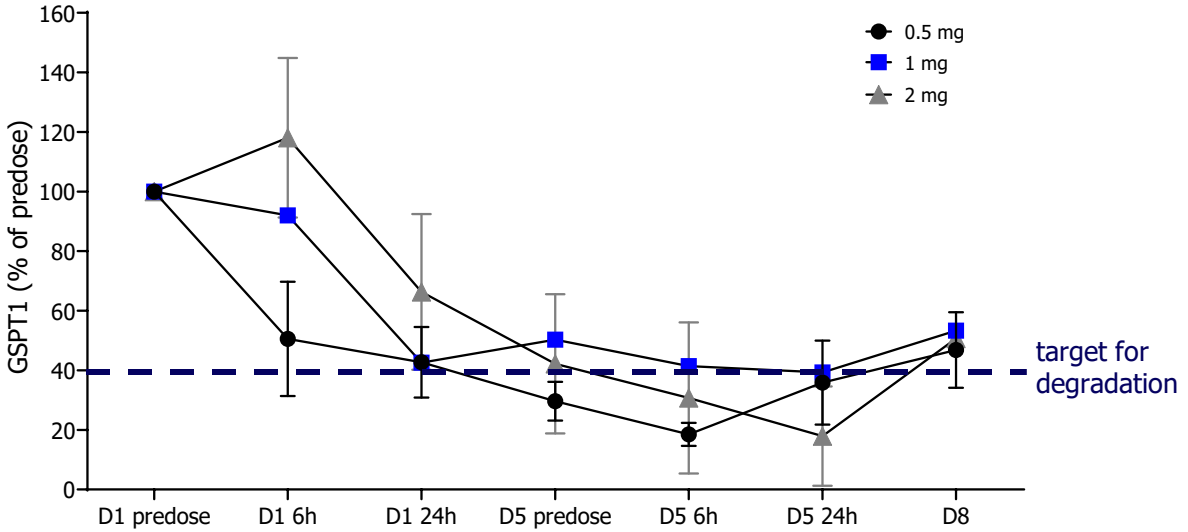
Summary of Pharmacokinetics and Pharmacodynamics

MRT-2359 displayed dose dependent plasma exposure



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

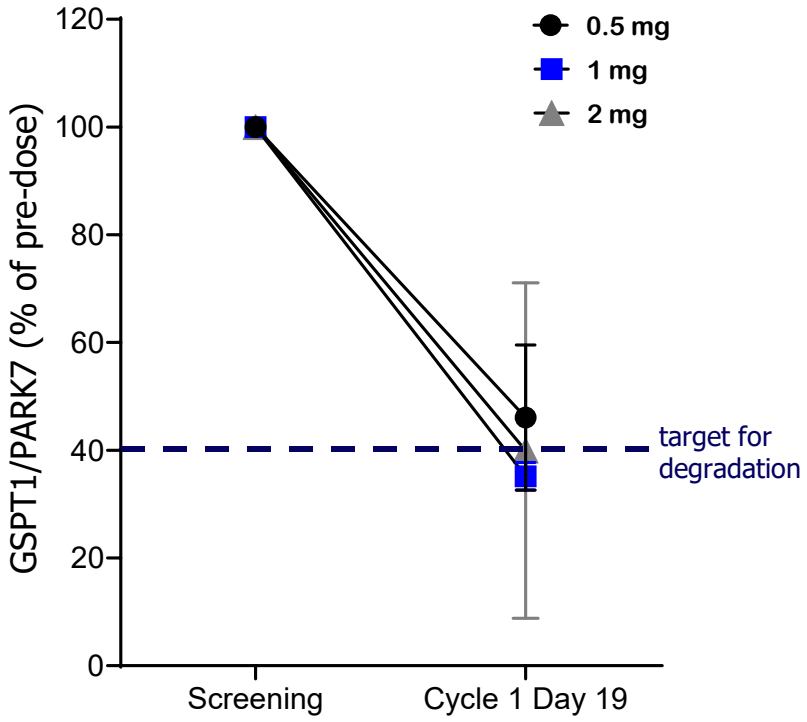
MRT-2359 displayed deep GSPT1 degradation in PBMCs at all dose levels



- 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

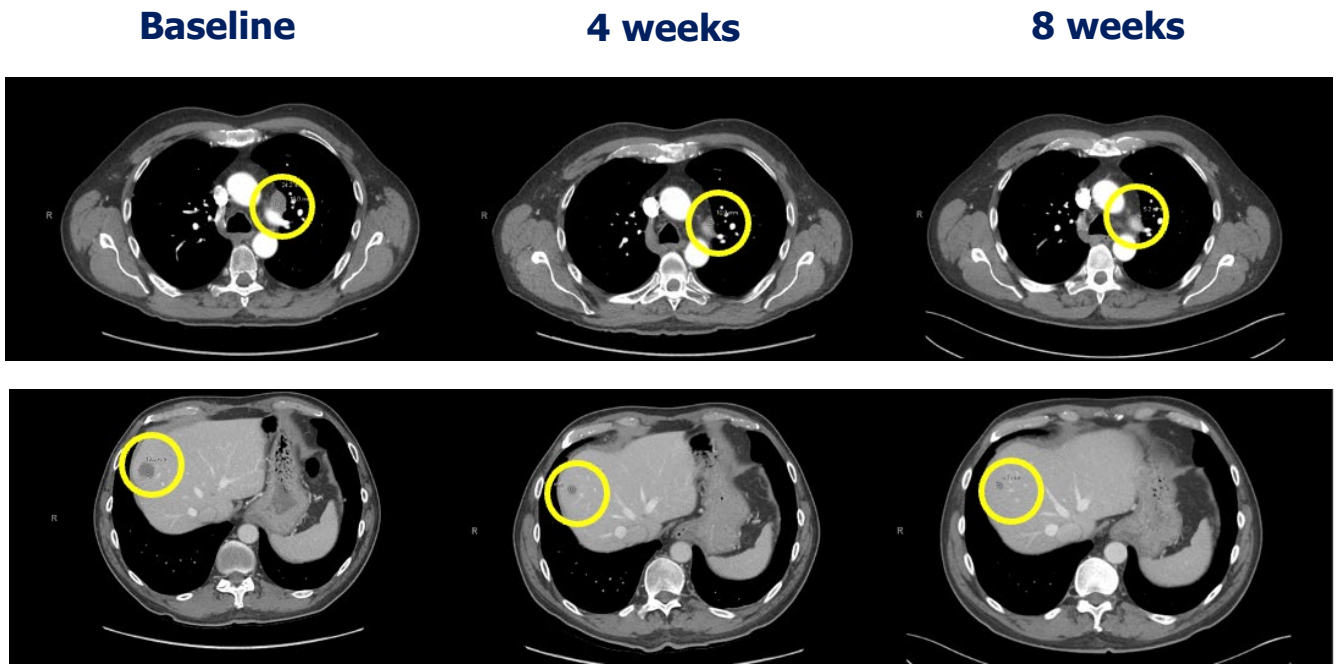
AE Preferred Term	0.5 mg (N=9)[##]		1 mg (N=7)[##]		2 mg (N=5) [##]		Overall (N=21)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Thrombocytopenia[###]	0	0	0	0	4 (80%)	3 (60%)[***]	4 (19%)	3 (14%)
Neutropenia[*]	0	0	0	0	2 (40%)	1 (20%)	2 (10%)	1 (5%)
Leukopenia	0	0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

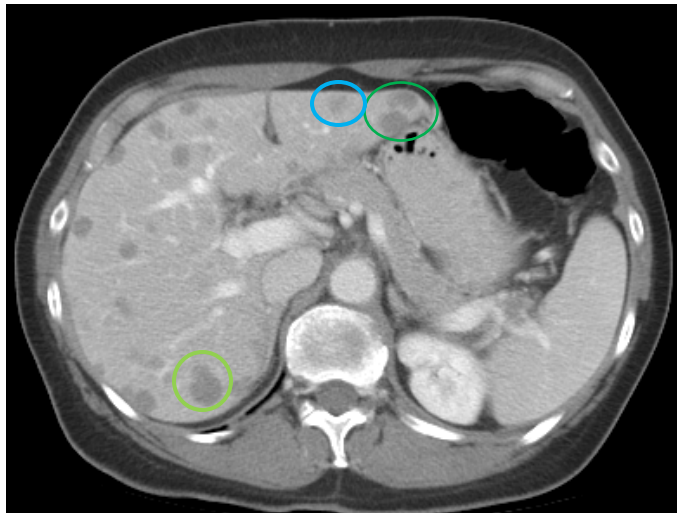
- High Grade (HG) neuroendocrine bladder cancer
- Baseline tumor biopsy demonstrated high N-MYC expression
- 4 prior lines of therapy including chemotherapy and pembrolizumab
- Patient initiated on 2 mg for first 5/9 regimen, then lowered to 1 mg and 0.5 mg and remains on therapy (> 3 month)
- CT scan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



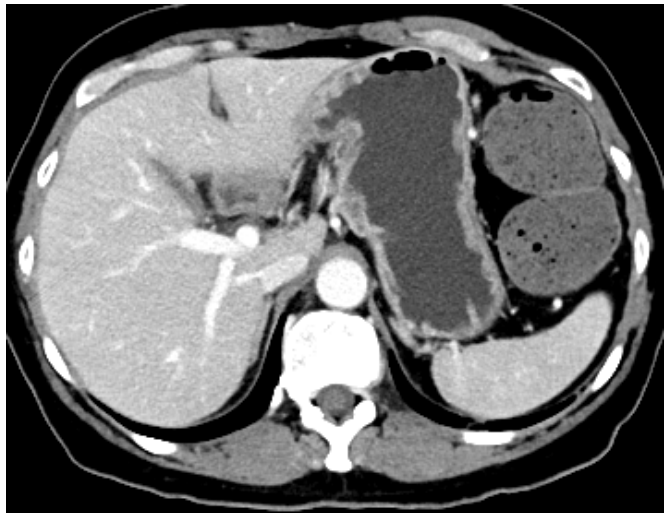
Unconfirmed PR in NSCLC with SCLC/NE Transformation

- 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

Baseline



3 weeks



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

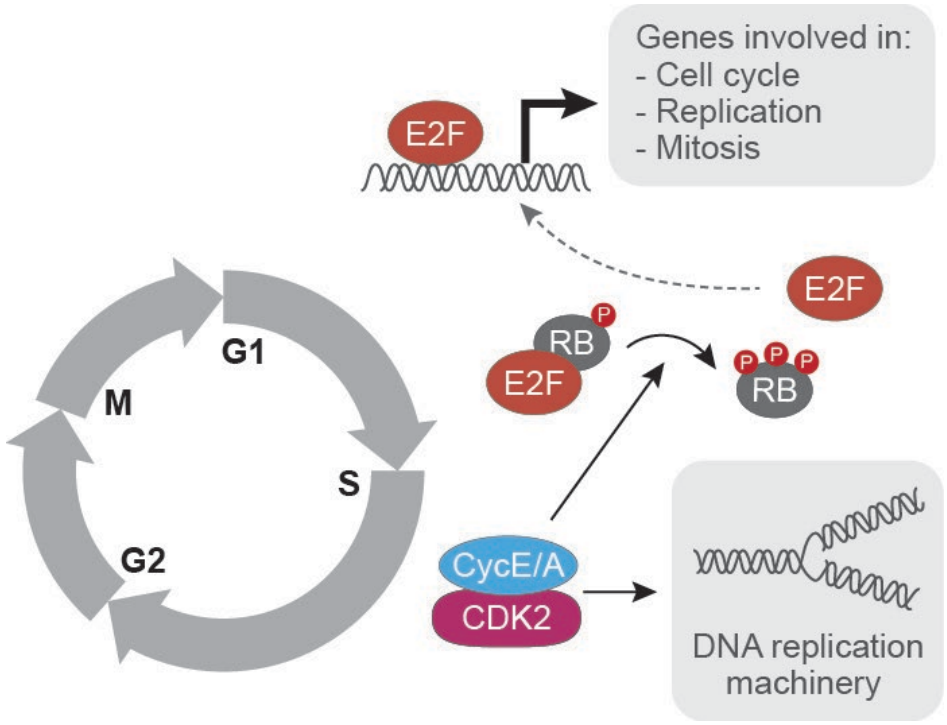
- Currently dosing 1.5 mg, expected to complete DLT observation period by end of October
- Based on favorable tox profile, Company initiating intermittent dosing regimen of 21 days on and 7 days off drug (21/7)

Monte Rosa Therapeutics

CDK2 Program

CDK2 as a Target for Selected Solid Tumors

CDK2 is one of the key regulators of the cell cycle



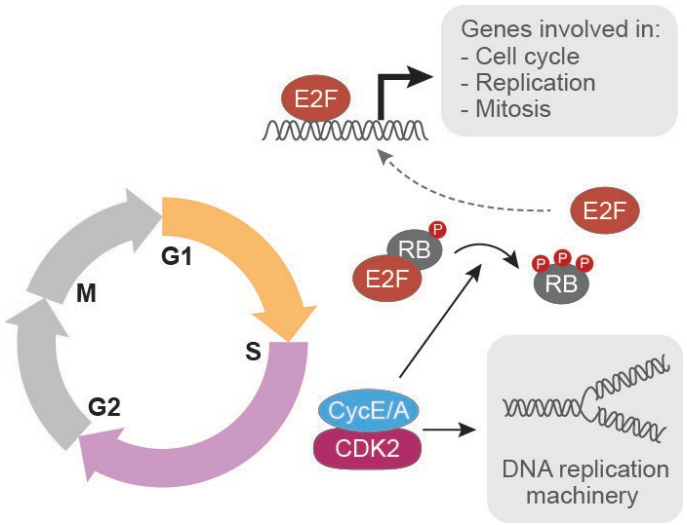
Therapeutic hypothesis: Tumors with CDK2 pathway activation by high CyclinE1/E2 expression

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)

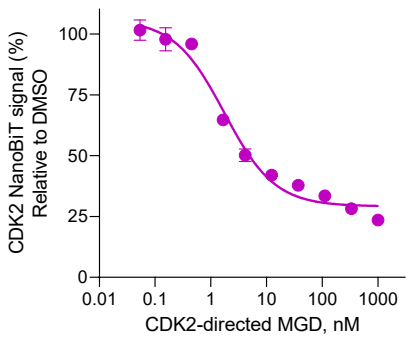
CDK2 Degradation Affects E2F Downstream Proteins and Inhibits Proliferation of CDK2-dependent Cancer Cells

CDK2 is one of the key regulators of the cell cycle

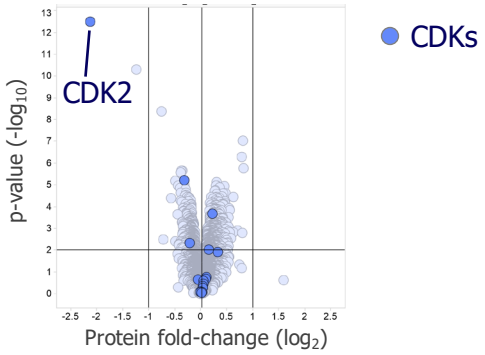


MGD-induced selective degradation of CDK2 results in reduction of E2F downstream proteins and inhibition of proliferation

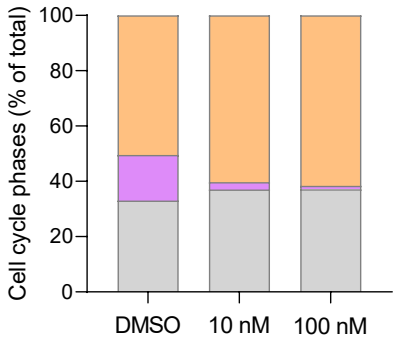
CDK2 - NanoBiT



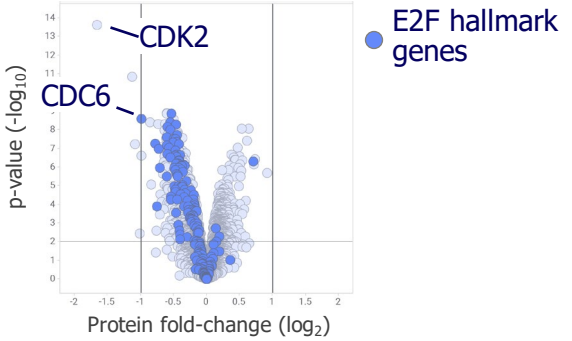
Proteomics



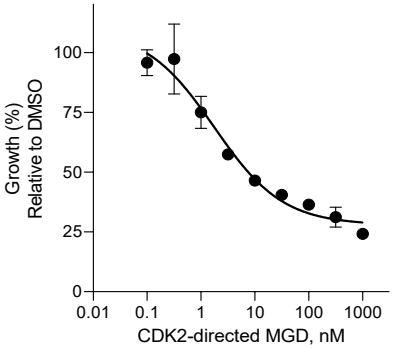
Cell cycle profile



E2F target proteins



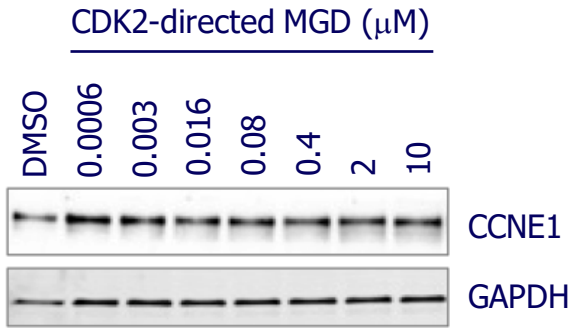
Proliferation



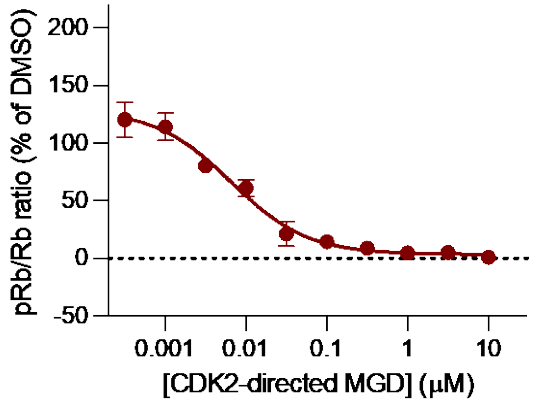
MDA-MB-157 - Cell cycle (48 hr), TMT Proteomics (24hr) and CyQuant (7d)

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

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

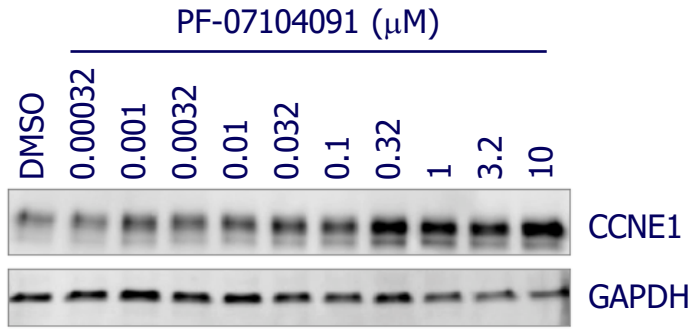


MDA-MB-157 cells, 24h

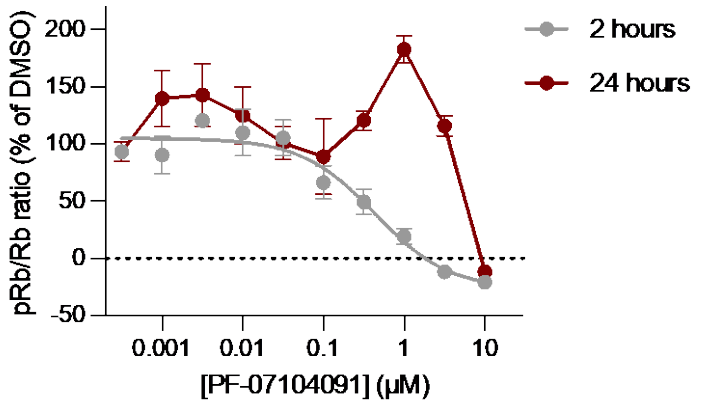


MDA-MB-157 cells, pRb (S780)/total Rb multiplex AlphaLISA, 24h

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

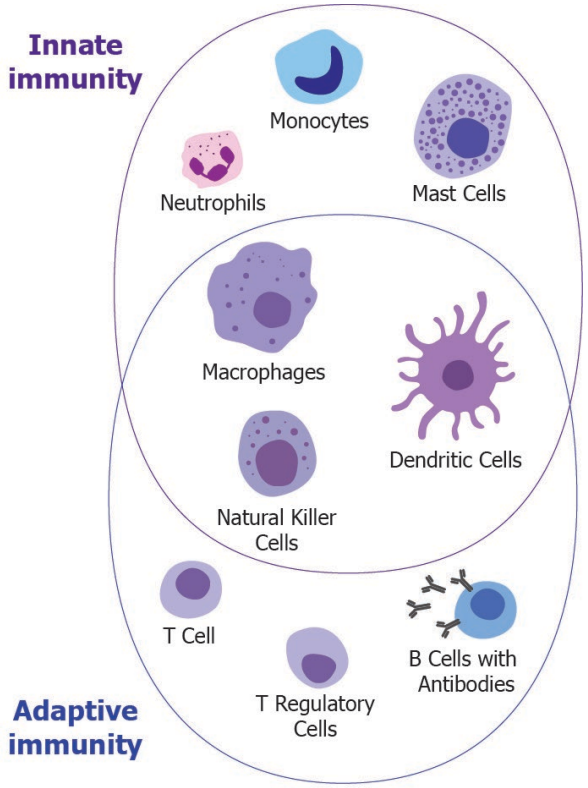
Inflammation and Immunology (I&I) Programs

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

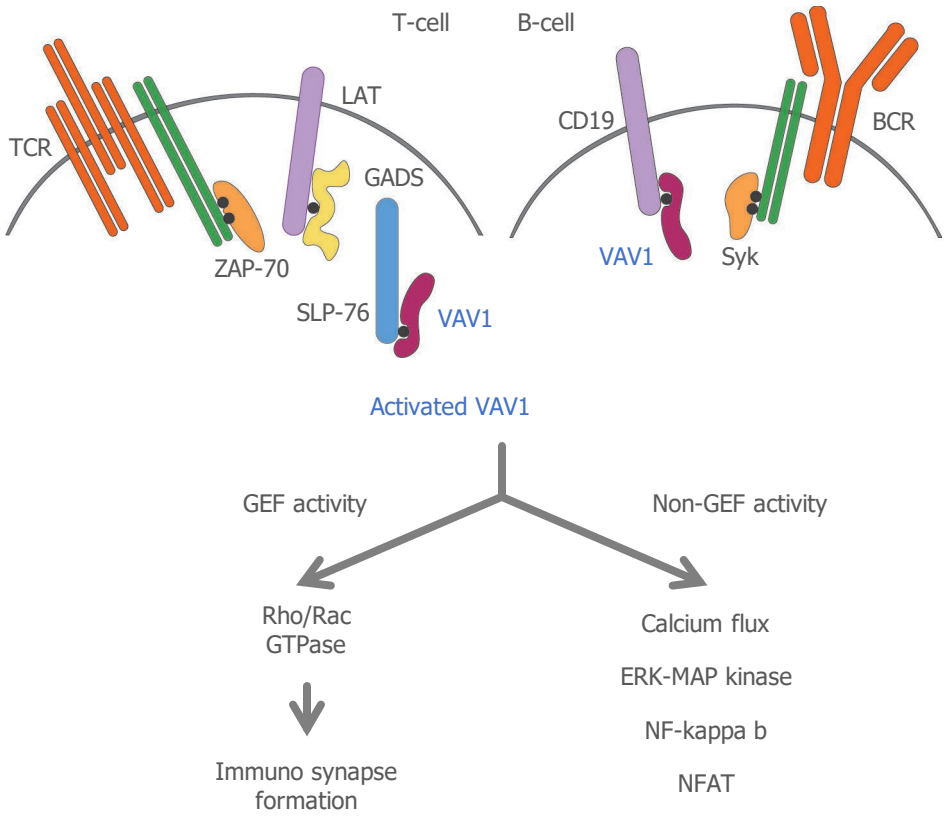
Additional indications

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:

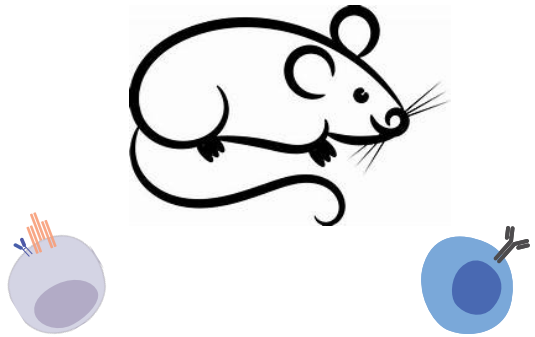
- Autoimmune disorders including rheumatoid arthritis (6.2M patients), multiple sclerosis (1.3M patients), myasthenia gravis (36K – 60K patients in US), and acute graft-versus-host disease (10K patients)

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

$VAV1^{-/-}$ mice



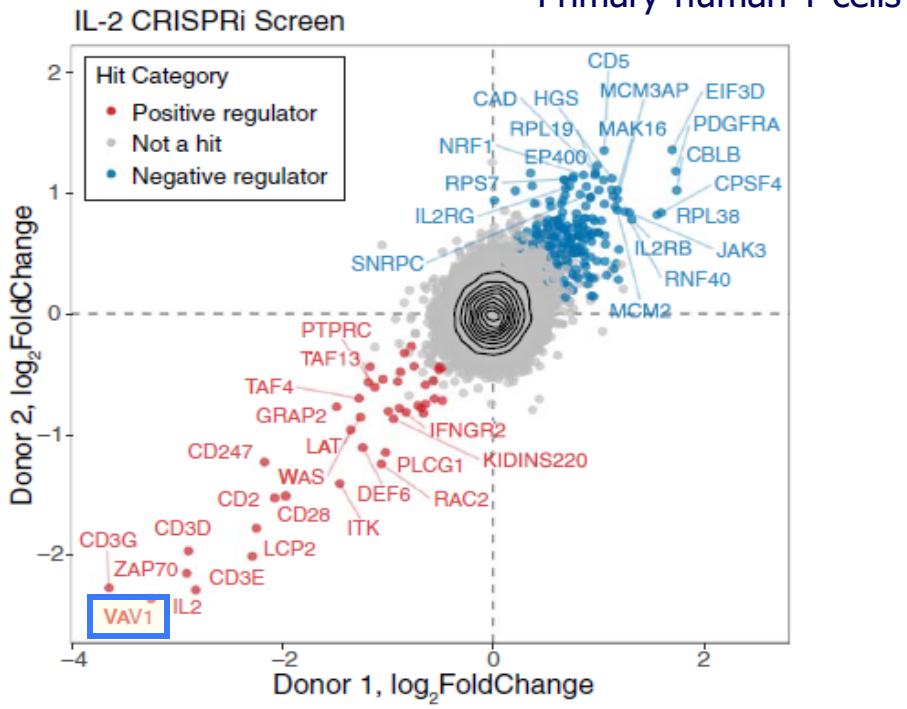
T-cell function **B-cell function**

- 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

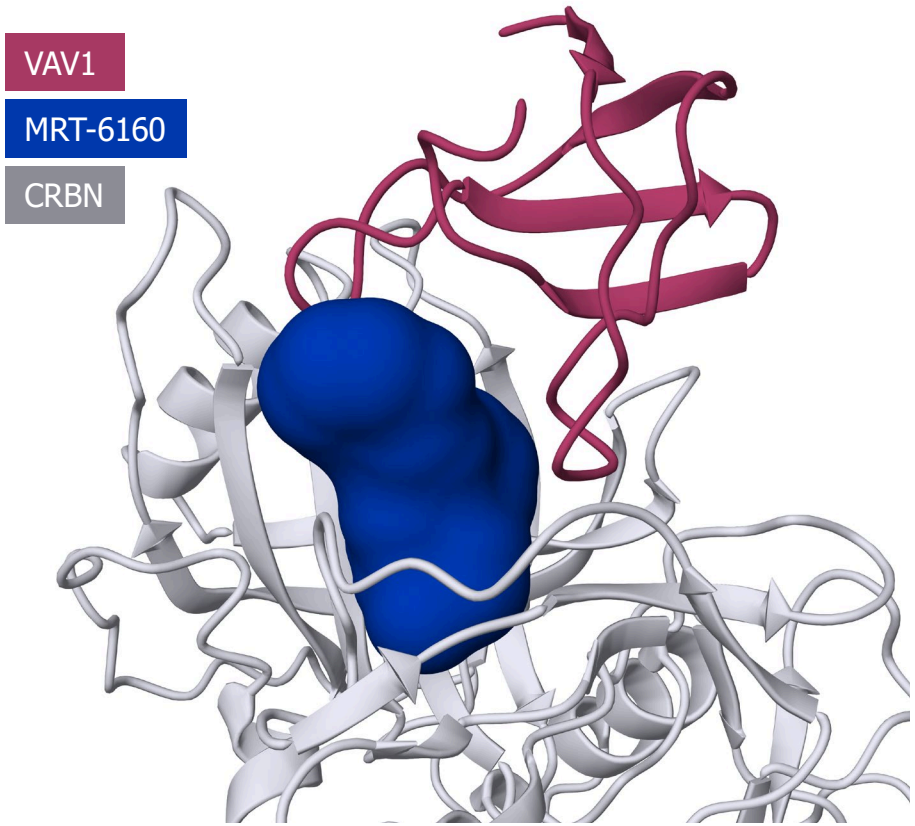
Primary human T cells



Schmidt et al., Science 2022

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

VAV1 ternary complex (Cryo-EM)

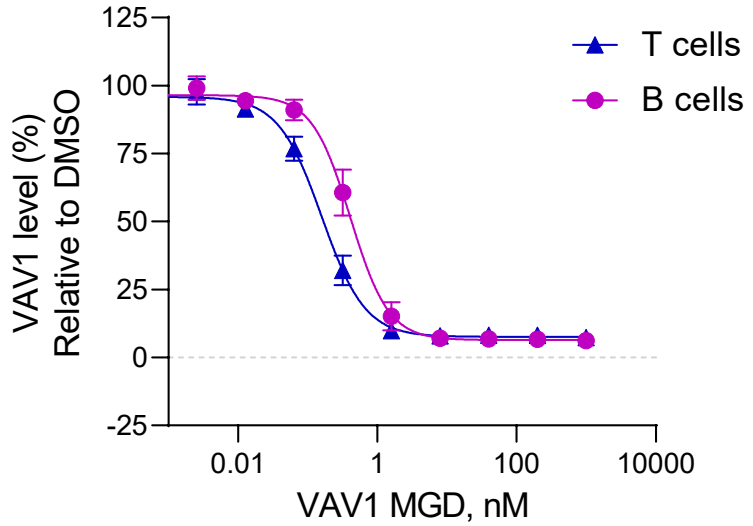


Cryo-EM structure of MRT-6160 in ternary complex with CRBN and VAV1

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

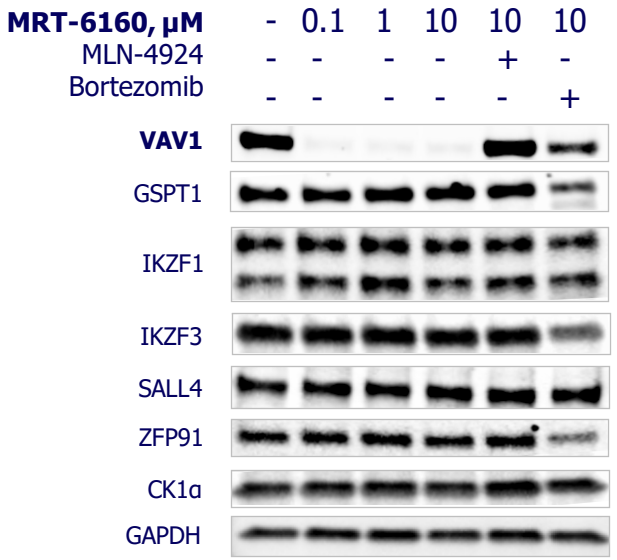
MRT-6160 is a Potent and Selective VAV1-directed MGD

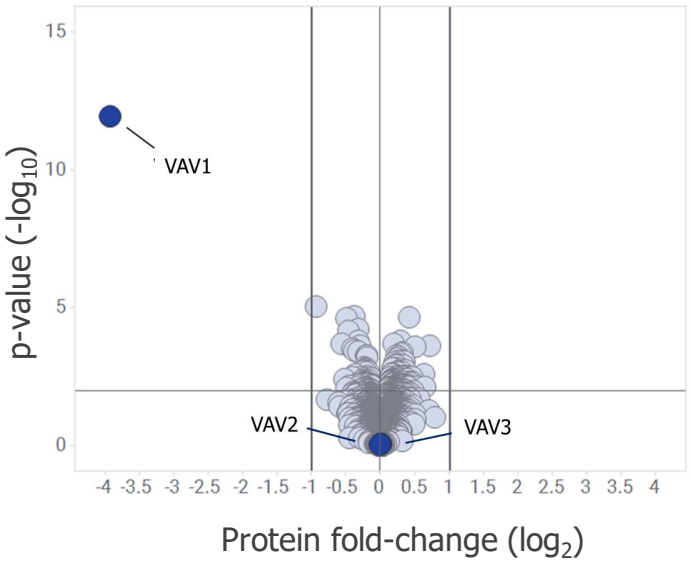
MRT-6160 is a potent VAV1-directed MGD



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

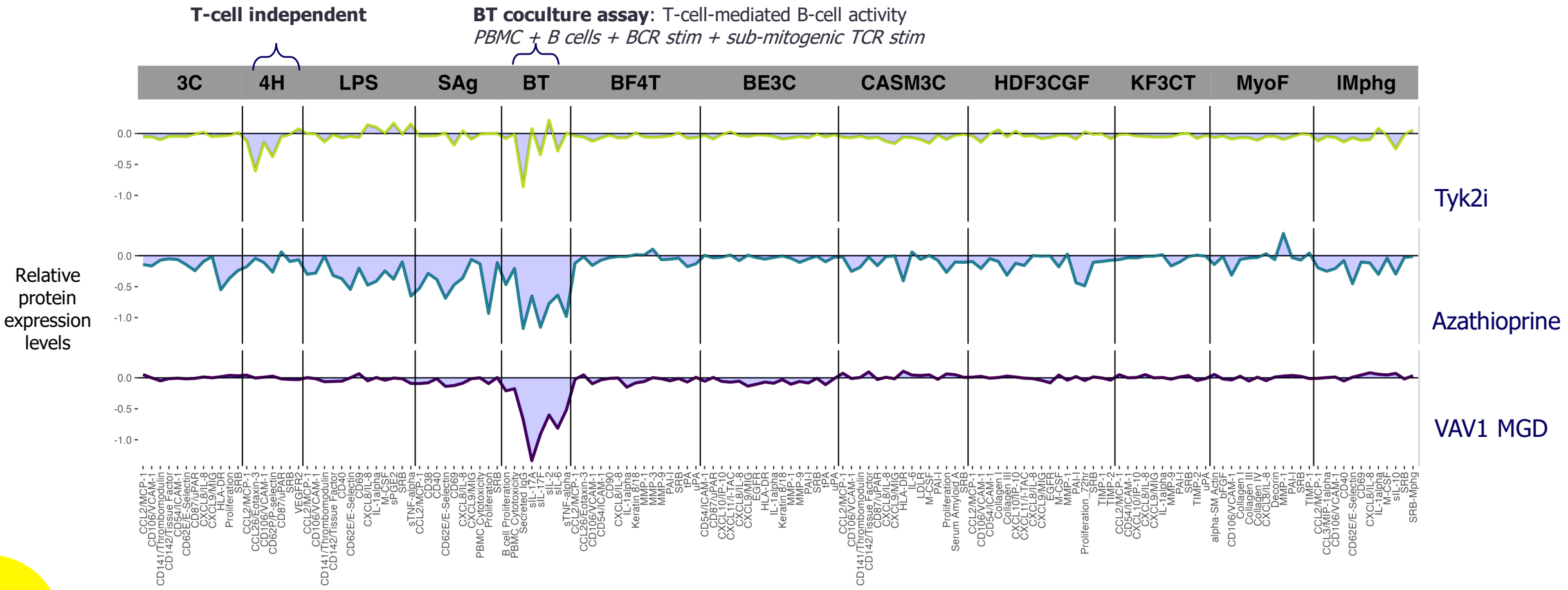
MRT-6160 induces selective VAV1 degradation and has a favorable ADME/DMPK profile





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

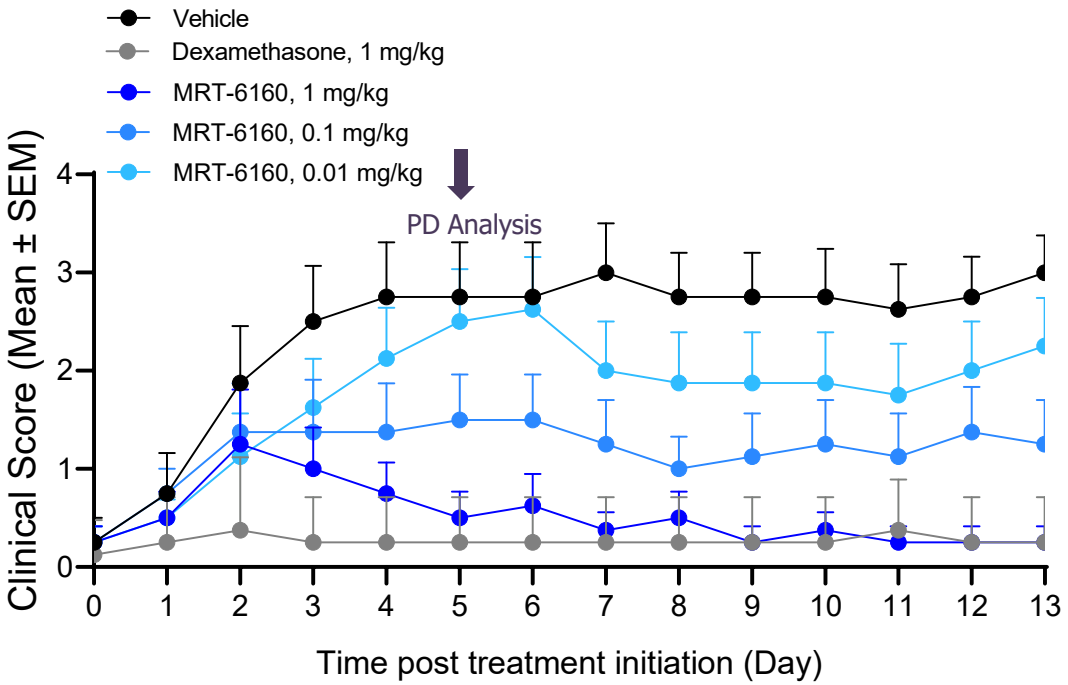
Azathioprine, 100 uM

VAV1 MGD, MRT-6160, 1000 nM

** Experiment performed by Eurofins*

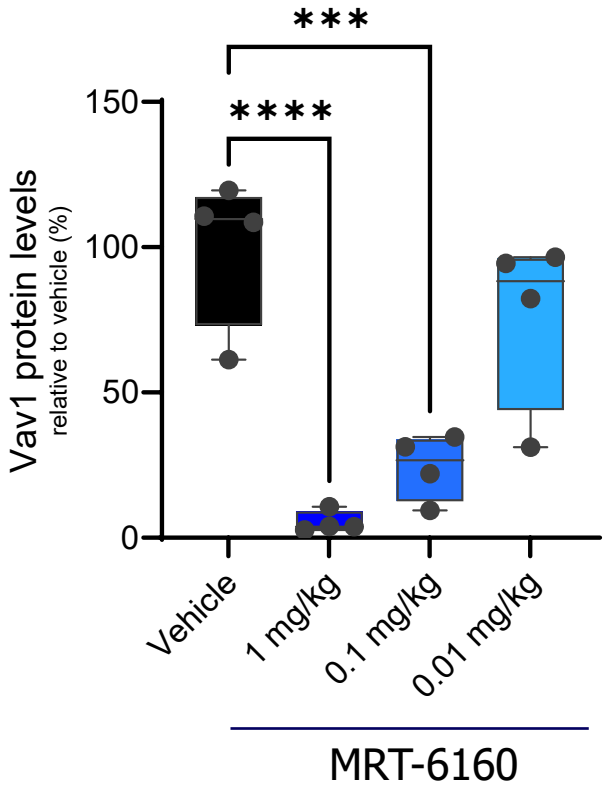
MRT-6160 Elicits Dose-Dependent Efficacy in T-cell-mediated Multiple Sclerosis Autoimmune Disease Model

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

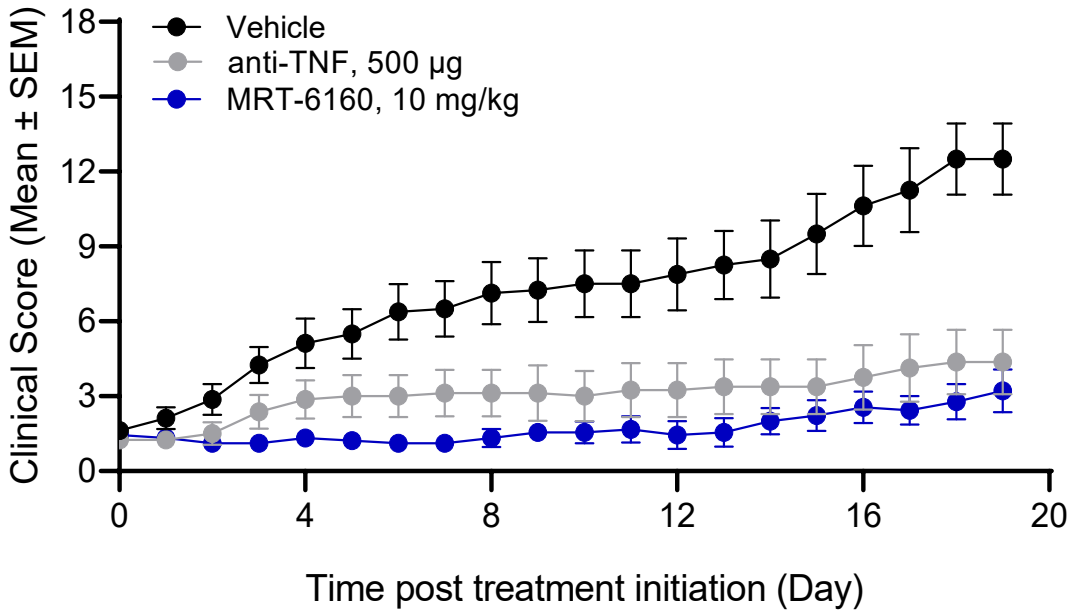
MRT-6160-mediated activity correlates with VAV1 levels



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

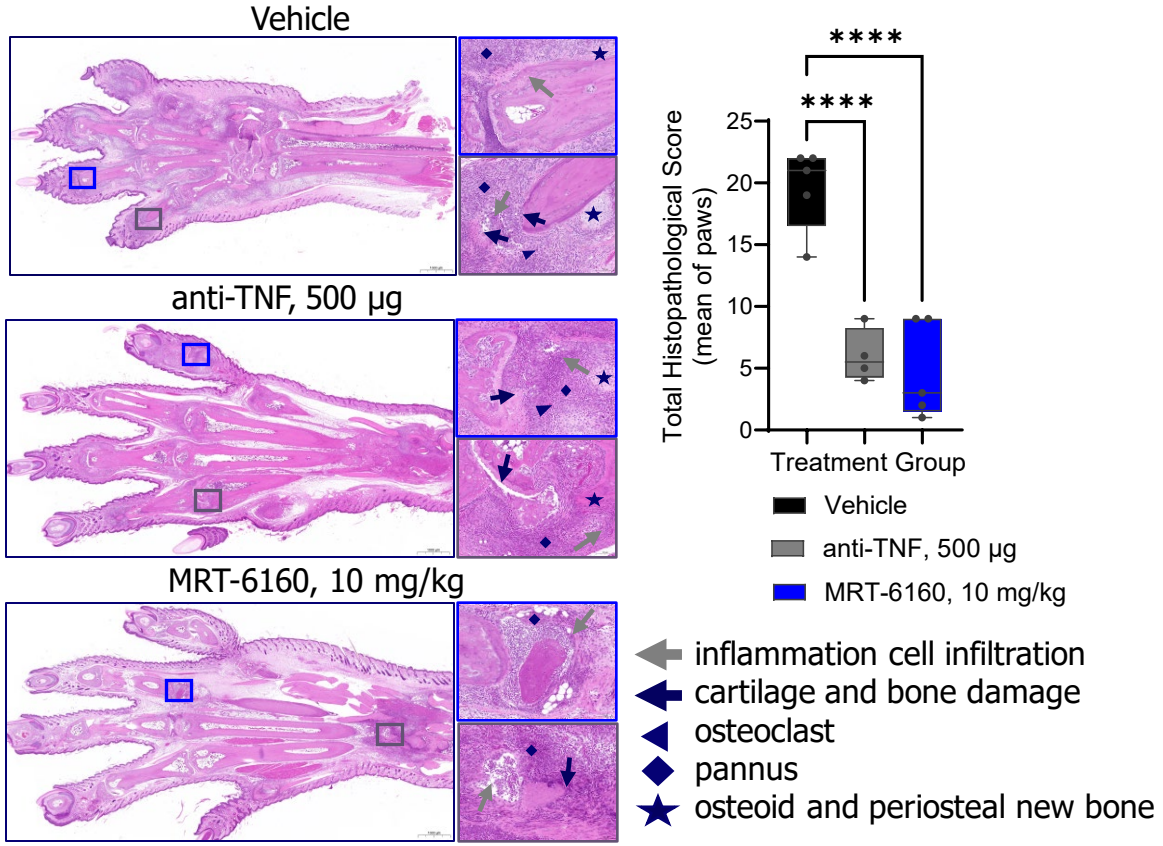
MRT-6160 Inhibits Disease Progression and Joint Inflammation/Damage in a T/B-cell-mediated Rheumatoid Arthritis Disease Model

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

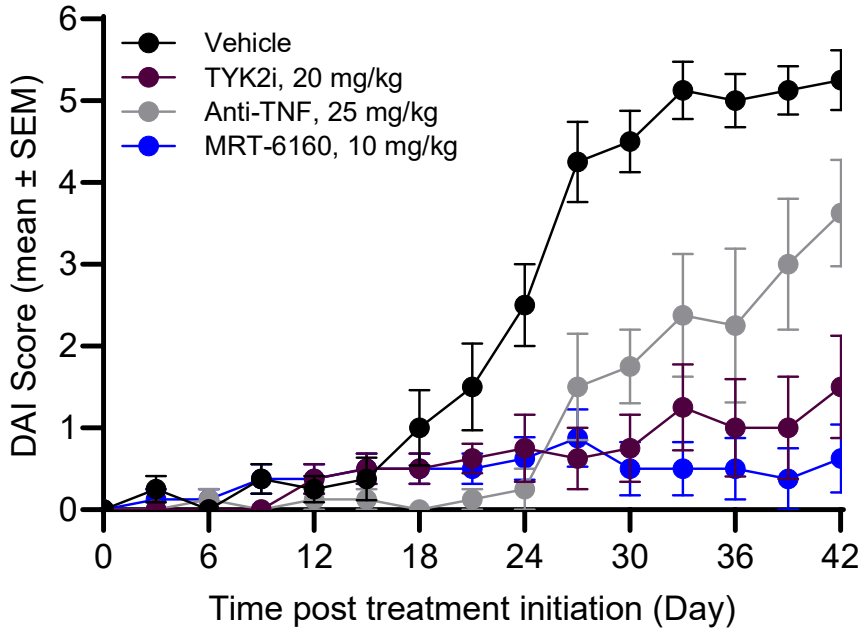
MRT-6160 inhibits joint inflammation and damage



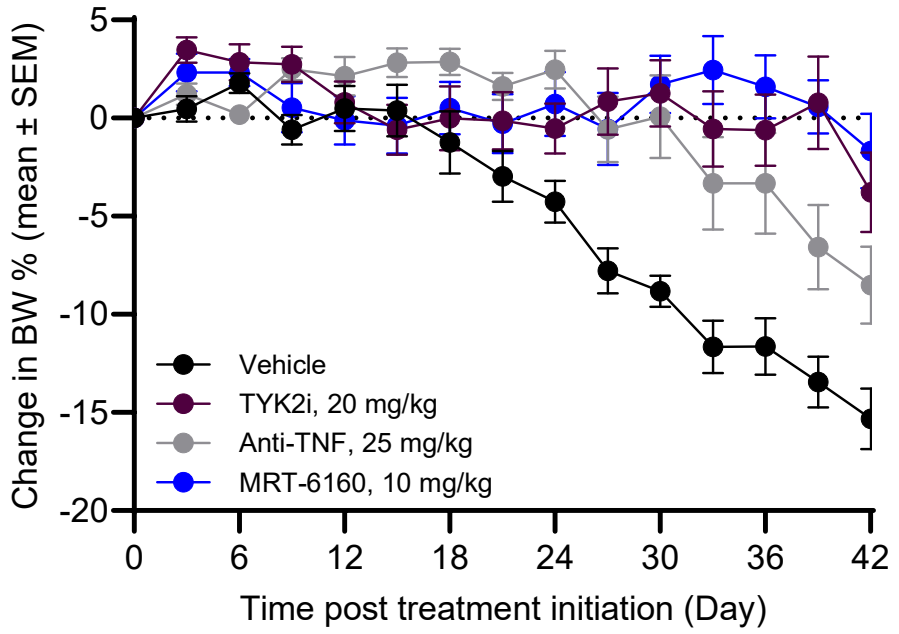
Histopathology performed on paws at end of study, total score is mean of parameters indicated, and representative images shown

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



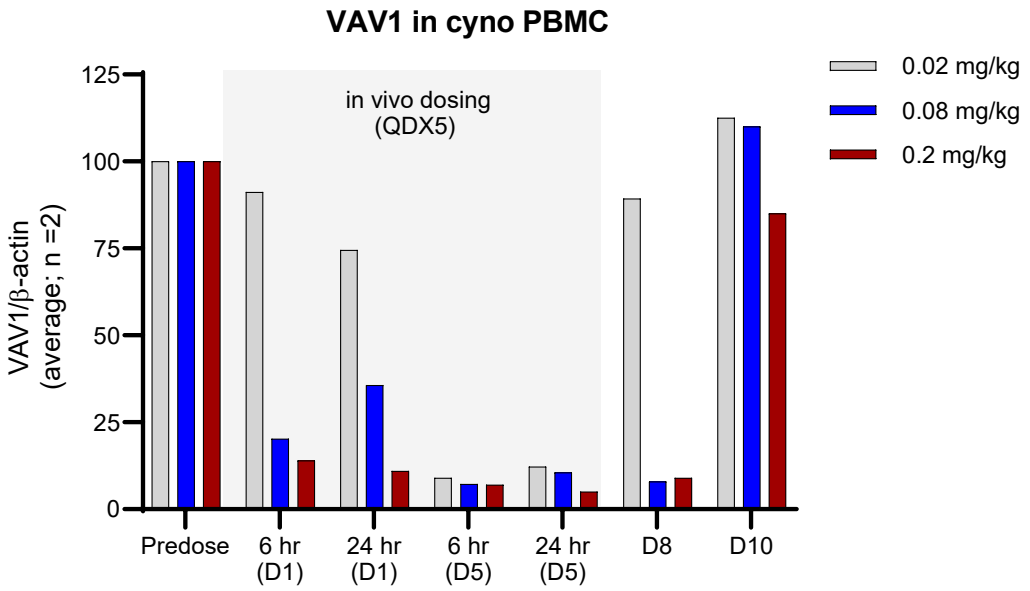
CD4+ T cell transfer-induced colitis model

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

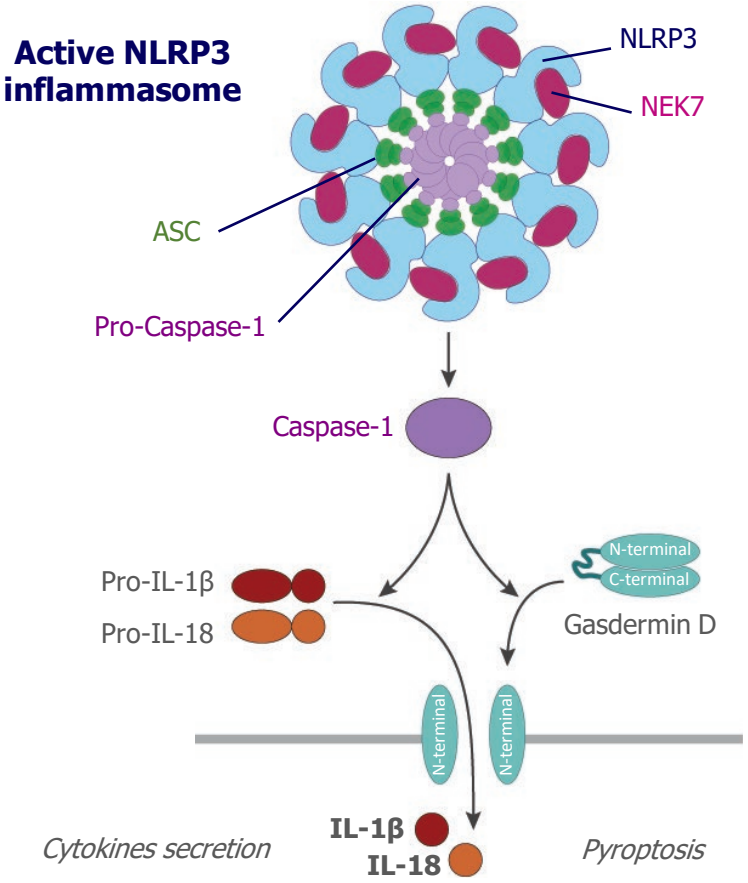
- MRT-6160 is a highly selective VAV1-directed MGD designed through our QuEEN™ platform and the first MGD being developed specifically for a non-oncology indication
- Attenuates multiple aspects of T- and B-cell receptor signaling in relevant preclinical models
- Engages VAV1 through a novel binding 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

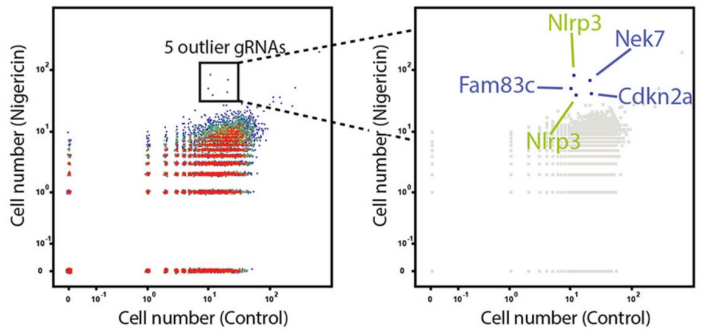
Clinical opportunity: First-in-class NEK7 degraders for

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

NEK7 as a Target to Attenuate NLRP3 Inflammasome Disease Activity

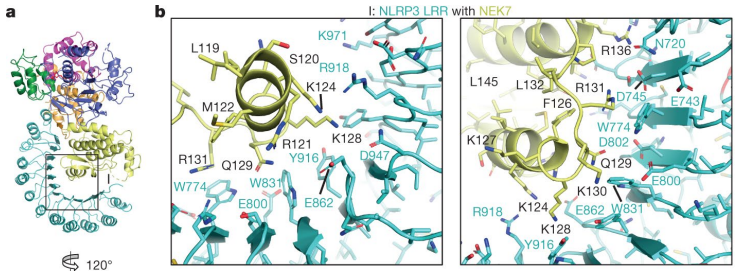
NEK7 is essential for NLRP3 inflammasome activation

Functional role for NEK7 in NLRP3 inflammasome



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

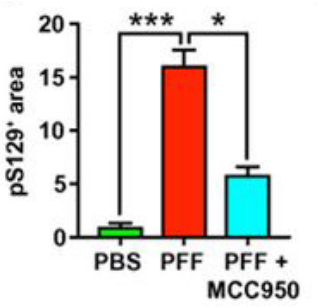
Structural licensing of NLRP3 by NEK7 binding



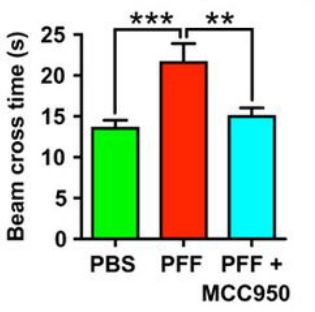
Sharif et al., Nature 2019

Inflammasome modulation reduces neuroinflammation in PD models

pS129 α-synuclein in the substantia nigra



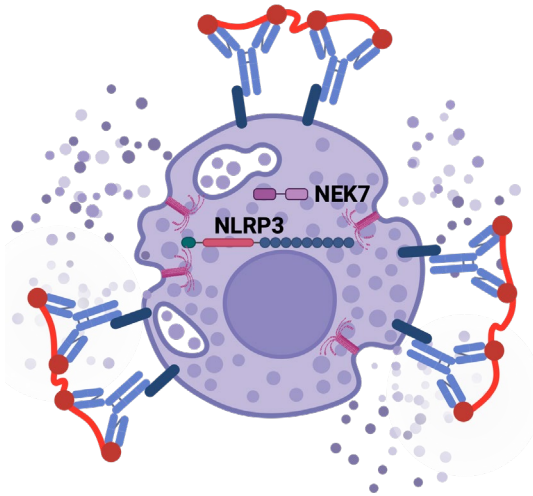
Balance beam (8 months)



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

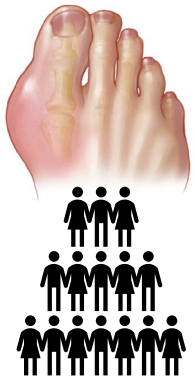


Adapted from Abraham et al. Research Square 2023

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

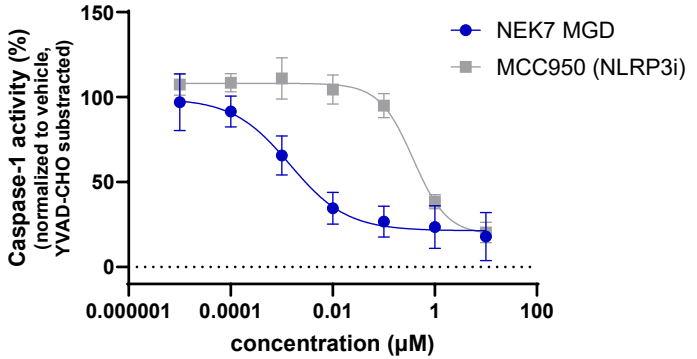
- Strong link to NLRP3 biology
- Unwanted side effects and contra-indications with SOC agents (e.g. NSAIDs, colchicine)
- Large numbers of patients with poorly controlled disease
- Need for rapid relief (acute) and fewer flares (chronic)

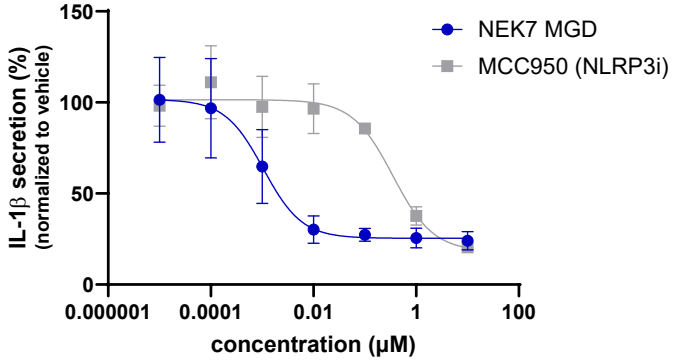
Monosodium Urate (MSU) crystals

Monocyte/macrophage

caspase-1 activation
IL-1β, IL-18 release

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

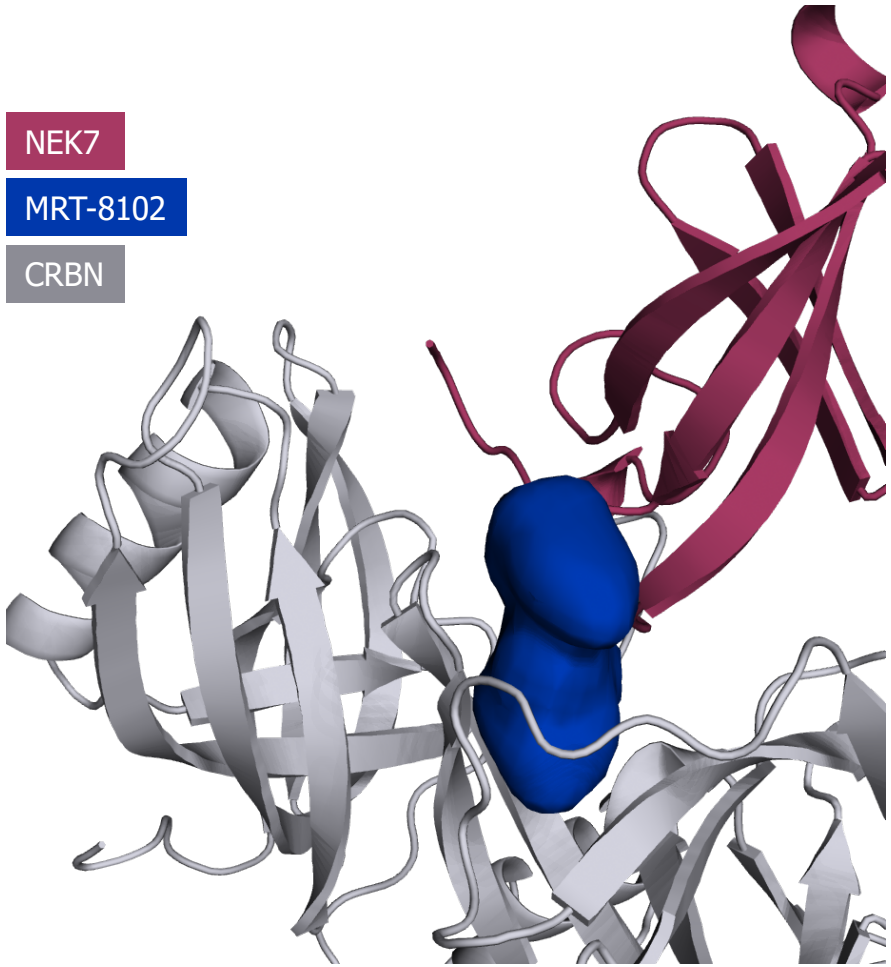




Human monocyte-derived macrophages
LPS + MSU stimulation
Pretreatment with molecular glue degrader (MGD) or NLRP3 inhibitor (NLRP3i)

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

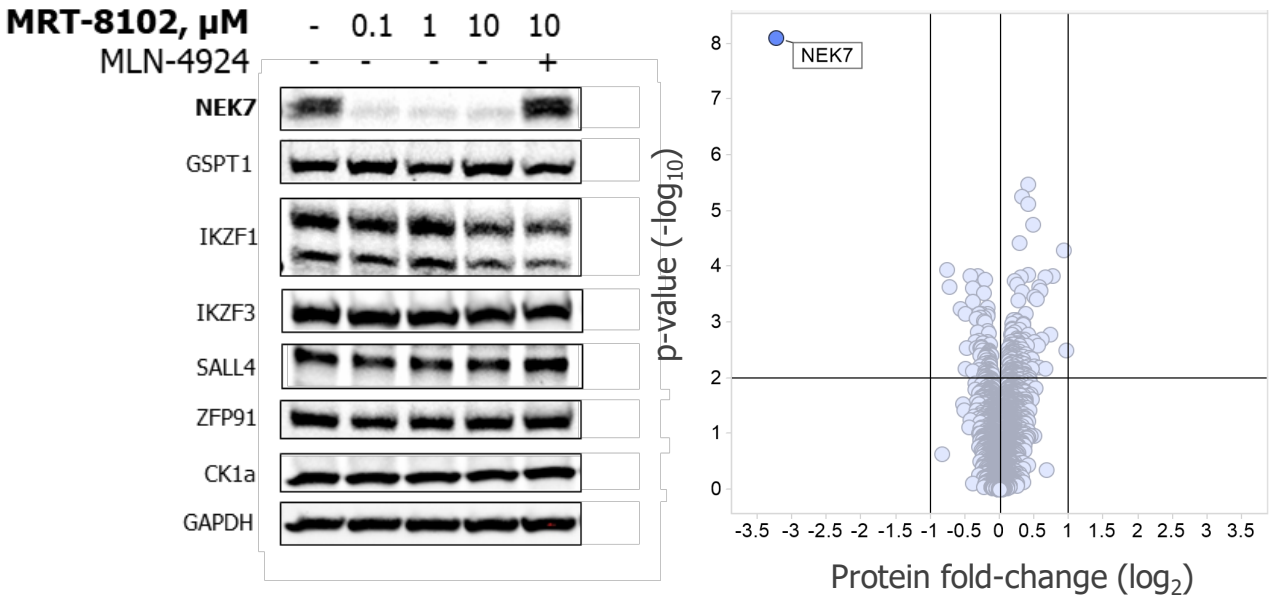
NEK7 Ternary Complex (Crystal Structure)



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

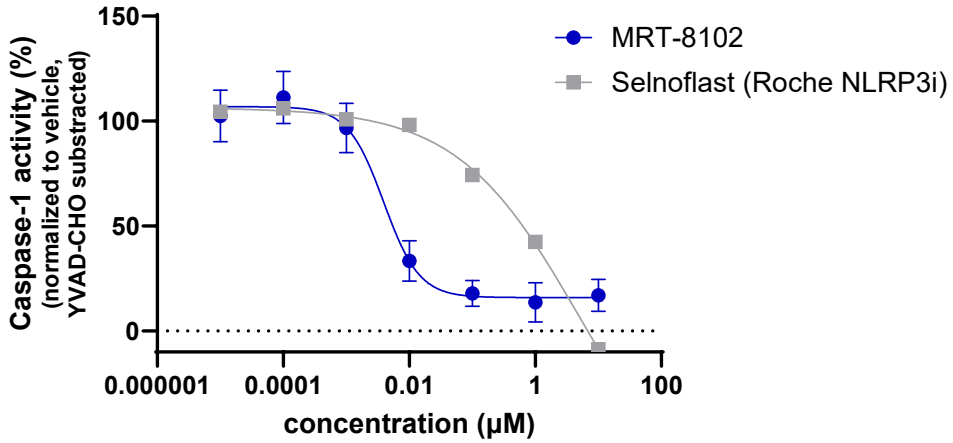


6 hr treatment in Kelly (SALL4) or MM.1S
2 μM MLN-4924, 30 min pre-treatment

MRT-8102 at 10 μM in hPBMC, 24h

Additional cell lines screened:
U937, Kelly and MM1S

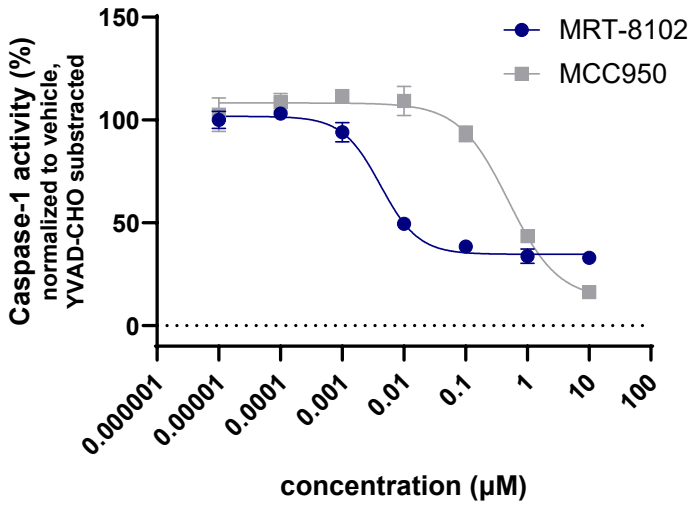
MRT-8102 potently suppresses inflammasome activation in primary human macrophages



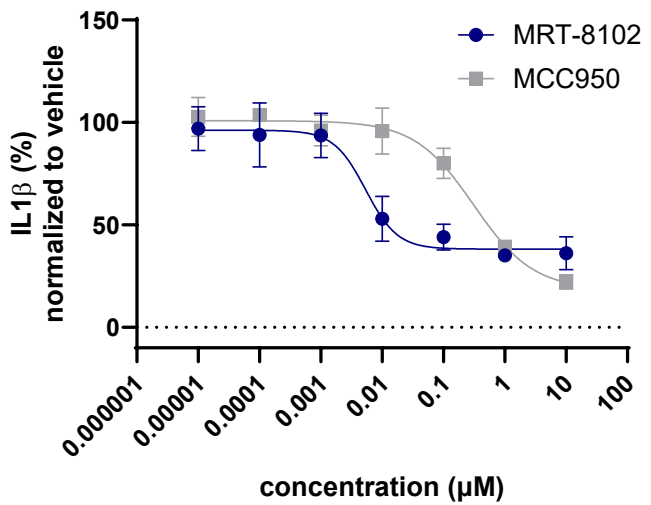
Human monocyte-derived macrophage (hMDM) assay
LPS + MSU stimulation; pre-treatment with MGD/NLRP3i
Similar reduction in IL-1β

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

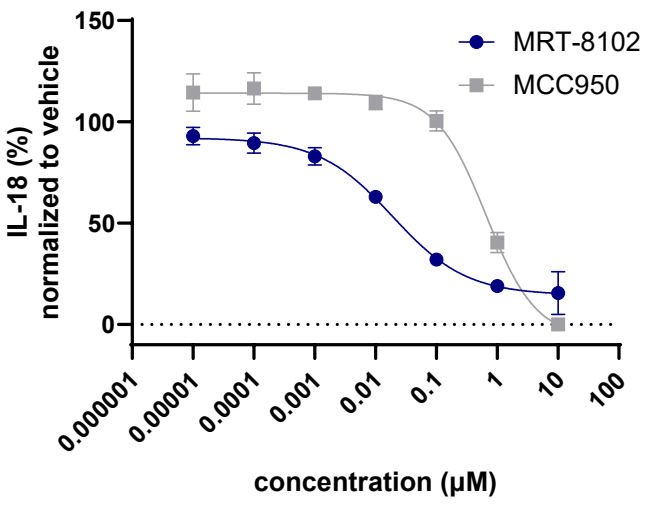
MRT-8102 inhibits caspase-1 activity in hMDMs after stimulation



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



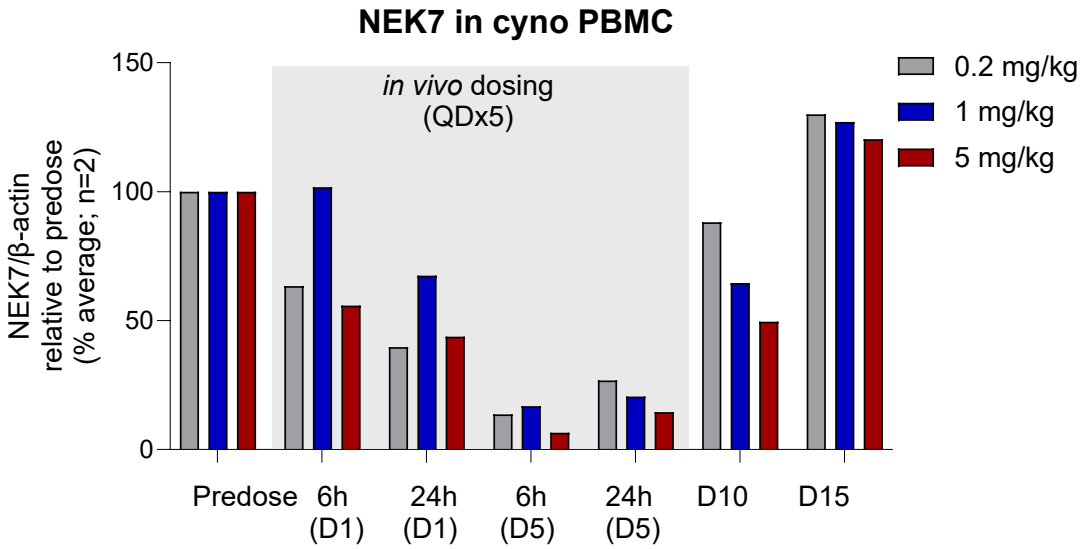
MRT-8102 inhibits IL-18 secretion by hMDMs after stimulation



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

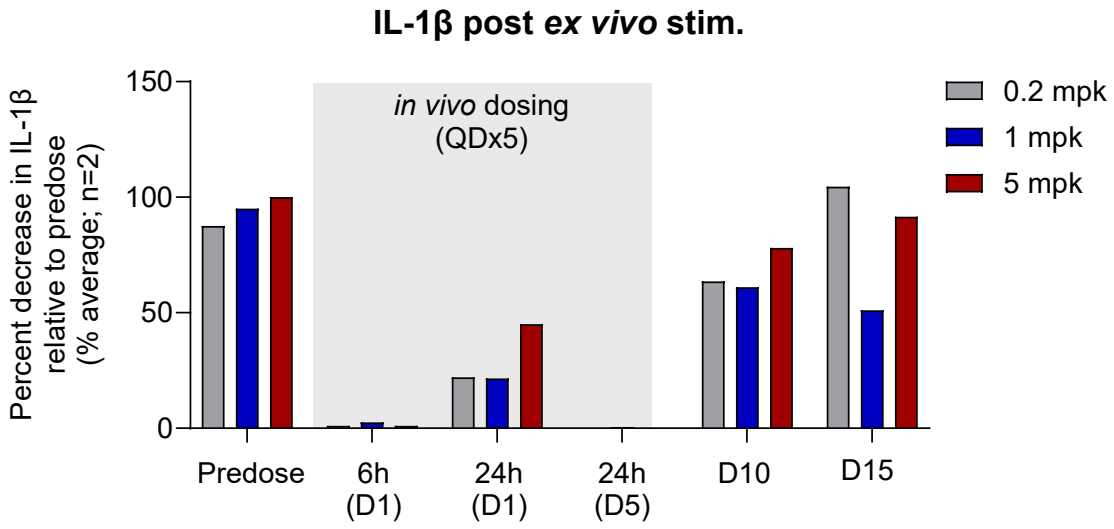
Suppression of *Ex Vivo* Inflammasome Activation Following Degradation of NEK7 in Non-human Primates

MRT-8102 induces NEK7 degradation *in vivo*



No clinical observations reported

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



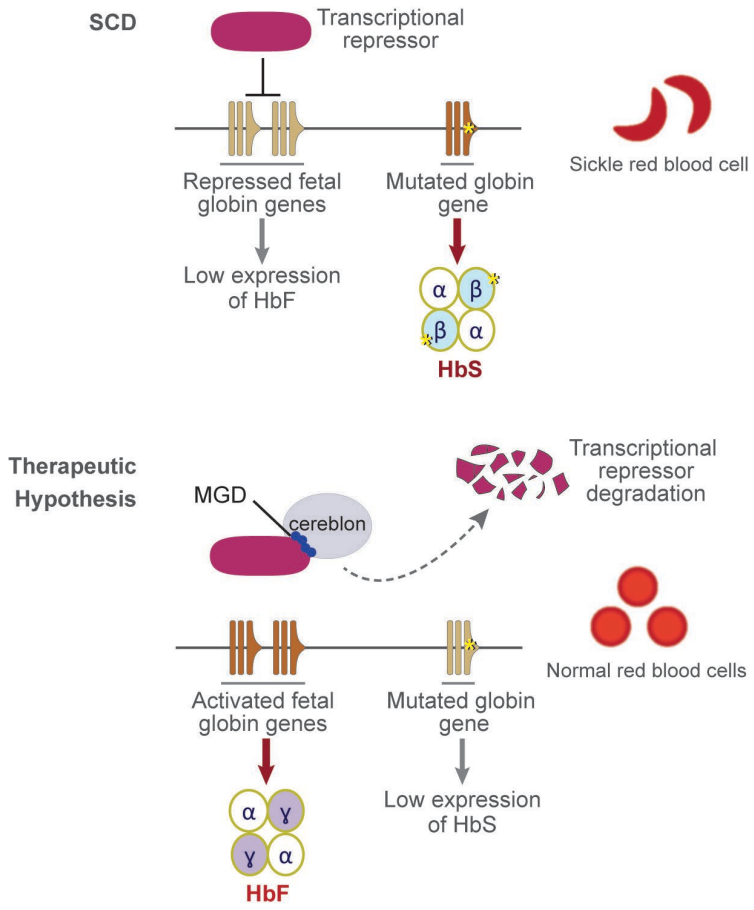
IL-1β in plasma after *ex vivo* stimulation with LPS+nigericin

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

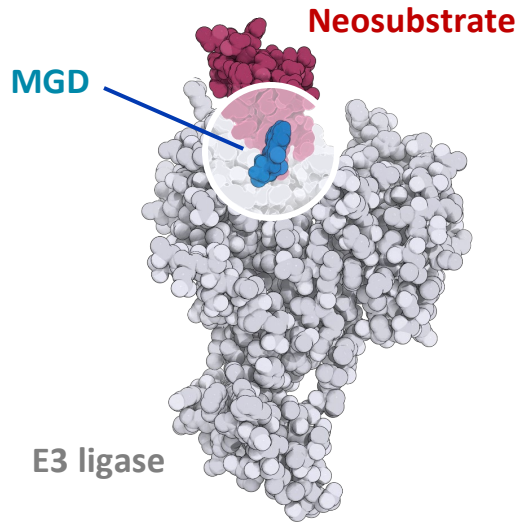
Our MGD Library

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

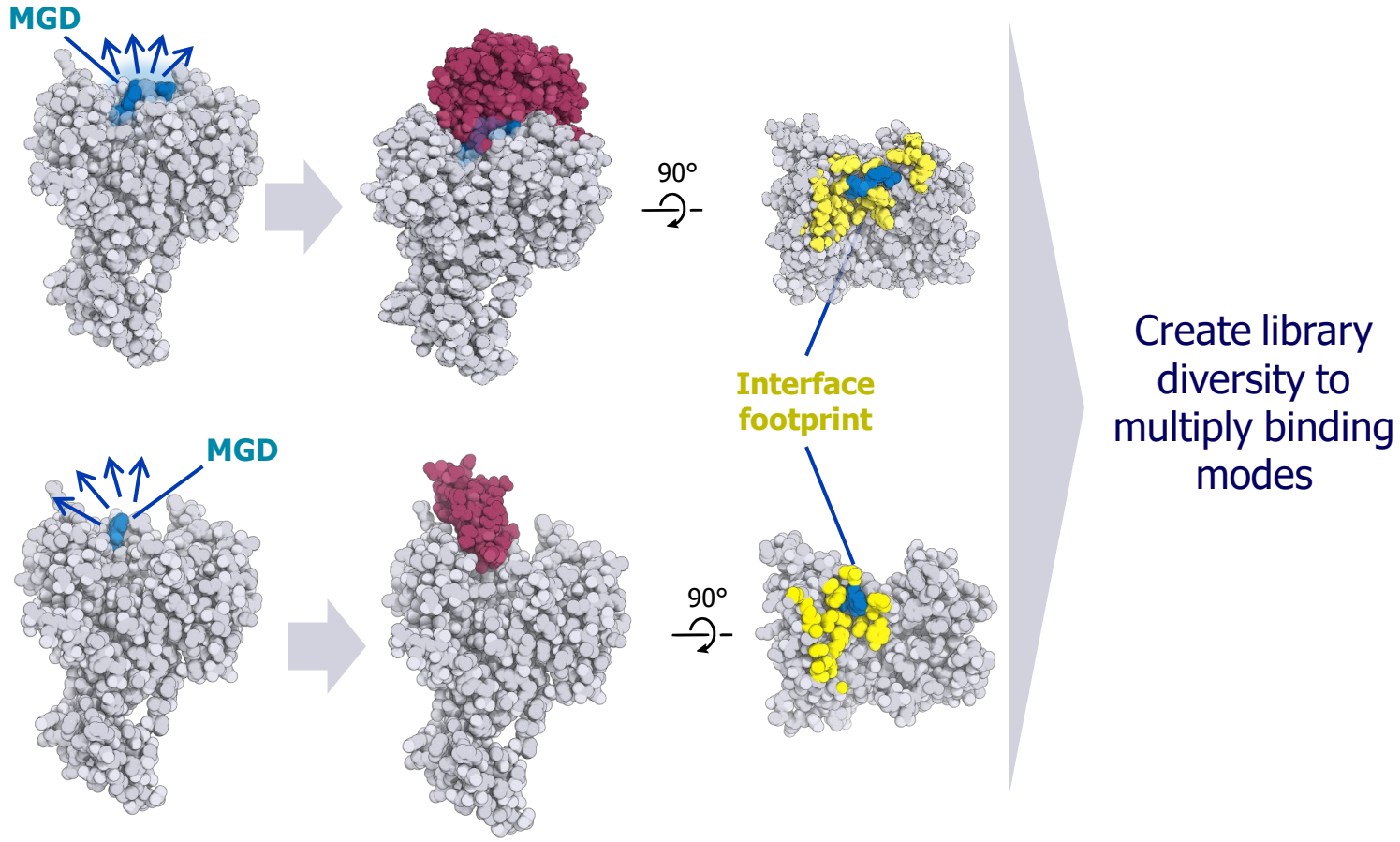
Multiple points of contact mediate formation of ternary complex



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

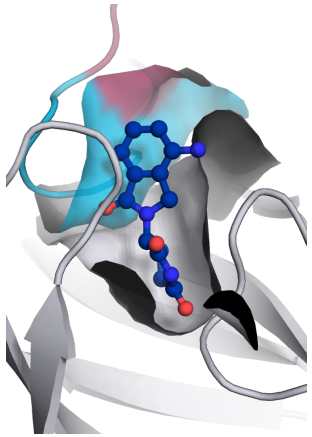


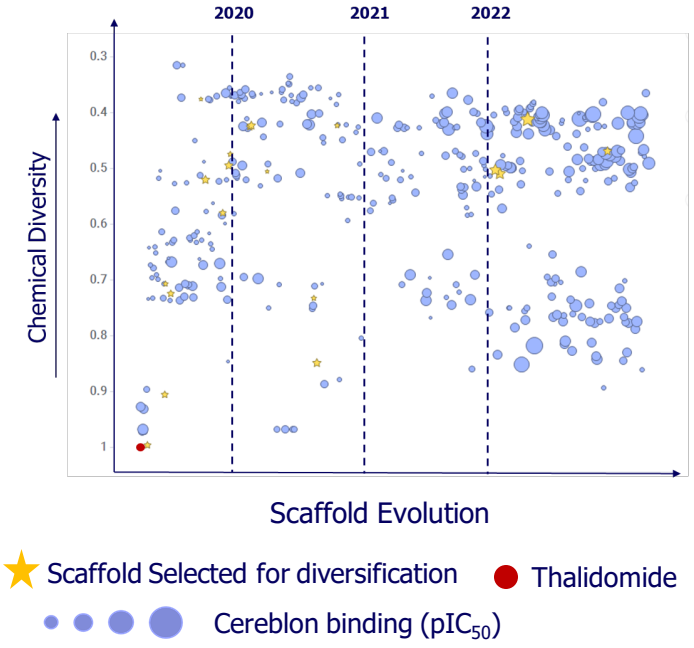
Create library diversity to multiply binding modes

Library Expansion Unlocks Novel Degron and Target Space

Ligase binding

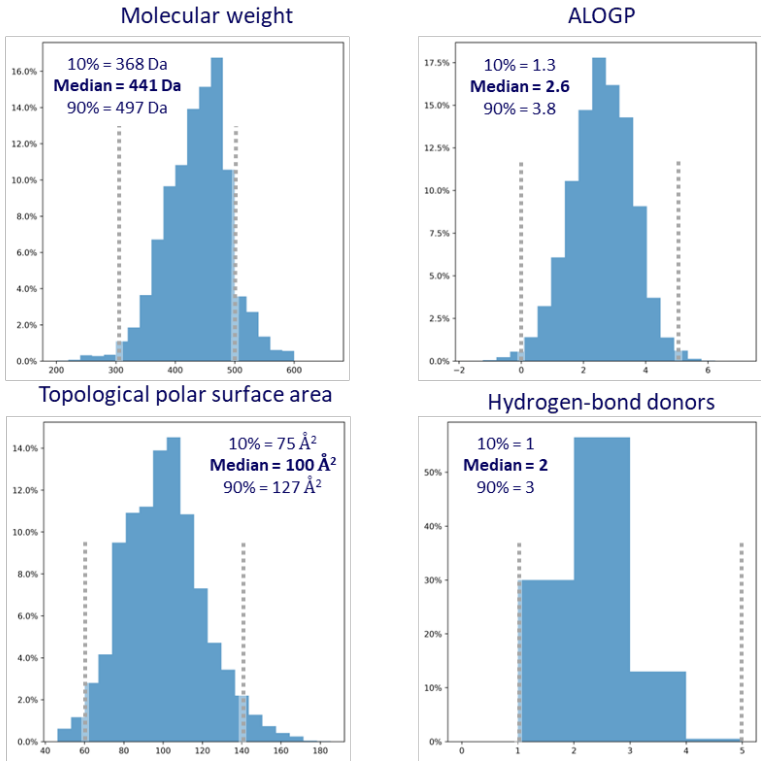
Structurally diverse scaffolds retain potent CRBN binding





Properties

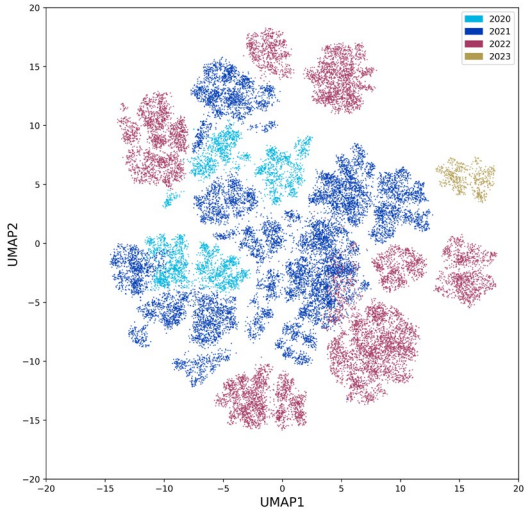
Well within drug-like property space



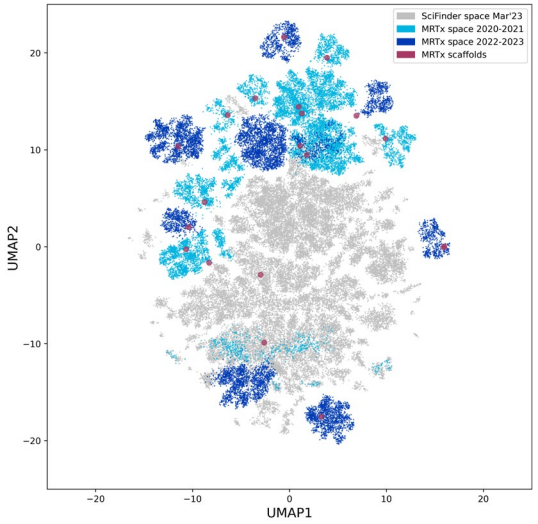
Teaching Cereblon New Tricks

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

Creating diverse and proprietary chemical space …



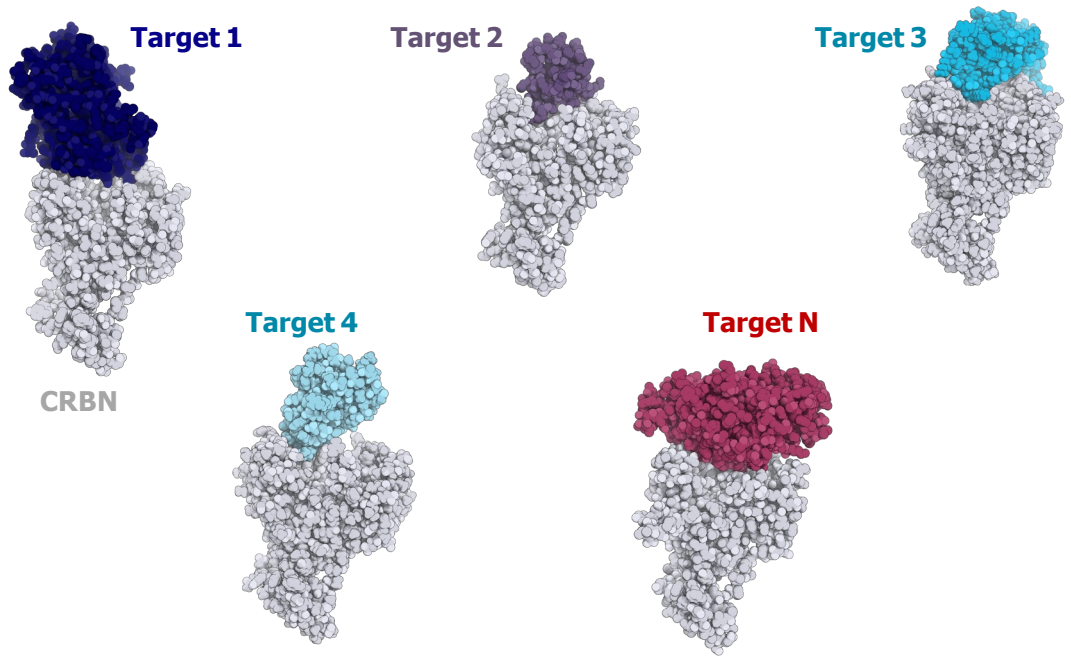
Clearly differentiated sub-libraries



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 Biomedicine
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 & RICHARDSON

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

abbvie
Lilly

Jennifer Champoux
Chief People & Operations Officer

H3 Biomedicine
NOVARTIS


Thank You
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