From Serendipity to Rational Design

Taking Molecular Glue Degraders to New Heights | March 2024

Monte Rosa Therapeutics

Forward-Looking Statements

This communication includes express and implied "forward-looking statements," including forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include all statements that are not historical facts and, in some cases, can be identified by terms such as "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "potential," "continue," "ongoing," or the negative of these terms, or other comparable terminology intended to identify statements about the future. Forward-looking statements contained herein include, but are not limited to, statements about our product development activities, our ability to grow our product pipeline, our ongoing clinical development of our GSPT1 degrader referred to as MRT-2359, including our expectations for the nature, significance, and timing for our disclosure of any initial data from our Phase 1/2 clinical trial of MRT-2359 in MYC-driven solid tumors, timing for our identification and any disclosure of a recommended phase 2 dose for MRT-2359, statements the Company's QuEEN™ discovery engine and the Company's view of its potential to identify degradable protein targets and rationally design MGDs with unprecedented selectivity, statements about our collaboration with Roche, statements about the advancement and timeline of our preclinical and clinical programs, pipeline and the various products therein, including the ongoing development of our VAV1-directed degrader, referred to as MRT-6160, the planned submission of an IND to the FDA for MRT-6160 in Q2 2024, and our expectations of timing for commencing any Phase 1 single ascending dose / multiple ascending dose (SAD/MAD) study initiation in healthy volunteers, our expectations regarding the potential clinical benefit for our programs and our expectations of timings for the program, the ongoing development of our NEK7-directed degrader, referred to as MRT-8102, the planned submission of an IND to the FDA for MRT-8102 in the first quarter of 2025, and our expectations of timing for clinical advancement for MRT-8102, statements around the identification and the timing of a development candidate for CDK2 and other programs, statements around the advancement and application of our platform, and statements concerning our expectations regarding our ability to nominate and the timing of our nominations of additional targets, product candidates, and development candidates, as well as our expectations of success for our programs and the strength of our financial position, our use of capital, expenses and other financial results in the future, availability of funding for existing programs, ability to fund operations into the first half of 2026, among others. By their nature, these statements are subject to numerous risks and uncertainties, including those risks and uncertainties set forth in our most recent Annual Report on Form 10-K for the year ended December 31, 2023, filed with the U.S. Securities and Exchange Commission on March 14, 2024, and any subsequent filings, that could cause actual results, performance or achievement to differ materially and adversely from those anticipated or implied in the statements. You should not rely upon forward-looking statements as predictions of future events. Although our management believes that the expectations reflected in our statements are reasonable, we cannot guarantee that the future results, performance, or events and circumstances described in the forward-looking statements will be achieved or occur. Recipients are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date such statements are made and should not be construed as statements of fact. We undertake no obligation to publicly update any forward-looking statements, whether, as a result of, new information, any future presentations, or otherwise, except as required by applicable law. Certain information contained in these materials and any statements made orally during any presentation of these materials that relate to the materials or are based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party studies, publications, surveys and other data to be reliable as of the date of these materials, we have not independently verified, and make no representations as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, no independent source has evaluated the reasonableness or accuracy of our internal estimates or research and no reliance should be made on any information or statements made in these materials relating to or based on such internal estimates and research.

Monte Rosa Therapeutics – Company Overview

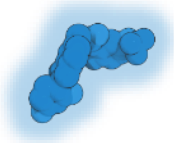
Taking molecular glue degraders (MGDs) to new heights

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

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

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

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



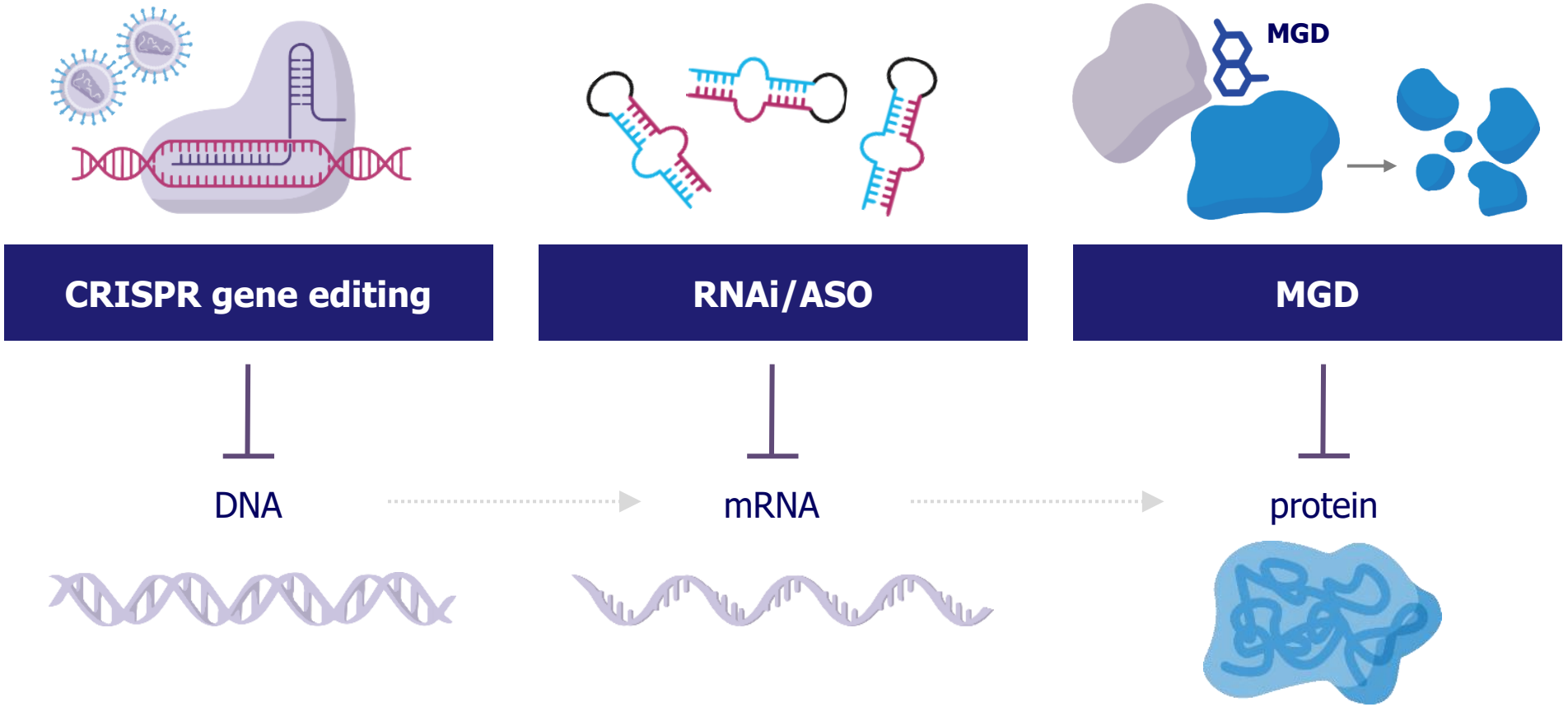
MRT-6160, highly selective VAV1-directed MGD, being rapidly advanced with IND expected in mid-2024; broad potential applications across autoimmune diseases

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

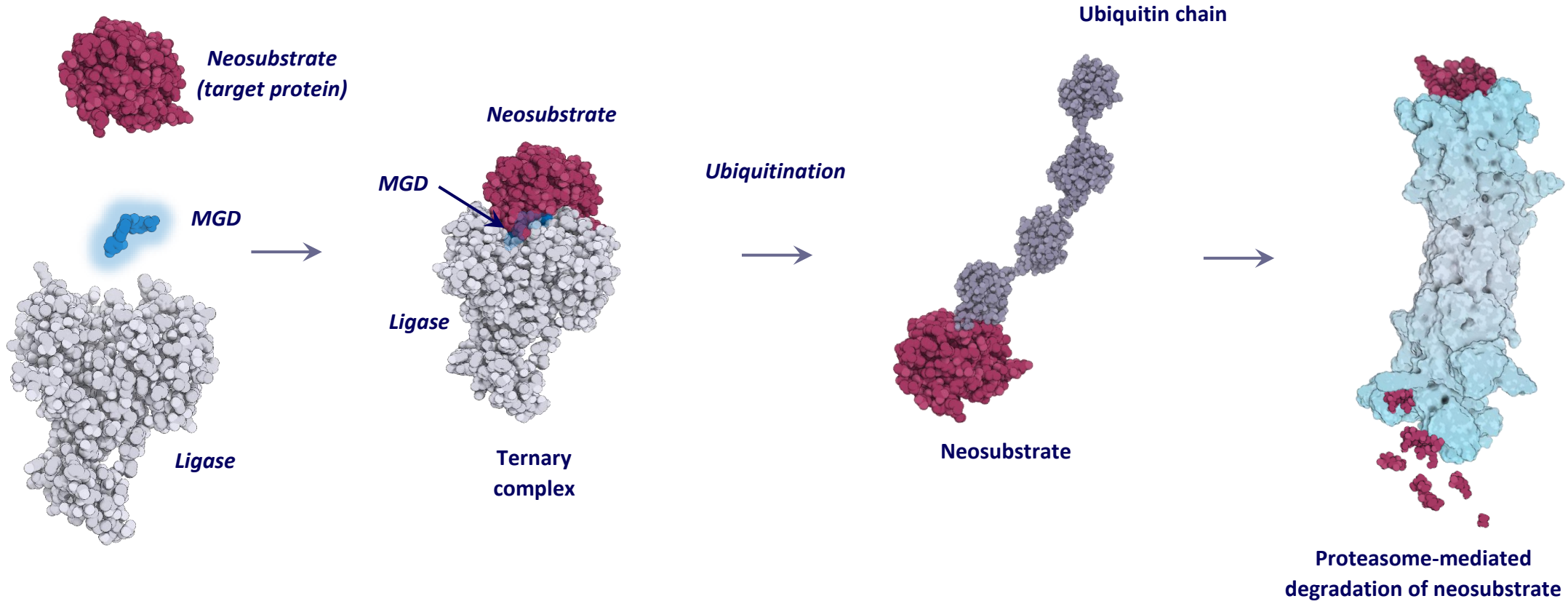
Strong financial position providing cash runway into H1 2026 and through multiple anticipated clinical readouts, including MRT-2359 Phase 1/2 and SAD/MAD for VAV1 and NEK7

Three Ways to Eliminate a Disease-Causing Protein

MGDs can directly and precisely target proteins that cause disease



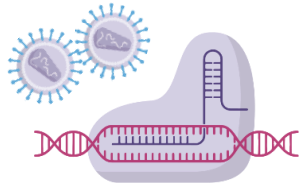
Our Molecular Glue Degraders (MGDs) Edit the Proteome



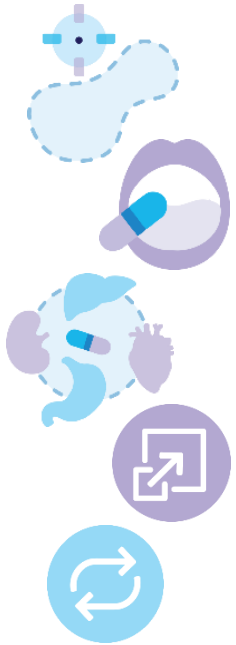
Monte Rosa's rationally designed MGDs have potential applications in Oncology, Immunology, Neuroscience and other therapeutic areas

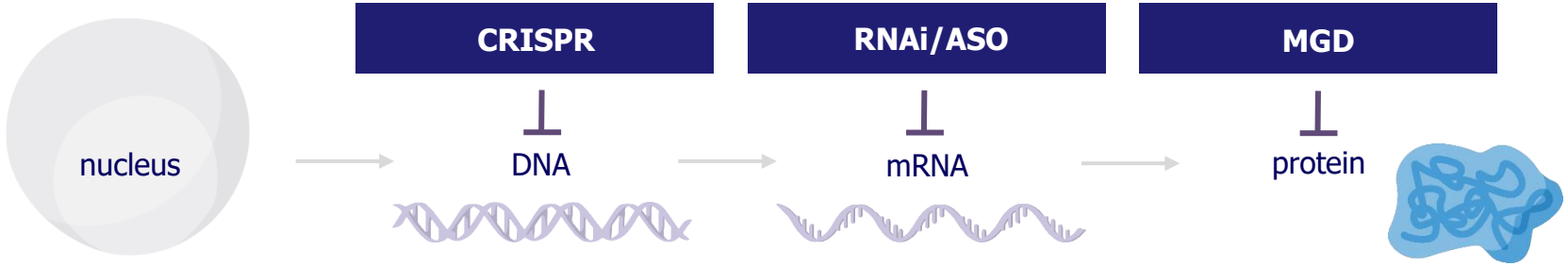
Molecular Glue Degraders (MGDs) – A Highly Differentiated Modality

Advantages of large molecule modalities with orally dosed small molecules



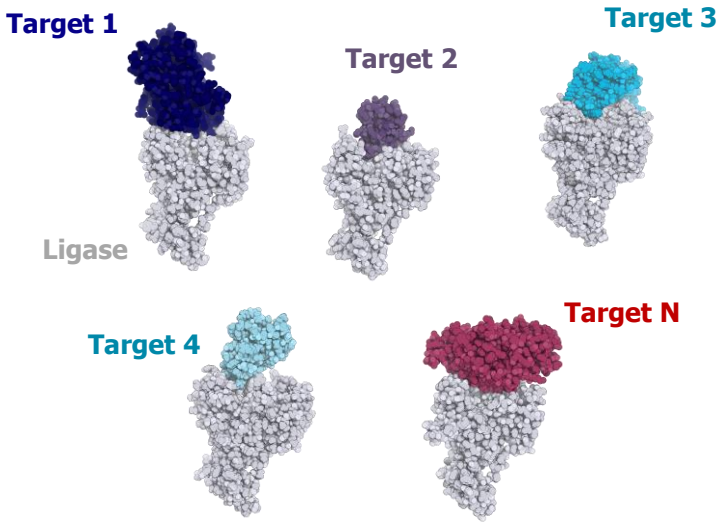
Properties	CRISPR	RNAi/ASO	MGD
Address undruggable space	✓	✓	✓
Orally bioavailable			✓
Systemic distribution			✓
Scalable manufacturing			✓
Reversible		✓	✓





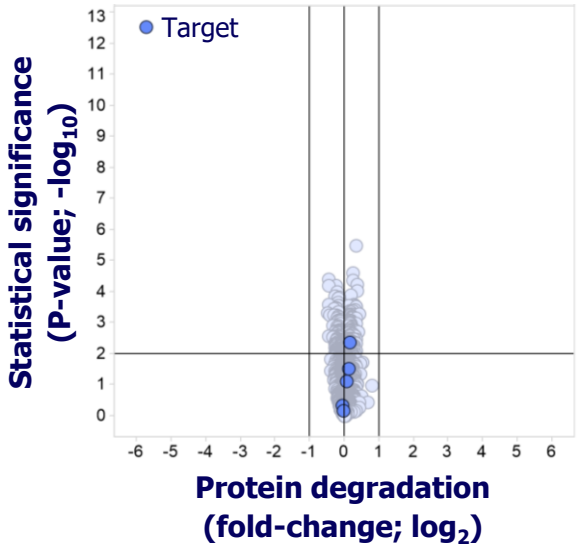
Key Advantages of Our Rationally Designed MGDs

Unique Target Space



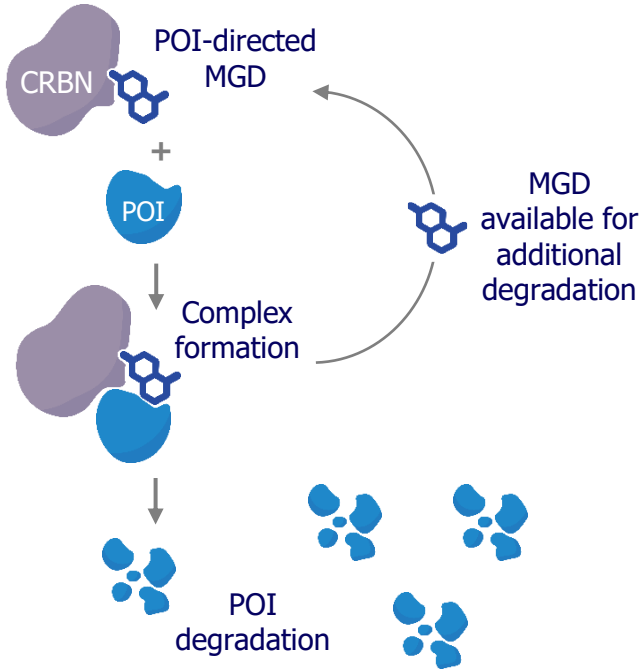
Disease-agnostic platform with initial focus on highly credentialed, undruggable oncology and immunology/inflammation targets

Unprecedented Selectivity



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

Catalytic Mechanism of Action



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

POI = protein of interest

Monte Rosa Therapeutics – Key Firsts and Accomplishments

From serendipity to rational design of MGDs

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

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

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

Progressed VAV1 MGD MRT-6160 and NEK7 MGD MRT-8102 into IND enabling studies; MRT-6160 is the *first* known MGD specifically developed for a non-oncology indication

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

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

* Based on optimal PD modulation in preclinical studies

Monte Rosa Therapeutics

Portfolio

Monte Rosa Pipeline and Upcoming Milestones

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

Oncology Immunology Inflammation Various

Monte Rosa Therapeutics

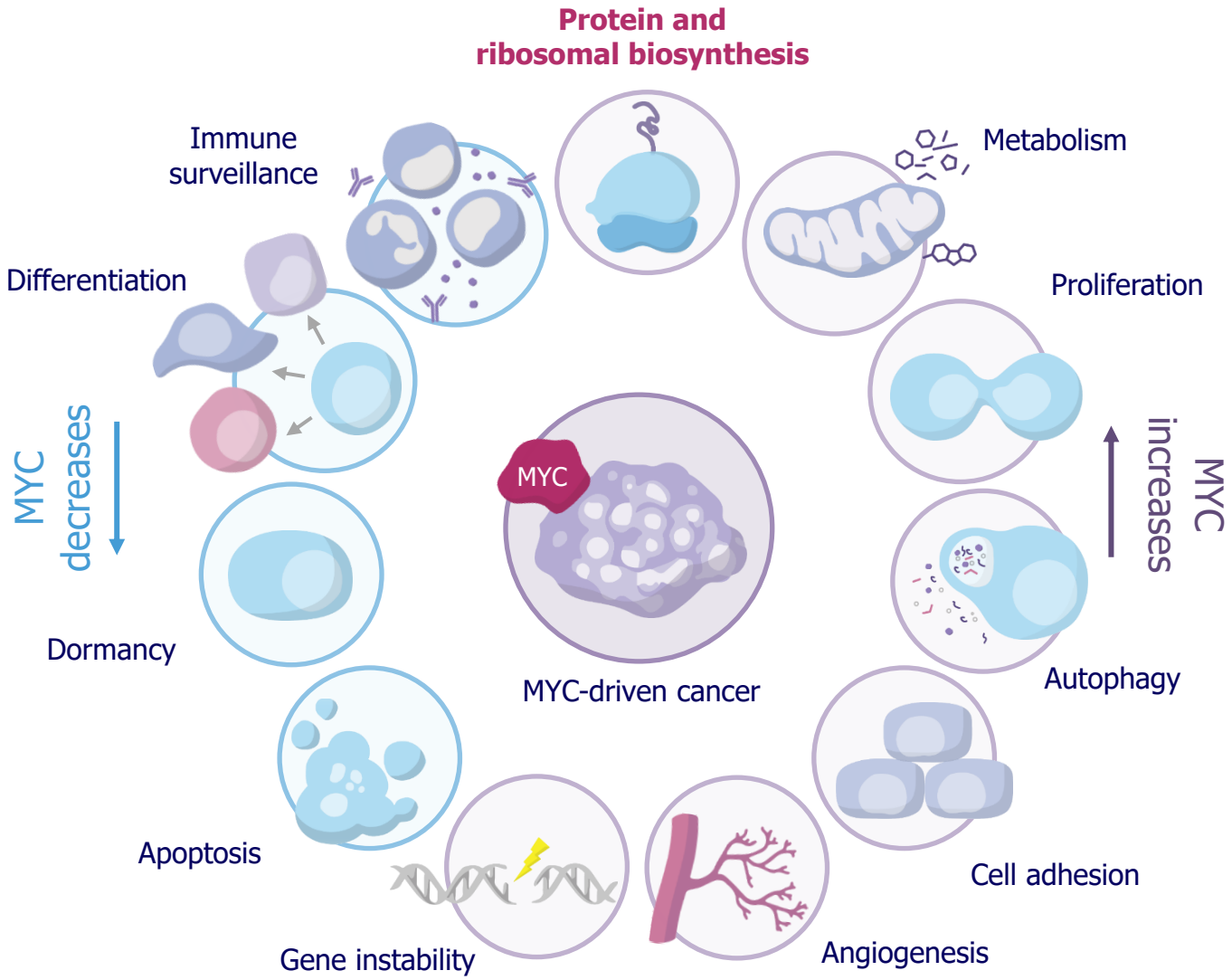
GSPT1 program (MRT-2359)

MYC is a Key Regulator of Cancer Growth and Immune Evasion

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

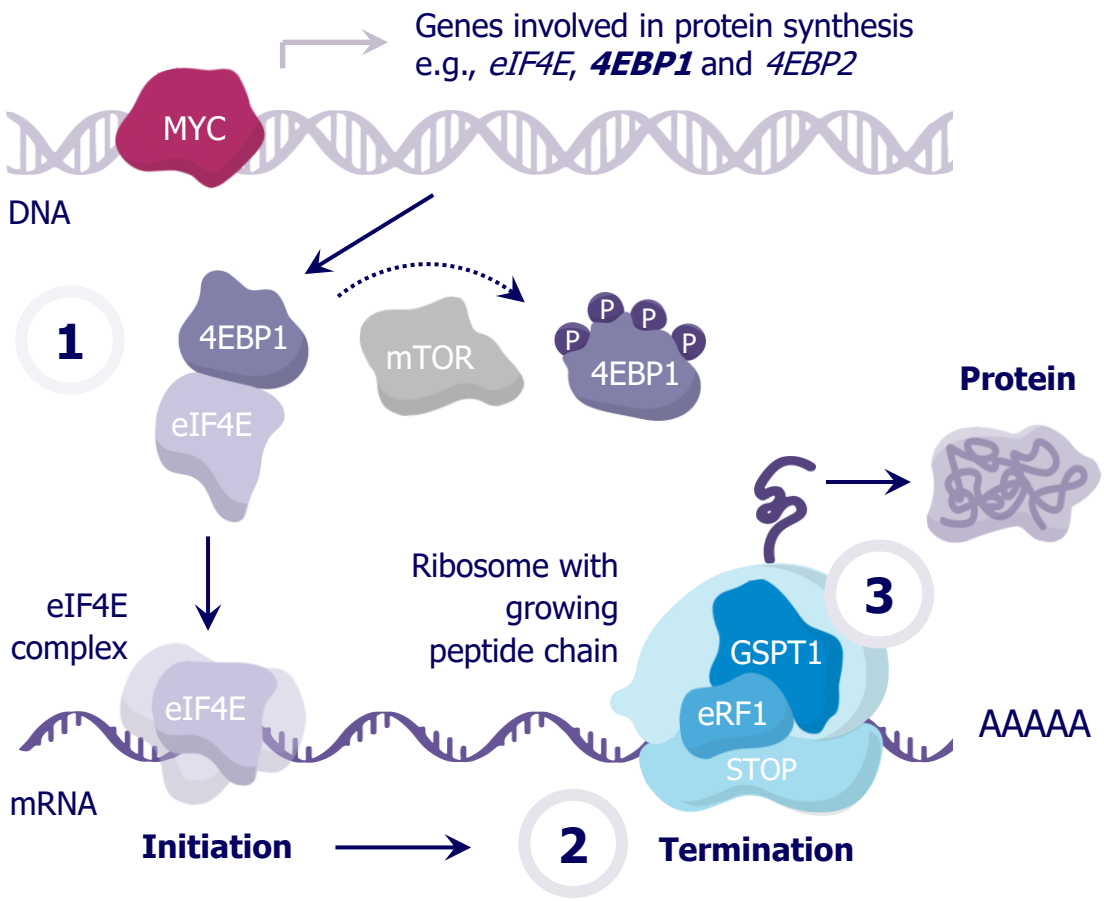
- MRT-2359 is designed to specifically target MYC-driven tumors

MYC Impacts Many "Hallmarks of Cancer"



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

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



1

Addiction

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

2

Dependency

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

3

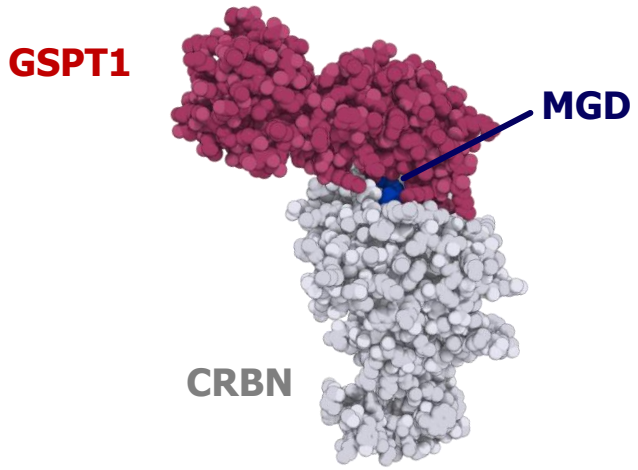
Therapeutic vulnerability

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

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

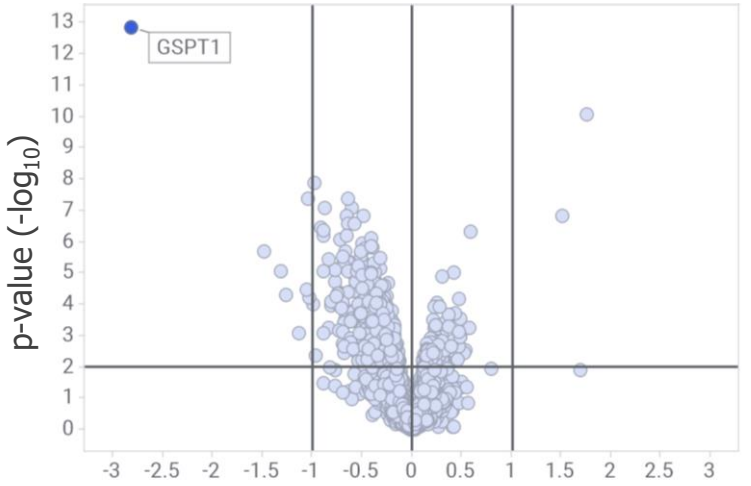
MRT-2359 is a potent GSPT1-directed MGD

Ternary complex modelling



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

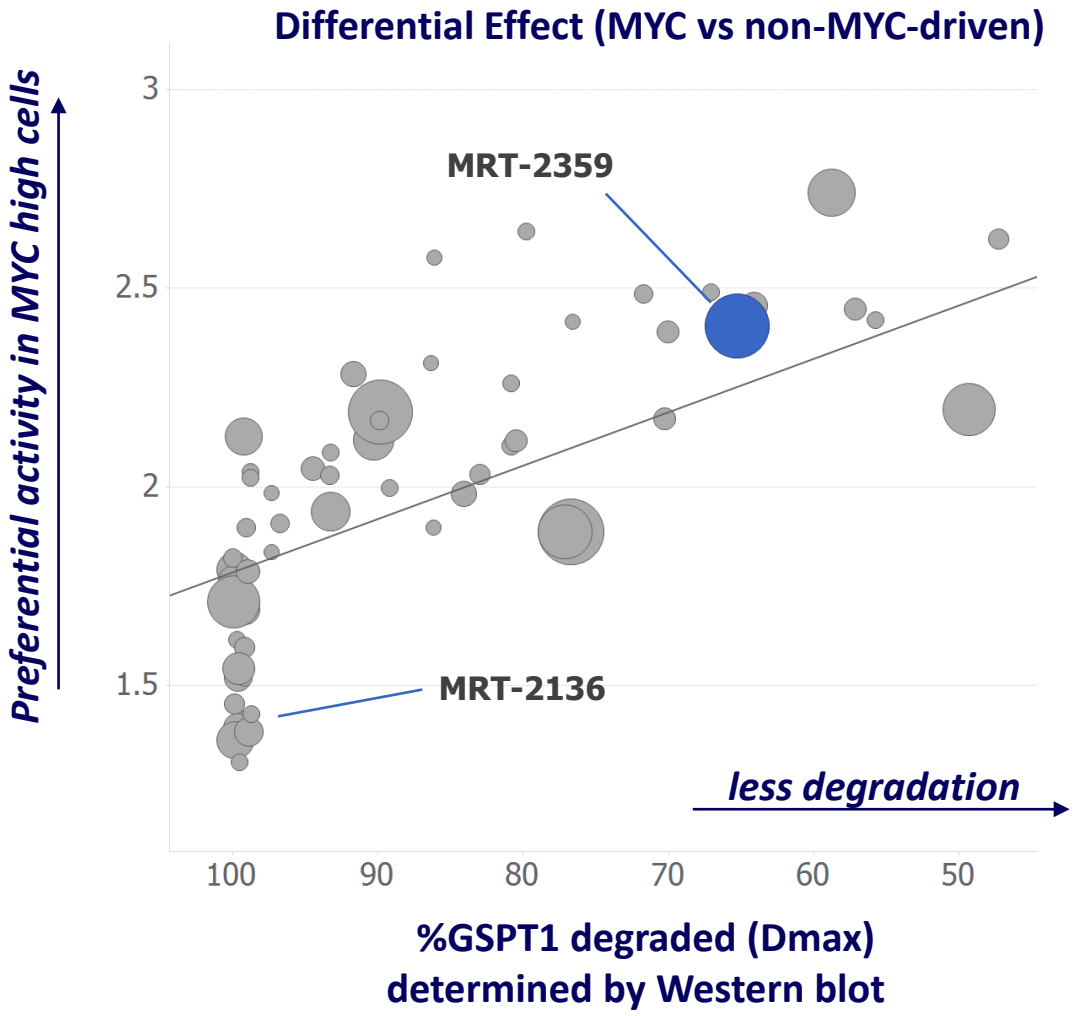
MRT-2359 induces selective GSPT1 degradation and shows favorable ADME/DMPK profile



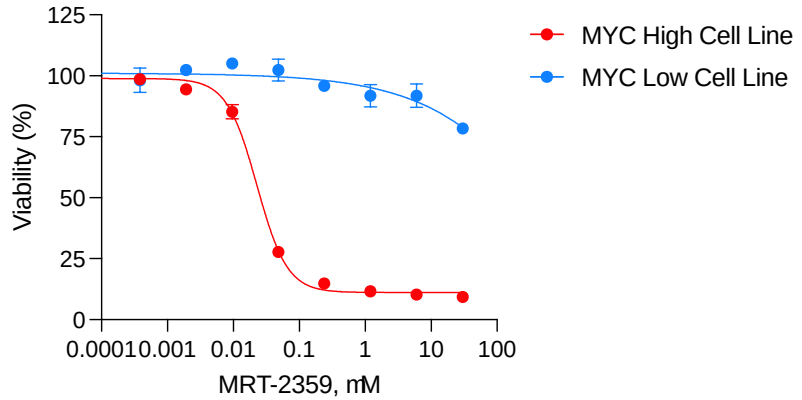
No degradation of other known cereblon neosubstrates

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

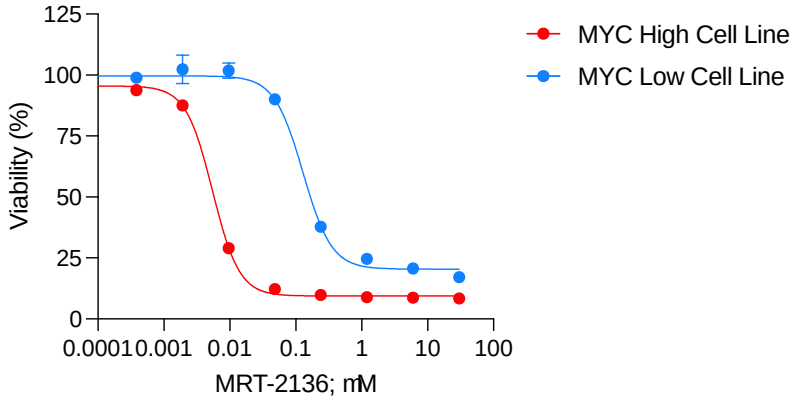
MRT-2359 Has Optimized Depth of Degradation To Achieve Preferential Activity in MYC High Cancer Cells



MRT-2359 displays preferential activity in MYC driven NSCLC cells



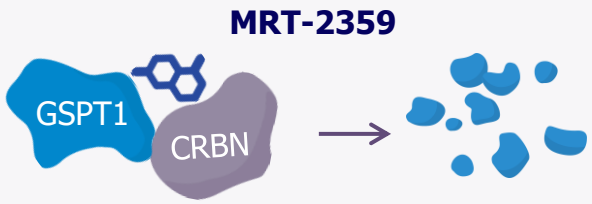
Non-optimal GSPT1 MGD (MRT-2136) shows limited preferential activity



Three Mechanisms Driving Preferential Activity in MYC High Tumor Cells

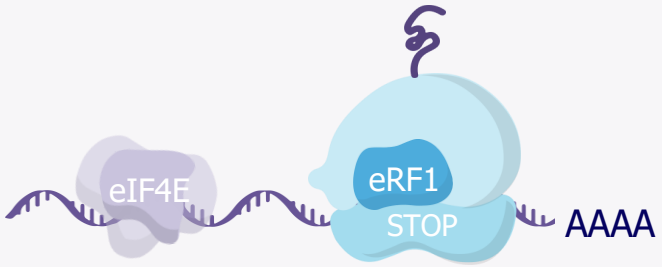
Preferential GSPT1 degradation

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



Inhibition of translation

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

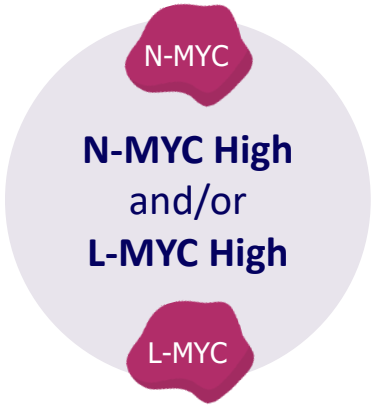


MYC down-modulation

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

Large Potential Opportunities in MYC-Driven Tumors

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



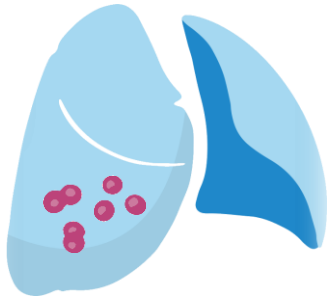
SCLC (70-80% L/N-MYC high)

NSCLC

N-MYC high (5-10%)

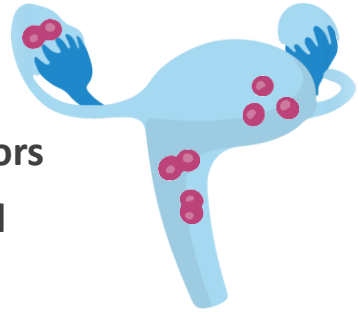
SCLC/NE transformation

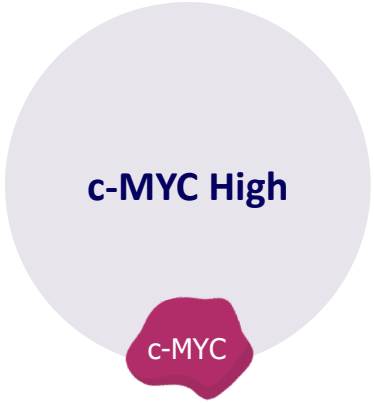
Neuroendocrine lung cancer



Neuroendocrine tumors

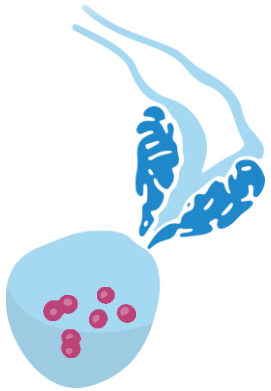
L-/N-MYC amplified tumors





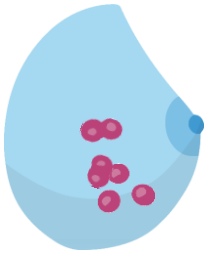
Prostate cancer

Including ARV7 positive



Breast cancer

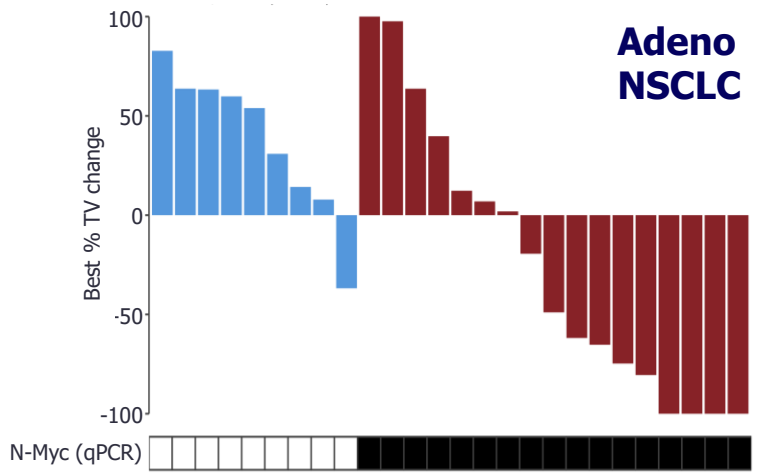
ER positive metastatic

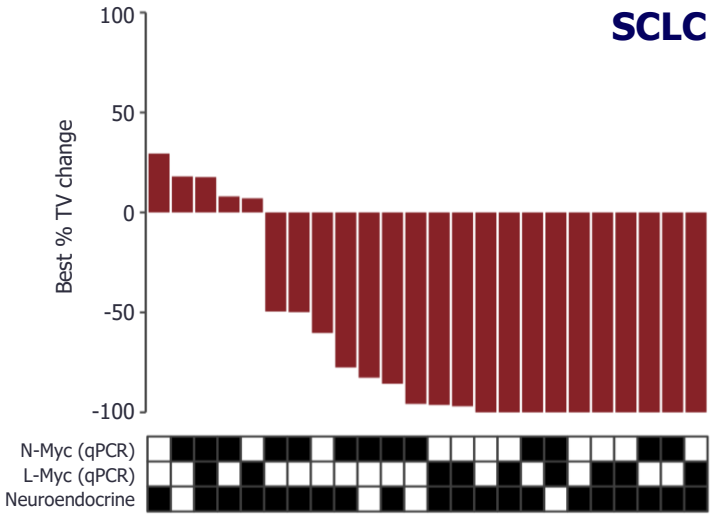


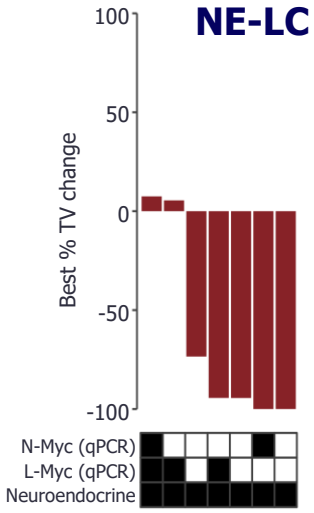
Preclinical Validation of Activity of MRT-2359 in Lung Cancer PDX Models

Collection of PDX models

MRT-2359
10 mg/kg QD

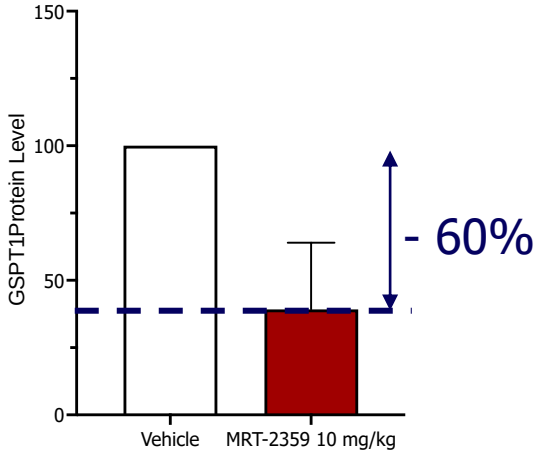






PD modulation

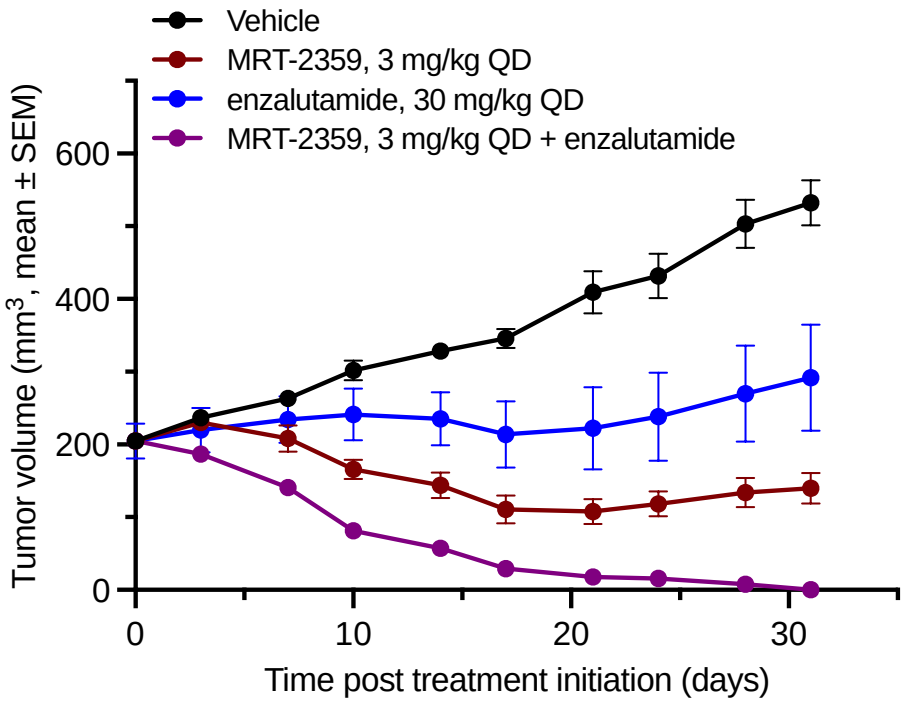
Targeted mass spectrometry
in 7 representative models



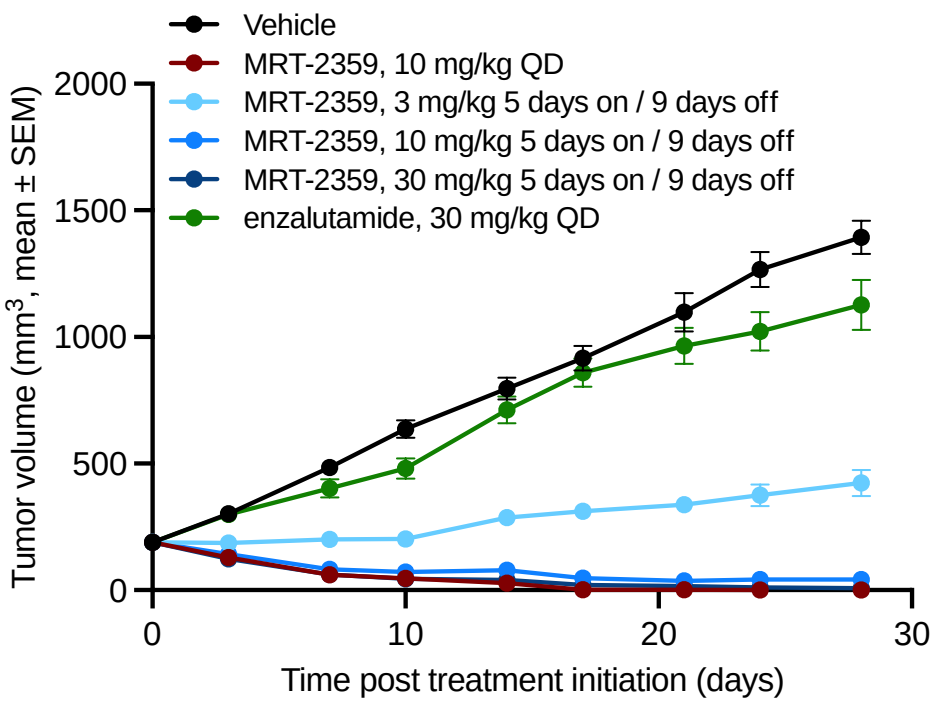
biomarker negative biomarker positive

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

MRT-2359 displays activity in castrate resistant VCAP model

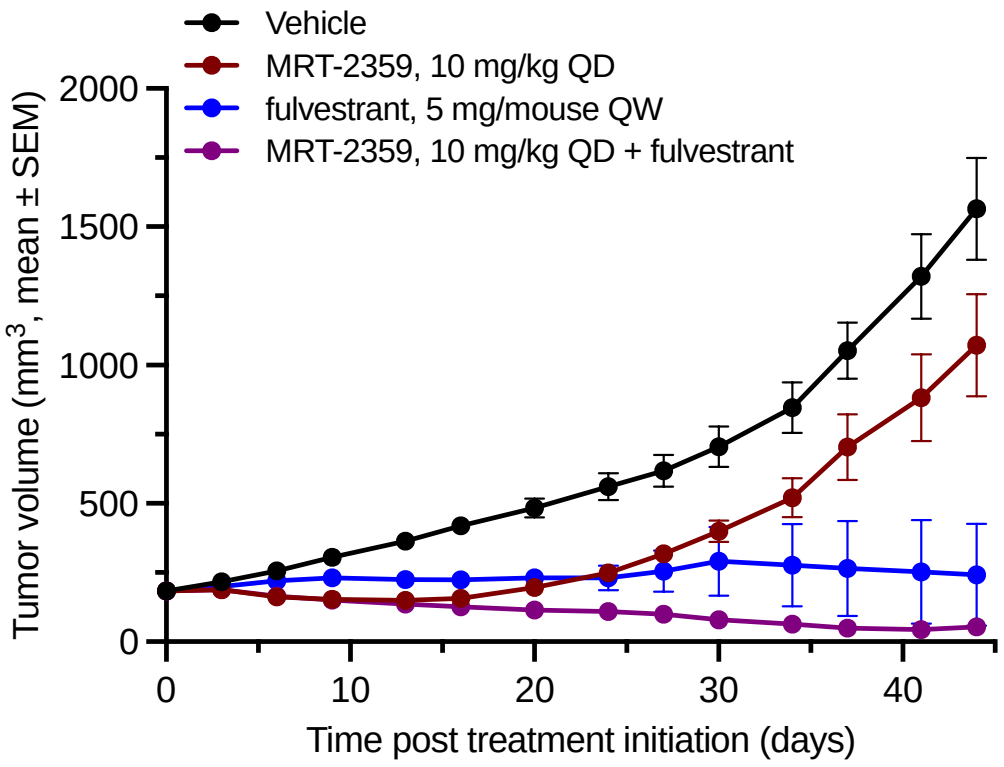


MRT-2359 displays activity in ARV7 driven 22RV1 model



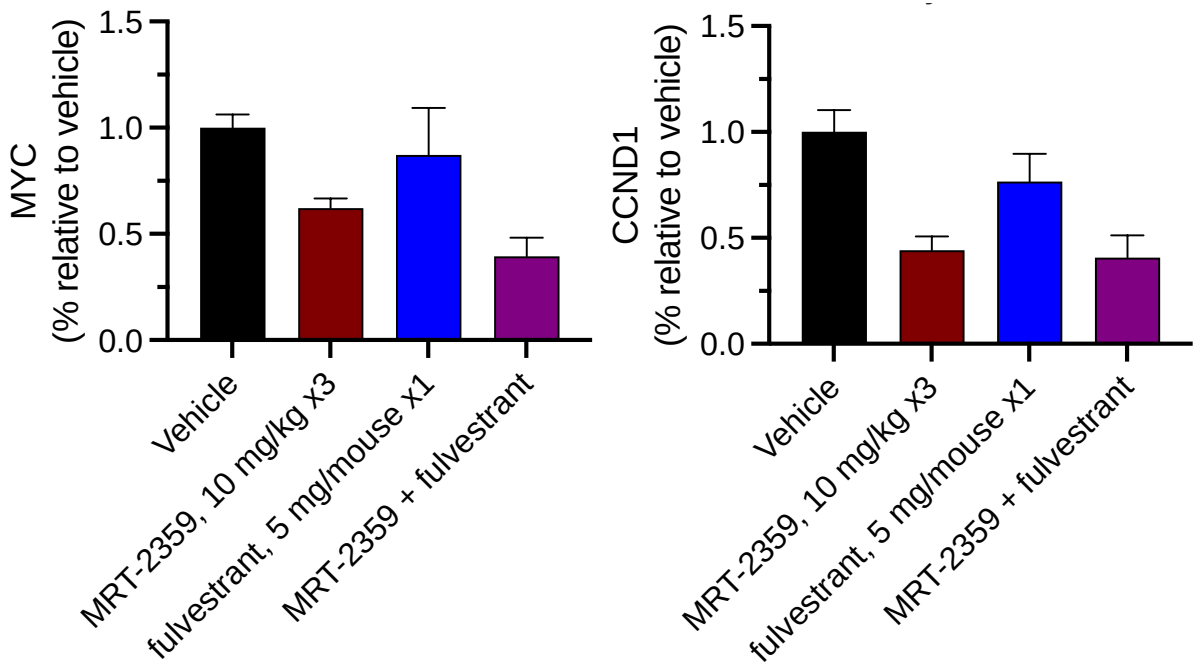
MRT-2359 Leads to Tumor Regressions in Preclinical Model of ER-positive Breast Cancer

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



MCF7 Breast CDX (ER+, HER2-)

MRT-2359 reduces MYC and CCND1 *in vivo*



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

Phase 1: Dose Escalation

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

RP2D (expected Q2 2024)

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

Backfill: Up to 6 additional pts for each dose level

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

Phase 2: Expansion Cohorts

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

* Efficacy guided stratification per N-/L-MYC expression
** Retrospective stratification per N-/L-MYC expression
*** Planned cohorts, to be confirmed

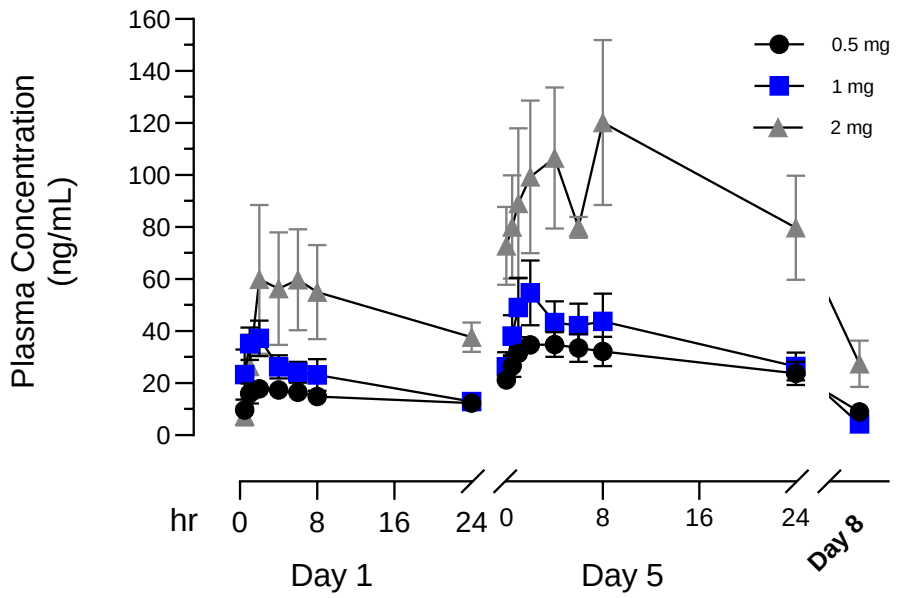
MRT-2359 Phase I Interim Data – October 2023

Objectives of Phase I interim analysis

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

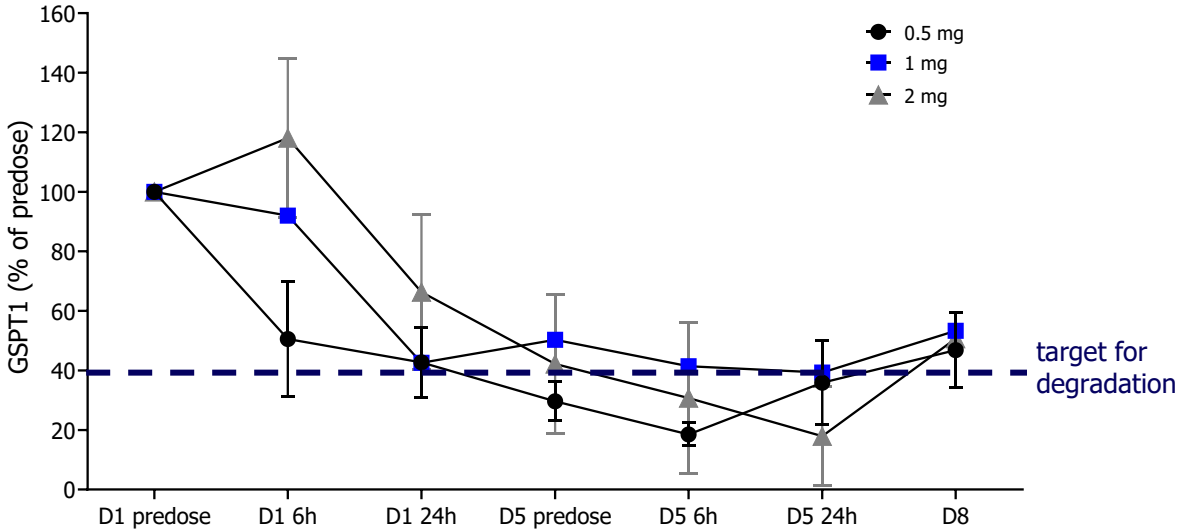
MRT-2359 Induces Optimal GSPT1 Degradation in PBMCs*

MRT-2359 displayed dose dependent plasma exposure



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

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

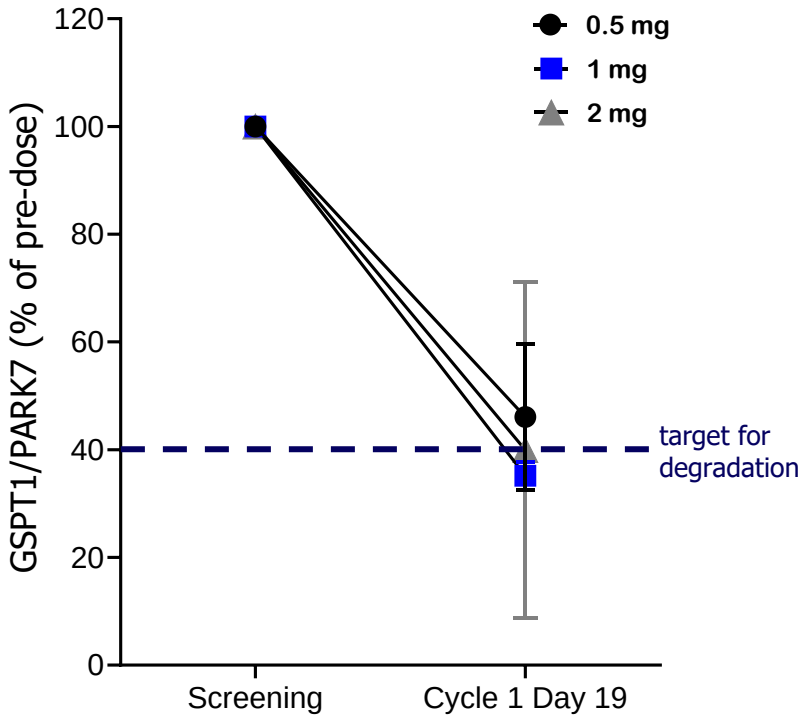


- GSPT1 expression assessed using targeted mass spectrometry
- PD modulation in PBMCs observed across all dose levels; level of degradation (~ 60%) in line with maximal degradation observed in preclinical studies using the same method
- Level of degradation equivalent across all dose levels, suggesting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

* as presented on 10/17/23

MRT-2359 Induces Optimal GSPT1 Degradation in Tissue Biopsies*

MRT-2359 reduced GSPT1 protein expression in human tissue biopsies



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

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

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

No observed clinically significant hypocalcemia or hypotension/cytokine release syndrome

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

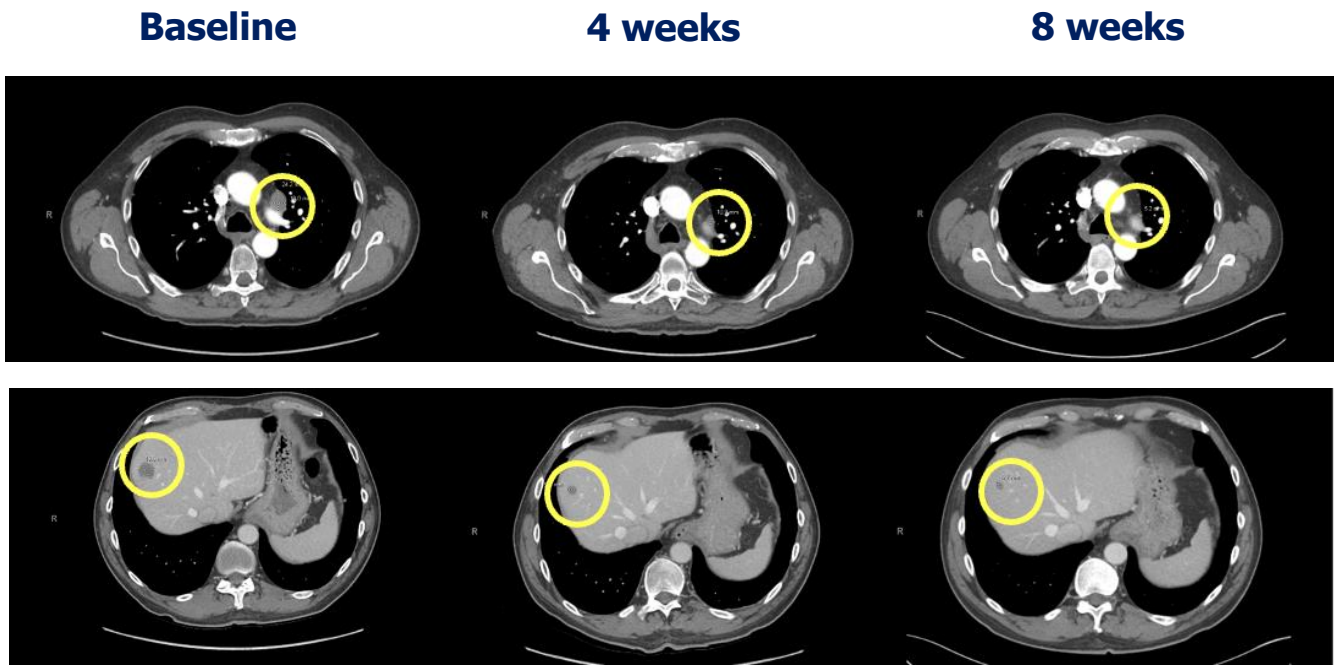
Note: As presented on 10/17/23

[#] Data cut-off: 7 SEP 2023
[##] MRT-2359 was given orally daily on the 5 days on and 9 days off schedule
[###] Data combined for 'thrombocytopenia' and 'platelet count decreased'

[*] Data combined for 'neutropenia' and 'neutrophil count decreased'
[**] Data combined for 'diarrhea' and 'feces soft'
[***] Dose limiting toxicity: Grade 4 thrombocytopenia in 2 patients

Confirmed Partial Response in High Grade Neuroendocrine Bladder Cancer*

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

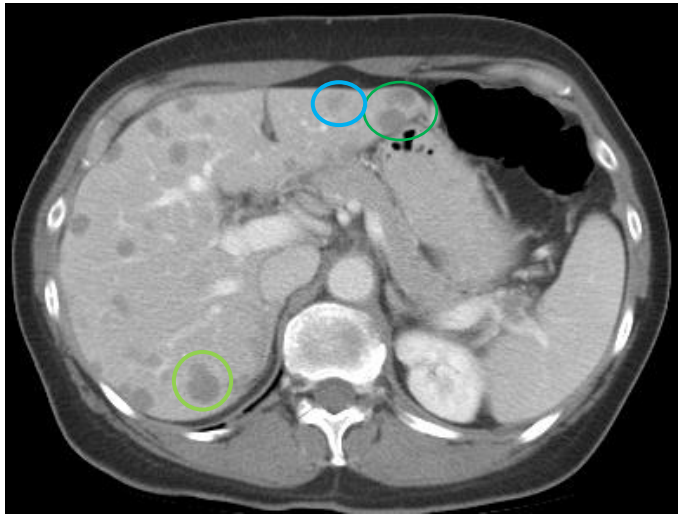


* as presented on 10/17/23

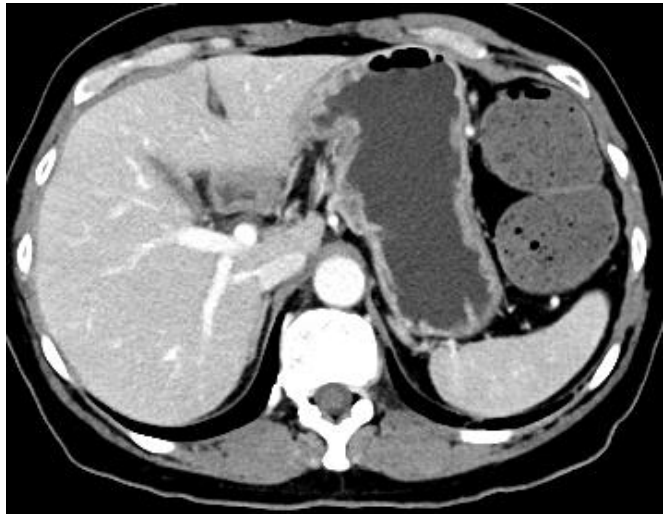
Unconfirmed Partial Response in NSCLC with SCLC/NE Transformation*

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

Baseline



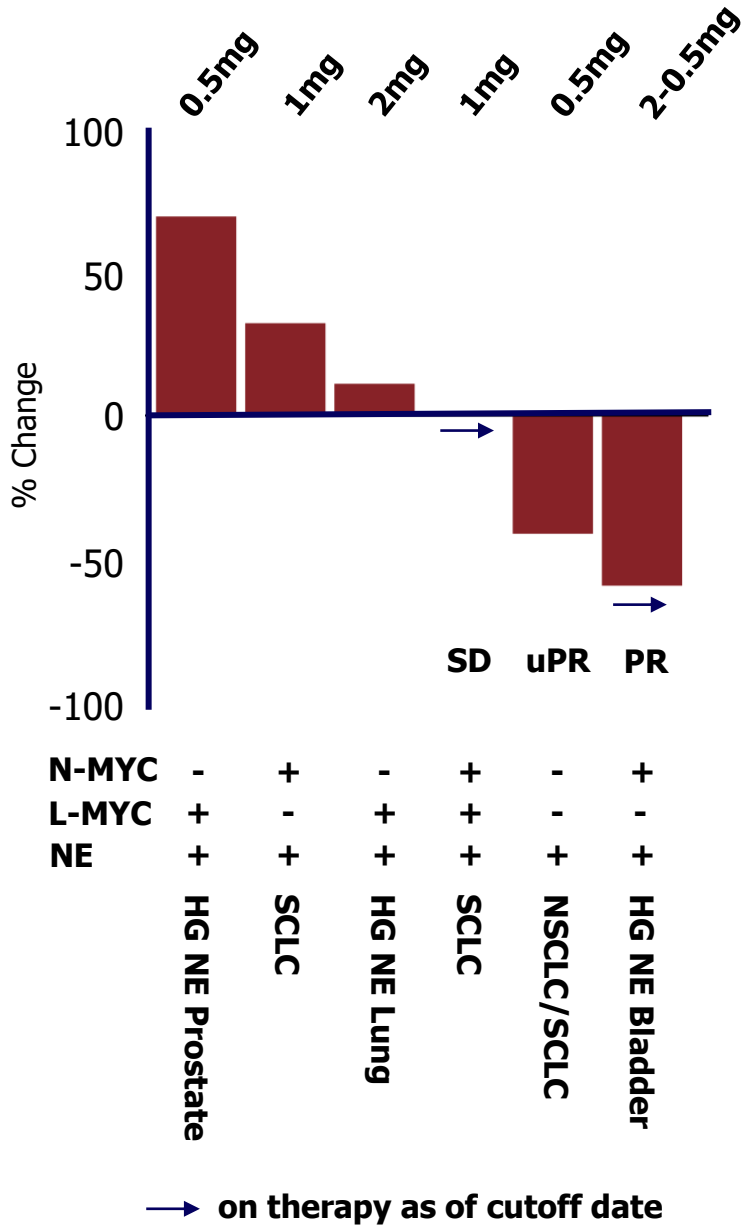
3 weeks



* as presented on 10/17/23

MRT-2359-001 – Preliminary Efficacy Data*

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



* as presented on 10/17/23

Favorable Safety at Clinically Active Doses*

Safety profile supports further development

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

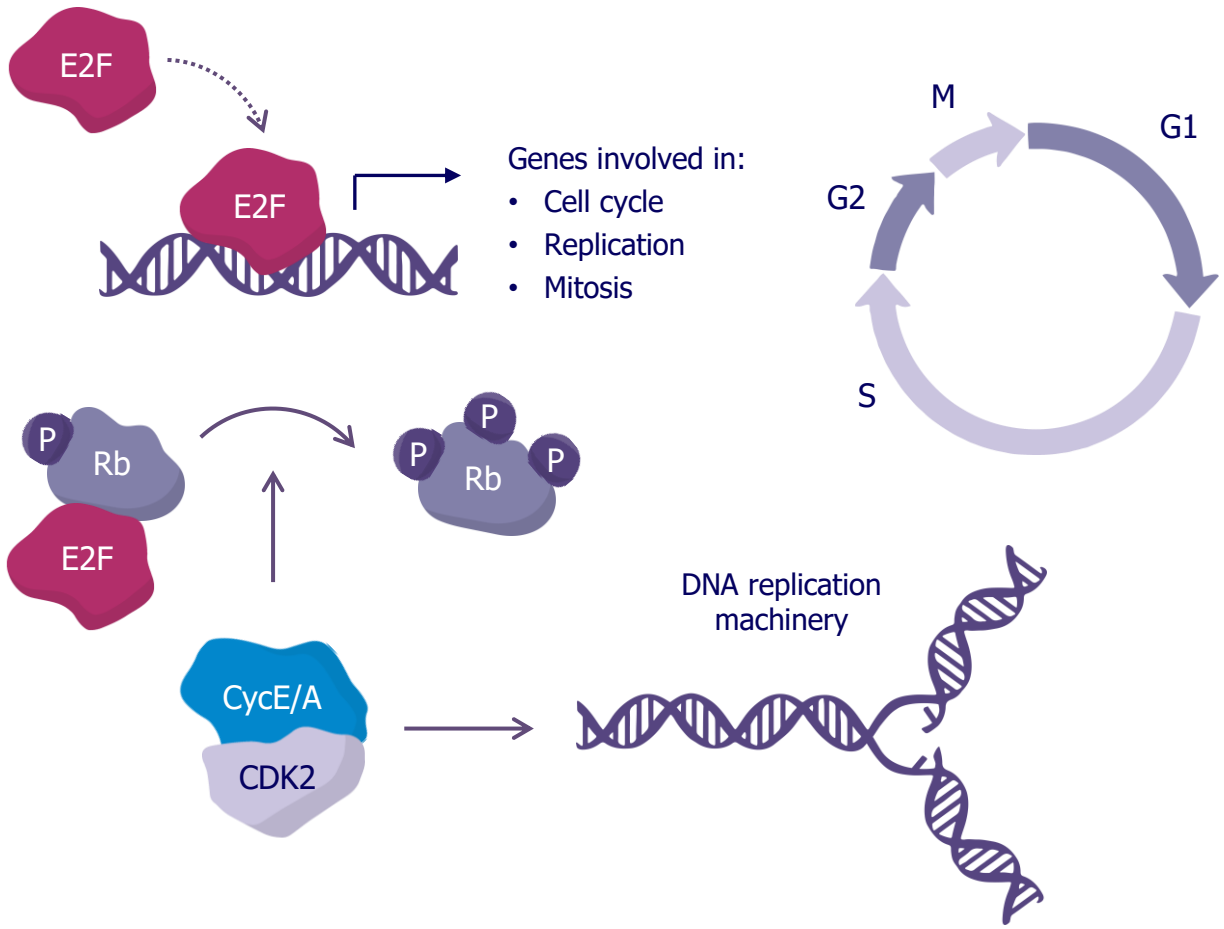
* as presented on 10/17/23

Monte Rosa Therapeutics

CDK2 Program

CDK2 as a Key Driver of Cell Cycle Progression in Cancer

CDK2 a key cell cycle regulator



Therapeutic hypothesis:

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

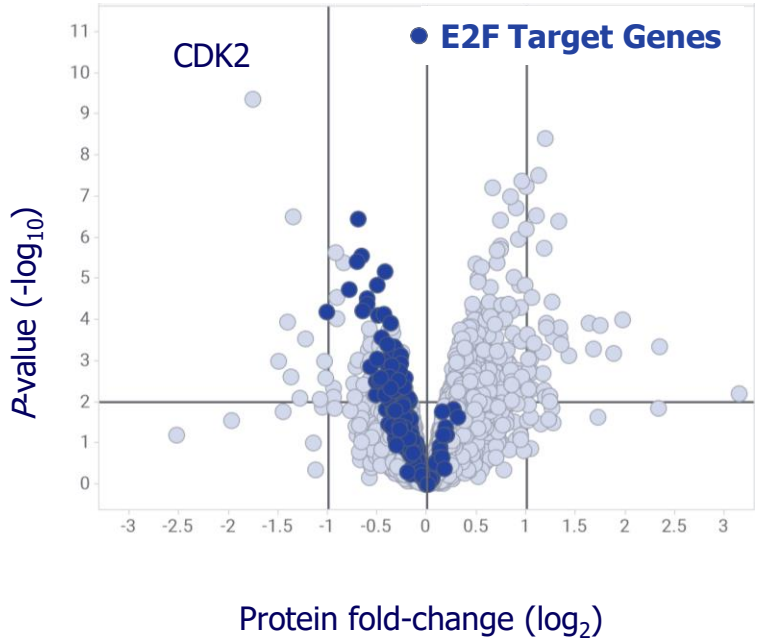
Clinical Opportunity:

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

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

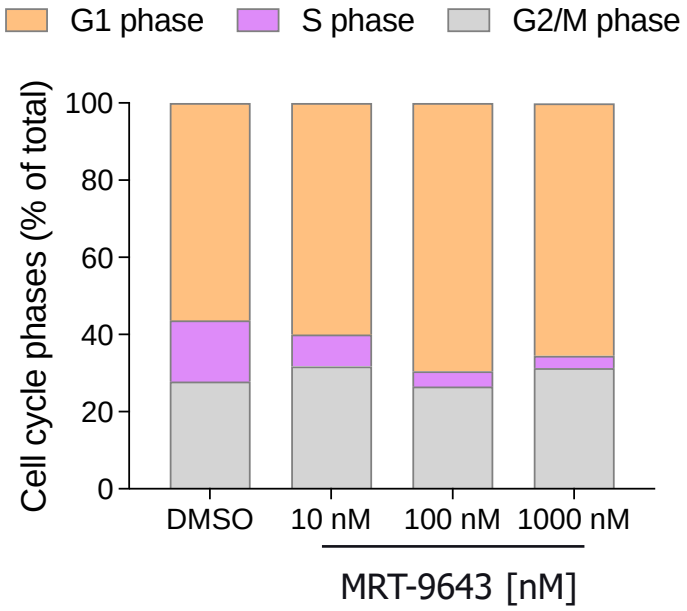
Orally Bioavailable MGD MRT-9643 is Selective and Shows Biological Activity in a CDK2 Dependent Cell Line

Selective CDK2 degradation reduces E2F pathway genes



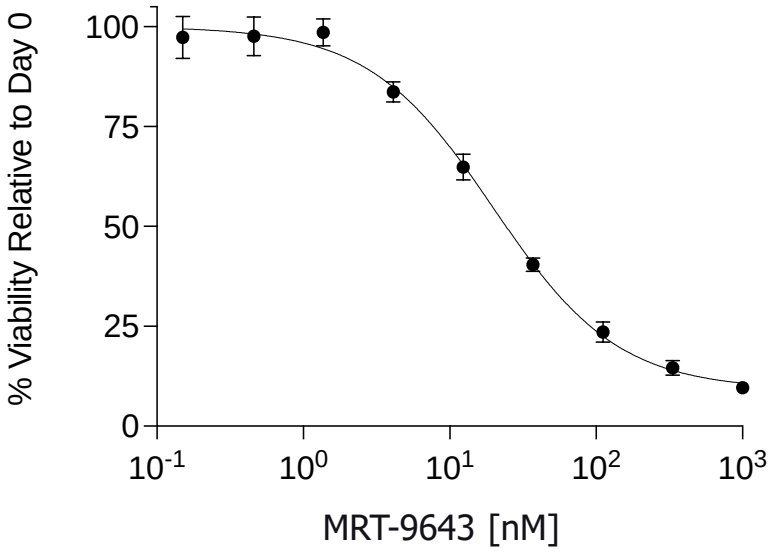
TMT Proteomics (24 hr/1 μM)
MDA-MB-157

CDK2 degradation arrest CDK2-dependent cells in G1 phase



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

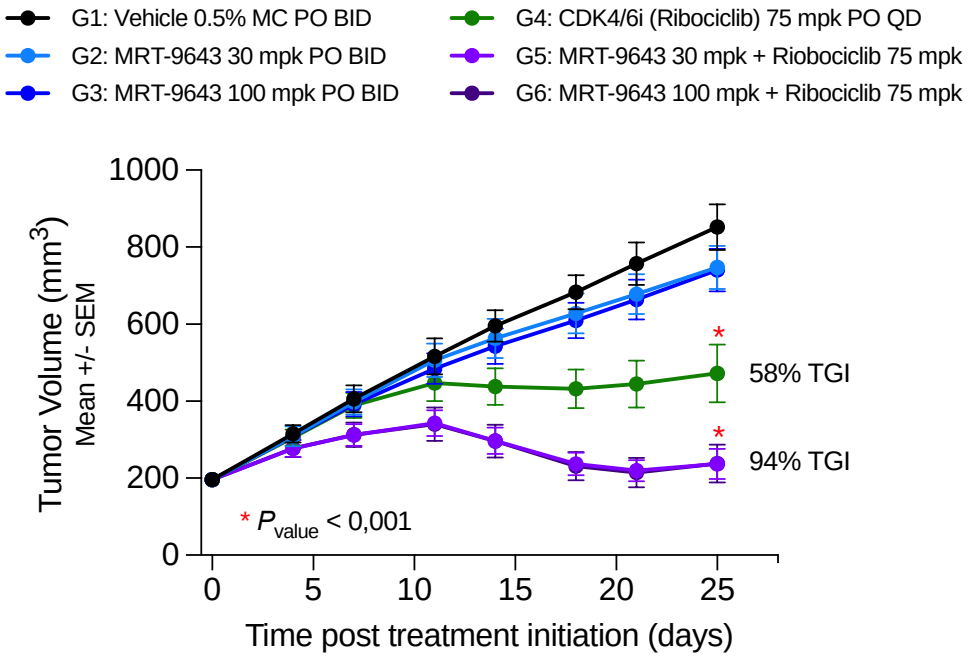
CDK2-directed MGD inhibits proliferation of CDK2 dependent cells



CyQuant Assay (7 d)
MDA-MB-157

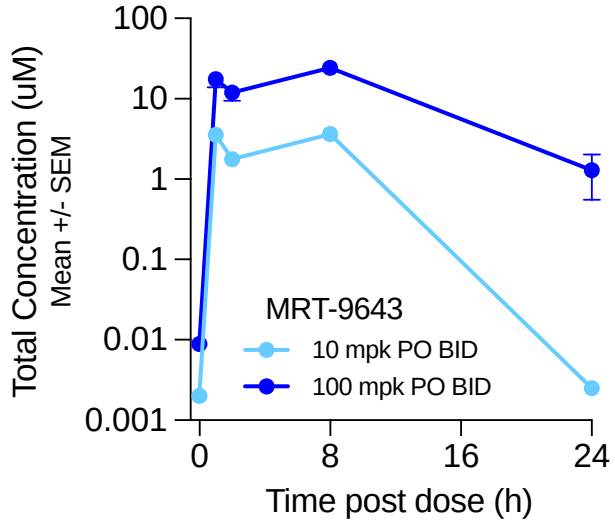
Orally Bioavailable MGD MRT-9643 Demonstrates Activity as Single Agent and in Combination with CDK4/6i in ER+ Breast Cancer

Orally dosed CDK2 MGD induces strong TGI in combination with CDK4/6i *in vivo*

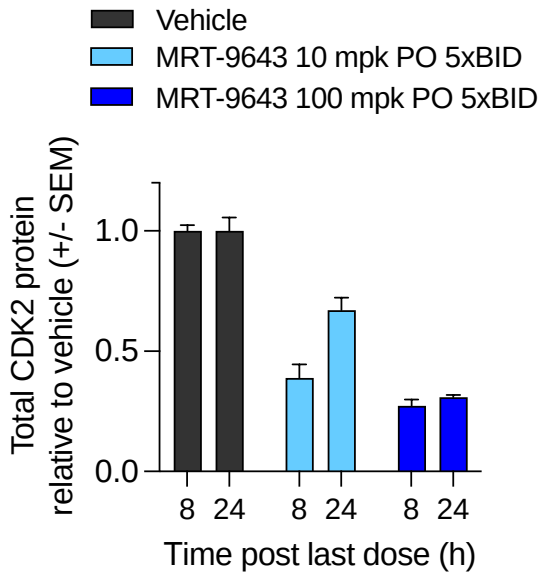


Efficacy evaluation, 25-day treatment
MCF7 ER+ BC CDX Model

CDK2 MGD is orally bioavailable and degrades CDK2 *in vivo*



Plasma PK exposure
MCF7 ER+ BC CDX



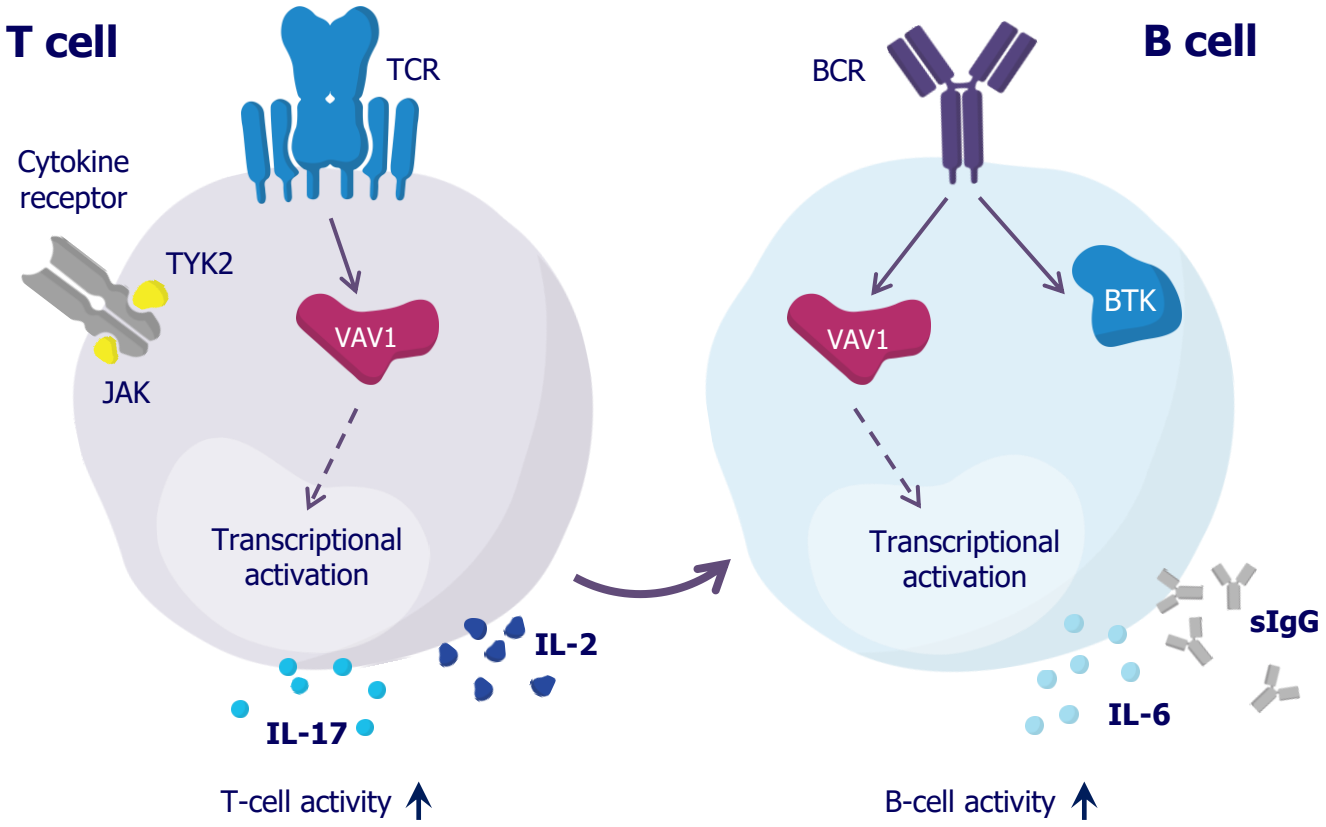
Oral PK/PD study
HCC1159 BC CDX

Monte Rosa Therapeutics

VAV1 Program (MRT-6160)

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

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



VAV1 signaling increases cytokine production, proliferation, and differentiation

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

Therapeutic hypothesis:

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

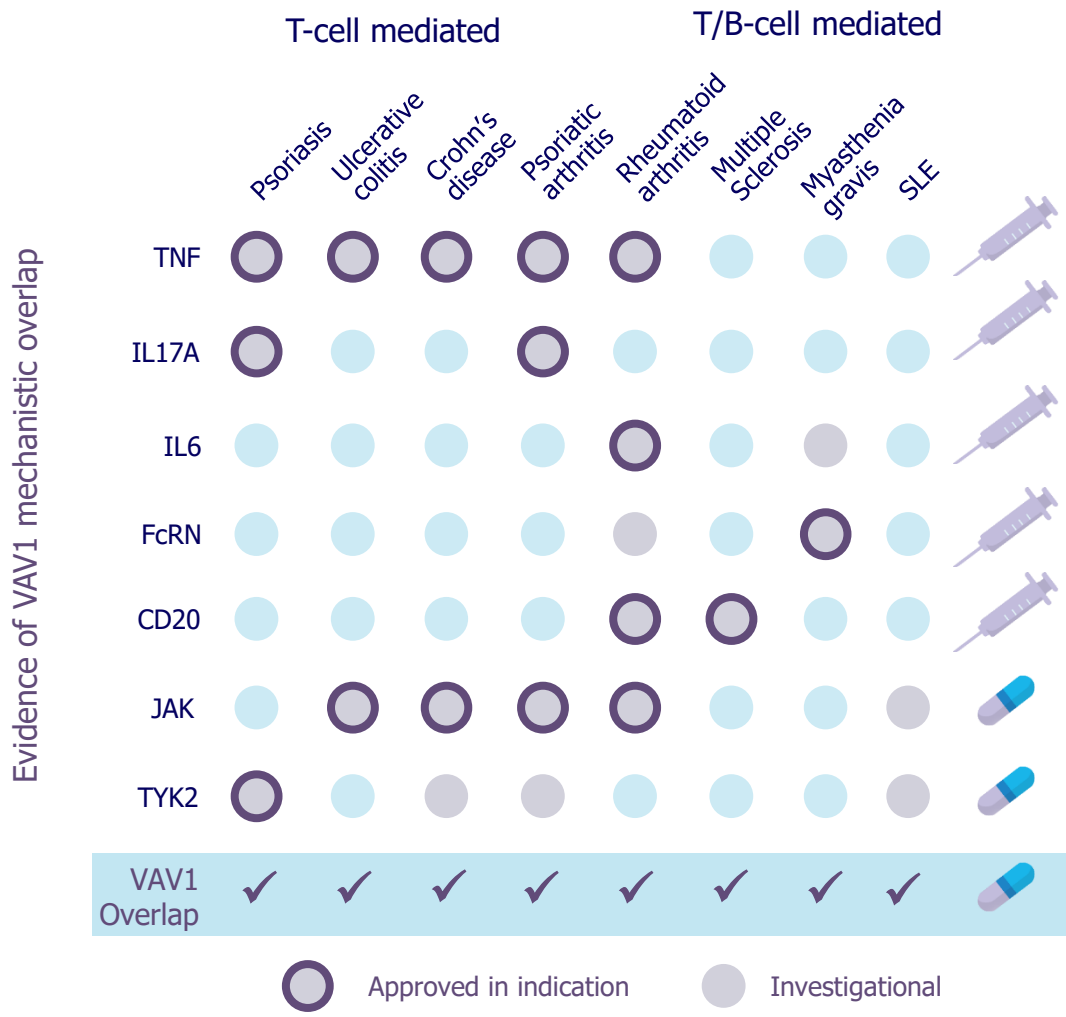
Clinical Opportunity:

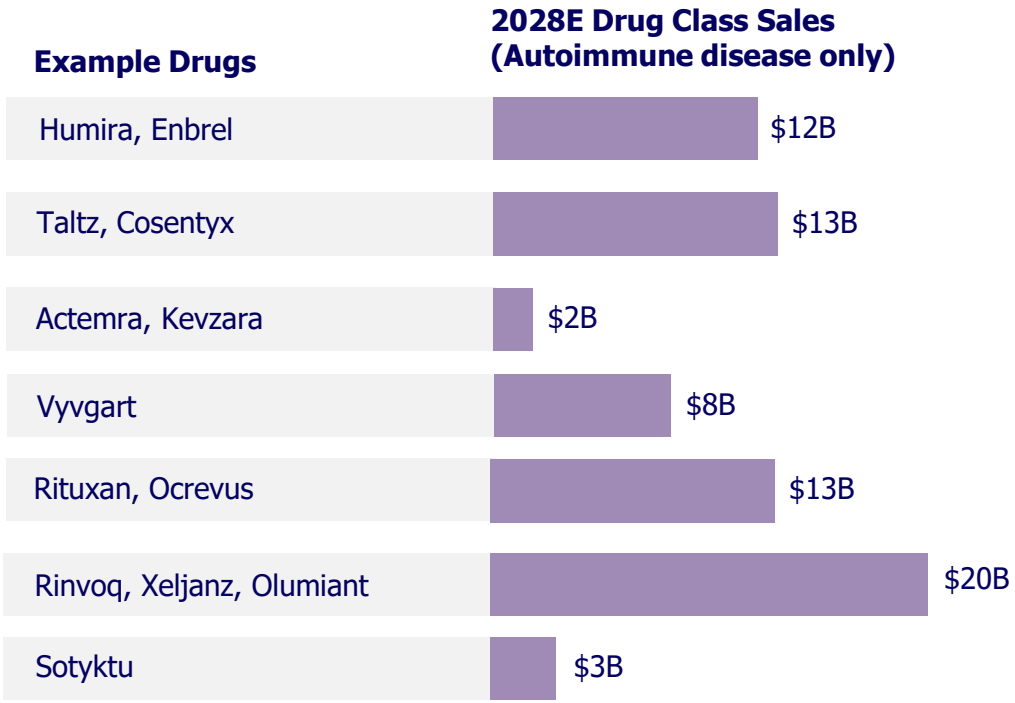
Autoimmune disorders including rheumatoid arthritis (6.2M patients), multiple sclerosis (1.3M patients), and myasthenia gravis (36K – 60K patients in US)

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

VAV1: Unique Mechanism with Broad Potential Applications

Potential to address multiple autoimmune diseases with safe, oral therapy

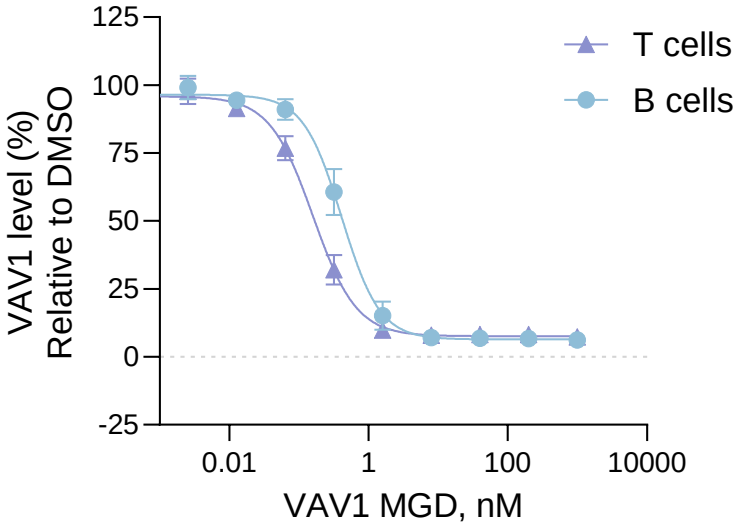




Note: Chart adapted from Hosack et al., Nat Rev Immunol 2023. Drug class sales from Evaluate Pharma. 2028E sales may include sales from anticipated future approvals.

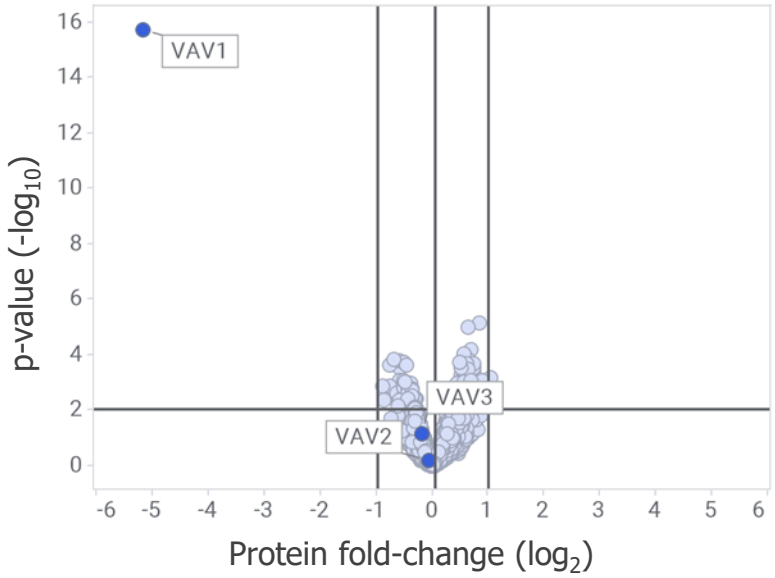
MRT-6160 is a Potent and Selective VAV1-directed MGD

MRT-6160 is a potent VAV1-directed MGD



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

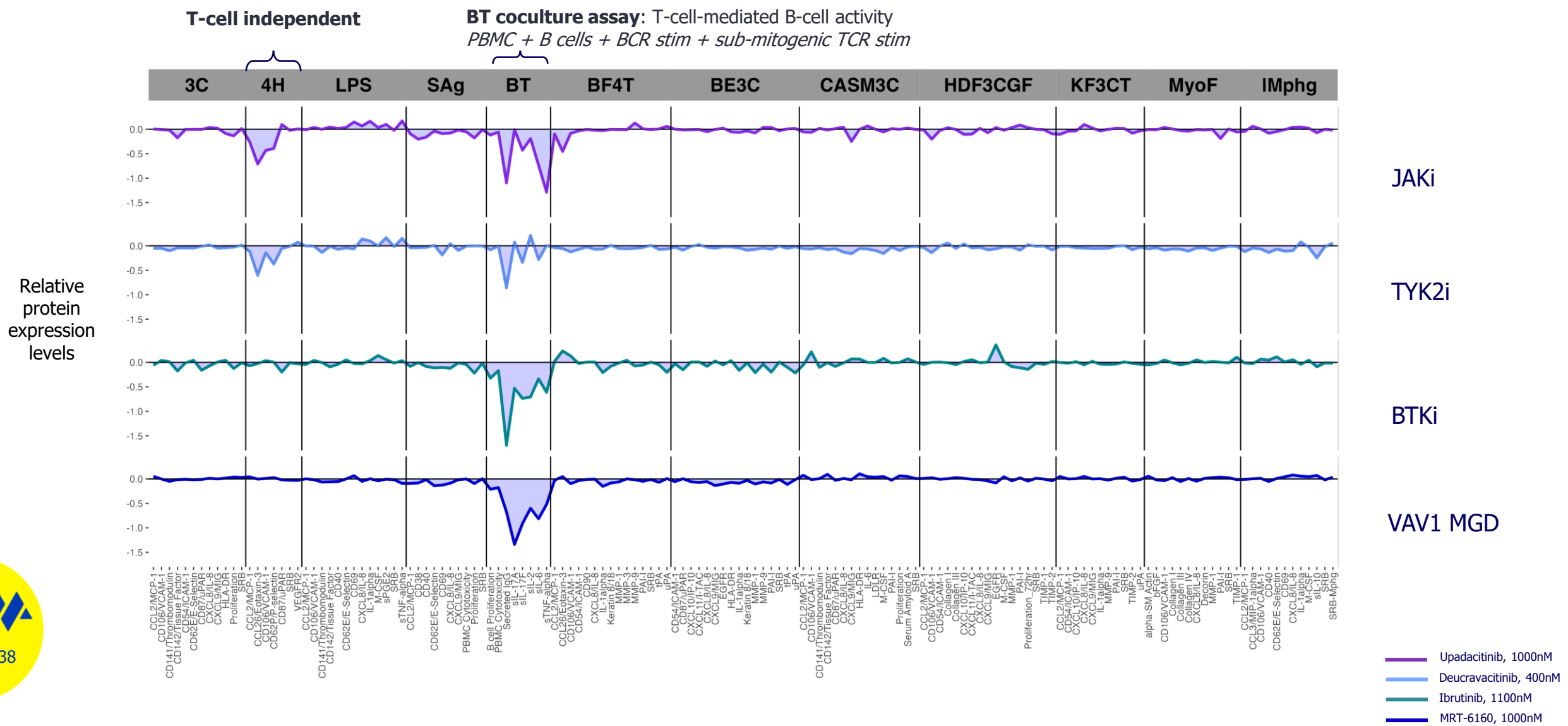
MRT-6160 induces highly selective VAV1 degradation and has a favorable ADME/DMPK profile



No degradation of other known cereblon neosubstrates

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

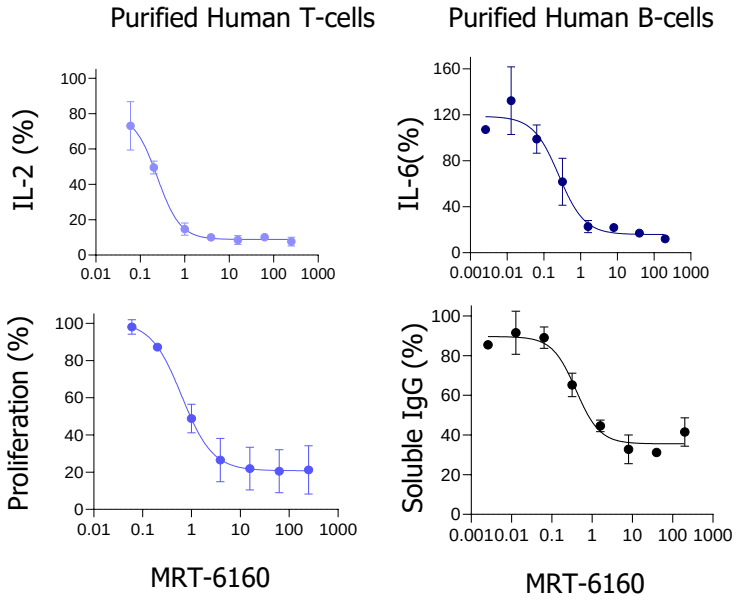
MRT-6160 Demonstrates Differentiated Activity (BioMAP) Profile



MRT-6160 Attenuates T- and B-Cell Activity and Cytokine Production

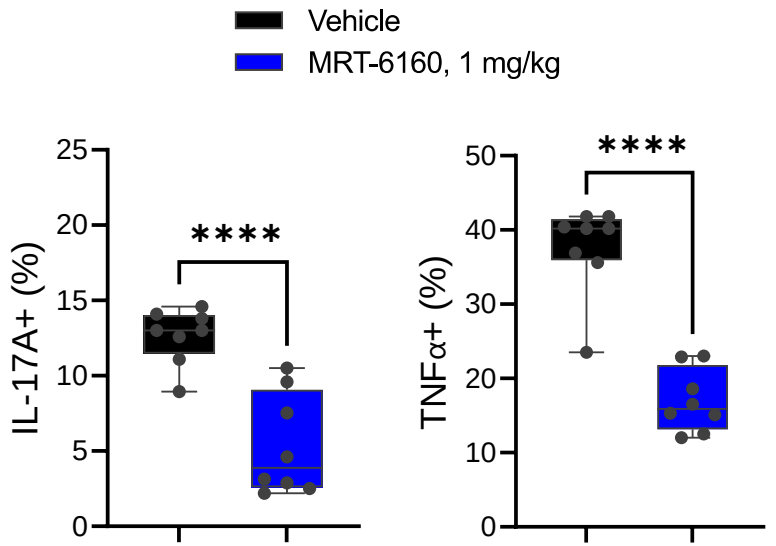
Experimental demonstration of activity overlapping with clinically validated mechanisms

Direct impact on T-cell and B-cell effector functions



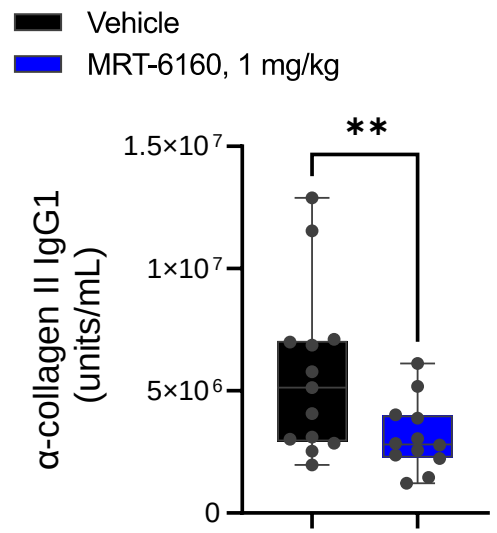
Antigen receptor *ex-vivo* stimulated human lymphocytes

Attenuation of disease-relevant cytokines (IL-17A, TNFα)



Ex-vivo stimulated CD4+ T cells from T-cell transfer-induced colitis model

Reduction of T-cell dependent antibodies against self-antigens (auto-Ab production)



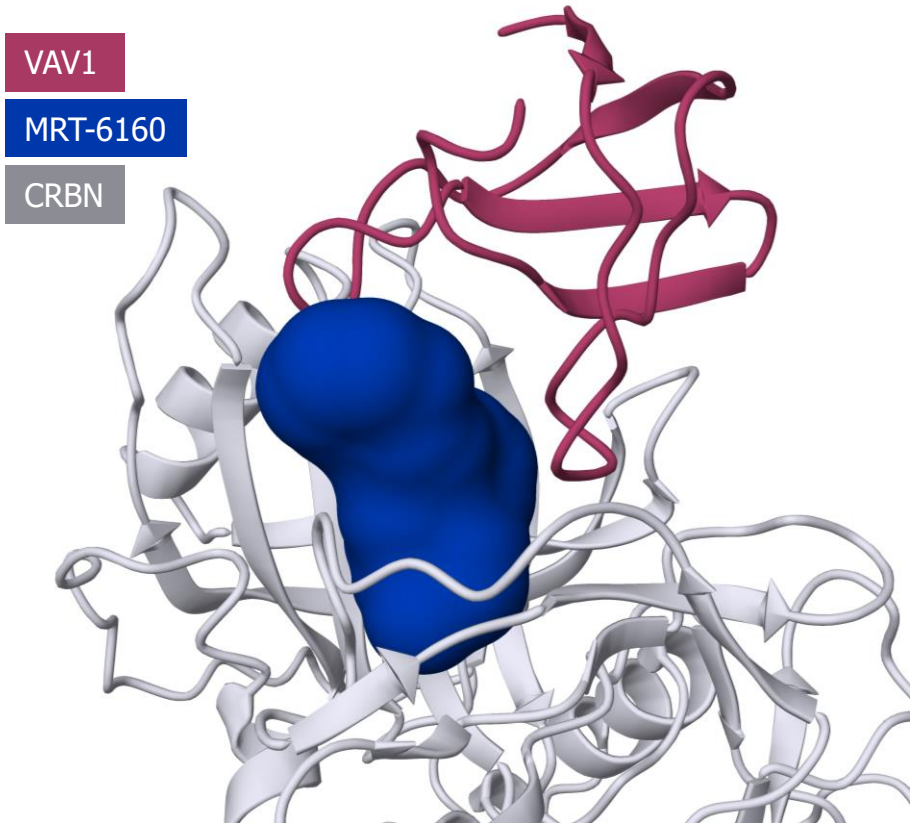
Serum assayed from collagen-induced arthritis model

VAV1 MOA Overlap

- ✓ JAKi
- ✓ IL6 antagonists
- ✓ BTKi
- ✓ anti-CD20
- ✓ TYK2i
- ✓ IL17A/F antagonists
- ✓ anti-TNFα
- ✓ anti-FcRN

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

VAV1 ternary complex (Cryo-EM)



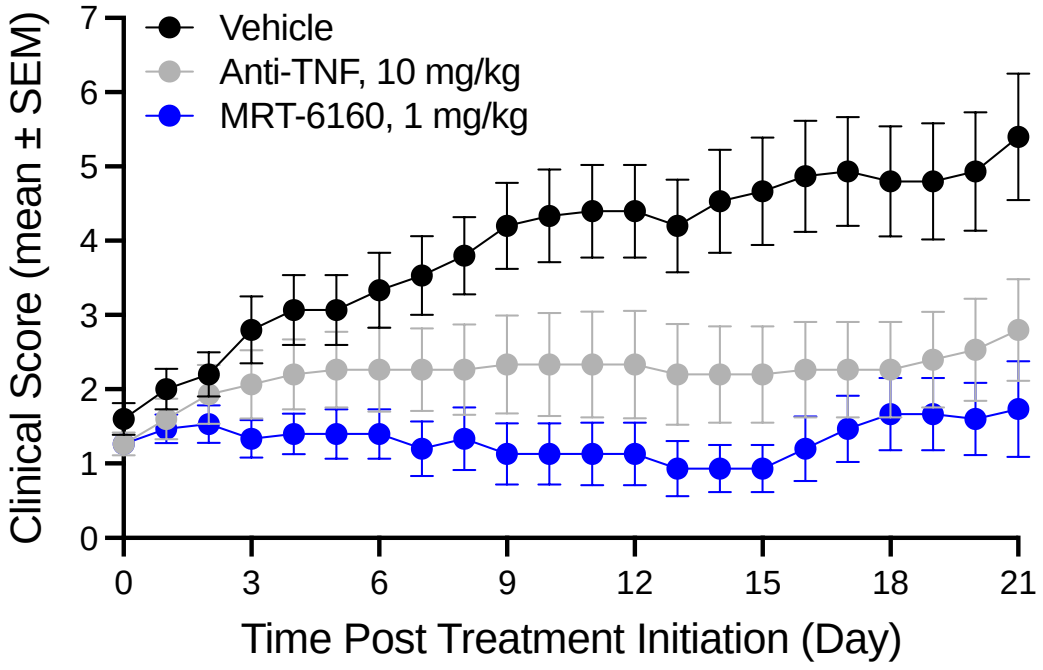
Cryo-EM structure of MRT-6160 in ternary complex with CRBN and VAV1

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)
Counterscreens (panel with 98 targets)	No inhibition

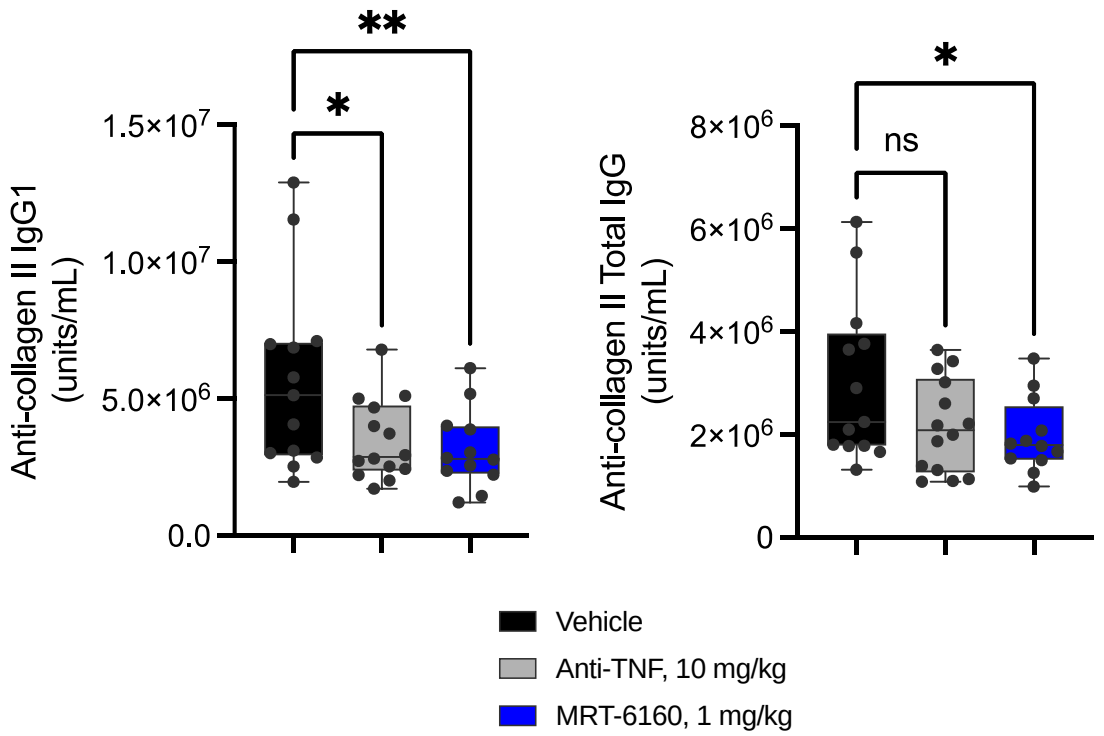
Preclinical GLP tox studies in rats and NHPs demonstrates highly favorable profile including no significant changes in peripheral immunophenotyping assessments

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

MRT-6160 inhibits disease progression



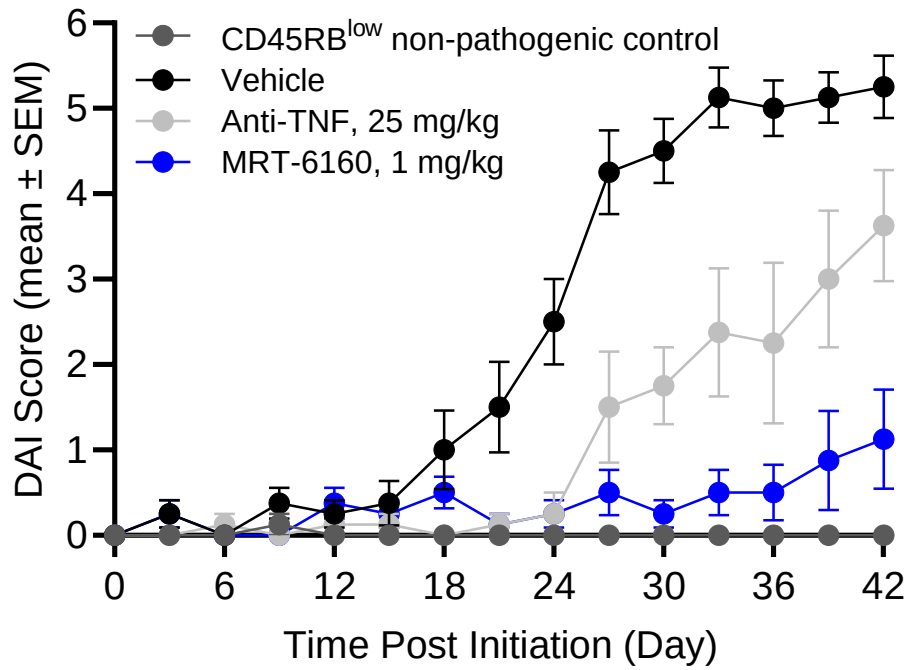
MRT-6160 inhibits anti-collagen II auto-antibodies



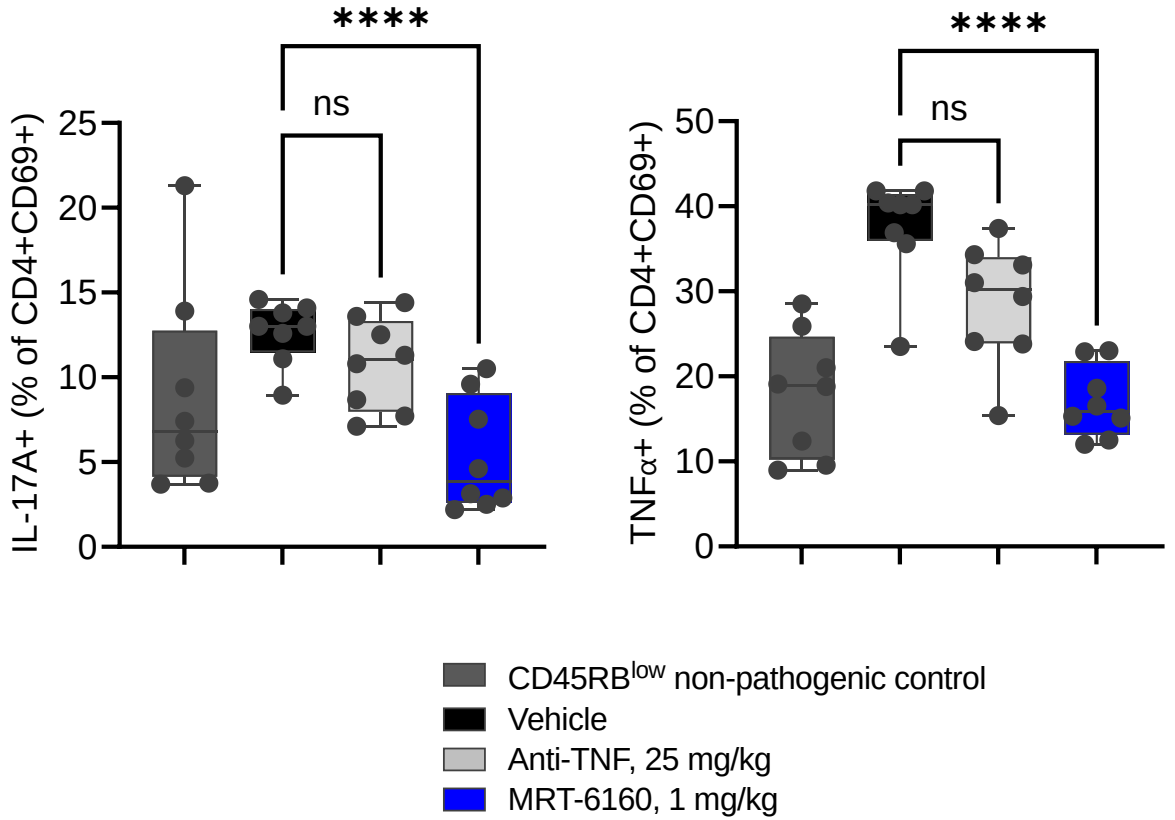
Collagen-induced arthritis T/B-cell (auto-antibody) driven model

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

MRT-6160 inhibits disease progression in a model of colitis



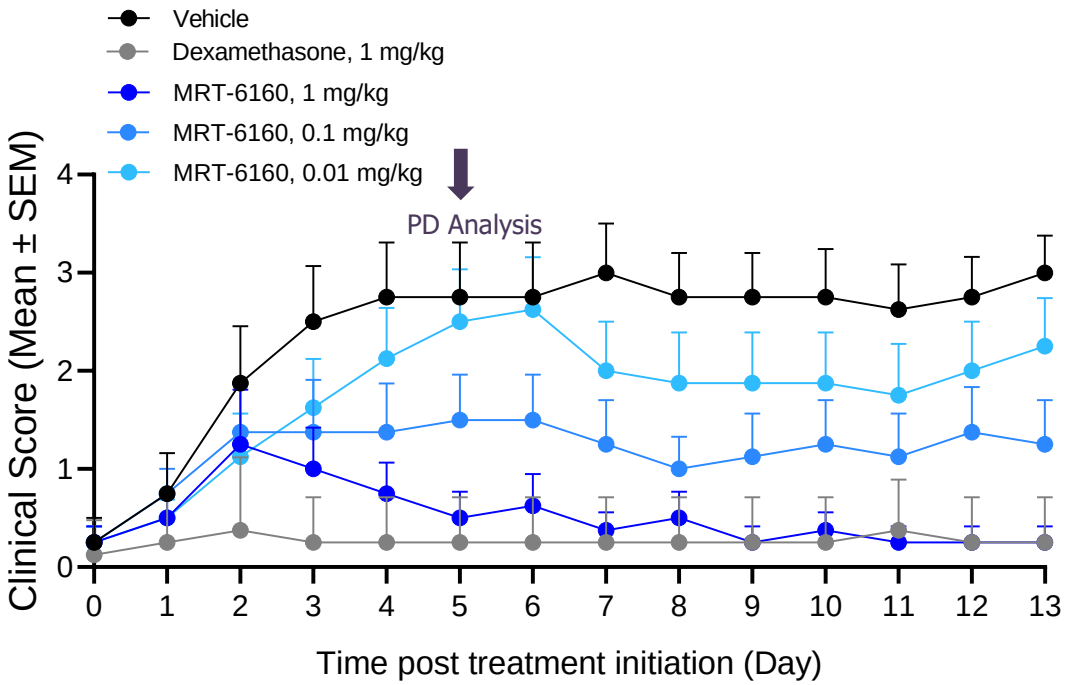
MRT-6160 reduces pro-inflammatory cytokine production by CD4+ T cells



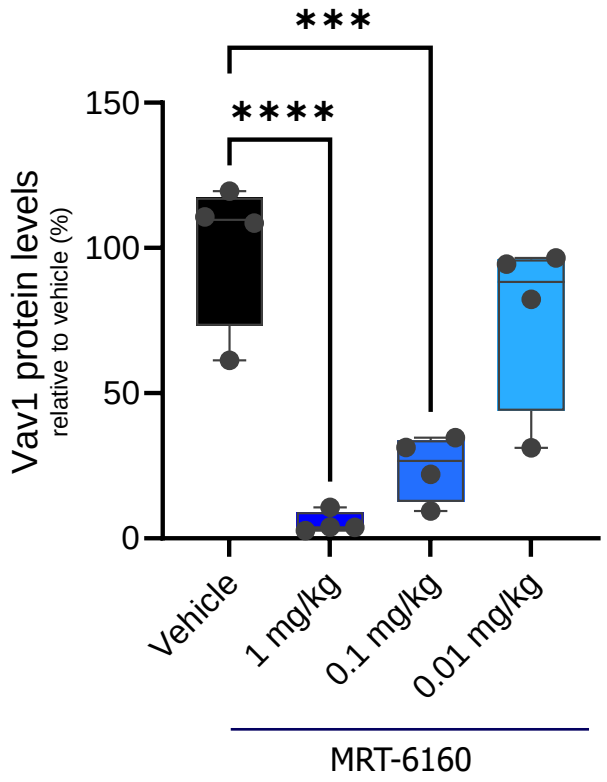
CD4+ T cell transfer-induced colitis model

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

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

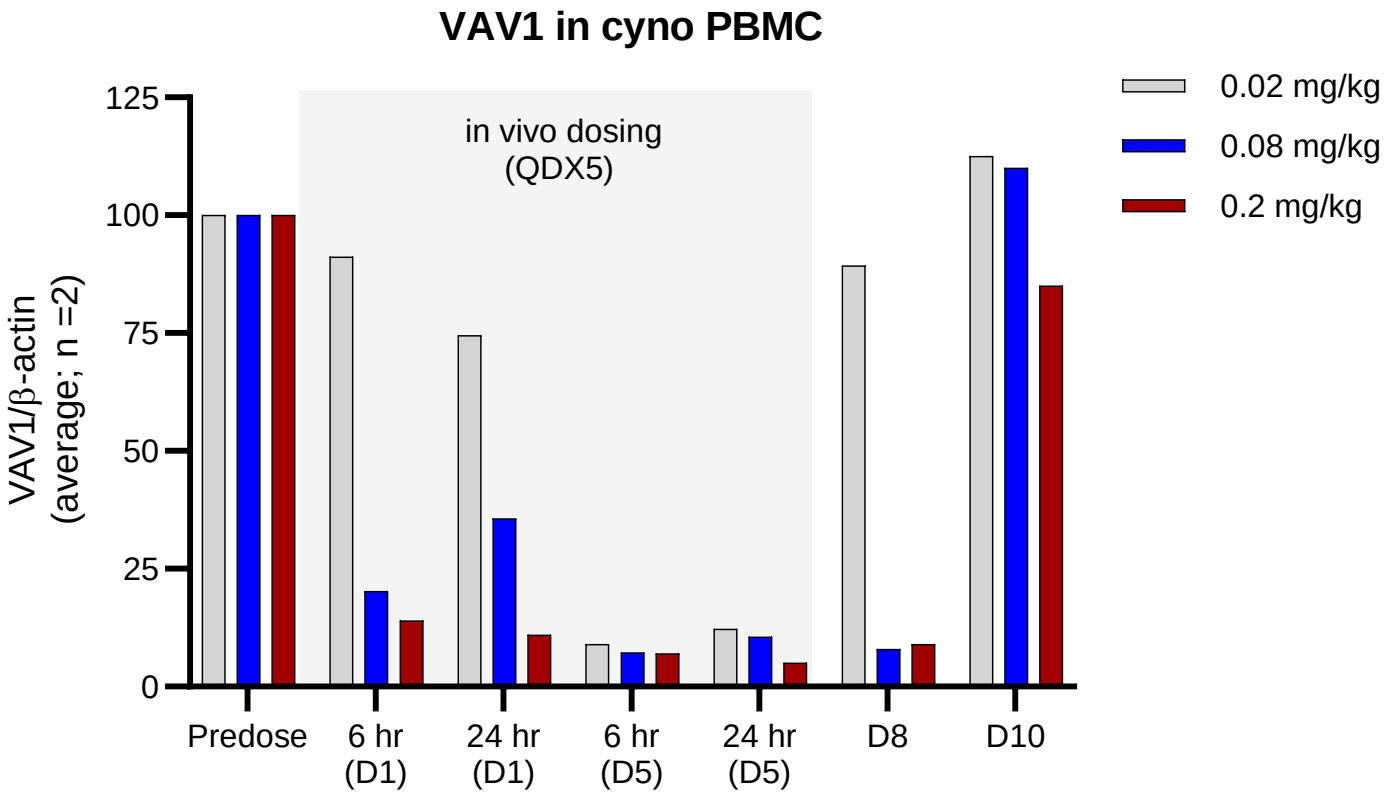


MRT-6160-mediated activity correlates with VAV1 levels



T-cell mediated experimental autoimmune encephalitis (EAE) model

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



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

Preliminary MRT-6160 Development Plan through Early POC

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

Phase 1 SAD/MAD in Healthy Volunteers

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

Potential Early Proof-of-Concept Indications

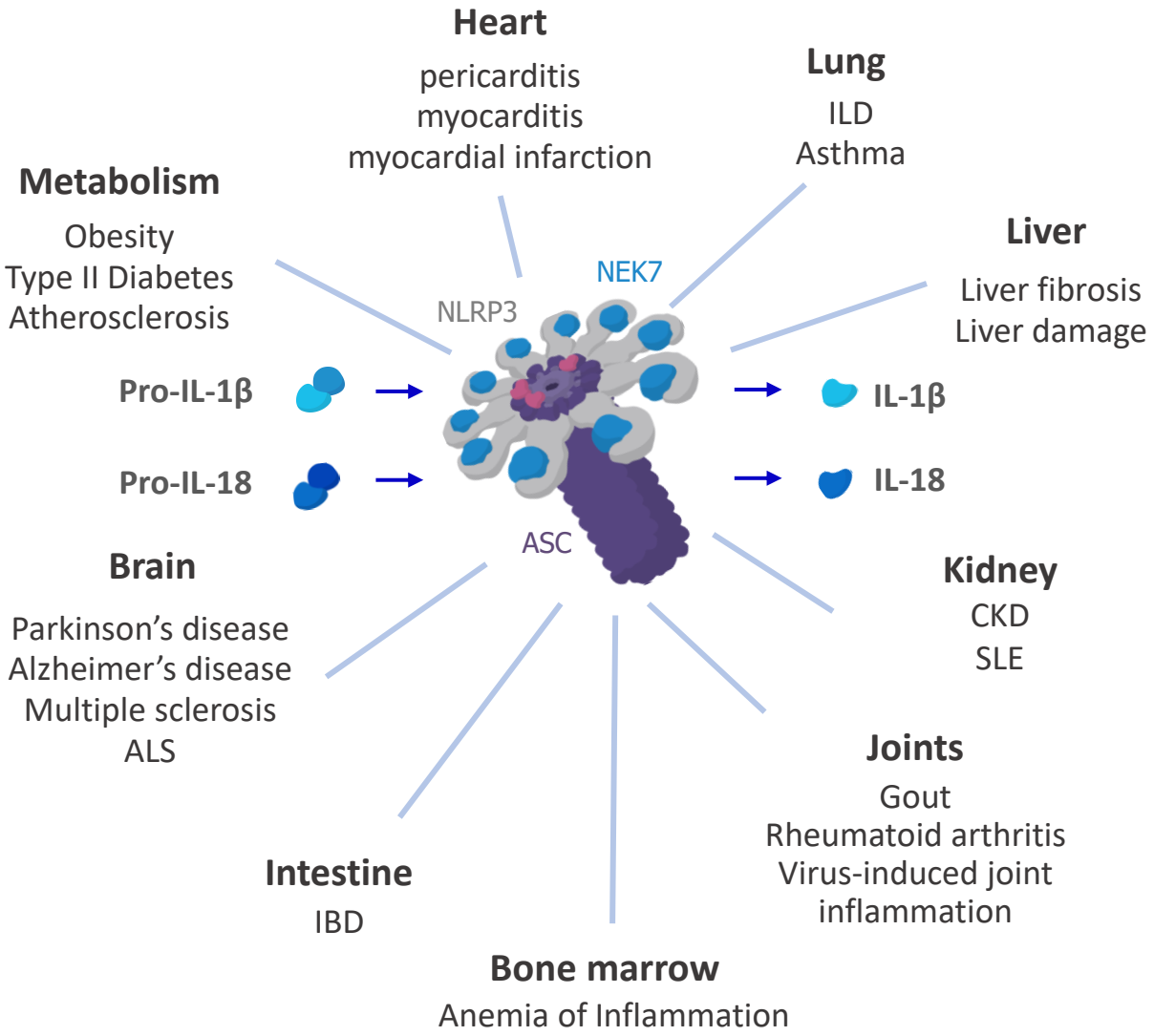
- **Gastroenterology** – Ulcerative colitis
- **Rheumatology**
  - Rheumatoid arthritis
  - Axial spondyloarthritis
- **Neurology**
  - Multiple sclerosis
  - Myasthenia gravis
- **Dermatology**
  - Psoriasis
  - Cutaneous lupus erythematosus

SAD/MAD study expected to initiate mid-2024

Monte Rosa Therapeutics

NEK7 Program (MRT-8102)

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



Therapeutic hypothesis:

Activation of the NLRP3 inflammasome critically depends on NEK7

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

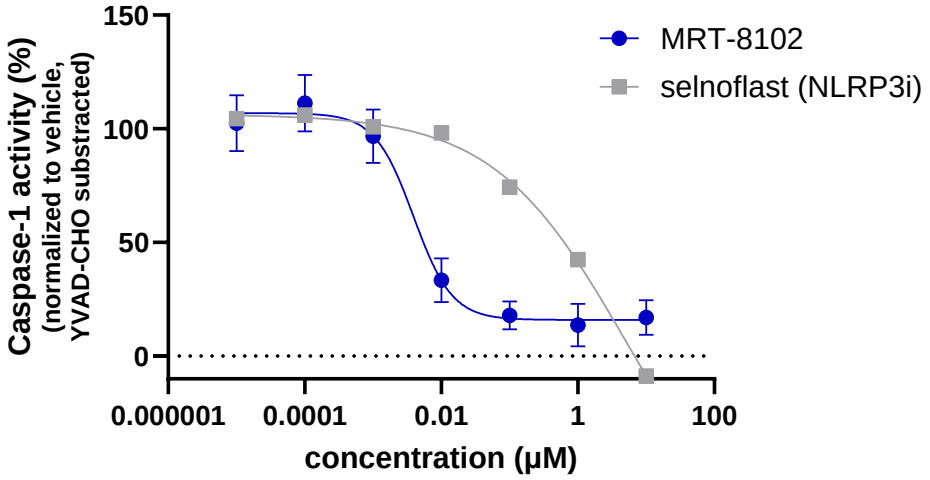
Consequently, NEK7 degradation has the potential to become an important treatment modality for a variety of inflammatory diseases

Clinical Opportunity:

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

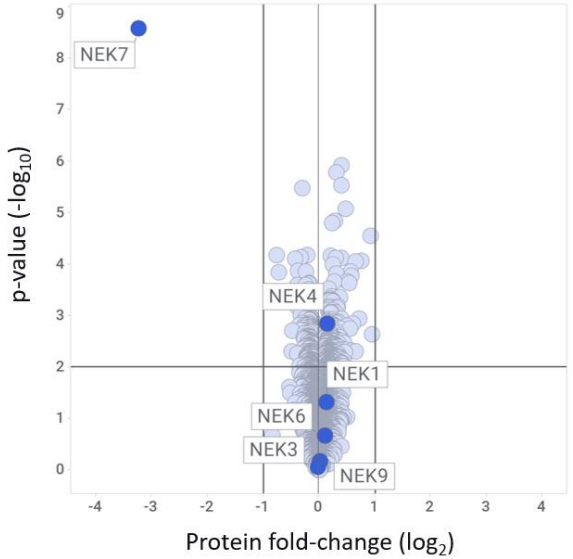
MRT-8102 is a Potent and Selective NEK7-directed MGD

MRT-8102 potently suppresses inflammasome activation in primary human macrophages



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

MRT-8102 induces highly selective NEK7 degradation

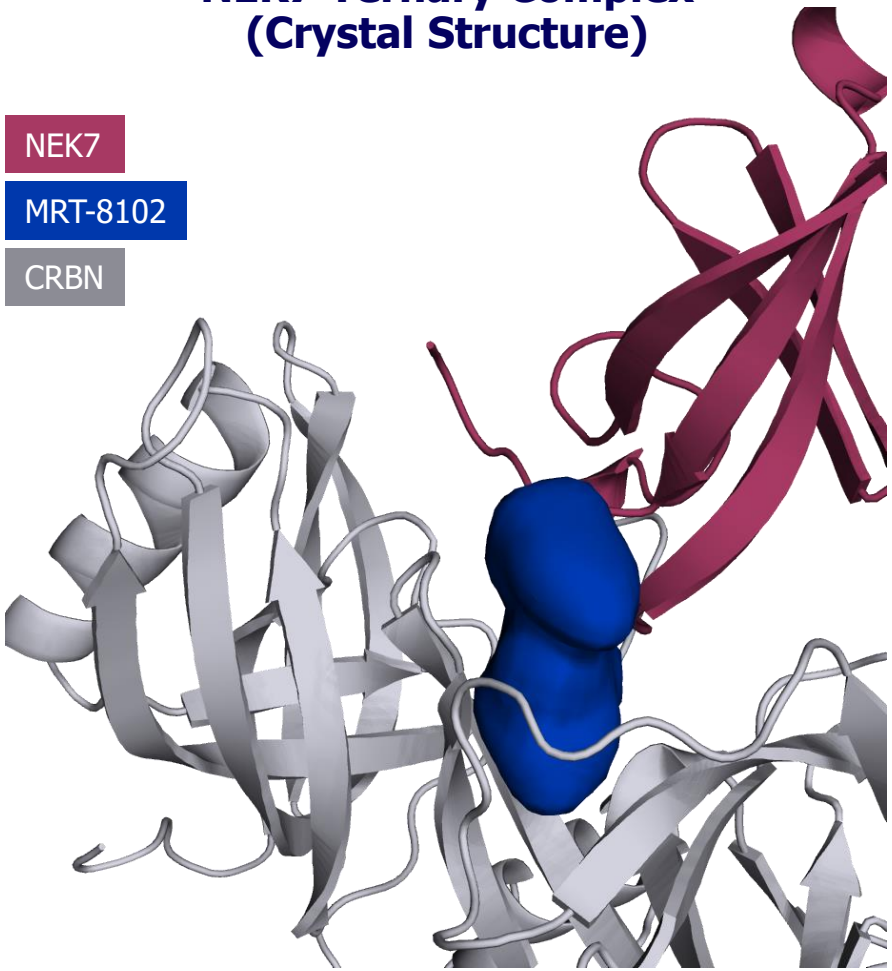


No degradation of other known cereblon neosubstrates

ADMET profile	
hERG	No inhibition
Oral bioavailability	Yes

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

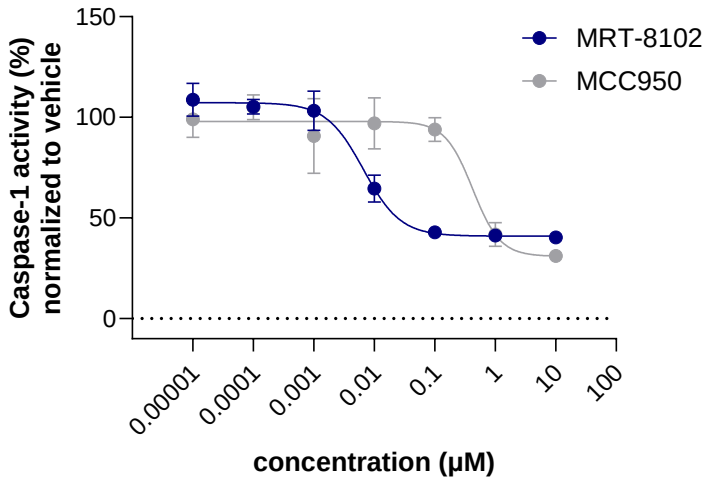
NEK7 Ternary Complex (Crystal Structure)



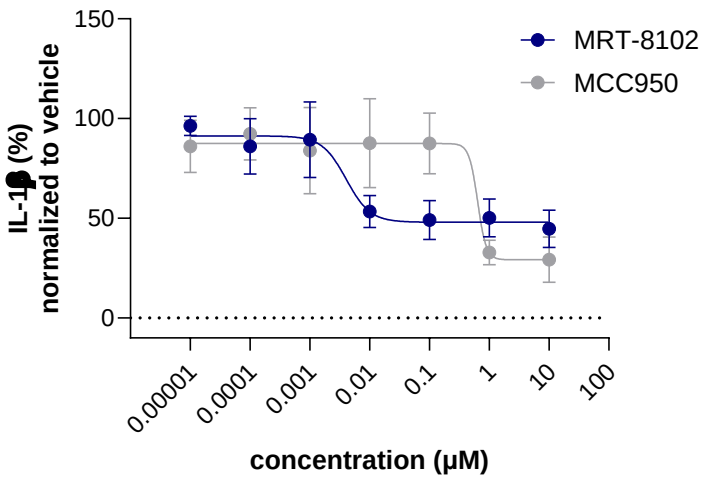
MGD Activity Profile	
CRBN Binding (HTRF, IC_{50})	0.2 µM
NEK7 Degradation (CAL51, DC_{50} /Dmax)	10 nM / 89%
Selectivity (TMT proteomics)	Excellent selectivity profile in different cell lines
Physicochemical Properties	
LogD	1.47
MW	<450
Thermodynamic Solubility	166 µM
ADMET Profile	
Oral Bioavailability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

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

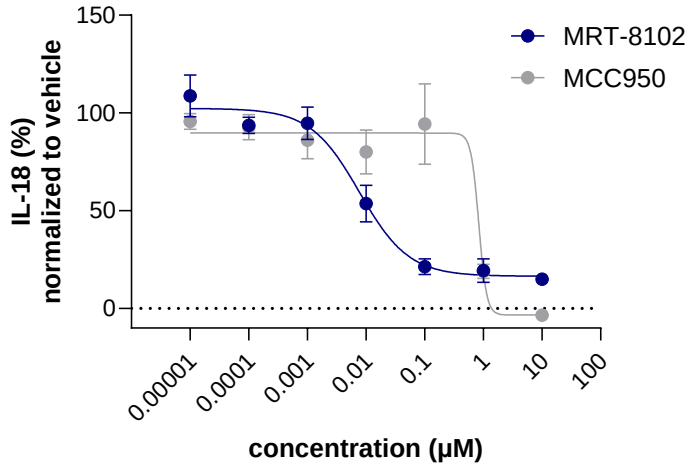
MRT-8102 inhibits caspase-1 activity in hMDMs after stimulation



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

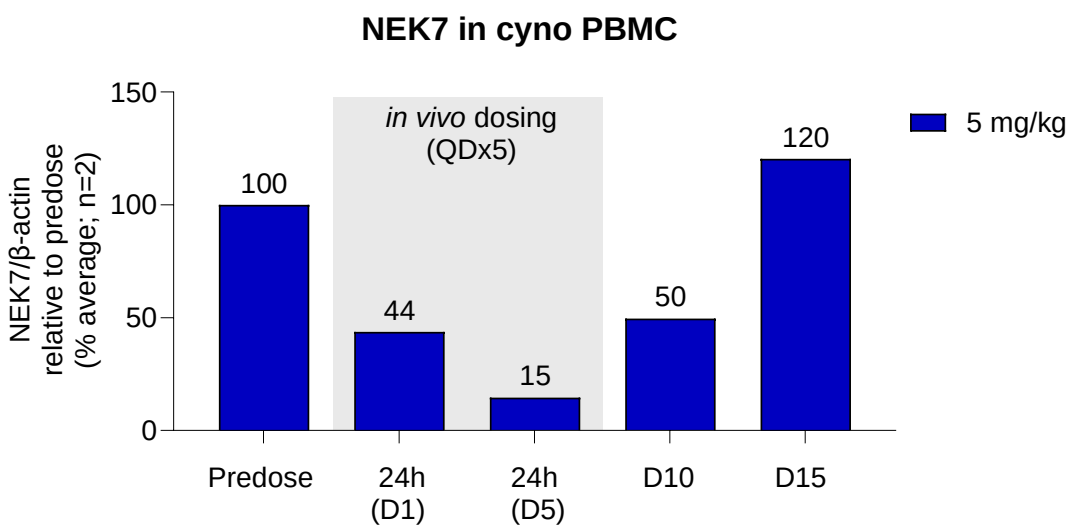


MRT-8102 inhibits IL-18 secretion by hMDMs after stimulation



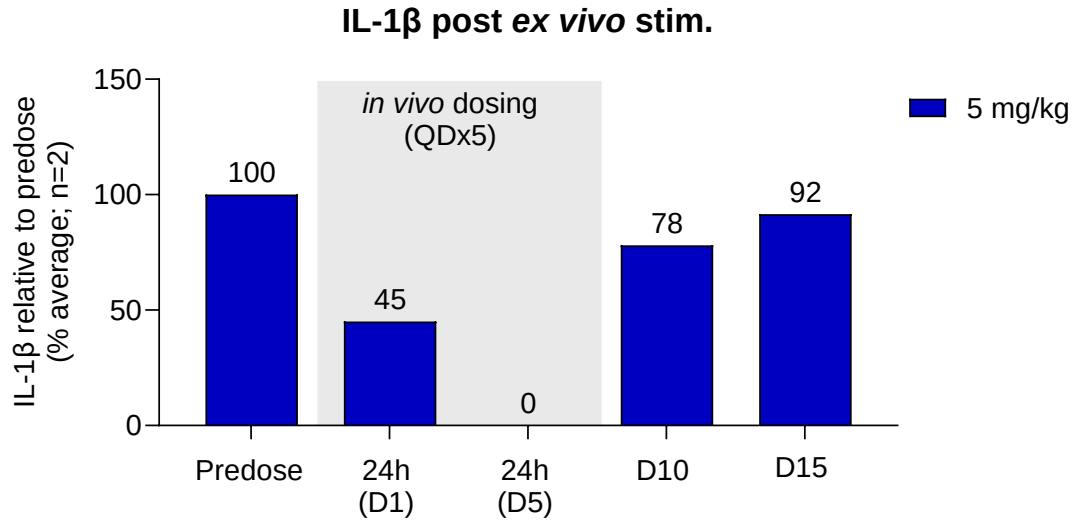
Suppression of *Ex Vivo* Inflammasome Activation Following Degradation of NEK7 After Single and Multi-dose Study in Non-human Primates

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



No clinical observations reported

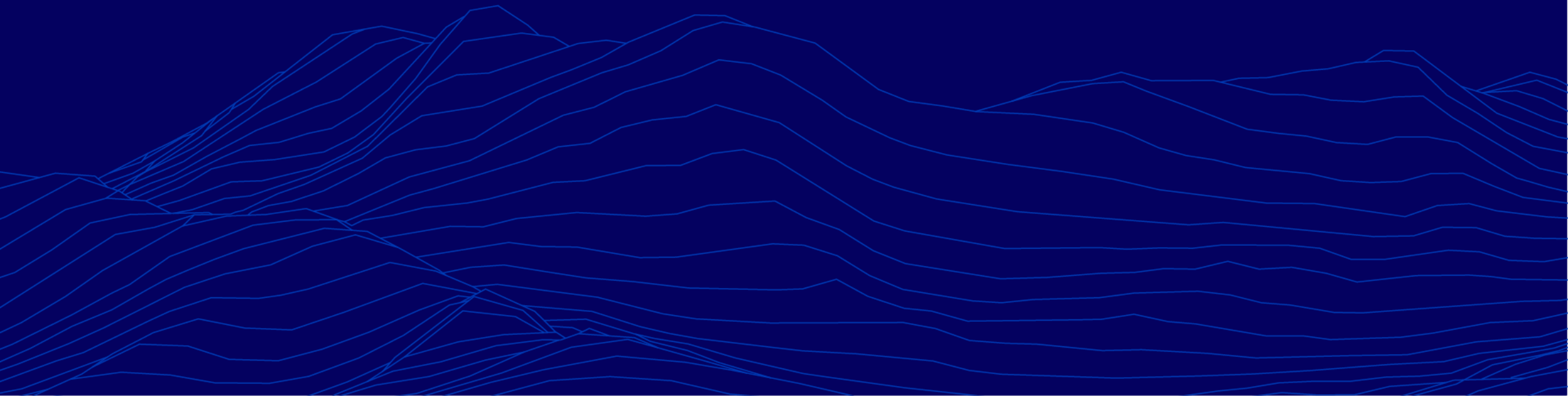
In vivo NEK7 degradation leads to inhibition of NLRP3 inflammasome in _ex vivo_ stimulation assay



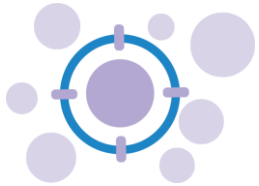
- IL-1β in plasma after *ex vivo* stimulation with LPS + nigericin
- Similar results for Caspase-1 activity from same study
- Follow-up study with 1 mg/kg MRT-8102, *i.v.* at 4 hr showed similar results

Monte Rosa Therapeutics

QuEEN™ Discovery Engine

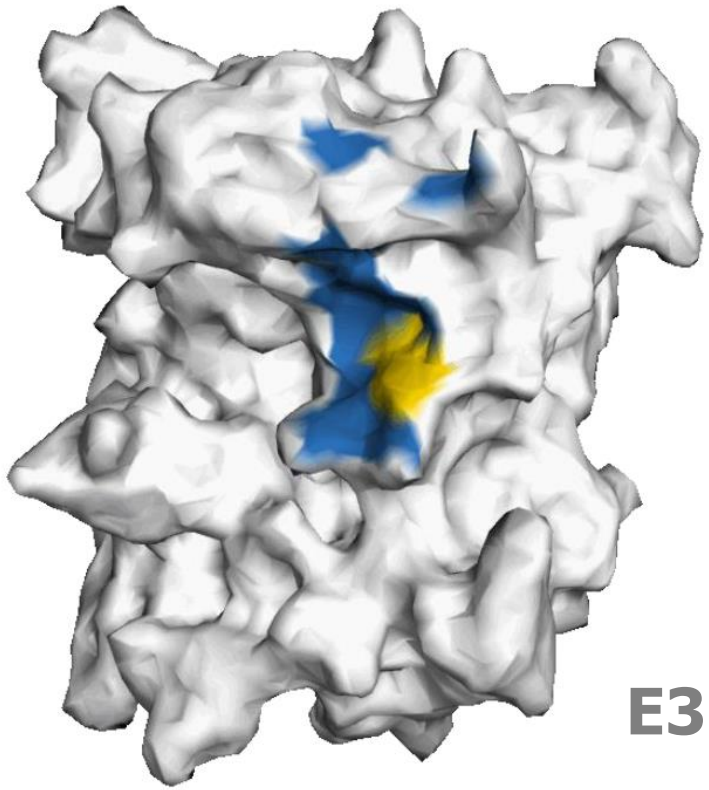


Overcoming Past Limitations of Molecular Glue Degraders

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

Our Critical Insight: Surfaces are Critical for MGD Discovery

Surfaces, not structures, mediate PPIs and targeted protein degradation

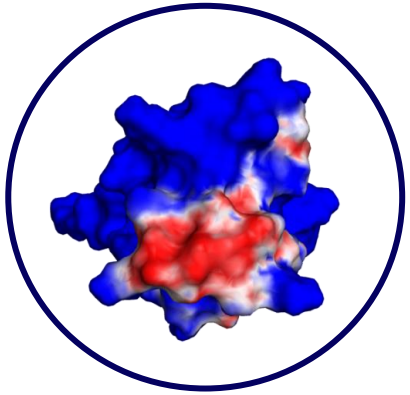


E3 ligase

Neosubstrate footprint
MGD footprint

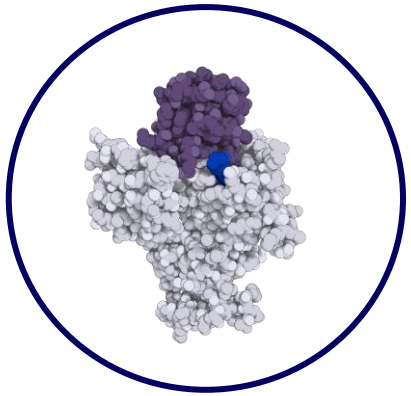
- Rationally-designed MGDs create diverse E3 ligase neosurfaces, enabling recruitment of new targets
- Our geometric deep learning algorithms use surfaces to **predict** targets.
- Our surface-based algorithms **design** MGDs to recruit targets.
- Our platforms generate **actionable data-at-scale** to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

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



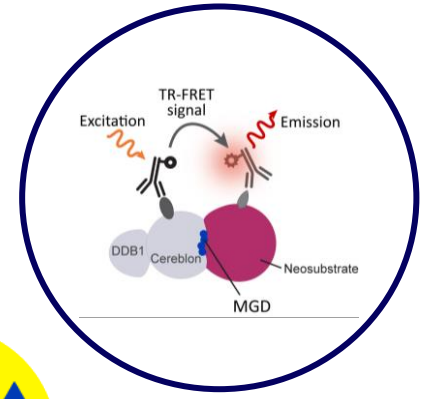
AI/ML

In silico discovery using proprietary AI-powered algorithms



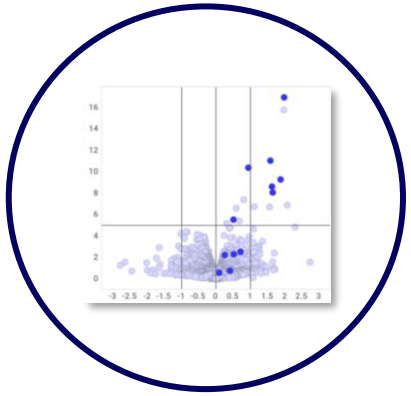
Structure-based Design

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



Proximity Screening

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

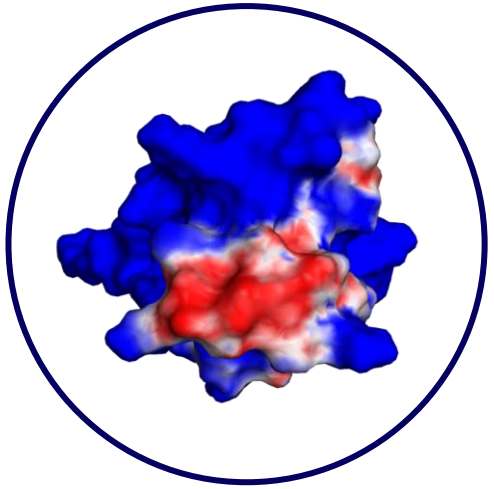


Proteomics

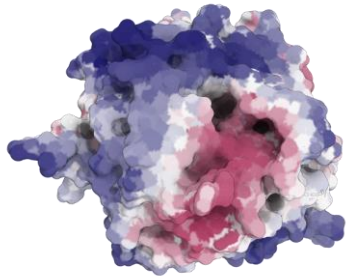
Integrated proteomics engine and database to identify novel targets and explore cellular complex formation and protein degradation

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

Proprietary AI/ML engines

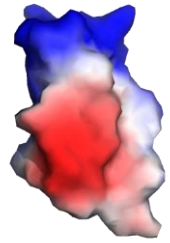


Ligase reprogrammability



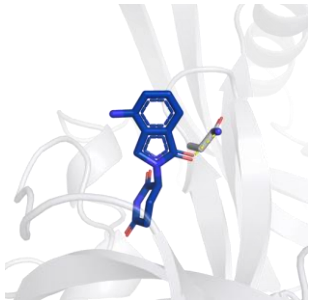
Discover protein interaction hotspots

Target identification



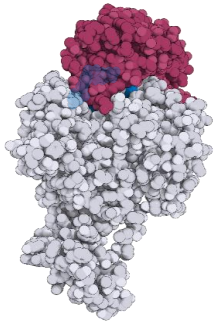
Match interaction sites on neosubstrates

MGD discovery



Generate MGDs with drug-like properties

In silico screening



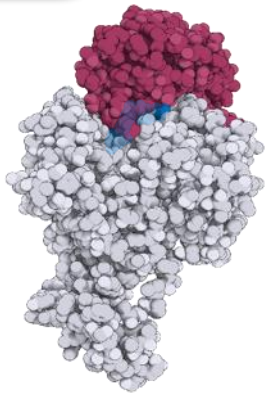
Screen for activity in ternary complexes

QuEEN™: How it Works

Predict

Target and ligase ID

Surface-centric
discovery process



Design

AI-powered chemistry

Surface-aware MGD
generation & optimization

Test & Train

Actionable data-at-scale

Proteomics
Virtual screens
Structural biology
High throughput screens

QuEEN™ Toolbox to Rapid Discovery Oral MGDs

Predict

Target and ligase ID

Surface-centric
discovery process

Design

AI-powered chemistry

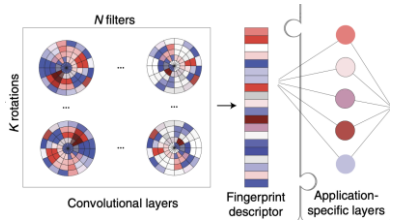
Surface-aware MGD
generation & optimization

Test & Train

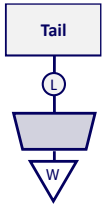
Actionable data-at-scale

Proteomics
Virtual screens
Structural biology
High throughput screens

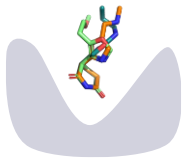
fAIceit™ Ultra-fast fingerprint search for surface-based matchmaking



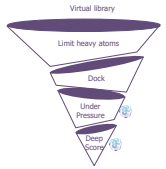
FLASH™
virtual library



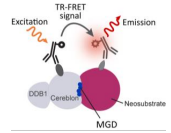
HitMan™
diverse library



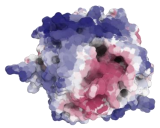
Headlong™
virtual screens



HT library screening

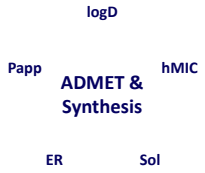


E3 ligase
reprogrammability

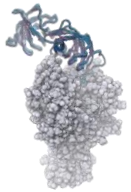


fAIceit mimicry
target ID

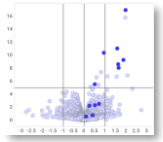
GlueAID™
ADMET & synthesis



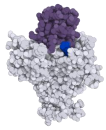
Rhapsody™
ternary complexes



Proteomics
mass-spec farm



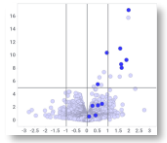
Structural biology
X-ray & cryo-EM



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

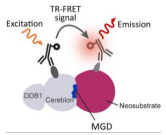
Lab experimentation

Proteomics
mass-spec farm



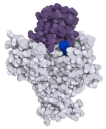
34 million
protein measurements

HT library screening



6 million
MGD activity measurements

Structural biology
X-ray & cryo-EM



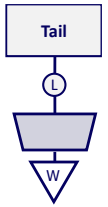
>100
structures

in silico experimentation

fAIceit mimicry
target ID

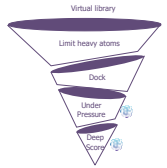
250 billion
protein surface matchings

FLASH™
virtual library



37 billion
virtual MGDs

Headlong™
virtual screens



651 million
compounds screened

Cloud First and Cloud Native

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

Monte Rosa Therapeutics

Team

World-Class Leadership

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

Markus Warmuth, M.D.
Chief Executive Officer

H3 Biomedicine
NOVARTIS

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

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

Andrew Funderburk
SVP, Investor Relations and Strategic Finance

Kendall Investor Relations
Health Advances


Thank You
Monte Rosa
Therapeutics