Proteome Editing Through Molecular Glue Degraders

Innovating Beyond New Heights | January 2025

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 ability to grow our product pipeline, statements around the Company's QuEEN™ discovery engine and the Company's view of its potential to identify degradable protein targets and rationally design MGDs with unprecedented selectivity, statements related to the Company's strategic agreements, goals of such agreements, including the ability to accelerate and broaden scope of clinical development of MRT-6160 while retaining substantial value for the Company, as well as to expand platform reach to discover and develop MGDs against previously undruggable targets in cancer and neurological diseases, statements related to any milestone provided under the strategic agreements, royalty or other payments related thereto and the ability of such payments to extend our runway, statements around the productivity of the QuEEN discovery engine and the potential of the Company's MGDs against a broad spectrum of targets, statements about the advancement and timeline of its preclinical and clinical programs, pipeline and the various products therein, statements around multiple anticipated preclinical and/or clinical readouts and their expected timing, including results from proof-of-concept patient studies, statements related to regulatory submissions, including timing thereof, and interactions with regulatory authorities, the applicability of candidates to various indications, the expected potential clinical benefit of any of our candidates, statements around advancement and application of our pipeline and application of our platform, statements concerning our expectations regarding our ability to identify, nominate and the timing of our nominations of additional targets, product candidates, and development candidates, statements around our ability to capitalize on and potential benefits resulting from our research and translational insights as well as our the ability to optimize collaborations with industry partners on our development programs, obligations under our collaboration agreements, expectations around the receipt of any payments under such agreements and the future development and commercialization of various products, our use of capital, expenses and other financial results in the future, availability of funding for existing programs, ability to fund operations into 2028 through multiple anticipated proof-of-concept patient study readouts, as well as our expectations of success for our programs, strength of collaboration relationships and the strength of our financial position, among others. By their nature, these statements are subject to numerous risks and uncertainties, including those risks and uncertainties set forth in our most recent Annual Report on Form 10-K for the year ended December 31, 2023, filed with the U.S. Securities and Exchange Commission on March 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. These materials remain the proprietary intellectual property of Monte Rosa Therapeutics and should not be distributed or reproduced in whole or in part without the prior written consent of Monte Rosa Therapeutics.

Monte Rosa Therapeutics – Company Overview

Proteome editing with molecular glue degraders

Arsenal of rationally designed MGDs to edit the proteome by degrading proteins with unprecedented precision

Industry-leading discovery engine combining use of **AI *with* experimental platform** to enable **rational design of novel MGDs**

Collaboration with Roche – expands **platform reach into neurology**

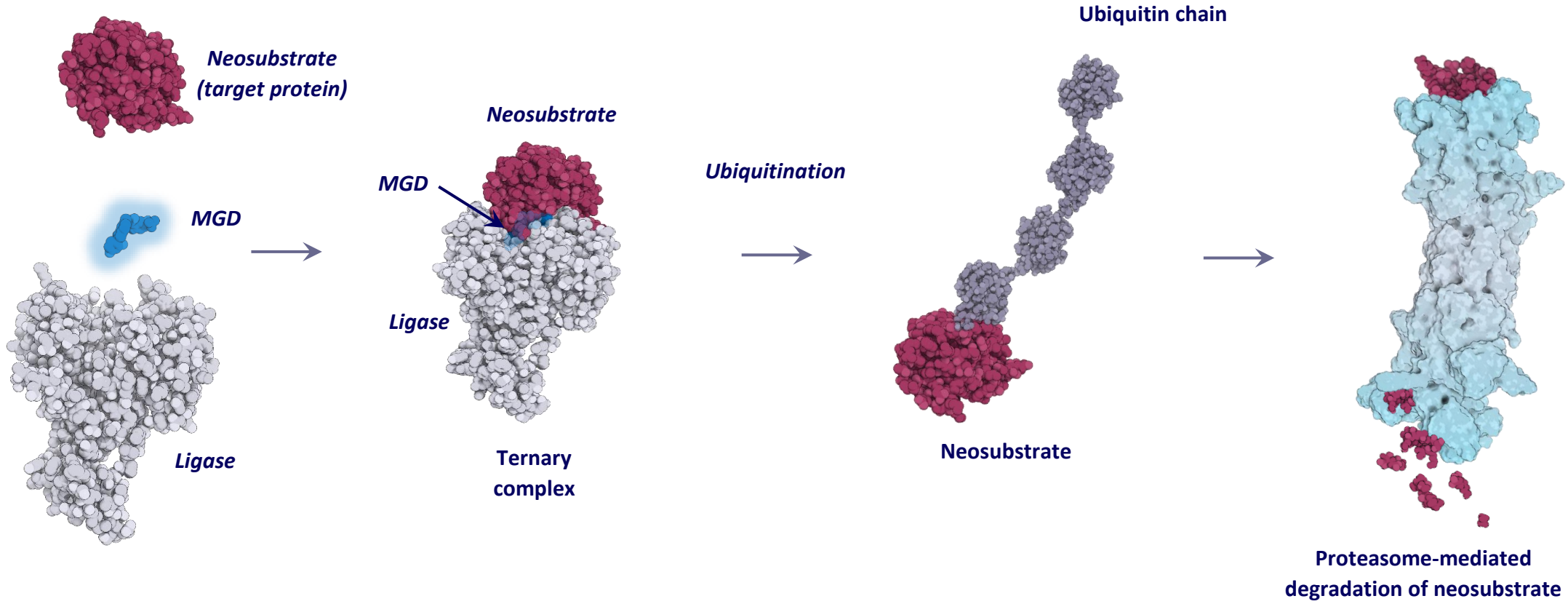
Phase 1/2 clinical study ongoing with MRT-2359 being explored in MYC-driven cancers; **additional Phase 1 data expected Q1 2025**

MRT-6160, highly selective VAV1-directed MGD for I&I conditions, **Phase 1 data expected Q1 2025 – global license to Novartis with US P&L share**

MRT-8102, highly selective NEK7-directed MGD for IL-1β/NLRP3-driven inflammatory diseases with **IND submission anticipated H1 2025**

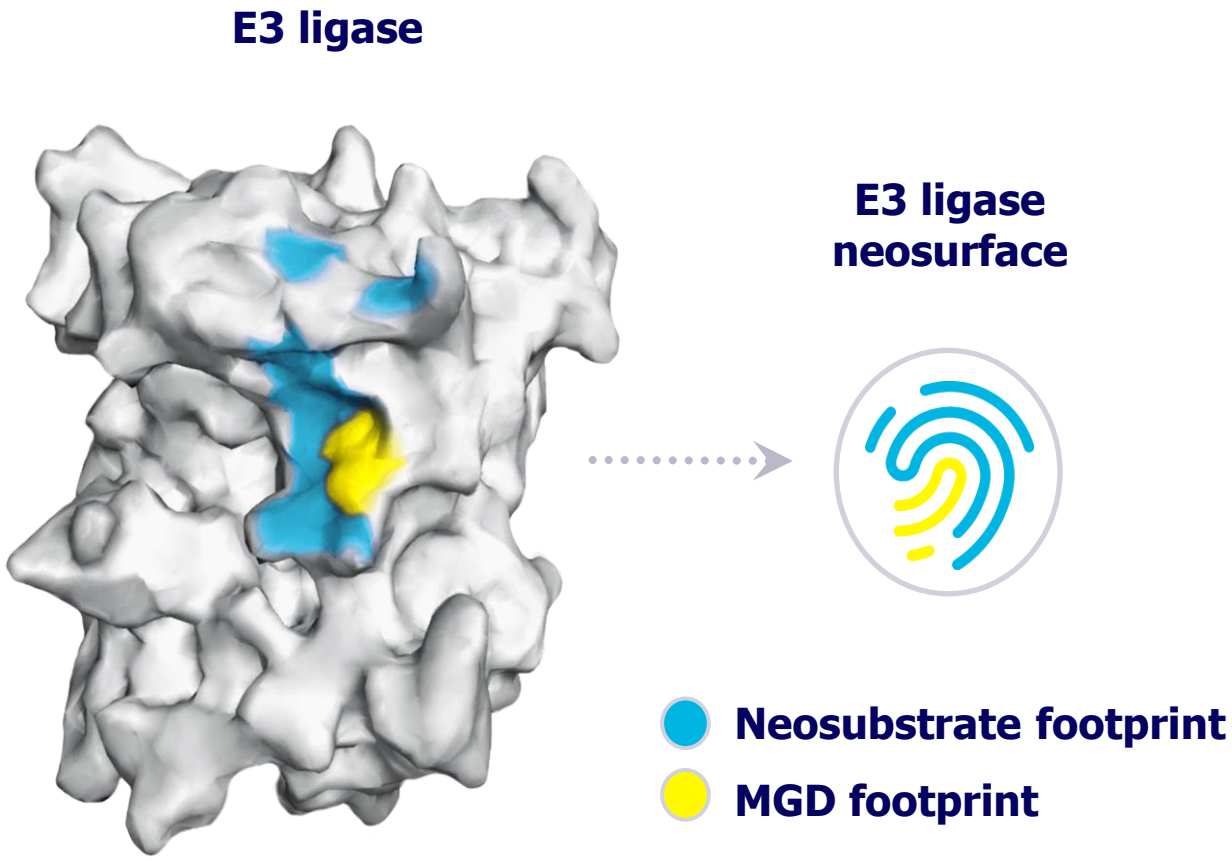
Strong financial position providing **cash runway into 2028** through multiple anticipated proof-of-concept clinical readouts

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

Key Insights into Surface Interactions Drive Only-in-Class MGD Designs



Interrogating surfaces using geometric deep learning informs reprogrammable ligase and matching target space...

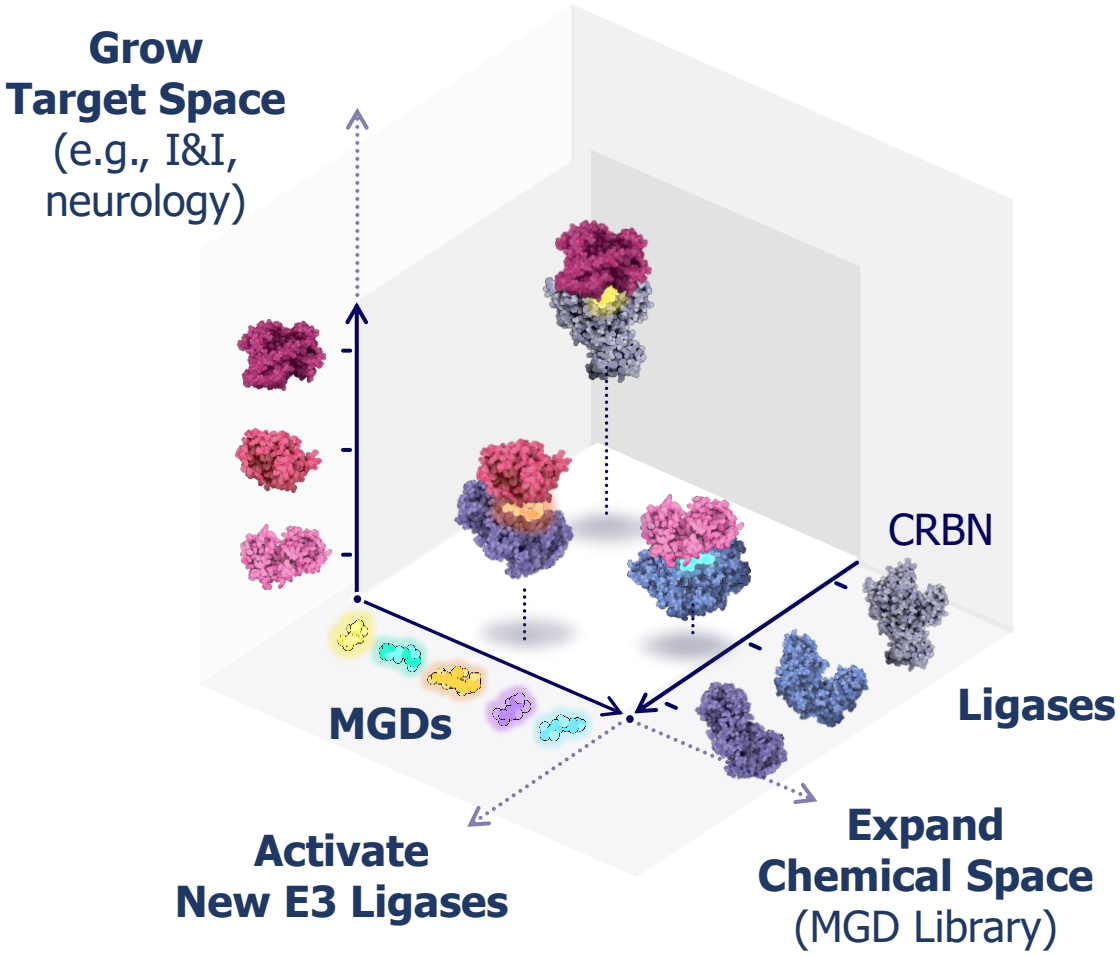
Key Insights into Surface Interactions Drive Only-in-Class MGD Designs

...and creates broad opportunity

to eliminate undruggable,

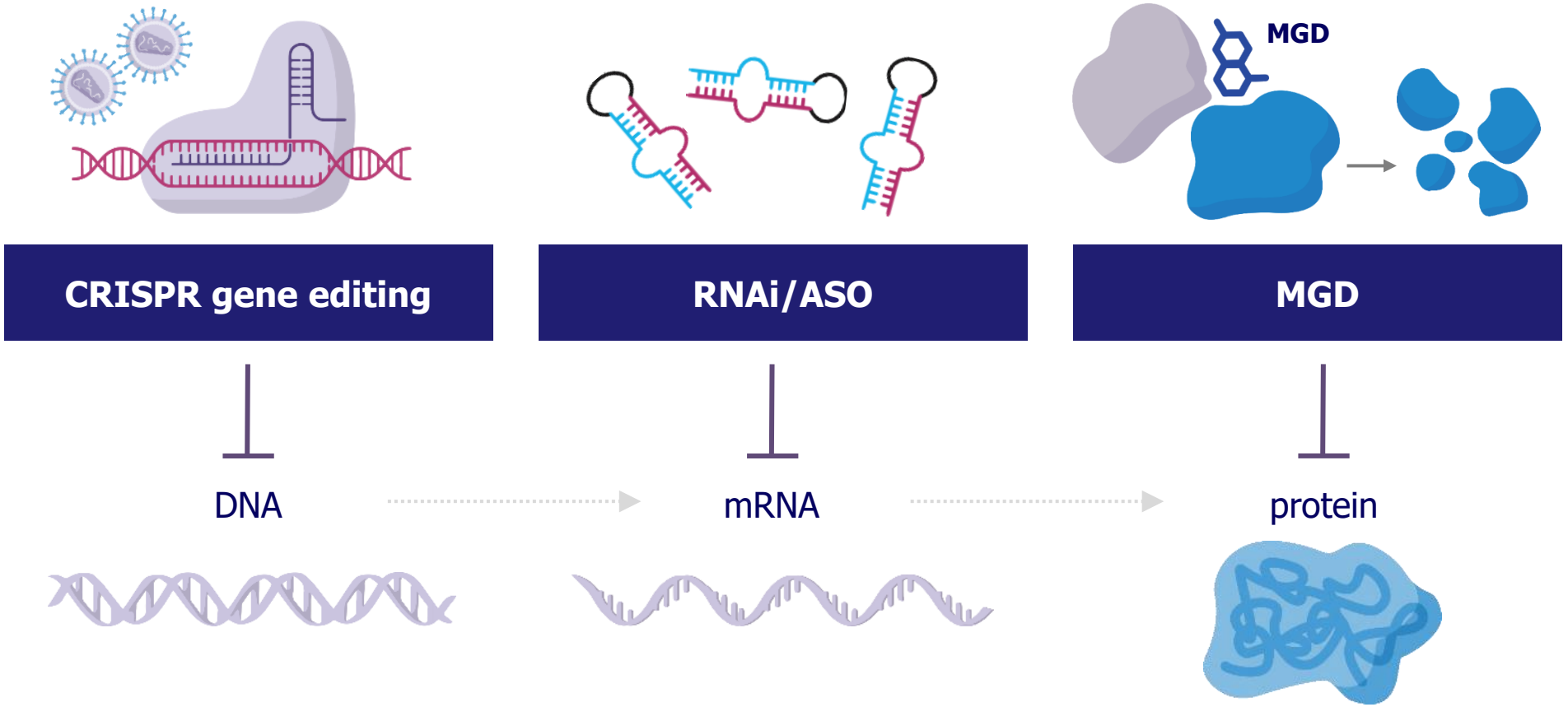
disease-driving proteins through

"only-in-class" MGDs



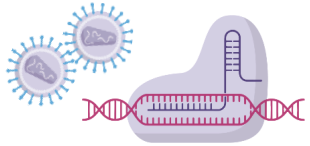
Three Ways to Eliminate a Disease-Causing Protein

MGDs can directly and precisely target proteins that cause disease

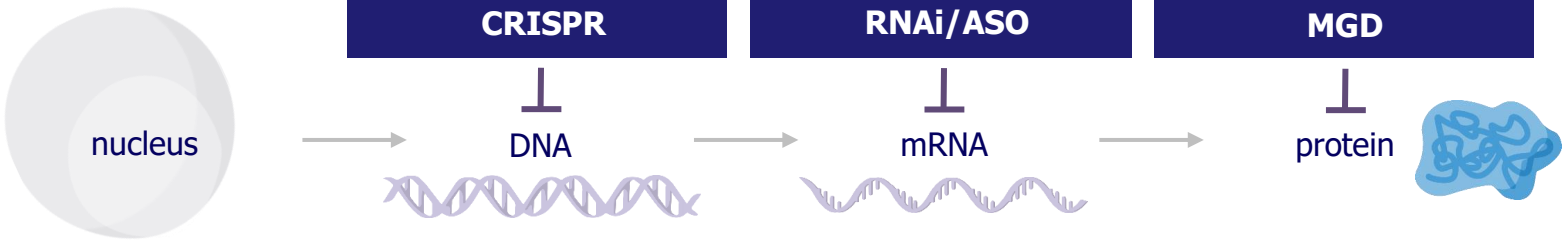


Three Ways to Eliminate a Disease-Causing Protein

MGDs provide advantages of large molecule modalities with orally dosed small molecules

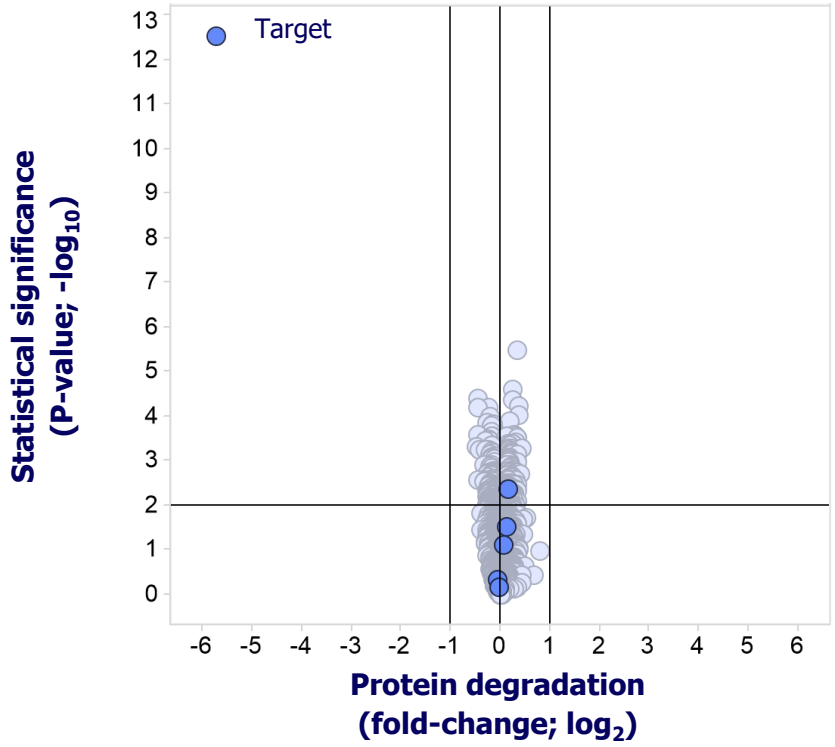


Properties	CRISPR	RNAi/ASO	MGD
Address undruggable space	✓	✓	✓
Highly selective	✓	✓	✓
Orally bioavailable			✓
Systemic distribution			✓
Scalable manufacturing			✓
Reversible		✓	✓



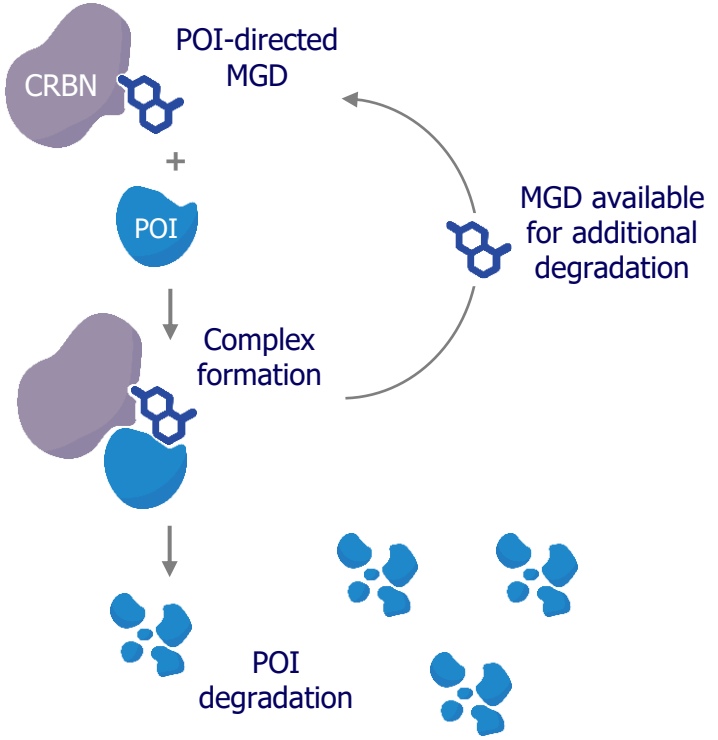
Key Advantages of Our Rationally Designed MGDs

Unprecedented Selectivity



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

Catalytic Mechanism of Action

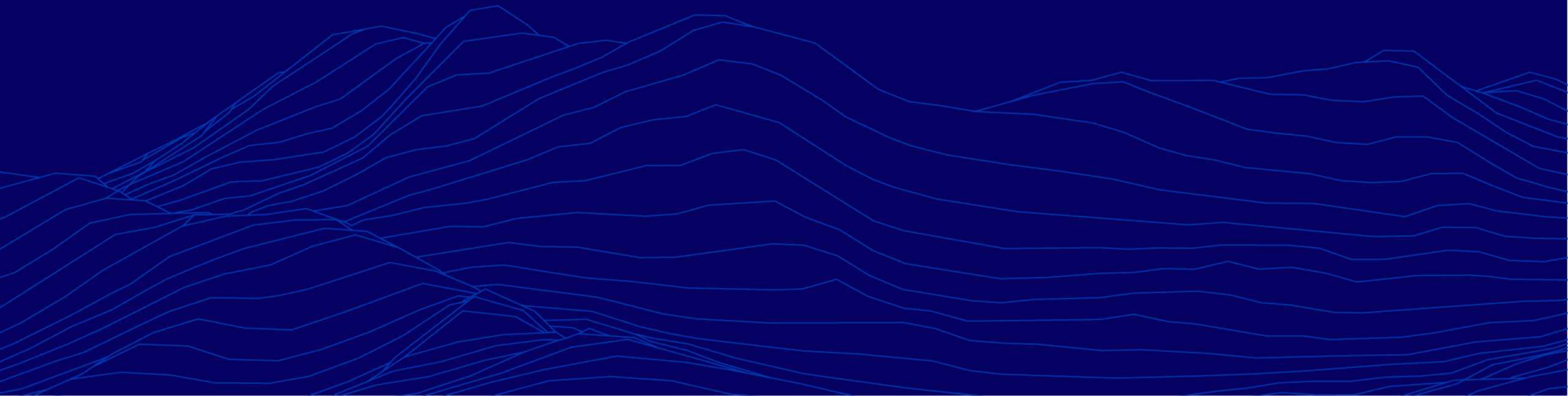


Long lasting, catalytic protein degradation effect creates differentiated target product profiles

POI = protein of interest

Monte Rosa Therapeutics

Portfolio and Partnerships



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				Additional Phase 1 data in Q1 2025	
VAV1	MRT-6160	Autoimmune Disease – Systemic and CNS				Phase 1 data in Q1 2025	NOVARTIS *
NEK7	MRT-8102	IL-1β/NLRP3 driven Inflammatory Diseases				IND submission in H1 2025	
	LO (2^{nd} generation)					Development candidate in H2 2025	
CDK2	LO	Breast Cancer				Development candidate in H1 2025	
CCNE1 (Cyclin E1)	LO	CCNE1 amplified tumors				Development candidate	
Discovery Targets	-	Multiple				Lead optimization	
Discovery Targets	-	Oncology and Neurological Diseases				Undisclosed	Roche

Oncology Immunology Inflammation Various

* Monte Rosa has an exclusive global license agreement with Novartis for this asset.

Portfolio Strategy

	2020 – 2024	2025+
Strategic Goal	**Build discovery capability with focused disease interest**	**Expand portfolio with broader therapeutic area lenses via our powerful discovery engine**
Therapeutic Areas of Focus	*Oncology*, *I&I* 	*Cardiovascular*, *Metabolic*, *Genetic* 
MRTx Pipeline Expansion	• GSPT1 • CDK2 • CCNE1 • VAV1 (NOVARTIS) • NEK7	**Current programs + emerging novel projects**

Creating Value through Strategic Agreements

	NOVARTIS	Roche
Scope	Global license agreement to advance VAV1-directed molecular glue degraders including MRT-6160 (announced Oct. 2024)	Strategic collaboration to discover novel MGDs targeting cancer and neurological diseases (announced Oct. 2023)
Financials	• $150M upfront payment • Eligible for up to $2.1B in development, regulatory, and sales milestones, beginning upon initiation of Phase 2 studies • Eligible for US P&L share and ex-US tiered royalties	• $50M upfront payment • Eligible for preclinical, clinical, commercial and sales milestone payments >$2B and tiered royalties
Strategic Goal	Accelerate and broaden scope of clinical development of MRT-6160 while retaining substantial value for Monte Rosa	Expand platform reach to discover and develop MGDs against previously undruggable targets in cancer and neurological diseases

Notes: Under the terms of the Novartis agreement, Novartis will obtain exclusive worldwide rights to develop, manufacture and commercialize MRT-6160 and other VAV1 MGDs and will be responsible for all clinical development and commercialization, starting with Phase 2 clinical studies. Monte Rosa remains responsible for completion of the ongoing Phase 1 clinical study of MRT-6160. Monte Rosa will co-fund any Phase 3 clinical development and will share any profits and losses associated with the manufacturing and commercialization of MRT-6160 in the U.S. Under the terms of the Roche agreement, Monte Rosa Therapeutics will lead discovery and preclinical activities against multiple select cancer and neurological disease targets to a defined point. Roche gains the right to exclusively pursue further preclinical and clinical development of the compounds.

Monte Rosa Therapeutics

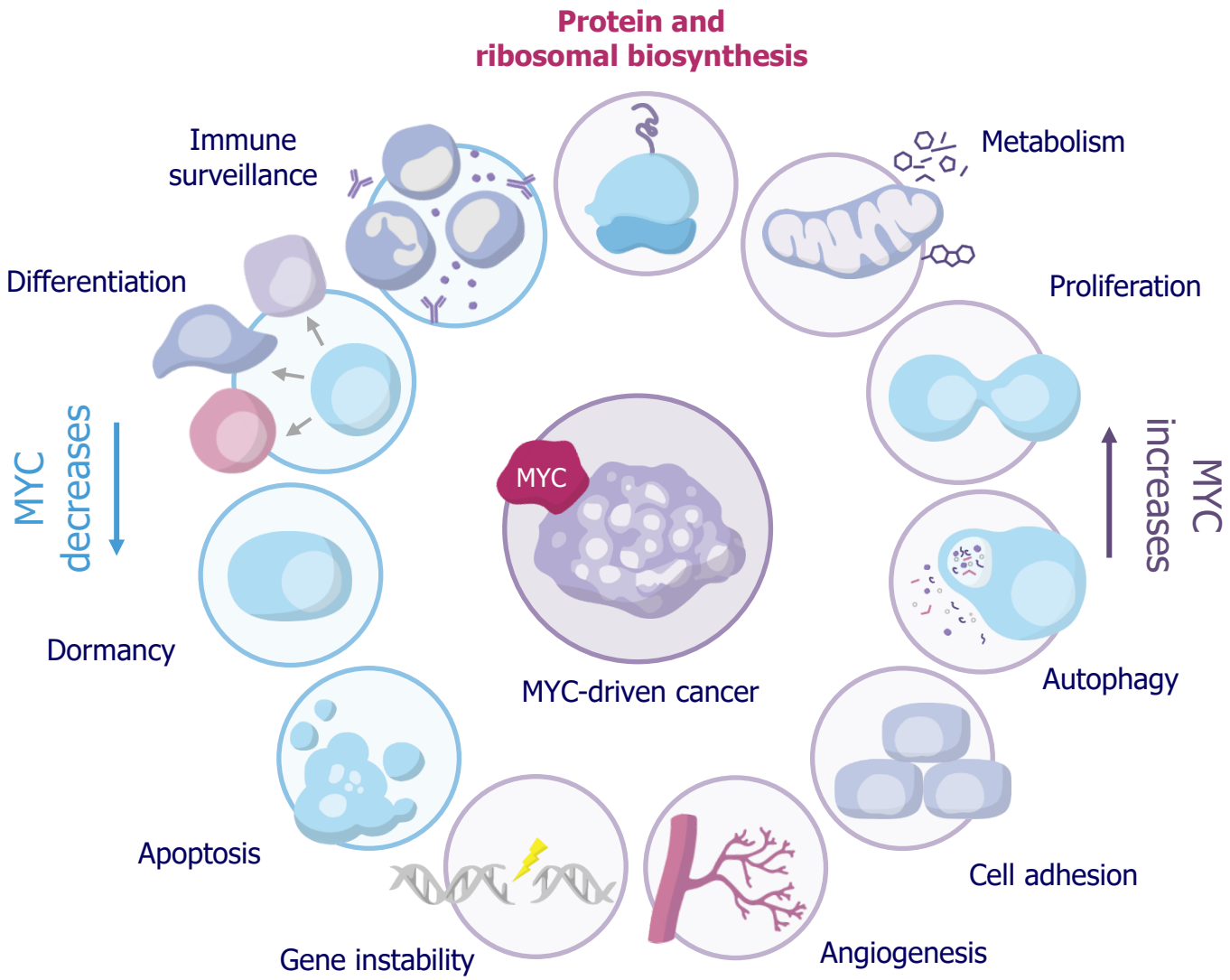
GSPT1 program (MRT-2359)

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

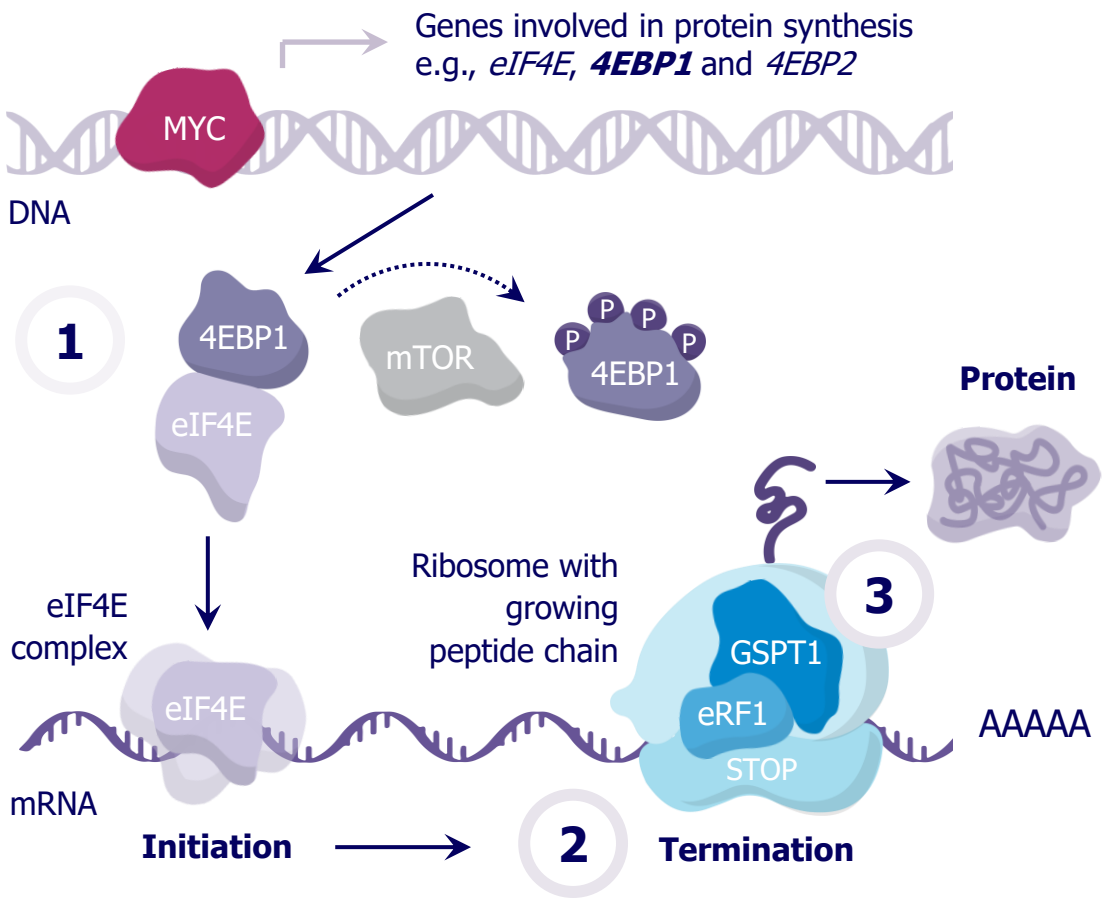
- MRT-2359 is designed to specifically target MYC-driven tumors

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

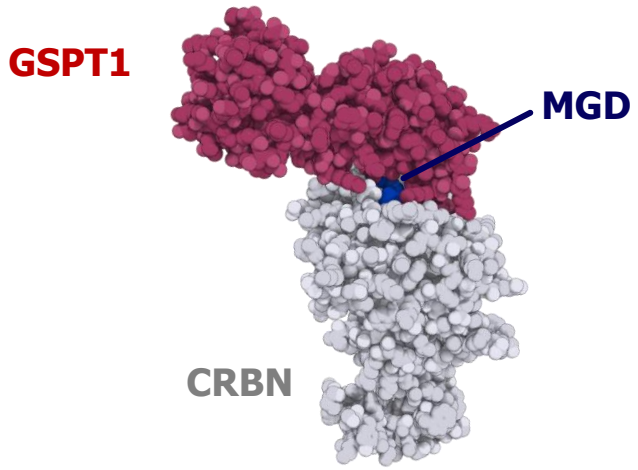
Therapeutic vulnerability

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

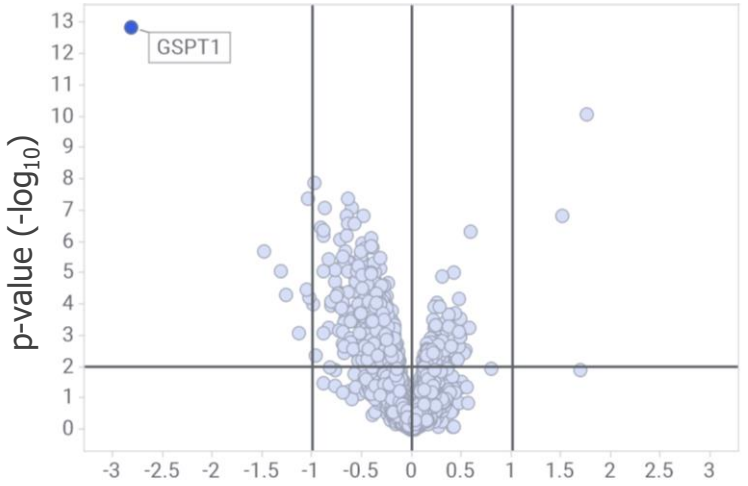
MRT-2359 is a potent GSPT1-directed MGD

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

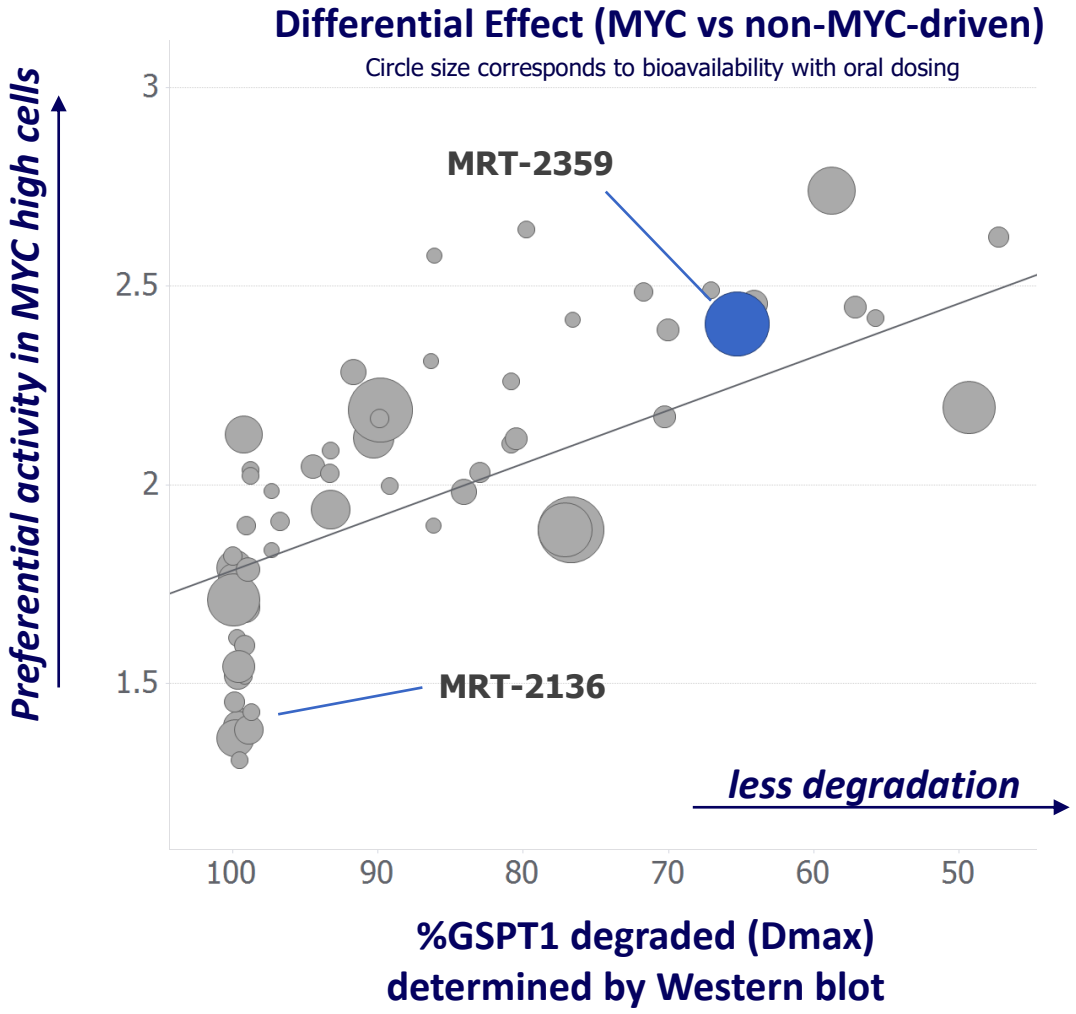
MRT-2359 induces selective GSPT1 degradation and shows favorable ADME/DMPK profile



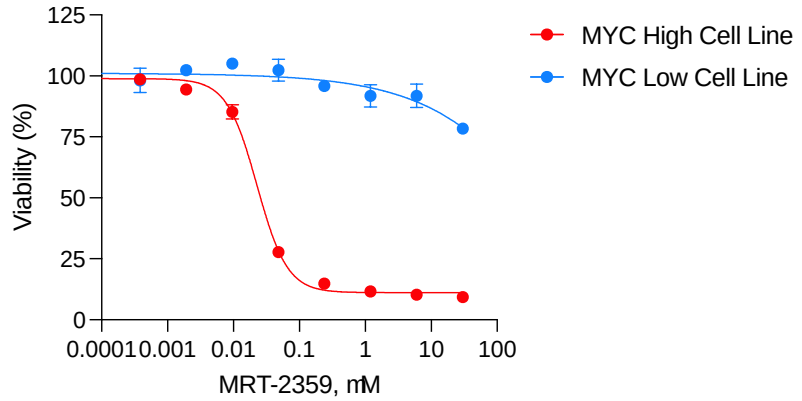
No degradation of other known cereblon neosubstrates

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

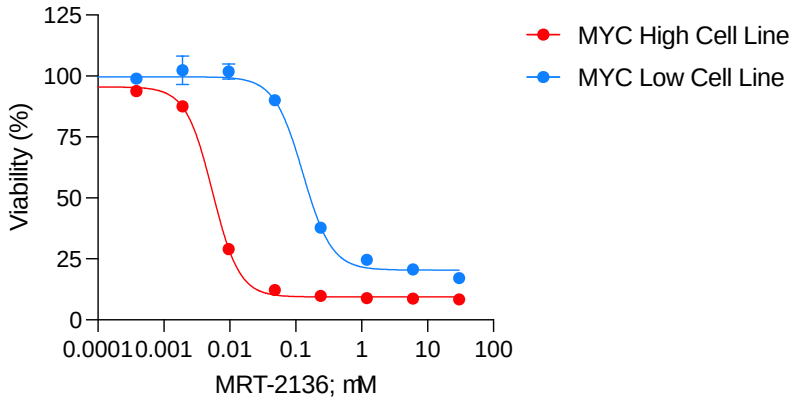
MRT-2359 Has Optimized Depth of Degradation To Achieve Preferential Activity in MYC High Cancer Cells



MRT-2359 displays preferential activity in MYC driven NSCLC cells



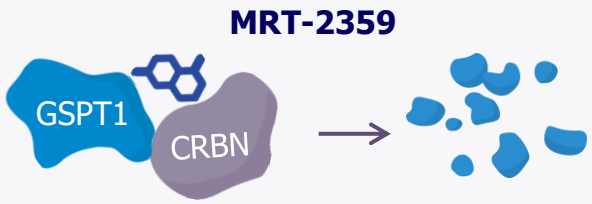
Non-optimal GSPT1 MGD (MRT-2136) shows limited preferential activity



Three Mechanisms Driving Preferential Activity in MYC High Tumor Cells

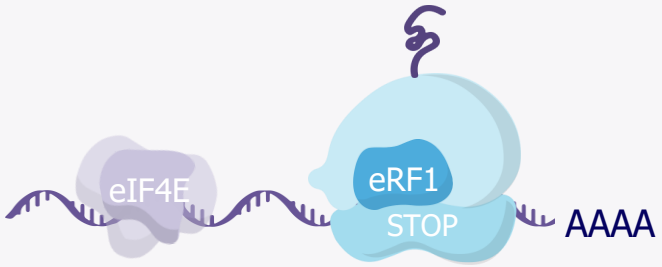
Preferential GSPT1 degradation

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



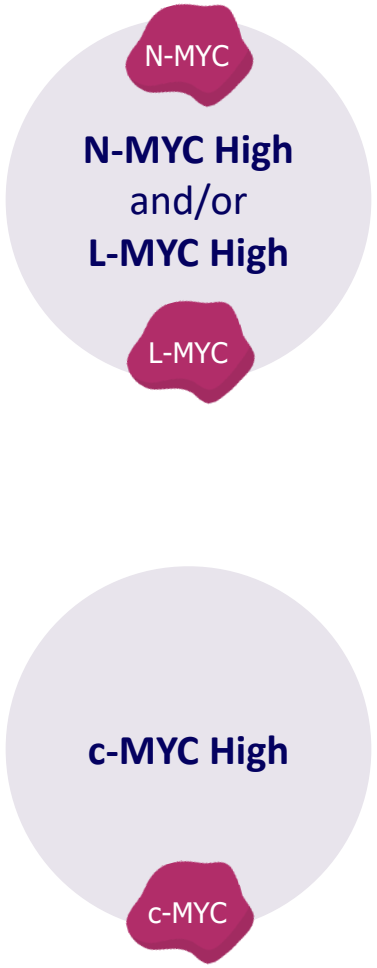
MYC down-modulation

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

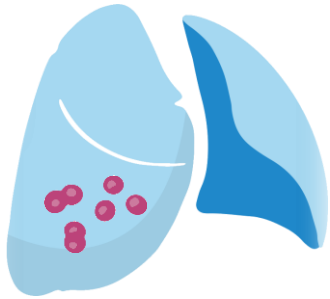
Indication Size



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

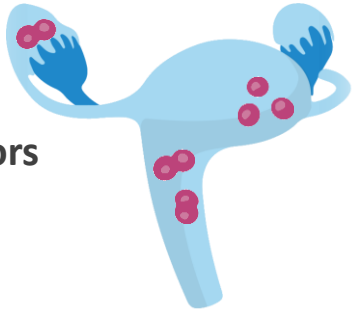
NSCLC
N-MYC high (5-10%)
SCLC/NE transformation

Neuroendocrine lung cancer

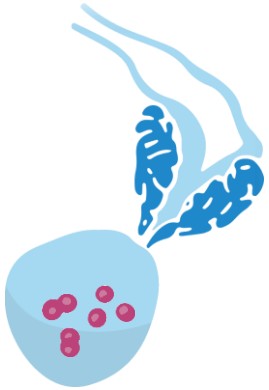


Neuroendocrine tumors

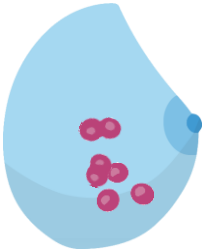
L-/N-MYC amplified tumors



Prostate cancer
AR positive including
AR-V7



Breast cancer
ER positive metastatic

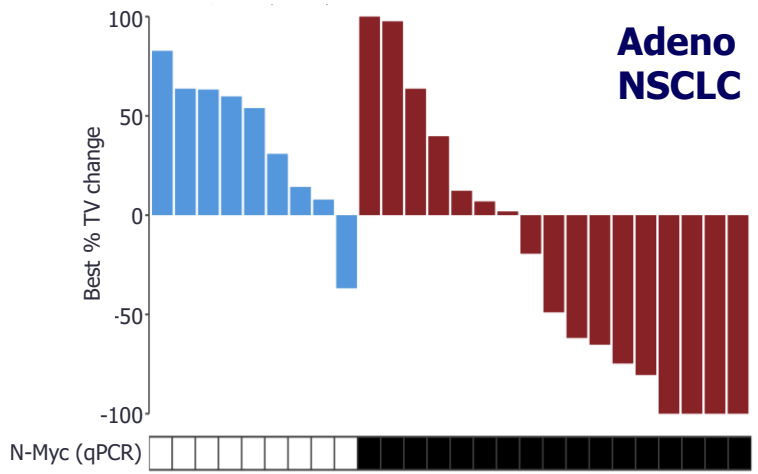


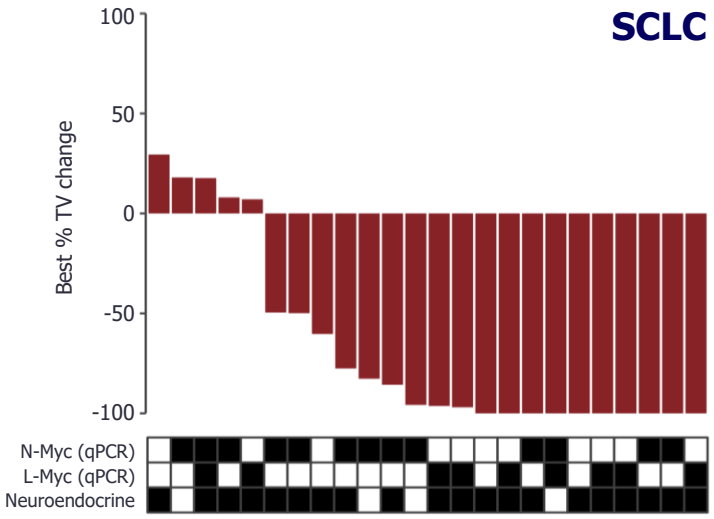
and others…

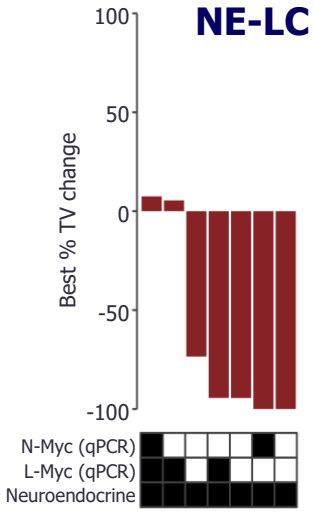
Preclinical Validation of Activity of MRT-2359 in Lung Cancer PDX Models

Collection of PDX models

MRT-2359
10 mg/kg QD

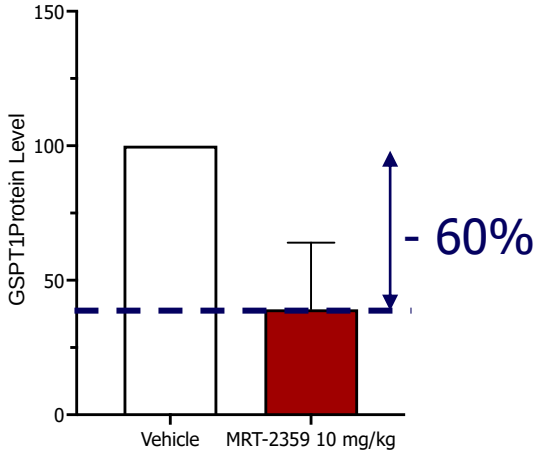






PD modulation

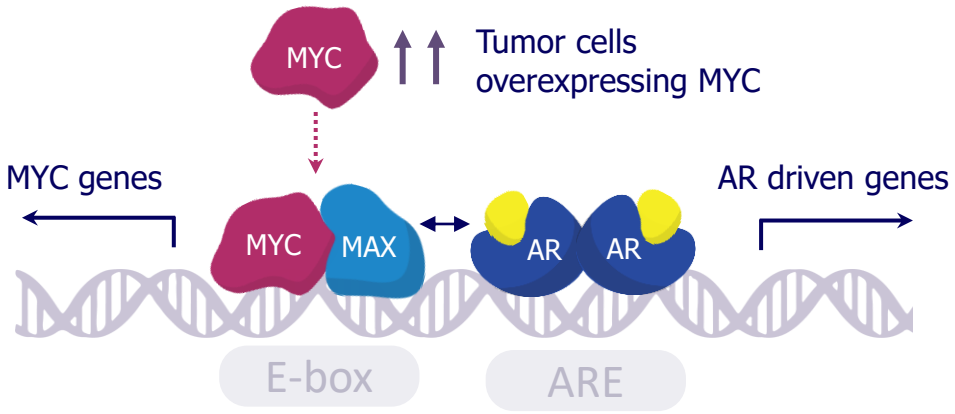
Targeted mass spectrometry
in 7 representative models



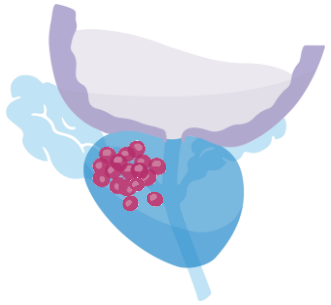
biomarker negative biomarker positive

MRT-2359 disrupts MYC and AR Signaling in Prostate Cancer

MYC overexpression drives AR dependence and therapy resistance in CRPC

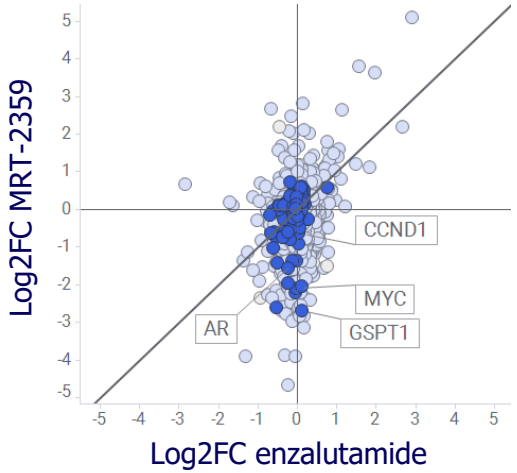


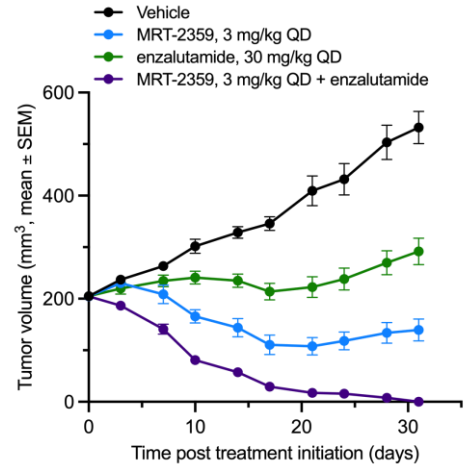
- Sustained tumor growth
- Therapy resistance



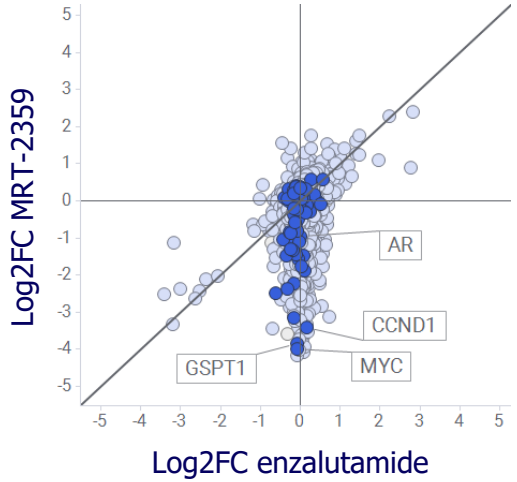
MRT-2359 inhibits expression of AR-regulated genes and has significant activity in human prostate cancer models

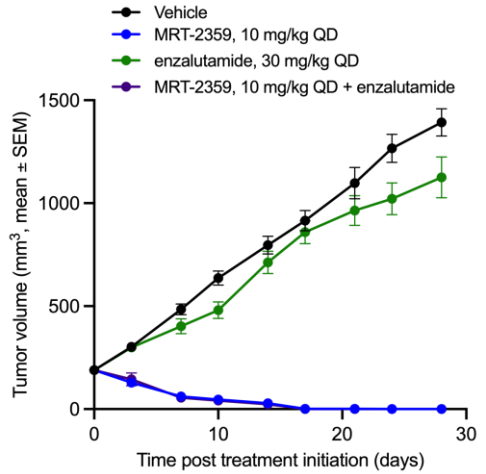
VCaP (AR-V7 low)





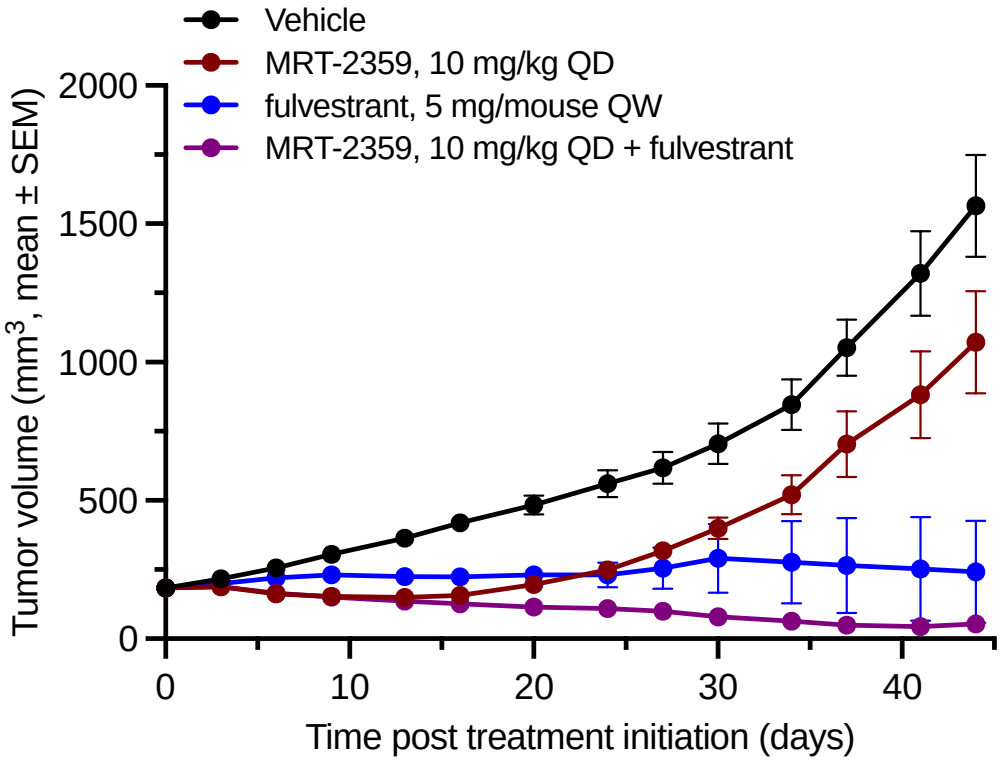
22RV1 (AR-V7 high)





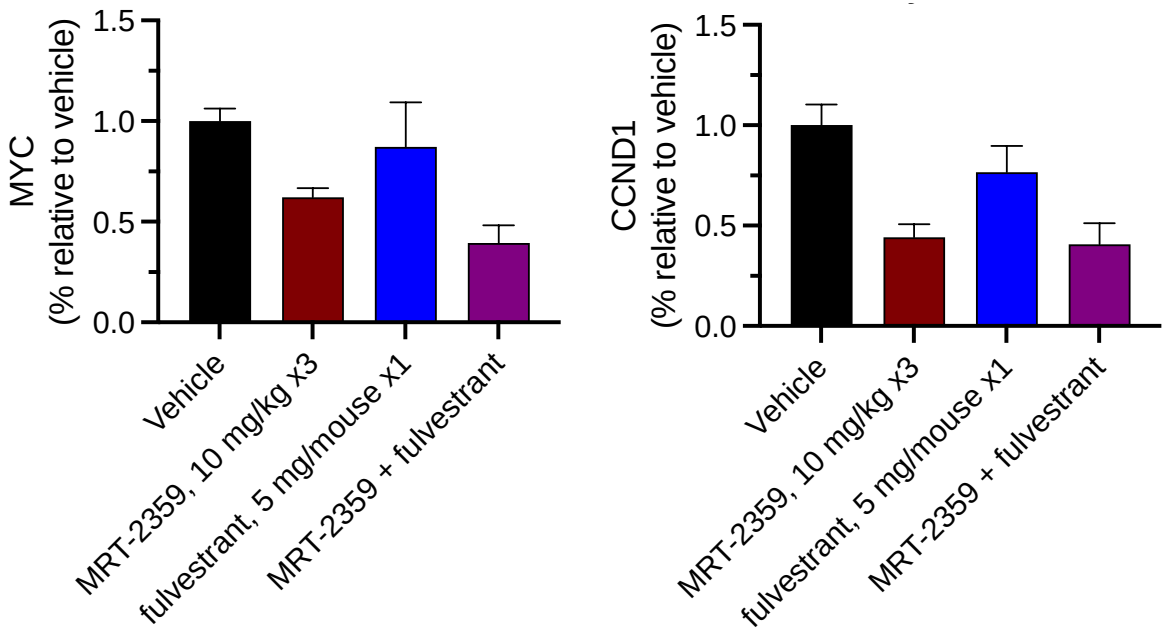
MRT-2359 Leads to Tumor Regressions in Preclinical Model of ER-positive Breast Cancer

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



MCF7 Breast CDX (ER+, HER2-)

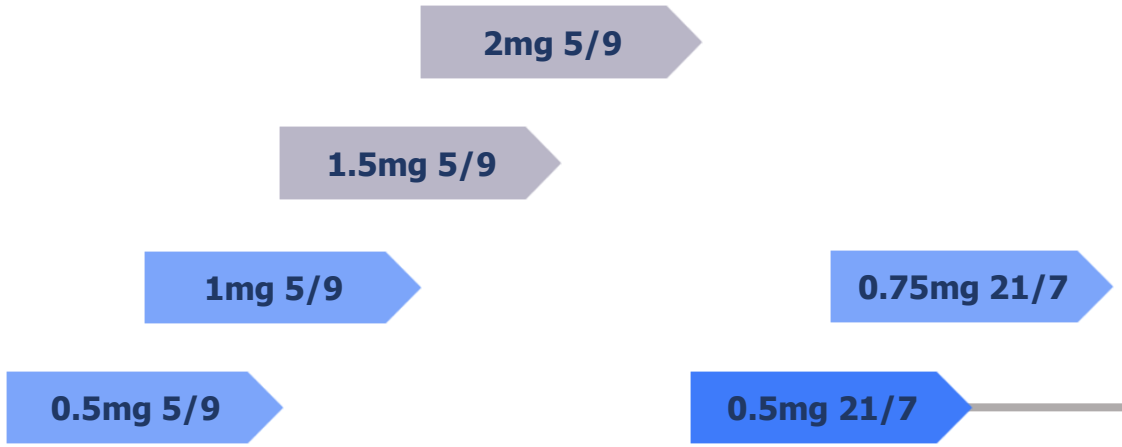
MRT-2359 reduces MYC and CCND1 *in vivo*



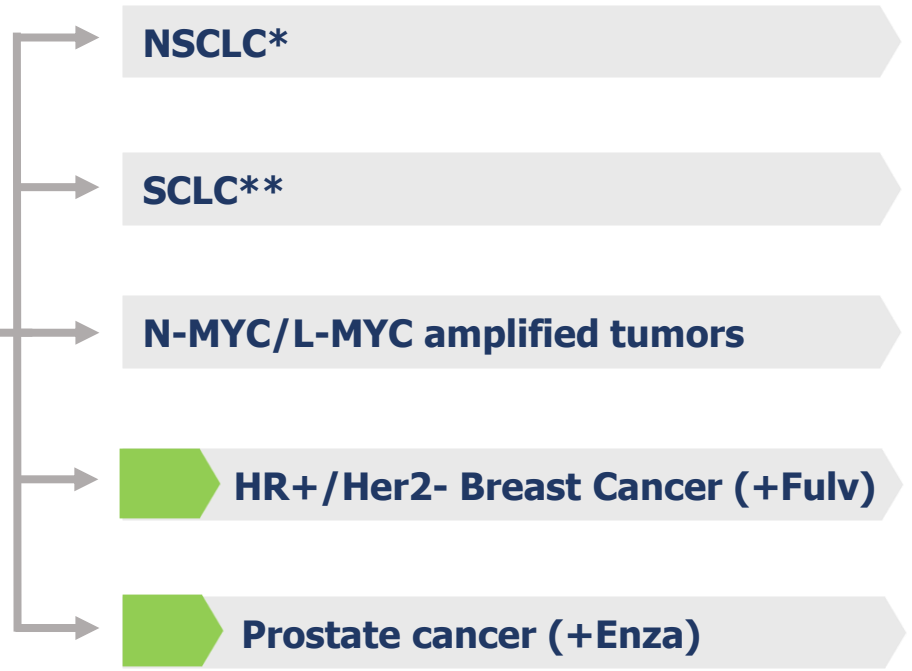
MRT-2359-001 Phase 1/2 Clinical Study Design

Phase 1: Dose Escalation

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



Phase 2: Possible Expansion Cohorts



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

Safety assessments initiated

0.5mg 21/7 identified as RP2D

Data update expected in Q1 2025

5/9 = 5 days on drug, 9 days off drug; 21/7 = 21 days on drug, 7 days off drug; RP2D = recommended Phase 2 dose

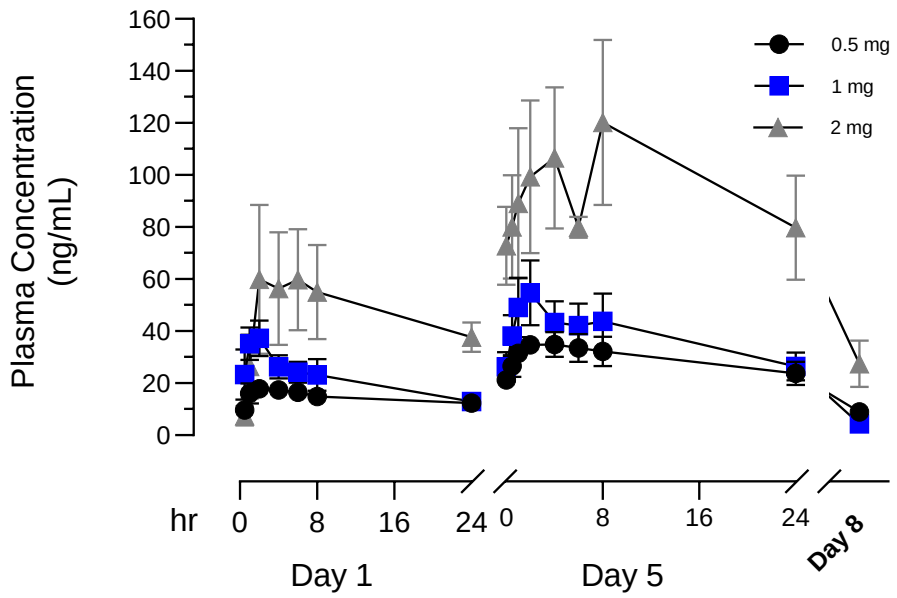
MRT-2359 Phase I Interim Data – October 2023

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

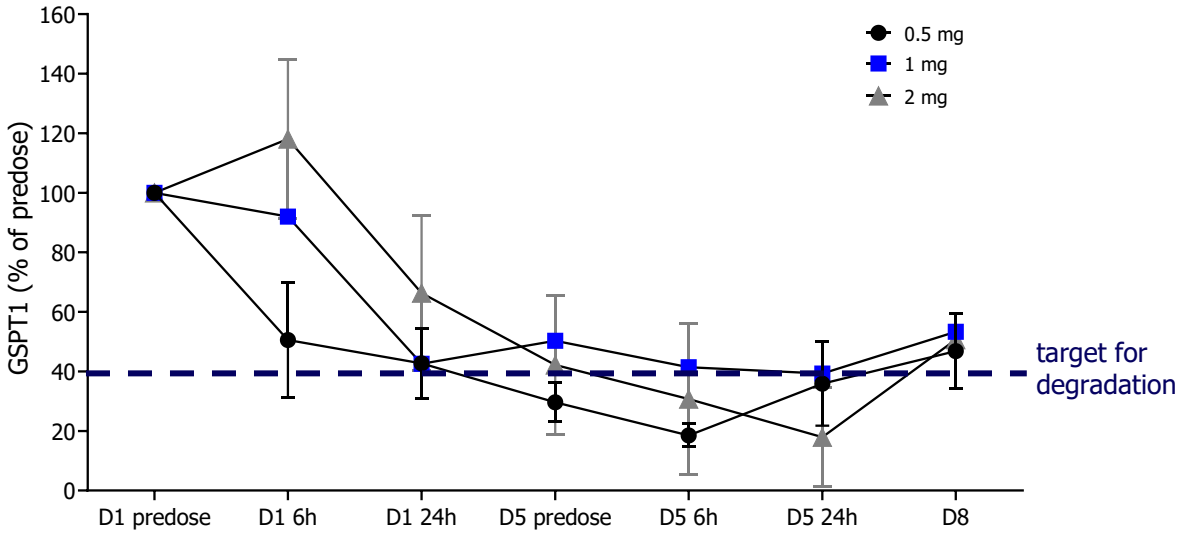
MRT-2359 Induces Optimal GSPT1 Degradation in PBMCs*

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

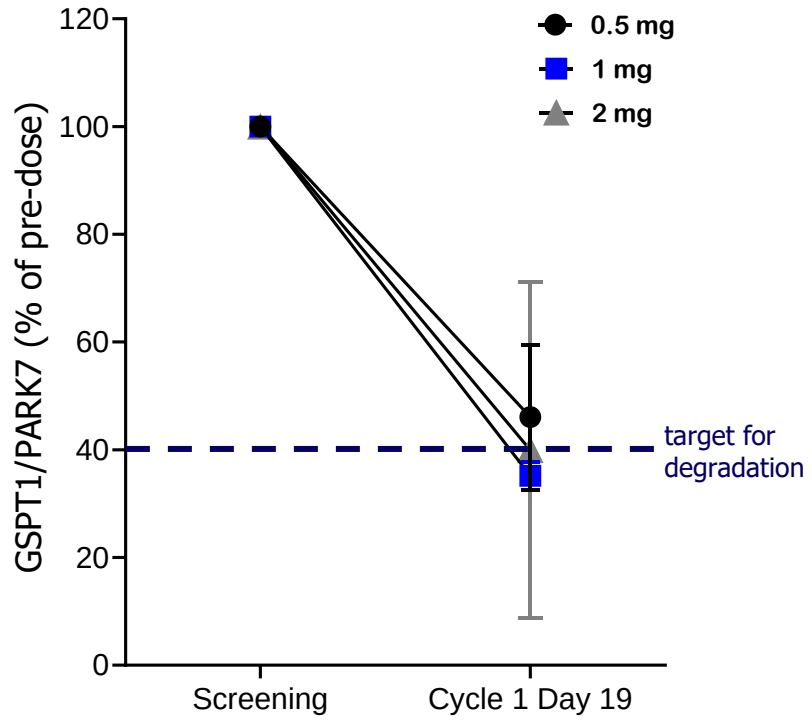


- GSPT1 expression assessed using targeted mass spectrometry
- PD modulation in PBMCs observed across all dose levels; level of degradation (~ 60%) in line with maximal degradation observed in preclinical studies using the same method
- Level of degradation equivalent across all dose levels, suggesting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

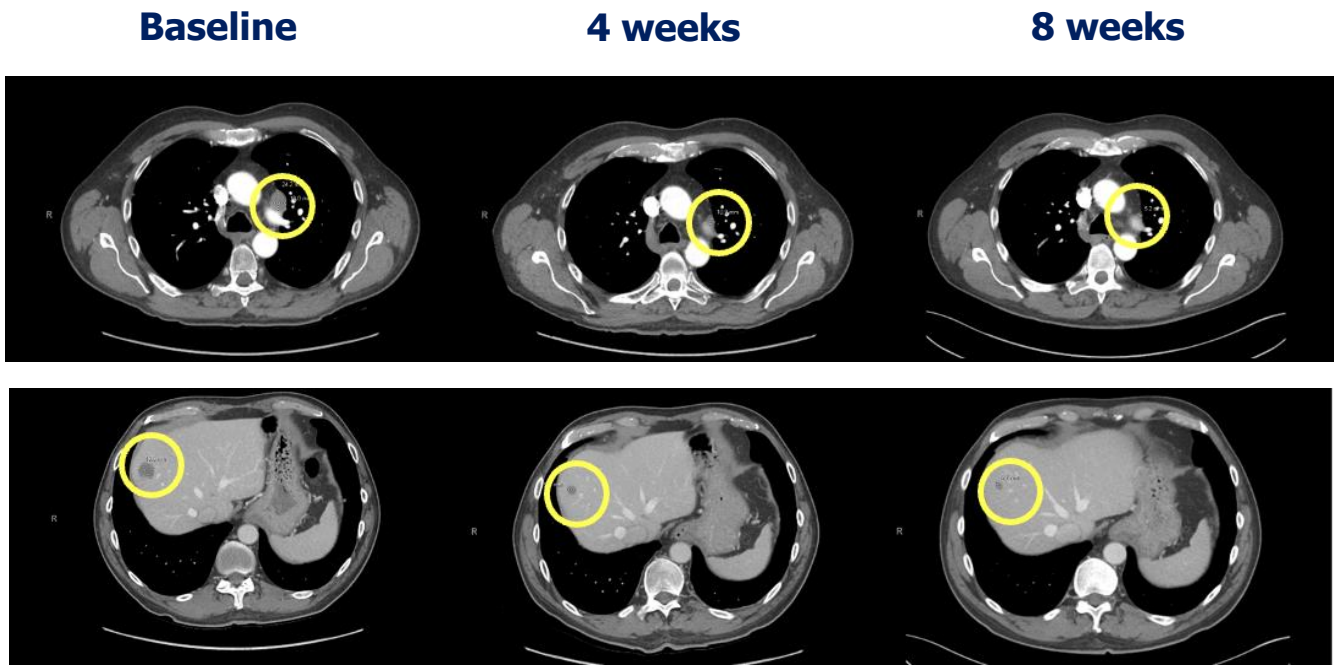
Note: As presented on 10/17/23

[#] 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)

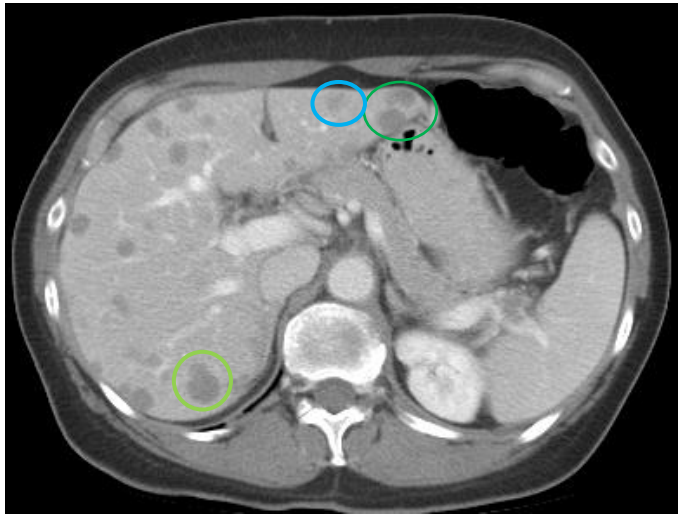


* as presented on 10/17/23

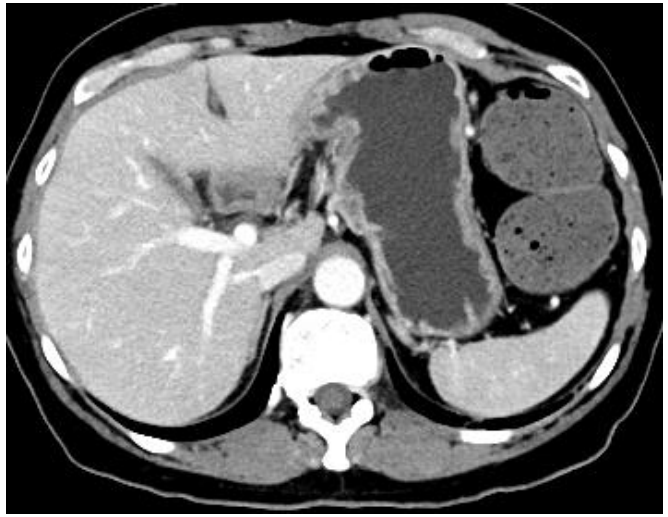
Unconfirmed Partial Response in NSCLC with SCLC/NE Transformation*

- 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



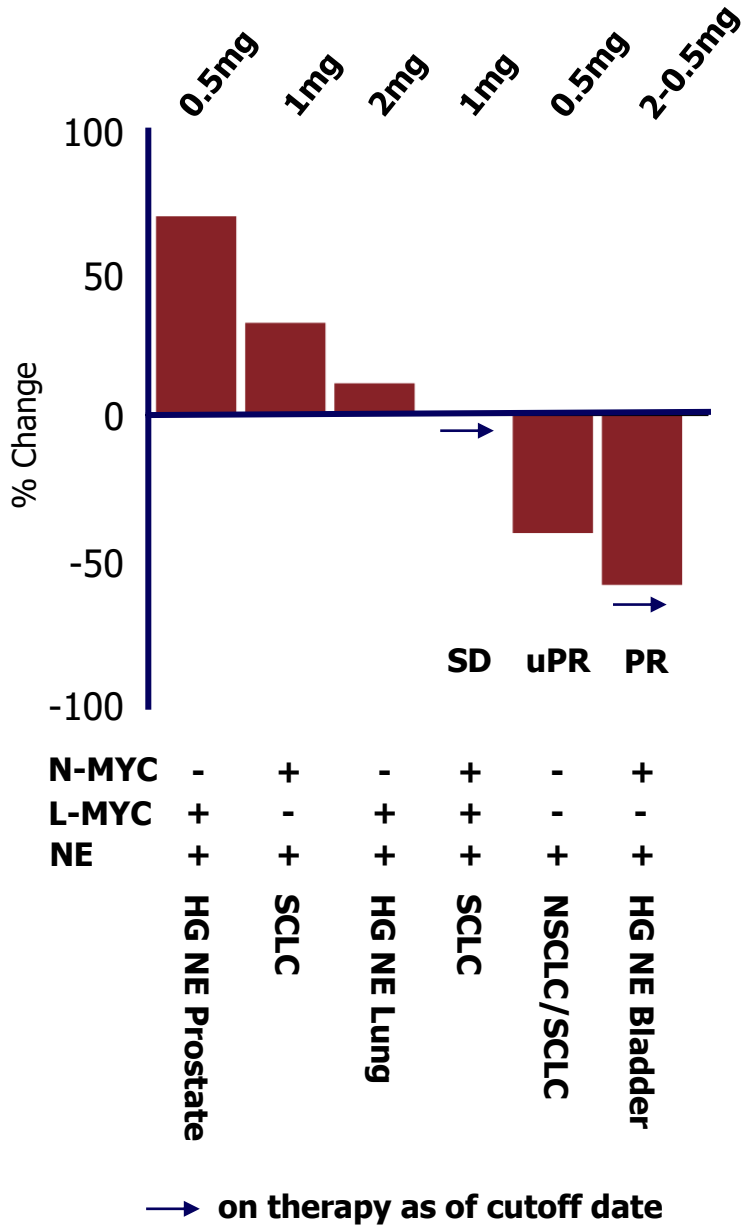
3 weeks



* 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 Profile at Clinically Active Doses*

Safety profile supports further development

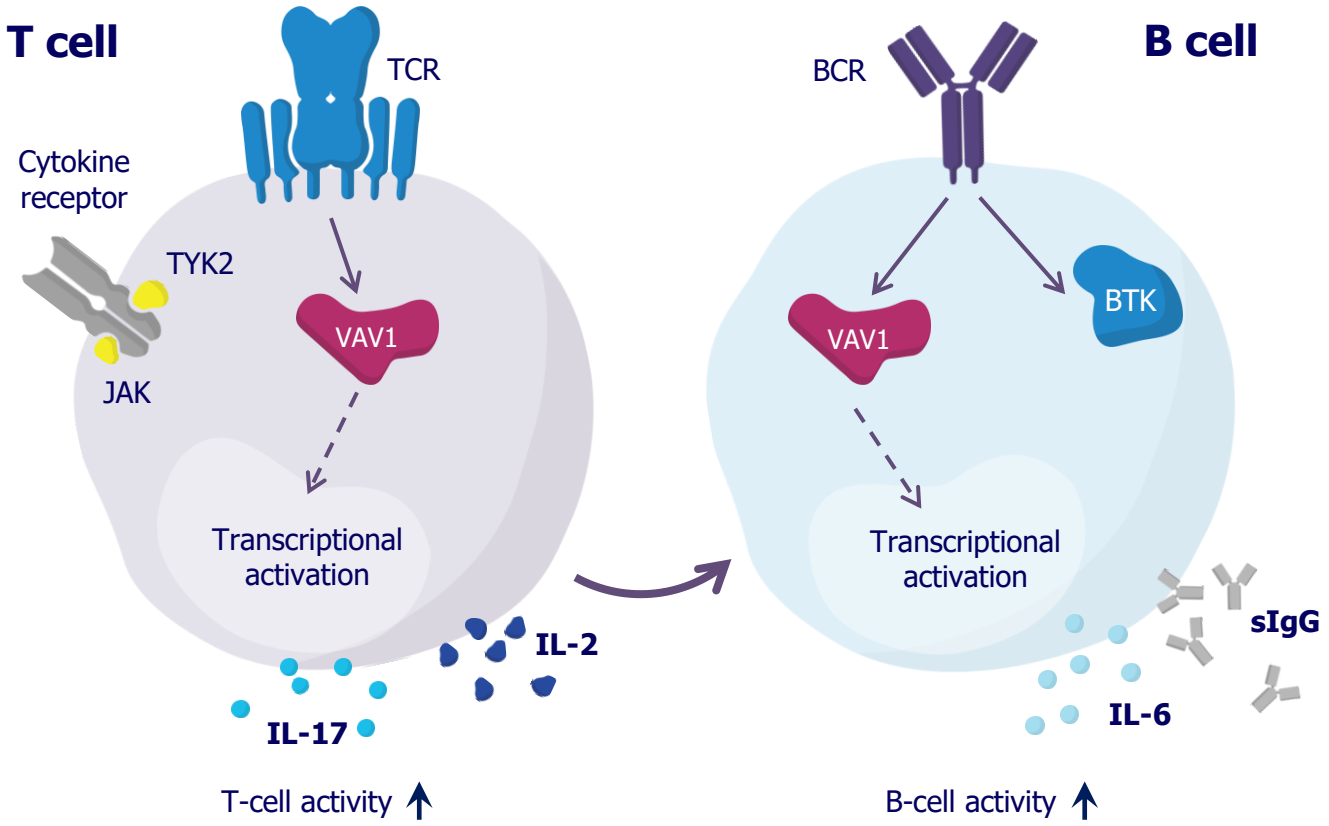
- Preferential and more rapid degradation of GSPT1 in MYC high tumor cells enables favorable adverse event (AE) profile at clinically active doses of 0.5 and 1 mg – no Grade ≥3 AEs
  - Grade 1-2 AEs primarily GI-related and manageable
- No observations of previously reported limitations of other GSPT1-targeted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

* as presented on 10/17/23

Monte Rosa Therapeutics

VAV1 Program (MRT-6160)

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



VAV1 signaling increases cytokine production, proliferation, and differentiation

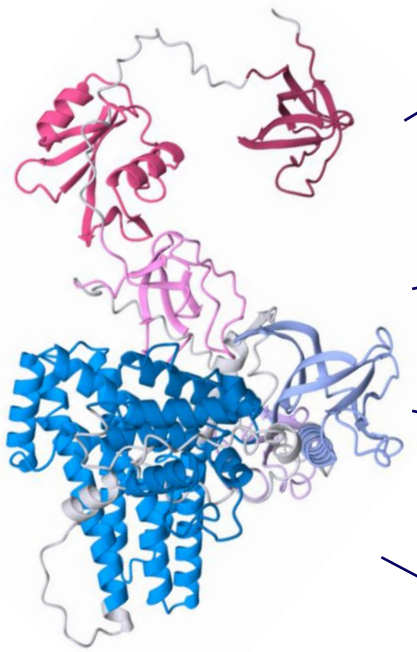
- Pivotal scaffolding protein and signaling molecule **downstream of both the T-cell and B-cell**
- VAV1 degradation impacts both T- & B-cell function, with the **potential to treat a broad set of immune-mediated diseases**

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.

VAV1 is an Upstream Targeting Node Associated with Clinically Validated Pathways

VAV1 signaling is associated with several T and B cell immunologic outcomes

Clinically validated pathway in autoimmune/inflammatory disease



VAV1

T cell activation

ORENCIA® (abatacept)

RINVOQ® upadacitinib

B cell activation/Plasma cell differentiation (Antibody production)

Rituxan® Rituximab

VYVGART® Hytrulo

Th17 response

Cosentyx® (secukinumab)

omvoh™ (mirikizumab-mrkz) 300 mg/15 mL infusion | 100 mg/mL injection

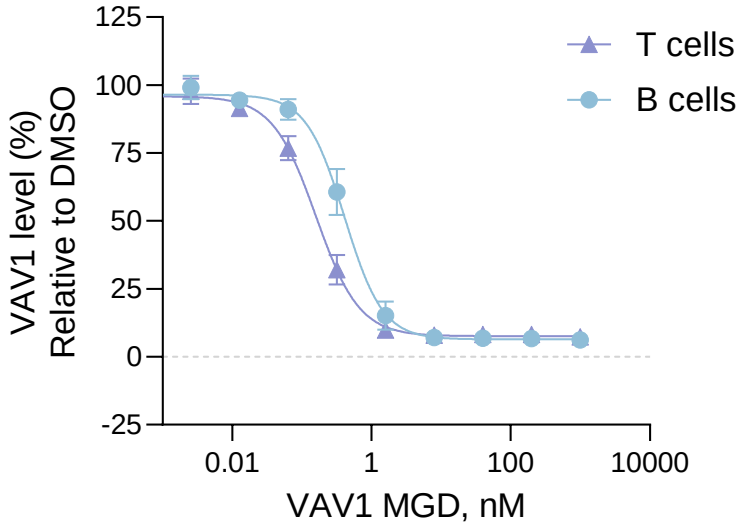
Pro-inflammatory cytokine production

HUMIRA® adalimumab

ACTEMRA® tocilizumab

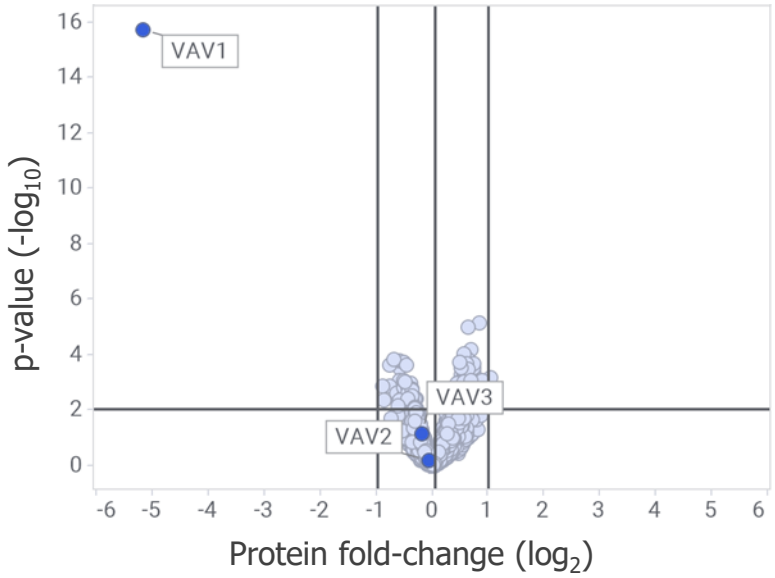
MRT-6160 is a Potent and Highly Selective VAV1-directed MGD

MRT-6160 is a potent VAV1-directed MGD



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

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

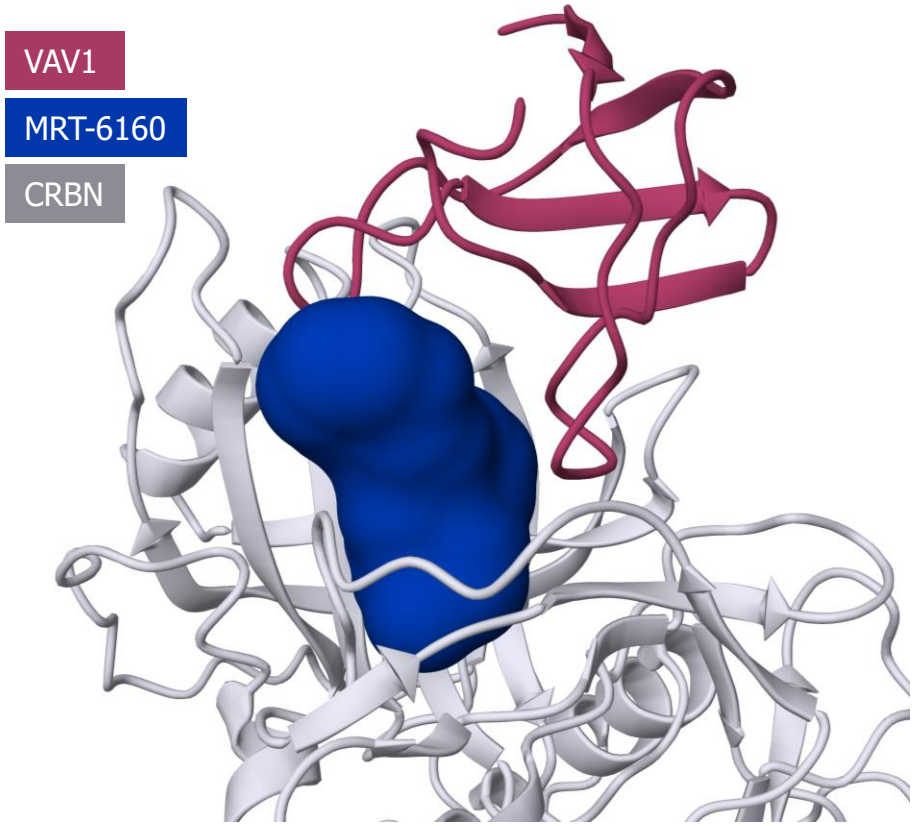


No degradation of other known cereblon neosubstrates

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

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

VAV1 ternary complex (Cryo-EM)



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

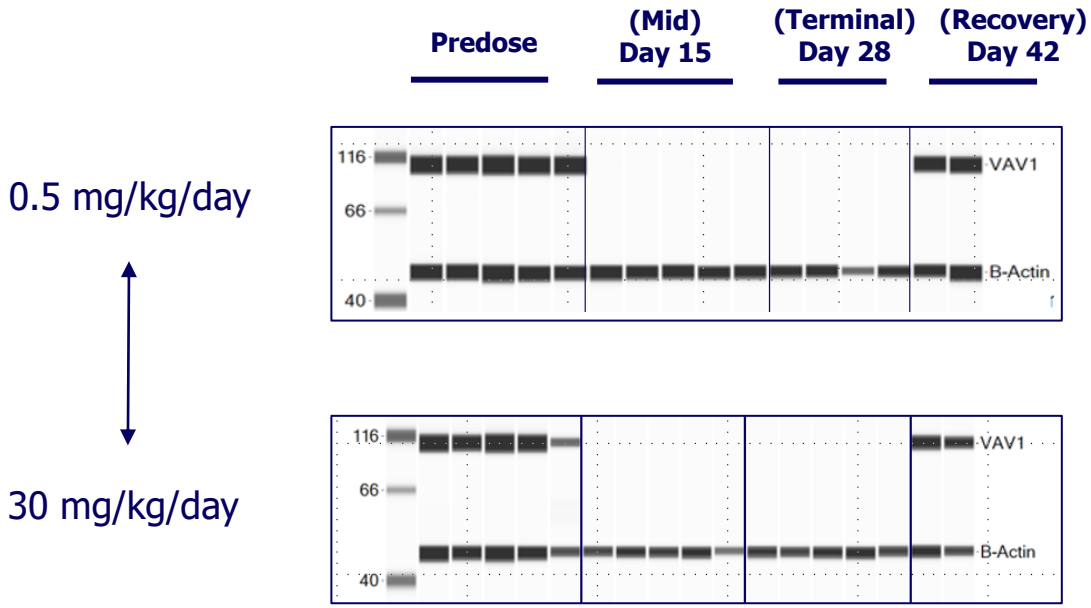
MGD Activity Profile	
CRBN Binding (HTRF, IC_{50})	0.67 µM
VAV1 Ternary Complex (HTRF, EC_{50})	11 nM
VAV1 Degradation (Jurkat, DC_{50} /Dmax)	7 nM / 97%
Selectivity (TMT proteomics)	Large VAV1 selectivity window
Physicochemical Properties	
LogD	1.5
MW	<400
Thermodynamic Solubility	7 µM
ADMET Profile	
Oral bioavailability (all species)	> 50 %
Metabolite Profile (*in vitro*)	No unique human metabolites or GSH adducts (mics)
CYP DDI (9 isoforms)	IC_{50} > 30 µM
Safety Pharmacology	
Mini-Ames	Negative
hERG inhibition (patch clamp)	No inhibition (EC_{50} > 30 µM)
Counterscreens (panel with 98 targets)	No inhibition

28-day GLP Toxicology Studies Establish Highly Favorable Safety Margins

28-day GLP Toxicology Summary

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

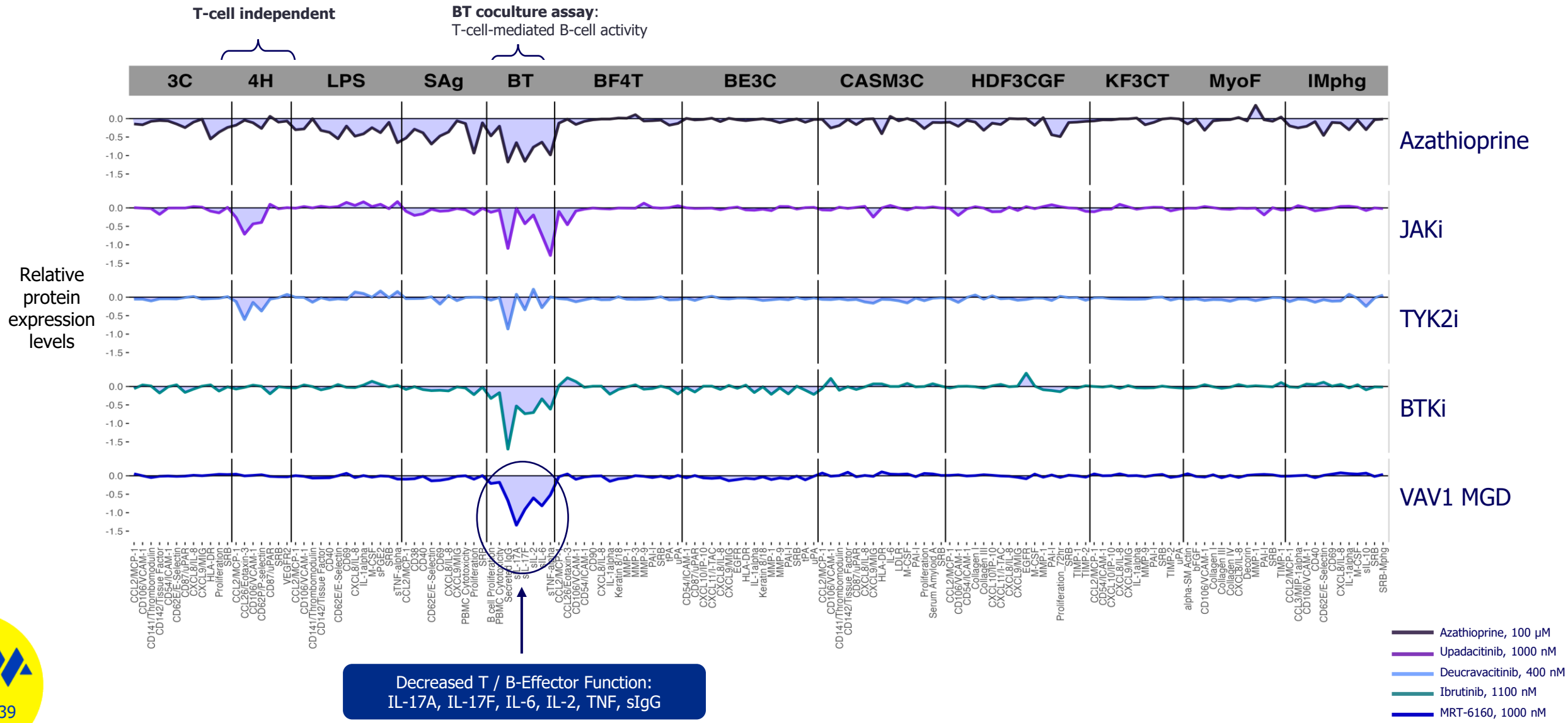
Robust VAV1 degradation and recovery observed in both low and high dose groups in cyno GLP tox study



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

NOAEL = no observed adverse effect level

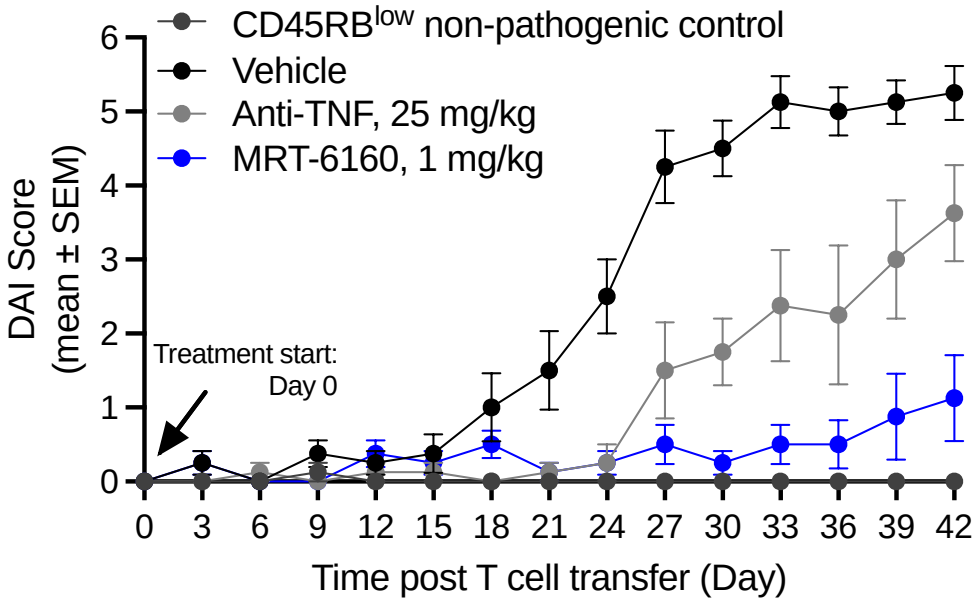
MRT-6160 Blocks T-cell-Mediated B-cell Activity in BioMAP® Profile



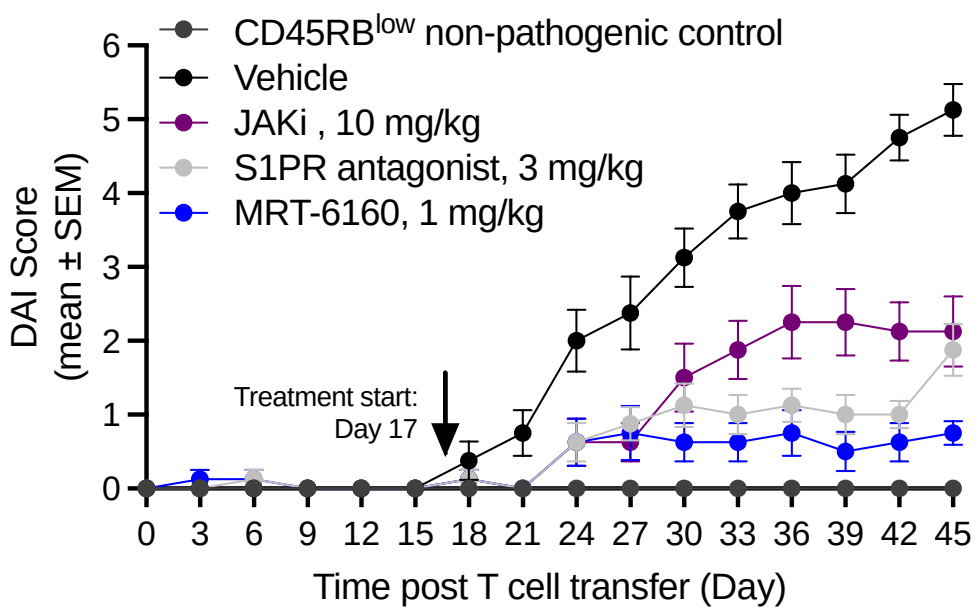
BioMAP® Diversity Plus Platform (Eurofins). Shark tooth plots show relative expression levels of indicated proteins in Drug treated vs. DMSO controls. 3C/4H, Venular endothelial cells; LPS/SAg, Venular endothelial cells + PBMC; BT, PBMC + B cells; BF4T, Bronchial epithelial cells + dermal fibroblasts; BE3C. Bronchial epithelial cells; CASM3C, Coronary artery smooth muscle cells; HDF5CGF, Dermal fibroblasts; KF3CT, keratinocytes + dermal fibroblasts; MyoF, lung fibroblasts; IMphg, macrophages + venular epithelial cells

MRT-6160 Ameliorates T Cell Transfer-Induced Colitis Better than Standard of Care

Treatment initiated at time of model induction on Day 0



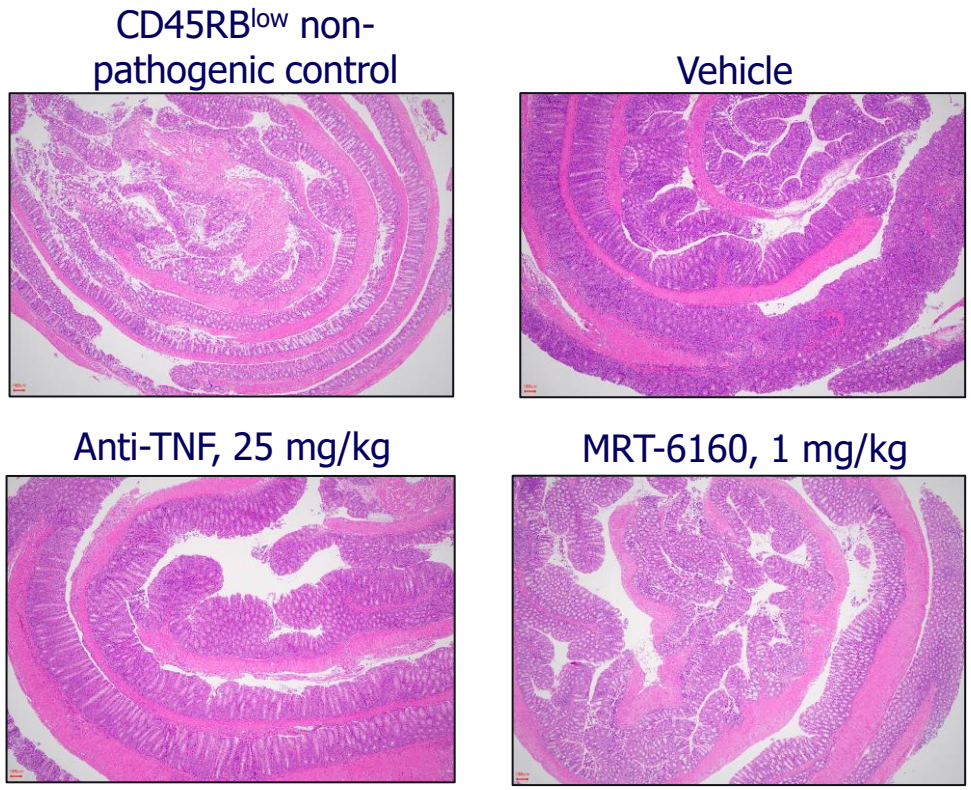
Treatment initiated in therapeutic setting on Day 17 following disease induction



Non-pathogenic CD45RB^{low} or pathogenic CD45RB^{high} cells were transferred into SCID mice to induce colitis. Mice were treated with vehicle, MRT-6160 (PO QD), or anti-TNF (IP Q3D) from Day 0 to Day 42 and assessed for disease every 3 days (*left*) or with vehicle, MRT-6160, or S1PR antagonist (etrasimod; PO QD), or JAKi (upadacitinib; PO BID) from Day 17 to Day 45 and assessed for disease every 3 days (*right*)

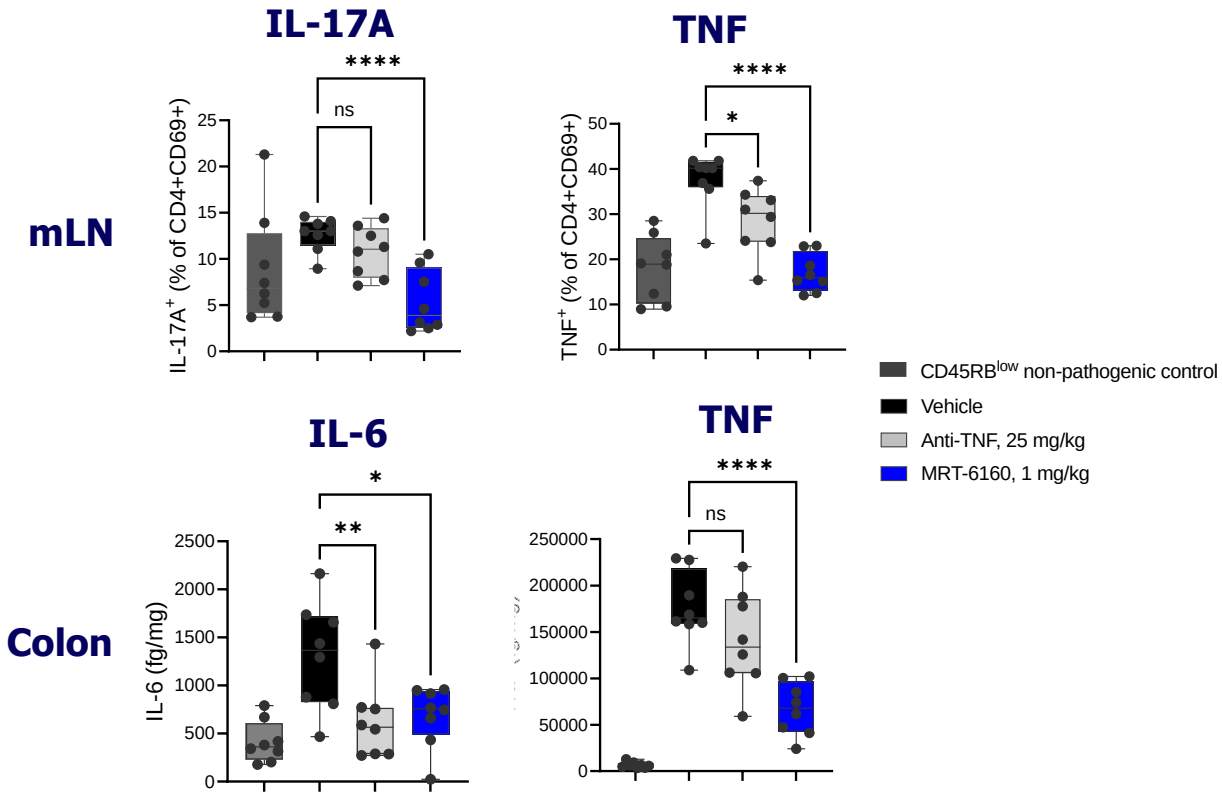
MRT-6160 Reduces Inflammation-Mediated Damage of the Colon and Cytokine Production in a T-Cell Transfer Model of Ulcerative Colitis

MRT-6160 reduces inflammation-mediated damage and swelling of the colon



Hematoxylin and eosin-stained histopathology sections from colon at end of study

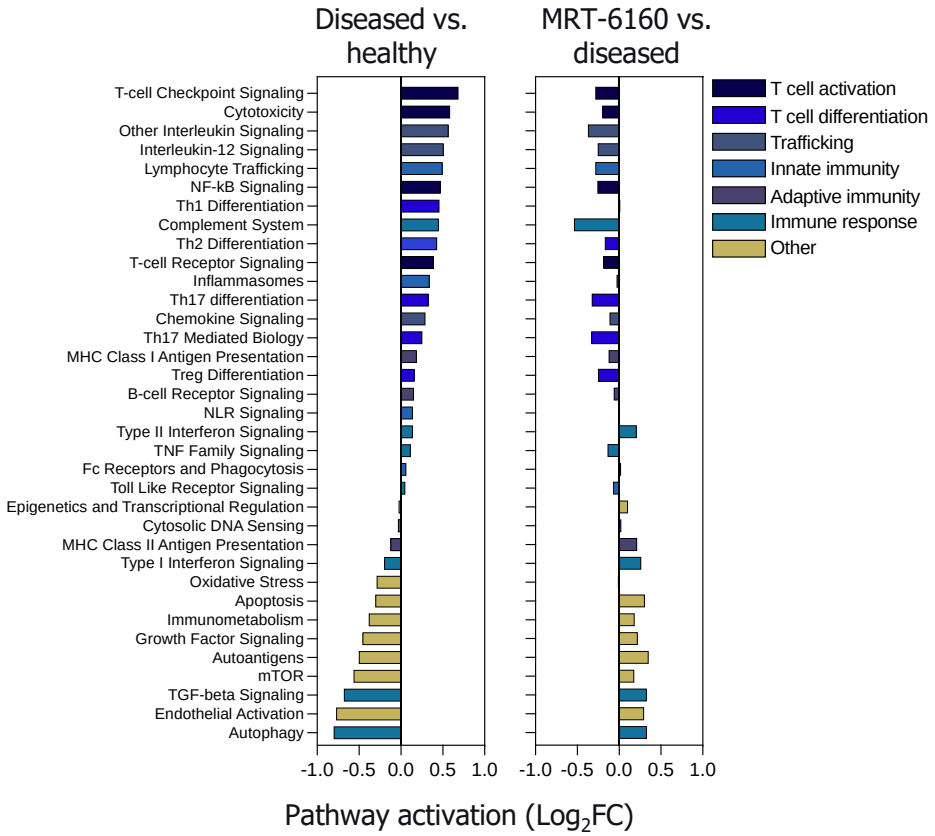
MRT-6160 reduces cytokine production in the mesenteric lymph node and colon



Flow cytometric (*upper row*) and cytokine bead array (*lower row*) analysis of mesenteric lymph node CD4+ T cells and colon tissue respectively

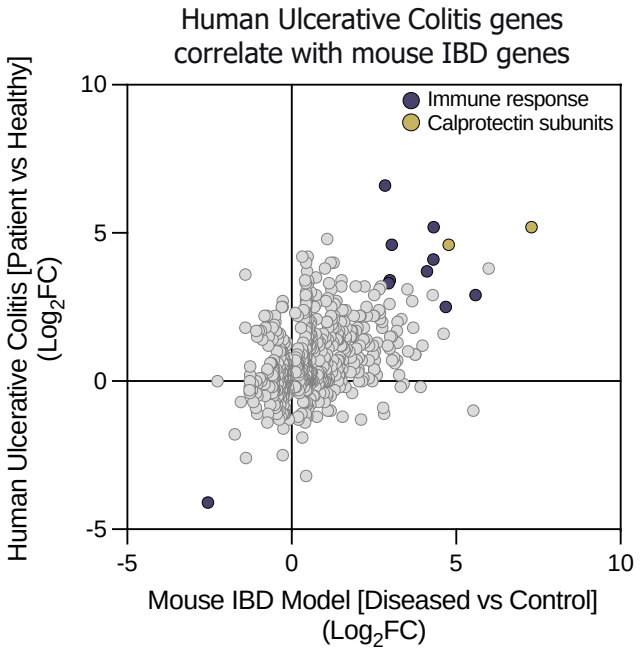
MRT-6160 Reduces Expression of Human Disease-Relevant Pro-Inflammatory and Disease-Associated Genes

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

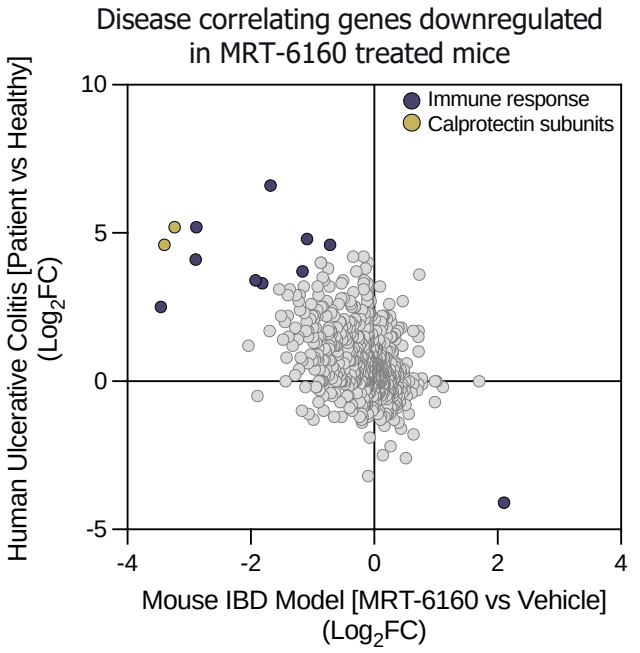


RNA from mouse colon at study termination was assessed using the NanoString nCounter Mouse Autoimmune Profiling Panel

MRT-6160 attenuates expression of human Ulcerative Colitis-relevant pro-inflammatory genes



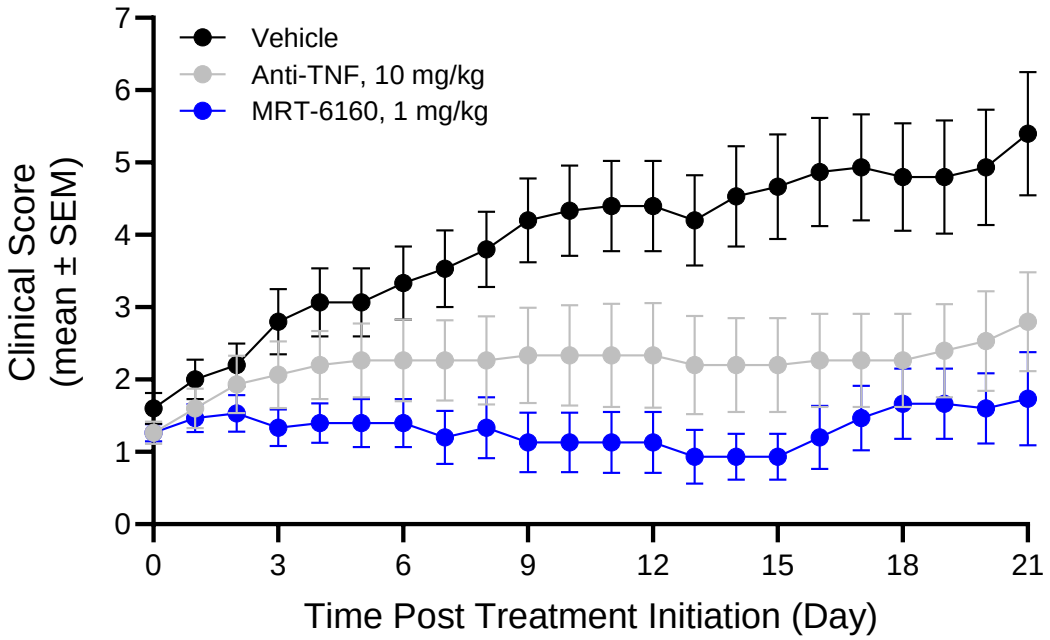
Vehicle vs. Control differential expression in the IBD mouse model was mapped to human ulcerative colitis vs healthy differential expression



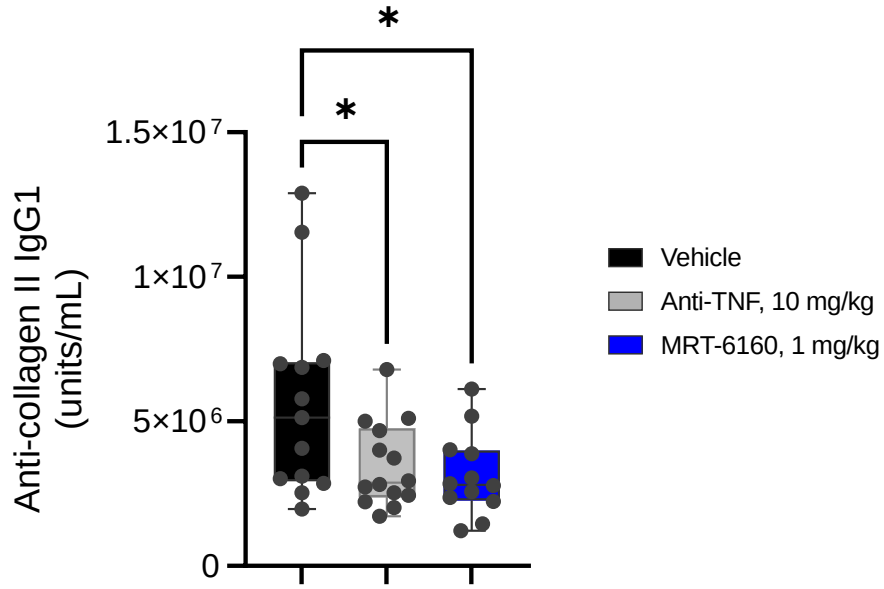
MRT-6160 vs Vehicle differential expression in the IBD mouse model was mapped to human ulcerative colitis vs healthy differential expression

MRT-6160 Inhibits Disease Progression, Joint Inflammation & Auto-Antibody Production in a Rheumatoid Arthritis Disease Model

MRT-6160 inhibits disease progression



MRT-6160 inhibits anti-collagen II auto-antibodies

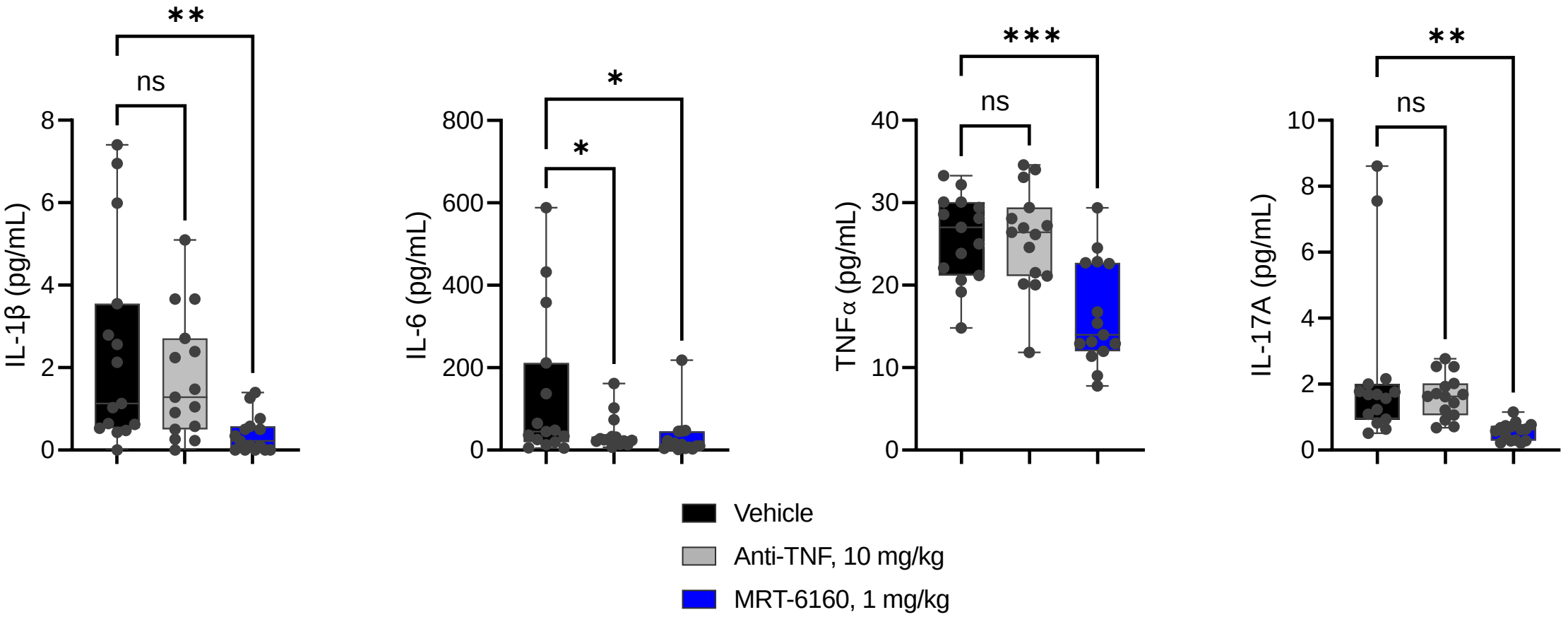


Collagen-induced arthritis T/B-cell (auto-antibody) driven model

Mice were immunized with bovine collagen II twice 21 days apart and enrolled into treatment groups at disease onset

Dosing: Vehicle, MRT-6160, or anti-TNF (IP BIW) for 22 days starting at disease onset

MRT-6160 Reduces Pro-Inflammatory Cytokine Production in a Rheumatoid Arthritis Disease Model



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

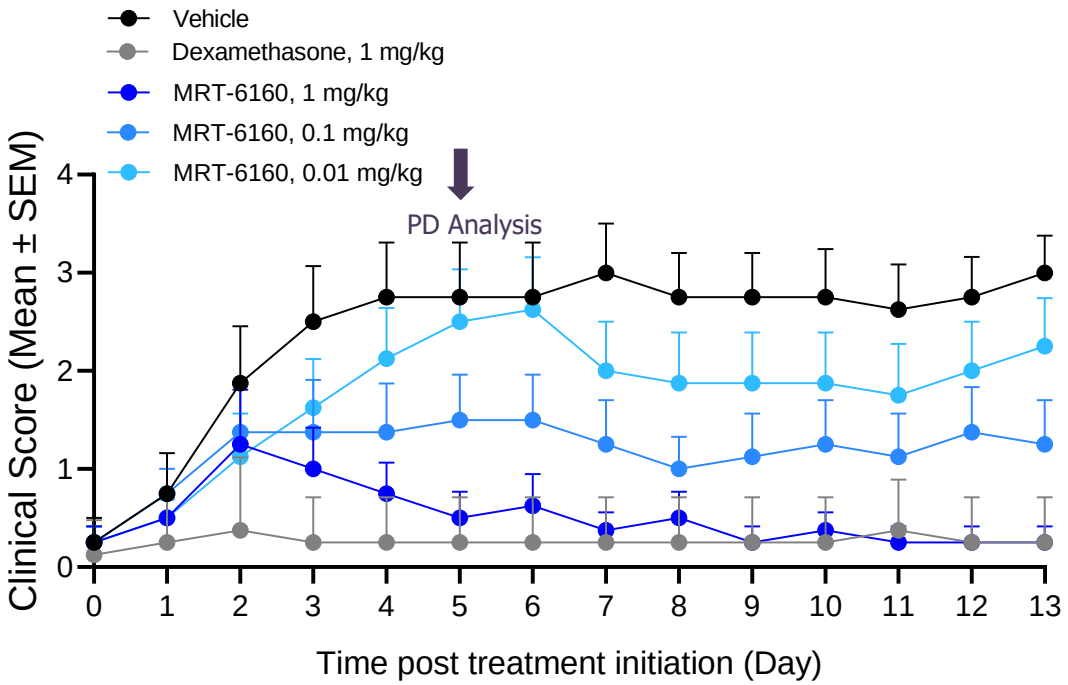
Dosing: Vehicle, MRT-6160; PO QD. Anti-TNF; IP BIW.

Mice were treated for 21 days from disease onset (Day 0)

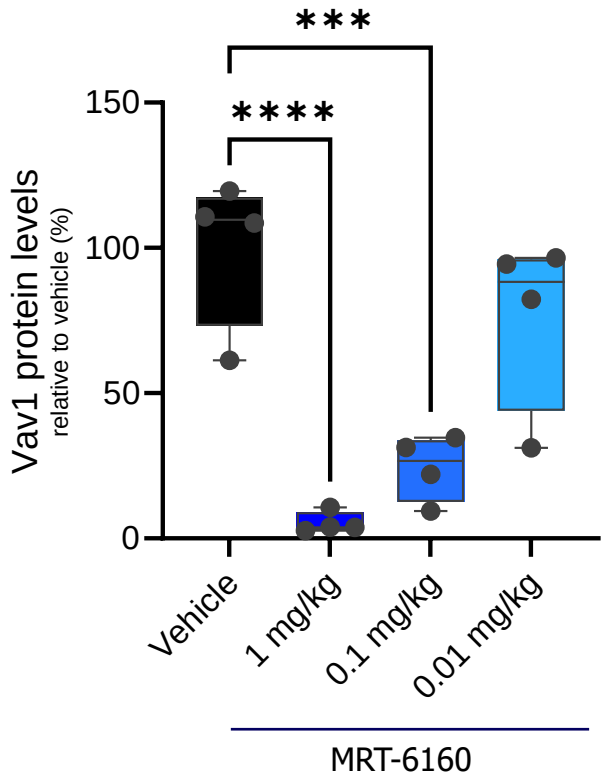
Serum cytokine analysis on Day 21

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

C57BL/6 mice were immunized with MOG35-55 peptide on Day -12 then administered pertussis toxin (Days -12 and -10). Mice were assessed for disease daily. On Day 0, mice were treated with vehicle or MRT-6160 (PO QD) (left). On Day 5, the spinal cords of satellite mice were assessed for Vav1 levels by western blot (right).

Phase 1 Biomarker Strategy to Demonstrate MRT-6160 Pharmacodynamic Effects

Phase 1 SAD/MAD in Healthy Volunteers

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

VAV1 protein degradation

- Flow cytometry on T and B cells: whole blood (WB)
- Potential: Mature B cell typing in MAD

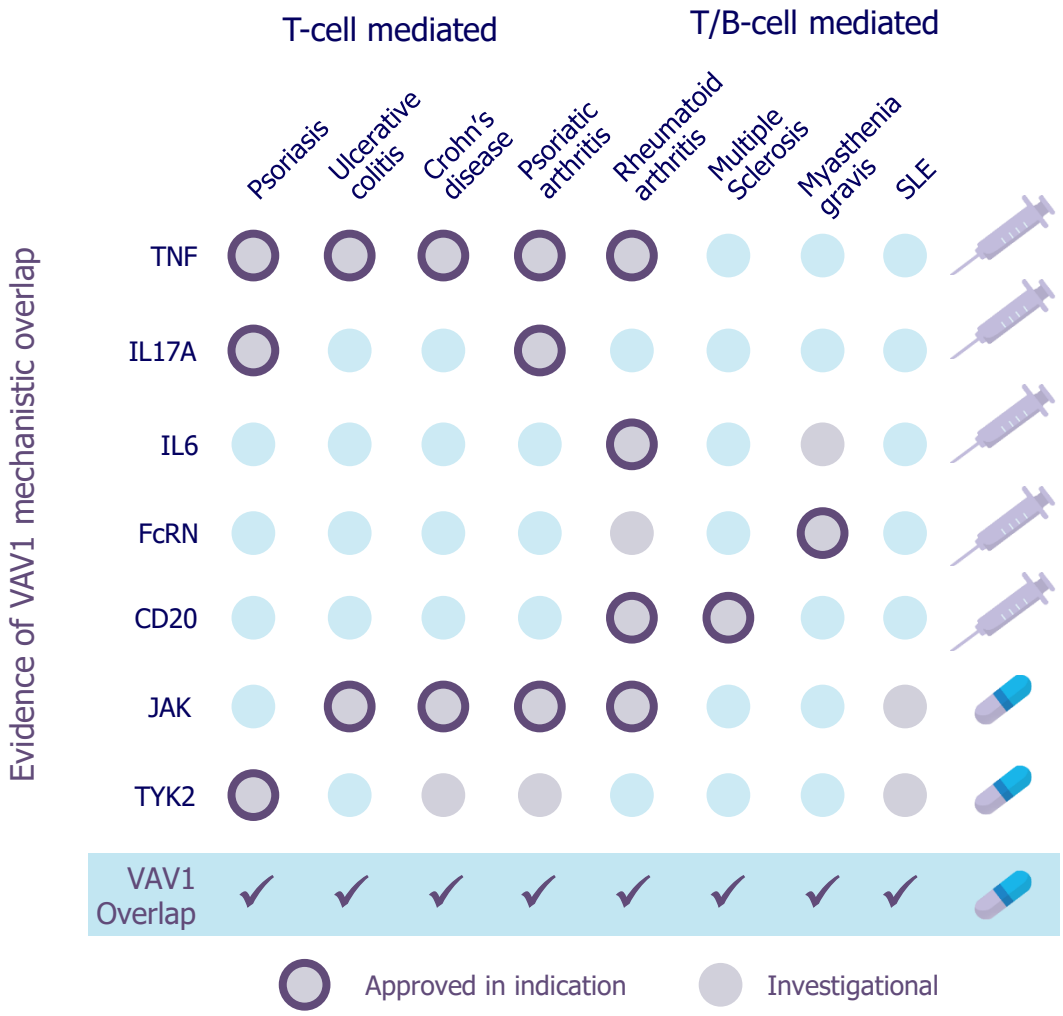
Key downstream PD

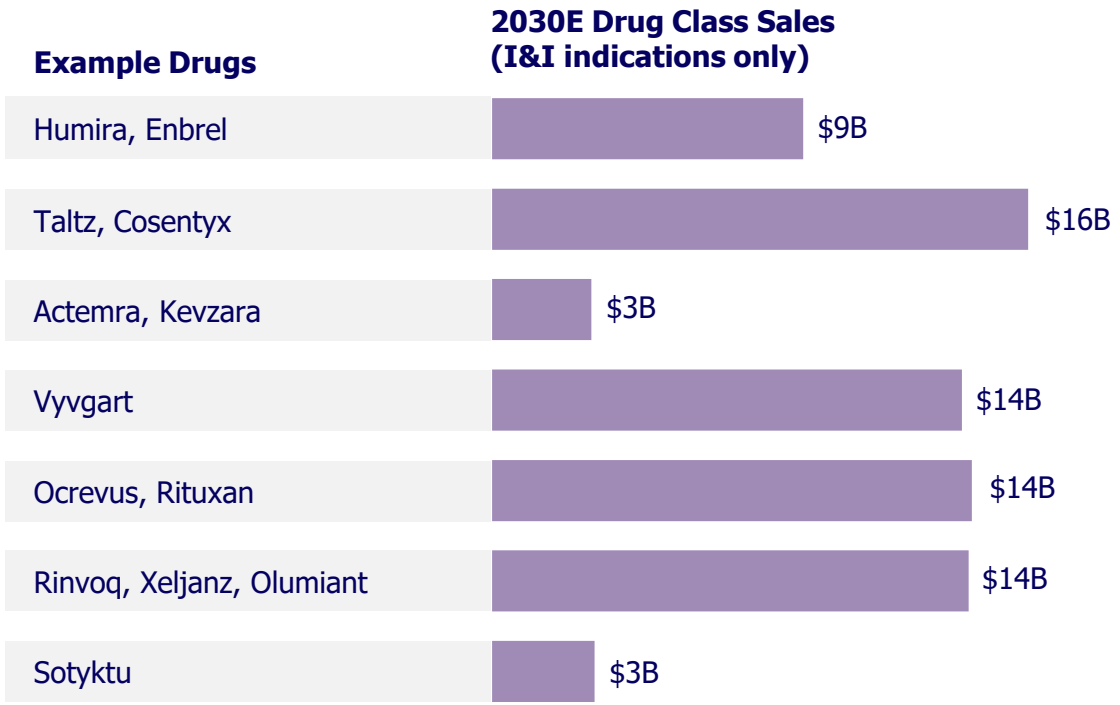
- Flow cytometry for CD69 protein on T & B cells: WB
- Immunoassay for IL-2, IL-6, IL-17
- hs C-reactive protein

Phase 1 SAD/MAD study ongoing, clinical data anticipated in Q1 2025

VAV1: Unique Mechanism with Broad Potential Applications

Potential to address multiple autoimmune diseases with safe, oral therapy



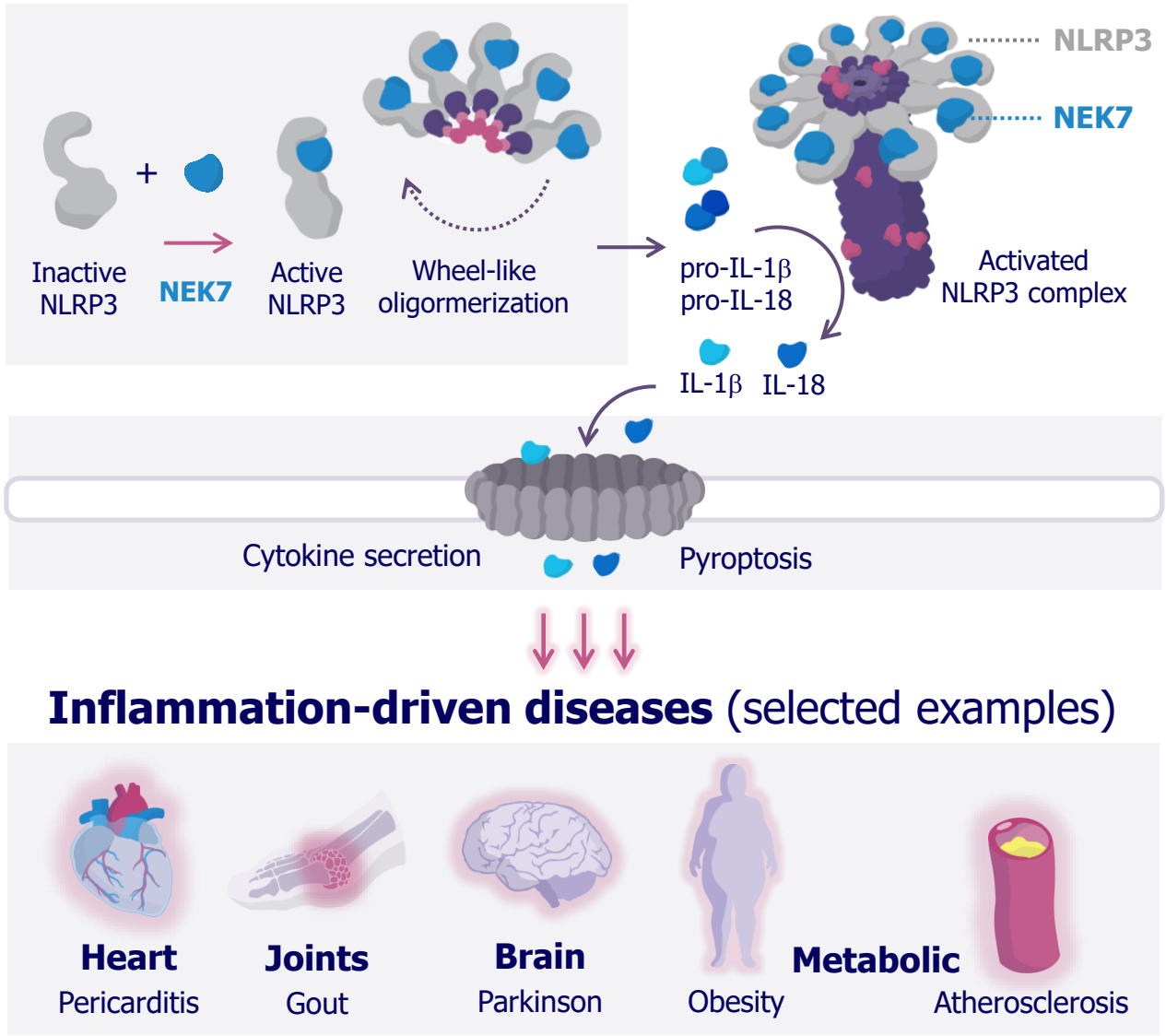


Note: Chart adapted from Hosack et al., Nat Rev Immunol 2023. Drug class sales from Evaluate Pharma. 2030E sales may include sales from anticipated future approvals.

Monte Rosa Therapeutics

NEK7 Program (MRT-8102)

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



NEK7 enables NLRP3 assembly in a kinase-independent manner

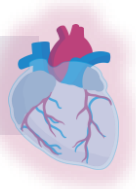
NEK7-deficient macrophages are severely impaired in **IL-1β and IL-18** secretion

NEK7 degradation has the potential to become an important treatment for **inflammation-driven diseases**

IL-1/NLRP3 Signaling is a Clinically Validated Pathway

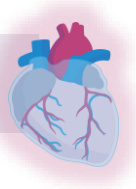
Cardio-immunology

Recurrent pericarditis



Rilonacept (IL-1α/β) – approved for recurrent pericarditis

Atherosclerotic cardiovascular disease



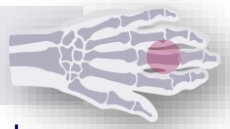
Canakinumab (IL-1β) – reduction in cardiac events

Rheumatology

Gout

Canakinumab (IL-1β) – approved for gout flares

Osteoarthritis



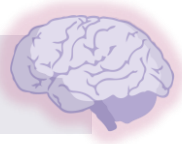
Canakinumab (IL-1β) – decreased rates of knee and hip replacement

Autoinflammation
CAPS CINCA NOMID

Anakinra (IL-1R), canakinumab (IL-1β), rilonacept (IL-1 α/β) – approved for CAPS and NOMID

Neurology

Neuroinflammation
Epilepsy



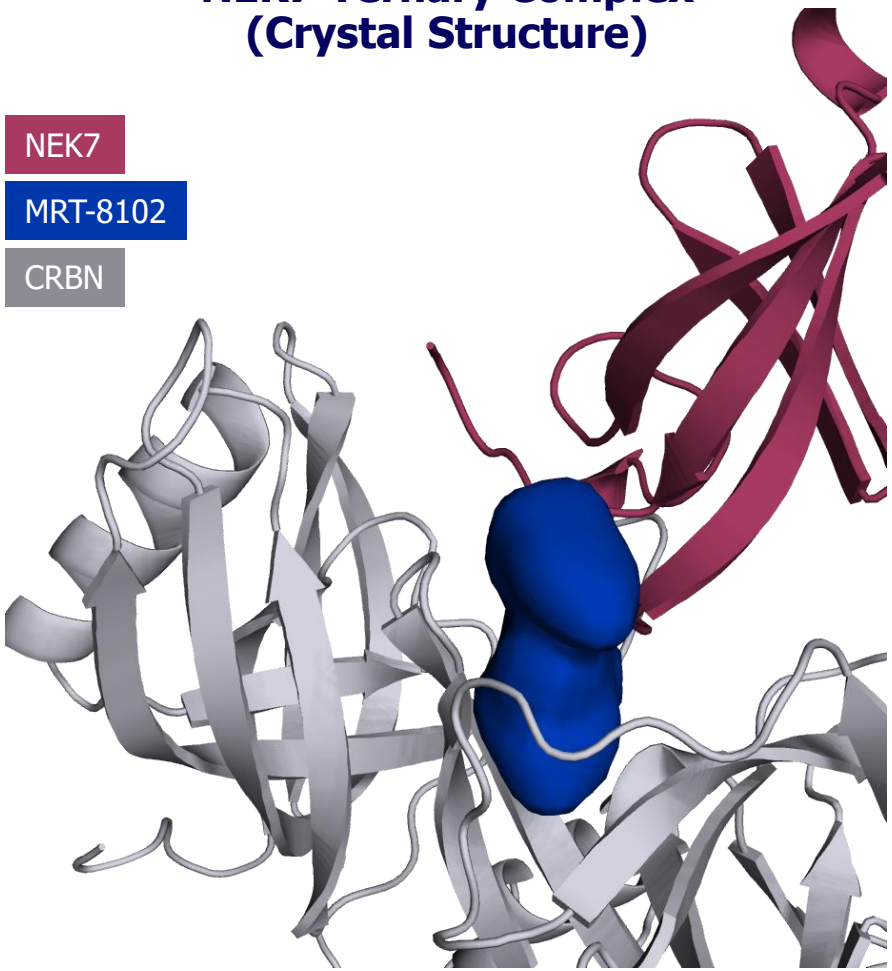
Belnacasan (CASP1) – reduction in seizures

Metabolic
Weight loss

Multiple NLRP3 agents being studied for weight loss

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

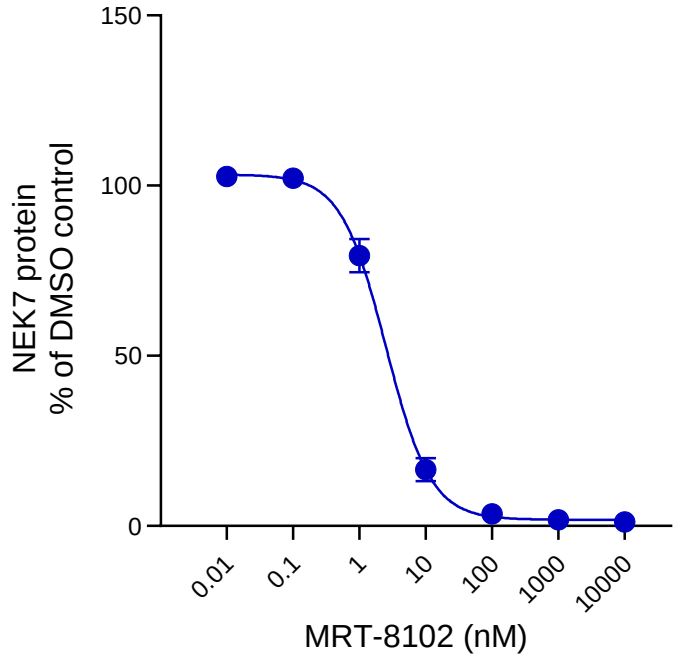
NEK7 Ternary Complex (Crystal Structure)



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

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

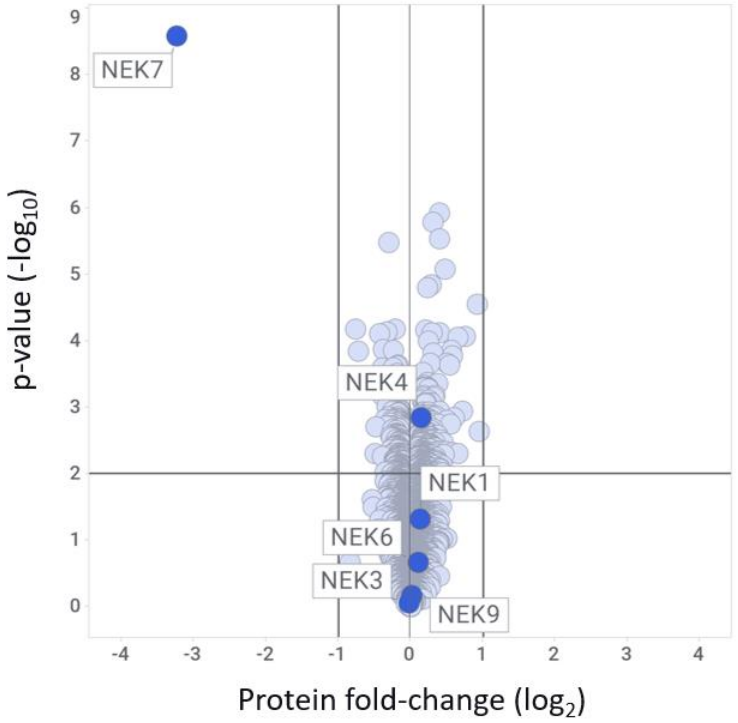
MRT-8102 potently degrades NEK7



Human PBMC
24 h treatment

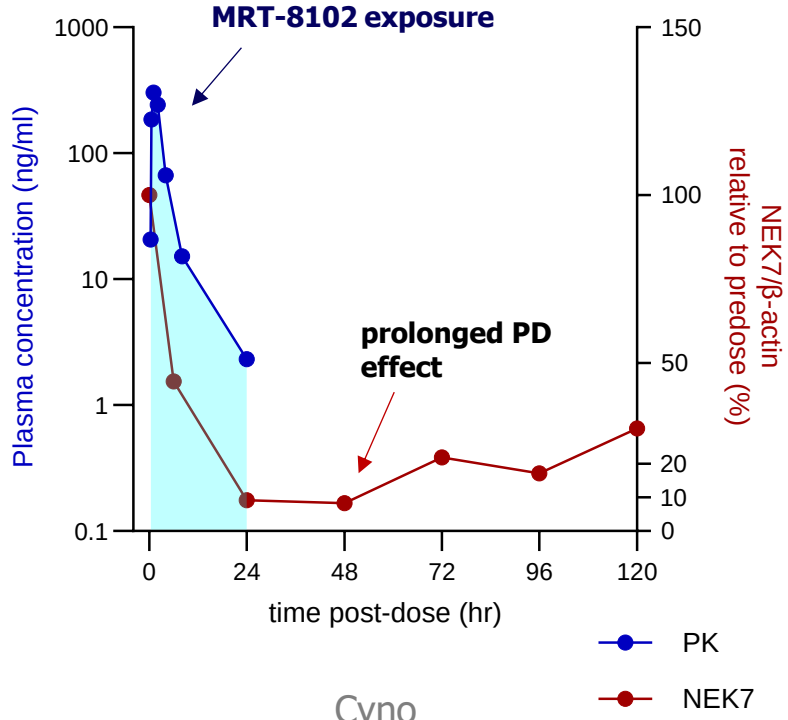
DC_{50} = 2.5 nM

MRT-8102 induces highly selective NEK7 degradation



No degradation of other known CRBN neosubstrates

MRT-8102 exposure results in prolonged PD effect

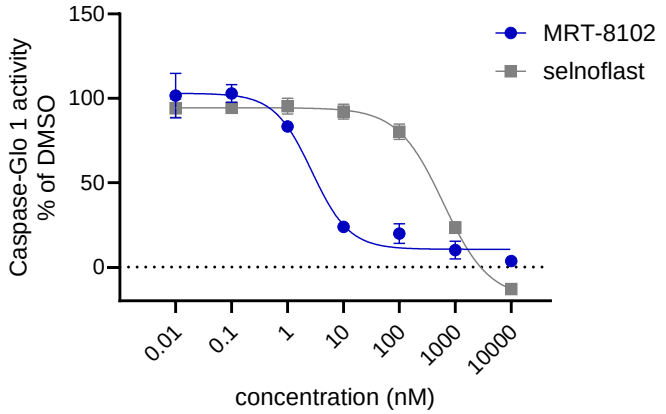


Cyno
10 mg/kg single-dose

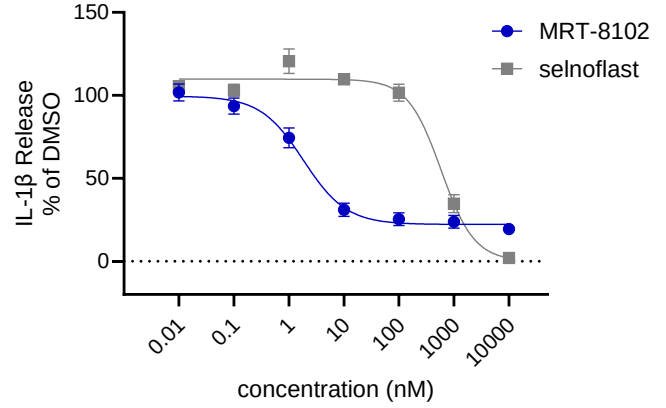
MRT-8102 Leads to Potent Inhibition of NLRP3 Inflammasome *In Vitro*

Reduced caspase-1 and IL-1β in human monocyte-derived macrophages

Caspase-1

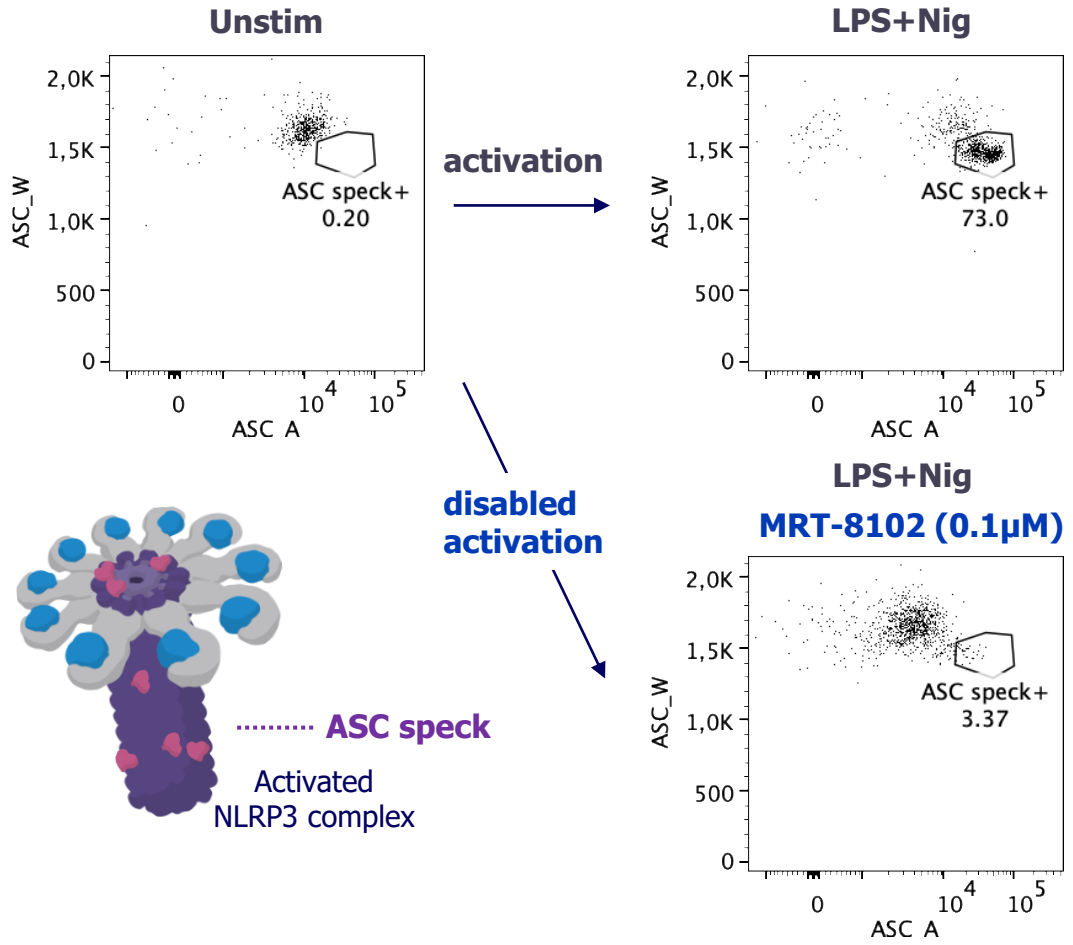


IL-1β



LPS + Nigericin

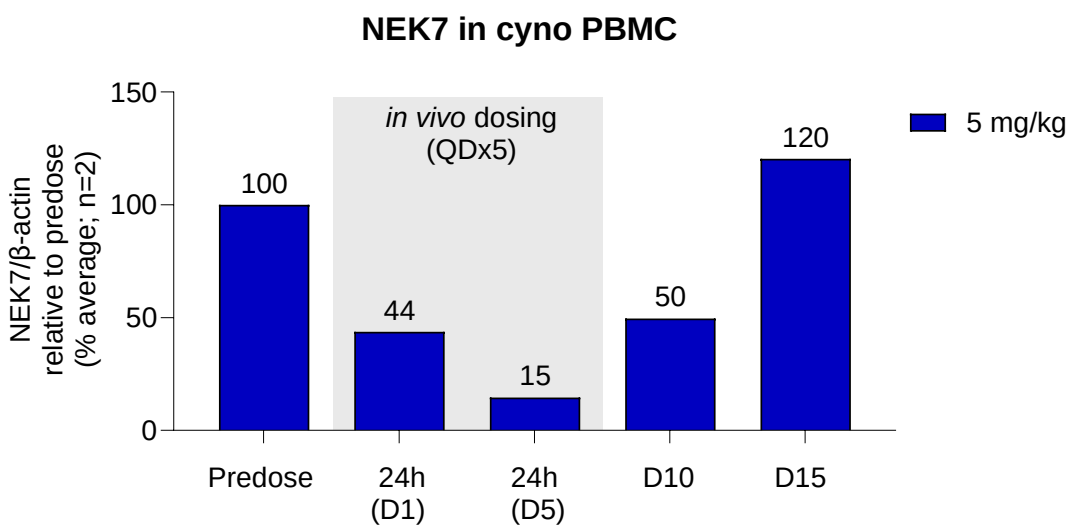
Reduced inflammasome activation (ASC speck formation) in human whole blood



Gating strategy: Single cells_CD45+_CD66b-_CD14+

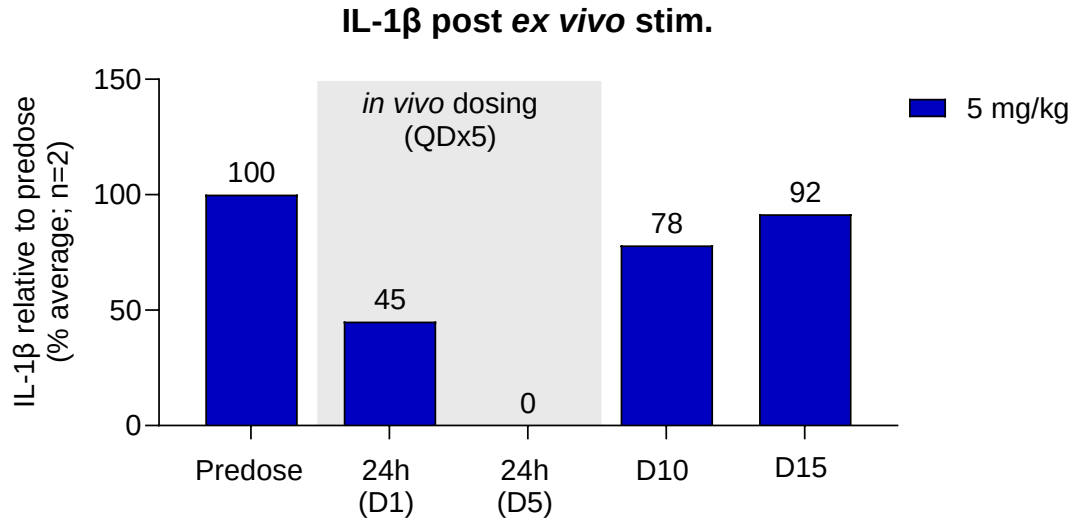
Suppression of *Ex Vivo* Inflammasome Activation Following Degradation of NEK7 After Single and Multi-dose Study in Non-human Primates

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



No clinical observations reported

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

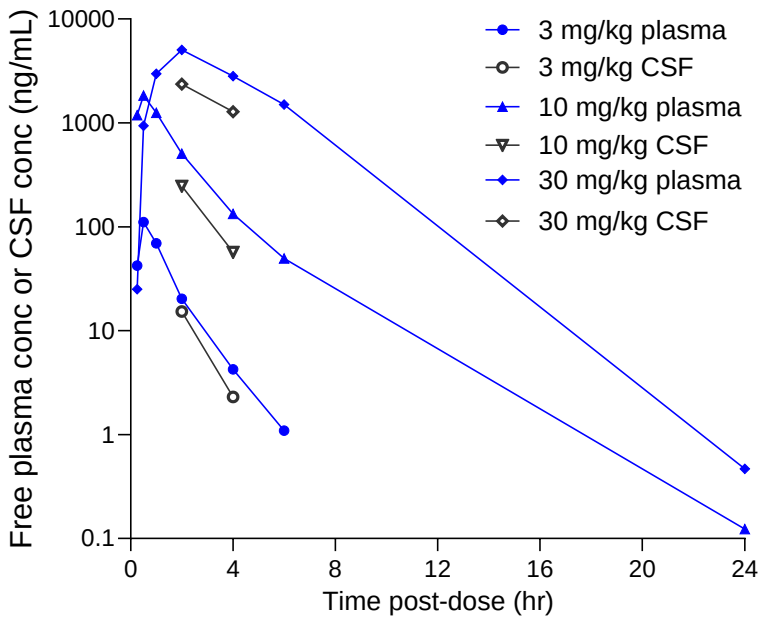


- IL-1β in plasma after *ex vivo* stimulation with LPS + nigericin
- Similar results for Caspase-1 activity from same study
- Follow-up study with 1 mg/kg MRT-8102, *i.v.* at 4 hr showed similar results

MRT-8102 Displays Significant Blood Brain Barrier Penetration

MRT-8102 displays CNS-penetrance

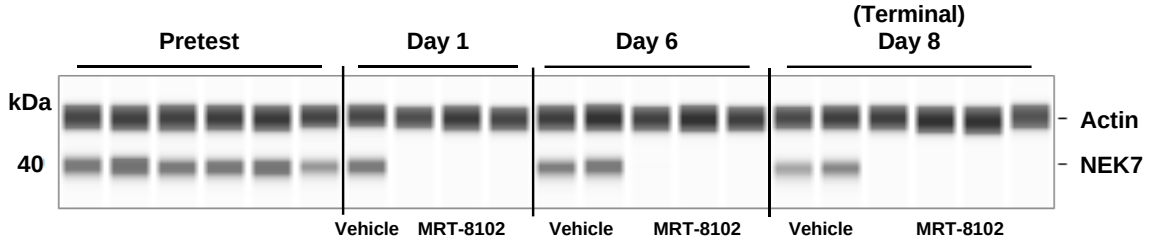
Single dose p.o.



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

Significant NEK7 degradation in various brain regions 24h post treatment

PBMCs



Brain

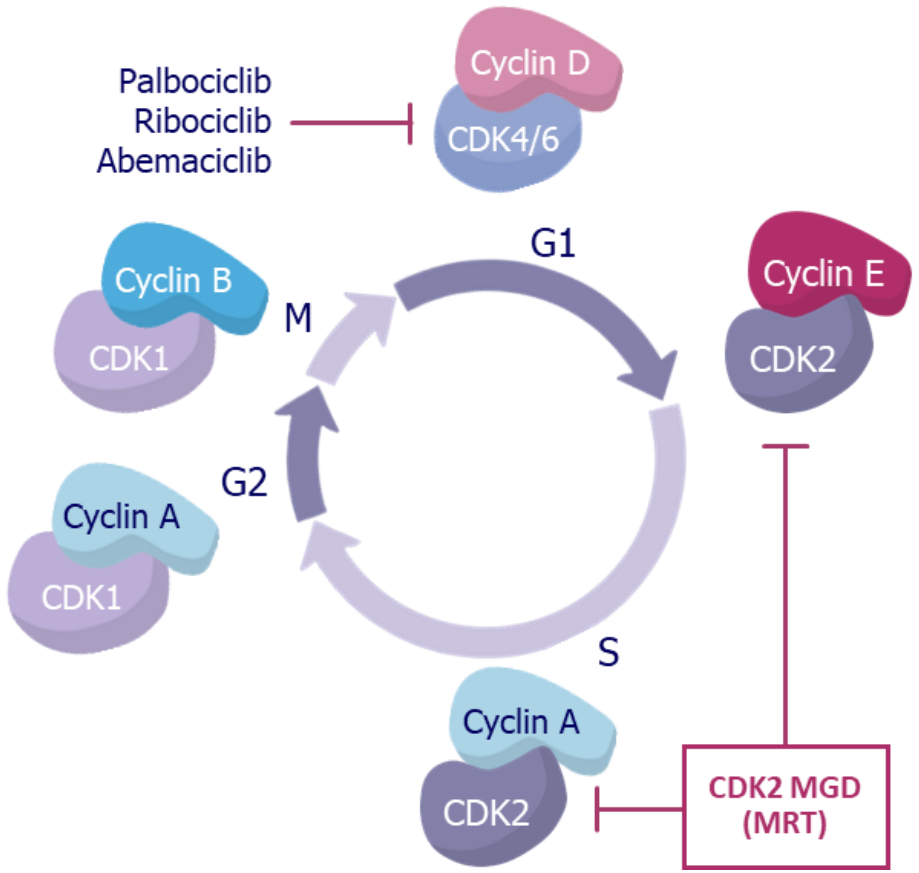
Daily dose of 30 mg/kg MRT-8102 for 7 days
Analysis on day 8 (24 hr post-final dose) by JESS Simple Western

Monte Rosa Therapeutics

CDK2 Program

CDK2 is a Key Driver of Cell Cycle Progression in Cancer

CDK2: a key cell cycle regulator



Therapeutic hypothesis:

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

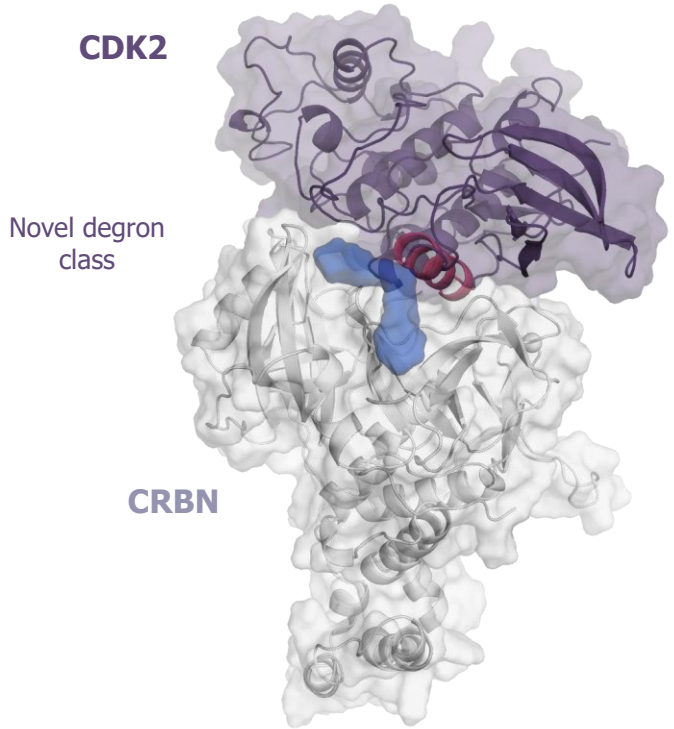
Clinical Opportunity:

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

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

MRT-9643 is a Potent, Highly Selective CDK2 MGD with a Favorable Drug-like Profile

CDK2 ternary complex (Cryo-EM)

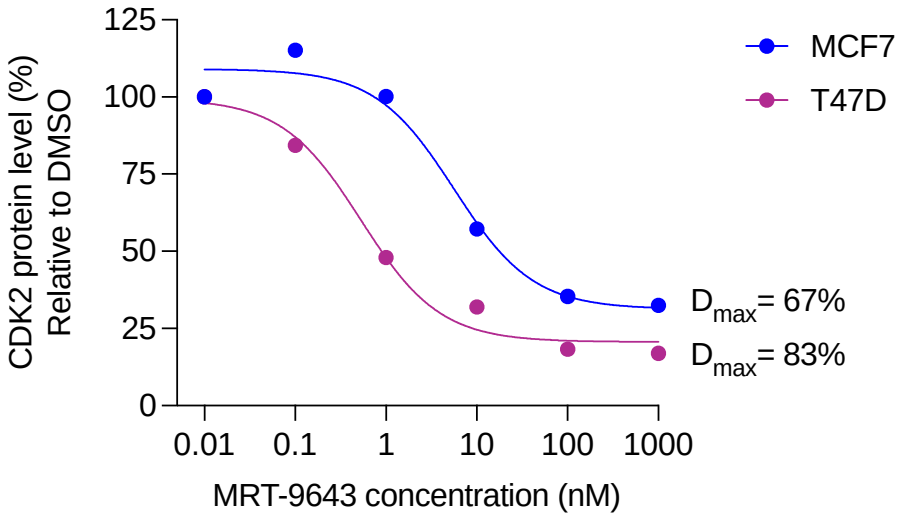


CDK2-MGD-CRBN-DDB1 cryo-EM structure
(DDB1 not shown)

MGD Activity Profile	
CRBN Binding (HTRF, IC_{50})	0.3 µM
CDK2 Ternary Complex (HTRF, EC_{50})	6 nM
CDK2 Degradation (HEK, DC_{50} /Dmax)	56 nM / 64%
Selectivity (TMT proteomics in MCF7)	Large CDK2 selectivity window
Physicochemical Properties	
LogD	3.2
MW	511.45
kinetic Solubility	79 µM
ADMET Profile	
Oral bioavailability (all species)	nd
Metabolite Profile (*in vitro*)	No unique human metabolites and 0.52% GSH adducts (mics)
CYP DDI (5 isoforms)	IC_{50} 15 - > 50 µM
Safety Pharmacology	
Mini-Ames	Negative
hERG inhibition (patch clamp)	4.4 µM
Counterscreens (panel with 98 targets)	Not done

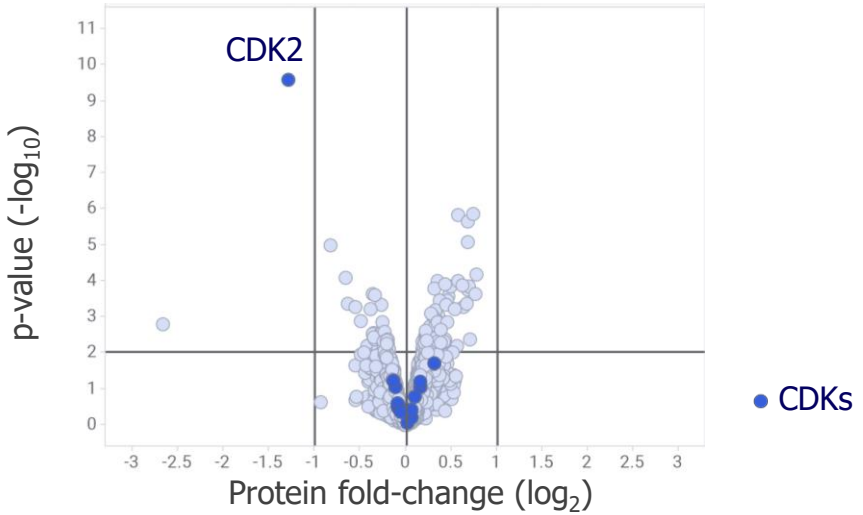
MRT-9643 is a Potent and Highly Selective CDK2-directed MGD

MRT-9643 is a potent CDK2-directed MGD



in vitro data	
CRBN binding, IC_{50}	289 nM
Ternary complex, EC_{50}	6 nM
Degradation, DC_{50} / D_{max} (HEK 293)	56 nM / 64 %

MRT-9643 induces highly selective CDK2 degradation and has a favorable ADME/DMPK profile



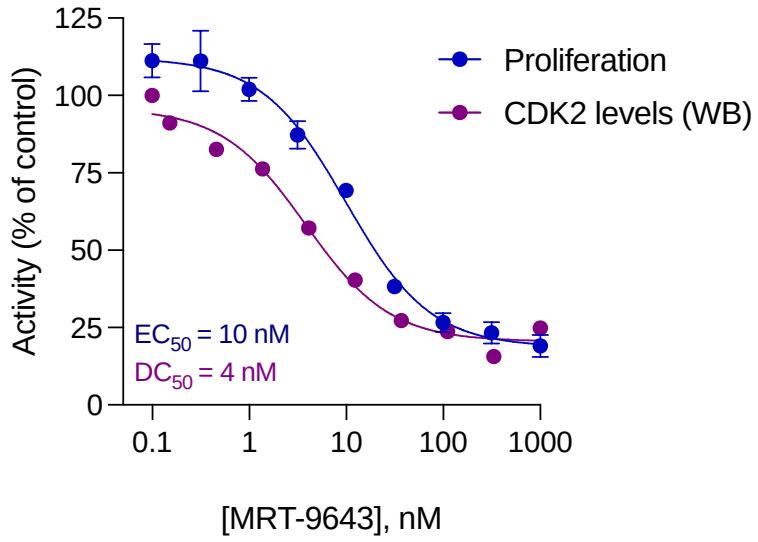
TMT Proteomics (24 hr/1 µM), MCF7 cells

No degradation of other known cereblon neosubstrates

ADMET profile	
CYP DDIs	IC_{50} 15 - >50 µM
hERG inhibition patch clamp	EC_{50} 4.4 µM
Oral bioavailability all species	nd

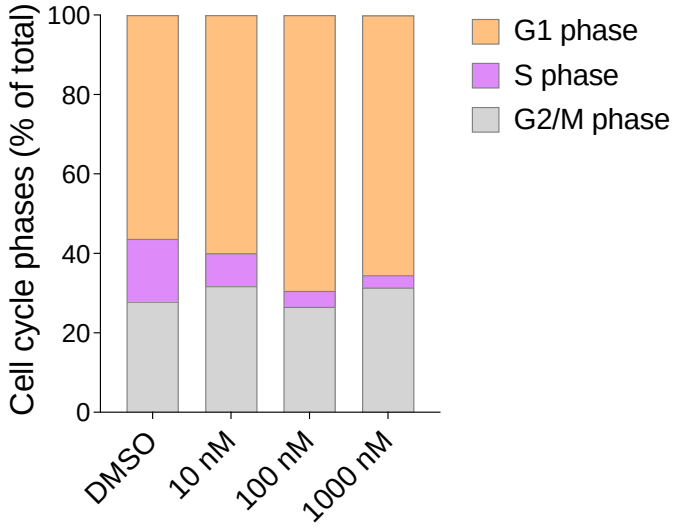
MRT-9643 Inhibits Proliferation of CDK2-dependent Cancer Cells

CDK2 degradation inhibits proliferation



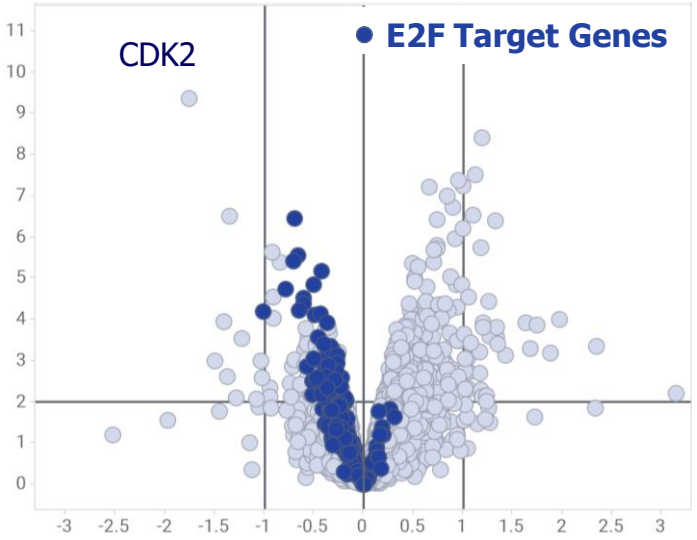
WB degradation (24 hr) MDA-MB-157
CyQuant proliferation assay (7 d) MDA-MB-157

CDK2 degradation arrests CDK2-dependent cells in G1 phase



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

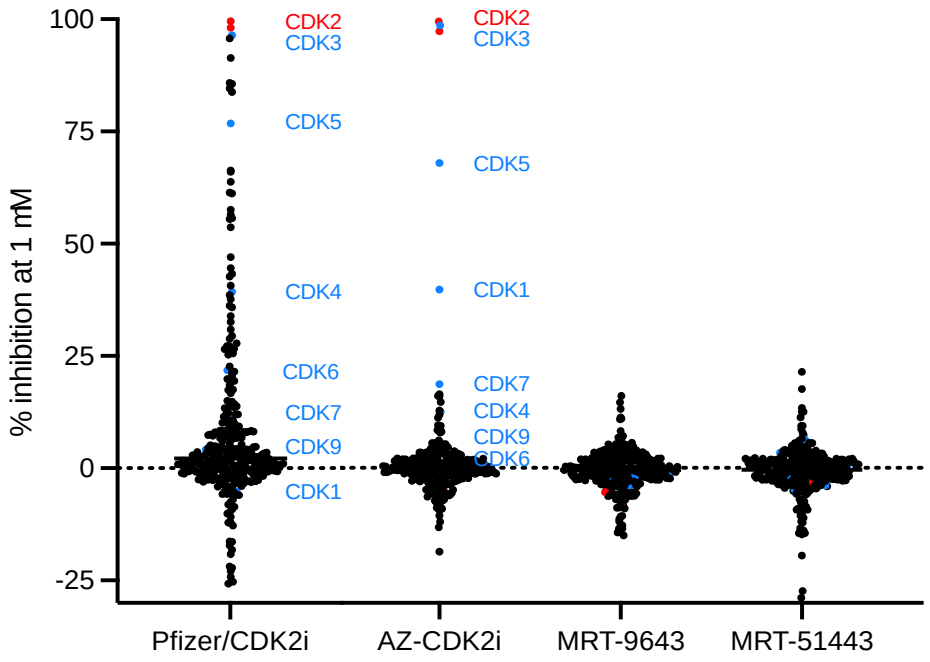
CDK2 degradation results in reduction of E2F pathway proteins



TMT Proteomics (24 hr/1μM)
MDA-MB-157

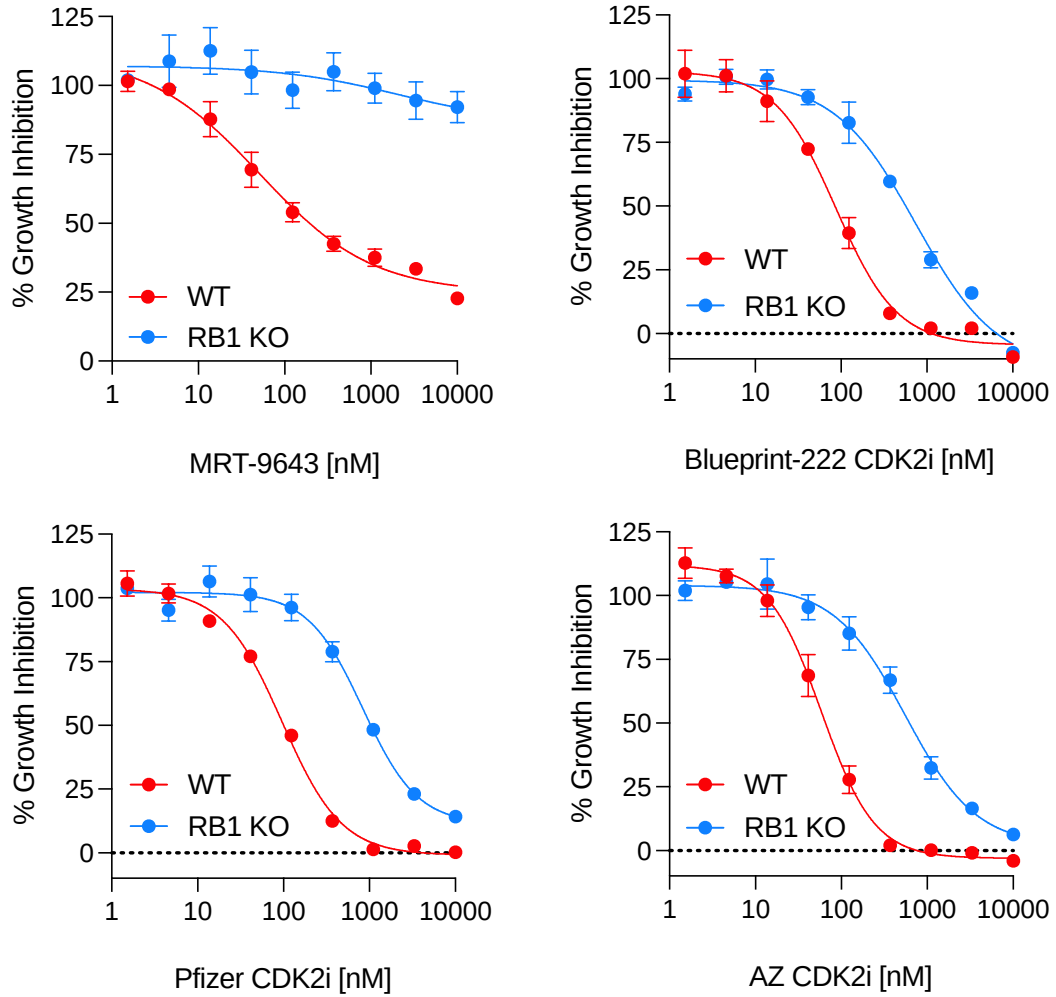
MRT-9643 Displays Superior Selectivity Compared to Clinical CDK2 Inhibitors

Clinical-stage CDK2 inhibitors demonstrate off target activity in biochemical kinome profiling



Carna Mobility Shift Assay; 1 µM CDK2i or CDK2 MGD, across 323 human kinases

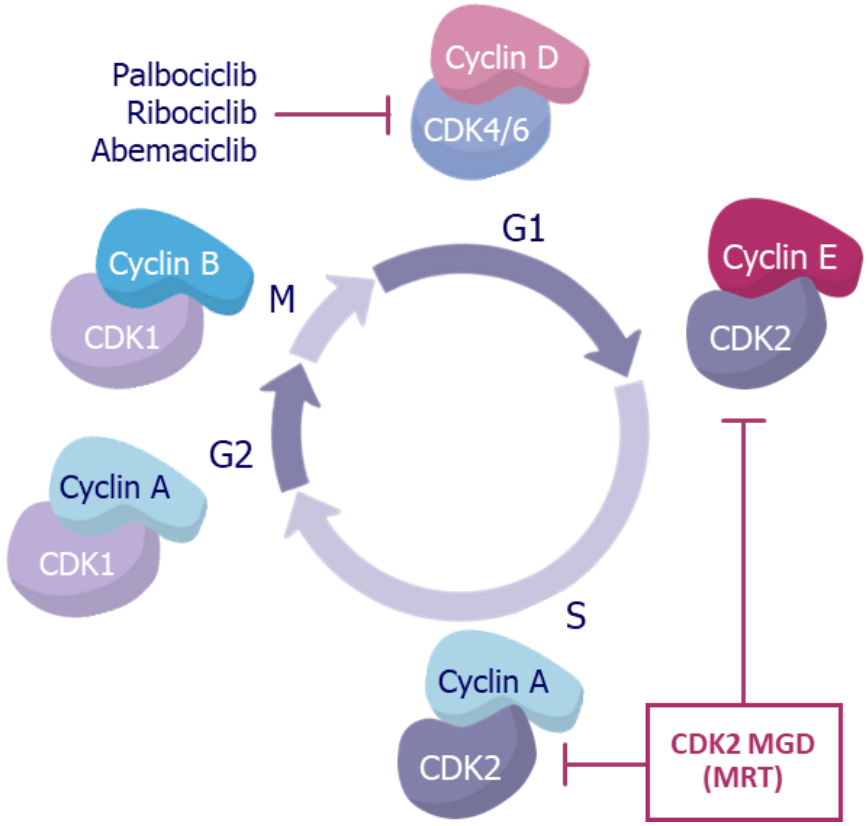
CDK2 inhibitors but not CDK2 MGDs display activity in CDK2-independent RB1 KO line



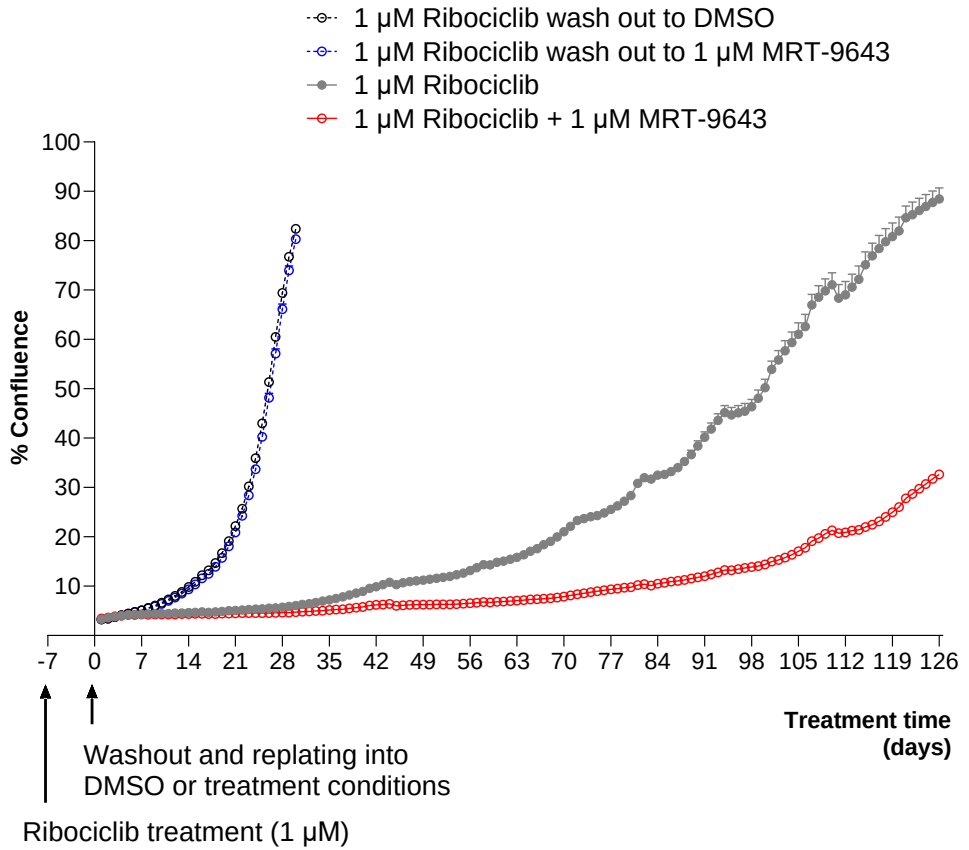
7-day CyQuant Assay; MDA-MB-157 cell line

CDK2 MGD/Ribociclib Combination Delays Resistance Onset in ER+ Model *in vitro*

CDK2 MGD and CDK4/6 inhibitor combination



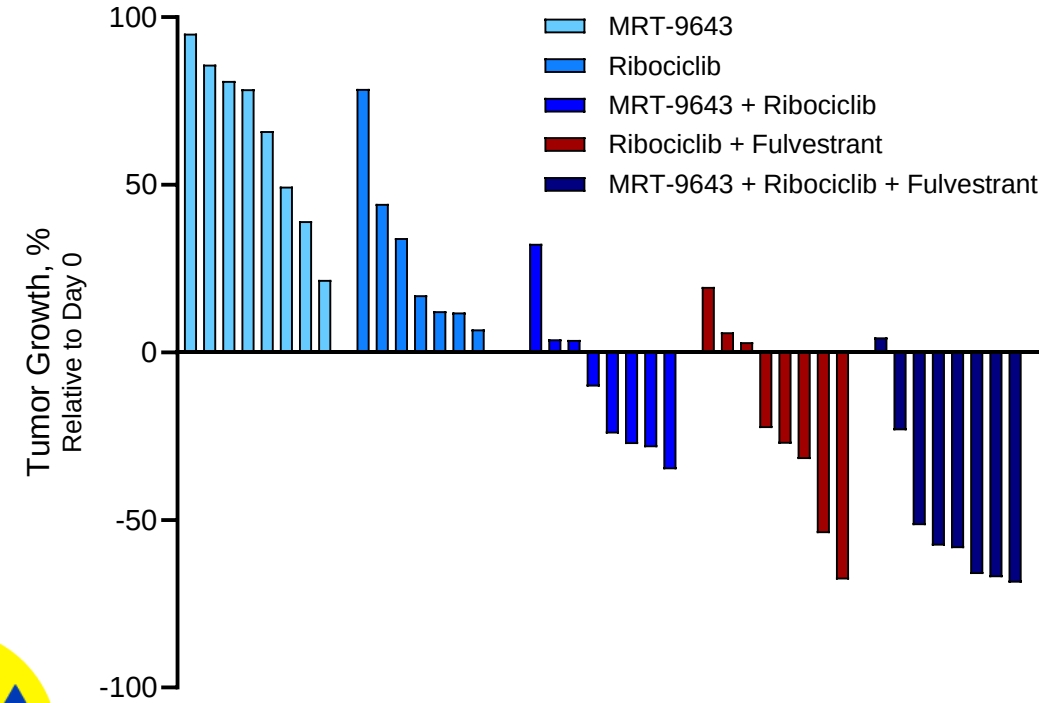
MRT-9643/ribociclib combination delays resistance onset in ER+ model *in vitro*



Incucyte confluence monitoring, MCF7

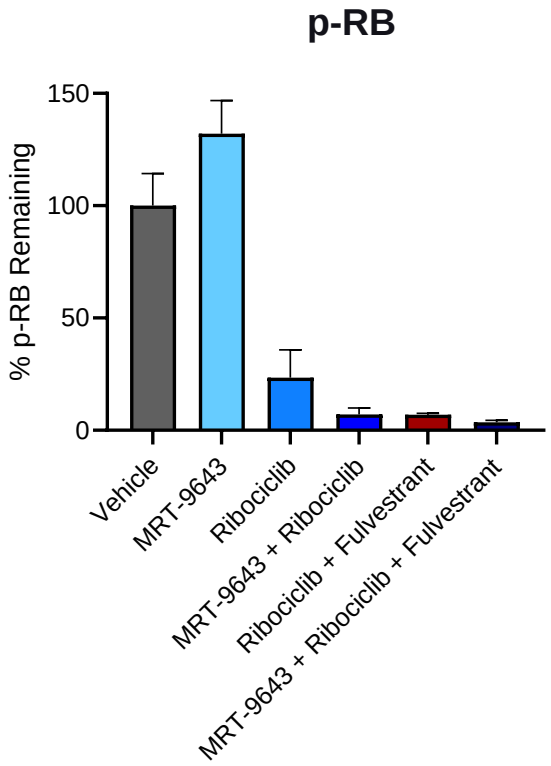
CDK2 MGD Demonstrates Activity in Combination with CDK4/6 Inhibitor (and Fulvestrant) in ER+ Breast Cancer (MCF7)

MRT-9643 induces robust tumor regression in combination with CDK4/6 inhibition and fulvestrant

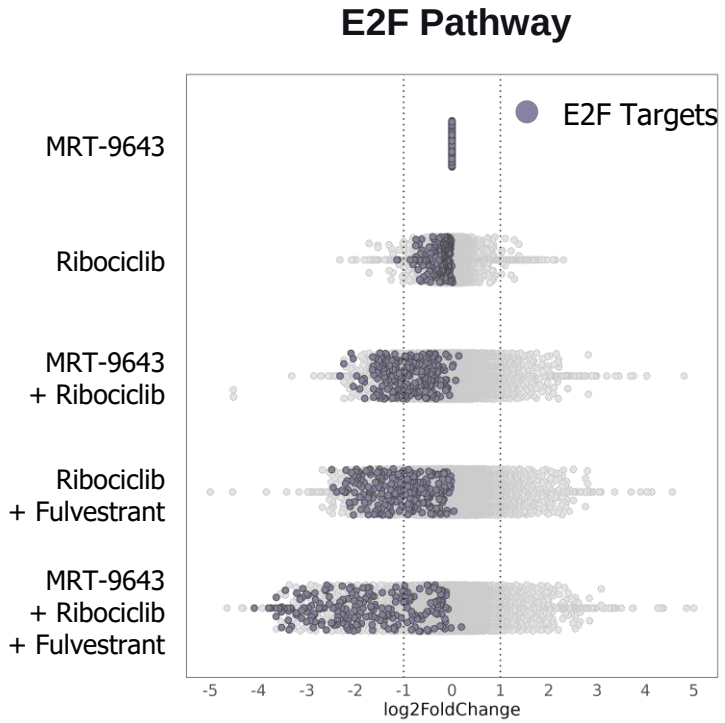


28-day efficacy evaluation in MCF7 CDX Model (MRT-9643 dosed at 30 mpk BID)

MRT-9643 induces robust pathway suppression in combination with breast cancer SoC



Western blot analysis
Day 28 PD, 1 hr post second BID dose



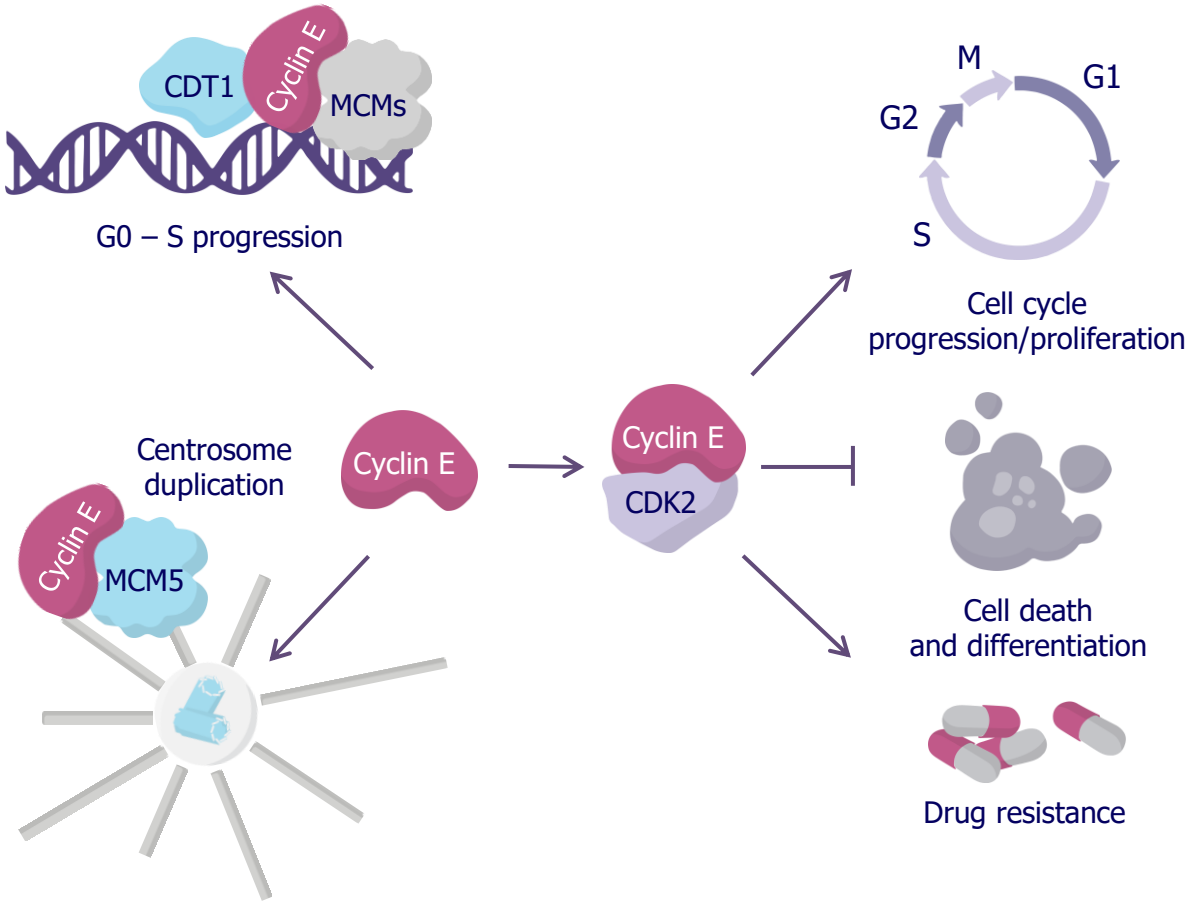
RNA-Seq analysis (fold change relative to vehicle) Day 28 PD, 1 hr post second BID dose

Monte Rosa Therapeutics

CCNE1 Program

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

Cyclin E drives multiple hallmark cancer mechanisms



Therapeutic hypothesis:

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

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

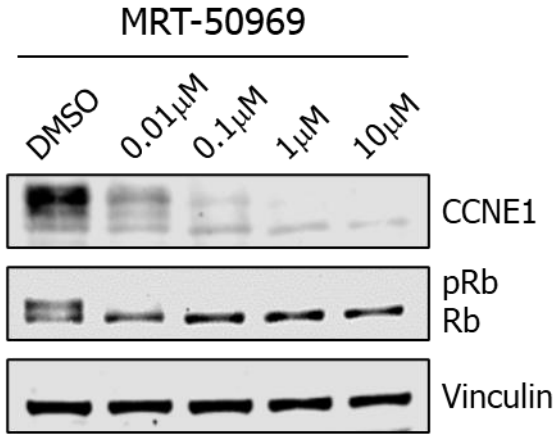
Clinical opportunity:

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

- Ovarian (~19%), endometrial (~10%), and gastric (~10%) cancer
- Breast cancer and others

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

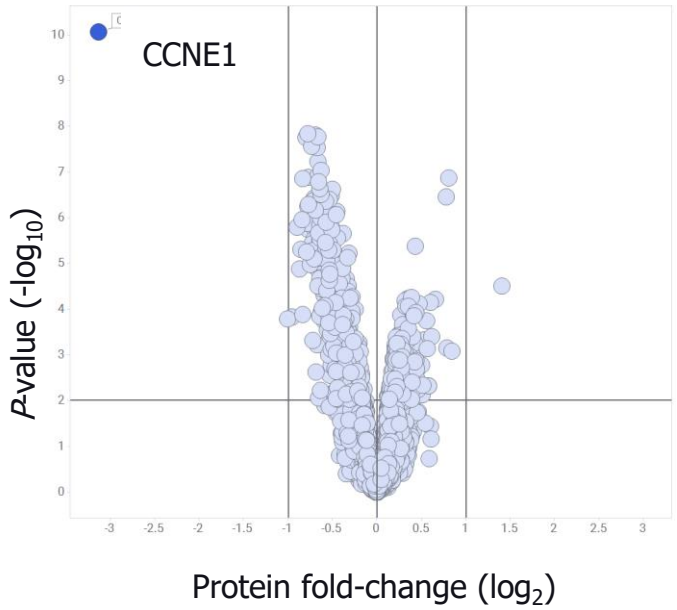
CCNE1 degradation leads to downstream pathway suppression



In vitro data	
CRBN binding, IC_{50}	0.15 μM
Ternary complex, EC_{50}	3 nM
Degradation, DC_{50}/D_{max}	3 nM / 94 %

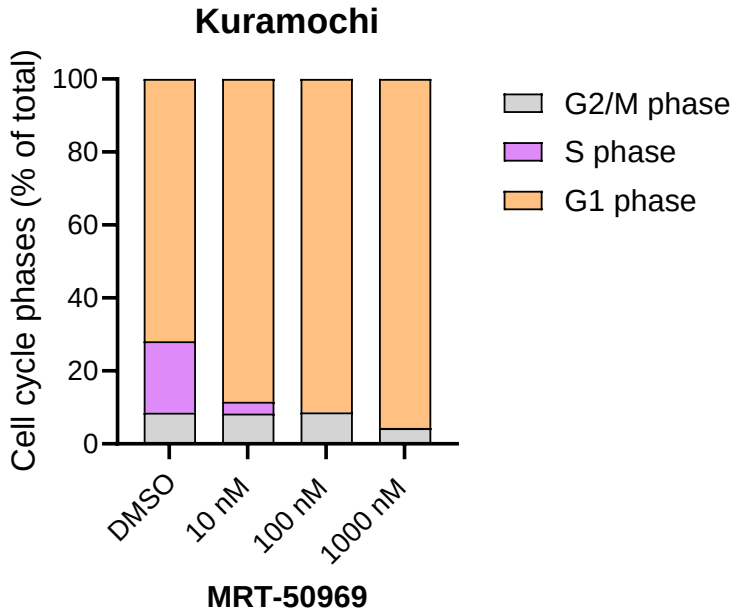
Western blot, OVISE, 24h

MRT-50969 is highly selective for CCNE1



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

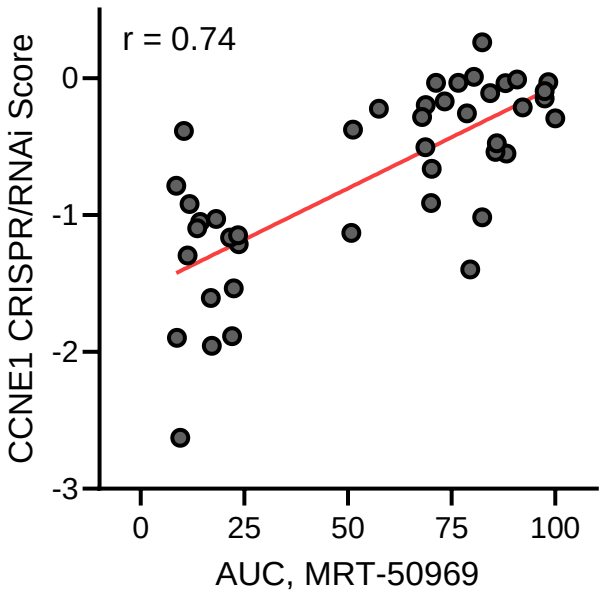
MRT-50969 induces robust G1/S cell cycle arrest



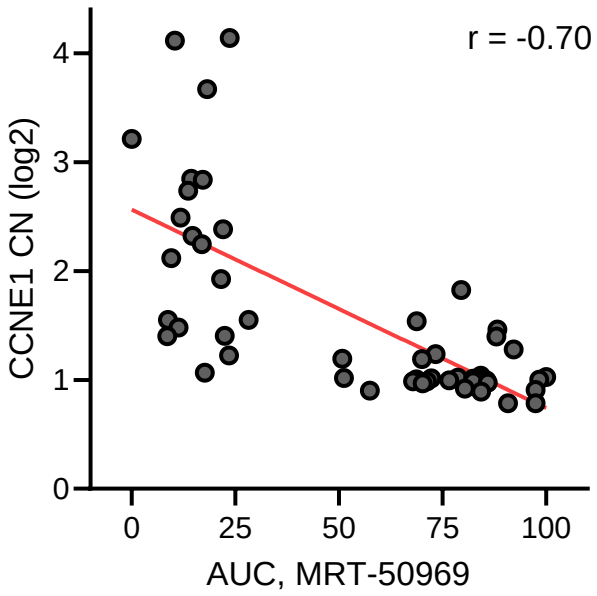
FACS, EdU incorporation, 48h

CCNE1 MGD Sensitivity is Highly Correlated with CCNE1 Gene Dependency, Copy Number and Expression

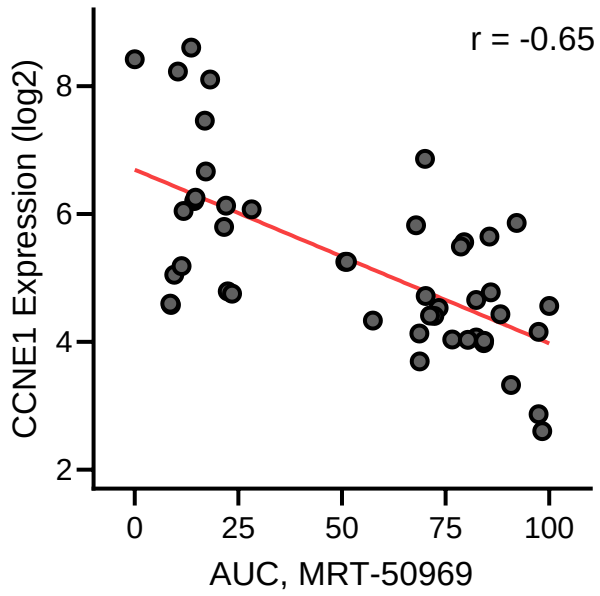
Gene Dependency



Copy Number

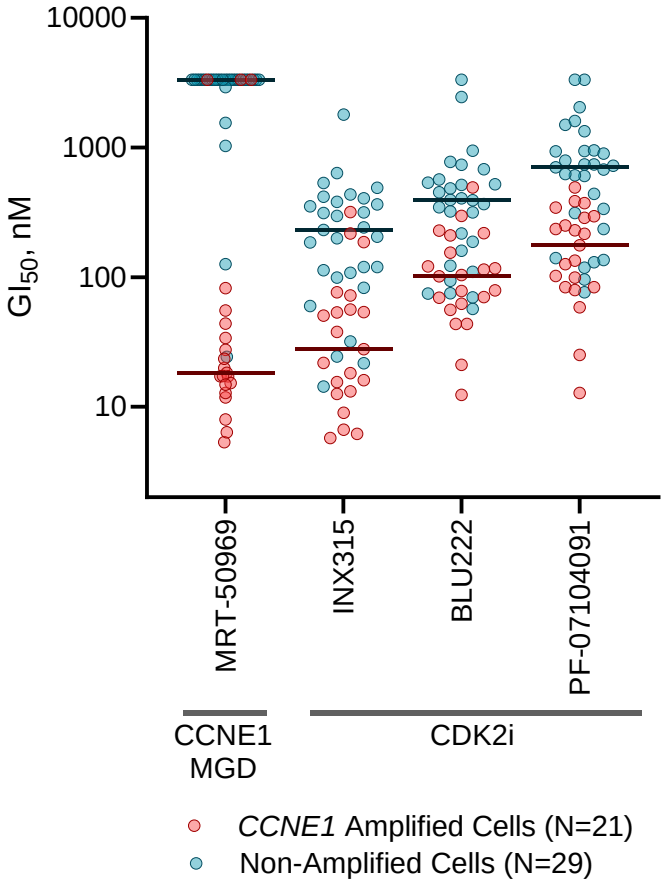


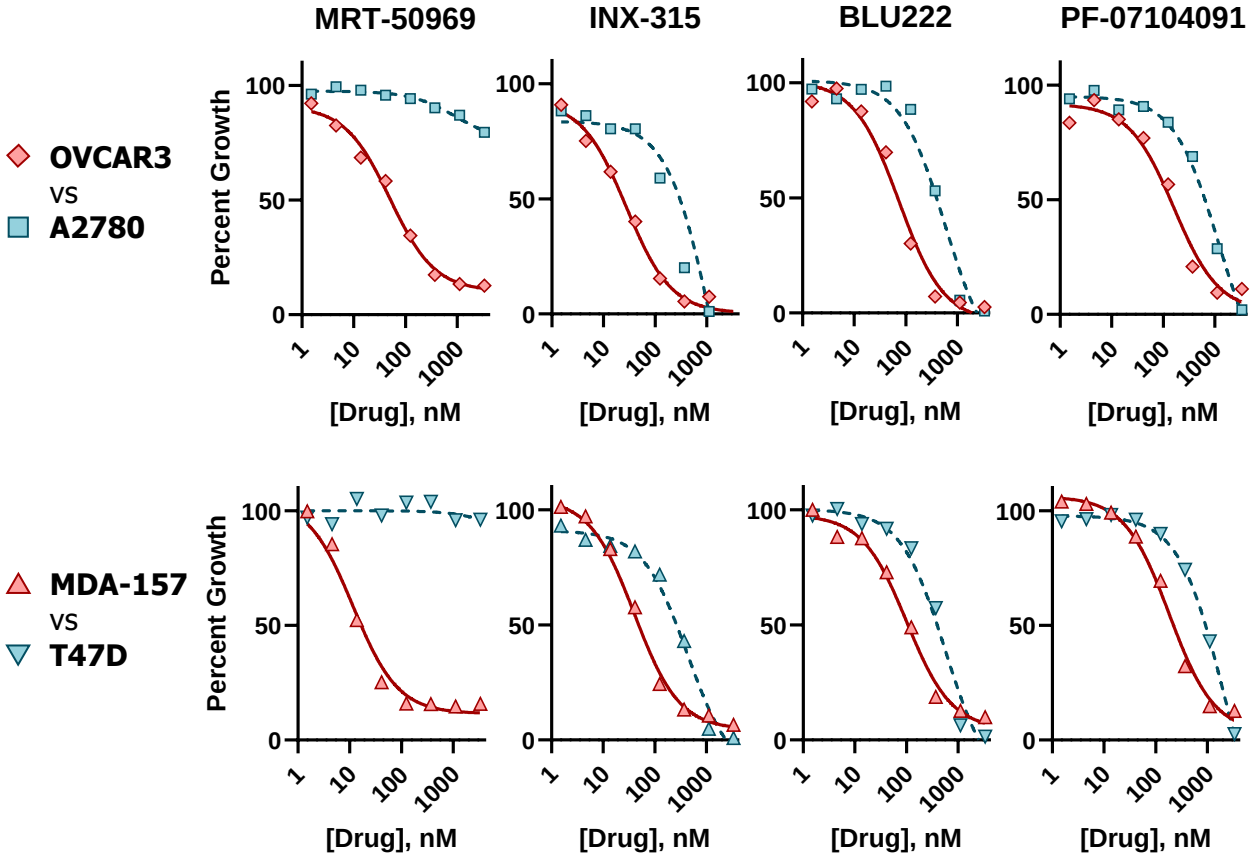
mRNA Expression



5 Day CyQuant assay, 50 cancer cell line panel;
Gene dependency and genomics data from DepMap/Broad Institute

MRT-50969 Shows Superior Differential Activity in *CCNE1* Dependent Cell Lines Compared to Clinical-Stage CDK2 Inhibitors



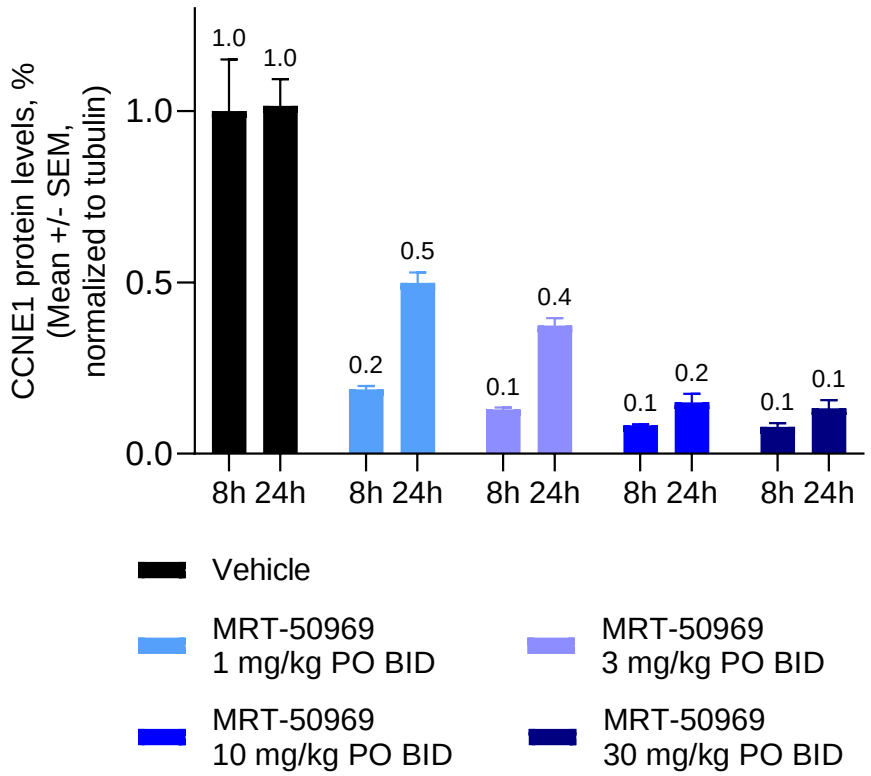


5 Day CyQuant assay, bars indicate median GI_{50}

GI_{50} = growth inhibition 50%, the concentration of drug required to inhibit the growth of cancer cells in vitro by 50%

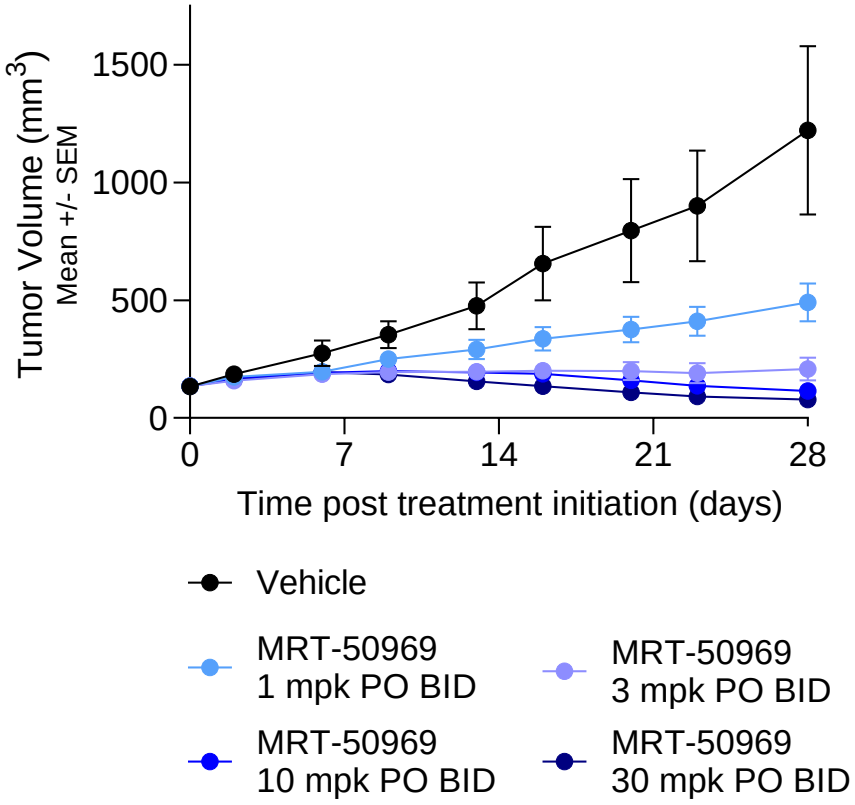
MRT-50969 Inhibits Tumor Growth in a CCNE1 Amplified Breast Cancer Model *in vivo*

MRT-50969 degrades CCNE1 *in vivo*



Day 28/8h and 24h PD, Western blot, HCC1569 CDX

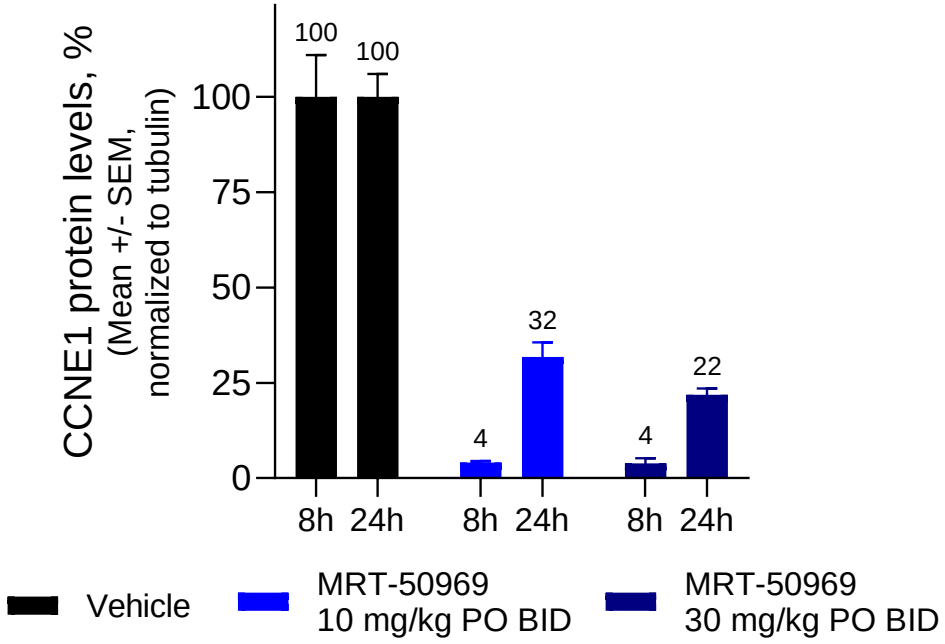
MRT-50969 inhibits tumor growth in CCNE1 amplified breast cancer model



HCC1569 CDX, 28-day efficacy study

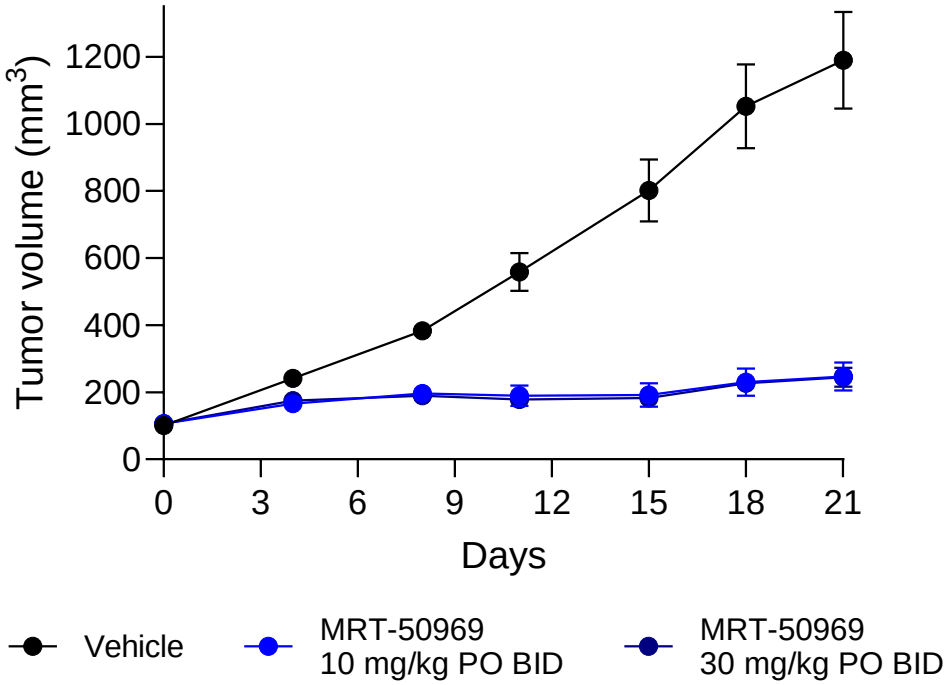
MRT-50969 Inhibits Tumor Growth in a CCNE1 Amplified Gastric Cancer Model *in vivo*

MRT-50969 degrades CCNE1 *in vivo*



Day 21/8h and 24h PD, Western blot, MKN1 CDX

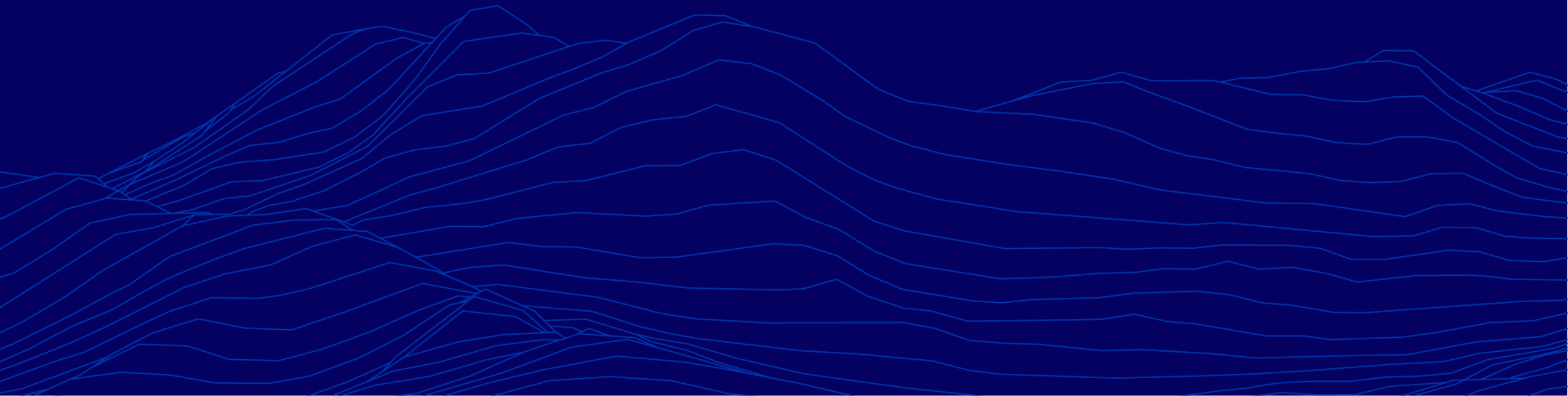
MRT-50969 inhibits tumor growth in CCNE1 amplified gastric cancer model



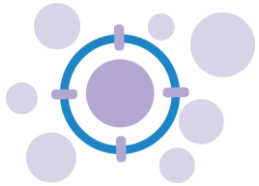
21-day efficacy study in MKN1 CDX model

Monte Rosa Therapeutics

QuEEN™ Discovery Engine



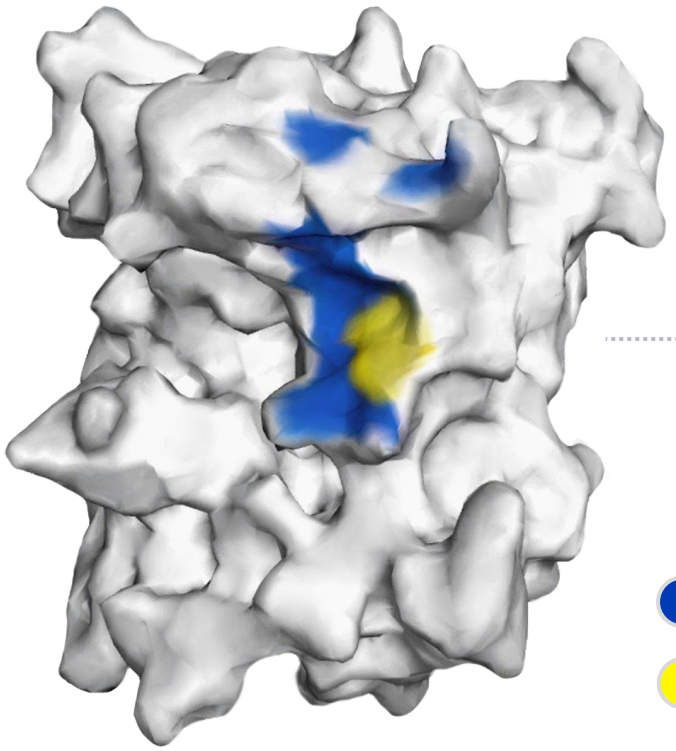
Overcoming Past Limitations of Molecular Glue Degraders

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

Our Critical Insight: Surfaces are Critical for MGD Discovery

Surfaces, not structures, mediate PPIs and targeted protein degradation

E3 ligase



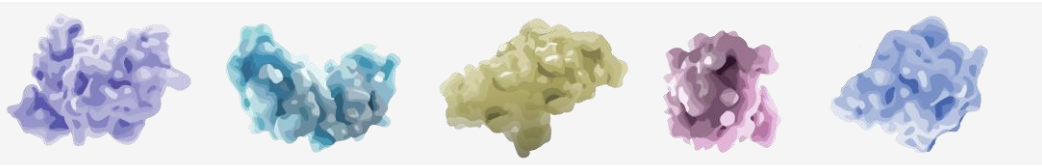
E3 ligase neosurface

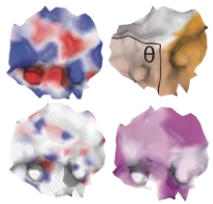
- Neosubstrate footprint
- MGD footprint

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

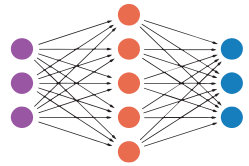
GlueShot: *de novo* MGD Design for Novel Targets

Protein structures	*AF, Rosetta, PDB*
Surface fingerprint	***fAIceit™***
Fingerprint matching	***Headlong™ & fAIceit™***
Surface of MGD + ligase	***COSMOS™***
Virtual library	***FLASH™ & GlueAID™***
E3 ligase structures	*AF, Rosetta, PDB*

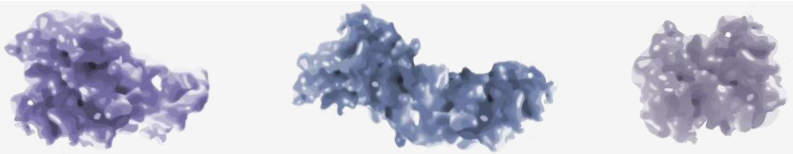




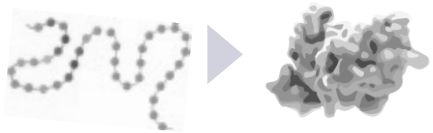
Geometric and chemical surface characterization

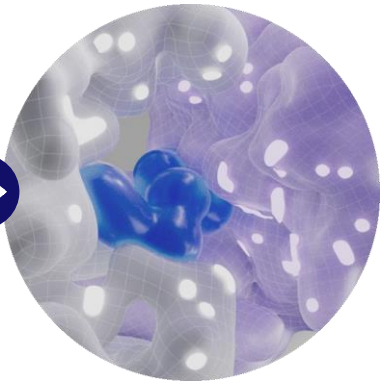


Neosubstrate footprint
MGD + ligase footprint



Nobel prize

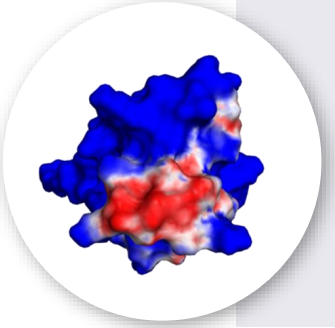




MGDs that induce PPIs with drug-like properties

QuEEN™ Unique Capabilities

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



AI/ML

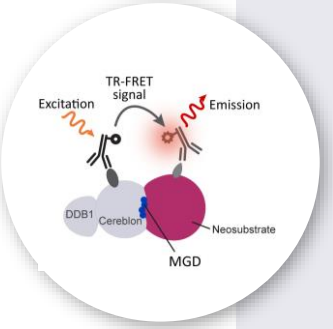
In silico discovery using proprietary AI-powered algorithms

Structure-based Design

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

MGD Library

Growing 50K compound library for novel degron and target space exploration

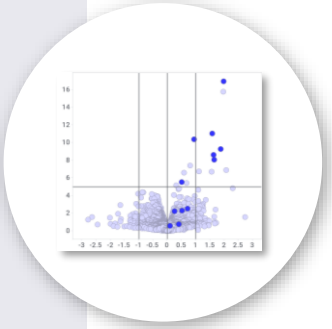


Proximity Screening

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

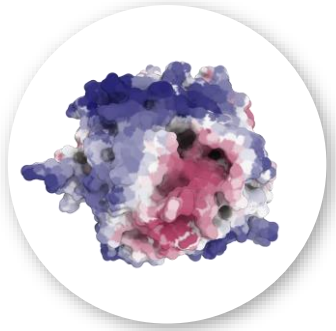


Proprietary AI/ML Engines Enable the Discovery of Reprogrammable Ligases, Neosubstrates, and Selective MGDs

Proprietary AI/ML engines

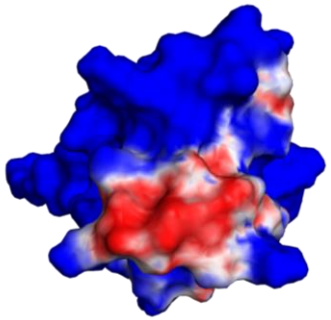
Target ID

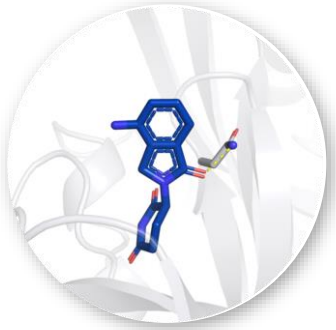
Guided by surface mimicry



Ligase matching

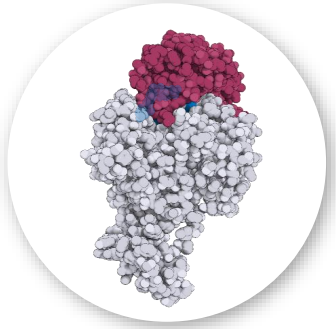
PPI propensity & surface complementarity





MGD discovery

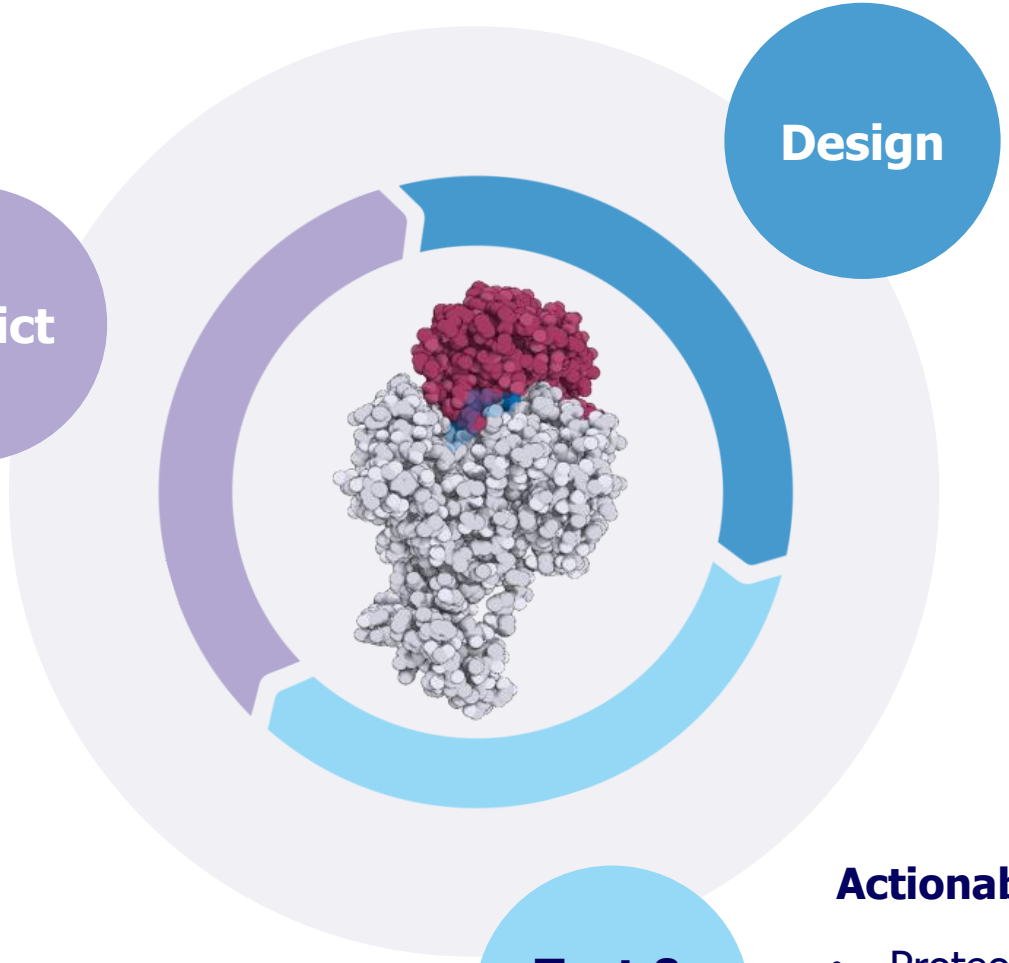
Generate MGDs with drug-like properties



***In silico* screening**

Screen for activity in ternary complexes

QuEEN™: How it Works



Target and ligase ID

- Surface-centric discovery process

AI-powered chemistry

- Surface-aware MGD generation & optimization

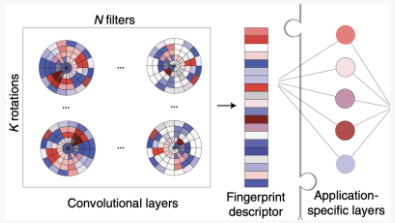
Actionable data-at-scale

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

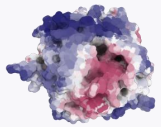
QuEEN™ Toolbox to Rapid Discovery of Oral MGDs

Predict
Target & ligase ID

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



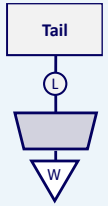
E3 ligase
reprogrammability



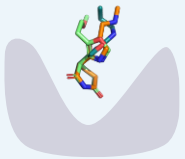
fAIceit mimicry
target ID

Design
AI-powered chemistry

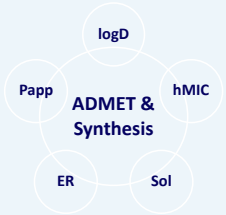
FLASH™
virtual library



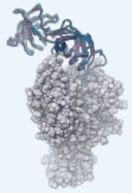
HitMan™
diverse library



GlueAID™
ADMET & synthesis

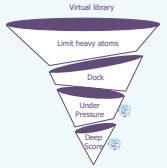


Rhapsody™
ternary complexes

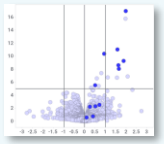


Test & Train
Actionable data-at-scale

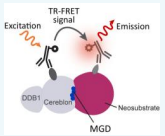
Headlong™
virtual screens



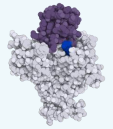
Proteomics
mass-spec farm



HT library screening



Structural biology
X-ray & cryo-EM



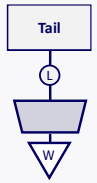
Algorithms Use MGD-focused, Moated Data to Identify Targets and Design MGDs

in silico experimentation

fAIceit mimicry
target ID

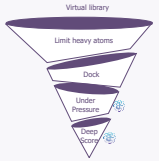
250
BILLION
Protein surface matchings

FLASH™
virtual library



37
BILLION
Virtual MGDs

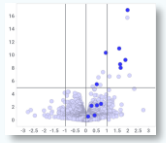
Headlong™
virtual screens



651
MILLION
Compounds screened

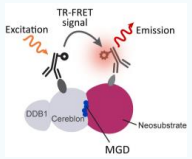
Lab experimentation

Proteomics
mass-spec farm



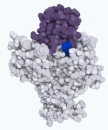
37
MILLION
protein measurements

HT library screening



6.5
MILLION
MGD activity measurements

Structural biology
X-ray & cryo-EM



>125
Structures

Cloud First and Cloud Native

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

Monte Rosa Therapeutics

Team

World-Class Leadership

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

Markus Warmuth, M.D.
Chief Executive Officer

H3 Biomedicine
Novartis

Sharon Townson, Ph.D.
Chief Scientific Officer

Kymera Therapeutics
Warp Drive Bio

John Castle, Ph.D.
Chief Data and Information Officer

agenus
BioNTech

Magnus Walter, DPhil
SVP, Drug Discovery

AbbVie
Lilly

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

The University of Texas MD Anderson Cancer Center

Phil Nickson, Ph.D., J.D.
Chief Business and Legal Officer

Momenta
FISH & RICHARDSON

Jennifer Champoux
Chief Operating Officer

H3 Biomedicine
Novartis

Andrew Funderburk
SVP, Investor Relations and Strategic Finance

Kendall Investor Relations
Health Advances


Thank You
Monte Rosa
Therapeutics