From Serendipity to Rational Design

Taking Molecular Glue Degraders to New Heights | August 2022

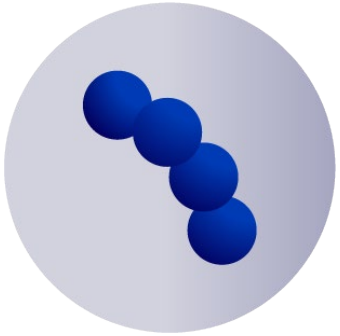
Monte Rosa Therapeutics

Forward-Looking Statements

These materials include express and implied "forward-looking statements," including forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward looking statements include all statements that are not historical facts, and in some cases, can be identified by terms such as "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "potential," "continue," "ongoing," or the negative of these terms, or other comparable terminology intended to identify statements about the future. Forward-looking statements contained in herein include, but are not limited to, statements about our product development activities, including our expectations around MRT-2359 and the ongoing development of our QuEEN™ platform, and the advancement of our pipeline and the various products therein, our expectations of timing for FDA clearance of our IND for MRT-2359, our expectations of timing for initiation of our clinical trial for MRT-2359, our ability to initiate and the timing of initiation of additional lead optimization programs, and our expectations regarding our ability to nominate and the timing of our nominations of additional development candidates. By their nature, these statements are subject to numerous risks and uncertainties, including the impact that the current COVID-19 pandemic will have on our development activities and operations, as well as those risks and uncertainties set forth in our Annual Report on Form 10-K for the fourth quarter and full year ended December 31, 2021 filed, with the US Securities and Exchange Commission on March 29, 2022, and any subsequent filings, including our Quarterly Report on Form 10-Q for the second quarter of 2022 ending on June 30, filed on August 11, 2022, 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 Highlights

Taking molecular glue degraders (MGDs) to new heights



Next-generation molecular glue-based targeted protein degradation platform developing breakthrough small molecule drugs that selectively degrade therapeutically-relevant proteins

Targeting the undruggable proteome via AI-based degron prediction & rational design of highly selective MGDs

IND filed for GSPT1 program with clinical development planned in Myc-driven tumors

Five disclosed programs targeting high unmet medical needs in oncology and non-oncology indications

World-class leadership & SAB with deep drug discovery know-how and development expertise in precision medicine

World-Class Leadership

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

Markus Warmuth, M.D.
Chief Executive Officer

H3 Biomedicine
NOVARTIS

Ajim Tamboli, CFA
Chief Financial Officer

COLUMBIA THREADNEEDLE INVESTMENTS
LEHMAN BROTHERS

Owen Wallace, Ph.D.
Chief Scientific Officer

Fulcrum Therapeutics
NOVARTIS

Sharon Townson, Ph.D.
Chief Technology Officer

KYMERA
Warp Drive Bio

John Castle, Ph.D.
Chief Data Scientist

agenus
BIONTECH

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

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

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

Lilly
Boehringer Ingelheim

Silvia Buonamici, Ph.D.
SVP, Drug Discovery Biology

H3 Biomedicine
NOVARTIS

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

Momenta
FISH & RICHARDSON

Jennifer Champoux,
SVP, Operations

H3 Biomedicine
NOVARTIS

Strong Cash Position and Investor Support

Over $455M raised since 2020 with top tier investors provides runway into late 2024

Series A	Series B	Series C	IPO	
$32.5M	**$96.0M**	**$95.0M**	**$255.6M***	**$299.5M Cash†**
April 14, 2020	September 14, 2020	March 11, 2021	June 28, 2021	as of June 30, 2022

* Aggregate IPO gross proceeds were approximately $255.6 million before deducting underwriting discounts and commissions and other offering expenses and include an additional $33.3 million in gross proceeds the company received as part of its IPO from the full exercise of the underwriters' option to purchase up to an additional 1,755,000 shares of common stock at the public offering price of $19.00 per share.

† Includes cash, cash equivalents, restricted cash and marketable securities as of June 30, 2022

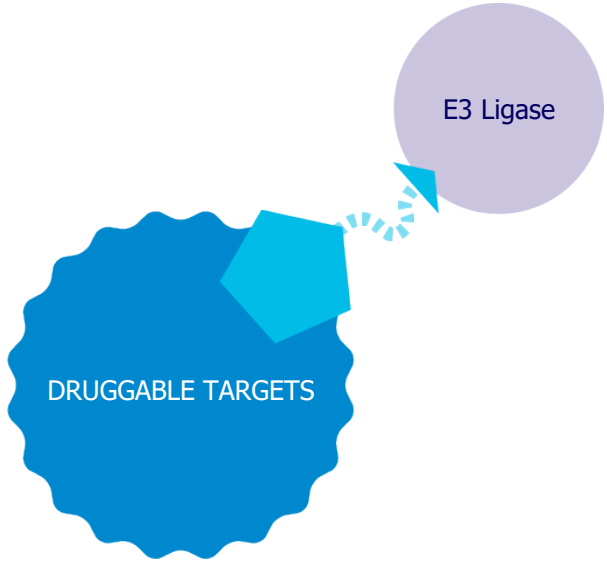
Molecular Glue Degraders (MGDs)

Expanding target space, fostering a new generation of drugs

INHIBITOR

Drugging
the Druggable

PROTAC



Redrugging
the Druggable

MGDs

Drugging
the Undruggable

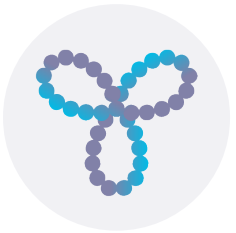
Expanding the Degradable Proteome

Target Space

The Next Generation of Precision Medicine-based Small Molecule Drugs

Selectively editing the human proteome with rationally designed MGDs

Traditional small molecule inhibitors



Therapeutic Antibodies

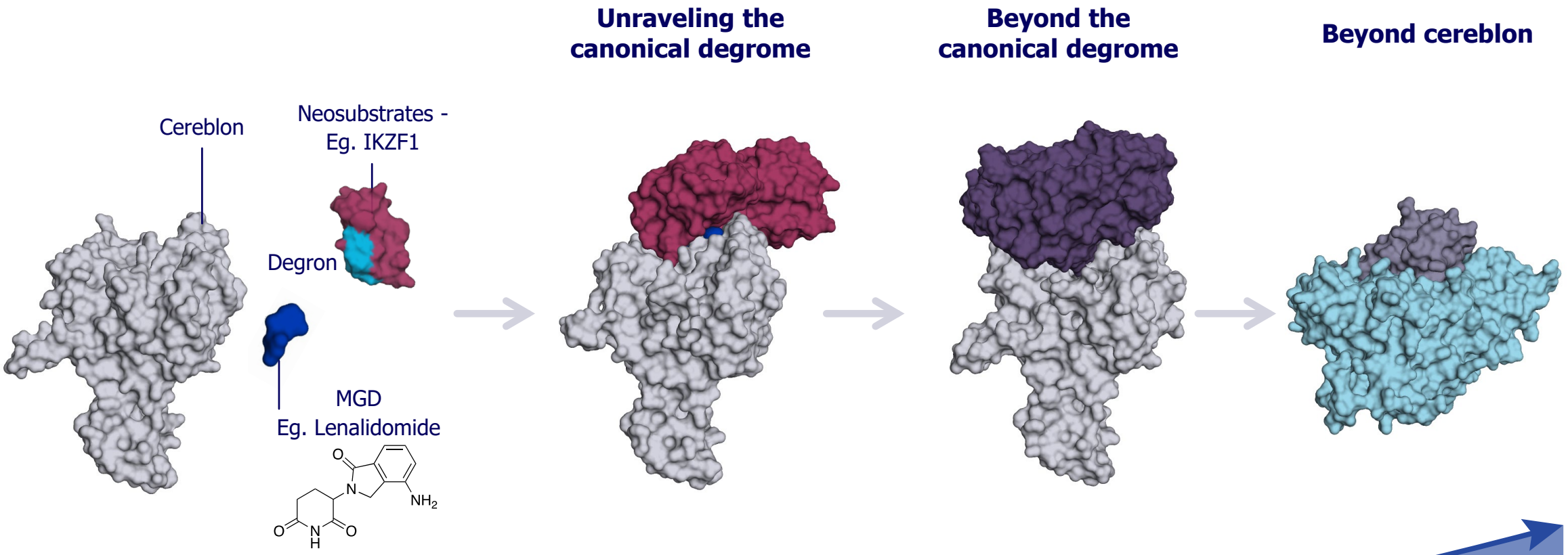
MGDs

RNAi, RNA Editing

CRISPR/Gene Therapy

	Traditional small molecule inhibitors	Therapeutic Antibodies	MGDs	RNAi, RNA Editing	CRISPR/Gene Therapy
Ability to access undruggable space	✗	✓	✓	✓	✓
Cellular permeability	✓	✗	✓	✓	✓
Oral bioavailability	✓	✗	✓	✗	✗
Systemic distribution	✓	✓	✓	✗	✗
CNS Penetration	✓	✗	✓	✗	✗
Manufacturing scalability	✓	✓	✓	✗	✗

Our Rational Approach to Unleash the Full Potential of MGDs



Monte Rosa Therapeutics

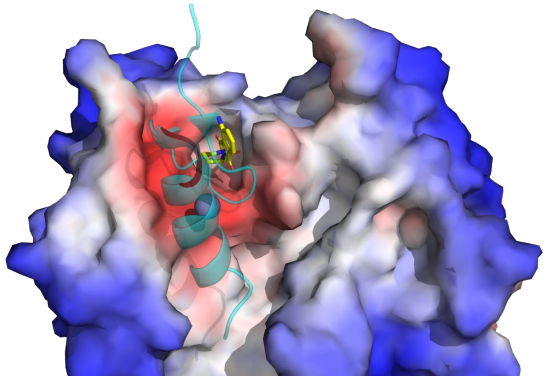
QuEEN™ Discovery Platform

Quantitative and Engineered Elimination of Neosubstrates

QuEEN™ Discovery Platform: A Target-Centric Approach to MGDs

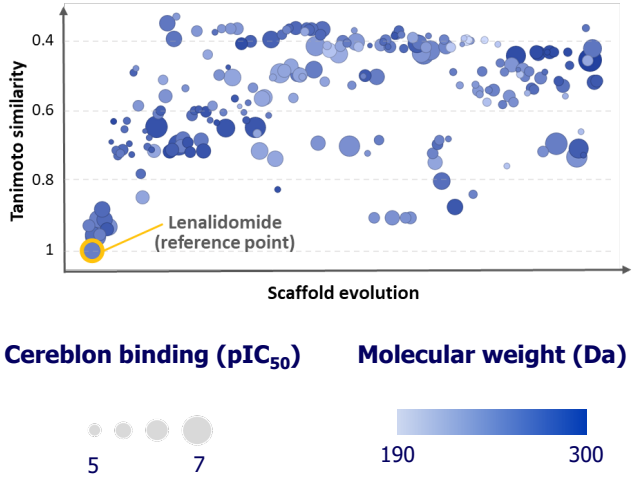
AI Engines OneVision™ and Rhapsody™

In silico degron & ternary complex discovery using proprietary AI-powered algorithms



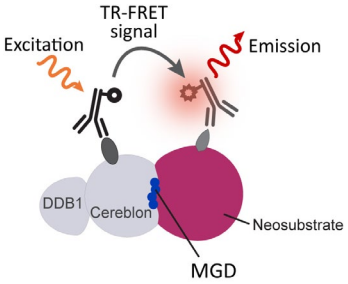
Proprietary MGD library

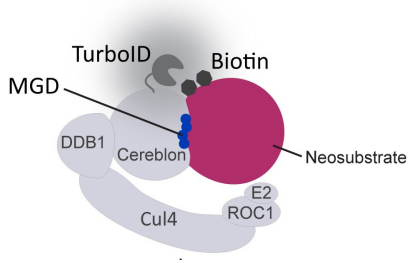
Rationally designed, diverse and growing library engaging a variety of degrons



Glueomics™ toolbox

Specialized suite of *in vitro* & *in silico* assays to discover, optimize and advance MGDs as clinical candidates

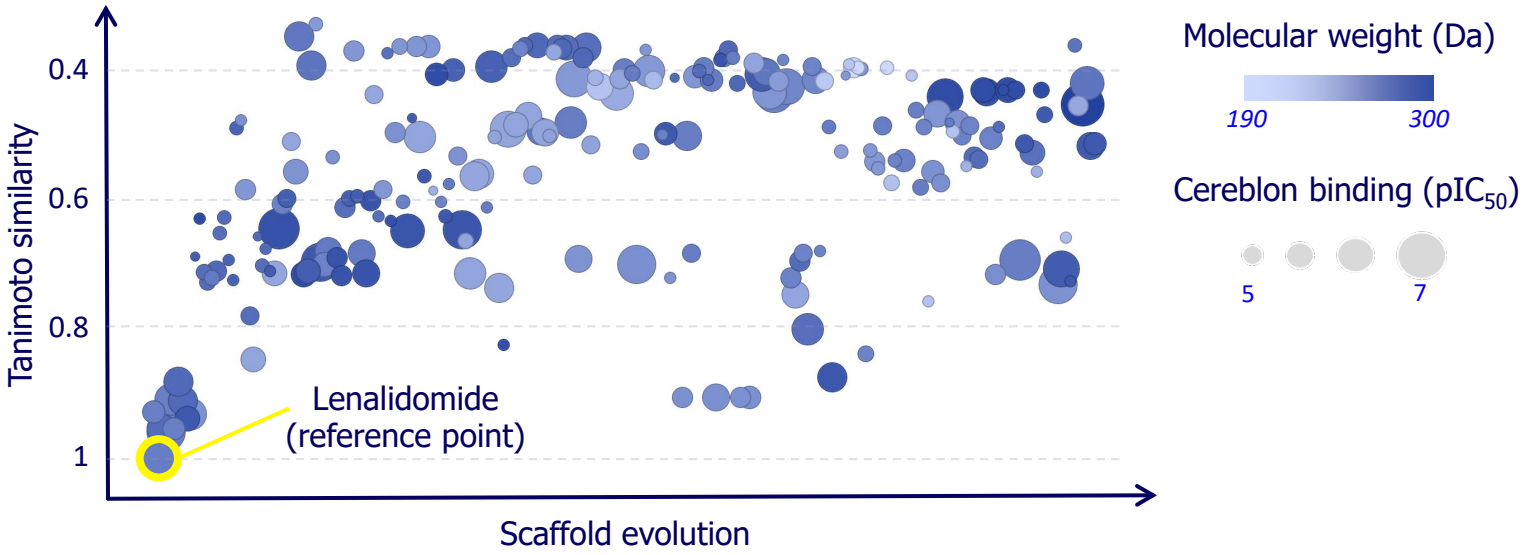




Accessing a large pool of undruggable targets with a diverse MGD library

Increasing Novelty and Structural Diversity to Match the Target Space

Increasing MGD scaffold diversity



MGD library is derived from **> 400 unique low molecular weight scaffolds** with **favorable CRBN binding** affinities

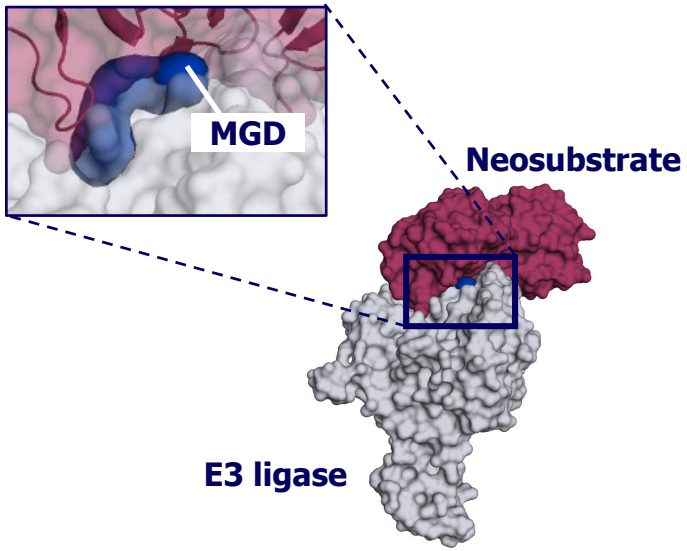
Library design and expansion

- Design focused on optimal drug-like properties
- High structural diversity and novelty
- Current library size 20K MGDs

MGDs Reprogram the Cereblon Surface

Remodeled MGD-CRBN surface enables selective engagement of neosubstrates

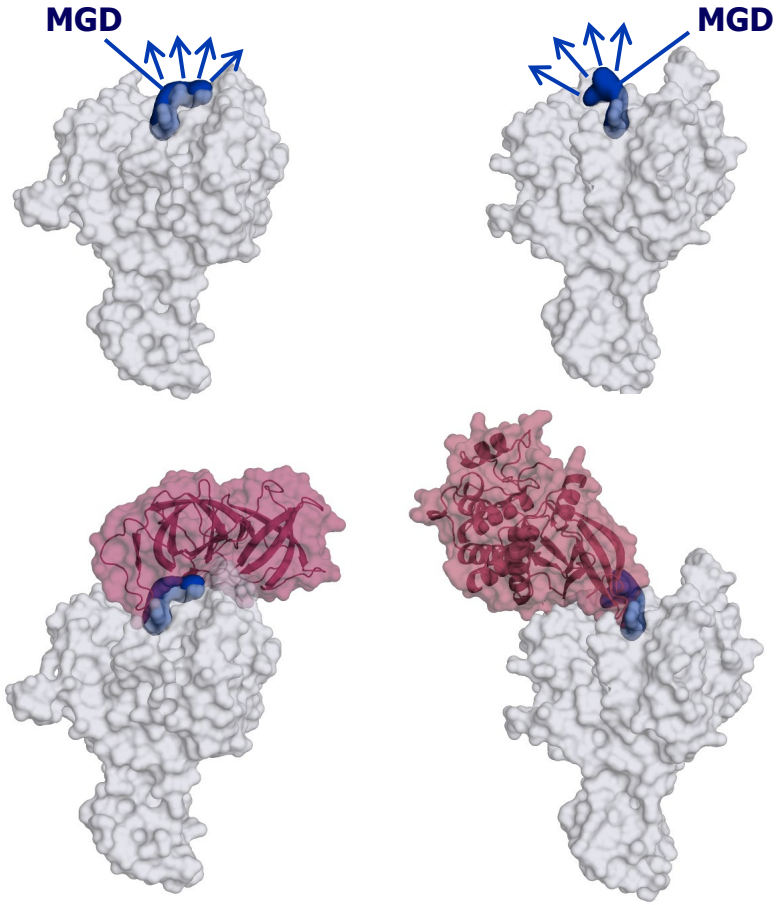
Multiple points of contact for dialing in selectivity and potency



Effective ternary complex generation involves

- MGD-cereblon interactions
- MGD-neosubstrate interactions
- CRBN-neosubstrate interactions

MGDs are rationally designed to exploit key contacts to selectively engage different neosubstrates



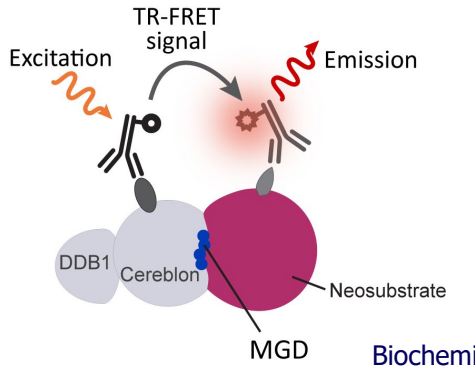
MGDs reshape the cereblon surface through different exit vector geometries

Neosubstrates are engaged selectively through unique interactions with both MGD and cereblon

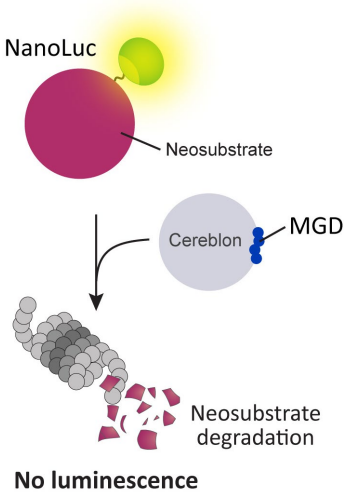
Glueomics™ Toolbox Accelerates Identification of MGDs

Multiple assays enable rapid identification and validation of MGDs for novel targets

in vitro screens

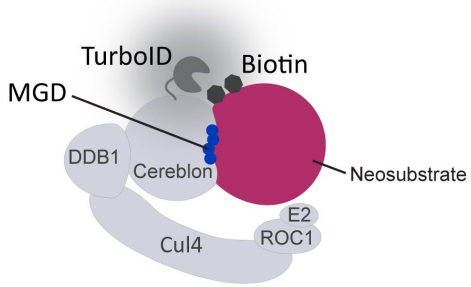


Biochemical



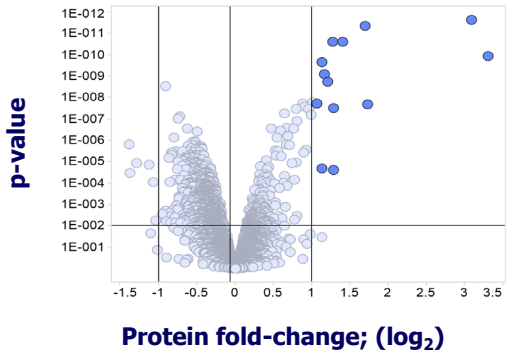
Cellular

Chemoproteomics - proximity



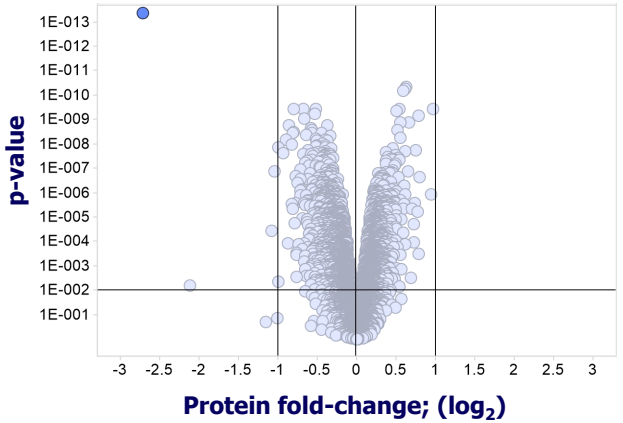
IP using streptavidin beads

Mass spectrometry



Turbo-ID

Proteome-wide expression



TMT Proteomics to evaluate:

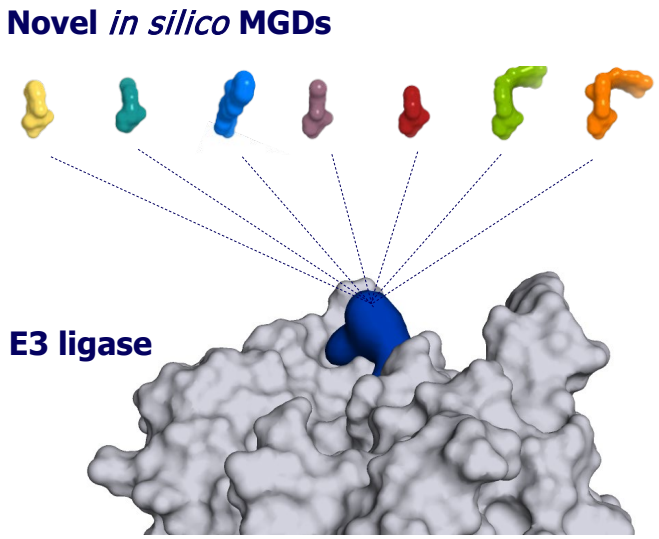
- Proteome-wide changes in protein levels
- MGD selectivity

Rhapsody, QuEEN's *in silico* Engine

A suite of proprietary AI-powered algorithms to design, discover and develop MGDs

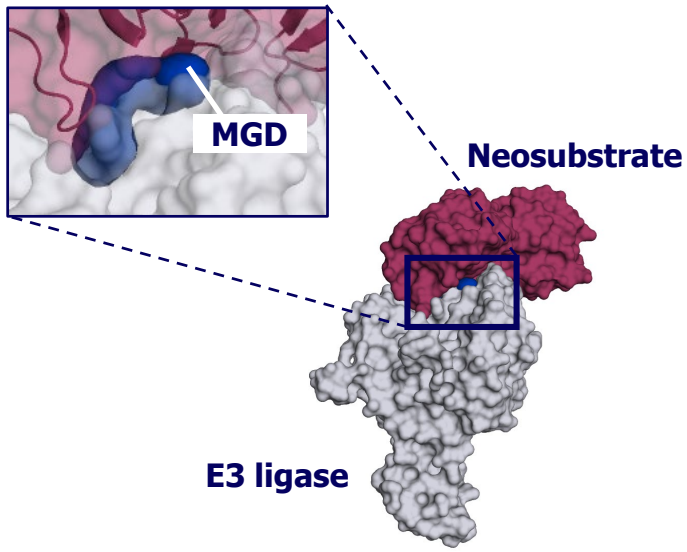
in silico library generation

Creation and E3 ligase docking of novel MGDs, expanding our library to engage more targets



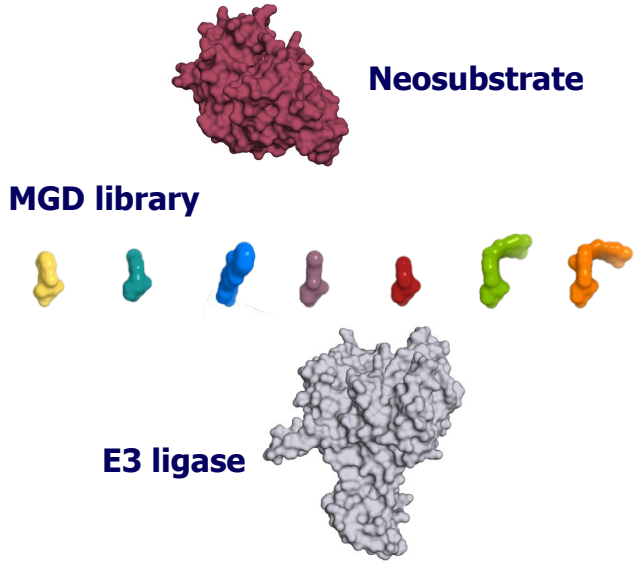
in silico ternary complex models

Ternary complex models enabling MRT scientists to engineer and optimize selective MGDs



in silico MGD screening

Computational screening identifying and prioritizing hits inducing binding and selective degradation



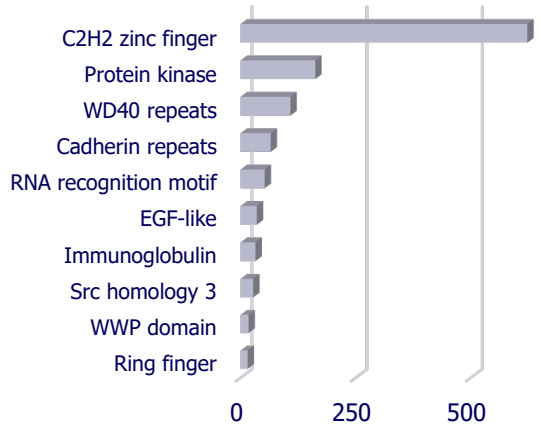
Taking MGD discovery *in silico* to accelerate discovery

A Rich, Differentiated Target Space Across Protein Domains and Diseases

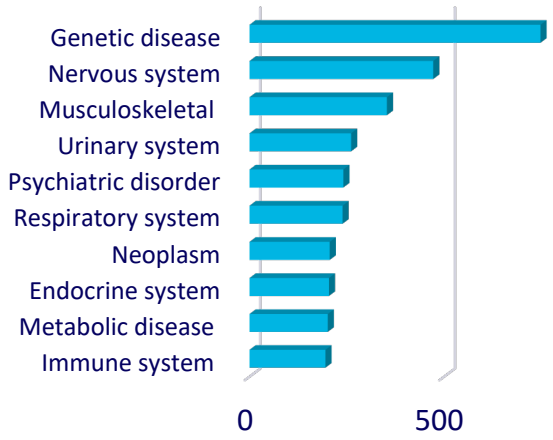
G-Loop centric Degron Encyclopedia

>3000 proteins contain a predicted G-loop structure

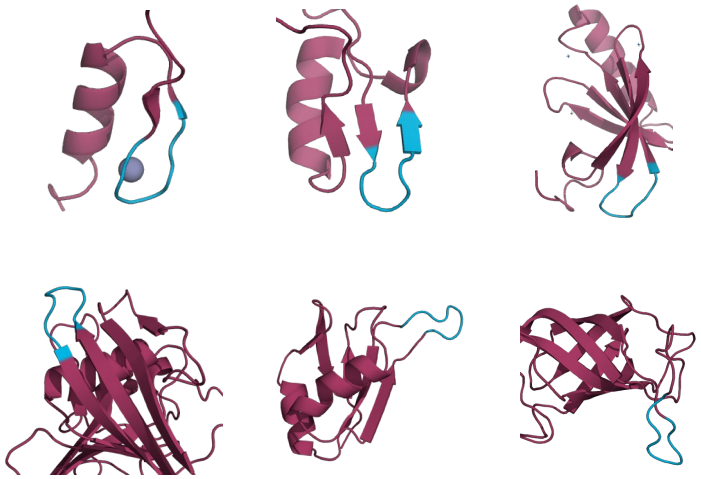
Degron-containing domains



Broad disease landscape



Predicted degrons



Diverse protein domains and classes

>85% degrons have unique sequence

>75% undruggable

Many highly credentialed targets

Leveraging a Leading Drug Discovery Platform

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

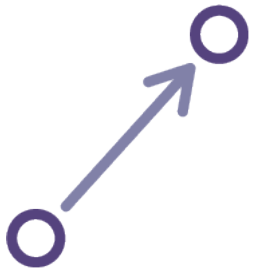
Monte Rosa's High-Value Proprietary Pipeline

Targets

Undruggable and inadequately drugged degron-containing proteins

Targeting non-catalytic and scaffolding functions

High level of target validation, preclinically and clinically



Clinical Path

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

Opportunity for rapid clinical PoC for MOA and efficacy

Patient Benefit

Address high unmet needs

Potential to address a wide range of therapeutically-relevant proteins in oncology and beyond

Create synergies within therapeutic areas

Monte Rosa Pipeline

Rapidly advancing wholly owned MGD programs targeting undruggable proteins

Target / Program	Indication(s)	Discovery	IND-Enabling	Clinical	Next Anticipated Milestones	Ownership
GSPT1	NSCLC, SCLC and other Myc-driven Malignancies				Initiate Phase 1/2	
CDK2	Ovarian Cancer, Breast Cancer				IND-Enabling Studies	
NEK7	Inflammatory Diseases					
VAV1	T and B Cell Malignancies, Autoimmune Disease				Lead Optimization	
BCL11A	SCD, β-Thalassemia					
Undisclosed	Multiple					

Oncology Autoinflammation Oncology / immunology Genetic diseases

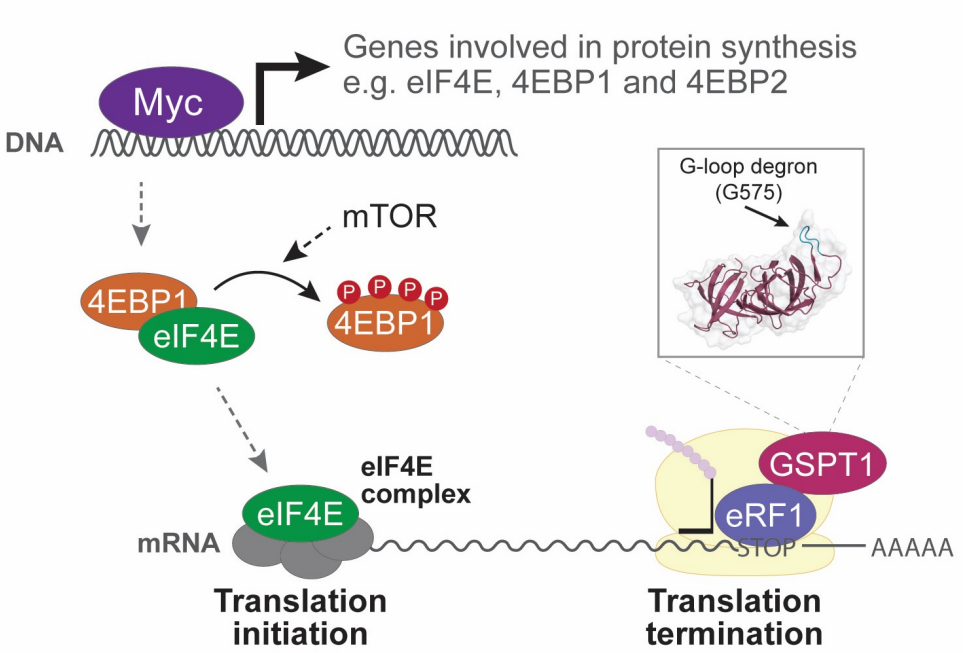
Monte Rosa Therapeutics

GSPT1 Program

Targeting Myc-driven Tumors and Their Addiction to Protein Translation

GSPT1 is a key regulator and vulnerability of Myc-induced translational addiction

Myc hijacks the cellular protein translation machinery creating a vulnerability to GSPT1 degradation



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

- Myc regulates the expression of key genes related to protein translation, including the master regulator 4EBP1 and eIF4E

This addiction to protein translation creates a **dependency** to the translation termination factor GSPT1 a degron-containing protein

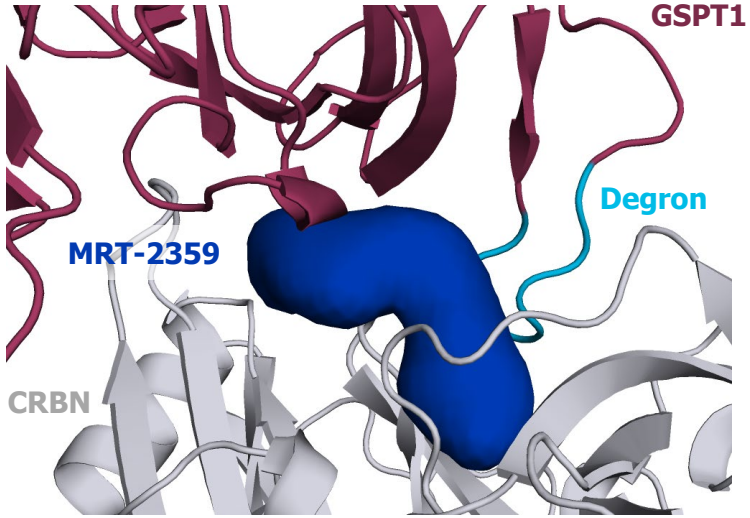
GSPT1 MGDs exploit this **vulnerability** by:

- Disrupting protein translation output
- Reducing Myc-oncogenic signaling

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

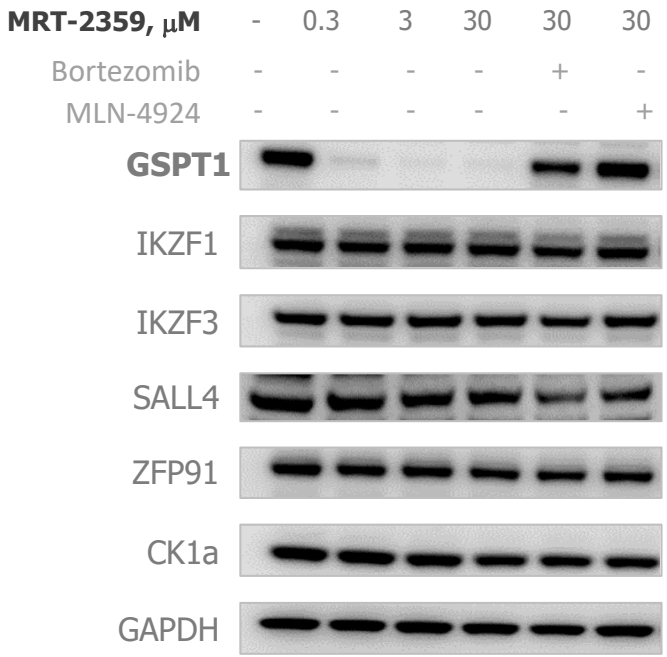
MRT-2359 is a potent inducer of GSPT1-cereblon proximity

Ternary complex model



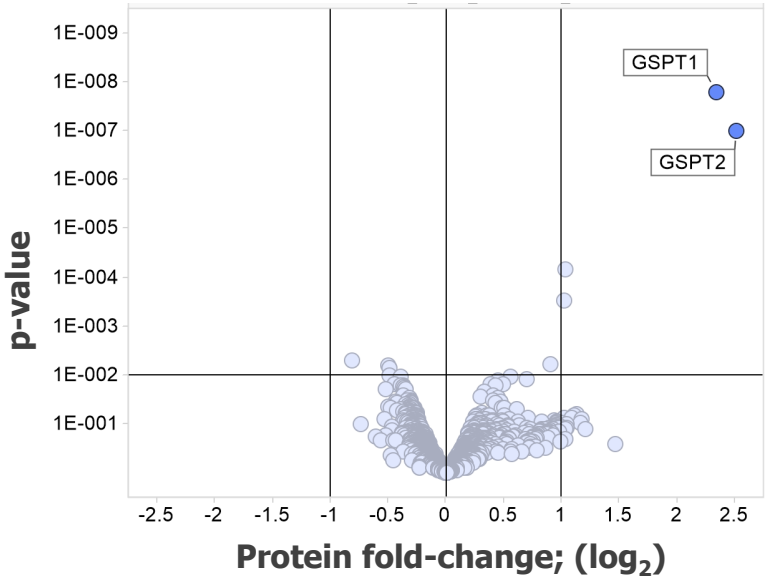
in vitro data	
CRBN binding, K_i	113 nM
Ternary complex, EC_{50}	< 7 nM
Degradation, DC_{50}	80 nM

MRT-2359 is a selective GSPT1-directed MGD



6hr post treatment in MM1S and Kelly (SALL4)

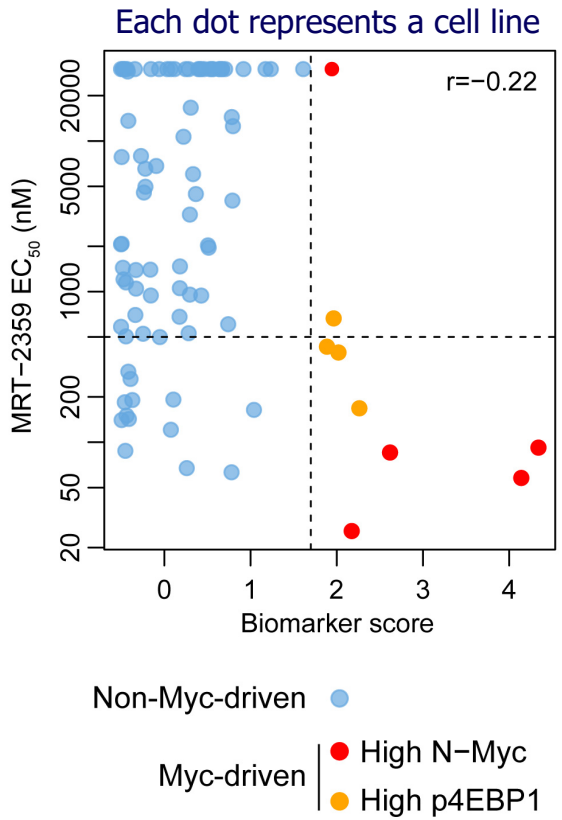
Proximity – Turbo ID



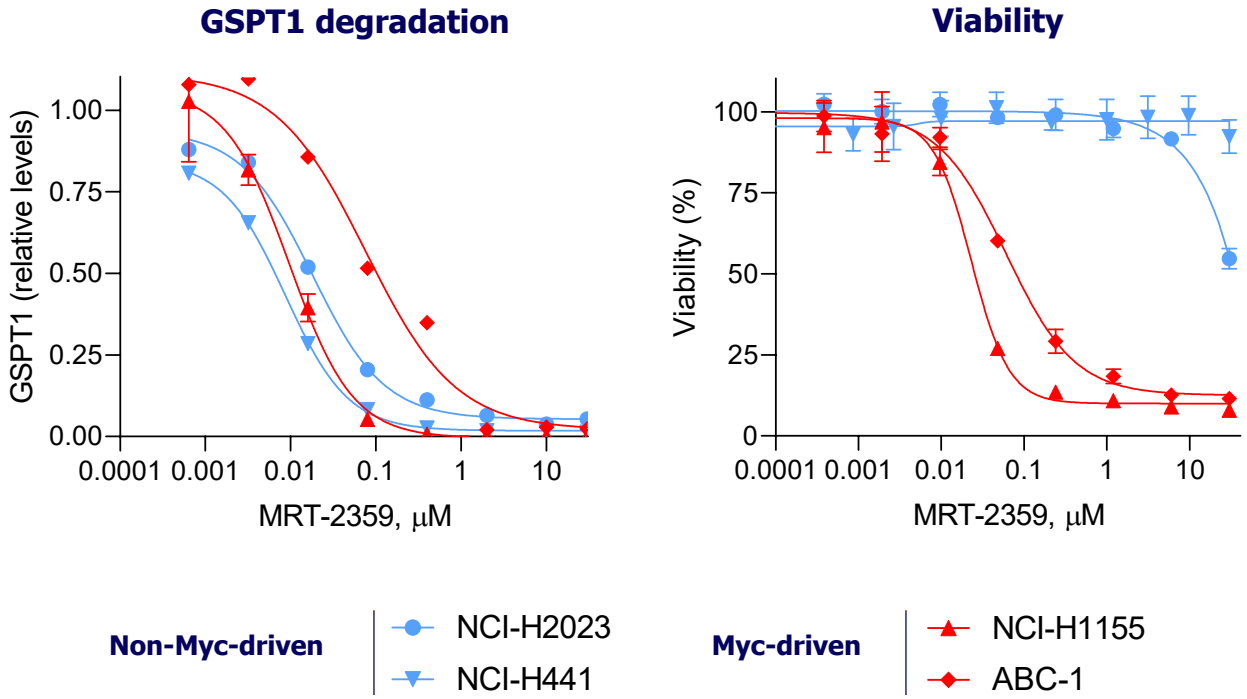
1hr post treatment

Myc-driven NSCLC Lines are Highly Sensitive to MRT-2359

Myc-driven NSCLC cell lines are sensitive to MRT-2359



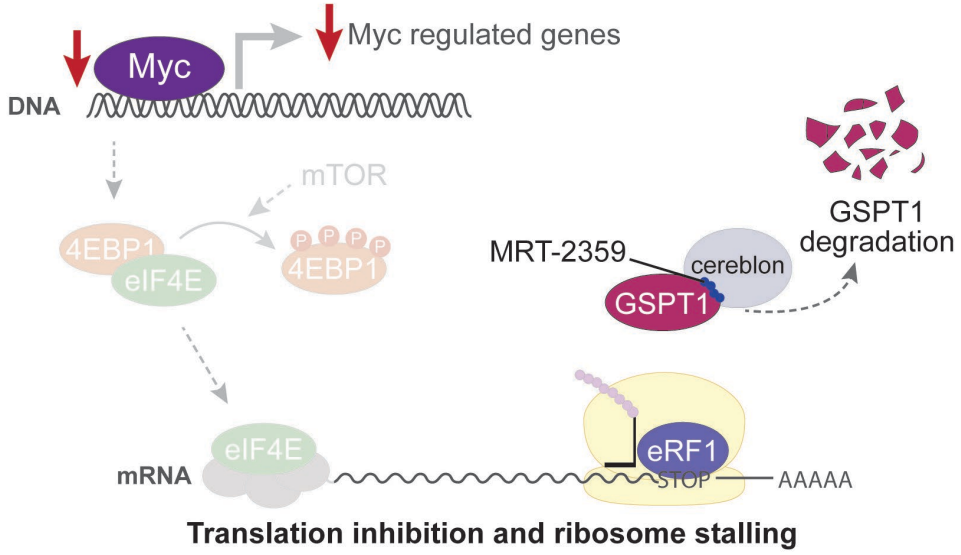
MRT-2359 induces GSPT1 degradation in all cell models, but selective killing in high N-Myc lines only



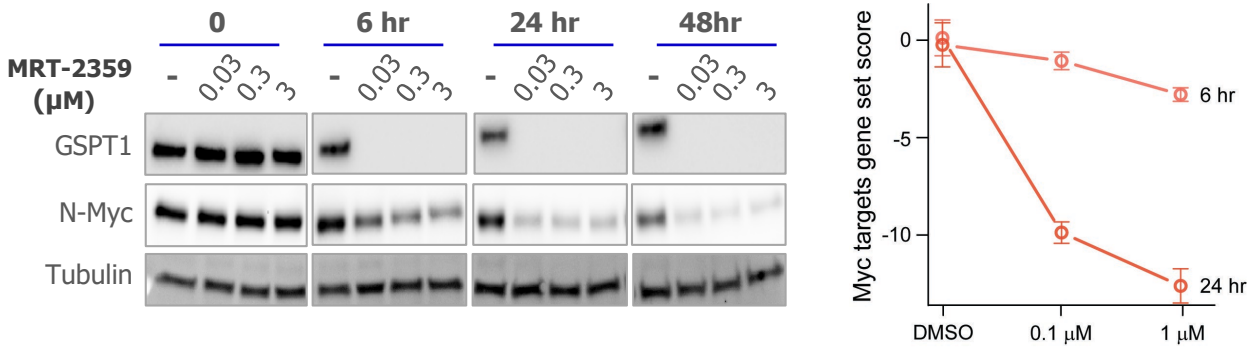
GSPT1 western blot at 6 hr (N-Myc high) and 24 hr (low). 72 hr viability assay (CTG)

MRT-2359 Affects N-Myc Pathway only in Myc-driven Cells

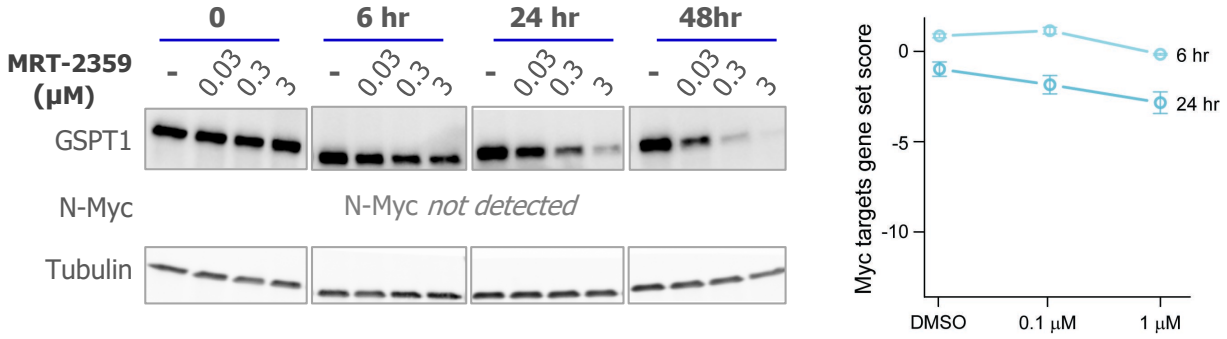
GSPT1-directed MGD degradation affects translation, a critical vulnerability of Myc-driven cells



Myc-driven (NCI-H1155)



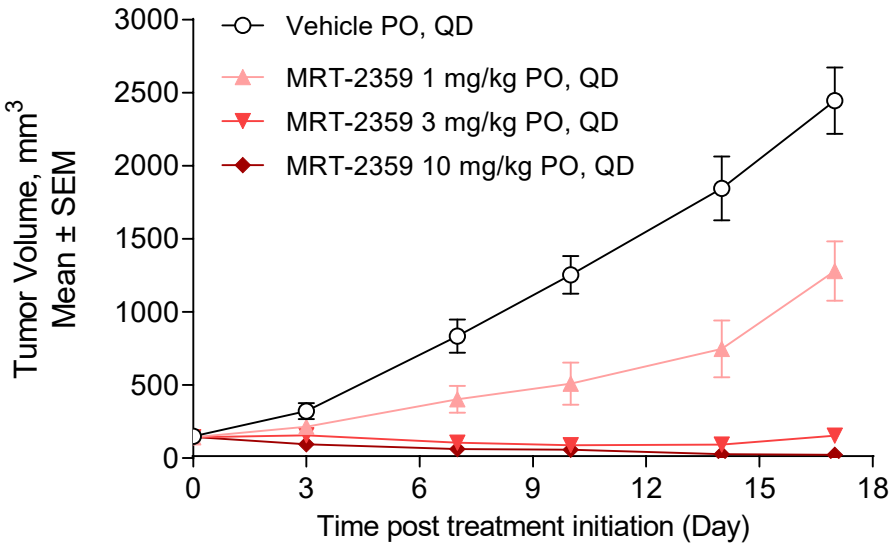
Non-Myc-driven (NCI-H2023)



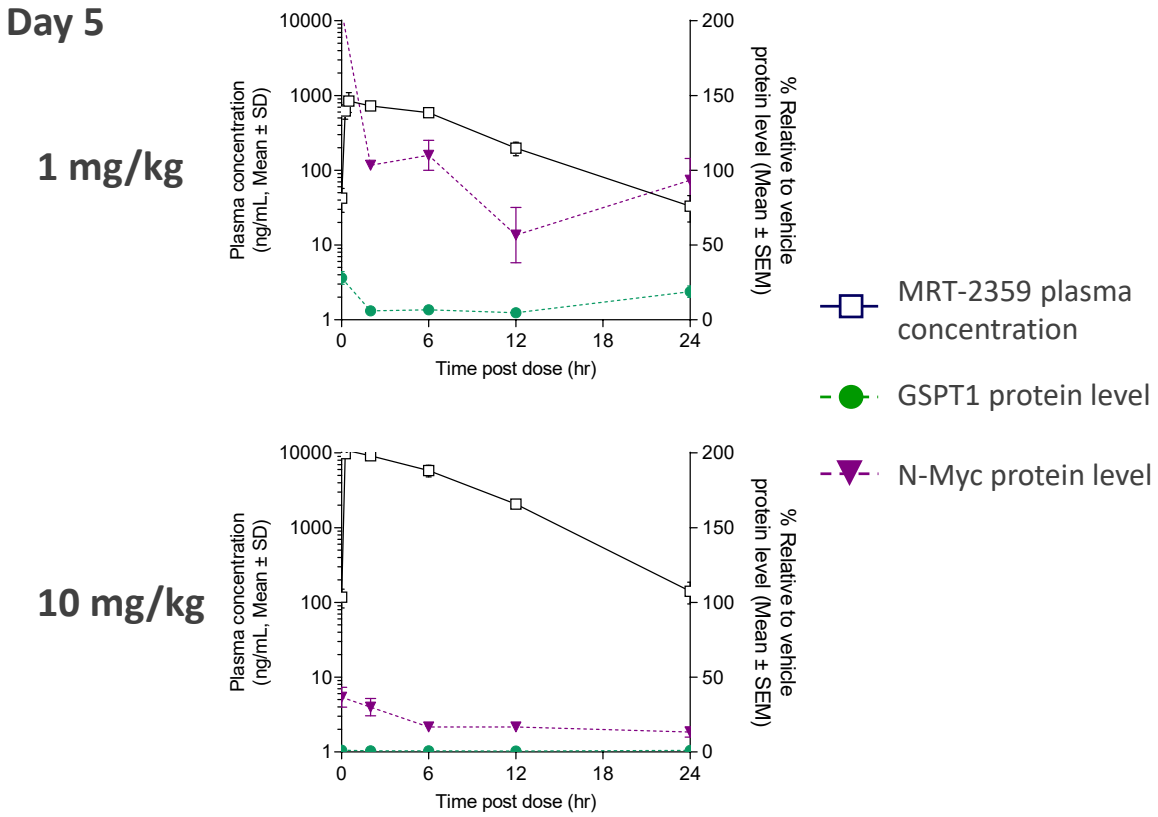
MRT-2359 Induces Tumor Regressions in N-Myc-driven Xenograft Models

Oral dosing of MRT-2359 shows anti-tumor activity and regressions in NCI-1155

Similar observations in other high N-Myc expression models (ABC-1, NCI-H1770)

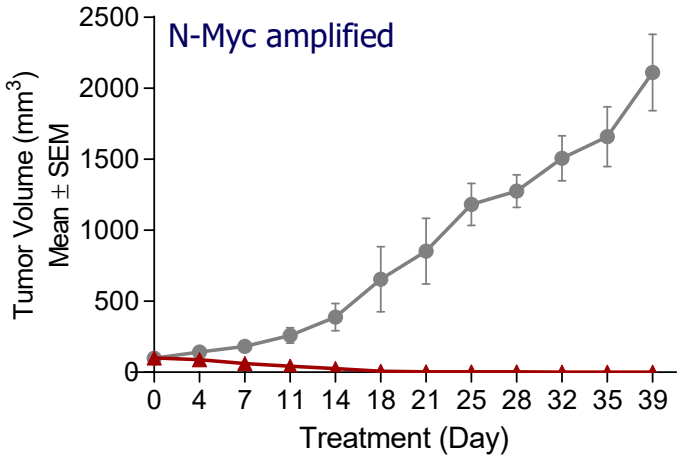


Dose- and time-dependent degradation of GSPT1 is associated with N-Myc downregulation

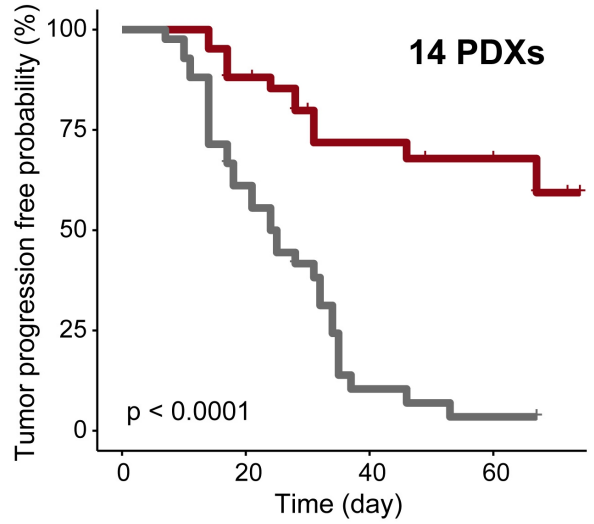


MRT-2359 Anti-tumor Activity in L- or N-Myc-positive NSCLC PDXs

HIGH
L−Myc or N−Myc expression

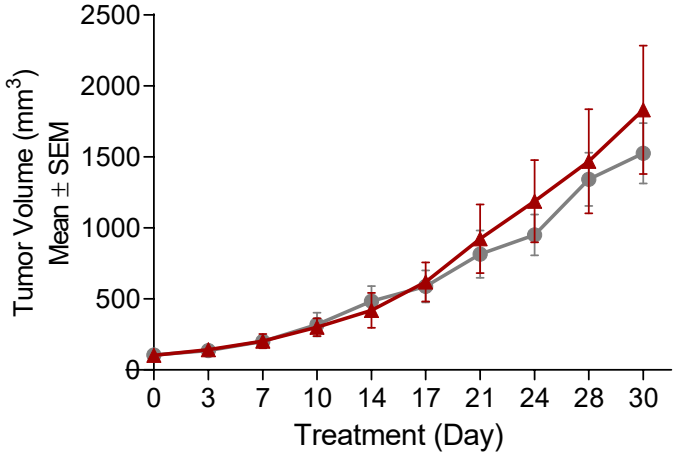


Tumor progression to ≥800 mm³

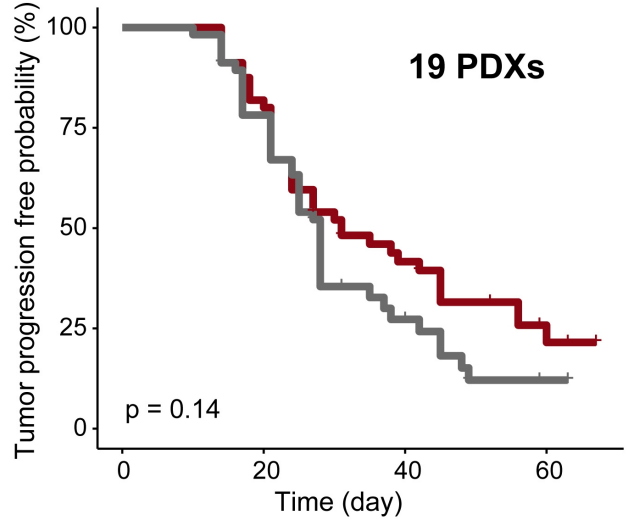


Vehicle
MRT-2359 10 mg/kg PO, QD

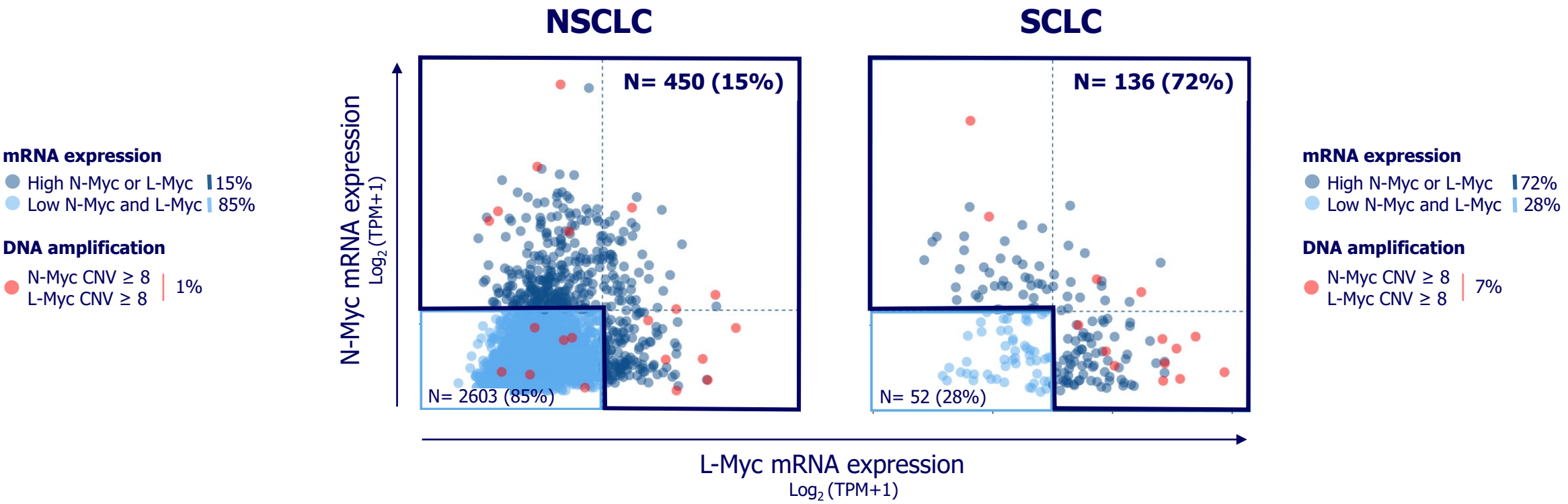
LOW
L−Myc and N−Myc expression



Tumor progression to ≥800 mm³



Real-world Data Identify High Frequency of Myc-driven Lung Cancer Patients

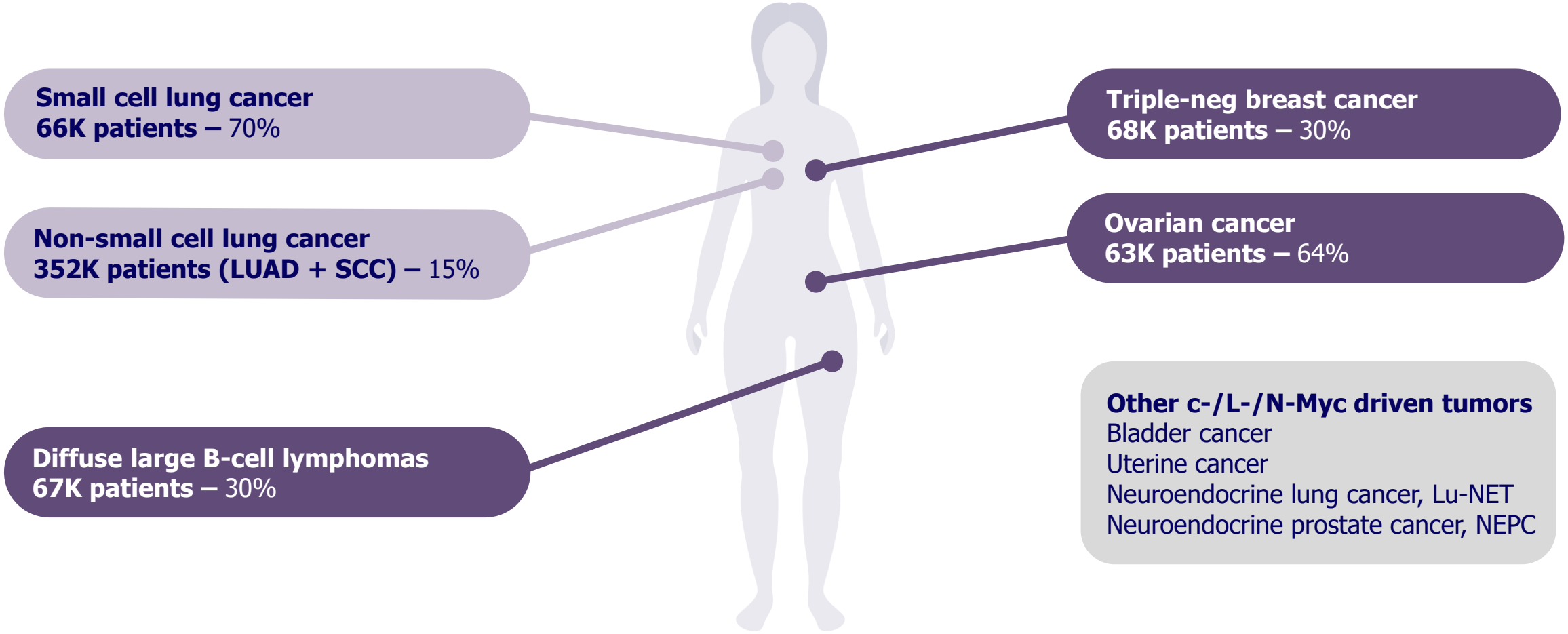


Analyses of real-world molecular and genomic data on 3241 lung cancers performed in collaboration with Tempus Inc.

15% of NSCLC and 72% of SCLC patients with high L-Myc or N-Myc mRNA expression similar to Myc expression levels in NSCLC PDX models

Targeting Myc-positive Tumors with MRT-2359

Potential indications and patient stratification hypotheses



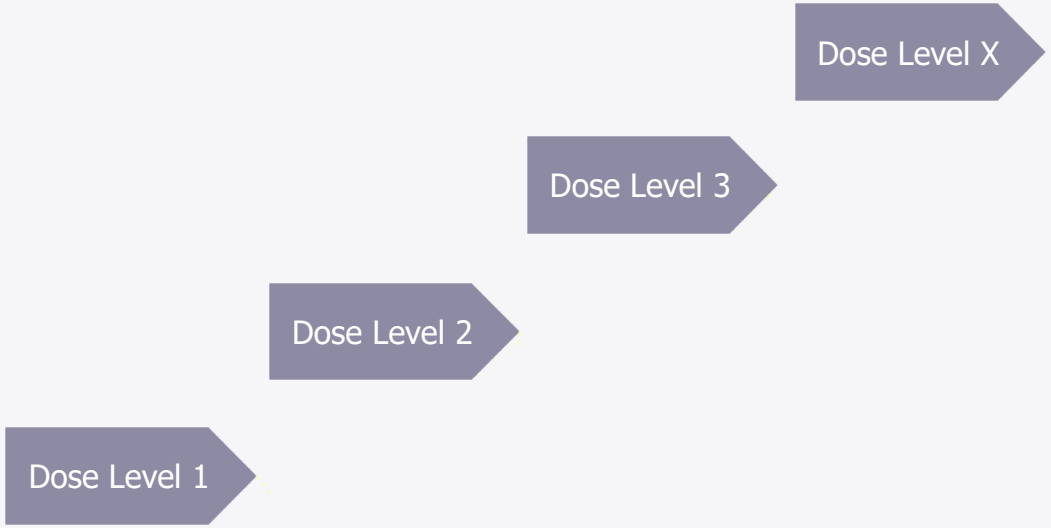
Patient diagnosed incidence #s, major markets (US, EU and JP): Decision Resources Group (DRG)
Patient stratification %s: Schaub - Cell Systems 2018; Massó-Vallés – Exp. Op. therapeutic targets 2020; Sesques and Johnson - Blood 2016

MRT-2359-001 Phase 1/2 Clinical Development

Phase 1 dose escalation

BOIN design

Lung cancer (NSCLC, SCLC), solid tumors with L-/N-Myc amplification and diffuse large B-cell lymphomas



RP2D

Phase 2 expansion cohorts

NSCLC – Enriched for high L-/N-Myc expression

SCLC – Enriched for high L-/N-Myc expression

Solid tumors – L-/N-Myc amplification

Targeting Myc-addicted Tumors with MRT-2359

Rationally designed **potent and selective** GSPT1-directed MGD

Favorable **drug-like properties** and ADMET profile

Orally bioavailable development candidate

Robust **antitumor activity** in **multiple tumor models**

IND filed in August 2022

Patient stratification hypothesis developed

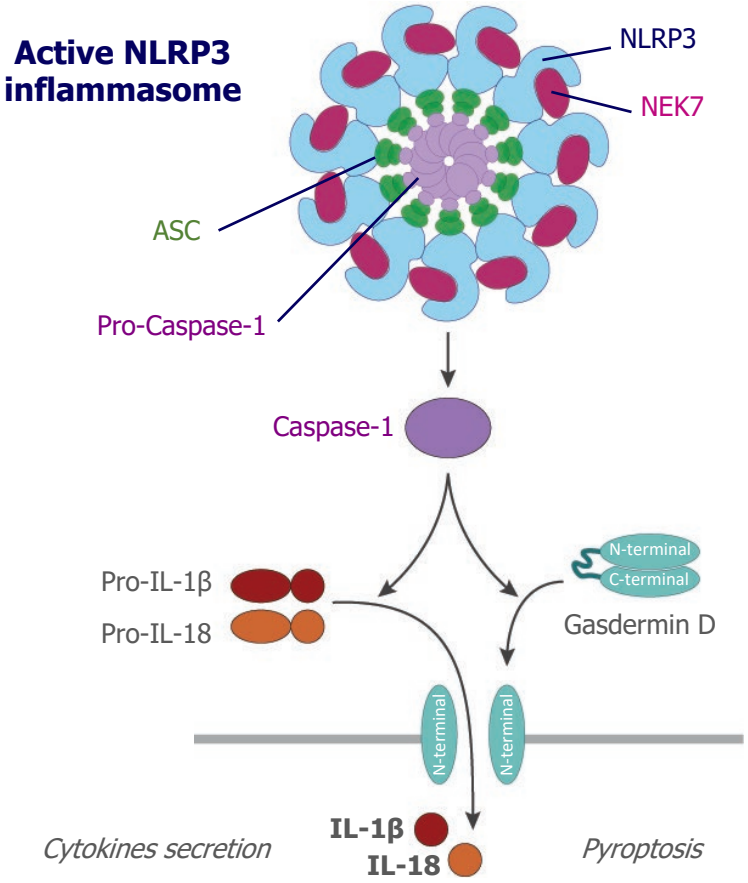
Initiate Phase 1/2 in Q4 2022, subject to FDA clearance of IND

Monte Rosa Therapeutics

NEK7 Program

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

NEK7 is an essential regulator of the inflammasome



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

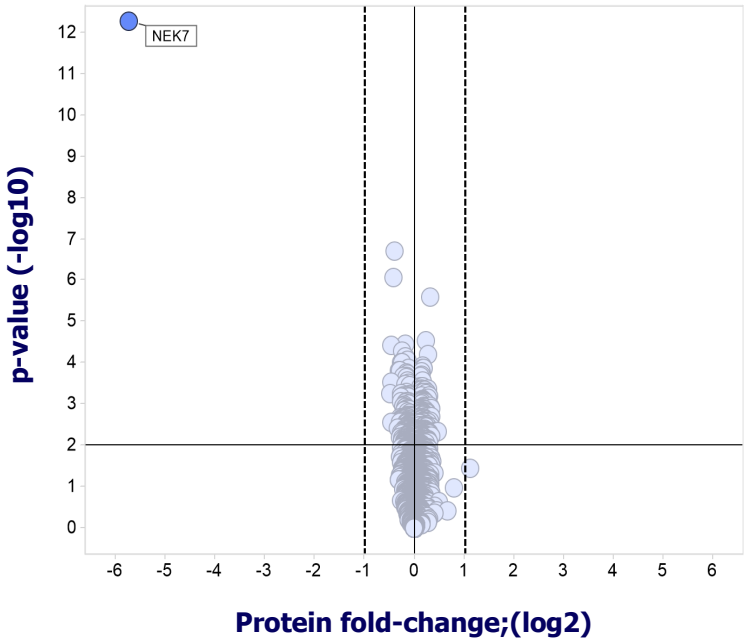
- NEK7 licenses NLRP3 assembly in a kinase independent manner
- NEK7-deficient macrophages are severely impaired in IL-1β and IL-18 secretion

Clinical opportunity: First-in-class NEK7 degraders for

- Over-activated NLRP3 inflammasome: metabolic pathologies, cardiovascular diseases, inflammatory issues and neurologic disorders
- NLRP3 activating mutations: Cryopyrin-associated periodic syndromes (CAPS)

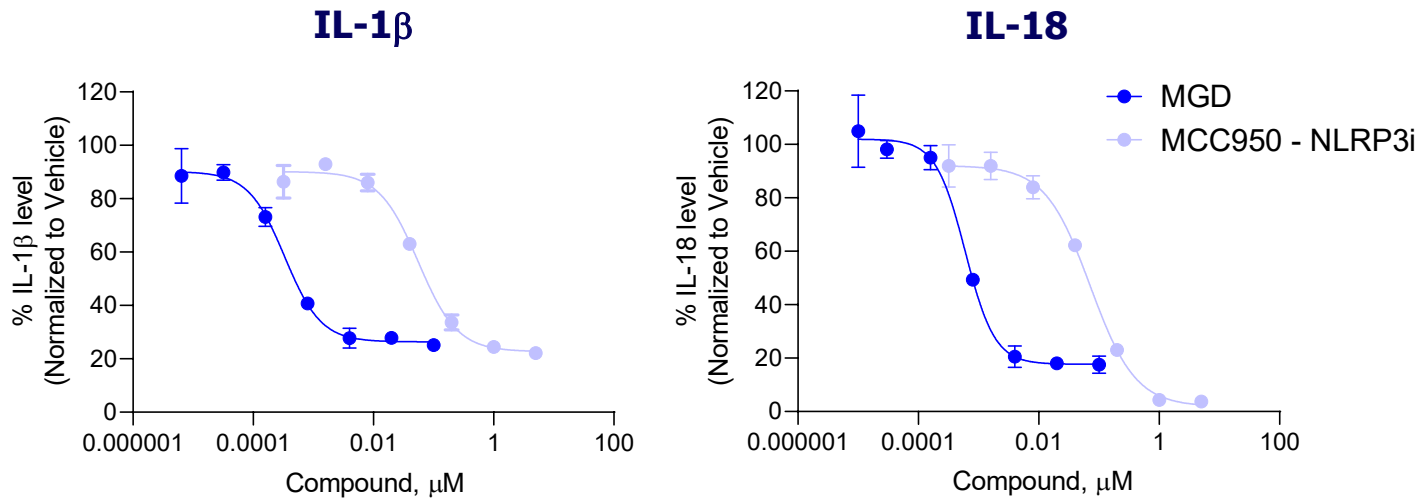
NEK7-directed MGDs modulate NLRP3 Pathway in human macrophages

NEK7-directed MGD shows high selectivity



TMT Proteomics – U937 24hr post treatment

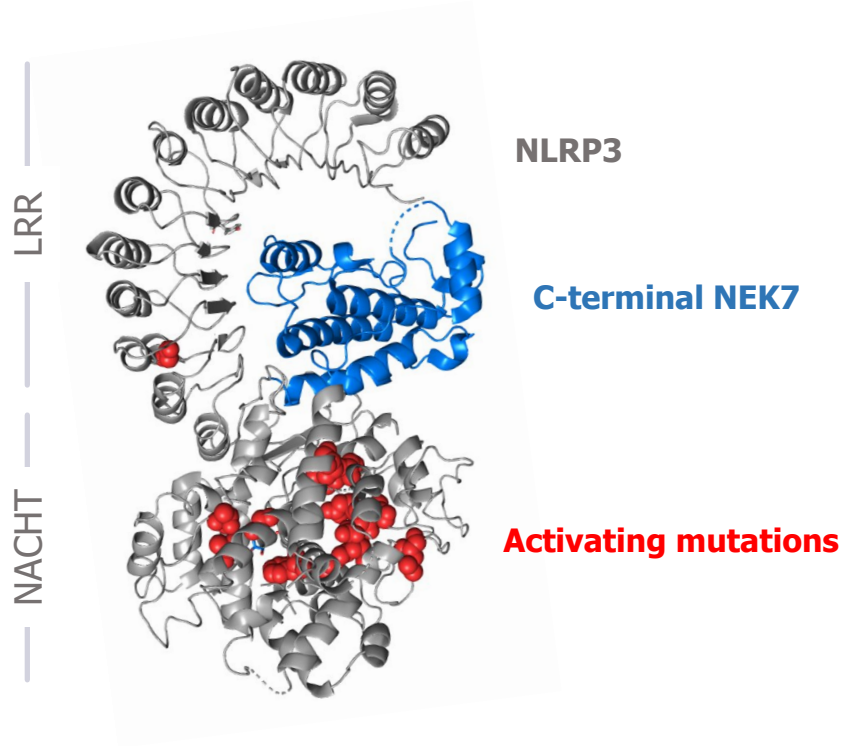
NEK7-directed MGD compared to NLRP3 inhibitor



IL-1β and IL-18 release - human macrophages LPS/MSU stimulated 24 hr post treatment

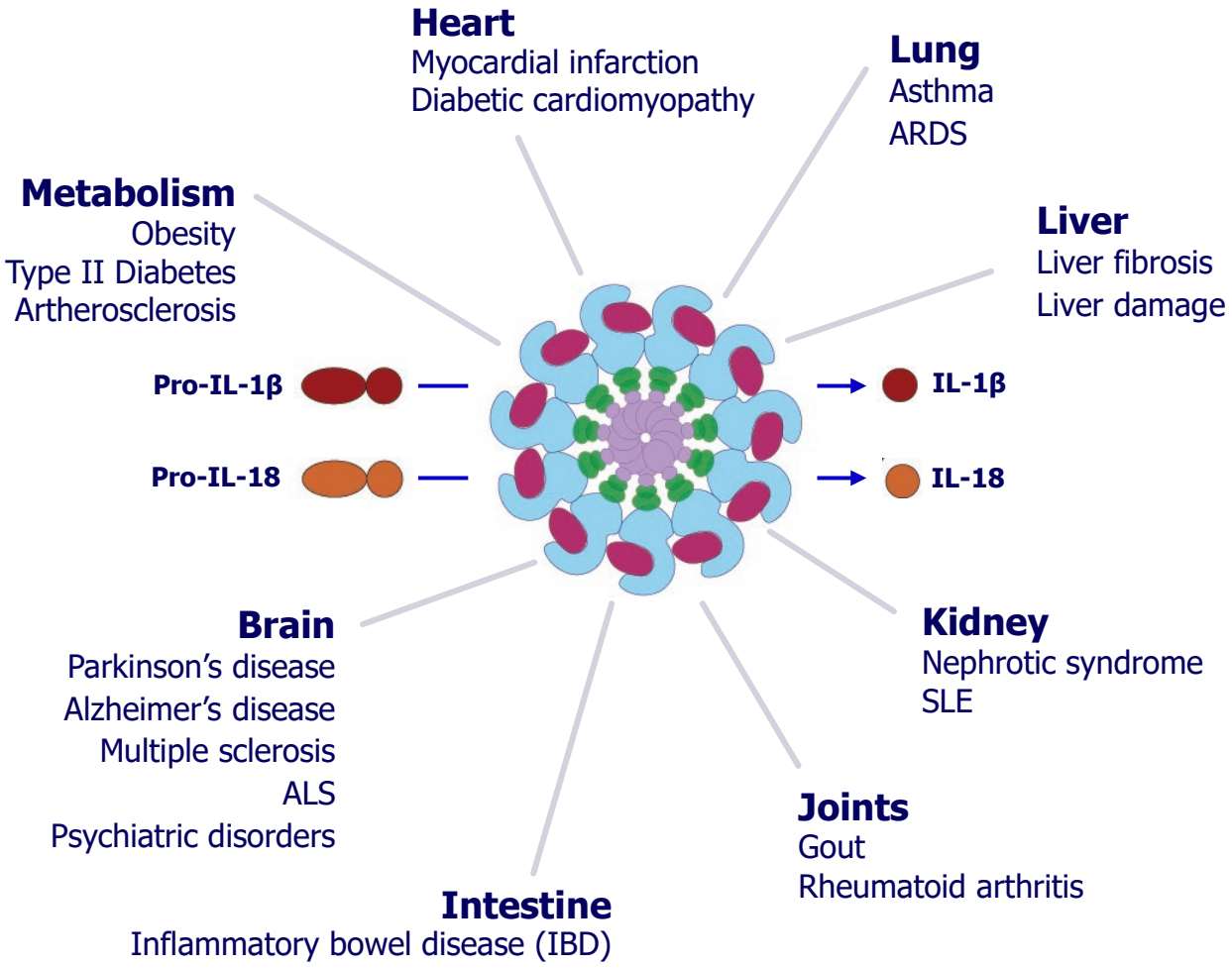
Overactivation of the NLRP3 Inflammasome in Diseases

NLRP3 activating mutations



NLRP3 mutations found in CAPS (Cryopyrin-associated periodic syndromes – MWS*, FCAS**, CINCA/NOMID# Syndrome) might stabilize the active form of NLRP3

Over-activated NLRP3 inflammasome



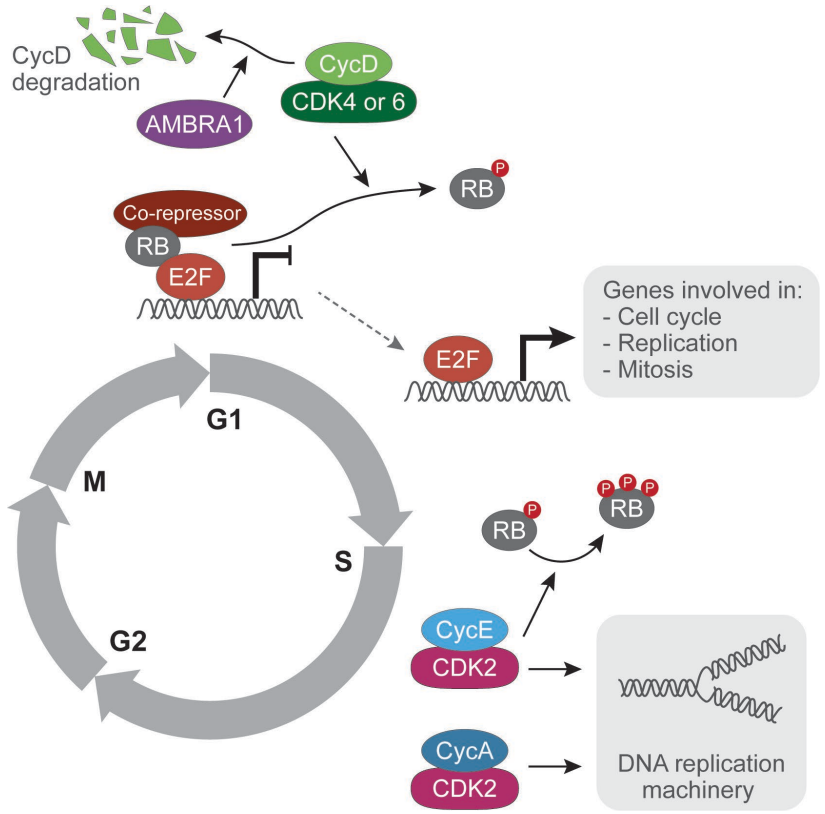
*Muckle-Wells Syndrome
**familial cold autoinflammatory syndrome, #Chronic infantile neurological cutaneous and articular/neonatal onset multisystem inflammatory disease

Monte Rosa Therapeutics

CDK2 Program

CDK2 as a Target for Selected Solid Tumors

CDK2 is one of the key regulators of the cell cycle



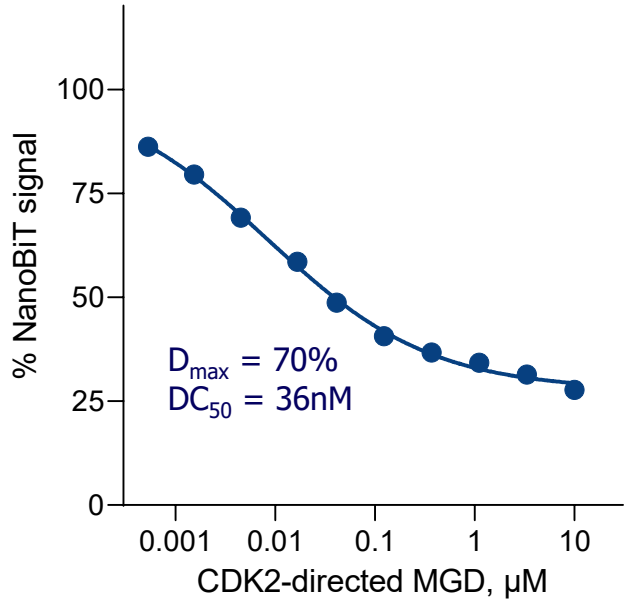
Therapeutic hypothesis: Tumors with CDK2 pathway activation by:

- CyclinE1/E2 amplification or loss of AMBRA1
- Loss of RB

Clinical Opportunity: CDK2 driven cancers: ER positive breast cancer pre and post treatment with CDK4/6 inhibitors (444K patients), ovarian cancer (63K patients), and endometrial cancer (118K patients)

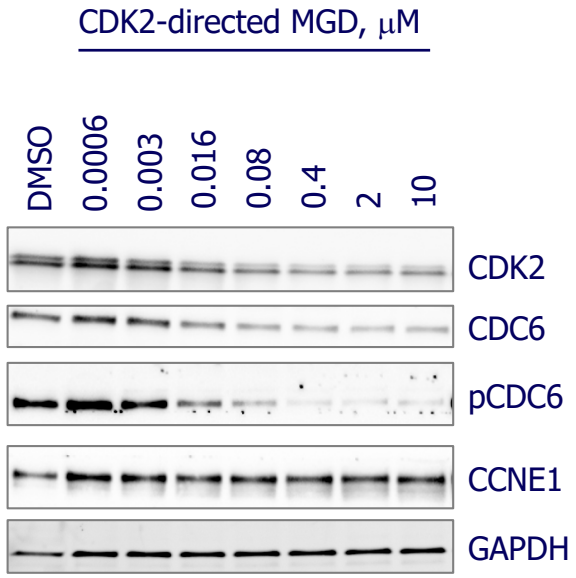
CDK2-directed MGD Shows Biological Activity in a CDK2-dependent Cell Line

CDK2-directed MGD induces CDK2 degradation



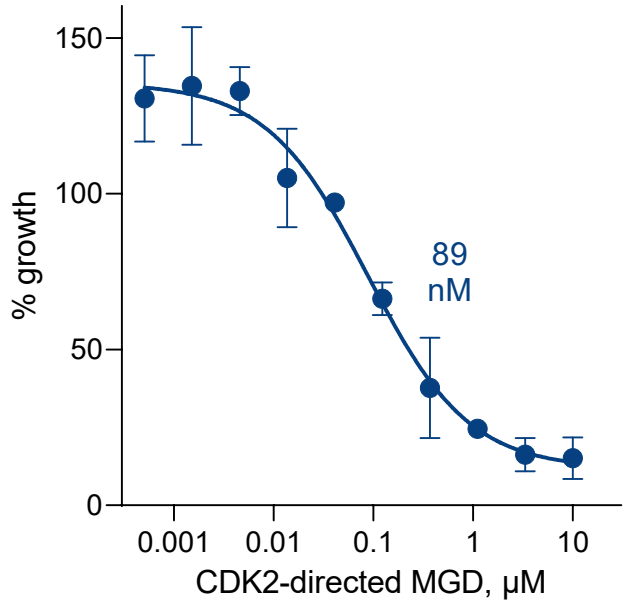
NanoBiT assay in HEK293 cells, 24h

CDK2-directed MGD reduces CDC6 protein



MDA-MB-157 cells, 24h

CDK2-directed MGD inhibits proliferation



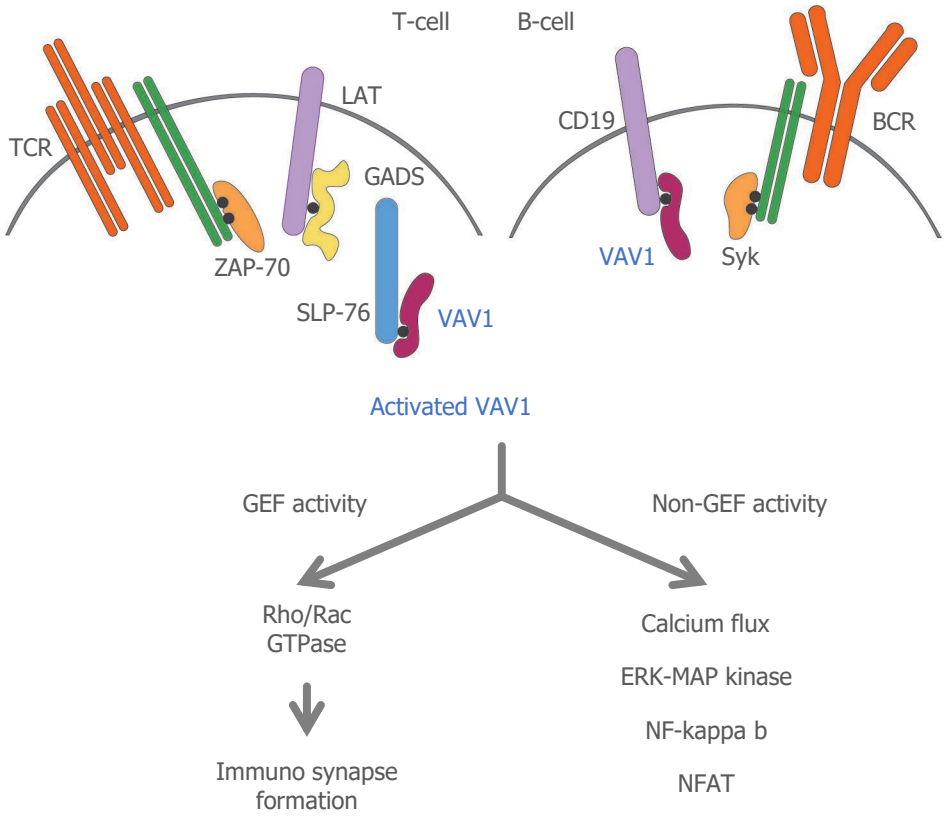
CyQuant assay in MDA-MB-157 cells, 7d

Monte Rosa Therapeutics

VAV1 Program

VAV1 as a Target for Autoimmune Disease

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



Therapeutic hypothesis: Diseases with VAV1 activating mutations or autoimmune disorders

- VAV1 activation mutations identified in leukemia, lymphoma and lung cancer
- VAV1 KO mice improved multiple autoimmune models

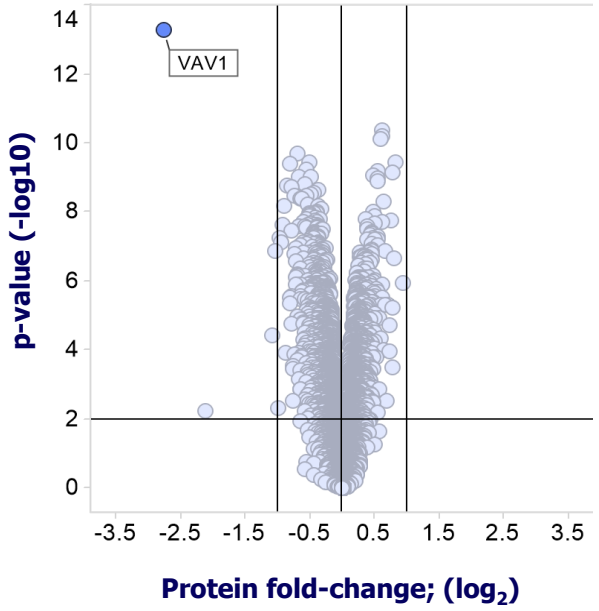
Clinical Opportunity: First-in-class VAV1 degraders for

- T-cell and B-cell lymphomas: DLBCL (66K patients) and Burkitt lymphoma
- Autoimmune disorders including MS (1.2M patients), myasthenia gravis (36K – 60K patients in US), and acute graft-versus-host disease (10K patients)

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

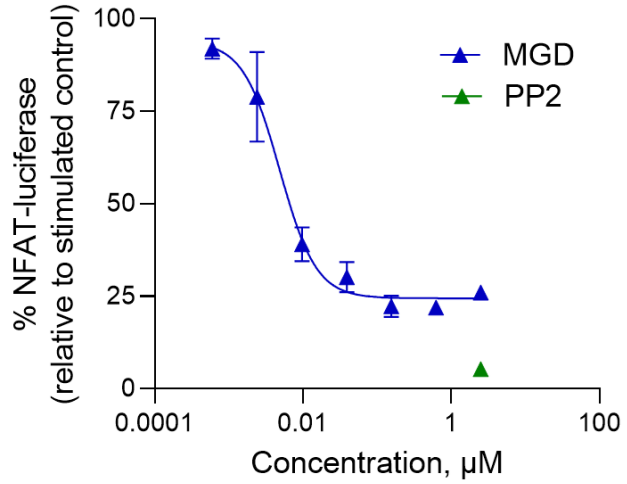
VAV1-directed MGDs Demonstrate Pharmacodynamic Activity in T Cells

VAV1-directed MGD shows high selectivity



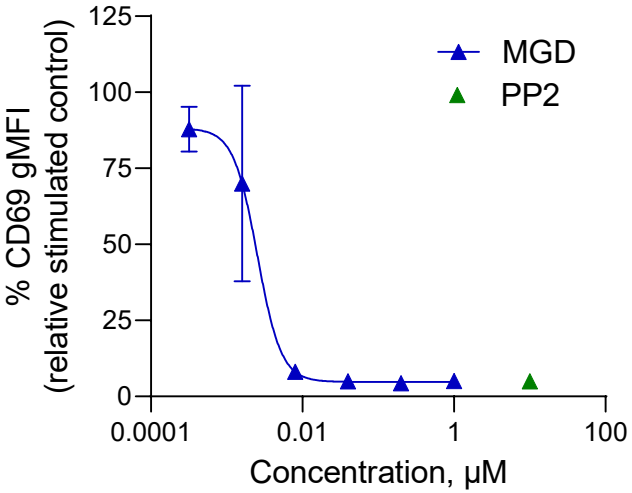
TMT Proteomics – Jurkat 24hr post treatment

VAV1-directed MGD inhibits NFAT-luciferase activity



NFAT-luciferase assay – Jurkat
24 hr MGD pre-treatment + 18 hr anti-CD3 stimulation
PP2 - Src family kinase inhibitor

VAV1-directed MGD inhibits CD69 expression in primary T cells



CD69 FACS - Human primary T-cells
6 hr MGD pre-treatment + 16 hr anti-CD3 stimulation
PP2 - Src family kinase inhibitor

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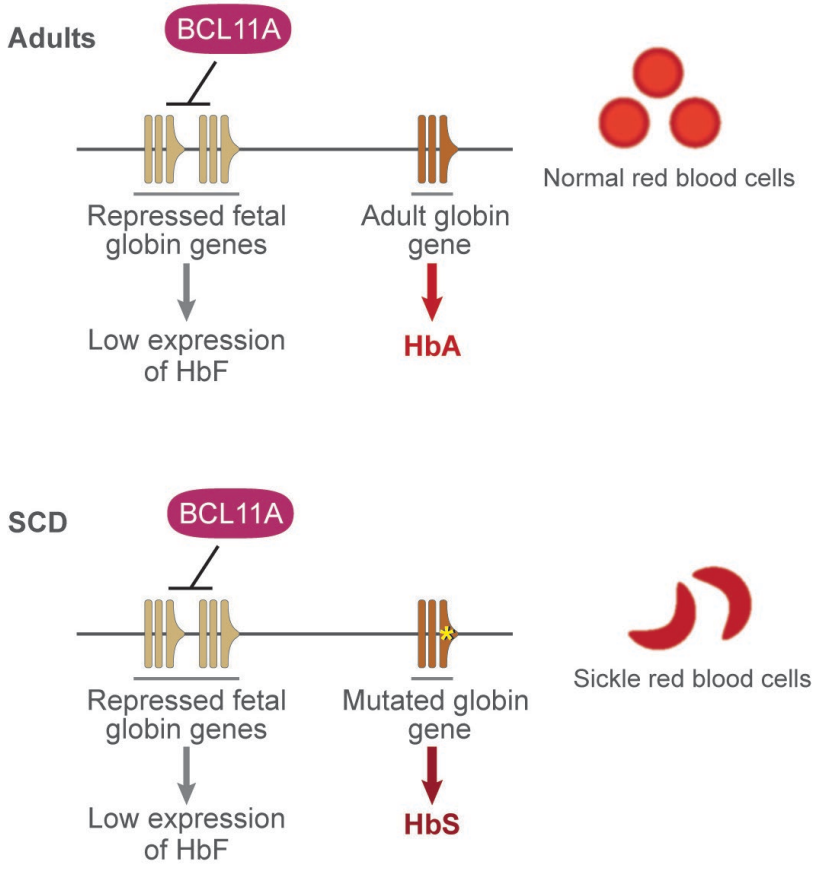
BCL11A Program

BCL11A as a Target for Hemoglobinopathies (SCD and β-Thalassemia)

BCL11A is the zinc finger transcription repressor of the fetal globin genes



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

Clinical Opportunity: First-in-class BCL11A degraders for

- Sickle cell disease (SCD)
  - 155,000 patients (US and EU)
  - >6M patients (ROW)
- β-thalassemia
  - 17,000 patients (US and EU)

Patient diagnosed prevalence #s: DRG; www.notaloneinsicklecell.com

Monte Rosa Therapeutics

Summary

Monte Rosa Therapeutics

From serendipity to rational design of MGDs

Molecular glue-based targeted protein degradation platform developing breakthrough small molecule therapeutics that selectively degrade disease-causing proteins

Proprietary, **target-centric** drug discovery platform enabling **rational design**, and anticipated rapid development, of molecular glue-based degraders targeting the **undruggable proteome in oncology** and **non-oncology disease**

Initial platform focus on **cereblon-mediated protein degradation** with **hundreds of potential targets** to address

Extensive and compelling pre-clinical *in vivo* data for GSPT1 program, demonstrating **potent anti-tumor activity** in Myc-driven tumor models with development candidate MRT-2359

Initiation of Phase 1/2 trial for MRT-2359 for the treatment of Myc-driven tumors including lung cancer planned for Q4 2022, subject to FDA clearance of IND; additional programs at various stages of lead optimization and discovery

Potential to reprogram other E3 ligases to access more of the undruggable proteome through other degrons


Thank You
Monte Rosa
Therapeutics