

# From Serendipity to Rational Design

Taking Molecular Glue Degradors to New Heights | June 2022



**Monte Rosa**  
Therapeutics

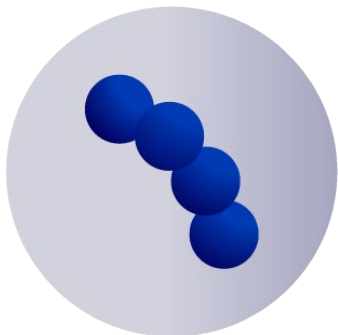
# Forward-Looking Statements

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 these materials include, but are not limited to, statements about our product development activities, including our expectations around the ongoing development of our QuEEN™ platform, the advancement of our pipeline and the various products therein, including -the expected timing for filing our IND for our lead GSPT1-directed MGD product candidate, MRT-2359, and the advancement of our additional programs, including NEK7, CDK2, VAV1, and BCL11A, the expansion of our compound and degron libraries, our ability to identify additional molecular glue degraders, and our scientific predictions around clinical opportunities for our programs, including GSPT1. 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 first quarter of 2022 ending on March 31, filed on May 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, it has not independently verified, and makes 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.

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# 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 for GSPT1 program expected in 2022** 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



**Ajim Tamboli, CFA**  
Chief Financial Officer



**Owen Wallace, Ph.D.**  
Chief Scientific Officer



**Sharon Townson, Ph.D.**  
Chief Technology Officer



**John Castle, Ph.D.**  
Chief Data Scientist



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



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



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



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

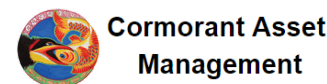


**Jennifer Champoux**  
SVP, Operations



# Strong Cash Position and Investor Support

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

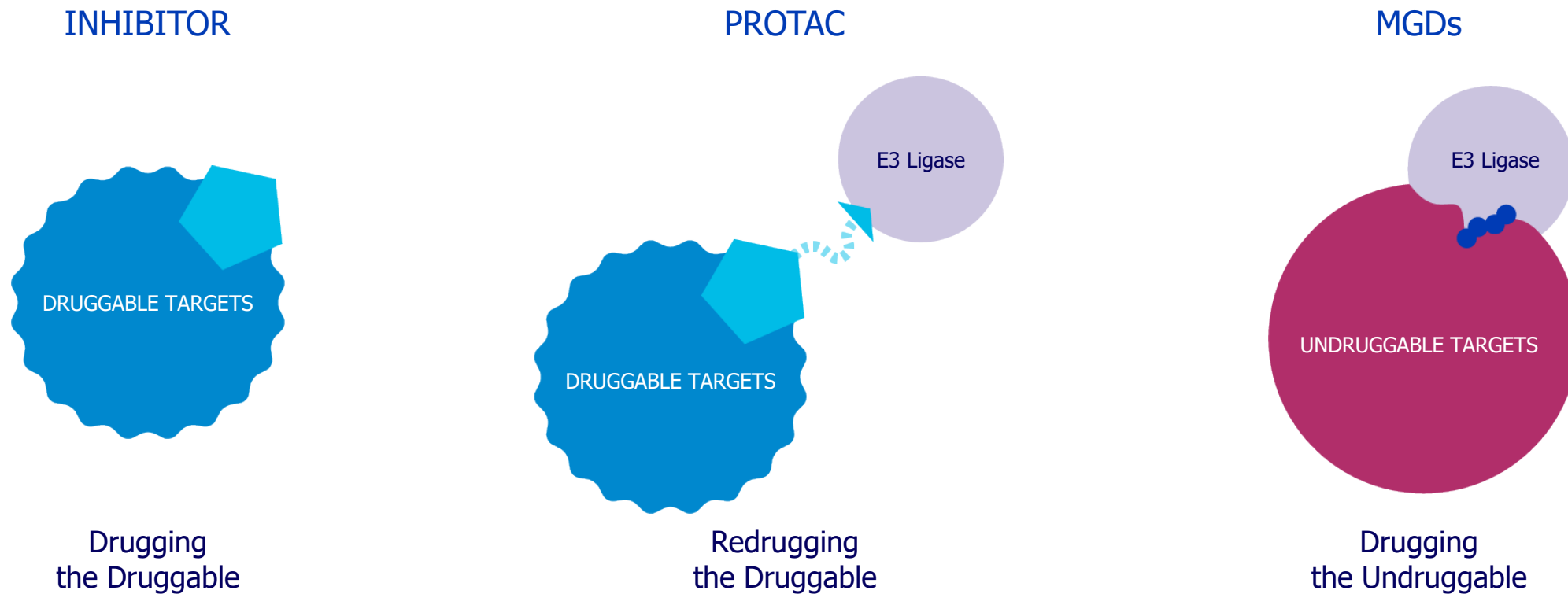


Aggregate IPO gross proceeds were approximately \$255.6 million before deducting underwriting discounts and commissions and other offering expenses and include an additional \$33.3 million in gross proceeds the company received as part of its IPO from the full exercise of the underwriters' option to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



# Molecular Glue Degraders (MGDs)

Expanding target space, fostering a new generation of drugs



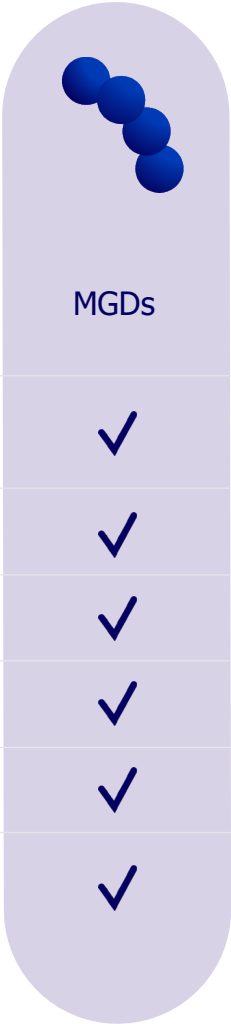




Expanding the Degradable Proteome

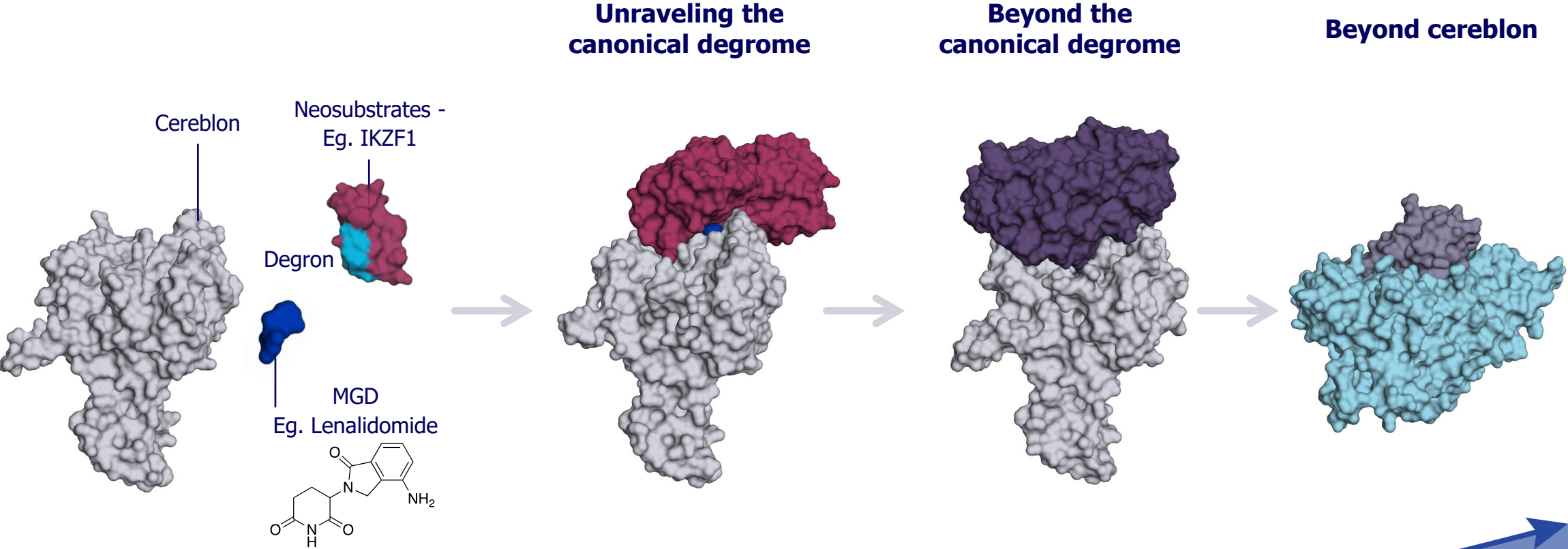
Target Space

# 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
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



Expanding the Degradable Proteome

Chemical Space

Target Space

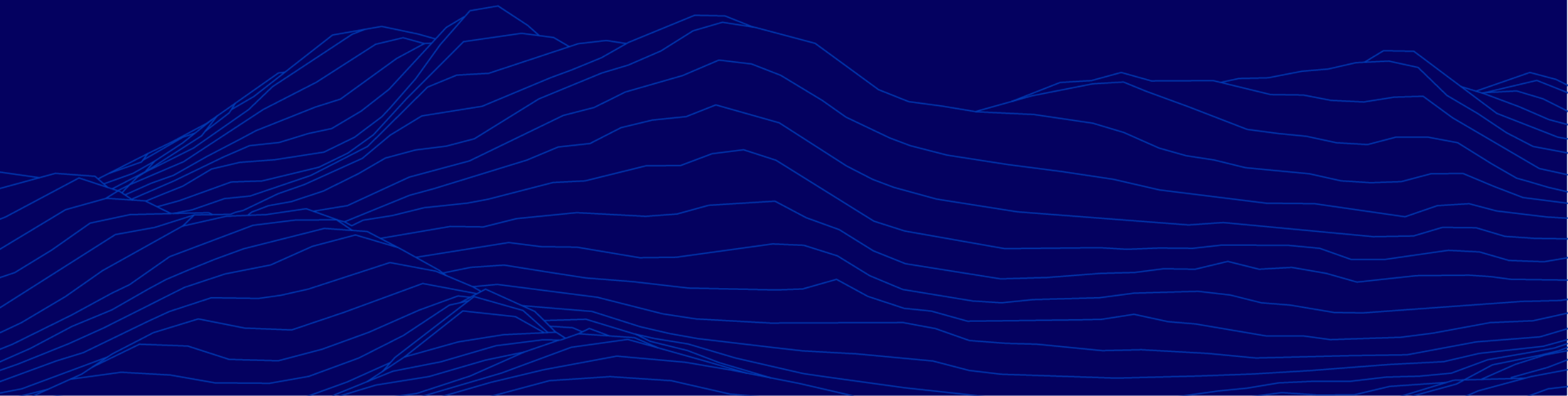






# QuEEN™ Discovery Platform

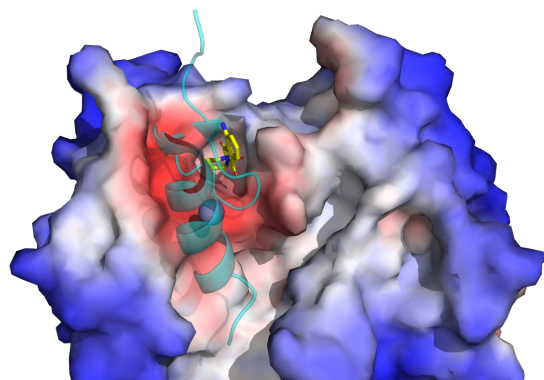
Quantitative and Engineered Elimination of Neosubstrates



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

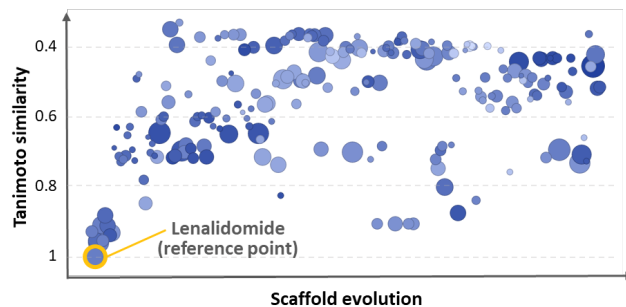
## AI Engines OneVision™ and Rhapsody™

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



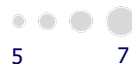
## Proprietary MGD library

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



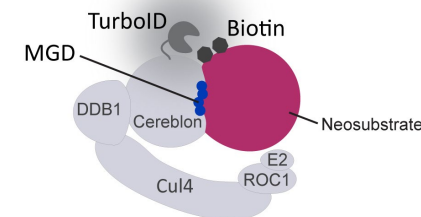
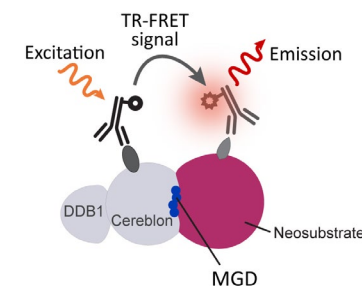
Cereblon binding (pIC<sub>50</sub>)

Molecular weight (Da)



## Glueomics™ toolbox

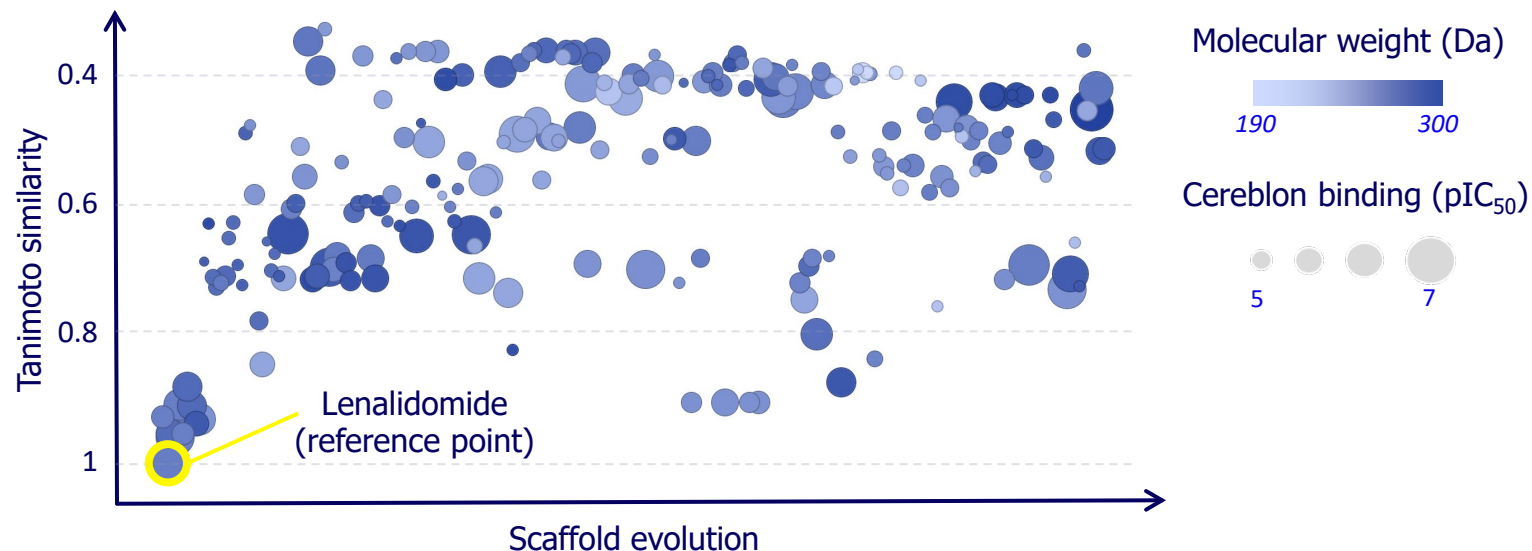
Specialized suite of *in vitro* & *in silico* assays to discover, optimize and advance MGDs as clinical candidates



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



## Library design and expansion

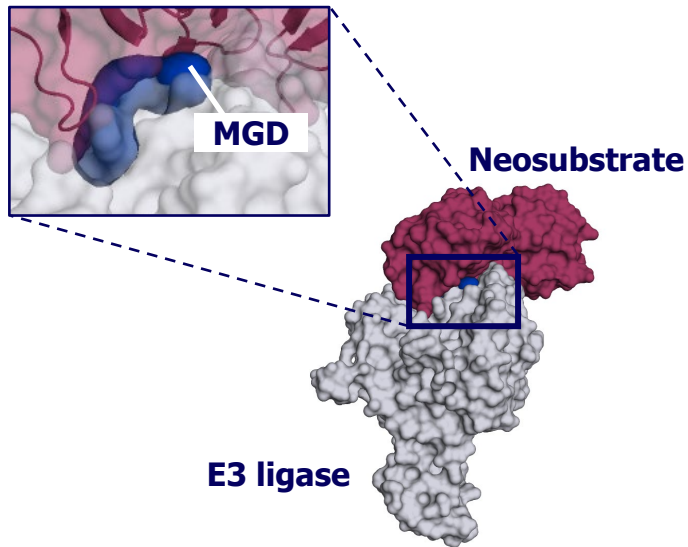
- Design focused on optimal drug-like properties
- High structural diversity and novelty
- Current library size 20K MGDs

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

# MGDs Reprogram the Cereblon Surface

Remodeled MGD-CRBN surface enables selective engagement of neosubstrates

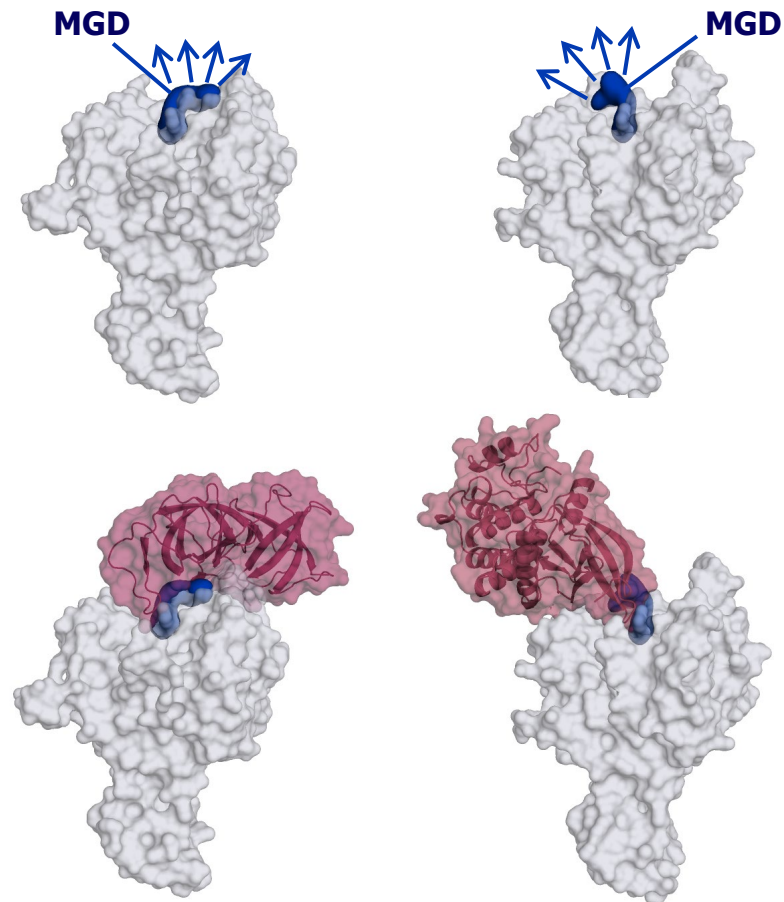
**Multiple points of contact for dialing in selectivity and potency**



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**



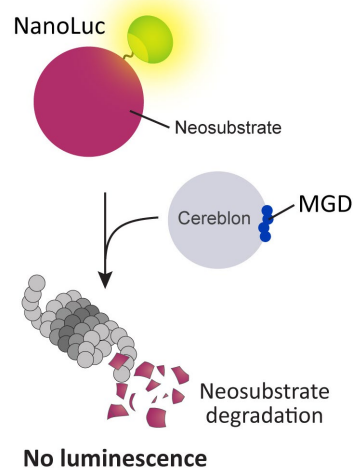
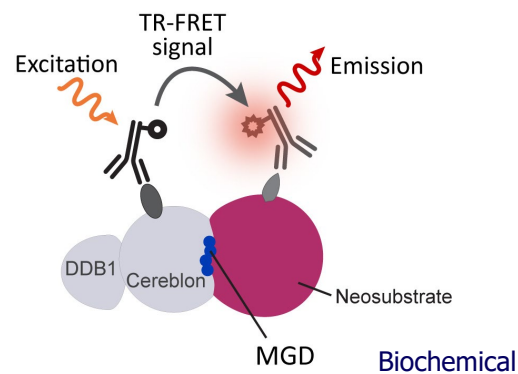
MGDs reshape the cereblon surface through different exit vector geometries

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

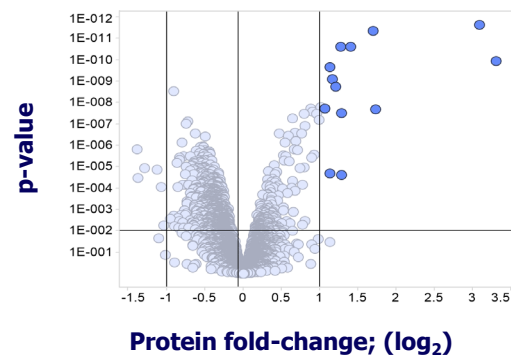
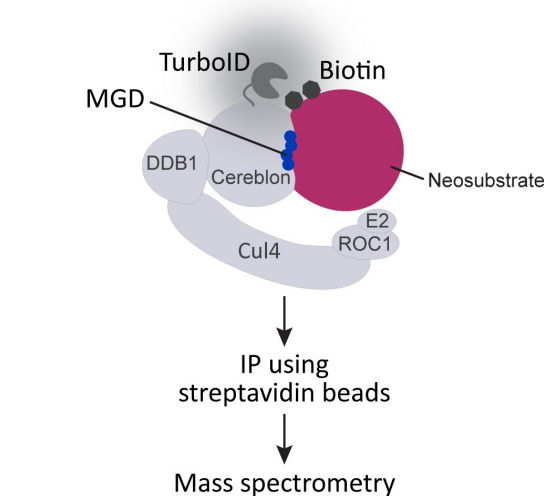
# Glueomics™ Toolbox Accelerates Identification of MGDs

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

## *in vitro* screens

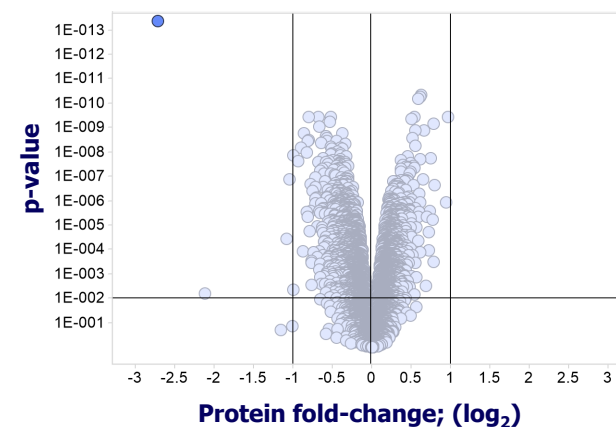


## Chemoproteomics - proximity



Turbo-ID

## Proteome-wide expression



TMT Proteomics to evaluate:

- Proteome-wide changes in protein levels
- MGD selectivity

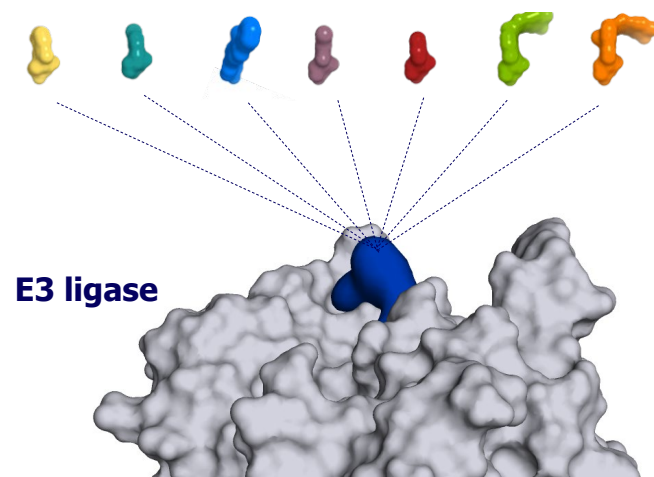
# Rhapsody, QuEEN's *in silico* Engine

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

## *in silico* library generation

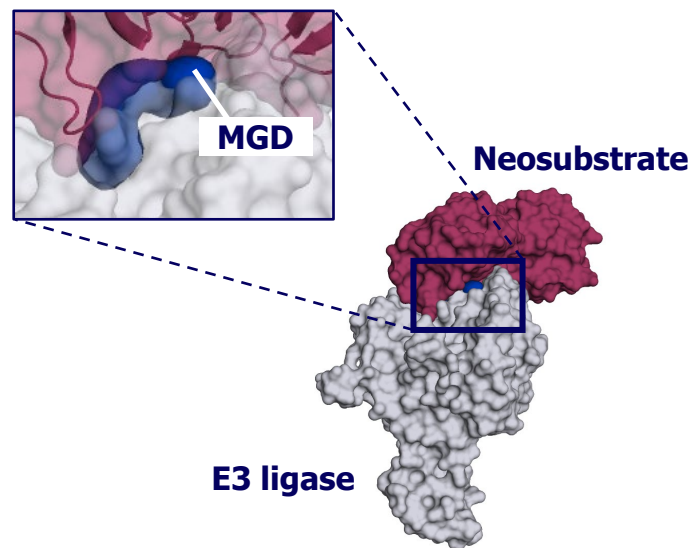
Creation and E3 ligase docking of novel MGDs, expanding our library to engage more targets

### Novel *in silico* MGDs



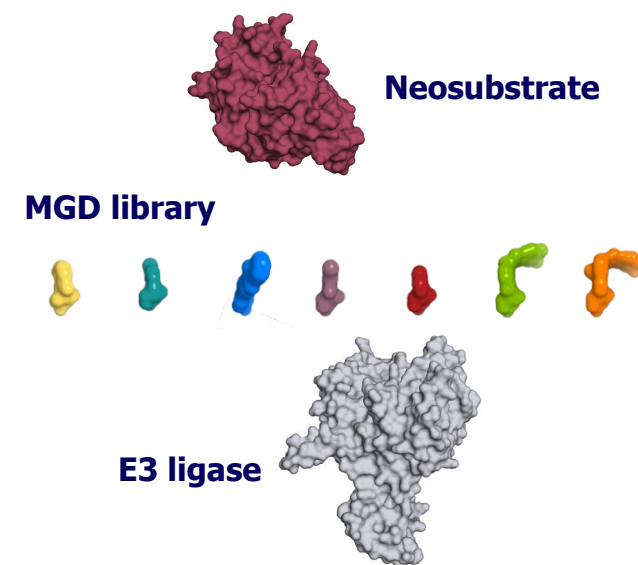
## *in silico* ternary complex models

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

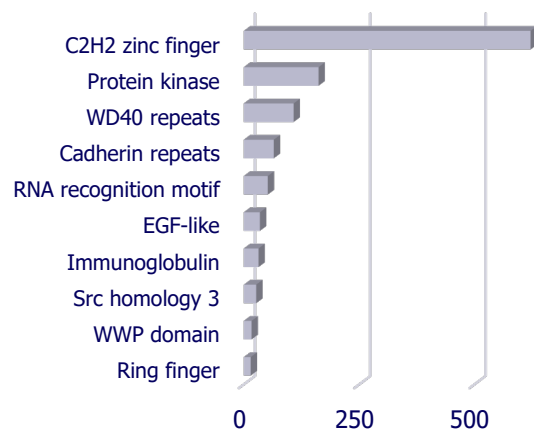


# A Rich, Differentiated Target Space Across Protein Domains and Diseases

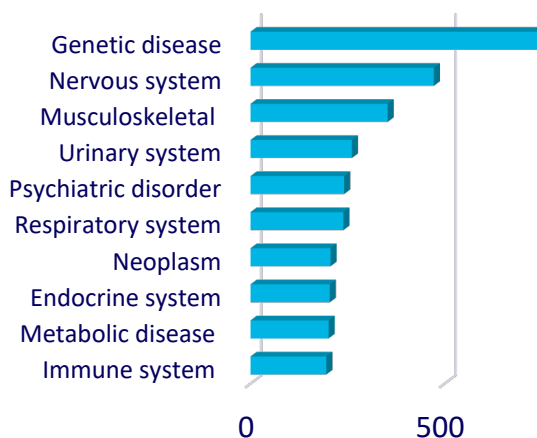
## G-Loop centric Degron Encyclopedia

>3000 proteins contain a predicted G-loop structure

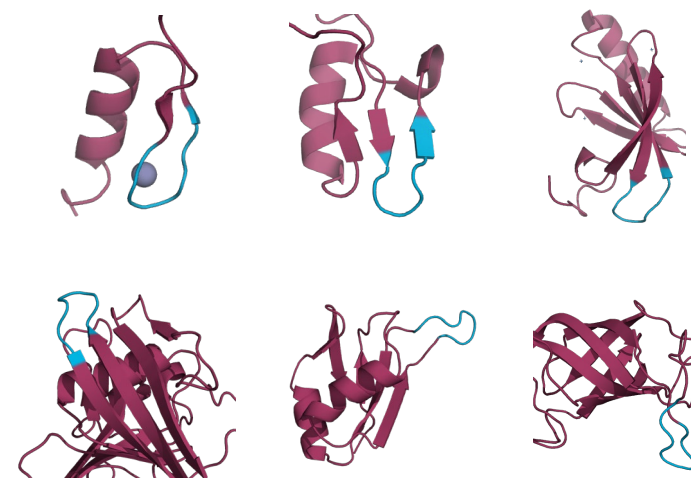
### Degron-containing domains



### 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

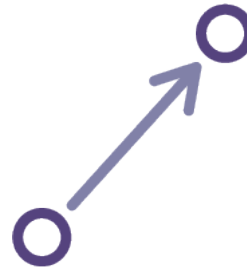


### Targets

Undruggable and inadequately  
drugged degran-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				IND filing mid-2022	
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					

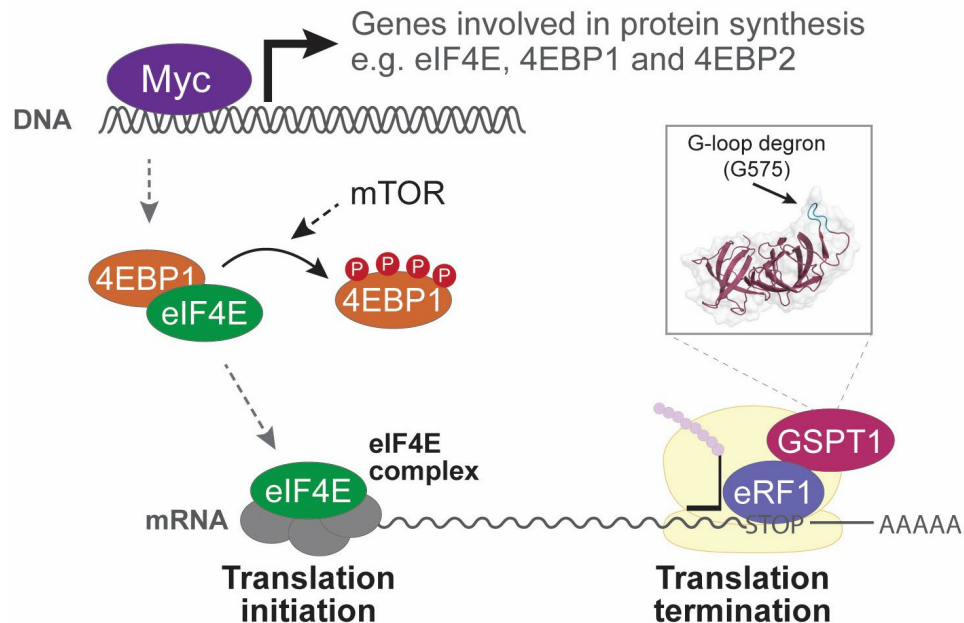


# GSPT1 Program

# 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

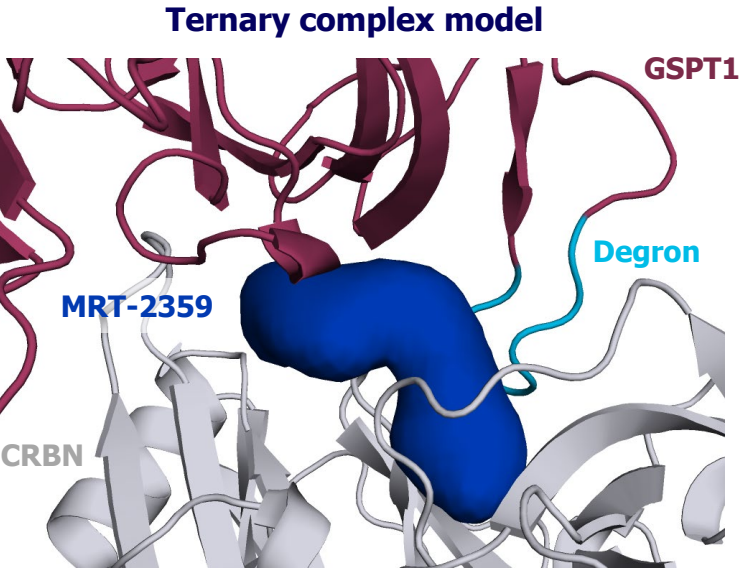
GSPT1 MGDs exploit this **vulnerability** by:

- Disrupting protein translation output
- Reducing Myc-oncogenic signaling

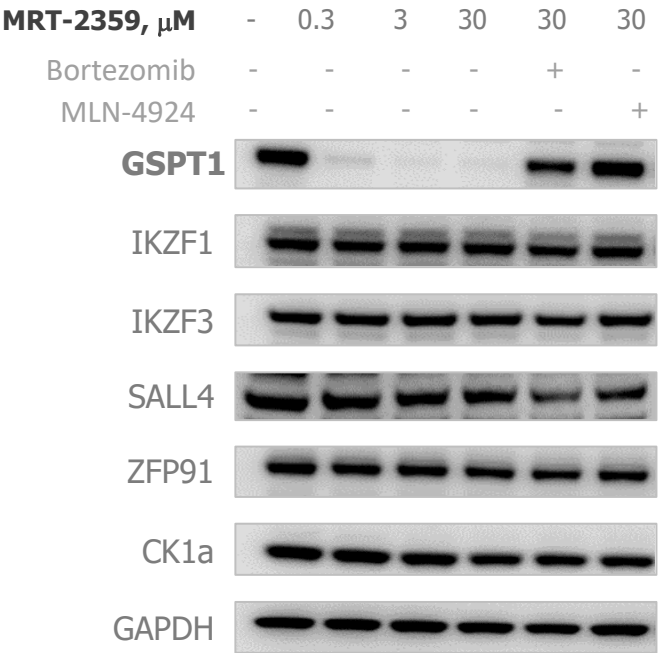
# MRT-2359 is a Potent and Selective GSPT1-directed MGD

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

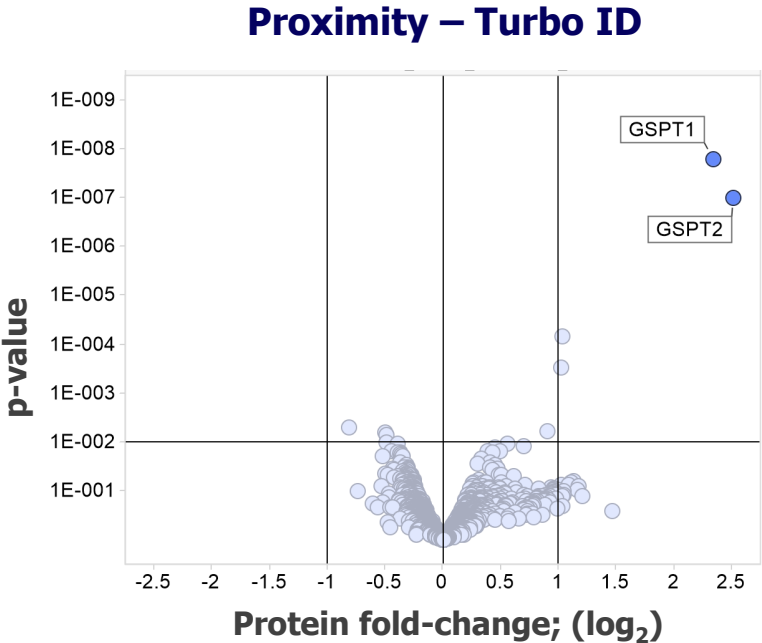
MRT-2359 is a selective GSPT1-directed MGD



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



6hr post treatment in MM1S and Kelly (SALL4)

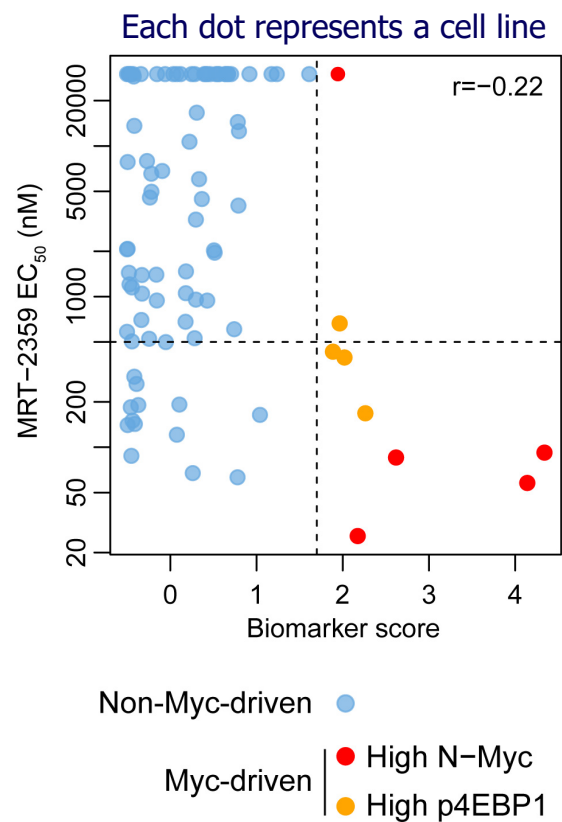


1hr post treatment

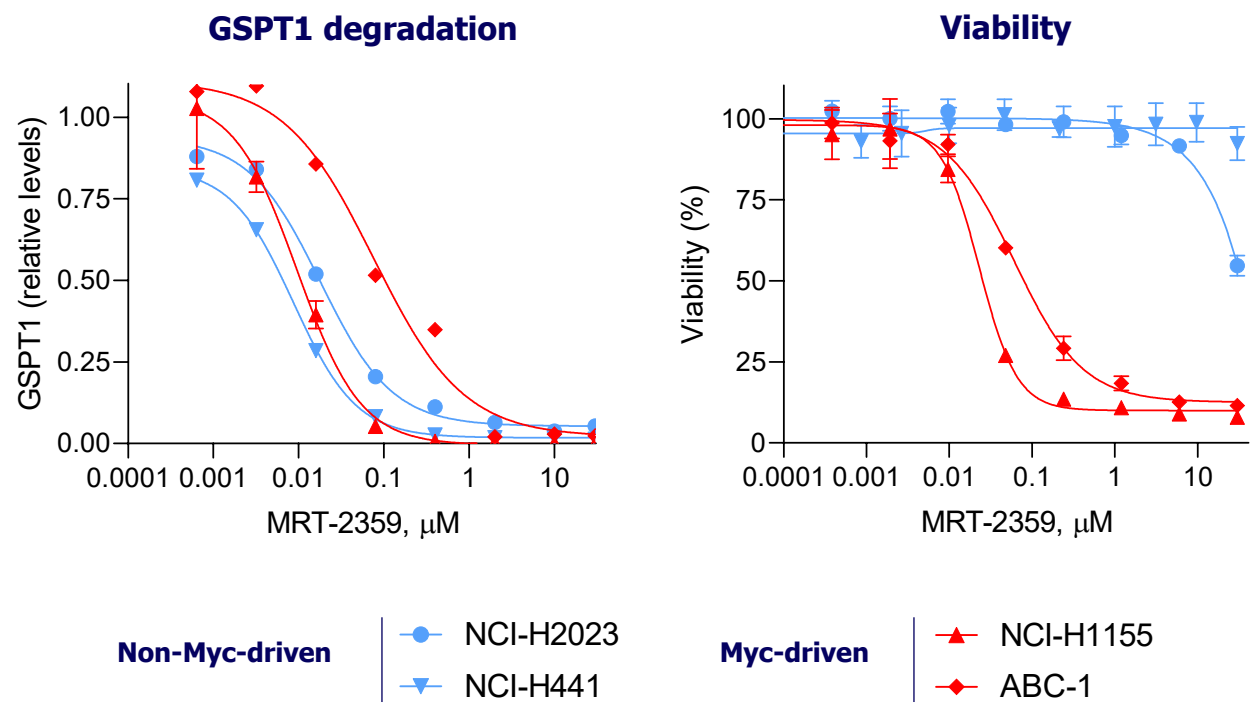


# Myc-driven NSCLC Lines are Highly Sensitive to MRT-2359

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



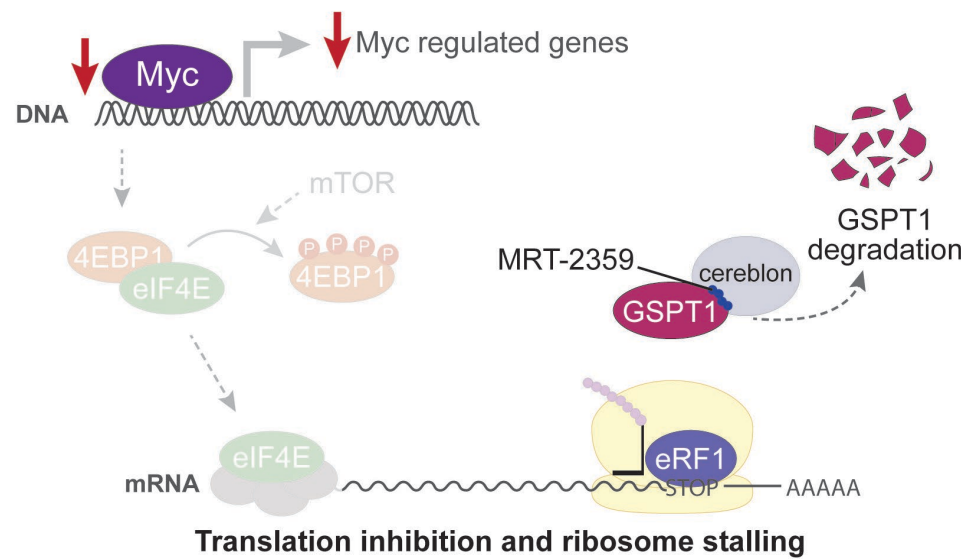
**MRT-2359 induces GSPT1 degradation in all cell models, but selective killing in high N-Myc lines only**



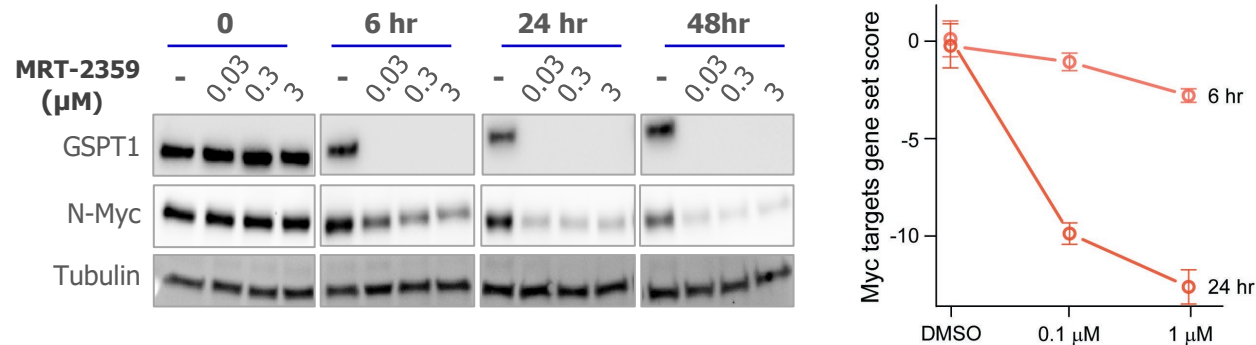
GSPT1 western blot at 6 hr (N-Myc high) and 24 hr (low). 72 hr viability assay (CTG)

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

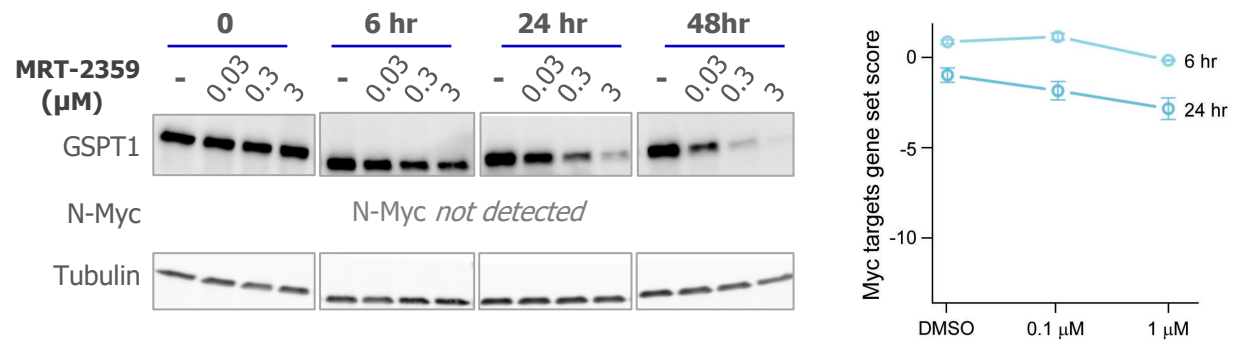
## GSPT1-directed MGD degradation affects translation, a critical vulnerability of Myc-driven cells



### Myc-driven (NCI-H1155)



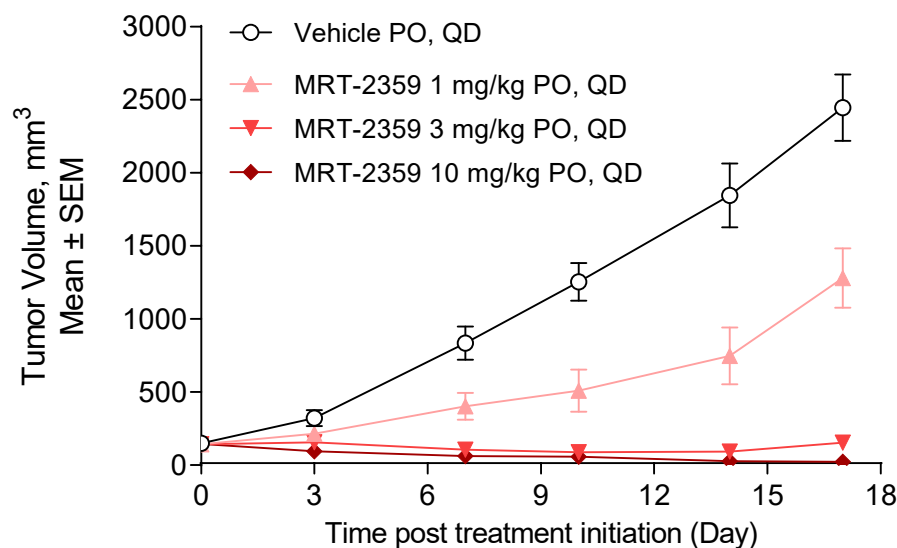
### Non-Myc-driven (NCI-H2023)



# 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

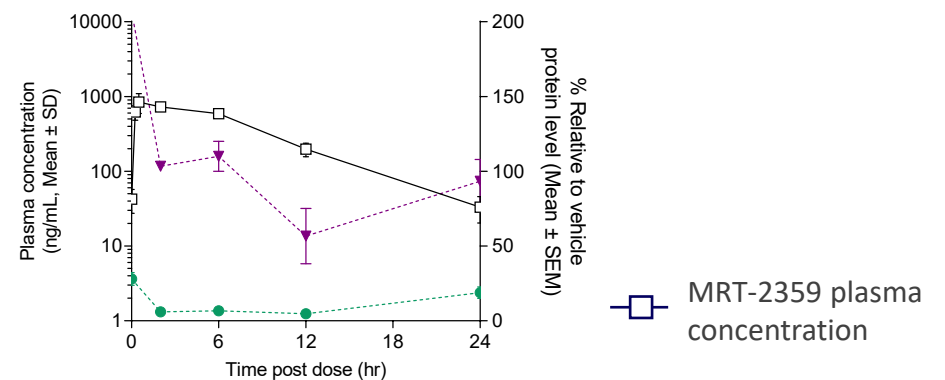
*Similar observations in other high N-Myc expression models (ABC-1, NCI-H1770)*



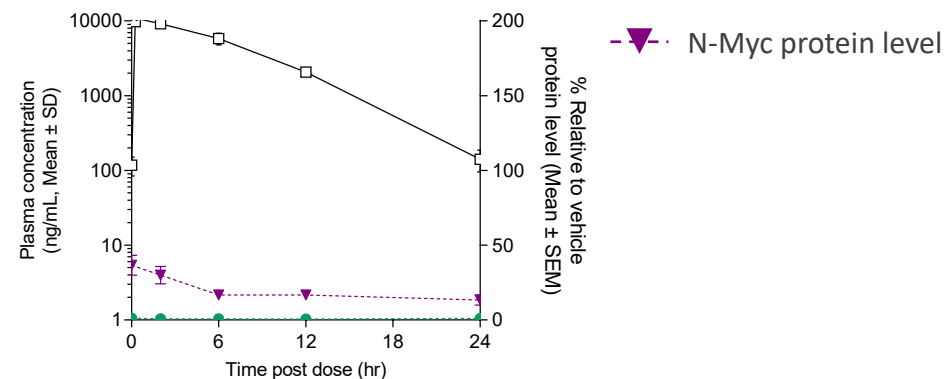
## Dose- and time-dependent degradation of GSPT1 is associated with N-Myc downregulation

Day 5

1 mg/kg

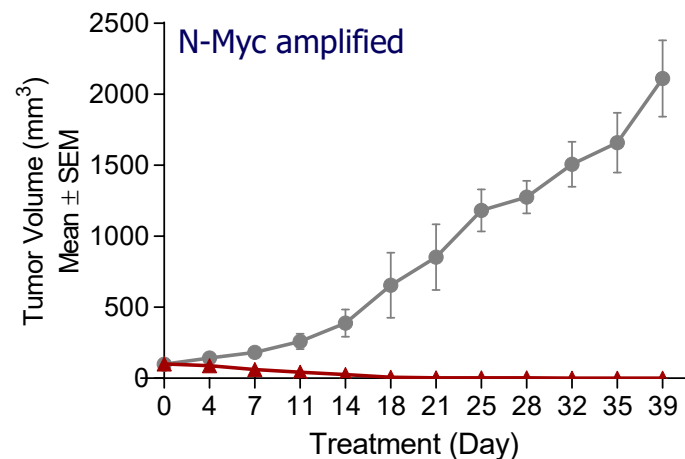


10 mg/kg

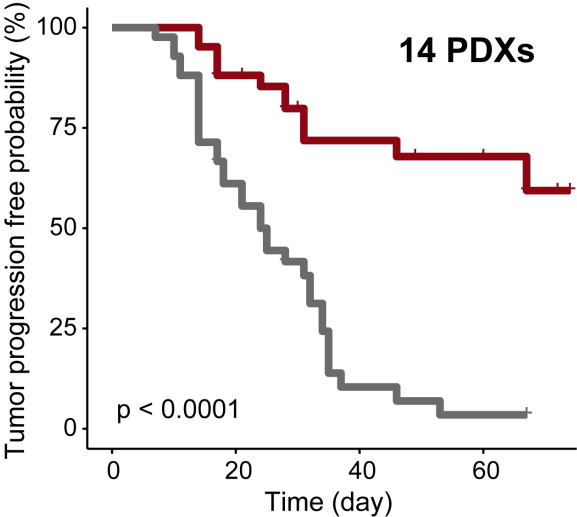


# MRT-2359 Anti-tumor Activity in L- or N-Myc-positive NSCLC PDXs

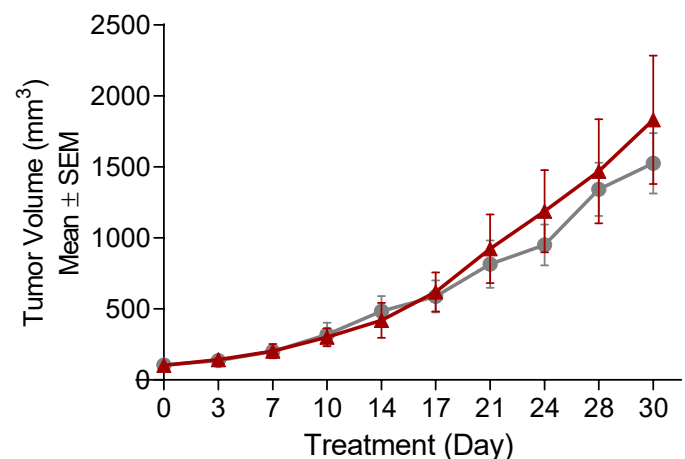
**HIGH**  
L-Myc or N-Myc  
expression



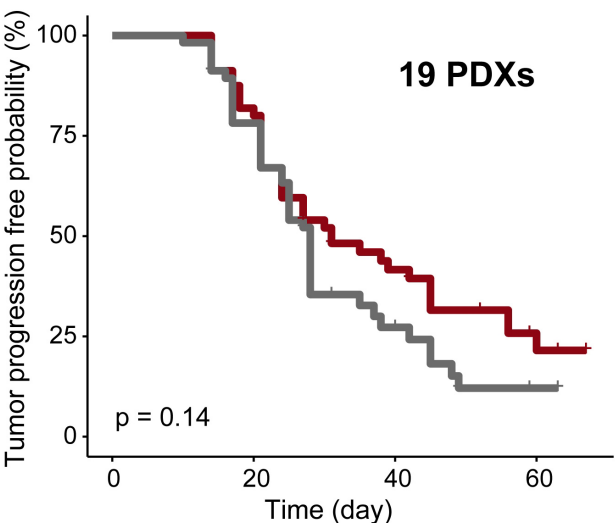
→  
Tumor progression  
to ≥800 mm<sup>3</sup>



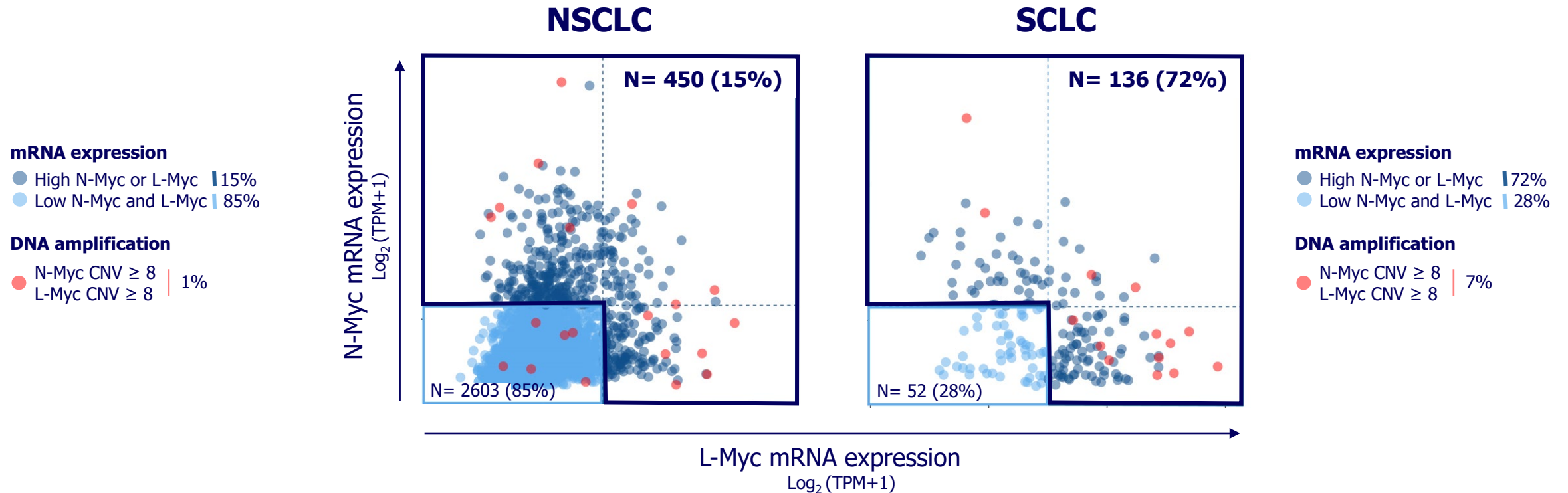
**LOW**  
L-Myc and N-Myc  
expression



→  
Tumor progression  
to ≥800 mm<sup>3</sup>



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

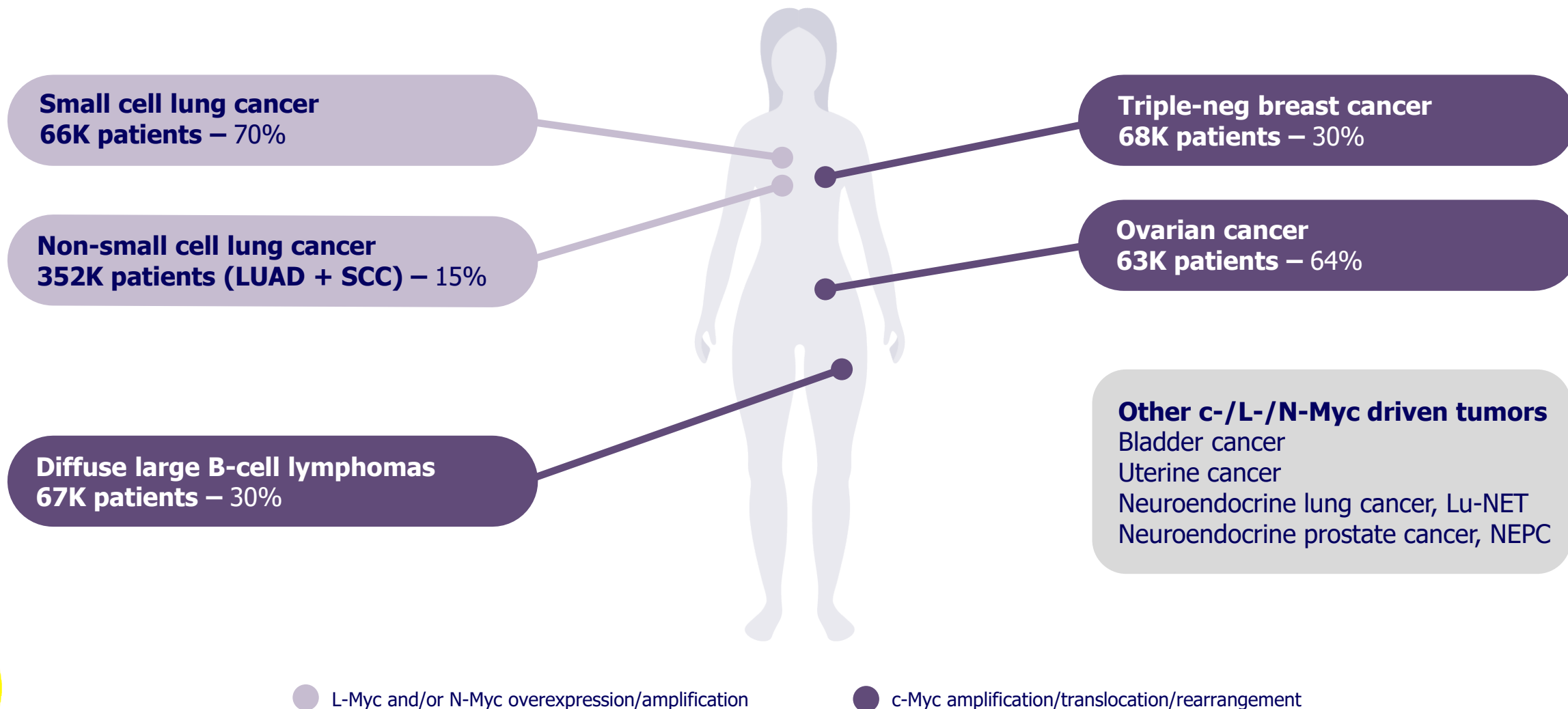


Analyses of real-world molecular and genomic data on 3241 lung cancers performed in collaboration with Tempus Inc.

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

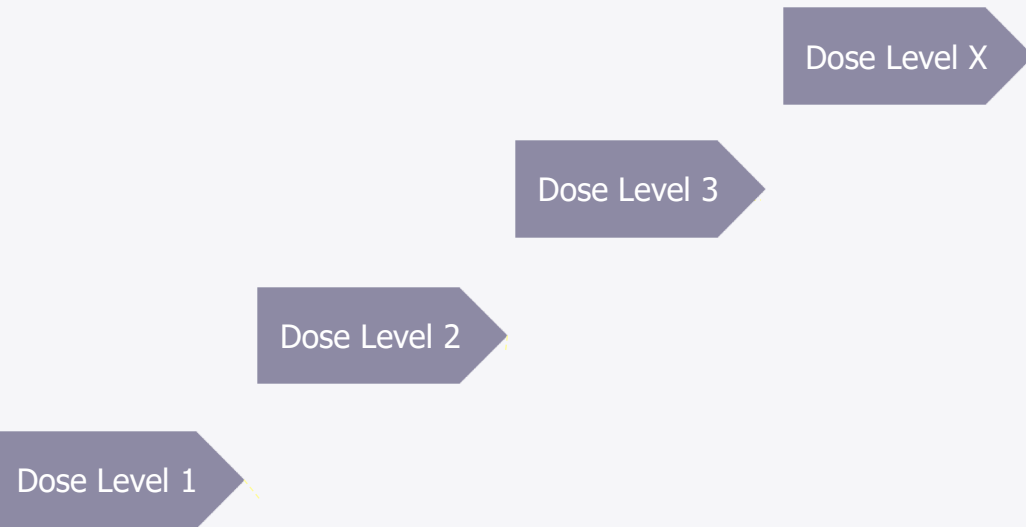


# MRT-2359-001 Phase 1/2 Clinical Development

## 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**

Completing **IND-enabling** activities

**Patient stratification hypothesis** developed

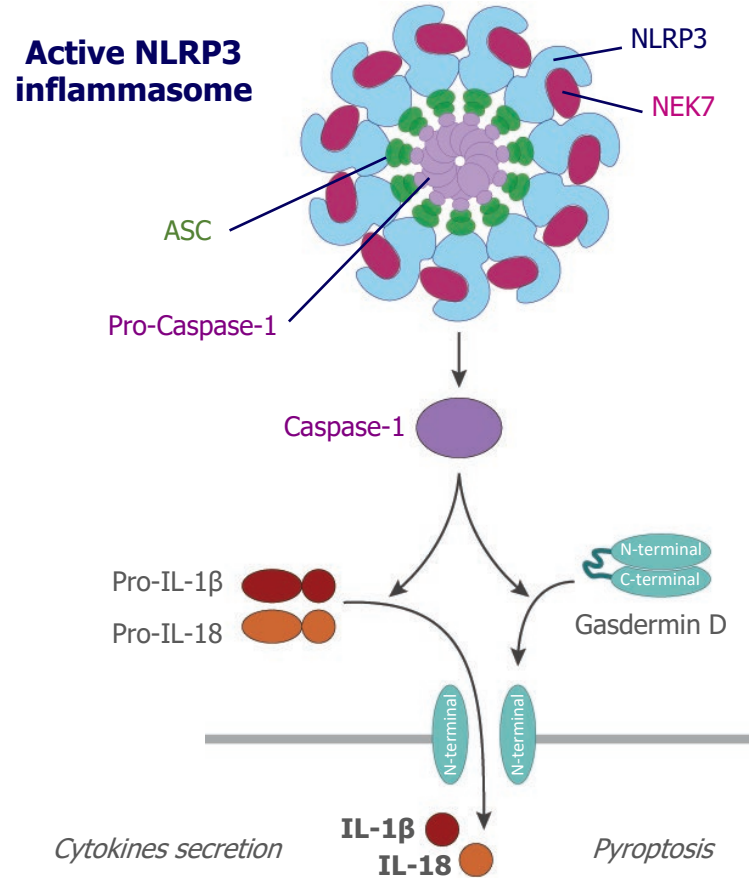
**IND filing  
expected in  
mid-2022**



# 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

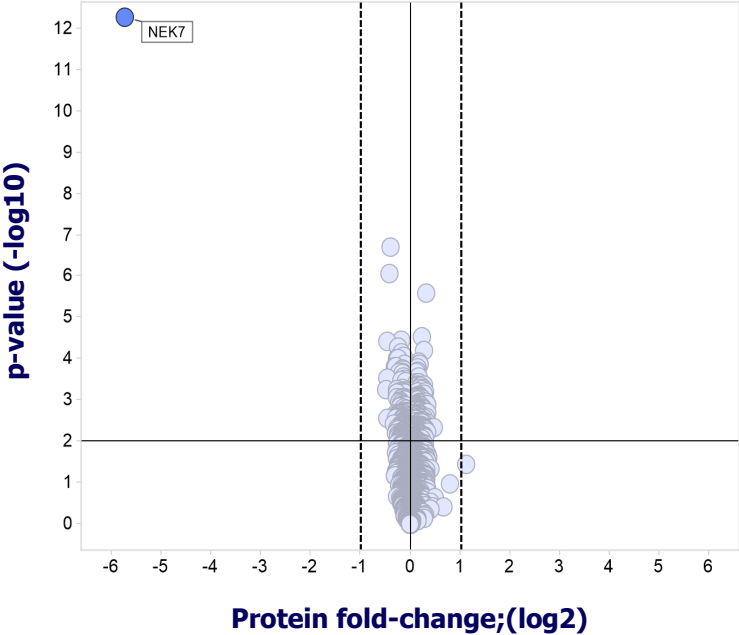
- NEK7 licenses NLRP3 assembly in a kinase independent manner
- NEK7-deficient macrophages are severely impaired in IL-1 $\beta$  and IL-18 secretion

**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)

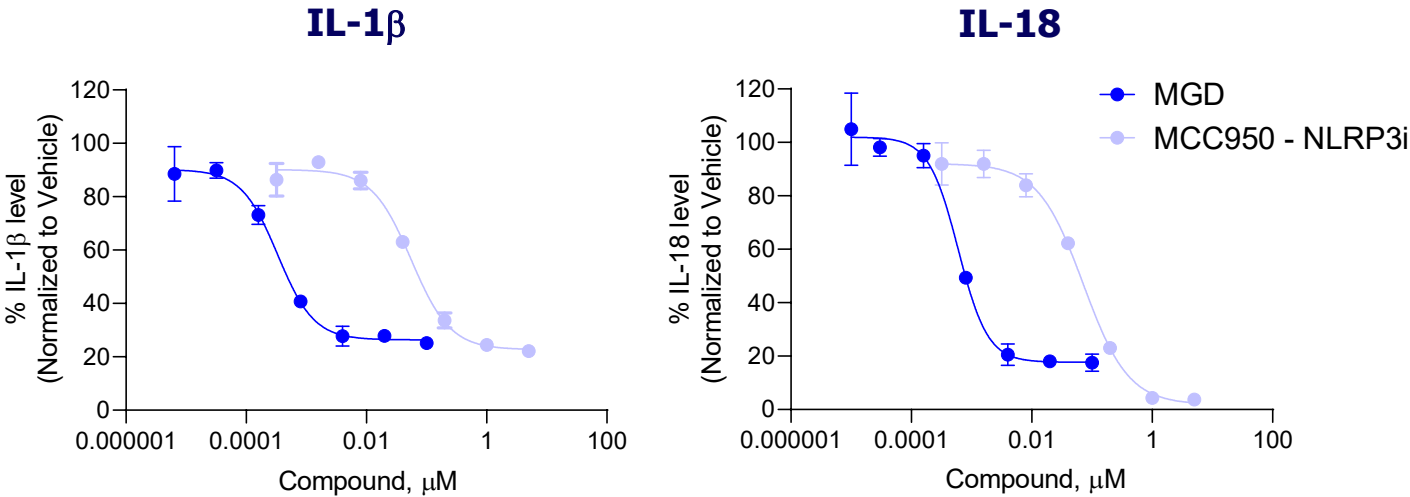
# NEK7-directed MGDs modulate NLRP3 Pathway in human macrophages

NEK7-directed MGD shows high selectivity



TMT Proteomics – U937 24hr post treatment

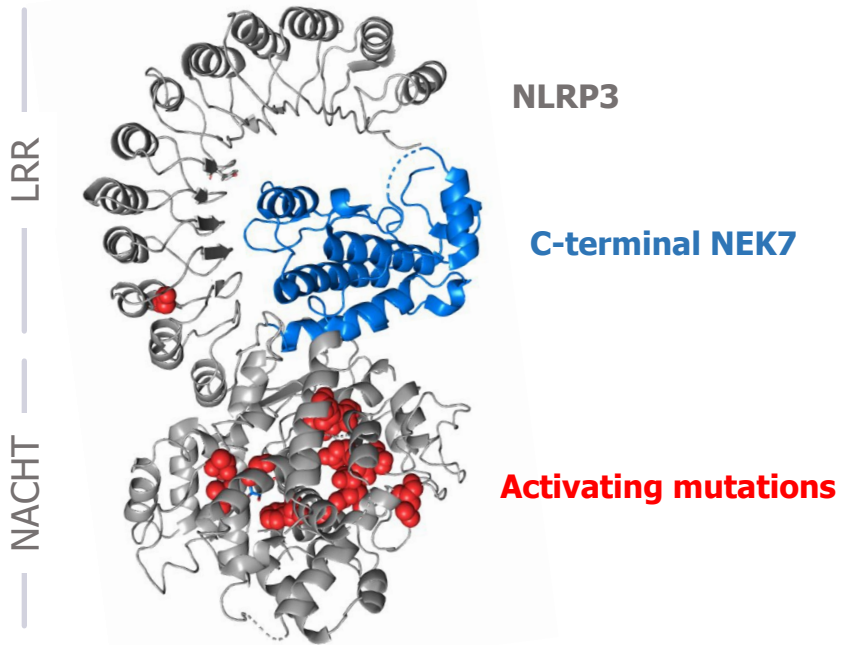
NEK7-directed MGD compared to NLRP3 inhibitor



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

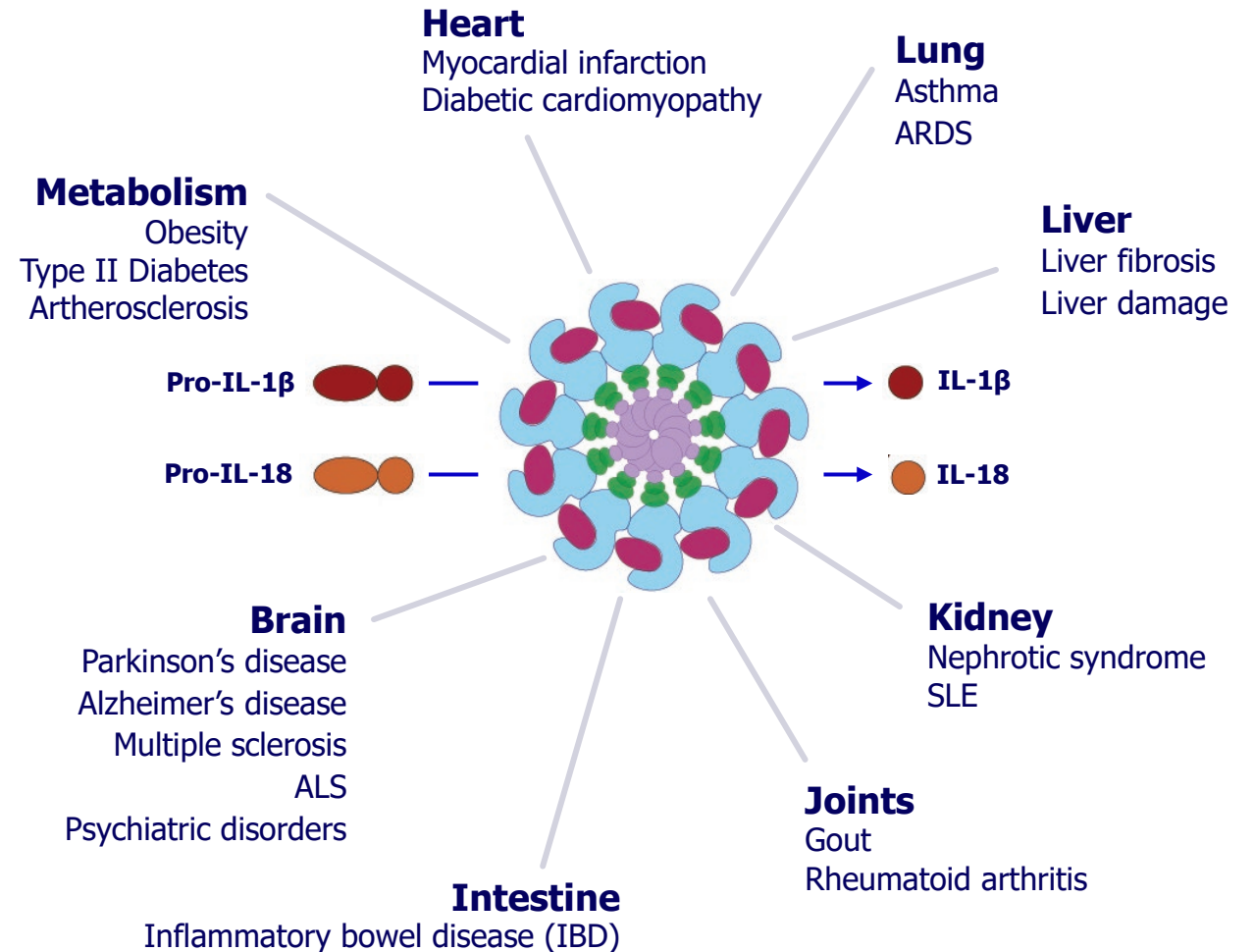
# Overactivation of the NLRP3 Inflammasome in Diseases

## 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

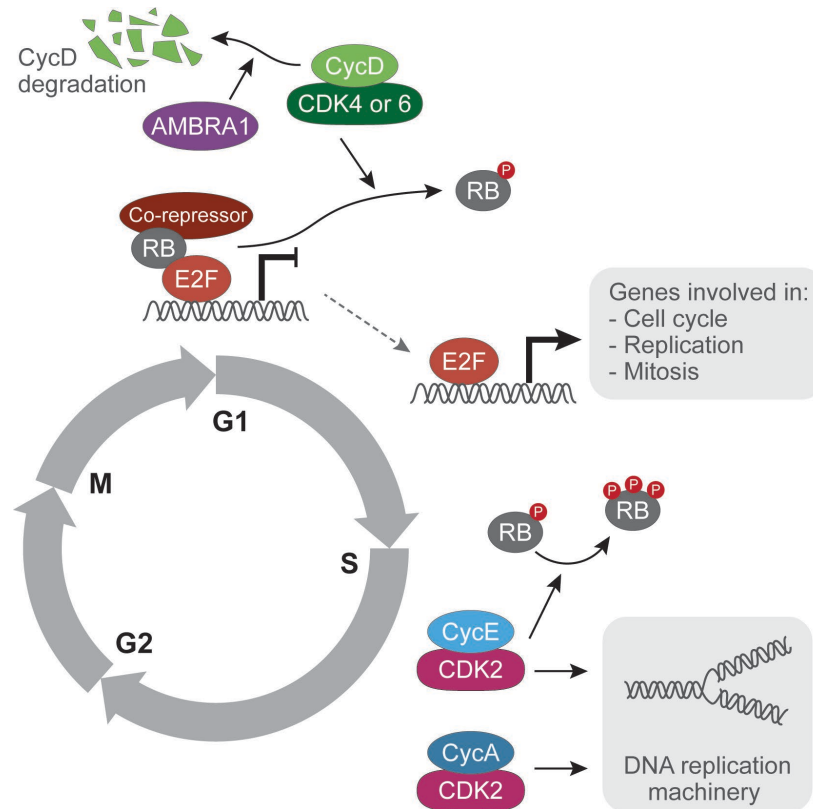




# CDK2 Program

# CDK2 as a Target for Selected Solid Tumors

**CDK2 is one of the key regulators of the cell cycle**



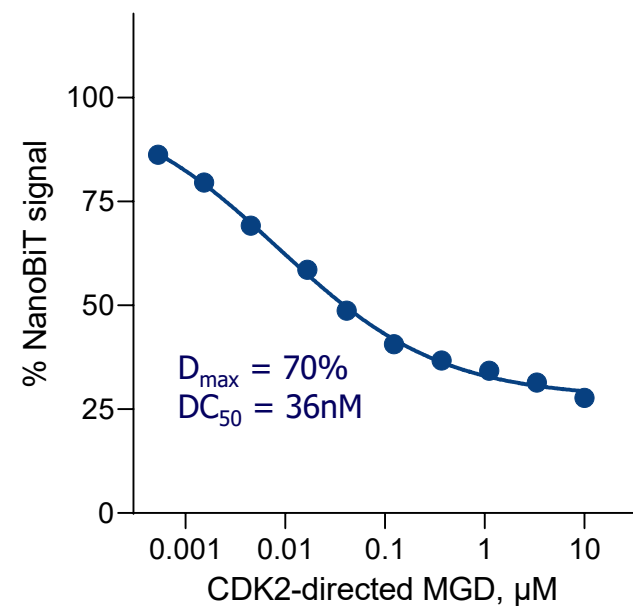
**Therapeutic hypothesis:** Tumors with CDK2 pathway activation by:

- 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)

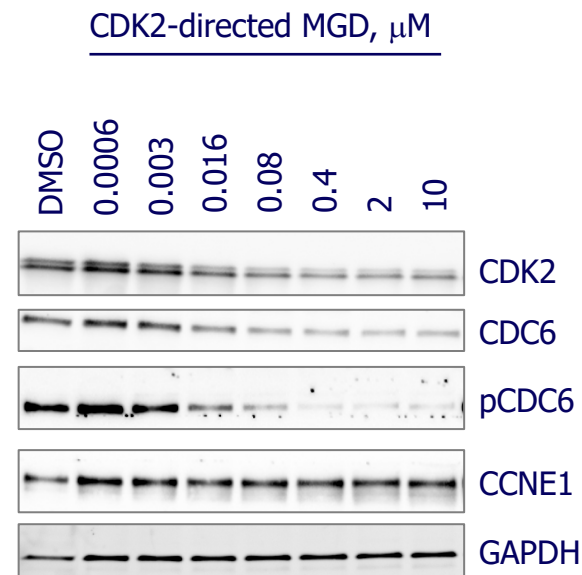
# CDK2-directed MGD Shows Biological Activity in a CDK2-dependent Cell Line

**CDK2-directed MGD induces CDK2 degradation**



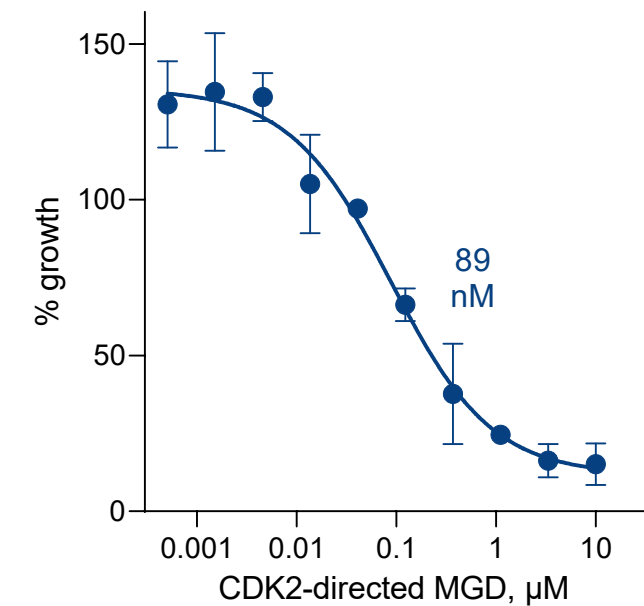
NanoBiT assay in HEK293 cells, 24h

**CDK2-directed MGD reduces CDC6 protein**



MDA-MB-157 cells, 24h

**CDK2-directed MGD inhibits proliferation**



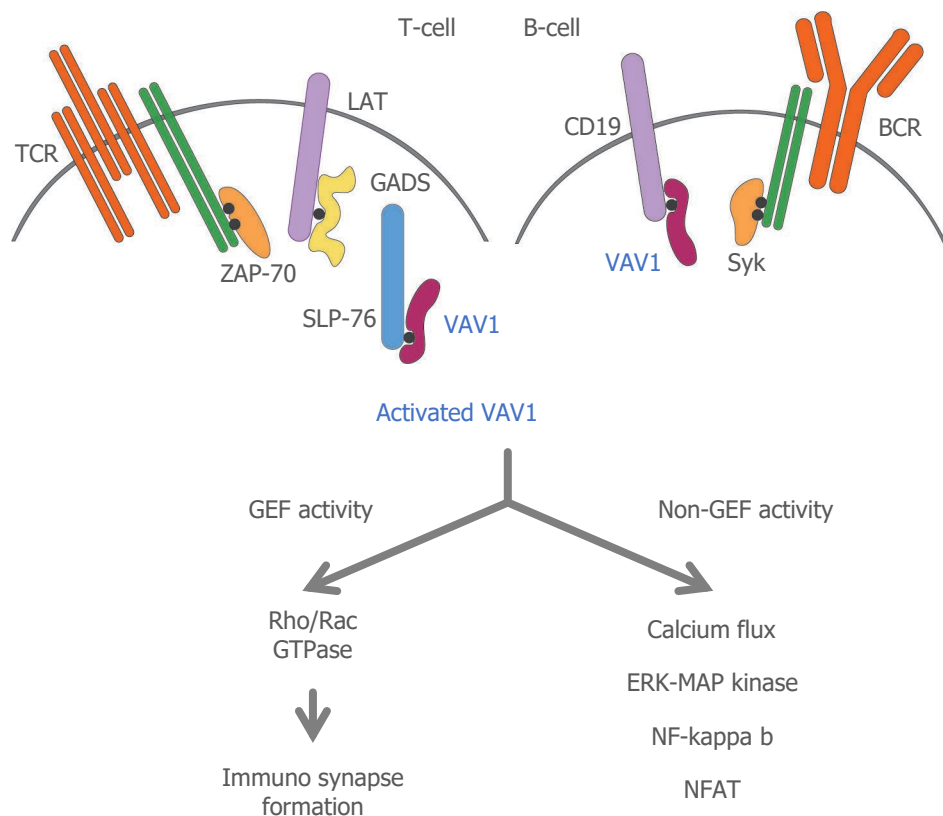
CyQuant assay in MDA-MB-157 cells, 7d



# 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

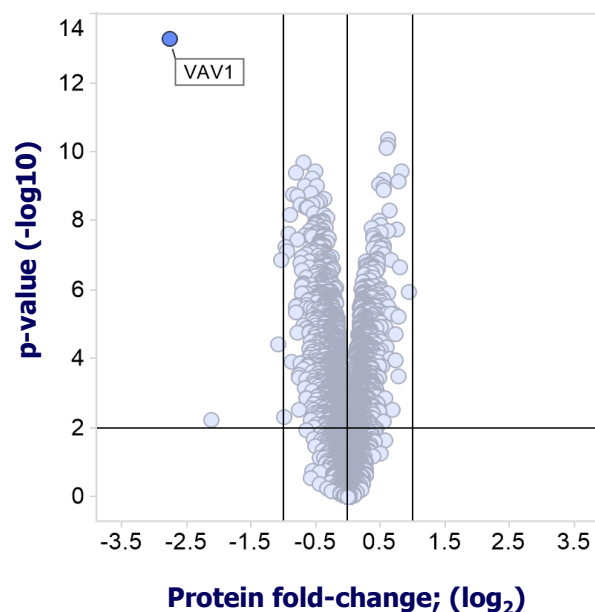
**Clinical Opportunity:** First-in-class VAV1 degraders for

- 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)

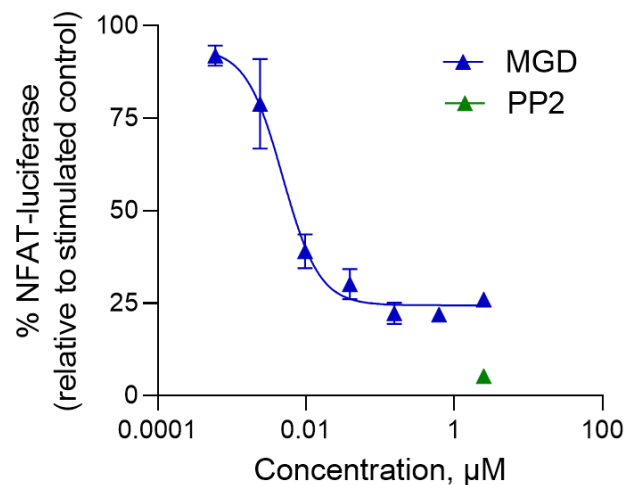
Patient diagnosed prevalence and incidence #s, major markets (US, EU and JP): DRG; myasthenia.org

# VAV1-directed MGDs Demonstrate Pharmacodynamic Activity in T Cells

## VAV1-directed MGD shows high selectivity

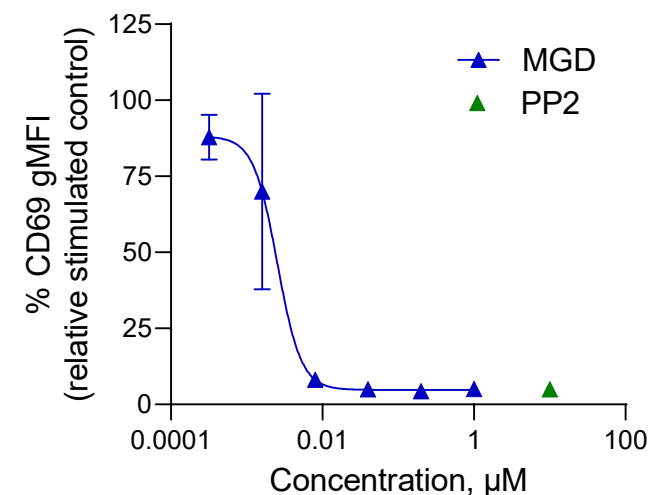


## VAV1-directed MGD inhibits NFAT-luciferase activity



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

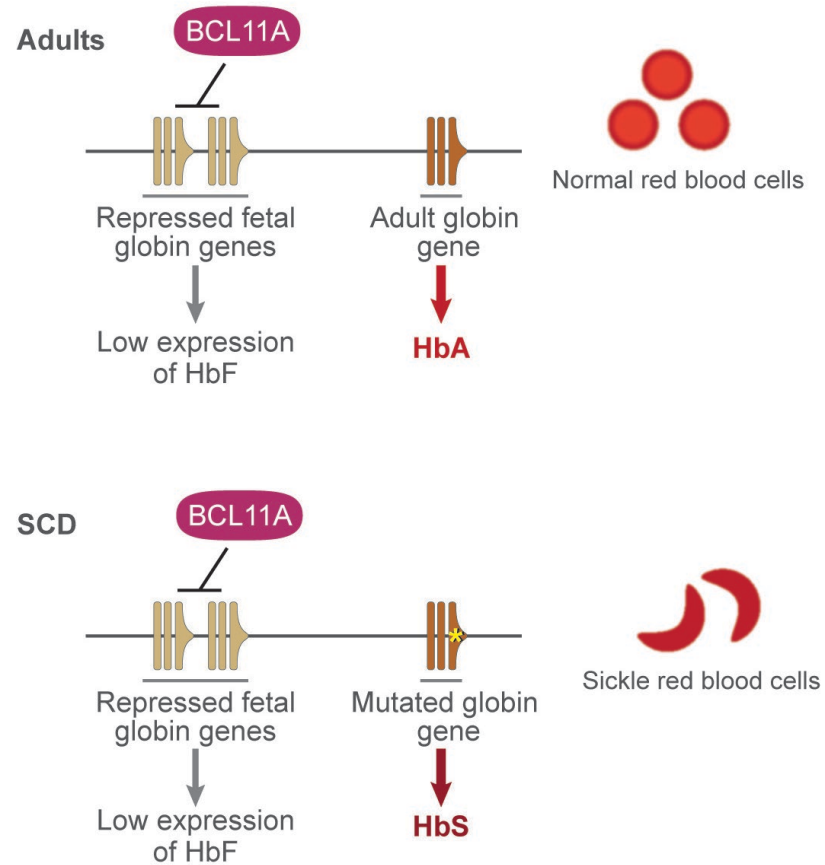


# BCL11A Program



# BCL11A as a Target for Hemoglobinopathies (SCD and $\beta$ -Thalassemia)

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



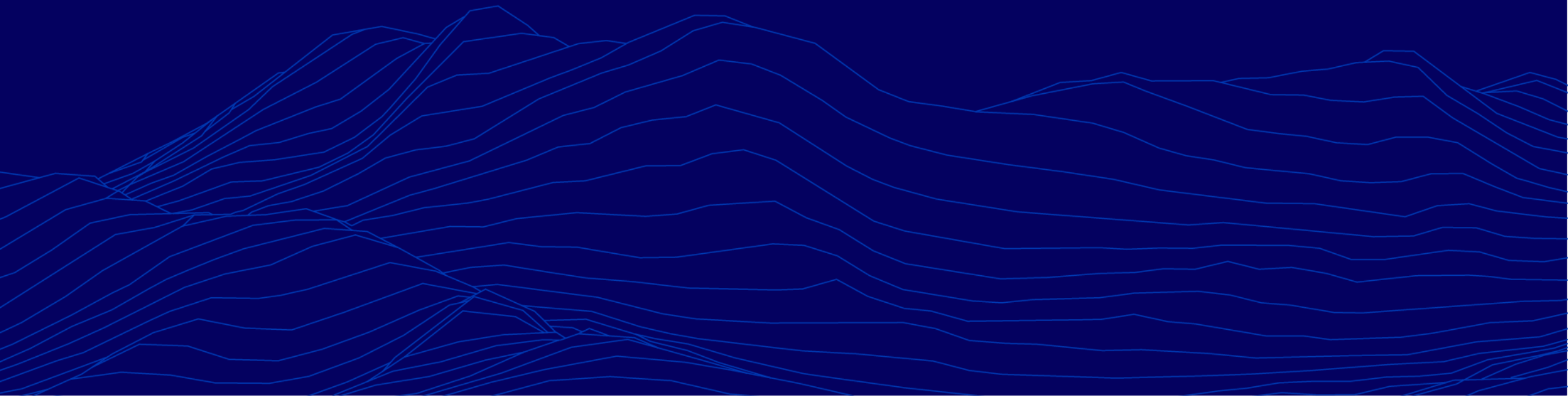
**Therapeutic hypothesis:** Reactivate expression of fetal hemoglobin (HbF) to compensate for mutated adult globin

**Clinical Opportunity:** First-in-class BCL11A degraders for

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



# 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

**IND filing for GSPT1 program expected in mid-2022**; additional programs at various stages of discovery

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



Thank You

