Monte Rosa
THERAPEUTICS

From Serendipity to Rational Design

Taking Molecular Glue Degraders to New Heights

Sept 2021

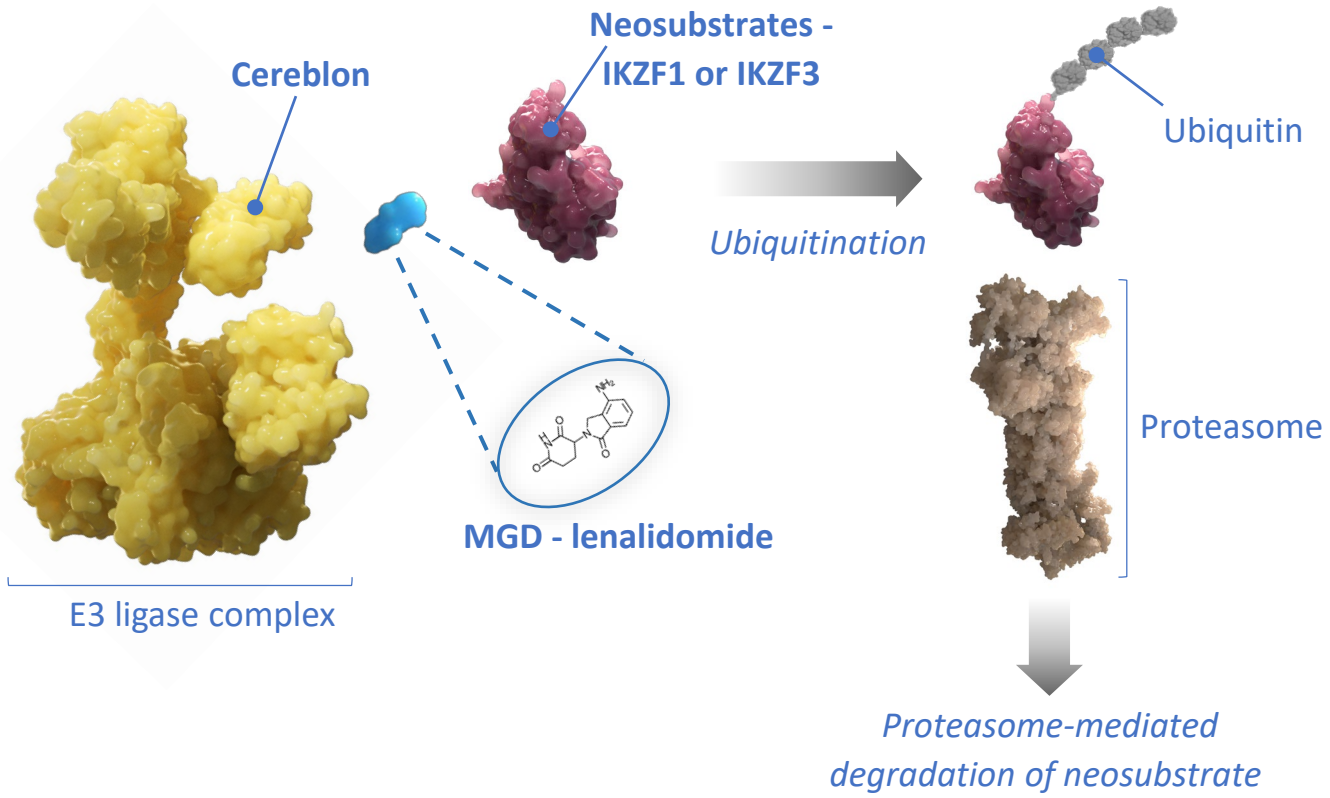
Monte Rosa Therapeutics Overview

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
- **DC selection for lead program in 2021** for GSPT1 degrader targeting Myc-driven cancers
- **Multiple identified programs** targeting high unmet medical needs in oncology and non-oncology indications
- **Experienced leadership & SAB** with deep drug discovery and development expertise and know-how

Molecular Glue Degraders

A powerful and differentiated approach to eradicate disease-causing proteins



- ✓ **Undruggable** target space
- ✓ Favorable **drug-like** properties
- ✓ Clinically **validated**
- ✓ **Systematic** and **selective** reprogramming
- ✓ **Broad** therapeutic application

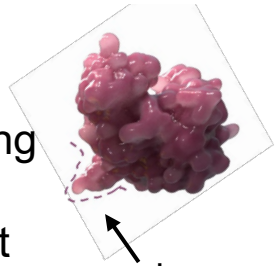
Systematic Chemical Reprogramming of E3 Ligases using MGDs

QuEEN™ Discovery Platform: Transformational Approach to MGDs

Building a unique portfolio of precision medicines addressing high unmet medical need

Degron Encyclopedia

Degron identification using an AI-powered deep neural net (DNN)

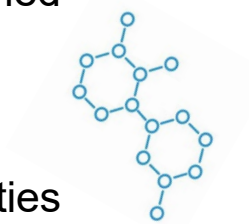


Proprietary Library

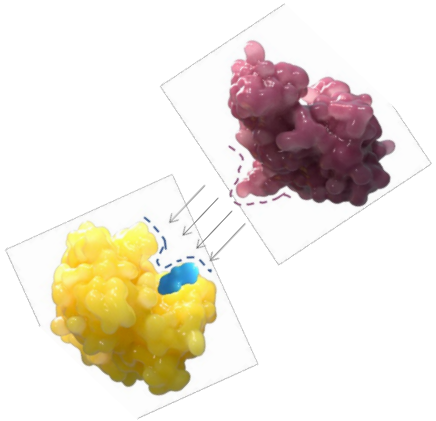
Rationally designed

Diverse and growing library

Drug-like properties



Glueomics Toolbox



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

Proprietary pipeline

- Highly selective MGDs for undruggable and inadequately drugged degron-containing proteins
- Programs with biomarker-based patient selection strategy and clear path to the clinic
- Potential to address a wide range of disease-relevant proteins in oncology and beyond

One Vision™ Modules Connects Novel Degrons to Degraders

Modular AI algorithm suite maximizes external databases to discover targets and MGDs

Inputs

Sequences

UniProt

Structures

RCSB PDB PROTEIN DATA BANK

AlphaFold2

One Vision™
Integrated Degron Mining

Topology
BC Score

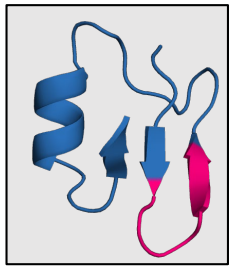
Sequence
DNN

…CKKSGEK…

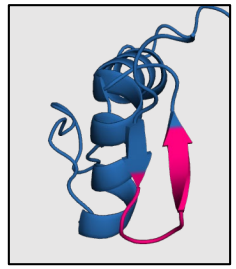
Surface
MASIF

Algorithms trained using MRT lab data

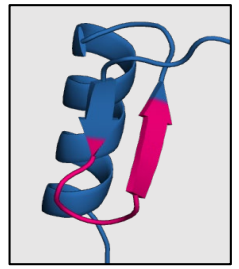
Degron Encyclopedia™



Target X



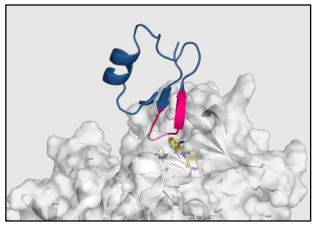
Target Y



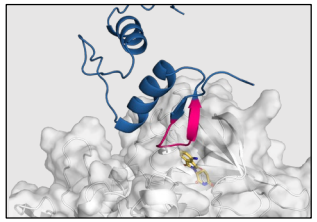
Target Z

~3,000 proteins

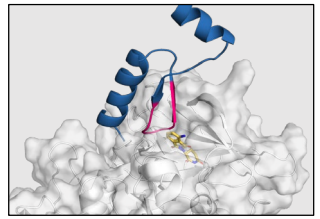
Rhapsody™



Target X



Target Y



Target Z

in silico ternary complex modeling & MGD screening

New Chemical Space: MGD Anatomy and Evolving MGD Library

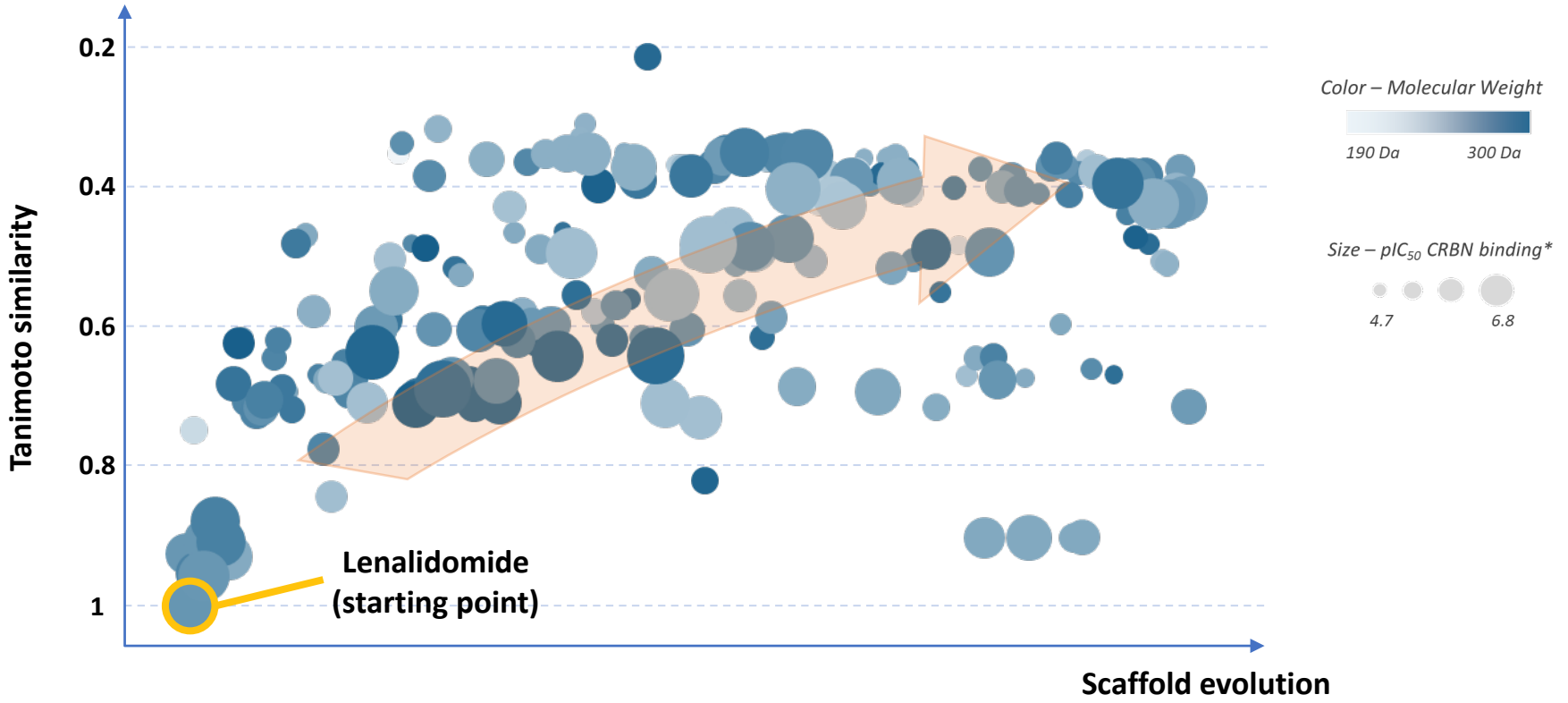
Increasing novelty and structural diversity to match the target space

Understanding MGD Anatomy

Core
Degron domain

Warhead
Cereblon binding domain

Increasing the Core-Warhead Chemical Diversity



>200 unique scaffolds validated with **increasing diversity**, confirmed **binding** and **structural insights**

Glueomics Toolbox - Biomolecular Sciences

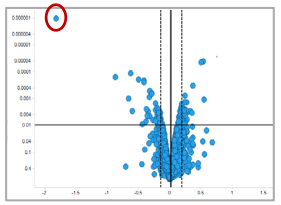
A suite of compound profiling assays to support platform and pipeline

Platform
(Degron Prediction, New Target Space)

Target ID & Validation
Degron Discovery

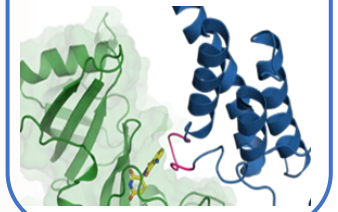
Quantitative Proteomics

Proteome-wide quantitation



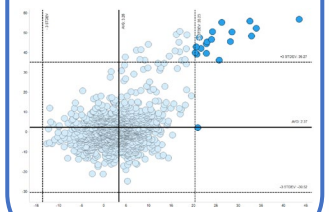
Structural Biology

Crystallography/ Cryo-EM



Cellular Profiling

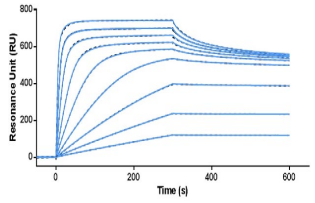
HiBiT/IF/Nano-BRET



Transcriptomics

Biochemistry/Biophysics

SPR/FP/MST/HTRF



Structure-Degradation Relationship to Drive Chemistry Optimization

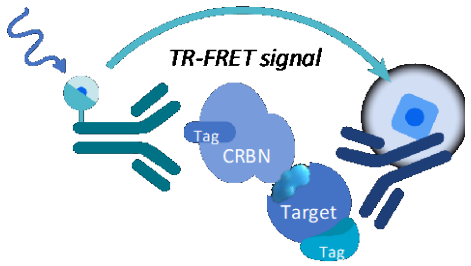
Pipeline
(Lead Optimization)

Fully integrated workflow enabling target ID, validation and rapid design-build-test cycles for chemistry optimization

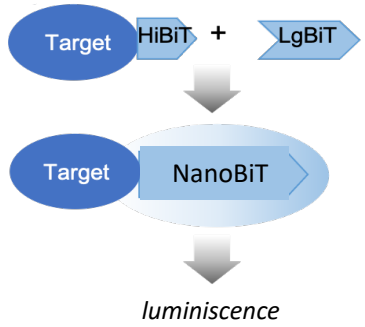
In-house Capabilities Accelerate Prediction-to-Validation

Matching target space to chemical space

In-vitro Screens

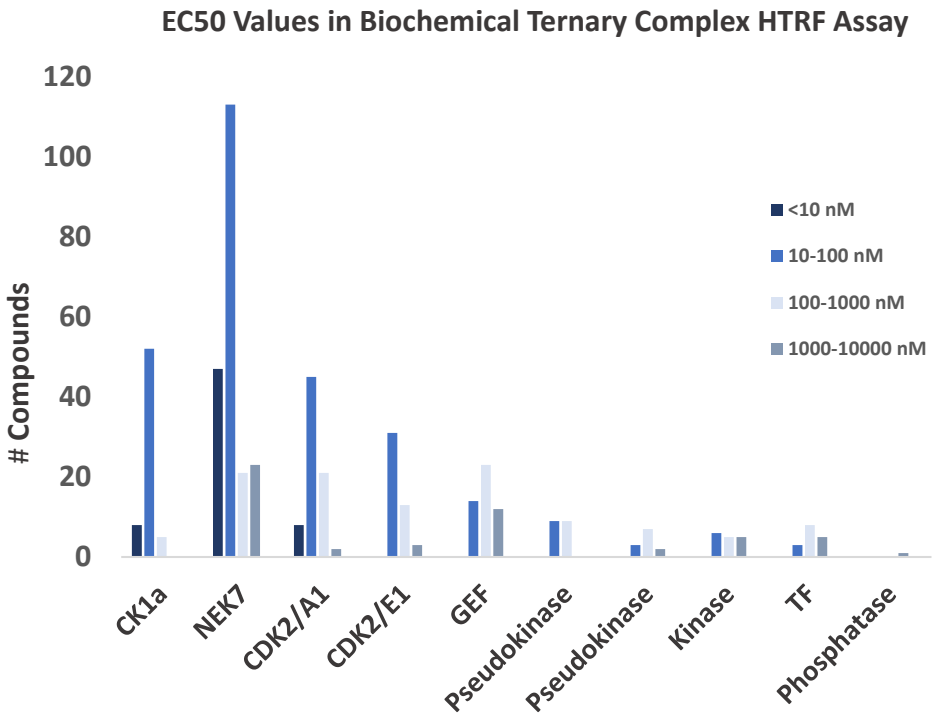


biochemical

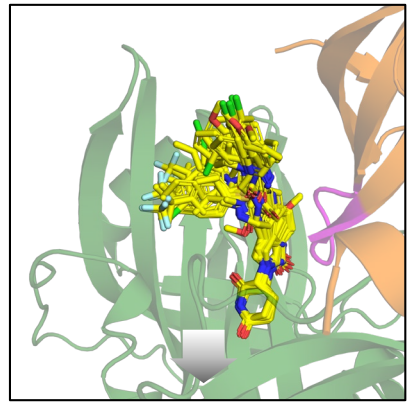


cellular

Results



In-silico Screens



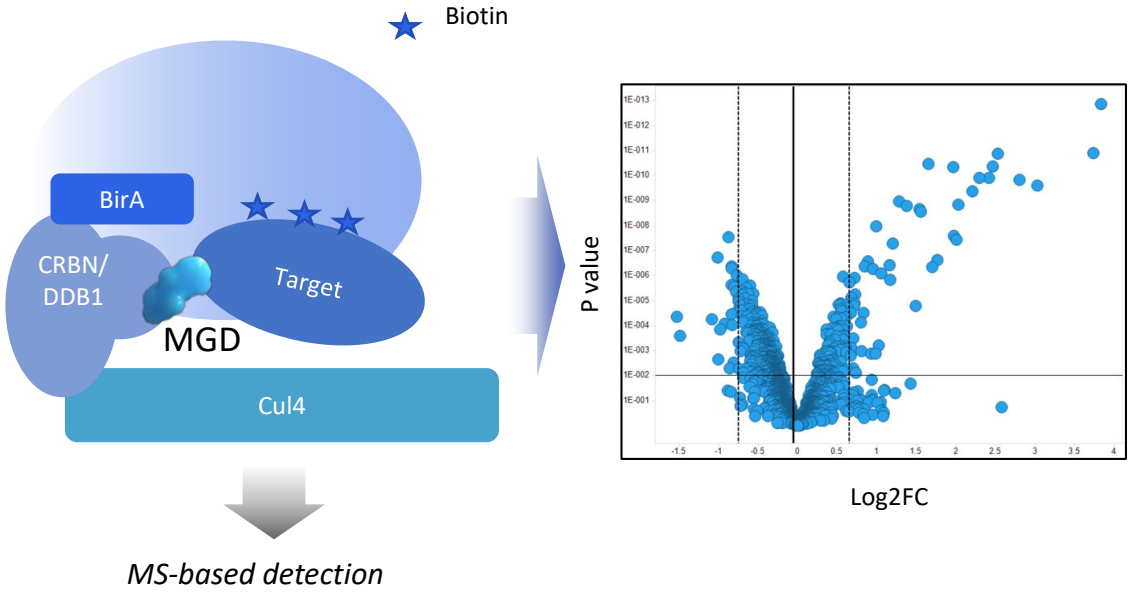
In-silico prediction of ternary complex formation using Rhapsody™

Multiple screening formats enable **rapid identification** and **validation** of **MGDs** for **novel G-loop targets**

Chemocentric exploration of MGD space

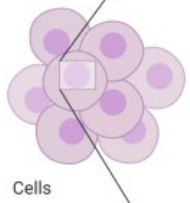
Exploring target space in a degron agnostic fashion through cellular assays

HT Proteomics



Turbo-ID proximity ligation labels
CRBN-proximal proteins with biotin

Cell Based Phenotypic Screens



Unbiased cellular screens
e.g. reporter assays, synthetic lethality phenotypic models

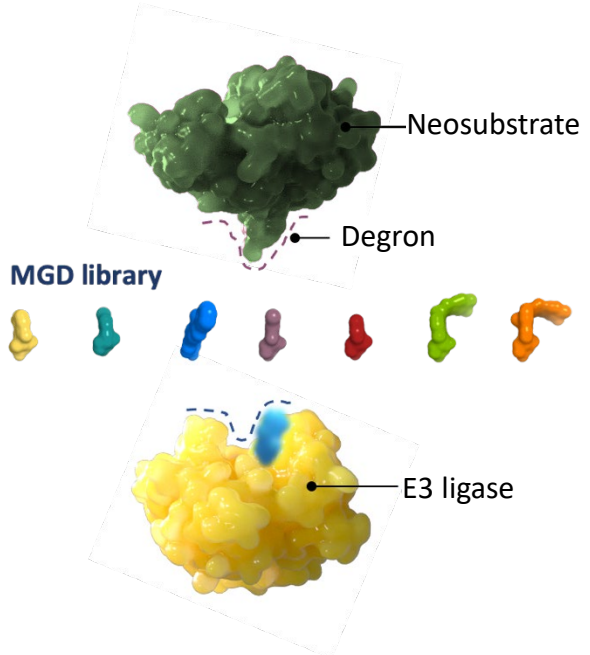
Transcriptomics

Rapid target deconvolution enabled through multiple genetic and chemical tools

Rhapsody, QuEEN's *in silico* MGD Engine

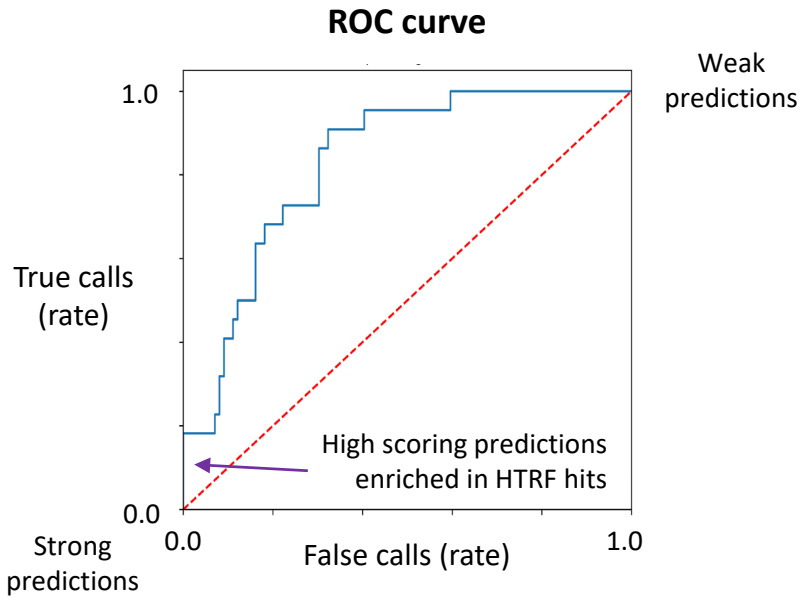
in-silico screening identifies hits for evaluation and predictive models

in silico MGD screen



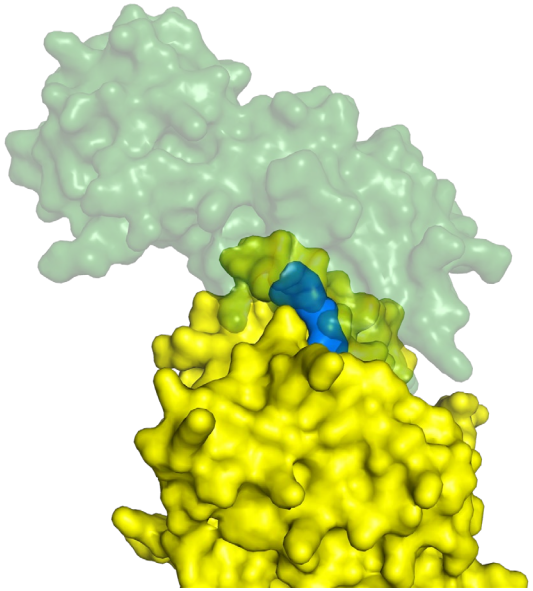
Screen ternary complexes

Compare GSPT1 in silico hits to lab



Rhapsody prioritizes MGDs identified in HTRF screens

Predictive models



GSPT1-MRT-048-cereblon

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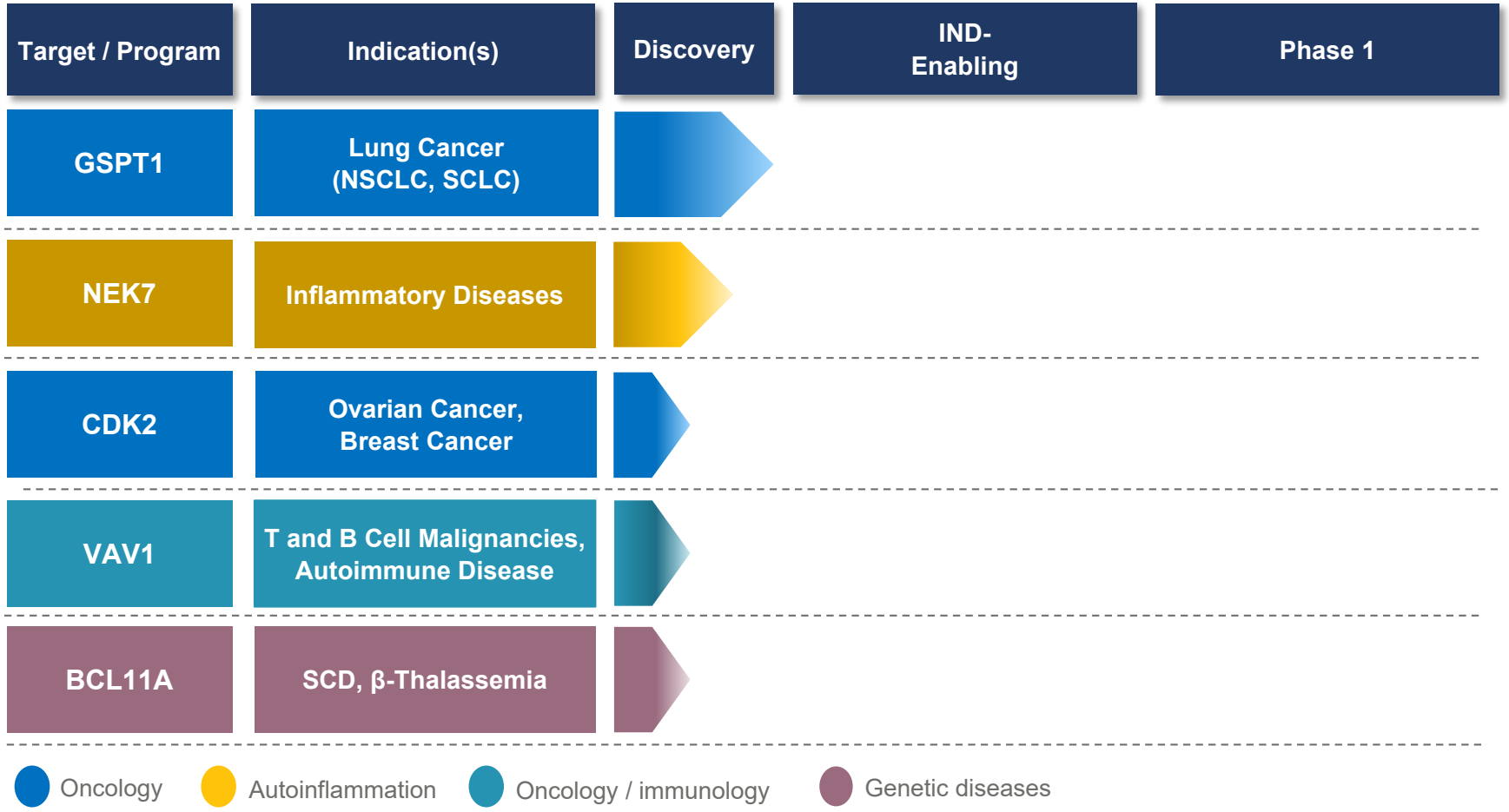
Monte Rosa Pipeline

Monte Rosa Pipeline

Rapidly advancing wholly owned MGD programs



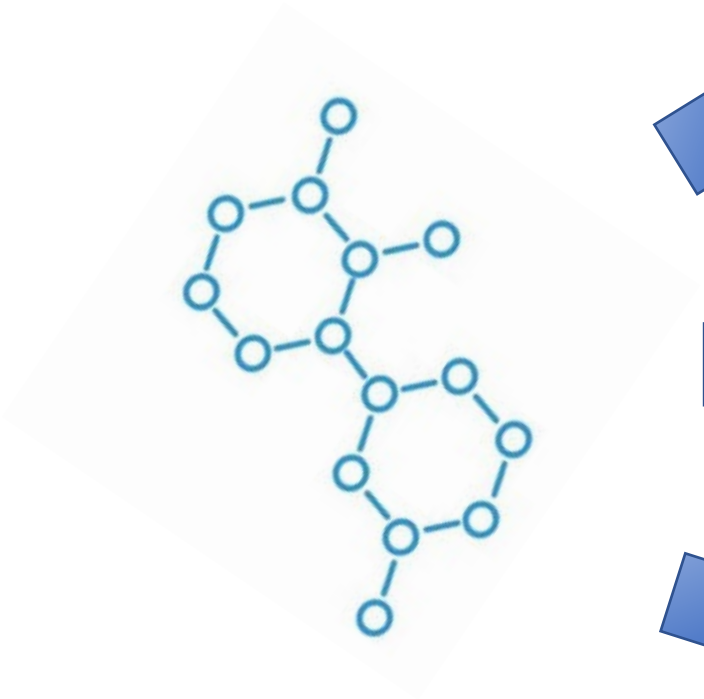
+ other undisclosed programs

Vignette

Rationally designing MGDs with highly selective degradation profiles

Selectivity of MGDs

Multiple Approaches to Achieve Desired Selectivity



Selective screening hits from our MGD Library
e.g., NEK7 for inflammatory disorders

Medicinal chemistry optimization against known neosubstrates
e.g., GSPT1 for MYC-driven cancers

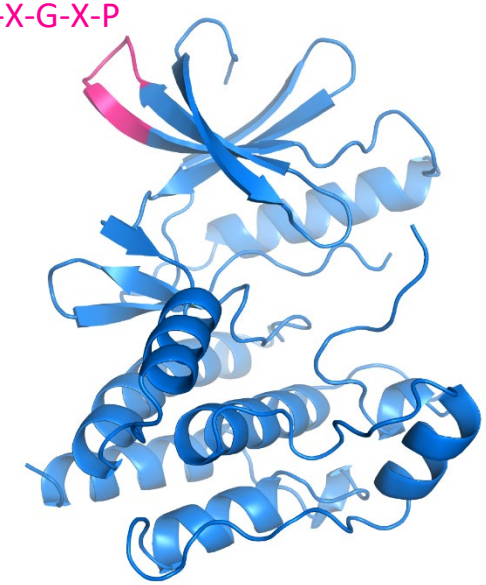
Medicinal chemistry optimization against other proteins and family members
e.g., CDK2 for solid tumors

NEK7: Hits Identified from MGD Library Screen

NEK7 is a key component of the NLRP3 inflammasome

NEK7 contains a highly defined degron

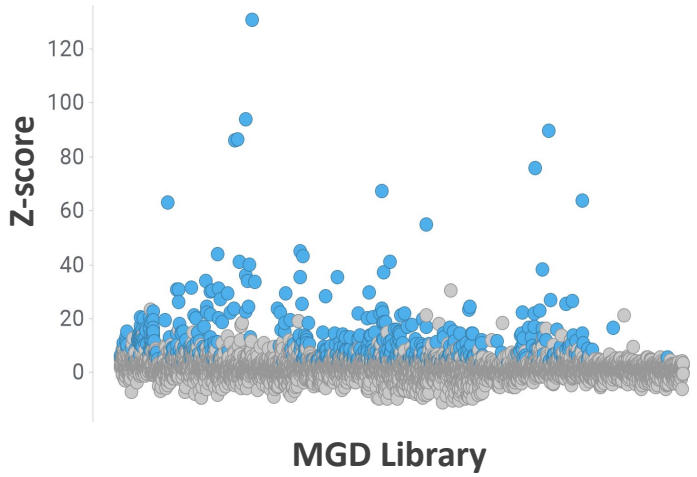
Degron
X-L-X-X-G-X-P



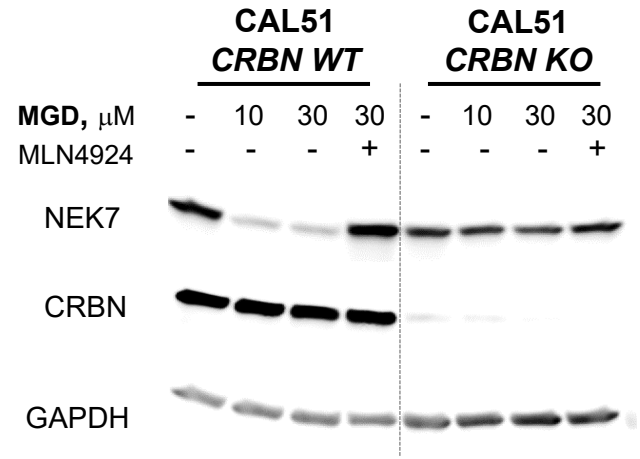
High structural similarity to CK1α

Library screen identifies multiple MGDs to NEK7

Ternary complex formation assay (HTRF)



NEK7-directed MGD activity is cereblon-dependent

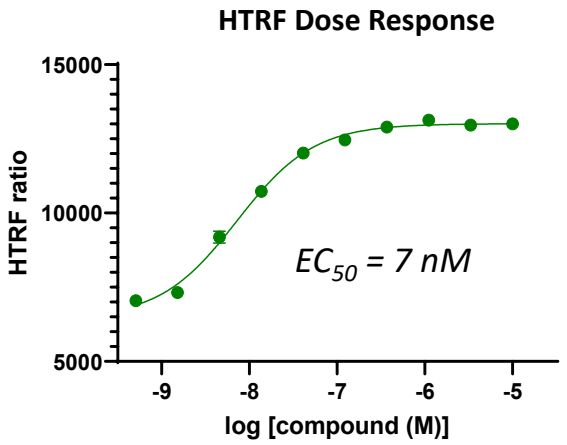


Western blot – 6hr post treatment

NEK7-directed MGDs are Selective for NEK7

Selectivity confirmed biochemically and by proteomics profiling

MGDs are biochemically selective for NEK7

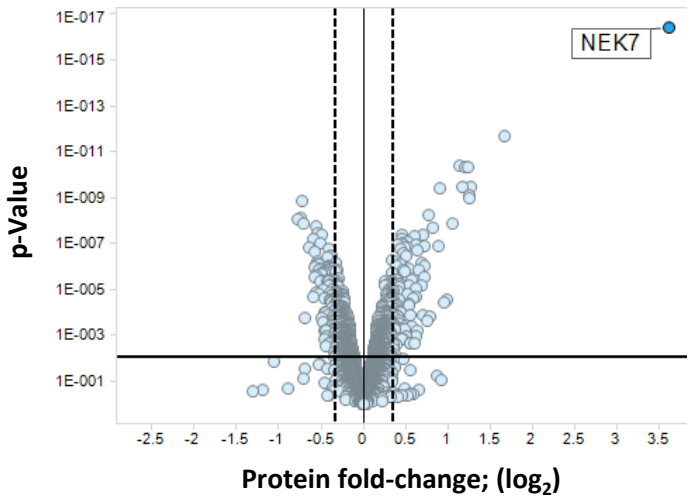


Single-point HTRF screen selectivity

Target	Z-score
NEK7	**21.9**
CK1α	-0.2
GSPT1	1.1
XXXX	1.4
XXXX	0.3
XXXX	0.7
XXXX	1.0
XXXX	0.9
XXXX	0.0
XXXX	-0.1

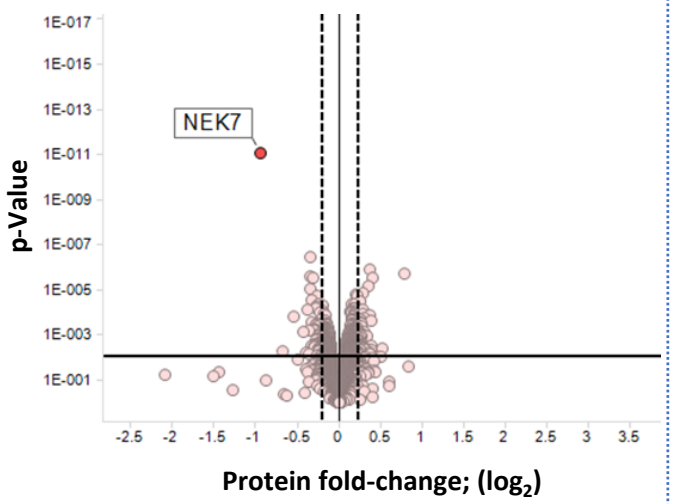
Ternary HTRF assay

MGDs promotes NEK7-CRBN proximity



Turbo-ID Proximity Assay – 6hr post treatment

MGDs promotes selective degradation of NEK7

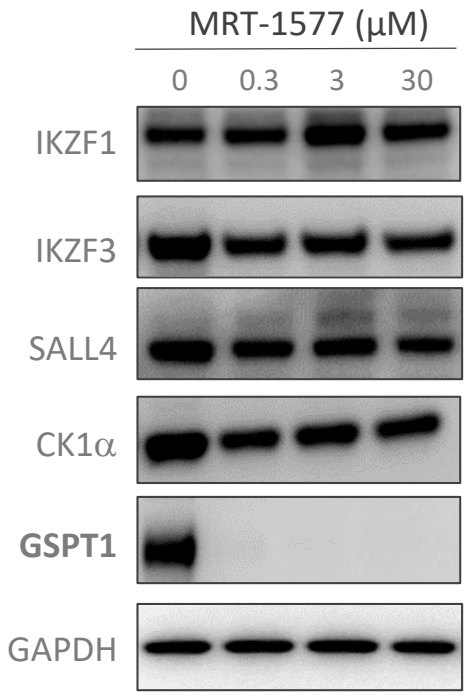


Proteomics – 24hr post treatment

GSPT1: Optimization of Compounds for Selectivity

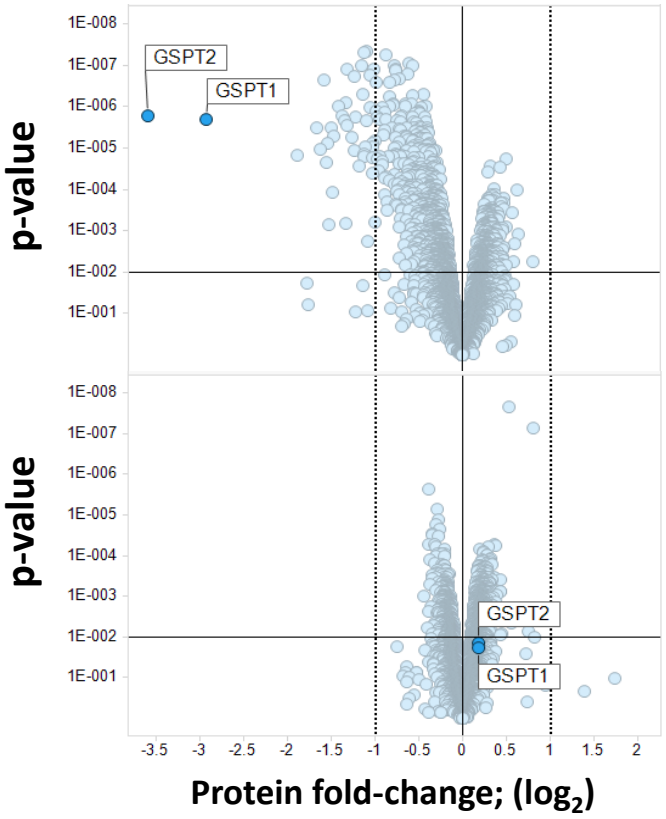
GSPT1-directed MGD downregulates GSPT1, but not other known cereblon-neosubstrates

Selectivity vs known cereblon-neosubstrates



Western blot – 6hr post treatment

GSPT1-directed MGD is highly selective



GSPT1 wild-type

GSPT1 G575N

575 N creates a steric clash precluding binding of GSPT1 to cereblon/MGD complex

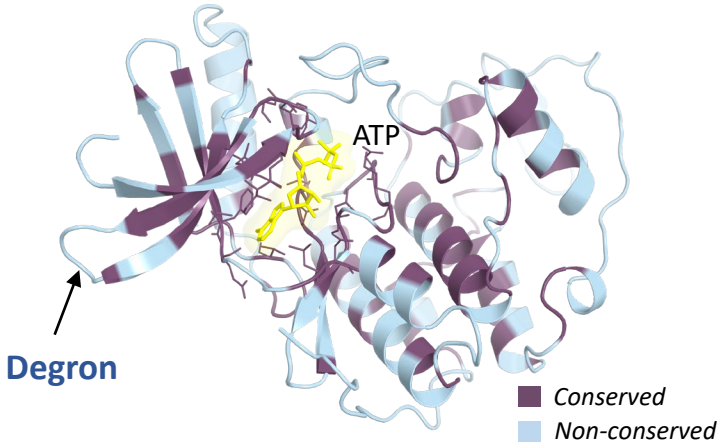
Proteomics – 6hr post treatment

CDKs Have Highly Similar ATP-binding Sites but Unique Degron Sequence

CDK2 biochemical hits are selective over CDK1, CDK4 and CDK9

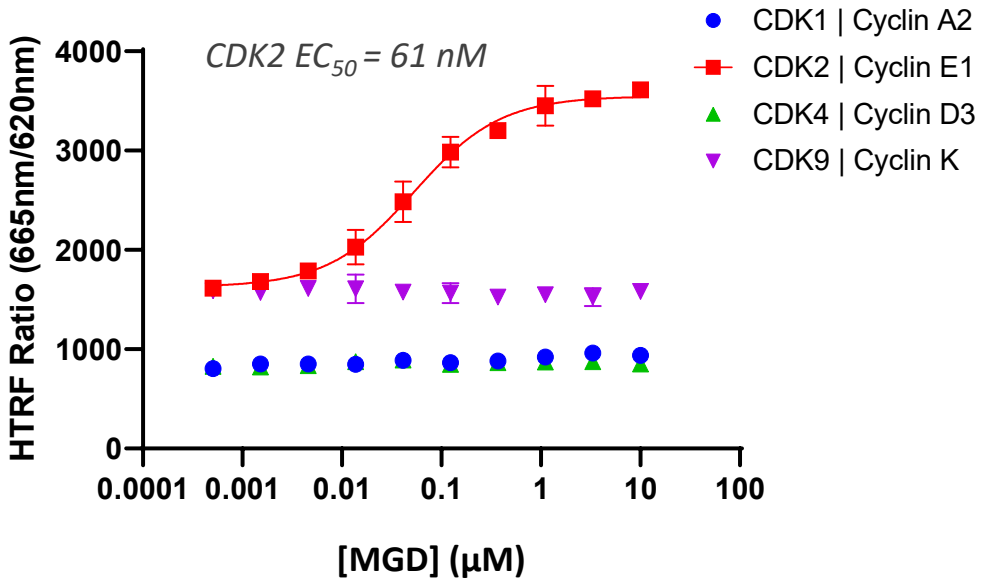
Degron sequence is diverse amongst CDK family members

Example: CDK2 and CDK4 structural similarity



- High ATP-binding site conservation
- Degron sequences have low homology

MGDs are biochemically selective for CDK2 over other CDK family members



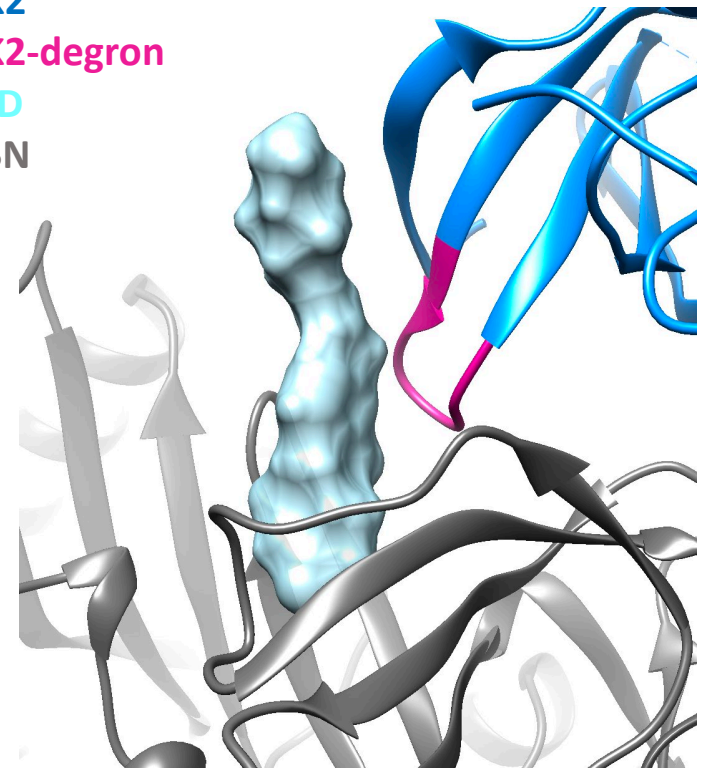
✓ Potential to identify **selective MGDs** to closely related **cyclin-dependent kinases**

Rationally Optimized CDK2-Directed MGDs are Selective Degraders

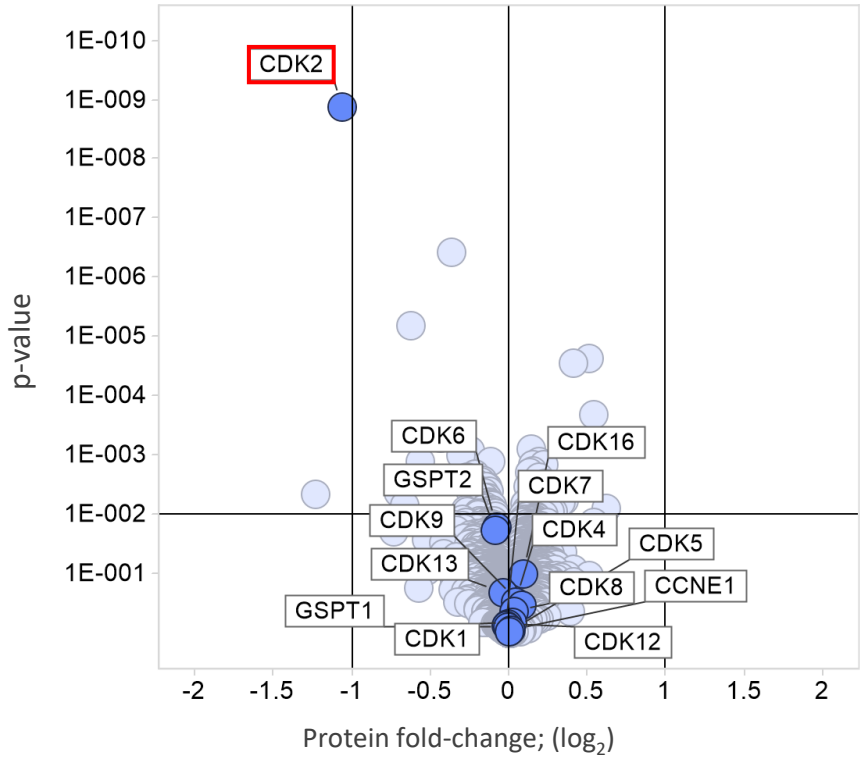
Demonstration of selective CDK2 degradation with MGD treated cells

Rhapsody™ homology model enables rapid chemistry optimization

CDK2
CDK2-degron
MGD
CRBN



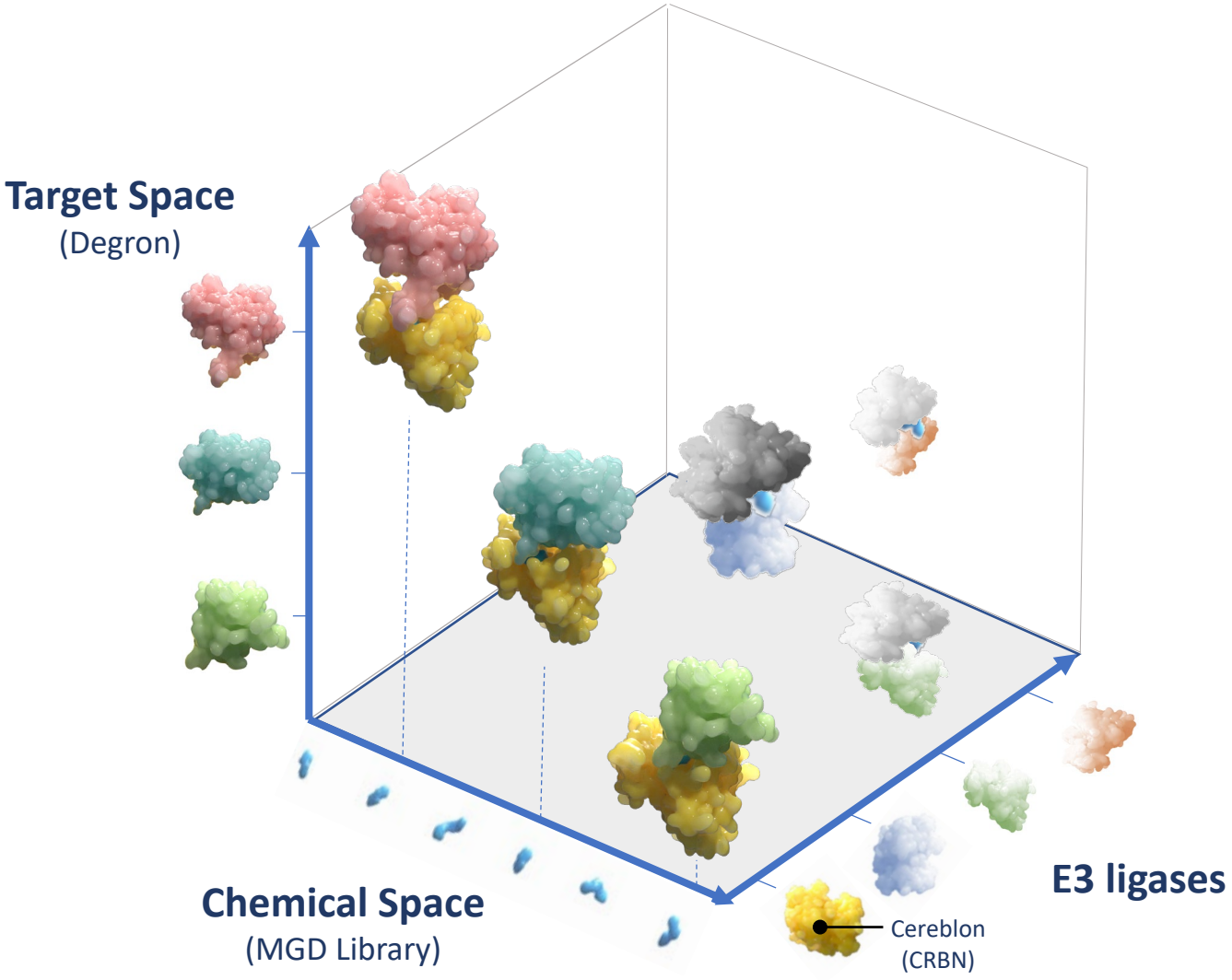
Rationally optimized MGDs selectively degrade CDK2



TMT-Proteomics (HEK293) –24hr post treatment

Unlocking the Full Potential of Protein Degradation with MGDs

Quantitative and engineered elimination of proteins across a broad spectrum of diseases



- Oncology
- Immunology
- Inflammation
- Metabolic disorders
- Neurodegeneration
- Genetic diseases

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Thank You