



Monte Rosa
THERAPEUTICS

Molecular Glue Degraders: *From Serendipity to Rational Design*

4th Annual TPD Summit - October 27, 2021

Monte Rosa Therapeutics Overview

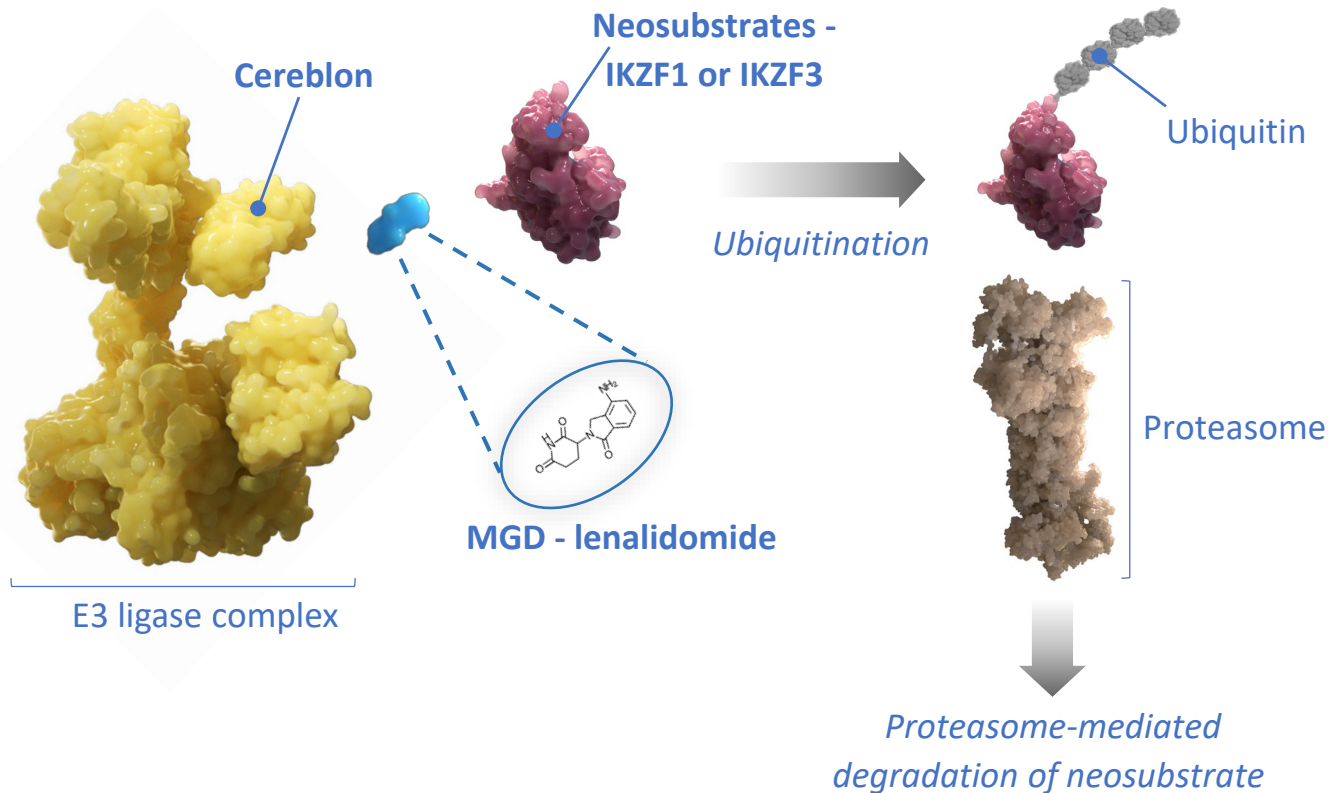
Taking molecular glue degraders (MGDs) to new heights

- **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 degran 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 (MGDs)

A powerful and differentiated approach to eradicate disease-causing proteins



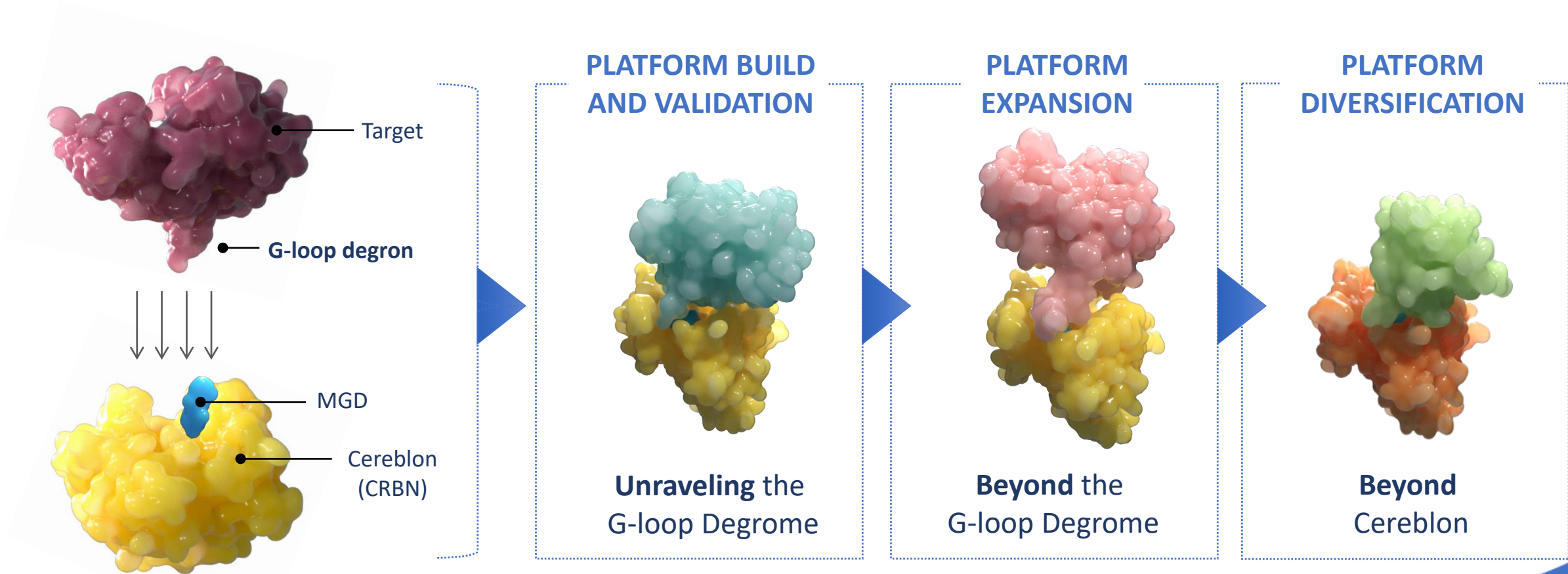
- ✓ Undruggable target space
- ✓ Favorable **drug-like** properties
- ✓ Clinically **validated**
- ✓ **Systematic and selective** reprogramming
- ✓ **Broad** therapeutic application

Systematic Chemical Reprogramming of E3 Ligases using MGDs



Cereblon (CRBN), the G-loop Degron and Beyond

A rational approach to unleash the full potential of MGDs

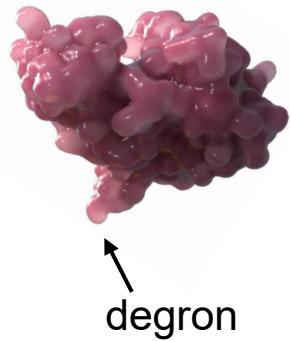


EXPANDING THE DEGRADABLE
PROTEOME BY RATIONAL DESIGN

QuEEN™ Discovery Platform: A Transformational Approach to MGDs

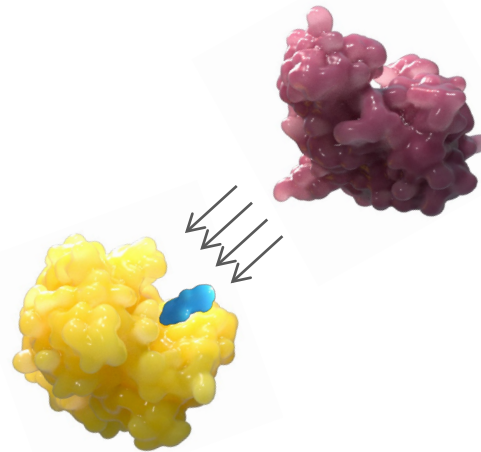
Building a unique portfolio of precision medicines addressing high unmet medical needs

Degron Encyclopedia



Degron discovery using our AI-powered algorithm

Glueomics™ Toolbox



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

Proprietary Library



Rationally designed, diverse and growing library with drug-like properties



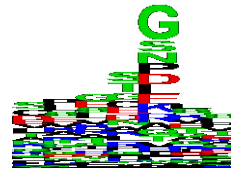
The Degron Encyclopedia

A rich, differentiated target space across protein domains and diseases

Integrated Degron Mining

Sequence

Deep Neural Net



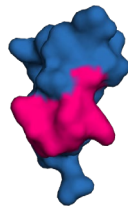
Topology

Loop scoring



Surface

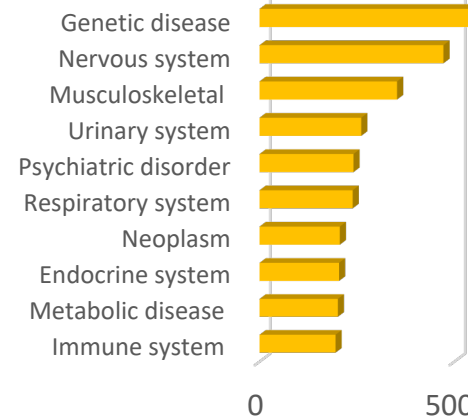
Surface geometry



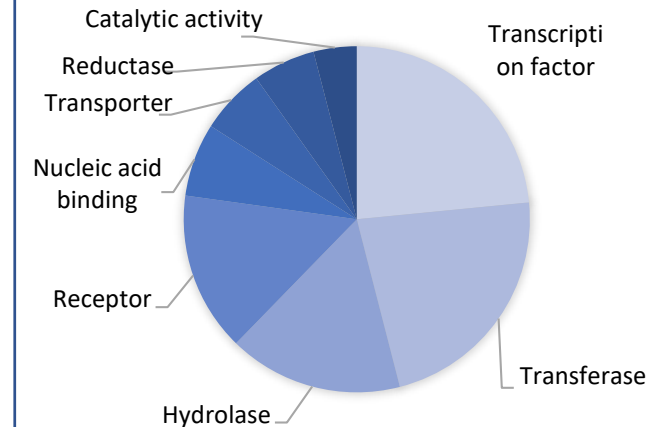
Degron Encyclopedia

>3000 predicted degron-containing proteins

Broad disease landscape



Top protein classes



**Many highly
credentialed targets**

>75% undruggable

**>85% degrons have
unique sequence**

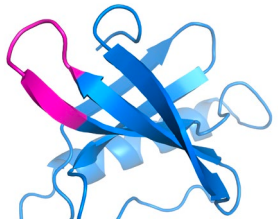


Expanding the Target Space by Identifying More Degrons

Example of degron-containing proteins in different diseases

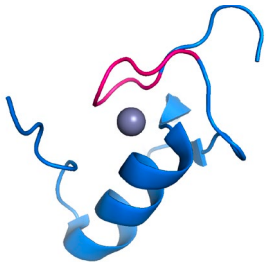
Immunology/ Inflammation

Kinase



Inflammation

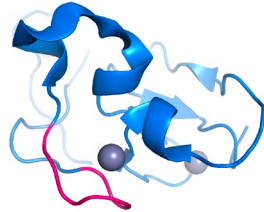
DNA binding



T-cell development

Cancer

Demethylase



Solid tumors

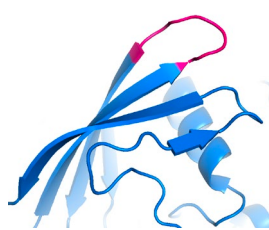
GEF



Hematological cancers

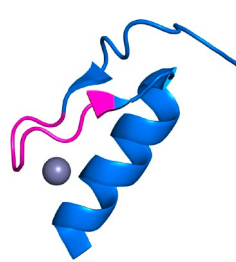
I-O

Phosphatase



T-cell exhaustion

DNA binding



Tregs

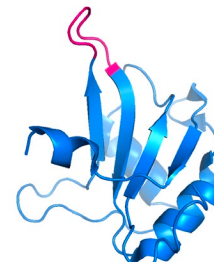
Neurology

DNA binding



ALS

RNA binding



ALS

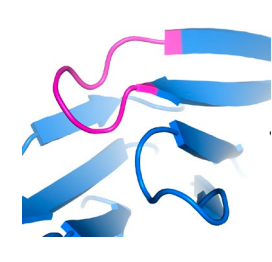
Genetic Diseases

DNA binding



Blood

WD repeat



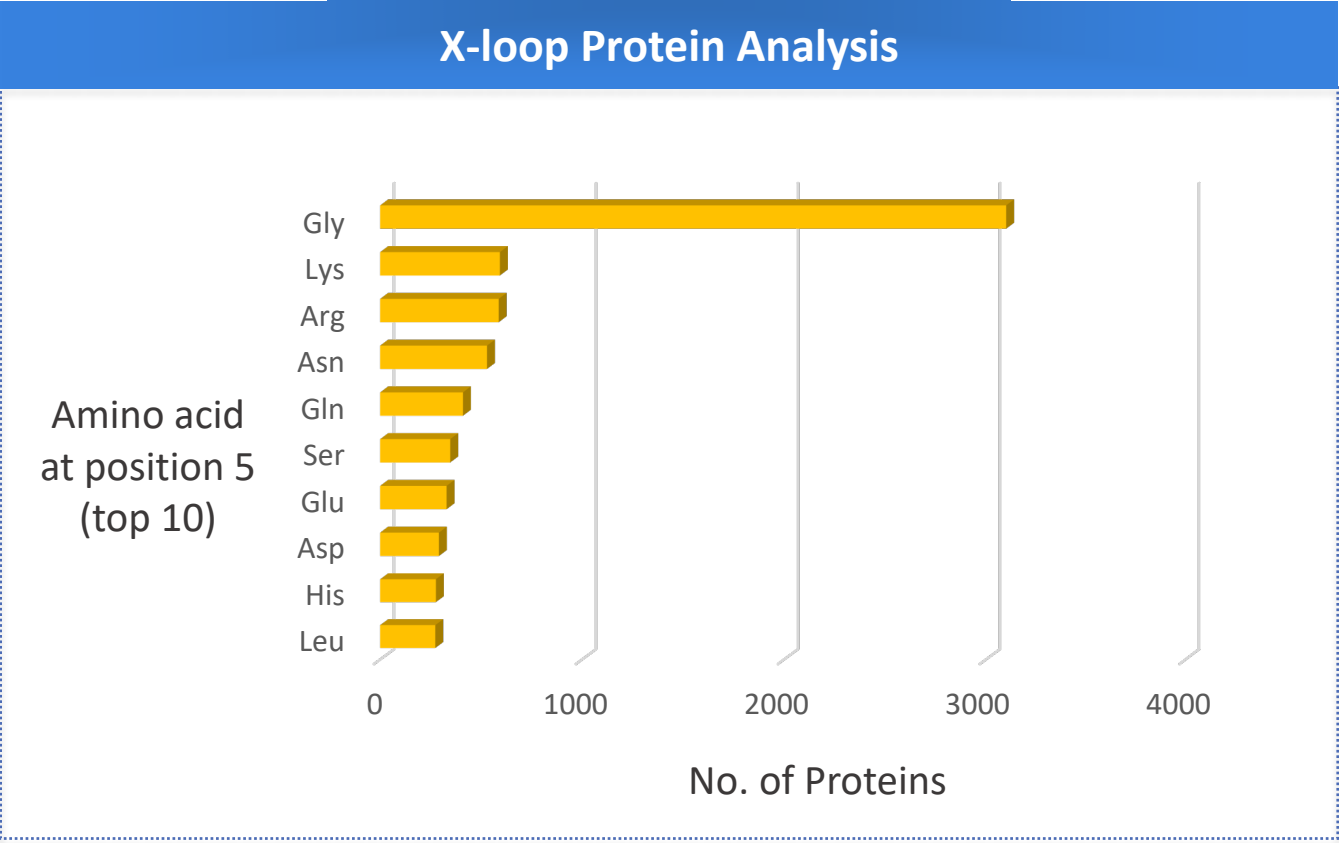
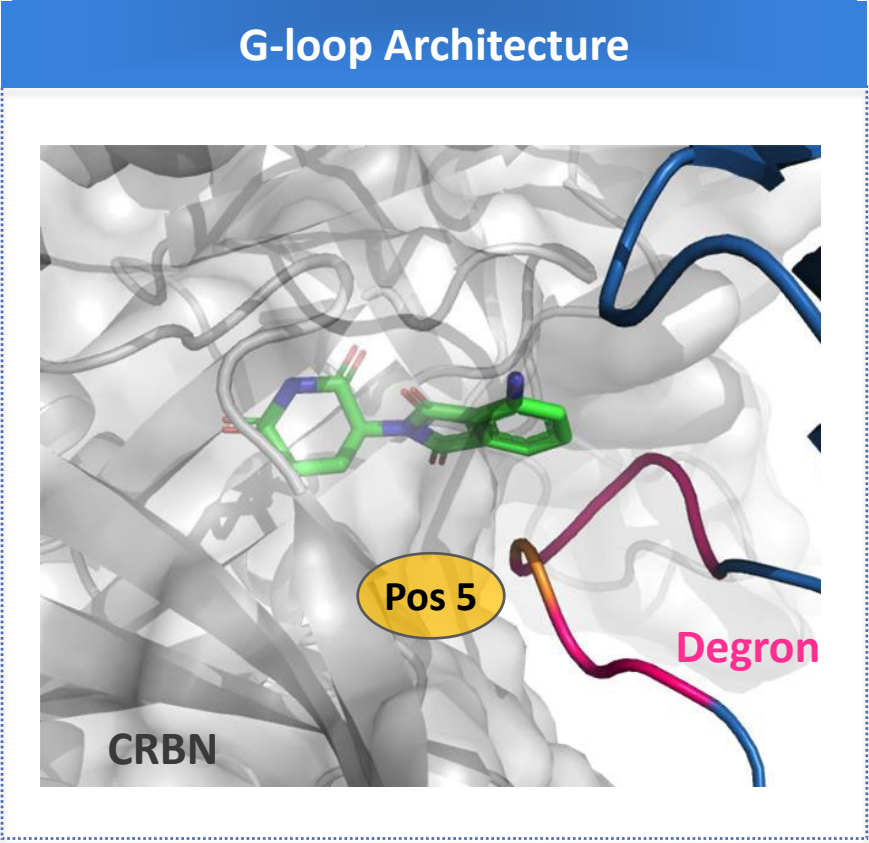
Spastic Paraplegia

>85% of degrons have a unique sequence, providing a unique handle to engage MGD chemical matter



Expanding the Target Space by Identifying More Degrons

Additional structural loops revealed beyond the G-loop degrome



X-loop degrons further expand the list of proteins potentially amenable to a MGD approach



New Chemical Space: MGD Anatomy and Evolving MGD Library

Increasing novelty and structural diversity to match the target space

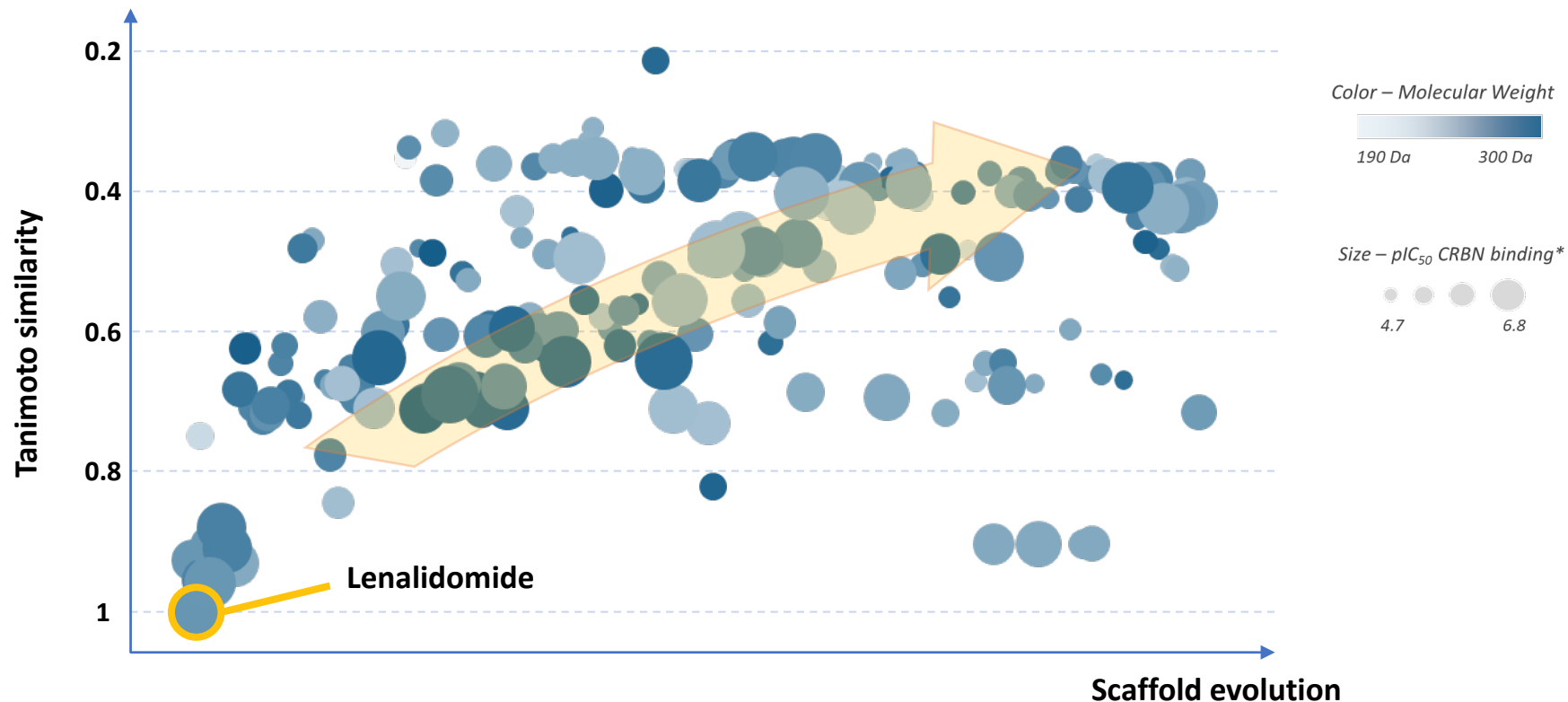
MGD Anatomy



Core
Degron domain

Warhead
Cereblon
binding domain

Increasing the Core-Warhead Chemical Diversity

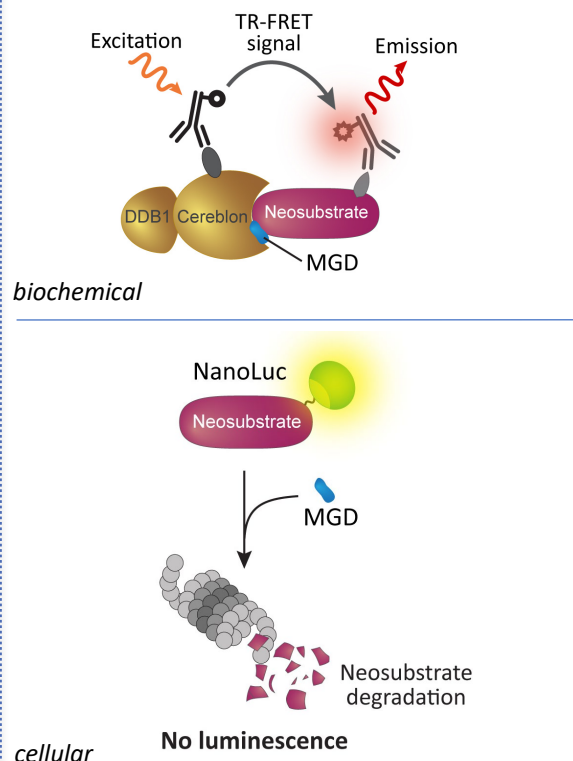


>200 unique scaffolds validated with increasing diversity, confirmed binding and structural insights

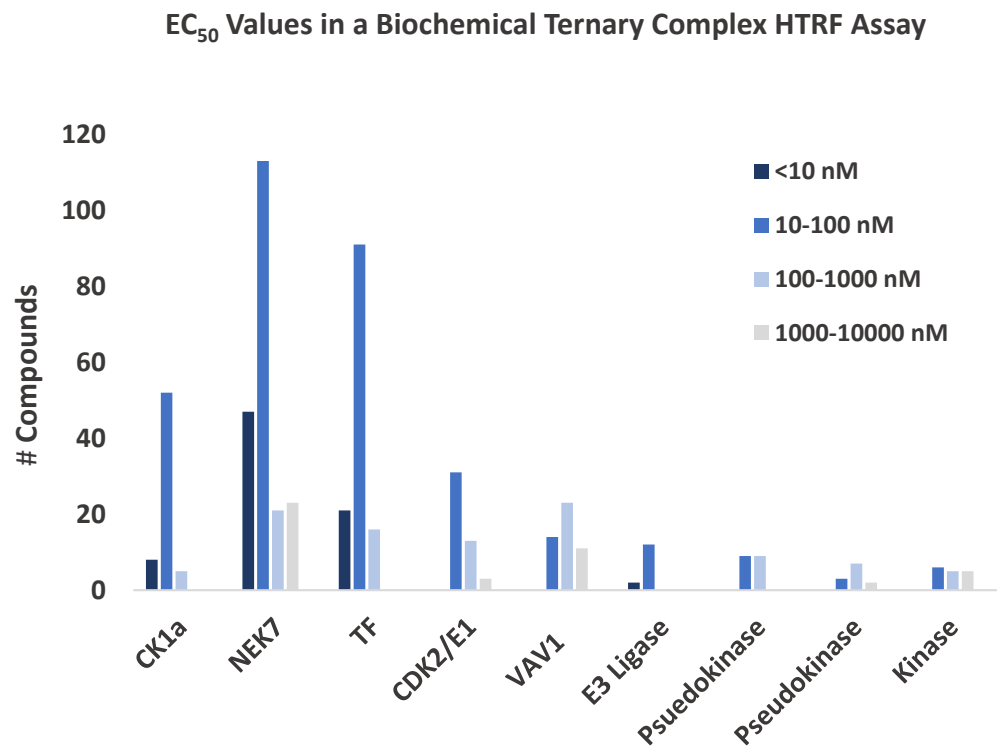
Glueomics™ Toolbox Accelerates Identification of MGDs

Matching target space to chemical space

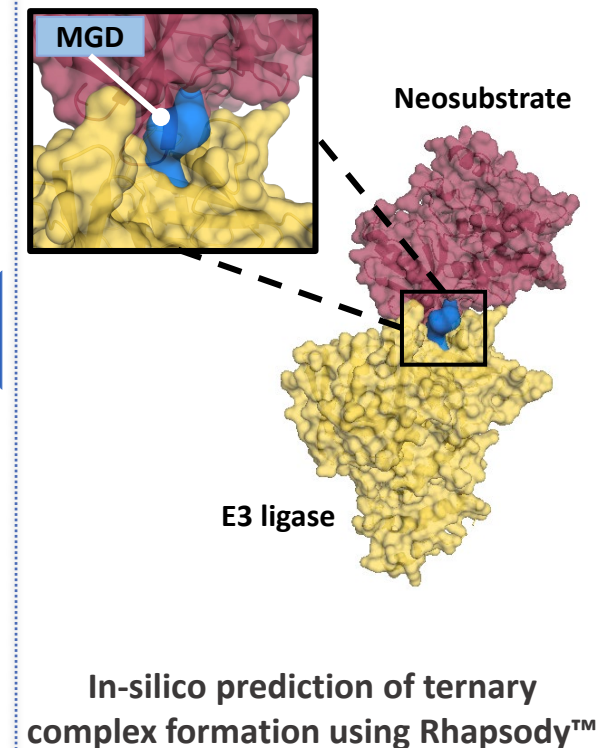
In vitro Screens



Results



In-silico Screens

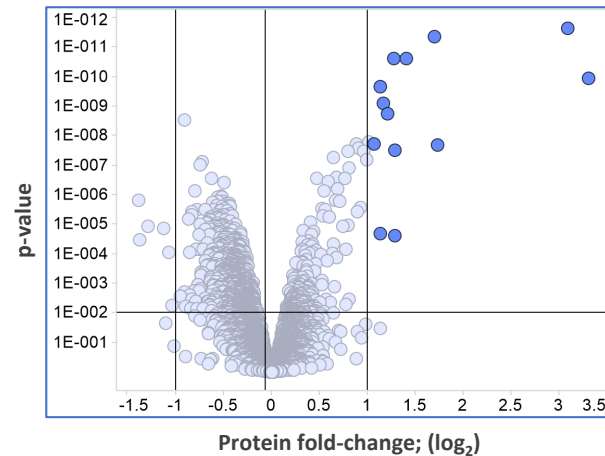
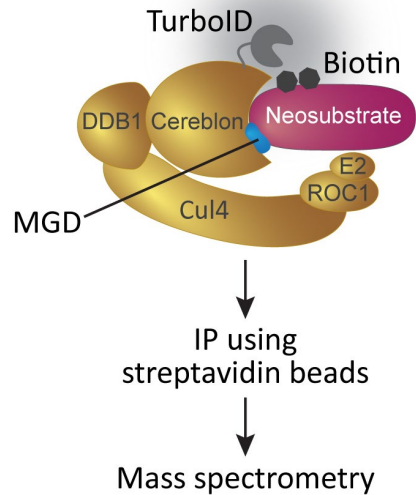


Multiple screening formats enable rapid identification and validation of MGDs for novel degron containing targets

Glueomics™ Toolbox Accelerates Exploration of MGD Space

Exploring target space through chemoproteomics

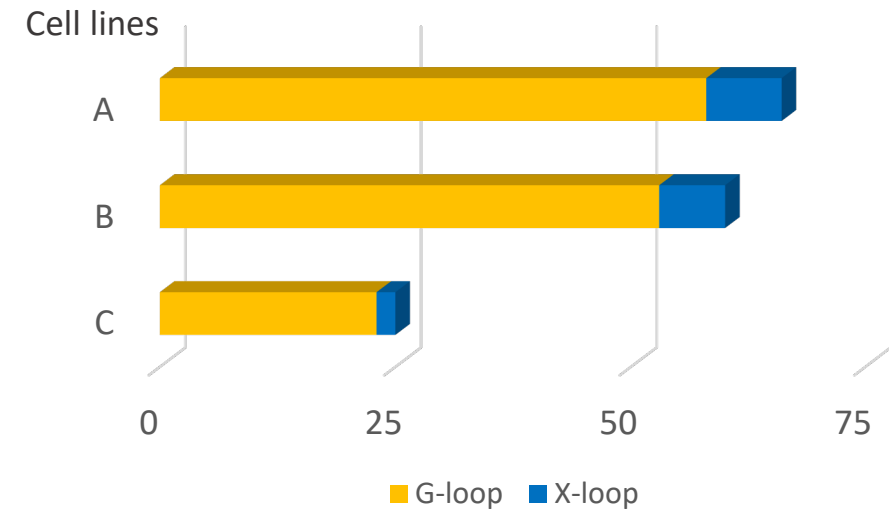
Proteomics



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

Target Space

Turbo-ID data for 15 representative MGDs



Unbiased discovery of novel and known
degron containing proteins

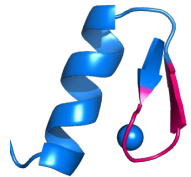
Chemoproteomics enables rapid target deconvolution and identification of novel degron containing targets



Chemoproteomics Accelerates Prediction-to-Validation

Experimental validation of targets using MS proximity (TurboID) and degradation assays

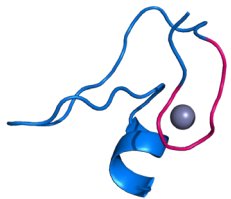
Transcription Factor A



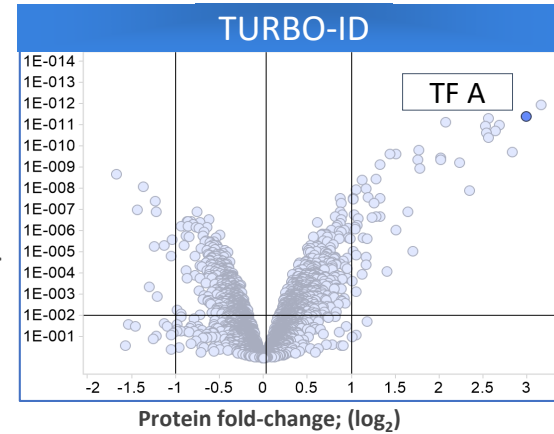
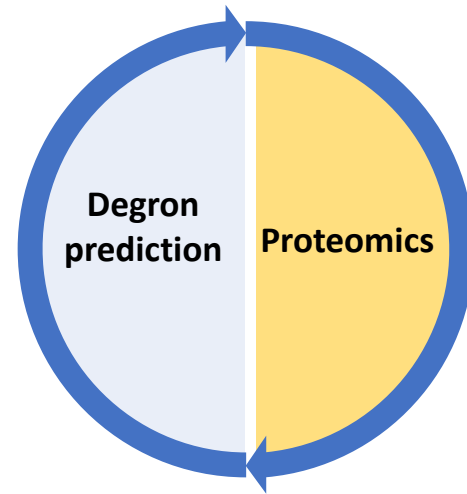
Sickle cell disease

Novel predicted degrons

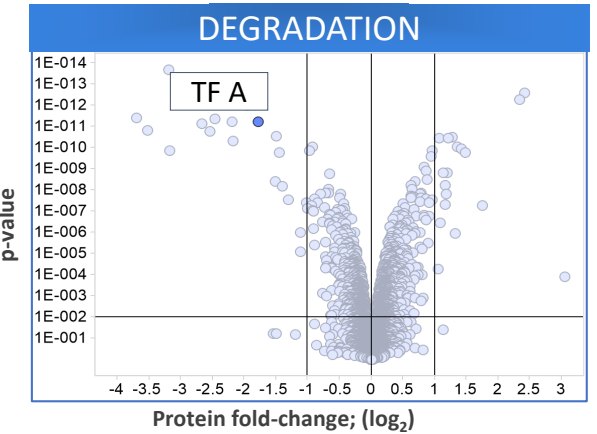
Transcription Factor B



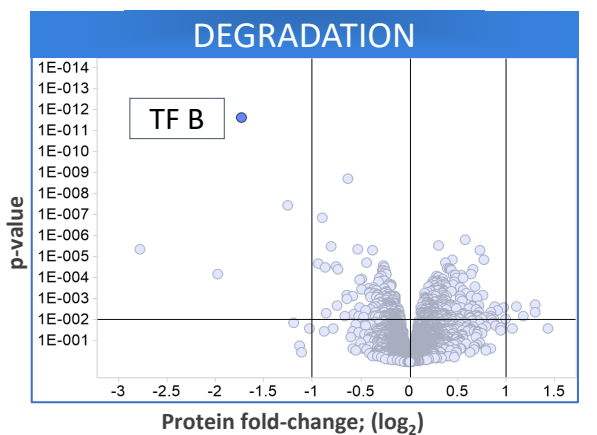
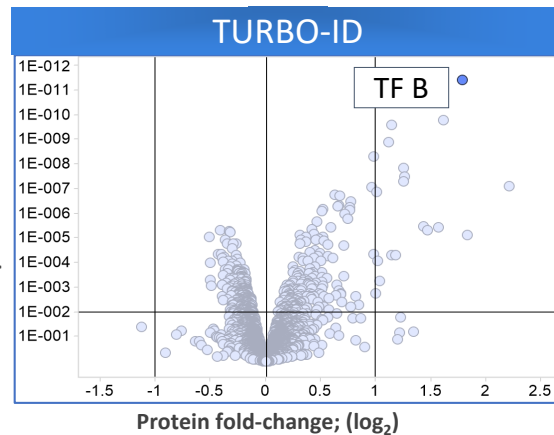
hematologic malignancies



MGDs induce CRBN proximity

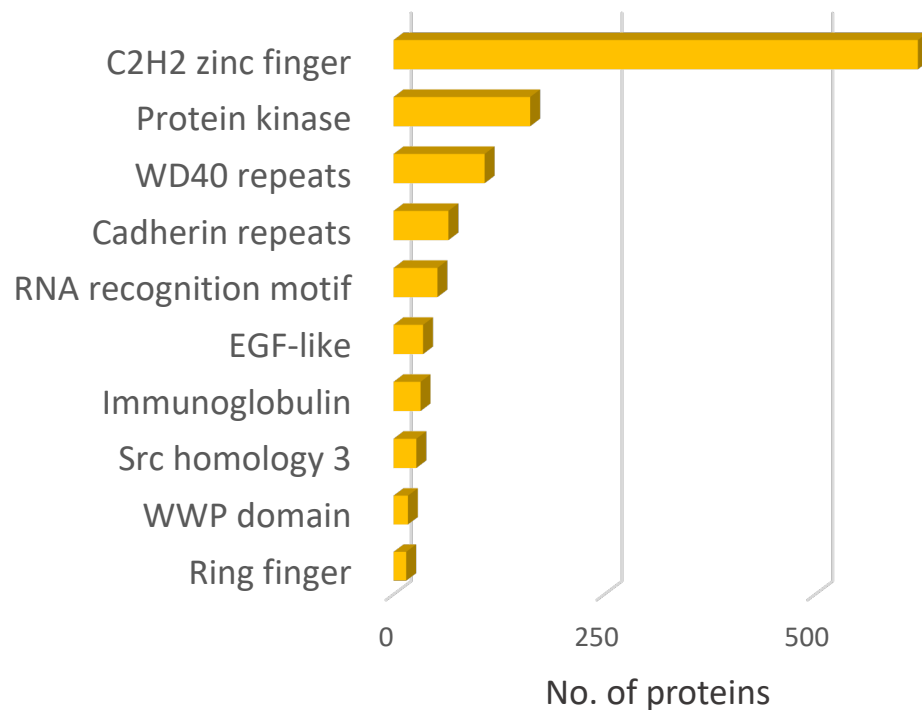


MGDs promote degradation



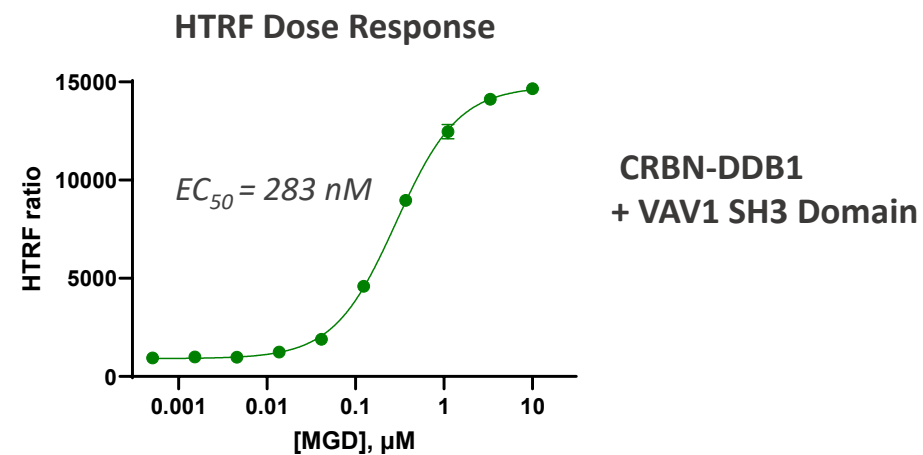
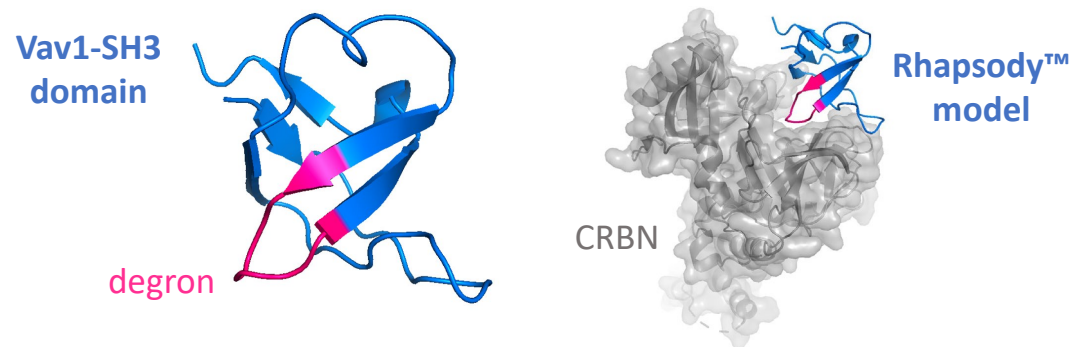
Multiple Protein Domains Contain Degrons

Degron-containing Protein Domains



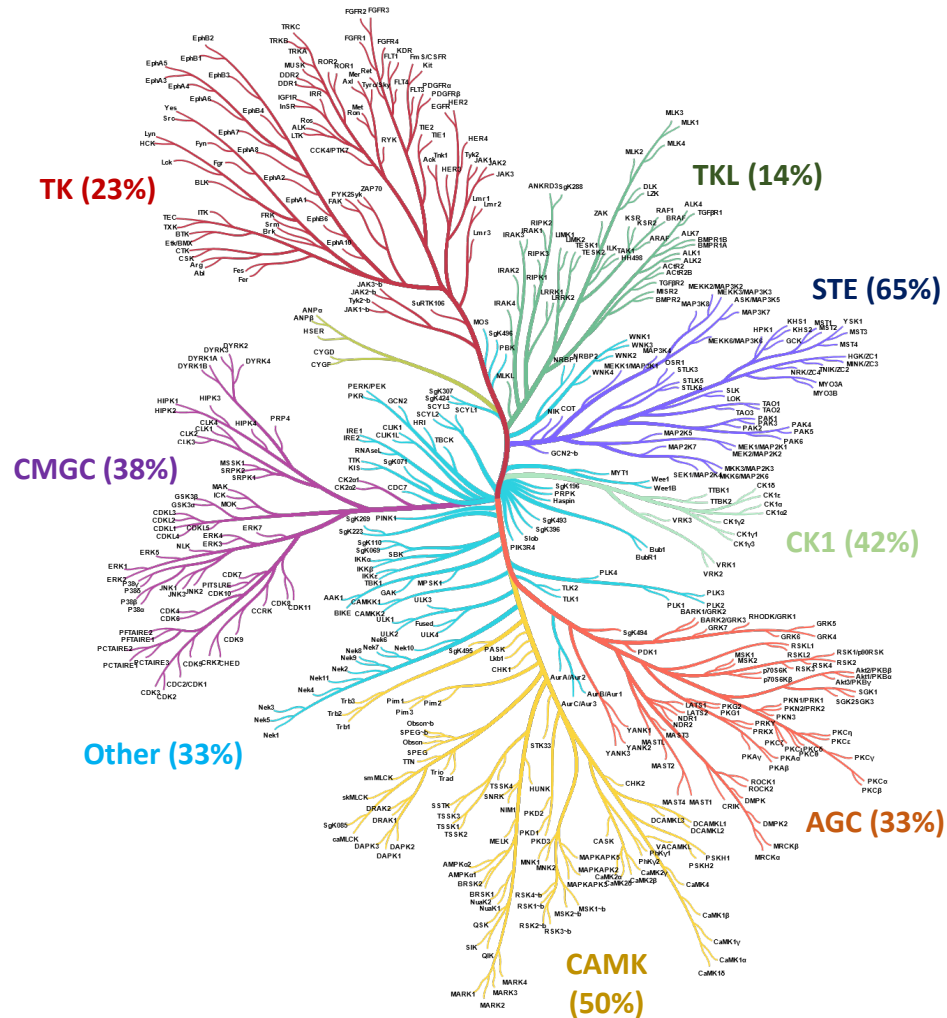
Top 10 degron-containing domains

VAV1-directed MGDs Target the SH3 Domain



Many Kinases Contain Degrons

An opportunity to selectively degrade tough-to-selectively inhibit proteins



Degrome

Kinases with degrons

- Over 170 human kinases have predicted degrons
- Degrons occur in kinase, SH3 and other domains
- Includes multiple kinases with scaffolding functions

Uniqueness

Degrans provide a unique selectivity handle

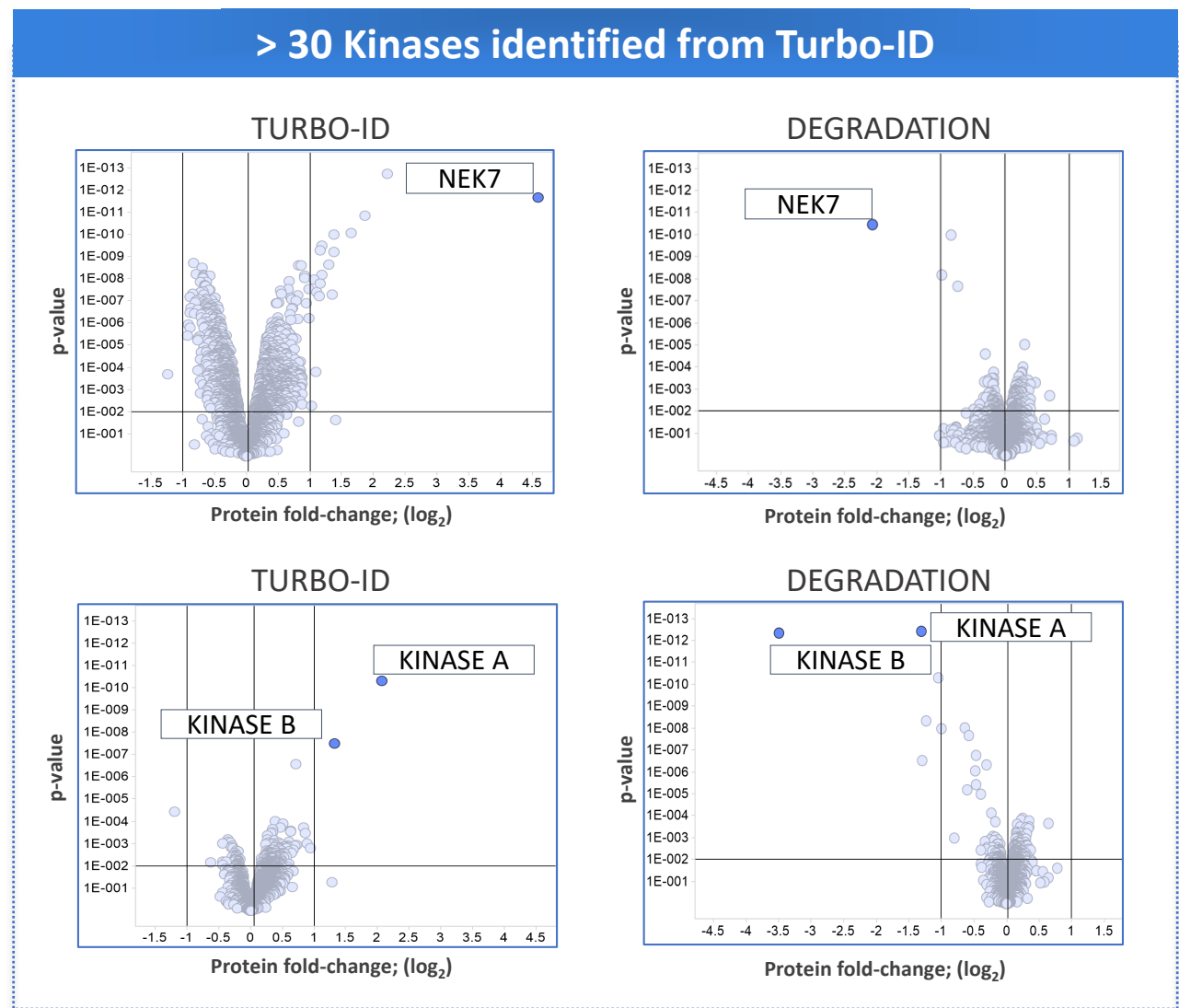
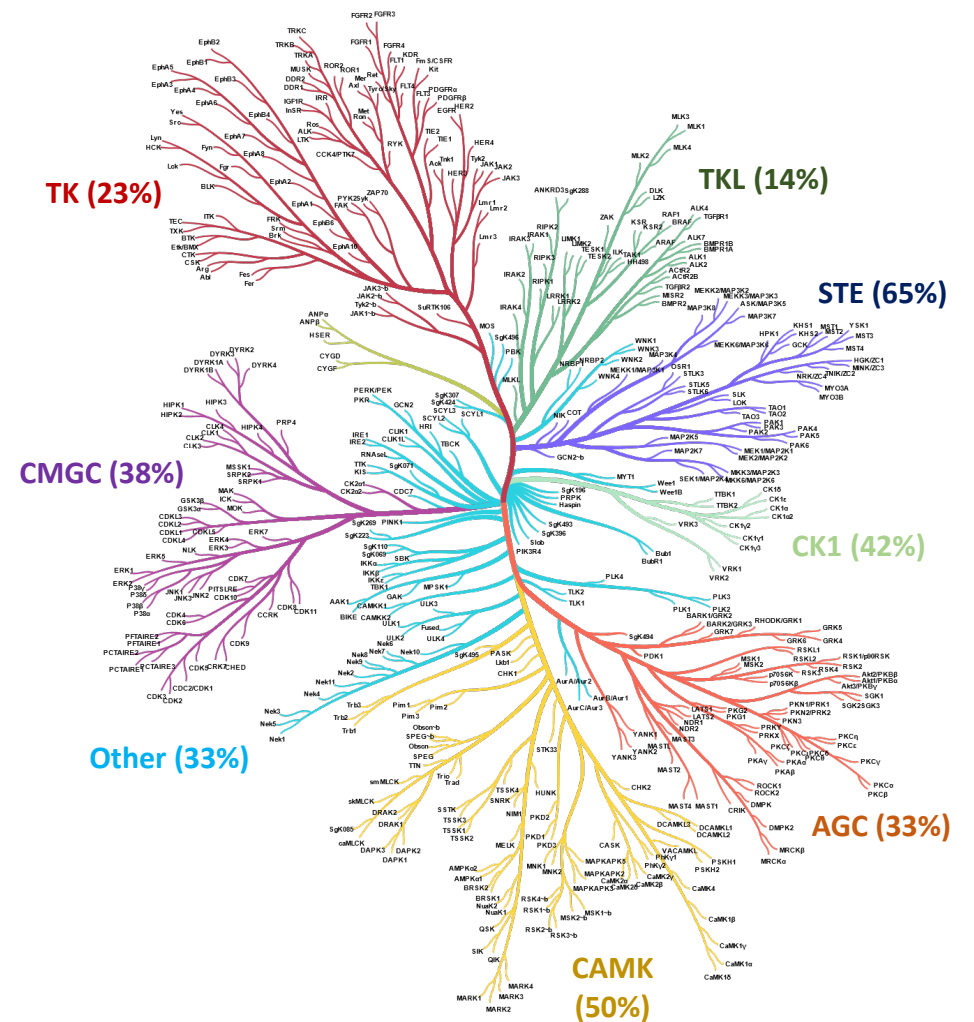
- Typically, degrons occur outside conserved regions
- Sequence homology is more diverse than binding pockets, allowing for more selective engagement

% kinase families with a predicted degron



Many Kinases Contain Degrons

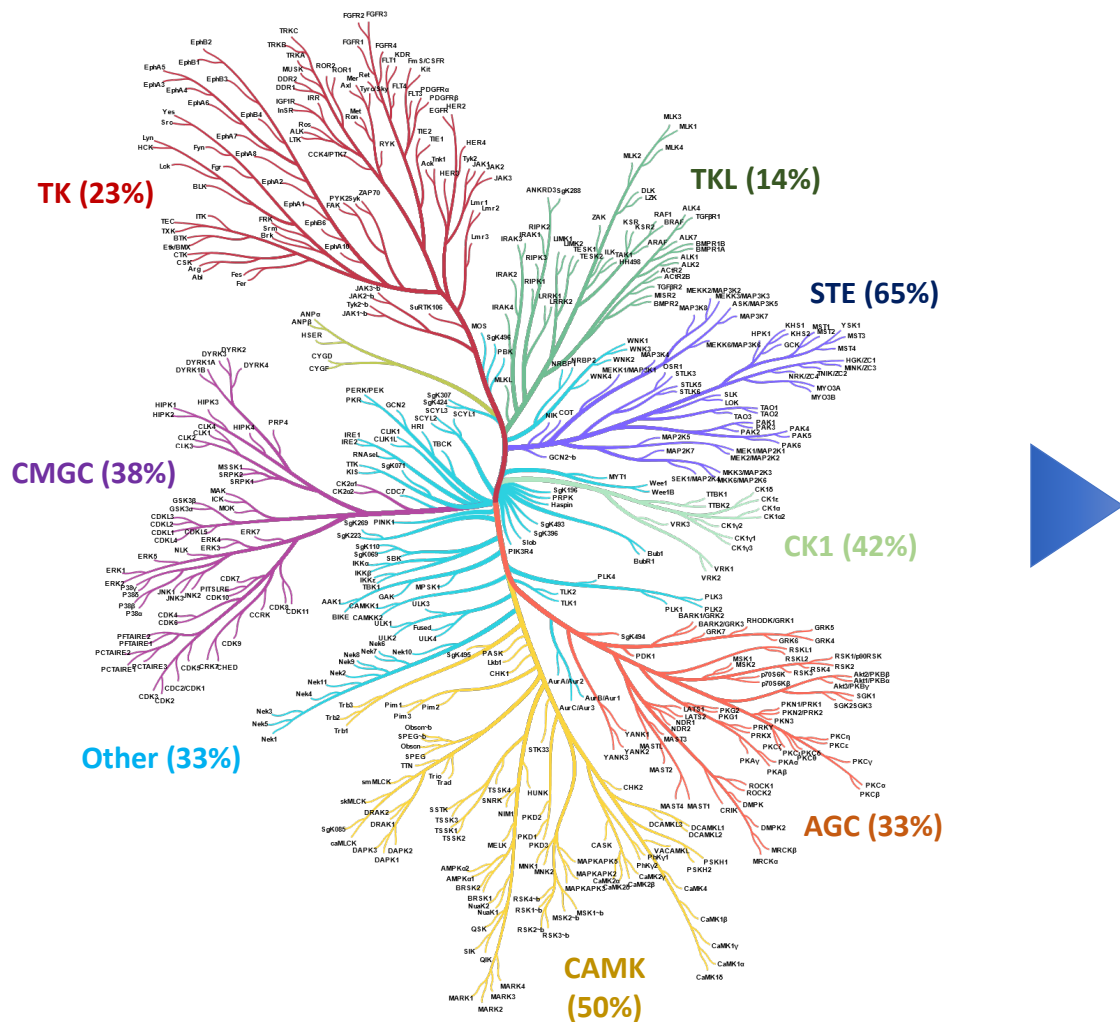
An opportunity to selectively degrade tough-to-selectively inhibit proteins



% kinase families with a predicted degron

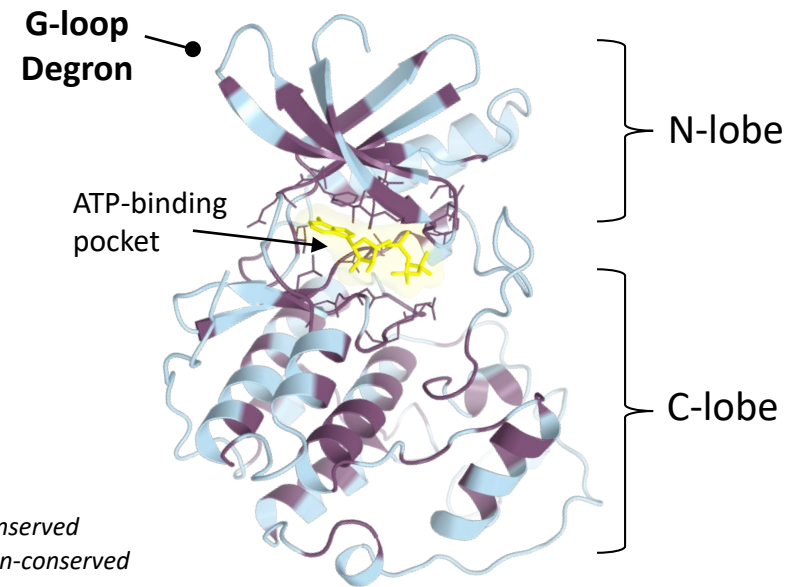
Many Kinases Contain Degrons

An opportunity to selectively degrade tough-to-selectively inhibit proteins



Degron sequence is diverse amongst CDK family members

Example: CDK2 and CDK4 structural similarity



- High ATP-binding site conservation
- Low homology in the degron sequence

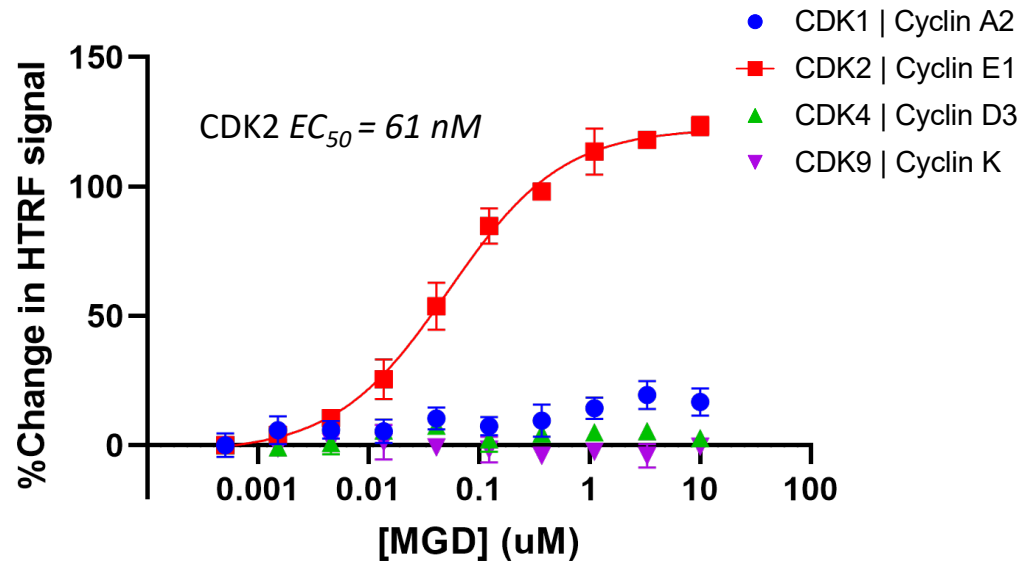
% kinase families with a predicted degron



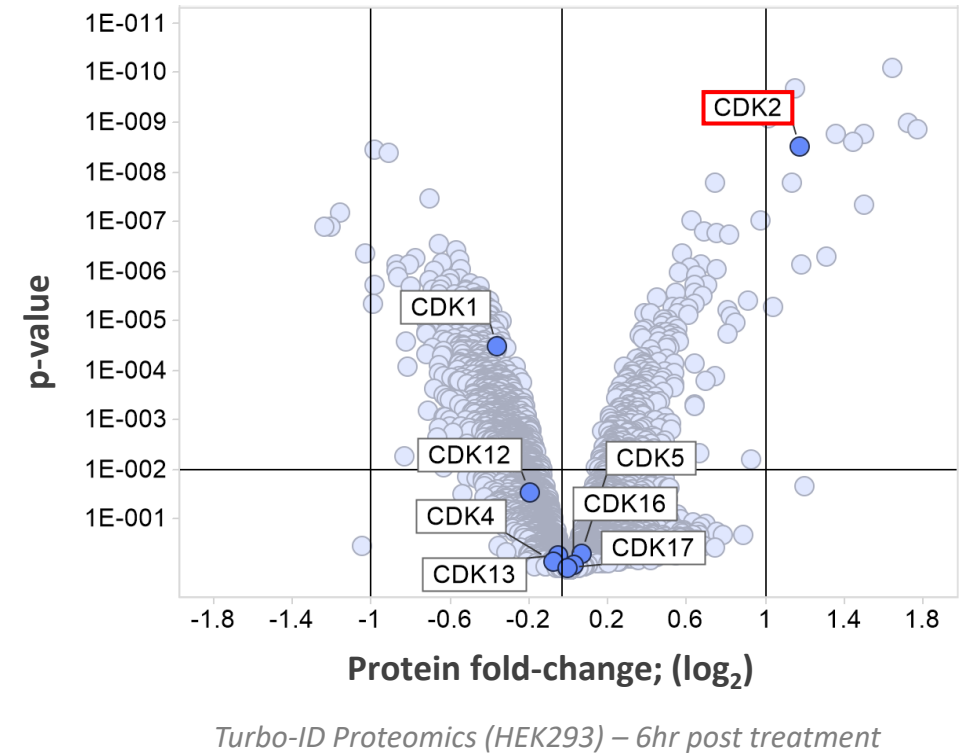
CDK2-Directed MGDs are Selective over other CDKs

MGDs identified through biochemical screens induce cellular proximity with CRBN

MGDs are biochemically selective over CDK1, CDK4 and CDK9



MGDs promote CDK2-cereblon proximity and are selective over other CDKs

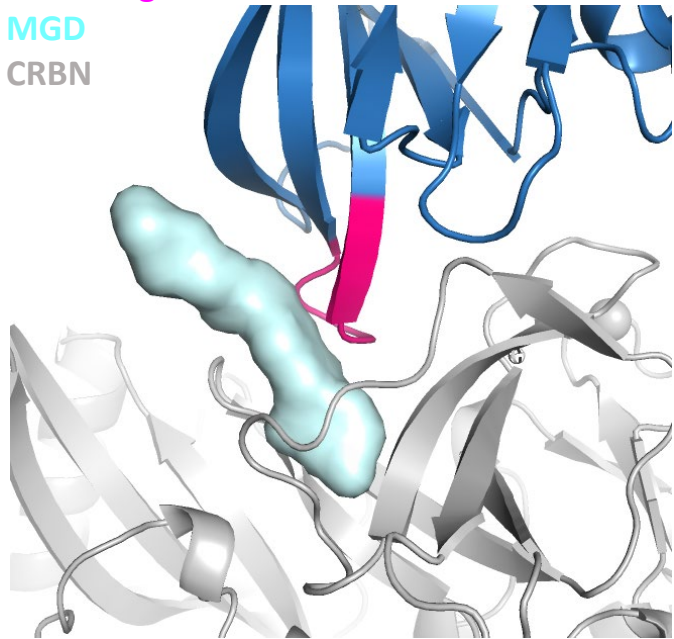


Rationally Designed CDK2-Directed MGDs are Selective Degraders

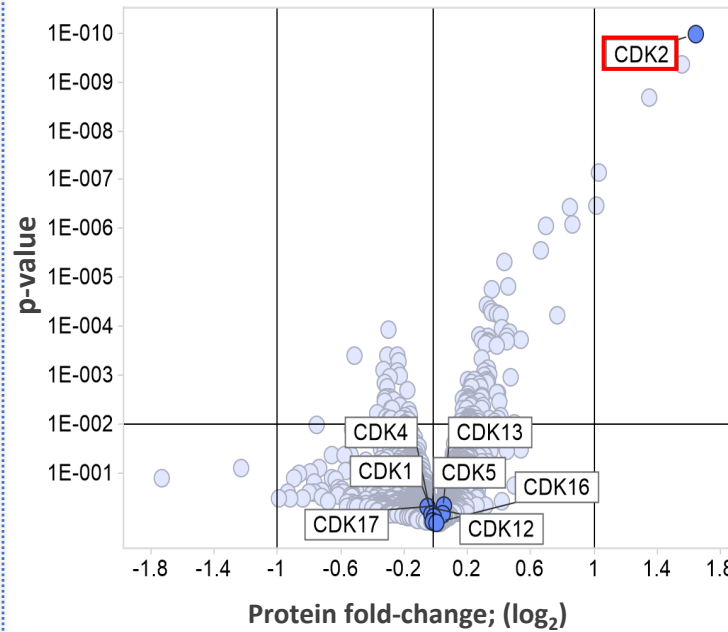
Demonstration of selective CDK2 degradation with MGD treated cells

Rhapsody™ model enables rapid chemistry optimization

CDK2
CDK2-degron
MGD
CRBN

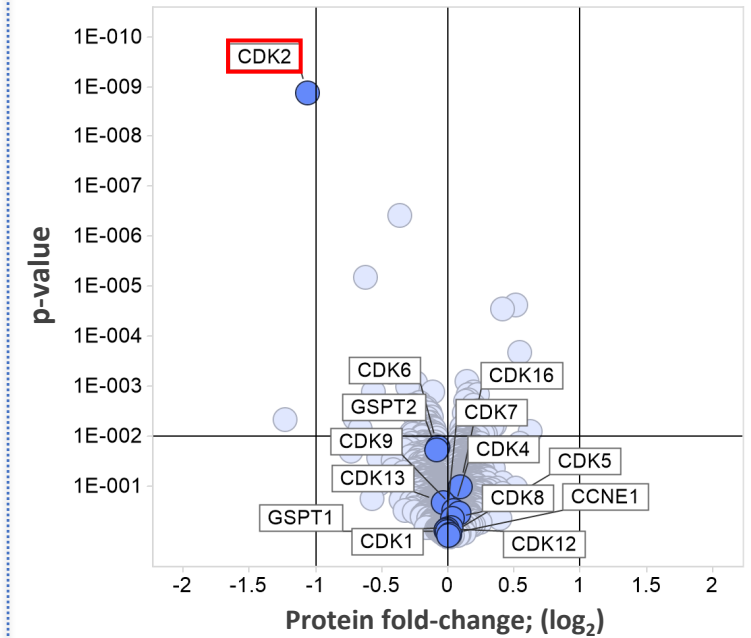


Rationally designed MGDs promote more selective CRBN proximity



Turbo-ID (HEK293) – 6hr post treatment

Rationally designed MGDs selectively degrade CDK2

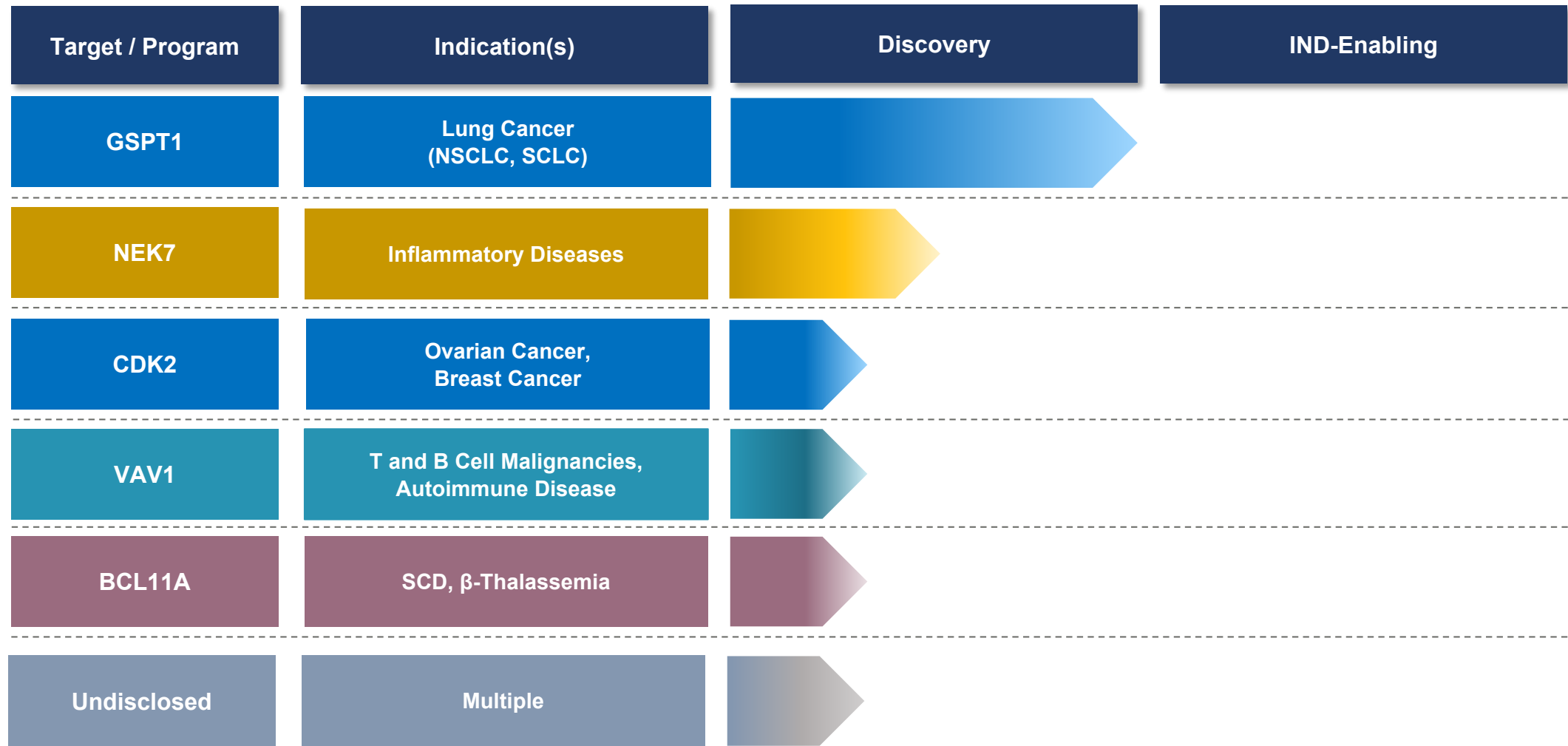


TMT-Proteomics (HEK293) – 24hr post treatment



Monte Rosa Pipeline

Rapidly advancing wholly owned MGD programs



Oncology

Autoinflammation

Oncology / immunology

Genetic diseases





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THERAPEUTICS

Thank You
