



Monte Rosa
THERAPEUTICS

Molecular Glue Degraders: *From Serendipity to Rational Design*

4th Annual TPD Summit - October 27, 2021



Monte Rosa Therapeutics Overview

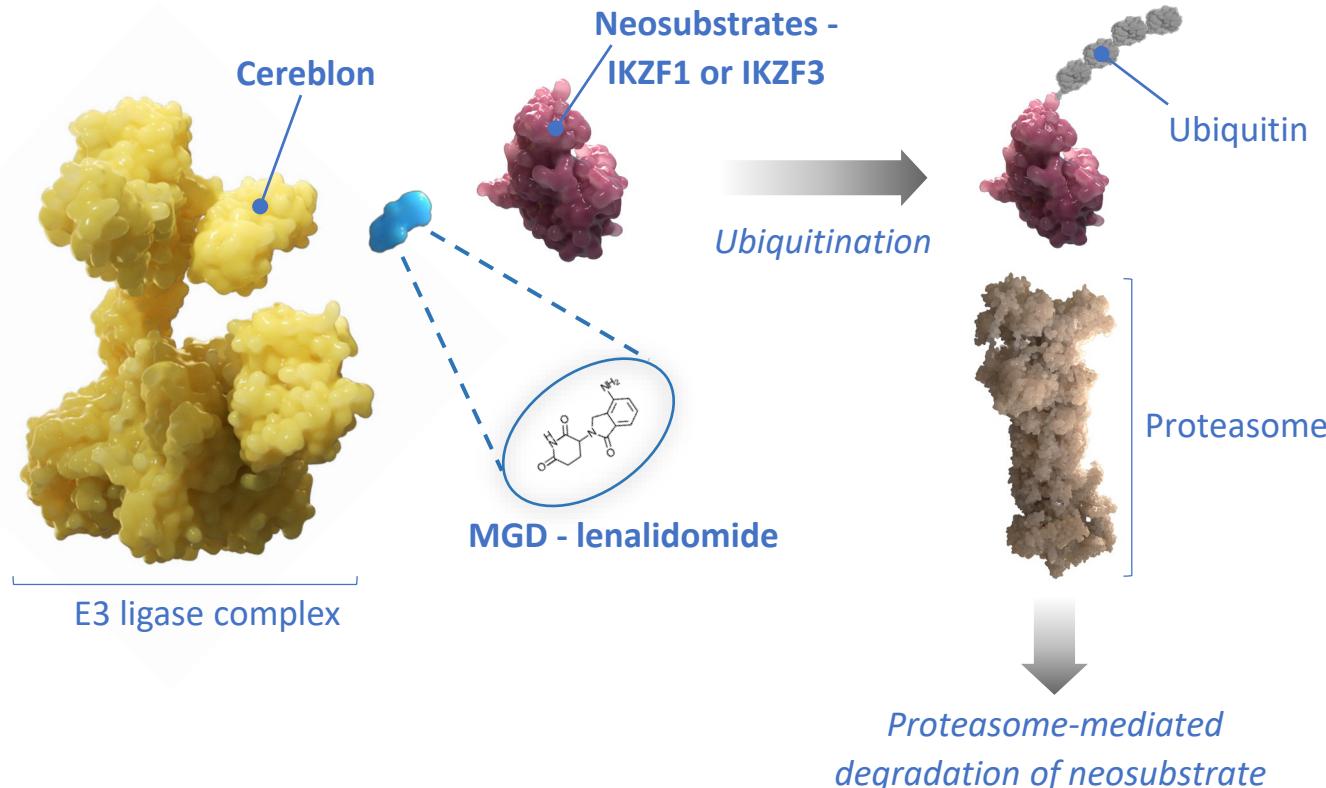
Taking molecular glue degraders (MGDs) to new heights

- 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 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 (MGDs)

A powerful and differentiated approach to eradicate disease-causing proteins

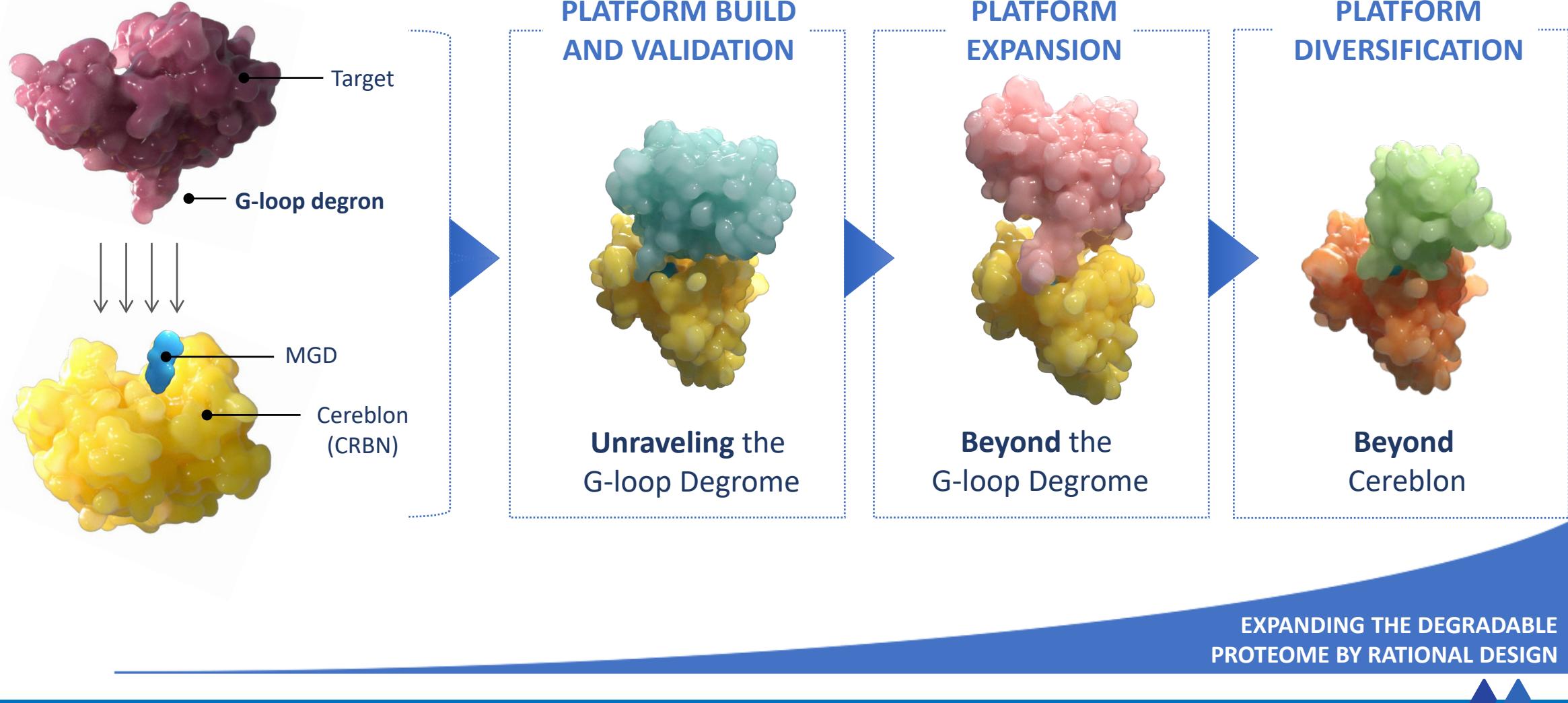


- ✓ Undruggable target space
- ✓ Favorable **drug-like** properties
- ✓ Clinically **validated**
- ✓ Systematic and **selective** reprogramming
- ✓ Broad therapeutic application

Systematic Chemical Reprogramming of E3 Ligases using MGDs

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

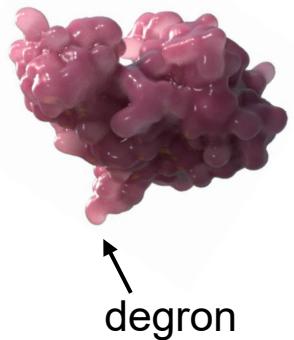
A rational approach to unleash the full potential of MGDs



QuEEN™ Discovery Platform: A Transformational Approach to MGDs

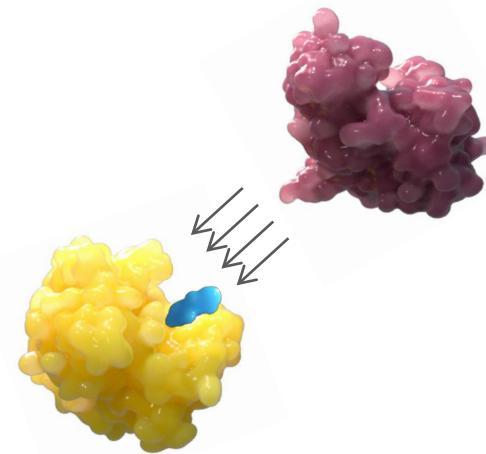
Building a unique portfolio of precision medicines addressing high unmet medical needs

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



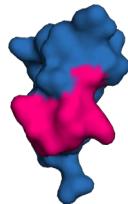
Topology

Loop scoring



Surface

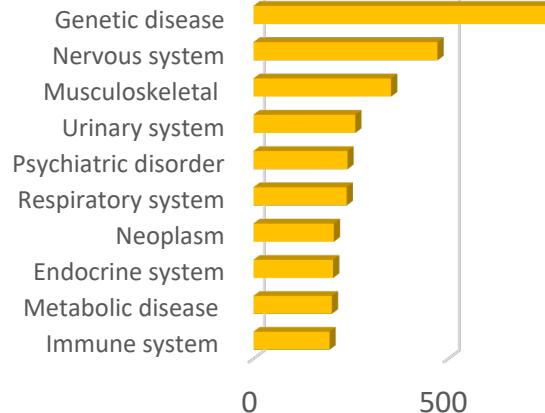
Surface geometry



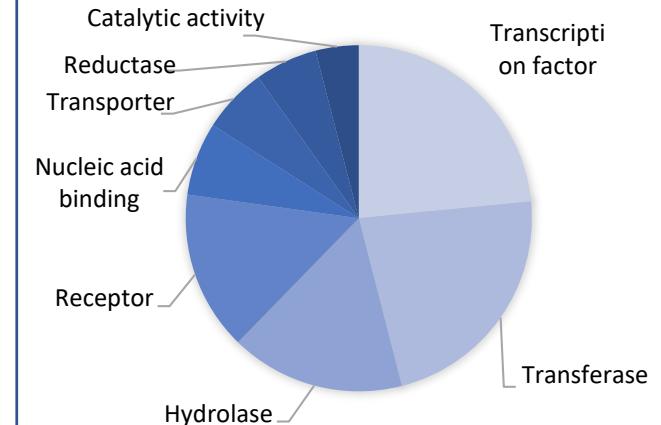
Degron Encyclopedia

>3000 predicted degron-containing proteins

Broad disease landscape



Top protein classes



**Many highly
credentialed targets**

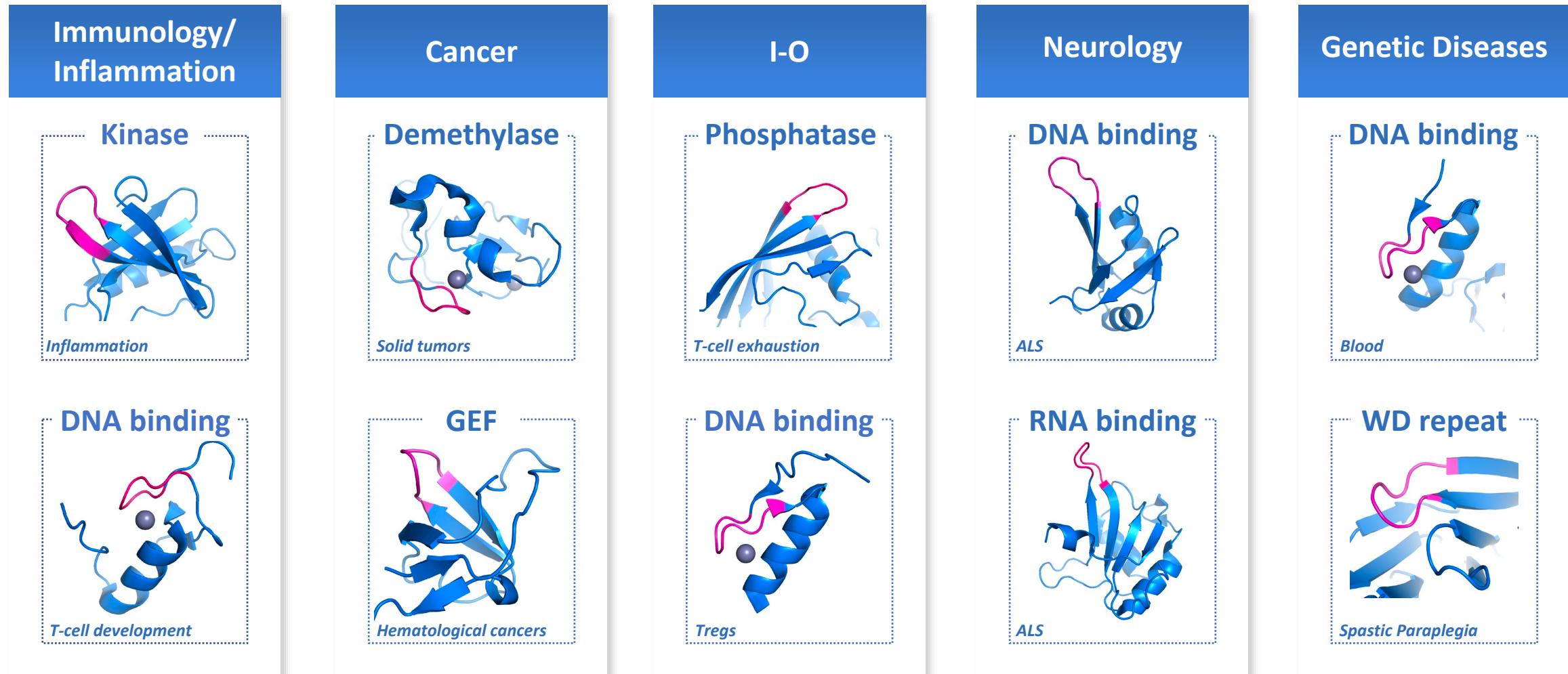
>75% undruggable

**>85% degrons have
unique sequence**



Expanding the Target Space by Identifying More Degrons

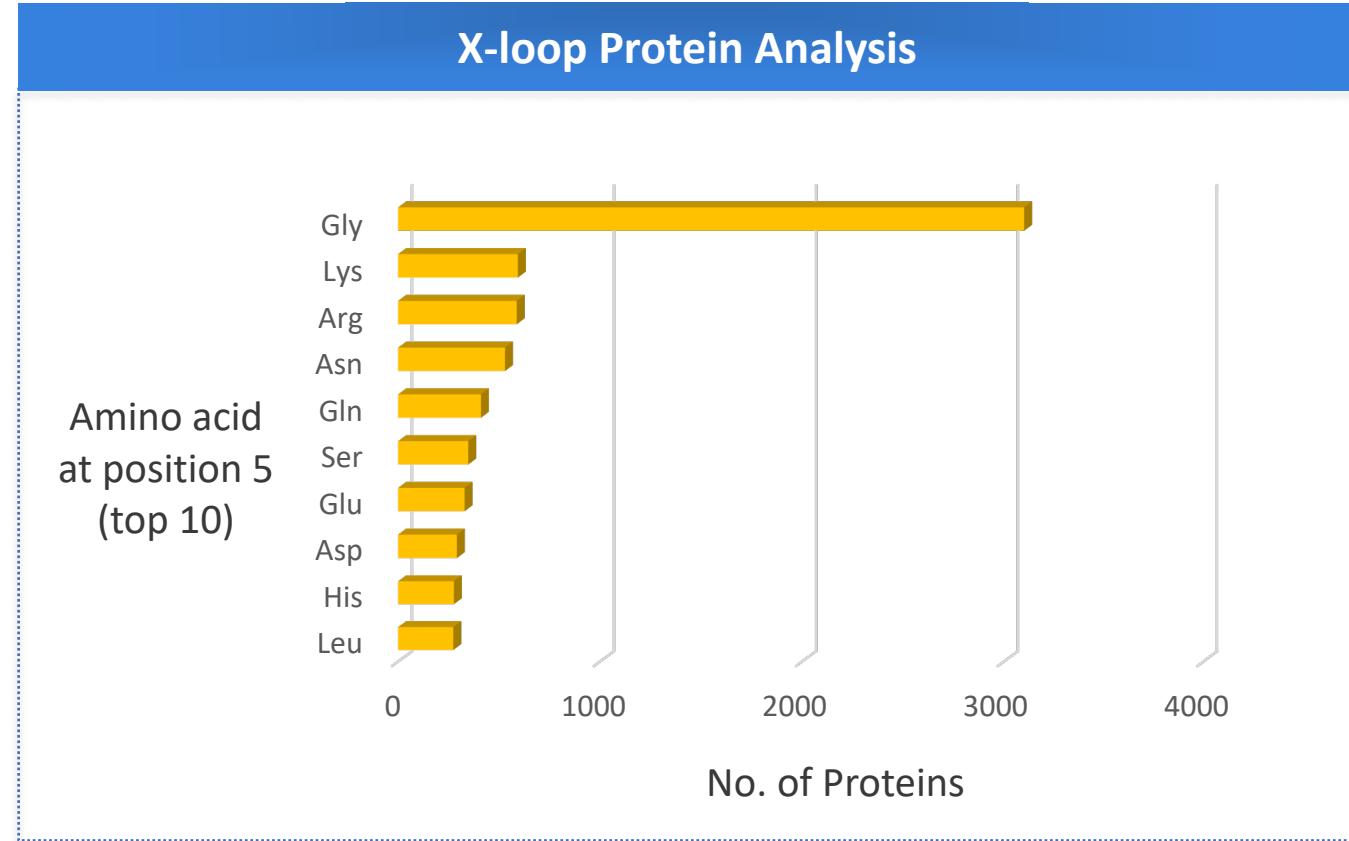
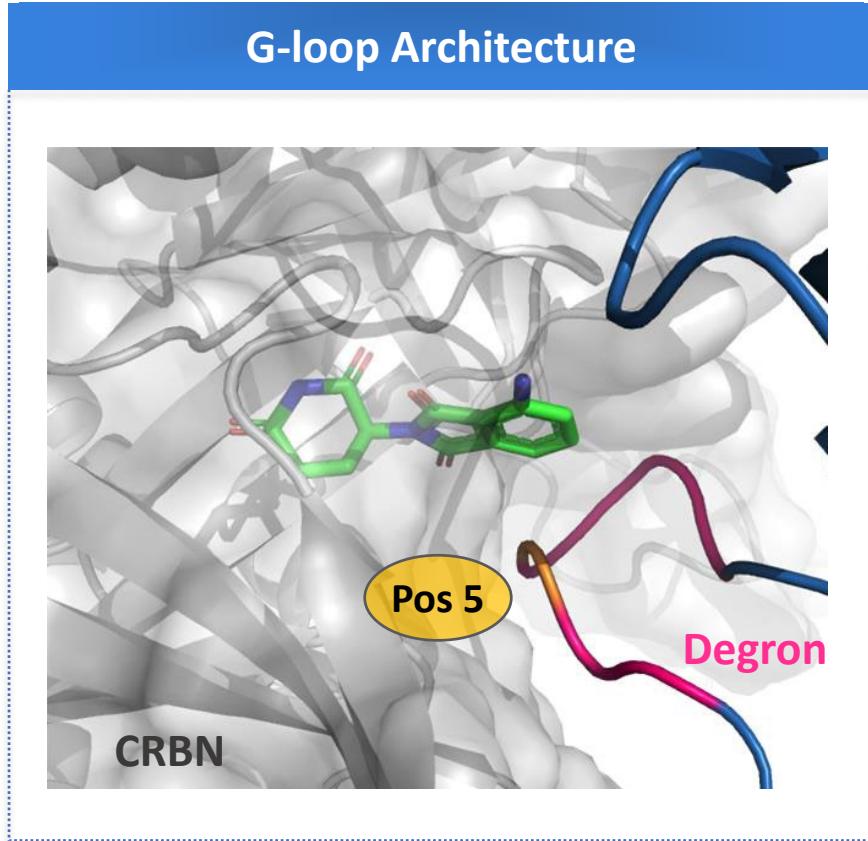
Example of degron-containing proteins in different diseases



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

Expanding the Target Space by Identifying More Degrons

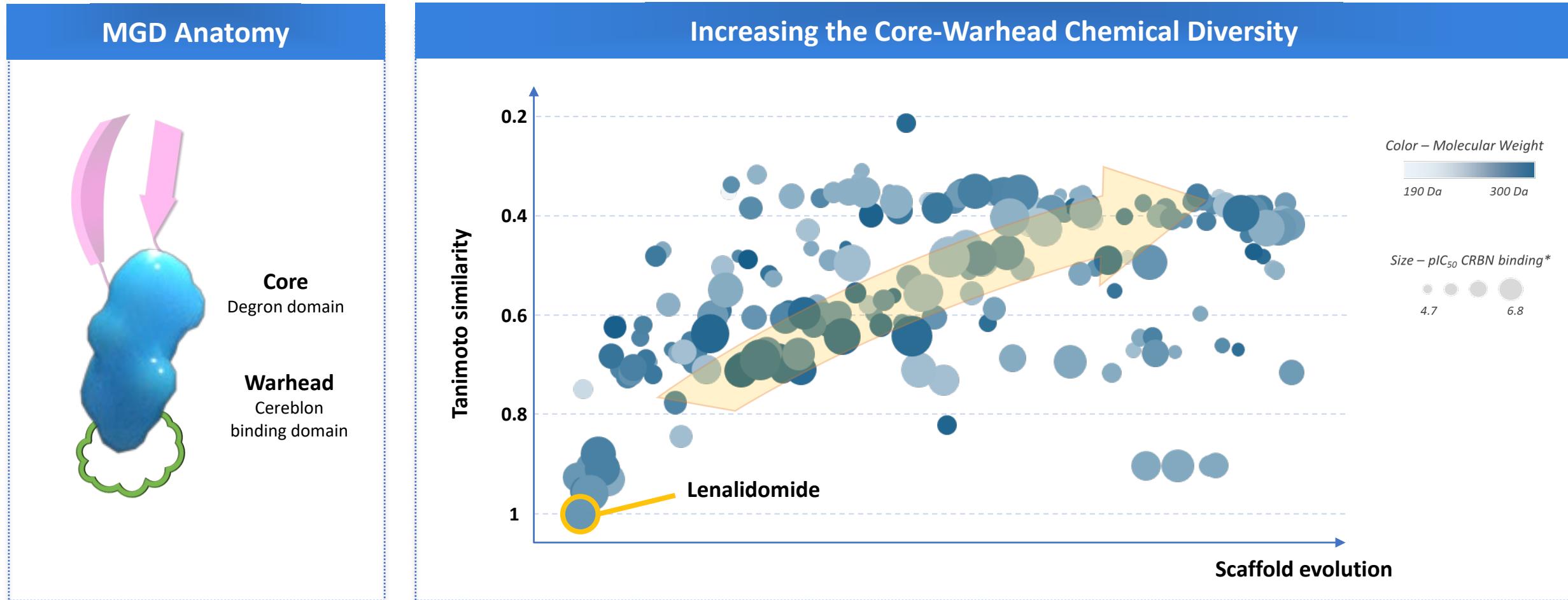
Additional structural loops revealed beyond the G-loop degrome



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

New Chemical Space: MGD Anatomy and Evolving MGD Library

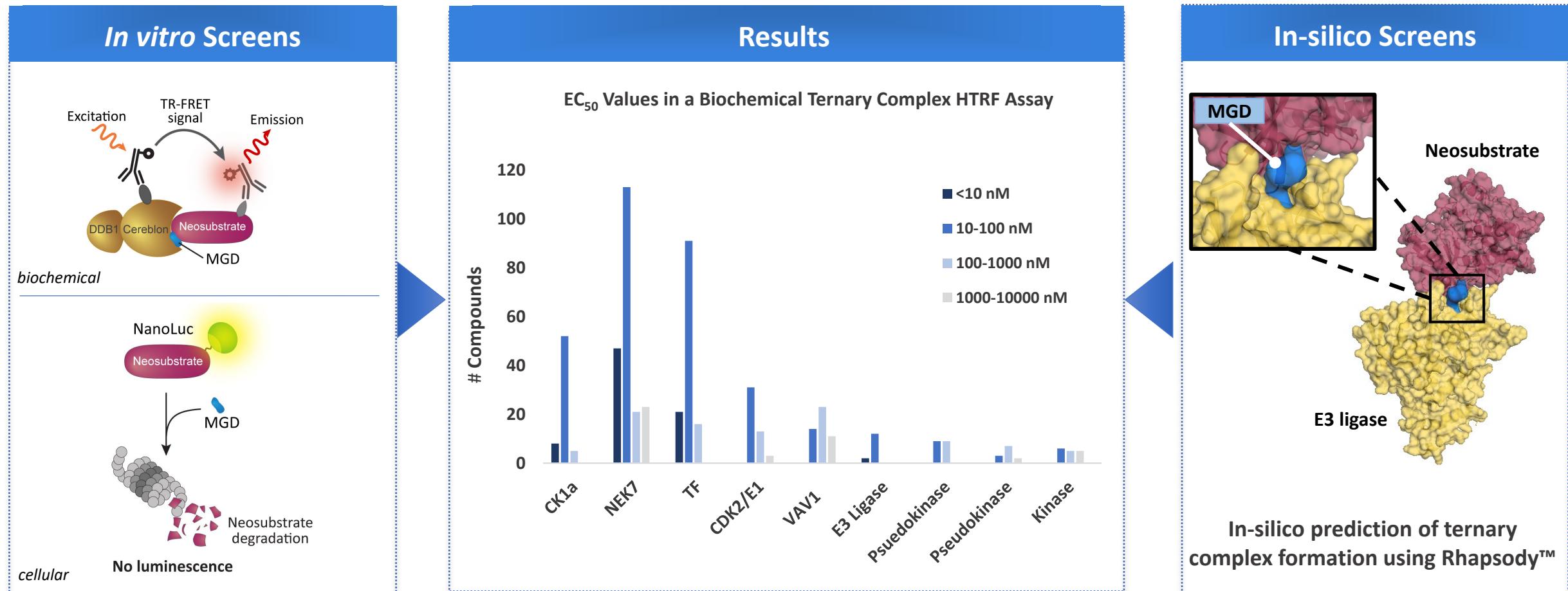
Increasing novelty and structural diversity to match the target space



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

Glueomics™ Toolbox Accelerates Identification of MGDs

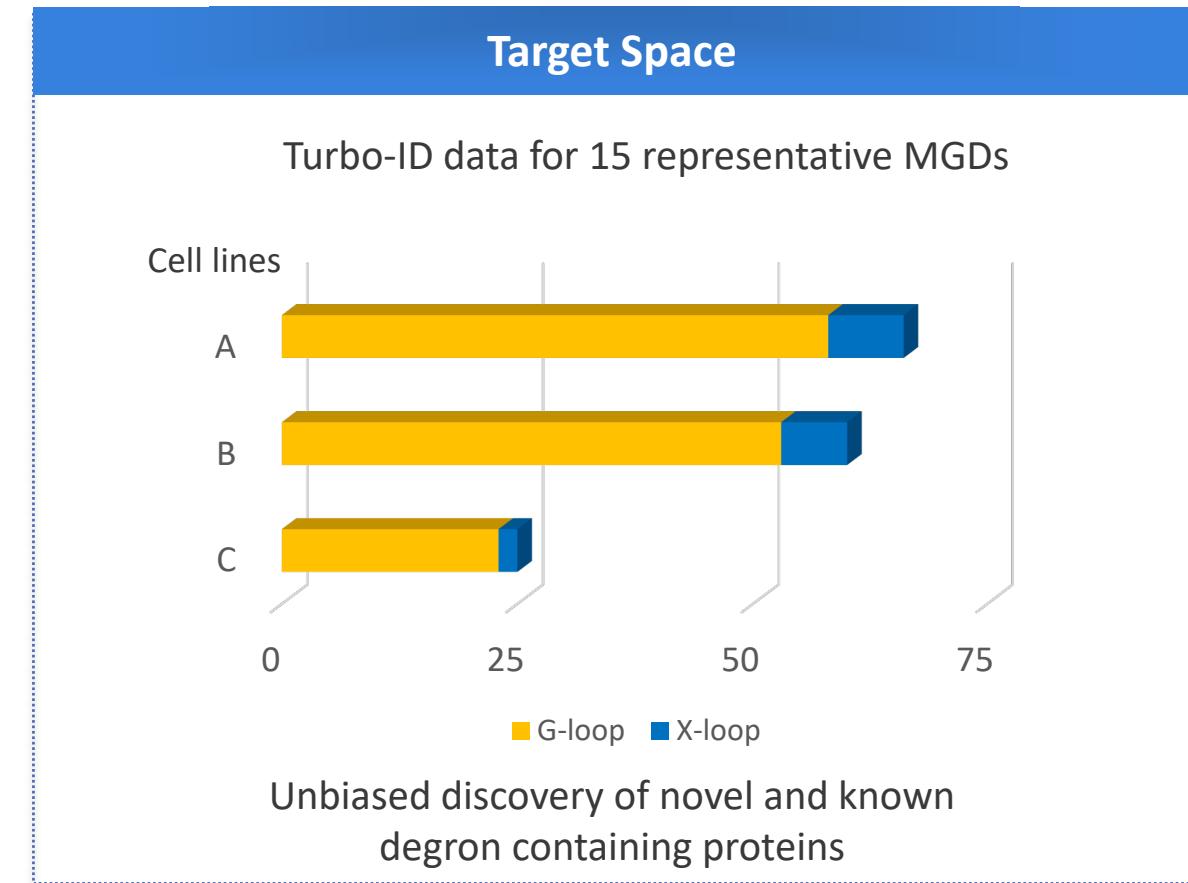
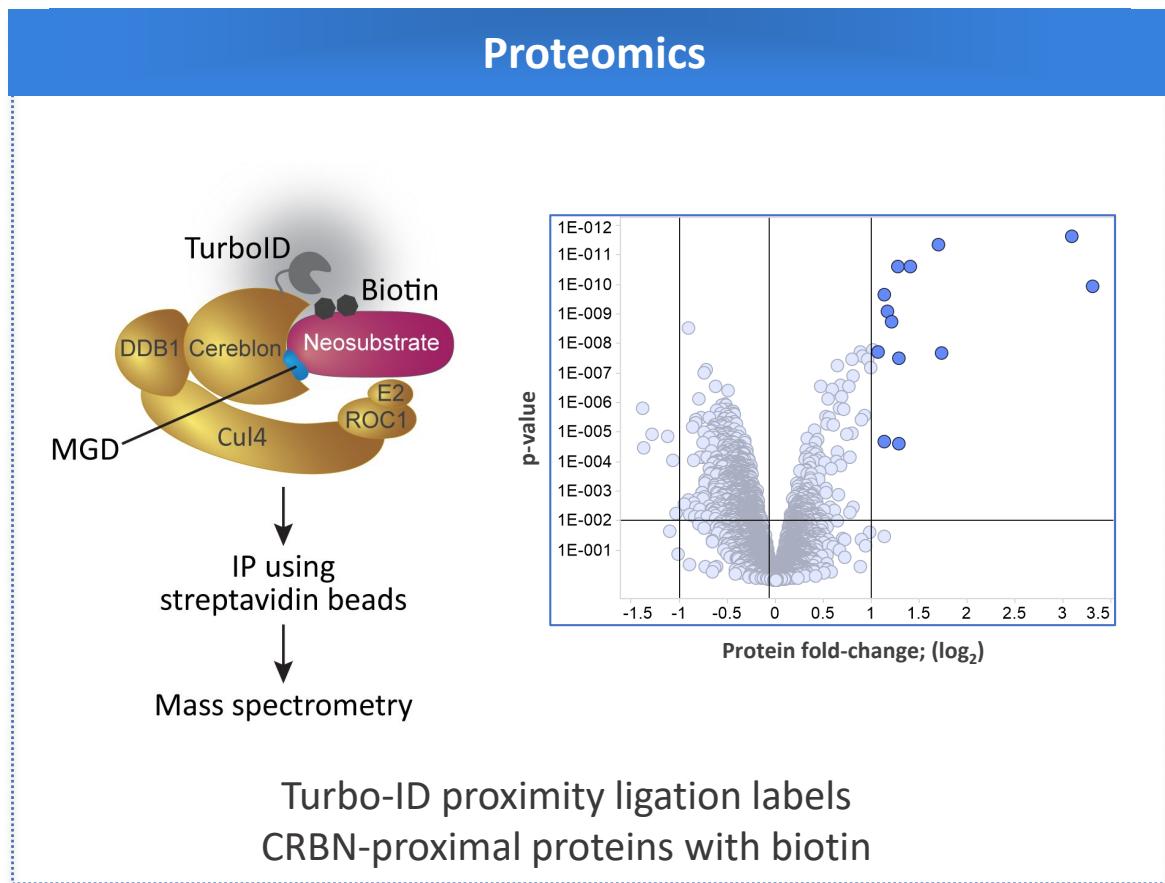
Matching target space to chemical space



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

Glueomics™ Toolbox Accelerates Exploration of MGD Space

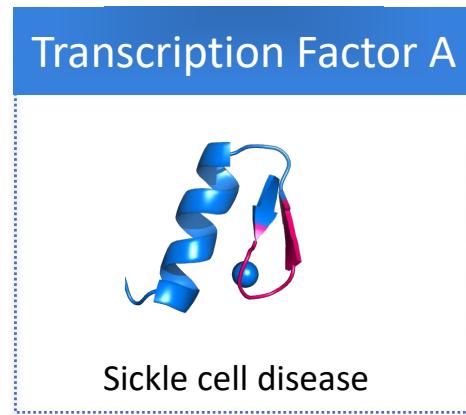
Exploring target space through chemoproteomics



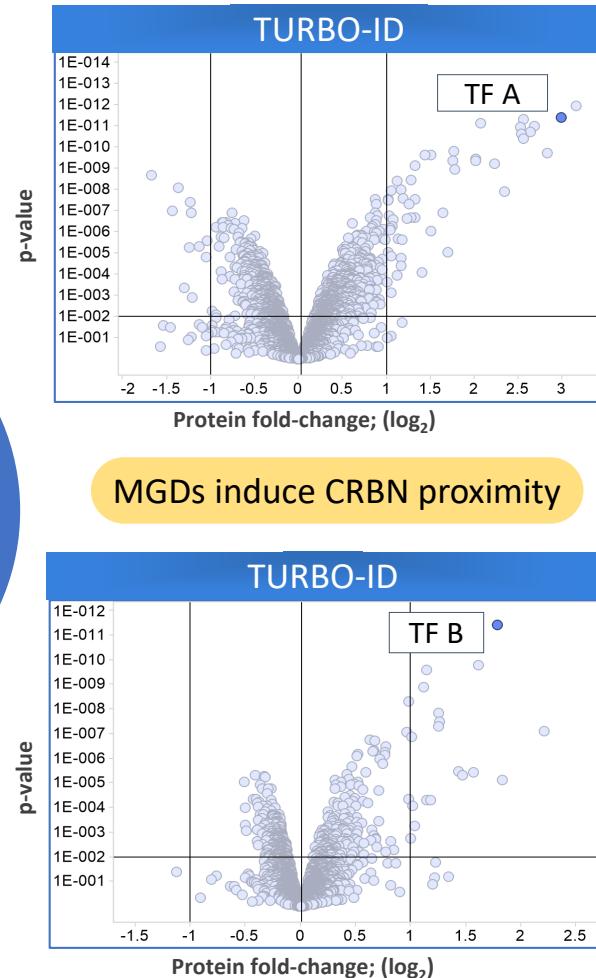
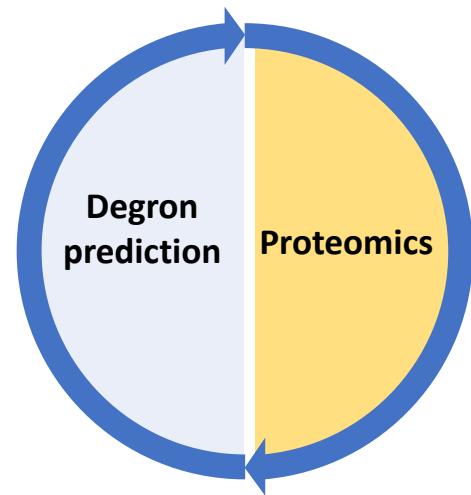
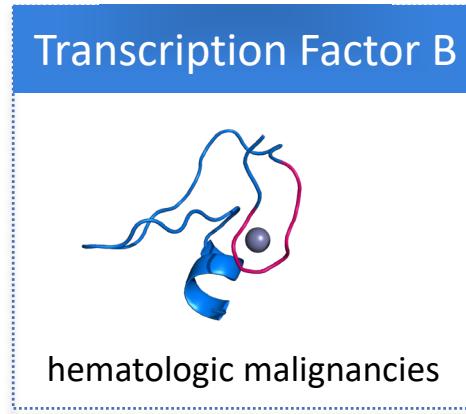
Chemoproteomics enables rapid target deconvolution and identification of novel degron containing targets

Chemoproteomics Accelerates Prediction-to-Validation

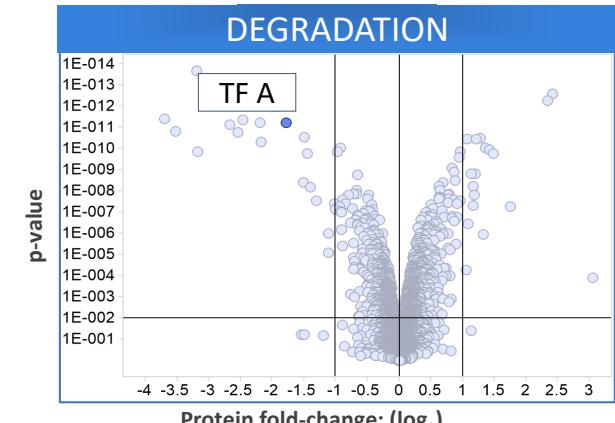
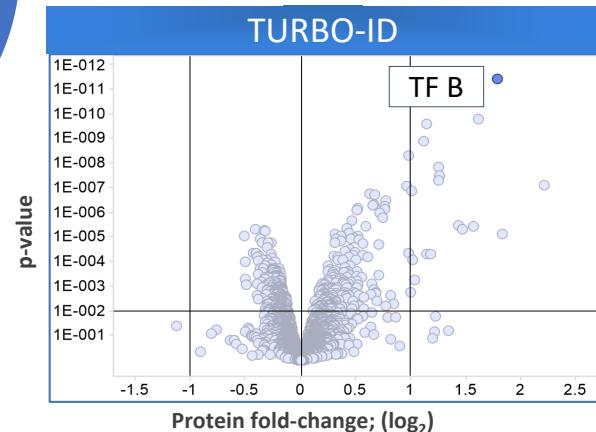
Experimental validation of targets using MS proximity (TurbolD) and degradation assays



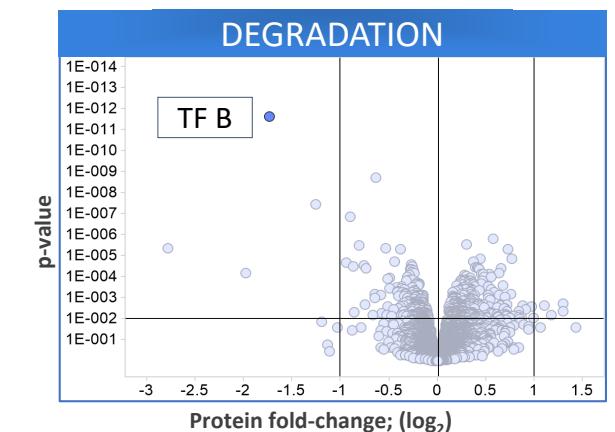
Novel predicted degrons



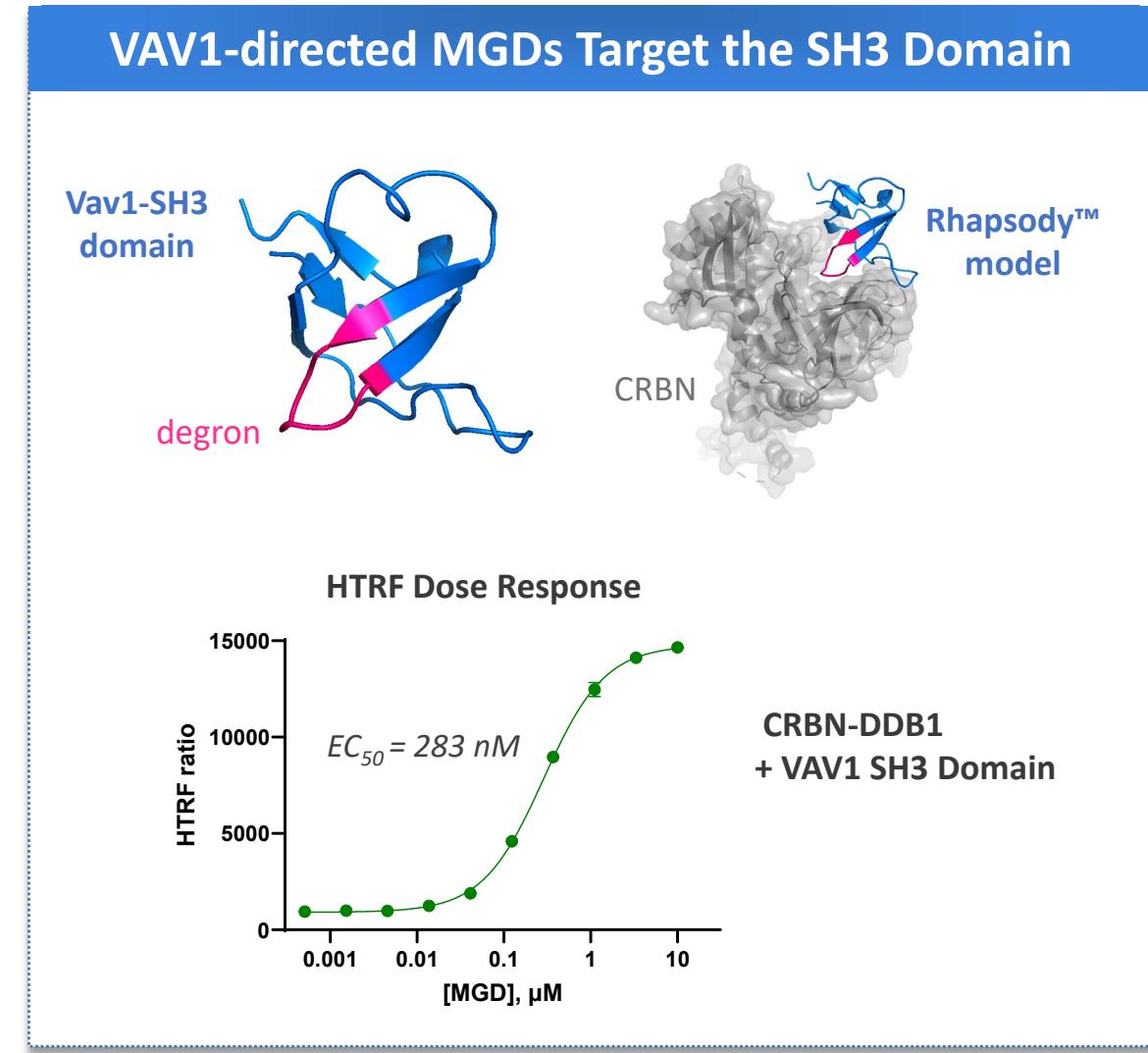
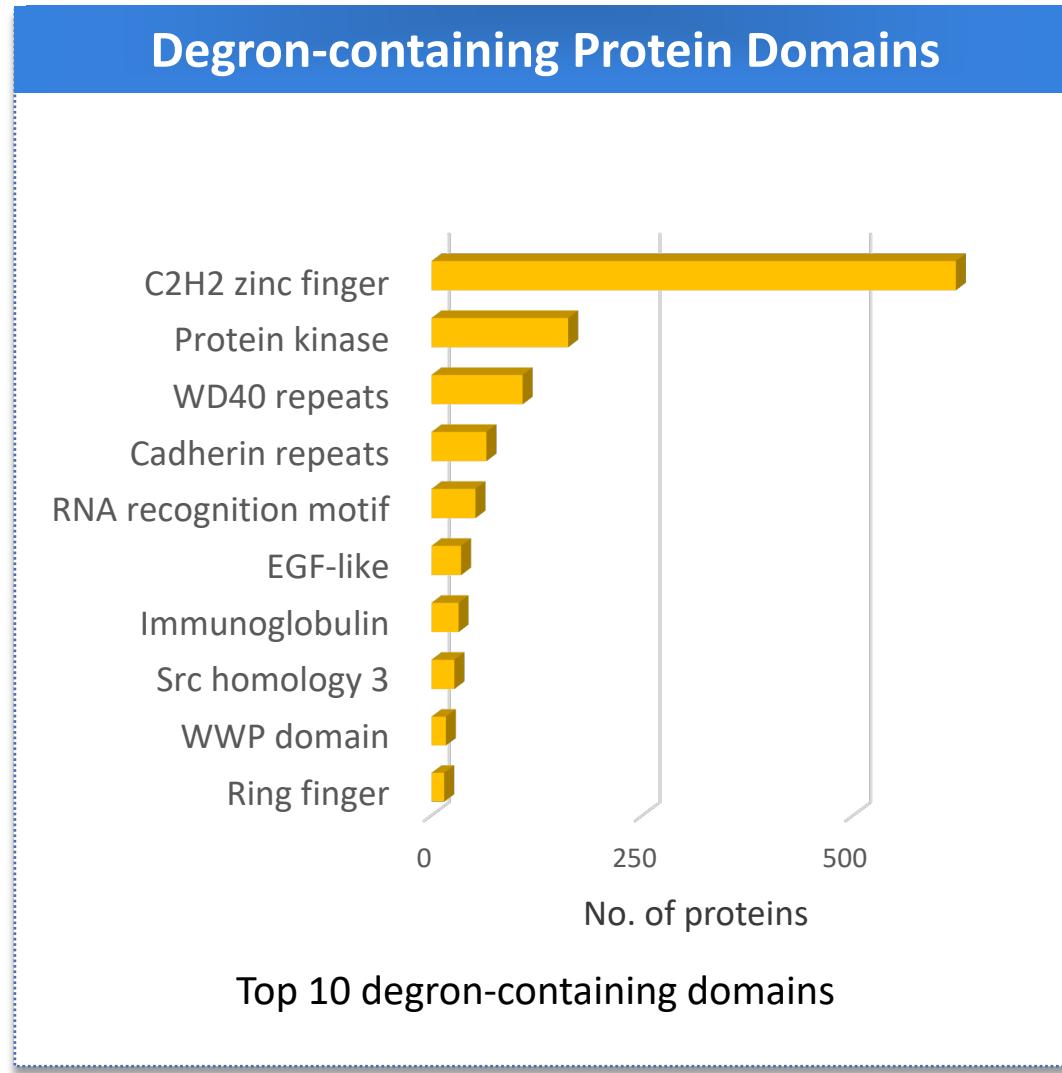
MGDs induce CRBN proximity



MGDs promote degradation

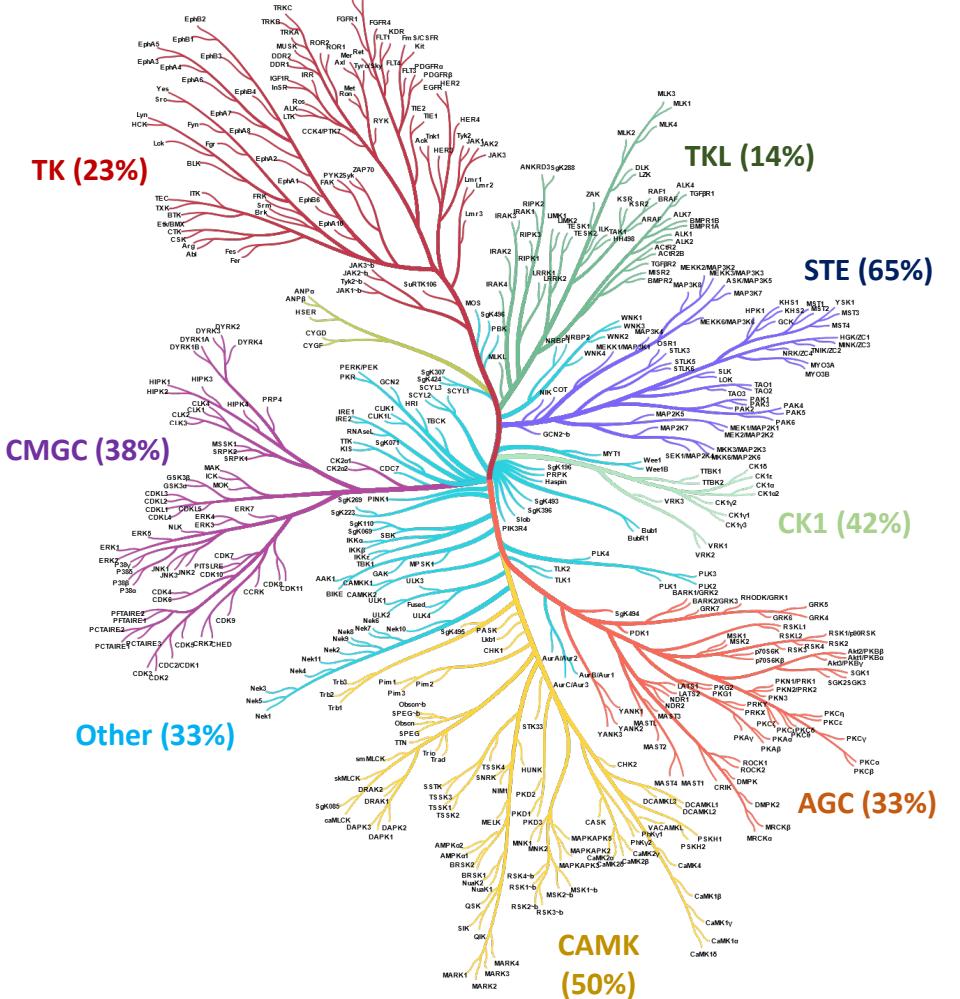


Multiple Protein Domains Contain Degrons



Many Kinases Contain Degrons

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



% kinase families with a predicted degron

Degrome

Uniqueness

Kinases with degrons

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

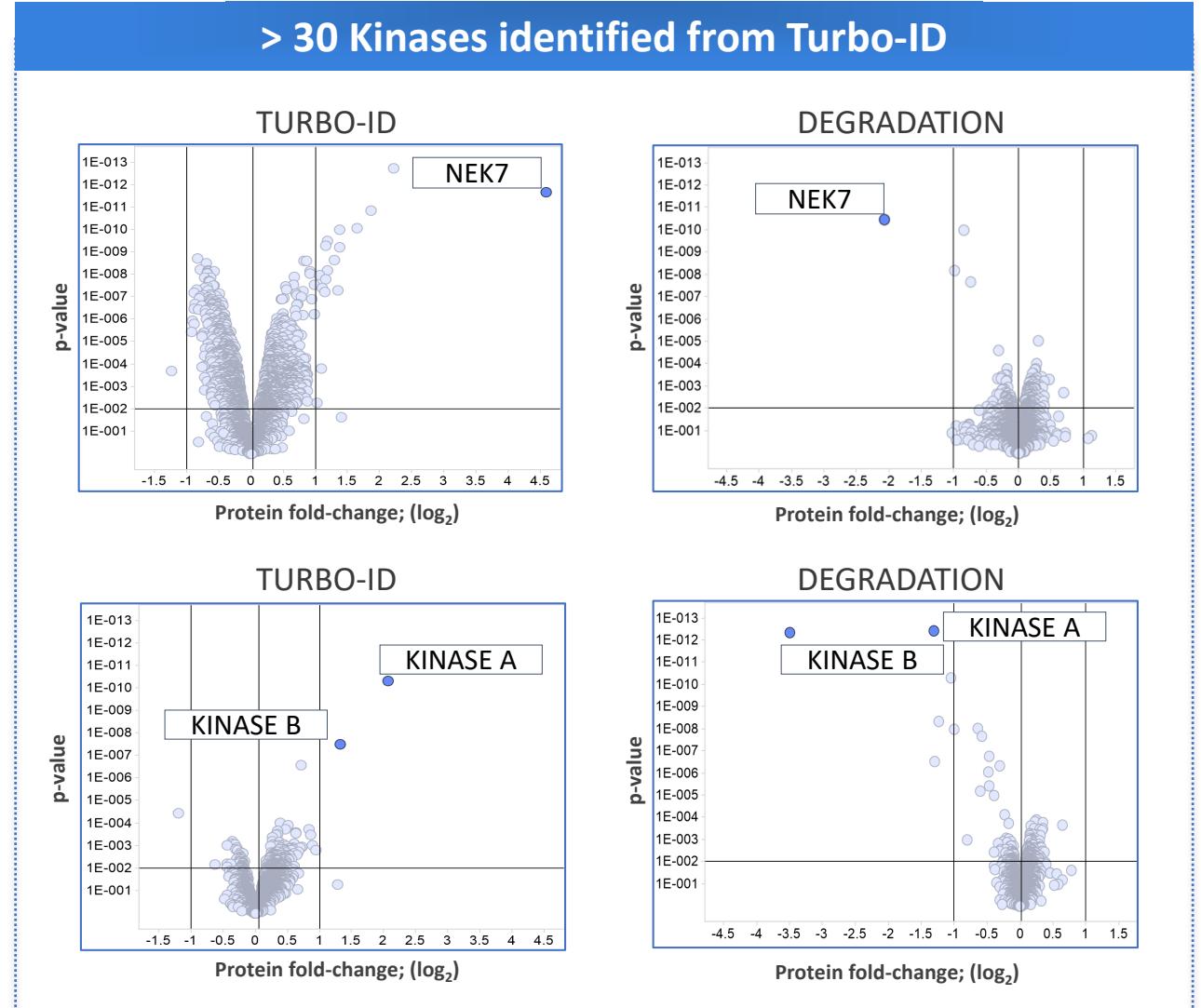
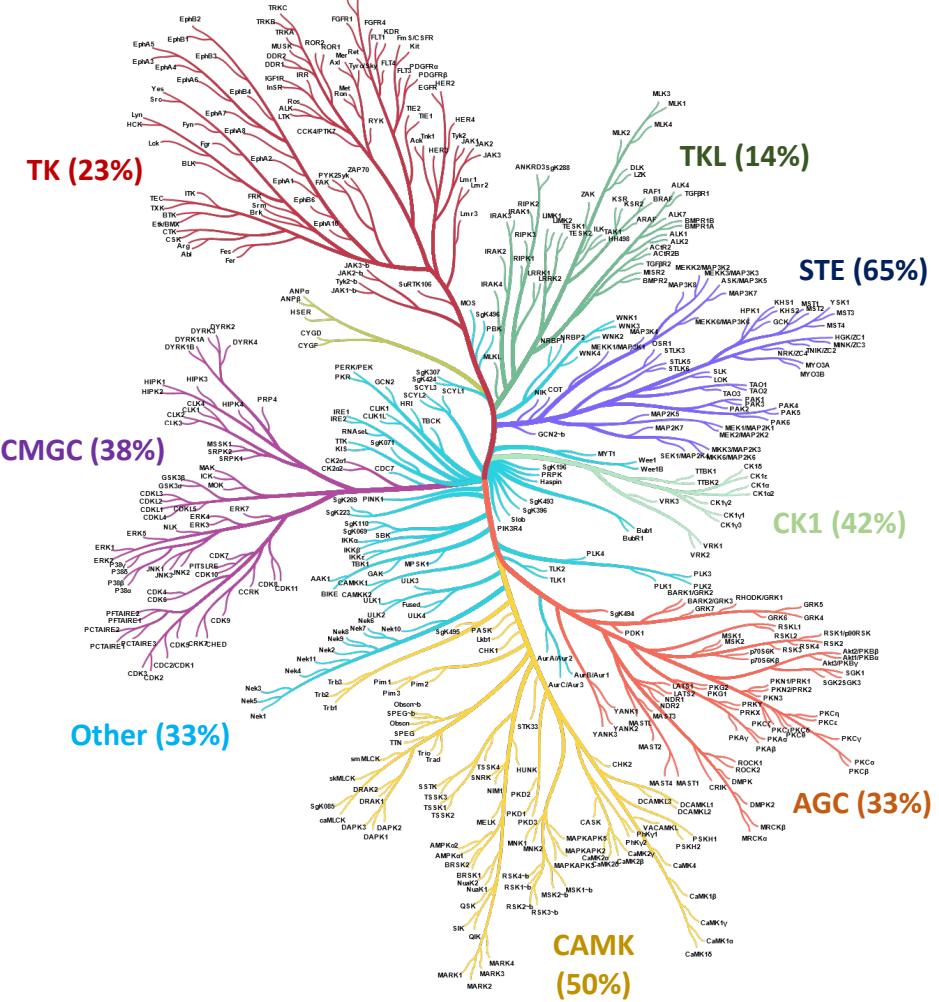
Degrongs provide a unique selectivity handle

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



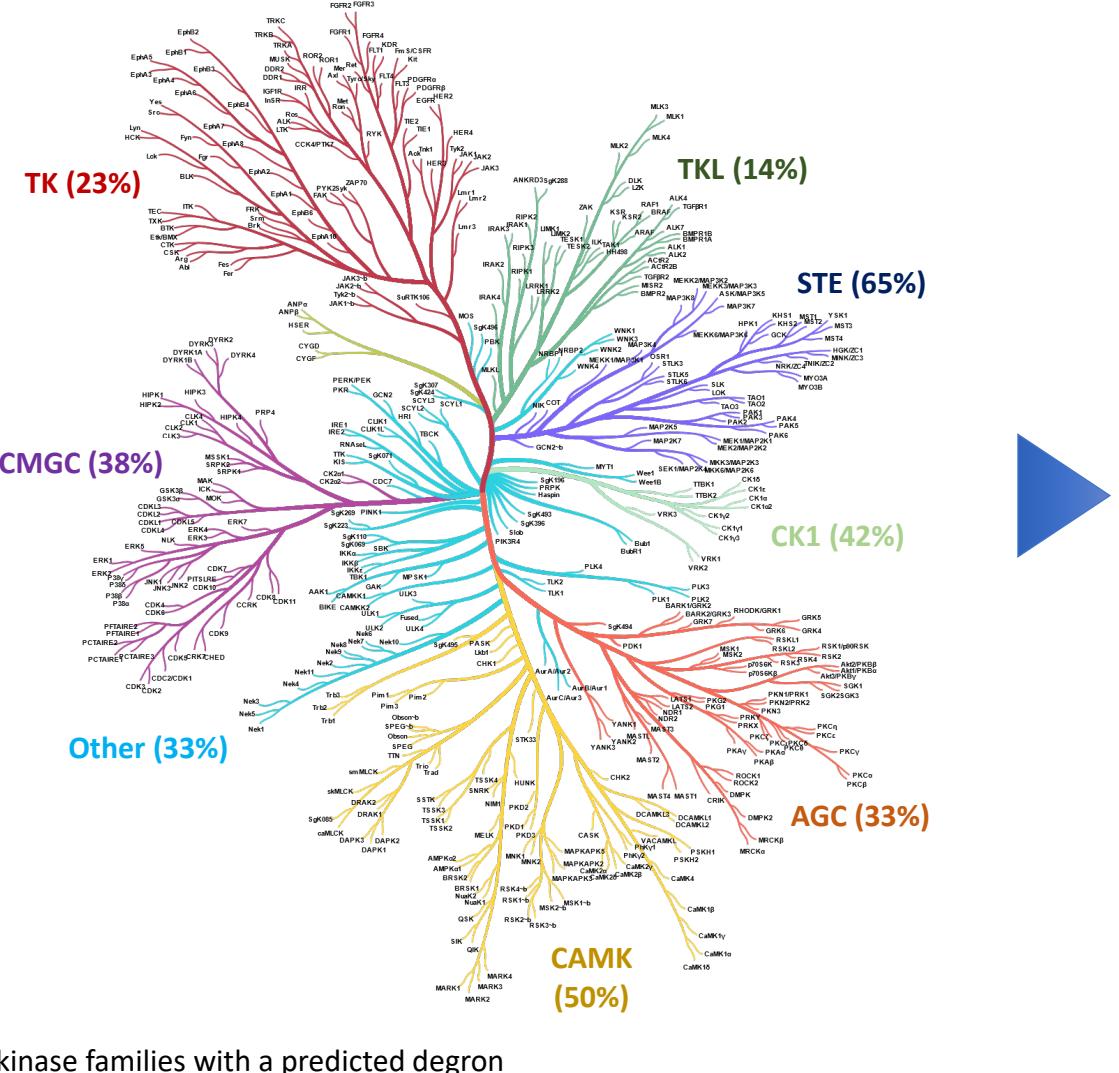
Many Kinases Contain Degrons

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



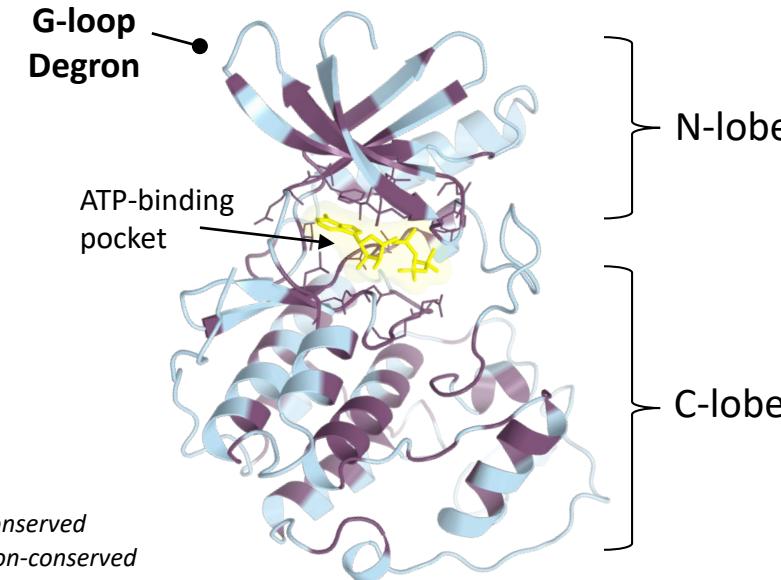
Many Kinases Contain Degrons

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



Degron sequence is diverse amongst CDK family members

Example: CDK2 and CDK4 structural similarity



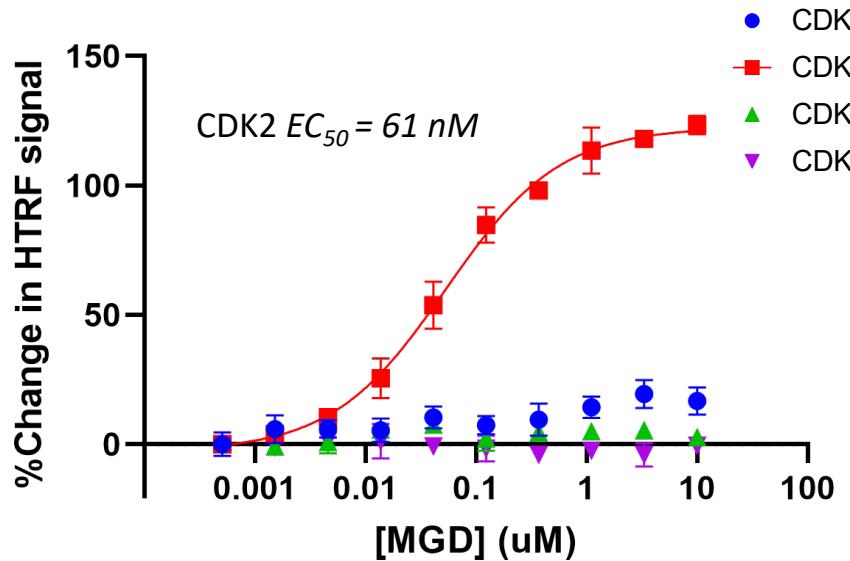
- High ATP-binding site conservation
- Low homology in the degron sequence



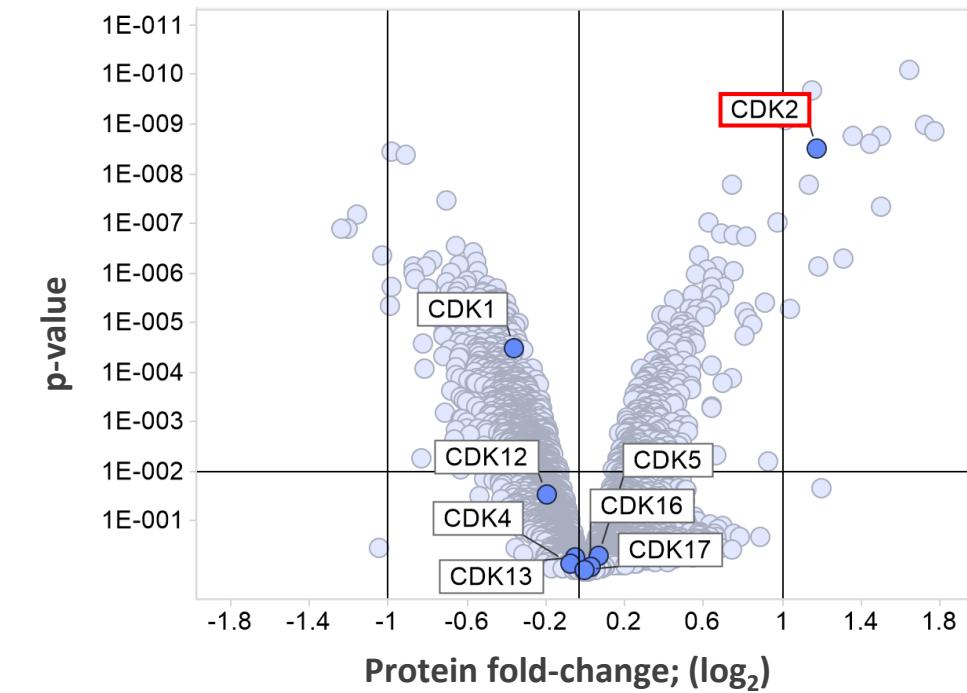
CDK2-Directed MGDs are Selective over other CDKs

MGDs identified through biochemical screens induce cellular proximity with CCRBN

MGDs are biochemically selective over CDK1,
CDK4 and CDK9



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

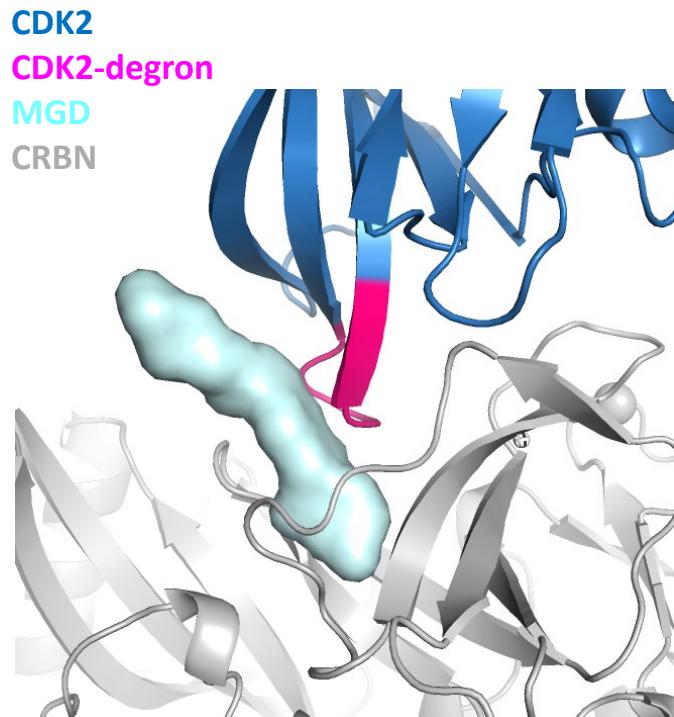


Turbo-ID Proteomics (HEK293) – 6hr post treatment

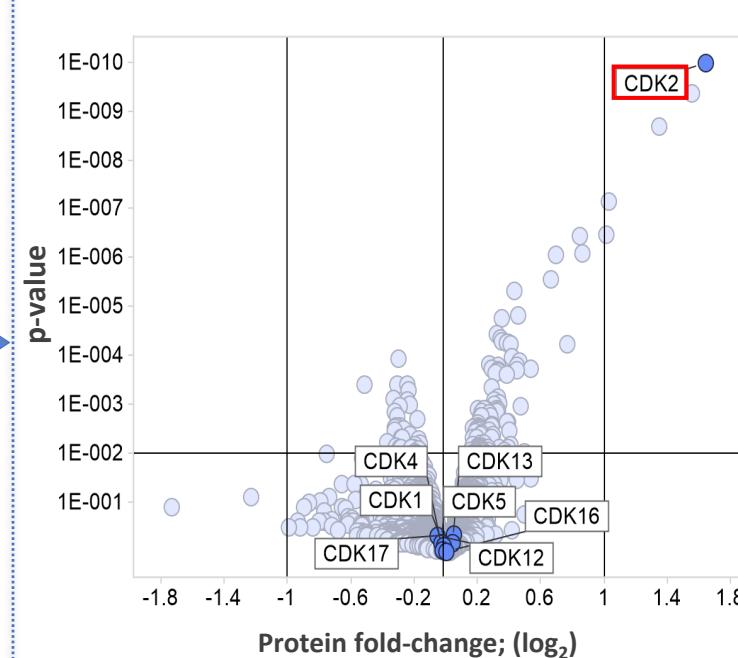
Rationally Designed CDK2-Directed MGDs are Selective Degraders

Demonstration of selective CDK2 degradation with MGD treated cells

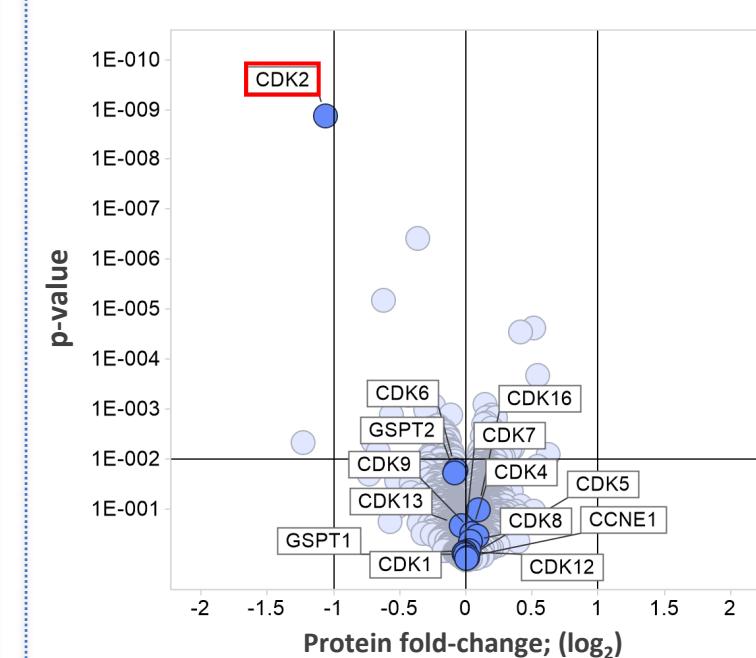
Rhapsody™ model enables rapid chemistry optimization



Rationally designed MGDs promote more selective CRBN proximity



Rationally designed MGDs selectively degrade CDK2



Monte Rosa Pipeline

Rapidly advancing wholly owned MGD programs

Target / Program	Indication(s)	Discovery	IND-Enabling
GSPT1	Lung Cancer (NSCLC, SCLC)		
NEK7	Inflammatory Diseases		
CDK2	Ovarian Cancer, Breast Cancer		
VAV1	T and B Cell Malignancies, Autoimmune Disease		
BCL11A	SCD, β-Thalassemia		
Undisclosed	Multiple		



Oncology



Autoinflammation



Oncology / immunology



Genetic diseases



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Thank You

