From Serendipity to Rational Design

Taking Molecular Glue Degraders to New Heights | 2nd Annual TPD Europe Summit, March 17, 2022

Amine Sadok, PhD

Sr Director - Head of Discovery Technologies

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 and in silico tools, the advancement of our pipeline and the various products therein, including -the timing for filing our IND for our GSPT1 program and the advancement of additional programs, 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 for GSPT1 program. 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 Quarterly Report on Form 10-Q for the third quarter ended September 30, 2021 filed with the US Securities and Exchange Commission, and any subsequent filings, 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.

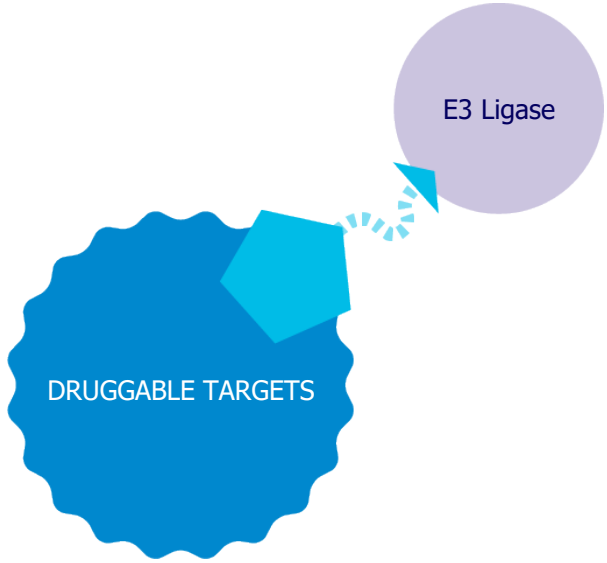
Molecular Glue Degraders (MGDs)

Expanding target space, fostering a new generation of drugs

INHIBITOR

Drugging
the Druggable

PROTAC



Redrugging
the Druggable

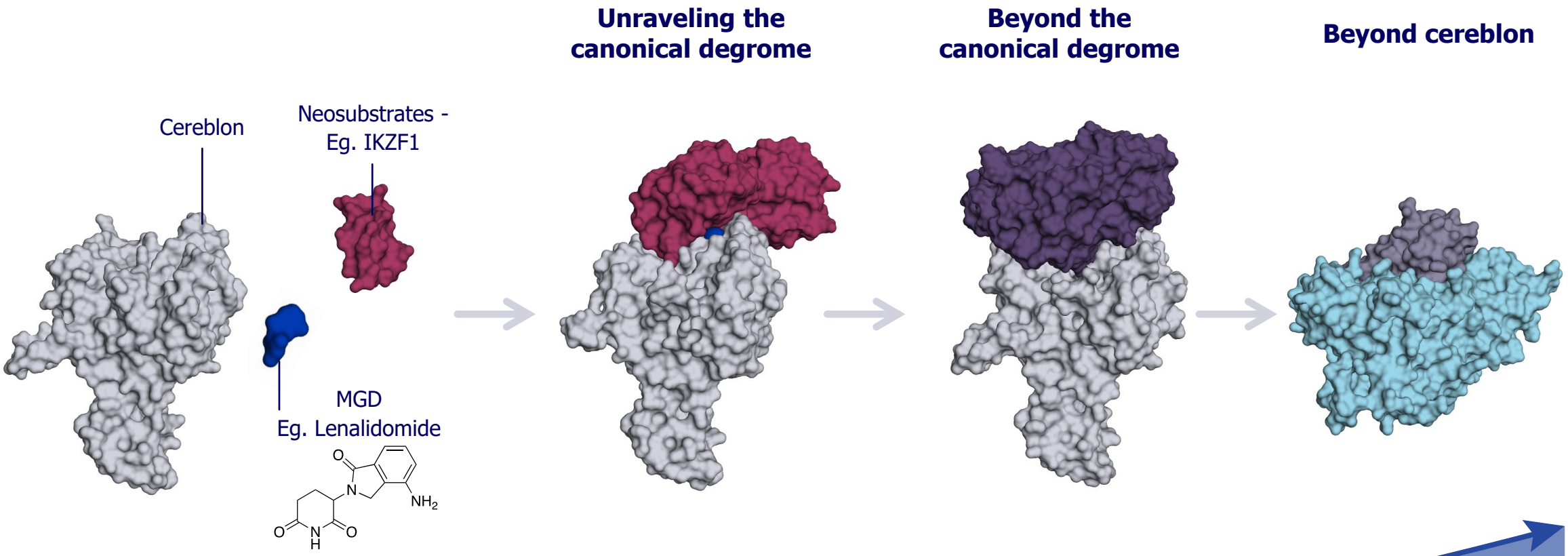
MGDs

Drugging
the Undruggable

Expanding the Degradable Proteome

Target Space

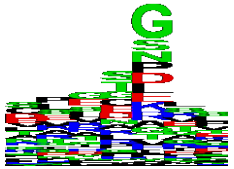
Our Rational Approach to Unleash the Full Potential of MGDs



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

Degron encyclopedia

Degron discovery using proprietary AI-powered algorithm



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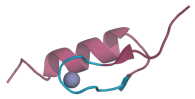
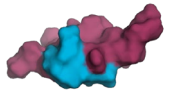


Topology

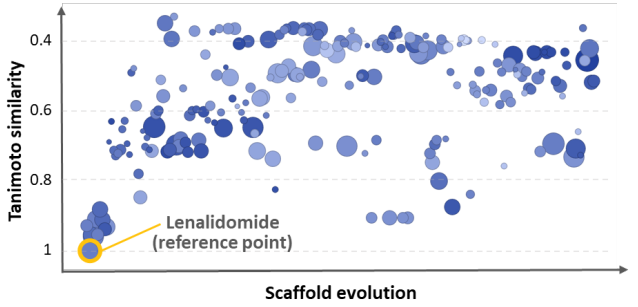


Surface

1000s of proteins across multiple degrons

Proprietary MGD library

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



Cereblon binding (pIC_{50})

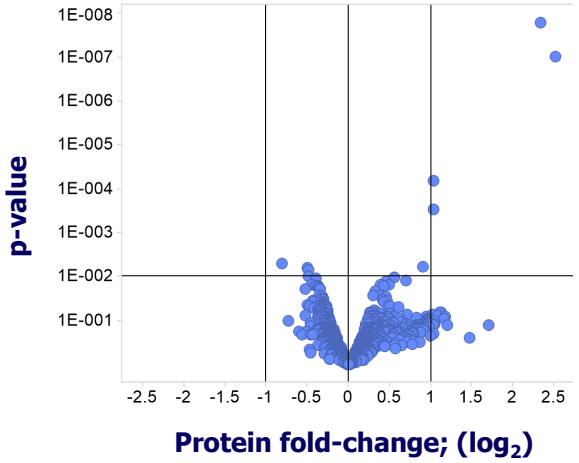
5 7

Molecular weight (Da)

190 300

Glueomics™ toolbox

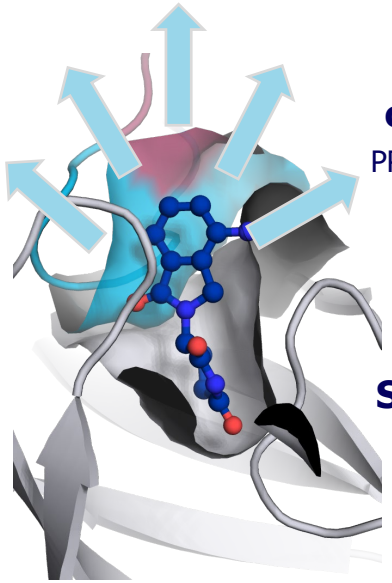
Specialized suite of *in vitro* and *in silico* assays to discover, optimize and advance MGDs as clinical candidates



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

Expanding MGD Exit Vectorology Engages Novel Degron Classes

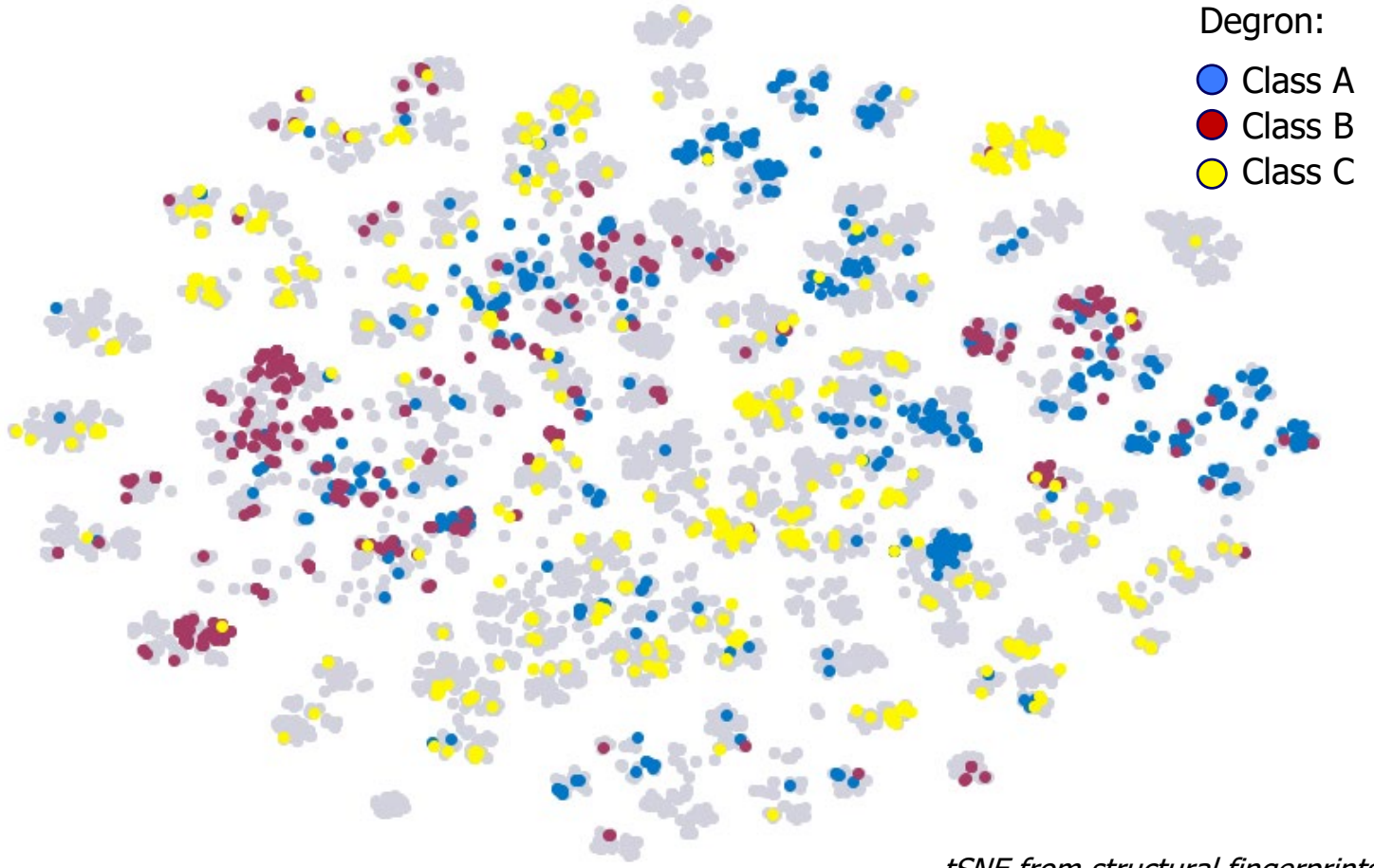
MGD diversification



Side-chains
PPI domain

400+ Scaffolds

Expanded MGD diversity engages more degron classes

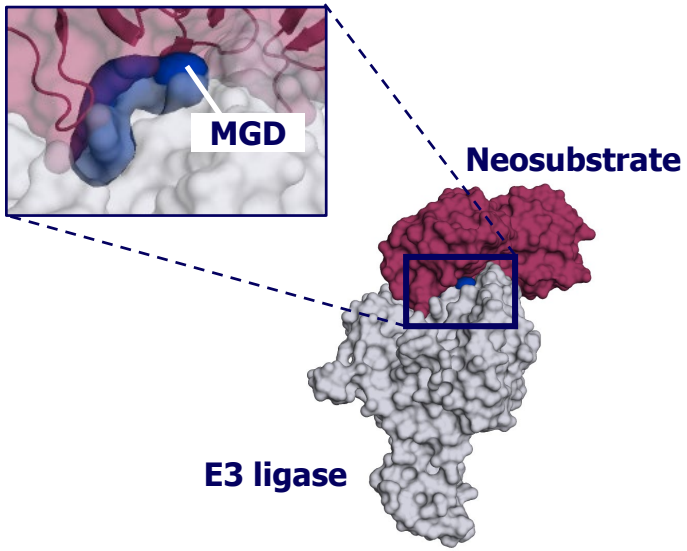


tSNE from structural fingerprints

MGDs Reprogram the Cereblon Surface

Remodeled MGD-CRBN surface enables selective engagement of neosubstrates

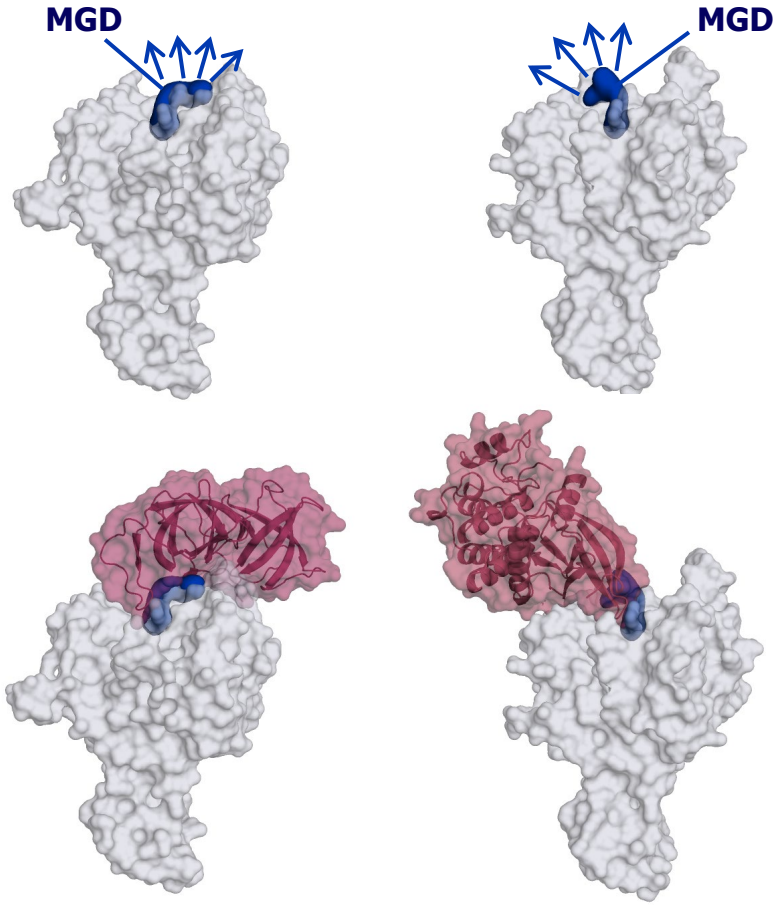
Multiple points of contact for dialing in selectivity and potency



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



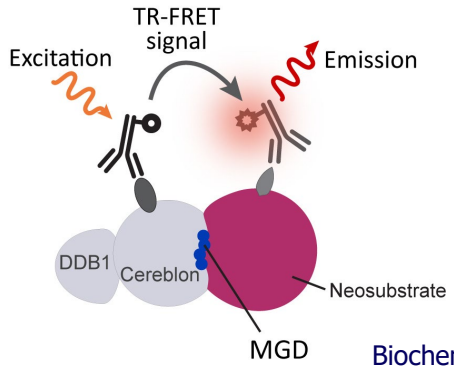
MGDs reshape the cereblon surface through different exit vector geometries

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

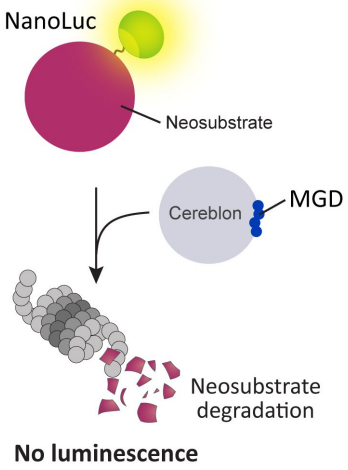
Glueomics™ Toolbox Accelerates Identification of MGDs

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

in vitro screens

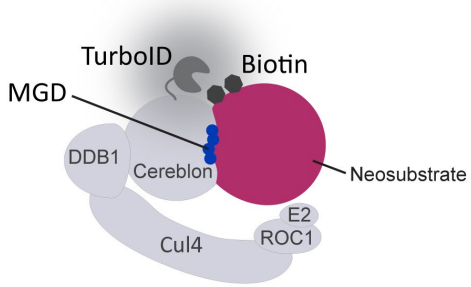


Biochemical



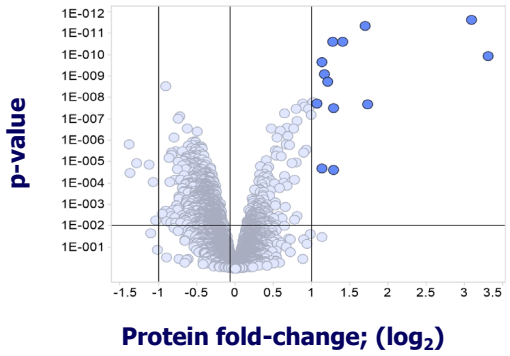
Cellular

Chemoproteomics - proximity



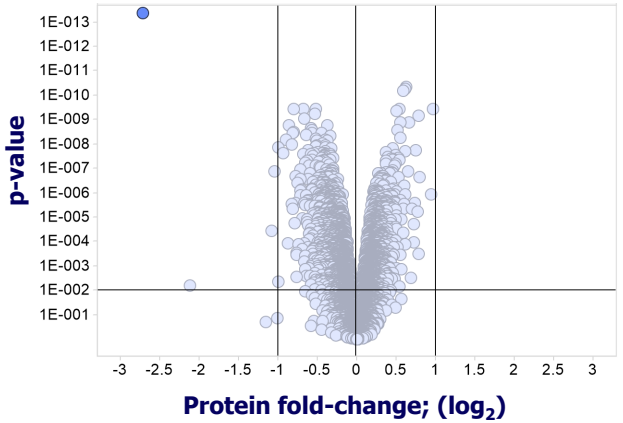
IP using
streptavidin beads

Mass spectrometry



Turbo-ID

Proteome-wide expression



TMT Proteomics to evaluate:

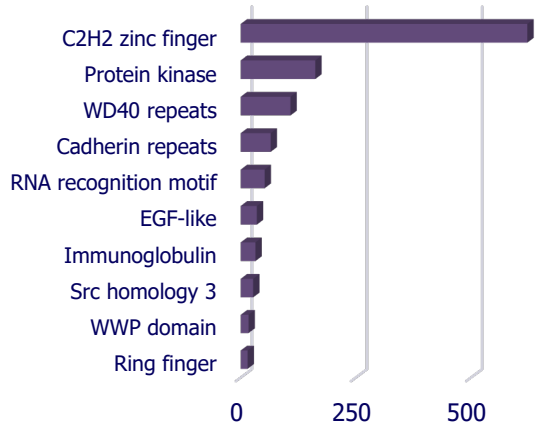
- Proteome-wide changes in protein levels
- MGD selectivity

A Rich, Differentiated Target Space Across Protein Domains and Diseases

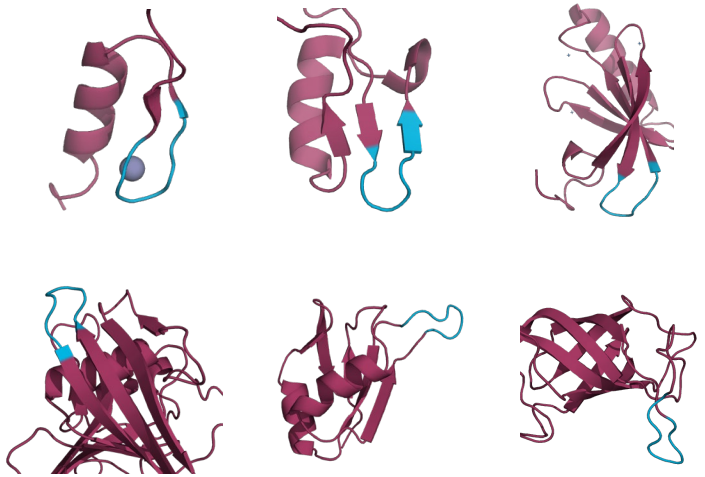
Degron Encyclopedia

>3000 proteins containing a predicted loop degron

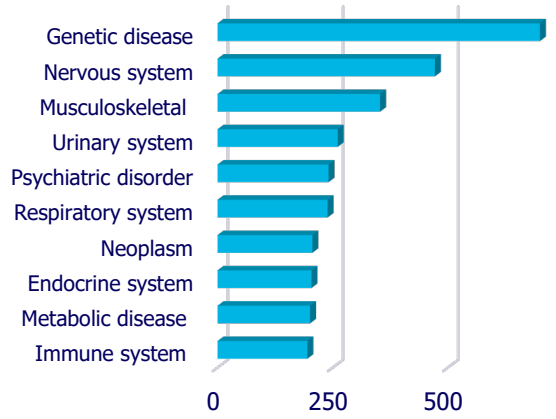
Degron-containing domains



Predicted degrons



Broad disease landscape



Diverse protein domains and classes

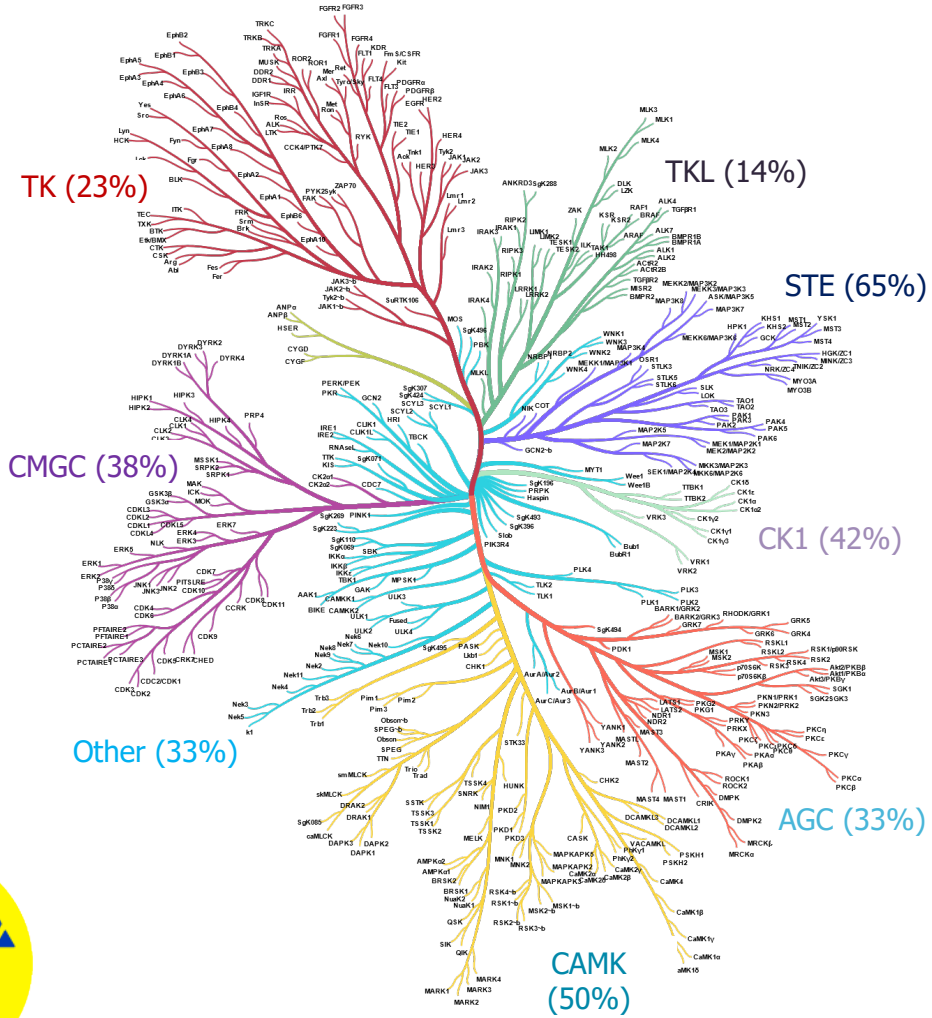
>85% degrons have unique sequence

>75% undruggable

Many highly credentialed targets

Degron Encyclopedia Predicts Degrons in Specific Kinases

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



% kinase families with a predicted degron

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

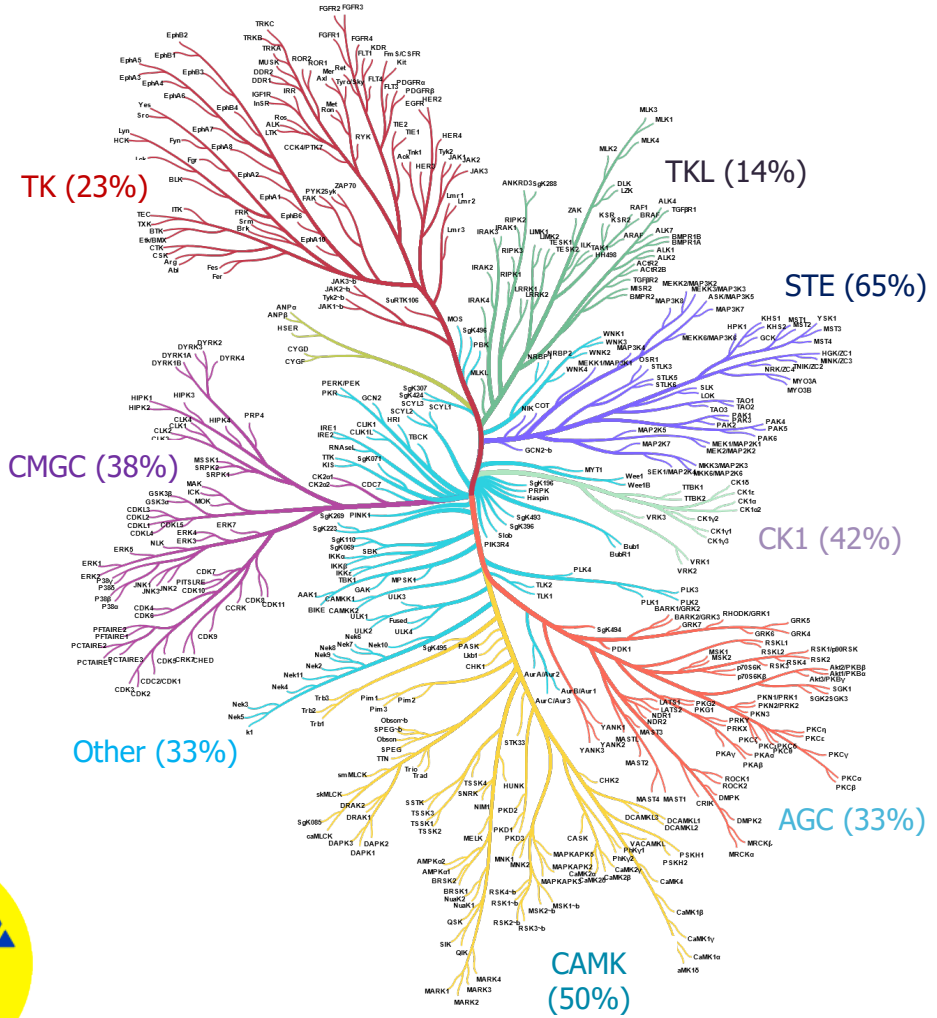
Uniqueness

Degrons provide a unique selectivity handle

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

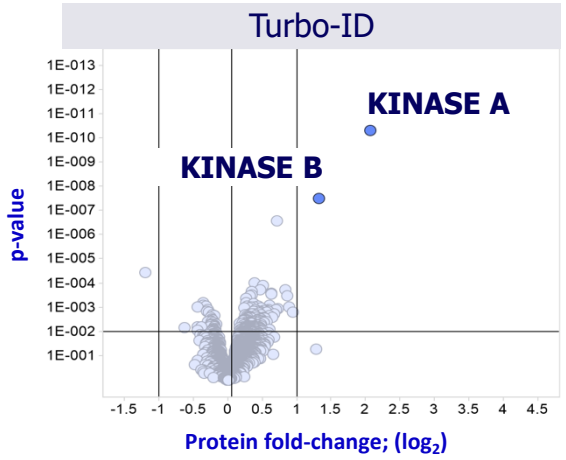
Degron Encyclopedia Predicts Degrons in Specific Kinases

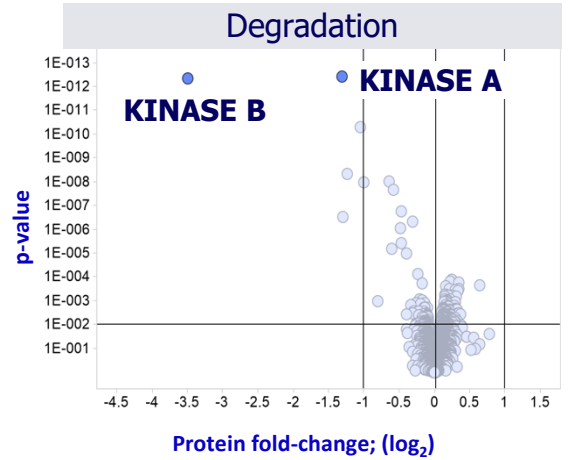
Chemoproteomics confirm neosubstrate induced proximity and degradation

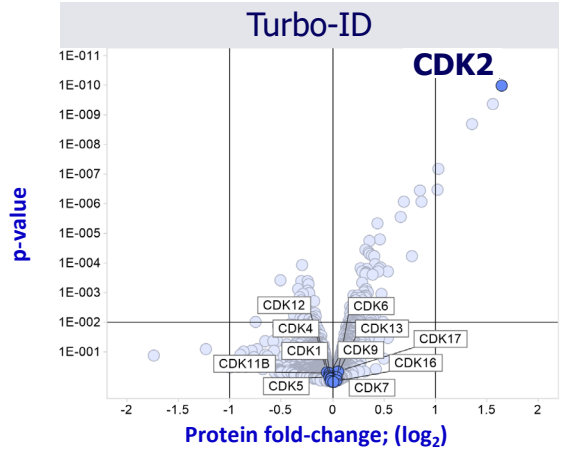


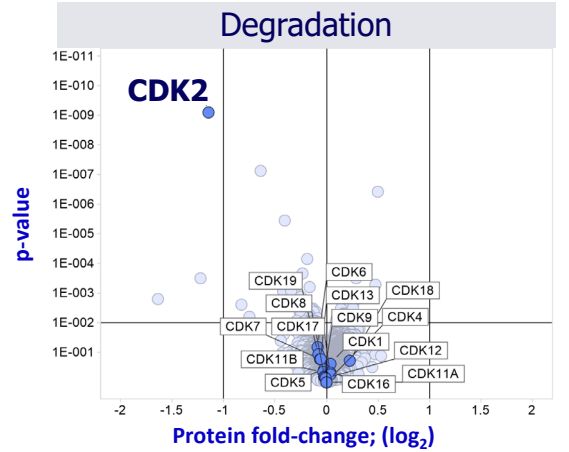
% kinase families with a predicted degron

> 30 kinases identified from Turbo-ID



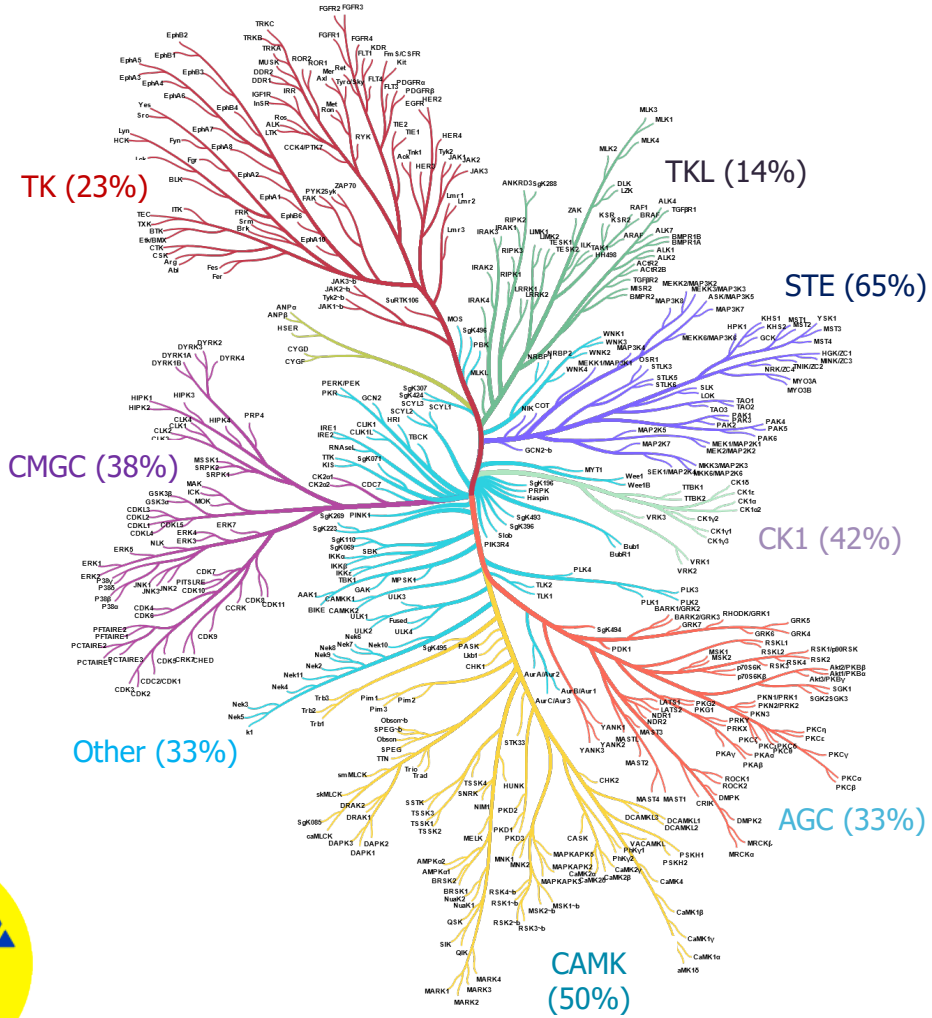






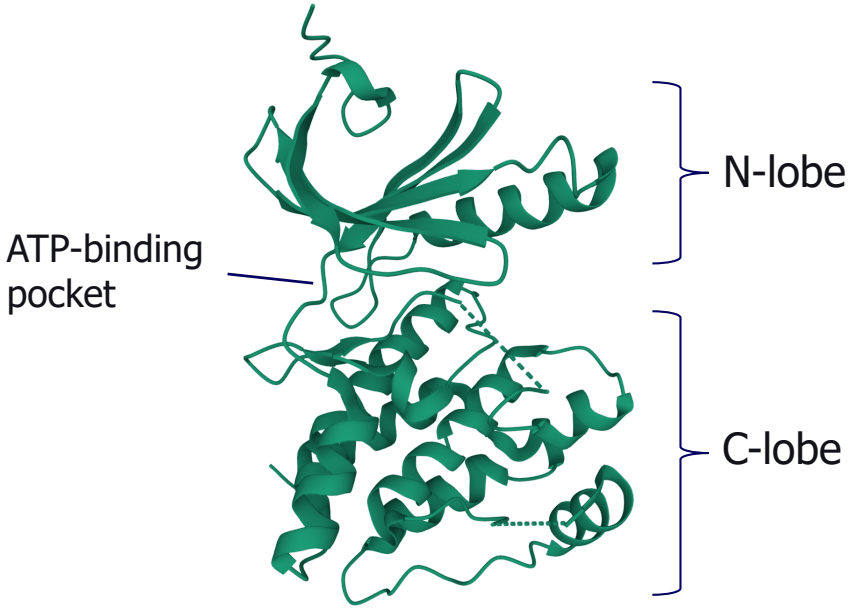
Degron Encyclopedia Predicts NEK7 has Unique Degron

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



% kinase families with a predicted degron

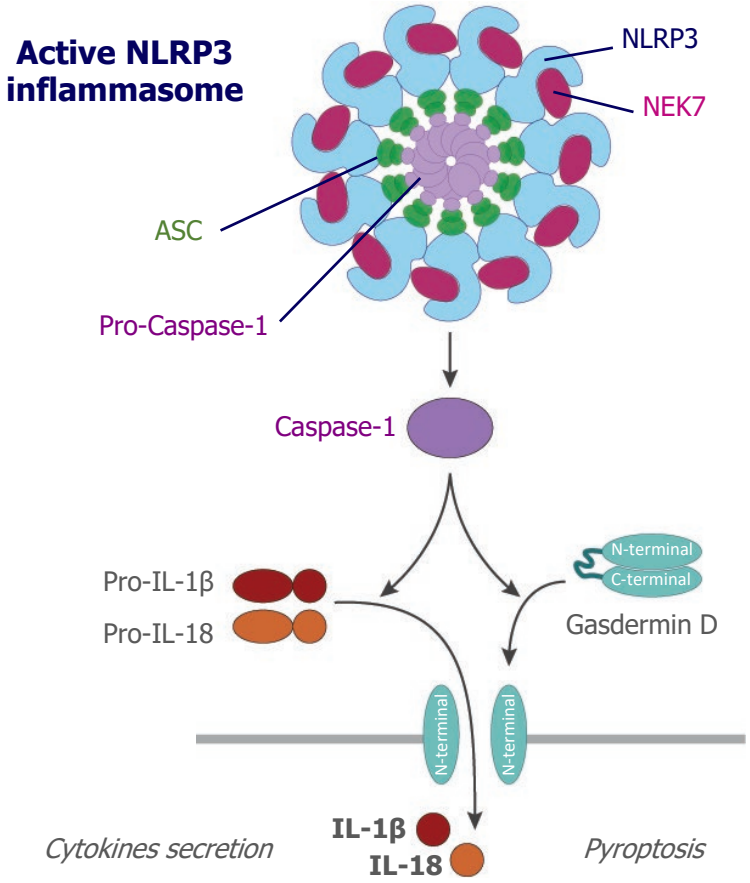
NEK7 degron sequence is unique among NEK family



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

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

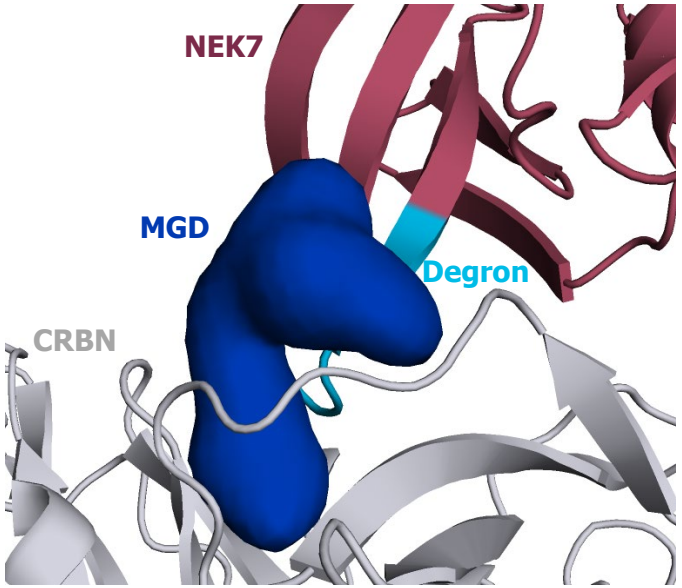
- NEK7 licenses NLRP3 assembly in a kinase independent manner
- NEK7-deficient macrophages are severely impaired in IL-1β and IL-18 secretion

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)

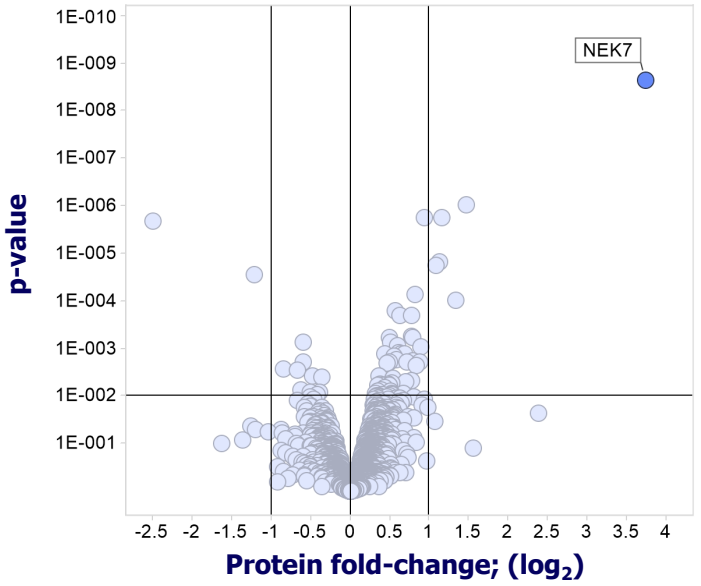
Rationally Designed NEK7-Directed MGDs are Selective

Rhapsody model enables rapid chemistry optimization



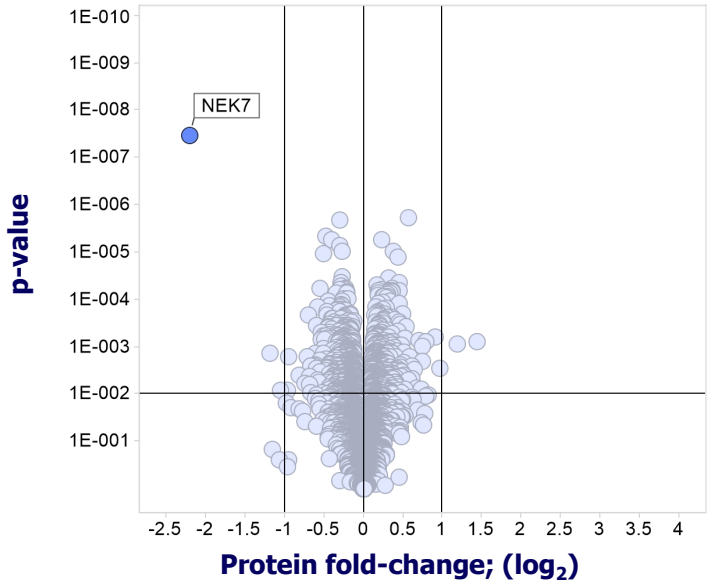
in vitro data	
CRBN binding, K_i	48 nM
Ternary complex, EC_{50}	20 nM
Degradation, DC_{50}	10 nM

Rationally designed MGDs promote selective CRBN proximity



Turbo-ID – 6hr post treatment

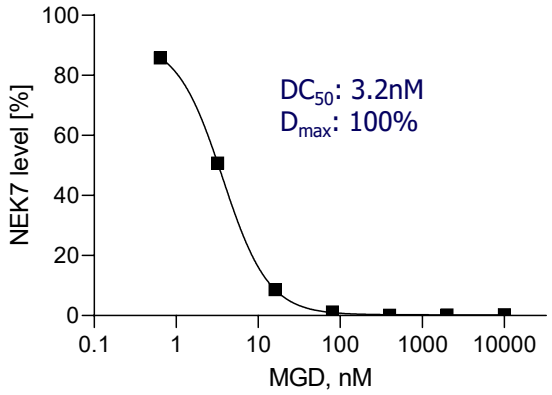
NEK7-directed MGD promotes selective degradation of NEK7

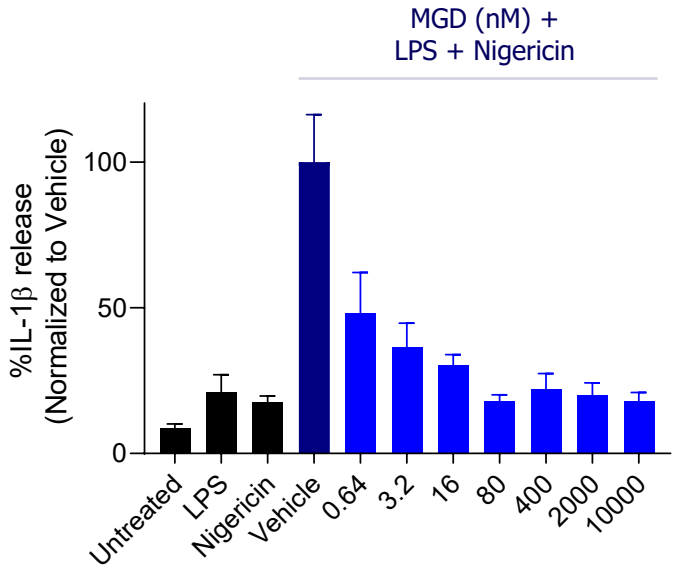


TMT-Proteomics – 24hr post treatment

NEK7-directed MGDs Modulate NLRP3 Pathway in Human Macrophages

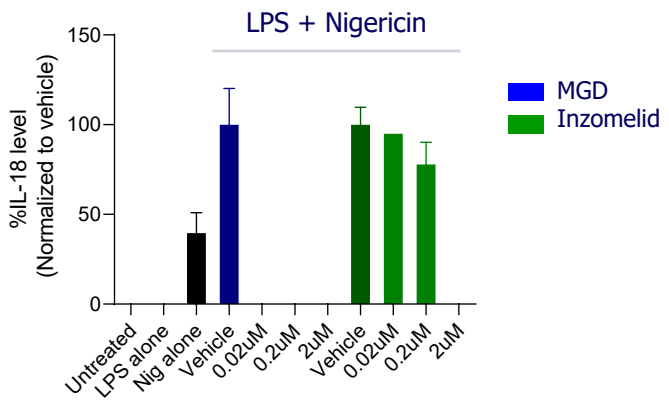
MGDs promotes NEK7 degradation and pathway engagement in hMDMs



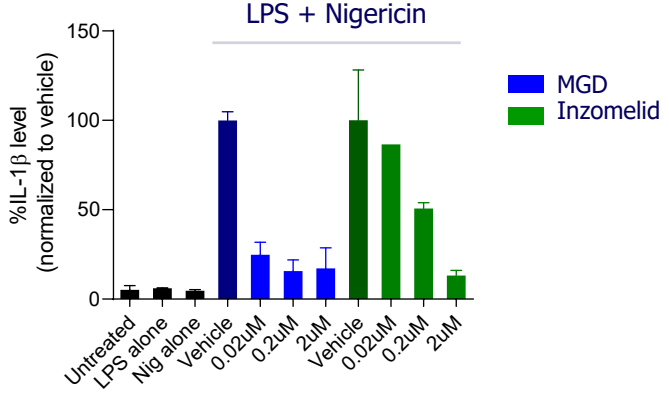


NEK7-directed MGD compared to NLRP3 inhibitor

IL-18



IL-1β



Western blot – 24 hr

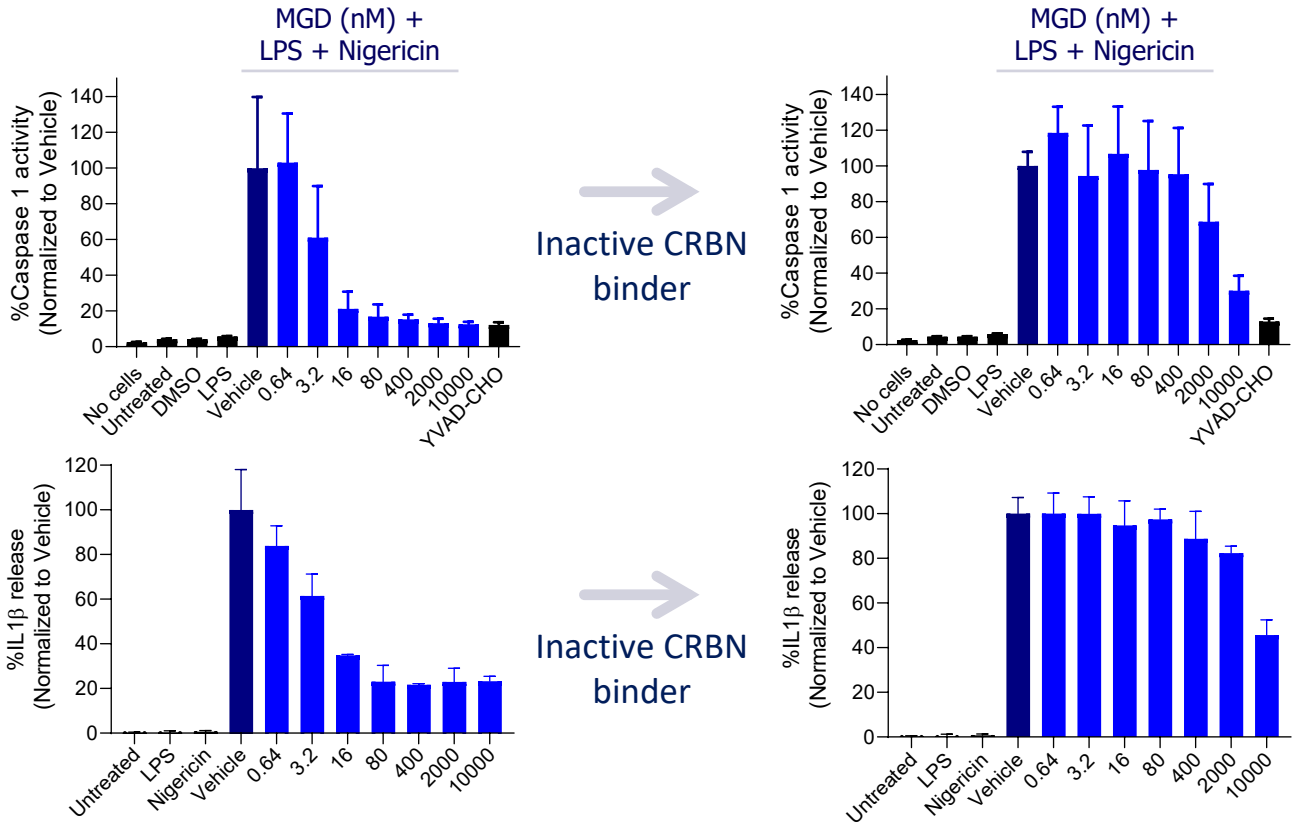
Treatment (6hr) of primed hMDMs

Treatment (20 hr) of primed hMDMs

CASP1 and LDH showed similar profile

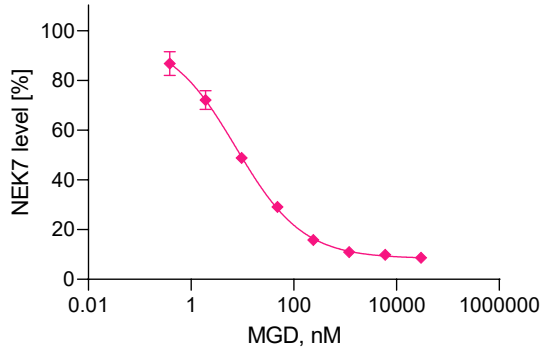
MGD Induced NEK7 Degradation is CRBN- and Degron-Dependent

NEK7-directed MGD is CRBN-dependent and rescues NLRP3 pathway modulation

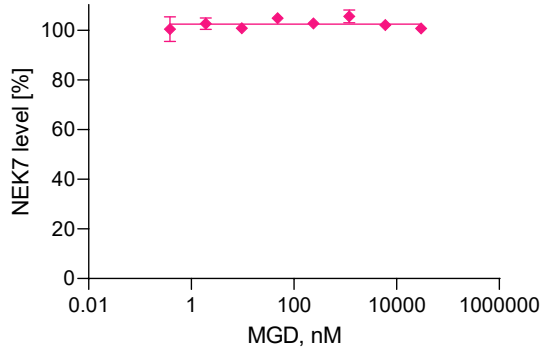


NEK7 MGD induced CRBN interaction Requires Degron

NEK7 WT

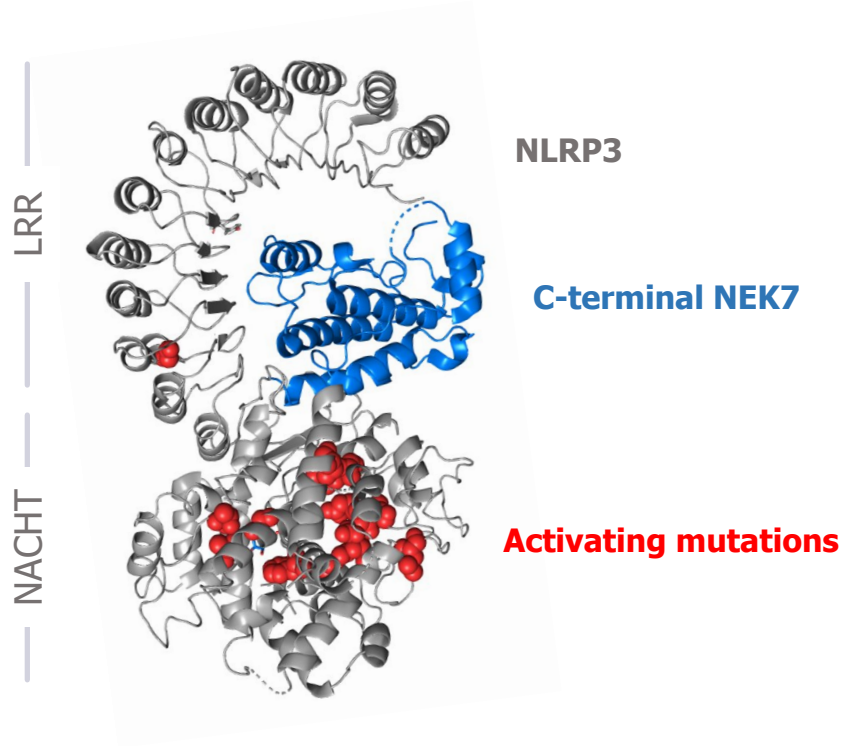


NEK7 Xmut



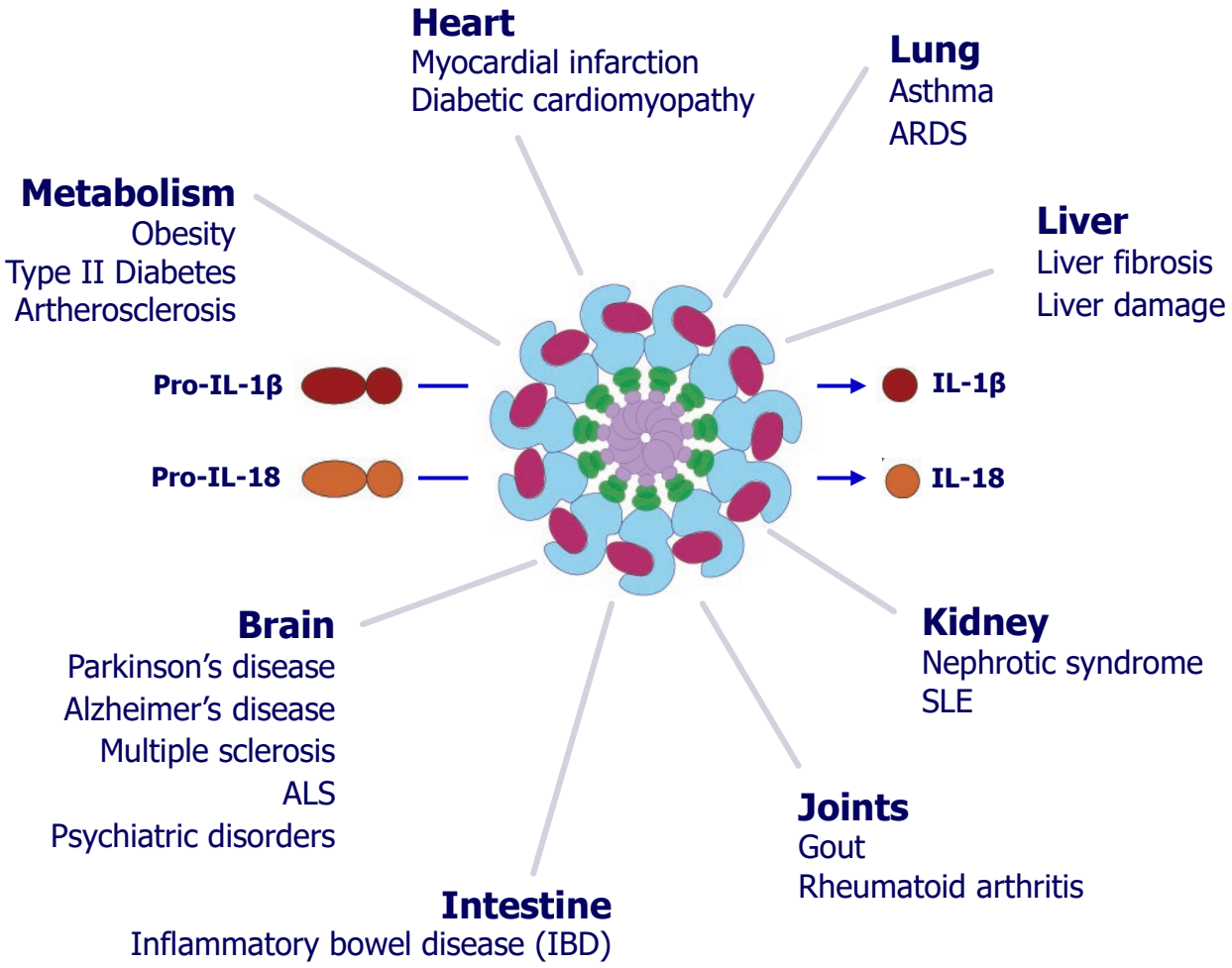
Overactivation of the NLRP3 Inflammasome in Diseases

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 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	
NEK7	Inflammatory Diseases				IND-Enabling Studies	
CDK2	Ovarian Cancer, Breast Cancer					
VAV1	T and B Cell Malignancies, Autoimmune Disease				Lead Optimization	
BCL11A	SCD, β-Thalassemia					
Undisclosed	Multiple					

Oncology Autoinflammation Oncology / immunology Genetic diseases


Thank You
Monte Rosa
Therapeutics