C4 Therapeutics

Monofunctional Degradation Activating Compounds: From Platform Development to the Clinic

Discovery on Target – Next Generation Protein Degraders

Forward-looking Statements and Intellectual Property

Forward-looking Statements

The following presentation contains forward-looking statements. All statements other than statements of historical fact are forward-looking statements, which are often indicated by terms such as "anticipate," "believe," "could," "estimate," "expect," "goal," "intend," "look forward to," "may," "plan," "potential," "predict," "project," "should," "will," "would" and similar expressions. These forward-looking statements include, but are not limited to, statements regarding the therapeutic potential of C4 Therapeutics, Inc.'s technology and products. These forward-looking statements are not promises or guarantees and involve substantial risks and uncertainties. Among the factors that could cause actual results to differ materially from those described or projected herein include uncertainties associated generally with research and development, clinical trials and related regulatory reviews and approvals, as well as the fact that the product candidates that we are developing or may develop may not demonstrate success in clinical trials. Prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. C4 Therapeutics, Inc. undertakes no obligation to update or revise the information contained in this presentation, whether as a result of new information, future events or circumstances or otherwise.

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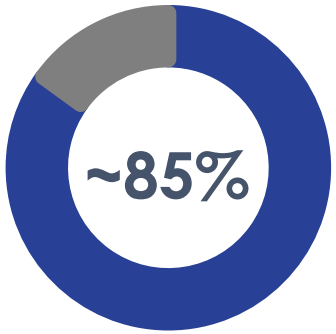
Targeted Protein Degradation Has the Potential to Transform Treatment of Disease



TPD Has an Expansive Target Landscape

85% of proteins are currently undruggable or poorly drugged

TPD Offers a Powerful Modality

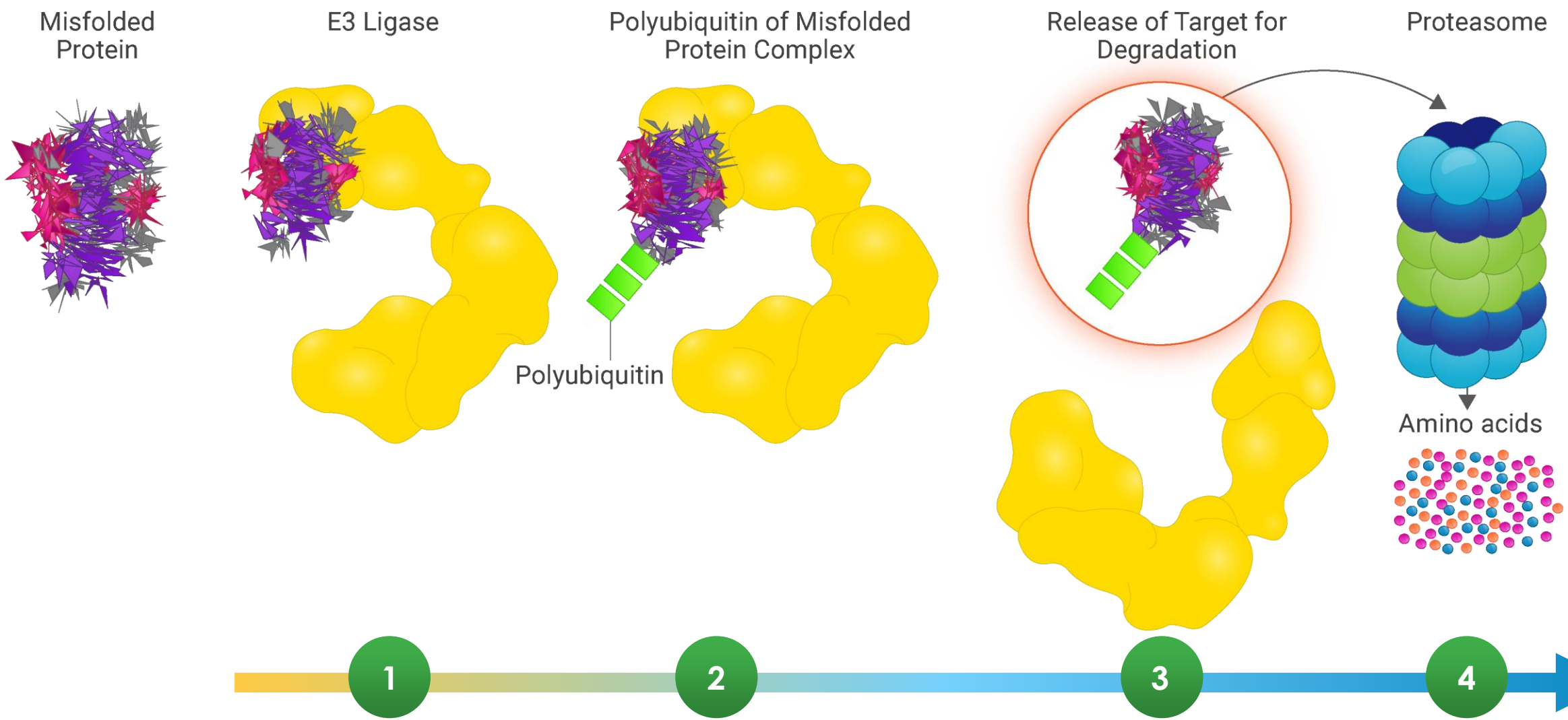
Benefits of genetic knockdown with a small molecule approach

C4T's TORPEDO platform creates therapeutic candidates that have the potential to improve patient care

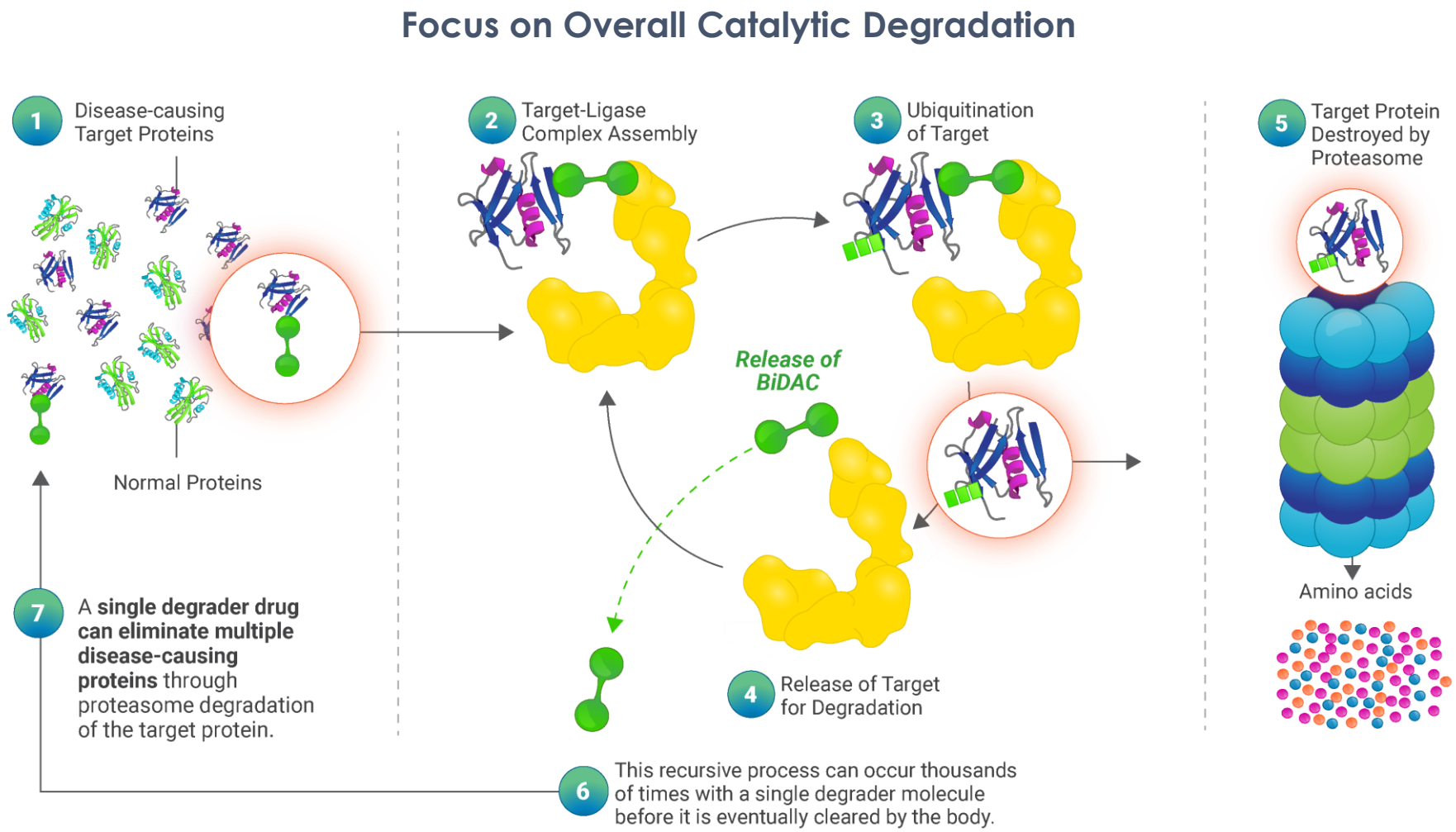
- Overcome Resistance
- Drug Undruggable Targets
- Improve Treatment Options

Source: Hopkins, A., Groom, C. The druggable genome. Nat Rev Drug Discov 1, 727–730 (2002).

The Human Body Has A Natural Process to Destroy Unwanted Proteins

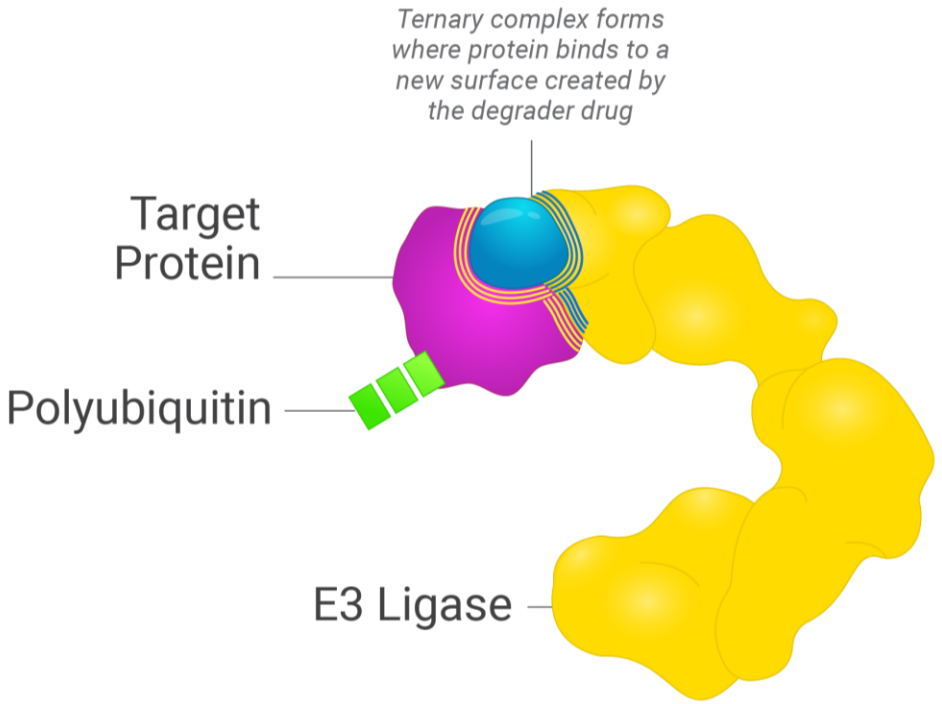


Targeted Protein Degradation Leverages the Body's Natural Process to Destroy Disease-Causing Proteins

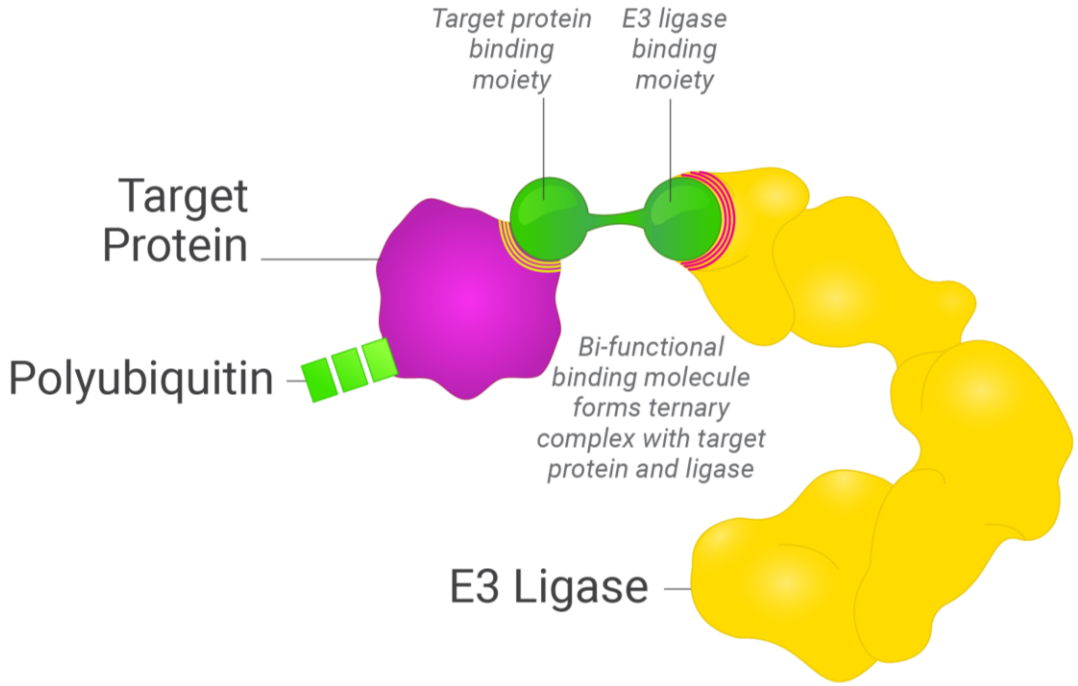


TORPEDO Platform Offers Flexibility to Design MonoDAC and BiDAC Degraders

MonoDAC Degrader

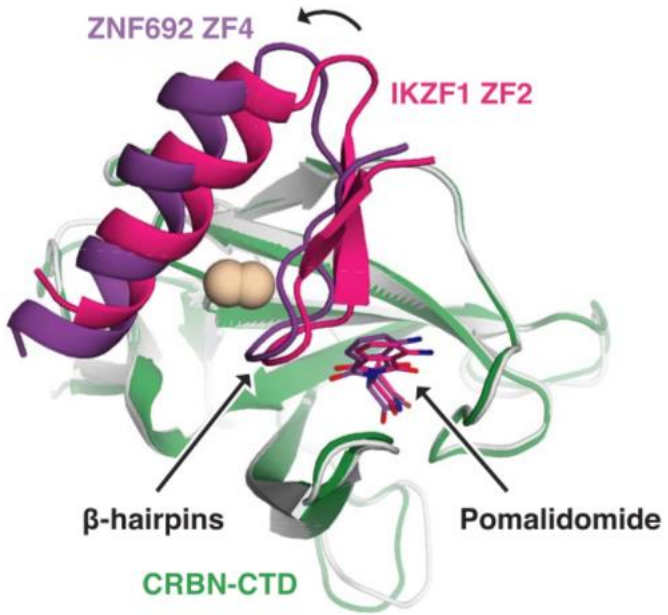


BiDAC Degrader

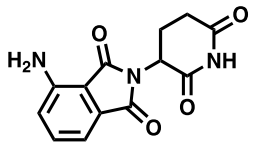


Flexibility to Address Different Targets with Tailored Approach

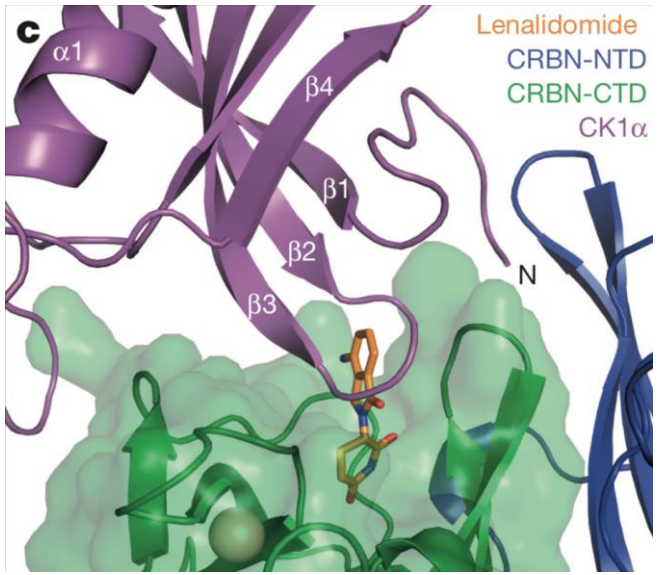
Molecular Glue Degraders (MGDs) in the Literature



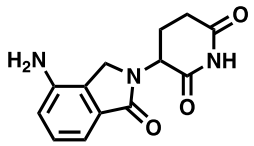
Thalidomide-related Zinc Finger degraders



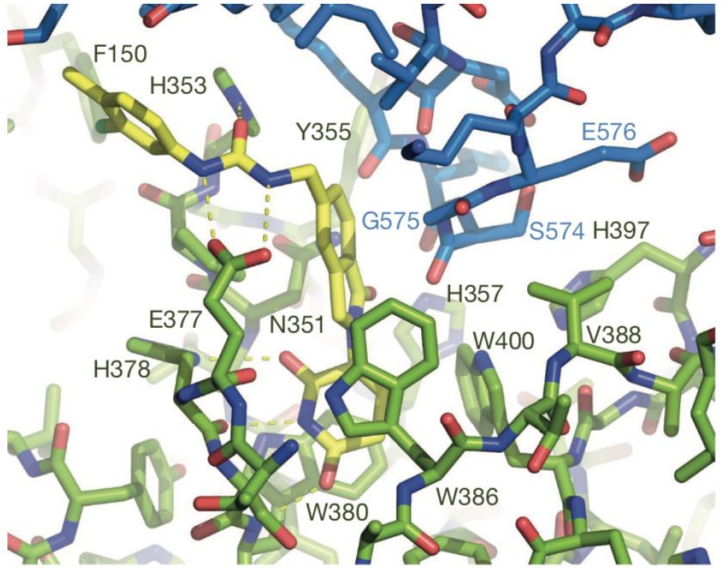
Science **2018**, *362(6414)*, eaat0572



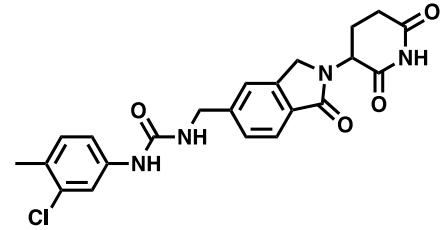
Lenalidomide, CK1-α degrader



Nature **2016**, *532(7597)*, 127

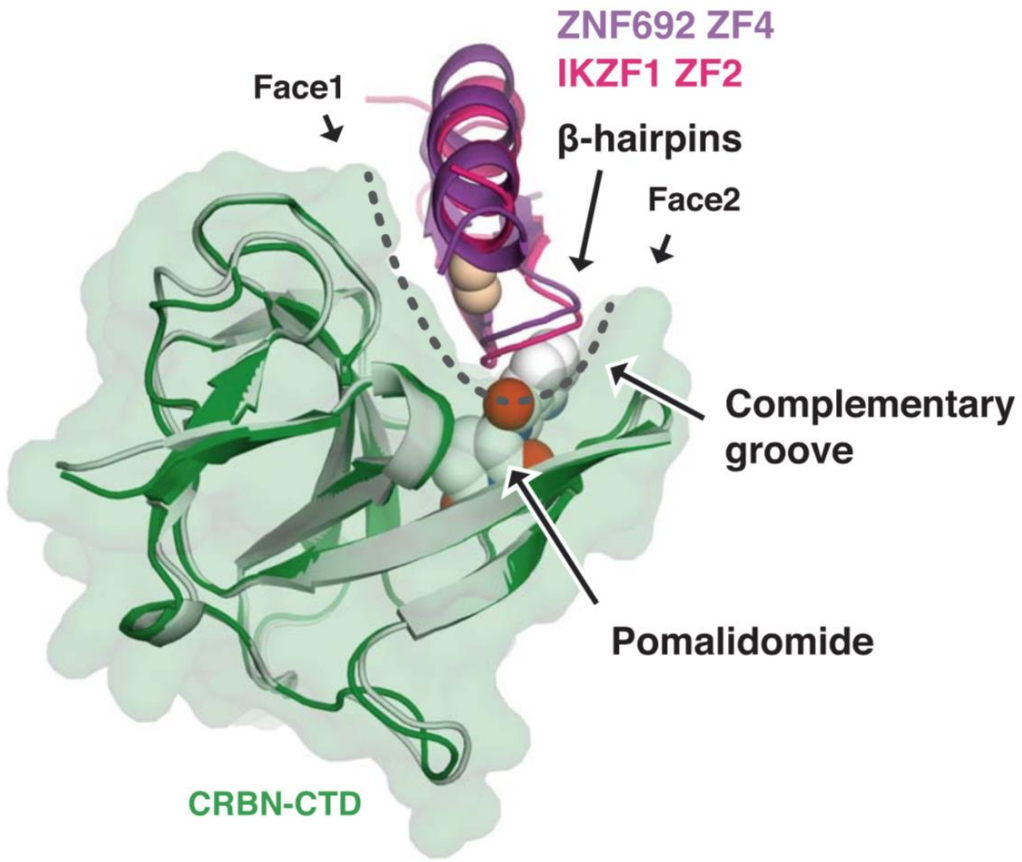


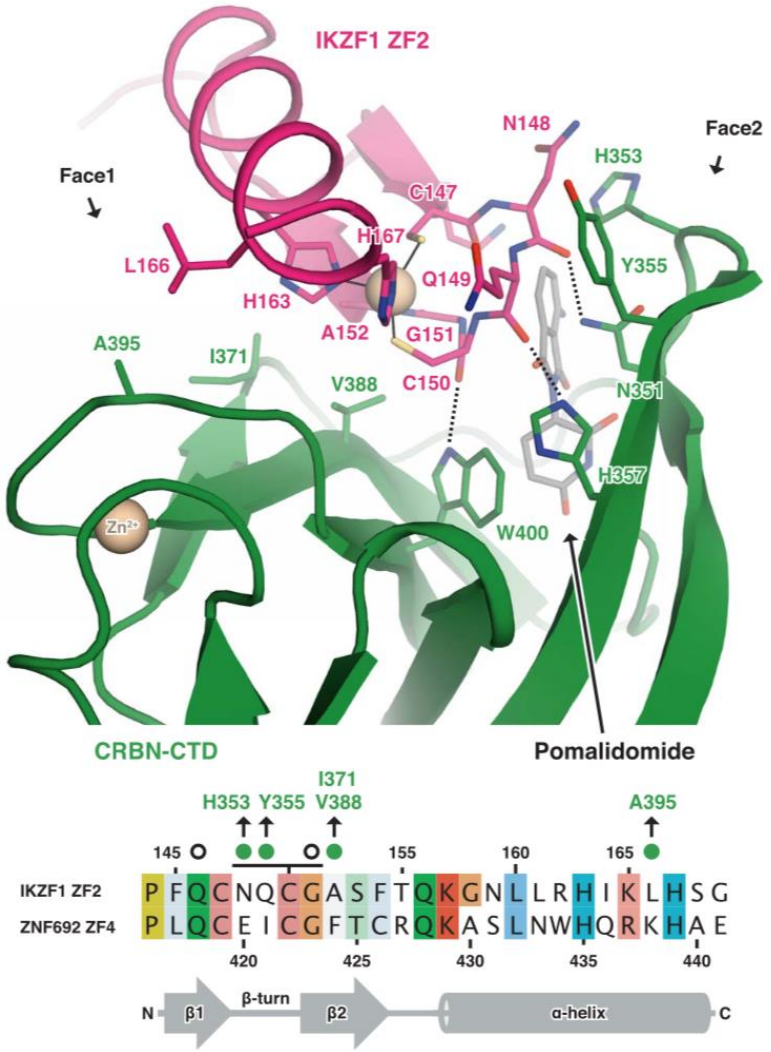
CC-885/90009 GSPT1 degraders



Nature **2016**, *535(7611)*, 252

MGDs in the Literature





β-turn is the primary recognition element, 2nd interactions play a role in activity and selectivity

Science **2018**, *362(6414)*, eaat0572

Why MonoDAC Degraders and Molecular Glue Degraders?

Disease Target and Potential for New Medicines

- Access to Undruggable/or Unliganddable Targets
- MonoDAC degraders and MGDs exhibit degradation-only pharmacology

Drug Properties and Performance

- Access to degrader drug candidates within more traditional Rule of 5 physicochemical property space

MonoDAC Degraders and MGDs should be aligned to the right target and clinical opportunities

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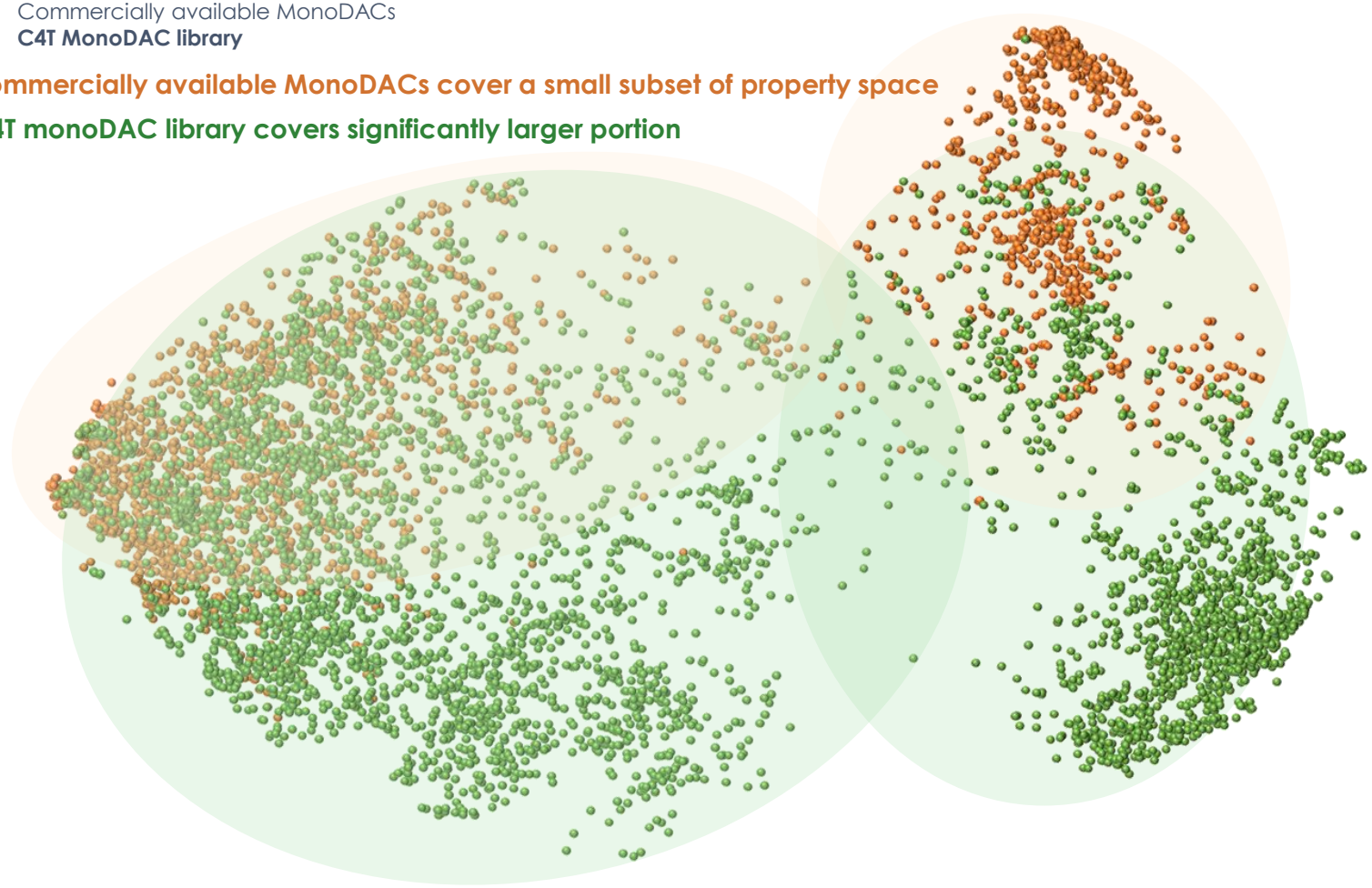
Identification and Characterization of MonoDAC CFT7455

C4T MonoDAC Library: Expanding the Cereblon Toolbox

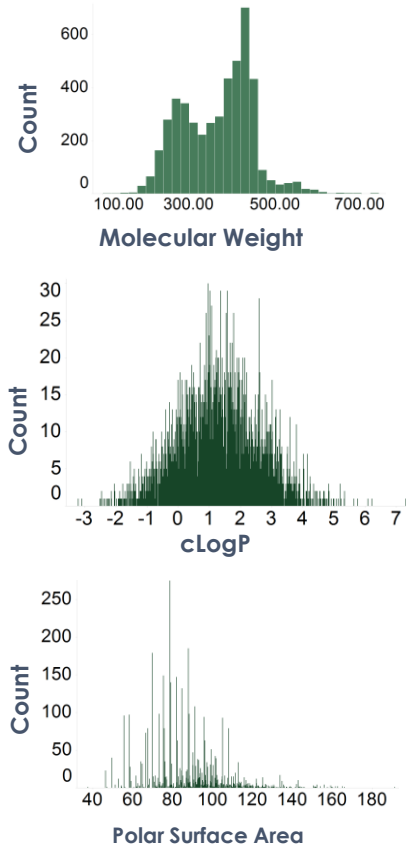
Commercially available MonoDACs
C4T MonoDAC library

Commercially available MonoDACs cover a small subset of property space

C4T monoDAC library covers significantly larger portion



Drug-like property space



>5,000 membered library constructed from >200 unique scaffolds to maximize MonoDAC structural diversity and CRBN surface remodeling

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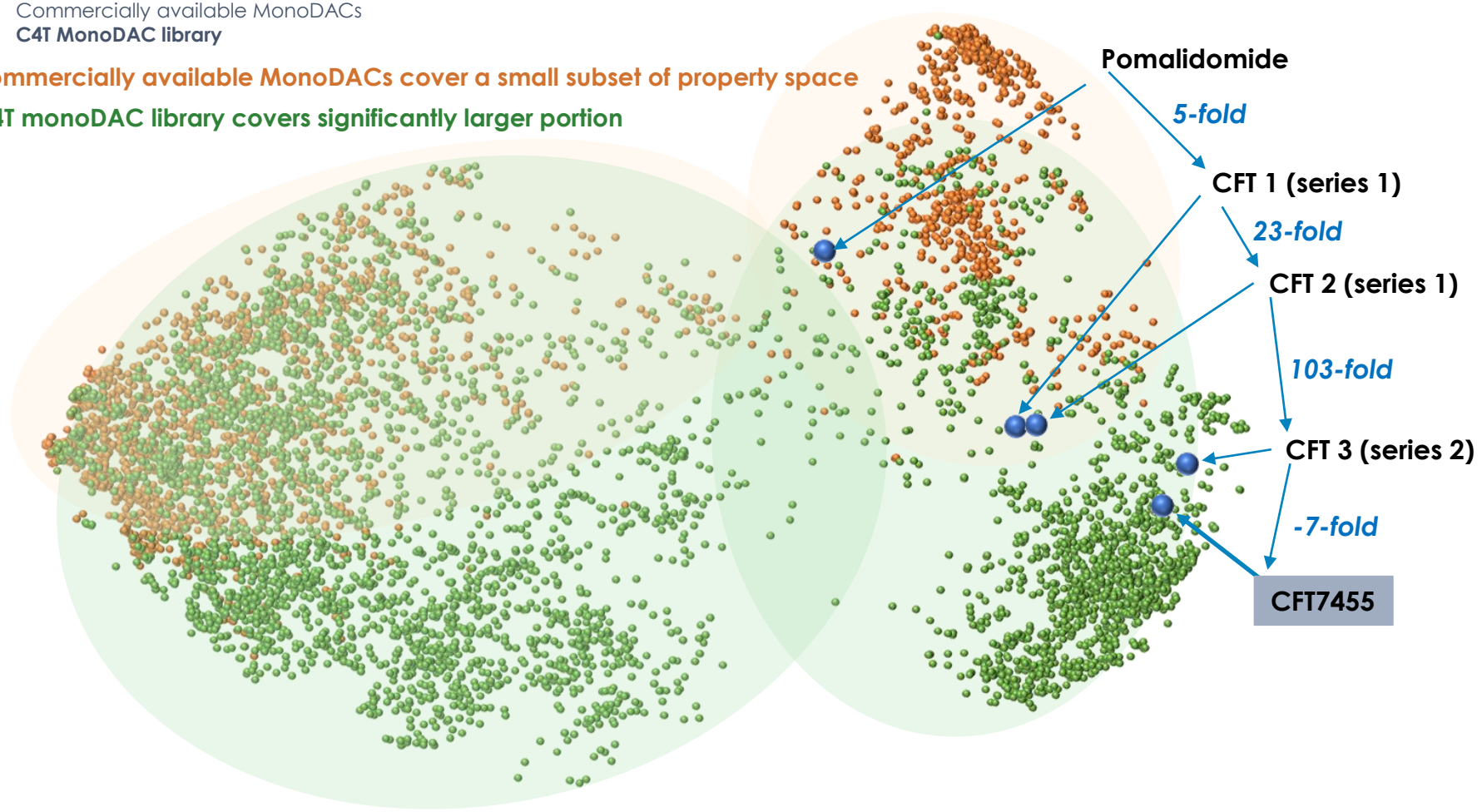
C4T MonoDAC Library in Action

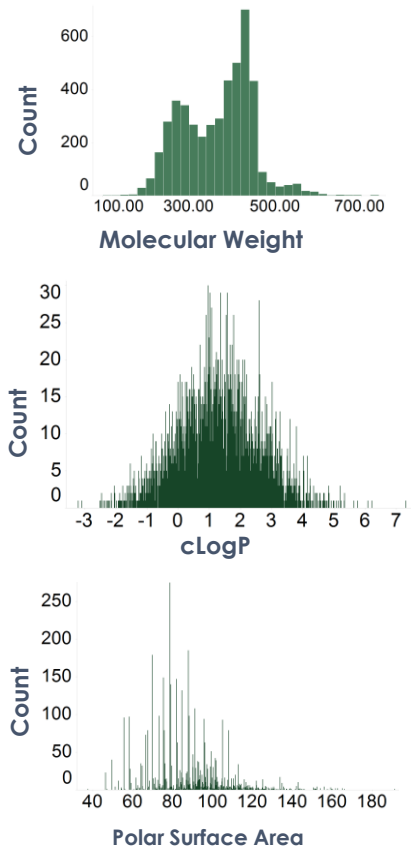
Commercially available MonoDACs
C4T MonoDAC library

Commercially available MonoDACs cover a small subset of property space

C4T monoDAC library covers significantly larger portion



Drug-like property space

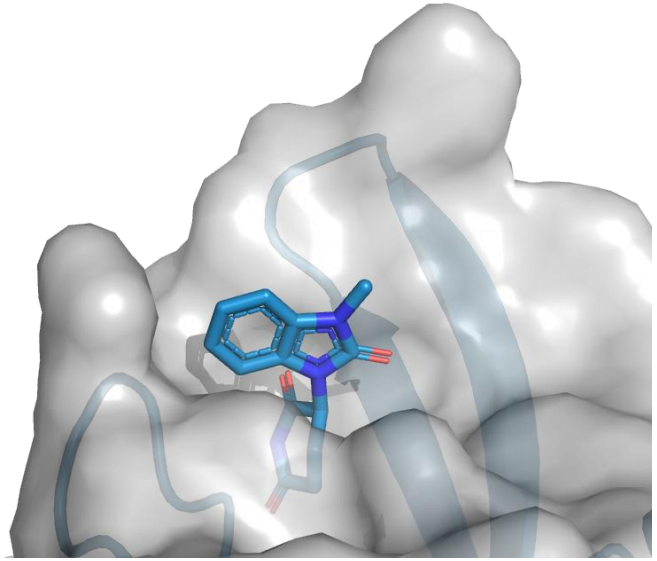


C4T MonoDAC Library has produced hits to novel MonoDAC Targets and a development candidate

Deep Structural Design Expertise of MonoDAC Degraders

Benzoimidazolone

C4T unpublished
1.17 Å

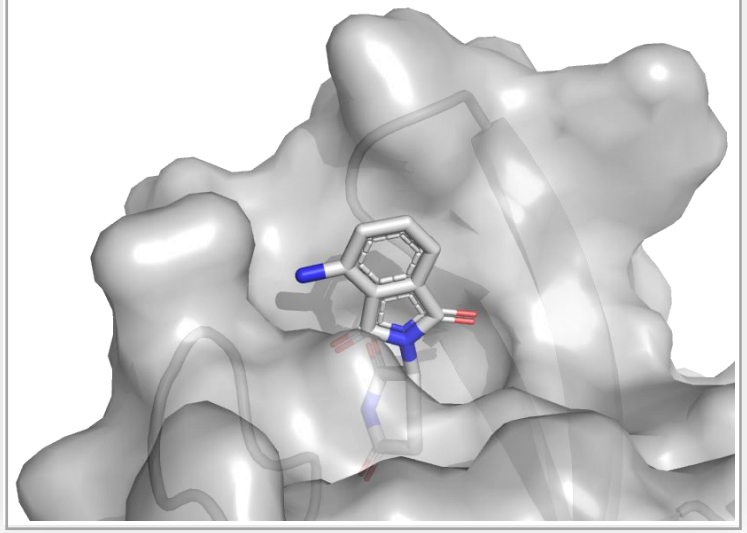


Compound 4
CRBN FP K_D = 830 nM

IKZF1▼

Pomalidomide

PDB 6h0f



Pomalidomide
K_D = 1600 nM

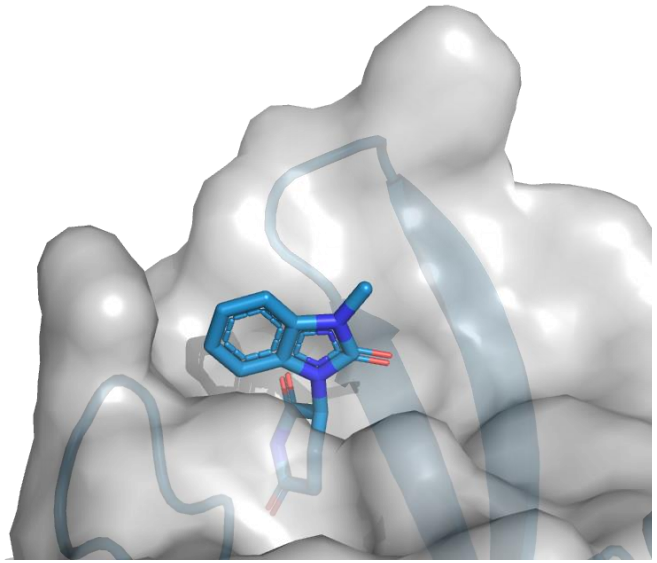
IKZF1▼

Deep Structural Design Expertise of MonoDAC Degraders

Benzoimidazolone

C4T unpublished

1.17 Å



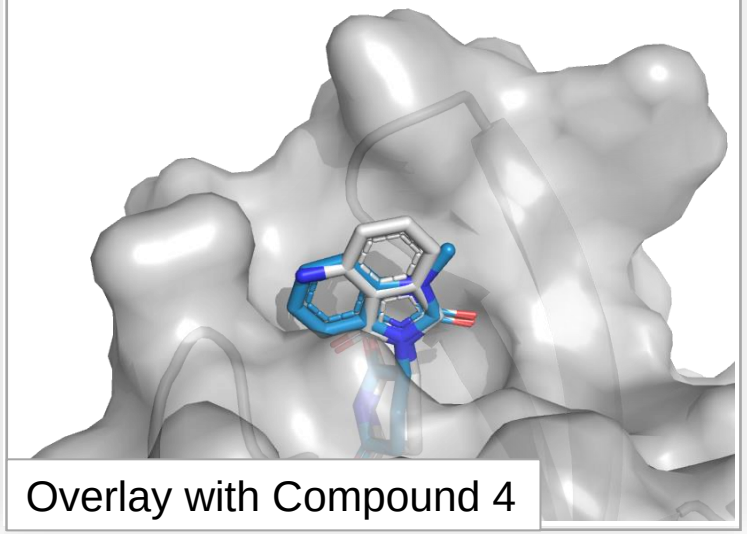
Compound 4

CRBN FP K_D = 830 nM

IKZF1▼

Pomalidomide

PDB 6h0f



Overlay with Compound 4

Pomalidomide

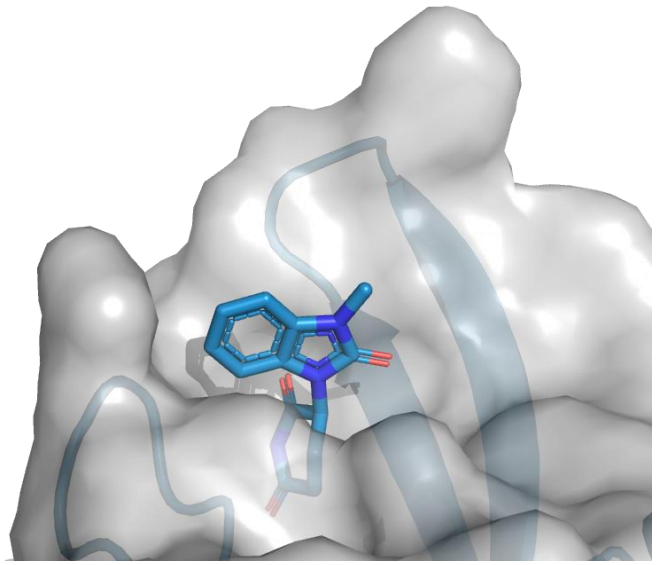
K_D = 1600 nM

IKZF1▼

CRBN, cereblon; FP, fluorescence polarization; IKZF1, Ikaros family zinc finger protein 1.

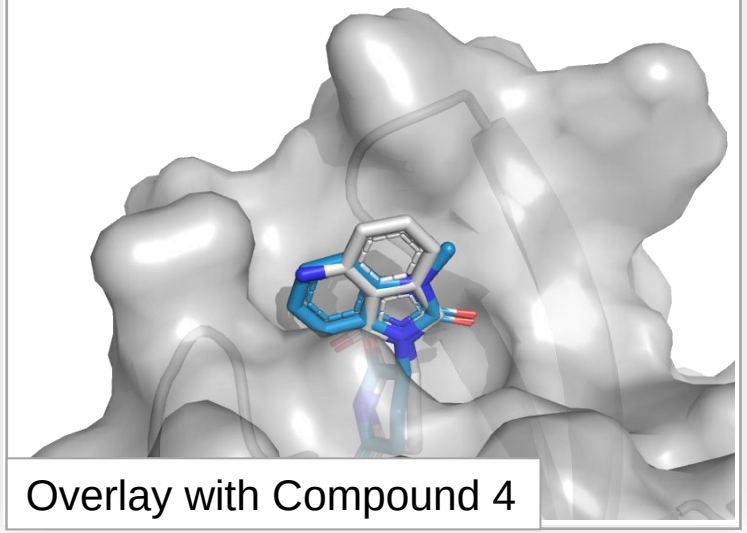
Deep Structural Design Expertise of MonoDAC Degraders

Benzoimidazolone
C4T unpublished
1.17 Å



Compound 4
CRBN FP K_D = 830 nM
IKZF1▼

Pomalidomide
PDB 6h0f

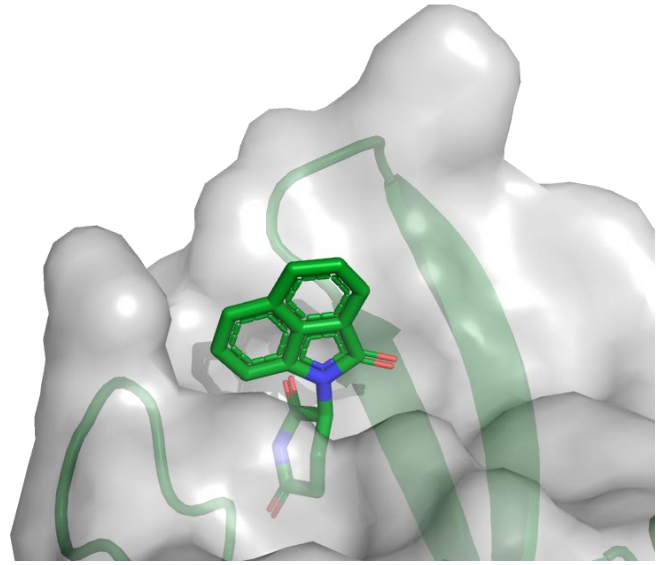


Overlay with Compound 4

Pomalidomide
K_D = 1600 nM
IKZF1▼

50-fold affinity increase

Benzoisoindolinone
C4T unpublished
1.06 Å

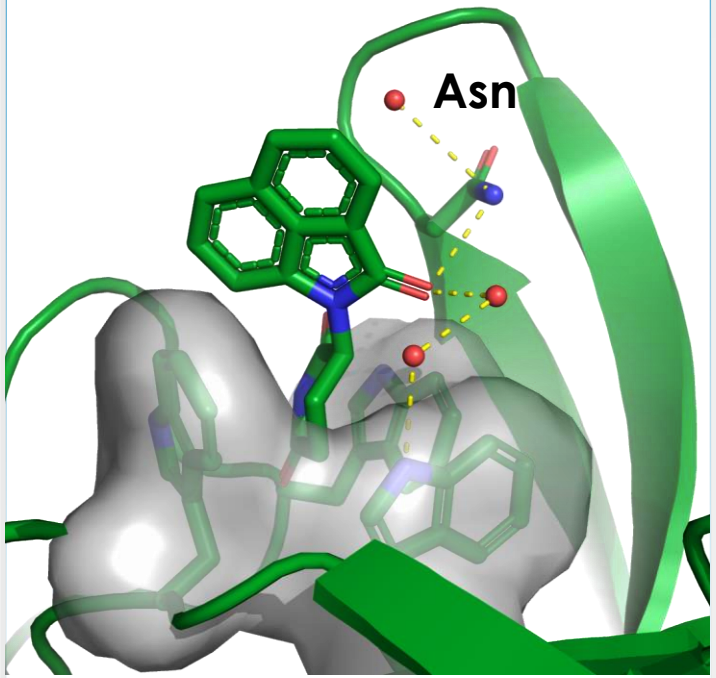


Compound 5
K_D = 34 nM
IKZF1▼

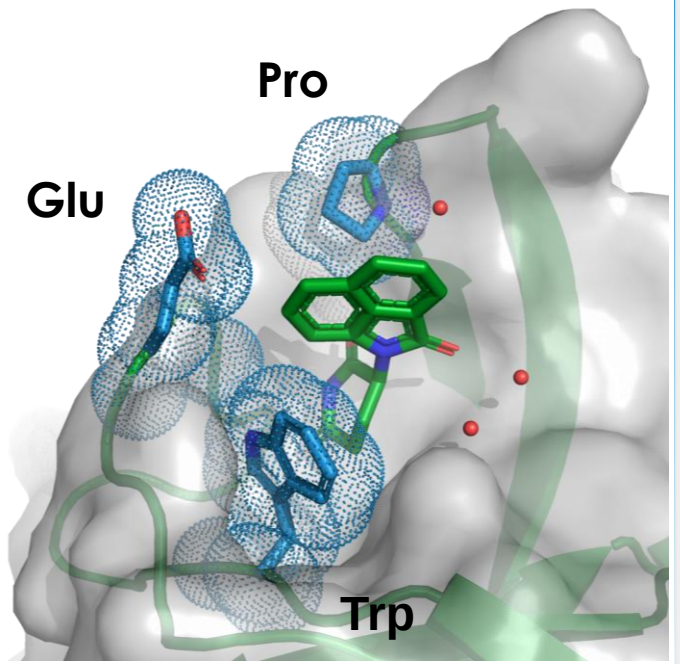
CRBN, cereblon; FP, fluorescence polarization; IKZF1, Ikaros family zinc finger protein 1.

Exploring CRBN Interactions with the Potent Tricyclic Core

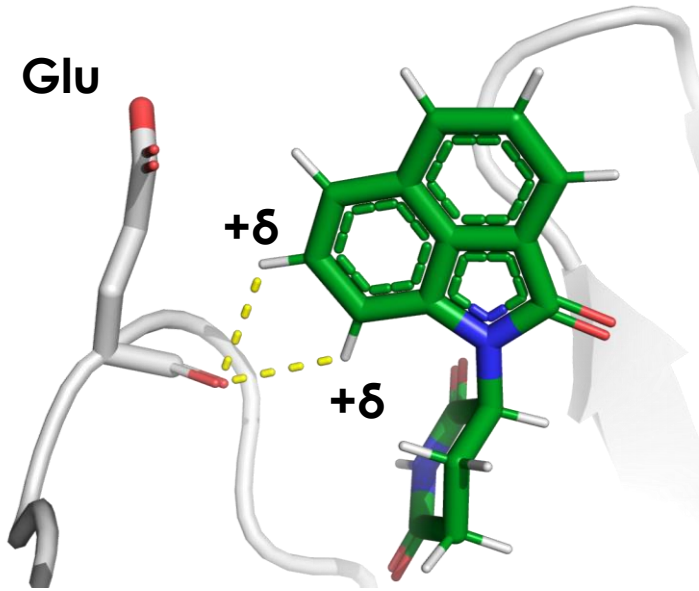
Tri-Trp Pocket Interactions



Increased Hydrophobic Contacts with CRBN



+δ Aromatic C-H Interactions with Backbone Carbonyl



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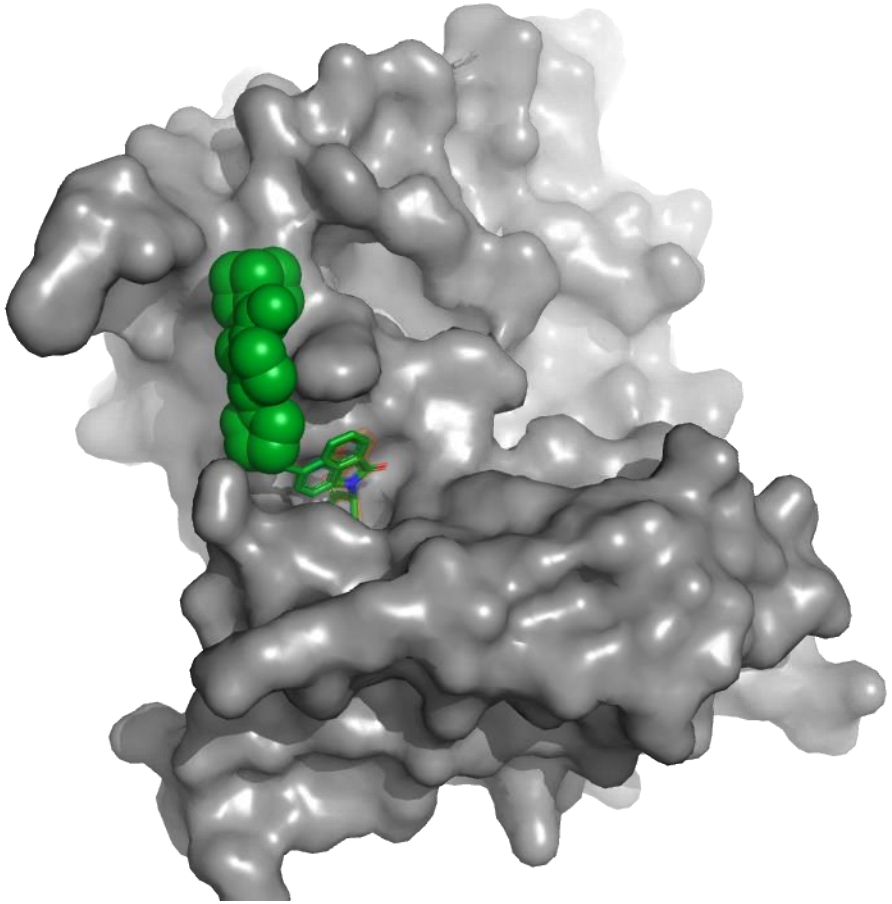
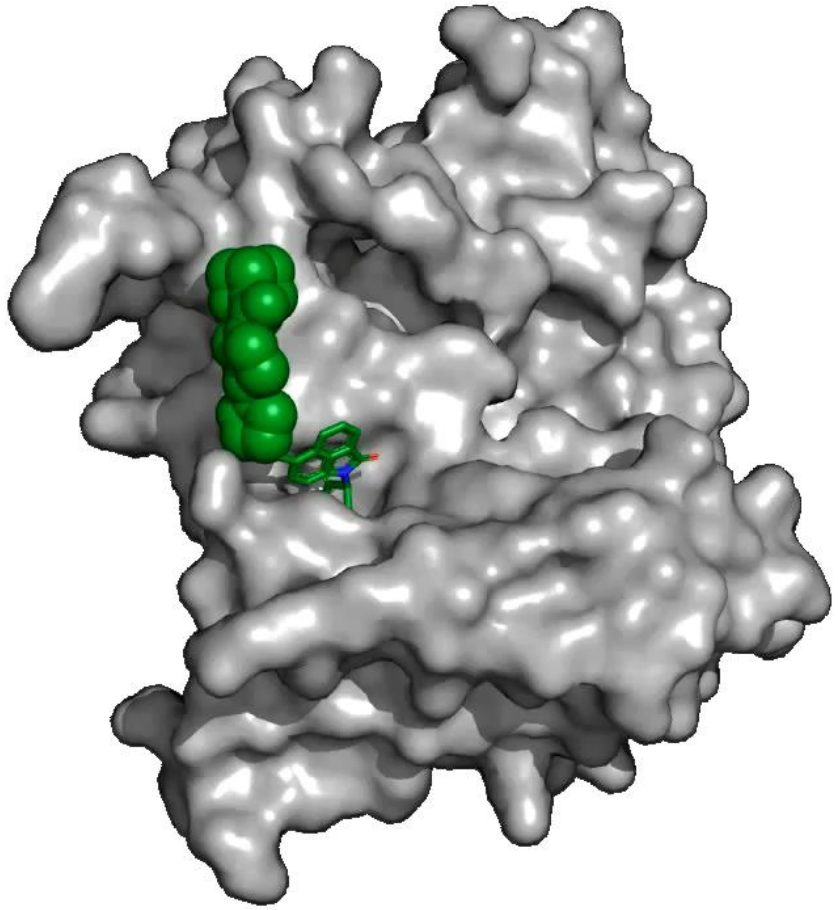
Design Beyond the Tricyclic Core - Crystallography and Ternary Complex Models

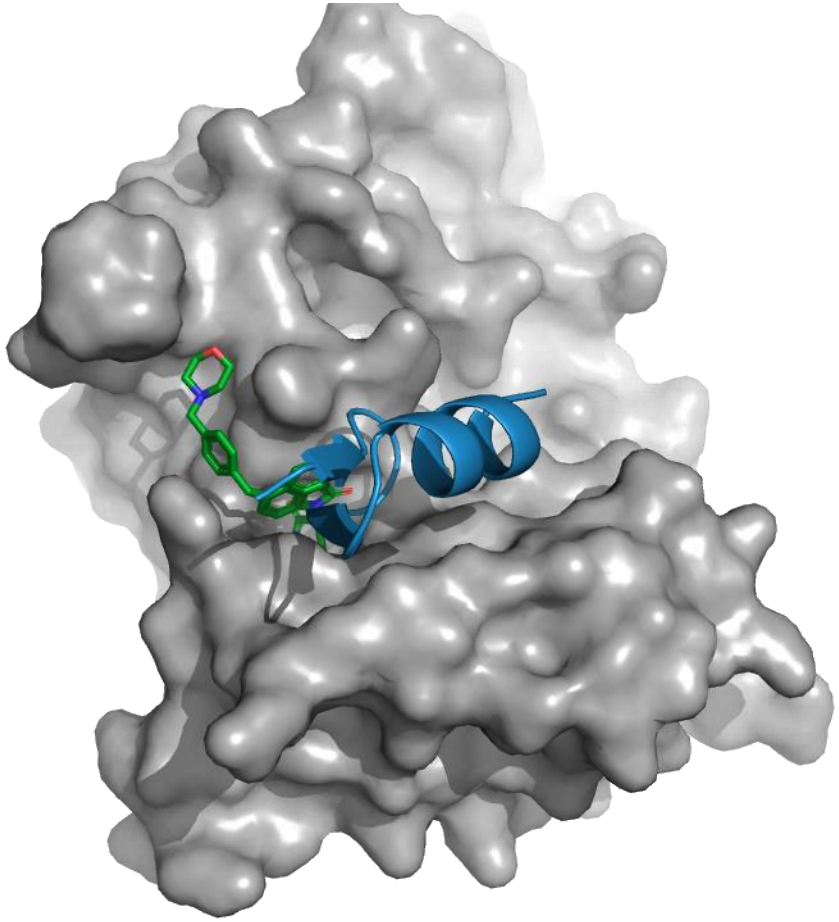


PDB 4tz4

Design Beyond the Tricyclic Core - Crystallography and Ternary Complex Models



Design Beyond the Tricyclic Core - Crystallography and Ternary Complex Models



C4T unpublished structure
Blue cartoon = IKZF1 model

Summary: Deep structural understanding of CRBN was critical in developing CFT7455

- **MonoDAC library provides coverage of diverse chemical space**
- **Structural understanding of CRBN binding yielded potent tricycle core**
- **Further designs extend beyond the Tri-Trp pocket; alter CRBN surface**
- **Result of the chemistry campaign was CFT7455 – a potent CRBN binder with fast, selective degradation of IKZF1/3 that has made it to the clinic**

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Finding MonoDAC Hits to Novel Neosubstrates

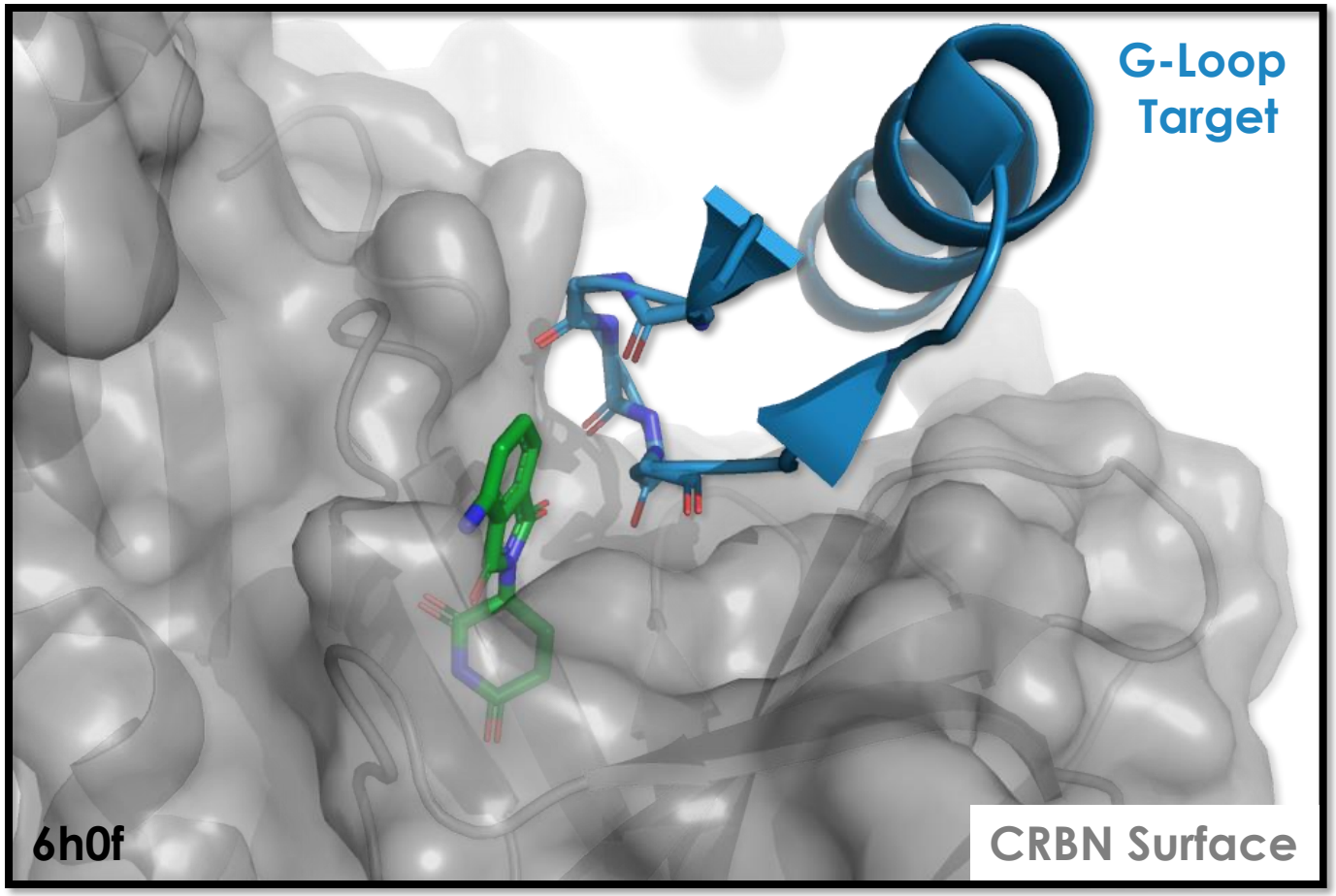
Strategic Approach to MonoDAC Hit Identification

In Silico Ternary Complex Design	Ternary Complex Identification	Cellular Degradation
• Identify G-loop containing proteins across the proteome • Generate ternary complex models that inspire new monoDAC design • *Approach does not necessarily identify productive degraders*	• Develop high-throughput biochemical methods to identify ternary complex formation • Develop high-throughput cellular assay methods to identify ternary complex formation • *Approaches do not identify productive degraders*	• HiBiT assay – mechanism-informed reduction of target protein levels • *Off-target/off-mechanism and off-target/on-mechanism activity could confound hit identification*

A comprehensive approach that will also identify and expand MonoDAC degrons

In Silico: Canonical G-Loop Protein MonoDAC Design

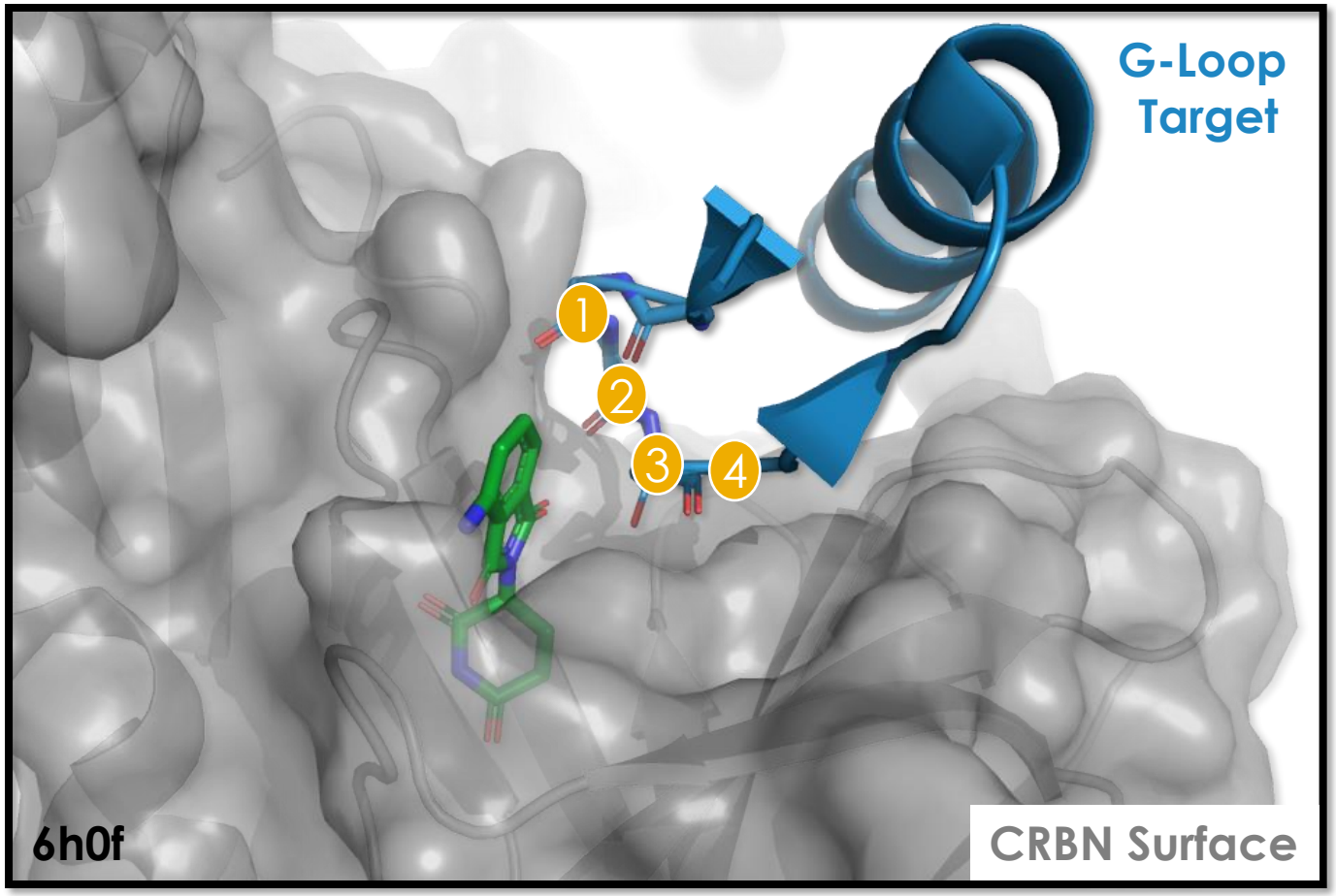
1. Model G-Loop



In Silico: Canonical G-Loop Protein MonoDAC Design

1. Model G-Loop

2. Examine amino acid sidechains



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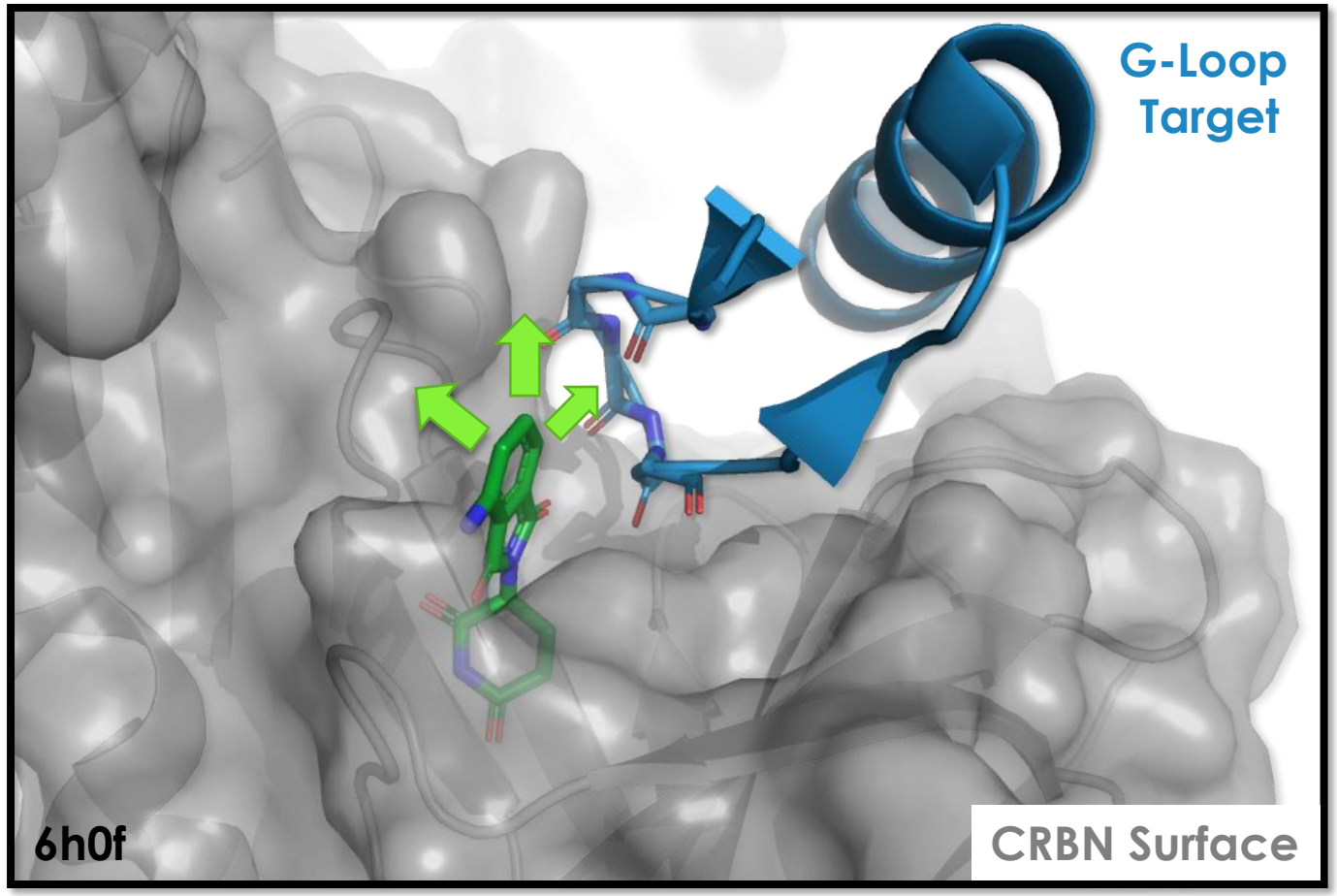
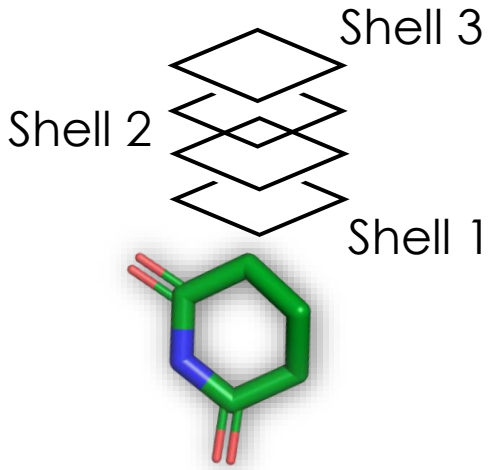
In Silico: Canonical G-Loop Protein MonoDAC Design

1. Model G-Loop

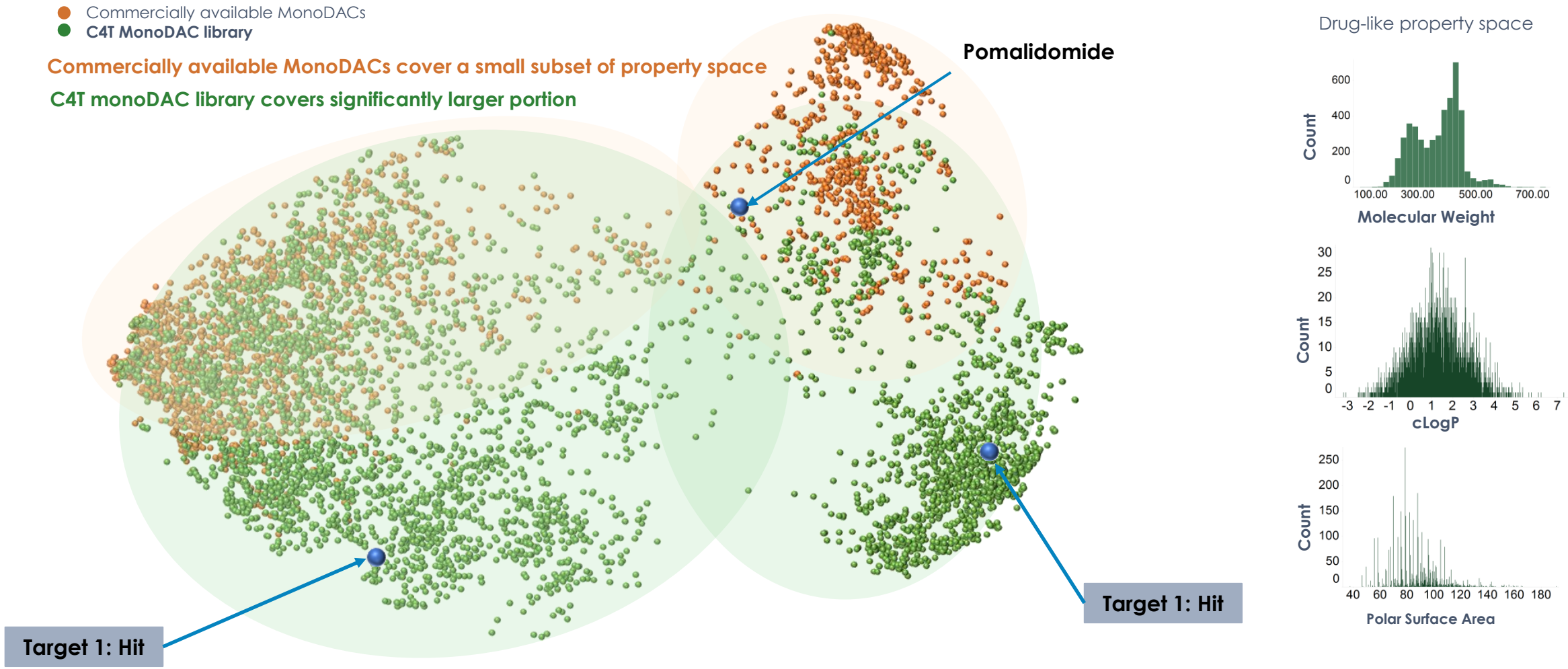
2. Examine amino acid sidechains

3. Grow CRBN ligands from novel scaffolds





C4T MonoDAC Library in Action – *In Silico* Ternary Complex Design



C4T MonoDAC Library has produced hits to novel MonoDAC Targets and a development candidate

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In Silico: Test Designed MonoDACs Against Canonical G-Loop Protein

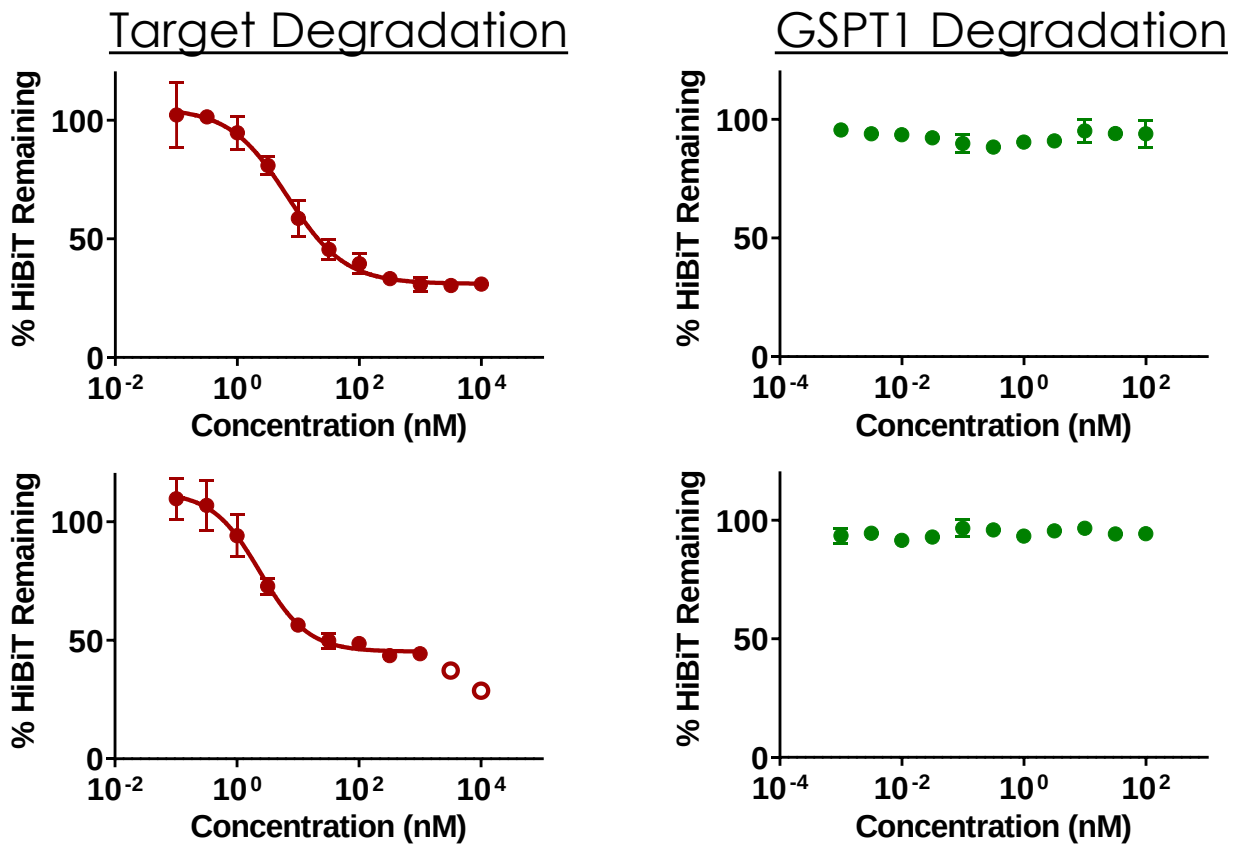
Funnel Assessing *In Silico* Designs

38 Designed compounds to accommodate G-loop of target protein

14 Hits showing degradation less than 80% E_{max}

14 Pass the GSPT1 filter

Example: Two Hits From Screen Degrade Target 1 & Spare GSPT1

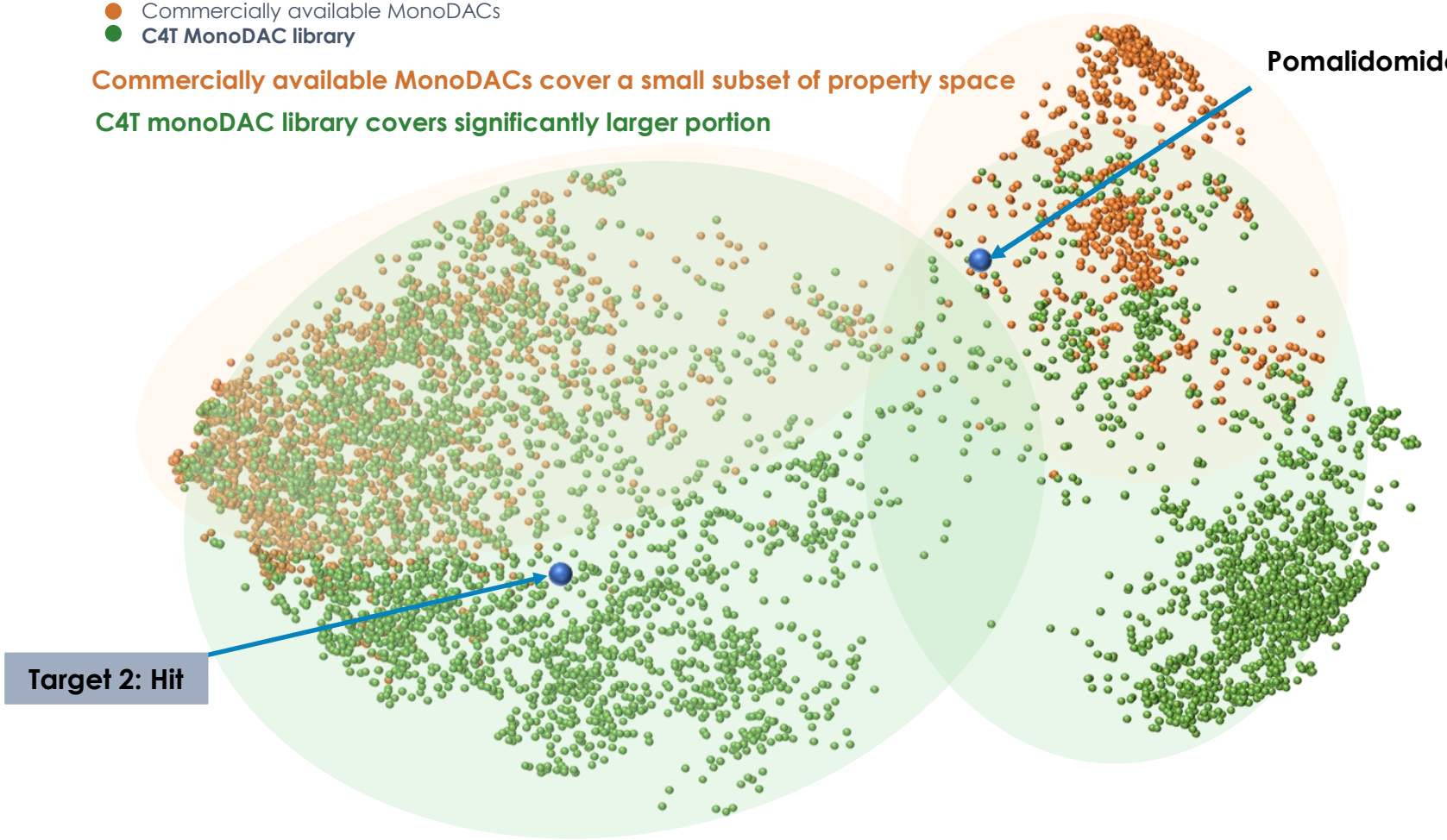


C4T MonoDAC Library in Action – Cellular Degradation of Specific Target

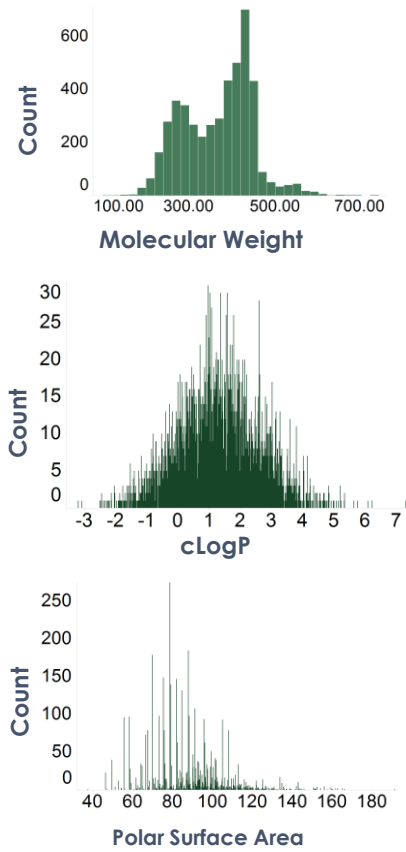
Commercially available MonoDACs
C4T MonoDAC library

Commercially available MonoDACs cover a small subset of property space

C4T monoDAC library covers significantly larger portion



Drug-like property space



C4T MonoDAC Library has produced hits to novel MonoDAC Targets and a development candidate

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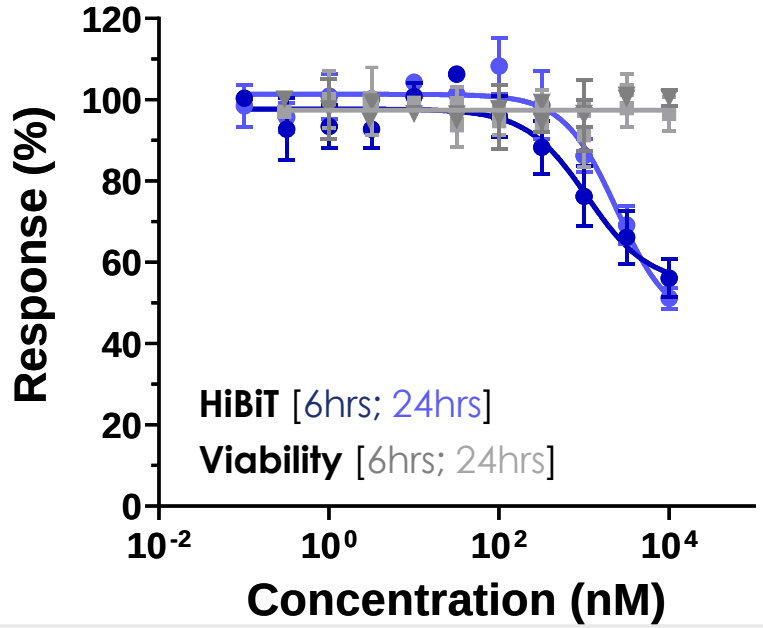
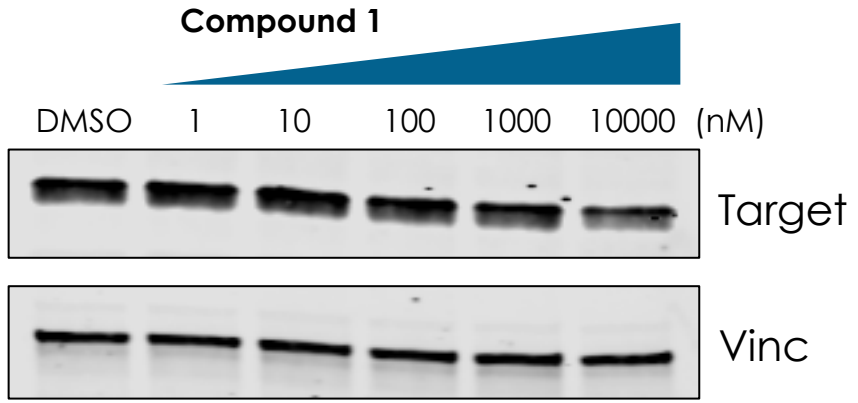
C4T MonoDAC Library in Action – Cellular Degradation of Target 2

HiBiT Cellular Degradation
Dose-Response Hit Identification



Endogenous Degradation
Western Blot

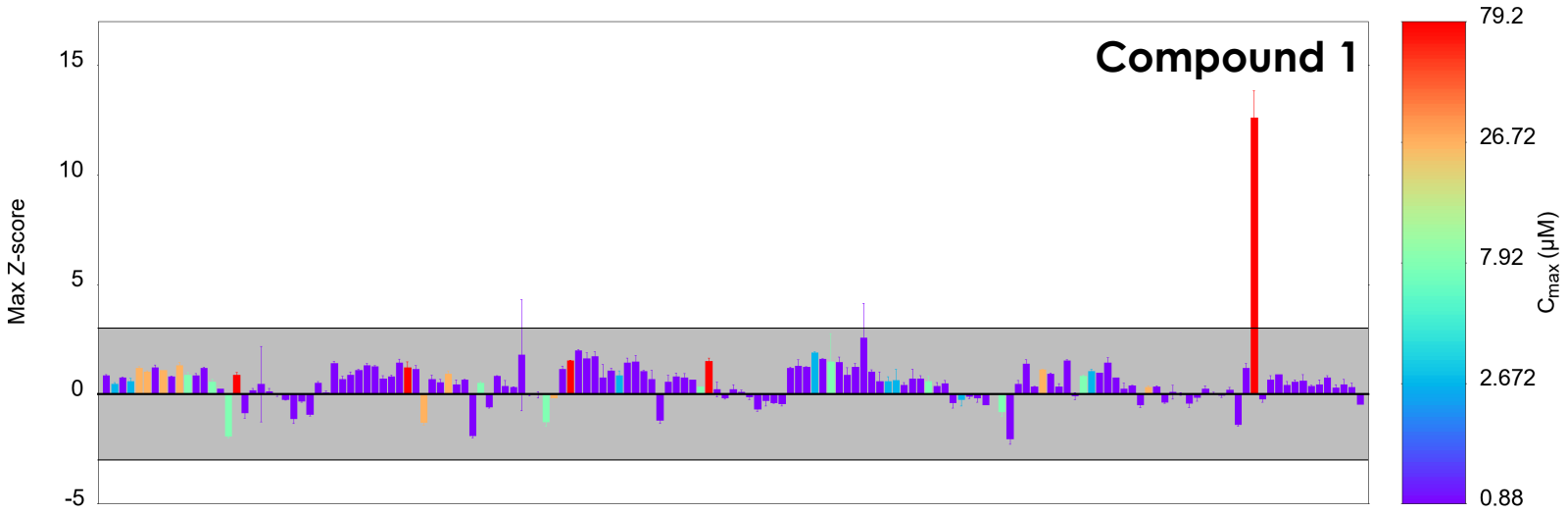


- 6hr Timepoint
- 73% Remaining

Identified hit reduces tagged and endogenous Target 2 protein levels

C4T MonoDAC Library in Action – Biochemical Ternary Complex

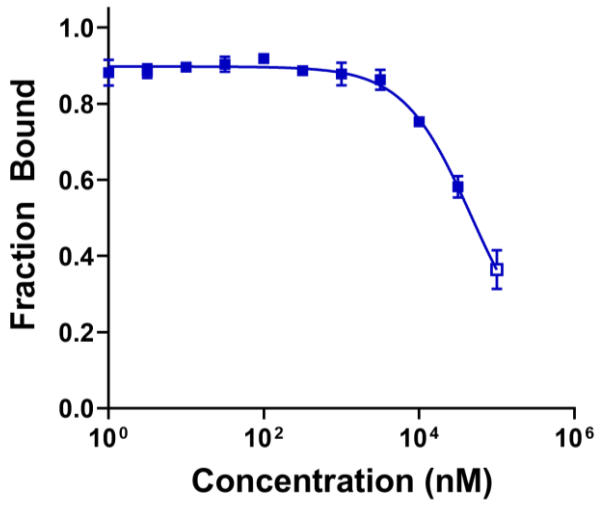
- AlphaLISA assay format
- Ternary complex between Target 2 and CRBN-DDB1
- Analysis of library subset shown



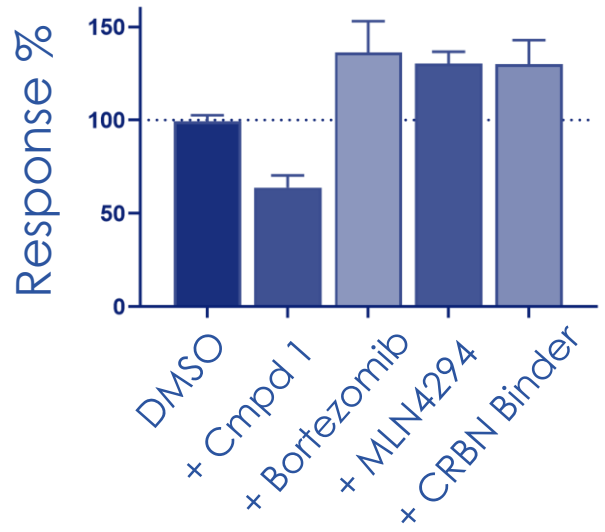
Biochemical screen of the MonoDAC library identifies the same hit compound

C4T MonoDAC Library – Hit Validation for Compound 1

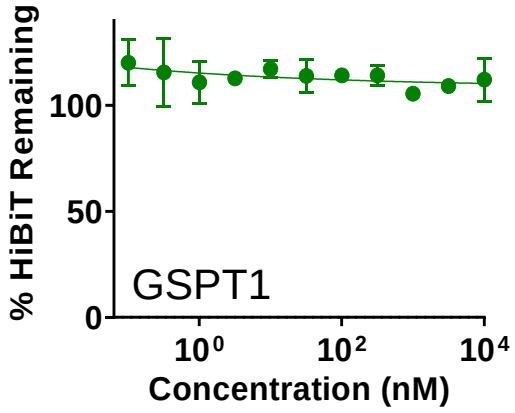
CRBN Engagement
Biochemical FP Assay



Mechanism of Action
HiBiT Competition



Canonical G-Loop Anti-Targets

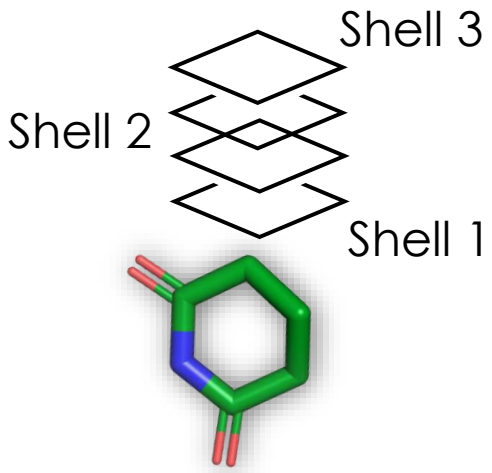


No degradation of IKZF1 or SALL4

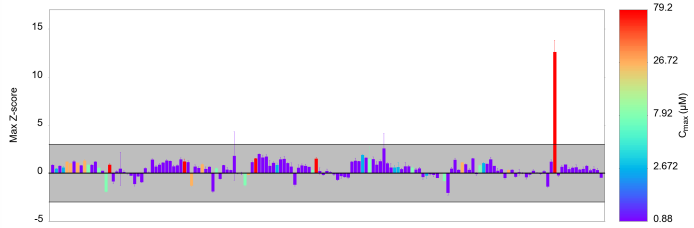
Compound 1 demonstrates selective on-target, on-mechanism degradation of Target 2

Strategic Approach to MonoDAC Screening

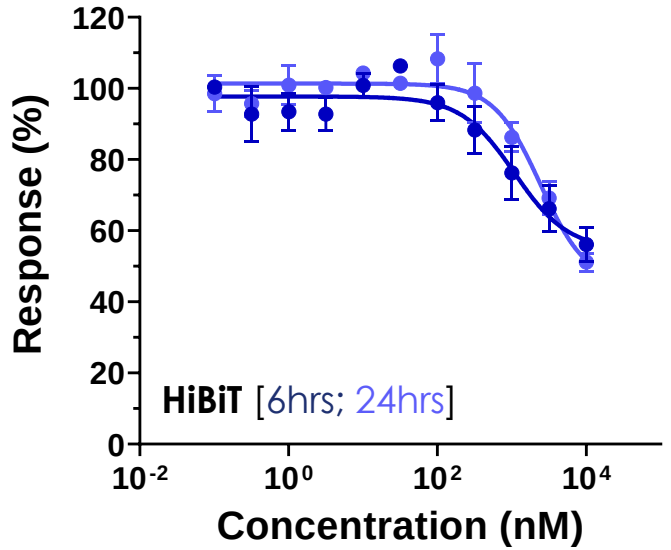
In Silico Ternary Complex Design



Ternary Complex Identification



Cellular Degradation



A comprehensive approach to identify and expand MonoDAC degrons

Thank You C4T Team