C4 Therapeutics

Addressing Challenging Therapeutic Targets Using Innovative Bifunctional Degrader Approaches

6th Annual TPD Summit,

October 31, 2023

Mathew E. Sowa, PhD

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. The forward-looking statements included in this presentation are subject to a variety of risks and uncertainties, including those set forth in our most recent and future filings with the Securities and Exchange Commission. Our actual results could vary significantly from those anticipated in this presentation, and our financial condition and results of operations could be materially adversely affected. 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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Disclosure Information

Mathew E. Sowa, PhD

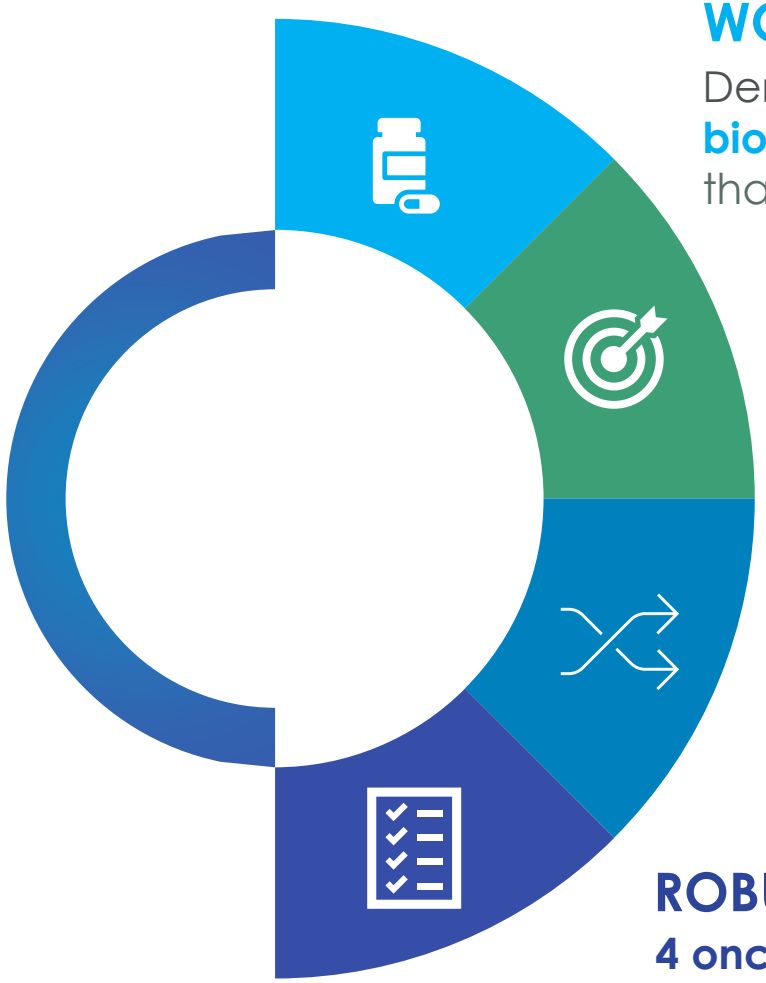
I have the following financial relationships to disclose:

- Stockholder in: C4 Therapeutics, Inc.
- Employee of: C4 Therapeutics, Inc.

C4T is a Leader in Delivering on the Promise of Targeted Protein Degradation

Our Mission

To deliver on the promise of targeted protein degradation science to create a new generation of medicines that transform patients' lives



WORLD-CLASS DEGRADER PLATFORM

Demonstrated ability to design **orally bioavailable, catalytically efficient degraders** that maximize the benefits of degradation

RIGOROUS TARGET SELECTION

Focus on targets with a **clear degrader rationale**

BROAD DEGRADER APPROACH

Only company with both **MonoDAC and BiDAC degraders** in the clinic

ROBUST CLINICAL PIPELINE

4 oncology degraders against targets of high unmet need

C4T's TORPEDO Platform Efficiently Designs Potent Targeted Protein Degrader Medicines

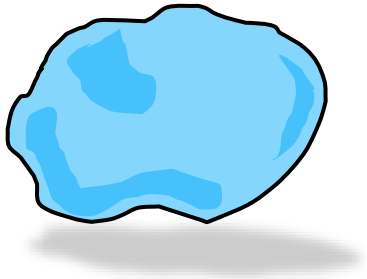
Focus on Catalytic Efficiency	Optimization of overall degradation process results in maximal efficacy
Ability to Design, Analyze & Predict Degrader Performance	Rapid delivery of potent drug candidates through informed and efficient drug discovery
Ability to Develop Both MonoDAC & BiDAC Degraders	Flexibility to address different targets with tailored approach

Robust Pipeline of Degrader Medicines Pursuing Multiple Targets in Oncology

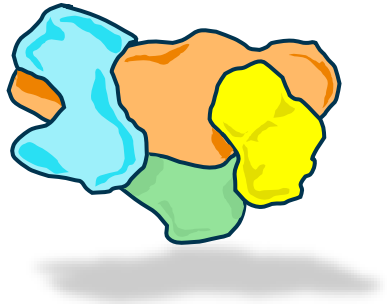
Program	Target	Indications	Discovery	Pre-clinical	Early phase development	Late phase development	Rights
CFT7455	**IKZF1/3**	Multiple Myeloma & Non-Hodgkin's Lymphoma					
CFT8634	**BRD9**	Synovial Sarcoma & SMARCB1-null Cancers					
CFT1946	**BRAF-V600**	V600 Mutant Cancers					
CFT8919[1]	**EGFR L858R**	Non-Small Cell Lung Cancer					
Chromatin Regulating Targets		Various Cancers					
Oncogenic Signaling Targets		Various Cancers					
Transcription Factor Targets		Various Cancers					

1. Exclusive Licensing Agreement with Betta Pharmaceuticals for the development and commercialization in Greater China

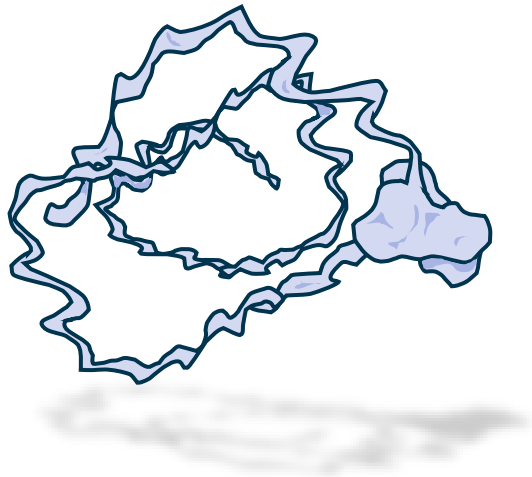
Targeted Protein Degradation Has the Potential to Transform the Treatment of Disease



"flat surface" proteins



scaffolding proteins



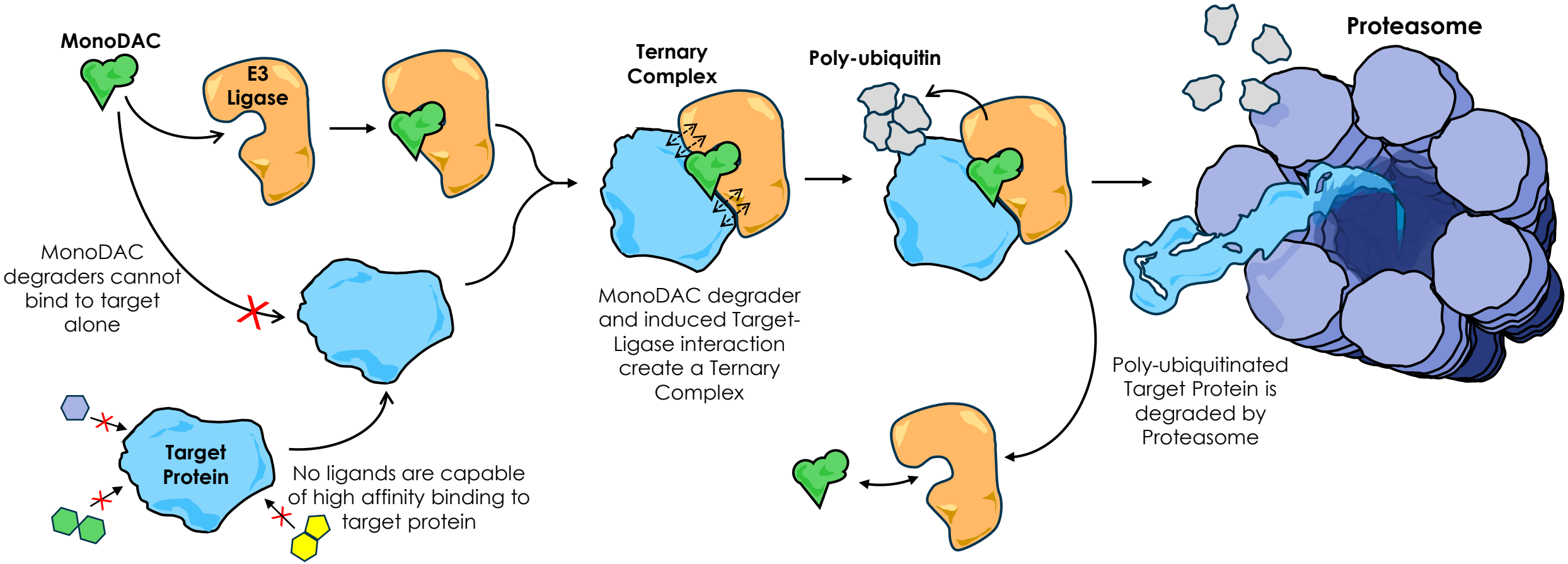
Intrinsically disordered proteins

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

- Overcome Resistance
- Drug Undruggable Targets
- Improve Treatment Options

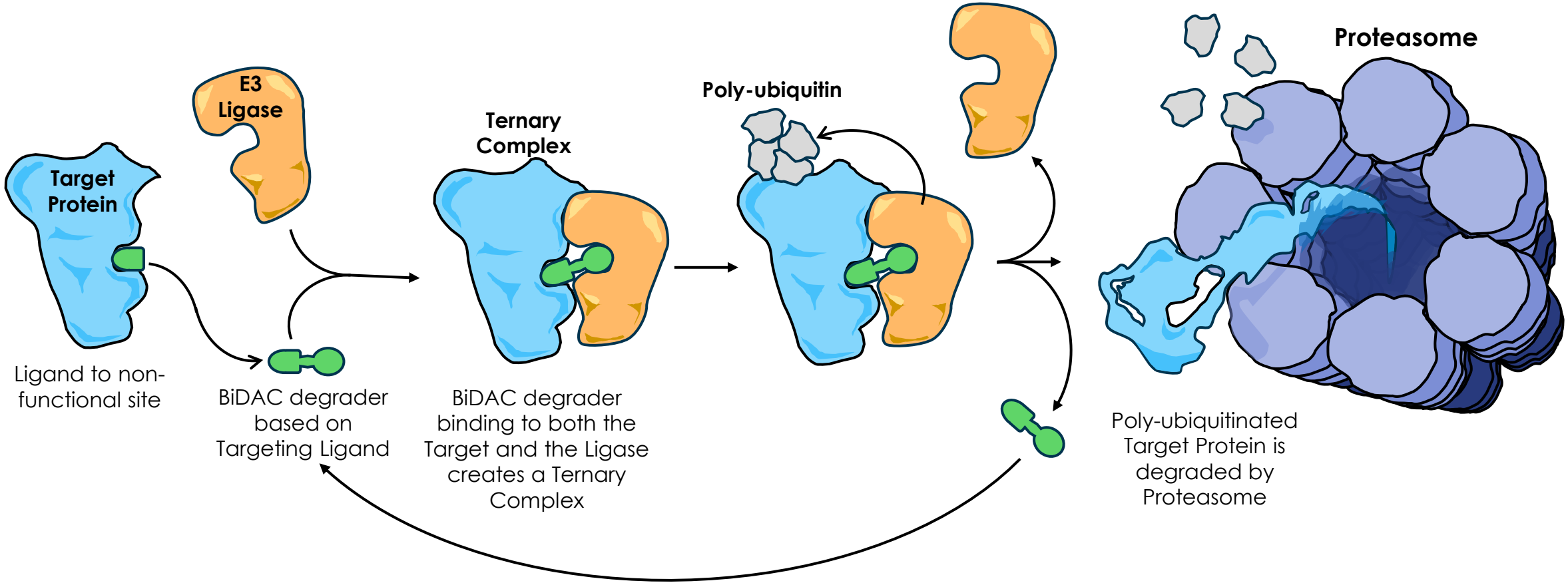
Utilizing TPD to Drug "Undruggable" Targets: MonoDAC Degraders

MonoDAC degraders (aka "molecular glue degraders") promote novel E3 ligase-target protein PPIs that allow binding to conventionally undruggable surfaces



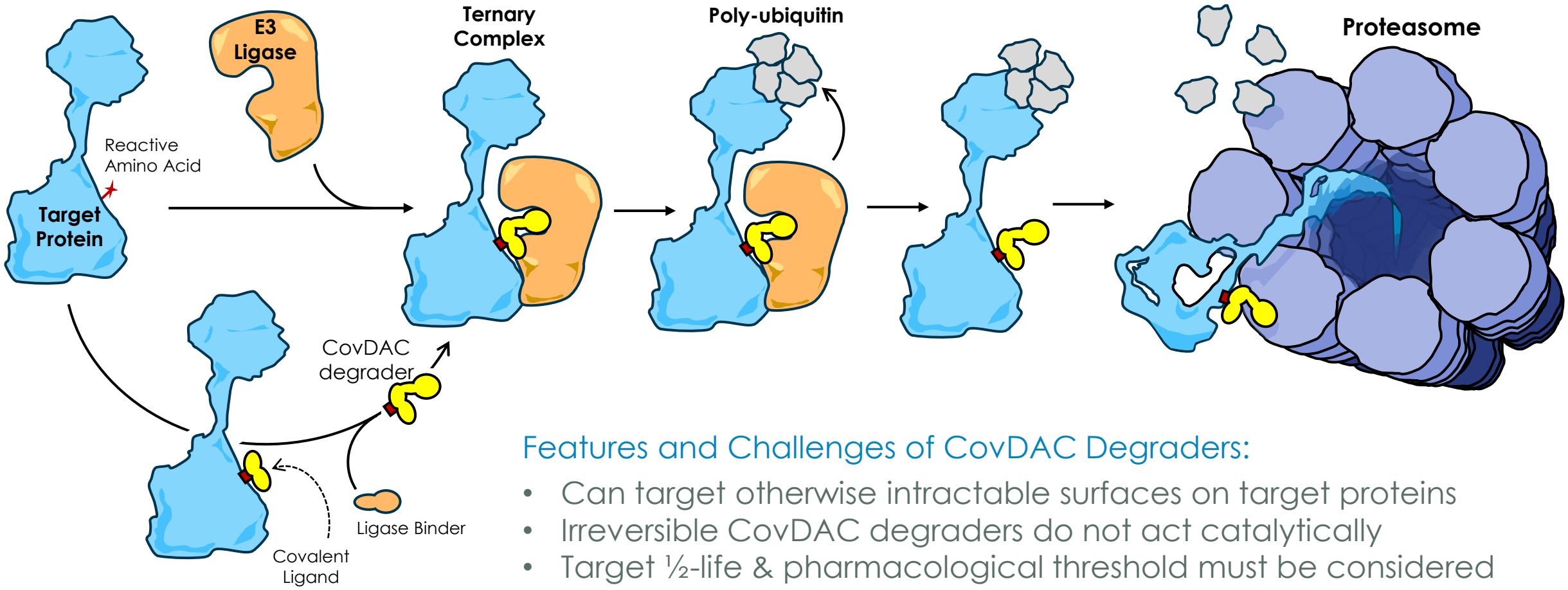
Utilizing TPD to Drug "Undruggable" Targets: BiDAC Degraders

BiDAC degraders can degrade a target protein even when the targeting ligand does not interact with a functionally relevant site



Utilizing TPD to Drug "Undruggable" Targets: CovDAC Degraders

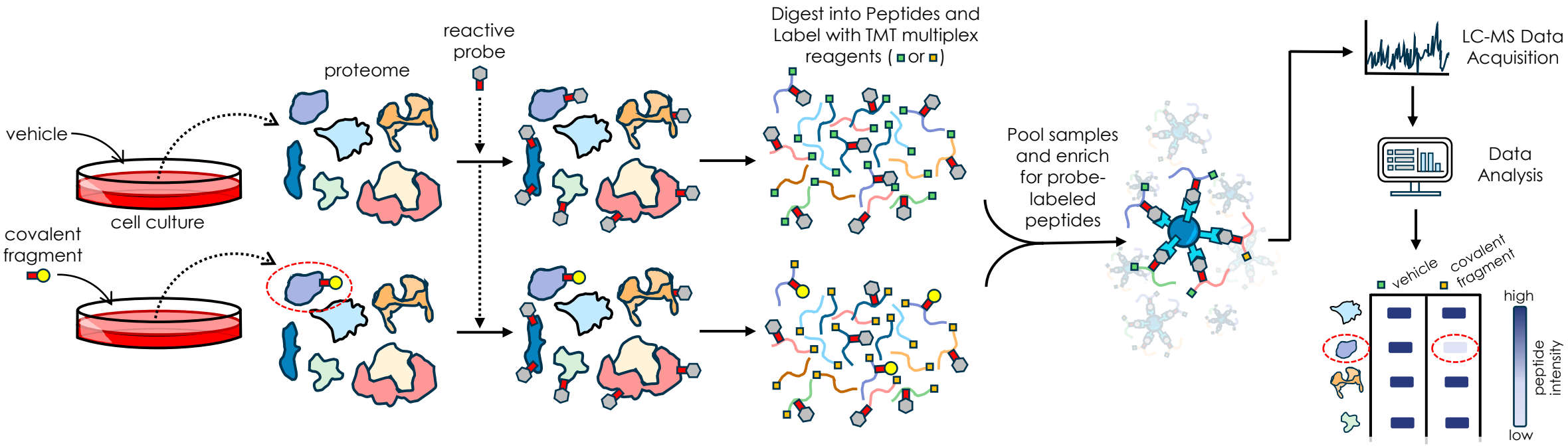
CovDAC (Covalent Degradation Activating Compound) degraders employ covalent targeting ligands to access surfaces that are difficult for reversible compounds to bind



Features and Challenges of CovDAC Degraders:

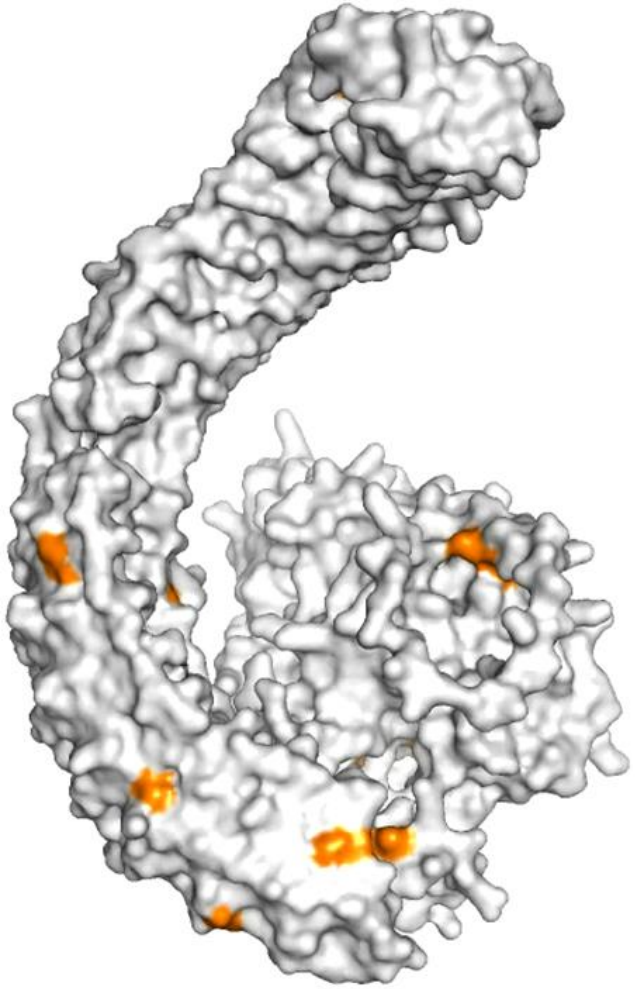
- Can target otherwise intractable surfaces on target proteins
- Irreversible CovDAC degraders do not act catalytically
- Target ½-life & pharmacological threshold must be considered

Chemoproteomics Screens for Covalent Target Ligand Identification

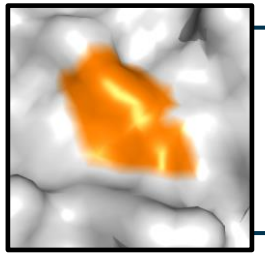


- Chemoproteomics screening is a cellular assay that enables identification of small molecule binding sites via labeling of reactive residues on proteins
- A screening campaign can provide fragment hits across the accessible reactive proteome of the chosen cell type

Utilizing Covalent Targeting Ligands to Design CovDAC and BiDAC Degraders for "Undruggable" Targets

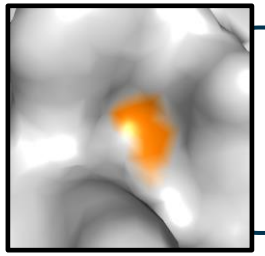


flat surface



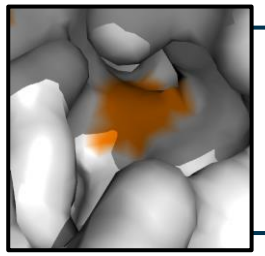
Improve covalent reactivity and use adjacent target protein and E3 ligase surfaces to leverage ternary complex interactions

shallow pocket



Combine PPI with additional pocket features to improve binding and potentially convert from covalent to reversible binding ligands

deep pocket



Use pocket features to improve selectivity and binding properties; can utilize to convert from covalent to reversible binding ligands

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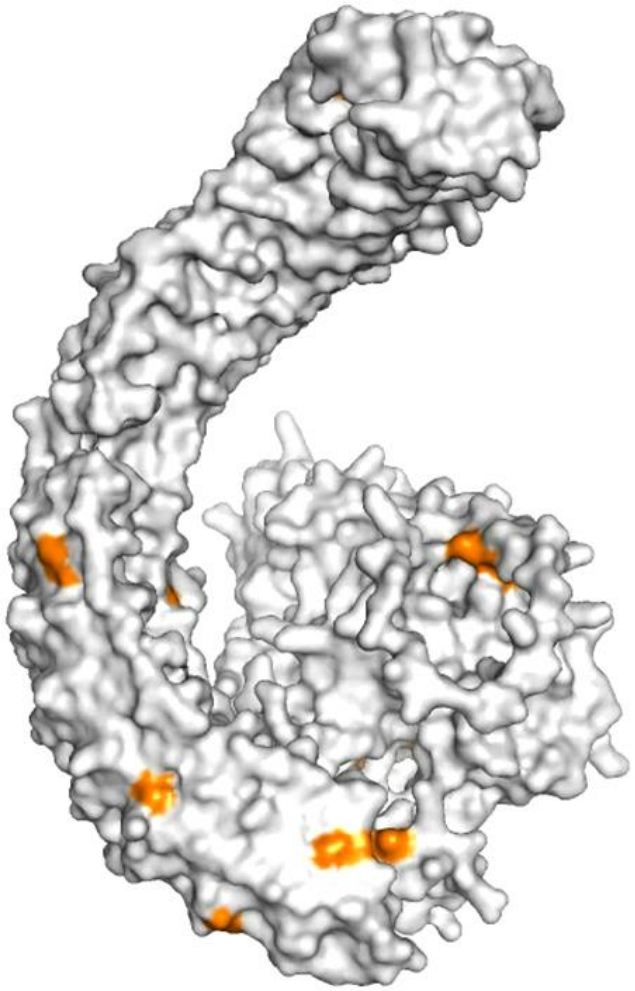
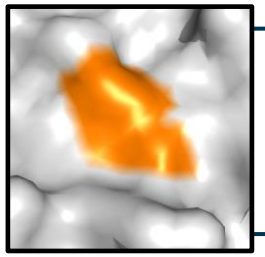
Utilizing Covalent Targeting Ligands to Design CovDAC and BiDAC Degraders for "Undruggable" Targets



flat surface



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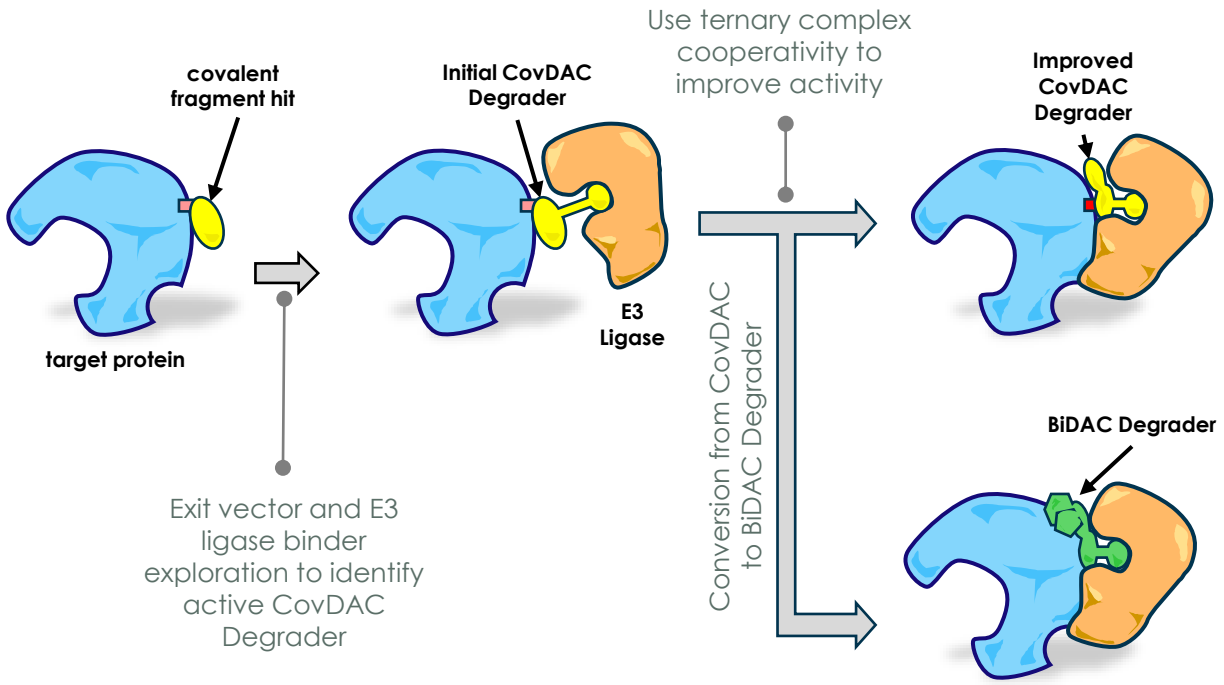

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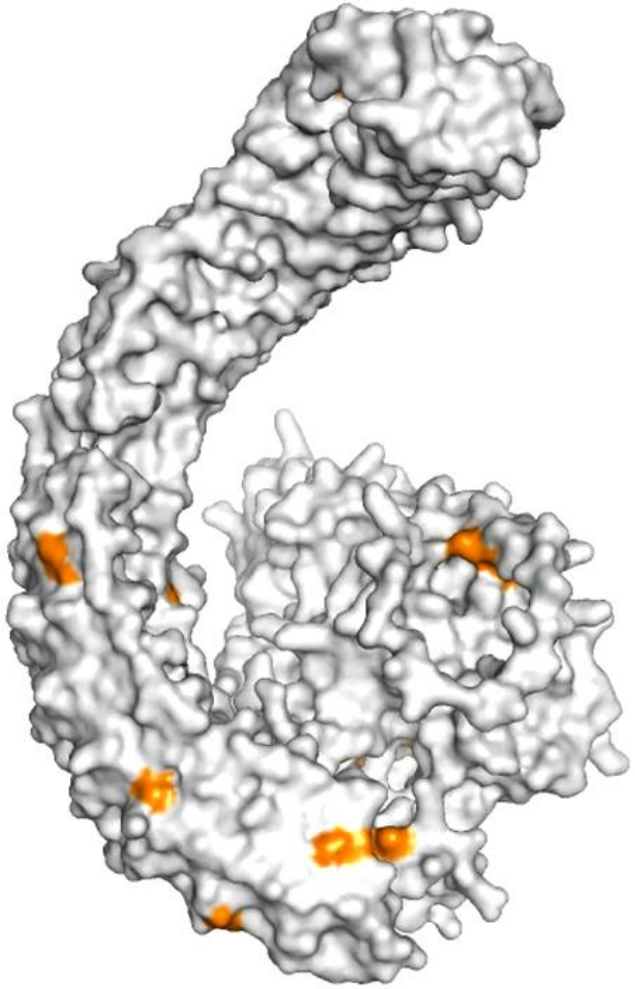
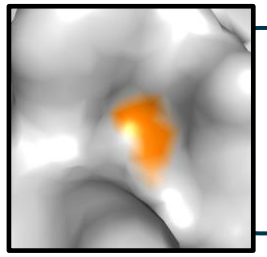


shallow pocket



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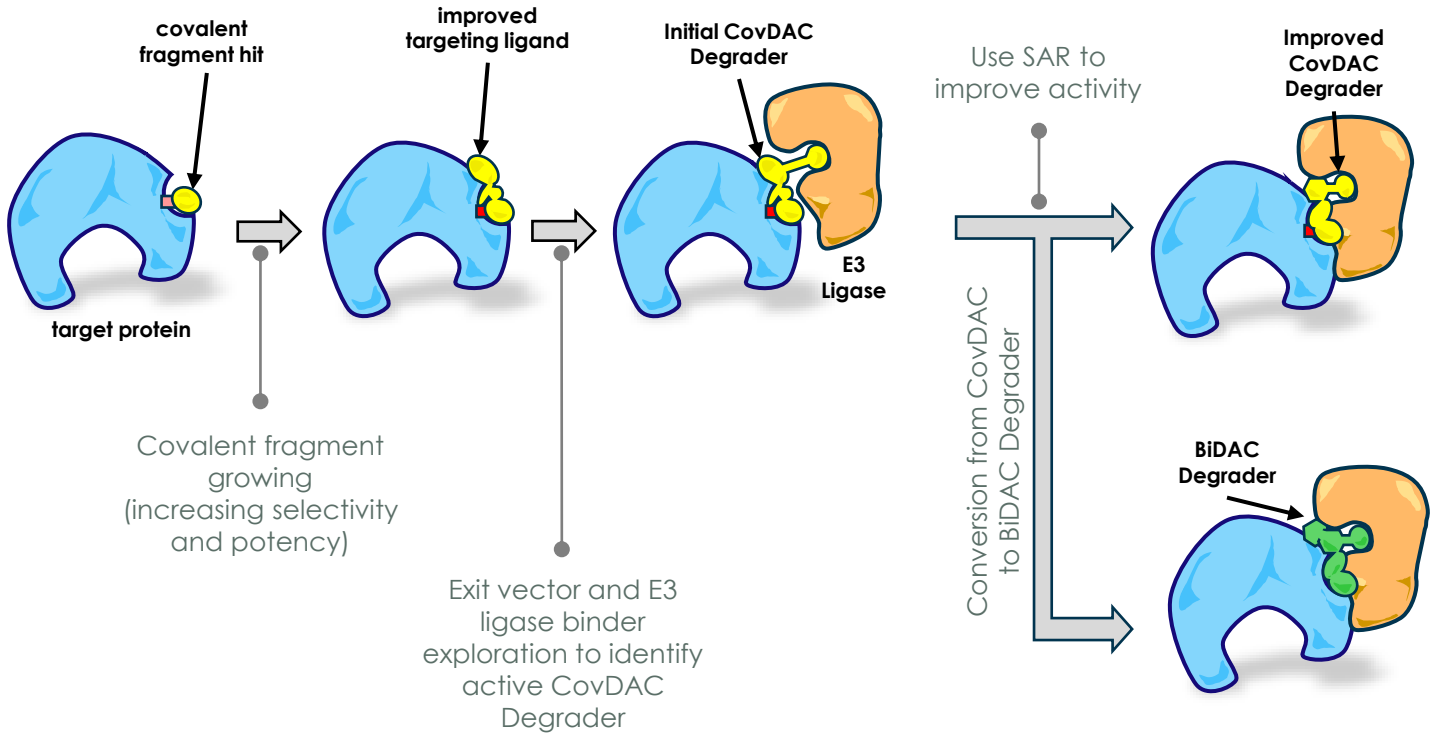

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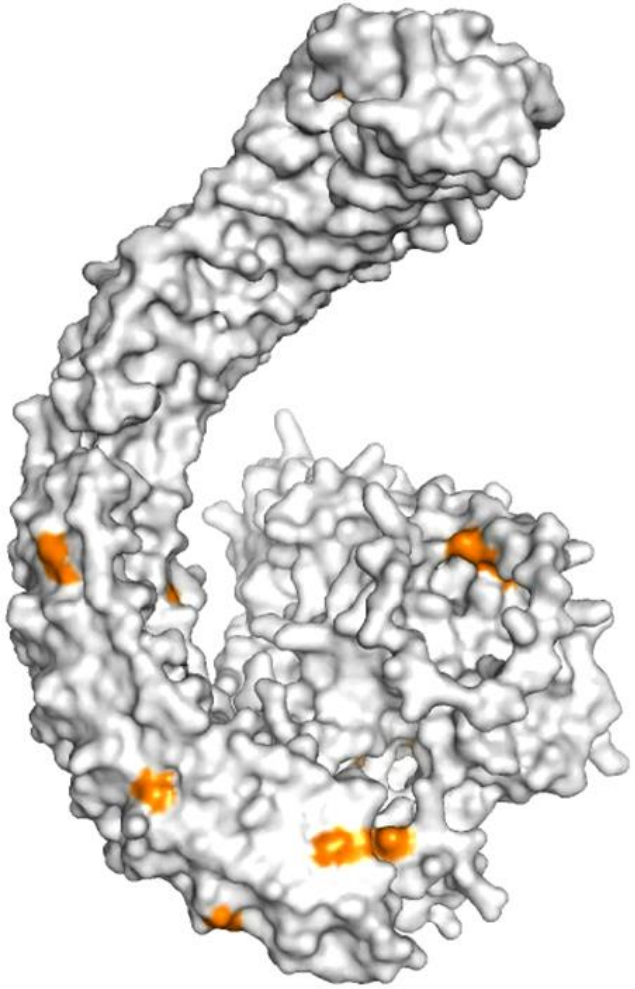

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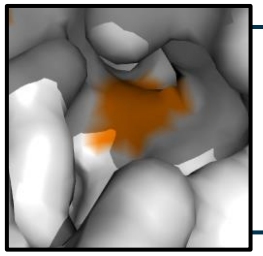
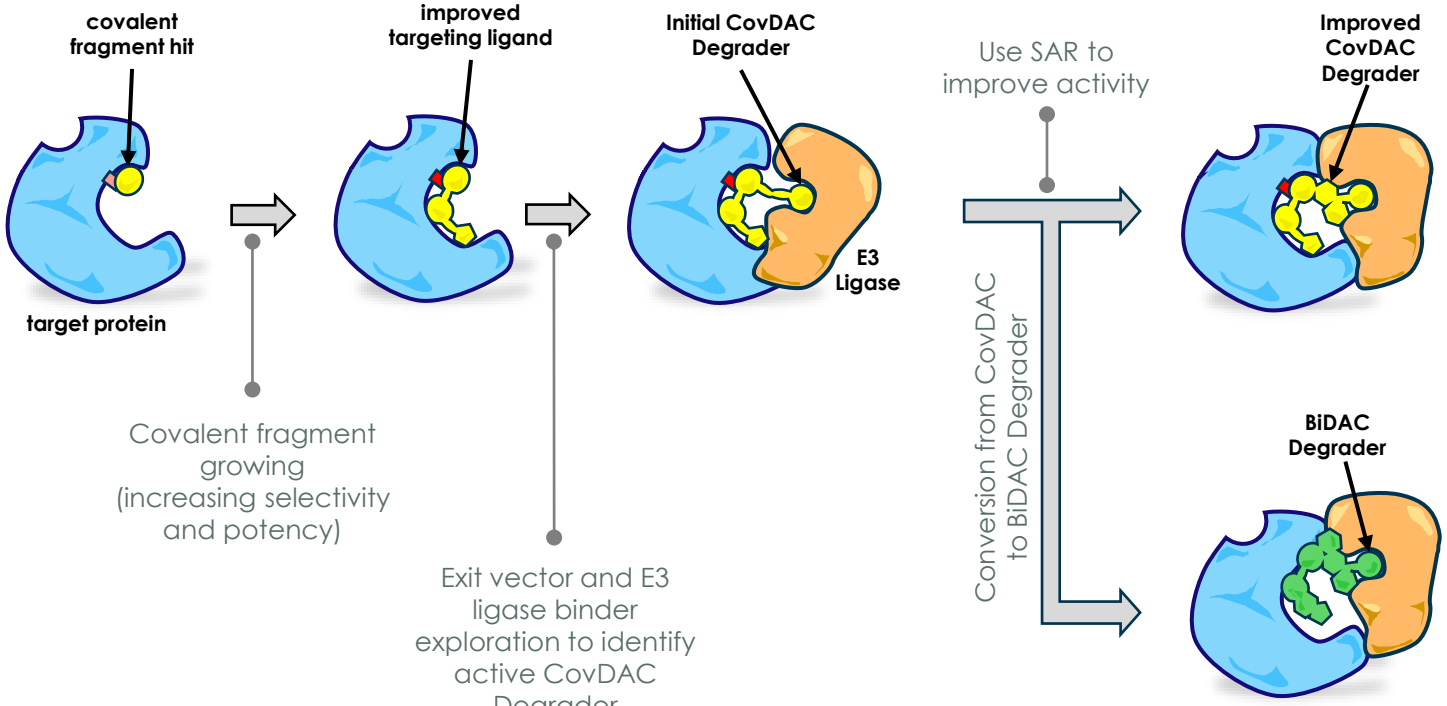


Use pocket features to improve selectivity and binding properties; can utilize to convert from covalent to reversible binding ligands



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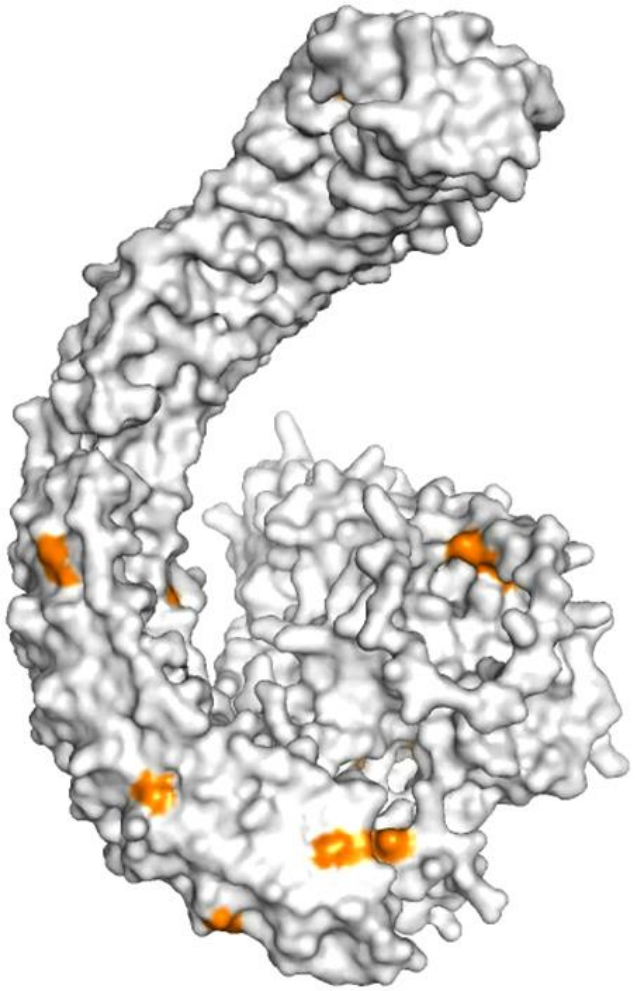

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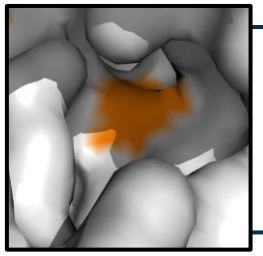

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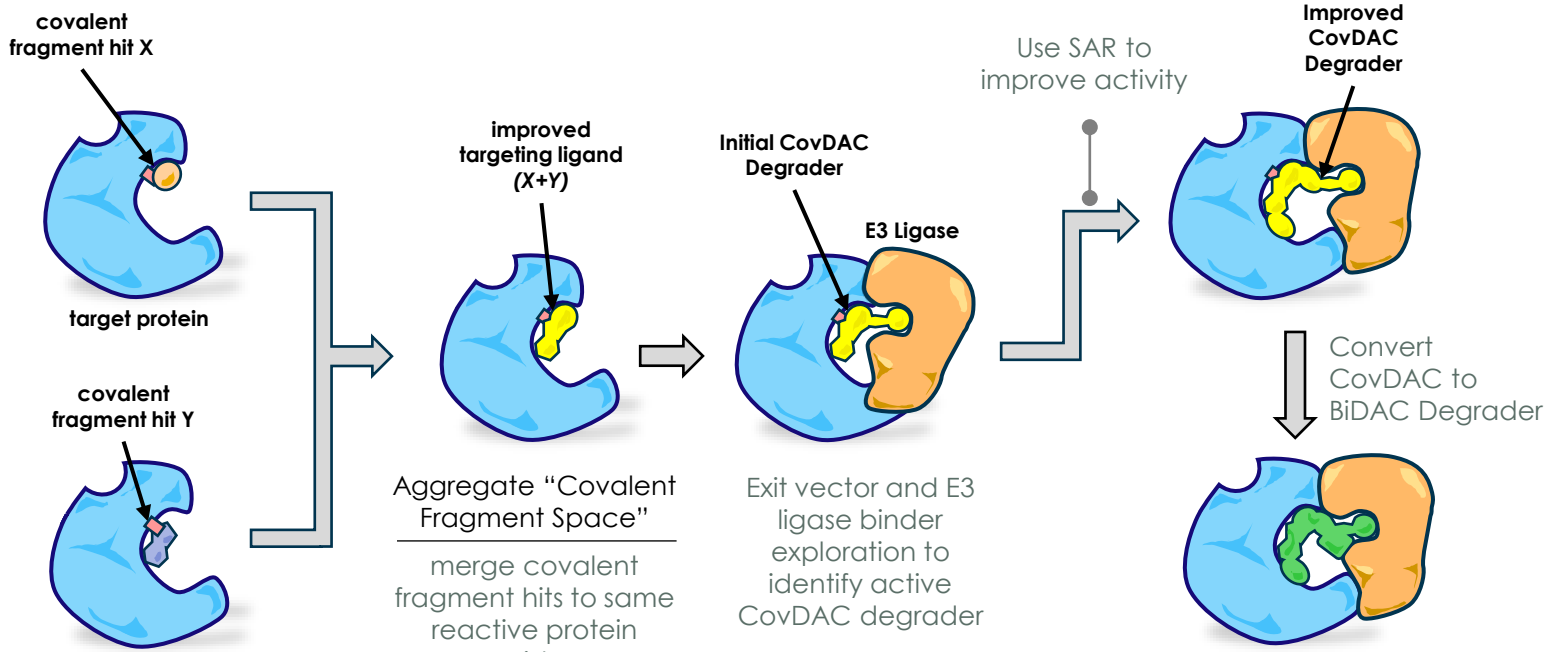

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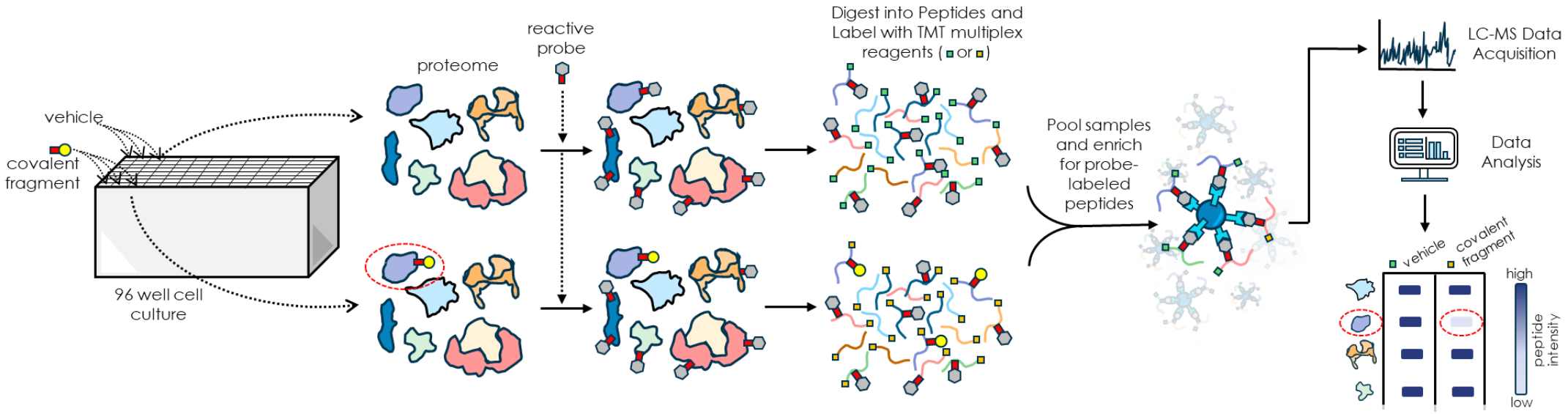
C4T Cysteine-Targeted Chemoproteomic Screen with OmicScouts

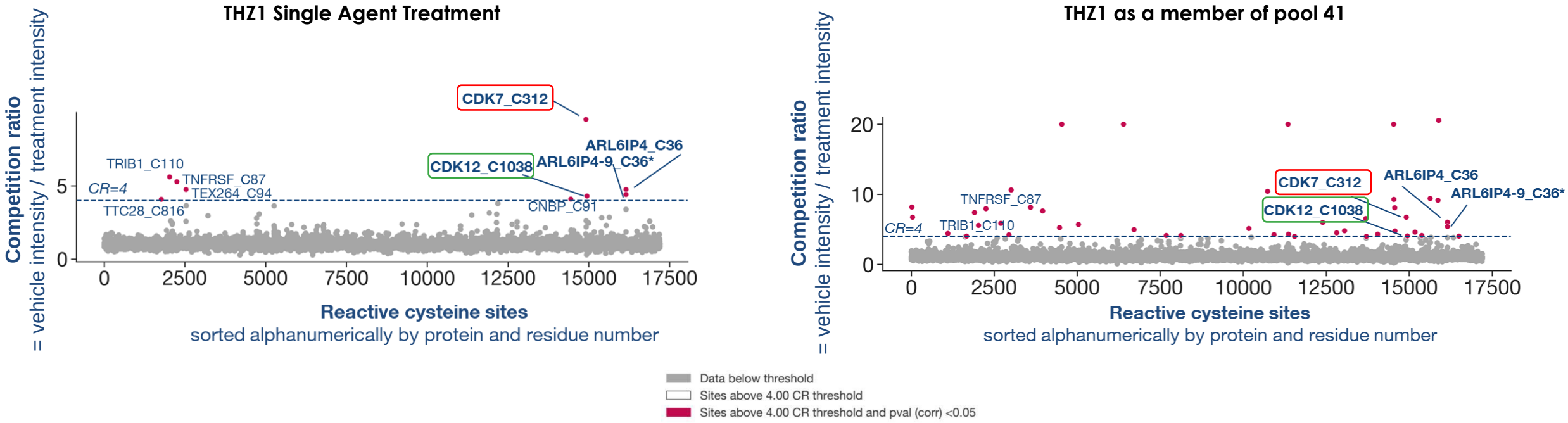


	Kuljanin et al.*	C4T CysScout Pilot study with OmicScouts
# fragments screened	285	265
Pooled?	No	Screened in pools of 5 fragments
# Cell lines	3	1
# Cysteine sites identified	>20k per cell line, ~30k across 3 cell lines	~30k
# unique proteins	>6k per cell line, ~7k across 3 cell lines	~10k

*Kuljanin M, et al. *Nat Biotechnol*. 2021 May;39(5):630-641

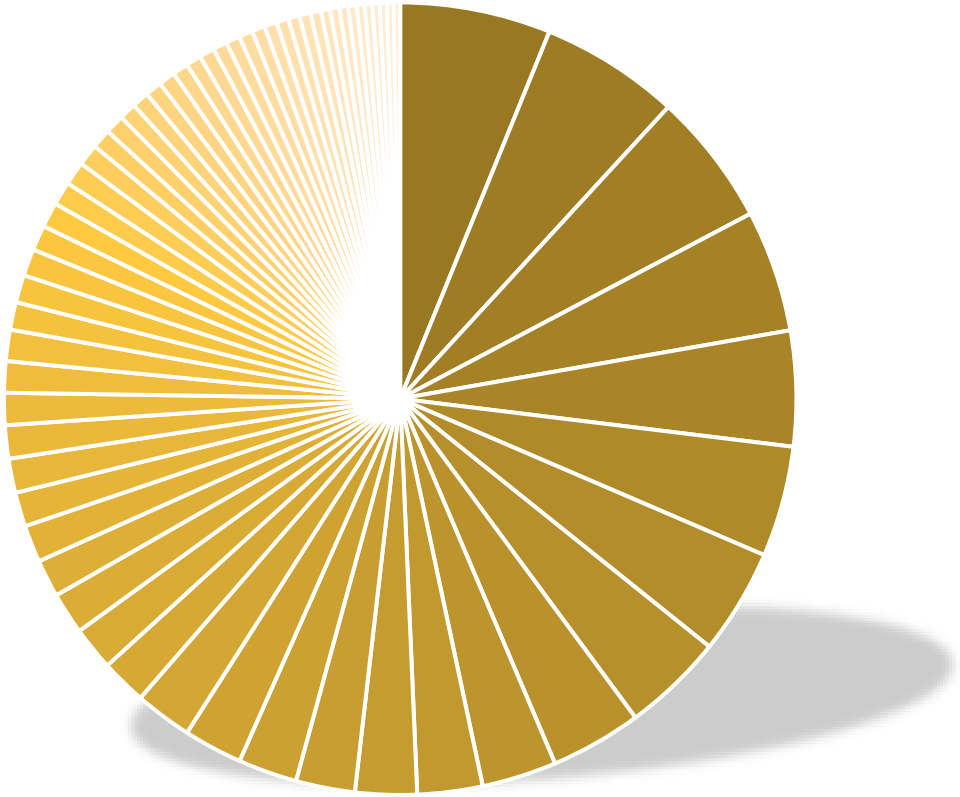
C4T Cysteine-Targeted Chemoproteomic Screen: Positive Control and Proof of Concept for Pooling Strategy

- THZ1 was used as a positive control for the assay and as a test case for the pooling methodology
  - Correctly identified CDK7 and CDK12 as the predominant protein targets as a single agent and as part of a 5-member pool

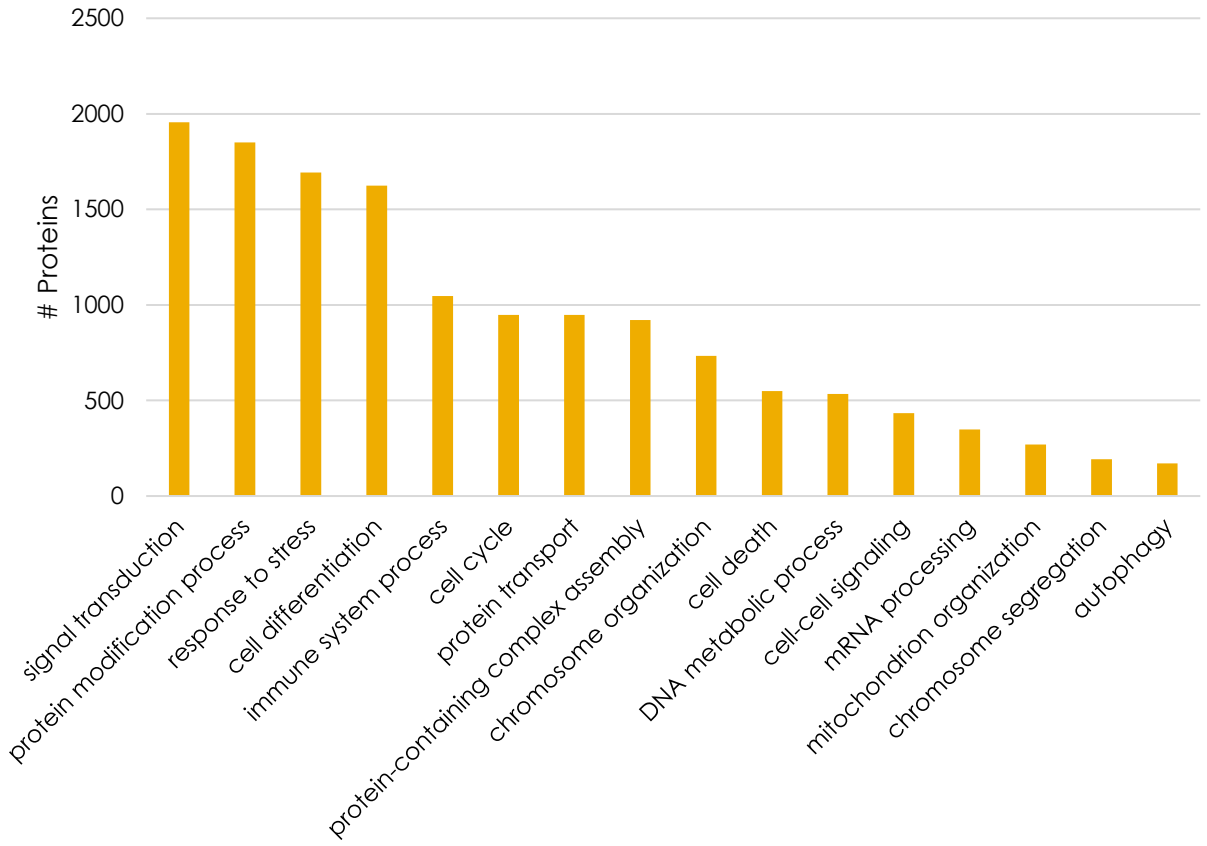


C4T Cysteine-Targeted Chemoproteomic Screen: Wide Array of Identified Cellular Processes Demonstrates Lack of Any Pathway Bias

63 GO Cellular Process Classes with ≥100 proteins



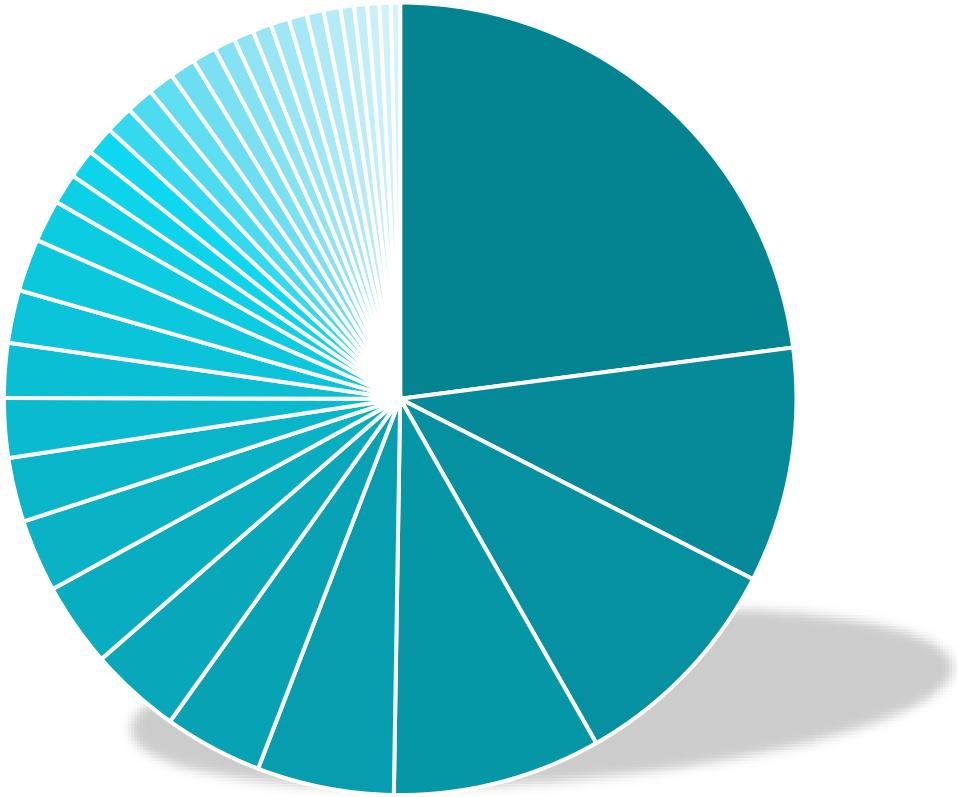
Selected Examples of Cellular Process Classes



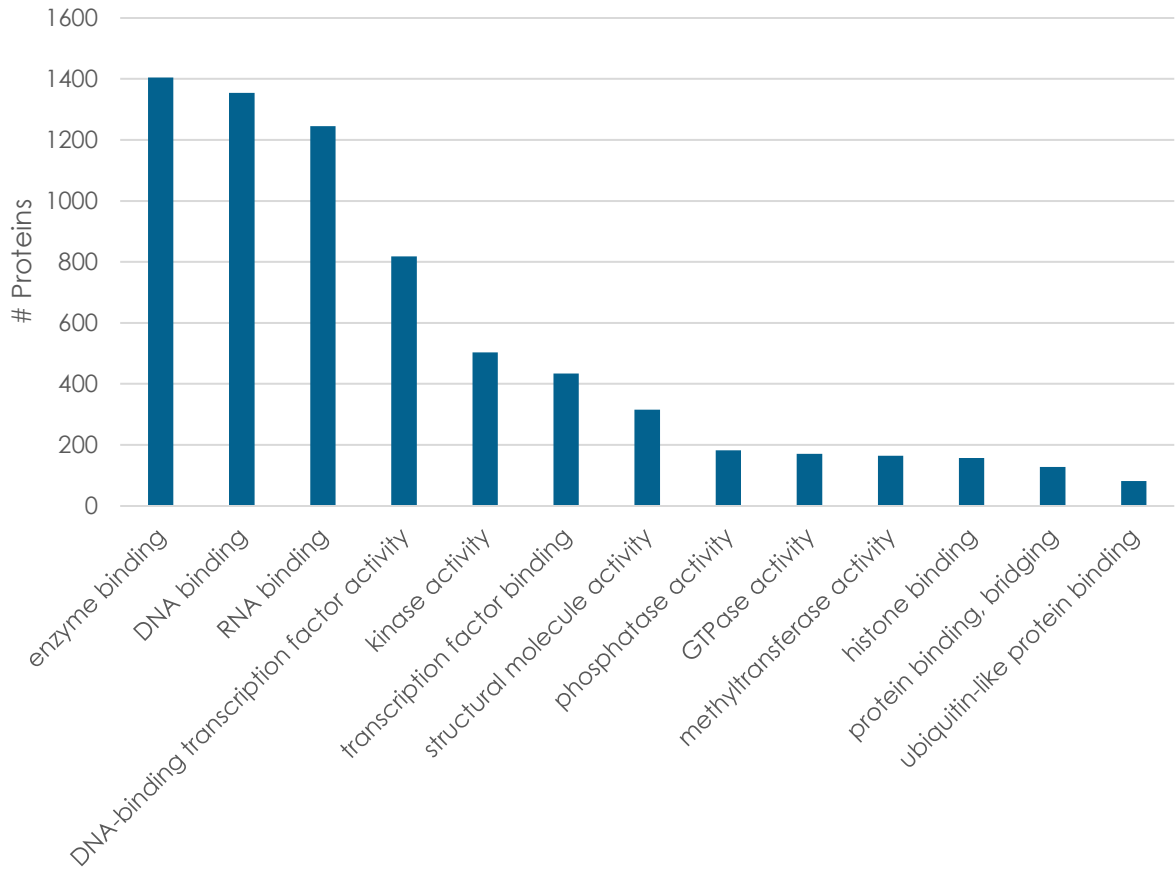
"cellular process" defined by GO process annotation

C4T Cysteine-Targeted Chemoproteomic Screen: Multiple "Undruggable" Protein Classes are Identified

35 GO Protein Functional Classes with ≥50 proteins



Selected Examples of Protein Functional Classes



"protein classes" defined by GO functional annotation

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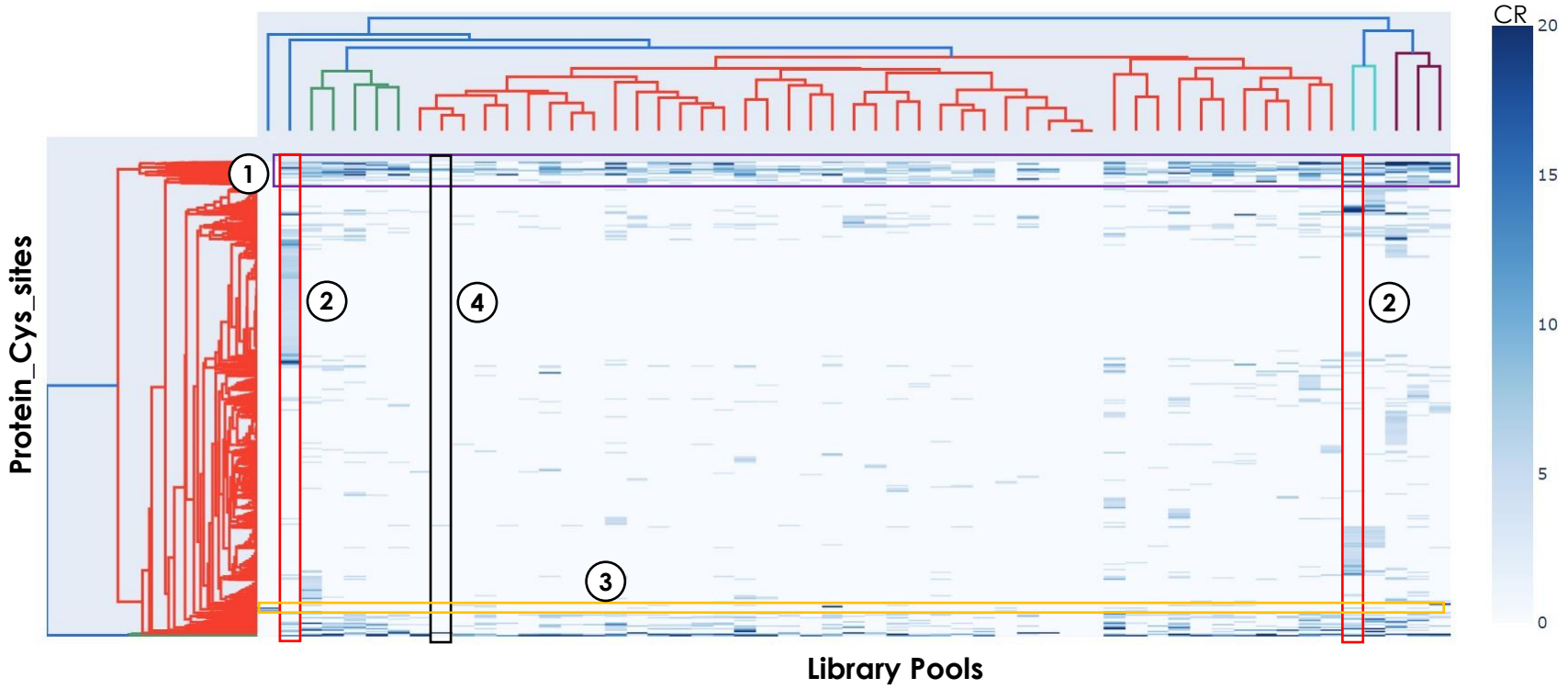
C4T Cysteine-Targeted Chemoproteomic Screen: Overview of Statistically Significant Sites across the Proteome

- Quantitated cysteine sites across the proteome with a p-value < 0.05 and a competition ratio (CR) ≥ 4



The clustermap illustrates that there are:

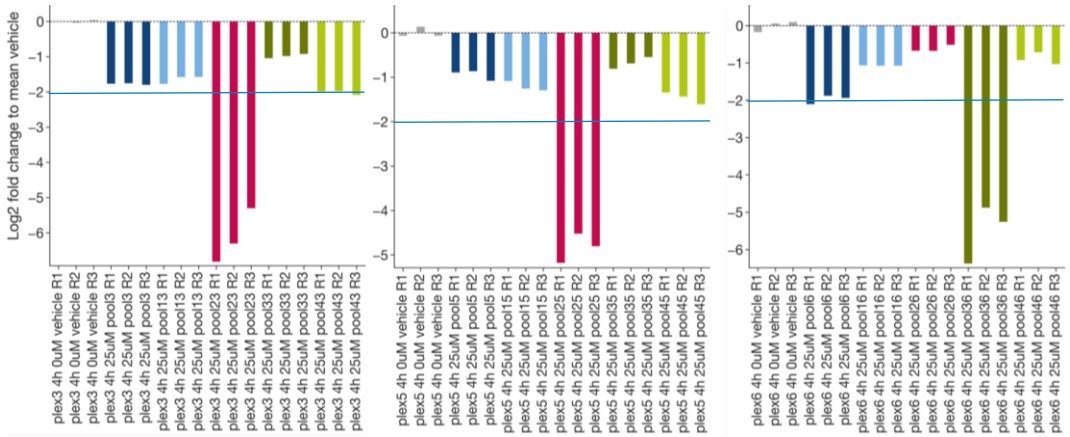
1. Commonly labeled protein sites across most pools
2. Pools that contain promiscuous fragments
3. Rare protein sites that are labeled in few to 1 pool(s)
4. Pools that contain very protein site specific reactive fragments

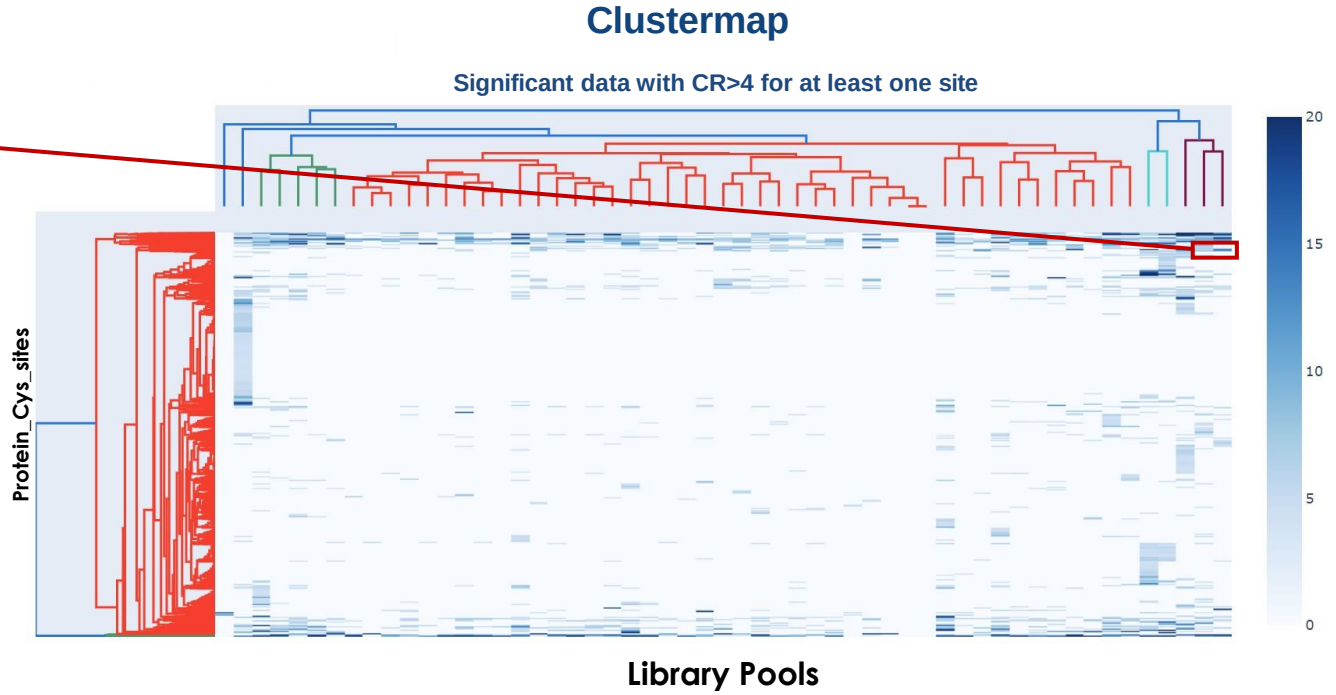
C4T Cysteine-Targeted Chemoproteomic Screen: Overview of Statistically Significant Sites across the Proteome

- Quantitated cysteine sites across the proteome with a p-value < 0.05 and a competition ratio (CR) ≥ 4

POI-21_Cys*X*

Significantly targeted by pools 23, 25, and 36





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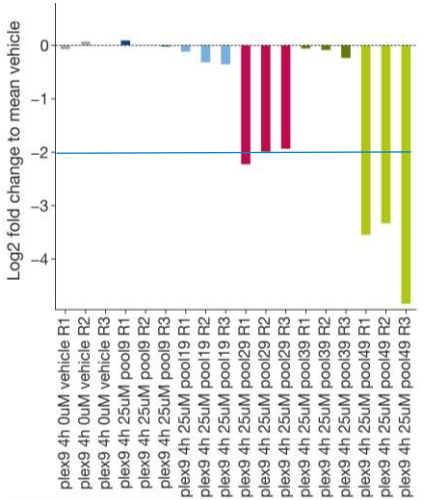
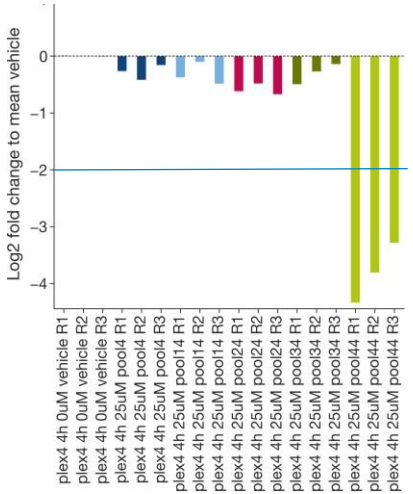


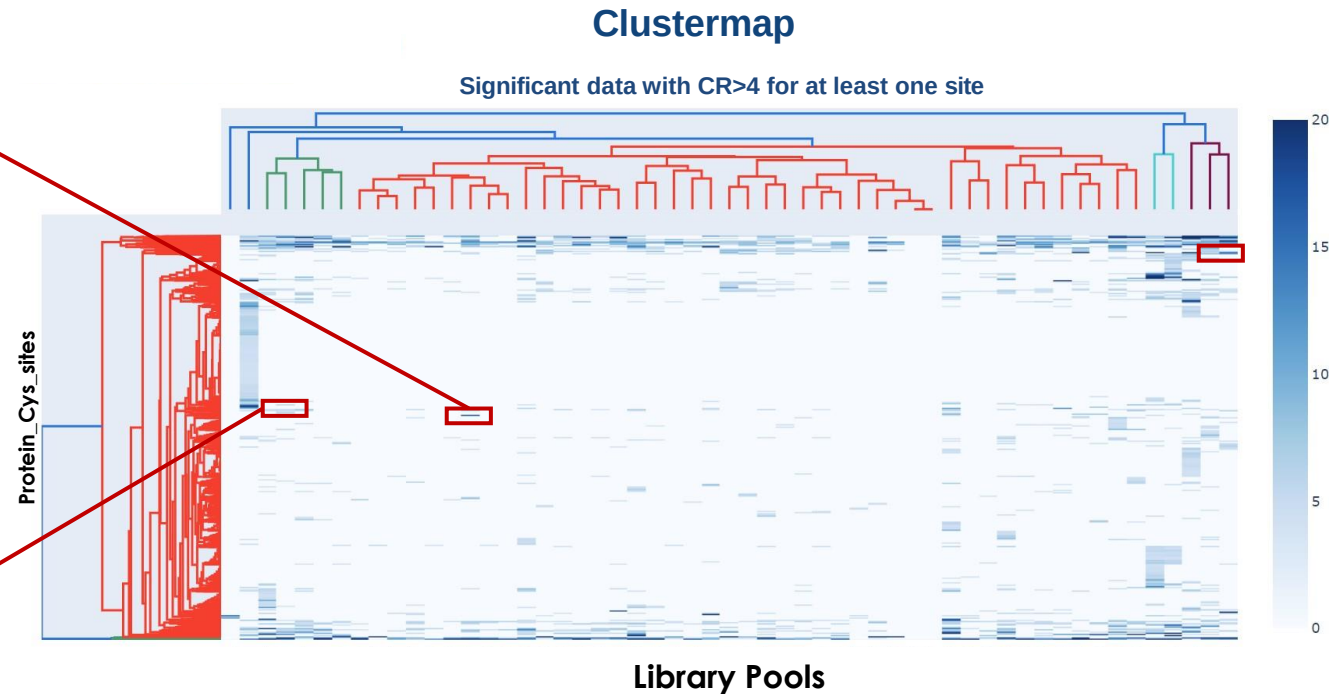
POI-31_Cys*X*

Significantly targeted predominantly by pool 49 and pool 29

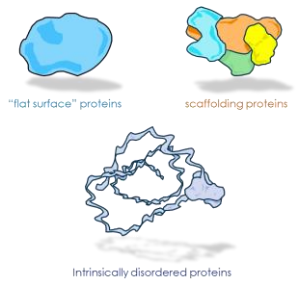


POI-73_Cys*X*

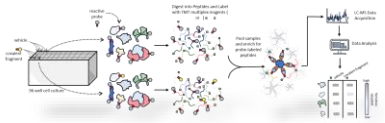
Significantly targeted ***only*** by pool 44



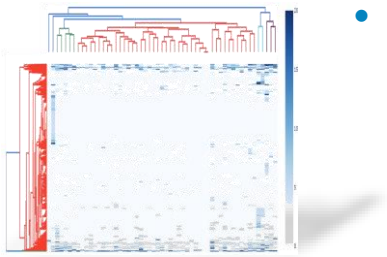
Summary and Conclusions



- Targeted Protein Degradation is well suited to target the "undruggable" proteome for the treatment of human disease
  - Ligand discovery against high value "undruggable" targets remains a bottleneck
  - Covalent target ligand-based approaches could help address this challenge



- Chemoproteomic screening offers a path to identify starting points for developing degraders targeting "undruggable" proteins



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- Working closely with OmicScouts, C4T has conducted a pilot chemoproteomic screen
  - Numerous proteins considered undruggable were identified across a wide range of biological processes
  - A significant fraction of these contain ligandable sites providing opportunities to develop degraders for the most difficult to drug proteins involved with human disease

Thank You!

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- Hope Flaxman
- Scott Mills
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- Michael Thomenius
- Roy Pollock
- Chris Nasveschuk
- Jim Henderson

- The omicscouts Team!