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MOPED™ : A Novel Platform for the Discovery of Molecular Glues

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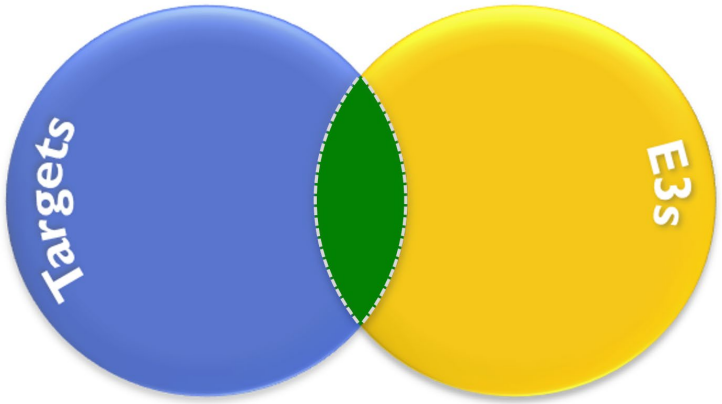
Vice President, Molecular Technology

Proteovant breaks through current limits of TPD

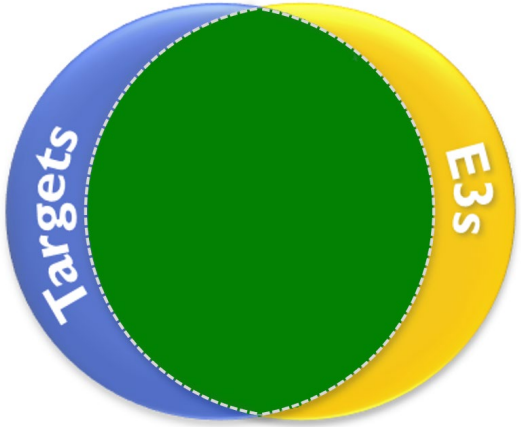
Target-centric approach coupled with AI enabled Platforms transforms UPS Degrader Drug Discovery

Majority of TPD landscape



Current scope of protein targets and E3s

Proteovant advantage



Expanding the universe of protein targets and E3s

Heterobifunctional degraders primarily use CRBN and VHL
Molecular glue degrader companies predominantly exploit CRBN or phenotypic discovery
Proteovant proprietary ternary complex focused TPD platforms enable access to a wider range of targets and E3s

Why targeted protein degradation?

Protein degradation offers advantages over other modalities

Targeted Protein Degradation

1. **Impact all protein functions** — Target enzymatic and non-enzymatic roles
2. **High selectivity potential** — Opportunity to target less conserved regions of the protein of interest vs. related family members
3. **Expand target space** — Target historically "undruggable" proteins
4. **Event-driven pharmacology** — Catalytic mechanism reduces the drug concentration required at site of action

TPD technologies have different strengths

Challenges limit each of the technologies for drug discovery in various ways

TPD type	molecular weight	compound absorption	target biomolecules	mechanism	molecular structure design
HyT-PD	moderate	moderate	POI	various	easy
PROTAC	high	hard	POI and E3	UPS	moderate
Molecular Glue	low	easy	POI and E3	UPS	hard
TRAFTAC	high	hard	POI (transcription factors) and E3	UPS	hard
AID Tag	moderate	moderate	POI and E3 (SCF)	UPS	easy
HEMTAC	high	hard	POI and HSP90	UPS	hard
SNIPER	high	hard	POI and E3 (IAP)	UPS	moderate
AUTAC	high	hard	POI	autophagy-lysosome	moderate
ATTEC	high	hard	POI and LC3	autophagy-lysosome	hard
LYTAC	high	easy	POI and LTR	endocytosis-lysosome	moderate
AUTOTAC	high	hard	POI and P62	autophagy-lysosome	hard

He et. al. European Journal of Medicinal Chemistry Volume 260 (2023) 115741

Molecular glues have advantages as oral therapeutics

A significant unsolved discovery challenge

Molecular glues have favorable properties for safe oral drugs

- Drug like physiochemical space
- Minimal binary biological effects, due to weak binding to one or both of the individual partners
- Selectivity through strong dependence on protein surfaces
- Efficacy not blunted by Hook effect

Glue discovery is an unsolved problem

- Glue discovery is high risk / high reward with most examples being serendipitous
- Steep SAR challenges chemical optimization
- Billions of possible combinations require a novel discovery approach

Interest in molecular glue technology highlights the unsolved discovery challenge

Disclosed deals since January 2022

Announcement Date	Licensor	Licensee	Headline	Upfront Payment	Total Biobucks
9/20/2023	Orionis	Genentech	Orionis Biosciences Announces Collaboration with Genentech to Discover and Develop Molecular Glue Class Medicines	$47M	>$2B
4/5/2023	Biotheryx	Incyte	Biotheryx Announces Research Collaboration And License Agreement With Incyte For Discovery Of Targeted Protein Degraders For Novel Oncology Targets	$7M	$360M (per target; option for additional)
4/5/2023	Proxygen	Merck	Proxygen Announces Collaboration And License Agreement With MSD For The Discovery And Development Of Novel Molecular Glue Degraders	Yes; amount undisclosed	$2.55B
10/4/2022	Synthex	BMS	Synthex And Bristol Myers Squibb Enter Into A Research Collaboration To Discover And Develop Targeted Protein Degradation (TPD) Therapeutics	Yes (cash and equity investment); amount undisclosed	Over $550M
8/25/2022	A-Alpha Bio	BMS	A-alpha Bio Announces Collaboration With Bristol Myers Squibb To Discover Molecular Glue Targets For Protein Degradation	Yes; amount undisclosed	Undisclosed
6/2/2022	Proxygen	Merck KGaA	Proxygen Announces Strategic Collaboration With Merck To Develop Molecular Glue Degraders	Yes; amount undisclosed	€495M ($554M)
5/10/2022	Evotec	BMS	Evotec And Bristol Myers Squibb Extend And Expand Strategic Partnership In Protein Degradation	$200M	$5B
4/28/2022	Plexium	AbbVie	Abbvie And Plexium Enter Into Multi-target Strategic Collaboration To Develop And Commercialize Targeted Protein Degradation Therapies For Neurological Conditions	Yes; amount undisclosed	Undisclosed
2/3/2022	Plexium	Amgen	Amgen And Plexium Announce Multi-year, Drug Discovery Collaboration To Identify Novel Targeted Protein Degradation Therapies	Undisclosed	Over $500M
1/25/2022	Yeda	Monte Rosa	Monte Rosa Therapeutics And Yeda, The Commercial Arm Of The Weizmann Institute Of Science, Announce License And Research Collaboration To Accelerate Discovery Of Novel Covalent Molecular Glue Degraders	Undisclosed	Undisclosed

MOPED™ is an innovative platform for glue discovery

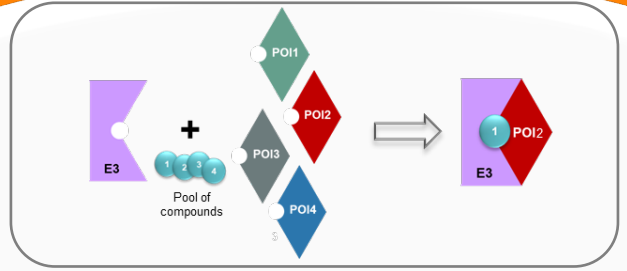
MOlecular **P**roximity **E**nabled **D**etection (MOPED™)

INCREASING ACCESS TO TARGETS

Discovering novel molecular glues directed to structured and unstructured protein regions

EXPANDING E3 OPPORTUNITIES

Finding novel molecular glues using known E3s, target matched E3s, and/or E3 agnostic



Biochemical workflow to discover glues for a defined drug target and pre-selected E3s

Multiplexing compounds, targets, and/or E3s for speed and efficiency

INCREASING NUMBER OF LEADS

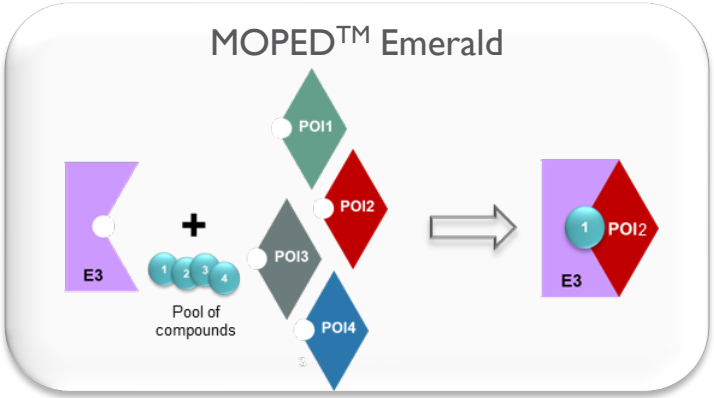
Exploring potential biological functions of molecular glues beyond TPD

BROADENING BIOLOGICAL IMPACT

MOPED™ Emerald: Biochemistry designed for molecular glue discovery

Sensitivity to find the weak hits

- Biochemical assay to measure ternary complex formation
  - Assay format gives high sensitivity for weak hits
  - E3s are tested individually and include widely used E3s and target matched E3s
  - Pools of compounds and POIs are tested for efficient screening
- Technology developed and validated
  - High-throughput 1536 well assay
  - Well-established oncology target A with known degraders was screened, and glues were identified that degrade the target



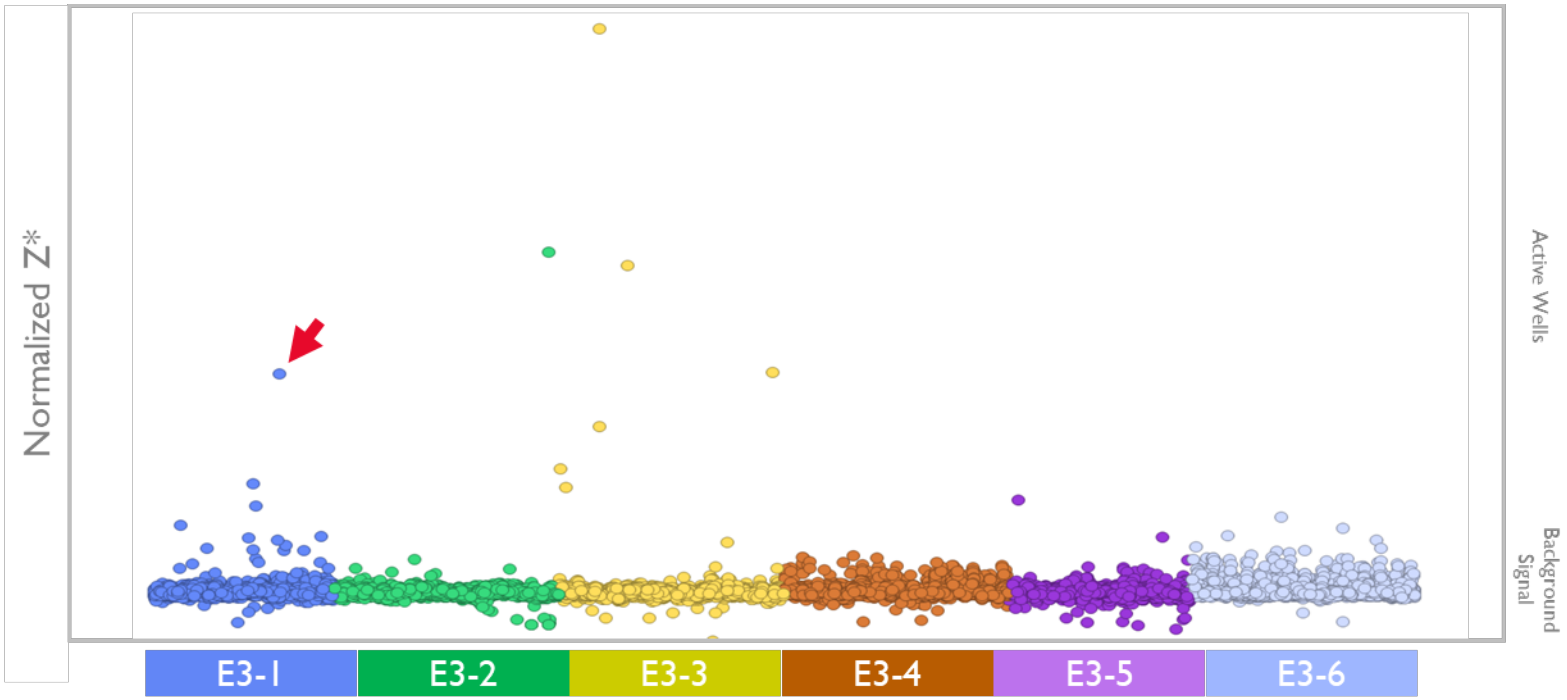
MOPED™ Emerald: Glue screening for target A

Well established oncology target with known glue degraders

- Target A
  - High value oncology target
  - Multi-domain protein
  - Known glue degraders
- Screen design
  - 460,000 compound Enamine hit locator library
  - 6 E3s
  - 3 of the ordered domains
- Each multiplexed screening well contained a mix of the three domains, one E3, and ~100 compounds

Primary Emerald screen of target A against six E3s

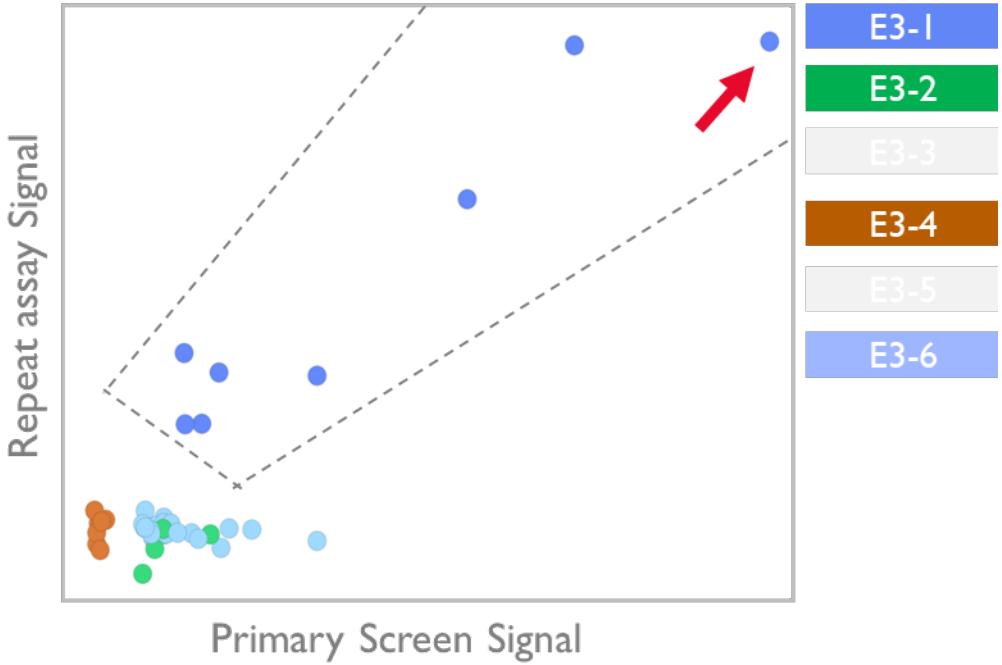
Diversity library tested against each of 6 E3s identified active wells



Target A active well confirmation

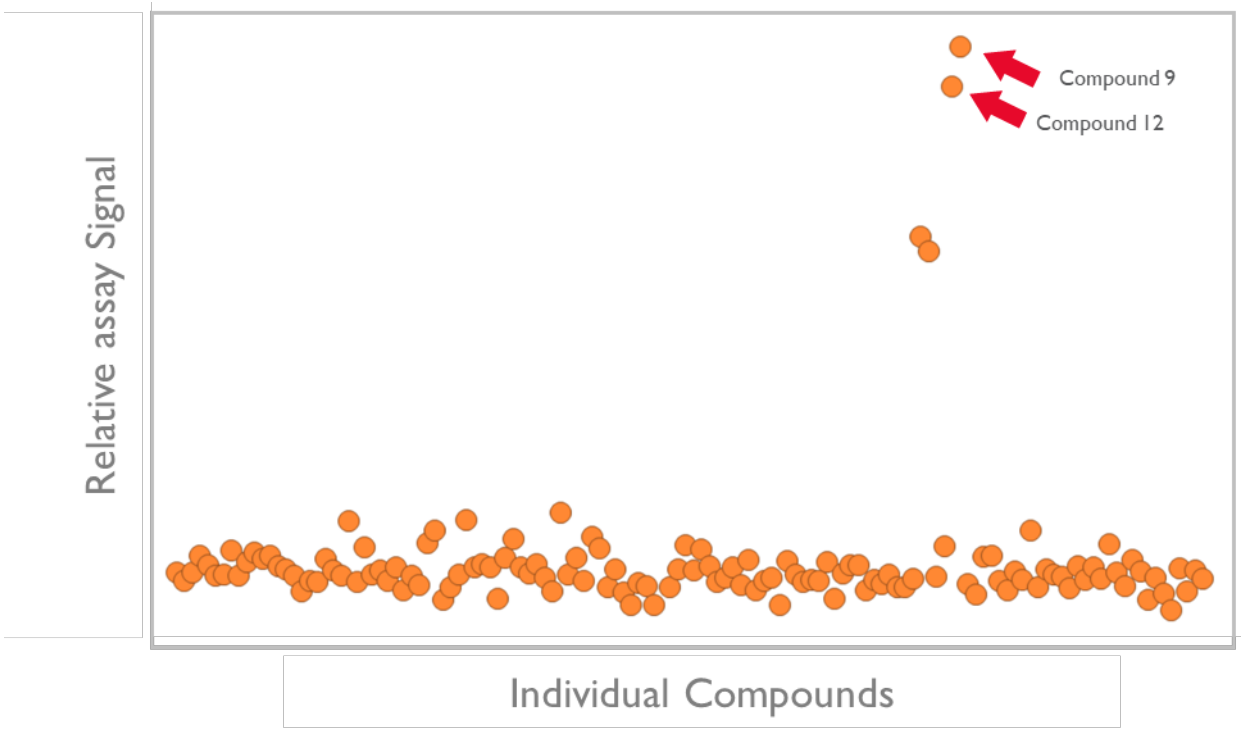
One E3 had active wells that repeat

- Active wells from 4 E3s were retested in triplicate
- Compound pools showing activity across multiple E3s are discarded
- Rate of primary screen confirmation is E3 dependent
- One E3s had wells that confirmed



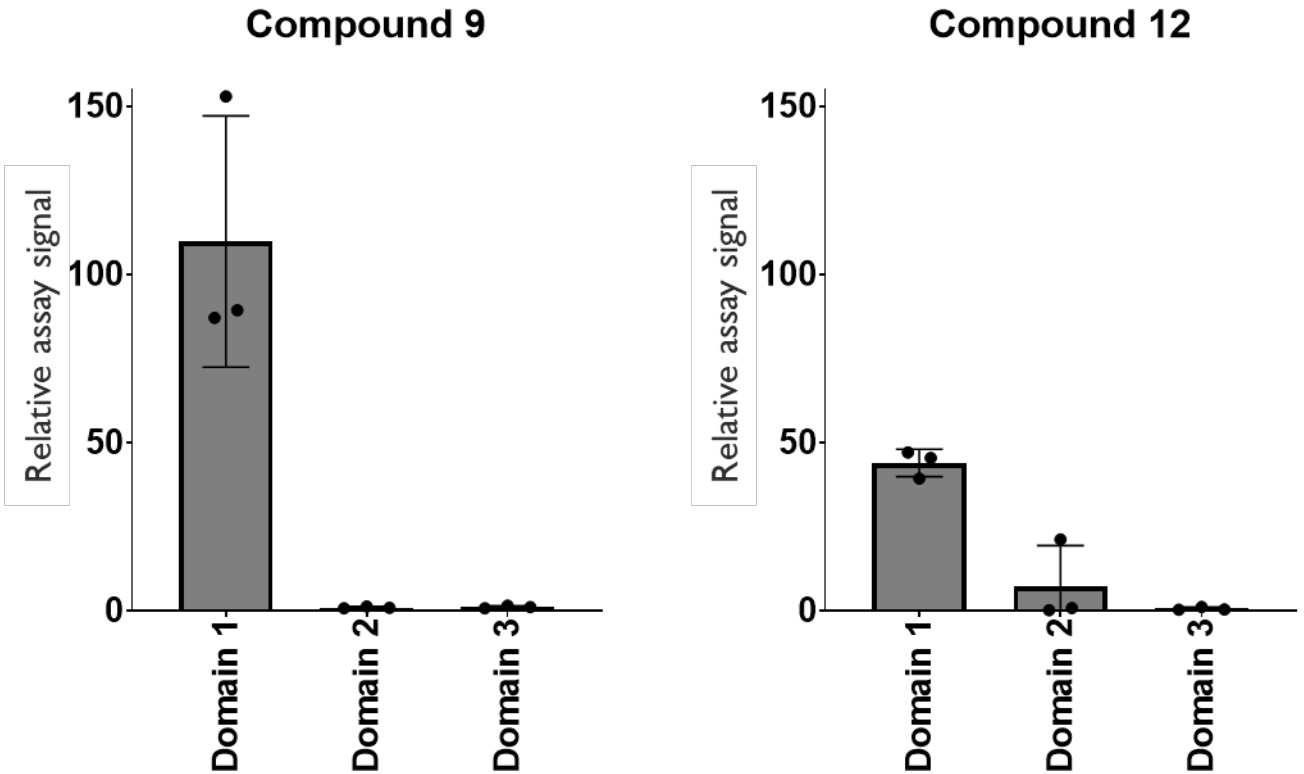
Target A deconvolution of one compound pool

Pool activity is from four compounds in this individual well



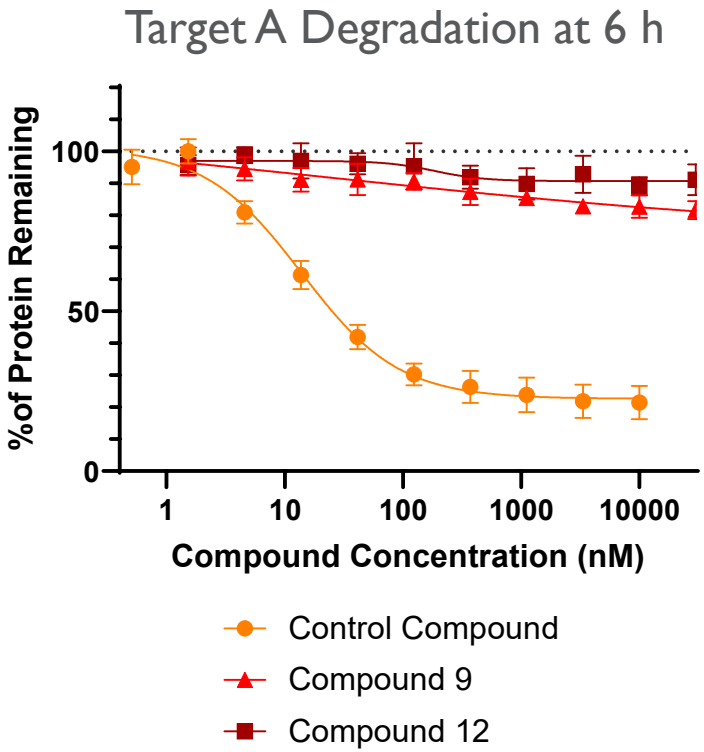
Target A hits are selective to one of the protein domains

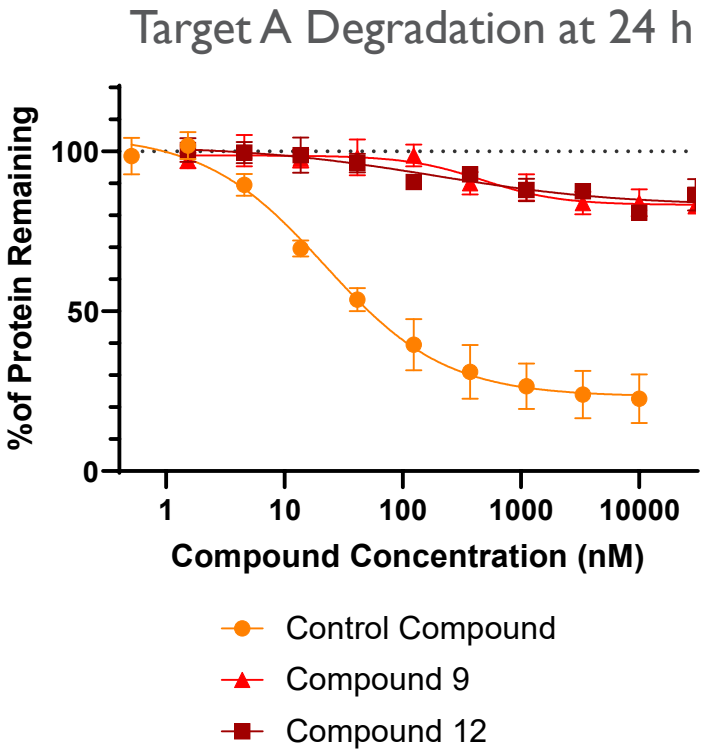
Compounds 9 and 12 leverage one E3 and a single protein domain



Target A hits are weak degraders

Two compounds from the screening library show degradation of target A in a HiBIT assay





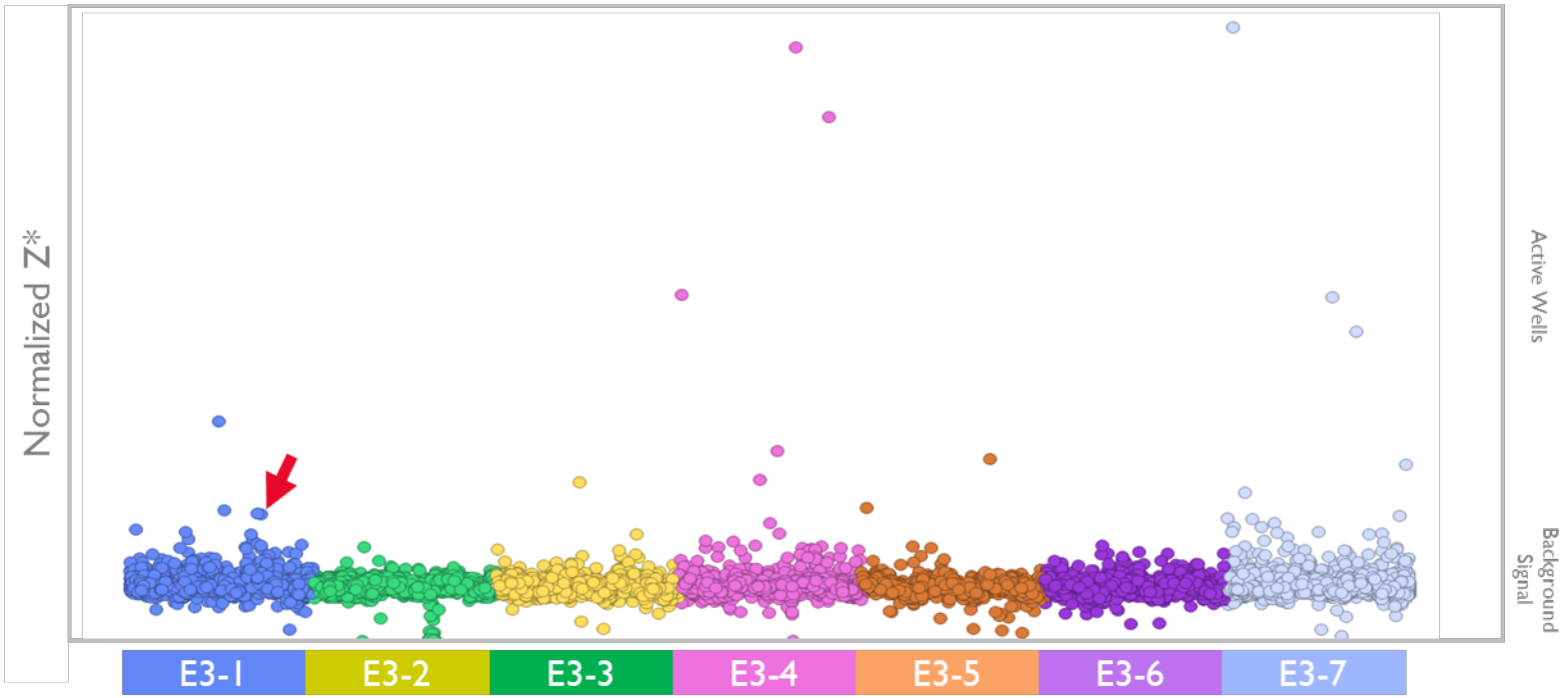
MOPED™ Emerald: Glue screening for target B

Challenging oncology target of interest across pharma

- Target B
  - High value oncology target
  - Multi-domain protein
  - Challenging to identify potent inhibitors
- Screen design
  - 460,000 compound Enamine hit locator library
  - 7 E3s
  - 3 of the ordered domains
- Each multiplexed screening well contained a mix of the three domains, one E3, and ~100 compounds

Primary Emerald screen of target B against seven E3s

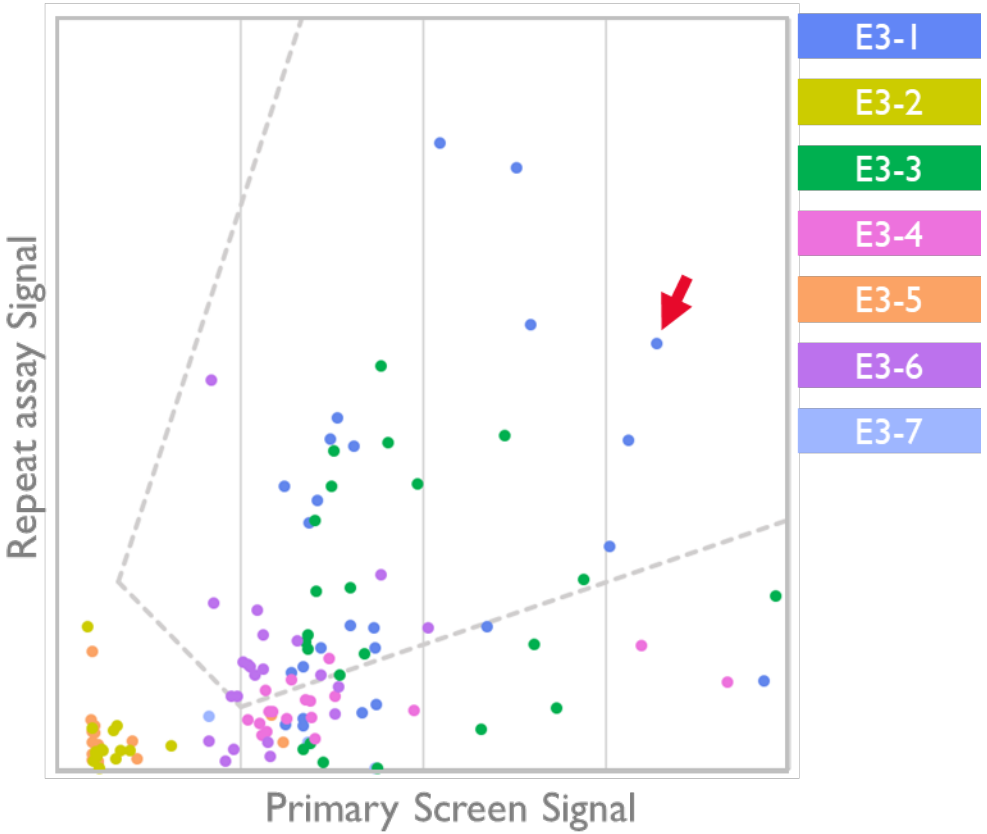
Diversity library tested against each of 7 E3s identified active wells



Target B active well confirmation

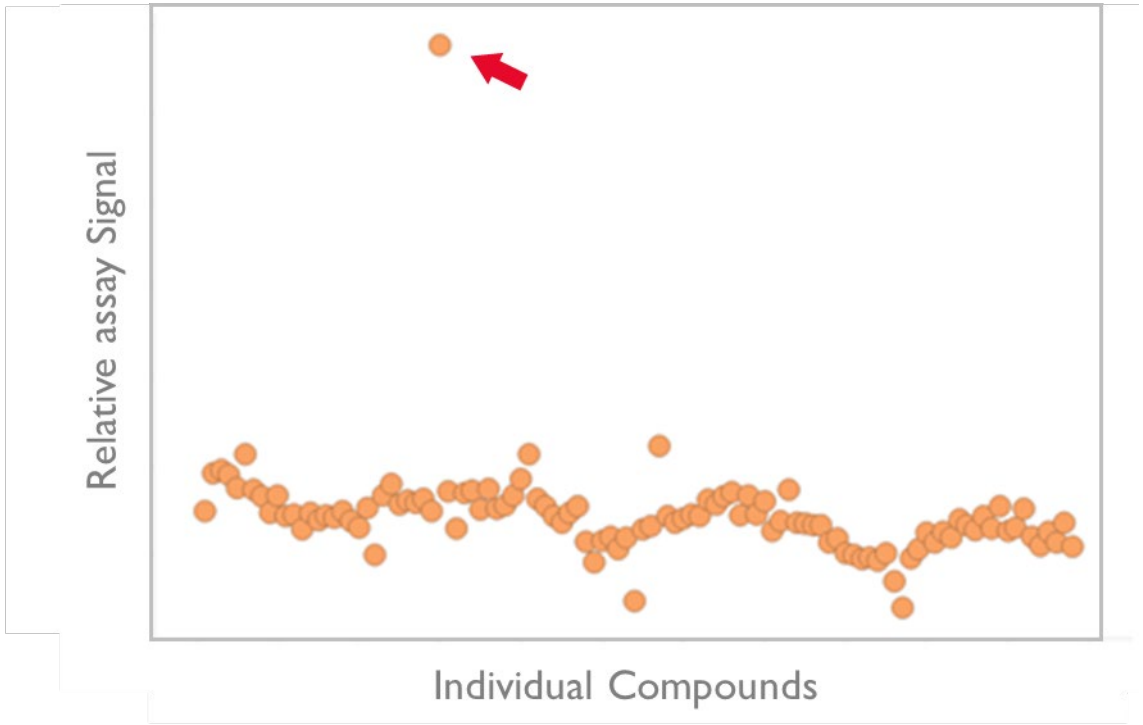
4 E3s had active wells that repeated

- Active wells from 7 E3s were retested in triplicates
- Compound pools showing activity across multiple E3s are discarded
- Rate of primary screen confirmation is E3 dependent
- Four E3s had wells that confirmed



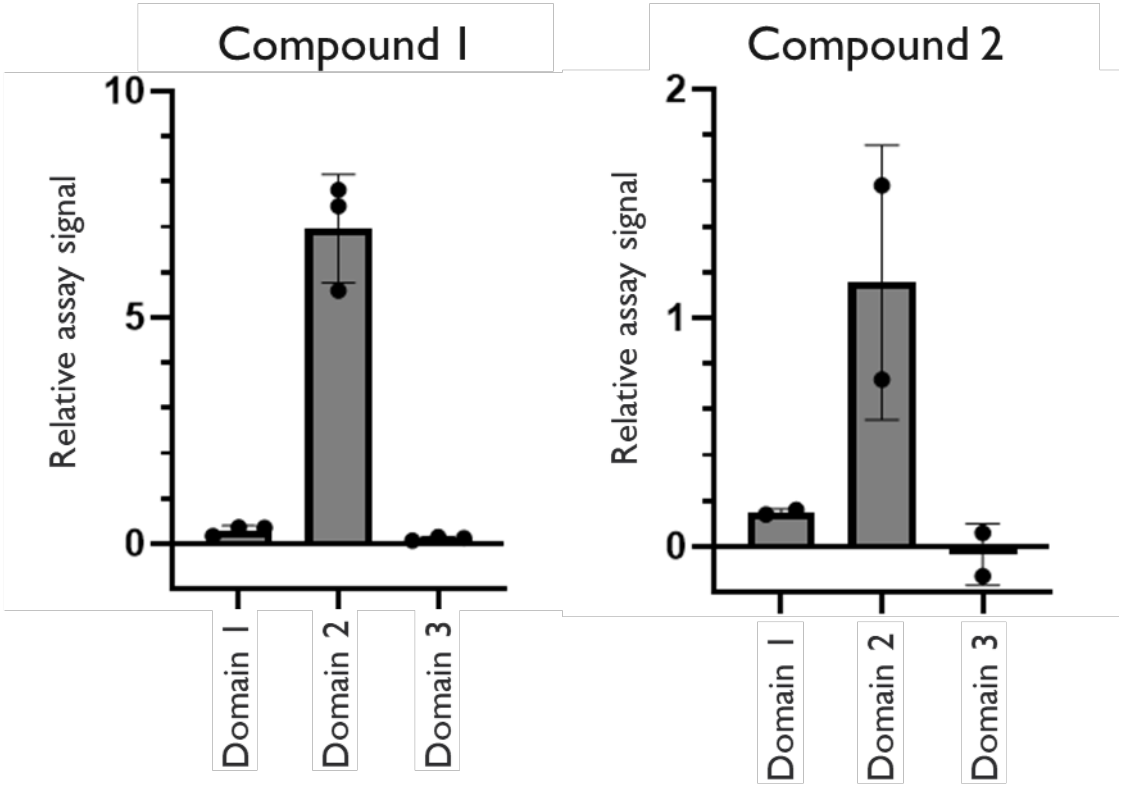
Target B deconvolution of one compound pool

Pool activity is from one compound in this individual well



Target B hits are selective to one of the protein domains

Compounds 1 and 2 leverage one E3 and a single protein domain

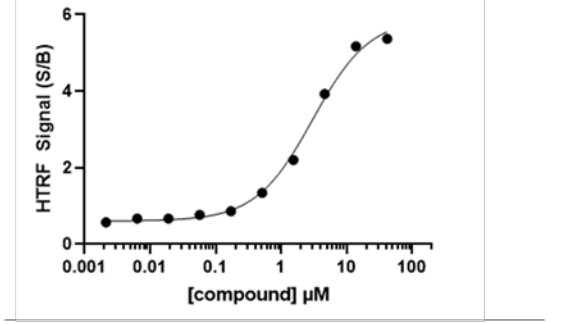


MOPED™ Emerald: Target B hits form ternary complexes

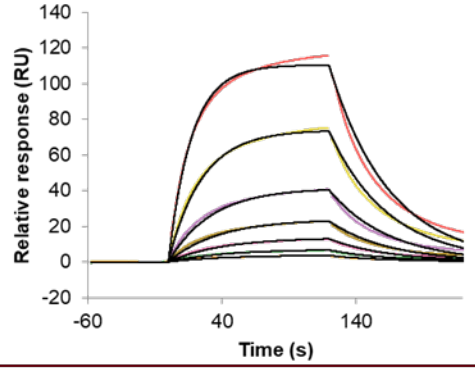
Compound 1 and compound 2 have distinct ternary complex kinetics

Compound 1

HTRF shows 5.1 µM ternary complex EC_{50}

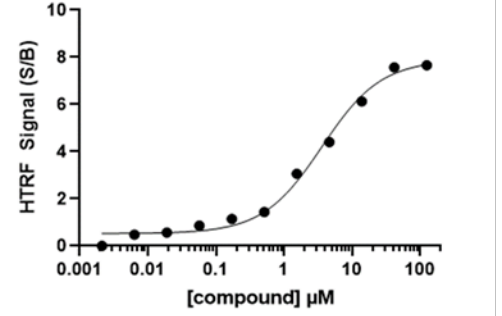


SPR shows 1.3 µM ternary complex K_D

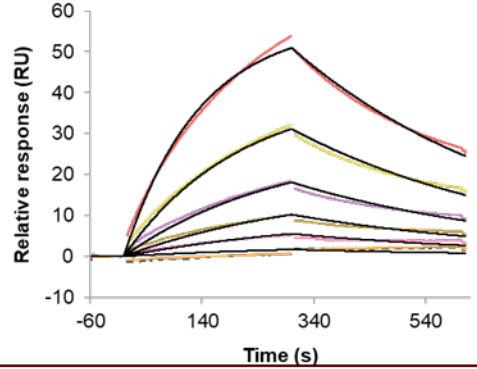


Compound 2

HTRF shows 12.4 µM ternary complex EC_{50}

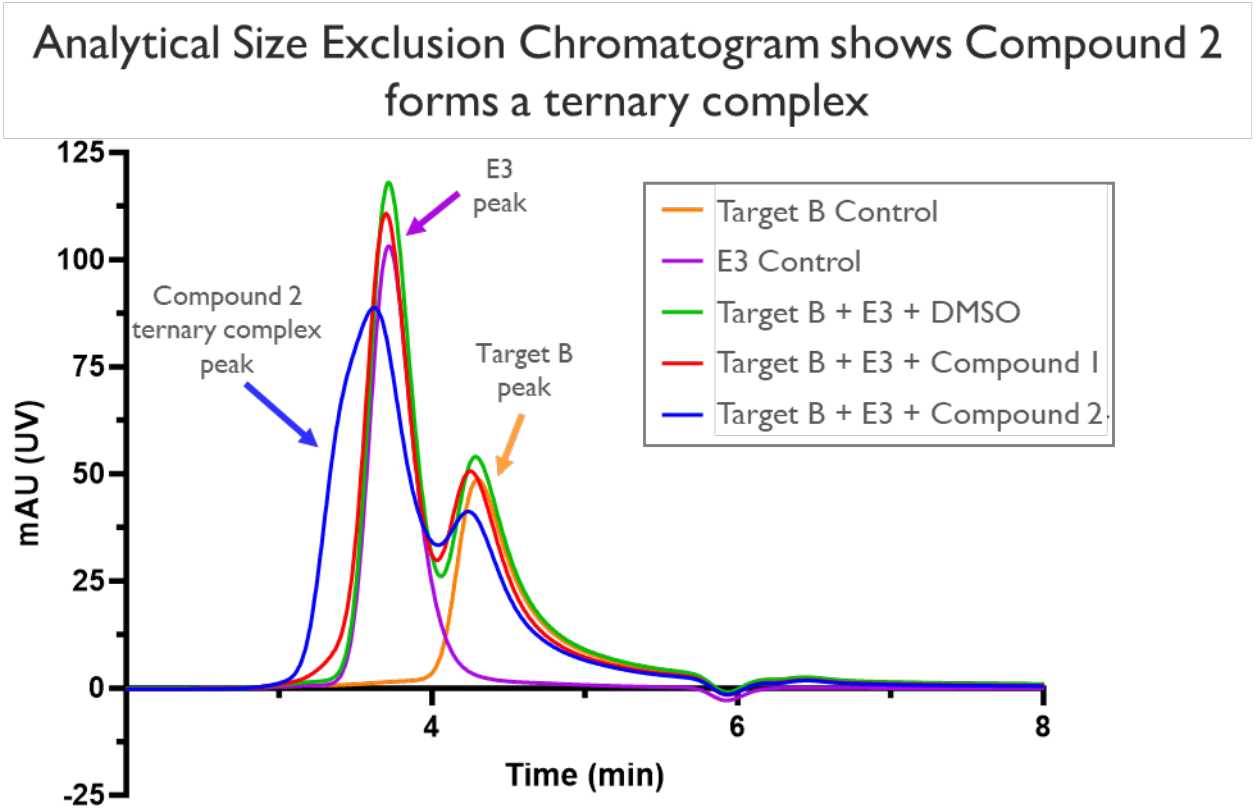


SPR shows 0.9 µM ternary complex K_D



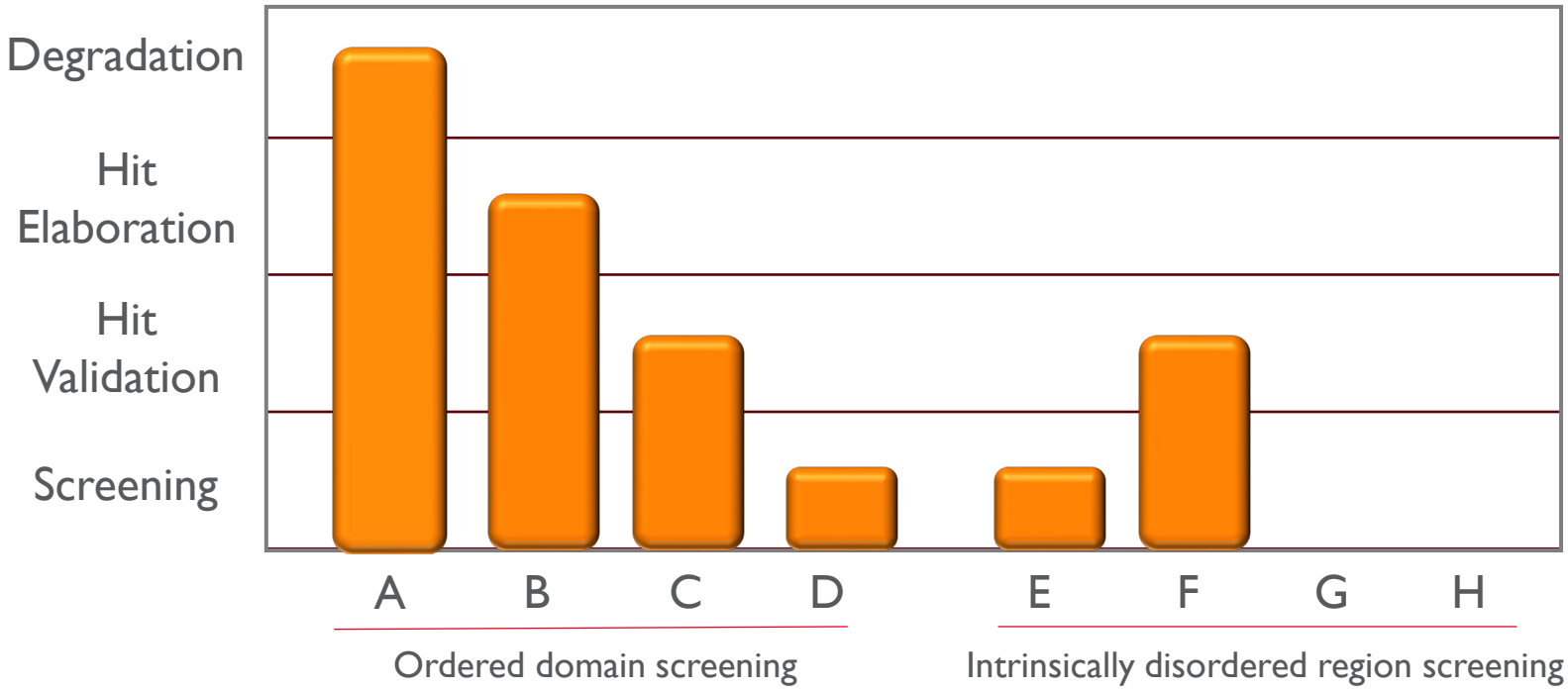
MOPED™ Emerald: Target B hits form ternary complexes

Ternary complex formed in the presence of compound 2 as demonstrated by aSEC



MOPED™ Emerald: 6 unique proteins screened to date

Workflow is fully enabled with hits progressing



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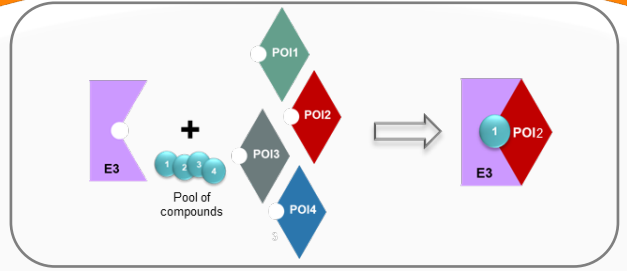

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Contributors

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Thank-you