



Enabling and Accelerating Targeted Protein Degraders and Molecular Glues Drug Discovery through a Global Open Access Platform

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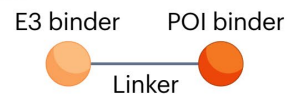


Targeted Protein Degradation via PROTACs and Molecular Glues Degraders

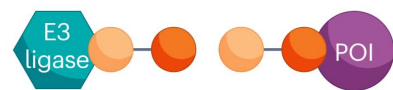
a PROTACs

Compound can bind target and E3 ubiquitin ligase independently to induce ternary complex

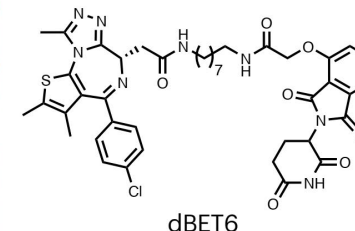
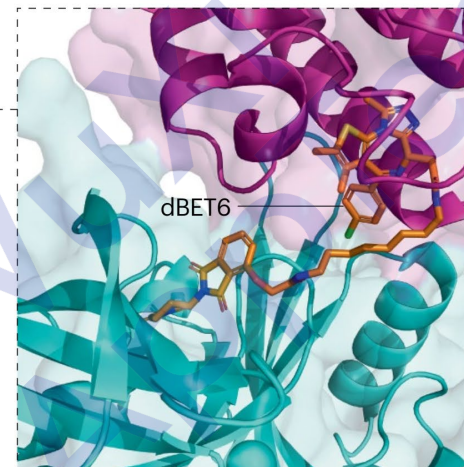
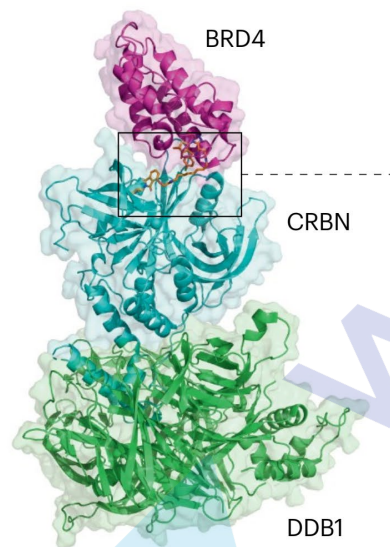
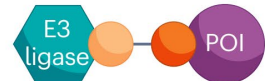
PROTAC



Binary complexes



Ternary complex



b Molecular glue degraders

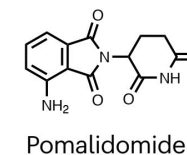
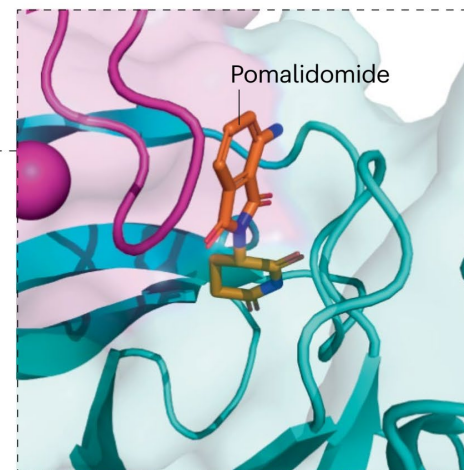
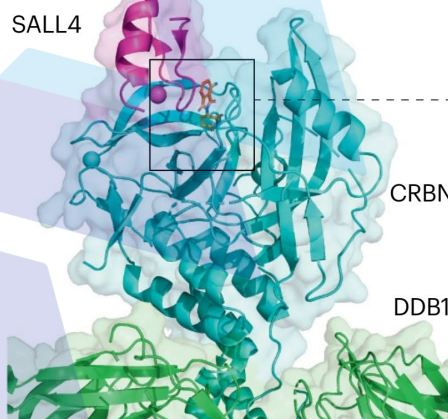
Compound only binds target or E3 ligase. Binary binding generates a neo-surface that recruits the other protein and induces ternary complex formation

Glue E3-POI binder

Binary complex

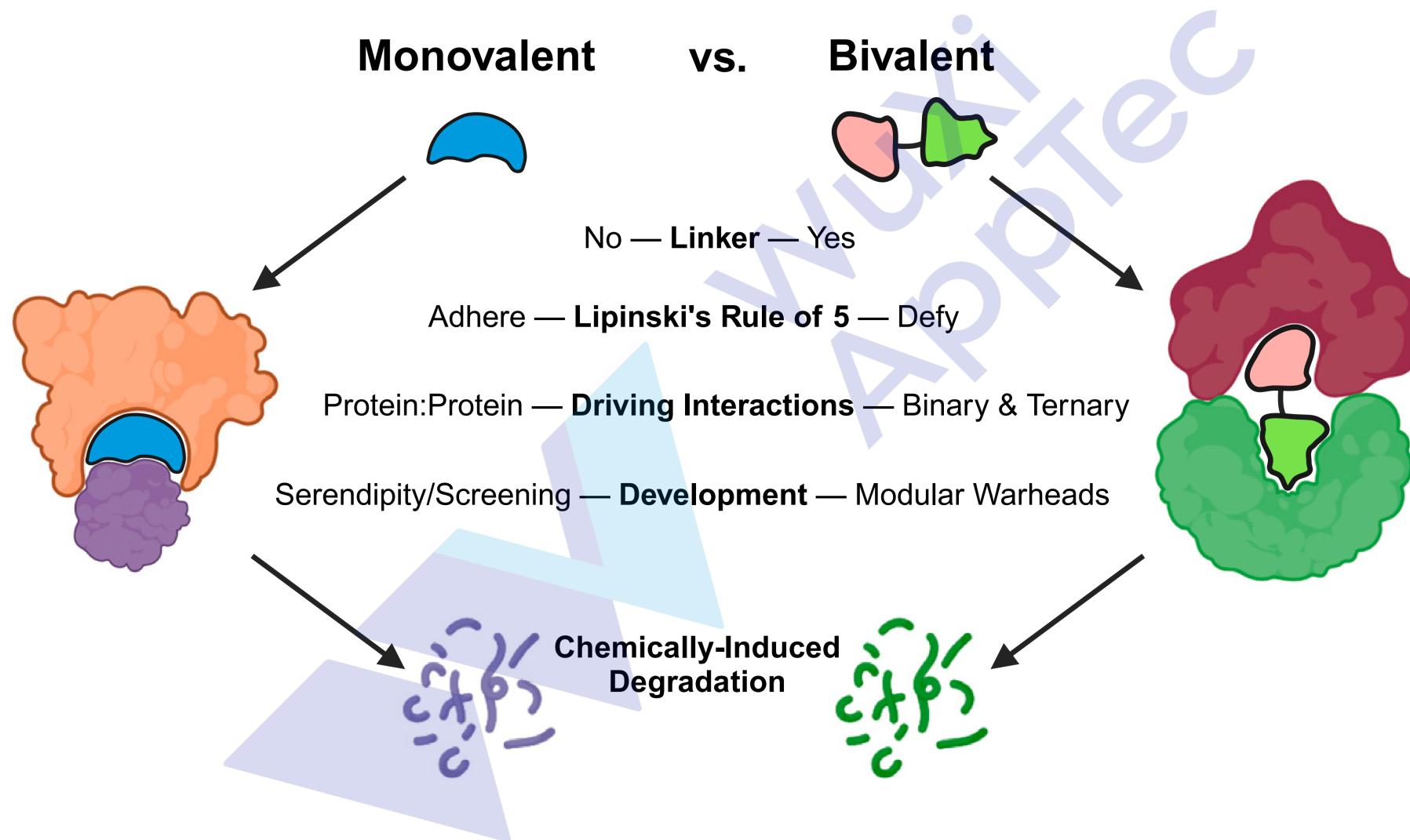


Ternary complex



Source: Targeted protein degradation for cancer therapy, M. Hinterdorfer et al., *Nat. Rev. Cancer*, **2025**, 25, 493-516.

Comparison of Monovalent and Bivalent Degraders Properties



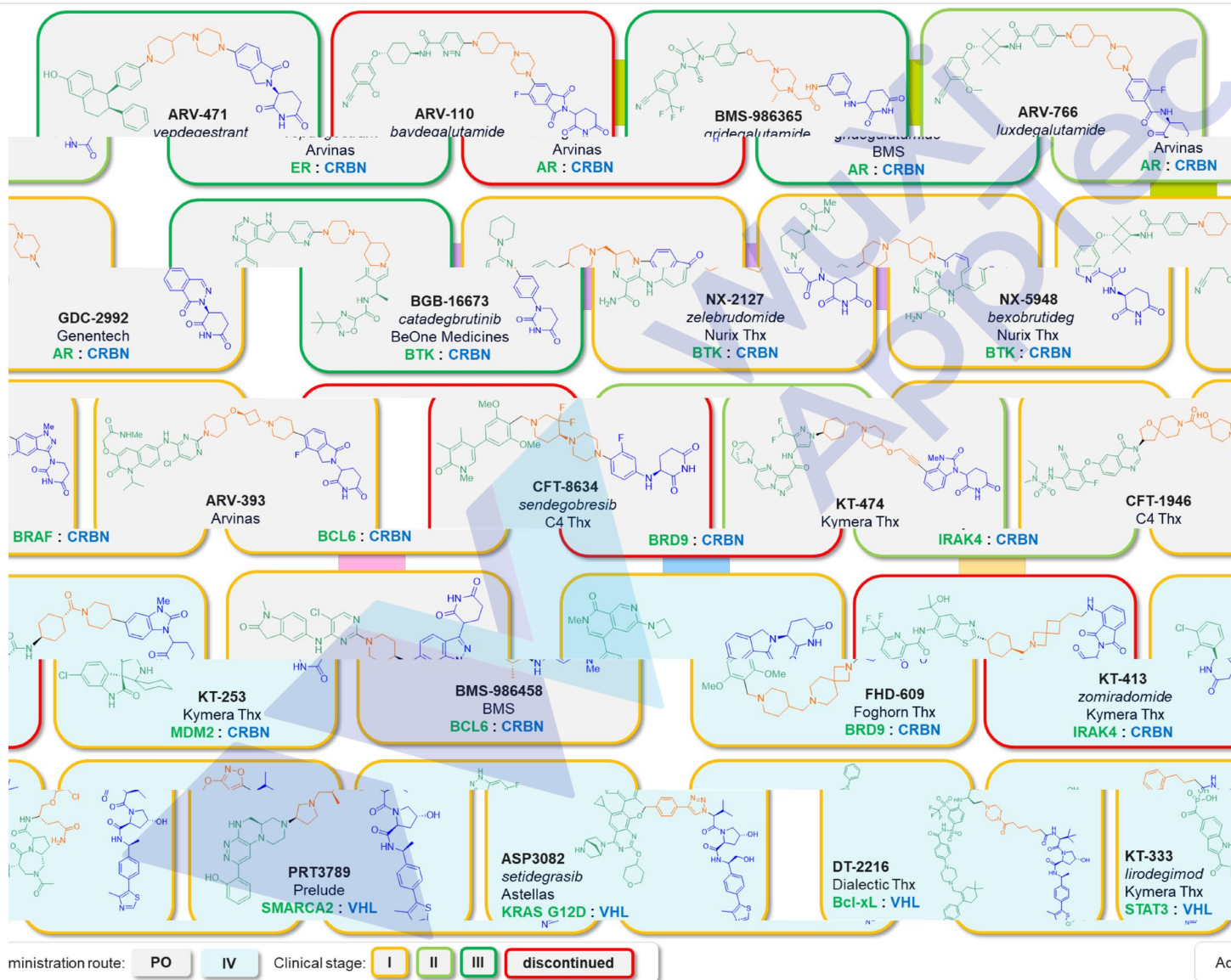
Source: Next steps for targeted protein degradation, M.W. Krone & C.M. Crews, *Cell Chem. Biol.*, **2025**, 32, 219-226.

Molecular Glues in Clinical Development

Degrader	Company	Phase	Target	E3	Indication
Molecular glue degraders					
CC-220	BMS	III	IKZF1/3	CRBN	Multiple myeloma (lymphoma, phase I)
CC-92480	BMS	III	IKZF1/3	CRBN	Multiple myeloma
CC-99282	BMS	II	IKZF1/3	CRBN	Lymphoma
E7820	Eisai	II	RBM39	DCAF15	Myeloid cancers
CC-122	BMS	I	IKZF1/3	CRBN	Lymphoma
CFT-7455	C4	I	IKZF1/3	CRBN	Multiple myeloma and lymphoma
KPG-818	Kangpu	I	IKZF1/3	CRBN	Systemic lupus erythematosus, multiple myeloma and lymphoma
ICP-490	Innocare	I	-	CRBN	Multiple myeloma and diffuse large B cell lymphoma
KPG-121	Kangpu	I	IKZF1/3, CK1a	CRBN	Prostate cancer
BTX-1188	BioTheryX	I	GSPT1,IKZF1/3	CRBN	Haematological and solid malignancies
CC-90009	BMS	I	GSPT1	CRBN	Acute myeloid leukaemia and myelodysplastic syndrome
MRT-2359	Monte Rosa	I / II	GSPT1	CRBN	MYC-driven solid tumours
NVP-DKY709	Novartis	I	IKZF2/4	CRBN	Solid tumours
TQB3820	Sino	I	IKZF1/3	CRBN	Multiple myeloma
Lenalidomide analogue	Starton	I	IKZF1/3	CRBN	Multiple myeloma

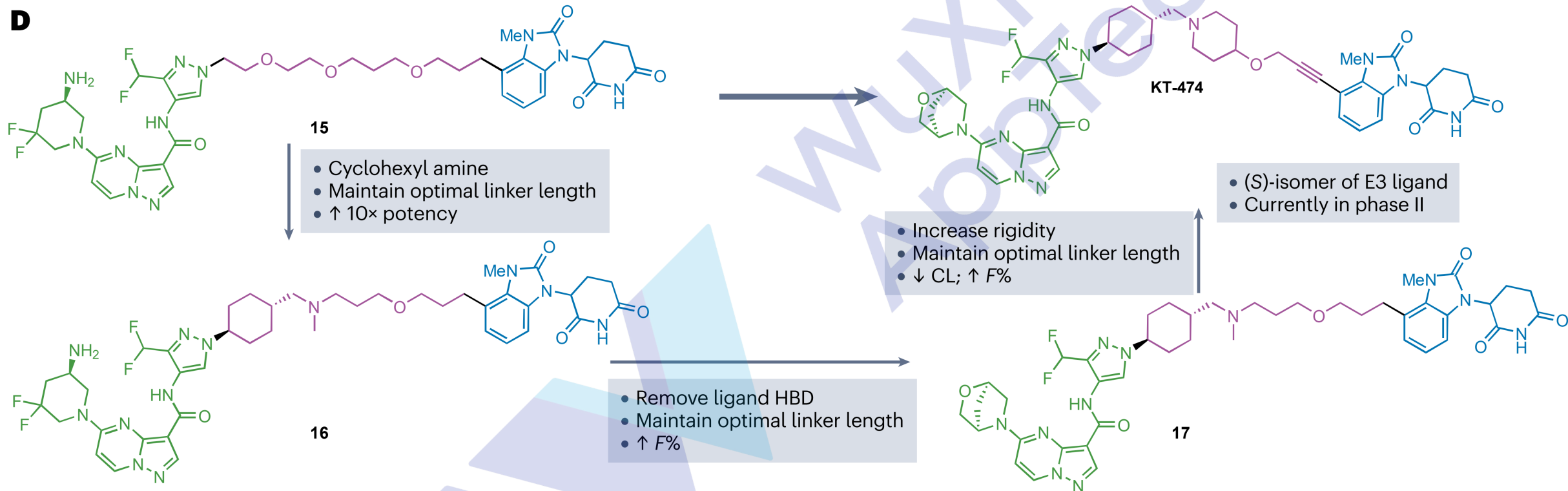
Source: Targeted protein degradation: from mechanisms to clinic, Jonathan M. Tsai, et al., *Nat. Rev. Mol. Cell Biol.*, **2024**, 25, 740-757.

PROTACs in Clinical Development



Source: Lessons learned in linking PROTACs from discovery to the clinic, A. Pike et al., *Nat. Rev. Chem.*, 2026, 10,117-132.

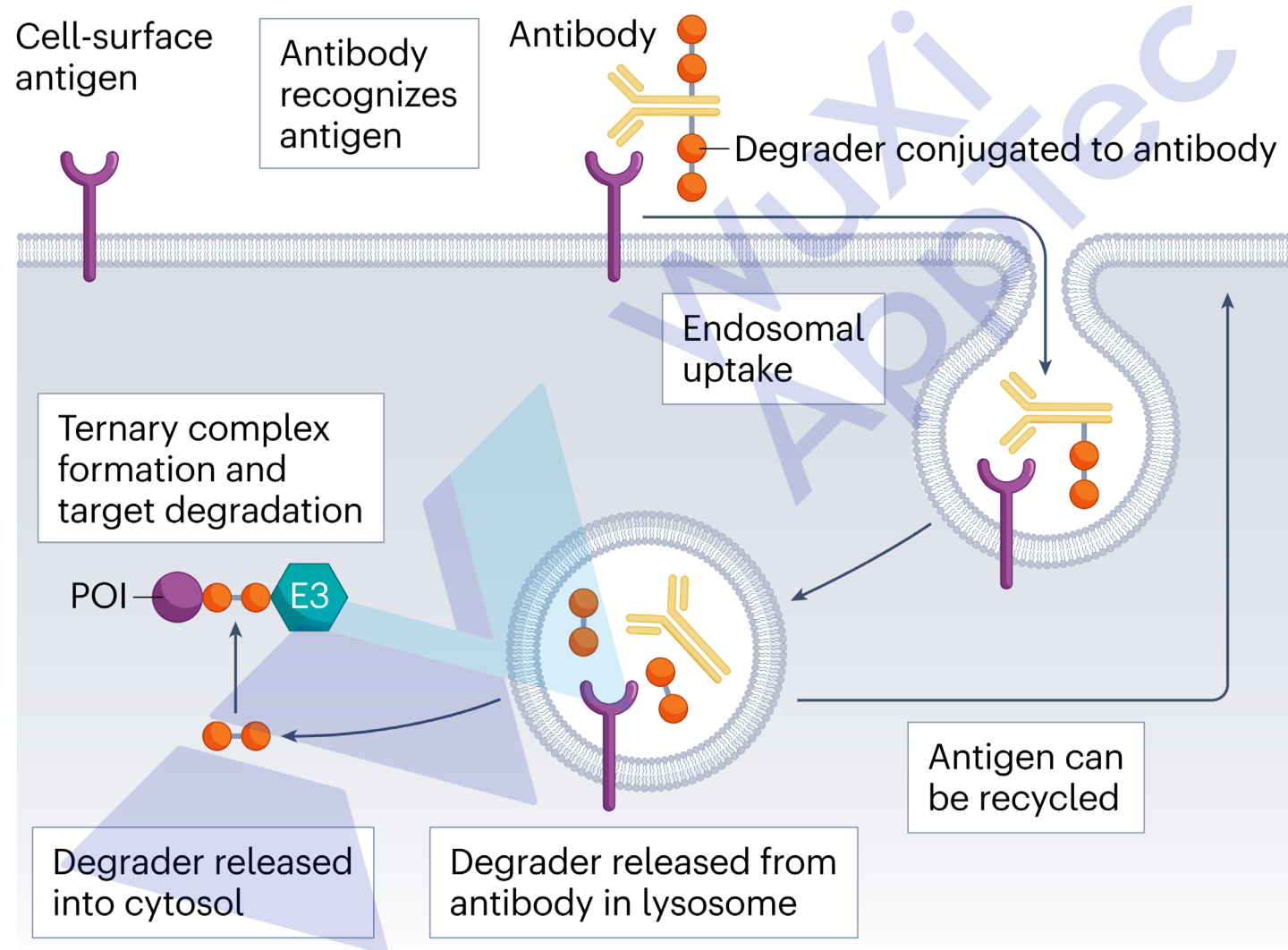
The Design Evolution of A Clinical PROTAC – KT-474



Source:

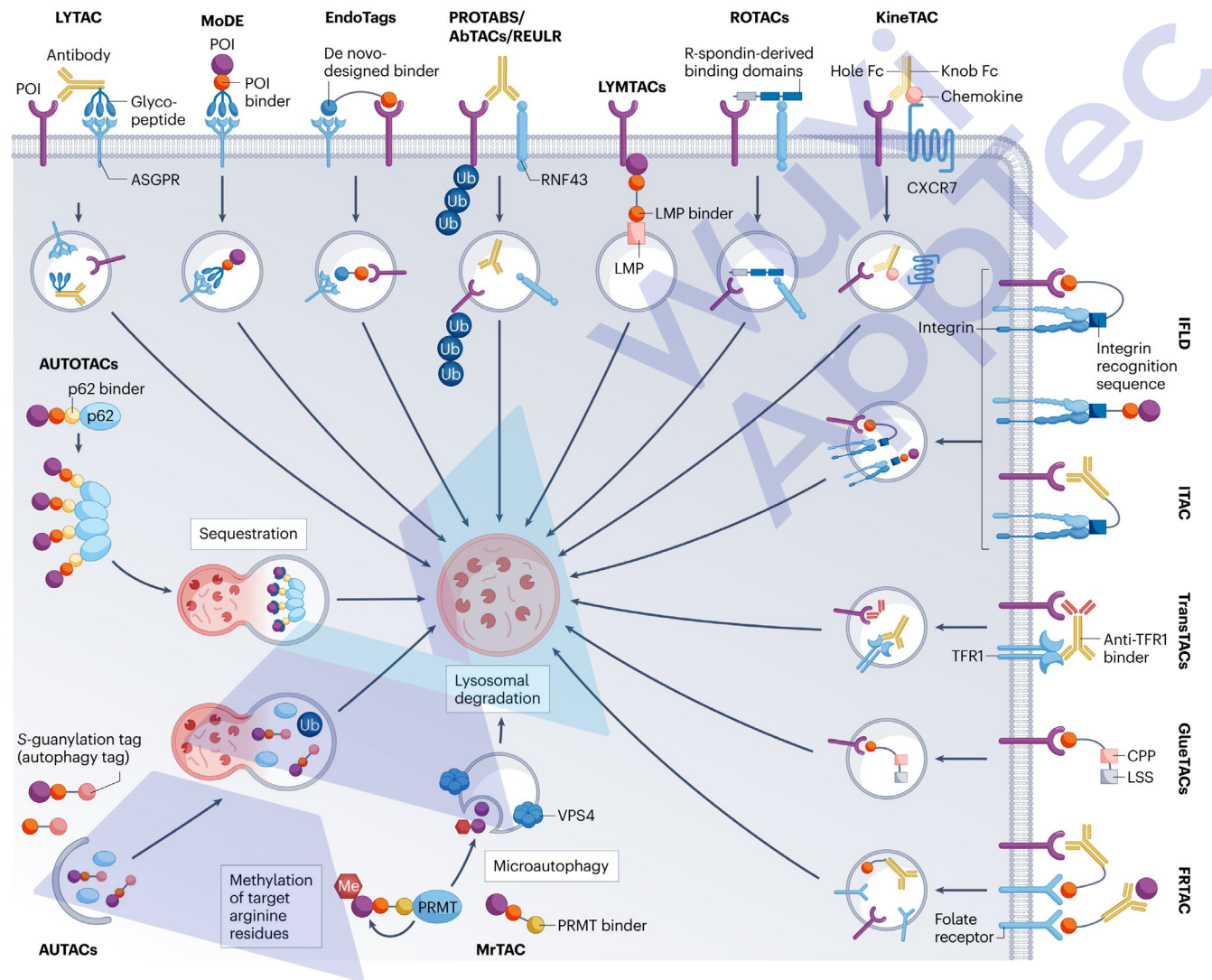
1. Discovery of KT-474 a potent, selective, and orally bioavailable IRAK4 degrader for the treatment of autoimmune disease, X. Zheng et al., *J. Med. Chem.* **2024**, 67, 18022-18037.
2. Lessons learned in linking PROTACs from discovery to the clinic, A. Pike et al., *Nat. Rev. Chem.*, **2026**, 10,117-132.

Degrader-Antibody Conjugates (DACs) – New TPD Approach



Source: Targeted protein degradation for cancer therapy, M. Hinterdorfer et al., *Nat. Rev. Cancer*, **2025**, 25, 493-516.

Non-Ubiquitin-Proteasome System-Based TPD Modalities



Source: Targeted protein degradation for cancer therapy, M. Hinterdorfer et al., *Nat. Rev. Cancer*, **2025**, 25, 493-516.

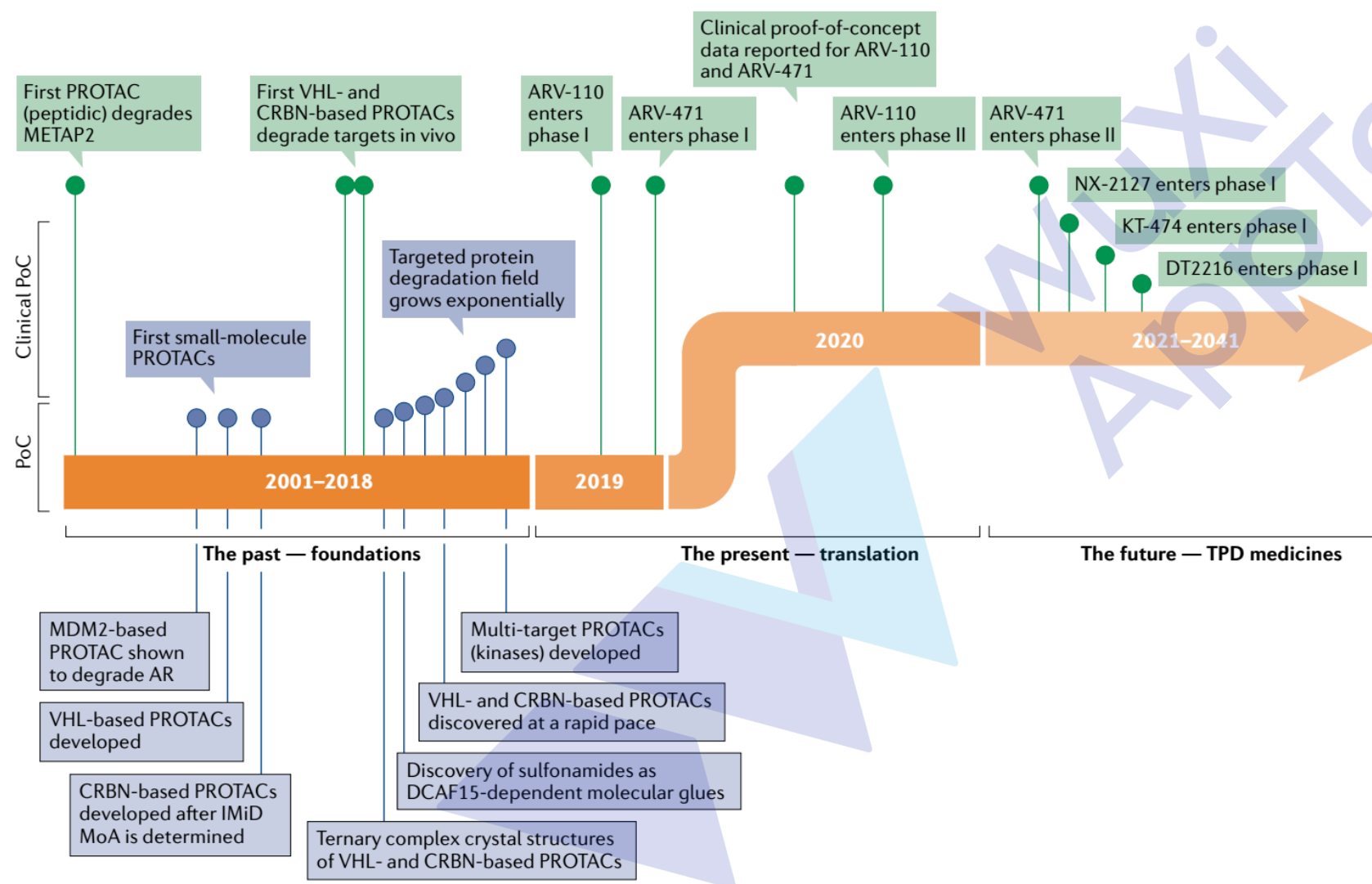
There Are Advantages of TPDs as Therapeutics

Therapeutic modality	PROTACs/ molecular glues	Small-molecule inhibitors	Gene-based strategies	bioPROTAC	oligoTAC	LYTAC	ATTEC	AUTAC	abTAC
Target scaffolding functions	✓		✓	✓	✓	✓	✓	✓	✓
Potential to treat undruggable proteins	✓		✓	✓	✓	✓	✓	✓	✓
Iterative mechanism of action	✓		✓	✓	✓	✓	✓	✓	
Broad tissue penetration	✓					✓	✓	✓	
Orally bioavailable	✓	✓							
Ease of manufacturing	✓	✓		✓	✓	✓	✓	✓	
Preclinical validation, proof-of-concept established	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical validation	✓ (Phase II for PROTACs)	✓	✓						

- Catalytic-based event-driven depletion of targeted protein.
- Recycling and catalytic mechanism enables sub-stoichiometric degradation and prolonged duration.
- Protein binding instead of active site occupancy - chemistry diversity and solutions to undruggable targets.
- Ternary-complex-formation grants extra selectivity and cooperativity optimization.

Source: PROTAC targeted protein degraders: the past is prologue, Miklós Békés, et al., *Nat. Rev. Drug Disc.*, **2022**, 21, 181–200.

Some Key Milestones Await TPDs



- Successful clinical trials & regulatory approval, including non-druggable targets.
- Demonstrating target classes best served by degradation over inhibition.
- Expanding E3 ubiquitin ligases employed - tissue specificity.
- Extending beyond oncology therapeutics.
- Clinical validating new TPD modalities e.g. LYTACS, AUTACs.

Source: PROTAC targeted protein degraders: the past is prologue, Miklós Békés, et al., *Nat. Rev. Drug Disc.*, **2022**, 21, 181–200.

There Are Challenges in TPD Discovery

Hard to design



- Compound design remains largely empirical as target binding affinity does not predict activity.
- Many compounds need to be synthesized and tested to find functionally active degraders.

Hard to make



- Synthesis is lengthy requiring the right sequential assembly of the target protein binder, linker, and E3 binder.
- Purification requires special solvent and column conditions by trial and error - compounds have poor solubility and prone to epimerization.

Hard to optimize



- Compounds are typically “beyond the rule of 5” with low solubility.
- Many compounds need to be synthesized and tested in animal studies to find orally bioavailable degraders.

We Have a TPD Discovery Platform

Chemistry

- **>1,100** discovery chemists, with strong experiences in the linkers, E3 ligase ligands and target protein ligands synthesis since 2016.
- **>180** clients/collaborations.
- **2,800+** linkers are available.
- **200+** ligands are available.
- **>200** methods of Prep-HPLC and chiral-SFC analysis and purification.
- **>238,000** Targeted Protein Degraders successfully delivered.
- Delivered **>80** PCCs.

TPD Discovery Platform

Biology

Biochemical/Biophysical Assays:

- POI-PROTAC or E3-PROTAC binary binding assay (TR-FRET, FP, SPR, MST/TRIC).
- POI-PROTAC-E3 ternary complex formation assay (TR-FRET, AlphaScreen, SPR, MST/TRIC).
- POI ubiquitination assay (TR-FRET, AlphaScreen).

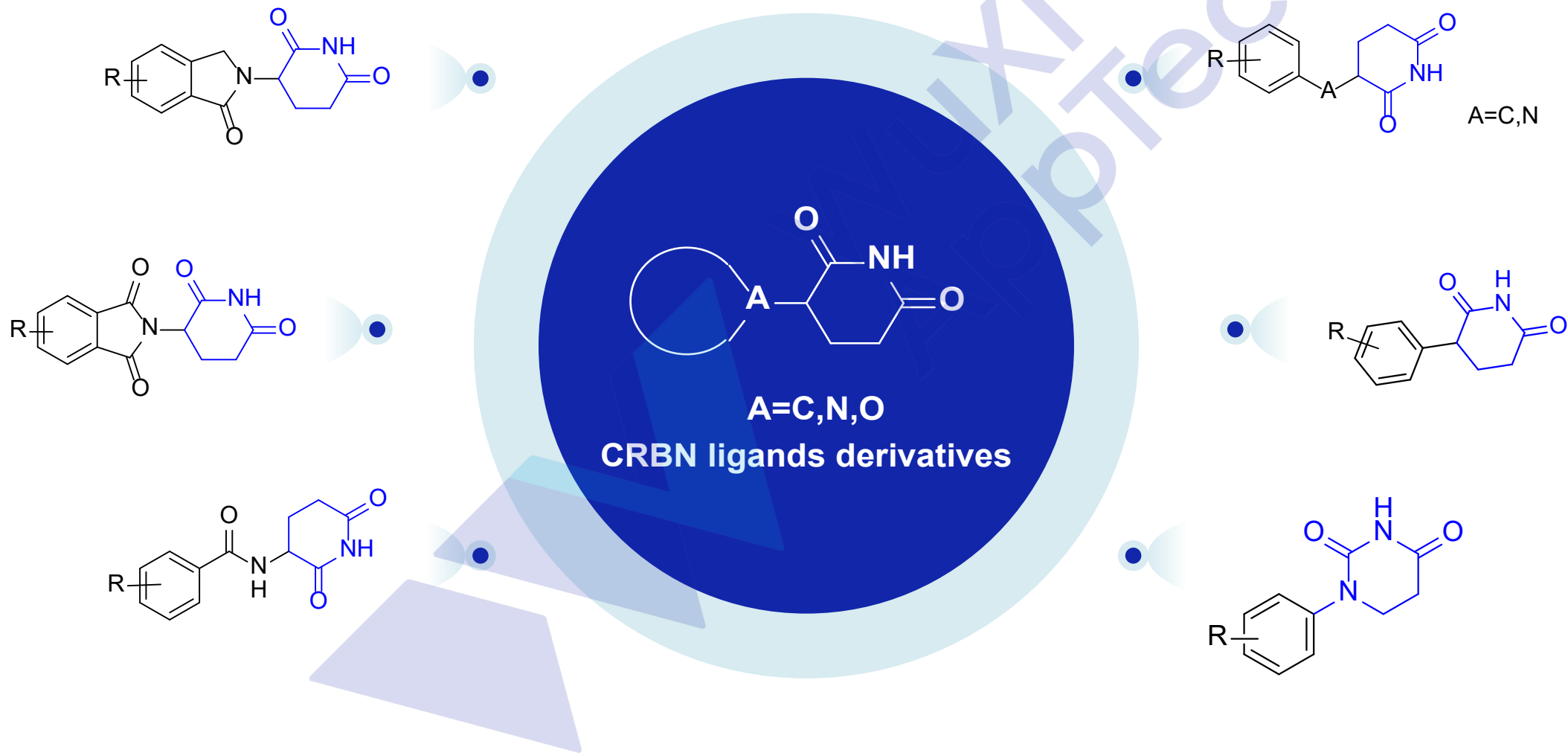
Cellular Assays:

- POI or E3 engagement assay (NanoBRET).
- POI-PROTAC-E3 ternary complex formation assay (NanoBiT, NanoBRET).
- POI ubiquitination assay (IP-WB, PROTAC Assay Plate, NanoBRET).
- POI degradation assay (HiBiT, In-cell Western, ELISA, AlphaLISA, TR-FRET).

In Vivo Pharmacology:

- PK/PD studies and ADME/Tox studies.

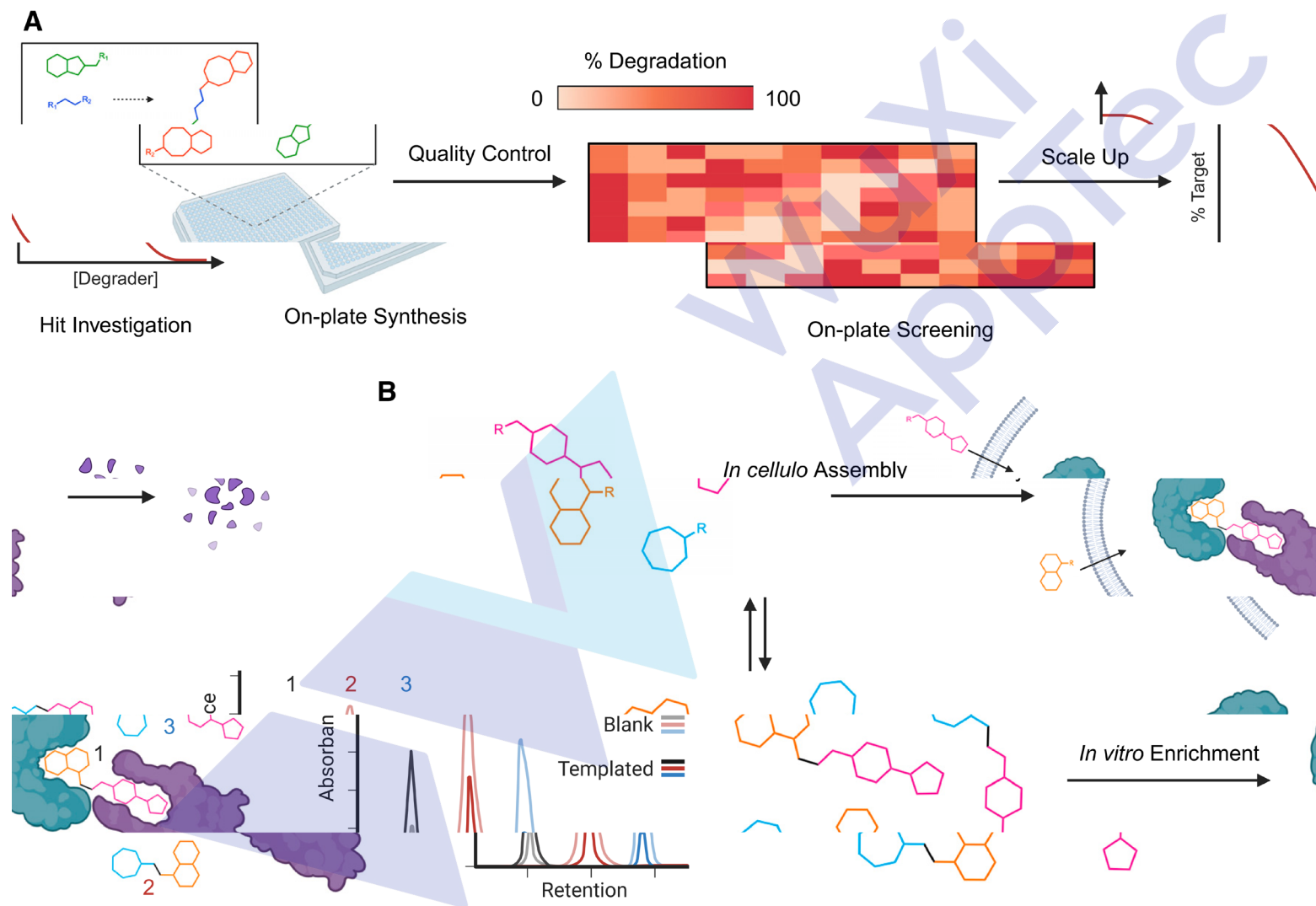
E3 Ligase Ligands for TPD Synthesis



TPD Purification Challenges and Our Solutions

Challenges		Solutions	
Poor Solubility	• Limited throughput for HPLC purification • Easily over pressured prep-HPLC system • Low purification recovery	Method Development	• Over 200 different conditions screened with various columns and modifiers • Diversified techniques: RP-HPLC; NP-HPLC; SFC
Poor Stability	• Limitations to use common HPLC modifiers • Broad peak shape and low resolution • In time purification and work-up	Instrument Modification	• Innovative on-line dilution system was designed by WuXi purification team specifically for PROTACs • Two columns with different particle size to reduce solvent effect
High Polarity	• Poor retention on commonly used RP-HPLC • Highly polar solvents needed for SFC • Multi-steps purification needed	Proven Experiences	• Purified over 120,000 PROTACs with over 95% first time success rate • Established general guideline for separation condition based on structure functionalities

Direct-to-Biology Approaches for Higher Throughput Degradable Synthesis

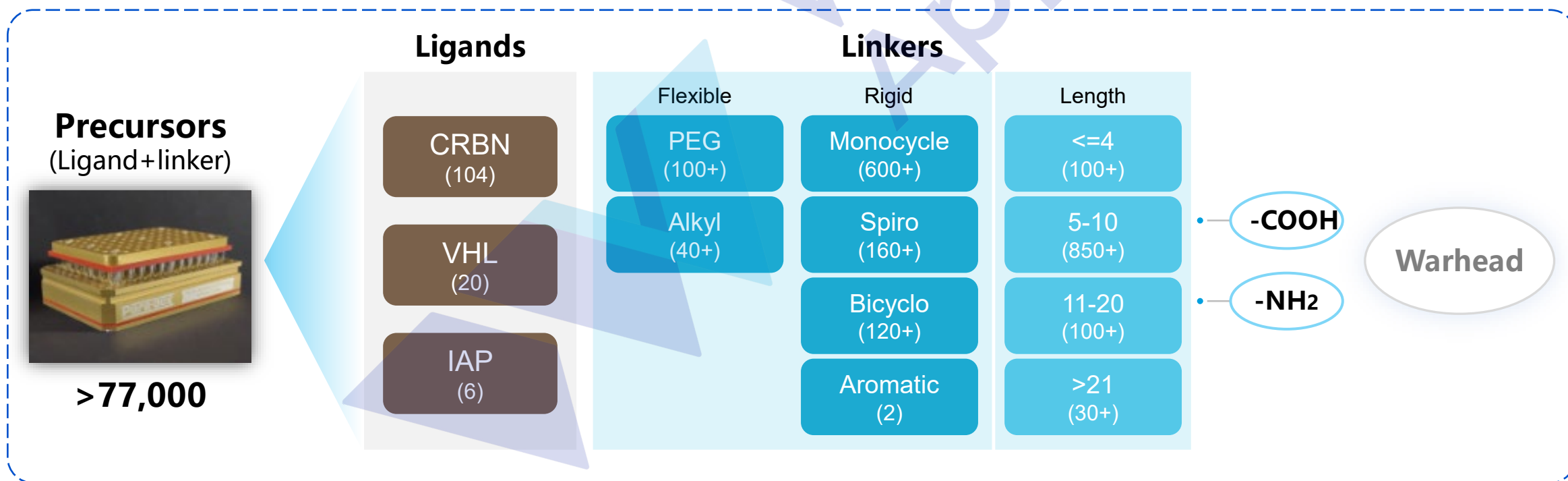


Source: Next steps for targeted protein degradation, M.W. Krone & C.M. Crews, *Cell Chem. Biol.*, **2025**, 32, 219-226.

Our Building Blocks for Direct to Biology

Over 69,000 Precursors Can Be Rapidly Assembled within 2 Weeks

- > 200 ligands are in stock, which include popular CRBN, novel CRBN, VHL and IAP
- > 2,800 linkers are in stock, which cover flexible, rigid linker molecule
- Diversified length linkers are listed to support the molecule design



Our Chemistry Tools for Direct to Biology

Types of Reactions that Can Be Developed for the Direct to Biology Approach

Reductive Amination	Thiol-involved Michael Addition	Photochemistry
$\text{Ar}-\text{CHO} + \text{H}_2\text{N}-\text{R} \xrightarrow{[\text{R}]} \text{Ar}-\text{CH}_2-\text{NH}-\text{R}$	$\text{R}^1-\text{C}(=\text{O})-\text{CH}=\text{CH}_2 + \text{HS}-\text{R}^2 \longrightarrow \text{R}^1-\text{C}(=\text{O})-\text{CH}_2-\text{S}-\text{R}^2$	$\text{R}^1-\text{C}_6\text{H}_3(\text{NO}_2)\text{CH}_2\text{OH} + \text{H}_2\text{N}-\text{R}^3 \xrightarrow{h\nu} \text{R}^1-\text{C}_6\text{H}_3(\text{NO}_2)\text{CH}_2-\text{NH}-\text{C}(=\text{O})-\text{NH}-\text{R}^3$
Hydrozone Formation	Multicomponent Reaction	SNAr and SN2 Substitution
$\text{Ar}-\text{CHO} + \text{H}_2\text{N}-\text{NH}-\text{C}(=\text{O})-\text{R} \longrightarrow \text{Ar}-\text{CH}=\text{N}-\text{NH}-\text{C}(=\text{O})-\text{R}$	$\text{R}^1-\text{CHO} + \text{R}^2-\text{COOH} + \text{R}^3-\text{NC} \longrightarrow \text{R}^2-\text{O}-\text{C}(=\text{O})-\text{CH}(\text{R}^1)-\text{C}(=\text{O})-\text{NH}-\text{R}^3$	$\text{R}^1-\text{NH}-\text{C}(=\text{O})-\text{CH}_2\text{Cl} + \text{H}_2\text{N}-\text{R}^2 \longrightarrow \text{R}^1-\text{NH}-\text{C}(=\text{O})-\text{CH}_2-\text{NH}-\text{R}^2$
Cyclization Involving Cysteine	Sulfur(VI) Fluoride Condensation	Click Reaction
$\text{Ar}-\text{CN} + \text{HS}-\text{CH}_2-\text{CH}(\text{NH}_2)-\text{C}(=\text{O})-\text{NH}-\text{R} \longrightarrow \text{Ar}-\text{C}(=\text{S})-\text{N}(\text{CH}_2\text{S})-\text{C}(=\text{O})-\text{NH}-\text{R}$	$\text{R}^1-\text{C}_6\text{H}_4-\text{SO}_2\text{F} + \text{H}_2\text{N}-\text{R}^2 \text{ or } \text{OH} \longrightarrow \text{R}^1-\text{C}_6\text{H}_4-\text{SO}_2-\text{NH}-\text{R}^2 \text{ or } \text{O}$	$\text{R}^1-\text{C}_8\text{H}_{15} + \text{N}_3-\text{R}^2 \longrightarrow \text{R}^1-\text{C}_8\text{H}_{15}-\text{N}_3-\text{R}^2$

