CeTPD Journal Club

April – May 2026

Targeted protein degradation, medicinal chemistry, chemical structural biology & cell biology

Centre for Targeted Protein Degradation
University of Dundee

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MEET THIS MONTH'S EDITORS

Click here for info on the editor

SUZANNE O'CONNOR

Suzanne received her undergraduate degree in Medicinal Chemistry from Trinity College Dublin, Ireland and her MRes in Drug Discovery & Development from Imperial College London, where her research focused on the development of antibody drug conjugates. She then joined AstraZeneca working on a variety of oncology drug discovery projects. She moved to the Institute of Cancer Research for her PhD in Fragment Based Drug Discovery with Professor Ian Collins and then joined Evotec as a senior scientist developing molecules for the treatment of chronic pain. Suzanne joined the Ciulli group in 2021 where she led multidisciplinary teams for PROTAC drug discovery projects in oncology, in collaboration with Boehringer Ingelheim and since July 2024 is a Team Leader for our KOODAC team, specialising in paediatric cancers.

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LIAM MARTIN

Liam completed his BSc in Biomolecular Science at the University of St Andrews in 2015, before moving to University College London for an MRes in Drug Discovery. He remained at UCL for his PhD studies with Profs Helen Hailes and Sanjib Bhakta, focusing on the development of novel antitubercular agents. He entered the TPD field as a postdoc in the group of Dr David France at the University of Glasgow and then moved to Dundee in 2022 to take up a medicinal chemistry position in the AC-BI team. As of June 2024, Liam is medicinal chemist in the KOODAC team, developing protein degraders to address challenging paediatric cancers.

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HANNAH PETERS

Hannah completed her MSci Chemistry with Medicinal Chemistry degree at Imperial College London and conducted her MSci project under the supervision of Professor Ed Tate, where she developed high-throughput proteomics platforms for molecular glue discovery. From June-Sept 2024, Hannah completed a 10-week internship in the Ciulli Group working on the structural and biophysical validation of dual-ligase recruiting SMARCA2/4 molecular glue degraders. She returned to re-join the group in September 2025.

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ROBERTA IBBA

She graduated in Pharmaceutical Chemistry and Technology at the University of Sassari and obtained her PhD from the University of Cagliari, including a nine-month research visit at the University of Oxford. Following postdoctoral positions at the Universities of Siena and Sassari, she joined the CeTPD as a Visiting Postdoctoral Fellow in 2023 and was appointed Postdoctoral Scientist in February 2024. Since June 2024, she has been part of the KOODAC team and was awarded an individual fellowship from the Italian Association for Cancer Research (AIRC), enabling her to lead an independent research programme focused on developing novel approaches to target oncogenic drivers in paediatric cancers.

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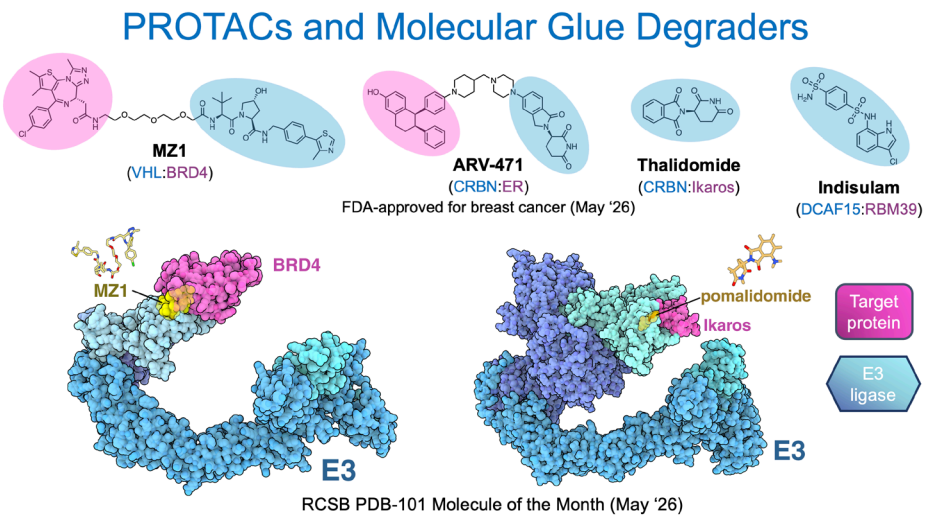
FEATURE OF THE MONTH

| *Alessio*

What the first PROTAC approval means for the TPD field

On the 1st May 2026, the FDA approved ARV-471 (vepdegestrant) for a subset of patients with advanced or metastatic breast cancer — making it the first-ever PROTAC drug to reach patients for labelled use. On the very same day, the RCSB Protein Data Bank chose PROTACs and Molecular Glue Degraders as their Molecules of the Month for May 2026 (see image). Perhaps a coincidence? As I shared with the community on LinkedIn then, it's a major milestone and a feel-good moment for the field. It warrants time to celebrate, and also time for some reflections.



So, what does the approval mean today and what can we expect next?

First, there is no doubt that this is one of many key moments and achievements that have been witnessed in the "PROTAC journey" over the past 15 years. It warranted immediate updates to a few of my lecture slides! It is reminiscent of the FDA approval of Imatinib (Gleevec) as the first kinase inhibitor, after decades of scepticism and naysaying towards targeting protein kinases with small molecules. That was 10th May, 2001; exactly 25 years later. Since then, the field of kinase inhibitors has seen approvals reaching 100 just in November last year (Nature Reviews). If the PROTAC field was to even mirror such an impressive volley of medicines approvals in the same period of time, that will be a true metric of impact and success.

While this is indeed an important milestone, there are caveats to this specific case. In a randomised Phase III trial head-to-head with standard of care fulvestrant, vepdegestrant showed efficacy in a limited subset of patients with advanced or metastatic breast cancer (bearing ESR1 mutations) - but not in patients without the mutations. The bad news is the restriction will limit the impact of the drug in the broader breast cancer patient population, suggesting that the compound will be unlikely to dramatically move the needle in that space. The good news is that this limitation seems to be more to do with the actual context of the trial and biology, than it has to do with the PROTAC modality itself. The tests were done in heavily pre-treated patients, which included prior use of approved selective-estrogen receptor degraders (SERDs). Potentially, it highlights

the need to re-consider ER target vulnerability to degradation as a therapeutic concept in breast cancer. In reflection, ER (and AR) seemed obvious targets and were certainly favourite ones amongst many investors and pharmaceutical companies in the early days of PROTACs. While there were conflicting views, I vividly recall strong opinions that the field should prioritise ER and AR because they were perceived as "most highly validated" drug targets. What was perceived to be "de-risked, sound" biology was felt needed to de-risk an unproven drug modality. But biology is complex, indeed, and it rules.

Looking forward, with >40 PROTAC drugs in clinical trials (see our review here), against a plethora of protein targets, an expanding range of diseases and therapeutic concepts also beyond oncology, two E3 ligases (CRBN and VHL) now well established as recruiters (and more coming, such DCAF16 with Amphista's AMX-883), the pipeline looks healthy and the landscape conducive to many more approvals to follow.

So, it certainly is a fantastic moment. "Large" molecules that many thought it impossible to make into medicines that would ever work in patients have proven that feat to be achievable. It has taken over a decade, but thanks to the crucial improvements of E3 binders smaller, more drug-like ligands, and some sweet-spot of linkerology, PROTACs now do behave like small molecules. PROTACs and the more compact molecular glues keep degrading potently, rapidly and highly selectively, essentially any proteins that they can redirect and stick to ubiquitin E3 ligases. The sky seems to be the limit, and visionaries and believers will feel vindicated. Many naysayers (though they may not admit now) will finally become converted. Many more people will follow suit and jump on the bandwagon. What reassured me about our field is that the science is sound, it works, and, as an open, vibrant and colleagiate community, we keep learning and improving, and rapidly implement new technologies to accelerate and optimise how we arrive at such molecules at the end of the journey. That ensures we stay humble and on the right track. Furthermore, the broad applicability of protein degraders across multiple therapeutic areas, indications and targets, and the ease of delivery of small molecules, together compound to usher even greater future impact. It could not be a more exciting time to start degrading!

TARGETED PROTEIN DEGRADATION

CHEMISTRY | STRUCTURAL BIOLOGY & BIOPHYSICS | CELL BIOLOGY | MODELLING

"Every two months, we spotlight the latest and most significant literature in the field of targeted protein degradation, spanning chemistry, biophysics, cell biology, and computational modeling"

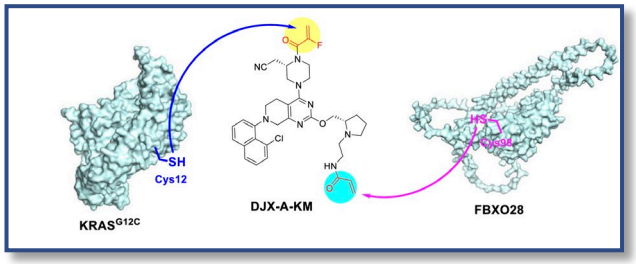
Literature review from 21st March to 20th May 2026

| *Roberta*

Small-molecule degraders for oncogenic KRAS^{G12C} and pan-KRAS mutations

Jianxiong Deng,§ Shujun Shen,§ Lei Huang,§ Fang Xu§, Weizhen Huang,§ …, Tongzheng Liu,* Yi Tan* & Zhengqiu Li*

Nat. Commun. **2026**, 17, 4425



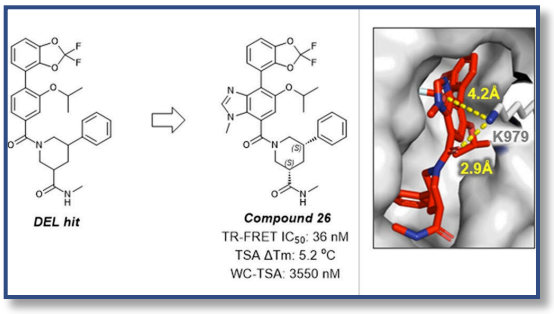
To overcome the molecular weight and permeability limitations of conventional KRAS^{G12C} PROTACs, the authors append an acrylamide warhead via a short ethylamine linker onto the prolinol moiety of MRTX849, adding only ~10% molecular weight. The resulting DJX-A-KM achieves near-complete KRAS^{G12C} degradation (DC_{50} = 2 nM, D_{max} = 98%) with ~66% degradation within 2 hours and sustained suppression for up to 60 hours post-washout. Co-immunoprecipitation mass spectrometry and cysteine-directed ABPP converge on FBXO28 as the covalently recruited E3 ligase, with Cys98 confirmed as the critical modification site. The strategy extends to pan-KRAS degradation through DS-01, which incorporates the same acrylamide–prolinol motif into a broad-spectrum KRAS ligand and achieves potent degradation across six common KRAS mutants. Both compounds demonstrate significant tumour growth inhibition in xenograft models.

This paper presents an elegant minimalist degrader design that circumvents classical PROTAC liabilities through dual covalent engagement. The identification of FBXO28 as a recruitable E3 significantly expands the available E3 toolkit. Key questions remain around sub-stoichiometric activity and potential off-target covalent labelling from the acrylamide–prolinol scaffold. Nonetheless, the generalisation to pan-KRAS degradation and the conceptual blueprint of exploiting endogenous target–E3 proximity to minimise molecular weight are broadly applicable advances.

| *Liam*

DNA-Encoded Library (DEL) Selection Identifies a Distinct DDB1 Binding Site

Shiva Krishna,§ Reddy Guduru,§ John P. Caldwell,§ Katherine M. Digianantonio,§ Sarah M. Prophet,§ Song Yang§...Miklós Békés*
ACS Med. Chem. Lett. **2026**, *17, 4, 757–767*



A team from Arvinas reports the identification of a potent ligand for DNA damage-binding protein 1 (DDB1). DDB1 is well known to the TPD field as an adaptor protein which recruits DDB1-CUL4-associated factors (DCAFs) to the CUL4 E3 scaffold. Previous reports of DDB1 recruiting PROTACs and molecular glues have generated interest in recruiting target proteins directly to DDB1 for degradation, rather than via a DCAF substrate receptor.

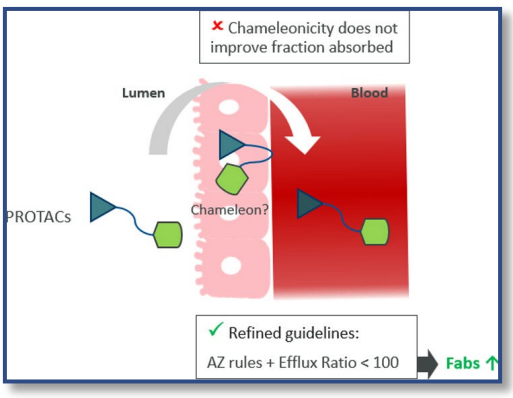
To identify a ligand suitable for degrader development, the authors screened a 1.2 billion molecule DNA-encoded library against DDB1 and identified a singleton hit. They then used computer-aided drug design to optimise this hit into a potent DDB1 ligand. The authors note that this ligand binds at a site on DDB1 which has so far not been liganded and, intriguingly, that ligand binding appears to induce a conformational change in DDB1 which would preclude the binding of DCAFs.

This is a neat bit of early-stage hit optimisation. While the authors do not present any degrader molecules developed using their DDB1 ligand, hopefully, this will be followed up soon, either by Arvinas themselves or another research team. The suggestion that this ligand may serve as an allosteric inhibitor of DCAF-DDB1 PPIs is of general interest to the field and it may find use as a tool compound to probe DDB1-mediated biology. This compound may also be used to validate DCAF-dependent degradation, in a way that is analogous to the use of proteasome or neddylation inhibitors to demonstrate proteasomal and ubiquitin-dependent degradation, respectively.

| *Suzanne*

Evaluation of Oral PROTAC Guidelines: Efflux ratio outweighs chameleonicity descriptors

Claire Le Manach,§* Jenny Viklund,§* Karolina Kwapien, Susanne Winiwarter
ACS Med. Chem. Lett. **2026**, *17, 4, 890–899*



The need for developing orally bioavailable PROTACs has become essential with the increasing interest in this modality for the treatment of chronic diseases. This paper looks to expand our knowledge by searching for an additional descriptor - chameleonicity - to identify likely oral candidates. However, despite analysis of experimental chameleonicity parameters Chamelogk and ePSA:TPSA ratio, unexpectedly, no correlation was observed for oral absorption of AZ PROTACs and six clinical PROTACs studied. Using a multiparameter score that

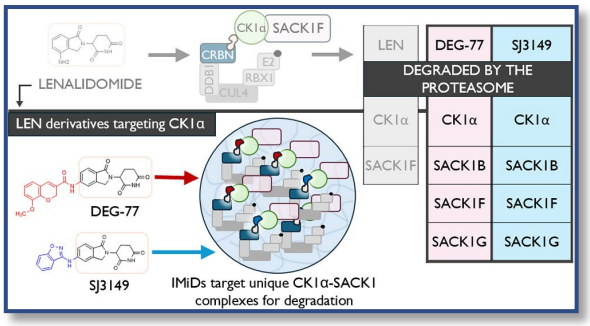
includes calculated chameleonicity (Bifunctional Bioavailability Index), only marginally enriched orally bioavailable compounds. Instead, the authors highlighted efflux ratio from Caco2 assays as a valuable method to filter our poorly absorbed compounds ahead of *in vivo* testing, with 89% of compounds with Efflux Ratio > 100 having an oral absorption in mouse (mFabs) < 0.2 while an Efflux Ratio < 20 gave a good chance of mFabs >0.3, especially for compounds in the oral space (ChromLogD 3-7 and ePSA 110-150) in their data set.

Whilst there have been great advances in the development of orally bioavailable PROTACs, with notable publications from Arvinas and AstraZeneca on guidelines for success, the process still relies heavily on empirical design and *in vivo* experiments. Unfortunately, PROTACs tend to perform poorly in standard Caco2 experiments, but where data is available, it can at least be used to filter out compounds for *in vivo* testing, when combined with previous guidelines for the oral space.

| *Roberta*

The Contribution of Native Protein Complexes to Targeted Protein Degradation

*Lorraine Glennie,§ Nicole M. Curnutt, Gajanan Sathe, …, Gopal P. Sapkota**
ACS Chem. Bio. ***2026****, 21, 1095–1111*

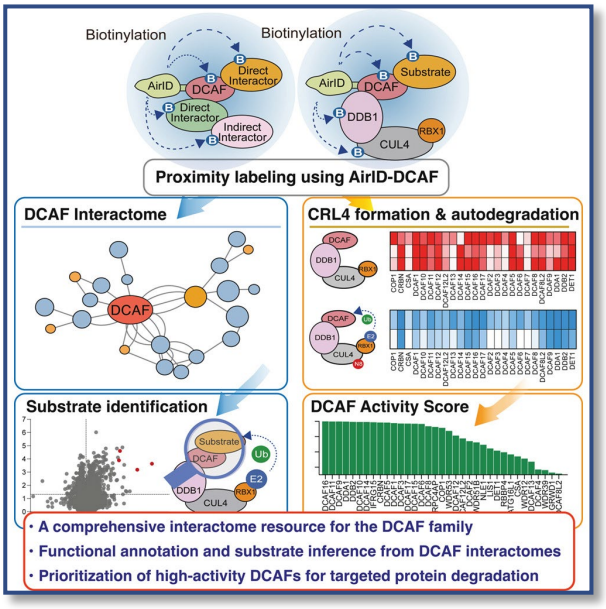


Using CK1α and its eight SACK1 scaffolding partners as a model system, Glennie and colleagues demonstrate that potent CK1α-selective lenalidomide-derived molecular glue degraders (namely DEG and SJ series) could co-degrade multiple SACK1 proteins — including SACK1B, SACK1F, SACK1G and mitotic SACK1D — with the same degradation kinetic of CK1α itself. MoA elucidation, proved that co-degradation relies on both CK1α and CRBN, and is blocked by MG132 but not by autophagy-lysosomal inhibitor (bafilomycin A1), confirming proteasomal dependence. The requirement for direct protein–protein interaction is then validated using patient-derived fibroblasts harbouring the CK1α-binding-deficient SACK1G^{R265P} mutation: DEG-77 degrades CK1α normally in these cells but completely fails to co-deplete SACK1G^{R265P}. Structural differences between the DEG and SJ series produce subtle differences in which CK1α–SACK1 complexes are targeted, suggesting the importance of ternary complex geometry for dictating productive ubiquitylation.

This study makes an important conceptual contribution by demonstrating that indirect degradation of complex partners is still dependent and mechanistically rationalised by direct protein–protein interaction with the POI. The patient fibroblast experiments are a particularly clean validation of this principle. The work highlights that the multiprotein complex of a POI should be considered explicitly in degrader design — both as a potential liability and as an opportunity to selectively target specific subcellular functions of a multifaceted protein.

An interactome-based framework for DDB1- and CUL4-associated factor prioritisation in targeted protein degradation

Satoshi Yamanaka,§*..., Hidetaka Kosako*, Tatsuya Sawasaki*
Mol. Cell, ***2026,*** *86,7*



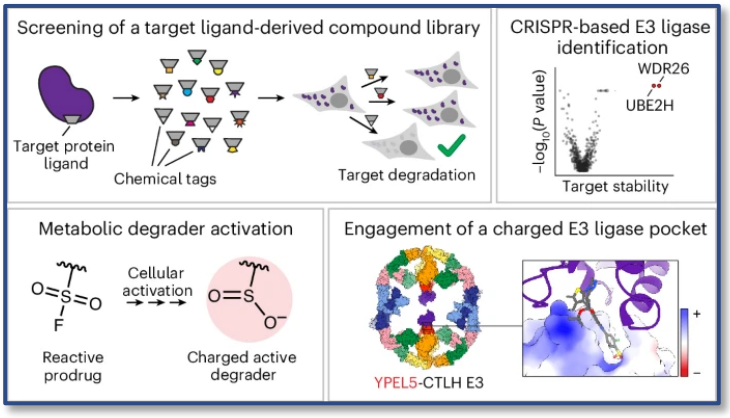
The authors present a massive effort to characterise the functional roles, natural substrates and catalytic activity of 60 human CRL4^{DCAF} E3 ligase complexes. Central to this work is the generation of 60 cells lines, each containing a different AirID-tagged DCAF protein. To validate that each DCAF was in-fact able to form a CRL4^{DCAF} complex, an *in vitro* AlphaScreen-based assay was used to confirm DCAF-DDB1 interaction while proximity biotinylation of other CRL4-associated proteins in cellulo was used to provide evidence of CRL4^{DCAF} complex assembly. The catalytic activity of the CRL4^{DCAF} complexes was then assessed by using quantitative proteomics to determine the degree to which each DCAF underwent auto-degradation when deneddylation was supressed by small molecule inhibition of the CAP9 signalosome. Proximity biotinylation experiments were used to build a comprehensive interactome for the 48 DCAFs which were found to form active CRL4^{DCAF} complexes. From these interactomes the authors are able to infer the cellular pathways which are likely to be regulated by each DCAF. Elegant integration of proximity biotinylation experiments with quantitative proteomics and RNA-seq then allowed the differentiation of interactors from true substrates.

This was an impressive and comprehensive body of work from the authors. Their findings will provide a very useful resource for the field as we seek to expand the range of E3 ligases that we can recruit for TPD. Their work on substrate identification will be of immediate interest to those employing a biology-first approach to molecular glue discovery.

| *Hannah*

Charged molecular glue discovery enabled by targeted degron display

Zhe Zhuang,§ Woong Sub Byun,§ Jakub Chrustowicz,§..., Brenda A. Schulman* & Nathanael S. Gray*
Nat. Chem. Biol. **2026**, *https://doi.org/10.1038/s41589-026-02182-5.*



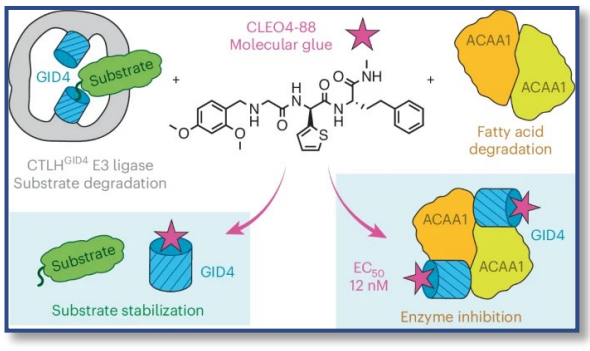
Utilising a target-centric chemical screening strategy, the authors screened sulfonyl-fluoride functionalised JQ1 ligand derivatives in a BRD4-HiBiT assay. This led to the discovery of ZZ1, a metabolically-activated electrostatic molecular glue that induces degradation of BET proteins through recruitment of the previously undrugged YPEL5-CTHL E3 complex. Unexpectedly, ZZ1 does not recruit YPEL5-CTHL covalently via the sulfonyl-fluoride moiety. Instead, it acts as a prodrug that converts into the active acidic sulfinic acid metabolite, which projects into the basic environment of the YPEL5 binding pocket. Structural analysis of the $BRD4^{BD1}$-bound YPEL5-CTHL via cryo-EM was critical in elucidating the mechanism of ZZ1-indued ternary complex formation and guided subsequent structure-based optimisation of ZZ1 to yield the superior degrader ZZ2, which demonstrated increased degradation potency, $BRD4^{BD1}$ ubiquitination and more stable ternary complex formation.

This study further reinforces how chemical elaboration of existing POI ligands can be a fruitful avenue for molecular glue discovery and enable recruitment of novel E3 ligases. However, the authors were unable to extend the 'c-Glue' concept to other targets beyond BRD4, raising important questions on the broader recruitment potential for CTHL. More broadly, this work also highlights the potential for incorporating charged degron mimetics- or prodrug variants thereof- into ligands for the rational design of molecular glue degraders.

| *Suzanne*

The molecular glue CLEO4-88 inhibits the ACAA1 thiolase by induced binding to GID4

Chetan K. Chana, Ines Ben Makhlouf,§ Jaeyoun Kim,§ April J. Y. Yu,§ Nathalie Moatti,§ Stephen Orlicky,§ Cassandra J. Wong,§ Leon Baronijan,§* ... Frank Sicheri*
Nat. Chem. Biol. **2026**, *https://doi.org/10.1038/s41589-026-02183-4*



Chana *et al.* explored small molecule ligands of the E3 ligase CTLH subunit GID4, looking for molecular glue activity. Using DEL and fragment screening, they identified potent small molecules that bind to the degron-binding pocket of GID4 and searched for any serendipitous interactions with new proteins using proteomics. Their efforts led to the discovery of a 12.5 nM molecular glue between GID4 and ACAA1, a peroxisomal

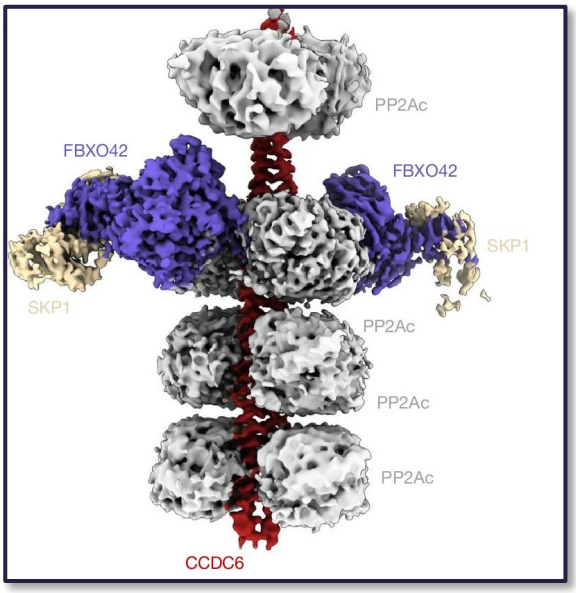
thiolase. By solving a 2.3 Å crystal structure of the ternary complex they revealed an allosteric mechanism whereby the glue binds solely to GID4, inducing the necessary conformational change to then recruit ACAA1. This mechanism inhibits the catalytic activity of ACAA1 but does not lead to its degradation because GID4 binds to ACAA1 and to its immediate partner ARMC8a in CTLH complexes using a common surface.

As the number of E3 ligases explored for TPD has been limited by the lack of suitable ligands for them, it's fantastic to see new ligands emerging and the characterisation of new molecular glue interactions.

| *Hannah*

Template-driven scaffolding of SCF^{FBXO42} regulates PP2A degradation

Sebastien Coassolo,§ Nairie Michaelian,§ Timurs Maculins,§..., Peter L. Hsu* & Robert L. Yauch*
Nature ***2026**, 654, 250–260*



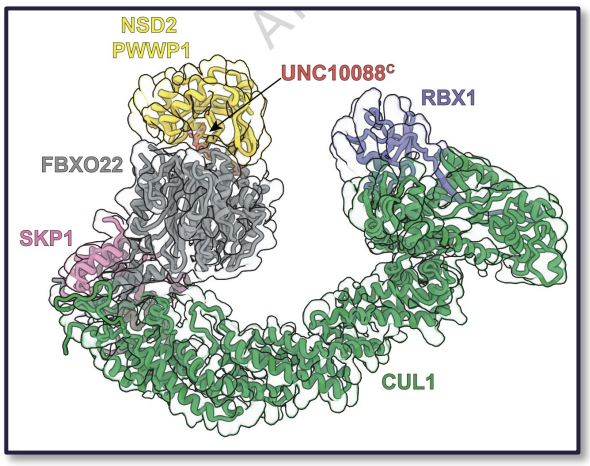
Although FBXO42 has been previously linked to the regulation of p53 and other putative substrates, the authors demonstrate that FBXO42 remains essential in TP53-deficient backgrounds, indicating the presence of a missing critical substrate(s) regulated by FBXO42 in cancer cell growth. In this study, the authors reveal that FBXO42 targets the catalytic subunit of PP2A for ubiquitination and degradation through a recognition mechanism involving the assembly of a complex consisting of multiple PP2Ac monomers bound to the coiled-coil protein CCDC6. Notably, LCTM1-mediated PP2Ac C-terminal carboxy-methylation contributes directly to PP2Ac engagement by FBXO42. Cryo-EM structural analysis revealed FBXO42 recognises the quaternary assembly of the CCDC6-PP2Ac complex, with the C-terminal carboxy-methyl group of PP2Ac buried within the central cavity of the FBXO42 Kelch domain. Strikingly, unlike other reported multicomponent E3 ligase recognition mechanisms, in which the ligase establishes direct contacts with multiple components of the substrate assembly, CCDC6 has no direct interface with FBXO42. Instead, CCDC6 functions only to rearrange PP2Ac into a structure facilitating recognition by the E3, leading the authors to term this as a "template-driven" mode of action.

Through a combination of biochemical and structural studies, the authors elegantly define a unique mechanism for PP2A control through the ubiquitin-proteome system. This study highlights the critical role of posttranslational modifications, in this case C-terminal carboxy methylation, for E3 ligase substrate recognition and reveal a unique template-driven mode of action, whereby a non-substrate template protein is required to rearrange the substrate into a form that can be recognised by the E3. This demonstrates an additional layer involved in substrate regulation, whereby expression levels of template proteins can potentially influence stability of substrates, and raises the possibility that other substrate interactions may be governed through a similar template-driven mechanism

Structural basis of NSD2 degradation via targeted recruitment of SCF-FBXO22

Kevin C. Robertson,§ Sascha J. Amann,§ Tongkun Liu,§..., David Haselbach,* Lindsey I. James* & Nicholas G. Brown*

Nat. Commun. ***2026, in press****. https://doi.org/10.1038/s41467-026-72235-9*



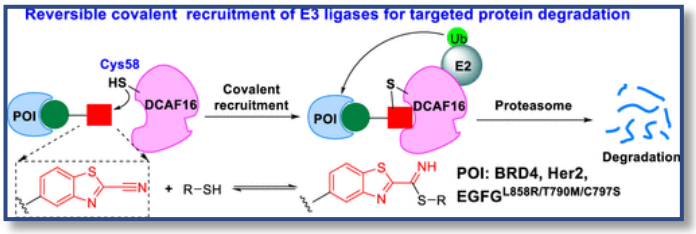
Despite the development of numerous FBXO22-recruiting degraders, a structure of FBXO22 in complex with a neosubstrate has not yet been reported. In this study, the authors elucidate the structural basis for degrader-induced NSD2 recruitment to FBXO22 using cryo-EM, providing a framework for the rational design of next-generation FBOX22-recruiting NSD2 degraders. UNC10088 and close analogue UNC8732 have been previously demonstrated to undergo conversion into their active aldehyde derivatives by hydrolysis or amine oxidase-mediated metabolism, respectively, enabling covalent recruitment of FBXO22 via Cys326. As expected, the cryo-EM structure revealed electron density corresponding to a hemithioacetal linkage formed between the UNC10088 and Cys326 of FBXO22. In addition, the structure revealed favourable direct protein-protein interactions between NSD2 and FBXO22; mutations at this surface interface dramatically reduced FBXO22-dependent NSD2 ubiquitination and ternary complex formation. Importantly, the structure also suggested larger or alternative warheads could be accommodated to engage Cys326. Guided by these structural insights, the authors undertook a medicinal chemistry campaign focused on benzaldehyde-based analogues, leading to the identification of UNC10415667 and UNC12149, which induce potent NSD2 degradation and ubiquitination while eliminating the need for metabolic activation. Interestingly, these degraders recruit NSD2 to a region of FBXO22 that is distinct from the binding site used by its native substrate, BACH1. The authors were able to solve the structure of FBXO22 bound simultaneously to NSD2 and BACH1, indicating that recruiting neo substrates to FBXO22 without perturbing native substrate degradation is possible.

Given the recent surge in interest in FBXO22 within the targeted protein degradation field, it is exciting to finally see the structural basis for NSD2-recruitment to FBXO22 revealed. These findings provide important design principles for the development of FBXO22-recruiting degraders against additional therapeutic targets. To date, a common strategy for identifying ligandable E3 ligase surfaces has been to exploit interfaces involved in endogenous substrate recognition. In contrast, this discovery of a FBXO22 binding site distinct from that used by BACH1, and potentially other native FBXO22 substrates, emphasises that recruiting E3s via allosteric sites is possible. This finding may help mitigate concerns more broadly that degrader-mediated recruitment of E3 ligases could potentially disrupt the ubiquitination and degradation of endogenous substrates.

| *Suzanne*

New reversible covalent warheads: Cyano benzothiazoles recruiting DCAF16 for targeted protein degradation

Jixian Zhang… Yi Tan, Tongzheng Liu,* and Zhengqiu Li**
J. Med. Chem. ***2026****, 69, 9, 11620–11637*



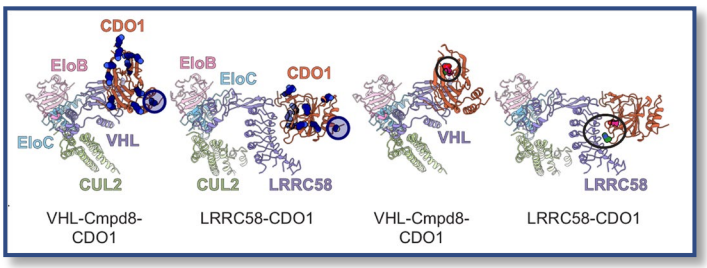
The authors sought to chemically modify N-terminal cysteine residues to explore the effect on modulating protein function as these residues are known to perform key biological functions, including sensing oxygen and oxidative stress and the coordination of proteostatic responses through post-translational modifications. They used affinity-based protein profiling and a library of electrophilic probes to systematically map ligandable native N-terminal cysteine residues across multiple cancer cell lines. The cyanobenzothiazole probes used can also form reversible thioimidate linkages with non-N-terminal cysteine thiols. Integrating the cyanobenzotriazole to a JQ1 ligand was found to induce proteosomal-dependent degradation of BRD4 by modifying the conserved cysteine C58 of the E3 ligase adapter DCAF16. Conjugation of the cyanobenzotriazole to tucatinib and brigatinib was found to degrade HER2 and EGFR L858R/T790M/C797S mutant respectively.

While covalent targeting has been achieved for quite a number of E3 ligases, reversible covalent ligands can offer advantages such as durable target engagement with potentially improved safety. It is great to see that this benzotriazole conjugation approach is applicable to other proteins beyond BRD4, to transform ligands into molecular glues. It is worth mentioning that Amphista's AMPTX1, a reversibly covalent BRD9 degrader, also engages the C58 of DCAF16.

| *Roberta*

Cysteine availability tunes ubiquitin signaling via inverse stability of LRRC58 E3 ligase and its substrate CDO1

*Gisele A. Andree, § Luca J. Stier, § …, Brenda A. Schulman**
Nat. Commun. ***2026****, 17, 4196*



Using active CRL profiling — a quantitative proteomics approach enriching neddylated E3 complexes — Andree, Stier and colleagues identify LRRC58 as the long-sought E3 receptor for cysteine-dependent CDO1 degradation. LRRC58 accumulates post-transcriptionally under cysteine starvation by suppression of its own autodegradation, and shows a striking inverse abundance relationship with CDO1 across five human cell lines. LRRC58 knockout stabilises CDO1 under starvation, while biochemical reconstitution confirms that LRRC58 assembles functional CUL2- or CUL5-based CRLs that ubiquitylate CDO1 in an LRRC58-dependent manner. Systematic Lys→Arg scanning reveals that the endogenous pathway targets CDO1 almost exclusively at Lys8, whereas the VHL-based molecular glue Cmpd8 bypasses this constraint and modifies multiple

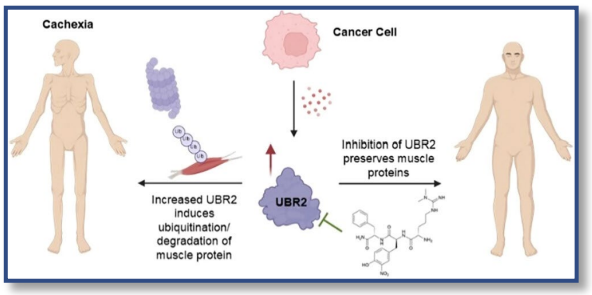
lysines. Cryo-EM structures at 3.73 Å (CUL2) and 2.95 Å (CUL5) show LRRC58 gripping CDO1 through nine LRRs and a unique C-cap, geometrically positioning Lys8 as the sole residue within 20 Å of the catalytic active site. Notably, CDO1 patient mutations (E143K, H147K) that impair endogenous degradation retain full susceptibility to Cmpd8, providing proof-of-concept for orthogonal degrader rescue of disease-associated variants.

This work elegantly closes a 50-year-old mechanistic gap, and the structural explanation of single-lysine selectivity through geometric positioning is a genuinely important advance for the CRL field. The comparison with Cmpd8/VHL is a neat illustration of how pharmacological degraders can bypass the constraints of endogenous pathways — directly relevant for targeting disease variants that have escaped their natural E3. One key question the paper leaves open, and which the authors acknowledge, is how cysteine levels are actually sensed at the molecular level — whether through LRRC58 directly, a cysteine-responsive co-factor, or another cellular mechanism entirely. Answering this will be essential to fully understand the regulatory logic of this pathway.

| *Roberta*

Development of High-Affinity Ligands for Human UBR2

*Shih-Ting Huang,§ Abdelfattah Faouzi,§…,Yuan Chen**
J. Med. Chem. ***2026****, 69, 11738–11751*

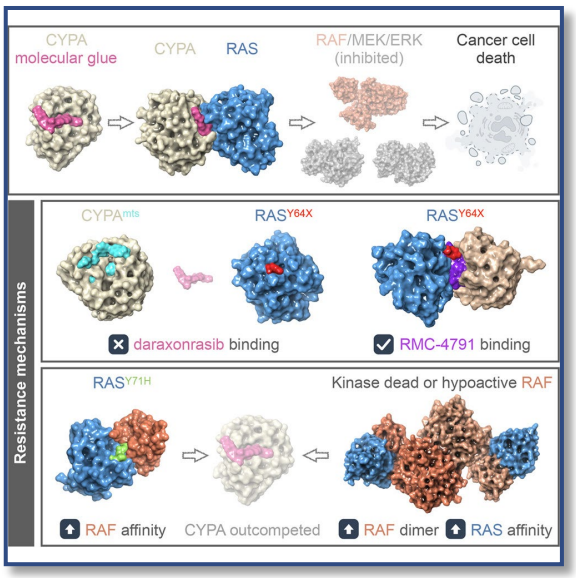


UBR2 belongs to the UBR box-containing E3 ligases (UBR proteins) that recognize the N-termini of their target proteins, known as N-degrons, for degradation. Despite UBR2 being a validated driver of cancer- and diabetes-induced cachexia, no well-characterised pharmacological inhibitors have been reported, partly due to the shallow substrate-binding pocket of the UBR box domain. Through a systematic peptidomimetic SAR campaign incorporating unnatural amino acids, Huang, Faouzi and colleagues develop tripeptide ligands binding UBR2 with K_d of 20–40 nM — ~100-fold improvements over natural counterparts — and 10-fold selectivity over UBR1. High-resolution co-crystal structures (~1.2 Å) reveal that a trifluoroethyl-arginine at position 1 enhances electrostatic interactions, while 3-nitro-L-tyrosine at position 2 forms two additional hydrogen bonds with Gly144/Gly146 absent in natural peptide complexes. In a C2C12 myotube cachexia model driven by KPC cancer cell-conditioned media, the lead compound **26** (2.5 μM) restored myosin heavy chain levels and myotube morphology to near-normal.

This work demonstrates for the first time that UBR box domains are tractable for high-affinity ligand development, providing a clear structural rationale and a validated pharmacophore model. The 10-fold selectivity over UBR1 is therapeutically meaningful given their distinct disease associations. The cellular cachexia data provide an encouraging proof-of-concept. Improving the proteolytic stability of these peptidic scaffolds — as evidenced by the pulsed dosing required in the cellular model — will be the critical next step, and the high-resolution structural data now available should guide that optimisation.

Disrupted molecular glue complex drives RAS inhibitor resistance

*Ben Sang,§ Ling Feng Ye,§ Zheng Fu,§ Yasin Pourfarjam,§...Piro Lito**
Cell ***2026****, 189, 2918-2933.e17*



The tricomplex pan-RAS(ON) inhibitor Daraxonrasib, developed by Revolution Medicines, represents a major development in targeted therapies for RAS-dependent cancers. Acting as molecular glue for RAS and CYPA, Daraxonrasib inhibits the RAS-RAF protein-protein interaction required for oncogenic signalling via the RAF-MEK-ERK pathway. In this study, the authors use patient samples as well as a systematic base editing screens to identify mutations which contribute to Daraxonrasib resistance.

Through structural and functional studies they characterise mutations in KRAS and BRAF, which either destabilise the Daraxonrasib-induced ternary complex or increase the stability of the RAS-RAF interaction. Curiously, they find that hypoactive or kinase-dead mutants of BRAF are able to out-compete Daraxonrasib-induced the inhibition of the RAS-RAF interaction. They suggest that this may be due enhanced RAF dimerisation, which leads to increased affinity of RAF for RAS, ultimately displacing Daraxonrasib and CYPA. The structural basis for this mechanism, however, remains undetermined.

The authors go on to propose that the use of alternative tricomplex inhibitors or combination therapy with inhibitors of RAF dimerisation may be effective approaches to overcome some of the key resistance mechanisms identified.

This is a very timely and important study given recent interest in Revolution Medicines tricomplex approach to KRAS inhibition. While Daraxonrasib is not a degrader, there are still lessons to be learned here for the broader field of induced proximity. That tricomplex-disrupting mutations were observed on CYPA, KRAS and BRAF suggests that the number of such mutations will likely increase with the number (and likely size) of interaction surfaces which are involved in PPI-driven modalities. For TPD, this logic can be extended to include the PPIs involved in assembly of CRL complexes, as has been shown by others.

PRE-PRINTS

| *Suzanne*

PROTAC internalization and target degradation require clathrin-mediated endocytosis

Hao-Yang Liu, …, Hong-Yu Li,* Jeanne C. Stachowiak*

The authors were interested in understanding how PROTACs enter cells. Although passive diffusion is often assumed, active transport may be required for molecules of such high molecular weight. Previous work showed that the fatty acid transporter CD36 is a receptor for PROTACs, required for cellular uptake and function. They show here that clathrin mediated endocytosis is required for the function of PROTACs, using different E3 ligases (VHL, MDM2, CRBN) against multiple targets (BRD4, AR). Genetic or pharmacological disruption of clathrin assembly abolishes all detectable PROTAC induced protein degradation. In the proposed model, binding of PROTACs to CD36 leads to their recruitment to sites of clathrin-mediated endocytosis, followed by PROTAC internalization and release inside the cell. A highly interesting read for anyone looking at optimizing PROTAC cellular uptake.

| *Suzanne*

Identification and SAR optimization of FBXO22-mediated TEAD Targeted Glue™ degraders

Martin Fisher, …, Marta Carrara*

Amphista report the discovery and development of their potent and fast TEAD molecular glue degrader. The amine-based TEAD degrader undergoes oxidation to the active aldehyde, which then reversibly covalently engages the Cys326 of FBX022. Proteomics studies show good selectivity and on-target pathway modulation. It's particularly nice to see the development of more degraders using E3 ligases beyond VHL and CRBN. It would be interesting to explore whether this relatively small morpholine-amide FBX022 binder could be conjugated onto other POI ligands to transform them into degraders.

| *Hannah*

Metabolic glues as a means of purine sensing and chemotherapeutic response

Samuel R. Witus, ..., Michael Rapé*

Whilst plant hormones and therapeutic compounds are known to act as molecular glues, up until now there have been no reported endogenous molecular glues in human cells. In this seminal work from the Rapé lab, they demonstrate that *de novo* purine synthesis is regulated by glues derived from endogenous metabolites, termed 'metabolic glues'. Purine nucleotides act as molecular glues that anchor the rate-limiting enzyme of purine biosynthesis (PPAT) to its inhibitor NUDT5. This allows cells to monitor purine levels and establish essential feedback controls of their synthesis. Chemotherapeutics targeting purine metabolism, such as methotrexate, act as molecular glues of the same PPAT:NUDT5 complex, but glue with increased potency and adopt an altered binding mode, leading the authors to exploit this structural flexibility to design molecular glues with increased thiopurine efficiency.

bioRχiv **Localized heme sensing through a ternary molecular glue**

Michael Heider, ..., Michael Rapé*

Here, the authors demonstrate that cells use an endogenous glue strategy to monitor heme, which acts as a 'ternary molecular glue' bridging three polypeptides to trigger the degradation of the transcriptional repressor BACH1 through FEM1B. Since heme engages the mitochondrial-binding motif of FEM1B, this triggers a localised stress response and ensures only cytoplasmic FEM1B can degrade BACH1. Therefore, cells are protected from accumulation of toxic cytoplasmic heme but a response during times of ETC-production is avoided.

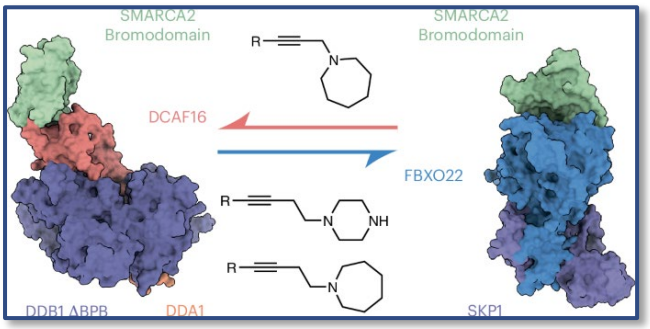
PAPERS AND PRE-PRINTS FROM CeTPD

| *Alejandro and Valentina*

Dual E3 Ligase Recruitment by Monovalent Degraders for Tunable SMARCA2/4 Degradation

Valentina A. Spiteri§, Dmitri Segal§, Alejandro Correa-Sáez§, …, Alessio Ciulli*, Georg E. Winter*
Nat. Chem. Biol. ***2026****, https://doi.org/10.1038/s41589-026-02224-y*

CeTPD authors (past and present): Valentina A. Spiteri, Alejandro Correa-Sáez, Kentaro Iso, Ryan Casement, Mark A. Nakasone, Gajanan Sathe, Hannah E. Peters, Mark Doward, Angus D. Cowan, Alessio Ciulli



Molecular glue degraders (MGDs) are monovalent compounds that direct E3 ligases toward neo-substrates for proteasomal degradation. All characterised MGDs to date recruit a single E3 ligase, leaving them vulnerable to resistance via ligase loss or mutation. This paper in collaboration with Georg Winter´s group overturns that paradigm by showing that a single monovalent degrader can simultaneously engage two structurally unrelated E3 ligase substrate receptors—DCAF16 and FBXO22—to degrade SMARCA2/4 in a functionally redundant manner. **Compound 1** bears a propargyl-azepane tail that covalently engages DCAF16 at C173, a previously uncharacterized cysteine resolved here by cryo-EM. Single knockouts of either ligase only partially rescue degradation; double knockout fully abrogates it, confirming genuine redundancy. Strikingly, the system is chemically tuneable: minimal structural changes to the degradation tail—adding one methylene group (**Compound 3**) or altering ring size (**Compound 2**)—shift the dominant ligase from DCAF16 to FBXO22. Genetic tunability is also demonstrated via DMS-identified DCAF16-L59W, a gain-of-function mutation that stabilises a key π-stacking interaction and synthetically enforces DCAF16 dependency for Compounds 2 and 3. Together, these findings establish dual-ligase engagement as a new design principle for overcoming degrader resistance.

| *Conner*

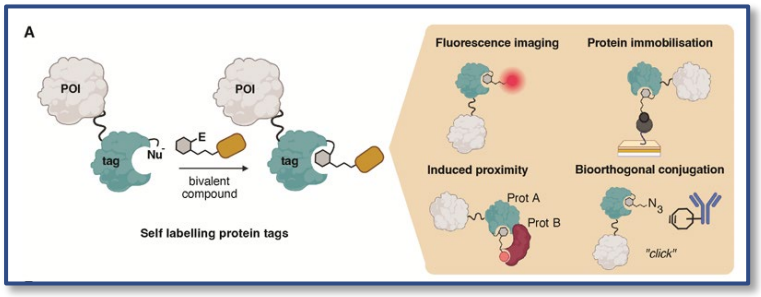
BromoCatch: a self-labelling tag platform for protein modification and live cell imaging

*Maria Rodriguez-Rios,§ Conner Craigon,§ Mark A. Nakasone, …, Alessio Ciulli**
Nat. Commun. ***2026, in press****. https://www.nature.com/articles/s41467-026-72539-w*

CeTPD (Past and Present): Maria Rodriguez-Rios, Conner Craigon, Mark A. Nakasone, Gajanan Sathe, Adam G. Bond, Mark Dorward, Alessio Ciulli

The Ciulli lab has recently finalised a publication describing the BromoCatch self-labelling tag system, a 13.1 kDa engineered tag that employs a para-acrylamide warhead to covalently

tether probes to a cysteine-engineered variant of the BromoTag system. BromoCatch is designed as a smaller alternative to the larger self-labelling systems such as HaloTag and SNAP-tag, overcoming the constraints of tag size and protein fitness. This platform enables rapid, selective, and irreversible labelling of tagged proteins with synthetic ligands, providing a versatile strategy for proximity-driven applications. The study demonstrates that BromoCatch supports efficient probe conjugation under both *in vitro* and live-cell conditions, facilitating targeted biotinylation, induced protein degradation via recruitment of VHL, and fluorescent labelling. Importantly, the system exhibits favourable kinetics, specificity, and minimal off-target reactivity, making it a robust tool for chemical biology applications and for studying protein function, localisation, and dynamics in complex biological environments.



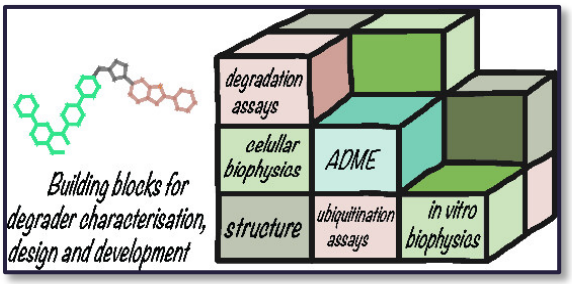
| *Alessandra*

Methods to Study the Molecular Mechanism and Drive the Design of Protein Degraders

Charlotte Crowe and Alessio Ciulli*
Chem. Rev., ***2026***,*126, 5755−5791*

CeTPD authors (past and present): Charlotte Crowe and Alessio Ciulli

This review serves as an up-to-date and practical "how-to-degrade" guide and is an excellent starting point for researchers who are new to the TPD field. It provides a comprehensive overview of how degraders function and outlines the key parameters and experimental methods used to study each stage of the degradation mechanism.



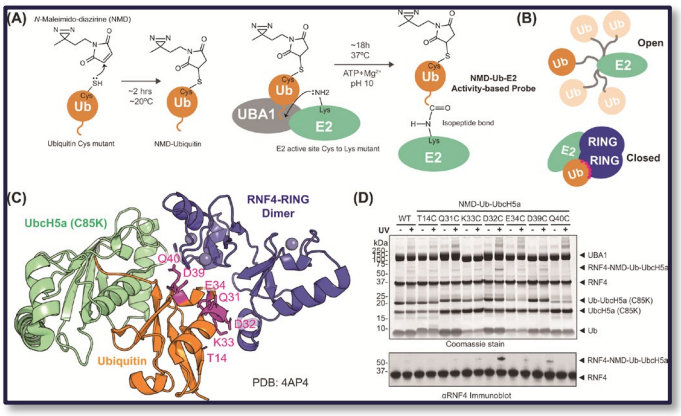
It is structured in a way that appeals to readers with different scientific backgrounds and interests, with different key sections focusing on: ***1)*** *Mechanisms and parameters for evaluating small-molecule degrader efficacy.* ***2)*** *Cellular permeability and intracellular availability of degraders,* ***3)*** *Small-molecule degrader-mediated binary binding and ternary complex formation,* ***4)*** *Methods to evaluate target protein ubiquitination,* ***5)*** *Small-molecule-mediated degradation,* ***6)*** *Implications and applications for drug development.* A major takeaway from this review is that successful degrader development requires a detailed understanding of every step involved in targeted protein degradation, including target binding, ternary complex formation, ubiquitination, and cellular degradation. The authors emphasise the importance of combining biochemical, biophysical, cellular, and structural approaches to evaluate degrader activity and optimise performance. *In vitro* and cellular assays provide complementary information while structural techniques such as X-ray crystallography and cryo-EM support rational molecular design. The authors also highlight an important practical challenge in the field: many of these assays are technically demanding, resource-intensive, and low-throughput; therefore, selecting the right assays at the appropriate stage of the drug discovery process is critical.

| *Mark and Sarah*

Photocrosslinking Activity-Based Probes to Capture the Dynamics of Ubiquitin RING E3 Ligase Interactions

Sarah F Chandler,…, Alessio Ciulli, Ronald T. Hay*
Biochem. J ***2026****, 483 (7), 1115–1130*

CeTPD authors (past and present): Sarah F Chandler, Mark A. Nakasone, Nikolai Makuhin, Alessio Ciulli



This study describes an innovative workflow to capture the transient dynamics of the E2~Ub intermediate with RING E3 ligases via photo cross-linking and mass spec analysis. By incorporating a light-activated N-Maleimido Diazirine (NMD) crosslinker at an engineered cysteine on Ub loaded on E2 (E2~Ub), researchers successfully "trapped" active E2~Ub/E3 conformations in solution, overcoming the limitations of traditional crystallography. Importantly, the case study on the homodimeric CHIP provides insight for a 2:2 stoichiometry, refining existing asymmetrical models. Beyond static snapshots, the approach maps "ensemble proximity," revealing how disordered protein regions and mobile termini frequently contact the catalytic machinery during ubiquitination. New interactions between E2~Ub and RING E3s were discovered and provide additional insights beyond X-ray crystal structures. The study's broad importance lies in its hybrid methodology, pairing experimental crosslinking with RF-diffusion and integrative modelling to correlate molecular distances in 3D. Overall, this represents a roadmap for investigating the ~600 human RING E3 ligases, which present major challenges to X-ray crystallography and cryo-EM. By unmasking the secret motions of these enzymes, this work significantly advances our understanding of the underlying mechanisms of ubiquitination and targeted protein degradation.

| *Alessandra*

ChemRxiv™

Proximity Binding Assay for PROTAC Ternary Complex Analysis

Charlotte Crowe, …, Alessio Ciulli*
CeTPD authors (past and present): Charlotte Crowe and Alessio Ciulli

Here, the authors present the validation a novel proximity binding assay developed by Dynamic Biosensors GmbH for simultaneous analysis of binary and ternary protein interactions on a heliX® biosensors. Target proteins and ubiquitin E3 ligase substrate are tethered to flexible swivel arms on a Y-shaped DNA scaffold, promoting close proximity upon engagement with PROTAC molecules. Interaction states are distinguished using fluorescence-based readouts: ternary complexes are detected via FRET, while binary interactions are monitored through fluorescence quenching, enabling real-time kinetic analysis of complex formation and dissociation. The platform was validated using CRBN and VHL E3 ligases together with clinically relevant PROTACs. This approach enables comparison of ternary interaction kinetics, identification of kinetically stable ternary complexes, and high-throughput screening, while expanding the repertoire of available biophysical tools.

bioRχiv

Exploration of targeted electrophilic kinase probes identifies a covalent ULK1 degrader

*Nur Mehpare Kocaturk,§ Adam L. Pinto,§ …, William Farnaby**

CeTPD authors (past and present): Nur Mehpare Kocaturk, Adam L. Pinto, Matylda Izert-Nowakowska, Gajanan Sathe, Qasim Ashraf, William Farnaby

In this preprint from the Farnaby group, we describe a chemoproteomic strategy to identify monovalent electrophilic kinase degraders. We used pan-kinase targeting molecules to enable assessment of the modulation of hundreds of kinases, using just a handful of compounds. Termed "KinoGlus," these molecules were synthesised by decorating a promiscuous kinase ATP-site binding scaffold with solvent-exposed electrophilic warheads, able to either irreversibly capture effector proteins, or *cis*-label kinases. Profiling the effects of these multi-targeted probes on kinase abundance allowed us to nominate several kinases, including ULK1, as degradable hits. Transplanting the chloroacetamide handle of KinoGlu 1 onto an ULK1-targeted scaffold yielded ALP-1, which can effectively degrade ULK1. This degradation was confirmed to be post-translational and require the presence of both the electrophile and kinase hinge-binding. ALP-1 robustly suppresses ULK1-mediated ATG14 phosphorylation and starvation-induced autophagy beyond the levels achievable with an inhibitor. Mechanism-of-action studies point to E1 ligase and lysosomal, rather than proteasomal, dependence. Furthermore, intact protein mass spectrometry confirmed that ALP-1 directly, covalently engages the ULK1 kinase domain.
We present proof-of-concept for electrophilic scout molecules being a route into kinase degrader discovery. The unexpected finding that ALP-1 covalently labels ULK1 itself *in vitro*, raises intriguing questions about the relationship between *cis*- target engagement of ULK1 and its induced degradation in cells. Mechanistic studies ongoing in the lab will be important to delineate these contributions and guide future optimisation.

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