CeTPD Journal Club

February – March 2025

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

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info on the editor

ANGUS COWAN

Angus completed his Bachelor of Biotechnology with Honours at Monash University in 2011. He obtained his PhD in 2017 at WEHI (Melbourne) with Profs Peter Czabotar and the Peter Colman. Following a 2 year postdoc with Prof Czabtoar, he joined Ciulli group January 2020. Supported by a Marie Skłodowska-Curie Fellowship, Angus' work on structural and biophysical characterisation of DCAF11- and DCAF16-recruiting degrader molecules was part of a large collaborative effort that uncovered a new modailty: intramolecular bivalent glues. He joined the AC-BI collaboration team as a Senior Drug Discovery Scientist in structural biology and biophysics in October 2023.

LinkedIn: https://www.linkedin.com/in/angus-cowan-14a26714b/

STEFAN DJUKIC

Stefan completed his bachelor and MSc studies in biology and molecular biology at University of Novi Sad, Serbia, after which he moved to Prague, CZ and joined Pavlina Rezacova's Structural biology group at Institute of Organic Chemistry and Biochemistry where he utilized X-ray crystallography to study medicinally relevant enzymes and their inhibitors. After earning his PhD from Charles University, he joined CeTPD's AC-BI collaboration team as a scientist in structural biology/biophysics.

LinkedIn: https://www.linkedin.com/in/stefan-djukic-7538581ba/

GAJANAN SATHE

Gajanan earned his Ph.D. from the Institute of Bioinformatics, Bangalore, and Johns Hopkins University, where he applied mass spectrometry-based proteomics to study cellular signalling and identify Alzheimer's biomarkers. After returning to India, he helped set up proteomics facilities at NIMHANS. In 2020, he joined Professor Sapkota's lab as a postdoc, optimizing global ubiquitination and phosphoproteomics workflows to study targeted protein degradation. His work led to insights into PROTAC-mediated ubiquitination, PP2A substrates, and targeted TAU dephosphorylation. In 2024, he joined the Centre as a Senior Scientist to lead proteomics efforts.

LinkedIn:https://www.linkedin.com/in/dr-gajanan-sathe-86739819/

GIORGIA KIDD

Giorgia finished her MChem in Pure and Applied Chemistry from the University of Strathclyde in 2016, and continued her studies towards a PhD there in the group of Prof. William Kerr investigating iridium-catalysed hydrogen isotope exchange and hydrogenation procedures. Having completed this in 2021, Giorgia joined the group within the AC-BI team as a medicinal chemist.

𝕏: @justgiorgia
LinkedIn: https://uk.linkedin.com/in/giorgia-kidd-9a9257104

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"

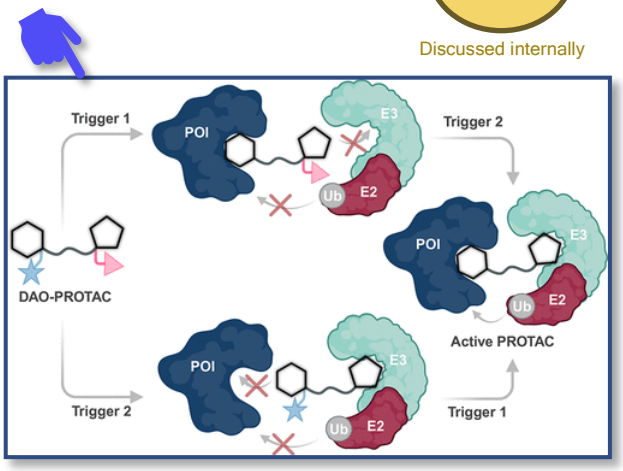
Literature review from 21st January to 20th March 2025

| *Giorgia*

Dual-Action-Only PROTACs

Ranit Dutta,§ Anirudh Devarajan,§ Amelia Talluri, Ritam Das, and S. Thayumanavan*
J. Am. Chem. Soc. **2025**, 147, 11, 9074–9078

Discussed internally



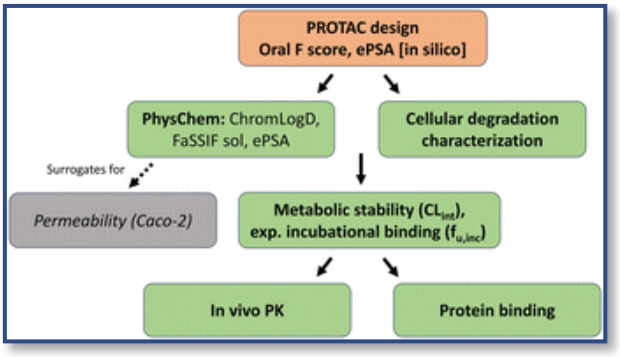
The authors have developed an activating strategy for PROTACs which are exposed to disease-like environments. Their chosen conditions aimed to have activation of PROTACS in condition of both hypoxia and cathepsin-L overexpression, both present in cancer cells. This strategy was proposed to prevent the inherent toxicity which has been observed with some PROTACtable targets, notably the thoroughly studied and yet unseen in the clinic, BRD4. In this study, both functional sites of the PROTAC are masked by protecting groups which are cleavable in the disease conditions, leading to the modification of BRD-4 directed dBet1 by appending a nitroaryl to JQ1, along with the formation of a ternary amide at the CRBN ligand side that produces an unfunctional PROTAC (DAO-PROTAC). This is dual activated and able to degrade BRD4 exclusively under conditions of both hypoxia and Cath-L expression. Comparing the toxicity of this DAO-PROTAC to the parent dBet1 shows much improved tolerability in healthy HEK-293 cells. This strategy was shown to be applicable to another target through modification of THAL-SNS-032, which was developed to target CDK9. Again, the DAO-PROTAC has comparable activity to the parent PROTAC only once the unmasking conditions are fulfilled. The unmasked PROTAC has comparable cytotoxicity to the parent one, but with the benefit to be present only under disease conditions.

Overall, this is a promising strategy for the modification of previously promising compounds which were seen to have toxicity, or for the development of compounds for targets where toxicity has been an inherent problem. Since the authors thought about generalisability from the start, this might be applicable in its current form to other targets/PROTACs where toxicity of healthy cells has been an issue until now.

| Giorgia

In vitro and *in vivo* ADME of heterobifunctional degraders: a tailored approach to optimize DMPK properties of PROTACs©

Christine Katharina Maurer, ..., and Heide Marika Duevel*
RSC Med. Chem., ***2025***, *https://doi.org/10.1039/D4MD00854E*



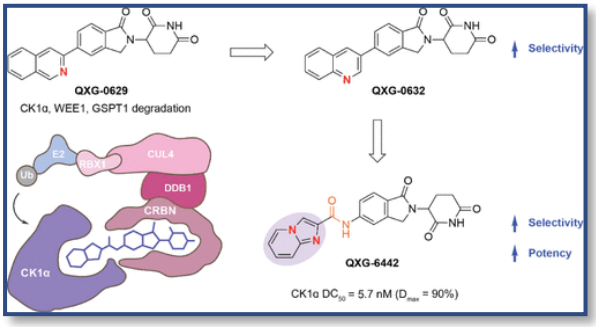
The increasing development of new modalities, such as PROTACs and other bifunctional molecules, has created a need to better understand their design for use in medicines. The community has built good understanding of what is required to develop beyond rule of 5 compounds for the best chance of oral bioavailability. Oral bioavailability, and eventually dose in humans is calculated using a range of parameters. These are determined through DMPK assays, many of which were developed and are well understood for small molecules. These classical experiments however show incompatibilities or issues with bRo5 compound such as PROTACs due to their increased size and lipophilicity and thus, decreased solubility and permeability. In this paper, the authors discuss the assay modifications that have been applied to traditional protocols to make them more robust for the screening of PROTACs and whether such assay could be generalizable, or need be applicable on a series-by-series basis. They also discuss the current state of the art for the prediction of mouse bioavailability and propose a new *in silico* methodology for this prediction using molecular weight and number of hydrogen bond acceptors and donors. This model has been integrated into their early PROTAC design and optimisation strategies.

This would be a great read for anyone working on PROTAC drug discovery programs to assess what assays may be applicable and to become familiar with what issues might be encountered in DMPK profiling of PROTACs.

| Giorgia

Development of Potent and Selective CK1a Molecular Glue Degraders

Qixiang Geng,§ Zixuan Jiang,§ ..., and Nathanael Gray*
J. Med. Chem. ***2025***, *68, 3, 3180–3196*



Due to their more drug-like properties, molecular glues are an interesting modality for targeted protein degradation. However, systemic design of molecular glues can be challenging as they can bind to shallow pockets on your protein of interest. In this study, Geng and Jiang *et al.* utilise the privileged IMiD core as seen in known molecular glues such as pomalidamide and lenalidamide. They diversify these cores through common transformations such as amide couplings and metal-mediated cross couplings in order to form a diversified chemical library to find glues of CK1a. Their initial hit is promiscuous, degrading CK1a along with GSPT1, WEE1, and IKZF2,

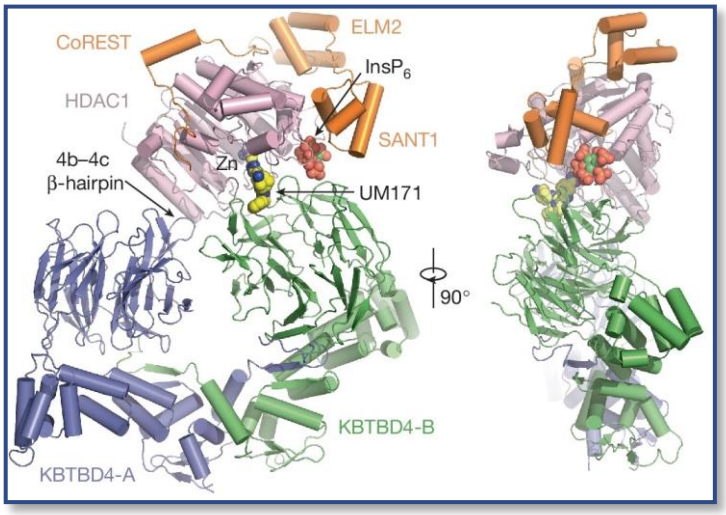
however, small modifications to the structure produced cleaner, more potent molecules. They confirmed the selectivity profile *via* proteomic analysis and delved into the structure activity relationships further using molecular docking. This analysis allowed them to further tweak their designs to improve potency further.

This study sits in a nice middle point between serendipitous discovery of molecular glue degraders and design of such molecules, using a well-known starting point of the IMiD compounds for further decoration.

| *Angus*

UM171 glues asymmetric CRL3–HDAC1/2 assembly to degrade CoREST corepressors

Megan J. R. Yeo,§ Olivia Zhang,§ Xiaowen Xie,§ Eunju Nam,§ …, Brian B. Liau* and Ning Zheng*
Nature **2025**, 639, 232-240



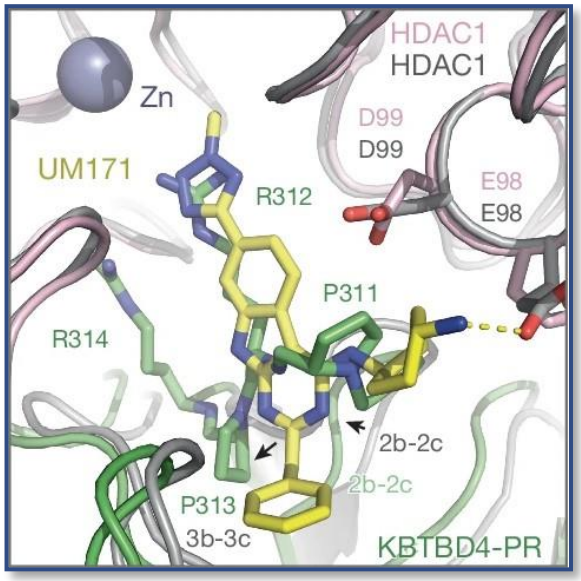
In this paper, the authors comprehensively unravel and characterise the mechanism of action of a potent inducer of hematopoietic stem cell proliferation UM171, known to induce degradation of the LSD1-HDAC-CoREST (LHC) corepressor complex through the $CRL3^{KBTBD4}$ E3 ligase. Using proteomics, fluorescent reporters, and chemical inhibitors, HDAC1/2 are identified as the primary target of UM171 that enables ubiquitination and degradation of CoREST proteins in the LHC corepressor complex by $CRL3^{KBTBD4}$. Through biochemical experiments, the authors define the minimum components of the complex induced by UM171 for structural investigation: KBTBD4, HDAC1 or HDAC2, ELM2-SANT1 domains of CoREST UM171 and inositol hexakisphosphate ($InsP_6$). The cryo-EM structure of the complex reveals a novel bimolecular gluing mechanism, where UM171 induces asymmetric engagement of HDAC1 through the dimeric KBTBD4, with $InsP_6$ acts as a second molecular glue that simultaneously engages KBTBD4, HDAC1 and CoREST. Finally, base editor scanning of KBTBD4 and HDAC1 is used to define regions of importance for UM171-induced degradation of CoREST.

A remarkable paper both in terms of the breadth and depth of characterisation as well as findings. Not only is it the first structural characterisation of molecular glue that recruits a dimeric CRL3 E3 ligase complex, but also the first example of a bimolecular gluing system. How many other small molecule gluing systems rely on, or are enhanced by, biomolecular co-glues found in cells? This paper suggests anyone struggling to reconstitute a glue system in vitro should look for co-glues.

| *Angus*

Converging mechanism of UM171 and KBTBD4 neomorphic cancer mutations

Xiaowen Xie,§ Olivia Zhang,§ Megan J. R. Yeo,§ Ceejay Lee,§ … , Ning Zheng* and Brian B. Liau*
Nature **2025,** 639, 241-249



Back-to-back with the previous article, this study elucidates how gain-of-function mutations in the CRL3 E3 ligase receptor KBTBD4 lead to aberrant protein-protein interactions (PPIs) that drive medulloblastoma (MB), a common childhood brain tumour. The authors demonstrate that these mutations promote the degradation of the corepressor CoREST by engaging the LSD1-HDAC-CoREST complex component HDAC1/2 through altered PPIs, a mechanism that is mimicked by UM171. Deep mutational scanning is used map the landscape of the 2b-2c mutational hotspot in KBTBD4, revealing that both point mutations and insertions can contribute to neomorphic activity, with insertions being particularly effective. Remarkably, the cryo-EM structures of KBTBD4 2b-2c insertion mutants in complex with HDAC1-CoREST reveal a conformation analogous to the UM171-induced complex. In this case, the mutated 2b-2c loop adopts a structure that inserts a bulky side chain into the HDAC1 active site, mimicking the N-methyl tetrazole moiety of UM171. Based on this, the authors investigate HDAC inhibitors as a potential way to block the interaction between neomorphic KBTBD4 mutants and HDAC, demonstrating the inhibitors block CoREST degradation by KBTBD4 mutants. Finally, they show KBTBD4 mutant MB PDX models are more sensitive to treatment with an HDAC inhibitor than KBTBD4 WT.

Another tour de force involving deep mechanistic characterisation through multidisciplinary approaches. Along with the companion study on UM171, this article leaves the reader with thought-provoking questions. Will future molecular glues be designed based on careful investigation of neomorphic gain-of-function hotspots? I look forward to studies exploring this idea.

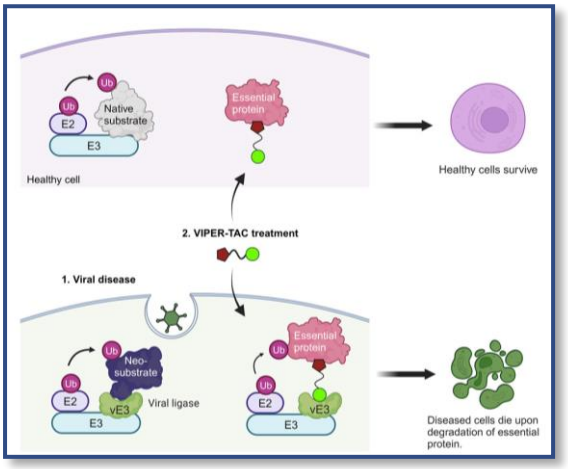
| *Angus*

VIPER-TACs leverage viral E3 ligases for disease-specific targeted protein degradation

Kyle Mangano, …, Patrick Ryan Potts
Cell Chem. Biol., **2025,** 32(3), 423-433

In this proof-of-concept study from Amgen, the authors develop viral E3 pan-essential removing targeting chimeras (VIPER-TACs), which recruit virally encoded E3 ubiquitin ligases to specifically degrade target proteins in virally infected cells. They first develop a chemically inducible

dimerisation system using FKBP12^{F36V} and MTH1 tags and bifunctional molecules with ligands for both proteins to explore the potential of viral E3's to degrade target proteins. The system shows many viral E3's are capable of degrading host proteins, including the human papillomavirus (HPV) E6 protein. In an engineered model of HPV-positive cervical cancer cell expressing MTH1-tagged E6 protein, VIPER-TAC treatment induced selective degradation of essential protein SARS1 tagged with FKBP12^{F36V}, leading to cell death.



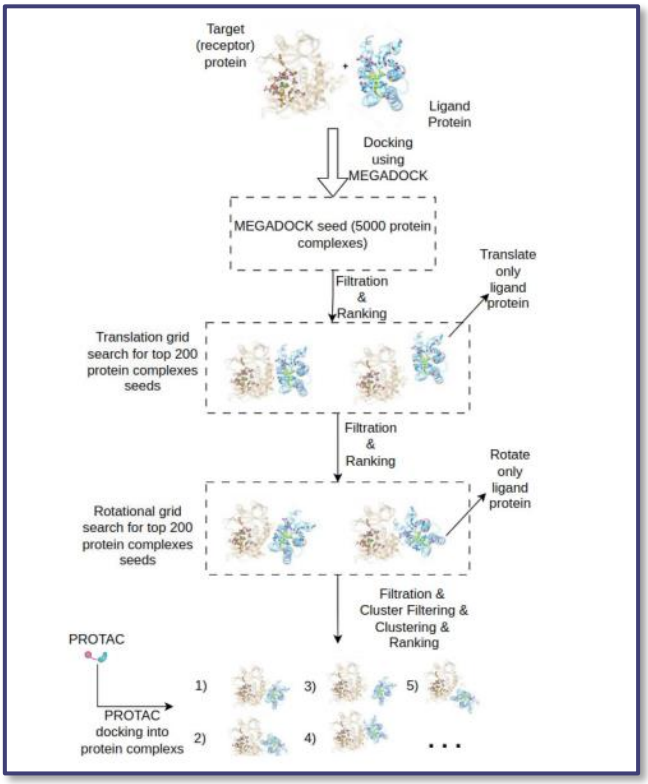
Tissue specificity was one of the early promises of TPD that has proven challenging to realise so far. This is a very clever idea to find tissue specificity in virally infected cells and could potentially have many applications in treatment of viral infections and in virally driven cancers.

| *Stefan*

MEGA PROTAC, MEGA DOCK-based PROTAC mediated ternary complex formation pipeline with sequential filtering and rank aggregation

*Sadettin Y. Ugurlu §, David McDonald, … Shan He**
Sci. Rep., ***2025***, *15, 5545*

PROTAC design is often limited by the lack of structural insight into the ternary complex formation. There are several molecular docking-based and optimization pipelines that were designed to predict ternary complexes, but they are showing limited predictive performance in the quality of the structure and their ranks. In this paper, the authors describe MEGA PROTAC, a pipeline that uses MEGADOCK to generate protein-protein complexes (PPCs). Docking results form an initial dataset which then goes through a sequential filtration strategy that is combined with rank aggregation to decide on complexes suitable for grid search which is used separately for translation and rotation. The remaining PPCs are grouped into clusters and filtered by energy score of the proteins in each cluster. Another rank aggregation is used as a criterion to select the best PPCs, which are then used as receptors for PROTAC docking by MEGADOCK. MEGA PROTAC was compared to state-of-the-art method BOTCP, and it outperformed it on 16/22 test cases, validating MEGA PROTAC as a reliable pre-refinement tool.

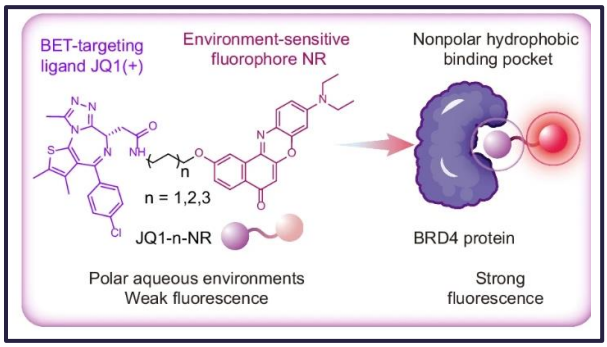


The paper brings a new ternary structure prediction pipeline which outperforms existing methods by utilizing a combination of MEGADOCK's speed with a new filtration strategy that utilizes several different ranking criteria improving the accuracy of the models.

| *Stefan*

Non-invasive in vivo monitoring of PROTAC-mediated protein degradation using an environment-sensitive reporter

*Tao Li§ Qingyu Zong,§ .... Youyong Yuan**
Nat. Commun., **2025**, *16, 1892*



PROTAC degradation efficiency is usually measured by quantifying POIs abundance through Western blotting or using various protein tags, all of which are limited to in vitro experiments. This paper proposes a new method for non-invasive quantification of protein degradation *in vivo* by environment-sensitive reporters (ESR), which are heterobifunctional molecules composed of POIs-target ligand and environment-sensitive fluorophore which are connected through a linker. In polar environments, the excited fluorophore releases the energy through non-radiative transitions resulting in weak fluorescence, while hydrophobic environments (such as POI binding sites) enhances the fluorescence signal. To test the method, authors synthesized a small BRD4 PROTAC library which they screened against several cell lines and used both ESR and Western blot to quantify degradation. Further, they compared two methods *in vivo* (using tumour-bearing mice). The results showed high correlation between WB signal and ESR signal across all the experiments. Moreover, level of ESR signal three days after PROTAC treatment showed to be a suitable indicator for early prediction of therapeutic efficacy of PROTACs in vivo. To validate the generality of the strategy, they repeated the experiments by monitoring GPX4 protein degradation.

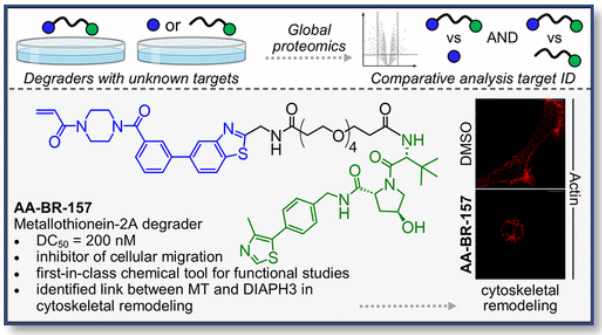
This paper presents an elegant solution for assessing efficacy of degraders *in vivo*. Utilization of environment-sensitive fluorophores seem to be a reliable method with the only limitation being the requirement for a good POIs binder.

| *Gajanan*

Chemoproteomics-Enabled PROTAC Discovery for Metallothionein in Cancer

*Brittney Racioppo, Dany Pechalri,…, Alexander Adibekian**
J. Am. Chem. Soc., ***2025***, *147, 7817-7828*

In this article, the authors present a chemoproteomic platform for the rapid screening of target-agnostic degraders without the need for prior optimization. They treated cells with a PROTAC



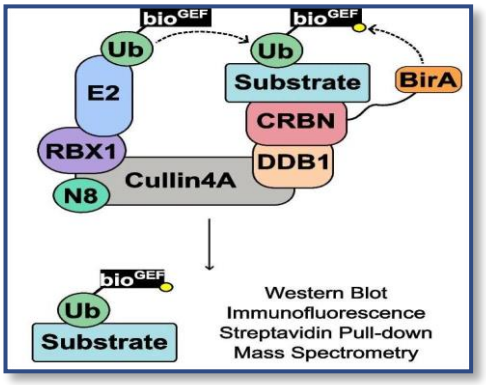
compound, its individual components - namely the E3 ligase recruiter-linker conjugate and the POI-binding ligand - followed by global MS-based proteomics analysis. The use of these control probes enable the filtering of protein abundance changes caused by either the warhead or the E3 ligase recruiter alone, thereby improving confidence in identifying direct cellular targets of the degrader. This approach led to the discovery and validation of several first-in-class covalent and non-covalent degraders and ligands targeting previously "undruggable" proteins of high therapeutic interest, including metallothionein 2A (MT2A), RAS GTPase-activating protein 3 (RASA3), and transmembrane protein 189 (TMEM189). The MT2A degrader was further characterized through ternary complex formation assays and identification of its covalent binding site. Subsequent optimization of the MT2A-targeting degrader focused on fine-tuning linker length and composition to enhance activity. Biological assays with the optimized PROTAC, AA-BR-157, demonstrated its ability to inhibit cellular migration and modulate DIAPH3 expression and cytoskeletal remodelling, further validating its functional impact.

This study presents a robust chemoproteomic platform for rapid, target-agnostic degrader discovery without prior optimization. Rigorous controls aid in confident target validation, leading to first-in-class degraders against challenging proteins like MT2A. However, the biological link to DIAPH3-mediated cytoskeletal remodelling is weak, and structural insights into the PROTAC–VHL–MT2A ternary complex are lacking.

| *Gajanan*

Cullin-RING ligase BioE3 reveals molecular-glue-induced neosubstrates and rewiring of the endogenous Cereblon ubiquitome

Laura Merino-Cacho,…, Rosa Barrio & James D. Sutherland**
Cell Commun. Signal, ***2025****, doi: 10.1186/s12964-025-02091-5.*



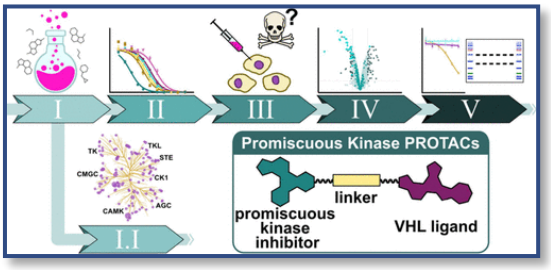
In this article, the authors utilized the BioE3 approach to identify both endogenous substrates of CRBN and neosubstrates induced by immunomodulatory drugs (iMiDs). By fusing the biotin ligase BirA to the N-terminus of CRBN, they achieved specific biotinylation in HEK293FT and U2OS-TRIPZ-bioGEFUb cells. Using this system, they validated Spalt-like 4 (SALL4) as a neosubstrate following pomalidomide treatment, demonstrating the effectiveness of the CRBN-BioE3 platform in capturing neosubstrate interactions. Proteomic analysis further uncovered both known and novel endogenous CRBN substrates, as well as potential pomalidomide-induced neosubstrates—including Cold Shock Domain Containing E1 (CSDE1)—with additional support from orthogonal validation and computational modelling to investigate potential binding sites.

The authors present application of the BioE3 approach to profile both endogenous and drug-induced neosubstrates of CRBN. The fusion of BirA to CRBN, coupled with the bioGEFUb system, enables robust and proximity-dependent biotinylation, facilitating substrate capture. The validation of SALL4 as a neosubstrate and the identification of novel candidates such as CSDE1 underscore the utility of this strategy. Overall, the study provides a valuable framework for substrate discovery in the context of targeted protein degradation.

| *Giorgia*

Workflow for E3 Ligase Ligand Validation for PROTAC Development

*Nebojša Miletić,§ Janik Weckesser,§ ….., and Stefan Knapp**
ACS Chem. Biol. ***2025****, 20, 2, 507–521*



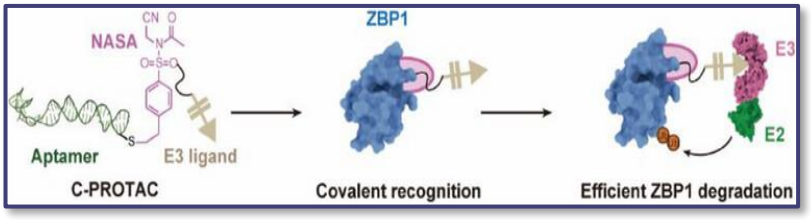
The authors highlight a current limitation in PROTAC drug discovery, being that only a small number of E3 ligases have been co-opted for use in degradation, mainly CRBN and VHL. The paper describes a workflow for validation of new E3 ligases using promiscuous kinase ligands to assess whether they may be used generally for degradation. A small library of PROTACs with these varying promiscuous binders were synthesised and assayed for various properties which can aid in functionality (such as permeability and target engagement). Differential scanning fluorimetry was used with 100 kinases and in the initial screen, 80 showed a significant shift in melting temperature, predicting binding. Further analysis of the interactable kinome was made using chemoproteomics method, i.e., Kinobeads, to validate what kinases were targeted with which PROTAC. UPS dependant degradation was assessed using western blotting and proteomics analysis to probe the change in protein levels. Overall, while in this exemplar study VHL E3 ligase was used, this workflow can be applied to new E3 ligases for validation of their function and utility.

This workflow will be really valuable to help quickly validate any new E3 ligases for utility before application to specific targets, especially as many assays used can be transferred to direct-to-biology or high-throughput methods.

| Stefan

Targeted Degradation of ZBP1 with Covalent PROTACs for Anti-Inflammatory Treatment of Infections

*Rentang Huang, § ... , Shu-Lin Liu**
Angew. Chem. Int. Ed., 2025, e202423524



Z-DNA binding protein 1 (ZDB1) is a pathogen sensing protein which triggers the immune response by recognizing Z-DNA and Z-RNA, which further promotes apoptosis and the release of proinflammatory cytokines. Excessive activation of ZDB1 can lead to organ damage, necrosis and systematic inflammation. While ZDB1 inhibition is the critical target for immune response control, no widely recognized specific inhibitors are known. The authors tackle this problem by trying an interesting approach which is to induce proximity between ZDB1 and E3 ligase via covalent PROTACs (C-PROTACs) which would have DNA aptamer as ZDB1 binder, *N*-acyl-*N*-alkyl sulfonamide (NASA) as part of the liner and VHL ligand. *In vitro* validation of this approach showed the C-PROTAC treatments not only prevents cell deaths but also leads to restoration of cellular function. *In vivo* experiments on viral pneumonia models showed that C-PROTAC treatment led to decrease in proinflammatory cytokines leading to a decrease in the intensity of inflammatory response, while improving the pathological changes on lungs. No pathological changes were observed on other organs further demonstrating therapeutic potential of ZDB1 degradation.

This paper is a great example of PROTACs succeeding where traditional drugs failed. Covalent PROTACs is an emerging field and combining it with DNA aptamers opens many new possibilities. Also, validation of ZDB1 as a target can be a huge step towards development of new anti-viral and anti-inflammatory treatments.

PRE-PRINTS

bioRχiv

Discovery of a VHL molecular glue degrader of GEMIN3 by Picowell RNA-seq

Jonathan W. Bushman,..., Jaeki Min & Patrick Ryan Potts**

Building on the extensive existing chemistry of VHL inhibitors, this study aims to identify new molecular glues and novel targets for the second most widely used E3 ligase in targeted protein degradation (TPD). Here, the authors report the discovery of the VHL molecular glue dGEM3 using an ultra-high-throughput Picowell RNA-seq screening platform—a unique approach that combines a biased, E3 ligase-focused DNA-encoded chemical library (DEL) with an unbiased RNA-seq readout. The work highlights the potential to reprogram VHL for new targets and provides valuable mechanistic insights into degron recognition and ternary complex dynamics—advancing the field of molecular glue–based TPD.

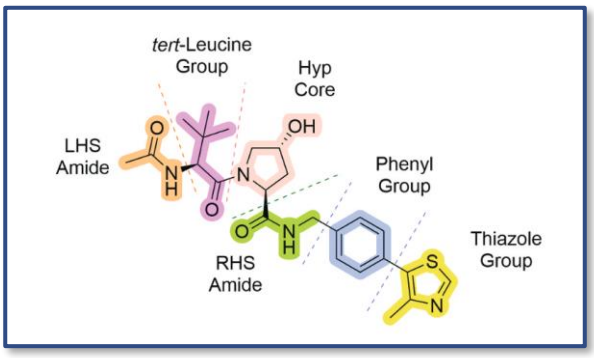
PAPERS AND PREPRINTS FROM CeTPD

| *Alex*

A patent review of von Hippel-Lindau (VHL)-recruiting chemical matter: E3 ligase *ligands for PROTACs and targeted protein degradation (2019–present)*

*Aina Urbina, § Alex J. Hallatt, § Jack Robertson,§ and Alessio Ciulli**
Expert Opinion on Therapeutic Patents, ***2025****, 35, 3, 197–238.*

CeTPD authors: Aina Urbina, Alex J. Hallatt, Jack Robertson, Alessio Ciulli



In this review, the authors provide a summary of any novel changes to the VHL chemotype reported in **patent literature since 2019**. Over 150 patents were covered in the initial screening and effort was made to exclude any modifications that had been reported prior to 2019, with a few exceptions that were highlighted early on. The scope of the review covers both monovalent VHL binders as well as VHL ligands used in bivalent binders, such as PROTACs and antibody-drug conjugates (ADCs). Where possible, biological data associated to the reported compounds was also reported, so that key structure-activity relationships (SAR) could be extracted despite the heterogenous nature of patents.

The review was structured by breaking down the **VHL chemotype into 6 key regions** (*above*) so that the reported modifications could be clustered by the relevant region where the change had taken place. Some regions had extensive reported changes, such as the LHS amide and phenyl group, whilst others had only limited reported modifications, such as the hydroxyproline core. The review also **highlighted some emerging trends in combatting the potential drawbacks of VHL ligands**, such as the introduction of solubilising groups at the solvent-exposed benzylic position and the bioisosteric replacement of both the LHS and RHS amides with heterocycles. Overall, this review shows that there is still considerable interest in VHL-based therapeutics, especially from (bio)pharmaceutical companies.

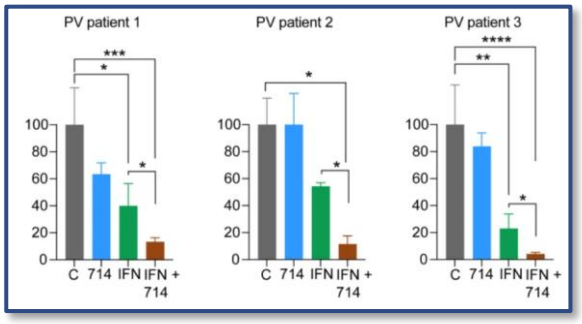
"Writing this patent review was both tough and rewarding! Whilst trying to extract data from >100 patents in a clear and cohesive way was a challenge, the end result is a valuable resource for the community and should help to guide future developments in the next generation of VHL-based therapeutics." – Alex H.

| *Dylan*

Loss of *Socs2 improves molecular responses to IFNa in a mouse model of myeloproliferative neoplasms driven by JAK2-V617F*

*Mar Usart ,…, Radek C. Skoda**
Nature Leukemia ***2025****, 39, 876–887*

CeTPD authors: Dylan Lynch, Nikolai Makukhin, Alessio Ciulli



In this paper, **the role of SOCS2 (suppressor of cytokine signalling 2) in modulating responses to pegylated interferon alpha (pegIFNa) is investigated.** PegIFNa induces a therapeutic response in a subset of patients with myeloproliferative neoplasms (MPN), a group of rare blood cancers that originate in the bone marrow. The authors identified that SOCS2 deletion in JAK2-V617F mutant mice results in an increased sensitivity to cytokines, and that subsequent pegIFNa treatment enhanced the depletion of JAK2-mutant hematopoietic stem cells in the case of SOCS2 deletion. These findings, in the first part of the paper, demonstrate that ablation of SOCS2 enhances the effectiveness of pegIFNa. The authors then used the SOCS2 inhibitor MN714, designed and synthesised in CeTPD, in combination with IFNa (Fig. 1). This displayed better efficacy than IFNa alone in reducing CD34+ cells from patients with polycythaemia vera (PV) in vitro. Overall, this poises inhibition of SOCS2 as a possible method to improve these deep molecular responses to pegIFNa in MPN patients with JAK2-V617F mutations.

| *Andreas*

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Discovery of a CNS active GSK3 degrader using orthogonally reactive linker screening

*Andreas Holmqvist,§ Nur M. Kocaturk,§ …, William Farnaby**

CeTPD authors: Andreas Holmqvist, Nur M. Kocaturk, Kristiina Juvonen, William Farnaby

In this first preprint from the **Farnaby Lab**, the team developed a **direct-to-biology (D2B)** screening approach using orthogonally reactive linkers to enable the discovery of a CNS-active degrader of glycogen synthase kinase 3 (GSK3), a long-standing and challenging neurological target. Using this approach, the team identified a **potent**, **selective**, and **rapid degrader of GSK3α and GSK3β** in cells, which exhibited broad kinome selectivity, and *in vivo* CNS degradation, showcasing the power of this approach for advancing brain-penetrant targeted protein degraders.

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Centre for Targeted Protein Degradation
School of Life Sciences
1 James Lindsay Place,
Dundee,
DD1 5JJ

Journal club – website

@alessiociulli @Farnaby84 @FarnabyLab @UoDCeTPD @DeLaCuadraBaste @Holmqvist89