CeTPD Journal Club

December 2025 – January 2026

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

Centre for Targeted Protein Degradation
University of Dundee

innovate
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MEET THIS MONTH'S EDITORS

Click here for info on the editor

ALESSANDRA SALERNO

Alessandra obtained her MSc degree in Chemistry and Pharmaceutical Technologies from the University of Bologna in 2019, followed by a PhD from the same institution in 2023, during which she undertook several research stays abroad. She moved to Dundee on two occasions: first in June 2022, when she joined the Ciulli Group for six months as a visiting PhD student to expand her expertise in the PROTAC field, and again in June 2023, when she began her postdoctoral research after being awarded a Marie Curie Individual Fellowship. In her spare time, she enjoys travelling, reading, and photography, and she is also responsible for editing every issue of this journal club.

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RUBÉN PRIETO DÍAZ

Rubén graduated with a degree in Pharmacy and a Master's in Drug R&D from the University of Santiago de Compostela. He completed his PhD in 2023 in the group of Prof. Sotelo, focusing on multicomponent chemistry applied to the design of small molecules. After a short postdoctoral stint at Uppsala University, he was awarded a postdoctoral fellowship by the Xunta de Galicia. In January 2025, he joined Alessio's group as part of his fellowship. Outside of the lab, Rubén enjoys traveling, reading, and playing basketball.

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ZHER YIN TAN

Zher Yin obtained his PhD in Chemistry at Harvard University under the co-supervision of Prof. Ramnik Xavier and Prof. Stuart Schreiber, where he worked on leveraging novel chemical biology tools to discover autophagy modulators. He joined CeTPD in 2025 where he works on discovering molecular glues to tackle Parkinson's Disease. In his free time, he enjoys playing badminton and listening to music.

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ALEX HALLATT

Alex obtained his MChem at Newcastle University in 2019, which included a 12-month placement at GSK, Stevenage. He then stayed at Newcastle University to obtain his PhD in 2023, working with Dr. Celine Cano and Prof. Mike Waring to develop heterobifunctional degraders of the metabolic target, glucokinase. Alex has been working in the Ciulli Group at CeTPD since 2023, first working on degraders using weak affinity ligands and more recently as part of the LITE initiative focusing on degrading the high-interest Parkinson's Disease target, LRRK2. Alex is also a board member of the EFMC Young Scientist Network (YSN) which aims to foster collaboration and training between young European med chemists and chemical biologists.

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TARGETED PROTEIN DEGRADATION

CHEMISTRY | STRUCTURAL BIOLOGY & BIOPHYSICS | CELL BIOLOGY | MODELLING

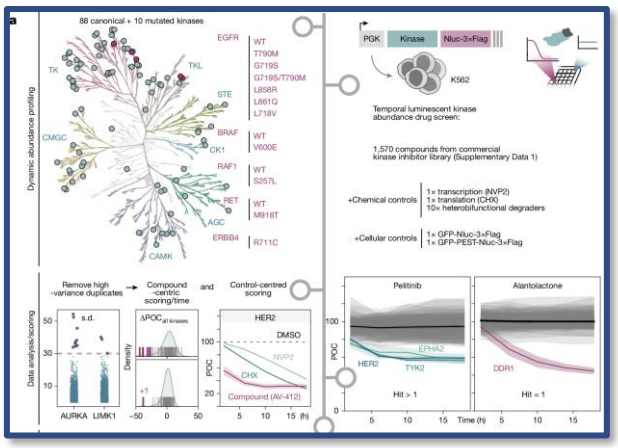
"Every two months, we spotlight the latest and most significant literature in the field of targeted protein degradation, spanning chemistry, biophysics, cell biology, and computational modelling"

Literature review from 21st November to 20th January 2026

| *Zher Yin*

Inhibitors supercharge kinase turnover through native proteolytic circuits

Natalie S. Scholes, ..., Georg E. Winter*
Nature ***2026****, 649, 1032–1041*



It has been observed that kinase inhibitors could lower target protein levels. To better understand this, the authors developed a bioluminescence platform to study various proteins and kinase inhibitors. They produced a dataset to profile kinases and their mutants and found trends that influence inhibitor-mediated kinase destabilisation.

HSP90-mediated protein degradation has been explored as a new approach for protein degradation, and the authors followed up on three kinases that are degraded with different extent of interactions with HSP90. While TAK285-mediated degradation of BLK is sensitive to HSP90 inhibition, the authors showed that TAK285 dissociates BLK to the cytoplasm where it is less stable, leading to lowered BLK levels. The stabilities of the other two proteins that were investigated were not sensitive to HSP90, but the authors demonstrated the mode of degradation for them through different E3 ligases or through the lysosome.

This paper is a great resource for groups interested in kinases and highlights that the modes of action for kinases are not restricted to just enzymatic inhibition. It also combines high-throughput profiling with deep mechanistic studies to illuminate possible biological activities arising from simple enzymatic inhibition. There are many takeaways possible from this dataset, for example, how mutations affect stability, novel degradation machinery dependent on phosphorylation states, or possibilities of inhibitors acting as molecular glues. This study invites more in-depth characterisation of any kinase inhibitors, which might lead to exciting, unexpected discoveries.

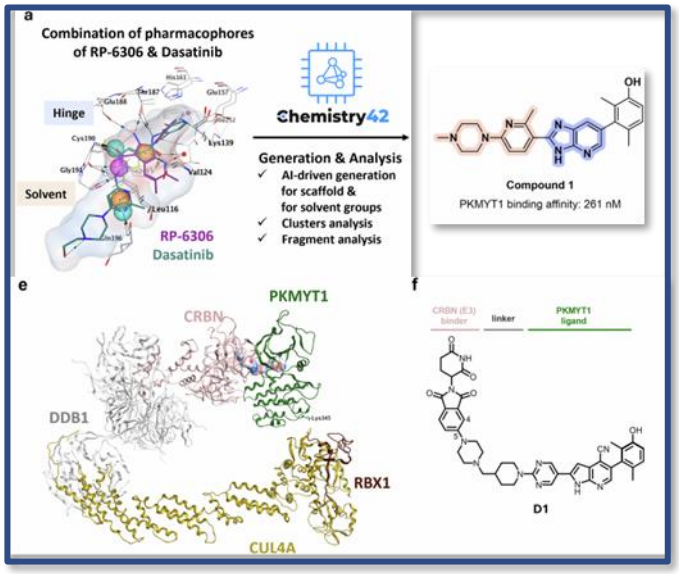
| Zher Yin

Discovery of a bifunctional PKMYT1- targeting PROTAC empowered by AI generation

Yazhou Wang§, Xiaomin Wang§, Tingting Liu§, …, Xin Cai*, Xiao Ding*, Alex Zhavoronkov*

Nat. Commun. ***2025*** *16(1), 10759-10776*

Discussed internally



The authors employed the Generative AI tool Chemistry42 to design a new PKYMT1 inhibitor based on pharmacophores of known inhibitors, prioritising synthetic ease and predicted off-target selectivity. The designed inhibitor was optimised for PK properties, and the top candidate was incorporated into CRBN-recruiting PROTACs using computational modelling of the ternary complex using MOE and Generative AI. The PROTAC was further optimised through linker exploration, resulting in a compound with improved degradation and selectivity, and prolonged inhibitory activity compared to the parent ligand. The authors also performed necessary control experiments to validate the mechanism of action.

Their mouse studies demonstrated degradation of PKYMT1 and inhibition of the downstream pCDK1 *in vivo*. Surprisingly, when dosed to similar pCDK1 inhibition levels, the parent inhibitor displayed superior antitumour activity compared to the PROTAC, possibly attributed to off-target effects. Overall, this study showcased the incorporation of Generative AI in the hit-finding and optimisation process, and invites further examination of PKYMT1 as a drug target.

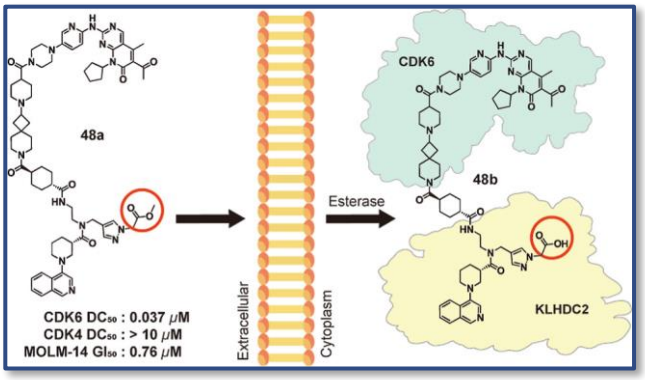
As AI tools advance, it is always interesting to assess their applications in the drug discovery process. While the authors discovered a potent and selective inhibitor and degrader using Generative AI, it is important to consider the novelty of the structures, especially comparing it to the parent compounds. The paper used traditional medicinal chemistry optimisation to explore linkerology after their initial design, which perhaps points towards limitations of Generative AI in this context, highlighting the importance of synthesising and testing analogues. The continual evolution of application of AI in the drug discovery process will be followed with great excitement.

| *Alex*

Selective CDK6 Degradation via the KLHDC2 E3 Ubiquitin Ligase

Eunhye Jeon§, Younghoon Kim§, Hyunwoo Ahn§, …, Nathanael S. Gray*, Taebo Sim*
J. Med. Chem. ***2025***, *68, 25539−25568*

Discussed internally



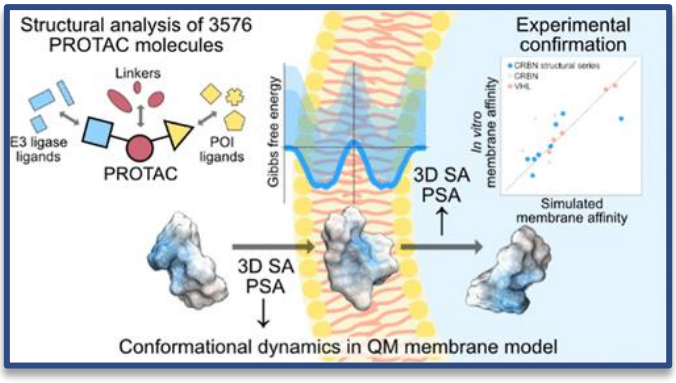
In this study the authors use a combination of computational and empirical methods to develop a new series of ligands for the E3 ligase KLHDC2. The new ligands were inspired by the natural KLHDC2 substrate, the C-terminal degron Ala-Gly-Gly motif, and a handful of existing KLHDC2 ligands from Arvinas and Kymera. These ligands were then used to synthesise a library of bifunctional molecules based on the CDK4/6 inhibitor, Palbociclib. A series of degraders which showed preferential degradation of CDK6 over CDK4 was optimised further by refinement of the KLHDC2 binder and the linker. These tool compounds selectively degraded CDK6 in various leukaemia cell lines, which was nicely validated by global proteomics, and showed greater tumour growth inhibition than palbociclib and a comparable CRBN-based CDK6 degrader in a mouse xenograft model.

This work does a great job of setting the scene and showcasing the current state-of-play of KLHDC2 ligands before demonstrating its findings and reminds us that the toolbox of recruitable E3 ligases certainly goes beyond CRBN and VHL. It would have been nice to see how the linkerology was optimised to favour this rigid linker in particular, as well as how the compounds might be further developed to achieve greater efficacy and oral bioavailability.

| *Alessandra*

Conformational Dynamics in the Cell Membrane Interactions of Bispecific Targeted Degrader Therapeutics

Emma Inganäs...Pär Matsson**
J. Med. Chem. **2025**, 68, 24, 25881–25898



This study explores how PROTAC molecular design influences interactions with cellular membranes by combining large-scale data analysis with advanced computational modelling. The authors first analysed PROTAC large 2D molecular descriptors and then used 3D conformational sampling to investigate environment-dependent polarity in aqueous and membrane-like conditions. The results show that PROTACs can shield polar surface area in membrane environments through conformational folding, a process driven primarily by

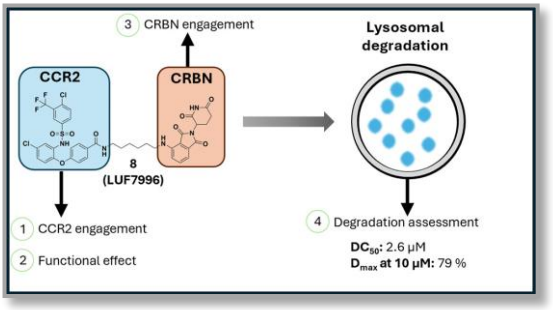
linker flexibility. Importantly, overall molecular folding was found to be more influential than linker folding alone in reducing exposed polarity and promoting membrane interaction.
A key strength of the work is the validation of COSMO-based computational predictions using an established experimental membrane-binding platform, demonstrating a strong correlation between predicted computational interaction energy minima and experimental data. The validated model was subsequently applied to a larger dataset to link membrane affinity with physicochemical properties such as logP and PSA, and to compare linker- and E3 ligase-dependent effects across paired compounds.

While the field is still debating the most effective strategies to understand and improve PROTAC cellular permeability, this study provides valuable insights into PROTAC–membrane interactions and highlights opportunities for rational permeability optimisation through balanced linker and E3 ligand design.

| *Rubén*

Leveraging Targeted Protein Degradation for G Protein-Coupled Receptors: The Development of CCR2 Molecular Degraders

Khaled Essa§, Natalia V. Ortiz Zacarías§, …, Daan van de Es,* Laura Heitman*
J. Med. Chem. **2025**, 68, 24, 26525–26546



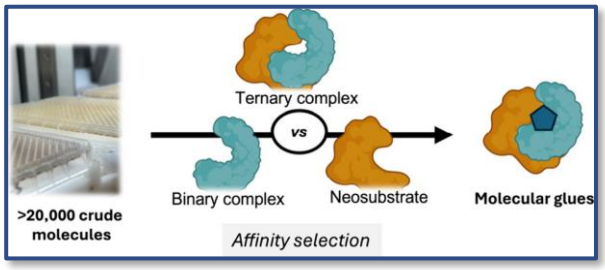
This paper explores the application of targeted protein degradation to G protein-coupled receptors, a major class of membrane proteins and drug targets, focusing on CCR2 as a pharmacologically relevant example. Using an intracellular allosteric CCR2 ligand as the POI binder, the authors design a series of CCR2 degraders by linking this ligand to different E3 ligase recruiters through varied linker architectures.
Among the compounds tested, CRBN-recruiting degraders show sustained and concentration-dependent degradation of CCR2, with LUF7996 emerging as the most effective example. Mechanistic studies indicate that CCR2 degradation proceeds through a lysosomal, rather than proteasomal one, consistent with known GPCR trafficking and turnover mechanisms. Importantly, the authors demonstrate degradation of endogenous CCR2 and show that compound 8 (LUF7996) effectively inhibits CCL2-induced monocyte migration, providing functional validation in a disease-relevant cellular context. The study is supported by a comprehensive workflow combining target engagement, functional assays and real-time degradation measurements.

What makes this study particularly interesting is that it shows how targeted protein degradation can be extended to GPCRs by exploiting intracellular allosteric binding sites. Although such ligands are not trivial to identify, the work provides a clear and practical framework for driving lysosome-dependent degradation of an endogenous membrane receptor and linking molecular design to functional cellular outcomes.

| *Zher Yin*

Direct-to-Biology Enabled Molecular Glue Discovery

Maowei Hu…Daniel J. Blair*
J Am Chem Soc ***2026****, 148, 1, 20–27*



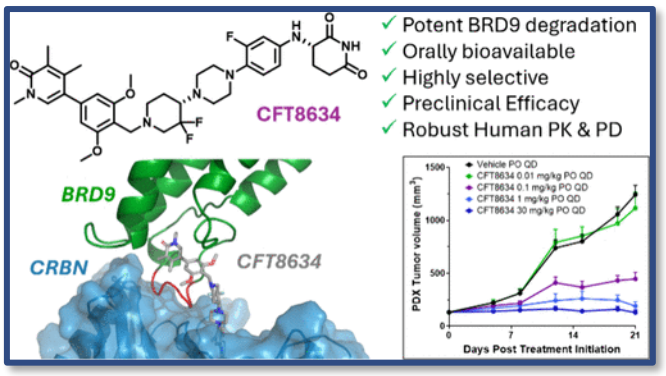
Affinity Selection Mass Spectrometry (ASMS) is emerging as a powerful technique to screen for binders. In this study, the authors extended ASMS to screening for molecular glues using SEC followed by LC-MS, based on the diminished rates of dissociation of ternary complexes. After verifying their system could enrich for ternary complexes over binary complexes using well-established molecular glues, they employed High Throughput Chemistry and Direct-to-Biology (HTC-D2B) to generate and test pools of MS/MS barcoded compounds. This resulted in submicromolar potency molecular glue degraders of LCK comprising of novel chemical matter. Overall, this study highlights a successful example of using ASMS and HTC-D2B to discover molecular glues, which improve the efficiency of identifying new molecular glues.

Discovering novel molecular glues is no easy task. Many groups have tackled this challenge using various approaches, from array-based screening with purified compound libraries, to pooled screening of enormous libraries such as the case of DNA-encoded libraries. ASMS combined with HTC-D2B taps on the strengths of both approaches, assessing large library sizes through pooled screening, yet allowing QC for individual molecules. Overall, this study provides a nice proof-of-concept using ASMS to discover glues, and hopefully more applications will soon follow.

| *Alessandra*

Discovery of CFT8634, a Potent, Selective, and Orally Bioavailable Heterobifunctional Degrader of BRD9

Katrina L. Jackson* et al.
J. Med. Chem. ***2025****, 68, 23, 24848–24868*



BRD9 has emerged as a promising target for targeted protein degradation, as bromodomain inhibition alone does not induce synthetic lethality in synovial sarcoma or MRT cells, with BRD9 retaining chromatin access *via* an alternative domain. To address the unmet need, C4 Therapeutics developed a selective, orally bioavailable heterobifunctional degrader of BRD9. The team's efforts applied a classical three-part optimisation strategy: modifying the CRBN-binding moiety to reduce metabolic liabilities and off-target effects, refining linker chemistry, including linker excision strategies and halogen substitutions to tune lipophilicity and clearance, and adjusting the POI scaffold to optimise physicochemical properties such as TPSA and hydrogen-bonding.

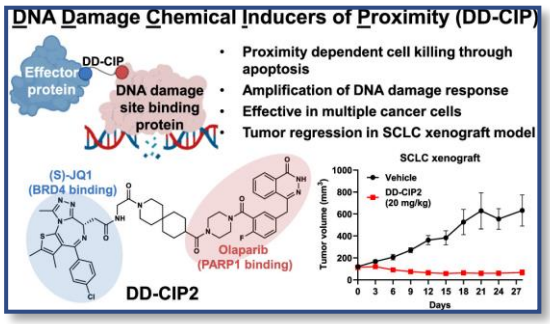
Structural and HDX-MS studies underscored the importance of stereochemistry and linker design in achieving isoform-selective degradation, with only one of four stereoisomers advancing based on PK, selectivity, and CYP3A4 profile. The optimised compound, CFT8634, demonstrated robust proteomic selectivity, favourable *in vivo* pharmacokinetics, and activity in cell and patient-derived models, advancing to a Phase 1 clinical trial. While clinical data confirmed oral bioavailability and target engagement, BRD9 degradation alone produced modest efficacy, highlighting the need for a polypharmacological approach, and unexpected cardiac toxicities curtailed the further advancement.

Despite the lack of a resolved ternary complex structure, this campaign demonstrates how rigorous ligand-based SAR can drive the development of heterobifunctional degraders toward clinical application. The work illustrates the challenges of translating preclinical models to humans, providing valuable lessons for medicinal chemists. A must-read example of how careful optimisation can guide and advance complex degrader programs.

| *Rubén*

Design and Development of DNA Damage Chemical Inducers of Proximity for Targeted Cancer Therapy

Tian Qiu§, Yeuan Ting Lee§, …, Nathanael S. Gray*
J. Am. Chem. Soc. ***2026,*** *148, 1, 1153–1163*



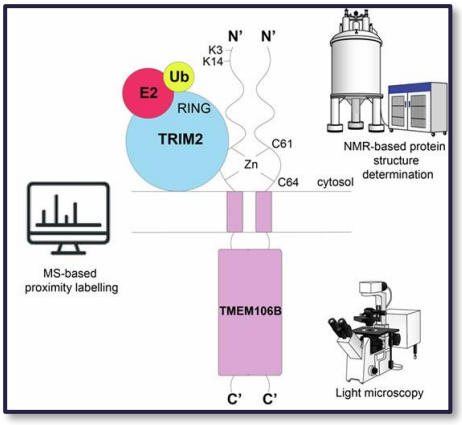
This paper reports the design and development of DNA damage chemical inducers of proximity (DD-CIPs), bivalent small molecules that rewire the DNA damage response by inducing proximity between PARP1/2 and the chromatin regulator BRD4. By covalently linking PARP inhibitors to a BRD4 ligand the authors establish a proximity-driven mechanism that is distinct from classical PARP inhibition or dual PARP/BRD4 blockade.
The study shows that DD-CIPs induce formation of a PARP–BRD4 complex, triggering DNA damage signalling, cell cycle arrest and apoptosis. A focused linker optimisation leads to DD-CIP2, a metabolically improved compound with nanomolar activity across a broad range of blood and solid cancer cell lines, including homologous recombination–proficient models. The strength of the work lies in the combination of detailed mechanistic studies with solid in vivo validation, showing significant tumour regression in a small-cell lung cancer xenograft model at well-tolerated doses.

The study nicely illustrates how careful linker design can be used to fine-tune proximity and downstream biology. The connection between molecular design, induced PARP–BRD4 proximity and DNA damage signalling is very well established.

| *Alessandra*

TRIM2 E3 ligase substrate discovery reveals zinc-mediated regulation of TMEM106B in the endolysosomal pathway

Cecilia Perez-Borrajero… Janosch Hennig*
EMBO Rep. ***2025****, doi: 10.1038/s44319-025-00667-3*



This study focuses on identifying native cellular interactors of the mammalian E3 ubiquitin ligase TRIM2 by employing a proximity-labelling strategy that selectively biotinylates nearby ubiquitinated substrates, building on the previously described BioE3 approach (*Nat Commun* 14, 7656, **2023**). By adapting this recently developed ubiquitin-specific proximity-labelling tool, the authors were able to systematically identify TRIM2 substrates directly in cells.
Using this approach, the study reveals that TRIM2 preferentially targets proteins associated with the endolysosomal pathway including TMEM106B. Through an integrated set of biochemical and structural experiments, including in vitro ubiquitination assays and NMR spectroscopy with ^{15}N-labelled TMEM106B, the authors demonstrate that TRIM2 ubiquitinates TMEM106B at lysine residues within its cytosolic *N*-terminal region. Substrate recognition is mediated by a direct interaction between TRIM2 and a newly identified zinc-coordination motif in TMEM106B. This motif promotes homodimerization, enables specific protein–protein interactions, and plays a key role in regulating lysosomal size.

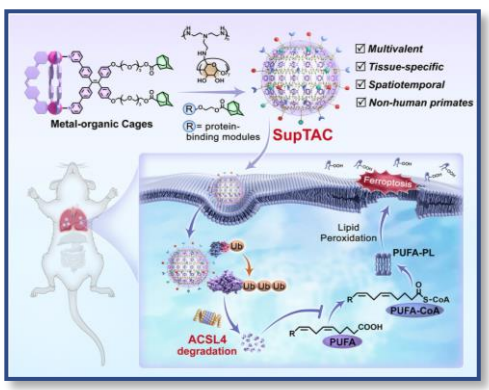
A major challenge in elucidating E3 ubiquitin ligase function is the comprehensive identification of their cellular substrates, degrons, and recognition motifs, a task complicated by the highly transient nature of ubiquitination within signalling complexes. This work demonstrates how ubiquitin-focused proximity-labelling strategies can overcome these limitations, enabling deeper insights into the biology of underexplored E3 ligases and their roles in cellular homeostasis.

| *Rubén*

Multimodal supramolecular targeting chimeras enable spatiotemporally resolved protein degradation *in vivo*

Ji Liu… Ming Wang*
Cell ***2026.*** doi.org/10.1016/j.cell.2025.12.007

Discussed internally



This paper describes the development of supramolecular targeting chimeras (SupTACs), a platform designed to achieve spatiotemporally controlled protein degradation *in vivo* without relying on classical covalently linked bifunctional degraders.
SupTACs are assembled through non-covalent interactions between adamantane-modified ligands and β-cyclodextrin-based nanoparticles, enabling multivalent co-presentation of E3 ligase recruiters and target-binding ligands. Using this approach, the authors demonstrate

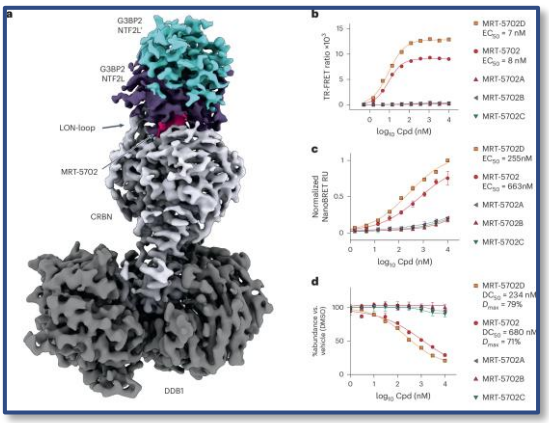
efficient proteasome-dependent degradation of several targets, including BRD4, MEK and ACSL4. A key result is the ability to bias degradation toward specific tissues *in vivo* by tuning nanoparticle properties and exploiting protein corona effects. The study further introduces chemically caged SupTACs, allowing temporal control of degradation through bioorthogonal activation. In addition, the system is shown to support proximity-induced phosphorylation, illustrating that the platform is not limited to degradation.

This paper presents a very solid and well-executed study, with carefully designed experiments that clearly support the authors' conclusions. The extensive *in vitro* and *in vivo* validation, including several species, together with a clear mechanistic rationale, makes the work convincing and very well grounded.

| *Alex*

Cereblon induces G3BP2 neosubstrate degradation using molecular surface mimicry

Stefano Annunziato§, Chao Quan §, Etienne J. Donckele§, …, Pablo Gainza*, Georg Petzold*
Nat. Struct. Mol. Biol. **2026** doi.org/10.1038/s41594-025-01738-8



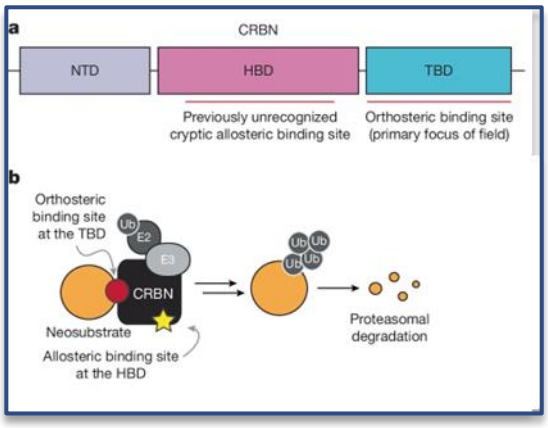
This paper from workers at Monte Rosa describes the identification of the cereblon (CRBN) neosubstrate, G3BP2, which lacks the canonical G-loop degron motif typically found in CRBN neosubstrates. Building on from previous work, which mapped CRBN target space by computational mining of the human proteome for potential G-loop degron mimetics, unbiased global proteomics was used to screen for new CRBN-based molecular glue degraders. Compound MRT-5702 was identified, which reduced G3BP2 levels in a neddylation-, proteasome- and CRBN-dependent manner. A blend of biochemical, computational and structural methods was used to elucidate the rationale behind G3BP2 recruitment despite lacking the key degron motif. The authors demonstrate that when MRT-5702 binds to CRBN, the CRBN surface mimics USP10, a natural interactor of G3BP2, and that this mimicry is what drives the CRBN-G3BP2 interaction.

Another paper from Monte Rosa showcasing that G-loops are not essential for cereblon recruitment and that the plasticity of cereblon is likely to explain why it is able to degrade so many neosubstrates. I particularly liked the hypothesis that the G-loop interacting region is only a small fraction of the >1,000 Å² extended PPI hotspot of CRBN^{closed} and that perhaps the full potential of cereblon recruitment is yet to be discovered with new degron motifs beyond the G-loop.

| Alex

Identification of an allosteric site on the E3 ligase adapter cereblon

Vanessa N. Dippon§, …, Andrew B. Benowitz*, Christina M. Woo*
Nature, **2026**, doi.org/10.1038/s41586-025-09994-w



This paper describes the discovery of SB-405483, a novel ligand for the E3 ligase cereblon (CRBN) which binds to a previously unknown cryptic allosteric site in the helical bundle domain (HBD). This novel compound was discovered serendipitously during a HTS campaign to find new orthosteric ligands but where a gain-of-signal was observed during screening by TR-FRET instead of the expected loss-of-signal. After ruling out assay interference, direct binding to cereblon was validated using affinity selection mass spectrometry (AS-MS). The allosteric nature of SB-405483 was confirmed by biochemical methods and by a cocrystal structure of it bound to the CRBN-DDB1 complex alongside lenalidomide in the thalidomide-binding domain (TBD). The authors then go on to show that SB-405483 can modulate neosubstrate recognition when >100 orthosteric ligands are each bound at the CRBN TBD interface, and that this can either potentiate or inhibit their neosubstrate degradation. The paper concludes with strong structural evidence for the molecular mechanism of action, suggesting that SB-405483 binds to CRBN during a previously unobserved intermediate state (CRBNint) and then promotes the closed conformation (CRBNclosed) which enhances orthosteric ligand binding.

Yet another CRBN tour-de-force from the group of Christina Woo, this time in collaboration with GSK, using a variety of in vitro and cellular methods to validate and profile the first allosteric ligand for CRBN and to structurally interrogate its binding site and mechanism of action. This work opens the door to aid molecular glue discovery and to show the importance of following up on surprising assay outcomes… you never know what you might find!

PRE-PRINTS

| *Alex*

A unified platform for the rapid assembly of glutarimides for Cereblon E3 ligase modulatory drugs

David M. Whalley*, Olivier Lorthioir*, ..., Alfie Woodhouse

This pre-print describes the development of a platform for the rapid synthesis of glutarimides, such as CRBN binders, with a particular focus on high-throughput experimentation (HTE) which although not explicitly demonstrated, could be coupled with direct-to-biology workflows. Interestingly, while most approaches for the synthesis of ImiDs focus on the disconnections exocyclic to the glutarimide motif, this approach involves the late-stage formation of the glutarimide ring using a sequence of organocatalysed C–N bond formation, metal-free Giese addition and acid-mediated cyclisation.

| *Alessandra*

Design of Tissue-Selective PROTACs Through Recruiting E3 Ligase Scaffolding Protein MAGEA11

Isabella E. Jacobsen...William C.K. Pomerantz* and Gunda I. Georg*

This pre-print highlights the potential of tissue-specific E3 ligases in targeted protein degradation. The authors report the first PROTAC recruiting the cancer-restricted E3 ligase scaffolding protein MAGEA11 to degrade BET proteins. Notably, the degrader shows no activity in non-cancerous, MAGEA11-deficient HEK293T cells, demonstrating tumour-specific selectivity. This work underscores the promise of exploiting tissue-specific ligases for precision degradation. It remains to be explored how broadly MAGEA11-mediated degradation can be applied beyond bromodomain proteins.

| *Rubén*

Discovery of Non-Degradative Covalent Molecular Glues for Transcriptional Reprogramming

Tuong Nghi Duong, ..., Daniel K. Nomura*

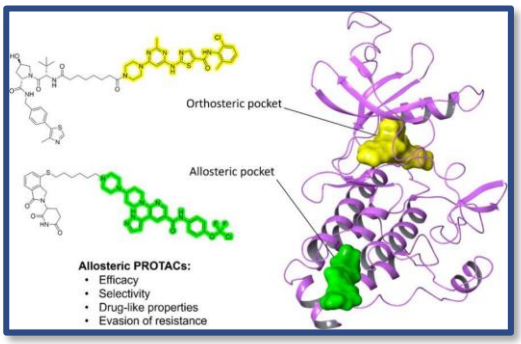
This preprint reports the discovery of non-degradative covalent molecular glues that rewire transcription through induced proximity rather than protein degradation. Using an electrophile-enabled, chemoproteomics-guided approach, the authors identify a BCL6-based molecular glue that recruits BRD9, leading to suppression of MYC transcription and derepression of BCL6 target genes in lymphoma models.

PAPERS AND PRE-PRINTS FROM CeTPD

| *Suzanne*

Allosteric PROTACs:Expanding the Horizon of Targeted Protein Degradation

Aileen Frost§, Suzanne O'Connor§ and Alessio Ciulli*
J. Am. Chem. Soc. ***2026****. https://doi.org/10.1021/jacs.5c14840*



A key promise of PROTACs is that proximity alone —not inhibition— is required, allowing binding anywhere on the protein surface to trigger degradation. Yet despite this conceptual freedom, most PROTACs to date have been built from orthosteric inhibitors. The use of allosteric or functionally silent ligands remains a largely untapped opportunity. In this Perspective, we spotlight pioneering efforts in allosteric PROTAC design and explore how such strategies could unlock improved outcomes for target selectivity, efficacy, and resistance management while also modulating physicochemical properties to enhance *in vivo* performance. We further discuss the practical and conceptual challenges and the advances needed to make allosteric targeting a mainstream strategy in the design of protein degraders and other proximity-inducing molecules.

| *Zher Yin*

bioRχiv

Linker-rigidified VHL homodimerizers convert degraders into stabilizers of non-ubiquitinable ternary complexes

Charlotte Crowe…Alessio Ciulli*

CeTPD authors (past and present): Charlotte Crowe, Alessandra Salerno, Gajanan Sathe and Alessio Ciulli

This paper describes a cryo-EM structure of the CRL2VHL E3 ligase dimerised by the VHL homo-PROTAC CM11. Guided by this structure, the authors designed side-by-side, linker-rigidified VHL homodimerisers that bias the relative VHL orientation away from the E2~Ub active site, contrasting the flexible, head-to-head PEG linkage of CM11. Biophysical binding and in vitro ubiquitination assays show that these compounds form stable, long-lived and compact ternary complexes that are incompatible with VHL cross-ubiquitination. In cells, the compounds stabilise VHL and concomitantly inhibit it to elevate HIF-1a levels. The authors show that a stable ternary complex can be non-productive for ubiquitination, and linker architecture can reprogram degraders into stabilisers by controlling target ubiquitinability.

| *Zher Yin*

Induced ubiquitination of the partially disordered Estrogen Receptor alpha protein via a 14-3-3-directed molecular glue-based PROTAC design

Carlo J.A. Verhoef§, Charlotte Crowe§, …, Alessio Ciulli*, Peter Cossar*

CeTPD authors (past and present): Charlotte Crowe, Mark A. Nakasone, Aitana DeLaCuadra-Basté, Tessa Harzing, Gajajan Sathe, Kentaro Iso, Alessio Ciulli and Peter Cossar

This paper describes the development and biophysical/biochemical characterisation of a molecular glue-based PROTAC (^{MG}PROTAC). This molecule conjugates a fusicoccin molecular glue stabiliser to a VHL-recruiting ligand to capture and ubiquitinate the 14-3-3/estrogen receptor alpha complex.

| *Zher Yin*

Native Mass Spectrometry Analysis of a Cullin RING Ubiquitin E3 Ligase Complex in the Context of Targeted Protein Degradation

Louise Sternicki§… Sally-Ann Poulsen*

CeTPD authors (past and present): Charlotte Crowe, Lianne H. E. Wieske and Alessio Ciulli

This paper establishes conditions and methodology to analyse and interpret native mass spectrometry (nMS) of the full-length pentameric E3 ligase CRL2VHL in complex with MZ1/Brd4BD2 and ACBI3/KRAS and recruiting the ubiquitin-loaded E2 UBE2R1. The authors characterise binary, ternary and higher order complexes productive for neo-substrate ubiquitination and degradation.

| *Suzanne*

Tuning the open-close equilibrium of Cereblon with small molecules influences protein degradation

Suzanne O'Connor §, Zoe J. Rutter §, …, Kirsten McAulay*, Theodor Theis*, Alessio Ciulli*

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Upon binding ligands and molecular glues, CRBN undergoes a significant structural rearrangement from an open to closed state, defined by the positioning of the thalidomide-binding domain (TBD) with respect to the Lon domain. However, the exact molecular basis for this ligand-induced conformational change and its implication to neo-substrate degradation remain elusive. During our campaign to discover novel CRBN binders, we identified CRBN binders that either induce CRBN closure or do not and profiled them using various biophysical techniques. Our study reveals new molecular insights into the structural basis for how CRBN open-closed equilibrium is directly modulated by compound binding and impacts target degradability by CRBN, with important implications to the design of PROTACs and molecular glue degraders.

OTHER PAPER HIGHLIGHTS

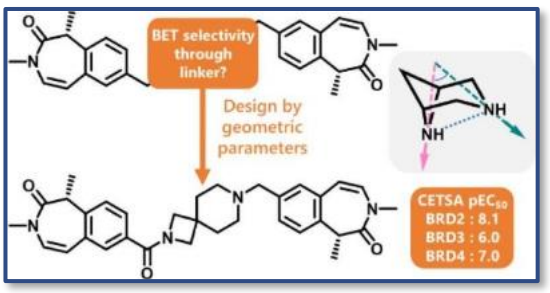
CHEMISTRY

MODELLING

| *Alex*

BET Isoform Selectivity through Diverse Linkers for Bivalent Inhibitors: GSK785, a BRD2/4-Selective Bivalent BET Inhibitor

Francesco Rianjongdee§ et al.*
J. Med. Chem. ***2026****, 69, 895−917*



This paper describes the rational design of GSK785 as a bivalent dual BRD2/4- BET inhibitor with unprecedented selectivity over the highly-conserved isoform, BRD3. Bivalent ligands can simultaneously bind to both the BD1 and BD2 domains of BET proteins, and the authors hypothesised that isoform selectivity could be achieved by using a rigidified linker that bears the optimal length and angular vectors for BRD2 and BRD4, whilst being an unfavourable geometry for BRD3. To this end, a series of bivalent inhibitors bearing conformationally restricted diamines (CRDAs) were synthesised via a diversity-orientated approach and led to the discovery of GSK785 (see Figure).

Although not a TPD paper in its own right, the design and synthetic considerations of bivalent inhibitors can translate quite nicely into the development of bivalent degraders. I think the approach utilised in this paper provides a nice framework for how next-generation bivalent degraders could be rationally designed, synthesised and evaluated to maximise the efficiency of linkerology. Additionally, achieving isoform selectivity for bromodomains which share such high homology between isoforms is no small feat!

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