



CeTPD Journal Club

August – September 2026

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



Centre for Targeted
Protein Degradation
University of Dundee

innovate
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TABLE OF CONTENTS

MEET THIS MONTH'S EDITORS	1
TARGETED PROTEIN DEGRADATION	1
De Novo-Designed Bifunctional Proteins for Targeted Protein Degradation	1
Bram Mylemans, ..., Derek N. Woolfson*	
J. Am. Chem. Soc. 2026 , 148 (32), 34311–34319.	
Generalizable Strategies for the Synthesis of Cereblon-Recruiting PROTAC Prodrugs	2
Aiden X. Wang, ..., Jeremiah A. Johnson*	
Angew. Chem. Int. Ed. 2026 , 65 (40), e3238473.	
Engineering Nonpathogenic Bacteria for Synergistic Tumor-Targeted Protein Degradation and Immunotherapy by Checkpoint-Inhibiting Nanobodies	2
Xingping Hu [§] , Yu Chen [§] , ..., Jinghua Ren*, Hongwei Duan*	
J. Am. Chem. Soc. 2026 , 148 (32), 34393–34405.	
Discovery of Highly Potent and Selective, Orally Bioavailable BTK-Targeting PROTACs Featuring Novel CRBN-Binding Warheads	3
Alexey B. Mantsoyov*, ... , Alex Zhavoronkov*	
J. Med. Chem. 2026 , 69 (17), 20494–20519.	
Structure-Guided Optimization of a Molecular Glue Targeting the KBTBD4-HDAC1/2 Complex	4
Timea Baló, ..., Andras Kotschy*	
Chem Med. Chem. 2026 , 21, 16, e70451.	
Click-Activated Supramolecular Targeting Chimeras for Spatiotemporally Resolved Protein Degradation <i>In Vivo</i>	4
Yongsong Zhang, Ji Liu, Tianyu Ma & Ming Wang*	
Angew. Chem. Int. Ed. 2026 , e2233329.	
TRI-611, a selective, brain-penetrant molecular glue degrader of ALK	5
Andrew R. Conery, Daniel S. La, ..., Vito J. Palombella*	
Nature 2026 , 658, 241–249.	
Linker Optimization of cMYC RIBOTAC for Efficient cMYC Modulation	6
Sivakumar Komachankandy, Jinseo Heo, Yerin Kim, Wonpil Im, Yeongju Lee*	
Chem Med. Chem. 2026 , 21, 18, 1860-7179.	
Blood-Brain Barrier-Permeable Macrocyclic Chimeras (BmTACs) for Targeted Protein Degradation in the Aging Brain	6
Licong Peng, Qihang Li, Zhizhi Li, Guozhen Bai, Yuan Tian,* Shaobing Zhou*	
J. Am. Chem. Soc. 2026 , 148 (38), 41137–41150.	
Discovery of Potent and Selective VHL-Recruiting PROTAC Degraders Targeting EGFR with Improved Developability and Potent Anti-NSCLC Efficacy	7
Xiang Ni, ..., Kuojun Zhang*	
J Med. Chem. 2026 , DOI: 10.1021/acs.jmedchem.6c01893.	
A 2-in-1 Strategy for the Discovery of Compact HDAC8 Protac Degraders	8
Yi Liu [§] , Nikee Awasthee [§] , Yufeng Xiao [§] , ..., Daiqing Liao*, Guangrong Zheng*	
J. Med. Chem. 2026 , 69 (18): 21381–21397.	
PRE-PRINTS	9
Direct-to-Biology Bifunctional Screening Reveals Noncanonical Mechanisms of Targeted Protein Degradation	9
Clara Gathmann, ..., Christopher G. Parker*	
Reprogramming VHL with molecular glues enables selective degradation of caspase-2	9
Jianzhong Hu, ..., Jaeki Min*	
Cereblon on Steroids: Beyond the Canonical Ligand Space	9
Alexander Herrmann, ..., Marcus D. Hartmann*	

METTL3 promotes human coronavirus replication through an interferon-independent mechanism _____ 9
Ikshita Dinesh, ..., Hannah M. Burgess* _____

PAPERS AND PRE-PRINTS FROM CETPD _____ **10**

Induced ubiquitination of the partially disordered estrogen receptor alpha via a 14-3-3 directed molecular glue-PROTAC _____ 10

Carlo J. A. Verhoef,[§] Charlotte Crowe,[§] ..., Alessio Ciulli,* Peter J. Cossar* _____
Nat. Commun. **2026**, 17 (1), 8696 _____

Linkerology in PROTACs: learnings for proximity-inducing therapeutics _____ 11

Rubén Prieto-Díaz,[§] Aina Urbina,[§] María Rodríguez-Ríos, [§] Alessio Ciulli# _____
Trends Biochem. Sci. **2026**, 51 (9), 868–895. <https://doi.org/10.1016/j.tibs.2026.07.004> _____

MEET THIS MONTH'S EDITORS



[Click here for info on the editor](#)

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 working on oncology targets, and the LITE team targeting LRRK2 in 2026. In her spare time, she enjoys playing video games, traveling, and looking after her plants.

LinkedIn: [Giorgia Kidd | LinkedIn](#)



Jane Costello

Jane finished her MChem in Chemistry with a year in industry from the University of York in 2025, after completing her year in industry at Nxera Pharmaceuticals in Cambridge working as a synthetic and medicinal chemist. In December 2025, Jane joined the Cossar group starting a PhD working on creating molecular glues for TDP43. In her spare time, she enjoys hiking, doing arts & crafts and playing guitar.

LinkedIn: [Jane Costello | LinkedIn](#)



Wednesday McIntosh

Following her bachelors and masters degrees at the University of Dundee, Wednesday is carrying out a BBSCR EastBio/Syngenta PhD studentship under Professor Alessio Ciulli and Dr Piers Hemsley. She is interested in translating mammalian biotechnology into agriculture, focussing on targeted protein degradation in plants, and enjoys working on both the biological and chemical sides of her project.

LinkedIn: [Wednesday McIntosh | LinkedIn](#)



Conner Craigon

Conner holds a PhD in Cell Biology from the University of Dundee, graduating in 2022, where he, specialising in chemical biology and targeted protein degradation. His research focused on developing innovative technologies for the degradation of cellular proteins. Following his PhD, he continued his academic career as a Postdoctoral Research Associate at CeTPD. His work has contributed to the development of novel research technologies, including the BromoTag® and BromoCatch® systems.

LinkedIn: [Conner Craigon | LinkedIn](#)

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 July to 20th September 2026

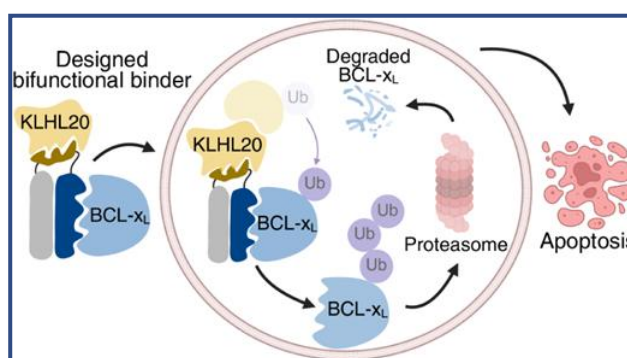
| *Giorgia*

De Novo-Designed Bifunctional Proteins for Targeted Protein Degradation

Bram Mylemans, ..., Derek N. Woolfson*
J. Am. Chem. Soc. **2026**, 148 (32), 34311–34319.

In a new approach to protein degradation, members of the Woolfson group have leveraged modern protein structure prediction methods such as AlphaFold and Rosetta to design short linear motifs (SLiMs). These SLiMs were designed to recruit their chosen target of BCL-xL, of interest in oncology, and currently underutilised E3 ligase, KLHL20 for ubiquitination, expanding the E3 ligase toolbox.

This molecular modelling approach yielded bifunctional peptides which interacted with either of the binding partners well in Fluorescence Anisotropy (FA) assays. The ternary complex is productive, and a moderate level of degradation was seen. While the PROTAC degrader DT2216 does still perform better than the peptide system, as a proof of concept, this work represents a new avenue for protein degradation with delivery and targeting complementarity versus small molecule PROTAC degraders.



This paper leverages new technologies such as protein structure prediction, and new E3 ligases to push the boundaries of previous work in the field. I think it will be interesting to see how much this methodology is picked up by the community and whether it can be pushed to PROTAC peptide therapeutics in the future!

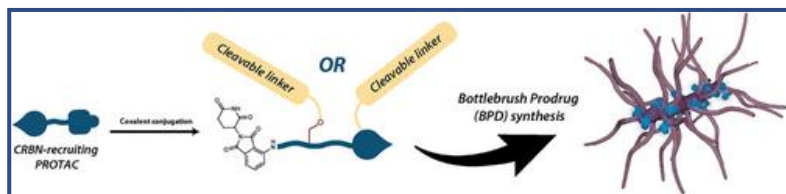
| *Giorgia*

Generalizable Strategies for the Synthesis of Cereblon-Recruiting PROTAC Prodrugs

Aiden X. Wang, ..., Jeremiah A. Johnson*
Angew. Chem. Int. Ed. **2026**, 65 (40), e3238473.

To address some of the common hurdles found in PROTAC development such as poor permeability and complex *in vivo* pharmacokinetics, prodrug strategies can be employed. For VHL there have been many prodrug strategies available, but currently less are reported for CRBN, in part as it has fewer functional handles for exploiting. The team in the Johnson lab aimed to use prodrug strategies on recently reported model systems, such as ARV825, and a CDK9 targeting CDK9, using methods that would be transferable to other CRBN ligand based PROTACs.

Ultimately, they wanted to generate macromolecular bottle brush structures with the PROTACs, as a nanoparticle delivery system that might also help to overcome some of the caveats with PROTACs *in vivo*. These were formed, and found to be functional both *in vitro* and *in vivo*, emphasising that this could be a useful strategy in CRBN PROTAC drug discovery. While all the model compounds use classical glutarimide based CRBN ligands, the prodrug moieties were not directly within this motif, and so the work might be transferable to newer generation CRBN ligands such as amino glutarimides and dihydrouacils



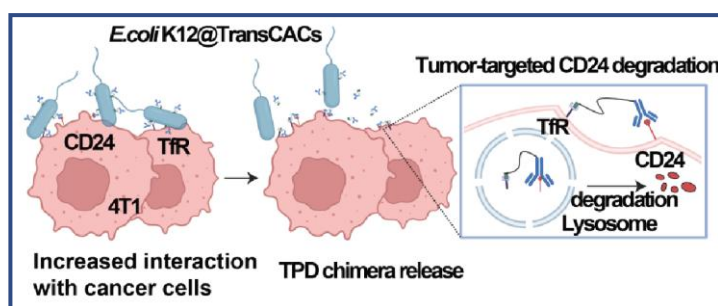
Knowing firsthand that PROTAC drug discovery can come with many hurdles, I enjoyed reading about these new tricks for the medicinal chemist's arsenal. I think time will tell whether they are general and if the desired effect can be achieved in different tissues/disease states.

| *Conner*

Engineering Nonpathogenic Bacteria for Synergistic Tumor-Targeted Protein Degradation and Immunotherapy by Checkpoint-Inhibiting Nanobodies

Xingping Hu[§], Yu Chen[§], ..., Jinghua Ren*, Hongwei Duan*
J. Am. Chem. Soc. **2026**, 148 (32), 34393–34405.

This study developed engineered non-pathogenic *E. coli* K-12 as a tumour-targeted delivery platform that combines targeted protein degradation with immune checkpoint inhibition. By exploiting the ability of engineered bacteria to preferentially colonise the hypoxic and immunosuppressive tumour microenvironment, the system enables local production and delivery of protein-degrading agents and checkpoint-blocking



nanobodies directly within tumours. The platform targets CD24 for degradation, reducing tumour-promoting signalling and immune evasion, while simultaneously blocking PD-L1 to enhance antitumour immune responses. *In vivo*, the combined treatment produced greater tumour suppression than either strategy alone, demonstrating the potential of programmable bacteria as multifunctional and tumour-selective cancer therapeutics.



A strength of the study is the integration of targeted protein degradation and immune checkpoint inhibition within a single tumour-localised delivery platform. The use of engineered bacteria enables local therapeutic production, potentially reducing systemic exposure and associated toxicity. However, clinical translation remains challenging due to the complexity of using live bacteria, particularly the need to control bacterial colonisation, therapeutic expression and clearance, alongside potential risks of inflammation, bacterial dissemination and infection.

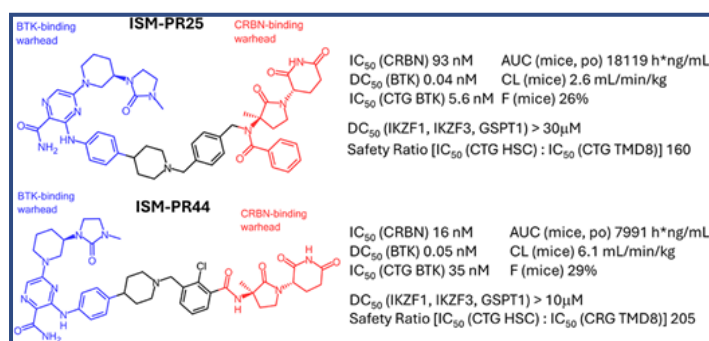
| Wednesday

Discovery of Highly Potent and Selective, Orally Bioavailable BTK-Targeting PROTACs Featuring Novel CRBN-Binding Warheads

Alexey B. Mantsyzov*, ... , Alex Zhavoronkov*
J. Med. Chem. **2026**, 69 (17), 20494–20519.

With the goal to develop PROTACs that target Bruton's Tyrosine Kinase (BTK), a key therapeutic target for many blood cancers, the authors have discovered novel Cereblon (CRBN) warheads using AI assistance. Using the core binding components known from CRBN binder lenalidomide, the team generated new warheads containing a second chiral centre with greater three-dimensionality and lower cLogP. These warheads were able to form new hydrogen bonds with CRBN and showed no degradation of known lenalidomide neosubstrates associated with off-target effects. Using the established BTK warhead from PROTAC NX-5948, the CRBN warheads were screened in various *in vitro* and *in vivo* studies combined with a selection of piperidine and acyl linkers.

The studies found many PROTACs with potent degradation of BTK, however, many were limited by poor oral bioavailability and cellular toxicity. Overall, the authors discovered two potential leads for further pre-clinical development, ISM-PR25 and ISM-PR44, which are potent, show good degradation with acceptable bioavailability and low cellular toxicity.



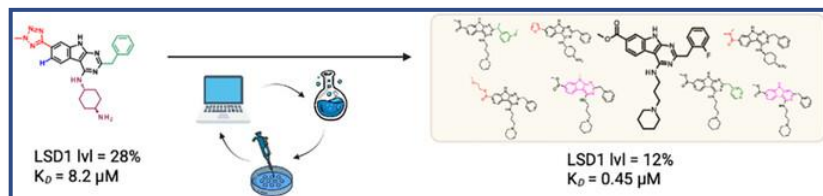
It is interesting to see the application of AI in generating novel E3 ligase ligands and being able to see their progress through the *in vitro* and *in vivo* studies. This paper shows the work that is being done to speed up the drug discovery process with the tools that we now have available to us, such as AI.

| Jane

Structure-Guided Optimization of a Molecular Glue Targeting the KBTBD4-HDAC1/2 Complex

Timea Balo, ..., Andras Kotschy*
Chem Med. Chem. **2026**, 21, 16, e70451.

The authors describe their cryo-EM structure-based optimisation of the molecular glue UM171. Balo *et al.* aim to use structure-activity relationship (SAR) data to rationally optimise the structure of UM171 for greater affinity of the KBTBD4-HDAC1/2 interaction. Formation of the KBTBD4-HDAC1/2 complex results in increased degradation of LSD1. The optimisation involved testing analogues of UM171 to investigate interactions in each pocket of the protein interface. The authors showcased the impact of introducing alternative functional groups, hydrophobic regions, alternative stereochemistry and rigidification of the glue. Highlights included utilising the cryo-EM structure to guide analogue design and using controls to determine the impact of solvent exposure in results. The group achieved a 20-fold improvement in glue activity based on ternary complex stability, as well as improved LSD1 degradation.



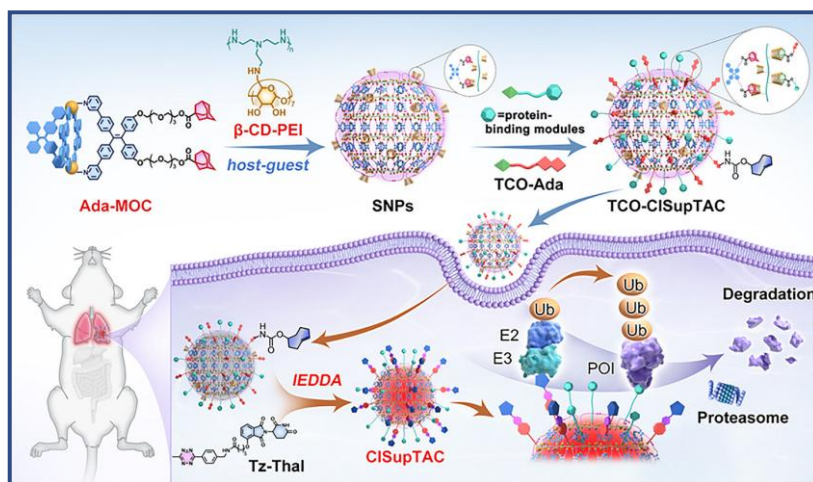
The rational design of molecular glues based on SAR data is a cutting-edge developing area of drug discovery, making papers like this beneficial for the wider scientific community. Unfortunately, in this case some of the results leading to loss of activity were difficult to rationalise based on the SAR data.

| Conner

Click-Activated Supramolecular Targeting Chimeras for Spatiotemporally Resolved Protein Degradation *In Vivo*

Yongsong Zhang, Ji Liu, Tianyu Ma & Ming Wang*
Angew. Chem. Int. Ed. **2026**, e2233329.

This study introduces click-activated supramolecular targeting chimeras (CISupTACs) as a modular platform for spatially and temporally controlled targeted protein degradation *in vivo*. The approach uses a two-step system in which tissue-targeting nanoparticles containing a protein-binding ligand and trans-cyclooctene (TCO) accumulate at the desired site. Subsequent administration of a tetrazine-conjugated E3 ligase recruiter triggers an inverse electron-demand Diels–Alder (IEDDA) reaction, assembling an active



degrader in situ and promoting target ubiquitylation and degradation. The platform was validated against ACSL4, demonstrating selective degradation and suppression of ferroptosis in vitro, and FoxO1, where lung-selective degradation reduced pulmonary inflammation and improved vascular barrier integrity in a mouse model of acute lung injury. Notably, the IEDDA-based strategy demonstrated faster activation and degradation kinetics than an alternative Staudinger reaction-based approach.



A key strength of CIsupTACs is the spatial control achieved through local chemical activation, offering a modular alternative to constitutively active degraders and potentially reducing systemic toxicity. However, the requirement for multiple components introduces delivery and reaction-efficiency challenges, while relatively modest degradation ($D_{\max}$) may limit efficacy compared with conventional bifunctional degraders.

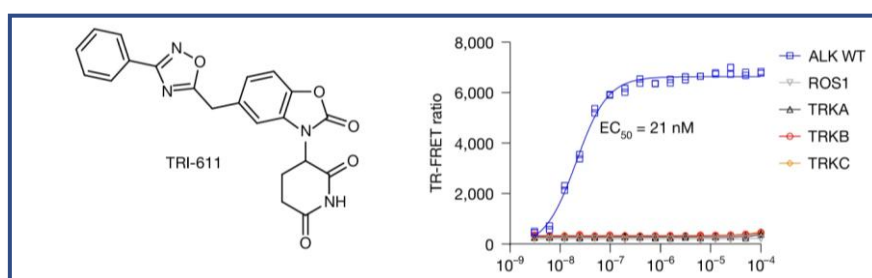
| *Conner*

TRI-611, a selective, brain-penetrant molecular glue degrader of ALK

Andrew R. Conery, Daniel S. La, ..., Vito J. Palombella*
Nature **2026**, 658, 241–249.

This study introduces TRI-611, a potent, selective and brain-penetrant molecular glue degrader designed to eliminate oncogenic ALK fusion proteins in ALK-positive non-small-cell lung cancer (NSCLC). TRI-611 promotes formation of a ternary complex between ALK

and the CRBN E3 ligase, driving ALK ubiquitination and proteasomal degradation through a previously unrecognised binding interface on the kinase domain. It remains active against several TKI-resistant ALK variants and shows strong proteome-wide selectivity. Importantly, oral dosing produces marked tumour regression in both subcutaneous and intracranial models, while combination with ALK tyrosine kinase inhibitors gives deeper and more durable antitumour responses.

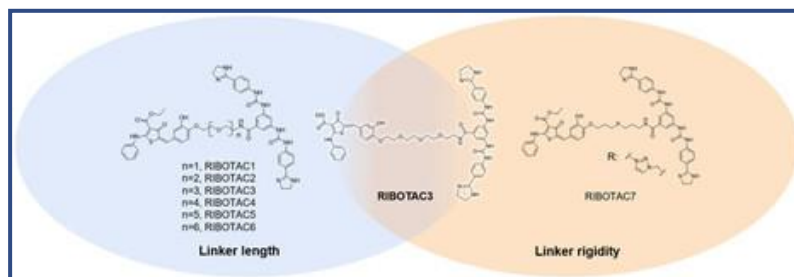


A key strength of this study is its extensive mechanistic characterisation, revealing a non-G-loop-dependent CRBN neosubstrate interface that may improve degradation selectivity. Activity against TKI-resistant ALK mutants and intracranial tumours further highlights its therapeutic potential. However, efficacy remains preclinical, and the emergence of resistance and long-term selectivity in patients remain uncertain.

Linker Optimization of cMYC RIBOTAC for Efficient cMYC Modulation

Sivakumar Komachankandy, Jinseo Heo, Yerin Kim, Wonpil Im, Yeongju Lee*
Chem Med. Chem. **2026**, 21, 18, 1860-7179.

Komachankandy *et al.* present their work on linker optimisation of the ribonuclease-targeting chimeras (RIBOTACs). Previous optimisation had focused on RNase L-recruiting motifs and RNA-binding ligands; however, the impact of linker length and rigidity had not been systematically investigated. This work highlights the importance of linker design to achieve optimal inter-component distance for efficient RNA degradation. In particular, the group demonstrated with unchanged RNA-binding and RNase L-recruiting motifs, extension of the PEG5-7 linkers prevented degradation while maintaining RNA-binding affinity, showcasing how length can prevent function. Aside from linker length, rigidification was investigated with the aim of improving spatial control. A triazole-based rigid linker was designed but had reduced binding affinity, loss of RNA cleavage activity and loss of cellular activity. The triazole-based linker's unfavourable results indicated conformational constraints would negatively impact the dynamic spatial alignment required for productive RNA degradation.

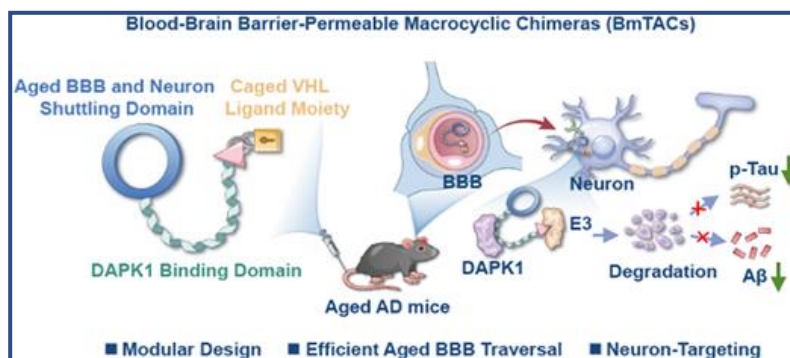


Overall, this work is a good example of systematically investigating the importance of linker design, particularly linker length, which was demonstrated to have a significant impact. However, only the rigid triazole-based linker was designed to investigate the impact of rigidification on spatial control, it would be interesting to see other rigid analogues tested that promote different geometry.

Blood-Brain Barrier-Permeable Macrocyclic Chimeras (BmTACs) for Targeted Protein Degradation in the Aging Brain

Licong Peng, Qihang Li, Zhizhi Li, Guozhen Bai, Yuan Tian,* Shaobing Zhou*
J. Am. Chem. Soc. **2026**, 148 (38), 41137–41150.

Targeting neurogenerative diseases such as Alzheimer's with TPD introduces the further complication of having to cross the blood brain barrier with large, beyond rule of 5 molecules. Methods to improve BBB penetration have been described before, taking advantage of a molecules chameleonicity, using Prodrug strategies, or via encapsulation for example.



In this paper, to cross the BBB, the macrocyclic moiety of the molecule is functioning as a neuron shuttling domain to allow the molecule to enter the neuron. There is a reactive oxygen species (ROS) cleavable prodrug motif on the VHL portion of the molecule which should allow activation of the E3 ligase binder in the high ROS environment of Alzheimer's lesions.

Despite the large size of the molecule, it is shown to give good degradation of DAPK1 *in vitro*, as well as 55% degradation *in vivo*. Fluorescence microscopy showed that the peptidic PROTAC was transported into the cell. As well as the effect on protein levels, the rats with induced Alzheimer's treated with the molecule performed better in the Morris water maze test, showing improved special memory.

Overall, this study used multiple new methodologies in PROTACs to achieve a molecule that, despite its large size, was able to have an *in vivo* and therapeutic effect.



This work used a lot of different ideas together to make steps forwards towards PROTACs that are functional in the brain. I liked that while the methodology as a whole could be something that other groups implement, they can also be inspired by parts such as the shuttling peptide or VHL prodrug moiety.

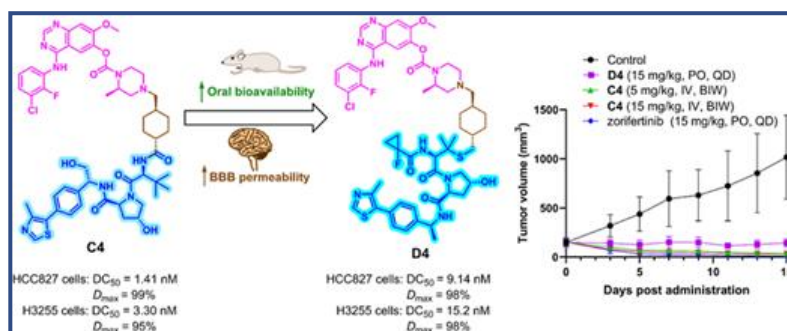
| Jane

Discovery of Potent and Selective VHL-Recruiting PROTAC Degraders Targeting EGFR with Improved Developability and Potent Anti-NSCLC Efficacy

Xiang Ni, ..., Kuojun Zhang*

J Med. Chem. **2026**, DOI: 10.1021/acs.jmedchem.6c01893.

Ni *et al.* aimed to develop an alternative to epidermal growth factor receptor (EGFR) kinase inhibitors for the treatment of non-small cell lung cancer (NSCLC), due to their longer-term problem of acquired resistance to inhibition. The authors achieved this by creating a VHL-recruiting PROTAC degrader targeting EGFR. The paper covers their comprehensive structure-activity relationship (SAR) optimisation of the E3 ligase ligand and linker moieties. Previous limitations of EGFR PROTAC degraders included high dosing frequency, poor oral bioavailability and lack of brain exposure, however in this paper EGFR PROTAC degrader D4 developed is orally bioavailable and able to penetrate the BBB in mice, as well as selectively and rapidly degrading EGFR. Another EGFR PROTAC degrader presented in this paper, C4, caused significant tumour regression at low intravenous doses with a reduced dosing frequency of twice weekly in a HCC827 xenograft model.





The authors demonstrate systematic SAR optimisation overcoming previous EGFR PROTAC degrader associated issues such as poor oral bioavailability, lack of brain exposure and high dosing frequency. It would be interesting to see if the most promising degraders in the paper (C4 and D4) can overcome all clinically relevant EGFR resistance mutations.

| Wednesday

A 2-in-1 Strategy for the Discovery of Compact HDAC8 Protac Degraders

Yi Liu[§], Nikee Awasthee[§], Yufeng Xiao[§], ..., Daiqing Liao*, Guangrong Zheng*
J. Med. Chem. **2026**, 69 (18): 21381–21397.

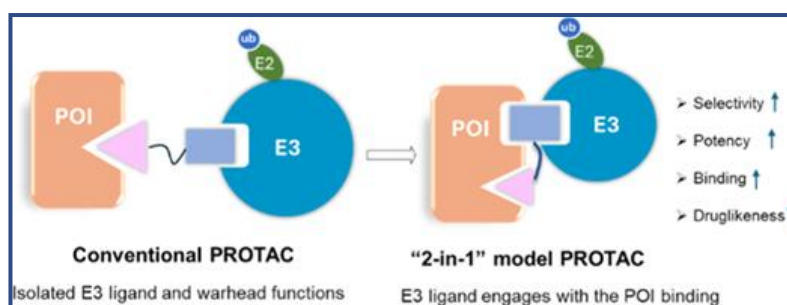
Building on their previously discovered HDAC8 PROTACs, the authors work to design a degrader where the E3 ligase ligand can also engage the protein of interest (POI).

While creating smaller degraders with more favourable physicochemical properties, this “2-in-1” strategy also

opens the opportunity to target areas on the POI that allow specificity over other proteins.

In this work, the authors design a potent degrader containing a HDAC8 warhead, a short rigid linker and a Cereblon ligand that also acts as a capping group, engaging residues around the HDAC8 binding pocket. This degrader showed improved selectivity for HDAC8 over other Class I HDACs, particularly HDAC3, which had previously been subject to off-target degradation. However, proteomics studies identified that the new degrader showed some degradation towards Class II HDACs, which hadn't been seen before.

Overall, the authors have designed some of the smallest HDAC8 degraders to date, showing *in vivo* degradation and have demonstrated an approach for adjusting the selectivity and physicochemical properties of PROTACs.



This paper highlights new ways to improve existing PROTAC design. It would be interesting to see whether this kind of strategy could also be used in the development of molecular glues.

PRE-PRINTS



ChemRxiv™

Direct-to-Biology Bifunctional Screening Reveals Noncanonical Mechanisms of Targeted Protein Degradation

| [Giorgia](#)

Clara Gathmann, ..., Christopher G. Parker*

Starting with a BRD4 reporter assay, the authors discovered a catechol containing PROTAC degrader, but with the knowledge that this motif can convert to electrophilic ortho-quinone and quinone methide species, they investigated the structure further. They truncated their PROTAC to generate electrophilic glues which were active and further expanded this to a glue for BRD2.

bioRxiv

Reprogramming VHL with molecular glues enables selective degradation of caspase-2

| [Jane](#)

Jianzhong Hu, ..., Jaeki Min*

The authors achieved both their aims of creating a selective chemical probe for caspase-2 degradation studies as well as expanding the target space of VHL. It will be interesting to see how this work is built upon such as further medicinal chemistry optimisation of the probes and investigating recruiting VHL for the degradation of other targets after the demonstration its neosubstrate landscape is broader than previously thought.

| [Wednesday](#)

bioRxiv

Cereblon on Steroids: Beyond the Canonical Ligand Space

Alexander Herrmann, ..., Marcus D. Hartmann*

To broaden the landscape of Cereblon (CRBN) ligands, the authors carried out high throughput screens and identified a series of new structures that engage CRBN, particularly steroidal scaffolds and bicyclic lactams. Additionally, the identified ligand classes didn't show detectable degradation of typical CRBN neosubstrates. Overall, this work identified new CRBN-binding scaffolds that could be used for targeted protein degradation.

| [Conner](#)

bioRxiv

METTL3 promotes human coronavirus replication through an interferon-independent mechanism

Ikshita Dinesh, ..., Hannah M. Burgess*

This study demonstrates that the RNA methyltransferase METTL3 promotes human coronavirus replication independently of interferon signalling, with targeted degradation of METTL3 reducing viral RNA and protein accumulation. A key strength of the study is the use of both a selective METTL3 inhibitor and a PROTAC degrader, providing complementary evidence for METTL3's role in viral replication and highlighting its potential as a host-directed antiviral target.

PAPERS AND PRE-PRINTS FROM CeTPD

| Aitana

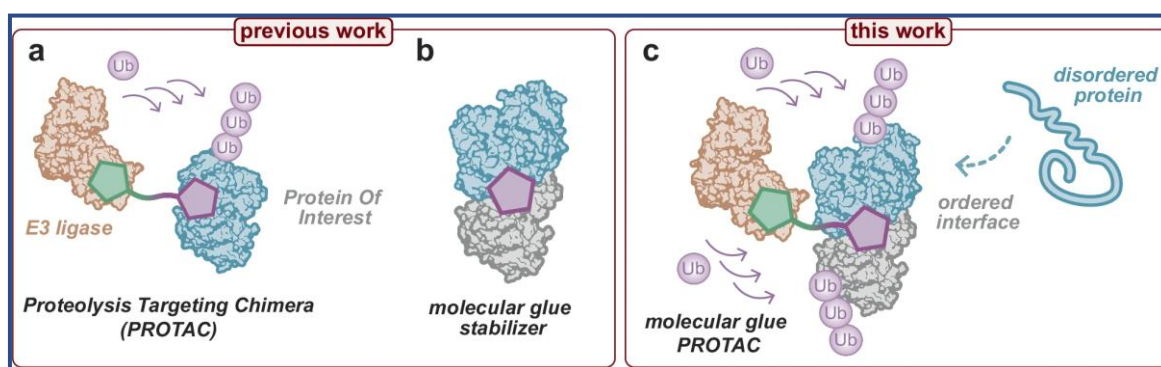
Induced ubiquitination of the partially disordered estrogen receptor alpha via a 14-3-3 directed molecular glue-PROTAC

Carlo J. A. Verhoef,[§] Charlotte Crowe,[§], Alessio Ciulli,^{*} Peter J. Cossar^{*}*Nat. Commun.* **2026**, 17 (1), 8696

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

This paper describes the development of a molecular glue-based PROTAC (MGPROTAC), by using a molecular glue stabiliser (FC-NAC) conjugated to the VHL ligand (VH032), which brings the 14-3-3/Estrogen receptor α (ER α) complex in close proximity to VHL. In this system, the molecular glue functions as the ligand for a protein complex, stabilising an interface between a partially disordered target and a scaffold protein. A panel of FC-NAC-VH032 chimeras were synthesized with different linker lengths and two distinct chemical compositions, polyethylene glycol (PEG) or alkyl. Fluorescence anisotropy (FA) assay and VHL target engagement experiments showed that MGPROTACs effectively engaged both 14-3-3/ER α and VHL. Further biophysical characterisation revealed distinct linker-dependent cooperativities across the panel; specifically, longer apolar linkers promote strong positive cooperativity up to an optimal length (CV2a, 11 atoms). Cryo-EM showed that the most cooperative MGPROTAC, CV2a, induces a neo-protein-protein interface between the VHL β -domain and the 14-3-3 ζ α 8/ α 9 helices. Molecular dynamics (MD) simulations suggest that a hydrogen bond between VHL Tyr112 and 14-3-3 ζ Tyr211 serves as the key hotspot interaction. The MGPROTACs drove rapid, UBE2D2-dependent in vitro ubiquitination of the 14-3-3 ζ /ER α complex and linker design also tuned site selectivity: CV3a biased ubiquitination towards 14-3-3 ζ , whereas CV2a preferentially modified ER α . However, CV2a did not reduce ER α levels in MCF-7 cells, despite engaging VHL and enriching the 14-3-3/ER α complex by IP-MS. We hypothesise that this could be due to polypharmacology across the 14-3-3 interactome, which would dilute effective ternary complex formation with ER α , a short-lived quaternary complex in cells, or efflux.

Overall, the study shows that induced proximity can be extended beyond single, well-folded proteins to protein complexes with disordered regions, and that linker design tunes both cooperativity and ubiquitination site selectivity. This study is framed as a proof-of-concept rather than a validated tool to study ER α biology.



Linkerology in PROTACs: learnings for proximity-inducing therapeutics

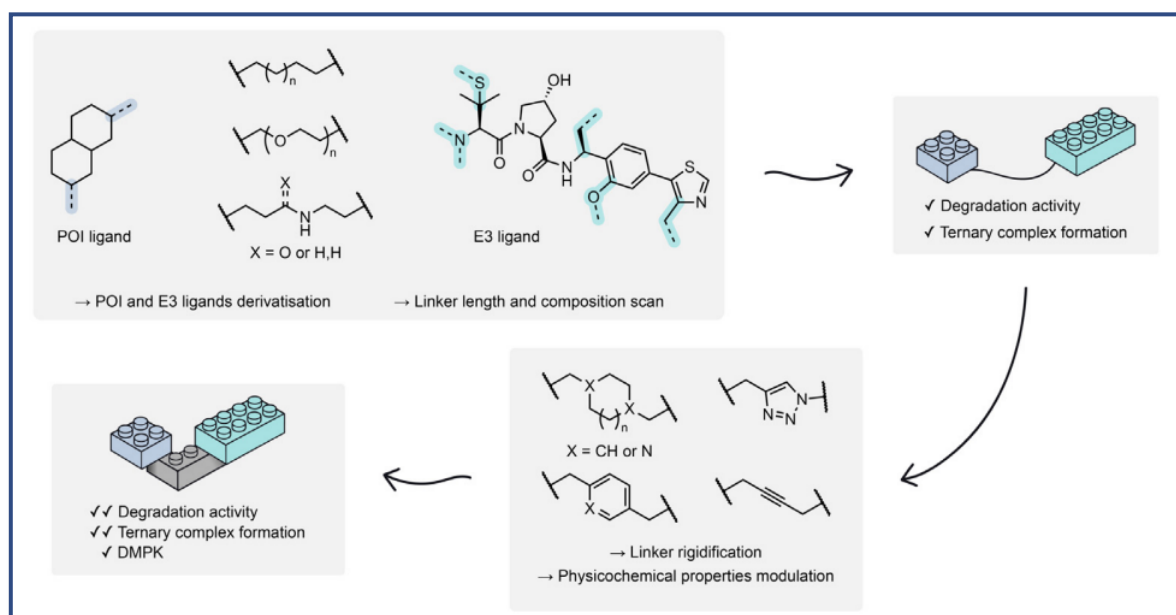
Rubén Prieto-Díaz,[§] Aina Urbina,[§] María Rodríguez-Ríos,[§] Alessio Ciulli[#]

Trends Biochem. Sci. **2026**, 51 (9), 868–895. <https://doi.org/10.1016/j.tibs.2026.07.004>

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This review introduces linkerology as a design framework for PROTACs, treating the linker as an active determinant of ternary complex geometry, cooperativity and ADME behaviour. Linker optimisation should not be viewed simply as adjusting length and flexibility. It is a multidimensional medicinal chemistry problem involving composition, attachment vectors, rigidity, polarity and conformational preference. A cheminformatic analysis of over 2700 linkers from PROTAC-DB, annotated against eight chemotypes under a non-exclusive scheme, showed that over 70% are hybrids and confirmed a bias towards flexible alkylic and (poly)ether motifs. The 20 disclosed clinical-stage PROTACs diverge sharply from this published landscape; specifically, alicyclic motifs rise from 12.2% to 48.5%, amide and linear amine content falls from 20.0% to 3.0%, no PEG architecture is retained, and all linkers fall within 7–15 Å with fewer than seven rotatable bonds. Two case studies show how this is reached in practice: rigidification and replacement of a polar ether oxygen by an acetylene improved potency, reduced efflux and increased oral exposure in KT-474, whereas in CFT8634 a gem-difluoro moiety modulating pKa contributed in part to an increase in bioavailability from 1% to 74%. However, the clinical dataset is small, so whether this convergence reflects translational selection or shared medicinal chemistry practice remains unclear.

Overall, linker design should be treated as a primary parameter from the earliest stages of degrader discovery rather than a late optimisation step, and these principles will need extending to emerging induced-proximity modalities. It is framed as a forward-looking framework rather than validated design rules.





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