CeTPD Journal Club

June – July 2026

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

Centre for Targeted Protein Degradation
University of Dundee

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MEET THIS MONTH'S EDITORS

Click here for info on the editor

Alexandra Teslenko

Alexandra, originally from Belarus, is a biochemist passionate about understanding how protein modifications regulate cellular processes. She completed her undergraduate studies in biochemistry at Heidelberg University. She then pursued her interdisciplinary Ph.D. with Prof. Beat Fierz at EPFL Lausanne, Switzerland, focusing on the single-molecule biophysics of the chromatin writer PRC1 and its ubiquitination kinetics in the context of transcriptional repression. Fascinated by the ability of E3 ligases to control protein fate and degrade the undruggable, Alexandra joined the KOODAC team as a structural biologist.

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Jack Robertson

Jack started off as an undergraduate at Newcastle University, completing his masters in Chemistry with Medicinal Chemistry, before having a stint as a process chemist. Subsequently, he moved to undertake a PhD in Chemical biology under Prof. Glenn Burley at the University of Strathclyde. Here he focussed on developing peptidomimetics for application in Cell-Penetrating Peptides combining both synthetic chemistry and cell biology techniques. He moved to Dundee as part of the AC-Almirall team in April 2021 as a chemical biologist before joining the LITE team in January 2025.

Elisha McCrory

Elisha is originally from Durham, UK and completed both her BSc and MSc in Pharmacology at the University of Liverpool in 2019. Elisha completed her PhD in the lab of Prof. Sir. Philip Cohen at the MRC-PPU, University of Dundee in 2023 where she worked on identifying sites of atypical ubiquitin attachment onto the hydroxyl groups of serine and threonine residues of proteins and onto hydroxyl groups of sugars. Elisha joined the AC-BI team in December 2023 as a Cell Biologist.

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Hannah Mortlock

Hannah, originally from Dumfries, completed her MChem in Chemistry with Medicinal Chemistry at the University of St Andrews. As part of her degree, she completed a year in industry working for Sygnature Discovery in Nottingham, a drug discovery CRO. While there, she worked on developing high-throughput chemistry methods to create libraries of PROTACs for cancer therapies. In September 2025, she joined the Farnaby Group for her PhD developing targeted mitochondria degradation.

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TARGETED PROTEIN DEGRADATION

CHEMISTRY | STRUCTURAL BIOLOGY & BIOPHYSICS | CELL BIOLOGY | MODELLING

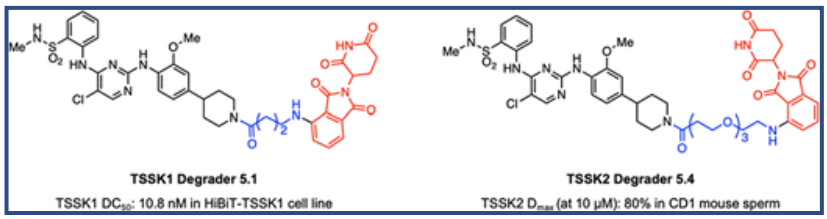
"Every two months, we spotlight the latest and most significant literature in the field of targeted protein degradation, spanning chemistry, biophysics, cell biology, and computational modelling"

Literature review from 21st May to 20th July 2026

| *Hannah*

Development of TSSK1 and TSSK2 Targeted Degraders Reveals Sperm Machinery for Protein Degradation and Potential for Nonhormonal Male Contraception

Jarrett A. Holdaway, …, Gunda I. Georg*
J. Med. Chem. (2026) 69 (12): 14236–14254.



In this work, the a previously reported potent ATP-site inhibitor for TSKK1/2 (IC_{50}: 0.88 nM/66 nM) that was not further developed due to broad nonselectivity was converted into a more selective heterobifunctional degrader. TSKK1 and 2 are members of a testis-specific serine/threonine kinase family that have essential roles in sperm production. The authors synthesised a small selection of alkyl and PEG-linked pomalidomide heterobifunctionals. These showed nM CRBN-mediated proteasomal-dependent degradation of TSKK1 in a Nano-Glo HiBiT Lytic stable cell line. Despite very poor pharmacokinetic properties, these degraders degraded TSSK2 in mouse sperm cells at μM concentrations after 4 hours; the resulting impaired sperm mobility (up to 97%) led to a strong reduction of in vitro fertilisation.

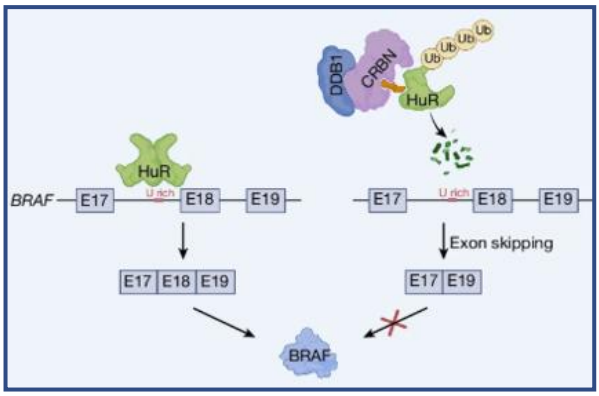
This first use of TPD in sperm shows a proof of concept as a strategy for the development of non-hormonal male contraception. Pleasingly, the heterobifunctional displayed improved selectivity of the broadly nonselective parent inhibitor. However, this degrader series will require significant medicinal chemistry efforts to overcome the very poor observed pharmacokinetics if a comprehensive in vivo characterisation of the reversibility, safety and effectiveness of this strategy is to be achieved. The group recently presented a poster, showing efforts towards a prodrug strategy that could be a promising route to improve PK.

| Elisha

Molecular glue degraders of HuR suppress BRAF-mutant colorectal cancer

Xiaociu Lu§,Xiuyun Wang§, Zheng Yang§, Xusheng Wang§, …, Hao Dou*, Hexiu Su* and Yong Cang*
Nature ***655****, 780–789 (2026)*

BRAF-mutant colorectal cancer (CRC) remains one of the most challenging therapeutic subtypes, with traditional BRAF inhibitor treatment often being ineffective. Here, the authors use HTRF and parallel global proteomics screening to identify dHuR as a molecular glue degrader targeting Human RNA-binding protein (HuR). HuR is frequently over-expressed in the cytoplasm of cancer cells allowing enhanced expression of proteins that promote tumour growth and resistance to therapies.



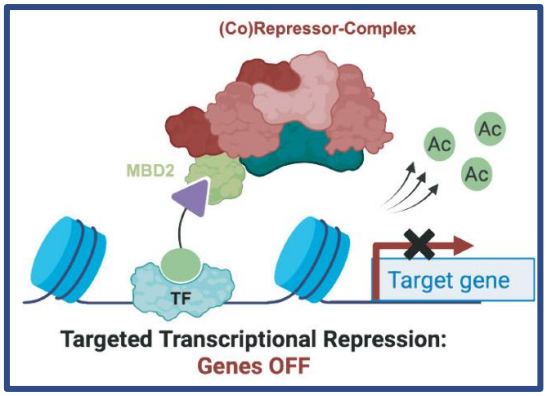
Cryo-EM revealed that dHuR engages the β-hairpin G-loop degron similarly to other CRBN neosubstrates, with G58 being the key modulator of this interaction. Interestingly, the authors identified a specificity of dHuRs for BRAF-mutant cell lines over BRAF WT CRC lines. Mechanistic studies demonstrated that dHuRs promoted exon-18 skipping and inefficient translation thus, leading to lower BRAF expression. Further analysis identified that dHuRs are successful in BRAF-inhibitor resistant cells and demonstrated enhanced activity in combination with EGFR and MEK inhibition. Initial in vivo tolerability studies demonstrate minimal body weight reduction as well as biomarker reduction at efficacious dose. Excitingly, clinical candidate **DEG6498** has since been approved for clinical development in advanced solid tumours.

This paper uncovers a very exciting novel therapeutic strategy for BRAF-mutated CRC, with potential to overcome resistance to BRAF inhibitors. While PDX models supported the combination approach, further characterisation in clinically derived resistant samples as well as understanding the effects of global HuR degradation will be key for progression of these compounds. Keeping our eyes peeled for clinical developments in the future!

| Alexandra

Targeted Transcriptional Repression by Induced Proximity

Christian E. Stieger, Xinru Chen, Christina C. Kuismi, ... , Daniel K. Nomura**
ACS Cent. Sci. (2026) 12 (7): 1008–1020.



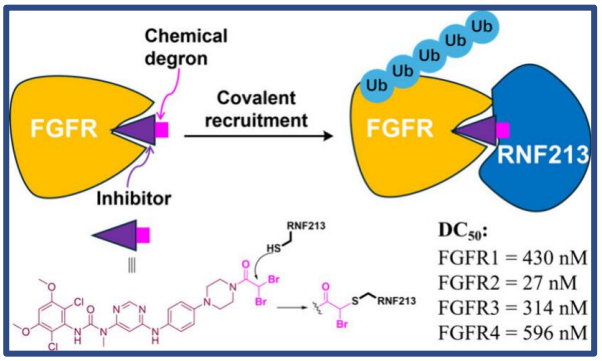
In this work, Stieger et al. present Transcriptional Repression via Active Chemical Epigenetic Reprogramming (**TRACER**), an induced-proximity strategy employing heterobifunctional molecules to recruit endogenous transcriptional co-repressor machinery to a target transcription factor (TF). TRACER induces proximity between the TFs estrogen receptor (ER) or androgen receptor (AR) and the methyl-CpG-binding domain protein 2 (MBD2), a component of the Nucleosome Remodeling and Deacetylase (NuRD) co-repressor complex, to drive epigenetic silencing of transcription factor-controlled genes. Transcriptional profiling confirmed downregulation of canonical TF target genes, including ESR1 and GREB1 by RT-qPCR and quantitative proteomics, reduced chromatin accessibility (ATAC-Seq) and target RNA expression (RNA-Seq), while dependent on HDAC activity and MBD2 expression. Notably, TRACER retained transcriptional repression across varying linker lengths between the TF ligand and MBD2 warhead, indicating no requirement for a restrained ternary geometry. Cellular target engagement was confirmed by photoaffinity-based chemoproteomics and affinity selection mass spectrometry (AS-MS). However, genome-wide profiling to assess potential off-target epigenetic remodelling remains to be established.

TRACER strategy expands the TCIPs methods for transcriptional rewriting, leveraging endogenous co-repressor machinery to silence TF-controlled genes. Structural reconstitution of the ternary complex formed by TRACER ligands, target TF, MBD2 with the full NuRD complex will provide critical mechanistic insight into epigenetic control through TRACERs.

| Jack

Molecular Glues Recruiting RNF213 As an E3 Ligase for Targeted Protein Degradation: A Minimal Dibromoacetamide Warhead As a Recruitment Ligand

Jingyi Jiang§, Yubin Chen§, Rui Wan§, ..., Tongzheng Liu, Yi Tan*, Zhengqiu Li**
J. Am. Chem. Soc. 2026, 148, 2, 27203–27218.



Research here by Jiang et al. utilises RNF213 as an E3 ligase to degrade fibroblast growth factor receptors (FGFRs). Starting from FGFR inhibitor Infigratinib, a series of molecular glues were synthesised with electrophilic reactive handles. Dibromoacetamide containing **CYB-5067** was identified as a potent degrader of FGFR2 (DC_{50} 27 nM, D_{max} 96%). Notably, **CYB-5067** demonstrated comparable FGFR2 degradation to CRBN based

PROTAC **LC-MB12**. Co-IP/MS experiments identified the E3 ligase responsible for degradation as RNF213 and subsequent knockdown of RNF213 abolished degradation of FGFR2. A combination of iso-TOP-ABPP and site-directed mutagenesis experiments identified C1748 of RNF213 as the residue that reacts with **CYB-5067**. **CYB-5067** showcased *in vivo* activity in a xenograft model showing tumour growth inhibition of 94.6%, comparable to the inhibitor Infigratinib, at 30 mg/kg dose. The dibromoacetemide utility was demonstrated with the synthesis of CDK12 degrader **LCX-1304** (DC_{50} 252 nM, D_{max} 80%) and WEE1 degrader **DJX-3025** (DC_{50} 68 nM, D_{max} 94%).

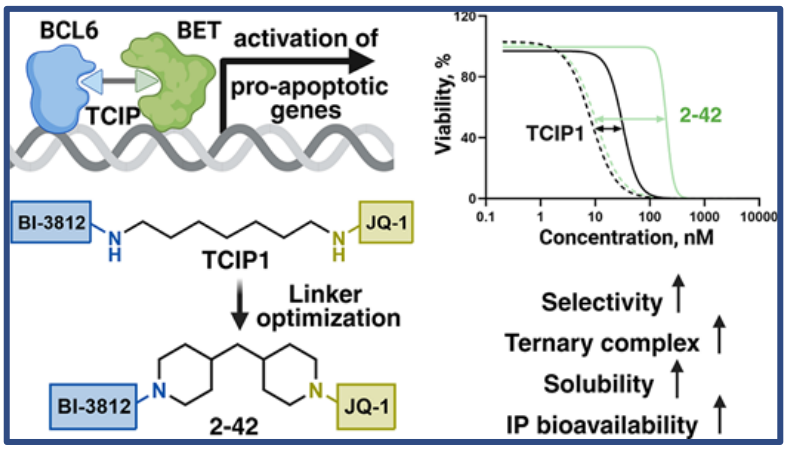
This extensive work identified dibromacetamides as useful handles for molecular glue design, importantly showing their activity against multiple target proteins. The authors al highlight the effectiveness of RNF213 as an E3 ligase that has value in addition to common ligases employed in TPD, primarily VHL and CRBN.

| *Alexandra*

Design of Potent and Selective BCL6 Transcriptional Chemical Inducers of Proximity through Linker Optimization

*Fang-Chi Chan§, Veronika M. Shoba§, Oleh Shyshlyk§, Andrii Frolov§, …, Armand B. Cognetta, III, * and Oleksandr O. Grygorenko**
J. Med. Chem. (2026) 69 (13): 15668–15684.

B-cell lymphoma 6 (BCL6) is a transcriptional repressor silencing pro-apoptotic genes, driving uncontrolled B-cell proliferation and tumorigenesis. While BCL6 inhibitors and PROTACs operate through loss-of-function mechanisms, Transcriptional Chemical Inducers of Proximity (TCIPs) offer a gain-of-function alternative by recruiting transcriptional coactivators to BCL6-bound genomic loci, inducing pro-apoptotic gene expression.



Chang et al. present systematic linker engineering of heterobifunctional BCL6-BRD4 TCIPs derived from **BI-3812** and **JQ1**, screening 65 structurally diverse linkers across acyclic, aryl, saturated and spirocyclic architectures. Viability assays in BCL6+ cell lines (SUDHL-5 and KARPAS-422) with the BCL6-negative cell line MV4-11 indicated the main SAR: Linker rigidification through saturated, benzene or spirocyclic ring incorporation improved cellular selectivity and ternary complex formation; heteroatom insertion into flexible linkers reduced both activity and selectivity while a heteroatom within a more rigid linker did not negatively affect activity or ternary complex formation. Lead compound **2–42**, bearing a conformationally constrained bis-piperidine linker, demonstrated superior ternary complex formation, rationalized by MD simulations through linker preorganization and reduced bound-state conformational strain. *In vivo*, **2–42** achieved the highest plasma exposure among leads, while *in cellular*, the BI-3812 cellular competition rescued the 2-42-induced degradation, confirming a ternary-driven mechanism.

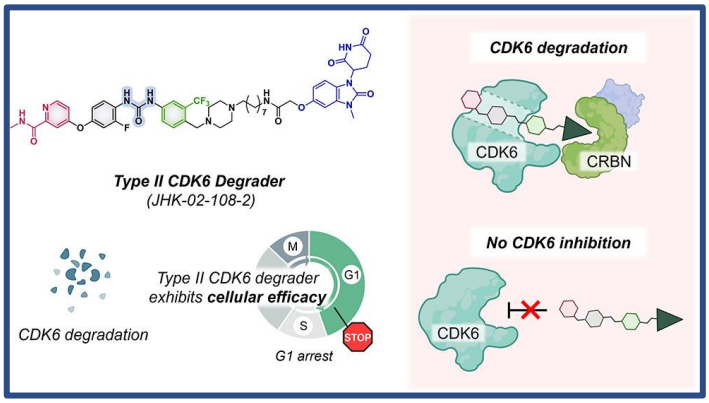
Linker optimisation can substantially improve cellular potency, selectivity, solubility, metabolic stability, and *in vivo* exposure. Poor permeability remains the key limitation for oral bioavailability, mainly depending on the structure of the linked warheads.

| *Jack*

A Type II CDK6 Degrader Enables Cellular Targeting beyond the Limits of Type Inhibition

Ji Hyeon Kim, Caitlin E. Mills, ..., Katherine A. Donovan*, Eric S. Fischer*, Nathanael S. Gray*

J. Am. Chem. Soc. ***2026****, 148, 26, 27951–27964l.*



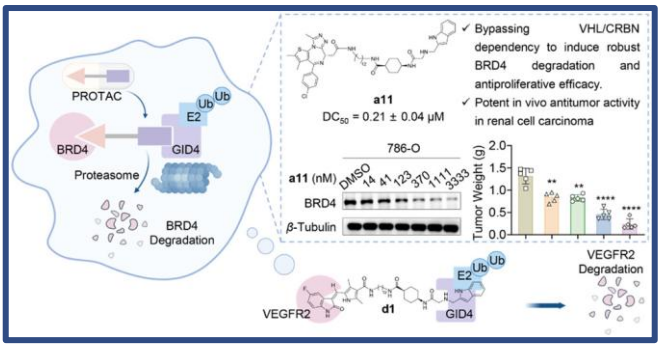
Type II inhibition of cyclin dependant kinases (CDKs) has proved challenging, often showing poor cellular potency. This work showcases the ability to take a pan-kinase type II inhibitor and develop selective CDK PROTACs. Regorafenib was repurposed for PROTAC synthesis and a series of CRBN recruiting degraders were synthesised. The panel of compounds included 4 varying CRBN ligands and 6 different linear linkers. From the series several compounds were identified as CDK5/6 degraders with **JHK-02-108-2** being highlighted as a potent and crucially the only selective CDK6 degrader. **JHK-02-108-2** exhibited sustained degradation over 24 h and no hook effects, an improvement on type I based CDK6 degrader **BSJ-03-123**. As CDK6 has been reported as a potential target for treating Glioblastoma (GBM) and acute myeloid leukaemia (AML). To assess their approach, experiments were conducted using GBM and AML cell lines. For GBM type cells, growth inhibition of IC_{50} 640 nM and DC_{50} 11 nM were observed but the growth inhibition was less pronounced in AML cell models.

The work highlighted here demonstrates the strength of the PROTAC approach, being able to take a weak inactive inhibitor and develop a cell active, target selective, compound. More work is required to understand CDK6 biology in the context of AML and GBM to explain the differing results in cell models presented.

| *Jack*

GID4-Recruiting PROTACs for BRD4 Degradation Overcome Resistance Driven by CRBN and VHL Deficiency

Yecheng Tang§, Mingming Zhang§, Yuxin Fang§, …, Chunquan Sheng*, Guoqiang Dong*
J.Med.Chem, ***2026****, 69,16704-16721.*



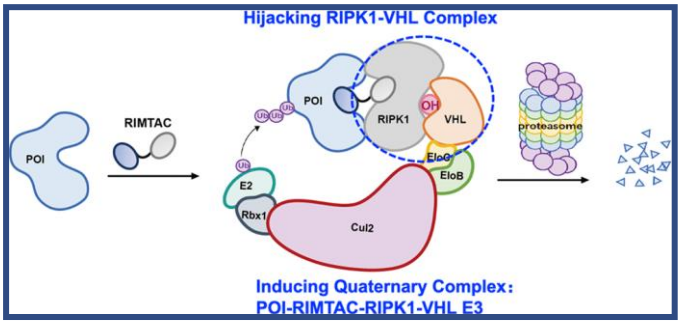
To date the vast majority of PROTAC molecules rely on either CRBN or VHL as their E3 ligase binding partner. The work reported here uses glucose-induced degradation protein 4 homologue (GID4) ligands to develop PROTACs that can induce BRD4 and VEGFR2 degradation in VHL and CRBN resistant cell models. By employing truncated GID4 ligand PFI-7 and linking to BRD4 binding JQ-1 a series of BRD4 degrader molecules were identified. The most potent compound **a11** demonstrated a DC_{50} of 210 nM in both anon-expressing VHL (786-O) and a CRBN-KO cell line. Compound **a11** showcased *in vivo* efficacy in a 786-O xenograft model with tumour growth inhibition of 67% after IP dosing and did not show any signs pathological alterations to major organs. Finally, a VEGFR2 PROTAC was developed using the truncated PFI-7 ligand. The PROTAC, **d1**, was able to degrade VEGFR2 with a DC_{50} of 340 nM, highlighting the utility of GID4 mediated degradation beyond BRD4.

This promising research highlights the potential of GID4 ligands in the PROTAC field and utilised simplified ligands to facilitate synthesis of PROTACs. The work also shows the benefit of GID4 PROTACs to target renal cell carcinoma that lack expression of VHL.

| *Hannah*

RIMTAC: A Novel Degrader Design Platform by Indirect VHL-Recruitment via RIPK1

Chang Shen§, Hanyin Sun§, …, Bo Zhao*, Mingyan Zhu*, Yudao Shen*
J. Med. Chem. (2026) 69 (14): 17093–17117.



The authors establish RIPK1-Mediated TArgeting Chimeras (RIMTACs) as a new class of degraders which indirectly recruit VHL through an endogenous interaction. RIPK1, a key regulator of apoptosis, necroptosis and inflammation, forms a complex with VHL except under severe hypoxia. Hydroxylated RIPK1 Pro195 mediates this interaction with VHL. The authors hypothesised that this endogenous interaction could be harnessed for TPD because RIPK1 stability is not influenced by VHL. Bifunctional molecules synthesised from a RIPK1 ligand, simple alkyl and PEG linkers and ligands for BRD4, ATK and JAK1, respectively, showed dose- and time-dependent degradation of their targets. The BRD4 degraders were the most potent, with

compound 10: DC_{50} 54.12 nM, D_{max} 83.3% after 24 h in HEK293 cells. RIMTACs were validated to be UPS-dependent degraders since, for each POI, co-treatment with the proteasomal inhibitor **MG132** and neddylation inhibitor MLN4924 rescued degradation, mRNA expression was unaffected, and RIMTAC washout recovered protein levels. The quaternary VHL-RIPK1-RIMTAC-POI complex was required for each POI, as knockout or inhibition of VHL and siRNA knockdown of RIPK1 and the POI rescued the observed degradation.

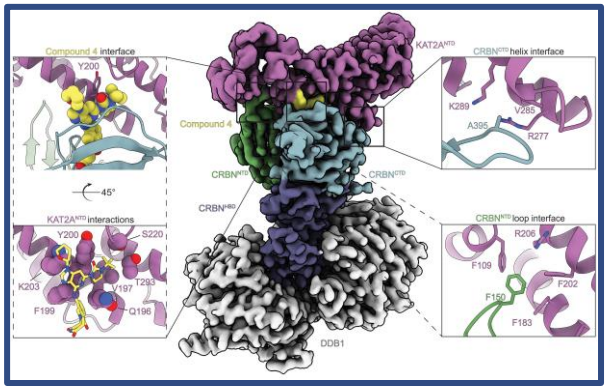
The authors successfully validate RIMTACs for three kinase targets: BRD4, AKT and JAK1. These recruit VHL indirectly for UPS-dependent TPD through the endogenous RIPK1-VHL interaction, providing another strategy in the TPD toolbox.

| *Alexandra*

Degron-independent recruitment of KAT2A expands the target space of CRBN molecular glues

*Samuel Ojeda§, Meng Wang§, …, Eric S. Fischer**
Science ***393****, 188–194 (2026).*

Molecular glues (MGs) are degrader molecules that function in the absence of a well-defined drug-binding pocket. Structural studies have indicated a common CRBN-based degron motif on the POI: the beta-hairpin G-loop. Ojeda et al. present the first MG that operates through a degron-independent binding mode, identified via target-agnostic global degradation proteomics and immunoprecipitation mass spectrometry (IP-MS).



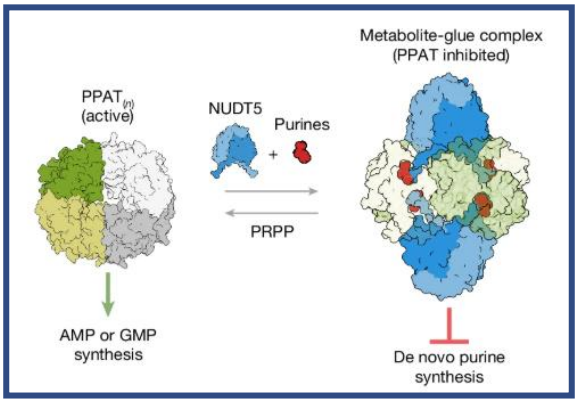
The optimised MG **4** selectively targets the non-catalytic N-terminal domain (NTD) of lysine acetyltransferase KAT2A without off-target activity against the closely related KAT2B. Structural characterization revealed a degron-independent binding mode in which compound **4** promotes a large PPI interface with CRBN, distinct from canonical immunomodulatory imide drug (IMiD) degron interactions. MG **4** recruits KAT2A-NTD via a globular helical domain mediated by a solvent-exposed tyrosine Y200, while the helical interface of KAT2A interacts with the zinc-coordinating region of CRBN-CTD and with a loop interface between F150 on CRBN-NTD and KAT2A-NTD. In AML cell lines (EOL-1, MV4;11), **4** selectively degraded KAT2A, reduced H3K9 acetylation in a neddylation- and proteasome-dependent manner and demonstrated antiproliferative activity. *In vivo*, **4** reduced leukemic burden and H3K9Ac levels in CD45+ cells, confirming KAT2A degradation.

The authors expand the landscape of CRBN-mediated MG interactions and present the first MG that functions in the absence of G-loop degron motifs or its structural mimic, while exploiting binding to non-catalytic domains for improved selectivity.

| Elisha

Metabolite glues as a means of purine sensing and chemotherapeutic response

Samuel R. Witus, Megan M. Kober, Heegwang Roh …, Michael Rapé*.
Nature (2026) ***655****, 1300–1308*



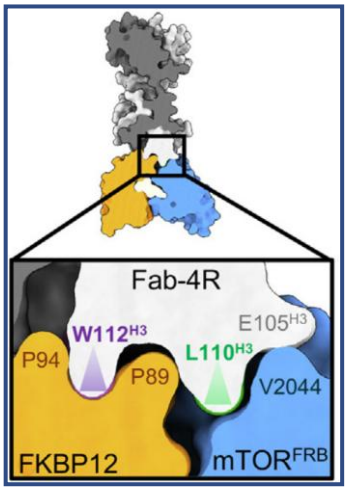
In this article, Witus et al. describe 'metabolite glues', endogenous purine nucleotides acting as molecular glues within cells. They identify AMP, amongst other purine nucleotides, as key regulators of the interaction between the rate-limiting enzyme of purine synthesis, PPAT and its inhibitor, NUDT5. Using Cryo-EM structural analysis the authors demonstrate that the C-terminal tail of NUDT5 is anchored within the PPAT binding site by AMP, preventing unnecessary activation of the de novo purine synthesis pathway, an energetically costly pathway for cells. The presence of AMP prevents the endogenous substrate of PPAT, PRPP from disassociating the complex and thus, limits de novo purine synthesis. This describes an important regulatory feature of the complex for nutrient sensing and maintaining metabolic balance.
Moreover, the authors uncover how thiopurine chemotherapeutic agents such as 6-MP, exert their effects in part, by binding to PPAT and inhibiting the purine synthesis pathway. Although they exploit a different binding mode to endogenous AMP, these thiopurines bind more potently via the glue pocket and allow bypassing of the dissociation of the complex by PRPP. Furthermore, by exploring the structurally flexible binding site, the authors demonstrate ways to improve current therapeutic agents that may improve efficacy whilst decreasing side effects

This paper gives an interesting translational insight into the mechanism of current chemotherapeutic agents and suggests improvements for future therapies. An exciting contribution for both biology and future drug design!

| Elisha

Epitope-guided Detection of a Molecular Glue-induced Ternary Complex Using Engineered Synthetic Antibody Fragments

Kelly M O'Leary, Tomasz Slezak, Duc Anh Le, Anthony A. Kossiakoff*
Journal of Molecular Biology (2026), ***438***



Having good tools for selectively isolating molecular-glue induced ternary complexes from cells remains a challenge. Here, the authors utilise a phage display pipeline to identify synthetic antibody fragments able to identify the rapamycin-induced FKBP12-mTOR ternary complex.
--The authors generated three fragments with distinct binding modes (1A, 2C and 4R). X-Ray crystallography of Fab-4R demonstrated its unique binding mode by burying residues L110 and

W112 into hydrophobic pockets on mTOR and FKBP12 respectively, forming a 'clamp'. This gave 4R its heightened affinity towards the rapamycin-induced ternary complex with little affinity to each of the proteins separately. The authors then also reformatted Fab-4R into scFv-4R, allowing its expression within cells. scFv-4R successfully retained its affinity and the authors highlight further exploration of fluorescent-markers or other reporters may be of interest.

The authors also include a framework for rational engineering of antibodies against protein-protein interactions including epitope size, location and affinity.

An interesting tool for antibody-based detection of ternary complexes. Very much looking forward to seeing whether this can be expanded to other molecular glue targets.

PRE-PRINTS

| *Jack*

ChemRxiv™

Rapid two-step multicomponent synthesis and structure-degradation relationships of selective HDAC6 PROTAC degraders

*Mikhail Tsymliakov..... Finn K. Hansen**

Tsymliakov et al. report a synthesis of selective CRBN mediated HDAC6 degraders via Ugi chemistry for rapid assembly of PROTAC molecules. The Ugi reaction is used to assemble CRBN ligand, linker and HDAC ligand in one step, subsequently streamlining the synthesis of the target PROTACs. From the panel of 11 PROTACs synthesised 4 were identified as potent nanomolar degraders, that were selective for HDAC6 over both HDAC 1 and HDAC2. This works highlights the value of multicomponent chemistry in PROTAC synthesis in addition to valuable SAR for selective HDAC degradation. It would be of interest if the synthetic strategy could be adapted to other PROTAC series or employed in a high-throughput plate-based chemistry setting.

|*Alexandra*

bioRχiv

Induced Estrogen Receptor SUMOylation drives SERD activity

Matthias Hinterndorfer§, Caroline Schätz§, Stefan Schmitt§, ..., Anna C. Obenauf, Nicolas H. Thomä*, Georg E. Winter**

Selective estrogen receptor degraders (SERDs) have long been assumed to exert their therapeutic efficacy through degradation of ERa. Here, the authors systematically decouple SERD-induced SUMOylation effect from proteasomal degradation using orthogonal CRISPR/Cas9 screens, proximity labelling, cellular interaction assays, in vitro SUMOylation assays and CryoEM. Hinterndorfer et al. show that SERDs induce SUMOylation of ERa, priming the receptor degradation mediated via the SUMO-targeting ubiquitin ligases (STUbLs). The inhibition of STUbLs increases cell sensitivity to SERDs, demonstrating that ERa degradation is not required for SERD efficacy. The authors present a novel mechanism of SERDs, where the SUMOylated ERa recruits a transcriptional co-repressor (including NuRD) to chromatin, which silences estrogen signalling more effectively than complete ERa loss-of-function through inhibition or degradation. This work introduces a SUMOylation-induced transcriptional control as a drug targeting mechanism

| *Hannah*

ChemRxiv™

Predicting PROTAC Oral Bioavailability with Physics-Based Foundation Model Finetuning

Davide Boldoni, Jesko Fabian Kaiser, Heide Marika Duevel*, Christin Rakers**

Merck reports a deep learning framework to predict oral bioavailability. The large PROTAC data sets required for robust machine learning are not yet available, and so the authors attempt to pretrain the model with both small molecules and PROTACs. Pretraining approaches are complex and computationally expensive. The authors find these to be justified when the fine-tuning dataset is sufficiently relevant for the model's intended use, making this model useful for prioritising new designs in an established series. However, for ranking novel PROTACs, a robust model remains elusive; multiparameter scoring approaches therefore are still the best current solution.

bioRχiv

Discovery of CDK4-selective molecular glue degraders by high-throughput proteomics

*Patrick R.A Zanon, Bachuki Shashikadze, Denise Winkler,…,Henrik Daub**

Here, the authors report **NE26394**, a selective glue degrader targeting CDK4 whist sparing other CDK family members such as CDK6. **NE26394** is an optimised derivative of a hit identified during unbiased high-throughput proteomics of a CRBN-directed compound library of several thousand compounds. Interestingly, the authors report that CDK4 degradation relies on co-recruitment of INK4 family proteins, generating heterodimers that allow CRBN recognition. This work nicely highlights the power of proteomics in the molecular glue discovery pipeline.

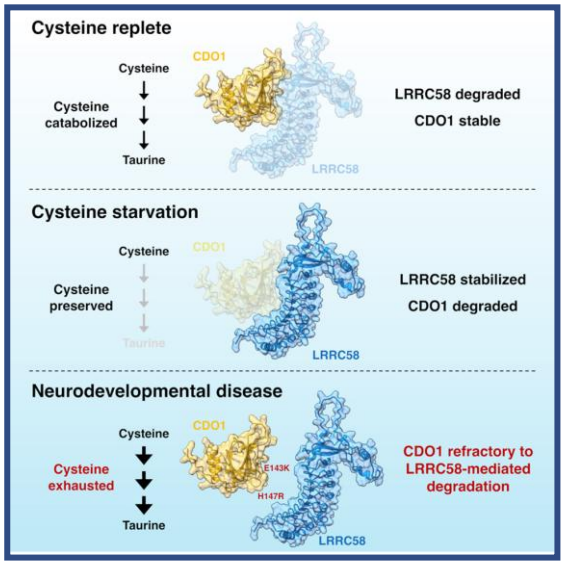
PAPERS AND PRE-PRINTS FROM CeTPD

| *Lianne*

LRRC58 defines an E3 ubiquitin ligase complex sensitive to cysteine abundance

*Dylan E. Ramage, …, Richard T. Timms**
Mol Cell, **2026**, 86(14), 2828-2842

CeTPD authors (past and present): Lianne H. E. Wieske, Charlotte Crowe, Mark A. Nakasone, Kevin Haubrich, Mark Dorward and Alessio Ciulli



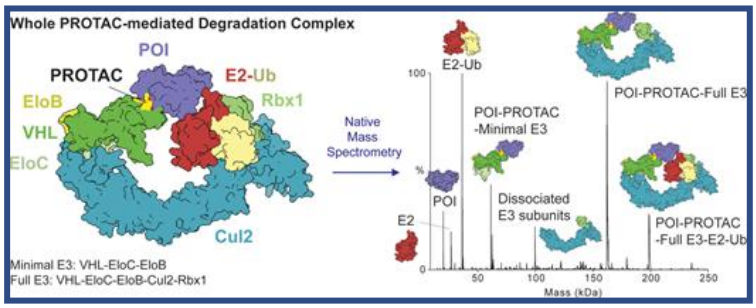
This paper brings us one step closer to understanding cellular cysteine regulation. This study shows that CDO1 levels are regulated by the ubiquitin-proteasome system (UPS) in response to extracellular cystine concentration. The substrate receptor LRRC58 is able to interact with and degrade CDO1. It was found that CDO1 as well as LRRC58 abundance was correlated to intracellular cysteine levels, and both appear to be regulated by the UPS. CDO1 abundance increased upon high cysteine concentrations, whereas LRRC58 levels showed an inverse correlation to cysteine concentrations. Unlike most substrate receptors reported so far, LRRC58 is able to complex with more than one cullin scaffold, and has been shown to form functional $CRL2^{LRRC58}$ and $CRL5^{LRRC58}$ complexes. Through saturation mutagenesis profiling, a structural model for the CDO1-LRRC58 interaction was established. Furthermore, several residues at the C-terminus of LRRC58 were identified as responsible for cysteine-dependent instability. The data show that LRRC58 E3-complexes are responsible for CDO1 ubiquitination, but it is not entirely clear what substrate receptor is involved in LRRC58 regulation.

| *Lianne*

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

*Louise M. Sternicki, …, Sally-Ann Poulsen**
Anal Chem, **2026**, 98(27), 20377-20388

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



When designing a novel chemical degrader, validation of ternary complex formation between the POI and the E3 ligase complex is crucial. Although structural methods such as cryo-EM and X-ray crystallography are the most informative, they are time-consuming and expensive. This paper shows that native mass spectrometry (nMS) can be used to characterise binary, ternary and higher-order complex formation of $CRL2^{VHL}$, using two different target proteins. The first $CRL2^{VHL}$ system consisted of $BRD4^{BD2}$ with PROTAC MZ1, and the second involved KRAS with PROTAC ACBI3. nMS was able to capture all relevant complexes for both $BRD4^{BD2}$/MZ1 and KRAS/ACBI3 with the E3 ($CRL2^{VHL}$) complex alone as well as with the full E2-E3 complex. The authors anticipate that these findings will open avenues for nMS to integrate as an alternative experimental method enabling scalable characterisation of the intricate high-mass multiprotein interactions central to biological mechanisms of action.

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