CeTPD Journal Club

October – November 2024

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

Centre for Targeted Protein Degradation
University of Dundee

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TABLE OF CONTENTS

MEET THIS MONTH'S EDITORS

Click here for info on the editor

CONNER CRAIGON

Conner completed his MRes and recently his PhD at the Univeristy of Dundee. He is currently working in an academic postdoctoral position in the Ciulli group as a cell biologist.

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CALUM McLAUGHLIN

Calum joined the Centre for Targeted Protein Degradation in September 2022 as a postdoctoral researcher in biological chemistry in the academic lab of Prof. Alessio Ciulli, working on a project in collaboration with Amgen. Previously, he was an Alexander von Humboldt postdoctoral research fellow in photochemistry in the group of Prof. Ryan Gilmour at the Westfälische Wilhelms-Universität Münster (Germany) and carried out his PhD at the University of St Andrews in the lab of Prof. Andrew Smith researching enantioselective organocatalysis.

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AINA URBINA TEIXIDOR

Aina completed her undergraduate degree in Pharmacy before pursuing her Ph.D. in Organic Chemistry in the research group of Prof. Joan Bosch and Prof. Mercedes Amat at the University of Barcelona. In May 2021, she joined the Centre for Targeted Protein Degradation as a medicinal chemist in the AC-Almirall collaboration to develop novel PROTACs, keen on expanding her knowledge of structure-based drug design and protein-ligand interactions.

LinkedIn: www.linkedin.com/in/aurbinateixidor/

PETR ZHMUROV

Pete obtained his PhD in Organic Chemistry at the Zelinsky Institute of Organic Chemistry (RAS) under the supervision of Prof. Alexey Sukhorukov. Following his PhD, he worked as a postdoctoral scientist at the Saint Petersburg State University in the Prof. Mikhail Krasavin group where he developed an interest in PROTACs. He joined the Centre for Targeted Protein Degradation as a medicinal chemist in February 2022 in the AC-Boehringer Ingelheim collaboration.

LinkedIn: Petr Zhmurov | 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"

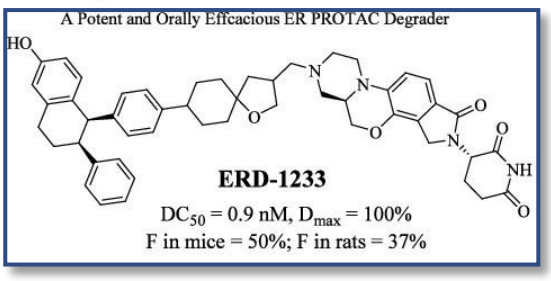
Literature review from 21st September to 20th November 2024

| *Aina*

Discovery of ERD-1233 as a Potent and Orally Efficacious Estrogen Receptor PROTAC Degrader for the Treatment of ER+ Human Breast Cancer

Ranjan Kumar Acharyya,§ Rohan Kalyan Rej,§ Biao Hu,§ Zhixiang Chen,§ Dimin Wu,§ … , Shaomeng Wang*

J. Med. Chem. **2024**, *67*, 19010-19037



Targeting ER+ is a promising therapeutic strategy for the treatment of ER+ breast cancer, which is the most common subtype of breast cancer (70%, based on 2017–2021 cases).[1] The authors describe here the efforts to develop potent and orally efficacious ER PROTACs using their novel and potent cereblon ligand (RR-11055) and Lasofoxifene as the ER binging moiety. Through an extensive linker optimisation involving rigidification and amide removal, they developed ERD-1233 which achieved maximal degradation with DC_{50} of 0.9 nM. This compound proved to have excellent microsomal and plasma stability, no significant hERG or CYP inhibition, oral bioavailability (F = 50 and 37% in mice and rats, respectively) and to achieve 68% tumour regression after oral administration at 20 mg/kg in the MCF-7 xenograft tumor model. Overall, the authors suggested that ERD-1233 has several advantages over ARV-471, Arvinas ER PROTAC in Phase 3 of clinical trials.

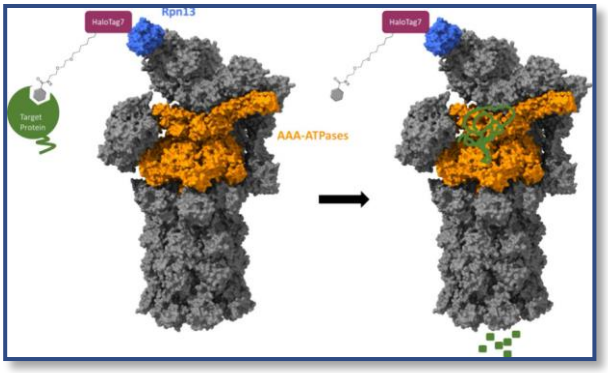
Shaomeng Wang's lab have developed a very interesting ER targeting PROTAC, showing excellent potency, good oral bioavailability and efficacy *in vivo*. Further extensive evaluation of the compound, showing its selectivity in a global level by proteomics and proving its PROTAC mechanism of action, would be necessary for a more complete assessment of ER-1233.

1. https://seer.cancer.gov/statfacts/html/breast-subtypes.html (accessed 19/11/2024)

| *Calum*

Recruitment to the Proteasome Is Necessary but Not Sufficient for Chemically Induced, Ubiquitin-Independent Degradation of Native Proteins

Madeline Balzarini, … , Thomas Kodadek*
ACS Chem. Biol. **2024**, *19*, 11, 2323–2335



In TPD, one challenge faced is that ternary complex formation is sometimes not sufficient for target degradation. Factors which can lead to this include (i) unsuitable alignment to Ub, or lack, of substrate acceptor lysine residues, (ii) E3 ligase tissue expression and localisation, and (iii) resistance to degraders through mutations or down-regulation of the E3 ligase.

Kodadek and co-workers report the development of Direct Proteasome Degraders (DPDs), which aim to by-pass the requirement for E3 ligase engagement and substrate poly-ubiquitination by utilising chemical dimerisers that induce proximity of POIs to the 26S proteasome. The authors clearly delineate their decision for choosing the proteasomal protein Rpn13 and have established an Rpn13(1−128)-HALO-FLAG cell line to analyse the DPD-mediated degradation of native proteins. JQ1-Halo DPDs were shown to selectively degrade BRD2, and relevant control experiments were conducted to demonstrate that this is a ubiquitin-independent process using inhibitors of NEDD8 and UBA1. A similar study was also carried out to demonstrate the degradation of CDK9. Global proteomics analysis, coimmunoprecipitation and siRNA knock down experiments were undertaken in attempt to rationalise the selectivity for BRD2 degradation over BRD4 and BRD3. The authors speculate that the selectivity is due to the differences of the unstructured region of BRD2 vs BRD4 that are engaged by the AAA ATPases, and less efficient recruitment to the proteasome in the case of BRD3. It is also noted that in contrast to PROTACs, which are highly dependent on linkerology, once the linker of the DPD is long enough, presumably to allow the ATPases to reach an unstructured region of BRD2, a further increase in linker length does not reduce activity. It will be interesting to determine if this is a singular occurrence or if this is a general distinction of DPDs to PROTACs, which will only be answered when more proteins are degraded using this approach.

I enjoyed reading this comprehensive study, it is a nice story with carefully planned experiments. This area has received less attention than Ub-dependent TPD, primarily due to the lack of proteasome ligands that do not interfere with core functions of the proteasome. With the recent reports of ligands for Rpm13 and PSMD2,[1,2] it will be intriguing to see what happens next in this space.

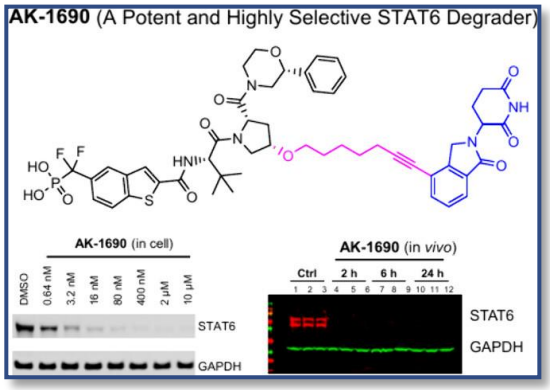
1. E. M. H. Ali, C. A. Loy, D. J. Trader, *BioRXiv*, 2024, DOI = 10.1101/2024.01.20.576376.

2. C. Bashore *et. al.*, *Nat. Chem. Biol.*, **2023**, *19*, 55.

| *Aina*

Discovery of AK-1690: A Potent and Highly Selective STAT6 PROTAC Degrader

Atsunori Kaneshige, Yiqing Yang, … , Shaomeng Wang*
J. Med. Chem. **Article ASAP** *DOI: 10.1021/acs.jmedchem.4c01009*



In this paper, the authors describe their medicinal chemistry efforts towards the development of several high-affinity and selective STAT6 ligands, starting from a previously reported STAT6 ligand with moderate affinity (K_i = 3.5 μM). The most potent ligand from this series, AK-068, with a K_i = 6 nM, was utilised for the design of STAT6 PROTAC degraders. From all the PROTACs reported, all lenalidomide-based with linear linkers, AK-1690 proved to be the most potent one (DC_{50} = 1 nM and D_{max} > 95% in MV4;11 cells). Further evaluation demonstrated that AK-1690 is selective for STAT6 against other STAT proteins, that follows a PROTAC mechanism of action and that has no effect on cereblon neo-substrates IKZF1 and IKZF3 at concentrations up to 10 μM. Finally, the authors proved the plasma and microsomal stability of AK-1690 and its effectiveness depleting STAT6 *in vivo* in mouse tissues.

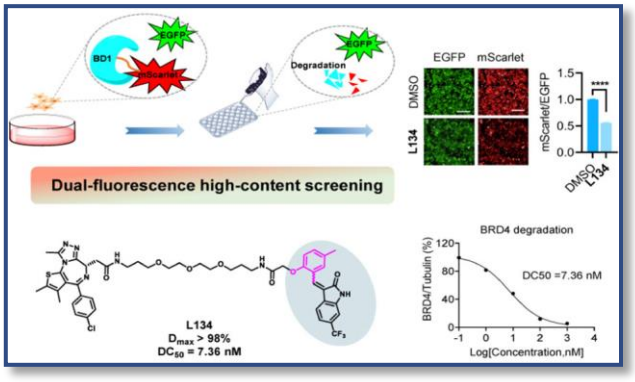
Shaomeng Wang's lab have rationally designed a potent and selective STAT6 PROTAC, showing *in vivo* efficacy, that can be used as a tool compound and potential lead for further optimisation. With the first-in-class oral STAT6 degrader entering clinical trials,[1] it is worth keeping an eye on further developments regarding STAT6 degradation.

1. https://investors.kymeratx.com/news-releases/news-release-details/kymera-therapeutics-announces-fda-clearance-investigational-0/ (accessed 19/11/2024)

| *Calum*

Design, Synthesis, and Activity Evaluation of BRD4 PROTAC Based on Alkenyl Oxindole-DCAF11 Pair

Man Zhao,§ Wenjing Ma,§ Jinyi Liang,§ … , Min Li,* Yuyang Liu,* Liang Hong,* and Guofeng Li*
J. Med. Chem. **2024**, *67*, 19428−19447



Despite the wide range present in human cells, only a limited number of E3 ubiquitin ligases have been exploited for application in TPD (such as VHL, CRBN, IAP, and MDM2) with many approaches generally relying on the most ubiquitously expressed VHL and CRBN. There is a clear need to expand the repertoire of functional E3 ligases to fulfil the potential of PROTACs. Considerable efforts are currently focussing on translating the success of CRBN ligands to other DDB1-CUL4 associated factors (DCAF) proteins. Recently, this lab and others have discovered

electrophilic PROTACs which can covalently engage the E3 ligase substrate adaptor protein DCAF11.

Previously, the authors reported a series of BRD4-DCAF11 PROTACs which utilised an alkenyl oxindole warhead to recruit DCAF11. In this article, structural modifications to the aromatic rings of the alkenyl oxindole skeleton have been made and the structure−activity relationship of a suite of PROTACs targeting BRD4 has been investigated. It was found that the activity of these degraders is significantly influenced by the substituents and positions around the scaffold of the alkenyl oxindole moiety. Utilising a dual-fluorescence reporter high-throughput screening system for BRD4 degradation, compound L134 was identified as a potent BRD4 degrader (D_{max} > 98%, DC_{50} = 7.36 nM). Extensive mechanistic experiments were performed to demonstrate that the degradation was mediated by the E3 ubiquitin ligase DCAF11 and proceeds through the ubiquitin-proteasome pathway.

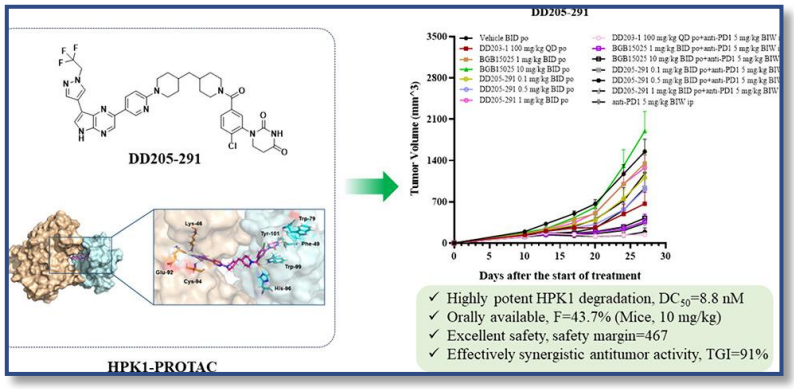
L134 has been identified as a potent BRD4 degrader, covalently recruiting the E3 ligase substrate adaptor protein DCAF11 through an alkenyl oxindole warhead. It will be interesting to see what other proteins can be degraded harnessing DCAF11 recruitment in the future.

| *Calum*

Discovery of Novel PROTAC-Based HPK1 Degraders with High Potency and Selectivity for Cancer Immunotherapy

Zhimin Zhang, … , Dongzhou Liu*

J. Med. Chem. **2024**, 67, 21, 18682–18698



Hematopoietic progenitor kinase 1 (HPK1, MAP4K1) is a serine/threonine kinase part of the MAP4K family, predominantly found in immune cells and is recognised as a negative regulator of TCR signalling. Deprivation of the HPK1 function suppresses tumour growth, providing an attractive strategy for cancer immunotherapy. Whilst there are several HPK1 inhibitors in (pre)clinical studies showing satisfactory outcomes, these cannot not disturb the signalling emitted from the non-kinase scaffolding domain, leading to a suboptimal immune response.

The authors posited that a PROTAC approach would enable superior efficacy to be achieved. Starting from a previously developed in-house inhibitor as the POI ligand and phenyl dihydrouracil as the CRBN recruiter of choice, a range of linker motifs were systematic assessed in the quest for a HPK1-PROTAC with high potency and oral bioavailability. Whilst linear linkers were amenable, rigid dipiperazine structures provided optimal HPK1 degradation. Structure-activity relationship investigations of the POI binder led to a further enhancement of degradation efficiency, with DD205-291 being identified as a potent degrader (DC_{50} = 8.8 nM, D_{max} = 94%). DD205-291 inhibited SLP-76 phosphorylation and demonstrated stimulation activity for immunomodulatory factors. Mechanistic experiments indicated that the process was dependent on ternary complex formation, ubiquitination, and proteasomal degradation. Additional studies showed favourable PK−PD characteristics both in vitro and in vivo, including

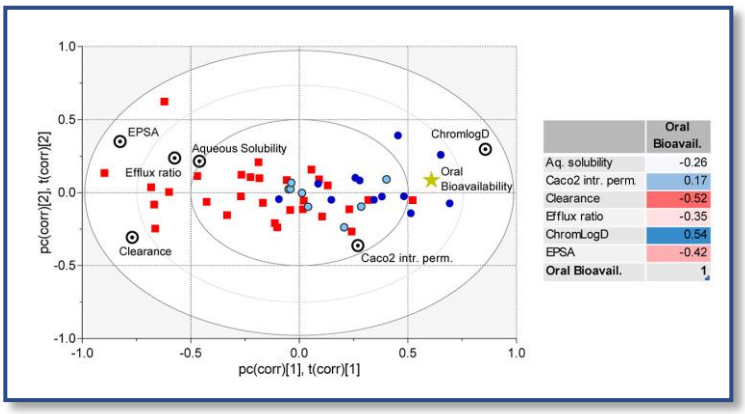
good metabolic stability, oral exposure, and bioavailability, whilst displaying in vivo antitumor activity.

Liu and co-workers have developed a novel HPK1 PROTAC for cancer immunotherapy. It was fascinating to read the story of how an inhibitor can be beneficially translated to a PROTAC modality, providing a preclinical candidate. This study was comprehensive and definitely worth a read, in my opinion!

| *Pete*

Closing the Design–Make–Test–Analyze Loop: Interplay between Experiments and Predictions Drives PROTACs Bioavailability

Authors Zulma Santisteban … , Thomas Lundbäck,* Tomas Leek* and Johan Wernevik*
J. Med. Chem. **2024**, *67*, 22, *20242–20257*



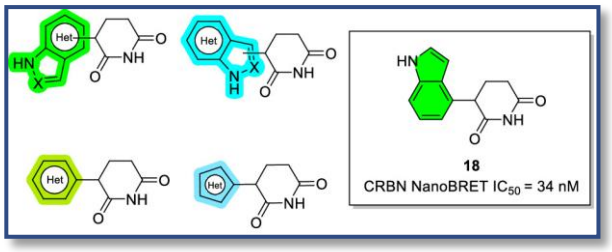
Lipophilicity is a key structural property of a drug that affects its absorption, distribution, metabolism, excretion, and pharmacological activity. Sufficient lipophilicity is required for passive uptake over the cell membrane; however, it could also cause poor water solubility, which can limit drug absorption and increase nonspecific binding to proteins or tissues.
Another commonly used metric for predicting drug passive cellular uptake is the experimental polar surface area (EPSA). This method conditions promote intramolecular hydrogen bonding, providing better prediction of the conformation assumed by molecules in solution. This conformational change can affect molecule size and polarity—parameters which also show a decent correlation with permeability. This effect is especially important for bRo5 compounds such as macrocyclic peptides and PROTACs.
In this study, researchers from AstraZeneca demonstrated the use of in-house developed automated chromatographic LogD and EPSA assay for PROTACs, highlighting advantages of the former over the shake-flask method, while also noting only a weak correlation with LogD predictions. They also showed with contribution coefficients that bioavailability correlates positively with ChromLogD, while a negative correlation is observed for EPSA, clearance, and to some extent, efflux ratio. Solubility and permeability appear to have a smaller influence on oral bioavailability.

This study showed how the implementation of two chromatographic high-throughput assays can significantly speed up the optimisation of physicochemical and DMPK characteristics of drug candidates.

| *Pete*

Heteroaryl Glutarimides and Dihydrouracils as Cereblon Ligand Scaffolds for Molecular Glue Degrader Discovery

Yuebiao Zhou*, …, Christian Nilewski*
ACS Med. Chem. Lett. **Article ASAP** *DOI: 10.1021/acsmedchemlett.4c00445*



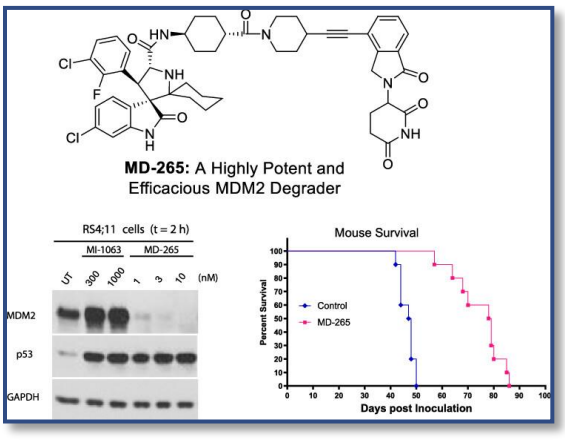
An excellent paper from Genentech scientists discusses novel indole and indazole-based CRBN ligands as warheads for molecular glue degraders. They selected the recently published phenyl glutarimide as a SAR starting point. Even though it was ten times weaker than Lenalidomide, it showed better hydrolytic stability.
Using molecular modelling and CRBN ternary complex crystal structures, they synthesised different regioisomers of indazolyl- and indolyl glutarimides. The authors found that 4-indolyl glutarimide exhibits slightly higher affinity compared to Lenalidomide and more than five times better chemical stability. The indazole analogue had weaker binding due to their lower lipophilicity (resulting in very close ligand-lipophilicity efficiency).
To further improve chemical stability, they replaced the glutarimide with a non-racemisable dihydrouracil. Unfortunately, this resulted in a tenfold loss of potency.

This paper opens a door for the development of new more stable CRBN ligands. It will be interesting to see how that approach develops to provide more potent and stable degraders.

| *Pete*

Discovery of MD-265: A Potent MDM2 Degrader That Achieves Complete Tumor Regression and Improves Long-Term Survival of Mice with Leukemia

Angelo Aguilar, …, Shaomeng Wang*
J. Med. Chem. **2024**, *67*, 21, *19503–19518*



Previously, Wang's group reported the discovery of MD-224, a first-in-class PROTAC degrader of the murine double minute 2 (MDM2) protein. This protein inhibits the tumour suppression function of the non-mutated tumour suppressor p53. Replacing the benzamide moiety in MD-224 with a cycloalkyl linker led to a fourfold increase in degrading potency. Rigidifying the flexible 4-pentyn-1-amine linker by converting it to a 4-ethynyl-piperidine analogue preserved the antiproliferation activity, but also demonstrated antiproliferative activity against p53 mutated cell line, caused by GSPT1 degradation. Both lead compounds achieved complete tumour regression in the xenograft model.
Combining linker rigidification and non-aromatic cycloalkyl structural fragments in one molecule led to the development of MD-265. This degrader achieved sub nanomolar cell growth inhibition

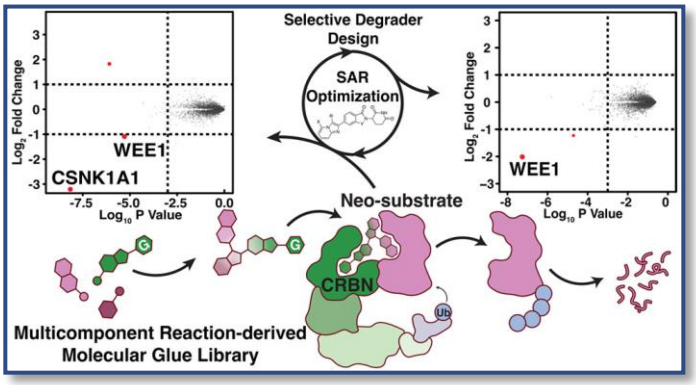
(wild-type RS4;11) and inhibited cell growth in another nine acute leukaemia cell lines (5-200 nM), also showing no GSPT1 degradation.
It was previously reported that treatment with a potent MDM2 inhibitor could lead to quick tumour regrowth and resistance development, based on p53 mutation. Treatment with MD-265 not only induced complete tumour regression, but the regrown tumour was shown to be responsive to a second round of treatment.

Another great example of PROTAC rational design from Wang's group. This SAR optimisation will be in the linkerology textbooks.

| *Pete*

Discovery of CRBN-Dependent WEE1 Molecular Glue Degraders from a Multicomponent Combinatorial Library

Hlib Razumkov, …, Eric S. Fischer*, Nathanael S. Gray*
J. Am. Chem. Soc. ***2024****,* 146, 46, *31433–31443*



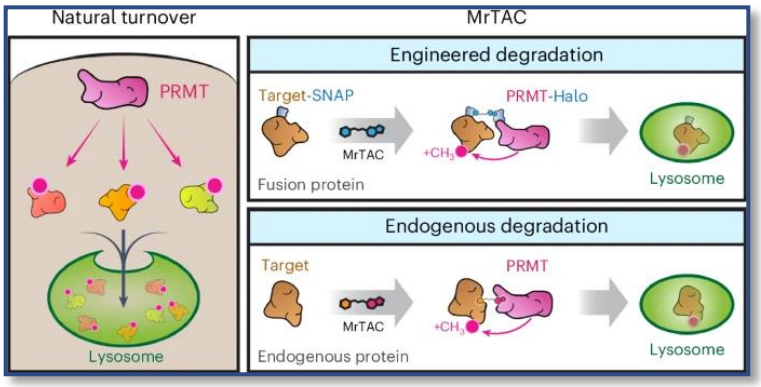
The multicomponent reaction strategy has proven its efficacy for the rapid synthesis of large and diverse screening libraries of bioactive compounds. In this paper, the authors demonstrated that this approach could be applied as a rapid and efficient glutarimide derivatisation strategy. They used the Groebke−Blackburn−Bienaymé reaction to synthesise over 200 novel molecular glues, starting from a small set of common glutarimide-containing aldehydes. Screening the resulting library led to the discovery of novel WEE1/CK1a dual degraders. After additional structural optimisation, a selective WEE1 degrader was obtained; however, this selective degrader exhibited only mild cytotoxic effects and did not decrease relative proliferation below 50% and only modest increase in cytotoxicity during co-treatment with DNA-damaging chemotherapy agent.

The application of multicomponent reactions for the synthesis of molecular glue libraries could streamline hit identification and subsequent structure optimisation. I can't wait to see more examples of this strategy.

| Conner

Methylarginine targeting chimeras for lysosomal degradation of intracellular proteins

Laurence J. Seabrook…. Lauren V. Albrecht
Nat Chem Biol, ***2024***, *20, 1566–1576*



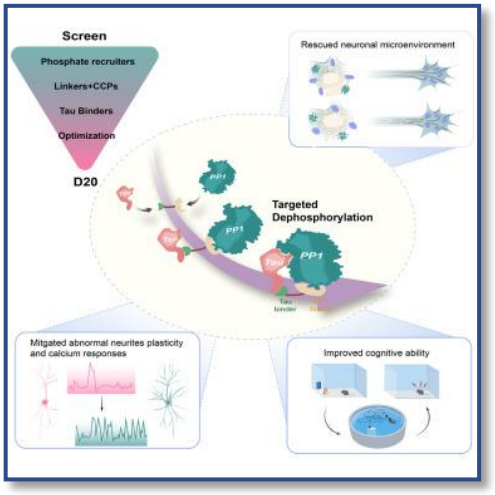
The authors present a methodology leveraging endogenous arginine methyltransferases (PRMTs) to trigger substrate degradation through arginine methylation. Their approach, named 'MrTAC,' utilizes a heterobifunctional small molecule to recruit PRMT1 to target proteins, initiating degradation in lysosomes via the microautophagy pathway. The study highlights MrTAC's effectiveness in degrading key cancer targets—BRD4, GSK3B, MYC, and HDAC6 — across various cell lines, timeframes, and dosages. Overall, MrTAC showcases the potential of harnessing endogenous lysosomal proteolysis to develop a novel class of small-molecule degraders.

This work from the Albrecht lab has exciting implications for the field of TPD. Their work demonstrates for the first time the usurpation of the micro autophagy pathway in degrading targeted proteins and its broad use against multiple high profile cancer targets in a fast and potent autophagy-mediated mechanism of action. Moving forward from this work, it would be interesting to see this work move away from the use of the HaloTag® technology onto the development of bifunctional compounds utilising currently developed inhibitors against PRMT to determine if the retain the autophagy mediated degradation and open up the TPD field towards using micro autophagy as an alternative to ubiquitin mediated degradation.

| Conner

A tau dephosphorylation-targeting chimera selectively recruits protein phosphatase-1 to ameliorate Alzheimer's disease and tauopathies

Yue Xiao, Linyu Wei,…· Xiaochuan Wang, Jie Zheng,* Jian-Zhi Wang**
Cell Chem Biol., ***2024,*** *17;31(10), 1787-1799*

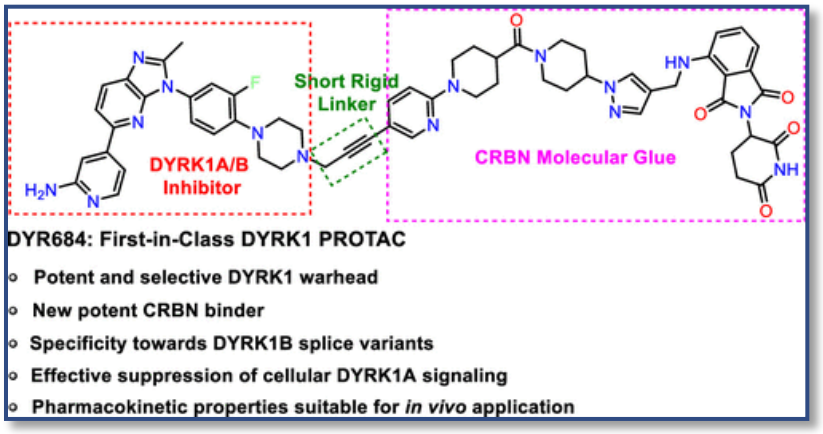


Abnormal accumulation of hyperphosphorylated tau (pTau) is a major cause of neurodegeneration in Alzheimer's disease (AD) and related tauopathies. The authors here describe the development of the D20 chimeric peptide that recruits PP1, a tau phosphatase. In both cultured primary hippocampal neurons and mouse models for AD or related tauopathies, the authors demonstrate that D20 is able to significantly reduce pTau by dephosphorylation at multiple AD-related sites and total tau. Highlights of the paper include demonstrating that multiple-dose administration of D20 through tail vein injection in 3xTg AD mice effectively ameliorated tau-associated pathologies with improved cognitive functions and that D20 was shown to not cause detectable toxicity in cultured neurons, neural cells, or peripheral organs in mice.

This work by the Jian-Zhi Wang lab expands upon the chemical space of DEPTAC (DEPhosphorylation TArgeting Chimera) through their best chimeric molecule D20, which they show demonstrates a significant reduction in tau phosphorylation both in cells and in vivo, as well as a reduction in tau-related pathology in mice, without exhibiting toxicity. Critically they show that D20 can effectively penetrate the blood-brain barrier in vivo. However, a current limitation in the DEPTAC compounds is their reliance in mice, which do not fully capture the complexity of Alzheimer's disease in humans. Future research on D20 and other related molecules should focus on utilising more advanced disease models to better understand its potential therapeutic benefits of these molecules in humans.

Discovery and Functional Characterization of a Potent, Selective, and Metabolically Stable PROTAC of the Protein Kinases DYRK1A and DYRK1B

Gerrit Wilms, Kevin Schofield, ...Walter Becker, Christopher Hulme**
J. Med. Chem. ***2024,*** *67, 17259−17289*



DYRK1A and DYRK1B are closely related protein kinases that are involved in pathological processes such as neurodegeneration, cancer development, and adaptive immune homeostasis. Herein, the authors report the development of the first DYRK1 proteolysis targeting chimeras (PROTACs) that combine a new ATP-competitive DYRK1 inhibitor with ligands for the E3 ubiquitin ligase component cereblon (CRBN) to induce ubiquitination and subsequent proteasomal degradation of DYRK1A and DYRK1B. Highlights from the paper include DYR684 their lead compound promotes fast, efficient, potent, and selective degradation of DYRK1A in cell-based assays and compared to competitive kinase inhibition, targeted degradation of DYRK1 by DYR684 provided improved suppression of downstream signalling. This research highlights the possibility of targeting DYRKs via PROTAC-mediated degradation.

This work by the Hulme lab presents an impressive breakthrough in developing the first PROTACs targeting the disease-causing kinases DYRK1A and DYRK1B. Notably, the study reveals that a splice variant of DYRK1B exhibits resistance to degradation by their most effective PROTAC molecule, DYR684. This intriguing observation highlights the need for future research to uncover the structural mechanisms underlying this resistance. Such insights could enable the design of tuneable degraders or the development of PROTACs selectively targeting either DYRK1A or DYRK1B.

PRE-PRINTS

| *Aina*

ChemRxiv™ Rational Design of CDK12/13 and BRD4 Molecular Glue Degraders

*Zhe Zhuang,§ Woong Sub Byun,§ … , Nathanael S. Gray**

Although designing molecular glue degraders has proven to be challenging and sometimes relies on serendipity, the authors of this paper explore the incorporation of gluing moieties in parenteral inhibitors to transform them in molecular glue degraders. Particularly successful is the design of ZZ3 as a potent CDK12/13 degrader, with the introduction of a phenyl amide into a CDK12/13 binder. It will be interesting to see if this strategy can be broadly applied to other protein binders for its degradation.

| *Aina*

bioRχiv Development of Potent and Selective CK1α Molecular Glue Degraders

*Qixiang Geng,§ Zixuan Jiang,§ … , Nathanael S. Gray**

In this paper, the authors identified a molecular glue that induces potent and selective CK1α degradation, through explorative synthesis of a glutarimide-based library, scaffold hopping and rational modification, understanding the SAR associated with the gluing moiety. Considering that CC-91633, a CK1α molecular glue from BMS, entered Phase 1 clinical trials, it is important to better understand the structural basis for CK1α–CRBN recognition.

| *Pete*

bioRχiv Degraders Discovery of electrophilic degraders that exploit SNAr chemistry

*Qixiang Geng,§ Zixuan Jiang,§ … , Nathanael S. Gray**

This preprint showed application of SNAr chemistry for the design of electrophilic protein degraders. Attaching an SNAr warhead onto a BRD4 inhibitor led to the discovery of BRD4 degraders with low picomolar potency. Moreover, SNAr covalent warheads can recruit various E3 ubiquitin ligases, like DCAF11 and DCAF16 to generate degraders targeting AURKA, AURKB, PTK2B, ITK, LIMK2, CDK4, CDK6, CDK12, and WEE1.

ChemRxiv™

Computation, *Synthesis and NMR Investigations of PROTAC Linker Conformation, Chamaleonicity and their Impacts on the Mode of Action*

Hao Lan, ..., Alessio Ciulli, Craig P. Butts* and Varinder K. Aggarwal*

Based on well-known VHL-based BET degraders MZ1 and ARV771 authors designed two new BRD4 degraders HL1 and HL1CON with flexible hydrophilic and semi-rigid hydrophobic linkers. The rigidity of the latter one was developed to potentially stabilize the MZ1-type ternary complex similarly to HL1 and to improve membrane permeability. However, HL1CON exhibits non-chameleonic hydrophobic collapse in different solutions as well as in VHL binary complexes.

OTHER PAPER HIGHLIGHTS

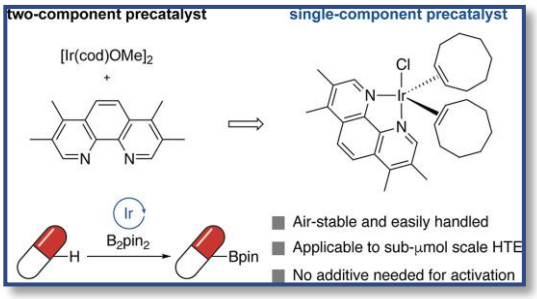
CHEMISTRY | STRUCTURAL BIOLOGY & BIOPHYSICS | CELL BIOLOGY | MODELLING

| *Pete*

An Air-Stable, Single-Component Iridium Precatalyst for the Borylation of C–H Bonds on Large to Miniaturized Scales

Kyan A. D'Angelo, Chris LaBrian, ..., Noah P. Tu*, Shashank Shekhar* and John F. Hartwig*
J. Am. Chem. Soc. ***2024***, 146, 47, *32717–32729*

There is a report of a single-component iridium precatalyst for of aryl and heteroaryl C-H borylation. This precatalyst is air-stable, reacts with higher turnovers without losing comparable selectivity. It also can be used in high-throughput small-scale systems.

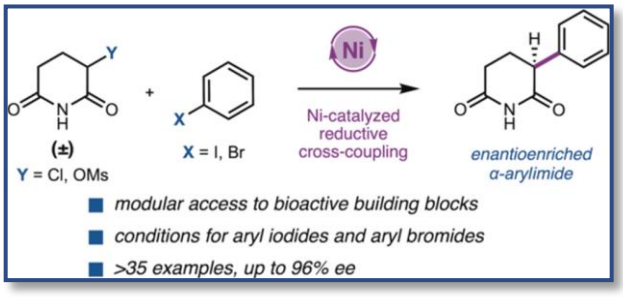


| *Pete*

Catalyzed Asymmetric Reductive Arylation of a-Substituted Imides

*Li-Ming Chen...., Sarah E. Reisman**
J. Am. Chem. Soc. ***2024***, 146, 43, *29523–29530*

In this paper, the authors describe Ni-catalysed asymmetric reductive cross-coupling of racemic imide electrophiles and (hetero)aryl halides. This reaction provides access to enantioenriched a-arylglutarimide motifs, which can be exploited for the development of novel CRBN binders. The racemisation rate of a-phenylglutarimides with various substitutions is also discussed.



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