# CeTPD Journal Club

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


July 2023

Centre for Targeted Protein Degradation
University of Dundee

innovate
collaborate
inspire

Journal Club

# Content

# Meet this Month's Editors

This month's editors are (from left to right): Angus Cowan, Shakil Khan, and Xingui Liu

*"TPD is a rapidly developing field, I'm glad to contribute to making new work more accessible and digestible through Journal Club"*

Angus obtained his PhD in 2017 at the Walter and Eliza Hall Institute (Melbourne) under the supervision of Professors Peter Czabotar and Peter Colman, investigating the structure and function of pro-apoptotic BCL-2 family proteins. After a 2 year postdoc working as part of an academic team collaborating with an industry partner to develop modulators of necroptosis, he joined Ciulli group in January 2020. Angus' research focuses on structural and functional investigation of substrate receptors of CRL4 E3 ligases, with a view to exploiting them for targeted protein degradation.

*"This Journal Club is an amazing resource to keep us up-to-date with the latest discoveries in the targeted protein degradation field."*

Shakil completed his MRes in Drug Discovery at the University of Aberdeen and his PhD under the supervision of Dr Xuming Zhang at Aston University. Here, Shakil's doctoral research centered around identifying novel binding partners to ion channels involved in pain. Shakil joined the Ciulli Group in August 2021 as a Cell Biologist as part of the PROTAC Drug Discovery collaboration with Boehringer Ingelheim.

"*Editing Journal club is a great team work and I feel proud to contribute to the TPD field in this way."*

Xingui Joined the Ciulli group as a postdoctoral scientist in Jan 2021. Before joining the Ciulli group, she worked as postdoc associate at the University of Florida where she was trained in drug discovery research in TPD. She completed her PhD in medicinal chemistry at the University of Arkansas for Medical Sciences and obtained her undergraduate degree in pharmacy and Master degree in medicinal chemistry from the China Pharmaceutical University and East China Normal University, separately.

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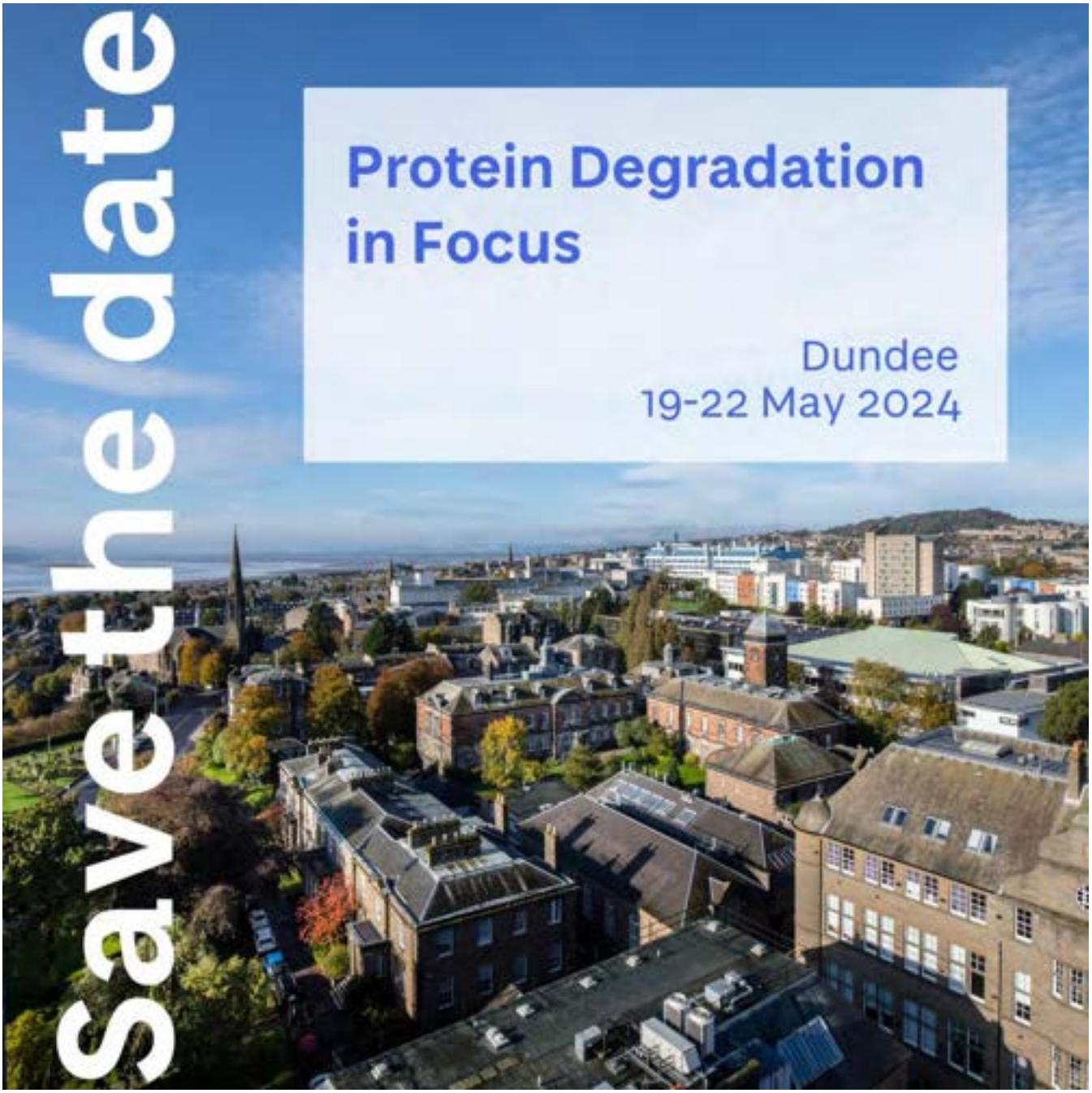
## Save the Date "*Protein Degradation in Focus: a Special Symposium to Celebrate the Opening of CeTPD in Dundee*"




We invite you to save the date for the 2024 Symposium "***Protein Degradation in Focus: A Special Symposium to Celebrate the Opening of CeTPD in Dundee***" taking place 19 to 22 May 2024 at the School of Life Sciences, University of Dundee.

More information and registration to follow soon. We hope that you'll be able to join us!

The Scientific Organisers
Alessio Ciulli, Brenda Schulman, Craig Crews, Valentina Spiteri and Charlotte Crowe

# Back of the Napkin – Inspiring Stories from Scientific Pioneers

Contributor: Alex Moloney. Twitter @MoloneyAlex

A discovery is often the serendipitous encounter of an accident and a prepared mind. Yet, the fascinating stories behind discoveries are intricate tales of their own. Sometimes, ideas are born during brainstorming sessions or from a flash of inspiration that can be captured in hasty scribbles on the back of a napkin. Inspired by this very notion, Bio-Techne presents a new podcast called "Back of the Napkin" (BotN), which delves into the careers of scientific pioneers, unraveling the untold stories that have sparked game-changing ideas and breakthroughs.

BotN seeks to unveil the essence of those light bulb moments, the instances when ideas materialize into reality. It explores the creative processes behind the genesis of novel concepts and navigating the obstacles encountered along the way. With insightful questions and thought-provoking discussions, the podcast presents new ideas on fostering innovation while remaining relatable and empowering to its listeners.

Series 1 of BotN is a collection of 6 episodes featuring ingenious minds in the life sciences. Among them are trailblazers like Matthew Disney, inventor of ribonuclease targeting chimeras (RIBOTACs), and Jennifer Petter, the Founder and Chief Innovation Officer at Arrakis Therapeutics. Episode three is recorded at the CeTPD and features the Founder and Director of the facility, Alessio Ciulli. Additionally, chemical biology pioneers like Neal Devaraj and drug discovery visionaries Amy Ripka and Michelle Arkin add their own unique tales to the mix, each sharing valuable insights into their landmark contributions to science.

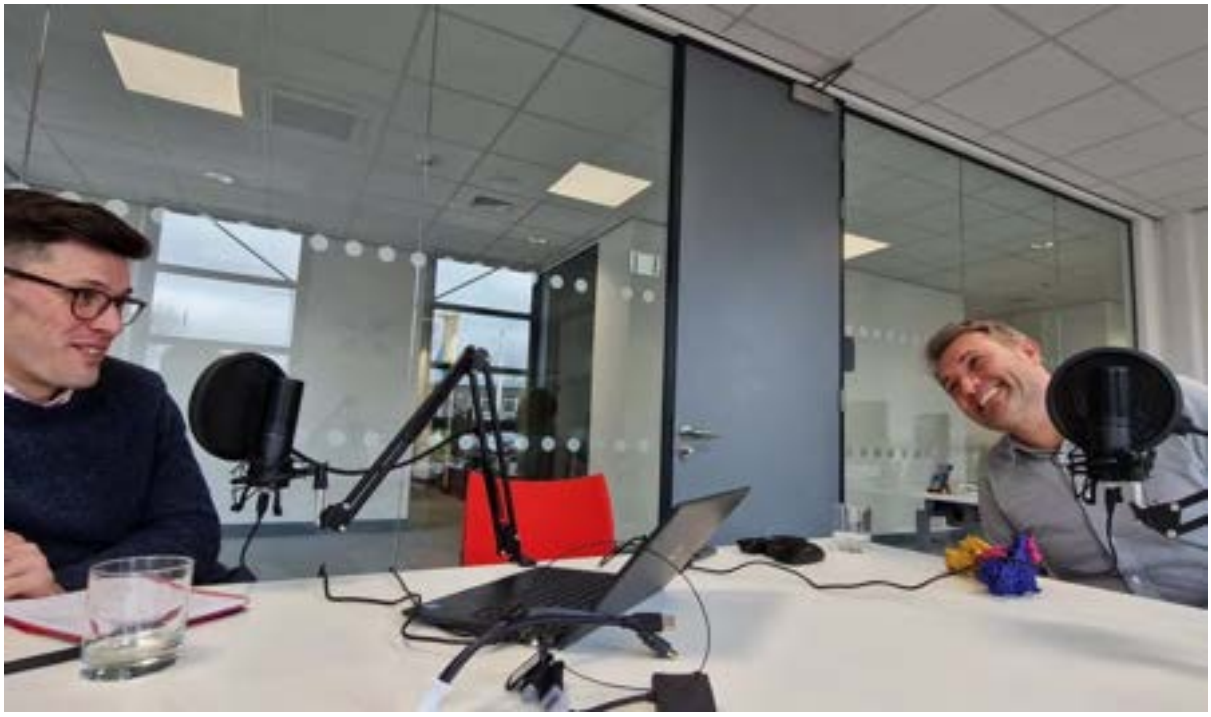


*Figure 1: Recording underway for Episode 3 with CeTPD Founder and Director, Alessio Ciulli. "At the forefront of targeted protein degradation"*

A common thread unites each episode; the unmistakable passion driving these remarkable individuals in their pursuits. From revolutionising enabling technologies in chemical biology to developing groundbreaking therapeutics for Parkinson's disease, each guest shares an unquestionable dedication to driving science forward through their individual contributions.

In true homage to the podcast's name, every guest leaves behind a personalized scribble on the back of a napkin. These humble pieces of tissue paper not only serve as podcast memorabilia but as constant reminders that greatness can arise from the simplest beginnings, a 5"x5" canvas of creativity.

"Back of the Napkin" promises to ignite your curiosity, inspire your imagination, and kindle your own sparks of innovation. Welcome to a world where extraordinary discoveries are born, one napkin at a time.

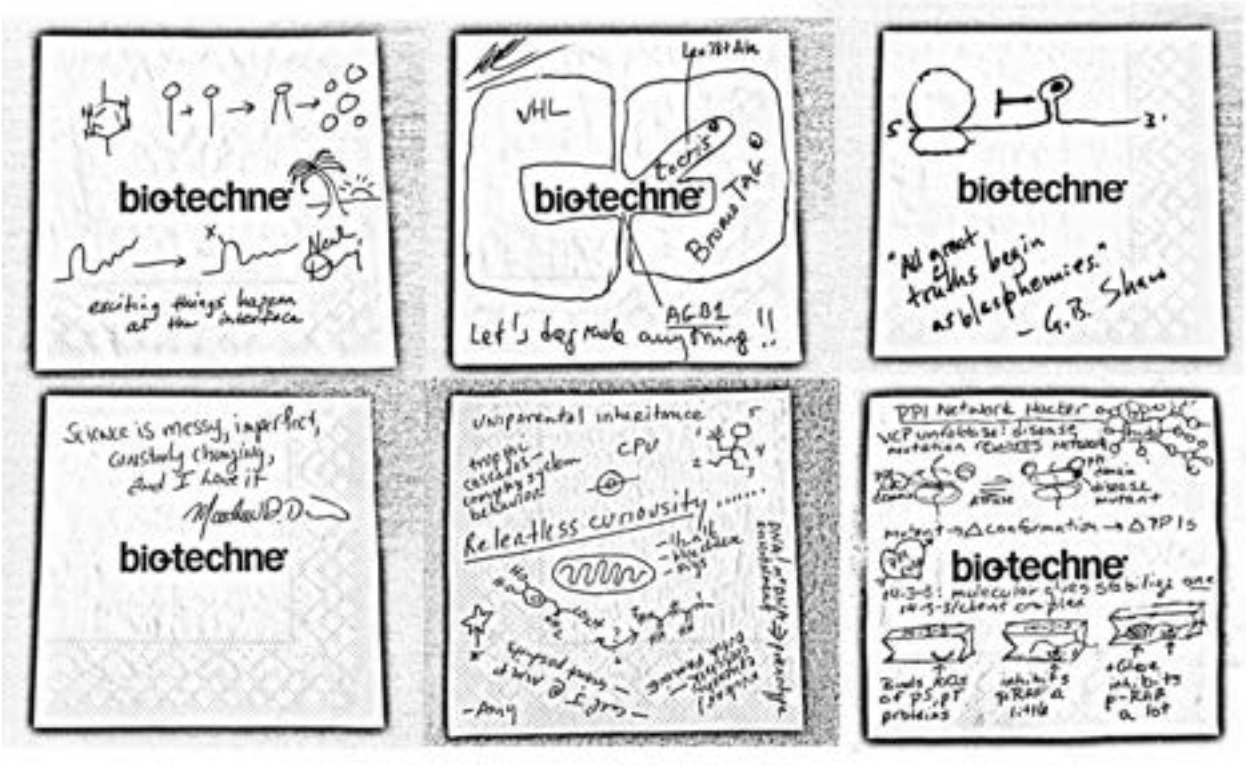



*Figure 2: Napkins from the Series 1 guests. Top left: Neal Devaraj. Top middle: Alessio Ciulli. Top right: Jennifer Petter. Bottom left: Matthew Disney. Bottom middle: Amy Ripka. Bottom right: Michelle Arkin.*

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BACK OF THE NAPKIN

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# Targeted Protein Degradation

Chemistry | Structural Biology/Biophysics | Cell Biology

Contributor: Xingui

## Expanding Chemical Probe Space: Quality Criteria for Covalent and Degrader Probes

Ingo V. Hartung*, Joachim Rudolph, Mary M. Mader, Monique P. C. Mulder, and Paul Workmango

*J. Med. Chem.* **2023**, 66, 9297–9312

| Quality Criteria | Reversible Chemical Probes | Covalent Chemical Probes | Degrader Chemical Probes |
|---|---|---|---|
| Potency | Biochemical < 100 nM<br>Cellular < 1 μM | Provide $k_{inact}/K_I$<br>Cellular < 1 μM | $DC_{50}$ < 1 μM<br>$D_{max}$ > 80% |
| Selectivity | > 30-fold within family<br>+ safety panels | > 30-fold to neighbors<br>+ unbiased proteomics<br>+ safety panels | > 30-fold to neighbors<br>+ unbiased proteomics<br>+ safety panels |
| Target Engagement | Biophysical proof of on-target activity | Identify site of covalent labeling | Proof of on-target & on-E3 activity |
| Chemical Matter | Denisk potentially promiscuous or PAINs motifs | | |
| Control Compounds | > 100-fold weaker on target | Intact warhead,<br>> 100-fold weaker on target | Intact target binder,<br>> 100-fold weaker on E3 |
| Stability & Reactivity | Stable in relevant media | Avoid excessive chemical reactivity | Avoid fast deterioration of structural integrity |

Chemical probes are cell-active, selective, highly validated research tools that can be used to decipher the biology of their targets. High-quality probes represent a critical component in both basic research and drug discovery and applying quality criteria has been an accepted practice among scientific communities (e.g. Chemcal Probes. Org, SGC, EUbOPEN). With the chemical space of probes expanding from reversible molecules to covalent and bivalent molecules, new quality criteria tailored for these new modalities are 5arranted. This review paper by Hartung et al. met this need by proposing potency, selectivity, and chemical matter criteria for covalent and bifunctional degrader probes.

These criteria are set based on the development pathways of successful probes. They can serve as guidelines for covalent and bivalent degraders probes and for drugs development.

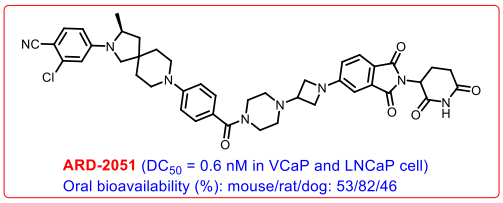
Cell Biology | Chemistry | Structural Biology/Biophysics

Contributor: Xingui

## Discovery of ARD-2051 as a Potent and Orally Efficacious Proteolysis Targeting Chimera (PROTAC) Degrader of Androgen Receptor for the Treatment of Advanced Prostate Cancer

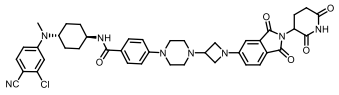
Xin Han§, Lijie Zhao§, Weiguo Xiang§, Bukeyan Miao§, Chong Qin§, Mi Wang§, …, Shaomeng Wang*

*J. Med. Chem.* **2023**, 66, 8822–8843

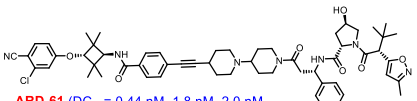



**ARD-2051** ($DC_{50}$ = 0.6 nM in VCaP and LNCaP cell)
Oral bioavailability (%): mouse/rat/dog: 53/82/46

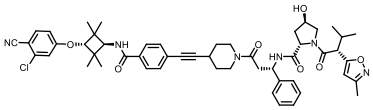
Androgen receptor (AR) is one of the most popular targets for PROTACs with at least 6 AR PROTAC degraders (AC176, ARV-766, ARV-110, GT20029, HP518, and CC-94676) in clinical trials. Most of them are CRBN-based and orally bioavailable PROTACs. In this new issue of J. Med. Chem, Wang's group reported another very potent and orally bioavailable AR PROTAC, named ARD-2051, adding to the long list of AR PROTACs his group has reported previously (e.g. ARD-2585, ARD-61, ARD-266, and ARD-69).



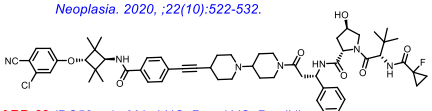
**ARD-2585** ($DC_{50}$ = 0.04-0.1 nM in VCap and LNCaP, oral bioavailability in mice = 51%)
*J. Med. Chem. 2021, 64, 18, 13487–13509*



**ARD-61** ($DC_{50}$= 0.44 nM, 1.8 nM, 2.0 nM, 2.4 nM and 3.0 nM in the MDA-MB-453, MCF-7, BT-549, HCC1428 and MDA-MB-415 cell lines separately, degrades AR in vivo after IP injection)
*Neoplasia. 2020, ;22(10):522-532.*



**ARD-266** ($DC_{50}$ = 0.5 nM in LNCaP and $DC_{50}$ = 1.0 nM in VCaP)
*J. Med. Chem. 2019, 62, 24, 11218–11231*



**ARD-69** (DC50 < 1 nM in LNCaP and VCaP cell line, degrades AR in vivo after IP injection)
*J. Med. Chem. 2019, 62, 2, 941–964*

This round of medicinal chemistry campaign is based on ARD-2585, aiming to improve its oral bioavailability in rat, probably because pharmacokinetic profiles in rat are more transferable to human. They started their modification by optimizing their warhead guided by computational modelling and found improving the binding affinity to warhead could significantly increase degradation potency. After two rounds of iterative structure modifications on the linkers and warheads and pharmacokinetic profillings, ARD-2051 was obtained as the best new degrader that showed better pharmacokinetic and pharmacodynamic profiles than ARV-110, the first AR PROTAC degrader in Phase 3 clinical trial, and could be promising candidate for preclinical evaluation. Newer generations of AR degraders with modifications on the E3 ligase ligand are likely to follow up as this moiety has not been touched in this series of compounds.

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Cell Biology | Chemistry | Computational Chemistry | Modelling/Simulation | Structural Biology/Biophysics

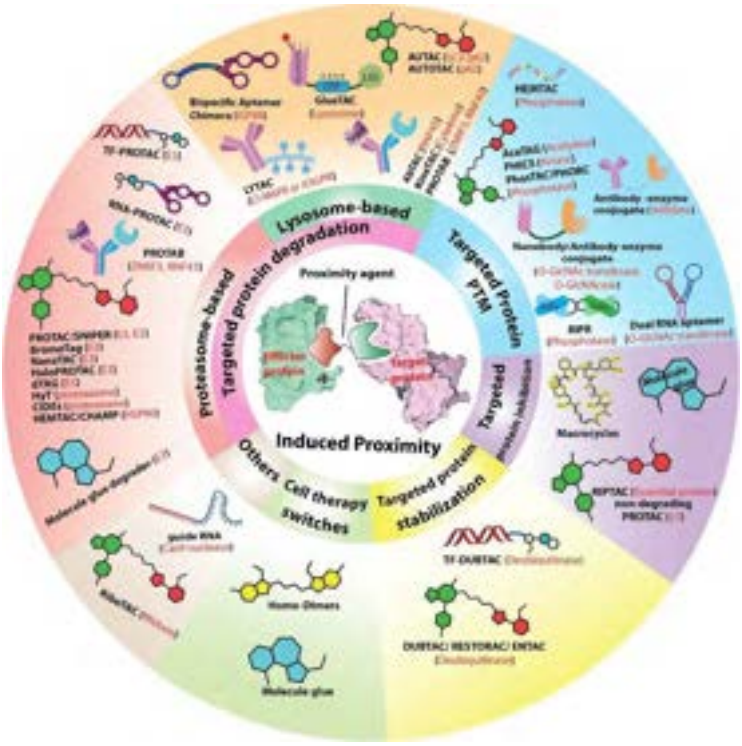
Contributor: Xingui

## Proximity-Based Modalities for Biology and Medicine

Xingui Liu[§] and Alessio Ciulli*

*ACS Cent. Sci.* **2023**, 9, 1269–1284

Proximity-based modalities are emerging drug discovery strategies. They work through various different mechanisms of action, including targeted protein degradation, targeted protein post-translational modification, targeted protein inhibition, targeted protein stabilization, cell therapy switches, and many others. Nevertheless, not all induced proximity modalities are created equal and they come with advantages and challenges. In this outlook paper, Alessio and I present you with the brief introduction of all the modalities, their developing histories, current development stages, future development prospects, and more importantly, the opportunities and challenges the field has to address to better apply these modalities to both basic research and drug discovery.




We hope this is a timely presentation to the field when the the molecular glue and PROTAC degraders are rising meteorically with many of them being approved or advanced into clinic studies, and new proximity-based modalities are surging at a ever faster speeds. We also hope you find this outlook useful and that it will inspire the next steps in the field. It is worth noting that although we have focused the induced proximity between protein and protein (or nucleic acid) in this outlook paper, using bifunctional molecules to bridge cell-cell interaction or cell-antibody interaction are also actively pursued in the fields of Immunology and Oncology.

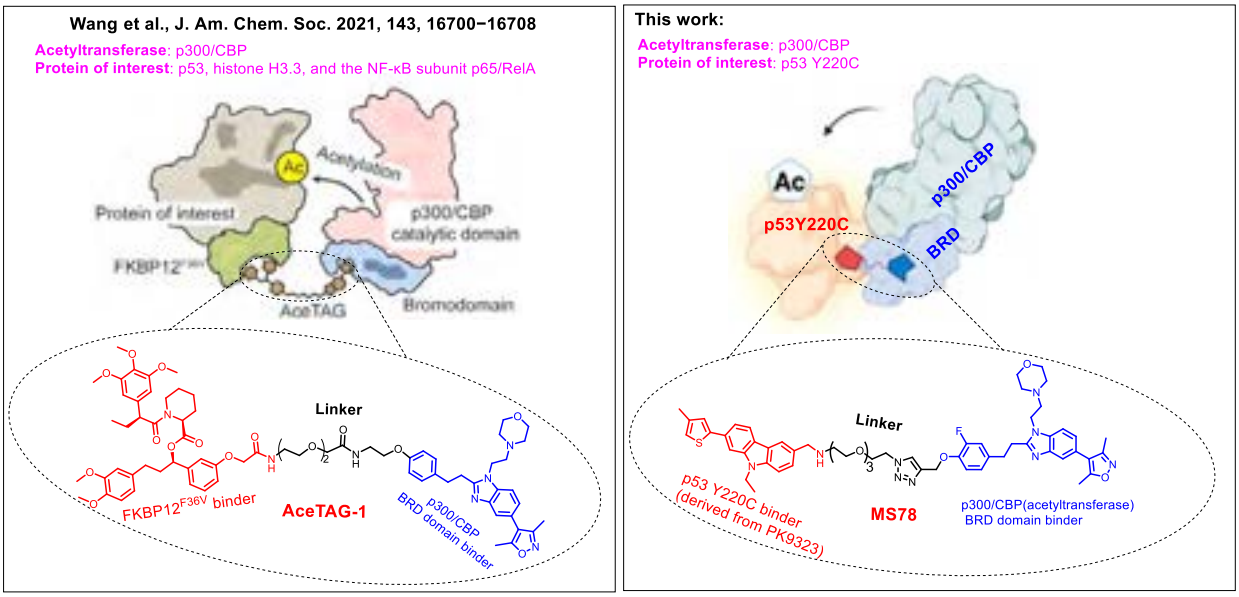
Cell Biology Chemistry

Contributor: Xingui

**Acetylation Targeting Chimera Enables Acetylation of the Tumor Suppressor p53**

Md Kabir§, Ning Sun§, Xiaoping Hu§, …, Jian Jin*

*J. Am. Chem. Soc.* **2023**, 145, 14932-14944




Acetylation Targeting Chimera (AceTAC) is heterobifunctional molecule composed of an acetyltransferase binding moiety, a linker, and a protein of interest binding moiety. It can induce target protein acetylation through induced proximity between a catalytically active acetyltransferase and protein of interest (POI). The first proof-of-concept AceTAC (called AceTAG in Wang's paper) (*J. Am. Chem. Soc. 2021, 143, 16700−16708*) hijacked the bromodomain (non-catalytic) of acetyltransferase p300/CBP and relied on FKBP12$^{F36V}$ fusion protein systems to recruit protein of interest. This artificial fusion protein system, although versatile for targeting diverse POI and great as chemical biology tools for proof-of-concept studies, has limited translational potential.

In this new issue of *J. Am. Chem. Soc,* Kabir, et al. reported new AceTAC molecule named **MS78**. **MS78** can induce the acetylation of endogenous p53Y220C by engaging p53Y220C through p53Y220C stabilizer derivative and hijacking the p300/CBP at the bromodomain. The induced acetylation of p53Y220C by **MS78** is time-dependent, concentration-dependent, and p300/CBP-dependent, and more importantly, p53Y220C acetylation activates its tumor suppressing effect and leads to pharmacological benefits, including inhibiting cell growth selectively in cancer cell lines that endogenously express p53Y220C and inducing downstream signaling of canonical and noncanonical p53 pathways in a mechanism different to the existing p53 stabilizers.

While further investigations on mechanisms (e.g. the acetylation lysine sites and the exact signalling pathways modified) and potency improvement are warranted for in vivo efficacy studies and for translational purposes, this study provided a valuable tool to study the functions of p53Y220C acetylation in cancers harboring the p53Y220C mutation and offered a starting point for treating cancers through pharmacologic activation of tumor-suppressor proteins.

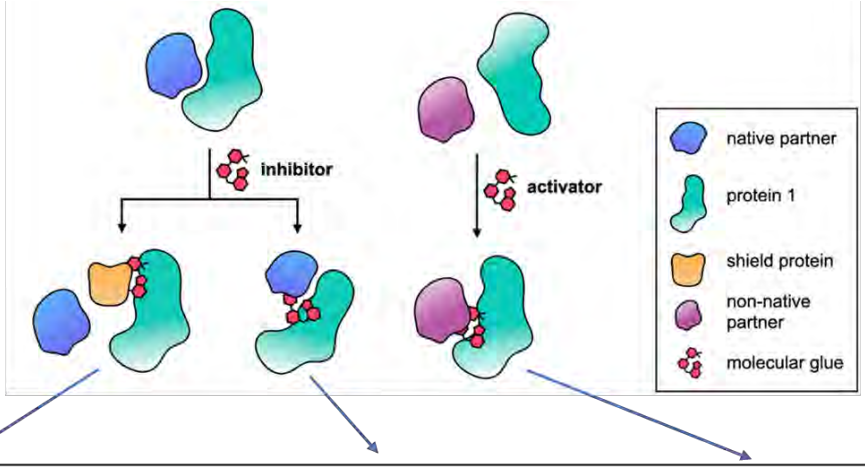
Cell Biology | Chemistry | Computational Chemistry | Modelling/Simulation | Structural Biology/Biophysics

Contributor: Xingui

## Molecular Glue Discovery: Current and Future Approaches

Jeffrey A. Dewey[§], …, Gyorgy Babnigg*

*J. Med. Chem.* **2023**, 66, 9278–9296




| | Type 1: Shielding | Type 2: Redirecting | Type 3: Novel activity |
|---|---|---|---|
| **Mechanism** | Achieve endogenous PPI inhibition by inducing a non-native PPI to physically block the target protein's endogenous activity. | Bind to endogenous PPI and redirect its conformation or dynamics to abrogate, or occasionally enhance activity. | Induce a non-native PPI to produce a novel activity between those proteins. |
| **Examples** | rapamycin, tacrolimus, and cyclosporine | tafamidis, paclitaxel, lenalidomide, and dexrazoxane | thalidomide, pomalidomide |
| **Assays for Discovery via ABMs** | Viral replication assay | Mouse studies and SAR, Cell killing, In vitro aggregation assay, Fluorescent biosensor assay, Actin polymerization, In vitro enzyme complex reconstitution, SAR, Chemogenomics, Mutant selective cell killing, Transcription factor luciferase assay | Mouse studies and SAR, Patch clamp, Cell killing, SAR, Mutant selective cell killing, Transcription factor luciferase assay |
| **Assays for Discovery via IDMs** | HTRF, FP, Docking | Mass spectrometry, Docking, ELISA, SPR, Covalent Fragment MS, Covalent Fragment X-Ray crystallography, FP | Surface binding fluorescence, Crystallization, Oblique-incidence reflective difference (OI-RD) microscopy, FP, TR-FRET |

Modulating protein-protein interaction with molecular glue represents an attractive therapeutic strategy. However, the discovery of molecular glues largely remains a fortuitous process, with rational discovery strategies only slowly emerging. This review paper by Dewey *et. Al* classifies current molecule glues into three types and reviews the methods and approaches (e.g. activity-based methods (ABMs) and interaction detection methods (IDMs)) that have led to the identification of small-molecule molecular glues. Molecular glue discovery examples are also showcased for each approach.

By highlighting the advantages and listing the challenges of each method, this review provides a handbook for molecular glue discovery and can potentially inspire new discovery strategies based on the biology of the targets which will embolden research teams to rationally discover new molecular glues for clinically relevant disease targets.

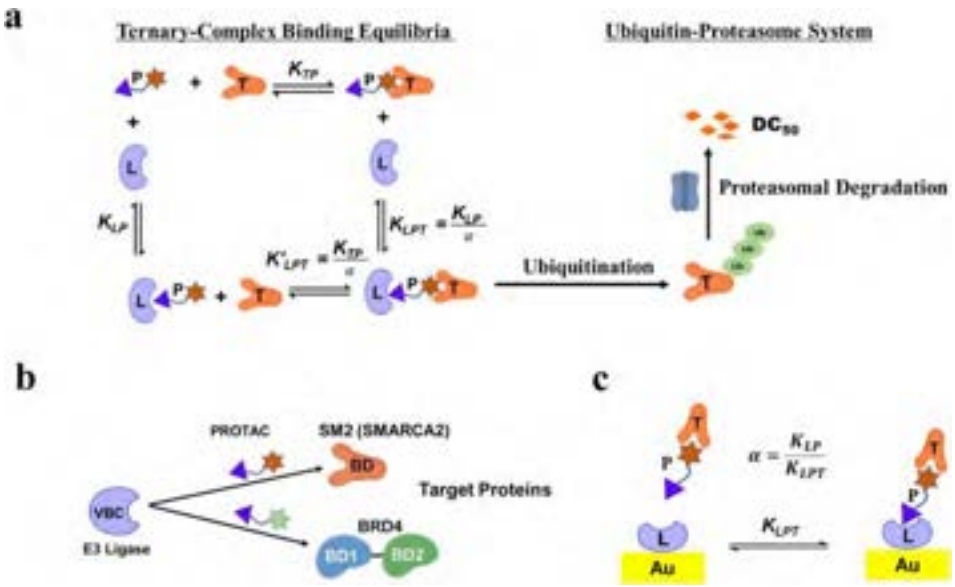
Cell Biology | Chemistry | Modelling/Simulation | Structural Biology/Biophysics

Contributor: Angus

**Affinity and cooperativity modulate ternary complex formation to drive targeted protein degradation**

Ryan P. Wurz[§], …, Dane Mohl*, Amit Vaish*
*Nat. Commun.* **2023**, 14, 4177

Degradation of target proteins by PROTACs is an outcome influenced by many factors. This paper attempts to evaluate the relationships between cellular activity, biophysical properties and predicted ternary complexes of sets of SMARCA2- or BRD4-degrading, VHL-recruiting PROTACs, building on previous work in the field. The authors find a positive correlation between degradation in cells and both ternary complex affinity and cooperativity, supporting previous reports in the literature for these systems.



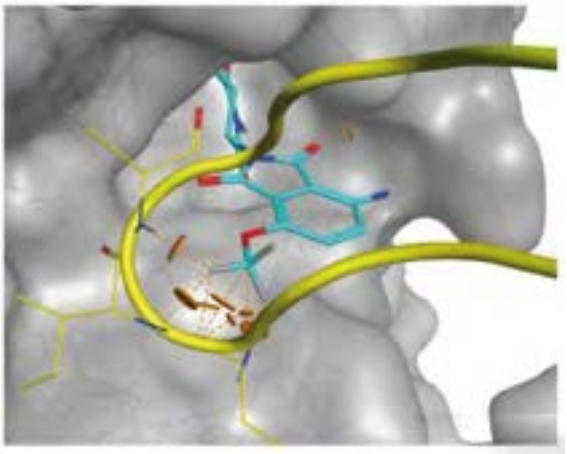

Understanding and predicting PROTAC activity in cells is a difficult undertaking, requiring many techniques to build a full picture. This work supports previous observations in the field for VHL-recruiting PROTACS targeting BRD4 or SMARCA2, emphasising the importance of positive cooperativity for efficient degradation in these systems. The mathematical framework for analysing and describing SPR data of ternary complexes developed here will be useful to many in the field.

Cell Biology | Chemistry | Modelling/Simulation | Structural Biology/Biophysics

Contributor: Angus

**A degron blocking strategy towards improved CRL4CRBN recruiting PROTAC selectivity**

Habib Bouguenina[§*], …, John J. Caldwell*
*Chembiochem* **2023**, DOI: 10.1002/cbic.202300351



While IMiD/CELMoD-derived PROTACs have been shown to be highly effective degraders, there are concerns over retained degradation of neosubstrates of the monovalent parent compounds such as IKZF1, SALL4 and GSPT1. Ideally, CRBN-recruiting PROTACs would only degrade their intended targets, with minimal off-target degradation. The authors of this paper take a structure-guided "degron blocking" approach, adding a methoxy group to sterically block binding of the glycine β-hairpin loop of IMiD/CELMoD neosubstrates. Analogues of IMiD/CELMoD compounds retained CRBN binding but did not degrade neosubstrates SALL4, IKZF2, SALL4, GSPT1 or CK1α. A pomalidomide-based and degron-blocked BRD9-degrading PROTAC was tested, showing improved target specificity in comparison to the equivalent non-degron-blocked PROTAC. Finally, simulations of ternary complexes was used to identify putative protein-protein interfaces between BRD9 and CRBN which were probed experimentally, with minimal differences observed for the degron-blocked vs. parent PROTAC.

While not all IMiD/CELMoD-derived PROTACs suffer from off-target degradation, those that do could benefit from this clever and simple degron blocking strategy.

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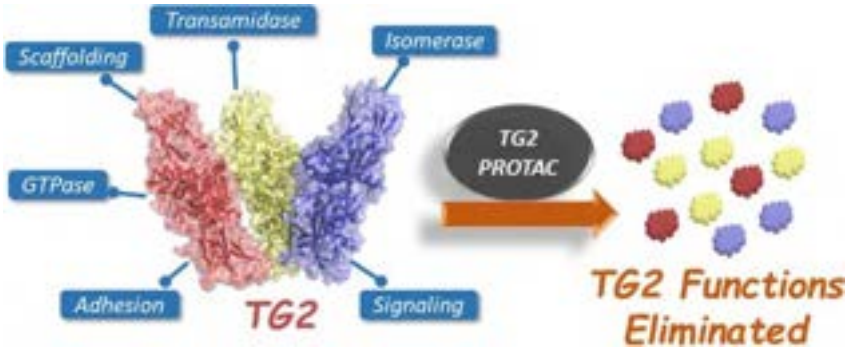
Cell Biology | Chemistry | Modelling/Simulation | Structural Biology/Biophysics

Contributor: Angus

**Discovery and Characterization of PROTACs Targeting Tissue Transglutaminase (TG2)**

Andres Valdivia[§], …, Daniela Matei*, Gary E. Schiltz*
*J. Med. Chem.* **2023**, 66, 9445–9465




Proteins with multiple pathogenic functions in disease are attractive targets for TPD, as all functions are inhibited by degradation of the protein. Tissue transglutaminase 2 (TG2) is one such protein that has several pro-tumorigenic functions in cancer. In this work, the authors synthesise a small library of TG2 PROTACs and test their activity in ovarian cancer cell lines. Two VHL-recruiting PROTACs showed proteasome-dependent degradation that is abolished in control compounds that do not bind VHL. The active PROTACs inhibited cancer cell migration and adhesion to fibronectin while the control compounds did not.

This paper provides a promising starting point for the development of PROTACs targeting TG2. Further validation looking at ternary complex formation in biophysical and cellular assays is warranted, and along with structural information will help inform SAR campaigns to develop more potent degraders.

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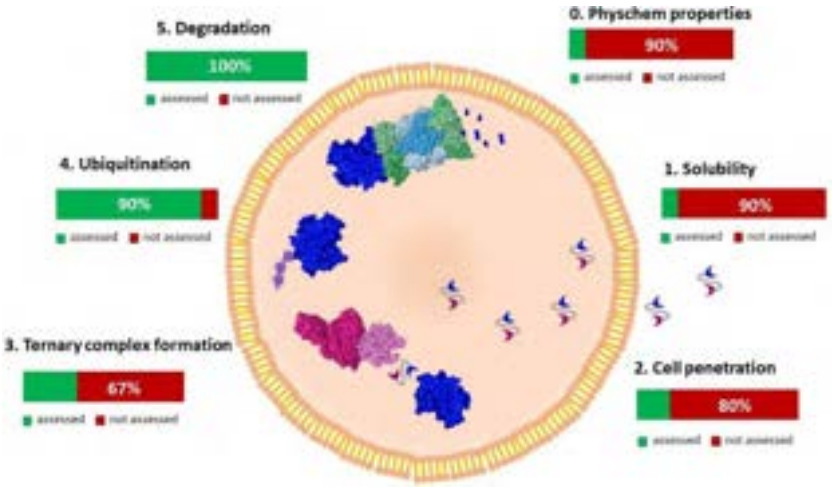
Cell Biology | Chemistry | Structural Biology/Biophysics

Contributor: Angus

**The Quest for Oral PROTAC drugs: Evaluating the Weaknesses of the Screening Pipeline**

Giulia Apprato[§], Giuseppe Ermondi, and Giulia Caron*
*ACS Med. Chem. Lett.* **2023**, 14, 879-883




In this targeted bibliographic review of recent PROTAC articles from the *Journal of Medicinal Chemistry* and *ACS Medicinal Chemistry Letters*, the authors assess reporting of 6 elements relevant to the PROTAC mechanism of action in pre-clinical settings. These include physchem properties, solubility, cell penetration, ternary complex formation, ubiquitination and degradation. They highlight relevant techniques in each category and call for more systematic evaluation of PROTACs, particularly for physicochemical, solubility, permeability and ternary complex formation data which are underinvestigated.

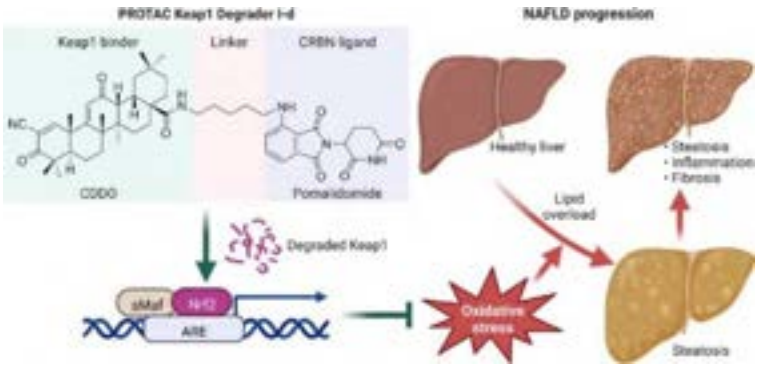
This is a useful primer for anyone entering the PROTAC/TPD field and highlights its highly multidisciplinary nature (as indicated by the colourful discipline headers above each entry in this journal club). While all the aspects of pre-clinical degrader development mentioned here are important, not all research groups interested in degraders will have the technical experitise or equipment to assess them all, as acknowledged by the authors. This review should not discourage such groups from entering the field, rather, it should encourage collaboration between groups with different expertise in order to contribute more complete data and maximise impact in this developing field.

Cell Biology | Chemistry | Modelling/Simulation | Structural Biology/Biophysics

Contributor: Shakil

**Discovery of NAFLD-Improving Agents by Promoting the Degradation of Keap1**

Mingming Qi[§], Hui Zhong[§], Zhaoyan Cheng[§], …, , Li Chen*, Jianbo Sun*
*J. Med. Chem.* **2023**, *66*, 9184–9200




Activation of Nrf2 by Keap1 inhibition has been shown to be a key contributing factor to non-alcoholic fatty liver disease (NAFLD). A variety of Keap1 inhibitors, such as bardoxolone methyl, olitipraz and isothiocynate, have been developed and covalently bind to cysteine residue of Keap1. However, these inhibitors have weak selectivity towards Keap1 and may bind to other cysteine rich proteins causing off target effects.

The authors showed that PROTACs may help overcome the off-target effects of these inhibitors. Compared with 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) alone, PROTACs I-d, containing CDDO as POI ligand and pomalidomide as the CRBN ligand, showed improved inhibition of hepatic steatosis, steatohepatitis, and fibrosis in *in vivo* and *in vitro* models of NAFLD. Compound I-d also showed lower *in vivo* toxicity than CDDO.

This paper demonstrates the potential of PROTACs to overcome the toxicity effects of Keap1 inhibitors. Further validation is required to show if compound I-d selectively degrades Keap1.

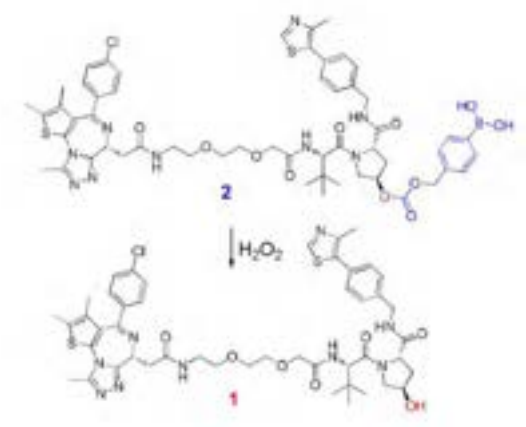
Cell Biology | Chemistry

Contributor: Shakil

**Hydrogen Peroxide-Inducible PROTACs for Targeted Protein Degradation in Cancer Cells**

Dehao Yu[§], Heli Fan[§*], Zhili Zhou[§], …, Huabing Sun*
*Chembiochem* **2023**, DOI: 10.1002/cbic.202300422

Degrading BRD4 using PROTACs has been shown to cause side effects such as skin disorders because BRD4 is expressed in both cancer and normal cells. Recently, light-responsive PROTACs can achieve good selectivity towards target cells, and only degrade POIs upon photoirradiation. However, this is only applicable to cancers that are accessible to photoirradiation.




Cancer cells contain higher levels of reactive oxygen species (ROS) compared to normal cells, with $H_20_2$ shown to be the most stable and abundant ROS. In this issue, Yu *et al.,* develop a $H_2O_2$-inducible PROTACs that can degrade BRD4 in cancer cells, without affecting BRD4 in normal cells. The addition of arylboronic acid caging group to the VHL E3 ligase ligand can selectively react with $H_2O_2$ to release the active PROTAC.

This is a novel approach to improve selectivity of PROTACs. It would be interesting to see if this concept can be applied to CRBN based PROTACs. Further *in vivo* work is required to understand what effect the addition of arylboronic acid caging group has on PK/PD profile of the compound.

Cell Biology | Chemistry | Computational Chemistry

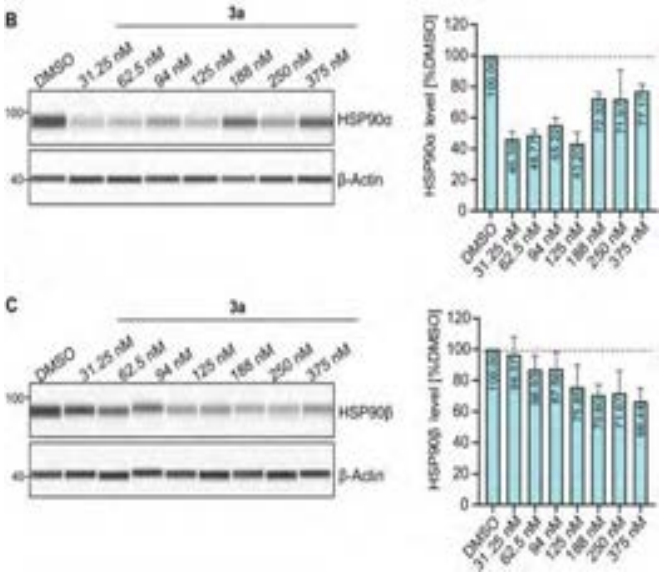
Contributor: Shakil

**Development of the first geldanamycin-based HSP90 degraders**

Silas Wurnig[§], Melina Vogt[§] …, Sanil Bhatia*, Finn Kristian Hansen*
*Front. Chem.* **2023,** *11,* 1219883

HSP of 90 kDa (HSP90) is elevated in a variety of cancer types suggesting a role in malignant cell growth and survival. HSP90 inhibitors can cause acquired resistance and dose-limiting toxicities, however, PROTACs may be able to overcome these issues.

In this paper, the authors designed a series of PROTACs by attaching a CRBN-recruiting, pomalidomide-derived ligand via various alkyl- or PEG-based linkers of different chain lengths to Geldanamycin, a potent HSP90 inhibitor. These series of PROTACs were tested in K562 leukaemia cells and showed that compound 3a with a PEG2-based linker caused the strongest degradation of HSP90α and HSP90β. Compound 3a showed a Dmax of 57% against HSP90α and 34% for HSP90β. Further work is required to understand the *in vivo* efficacy of compound 3a.




Cell Biology | Chemistry

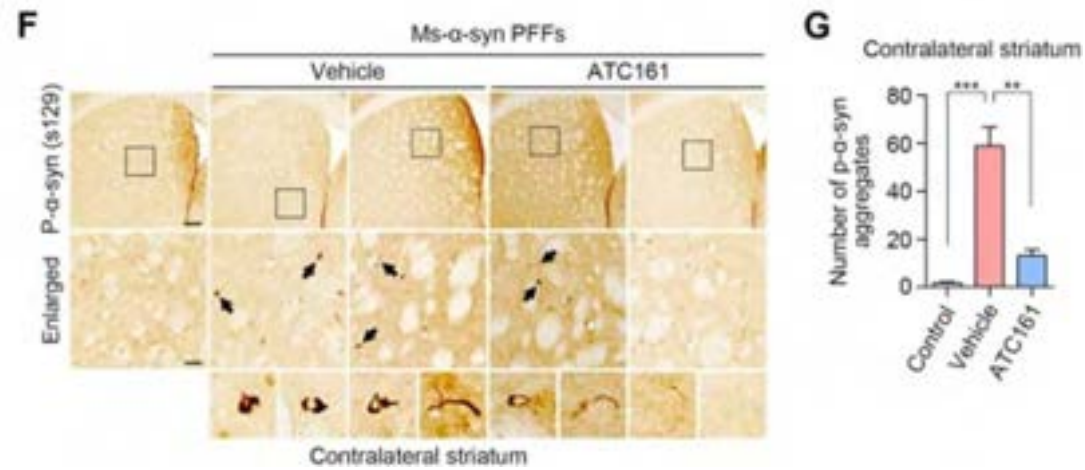
Contributor: Shakil

**Targeted degradation of α-synuclein aggregates in Parkinson's disease using the AUTOTAC technology**

Jihoon Lee[§], Ki Woon Sung[§], Eun-Jin Bae[§],…, Young Ho Suh*, Yong Tae Kwon*
*Mol. Neurodegener.* **2023**, 18, 41

Parkinson currently has no disease modifying therapeutics in clinic. Korgbo (ACS Med. Chem. Lett. 2020, 11) developed a PROTAC that can degrade A53T α-syn in HEK293 cells. However, there are still questions how PROTACs can degrade α-sync oligomers, fibrils, or aggregates.

AUTACs could be a valuable tool in removal of large α-sync aggregates. Here, the authors designed an AUTAC, ATC161, which contains a target binding ligand of anle138b and autophagy-targeting ligand that binds to the ZZ domain of p62. ATC161 is the first molecule to demonstrate degradation of α-syn aggregates in vivo and in vitro. Furthermore, ATC161 is an orally administrable drug that will enter phase 1 clinical study and will be interesting to see the development of ATC161.



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