CeTPD Journal Club

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

May 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): Loudes Acosta Benavides, Alejandro Correa Sáez and Mark Nakasone

"The Journal Club is a fantastic idea that makes it easier to keep up to date. It's great that the whole CeTPD collaborates to highlight TPD-related news. ."

Lourdes comes from Madrid, Spain. She completed a double degree in Pharmacy and Biotechnology at San Pablo CEU University, where she decided to continue her studies by doing a PhD in medicinal chemistry. There she works on the synthesis of PROTACs to achieve CK2 degradation.

"The Journal Club serves as a valuable resource for anyone interested in TPD. It is a great way to stay up-to-date on the latest research and to learn about new methods and findings."

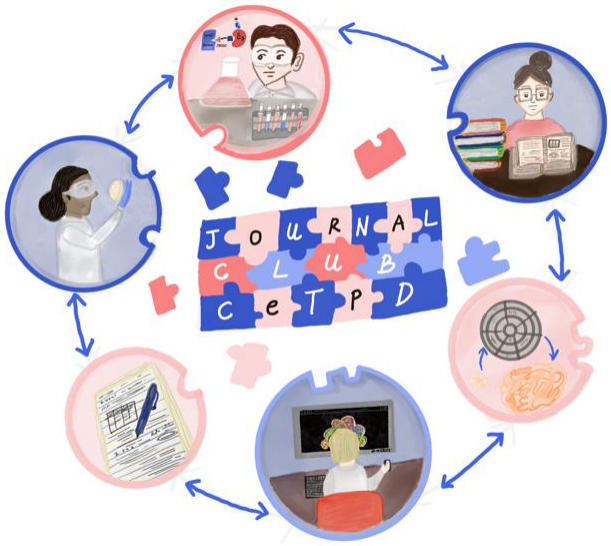
Alejandro joined the Ciulli group as a postdoctoral scientist in February 2023. He completed his undergraduate degree as well as his PhD in Biomedicine at the University of Córdoba (Spain). His research encompassed the fields of protein biochemistry, molecular biology, cell signalling, and drug discovery. He joined the lab as a molecular biologist to work on innovative strategies to characterize novel ligases to be employed in TPD.

"*The JC is unique resource for understanding trends in TPD."*

Mark began his path in research as an undergraduate researcher at McDaniel College (USA), studying protein-foldingunder Melanie R. Nilsson. In 2008 Mark entered the ubiquitin field as a graduate student in David Fushman's NMR lab at the University of Maryland. For his doctoral work, Mark carried out the first structural study on "complex"polymeric ubiquitin. Upon earning his doctorate in 2013, the presidentially appointed Fulbright board awarded Marka two year fellowship to carry out his ubiquitin research at the Technion in Haifa, Israel. While hosted in Michael H.Glickman's lab, Mark undertook many collaborative projects and discovered the substrate preferences ofproteasome-associated deubiquitinases. In 2016 Mark joined Danny T. Huang's lab at the CRUK Beatson Institute in Glasgow. As an ERC research fellow, Mark characterised biologics that inhibit E3 ligases, novel ADP-ribosylated ubiquitin, and developed chemical methods to isolate E2/E3/substrate transition complexes for cryo-EM and X-raycrystallography. In April 2022, Mark joined CeTPD to further explore the potential of E3 ligases.

CeTPD Outreach Café Science: Engaging with the Community

Contributor: **Dr Selma Gulyurtlu** and illustrator **Padma Srinivasan**



Special Acknowledgement: Public Engagement Officer, Shabnam Wasim, for her help, guidance and community contacts and Dr Amy Cameron, Public Engagement and Communications Officer

This month, CeTPD Outreach dealt their hand in the community! As a centre, we are committed to raising awareness of our research and inspiring others. Our director, Prof. Ciulli, was a great example of this when he took his expertise to a community group in Dunkeld to give a Café Science talk. In this talk he discussed multiple aspects of TPD, PROTAC drug design and development, and what we do in the centre. Members of Café Sci were so energised by his talk that they asked to visit our centre to see the facilities.

Thus, CeTPD Outreach welcomed 6 members for a tour of the facilities, where different members of our centre engaged with the group and explained the different facilities that help us conduct our research. We started with Dr David Zollman, AC-Almirall industry collaboration team leader with background in Structural Biology and Biophysics, who gave an insight into our biophysics suite. The group moved onto an explanation of the peptide synthesiser by Dr Jack Robertson, AC-Almirall Scientist in Medicinal Chemistry/Chemical Biology (See Fig.1). Dr Selma Gulyurtlu (AC-Almirall Scientist in Cell Biology) provided an overview of the different biology labs, including cell and tissue culture, and the techniques used to assess cell behaviour to our compounds. Additionally, this also included an in-depth description of protein purification by AC-BI associate scientist in Structural Biology and Biophysics, Denzel Gonzales. Henceforth, Dr Giorgia Kidd (AC-BI Scientist in Medicinal/Organic Chemistry) took the group through the chemistry labs and the different tools that allow characterisation of compounds. The tour finished with Dr Alena Kroupova, AC-Almirall Scientist in Structural Biology and Biophysics, in the crystallisation lab who had some crystals ready to show the group!

We ended our session with a “Meet the CeTPDer” session where different scientists across the centre came to provide a discussion into their experience in the field. Other than the already mentioned Prof. Ciulli, Dr Selma Gulyurtlu, Dr Giorgia Kidd and Denzel Gonzales, this session included Principal Investigator Dr Will Farnaby, AC-BI Industry Collaboration team leader Dr Kirsten McAulay, AC-BI Scientist in Computational Chemistry Dr Sohini Chakraborti, Postdoctoral Research Associate Dr Conner Craigon, Postdoctoral Research Scientist in Medicinal Chemistry Dr Maria Rodriguez-Rios, Postdoctoral Research Fellow Claudia Diehl, Doctoral Candidate Charlotte Crowe and Doctoral Candidate Aitana De La Cuadra Baste.

(A)  (B) 

Figure 1: Photos of the Café Sci group touring CeTPD. (A) Image of the group with tour organisers Dr Selma Gulyurtlu and Dr Giorgia Kidd, situated in the main biology lab. (B) Image of the group receiving an explanation into the peptide synthesiser by Dr Jack Robertson

Feedback from this session was extremely positive, including the note "It was our pleasure to come to the labs this morning with Café Science. We thoroughly enjoyed the visit, and it was great to witness the enthusiasm of all your staff". Overall, this was a great stepping stone to our 2-part Café Science programme that we also launched this month. This programme was developed in collaboration with Public Engagement Officer, Shabnam Wasim, with our target audience being the elderly community, and was launched with our first community group: The Beehive group from Menzieshill Community Centre.

This programme consists of two separate days of visits, where the first visit our scientists travel to the group's community centre to give a Café Science talk and mediate a discussion about Targeted Protein Degradation, why it is important, and how we investigate it as a team of scientists. In the second visit, the group then visits the centre for a tour, a chance to try some of our Outreach activities/games and continue our discussion of the new modality.

For our first visit, Dr Aileen Frost (Medicinal/Organic Chemistry) and Dr Valentina Spiteri (Structural Biology and Biophysics) (see Fig.2) travelled to the Menzieshill Community centre to give the first CeTPD Outreach Café Science talk. In this talk they started with an overview on what proteins are, how important they are in the body, and what can happen if they don't function correctly. They led onto an overview on traditional medicines and how they work, focussing on paracetamol as an example. This allowed our scientists to open the discussion into why we need to develop new medicinal modalities. They described TPD as instead of blocking a problematic protein's function, to remove the protein altogether. They finished their session by describing that we work as a big team in the centre involving several different disciplines.

In addition, this event also encompassed several break-out sessions where we trialled some of our CeTPD Outreach games. This included looking at 3D protein structures developed by X-Ray crystallography, which were images from our developed card game "Ink Blot Proteins" designed by Claudia Diehl. This created a discussion on how proteins have different shapes, why that is important and how that can be exploited when designing new medicines. We also trialled "Form the Ternary Complex", developed by Dr Sohini Chakraborti, a card game that looks at the 5 components in a ternary complex structure: the protein of interest, the PROTAC that is split into 2 binders and a linker, and the E3 ligase. This helped to build the understanding of what PROTACs look like, and how they work.

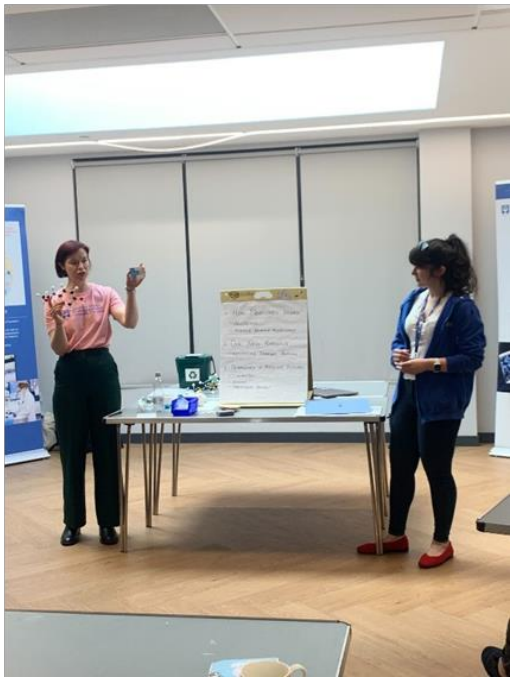
(A)  (B) 

Figure 2: Photos of CeTPD Outreach Team visiting the local community Beehive group at Menzieshill Community Centre. (A) From left to right, Dr Aileen Frost and Dr Valentina Spiteri before their Café Science talk on Targeted Protein Degradation (B) Aileen and Valentina during their talk discussing how many molecules of paracetamol there are in a 500mg tablet.

Feedback from our first session was extremely positive and collected verbally. Some of the feedback included "I lived in Dundee all my life and never really knew what type of science was happening, but these girls explained it so well today", "a wonderful and enthusiastic young group, very refreshing to see our future is in such capable hands" and "I'm proud to be from Dundee, it really is a City of Discovery".

The following week we welcomed the Beehive group into CeTPD for a tour of the facilities (see Fig.3). This was led by Dr Selma Gulyurtlu and Dr Giorgia Kidd. Following a brief re-introduction into the importance of proteins and the function of the degrader, Selma started the tour going through all the aspects, labs and machinery involved in biology, starting in our biophysics suite, moving into the fermentation suite, then the main biology lab, cell/tissue culture and ending in the crystallisation lab. Giorgia then took over the tour to discuss all things Chemistry, such as how we synthesise the new chemical entities in our labs, and how we get them ready for testing.

We ended our programme with another "Meet the CeTPDer" session where different scientists from our centre came to say hello, discussed their experience and background. This included a return of our Senior Scientist Aileen, together with Dr Maria Rodriguez-Rios, Scientist in Medicinal/Organic chemistry Dr Qingzhi Zhang, Senior Scientist in Mass Spectrometry and Cellular Proteomics Dr Manjula Nagala, Dr Sohini Chakraborti and Masters research student Beth Forrester. In this session they were also offered the option to take away supplies to knit or crochet a bubbling conical flask, an activity that was modelled by the director's personal assistant, Diane Purves.

(A)

(B)

(C)

Figure 3: Photo of the CeTPD Outreach giving a tour of CeTPD to the Beehive community group. (A) Dr Giorgia Kidd leading the tour through the Chemistry labs explaining the processes of synthesis and characterisation of compounds. (B) Dr Selma Gulyurtlu in the Crystallisation lab giving a general overview of the processes in structural biology. (C) Our "Meet the CeTPDer" session with activities, games, refreshments and CeTPD Outreach volunteers.

Feedback from this session continued extremely positive. Here were some of the comments: "Oh wonderful, just wonderful", "I can't wait to tell my nephew about this visit, he will be so happy as he works in a lab too!", "My word, what a centre and what a team! And all happening right here in Dundee too – I'm beaming with pride to be a Dundonian" and "Amazing how all this technology works, and how it all comes together for the greater good. It has really opened my old eyes in this field".

Overall, the success of this event has energized our team and centre, and it is now our ambition to implement this 2-day programme in other elderly community groups across Dundee. Well done to everyone involved in a very successful public engagement month!

CeTPD takes on Barcelona for the 2023 Proximity-inducing pharmacology conference

Contributor: **Dr Mark Nakasone**

Cristina Mayor-Ruiz (Institue for Research in Biomedicine, Spain) is a rising star in TPD and recently organized the 2023 *Proximity-inducing pharmacology: Targeted protein degradation and beyond* conference in Barcelona, Spain held from 22-24 May. CeTPD was well represented with three speakers Alessio Ciulli, Will Farnaby, and Angus Cowan along with poster presentations from Oliver Hsia, Javier Perez-Areales, Valentina Spiteri, Alena Kroupova, and Mark Nakasone. This unique conference attracted key figures in TPD from around the world and reached capacity shortly after registration opened. In addition, many Ciulli lab/CeTPD alumni were united in Barcelona. This meeting was inspiring and CeTPD will continue the tradition hosting the conference in Dundee for May 2024, followed by George Winter for Vienna, Austria for 2025.

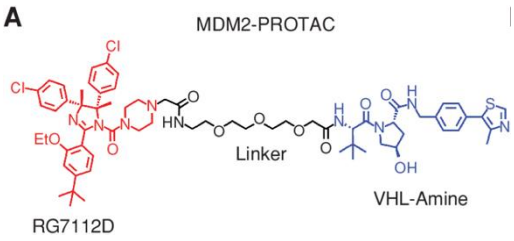
Targeted Protein Degradation

Cell Biology

Contributor: Alejandro

Targeted MDM2 Degradation Reveals a New Vulnerability for p53-Inactivated Triple-Negative Breast Cancer

Clare M Adams[§], …, Joseph M Salvino*, Christine M Eischen*
Cancer Discov. **2023**, *13(5)*, 1210



Previous studies have shown that MDM2 ligase is still required for growth and survival in p53-mutant triple-negative breast cancer (TNBC) cells. This research builds on this work by presenting a new therapeutic strategy for TNBC cancer cells. This strategy targets MDM2 degradation, which causes apoptosis in p53-inactivated TNBC cells, while sparing normal cells. A novel MDM2-degrading PROTAC has shown promise in the treatment of TNBC. The PROTAC was shown to eliminate TNBC cells in 2D and 3D cultures, as well as in patient explants. It was also stable in vivo and showed on-target efficacy in TNBC xenograft-bearing mice, significantly extending survival. Transcriptomic analyses revealed upregulation of p53 family target genes in cells treated with the PROTAC. Moreover, the researcher also showed that TAp73, a p53 family member, was activated and required for MDM2-PROTAC-induced apoptosis.

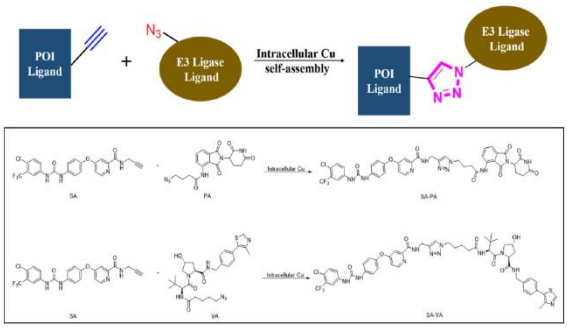
The data presented here challenges the current understanding of the MDM2/p53 paradigm and shows that MDM2 is required for p53-inactivated TNBC cell survival, and PROTAC-targeted MDM2 degradation is an innovative potential therapeutic strategy for TNBC and superior to existing MDM2 inhibitors.

Cell Biology | Chemistry

Contributor: Lourdes

Discovery of intracellular self-assembly protein degraders driven by tumor-specific activatable bioorthogonal reaction

Ru Si[§], …, Jie Zhang*
Eur. J. Med. Chem. **2023**, 257, 115497



Proteolysis Targeting Chimera's (PROTAC's) present worse membrane permeability and bioavailability than traditional inhibitors. These disadvantages are due to their large molecular weight. This research brings an alternative to avoid these problems. They divide the PROTAC molecule in two smaller precursors capable of assembling in the intracellular media of tumoral cells.

In this study they demonstrate that the precursors can assemble in to a PROTAC through a CuAAC reaction without adding an external catalyst. This reaction occurs only in tumoral cells due to the higher content of copper in this type of tissues. They also achieve the degradation of the proteins of interest, VEGFR-2 and EphB4. The strategy presented in this article might help avoiding the principal issues with PROTACs. It's true that the VHL precursor still present some permeability problems, but it might be easier to solve those than the complete PROTAC ones. Also, it's a good point how they take advantage of the intracellular properties of tumoral cells to achieve selectivity against this specific tissue. I am just curious to see if this technique could be transferred to in vivo models.

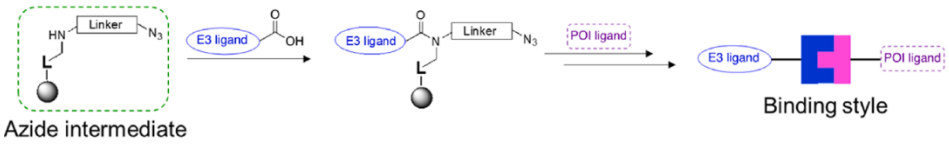
Chemistry

Contributor: Lourdes

Development of versatile solid-phase methods for syntheses of PROTACs with diverse E3 ligands

Hanqiao Xu[§], Takashi Kurohara[§], …, Yosuke Demizu*

Bioorg. Med. Chem. **2023**, 86, 117293



Solid-phase organic synthesis (SPOS) has been traditionaly used for peptide and oligonucleotide synthesis. It does not require a workup in each step, so it helps to reduce the effort and time of the global synthesis. Due to these advantages, it has been used in the past for the synthesis of PROTACs, specifically for CRBN binders with alkyl linkers. In this work they propose a new route that can be used for VHL and CRBN recruiting PROTACs with different linker compositions. They use SPOS to reach the synthesis of six PROTACs combining three E3 ligands: VH032, LCL161 and pomalidomide, with alkyl and PEG linkers, and with JQ1, a ligand of BRD4, the protein of interest. The connexions between the three parts of the PROTAC were done by amide couplings. The products obtained showed moderate or lower degradation activity against BRD4 compared to the positive controls, this may be due to the increased rigidity caused by the amide bonds.

In conclusion, they propose a SPOS that can be used to achieve PROTACs with the ability of recruit different E3 ligases in a rapid manner. It also allows the use of several types of linkers to introduce variability. The only disadvantage is that it is limited to one type of chemistry, the coupling between a carboxylic acid and an amine to form an amide, these leads to the reduction of the flexibility of the compounds and the increase of its lipophobicity.

Cell Biology | Chemistry

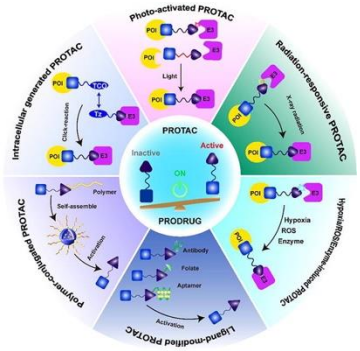
Contributor: Alejandro

Stimuli-activatable PROTACs for precise protein degradation and cancer therapy

Jing Gao[§], …, Zhiai Xu*,Haijun Yu *

Sci Bull. 2023, 68, 1069

This review presents a comprehensive overview of the current state of research in stimuli-activatable PROTAC. The authors emphasize the significance of controlling the off-target effects of PROTACs in order to mitigate systemic toxicity and enhance their clinical applicability through protein degradation. In order to achieve this objective, prodrug PROTACs have been designed to respond to various external and internal stimuli, including light, X-ray, hypoxia, ROS (reactive oxygen species), specific enzymes, and reduction, thereby facilitating direct activation of the PROTAC within tumor cells. Furthermore, the incorporation of multifunctional components, such as antibodies, folate, and aptamers, into the PROTAC structure enables the attainment of cell selectivity.



The integration of stimuli-responsive PROTACs with nanomedicine delivery systems (nanoparticles or liposomes) might offers a promising avenue for improving pharmacokinetic profiles and enhancing tumor tissue accumulation. This approach has the potential to improve precise cancer therapy by maximizing therapeutic efficacy while minimizing off-target effects.

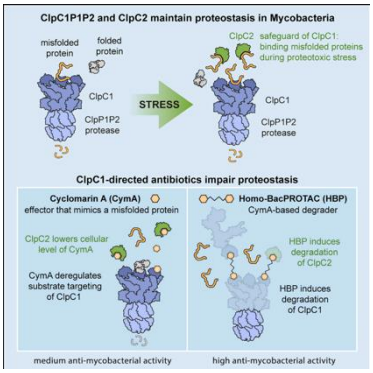
Cell Biology | Structural Biology/Biophysics

Contributor: Mark

Clp-targeting BacPROTACs impair mycobacterial proteostasis and survival

David M. Hoi §, Sabryna Junker §, Lukas Junk§, …, Rainer Kalscheuer *, and Tim Clausen*

Cell. 2023, 186(10), 2176-2192.e22



In this study, Hoi *et al.* continue pioneering work from the Clausen lab on TPD in bacteria "BacPROTACs." Unlike humans and other eukaryotes, they exploit the ClpC1:ClpP1P2 proteases in mycobacteria. Using cyclomarin A and ecumicin as a starting point, they exploit ClpC2 binding to create a homo-BacPROTAC. This set of dual cyclomarin A heads results in degradation of ClpC1 and associated ClipC2. Extensive proteomics confirm their findings and *Mycobacterium tuberculosis* viability assay shows improved efficacy from the initial antibiotics.

The approach of Hoi *et al.* Is a great example of repurposing and improving existing molecules. There are many similar concepts to conventional TPD in eukaryotes, including how homo-PROTACs can induce degradation of a target through dual warheads. In general, development of BacPROTACs from several studies is emerging as a promising class of antibiotics for pathogenic bacteria with unment needs.

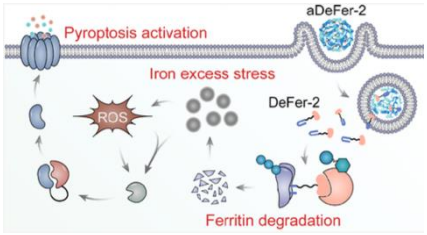
Cell Biology

Contributor: Mark

Small-Molecule Ferritin Degrader as a Pyroptosis Inducer

Yu Chen§, …, and Quanyin Hu*

J. Am. Chem. Soc. 2023, 145(17), 9815-9824



Altered metabolism and nutrient concentrations in the tumor microenvironment distinguish malignancies from health cells and tissue. Chen and co-workers have harnessed TPD to develop degraders for ferritin, which results in a spike of intracellular iron and cell death through caspase 3-GSDME-mediated pyroptosis. Interestingly, the long-chain fatty acid, oleic acid was selected as the ferritin recruiter as it selects the interface between ferritin dimers. The classic VH032 ligand for VHL was used as the E3 warhead, and assay in B16F10 melanoma cells lead to the optimal linker for the DerFer-2 degrader. In vitro, ITC confirmed the affinity of DeFer-2 and ferritin to be in the low micromolar range. Proteomics and Western blot showed decrease in ferritin, while intracellular free iron content was determined spectroscopically. Light microscopy unambiguously confirmed pyroptosis was induced by DeFer-2 leading to ROS stress and cell death.

Chemically the DeFer-2 degrader has a long-chain unsaturated fatty acid, which prevents challenges for delivery. To overcome this Chen et al. devised an albumin nanostructure to introduce B16F10 cells and mice. This combination improved survival in their mouse model and notably had little side effects, as cancer cells are much more vulnerable to pyroptosis.

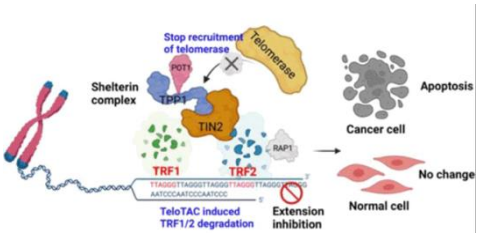
Cell Biology | Chemistry | Computational Chemistry | Modelling/Simulation | Structural Biology/Biophysics

Contributor: Mark

Telomere Targeting Chimera Enables Targeted Destruction of Telomeric Repeat-Binding Factor Proteins

Zhen Wang[§], Jing Liu[§],…, Jian Jin*, and Wenyi Wei*

J. Am. Chem. Soc. 2023, 145(19), 10872-10879



Surveillance and methods to quantify Telomeres has emerged as an important area of cellular viability, aging, and disease. In caner telomeric repeat-binding factor 1 and 2 (TRF1 & TRF2) are upregulated and stabilize the telosome, to maintain telomere length and promote viability. As a first-in-class study, Wang et al. of the Wei lab report VHL based degraders of TRF1 and TRF2. Similar to transcription factor targeting PROTACs (TRAFTACs), the telomere-targeting chimeras (TeloTACs) reported in this study utilize a specific DNA oligonucleotide to recruit through a conventional E3 ligase warhead. Much work was carried out to determine the sequence of TTAGGGG repeats for TeloTACs to work. Their cell-based assays coupled with light microscopy clearly show TeloTACs exploit cancer's need for elevated telomerase activity.

Together with TRAFTACs, TeloTACs collectively demonstrate proof of concept studies that such "chimeras" of DNA oligonucleotides and small molecules can be combined to achieve specificity for challenging targets. The dependence on the telomere is a key difference between health vs. cancer cells. Wang et al. Have rationally designed several versions of TeloTACs optimizing mainly the DNA sequences and linker, yet most TeloTACs are much larger (~10 kDa) than conventional PROTACs (~1 kDa). While the DNA oligonucleotide greatly aids with target specificity, turning such molecules into therapeutics remains a major obstacle.

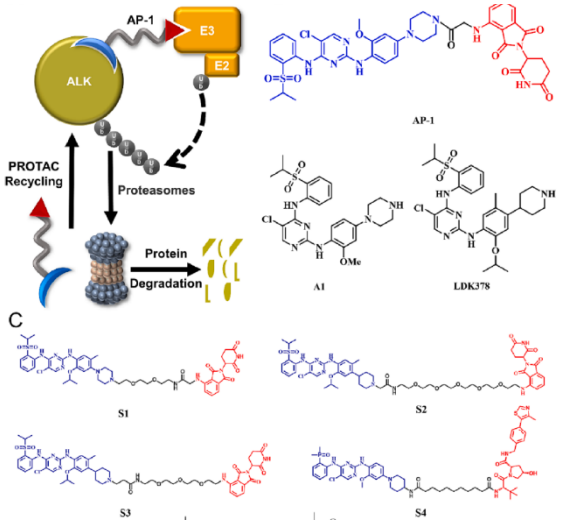
Cell Biology | Chemistry

Contributor: Lourdes

Discovery of a miniaturized PROTAC with potent activity and high selectivity

Lidong Gong[§], Ridong Li[§], …, Tiancheng Li*, Zhiqiang Lin*

Bioorg. Chem. **2023**, *136*, 106556



Anaplastic lymphoma kinase (ALK) inhibitors have demonstrated their efficacy in cancer patients. However, many ALK mutants are resistant to this type of drugs. This is why, in this study they propose the use of PROTACs as an alternative. ALK PROTACs have been previously synthetized, but due to their large molecular weigh they end up having poor druggability. To solve this problem, in this article they propose to go ahead with a simpler design in which they have shorten the linker to a 2 carbon length and reduce the size of the POI ligand to the active sites only. With the PROTAC synthetized (AP-1) they have performed degradation assays in different ALK variants to confirm it can be used for different mutations. Also, *in vivo* experiments proved that the degradation of ALK by AP-1 could significantly inhibit the growth of tumors.

Modifications in the length and flexibility of the linker are often done to improve the activity of the PROTACs. Many of these modifications tend to go towards longer and more flexible linkers to asure that both ends of the PROTAC can bind to their respective proteins in an easier way. These leads to the increase of the molecular weight and consequently to the reduction of permeability. In this paper they demonstrate that shortening the length of the linker does not imply a loss of activity. This might not be useful for all the targets, but it is an interesting measure to have in consideration.

Chemistry

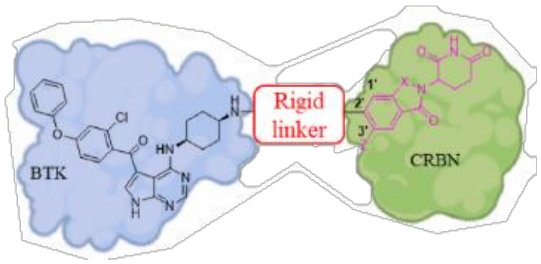
Contributor: Lourdes

Discovery of novel BTK PROTACs with improved metabolic stability via linker rigidification strategy

Song Chen[§], …, Xufen Yu*, Yonghui Wang*

Eur. J. Med. Chem. **2023**, 255, 115403

Bruton's tyrosine kinase (BTK) is an enzyme related with the proliferation and survival of B lymphocytes. It's aberrant activation is associated with hematocellular malignancies. Some covalent binding inhibitors have been developed against BTK. However, C481S mutation is resistant to this strategy, that's why they propose PROTACs as a therapeutic alternative, using ARQ-531, a reversible non-covalent inhibitor as ligand for the protein of interest.



In this study they have discovered a series of novel BTK PROTACs based on ARQ-531. They have also explored the SAR of rigid linkers and CRBN E3 ligase ligands to achieve an active PROTAC with improved metabolic stability. Furthermore, they are trying to achieve oral bioavailability, but it's still under investigation.

Other Paper Highlights

Cell Biology | Modelling/Simulation | Structural Biology/Biophysics

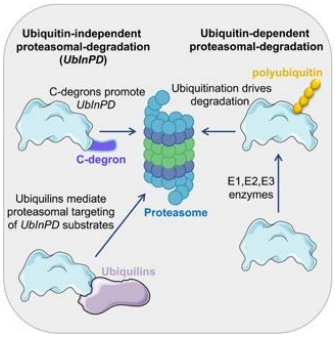
Contributor: Alejandro

Ubiquitin-independent proteasomal degradation driven by C-degron pathways

Yaara Makaros[§], …, Itay Koren*

Mol Cell. 2023, 83(11),1921

This paper provides novel insights into ubiquitin-independent proteasomal degradation (UbInPD), a less understood process compared to the well-characterized canonical mode of protein degradation through ubiquitin conjugation within the ubiquitin-proteasome system (UPS). The study reveals the prevalence of degrons that promote UbInPD, highlighting their crucial roles in Protein Quality Control (PQC). Utilizing a high-throughput degron identification platform (GPS-peptidome), the authors identified a repertoire of C-terminal degrons, termed "C-degrons". Additionally, they identified 69 full-length proteins regulated by UbInPD. To gain further insights, the authors performed a triple Knock Out experiment targeting the Ubiquilin family members, revealing their involvement in facilitating the targeting of UbInPD substrates to the proteasome. This emphasizes the critical role of the Ubiquilin family in orchestrating the UbInPD pathway.



In conclusion, this study paves the way for investigating the mechanisms underlying UbInPD and raises the question of how protein degradation through this pathway is influenced by environmental stresses and other stimuli. Exploring the regulation and dynamics of UbInPD in response to cellular cues could provide valuable insights into protein homeostasis and contribute to the development of therapeutic interventions targeting protein degradation pathways.

Computational Chemistry | Modelling/Simulation | Structural Biology/Biophysics

Contributor: Mark

Automated model building and protein identification in cryo-EM

Kiarash Jamali[§], …, Sjors H.W. Scheres*

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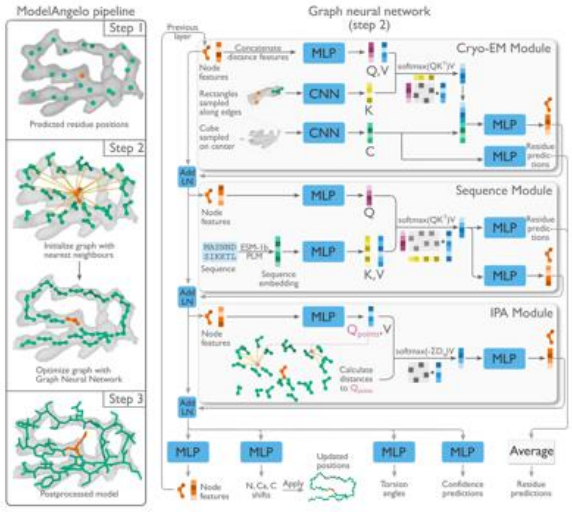
Model building in low-medium resolution maps is a major challenge and a common obstacle for cryo-EM. Although many postprocessing protocols can improve maps and there are map-to-model validation conventions (e.g. Q-score), much human bias can be introduced at model building. In this preprint, Jamali *et al*. improve on their ModelAngelo package for automated model building in cryo-EM maps. In short, ModelAngelo is a machine learning approach that combines sequence information to build atomic models in cryo-EM maps. The first release of ModelAngelo could only build proteins, but this current version (v1.0.1) can build amino acids and nucleotides. Certainly, ModelAngelo outperforms humans and for increasingly larger complexes ModelAngelo really shines. Jamali *et al*. demonstrate this on the 16.7MDa “single-PBS-PSII-PSI-LHC super complex” and built in new parts of the map.



For CeTPD the rapid development of cryo-EM software is of great importance. As early adopters of ModelAngelo we routinely use this software to better understand our preliminary 3.5-5.0 Å maps. ModelAngelo runs fast and is user friendly as a standalone Anaconda package. Similar to AlphaFold2, ModelAngelo will improve with more high resolution cryo-EM structures. Software such as ModelAngelo represent future direction of cryo-EM workflows and the fully opensource nature of software from the Scheres laboratory is the ideal standard.

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