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Introduction to the themed collection on 'Induced-Proximity Pharmacology'

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The field of induced-proximity pharmacology is a burgeoning area of drug discovery with a myriad of opportunities for the medicinal chemist. The field has been dominated by the success of heterobifunctional small molecule protein degraders called proteolysis-targeting chimeras (PROTACs) that chemically tether a ligand for an E3 ubiquitin ligase to a ligand for a protein-of-interest (POI). PROTACs induce the proximity of the E3 with the POI, which mediates its polyubiquitination and subsequent proteasomal degradation. However, a plethora of innovative modalities that exploit induced proximity have started to gain traction that promise to deliver novel ways to deplete or modulate therapeutic targets. We were motivated to guest edit a themed collection in *RSC Medicinal Chemistry* that not only captures some of the exciting new developments in the field of PROTAC research, but also covers new approaches to induced-proximity pharmacology and the challenges faced by medicinal chemists working in the area.

As it is typical for new drug modalities, PROTACs have initially been applied to areas of well-understood biology with remaining clinical needs, such as the estrogen receptor for treating ER-positive breast cancer. The considerable chemical diversity of now-available ER degraders is reviewed by Peng *et al.* (**https://doi.org/10.1039/D4MD00961D**). This themed collection also highlights the significant breadth of novel therapeutic opportunities afforded by the modality in research and development. Notably, Sun *et al.* (**https://doi.org/10.1039/D4MD00252K**) report first-in-class MELK degraders for the treatment of Burkitt's lymphoma, and KDM3 PROTACs are described by Zaman *et al.* (**https://doi.org/10.1039/D4MD00122B**) to eliminate colorectal cancer stem cells. Jin *et al.* (**https://doi.org/10.1039/D5MD00316D**) present the design and evaluation of pyrrolobenzodiazepine-based PROTACs that degrade the RelA/p65 subunit of NF-κB, a target that has evaded the discovery of direct inhibitor drugs. PROTAC degraders of the anti-apoptotic protein Bcl-xL were described previously, but in this themed collection Zhang *et al.* (**https://doi.org/10.1039/D5MD00119F**) have developed a highly potent and *in vivo* active degrader with improved platelet toxicity. Galla *et al.* (**https://doi.org/10.1039/D4MD00142G**) review PROTACs that have been designed to degrade targets involved in inflammation and autoimmunity, signifying an important expansion of the field to research indications beyond cancer. The variety of chemical structures, targets, and indications being addressed continues to expand, with several PROTACs currently in active clinical development for inflammatory diseases. Importantly, the disadvantages of conventional therapies are described (such as low efficacy, short pharmacodynamic duration, and poor selectivity), which contextualize the need for innovative approaches such as targeted protein degradation.

Investigation of alternative modes of administration will also reveal new avenues to advance therapeutic degraders. Hemmerling *et al.* (**https://doi.org/10.1039/D5MD00173K**) detail the design and development of inhaled bromodomain and extra-terminal-domain (BET) PROTACs for the potential treatment of lung diseases such as idiopathic pulmonary fibrosis (IPF). Non-systemic approaches such as this deliver high local concentrations of the drug at the site of action to drive high efficacy, while reducing systemic exposure to mitigate toxicities and improve therapeutic indices. This work describes key design parameters and general insights for the future development of topical and inhaled degraders. Hales *et al.* (**https://doi.org/10.1039/D5MD00118H**) also report opportunities for PROTACs beyond cancer, focusing on the degradation of hepatitis B virus antigen. The authors detail an important caveat of relevance to the field, as they found that the mode-of-action of their heterobifunctional degrader did not

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proceed through the expected induced-proximity mechanism. The work highlights the need for rigorous mechanistic studies to elucidate the specific means by which degraders exert their pharmacological effects.

There are several important features of PROTAC degraders that are reported and reviewed in this themed collection. PROTACs often possess improved selectivity over traditional inhibitors due to the complexity of their pharmacology and the need to induce productive protein–protein interactions that lie outside of the ligand binding site. The high selectivity that PROTACs are able to confer was demonstrated by Marsh *et al.* (**https://doi.org/10.1039/D4MD00969J**) in their development of selective degraders of the chromatin reader p300 over its paralog CREBBP. This work may help further the development of p300 selective degraders that exploit paralog-dependent synthetic lethality in cancers with loss-of-function mutations in *CREBBP*. Another key advantage of degradation over traditional inhibitors is the potential for enhanced efficacy that phenocopies genetic methods of protein depletion. Pogash and Fletcher (**https://doi.org/10.1039/D5MD00095E**) review degraders of kinases that address scaffolding functions through event-driven pharmacology, *versus* occupancy-driven ATP-site inhibitors, with a focus on kinases associated with cancers, FAK and AURKA.

Heterobifunctional PROTACs are, by their very nature, considerably larger than traditional oral drugs, and are thus outside of the Lipinski rule of 5 (Ro5). The physicochemical demands needed to progress such molecules often provides significant challenges for the medicinal chemist to ensure the properties of the molecules are optimal for future development. The opinion article by Scott, Michaelides and Schade (**https://doi.org/10.1039/D4MD00769G**) shares important insights regarding the advancement of PROTACs towards the clinic, and frameworks that guide their optimization are provided that will be very useful to practitioners. The research article by Maurer *et al.* (**https://doi.org/10.1039/D4MD00854E**) further outlines opportunities for using computational predictions to guide the optimization of PROTACs towards desired pharmacokinetic properties, helping to overcome an overreliance on animal testing.

Zerfas *et al.* (**https://doi.org/10.1039/D5MD00028A**) demonstrate the design of the first PROTAC degraders of the endoplasmic reticulum-resident protein IRE1α using structure-based optimization of the ternary complex which delivered a truncated heterobifunctional molecule with physiochemistry closer to that of molecular glues than traditional PROTACs. This work suggests that merged pharmacophore strategies may yield 'linkerless' bivalent small molecules in the future. Yang *et al.* (**https://doi.org/10.1039/D4MD00962B**) also focused on ternary complex optimization and introduced the metric of protein frustration, a concept traditionally used to understand protein folding, to define suboptimal ('frustrated') residues at the protein–protein interface. The method recapitulated the degradation efficacy of a series of BRD4 PROTACs and could be applied to molecular design strategies in the future.

The themed collection covers some of the significant advances being made in the development of new PROTAC-related technologies. Despite the increasing application of rational structure-based design approaches mentioned above, there is still a level of empiricism in the development of efficacious degraders, and new parallel medicinal chemistry methods are required to facilitate the rapid generation of structure–degradation relationships. Stevens *et al.* (**https://doi.org/10.1039/D4MD00760C**) describe the high-throughput nanoscale synthesis and direct-to-biology screening of PROTAC libraries to efficiently probe a variety of different linker chemistries. Interestingly, they found that even within a set of compounds with 20–40% purity, 84% gave DC_{50} values within the assay error. In another synthetic chemistry-enabled strategy, Zhao *et al.* (**https://doi.org/10.1039/D4MD00824C**) report the use of copper-mediated azide–alkyne cycloaddition click chemistry to facilitate the preparation of PROTAC degraders of tyrosyl-DNA phosphodiesterase 1 (TDP1). Wurnig *et al.* (**https://doi.org/10.1039/D4MD00972J**) describe the incorporation of a photoswitch into the linker of an HDAC6 PROTAC to create photochemically targeted chimeras (PHOTACs) that enable the precise spatiotemporal control of target levels. This approach could be applied to optically control other POIs and deliver precision therapeutics with improved safety.

Most PROTACs employ ligands for CRBN or VHL, but there are 600 E3s that could in theory be recruited to considerably expand the scope of the modality, and new methods are required to generate ligands for these ligases to facilitate subsequent PROTAC development. Riha *et al.* (**https://doi.org/10.1039/D4MD00681J**) utilized a DCAF16–SPIN4 interaction assay to identify and optimize covalent ligands of the DCAF16 ubiquitin ligase that were subsequently converted into PROTAC-based degraders of FKBP12.

The themed collection also covers alternative degrader modalities. Naganuma *et al.* (**https://doi.org/10.1039/D4MD00546E**) present a strategy to enhance delivery of PROTACs employing heteroduplex oligonucleotide warheads that are conjugated to a hydrophobic cell-penetrating peptide (CPP). The CPP mediates cellular entry and RNase H-mediated RNA strand cleavage, and CPP detachment releases the active decoy oligonucleotide-based PROTAC into the cytosol. Harris and Trader (**https://doi.org/10.1039/D4MD00787E**) review the various degrons recognized by E3 ligases which have inspired the design of diverse heterobifunctional degrader molecules that utilize 'degron-like' motifs. Such compounds employ N-degron residues or hydrophobic tags, and opportunities for the development of molecules that mediate direct recruitment of POIs to the proteasome are also described. Similarly, Guo, Yang and Cherney

(https://doi.org/10.1039/D4MD00718B) review the recent emergence of degraders now employing non-E3 substrate receptor ligands and that function through the recruitment of E2 ubiquitin-conjugating enzymes, substrate adaptors and E3 chaperone proteins, as well as direct-to-proteasome approaches. Gao *et al.* (https://doi.org/10.1039/D4MD00320A) exploit the hydrophobic tagging technique to design degraders of the immune checkpoint target PD-L1. The PD-L1 ligand BMS-220 was linked to a new hydrophobic tag, the 4,4′-bifluorobenzhydrylpiperazinyl motif, to effect proteasome-mediated degradation.

Molecular glue degraders often possess more traditional Ro5 physicochemistry than heterobifunctional molecules yet maintain the same induced-proximity mode-of-action. To help advance cereblon-based molecular glue degraders through lead optimization (LO), Jia *et al.* (https://doi.org/10.1039/D4MD00870G) develop efficiency metrics that capture both potency and depth of degradation. The approach was used to retrospectively track the optimization of a glue degrader series that eventually delivered golcadomide, which is currently in clinical trials. It will be interesting to see these metrics used prospectively in LO strategies. Proteomics and functional genomics screens in cancer cell lines by Coomar *et al.* (https://doi.org/10.1039/D5MD00054H) discovered that the anthelmintic drug niclosamide triggered the proteasomal degradation of cyclin D1, which was mediated by the E3 ligase $CRL4^{AMBRA1}$. Although the degradation did not appear to proceed *via* a molecular glue mechanism but rather through disruption of the mitochondrial membrane potential, the techniques the group employed to reveal this mode-of-action will be of broad interest to the degradation community.

There has been a surge in interest in exploring non-degrader glues and Oberheide *et al.* (https://doi.org/10.1039/D4MD00833B) employ a novel reversible covalent tethering technique to identify a series of glues for tau/14-3-3. These fragment-like stabilizers will allow for exploration of the role of 14-3-3 in tau aggregation. The application of covalent chemical biology to the area of induced-proximity pharmacology is clearly a growing opportunity and Jones (https://doi.org/10.1039/D4MD00388H) covers the emerging field of synthetic neofunctionalization of protein surfaces in cells.

This themed collection reflects the tremendous variety of therapeutic modalities and chemical biology technologies being developed in the pursuit of small molecules that mediate their pharmacology through induced protein proximity. Noticeably, most articles and reviews describe the use of PROTACs to mediate targeted degradation, which is not surprising considering the incredible progress the field has made recently. In the coming years, we will no doubt see medicinal chemistry advances in other areas of induced-proximity pharmacology, including the recruitment of enzymes that mediate alternative gain-of-function post-translational modifications and synthetic biology approaches to rewire signaling complexes. The field of medicinal chemistry is clearly entering an exciting era of modality diversification that we all hope will expand the druggable proteome to deliver safer medicines with transformational efficacy to patients.