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EDITORIAL

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Alessio Ciulli holds the Personal Chair of Chemical and Structural Biology at the School of Life Sciences, University of Dundee. His research interests are on the development of small molecules targeting protein-protein interactions and inducing protein degradation. His group has made significant contributions to selective chemical intervention on important PPI targets. Initially in collaboration with the Crews Lab, they pioneered the structure-guided design of drug-like ligands for the von Hippel-Lindau E3 ligase, and later in independent work reported one of the first degrader molecules originated from their VHL ligands. These discoveries jump-started the PROTAC field and led to significant commercial impact across academia and biopharma worldwide. More recently, Alessio's Lab has illuminated important structural and mechanistic insights into the molecular recognition and mechanism of action of PROTACs, including the first crystal structure of a PROTAC ternary complex. Collectively Alessio's discoveries have contributed to making targeted protein degradation a realistic and effective drug discovery modality. Alessio graduated in Chemistry (University of Florence, 2002) and obtained his PhD in Chemical Biology (University of Cambridge, 2006) studying protein-ligand interactions. Following post-doctoral research on fragment-based drug design, and a 3-months HFSP visiting Fellowship at Yale University, he returned to Cambridge to start his independent career in 2009. In 2013 Alessio moved his laboratory to Dundee and was promoted to Professor in October 2016. He is a Fellow of the Royal Society of Chemistry.

William Farnaby is currently a team leader in medicinal chemistry and chemical biology at the School of Life Sciences, University of Dundee. Since 2016 he has led a multi-disciplinary team of drug discovery scientists, within the group of Professor Alessio Ciulli, focussed on the development of the next generation of bivalent degrader molecules as drugs to treat disease. This team is engaged in a unique collaboration model with scientists at Boehringer Ingelheim that aims to discover PROTACs to address areas of critical unmet medical need. William has led and progressed protein degradation projects through multiple stages of the drug discovery process and in doing so continues to contribute significantly to the advance of rational degrader design, synthesis and methods of biochemical and cellular evaluation. Prior to this William worked at Takeda Cambridge as a senior medicinal chemist. He contributed to a number of successful projects within the CNS therapeutic area, including programs to develop novel chemical matter to accelerate early stage CNS drug discovery and co-invented two clinical candidates currently under investigation.

Until recently, small molecule drug discovery has been dominated by occupancy driven modalities relying on the persistent action of a drug on a target protein to induce a therapeutic response. For many years, the tantalising prospect of inducing protein degradation with small molecules offered promise but remained experimentally challenging. Today, supported by key advances over recent years and emerging clinical validation, protein degradation is rapidly becoming one of the biggest shifts in approach the drug discovery community has seen for decades. Medicinal chemists are redefining their 'rule' book and their definition of what is required of a small molecule to be efficacious and

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developable. The potential to dissect biological circuits in a post-translational setting, enabled by targeted protein degradation, is likely to greatly accelerate target identification and validation. Moreover the scope of proteins, domains and pathways that may be addressed by this approach is still unexposed, and primed for expansion as our perception of what is druggable continues to evolve. As an increasing number of drug discovery projects across industry and academia progress towards pre-clinical and clinical evaluation, we are delighted to present a collection of reviews that aim to highlight how targeted protein degradation has impacted drug discovery to date, the tools available, and the challenges and opportunities that lie ahead. All of the authors are leaders in their field, have themselves contributed critically to what we know today, and as active practitioners continue to shape the future of protein degradation drug discovery.

Our special issue gets off to a flying start with three plenary reviews. The first by Chopra *et al.* provides a critical overview on the use of small molecules to intercept the ubiquitin proteasome system for inducing protein degradation [1]. The authors nicely compare and contrast approaches employing bivalent Proteolysis Targeting Chimeras (PROTACs) with monovalent 'molecular glues' which they refer to as 'DCAF binding templates', to hijack E3 ubiquitin ligases to induce protein degradation. A historical perspective is given by Petterson and Crews on the key milestones on development of the PROTAC approach to date [2]. The main advantages and potential challenges that may be observed over other modalities as the first PROTAC compounds progress to the clinic are also discussed. The last decade has observed key discoveries in uncovering the neosubstrate protein targets and E3 ligase binding mode of the immunomodulatory drugs thalidomide and lenalidomide, as well as the emergence of other potential glues such as indisulam that may also redirect E3 ligase recruitment. Chamberlain and Cathers provide a timely review of this narrative as the field evolves from revealing the mode of action of these molecules to exploiting these findings towards more targeted therapeutic approaches [3].

In the field of bivalent small molecules, specific and non-genetic inhibitor of apoptosis protein (IAP)-dependent protein erasers (also known as SNIPERs) as well as PROTACs targeting BET bromodomain proteins have both been instrumental in demonstrating that small-molecule mediated protein degradation may be achieved at low concentration and with exceptional selectivity. These two approaches are featured in reviews by Naito *et al.* [4] and Yang *et al.* [5], respectively. Emerging from much of this research has been a desire to rationalise the process of evaluating and designing the next generation of bivalent degraders. Zhang *et al.* provide a concise overview of progress with regards to understanding ternary complex formation, its contribution to the PROTAC-induced degradation process and how the field may use the structural and biophysical data that are beginning to emerge to drive biochemical and cellular activities and to dissect the critical factors in compound discovery [6]. As bivalent small molecule degraders become more and more an established part of the drug discovery armoury, questions are being asked and key lessons learned in the *in vivo* application of such compounds. The speed and efficiency with which these challenges are met will be one of the critical factors in delivering on the promise of this modality. In this context, Watt *et al.* describe experiences shared in the public domain to date in the *in vivo* profiling of PROTACs [7].

As the hunger for accelerating drug discovery in the protein degradation space increases, so does the need to improve and expand the toolbox. A review by Daniels *et al.* details the development of cellular methods to monitor critical components of induced protein degradation [8]. This is an area that has matured considerably in recent months and years, with increasing options for higher throughput and more informative assays. Quantitative proteomics applications that may unveil the effects of degraders on cellular protein homeostasis are now established as a critical element of any scientific endeavour in the field. In this context Grandi and Bantscheff summarise advancements in mass spectrometry based chemoproteomic methods [9]. Alongside an expanding analytical toolbox, chemical biologists continue to provide solutions for investigating functional consequences of selective post translational depletion of proteins. Yesbolatova *et al.* provide a concise review of ligand-induced genetic degradation, whereby a target gene of interest is fused to a general 'degron tag' for which a degrader molecule exists [10]. Such methods can be very valuable to de-risk potential therapeutic targets by (de)validating them prior to developing specific ligands or degraders against. In a similar vein, but with a focus on cancer biology, Mayor-Ruiz and Winter describe lessons that have been learned by acutely inducing protein degradation to perturb critical cellular processes and pathways, and how the methods employed fare when compared to other established approaches such as genetic silencing and enzyme inhibition [11].

Finally, the modulation of protein homeostasis *via* a distinct approach – the inhibition of deubiquitinating enzymes – is discussed by Wertz and Murray. An ever growing and emerging area of drug discovery research in its own right, the focus of this review is on the biological function, structural biology and attempts to drug the well-characterized USP7 and USP14 enzymes [12].

The editors would like to thank all the authors and referees for their valued and insightful contributions. We hope that this special issue will act as a gateway for drug hunters from all fields and therapeutic areas interested in understanding the potential of targeted protein degradation. It is also our hope that it will provide a timely and illuminating perspective on the technological accomplishments, current challenges, and future opportunities in the field.

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