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Chasing molecular glue degraders: screening approaches

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Protein–protein interactions (PPIs) govern all biological processes. Some small molecules modulate PPIs through induced protein proximity. In particular, molecular glue degraders are monovalent compounds that orchestrate interactions between a target protein and an E3 ubiquitin ligase, prompting the proteasomal degradation of the former. This and other pharmacological strategies of targeted protein degradation (*e.g.* proteolysis-targeting chimeras – PROTACs) overcome some limitations of traditional occupancy-based therapeutics. Here, we provide an overview of the "molecular glue" concept, with a special focus on natural and synthetic inducers of proximity to E3s. We then briefly highlight the serendipitous discoveries of some clinical and preclinical molecular glue degraders, and discuss the first examples of intentional discoveries. Specifically, we outline the different screening strategies reported in this rapidly evolving arena and our thoughts on future perspectives. By mastering the ability to influence PPIs, molecular glue degraders can induce the degradation of unliganddable proteins, thus providing an exciting path forward to broaden the targetable proteome.

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1. Introduction

More than 300 000 protein–protein interactions (PPIs) occur in human cells and they are involved in all physiological processes, including disease.[1] Recent decades have witnessed the capacity of many small-molecule drugs to modulate PPIs. The inhibition of PPIs has arguably received more attention in the past and has proved to be challenging but still feasible.[2,3] In contrast, inducing PPIs was long considered almost unachievable. Although PPI stabilizers and inducers are still scarce, innovations around proximity-inducing chemotypes are gaining momentum and offer attractive new options in pharmacotherapeutics. Excellent reviews have recently discussed a variety of proximity-inducing concepts.[4,5] The discovery of natural and synthetic small-molecule compounds that operate through a "molecular glue" (MG) mode

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of action has provided us with inspiring examples of how such molecules can orchestrate PPIs.[5–9] MGs are defined herein as monovalent small molecules that strengthen/trigger contacts between two proteins, binding at the interface of said two protein surfaces. FK506, rapamycin, and cyclosporine A are prime examples. An interesting type of MGs are "MG degraders", which prompt the destabilization of a target protein by induced/stabilized proximity to an E3 ubiquitin ligase. Auxin and thalidomide exemplify this mode of action. MG degraders will be the major focus of this review. This twist of the "MG concept" towards eliciting protein destruction, together with breakthroughs using bivalent molecules (*e.g.*, proteolysis targeting chimeras – PROTACs),[10–16] have inspired new paradigms on how to inactivate disease-relevant proteins: the targeted protein degradation (TPD) approach.

TPD is a pharmacological strategy based on drugs (degraders) that destabilize proteins by hijacking the intracellular proteolysis machinery. This strategy has garnered significant attention in the last year owing to its potential to modulate the abundance of proteins that are difficult to target with conventional inhibitors. Degraders can be multivalent (*e.g.*, PROTACs) or monovalent (*e.g.*, MG degraders) depending on their modularity (Fig. 1). In the following sections, we first offer a TPD-focused contextualization of MG degraders. We then briefly illustrate the "MG" and "MG degrader" concepts. Finally, we discuss how the discovery of MG degraders is moving from initial accidental findings to intentional strategies and developments, and lay out the prospects and challenges ahead.

2. Targeted protein degradation (TPD): multivalent and monovalent degraders

TPD has caused great excitement in drug discovery in recent years as an important complementation and alternative to inhibitor-based therapeutics.[10–13,16] Recent advances in this field hold the promise to expand the druggable space. TPD is based on the drug-induced appropriation of one of the cell's natural protein removal systems. To date, most work on TPD has focused on the chemical rewiring of the ubiquitin–proteasome system (UPS), but additional approaches harnessing other protein homeostasis machinery have been described. Examples include: lysosome-targeting chimeras (LYTACs),[17] autophagosome-tethering compounds (ATTECs),[18,19] autophagy-targeting chimeras (AUTACs and AUTOTACs)[20,21] and bacterial protease-targeting chimeras (BacPROTACs).[22] For conciseness, here we will cover UPS-dependent TPD.

Small-molecule drugs referred to as degraders induce proximity between a target protein of interest (sometimes called "neosubstrate") and an E3 ubiquitin ligase. The productive formation of target:degrader:E3 ternary complexes results in polyubiquitination and subsequent proteasomal degradation of the target. Whereas traditional inhibitors are based on occupancy, degraders are event-driven and thus have a catalytic mechanism of action due to their dissociation after promoting target polyubiquitination. A simple way to classify degraders is based on the number of chemical moieties in the small molecule. Hence, degraders can be multivalent or monovalent (Fig. 1).

Within the multivalent degraders, heterobifunctional molecules known as proteolysis targeting chimeras (or PROTACs) have paved the way (Fig. 1). In 2001, Crews, Deshaies and colleagues used E3 peptidic ligands to show that an E3 could be bridged to a protein of interest and prompt the degradation of the latter.[23] Peptidic PROTACs progressed to fully-synthetic designs that bind target and E3 with dedicated warheads connected by a linker.[24–29] Recently, trivalent PROTACs have also been developed.[30] Due to their modular architecture, PROTACs can be easily adapted to a spectrum of targets. This modularity poses potential challenges for their clinical use as

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Cristina Mayor-Ruiz

Cristina Mayor-Ruiz obtained her PhD at the CNIO (Madrid, 2018) under the supervision of Dr. Fernández-Capetillo, where she studied mechanisms of resistance to anticancer therapies. In 2018, she joined the lab of Dr. Winter (CeMM, Vienna) for her postdoc, focusing on chemical biology around degraders. Since 2021 she leads the "Targeted protein degradation & drug discovery lab" at IRB Barcelona. Her research focuses on developing proximity-inducing drugs with therapeutic interest, and on tackling biological questions that involve (dys)regulation dynamics of E3 ubiquitin ligases. Dr. Mayor-Ruiz has been honored with national and international awards, such as an ERC Starting grant.

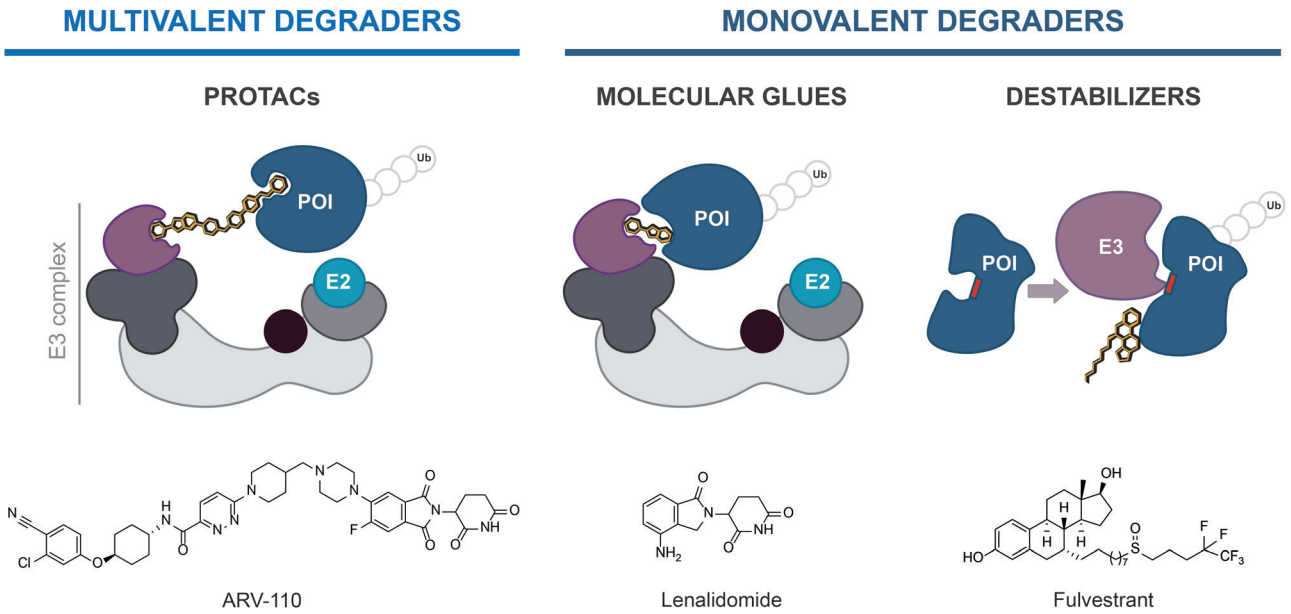

Fig. 1 Types of degraders. Multivalent degraders bind E3 and target with dedicated warheads that are connected by a linker (left, bivalent PROTACs are depicted). ARV-110 (AR degrader in clinical trials) is shown as an example below (bottom left). Monovalent degraders (right) are linker-less molecules and comprise: molecular glue (MG) degraders and destabilizers. MG degraders induce/stabilize direct E3:target interactions. Destabilizers drive the target protein to a vulnerable state *via* different phenomena (the exposure of hydrophobic region upon drug binding is shown). This susceptible state is then recognized by the degradation machinery (*e.g.*, E3s). The chemical structures of the clinically approved drugs lenalidomide (IKZF1/3, CK1α MG degrader) and fulvestrant (ER destabilizer) are shown (bottom middle and right). POI: protein of interest. Ub: ubiquitin. The E3 complex depicted represents a prototypical multi-subunit ligase of the Cullin-RING ligase family.

their physicochemical properties breach the typical limits for small-molecule oral drugs. Such suboptimal parameters can be partially counterbalanced by the catalytic mode of action of PROTACs. Indeed, this exciting technology is currently transitioning to the clinic, with several PROTACs now in clinical trials.[16,31] PROTACs have been extensively reviewed elsewhere.[12–16,32,33]

Monovalent degraders (Fig. 1) are single linker-less molecules that induce the degradation of proteins by orchestrating (1) indirect E3:target dimerizations (destabilizers[34–36] – *e.g.*, fulvestrant) or (2) direct E3:target interactions (MG degraders[37–40] – *e.g.*, lenalidomide). Destabilizers drive the target to a vulnerable state for further E3 recognition. Revealing a degron, increasing surface hydrophobicity, inducing polymerization, or preventing protective interactions are some of the vulnerable states triggered by destabilizers. While the mode of action of destabilizers (sometimes called monomeric degraders) is commonly non-obvious, insights are emerging. We referred the readers to recent reviews for further information.[34–36] MG degraders strengthen or prompt direct E3:target interactions that are typically highly cooperative. Conversely, PROTACs are often not designed to capitalize on cooperative interfaces, although there are examples that also orchestrate large PPIs.[41–43] MG degraders usually have no affinity for at least one of the two proteins in isolation. Serendipitous discoveries have illustrated the great potential of this type of degraders. In this regard, apart from sharing major advantages of PROTACs (*e.g.*, degradation of targets, a catalytic mechanism of action), MG degraders have four key differences: (i) favorable drug-like properties that often fall within the Lipinski's "rule of 5" (Fig. 2);[35] (ii) can induce the degradation of target proteins otherwise deemed unligandable (*e.g.*, IKZF1/3, RBM39);[44–55] (iii) have non-saturable kinetics (no hook effect due to formation of binary complexes); and (iv) they are already a therapeutic reality.[56–67] However, the lack of systematic technologies to develop or even detect such molecules has hampered broad translational efforts.

In the next section, we briefly illustrate the "MG" and "MG degrader" concepts, covering from natural to synthetic compounds that greatly exemplify the potential of PPI modulation by small molecules.

3. The "molecular glue" concept

MGs are monovalent small molecules that bridge two proteins by orchestrating/catalyzing PPIs. These interactions are not saturable, differentiating MGs from bivalent inducers of proximity. MGs are typically characterized by the lack of affinity to at least one protein partner, and they often prompt highly cooperative PPIs. Several interpretations of this concept can be found in the literature. Recently, the Zheng lab postulated that most, if not all, MGs act on proteins that already have a basal propensity to interact with each other, thus also differentiating this pharmacology from bifunctional molecules like PROTACs.[77] PPI "chemical stabilizers" can be defined as a subtype of MGs in which the two partner proteins have considerable basal affinity in the absence of the small molecule.[6,8,40] Intramolecular MGs (hence, involving only

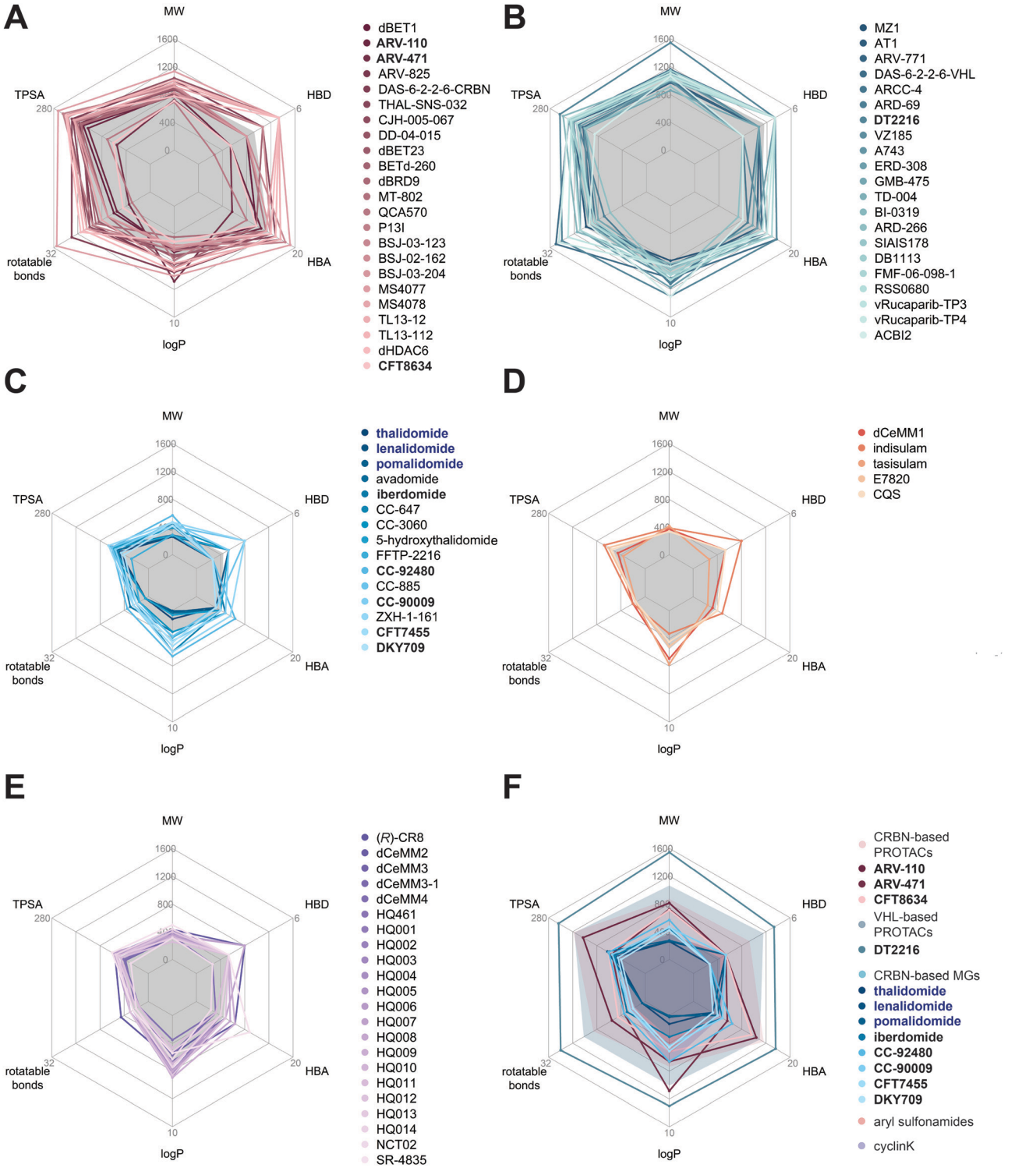

Fig. 2 Chemical properties of molecular glue (MG) degraders *vs.* bivalent PROTACs. Radar plots showing molecular weight (MW), estimated topological polar surface area (TPSA), number of rotatable bonds, octanol–water partition coefficient (log*P*), hydrogen bond acceptors (HBA), and hydrogen bond donors (HBD). Blue bold: MG degraders clinically approved. Black bold: degraders in clinical trials. In A–D, the average for each graph is shown in grey. Properties of selected bivalent degraders are shown in (A and B): (A) CRBN-based PROTACs (n = 23); (B) VHL-based PROTACs (n = 21). For these analyses, we selected the most cited PROTACs against common targets (as reported in the open-access database PROTAC-DB)[68] and PROTACs in clinical trials with disclosed structure. We also include an example of a VHL-based bioavailable PROTAC (ACBI2).[69] MG degraders are shown in (C–E): (C) CRBN-based MG degraders (n = 15); (D) aryl sulfonamides (n = 5); (E) cyclin K MG degraders (n = 22). (F) Radar plot combining average properties of each subgroup. Degraders approved (blue bold) or in clinical trials (black bold) are highlighted. Chemical properties were either obtained from ChEMBL or calculated using ChemDraw v.20.1.0.112 and Marvin v.22.11.0, ChemAxon.

one protein) are also an emergent subclass. Of note, the direct glue-like mode of action differs from allosteric stabilizers of PPIs like paclitaxel.

We like to think of MG degraders simply as a subtype of MGs that hold a protein to an E3 ligase so that the targeted protein is tagged for proteasomal destruction. In the following subsections, we outline examples of natural and synthetic MGs with and without degradative capacity (Fig. 3).

3.1 Natural compounds

3.1.1 Natural non-degradative molecular glues. Retrospective studies have shown that a growing number of natural products exert their physiological activity through an MG-like mechanism of action. We provide here some examples that function as protein–protein tethers without a degradative outcome, thus promoting/enhancing PPIs in which none of the proteins involved is an E3 ubiquitin ligase. In the early 1990s, the term MG was used to describe the mode of action of microbial macrolides such as FK506 (Fig. 3A), rapamycin and the cyclic peptide cyclosporin A (Fig. 4). The former two bind to FKPB12 and these binary complexes induce inhibitory interactions with calcineurin and FRAP (later mTOR, mammalian Target of Rapamycin), respectively.[78,79] Another example of an MG is Cyclosporin A, which forms a binary complex with cyclophilin able to bind and inhibit calcineurin.[80,81] These findings spurred the discovery of additional compounds with similar MG properties.[82] Often called ''chemical stabilizers'', fusicoccanes (*e.g.*, fusicoccin A, cotylenin A) induce the targeted stabilization between the 14-3-3 proteins and part of its interactome (Fig. 4).[83–85] The fungal metabolite brefeldin A (Fig. 4), a macrocyclic lactone used to study membrane trafficking, inhibits Golgi functions by stabilizing ARF(GDP) with its guanine exchange factor ARNO.[86,87] We also find examples in plant biology: brassinosteroids are phytohormones that function as MGs by linking the membrane receptor kinase BRI1 to its co-receptors (Fig. 3A and 4).[71,88]

3.1.2 Natural molecular glue degraders: rewiring the ubiquitination pathway, lessons from plants and viruses. Natural MG degraders comprise a remarkable subtype of MGs. They induce the degradation of a target protein by induced proximity to an E3 ubiquitin ligase. The prime example of a natural MG degrader is the plant hormone auxin (Fig. 3B and 5).[72,89] In 2007, Tan *et al.* showed that auxin promotes the degradation of the family of transcription repressors AUX/IAA by enhancing weak existing interactions with TIR1 (part of the E3 ligase complex SCF^{TIR1}).[72] The X-ray structures revealed that auxin complements a suboptimal interface, facilitating nanomolar protein–E3 interactions. Methyl jasmonate is another plant hormone with a similar mechanism (Fig. 3B and 5). This hormone glues the E3 ligase SCF^{COI1} to the transcriptional repressor JAZ.[73]

Beyond plant biology, viruses are inspiring examples of E3 hijacking, in this case, to evade the host's defense mechanisms.[90,91] Viral proteins bind and thereby redirect specific E3 ligases to ubiquitinate certain host proteins and enhance viral replication. Peter Howley's group reported the first example of viral hijacking back in the early 1990s.[92–94] Studying the human papillomavirus protein E6, they discovered that E6 induces interactions between two host proteins: TP53, involved in viral surveillance, and one that they named E6-associated protein (E6-AP). Of note, E6-AP then founded a new class of E3 ubiquitin ligases, now called HECTs (from Homolog to E6-AP carboxyl terminus) with around 30 members in humans. In 1998, Howley and colleagues proposed that the fusion of proteins such as E6 could be used to trigger the degradation of other proteins of interest beyond TP53. This was perhaps the earliest documented notion around TPD (WO2000022110A2). Additional viral factors provide us with a wealth of examples of E3 hijacking. For instance, the Vif protein of the human immunodeficiency virus (HIV) hijacks CRL5 and binds the co-transcription factor CBF-β leading to degradation of A3F and A3G, proteins that block viral replication.[95–97] Hijacking of $CRL1^{\beta\text{-}TRCP}$ also enables HIV to evade host immunity.[98] The V protein of simian virus 5 (SV5 V) binds the CRL4 adaptor DDB1, bringing in proximity the host STAT2/STAT1 heterodimers. Ubiquitination and further degradation of STAT1 largely diminishes interferon response to viral infection.[99,100] In addition to hormone plants and viral factors, some *Streptomyces*-derived manumycin polyketides (asukamycin and manumycin A) have been reported to rewire E3s (Fig. 5). These natural products seem to function as covalent MG degraders that engage UBR7 (a putative E3) and TP53.[101] Recently reported in mammalian cells by the Rape lab, $CUL2^{FEM1B}$ relies on Zn^{2+} ions as ''MGs'' to selectively recruit reduced FNIP1 (and not oxidized FNIP1) during reductive stress, thereby explaining how an E3 ligase can discriminate targets based on redox state.[102]

All the aforementioned natural products, degraders or not, exert their physiological activity using an MG-like mode of action. Some of these molecules have been used for many years as therapeutic agents, like the immunosuppressants FK506 (*e.g.*, Prograf), rapamycin (Rapamune) and cyclosporin A (*e.g.*, Sandimmun). Others, like auxin, are widely used in research.[103] The discovery that simple synthetic compounds can also serve as MGs has driven even greater interest in this seemingly rare type of small molecules.

3.2 Synthetic molecular glues

3.2.1 Synthetic non-degradative molecular glues. We briefly outline examples of non-natural MGs that function outside the UPS:

Synstab A is a simple synthetic compound discovered in 2001 that, by functioning as a MG, promotes microtubule formation.[104] DNMDP and related small molecules induce interaction between the phosphodiesterase PDE3A and SLFN12 (Fig. 3C and 6), leading to a cytotoxic effect in cancer cells with high expression of both proteins.[75,105] In 2020, structural studies with trametinib, unlike other MEK inhibitors revealed that it glues MEK to KSR (Fig. 3C and 6).[106] The same group developed trametiglue, a more potent derivative (Fig. 6).

The sequestering of binding partners in stabilized dimeric protein complexes is a valid strategy for modulating PPIs *via* MGs. Max homodimer stabilization is an example. A small-molecule

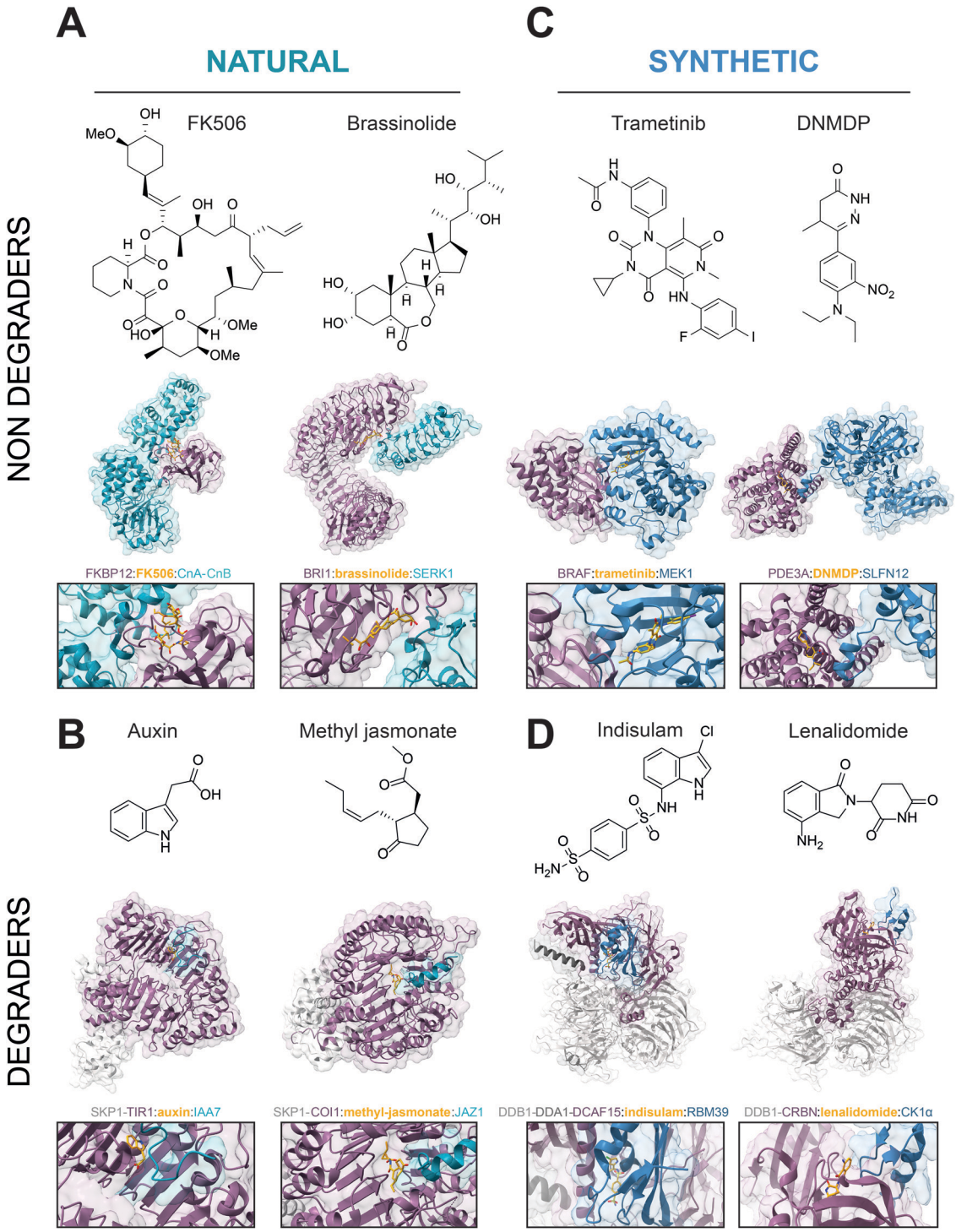

Fig. 3 Natural and synthetic molecular glues (MGs). (A and B) Selected examples of natural MGs. (A) Natural non-degradative MGs: FK506 structure and FKBP12:FK506:CnA-CnB complex (PDB: 6TZ6, left);[70] brassinolide structure and BRI1:brassinolide:SERK1 complex (PDB: 4LSX, right).[71] (B) Natural MG degraders: auxin structure and SKP1:TIR1:auxin:IAA7 complex (PDB: 2P1Q, left);[72] methyl jasmonate structure and SKP1:COI1:methyl jasmonate:JAZ1 complex (PDB: 3OGM, right).[73] (C and D) Examples of synthetic MGs. (C) Synthetic non-degradative MGs: BRAF–trametinib–MEK1 complex (PDB: 7M0Y, left);[74] DNMDP structure and PDE3A:DNMDP:SLFN12 complex (PDB: 7LRD, right).[75] (D) Selected synthetic MG degraders: DDB1–DDA1–DCAF15: indisulam:RBM39 X-ray (PDB: 6Q0W, left);[55] DDB1-CRBN:lenalidomide:CK1α X-ray structure (PDB: 5FQD, right).[76]

microarray screen identified binders of purified Max.[107] KI-MS2-008 (Fig. 6), an optimized analog of one of the drug hits, stabilizes Max homodimers and thus renders Max less capable of binding Myc.[107] Additional examples are RO2443, which prevents MDMX binding to p53 by stabilizing an inactive MDMX homodimer,[108] or JH-RE-06, which induces REV1 dimerization to block the

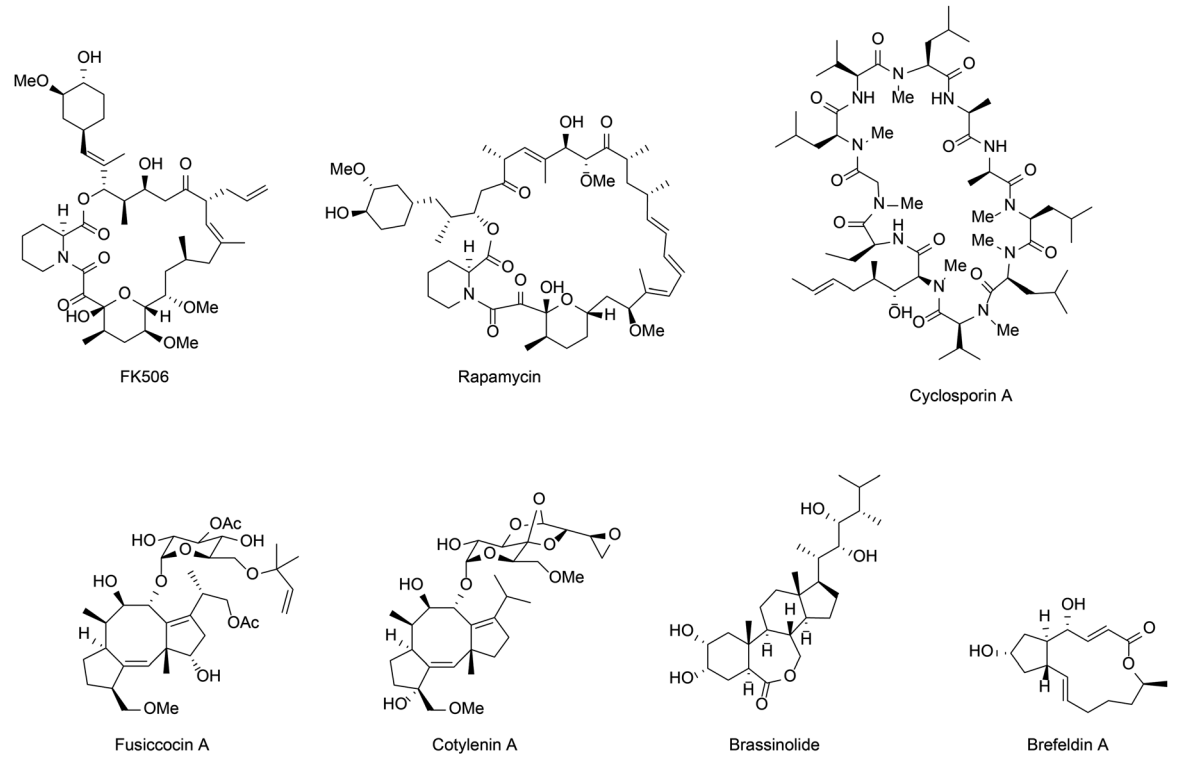

Fig. 4 Chemical structures of natural non-degradative molecular glues.

REV1–REV7 interaction (Fig. 6).[109] Simple synthetic compounds can also function as intramolecular glues, as shown by SHP099[110,111] and ET070 (Fig. 6),[112] which correct the hyperactivation of mutant SHP2 by stabilizing its closed conformation.

To date, less attention has been given to covalent MGs: RM-018 is a recently published example (Fig. 6).[113] It binds cyclophilin A, and this binary complex can associate with the active state of $KRAS^{G12C}$ and form a covalent bond. Interestingly, $KRAS^{Y96D}$ confers resistance to currently approved (non-glue-like) covalent $KRAS^{G12C}$ inhibitors, and RM-018 overcomes such $KRAS^{G12C/Y96D}$-mediated resistance.

A first-in-class (potential) MG is ceapin-A7 (Fig. 6), which acts as a tether between two organelles. Ceapin-A7 induces the neomorphic association of ATF6α in the endoplasmic reticulum with ABCD3 in the peroxisome, hence acting as an inter-organelle glue.[114] Confirmation of the ternary complex, or biochemical reconstitution of the drug-induced proximity is pending. Nevertheless, this example opens up a roadmap for the chemical modulation of organelle–organelle interactions.

Many other notable examples of synthetic MGs have been reported.[5–8,115] These examples provided proof of concept that simple, non-natural compounds can also induce PPIs.

3.2.2 Synthetic molecular glue degraders: serendipitous discoveries. Regarding synthetic MG degraders, serendipity has driven the discovery of structurally simple compounds with anticancer activities (Fig. 7). Retrospective analyses showed the MG-like mode of action of those compounds.

The prime examples of synthetic MG degraders are thalidomide (Fig. 7) and its analogs/derivatives (the immunomodulatory imide drugs – IMiDs). Seminal biochemical and structural studies uncovered that IMiD binding to the E3 $CRL4^{CRBN}$ leads to the induced degradation of several targets.[44–50] In brief, IMiDs were first shown to trigger CRBN-dependent proteasomal degradation of the C2H2-type zing-finger transcription factors Ikaros (IKZF1) and Aiolos (IKZF3).[46–48] Shortly after, lenalidomide (Fig. 3D) was shown to also induce the degradation of the kinase CK1α, while the structurally similar thalidomide and pomalidomide do not.[50] Therefore, small differences in the chemical structure could drive substantial differences in the specific set of proteins targeted for degradation. A broad target accommodation has been shown for IMiD derivatives. Currently, thalidomide, lenalidomide and pomalidomide are used in a variety of clinical settings,[59] thus providing evidence that MG degraders are an efficacious therapeutic strategy. Of note, IMiDs have also fueled PROTAC developments. In 2015, Winter *et al.* reported the first *in vivo*-compatible PROTAC (dBET1) by conjugation of an IMiD-like phthalimide moiety to the BET-bromodomain inhibitor JQ1.[27] The same year, Lu *et al.* also generated IMiD-based PROTACs.[116]

The second type of synthetic glue degraders reported is comprised by aryl sulfonamides, such as indisulam and E7820 (Fig. 3D and 7). Retrospective studies showed that they hijack $CRL4^{DCAF15}$ to degrade the splicing factor RBM39 and its paralog RBM23.[51–55] The pre-mRNA splicing factor PRPF39[117] and HIF1-β[118] are additional targets of some aryl sulfonamides. No aryl sulfonamide has merited approval to date. Earlier phase II clinical trials with indisulam and E7820 showed limited efficacy.[119–126] The current understanding of their mechanism of action may enable better patient stratification.

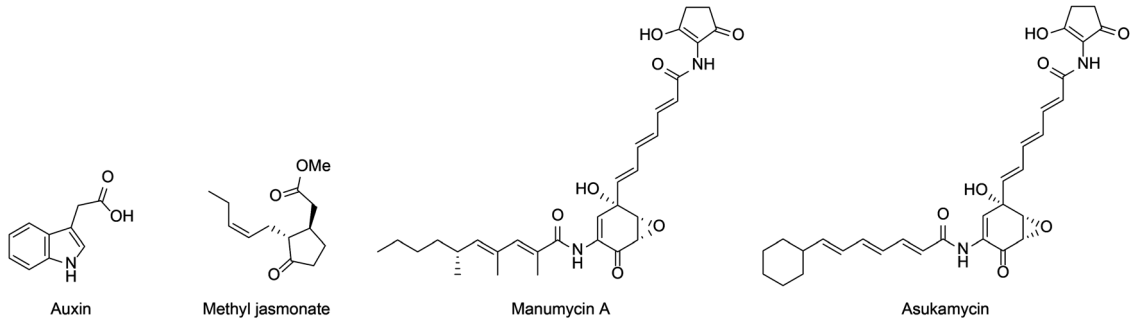

Fig. 5 Chemical structures of natural molecular glue degraders.

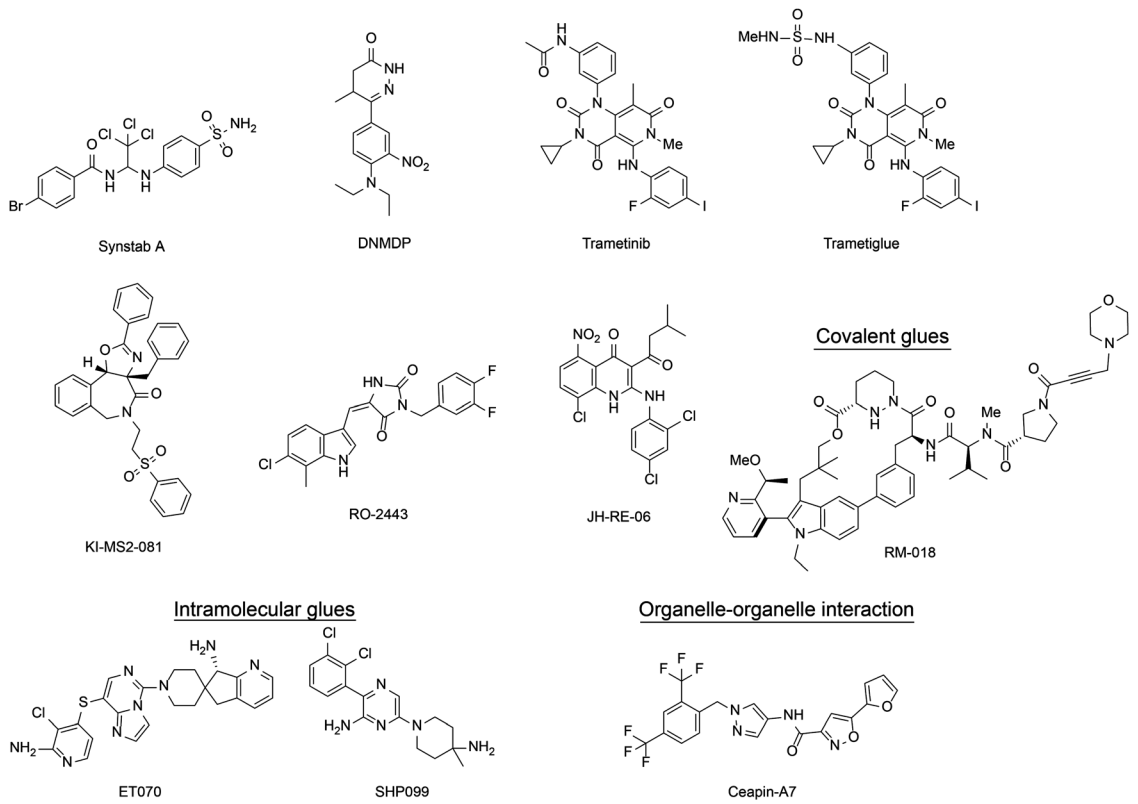

Fig. 6 Chemical structures of synthetic non-degradative molecular glues.

Whereas IMiDs show a nanomolar affinity for CRBN, aryl sulfonamides have much weaker binding to DCAF15 alone. The weak binary affinity is compensated by a large DCAF15–RBM39 interaction surface, twice as big as the CRBN–target interaction area facilitated by IMiDs. Sulfonamides have proven that MG degraders do not necessarily depend on high-affinity binding to the E3 in isolation. Conceptually, this suggests that non-ligandable E3s are also valuable for drug development campaigns. This notion may also extend to PROTAC development: a novel DCAF15-based PROTAC against BRD4, named DP1, has recently been reported.[127] IMiDs and aryl sulfonamides have been extensively reviewed elsewhere.[38,59,128–130]

Screens for inhibitors of BCL6, a known oncogenic driver in lymphoma, led to the unintended discovery of monovalent degraders of BCL6.[131,132] In an elegant study, Słabicki *et al.* addressed the mechanism of action of one of these compounds, namely BI-3802 (Fig. 7).[133] The authors revealed that BCL6 destabilization was elicited *via* compound-induced polymerization. BCL6 normally forms homodimers through its BTB domain. The authors showed that BI-3802 facilitates the self-assembly of a symmetric dimer into polymers. Binding at opposing sides of the BCL6 homodimer, the hydrophobic parts of BI-3802 that are solvent-exposed engage in interactions with another homodimer, thereby inducing BCL6 polymerization. These filaments led to an exacerbated ubiquitination by SIAH1, an E3 ligase of the RING family. This mechanism of action is at the interface of the two monovalent degrader subcategories (MG degraders and destabilizers, Fig. 1). BI-3802 does not directly glue BCL6 to the involved E3

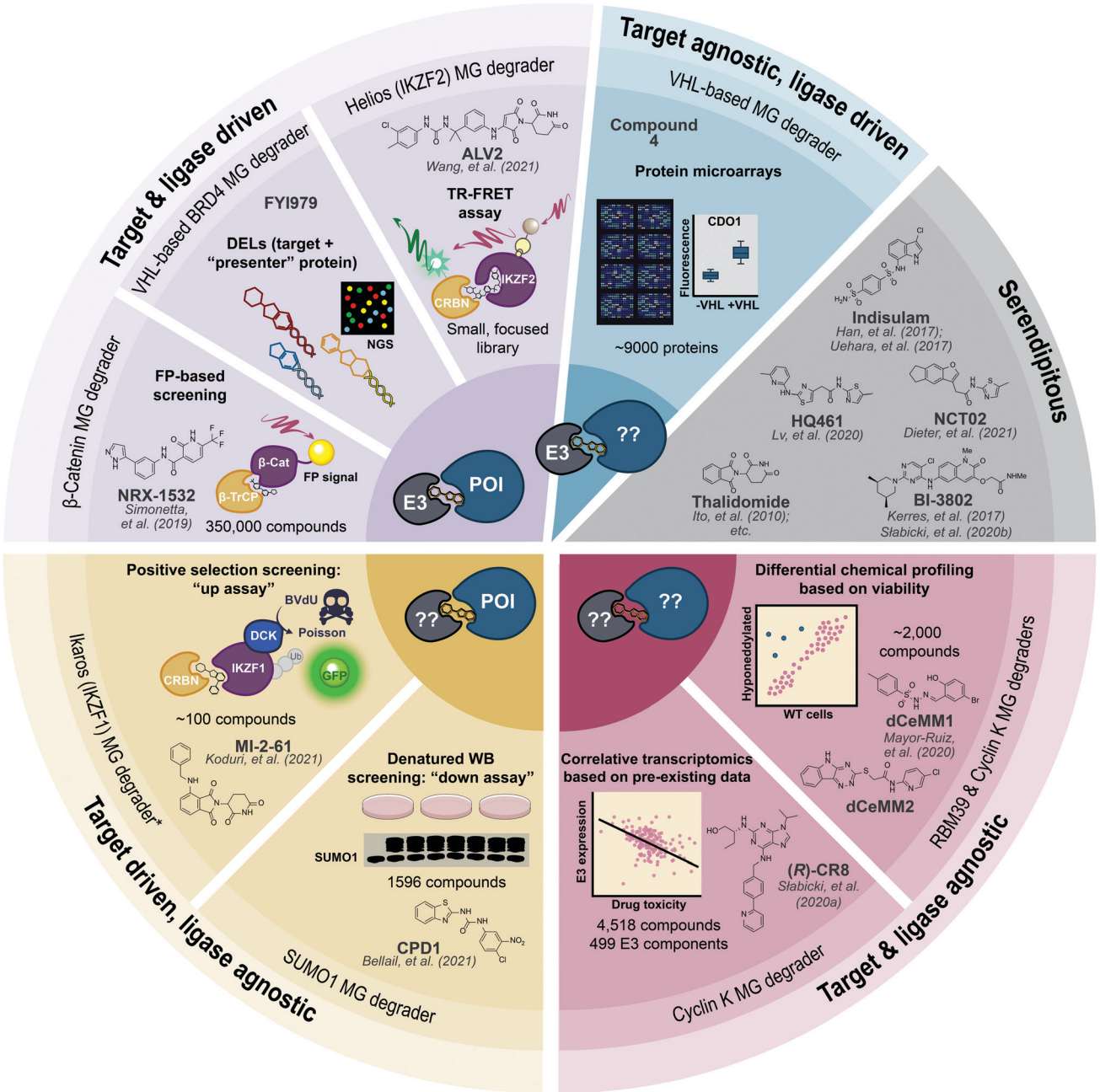

Fig. 7 From serendipity to intentional discovery of synthetic molecular glue (MG) degraders. Depiction of strategies towards MG degrader discovery categorized as indicated in the outer circle and schematically represented in the inner circle. The following information is indicated: type of screen, chemical diversity of the compound library used, small-molecule hit name and chemical structure (if disclosed), and paper reference (only for published strategies). POI: protein of interest. TR-FRET: time-resolved fluorescence energy transfer. DELs: DNA-encoded libraries. FP: fluorescence polarization. β-Cat: β-Catenin. WB: western blot. WT: wild type. *IKZF1 MG degrader: although the compounds used were IMiD derivatives, we have classified this strategy as E3-agnostic given the foreseen potential of the screening assay beyond CRBN and IMiD scaffolds.

but rather induces indirect "dimerization" between the polymerized protein and the E3. Interestingly, SIAH1 mediates the degradation of both endogenous and compound-dependent aggregated BCL6. The concept of ligand-induced polymerization and subsequent protein destabilization offers appealing new opportunities for TPD. This mechanism of action may be shared with other monovalent degraders reported in the literature whose precise mode of action has yet to be elucidated.

Strategies searching for polymerization-inducing molecules (either in biochemical or cell-based screens) and coupled with a target expression reporter may help find similar degraders, specially against proteins that form symmetric dimers.

Apart from the three examples outlined, two cyclin K (CycK) degraders were found without intendedly looking for MG degraders: HQ461 and NCT02 (Fig. 7).[134,135] These examples are discussed in the Section 4.1 below.

Notably, all the aforementioned MG degraders, whether natural or synthetic, share a common feature, namely their capacity to induce the degradation of target proteins otherwise deemed non-ligandable (*e.g.*, transcription factors). In addition, most of them hijack E3s of the cullin RING ligase (CRL) family. CRLs are the largest family of E3 ubiquitin ligases. These E3s are multisubunit complexes formed by a cullin scaffold, an adaptor protein, a substrate receptor and a RING protein subunit.[136,137] CRLs orchestrate an impressive array of eukaryotic processes and their dysregulation underlies many pathologies. Such physiological impact depends on dynamic and tightly coordinated interactions between CLRs and certain positive and negative regulators.[137–140] Several functional genomics campaigns in recent years have helped map how the repertoire of CLRs and their regulators shape degrader efficacy, thus also outlining putative resistance mechanisms.[141–151]

4. Synthetic molecular glue degraders: the first intentional discoveries

The discovery of synthetic MG degraders has been driven mostly by fortuity, as outlined above. Chemical diversification of known glue degraders, especially IMiDs, has delivered derivatives that are even approaching the clinic.[16,31] Of course, such chemical diversification has a narrow focus on particular E3s and chemical scaffolds. Examples of strategies for the systematic development or identification of novel MG degraders are still limited.[152] Recently, we and others have challenged the ''unintended discovery'' notion around these molecules. In this section, we discuss the first examples of intentional strategies for delivering MG degraders, falling into binary combinations of the following categories: target-agnostic, E3-agnostic, target-driven and E3-driven (Fig. 7).

4.1 Target- and E3-agnostic intentional strategies of discovery

In 2020, three groups independently reported the discovery of structurally different CycK MG degraders (Fig. 7 and 8). Although all the studies converged on the identification of compounds with the same mechanism of action, they used distinct strategies as a starting point. Słabicki *et al.* and Mayor-Ruiz *et al.* leveraged target- and E3-agnostic approaches.[153,154] Lv *et al.* performed a target-driven approach looking for NRF2 inhibitors, which then led to the identification of an MG degrader against a different target (CycK).[134]

Słabicki *et al.* conducted a data-mining exercise in which the transcriptional expression of several E3 ligase components in cancer cell lines was correlated to pre-existing data of drug sensitivity.[153] First, they showed that DCAF15 expression correlated with aryl sulfonamide toxicity. In addition, the cytotoxicity of (*R*)-CR8, a known pan-CDK inhibitor, correlated with the expression of the CRL adaptor DDB1. Słabicki *et al.* then proved that (*R*)-CR8 induces selective degradation of CycK in a DDB1-dependent manner.

Mayor-Ruiz *et al.* developed a phenotypic cell-based strategy[154] based on hyponeddylated models previously engineered by the same group.[141] CRLs are activated by reversible NEDD8 conjugation in the cullin component. Neddylation activates CRL-dependent ubiquitination through NEDD8 nucleation of ubiquitin ligation assembly[155] and also stabilizes CRLs by blocking CAND1 from exchanging substrate receptors.[156] UBE2M is an essential E2 enzyme in the neddylation cascade whose impaired function confers degrader resistance through the inactivation of a substantial number of CRL complexes.[141] Taking advantage of UBE2M mutant cancer cells, Mayor-Ruiz *et al.* established a scalable drug screening strategy based on differential viability of WT *vs.* UBE2M^{mut} cell models. First, a novel sulfonamide scaffold (dCeMM1) was found to hijack CRL4^{DCAF15} to selectively degrade RBM39, thus validating the chemical profiling strategy. In addition, three small-molecule drugs (dCeMM2/3/4) were identified as dependent on functional CRLs to exert their toxicity. Through an extensive and orthogonal effort aimed at dual target–E3 identification, these chemical entities were proved to be CycK MG degraders.[154] Of note, the Nomura lab very recently used a similar strategy (WT *vs.* siUBE2M transfection in HAP1 cells) to screen a library of 750 covalent fragments. The fragment EN450 was reported to have a differential effect in WT *vs.* siUBE2M cells and proposed to act as a MG that binds covalently to the E2 UBE2D to induce degradation of NFKB1.[157]

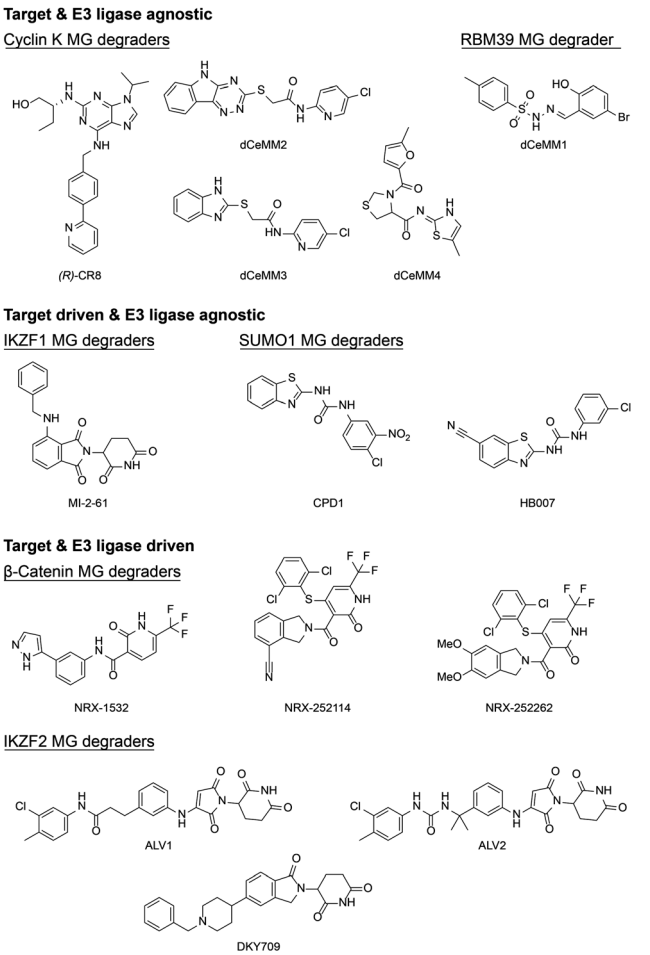

Fig. 8 Chemical structures of molecular glue degraders intentionally discovered/developed.

Finally, Lv *et al.* used a luciferase-based screen to identify NRF2 inhibitors. This exercise led to the identification of HQ461 (Fig. 7).[134] Through a target deconvolution campaign that included gain-of-function screenings based on hypermutation, the authors demonstrated that HQ461 was yet another CycK MG degrader. The chemical basis for optimizing HQ461 was dissected through a structure–activity relationship study, which found a 3-fold more potent analog: HQ0015 (DC_{50}: 41 nM).[134]

Deciphering the mechanisms of action of (*R*)-CR8, dCeMM2/3/4 and HQ461 was enabled by comprehensive multi-omics campaigns. Importantly, all the studies converged on a unifying and unprecedented mechanism of action: drug binding to the active site of the usual CycK partner CDK12 (and, presumably, the paralog CDK13) strengthened the dimerization between CDK12–CycK and the CRL adaptor DDB1, in the absence of a dedicated substrate receptor. CDK12/13 thus act in a substrate receptor-like manner, positioning CycK in a zone of the partial CRL4 complex that is accessible for the E2-mediated ubiquitin transfer. Extensive profiling, including a 3.5 Å structure solved by Słabicki *et al.*, confirmed the DDB1:CR8:DK12–CycK complex and revealed a substantial protein–protein interface (~2100 Å).[153] DDB1 and CDK12–CycK have a basal affinity of ~50 μM, which is strengthened ~1000 fold in the presence of the MG degraders. Interestingly, no biological role has been attributed so far to this low-affinity DDB1–kinase interaction, which is also expected within cells. Although CycK is the primary destabilized target, these compounds also have an effect on CDK12 levels. In cells, CDK12 binds to CycK to form a functional active complex. Lv *et al.* showed that CRISPR inactivation of CycK also reduces CDK12 levels.[134] Therefore, the observed concomitant destabilization of CDK12 is likely due to the MG-induced CycK degradation and not to CRL "auto-degradation" after long compound exposure as observed for canonical substrate receptors like CRBN.[44,158]

In 2021, Dieter *et al.* reported the serendipitous discovery of another chemically distinct CycK glue degrader: NCT02 (Fig. 7). The authors conducted a drug screen with a library of 80 000 non-characterized small molecules looking for compounds with a cytotoxic effect in patient-derived colorectal cancer spheroids.[135] Characterization of the top hit, NCT02, revealed that it induces the degradation of CycK and CDK12. Interestingly, the ATP-competitive CDK12/13 inhibitor SR-4835 was also shown to act as a CycK degrader. SR-4835 was further tested *in vivo* showing a potent anti-tumor activity. Degradation of CycK and CDK12 was identified as a potential vulnerability in a specific subgroup of colorectal cancer patients, namely the CMS4 subtype (TP53-deficient or mutant tumors with a mesenchymal phenotype).

A recent patent from Bayer disclosed pyrazolotriazines series that also induce CDK12 and/or CycK degradation (WO2021116178).

All these findings illustrated a novel mechanism by which an MG degrader induces target degradation through the orchestration of a distant PPI rather than by directly reprogramming the target–E3 interface. Whereas none of the targets of auxin, IMiDs or sulfonamides are ligandable in the absence of the E3 ligase, the CycK degraders have affinity for the CDK12–CycK target complex in isolation (specifically, for the kinase). On the other hand, these compounds recruit an E3 component (DDB1), which was considered unligandable, as aryl sulfonamides showed with DCAF15. Of note, the CycK MGs proved that it is indeed possible to rewire a CRL adaptor instead of the substrate receptor and still achieve target degradation. Pinch *et al.* provided further evidence of this notion by showing that PROTAC-based hijacking of SKP1, the adaptor for CRL1 (SCF) complexes, also leads to TPD.[159] The authors applied "COFFEE" (maleimide–thiol chemistry for covalent functionalization followed by E3 electroporation) to bypass the need for specific E3 binders.[159]

Why such a remarkable diversity of chemical entities can converge in the induced degradation of CycK remains to be fully elucidated. The basal low-affinity detected between DDB1 and CDK12–CycK suggests that any molecule that fits into that interface cavity may enhance their binding. If a certain affinity threshold for the ternary complex is achieved and with proper geometry, it will translate to CycK degradation. Whether other CDKs or additional targets outside this superfamily can be redirected to DDB1 *via* a similar MG mechanism remains to be seen.

4.2 Target-agnostic and E3-driven strategies

VHL and CRBN are the most exploited E3s in the TPD field. CRBN has been successfully hijacked by many PROTACs and also by MG degraders (IMiDs). Many VHL-dependent PROTACs have also been reported. However, MG degraders rewiring VHL were still lacking until recently. Novartis (NIBR) has disclosed in some scientific settings a prototypical example of an E3-driven target-agnostic strategy based on protein microarrays (unpublished).‡ This strategy was used to screen for compound-induced interactions between VHL and thousands of proteins. Several small molecules (*e.g.*, "compound 4") were found to bind VHL to CDO1, a critical regulator of cysteine metabolism, prompting polyubiquitination and subsequent proteasomal degradation of CDO1 (Fig. 7). X-ray structures of the ternary complex confirmed the MG mode of action.[160] Although the scalability of protein microarrays may seem limited, this example provides yet another validated avenue towards intended discoveries of MG degraders. Examples of E3-driven target-agnostic approaches for MG degrader discovery are scarce. The development of additional cell-based assays and strategies is expected to help unlock tissue-specific E3-dependent vulnerabilities.

4.3 Target-driven and ligase-agnostic strategies

4.3.1 Discovery of IKZF1 molecular glue degraders *via* "up assays". Using the degradation of a protein of interest as a

‡ J. E. Bradner (NIBR) presented in part at (at least) the "Hanson Wade TPD conference", Oct 2020 and the "Dana-Farber Targeted Degradation Webinar Series", Feb 2021. G. Michaud (NIBR) presented in part at (at least) the Translational Chemical Biology conference, Oct 2020 (advertised in **https://www.nature.com/articles/d42473-020-00441-0**).

readout in cellular screening assays seems like a straightforward path to find MG degraders from a drug library. However, this kind of ''signal-down'' strategy can be confounding and it is usually noisier than positive selection methods. Koduri *et al.* published a target-driven E3-agnostic positive selection assay (''up assay'') to identify monovalent degraders of IKZF1.[161] In brief, the authors engineered a reporter system that converts protein loss into a positive selection output (resistance). To this end, they fused a modified version of the enzyme deoxycytidine kinase (DCK) to IKZF1. DCK converts the non-natural nucleoside BVdU into a toxic compound. Hence, degradation of the fusion protein prevents the DCK-mediated toxin conversion of BVdU. Chemical screens coupled to co-treatment with BVdU allowed them to identify novel IMiD-like MG degraders of IKZF1 *via* the concomitant resistance (*e.g.*, MI-2-61) (Fig. 7 and 8). Koduri *et al.* interrogated around 100 newly synthesized analogs of pomalidomide, including the classical IKZF1 degraders and a small library of uncharacterized IMiDs reported in the literature. Although IMiD derivatives were used for the screening, we have classified this strategy as E3-agnostic, given the foreseen potential beyond CRBN and IMiD scaffolds. Indeed, using a small library of compounds enriched in (non-IMiD-like) metabolic inhibitors, the authors found that the compound Spautin-1 induces IKZF1 destabilization in a CRBN-independent manner. The exact mechanism of action of this IKZF1 monovalent degrader remains to be elucidated.

Overall, this study provided proof of principle of how phenotypic ''up assays'' based on degradation of the protein of interest can be used to identify glue degraders.

4.3.2 SUMO1 degraders identified *via* denatured western blot screening. Bellail *et al.* set out to identify monovalent degraders to selectively target SUMO1 conjugation in cancer. Directly relying on SUMO1 levels, they used denatured western blotting[162] as a strategy to distinguish between SUMO1 and SUMO2/3 conjugation. The authors screened the NCI drug-like library of 1596 compounds in search of SUMO1 degraders and identified the small-molecule hit CPD1, which was then optimized to the lead compound HB007 (Fig. 7 and 8).[163] Bellail *et al.* found FBXO42 (a CRL1 substrate receptor) and CAPRIN1 as drug interactors, using genome-scale CRISPR screens and HB007-based pull-down proteomics. Degradation selectivity of CPD1 and HB007 was not assessed through quantitative expression proteomics. Given that SUMO1 conjugation regulates the ubiquitination and degradation of many substrate proteins, the authors argued that it is indeed difficult to disentangle the primary (SUMO1 degradation) and secondary events. Although structural and biophysical confirmation of an MG-like mode of action is pending, the mechanism proposed is as follows: HB007 induces the interaction of CAPRIN1 with FBXO42, then recruiting SUMO1 (or SUMO1-conjugated proteins) to the CAPRIN1–CUL1–FBXO42 ligase complex, where SUMO1 is ubiquitinated. This is an example of a putative MG degrader identified using protein destabilization directly as a readout, in this case in a ''signal-down'' setup.

The best-suited screening approaches and readouts depend on the specific protein of interest. The assay applied in this study seems highly labor-intensive (western blotting), but proved to be valid to distinguish between SUMO1 and SUMO2/3 conjugation. Other assay methodologies to detect target levels have been very useful for the TPD field when aiming for high-throughput and accurate measurements (*e.g.*, ELISA or the HiBit–LgBit split nanoluciferase system).[164] Recently, Payne *et al.* applied time-resolved fluorescence resonance energy (TR-FRET) to profile PROTAC-induced degradation of BRD4.[165] By combining a fluorescent JQ1-based tracer with a primary BRD4 antibody and a labeled nano-secondary antibody, the authors were able to monitor BRD4 levels. The assay was miniaturized to a 96-well plate format, enabling the scalable profiling of molecules in unmodified biological systems.

4.4 Target- and ligase-driven strategies

4.4.1 β-Catenin molecular glue degraders. MG degraders that restore an E3–substrate pairing lost in disease are a particularly appealing therapeutic option. In 2019, Simonetta *et al.* identified and further optimized small molecules that enhanced the lost interaction between $CRL1^{\beta\text{-}TrCP}$ and mutant β-catenin.[166] A β-catenin phosphodegron that includes Ser33 and Ser37 is recognized by $CRL1^{\beta\text{-}TrCP}$. When mutated in cancer, this leads to β-catenin stabilization and, thereby, facilitates oncogenic transcriptional programs. The team focused on Ser37 as a hot-spot mutation. Building on a pSer33/Ser37 phosphodegron peptide with weak binding to the E3, Simonetta *et al.* established a robust high-throughput biochemical screen based on fluorescence polarization and surveyed a collection of 350 000 small compounds. This campaign identified several compounds, like NRX-1532, able to enhance the binding and $CRL1^{\beta\text{-}TrCP}$-dependent ubiquitination of mutant β-catenin (Fig. 7 and 8).[166] In an impressive optimization process that strategically prioritized molecular modifications at the β-catenin:β-TrCP interface, the potency of the original hit NRX-1532 was improved up to 10 000-fold in the derivatives NRX-252114 and NRX-252262. Unlike other glue degraders, these compounds do not exhibit any affinity for the E3 alone and the induced dimerization is mostly based on the high cooperativity of the ternary complex.

The described screening approach proved that it is possible to deliver MG degraders that restore the lost binding of an E3 ligase to its native protein substrates. This study is a blueprint for similar future endeavors towards intentional target- and E3-driven developments of MG degraders.

4.4.2 Development of Helios (IKZF2) molecular glue degraders. In 2021, Wang *et al.* reported the structure-guided development of CRBN-dependent MG degraders of Helios (IKZF2), a transcription factor involved in immunosuppression.[167]

Regulatory T cells (Tregs) are a specialized subpopulation that maintains normal homeostasis and self-tolerance to immune responses, but also represses the antitumor immune response. Helios is critical for maintaining the identity and suppressive activity of Tregs, and mouse models with Helios-deficient Treg cells have shown enhanced antitumor immunity.[168] Therefore, the team set out to repurpose CRBN to target Helios for degradation.

Ikaros (IKZF1) and Aiolos (IKZF3) are the only transcription factors within the Ikaros family degraded by canonical IMiDs. The presence of a glutamine residue in their second zing-finger domain enables IMiD-induced degradation,[47] while the histidine residues in Helios (IKZF2) do not. The authors reasoned that a more flexible CRBN-binding core could accommodate a key Helios histidine residue, based on the realization that the IMiD CC-885 can indeed induce a weak dimerization between CRBN and a mutant version of IKZF1 in which Gln146 is a histidine.[169] First, Wang *et al.* synthesized the IMiD derivative ALV-02-146-03 and checked that it could engage CRBN. They then used a CRBN:Helios dimerization assay based on TR-FRET, and screened a small focused library of analogs. Several rounds of optimization led to ALV1 and ALV2 (Fig. 7 and 8). The former induces CRBN-dependent degradation of Helios and also retains Ikaros destabilization, while the latter has relative selectivity for Helios. Of note, Eos (IKZF4) also encodes a histidine residue at the same position as Helios, hence ALV1 and ALV2 also induce Eos destabilization.[167] Helios degradation weakened the anergic phenotype (T cell unresponsiveness) and reduced the suppressive activity of Treg cells. The Helios glue degrader DKY709 (Fig. 8) from Novartis is in Phase I for solid cancers (currently tested as monotherapy and in combination with spartalizumab, an anti-PD-1).[16,31]

Although intentional, the discussed strategy built on the abundant structural information available for other members of the Ikaros family in complex with canonical IMiDs and CRBN. Nevertheless, similar structure-guided efforts may yield MG degraders for other previously unligandable targets by reprogramming E3 ligase substrate specificity.

4.4.3 DNA-encoded libraries deliver VHL-dependent glue degraders of BRD4. VHL-focused approaches to discover MG degraders, both in a target-agnostic (see Section 4.2) and in a target-driven fashion, have been covered at several scientific events.§ Although not yet published, we provide a succinct description.

Conceptualized by Brenner and Lerner,[170] DNA encoded libraries (DELs) are increasingly being adopted in drug discovery. This technology involves the generation of large mixtures of compounds through synthetic chemistry cycles that introduce diverse building blocks encoded by unique DNA tags. Several cycles of affinity selection, typically involving an immobilized target protein, yield binders to the protein of interest from such mixtures. These binders are identifiable by sequencing the DNA tags uniquely associated with each compound. DELs have allowed the screening of drug collections with an unprecedented chemical diversity.[171]

Stuart Schreiber's lab and colleagues have established DOSEDO (diversity-oriented synthesis encoded by DNA oligonucleotides) for the scalable synthesis of DNA-barcoded compounds. The resulting DELs have been applied to MG discovery for preselected targets by screening for cooperative binding. Differential interrogation of the DELs for a target protein in the absence and presence of "presenter" proteins brought about the discovery of presenter-dependent binders that can be decoded by DNA sequencing (Fig. 7). Using BRD4 as a preselected target and VHL as a presenter, the MG degrader FYI979 was found (unpublished).

The progress achieved with DELs during the last two decades has transformed this technology into a powerful tool to identify binders.[171] The use of DELs in setups similar to the example discussed showcases exciting new possibilities to facilitate the intentional discovery of MG degraders in a target- and/or E3-driven fashion.

4.4.4 Computational modeling and virtual screening: closer to assisting the rational development of MG degraders? Computer-aided drug design has helped expedite the development of small-molecule inhibitors.[172,173] Likewise, computational modeling is expected to assist the drug discovery process in the TPD field.

Most TPD-related computational efforts to date have focused on rationalizing PROTAC-induced ternary complex formation. In 2018, Nowak *et al.* applied *in silico* protein–protein docking frameworks to identify low-energy binding modes that guided the design of BRD4 selective PROTACs.[42] Soon after, Drummond and Williams proposed four methods that combined linker conformational searches with protein–protein docking, leading to virtual models of ternary complexes that resembled known crystal structures.[174,175] Similarly, Zaidman *et al.* developed the method PRosettaC and performed retrospective PROTAC studies that delivered near-native ternary complexes.[176] The aforementioned pipelines were subsequently improved by Weng *et al.* by combining FRODOCK's protein docking with rounds of filtering, re-scoring, and final RosettaDock's refinements.[177] In addition, Bai *et al.* were able to correlate target degradation with the frequency of ternary complex formation of a small set of PROTACs with different linker lengths.[178] The latest studies have incorporated molecular dynamics as a more thorough computational approach to assess PROTAC-related thermodynamics.[179–181] Moreover, some recent studies have shown that only the ternary complex models with optimal target-lysine accessibility for the E2 could predict target degradation outcomes.[181–183] All these examples evidenced that computational modeling has the potential to help guide and predict drug-induced ternary complex formation.

The rapidly growing literature of computational methods, albeit mainly PROTAC-oriented, sets the grounds for modeling proximity-inducing pharmacology, including MG degraders. Nonetheless, important differences should be noted when computationally rationalizing MGs *vs.* PROTACs. While the PROTAC's warhead–linker–warhead nature contributes important hints of protein–protein binding modes, MG modeling can be a blank canvas to start with. Prioritization of the best E3–target pair(s) is paramount for prospective target-driven MG designs. *In silico* protein–protein docking provides an attractive surrogate to *in vitro* experiments and could, in theory, assist E3–target pair prioritization by predicting geometrically compatible PPIs. However, accurate predictions require computationally expensive methods (*e.g.*, metadynamics-based

§ S. L. Schreiber presented in part at (at least) the conference "Induced Proximity-Based Drug Discovery Summit", June 2021.

dissociation free energy),[184] thereby dramatically limiting the number of screenable pairs. Insights into which E3–target regions are prone to contribute stable PPIs will be particularly valuable for prioritizing complexes derived from protein–protein dockings. In principle, these models could highlight cavities at protein–protein interfaces; virtual drug screening combined with refinement techniques could help find molecules able to fit into those cavities and enhance the target–E3 affinity.

Computer-aided drug design can be a powerful tool in searching for promising candidates, especially when used in tandem with chemical biology, structural biology, and phenotypic screening procedures. Hence, further investigation on MG principles, together with the increasing availability of ternary complex structures, will boost future retrospective *in silico* studies. More sophisticated techniques that address the shortcomings of existing computational approaches will be required for prospective endeavours. That said, the current trend of *in silico* protocols suggests that we are a step closer to computationally assisting the design of MG degraders and PROTACs.

5. Conclusions and outlook

The TPD field has made spectacular progress in recent years, and the generalizability of the approach is undeniable. We are witnessing exciting times on multiple fronts: some approved drugs are known to act as MG degraders, several PROTACs are in clinical trials, novel TPD approaches continue to appear, and a plethora of strategies and rules to rationally develop these pharmacological modalities is emerging. Beyond therapeutics, degraders have proved to be powerful research tools for precise and fast perturbation of the proteome at timescales that are unachievable for genetic strategies.

In this review, we have addressed how the discovery of MG degraders is evolving from fortuitous to intentional developments. The examples provided have brought with them important lessons about compound-induced proximity as efficient therapeutics. Furthermore, the MG degraders discussed evidence that these chemical entities are more frequent than we foresaw. Exhaustive mechanistic characterizations have revealed unprecedented modes of action to elicit productive TPD, such as rewiring a partial CRL complex[134,153,154] or inducing protein polymerization.[133]

The theoretical E3–target pairings induced/facilitated by MG degraders seem almost unlimited if we account for $>20\,000$ proteins and about 600 human E3s, (even more, if we consider all the components of multi-subunit E3s). However, recent studies have scaled-down these numbers to more realistic prospects: exhaustive thermodynamic characterization of prototypical MGs outlined that a minimum level of intrinsic affinity between E3 and target may be required.[77] Therefore, intentional developments of MG degraders should probably prioritize E3–target pairs with detectable affinity. The exact threshold of natural weak PPIs needed for a given molecule to act as an MG remains to be determined.

We envisage that phenotypic screens will continue to be pivotal for the discovery of glue degraders, building on more sophisticated preclinical models, informative counter screens, and target deconvolution methodologies. The use of cellular systems helps prioritize hit matter with drug-like properties and enables the interrogation of full-length proteins in their native environment. We believe that target-agnostic discovery of MG degraders will help unlock disease-relevant vulnerabilities, including undruggable targets. A deeper understanding of drug-induced interfaces and cooperative binding should also further the development of MG degraders. Structural hypotheses and models to determine drug-assisted target–E3 gluing are becoming more and more accurate. Accordingly, structure-based drug discovery, together with *in silico* modeling and virtual screening are expected to greatly facilitate MG designs. Furthermore, technological progress in high-throughput proteomics will further help accelerate drug discovery in this area. To conclude, the advances in the TPD field have fueled interest in other proximity-inducing concepts whose evolution will be interesting to follow in the coming years.[185–189] As our understanding of the molecular features that govern drug-induced productive PPIs grows and the use of this pharmacology in disease matures, new breakthroughs are sure to follow.

Conflicts of interest

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