CellPress

Cell Chemical Biology

Review

The rise of degrader drugs

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https://doi.org/10.1016/j.chembiol.2023.06.020

SUMMARY

The cancer genomics revolution has served up a plethora of promising and challenging targets for the drug discovery community. The field of targeted protein degradation (TPD) uses small molecules to reprogram the protein homeostasis system to destroy desired target proteins. In the last decade, remarkable progress has enabled the rational development of degraders for a large number of target proteins, with over 20 molecules targeting more than 12 proteins entering clinical development. While TPD has been fully credentialed by the prior development of immunomodulatory drug (IMiD) class for the treatment of multiple myeloma, the field is poised for a "Gleevec moment" in which robust clinical efficacy of a rationally developed novel degrader against a preselected target is firmly established. Here, we endeavor to provide a high-level evaluation of exciting developments in the field and comment on steps that may realize the full potential of this new therapeutic modality.

INTRODUCTION

Birth of the TPD field

Manipulating proteins in an *in vivo* setting with chemistry is the pillar for chemical biology as well as drug discovery.[1,2] Back in 2005, Stuart Schreiber elucidated his foresights in chemical biology, highlighting four grand goals to be reached, one of which was "identifying small-molecule modulators for each individual function of all human proteins."[3] Given that nature often regulates biochemical processes by creating proximity through scaffolding proteins or phase-separated condensates, small molecules capable of mimicking nature's proximity induction could cf. novel functions beyond canonical "inhibitors" or "activators" paradigm, thus offering a path to vastly expanding the number of targets accessible to chemical perturbation. The first well-documented example of this type of molecule, commonly referred to as "molecular glues"[4] or "chemical inducers of proximity (CIP),"[5] is the macrolide natural product FK506[6] (Figure 1A), a molecule that simultaneously binds proteins FK506-binding protein 12 (FKBP12) and calcineurin. Formation of this complex reduces the peptidyl-prolyl *cis*-trans isomerase activity of FKBP12 as well as the phosphatase activity of calcineurin. In the three decades since the groundbreaking work on FK506, many other proximity-inducing small molecules such as FK1012[7] (Figure 1A), a homodimer of FK506, have been uncovered that can rewire cellular circuitry.[4,5,8,9] Among them, a class of bivalent small molecules capable of recruiting ubiquitin ligase complexes to result in protein degradation was conceptualized[10,11] and reduced to practice.[12] The first successful example involved the use of a peptide moiety to bind, recruit, and redirect the activity of an E3 ubiquitin ligase complex called the Skp1-Cullin-F-box (SCF) containing complex toward the protein methionine aminopeptidase-2 (MetAP-2).[12] Due to its chimeric (bivalent) nature, the synthetic molecule engages both the F-box protein $SCF^{\beta\text{-}TRCP}$ and MetAp-2, leading to the ubiquitination of the latter and its subsequent proteasome-mediated degradation. This pioneering study solidified the principle of designing bivalent degraders, in which both the E3 ubiquitin ligase- and the target protein-binding ligands are small molecules and are therefore more favored in drug development. Thereafter, efforts to avoid the use of peptide ligands resulted in the creation of a large number of bivalent degraders based on von Hippel-Lindau (VHL) ligands, which recruit the $CRL2^{VHL}$ E3 ubiquitin ligase.[13–15]

Concurrent with these efforts, another long-standing mystery in modern pharmacology began to be unraveled. Studies on the mechanism of action (MOA) of the once infamous teratogenic drug thalidomide (Figure 1B) had revealed that this molecule binds to the E3 ubiquitin ligase $CRL4^{CRBN}$.[16] Subsequent studies of this immunomodulatory drug (IMiD) class demonstrated that the IMiDs do not act as inhibitors of cereblon (CRBN), but rather act by redirecting CRBN neomorphic degradation activity against neosubstrates such as Ikaros family zinc finger protein 1 (IKZF1), IKZF3, and the teratogenicity-causing spalt-like transcription factor 4 (SALL4).[17–21] These discoveries led to the independent development of another series of bivalent degraders, namely the use of IMiDs and IMiD derivatives to recruit CRBN for targeted degradation.[22,23] In principle, by harnessing the cell's own protein disposal system (not only the ubiquitin-proteasome system [UPS] but also the autophagy-lysosome system [ALS]), the degrader molecules draw a target protein into proximity with an otherwise unrelated disposal machinery protein to

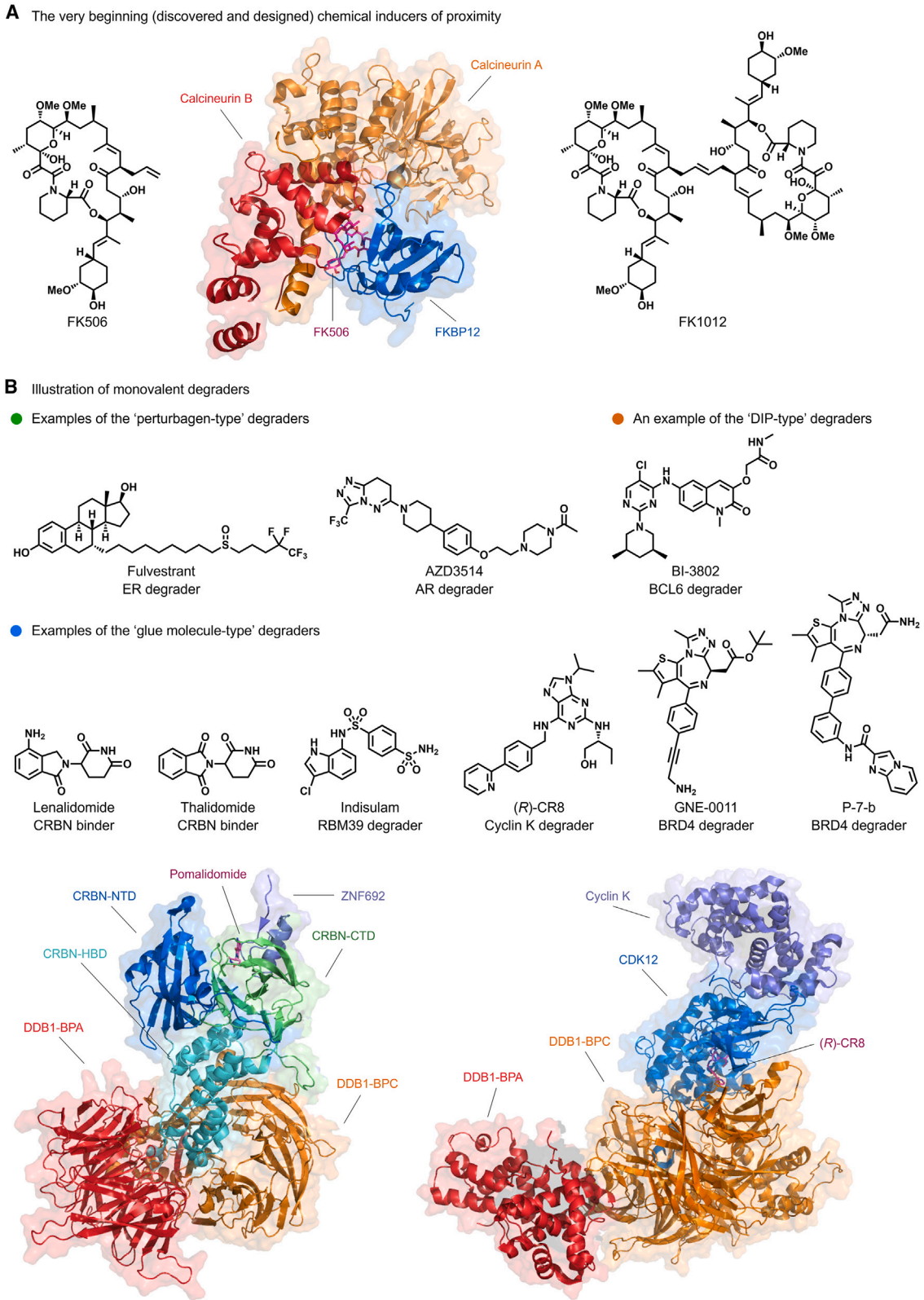

Figure 1. Schematic representation of proximity-inducing protein degraders

(A) Chemical structures of FK506 and FK1012 and a structural model of the Aspergillus fumigatus calcineurin A-calcineurin B-FKBP12-FK506 complex (PDB ID 6TZ7). (B) Illustration of monovalent degraders. The structural models of the human DDB1-CRBN-pomalidomide-ZNF692 complex (PDB ID 6H0G) and the human DDB1-(*R*)-CR8-CDK12-cyclin K complex (PDB ID 6TD3) are shown as cartoon representations.

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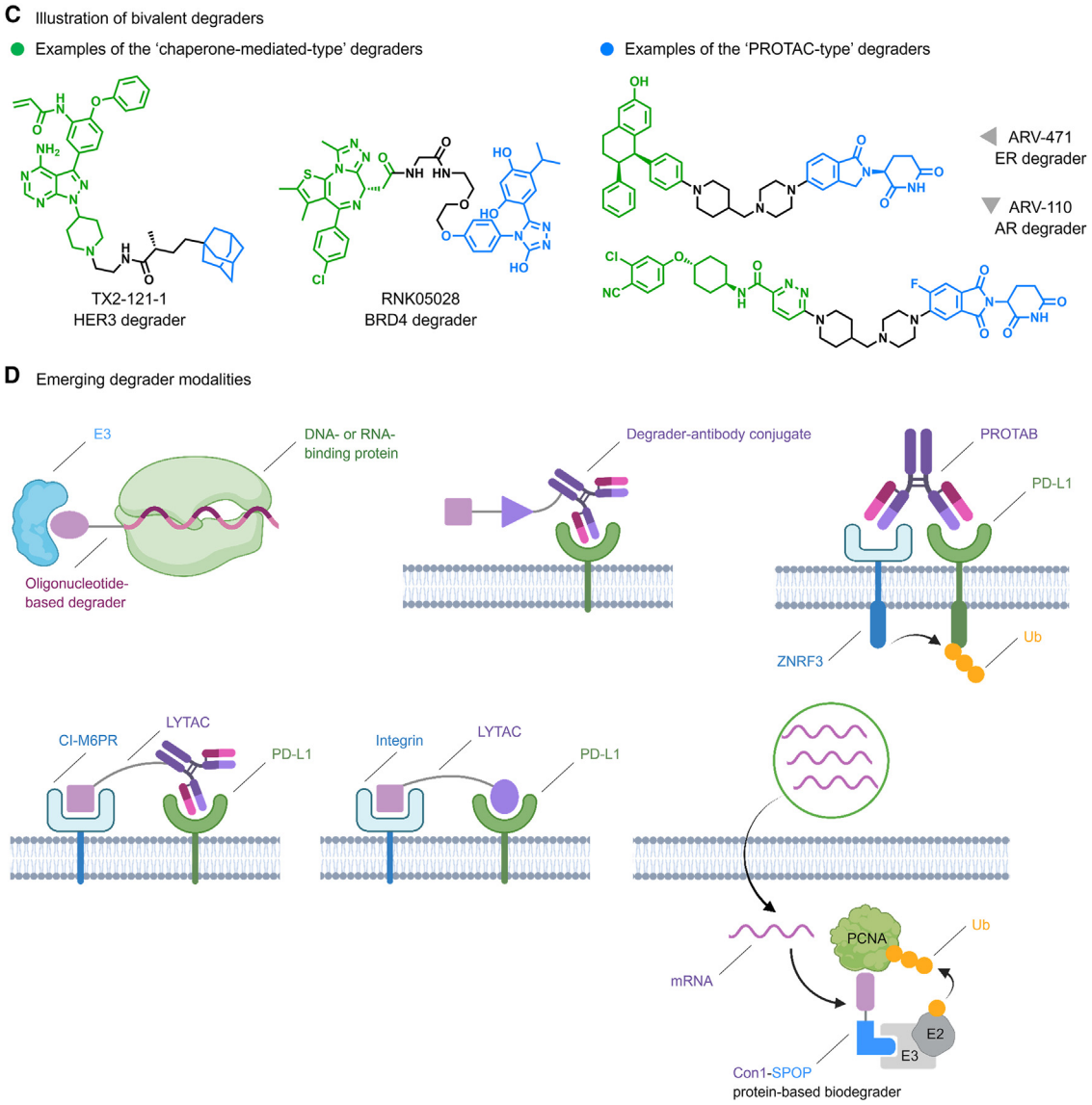

Figure 1. ***continued***
(C) Illustration of bivalent degraders.
(D) Schematic representation of selected emerging degrader modalities. Abbreviations are as follows: Con1, consensus motif 1; DIP, drug-induced polymerization; PROTAB, proteolysis targeting antibodies; SPOP, speckle-type POZ protein.

form a complex, thereby initiating the elimination process to clear any unwanted proteins. This MOA contrasts with conventional small molecules, which exert stoichiometric, "constant occupancy"-driven pharmacology. That is, the degrader molecules shift to sub-stoichiometric (iterative), "transient event"-driven degradation pharmacology, regardless of where the ligand binds on the target protein, while also relaxing the requirements for ligand binding affinity. In this regard, eliminating therapeutically relevant scaffolding role of a target protein, as well as overcoming drug resistance that impairs inhibitor binding or increases protein copies becomes feasible. The realization of efficient protein degradation by small molecules has thus generated tremendous excitement about the potential of targeted protein degradation (TPD) as a powerful chemical tool and as a promising drug modality. On this basis, the development of degradation tag fusion strategies such as the auxin-inducible degron (AID) system (combines the fusion of a target protein to AID degron with the use of the plant hormone auxin)[24–26] and the dTAG system (combines the fusion of a target protein to mutant $FKBP12^{F36V}$ with the use of a bivalent degrader)[27] enables more rapid loss-of-function studies compared to nucleic acid-based approaches, allowing for target-specific biological investigation with kinetic resolution as well as allowing for target validation in the context of drug discovery.[28,29] Collectively, the early insights that pharmacological effects can arise from target degradation and that small-molecule ligands of E3 ubiquitin ligases can be rationally used for targeted degradation set the stage for the subsequent surge of interest in TPD.

Monovalent and bivalent small-molecule degraders as the main TPD modalities

Small-molecule protein degraders commonly act in a monovalent or bivalent manner, which primarily differ in their chemical composition and MOAs. To recap briefly, monovalent degraders consist of only one binding ligand and have a low molecular weight, which makes them hard to be visually distinguished from conventional inhibitors, and therefore, can be optimized following most of the established drug development paradigms, provided that in the case of any steep structure-activity relationship (SAR) observed, these optimizations of structure-property relationship (SPR) should not alter the function of the small molecule as a degrader. Mechanistically, monovalent degraders, in most cases, could either act as perturbagens, driving a target protein to form a susceptible conformational state that can be disposed of, or act as glue molecules that preferentially bind to the target protein or the disposal machinery protein, modifying its surface and causing it to complementarily interact with the other one through induced protein-protein interactions (PPIs). The most representative of the "perturbagen-type" degraders is fulvestrant[30] (Figure 1B), a selective estrogen receptor degrader (SERD) drug for the treatment of hormone-receptor (HR) positive advanced breast cancer. Reminiscent of fulvestrant, the selective androgen receptor degrader (SARD) AZD3514[31] (Figure 1B) also falls into this category. For "glue molecule"-type degraders, the IMiDs and IMiD derivatives represent the most heavily investigated compound class.[32,33] Indisulam (Figure 1B) has also similarly been shown to direct another E3 ubiquitin ligase $CRL4^{DCAF15}$ to degrade the splicing factor RNA-binding motif protein 39 (RBM39).[34–38] In addition, the cyclin K degraders such as CR8[39–41] (Figure 1B) represent an alternative scenario in which they preferentially bind to the target protein cyclin-dependent kinase 12 (CDK12). Furthermore, as a rare instance, the degradation mechanism of the B cell lymphoma 6 (BCL6) degrader BI-3802 (Figure 1B) uniquely involves promoting the polymerization of BCL6, thereby facilitating its recognition and ubiquitination by the E3 ubiquitin ligase seven in absentia homolog 1 (SIAH1).[42,43] Nevertheless, despite the favorable prospects for drug development, the discovery of new monovalent degraders has been trailing behind the discovery of new bivalent degraders.[44] This is in large part due to the lack of rational discovery strategies, making the system heavily reliant on serendipitous characterizations. As such, the academic and industrial research communities are presently evolving new screening strategies and screening funnels to accelerate monovalent degrader hit identification and drug discovery. In lieu of a comprehensive list, the audience is encouraged to peruse previous elegant reviews for more details on monovalent degraders.[4,45–50]

The major advantage of bivalent degraders over monovalent degraders is that they are amenable to rational design. Compositionally, these molecules consist of two binding ligands connected by a linker moiety, where each ligand binds to a target protein and a disposal machinery protein, respectively, to achieve spatial proximity. Thus, applying the bivalent degrader approach is a straightforward and well-trodden path that requires only chemistry efforts to adjust the linker length, determination of a viable exit vector for the ligand of the target protein, and selection of an appropriate ligand of the disposal machinery protein as needed. In this regard, the number of bivalent degraders has grown exponentially,[51] and bivalent modalities such as the chaperone-mediated chimeras[52–55] (Figure 1C), proteolysis-targeting chimeras (PROTACs)[56–58] (Figure 1C), and lysosome-targeting chimeras (LYTACs)[59–61] (Figure 1D) continue to expand the landscape of degradable targets.[62] On the other hand, bivalent degraders possess larger molecular weights than typical small-molecule drugs, posing more challenges in medicinal chemistry to achieve requisite properties for oral delivery, central nervous system (CNS) exposure, formulation, and metabolite-related toxicity. Nevertheless, more than 10 PROTAC-based bivalent degraders have entered clinical trials,[44,63] with the most advanced estrogen receptor (ER) degrader, ARV-471 (Figure 1C), having progressed to phase III trials. Furthermore, the intensive interest in developing PROTAC drugs has yielded a wealth of insights on optimizing drug-like properties,[64–68] providing a clear framework for future development. In lieu of a comprehensive list, the audience is encouraged to peruse previous insightful reviews for more details on bivalent degraders, particularly a trajectory from concept to practice.[56,58,69–72]

Collectively, the TPD field has never been more electrified than it is today, with a large number of pharmaceutical and biotechnology companies entering the space to translate more therapeutic hypotheses into clinical investigations. In what follows, we present our observations and reflections on the translational opportunities in the TPD field, discuss the implications of current trends, and suggest steps that may realize the full potential of this new therapeutic modality. We recognize that it is not possible to cover all aspects in depth in a single article. Instead, we provide a general commentary along with crucial references as a roadmap to guide the audience in building a more comprehensive understanding of the TPD landscape.

TRANSLATIONAL OPPORTUNITIES IN TPD

Overview of pure plays and partnerships on the TPD track

Since the launch of Nurix and Arvinas, the first two TPD-focused companies, there has been significant investment in the TPD sector,[73] resulting in a large number of new companies and partnerships. Here, we provide a general summary of selected TPD-focused companies to illustrate the rapid growth and diversity of platforms and approaches. As shown in Table 1, while there is consensus that the promise of TPD is to drug previously undruggable targets, several companies have opted to mitigate biological risk by focusing on clinically credentialed targets (e.g., androgen receptor [AR], ER, Bruton's tyrosine kinase [BTK], epidermal growth factor receptor [EGFR], Kirsten rat sarcoma viral oncogene homolog [KRAS], and v-Raf murine sarcoma viral oncogene homolog B1 [BRAF]) in the hope of either addressing clinical resistance to inhibitor drugs or achieving better efficacy than the corresponding inhibitor drugs. For example, Arvinas's lead AR degrader ARV-110 (Figure 1C) and lead ER degrader ARV-471 were the first two PROTAC molecules to enter phase II trials, and the field eagerly awaits the results of these. In contrast, several other companies have opted to explore new degradable targets. For example, Fimecs is exploiting the diversity-oriented synthesis (DOS) approach aimed at degrading

Table 1. Selected TPD contributors and their pipelines

Pure Play	Partnership[a]	Pipeline	Indication
ARVINAS	P2, P4, P15, B1	AR, ER, MYC, BCL6, HPK1, $KRAS^{G12D/V}$	Oncology
nurix	P10, P13	BTK, CBL-B, IRAK4, ligands of novel E3 ligases (DEL-based)	Oncology, inflammation
vividion THERAPEUTICS	P1, P15, P18	Covalent ligands of novel E3 ligases (chemoproteomics-based)	Oncology
KYMERA	P10, P16, P17	STAT3, MDM2, IRAK4	Oncology, inflammation
FOGHORN THERAPEUTICS	B5	BRD9, SMARCA2, ARID1B	Oncology
C4 Therapeutics	P1, B4	BRD9, BRAF, EGFR, IKZF1/3	Oncology
AMPHISTA THERAPEUTICS	P5, P9	Bivalent degraders (Eclipsys-based)	Oncology
FRONTIER MEDICINES	P7	Covalent ligands of novel E3 ligases (chemoproteomics, AI-based)	Oncology
CelerisTx	P5, P19	Bivalent degraders (AI-based)	Oncology, neurodegeneration
VANTAI	P3, P19, B2	Ligands of novel E3 ligases (AI-based)	Oncology
FIMECS	P8, P20	IRAK3, TRIB1, ILK (DOS-based)	Oncology
cullgen		NTRK, ligands of novel E3 ligases	Oncology
Prelude THERAPEUTICS		SMARCA2	Oncology
RANOK Therapeutics	P2	CHAMPs - BRD4	Oncology
LYCIA	P14	LYTACs	Immunology, pain
ROIVANT SCIENCES		Acquisition of Oncopia and Silicon, powered by VantAI	Oncology
proteovant THERAPEUTICS	B2	AR, STAT3, SMARCA2/4, P300 $KRAS^{G12D}$, IKZF2	Oncology
Captor Therapeutics®		MCL-1, GSPT1	Oncology
A-ALPHA BIO	P9	Monovalent degraders (AlphaSeq-based)	Oncology
TRIANA Biomedicines	P2	Monovalent degraders (AI, DEL-based)	Oncology
Plexium	P11	Monovalent degraders - CDK2, BRD4, IKZF2, SMARCA2	Oncology
DUNAD therapeutics	P6	Monovalent covalent degraders	Oncology
SEED THERAPEUTICS	P14	Monovalent degraders - $KRAS^{G12D}$	Oncology
	P5, P19	Monovalent degraders	Oncology
DeuteR	B3	Monovalent degraders	Oncology
evotec	P9	Monovalent degraders (PanOmics, PanHunter, AI-based)	Oncology, neurodegeneration
ORIONIS™ BIOSCIENCES	P6	Monovalent degraders (Allo-Glue-based)	Oncology
Monte Rosa Therapeutics		Monovalent degraders - GSPT1, NEK7, CDK2, VAV1, BCL11A	Oncology, immunology, anemia
NEOMORPH		Monovalent degraders	Oncology
biotheryx		GSPT1+IKZF1/3, SOS1, CDK2/4/6, PDE4	Oncology, inflammation
ORIGAMI Therapeutics		HTT	Neurodegeneration
PAQ Therapeutics		ATTEC	Oncology, neurodegeneration
ORUM THERAPEUTICS		GSPT1, PROTAB	Oncology
Ubix Therapeutics		BTK	Oncology
DIALECTIC THERAPEUTICS		$BCL\text{-}X_L$, BCL-2	Oncology
Other contributors			
stablix, DEGRON, NEOsphere, epd, AUTOTAC, Cedilla, VICINITAS THERAPEUTICS, POLYPROX THERAPEUTICS, Differentiated Therapeutics, CUTRUN TX, casma, Amgen, Coho Therapeutics, Accutar Biotech, Orthbio, HINOVA, TREELINE, AVILAR THERAPEUTICS, PHOREMOST, Progenra, TRILO THERAPEUTICS			

AI, artificial intelligence; ATTEC, autophagosome-tethering compound; CHAMP, chaperone-mediated protein degrader; DEL, DNA-encoded chemical library; DOS, diversity-oriented synthesis.

[a] Partnered programs are generally undisclosed.

pseudokinases such as interleukin-1 receptor-associated kinase 3 (IRAK3), tribbles homolog 1 (TRIB1), and integrin-linked protein kinase (ILK). Pseudokinases possess inactivating mutations in critical catalytic motifs and therefore signal primarily through noncatalytic mechanisms, which drive certain diseases in human pathophysiology.[74] As links between well-characterized biology and untamed diseases are validated, targeting pseudokinases for degradation is believed to hold great opportunities. Several other noteworthy features are also demonstrated in Table 1. First, oncology remains the most sought-after therapeutic indication, while other therapeutic areas such as neurodegeneration, inflammation, immunology, pain, anti-infectives, and anemia are only beginning to be explored, which is motivated by unmet medical needs, successful precedents of approved IMiDs, and profit potential. It is worth mentioning that, in non-oncology indications, Kymera's lead IRAK4 degrader KT-474 has exhibited systemic anti-inflammatory effects in patients with inflammatory and autoimmune diseases, such as atopic dermatitis (AD) and hidradenitis suppurativa (HS). Second, chasing glue molecule-type degraders is of burgeoning interest. Most of these type of degraders have been developed by chemical analoging from chemotypes like IMiDs as well as building out chemical diversity that binds to the thalidomide-binding domain on CRBN. For example, large chemical libraries of CRBN ligands are being created and screened using a combination of unbiased chemoproteomics screening, target-based screening, degron identification, and molecular docking. Consequently, CRBN has been chemically reprogrammed to cf. neomorphic degradation activity against neosubstrates such as IKZF2,[75] G1 to S phase transition 1 (GSPT1),[76] widely interspaced zinc finger (WIZ),[77] CDK2,[78] never in mitosis gene a (NIMA) related kinase 7 (NEK7), BCL11A, and VAV1 (see Monte Rosa's pipeline in Table 1). With recent structural insights into IMID-triggered allosteric rearrangement of CRBN from an ''open'' conformation to a ''closed'' conformation, a deeper structural understanding is emerging, providing chemists with ideas on how to make more efficient CRBN-based degraders.[79–81] Not only that, but more research is underway in the hope of drawing a roadmap for the discovery of a new glue molecule-type of degraders. In addition to the aforementioned BCL6 degraders, RBM39 degraders, and cyclin K degraders, Genentech and Plexium are exploring new approaches to target BRD4 (see GNE-0011, [82–84] and P-7-b[85] in Figure 1B) and CDK2. Third, expanding the landscape of E3 ubiquitin ligases[58,86–89] that can be harnessed for TPD is gaining attention, as new E3 ubiquitin ligases offer the potential not only to achieve tissue-level selectivity to mitigate safety risks for certain targets but also to overcome resistance to VHL and CRBN-based degraders.[90–95] Toward this goal, several recent studies have highlighted the potential of DNA-encoded chemical library (DEL) screening[96] and chemoproteomic-enabled covalent ligand discovery[97–101] to reveal new ligandable E3 ubiquitin ligases such as glucose-induced degradation protein 4 homolog (GID4),[102] DDB1- and CUL4-associated factors (DCAFs),[103–106] ring finger proteins (RNFs),[107,108] and protein fem-1 homolog B (FEM1B).[109] Lastly, the artificial intelligence (AI)-enabled drug discovery wave[110] is pouring into the TPD field, with the ambitions to become game-changers. Companies such as Celeris, VantAI, Roivant, Triana, and Evotec are working to impact and accelerate ways to optimize bivalent degraders,[111] identify novel E3 ubiquitin ligase ligands, and discover monovalent degraders. Most importantly, however, it remains to be seen whether these AI-focused startups will be able to translate preclinical programs into clinical success. Collectively, the disease target portfolio in the pipeline of the TPD companies reflects the trends in degrader drug discovery and development.

Uncovering the opportunities hidden beneath the iceberg

Given that the potential of TPD has been widely noted, its applications are rapidly diversifying in combination with other fields, including synthetic biology, protein engineering, and nucleic acid regulation. For example, the TPD strategy is being used to achieve chemical control of potentially fatal overactive immune response-associated toxicities in chimeric antigen receptor (CAR) T cell therapy by creating an IMiD-gated, OFF-switch degradable CAR fused with a zinc-finger degron tag.[112,113] Besides, degrader-antibody conjugates (Figure 1D) derived from antibody-drug conjugates (ADCs) are being created to enable ''biological missile''-guided, tumor- or tissue-specific degradation.[114–119] Likewise, bispecific antibody degraders were shown to repurpose the membrane-bound E3 ubiquitin ligases RNF43 and ZNRF3 to drive efficient degradation of transmembrane proteins such as programmed cell death ligand 1 (PD-L1), EGFR, and insulin-like growth factor 1 receptor (IGF1R) (Figure 1D).[120–122] Similar to the membrane-bound E3 ubiquitin ligases, cell-surface lysosome-targeting receptors (e.g., the cation-independent mannose-6-phosphate receptor [CI-M6PR], the asialoglycoprotein receptor [ASGPR], and the integrins) have also been shown to be co-opted to shuttle disease-relevant transmembrane proteins (e.g., apolipoprotein E4 [ApoE4], EGFR, cluster of differentiation 71 [CD71], and PD-L1) into lysosome for degradation (Figure 1D).[59–61,123] Moreover, protein-based biological degraders (biodegraders) (Figure 1D), which center on the intracellular expression of a chimeric protein consisting of a high-affinity target-binding domain fused to an engineered E3 ubiquitin ligase adapter, have been shown to be capable of hosing up formidable oncotargets such as the proliferating cell nuclear antigen (PCNA) after delivery of the degrader mRNA using lipid nanoparticles.[124–126] In other respects, oligonucleotides are being employed to capture RNA- and DNA-binding proteins that lack well-defined ligandable pockets (Figure 1D),[127–129] pushing the boundaries of degradable genome considerably. Regarding applications in the field of anti-infections, the X-protein of the hepatitis B virus (HBV) and the NS3/4A protease of the hepatitis C virus (HCV) have been shown to be suitable for the TPD approach.[130,131] In a similar context, PROTAC influenza viruses in host cells have been designed to function as live-attenuated whole pathogen vaccine,[132] while the degradation machinery (the ClpCP protease) in mycobacteria have been programmed to degrade bacteria's own proteins.[133] In addition to inducing ubiquitination, emerging proximity-inducing modalities are also expected to induce other post-transcriptional modifications (PTM), such as deubiquitination,[134] dephosphorylation,[135] phosphorylation,[136,137] and acetylation,[138] for targeted protein stabilization, deactivation, activation, localization, etc. For example, the deubiquitinase OTUB1 has been shown to be hijacked to stabilize cystic fibrosis causative mutant ΔF508-cystic fibrosis transmembrane conductance

regulator (CFTR) protein levels, thereby improving its proper function in chloride channel conductance.[134] This strategy also applies to the tumor suppressor kinase WEE1 in hepatoma cells, enabling Vicinitas Therapeutics to launch with the aim of saving more needed proteins from destruction. Likewise, the AMP-activated protein kinase (AMPK) and the protein kinase C (PKC) have been demonstrated to be hijacked to induce neophosphorylation,[136,137] enabling Photys Therapeutics to launch with the aim of modulating and repairing disease-driving proteins. Taken together, these innovative works further fuel the field and create more translational opportunities.

Implementing the "5Rs" principle for successful translation

In 2014, AstraZeneca provided a useful five-dimensional framework (known as "5Rs": right target, right tissue, right safety, right patients, and right commercial potential) to guide the research and development of small-molecule drugs.[139,140] This framework remains instructive today for advancing new chemical modalities into the right direction of clinical studies. For TPD, the most important lesson that can be learned from the "5Rs" is to find the best scenario for its use, where degradation strategy outperforms conventional inhibition strategy. For example, untamed transcription factors,[141] scaffold proteins or proteins with scaffolding functions,[142] protein aggregates or aggregate-prone proteins,[143] overexpressed proteins with slow resynthesis rates, enzymes with resistance mutations that impair synthetic inhibitor binding or have extremely high affinity for their endogenous ligands,[72] and other "undrugged" disease-causing proteins or proteins implicated in disease-associated signaling are amenable to the TPD approach. Ultimately, the measure of effectiveness will be that a TPD therapy either outperforms existing standard-of-care treatment or become the first-in-class treatment for its indication. A good example is the development of degraders for the transcription factor signal transducer and activator of transcription 3 (STAT3) for the treatment of STAT3-driven hematological malignancies. Given that monomeric STAT3 still has transcriptional factor activity, STAT3 inhibitors that act by blocking STAT3 dimerization are only partially effective. Therefore, a degradation approach would be favored over an inhibition approach. Accordingly, a bivalent STAT3 degrader SD-36[144–146] (Figure 2) was discovered and more recently, a covalent monovalent STAT3/5 dual degrader JPX-1188[147,148] (structure unknown) developed by Janpix (owned by Centessa Pharmaceuticals) is approaching to the clinic. The second lesson that can be learned from the "5Rs" is to selectively achieve desired pharmacology in the intended site of action, particularly the "on-target-off-tissue drug engagement" issue that determines the therapeutic window. In previous successful practices, the strategy adopted tended to focus on the optimization of the permeability property, which can be illustrated by two recent cases. In the first case, to minimize the risk of tropomyosin receptor kinase A (TrkA) engagement in the CNS, peripherally restricted TrkA inhibitors were achieved by making them substrates for the blood-brain barrier (BBB) efflux transporters (Figure 2).[149] In the second case, to confine the pharmacology of mammalian target of rapamycin (mTOR) inhibition to the CNS and not elsewhere, drug combination of a brain-permeable bitopic mTOR inhibitor whose function requires FKBP12 and a brain-impermeable FKBP12 ligand was used to enable the brain-restricted mTOR inhibition (Figure 2).[150–153] Regarding TPD, an additional layer to increase "on-target-on-tissue" specificity is to pair cell-specific or tissue-specific ubiquitin ligases, which is the consensus in the field.[86,88,89,154] A notable case is the development of BCL-X_L degraders DT2216 and 753b, which targets VHL that is poorly expressed in platelets, thus addressing the on-target platelet toxicity associated with BCL-X_L inhibition (Figure 2).[155–157] That said, mapping degradation pairs in disease settings will facilitate successful translation.

Breaking free of the shackle of Lipinski's rule of 5: Co-opting uptake transporters

The oral route remains the most convenient and cost-effective way to administer a drug. As mentioned earlier, the development of orally available bivalent drugs is far more challenging than that of orally available inhibitor drugs.[158] Therefore, much emphasis has been placed on the delivery system,[68] the metabolism,[64,159] and the solubility and permeability, with the latter being linked to physicochemical properties that are generally guided by Lipinski's rule of 5 (Ro5).[160] Ro5 allows simple prediction for the highest probability of a compound to achieve good oral absorption based on a physicochemical rationale, and has served as empirical guidelines for structural properties of drug-like compounds for over 25 years[161,162] However, overinterpretation or misinterpretation of the rule can cause problems, especially in the field of TPD where compounds can be active even at vanishingly low concentrations and are subject to complex conformational dynamics.[163,164] It is important to highlight that the rule obviously does not apply to compounds intended for non-oral routes of administration and, more often overlooked, to compounds that are substrates for biological uptake transporters (Figure 3A).[165] Three examples are highlighted here to further elucidate the latter exception as a way to inspire bivalent degrader drug development. The first example is the HCV nonstructural protein 5A (HCV-NS5A) replication complex inhibitors. Since the disclosure of daclatasvir,[166,167] this class of C_2-symmetric inhibitors including ledipasvir, elbasvir, velpatasvir, ombitasvir, and pibrentasvir (Figure 3B) have been developed and approved for the treatment of chronic HCV.[168–170] With a molecular weight in the range of 738.9–1113.2 Da, these large-size inhibitors are predicted to have poor oral bioavailability according to the Ro5. However, it was found that the $_L$-Pro-$_L$-Val dipeptide subunit present in these molecules can be recognized by a transporter, thus ensuring a high plasma exposure via the oral route.[171] The second example is the BCL-2/BCL-X_L dual inhibitor navitoclax (ABT-263) and the BCL-2 inhibitor venetoclax (ABT-199) (Figure 3C), developed to treat relapsed or refractory chronic lymphoid leukemia. Both molecules are suitable for oral delivery, albeit with molecular weights of 974.6 and 868.5 Da, respectively.[172–174] Although navitoclax and venetoclax violate the Ro5, it was found that transport by the intestinal lymphatics[175] plays a sizable role in their absorption and may secondarily enhance systemic exposure by avoiding the hepatic first-pass effect.[176] The third example is the aforementioned bitopic mTOR inhibitor RapaLink-1 (Figure 2B),[150–153] which possess a molecular weight of 1784.2 Da, even beyond that of typical bivalent degraders. The high *in vivo* activity of RapaLink-1 and its structural analog RMC-5552[177] (currently in

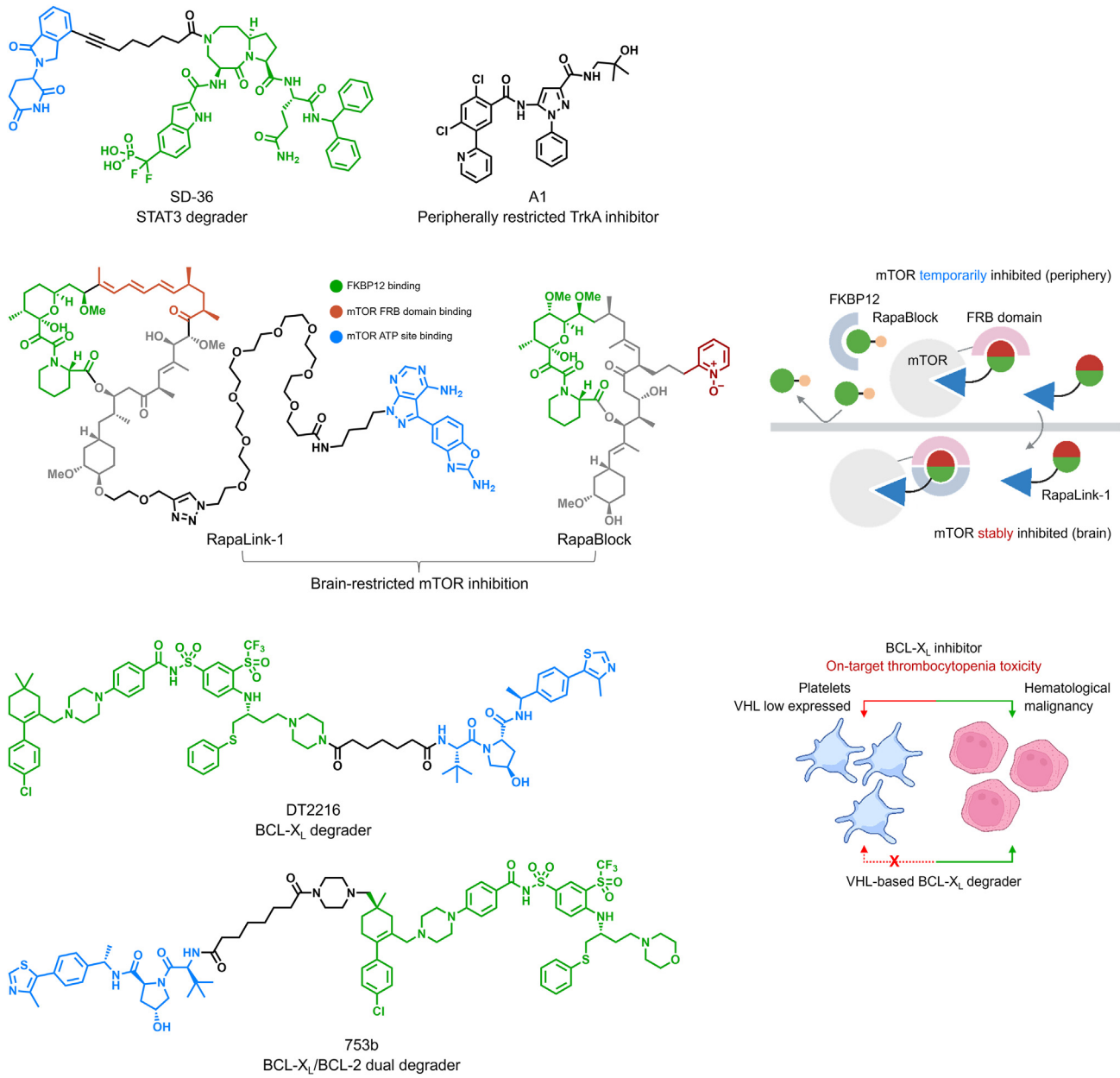

Figure 2. Chemical structures of SD-36, RapaLink-1, RapaBlock, DT2216, and 753b
The mechanisms of action of brain-restricted mTOR inhibition and platelet-sparing BCL-X_L degradation are shown with cartoons.

clinical trials) implies their good cell permeability, suggesting that there may be a cellular uptake mechanism that assists the cytoplasmic entry of such compounds. By using complementary genome-scale chemical-genetic methods, interferon-incused transmembrane proteins (IFITMs) were found to promote the cellular uptake of these linked bitopic molecules in a pattern where longer linker length correlated with greater IFITM assistance.[178] This finding provides clues for other linked chemotypes to exploit this uptake pathway. Collectively, exploiting intestinal and brain uptake transporters[179] for bivalent degrader drug absorption could be a unique direction to address the oral bioavailability conundrum and the CNS exposure conundrum.

CONCLUSIONS

The past two decades have witnessed an incredible paradigm shift in the field of chemical biology and drug discovery, with many new therapeutic modalities being innovated and proved.[180,181] After being electrified since its launch, TPD is experiencing a critical transition from "gold rush"[182] to a "Gleevec moment". Just as the regulatory approval of Gleevec has inspired the subsequent launch of over 80 marketed kinase inhibitor drugs,[183] the first degrader drug to be developed with prior knowledge of the identity of its target protein will also lead the way to more success. In particular, the clinical results

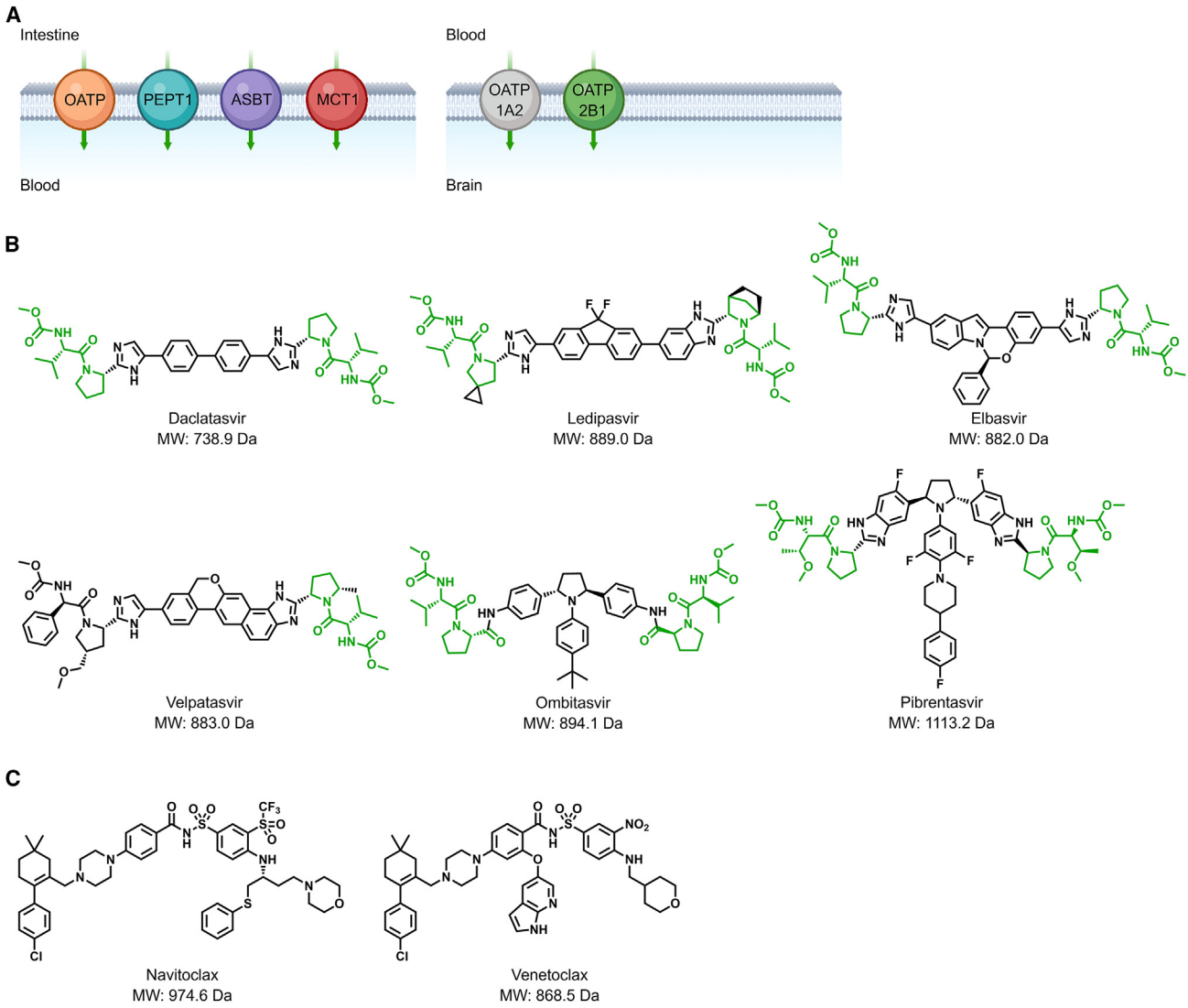

Figure 3. Schematic representation of uptake transporters-assisted drug absorption

(A) Selected human uptake transporters in the intestinal epithelia cell membrane and blood-brain barrier.

(B) Chemical structures of selected HCV-NS5A inhibitor drugs with the $_{L}$-Pro-$_{L}$-Val dipeptide subunit colored in green.

(C) Chemical structures of the BCL-2/BCL-X_L dual inhibitor navitoclax and the BCL-2 inhibitor drug venetoclax. Abbreviations are as follows: ASBT, ileal apical sodium/bile acid co-transporter; MCT1, monocarboxylic acid transporter 1; OATP, organic anion transporting polypeptide; PEPT1, peptide transporter 1.

of a range of bivalent degrader drug candidates will tip the balance in the dispute over whether the benefits of this large molecule-weight modality are hype or useful medicines. We believe that the preclinical development challenges of bivalent degraders for oral delivery will not matter much to the pharmaceutical industry, although the ways in which the pharmaceutical industry is achieving this goal have not been fully communicated to date. Regarding monovalent degraders, as knowledge grows in discovery paradigms, mechanistic understandings, mechanism-indication pairs,[184] and safety-toxicology assessments,[185] the field should be poised to see new drugs that differ from the IMiD class. Collectively, we have briefly navigated the rise of the ever-expanding degrader modality and have commented on the transformation and innovation efforts concerning it. The audience should at most take this article as a tutorial preface to the magnum opus that brings together the wisdom of the entire TPD field. We encourage the audience to peruse those elegant research papers for a more comprehensive view. Going forward, we expect protein degraders to serve as an interdisciplinary link in connecting genetics, pathophysiology, chemical biology, and translational medicine, and as a new case from basic science to unprecedented medicines. While the discovery of ubiquitin-mediated protein degradation and the discovery of the mechanisms of autophagy were awarded Nobel Prizes in 2004 and 2016, respectively, we believe that these two great works will continue their impact by transforming formidable diseases (e.g., the Cancer Moonshot) with degrader therapy, which should not just offer patients new treatment options, but should bring them real benefits that were not available with any previous treatment.

SIGNIFICANCE

With remarkable progress made in the field of targeted protein degradation, a substantial number of therapeutic hypotheses have been or are currently being translated into clinical investigations, signaling the impending arrival of a "Gleevec moment". In this context, we endeavor to promptly present our observations and reflections, highlighting translational opportunities and approaches, with the aim of suggesting steps that may unlock the full potential of degrader therapeutics.

ACKNOWLEDGMENTS

The authors thank Dr. Milka Kostic (Dana-Farber Cancer Institute, Twitter: @MilkaKostic), Dr. Eric S. Fischer (Dana-Farber Cancer Institute), Dr. Lyn H. Jones (Dana-Farber Cancer Institute), Dr. Stewart L. Fisher (C4 Therapeutics), and Dr. Christopher G. Nasveschuk (C4 Therapeutics) for their assistance with critical reading and scientific editing of the manuscript. The authors thank Dr. Jie Jiang (Dana-Farber Cancer Institute) for her assistance with literature collection. The authors also wish to thank the large number of investigators who have contributed to many aspects of this topic and apologize if the authors failed to cite some relevant work. M.T. is a CPRIT scholar in cancer research and M.T. thanks the Cancer Prevention and Research Institute of Texas (CPRIT) for research funding support (RR220012).

AUTHOR CONTRIBUTIONS

Conceptualization, M.T. and N.S.G.; Writing – Original Draft, M.T.; Writing – Review & Editing, M.T. and N.S.G.

DECLARATION OF INTERESTS

The authors declare the following competing financial interest(s): N.S.G. is a founder, a science advisory board member, and an equity holder in Syros, Lighthorse, Inception, C4, B2S, Allorion, Voronoi, Matchpoint, CobroVentures, GSK, Shenandoah (board member), Larkspur (board member), and Soltego (board member). The Gray lab receives or has received research funding from Novartis, Takeda, Astellas, Taiho, Janssen, Kinogen, Voronoi, Arbella, Epiphanes, Deerfield, Springworks, Interline, and Sanofi.

INCLUSION AND DIVERSITY

We support inclusive, diverse, and equitable conduct of research.

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