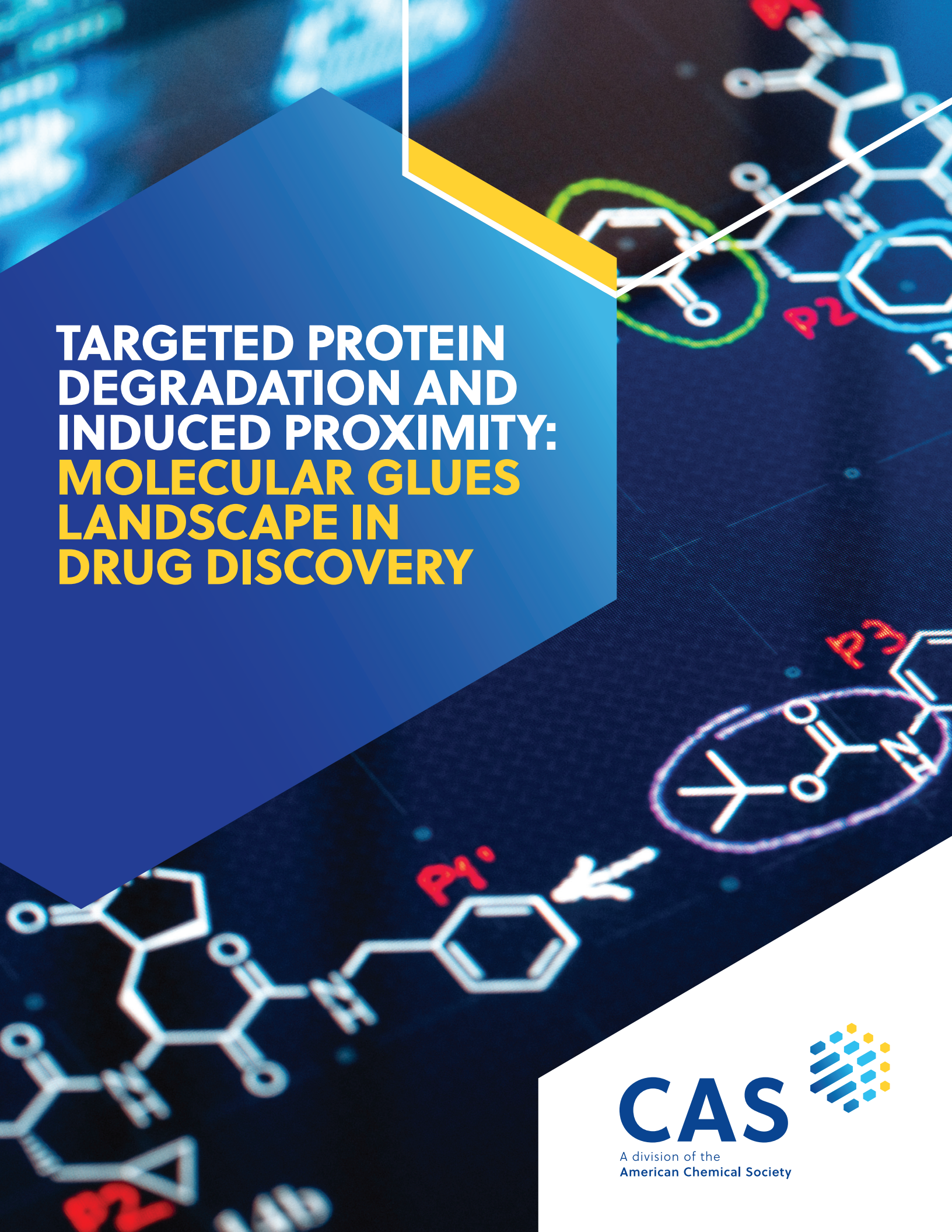

TARGETED PROTEIN DEGRADATION AND INDUCED PROXIMITY: MOLECULAR GLUES LANDSCAPE IN DRUG DISCOVERY

CAS

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Introduction

Induced-proximity targeted protein degradation (TPD) is a ground-breaking strategy in drug discovery that has emerged during the last decade.[1–3] In TPDs, undruggable disease-causing proteins are recruited for rapid destruction and elimination via the ubiquitin-proteasome pathway, which is a major mechanism for protein degradation and homeostasis.[1–5] The ubiquitin-proteasome pathway is part of the cellular housekeeping processes and occurs through an enzyme cascade, which results in protein ubiquitination and subsequent degradation.[4,5] The ubiquitin-proteasome system (UPS) is a major mechanism for cellular protein degradation and maintaining protein homeostasis, which is a part of the regular cellular housekeeping processes. Therefore, signifying the potential breadth of TPD applications being almost unlimited. The UPS process involves an enzyme cascade that results in the ubiquitination of the protein of interest (POI).

Ubiquitination is key to both proteasomal- and autophagy-mediated protein degradation, entailing E3 ligases as the critical components of the cascade. Of more than 600 E3 ubiquitin ligases encoded by the human genome, there are only a few that have been exploited for targeted protein degradation. Subunits of ubiquitin ligase can be targeted by molecular glue degraders, which cause a conformational change that promotes the formation of a ternary complex with the POI, prompting ubiquitin transfer and subsequent proteasomal degradation of the POI.[6,7] Identifying successful strategies for discovering ligands to POIs that bind to E3 ligases has become an attractive and exciting research objective and can lead to new therapies for diseases such as cancer, inflammatory and immune diseases, and infections, many of which are driven by the aberrant expression of a pathogenic protein.[1–3]

Compared with traditional pharmacological target protein inhibition, the protein degradation approach has significant advantages. Degraders act via transient binding rather than competitive occupancy and successfully dissociate after promoting polyubiquitination of the disease-causing protein. Consequently, a single degrader can destroy many copies of a pathogenic protein, thereby providing greater efficiency at very low doses. While protein inhibitors simply block the active site of a pathogenic protein, degraders remove all of its functions, providing higher sensitivity to drug-resistant targets and an improved chance of affecting the nonenzymatic protein function.[8–10]

The development of therapeutic chimeric degraders has advanced considerably over the past two decades.[11,12] The earliest description of a chimeric degrader used to exploit the ubiquitin-driven natural protein degradation for therapeutic purposes was in a patent filed in 1999 by Proteinix, which aimed to use small molecules for the recruitment of E3 ligases to degrade a POI.[13] In 2001, the first in vitro proof-of-concept study was published, demonstrating that a peptide-based protein-targeting chimeric molecule, Protac-1, which recruits the E3 ligase β-TrCP, successfully led to the degradation of a cancer-associated protein, MetAP2; thus, the term PROTAC (PROteolysis-TArgeting Chimera) was coined.[14]

This was followed by the development of a peptide from HIF1α, which binds the VHL E3 ligase, and the creation of cell-penetrating PROTACs, which degrade a variety of proteins at various locations.[15,16] Early PROTACs were large-molecular structures; the first report of a small molecule androgen receptor (AR) degrader using nutlin-3 for recruiting MDM2 was published in 2008.[17] The subsequent

discovery of small-molecule mimetics of the HIF1α peptide expedited the rational design of small molecular PROTACs.[18–20] To date, few proximity-induced TPDs have reached clinical testing, but clinical trials of two targeted protein degraders commenced in 2019. These involve PROTACs ARV-110 (NCT03888612) and ARV-471 (NCT04072952), which target the androgen and estrogen receptors, respectively; both have proceeded to Phase II trials. Multiple other commercial protein degraders are in development.[10]

The discovery of molecular glues further advanced the strategies of TPD which interact with two protein surfaces (E3 ligase and target protein) to induce and enhance the affinity of these two proteins.[21] Molecular glues include thalidomide and its analogues, lenalidomide and pomalidomide (immunomodulatory imide drugs), which target the E3 ligase, cereblon.[22] Multiple protein degraders that target various androgen and estrogen receptors, and other disease-associated proteins, have now been identified.[23–26]

The first rational discovery of a molecular glue between a ligase and a substrate involved a series of compounds that enhanced the interaction between the oncogenic transcription factor, β-catenin and its cognate E3 ligase, SCF β-TrCP.[27] Molecular glues have been identified with various other mechanisms of action, including autophagy-mediated protein degradation, MEK sub-complex stabilization, KRAS mutant inhibition, α-tubulin polymerization stabilization, and FK506-binding protein 12 (FKBP12) protein degradation.[28] To assess recent advances in molecular glue research, particularly in medicinal chemistry and drug discovery, this white paper will examine the relevant publication data from the CAS Content Collection™.

Proximity-induced targeted protein degradation and molecular glues

Molecular glues are monovalent small molecules (<500 Da) that chemically induce the proximity of target proteins with E3 ubiquitin ligases to ubiquitinate and degrade specific proteins via the proteasome (**Figure 1A**).[6] Molecular glue degraders have been serendipitously discovered and interact with a variety of target proteins that are difficult to predict, exhibiting distinct biological activities by inducing and enhancing the interaction of two proteins that otherwise do not show a native affinity for each other.[29–31] Comparatively, PROTACs are bivalent molecules consisting of two moieties, one binding to the POI and the other to E3 ligase, joined by a linker (**Figure 1B**). Upon polyubiquitylation and subsequent degradation of the POI, these small molecule degraders are recycled to repeat this process and thus have a catalytic mechanism of action.[32] The rational discovery of most PROTACs is on the basis of the binding mode of E3 ligases with the target proteins, followed by the choice of an appropriate site in the E3 ligase to extend the linker and E3 ligase-binding groups.[32] Thus, the target proteins of PROTACs are predictable.

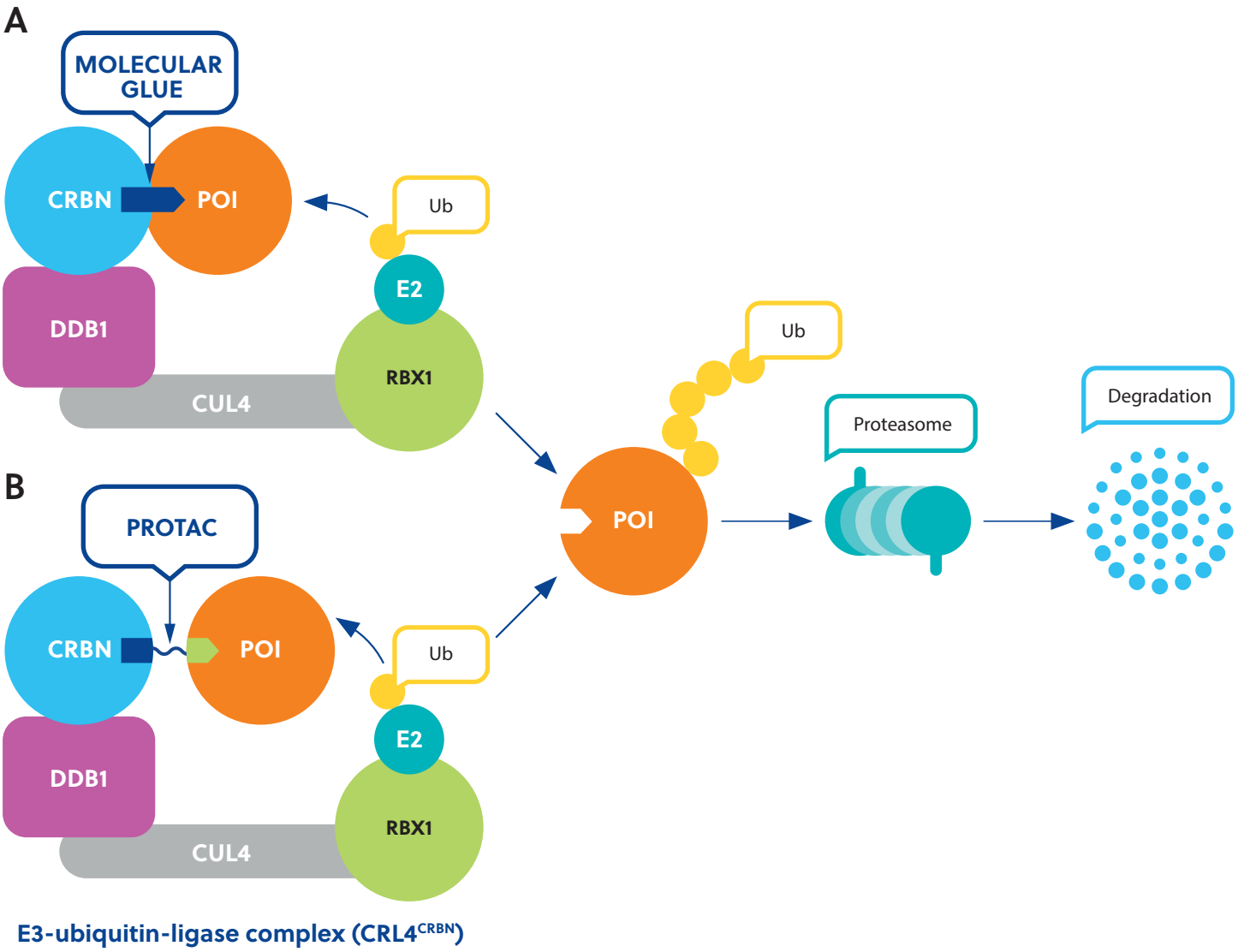


Figure 1. Schematic presentation of the degradation of a protein of interest (POI) via the ubiquitin (Ub)-proteasome system using a molecular glue (A) or PROTAC (B) bound to the E3 ubiquitin ligase CUL4–RBX1–DDB1–CRBN (CRL4CRBN) complex

Molecular glues are expected to have better pharmacological properties compared with PROTACs; they are much smaller and can therefore follow Lipinski's rule of five for drug conformity, which defines the molecular properties important for drug pharmacokinetics.[33] They are expected to have higher membrane permeability, improved cellular uptake and in general, should be less likely than PROTACs to pose a significant challenge for blood-brain barrier penetration, which is an important requirement for treating central nervous system disorders. A comparison of the key properties of molecular glues and PROTACs is provided in **Table 1**.

Table 1. Comparison between Molecular Glues and PROTACS

	Molecular glues	PROTACs
Feature	Monovalent	Bivalent
Linker	No	Yes
Molecular weight	<500 Da	700–1000 Da
Lipinski's rule of 5	Within	Defy
Target	To be determined	Predictable
Binding pocket	Not required	Required
Binding affinity	Weak binding affinities for either E3 ligase or target protein is needed, displaying an event- driven catalytic mechanism of action	Binding E3 ligase and the target protein, two ligands are connected by a linker

Small molecule glues have also been shown to reprogram the binding partners of scaffolding proteins or to enhance the endogenous interaction between two proteins.[34] Molecular glues stabilize the interactions between proteins instead of inhibiting these interactions. Thus, they provide new therapeutic mechanisms and potentially unexplored substrates for targeting. Moreover, molecular glues would be expected to be synthetically more tractable, with a more straightforward structure-activity relationship than PROTACs.[35] However, an important advantage of PROTACs is their versatility; they allow for modular design to rapidly connect one enzyme with many targets.[36]

Being much smaller than the average PROTAC, molecular glues are more likely to find binding sites on any given protein and thereby probe a larger area of possible surfaces for molecular glue effects.[35] On the other hand, it makes the design and identification of molecular glues extremely difficult.[37] Indeed, until recently, molecular glue identification has relied primarily on serendipity, but a shift toward rational design is emerging to facilitate drug discovery and the target of undruggable proteins, as discussed in a later section.[11] Early examples are beginning to emerge that rationalize some of these concepts to develop molecular glue degraders with new functions. However, there is still much to be learned.[37]

The landscape of molecular glue research: Overview of CAS literature search findings

The CAS Content Collection represents the largest human-curated collection of published scientific knowledge.[38] It is particularly useful for the quantitative analysis of global scientific publications against variables such as time, research area, formulation, application, disease association, and chemical composition. Currently, the collection has over 1,000 TPD-related publications, primarily including journal articles and patents. **Figure 2** shows the explosive growth in both publications and patents on protein degraders over the past decade, from just single digits in 2014 up to hundreds of publications in the last 2–3 years.

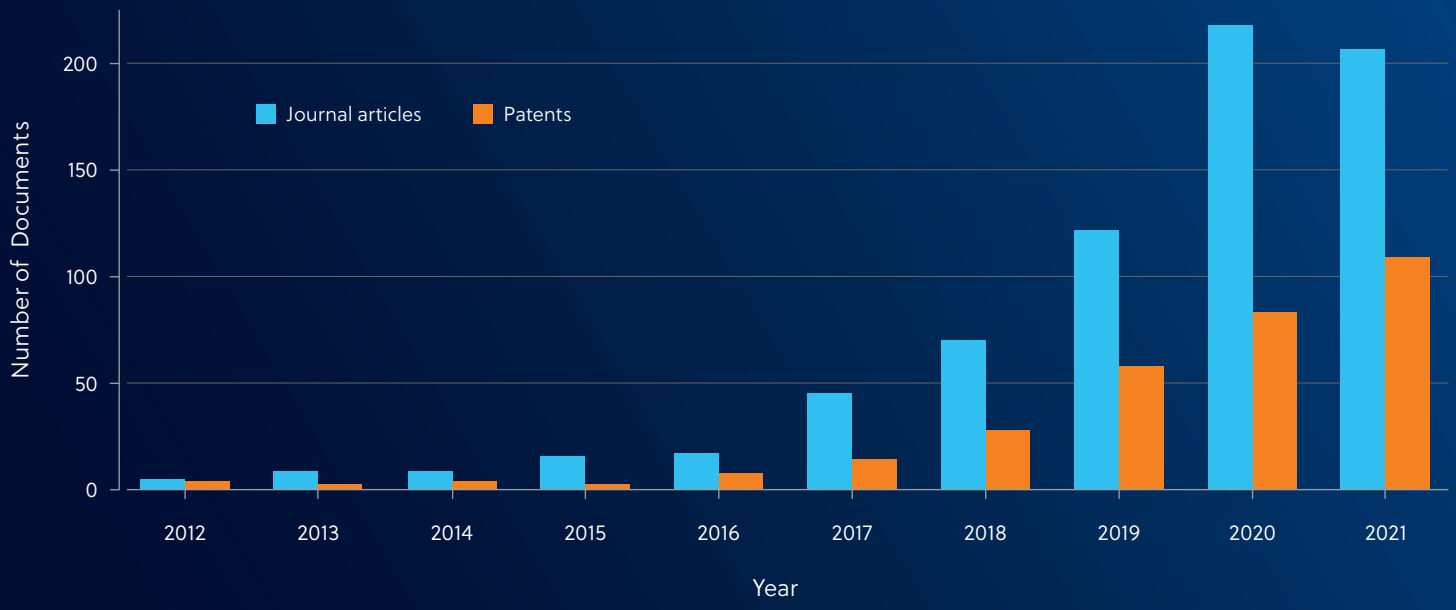


Figure 2. Trends in the protein degraders-related number of publications in the last decade, including journal articles and patents

Further analysis shows that the largest number of journal publications on protein degraders were from the United States, China, the United Kingdom, Japan and Germany, among others (**Figure 3A**). The largest numbers of protein degrader-related patent filings were from China and the United States (**Figure 3C**). Among research institutions, the Dana-Farber Cancer Institute and the University of Dundee published the largest number of TPD-related journal articles (**Figure 3B**). A list of journals that frequently publish TPD-related articles is presented in **Figure 3D**. This shows the importance of TPD in medical research, with the Journal of Medicinal Chemistry and the European Journal of Medicinal Chemistry having the greatest number of TPD-related articles.

A

Country	Journal Publication
United States	259
China	215
United Kingdom	59
Japan	44
Germany	27
India	17
Switzerland	13
Austria	12
Netherlands	12
Russian Federation	12

B

Organization	Journal Publication
Dana-Farber Cancer Institute	20
University of Dundee	20
Yale University	16
University of Michigan	15
University of California	14
China Pharmaceutical University	10
University of Kentucky	10
Chinese Academy of Sciences	9
Icahn School of Medicine at Mount Sinai	9
National Institute of Health Sciences	9
University of Florida	9
Tslnghua University	8

C

Country	Patents
China	122
United States	112
Japan	18
S. Korea	18
Germany	11
Switzerland	10
France	8
Austria	6
United Kingdom	4

D

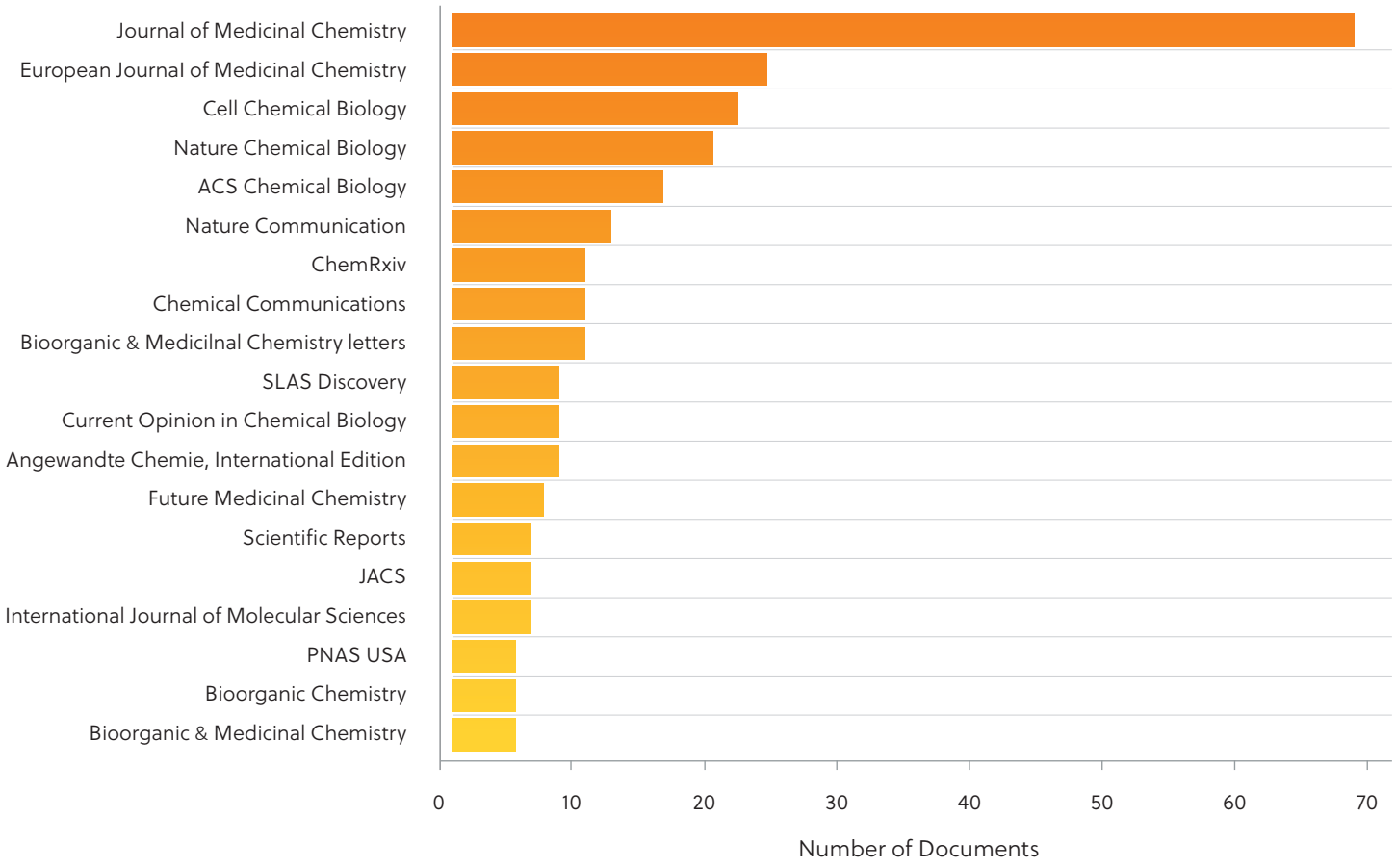
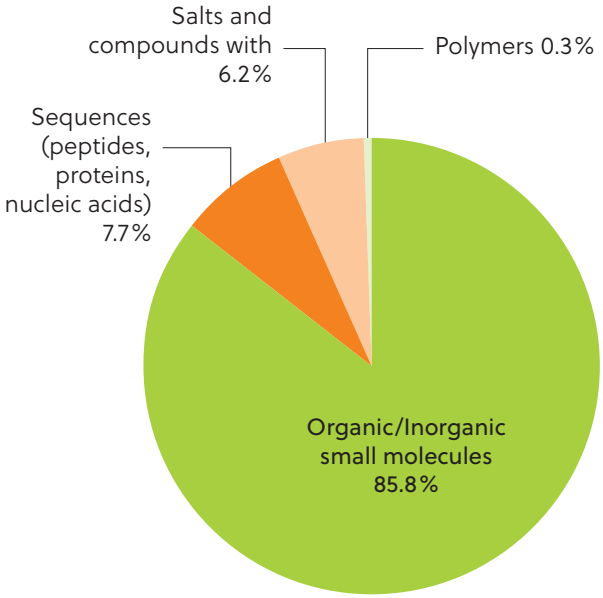


Figure 3. Top countries (A), organizations (B), and scientific journals (D) publishing TPD-related journal articles, and top countries filing TPD-related patents (C)

Analysis of the TPD literature by chemical type indicates domination by small molecules (85.8%), followed by biosequences (7.7%), including peptides, proteins, nucleic acids, and salts (6.2%) (**Figure 4, left panel**). This contrasts with the early protein-targeting chimeric molecules that were peptide-based; the first invention and design of a small molecule androgen receptor degrader using nutlin-3 for recruiting the E3 ubiquitin-protein ligase MDM2 (mouse double minute 2 homolog) was published in 2008.[17]

The roles of TPD substances in protein degrader-related research are shown in the **right panel of Figure 4**. Protein degraders are synthesized via multistep chemical reactions, which explains the dominance of the synthesis-related roles of synthetic preparation and reactant in the literature analysis results. Therapeutic use and pharmacological activity are therapy-related, reflecting the emerging role of protein degraders in medical practice. It is clear that significantly greater numbers of compounds indexed in the CAS Content Collection originated from patents.



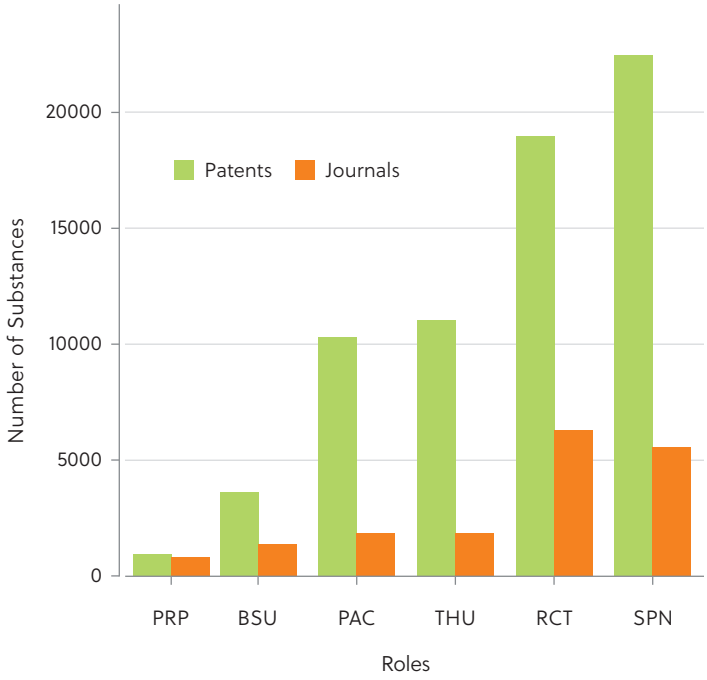


Figure 4. Classes of substances represented in the TPD-related documents (left panel) and their role indicators according to CAS Content Collection (SPN, synthetic preparation; RCT, reactant; THU, therapeutic use; PAC, pharmacological activity; BSU, biological study (unclassified); PRP, properties)

An analysis of the variety of diseases targeted by protein degraders found in the CAS Content Collection showed the largest portion (44%) of the publications were associated with cancer treatment (e.g., breast and prostate cancer, multiple myeloma, and leukemia; **Figure 5**). Neurodegenerative, infectious, inflammatory, autoimmune, and metabolic diseases were also highly represented.

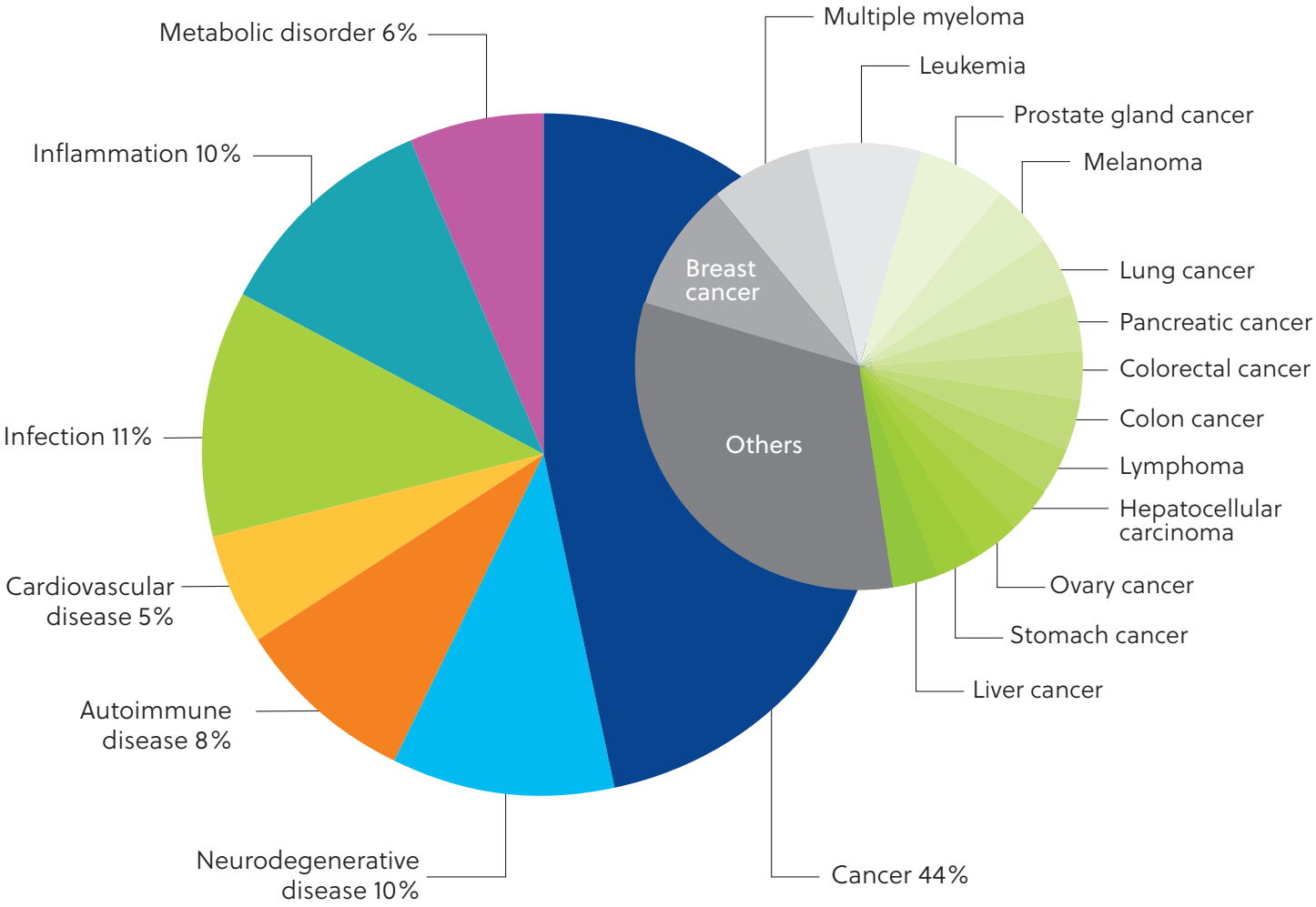


Figure 5. Distribution of protein degrader-related publications in the CAS Content Collection with respect to targeted diseases

In the literature analysis, CRBN, VHL, and MDM2 were found to be the most popular types of E3 ligases used to recruit TPDs to induce ubiquitination and subsequent proteasomal degradation of target proteins in cancer, inflammation, neurodegenerative, autoimmune, and infectious diseases (**Table 2**).

Table 2. Correlation of the number of protein degrader-related publications in the CAS Content Collection for the three most widely used E3 ligases with their targeted diseases (percentages are from the total number of protein degrader-related publications)

	Cancer	Inflammation	Neuro-degenerative diseases	Autoimmune diseases	Infectious diseases
CRBN	20.1%	3.2%	2.3%	2.1%	1.7%
VHL	12.6%	1.5%	0.9%	1.1%	0.8%
MDM2	2.6%	0.8%	0.4%	0.4%	0.2%

TPD literature trends during 2017–2021 (number of documents) showed that the largest number of publications were on PROTAC and E3 ubiquitin ligase, followed by cereblon, proteasome and ubiquitination (**Figure 6A**). Although documents on molecular glues and protein degraders were overall less numerous during this period, they were the key concepts (proportion of documents containing concepts) that showed explosive growth and interest from 2019 onwards. Other concepts including ubiquitination, E3 ligase, cereblon, PROTAC, and proteasome also showed strong continuing growth throughout 2017–2021 (**Figure 6B**).

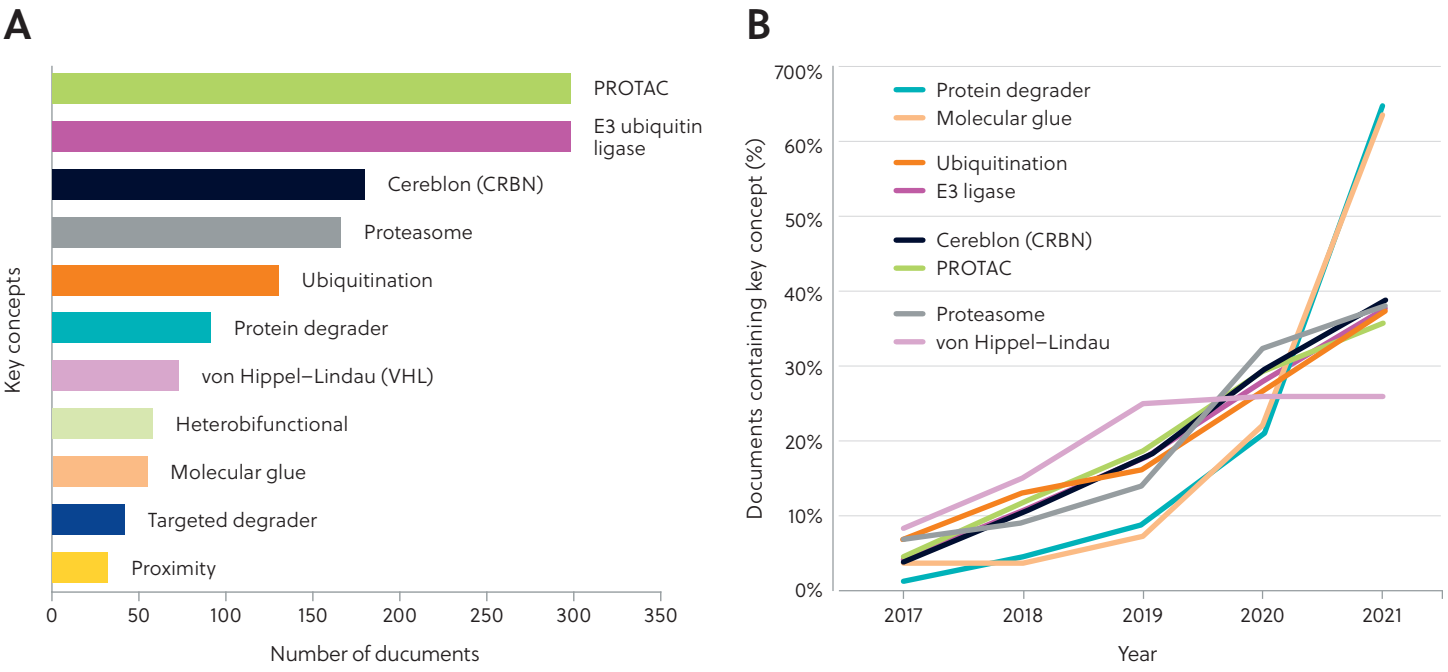


Figure 6 (A) Number of publications presenting key concepts related to TPDs during the years 2017–2021. (B) Trends in key concept presented in the articles related to TPDs during the years 2017–2021. Percentages are calculated with yearly publication numbers for each key concept, normalized by the total number of publications for the same concept in the same period

Table 3 summarizes the major E3 ligase recruiting TPDs, which is reflected in the number of documents contained within the CAS Content Collection. While CRBN remains the most frequently used recruiter, there is clearly much interest in a range of other types, indicating an emerging diversity in this approach.

Table 3. Number of documents in the CAS Content Collection related to E3 ligase recruiters exploited for targeted protein degradation

E3 ligase / subunit	Number of records
CRBN	309
VHL	207
MDM2	189
SCF	86
RNF	63
SKP	55
cIAP	50
DDB1	47
KEAP1	31
FBXO	23
UBR2	19
β-TrCP	9
DCAF	8
SIAH1	4
STUB1	4
ASB6	2
CDC34A	1
UBE4A	1

Advances in drug discovery approaches for molecular glue degraders

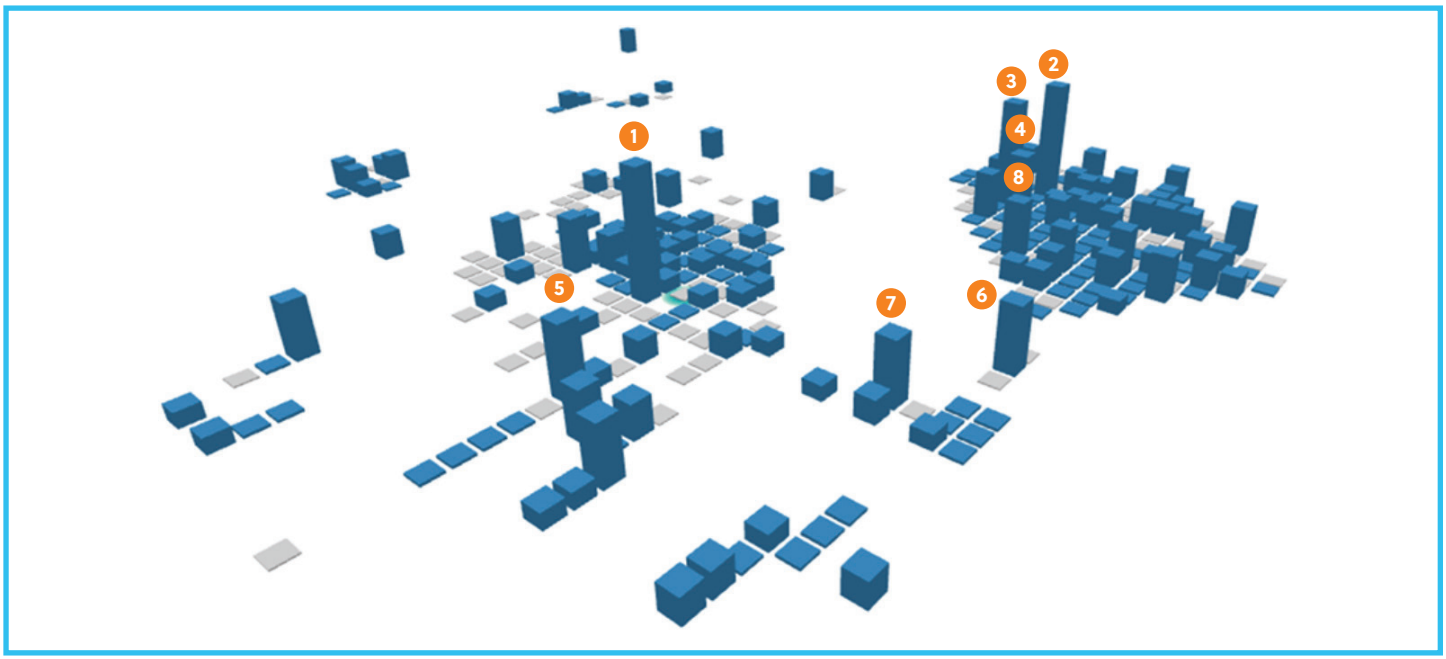
Research interest in molecular glue compounds is rapidly expanding the compilation of E3 ligases, molecular glues, their neosubstrates, and the associated diseases they aim to treat, particularly for the degradation of previously undruggable proteins. Molecular glues have been discovered firstly through serendipity but also through chemical library screening. For more details on the use of high throughput chemical library screening for the identification of molecular degraders, see our publication in cas.org/molecularglue. A developing and more targeted route to molecular glues is through rational design.[34,39] Mechanism of action, structure-activity relationship, and protein structure studies have laid the foundations for the structure-based drug design of molecular glues. These approaches have enabled the discovery and validation of various highly potent and selective molecular glues, some examples of which are given in **Table 4**.

Table 4. Pathway of molecular glue degrader discovery and structure guided drug design

Initial Discovery	Scaffold Definition	Optimization	Validation
– Serendipitous[22] – High throughput screens (HTS)[27,39,40] – Data mining[40,41]	– Crystallography[42,43] – Molecular Docking[44,45] – Structure activity relationship (SAR) studies[44,46,47]	– Protein-protein interaction assay of scaffold analogs[46] – E3 ligase-dependent activity assay of scaffold analogs[44,47]	– Binding assays[48] – Biochemical methods validating targeted degradation[47,49] – Cell-based activity assays[46] – Molecular docking analysis[47] – Crystallography[48,50]

Thalidomide was shown to be a molecular glue long after its first development as a therapeutic agent (with serious teratogenicity effects).[22,31,42,43,51,52] This efficacy proved the concept of E3 ligase-based targeted protein degradation as a therapeutic strategy, which stimulated the search for new molecular glues, E3 ligases, and their neosubstrate targets. Promising thalidomide-based analogs with reduced teratogenicity, enhanced potency and better target specificity are currently in development from the preclinical stage to the Phase II clinical stage. These analogs include CC-122,[47] CC-220,[50] CC90009,[46] CC-92480,[53] ZXH-1-161,[47] and SJ6986.[44] Using ChemScape software within SciFinder^{n},[54] a structure similarity analysis of the CAS Patent Content Collection for compounds with 90% similarity to thalidomide showed significant numbers of recent patents related to thalidomide-based analogs (**Figure 7**).

Chemscape map of compounds within 90% similarity limit to thalidomide used as protein degraders (SciFinder^n)



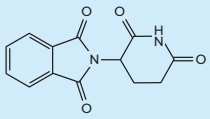
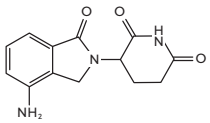
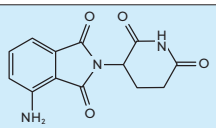
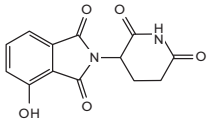
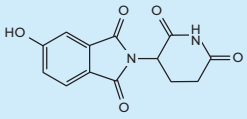
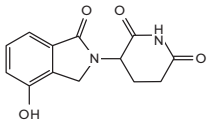
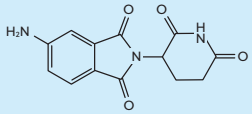
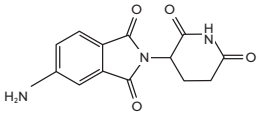
	Compound CAS #	Structure	Number of patents
1	50-35-1 (thalidomide)		1,060
2	191732-72-6 (lenalidomide)		962
3	19171-19-8 (pomalidomide)		496
4	5054-59-1		104
5	64567-60-8		39
6	1061604-41-8		28
7	191732-76-0		24
8	191732-70-4		23

Figure 7. A search in SciFinder^n for compounds within the 90% similarity limit to thalidomide used as protein degraders gave 219 compounds. Each column on the figure reflects a single compound, with the top 8 indicated by numbers. The distance between two columns reflects the similarity between these two compounds. The bar height reflects the number of patents related to a given compound in the development of molecular glues

Crystallization and mutational analysis have enabled an understanding of the interaction of CRBN with thalidomide and its analogs, including lenalidomide and pomalidomide.[42,43] The main pharmacophore structure is a conserved glutarimide ring that binds to CRBN and occupies a hydrophobic binding cavity between two CRBNβ sheets and the carbonyls at C2 and C6. Additionally, an amide at N1 forms hydrogen bonds with CRBN. This understanding has formed the basis for the structure-based design of new molecular glues.

Efforts to optimize the specificity and potency of molecular glues have resulted in promising new antitumor agents, including Bristol Myers Squibb (BMS)/Celgene's 2nd generation compounds CC-122, CC-220, and CC-885.[49,55,56] These were synthesized as part of focused combinatorial libraries retaining the main CRBN binding pharmacophore glutarimide ring, with variations to the solvent-exposed ring. CC-122 shows enhanced proteasome dependent degradation of proteins, while CC-220 binds to CRBN with greater affinity than lenalidomide and pomalidomide.[49] In order to improve the poor toxicity profile of CC-885, BMS/Celgene developed analogs that improved antiproliferative activity against a broad panel of AML cell lines compared with normal cells. Using CC-885 as a structural template, SAR studies defined a scaffold with a difluoro acetamide linker that maintained a good in vitro selectivity index.[46] The recent discovery of the cereblon E3 ligase modulation drug (CELMoD) SJ6986 from a 415-compound focused chemical library with 30 scaffolds demonstrated the utility of evaluating the library by in silico molecular docking analysis and the evaluation of physiochemical descriptors, prior to phenotypic screening.[57]

Once favorable molecular glue drug candidates are identified, their therapeutic specificity and potency need to be further validated. This is achieved by determining their mode of action and functional bioactivity. Validation assays to confirm the chemical interactions of lead CELMods have included crystallography,[48] docking analysis,[44] fluorescence polarization assays,[44] TR-FRET,[47] and co-precipitation[48] or pull-down assays.[48] Targets of degradation have been validated by immunoblotting,[44,46,47] chemiluminescence based assays,[50] and expression proteomic analysis.[44,47,49]

Methods for confirmation of the cellular activity of CELMods of interest have included antiproliferation assays across specific cell lines to validate the cell line specificity, potency, and therapeutic value of lead compounds.[44,46]

E3 ubiquitin ligases recognize their substrates through degrons, which are short sections of the primary protein sequence that are necessary and sufficient for interaction with substrate receptors of ubiquitin ligases.[58] Chemoproteomics can provide a useful approach for identifying proteins from the human proteome with favorable degron features, making these targets feasible candidates for recruitment to CRBN.[59] Sources of optimal degraders could potentially be searched for among existing focused chemical library collections or through constructing new in silico assisted custom-designed chemical libraries tailored for chemical feasibility and spatial diversity within the new CRBN-neosubstrate binding cavity space.[42] These approaches can be substantially enhanced using the CAS SciFinder^{n} resource, which provides current and accurate substance and reaction information, chemical structures, properties, experimental schemes, and regulatory information in a comprehensive chemical database.[54]

An alternative approach to identifying new molecular glues is to use DNA-encoded chemical library (DECL) technology.[60–65] In this approach, candidate small molecules are covalently linked to DNA sequences carrying readable information about the compound. This form of 'DNA-tagging' enables efficient synthesis, handling, and interrogation of vast numbers of chemically synthesized, drug-like compounds. Billions of these compounds forming DNA-encoded libraries can be screened for binding to proteins and numerous bioactive compounds have been identified this way. Some of these compounds have detected otherwise unknown allosteric binding sites on target proteins and others have been used to unravel complex biology. More recent improvements in compound design and selection methods have increased the value and potential of DECLs for the discovery of protein-binding compounds including molecular glues.[61,62,65]

Recently discovered molecular glues, E3 ubiquitin ligases, and target proteins

The most investigated molecular glues are small molecules that bind the E3 ligase CRBN and the aryl sulfonamides that engage DCAF15.[66,67] Other molecular glues induce protein degradation through various mechanisms of action, including autophagy-mediated protein degradation, protein-protein interaction stabilization, KRAS mutant inhibition, microtubule polymerization stabilization, PI3K inhibition, FKBP12 protein binding, and inhibition of mTOR. The number of known molecular glue types and structures is already considerable and is growing. A summary of these types, with examples and CAS registration numbers, is provided in **Table 5**.
The range of different types and target proteins indicate that molecular glues have potential impact across of wide range of diseases, including numerous types of cancers, autoimmune, and neurodegenerative diseases. It also indicates an extensive range of different mechanisms of action against previously undruggable targets and helps explain the rapidly increasing research interest in molecular glues in recent years. While the majority of discovered molecular glues utilize E3 ligase to degrade target proteins, some have emerged that are non-E3 ligase utilizing and use other mechanisms such as autophagosome-tethering, protein-protein interaction stabilization, and KRAS mutant inhibition. In addition, certain natural molecular glues have been identified, such as cyclosporin A and Lupkynis, which have anti-inflammatory properties. These developments indicate an important broadening of molecular glue approaches and a potentially more diverse range of activities.

Table 5. Overview of discovered molecular glues and their applications. Further details on the types of protein degradation can be found at cas.org/molecularglue

Types of protein degradation	Description	Examples: CAS REG numbers
E3 ligase utilizing targeted protein degraders		
Transcription factors IKZF1 and IKZF3 degradation	Lymphocyte lineage transcription factors - key regulators for survival of malignant plasma cell in multiple myeloma - considered undruggable due to lack of druggable binding pockets.	Revlimid: 191732-72-6[34] Thalidomide: 50-35-1[52] Pomalyst: 19171-19-8[39]
Cyclin K and CDK12 degradation	Drug targets to treat cyclin E1-overexpressing tumors of human tumorigenesis.	CR8: 294646-77-8[68] Glue01: 1226443-41-9[69] HQ005: 2750644-31-4[40]
Casein kinase 1α (CK1α) degradation	Member of CK1 family of proteins that regulate various signaling pathways involving autoimmune diseases, neurodegenerative diseases, and cancer.	FPFT-2216: 2367619-87-0[70] TMX-4116: 2766385-56-0[71]
G1 to S phase transition protein 1 (GSPT1) degradation	Translation termination factor GSPT1 is overexpressed and oncogenic in several cancers.	Eragidomide: 1860875-51-9[10] BTX-1188: CAS REG not available[72] MG-277: 2411085-89-5[73]
Sal-like protein 4 (SALL4) degradation	SALL4, a spalt-like developmental transcription factor, is important for limb development. Thalidomide and derivatives induce degradation of SALL4 - likely reason for the observed birth defects.	Thalidomide: 50-35-1[51] Pomalidomide: 19171-19-8[51] Lenalidomide: 191732-72-6[51]
RNA-binding motif protein 39 (RBM39) degradation	RNA-binding protein involved in transcriptional co-regulation and alternative RNA splicing.	Indisulam: 165668-41-7[74] E7820: 289483-69-8[75] dCeMM1: 118719-16-7[34]
β-catenin degradation	Oncogenic transcription factors remain extremely challenging proteins to target, despite being implicated in multiple diseases.	NRX-252114: 2763260-39-3[27] NRX-252262: 2438637-61-5[27]
Tumor protein p53 stabilization and activation	Acts as a tumor suppressor - regulates cell division by keeping cells from growing and proliferating in an uncontrolled way.	Asukamycin: 61116-33-4[34] Manumycin: 52665-74-4[76]
BCL6 protein degradation	Targeting BCL6 protein is an effective therapeutic approach for treating diffuse large B-cell lymphoma (DLBCL).	BI-3802: 2166387-65-9[77] CCT369260: 2253878-44-1[78]

Table 5. Overview of discovered molecular glues and their applications. Further details on the types of protein degradation can be found at cas.org/molecularglue

Types of protein degradation	Description	Examples: CAS REG numbers
Non E3-ligase molecular glues		
Autophagy mediated protein degradation	Autophagosome-tethering compounds (ATTECs) - type of molecular glue that tether the POI to autophagosomes by direct binding of POI and autophagosome protein LC3.	10O5: 220904-83-6[37] 8F20: CAS REG not available[37] AN1: 486443-73-6[28] AN2: 7758-73-8[28]
Protein-protein interaction stabilizers	– 14-3-3 protein stabilization: A highly conserved class of adapter proteins involved in regulation of several hundred proteins. – MAX homodimer stabilization: mediates various cellular functions such as proliferation, differentiation, and apoptosis. – MEK sub-complexes stabilization: binds MEK but also engages the kinase suppressor of Ras (KSR) at the complex interface.	Raf, p53, Cdc25, Cdk2, and histone deacetylases (HDACs): CAS REGs not available[79] KI-MS2-008: CAS REG not available[80] Trametinib: 871700-17-3[81]
KRAS mutant inhibition	Frequent oncogenic driver in solid tumors, including non-small cell lung cancer (NSCLC) - previously thought to be an "undruggable" target e.g., RM-018 and RM-108-like molecular glues.	RM-018: 2641993-55-5[82] RMC-6291: CAS REG not available[83]
Tubulin polymerization stabilization	Prevent cell division by promoting assembly of stable microtubules especially from β-tubulin heterodimers and inhibit their depolymerization.	Discodermolide: 127943-53-7[84] Paclitaxel: 33069-62-4[85]
PI3K inhibition	Plays a central role in tumor cell proliferation with p110α as the most frequently mutated subunit.	Fusicoccin A: 20108-30-9[86] Epibestatin: 61046-23-9[87] Trametinib: 871700-17-3[81]
FK506-binding protein binding	Engages three target proteins - calcineurin, mTOR, and CEP250 - with specifically interacting different amino acid residues at the binding sites.	FK506: 104987-11-3[88] Rapamycin: 53123-88-9[89] FK1012: 152406-17-2[90]
Natural molecular glue degraders		
Various molecular glue degraders	Some natural compounds that were found to function as molecular glues e.g., Cyclosporin A and voclosporin which bind to cyclophilin 18 (Cyp18)-CsA complex - blocks cytokine transcription in T-cells, and sanglifehrin A which inhibits T- and B-cell proliferation.	Cyclosporin A: 59865-13-3[91] Lupkynis: 515814-01-4[92] Sanglifehrin A: 187148-13-6[93]

Commercial and institutional development of molecular glue therapies and diseases targeted

While many potential molecular glues have been identified, very few have been assessed so far for therapeutic efficacy in the clinic and even fewer have received regulatory approval. A selection of promising companies that have molecular glue therapies in preclinical development are listed in **Table 6**; these are mainly intended for use in a variety of cancers, neurodegenerative, and inflammatory diseases for which there are substantial unmet clinical needs. These companies are mainly based in the US and Europe.

Table 6. Companies with molecular glue therapies in preclinical development

Organization	Highlights
Ranok (Hangzhou, China)	Drug candidate RNK05047 entering clinical trials first half of 2022 for treatment of solid tumors and lymphomas.[94]
Monte Rosa Therapeutics (Boston, MA, USA)	Initiated IND-enabling activities for its lead program targeting GSPT1 for oncology treatment and beyond. IND application to be submitted to the FDA mid-2022. Drug discovery phase for other molecular glues targeting solid/liquid tumors, autoimmune diseases, and blood diseases.[95]
Plexium/Partnered with Amgen (San Diego, CA, USA)	Lead optimization phase for a cereblon molecular glue targeting IKZF2 for the treatment of immune disease and cancer. Drug discovery phase for a disclosed novel E3 ligase molecular glue and also undisclosed partnered molecular glue programs.[96]
Frontier Medicines/Partnered with AbbVie (San Francisco, CA, USA)	Drug discovery phase to develop small molecule covalent drugs against intractable immunology and oncology targets.[97]
f5 Therapeutics (San Diego, CA, USA)	The pipeline of molecular candidates for hepatocellular carcinoma, breast cancer, lung cancer, head and neck cancer, colorectal cancer, gastric cancer, multiple sclerosis, rheumatoid arthritis, nonalcoholic steatohepatitis, and liver fibrosis.[98]
Ambagon Therapeutics/ Partnered with BMS and Merck (San Carlos, CA, USA)	Drug discovery phase with five early discovery oncology treatment compounds. Focusing on targeting gene signaling and expression, disrupting the cell cycle, along with other cancer-causing dysregulations. Ambagon expects to have at least one development candidate by the second quarter of 2023.[99]
Captor (Wrocław, Poland)	Drug candidates for hepatocellular carcinoma and autoimmune liquid tumors.[100]
Amphista Therapeutics (London, UK)	Aims to move beyond use of Ubiquitin E3 ligase cereblon. They will initially focus on cancer treatments, with the possibility of branching out to treat neurological, neurodegenerative, and immunological disease along with other areas of high unmet medical need in the future.[101]
Dunad Therapeutics (Cambridge, UK)	Drug discovery phase utilizing central nervous system accessible therapeutics.[102]
Proxygen/Partnered with Boehringer Ingelheim (Vienna, Austria)	Drug discovery phase treating lung and gastrointestinal cancers.[103]
Neomorph/Partnered with Dana Farber Cancer Institute (San Diego, CA, USA)	Drug discovery phase to advance their molecular glue development pipeline against undruggable targets.[104]
Seed Therapeutics/Partnered with Lilly (New York, NY, USA)	Drug discovery phase with molecular glue pipeline candidates treating cancers, neurodegenerative disesaes, and infectious diseases. Their lead compound targets the KRAS oncogene.[105]
Pin Therapeutics (Seoul, South Korea)	Drug discovery phase.[106]
Venquis Therapeutics, (San Diego, California, USA)	Drug discovery phase for cancer and degenerative diseases.[107]
IRB Barcelona/Partnered with Almirall (Barcelona, Spain)	Drug discovery phase for skin disease treatment.[108]
Shanghai Dage Biomedical Technology Co., Ltd. (Shanghai, China)	Pipeline of molecular glues addressing targets for cancers, inflammatory disease, and metabolic disease. Lead optimization phase for oncology molecular glue candidates.[109]
Triana Biomedicines (Waltham, MA, USA)	Launched recently in April 2022 to establish a rationally designed molecular glue pipeline to treat inadequately addressed diseases.[110]
Evotec/Partnered with BMS (Hamburg, Germany)	Drug discovery phase to develop pipeline of molecular glue degraders.[111]

Several other companies have a promising range of molecular glue compounds in various stages of clinical development that aim to treat many different solid and liquid tumors, inflammatory conditions, and autoimmune diseases, such as systemic lupus erythematosus (**Figure 8**). Some of these companies are developing molecular glues against single diseases or therapeutic areas. Others, such as Bristol Myers Squibb and Eisai, are developing them against multiple disease indications.

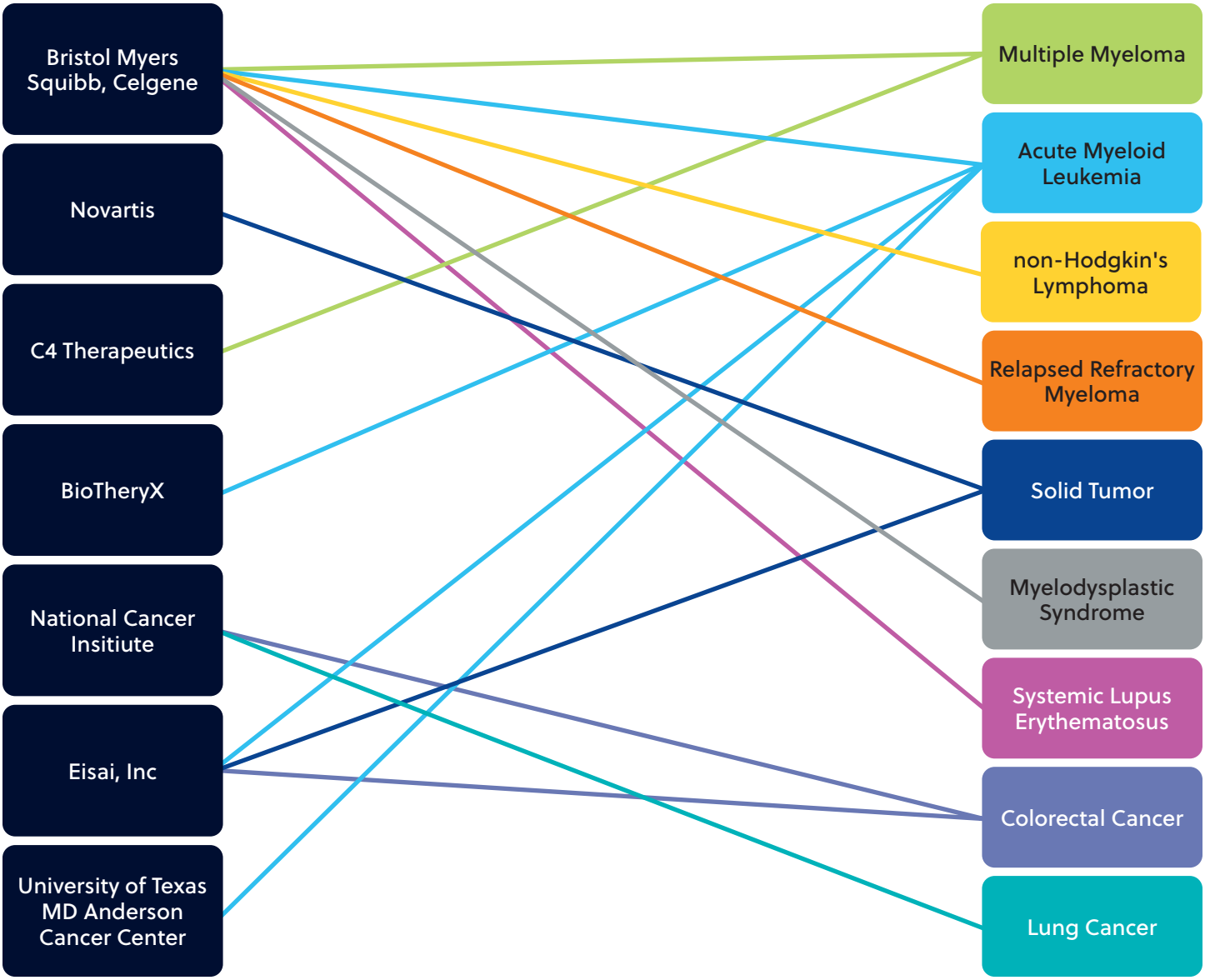


Figure 8. Companies and research organizations with discovered molecular glues in the clinical development pipeline, alongside the diseases they treat

Recent notable molecular glue patents

The CAS Content Collection searches indicated a growing number of patents related to molecular glues. Most of these cover large libraries of compounds and their synthesis routes with in vitro and in vivo testing results. Some of the recent and noteworthy patents and their originators include WO 2021/053555, which was filed by Novartis (Basel, Switzerland) for 18 compounds that bind to and alter the specificity of the CRBN complex to induce ubiquitination and degradation of an unspecified protein. Another patent, WO 2021/249517, was filed by National Institute of Biological Sciences (Beijing, China) for 31 molecular glues which trigger the poly-ubiquitination and degradation of cyclin K creating a modified CDK12 protein binding DDB1 of DDB1-CUL4-RBX1. Patent WO 2020/006264, filed by the Dana-Farber Cancer Institute (Boston, MA, USA), is for 61 ligands to CRBN with immunomodulatory activity. Additionally, patent WO 2008/115516 has been filed by the BMS/Celgene Corporation (Summit NJ, USA), for 4′-O-substituted isoindoline derivative compounds, while WO 2021/126805 has been filed by Orionis Biosciences (Gent, Belgium) for an agent to treat disease through the recruitment and/or ubiquitination and/or degradation of proteins, such as argininosuccinate synthetase. Additional molecular glue-related patents can be found at cas.org/moleculargluе.

Summary and conclusion

Induced-proximity TPD has recently emerged as an approach to drug discovery and development, demonstrating huge potential.[1–3] Over the past decade, PROTACS and molecular glues have created much excitement and interest from numerous pharmaceutical companies and research institutions, which have recognized their therapeutic possibilities.[25,32,77,89] Molecular glue-type binding is a new modality option in which the actions of E3 ligases are reprogrammed by monovalent small molecules. This approach is creating new routes for the degradation of otherwise undruggable protein targets in numerous serious diseases.[4,5] Searches of the CAS Content Collection show that inducing protein degradation via these small molecules is attracting widespread and increasing interest as a promising therapeutic paradigm. The molecular glues identified in the CAS analyses predominantly use cereblon E3 ligase but there is much effort to move beyond this one approach to harness alternative enzyme systems. This trend may significantly expand the range of molecular glues available and potentially increase their efficacy.

The understanding of molecular glue modes of action and design principles is incomplete; thus, advanced research is essential to better design and exploit these compounds.[32,35,37,89] The current methods of novel molecular glue discovery have largely relied on intensive high-throughput screening, followed by systematic validation.[32]

The lack of efficient rational design strategies may hold back the development of new and more efficient compounds and their assessment and validation for varying indications. The development of new computational tools to model and predict the binding mode of molecular glue-induced protein-protein interaction complexes could be a valuable approach for virtual screening and a structure-based rational design of new molecular glues.[45] Advances in crystallization and improved understanding of protein docking further improve molecular glue development.[27,87,89] In addition, the emergence of DECL technology and its further development in compound design provides the opportunity to rapidly screen billions of candidate molecules for target protein binding.[61,62,65] All these developments are collectively enabling a transition from serendipity to rational design.[34]

Overall, published articles and patents found in the CAS Content Collection indicate a rapidly advancing knowledge of the mechanisms of the molecular glue operation and number of potentially useful compounds with therapeutic properties. Elucidating the structural biology and medicinal chemistry of these compounds and the proteins they bind to are of utmost importance in progressing the targeted protein degradation strategy used by molecular glues into valuable and practical applications in the clinic.

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