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# Opportunities in proximity modulation: Bridging academia and industry

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## SUMMARY

In the past decade, exciting therapeutic strategies to harness the ubiquitin-proteasome system (UPS) for degradation of target proteins have emerged. Proximity-inducing modalities are at the center of these strategies and act by modulating protein-protein interactions. While we are still learning to harvest this approach, it holds tremendous promise for developing treatments for hitherto undruggable proteins. Here, we discuss how academic efforts and academic-industrial collaboration have advanced the development of therapeutic modalities based on the principle of proximity induction. We make a case for forming a global academia-industry alliance to enhance access to training and expertise while accelerating innovation and translation from ground-breaking ideas to proof of concept in the clinic.

## INTRODUCTION

Proximity induction is a powerful mechanism utilizing small molecules to reprogram cellular machineries and trigger novel biological functions. The pharmaceutically best understood outcome of proximity induction is targeted protein degradation (TPD). TPD selectively removes disease-relevant proteins by exploiting cellular degradation systems. It relies on small molecules to mediate protein-protein interactions between target proteins and effectors such as E3 ligases, bringing the two in close vicinity and altering their specificity. This mode of action provides exciting opportunities to expand the target space beyond what is druggable now.

Currently, the most pursued modalities in the TPD field are proteolysis-targeting chimeras (PROTACs[1]) and molecular glue degraders (MGDs). PROTACs are bifunctional small molecules that bind E3 ligase and target through separate moieties, without the need for the two proteins to interact directly (Figure 1). In contrast, MGDs are monovalent and act as an adhesive—they bind, often weakly, to only one of the two partners before orchestrating a ternary complex with the second partner and, hence, depend on direct interactions between target and effector. New types of proximity-modulating strategies that go beyond traditional PROTAC and MGD principles continue to rapidly emerge, as well as exciting applications of proximity induction beyond degradation (Table 1).

While mechanisms for intracellular protein degradation via the ubiquitin-proteasome system (UPS) had been known for some time, earning the Nobel Prize for Chemistry in 2004, the ability to hijack this system for therapeutic benefit long remained elusive. Over the past decade, however, crucial advancements in the development of protein degraders as therapeutic modality have energized the TPD field. A small but rising number of clinical trials[2,3] highlights the advantages of PROTACs over conventional inhibitors (Table 1) raising significant interest from the pharmaceutical industry. Similar to other ground-breaking new modalities such as mRNA therapeutics, academic scientists have been important drivers of innovations in the field. In the hunt for innovation, drug discovery has undergone a substantial shift. Nowadays academic institutions play an increasingly critical role in the early phases of the value chain, with an estimated 30% of approved small-molecule entities having been developed with contributions of academic scientists or through companies founded by publicly funded academic inventors.[4] The challenge remains; however, how academic discoveries can be best translated into patient benefit.

Discoveries from the TPD community have highlighted the potential for fruitful collaboration between academia and industry to de-risk and push forward this promising therapeutic modality. This exemplifies how academia and industry can leverage their respective strengths and acknowledge each other's limitations, while advancing new therapeutic strategies and tackling global challenges. For both PROTACs and MGDs, significant concerns were voiced early on with respect to their broad clinical applicability. For PROTACs, these were mainly related to physicochemical properties and high molecular weight. For MGDs, doubts

 

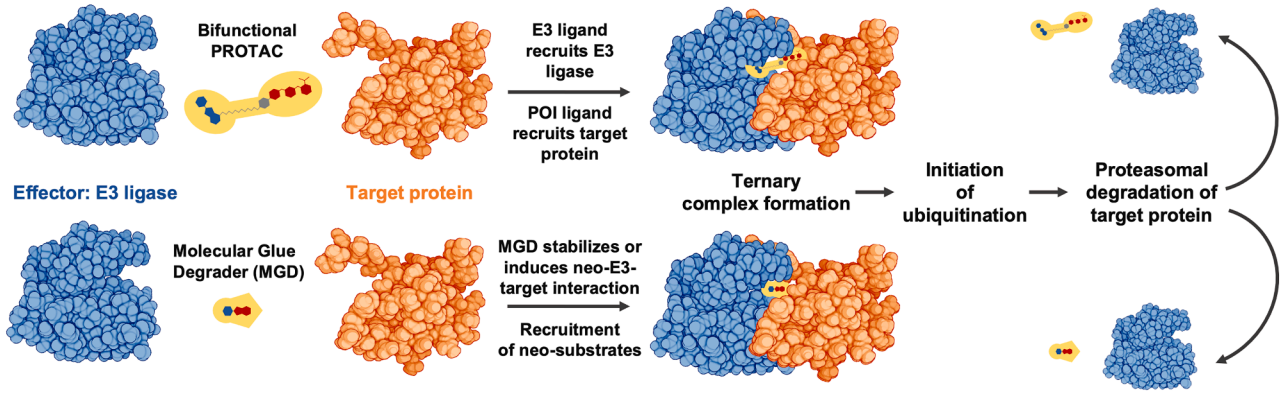


**Figure 1. Mechanism of action of PROTACs and MGDs**
Both modalities form a ternary complex with target protein and an E3 ligase that initiates target protein ubiquitination, followed by proteasomal degradation (created with elements from BioRender.com/auxdzv5).

were raised if the success of clinical-stage glue degraders—all identified by serendipity—could be repeated by rational discovery strategies. De-risking and proving principles for TPD has relied largely on academic efforts, helping to boost it as a promising mode of action.

## EVOLVING WORLD OF PROTACs: FROM CONCEPT TO DRUG

In 1999, a patent proposed the idea that a bifunctional small molecule might allow recruitment of a protein to the UPS to trigger targeted degradation.[5] In 2001, this idea was put into first practice through a bifunctional molecule named "PROTAC," comprising a high-affinity covalent ligand for MetAP-2, joined via a linear linker to a peptide binder of the $SCF^{\beta\text{-}TRCP}$ E3 ligase.[6] This PROTAC mediated ubiquitination of MetAP-2 *in vitro* and in *Xenopus laevis* eggs.[6] This and other early PROTACs, while providing proof of concept, were peptidic in nature and had poor drug-like properties, limiting their further development. It took another decade until much smaller, high-affinity, and highly specific small-molecule ligands to von Hippel-Lindau (VHL)[7] and a second E3 ligase, the Cullin4 RING component cereblon (CRBN) were developed.[8,9] These E3 ligands enabled design of significantly improved PROTAC molecules with respect to degradation potency, speed, and selectivity profiles. Four papers published in spring of 2015 document the ground-breaking nature of this advancement[10–13] and testify the early roots of academic-industrial collaboration in this field: while many early efforts were purely academic driven, one involved Arvinas, a biotech spin-out of Yale University, others a collaboration between GSK, Cellzome, Arvinas, Novartis, and academic institutions. As a news article stated—it was "prime time for PROTACs."[14]

**Table 1. Advantages of PROTACs and MGDs over conventional small-molecule inhibitors**

| |
|---|
| Catalytic mechanism of action (sub-stoichiometric amounts needed, lower doses, potentially lower toxicity) |
| Targeted degradation of disease-relevant target proteins rather than transient inhibition (prolonged biologic effect, potentially lower doses needed) |
| No high affinity binding needed (especially for MGDs) |
| Dual layer of specificity (PROTACs) |
| Tissue specificity may be achieved by utilizing tissue-specific E3 ligases |
| Applicable to the undruggable proteins lacking accessible binding sites |
| Less sensible to point mutations causing resistance mechanisms |

The PROTAC field has since continued to advance at a fast pace, with major innovations coming from both academia and industry. An ever-increasing number of intracellular target proteins have been degraded with PROTACs, and compounds are currently tested in clinical trials for cancer and other indications. Diverse discovery chemistry approaches are pursued, from rational design approaches based on structure[15] to automated chemical synthesis and high-throughput screening of PROTACs directly in cells in a "direct-to-biology" strategy.[16] Chemistry creativity has expanded functionality to trivalent PROTACs and beyond,[17] macrocyclization,[18] light-activation,[19] and other pro-drug strategies,[20] covalency at the E3 ligase and target side,[21,22] and conjugation of degraders as cytotoxic payload for degrader-antibody conjugates (DACs).[23] Structural and mechanistic understanding of PROTAC function has exploded from pioneering crystallographic studies of VHL-/CRBN-based ternary complexes[24,25] to more recent cryoelectron microscopy (cryo-EM) studies involving whole CRL complexes engaged with both target protein and E2-conjugating enzymes captured in the process of ubiquitin transfer.[26,27] Several advantages of PROTACs over inhibitors arise from their unique proximity-inducing mechanism (Table 1).

To degrade hitherto inaccessible targets, PROTAC-recruitable protein fusion tags for inducible degron strategies were developed, such as dTAG[28] and BromoTag,[29] that enable a fast probing of protein's biological function and are widely used for biomedical research in cell lines and *in vivo*. As the target space expanded, bio-PROTACs and related protein-based approaches have allowed the recruitment of different E3 ligases.[30]

The expansion of the clinically relevant E3 ligase space is, however, one of the big challenges in the field. More than 600 E3 ligases exist, yet the structure, dynamic regulation, and function of most remain largely uncharacterized. Major efforts have been directed toward the design of novel E3 ligase ligands,[31] albeit to date these efforts have led to only a few effective PROTAC degraders.[32,33] All current PROTACs in the clinic where the E3 ligase is known are either CRBN or VHL based, as are most active molecules reported in literature. Considering that several companies have not disclosed the E3 ligases recruited by their compounds, this may soon change. E3 ligase abundance in target tissue is of course a prerequisite for degrader efficacy. At the same time, tissue-specific expression of yet unexploited E3 ligases holds potential for fewer side effects. Mapping the human E3 ligome is an ongoing, time intensive, and complex effort largely performed in academic laboratories. Industrial-academic partnerships in this area could substantially accelerate the speed of translating this knowledge into innovation in drug development pipelines.

Despite all voiced concerns, PROTACs have been optimized and shown to be orally bioavailable and efficacious, from animal models to human patients, and to penetrate and be active in the central nervous system (CNS) and in the brain.[34] As PROTACs need to bind both E3 ligase and target protein, their rise has reignited efforts to discover novel small-molecule-binding ligands for proteins, including biophysical fragment/ligand screening,[35] fragment profiling in intact cells,[36] and DNA-encoded library (DEL) screening.[37] In summary, the PROTAC field remains bright and wide open for innovation in many aspects from fundamental understanding of their mechanisms to advancing their design, development, and delivery as transformative medicines.

## MGDs: FROM SERENDIPITY TO INTELLIGENT HUNTING AND DESIGN

While the term "molecular glue" was coined in the early 1990s, referring to microbial macrolides (such as FK506, cyclosporin, and rapamycin),[38] the mechanism of MGDs was first discovered through studies on the phytohormone auxin that regulates gene expression by mediating degradation of transcriptional repressors.[39]

The entire concept gained pharmaceutical relevance when the biological mechanism of thalidomide and analogs (IMiDs, immunomodulatory imide drugs) was revealed—long after the first use of IMiDs in humans. Seminal, academic-led studies first uncovered that thalidomide targets E3 ligase component CRBN,[8] followed by showing that IMiD binding to $CRL4^{CRBN}$ leads to ubiquitination and degradation of, among others, transcription factors IKZF1/3, rather than inhibition of CRBN.[8,9,40,41] This was followed by studies that provided structural insights and first evidence of a broad scope of potential neosubstrates.[42] In parallel, some aryl sulfonamides, such as indisulam, were found to hijack $CRL4^{DCAF15}$ and degrade the splicing factor RBM39.[43,44] Together these findings hinted at MGDs being more frequent than initially thought. Importantly, these first MGDs, whether natural or synthetic, shared appealing features such as the degradation of some target proteins without binding pockets and the lack of affinity for at least one of the two proteins involved. In addition, IMiDs' long-standing clinical success in treating blood cancers already validated the therapeutic potential of glue-mediated degradation strategies. Yet, it remained unclear if MGDs could be discovered by rational approaches.

Proof of principle for rationally tuning degradation specificity by adapting the glue compound emerged from $CRL4^{CRBN}$ and its degradation of diverse zinc-finger substrates, ultimately paving the way for development of compounds that specifically caused IKZF2 degradation.[45,46] Subsequent approaches illustrated that MGDs are not only discovered fortuitously.[47,48] For example, in 2019 biochemical screening was coupled with structure-based optimization to find MGDs that restore the interaction of $CRL1^{\beta\text{-}TRCP}$ with mutant β-catenin.[49] Soon after, other studies reported the discovery of structurally different cyclin K (CycK) MGDs.[50–52] In 2021, new CRBN-based MGDs were rationally discovered by positive selection screens to identify degraders of IKZF1.[53]

Molecular understanding of IMiDs and aryl sulfonamides raised the question whether other E3 ligases could be recruited via MGDs. A Novartis Biomedical Research team explored whether known VHL ligands harbor MGD potential.[54] This led to the surprising finding that a complex of VHL, Elongin B, and Elongin C (VBC) could be glued to the protein cysteine dioxygenase 1 (CDO1) in a compound-dependent manner. Other approaches successfully explored dynamic tracing of ligase abundance[55] or cell morphological profiling[56] for MGD discovery. It is noteworthy that these initial proof-of-concept experiments allowed to parse fundamental insights in ligase regulation into high-throughput assay formats without focusing on a predefined target space.

We have seen innovation in target-focused MGD discovery approaches, which is an area driven so far largely by industrial-academic collaborations between Broad/Harvard scientists and Novartis Biomedical Research. Leveraging the power of DEL selections, cooperative, VHL-dependent degraders of BRD4 and BRD9 could be identified.[57,58] These compounds structurally resembled more closely PROTACs than conventional MGDs. What remains to be seen is how much additional chemical optimization will be required in ensuing hit-to-lead campaigns and to which extent the relatively high molecular weight of these compounds can be reduced. Another strategy for target-centric MGD discovery is to generate chemical derivatives of target binders (warheads), thereby chemically adapting to the surface topology of the target protein. This has led to novel, highly cooperative degraders of the gene control factor ENL.[59] Some parts of the molecule that form the covalent anchor and extrude from the binding pocket appear to be transferrable and can be grafted onto a suite of structurally varied inhibitors with retained target degradation potency.[60,61]

In addition to focused strategies for identifying MGD candidates, mechanistic studies of serendipitously identified degraders have often revealed unanticipated and differentiated molecular mechanisms of action. The BCL6 degrader BI-3802[62] was shown to function through drug-induced polymerization of BCL6 into filaments, thereby facilitating their degradation by the E3 ligase SIAH1.[63] The monovalent BRD2/4 degrader GNE-0011,[64] a propargyl-amine analog of BET inhibitor JQ1, and later-designed MMH1 and MMH2 analogs, were shown to

**Table 2. Proximity-inducing modalities that reprogram distinct cellular machinery to achieve a broad range of biological outcomes**

| Recruited effectors | Modalities | Targets | Reprogrammed mechanisms | Biological effect |
|---|---|---|---|---|
| E3 ubiquitin ligase | proteolysis-targeting chimera (PROTAC)<br>molecular glue degrader (MGD)<br>degrader-antibody conjugate (DAC)<br>molecular glue-antibody conjugate (MAC)[69] | intracellular proteins | ubiquitination | degradation |
| Deubiquitinase | deubiquitinase-targeting chimera (DUBTAC) | intracellular proteins | deubiquitination | stabilization |
| Kinase | phosphorylation-inducing chimeric small molecule (PHICS)[70] | intracellular proteins | phosphorylation | modulation of signaling pathways |
| Phosphatase | phosphorylation-targeting chimera (PhosTAC)[71]<br>phosphatase-recruiting chimera (PhoRC)[72]<br>affinity-directed phosphatase (AdPhosphatase)[73] | intracellular proteins | dephosphorylation | modulation of signaling pathways |
| Histone acetyltransferase<br>Lysine acetyltransferase | acetylation-targeting chimera (AceTAC)[74]<br>acetylation tagging system (AceTAG)[75] | intracellular proteins | acetylation | gene regulation |
| Lysosomal-targeting receptors (LTRs) | lysosome-targeting chimera (LYTAC) | extracellular proteins | lysosomal trafficking/ endocytosis | degradation |
| LC3/GABARAP | autophagy-targeting chimera (AUTAC)<br>autophagosome-tethering compounds (ATTECs) | intracellular proteins or organelles | autophagy | degradation |
| Cell surface/ membrane-bound E3 ligases | proteolysis-targeting antibody (PROTAB) | membrane-associated proteins | ubiquitination | degradation |
| Transcription factors or cancer drivers | transcriptional/epigenetic chemical inducers of proximity (TCIPs) | epigenetic modifiers | localization | cell death signaling |
| Diverse | small-molecule-nanobody conjugate inducer of proximity (SNACIP) | intracellular proteins/ structures | dimerization | relocation, signaling, transport, ferroptosis |

leverage the surface complementarity between BRD2/4 and the E3 ligase DCAF16 to covalently cross-react and consequently induce BRD2/4 degradation.[65] This approach of "template-assisted covalency" could be expanded to stabilize and functionalize additional interactions between targets and E3 ligases where an underpinning surface complementarity is given, but where interactions are too transient to cause target ubiquitination in absence of the compound.[66] A complementary strategy to leverage such intrinsic protein-E3 ligase interactions is via intramolecular bivalent glues (IBGs),[67] which function by bridging two domains of the target protein in *cis*, thereby nucleating a basal E3 ligase interaction. The common denominator of these studies is that they frequently rely on integrating unbiased approaches, such as genome-scale CRISPR screens, with focused biochemical reconstitutions and structural and biophysical investigations of the underlying ternary complex.

In summary, MGDs remain a vibrant and expanding arena for innovation, extending from basic molecular insights to the development of transformative medical treatments. Yet, the challenge to design MGDs tailored for specific targets remain at the cutting edge of the field, with this clearly being an area where early-stage academic-industrial collaborations will be highly synergistic.

## NEW MODALITIES OF INDUCED PROXIMITY

In recent years, several strategies for direct-to-proteasome degraders have emerged. A study from Genentech suggested a hitherto unknown TDP mechanism involving direct recruitment of target proteins to the 26S proteasome without requiring E3 ligase-dependent ubiquitination.[68] An improved understanding of the fundamental regulation of the 26S proteasome will advance direct degradation concepts that "cut out the middle man." Rapid benchmarking of this and other emerging modalities again offers exciting opportunities for joint industrial-academic collaborations.

Expanding the concept of proximity induction beyond TPD, other modalities have emerged that recruit different types of enzymes to a target protein, thereby achieving other defined biological outcomes, tailored to specific therapeutic needs (Table 2). They could, for example, enhance protein levels and/or activity, or modulate other post-translational protein

modifications (PTMs). Moreover, innovative proximity-inducing approaches allow for targeting protein populations such as extracellular and cell surface proteins, thereby further expanding the therapeutic scope.

A team from UC Berkeley and Novartis Biomedical Research published deubiquitinase-targeting chimeras (DUBTACs) as a strategy designed to selectively stabilize proteins by harnessing the cell's deubiquitination machinery.[76] DUBTACs function similarly to PROTACs, but recruit a deubiquitinase instead of an E3 ligase. By removing ubiquitin chains from targeted proteins, DUBTACs help prevent their degradation, making the approach particularly useful in diseases where protein loss or dysfunction is a factor.[77,78]

While PROTACs and DUBTACs modulate the ubiquitination and thus stability of target proteins, other strategies have emerged to manipulate PTMs such as phosphorylation or acetylation of proteins, thereby potentially altering protein activation status transiently and precisely control target protein activity, influencing critical cellular processes such as apoptosis or proliferation (Table 2). Similarly, small molecule-nanobody conjugate inducers of proximity (SNACIPs) have been developed to redirect specific endogenous proteins to a desired intracellular location[79] and transcriptional/epigenetic chemical inducers of proximity (TCIPs) to (re-)direct endogenous transcriptional regulators, such as transcriptional kinases or transcription factors, to therapeutic target genes.[80,81] Such approaches demonstrate the potential of induced-proximity technology for precise spatial control over endogenous protein activity, impacting processes such as cell division and signaling.

Targets can also be directed to the lysosome to achieve efficient degradation, thereby expanding the scope beyond proteins to other cellular structures. Substrates can reach the lysosomes by endocytosis or autophagy—both pathways are exploited for proximity-induced degradation. For example, lysosome-targeting chimeras (LYTACs) specifically target extracellular and membrane proteins by recruiting lysosome-shuttling receptors, such as cation-independent mannose-6-phosphate receptor (CI-M6PR) or transferrin receptor (TfR), to a target protein facilitating its lysosomal delivery.[82–84] Additionally, LYTACs have been developed for recruiting asialoglycoprotein receptors (ASGPRs)[85] and insulin-like growth factor 2 receptors (IGF2Rs).[86]

Autophagy-targeting chimeras (AUTACs) or autophagosome-tethering compounds (ATTECs) harness autophagy to target large structures like aggregated proteins, organelles, or pathogens to the lysosome. AUTACs label substrates with an "S-guanylation" marker, promoting Lys63-linked polyubiquitination recognized by cellular autophagy receptors, which then recruit the autophagosome.[87] On the other side, ATTEC approaches are using LC3/GABARAP binders to induce proximity of substrates to the autophagy-lysosome system leading to their degradation).

An alternative approach for degrading proteins present in the cell membrane is the use of proteolysis-targeting antibodies (PROTABs), which employ hetero-bispecific chimeric antibodies designed to connect E3 ligases with undesired cell surface proteins, such as oncogenic receptors.[88,89] This interaction promotes the oligomerization and ubiquitylation of these proteins, facilitating their internalization and degradation via the lysosomal pathway. PROTABs are not only highly specific but also effectively bypass the challenge of intracellular compound delivery and offer a method to degrade cell membrane proteins that are considered undruggable.

Leveraging the well-established concept and modality of antibody-drug conjugates (ADCs), DACs take advantage of the specificity of antibodies, coupling them with heterobifunctional degraders.[90] This targeted delivery not only minimizes collateral damage of the cytotoxic agent to healthy cells but also can enhance compound penetration and protein degradation in the targeted tissue, with preclinical studies demonstrating up to a 1,000-fold improvement in efficacy and therapeutic windows. Several DACs are progressing through clinical stages.

The major next challenge for new tools inducing proximity lays in developing specific chemical ligands to recruit target proteins to a chosen mediator or effector (e.g., E3 ligase, DUB, kinase, and phosphatase) while retaining catalytic activity of the latter.

## AI MEETS PROXIMITY INDUCTION

Designing heterobifunctional compounds remains challenging, especially when aiming for oral bioavailability.[91] Therapeutic application of PROTACs has initially been limited by issues like poor cell permeability/uptake, suboptimal pharmacokinetics and pharmacodynamics associated with their high molecular weight, as well as the restricted scope of addressable targets. However, recent advancements have addressed many of these limitations, and numerous PROTACs now demonstrate oral efficacy and even CNS/blood-brain barrier penetration, expanding their potential for treating CNS disorders.[92,93] While progress has been substantial, some challenges persist, particularly in optimizing drug-like properties, diversifying target option, and confirming or elucidating new bona fide mechanisms but also regarding the identification of effectors (ligases, phosphatases, etc.) to enhance therapeutic versatility.

Since its inception, the field of proximity induction has been highly multi-disciplinary, involving chemical and structural biology, biochemistry and cell biology, pharmacology and medicinal chemistry, as well as computational biology. Discoveries will continue to emerge from phenotypic cellular screens and structural elucidations, driven by increasing insights into compound-enabled protein-protein interactions. The extent to which these are hardwired and can be reprogrammed specifically with small-molecule compounds remains at the center of the field. For leveraging the growing body of experimental data, however, computational approaches are becoming more than just powerful acceleratory tools, with first applications for MGD discovery already emerging by virtually mining the CRBN target space.[94] AI/machine learning (ML)-driven platforms are being increasingly applied to drug design and are thus expected to have a significant impact on the fields of TPD and proximity induction as well. Virtual screening efforts, *in silico* prioritization of E3-target pairs, generative models for ligand design, AI and ML models interpreting wet lab screening data, AI-aided ligand prediction, and hit identification all are already accelerating discoveries.[95–97]

AlphaFold2 was already successfully leveraged for computer-aided design of endocytosis-triggering binding proteins

(EndoTags).[98] Within the fast-evolving landscape of computational tools such as AlphaFold3 or Boltz-2, this area is sure to gain even more momentum.[99,100] Synergy of computational and experimental approaches is likely to play an important role in advancing discoveries in the field. Integration of additional large-scale datasets into multi-modal foundation models will further refine our ability to predict actionable protein interfaces and to design molecular glues that stabilize them for therapeutic applications. Predicting dynamics of protein interactions, however, remains a major challenge that is at the cutting edge of current simulation capabilities. In the future, emerging technologies such as time-resolved cryo-EM and dynamics-informed AI may improve the quality of these predictions. Given the wealth of non-public structural, dynamic small-molecule data in industry, this would be particularly fruitful area for academia/industry collaboration.

## UNITING FORCES FOR ACCELERATED TRANSLATION

Over 10 years after the pivotal disclosures of VHL- and CRBN-based ligands for PROTACs and the glue-based mechanism of action of IMiDs, clinical validation is well underway, and over 90 biotech and large pharma companies claim to operate in the broad field of TPD. Looking back, academia-industry collaborations have tremendously accelerated the field, while an enormous amount of venture funding fueled R&D efforts in emerging companies. Academic TPD hot spots developed into vibrant ecosystems driven by fruitful collaborations, attracting more investment to achieve the shared goal of bringing the promising action mode into the clinic. Big biopharma deals followed rapidly and exponentially, allowing numerous spin-out companies to advance through clinical phases and enabling large pharmaceutical companies to capitalize on the opportunity.

The strength of industrial drug discovery lies undoubtedly in its vast experience, its professional infrastructure, the resources available, and the high level of scrutiny ultimately needed to get a drug to patients. It is after all typically the biopharma industry that advances drugs through the clinic to the bedside. Yet, failure rates in drug discovery are high in all phases of the preclinical and clinical development process. Particularly in cases with no existing clinical proof of concept, the risk of potential failure, wasting precious time and resources, is a substantial threat to any business case.

Academic research has historically been slowed down by limited resources and the range of expertise required to drive new modalities forward, yet it offers an important advantage that industry usually lacks: having the freedom to explore previously untrodden experimental avenues as well as having the required time to pursue them. This provides a high potential to develop disruptive ideas. Therefore, it is not surprising that academic-industrial interests came together in many flavors to drive the TPD field forward: by joint discovery platforms or partnerships (e.g., between Yale/University of Cambridge/GSK, between Boehringer Ingelheim/University of Dundee, UC Berkeley/Novartis, Dana-Farber Cancer Institute/Deerfield management, etc.), by spinning out or reorienting previously spun-out companies (e.g., Arvinas/Yale, Nurix Therapeutics/UCSF and UC Berkeley/UC San Francisco, C4 Therapeutics/Harvard, Monte Rosa Therapeutics/Institute of Cancer Research/Cancer Research UK, Friedrich Miescher Institute/Novartis, Proxygen/CeMM, Amphista Therapeutics/Dundee), or by pulling heavy academic advice into venture-funded companies (e.g., Kymera Therapeutics, VantAI, Zenith Therapeutics, Lyterian Therapeutics). While these efforts were mostly based in the US, hotspots of academic-industrial collaboration in Europe emerged early on in Vienna, Dundee, and Basel, and more recently Barcelona, Frankfurt, and Lausanne came on board by accruing a critical mass of academic expertise, infrastructure, institutional, and third-party funding. Research efforts into TPD at these European sites are highly complementary with a distinct focus and expertise at each hub (Figure 2). A shared feature of all sites, however, is the existence of a broad range of tightly integrated academic disciplines needed to succeed in understanding and advancing proximity-inducing drugs, from medicinal chemistry, structural biology, and biophysics to biochemistry, cell biology, bioinformatics, and preclinical capabilities.

The lineup of PROTACs and MGDs advancing through clinical trials[2,3] highlights the effectiveness and impact of these collaborative ecosystems. The insights generated by academic mechanistic research, e.g., on the action of IMiDs, have also helped to better understand how undesired off-target effects can potentially be addressed.[101,102]

## ESTABLISHING AN ACADEMIC-INDUSTRY ALLIANCE

Individual collaborations between scientists working at academic hubs have been highly productive in the past, proving that the entire TPD community would benefit from tightening the so-far loose links between the different centers. Until now, however, there have not yet been large-scale international consortia to facilitate efforts and fuel innovation in TPD and the broader field of proximity induction. The initiation of such networks is a natural task of academic hubs and different highly successful role models exist in other areas of biomedical research. The Cancer Dependency Map (DepMap) Consortium is a public-private partnership run by the Broad Institute (Cambridge, USA) dedicated to systematically catalog cancer vulnerabilities and providing the research community with key datasets as well as analytical and visualization tools. Industry partners can nominate compounds for screening and get access to the portal for interrogating their private datasets.

EUbOpen was a public-private partnership funded under the EU Innovative Medicines Initiative (IMI) from 2020 to 2025 with the main objective to assemble an open access chemogenomic compound library and establish an infrastructure to identify and characterize chemical probes and binding ligands with a focus on E3 ubiquitin ligases.

EU-OPENSCREEN was established as a European Research Infrastructure Consortium (ERIC) in 2018, integrating high-capacity screening resources across nine European countries, providing chemical biology tools and data resources for early-stage drug discovery. For collaborations with industry, a pre-competitive open innovation model is used. The consortium itself has been a partner in numerous EU-funded projects.

To fully realize the benefits of the still largely uncharted space of proximity induction and develop needed technologies,

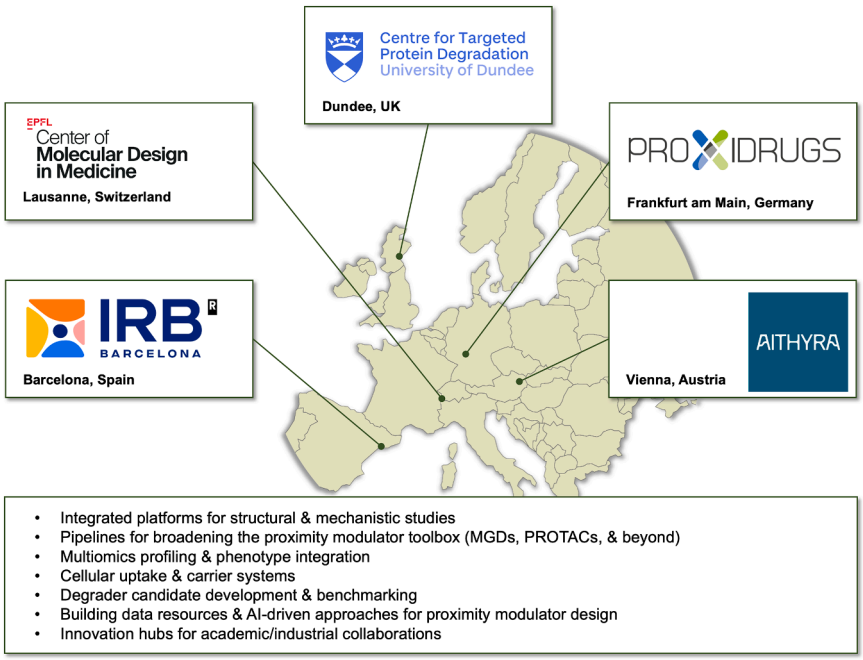


**Figure 2. Founding members of a multi-center academic alliance sharing expertise to train future scientists and explore new therapeutic modalities.**

The network fosters innovation in proximity induction. By uniting experts in academia and industry, it aims to accelerate translation and connect researchers in Europe and beyond.

platforms, and databases, we see similar exciting opportunities for global collaborative alliances, where academics across disciplines and countries join forces, together with industrial scientists and founders of spin-off companies, with the purpose of accelerating early drug discovery, technology transfer, and educating the next generation of researchers. As outlined above, looking back into the history of the still young field of TPD and proximity induction, there are multiple examples supporting the validity of such an approach. As a field, we have already embraced many initiatives—best-practice guidelines, workshops, conferences, webinar series, networking groups (e.g., the "Women in TPD and Induced Proximity" initiative)—that can serve as stepping stones to catalyze professional alliances.

While it is essential to maintain the established close ties within each of the regional ecosystems, connecting academic centers across regions opens opportunities for the expansion of the broader field of proximity induction. Especially at early stages of the discovery cycle, the sharing of valuable resources, information, and expertise will deliver significant benefits to all partners involved and allow for the development of innovative concepts and expansion of research capabilities. For example, by leveraging and co-developing digital and experimental platforms, these collaborations can help promote novel drug modalities across the field. In addition, the integration of academic insights into the drug discovery process can be particularly valuable for emerging drug modalities that require specialized knowledge.

Looking ahead, we envision to go far beyond our own current efforts and engage with the broader community within and beyond Europe. In a first step, we aspire to secure both public and private funding to better connect our relevant centers and interested groups.

We envision this model to unify academic strengths and ensure that academic drug discovery remains a highly attractive partner. Such a multi-center network could go significantly further in developing modalities and has the combined resources and expertise akin to a medium size pharma company. The goal of this network would not be to develop market-ready drugs, or compete with industry, but to share resources and knowledge to excel at our core tasks: training the next generation of researchers and scientific leaders, exploring innovative therapeutic approaches, and ensuring a smooth transfer into application. Exploratory bench time, in the end, is a key strength of academic research. Many novel approaches require prolonged exploration and multiple angles to assess their viability, and academic models and alliances are well positioned to explore these. We envision that these alliances will be particularly productive in developing needed technological approaches and integrating existing platforms, e.g., in effector-target matching (wet lab and *in silico* driven); in benchmarking novel effectors, ligands, compounds, and assays; in exploring alternative modes of proximity induction; and in developing *in vivo* models, e.g., to study mechanism of transport across biological barriers.

In initiating such an alliance, we are driven by our common understanding of academic constraints, as well as benefits/rewards emerging from spinning out and collaborating with private entities to create a vibrant ecosystem. Such ecosystem will favor discoveries that frequently only materialize at a certain scale. Moreover, such an alliance will have a potential to bring together the best from both worlds (academia and industry) leading to more efficient development of new therapeutics and their successful clinical use. We call upon colleagues from both academia and industry to join the effort.

## AUTHOR CONTRIBUTIONS

Conceptualization and writing, A.C., I.D., K.K., C.M.-R., N.H.T., and G.E.W.

## DECLARATION OF INTERESTS

I.D. is a founder/shareholder of Vivlion GmbH and a member of its scientific advisory board. I.D. is a member of the scientific advisory board of the Boehringer Ingelheim Foundation, the expert committee (for international research leader grants) of the Novo Nordisk Foundation, and of the advisory board of *Cell* and *Molecular Cell*. I.D. was a founder and consultant of Caraway Therapeutics Inc. The Mayor-Ruiz lab has received or receives research funding from Almirall and Aelin Tx. C.M.-R. is part of the SAB of Avammune Tx. G.E.W. is scientific founder and shareholder of Proxygen and Solgate Therapeutics and shareholder of Cellgate Therapeutics. G.E.W. is on the Scientific Advisory Board of Proxygen and Nexo Therapeutics. The Winter laboratory has received research funding from Pfizer. The A.C. laboratory at the University of Dundee receives or has received sponsored research support from Almirall, Amgen, Amphista Therapeutics, Boehringer Ingelheim, Eisai, GSK, Merck KGaA, Nurix Therapeutics, Ono Pharmaceuticals, and Tocris-BioTechne. A.C. is a scientific founder and shareholder of Amphista Therapeutics, a company that is developing TPD therapeutic platforms. A.C. is on the Scientific Advisory Board of ProtOS Bio. G.E.W., C.M-R, and A.C. are inventors on several patents and patent applications covering small-molecule degraders and degrader discovery approaches. K.K. is a founder, shareholder, and part-time employee (Head of Business Development, 20%) of Vivlion GmbH. N.H.T. has consulted for Monte Rosa, Boehringer Ingelheim, Astra Zeneca, Ridgeline Therapeutics, Red Ridge Bio, and is a founder and shareholder of Zenith Therapeutics. The N.H.T. lab receives funding from Merck KG, Astra Zeneca, as well as Novartis.

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