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Innovation-driven drug discovery: Frontier exploration and breakthrough

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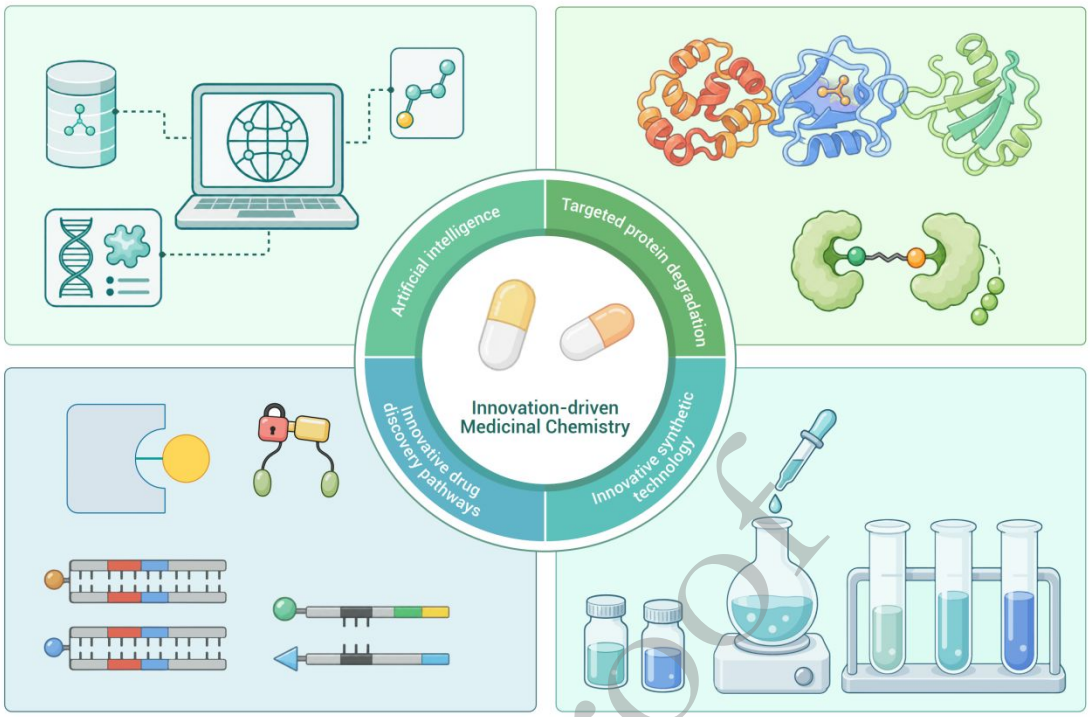
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- This review summarizes innovative small-molecule drug-discovery technologies from 2020-2025.
- Though these tools expand druggable targets, they several bottlenecks.
- Future progress relies on interdisciplinary integration and closed-loop data-algorithm-experiment validation.

ABSTRACT

The progress of drug discovery to the market typically requires 12 to 15 years, during which substantial financial investments are continuously made for various research and testing activities. The complexity and multifactorial nature of the disease, the complexity of the drug development process, the size of the chemical space to be explored, and stringent regulatory requirements are all current challenges. In recent years, the application of various emerging technologies in drug discovery has been increasing, offering the potential to reduce development costs. This review introduces several innovative approaches such as artificial intelligence-driven drug discovery, targeted protein degradation, interdisciplinary integration, and new synthetic technologies. These advancements can lead to a reduction in the overall cost of drug discovery. Additionally, we summarize the challenges and future directions associated with each technology discussed herein. We hope that these innovations will provide significant support in the field of drug development.

Drug development faces many challenges, including high costs, long lead times, and low success rates. Developing a new drug requires an average investment of about $2.6 billion, takes 12 to 15 years, and has a success rate of less than 10 percent in the clinical trial phase.[1] The multifactorial nature of the disease, the complexity of the drug development process, the size of the chemical space to be explored (approximately 10^{60}-10^{100}), and stringent regulatory requirements are all current challenges (Figure 1).[2] To overcome these challenges, scientists have been actively exploring new technologies and methods to improve the drug development process, and continuous innovation will inject new vitality into drug development.

In the vigorous development of modern medicine and life sciences, innovation-driven drug discovery is, with its unique charm and powerful driving force, becoming a key force leading the innovation and progress in the medical field. Artificial intelligence (AI) technology can assist researchers in identifying reliable targets for complex diseases, thereby accelerating the drug discovery process. The development of targeted protein degradation (TPD) techniques and covalent drugs has opened new avenues for discovering challenging druggable targets. DNA-encoded libraries (DEL) serve as revolutionary tools for ultra-high-throughput screening and provide the foundational infrastructure for systematically expanding the druggable space. These technologies integrate cutting-edge theories and advanced techniques from multiple disciplines. They are dedicated to conducting in-depth analyses of disease mechanisms at the molecular level, exploring potential drug targets, and developing innovative pharmaceuticals with enhanced efficacy and reduced toxicity through precise design and optimization (Figure 1).[3,4] This process not only requires a solid chemical foundation, but also cannot be separated from the deep intersection and collaborative innovation in multiple fields such as biology, pharmacology, and informatics, opening

up a new path full of hope and challenges for the cause of human health.

This Review surveys highly innovative drug discovery publications from Top journals and explores the latest applications of innovative technologies in small molecule drug development over the past five years (2020–2025). It encompasses various stages, including target discovery, database construction, drug design, drug synthesis, and the identification of multifunctional molecules. Additionally, we discuss the challenges and opportunities faced in these fields. We hope that in this era of innovation, researchers can accelerate drug discovery and provide patients with a broader range of options.

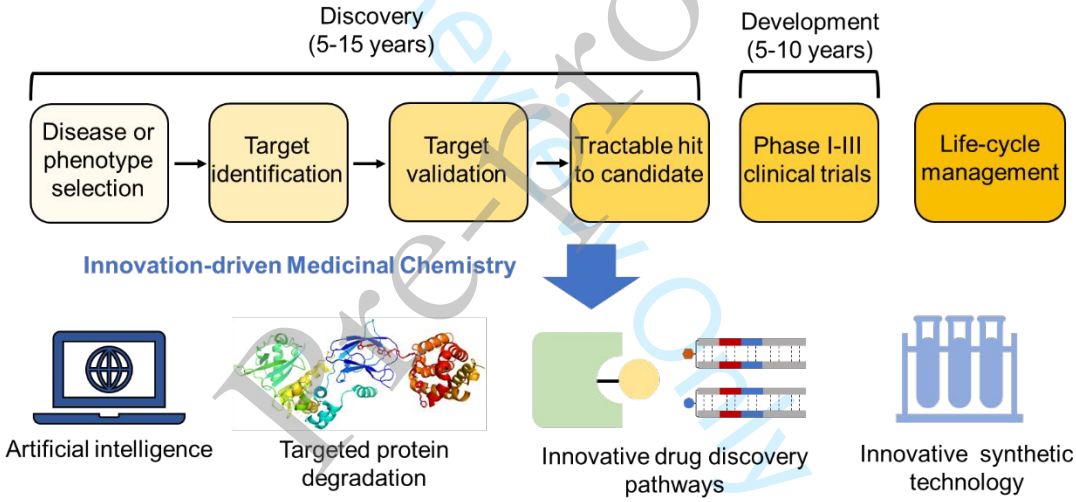


Figure 1. Overview of the role of innovation-driven drug discovery in the drug development pipeline. The drug development pipeline consists of several essential stages, including target identification, drug discovery, preclinical studies, clinical trials, regulatory agency review, and post-market surveillance. The innovation-driven medicinal chemistry has infused new vitality into the field of drug discovery.

AI-driven drug discovery

The emergence of AlphaGo in 2016 catalyzed the widespread integration of deep learning into pharmaceutical research. In 2020, a Massachusetts Institute of Technology team leveraged AI to discover halicin, a novel antibiotic that demonstrates AI's capability to explore unprecedented chemical space. DSP-1181, the world's first small-molecule drug wholly designed by AI, entered clinical trials and substantially shortened the drug development timeline. In 2021, AlphaFold 2 achieved unprecedented accuracy in predicting protein folding, providing a critical foundation for structure-based drug design. Concurrently, Insilico Medicine successfully implemented an end-to-end AI-driven drug discovery platform and advanced its candidate into clinical development. Among these, Rentosertib demonstrated positive results in the GENESIS-IPF Phase IIa clinical trial (NCT05938920). Since then, multiple AI-designed drug candidates have progressed into Phase I/II clinical trials. In recent years, continuous breakthroughs in generative AI, together with the progressive maturation of regulatory frameworks, have propelled AI-powered drug development further into mid- and late-stage clinical studies. This advancement not only significantly reduces R&D costs and shortens development cycles but also expands access to previously intractable therapeutic targets and molecular spaces, thereby fundamentally reshaping the technological paradigm of modern drug discovery. In 2024, AlphaFold 3 was released, extending predictive capability to protein–protein and protein–ligand complexes; notably, the pioneering researchers behind these advances were awarded the Nobel Prize in Chemistry the same year, signifying that AI-driven drug design has entered a new phase characterized by rigorous clinical validation and accelerated industrial translation. The advent of AI technologies, especially large language models (LLMs)[5] and generative AI[6], promises to change this. With the development of AI technology in the whole process of drug discovery, it has been applied in disease target identification,[7,8] drug

discovery,[9–11] preclinical and clinical research,[12,13] and post-marketing surveillance.[14–16]

Key breakthroughs in AI-driven drug discovery center on paradigm-shifting innovations across the entire R&D value chain. Leveraging AI models such as the AlphaFold series, high-accuracy, rapid prediction of protein structures has been achieved, significantly expanding the scope of druggable targets. Integrated multi-omics knowledge graphs, large language models, and graph neural networks enable efficient identification of novel disease targets, substantially shortening target discovery timelines.[17,18] Generative AI approaches represented by diffusion models and Transformer architectures overcome limitations inherent in existing compound libraries by *de novo* designing novel drug molecules while simultaneously optimizing their drug-like properties;[19,20] when coupled with ultra-fast virtual screening of billion-scale molecular libraries, these methods dramatically reduce screening costs and eliminate unnecessary synthetic efforts.[21] Furthermore, AI enables precise prediction of ADMET profiles and toxicity risks to markedly improve clinical success rates.[22] Finally, the tight integration of AI-powered molecular design, retrosynthetic planning, and automated synthesis establishes a R&D system, delivering transformative improvements in both development efficiency and overall success probability of novel therapeutics.

The efficiency of AI in screening and prediction significantly reduces the need for repetitive laboratory experiments, thereby accelerating each phase of drug discovery and saving valuable time. With precise target localization, rational drug design, and scientifically sound clinical trial planning facilitated by AI, the success rate of drug development is enhanced while the risk of failure is minimized. This advancement fosters innovation in drug development and promotes the evolution of personalized medicine. This section will explore the profound impact of AI on all aspects of drug discovery.

Target identification

AI has the capability to identify potential targets, predict target functions, and validate their efficacy, thereby rapidly pinpointing drug development objectives and avoiding blind exploration. It can discern differential gene-encoded proteins associated with disease states from vast datasets to serve as viable targets. AI technologies leverage advanced algorithms including graph neural networks (GNNs), biomedical LLMs, autoencoders, and deep learning to construct disease–gene–protein association networks, enabling efficient identification, prioritization, and preliminary druggability assessment of potential therapeutic targets.

Among these, GNNs excel at uncovering latent relational patterns within multi-omics data, thereby facilitating the identification of disease-driving genes and critical biological pathways while significantly reducing the likelihood of false-positive target selection. Biomedical LLMs, integrated with knowledge graph methodologies, automatically extract target–disease and target–drug associations from vast scientific literature repositories, accelerating the discovery of novel indications for existing drugs and revealing weak yet biologically meaningful target–disease links that may have been overlooked by conventional experimental approaches. In traditional processes, it takes an average of 3 to 5 years for a target to progress from biological clues to preclinical validation. However, the LLM-agent pipeline compresses hypothesis generation, evidence integration, and preliminary validation down to a matter of months. As data and feedback iterate, this approach continuously expands the landscape of targets that can be industrialized.

Fibrosis often occurs in the mid to late stages of chronic diseases and is observed in various organs, including the lungs, kidneys, and liver.[23,24] Currently, treatment options for fibrosis are

limited, with no approved drugs specifically targeting renal fibrosis. By employing the AI platform PandaOmics,[25] a comprehensive analysis was conducted on multi-omics data from a series of clinical samples related to fibrosis as well as relevant clinical datasets, aiming to identify proteins closely associated with this condition. Additionally, data pertaining to renal fibrosis were analyzed in hopes of uncovering common therapeutic targets across different organs. Based on differential expression data derived from fibrotic tissues, an interaction network of differentially expressed proteins within cells was constructed. Core proteins from this network were subsequently selected for further investigation. Among the identified protein targets, three additional criteria were applied: 1) accessibility by small molecule drugs; 2) involvement as proteins or receptor kinases; 3) lack of extensive prior research. After applying these filtering conditions, five potential drug targets were identified; among them, TRAF2- and NCK-interacting kinase emerged as the most significant candidates, validated through siRNA methods. Subsequently, based on this target, INS018_055 was identified through the processes of compound generation and structure optimization, exhibiting favorable characteristics in terms of safety, tolerability, and pharmacokinetics.[3] The Phase IIa clinical trial in China (NCT05938920) has now been completed.

Protein structure prediction

AI models, such as AlphaFold,[26–28] are capable of accurately predicting the three-dimensional (3D) structures of proteins. By inputting amino acid sequences and utilizing neural network computations, these models output atomic-level 3D structures. They employ techniques such as multiple sequence alignment, geometric constraints, and attention mechanisms to capture critical information about proteins, resulting in high structural prediction accuracy. This capability

addresses numerous structural challenges that traditional experimental methods often struggle to resolve. The ability of AI to predict protein structures significantly aids in drug design and optimization. By designing drugs based on the structure of target proteins, it enhances both success rates and efficiency while advancing the development of personalized medicine.

Frank Noé *et al.* demonstrated that the AlphaFold 2 model performs comparably to experimentally determined structures in large-scale virtual screening campaigns. In certain aspects, it even surpasses them. Notably, compounds designed based on AlphaFold 2-predicted structures of the 5-HT2A receptor exhibited enhanced potency and selectivity. Cryo-EM validation confirmed the high accuracy of the AlphaFold 2 predictions and further revealed that AlphaFold 2 successfully captured low-energy conformational states not resolved in the experimental structures. Although experimentally determined structures have traditionally been regarded as the gold standard, the AlphaFold 2 model holds significant promise for ligand discovery.[29]

Parkinson's disease is the second most common neurodegenerative disorder, following Alzheimer's disease, and it severely impacts patients' daily lives, with high rates of disability and mortality.[30–32] Through large-scale genome-wide association studies in diverse populations, FAM171A2 has been identified as a risk gene for Parkinson's disease. This protein plays a crucial role in promoting the pathological spread of α-synuclein. By utilizing AI for protein structure prediction and virtual screening techniques, researchers successfully identified a small molecule (Bemcentinib) from 7,173 compounds that effectively inhibits (IC_{50} = 19.1 μM) the binding between FAM171A2 and pathological α-synuclein. Additionally, this small molecule suppresses the uptake of pathogenic protein fibers by dopaminergic neurons.[33]

Molecular generators and synthesis of molecules

AI has the capability to rapidly generate and screen a vast array of candidate drug molecules, significantly reducing the time required from drug target discovery to the identification of potential candidates. Utilizing advanced AI technologies such as generative adversarial networks, it is possible to swiftly design drug molecules with specific activities and properties, thereby circumventing the cumbersome trial-and-error processes inherent in traditional drug design. Furthermore, by leveraging structural and functional information about targets, AI can accurately design drug molecules that are well-matched to these targets. By employing deep learning algorithms to analyze binding pockets of target proteins, AI can predict the binding modes and affinities between drug molecules and their targets. This enables the design of highly active and selective pharmaceutical compounds.

The current latest generation models are characterized by multi-architecture integration, efficient inference, and cross-modal generation. The mainstream generation models mainly include transformer models, diffusion models, reinforcement learning generation models, and GNN generation models. The transformer model achieves powerful global sequence modeling and parallel computing capabilities through self-attention mechanisms, excels at capturing long-range dependencies, and has excellent cross-modal generalization, making it the fundamental architecture for LLMs and multimodal generation; the diffusion model generates high-quality content through gradual denoising, has stable training and strong controllability, and performs well in high-fidelity image, audio, and molecular structure generation; the reinforcement learning-based generation models optimize generation strategies with reward signals, can effectively align human preferences, and enhance the practicality, safety, and decision coherence of generated content; the GNN model

focuses on the generation and modeling of graph-structured data, can precisely capture topological relationships, and has unique advantages in structured scenarios such as molecular design and knowledge graph completion.

Based on the structural characteristics of target molecules and existing knowledge of chemical reactions, AI is capable of devising efficient synthetic routes. It takes into account various factors such as reaction yield, cost, and safety considerations, providing chemists with optimized synthesis strategies. Through extensive analysis of chemical reaction data, AI can assess the feasibility of different reaction pathways, assisting in selecting the most effective synthetic route.

The rapid iteration of the design-manufacture-test-analyze cycle in drug discovery is crucial for enhancing decision-making efficiency and accelerating pharmaceutical development.[34–36] Existing methods face bottlenecks in automation and efficiency, particularly in chemical synthesis and biological activity validation. To address these challenges, an automated drug design framework has been developed by integrating generative deep learning models with microfluidic chip synthesis. Through pre-training and fine-tuning of deep learning models, molecular structures with specific biological activities and synthetic feasibility are generated, while microfluidic technology facilitates automated synthesis and preliminary screening. This approach has already been applied to the discovery of liver X receptor agonists, showing promise in expediting the drug discovery process and improving research and development efficiency.[37]

Generative AI is driving the transformation of drug discovery from trial and error to precise design through technologies such as modular reactions, latent space optimization, and 3D structural perception. Its core advantage lies in efficiently exploring chemical spaces, balancing multiple target attributes, and accelerating the iteration of candidate drugs through experimental validation.

The ClickGen model employs click chemistry (such as CuAAC reactions) and amide reactions as modular assembly rules, integrating reinforcement learning and image completion techniques to ensure the synthetic feasibility and biological activity of generated molecules. By incorporating predefined reaction rules into the generation process, this model addresses the challenges associated with synthesis difficulty that are prevalent in traditional methods (Figure 2A). In the design of drugs targeting poly(ADP-ribose) polymerase 1 (PARP1), this method demonstrates a significant advantage in efficiency, completing the design, synthesis, and biological activity testing of lead compounds within just 20 days. This is notably more efficient compared to traditional drug design approaches. In biological activity assays, two candidate compounds exhibited excellent anti-proliferative activity, low toxicity, and nanomolar-level inhibitory activity against PARP1. This method represents a novel paradigm in the field of molecular generation and holds promise for advancing AI-driven automated experiments and closed-loop molecular design, thereby providing new possibilities for drug development.[38]

The functionalization of late-stage drug candidates represents a cost-effective approach to optimizing drug properties; however, the chemical complexity of drug molecules poses significant challenges for late-stage diversification.[39] By employing a late-stage functionalization platform that integrates geometric deep learning and high-throughput reaction screening, computational models can predict reaction yields and substrate reactivity, classify the activity of novel reactions, and accurately capture the regioselectivity of major products. By combining GNNs with high-throughput experimentation, molecular graph representations are significantly enhanced through 2D, 3D, and quantum chemical information, leading to improved predictive accuracy. Numerous opportunities for structural diversification have been successfully identified among 23 commercial

drug molecules. The predictive model demonstrates exceptional performance in terms of reaction yield and regioselectivity, providing robust tools for future drug development with the potential to accelerate drug optimization and new compound discovery.[40]

Comprehensive small molecules drug discovery platform

An AI-driven, one-stop platform that provides a clean, convenient, and cloud-based interface to streamline early drug discovery workflows. By seamlessly integrating a variety of innovative AI algorithms including molecular docking, quantitative structure activity relationship modeling, molecular generation, ADMET (absorption, distribution, metabolism, excretion, and toxicity) prediction, and virtual screening, comprehensive platforms such as DrugFlow[41–46] offer effective AI solutions for nearly all critical stages in early drug discovery.

Hypoxia-inducing factor proline hydroxylase (PHD) inhibitors have been approved for the treatment of renal anemia, but have failed clinical trials in inflammatory bowel disease (IBD) due to lack of efficacy. The AI platform identifies the PHD1 and PHD2–hypoxia-inducible factor 1α (HIF1α) axis as therapeutic targets for IBD because they play a key role in regulating mucus production, tight junction formation, immunosuppressive metabolite production, and wound healing. Chemistry42 is an advanced platform for the discovery of small molecule drugs. It efficiently facilitates hit identification, hit-to-lead transitions, and lead optimization processes.[47] Using Chemistry42 platform, the structure-based drug design module, combined with Alchemistry binding free energy estimation and ADMET analysis, ISM012-042 was designed (Figure 2B). ISM012-042 showed a unique binding mechanism to PHD2 through crystal structure analysis, and inhibited PHD1 and PHD2 with IC_{50} values of 1.9 nM and 2.5 nM, respectively. The study demonstrates the

potential of AI in drug design, and the drug has received regulatory approval to begin a Phase I clinical trial (NCT06012578), promising a more effective treatment option for patients with IBD.[48]

With advances in technology, AI and automation are increasingly driving innovation in drug discovery and development. At the core of this transformation lie LLMs, generative AI, and reaction-chain reasoning, which enable end-to-end intelligent automation of retrosynthetic planning, reaction condition prediction, and optimization of yield and selectivity. Representative models including SynFormer, ReaSyn, and Chemma achieve multi-step synthetic route inference and exploration of novel chemical transformations without reliance on quantum computing. Integrated within human–machine collaborative frameworks, these models significantly reduce experimental trial-and-error iterations, thereby accelerating the discovery of new molecular entities and innovative reaction methodologies.

Concurrently, automated synthesis robots are rapidly evolving toward autonomy, modularity, and closed-loop operation. Platforms such as RoboChem equipped with AI-driven decision-making modules can autonomously execute synthesis, optimization, and scale-up around the clock, performing over one thousand reaction screenings per day with a throughput vastly exceeding that of conventional laboratory workflows. Furthermore, intelligent laboratories integrating natural-language interfaces and mobile robotic systems enable flexible deployment and automated execution of hazardous reactions. Together, AI and robotics are synergistically transforming pharmaceutical synthesis from empirical trial-and-error into a fully intelligent, closed-loop R&D paradigm that integrates AI-driven molecular design, robot-executed synthesis and real-time adaptive optimization.

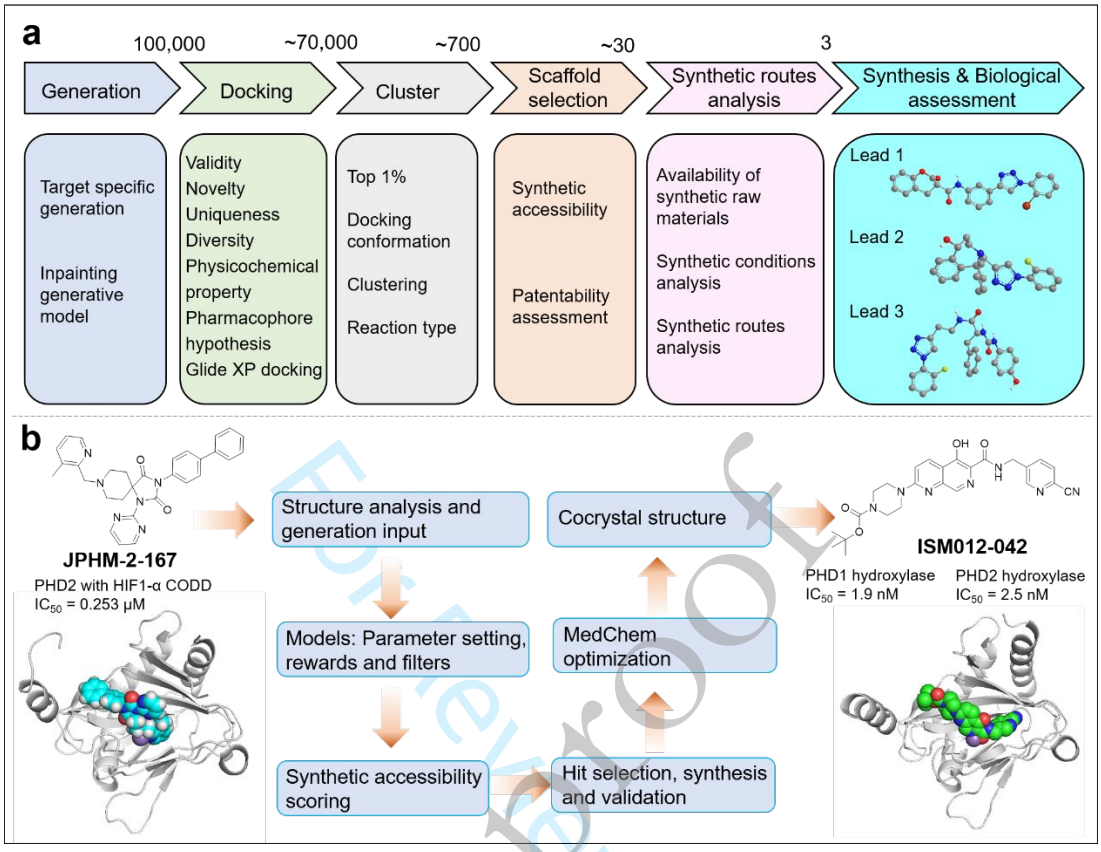


Figure 2. AI-driven synthesis planning and comprehensive small molecules drug discovery platform. (A) Workflow for virtual screening of the molecules generated by the ClickGen model to identify lead compounds. (B) AI-powered workflow of ISM012-042's discovery and design. CODD, C-terminal oxygen-dependent degradation domains, PDB ID on the left: 6QGV; PDB ID on the right: 8Y0V.

Challenges and future directions

Despite advances in AI technology, currently, the majority of molecules identified by AI are in Phase I clinical trials, with only a few having progressed to Phase II clinical trials and beyond, highlighting the complexity of drug development. Current AI-driven drug discovery has already encountered several representative clinical failures. For instance, Verge Genomics' amyotrophic

lateral sclerosis candidate drug VRG50635 developed through AI-based target identification leveraging human brain tissue data failed to meet its pre-specified efficacy endpoints in Phase I clinical trials. Similarly, BenevolentAI's BEN-2293 was discontinued during its Phase IIa trial for atopic dermatitis due to insufficient therapeutic efficacy. Existing AI algorithms predominantly prioritize chemical space fitting while lacking a mechanistic understanding of real-world physiological systems. Modeling efforts remain overly focused on molecular target affinity and neglect critical *in vivo* factors such as pharmacokinetics, organ-specific toxicity, disease-specific microenvironments, and systemic pathway compensation. Compounding these limitations are accelerated development timelines and the frequent omission of rigorous target validation and comprehensive preclinical assessment. Consequently, candidates demonstrating robust activity *in vitro*, in cellular assays, and in animal models often fail to translate into clinical success.

Currently, the performance of AI models is heavily relying on the quality of training data. However, in the field of drug discovery, data often suffers from issues such as inaccuracies, incompleteness, and inconsistencies. These problems can lead to models yielding erroneous patterns, thereby affecting the accuracy of predictions. Furthermore, these data originate from diverse sources with varying formats and standards, making integration and analysis challenging.[49]

In addition to data-related concerns, the predictive accuracy of algorithms and models in drug discovery remains limited, particularly when addressing complex biological systems and disease mechanisms. AI models may struggle to fully capture the intricacies and uncertainties involved in predicting a drug's metabolic processes within the body, its interactions with targets, as well as potential toxic side effects.[50] In the field of protein structure prediction, AlphaFold yield only static structural models and face significant limitations in modeling intrinsically disordered regions,

ligand-bound states, post-translational modifications, and large multi-component assemblies.[51] Future efforts should integrate molecular dynamics simulations, small-molecule docking, and multi-source experimental constraints to develop novel predictive models capable of capturing dynamic conformational ensembles, thereby establishing an integrative structural biology research paradigm.

In response to these challenges, it is essential to establish a unified and standardized drug research and development database that integrates data from various sources. Additionally, promoting the circulation and sharing of data is crucial. By formulating reasonable data-sharing policies and incentive mechanisms, researchers can provide richer data resources for the application of AI in drug discovery.

Regarding model interpretability and reliability, it is important to research and develop technologies and methods that can elucidate the decision-making processes and outcomes of AI models. Techniques such as feature importance analysis and local interpretable model-agnostic explanations should be employed to enhance transparency and trustworthiness. This will enable researchers and clinicians to better understand and accept the predictive results generated by AI.

Furthermore, continuous optimization and improvement of existing AI algorithms are necessary to enhance their predictive accuracy, generalization capabilities, and computational efficiency. Developing more advanced deep learning architectures, refining reinforcement learning strategies, or exploring new machine learning methodologies will better address the complex issues encountered in drug discovery. Given the growing capabilities of AI and the pace of progress, the prospects for AI in accelerating drug development are bright.

TPD-ubiquitin-proteasome system

Since its initial proposal in 2001, proteolysis-targeting chimeras (PROTAC) technology has undergone over two decades of development, with approximately forty PROTAC-based drug candidates having advanced into clinical trials to date. In 2010, cereblon was identified as a critical E3 ubiquitin ligase; in 2012, the VHL ligand was successfully developed, both breakthroughs providing essential molecular tools for PROTAC design. In 2013, Arvinas was founded to advance the industrialization of TPD; in 2019, ARV-110 became the first PROTAC to enter clinical development globally. In 2022, ARV-471 (vepdegestrant) demonstrated success in Phase II clinical trials; on August 8, 2025, the U.S. Food and Drug Administration (FDA) officially accepted the marketing application for vepdegestrant. Vepdegestrant has been granted Fast Track designation by the FDA, positions it as a leading candidate to become the world's first approved PROTAC therapeutic. Concurrently, following the mechanistic elucidation of thalidomide-class drugs in 2010, the molecular glue field has witnessed rapid growth, with multiple molecular glues now in clinical development, thereby further enriching the TPD technology landscape.

TPD is a groundbreaking approach in molecular therapeutics that selectively eliminates specific proteins by leveraging the cell's intrinsic protein degradation systems. TPD technology achieves the elimination of specific proteins by inducing endogenous degradation systems within cells, such as the ubiquitin-proteasome system and lysosomal pathways. This approach showcases distinct advantages, especially in addressing traditional undruggable targets that do not possess well-defined ligand-binding pockets.[52–55] The core advantage resides in its ability to bind to any accessible region on the protein surface. With the integration of multimodal data, the development of novel E3 ligases, and advancements in personalized medicine, TPD is expected to reshape treatment paradigms in fields such as oncology and immune diseases, providing a new framework for tackling major

illnesses.

Moving beyond the conventional small-molecule occupancy-based inhibition model, TPD leverages degradation mechanisms to overcome the undruggable bottleneck for a broad spectrum of disease-relevant proteins. Early-generation PROTACs evolved from peptide-based scaffolds to orally bioavailable small molecules. Molecular glues represented by thalidomide analogs elucidated the mechanistic basis of E3 ligase–target protein engagement, enabling efficient intracellular clearance of soluble pathogenic proteins. Subsequently, novel modalities including lysosome-targeting chimeras (LYTACs), endoplasmic reticulum–associated degradation enhancers (ERADECs),[56] and folate receptor targeting chimeras (FRTACs)[57] have emerged. These modalities harness the lysosomal, endoplasmic reticulum–associated degradation pathways respectively to address previously intractable targets such as membrane-bound and extracellular proteins, thereby substantially expanding the druggable target landscape. Vepdegestrant, the world's first FDA-approved PROTAC therapeutic, marked a pivotal milestone in the transition of TPD from bench-scale discovery to commercialized clinical application. Concurrently, AI-powered tools have accelerated progress by enabling precise prediction of ternary complex conformations and *de novo* design of degraders.[58] Parallel efforts to discover and engineer novel E3 ligase ligands including TRIM21[59] have further advanced selective degradation of polymeric pathogenic proteins and spatiotemporally controlled degradation in specific tissues, collectively establishing a comprehensive, robust, and increasingly sophisticated TPD R&D ecosystem.

PROTACs are heterobifunctional small molecules that recruit E3 ubiquitin ligases to induce ubiquitination and subsequent proteasomal degradation of target proteins. Their modular architecture enables rational design with relatively low development barriers and high target

selectivity. PROTACs are broadly applicable to intracellular targets amenable to small-molecule engagement, particularly advantageous in overcoming resistance to kinase inhibitors. However, their large molecular weight often compromises cell permeability and oral bioavailability, and they are susceptible to the hook effect, wherein high concentrations impair ternary complex formation and reduce degradation efficiency.

Molecular glues are monofunctional small molecules that induce or stabilize neo-protein–protein interactions between an E3 ligase and a target protein, thereby promoting target ubiquitination and degradation. Owing to their compact size, absence of a linker moiety, and favorable drug-like properties, including high oral absorption and no hook effect, molecular glues exhibit superior developability. They are especially suited for traditionally undruggable intracellular targets. Nevertheless, their mechanism relies critically on remodeling protein–protein interfaces, rendering rational design highly challenging; moreover, their utility is constrained by the limited repertoire of E3 ligases amenable to productive engagement.

LYTACs mediate TPD via lysosomal trafficking rather than the ubiquitin–proteasome system. By bridging extracellular or membrane-bound targets to lysosome-resident receptors, LYTACs enable selective degradation of proteins inaccessible to proteasomal machinery, including aggregated and heavily glycosylated proteins. This expands the scope of TPD beyond intracellular targets, a key limitation of both PROTACs and molecular glues. However, LYTACs suffer from large molecular size, potential immunogenicity, suboptimal pharmacokinetic properties (e.g., poor *in vivo* stability and delivery challenges), and intrinsic inability to engage intracellular targets.

In summary, PROTACs are the preferred modality for intracellular, ligandable targets; molecular glues offer optimal balance of oral bioavailability and efficacy against intracellular, historically

undruggable targets; and LYTACs uniquely address extracellular, membrane-associated, and aggregation-prone proteins, constituting their primary therapeutic niche. Currently, over 50 PROTAC candidates are undergoing clinical trials. The potential applications encompass a variety of diseases, including hematologic malignancies, solid tumors, and autoimmune disorders.

In vivo self-assembly of PROTACs

TPD is a recently emerging therapeutic approach aimed at achieving precise treatment by degrading protein of interest (POI). TPD can be subdivided into nearly 10 different technical routes according to the specific principle of action, among which molecular glue and PROTAC technology are the fastest developing. However, traditional TPD methods such as PROTACs have the problems of low efficiency and insufficient accumulation of target sites *in vivo*, which limits their application.[60]

To enhance the pharmacological properties of PROTACs, traditional high molecular weight PROTACs were first divided into two smaller drug-like precursors that can self-assemble to form functional PROTACs via a bioorthogonal reaction. Subsequently, optimal precursors were individually encapsulated within cyclic peptide-modified liposomes to create nano-PROTACs (Figure 3A). This approach facilitates tumor-targeted delivery and enables in situ self-assembly to generate PROTACs within tumor cells. These PROTACs signify a pivotal advancement in the clinical translation, aimed at developing precise targeted therapies for cancer treatment.[61]

ClickRNA-PROTAC

The application of PROTAC drugs in cancer therapy is limited by the differential expression of

E3 ubiquitin ligases across various tumors and a lack of tumor specificity.[62] To address this issue, ClickRNA-PROTAC utilizes mRNA transfection to express a fusion protein that covalently tags E3 ubiquitin ligases in live cells (Figure 3B). This fusion protein is then functionalized using ligands modified with dibenzocyclooctyne. Subsequently, bioorthogonal click chemistry facilitates the coupling of azide-tagged POIs to the fusion protein, thereby inducing the ubiquitination and degradation of POIs. Additionally, by employing an AI-based base editing strategy that leverages UAG stop codons for tumor-specific mRNA (Figure 3B) translation regulation, ClickRNA-PROTAC selectively degrades POIs within tumor cells. Notably, this strategy allows for effective degradation of multiple proteins, including BRD4, KRAS, and NFκB, simply by changing the warhead molecule.[63]

Multivalent targeting chimeras

Immunotherapy has shown limited efficacy in solid tumors, primarily due to the complexity and heterogeneity of the tumor-immune microenvironment (TIME).[64–66] Current strategies are often restricted to the activation of a single type of immune cell, which is insufficient to address the intricacies of TIME.[67–69] Consequently, a tri-valent orthogonal coupling arm technology has been developed to facilitate the specific and efficient integration of multiple therapeutic modules. This approach facilitates the construction of multi-modal targeted chimeras (multi-TAC), capable of simultaneously recruiting and activating various immune cells within TIME.

In *in vitro* cell experiments and three humanized mouse models, the EGFR-CD3-PDL1 multi-TAC demonstrated exceptional anti-tumor immune efficacy (Figure 3C). Evaluations using patient-derived tumor models indicated that its recruitment of activated T cells and dendritic cells

synergistically resulted in an enhanced anti-tumor immune response, achieving an overall effective rate of 75%. The highly modular and programmable characteristics of multi-TAC suggest broad application prospects in immunotherapy and other fields, potentially providing new directions for cancer immunotherapy.[70]

The multivalent PROTAC based on DNA tetrahedra leverages the programmability and modifiability of DNA tetrahedra, integrating tumor cell-targeting modules, E3 ubiquitin ligase recognition modules, and multiple target protein recognition modules to achieve efficient degradation and tumor-specific targeting.[71–74] The tetrahedral PROTAC exhibits remarkable efficiency in degrading the STAT3 protein and demonstrates significant anti-tumor effects in both *in vitro* and *in vivo* studies, substantially surpassing the performance of traditional bivalent PROTACs. This provides a novel approach for designing new multivalent PROTACs and holds promise for advancing the application of DNA framework-based multivalent PROTACs in cancer therapy.[75]

Despite the advantages and remarkable successes achieved, designing PROTACs that effectively function as intended in cells or *in vivo* can be challenging. This often necessitates extensive chemical optimization to attain significant levels of TPD.[76–78] Current PROTACs rely on a single E3 ligase, which can easily lead to the development of resistance.[79–81] To address this issue, a trivalent PROTAC has been designed that employs a branched trifunctional linker to concurrently recruit cereblon (CRBN), von Hippel-Lindau (VHL), and Bromo- and Extra-Terminal (BET)-targeting ligands (Figure 3D). By employing structure-activity relationship optimization strategies, dual E3 ligase-recruiting PROTACs have been developed, demonstrating synergistic effects in promoting degradation.[82]

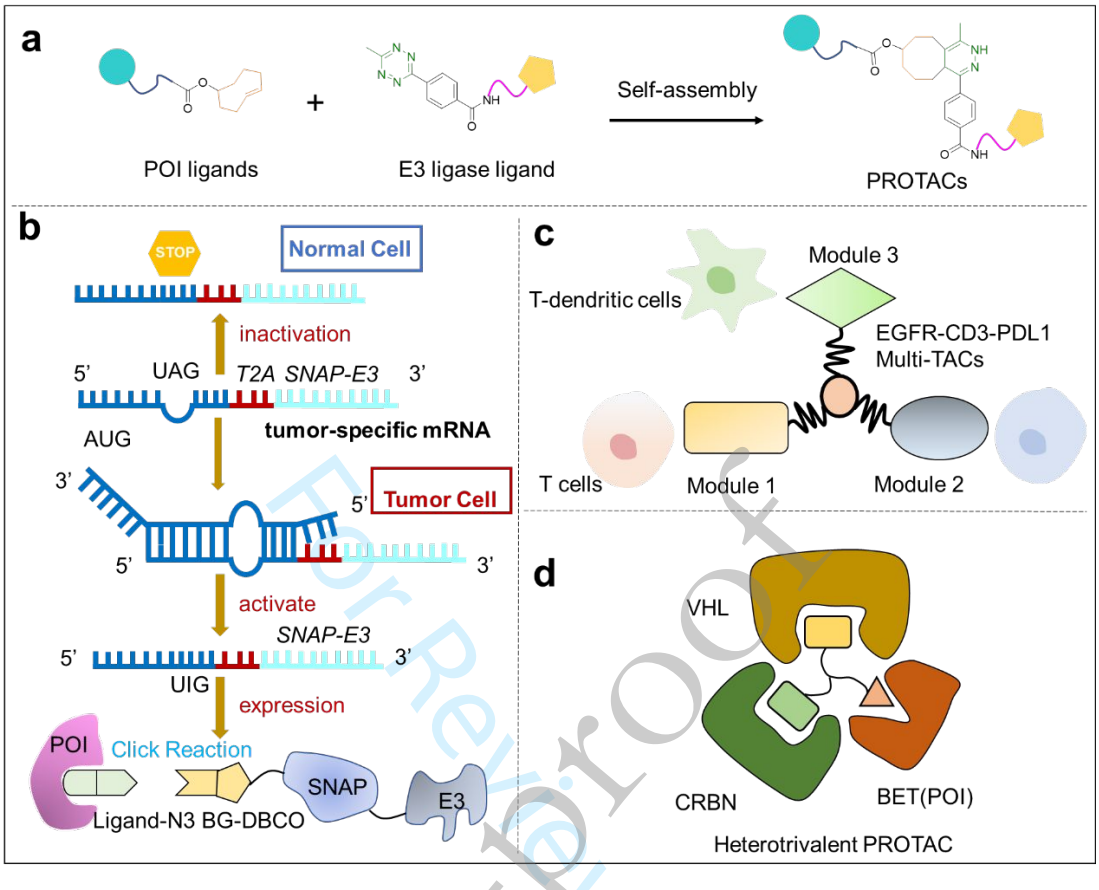


Figure 3. TPD technology based on PROTAC. (A) Bioorthogonal reaction-enabled self-assembly. (B) Scheme of ClickRNA-PROTAC. mRNA of the SNAPTag-E3 ubiquitin ligase (SNAP-E3) fusion protein are delivered by lipid nanoparticles, and then the diphenylcyclooctyne-conjugated benzylguanine (BG-DBCO) and azide-conjugated ligand of POI (Ligand-N3) are administered sequentially. In tumor cells, ClickRNA-PROTAC can be activated by tumor-specific mRNA, leading to the expression of SNAP-E3 fusion protein, which couples to BG-DBCO and Ligand-N3 to form a protein complex that ubiquitinates and degrades the POI. In normal cells, as there is no tumor-specific mRNA to activate the base editing system, the SNAP-E3 cannot be translated. (**C**) The T-Linker technology enables modular and programmable integration of multiple therapeutic modules into single agents, termed multi-TACs, which support multiple immune cell co-engagement in TIME. (D) Simplified structure of a heterotrivalent PROTAC labeled with optimal

linker lengths required between each ligand to have active VHL/CRBN driven BET degradation and to avoid cross-ligase degradation of VHL and/or CRBN.

Rational design of molecular glues

The interaction between proteins, known as PPIs, is crucial for human cells and their molecular recognition, serving as a fundamental aspect of biological processes.[83–86] Molecular glues that can induce or stabilize PPIs are revolutionizing the clinical approach to modulate protein interactions.[87] For example, it can induce the target protein to come into proximity with ubiquitin ligases, thereby facilitating the degradation of the target protein via the ubiquitin-proteasome system. A total of three molecular glue drugs have been approved for market release globally, namely thalidomide, lenalidomide, and pomalidomide. In clinical practice, there are numerous other molecular glue candidates under investigation, including Celgene's CC-220, CC-99282, CC-92480, and CC-9009, as well as BMS's BMS-986470. The primary applications include multiple myeloma, systemic lupus erythematosus, sickle cell disease, and lymphoma. In recent decades, the discovery of molecular glues has primarily relied on serendipitous findings, phenotypic screening, and mechanism validation.[88–97] However, there has been an increasing trend in utilizing systematic screening methods to identify molecular glues.[98,99]

The CDK12 inhibitor SR-4835[100] induces the degradation of cyclin K by linking CDK12-cyclin K to the DDB1-Cullin 4-RING box protein-1 E3 ligase, thereby achieving this effect in the absence of CRBN substrate receptor. Through molecular dynamics simulations, key sites on the PPI were identified that stabilize the CDK12-DDB1 complex, thereby facilitating the subsequent degradation of cyclin K. DDB1-Pro 951 is relatively distant from SR-4835, located in the outer pocket.

Molecular dynamics simulations reveal that residues surrounding the outer pocket can further enhance allosteric effects. Using SR-4835 as a lead compound, a series of piperazine derivatives were initially synthesized by converting morpholine into an easily modifiable piperazine. Additionally, based on the unfavorable spatial interactions of the methylimidazole group, increasing molecular flexibility has proven to be an effective modification strategy, resulting in the identification of compounds with enhanced activity. The final outcome of the structure-activity relationship study resulted in the identification of the compound LL-K12-18, which exhibited potent gene transcription inhibition and anti-proliferative effects in tumor cells; compared to its precursor compound SR-4835, its activity against MDA-MB-231 and MDA-MB-468 cells was increased by 88-fold and 307-fold, respectively (Figure 4A). These findings underscore the potential of the dual-site approach in disrupting CDK12 function and provide a framework for designing cyclin K molecular glues based on structural insights.[101]

Bivalent glue

Intramolecular bivalent glue 1 (IBG1) is a class of PROTAC degraders reported in patents, composed of the BET inhibitor JQ1 and the aryl sulfonamide ligand E7820 linked together. It has been shown to induce efficient degradation of BRD4 across multiple cell lines. Investigations into its degradation mechanism revealed that IBG1 requires both bromodomains of BRD4 to be simultaneously engaged, as a single bromodomain is insufficient for inducing degradation. Under the influence of IBG1, both bromodomains 1 (BD1) and BD2 domains interact with DCAF16 concurrently. The JQ1 core within IBG1 binds to BD2 while the E7820 core interacts with BD1. By keeping the linker constant and replacing the E7820 component with JQ1, IBG3 was obtained

(Figure 4B). Experimental results indicate that IBG3 functions as a more efficient molecular bivalent glue. Structural analysis has unveiled an entirely new degradation mechanism: small molecules induce dimerization of target proteins through dual structural domains, modulating interactions between target proteins and E3 ligases by modifying protein surfaces, ultimately leading to degradation via the ubiquitin-proteasome pathway.[102]

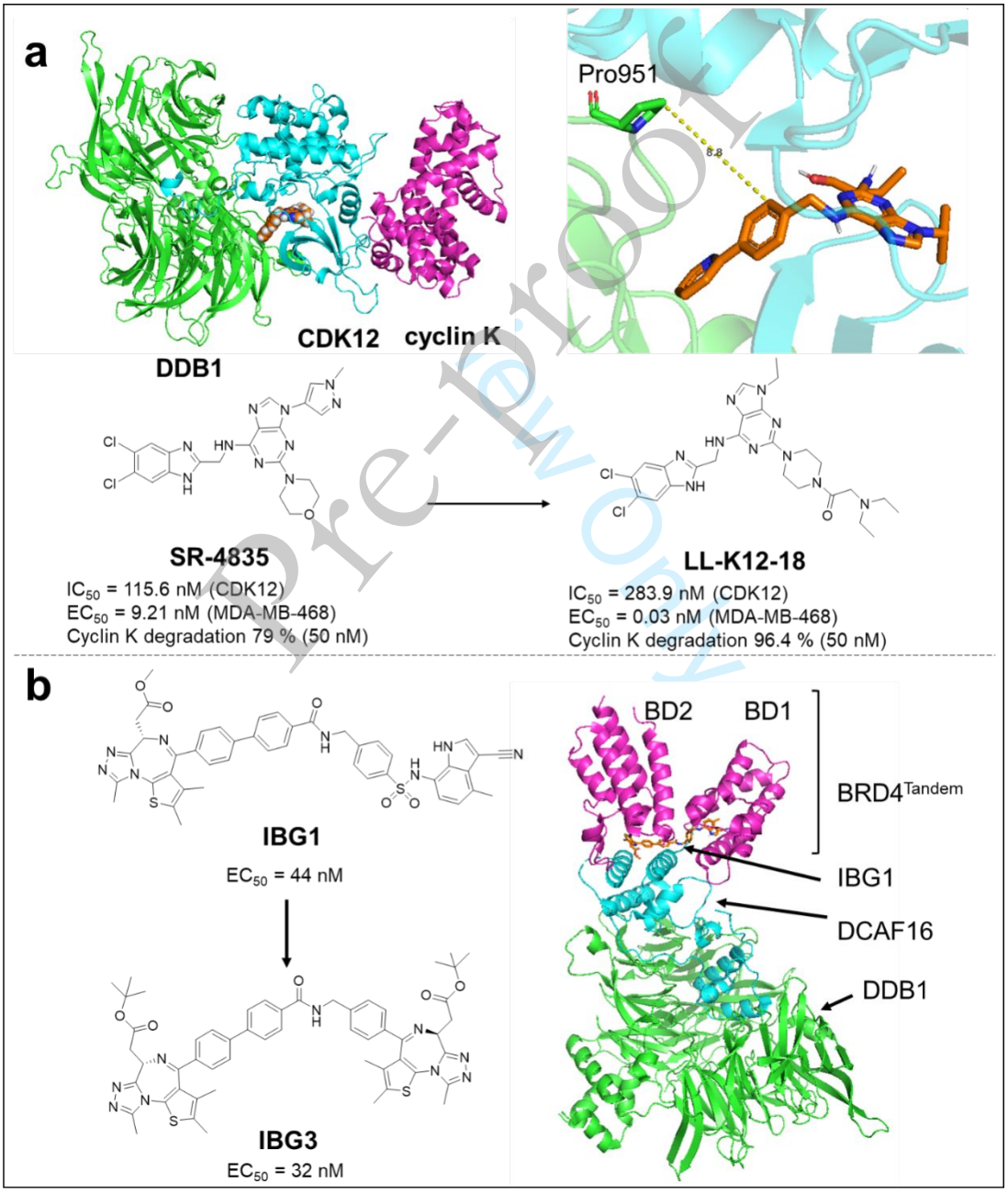


Figure 4. TPD technology based on molecular glues. (A) The structure of tetramer complex (PDB ID: 6TD3). And derivation direction for dual-site molecular glues. (B) The design strategy of bivalent glue. Model of the complex formed between DCAF16, DDB1(ΔBPB), $BRD4^{Tandem}$ (BD1 and BD2) and IBG1 (PDB ID: 8OV6).

Challenges and future directions

Although Arvinas' PROTAC degrader vepdegestrant marketed as Veppanu and co-developed with Pfizer secured U.S. FDA approval on May 1, 2026, multiple setbacks still persist across the clinical development of PROTAC agents. Arvinas' ARV-110 produced desirable therapeutic responses only among metastatic castration resistant prostate cancer mCRPC patients carrying AR T878X or H875Y mutations while delivering negligible clinical gains for general mCRPC cohorts. Foghorn Therapeutics' BRD9 degrader FHD609 enables robust BRD9 degradation yet triggers dose dependent QTc interval prolongation and subsequent clinical hold. C4 Therapeutics' CFT8634 attains strong BRD9 knockdown as well but lacks adequate antitumor effects against synovial sarcoma and SMARCB1 deficient solid tumors to sustain further clinical advancement.[103]

The bifunctional nature of PROTAC molecules endows them with the ability to facilitate targeted degradation, yet their molecular weight typically exceeds 800 Da, making them prone to non-specific binding with off-target proteins. Currently, fewer than 2% of human E3 ligases (such as CRBN and VHL) are widely utilized in PROTAC design. This reliance gives rise to two major issues: first, there is a risk of drug resistance, as tumor cells may evade degradation by downregulating VHL expression; second, target coverage is limited, with approximately 30% of oncogenic proteins being ineffective for degradation through existing E3 ligases.

In response to these challenges, groundbreaking innovative directions have emerged, such as molecular glues and self-assembling technologies. Additionally, in-depth exploration of E3 ligases has led to the identification of candidates with drug development potential, providing opportunities for the development of new degradation pathways. The application of targeted delivery technologies, including nanocarriers and cell membrane camouflage, can significantly enhance degradation efficiency by several folds. Furthermore, strategies involving generative model applications and multi-omics data integration enable the use of AI to simulate and construct predictive models aimed at optimizing target selection and discovering novel specific linkers.

TPD-lysosomal pathways

The lysosomal degradation pathway is a crucial mechanism for the intracellular degradation of proteins and other substances. It primarily mediates the breakdown of proteins and organelles through processes such as endocytosis, phagocytosis, and autophagy. Researchers have developed a variety of modular and highly selective novel degradation strategies. These strategies leverage distinct mechanisms of action and diverse carrier formats to enable systematic, efficient degradation of extracellular proteins, membrane proteins, and even tumor-specific proteins.

The ubiquitin-proteasome system mainly targets short-lived intracellular proteins and certain abnormal proteins for degradation. In contrast, the lysosomal degradation pathway predominantly degrades long-lived proteins, protein aggregates, invading bacteria and viruses, as well as damaged organelles; it can also degrade extracellular proteins. The ubiquitin-proteasome system requires the participation of various components including ubiquitin-activating enzymes, ubiquitin-conjugating enzymes, E3 ubiquitin ligases, and proteasomes. Conversely, the lysosomal degradation pathway

relies on an array of hydrolytic enzymes found within lysosomes such as acid phosphatases and cathepsins to facilitate its functions.

Lysosomal degradation mediated by endocytic receptors

For lysosomal-targeted protein degradation, commonly used receptors such as the cation-independent mannose-6-phosphate receptor and the asialoglycoprotein receptor typically require ligands capable of multivalent binding to become activated.[104,105] This imposes higher demands on the design and synthesis of degradation molecules. Therefore, the development of a platform for synthesizing simple, flexible, and versatile modular constructs of novel targeted protein degradation inducers will facilitate the advancement and application of targeted protein degradation strategies.

Endogenous ligands trigger the endocytosis and lysosomal transport of cell surface receptors;[104–106] however, the lack of natural ligands that can effectively induce endocytosis has further narrowed their applicability.[107–109] To address this issue, advanced computational methods have been employed to develop a synthetic protein known as EndoTags, which specifically binds to cell surface receptors involved in the endocytic process, thereby facilitating endocytosis. By attaching EndoTags to other proteins that recognize and bind disease-related targets, researchers have created a protein-based lysosomal targeting chimera capable of efficiently directing unwanted proteins to lysosomes for degradation.[110]

A strategy for constructing lysosome-targeting non-covalent degraders based on co-assembly, termed lysosome-targeting co-assembly, has been developed (Figure 5A). This assembly is a modular supramolecular co-assembly system composed of two self-assembling peptide-based ligands that can simultaneously bind to receptors with endocytic capabilities on the cell membrane

(such as class A scavenger receptor, SR-A) and target proteins for degradation. It induces an SR-A-mediated cellular uptake pathway to transport the target proteins into lysosomes for degradation. This strategy successfully facilitated the lysosomal degradation of extracellular protein interleukin-17A (IL-17A) and membrane protein PD-L1 in various cell lines expressing SR-A receptors. Notably, the co-assembled degrader targeting IL-17A significantly reduced the levels of IL-17A at skin lesions in a psoriasis model mouse, alleviating psoriatic-like inflammation in these mice.[111]

The degradation of extracellular proteins within the lysosome has been advanced significantly.[104,112,113] However, there have been limited achievements in the selective degradation of protein targets in disease-relevant cells or tissues, which would greatly facilitate the advancement of precision medicine. Furthermore, most degraders remain inaccessible due to their inherent complexity. A class of easily accessible FRTACs has been reported, which specifically target the folate receptor predominantly expressed on malignant cells. These chimeras are designed to degrade extracellular soluble and membrane-associated cancer-related proteins both *in vitro* and *in vivo*. FRTAC serves as a comprehensive platform dedicated to the development of more precise and effective chemical probes and therapeutics aimed at advancing the study and treatment of cancer.[57]

Transferrin receptor 1 (TfR1) is highly expressed in cancer cells and activated T cells, and its internalization occurs at a rapid pace.[114–116] Based on this characteristic, by bringing the target protein on the membrane into proximity with TfR1, efficient degradation of membrane proteins can be achieved, thereby facilitating tumor treatment. TfR-targeting chimeras were designed to connect the target protein with TfR1, facilitating their entry into the cell from the surface. Subsequently, the target protein is delivered to lysosomes for degradation, which serves as a strategy for membrane protein regulation and cancer therapy. This approach addresses issues related to EGFR-driven

cancer resistance and has demonstrated promising results in mouse experiments.[117]

Tumor microenvironment-targeted chimeric protein degradation

The design of a tumor microenvironment-targeted chimeric protein degradation system, termed membrane protein degraders (Pro-MPD), is aimed at the specific activation and degradation of membrane proteins in situ within tumors. This system relies on protease activation of transmembrane peptides within the tumor microenvironment to trigger the internalization and subsequent degradation of target proteins. In normal tissues, due to the absence of relevant proteases (MMP2/9), the degradation chimeras merely bind without undergoing degradation, thereby ensuring specificity for tumor sites. Pro-MPD incorporates transmembrane peptides that can be cleaved and activated by proteases. A masking peptide composed of negatively charged amino acids temporarily inactivates these transmembrane peptides, thereby facilitating targeted delivery and specific degradation within tumors. Pro-MPD presents a universal strategy for developing conditionally activated MPDs while minimizing unintended systemic toxicity caused by non-tumor-related degradations. This approach presents novel targeted therapeutic strategies for tackling undruggable membrane protein targets.[118]

Novel biomaterial-mediated lysosomal degradation

By combining heat shock protein 90 (HSP90) in platelets with the ligand of the POI, degrader platelets (DePLT) capable of degrading the target protein can be constructed and selectively enriched in the bleeding part. DePLT transfers POI ligand-labeled HSP90 to cancer cells through the release of platelet-derived microparticles, activates the ubiquitin-proteasome system to degrade

intracellular target proteins. DePLT binds to the extracellular target protein by releasing free pre-labeled HSP90 and redirecting it to lysosomal degradation (Figure 5B). By constructing ligand tag HSP90 (iHAC) targeting BRD4 protein in mouse breast cancer cells, BRD4 protein in cancer cells can be effectively degraded at 0.16 μM and 20 μM.[119]

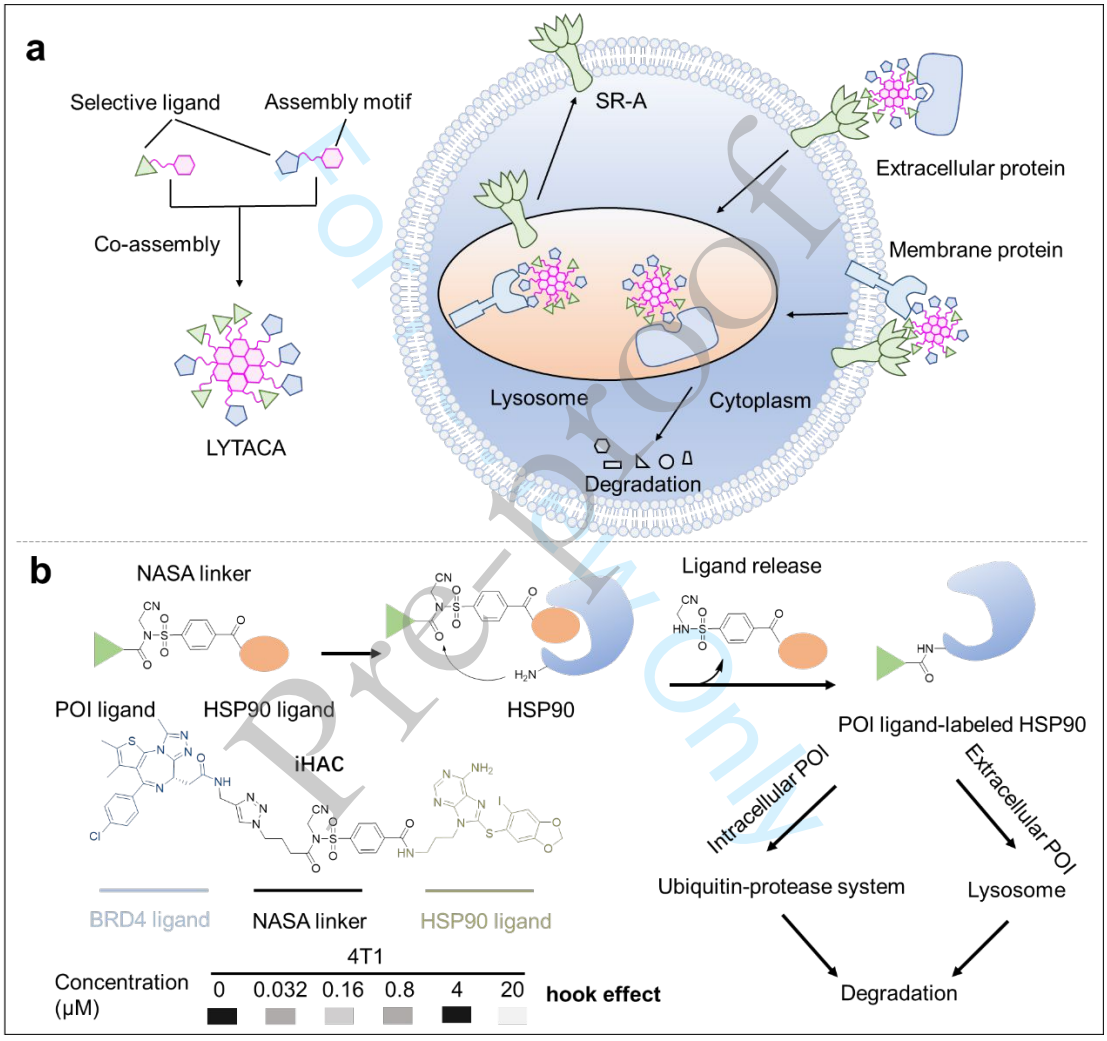


Figure 5. TPD technology based on lysosomal degradation. (A) LYTACA strategy for protein degradation of both extracellular and membrane proteins. LYTACA is based on a modular supramolecular co-assembly system consisting of two selective ligands with an assembly motif. The constructed non-covalent degrader, LYTACA, can bind to cell membrane receptors and the protein of interest simultaneously, resulting in internalization and subsequent lysosome degradation. (B)

Schematic illustration of platelet-based protein degraders with covalently labeled HSP90 yielding TPD. Engineered platelets (DePLTs), were developed through ligand-directed covalent labeling with POI ligands tethered to HSP90. These specialized platelets possess the ability to selectively target postsurgical areas and activate in response to their inherent tropism for hemorrhage. Depending on the specific POI ligands attached, DePLTs can facilitate the transfer of labeled HSP90 to cancer cells via plasma membrane particles, thereby inducing degradation of intracellular POIs through the ubiquitin-proteasome system. Alternatively, DePLTs may release prelabeled free HSP90, which redirects extracellular POIs towards lysosomal pathways for proteolysis. Immunoblot analysis of BRD4 degradation in 4T1 cells after iHAC treatment. NASA, *N*-acyl-*N*-alkyl sulfonamide.

Challenges and future directions

The targeting of lysosomes through chimeric constructs relies on glycosylation modifications or receptor-ligand interactions to direct target proteins to the lysosome. However, the non-specific coupling of sugar structures with antibodies results in a high off-target clearance rate. Additionally, these receptors are prone to being occupied by endogenous ligands, which can adversely affect degradation efficiency. Furthermore, lysosomal-targeting molecules (such as antibody conjugates) typically have a large molecular weight, making it challenging for them to penetrate the dense stroma of solid tumors.

In order to advance the feasibility of this strategy, researchers have developed a flexible scaffold for lysosome-targeting chimeras that can be tailored to accommodate various target proteins. Concurrently, ongoing research is focused on delivery systems; the DePLT technology utilizes

platelet-derived microparticles to deliver HSP90 while simultaneously degrading intracellular BRD4 and extracellular PD-L1. Furthermore, innovative mechanisms have been discovered, including systems that leverage TfR1 and folate receptor for degradation purposes.

Innovative drug design strategy

The traditional drug design strategies, while having achieved significant success and resulting in the market launch of numerous medications, face challenges when targeting single molecular structures. These challenges include low efficacy, the development of resistance, and poor pharmacokinetic properties. Consequently, a range of innovative drug design strategies has emerged. Examples include covalent drugs, multi-target drugs, and prodrugs. These approaches have the potential to overcome the limitations associated with conventional targeted drug design.

The strategy of interdisciplinary integration in drug development represents an innovative approach to drug development that combines theories, methods, and technologies from multiple disciplines.[120] By integrating diverse fields of study, innovative drug design effectively addresses the limitations inherent in traditional drug discovery processes. These approaches not only offer a more comprehensive and profound perspective but also provide improved tools for pharmaceutical research and development.

Covalent drugs

Covalent inhibitors are a class of small molecule compounds that bind to target proteins through covalent bonds to inhibit their biological activity.[121] Covalent inhibitors can form covalent bonds with specific amino acid residues in target proteins (such as cysteine, serine, etc.), resulting in

protein conformational changes and inhibiting its activity.[122,123]

Lysine (Lys) and tyrosine (Tyr) are usually located near ligand binding sites and have been identified as potential alternative nucleophiles for covalent targeting. Sulfonyl fluoride (SF) can not only react with common nucleophilic amino acid residues such as serine (Ser) and threonine (Thr), but also specifically modify Tyr, Lys, cysteine (Cys) and histidine (His). This makes applications in covalent drug design promising, especially in the development of drugs against difficult-to-produce targets.[124–127]

The activity-based proteome profiling technology was employed to identify the reactive protein profile of SF electrophilic probes, leading to the selection of a protein library capable of reacting with the SF warhead (Figure 6A). Additionally, the SF warhead was incorporated into the construction of a DEL, resulting in the design and synthesis of a diverse array of theoretical compounds totaling 67 million covalent DELs. Subsequently, three target proteins (phosphoglycerate mutase 1, glutathione S-transferase 1, and dipeptidyl peptidase 3) with distinct catalytic functions were selected as model proteins for the universal validation of DEL covalent screening. The results successfully yielded high-activity lead compounds (IC_{50} = 0.07 μM).[128]

In the discovery of covalent inhibitors, the utilization of covalent DEL technology, combined with molecular docking and medicinal chemistry optimization, represents a viable strategy. This approach has led to the identification of novel covalent inhibitors targeting non-structural proteins of SARS-CoV-2. Through X-ray crystallography and molecular dynamics simulations, the binding modes of these inhibitors with their target proteins have been elucidated, providing a structural foundation for drug design and optimization. These compounds not only serve as valuable chemical probes for target validation but also present promising candidates for the development of antiviral

therapies against SARS-CoV-2.[129]

Therapeutic radiopharmaceuticals must achieve sustainable tumor targeting and rapid clearance of healthy tissue, which remains a major challenge.[130,131] A targeted ligation strategy that selectively immobilizes the radiopharmaceutical onto the target protein in the tumor would be an ideal solution. A radiopharmaceutical link based on sulfur (VI) fluoro exchange (SuFEx) chemistry used to prevent rapid tumor clearance (Figure 6B). In mice, SuFEx-engineered fibroblast activation protein inhibitor showed a 257 percent increase in tumor uptake and a 13-fold increase in tumor retention compared to the original inhibitor. Ingestion in healthy tissue was rapidly eliminated.[132]

Currently, all FDA-approved covalent small molecules contain a single electrophile, which presents a straightforward pathway for the development of acquired resistance.[133,134] A systematic analysis of human proteins in the Protein Data Bank was conducted to identify approximately 400 unique targets amenable to dual covalent inhibitors. The compound ZNL-0056 is an ATP-competitive inhibitor that forms two covalent bonds with cysteine residues in EGFR, demonstrating sustained efficacy against single cysteine mutants (Figure 6C). Consequently, molecular bidents represent a novel pharmacological modality with the potential to enhance selectivity, potency, and resistance profiles in drug development.[135]

Covalent drug molecules may inadvertently engage in non-specific interactions with other proteins that possess similar structures or active sites. This can lead to off-target effects and trigger adverse reactions. In addition to the active site, drug molecules may also covalently bind to other regions of the target protein. Such interactions not only have the potential to impact the therapeutic efficacy of the drug but may also result in abnormal protein function, thereby increasing toxicity risks. Furthermore, akin to non-covalent drugs, prolonged use of covalent drugs could induce

mutations in the target protein. These mutations might alter the binding sites for the drug, consequently diminishing its binding capacity and leading to the development of resistance.[136]

Therefore, it is essential to conduct in-depth research and optimization of drug molecular structures to enhance their selective recognition capabilities towards target proteins while minimizing interactions with non-target proteins. Designing covalent warheads with specific structural features can enable more precise covalent binding to the active sites or particular domains of target proteins. Additionally, developing novel targeted delivery systems, such as nanocarriers and antibody-drug conjugates, allows for the specific delivery of covalent drugs to affected areas. This approach increases the concentration of drugs within target tissues while reducing distribution in non-target tissues, thereby mitigating off-target effects and toxicity risks.

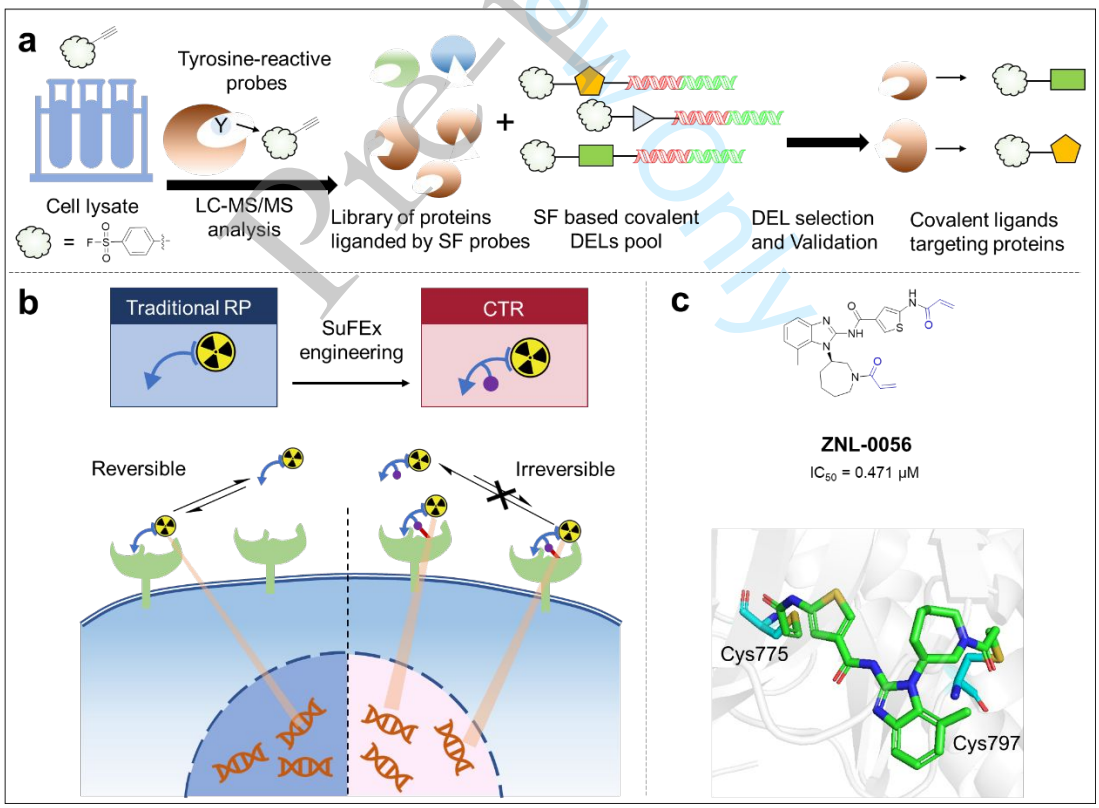


Figure 6. Representative strategies for the design of covalent drugs. (A) The proposed ABPP-

CoDEL selection method. The SF-based probes are used to identify the probe-modified proteins that are selected for SF-based CoDEL selection. After washing out, the hit compounds are encoded, of which the model of action is next validated. (B) Schematic representation of the potential benefits of covalent targeted radioligands over traditional radiopharmaceuticals for targeted radionuclide therapy. (C) ZNL-0056 co-crystal structure with EGFR T790M/V948R (PDB ID: 8EME).

Dual-target (one stone, two birds)

The dual-target drug design strategy represents an innovative approach in pharmaceutical research and development, aimed at creating drug molecules that can simultaneously interact with two or more disease-related targets. This strategy enhances therapeutic efficacy by concurrently modulating multiple disease pathways, thereby reducing the likelihood of resistance development and potentially minimizing adverse effects associated with the medication.[137–142]

Dual-target drug design, as an important strategy in modern innovative drug research and development, can be mainly classified into four core methods: drug effect group combination, fragment connection, molecular hybridization, and multi-target optimization guided. The drug effect group combination method extracts and reasonably integrates the key drug effect groups of two targets, enabling a single molecule to simultaneously meet the binding requirements of both targets. It has the characteristics of compact molecules and excellent pharmacological properties, and is mainly used in drug design for targets such as kinases and GPCR. The fragment connection method uses flexible or rigid connecting arms to covalently couple the active ligands that act on two targets, with a direct design concept and wide applicability. The typical representative is PROTAC and other dual-function degrading molecules. The molecular hybridization method focuses on

directly fusing the parent nuclei or dominant structures of two active molecules, facilitating the acquisition of novel chemical types. It is commonly applied in the modification of natural products and the development of heterocyclic drugs. The multi-target optimization guided by AI is based on machine learning, deep learning, and multi-objective optimization algorithms, synchronously balancing parameters such as affinity to the dual targets, ADMET properties, and synthetic accessibility, achieving efficient design and molecular optimization. It is widely used in the drug research and development of complex diseases such as antitumor, neurodegenerative diseases, and anti-resistant pathogens.

Glioblastoma is a highly aggressive brain tumor that currently lacks effective treatment options.[143] The mammalian target of rapamycin (mTOR) plays a crucial role in regulating cell growth, metabolism, survival, and immune responses.[144] The G1 to S phase transition 1 gene (GSPT1) primarily regulates the termination process of protein translation and is closely associated with the development of various tumors.[145] By combining mTOR inhibition with the selective degradation of GSPT1, a novel bifunctional molecule YB-3−17 has been designed (Figure 7A). Compared to monotherapy, YB-3−17 exhibits enhanced efficacy in tumor cell lines, effectively achieving a dual benefit. YB-3−17 significantly inhibited the phosphorylation of S6K and 4EBP1 proteins in U87 cells in a concentration- and time-dependent manner, indicating its substantial impact on the mTORC1 signaling pathway. Additionally, the degradation of GSPT1 induced by YB-3−17 could be blocked by proteasome inhibitors but not by MLN0128. This finding suggests that the degradation of GSPT1 is dependent on the proteasome system rather than being associated with mTOR, thereby demonstrating the specificity of YB-3-17's action on GSPT1 through the proteasomal pathway.[146]

Host-targeting antivirals offer both preventive and therapeutic strategies to address resistance and manage potential outbreaks of emerging coronaviruses.[147] Cathepsin L (CTSL) and calpain-1 (CAPN1) are host cysteine proteases that play critical roles in the entry of coronaviruses into cells as well as in the immune response associated with infection.[148–151] Based on structure-based drug design, dual-target inhibitor, **14a**, have been developed to simultaneously target the CTSL and CAPN1 (Figure 7B). These proteins play a crucial role in the entry of coronaviruses into cells and in immune responses associated with infection. Through X-ray crystallographic analysis, the covalent binding modes of **14a** with CTSL and CAPN1 were elucidated, providing a structural foundation for the development of broad-spectrum antiviral agents against coronaviruses.[152]

Determining a suitable combination of multiple targets for multi-target drugs presents a significant challenge.[153] These targets must play crucial synergistic roles in the pathogenesis and progression of diseases, and their simultaneous targeting should yield substantial therapeutic effects. Designing drug molecules that can effectively bind to multiple targets is complex; it requires balancing the binding affinity and selectivity of the drug for different targets while avoiding unnecessary off-target effects. Network pharmacology tools (e.g., Cytoscape, STRING, and NetworkAnalyst) enable the construction of disease–target interaction networks and the identification of core hub nodes. Target prediction tools (e.g., SwissTargetPrediction, PharmMapper, and SuperPred) support multi-target prediction as well as off-target risk assessment.

In the design of such drugs, it is essential to employ computer-aided drug design and AI technologies to conduct an in-depth study of the structure and function of target proteins. The goal is to develop multi-target drug molecules with enhanced affinity, selectivity, and stability. By optimizing the drug's structure, precise regulation of multiple targets can be achieved, thereby

improving therapeutic efficacy. Simultaneously, it is important to establish high-throughput screening models and evaluation methods suitable for multi-target drugs to enhance the efficiency and accuracy of drug screening. Utilizing advanced analytical techniques and bioinformatics tools will facilitate a comprehensive investigation into the interaction mechanisms between drugs and multiple targets, providing valuable guidance for drug optimization.

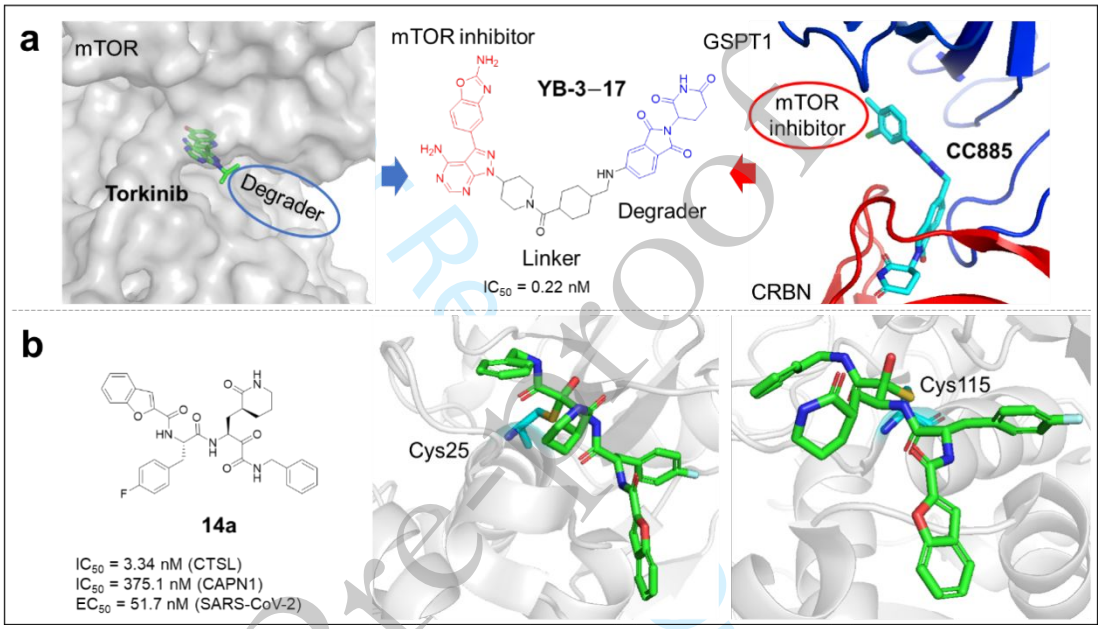


Figure 7. Design strategies for dual-target drugs. (A) The design and synthesis strategy of YB-3−17. Enzymatic inhibition rate of mTOR protein after treated with YB-3−17, PDB ID on the left: 4JT5; PDB ID on the right: 5HXB. (B) Crystal structures of human CTSL (PDB ID: 7W33) and CAPN1 protease core (PDB ID: 7W7O) in complex with **14a**, respectively.

Prodrug strategy

Prodrugs are derivatives of therapeutic agents specifically designed to enhance the pharmacokinetic profile of the drug. In a prodrug, the pharmacological activity of the active compound is concealed and subsequently restored within the human body through bioconversion, a

process that is typically facilitated by enzymatic action.[154]

Ribozymes-targeted chimeras (RIBOTAC) represent an emerging strategy for targeted therapy.[155] However, research on the selective activation of RIBOTAC by bioorthogonal or cell-specific triggers has yet to be explored. Developing a strategy for on-demand RNA degradation to achieve precise cancer treatment can address the challenge of existing RNA-targeted small molecules lacking selectivity. A strategy to activate specific organizations or cells while minimizing side effects on non-target tissues is the prodrug approach.

The RNA G-quadruplex (G4) binding agent is conjugated with a cage-like ribonuclease recruitment moiety.[156,157] This recruitment moiety can be developed through bioorthogonal reactions, tumor-specific enzymes, or metabolic degradation to establish an inducible RIBOTAC (iRIBOTAC) strategy (Figure 8). The strategy has designed various iRIBOTACs that can be activated by different triggers, including phosphine-mediated Staudinger reactions, NQO1-catalyzed reductions, boronic esters responsive to H_2O_2, and selenocysteine-responsive dinitrophenyl sulfonamides. This approach enables the spatiotemporal control of G4 RNA degradation. The strategy demonstrated a high efficiency in degrading G4 RNA in both *in vitro* and *in vivo* experiments. It was able to induce apoptosis and achieve specific tumor imaging and growth inhibition in mouse models. This approach offers a novel precision treatment strategy for cancer therapy, enabling selective cytotoxicity against tumor cells through on-demand activation. It holds promise for reducing side effects while enhancing therapeutic efficacy.[158]

Prodrugs are designed to be converted into active drugs through specific mechanisms; however, achieving precise targeting of pathological sites remains a significant challenge. The efficiency with which prodrugs convert to their active forms in the body may be relatively low, potentially leading

to suboptimal therapeutic outcomes. This is particularly critical in diseases such as cancer treatment, where high concentrations of active drugs are required; insufficient conversion efficiency may hinder effective suppression of tumor cells.[159]

To address this issue, novel targeting groups and delivery systems can be employed to enhance the specificity of prodrugs. Developing targeted delivery systems based on antibodies, peptides, or nanomaterials can facilitate the precise delivery of prodrugs to affected areas, thereby improving therapeutic efficacy while minimizing side effects. Furthermore, it is essential to conduct in-depth research on the conversion mechanisms of prodrugs within the body. This includes investigating the types of enzymes involved in conversion processes, metabolic pathways, and various influencing factors. By integrating both *in vitro* models and *in vivo* experiments, researchers can elucidate the conversion process of prodrugs and provide a foundation for optimizing their design and enhancing conversion efficiency.

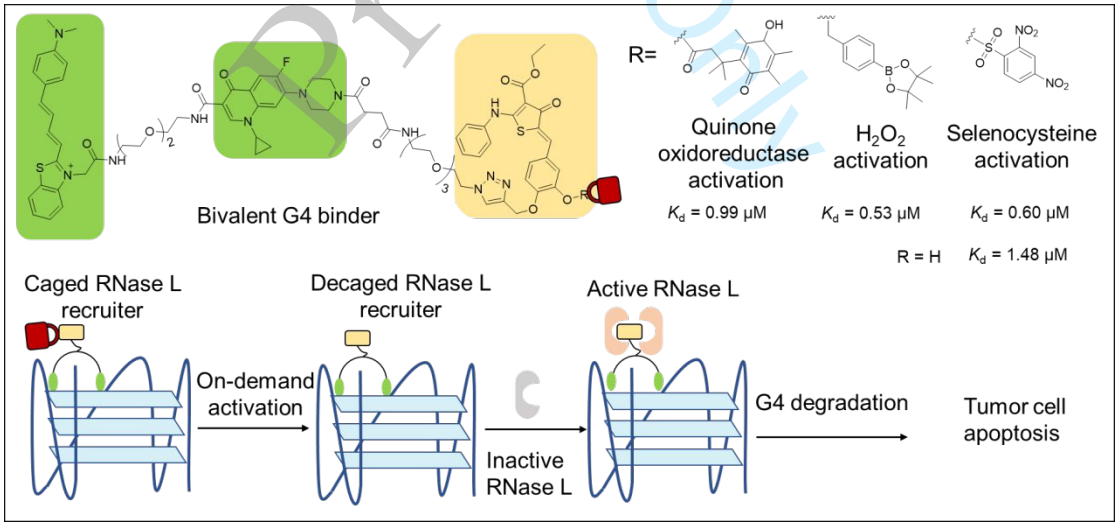


Figure 8. Design of the iRIBOTAC. Schematic illustration and structures of iRIBOTAC for on-demand G4 degradation and cell death induction. Dissociation constants of bivalent G4 binders toward c-Myc RNA G4.

DEL

DEL technology, first conceptualized in 1992 by Sydney Brenner and Richard A. Lerner, has undergone more than three decades of continuous development. It has followed a distinct evolutionary trajectory, advancing from theoretical conception to industrial-scale application, and shifting from library construction driven by scale expansion to rational design guided by structural insights. In its early stage, DEL relied predominantly on the one-bead-one-compound strategy performed on solid-phase supports; however, progress was initially constrained by limitations in synthetic compatibility and achievable library size. A pivotal technological turning point emerged in 2004, with the establishment of several key methodologies including DNA-templated synthesis, encoding-enabled self-assembled chemical libraries, and solution-phase split-and-pool synthesis. These advances enabled a fundamental transition from heterogeneous solid-phase to homogeneous solution-phase synthesis and laid the foundational technical framework for modern DEL platforms. Following 2009, the widespread adoption of next-generation sequencing technologies and the systematic development of numerous DNA-compatible organic reactions propelled DEL into a phase of industrial maturity. It is now broadly deployed across pharmaceutical R&D for hit identification and lead generation. Library sizes rapidly expanded into the tens of billions range, while screening paradigms evolved beyond purified protein systems to encompass more physiologically relevant environments, such as cell lysates, thereby enhancing biological relevance and translational potential. Since 2018, DEL technology has advanced further toward precision and interdisciplinary integration. Emphasis has shifted to rationally designed library formats including focused libraries, covalent DELs, and macrocyclic or three-dimensional molecular scaffolds. Deep

synergies have also been forged with cutting-edge modalities such as AI-driven library design and analysis, PROTACs and molecular glues, and live-cell-based screening. These integrations are progressively overcoming historical challenges associated with undruggable targets, continuously expanding the scope of accessible chemical space and therapeutic applications. Today, DEL stands as an indispensable core platform technology in modern drug discovery.

DELs provide a rapid and cost-effective platform for screening extensive compound libraries against biological targets. Most DELs are constructed in a single-pharmacophore format, comprising three or four building blocks synthesized through the combinatorial split-and-mix methodology.[160,161] Additionally, dual-pharmacophore DELs, such as the encoded self-assembling chemical library, have been developed.[162] In these libraries, two sets of small molecules are displayed on the respective strands of DNA duplexes, thereby facilitating the selection of synergistic binder pairs. However, dual-pharmacophore DELs identify distinct binders that necessitate subsequent linking to achieve the complete ligands, a process that is often fraught with challenges.[163]

A protein-templated DEL selection approach has been reported, which can identify complete ligand/inhibitor structures from DNA-encoded dynamic libraries without the necessity for subsequent fragment linking (Figure 9A). This method is based on dynamic DNA hybridization and target-templated in situ ligand synthesis. It incorporates and encodes linker structures within the library, alongside the building blocks, allowing them to be sampled by the target protein. The system was employed to screen multiple targets, and during the evaluation of the non-structural protein 13 (NSP13) helicase of SARS-CoV-2, it was observed that at a high concentration of 200 μM, most compounds exhibited over 80% inhibition of NSP13's ATPase activity. Among these, compound

N-1 demonstrated the highest inhibitory potency, with an IC_{50} value of 1.51 μM.[164]

With the advancement of DEL technology, the use of DEL reagent kits enables rapid screening of drug targets. Notably, affinity screening using DEL against SARS-CoV-2 and other variants of coronaviruses has led to the identification of a series of promising non-covalent hits (DEL7). Subsequently, structural studies were conducted to optimize these hits and investigate their mechanisms of action (Figure 9B). It was found that these compounds (**29**) exhibit distinct binding modes compared to the main protease inhibitor Nirmatrelvir, suggesting their potential as novel therapeutic agents capable of overcoming resistance to Nirmatrelvir and its complexes.[165]

Lead compounds identified through DEL screens often exhibit higher molecular weights, which presents challenges in the drug development process. Conventional DEL methodologies have been refined by integrating alternative techniques, such as photo cross-linking screening, to augment chemical diversity. The compounds identified through this approach demonstrate lower molecular weights and improved modification potential compared to conventional DEL molecules. This research highlights the synergistic relationship between DEL and AI technologies, thereby advancing the field of drug discovery.[166]

Currently, the construction of a large-scale DEL with adequate complexity poses significant challenges.[167] Ensuring that the compounds within the library possess adequate chemical diversity and quality is crucial. Although DEL technology has enhanced screening efficiency, several limitations persist. It is essential to guarantee that each compound can adequately interact with the target protein and undergo reaction; however, this may be influenced by factors such as compound solubility, stability, and the expression levels of the target protein.

Due to various interfering factors during the screening process, false positive and false negative

results may occur.[168,169] False positives can lead to wasted time and resources in subsequent validation efforts, while false negatives might result in missed opportunities for identifying promising compounds. Therefore, there is an urgent need to develop more reliable screening methods and validation strategies to mitigate these error rates.

In the expansion and optimization of libraries, it is essential to introduce a greater variety of chemical types, scaffold structures, and functional groups to further broaden the chemical space of DELs. This approach will enhance the opportunities for discovering novel active compounds. Simultaneously, optimizing the composition and design of these libraries is crucial to ensure both diversity and quality of the compounds. Moreover, developing more efficient and flexible methods for compound synthesis and DNA labeling techniques can significantly improve the efficiency and quality of library construction. Employing new technologies such as click chemistry can facilitate faster and more specific connections between compounds and their DNA tags. Additionally, refining screening methods and equipment will enhance throughput, efficiency, and sensitivity in screening processes. By integrating microfluidic technology or high-content screening techniques, researchers can achieve more precise detection of interactions between compounds and target proteins.

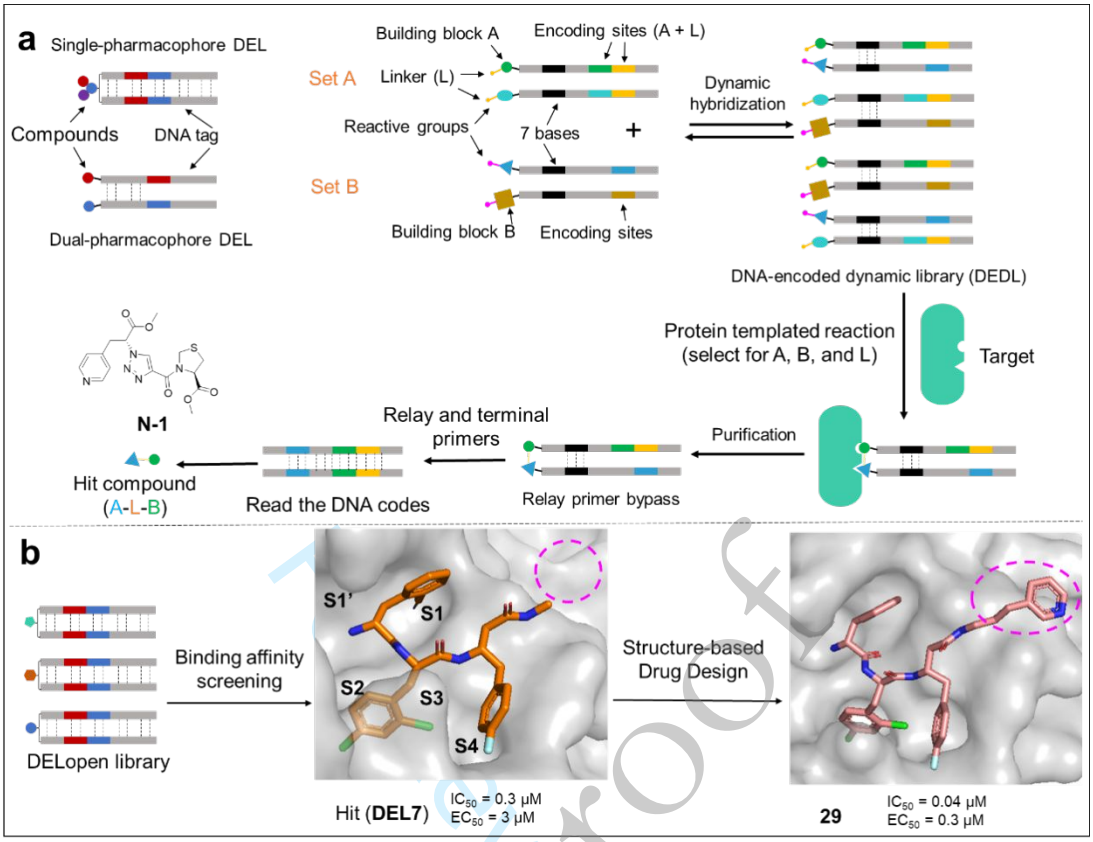


Figure 9. The representative application of DEL in drug screening. (A) Protein-templated DEDL selection method. Two sets of DNA-encoded small molecules with a short complementary region form the dynamic library. Besides the building blocks, a linker motif (L) is encoded in set A. The DNAs contain a pair of reactive groups. Adding the target shifts the equilibrium and promotes in situ ligand synthesis. Next, the conjugated duplexes are gel-purified, and the selected building blocks and the linker are decoded with relay primer bypass PCR and sequencing to identify the full ligand (A–L–B). (B) The discovery process of compound **29** (PDB ID: 8UDF and 8UEA).

Innovative synthetic technology

The technology of drug synthesis refers to the techniques and methods used to convert simple organic or inorganic raw materials into drug molecules through chemical or biochemical reactions. With advancements in technology, changes in disease patterns, and an increasing demand for health

among the populace, it is of paramount importance to develop efficient, precise, and sustainable drug synthesis technologies.[170] Within the innovative drug synthesis technology framework, modular synthesis serves as a unifying molecular construction paradigm that emphasizes deconstructing complex drug architectures into discrete, functionally defined building blocks for independent assembly. Multicomponent reactions represent an efficient implementation of this modular philosophy, enabling the concurrent integration of multiple building blocks in a single synthetic operation, thereby markedly enhancing both synthetic efficiency and molecular diversity. SuFEx click chemistry, in turn, provides a precise, robust, and operationally mild core ligation tool for modular assembly. Collectively, these three strategic elements constitute a modern drug synthesis platform characterized by high efficiency, exceptional precision, and broad structural diversity. By improving efficiency, expanding structural diversity, and enhancing functionalization capabilities, these approaches provide new tools for the precise construction and high-throughput screening of complex pharmaceutical compounds.

Modular synthesis method

Modular reaction is a strategy that involves decomposing the reaction process into multiple independent modules, which can then be combined to achieve specific chemical reactions or synthesis objectives. The concept of modular reactions is widely applied in click chemistry.[171,172] Click chemistry is a modular, highly selective, mild-condition coupling reaction that enables the efficient and rapid synthesis of functional molecules. The reaction occurs at room temperature to moderate temperatures and offers advantages such as speed, high selectivity, and the absence of harsh reaction conditions or complex purification steps. This makes it particularly suitable for

generating models and has led to its extensive application in drug development, materials science, and biological labeling fields.

The predominant approach to the discovery of PROTACs primarily relies on an empirical design-synthesis-evaluation process, which involves numerous cycles of labor-intensive synthesis, purification, and bioassay data collection.[173–175] Consequently, there is a pressing need for the development of innovative methods to expedite PROTAC synthesis and facilitate the exploration of chemical space. A direct-to-biology strategy has been reported to enhance the synthesis of PROTAC libraries on plates, facilitating the seamless transfer of reaction products to cell-based bioassays without necessitating additional purification (Figure 10A). By integrating amide coupling with light-induced primary amines and *o*-nitrobenzyl alcohols cyclization (PANAC) photo click chemistry into a plate-based synthetic process, this approach yields PROTAC libraries characterized by high efficiency and structural diversity.[176]

Multicomponent reactions

Compared to traditional multi-step reaction sequences, multicomponent reactions allow for the simultaneous formation of multiple chemical bonds in a single step. This significantly reduces the number of syntheses steps and shortens reaction times.[177] Multicomponent reactions are capable of efficiently synthesizing structurally diverse compounds. Due to their ability to combine various functional groups and frameworks in one reaction, they are particularly well-suited for constructing libraries containing compounds with multiple structural types.

In order to develop new CRBN-based molecular glue degraders, especially selective degraders targeting Wee-like protein kinase (WEE1) for more effective cancer treatment, existing methods

face challenges in efficiently synthesizing a diverse library of molecular glues while lacking sufficient selectivity for specific targets. To address this issue, a library of pentanoyl imine derivatives was synthesized using the Groebke−Blackburn−Bienayme three-component reaction. Through high-throughput screening and structure-activity relationship studies, selective WEE1 degraders were identified. Additionally, cryo-electron microscopy was employed to elucidate the structure of their complex with CRBN, providing a structural basis for rational design. These degraders exhibit significant WEE1 degradation capability and anti-proliferative effects across various tumor cell lines, providing a potential starting point for the development of new cancer therapeutics. Notably, they demonstrate synergistic anti-proliferative effects when used in conjunction with DNA-damaging chemotherapeutic agents.[178]

Many pharmaceutical molecules possess complex structures and lengthy synthesis routes, necessitating multiple reaction steps. This complexity often results in low overall yields and high production costs, which are not conducive to large-scale manufacturing. Therefore, it is essential to develop efficient and highly selective novel synthetic reactions and catalysts while adhering to the principles of green chemistry.[179,180] This includes advancing atom-economical reactions, catalytic processes, solvent alternatives, and the utilization of renewable resources. Moreover, employing automated equipment and continuous flow technologies can facilitate the continuous automation and modularization of drug synthesis. These advancements will enhance production efficiency and quality control standards, while simultaneously reducing pollution.

SuFEx

The click chemistry approach has emerged as a powerful strategy for constructing highly modular

chemical libraries.[181] However, the development of new click reactions and the unlocking of novel clickable building blocks remain significant challenges. The dual-click strategy of sequentially connecting widely used carboxylic acids and amines with fluorosulfonyl isocyanate (FSO_2NCO) is achieved through a modular approach involving amination/SuFEx processes. The method allows for the convenient acquisition of a chemical library comprising *N*-fluorosulfonyl amides ($RCONHSO_2F$) and *N*-acyl sulfonamides ($RCONHSO_2NR'R''$) under simple and practical conditions, achieving near-quantitative yields (Figure 10B). The preliminary biological activity screening of these compounds indicates that some of them exhibit significant antibacterial activity against Gram-positive bacteria, specifically *Staphylococcus aureus* and drug-resistant MRSA, with a minimum inhibitory concentration (MIC) as low as 6.25 $\mu g \cdot mL^{-1}$. These results provide compelling evidence for the potential application of modular click chemistry libraries as an enabling technology in high-throughput drug discovery.[182]

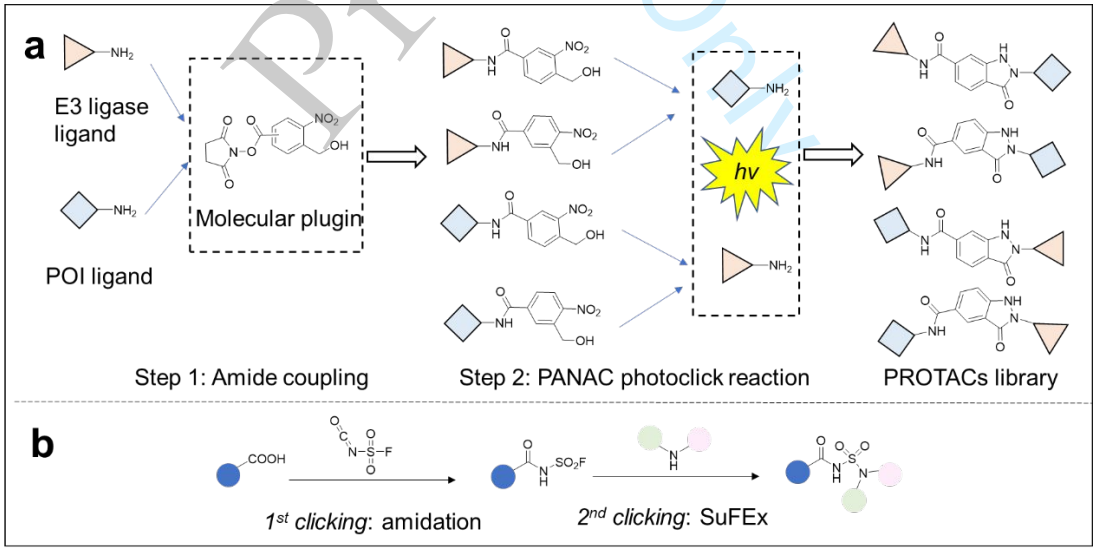


Figure 10. Advancements in synthesis technology facilitate drug discovery. (A) The conjugation strategies for direct modular assembly of PROTACs through amide coupling via molecular plugin

(*o*-NBA-NHS-1 or *o*-NBA-NHS-2), and photo click chemistry in plate. (B) A modular double-clicking strategy for the ligation of carboxylic acids and amines.

Conclusion

Although AI, TPD, innovative molecular design, and intelligent synthesis technologies have collectively established a new paradigm for drug discovery. These advances significantly shorten development timelines, expand the druggable chemical space, and enable the targeting of historically undruggable targets. The innovation-driven drug development landscape remains fundamentally constrained by the persistent mismatch between rapid technological advancement and slow clinical translation. Its underlying limitations and systemic risks warrant serious attention.

AI-enabled drug discovery acts as the intelligent underlying support for new drug research and development. It will evolve progressively via modular industrial deployment and original innovative exploration in the future. Commercial applications will materialize in the short run through target screening, molecular design and clinical optimization. In the medium term, multimodal large models will facilitate the construction of an interpretable, iterable and automatic R&D framework. Long-term priorities lie in tapping into historically undruggable targets and advancing personalized precision pharmaceutical production. Its clinical translation is currently hampered by multiple prominent constraints. Major challenges include limited predictive accuracy of models stemming from incomplete and inadequately annotated biomedical datasets, insufficient algorithm interpretability that impairs regulatory review compliance, and low consistency between computational predictions and wet-lab verification, all of which curb the practical rollout of relevant technologies. For the formulation of industrial standards, stakeholders should build a complete

institutional system covering compliance and full traceability criteria for pharmaceutical R&D data powered by AI, verified efficacy benchmarks for computational models, and uniform specifications governing algorithm interpretability. It is also essential to draw a clear distinction between AI-aided research data and documents submitted for pharmaceutical registration, alongside refined criteria for commercial service management and project pipeline assessment. These efforts will jointly formulate industry norms for intelligent drug R&D compatible with existing pharmaceutical regulatory requirements.

TPD represents an innovative molecular paradigm that overcomes the limitations of conventional small-molecule therapeutics. Looking ahead, the field is poised to evolve into a diversified technological landscape. PROTACs will continue to undergo optimization for improved drug-like properties and an expanded repertoire of exploitable E3 ubiquitin ligases to advance clinical pipeline development. Molecular glues will leverage their favorable pharmacokinetic and synthetic profiles to steadily progress toward regulatory approval. And emerging modalities such as LYTACs and AUTACs will gradually address the long-standing challenges of extracellular protein and protein complex degradation, thereby broadening therapeutic applications into inflammatory and neurodegenerative disorders. PROTACs suffer from relatively large molecular weights and low membrane permeability, imposing prominent restrictions on their druggability and hindering clinical translation. Their capability to induce irreversible target degradation triggers safety worries, especially concerning off-target toxic effects during long-term repeated administration. Additional clinical obstacles consist of widespread target homogeneity, unsatisfactory drug delivery performance and the progressive emergence of drug resistance. To address these challenges, a tiered, technology-specific regulatory standard system must be established. This includes distinct

physicochemical quality control criteria and degradation efficiency benchmarks for each TPD modality; dedicated evaluation guidelines for off-target proteome profiling and tissue distribution assessment; a dual-endpoint evaluation framework integrating quantitative protein degradation rate with clinically meaningful efficacy endpoints; and harmonized protocols for assessing specificity-related toxicity and long-term safety to fill critical gaps in current regulatory standards for the TPD field.

Synthetic chemistry serves as the core manufacturing enabler for innovative drug development spanning laboratory research, clinical translation and commercial-scale production. Looking ahead, it will evolve along a stratified pathway. Intelligent small-scale synthesis, environmentally sustainable pilot-scale manufacturing, and domestically sourced large-scale production. At the front end, AI-driven retrosynthetic planning and automated synthesis platforms will enable high-throughput, rapid preparation of complex molecules. In the midstream, continuous-flow processing and green catalytic technologies will address critical challenges in process scale-up for complex pharmaceuticals while significantly reducing waste generation. At the downstream stage, reliance on domestically produced reagents will underpin a robust, cost-efficient supply chain for the large-scale manufacturing of novel therapeutics. Currently, a key bottleneck impeding the clinical translation of new drugs lies in the substantial gap between laboratory-scale synthetic processes and industrial-scale production. This challenge is exacerbated by the intricate impurity profiles of complex innovative molecules, the high capital and operational costs associated with greening synthetic processes, and the resulting tension between sustainability imperatives and economic viability. To overcome these barriers, industry-standardization efforts must establish a three-tiered process validation framework for small-scale, pilot-scale, and commercial-scale manufacturing

alongside quantitative metrics for green synthesis, including atom economy and waste emission thresholds. For complex innovative active pharmaceutical ingredients, such as those TPD, dedicated standards are required for impurity identification, traceability, and permissible limits. Furthermore, regulatory-compliant standards must be developed for the calibration of automated synthesis equipment and for end-to-end experimental data traceability to secure full alignment with the evolving demands of cutting-edge drug discovery and industrialization.

In future, the core breakthroughs in drug discovery will no longer hinge on incremental advances in isolated technologies, but rather on a systemic innovation characterized by deep interdisciplinary integration, a closed-loop paradigm linking data, algorithms, and experimental validation, and balanced emphasis on fundamental mechanistic understanding and engineering-driven translation. A standardized, high-quality, multimodal, and openly shared drug discovery data infrastructure must be established. Critical bottlenecks including AI model interpretability and the faithful computational modeling of complex biological systems must be overcome. The E3 ligase repertoire must be expanded. Targeted delivery and conditionally activated modalities must be advanced to address the druggability and target specificity challenges inherent in TPD. Covalent binding, dual-target modulation, and degradation strategies must be seamlessly integrated with AI-powered molecular design to build a more efficient and safer drug molecule creation platform. Synthetic methodologies must evolve toward atom economy, green and sustainable practices, and automated, intelligent operation. This evolution will bridge the final gap between laboratory-scale innovation and industrial-scale translation.

Considering that researchers are continuously exploring these technologies, we have witnessed advancements such as intramolecular bivalent ligands and novel strategies like TfR-targeting

chimeras and FRTAC that inject fresh vitality into these methods. It is precisely through ongoing innovation that drug discovery continues to progress. We can maintain a prudent optimism regarding the prospects of innovation-driven drug discovery.

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AUTHOR CONTRIBUTIONS

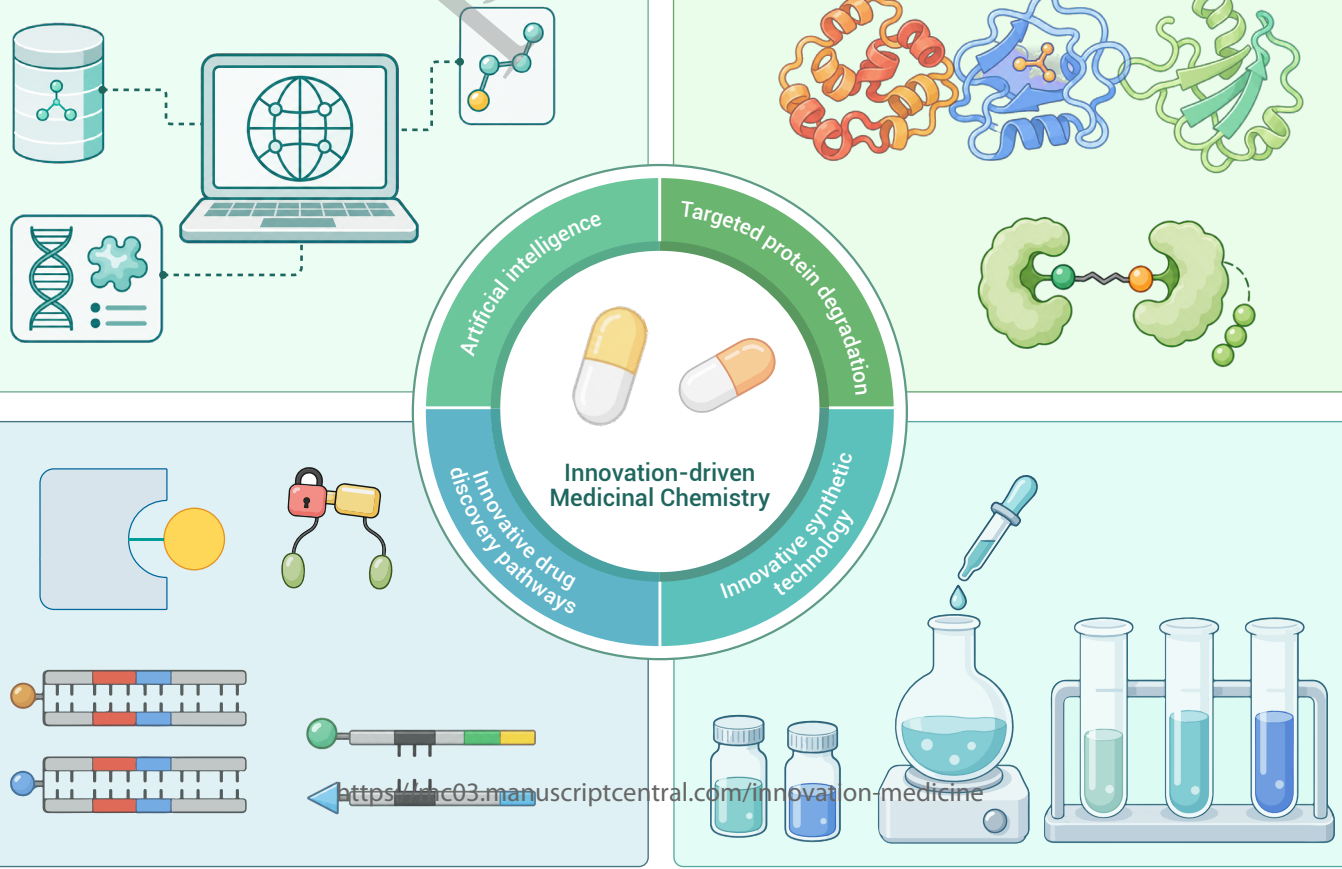
Shaoqing Du: Writing-original draft, Xueping Hu: Writing-original draft, Erik De Clercq: Writing-review & editing, Xinyong Liu: Writing-review & editing, Peng Zhan: Writing-review & editing. All authors contributed to and approved the manuscript.

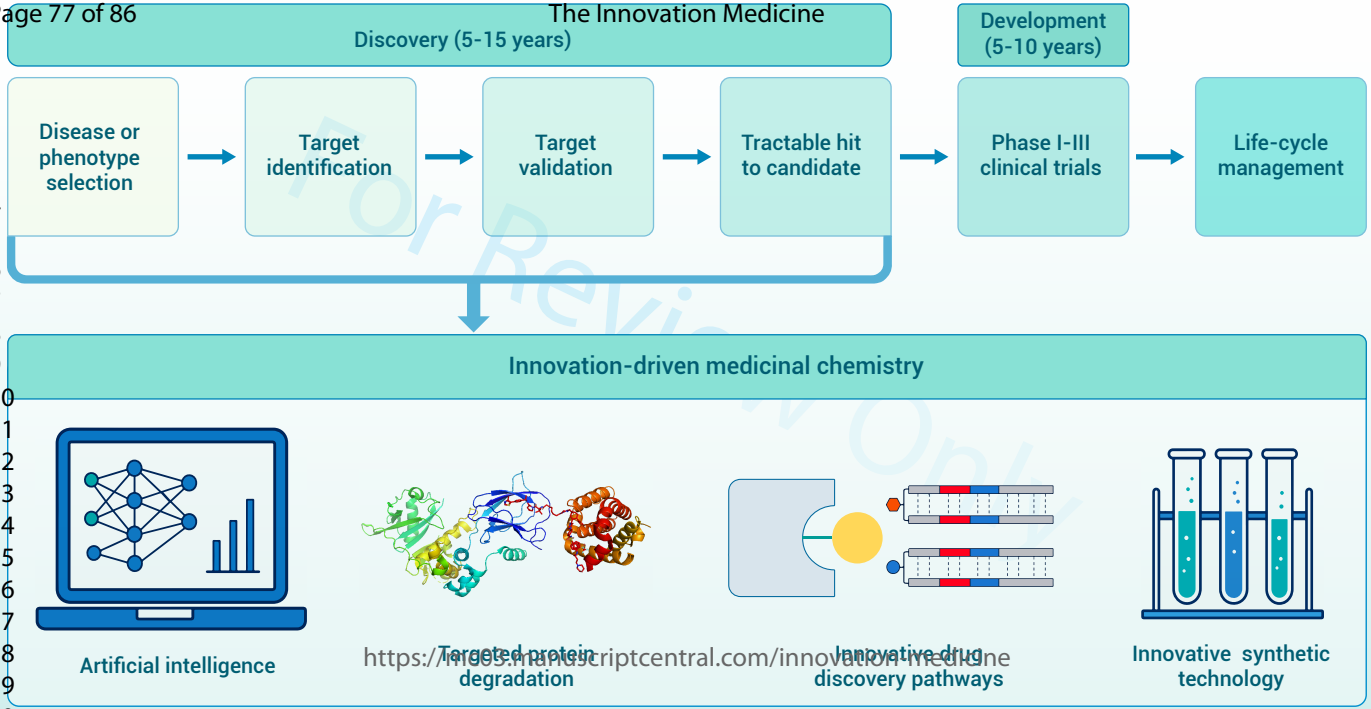
DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

Data are available from the corresponding author upon reasonable request.

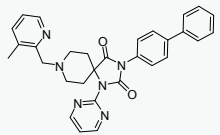




A

100,000	~70,000	100	30	3
Generation	Docking	Cluster	Scaffold selection	Synthetic routes analysis	Synthesis & Biological assessment
Target specific generation Inpainting generative model	Validity Novelty Uniqueness Diversity Physicochemical property Pharmacophore hypothesis Glide XP docking	Top 1% Docking conformation Clustering Reaction type	Synthetic accessibility Patentability assessment	Availability of synthetic raw materials Synthetic conditions analysis Synthetic routes analysis	Lead 1 Lead 2 Lead 3

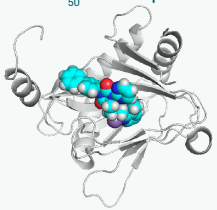
B



JPHM-2-167

PHD2 with HIF1-α CODD

IC_{50} = 0.253 μM



Structure analysis and generation input

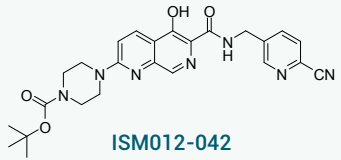
Models: Parameter setting, rewards and filters

Synthetic accessibility scoring

Hit selection, synthesis and validation

MedChem optimization

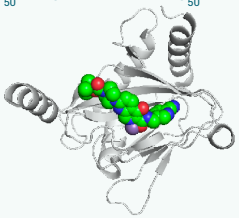
Cocrystal structure

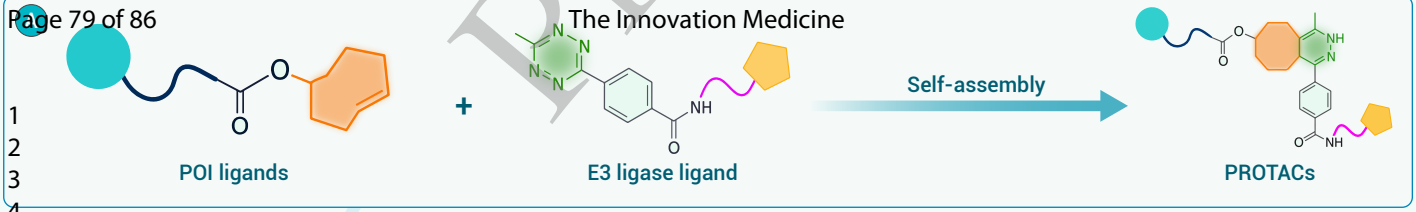


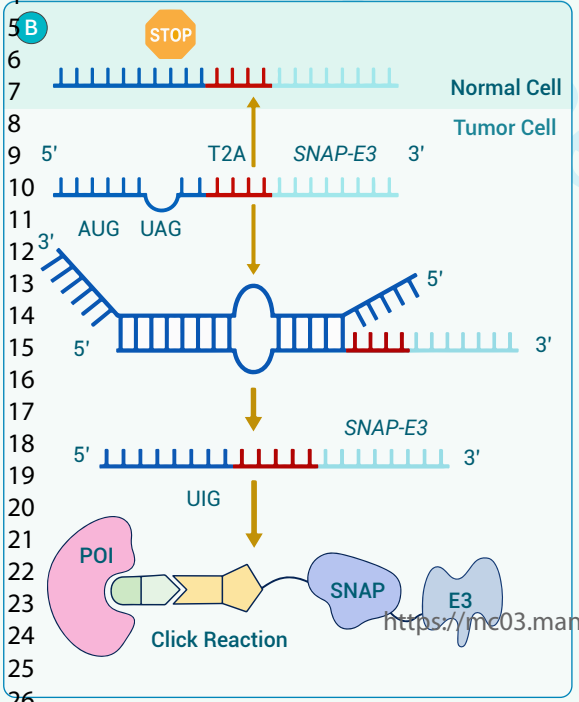
ISM012-042

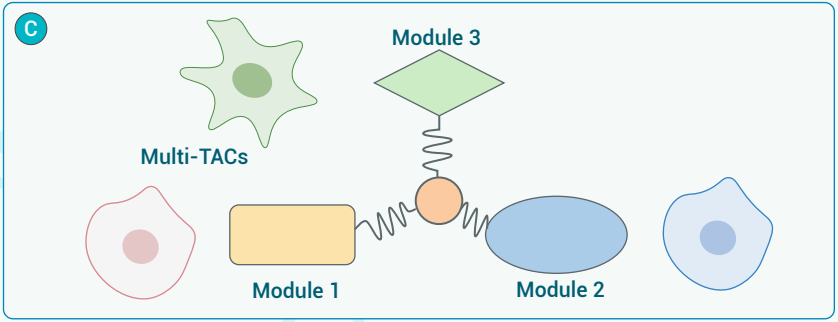
PHD1 hydroxylase IC_{50} = 1.9 nM

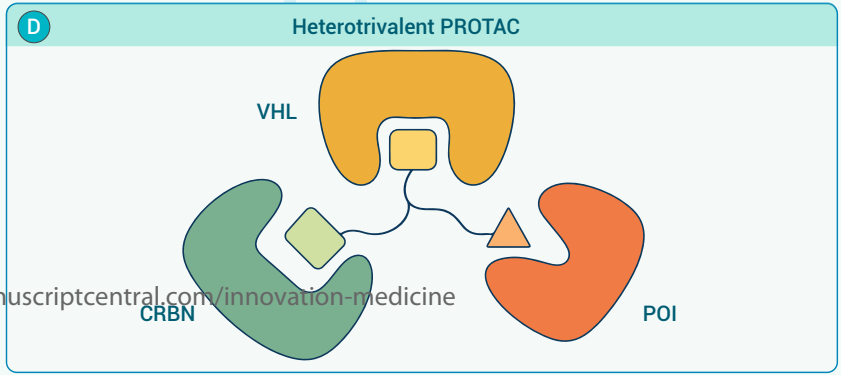
PHD2 hydroxylase IC_{50} = 2.5 nM











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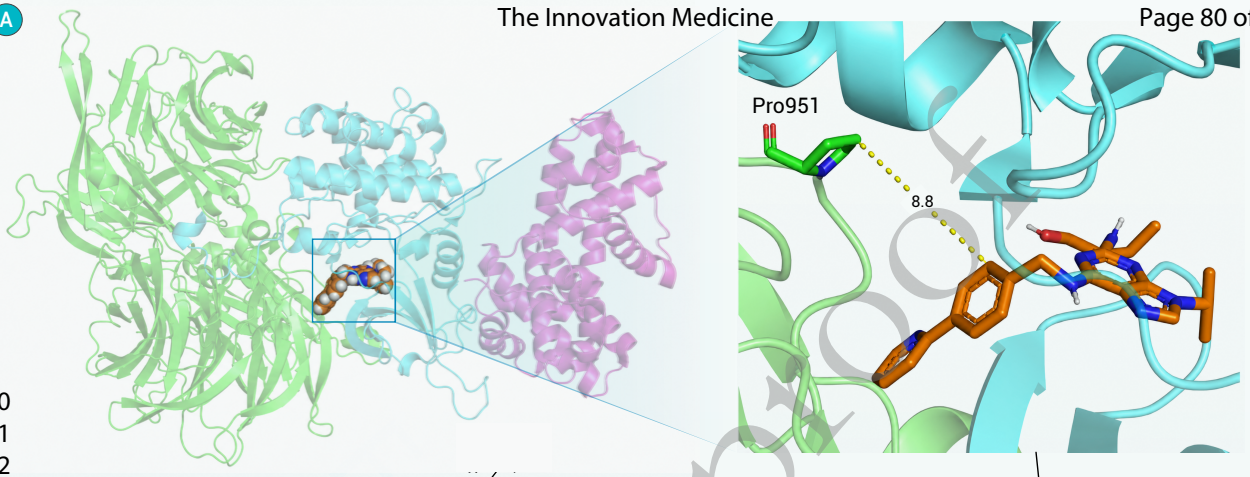
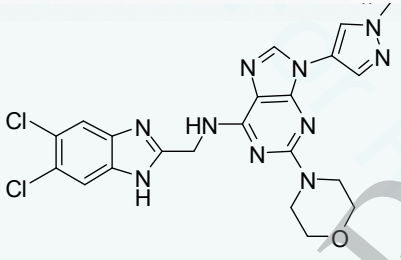
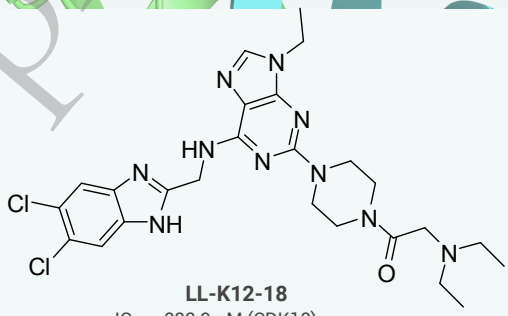




SR-4835

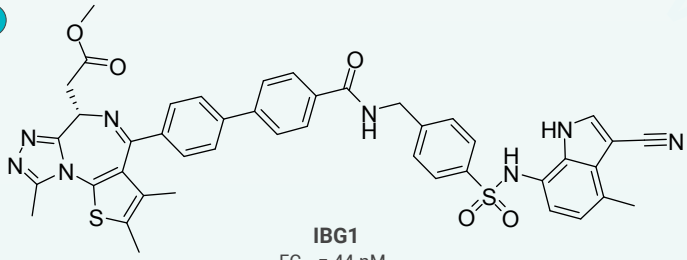
IC_{50} = 115.6 nM (CDK12)
EC_{50} = 9.21 nM (MDA-MB-468)
Cyclin K degradation 79 % (50 nM)



LL-K12-18

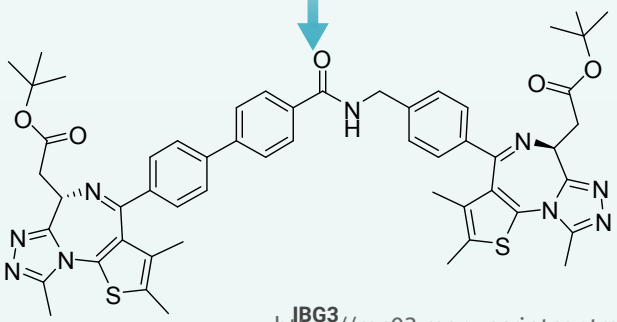
IC_{50} = 283.9 nM (CDK12)
EC_{50} = 0.03 nM (MDA-MB-468)
Cyclin K degradation 96.4 % (50 nM)

B



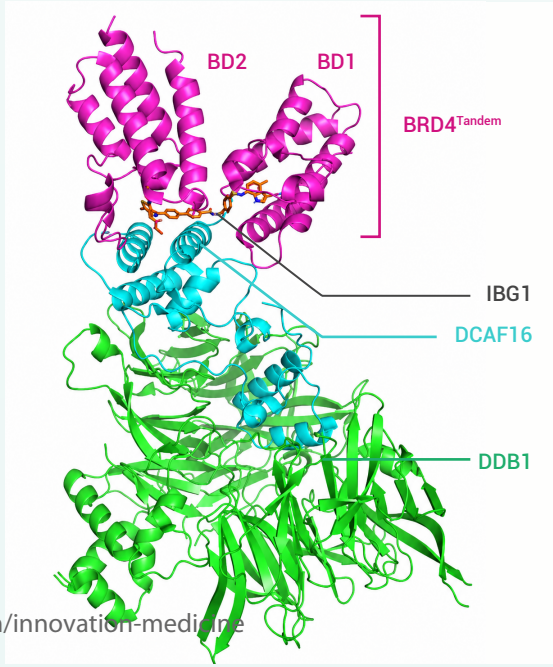
IBG1

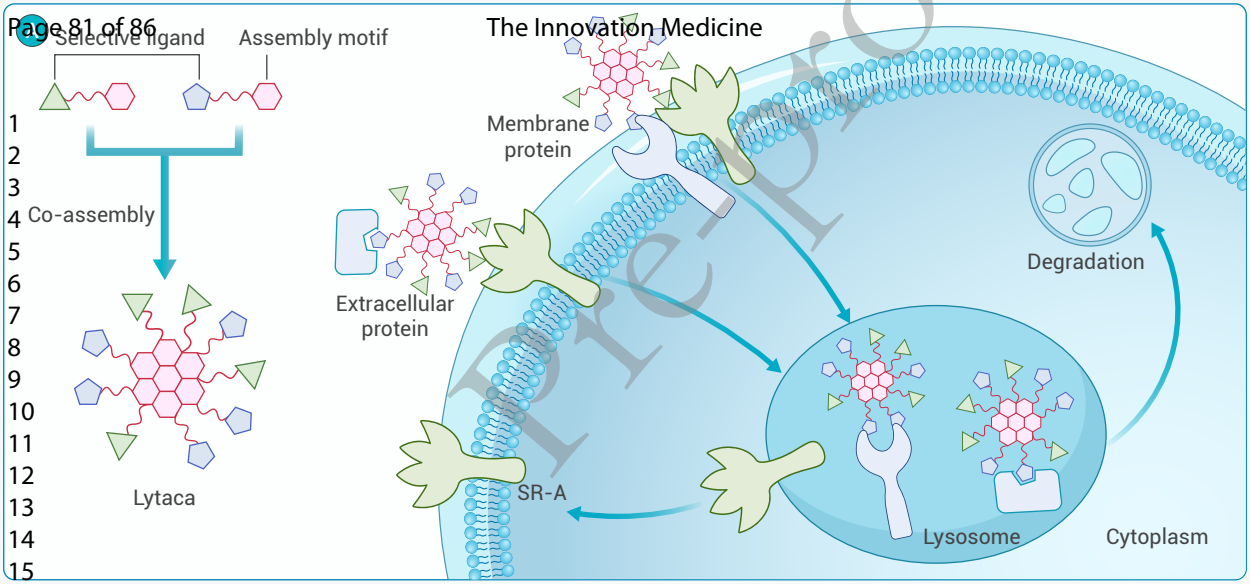
EC_{50} = 44 nM

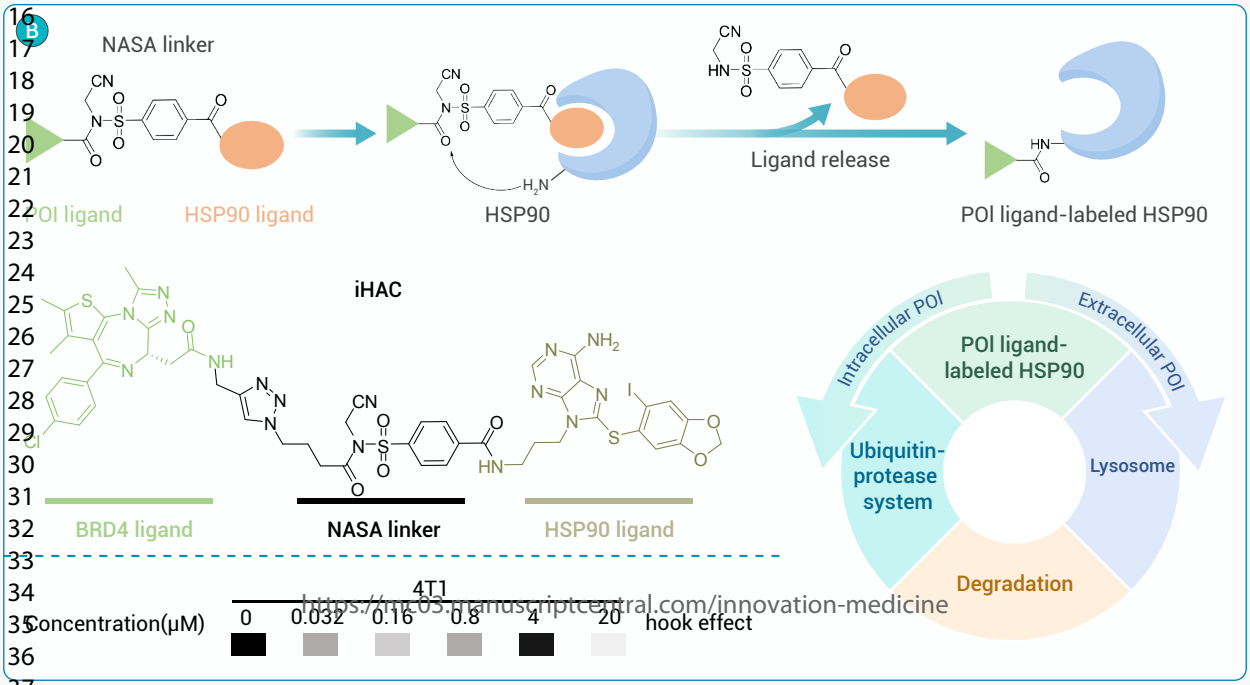


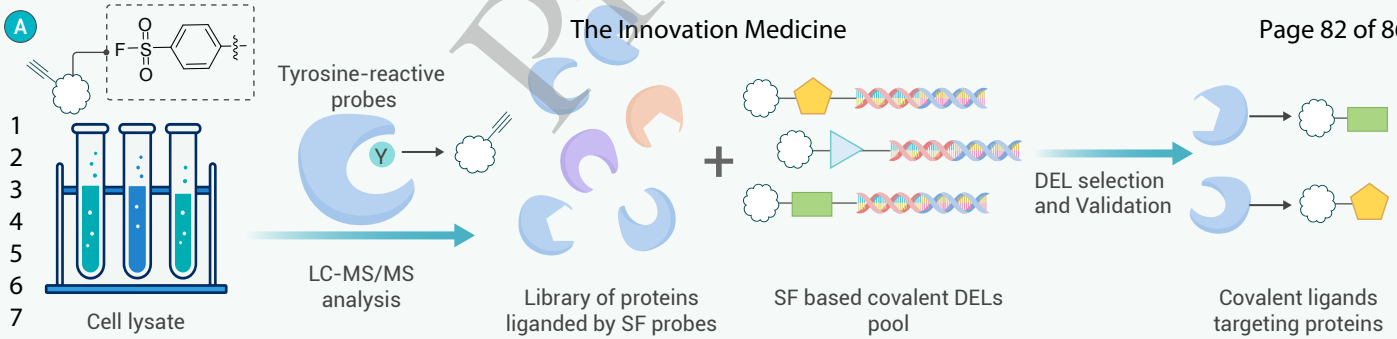
IBG3

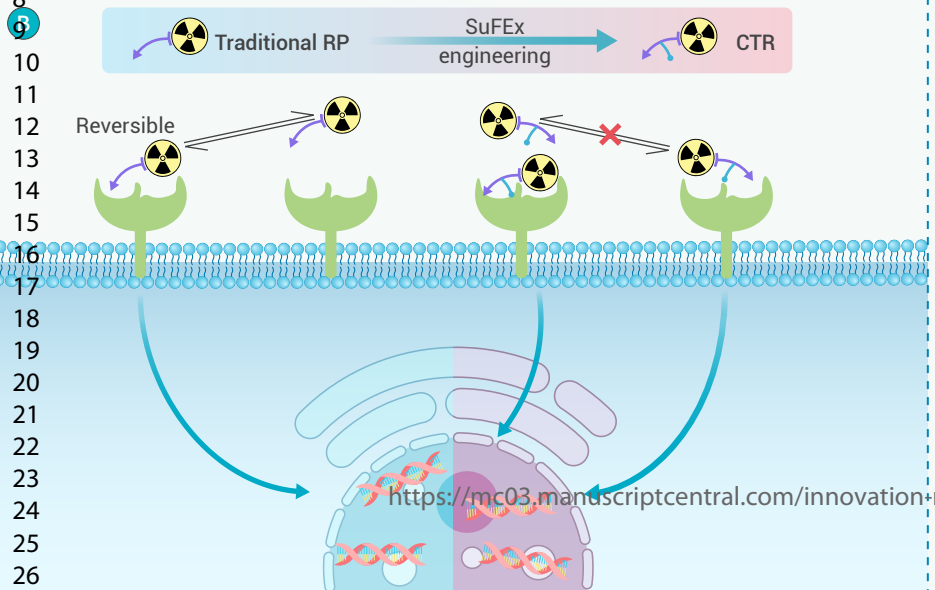
EC_{50} = 32 nM

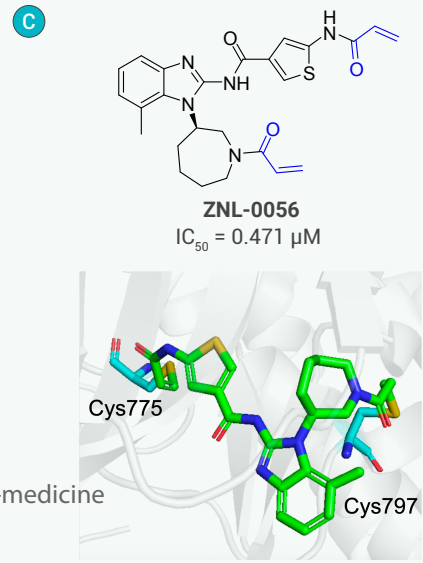


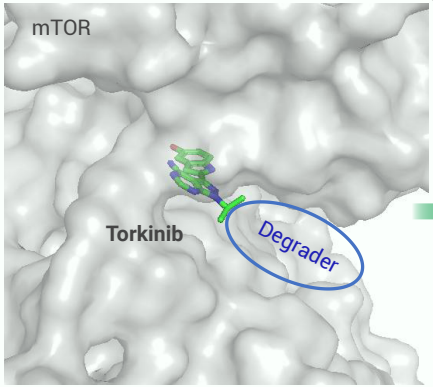


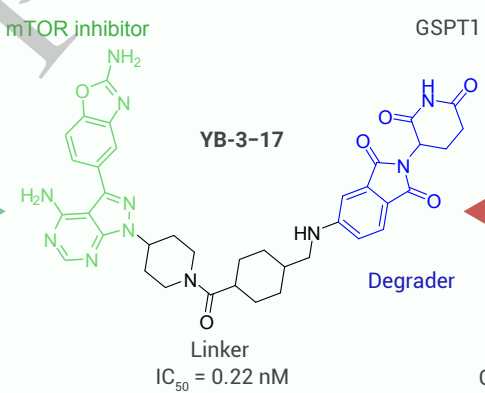


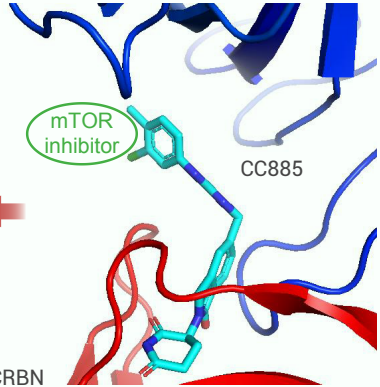












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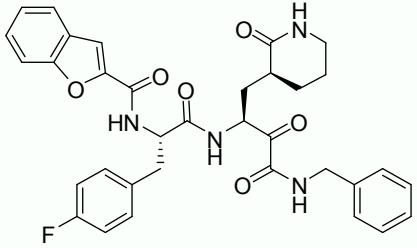

14a

IC_{50} = 3.34 nM (CTSL)
IC_{50} = 375.1 nM (CAPN1)
EC_{50} = 51.7 nM (SARS-CoV-2)