

Commentary

How new drug R&D can solve intractable scientific problems and meet clinical needs: insights from analysis of typical use cases

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ABSTRACT

New drug research and development (R&D) faces critical challenges such as drug resistance, ineffectiveness of single-target interventions, “undruggable” targets, long cycles, and high costs. This article analyzes five typical use cases to illustrate breakthrough strategies for addressing these issues. Innovations include the identification of dual-target antibiotics (paenimicin) and phospholipid-targeting antifungals (mandimycin) that overcome microbial resistance via mining silent biosynthetic gene clusters; development of “molecular glue” compounds (D927 and BBO-10203) that regulate protein-protein interactions, thus addressing insulin resistance and tumor drug resistance; AI-driven discovery of the TNIK inhibitor rentosertib for reversing pulmonary fibrosis; use of protein interface remodeling to develop the KRAS G12D inhibitor zoldonrasib for “undruggable” targets; and repurposing of existing drug combinations (letrozole plus irinotecan), on the basis of multi-omics data for Alzheimer's disease. These use cases demonstrate how interdisciplinary technologies (e.g., AI and structural biology) and strategic innovations (multi-target design and drug repurposing) can drive a transformation from experience-driven to precision and intelligence-driven R&D, and provides a reference for meeting intractable clinical needs.

Keywords: new drug R&D, drug resistance, dual-target strategy, AI-driven R&D, undruggable targets, drug repurposing, protein-protein interactions

New drug research and development (R&D) is a systematic engineering endeavor in the pharmaceutical field that is important yet fraught with major challenges. Its core mission is to address unmet clinical needs, unravel the complex mechanisms underlying disease occurrence and progression, and develop safe and effective therapeutic interventions. However, this process faces multiple obstacles: because traditional targets are prone to drug resistance, therapeutic efficacy is frequently diminished; because most diseases exhibit multifactorial pathological characteristics, single-target interventions are often ineffective; and because numerous key targets have structural properties that make them “undruggable,” the design of specific molecules for intervention is difficult. Moreover, long R&D cycles, high costs, and high failure rates have long constrained new drug

output. In recent years, through integrating interdisciplinary technologies, researchers have achieved breakthroughs in addressing drug resistance and druggability barriers, and shortening the R&D cycle, through innovative technical strategies. This article systematically analyzes the core ideas and technical pathways for overcoming intractable scientific problems in new drug R&D through five typical use cases, to provide a reference for research in related fields.

1. CASE 1: SOLVING THE DRUG RESISTANCE DILEMMA: FROM DUAL-TARGET ANTIBIOTICS TO PHOSPHOLIPID-TARGETING ANTIFUNGALS [1, 2]

Globally, multidrug-resistant (MDR) microbial infections have emerged as an “invisible plague” threatening

human health. In 2021 alone, drug-resistant bacterial infections caused approximately 1.14 million deaths, and pan-resistant fungi (such as *Candida auris* resistant to all four classes of antifungals) have led to scenarios of no available drugs for clinical treatment. Traditional anti-infective drugs have drawbacks including single-target-induced resistance, high toxicity, and poor water solubility. A team led by Zongqiang Wang from China Pharmaceutical University has developed paenimicin (targeting MDR bacteria) and mandimycin (targeting fungal phospholipids), which provide new solutions to drug resistance (Figure 1).

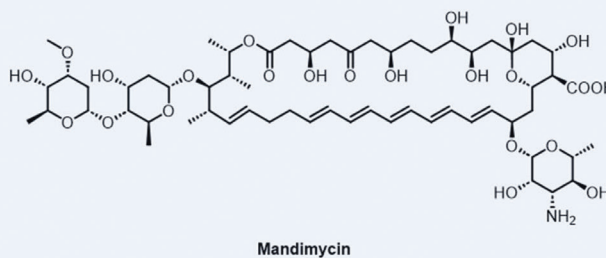
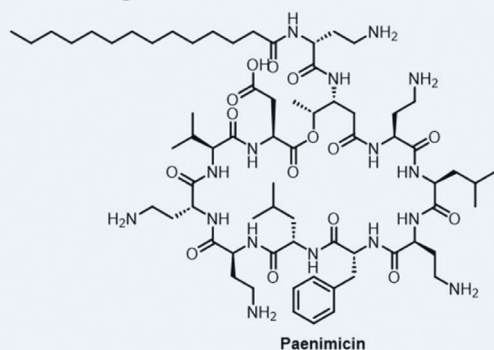
1.1 Innovative breakthroughs amid the drug resistance crisis: dual fronts against bacteria and fungi

Although the discovery of antibiotics and antifungals was a milestone in modern medicine, rapid emergence

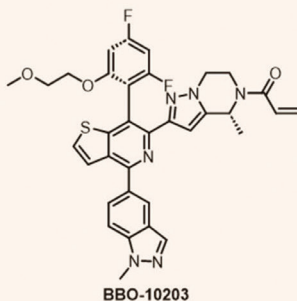
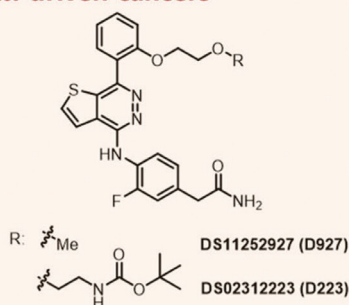
of resistance is currently undermining progress. Bacteria develop resistance via gene mutations or acquiring resistance genes, whereas fungi develop resistance through target modification or enhanced drug efflux. Traditional drug development is trapped in a cycle of high repetition and low innovation: 70% of clinical antibiotics derive from microbial secondary metabolites, yet conventional culture-based screening often rediscovers known compounds while leaving silent biosynthetic gene clusters (BGCs) underexplored.

To address bacterial resistance, researchers have focused on Paenibacillaceae, a rich source of antibiotics such as colistin and gramicidin, which bear numerous unexplored silent BGCs. By using the synthetic bioinformatic natural product (synBNP) strategy and peptide optimization technology, they bypassed traditional culture barriers, and directly predicted and synthesized potential active peptides from genomic data. Analysis of 1,245 public genomes and 11 laboratory

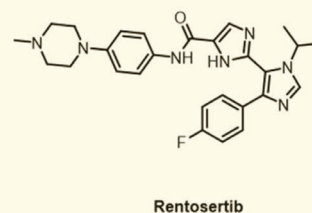
➤ Multidrug-resistant microbial infections



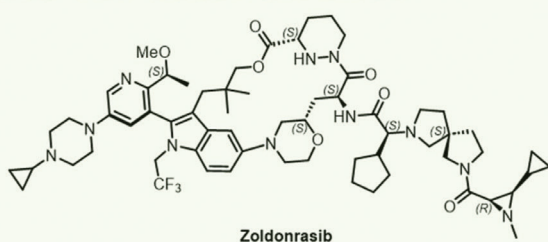
➤ PI3K α -driven cancers



➤ Idiopathic pulmonary fibrosis



➤ KRAS-G12D-mutant solid tumors



➤ Alzheimer's disease

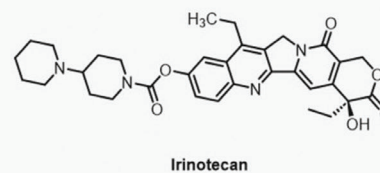
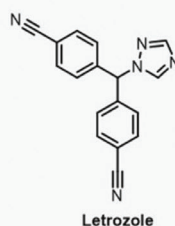


Figure 1 | Chemical structural formulas of representative compounds or drugs described herein.

Commentary

strain genomes identified a silent non-ribosomal peptide synthetase (NRPS) gene cluster and led to the discovery of paenimicin, a novel 11-mer depsilipo peptide antibiotic.

In antifungal research, traditional drugs (e.g., amphotericin B) primarily target ergosterol, with single-target resistance, high nephrotoxicity (incidence of renal adverse events as high as 80% in clinical settings), and poor water solubility (0.83 µg/mL). The researchers built a phylogeny-guided natural product discovery platform. By using glycosyltransferases involved in mycosamine transfer as molecular markers, they constructed a phylogenetic tree and identified evolutionarily unique gene clusters from 316,123 bacterial genomes. Subsequently, mandimycin, a novel polyene macrolide from *Streptomyces netropsis*, was discovered.

1.2 Mechanistic innovation: transformative dual-target and non-traditional target strategies

Paenimicin's breakthrough lies in its "dual-front" targeting mechanism. Unlike single-target antibiotics, it simultaneously binds the phosphate/hydroxyl groups of lipid A (in Gram-negative bacteria) and phosphate groups of teichoic acids (lipoteichoic acid/wall teichoic acid in Gram-positive bacteria). Molecular dynamics simulations have indicated that its positively charged diaminobutyric acid residues form electrostatic interactions with lipid A's phosphate groups, and the fifth amino acid forms hydrogen bonds with glucosamine's C-6 hydroxyl, thus conferring potency against colistin-resistant strains (MIC = 2 µg/mL). In contrast, colistin can be evaded through phosphoethanolamine modification.

In Gram-positive bacteria, paenimicin binds lipoteichoic acid with a K_d of 5.61 µM, disrupts membranes, and causes potassium efflux. Critically, no resistant mutants emerged in 30-day serial passage experiments, even in high-concentration cultures (10^9 CFU/mL), thus confirming the resistance-evading effect of this dual targeting.

Mandimycin is not dependent on ergosterol, and it targets fungal membrane phospholipids (e.g., phosphatidylinositol and phosphatidylglycerol). Its phosphatidylinositol binding (K_d = 21.9 µM) surpasses amphotericin B's ergosterol binding (K_d = 26.1 µM), according to isothermal titration calorimetry experiments. This interaction is mediated by a dideoxysaccharide consisting of digitoxose and 3-O-methyldigitoxose units. Knocking out the *mandQ* gene (responsible for disaccharide transfer) leads to production of mandimycin B, whose lack of phospholipid binding results in a shift to ergosterol dependence and 2–4 fold decreased activity. Mechanistically, membrane disruption causes rapid potassium efflux and *Candida albicans* collapse within 8 hours. No resistance has been observed at 8x the MIC, and this compound remains potent against amphotericin B-resistant strains (MIC = 0.125–2 µg/mL).

1.3 From laboratory to clinic: safety and efficacy breakthroughs

Favorable druggability is key for clinical translation. Paenimicin exhibits excellent pharmacokinetics, including a subcutaneous bioavailability of $102\% \pm 13\%$, a 20.2-hour half-life (10x that of colistin), and a longer half-life after subcutaneous than intravenous injection. Moreover, it has shown ultra-low toxicity ($HC_{50} > 100$ µg/mL against HepG2 cells; $LD_{50} > 500$ mg/kg) and no obvious renal toxicity in mice (40 mg/kg for 7 days). In animal models, 20 mg/kg has been found to decrease carbapenem-resistant *Acinetobacter baumannii* burden by $2.40 \log_{10}$, colistin-resistant Enterobacteriales by $>3 \log_{10}$, and methicillin-resistant *Staphylococcus aureus* by $5.90 \log_{10}$ (performing comparably to vancomycin).

Mandimycin solves the drawbacks of polyene, including water solubility (8.07 mg/mL, 9,700x that of amphotericin B), thus enabling easy administration, and its IC_{50} against renal HK-2 cells (48.28–88.67 µM) is 7–22x that of amphotericin B. After 30 mg/kg intravenous injection, mice show no obvious renal injury, whereas severe damage is observed after administration of 2 mg/kg amphotericin B. Moreover, this compound is effective against WHO-prioritized MDR fungi (MIC = 0.25–2 µg/mL for *C. albicans*/*C. auris*; 0.125 µg/mL for *Cryptococcus neoformans*). In invasive candidiasis mouse models, 10 mg/kg achieves 100% survival in invasive candidiasis; decreases amphotericin B-resistant *C. auris* burden by $2.3 \log_{10}$; and lowers vaginal fungal load by $2.51 \log_{10}$ while decreasing inflammation.

1.4 Scientific insights and clinical value: a new paradigm for anti-infective R&D

These successes offer critical insights. Regarding discovery strategies, synBNP and phylogeny-guided screening bypass culture limits, thus enabling mining of silent BGCs from genomes to boost efficiency. This "gene-to-structure" approach is scalable to other microorganisms. Regarding target design, dual targets (paenimicin) and non-traditional targets (mandimycin) avoid single-target resistance. Their "dual-locking" on bacterial membranes and multi-point phospholipid attack hinder resistance via simple mutations, thereby guiding the design of long-acting drugs.

Regarding druggability optimization, structural modifications (paenimicin's cyclization decreasing serum binding, and mandimycin's dideoxy sugar enhancing solubility) demonstrate a valuable structure-function linkage for natural product optimization. Clinically, they serve as last-line defenses: paenimicin targets colistin-resistant Gram-negative bacteria and methicillin-resistant *S. aureus*, whereas mandimycin targets amphotericin B-resistant fungi (e.g., pan-resistant *C. auris*) and has strong potential for use in immunocompromised patients. These advances have reshaped anti-infective R&D. The use of evolutionary perspectives to mine natural products, the development of multi-target strategies,

and the use of structural optimization provide a promising route to overcome microbial resistance.

2. CASE 2: METABOLIC AND CANCER DUAL-TARGET DRUGS REGULATING PROTEIN-PROTEIN INTERACTIONS: ADDRESSING SIMULTANEOUS RESISTANCE TO INSULIN AND TUMOR DRUGS [3, 4]

In diabetes treatment, insulin resistance limits the efficacy of existing drugs, and traditional PI3K inhibitors tend to cause adverse effects such as hyperglycemia. In cancer treatment, abnormal activation of PI3K α is a key driver of tumor progression; however, because existing inhibitors cannot distinguish the PI3K α activity in normal tissues vs. tumor tissues, their clinical application is restricted. For example, the incidence of hyperglycemia with PI3K α inhibitors in tumor treatment exceeds 30%, thus severely affecting the implementation of treatment regimens and patient tolerance.

Terayama et al. [4] have developed “molecular glue” compounds (D223 and D927), which stabilize the conformation of the RAS-binding domain of PI3K α ; promote the binding of RAS and PI3K α ; and thereby activate glucose uptake pathways without a need for insulin (Figure 1). A derivative compound, BBO-10203, achieves selective inhibition of tumor PI3K α activity by covalently binding PI3K α and blocking RAS interaction (Figure 1).

D927 rapidly decreases blood glucose in Zucker obese rat models, increases the glucose infusion rate by 30%, and markedly enhances skeletal muscle glucose uptake. In addition, BBO-10203 effectively inhibits AKT phosphorylation in HER2-amplified tumor models ($IC_{50} = 6$ nM) without hyperglycemic adverse effects. Combination treatment with BBO-10203 and CDK4/6 inhibitors has achieved a tumor regression rate of 80%. Mechanistic studies have indicated that D927 activates the glucose transporter GLUT4 by enhancing RAS-PI3K α interaction, whereas BBO-10203 achieves precise inhibition by specifically blocking the RAS-PI3K α signaling pathway in tumor cells (Figure 2).

D927 provides a new therapeutic direction for insulin-resistant diabetes and is particularly suitable for patients with insufficient insulin secretion. BBO-10203 offers a highly selective treatment regimen for PI3K α -driven tumors (such as HER2-positive breast cancer). This strategy validates the dual application value of protein-protein interaction regulation in the metabolic and tumor fields. For other disease areas, developing “functionally selective” drugs by precisely regulating protein interaction interfaces has potential to simultaneously increase efficacy and decrease adverse effects, thus providing an important reference for target intervention in neurodegenerative diseases, autoimmune diseases, and other fields.

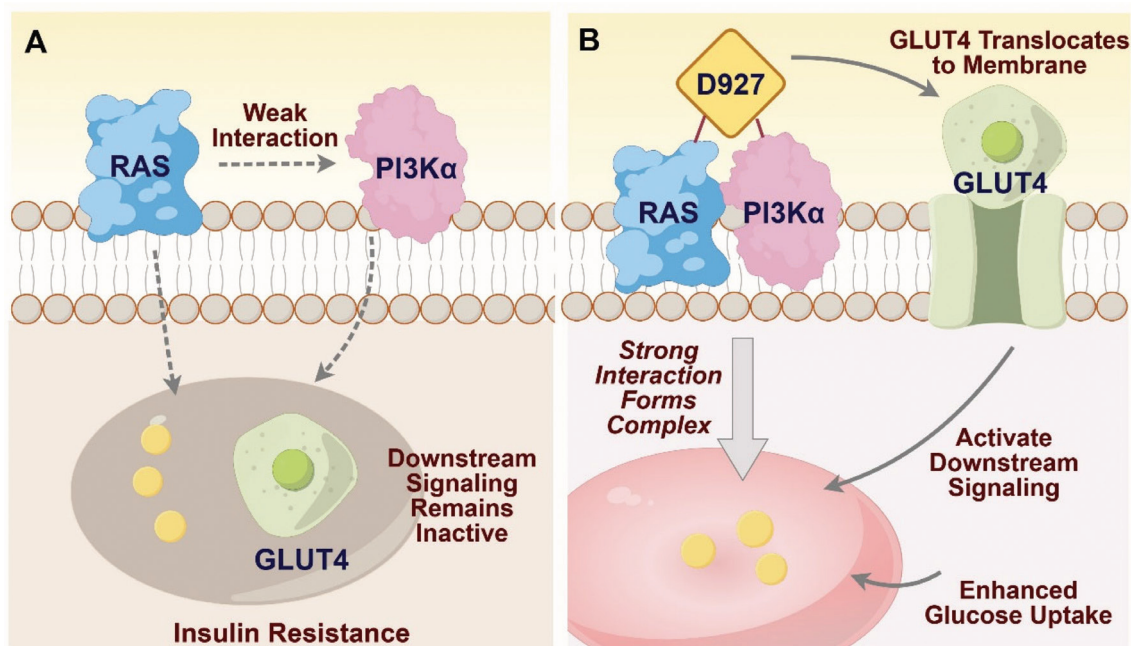


Figure 2 | Schematic diagram of the “molecular glue” D927 in regulating RAS-PI3K α interaction and ameliorating insulin resistance.

In the insulin-resistant state (A), the weak interaction between RAS and the RAS-binding domain (RBD) of PI3K α leads to inactive downstream signaling; the glucose transporter GLUT4 remains trapped in intracellular vesicles, thus resulting in insufficient glucose uptake. After D927 treatment (B), D927 binds the RBD of PI3K α and stabilizes its conformation, thereby promoting the formation of a stable RAS-PI3K α complex. The subsequent activation of downstream signaling cascades drives GLUT4 translocation to the cell membrane and enhances glucose uptake independently of insulin.

Commentary

3. CASE 3: AI-DRIVEN R&D OF PULMONARY FIBROSIS DRUGS: FROM TARGET DISCOVERY TO CLINICAL REVERSAL [5]

Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal disease. Existing drugs (such as nintedanib) can only slow disease progression but cannot reverse the decline in lung function, and precise targets are lacking. Because the 5-year survival rate of patients with IPF is below 30%, effective therapeutic approaches are urgently needed.

Xu et al. [5] have identified TNIK as a key regulatory target for IPF by using the generative AI platform PandaOmics and designed the small-molecule inhibitor rentosertib, which targets the multiple profibrotic and proinflammatory functions of TNIK (Figure 1). In a phase IIa clinical trial, patients receiving 60 mg once daily showed an increase in forced vital capacity of 98.4 mL from baseline (95% confidence interval 10.9–185.9), representing a obvious improvement over the –20.3 mL observed in the placebo group. Serum proteomic analysis revealed downregulated expression of fibrosis-associated proteins (such as COL1A1 and MMP10). The drug was well tolerated and had a treatment-related serious adverse event rate below 12%. Mechanistic studies indicated that rentosertib decreases the secretion of profibrotic cytokines and promotes fibroblast apoptosis by inhibiting the TNIK-mediated TAK1-NF- κ B pathway. With the AI platform, the cycle from target discovery to clinical research was shortened to 30 months, thus markedly attenuating the traditional drug development timeline.

Rentosertib, the first drug showing potential to reverse lung function, has provided a revolutionary breakthrough in IPF treatment. Its AI-driven target discovery and drug design paradigm have validated the value of AI in target prediction and compound design, particularly for diseases with complex etiologies that are difficult to address with traditional methods (such as neurodegenerative diseases and rare diseases). This pathway promotes a transformation from experience-driven to data-intelligence-driven drug R&D.

4. CASE 4: DEVELOPMENT OF KRAS G12D INHIBITORS BY REMODELING PROTEIN INTERFACES: A NEW PARADIGM FOR “UNDRUGGABLE” TARGETS [6]

KRAS G12D is among the most common mutation types in solid tumors. The encoded protein's aspartic acid has low nucleophilicity, and the lack of traditional surface small-molecule binding pockets hinders targeting with traditional drug design methods, thus resulting in a long-term lack of effective therapeutic drugs in clinical practice. For example, the 5-year survival rate of patients with KRAS G12D mutated pancreatic cancer is below 5%, thus representing an extremely urgent treatment need.

Weller et al. [6] have designed small-molecule compounds based on cyclosporin A (CYPA). By using CYPA to form a new protein interface with KRAS G12D, the aziridine warhead is precisely positioned through a rigid linker to achieve covalent inhibition of G12D. The candidate drug zoldonrasib has achieved an objective response rate of 60% and a disease control rate of 77% in 30 KRAS G12D tumor models (Figure 1). In animal models, the tumor doubling time was markedly prolonged (median 10 days in the control group vs. not reached in the treatment group), and deep and durable tumor regression was achieved in pancreatic cancer and lung cancer models. Mechanistic studies have indicated that zoldonrasib specifically modifies the G12D residue by inducing the formation of a CYPA-KRAS G12D complex, thus blocking its interaction with downstream effector proteins. This strategy avoids interference with wild-type KRAS and markedly enhances safety.

Zoldonrasib, the first potent candidate drug for refractory cancers with KRAS G12D mutations (such as pancreatic cancer and colorectal cancer), has entered phase I clinical trials. Its protein interface remodeling strategy overcomes the limitations of traditional target druggability, thus offering a promotable technical route for targeted therapy of other “undruggable” proteins, which is particularly suitable for difficult-to-target targets such as viral proteins and transcription factors.

5. CASE 5: COMBINING EXISTING DRUGS FOR ALZHEIMER'S DISEASE TREATMENT: A BREAKTHROUGH IN HUMAN DATA-DRIVEN PRECISION MEDICINE [7]

Alzheimer's disease (AD), a multifactorial neurodegenerative disease, has long perplexed the academic community because of its pathological heterogeneity (such as A β plaques, tau tangles, neuroinflammation, and cell type-specific gene dysregulation). The failure rate of traditional single-target therapies is as high as 98%, and existing treatments can only alleviate symptoms but cannot halt disease progression. More than 50 million people are affected worldwide, and this number is expected to triple by 2050, with annual costs exceeding one trillion US dollars. Therefore, effective therapeutic approaches are urgently needed.

Li et al. [7] have proposed a cell-type-directed network correction therapy. The authors used three types of human data sources: cross-study single-cell transcriptomic data (analysis of 179,690 nuclei, which identified differential expression profiles in six key pathological cell types including neurons and glial cells); the Connectivity Map drug perturbation database (screening for drugs with potential to reverse AD gene networks); and millions of electronic medical records (from the UC health system) to verify the association between drugs and AD risk. Through computational biology methods, they identified a combination regimen using the existing

drugs letrozole (targeting neurons) and irinotecan (targeting glial cells) (**Figure 1**).

In A β and tau dual-pathology mouse models, this combination therapy markedly ameliorated short-term and long-term spatial memory (increase in target quadrant residence time at 24 hours and 72 hours to >80%, $p < 0.005$), and decreased AD pathological damage (40% decrease in A β plaques, 32% decrease in p-tau, marked recovery of hippocampal volume ($p = 0.0003$), and restored neuron density in the CA1 region). Electronic medical record data indicated that patients treated with letrozole or irinotecan had a 53.4% (relative risk 0.466) and 80.5% (relative risk 0.195) AD risk reduction, respectively. Single-cell sequencing confirmed that this therapy reversed abnormal gene networks in neuronal synaptic pathways and glial cell inflammatory responses. Both drugs are FDA approved and have established safety profiles, thus markedly shortening the clinical translation cycle. This paradigm provides a precision medicine framework for multifactorial diseases, and might promote personalized treatments based on patients' transcriptomic and clinical characteristics.

This study validates the efficiency of repurposing existing drugs and demonstrates the core value of multi-omics data integration in R&D for complex diseases, thus providing a paradigm for multi-target treatment of cancers, cardiovascular diseases, and other multifactorial diseases.

6. SUMMARY AND OUTLOOK

The above use cases demonstrate the value of new drug R&D in solving intractable scientific problems, including addressing unmet clinical needs (e.g., drug-resistant infections, irreversible fibrosis, difficult-to-target mutations, and multifactorial neurodegenerative diseases) through technological innovation (e.g., phylogeny-guided screening, AI design, protein interface remodeling, and multi-omics integration) and strategic innovation (mining non-traditional targets, regulating protein interactions, and repurposing and combining existing drugs), thus achieving breakthroughs in precision treatment for previously “undruggable” targets.

Each use case presents a unique R&D paradigm. The antifungal drug mandimycin avoids drug resistance by mining non-traditional targets (phospholipids), thereby validating the value of innovative natural product screening strategies. Metabolic and cancer dual-target drugs achieve functional selectivity by regulating protein interactions (enhancing/blocking RAS-PI3K α binding), thereby providing ideas for cross-disease target intervention. The AI-driven R&D of rentosertib demonstrates the value of data intelligence in accelerating R&D for complex diseases by shortening R&D cycles. Zoldonrasib overcomes the “undruggable” bottleneck of KRAS G12D through protein interface remodeling and expands the boundaries of covalent drug design. Finally, the existing drug combination strategy for AD

achieves precise network correction based on multi-omics integration and highlights the efficiency of existing drug repurposing in multifactorial diseases.

In the future, with deepening integration of interdisciplinary fields (such as AI and pharmacy, structural biology, chemistry, multi-omics, and computational biology), new drug R&D is expected to solve scientific problems with enhanced accuracy. The systematic mining of non-traditional targets may further enrich treatment options; protein interaction regulation technologies may drive the development of more functionally selective drugs; AI and multi-omics technologies may accelerate R&D for complex diseases; protein interface remodeling strategies may provide solutions for more “undruggable” targets; and existing drug repurposing and combination may become important pathways for treating multifactorial diseases. These innovations are expected to further promote the transformation from experience-driven to precision and intelligence-driven R&D for new drugs, thus bringing hope for cures for more diseases.

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AUTHOR CONTRIBUTIONS

Yuning Song, Peng Zhan, and Haiyong Jia conceived the idea. Mei Wang and Kai Song wrote the draft manuscript. Yuning Song, Peng Zhan, and Haiyong Jia revised the manuscript. All authors have read and approved submission of the final manuscript.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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Commentary

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