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Tuning complex life networks: Single-molecule multi-target strategies transforming metabolic disease treatment

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Dear Editor,

The evolution of drug discovery paradigms in metabolic diseases is fundamentally driven by in-depth mechanistic insights into disease pathogenesis and advances in innovative technologies. For decades, therapeutic development has largely followed a single-target paradigm, aiming to correct disease by modulating individual proteins. While this strategy has yielded many successful medicines, its limitations have become increasingly apparent in complex disorders.[1]

However, compared with many other diseases, metabolic disorders are characterized by systemic, multi-organ dysfunction involving tightly interconnected metabolic, inflammatory, endocrine, and immune pathways. As a result, pathological progression is rarely driven by a single molecular abnormality but instead arises from network-level disturbances in biological homeostasis. The intrinsic complexity of biological networks, characterized by feedback regulation and compensatory mechanisms, often limits the long-term efficacy of highly selective interventions.

Although combination therapies can achieve multi-pathway modulation, they frequently suffer from pharmacokinetic mismatches, drug–drug interactions, and poor patient compliance. These challenges have stimulated growing interest in single-molecule multi-target therapeutics, which seek to coordinate multiple disease-relevant pathways through a single chemical entity. By restoring network homeostasis rather than modulating isolated targets, this strategy offers a promising framework for addressing the complexity of metabolic diseases (Figure 1).

RATIONAL CONSTRUCTION OF TARGET COMBINATIONS: MECHANISTIC DECODING AND SYNERGISTIC REPROGRAMMING OF COMPLEX PATHOLOGICAL NETWORKS

A series of cutting-edge studies have verified the strengths of the multi-target drug discovery paradigm. In regulating uric acid homeostasis and suppressing inflammation, the "single-molecule, multi-target" strategy exhibits promising translational prospects. Traditional urate-lowering medicines such as febuxostat and lesinurad can reduce serum uric acid, yet they hardly relieve acute inflammation of gouty arthritis and carry potential toxicity upon long-term administration. Conversely, purely anti-inflammatory treatments often address only symptoms rather than pathogenesis, and they fail to fundamentally resolve hyperuricemia, which is a root metabolic factor. In 2025, our team published a study in *Nature Communications* that provided an innovative solution through natural product–guided phenotypic drug discovery.[2] Phenotypic drug discovery is not a regression to empirical trial-and-error but a rational, systems-level strategy. It "black-boxes" the molecular network complexity within the human body, directly anchoring on the overall therapeutic phenotype of uric acid reduction and anti-inflammation rather than being entangled in isolated target details, which follows the core principle of systems biology that systemic phenotypic evaluation delivers more reliable therapeutic efficacy signals. The study used *β*-carboline-1-propionic acid, an active component of *Eurycoma longifolia*, as the lead, constructing a URAT1/NLRP3 dual-target pharmacophore model to achieve a single-molecule, multi-effect design that simultaneously inhibits URAT1/OAT4/GLUT9 urate transport and targets NLRP3 inflammation. Compound 32, which synergistically inhibited urate transport pathways and precisely modulated inflammatory nodes, achieving a uric acid reduction rate of 93.42% (superior to lesinurad) and effectively alleviating joint inflammation. Acute toxicity testing showed no significant adverse effects even at a dose of 1000 mg/kg. This study validates that moving beyond mechanistic single-point interventions and adopting phenotype-oriented multi-target design is a feasible paradigm for achieving highly effective and low-toxicity therapy.

Similarly, current single-target and partial multi-target drugs still exhibit clear clinical limitations in the treatment of dysregulated glucose and lipid metabolism. Semaglutide-based GLP-1R single-target agents and GLP-1R/GIPR dual-target agents, such as tirzepatide and RAY1225, have demonstrated remarkable efficacy in weight reduction and glycemic control. Notably, RAY1225 had progressed into Phase 2 clinical trials, highlighting the growing clinical validation of dual-incretin strategies. However, these agents remain limited in addressing broader metabolic dysfunction, including insulin sensitization, chronic inflammation, and comprehensive hepatic protection.[3] Meanwhile, the PPARα/γ/δ triple agonist Lanifibranor effectively improves liver fibrosis in MASH Phase 2b trials but shows weak weight-loss and glucose-lowering effects, requires high dosing (30 mg/kg), and is associated with adverse effects such as weight gain, anemia, and fluid retention.[4]

In 2026, the Müller team published a study in *Nature* presenting a single-molecule quintuple agonist that offers an optimal solution to this challenge.[5] By covalently linking GLP-1R/GIPR dual-target activity with PPARα/γ/δ triple-target activity, they successfully constructed a five-target compound. This molecule, through synergistic action of incretin and PPAR pathways, further reduced body weight, food intake, and hyperglycemia in obese and insulin-resistant mice. Moreover, precise targeted delivery mediated by incretin receptors reduced the effective dose to 10 nmol/kg—nearly 6,900-fold lower than Lanifibranor alone (68.98 μmol/kg)—while largely mitigating common adverse effects og traditional PPAR agonist such as anemia and fluid retention, providing a new high-efficacy, low-toxicity approach for comprehensive treatment of dysregulated glucose and lipid metabolism and related complications.

Although Alzheimer's disease (AD) is traditionally classified as a neurodegenerative disorder, growing evidence links its progression to metabolic dysfunction, chronic inflammation, circadian disruption, and aging, making it a representative network disease suitable for multi-target intervention. Because biological aging is a major driver of AD progression, therapies capable of simultaneously modulating aging-related and neurodegenerative pathways are particularly attractive. In 2026, the Li team developed the AI-driven platform PTD-DEP to identify compounds with coordinated anti-aging and anti-AD activities.[6] From a library of 92 anti-insomnia drugs, melatonin was selected as the optimal candidate. Mechanistic studies revealed that melatonin directly targets p300 and restores BMAL1-dependent circadian regulation, thereby improving redox homeostasis and promoting neuroprotection. This work demonstrates the potential of AI-guided discovery to identify single molecules that simultaneously regulate interconnected pathological networks.

In summary, the development of multi-target drugs is not only about constructing new molecules but also involves in-depth exploration and precise reprogramming of the mechanisms of existing molecules, thereby achieving systematic regulation of complex disease pathological networks.

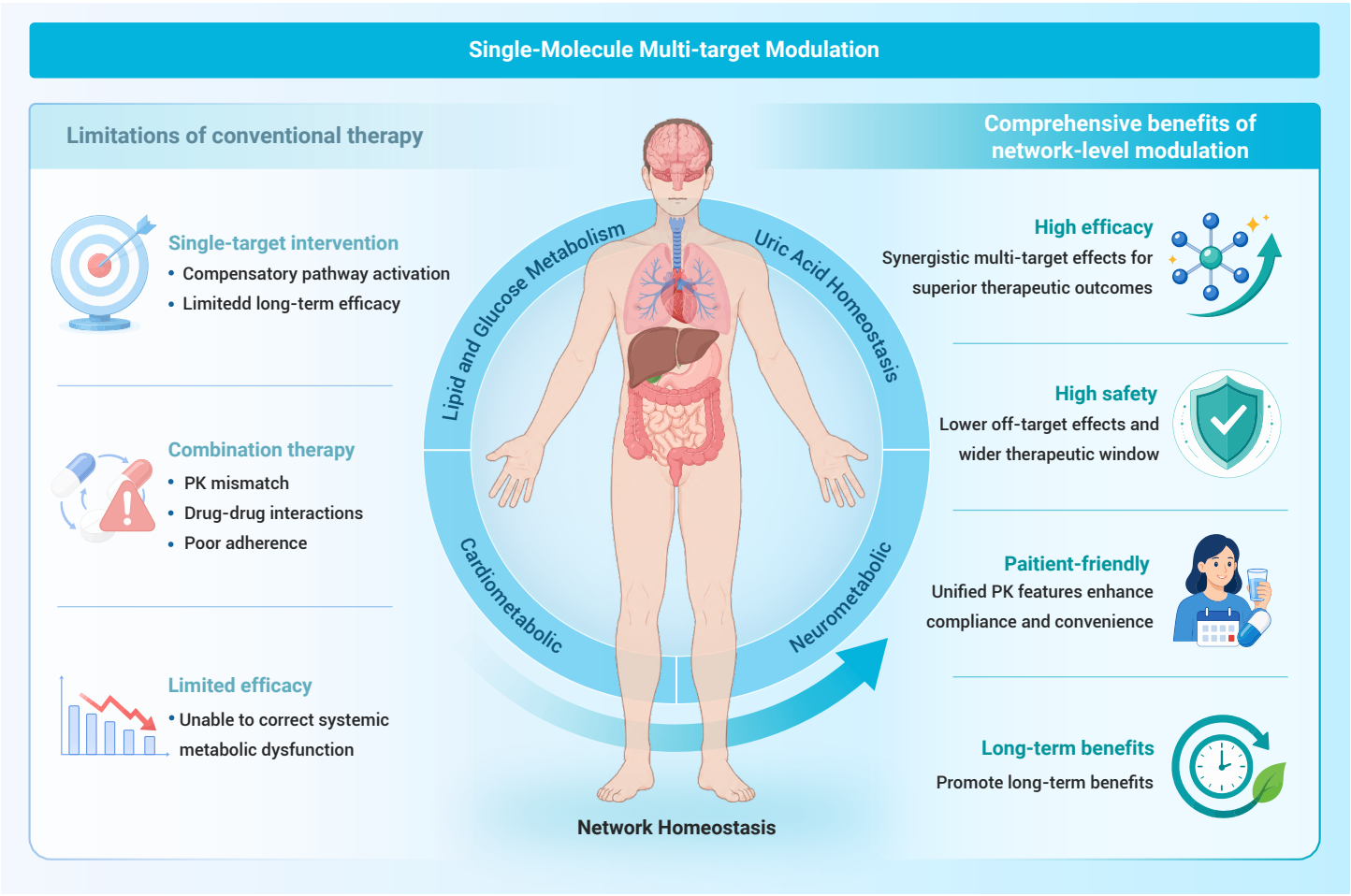

Figure 1. Comparative analysis of single-molecule multi-target drugs and traditional therapeutic strategies for metabolic diseases

THE ART OF SYSTEMIC REGULATION: DESIGN PRINCIPLES AND EFFICACY-BALANCING STRATEGIES FOR MULTI-TARGET DRUGS

The main challenge in multi-target drug design is to move beyond simple target stacking. Instead, effective designs should emphasize synergistic complementarity and balanced regulation. Targets within the same pathway can cooperate to enhance efficacy and prevent compensatory escape mechanisms, while targets across distinct pathological axes enable network-level intervention. Importantly, the activity of each target must be carefully balanced: core targets should strongly inhibit key pathological nodes, whereas auxiliary targets should provide moderate modulation to maintain network homeostasis and minimize toxicity.[7] This represents the "art of systemic regulation" in multi-target drug design.

For example, in obesity treatment, potent GLP-1R activation can drive weight loss, while moderate PPAR modulation improves metabolic health, achieving greater clinical tolerability than indiscriminate strong intervention. It can be seen that rather than acting on redundant pathways, optimal target pairs regulate distinct yet interconnected pathological processes, thereby simultaneously suppressing disease-driving mechanisms while reinforcing endogenous compensatory networks. Compared with combination therapies, single-molecule multi-target agents offer unified pharmacokinetics, reduced drug–drug interaction risk, and simplified dosing regimens. Nevertheless, integrating multiple pharmacological activities into one molecule while maintaining favorable physicochemical and pharmacokinetic properties remains a major medicinal chemistry challenge.

AI-ENABLED PRECISION REGULATION: ENTERING A PROGRAMMABLE AND PREDICTABLE PARADIGM FOR MULTI-TARGET DRUG DEVELOPMENT

Achieving precise network-level modulation via multi-target drugs cannot be accomplished through traditional empirical trial-and-error strategies, which fail to satisfy the regulatory requirements of complex biological systems, while mechanistic single-point intervention is also inadequate to overcome systemic compensatory barriers. Currently, the drug development pathway is transitioning from empirical medicine to an AI-enabled era of precise regulation in complex systems: natural product–guided phenotypic screening anchors the overall therapeutic effect, avoiding entanglement in molecular details; rational integration of pharmacophores constructs a multi-target synergistic scaffold; meanwhile, generative AI brings a fundamental logic revolution—technologies such as LaMGen (LLM-driven 3D molecular generation) and EVOSYNTH (evolutionary optimization with synthesis feasibility assessment) break through the mechanical limitations of traditional target-based design,[8,9] enabling prediction and generation of single-molecule, multi-target entities that align with pathological network regulation, match overall phenotypic requirements, and possess drug-like properties. This advances drug development from "component-level trial-and-error" to "system-level customization".

This signifies that multi-target design is transitioning from a random, highly inspiration-dependent empirical exploration to a programmable and predictable engineering process. By integrating pathway analysis, transcriptome simulation, and single-cell perturbation profiles, AI can assess a molecule's "efficacy-toxicity" balance computationally before synthesis. This integrated approach is ushering in an era of personalized, network-tailored therapies for complex metabolic diseases.

CONCLUSION AND OUTLOOK: CENTERED ON HOMEOSTASIS REMODELING, USHERING IN A NEW ERA OF PRECISION THERAPY FOR METABOLIC DISEASES

In summary, metabolic diseases are complex network disorders driven by the dynamic interplay of multiple pathological pathways. A key breakthrough

in their treatment lies in moving beyond the traditional single-target paradigm and toward coordinated regulation of biological systems at the network level. The single-molecule multi-target strategy is centered on the concept of homeostasis remodeling, enabling simultaneous intervention at multiple disease-relevant nodes through a single chemical entity. By strongly inhibiting key pathological processes *via* core targets while gently modulating network balance through auxiliary targets, this approach has the potential to enhance therapeutic efficacy while reducing systemic adverse effects, meeting the clinical demand for long-term treatment of metabolic diseases.

Despite these advantages, important challenges remain. Unified pharmacokinetics, while reducing drug–drug interactions and improving compliance, also limits independent dose optimization across targets. A dose sufficient to achieve efficacy at one target may result in excessive modulation of another, thereby increasing the risk of on-target toxicity.[10] This challenge is particularly relevant in metabolic diseases, where therapeutic targets are often distributed across multiple organs and regulatory systems. The overarching goal of multi-target drug design is to maximize therapeutic benefit while minimizing dose-dependent toxicity within a unified pharmacokinetic framework.

Evidence from recent studies supports the value of multi-target strategies in gout, metabolic disorders, and Alzheimer's disease. Meanwhile, the "multi-component, multi-target, multi-pathway" concept of traditional Chinese medicine provides a complementary source of inspiration, with its active constituents serving as scaffolds for modern multi-target drug design.

In the future, with in-depth insights into disease mechanisms from systems biology and the convergence of AI, synthetic biology, cryo-electron microscopy, organ-on-a-chip and other technologies, single-molecule, multi-target drugs will accelerate from laboratory innovations to mainstream clinical applications. Future efforts should focus on optimizing target balancing and minimizing off-target liabilities to fully realize their therapeutic potential. Ultimately, the systemic intervention strategy of single-molecule, multi-target drugs will drive a transformative shift in metabolic disease therapy from symptomatic relief to etiological intervention, offering safer, longer-lasting, and more precise therapeutic hope for hundreds of millions of patients worldwide.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

Peng Zhan is an Editorial Board member of The Innovation Drug Discovery and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and their research group. The other authors declare no conflicts of interest.