Multidisciplinary convergence drives next-generation drug discovery: A new paradigm

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The evolution of drug discovery paradigms has always been intimately connected to the profundity of human understanding into the molecular mechanisms of disease and the capacity for technological innovation. From the serendipitous screening of natural products based on empirical observations to rational drug design targeting specific molecules in the late 20th century, each revolution has been accompanied by a fundamental reconstruction of methodologies and theoretical frameworks. However, in tackling complex diseases such as cancer, Alzheimer's disease, and metabolic syndrome, the traditional "single-target, single-drug" development model reveals significant limitations: clinical trial success rates remain persistently low, and the return on research investment is declining. Modern systems biology research reveals that most chronic diseases are actually dynamic network dysfunctions arising from the interaction of multiple genes, signaling pathways, cell types, and microenvironments. In contemporary drug discovery paradigms, the dynamic interplay between chemical systems and target entities has been integrated into a novel research framework. Drawing upon the principles of Constitutional Dynamic Chemistry, pharmaceutical agents achieve structural adaptive matching through reversible interactions with biological targets.[1] This process can be conceptualized as the target orchestrating and assembling its optimally compatible drug molecule, thereby extending and transcending the static interpretation of the classical "lock-and-key model" at a systems level. In this context, multidisciplinary convergence is emerging not merely as an incremental improvement but as a fundamentally new paradigm—a comprehensive reconfiguration of the logic, tools, and ecosystem of drug discovery. It represents the inevitable path to overcoming current R&D bottlenecks, propelling comprehensive innovation across the entire chain—from systemic disease understanding and technological integration to the reconstruction of the drug discovery ecosystem.

Figure 1. Multidisciplinary technologies intersection in reshaping drug discovery This schematic illustrates the shift from a traditional, single-target linear pipeline toward a dynamic, iterative ecosystem in which data, tools, and insights from diverse fields interact synergistically across the entire process.

COGNITIVE SHIFT: FROM SINGLE-TARGET INTERVENTION TO SYSTEMIC NETWORK MODULATION

Traditional drug discovery is rooted in a reductionist paradigm, aiming to correct pathological states by inhibiting or activating a specific protein target. This strategy has proven highly effective for diseases with clear, singular causative factors, such as infectious diseases, yet it struggles against systemic illnesses like neurodegenerative disorders, autoimmune diseases, and complex cancers. For instance, decades of drug development targeting beta-amyloid (Aβ) for Alzheimer's disease have repeatedly ended in failure, indicating that intervention at a single target is insufficient to reverse the complex network pathology involving protein misfolding, neuroinflammation, synaptic dysfunction, and vascular damage.[2]

The cognitive advancement propelled by multidisciplinary convergence manifests in the establishment of frameworks such as systems pharmacology and network medicine. Its core lies in understanding disease from the perspective of molecular interaction networks and system dynamics, thereby identifying intervention points. By integrating multi-omics data (such as genomics, proteomics, metabolomics, and epigenomics) with computational

modeling, researchers can construct disease-specific molecular interaction networks. Such "systemic targets" often reside at the convergence points of multiple pathological pathways, and modulating them holds greater promise for effectively restoring network homeostasis. This systems-oriented approach is already yielding promising strategies in areas like cancer immunotherapy and inflammatory disease, where interventions are designed to modulate immune network states rather than single checkpoints.

TECHNOLOGICAL FUSION: RESHAPING THE ENTIRE DRUG DISCOVERY PIPELINE TOWARD ADAPTIVE AND DYNAMIC DISCOVERY

The transformation in cognitive approach requires a parallel evolution in the technological framework. Multidisciplinary integration is fundamentally restructuring the key phases of drug discovery, including target identification, lead compound optimization, drug delivery, and preclinical assessment (Figure 1). These stages no longer progress in isolation but are interconnected. For example, computational models inform the design of novel biologics and delivery systems, which are then tested in advanced engineered models; resulting experimental data subsequently refine the initial predictions. This closed-loop, iterative process characterizes the adaptive and dynamic engine of modern discovery.

Computational and data-driven drug design

Computational methods, spearheaded by artificial intelligence (AI), are profoundly empowering target discovery and medicinal chemistry. Machine learning models can mine potential targets and biomarkers from vast biomedical datasets; generative AI can further enable the *de novo* design of novel molecular entities with ideal physicochemical and binding properties, vastly expanding the explorable chemical space. In natural product development, AI-assisted structure elucidation, biosynthetic pathway prediction, and structure-activity relationship optimization significantly enhance the efficiency of derivatization and structural modification. Concurrently, the integration of AI with high-throughput screening data enables more accurate prediction of compound pharmacokinetics and toxicity profiles, accelerating the ADMET optimization process for lead compounds.[3]

Co-evolution of biologics and delivery technologies

The rise of biomacromolecular drugs (e.g., monoclonal antibodies, bispecific antibodies, fusion proteins), is itself a product of the intersection of structural biology, protein engineering, and synthetic biology, so too is the advent of cell and gene therapies.[4] This convergent approach is equally pivotal for emerging modalities such as proteolysis-targeting chimeras (PROTACs), molecular glues, and RNA-targeting small molecules, where chemistry, biology, and informatics intersect to drug challenging targets. Technologies like cryo-electron microscopy have made it possible to resolve target-drug complex structures at near-atomic resolution, underpinning structure-based precision design. In the field of drug delivery, the introduction of materials science and nanotechnology has catalyzed the development of advanced delivery platforms such as lipid nanoparticles, exosome-based carriers, and stimuli-responsive nanosystems. These innovations have markedly improved the targeting capability, stability, and intracellular delivery efficiency of nucleic acid-based drugs, peptides, and protein therapeutics.

Innovation in engineered models and high-throughput experimental systems

The integration of microfluidic technology, automated experimental platforms, and organoids/organs-on-chips is propelling preclinical models towards higher throughput and greater physiological relevance. For instance, microfluidic-based "organ-on-a-chip" systems can simulate human tissue barriers, three-dimensional cellular architectures, and dynamic fluidic microenvironments. They provide more physiologically relevant predictive models for assessing drug permeation, metabolism, and organ-specific toxicity, offering the potential to reduce late-stage R&D failures attributable to the limitations of traditional preclinical models.

ECOSYSTEM RESTRUCTURING: BUILDING AN OPEN AND COLLABORATIVE R&D ECOSYSTEM

Multidisciplinary convergence not only transforms technological pathways but also drives the R&D ecosystem from an isolated, linear model towards a new paradigm characterized by openness, networking, and collaboration.

Establishment of academia-industry-clinical collaborative networks

To bridge the "valley of death" between basic research discovery and clinical translation, numerous large-scale collaborative research initiatives have emerged globally. Examples include the U.S. Accelerating Medicines Partnership, Europe's Innovative Medicines Initiative, and China's Major National Science and Technology Project for Significant New Drugs Development. By integrating resources from academia, industry, healthcare institutions, and regulatory bodies, these consortia focus on major disease areas, jointly advancing end-to-end research from target validation to proof-of-concept, thereby significantly shortening the R&D timeline.

The rise of open science and data-sharing platforms

International open science initiatives, such as the Human Cell Atlas and Open Targets, are dedicated to building standardized, publicly accessible large-scale biomedical databases and tool platforms. These platforms dismantle data silos, lower the barriers to entry for research, and enable investigators worldwide—including resource-limited small and medium-sized enterprises and academic teams—to conduct target discovery and validation based on high-quality data resources, substantially enhancing the overall innovation efficiency of the field.

CONCLUSION

The new paradigm in drug discovery driven by multidisciplinary convergence represents a profound transformation encompassing the reconfiguration of cognitive frameworks, the fusion of technological systems, and the restructuring of innovation ecosystems. It conceptualizes diseases as dynamic networks of multi-level interactions, thereby leveraging artificial intelligence and big data as core engines of convergent technologies to achieve systematic deconstruction and intervention of complex disease networks.[5] Within this paradigm, emerging methodologies such as AI-driven target discovery and virtual screening, big data-based biological network modeling, generative AI-assisted de novo molecular design, and intelligent delivery system optimization are fundamentally enhancing the precision and efficiency across the entire pipeline-from target identification to preclinical evaluation. Concurrently, open and collaborative research ecosystems, by sharing large-scale, high-quality multi-omics and clinical data, provide indispensable "fuel" for these advanced computational tools, thereby accelerating knowledge discovery and translational application. Although critical challenges remain on the path ahead, this paradigm is undoubtedly steering drug discovery into a new era characterized by greater precision, enhanced creativity, and an improved capacity to address complex diseases. Future success will belong to those research communities capable of mastering complexity, breaking down disciplinary barriers, and engaging in profound collaboration. In summary, this profound paradigm shift moves beyond the static "lock-and-key" model toward an adaptive, responsive approach that mirrors the dynamic, adaptive, and evolving nature of living systems.

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AUTHOR CONTRIBUTIONS

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

DECLARATION OF INTERESTS

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