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The Innovation Drug Discovery

Integrating diverse drug modalities and reshaping the clinical translation ecosystem in next-generation therapeutics

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The explosive development of next-generation therapeutic modalities including proteolysis-targeting chimeras (PROTACs), nucleic acid therapeutics, gene editing, and antibody-drug conjugates (ADCs) is redefining the landscape of modern drug discovery. However, the widening gap between the accelerating pace of molecular innovation and the declining success rate of clinical translation constitutes a sharp paradox. Numerous highly promising candidate molecules stall at the preclinical or early clinical stage, reflecting a systemic mismatch across the entire chain from laboratory research to clinical practice. Unlike a conventional technological bottleneck, which can be resolved by optimizing a single stage, a systemic mismatch arises when one stage's output cannot meet the next stage's operational requirements. This reflects a broader shift in modern drug discovery: it no longer relies on isolated breakthroughs but operates as a tightly interconnected network (Figure 1). Specifically, we examine this systemic mismatch through four interconnected dimensions: molecular-manufacturability design coupling; AI- and multi-omics-driven integration of traditional Chinese medicine (TCM) with emerging therapies; preclinical model limitations and multimodal evidence integration; and adaptive regulatory science. Molecular innovation expands the design space but raises manufacturing and characterization demands. AI- and multi-omics-guided TCM integration further broadens this space, while candidate complexity exacerbates manufacturing and validation bottlenecks. These expanding spaces expose conventional preclinical models' limited predictivity, and ensuing evidentiary uncertainty enters clinical and regulatory decisions. Regulatory flexibility or rigidity then shapes early technology selection and development. Together, these dimensions form a feedback loop among innovation, manufacturing, evaluation, and regulation, generating structural mismatch across drug development.

NEW-MODALITY TRANSLATION DEMANDS TIGHT MOLECULAR-MANUFACTURABILITY DESIGN COUPLING

Next-generation modalities such as PROTACs, ADCs, oligonucleotides, and gene editing-based therapeutics each have distinct mechanisms. For example, PROTACs degrade target proteins *via* intracellular degradation systems instead of inhibiting them, whereas ADCs deliver cytotoxic payloads to cancer cells *via* antibody mediated targeting. Despite their revolutionary mechanistic potential, these modalities face formidable clinical translation challenges. For traditional small-molecule drugs, manufacturing is frequently regarded as a downstream consideration following molecule selection. Chemistry, Manufacturing and Controls (CMC) is traditionally considered a final-stage concern in the small-molecule research and development (R&D) pipeline. However, for next-generation drug modalities such as ADCs and PROTACs, this linear sequential logic is no longer sufficient. Clinical translation of new drug modalities requires tight coupling between molecular design and CMC, rather than a sequential process. For instance, PROTACs often exhibit poor solubility and membrane permeability. CMC should be tackled during initial design, rather than being deferred to the scale-up phase. Without a suitable crystal form or formulation to improve bioavailability, a PROTAC candidate will face early-stage failure. Therefore, the translational bottleneck for next-generation therapeutics is a structural mismatch between molecular design and systemic manufacturability-tolerability.

ARTIFICIAL INTELLIGENCE (AI) AND MULTI-OMICS FOSTER CROSS-DISCIPLINARY TCM-NEW MODALITY INTEGRATION

TCM has long faced a black-box dilemma, with unclear pharmacologically active substances and unknown targets. This dilemma may stem from a structural mismatch between TCM's holistic multi-target regulation and modern medicine's single-target reductionist paradigm, with the former embracing multi-components and the latter relying on single drugs. In recent years, the deep integration of AI and multi-omics technologies has fundamentally empowered TCM pharmacology with novel methodological capabilities.

AI-driven models are systematically deconstructing the traditional black-box nature of TCM in target prediction. For instance, Shao and colleagues first identified extremely early-stage gastric cancer cells in a population with Qi deficiency and damp-heat.[1] This discovery enabled gastric cancer warning up to 10 months in advance and subsequently led to a TCM formulation for tumour prevention and treatment. This clinical problem-driven and AI-targeted screening paradigm is reshaping new TCM drug development. Moreover, AI's advanced data analysis and nonlinear modeling also drive TCM pharmacology toward precision medicine and thus facilitate the discovery of novel TCM targets. Integrating genomics, transcriptomics, proteomics, and metabolomics enables systematic understanding of TCM's multi-target mechanisms, moving beyond the traditional single-omics limitation in elucidating its active material basis.

THE LIMITATIONS OF PRECLINICAL MODELS NECESSITATE A NEW PARADIGM OF MULTI-MODAL EVIDENCE INTEGRATION

Animal models have long served as the gold standard for preclinical evaluation, but their predictive value is now being questioned. In cancer research, the reported rate of successful translation from animal models to clinical trials has been less than 8%.[2] In April 2025, the U.S. Food and Drug Administration (FDA) released a roadmap for reducing animal testing in preclinical safety studies, explicitly acknowledging that animal studies have been poor predictors of therapeutic success in common diseases, including cancer, Alzheimer's disease, and inflammatory diseases. Moreover, the FDA announced a historic plan to phase out animal testing requirements for monoclonal antibodies and other drugs. These requirements will be replaced with New Approach Methodologies (NAMs), such as AI-driven computational toxicology models, cell-based assays, and organoid toxicity evaluation.

This paradigm shift, the most profound in nearly half a century, is fraught with uncertainties and unknowns. Organoid and organ-on-a-chip platforms encounter challenges such as low functional maturity, high batch-to-batch variability, and the absence of Good Manufacturing Practice (GMP)-compliant manufacturing standards. AI-discovered molecules have shown an 80%-90% Phase I clinical success rate, referring to the proportion of drug candidates that met the study-defined criteria for Phase I success, which is higher than the historical average of 40%-65%.[3] However, their advantages at Phase II and later stages have not yet been observed. Critically, no AI-discovered drug has yet gained marketing approval to date. These clinical dilemmas require us to move beyond the simplistic animal-versus-non-animal binary in

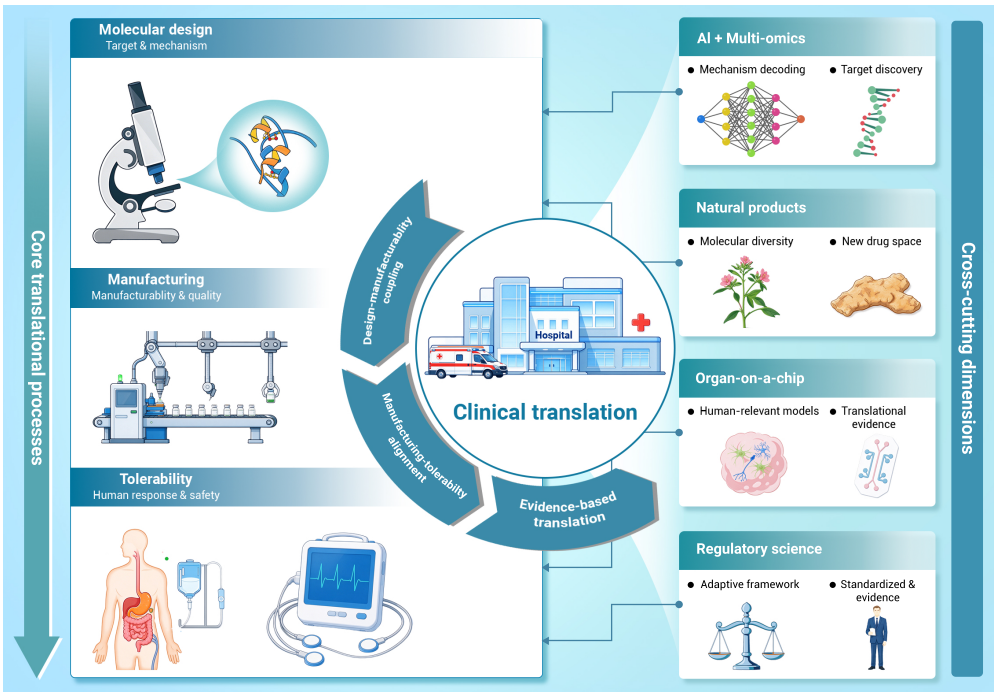


Figure 1. Structural causes of the translational gap from technological, model, and regulatory bottlenecks. "Design-manufacturability coupling" directly maps onto molecular design-scale-up adaptation and is further challenged by AI- and multi-omics-driven TCM integration, while "Manufacturability-tolerability alignment" translates these upstream design and manufacturing pressures into downstream safety and tolerability requirements. "Evidence-based translation" then links preclinical model limitations and multimodal evidence integration with adaptive regulatory science, showing how evidentiary uncertainty and regulatory feedback jointly shape the translation of these technologies.

preclinical modeling and to build a new paradigm of multi-modal evidence integration. This paradigm combines computational predictions, organ-on-a-chip, organoids, human genetics data, and real-world clinical data into a weighted evidence system rather than relying on any single model's verdict.

EVOLUTION OF REGULATORY SCIENCE DEMANDS AN ADAPTIVE REGULATORY FRAMEWORK

Regulatory lag has always been the greatest institutional bottleneck for innovative drug translation. The traditional linear approval paradigm, animals before humans, safety before efficacy, is increasingly inadequate for new modalities like gene editing and personalized therapies. The Plausible Mechanism Pathway, a November 2025 FDA regulatory breakthrough, allows licensure decisions based on plausible scientific mechanism and accumulated evidence without feasible randomized controlled trials.[4] Despite such progress, regulatory innovation still faces deep tensions from both the inapplicability of a one-size-fits-all framework to heterogeneous new drug modalities and the impediment of clinical translation by a lack of standardized analytical methodologies and long-term toxicological data. Besides, relaxed evidentiary standards may let therapies advance with limited safety data, raising adverse event risk, and complicating benefit-risk assessment. Divergent jurisdictional requirements cause coordination challenges, fragmented approvals, inconsistent labeling, and delayed development. Expedited pathways may reward speed over validation, distorting incentives, and reducing confirmatory trials and safety monitoring. Notably, these risks do not negate the value of regulatory innovation, but they must be explicitly weighed against its benefits within an adaptive regulatory framework. More fundamentally, the next frontier of drug regulatory science is not accelerated approval alone but the redesign of an adaptive regulatory framework capable of supporting sound decision-making under conditions of incomplete information.

OUTLOOK

The translational gap in next-generation therapeutics arises not from the inadequacy of any single technology, but from the structural misalignment of the entire drug R&D paradigm. Bridging the translational gap for far more complex new modalities demands rational paradigm shifts at three distinct levels rather than applying linear processes designed for small molecules. At the cognitive level, we need to shift from drug-centric thinking to a systems perspective, one that views drug metabolic rhythms, drug delivery, manufacturing, regulation, and clinical practice as an integrated continuum, not as independent links for separate optimization. For example, conventional growth hormone therapy, based on daily injections, disregards the hormone's circadian pulsatile release. In contrast, biomimetic rhythmic delivery demonstrates efficacy as a function of dynamic coupling across drug molecules, delivery systems, and the host organism.[5] At the methodological level, we need to embrace multimodal evidence integration combining AI predictions, organ-on-a-chip, organoids, human genetics, and real-world data into a dynamically updated evidence network. For instance, organoids integrating 3D architecture, cell-cell interactions, and regenerative signals can serve both as screening models and delivery vehicles, with cross-validation against complementary evidence redefining drug assessment. At the institutional level, we need to proactively shape regulatory science by designing adaptive frameworks in parallel with technological development, rather than waiting for technologies to mature before setting standards. Within the next 5-10 years, the most realistic clinical translation will likely occur in these frontier areas such as AI foundation models with multimodal multi-omics for TCM-modern therapeutic integration, generative AI and computational protein/peptide design for target discovery, patient-derived organoids for human-relevant preclinical efficacy and safety prediction, and model-informed drug development for regulatory and clinical decision-making.

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AUTHOR CONTRIBUTIONS

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

DECLARATION OF INTERESTS

The authors declare no competing interests.