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## Gaps between medical biology and AI drug discovery

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**Drug discovery is a complex, iterative process spanning biology, chemistry, pharmacology, and computational sciences. Artificial intelligence (AI) can accelerate this process but often misaligns with biological realities. Here, we highlight three crucial gaps in AI-driven drug discovery. First, conflating binding affinity with bioactivity ignores distinct experimental setups. Second, reliance on simplified bioactivity metrics limits the ability of AI models to capture richer biological contexts. Third, AI applications remain fragmented, addressing isolated tasks rather than integrating insights across pipeline stages. To bridge these gaps, we propose a biologically contextualized AI framework and provide guidelines for researchers in both medical biology and AI drug discovery.**

**Keywords: drug discovery; artificial intelligence; medical biology**

FEATURE

### Introduction

Drug discovery is a complex, multistage process involving target identification, hit discovery, lead optimization, preclinical testing, and clinical trials. Each stage presents unique challenges and requires a combination of experimental precision and interpretive expertise to identify and develop safe, effective therapeutic agents. Despite the significant progress achieved in medical biology, drug discovery remains a time-intensive, costly endeavor with high failure rates, particularly during the later stages of preclinical and clinical testing.[(p1)] This persistent inefficiency underscores the pressing need for innovative approaches to accelerate and enhance the drug discovery pipeline.

AI offers transformative potential in drug discovery, leveraging its capabilities to analyze large data sets, model molecular interactions, and optimize candidate molecules.[(p2)] AI applications have shown particular promise in virtual screening, bioactivity prediction, and multiobjective molecular design.[(p3)] However, current AI methodologies often fall short of addressing the full complexity of medical biology, leaving crucial gaps unaddressed. These hinder AI from realizing its potential as a comprehensive solution for drug discovery.

First, binding affinity and bioactivity are fundamentally different concepts, yet many AI-driven drug discovery methods use the same model to predict both.[(p4),(p5)] Binding affinity measures the strength of the interaction between a molecule and its target, whereas bioactivity reflects the broader biological effects of a compound. Even within the same measurement type, experimental methods and assay conditions can vary significantly,[(p6),(p7),(p8)] affecting the values obtained. Therefore, applying the same model across these contexts can introduce inaccuracies. Accurate bioactivity prediction requires additional design: efforts to model the active site availability through spatial emptiness,[(p9)] promising strategies of modeling various molecular interactions via docking and graph neural networks,[(p10)] and integrating


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assay conditions through mechanistic equations, such as Cheng–Prusoff[p11] and Hill[p12] equations. Without these, including, but not limited to, the above-mentioned designs, AI models are biased toward their simplified training data and find it hard to capture underlying complexities clearly.

Second, the over-reliance on simplified bioactivity metrics, such as single-point $EC_{50}$ or Ki values, limits the depth of information available for AI models. Condition–value curves, which provide a richer representation of molecular behavior under varying conditions, remain underutilized in AI workflows despite their potential to reveal nuanced insights.[p13] These data, if integrated effectively, could enhance the predictive power of AI models and help uncover previously unknown biological mechanisms.

Finally, the fragmented application of AI across distinct stages of drug discovery poses a significant limitation. Many AI tools are developed for specific tasks, such as target identification or lead optimization, without addressing the iterative nature of the drug discovery pipeline. Failures in preclinical or clinical testing often necessitate revisiting earlier stages, requiring large-scale rescreening of candidates and contributing to the inefficiency and costliness of the process. Attempts to integrate AI across multiple stages, such as combining hit identification with lead optimization through multiobjective molecular design, have shown promise,[p14] but broader, holistic approaches remain underexplored.[p15]

Here, we critically examine these three gaps between medical biology and AI drug discovery and highlight how these misalignments limit the effectiveness of current AI methodologies. By addressing these challenges, we aim to outline a path toward a more integrated, biologically informed application of AI in drug discovery that spans the entire pipeline.

## Gap 1: misinterpreting binding affinity and bioactivity in AI models

Binding affinity and bioactivity are fundamentally different concepts, yet many AI-driven drug discovery methods use the same model to predict both. By definition, bioactivity refers to the ability of a substance to induce biological effects within living systems, typically describing how molecules, drugs, or chemicals influence organisms.[p10] By contrast, binding affinity is the strength of the interaction between a biomolecule and its binding partner.[p16] They do not have a monotonic relationship. A lower binding affinity can be compensated by a lower molecular weight and more lipophilic nature for allosteric modulators, leading to similar binding efficiency and surface efficiency indices (Figure 1).[p17]

### *Impact of measurement variability*

Although related, bioactivity and binding affinity are assessed through distinct experimental techniques that introduce significant variability into the data used for AI-driven predictions. Bioactivity is typically measured through functional assays that evaluate physiological or biochemical effects, such as changes in cell viability[p6] and receptor activation,[p18] usually measured by the concentration of

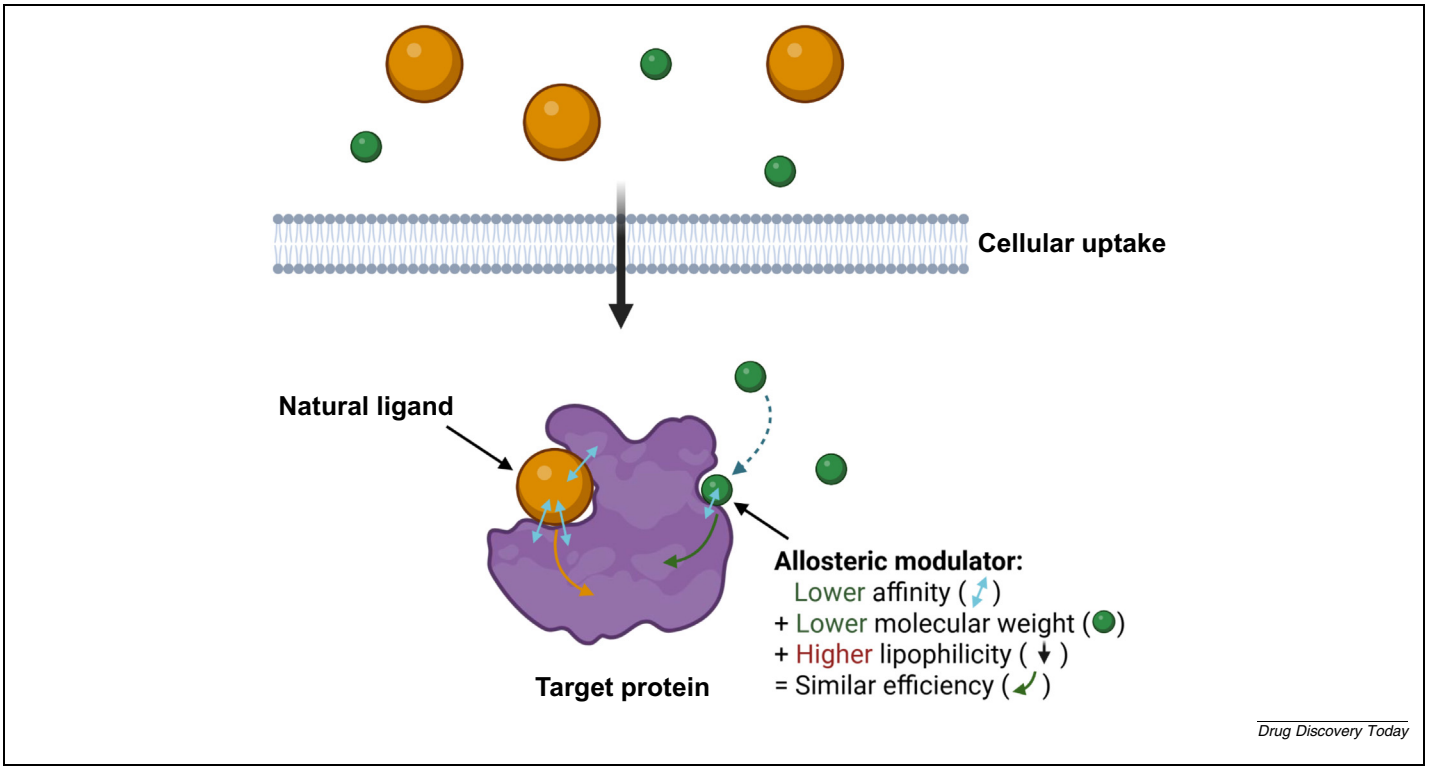


**FIGURE 1**

Binding affinity and bioactivity. Lower binding affinity can be offset by smaller molecular weight and higher lipophilicity, leading to similar binding efficiency or bioactivity. The natural ligand (orange) has a strong binding affinity but a larger molecular weight, whereas the allosteric modulator (green) compensates through reduced size and increased lipophilicity. The higher lipophilicity enhances cellular uptake and increases the concentration of the allosteric modulator around the target protein, contributing to similar binding efficiency[p17] and effective interaction with the target protein. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the compounded needed to induce/reduce a 50% response ($EC_{50}/IC_{50}$). By contrast, binding affinity is usually quantified using equilibrium dissociation constants ($K_D$), obtained via biophysical methods such as surface plasmon resonance (SPR)[p7] and fluorescence anisotropy,[p8] which measure the strength and stability of molecular interactions.

This diversity in assay approaches introduces inconsistencies, even when measuring the same bioactivity metric. For example, the $K_i$ value for the human A2A receptor (CHEMBL251) can be derived through very different methods. The CHEMBL2417388[p19] assay uses scintillation counting to measure [3H]ZM241385 displacement from A2A receptors expressed in HEK293 cell membranes under controlled conditions over 60 min. By contrast, the CHEMBL1133401[p20] assay assesses the inhibition of human neutrophil activation, reflecting a more complex physiological environment. Whereas the [3H]ZM241385 displacement assay directly measures the binding affinity, the neutrophil activation assay[p18] incorporates additional biological processes to measure the bioactivity, leading to variations in the reported $K_i$ values.

These discrepancies challenge AI models,[p21],[p22],[p23] which often rely on standardized bioactivity data and overlook nuances such as assay conditions and interaction complexities. As a result, the models often struggle to generalize,[p24] particularly when the training data combine results from assays with differing measurement contexts.[p25] For example, functional assays[p26] that involve cell-based systems may introduce variability resulting from biological noise, whereas controlled biophysical assays[p27] provide more direct and reproducible measurements but lack physiological context.

By neglecting these methodological variations, AI models risk oversimplifying complex bioactivity relationships, leading to inaccurate predictions or poor model transferability across data sets. To improve bioactivity prediction, which more closely reflects drug efficacy, additional model designs are needed beyond those used for binding affinity. For example, AI models can be extended to evaluate how the active sites are blocked by ligand binding poses, molecular docking can be used to generate reference data that mimic collective molecular behavior under experimental setups for AI models, and assay conditions (e.g., protein or substrate concentrations) can be incorporated through mechanistic equations, such as the Cheng–Prusoff[p11] and Hill[p12] equations, to connect experimental context with observed bioactivity outcomes. Accounting for these measurement variabilities enables AI models to distinguish between assay-dependent artifacts and true molecular interactions, enhancing their robustness and reliability for real-world drug discovery applications.

### *Challenges in unified bioactivity modeling*

Current AI models often fail to capture assay-specific differences because of heterogeneous experimental methods and data aggregation. This limits prediction accuracy and biological relevance. Preliminary attempts[p28] using text embeddings to include assay type descriptions show modest improvement, but remain insufficient. A detailed discussion on assay-informed modeling and related challenges is provided in the Note S1 in the supplemental information online.

## Gap 2: overreliance on simplified bioactivity metrics in AI

Figure 2 highlights the disconnect between traditional bioactivity measurements, the simplified metrics used in AI applications, and the deeper biological mechanisms at play in drug discovery. Standardized bioactivity values, such as $IC_{50}$ or $EC_{50}$, dominate data sets, including ChEMBL[p29] and PubChem.[p30] Although these metrics are invaluable for benchmarking and comparative studies, they often fail to encapsulate the complexity of experimental conditions or the intricate molecular interactions underpinning drug efficacy. Factors, such as assay type, experimental protocols, cellular context, and molecular environments, including cofactors,[p31] receptor complexes,[p32] or protein crowding in cellular milieus,[p33] can significantly influence bioactivity measurements, but are rarely accounted for in these standardized values.

The reliance on simplified bioactivity metrics in AI models overlooks the richness of raw experimental outputs (Figure 2). For instance, whereas traditional measurements capture cellular responses (Figure 2a), AI applications often reduce these to standardized metrics derived from data sets (Figure 2b). This reduction omits crucial details about intracellular pathways and molecular interactions (Figure 2c), which could provide deeper insights into drug mechanisms. Integrating AI with richer experimental data (Figure 2d) could uncover new targets and mechanisms, addressing limitations in linear drug discovery. Moreover, poorly designed *in vitro* experiments featuring unrealistic exposures can generate misleading results,[p34] including data irrelevant to *in vivo* conditions or artifacts arising from toxicity. Such limitations further compromise the reliability of standardized metrics and risk propagating errors when incorporated into AI models.[p10],[p14],[p35],[p36],[p37],[p38],[p39],[p40],[p41],[p42],[p43],[p44],[p45],[p46],[p47],[p48],[p49],[p50],[p51],[p52],[p53],[p54],[p55],[p56],[p57],[p58],[p59],[p60],[p61],[p62],[p63],[p64],[p65],[p66],[p67],[p68]

AI models[p21],[p22],[p23] trained solely on simplified metrics often fail to account for essential variables, such as assay-specific conditions, measurement techniques, and context-dependent molecular interactions. For example, two compounds with similar $IC_{50}$ values might exhibit vastly different therapeutic outcomes as a result of divergent modes of action or molecular binding profiles.[p69] Moreover, standardized metrics often neglect crucial factors, such as *in vivo* bioavailability and tissue distribution, which are pivotal for drug efficacy.[p70] Addressing these gaps requires a paradigm shift toward integrating detailed experimental data, molecular interaction networks, and context-specific biological information into AI-driven drug discovery workflows.

### *Potential solutions*

Condition-value curves capture detailed, dynamic bioactivity responses beyond single metrics, enabling AI models to learn nuanced molecular behaviors. Probabilistic predictions quantify uncertainty and better handle experimental variability, guiding more confident decision-making. Together, these approaches can improve prediction accuracy and interpretability in drug discovery. A full discussion is provided in Notes S2 and S3 in the supplemental information online.

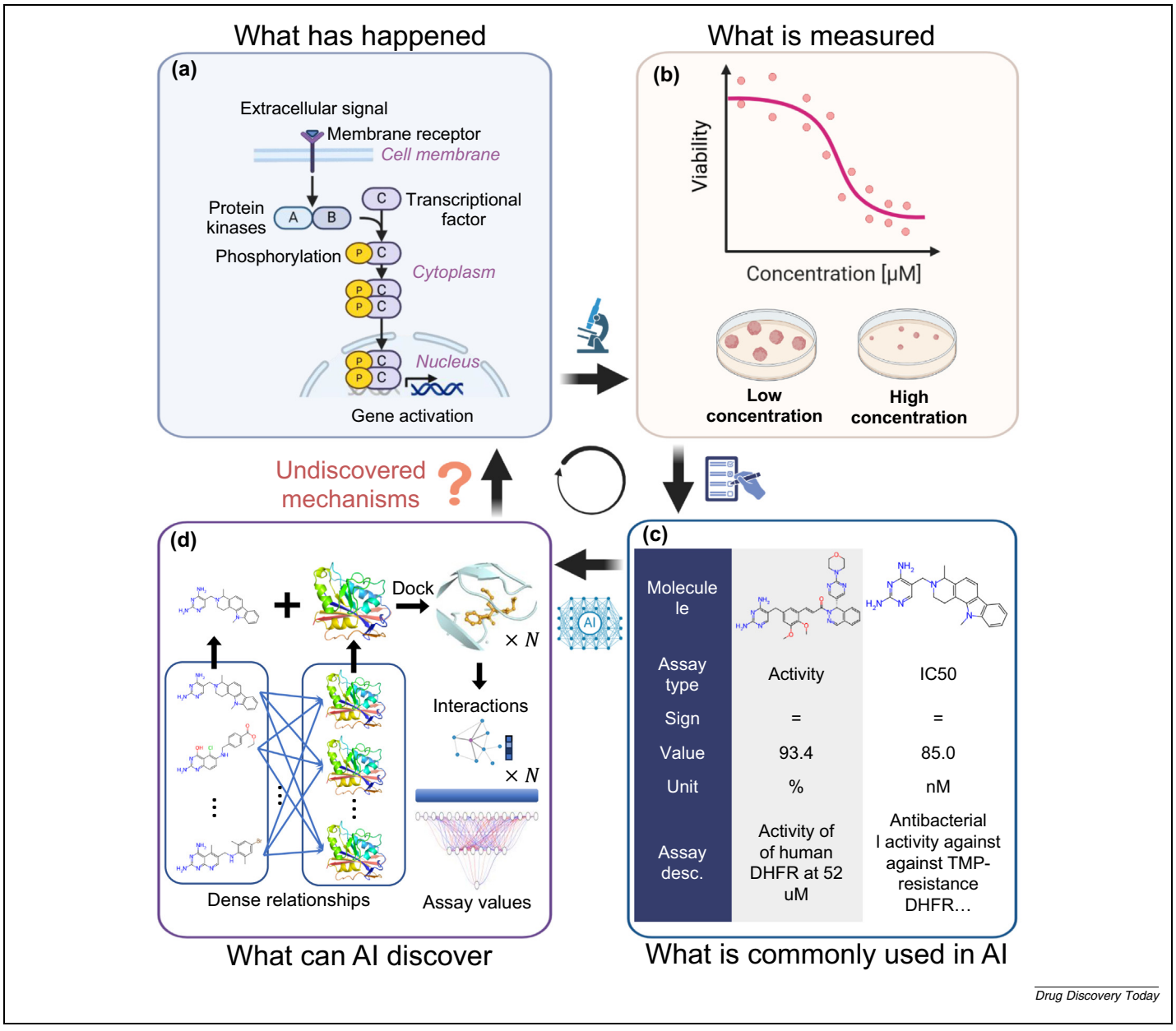


**FIGURE 2**

Bridging experimental and predictive insights: limitations and potential of artificial intelligence (AI) in drug discovery. **(a)** 'What has happened': intracellular pathways modulated by drug molecules, from receptor signaling to gene activation. **(b)** What is measured': measurement of cellular responses (e.g., viability) across varying drug concentrations, reflecting experimental outputs. **(c)** 'What is commonly used in AI': simplified bioactivity metrics (e.g., $IC_{50}$) typically used in AI models, extracted from standardized data sets. **(d)** 'What can AI discover': potential of AI to infer molecular interactions, predict assay values, and identify native-like binding modes, enabling insights into new drug targets. This perspective underscores the transition from linear drug discovery pipelines to iterative AI-assisted discovery, emphasizing the integration of *in situ* measurements and AI-predicted interactions to improve success rates.

### Gap 3: fragmented AI use in drug discovery

We conducted a survey of AI applications across all stages of the drug discovery pipeline, highlighting recent, comprehensive, and pioneering studies for each stage (Figure 3). These works demonstrate the growing impact of AI on tasks such as drug target identification, virtual screening, absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction, and clinical pharmacology. Within these applications, AI models can predict well but are often hard to interpret. Existing explainable AI tools give limited biological insight and rarely integrate multiscale data. Combining mechanistic models, knowledge graphs, and causal methods could improve trust and actionability. A full discussion is provided in Note S4 in the supplemental information online.

Nevertheless, Figure 3 also underscores the fragmented nature of current AI approaches. Most models are tailored to solve isolated problems rather than providing integrated solutions across the pipeline. This fragmentation is problematic given the iterative and interconnected nature of drug discovery, where downstream failures are rarely considered during earlier stages.

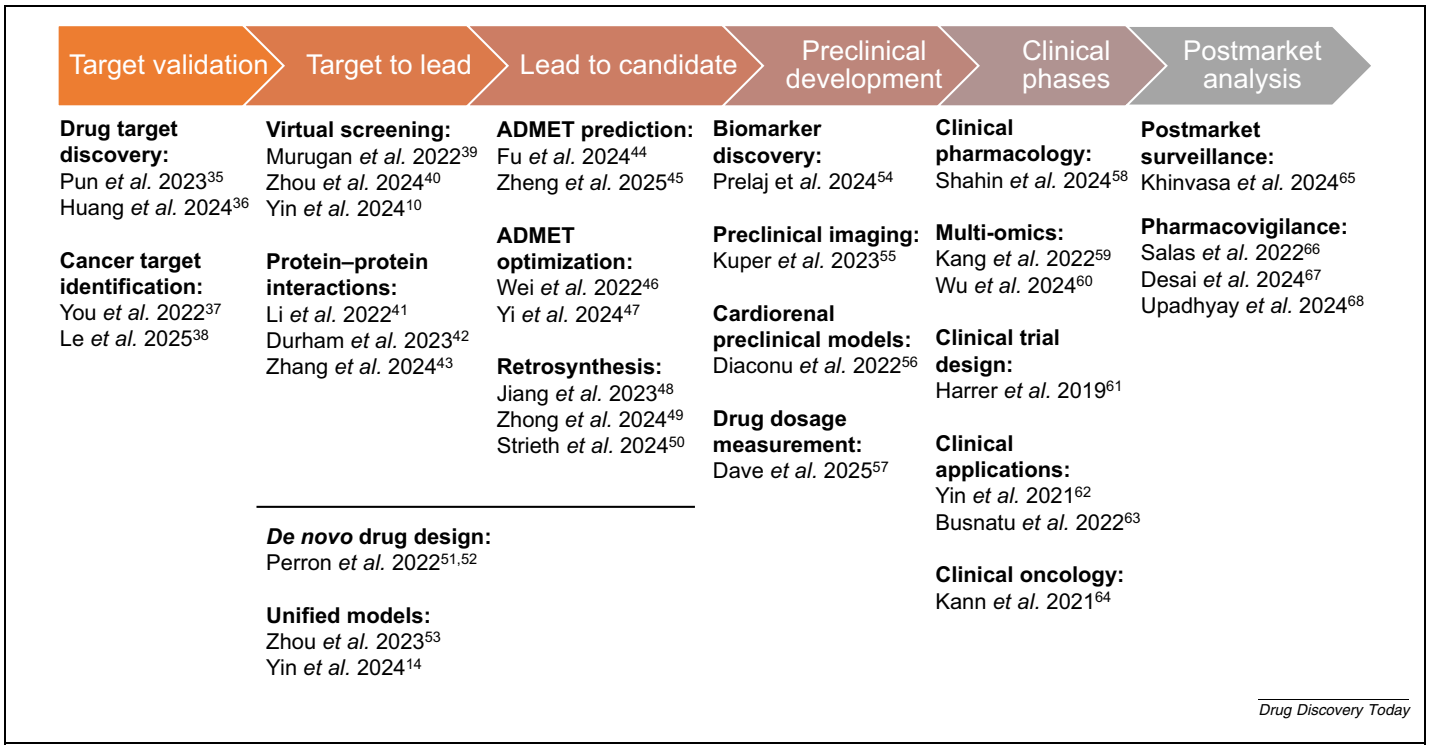


**FIGURE 3**

Recent publications on artificial intelligence (AI) drug discovery. AI methods are applied independently across drug discovery stages, from target validation to postmarket analysis. Publications highlight key advancements and pioneering efforts.[p10],[p14],[p35],[p36],[p37],[p38],[p39],[p40],[p41],[p42],[p43],[p44],[p45],[p46],[p47],[p48],[p49],[p50],[p51],[p52],[p53],[p54],[p55],[p56],[p57],[p58],[p59],[p60],[p61],[p62],[p63],[p64],[p65],[p66],[p67],[p68] Abbreviation: ADMET, absorption, distribution, metabolism, excretion, toxicity.

As an attempt to integrate the 'Target to lead' and 'Lead to candidate' stages, *de novo* design methods[p51],[p52] typically attempt to generate 'pseudo' drug candidates. These are molecules predicted to be drug-like based on feedback from well-trained bioactivity and property prediction models. However, these predictive models are usually trained without consideration for their subsequent use in molecular generation or optimization.

We argue that such prediction models themselves could be directly extended to generate true (i.e., experimentally validated rather than predicted) drug candidates.[p14] This is because predictive models already capture inherent structure–activity and structure–property relationships, effectively learning an internal representation of the chemical–biological space that generative agents struggle to explore comprehensively. The development of such unified models points to a way of addressing the gaps introduced by fragmented AI use in drug discovery.

Although extending predictive models could yield experimentally validated candidates, their success ultimately depends on biological translation. Many candidates still fail in preclinical or clinical stages because of overlooked *in vivo* barriers and 'undruggable' targets.[p71] Incorporating physiological constraints and simulating complex biological systems [e.g., physiologically based pharmacokinetic (PBPK) models or disease microenvironments] could improve translation to real-world efficacy. A full discussion is provided in the Notes S5 and S6 in the supplemental information online.

### *Emerging directions*

Drug repurposing, foundation models, and emerging agentic workflows offer a potential route toward overcoming this fragmentation. Drug repurposing[p72] represents a prominent AI application that can mitigate this gap: by evaluating existing drug compounds for new indications, AI can leverage previously generated molecules and clinical data, reducing the need for *de novo* design while still connecting early- and late-stage predictions. Unlike task-specific models, foundation models trained on large-scale, heterogeneous biomedical and chemical data sets[p73] can serve as versatile backbones adaptable across multiple stages of the pipeline. In parallel, agentic workflows represent a shift from static prediction toward dynamic, decision-making systems that can autonomously design, test, and iteratively refine molecules by interacting with both predictive models and experimental feedback.[p74] Such workflows could, in principle, close the loop between target discovery, compound generation, and validation, addressing the disconnect between early-stage design and late-stage outcomes. However, their effectiveness remains limited by the availability of high-quality, multimodal training data and by challenges in ensuring interpretability, reproducibility, and safe deployment.[p75]

## Toward a holistic AI framework for drug discovery

AI has revolutionized drug discovery, yet its application remains constrained by oversimplified assumptions and fragmented implementation across the development pipeline. A fundamental limitation is the reductionist approach to

**TABLE 1**

**Guidelines for medical biology and AI drug discovery researchers to advance a biologically contextualized AI framework.**

| For medical biology researchers | For AI drug discovery researchers |
|---|---|
| (1) Be very clear when using biological terms. Your words are often taken as biological truth by AI researchers | (1) Be sensitive to biological concepts. AI will not correct human misconceptions |
| (2) Believe everything you know can be used in AI models; thus, write it all down in an organized way | (2) Truth is richer than standards. Standards are useful, but they should not blind you to biological complexity |
| (3) Show your research in a holistic biological framework. This helps AI researchers come up with new ideas for modeling the biological world | (3) Aim to reveal holistic biological understanding for AI models. Biology contains the answers, but they must be expressed in forms that models can learn from |

biological data, such as equating binding affinity with bioactivity, despite the latter being influenced by complex physiological interactions. Similarly, reliance on single-value bioactivity metrics (e.g., $EC_{50}$) overlooks richer condition-dependent dynamics that could improve predictive accuracy.

To address these gaps, we propose a biologically contextualized AI framework (Figure S1 and Note S7 in the supplemental information online), which serves as both a conceptual map and a practical guide. Each element of the framework is linked to concrete actions, such as incorporating richer data sets, designing iterative AI–experiment feedback loops, and aligning computational predictions with physiological contexts. It also brings several technical and policy barriers to the forefront. For instance, although predicted structure models, such as AlphaFold,[p76] have the potential to significantly accelerate both fundamental and translational research, they are not experimentally validated and cannot be regarded as ground truth. Challenges remain to capturing protein dynamics, predicting multichain structures, interpreting protein function, and assessing model quality.[p77] Similarly, real-world medical data sets are typically small, domain specific, and imbalanced, which limits the effectiveness of self-supervised learning approaches.[p78] Gold-standard genomic data sets also underrepresent non-European populations, creating inequities and constraining our understanding of human disease.[p79] Nonclassical targets frequently lack sufficient data records, making them impractical when time and resources are constrained. In addition, the potential misuse of AI raises concerns about the sharing of medical records[p80]; ensuring security and patient consent is essential before institutes and clinics can share data for AI research.

To further operationalize this vision, we provide guidelines for medical biology and AI drug discovery researchers (Table 1).

## Concluding remarks

Bridging the gaps between medical biology and AI-driven drug discovery requires a fundamental shift from reductionist, task-specific algorithms toward holistic, biologically grounded frameworks. As outlined here, misinterpretations of binding affinity and bioactivity, underutilization of rich experimental data, and fragmented AI applications across the drug discovery pipeline collectively limit the translational impact of current approaches. By integrating multiscale biological knowledge, experimental metadata, and iterative feedback loops, a biologically contextualized AI framework can better capture the complexity of living systems and align predictions with therapeutic realities. Yet, realizing this vision is constrained by barriers spanning structural biology (e.g., limited validation of predicted models), biological complexity (e.g., protein dynamics and nonclassical targets), data limitations (e.g., small, biased, and imbalanced data sets), and ethical concerns (e.g., privacy and equitable access). Realizing the full potential of AI in drug discovery depends on closing these gaps and barriers, unifying computational and experimental efforts into a cohesive, adaptive, and biologically informed discovery process.

## Author contributions

**Y.Y.:** conceptualization, investigation, methodology, visualization, writing – original draft. **A.F.:** investigation, visualization, writing – review and editing. **L.W.:** funding acquisition, project administration, supervision, writing – review and editing.

## CRediT authorship contribution statement

**Yueming Yin:** Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **Afu Fu:** Writing – review & editing, Visualization, Investigation. **Lipo Wang:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

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## Declarations of interest

The authors declare that they have no conflicts of interest.

## Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.drudis.2025.104512.

## Data availability

Supplementary information is available online together with this article.

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