

Artificial intelligence in drug development

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Drug development is a complex and time-consuming endeavor that traditionally relies on the experience of drug developers and trial-and-error experimentation. The advent of artificial intelligence (AI) technologies, particularly emerging large language models and generative AI, is poised to redefine this paradigm. The integration of AI-driven methodologies into the drug development pipeline has already heralded subtle yet meaningful enhancements in both the efficiency and effectiveness of this process. Here we present an overview of recent advancements in AI applications across the entire drug development workflow, encompassing the identification of disease targets, drug discovery, preclinical and clinical studies, and post-market surveillance. Lastly, we critically examine the prevailing challenges to highlight promising future research directions in AI-augmented drug development.

Drug development is a multifaceted process aimed at developing new medications to treat diseases. It involves several stages, including target identification, drug discovery, preclinical studies, clinical trials, regulatory approval and post-market surveillance. Drug development currently faces numerous challenges, including high costs, long time frames and low success rates^{1,2}. On average, developing a new drug requires a substantial investment of approximately US\$2.6 billion and may take 12 to 15 years to complete³. Unfortunately, the success rate of new drugs, even at the clinical trial stage, is less than 10%. Several factors are responsible. Fundamentally, diseases are often complex and multifactorial, posing difficulties in identifying effective treatments. The drug development process itself is also complex, involving multiple stages where setbacks can doom the entire process. Additionally, the vast chemical space that needs to be explored in search of a potential drug candidate is estimated to be on the order of 10^{60-100} , making drug discovery comparable to finding a needle in a haystack⁴. Lastly, regulatory requirements are stringent, and meeting the standards for safety, efficacy and quality can be a time-consuming and costly endeavor. To overcome these challenges, scientists have been actively exploring new technologies and methods to improve the drug development process—with AI being poised to radically alter this field.

Recent advancements in AI, including image recognition, natural language processing (NLP) and computer vision, have shown particular promise for addressing key challenges in drug development⁵. In particular, large language models (LLMs) such as ChatGPT⁶ and Gemini⁷, and generative AI such as Sora⁸, have demonstrated capabilities that, in some instances, already surpass human intelligence. AI's ability to process vast amounts of data promises to greatly accelerate and improve the drug development process^{5,9}. Consequently, pharmaceutical companies, biotech firms and research institutions are increasingly adopting AI-driven approaches to surmount the obstacles inherent in traditional methods^{10,11}. AI has proven valuable in analyzing complex biological systems^{12,13}, identifying disease biomarkers and potential drug targets^{14–16}, simulating drug–target interactions^{17,18}, predicting the safety and efficacy of drug candidates^{19–21} and managing clinical trials^{22,23} (Fig. 1). However, it is important to recognize that AI-powered drug development still faces several unique challenges. Without effective solutions to these obstacles, the promise of AI may not be fully realized.

This Review explores the state-of-the-art applications of AI in small-molecule drug development since 2019; for insights into research conducted before 2019, readers are encouraged to consult previous

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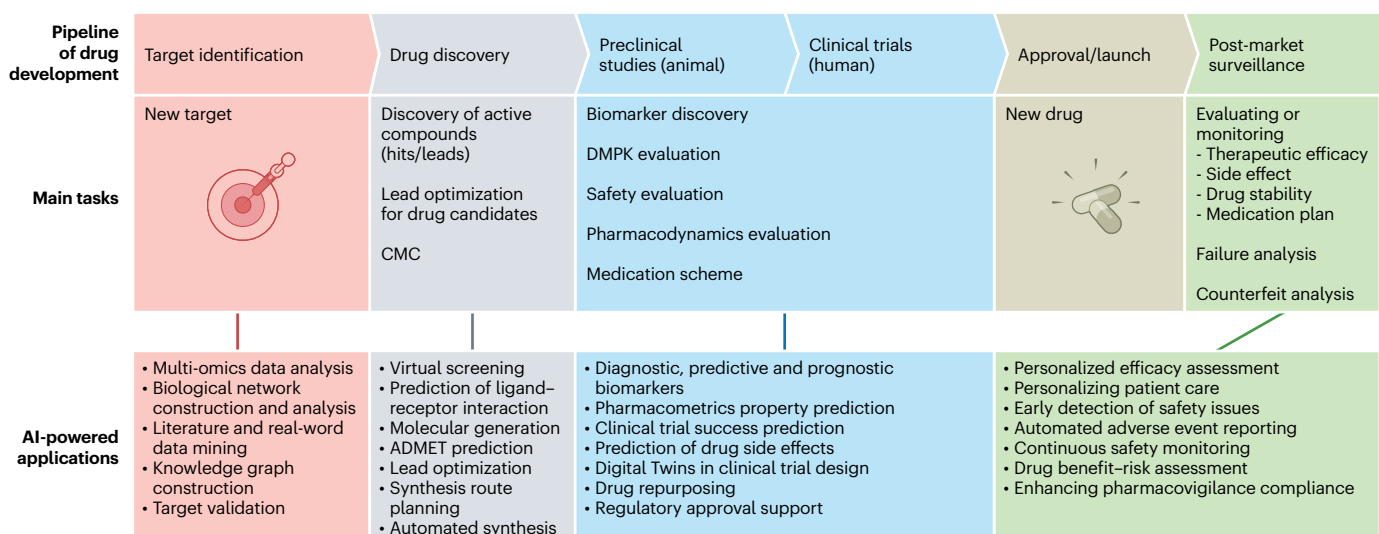


Fig. 1 | Overview of AI applications in the drug development pipeline. The drug development pipeline encompasses several critical stages, including target identification, drug discovery, preclinical studies, clinical trials, regulatory agency review and post-market surveillance. AI technologies have potential

applications across nearly all these stages. CMC, chemical manufacturing and control; DMPK, drug metabolism and pharmacokinetics. All structural figures were created using the UCSF ChimeraX 1.7.1 software²⁴⁷.

comprehensive reviews^{2,24,25}. For more detailed information on AI for natural product drug discovery, please refer to the latest review²⁰. In this Review, we first describe AI-powered drug discovery, from target identification up to synthesis planning, and AI applications within clinical stages of drug development—including biomarker discovery, drug repurposing, prediction of pharmacokinetic properties and toxicity, and clinical trial conduct. Finally, we discuss the challenges faced by AI-powered drug development and outline future directions for the field. We hope to illuminate a new era of innovation, efficiency and precision in drug development that is expected to expedite delivery of new and better medicines to patients.

AI-driven drug discovery

In recent years, AI has emerged as a transformative force in the field of drug discovery, revolutionizing traditional methodologies and enhancing efficiency across multiple stages of the process. This section will explore the profound impact of AI on various aspects of drug discovery, including target identification, virtual screening, de novo design, ADMET (absorption, distribution, metabolism, excretion and toxicity) predictions, and synthesis planning and automating synthesis and drug discovery. By leveraging advanced algorithms and techniques, researchers are now able to accelerate the discovery of novel therapeutic agents, improve the accuracy of predictions and reduce the overall time and costs associated with drug development.

Target identification

The identification of small-molecule targets, such as proteins or nucleic acids, is a critical process in drug discovery. Traditional methods such as affinity pull-down and whole-genome knockdown screening are widely used, but tend to be time consuming and labor intensive, with high failure rates.

Advances in AI technology are revolutionizing this field by enabling the analysis of large datasets within complex biological networks. AI facilitates the identification of disease-related molecular patterns and causal relationships by constructing multi-omics data networks, thus facilitating the discovery of candidate drug targets^{26–31}. For example, recent research uses NLP techniques (such as word2vec embeddings) to map gene functions into high-dimensional space, enhancing the sensitivity of target identification despite the sparsity

of gene function overlap²⁶. Nonetheless, integrating multi-omics data efficiently and ensuring the interpretability of AI models are challenging tasks. Graph deep learning technology addresses these by merging graph structures with deep learning, focusing on graph nodes related to key features (for example, atom type, charge) to effectively identify candidate targets. A recent study successfully developed an interpretable framework using multi-omics network graphs with graph attention mechanisms to predict cancer genes effectively³².

Furthermore, integrating multi-omics data with scientific and medical literature into knowledge graphs allows AI to discern relationships between genes and disease pathways^{33–35}. Biomedical LLMs, when deeply integrated with biological networks or knowledge graph functions, provide efficient and precise methods for linking diseases, genes and biological processes³⁶. For instance, the PandaOmics platform (<https://pharma.ai/pandaomics/>) successfully utilized multi-omics data and biological network analysis to recognize TRAF2- and NCK-interacting kinase as a potential target for anti-fibrotic therapy, leading to the development of a specific TRAF2- and NCK-interacting kinase inhibitor (INSO18_055)³⁷. However, the potential publication biases in the literature suggest a need for supplementary methods to ensure the identification of novel and relevant targets.

Real-world data, such as medical records, self-reports, electronic health records (EHRs) and insurance claims, provide essential contextual information for understanding complex diseases and facilitating target discovery^{38–40}. However, real-world data often contain unstructured text, lack standardization and may include biases, limiting their application in this context. While high-quality, curated datasets are crucial for training models, real-world data are inherently noisy and complicated by the confluence of multiple diseases. Nonetheless, recent studies have shown that despite these issues, noisy real-world data can train effective models³⁸, advancing the potential for gene discovery and candidate drug targets in noisy medical record and non-expert disease labeling scenarios. Enhancing model generalizability across diverse populations remains a major challenge, especially for diseases with low labeling or prevalence rates⁴⁰. As real-world and multi-omics data grow richer, utilizing advanced data mining algorithms and expert knowledge will further enhance their integration, significantly improving the success rate of target discovery.

Virtual screening

Virtual screening is a critical strategy for efficiently identifying potential lead compounds or drug candidates⁹. The rapid expansion of compound libraries necessitates accelerated virtual screening of ultra-large libraries⁴¹, prompting advancements in AI technologies for ligand docking^{42,43}. AI-based receptor–ligand docking models can predict ligand spatial transformations, directly generate complex atomic coordinates using algorithms like equivariant neural networks^{44–46} and learn the probability density distribution of receptor–ligand distances to generate binding poses^{47–49}. Notably, recent receptor–ligand co-folding networks based on AlphaFold2 and RosettaFold show promise in predicting complex structures directly from sequence information^{50–53}. However, they may produce unrealistic ligand conformations due to insufficient learning of physical constraints, necessitating post-processing (for example, energy minimization) or geometric constraints to optimize docking pose validity. However, deep learning-based binding pose prediction models have yet to outperform physics-based methods⁵⁴ in pocket-oriented docking tasks, and they often inadequately consider receptor pocket flexibility. Additionally, predicting precise receptor–ligand interaction remains a challenge. While early machine learning successes in affinity prediction have sparked interest in deep learning models^{42,55}, and these models may outperform traditional scoring functions by handling both three-dimensional structural⁵⁶ and nonstructural data^{57–64}, their performance heavily depends on ligand pose accuracy and is primarily suitable for known receptor structures.

When target structures are absent or incomplete, the direct application of docking-based virtual screening is impractical. As an alternative, AI techniques may be used in sequence-based prediction methods⁶⁵. However, such methods often struggle to capture the complexity of three-dimensional protein–ligand interactions, complicating accurate predictions of how binding pose changes affect interaction strength.

While targeted drug development is effective for defined targets, many diseases lack such targets. Phenotype-based virtual screening is thus crucial for diseases with undefined targets (for example, rare diseases) and broadly phenotypic diseases (for example, aging)^{66–72}. A recent study used nuclear morphology and machine learning to identify compounds inducing senescence in cancer cells⁷³; similar strategies are also promising for antibiotic discovery⁶⁸. However, such models often depend on case-specific phenotypic data and struggle with generalization. Furthermore, AI-based activity prediction solely relying on ligand chemical structures faces challenges like data sparsity and imbalance, and activity cliffs⁷⁴. Recent studies suggest that integrating related biological information like cell morphology and transcriptional profiles can enhance model performance⁷⁵, offering a new direction for more accurate activity prediction.

Current virtual screening models generally focus on specific tasks such as scoring⁷⁶, pose optimization⁴⁸ or screening⁷⁷, emphasizing the need to develop universal models capable of handling multiple tasks⁷⁸. Incorporating inductive biases (which refer to the model's inherent tendency to prioritize certain types of solutions over others) or data augmentation (which refers to techniques used to artificially expand the diversity of a training dataset without collecting new data) might improve model generalizability^{79,80}. Furthermore, the exponential growth of commercial compound collections to billions makes comprehensive screening computationally infeasible⁸¹. Meanwhile, the available molecular libraries cover only a small portion of the druggable chemical space, which continues to expand—creating both opportunities and challenges in navigating and screening for bioactive molecules.

In response to these challenges, techniques like active learning and Bayesian optimization⁸² are effective methods for addressing the chemical space search problem, becoming key to enhancing virtual screening efficiency. The integration of quantum mechanics with AI offers new tools for chemical space exploration⁸³, while molecular

dynamics simulations add depth to protein–ligand interactions, addressing issues of binding affinity and selectivity to improve model accuracy⁸⁴. Simultaneously, by generating custom virtual libraries for specific targets or compound types, deep generative models substantially narrow search spaces and enhance screening efficiency^{85–87}. For instance, our conditional recurrent neural network generated a custom library that identified an efficient and selective RIPK1 inhibitor in cell and animal models⁸⁶.

De novo design

De novo drug design involves autonomously creating new chemical structures to optimally satisfy desired molecular features. Traditional methods, including structure-based, ligand-based and pharmacophore-based designs, are manual and rely on expert designers and explicit rules. AI, particularly deep learning, has enabled the automated identification of novel structures that meet specific requirements, bypassing traditional expertise. This technology has been successfully applied in developing small-molecule inhibitors⁸⁷, PROTACs⁸⁸, peptides^{89–91} and functional proteins^{92,93} that are validated through wet-lab experiments, ushering in a more efficient and innovative drug discovery era.

In deep learning-driven de novo design (Fig. 2), the molecular generation component is central, normally using chemical language or graph-based models. Chemical language models convert molecular generation tasks into sequence generation^{85,87,94–97} such as SMILES string ('simplified molecular input line entry system', a notation system that represents a chemical structure in a linear text format). Although extensive pretraining is required and may produce invalid SMILES due to syntactic errors, these errors can aid model self-correction by filtering improbable samples⁹⁸. Models like long short-term memory models (a type of deep learning model that analyzes sequential data) face information compression bottlenecks, hindering the learning of global sequence attributes, which suggests a need for architectures such as Transformers to better capture global properties. Recent research integrates structured state–space sequences into chemical language models to reveal high chemical space similarity and alignment with key natural product design features, proving the model's utility in de novo design⁹⁹.

Conversely, graph-based models represent molecules as graphs, generating structures using autoregressive or non-autoregressive strategies^{100–103}. Autoregressive approaches construct molecules atom by atom, which can lead to chemically implausible intermediates and introduce bias^{101,102}. In contrast, non-autoregressive methods generate entire molecular graphs at once but need extra steps to ensure the graph's validity, as these models' limited perception of molecular topological structures can induce flawed structures¹⁰⁴.

Given the vastness of the drug-like chemical space, de novo generation often guides design toward target features, using optimization mechanisms such as scoring functions based on metrics including similarity to known active molecules and predicted bioactivity. Incorporating reinforcement learning for iterative optimization is an effective approach⁹⁴, yet designing appropriate scoring functions is challenging as directly quantifying objectives like synthetic feasibility or drug likeness is difficult, often leading to unintended consequences¹⁰⁵. Furthermore, reinforcement learning's extensive optimization steps highlight challenges in sample efficiency, which active or curriculum learning^{106–108} strategies may mitigate.

Beyond introducing scoring functions, incorporating constraints—such as disease-related gene expression features¹⁰⁹, pharmacophores¹¹⁰, protein sequences⁸⁷ or structures^{102,111–114}, binding affinity¹¹⁵ and protein–ligand interactions^{116,117}—can also direct models toward generating desired molecules. For instance, our PocketFlow model, conditioned on protein pockets, effectively generated experimentally validated active compounds against HAT1 and YTHDC1 targets, showcasing its drug design capabilities¹⁰². Additionally, models can refine leads by

restricting outputs to specific scaffolds or fragments from desired candidates, albeit at the cost of limiting chemical diversity¹¹⁸.

ADMET

ADMET plays a critical role in determining drug efficacy and safety. While wet-lab evaluations are required for market approval and cannot be fully replaced by simulations, early-stage ADMET predictions can help reduce failures due to poor characteristics¹¹⁹. AI has emerged as a valuable tool for predicting ADMET properties using predefined features like molecular fingerprints or descriptors. For instance, Bayer's in silico ADMET platform uses machine learning techniques such as random forest and support vector machines, using descriptors like circular extended connectivity fingerprints to ensure accuracy and relevance¹²⁰. Over the past decades, various descriptors for ADMET predictions have been developed^{121–124}. However, feature engineering involved in these feature-based methods remains complex and limits generality and flexibility.

Deep learning now drives ADMET prediction, automatically extracting meaningful features from simple input data. Various neural network architectures, including transformers (designed to effectively handle sequential data)^{125–127}, convolutional neural networks (a type of deep learning model commonly used for image and video recognition tasks)¹²⁸ and, more recently, graph neural networks (deep learning models for processing graph-structured data, such as molecular structures)^{78,129}, excel in modeling molecular properties from formats such as SMILES strings and molecular graphs. Among them, SMILES strings offer compact molecular representation and can distinctly express substructures like branches, rings and chirality, but lack topological awareness—whereas graph neural networks (like the GeoGNN model¹²⁹) incorporate geometric information, providing superior performance in ADMET prediction. Indeed, a recent study¹²⁶ indicates that transformer models using SMILES input struggle with complete structure recognition. For predictions involving properties like toxicity, the performance of representations generated by these models might saturate before training progresses, showing limited improvement after training.

Despite the advances propelled by novel deep learning algorithms, the field still faces challenges. High costs and considerable time investments lead to scarce labeled data in ADMET predictions, leading to potential overfitting. Unsupervised and self-supervised learning offers solutions, and while large transformer-based models show promise in other fields, their use in ADMET prediction remains underexplored. A recent study¹³⁰ indicates that although SMILES language does not encode molecular topology directly, carefully designed self-supervised training with contextual transformers equipped with linear attention mechanisms can effectively learn implicit structure–property relationships, bolstering confidence in applying large-scale self-supervised models for ADMET predictions.

Furthermore, molecular representation is critical for AI performance. High-dimensional representations typically provide richer information than low-dimensional ones. However, recent studies indicate that integrating multiple levels of molecular representation can substantially enhance learning, leading to more comprehensive, generalizable and robust ADMET prediction^{78,131,132}. This suggests that multimodal ADMET models using multiple representations simultaneously holds promise, although the optimal combination of data types is still unresolved.

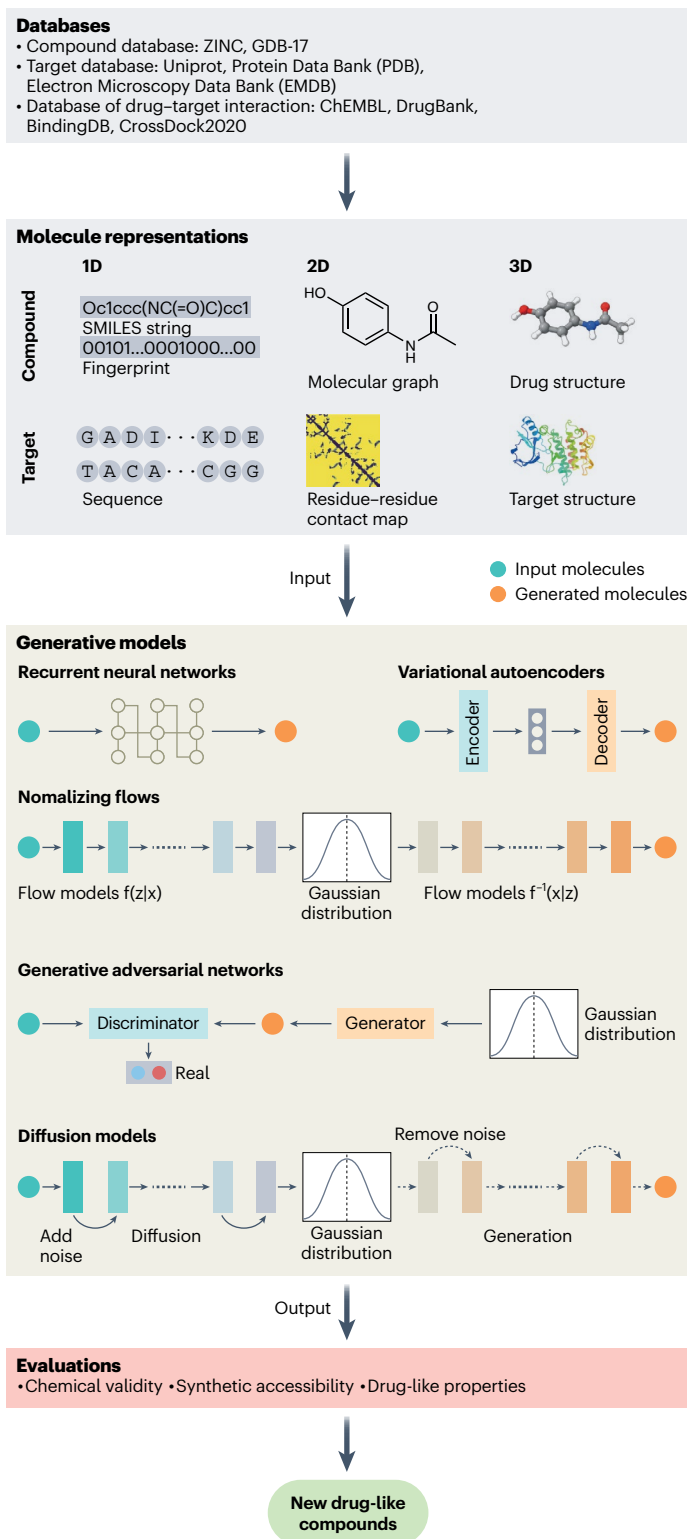


Fig. 2 | Pipeline for AI-driven molecular generation in drug discovery.

Molecular representations—one-dimensional (1D), two-dimensional (2D) and three-dimensional (3D) structures—are derived from diverse compound, target and drug–target interaction databases and are used to train AI models such as generative adversarial networks (a type of neural network architecture consisting of two competing networks, a generator and a discriminator, working together to create realistic data samples), recurrent neural networks (used for processing sequential data), variational autoencoders (generative models that learn to encode input data into a latent space and then decode it back to reconstruct the original data), normalizing flows (a class of generative models that transform a simple probability distribution into a more complex one through a series of invertible transformations) and diffusion models (generative models that create data by simulating a diffusion process). These models generate novel molecules, which are subsequently assessed for chemical validity, synthetic accessibility and drug-like properties, which ultimately enables the identification of new drug-like compounds. All structural figures were created using the UCSF ChimeraX 1.7.1 software²⁴⁷.

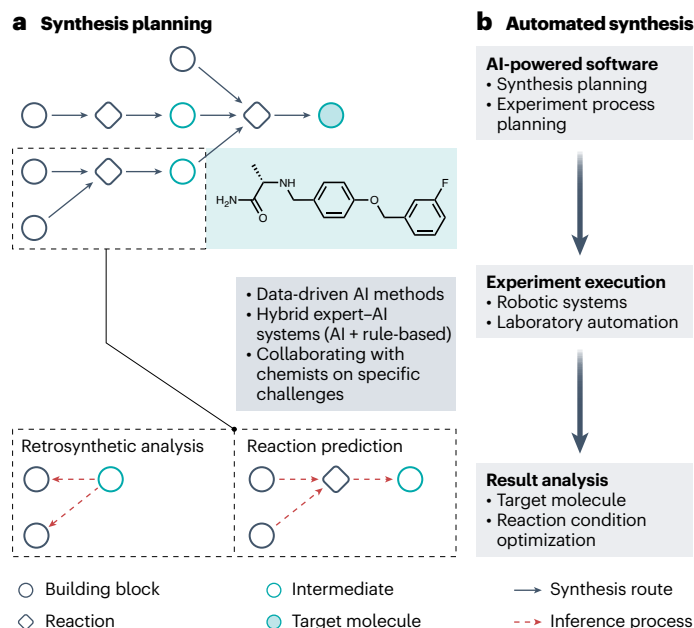


Fig. 3 | AI-driven synthesis planning and automation in drug discovery.

a, Synthesis planning. The synthesis planning process commences with retrosynthetic analysis that breaks down target molecules into commercially available or known building blocks, followed by reaction prediction to anticipate the required chemical reactions and conditions for synthesizing the target molecule. **b, Automated synthesis.** The schematic diagram illustrates the seamless integration of AI-driven software with experimental execution and result analysis within the automated synthesis process.

Interpretability remains a major challenge. Understanding model parameters in ADMET predictions helps reveal the relationships between molecular substructures and properties^{133,134}. Attention mechanisms, which allow a model to focus on important parts of the input data, can enhance interpretability by identifying key atoms or groups¹³⁵. Integrating chemical knowledge¹³⁶ can further enhance interpretability, but expanding models to achieve comprehensive chemical understanding remains challenging.

Synthesis planning and automating synthesis and drug discovery

Chemical synthesis, one of the bottlenecks in small-molecule drug discovery, is a highly technical and extremely laborious task. Computer-aided synthesis planning (CASP) and automatic synthesis of organic compounds can help alleviate the burden of repetitive laborious tasks for chemists, enabling them to engage in more innovative works^{137,138}. With the rapid development of AI, the pharmaceutical industry and academia are becoming increasingly interested in achieving intelligence and automation in this process^{138–141,142}.

CASP has been used as a tool to assist chemists in determining reaction routes via retrosynthesis analysis, a problem-solving technique in which target molecules are recursively transformed into increasingly simpler precursors (Fig. 3a). Early CASP programs were rule based (for example, logic and heuristics applied to synthetic analysis, simulation and evaluation of chemical synthesis¹⁴³ and retrosynthesis-based assessment of synthetic accessibility¹⁴⁴ programs). Since then, a range of machine learning techniques, particularly deep learning models, have been developed—yielding gradual improvements in the synthesis planning of artificial small molecules^{145–147} and natural products^{148,149}. Recently, the transformer model has also been applied to retrosynthetic analysis^{150,151}, prediction of regioselectivity (the preference of a chemical reaction to occur at one particular location over another on a molecule with multiple possible reactive sites) and

stereoselectivity (the preference of a reaction to produce one stereoisomer over another when multiple stereoisomeric products are possible¹⁵² and reaction fingerprint extraction¹⁵³. Concerns regarding the adequacy of purely data-driven AI methods for complex synthesis planning have spurred the development of hybrid expert-AI systems that incorporate chemical rules^{145,146}. Most current deep learning approaches, however, are unexplainable, showing as ‘black boxes’ that offer limited insights. To tackle this challenge, a new retrosynthesis prediction model, RetroExplainer, was recently introduced with an interpretable deep learning framework that reframes the retrosynthesis task as a molecular assembly process. RetroExplainer has shown superior performance compared to state-of-the-art retrosynthesis methods. Notably, its molecular assembly approach enhances interpretability, enabling transparent decision-making and quantitative attribution¹⁵⁴.

Automated synthesis of organic compounds represents a cutting-edge frontier in the field of chemistry-related fields (Fig. 3b), including medicinal chemistry. An optimal automated synthesis platform would seamlessly integrate and streamline various components of the chemical development process, including CASP as well as automated experiment setup and optimization, and robotically executed chemical synthesis, separation and purification. Recently, deep learning-powered automated flow chemistry^{145,147,155,156} and solid-phase synthesis¹⁵⁷ techniques for pharmaceutical compound synthesis have gained considerable attention. In particular, automated synthesis combined with designing, testing and analyzing technologies forms an automated central process of drug discovery called the design-make-test-analysis (DMTA) cycle. By leveraging deep learning, the efficiency of the DMTA cycle has been substantially improved, accelerating the discovery of hit and lead compounds for drug discovery^{147,155,158}. For example, by using an AI-powered DMTA platform with deep learning for molecular design and microfluidics for on-chip chemical synthesis, liver X receptor agonists were generated from scratch¹⁴⁷. In addition, LLMs^{159,160} are believed to ‘understand’ human natural language, enabling automation platforms to provide tailored solutions for specific challenges based on concise inputs from researchers. Although automated synthesis and the automated DMTA cycle have great prospects, their development is still in the infancy stage. Many technical challenges remain, including requirements to reduce solid formation to avoid blockage, predict solubility in nonaqueous solvents and at different temperatures, estimate optimal purification methods and optimize multistep reactions.

Following the planning and synthesis of new drug compounds, AI technology facilitates the *in vivo* validation of the mechanism of action (MOA) of new drugs. In high-content screening, by monitoring the real-time changes in omics data, AI technologies would generalize these features and develop a model that is capable of deciphering the molecular and cellular MOA of a new compound and its associated pharmacokinetics, pharmacodynamics, toxicology and bioavailability properties (Fig. 4)^{161–164}.

AI in clinical trials and real-world practice

AI is increasingly guiding various aspects of clinical trials by analyzing patient data, including genetic information, clinical history and lifestyle factors. Applying AI methods to such data helps to identify biomarkers and patient characteristics that influence drug responses, enabling more efficient and informative trial designs. By optimizing parameters like patient selection, treatment regimens and outcome measurements, AI has the potential to boost trial success and accelerate the translation of candidate drugs into clinical practice. Real-world data also offer a rich source of information from which AI applications can predict adverse events, drug–drug interactions and other outcomes. The sections below describe key applications of AI to the clinical stages of drug development.

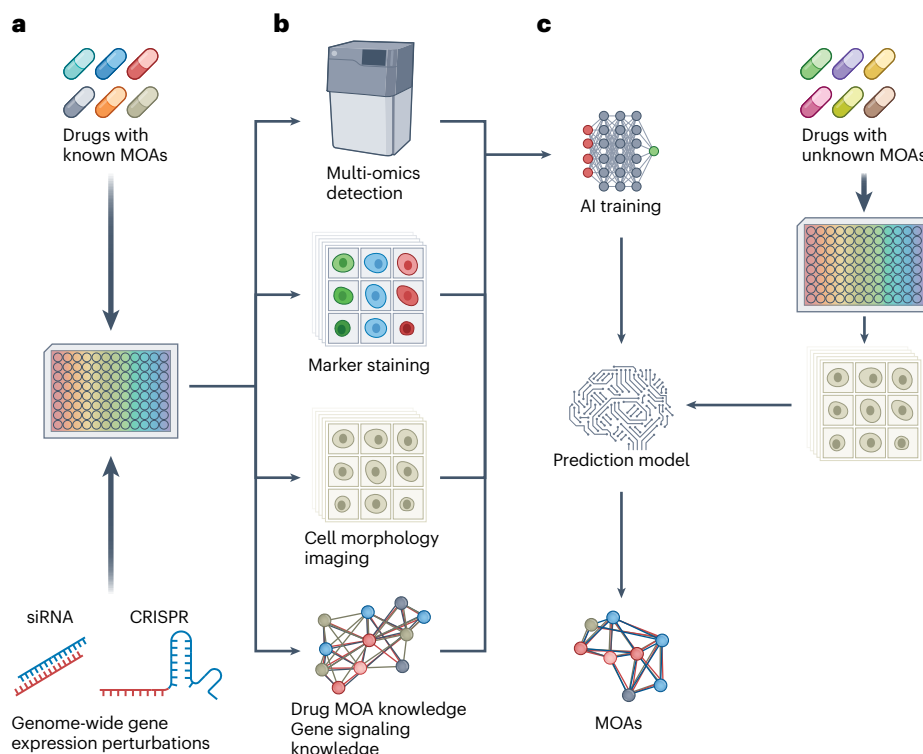


Fig. 4 | AI-driven MOA prediction using high-content screening and multi-omics data. **a**, In high-content screening, cells are cultured in multi-well plates, treated with a diverse range of drugs with known MOAs or signaling pathways (upper) and genome-wide gene expression perturbations (lower) are applied to different wells. CRISPR, clustered regularly interspaced short palindromic repeats; siRNA, small interfering RNA. **b**, Within each well, data on multi-omics features, marker staining patterns and cell morphology characteristics over time

are combined with knowledge of the corresponding MOAs or gene signaling pathway changes and used to train an AI model to understand the effect of each drug on cellular networks. **c**, As a result, this AI model will be able to predict the MOA of a new compound with similar multi-omics and cell morphology features. Parts **b** and **c** network images adapted from STRING²⁴⁸ under a Creative Commons license CC BY 4.0.

Biomarker discovery

Biomarkers serve as biological indices for objectively measuring and assessing normal versus pathological processes and responses to treatment, holding massive utility across medicine, biotechnology and biopharmaceuticals. However, traditional hypothesis-driven biomarker discovery methods are often inefficient while failing to address disease complexity comprehensively. These methods are time consuming and require substantial resources for hypothesis validation, while the constraints of limited sample sizes hinder broad validation across diverse populations.

Recent advancements in AI have dramatically enhanced biomarker discovery. AI models excel in identifying diagnostic biomarkers, offering predictive insights and diagnostic references for clinical pathology¹⁶⁵. A notable example is the ‘nuclei.io’ digital pathology framework¹⁶⁶, which merges active learning with real-time human–computer interaction. This helps to provide precise feedback to pathologists based on nuclear statistical data, by efficiently building datasets and AI models for various surgical pathology tasks, substantially boosting diagnostic accuracy and efficiency.

AI further excels in identifying prognostic biomarkers crucial for predicting disease progression and patient survival, thus enabling targeted and personalized treatments. For example, deep learning models can delineate CD8⁺ T cell morphology in blood samples as effective sepsis prognostic indicators¹⁶⁷, differentiate nuclear features marking cellular senescence¹⁶⁸ and identify proteomic biomarkers to accurately¹⁶⁹ predict liver disease outcomes. AI also predicts prognostic biomarkers for various cancers, delivering precise risk scores for survival, recurrence and metastasis. Notably, survival analysis models using graph neural networks outperform existing models, effectively

distinguishing risk groups beyond traditional clinical grading and staging^{170,171}—emphasizing AI’s potential in prognosis enhancement and the critical collaboration between pathologists and AI.

In drug development, identifying predictive biomarkers is crucial to enhancing research success by selecting patient populations most likely to benefit from treatments. These discoveries demand rigorous prospective clinical validation. Although AI-based predictive biomarkers have not yet been applied in the clinic, proof-of-concept studies indicate that AI can forecast patient responses to therapies by predicting known biomarkers such as microsatellite instability^{172–183}. The complexity of biological systems necessitates the integration of multiple types of biological data, including protein–protein interactions, into AI models for more comprehensive predictions¹⁸⁴.

Faced with a scarcity of large, labeled datasets, researchers are deploying diverse strategies to optimize the use of AI in biomarker discovery. The integration of datasets from multiple sources shows great promise^{171,185,186}. Digital biomarkers from wearable sensors also expand the scope of discovery, by providing rich, longitudinal datasets^{187,188}. Identifying multimodal biomarkers through molecular diagnostics, radiomics and histopathological imaging provides new avenues for precision medicine^{23,171,189,190}. Moreover, swarm learning¹⁹¹ and automated dataset processing pipelines¹⁹² lay the groundwork for large-scale, secure data collection.

Nonetheless, AI models face challenges relating to heterogeneity that impede their translational efficiency to clinical trials. Some studies use deep learning to elucidate cellular and tissue-level heterogeneity and the diversity of tumor ecosystems, offering new avenues for disease subtype classification and patient stratification^{193–196}. Interpretability and trust are critical for clinical acceptance of AI models¹³³ and can be

enhanced by integrating prior medical knowledge¹⁹⁷ or embedding biological relationships into neural networks¹⁹⁸. Addressing bias in AI-driven biomarker discovery^{199–201} requires strategies such as validating models across geographically diverse patient cohorts²⁰² and developing fair and transparent algorithms^{203,204}. Robust validation and responsible data curation will facilitate biomarker identification and application, supporting future drug development and disease treatment.

Predicting pharmacometrics properties

Applying AI and big data tools can effectively address pharmacometric problems and offer a powerful tool for time-to-event analysis, particularly in handling high-dimensional data and nonlinear relationships in the hazard function. AI supports personalized treatment by optimizing dose–response relationships, improving drug safety profiles and refining therapeutic windows, which are central to resolving pharmacometric problems in precision medicine. Machine learning-based analysis of 442 small-molecule kinases and 2,145 adverse events enabled the discovery of novel kinase–adverse event pairs, enabling risk mitigation and the development of safer small-molecule kinase inhibitors²⁰⁵. The multi-omics variational autoencoders (MOVE) framework integrates multi-omics data to reveal drug interactions—such as the link between metformin and the gut microbiota—and compares drug responses across various omics modalities²⁰⁶. PharmBERT, a domain-specific language model, enhances drug safety by extracting crucial pharmacokinetics information from prescription labels²⁰⁷, helping to identify adverse reactions and drug interactions. AI also optimizes drug dosages by analyzing genetic and physiological data, leading to personalized treatment recommendations that improve outcomes. Furthermore, AI can analyze patients' genetic information, physiological characteristics and past treatment responses to provide personalized dosage adjustment recommendations for doctors, thereby optimizing treatment outcomes²⁰⁸.

Drug repurposing

In addition to new drug discovery, AI contributes to the drug pool by repurposing existing, approved drugs using large-scale biomedical datasets, thus speeding up the development of optimal treatments for various diseases. By discovering previously unidentified therapeutic properties of approved drugs, AI reduces both the time and cost associated with drug discovery. For instance, AI has accelerated the repurposing of drugs for coronavirus disease 2019 (ref. 209), highlighting the value of AI in finding brand new applications for existing medications. AI can also simulate clinical trials using real-world data (including EHRs and insurance claims) to facilitate drug repurposing. As an example of this approach, a deep learning recurrent neural network used causal inference and deep learning to analyze medical claims databases, effectively identifying potential drug candidates. Applied to a cohort of millions with coronary artery disease, it pinpointed drugs and combinations that enhanced outcomes³⁹.

Another deep learning-based approach to drug repurposing involves the application of deep neural networks to omics data, to classify drugs into therapeutic categories based on the transcriptional perturbations that they induce *in vitro*²¹⁰. One study leveraged perturbation samples from the LINCS Project (<https://lincsproject.org/>) and 12 therapeutic categories derived from MeSH, resulting in high classification accuracy—especially with pathway-level data across diverse biological systems and conditions—offering potential for drug repositioning²¹⁰. Feature attribution techniques, combined with ensembles of interpretable machine learning models, enhance the identification of gene expression signatures associated with synergistic drug responses. This strategy has been shown to improve feature interpretability and support the selection of optimal anticancer drug combinations informed by molecular insights²¹¹.

Furthermore, AI-based high-content screening could also be applied in drug repurposing (Fig. 4). A deep learning model, MitoReID,

was developed to identify MOAs through mitochondrial phenotyping. It offers a cost-effective, high-throughput solution for drug discovery and repurposing, validated with unseen drugs (which were not part of the training set) and validated *in vitro*¹⁶³. By analyzing 570,096 cell images, MitoReID achieved 76.32% accuracy in identifying MOAs of US Food and Drug Administration-approved drugs and successfully validated the cyclooxygenase-2 inhibition of epicatechin, a natural compound in tea. Nevertheless, many challenges experienced in other stages of AI-driven drug development apply to drug repurposing, including issues with data quality, model interpretability, generalizability, validation costs, regulatory hurdles, integration with existing pipelines and high computational demands, which hinder widespread adoption and practical implementation.

Improving trial efficiency and predicting outcomes

Clinical trials are often expensive, time consuming and inefficient, with the majority facing delays in registration or struggling to find sufficient volunteers. AI has the potential to optimize trial design, streamline recruitment and predict patient responses, improving trial efficiency and success rates while reducing costs and timelines. An advanced pipeline has been created that integrates multimodal datasets, generates molecular leads using AI, ranks them by efficacy and safety, and uses deep reinforcement learning to create patentable analogs for testing²¹². It also predicts phase I/II clinical trial outcomes by estimating side effects and pathway activation, improving prediction accuracy and identifying potential risks in drug portfolios. In real-world studies, AI can analyze data from EHRs, insurance claims and wearable devices to assess drug effectiveness and safety (Fig. 5). For example, a study using real-world data and the Trial Pathfinder tool simulated trial outcomes from EHR data of 61,094 patients with advanced lung cancer, revealing that relaxing trial criteria could double eligible patients and improve survival outcomes. This approach, validated across various cancers, supports more inclusive, safer trials²¹³.

The challenge of finding suitable patients who meet inclusion criteria can be mitigated by using Digital Twins, as explored by Unlearn.ai. This technology creates virtual replicas of participants, allowing them to serve as the control group, thereby increasing the number of participants in the experimental group and improving trial efficiency. Unlearn.ai secured a US\$12 million grant in April 2020 to advance this application (<https://medcitynews.com/2020/04/funding-roundup-company-creating-digital-twins-for-clinical-trials-raises-12m/>), and other companies like Novadiscovery and Jinkō are conducting digital twin-based clinical trial simulations for diseases such as lung cancer (<https://www.novainsilico.ai/new-demonstration-of-the-predictive-power-of-an-in-silico-clinical-trial-in-oncology/>). The proposed approach uses computer modeling grounded in gene expression and clinical data, incorporating deep learning and generative adversarial networks²¹⁴. By leveraging diverse health metrics, these Digital Twins offer quantitative insights into vital processes, deliver dynamic health guidance and optimize treatment strategies. This approach seeks to deepen the mathematical understanding of biological mechanisms, revolutionize clinical practices and fully personalize medical care²¹⁵, for example, by generating patient-specific models that predict survival probabilities based on drug inputs. These models can also enable the simulation of clinical trials and optimize trial parameters, enhancing the likelihood of success. But they are not without their challenges, including high computational costs, tricky workflow integration, ethical concerns and limited personalization. These issues impact patient simulation accuracy, trial designs and regulatory acceptance, thereby slowing innovation²¹⁵.

Beyond the clinical trial stage of drug development, AI can also analyze post-market surveillance data to support the safety, efficacy and quality of drugs. The development and concurrent use of alternative methods to identify and address safety concerns early in the

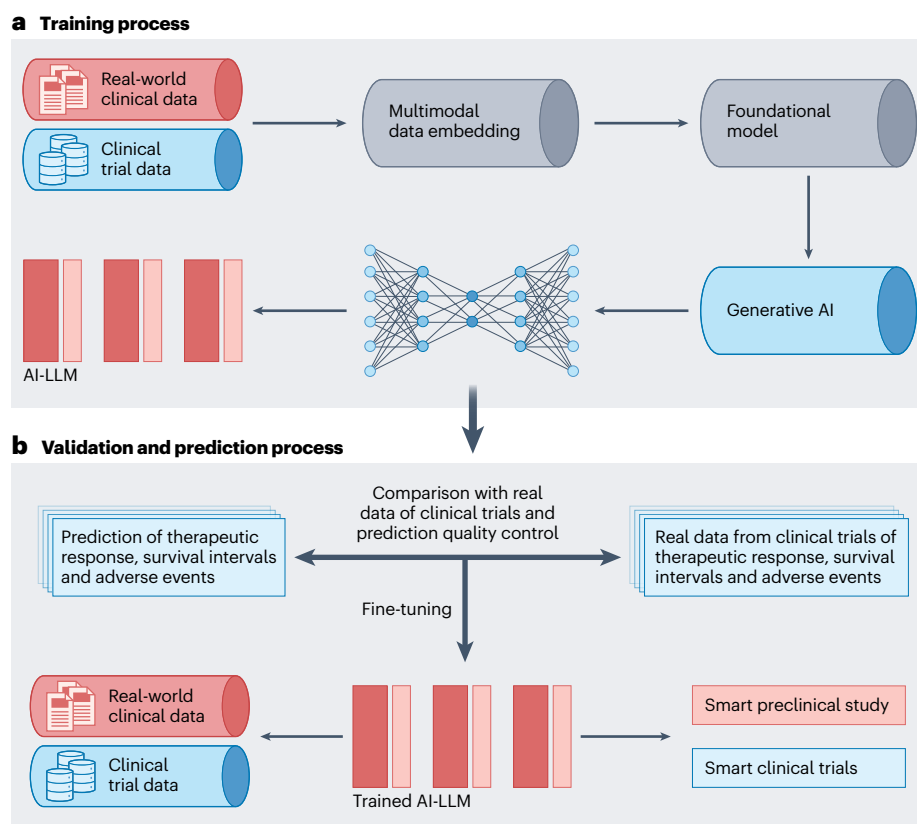


Fig. 5 | Utilizing AI capabilities to enhance both clinical trial processes and real-world medical practice. a. Training process: training involves using diverse clinical and trial data (EHRs, wearables, genomics, imaging) to develop an AI-LLM via multimodal embedding and generative AI. It assesses drug efficacy, optimizes trial protocols and enables smart preclinical and clinical studies. **b.** Validation

and prediction process: The AI-LLM is validated using real-world and clinical trial data, fine-tuned with therapeutic outcomes and adverse events. It predicts drug efficacy, assesses protocol feasibility and optimizes trials, enabling smart preclinical and clinical studies to accelerate drug development.

regulatory review process are essential for advancing regulatory science and optimizing drug development^{216,217}.

Challenges

Despite advancements, no AI-developed drugs have yet progressed beyond phase II trials, highlighting the complex nature of drug development. A key challenge is the lack of high-quality training data, due to high acquisition costs, privacy regulations and limited data sharing—especially for rare diseases or novel drug targets²¹⁸—which hinders the effectiveness of AI in identifying targets, biomarkers and other functions. Furthermore, available data often suffer from missing information, errors and biases, further reducing AI reliability. Drug discovery experiments can produce inconsistent results, and cost-saving measures may lead to incomplete data. Additionally, underrepresentation of ‘negative’ data (for example, unsuccessful experiments and negative trial outcomes) in the literature hinders a complete understanding of drug–target–disease interactions, efficacy and other clinical characteristics^{9,219}.

A key challenge in drug design is balancing multiple objectives for success. Current research often focuses too much on the chemical space, neglecting other key factors (such as druggability and synthesizability). While multi-objective design methods are improving^{220,221}, developing effective scoring functions (for example, for affinity prediction and bioactivity) remains complex and requires considerable experimentation. The absence of standardized evaluation processes further complicates model assessment^{222,223}, especially when conflicting objectives arise, such as maximizing similarity to known bioactive molecules while achieving structural novelty. Although benchmarking

platforms like MOSES²²⁴ and Guacamol²²⁵ exist, a consensus on best practices has not yet been reached.

Appropriate molecular representation is key in generative models. Traditional methods like SMILES and graphs are common²²⁶ and are being complemented by new, emerging data-driven approaches like hierarchical molecular graph self-supervised learning^{131,227,228}. Nevertheless, capturing complexity and ensuring synthesizability are difficult. Current methods for assessing synthetic feasibility are often imprecise, leading to discovery of unsynthesizable molecules. The integration of reaction knowledge into molecular generation shows promise, but needs improvement^{146,208}. Issues such as model interpretability, uncertainty in generating new molecules²⁰⁸ and bias²²⁹ have become focal points of academic interest. Effectively integrating bias control with uncertainty estimation is essential for improving the quality of generated molecules.

AI faces challenges with so-called ‘undruggable’ targets that lack suitable binding sites, including certain disordered proteins, transcription factors (such as MYC and IRF4) and protein–protein interactions. New AI methods and high-content screening (Fig. 4) to explore their conformational space and identify ligand binding sites could help overcome these obstacles.

Finally, technical challenges with algorithms and computing power limit AI’s use in drug development. Many AI algorithms used in drug development were designed for other fields and may not be fully suitable; for example, new algorithms based on NLP are needed to capture three-dimensional spatial interactions^{230,231}. Additionally, the high computational resources required by AI approaches pose barriers, especially for smaller research teams. Collaboration with

cloud providers and developing more efficient algorithms can help address these challenges. Further, AI drug development faces talent shortages and investment risks due to long cycles, low success rates and uncertain returns, affecting investor confidence.

Future directions

AI is revolutionizing the process of drug development by extracting critical insights from complex multi-omics biomedical data, identifying new biomarkers and detecting therapeutic targets and anomalies²³² to facilitate the discovery of lead compounds and drug candidates. Additionally, AI accelerates drug discovery, repurposing¹⁶ and toxicity prediction²³³, thus reducing time, cost and safety risks²³⁴. However, the journey toward fully realizing AI-enabled advancements in this area is ongoing, with many challenges to overcome and potential to be realized. Future efforts to address the challenges mentioned above should place particular emphasis on several key directions.

First, developing new strategies to address the data scarcity issue in AI-enabled drug development should be the top priority. Feasible strategies to enhance data sharing, establish data standards and develop new AI algorithms—such as ‘sparse’ AI methods that can produce accurate predictions from very limited data—are crucial. Multimodal pretrained models that integrate textual and chemical information offer promise in addressing the data scarcity, especially in zero-shot scenarios²³⁵. By integrating an array of data such as genomics, transcriptomics, disease-specific molecular pathways, protein interactions and clinical records, AI can also identify existing drugs with potential repurposing opportunities for neglected or orphan diseases²³⁶.

Current methods typically focus on single data types, thereby missing complex interrelations between various biological systems. Establishing effective multimodal fusion approaches can extract valuable insights from diverse sources and formats to advance drug development. With the rise of big data and GPU computing (based on a graphics processing unit, rather than a conventional central processing unit, or CPU), AI can now be applied to various data forms, including text, images and videos. Emerging models using omics data, including deep learning-based drug classification, show promise in drug efficacy prediction, mechanism identification and toxicity assessment, highlighting the future potential of multimodal AI in drug development^{210,212}.

Many current AI models are purely data driven, limiting their effectiveness in drug development due to the relative lack of sufficiently high-quality data. Because our life systems all adhere to the principles of physics (also called the First Principle), drugs also follow the constraints of physical laws without exception. Incorporating physical laws into existing data-driven AI algorithms is one future research direction that could help reduce data dependency and improve both the accuracy and generalizability of these models.

AI, especially LLMs, can ensure compliance with drug regulations by analyzing extensive documentation and keeping up with the latest requirements. This boosts efficiency, reduces risks of non-compliance and prevents delays in drug approval^{159,237–239}. Developing not just accurate, but also interpretable AI models is essential for building trust among drug developers, regulatory agencies, clinicians and patients by ensuring transparency and understanding in the decision-making process. These models can be incorporated early to optimize project funding and guide investments²³³ to accelerate drug development.

In the coming decades, AI’s role in medical modeling and simulation will be transformative. Advanced AI models will create ever more detailed virtual human simulations²⁴⁰, further enhancing our understanding of disease mechanisms²²³, drug actions and individual biological differences^{216,241}. Through simulations, AI can streamline clinical trial design and execution²⁴², testing different scenarios for best selection criteria²¹⁴ to accelerate patient recruitment and enhance trial representativeness²¹³. AI will also provide personalized medical decision support by analyzing health data and genomics, enabling

precise risk predictions, optimized treatments and improved surgical guidance^{243,244}. Medical education will benefit from AI-driven virtual reality, offering more realistic training scenarios and enhancing the quality of medical services²⁴⁵.

Conclusion

Overall, the continuing advancements in AI technologies are substantially improving the efficiency and cost-effectiveness of drug development. However, it is essential to recognize that AI is not omnipotent. The strength of AI technologies lies in analyzing big and complex data and aiding quick decision-making to complement human functions and augment human capabilities, but AI is not designed to entirely replace human ingenuity or authority. The drugs designed and properties predicted by AI still require validation through wet-lab experiments, and human input will still be needed to determine the direction of AI research and use. Nevertheless, given the ever-growing capabilities of AI and the pace of advancement, as well as the open sourcing of large models, including the recent AlphaFold3 (ref. 246), we can be judiciously optimistic about AI’s promise for accelerating drug development and benefiting human health.

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Competing interests

The authors declare no competing interests.

Additional information

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