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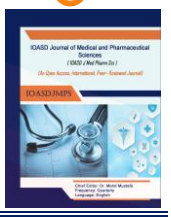

Predictive Roles of Artificial Intelligence in Pre-Clinical Studies: An Overview

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ABSTRACT

Animal testing in preclinical drug development has long raised scientific and ethical concerns. Artificial intelligence (AI), through its deep learning (DL) and machine learning (ML) sub-fields causing a paradigm shift in pre-clinical research by offering the potential to partially or fully reduce reliance on animal experimentation and to provide more human-relevant alternatives. This review examines the emerging roles of AI in preclinical drug development process which includes drug screening; pharmacodynamic and pharmacokinetic prediction; toxicity and carcinogenicity assessment; organ-on-chip technology, digital twins, virtual animal models, regulatory compliance, and autonomous AI agents while critically addressing the challenges and limitations that accompany this transition.

Keywords: Artificial intelligence (AI); Organ-on-chip; Digital twins; Animal models; AI agents.

Review Article

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1. INTRODUCTION

Drug discovery and development is among the most resource intensive and scientifically complex undertakings in medicine, typically spanning an average of 12 years from molecule identification to market approval (Singh *et al*., 2024). The drug development involves preclinical studies where the drug candidates are subjected for rigorous pharmacological characterization to validate their progression to clinical trials (Tripathi, 2023). Animal experimentation has historically been integrated to these preclinical studies (Gangwal & Lavecchia, 2025).

Nevertheless, drugs demonstrating efficacy in animal models frequently fail in human trials owing to interspecies physiological differences. Animal models are particularly limited in mimicking the complexity of certain diseases especially neurological disorders where genetic, environmental, physiological, emotional, and social factors jointly influence outcomes. Despite stringent guidelines for conducting animal experiments cruelty free, ethical concerns still persist particularly during the involvement of non-human primates like chimpanzees, monkeys etc in neuroscience research. These concerns have accelerated the adoption of alternative testing methods aligned with the 3R principle (*Replacement, Reduction, and Refinement*), integrating *in-silico* methods and AI into the preclinical workflow.

AI-supported alternatives such as organ-on-chip systems and digital twins are being developed to address the scientific, economic and ethical challenges of traditional testing. AI, DL and ML are emerging as transformative tools in this regard; however, these technologies remain in a research and development phase, and further validation is required before they can be considered replacements for traditional animal studies. Moreover, AI algorithms remain susceptible to bias inherited from their training data (Gangwal & Lavecchia, 2025). **Table 1** summarizes the comparative advantages and disadvantages of the principal preclinical testing approaches.

Table 1. Comparative overview of preclinical testing approaches

Model	Advantages	Disadvantages	Examples	Reference(s)
In vitro models	Inexpensive; rapid; suitable for high-throughput screening	Limited capacity to replicate whole-organism disease physiology	Organ-on-chip, Caco-2 cell line	Brahmankar & Jaiswal, 2022; Gollamudi, 2025
Animal models	Established standard for modelling human disease pathophysiology	Poorly replicate complex neurological and psychiatric conditions	Mouse, rat, dog, monkey	Tripathi, 2023; Gollamudi, 2025
In silico models	Time- and cost-efficient	Cannot fully replicate human physiology	ADMET Predictor	Bayan *et al*., 2024; Gollamudi, 2025
Artificial Intelligence	Rapid; can generate synthetic data from existing literature to model diseases lacking animal models	Still in a foundational stage; requires extensive validation	AnimalGAN	Gangwal & Lavecchia, 2025; Gollamudi, 2025

While AI technologies offer considerable promise for reducing reliance on animal models, animal studies remain indispensable in areas involving long-term and complex physiological investigations. A balanced strategy integrating AI with traditional animal studies is therefore warranted at the present stage. This review discusses the transformative role of AI across the preclinical drug development landscape.

2. AI IN DRUG SCREENING

Screening is typically the first step undertaken to detect the presence or absence of a specific pharmacodynamic activity. For example, α-amylase assay is used to screen antihyperglycaemic activity (Tripathi, 2025). With AI and its DL/ML sub-types, candidate compounds can be computationally screened against libraries containing millions of molecules to identify likely bioactivity, substantially reducing time and cost. AI models trained on large bioactivity repositories such as ChEMBL, PubChem, and ZINC enable researchers to identify compounds active against specific molecular targets (Singh *et al*., 2023). Notably, researchers at the Massachusetts Institute of Technology employed DL models trained across multiple databases and the medical literature to identify Halicin, a compound demonstrating activity against drug-resistant bacteria like Acinetobacter baumannii and Mycobacterium tuberculosis (Niazi, 2025).

3. AI IN PREDICTION OF PHARMACODYNAMIC ACTIVITY

Pharmacodynamics refers to the biochemical and physiological effects of a drug on the body (Tripathi, 2023). Early and accurate prediction of this activity reduces attrition in later-stage of human trials. Large language models (LLMs) such as BioBERT, ChemBERTa, PubMedBERT, and SciBERT are domain specific language models based on the '*Bidirectional Encoder Representations from Transformers'* (BERT) architecture increasingly used to predict drug-target interactions (Gangwal & Lavecchia, 2025). Early prediction of drug-target interaction is the first step in computational drug discovery. By using predictive models before expensive *in vitro* or *in vivo* testing, researchers can drastically reduce development costs, accelerate clinical timelines, prevent late state trial failure and effectively repurpose existing or even abandoned drugs bypassing much of the initial safety testing required for new molecules. DL algorithms generally outperform conventional ML approaches in this domain using tools like DeepDTA, WideDTA, and DeepAffinity and thereby employ protein sequencing to predict bioactivity (Gangwal & Lavecchia, 2025; Singh *et al*., 2024).

4. AI IN PREDICTION OF PHARMACOKINETICS

Pharmacokinetic parameters like absorption, distribution, metabolism and excretion (ADME) are critical determinants of clinical success and poor pharmacokinetic profiles remain a leading cause of candidate drug failure in clinical trials. Therefore, early assessment of ADME has become an established component of drug discovery (Jia & Gao, 2022). Traditional ADME evaluation relies on tedious *in vivo*, *in vitro*, and *in silico* procedures that are time and resource intensive; AI is increasingly exploited to streamline this process. Tools such as ADMETLab apply DL algorithms to predict drug absorption from molecular descriptors, while random forest and deep neural network models trained on large compound libraries estimate human intestinal absorption. AdmetSAR is a further example of an AI-based ADME prediction tool (Singh *et al*., 2023).

5. AI IN THE PREDICTION OF TOXICITY

Toxicity assessment is a central objective of preclinical trials. Traditionally testing requires at least two animal species which cause considerable cost and ethical burden (Tripathi, 2023). AI assisted toxicity prediction is gaining momentum, though there is need for extensive validation. AI Tools like DeepTox uses deep neural networks to predict toxicity while DeepDILI

models predict 'drug induced liver injury' (DILI). Notably, in an effort to replace the Draize eye-irritation test, US FDA's Center for Food Safety and Applied Nutrition has developed artificial neural network (ANN) based models for predicting ocular irritation (Gangwal & Lavecchia, 2025).

6. AI IN PREDICTION OF CARCINOGENICITY

Carcinogenicity is conventionally assessed through long-term exposure of the drugs in animals. AI based carcinogenicity prediction offers ethically and scientifically credible alternative. The FDA's National Center for Toxicological Research has developed DeepCrac, a tool for screening compounds for carcinogenic risk, thereby reducing reliance on animal testing. The STopTox model validated under 'Organisation for Economic Co-operation and Development' (OECD) guidelines, similarly predicts toxicity (Gangwal & Lavecchia, 2025; Singh *et al*., 2023).

7. AI AND ORGAN-ON-A-CHIP TECHNOLOGY

In 2010, Huh *et al*. developed the first 'lung-on-a-chip' device. This micro-fluidic device mimicked the physical and functional characteristics of human alveoli by co-culturing human alveolar epithelial cells and lung capillary endothelial cells on a flexible, porous silicone membrane. This was pioneered at Harvard University which paved the way for advanced 'organ-on-a-chip' technology. The technology has now expanded to simulate various human tissues including intestine, bone marrow and blood brain barrier thereby significantly improving drug development. This concept has since evolved toward 'patient-on-chip' systems in which individualized, patient-specific cell lines to recreate their unique genetic background and clinical data's are integrated with AI algorithms to generate personalized therapeutic response predictions. A principal limitation of this technology is the large volume of complex data generated, which poses challenges for interpretation and cross-laboratory standardization.

AI can address these challenges in several ways. ML algorithms can analyze large 'organ-on-a-chip' derived datasets to detect subtle cellular responses. DL algorithms facilitate the identification of novel biomarkers. Reinforcement learning algorithms can optimize experimental parameters such as flow rates and dosing regimens. Quris-AI company has combined organ-on-chip technology with AI algorithms to develop treatments for Fragile X syndrome, a condition for which no animal models currently exist (Gangwal & Lavecchia, 2025).

8. AI AND DIGITAL TWINS

A digital twin (DT) is a dynamically updated virtual replica of a patient, organ, biological system, or animal. It is generated from its physical counterpart which contains multidimensional, patient specific information to support decision making (Samei, 2025). In preclinical research, digital twins are used to construct virtual animals with AI providing the computational power to generate synthetic data that when integrated with DTs can predict diverse pharmacological parameters.

For instance, generative adversarial network (GAN) based rat DTs have been used to study hepatotoxicity by synthesizing liver transcriptomic data, while convolutional neural network (CNN) based DTs simulate neural responses in the mouse cortex, thereby reducing reliance on live-animal experimentation. *Aitia*, a company integrating AI with DTs through its Gemini platform, has modeled complex neurodegenerative diseases and cancers. It has given insights into Huntington's disease and amyotrophic lateral sclerosis. Similarly, *Deep Life* has pioneered DTs of human cells by integrating surge omics data with ML to model drug's action on diseased cells (Gangwal & Lavecchia, 2025).

9. AI-BASED VIRTUAL ANIMAL MODELS

Fully computational, AI enabled models capable of reproducing pharmacological responses represent a paradigm shift from live animal experimentation. The Virtual Dog model, developed by esqLABs, applies systems biology, multi-scale modeling and ML algorithms to simulate canine tissue and organ responses for predicting chronic toxicity, thereby reducing reliance on live dogs. AnimalGAN, another AI based tool developed by the FDA, simulates clinical pathology data for use in chemical safety evaluation. Further advances include Tox-GAN, which simulates cellular responses to chemical exposure and TransOrgan, a GAN based model mapping transcriptomic profiles across organs and sexes.

10. AI AND GOOD LABORATORY PRACTICE

Good Laboratory Practice (GLP) comprises a set of guidelines for governing the planning, execution, monitoring and reporting of non-clinical research laboratory studies (Pise *et al*., 2024). Regulatory authorities require laboratories to maintain authenticity, integrity, traceability and compliance with GLP guidelines. AI and ML have proven valuable in enhancing real time monitoring and anomaly detection. One such example is auto encoder based anomaly detection systems. Laboratories often generate large volumes of unstructured, heterogeneous data, which can be managed and analyzed through ML algorithms integrated with laboratory information management systems (LIMS) (Zai *et al*., 2025).

11. AI AGENTS AND PRECLINICAL STUDIES

A recent advancement in AI is the emergence of autonomous 'AI agents' or 'virtual scientists'. Such systems are capable of autonomously pursuing human defined goals through interaction with real world data and experimental systems. These agents can generate new hypothesis from existing literature and databases, validate them experimentally, and learn iteratively from

the outcomes. AI agents can substantially enhance toxicity prediction by integrating toxicological modeling with cheminformatics. For example, the company named *Human Chemical* has developed and employed AI agents to assess the toxicity of Cashmeran, a polycyclic musk compound used in perfumery, while other applications include identifying drug repurposing opportunities for spinal muscular atrophy (SMA) (Huynh *et al*., 2026).

12. CHALLENGES AND CONCERNS REGARDING AI IMPLEMENTATION

Though AI is emerging as a front runner in the drug discovery and development, its implementation in preclinical research faces several challenges. Robust AI models require large, high-quality datasets to train the AI models. Further, insufficient or poor-quality data compromises such models performance. On the other hand, excessive data acquisition can impose substantial cost burden on the organizations. Additional concerns include biasness of data's used to train AI models. Such models will generate 'black-box' nature of many algorithms, and there is a risk of model's hallucination. Data privacy and consent issues also arise regarding information used for AI driven research (Gonzalez *et al*., 2023; Paul *et al*., 2021). Regulatory challenges further persist owing to the absence of harmonized laws and guidelines for validating AI generated results submitted by research organizations.

13. CONCLUSION

Animal experimentation and *in vitro* methods remain the gold standard for preclinical drug testing. The field is progressively evolving toward more human-relevant models. AI holds immense potential to transform preclinical studies by reducing dependence on animal models. At present, AI functions as a complementary tool alongside animal studies for safety and efficacy testing. Nevertheless, the contribution of AI to the optimization and refinement of preclinical research is significant. With continued research and rigorous validation, AI may ultimately serve as a viable replacement for animal models addressing all the scientific and ethical concerns.

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