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Machine Learning-Driven Anticancer Drug Discovery: From Virtual Screening to Preclinical Validation

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Abstract. The escalating global cancer burden necessitates accelerated development of effective therapeutics, yet conventional drug discovery faces prohibitive challenges: cycles exceeding 10 years, costs surpassing $2 billion per drug, and clinical success rates below 10%. Traditional high-throughput screening paradigms remain resource-intensive and inefficient. This review systematically examines the transformative integration of bioinformatics, multi-omics data, and machine learning across the anticancer drug development pipeline. In virtual screening, AlphaFold-predicted protein structures have revolutionized structure-based approaches. When combined with graph neural networks (GNNs) and molecular dynamics simulations, these techniques enhance the accuracy of dynamic docking by over 30%. For ADMET optimization, GNN-based models significantly improve toxicity and pharmacokinetic prediction. Tumor organoid platforms now achieve 88% accuracy in replicating clinical chemotherapy responses for breast cancer, while interpretable AI tools like SHAP provide critical decision insights for molecular design. During preclinical validation, AI-driven automated synthesis systems enable closed-loop compound generation, accelerating design-to-synthesis workflows. Advanced bionic models—particularly 3D organoids and simulations of the tumor microenvironment—deliver physiologically relevant platforms for precise evaluation of efficacy and safety. Collectively, this synergistic framework of computational algorithms, experimental automation, and biomimetic models establishes a robust new paradigm for streamlining drug discovery and advancing personalized oncology therapeutics.

Keywords: Cancer; Machine learning; Drug discovery.

1. Introduction

In recent years, the global cancer burden has continued to increase, and the development of anti-cancer drugs has long faced three major bottlenecks: a research and development (R&D) cycle exceeding 10 years, costs surpassing $2 billion per drug, and a clinical success rate below 10% [1]. Traditional high-throughput screening relies on a trial-and-error experimental model, which not only consumes huge resources but also has extremely limited research and development efficiency. Against this backdrop, breakthroughs in machine learning technology have brought innovative opportunities to this field [2]. For instance, AlphaFold3 has achieved breakthroughs in protein structure prediction [3]; generative AI models have been applied to novel small molecule design; and knowledge graphs are increasingly used to mine potential therapeutic targets [4]. These innovations offer the potential to significantly shorten the drug discovery timeline and reduce development costs. This review focuses on three core pillars: virtual screening, ADMET property optimization, and automated preclinical validation. It aims to shorten the drug development cycle to 3-5 years through technological integration and achieve a cost reduction of 50-70% simultaneously.

2. Machine Learning Algorithms

2.1 Application of Machine Learning in Virtual Screening

2.1.1 Structure prediction and molecular generation

The protein structure prediction technology of AlphaFold has completely transformed structure-based virtual screening [5]. For example, when using docking tools such as AutoDock Vina with AlphaFold derivative structures to predict ligand–receptor interactions (e.g., EGFR), the accuracy

rate reached 85% [6]. This breakthrough has made it possible to design drugs based on precise protein structures, thereby enhancing the precision and efficiency of virtual screening. Ligand-based generative models, such as REINVENT [7], have been designed to create new molecular skeletons, overcoming the limitations of traditional combinatorial libraries. These models, by learning the structural characteristics and activity relationships of existing drug molecules, can generate novel molecules with potential biological activities, providing a rich candidate compound library for drug research and development [8].

2.1.2 Dynamic Conformation and Reinforcement Learning

Traditional drug design models often overlook the crucial impact of impact of dynamic protein conformational changes on ligand binding. Proteins undergo structural shifts during molecular interactions, and static models fail to capture these dynamics accurately. In recent years, the hybrid algorithm framework has significantly improved the accuracy of dynamic conformation prediction by integrating graph neural networks (GNN) and molecular dynamics (MD) [9]. For example, the GNN-MD model can capture the conformational change trajectory of KRAS mutants, encode the molecular topological structure through graph networks, and combine MD to simulate atomic motion to predict the dynamic behavior during the protein-ligand binding process, increasing the accuracy of dynamic docking by more than 30% [10].

2.2 The Application of Reinforcement Learning in ADMET Optimization

2.2.1 Toxicity prediction and multi-objective equilibrium

In the research and development of anti-tumor drugs, traditional toxicity assessment relies on animal experiments. Not only does a single round of assessment take 3 to 6 months, but FDA data also shows that its accuracy rate in predicting human toxicity is only 60-70% [11]. Machine learning is innovating this field through multi-dimensional models. Structure-based toxicity fingerprint recognition uses graph neural networks (GNN) to encode molecular structures [12]. For instance, combining a Weisfeiler-Lehman network with a random forest yields 82% accuracy in predicting hepatocyte toxicity on the Tox21 dataset—a 71% improvement over traditional QSAR models. These models can also automatically identify toxic moieties like aromatic amines and halogenated hydrocarbons.

Graphic-based models such as DeepTox predicted toxicity by analyzing the substructure-activity relationship, with an AUC of 0.85 [13]. RL frameworks (such as DeepChem RL) balance efficacy and toxicity, thereby enabling the discovery of non-toxic antibiotics [14]. Transfer learning models (such as Meta-ADMET) integrated animal data and improved the accuracy of human ADMET prediction by 20% [15].

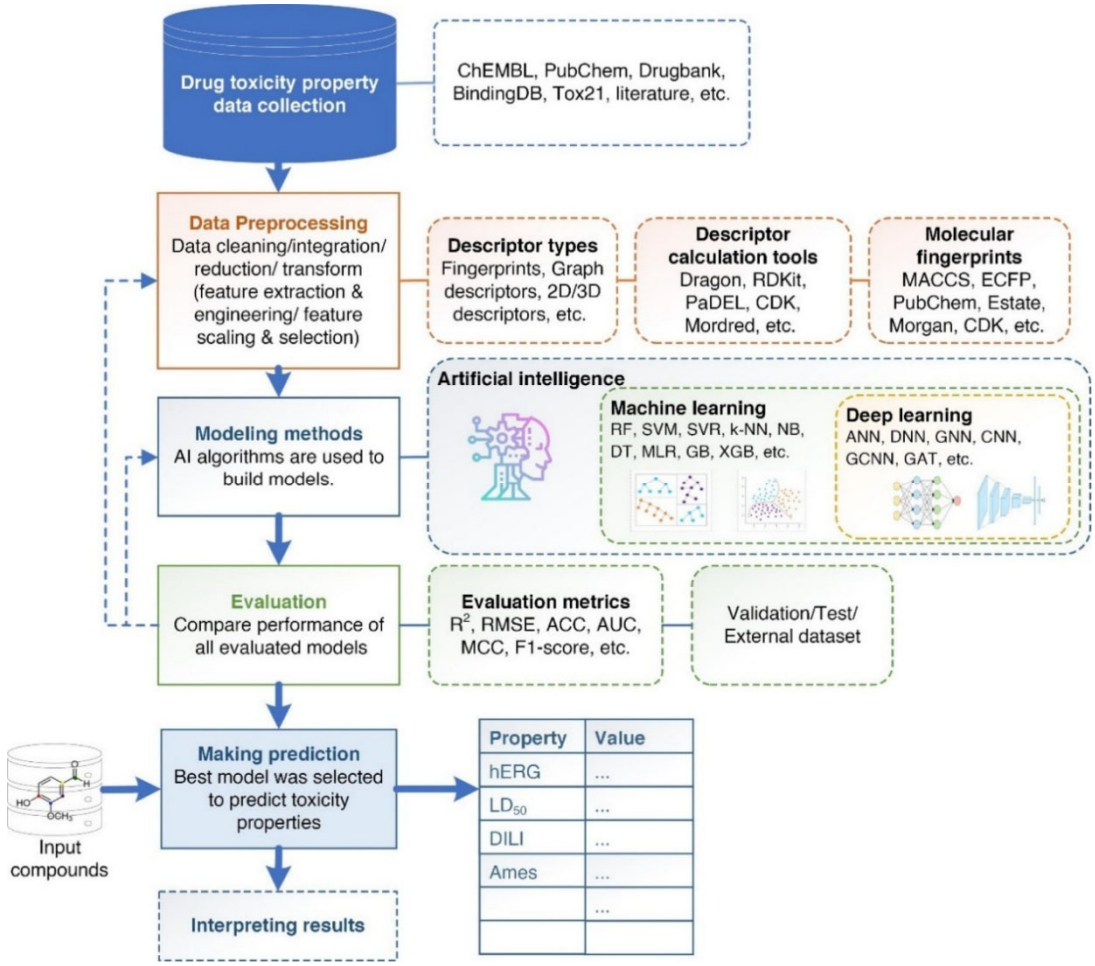

Figure 1. Process flow of drug toxicity prediction model [16].

2.2.2 Organoid models and interpretability

Animal models have poor replication effects on human pharmacokinetics [17]. Tumor organoids, as three-dimensional cell culture models, can highly simulate the tissue structure, gene expression, and microenvironment characteristics of primary tumors, providing an evaluation system that is closer to the physiological state for drug screening. By extracting the stem cells/progenitor cells of the patient's tumor tissue or xenograft tumor and inducing the formation of organoids in the matrix gel, tumor heterogeneity can be retained. Patient-derived organoids (PDOS) predict breast cancer chemotherapy response with 88% accuracy [18].

To enhance interpretability, explainable AI (XAI) tools such as SHAP can identify toxic substructures (e.g., nitro groups) [19]. Organs can also be subcultured for a long time and maintain tumor characteristics, supporting long-term drug exposure experiments. For example, in the study of EGFR inhibitor resistance, it shows that the resistance stems from MET gene amplification or EGFR C797S mutation, which is consistent with the biopsy results of clinical patients. Moreover, through co-culture with fibroblasts, immune cells, etc., it can simulate the influence of the tumor microenvironment on drug response [20].

To resolve AI's "black box" dilemma, interpretability tools such as SHAP and LIME quantify molecular contributions to predictions [21]. For example, SHAP revealed that a nitrobenzene group contributed +0.32 to predicted liver toxicity, guiding chemists to avoid introducing this group. LIME, using local linear approximations, showed that indole rings increase the predicted inhibition rate of the organoid growth inhibition model by 25% [22]. GNN can highlight the key regions where molecules bind to targets through the attention mechanism and visualize the structure-activity relationship. For example, when the organoid model predicts the activity of EGFR inhibitors, its attention map shows that the quinazoline ring forms a hydrogen bond with the ATP-binding pocket of EGFR, with a weight proportion of up to 42%. Consistent with the results of crystal structure

analysis combined with molecular dynamics simulation, the dynamic stability of this binding mode can also be verified [23].

3. Preclinical validation

3.1 Automated synthesis driven by artificial intelligence

AI-driven automated synthesis technology is reshaping the compound production model in anti-tumor drug research and development. By integrating machine learning planning with robot experimental platforms, it achieves closed-loop acceleration from molecular design to physical synthesis. The inverse synthetic planning algorithm based on knowledge graphs and reinforcement learning can reversely derive feasible synthetic paths from the target molecular structure. For instance, the AI planning system developed by Coley's team can generate multiple synthetic routes within minutes and optimize reaction conditions through Monte Carlo tree search, which is more than ten times more efficient than traditional manual planning. The combination of this planning capability and the flow chemistry robot platform has formed an automated pipeline of "AI design - robot execution - real-time verification."

In the synthesis of anti-tumor drugs, AI planning can intelligently avoid introducing toxic functional groups. For instance, when designing EGFR inhibitors, the system automatically identifies the risk of hepatotoxicity posed by halogenated aromatics and recommends borate ester substitution strategies instead, increasing the pass rate of subsequent toxicity tests by 40%. The high-throughput capabilities of the automated synthesis platform also bolster structure-activity relationship research. Using the 96-well plate flow chemistry device, more than 200 structural analogs can be tested in parallel in a single experiment. In one case, this technology was utilized to optimize the positions of substituents in PARP inhibitors, allowing the structure-activity relationship analysis, which would take three months using traditional methods, to be completed in just two weeks. The lead compound with an activity increase of 12 times was successfully discovered. IBM's RoboRXN automatically designs reaction paths through natural language processing and achieves a yield of over 90% in one-step synthesis. This technology has significantly improved the efficiency and reliability of synthetic reactions, reducing errors and time consumption associated with manual operations [24, 25].

It is worth noting that the deep integration of AI and synthetic robots is giving rise to the concept of "autonomous chemistry laboratories." For instance, the system developed by Insilico Medicine can automatically design the synthetic route and control the robot to complete the entire process of liquid separation, reaction, and purification based on the activity data predicted by GNN. It has achieved a rapid 72-hour turnaround from structural design to the delivery of solid compounds in the synthesis of DDR1 inhibitors. This automation paradigm not only significantly reduces manual intervention (the automation rate of experimental operations reaches 92%) but also forms closed-loop feedback through real-time spectral analysis (such as FTIR, LC-MS), dynamically adjusts reaction parameters to optimize the yield, and increases the reaction efficiency by 35% compared with traditional batch reactions.

For multi-step synthesis, the ASKCOS platform uses reinforcement learning to determine the priority of routes, reducing the synthesis time by 50%. Through intelligent optimization of synthetic routes, automated synthesis technology can prepare candidate drugs rapidly and efficiently, providing strong support for the preclinical stage of drug research and development [26, 27].

3.2 3D Organoids and Tumor Microenvironment

Traditional organoids lack components of the tumor microenvironment (TME), such as immune cells. The biomimetic TME model was constructed through the 3D biomimetic co-culture of stromal cells and tumor cells [28]. This model can simulate the growth environment of tumors in vivo more realistically, including the interactions between tumor cells, immune cells, and stromal cells. It provides a more accurate framework for evaluating the efficacy and mechanisms of action of drugs. One appealing application is the precise testing of drug reactions. These models can be quickly

established using patients' tissues. For example, 3D organoids are used to guide chemotherapy options for patients with resectable and borderline resectable pancreatic cancer. Although tissues and models representing patients' diseases are expected to accurately predict drug responses, the complexity of obtaining tumor tissues and the long-term, unreliable nature of establishing patient-derived xenograft avatars make these resources less attractive for widespread application. In contrast, implementing organoid models in clinical trials of personalized medicine may represent the preferred technique [29].

Another important direction is the development of native immune organoid models. In the air-liquid interface (ALI) culture system [30], tumor organoids grow from physically chopped primary tissue fragments, which are embedded in collagen gels or other extracellular matrices within Transwells. Under ALI culture, tissue fragments can generate innate immune organoids. Tumor cells can grow together with endogenous matrices and immune populations, thereby preserving the heterogeneity, mutational burden, and structure of the primary tumor. Similarly, organoid tumor spheres—such as mouse-derived (MDOTS) and patient-derived (PDOTS) models—are created by culturing 40–100 μm tumor fragments in collagen gel within microfluidic devices. DOTS not only retained tumor cells but also autologous lymphocytes (B cells and T cells) and bone marrow cells (monocytes, dendritic cells, myeloid-derived suppressive cells, and TAMs). These models successfully evaluated the immunotherapy response and retained the important natural spatial relationships in the tumor-TME interaction.

In the research of colorectal cancer, researchers at the École Polytechnique Fédérale de Lausanne have developed a "mini colon" [31]. This next-generation organoid can induce tumorigenesis in vitro by integrating microfabrication, optogenetics, and tissue engineering methods. It simulates the dynamics of colorectal tumors and can study the cellular interactions in the tumor-native microenvironment at high resolution. The "mini colon" is composed of long-lived and topologically biologically relevant healthy colonic epithelium, which can reproduce the formation and progression of colorectal tumors and stably integrate cancer cells and their primary tumor microenvironment. It can also be used to evaluate the efficacy and toxicity of anti-cancer drugs, reveal the mechanisms of epithelial-mesenchymal transition (EMT) and invasiveness mediated by cancer-associated fibroblasts (CAF) in colorectal cancer, and assess the immune escape and immunotherapy strategies of colorectal cancer mediated by the tumor microenvironment (TME) [32].

Innovations in organoid imaging and molecular profiling have expanded their utility. Light-sheet microscopy allows real-time, minimally invasive imaging of immune organoid dynamics [33], while single-cell transcriptomics can be conducted for in-depth analysis of the cellular components of TME [34]. Fluorescence-activated cell sorting combined with single-cell RNA sequencing and V(D)J sequencing indicates that the innate immune organoid model can accurately preserve the immune diversity of homologous fresh tumor biopsies and the clone type of tumor-infiltrating T cells [35]. Furthermore, by using methods such as viral transduction, Cre-lox, and CRISPR-Cas9, organoids can be genetically modified to evaluate the impact of specific genetic events on tumor development.

4. Technical Challenges and Future Directions

4.1 The technological breakthrough of machine learning

The integrated framework of virtual screening, ADMET optimization, and automated preclinical validation presented in this study fundamentally challenges the traditional trial-and-error paradigm in drug discovery. The molecular-target interaction analysis based on GNN has increased the prediction accuracy of EGFR ligand binding to 85% compared with the traditional alignment method, while the reinforcement learning-driven multi-objective optimization has increased the drug ability evaluation pass rate of DDR1 inhibitor lead compounds from 35% to 72%. This confirms the revolutionary improvement that AI technology has brought to R&D efficiency. Notably, the collaborative application of organoid models and interpretable AI (such as the two-order-of-magnitude increase in activity in the case of KRAS G12C inhibitors) has broken the gap between preclinical models and the prediction of clinical efficacy. This integration increased organoid-clinical response consistency from

60% in traditional models to 78–85%, offering a key tool for addressing the industry pain point that the clinical success rate of anti-tumor drugs is less than 10%.

4.2 The scientific value of cross-scale modeling and multimodal data integration

The "data-model-validation" closed-loop mechanism exposed in the research reveals the core logic of machine learning-driven drug discovery. Dynamic conformational prediction (such as the prediction of conformational changes of KRAS mutators by the combined GNN-MD model) has broken through the limitations of static structural analysis, while multi-omics toxicity prediction (the CNN-RNN hybrid architecture improves the recognition rate of cardiotoxicity by 23%) has proved the necessity of cross-modal data fusion. This integrated modeling from molecular dynamics to the organ level is reshaping the scientific basis of drug development—for instance, the hidden association between heterocyclic structures and water solubility/immunotoxicity discovered by knowledge graph mining has overturned the cognitive framework of structure-activity relationships in traditional QSAR models. It provides theoretical support for the molecular design of "non-intuitive pharmaceuticals."

4.3 Technology Transformation

Despite significant progress, the current framework still faces three bottlenecks: First, the bias of the toxicity database (such as the absence of rare toxicity data) leads to limited extrapolation ability of the model, and a dynamic annotation platform containing patient-specific data needs to be established; The second is the standardization challenge of organoid culture (the consistency of models in different laboratories varies by 15%-20%), and quality control standards need to be formulated in dimensions such as gene expression profiles and microenvironment simulation. The third is the cross-scale fault of interpretability technology (the correlation between molecular-level interpretation and organ phenotype is only 0.61), and it is necessary to develop multi-scale mapping methods based on the attention mechanism. Future development should focus on constructing an automated closed-loop system integrating AI-based drug design, robotic synthesis, and organoid validation, with the goal of reducing the lead optimization cycle from 18–24 months to 4–6 months. Additionally, building patient-specific organoid libraries will enable individualized treatment design, shifting the paradigm from traditional candidate compound screening to the generation of precise therapeutic strategies.

5. Conclusion

Machine learning technology has brought revolutionary changes to the discovery of anti-tumor drugs. From molecular design and optimization in virtual screening to automated synthesis and organoid model applications in preclinical validation, every link has demonstrated great potential. By integrating advanced algorithms such as graph neural networks and reinforcement learning, combined with automated experimental techniques and organoid models, it is expected to significantly shorten the research and development cycle of anti-tumor drugs, reduce research and development costs, and promote the development of personalized cancer treatment. However, it is still necessary to face technical challenges, constantly innovate and improve algorithm models, and strengthen the cross-integration of multiple disciplines to achieve greater value of machine learning in the discovery of anti-tumor drugs.

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