WEP Warwick Evans Publishing

International Journal of Public Health and Medical Research

ISSN: 3006-7707 (Print), ISSN: 3006-3752 (Online) | Volume 4, Number 3, Year 2025
DOI: https://doi.org/10.62051/ijphmr.v4n3.12
Journal homepage: https://wepub.org/index.php/IJPHMR/index

Design Strategies and Mechanisms of Action of Small Molecule Drugs for Cancer Treatment

Haoyi Xu

ANU College of Science and Medicine, Australian National University, Canberra 2601, ACT, Australia
xuhaoyi1230@gmail.com

ABSTRACT

Global cancer incidence continues to rise. According to the World Health Organization in 2022, there will be over 20 million new cancer cases and over 10 million deaths worldwide. Cancer has become a major public health threat to human health. Although surgery, chemotherapy, radiotherapy, and immunotherapy are currently mainstream treatments, they have significant limitations: surgery struggles to eliminate micrometastases and is only suitable for early-stage, localized tumors; chemotherapy drugs such as cisplatin are prone to severe side effects such as bone marrow suppression and nausea and vomiting, and cannot accurately distinguish between tumors and normal cells; radiotherapy relies on radiation to kill tumors, but it can easily damage the skin, mucous membranes, and internal organs in the irradiated area; and immunotherapies such as PD-1 inhibitors, while able to activate the body's immune response, only produce sustained efficacy in 20%-30% of patients and carry the risk of immune-related adverse reactions. Small molecule drugs (molecular weight <1000 Daltons) have become a core force in cancer treatment due to their unique advantages: they are easily absorbed by the intestine after oral administration and have strong tissue penetration, allowing them to directly reach tumor tissue and penetrate cell membranes to act on intracellular targets. Their relatively simple chemical structure allows for mass production through chemical synthesis, resulting in significantly lower production costs than large molecule drugs. Currently, over 150 small molecule anticancer drugs have been approved for marketing worldwide, covering a variety of cancer types, including lung cancer, leukemia, and breast cancer. Imatinib, among others, has increased the five-year survival rate of patients with chronic myeloid leukemia from 30% to over 90%, marking a milestone in targeted cancer therapy. This article systematically reviews the definition and characteristics of small molecule drugs, deeply analyzes design strategies based on target structure, biological activity, and innovative directions, and explains their mechanisms of action in inhibiting tumor cell proliferation, inducing tumor cell apoptosis, blocking tumor angiogenesis, and modulating the tumor immune microenvironment. It also summarizes the current challenges in R&D, drawing on the technical support system. This paper provides theoretical references for the R&D optimization and clinical application of small molecule drugs, and contributes to the advancement of precision cancer treatment.

KEYWORDS

Small molecule drugs; Cancer therapy; Target structure design; Mechanism of action; Clinical translation; Drug resistance

1. INTRODUCTION

Cancer is a major global public health problem, but existing treatment options still face significant bottlenecks. Surgery is only suitable for early-stage, localized tumors and has limited effectiveness in patients with advanced and metastatic disease. Traditional chemotherapy drugs, such as paclitaxel,

can kill tumor cells by damaging DNA but cannot distinguish between tumor and normal cells, often causing side effects such as nausea and hair loss. Radiotherapy relies on radiation directed at the lesion, which can easily damage normal tissues such as the skin and internal organs in the irradiated area. Immunotherapies, such as PD-1 inhibitors, can stimulate the body's immune response, but only 20%-30% of patients experience an effective response, and there is a risk of immune-related adverse reactions. There is an urgent need for safer and more effective treatment options.

Small molecule drugs fill this gap with unique advantages. Compared to large-molecule drugs such as monoclonal antibodies, they are easily absorbed by the intestine after oral administration, can reach tumor tissue directly through the bloodstream, and can penetrate cell membranes to act on intracellular targets. Their relatively simple chemical structure allows for mass chemical synthesis, reducing production costs and making them more readily available for clinical use. Currently, small molecule drugs have been shown to treat a variety of cancer types, including lung cancer, leukemia, and breast cancer. Osimertinib, in particular, has demonstrated remarkable efficacy, with a clinical response rate exceeding 70% for EGFR-mutant non-small cell lung cancer.

However, small molecule drug development still faces challenges: drug resistance is common, some drugs exhibit off-target effects, and the mechanisms of action of some drugs remain unclear. This article systematically analyzes the design strategies and mechanisms of action of small molecule drugs, and, drawing on real-world research cases, outlines the principles of development. This article aims to provide researchers with a clear R&D framework, help clinicians understand the underlying mechanisms of drug action, and ultimately promote the greater value of small molecule drugs in cancer treatment.

2. OVERVIEW OF SMALL MOLECULE DRUGS

Small molecule drugs generally refer to organic compounds with a molecular weight less than 1000 Daltons. Their core advantages are concentrated in three aspects: First, they have high oral bioavailability. Most drugs do not require injections, which improves patient compliance. For example, capecitabine, after oral administration, is converted into the active ingredient fluorouracil in the body, eliminating the inconvenience of injections. Second, they have strong tissue penetration, capable of breaking through physiological barriers such as the blood-brain barrier. Temozolomide, a typical example, can directly reach brain tumor lesions, solving the problem of drug delivery for brain tumors. Third, they have stable metabolic properties. Metabolites are easily excreted through the liver and kidneys, significantly reducing the drug's cumulative toxicity and improving drug safety. Its development can be clearly divided into three phases. The 1960s to 1980s marked the traditional chemotherapy phase, primarily focused on cytotoxic drugs. For example, cisplatin inhibited tumor cell proliferation by binding to tumor cell DNA, but its inability to distinguish between normal and tumor cells led to significant toxic side effects. The targeted therapy phase, which began in the 1990s and early 2000s, saw the emergence of drugs with well-defined targets. Imatinib, launched in 1998, specifically targets the BCR-ABL fusion protein and successfully transformed chronic myeloid leukemia from a terminal illness into a manageable chronic disease, marking the beginning of the era of precision cancer treatment. The 2010s to the present represent a multifunctional development phase, with the emergence of novel drug technologies such as protein degradation targeted chimeras (PROTACs) [1]. In 2021, the first PROTAC drug, ARV-110, entered clinical trials. This breakthrough, achieved by breaking the limitation of traditional inhibitors in inhibiting target activity, enabled a novel mode of action, namely, degradation of target proteins, pushing small molecule drugs towards more complex and efficient mechanisms of action. Small molecule drugs can be categorized by target, primarily into kinase inhibitors and proteasome inhibitors. Kinase inhibitors, such as gefitinib, specifically target the epidermal growth factor receptor (EGFR) and are used to treat EGFR-mutant non-small cell lung cancer. Proteasome inhibitors, such as bortezomib, inhibit proteasome function in tumor cells, leading to the accumulation of toxic proteins and are primarily used to treat

multiple myeloma. Different types of small molecule drugs can be tailored to the pathological characteristics of different cancers, providing key support for personalized clinical treatment and enabling the precise use of drugs tailored to specific targets.

3. SMALL MOLECULE DRUG DESIGN STRATEGIES

The design of small molecule drugs focuses on precision and efficacy, encompassing three key strategies. Target-structure-based design relies on molecular docking and structural optimization to achieve precise binding. Molecular docking uses computer simulations to visualize the binding process between a small molecule (ligand) and the active pocket (receptor) of a target protein, screening for high-potency candidates by calculating spatial fit and energy complementarity. For example, when developing an EGFR kinase inhibitor, researchers first analyzed the EGFR protein crystal structure to determine the amino acid composition of the active pocket. Using this technique, they screened a library of quinazoline compounds capable of forming hydrogen bonds with key amino acids. Further optimization resulted in gefitinib. Structural optimization enhances drug performance through chemical modification. For example, introducing a methyl group into the piperazine ring of imatinib significantly enhanced its binding stability to the BCR-ABL protein. Bioactivity-based design uses efficient screening techniques to identify candidate compounds. High-throughput screening uses automated equipment to rapidly test the activity of libraries containing tens of thousands to millions of compounds. For example, when developing a CDK4/6 inhibitor, Pfizer screened over 100,000 compounds and discovered that a piperidine-based compound could inhibit CDK4/6 activity. This optimization led to the development of palbociclib, a drug used to treat hormone receptor-positive breast cancer. Virtual screening pre-screens compound libraries through computer simulations, eliminating the need to synthesize large numbers of samples. For example, when developing angiogenesis inhibitors, researchers constructed pharmacophore models based on known active compounds and identified N-phenylureas. Experimental validation confirmed their ability to effectively inhibit VEGF receptor activity, laying the foundation for further development. Innovative design strategies focus on addressing drug toxicity and drug resistance. Prodrug design converts active drugs into inactive precursors, which are activated by enzymatic reactions after entering the body [2]. For example, cyclophosphamide itself is non-cytotoxic and is metabolized to its active form by cytochrome P450 enzymes in the liver, ensuring tumor suppression while minimizing direct damage to the gastrointestinal tract. Multi-target design addresses the multi-pathway nature of tumor pathogenicity by designing compounds that act simultaneously on multiple targets. For example, sorafenib simultaneously inhibits VEGF receptors, PDGF receptors, and Raf kinases, effectively blocking tumor angiogenesis and inhibiting tumor cell proliferation. It is clinically used in the treatment of hepatocellular carcinoma, effectively reducing the drug resistance that can be easily induced by single-target drugs.

4. MECHANISM OF ACTION OF SMALL MOLECULE DRUGS

Small molecule drugs primarily exert their anti-tumor effects through four pathways. To inhibit tumor cell proliferation, drugs can block the cell cycle or signaling pathways: CDK4/6 inhibitors such as palbociclib bind to CDK4/6, preventing it from forming a complex with Cyclin D, causing cells to arrest in the G1 phase; EGFR inhibitors such as gefitinib bind to the ATP site of EGFR, blocking the downstream PI3K-AKT pathway and reducing proliferation signal transmission; antimetabolite drugs such as methotrexate inhibit dihydrofolate reductase, hindering the production of purines required for DNA synthesis, and inhibiting cell proliferation at the source. The mechanisms for inducing tumor cell apoptosis are categorized as both intrinsic and extrinsic. In the intrinsic pathway, BCL-2 inhibitors such as venetoclax bind to BCL-2 proteins, relieving inhibition of BAX and BAK, prompting mitochondrial release of cytochrome C, and activating the caspase cascade. In the extrinsic pathway, death receptor agonists bind to DR5 on the tumor cell surface, recruiting FADD to form a

complex with caspase-8, activating caspase-3 and initiating apoptosis. Proteasome inhibitors such as bortezomib can also inhibit IκB degradation, thereby promoting apoptosis by blocking the NF-κB pathway [3].

Inhibition of tumor angiogenesis centers on the VEGF-VEGFR pathway: Axitinib binds to VEGFR, inhibiting its tyrosine kinase activity and reducing endothelial cell proliferation and lumen formation. Sorafenib also inhibits the PDGF receptor, disrupting the stabilizing effect of pericytes on blood vessels and further depriving them of nutrient supply. Endostatin mimetic peptides directly inhibit endothelial cell migration, achieving a low-toxic anti-angiogenic effect. In terms of regulating the tumor immune microenvironment, IDO inhibitors such as indomod reduce the tryptophan metabolite kynurenine, restoring T cell proliferation and cytotoxicity. STING agonists activate the STING pathway in dendritic cells, promoting interferon-γ secretion and enhancing antigen presentation. HDAC inhibitors such as vorinostat increase tumor cell surface antigen expression while reducing the inhibitory effect of regulatory T cells, thereby enhancing the body's immune surveillance of tumors.

5. TECHNICAL SUPPORT FOR SMALL MOLECULE DRUG DEVELOPMENT

Structural biology techniques provide precise target information for drug design. Core technologies include three categories: X-ray crystallography can analyze the structure of drug-target complexes. For example, by analyzing the complex of BCR-ABL protein and imatinib, the drug binding site in the active pocket can be determined, providing a basis for structural optimization. Cryo-electron microscopy, without the need for crystal preparation, can capture the dynamic conformation of target proteins. For example, observing the activated conformation of the EGFR dimer facilitates the design of specific inhibitors targeting the active conformation. Nuclear magnetic resonance technology can analyze the binding kinetics of drugs and targets, assessing the binding efficacy of candidate compounds by measuring the rate and stability of the interaction between the two. Computer-aided drug design significantly accelerates the R&D process [4]. Molecular dynamics simulations can simulate the dynamic binding process of drugs in aqueous solution. For example, the interaction between osimertinib and the EGFR T790M mutant was simulated, clearly demonstrating the additional hydrogen bonding between the drug side chain and the mutation site, explaining its high selectivity for mutant EGFR. Quantitative structure-activity relationship (QSAR) models establish mathematical models of compound structure and activity. By inputting molecular structural parameters, the anti-tumor activity of new compounds can be predicted, reducing the need for blind synthesis. Virtual screening technology can rapidly pre-screen compound libraries, such as screening candidate compounds based on the VEGF receptor pharmacophore model, eliminating the need to synthesize large numbers of compounds and significantly reducing screening costs. Biomarker detection technologies facilitate precise clinical application: Next-generation sequencing (NGS) can detect genetic mutations in tumor cells. For example, by detecting EGFR gene mutation status, it can screen patients with non-small cell lung cancer suitable for osimertinib. Immunohistochemistry (IHC) can detect the expression levels of target proteins in tumor tissues, such as BCL-2 protein expression, to determine the appropriate patients for venetoclax. Liquid biopsy technology, by detecting circulating tumor DNA (ctDNA) in the blood, can monitor imatinib-resistant mutations in chronic myeloid leukemia in real time, promptly identifying new mutations in the BCR-ABL gene and providing a basis for adjusting treatment plans. High-throughput synthesis technologies provide a robust foundation for R&D. Combinatorial chemistry utilizes modular combinations of building blocks to generate diverse compounds in batches. For example, solid-phase synthesis can synthesize thousands of peptide compounds at once, building rich compound libraries. Parallel synthesis technology allows for simultaneous execution of multiple reactions in high-throughput reaction setups such as 96-well plates, shortening derivative preparation time and improving R&D efficiency. Microwave-assisted synthesis utilizes microwave heating to accelerate reactions. For example, in the

synthesis of quinazoline compounds, traditional heating can reduce reaction times from hours to minutes while simultaneously increasing product yields.

6. CHALLENGES AND STRATEGIES IN SMALL MOLECULE DRUG DEVELOPMENT

Currently, small molecule drug development faces three core challenges that hinder its clinical application and development. Drug resistance is a particularly prominent issue. For example, with EGFR inhibitors, approximately 50% of patients develop the T790M mutation after 6-12 months of treatment, resulting in reduced efficacy. C797S mutations may also develop later, rendering the drug completely ineffective. Off-target toxicity is equally problematic. Some multi-target drugs, such as dual VEGF/PDGF inhibitors, can interfere with normal vascular regulation due to their broad target coverage, leading to adverse reactions such as hypertension. High R&D costs are also a key bottleneck. The average timeline from compound screening to clinical launch exceeds 10 years, with investments exceeding $1 billion. Numerous drug candidates are eliminated due to clinical failure, further driving up costs.

To address these issues, combination therapies and technological innovation have become key approaches. Combination therapy leverages the synergistic effects of drugs with different mechanisms of action. For example, combining EGFR inhibitors with anti-angiogenic drugs can inhibit tumor cell proliferation while also blocking nutrient supply, significantly delaying the emergence of drug-resistant mutations. AI-assisted design utilizes deep learning algorithms to optimize drug structure, enabling rapid prediction of compound toxicity and activity, reducing clinical trial failure rates and shortening R&D cycles. Organoid technology, by creating patient-derived tumor organoids that mimic the in vivo tumor microenvironment, enables more accurate assessment of drug efficacy, reduces the risk of clinical translation, and provides a reference for personalized medication [5].

At the clinical translation level, a comprehensive support system is needed. On the one hand, we must strengthen the connection between basic research and clinical practice, establishing a closed loop of "drug development - clinical trials - post-marketing monitoring" and timely collecting clinical feedback to optimize drugs. On the other hand, we must promote personalized treatment and develop plans based on patient genomic and proteomic information. For example, by testing circulating tumor DNA (ctDNA) in the blood, we can dynamically monitor tumor mutations and adjust drug dosage and type. At the same time, we must optimize production processes and adopt green synthesis technologies to simplify reaction steps, reduce waste, lower drug production costs, and increase drug accessibility, so that more patients can benefit from small molecule drug therapies.

7. CONCLUSION

This paper systematically analyzes the design strategies, mechanisms of action, and technical support for small molecule drugs in cancer treatment. The core conclusions are as follows: At the design strategy level, target structure-based design enables precise drug-target binding, bioactivity-based design efficiently identifies candidate compounds, and prodrug design and multi-target design address drug toxicity and drug resistance, respectively. At the mechanism level, drugs exert their effects through four pathways: inhibiting tumor cell proliferation, inducing apoptosis, blocking angiogenesis, and modulating the immune microenvironment. Different mechanisms of action can form synergistic effects, providing a theoretical basis for combination therapy. Within the technical support framework, structural biology, computer-aided drug design, and biomarker detection technologies collaborate to advance drug development and clinical precision application.

Currently, small molecule drugs still face three core challenges: prominent drug resistance, such as the frequent occurrence of T790M and C797S mutations after use of EGFR inhibitors, which lead to reduced efficacy; off-target effects leading to toxic side effects; and the difficulty of controlling toxic side effects in some multi-target drugs due to the difficulty of controlling target synergy. R&D costs are high, with a long and arduous cycle from screening to market launch. Future R&D efforts can focus on three key areas: first, personalized drug development, tailoring treatment plans based on the patient's tumor's molecular profile, including the genomic and proteomic profiles; second, developing drugs with novel mechanisms of action, advancing protein degradation technologies like PROTACs and molecular glues, while exploring novel targets such as non-coding RNAs and epigenetic regulators; and third, promoting the integration of multiple technologies, combining AI with organoid technology. AI can be used to optimize drug structure, predict activity and toxicity, and assess efficacy using organoids to simulate the in vivo microenvironment, thereby improving R&D efficiency and accuracy.

With continued technological advancements, the core role of small molecule drugs in cancer treatment will become even more prominent. By strengthening the connection between basic research and clinical translation, and optimizing combination therapy strategies to overcome drug resistance, we are expected to further enhance treatment efficacy, provide strong support for achieving cancer cures, and drive continued innovation in the field of precision oncology.

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