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Synergistic attack of "old drugs for new uses": repositioning strategies in cancer combination therapy

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Abstract

Cancer treatment faces severe challenges such as drug resistance, side effects, and high costs. The "repurposing old drugs" strategy, which involves repositioning approved drugs for non-oncology indications for cancer treatment, has opened up new avenues for developing efficient, low-toxicity, and rapidly translatable combination therapies. This strategy can not only accelerate clinical translation by leveraging known pharmacological and safety data but also generate synergistic effects with standard chemotherapy, targeted therapy, or immunotherapy by targeting non-classical pathways such as the tumor microenvironment, metabolic reprogramming, and epigenetic regulation. This paper aims to systematically review the repositioning strategies of non-oncology drugs in cancer combination therapies, focusing on their mechanisms of action, synergistic principles, high-throughput screening and computational prediction methods, as well as pre-clinical and clinical research progress based on models such as patient-derived organoids. The paper systematically analyzes the synergistic effects and potential of representative drugs such as metformin, statins, antimalarials, antipsychotics, non-steroidal anti-inflammatory drugs, β-blockers, antihistamines, and cardiovascular drugs. It also summarizes the current challenges in drug screening, mechanism validation, commercial incentives, clinical trial design, and safety re-evaluation, aiming to provide a theoretical basis and future research directions for optimizing cancer combination treatment strategies.

Keywords

drug repurposing, drug repositioning, cancer combination therapy, synergistic effect, non-oncological drugs, patient-derived organoids

Introduction

Cancer is a major global public health challenge and one of the most complex diseases faced by humanity. Despite significant progress in targeted therapy and immunotherapy, issues such as tumor heterogeneity, adaptive drug resistance, and metastasis remain major obstacles to curing cancer [1]. The field of cancer treatment has long faced severe challenges such as high costs, long development cycles, and high failure rates in new drug research and development [2]. Statistics show that the average development time for a new drug from early discovery to final approval for marketing often exceeds 10 years, and the cost may exceed $1 billion [3].

Against this backdrop, the "repurposing of old drugs" or drug repositioning strategy, as an appealing alternative, offers new possibilities for rapidly expanding the arsenal of anti-cancer therapies [4]. This strategy involves repurposing existing drugs that have been approved for treating other diseases for cancer treatment [5]. These drugs generally have known safety profiles, pharmacokinetic characteristics, and low costs, which can significantly accelerate the clinical translation process [6]. Drug repositioning adheres to the principle of polypharmacology, which posits that any drug with multi-target or off-target effects may exhibit multiple modes of action, thus providing a theoretical basis for discovering new therapeutic uses for diseases [2].

Combination therapy has emerged as a core strategy for enhancing efficacy and overcoming drug resistance by simultaneously targeting multiple oncogenic pathways. Within the framework of combination therapy, non-oncology drugs can synergize with traditional chemotherapy, targeted therapy, or immunotherapy. Through mechanisms such as multi-target attack, reversing drug resistance, and remodeling the tumor microenvironment (TME), they can enhance anti-tumor efficacy and potentially reduce side effects [7]. For instance, statins, initially used as lipid-lowering drugs, have been repurposed for cancer treatment. They can not only inhibit cancer cell proliferation as a single agent but also be combined with anti-cancer drugs to overcome drug resistance [8]. Similarly, the antifungal drug itraconazole has been re-evaluated for its anti-cancer potential due to its ability to inhibit angiogenesis and multiple oncogenic signaling pathways [9]. Antimalarial drugs and central nervous system (CNS) drugs have demonstrated promising anti-cancer properties, either as monotherapy or in combination with anti-tumor drugs [10]. Combination treatment strategies, especially the combination of repurposed drugs with standard therapies, have been proven to improve efficacy, reduce toxicity, and overcome drug resistance [11].

In the current era of precision medicine, while targeted therapies and immunotherapies have achieved remarkable success, their efficacy is often limited by the emergence of acquired resistance and the inherent heterogeneity of tumors, which frequently involve the activation of bypass signaling pathways [2, 7]. It is precisely here that the "repurposing old drugs" strategy offers a unique and irreplaceable value. Unlike the "vertical" inhibition of a single oncogenic driver, many non-oncology drugs, such as antipsychotics, antimalarials, and anti-inflammatory agents, inherently possess "horizontal" multi-target or off-target pharmacological properties [2]. This polypharmacology allows a single repurposed drug to simultaneously modulate a network of interconnected pathways-including metabolic reprogramming, epigenetic regulation, and the tumor immune microenvironment-which are often the very mechanisms driving resistance to highly specific therapies [7]. Therefore, within a combination therapy framework, these multi-target agents act as powerful "network disruptors." They can dismantle the compensatory survival circuits of tumor cells and remodel the immunosuppressive TME, thereby creating a "vulnerable window" that enhances the efficacy of standard-of-care chemotherapies, targeted agents, or immunotherapies [11]. This synergistic strategy, by attacking cancer on multiple fronts, represents a paradigm shift that complements the precision of new drug development with the network-level intervention of repurposed drugs, offering a more robust approach to tackling the complexity and adaptability of malignant tumors.

In recent years, with the in-depth understanding of the hallmarks of cancer and the development of technologies such as computational biology, high-throughput screening, and patient-derived tumor organoids (PDTOs), significant progress has been made in the systematic repositioning research of non-oncology drugs [6]. Computational techniques, databases, and literature retrieval can be used to

systematically screen approved non-oncology drugs with anti-cancer potential [4]. These drugs have a wide range of sources, including cardiovascular drugs, microbial drugs, small-molecule antibiotics, antiviral drugs, anti-inflammatory drugs, anti-neurodegenerative drugs, antipsychotic drugs, antidepressants, etc. [6]. Therefore, in-depth exploration of the repositioning strategies of non-oncology drugs in cancer combination therapies is of great systematic significance for promoting scientific research and clinical practice in this field. This review will conduct an in-depth analysis of its scientific basis, current status of clinical translation, and future prospects.

In this review, we move beyond a descriptive catalog of repurposed drugs to provide a critical, mechanism-based synthesis of the current state of the field. We systematically analyze the synergistic principles driving combination therapies, emphasizing the distinction between 'vertical' inhibition (highly specific targeted therapies) and 'horizontal' network disruption (multi-target repurposed drugs). Crucially, we introduce a hierarchical framework to evaluate the strength of evidence, differentiating between robust preclinical findings, early-phase clinical signals, and confirmatory trial results. We conclude by dissecting the key translational barriers and outlining a roadmap for the future, where precision repurposing, guided by biomarkers and computational models, can unlock the full potential of this strategy for patients.

Search strategy and methodology

This review was conducted following the principles of a semi-systematic review. We performed a comprehensive literature search across PubMed, Web of Science, and Scopus databases, focusing on publications from January 2016 to May 2026. The search strategy combined key terms related to drug repurposing (e.g., "drug repurposing", "drug repositioning", "old drugs for new uses", "repurposing") with terms related to cancer therapy (e.g., "cancer combination therapy", "synergistic effect", "tumor microenvironment", "chemotherapy sensitization") and specific non-oncological drug classes (e.g., "metformin", "statins", "antimalarials", "antipsychotics", "NSAIDs", "β-blockers").

Two authors (JY and XW) independently screened the titles and abstracts of all retrieved records to identify studies that investigated the repurposing of FDA-approved, non-oncology drugs for cancer treatment. We prioritized original research articles, systematic reviews, meta-analyses, and key clinical trials. We excluded conference abstracts, commentaries, and studies not written in English. The reference lists of included articles were also hand-searched to identify additional relevant studies.

Inclusion/Exclusion Criteria:

Inclusion: (1) Studies evaluating the anti-cancer activity of FDA-approved, non-oncology drugs; (2) Studies investigating synergistic effects when combined with standard chemotherapy, targeted therapy, or immunotherapy; (3) Studies providing mechanistic insights, preclinical data, or clinical outcomes.

Exclusion: (1) Studies on drugs already established as standard oncology treatments; (2) Studies focused solely on drug toxicity without an anti-cancer efficacy component; (3) In vitro studies lacking translational relevance to human cancers.

The final selection was based on the relevance to the review's focus on synergistic combination mechanisms and clinical translatability. The data were synthesized narratively, with a particular emphasis on critically evaluating the strength and maturity of the evidence for each repurposed drug. The level of evidence was classified as: Preclinical (in vitro/in vivo), Early-phase Clinical (Phase I/II), Confirmatory Clinical (Phase III/IV), or Observational/Epidemiological.

The scientific basis and advantages of the "repurposing old drugs" strategy

Core concepts and historical evolution of drug repurposing

Drug repositioning, also known as drug repurposing or reuse, refers to the application of "old drugs" that have been approved for specific indications to new therapeutic purposes [12]. This strategy is not a brand-new concept, and there are numerous successful cases of serendipitous discoveries in its historical development. For example, drugs such as aspirin, thalidomide, and sildenafil have all achieved a transition

from their original indications to new ones through "serendipitous discoveries" [13]. With the deepening understanding of cancer biology and the rise of data-driven methods, drug repositioning has shifted from serendipitous discovery to a more systematic and rational exploration [1]. Its core lies in leveraging the known safety, pharmacokinetic, and pharmacodynamic data of existing drugs to bypass the time-consuming and costly early stages of traditional new drug development, thereby accelerating the clinical translation of new therapies [14]. In the field of oncology, this strategy is particularly highly regarded as it can explore the potential of non-oncology drugs to target known or unknown vulnerabilities of cancer, providing a valuable opportunity to overcome the bottlenecks in cancer treatment [1].

Remarkable advantages compared to new drug R&D: cost, time, and safety

Compared with traditional de novo drug development, the "repurposing old drugs for new uses" strategy has significant advantages in terms of cost, time, and safety [8]. The traditional new drug development process is long, usually taking more than 10 years and billions of dollars in investment, and has an extremely high failure rate [9]. This high-investment, high-risk, and long-cycle model results in many patients, especially those with rare or drug-resistant cancers, being unable to access effective treatment in a timely manner.

Drug repositioning can significantly shorten the R&D time and reduce costs, as a large amount of data on the pharmacological properties, toxicological data, and formulation processes of candidate drugs have been accumulated, eliminating the need for repeated pre-clinical safety assessments [14, 15]. In terms of safety, repositioned drugs usually have a well-defined safety profile, and their clinical dosage and adverse reactions are well-known, which greatly reduces the risk of clinical development [8, 12]. For example, the anti-malaria drug artemisinin and its derivatives have been re-evaluated for their anti-cancer activity, and their known safety profiles facilitate rapid entry into clinical research [16]. Statins used for treating hypercholesterolemia and itraconazole used for anti-fungal treatment have also established a good safety record through long-term clinical application, laying the foundation for their repositioning research in cancer treatment [8, 9]. This approach can shorten the development time by several years and significantly reduce R&D costs, providing a fast and feasible solution to address the unmet medical needs in current cancer treatment. Especially for rare cancers, drug-resistant cancers, and malignancies lacking effective treatment methods, the drug repositioning strategy shows unique value. It can utilize the existing drug library to quickly screen out candidate drugs with potential anti-cancer activity, thus bypassing many obstacles in traditional new drug R&D [17]. In addition, the rise of computational methods such as artificial intelligence also provides a powerful tool for the efficient screening and prediction of new uses of existing drugs, further accelerating this process [18].

Utilizing the multi-target properties and synergistic treatment potential

Many non-oncological drugs, such as antipsychotics, antimalarials, and anthelmintics, possess the characteristic of multi-target action, which endows them with unique advantages in cancer combination therapies. These drugs can simultaneously interfere with multiple key signaling pathways related to cancer progression, such as autophagy, oxidative stress, and epigenetic regulation, thereby exerting multi-faceted impacts on cancer cells [16]. In combination therapies, these "old drugs" with multi-target characteristics can complement highly specific targeted drugs or traditional chemotherapy drugs. By attacking the "Achilles' heel" of cancer cells or disrupting their compensatory and survival mechanisms, a synergistic killing effect can be achieved, effectively overcoming the limitations of single-drug therapy, such as drug resistance [19]. For example, the antirheumatic drug auranofin disrupts the redox balance of cancer cells by inhibiting thioredoxin reductase, and when combined with an AKT inhibitor, it can produce a potent synergistic effect [20]. Similarly, cardiac glycosides induce cancer cell death in a Na/K-ATPase-dependent manner, and their action involves a sequential process of early autophagy activation and subsequent apoptosis induction, demonstrating their multi-mechanistic anti-cancer potential [21]. Benzimidazole anthelmintics, such as mebendazole and albendazole, have also been repositioned as promising anti-cancer candidates due to their multiple action mechanisms, including interfering with microtubule function, inhibiting angiogenesis, and regulating immune checkpoints [19]. This multi-target attack strategy can not

only improve the therapeutic effect but also potentially delay or overcome the drug resistance of cancer cells to single-targeted drugs. Therefore, in-depth exploration of the multi-target characteristics of non-oncological drugs and their rational integration into combination treatment regimens represents an important direction for the development of more effective anti-cancer strategies.

Critical analysis: While the multi-target nature of non-oncological drugs is often lauded as an advantage, it also presents a significant challenge for mechanistic deconvolution. Attributing a therapeutic effect to a single pathway when a drug interacts with dozens of targets can be misleading. For instance, the anti-cancer effects of metformin, historically attributed solely to AMP-activated protein kinase (AMPK) activation, are now known to involve complex interactions with the TME, immune cells, and the gut microbiome. This polypharmacology, while potentially beneficial for synergistic attack, complicates the identification of robust predictive biomarkers and increases the risk of off-target toxicities when combined with other agents. Future research must employ systems biology approaches to map the full target landscape of these drugs in the context of specific cancer genotypes.

Strategies for driving repositioning discoveries: computational biology, phenotypic screening, and clinical observation

The strategies driving drug repositioning discovery are mainly classified into three categories: disease-based strategies, target-based strategies, and drug-based strategies [22]. In recent years, the advancements in computational biology and artificial intelligence technologies have significantly promoted systematic repositioning research. Computational methods include network-based methods, machine learning/deep learning, text mining, and semantic analysis, etc. [23]. For example, network analysis methods predict new drug-disease associations by constructing drug-disease-target heterogeneous networks and using topological metrics [24, 25]. Gene expression profile-based methods, such as those using the Connectivity Map (CMap) and LINCS database, screen potential therapeutic drugs by "reversing disease characteristics" [26, 27]. In addition, phenotypic screening (e.g., high-throughput screening) and clinical observation remain important discovery approaches. Clinical observation may accidentally discover the efficacy of drugs for new indications, while systematic phenotypic screening can directly evaluate the effects of known compounds on specific disease phenotypes in cell or animal models [28]. These strategies complement each other and together form a multi-dimensional, data-driven drug repositioning discovery system [29, 30].

Key mechanisms of action of non-oncological drugs in cancer

Targeting tumor metabolism and energy homeostasis

Theoretical basis of tumor metabolic reprogramming and intervention

Abnormal energy metabolism and homeostasis imbalance in tumor cells are among their core characteristics. Targeting this process has become an important strategy for "repurposing old drugs". Tumor cells undergo metabolic reprogramming, such as enhancing glycolysis (Warburg effect) and altering mitochondrial function, to meet the bioenergetic and biosynthetic requirements for their rapid proliferation [31]. As the center of cellular energy metabolism and redox homeostasis, mitochondrial dysfunction is closely associated with tumor initiation, development, invasion, metastasis, and drug resistance [32]. Therefore, drug development targeting mitochondrial metabolic reprogramming provides new potential approaches for cancer treatment [33].

In preclinical models, the dual metabolic inhibition strategy that simultaneously targets oxidative phosphorylation and glycolysis can effectively disrupt the energy homeostasis of tumor cells, induce synthetic lethality, and demonstrate potent anti-tumor potential [34]. Additionally, single-atom nanozymes can disrupt the redox and energy metabolic homeostasis in the tumor area by mimicking multiple enzyme activities, thereby overcoming the limitations of current nanozyme catalytic therapies [35]. These studies reveal the feasibility of interfering with the tumor energy metabolic network and lay a theoretical foundation for the synergistic attack using non-tumor drugs. Mitochondrial calcium homeostasis and its regulation through the mitochondrial calcium uniporter (MCU) are also key links affecting the energy

metabolism, autophagy, and apoptosis of tumor cells, providing a new perspective for metabolic targeted therapy [36].

Hypoglycemic drugs: taking metformin as an example

Regulation of the AMPK/mechanistic target of rapamycin (mTOR) signaling pathway

Metformin is a classic representative targeting tumor metabolism. Its anti-cancer mechanism involves activating the AMPK pathway, inhibiting the mTOR signaling, and reducing the circulating insulin level, thereby interfering with the energy metabolism of cancer cells [37]. As a cellular energy sensor, AMPK plays a key role in maintaining energy balance. However, its role in cancer is context-dependent and may exhibit pro-tumor activity in some malignancies [37]. Metformin activates AMPK by inhibiting mitochondrial complex I, leading to an increase in the AMP/ATP ratio [38]. The activated AMPK phosphorylates and inhibits mTOR complex 1 (mTORC1), thereby inhibiting protein synthesis, cell growth, and proliferation, which is a key pathway for its inhibition of tumor growth [38, 39].

Effects on the TME and immune cell function

The anti-cancer effect of metformin is not limited to the direct metabolic inhibition of tumor cells but also has a profound impact on the TME and immune cell functions. Studies have shown that metformin can regulate the polarization of tumor-associated macrophages (TAMs) and reduce the infiltration of immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs), thereby improving the immunosuppressive TME [39]. In the context of diabetes, the high-glucose environment impairs the anti-tumor activity of Vγ9Vδ2 T cells, while metformin reverses this metabolic abnormality and restores the tumor immunosurveillance function of T cells by activating the AMPK pathway [40]. In addition, metformin can inhibit the expression of programmed death ligand 1 (PD-L1) and restore the activity of T lymphocytes by reducing the level of transforming growth factor-β1 (TGF-β1), thereby enhancing the response to immunotherapy [41]. Long non-coding RNAs (lncRNAs), as important epigenetic regulators, are also widely involved in the regulatory network of cancer metabolism and may interact with metabolic regulators such as metformin [42].

Synergistic effect with chemotherapy

In models such as glioma, the combination of metformin and temozolomide has shown a synergistic anti-tumor effect and improved survival rate, which reflects the strategy of enhancing the efficacy of traditional chemotherapy through metabolic intervention [43]. In preclinical studies of gastric cancer, the combination of metformin with chemotherapy regimens such as epirubicin, cisplatin, and 5-fluorouracil can synergistically increase cell apoptosis, reduce mitochondrial membrane potential, and inhibit cell proliferation and clonogenic ability, suggesting its potential as a chemotherapy sensitizer [44].

Statins

Statins, by inhibiting the mevalonate pathway, can not only reduce cholesterol but also affect the prenylation of small G proteins such as Ras and Rho, thereby inhibiting cancer cell proliferation and migration and inducing apoptosis [45]. Studies have shown that the disruption of cholesterol homeostasis can affect the energy metabolism of tumor cells. For example, in the Tasmanian devil facial tumor disease model, atorvastatin blocked the energy metabolism of tumor cells and inhibited tumor growth in vivo by inhibiting cholesterol synthesis [45]. This suggests that statins may affect multiple signaling pathways related to cell growth and survival by interfering with the synthesis of isoprenoid products downstream of the mevalonate pathway. Liver X nuclear receptor β (LXRβ) and its ligand 24S-hydroxycholesterol can drive tumor cell proliferation by promoting the metabolic switch of aerobic glycolysis, while statins can counteract this process [45]. Currently, the synergistic effect of statins in combination with chemotherapy is being evaluated in multiple clinical trials, aiming to verify their potential as chemotherapy sensitizers or independent anti-tumor drugs [43]. In addition, targeting the metabolic characteristics of cancer stem cells (CSCs) and using energy-interfering molecules to disrupt their cellular homeostasis is also a promising therapeutic approach, and statins may play a role in such strategies [46].

Regulation of the TME and immune response

Theoretical basis for the regulation of the TME

The TME is a complex ecosystem composed of tumor cells, immune cells, fibroblasts, blood vessels, and extracellular matrix (ECM). Its metabolic and immune status profoundly influences tumor progression and treatment response. Cells in the TME interact with each other through the exchange of metabolites and growth factors. This metabolic interaction is crucial for tumor growth, evolution, and the formation of an immunosuppressive microenvironment [47]. Therefore, regulating the metabolic and immune status of the TME has become another important direction for "repurposing old drugs".

Endoplasmic reticulum-mitochondria contact sites (MERCs), serving as a structural and biochemical platform for cellular metabolic homeostasis, play a crucial role when T cells respond to the stress of the TME. Targeting this interface can restore T cell metabolic homeostasis and enhance anti-tumor immunity [48]. Glucose, as a core energy substance, is essential for maintaining the functions of innate and acquired immunity. Glucose metabolic disorders can lead to impaired immune system function [49]. In tumor immunity, the remodeling of glucose metabolism directly affects the functions of immune cells and anti-tumor efficacy [49]. These studies provide a theoretical basis for non-tumor drugs to regulate the TME.

β-Blockers

β-blockers, such as propranolol, exhibit pleiotropic effects in regulating the TME by blocking the β-adrenergic signaling pathway. Chronic stress can influence tumor progression through the neuroendocrine system, in which β-adrenergic signaling plays an important role [50]. Propranolol can inhibit tumor-related angiogenesis, immune escape, and metastasis processes. Studies have shown that hypoxia-inducible factor-1α (HIF-1α) is a key regulator of metabolic reprogramming in tumor cells. In the hypoxic TME, HIF-1α interacts with estrogen-related receptor α (ERRα) to jointly promote tumor growth adaptation and resistance to pyroptosis, maintaining energy homeostasis [51]. β-blockers may reverse HIF1α-mediated chemotherapy resistance by affecting these pathways.

Preclinical and clinical observations have shown that the combination of propranolol with chemotherapeutic drugs such as 5-fluorouracil has a synergistic effect on tumors such as colorectal cancer [52]. The mechanism may involve reducing the inflammatory level of tumors and decreasing the infiltration of myeloid immunosuppressive cells, thereby improving the immunosuppressive state of the TME [53].

Antihistamines

Antihistamines such as cetirizine reshape the TME mainly by regulating the functions of tumor-associated immune cells. Histamine binds to the HRH1 receptor in the TME, inhibits the activity of $CD8^+$ T cells, promotes tumor growth, and leads to immunotherapy resistance. H1-antihistamines (e.g., cetirizine, loratadine) can relieve T-cell inhibition and enhance the response to immunotherapy by blocking this pathway [54]. Multiple clinical studies have shown that patients receiving a combination of H1-antihistamines and immune checkpoint inhibitors have better median overall survival (mOS) and median progression-free survival (mPFS) than those not using antihistamines. Moreover, cationic H1-antihistamines are particularly effective and have good safety [54]. This review systematically summarizes the mechanisms and clinical evidence of H1-antihistamines in enhancing the efficacy of immune checkpoint inhibitors, suggesting their potential clinical application value as low-cost immunotherapy adjuvants [54].

In addition, autophagy plays a complex role in supporting cancer growth and therapy resistance in the TME by regulating metabolic transformation, influencing cancer-associated fibroblasts (CAFs), and promoting immune escape [55]. The combination of autophagy-targeting drugs (such as chloroquine [CQ]) with immunotherapy also shows promise, and antihistamines may synergize with it by indirectly affecting the autophagy or metabolic state of immune cells [55]. These findings suggest that combining non-tumor drugs targeting TME metabolism/immunity with existing immunotherapies is an effective strategy to improve the response rate of cancer treatment [56].

Non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids

Inhibit the cyclooxygenase-2 (COX-2)/prostaglandin E2 (PGE2) pathway

NSAIDs and glucocorticoids play roles in cancer treatment by targeting inflammatory pathways. The main mechanism of action of NSAIDs is to inhibit COX-2, thereby reducing the synthesis of PGE2 [57]. PGE2 is a key pro-inflammatory and immunosuppressive mediator in the TME, which can promote tumor cell proliferation, invasion, angiogenesis, and inhibit anti-tumor immunity [57]. Selective COX-2 inhibitors have shown potential in the prevention and treatment of various cancers by blocking this pathway. In addition, studies have also explored dual inhibitors that simultaneously inhibit COX-2 and soluble epoxide hydrolase (sEH) to enhance anti-tumor activity and reduce gastrointestinal side effects [58].

Regulate immunosuppressive cells

Chronic inflammation serves as a crucial driving force in tumorigenesis and development and shapes the immunosuppressive TME. NSAIDs and glucocorticoids can modulate the composition and function of immune cells in the TME. For instance, they can influence the polarization of TAMs and inhibit their differentiation into the pro-tumor M2 phenotype [59]. Meanwhile, these drugs can also regulate the recruitment and activity of MDSCs, thereby alleviating their inhibition of T cell function [60]. Glucocorticoids also exert extensive anti-inflammatory and immunosuppressive effects by regulating transcription factors such as AP-1, NF-κB, and STAT. This may affect the expression of multidrug resistance-related transporters and potentially influence chemotherapy sensitivity [61].

Intervening in epigenetic regulation: rediscovery of histone deacetylase inhibitors (HDACi, e.g., valproic acid)

HDACi, such as valproic acid, are typical representatives of "old drugs for new uses" in the field of epigenetic regulation. HDAC removes acetyl groups from histones, leading to chromatin compaction and gene transcription inhibition. In cancer, the abnormal overexpression of HDAC results in the silencing of tumor suppressor genes [62, 63]. HDACi inhibits HDAC activity, increases histone acetylation levels, relaxes chromatin structure, and reactivates the expression of multiple genes, including tumor suppressor genes, thereby inducing cell cycle arrest, differentiation, and apoptosis of tumor cells [62, 64]. These drugs have been successfully applied in the treatment of certain hematological malignancies and have shown potential in the research of solid tumors such as glioblastoma and triple-negative breast cancer [63]. Moreover, HDACi can also produce synergistic effects with other epigenetic drugs such as DNA methyltransferase inhibitors, providing new ideas for combination therapy [65].

Inducing cell death and overcoming drug resistance

Overview of drug resistance mechanisms and intervention strategies

Overcoming drug resistance is a core challenge in cancer treatment. Inducing non-apoptotic cell death or reversing the multi-drug resistance mechanism provides a breakthrough for "repurposing old drugs". Tumor cells acquire drug resistance through metabolic reprogramming. For example, enhanced glycolysis, abnormal lipid metabolism, glutamine dependence, and mitochondrial dysfunction not only promote tumor growth and metastasis but also mediate drug resistance through multiple molecular mechanisms [66]. Non-coding RNAs (ncRNAs) play a key regulatory role in this process. They drive metabolic abnormalities related to drug resistance by regulating pathways such as glycolysis, lipid metabolism, mitochondrial function, and glutamine metabolism [66]. Therefore, targeting these metabolic pathways or the ncRNAs that regulate them is an emerging strategy to overcome drug resistance.

In non-small cell lung cancer (NSCLC), energy metabolic disorders can induce resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). Targeting the energy metabolism of NSCLC may be an effective way to alleviate TKI resistance [67]. Additionally, the interaction between mitochondria and autophagy profoundly influences cancer progression and chemotherapy resistance. Therapies targeting this interaction may lead to the development of more effective treatments [68].

Antimalarial drugs (e.g., artesunate, CQ/hydroxychloroquine [HCQ])

Antimalarial drugs such as artesunate and CQ/HCQ have been found to induce ferroptosis and inhibit autophagy. Ferroptosis is an iron-dependent form of cell death driven by lipid peroxidation. Drugs like artesunate may trigger ferroptosis by promoting reactive oxygen species (ROS) generation and disturbing iron metabolism [35].

CQ/HCQ, as classic lysosome inhibitors and autophagy inhibitors, have been clinically attempted for cancer treatment [55]. Autophagy plays a dual role in tumors. On the one hand, it can clear damaged organelles and inhibit tumorigenesis; on the other hand, its cytoprotective effect can maintain tumor survival and lead to treatment resistance [68]. As lysosomal acidification inhibitors, CQ/HCQ can block the fusion of autophagosomes with lysosomes, inhibit autophagic flux, thereby depriving tumor cells of their survival mechanisms and enhancing their sensitivity to chemotherapy or radiotherapy [69, 70]. In addition, they can also exert anti-cancer effects through multiple mechanisms, such as inducing endoplasmic reticulum stress, promoting apoptosis, eliminating CSCs, and regulating anti-tumor immunity (e.g., polarizing TAMs from the M2 pro-tumor type to the M1 anti-tumor type) [70].

When combined with chemotherapeutic drugs such as doxorubicin, antimalarial drugs can synergistically kill cancer cells, such as breast cancer cells. The mechanism may involve the amplification of chemotherapy-induced cellular stress by autophagy inhibition and the activation of the ferroptosis pathway [55]. However, clinical studies have shown that their anti-cancer effect as a single agent is limited, so they are often used in combination with conventional anti-cancer drugs as sensitizers [69]. Mitochondrial uncoupling, which changes the proton permeability of the inner mitochondrial membrane without synthesizing ATP, can regulate thermogenesis, glucose and lipid metabolism, and ROS production. Some small-molecule mitochondrial uncouplers have shown anti-cancer effects in preclinical models, and their action may also be related to the induction of a special mode of cell death [71].

CNS Drugs

Some CNS drugs, such as the antipsychotics fluoxetine and fluphenazine, have been found to inhibit multidrug resistance proteins (e.g., P-glycoprotein [P-gp]) or induce apoptosis in cancer cells. The overexpression of multidrug resistance proteins is one of the main reasons for the efflux pump-type resistance of cancer cells to chemotherapeutic drugs such as paclitaxel and doxorubicin [72]. These CNS drugs may act as inhibitors of P-gp, reducing the efflux of chemotherapeutic drugs from cells and thereby enhancing their intracellular concentration and toxicity.

The antipsychotic drug pimozide can induce tumor cell death, but its efficacy is regulated by peroxisomes. Peroxisomes support energy homeostasis through fatty acid oxidation and ether lipid synthesis, thereby resisting pimozide-induced apoptosis [73]. This reveals the importance of organelle metabolism in drug response. When combined with chemotherapeutic drugs such as paclitaxel, these CNS drugs can enhance the toxicity to cancer cells by inhibiting drug-resistant proteins or independently inducing apoptotic signals, reversing or delaying the development of drug resistance [74].

In addition, the antidepressant sertraline shows unique anti-tumor prospects in the “old drug new use” strategy, especially in targeting tumor metabolic vulnerabilities. Studies have found that some breast cancer and T-cell acute lymphoblastic leukemia cell lines are addicted to the serine/glycine synthesis pathway. Sertraline can interfere with this key metabolic pathway by inhibiting serine hydroxymethyltransferase, thereby selectively inhibiting the proliferation of such cancer cells [75]. Its anti-proliferative activity is further enhanced when combined with mitochondrial inhibitors (such as the antimalarial drug artemether). This combination can cause G1-S phase cell cycle arrest and shows a synergistic anti-tumor effect in a breast cancer mouse xenograft model. This discovery not only reveals a new mechanism by which sertraline exerts its anti-tumor effect through metabolic reprogramming but also provides new ideas for combination therapy for cancer subgroups dependent on serine/glycine synthesis.

In diffuse large B-cell lymphoma (DLBCL), metabolic reprogramming is closely associated with resistance to anti-cancer drugs. Targeting metabolic enzymes, metabolites, or their signal transduction pathways is an effective strategy to overcome chemotherapy resistance [72]. These findings suggest that repurposing drugs with known neuropharmacological effects provides an economical and rapid approach to overcoming multi-drug resistance in tumors.

Effects on ion channels and cell signaling: the anticancer potential of cardiovascular drugs (e.g., digoxin, verapamil)

Cardiovascular drugs such as digoxin (a Na^+/K^+-ATPase inhibitor) and verapamil (an L-type calcium channel blocker) have shown anticancer potential, mainly attributed to their regulation of ion channels and cellular signaling pathways. Ion channels play a crucial role in maintaining cell membrane potential, intracellular calcium homeostasis, and regulating cell proliferation, migration, and apoptosis, and many are abnormally expressed in cancer [76, 77]. For example, digoxin inhibits Na+/K+-ATPase, affects intracellular sodium and calcium ion concentrations, and then activates downstream signaling pathways to induce apoptosis of tumor cells. Verapamil blocks voltage-gated calcium channels, affects calcium ion influx, and may interfere with the proliferation and migration signals of tumor cells [78]. In addition, non-selective cation channels such as the transient receptor potential (TRP) channel family have also been found to be abnormally expressed in various cancers and are involved in tumor progression, making them potential drug targets [79, 80]. These "old drugs" provide new strategies for targeting the unique electrophysiological characteristics of tumor cells by regulating ion channels [81].

Summary of repurposed non-oncology drugs in cancer combination therapy

To provide a concise overview, the key characteristics of representative repurposed drugs discussed in this review are summarized in Table 1.

Table 1. The key characteristics of representative repurposed drugs.

Drug class	Representative agents	Original indication	Proposed anticancer mechanisms	Key synergistic partners	Clinical status/evidence level	Refs.
Biguanides	Metformin	Type 2 diabetes	AMPK/mTOR inhibition; TME modulation; PD-L1 downregulation	Chemotherapy (temozolomide, cisplatin); ICIs	Phase II/III; epidemiological support	[37–44, 122–124]
Statins	Atorvastatin, Simvastatin	Hypercholesterolemia	Mevalonate pathway inhibition; disrupts Ras/Rho prenylation	Chemotherapy; targeted therapy	Phase II ongoing; preclinical	[8, 45, 115]
Antimalarials	Artemisinin, CQ, HCQ	Malaria	Ferroptosis induction; autophagy inhibition (CQ/HCQ)	Chemotherapy (doxorubicin); radiotherapy	Phase II (mixed); repurposing challenges	[16, 55, 69, 70]
β-Blockers	Propranolol	Hypertension, arrhythmia	β-Adrenergic blockade; anti-angiogenic; immune modulation	Chemotherapy (5-fluorouracil)	Preclinical; retrospective observations	[50, 52, 53]
Antihistamines	Cetirizine, Loratadine	Allergies	HRH1 receptor blockade; restores $CD8^+$ T cell activity	ICIs	Observational; potential ICI adjuvant	[54]
NSAIDs	Aspirin, Celecoxib	Inflammation, pain	COX-2/PGE2 inhibition; converts "cold" tumors to "hot"	Immunotherapy (ICIs)	Preclinical; combination studies ongoing	[57, 125–127]
HDAC Inhibitors	Valproic acid	Epilepsy	HDAC inhibition; chromatin relaxation; gene reactivation	Chemotherapy (gemcitabine)	Phase II (e.g., VESPA trial)	[62–64, 112, 115]
Antipsychotics	Pimozide, Fluphenazine,	Psychiatric disorders	MDR inhibition (P-glycoprotein [P-gp]);	Chemotherapy (paclitaxel);	Preclinical; early clinical	[72–75]

Table 1. The key characteristics of representative repurposed drugs. (*continued*)

Drug class	Representative agents	Original indication	Proposed anticancer mechanisms	Key synergistic partners	Clinical status/evidence level	Refs.
	Sertraline		apoptosis induction; SHMT inhibition (sertraline)	mitochondrial inhibitors	exploration	
Cardiovascular Drugs	Digoxin, Verapamil	Heart failure, arrhythmia	Na^+/K^+-ATPase inhibition; calcium channel blockade	Chemotherapy	Preclinical	[76–78]

AMPK: AMP-activated protein kinase; COX-2: cyclooxygenase-2; CQ: chloroquine; HCQ: hydroxychloroquine; HDAC: histone deacetylase; ICIs: immune checkpoint inhibitors; mTOR: mechanistic target of rapamycin; PD-L1: programmed death ligand 1; PGE2: prostaglandin E2; TME: tumor microenvironment.

Construction principles and strategies of synergistic combination therapy

Complementary mechanism-based synergy: simultaneously blocking upstream and downstream or parallel pathways

The core of the mechanism-complementary synergistic strategy lies in simultaneously targeting multiple key signaling pathways involved in tumorigenesis and development. These pathways may have upstream-downstream relationships or act in parallel, thereby achieving multiple strikes against tumor cell proliferation and survival and overcoming the limitations of single therapies. This strategy, by combining drugs with different mechanisms of action, can more comprehensively inhibit tumor growth and delay the development of drug resistance.

For example, in breast cancer treatment, combining HER2-targeted antibody-drug conjugates (such as T-DXd) with therapies targeting specific tumor molecular subtypes can more precisely attack tumor cells [82]. In the treatment of NSCLC, the combined application of targeted drugs (such as crizotinib) against sensitive gene mutations (such as ROS1 fusion) and chemotherapy shows the potential for synergistic effects in neoadjuvant treatment before surgery, enabling major pathological response (MPR) and creating favorable conditions for subsequent surgery [83]. In addition, the combined use of chemotherapy drugs (such as carboplatin/paclitaxel) and immune checkpoint inhibitors (such as pembrolizumab) in the conversion treatment of locally advanced lung cancer also reflects a strategy of achieving synergistic therapeutic effects through the complementarity of different mechanisms (cytotoxicity and immune activation) [84]. This mechanism-based complementary combination therapy aims to maximize the therapeutic effect and improve patient prognosis through multi-targeted intervention.

Synthetic lethal synergism: exploiting tumor-specific vulnerabilities

The synthetic lethal synergistic strategy aims to leverage the unique genetic defects in tumor cells (such as mutations in DNA damage repair genes or epigenetic alterations) by pharmacologically inhibiting their complementary or backup pathways, thereby selectively killing tumor cells with minimal impact on normal cells. This strategy offers a novel approach for targeting the loss of traditionally "undruggable" tumor suppressor genes.

The most classic example is the application of poly(ADP-ribose) polymerase (PARP) inhibitors in *BRCA1/2*-mutated tumors [85]. Research has been continuously expanding the application scope of synthetic lethality. For instance, in ovarian cancer cells with normal *BRCA* gene function, the combined use of a PARP inhibitor (niraparib) and a chemotherapeutic drug (trabectedin) can induce synthetic lethal effects through the *p53*-dependent apoptotic pathway [86]. Additionally, new synthetic lethal pairs have been discovered, such as DNA ligase 1 (*LIG1*) and PARP in castration-resistant prostate cancer [87], as well as *SRC* kinase and *PARP1* in hepatocellular carcinoma [88]. Epigenetic changes, such as gene silencing caused by DNA methylation, also provide new targets for synthetic lethal therapies, namely "methylation synthetic lethality" [89]. Through computational methods such as artificial intelligence, synthetic lethal interactions can be systematically identified, and rational drug combinations can be designed accordingly, such as the combination of *MDM2* and *CDK9* inhibitors [90]. These advancements indicate that the synthetic

lethal strategy can effectively exploit the inherent vulnerabilities of tumor cells, opening up broad prospects for the development of precise and efficient combination therapies.

Microenvironment-modulating synergy: enhancing drug delivery and immune response

The microenvironment-regulating synergistic strategy focuses on altering the TME to overcome its inherent barriers such as immunosuppression, hypoxia, and high interstitial pressure, thereby enhancing the drug delivery efficiency and anti-tumor immune response of primary therapies (e.g., chemotherapy, radiotherapy, immunotherapy). The TME is a complex ecosystem composed of various cells (e.g., TAMs, regulatory T cells) and ECM, which often impedes the penetration of therapeutic drugs and promotes immune escape [91].

Significantly improved therapeutic outcomes can be achieved by modulating the TME. For example, the combination of anti-angiogenic drugs (such as nintedanib) and anti-PD-1 antibodies in the treatment of malignant pleural mesothelioma can reshape the TME by polarizing TAMs from M2 to M1 type and regulating immunosuppressive signals, resulting in a synergistic anti-tumor effect [92]. In liver metastatic colorectal cancer, an oral metronomic chemotherapy regimen (CAPOX) can modulate immune cells in the TME by activating the cGAS-STING pathway and exert a synergistic effect with anti-PD-1 antibodies [93]. Additionally, using nanomaterials (such as graphene oxide) or metal-organic framework materials for drug delivery can design intelligent delivery systems responsive to the TME. These systems can modulate the TME by catalytically decomposing hydrogen peroxide to relieve hypoxia and depleting glutathione, thereby enhancing the efficacy of chemodynamic therapy, sonodynamic therapy, or chemotherapy [94, 95]. These strategies, through active intervention in the TME, provide powerful means for improving drug distribution, activating anti-tumor immunity, and overcoming treatment resistance.

Toxicity-mitigating synergy: reducing the side effects of the primary therapy

The toxicity mitigation-based synergistic strategy aims to reduce or manage the toxic side effects caused by the main therapy while maintaining or enhancing anti-tumor efficacy through the combined application of drugs with different side effect profiles, thereby improving patients' tolerance and quality of life. This strategy is particularly suitable for patient populations requiring long-term treatment or being sensitive to the toxicity of traditional therapies.

For example, in cancer pain management, the combination of medical cannabis and opioids has shown the potential to effectively relieve pain while potentially reducing the opioid dosage and alleviating its associated toxicity in hospice inpatients, with good safety [96]. In the treatment of fibromyalgia, although the combination of alpha-lipoic acid and pregabalin did not show additive analgesic benefits, the study observed that the maximum tolerated dose, similar to that of monotherapy, could be achieved during combination therapy without increasing side effects, which provides support for the future development of combination therapies with complementary mechanisms and non-overlapping side effects [97]. In tumor treatment, for patients with NSCLC receiving the combination therapy of pembrolizumab and platinum-based chemotherapy, if acute kidney injury occurs, analysis using novel immunohistochemical markers (such as *p53* and PD-L1) can help identify whether the kidney injury is caused by platinum-based drugs or immune checkpoint inhibitors, thereby guiding clinical decision-making to protect renal function while ensuring the continuity of anti-tumor treatment [98]. These cases indicate that well-designed combination regimens can optimize the treatment window, maximizing efficacy while minimizing the treatment-related toxicity risks.

Screening and validation strategies for drug repositioning

Computational and data-driven discovery methods

Computational and data-driven methods have become the core engine for identifying potential anti-cancer candidate drugs in the "drug repurposing" strategy. By integrating bioinformatics, artificial intelligence, and network pharmacology, researchers can conduct large-scale analyses of drug-target interaction databases, gene expression profiles, and clinical electronic medical record data to predict the potential associations

between non-oncology drugs and key cancer pathways [99]. For instance, artificial intelligence models, which simulate intelligent behavior with minimal human intervention, have significantly accelerated the research process and reduced experimental costs through drug repositioning technologies [100].

In breast cancer drug resistance research, the computational drug repurposing method extracts drug resistance features by comparing the gene expression profiles of responders and non-responders to different treatment subtypes in the I-SPY 2 clinical trial. It then performs rank-based pattern matching using the drug perturbation profiles in the CMap database and successfully identifies compounds such as fulvestrant that may reverse drug resistance in multiple treatment and receptor subtypes [101]. These methods are not limited to single-drug discovery but also extend to the prediction of combination therapies. By using methods such as network analysis, regression-based machine learning, classifier models, and deep learning, combination cancer treatment regimens can be predicted. The progress of these computational methods provides a time- and cost-effective alternative for identifying novel and effective therapies [102].

Molecular docking and quantum mechanics studies provide profound insights into the synergistic mechanism of drug combinations at the theoretical level. For example, by screening the FDA-approved drug library using machine learning models and combining molecular docking and molecular dynamics simulations, potential PARP-1 inhibitors such as atazanavir and brexpiprazole can be identified, with better binding free energy than the control drugs [103]. Further quantum mechanics calculations, such as optimizing geometric structures and mapping electron densities, can confirm the Gibbs free energy of molecular structures, thereby verifying the enhanced stability after binding to the target [103]. In the discovery of Wee1 kinase inhibitors for triple-negative breast cancer, machine learning-based models effectively predicted the binding energy. Then, candidate drugs were screened through molecular docking and dynamics methods, and the synergistic effect of their combination with cisplatin was verified [104]. These computational tools together form a complete system from large-scale prediction to microscopic mechanism interpretation, laying a solid foundation for the study of synergistic mechanisms based on molecular interactions such as differences in electrostatic potential.

Application of PDTO models

PDTO models, serving as a bridge between basic research and clinical translation, have demonstrated great value in the screening and validation of non-oncology drug repositioning. PDTOs can highly mimic the tissue structure, genotype, and drug sensitivity heterogeneity of primary tumors, providing an ideal and individualized platform for in vitro screening and validation of repositioned drugs and their combination regimens [99]. The application of this model enables drug testing to be conducted under conditions closer to the human TME, thereby improving the accuracy of predicting clinical efficacy.

Patient-derived immunocompetent tumor organoids (PDITOs), which incorporate both tumor cells and immune cells, provide a promising platform for evaluating immunomodulatory drugs and predicting patient-specific immunotherapy responses. These models can be applied to screen immune checkpoint inhibitors and other immunotherapeutic agents, offering a more physiologically relevant alternative to conventional two-dimensional cultures [99]. Furthermore, PDTOs have been utilized to discover personalized treatment opportunities, including drug repurposing strategies, in various cancer types [99].

Studies have successfully used PDTOs for the discovery and validation of specific biomarkers. For example, in PDTO models of pancreatic ductal adenocarcinoma and NSCLC, biomarkers of auranofin sensitivity (such as low *CA12* expression) have been successfully screened, and the synergistic efficacy of its combined use with MK2206 has been verified, achieving “customized” drug repositioning tests targeting individualized tumor characteristics [99]. This process reflects the key role of PDTOs in translating computational predictions into experimental evidence.

Moreover, in studies on pancreatic cancer and melanoma with high fibrosis levels, although mouse models are mainly used, the evaluation of complex phenotypes involved in TME remodeling (such as reducing stiffness, restoring vascular function, improving perfusion, and alleviating hypoxia) is precisely

the key direction that PDTOs can simulate and study in the future [105, 106]. Machine learning models can even utilize drug combination screening data generated from platforms like PDTOs to go beyond traditional synergy score predictions and conduct dose-specific relative growth inhibition predictions, thereby providing support for reconstructing dose-response curves and prioritizing individualized combination therapies [107]. Therefore, PDTOs are not only a screening tool but also a core experimental system for integrating multi-omics data, validating computational predictions, and promoting the development of individualized cancer treatment strategies.

Integration from mechanistic research to population evidence

Successful drug repositioning is by no means an accidental discovery. It relies on the meticulous integration of preclinical mechanistic research and evidence from population-based epidemiology or retrospective studies. This process forms a complete evidence chain from phenomenon observation to theoretical verification and then to clinical validation.

Effective drug repositioning requires robust preclinical research to elucidate the mechanism of action of drugs on specific cancer pathways or targets [99]. For example, artificial intelligence and machine learning methods are widely used to identify systematic drug repositioning clues based on public databases, with particular emphasis on leveraging comprehensive target activity profiles to expand the drug's action spectrum to off-targets with therapeutic potential, thereby systematically advancing the repositioning process [108]. Computational models, such as those using pathway features and machine learning to simulate individual patients' responses to drugs, can predict drug efficacy by calibrating the pathway activity scores of disease samples. This serves as a proxy method for identifying potential candidate drugs and can even be used to decipher the drug's mechanism of action and propose combination therapy regimens [109].

However, mechanistic research alone is insufficient. Evidence from real-world populations is the key to supporting its clinical translation potential. The anti-cancer potential of statins and metformin initially stemmed from epidemiological observations, which found an association between the use of these drugs and improved prognosis in cancer patients [99]. These observational findings provided important directions for subsequent in-depth mechanistic studies in cell and animal experiments, ultimately propelling them into the formal clinical trial stage. This "clinical observation - mechanism exploration - clinical validation" model is a classic example of the drug repositioning pathway.

This integrated strategy is also applicable in the research on rare cancers such as chordoma. By constructing a Bayesian machine learning model using the published screening data of chordoma cell lines, potential compounds (such as the mTOR inhibitor AZD2014) can be predicted. Meanwhile, based on the understanding of the mechanisms of approved kinase inhibitors (such as afatinib and palbociclib), their synergistic effects can be verified in vitro, providing direct references for clinical combination therapy [110]. Additionally, the integrated analysis of network pharmacology and multi-omics data can systematically reveal the mechanism by which drugs (such as theophylline) affect liver cancer by regulating core targets. Based on this, potential synergistic drugs (such as chlorogenic acid and losartan) can be identified and then verified through in vitro and in vivo experiments, thus completing the closed loop from computational prediction to experimental evidence [111]. Therefore, combining population-based evidence with in-depth molecular mechanism research is the only way to reduce the risk of drug repositioning, improve the success rate, and ultimately achieve clinical translation.

An Integrated Model for Repurposing Discovery and Validation: The path from a computational prediction to a clinical trial is not linear but iterative. A holistic model would integrate: (1) AI/Machine Learning to computationally screen vast drug libraries and generate hypotheses based on tumor genomic profiles; (2) High-throughput Phenotypic Screening in patient-derived cell lines or 3D organoids to confirm anti-cancer activity; (3) Mechanistic Studies using CRISPR screens and multi-omics to decipher the drug's mode of action and identify putative biomarkers; (4) Validation in PDTOs to test efficacy in a patient-specific context and refine predictive biomarkers; and finally, (5) Biomarker-Driven Early-Phase Clinical

Trials enriched for the predicted responsive population. This closed-loop system is essential to de-risk the repurposing process and move beyond the "one-size-fits-all" failures of the past.

Preclinical and clinical progress of representative combination therapies

Combination of epigenetic modulators and chemotherapy

Epigenetic regulators, especially HDACi, have demonstrated significant synergistic potential in combination chemotherapy, which is an important manifestation of the "repurposing old drugs" strategy. Valproic acid, a classic anticonvulsant, has been proven to possess HDAC inhibitory activity and can enhance the sensitivity of tumor cells to chemotherapeutic drugs by altering chromatin structure and reactivating silenced tumor suppressor genes [112]. In solid tumors such as pancreatic cancer, chemotherapy resistance is the main cause of treatment failure, and epigenetic abnormalities play a crucial role in this process [113].

Preclinical studies support that the combination of valproic acid with chemotherapeutic drugs such as gemcitabine can produce a synergistic antitumor effect. The mechanism may involve reshaping the transcriptional program of tumor cells through epigenetic "priming", thereby overcoming inherent or acquired drug resistance [114]. Based on this principle, the VESPA Phase II clinical trial emerged, aiming to evaluate the efficacy and safety of valproic acid combined with simvastatin and then combined with the standard chemotherapy regimen in patients with metastatic pancreatic ductal adenocarcinoma. This study represents a cutting-edge exploration of repurposing non-oncology drugs (valproic acid, simvastatin) and forming a combination strategy with standard chemotherapy [115]. The scientific hypothesis is that the epigenetic regulatory effect of valproic acid may "prime" tumor cells, making them more sensitive to subsequent cytotoxic chemotherapy, while simvastatin may further enhance the efficacy by regulating the TME or metabolic pathways [116]. The core advantage of this combination strategy lies in the use of known safety data of marketed drugs, which is expected to accelerate clinical translation and provide new treatment hopes for pancreatic cancer patients with an extremely poor prognosis [117]. The combination of epigenetic drugs and chemotherapy has been proven to reverse drug resistance and enhance efficacy in a variety of hematological malignancies and solid tumors. The exploration of valproic acid in pancreatic cancer is a specific example in this broad field [118].

Repositioning of targeted CAFs

Targeting the TME, especially CAFs, has emerged as a novel strategy to overcome chemotherapy resistance and enhance therapeutic efficacy. CAFs create a niche that promotes tumor growth, immunosuppression, and drug resistance by secreting cytokines, growth factors, and remodeling the ECM [119]. The repurposing of the anti-fibrotic drug pirfenidone provides a powerful tool for this purpose.

Research has shown that pirfenidone can inhibit the activation and function of CAFs and reduce the excessive deposition of ECM, thereby reducing tissue interstitial pressure and improving the penetration and distribution of chemotherapeutic drugs in tumor tissues [113]. Moreover, pirfenidone can also regulate the immunosuppressive signals mediated by CAFs and may directly or indirectly affect the drug-resistant phenotypes of tumor cells, thus playing a role in enhancing the efficacy of chemotherapeutic drugs such as doxorubicin [120].

However, it remains a significant challenge to efficiently and specifically deliver pirfenidone to CAFs in tumor sites. Novel drug delivery systems, such as biomimetic liposomes, offer innovative solutions to this issue. These delivery systems can achieve active targeting through surface modification or stimulus-responsive drug release by leveraging the characteristics of the TME, thereby significantly increasing the local concentration of pirfenidone at the tumor site while reducing the side effects associated with systemic exposure [121]. For example, nanotechnology-based delivery systems have been used for the co-delivery of chemotherapeutic drugs and epigenetic regulators to overcome multidrug resistance, and the design concept is also applicable to CAF-targeted therapy [121]. By combining "old drugs" like pirfenidone with advanced targeted delivery technologies, the supporting structure of tumors can be more precisely disrupted, and CAF-driven chemoresistance can be reversed, opening up new avenues for combination

therapy based on TME regulation [119]. This strategy not only maximizes the therapeutic potential of repurposed drugs but also represents an important shift in cancer treatment from simply killing cancer cells to comprehensively regulating the tumor ecosystem.

Representative cases of drug combinations in clinical research

Trials of metformin combined with chemotherapy/targeted therapy in various solid tumors

As a classic hypoglycemic drug, the anti-tumor potential of metformin has been extensively explored in preclinical and clinical studies of various solid tumors. In ovarian cancer, a phase II clinical trial showed that neoadjuvant or adjuvant chemotherapy combined with metformin treatment could significantly reduce the number of CSCs in tumor tissues, enhance the in vitro sensitivity of tumors to cisplatin, and an extension of the overall survival of patients was observed [122]. In the field of breast cancer, studies have shown that metformin combined with neoadjuvant chemotherapy may increase the pathological complete response rate, especially in patients with a higher body mass index or the triple-positive (hormone receptor-positive/HER2-positive) subtype, where a trend of benefit was observed [123]. In a retrospective analysis of DLBCL, diabetic patients using metformin had better survival outcomes than non-users; preclinical studies further confirmed that metformin can synergize with traditional chemotherapy or rituximab and resensitize drug-resistant lymphomas [124].

Exploration of antidepressants (such as sertraline) and targeted therapies in leukemia

Sertraline shows unique anti-tumor prospects in the “repurposing old drugs” strategy. Studies have found that some breast cancer and T-cell acute lymphoblastic leukemia cell lines are addicted to the serine/glycine synthesis pathway. Sertraline can interfere with this key metabolic pathway by inhibiting serine hydroxymethyltransferase, thereby selectively inhibiting the proliferation of such cancer cells [75]. Its anti-proliferative activity is further enhanced when combined with mitochondrial inhibitors (such as the antimalarial drug artemether). This combination can cause cell cycle arrest at the G1-S phase and shows a synergistic anti-tumor effect in a breast cancer mouse xenograft model [75].

Combination of NSAIDs and immune checkpoint inhibitors

NSAIDs have emerged as a potential strategy to enhance the efficacy of immune checkpoint inhibitors by modulating the tumor immune microenvironment. Preclinical studies have shown that targeting the COX2/PGE2/EP2-4 pathway, whether using NSAIDs or PGE2 receptor antagonists, can rapidly convert “cold tumors” into “hot tumors”, that is, increase the infiltration and activation of effector T cells within the tumor [125]. In a colon cancer model, both celecoxib and naproxen significantly reduced the expression of PD-L1 in polyps, accompanied by an influx of $CD8^+$ T cells. This immunomodulatory effect is mainly dependent on the inhibition of COX-2 [126]. Clinical observational studies have also suggested that in patients with NSCLC, the use of NSAIDs may be associated with a lower objective response rate and shorter progression-free survival when used in combination with immune checkpoint inhibitors alone or in combination with chemotherapy [127]. This evidence indicates that the combination of NSAIDs and immunotherapy has complex biological effects, and its clinical translation requires more refined patient stratification and mechanistic studies. The apparent contradiction between preclinical mechanistic studies and clinical observations may stem from several factors. First, the timing, dosage, and duration of NSAID use in clinical settings differ substantially from carefully controlled preclinical protocols; chronic NSAID exposure may exert immunosuppressive effects that outweigh its acute immune-sensitizing actions [57, 59]. Second, the heterogeneity of patient populations—including differences in tumor mutational burden, baseline inflammatory status, and concurrent medications—may modulate the net effect of NSAIDs on immunotherapy outcomes [47, 60]. Third, the specific type of NSAID and its selectivity for COX-1 versus COX-2 may influence immune modulation differently, as suggested by the complex roles of the COX-2/PGE2 pathway in both promoting and suppressing anti-tumor immunity [60]. These observations underscore the need for biomarker-driven patient stratification in future clinical trials of NSAID-immunotherapy combinations.”

Critical analysis of clinical trials: lessons from CQ/HCQ

A comprehensive look at the clinical development of CQ/HCQ as an adjuvant cancer therapy provides critical lessons. Despite robust preclinical evidence showing that autophagy inhibition can sensitize tumors to chemotherapy, multiple phase I/II clinical trials combining HCQ with various agents (e.g., temozolomide in glioblastoma, bortezomib in multiple myeloma) have yielded only modest, or in many cases, disappointing results [69]. A critical analysis reveals several key limitations: 1) Trial design: Many trials were small, single-arm, and lacked a control group, making it difficult to attribute any observed benefit to the HCQ. 2) Endpoint selection: Most trials used overall survival or progression-free survival as endpoints, but the modest effect sizes demanded a large sample size to achieve statistical power—a feat not achieved. 3) Lack of predictive biomarkers: The most significant shortcoming was the absence of a reliable pharmacodynamic biomarker to confirm that HCQ was actually inhibiting autophagy in the patient's tumor at the administered dose. Without this, it was impossible to know whether the trial failed due to a lack of efficacy, or because the drug never hit its target. 4) Suboptimal dosing: Achieving a sufficient intra-tumoral concentration of HCQ to block autophagy is challenging, and dose escalation is often limited by its toxicity profile (e.g., gastrointestinal and retinal toxicity). The CQ/HCQ experience underscores that for drug repurposing in combination therapies to succeed, clinical trials must move beyond simply evaluating efficacy and must integrate correlative studies to validate target engagement and identify biomarkers for patient selection, even if this requires invasive tumor biopsies.

To provide a systematic and hierarchical overview of the clinical and translational evidence discussed above, we have classified the representative repurposed drugs into an evidence-based framework (Table 2). This classification distinguishes between promising early-phase clinical signals, robust preclinical findings with high translational potential, observational data, and failed or inconclusive clinical translation, thereby highlighting both the achievements and the remaining gaps in the field.

Table 2. Evidence hierarchy of repurposed non-oncology drugs in cancer combination therapy.

Evidence level	Representative drug(s)	Cancer type(s)	Key finding(s)	Refs.
I. Confirmatory clinical (Phase III/IV)	-	-	No non-oncology drug has yet achieved confirmatory Phase III evidence as a combination partner.	-
II. Promising early-phase Clinical (Phase I/II)	Metformin (+ chemo)	Ovarian, Breast, Lymphoma	Reduced cancer stem cells; enhanced chemosensitivity; improved survival in triple-positive breast cancer.	[122–124]
II. Promising early-phase clinical (Phase I/II)	Valproic acid (+ simvastatin/chemo)	Pancreatic ductal adenocarcinoma	VESPA trial ongoing; epigenetic "priming" to overcome chemoresistance.	[115]
III. Translational preclinical (In Vivo/Organoid)	Sertraline (+ artemether)	Breast cancer (Ser/Gly-addicted)	Potent synergy by targeting serine/glycine synthesis addiction; clear mechanistic basis.	[75]
III. Translational preclinical (In Vivo/Organoid)	Auranofin (+ AKT inhibitor)	Pancreatic cancer	PDTO models identified CA12 as a biomarker; personalized repurposing approach.	[99]
III. Translational preclinical (In Vivo/Organoid)	Pirfenidone (+ chemo)	Various	Remodels CAF-rich TME; improves drug penetration; novel delivery systems in development.	[113, 120]
IV. Observational/Epidemiological	Statins, Metformin	Various	Epidemiological associations with improved cancer outcomes; generated repurposing hypotheses.	[8, 99]
V. Inconclusive/Failed Translation	Chloroquine/Hydroxychloroquine	Glioblastoma, Multiple Myeloma	Preclinical synergy failed to translate; lack of pharmacodynamic biomarkers was a major shortcoming.	[69]

Interpretation of the Evidence Hierarchy: Several important observations emerge from this classification. First, a significant translational gap exists: despite hundreds of preclinical studies demonstrating synergy, no repurposed non-oncology drug has yet achieved Phase III confirmatory evidence as a combination partner in cancer therapy. Second, the most successful signals (e.g., metformin, valproic acid) share common features: they are mechanistically well-understood, target fundamental hallmarks of cancer (metabolism, epigenetics), and are being evaluated in biomarker-enriched or mechanistically driven trial designs. Third, the CQ experience serves as a cautionary tale, illustrating that robust preclinical autophagy inhibition does not guarantee clinical success without rigorous pharmacodynamic monitoring and patient selection. Collectively, these observations underscore that the path to clinical translation requires not only biological rationale but also trial designs that incorporate predictive biomarkers, pharmacokinetic/pharmacodynamic assessments, and adaptive strategies to identify responsive patient subsets. CAF: cancer-associated fibroblast; CQ: chloroquine; PDTO: patient-derived tumor organoid; TME: tumor microenvironment.

Repurposing for CNS tumors

Treatment of CNS tumors, especially pediatric brain tumors, faces a severe challenge from the blood-brain barrier (BBB), a natural barrier. Many effective chemotherapeutic drugs struggle to reach the intracerebral concentrations required for treatment [128]. Therefore, repurposing non-oncological drugs that have demonstrated good BBB penetration has become an important strategy for developing new therapies. These drugs include certain antibacterial and psychiatric drugs, which have the pharmacokinetic properties to enter the CNS and can be re-evaluated for their anti-tumor activity [129].

By screening the inhibitory effects of these "old drugs" on brain tumor cell lines or conducting rational repositioning based on their known molecular targets, potential therapeutic candidates can be rapidly identified [130]. However, relying solely on the BBB penetrability of the drugs may still be insufficient to achieve a sufficiently high exposure at the tumor site. To address this, combining with novel intracranial drug delivery technologies, such as convection-enhanced delivery (CED), can greatly enhance the therapeutic efficacy of repositioned drugs. The CED technique involves implanting a catheter in the tumor area or surrounding tissues and applying a pressure gradient, enabling a more extensive and uniform convective distribution of the therapeutic drugs within the brain parenchyma. This significantly increases the local drug concentration in the tumor while reducing systemic toxicity [130].

Combining repurposed drugs capable of penetrating the BBB with local delivery techniques such as CED constitutes a highly promising "double insurance" strategy: the drugs themselves possess CNS activity, while CED ensures their adequate exposure in the target area. This combined strategy brings new hope to pediatric neuro-oncology, offering the potential to overcome the limitations of traditional chemotherapy and providing more effective treatment options for refractory, recurrent, or surgically inoperable pediatric brain tumors [128]. Additionally, epigenetic drugs have also shown potential in the treatment of brain tumors, and their combination with CED technology may further optimize the therapeutic efficacy [131].

From clinical observation to confirmatory trials: lessons from successes and failures and the crucial role of biomarkers

The clinical translation process of the "repurposing old drugs" strategy is fraught with both successes and challenges. Taking CQ and its analogs as an example, although preclinical studies have shown their anti-cancer potential through multiple mechanisms such as regulating autophagy and inducing apoptosis, and they have entered clinical trials as an adjuvant therapy in combination with various anti-cancer drugs, most trials have only shown limited improvement in anti-cancer efficacy [69]. The reasons for the failure may include the acidic and hypoxic environment inside the tumor weakening the drug activity, as well as the lack of effective biomarkers to screen the patient population that may benefit.

These cases highlight the key from clinical observation to confirmatory trials: it is essential to have a deep understanding of the drug's mechanism of action, develop reliable predictive biomarkers for precise patient stratification, and optimize the timing and sequence of combination therapy. For example, a study has pointed out that administering metformin before chemotherapy may produce a better sensitization effect [132].

Effective biomarkers can be derived from multiple levels. At the molecular level, specific gene mutations or expression profiles are crucial. For example, in head and neck squamous cell carcinoma,

patients with PIK3CA gene alterations may gain survival benefits from the regular use of NSAIDs such as aspirin [133]. At the immune microenvironment level, the PD-L1 expression level (e.g., combined positive score [CPS]) is currently the main biomarker guiding the application of immune checkpoint inhibitors, but its predictive value is limited and needs to be combined with other biomarkers [134]. Emerging microbiome biomarkers also show potential. For instance, in rectal cancer, specific gut microbial characteristics (e.g., *Fusobacterium nucleatum*) are associated with the efficacy of chemoradiotherapy and are expected to be used for patient stratification [135]. In addition, circulating tumor cell counts, inflammatory indices (e.g., systemic inflammatory response index SIRI), and nutritional indicators have also been explored for prognosis prediction and risk stratification [136, 137]. Using a systematic drug screening platform (e.g., PRISM), the selective growth-inhibitory activity of non-oncology drugs can be predicted based on the molecular characteristics of cancer cell lines, which provides a potential molecular basis for patient stratification in clinical trials [138]. In the future, integrating multi-omics data to construct composite biomarker models will be the core direction for the personalized application of "old drug new use" combination therapies.

Challenges and translational barriers

Obstacles in intellectual property and commercial development

The application of the "repurposing old drugs" strategy in cancer combination therapies faces significant commercial incentive challenges. The core issue is that many non-oncology drugs awaiting repositioning have passed their patent protection periods and become generic drugs, which severely reduces the pharmaceutical companies' commercial motivation to invest substantial funds in clinical trials for new indications [139]. Although drug repositioning has the advantages of lower cost, shorter time, and higher success rate compared to traditional new drug development, due to the lack of patent protection for these drugs, it is difficult for enterprises to recoup their R&D investments through market exclusivity, resulting in limited commercial returns [139].

For example, disulfiram, a drug whose patent has expired, faces such challenges in the development of its anticancer potential. Although its combination with copper ions shows excellent anticancer efficacy, developing a new delivery system to form intellectual property is crucial for its product development and commercialization [140]. To overcome this "valley of death" in commercial development, several innovative strategies are being pursued. These include the development of novel formulations (e.g., nanoparticle-encapsulated drugs) which can be patented, thereby providing a commercial incentive to conduct the required clinical trials [140]. Similarly, pursuing orphan drug designation for rare cancers offers benefits such as market exclusivity and tax credits, making the repositioning of off-patent drugs economically viable for specific, underserved patient populations [139]. Furthermore, public-private partnerships (PPP) and non-profit initiatives, such as the Repurposing Drugs in Oncology (ReDO) project, are increasingly vital in bridging this gap by funding and facilitating trials for generic drugs with limited commercial appeal [139]. Similarly, CQ and its analogs, as ancient antimalarial drugs, also face a similar dilemma in the research of their repositioning for cancer adjuvant therapy. Most clinical trials have only shown limited improvement in anticancer effects, further reducing the attractiveness of commercial investment [69].

To promote the clinical development of such drugs, innovative funding models and incentive policies are required. PPP and regulatory incentive policies (such as priority review vouchers) are considered potential solutions [139]. In addition, through big data analysis of patents, it can be found that for drugs targeting specific targets (such as PI3K/AKT), the average time from patent application to approval for marketing is about 8.8 years. If this time is less than 10 years, a patent term extension of about 2 years may be obtained, which provides a certain commercial incentive reference for the repositioning development of some targeted drugs [141]. However, for the vast majority of non-oncology drugs whose patent terms have expired, their repositioning development still needs to rely on public funding support, the promotion of non-profit research institutions, and global policy adjustments aimed at promoting health equity to ensure that these potential therapies can benefit all patients [139].

Determination of the optimal dose and dosing regimen: anti-cancer dose vs. dose for the original indication

Determining the optimal dosage and administration regimen of non-oncology drugs in cancer combination therapies is a core challenge. The "therapeutic window" for cancer treatment may be significantly different from the conventional dosages for their original indications (such as anti-infection, lipid-lowering). For example, statins may require higher doses in cancer treatment to achieve the effects of inhibiting cell proliferation or inducing apoptosis, which may bring risks of adverse reactions beyond what is expected for their lipid-lowering effects [8]. For instance, while statins are generally well-tolerated at standard lipid-lowering doses (e.g., simvastatin 20–40 mg/day), the doses required to achieve direct anti-proliferative or pro-apoptotic effects in preclinical models are often several-fold higher (e.g., 10–20 μM in vitro). Translating this to clinical use raises a significant risk of dose-limiting toxicities, particularly hepatotoxicity and rhabdomyolysis [8]. Preclinical models have indicated a narrow therapeutic window, and phase I studies are urgently needed to define a maximum tolerated dose for cancer patients, as simply escalating to a high-dose statin regimen used in acute coronary syndromes is unlikely to be safe or tolerable chronically [8]. Similarly, CQ analogs need to reach a blood drug concentration sufficient to regulate autophagy or induce apoptosis in cancer treatment, which is different from their dosages for antimalarial or antirheumatic use [69]. The complexity of dose exploration lies in the need to strike a balance between efficacy and toxicity, especially when used in combination with standardized chemotherapy drugs with existing toxicity. Future research should be based on pharmacokinetic/pharmacodynamic models and systematically explore the optimal biologically effective doses of these old drugs as anticancer agents through well-designed early-stage clinical trials, rather than simply following the doses for their original indications [142].

Complexity of clinical trial design: endpoint selection and patient population

Evaluating the efficacy of repurposed drugs in combination therapies requires well-designed clinical trials to determine the optimal dosage, administration sequence, treatment cycle, and identify specific patient subgroups that may benefit, which constitutes the main complexity of clinical development [143]. The advantage of combination therapies lies in overcoming tumor heterogeneity and drug resistance through the synergistic action of multiple targets or pathways. For example, the combination of HDAC inhibitors with other targeted inhibitors (such as PI3K/mTOR, PARP, JAK, etc.) has been proven to have synergistic anti-cancer activity and can combat recurrent/refractory cancers [144, 145]. However, the realization of this synergistic effect is highly dependent on precise dosing regimens.

Clinical trial design also needs to consider the molecular characteristics of tumors and endpoint selection. For combination strategies aiming to enhance the efficacy of existing therapies or reverse drug resistance, it is challenging to select appropriate clinical endpoints (such as progression-free survival, overall survival) or biomarker surrogate endpoints [146]. Secondly, the heterogeneity of the patient population increases the difficulty of the trial. Cancer patients, especially elderly patients, vary greatly in comorbidities, physical status, and organ function, which affects treatment tolerance and outcomes [147]. The trial design needs to consider how to include a population that better represents real-world patients rather than strictly screened individuals. In addition, for some rare cancers or specific drug-resistant populations, conducting large-scale randomized controlled trials may not be feasible, and innovative trial design methods such as single-arm trials, adaptive designs, or the use of real-world data (RWD) are required [148]. To overcome these hurdles, innovative trial designs are essential. Adaptive trial designs allow for pre-specified modifications to the trial course based on interim results, such as dropping ineffective treatment arms or enriching for a responding biomarker-defined subgroup [148]. Platform trials, which evaluate multiple treatments simultaneously under a single master protocol, are particularly efficient for testing various repurposed drug combinations in biomarker-defined patient populations. Additionally, the use of RWD from electronic health records and registries is gaining regulatory acceptance as a complementary source of evidence, especially for rare cancers where conducting large RCTs is impractical.

Reassessment of off-target effects and safety

Although repurposed drugs generally have long-term safety data, when combined with potent anticancer drugs, they may produce unknown interactions or additive toxicity. Therefore, strict safety re-evaluation must be carried out in the new treatment context [149]. Anticancer drugs themselves may cause adverse reactions such as severe cardiovascular toxicity. When combined with repurposed drugs, the risk of toxicity superposition or the generation of new toxicity cannot be ignored [149]. For example, chemotherapy drugs such as anthracyclines and trastuzumab are known to have cardiotoxicity, and their combination with certain repurposed drugs may exacerbate this risk [149].

This re-evaluation is not limited to clinical observations but is also reflected in patent layouts. Many patents have focused on evaluating and reducing the cardiotoxicity of drugs, including anticancer drugs. For example, the use of bis(dioxopiperazine) or manganese compounds in combination with other selected anticancer drugs for cardioprotection [149]. In addition, innovations in drug delivery systems may also change the safety profiles of drugs. For instance, a nanodelivery system for doxorubicin has been developed to reduce its systemic and cardiotoxicity [150]. Similarly, when developing a new delivery system for disulfiram-copper complexes, evaluating the changes in its safety profile is a key step in addition to improving efficacy [140]. Therefore, for the combination strategy of "repurposing old drugs", systematic pre-clinical toxicology studies and well-designed phase I clinical trials must be carried out, with a focus on pharmacokinetic interactions, organ-specific toxicity (especially in the heart, liver, and kidneys), and the safety of long-term drug use.

Future development directions and prospects

Precision repositioning through the integration of artificial intelligence and multi-omics

The core driving force behind future drug repositioning strategies lies in the in-depth integration of artificial intelligence and multi-omics data. By integrating multi-dimensional information such as genomics, transcriptomics, proteomics, and metabolomics, artificial intelligence algorithms can predict effective drug combinations and identify predictive biomarkers with unprecedented accuracy [151]. For example, in female malignancies, AI-driven multi-omics integration is reshaping the opportunities for epigenetic therapy. By uncovering new drug-target-patient associations, it provides a precise tool to overcome the limitations and drug resistance of traditional therapies [151].

This integrative analysis is not limited to the single-omics level. Web server tools such as Mergeomics 2.0 can integrate data from various omics-association studies, clarify disease networks through enrichment analysis and key driver analysis, and predict potential drugs targeting disease processes using its integrated drug repositioning process [152]. Meanwhile, techniques such as single-cell RNA sequencing provide a powerful means to resolve the heterogeneity of the TME. By revealing the unique transcriptional characteristics of different cell sub-populations within tumors (e.g., specific CAF sub-populations), it can guide the selection of repositioned drugs targeting specific stromal cell populations, achieving more precise microenvironment intervention [153].

In complex diseases such as breast cancer, the molecular heterogeneity of tumors poses challenges to extracting representative features from multi-omics data. The novel bidirectional coordinated deep learning framework (e.g., BTOB-T) can more accurately predict the efficacy of new drugs by integrating proteomic and transcriptomic data and using Transformer-based models to extract gene representations, thereby optimizing repositioning strategies [154]. In addition, advanced methods such as graph deep learning, like STRGNN, demonstrate excellent accuracy in predicting drug-disease relationships by constructing multimodal networks containing proteins, RNAs, metabolites, and compounds and using topological regularization algorithms to select informative modalities [155]. AI-driven network pharmacology and systems biology methods contribute to understanding the mechanisms of action of multi-target drugs and rationally designing more effective drug combinations [156]. The development of these technologies marks the transition of drug repositioning from traditional empirical attempts to precise and predictable scientific exploration based on systems biology and computational intelligence.

A central tenet of this precision approach is the development of robust predictive biomarkers. These biomarkers can be derived from multiple levels of the tumor's biology. Molecular biomarkers, such as specific gene mutations (e.g., *PIK3CA*) or RNA expression signatures (e.g., the CMap), can identify tumors that are inherently sensitive to a repurposed drug [101, 133]. Immune microenvironment biomarkers, such as the PD-L1 CPS, although imperfect, are the current standard for guiding immunotherapy combinations [134]. More advanced techniques, such as multiplex immunohistochemistry, can characterize the complex immune cell infiltrate, providing a deeper insight into whether a repurposed drug (e.g., an NSAID) has successfully remodeled the TME. Emerging circulating biomarkers like tumor-educated platelets (TEPs) and circulating tumor DNA (ctDNA) offer the possibility of non-invasive, real-time monitoring of treatment response and resistance [136]. Finally, PDTOs are emerging as a powerful platform for functional biomarker discovery. By testing a panel of repurposed drugs on a patient's own organoids, one can directly assess sensitivity and identify "on/off" signals that correlate with response, enabling truly personalized combinatorial strategies [99]. The integration of multi-omics data with AI is not just about discovering new uses, but about building a comprehensive, multi-layered biomarker model that can guide patient selection from the bench to the bedside.

Optimization of novel drug delivery systems and combination strategies

To enhance the efficacy of repurposed drugs in cancer treatment and reduce systemic toxicity, the development of novel delivery systems is of utmost importance. Advanced technologies such as nanocarriers and antibody-drug conjugates can significantly improve the targeting and bioavailability of drugs in tumor tissues [157]. For instance, encapsulating repurposed drugs (e.g., NSAIDs, statins, or metformin) in functionalized nanoparticles can enhance their anti-tumor effects. This is attributed to the synergistic effects of nanocarrier functionalization, sustained drug release, and improved cellular uptake within tumors, thereby enabling the targeting of multiple cancer hallmarks [157]. In the treatment of lung cancer, radiolabeled drug delivery systems combined with imaging techniques such as positron emission tomography can achieve precise drug localization and real-time distribution monitoring, offering the possibility of personalized treatment strategies [158].

In addition to the innovation of delivery systems, optimizing combination therapy strategies is the key to attacking multiple vulnerable points of cancer and overcoming drug resistance. Exploring "three-drug" or "multi-drug" combination regimens has become a trend, aiming to systematically and synergistically attack tumors [159]. For example, in refractory tumors such as glioblastoma, the combined use of drugs such as metformin, epigallocatechin gallate, and temozolomide has demonstrated potential synergistic effects [160]. The concept of this combination strategy is also reflected in overcoming drug resistance in EGFR-mutated cancers. Combining new-generation EGFR tyrosine kinase inhibitors with immunotherapy or anti-angiogenic drugs is considered an important direction for improving patient prognosis [161].

Regarding the issue of multidrug resistance in lung cancer, the emerging treatment strategies are two-pronged. On the one hand, new-generation targeted drugs (such as KRAS G12C inhibitors and bispecific antibodies) are being developed. On the other hand, existing drugs (such as statins and disulfiram) are repurposed to target non-oncogenic vulnerabilities associated with drug resistance (such as autophagy and metabolic reprogramming). These repurposed drugs can serve as chemotherapy sensitizers to enhance the efficacy of tyrosine kinase inhibitors and immunotherapy [162]. Artificial intelligence plays a central role in optimizing these combination strategies. It can utilize high-throughput multi-omics data to provide information for the rational design of combination therapies and promote oncology to go beyond the limitations of single-target therapies through drug discovery and repositioning, response prediction, and clinical trial optimization [159].

Strengthen interdisciplinary collaboration and real-world evidence collection

To promote the successful translation of "old drugs for new uses" in cancer combination therapies, it is urgent to strengthen interdisciplinary cooperation and systematically collect real-world evidence. This requires the establishment of a close collaborative network among oncologists, pharmacologists,

computational biologists, medicinal chemists, and regulatory agencies to jointly build shared data platforms and biobanks [163]. For example, the design and implementation of precision oncology platform trials (such as the POP trial) are a prime example of such interdisciplinary and multi-institutional cooperation. It provides targeted treatment opportunities based on molecular alterations for patients with advanced malignancies through a structure similar to a drug rediscovery protocol and integrates clinical research into cancer care [164].

At the data level, retrospective analysis using real-world big data (such as electronic health records and medical insurance databases) can provide preliminary efficacy signals for promising drug repurposing combinations, thereby guiding the design of prospective clinical trials [165]. Large-scale biobanks associate genomic data with electronic health record data, and the availability of various public databases containing biological and clinical information provides rich resources for drug repurposing research using genomic data [165]. Organizations such as the Italian Foundation for the Network of Cancer Biotherapy have held expert think-tank meetings to bring together the wisdom from multiple parties in the field of immuno-oncology, review the current experience of immunotherapy, and plan new clinical studies. These meetings have emphasized the use of different methods such as artificial intelligence to find the most promising combination therapy partners [160].

In the aspect of clinical decision support, systems such as OncoPDSS integrate actionable evidence from multiple well-known resources. They can classify potentially effective and ineffective drug therapies centered on treatment based on the multi-omics alterations uploaded by users, and list relevant clinical trial information, thus assisting clinicians in making treatment decisions [166]. This closed-loop process from RWD to a structured knowledge base and then to clinical decision support has greatly accelerated the acquisition and application of precision oncology knowledge [163]. Ultimately, by strengthening cooperation and evidence collection, an iterative cycle from computational prediction, pre-clinical validation to real-world feedback can be constructed to continuously optimize the repositioning strategy, enabling it to benefit cancer patients more efficiently and safely.

Promote the regulatory and policy framework for "repurposing old drugs"

To fully exploit the potential of "repurposing old drugs" in cancer treatment, it is necessary to establish a corresponding regulatory and policy framework. Currently, the regulatory pathways are mainly targeted at new molecular entities. For the development of new indications for approved drugs, although the known safety data can accelerate the process, the evidence standards and approval procedures still need to be clarified and optimized [1]. Regulatory authorities need to develop flexible guidelines to recognize the research results based on real-world evidence, adaptive clinical trial designs, or biomarker-enriched populations, especially for refractory cancers with a limited number of patients [84]. At the policy level, data sharing should be encouraged, a public database containing drug repositioning candidate drugs should be established, and economic incentives such as tax incentives, R&D subsidies, or market exclusivity for new indications should be considered to attract pharmaceutical companies to invest [5]. Through regulatory science innovation and policy support, a more efficient and collaborative ecosystem can be built to accelerate the delivery of safe and effective "repurposing old drugs" solutions to cancer patients.

Reflections on translational failures

A critical and often overlooked question in drug repurposing is: why do many promising preclinical synergies fail to translate into clinical benefits? A systematic reflection on past failures reveals several recurring themes. First, the lack of robust predictive biomarkers is a primary culprit [69]. Without a tool to select patients whose tumors harbor the specific vulnerability being targeted, any potential efficacy signal is diluted in an unselected population. The failure of CQ/HCQ as an autophagy inhibitor in several phase II trials exemplifies this; despite robust preclinical evidence, the absence of a reliable biomarker to measure autophagy inhibition in patients made it impossible to confirm target engagement or optimize dosing [69]. Second, the reliance on simplistic preclinical models that do not recapitulate the complex human TME leads to an overestimation of efficacy. The immunosuppressive, hypoxic, and acidic TME can profoundly dampen

drug activity, a factor often missed in standard 2D cell culture. Third, inadequate clinical trial design, particularly the failure to account for the interaction between repurposed drugs and standard-of-care therapies (e.g., pharmacokinetic interactions), often results in unexpected toxicities or suboptimal drug exposure [147]. Finally, the heterogeneity of the patient population in terms of prior treatments, comorbidities, and performance status often creates a "noise" that obscures a genuine, yet modest, synergistic effect [147]. Moving forward, the integration of pharmacodynamic biomarkers, PDTO models for patient stratification, and adaptive trial designs is essential to de-risk the clinical translation of promising repurposed combinations and to ensure that a failure is genuinely due to a lack of efficacy, rather than a failure of the translational strategy itself.

Conclusions

The rise of the "repurposing old drugs" strategy in the field of cancer combination therapy marks a shift in the paradigm of cancer treatment from solely relying on the development of new drugs to the systematic integration that maximizes the value of existing drugs. From an expert's perspective, the core value of this strategy lies not only in its high cost- and time-saving advantages but also in its profound reflection of the renewed understanding of the complexity of tumor biology. Tumors are not isolated entities; their occurrence and development are closely intertwined with the overall physiological and pathological networks of the body, including metabolism, immunity, nerves, and inflammation. Therefore, using non-oncology drugs such as metabolic regulators, neuroactive drugs, and anti-inflammatory drugs for intervention is essentially a multi-dimensional reshaping of the "soil" on which tumors depend, thus forming a synergistic effect that complements the mechanisms of traditional therapies directly targeting tumor cells. This synergy goes beyond simple efficacy superposition and may break through the dilemma of drug resistance in existing therapies by interfering with metabolic dependence, reversing immune suppression, and inducing non-typical cell death such as ferroptosis.

However, translating this promising scientific concept into a clinical reality that benefits patients widely still requires a prudent balance between opportunities and challenges. On one hand, the integration of technologies such as patient-derived organoids, artificial intelligence, and multi-omics analysis is propelling drug repositioning into an era of "precision screening", which is expected to identify patient subgroups most likely to benefit and discover predictive biomarkers. This is the key to overcoming heterogeneity in clinical translation. On the other hand, we must face its inherent obstacles: insufficient commercial incentives for off-patent drugs may impede large-scale, high-quality clinical trials; re-evaluation of the known safety profile in the new context of combination therapy is crucial; and how to design sophisticated trials to confirm synergistic effects rather than simple additive effects.

Looking ahead, breakthroughs in this field will highly depend on the in-depth integration of multiple disciplines and technologies. Advances in computational biology, artificial intelligence, and machine learning models have made it possible to predict and optimize drug combinations from massive multi-omics data. Meanwhile, adopting adaptive clinical trial designs and integrating reasonable biomarkers to drive patient selection is the only way to achieve precision and high efficiency in the "repurposing old drugs" strategy. Novel delivery systems such as nanotechnology can enhance the targeted accumulation of drugs at tumor sites, improve efficacy, and reduce systemic toxicity. Systematically collecting and analyzing real-world evidence to supplement the deficiencies of randomized controlled trials provides a dynamic and long-term evidence-based basis for the optimization of treatment strategies.

In summary, by systematically exploring and integrating existing drug resources and optimizing their applications with cutting-edge technologies, "repurposing old drugs" is expected to become a crucial engine for enriching the arsenal of cancer combination therapies and propelling tumor treatment into a more efficient and accessible new stage. Ultimately, with lower development costs and faster translation speeds, it will provide global cancer patients with more effective, accessible, and personalized combination therapy options. This is not only an innovation in the technological approach but also an important evolution in the concept of clinical practice.

Looking forward, drug repurposing is positioned to expand rather than diminish in scope and impact. Several converging forces are actively clearing the historical financial and regulatory bottlenecks that have hindered this field. First, concerted efforts from governmental funding agencies and regulatory bodies are increasingly recognizing the value of drug repurposing, creating a more favorable environment for investment and innovation in this area. Second, regulatory frameworks are evolving to facilitate repurposing efforts, with initiatives aimed at updating labeling information and reducing uncertainty around existing drug use in new indications. Third, AI-driven high-throughput screening platforms and multi-omics integration are dramatically accelerating the identification of repurposing candidates, enabling systematic rather than serendipitous discovery [18, 100, 108, 151]. These developments, combined with the inherent cost and time advantages of repurposing over de novo drug development, suggest that the "old drugs for new uses" paradigm will become an increasingly integral component of the oncology therapeutic arsenal.

Abbreviations

AMPK: AMP-activated protein kinase

BBB: blood-brain barrier

CAFs: cancer-associated fibroblasts

CED: convection-enhanced delivery

CMap: Connectivity Map

CNS: central nervous system

COX-2: cyclooxygenase-2

CPS: combined positive score

CQ: chloroquine

CSCs: cancer stem cells

DLBCL: diffuse large B-cell lymphoma

ECM: extracellular matrix

EGFR-TKIs: epidermal growth factor receptor tyrosine kinase inhibitors

HCQ: hydroxychloroquine

HDACi: histone deacetylase inhibitors

HIF-1α: hypoxia-inducible factor-1α

MDSCs: myeloid-derived suppressor cells

mTOR: mechanistic target of rapamycin

ncRNA: non-coding RNA

NSAID: non-steroidal anti-inflammatory drug

NSCLC: non-small cell lung cancer

PARP: poly(ADP-ribose) polymerase

PD-L1: programmed death ligand 1

PDTO: patient-derived tumor organoid

PGE2: prostaglandin E2

P-gp: P-glycoprotein

PPP: public-private partnerships

ROS: reactive oxygen species

RWD: real-world data

TAMs: tumor-associated macrophages

TME: tumor microenvironment

Declarations

Author contributions

JY: Conceptualization, Writing—original draft, Writing—review & editing. XW: Conceptualization, Writing—original draft, Writing—review & editing. XZ: Investigation, Writing—review & editing. SZ: Investigation, Writing—review & editing. DX: Validation, Writing—review & editing. ZT: Validation, Writing—review & editing. ZY: Formal analysis, Writing—review & editing. CZ: Supervision, Project administration, Writing—review & editing, Funding acquisition. All authors read and approved the submitted version.

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The authors declare that they have no conflicts of interest.

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