

Chapter

Disease-Oriented Drug Repurposing in Lung Cancer: Targeting Metabolic Plasticity and Therapy Resistance

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Abstract

Lung cancer, particularly non-small cell lung cancer (NSCLC), remains a major clinical challenge because of its profound molecular heterogeneity, metabolic adaptability, and rapid development of therapeutic resistance. Although targeted therapies and immune checkpoint inhibitors have significantly improved patient outcomes, durable responses remain limited due to adaptive tumor evolution and metabolic rewiring. This chapter discusses disease-oriented drug repurposing as an emerging therapeutic framework that targets broader biological processes rather than isolated genetic alterations. By integrating findings from cancer metabolism, systems biology, network pharmacology, bioinformatics, and translational oncology, the chapter highlights how approved non-oncology drugs can be repurposed to modulate metabolic plasticity, tumor microenvironment dynamics, oxidative stress adaptation, autophagy, and resistance-associated signaling pathways. Particular emphasis is placed on combination therapeutic strategies, computational drug discovery, biomarker-guided approaches, and precision repurposing models. Collectively, disease-oriented repurposing represents a biologically rational and cost-effective strategy with substantial potential to improve therapeutic durability and overcome resistance in lung cancer, particularly when integrated with biomarker-guided patient selection, clinical validation, and careful consideration of translational barriers.

Keywords: lung cancer, drug repurposing, metabolic reprogramming, metabolic plasticity, therapy resistance

1. Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide and continues to impose a substantial global health burden, despite major advances in

diagnosis and treatment [1, 2]. Recent global cancer statistics indicate that lung cancer accounts for nearly one-fifth of cancer-related deaths, largely because many patients are diagnosed at advanced stages and eventually develop resistance to available therapies [1]. Although molecular diagnostics, targeted therapies, immunotherapy, and early detection strategies have improved clinical management, prognosis remains poor for many patients with advanced disease [2, 3].

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers and includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [3, 4]. SCLC is less common but is characterized by rapid proliferation, early metastatic dissemination, and aggressive clinical behavior [3]. One of the main biological characteristics of lung cancer is its high molecular and metabolic heterogeneity, which largely determines the variability of the response to therapy and the rapid development of drug resistance [5].

The identification of oncogenic driver alterations in Epidermal Growth Factor Receptor (EGFR), Anaplastic Lymphoma Kinase (ALK), c-ROS Oncogene 1 Receptor Tyrosine Kinase (ROS1), Rearranged During Transfection (RET), Mesenchymal–Epithelial Transition Factor (MET), and Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) has radically changed the therapeutic landscape of lung cancer over the last 20 years [6–8]. Tyrosine kinase inhibitors (TKIs) directed against these molecular aberrations have dramatically improved progression-free survival and quality of life in selected patient populations [7]. Similarly, immune checkpoint inhibitors targeting programmed death receptor-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) have transformed treatment strategies for advanced NSCLC [9, 10].

However, the remarkable adaptive capacity of lung tumors still limits durable responses [11, 12]. Under therapeutic pressure, cancer cells are continuously remodeling signaling pathways, metabolic programs, and interactions with the tumor microenvironment [13, 14]. These adaptive processes allow tumor cells to survive in conditions of hypoxia, nutrient deprivation, oxidative stress, and drug exposure, ultimately resulting in progression and relapse [15, 16].

Among the emerging hallmarks of cancer, metabolic reprogramming has gained increasing attention as a critical driver of tumor survival and therapeutic resistance [5, 13, 15]. Unlike normal cells, cancer cells exhibit large-scale metabolic reprogramming to support fast proliferation, biosynthesis, redox balance, and stress adaptation [16, 17]. Lung cancer cells dynamically rewire glucose, lipid, amino acid, and mitochondrial metabolism in response to hypoxia, nutrient deprivation, oxidative stress, and therapeutic pressure [14, 18]. Metabolic plasticity is a remarkable characteristic of lung tumors, allowing them to rapidly switch between glycolysis, oxidative phosphorylation, glutamine metabolism, lipid use, and autophagy depending on environmental conditions and treatment exposure [15, 18]. This phenomenon, commonly referred to as “metabolic plasticity,” is increasingly recognized as a central mechanism underlying therapeutic resistance [15, 18]. This metabolic plasticity supports rapid proliferation, redox balance, immune evasion, and microenvironmental adaptation, while also contributing to resistance against chemotherapy, targeted therapies, radiotherapy, and immunotherapy [9, 15, 19, 20]. Consequently, metabolic adaptation is increasingly viewed as a therapeutically exploitable vulnerability in lung cancer.

The metabolic phenotype of lung cancer is shaped by both intrinsic oncogenic signaling and extrinsic microenvironmental pressures. Alterations in KRAS, MYC,

EGFR, TP53, STK11, and KEAP1 directly influence glucose uptake, mitochondrial activity, oxidative stress responses, and anabolic metabolism [14, 15]. In parallel, hypoxia, inflammatory cytokines, immune suppression, and stromal interactions within the tumor microenvironment further reinforce metabolic adaptation and therapeutic escape [14, 19, 21]. At the same time, hypoxia, inflammatory cytokines, immune suppression, and stromal interactions in the tumor microenvironment promote metabolic adaptation and therapeutic escape [11, 20].

The conventional model of cancer treatment has mainly focused on targeting single molecular alterations. However, the clinical limitations of highly selective approaches have become apparent, particularly in biologically heterogeneous tumors, such as lung cancer [22, 23]. Tumors often develop secondary resistance mutations or bypass signaling pathways that circumvent therapeutic inhibition [7, 12, 20]. This has stimulated interest in more general disease-specific therapeutic approaches that can target adaptive cellular mechanisms common to several tumor subtypes.

In this respect, drug repurposing has become a desirable and economical approach in modern oncology [24, 25]. Drug repurposing or repositioning is the discovery of new anticancer uses for drugs that have already been approved or are under investigation for non-oncologic indications [24, 26, 27]. Repurposing has advantages over classical drug development, such as lower development costs, shorter translational timelines, and well-characterized safety profiles [24]. However, successful clinical translation requires more than biological plausibility; it depends on appropriate dosing, pharmacokinetic feasibility, biomarker-defined patient selection, and rigorous clinical validation.

Interestingly, a number of drugs not used in oncology have demonstrated anticancer activity by targeting cellular metabolism, mitochondrial function, inflammation, oxidative stress responses, autophagy, and immune signaling [28, 29]. For example, metformin inhibits mammalian target of rapamycin (mTOR) signaling and diminishes mitochondrial complex I activity, leading to impaired tumor proliferation and metabolic adaptation [28, 30]. Statins inhibit the mevalonate pathway and prenylation-dependent oncogenic signaling. Antiparasitic agents such as niclosamide and ivermectin target mitochondrial metabolism and cancer stem cell (CSC) survival [31, 32]. Similarly, autophagy inhibitors such as hydroxychloroquine can interfere with stress-adaptive survival pathways in resistant tumors [29, 33].

It is worth mentioning that disease-oriented drug repurposing is conceptually different from mutation-centered therapeutic methodologies. Disease-oriented strategies target broad hallmarks of cancer biology (rather than specific genomic alterations), including metabolic reprogramming, adaptation to oxidative stress, chronic inflammation, hypoxia signaling, immune suppression, and cellular plasticity [5, 34, 35]. Because these biological processes are common to a number of molecular subtypes, repurposed drugs may be more broadly useful and potentially provide more durable treatment effects.

Recent advances in systems biology, network pharmacology, artificial intelligence (AI), and multi-omics technologies have further accelerated repurposing research [34, 36]. Computational approaches now allow the integration of genomic, transcriptomic, proteomic, metabolomic, and clinical datasets to identify disease-associated networks and to predict drug–target interactions [34, 37]. These technologies have greatly contributed to the knowledge

of the adaptive systems underlying the progression of lung cancer and have allowed the identification of multitarget therapeutic strategies capable of overcoming resistance mechanisms.

This chapter highlights the emerging role of disease-oriented drug repurposing in lung cancer, with an emphasis on metabolic plasticity and therapy resistance. The discussion includes the most recent evidence in cancer metabolism, systems biology, network pharmacology, computational drug discovery, and translational oncology. Disease-focused repurposing, targeting adaptive biological processes instead of only individual oncogenic mutations, may provide a more complete and clinically efficacious strategy for future lung cancer treatment.

In addition to summarizing available evidence, the chapter critically discusses the limitations of repurposed agents, translational barriers, biomarker-guided selection, and the need for precision repurposing strategies in clinically heterogeneous lung cancer populations.

2. Genomic heterogeneity, tumor evolution, and metabolic reprogramming in lung cancer

A major challenge in lung cancer management is the considerable heterogeneity that exists between patients and within individual tumors [22, 23]. Lung cancers are composed of multiple subclonal populations that are constantly evolving under the selective pressure of therapeutic interventions and the tumor microenvironment [11, 22]. This active process of evolution is directly linked to metastasis, drug resistance, and disease relapse. Lung carcinogenesis is a multistep process, with progressive accumulation of genetic and epigenetic alterations in pathways regulating proliferation, apoptosis, DNA repair, immune regulation, and cellular metabolism [3, 5]. The most common oncogenic drivers in NSCLC are activating mutations in EGFR and KRAS, whereas tumor suppressor genes such as *TP53*, *STK11*, *KEAP1*, and *RB1* are frequently inactivated [3, 6]. Importantly, these are rarely changed in a vacuum. Instead, tumors acquire a complex network of molecular aberrations that, in concert, determine tumor phenotype, metastatic potential, and drug sensitivity [22].

Tumor evolution is strongly influenced by hypoxia, nutrient limitation, oxidative stress, inflammation, and exposure to anticancer therapies [14, 15]. Under these conditions, resistant cellular populations are selected through both genetic evolution and metabolic adaptation [23]. For example, EGFR-mutant tumors treated with TKIs frequently acquire secondary resistance mutations, such as T790M or activate bypass signaling pathways involving MET, HER2, or KRAS [12, 23, 38]. These adaptive mechanisms explain why therapies directed against single molecular targets often produce only transient clinical benefits.

Metabolic reprogramming is another defining feature of lung cancer biology [5, 13]. Cancer cells undergo extensive metabolic rewiring to support proliferation, biosynthesis, redox homeostasis, and survival under stressful conditions [15, 16]. In lung cancer, metabolic activity is directly regulated by oncogenic signaling pathways. KRAS activation promotes glycolysis, MYC enhances glutamine metabolism and mitochondrial biogenesis, while TP53 loss alters oxidative stress responses and mitochondrial respiration [15, 16]. Likewise, STK11/LKB1 deficiency

is strongly associated with altered energy metabolism and therapeutic resistance [39].

Hypoxia also induces metabolic adaptation through activation of hypoxia-inducible factor-1 alpha (HIF-1 α), leading to glycolysis, lactate production, angiogenesis, and glucose transporter expression [14, 15]. Metabolic reprogramming also contributes to immune suppression, autophagy induction, oxidative stress tolerance, and resistance to chemotherapy, targeted therapy, and immunotherapy [9, 19, 20, 22].

Genomic instability, tumor evolution, and metabolic plasticity contribute to the generation of highly plastic tumor populations that are difficult to eradicate by classical single-target strategies [22]. These observations have further increased interest in disease-oriented therapeutic strategies and drug repurposing approaches targeting broader adaptive survival mechanisms in lung cancer [24, 27, 28, 34, 40].

2.1 Aerobic glycolysis and the warburg effect

The Warburg effect was one of the early metabolic hallmarks of cancer, first described by Otto Warburg [41] in the 1920s. Warburg observed that cancer cells prefer to convert glucose to lactate, even in the presence of adequate oxygen – a phenomenon that is now known as aerobic glycolysis [17, 41].

Under normal physiological conditions, healthy cells predominantly depend on mitochondrial oxidative phosphorylation because it produces orders of magnitude more ATP per molecule of glucose [17]. In contrast, cancer cells often rely on glycolysis, although it is energetically less efficient [17, 42]. Although initially considered paradoxical, the Warburg effect is now understood to provide biological advantages that support tumor progression and adaptation [13, 17, 43].

Glycolytic metabolites are the first precursors for biosynthetic pathways for nucleotide, amino acid, and lipid synthesis [17]. Second, lactate accumulation acidifies the tumor microenvironment, resulting in extracellular matrix degradation, angiogenesis, invasion, and immune evasion [19, 21]. Third, glycolytic metabolism allows fast adaptation to the varying oxygen availability in the poorly vascularized areas of the tumor [13, 14].

Increased glucose uptake in lung cancer is frequently observed in imaging with fluorodeoxyglucose positron emission tomography (FDG-PET) [6, 44]. Increased expressions of glucose transporters, such as GLUT1 and glycolytic enzymes, such as hexokinase 2 (HK2), pyruvate kinase M2 (PKM2), and lactate dehydrogenase A (LDHA), have been associated with aggressive disease behavior and poor prognosis [13, 45].

Of note, aerobic glycolysis is a direct contributor to resistance to therapy [11, 46]. Glycolytic tumors often have enhanced antioxidant defenses, resistance to apoptosis, and increased tolerance to hypoxic stress [11, 15]. In addition, tumor microenvironments rich in lactate inhibit cytotoxic T-cell activity and favor the accumulation of immunosuppressive cell populations, resulting in decreased antitumor immunity [19].

These findings have highlighted glycolytic metabolism as a relevant therapeutic target in lung cancer. Some repurposed drugs, such as metformin, aspirin, and statins, have shown the capacity to alter glucose metabolism and improve treatment response in preclinical studies [28, 47].

2.2 Lipid, amino acid, and mitochondrial metabolism in lung cancer

Besides glucose metabolism, lung cancer cells are more dependent on lipid metabolism, amino acid utilization, and mitochondrial function to survive and progress [15, 16]. Rapid proliferation requires membrane components, signaling molecules, and alternative energy sources, all of which are provided by increased fatty acid synthesis and β -oxidation [18]. Lung tumors frequently overexpress enzymes such as fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC), which are associated with aggressive tumor behavior [15].

In addition, glutamine metabolism is crucial to the biology of lung cancer [15, 16]. Glutamine is a major source of carbon and nitrogen for nucleotide synthesis, antioxidant defense, and replenishment of tricarboxylic acid (TCA) cycle intermediates [16]. A fraction of lung cancers are significantly addicted to glutamine metabolism, which has been termed “glutamine addiction” [15].

Mitochondria continue to play a role in highly glycolytic tumors because they regulate ATP production, the generation of reactive oxygen species (ROS), apoptosis signaling, and adaptation to stress [16, 42]. Importantly, therapy-resistant populations and cancer stem-like populations often increase their dependence on oxidative phosphorylation as a compensatory survival mechanism upon exposure to chemotherapy or targeted therapy [11, 15].

2.3 Metabolic plasticity and therapeutic adaptation

Striking plasticity is a hallmark of lung cancer metabolism [14, 15, 17]. Depending on oxygen availability, nutrient supply, and therapeutic stress, tumor cells can dynamically switch between glycolysis, oxidative phosphorylation, fatty acid oxidation, glutamine utilization, and autophagy [15, 17]. This metabolic flexibility allows cancer cells to survive in harsh microenvironmental conditions and is one of the main causes of therapy failure. This metabolic adaptation is further reinforced by hypoxia, inflammatory signaling, stromal interactions, and nutrient competition in the tumor microenvironment [14, 17, 21, 48]. Therefore, tumors can frequently exploit alternative energy pathways when one metabolic pathway is therapeutically blocked [11, 46]. This explains why targeting a single metabolic pathway often results in transient therapeutic responses. The close relationship between metabolic plasticity and therapy resistance renders metabolism an increasingly attractive therapeutic target [46, 49]. Several repurposed drugs exert antitumor effects by interfering with adaptive metabolic pathways. Metformin and phenformin inhibit mitochondrial complex I activity, statins inhibit lipid biosynthesis by blocking the mevalonate pathway, and doxycycline inhibits mitochondrial protein synthesis [28, 50, 51]. The dynamic interactions among these metabolic pathways and their contribution to therapeutic adaptation are summarized in **Figure 1**.

Collectively, metabolic plasticity provides lung cancer cells with a survival advantage under therapeutic stress. Rather than representing a single pathway, it reflects an adaptive network involving glycolysis, oxidative phosphorylation, lipid metabolism, glutamine utilization, and autophagy. This network-level behavior supports the rationale for disease-oriented drug repurposing strategies that target multiple metabolic dependencies simultaneously [20, 28, 34].

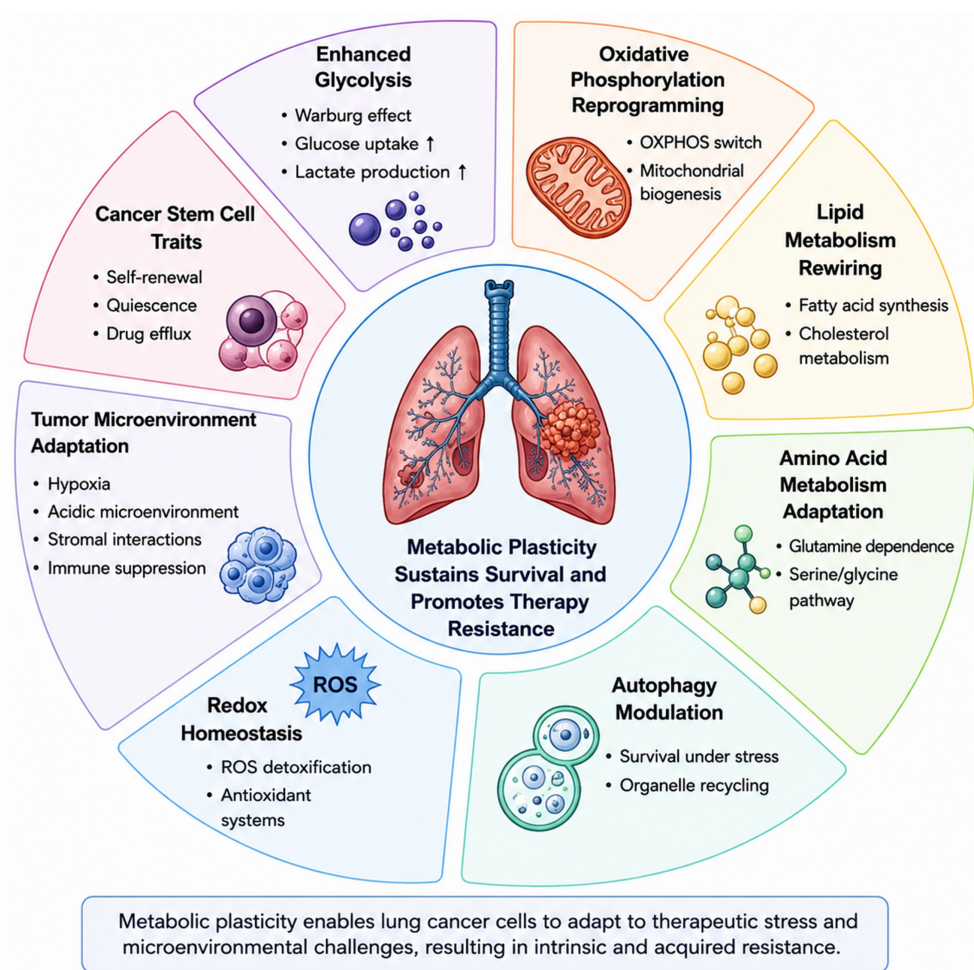


Figure 1. *Metabolic plasticity and therapy resistance in lung cancer. Metabolic plasticity enables lung cancer cells to dynamically switch between glycolysis, oxidative phosphorylation, lipid metabolism, glutamine utilization, and autophagy in response to hypoxia, nutrient deprivation, oxidative stress, and therapeutic pressure. These adaptive metabolic transitions support tumor survival, cancer stemness, immune evasion, and resistance to chemotherapy, targeted therapy, radiotherapy, and immunotherapy, highlighting metabolic adaptation as a central therapeutic vulnerability.*

3. Mechanisms of therapy resistance in lung cancer

Despite major therapeutic advances, therapy resistance remains a significant obstacle to achieving durable clinical responses and long-term survival in lung cancer [11, 12, 22]. Although many patients initially respond to chemotherapy, targeted therapy, radiotherapy, or immunotherapy, tumors frequently develop adaptive mechanisms to survive under therapeutic pressure [9, 11]. Resistance is mediated by genetic mutations, epigenetic modulations, metabolic reprogramming, remodeling of the tumor microenvironment, immune escape, and cellular plasticity [14, 15, 17].

Resistance development is a mirror of the evolutionary nature of lung cancer. During treatment, sensitive tumor cells are eliminated, whereas resistant subclones

survive and expand under selective therapeutic pressure [22]. Simultaneously, cancer cells activate stress-response pathways that support metabolic flexibility, oxidative-stress tolerance, and prosurvival signaling [15]. These interconnected processes ultimately give rise to highly plastic tumor populations capable of escaping various therapeutic modalities [11, 22].

3.1 Resistance to chemotherapy

Chemotherapy remains a mainstay of treatment for advanced NSCLC and SCLC, but its long-term efficacy is often limited by intrinsic and acquired resistance [3, 6]. One important mechanism of resistance is increased DNA repair capacity. Platinum-based agents cause DNA damage, but tumor cells resistant to these agents frequently enhance nucleotide excision repair and homologous recombination pathways, allowing survival after severe genomic damage [11]. Excision repair cross-complementation group 1 (ERCC1) has been significantly associated with platinum resistance in NSCLC [11].

The drug efflux transporters are another major player in chemoresistance. The overexpression of ATP-binding cassette (ABC) transporters, such as P-glycoprotein and multidrug resistance-associated proteins (MRPs), causes a decrease in the intracellular accumulation of cytotoxic drugs [11]. Changes in apoptotic signaling (e.g., loss of TP53, overexpression of BCL-2, activation of PI3K/AKT signaling) result in resistance to cell death caused by chemotherapy [11, 23].

Metabolic adaptation also contributes to chemoresistance. Resistant tumor cells often upregulate glycolysis, glutamine metabolism, antioxidant defenses, and mitochondrial flexibility to overcome the oxidative stress caused by cytotoxic therapy [14, 15, 17]. Hypoxia, inflammatory cytokines, interactions with the stroma, and immune suppression within the tumor microenvironment also promote resistant phenotypes [14, 17].

Chemoresistance is a complex process involving various genetic, metabolic, and microenvironmental adaptations [11, 22].

3.2 Resistance to EGFR and ALK-targeted therapies

Targeted therapies against EGFR mutations and ALK rearrangements have significantly improved the outcomes in selected NSCLC patients [6, 7, 12]. However, treatment almost inevitably leads to the development of resistance [12].

The development of secondary mutations in the EGFR kinase domain is among the best-characterized mechanisms of resistance in EGFR-mutant NSCLC [38]. The T790M mutation is often the driver of resistance to first-generation EGFR inhibitors, while mutations such as C797S may drive resistance to third-generation agents such as osimertinib [38]. Tumors may activate bypass signaling pathways (e.g., amplification of MET, activation of HER2, mutations of KRAS, or PI3K/AKT/mTOR signaling) and become less dependent on the activity of EGFR [12, 23, 38].

In ALK-positive tumors, secondary ALK mutations or activation of alternative proliferative pathways that reduce sensitivity to ALK inhibitors are also common [7]. In some cases, EGFR-mutant adenocarcinomas can undergo histological transformation to small cell lung cancer following prolonged targeted therapy, with aggressive clinical behavior and limited response to therapy [38].

Importantly, resistance to targeted therapy is not only genetic [15, 52]. Importantly, resistance to targeted therapy is not exclusively genetic. Epithelial-to-mesenchymal transition (EMT), autophagy activation, metabolic rewiring, and interactions with the tumor microenvironment also contribute substantially to therapeutic escape [20, 52]. Resistant tumors switch to oxidative phosphorylation to maintain ATP production as a compensatory survival mechanism when oncogenic pathways are inhibited [15, 46].

These findings emphasize the necessity of combinational therapeutic strategies that simultaneously target oncogenic drivers and adaptive survival mechanisms in resistant lung cancer [20, 34].

3.3 Adaptive resistance to immunotherapy

Immune checkpoint inhibitors against PD-1, PD-L1, and CTLA-4 have revolutionized the treatment of advanced lung cancer, but many patients experience primary or acquired resistance [9, 10]. An important mechanism is the defective presentation of antigens by tumor cells through the downregulation of MHC-I molecules or components of the antigen-processing machinery, leading to decreased recognition of the tumor by cytotoxic T lymphocytes [9]. Defects in interferon signaling may also impair immune activation and response to checkpoint blockade [9].

In addition, the tumor microenvironment is also important for immune resistance [19]. Tumors are enriched with immunosuppressive populations such as regulatory T cells, tumor-associated macrophages, and myeloid-derived suppressor cells, which suppress effective antitumor immunity [19]. Meanwhile, metabolic competition impairs the function of immune cells, as highly active tumor cells consume large amounts of glucose, amino acids, and oxygen, starving immune cells of the necessary metabolic resources [15, 19]. Beyond immune-cell exclusion and checkpoint activation, immunotherapy resistance is strongly shaped by metabolic dysfunction within the tumor microenvironment. Activated cytotoxic T cells require adequate glucose, amino acids, oxygen, and mitochondrial fitness to sustain proliferation, cytokine production, and tumor-cell killing. Highly glycolytic lung cancer cells compete for these nutrients and generate lactate-rich, acidic microenvironments that impair CD8⁺ T-cell effector function, promote T-cell exhaustion, and support immunosuppressive populations such as regulatory T cells and tumor-associated macrophages [19, 21, 48]. This metabolic competition creates a direct connection between tumor metabolism and checkpoint resistance, suggesting that restoration of immune-cell metabolic fitness may be necessary to improve responses to PD-1/PD-L1 blockade [53, 54].

Other tumors evade immunotherapy through the upregulation of alternative immune checkpoint pathways, decreased neoantigen expression, or stromal remodeling that impairs immune-cell infiltration [9]. These findings suggest that overcoming immunotherapy resistance will likely require more comprehensive therapeutic strategies to target metabolism, immune suppression, and adaptive signaling networks simultaneously [10, 19].

Therefore, it should not be viewed only as a failure of antigen recognition or checkpoint inhibition. It also reflects a metabolic imbalance in which tumor cells dominate nutrient use, acidify the microenvironment, and functionally exhaust antitumor immune cells.

3.4 CSCs and cellular plasticity

CSCs are a small but highly aggressive subpopulation of tumor cells with the ability for self-renewal, differentiation, and long-term tumor propagation [20]. In lung cancer, CSCs are highly associated with metastasis, recurrence, and therapy resistance. These cells are often relatively quiescent and less sensitive to chemotherapy and radiotherapy, which mainly target rapidly dividing cells [20].

CSCs have also been shown to possess increased DNA repair capacity, antioxidant defenses, and drug efflux activity [20]. Importantly, non-stem tumor cells can gain stem-like properties after therapeutic stress via processes such as EMT [52]. EMT facilitates invasion, metastasis, resistance to apoptosis, and metabolic adaptation [52].

CSCs are characterized by remarkable metabolic plasticity [15, 20]. CSCs can switch from glycolysis to oxidative phosphorylation to survive according to the environmental conditions [15]. Because of their adaptability, CSCs are particularly resistant to elimination by therapies that target single metabolic pathways [46]. Thus, targeting pathways involved in stemness and metabolic plasticity is increasingly considered critical for long-term disease control [20, 34].

3.5 Hypoxia, oxidative stress, and survival signaling

Impaired oxygenation is a common feature of lung tumors due to abnormal vascularization and rapid tumor growth [17, 21]. Under hypoxic conditions, cancer cells activate adaptive signaling pathways mediating survival, angiogenesis, metastasis, and therapy resistance [17]. HIF-1 α (hypoxia-inducible factor-1 alpha) is a central regulator of this response, promoting glycolysis, glucose transport, lactate production, and angiogenesis [15, 17]. Hypoxia also promotes EMT and immune suppression, leading to aggressive tumor behavior [19, 52].

Oxidative stress is also a major player in therapy resistance [15]. It is well known that many anticancer therapies induce ROS-mediated damage. Resistant tumor cells often acquire increased antioxidant capacity, such as through glutathione metabolism and NRF2 signaling, to counteract oxidative stress [17].

At the same time, activation of cell survival pathways such as PI3K/AKT/mTOR, MAPK, NF- κ B, and STAT3 is linked to proliferation, anti-apoptotic effects, and metabolic adaptation [11, 23, 55]. Metabolic reprogramming is closely associated with hypoxia and oxidative stress responses, and therefore, targeting these pathways is an appealing therapeutic strategy [46, 49]. Several repurposed drugs, able to interfere with mitochondrial metabolism, ROS regulation, or stress-adaptive signaling, are under investigation in resistant lung cancer models [20, 32].

3.6 Crosstalk between metabolism and drug resistance

Metabolic reprogramming is closely associated with therapy resistance in lung cancer [15, 46]. Resistance of tumor cells to treatment-induced stress is mediated by alterations in glucose metabolism, mitochondrial activity, lipid synthesis, and amino acid utilization [15, 17]. For instance, EGFR inhibitor-resistant tumors generally enhance their oxidative phosphorylation to exploit alternative energy sources, while chemotherapy-resistant cells enhance their glycolysis and antioxidant production

Resistance mechanism	Key biological features	Therapeutic consequence	Potential repurposing strategy
DNA repair enhancement	ERCC1 upregulation, homologous recombination	Platinum resistance	DNA repair–modulating combinations
Drug efflux activation	ABC transporter overexpression	Reduced intracellular drug accumulation	Efflux/survival pathway modulation
Metabolic rewiring	Glycolysis–OXPHOS switching, glutamine dependence	Survival under therapeutic stress	Metformin, phenformin, atovaquone
Autophagy activation	Stress-adaptive nutrient recycling	Chemotherapy and TKI resistance	Hydroxychloroquine, chloroquine
Cancer stem-cell persistence	Stemness, quiescence, metabolic flexibility	Relapse and metastasis	Doxycycline, niclosamide, ivermectin
Hypoxia adaptation	HIF-1 α activation, lactate accumulation	Immune suppression and radioresistance	Metformin, atovaquone
Immune metabolic exhaustion	Nutrient competition, lactate accumulation, T-cell dysfunction	Immunotherapy resistance	Metformin, aspirin/COX inhibitors, beta-blockers

Table 1.
Major mechanisms of therapy resistance in lung cancer and corresponding repurposing strategies.

[15, 46]. Immunotherapy-resistant tumors also create metabolically suppressive microenvironments that impair immune-cell function and promote immune escape [19].

Furthermore, metabolic pathways are strongly associated with epigenetic regulation and survival signaling networks [52]. Metabolites such as lactate, acetyl-CoA, succinate, and α -ketoglutarate have been shown to modulate the expression of genes associated with resistant phenotypes through chromatin remodeling [15, 52]. Importantly, tumor metabolism is highly dynamic, allowing cancer cells to rapidly switch between metabolic states in response to therapeutic pressure and environmental conditions [15, 17, 51].

This metabolic plasticity results in therapies targeting a single oncogenic pathway generally leading to only transient responses [46]. Therefore, disease-oriented strategies are shifting toward targeting broader metabolic vulnerabilities. Repurposed drugs targeting mitochondrial respiration, glycolysis, lipid metabolism, autophagy, and oxidative stress responses might be beneficial in overcoming resistance and improving the efficacy of existing lung cancer therapies [20, 29, 34] (see **Table 1**).

4. Principles of drug repurposing in oncology

4.1 Definition and historical perspective

Drug repurposing (also called drug repositioning) is the process of identifying new therapeutic uses for drugs developed for other diseases [20, 26]. The benefit of drug repurposing is that these drugs have available safety data, known pharmacokinetics, and available manufacturing processes to help reduce the

development time, cost, and uncertainty in the clinic compared to conventional drug discovery [20, 25].

Several important therapeutic advances have been due to the reuse of these. Thalidomide was developed as a sedative but was subsequently repurposed for multiple myeloma because of its immunomodulatory and antiangiogenic properties [20, 26]. Aspirin has also been of great interest for its possible anticancer properties via modulation of inflammation, platelet activity, and cyclooxygenase signaling [19, 56].

Recently, advances in molecular biology, systems medicine, and network pharmacology have spurred interest in repurposing strategies in oncology [34, 35]. Apart from drugs targeting tumor metabolism, angiogenesis, immune evasion, autophagy, and therapy resistance are also involved in other pathways [20, 56]. Lung cancer is especially a good candidate for this strategy because of its molecular heterogeneity, metabolic plasticity, and high ability for adaptive resistance [13, 14, 22].

However, the success of repurposing should not be evaluated solely based on biological plausibility. Increasing evidence indicates that clinical efficacy depends on appropriate patient selection, biomarker identification, pharmacokinetic optimization, and rational combination strategies.

4.2 Advantages of drug repurposing

The advantages of drug repurposing over conventional anticancer drug development have been described [20, 26]. In general, repurposed agents have faster, cheaper, and lower-risk clinical translation in terms of development because their toxicity and pharmacokinetic profiles are already known [20, 25].

Another important advantage is their multitarget biological activity [34]. Unlike highly selective targeted therapies, many of the repurposed drugs modulate multiple interconnected signaling and metabolic pathways simultaneously and may be especially beneficial in biologically heterogeneous tumors, such as lung cancer [22, 34].

Many repurposed drugs are inexpensive generic drugs that are already integrated into healthcare systems and thus may improve access to treatment globally [20, 56]. Furthermore, these agents present an attractive profile for use in combination therapy. Statins, hydroxychloroquine, and metformin are drugs shown to have the potential to enhance chemotherapy, targeted therapy, and immunotherapy by disrupting metabolic adaptation and survival signaling pathways [28].

But these advantages are not without significant drawbacks. Not all promising preclinical results lead to clinical benefit, and anticancer dosing strategies may be very different from those used in the original indication [20, 25]. However, the transformation of drugs remains an increasingly important strategy in translational oncology [20, 56].

Despite these advantages, drug repurposing also has important limitations. Many compounds demonstrating strong anticancer activity in experimental models have failed to reproduce similar efficacy in clinical trials because of inadequate tumor exposure, pharmacokinetic limitations, biological heterogeneity, or insufficient biomarker-guided patient selection. Therefore, successful repurposing requires both mechanistic rationale and rigorous clinical validation.

4.3 Drug repurposing pipelines and strategies

The modern drug repositioning employs a variety of complementary approaches [20, 34]. Target-based repurposing screens look for approved drugs targeting cancer-associated molecular pathways, while disease-oriented repurposing focuses on more general biological processes such as metabolic plasticity, inflammation, hypoxia adaptation, autophagy, and immune suppression [13, 14, 17, 19].

Another important approach is phenotypic screening, which screens drug libraries in cellular or animal models for compounds that can inhibit proliferation or reverse resistance [20, 57].

Moreover, without the need for prior knowledge of a specific molecular target, network pharmacology is becoming increasingly relevant in lung cancer, as shared resistance cannot be attributed to isolated molecular abnormalities but rather to interconnected signaling and metabolic networks [34, 35]. AI and machine learning are also being utilized to enable repurposing pipelines by integrating genomic, transcriptomic, proteomic, metabolomic, and clinical data to predict drug–disease relationships and identify promising therapeutic candidates [35, 36].

Modern repurposing pipelines increasingly integrate systems biology, network pharmacology, AI, and multi-omics data to prioritize compounds with the highest probability of clinical success, while reducing attrition during translational development.

4.4 Computational and experimental repurposing approaches

Computational biology is now playing a major role in drug repurposing research [34, 58]. Bioinformatics platforms compare disease-related gene expression profiles with drug-induced molecular profiles to identify compounds that reverse cancer-related pathways [58]. These analyses are usually conducted through public databases like TCGA, GEO, DrugBank, LINCS, and Connectivity Map [58, 59].

Molecular docking and virtual screening can be used to predict the interaction of approved drugs with cancer-related targets, and network pharmacology can help identify agents that modulate multiple pathways involved in resistance [20, 34].

However, computational predictions are not enough on their own and need to be validated experimentally [20]. *In vitro* studies, organoids, xenograft models, and genetically engineered mouse models remain crucial for confirming therapeutic activity and biological significance [9, 22, 60]. Finally, well-designed clinical trials are needed to assess efficacy, safety, dosing strategies, and biomarker-guided patient selection [20, 25].

Nevertheless, computational predictions should be considered hypothesis-generating rather than definitive evidence. Experimental validation using organoids, patient-derived xenografts, and prospective clinical studies remains indispensable before clinical implementation.

4.5 Regulatory and clinical considerations

However, drug repurposing is limited by many regulatory and clinical challenges, despite its therapeutic potential [20, 25]. Many of the repurposed drugs are generic

Advantages	Limitations
Reduced development cost	Limited commercial incentives
Established safety profile	Oncology dose may differ
Faster clinical translation	Pharmacokinetic limitations
Known pharmacology	Limited randomized clinical evidence
Combination therapy potential	Biomarker selection required
Cost-effective	Tumor heterogeneity

Table 2.
Advantages and limitations of drug repurposing in oncology.

medicines, and limited patent protection often reduces the commercial incentives for large oncology trials [20]. Therefore, a large part of the research in drug repurposing is supported by academic institutions, non-profit organizations, and public initiatives [20, 56].

Another important issue is the optimization of dose, as the anticancer activity may require concentrations or treatment schedules different from those used for the original indication [20, 25]. Furthermore, the biological heterogeneity of lung cancer implies that not all patients respond equally to the same repurposed therapy [22]. Therefore, biomarker-guided approaches may improve patient selection and therapeutic responsiveness [37, 61].

Moreover, clinical trials are often challenging to design, as these repurposed agents are frequently studied in combination with standard therapies, making it difficult to assess the contributions of single drugs [20]. Still, the rationale for disease-directed repurposing strategies in lung cancer is increasingly supported by an evolving appreciation of metabolic plasticity, tumor evolution, and adaptive resistance [11, 13, 17].

Another important challenge involves regulatory approval for new oncology indications. Since many repurposed agents are inexpensive generic drugs, commercial incentives for conducting large randomized oncology trials remain limited. Consequently, academic collaborations, cooperative clinical trial networks, and public funding initiatives are expected to play an increasingly important role in advancing precision repurposing strategies (see **Table 2**).

5. Disease-oriented drug repurposing framework in lung cancer

5.1 Concept of disease-oriented repurposing

Traditional lung cancer treatment strategies are primarily targeted at specific oncogenic alterations, such as EGFR mutations and ALK rearrangements [7, 12]. However, these strategies are frequently limited by tumor heterogeneity, metabolic adaptation, and resistance acquisition, despite significant progress in patient outcomes [11, 22]. Lung tumors are caused by complex interactions between genetic, metabolic, immune, and microenvironmental factors, rather than a single signaling pathway [15, 17, 52].

Disease-oriented drug repurposing focuses on these broader biological processes rather than individual mutations [20, 34]. This approach targets adaptive

mechanisms, including metabolic reprogramming, oxidative stress response, inflammation, hypoxia signaling, autophagy, immune suppression, and cellular plasticity [13, 17, 20]. These pathways are already targeted by multiple drugs not yet approved for oncology indications. Metformin targets mitochondrial metabolism and AMPK signaling, statins inhibit the mevalonate pathway, and anti-inflammatory agents suppress tumor-promoting inflammatory signaling [19, 28, 62].

These adaptive mechanisms are not unique to a single lung cancer subtype but are seen in several of them, suggesting that a disease-oriented repurposing may provide broader and more durable therapeutic benefits than mutation-specific therapies alone [20, 34]. (see **Figure 1**)

Importantly, disease-oriented repurposing should not be interpreted as a universal treatment strategy. Rather, it provides a biological framework that must be integrated with molecular profiling, metabolic phenotyping, and biomarker-guided patient stratification to maximize therapeutic benefit.

5.2 Targeting hallmarks of lung cancer

The disease-directed drug repurposing is in good agreement with the hallmarks of cancer framework, comprising sustained proliferative signaling, resistance to apoptosis, reprogramming of energy metabolism, angiogenesis, immune evasion, and metastasis [5]. Many repurposed drugs target several of these hallmarks [20, 34].

Metformin inhibits oxidative phosphorylation and mTOR signaling; statins interfere with cholesterol biosynthesis and oncogenic signaling; and aspirin inhibits inflammatory pathways that are involved in tumor progression [19, 28, 62]. Among these hallmarks, metabolic plasticity has emerged as an especially important therapeutic target, as lung tumors constantly reprogram their metabolism under conditions of hypoxia, nutrient deprivation, and therapeutic stress [15, 17].

Therefore, agents that rewire glycolysis, mitochondrial metabolism, lipid synthesis, or autophagy may reduce the adaptive capacity of resistant tumor cells and increase sensitivity to standard therapies [20, 29].

Because these hallmarks are highly interconnected, the simultaneous modulation of several biological processes may produce greater therapeutic benefits than the highly selective inhibition of individual oncogenic drivers.

5.3 Network-based understanding of disease pathways

Lung cancer development and therapeutic resistance are not determined by isolated molecular abnormalities but by interconnected biological networks [34, 35]. Network pharmacology is a systems biology approach that involves the analysis of interactions between genes, proteins, metabolites, signaling pathways, and therapeutic compounds [34].

Metabolic and inflammatory signaling networks are closely linked to key pathways such as EGFR, KRAS, PI3K/AKT/mTOR, HIF-1 α , and MYC [13, 17, 23]. Resistance often occurs via activation of compensatory pathways, thus limiting the benefit of single-molecule targeted therapies [11, 22].

Network-based approaches may allow the identification of critical pathway hubs and common biological vulnerabilities that could be better targeted by multitarget repurposed drugs [34, 35]. They also enable the rational design of combination therapies and more effective identification of promising therapeutic candidates [35, 58]. Rather than replacing conventional precision oncology, network pharmacology complements mutation-based approaches by identifying systems-level vulnerabilities that are not apparent from genomic alterations alone.

5.4 Multi-target therapeutic strategies

Classical targeted therapy is limited by its dependence on single molecular vulnerabilities [12, 38]. Tumors often adapt by activating bypass signaling, metabolic rewiring, or secondary mutations [7, 11].

The appeal of repurposed drugs is that many are broadly multitarget biologically active [20]. Metformin targets mitochondrial metabolism, AMPK signaling, mTOR activity, and immune regulation, while statins and antiparasitic agents target metabolism, inflammation, and CSC pathways [28, 32].

Multitarget effects could be particularly relevant to overcoming metabolic plasticity, whereby tumor cells switch dynamically between glycolysis and oxidative phosphorylation under therapeutic pressure [15, 46]. Thus, combination strategies with repurposed agents and standard therapies may improve treatment efficacy and delay the development of resistance [20, 34, 56].

Nevertheless, multitarget approaches also increase biological complexity. Rational selection of drug combinations should, therefore, be guided by mechanistic evidence, predictive biomarkers, and careful evaluation of pharmacodynamic interactions.

5.5 Precision medicine and systems pharmacology integration

It is likely that the future of disease-oriented repurposing will be based on the combination of precision medicine with systems pharmacology approaches [36, 61]. Genomic information alone is often insufficient to predict response to therapy because lung cancer behavior is modulated by metabolism, immune signaling, epigenetic regulation, and interactions within the tumor microenvironment [34, 37].

Recent advances in multi-omics technologies, single-cell sequencing, AI, and computational biology allow for a more comprehensive characterization of tumor biology [35–37, 60]. These tools may detect patient-specific susceptibilities and forecast responsiveness to repurposed therapies that target metabolic adaptation, inflammation, hypoxia, or oxidative stress pathways [36, 37].

With the advancement of systems biology and precision oncology, disease-oriented repurposing may be a more personalized approach to addressing therapy resistance and metabolic plasticity in lung cancer [34, 36]. The overall conceptual framework of disease-oriented drug repurposing in lung cancer is illustrated in **Figure 2**.

Ultimately, precision repurposing represents the convergence of disease-oriented biology and precision oncology, where treatment selection is based not only on genomic alterations but also on dynamic metabolic states, immune composition, and adaptive signaling networks.

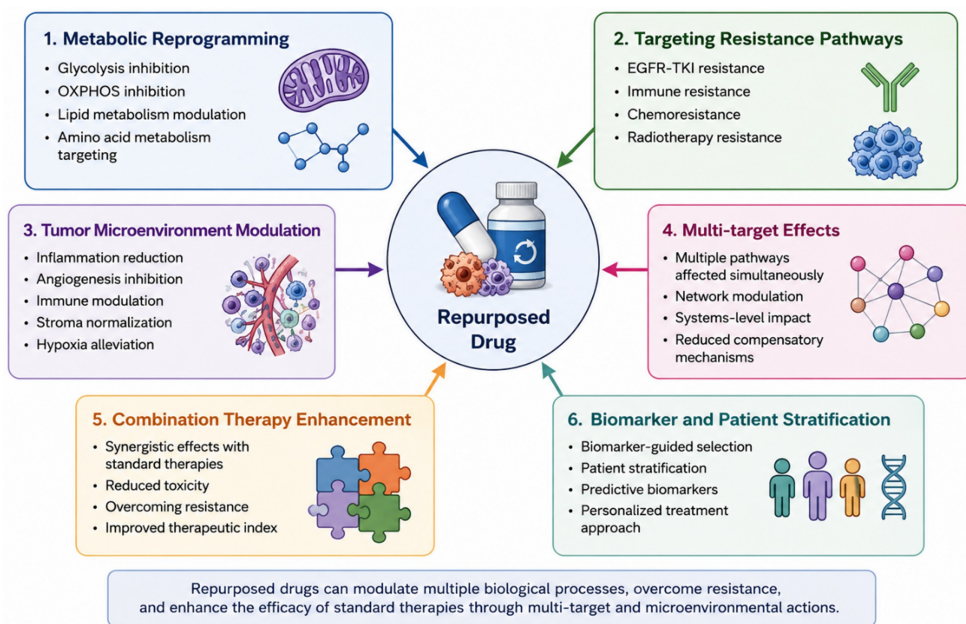


Figure 2. Disease-oriented drug repurposing framework in lung cancer. Disease-oriented drug repurposing targets shared biological processes underlying lung cancer progression rather than individual oncogenic mutations. By integrating metabolic reprogramming, inflammation, hypoxia signaling, oxidative stress, autophagy, immune suppression, and network pharmacology, repurposed drugs simultaneously modulate multiple adaptive pathways, thereby improving therapeutic responsiveness and reducing treatment resistance across diverse molecular subtypes.

6. Repurposed drugs targeting metabolic plasticity

Metabolic plasticity is increasingly recognized as a key driver of lung cancer tumor survival, progression, and therapy resistance [13, 17]. Unlike normal cells, lung cancer cells can dynamically switch between different metabolic states in response to changes in oxygen, nutrients, environmental stress, and therapeutic exposure [15, 17]. This plasticity enables the tumor to survive in hostile environments and plays a major role in resistance to chemotherapy, targeted therapy, radiotherapy, and immunotherapy [11, 46].

Metabolic adaptation is an umbrella term for multiple intertwined pathways [20, 25]. Therefore, there is a growing interest in repurposed drugs from non-oncology areas that can interfere with such processes. Several approved agents, initially developed for metabolic, infectious, cardiovascular, or inflammatory diseases, have shown anticancer activity by modulating mitochondrial function, glucose metabolism, lipid synthesis, oxidative stress, autophagy, and immune regulation [28, 29]. The major repurposed agents discussed in this section differ substantially in their level of mechanistic support, pharmacological feasibility, and clinical validation. Therefore, they should not be interpreted as equally mature therapeutic candidates. Some agents, such as metformin and statins, have relatively extensive epidemiological or clinical evidence, whereas others, including niclosamide, ivermectin, artesunate, and disulfiram, remain largely supported by preclinical data. This distinction is important when considering their translational relevance in lung cancer (see **Table 3**).

Drug	Original use	Main mechanism	Metabolic target	Resistance pathway	Clinical status
Metformin	Type 2 diabetes	Complex I inhibition, AMPK activation, mTOR suppression	Oxidative phosphorylation	EGFR-TKI resistance, metabolic adaptation	Phase II studies; mixed outcomes
Phenformin	Type 2 diabetes	Potent Complex I inhibition	Oxidative phosphorylation	OXPHOS-dependent resistant tumors	Preclinical; limited by lactic acidosis
Statins	Hypercholesterolemia	HMG-CoA reductase inhibition	Mevalonate/lipid metabolism	RAS/RHO prenylation, survival signaling	Observational studies; mixed clinical evidence
Aspirin	Anti-inflammatory/antiplatelet	COX inhibition, prostaglandin suppression	Inflammation-associated metabolism	Immune suppression, angiogenesis	Epidemiological evidence; limited prospective trials
Doxycycline	Antibiotic	Mitochondrial protein synthesis inhibition	Mitochondrial biogenesis	Cancer stem-cell survival	Preclinical evidence
Hydroxychloroquine	Antimalarial/autoimmune disease	Lysosomal inhibition, autophagy blockade	Autophagy-dependent metabolism	Stress-adaptive survival	Early-phase clinical studies
Niclosamide	Anthelmintic	Mitochondrial uncoupling, Wnt/STAT3 inhibition	Oxidative phosphorylation	Cancer stemness, EGFR-TKI resistance	Preclinical/early translational evidence
Disulfiram	Alcohol dependence	ALDH inhibition, ROS generation, NF- κ B modulation	Redox metabolism	Oxidative stress adaptation, CSC survival	Early oncology trials: not established in lung cancer
Ivermectin	Antiparasitic	PI3K/AKT/mTOR inhibition, mitochondrial dysfunction	Mitochondrial and signaling metabolism	Stemness, prosurvival signaling	Mainly preclinical evidence
Artesunate	Antimalarial	ROS generation, ferroptosis-related mechanisms	Iron/redox metabolism	Oxidative stress adaptation	Preclinical and early clinical exploration

Table 3.
Repurposed drugs targeting metabolic plasticity and therapy resistance in lung cancer.

6.1 Biguanides (metformin and phenformin)

Biguanides have garnered particular interest as repurposed metabolic agents due to their effects on tumor bioenergetics [28, 30]. Metformin is the most commonly used drug for type 2 diabetes mellitus, and it inhibits mitochondrial complex I activity, reduces ATP production, and activates AMP-activated Protein Kinase (AMPK), which is a key regulator of cellular energy homeostasis [28, 39, 63].

$$AMPK \uparrow \Rightarrow mTOR \downarrow$$

AMPK activation inhibits mTOR signaling and suppresses anabolic metabolism, leading to a reduction in protein synthesis, proliferation, and metabolic adaptation [28, 63].

Metformin suppresses tumor growth and reduces metastatic potential, as well as sensitivity to chemotherapy and EGFR inhibitors, in lung cancer models [28, 30]. It may also improve antitumor immunity via the relief of hypoxia and inflammatory signaling in the tumor microenvironment [19].

Phenformin inhibits oxidative phosphorylation even more strongly but is limited clinically due to an increased risk of lactic acidosis [39]. However, it is pertinent in tumors strongly dependent on mitochondrial metabolism [33, 39, 46].

From a translational perspective, metformin represents one of the most clinically mature repurposed agents in lung cancer; however, its therapeutic effects remain inconsistent across clinical studies. This inconsistency may reflect differences in diabetes status, tumor genotype, metabolic phenotype, drug exposure, and combination regimen. Phenformin is mechanistically attractive because of its stronger mitochondrial inhibition, but its toxicity profile limits clinical applicability. Therefore, future studies should identify tumor subgroups with clear oxidative phosphorylation dependency before considering biguanide-based therapeutic strategies.

6.2 Statins and cholesterol metabolism

Statins inhibit the rate-limiting enzyme of cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase [31, 62]. Besides their cardiovascular application, they have potential as anticancer agents by interfering with the mevalonate pathway and blocking prenylation-dependent oncogenic signaling [31, 62].

$$HMG - CoA \text{ Reductase } \downarrow \Rightarrow \text{Mevalonate Pathway } \downarrow$$

Membrane localization and signaling activity of proteins like RAS, RHO, and RAC require prenylation [62, 34]. These processes can be interfered with by statins and thus inhibit proliferation, migration, angiogenesis, and survival signaling [31, 62].

Several reports have shown synergistic effects of statins with EGFR inhibitors, particularly in resistant NSCLC [47, 59]. Statins may also work by interfering with the altered lipid metabolism, which is important for membrane biosynthesis and adaptation to tumor needs [15, 18].

The clinical interpretation of statins in lung cancer remains challenging. Although observational studies have suggested possible survival benefits, these findings may be influenced by confounding factors such as cardiovascular comorbidities, medication adherence, and differences in baseline patient characteristics. Prospective biomarker-guided trials are required to determine whether tumors with mevalonate pathway activation or prenylation-dependent signaling are more likely to benefit from statin-based combinations.

6.3 Antiparasitic agents (ivermectin and niclosamide)

Antiparasitic agents have been of interest due to their wide multitarget biological activities [32, 64]. By inhibiting PI3K/AKT/mTOR signaling, inducing mitochondrial dysfunction, and promoting oxidative stress-mediated apoptosis, ivermectin has demonstrated anticancer activity [64].

$$PI3K/AKT/mTOR \downarrow \Rightarrow Cell\ Survival \downarrow$$

Ivermectin may also target cancer stem-like cells and pathways involved in cellular plasticity and resistance to therapy [20, 64].

Niclosamide is a mitochondrial uncoupler, which disrupts oxidative phosphorylation and ATP production [32]. It also suppresses Wnt/ β -catenin, STAT3, NF- κ B, and Notch signaling pathways involved in resistance and stemness [32]. Preclinical studies have shown synergistic activity of niclosamide with EGFR inhibitors in resistant NSCLC [32].

Despite strong preclinical rationale, the clinical development of ivermectin and niclosamide in lung cancer remains limited. A major barrier is whether anticancer concentrations observed *in vitro* can be achieved safely in patients. Poor bioavailability, uncertain tumor penetration, and limited randomized clinical evidence currently restrict their translational application. These agents should, therefore, be considered promising experimental candidates rather than clinically established repurposed therapies.

6.4 Antifungal and antimicrobial drugs

Several antimicrobial and antifungal drugs have been reported to exhibit anticancer activity through their effects on mitochondrial metabolism, regulation of oxidative stress, and autophagy [44, 50].

Doxycycline inhibits mitochondrial protein synthesis because of the similarity between bacterial and mitochondrial ribosomes [50]. It also inhibits oxidative phosphorylation, diminishes ATP generation, and inhibits the survival of lung CSCs [20, 50].

Itraconazole also displayed anticancer properties by inhibiting angiogenesis, Hedgehog signaling, cholesterol trafficking, and mTOR-associated pathways [44]. Some antimicrobial agents have anti-inflammatory and immunomodulatory properties that may influence immune signaling associated with tumors [19].

The translational value of antimicrobial repurposing depends heavily on pharmacokinetic feasibility and tumor exposure. While doxycycline is biologically attractive for targeting mitochondrial translation and CSC metabolism, its anticancer activity may require prolonged exposure or combination strategies. Similarly,

itraconazole has demonstrated antiangiogenic and signaling effects, but its interactions with cytochrome P450 metabolism require careful attention in patients receiving targeted therapies or chemotherapy.

6.5 Anti-inflammatory drugs and COX inhibition

Chronic inflammation plays a central role in lung cancer progression, immune suppression, angiogenesis, and therapeutic resistance [19]. Cyclooxygenase-2 (COX-2) is frequently overexpressed in lung cancer and drives prostaglandin-mediated inflammatory signaling [19].

Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) inhibit cyclooxygenase activity, which is associated with inflammatory signaling and tumor progression [19, 56].



In addition to its anti-inflammatory effects, aspirin may also affect platelet function, angiogenesis, immune responses, and the formation of the metastatic niche [19]. Selective COX-2 inhibitors, such as celecoxib, have demonstrated anticancer activity, but there are concerns about cardiovascular toxicity [19].

Although anti-inflammatory repurposing is biologically plausible, clinical benefit is unlikely to be uniform across all patients. Tumors characterized by inflammatory signaling, prostaglandin activity, platelet activation, or immune-suppressive microenvironments may be more suitable candidates for aspirin or COX-targeted strategies. Cardiovascular, gastrointestinal, and bleeding risks must also be carefully considered when these agents are combined with anticancer therapies.

6.6 Beta-blockers and stress signaling

Beta-adrenergic signaling has been implicated in tumor proliferation, angiogenesis, metastasis, and immune suppression. Chronic stress activates sympathetic pathways that promote tumor progression through catecholamine signaling [19].

Beta-blockers, such as propranolol, inhibit adrenergic signaling and have been shown to have antiangiogenic, antiproliferative, and immunomodulatory effects in models of lung cancer [19]. These agents are also able to modulate mitochondrial function, oxidative stress response, and metabolic adaptation [15].

Despite the variability of clinical findings, retrospective studies indicate potential survival benefits among patients on beta-blockers during anticancer treatment [19].

Current evidence for beta-blockers in lung cancer is mainly observational, and results remain inconsistent. Their potential benefit may depend on tumor adrenergic signaling, stress biology, immune context, and treatment setting. Prospective studies are needed before beta-blockers can be recommended as routine adjunctive anticancer agents.

6.7 Mitochondrial metabolism inhibitors

Mitochondria remain important regulators of lung cancer metabolism, particularly in therapy-resistant and stem-like tumor populations [15, 20]. Some of

the repurposed agents disrupt mitochondrial oxidative phosphorylation and ATP production [28, 50].

The antimalarial drug atovaquone is a mitochondrial complex III inhibitor, which may reduce tumor hypoxia and enhance sensitivity to radiotherapy [46]. Atovaquone could deplete oxygen consumption, thereby increasing oxygen availability in hypoxic tumors [17].

$$\text{Oxidative Phosphorylation} \downarrow \Rightarrow \text{ATP Production} \downarrow$$

Resistance tumors are often dependent on oxidative phosphorylation. Thus, the combination of mitochondrial inhibitors with therapies targeting glycolysis may result in a more profound suppression of metabolic plasticity [46,49].

Mitochondrial metabolism inhibitors are particularly relevant for tumors that become dependent on oxidative phosphorylation during treatment resistance. However, mitochondrial targeting also raises toxicity concerns because normal tissues rely on oxidative phosphorylation. Future strategies should, therefore, prioritize therapeutic windows, tumor-selective metabolic dependencies, and pharmacodynamic biomarkers of mitochondrial inhibition.

6.8 Autophagy-modulating repurposed drugs

Autophagy is often employed by therapy-resistant lung cancer cells for the maintenance of metabolic homeostasis and to avoid apoptosis [33]. Chloroquine and hydroxychloroquine inhibit both lysosomal acidification and late-stage autophagy [29, 33]. These agents improve responses to chemotherapy, radiotherapy, targeted therapy, and immunotherapy in preclinical models of lung cancer by inhibiting stress-adaptive survival mechanisms [33].

$$\text{Autophagy} \downarrow \Rightarrow \text{Stress Survival} \downarrow$$

Inhibition of autophagy is particularly relevant in tumors with high metabolic plasticity, where intracellular recycling pathways are critical for survival under metabolic stress [15, 18, 20]. Several clinical trials are testing the combination of autophagy inhibitors with immunotherapy and targeted therapies in advanced lung cancer [29].

Although autophagy inhibition has a strong mechanistic rationale, clinical responses have been variable. One explanation is that autophagy may function differently depending on tumor stage, genotype, and treatment context. In addition, hydroxychloroquine may incompletely inhibit autophagy at clinically tolerable doses. These limitations highlight the need for pharmacodynamic biomarkers that confirm effective autophagy blockade within tumor tissue.

6.9 Comparative appraisal of repurposed metabolic therapies

Repurposed drugs targeting metabolic plasticity should be evaluated according to three major criteria: strength of mechanistic rationale, pharmacological feasibility, and level of clinical validation. Metformin has the strongest translational foundation among metabolism-directed repurposed drugs in lung cancer, but its clinical benefit remains inconsistent and is likely context-dependent. Statins and aspirin are attractive because of their safety profile and broad availability, yet much of their clinical support remains observational and is vulnerable to confounding.

In contrast, niclosamide, ivermectin, doxycycline, disulfiram, and artesunate demonstrate promising preclinical activity but require stronger pharmacokinetic and clinical validation before they can be considered mature therapeutic candidates. Hydroxychloroquine illustrates another important limitation: Even when the biological target is well-defined, clinically achievable dosing may not produce sufficient target inhibition in tumor tissue.

Collectively, these observations suggest that no single repurposed drug should be viewed as universally effective in lung cancer. Their greatest value is likely to emerge from rational, biomarker-guided combinations that target complementary metabolic and resistance pathways while maintaining acceptable safety and pharmacological feasibility.

7. Network pharmacology and bioinformatics approaches

Recent advances in computational biology, systems pharmacology, and AI have led to a transformation in the research of drug re-purposing in lung cancer [34]. Furthermore, lung cancer progression and therapy resistance involve highly interconnected signaling, metabolic, and immune pathways, making conventional single-target approaches frequently inadequate [22, 23]. At present, systems-level approaches integrate genomic, transcriptomic, proteomic, metabolomic, and clinical data to identify networks associated with disease and therapeutic vulnerabilities [34, 35, 37, 65].

Importantly, computational approaches should be viewed as decision-support tools rather than replacements for experimental validation. Although network pharmacology and AI substantially accelerate candidate prioritization, biological confirmation remains essential before clinical translation.

7.1 Systems biology and network pharmacology

In systems biology, cancer is viewed as an integrated biological network, not as a sequence of separate molecular events [34, 35]. In lung cancer, extensive crosstalk occurs between pathways involving EGFR, KRAS, PI3K/AKT/mTOR, MYC, HIF-1 α , and NRF2 as well as metabolic adaptation, inflammation, immune regulation, and oxidative stress responses [13, 17, 23]. The complexity of these networks accounts for the transient responses to therapies directed at a single oncogenic driver, as tumors activate compensatory pathways under therapeutic pressure [11, 23].

Network pharmacology and protein–protein interaction (PPI) analysis can help identify key signaling hubs and crosstalks of pathways involved in tumor development and resistance [34, 35]. Such approaches are particularly useful for repurposed drugs, which typically lead to multitarget rather than single-molecule biological effects [20, 34]. Drugs that modify mitochondrial activity, inflammation, autophagy, or metabolic signaling may thus influence multiple resistance-associated pathways simultaneously [28, 29].

One important advantage of systems biology is its ability to identify convergent biological vulnerabilities across genetically distinct tumors. Consequently, therapeutic strategies can be directed toward shared adaptive processes rather than individual driver mutations alone, thereby increasing the potential applicability of repurposed drugs across multiple lung cancer subtypes.

7.2 Multi-omics integration and biomarker discovery

Multi-omics integration, including genomics, transcriptomics, proteomics, metabolomics, epigenomics, and single-cell sequencing data, has been increasingly employed in lung cancer research in recent years [37, 60, 65, 66]. These technologies help achieve a more comprehensive understanding of tumor heterogeneity, metabolic plasticity, and therapy resistance [15, 46].

Integrated analyses can identify biomarkers related to sensitivity for repurposed drugs. For example, tumors exhibiting upregulated oxidative phosphorylation signatures may be more susceptible to mitochondrial inhibitors such as metformin or atovaquone [28, 30, 46]. Similarly, inflammatory or immune-related signatures may be utilized to predict responses to anti-inflammatory or immunomodulatory agents [19, 56].

Moreover, liquid biopsy technologies, including circulating tumor DNA and exosome analysis, provide an opportunity to monitor tumor evolution and treatment resistance dynamically during treatment [37, 61]. Such approaches could lead to more personalized and adaptive therapeutic strategies.

However, integrating multi-omics datasets into clinical decision-making remains challenging because different analytical platforms, sample quality, computational pipelines, and biological interpretation strategies may generate inconsistent results. Standardization and prospective validation, therefore, remain essential before routine clinical implementation.

7.3 AI and computational platforms

AI and machine learning are increasingly used for analyzing large biomedical datasets and predicting drug–disease relationships [35, 36]. Models based on AI can detect hidden molecular patterns, predict the response to therapy, optimize combinations of drugs, and accelerate virtual screening of approved drugs [35, 36, 59].

Public databases such as TCGA, GEO, DrugBank, Connectivity Map, LINCS, STRING, and BioGRID play an important role in computational repurposing studies [34, 37, 59]. These platforms allow for the analysis of gene-expression signatures, signaling pathways, protein interactions, and drug-induced molecular responses.

However, AI-driven approaches still require high-quality datasets and experimental validation [34–36]. Another important challenge involves the interpretability of AI models. While deep-learning algorithms often achieve high predictive performance, their decision-making processes may remain difficult to explain biologically. Future AI-driven repurposing platforms should, therefore, prioritize both predictive accuracy and mechanistic interpretability to facilitate clinical adoption. The integration of systems biology, multi-omics technologies, and AI into disease-oriented drug repurposing is summarized in **Figure 3**.

8. Combination strategies with repurposed drugs

Combination therapies are one of the most promising applications of drug repurposing in lung cancer [20, 56]. It is known that lung cancer is heterogeneous, metabolically plastic, and adaptively resistant, which limits the efficacy of monotherapy treatments [11, 22, 23]. Repurposed drugs can synergistically target

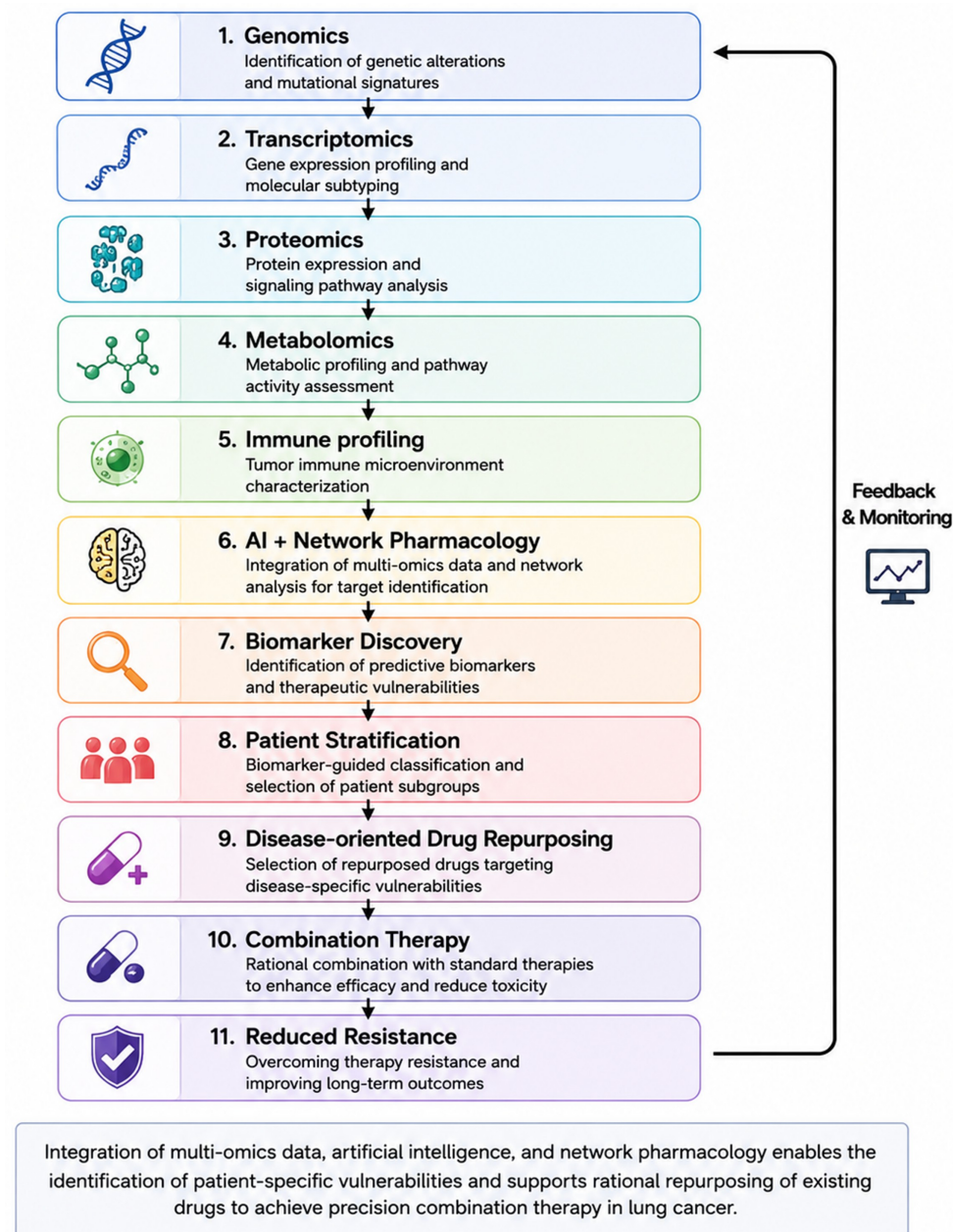


Figure 3.
Artificial intelligence and systems biology framework for disease-oriented drug repurposing. Integration of multi-omics datasets, network pharmacology, artificial intelligence, and computational biology facilitates the identification of disease-associated molecular networks and prioritization of repurposed therapeutic candidates. Computational predictions are subsequently validated using experimental models and biomarker-guided clinical studies to accelerate translational precision oncology.

metabolism, inflammation, autophagy, oxidative stress, and survival signaling pathways to improve the efficacy of chemotherapy, targeted therapy, and immunotherapy [34, 49].

Combination therapy has increasingly shifted from empirical drug pairing toward mechanism-driven therapeutic design. Rather than simply combining active agents, modern strategies attempt to simultaneously suppress complementary adaptive pathways responsible for therapeutic escape.

8.1 Combination with chemotherapy and targeted therapy

Repurposed drugs can interfere with adaptive stress-response pathways, sensitizing cells to chemotherapy [20]. Synergistic effects of metformin with platinum-based chemotherapy and EGFR inhibitors have been reported to be driven by the inhibition of mitochondrial metabolism, activation of AMPK, and suppression of mTOR signaling [28, 30].

$$AMPK \uparrow \Rightarrow mTOR \downarrow$$

Statins may also induce apoptosis through the inhibition of oncogenic signaling dependent on prenylation and the mevalonate pathway [31, 62].

Therapeutic response may be enhanced by autophagy inhibitors, such as chloroquine and hydroxychloroquine, because resistant tumor cells often depend on autophagy for survival during therapeutic stress [20, 29].

$$Autophagy \downarrow \Rightarrow Therapy\ Sensitivity \uparrow$$

Similarly, antiparasitic agents such as niclosamide and ivermectin modulate the STAT3, Wnt/ β -catenin, and PI3K/AKT signaling pathways associated with resistance [32, 64].

Targeted therapy is frequently associated with metabolic rewiring toward oxidative phosphorylation or other nutrient utilization pathways [46]. Thus, the combination of targeted agents with repurposed drugs modulating metabolism might be able to decrease tumor plasticity and increase the time to resistance [46, 49].

Nevertheless, the clinical success of these combinations remains variable. Several randomized studies evaluating metformin combined with platinum-based chemotherapy failed to demonstrate uniform survival benefits, indicating that metabolic phenotype and patient selection are likely major determinants of therapeutic response.

8.2 Enhancement of immunotherapy and overcoming resistance

Moreover, repositioning of drugs may also improve the response to immunotherapy by altering the tumor microenvironment [9, 19]. Metformin can reduce tumor hypoxia and improve T-cell function, while aspirin and other anti-inflammatory agents block prostaglandin-mediated immunosuppression [19, 28, 53, 56].

Beta-blockers could blunt adrenergic stress signaling involved in immune escape, and autophagy inhibitors improve antigen presentation and immune-mediated tumor cell killing [19].

Combination strategies are especially important to overcome acquired resistance [7, 11]. Resistant tumors are often due to metabolic adaptation, activation of

Biomarker	Biological phenotype	Repurposed drug	Standard therapy
High OXPHOS	Mitochondrial dependency	Metformin/Phenformin	EGFR-TKI
High glycolysis	Lactate-rich tumors	Aspirin/Statins	Immunotherapy
High autophagy	Stress adaptation	Hydroxychloroquine	Chemotherapy
High inflammatory signaling	COX-2 activation	Aspirin	PD-1 inhibitor
Cancer stem-cell markers	Stemness	Doxycycline/Niclosamide	Chemotherapy
STK11 mutation	Metabolic rewiring	Biguanides	Immunotherapy
KEAP1 mutation	Oxidative stress adaptation	Mitochondrial inhibitors	Targeted therapy

Table 4.
Biomarker-guided combination strategies for disease-oriented drug repurposing in lung cancer.

autophagy, phenotypic transformation, and survival of CSCs [20, 52]. Drugs such as metformin, doxycycline, niclosamide, and ivermectin have been shown to target these adaptive pathways and resistant stem-like populations [28, 50] (see **Table 4**).

Future studies should prioritize biomarker-guided combinations based on metabolic dependencies rather than applying identical combination strategies across genetically heterogeneous patient populations. Representative combination strategies integrating repurposed drugs with standard lung cancer therapies are summarized in **Figure 4**.

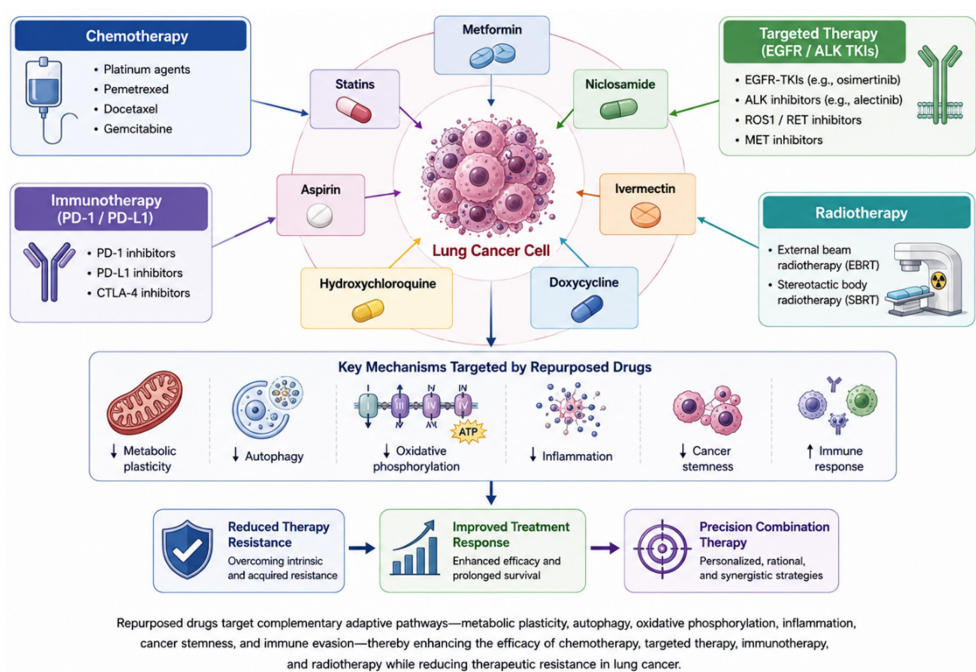


Figure 4.
Combination strategies of repurposed drugs with standard therapies in lung cancer. Repurposed drugs enhance the efficacy of chemotherapy, targeted therapy, immunotherapy, and radiotherapy by simultaneously targeting complementary adaptive pathways, including metabolic plasticity, mitochondrial function, autophagy, inflammation, oxidative phosphorylation, oxidative stress, immune suppression, and cancer stemness. These multitarget combination strategies may improve therapeutic response, delay resistance development, and support precision combination therapy in lung cancer.

8.3 Challenges in combination design

Despite compelling biological rationale, the clinical realization of repurposed drug combinations is hampered by a number of challenges [20, 25]. When used in combination with chemotherapy or targeted therapies, careful consideration should be given to optimal dosing, therapeutic sequencing, and drug–drug interactions [20].

Selection of patients is further complicated by tumor heterogeneity, as metabolic dependencies and resistance mechanisms vary greatly between patients [22, 37, 61]. Moreover, many promising preclinical findings fail to translate into clinical success due to differences in tumor biology, pharmacodynamics, and patient variability [20, 25].

Recent evidence indicates that metabolic competition between tumor cells and immune cells represents a major determinant of checkpoint inhibitor responsiveness. Activated CD8⁺ T lymphocytes require glucose, amino acids, oxygen, and mitochondrial integrity to sustain proliferation and cytotoxic function. Highly glycolytic tumors consume these nutrients and generate lactate-rich, acidic microenvironments that promote T-cell exhaustion, impair dendritic-cell activation, and increase the activity of immunosuppressive macrophages and regulatory T cells. Consequently, metabolic interventions may improve immunotherapy not only by targeting tumor cells but also by restoring immune-cell fitness [54].

Large-scale clinical trials are also limited by financial and regulatory barriers, especially for generic drugs where there is no strong commercial incentive [20]. However, combinatorial approaches targeting metabolic plasticity, immune suppression, and adaptive signaling networks are highly promising to enhance the durability of treatment and to overcome resistance in lung cancer [34, 49].

Therefore, combining immune checkpoint inhibitors with metabolism-targeting repurposed drugs represents a promising strategy to simultaneously restore antitumor immunity and reduce tumor metabolic adaptability.

9. Clinical evidence and translational perspectives

In lung cancer, drug repurposing is gaining more and more interest, as several approved non-oncology drugs can target tumor metabolism, autophagy, immune suppression, and therapy-resistance pathways [20, 29]. Most of the evidence is still at the pre-clinical level, but several re-purposed agents have entered clinical evaluation and demonstrated their translational promise [20, 25, 30]. Clinical success relies on a careful assessment of efficacy, safety, dosing, pharmacokinetics, and biomarker-guided patient selection [20, 25, 36, 61].

Although preclinical evidence has expanded rapidly, relatively few repurposed agents have demonstrated consistent efficacy in randomized clinical trials. This discrepancy illustrates the well-recognized translational gap between experimental models and clinical oncology. Differences in pharmacokinetics, tumor heterogeneity, patient selection, and treatment context frequently limit the successful translation of promising laboratory findings into routine clinical practice.

9.1 Preclinical validation studies

Repurposed drugs have exhibited promising anticancer activities in preclinical studies based on lung cancer cell lines, organoids, xenografts, and genetically engineered mouse models [20, 22, 60]. Metformin has demonstrated effects on reducing proliferation, inhibiting mitochondrial metabolism, decreasing EMT, and increasing sensitivity to chemotherapy and EGFR inhibitors [28, 30]. Statins inhibit the mevalonate pathway and potentially suppress signaling for proliferation, metastasis, and resistance [31, 62].

Antiparasitic agents, including niclosamide and ivermectin, target mitochondrial function, CSC pathways, Wnt/ β -catenin signaling, and oxidative-stress response [32, 64]. Autophagy inhibitors, such as chloroquine and hydroxychloroquine, have also been shown to improve the effects of chemotherapy, radiotherapy, and targeted therapies in resistant models [29].

Preclinical data, in general, suggest that repurposed drugs may be more effective in combination with standard anticancer therapies than as monotherapies [20, 56].

Importantly, not all preclinical models possess equal predictive value. Conventional two-dimensional cell cultures frequently overestimate drug efficacy because they fail to reproduce stromal interactions, immune-cell infiltration, metabolic gradients, and intratumoral heterogeneity. Consequently, organoids and patient-derived xenografts are increasingly considered more clinically relevant validation platforms.

9.2 Clinical trials and translational challenges

Metformin is the most investigated repurposed drug in lung cancer clinical studies [28, 30]. Metformin has been evaluated in retrospective and prospective studies in combination with chemotherapy, EGFR inhibitors, radiotherapy, and immunotherapy, but the results are still heterogeneous and seem to be highly influenced by tumor biology and patient selection [30, 61].

Several early-phase clinical trials have investigated metformin, hydroxychloroquine, itraconazole, and statins in combination with chemotherapy, targeted therapy, or immunotherapy. However, many studies have reported neutral or inconsistent outcomes, despite encouraging preclinical data. These findings suggest that successful repurposing depends not only on drug activity but also on appropriate patient stratification, metabolic phenotype, and rational combination design.

Hydroxychloroquine has been clinically tested for its ability to inhibit autophagy, while itraconazole, statins, and beta-blockers have shown potential benefits in selected patient populations [19, 44, 47]. However, definitive randomized clinical data are still lacking.

Tumor heterogeneity is a major translational barrier. Lung cancer subtypes are highly different in their metabolic dependencies, immune features, and resistance mechanisms, suggesting that repurposed therapies may only be effective in some biological subgroups [22, 37, 61].

Future clinical trials should, therefore, incorporate biomarker-guided enrollment, prospective metabolic profiling, and adaptive trial designs capable of identifying responsive biological subgroups rather than evaluating heterogeneous patient populations.

9.3 Safety, biomarkers, and precision medicine

The great advantage of repurposed drugs is that safety and pharmacokinetic data already exist [20, 26]. However, the anticancer activity may require different dosing schedules from the original indication, which may alter toxicity profiles and drug interactions [20, 25]. Therefore, careful evaluation of pharmacodynamics, tissue penetration, and long-term tolerability is still required.

The use of strategies based on biomarkers is gaining increasing importance for optimizing the use of repurposed therapies [36, 61]. Highly glycolytic tumors, oxidative-phosphorylation-dependent tumors, those with signatures of hypoxia, or those with altered metabolic pathways may respond differently to agents such as metformin, statins, or atovaquone [15, 17, 46, 49]. Genomic alterations, such as mutations in STK11 and KEAP1 may also be involved in the response to strategies targeting metabolism [22, 39].

Liquid biopsy technologies and AI-based multi-omics analysis are also advancing biomarker discovery and patient stratification [35–37, 61]. Such tools may provide more personalized strategies for repurposing that can be adapted to the dynamic biology of the tumor.

Therapeutic drug monitoring and pharmacodynamic biomarkers may become increasingly important for confirming adequate intratumoral target inhibition while minimizing systemic toxicity. Such strategies could improve dose optimization for repurposed agents whose anticancer mechanisms differ substantially from their original clinical indications.

9.4 Economic and global health implications

Most of the repurposed drugs are inexpensive, generic drugs that are already widely available globally, thus providing the possibility of a cost-effective therapeutic option [20, 56]. Agents including metformin, aspirin, statins, and hydroxychloroquine could improve access to adjunctive cancer therapies, especially in low- and middle-income countries, where targeted therapies and immunotherapies are still costly [20, 56].

However, large-scale clinical development is hampered by financial and regulatory barriers, as many repurposed drugs are not covered by patents and commercial incentives [20, 25]. Thus, academic institutions and public-funded collaborations are important actors in advancing clinical repurposing research.

With the advances in systems biology, precision medicine, and computational pharmacology, disease-oriented drug repurposing might be an increasingly important strategy to overcome metabolic plasticity and therapy resistance in lung cancer [34, 36].

Companion diagnostics are also expected to become increasingly important in disease-oriented repurposing. Rather than selecting patients solely according to genomic alterations, future diagnostic strategies will likely integrate metabolic signatures, immune phenotypes, circulating biomarkers, and AI-derived predictive models to support individualized therapeutic selection.

9.5 Economic perspective

Beyond reducing treatment costs, successful repurposing may improve global equity in precision oncology by expanding access to biologically rational

Challenge	Impact on translation	Potential solution
Tumor heterogeneity	Variable therapeutic response	Biomarker-guided trials
Pharmacokinetics	Inadequate tumor exposure	Dose optimization
Toxicity	Combination limitations	Therapeutic monitoring
Lack of biomarkers	Poor patient selection	Multi-omics integration
Limited randomized trials	Weak clinical evidence	International multicenter studies
Generic drug economics	Low commercial incentive	Academic/public funding

Table 5.
Major challenges limiting the clinical translation of repurposed drugs.

combination therapies in healthcare systems where novel targeted agents remain financially inaccessible (see **Table 5**).

10. Challenges, limitations, and future directions

Interest in disease-oriented drug repurposing for lung cancer is growing, but there are major biological, clinical, and translational challenges [20, 25]. Lung cancer is highly heterogeneous, with dynamic metabolic adaptation, tumor evolution, and therapy resistance [15, 22]. Repurposed drugs have provided promising opportunities to target these processes, but successful clinical translation necessitates improved biological understanding, better experimental models, and more precise therapeutic strategies [20, 60].

At the same time, advances in systems biology, AI, multi-omics technologies, and computational pharmacology are providing new opportunities for personalized repurposing approaches [34, 36].

10.1 Biological complexity and tumor adaptation

Lung tumors are constantly evolving through genetic mutation, epigenetic remodeling, metabolic rewiring, and tumor microenvironmental interaction [15, 22, 52]. Metabolic plasticity enables cancer cells to switch between glycolysis, oxidative phosphorylation, fatty-acid oxidation, glutamine metabolism, and autophagy in response to stress and therapy [15, 20, 46].

Glycolysis ↔ Oxidative Phosphorylation

Therefore, blocking a metabolic pathway often causes transient responses because tumors activate compensatory mechanisms for survival [46,49].

Intratumoral heterogeneity, with resistant subpopulations and cancer stem-like cells often having different metabolic and molecular profiles, provides another level of complexity in therapy [20, 22, 43]. Moreover, hypoxia, inflammation, immune suppression, stromal signaling, and nutrient competition in the tumor microenvironment greatly influence the therapeutic response and resistance [14, 19, 21].

10.2 Limitations of current repurposing models

Many of the repurposed drugs have promising preclinical activity but do not translate into consistent clinical success [20, 25]. Human tumors are metabolically heterogeneous and engage with immune cells in the context of a complex microenvironment, which is often not recapitulated by traditional cell-culture systems and animal models [22, 60].

Clinical studies are further limited by heterogeneous patient populations, insufficient biomarker stratification, and varying doses and pharmacokinetics [20, 25, 61]. The concentrations of drugs that are effective *in vitro* may not be achievable or tolerable in patients, and interactions with standard therapies may influence efficacy and toxicity [20, 25].

Financial and regulatory barriers also restrict large-scale clinical trials for off-patent drugs. [20]

10.3 Personalized repurposing strategies

Future strategies for repurposing will likely need to be personalized according to tumor-specific biological vulnerabilities [36, 61]. Tumors are heterogeneous in their metabolic dependencies, immune profiles, genomic aberrations, and resistance mechanisms, and thus one-size-fits-all treatment approaches are not effective for many patients [15, 22].

Biomarker-guided approaches may help to identify patients most likely to derive benefit from specific therapies. For example, tumors dependent on oxidative phosphorylation may be sensitive to mitochondrial inhibitors such as metformin or atovaquone, and inflammatory tumors may be sensitive to anti-inflammatory or immunomodulatory agents [19, 20, 28, 56].

Serial molecular profiling and dynamic monitoring by liquid biopsy as tumors evolve during treatment may allow real-time therapy changes [37, 61].

10.4 Emerging technologies and future opportunities

New technologies are broadening the translational potential of drug repurposing in lung cancer [36, 60]. With single-cell sequencing, organoids, and patient-derived xenografts [22, 60] we now have more accurate models of tumor heterogeneity and resistance evolution.

Metabolomics and spatial transcriptomics broaden the understanding of tumor metabolic organization and microenvironmental adaptation [15, 37, 45]. Synthetic lethality approaches can also uncover vulnerabilities associated with specific genetic or metabolic deficiencies [37, 61, 67].

Moreover, the nanotechnology-based delivery systems may improve intratumoral drug accumulation and decrease systemic toxicity [20, 68, 69].

10.5 Integration of AI, multi-omics, and precision oncology

AI, multi-omics integration, and precision oncology are progressively reshaping cancer therapeutics [35, 36, 61]. Machine learning techniques can be used to analyze genomic, transcriptomic, proteomic, metabolomic, imaging, and clinical data for the prediction of drug responsiveness and the identification of

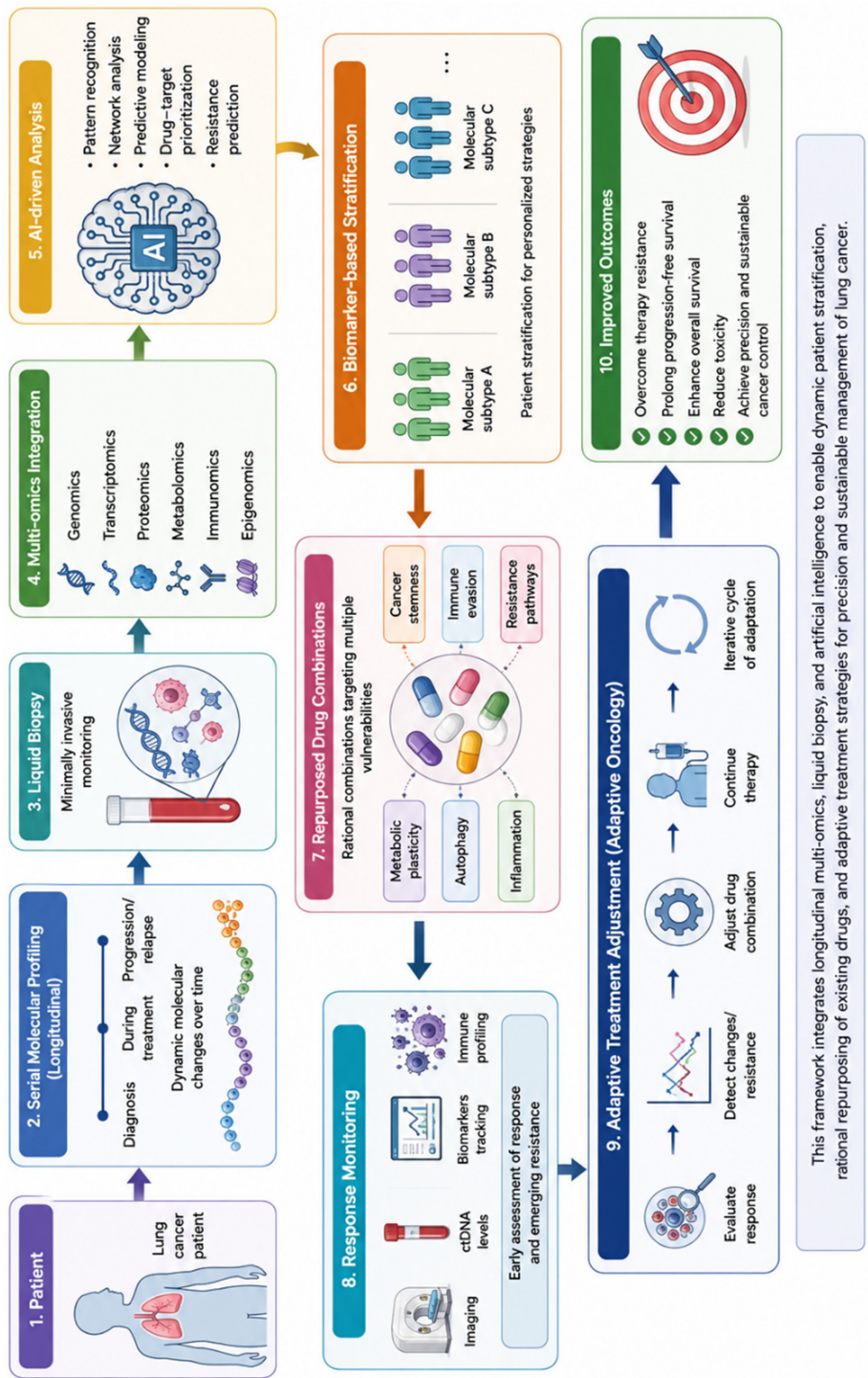


Figure 5. Future precision repurposing and adaptive oncology framework. A conceptual framework illustrating the future integration of serial molecular profiling, liquid biopsy, multi-omics technologies, artificial intelligence, biomarker-guided patient stratification, and adaptive combination therapy for disease-oriented drug repurposing in lung cancer. Continuous monitoring of tumor evolution enables dynamic therapeutic adjustment, supporting personalized treatment strategies aimed at overcoming metabolic plasticity and acquired therapy resistance.

repurposing candidates targeting metabolic and signaling vulnerabilities [35, 36, 65].

Multi-omics approaches integrate metabolism, immune regulation, epigenetics, signaling pathways, and microenvironmental interactions to provide systems-level insight into tumor biology [37, 66]. Such a transition steers precision oncology away from mutation-centric paradigms and toward more disease-oriented therapeutic paradigms [34, 35].

AI-driven prediction, coupled with real-time molecular profiling, may enable highly individualized repurposing strategies that can adapt to tumor evolution and overcome therapy resistance in advanced lung cancer [22, 34, 61].

A future perspective integrating adaptive precision oncology, longitudinal molecular profiling, AI, and disease-oriented drug repurposing is presented in **Figure 5**.

11. Conclusion

Lung cancer is one of the most biologically complex and therapeutically challenging malignancies in the world. Tumor heterogeneity, metabolic adaptability, and rapid emergence of therapy resistance limit long-term clinical outcomes, despite major advances in targeted therapies and immunotherapy [9, 11, 22]. These challenges emphasize the need for more comprehensive therapeutic strategies that can target the dynamic, interconnected biological processes driving tumor survival [34, 35].

Drug repurposing oriented toward diseases represents an attractive framework that goes beyond the classical mutation-centric approaches [20, 34]. This strategy targets common features of lung cancer biology, including metabolic reprogramming, adaptation to oxidative stress, inflammation, autophagy, immune suppression, hypoxia signaling, and microenvironmental remodeling - not just individual oncogenic alterations [13, 14, 19].

In lung cancer, metabolic plasticity is a particularly important therapeutic vulnerability [15, 17]. Tumor cells can toggle between different metabolic states. The property of tumor cells to survive under therapeutic stress contributes greatly to the development of resistance [46, 49].

$$\text{Metabolic Plasticity} \Rightarrow \text{Therapy Resistance}$$

Moreover, repurposed drugs such as metformin, statins, ivermectin, niclosamide, doxycycline, hydroxychloroquine, and aspirin have been demonstrated to interfere with adaptive processes, improving the response to chemotherapy, targeted therapy, radiotherapy, and immunotherapy [28, 29].

The advent of network pharmacology, systems biology, AI, and multi-omics technologies is accelerating the discovery of novel repurposing opportunities [34, 36]. Such tools allow a deeper understanding of the networks involved in the disease and encourage the design of more personalized therapeutic approaches adapted to the biology of individual tumors [36, 61].

Importantly, the future of disease-oriented repurposing will likely depend on dynamic precision-oncology frameworks that can incorporate real-time molecular profiling, AI-guided therapeutic prediction, and adaptive combination treatment design. Such approaches may facilitate continuous adjustment of therapy to tumor

Priority	Expected impact
Biomarker-guided patient selection	Improved therapeutic response
Multi-omics integration	Better target identification
AI-assisted drug prioritization	Faster discovery
Adaptive clinical trials	Improved translation
Precision combination therapy	Reduced resistance
Real-time molecular monitoring	Dynamic treatment optimization

Table 6.
Future priorities for disease-oriented drug repurposing.

evolution, metabolic adaptation, and the appearance of resistance during therapy. In this context, repurposed drugs may be incorporated as essential elements of systems-level cancer treatment rather than adjunctive agents [34, 67].

Disease-oriented repurposing is gaining momentum, despite significant challenges, including tumor heterogeneity, incomplete clinical validation, pharmacokinetic limitations, and regulatory barriers [20, 22, 25]. The future integration of computational pharmacology, biomarker-guided patient selection, and network-based therapeutic design might eventually lead to more durable, biologically informed treatment strategies in lung cancer [34, 36].

Disease-oriented drug repurposing is a biologically rational, cost-effective, and clinically promising strategy to overcome metabolic plasticity and therapy resistance in lung cancer [20, 34, 56]. As therapies for precision oncology evolve, repurposed therapies may be integrated more and more into next-generation personalized treatment paradigms to improve survival, therapeutic durability, and quality of life in patients with lung cancer [36, 61].

The novelty of this chapter lies in presenting drug repurposing from a disease-oriented perspective that prioritizes adaptive tumor biology over isolated genomic alterations. By integrating metabolic plasticity, systems biology, network pharmacology, AI, and precision oncology into a unified conceptual framework, this chapter highlights how repurposed drugs may be rationally incorporated into biomarker-guided therapeutic strategies. This integrative perspective provides a foundation for future research aimed at developing adaptive, systems-level treatment paradigms that respond to the dynamic evolution of lung cancer (see **Table 6**).

Precision oncology continues to evolve, and disease-oriented drug repurposing has the potential to shift from an adjunctive therapeutic concept toward an integral component of adaptive cancer management. The integration of computational pharmacology, real-time molecular profiling, and biomarker-guided combination therapy may ultimately enable more durable, individualized, and biologically informed treatment strategies for patients with lung cancer.

Conflict of Interest

There are no conflicts of interest associated with this chapter.

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