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Review Article

Beyond Current Therapies: *In Silico* Drug Repurposing as a Strategy to Overcome Tyrosine Kinase Inhibitor Resistance in NSCLC

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Abstract

Tyrosine kinase inhibitor (TKI) resistance in non-small cell lung cancer (NSCLC) poses a major challenge to the long-term success of current targeted treatments. This paper explores this clinical obstacle and advocates for *In Silico* drug repurposing as an essential, rapid strategy to discover new therapies for various resistance mechanisms, including mutations in EGFR, ALK, ROS1, and MET. By applying advanced computational techniques, combining extensive genomic and phenotypic data, and utilizing sophisticated machine learning, this method provides a transformative way to find new uses for existing drugs. This approach significantly reduces the long development times, high costs, and failure rates associated with traditional new drug discovery. Although preclinical results are promising and clinical efforts are underway, there are no approved repurposed drugs specifically targeting TKI resistance in NSCLC, which remains a significant therapeutic challenge. We highlight the need for focused research to turn *In Silico* findings into practical clinical solutions, broadening treatment options and improving patient care in NSCLC.

Keywords*: In Silico* Drug Repurposing, Tyrosine Kinase Inhibitor Resistance, Non-Small Cell Lung Cancer, Drug Resistance.

INTRODUCTION

Drug repurposing (known as repositioning) refers to a spectrum of methodologies focused on identifying novel therapeutic applications of pharmaceuticals that have already received regulatory approval or are under investigation in experimental stages. This approach leverages existing pharmacological data to explore alternative clinical uses beyond intended indications. There are several benefits to this approach, rather than creating a completely novel drug for a certain need [1]. The repurposing of drugs has become essential due to the global COVID-19 pandemic. The fast spread of diseases and the associated infection risks have made new treatments urgently needed. Advances in computational methods, along with accessible biomedical datasets like gene expression signatures, pharmaceutical databases, and online health communities, have driven the development of computational drug repositioning techniques. These methods mainly use data mining, machine learning, and network analyses[2,3]. Both experimental and computational techniques are used in the repurposing process, which aims to identify therapeutic targets not only for cancer but also for other diseases[4].

Lung cancer remains the leading cause of cancer-related deaths, with non-small-cell lung cancer (NSCLC) accounting for over 80% of cases worldwide[5,6].

Treatment of NSCLC via targeted kinase inhibition focuses on pathways involved in receptor-tyrosine-kinase-mediated inhibition of cell proliferation. *Anaplastic Lymphoma Kinase (ALK), Epidermal Growth Factor Receptor (EGFR), Mesenchymal-Epithelial Transition factor (MET), and ROS Proto-Oncogene 1 (ROS1)* are pharmaceutical targets for cell lung cancer treatment that are linked to the presence of oncogenic driver mutations in NSCLC[7,8].

Although significant progress has been made with TKIs, their effectiveness is constantly undermined by the development of resistance[9]. Given this ongoing clinical

challenge, this paper makes the case for and describes the strategic use of *In Silico* drug repurposing as a key approach to proactively identify and develop effective treatments that overcome TKI resistance in NSCLC. We explain how advanced computational methods, including the combination of genomic and phenomic data with artificial intelligence, can greatly speed up the discovery of new uses for existing drugs. Moreover, this work highlights the urgent need for future research to turn promising *In Silico* findings into robust clinical solutions, addressing the substantial unmet need for approved repurposed therapies in TKI-resistant NSCLC.

OVERVIEW OF TYROSINE KINASE INHIBITORS IN LUNG CANCER

Role of Tyrosine Kinases in Lung Cancer Pathogenesis

Receptor tyrosine kinases (RTKs) are transmembrane proteins with extracellular ligand-binding domains that phosphorylate tyrosine residues, triggering signaling pathways controlling cell proliferation, differentiation, and death. In lung cancers, various RTKs have been identified, where they act as proto-oncogenes contributing to malignant transformation, cell proliferation, motility, and survival [10-13].

The kinase remains inactive as a monomer until ligand binding induces dimerization and autophosphorylation, initiating a phosphorylation cascade [Figure 1, A][10,14,15,22].

In NSCLC, RTKs like EGFR, ALK, ROS1, and MET often become overexpressed or mutated, leading to uncontrolled cell proliferation. Tyrosine kinase inhibitors (TKIs) are used to target these aberrant signals, offering more effective treatments than chemotherapy[16,17].

Key mechanisms of RTK activation include:

- Gain-of-function mutations: Mutations in RTKs bypass normal regulation, driving tumor growth [18,15,22]. [Figure 1, C]
- Genomic amplification: Increased copies of RTK genes like EGFR and MET enhance signaling, contributing to cancer progression[19,20,22]. [Figure 1, D]
- Chromosomal rearrangements: Fusions, such as EML4-ALK in NSCLC, lead to continuous activation of RTKs, promoting tumorigenesis[21,22]. [Figure 1, B]

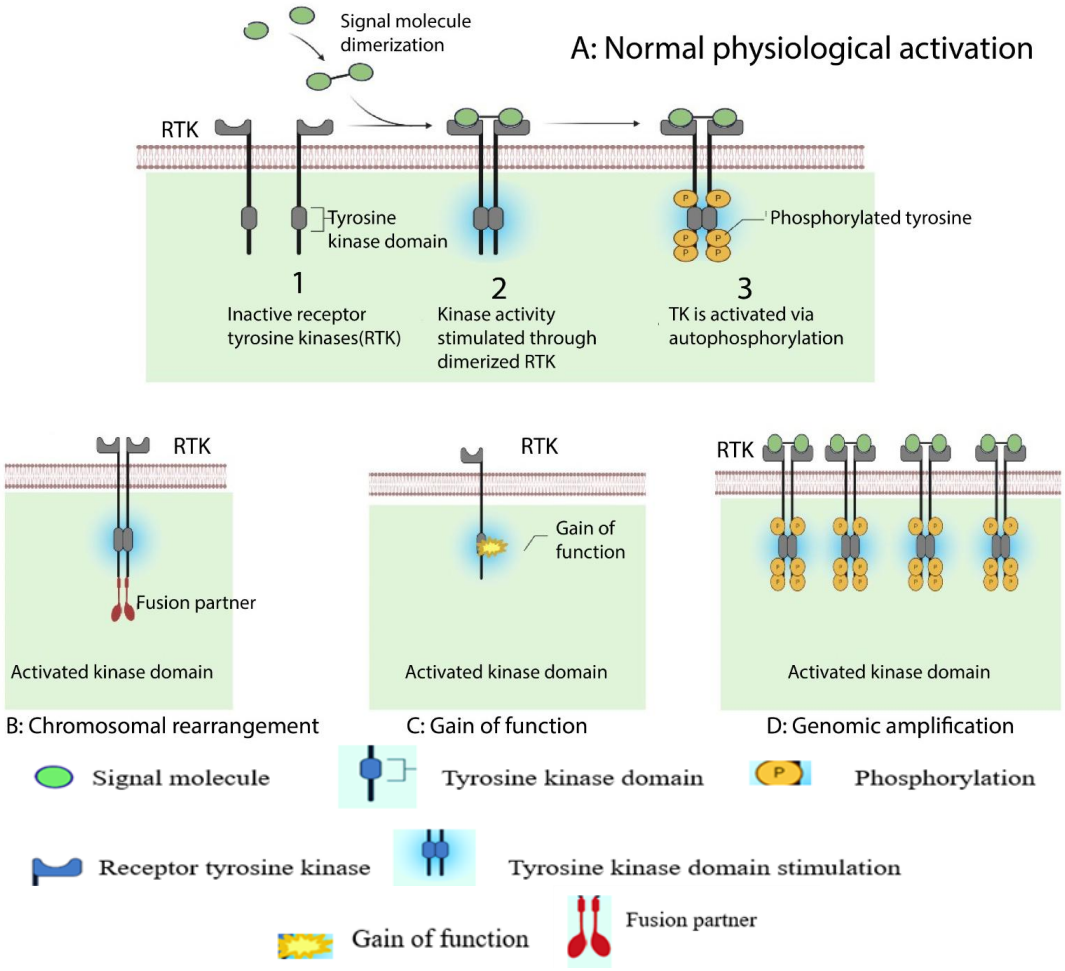

Figure 1: Mechanisms of Receptor Tyrosine Kinase Activation: Normal Physiological Processes (A) and Pathogenic Alterations (B, C, and D) [Created by BioRender.com]

FDA-APPROVED TKIs FOR NSCLC

Several therapeutic options are available for NSCLC, including surgery, radiation therapy, chemotherapy, targeted therapies, and immunotherapy, either alone or in combination[23]. The Food and Drug Administration has authorized 39 drugs for the treatment of NSCLC, of which 17 are tyrosine kinase inhibitors[24] [Table 1].

Starting with Del19/L858R mutations and moving on to target other variants, such as T790M, EGFR-TKIs have evolved in response to specific EGFR mutations, primarily targeting the allosteric and ATP-binding sites of EGFR to produce reversible or irreversible effects[25]. The first EGFR-TKI used to address the Del19/L858R mutation was gefitinib, which was approved in 2003(26). Mobocertinib is the newest EGFR-TKI approved for NSCLC that targets the *EGFR* exon 20 insertion mutation[27]. In contrast, osimertinib is a third-generation drug that targets the T790M mutation in cancer patients with EGFR sensitive or resistant tumors[28].

The discovery of ALK-TKIs was made possible by molecular characterization of non-small cell lung cancer, particularly by identifying the *EML4-ALK* fusion gene[29]. In 2011, the FDA approved crizotinib as a first-generation ALK inhibitor for the treatment of non-small cell lung cancer with *ALK* rearrangement[30]. There have been several ALK-TKIs developed after crizotinib, including ceritinib, alectinib, brigatinib, and lorlatinib[31]. Although crizotinib is effective in targeting *ALK, ROS1*, and *MET*, resistance can develop with extended use, mainly because it cannot cross the blood-brain barrier[32]. Improved brain penetration is a benefit of second-generation TKIs, such as ceritinib, alectinib, brigatinib, and lorlatinib, which solve the problem of the blood-brain barrier[31]. Nevertheless, it is important to note that resistance to TKIs continues to be a serious challenge, and this problem persists even with third-generation inhibitors[33].

Table 1: FDA-approved drugs as TKI in NSCLC

Drug	Category	Approval for NSCLC	Ref
Gefitinib	EGFR TKI	2003-2015 (first line)	26,34
Erlotinib	EGFR TKI	2004	26
Afatinib	EGFR TKI	2013	35
Osimertinib	EGFR TKI	2015	36
Alectinib	ALK Inhibitor	2015	37
Ceritinib	ALK Inhibitor	2014	38
Dabrafenib	BRAF Inhibitor	2017	39
Trametinib	MEK1/2 Inhibitor (EGFR mutation)	2017	39
Brigatinib	ALK Inhibitor	2017	27
Lorlatinib	ALK Inhibitor	2018	33
Dacomitinib	EGFR TKI (2nd Gen)	2018	40
Entrectinib	ALK, ROS1, TRK Inhibitor	2019	41
Capmatinib	MET Inhibitor	2020	42
Selpercatinib	RET Inhibitor	2020	43
Pralsetinib	RET Inhibitor	2020	44
Tepotinib	MET Inhibitor	2021	42
Mobocertinib	EGFR TKI (3rd Gen)	2021	27
Repotrectinib	ROS1 TKI	2023	45

Despite the existence of effective therapies for NSCLC, substantial death rates are still observed as a result of resistance to both on-target and off-target TKIs[46,25]. This persistent resistance remains a significant challenge; therefore, researchers need to explore new approaches to treat cancer[9].

MECHANISMS OF RESISTANCE TO TKI IN NSCLC

Understanding the diverse mechanisms by which NSCLC cells develop resistance to TKIs is fundamental, as these insights directly inform the design of effective counter-strategies.

Resistance to TKI therapies can be classified into primary (intrinsic) resistance and secondary (acquired) resistance. Primary resistance occurs when the treatment does not show a response from the beginning, typically indicated by disease progression within the first few months of starting TKI treatment. In contrast, secondary resistance develops over time, often following an initial phase of a positive therapeutic response [30].

Resistance to TKIs in NSCLC primarily arises from various molecular alterations that bypass the inhibitory effects of these drugs. These mechanisms can be broadly categorized into on-target mutations that directly affect drug binding and off-target activations of alternative signaling pathways. For instance, common on-target mutations, such as the EGFR T790M mutation, modify the ATP-binding pocket of the kinase, decreasing the affinity of first and second-generation TKIs[28,47]. Similarly, specific mutations in ALK and ROS1 can create steric hindrance or change protein conformation, obstructing effective drug binding. Other resistance mechanisms involve the activation of alternative receptor tyrosine kinases or downstream signaling components, which can circumvent the inhibited pathway [Table 2]. Understanding these basic molecular events is essential for developing strategies, including drug repurposing, to address TKI resistance [48–50]

Table 2: Common mutations associated with TKI resistance

RTK	Mutations	TKIs	Prevalence (%)	Ref
EGFR	T790M	Gefitinib	50–60%	47
	G796S/C797S		24.7%	
	L792X	Osimertinib	10.8%	51-53
ALK	G1202R	Crizotinib	2%	49
		Alectinib	21–29%	
		Ceritinib		
		Brigatinib		
	I1171T	Crizotinib	2%	
		Alectinib	12%	
	L1196M/Q	Crizotinib	7%	
ROS1	G2032R	Crizotinib	38%	50
		Lorlatinib	32%	
	D2033N	Crizotinib	2.4%	
	L2026M	Crizotinib	8%	48

IN SILICO STRATEGIES FOR DRUG REPURPOSING

In light of the complexities and costs associated with *de novo* drug discovery, *In Silico* drug repurposing represents a highly strategic and accelerated pathway to overcome TKI resistance. This approach leverages sophisticated computational methods to identify new therapeutic applications for existing, FDA-approved drugs, offering a significantly advantageous risk-benefit profile and mitigating development risks.

Computational approach

Despite substantial progress in the treatment of non-small cell lung cancer using therapies such as tyrosine kinase inhibitors, immunotherapy, and drug combinations, achieving a complete cure and enhancing overall survival rates, particularly in metastatic NSCLC, remains challenging. Drug resistance is a significant barrier that results in treatment failure, disease recurrence, and disease progression. Examples include resistance to Erlotinib and Crizotinib caused by mutations in targets such as *EGFR* and *ROS1*, respectively[54,55]. Given these challenges, *In Silico* drug repurposing emerges as a highly promising strategy, offering a more advantageous risk-benefit ratio and significantly mitigating development risks and costs compared to *de novo* drug discovery[56].

The drug repositioning approach involves computational and experimental strategies to identify novel therapeutic uses of existing drugs. New targets, dose regimens, and treatment techniques can be identified with the help of knowledge of pharmacological mechanisms, disease genomes, and molecular pathways[57].

Computational drug repositioning uses two main strategies to identify the novel therapeutic applications of known drugs. The target-based and drug-based approaches[58].

Within these overarching strategies, various *In Silico* methodologies are utilized, including network analyses, genomics and phenomics data integration, and increasingly, machine learning techniques [58–60].

Genome and Phenome approach

Computational techniques and network analysis have proven essential in discovering biomarker genes for the early identification and treatment of NSCLC. Researchers have employed co-expression network analysis to identify genes that may function as biomarkers while simultaneously assessing the effectiveness of current pharmacological interventions for NSCLC treatment [61,62]. Genetic data, such as genome-wide association studies (GWAS) and gene/protein networks, are used in network-based drug repurposing to identify novel applications for existing drugs. This approach enhances the identification of "druggable" genes near disease-linked targets, even if the targets themselves cannot be directly targeted[63].

The phenome, representing all phenotypic traits, provides a unique method for drug repositioning by connecting a drug's biological activities and adverse effects to disease phenotypes. This methodology relies on the concept that similarities between the symptoms of a disease and the adverse effects of a drug may suggest that the two conditions share the same biological pathways, thereby making the drug a potential treatment for the disease. This approach employs phenotypic data to identify novel therapeutic applications of current medications [59]. The integration of phenotypic data with other biological information, such as genomic data, can improve drug repositioning efforts and reveal new therapeutic applications for existing drugs. To anticipate novel drug-drug interactions and disease associations, computational models have been devised that integrate phenotypic similarities with genotype-disease relationships or drug-drug interaction data, even for diseases with unknown biological mechanisms. These methods use data from multiple sources to identify unknown connections and enhance the treatment options[64-66].

Machine Learning Based Methods

Machine learning is a potent tool in pharmaceutical research, providing solutions to numerous challenges in drug development. It can optimize clinical trials, predict drug-target interactions, expedite drug discovery, and reduce costs by analyzing large datasets and identifying patterns. ML serves as a critical catalyst for innovation in the pharmaceutical sector, with applications that involve the identification of prospective drug candidates and the customization of treatments[67]. ML algorithms can be applied in both target-based and drug-based repurposing strategies. For instance, in target-based approaches, ML can predict binding affinities between drugs and novel targets or identify cryptic protein pockets for binding. In drug-based approaches, ML can be used to analyze chemical similarities or shared biological activities across vast drug datasets to suggest new indications. A preliminary study explored the use of machine learning to predict how cancer cells respond to treatments based on their genomic and chemical profiles and suggested the possibility of drug repurposing[16,68-70].

DRUG REPURPOSING AS A STRATEGY TO OVERCOME TKI RESISTANCE

Studies indicate that the development of new cancer drugs faces a significantly higher failure rate after initial clinical trials (Phase 1), with only 3.4% progressing further. This contrasts with the development of drugs for cardiovascular, infectious, and autoimmune diseases, which demonstrate substantially higher success rates in the same early stages [71]. Therefore, repurposing existing drugs could help accelerate the discovery of cancer treatments more quickly and potentially reduce overall cancer mortality, especially non-small cell lung cancer[72].

Repurposing drugs for NSCLC

While the concept of drug repurposing offers significant promise for overcoming TKI resistance, it is critical to acknowledge the current landscape: to date, no repurposed drug has received regulatory approval specifically for addressing TKI resistance in NSCLC. This stark reality underscores the urgency for more targeted research and serves as the primary reason for the limited availability of extensive clinical data on approved repurposed agents in this specific context. Despite this, ongoing clinical trials and compelling preclinical studies provide strong proof-of-concept for the viability of this strategy. Table 3 presents a summary of ongoing clinical trials exploring the use of repurposed drugs, demonstrating the active pursuit of these therapies. Furthermore, preclinical studies highlight promising candidates and mechanisms by which repurposed drugs can bypass resistance [Table 4].

Table 3: Ongoing clinical trials exploring the use of repurposed drugs for treating NSCLC.

Trial ID	Phase	Planned End Date	Treatment Approach	Target Patient Group	Enrollment	Overall Objective
NCT03546829	Phase 1	December 2027	Vancomycin with focused radiation therapy	Early-stage NSCLC	40	Evaluate immune response and treatment effectiveness
NCT04980716	Phase 3	July 2026	Cardiovascular-related drugs (e.g., perindopril, statins, beta-blockers)	NSCLC patients with cardiovascular comorbidities	524	Assess overall survival and heart-related side effects
NCT05636592	Phase 1	December 2027	Statins plus PD-1/PD-L1 inhibitors	General NSCLC cases	250	Investigate tumor response and survival outcomes
NCT05445791	Phase 3	July 2025	Metformin	NSCLC patients with EGFR mutations	312	Focus on progression-free survival and treatment response rate
NCT05096663	Phase 2/3	December 2027	Combination of B12, Dexamethasone, various chemotherapies, and Ramucirumab	Advanced or recurrent NSCLC (Stage III/IV)	478	Study overall survival and progression-free survival

Table 4: A summary of drugs being evaluated in preclinical models for potential use in treating NSCLC.

Drug	First Indication	Targeted Cell Lines	Animal Studies	Mechanism(s) of Action	Outcomes/Effects	Ref
Atorvastatin	Treat hypercholesterolemia	NSCLC A-549 cells	-	Inhibits HMG-CoA reductase, modulates Akt/mTOR pathways, activates MAPK signaling, and triggers autophagy and ferroptosis	Suppresses tumor growth, induces apoptosis, enhances cancer treatment effectiveness	73-75
Celecoxib	A nonsteroidal anti-inflammatory drug employed in the treatment of osteoarthritis and dysmenorrhea	SGC-7901 cancer cells	-	Blocks COX-2, disrupts the PDK1/Akt signaling pathway, increases PPAR-γ and p53 expression	Triggers cell death, reduces tumor growth, halts cell cycle progression	76-78
Itraconazole	An antifungal agent utilized for the treatment of both systemic and superficial fungal infections	NSCLC xenograft models (LX-14, LX-7)	-	Inhibits endothelial cell migration, proliferation, and angiogenesis	Slows tumor growth, prolongs survival without tumor progression	79,80
Lovastatin	Employed to reduce elevated cholesterol and prevent cardiovascular disease	A549 lung cancer cells	-	Suppresses EGFR/Akt signaling, boosts AMPK activity, causes cells to exit the cell cycle and enter apoptosis	Inhibits cancer cell proliferation, promotes apoptosis, and interferes with cell survival pathways	81

Mebendazole	Broad-spectrum anthelmintic prescribed for intestinal parasitic infections	A549, H1299, H460, WI38	-	Inhibits microtubule formation, reduces cell motility, modulates p53 and STAT3 signaling	Triggers mitotic arrest, induces apoptosis, reduces cancer colony formation	82
Pitavastatin	A statin used to manage dyslipidemia and reduce cardiovascular risk	EGFR TKI-resistant NSCLC cell lines (A549, Calu6)	-	Inhibits EGFR/K-RAS, promotes apoptosis, disrupts tumor growth and angiogenesis	Reduces tumor growth, induces cell death	83
Simvastatin	Prescribed to reduce serum cholesterol and prevent atherosclerotic cardiovascular disease	Bm7 (R248W) p53 mutant cells, A459 cancer cells	Balb/C nude mice	Activates caspase-dependent apoptosis, promotes mutant p53 degradation, disrupts lipid raft formation	Decreases tumor cell motility, induces apoptosis, inhibits cell growth	84

CHALLENGES AND FUTURE DIRECTIONS

Despite these advances, computational drug repositioning models face significant hurdles in development and reliability. Simulating biological systems using theoretical methods is made more difficult by missing, biased, or inaccurate data. Experimental factors (e.g., patient, age and environment) can affect gene expression signatures, resulting in inconsistent and biased findings. Changes in gene expression in some pharmacological targets may not be significant, leading to misleading statistical outcomes. Without high-resolution structural data for drug targets, drug-target interactions are challenging to identify[85]. However, several obstacles limit the full potential of machine learning in drug repositioning. These include overfitting, unreliable biological data, difficulty in interpreting models, and the need for comprehensive clinical validation. There is a lack of high-quality consistent datasets, which restricts the credibility of ML models. To overcome these challenges, researchers developing more sophisticated methods to improve molecular structure representation and predictive accuracy, including deep learning models. Transparent insights into model predictions can also be obtained using interpretable ML approaches. Moreover, systematic and large-scale drug repositioning, as well as improved prediction accuracy, can be achieved by integrating various data sources, including chemical, omics, and clinical data. Despite these challenges, machine learning holds strong potential to revolutionize drug repositioning, especially as models improve in interpretability, robustness, and clinical validation[67].

CONCLUSION

Tyrosine kinase inhibitor (TKI) resistance in non-small cell lung cancer (NSCLC) remains a persistent challenge, necessitating innovative and accelerated therapeutic strategies. This paper advocates for *In Silico* drug repurposing as a potent and essential approach to overcome this critical barrier. By systematically leveraging computational methodologies, integrating genomic and phenotypic datasets, and deploying advanced machine learning, we can significantly accelerate the identification of novel indications for existing drugs. Despite promising preclinical and ongoing clinical efforts, the absence of approved repurposed drugs for TKI resistance in NSCLC underscores a significant unmet clinical need. Emphasizing repurposing offers a cost-effective solution, providing broader treatment access, especially for patients with limited income. Ultimately, *In Silico* drug repurposing is a strategic, efficient, and cost-effective pathway to expand the therapeutic arsenal against TKI-resistant NSCLC, representing a curcial imperative for improving patient outcomes and reshaping future treatment.

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