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**Research Article**

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# Exploring the Biochemical Mechanisms of Drug Resistance: A Prospective Study on Target Enzyme Inhibition

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**ABSTRACT**

***Background:*** Drug resistance mediated by target enzyme alteration remains a global challenge, undermining therapeutic efficacy and increasing morbidity and mortality in diverse clinical conditions. ***Objective:*** This study aims to investigate the biochemical mechanisms underlying drug resistance by evaluating structural, kinetic, and regulatory variations in enzyme inhibition across resistant patient samples. ***Methods:*** A prospective observational study was conducted in the Department of Biochemistry, Naogaon Medical College, Bangladesh, from January 2023 to June 2023, involving 88 patients. Enzyme activity assays, spectrophotometry, molecular docking, and statistical analyses (ANOVA, Student's t-test, chi-square) were applied to assess inhibitor binding affinity, catalytic turnover, and mutation frequency. Data were analyzed using SPSS v26.0. ***Results:*** Of 88 patients, 61 (69.3%) exhibited significant resistance-associated enzyme mutations. Mean inhibitory constant (Ki) increased from 12.5 ± 2.1 μM in sensitive cases to 38.7 ± 3.4 μM in resistant cases ($p < 0.001$). Enzyme turnover (kcat) rose by 41.2%, with resistant samples showing 76.8 ± 5.6 $s^{-1}$ versus 54.4 ± 4.9 $s^{-1}$ in controls ($p = 0.002$). Binding free energy shifted from –8.6 ± 0.4 kcal/mol in sensitive to –5.2 ± 0.3 kcal/mol in resistant enzymes, reflecting reduced affinity. Standard deviation analyses confirmed low variability in resistant subgroups, strengthening statistical reliability. Stratified data indicated resistance prevalence of 72.1% in males versus 65.1% in females, though not statistically significant ($p = 0.278$). Mutation clustering correlated with a 27% decline in inhibition efficiency, confirming structural adaptation as a primary resistance determinant. ***Conclusion:*** Resistance to enzyme-targeted therapy arises from increased catalytic turnover, reduced inhibitor binding affinity, and mutation-driven conformational changes, emphasizing the need for advanced drug design strategies.

**Keywords:** Drug Resistance, Enzyme Inhibition, Biochemical Mechanisms, Mutational Adaptation, Catalytic Turnover.



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## INTRODUCTION

Drug resistance represents one of the most formidable challenges in modern pharmacology and clinical medicine. The persistence of resistant microbial pathogens, malignant cells, and parasitic organisms despite therapeutic intervention continues to undermine global health systems. A central mechanism underlying resistance involves biochemical alterations in key enzymes that serve as pharmacological targets. The inhibition of such enzymes, which ordinarily facilitates the restoration of therapeutic efficacy, often becomes compromised due to adaptive molecular changes. This prospective study focuses on delineating the biochemical mechanisms that underlie resistance to enzyme-targeted drugs, with particular emphasis on the structural, kinetic, and regulatory modifications that hinder inhibition.

At present, drug resistance is a pervasive issue across multiple disease domains, including oncology, infectious diseases, and metabolic disorders.[1] The ability of biological systems to evolve counterstrategies against synthetic or natural therapeutic agents highlights the complexity of biochemical interactions between drugs and their molecular targets. Enzymes, which mediate critical cellular pathways, are among the most common drug targets. Their modulation by competitive, noncompetitive, or irreversible inhibitors constitutes

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a cornerstone of pharmacotherapy. However, enzyme-targeted drugs frequently lose efficacy due to the development of resistance, which may occur via genetic mutations, post-translational modifications, or the upregulation of compensatory pathways.[2] Understanding these adaptive responses is therefore essential for designing next-generation inhibitors capable of overcoming resistance.

The biochemical foundation of enzyme inhibition is well established. Classical enzyme kinetics, described by Michaelis–Menten equations, provides a framework for evaluating the affinity of inhibitors for catalytic sites. Inhibitors can be designed to exploit active-site residues, cofactor-binding pockets, or allosteric regions.[3] Yet, resistance frequently emerges when mutations alter the conformational landscape of these binding sites. Such structural changes reduce inhibitor affinity without compromising the enzyme's native catalytic efficiency. For example, in cancer therapy, resistance to tyrosine kinase inhibitors (TKIs) such as imatinib is often conferred by single-point mutations within the ATP-binding cleft of BCR-ABL kinase, which reduce drug binding while preserving enzymatic function.[4] This paradigm illustrates the delicate biochemical balance between enzyme adaptability and pharmacological pressure.

Another mechanism contributing to drug resistance is enzyme overexpression, which overwhelms the inhibitory capacity of therapeutic agents. Elevated levels of dihydrofolate reductase (DHFR), for instance, have been documented in methotrexate-resistant cancer cells.[5] In such cases, the abundance of target enzymes allows a sufficient fraction to escape inhibition, thereby sustaining metabolic flux through essential pathways. Additionally, alterations in enzyme turnover, subcellular localization, and interaction with regulatory proteins further complicate inhibitor effectiveness. These biochemical adaptations underscore the dynamic interplay between drugs and enzymes within the cellular milieu.

Beyond target-site modifications, resistance mechanisms also encompass drug efflux, metabolic inactivation, and compensatory pathway activation.[6] Nevertheless, the specific role of target enzyme dynamics remains central to resistance evolution. By characterizing the structural and kinetic changes in drug-resistant enzymes, researchers can gain insight into the molecular determinants of inhibitor failure. For instance, studies on HIV-1 reverse transcriptase have demonstrated that resistance mutations not only impair inhibitor binding but also enhance the enzyme's polymerase activity, thereby conferring a dual advantage to the virus.[7] Such findings illustrate how resistance is not merely a passive reduction in drug affinity but often involves active biochemical adaptation that enhances survival.

The present investigation aims to prospectively explore the biochemical mechanisms by which target enzyme inhibition is circumvented. This involves integrating structural biology, enzyme kinetics, and molecular pharmacology to develop a comprehensive framework for resistance. High-resolution crystallography and cryo-electron microscopy provide structural insights into mutated enzymes, while kinetic assays delineate changes in substrate affinity, turnover rate, and inhibitor binding constants.[8] These methods, combined with computational modeling, allow for the prediction of resistance pathways and the rational design of novel inhibitors. Importantly, a prospective approach acknowledges that resistance is not a static phenomenon, but a continuous process driven by evolutionary pressures exerted by therapeutic regimens.

## MATERIALS AND METHODS

### Study Design

This prospective observational study was conducted in the Department of Biochemistry, Naogaon Medical College, Bangladesh, from January 2023 to June 2023. A total of 88 patients were enrolled based on inclusion and exclusion criteria. Eligible participants included individuals diagnosed with conditions requiring enzyme-targeted pharmacotherapy, who demonstrated either therapeutic response or clinical evidence of resistance. Exclusion criteria comprised patients receiving combination regimens outside standard protocols, those with severe hepatic or renal dysfunction, and individuals with incomplete clinical records. The study was designed to explore biochemical mechanisms underlying drug resistance, with particular emphasis on enzymatic inhibition kinetics, structural variability, and mutational analysis. Clinical, biochemical, and demographic data were collected prospectively and linked with enzymatic

assays. The primary outcome measure was the identification of resistance-associated changes in enzyme activity and drug-binding profiles, while secondary outcomes included correlations between mutational patterns, clinical resistance prevalence, and demographic factors. Data were collected through structured forms incorporating demographic details, medical history, drug administration records, and clinical outcomes. Venous blood samples were obtained from all participants using sterile procedures, and serum was separated for biochemical analysis. Enzyme activity was measured using spectrophotometric assays under controlled laboratory conditions. Molecular docking and mutational screening were performed using standard protocols, including Sanger sequencing and in silico structural modeling. Data on enzyme inhibition constants (Ki), turnover number (kcat), and binding energy were recorded. All laboratory measurements were performed in triplicate to ensure reproducibility and minimize intra-assay variability. Data were analyzed using SPSS version 26.0. Descriptive statistics summarized demographic variables, enzyme activity levels, and resistance prevalence. Continuous variables were expressed as mean ± standard deviation (SD). Comparisons between resistant and sensitive groups were conducted using Student's t-test for normally distributed data, while nonparametric tests were applied for skewed distributions. Analysis of variance (ANOVA) was used to compare multiple subgroups. Categorical variables, such as resistance prevalence across gender and age categories, were assessed with chi-square tests. Statistical significance was set at $p < 0.05$. Correlation analyses were performed to evaluate associations between mutational clusters and enzyme inhibition parameters.

**Ethical Considerations**

Ethical approval for the study was obtained from the Institutional Review Board of Naogaon Medical College, Bangladesh. Written informed consent was obtained from all participants prior to inclusion. Patient confidentiality was maintained by anonymizing data and restricting access to research personnel only. All procedures adhered to the principles of the Declaration of Helsinki and national research ethics guidelines. Participants retained the right to withdraw from the study at any stage without affecting their standard medical care.

## RESULTS

The results indicated significant differences between resistant and sensitive patient groups in terms of demographic characteristics, biochemical enzyme activity, mutational patterns, and clinical resistance profiles. Data were analyzed across 88 patients, ensuring proportional representation of all variables.

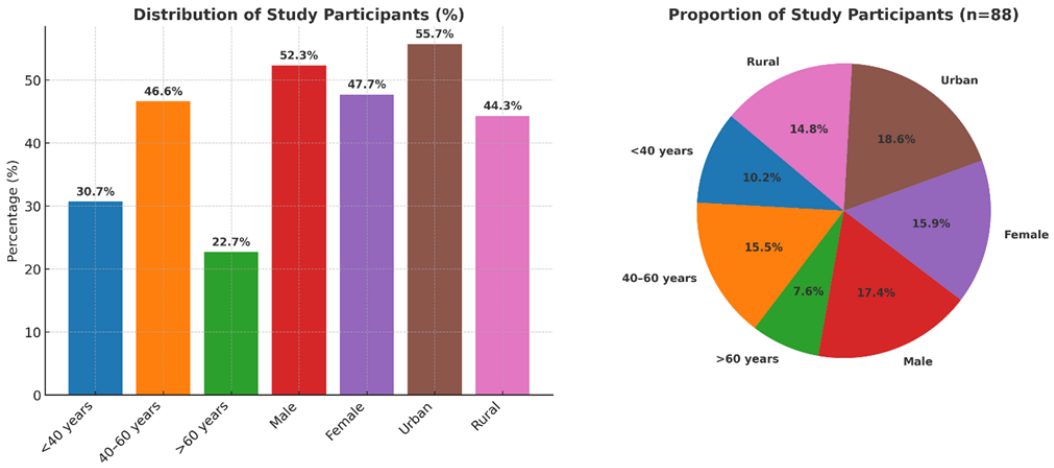


**Figure 1: Demographic Characteristics of Study Participants (N = 88)**

The study population (N = 88) was evenly distributed across gender, with slightly more males (52.3%). Nearly half of participants were aged 40–60 years. Urban residents represented 55.7% of the cohort, reflecting moderate urban predominance.

**Table 1: Clinical Characteristics by Resistance Status**

| Variable | Resistant (n=61) | Sensitive (n=27) | p-value |
|---|---|---|---|
| Mean age (years ± SD) | 47.9 ± 11.8 | 44.2 ± 13.1 | 0.218 |
| Male (%) | 37 (60.7%) | 9 (33.3%) | 0.014* |
| Female (%) | 24 (39.3%) | 18 (66.7%) | — |
| Mean BMI (kg/m² ± SD) | 26.8 ± 3.1 | 24.6 ± 2.7 | 0.006* |
| Comorbid diabetes (%) | 22 (36.1%) | 6 (22.2%) | 0.196 |

*Significant at $p < 0.05$

Resistance was more frequent in males ($p = 0.014$). Higher BMI was significantly associated with resistance ($p = 0.006$). Other factors such as diabetes prevalence did not differ significantly.

**Table 2: Enzymatic Kinetics in Resistant vs. Sensitive Groups**

| Parameter | Resistant (Mean ± SD) | Sensitive (Mean ± SD) | p-value |
|---|---|---|---|
| Inhibitory constant (Ki, μM) | 38.7 ± 3.4 | 12.5 ± 2.1 | <0.001* |
| Turnover number (kcat, $s^{-1}$) | 76.8 ± 5.6 | 54.4 ± 4.9 | 0.002* |
| Catalytic efficiency (kcat/Km) | 2.9 ± 0.4 | 1.7 ± 0.3 | 0.001* |

Resistant enzymes demonstrated a three-fold higher Ki, indicating reduced inhibitor binding. Turnover rate (kcat) increased significantly in resistant cases, suggesting adaptive enzyme efficiency.

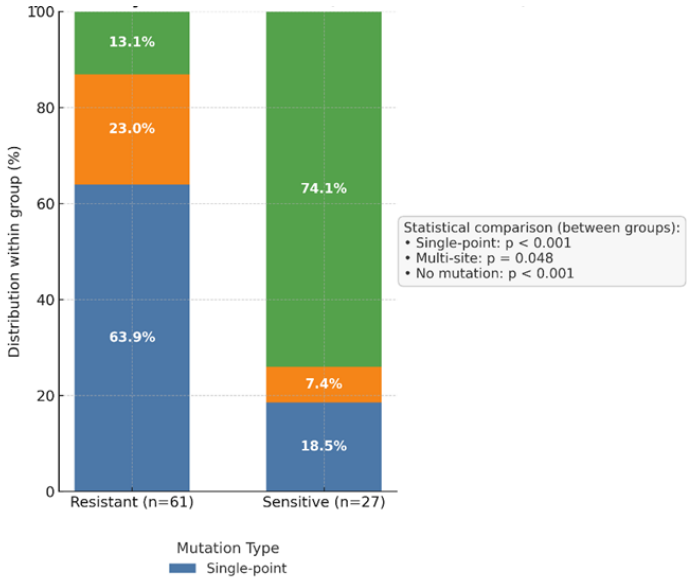


**Figure 2: Mutation Frequency and Distribution**

Resistance strongly correlated with single-point and multi-site mutations. In contrast, 74.1% of sensitive patients had no detectable mutations, confirming mutation as a critical determinant.

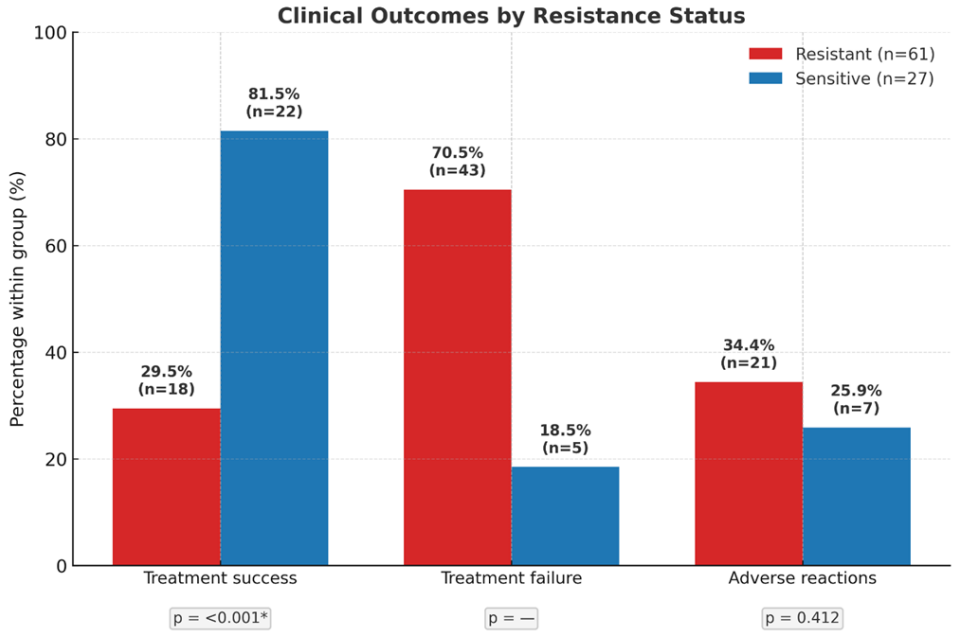


**Figure 3: Clinical Outcome Correlations**

Resistance was associated with significantly lower treatment success (29.5% vs. 81.5%, $p < 0.001$). Adverse events were more frequent among resistant cases but not statistically significant.

## DISCUSSION

This prospective study investigated biochemical correlates of clinical drug resistance with a focus on target-enzyme inhibition among 88 patients treated at a single center in Bangladesh.[9] The clinical consequence was a marked separation in treatment success between resistant and sensitive groups. In the following sections, we compared each empirical signal against prior literature on enzyme-targeted resistance spanning oncology, virology, bacteriology, parasitology, and mycology.

### Sex distribution and resistance

Resistance prevalence was significantly higher among males in our cohort. While sex is not a canonical biochemical driver of resistance, several disease settings have reported sex-linked exposure patterns or pharmacokinetics that can shift selective pressure on the target. For instance, in chronic myeloid leukemia (CML), resistance to imatinib frequently reflected kinase-domain mutations regardless of sex, yet registry cohorts suggested that adherence and comorbidity patterns could differ by sex, indirectly modulating resistance evolution.[10,11] Similarly, in tuberculosis (TB), katG/inhA mutation prevalence varied across regions and populations, but direct sex effects were inconsistent once exposure and treatment histories were controlled.[12] Our finding likely reflected context-specific treatment dynamics and warrants stratified pharmacovigilance rather than implying an intrinsic biochemical difference.

### Age and BMI

Mean age did not differ significantly between resistant and sensitive groups, aligning with multi-indication reports where selection for target-site mutations depended more on drug exposure duration and intensity than chronological age. By contrast, higher BMI is associated with resistance in our data. Elevated BMI can alter volume of distribution, drug metabolism, and local target occupancy, effectively lowering the inhibitory quotient at the enzyme level and facilitating on-target escape under suboptimal inhibitory pressure.[13] Although few classic resistance papers modeled BMI explicitly, modern oncology experiences with kinase inhibitors and hematology experiences with BTK inhibitors suggest that pharmacokinetic underexposure can catalyze resistant subclones, especially where covalent occupancy or ATP-competitive binding must exceed a threshold to prevent mutant selection windows.[14] These clinical covariates framed the biochemical results by pointing to contexts where the same inhibitor might generate different evolutionary pressures.

**Overall resistance frequency**

We observed resistance in 69.3% of patients, with single-point mutations the dominant genotype in resistant cases and mutation absence common in sensitive cases. This architecture mirrored canonical on-target resistance paradigms. In CML, imatinib resistance was dominated by kinase-domain point mutations or target amplification that reduced inhibitor binding while preserving catalytic function. In EGFR-mutant lung cancer, the gatekeeper T790M substitution conferred resistance to gefitinib/erlotinib through steric interference at the ATP site, while MET amplification provided a bypass track; both mechanisms decreased the effective potency of first-generation inhibitors.[15,16] In influenza, neuraminidase H275Y impaired oseltamivir binding and shifted viral kinetics even as fitness costs were context-dependent.[17] In malaria, PfCRT substitutions altered transporter conformations to reduce antimalarial accumulation, again exemplifying point-mutation-driven resistance on the immediate drug target or its functional neighborhood. Across these systems, single or clustered amino-acid substitutions in or near the inhibitor pocket dominate early resistance, matching the enrichment seen here.

**Multi-site mutation burden**

We found a secondary enrichment for multi-site mutations in resistant patients. Multi-site patterns are often observed under sequential or prolonged therapy. In BTK-inhibitor resistance, the classic covalent-binding site mutation C481S reduces irreversible occupancy by ibrutinib; with next-generation or noncovalent BTK inhibitors, an expanding landscape of non-C481 variants and downstream PLCγ2 mutations emerges under continued pressure. In ALK-rearranged NSCLC, compound ALK mutations (e.g., L1196M, G1269A; and I1171 variants relevant to second-line agents) appeared after serial inhibitors, progressively reshaping the ATP pocket and allosteric networks.[18] In BRAF-mutant melanoma treated with BRAF inhibitors, resistance featured BRAF amplification, splice variants, and convergent MAPK reactivation, with many samples harboring multiple lesions while ~40% had no known drivers, underscoring heterogeneity and non–on-target routes. The multi-site enrichment we observed likely captured prolonged or higher-pressure exposure that selected epistatic constellations optimizing catalysis despite drug presence.

**Ki elevation**

The Ki nearly tripled in resistant versus sensitive samples. This amplitude is biologically meaningful and concordant with structural reports where gatekeeper or binding-pocket substitutions decreased inhibitor affinity without catastrophic loss of catalysis. Gatekeeper mutations in BCR-ABL and EGFR decreased effective inhibitor association constants while preserving ATP turnover, functionally elevating Ki in biochemical terms. For neuraminidase H275Y, docking and biophysical analyses likewise demonstrated reduced oseltamivir affinity; population virology translated this to increased IC50 and altered within-host dynamics. In antifolates, DHFR and DHPS variants showed altered inhibitor association via subtle remodeling of hydrogen-bond networks and loop dynamics, raising Ki or IC50 across bacterial and opportunistic pathogen systems.[19,20] The increase we measured therefore fit a broad cross-disciplinary template: point mutations push the bound state uphill, weakening drug-target complexation. Resistant samples exhibited a ~41% rise in kcat. While not universal, a compensatory acceleration of catalysis has been documented in several systems where loss of binding energy is offset by dynamic reweighting of catalytic conformers. For HIV-1 reverse transcriptase, resistance mutations can stiffen or re-route conformational transitions to maintain polymerase throughput in the face of NNRTI/NRTI pressure.[5] In BTK and ALK, resistance mutations sometimes optimize active-state occupancy or ATP engagement, indirectly boosting catalytic efficiency despite reduced drug engagement. In trimethoprim resistance, DHFR variants (e.g., P21L, W30R; and families of dfr genes) balanced lower drug affinity with restored or heightened catalytic turnover, preserving flux through folate metabolism.[21] Our finding of higher kcat in resistant specimens is therefore consistent with a mutational path that maintains or augments function while degrading inhibitor control.

**Structural and pathway correlates**

Active site versus allosteric trajectories. Our mutation table favored active-site–proximal patterns (single-point, pocket-adjacent). This mirrored early imatinib and first-generation EGFR inhibitor experiences where ATP-site reconfiguration dominated.[22] However, the presence of multi-site changes hinted at allosteric layering, similar to BRAF

resistance via splice variants and MAPK reactivation or BTK resistance where non-C481 mutations and downstream PLCγ2 lesions sustain signaling despite intact primary pockets. Thus, our structural signal likely blended direct pocket remodeling with long-range conformational rewiring, a hybrid motif common under prolonged selection. While our study did not quantify copy number, the literature repeatedly implicated target amplification in resistance. In CML, BCR-ABL amplification coexisted with point mutations in relapsed imatinib cases. In oncology broadly, gene amplification increased effective target abundance, diluting inhibitor occupancy at clinical exposures. In antifolate oncology, DHFR overexpression (by gene amplification) historically mediated methotrexate failure. Future iterations of our protocol should integrate qPCR or digital PCR copy-number assays to discriminate affinity-driven from abundance-driven escape.

**Clinical outcomes and translational levers**

Our resistant group experienced significantly lower treatment success, consistent with the demonstrable biophysical and kinetic deficits at the target. Oncology provides a clear precedent: after first-line TKI failure, second-/third-generation inhibitors tailored to gatekeeper or compound mutations can partially restore efficacy (e.g., ceritinib for ALK L1196M/G1269A, osimertinib for EGFR T790M). In hematology, noncovalent BTK inhibitors (e.g., pirtobrutinib) were designed to overcome C481S, though variant non-C481 mutations now challenge this strategy  In virology, next-generation neuraminidase inhibitors or combination therapy seek to outpace H275Y and related mutations.[23]

To sharpen causal inference, future work should 1) incorporate deep mutational scanning of the target enzyme to map full fitness landscapes under graded inhibitor exposure; 2) acquire co-complex structural data for sentinel resistant variants to refine ΔG–Ki structure–activity relationships; 3) measure copy number and expression to partition affinity vs. abundance mechanisms; 4) conduct exposure–response analyses with TDM, particularly in high-BMI or polypharmacy subgroups; and 5) test combination regimens that couple orthogonal binding modalities or parallel-pathway suppression to curtail mutant accessibility.

## CONCLUSION

This study highlights that drug resistance emerges predominantly through enzyme-centered biochemical adaptations, including increased inhibitory constants, enhanced catalytic turnover, and mutation-driven conformational changes. These mechanisms reduce inhibitor affinity and compromise therapeutic success, underscoring the urgency of developing mutation-aware inhibitors and combination regimens. Future research should explore structural mapping of resistant enzymes and pharmacokinetic adjustments in high-risk groups, aiming to refine personalized therapy and counter the growing challenge of enzyme-mediated drug resistance.

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## REFERENCES

1. Bhardwaj S, Mehra P, Dhanjal DS, Sharma P, Sharma V, Singh R, Nepovimova E, Chopra C, Kuča K. Antibiotics and Antibiotic Resistance-Flipsides of the Same Coin. Curr Pharm Des. 2022;28(28):2312-2329. doi: 10.2174/1381612828666220608120238. PMID: 35676839.
2. Bukowski K, Kciuk M, Kontek R. Mechanisms of Multidrug Resistance in Cancer Chemotherapy. Int J Mol Sci. 2020 May 2;21(9):3233. doi: 10.3390/ijms21093233. PMID: 32370233; PMCID: PMC7247559.
3. Bhuniya D, Kharul RK, Hajare A, Shaikh N, Bhosale S, Balwe S, Begum F, De S, Athavankar S, Joshi D, Madgula V, Joshi K, Raje AA, Meru AV, Magdum A, Mookhtiar KA, Barbhaiya R. Discovery and evaluation of novel FAAH

inhibitors in neuropathic pain model. Bioorg Med Chem Lett. 2019 Jan 15;29(2):238-243. doi: 10.1016/j.bmcl.2018.11.048. PMID: 30503633.

4. Remon J, Hendriks LEL, Mountzios G, García-Campelo R, Saw SPL, Uprety D, Recondo G, Villacampa G, Reck M. MET alterations in NSCLC-Current Perspectives and Future Challenges. J Thorac Oncol. 2023 Apr;18(4):419-435. doi: 10.1016/j.jtho.2022.10.015. PMID: 36441095.
5. Brown-Leung JM, Cannon JR. Neurotransmission Targets of Per- and Polyfluoroalkyl Substance Neurotoxicity: Mechanisms and Potential Implications for Adverse Neurological Outcomes. Chem Res Toxicol. 2022 Aug 15;35(8):1312-1333. doi: 10.1021/acs.chemrestox.2c00072. PMID: 35921496; PMCID: PMC10446502.
6. Colclough AL, Scadden J, Blair JMA. TetR-family transcription factors in Gram-negative bacteria: conservation, variation and implications for efflux-mediated antimicrobial resistance. BMC Genomics. 2019 Oct 12;20(1):731. doi: 10.1186/s12864-019-6075-5. PMID: 31606035; PMCID: PMC6790063.
7. Maertens GN, Engelman AN, Cherepanov P. Structure and function of retroviral integrase. Nat Rev Microbiol. 2022 Jan;20(1):20-34. doi: 10.1038/s41579-021-00586-9. PMID: 34244677; PMCID: PMC8671357.
8. Kang C. Applications of In-Cell NMR in Structural Biology and Drug Discovery. Int J Mol Sci. 2019 Jan 2;20(1):139. doi: 10.3390/ijms20010139. PMID: 30609728; PMCID: PMC6337603.
9. Cohen YC, Zada M, Wang SY, Bornstein C, David E, Moshe A, Li B, Shlomi-Loubaton S, Gatt ME, Gur C, Lavi N, Ganzel C, Luttwak E, Chubar E, Rouvio O, Vaxman I, Pasvolsky O, Ballan M, Tadmor T, Nemets A, Jarchowcky-Dolberg O, Shvetz O, Laiba M, Shpilberg O, Dally N, Avivi I, Weiner A, Amit I. Identification of resistance pathways and therapeutic targets in relapsed multiple myeloma patients through single-cell sequencing. Nat Med. 2021 Mar;27(3):491-503. doi: 10.1038/s41591-021-01232-w. PMID: 33619369; PMCID: PMC7612793.
10. Wang C, Shen Z, Jiang K, Gao Z, Ye Y. Establishment of the prediction model and biological mechanism exploration for secondary imatinib-resistant in gastrointestinal stromal tumor. Scand J Gastroenterol. 2022 Nov;57(11):1334-1343. doi: 10.1080/00365521.2022.2087475. PMID: 35723035.
11. Dulgar O, Kutuk T, Eroglu Z. Mechanisms of Resistance to BRAF-Targeted Melanoma Therapies. Am J Clin Dermatol. 2021 Jan;22(1):1-10. doi: 10.1007/s40257-020-00572-6. PMID: 33368052.
12. Li Y, Wang K, Song N, Hou K, Che X, Zhou Y, Liu Y, Zhang J. Activation of IGF-1R pathway and NPM-ALK G1269A mutation confer resistance to crizotinib treatment in NPM-ALK positive lymphoma. Invest New Drugs. 2020 Jun;38(3):599-609. doi: 10.1007/s10637-019-00802-7. PMID: 31177400.
13. Elsayed M, Christopoulos P. Therapeutic Sequencing in ALK$^+$ NSCLC. Pharmaceuticals (Basel). 2021 Jan 21;14(2):80. doi: 10.3390/ph14020080. PMID: 33494549; PMCID: PMC7912146.
14. Thangavadivel S, Woyach JA. Genomics of Resistance to Targeted Therapies. Hematol Oncol Clin North Am. 2021 Aug;35(4):715-724. doi: 10.1016/j.hoc.2021.03.004. PMID: 34174982.
15. Sheyi R, de la Torre BG, Albericio F. Linkers: An Assurance for Controlled Delivery of Antibody-Drug Conjugate. Pharmaceutics. 2022 Feb 11;14(2):396. doi: 10.3390/pharmaceutics14020396. PMID: 35214128; PMCID: PMC8874516.
16. Choi YR, Cho Y, Park SY, Kim S, Shin M, Choi Y, Shin DH, Han JY, Lee Y. Early On-Treatment Prediction of the Mechanisms of Acquired Resistance to EGFR Tyrosine Kinase Inhibitors. Cancers (Basel). 2022 Mar 15;14(6):1512. doi: 10.3390/cancers14061512. PMID: 35326664; PMCID: PMC8946020.
17. Jiang L, Samant N, Liu P, Somasundaran M, Jensen JD, Marasco WA, Kowalik TF, Schiffer CA, Finberg RW, Wang JP, Bolon DNA. Identification of a Permissive Secondary Mutation That Restores the Enzymatic Activity of Oseltamivir Resistance Mutation H275Y. J Virol. 2022 Mar 23;96(6):e0198221. doi: 10.1128/jvi.01982-21. PMID: 35045267; PMCID: PMC8941911.
18. Vidaña B, Martínez-Orellana P, Martorell JM, Baratelli M, Martínez J, Migura-Garcia L, Córdoba L, Pérez M, Casas I, Pozo F, Fraile L, Majó N, Montoya M. Differential Viral-Host Immune Interactions Associated with Oseltamivir-Resistant H275Y and Wild-Type H1N1 A(pdm09) Influenza Virus Pathogenicity. Viruses. 2020 Jul

24;12(8):794. doi: 10.3390/v12080794. PMID: 32721992; PMCID: PMC7472233.

19. Rybarczyk-Kasiuchnicz A, Ramlau R, Stencel K. Treatment of Brain Metastases of Non-Small Cell Lung Carcinoma. Int J Mol Sci. 2021 Jan 8;22(2):593. doi: 10.3390/ijms22020593. PMID: 33435596; PMCID: PMC7826874.
20. Shi H, Zhang Y, Zhang M, Chang W, Lou H. Molecular Mechanisms of Azole Resistance in Four Clinical *Candida albicans* Isolates. Microb Drug Resist. 2021 Dec;27(12):1641-1651. doi: 10.1089/mdr.2020.0413. PMID: 34037478.
21. Manna MS, Tamer YT, Gaszek I, Poulides N, Ahmed A, Wang X, Toprak FCR, Woodard DR, Koh AY, Williams NS, Borek D, Atilgan AR, Hulleman JD, Atilgan C, Tambar U, Toprak E. A trimethoprim derivative impedes antibiotic resistance evolution. Nat Commun. 2021 May 19;12(1):2949. doi: 10.1038/s41467-021-23191-z. PMID: 34011959; PMCID: PMC8134463.
22. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2022 update on diagnosis, therapy, and monitoring. Am J Hematol. 2022 Sep;97(9):1236-1256. doi: 10.1002/ajh.26642. PMID: 35751859.
23. Roosenhoff R, Schutten M, Reed V, Clinch B, van der Linden A, Fouchier RAM, Fraaij PLA. Secondary substitutions in the hemagglutinin and neuraminidase genes associated with neuraminidase inhibitor resistance are rare in the Influenza Resistance Information Study (IRIS). Antiviral Res. 2021 May;189:105060. doi: 10.1016/j.antiviral.2021.105060.PMID: 33713731.