The Pharmaceutical and Chemical Journal, 2024, 11(6):76-83

Available online www.tpcj.org

Review Article

ISSN: 2349-7092
CODEN(USA): PCJHBA

Protein Kinase Inhibitors in Cancer Treatment: Mechanisms, Challenges, and Future Prospects

Zainab Munawar Ali, Dr. Bhupendra Vyas, Dr. Yuvraj Singh Sarangdevot

Faculty of Pharmacy, Bhupal Nobles' University, Udaipur

Abstract Protein kinase inhibitors (PKIs) have emerged as a cornerstone in modern oncology, offering targeted therapeutic approaches for various cancers by selectively inhibiting aberrant kinase activity. Protein kinases play a crucial role in cellular signaling, and their dysregulation contributes to tumor progression, metastasis, and drug resistance. Small-molecule inhibitors and monoclonal antibodies targeting kinases have demonstrated significant clinical success, particularly in treating hematologic malignancies and solid tumors. However, challenges such as drug resistance, off-target effects, and tumor heterogeneity limit their long-term efficacy. Emerging strategies, including allosteric inhibitors, PROTACs (Proteolysis-Targeting Chimeras), and AI-driven drug discovery, are shaping the future of PKI therapy. This review explores the mechanisms, challenges, and future prospects of PKIs in cancer treatment, highlighting advancements that aim to improve therapeutic outcomes and overcome existing limitations.

Keywords: Protein kinase inhibitors, Cancer, small-molecule inhibitors, kinase signaling pathways

Introduction

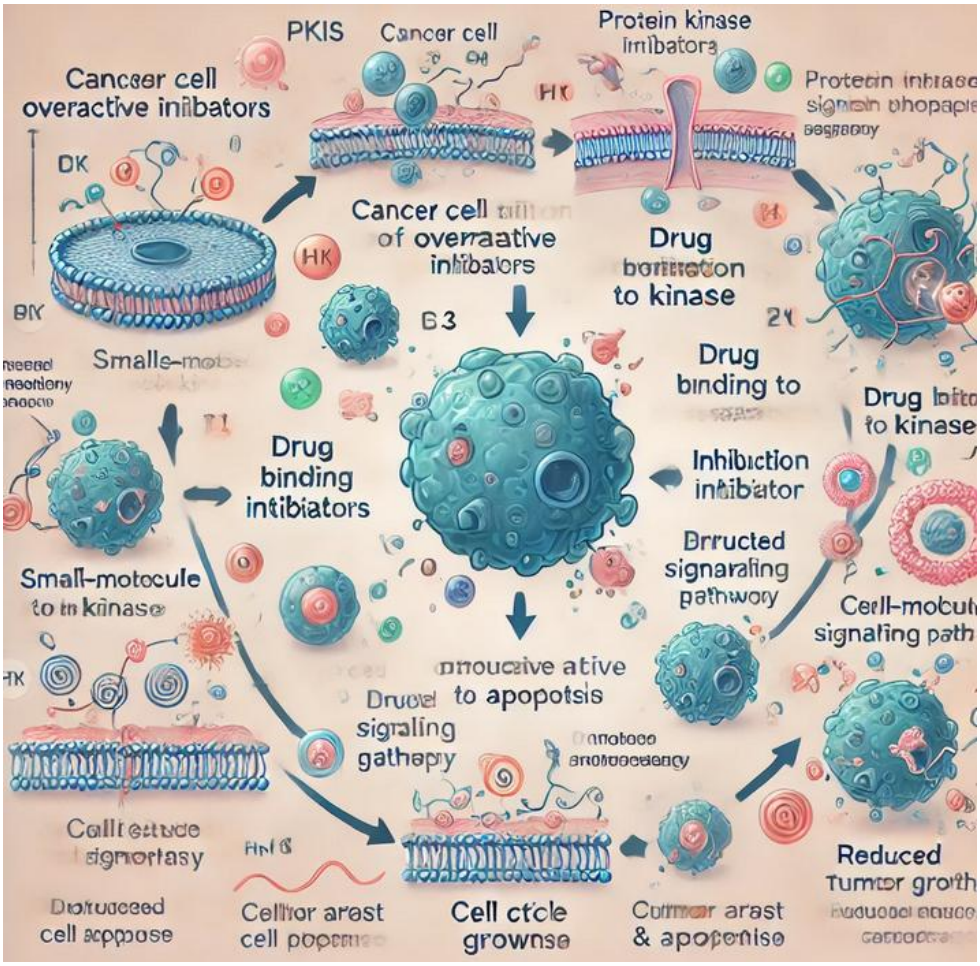
Cancer is a leading cause of morbidity and mortality worldwide, with an estimated 20 million new cases and 10 million deaths reported annually [1]. The disease burden varies across regions, influenced by genetic, environmental, and lifestyle factors. The most common cancers globally include lung, breast, colorectal, prostate, and liver cancers, with lung cancer being the leading cause of cancer-related deaths [2]. Risk factors such as smoking, obesity, infections (e.g., HPV, H. pylori), and exposure to carcinogens contribute significantly to cancer incidence. Advances in screening, early detection, and targeted therapies have improved survival rates, yet disparities persist, particularly in low-resource settings.

Protein kinases are essential enzymes that regulate various cellular processes by catalyzing the phosphorylation of proteins, a mechanism that controls cell signaling, growth, differentiation, and apoptosis [3]. These enzymes transfer a phosphate group from ATP to specific amino acid residues, modulating protein activity and signaling cascades. Protein kinases are broadly classified into tyrosine kinases and serine/threonine kinases**,** based on their substrate specificity [4].

Dysregulation of protein kinases plays a pivotal role in numerous diseases, particularly cancer, where aberrant kinase activity drives tumor growth and progression [5]. Mutations, overexpression, or chromosomal rearrangements in kinase genes lead to sustained activation of oncogenic pathways, making protein kinases attractive therapeutic targets. Small-molecule inhibitors and monoclonal antibodies targeting kinases have revolutionized cancer treatment, improving patient outcomes through precision medicine [6].

Protein kinases play a crucial role in regulating cellular functions such as growth, proliferation, differentiation, and apoptosis by phosphorylating target proteins [7]. In cancer, dysregulated kinase activity leads to uncontrolled cell

division, evasion of apoptosis, and increased metastasis. Mutations, gene amplifications, or overexpression of kinases like EGFR, HER2, BCR-ABL, and VEGFR drive tumor progression by hyperactivating oncogenic signaling pathways such as MAPK/ERK, PI3K/AKT, and JAK/STAT [8]**.** These aberrant signaling cascades promote angiogenesis, drug resistance, and immune evasion, making protein kinases critical targets for anticancer therapy. Inhibiting these kinases with targeted drugs has revolutionized cancer treatment, improving patient survival and outcomes [9].



Protein kinase inhibitors (PKIs) have transformed cancer treatment by specifically targeting dysregulated kinase signaling pathways that drive tumor growth and progression [10]. Unlike conventional chemotherapy, which affects both cancerous and healthy cells, PKIs offer a more selective approach, reducing toxicity and improving patient outcomes.

PKIs block the activity of oncogenic kinases such as EGFR, HER2, BCR-ABL, and VEGFR, thereby inhibiting cell proliferation, inducing apoptosis, and preventing angiogenesis [11]. Their use in targeted therapy has led to significant advancements in precision medicine, allowing for personalized treatments based on tumor-specific mutations.

Despite their success, challenges such as drug resistance, off-target effects, and tumor heterogeneity necessitate ongoing research to develop next-generation inhibitors [12]. Advances in computational drug discovery, combination therapies, and biomarker-based patient selection continue to refine PKI efficacy, making them a cornerstone of modern oncology.Objectives and scope of the review

Protein kinases are critical regulators of cellular signaling pathways that control growth, proliferation, differentiation, and apoptosis [13]. These enzymes function by transferring phosphate groups to target proteins, modulating their

activity and ensuring proper cellular function. However, in cancer, dysregulation of protein kinases leads to uncontrolled cell division, evasion of apoptosis, and increased tumor progression [14].

Protein kinases are broadly categorized into:

- Tyrosine Kinases (TKs) – Involved in growth factor signaling and often mutated in cancers (e.g., EGFR, HER2, BCR-ABL).
- Serine/Threonine Kinases (STKs) – Regulate cell cycle and survival pathways (e.g., RAF, AKT, CDKs).
- Dual-Specificity Kinases – Target both tyrosine and serine/threonine residues, influencing multiple cancer pathways.

Mechanisms of Protein Kinase Dysregulation in Cancer

- Gene Mutations & Amplifications – Mutations in kinase genes can result in constitutive activation, promoting oncogenesis (e.g., BRAF V600E in melanoma).
- Overexpression – Increased kinase expression leads to hyperactive signaling and uncontrolled proliferation (e.g., HER2 in breast cancer).
- Chromosomal Rearrangements – Fusion proteins like BCR-ABL drive leukemogenesis in chronic myeloid leukemia (CML).

Oncogenic Signaling Pathways Driven by Kinases

- MAPK/ERK Pathway – Promotes cell proliferation and survival (e.g., RAS-RAF-MEK-ERK cascade). PI3K/AKT/mTOR Pathway – Regulates metabolism, growth, and survival; frequently altered in cancer [15]. JAK/STAT Pathway – Involved in immune evasion and cytokine signaling in hematological malignancies.

Types of Protein kinase inhibitors (PKIs):

Protein kinase inhibitors (PKIs) are a crucial class of targeted cancer therapies designed to block the activity of protein kinases that drive tumor growth [16]. These inhibitors are broadly categorized into small-molecule inhibitors and monoclonal antibodies**,** each with distinct mechanisms and therapeutic advantages. Both types have significantly improved cancer treatment by selectively targeting dysregulated signaling pathways while minimizing damage to healthy cells [17].

Small-molecule inhibitors: are low-molecular-weight compounds that can easily penetrate cell membranes and bind directly to the kinase's active site [18]. These inhibitors typically compete with ATP for binding, thereby preventing phosphorylation and downstream signaling that promote cancer cell survival and proliferation. Some SMIs, such **as** Imatinib**,** Erlotinib**,** and Sorafenib**,** have shown remarkable success in treating cancers like chronic myeloid leukemia (CML), non-small cell lung cancer (NSCLC), and renal cell carcinoma [19]. The key advantages of SMIs include their ability to target intracellular kinases, their oral bioavailability, and ease of chemical modifications to enhance potency. However, challenges such as acquired drug resistance, off-target effects, and limited selectivity pose significant hurdles in their clinical application.

In contrast, monoclonal antibodies (mAbs) are large, protein-based drugs that primarily target extracellular domains of receptor tyrosine kinases (RTKs) [20]. These antibodies block ligand binding, preventing receptor activation and subsequent signaling cascades that drive cancer progression. Some mAbs, such as Trastuzumab**,** Cetuximab, and Bevacizumab**,** have been instrumental in treating cancers like breast, colorectal, and lung cancers. Beyond direct inhibition, mAbs can also induce immune-mediated cytotoxicity, enhancing the body's natural immune response against cancer cells [21]. The benefits of monoclonal antibodies include their high specificity, long half-life, and reduced off-target toxicity. However, they have limitations such as poor intracellular penetration, intravenous administration requirements, and potential immune reactions.

Both small-molecule inhibitors and monoclonal antibodies have transformed cancer treatment, offering more effective and less toxic alternatives to traditional chemotherapy [22]. Despite their success, the emergence of resistance mechanisms, limited efficacy in some cancers, and high treatment costs highlight the need for continuous research and innovation [23]. Future advancements in computational drug design, combination therapies, and biomarker-driven personalized treatments are expected to further optimize PKI efficacy and broaden their therapeutic applications in oncology.

Challenges in Protein Kinase Inhibitor Therapy

Despite the success of protein kinase inhibitors (PKIs) in targeted cancer therapy, several challenges limit their long-term efficacy and clinical application [24]. One of the major challenges is drug resistance, which can occur through various mechanisms such as secondary mutations in the kinase domain, activation of alternative signaling pathways, or overexpression of efflux transporters that reduce drug accumulation in cancer cells. For example, resistance to Imatinib in chronic myeloid leukemia (CML) is often caused by mutations in the BCR-ABL kinase domain, necessitating the development of second- and third-generation inhibitors like Dasatinib and Ponatinib [25].

Another significant challenge is off-target effects and toxicity, as many PKIs may unintentionally inhibit other kinases, leading to adverse side effects [26]. Since kinases play crucial roles in normal cellular functions, their inhibition can result in toxicities such as cardiovascular complications, liver toxicity, and skin reactions. For instance, Sorafenib and Sunitinib, which target multiple kinases, are associated with hypertension and hand-foot syndrome, limiting their tolerability in some patients [27]. The development of more selective inhibitors and personalized dosing strategies is essential to mitigate these side effects while maintaining therapeutic efficacy.

Tumor heterogeneity also poses a major challenge in PKI therapy. Cancer cells within the same tumor can exhibit genetic and molecular differences, leading to variable responses to kinase inhibitors [28]. This heterogeneity makes it difficult to achieve consistent and durable responses, as some cancer cells may inherently resist treatment or adapt over time. The use of combination therapies, where PKIs are paired with other targeted agents, chemotherapy, or immunotherapy, is being explored to overcome this challenge and improve patient outcomes [29].

Lastly, the high cost and accessibility of PKIs present a barrier to their widespread use, particularly in low- and middle-income countries [30]. Many kinase inhibitors are expensive due to the complexity of their development, clinical trials, and regulatory approvals. Additionally, the need for continuous monitoring and dose adjustments adds to the overall treatment cost. Addressing these financial and logistical barriers requires efforts from pharmaceutical companies, healthcare systems, and policymakers to make PKI therapies more affordable and accessible to all patients [31].

Despite these challenges, ongoing research and technological advancements, such as computational drug design, biomarker-driven therapies, and next-generation kinase inhibitors, continue to enhance the effectiveness of PKI therapy [32]. Overcoming resistance mechanisms, improving drug specificity, and integrating PKIs into combination treatment strategies will be key to maximizing their potential in modern oncology.

Emerging Strategies and Future Prospects

The continuous evolution of cancer therapy has led to the development of next-generation protein kinase inhibitors (PKIs) that aim to overcome resistance, improve selectivity, and enhance patient outcomes [34]. One promising approach is the design of covalent inhibitors, which form an irreversible bond with the kinase active site, leading to prolonged inhibition and reduced likelihood of resistance [34]. Drugs like Osimertinib, a third-generation EGFR inhibitor, have demonstrated success in overcoming resistance mutations in non-small cell lung cancer (NSCLC).

Another emerging strategy is the use of allosteric inhibitors, which bind to regulatory sites rather than the ATP-binding domain [35]. This approach provides greater specificity by targeting unique conformational states of kinases, minimizing off-target effects. For example, MK-2206, an allosteric AKT inhibitor, has shown potential in preclinical and clinical studies [36]. Additionally, dual and multi-target kinase inhibitors are being developed to block multiple oncogenic pathways simultaneously, reducing the ability of cancer cells to bypass therapy. Drugs like Lenvatinib and Cabozantinib, which target VEGFR, RET, and MET kinases, have shown effectiveness in resistant tumors [37].

Combination therapies are also gaining attention, where PKIs are used alongside chemotherapy, immunotherapy, or other targeted agents to enhance therapeutic efficacy [38]. Combining PKIs with immune checkpoint inhibitors (ICIs), such as nivolumab or pembrolizumab, has shown promising results in enhancing immune response and overcoming tumor resistance. Similarly, integrating PKIs with epigenetic modulators can help reprogram cancer cells to become more responsive to kinase inhibition [39].

Advancements in computational drug discovery and artificial intelligence (AI)-driven screening are revolutionizing PKI development [40]. Virtual screening, molecular docking, and deep learning algorithms are accelerating the identification of novel kinase inhibitors with improved selectivity and efficacy. Additionally, biomarker-driven precision medicine is helping to tailor PKI therapies based on an individual's tumor profile, ensuring maximum benefit while minimizing adverse effects [41].

Looking ahead, nanotechnology-based drug delivery systems and PROTAC (Proteolysis-Targeting Chimeras) technology represent exciting frontiers in PKI therapy. Nanoparticles can improve the bioavailability and targeted delivery of PKIs, while PROTACs offer a new approach by degrading oncogenic kinases rather than simply inhibiting them [42]. As research progresses, these innovations hold the potential to redefine the landscape of kinase-targeted cancer therapy, making treatments more effective, durable, and accessible to a broader patient population [43].

Conclusion and Future Directions

Protein kinase inhibitors (PKIs) have revolutionized cancer therapy by offering targeted treatment approaches that disrupt aberrant signaling pathways responsible for tumor growth and progression [44]. Over the years, both small-molecule inhibitors and monoclonal antibodies have demonstrated significant success in treating various cancers, including leukemia, lung, breast, and renal cancers. Despite these advancements, challenges such as drug resistance, tumor heterogeneity, off-target effects, and high treatment costs continue to limit their effectiveness [45]. The emergence of next-generation inhibitors, allosteric modulators, combination therapies, and precision medicine approaches has shown promise in addressing these limitations.

While PKIs have transformed oncology, several gaps in research remain. The development of resistance mechanisms against current PKIs underscores the need for novel inhibitors with improved selectivity and longer-lasting efficacy [46]. Additionally, the role of non-receptor kinases, kinase-independent functions, and tumor microenvironment interactions in cancer progression is not fully understood and requires further exploration [47]. Another critical area for improvement is drug affordability and accessibility, particularly in low- and middle-income countries, where the high cost of kinase inhibitors limits their widespread use [48].

Looking ahead, computational drug discovery, artificial intelligence-driven screening, and biomarker-based personalized therapies will play a crucial role in optimizing PKI development. The integration of nanotechnology, PROTACs (Proteolysis-Targeting Chimeras), and multi-target kinase inhibitors holds potential for enhancing drug delivery and overcoming resistance [49]. Additionally, the combination of PKIs with immunotherapy and epigenetic modulators may lead to more durable and effective cancer treatments [50]. As research advances, the next generation of kinase inhibitors is expected to offer greater precision, reduced toxicity, and enhanced therapeutic efficacy, ultimately improving patient outcomes in oncology.

References

[1]. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians, 68*(6), 394–424.

[2]. Mattiuzzi, C., & Lippi, G. (2019). Current cancer epidemiology. *Journal of Epidemiology and Global Health, 9*(4), 217–222.

[3]. Ardito, F., Giuliani, M., Perrone, D., Troiano, G., & Lo Muzio, L. (2017). The crucial role of protein phosphorylation in cell signaling and its use as targeted therapy. *International Journal of Molecular Medicine, 40*(2), 271–280.

[4]. Hardie, D. G. (1999). Plant protein serine/threonine kinases: Classification and functions. *Annual Review of Plant Biology, 50*(1), 97–131.

[5]. Quan, C., Xiao, J., Liu, L., Duan, Q., Yuan, P., & Zhu, F. (2017). Protein kinases as tumor biomarkers and therapeutic targets. *Current Pharmaceutical Design, 23*(29), 4209–4225.

[6]. Hojjat-Farsangi, M. (2014). Small-molecule inhibitors of the receptor tyrosine kinases: Promising tools for targeted cancer therapies. *International Journal of Molecular Sciences, 15*(8), 13768–13801.

[7]. Ardito, F., Giuliani, M., Perrone, D., Troiano, G., & Lo Muzio, L. (2017). The crucial role of protein phosphorylation in cell signaling and its use as targeted therapy. *International Journal of Molecular Medicine, 40*(2), 271–280.

[8]. Kim, M., Baek, M., & Kim, D. J. (2017). Protein tyrosine signaling and its potential therapeutic implications in carcinogenesis. *Current Pharmaceutical Design, 23*(29), 4226–4246.

[9]. Li, W., Croce, K., Steensma, D. P., McDermott, D. F., Ben-Yehuda, O., & Moslehi, J. (2015). Vascular and metabolic implications of novel targeted cancer therapies: Focus on kinase inhibitors. *Journal of the American College of Cardiology, 66*(10), 1160–1178.

[10]. Kannaiyan, R., & Mahadevan, D. (2018). A comprehensive review of protein kinase inhibitors for cancer therapy. *Expert Review of Anticancer Therapy, 18*(12), 1249–1270.

[11]. Attwood, M. M., Fabbro, D., Sokolov, A. V., Knapp, S., & Schiöth, H. B. (2021). Trends in kinase drug discovery: Targets, indications and inhibitor design. *Nature Reviews Drug Discovery, 20*(11), 839–861.

[12]. Catenacci, D. V. (2015). Next-generation clinical trials: Novel strategies to address the challenge of tumor molecular heterogeneity. *Molecular Oncology, 9*(5), 967–996.

[13]. Wada, T., & Penninger, J. M. (2004). Mitogen-activated protein kinases in apoptosis regulation. *Oncogene, 23*(16), 2838–2849.

[14]. Plati, J., Bucur, O., & Khosravi-Far, R. (2008). Dysregulation of apoptotic signaling in cancer: Molecular mechanisms and therapeutic opportunities. *Journal of Cellular Biochemistry, 104*(4), 1124–1149.

[15]. Ersahin, T., Tuncbag, N., & Cetin-Atalay, R. (2015). The PI3K/AKT/mTOR interactive pathway. *Molecular BioSystems, 11*(7), 1946–1954.

[16]. Kannaiyan, R., & Mahadevan, D. (2018). A comprehensive review of protein kinase inhibitors for cancer therapy. *Expert Review of Anticancer Therapy, 18*(12), 1249–1270.

[17]. Plati, J., Bucur, O., & Khosravi-Far, R. (2008). Dysregulation of apoptotic signaling in cancer: Molecular mechanisms and therapeutic opportunities. *Journal of Cellular Biochemistry, 104*(4), 1124–1149.

[18]. Toogood, P. L. (2002). Inhibition of protein−protein association by small molecules: Approaches and progress. *Journal of Medicinal Chemistry, 45*(8), 1543–1558.

[19]. Hojjat-Farsangi, M. (2014). Small-molecule inhibitors of the receptor tyrosine kinases: Promising tools for targeted cancer therapies. *International Journal of Molecular Sciences, 15*(8), 13768–13801.

[20]. Tolmachev, V., Stone-Elander, S., & Orlova, A. (2010). Radiolabelled receptor-tyrosine-kinase targeting drugs for patient stratification and monitoring of therapy response: Prospects and pitfalls. *The Lancet Oncology, 11*(10), 992–1000.

[21]. Seledtsov, V. I., Goncharov, A. G., & Seledtsova, G. V. (2015). Clinically feasible approaches to potentiating cancer cell-based immunotherapies. *Human Vaccines & Immunotherapeutics, 11*(4), 851–869.

[22]. Gerber, D. E. (2008). Targeted therapies: A new generation of cancer treatments. *American Family Physician, 77*(3), 311–319.

[23]. Paulus, R. A., Davis, K., & Steele, G. D. (2008). Continuous innovation in health care: Implications of the Geisinger experience. *Health Affairs, 27*(5), 1235–1245.

[24]. Attwood, M. M., Fabbro, D., Sokolov, A. V., Knapp, S., & Schiöth, H. B. (2021). Trends in kinase drug discovery: Targets, indications and inhibitor design. *Nature Reviews Drug Discovery, 20*(11), 839–861.

[25]. Soverini, S. (2023). Resistance mutations in CML and how we approach them. *Hematology, 2023*(1), 469–475.

[26]. Attwood, M. M., Fabbro, D., Sokolov, A. V., Knapp, S., & Schiöth, H. B. (2021). Trends in kinase drug discovery: Targets, indications and inhibitor design. *Nature Reviews Drug Discovery, 20*(11), 839–861.

[27]. Chu, D., Lacouture, M. E., Fillos, T., & Wu, S. (2008). Risk of hand-foot skin reaction with sorafenib: A systematic review and meta-analysis. *Acta Oncologica, 47*(2), 176–186.

[28]. Jänne, P. A., Gray, N., & Settleman, J. (2009). Factors underlying sensitivity of cancers to small-molecule kinase inhibitors. *Nature Reviews Drug Discovery, 8*(9), 709–723.

[29]. Morel, D., Jeffery, D., Aspeslagh, S., Almouzni, G., & Postel-Vinay, S. (2020). Combining epigenetic drugs with other therapies for solid tumours—Past lessons and future promise. *Nature Reviews Clinical Oncology, 17*(2), 91–107.

[30]. Akhlaq, A., McKinstry, B., Muhammad, K. B., & Sheikh, A. (2016). Barriers and facilitators to health information exchange in low-and middle-income country settings: A systematic review. *Health Policy and Planning, 31*(9), 1310–1325.

[31]. Badran, M. F. (2019). eHealth in Egypt: The demand-side perspective of implementing electronic health records. *Telecommunications Policy, 43*(6), 576–594.

[32]. Suehara, Y., Alex, D., Bowman, A., Middha, S., Zehir, A., Chakravarty, D., Wang, L., Jour, G., Nafa, K., Hayashi, T., & Jungbluth, A. A. (2019). Clinical genomic sequencing of pediatric and adult osteosarcoma reveals distinct molecular subsets with potentially targetable alterations. *Clinical Cancer Research, 25*(21), 6346–6356.

[33]. Murtuza, A., Bulbul, A., Shen, J. P., Keshavarzian, P., Woodward, B. D., Lopez-Diaz, F. J., Lippman, S. M., & Husain, H. (2019). Novel third-generation EGFR tyrosine kinase inhibitors and strategies to overcome therapeutic resistance in lung cancer. *Cancer Research, 79*(4), 689–698.

[34]. Baillie, T. A. (2016). Targeted covalent inhibitors for drug design. *Angewandte Chemie International Edition, 55*(43), 13408–13421.

[35]. Lu, S., Shen, Q., & Zhang, J. (2019). Allosteric methods and their applications: Facilitating the discovery of allosteric drugs and the investigation of allosteric mechanisms. *Accounts of Chemical Research, 52*(2), 492–500.

[36]. Konopleva, M. Y., Walter, R. B., Faderl, S. H., Jabbour, E. J., Zeng, Z., Borthakur, G., Huang, X., Kadia, T. M., Ruvolo, P. P., Feliu, J. B., & Lu, H. (2014). Preclinical and early clinical evaluation of the oral AKT inhibitor, MK-2206, for the treatment of acute myelogenous leukemia. *Clinical Cancer Research, 20*(8), 2226–2235.

[37]. Subbiah, V., Yang, D., Velcheti, V., Drilon, A., & Meric-Bernstam, F. (2020). State-of-the-art strategies for targeting RET-dependent cancers. *Journal of Clinical Oncology, 38*(11), 1209–1221.

[38]. Jin, H., Wang, L., & Bernards, R. (2023). Rational combinations of targeted cancer therapies: Background, advances, and challenges. *Nature Reviews Drug Discovery, 22*(3), 213–234.

[39]. Angus, S. P., Zawistowski, J. S., & Johnson, G. L. (2018). Epigenetic mechanisms regulating adaptive responses to targeted kinase inhibitors in cancer. *Annual Review of Pharmacology and Toxicology, 58*(1), 209–229.

[40]. Dhudum, R., Ganeshpurkar, A., & Pawar, A. (2024). Revolutionizing drug discovery: A comprehensive review of AI applications. *Drugs and Drug Candidates, 3*(1), 148–171.

[41]. Saini, K. S., Loi, S., de Azambuja, E., Metzger-Filho, O., Saini, M. L., Ignatiadis, M., Dancey, J. E., & Piccart-Gebhart, M. J. (2013). Targeting the PI3K/AKT/mTOR and Raf/MEK/ERK pathways in the treatment of breast cancer. *Cancer Treatment Reviews, 39*(8), 935–946.

[42]. Li, Y., Dong, Q., Mei, T., Zheng, M., Kumar, R. R., Yu, B., Wu, C., Zhang, H., & An, F. (2020). Nanosized modification strategies for improving the antitumor efficacy of MEK inhibitors. *Current Drug Targets, 21*(3), 228–251.

[43]. Guo, J., Zhou, Y., & Lu, X. (2023). Advances in protein kinase drug discovery through targeting gatekeeper mutations. *Expert Opinion on Drug Discovery, 18*(12), 1349–1366.

[44]. Kannaiyan, R., & Mahadevan, D. (2018). A comprehensive review of protein kinase inhibitors for cancer therapy. *Expert Review of Anticancer Therapy, 18*(12), 1249–1270.

[45]. Kamb, A., Wee, S., & Lengauer, C. (2007). Why is cancer drug discovery so difficult? *Nature Reviews Drug Discovery, 6*(2), 115–120.

[46]. Kuhn, D. J., Orlowski, R. Z., & Bjorklund, C. C. (2011). Second-generation proteasome inhibitors: Carfilzomib and immunoproteasome-specific inhibitors (IPSIs). *Current Cancer Drug Targets, 11*(3), 285–295.

[47]. Saraon, P., Pathmanathan, S., Snider, J., Lyakisheva, A., Wong, V., & Stagljar, I. (2021). Receptor tyrosine kinases and cancer: Oncogenic mechanisms and therapeutic approaches. *Oncogene, 40*(24), 4079–4093.

[48]. Barrios, C., de Lima Lopes, G., Yusof, M. M., Rubagumya, F., Rutkowski, P., & Sengar, M. (2023). Barriers in access to oncology drugs—A global crisis. *Nature Reviews Clinical Oncology, 20*(1), 7–15.

[49]. Yan, X. Y., Kang, Y. Y., Zhang, Z. Y., Huang, P., Yang, C., & Naranmandura, H. (2024). Therapeutic approaches targeting oncogenic proteins in myeloid leukemia: Challenges and perspectives. *Expert Opinion on Therapeutic Targets, 28*(12), 1131–1148.

[50]. Morel, D., Jeffery, D., Aspeslagh, S., Almouzni, G., & Postel-Vinay, S. (2020). Combining epigenetic drugs with other therapies for solid tumours—Past lessons and future promise. *Nature Reviews Clinical Oncology, 17*(2), 91–107.