Proceedings of ICMMGH 2026 Symposium: Cell and Molecular Biology: Understanding Immune Cell Functions
DOI: 10.54254/2753-8818/2026.PJ31162

Combined Use of Protein Kinase Inhibitors and Targeted Proteins in Cancer Therapy: New Broad Prospects for Cancer Treatment

Yaru Wang

Jinqiu International School, Qingdao, China
baiyi_135@qq.com

Abstract. Malignant tumors constitute a formidable global health challenge. Their high incidence and mortality have spurred the development of clinically safer and more effective novel therapeutics. Although treatments such as chemotherapy are widely used in clinical practice, their significant side effects greatly limit the treatment of cancer. The advent of molecular targeted therapy has ushered in a new era in cancer treatment and management. In the field of cancer treatment, PKN usually refers to protein kinase inhibitors, while TPD refers to targeted protein degradation technology.Protein kinase inhibitors(PKIs)are crucial for the treatment of cancer. However, these drugs often lose effectiveness as cancers develop resistance.Combining protein kinase inhibitors(PKIs)with targeted protein degradation(TPD)is a novel therapeutic approach. Through a systematic review of literature categorized into four thematic areas—'New therapeutic paradigms of protein kinase inhibitors,' 'Combination targeting of TPD and kinase inhibitors in cancer treatment,' 'Protein degradation,' and 'Cancer therapy'—the approaches and experiences in cancer treatment are summarized to explore the feasibility of combining PKN and TPD for cancer therapy. This article also explains how using PKIs and TPD together can achieve better outcomes than using either drug alone. For instance, in scenarios where tumors acquire alternative oncogenic signaling pathways or undergo target alterations, the combinatorial regimen exerts a more potent anti-tumor effect than either monotherapy alone.

Keywords: Protein kinase inhibitors, targeted degradation, combination therapy, drug resistance, drug development protein

1. Introduction

Protein kinases serve as pivotal regulators in core signaling pathways governing cell proliferation,survival,and metabolism. Dysregulation of these kinases significantly predisposes to carcinogenesis. Protein kinase inhibitors(PKIs)have been developed to target these kinases,such as imatinib and osimertinib. PKIs have ushered in a paradigm shift in cancer therapy, transitioning from conventional chemotherapy to precision targeted treatment. The essence of this treatment strategy lies in the ability of protein kinase inhibitors(PKIs)to competitively bind to the ATP-binding pocket of protein kinases,thereby inhibiting their activity and preventing the growth and

DOI: 10.54254/2753-8818/2026.PJ31162

proliferation of cancer cells. Nevertheless, this therapeutic strategy is not without limitations. For instance, acquired mutations within the kinase domain during treatment can diminish the binding affinity of PKIs, a phenomenon collectively termed drug resistance. This makes the treatment less than perfect. Therefore, currently, how to overcome the issue of drug resistance to protein kinase inhibitors is a major topic in the clinical treatment of cancer.

Targeted protein degradation (TPD) has emerged as a transformative technology amid this clinical predicament. TPD technology, especially proteolysis-targeting chimeras (PROTACs).PROTACs are bifunctional molecules characterized by one moiety that binds to the target protein and another that recruits an E3 ubiquitin ligase, which conjugates ubiquitin to the target protein and marks it for proteasomal degradation. Therefore, we can say that PKIs mainly inhibit the function of proteins, whereas TPD mainly prompts cells to directly eliminate proteins.

It is precisely because PKI and TPD work differently and have different effects that the combined use of PKI and TPD has become a potentially viable new treatment approach. Ideally, the combination of PKI and TPD as a targeted strategy, leveraging the complementary mechanisms of these two modalities, generates a strong synergistic effect.The combined use of PKI and TPD may become one of the main forms of cancer treatment in the future. This article will overview combination therapy, delineate the combinatorial mechanisms of PKI and TPD, and elaborate on the potential advantages and feasibility of this combinatorial strategy in cancer therapy.

2. Examples of using combination therapy in oncology

Combination therapy inherently offers the advantage of multi-level targeting of oncogenic signaling pathways. Cancer cells rely on aberrant signaling pathways for proliferation; a PKI can be deployed to target one component of the pathway, while a TPD agent targets another. For example, we can use KRAS drugs and EGFR PROTACs together. This dual attack is more effective and can prevent cancer from adapting.

For instance, in KRAS G12C mutated tumors, using a KRAS G12C PKI (such as Sotorasib) in combination with a PROTAC that degrades the upstream receptor (EGFR) or downstream effector (ERK) on the pathway can achieve vertical inhibition of the MAPK pathway, resulting in a more thorough and lasting anti-tumor effect [1].

2.1 Combined treatment regimens for testicular cancer

Prior to the advent of combination chemotherapy, metastatic testicular cancer was virtually uniformly fatal. Later, in 1977, fifty patients with disseminated testicular cancer were treated with a three-drug combination consisting of cisplatin, vinblastine, and bleomycin [2]. This regimen increased the cure rate of metastatic testicular cancer from less than 10% to over 70%. The investigators of this study are consequently recognized as pioneers in testicular cancer therapy. The regimen was later optimized to cisplatin+etoposide+bleomycin.Today, the cure rate for metastatic testicular cancer exceeds 95%.

Although there were two drug-related deaths during the trials of this regimen, 38 patients still survived, and 32 patients remained alive and disease-free for 6 to 30 months.Therefore, the investigators of the study concluded that this regimen represented a notable advancement in the management of patients with disseminated testicular cancer [2]. Notably, this successful case adequately validates the applicability of combination regimens in cancer therapy and supports their potential as a novel therapeutic modality.

DOI: 10.54254/2753-8818/2026.PJ31162

2.2 Multi-drug combined long-term treatment of acute lymphoblastic leukemia in children

In a multinational population study from five Nordic countries(Denmark,Finland,Iceland,Norway, and Sweden), 2,648 children under the age of 15 were diagnosed with acute lymphoblastic leukemia(ALL) between 1981 and 1996. By 1992, through the continuous intensification of multi-drug chemotherapy (incorporating high-dose methotrexate pulses) and the avoidance of cranial irradiation in the majority of children, a unified Nordic treatment protocol was established for all risk strata, replacing regional or national guidelines. During this experimental period, the incidence of ALL tended to stabilize [3]. It is clear that multi-drug treatment and long-term therapy represent an effective approach to treating ALL.

Several studies have highlighted that anti-leukemic agents can induce substantial adverse effects, and in certain patients, leukemia cell clones exhibit resistance to contemporary anti-leukemic therapies. Therefore, there is an urgent need to further improve treatment for pediatric ALL [4]. Treatment of ALL is hindered by drug resistance. Building on the previously mentioned combined treatment methods, it has been found that combination therapy can effectively address the issue of drug resistance. Therefore, combination treatment protocols can overcome many bottlenecks in the field of cancer therapy.

We have already introduced historical examples of combination therapy in cancer treatment and have a general understanding of how TPD and PKI work in the body. In the following, we will mainly discuss the medical mechanism of PKI and TPD when used together.

3. Investigating the mechanism of action of combined TPD and PKI in vivo

3.1 Mechanism of action of PKI and TPD used alone in cancer

Treatment To elucidate the combinatorial mechanism, it is first necessary to clarify the oncogenic role of protein kinases and the modes of action of individual agents. Protein kinases are indispensable in cellular signal transduction, orchestrating critical biological processes including cell growth, division, differentiation, and apoptosis. Dysregulated activation of these kinases—driven by gene mutations or other molecular aberrations—promotes uncontrolled cell proliferation, ultimately culminating in carcinogenesis. PKIs are a class of small molecule drugs that can specifically target and inhibit these abnormal kinase activities.

PKIs bind to the ATP-binding pockets of aberrant protein kinases, abrogating their ability to activate downstream signaling cascades, thereby suppressing uncontrolled cell proliferation and exerting anti-tumor effects. In essence, PKIs function as rationally designed molecular 'keys' that bind to the 'lock' of aberrant kinases (i.e., the ATP-binding pocket). Therefore, we often say that PKI, compared to traditional cancer treatments, is more targeted and causes less harm to the human body because it is not non-selective. Similarly, it is a representative form of targeted therapy.

BCR-ABL is a constitutively active tyrosine kinase that drives the pathogenesis of chronic myeloid leukemia (CML). Given that tyrosine kinase activity is indispensable for the oncogenic transforming capacity of BCR-ABL, kinase inhibitors represent a rational therapeutic strategy for CML. Phase II clinical trial data for imatinib demonstrated that this PKI elicited significant and durable hematologic and cytogenetic responses in CML patients with interferon-refractory disease [5]. Since then, the survival rate for CML has risen from less than 50%to 85-90%, and CML has transformed from a fatal disease to one that can be managed with chronic oral medication. This represents one of the great studies in the medical history of precision use of PKI.

DOI: 10.54254/2753-8818/2026.PJ31162

3.2 TPD used solely for cancer treatment

Currently, the most prominent TPD modalities include PROTACs and molecular glues. TPD agents merely require binding to any epitope of the target protein to mediate its complete degradation. This modality circumvents the prevalent issue of drug resistance, as it is not contingent on the integrity of the protein target's drug-binding pocket. The TPD field is advancing expeditiously, with numerous candidate agents having entered clinical trials and demonstrating promising efficacy.

TPD first entered clinical trials in 2019. The androgen receptor(AR)remains the main driver of castration-resistant prostate cancer as it progresses from localized disease to metastatic disease. Common resistance mechanisms encompass AR gene amplification or point mutations. Given these resistance mechanisms, leveraging PROTAC technology to degrade the AR protein constitutes a precise therapeutic strategy. Subsequently, ARV-110, an orally bioavailable small-molecule AR PROTAC degrader that facilitates AR ubiquitination and degradation, was described in the literature. Subsequently, preclinical data for ARV-110 demonstrated robust efficacy across multiple prostate cancer models [6]. This was a pioneering report in the field of TPD, proving both the safety and preliminary efficacy of PROTAC in humans.It also indicated that TPD can address the issue of resistance in cancer therapy.

3.3 Advantages of combining TPD and PKI

3.3.1 Challenges of drug resistance

PKI resistance frequently emanates from target-centric mutations or the activation of bypass signaling pathways. For target mutations, TPD can degrade the targets. As previously emphasized, TPD-based therapies circumvent the constraints of target mutation-driven resistance. When the target mutates, TPD can degrade the mutant protein, even if the PKI cannot bind to this mutation. Furthermore, the concurrent administration of PKIs and TPD agents enables the simultaneous inhibition of multiple critical signaling nodes, minimizing the propensity of cancer cells to evade therapeutic pressure via alternative bypass circuits.

For example, when tumors develop resistance to PKIs by activating bypass pathways such as c-MET, it is possible to use a combination of PKIs targeting the original target and TPD molecules targeting the bypass proteins. This approach concomitantly abrogates major tumor escape trajectories, potently suppressing the outgrowth of drug-resistant clones.This is also the most important reason for using them in combination.

Some oncogenic proteins are difficult to target with PKIs. However, TPD can generally target these proteins. Therefore, we can use PKIs for 'druggable' proteins and TPD for 'undruggable' proteins. This enables us to approach cancer from two distinct perspectives. The core merit of PKI-TPD combinatorial therapy resides in its capacity to elicit robust protein degradation and evoke profound anti-tumor cellular responses—an attribute that is particularly salient in surmounting target mutation-mediated resistance.

Numerous key mutations that confer resistance to PKIs (such as BTK C481S) may weaken PKI binding but do not necessarily affect the binding of PROTAC molecules. Consequently, PROTACs targeting the same oncoprotein can efficiently degrade these mutant isoforms and reinstate tumor cell cytotoxicity. Studies have confirmed that combining BTK PROTAC with BTK inhibitors can more thoroughly eliminate BTK protein and delay the development of resistance in lymphoma models [7].

DOI: 10.54254/2753-8818/2026.PJ31162

3.3.2 Mechanistic complementarity and synergistic effects

Although, so far, there is no clinical experimental data confirming that the combined use of TPD and PKI can be synergistic, we can try to construct a model based on their basic mechanisms of action and usage to speculate on the mechanism of action when used together.

PKIs reversibly abrogate the kinase activity of aberrant oncogenic kinases, thereby suppressing oncogenic signaling cascades that drive cancer cell proliferation. However, since the protein itself is inside the cell, it may be activated or mutated through other means. TPD directly eliminates kinase proteins, physically reducing their quantity and directly addressing the issue of mutations. Unfortunately, a potential issue with TPD is that it may not accurately remove abnormal proteins, and its indiscriminate use could be a broadly destructive assault on the patient's body. PKI, on the other hand, can help TPD quickly identify unsuitable proteins, thus preventing further cellular damage caused by TPD. While significantly alleviating patient burden, PKI rapidly suppresses signaling, and in combination with TPD clearing the proteins, can achieve profound and durable inhibition of protein kinase pathways.

If this proposed mechanistic model is validated in clinical trials, it will diversify cancer therapeutic modalities, reduce chemotherapy-related morbidity in patients, and substantially shorten the treatment course.

4. Discussion

Side effects are a major concern when using medications. In the combined use of TPD and PKI, the co-administration of these two agents may potentiate cumulative toxicity relative to monotherapy, underscoring the imperative to define safe dose thresholds and characterize the adverse event profiles associated with the combinatorial regimen. Additionally, for drugs that have not yet undergone trials, we still do not fully understand how the combination of TPD and PKI operates and interacts within the body.Issues such as managing overlapping toxicities from combination therapy, determining the optimal dosing regimen(sequential or simultaneous), and identifying biomarkers to predict therapeutic efficacy have not yet been addressed in this article. Future translational research should prioritize these unmet needs, with the objective of advancing this promising combinatorial regimen from preclinical development to clinical translation, ultimately benefiting a large number of cancer patients. If this technology is fully developed and popularized, it could signify the opening of a new frontier in targeted therapy. This holds great significance for the biopharmaceutical industry and represents a considerable contribution to improving human health.

Moreover, notably, no clinical evidence has yet corroborated the efficacy and safety of PKI-TPD combination therapy. Medical research relies on real data, so at this stage, the combined use of the two can only be considered a model or a proposal.

5. Conclusion

In summary, the combined application of protein kinase inhibitors (PKIs) and targeted protein degradation (TPD) embodies the paradigm shift in cancer targeted therapy from 'functional inhibition' to 'physical elimination.' Through combinational targeting, this strategy not only achieves deeper inhibition of signaling pathways but also directly circumvents resistance mediated by target mutations and bypass pathway activation, demonstrating unprecedented protein degradation capability and therapeutic potential. Despite inherent challenges, this field undoubtedly paves the

DOI: 10.54254/2753-8818/2026.PJ31162

way for a novel frontier in cancer therapeutics and constitutes a major breakthrough in the field of targeted cancer therapy.

References

[1] Wang Yali, Chen Xiuqiong, Zheng Kun, et al. Research progress on KRAS G12C inhibitor combined with other drugs for the treatment of KRAS G12C mutant non-small cell lung cancer [J]. Cancer, 2020, 39(9): 8.
[2] Lawrence H. Einhorn M.D., F.A.C.P, Donohue J .Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer - ScienceDirect [J].The Journal of Urology, 2002, 167(2): 928-932.
[3] Gustafsson G,Kreuger A,Clausen N,et al.Intensified treatment of acute childhood lymphoblastic leukaemia has improved prognosis,especially in non-high-risk patients: the Nordic experience of 2648 patients diagnosed between 1981 and 1996. Nordic Society of Paediatric Haematology and Oncology(NO [J].Acta Pdiatrica,2010,87(11): 1151-1161.DOI: 10.1111/j.1651-2227.1998.tb00923.x.
[4] Kager L .Pharmacogenomics to improve childhood acute lymphoblastic leukaemia therapy [J].memo - Magazine of European Medical Oncology, 2009, 2(2): 65-70.DOI: 10.1007/s12254-009-0110-1.
[5] Druker B J , Talpaz M , Resta D J , et al.Efficacy and Safety of a Specific Inhibitor of the BCR-ABL Tyrosine Kinase in Chronic Myeloid Leukemia [J].Massachussetts Medical Society, 2001(14).DOI: 10.1056/NEJM200104053441401.
[6] Neklesa T , Snyder L B , Willard R R , et al.ARV-110: An oral androgen receptor PROTAC degrader for prostate cancer. [J].Journal of Clinical Oncology, 2019, 37(7_suppl): 259-259.DOI: 10.1200/JCO.2019.37.7_suppl.259.
[7] Huang Junli. Design, synthesis and anti-inflammatory activity study of novel BTK-targeted PROTAC degradative agents [D]. Southern Medical University, 2023.