Decoding the PTEN paradox: Non-canonical PI3Kβ signaling opens new therapeutic avenues

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Received: April 1, 2026; Accepted: April 8, 2026; Published Online: April 13, 2026; https://doi.org/10.59717/j.xinn-drugdisc.2026.100015

Citation: Zhang J., Wang J., Li K., et al. (2026). Decoding the PTEN paradox: Non-canonical PI3Kβ signaling opens new therapeutic avenues. *The Innovation Drug Discovery* **1**:100015.

The loss of PTEN, a quintessential tumor suppressor, broadly fuels solid tumor progression, therapeutic resistance, and immune evasion. However, the lack of effective targeted strategies for these malignancies remains a major unmet clinical need. Previous studies have shown that PTEN deficiency not only hyperactivates PI3K signaling but also creates a selective dependency on PI3Kβ in multiple tumor contexts.[1] Notably, in PTEN-deficient breast cancer, PI3Kβ promotes immune evasion and resistance to immunotherapy.[2] In contrast to the clinical success of PI3Kα-selective inhibitors in genetically defined settings, PI3Kβ-selective kinase inhibitors have yielded limited and inconsistent activity in PTEN-deficient tumors, despite the robust antitumor effects of genetic PI3Kβ ablation. Recently, Tang *et al.* uncovered an underappreciated layer of PTEN biology by showing that PTEN directly dephosphorylates PI3Kβ at Y962 through its protein tyrosine phosphatase activity.[3] This study therefore reframes PTEN loss—long viewed as a difficult-to-drug tumor suppressor event—as a quantifiable, stratifiable, and potentially targetable signaling state centered on p-PI3Kβ^{Y962}.

In that work, Tang *et al.* leveraged BioID interactomics to systematically compare the interactomes of PI3Kα and PI3Kβ in PTEN-null triple-negative breast cancer (TNBC) cells. Rather than defining a simple linear pathway, their data support a PTEN-loss-driven phospho-signaling circuit in which impaired dephosphorylation permits accumulation of p-PI3Kβ^{Y962}, thereby strengthening the PI3Kβ–EPHA2 interaction and promoting assembly of a SRC–EPHA2–PI3Kβ complex. Mechanistically, both SRC and EPHA2 contribute to PI3Kβ phosphorylation, whereas Y962 phosphorylation is required for efficient EPHA2 binding. This phospho-state-associated complex couples enhanced p-AKT signaling with activation of the p-ERK/c-MYC axis, together driving tumor progression.

This signaling rewiring is especially important because it separates a clearly non-catalytic arm of PI3Kβ biology from its canonical lipid kinase function. By comparing kinase-dead and phosphorylation-site mutants, the authors showed that PI3Kβ-dependent ERK/c-MYC signaling could be maintained despite loss of lipid kinase activity, whereas disruption of Y962 phosphorylation markedly attenuated this output and suppressed tumor growth in multiple PTEN-null models. These findings do not fully explain the variable clinical performance of PI3Kβ catalytic inhibitors, but they provide a plausible mechanistic framework for why catalytic inhibition alone may be insufficient in PTEN-deficient cancers. Collectively, the data position p-PI3Kβ^{Y962} not simply as another phosphorylation event, but as a state-defined therapeutic vulnerability.

To bridge mechanism and translation, the authors generated a selective p-PI3Kβ^{Y962} antibody that robustly detected this phospho-state across PTEN-deficient cell lines and clinical specimens. Importantly, p-PI3Kβ^{Y962} inversely

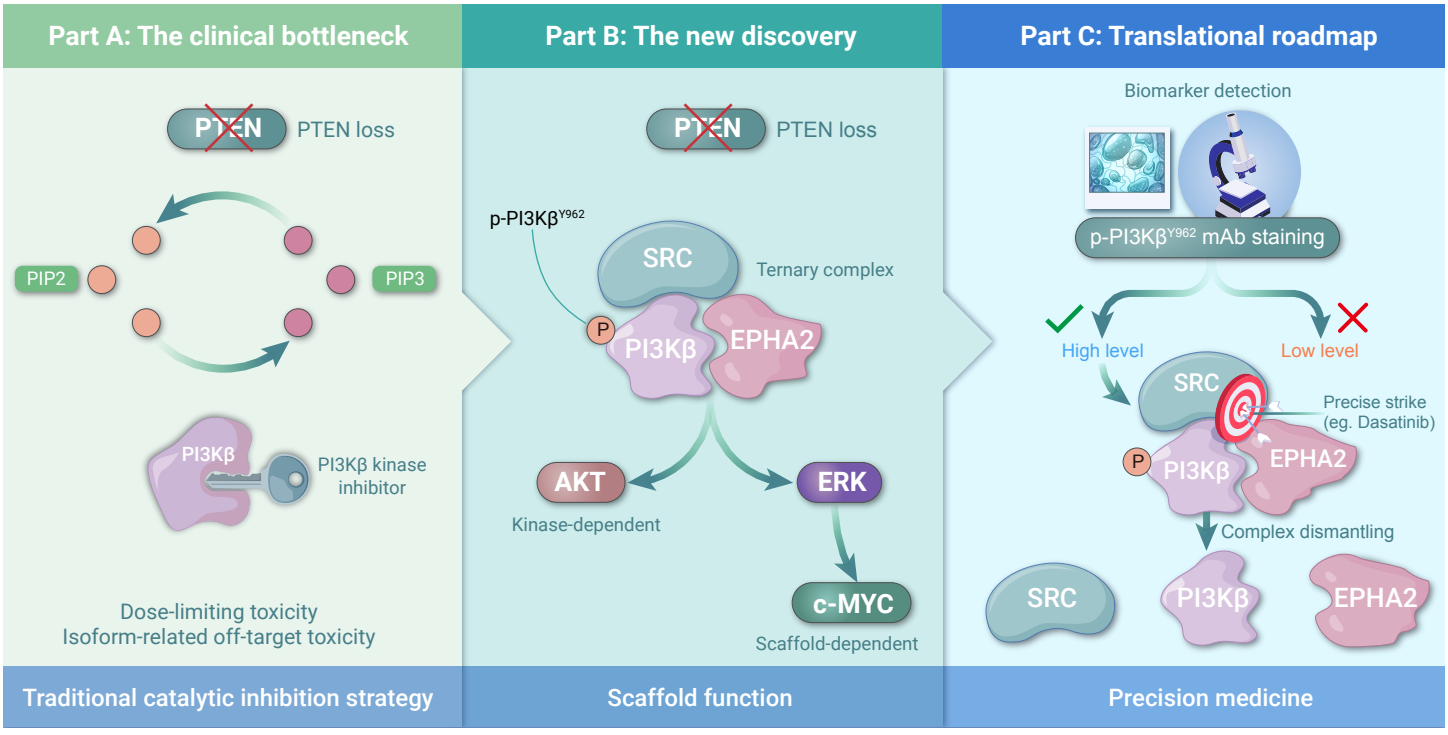

Figure 1. From PI3Kβ kinase activity blockade to state-selective PI3Kβ inhibition in PTEN-deficient tumors (A) Biological and clinical positioning of PI3Kβ. PI3Kβ-targeted catalytic inhibition has shown dose-limiting toxicity and isoform-related off-target toxicity in PTEN-deficient tumors. (B) PTEN-loss-driven phospho-signaling circuit. Loss of PTEN-mediated dephosphorylation permits accumulation of p-PI3Kβ^{Y962}, promotes SRC-EPHA2-PI3Kβ complex assembly, and potentiates the AKT and ERK/c-MYC pathways signaling transduction. (C) Translational roadmap. A clinically tractable proof-of-concept can begin with dasatinib repurposing and pharmacodynamic validation, followed by standardization of p-PI3Kβ^{Y962} assays, development of state-selective therapeutic modalities, and biomarker-guided clinical testing in PTEN-deficient tumors.

correlated with PTEN expression and was enriched in high-grade prostate tumors, supporting its potential as a prognostic biomarker and as a candidate stratification marker. Through a focused tyrosine kinase inhibitor screen, the authors further identified dasatinib—best viewed here as an FDA-approved SRC-family inhibitor with functional activity against the SRC/EPHA2/p-PI3Kβ^{Y962} signaling axis—as a tractable proof-of-concept agent. In preclinical models, dasatinib reduced p-PI3Kβ^{Y962}, dampened p-AKT and p-ERK/c-MYC signaling, and selectively inhibited PTEN-null tumor growth. Thus, rather than definitively establishing a clinically validated predictive biomarker, this study lays a strong preclinical foundation for biomarker-guided repurposing of dasatinib in PTEN-deficient tumors.

The structural and functional distinctiveness of p-PI3Kβ^{Y962} lies in the fact that it does not represent a classical small-molecule pocket, but rather a dynamic signaling state defined by phosphorylation-dependent complex assembly. From a pharmacological perspective, at least three therapeutic directions emerge. First, upstream kinase blockade is immediately actionable: because SRC and EPHA2 cooperate to sustain PI3Kβ Y962 phosphorylation, dasatinib provides a clinically available proof-of-concept for suppressing this oncogenic signaling. Second, a more exploratory strategy would be to disrupt the phosphorylation-dependent PI3Kβ–EPHA2/SRC interface through protein-protein interaction inhibitors or related modalities that destabilize this oncogenic complex. In this regard, the successful advent of covalent inhibitors targeting the PI3Kα–RAS binding domain serves as an instructive precedent for this targeted modality.[4] Third, if the key oncogenic contribution of PI3Kβ in this setting indeed depends partly on scaffold-like functions rather than catalytic output alone, degradation-based or state-selective silencing strategies may, in principle, provide a more complete way to extinguish this signaling state than catalytic inhibition alone.

Recent work has already expanded PI3Kβ biology beyond canonical lipid signaling. For example, He *et al.*[5] demonstrated that, under high-glucose conditions, PI3Kβ can act as a protein kinase to govern O-GlcNAcylation, fatty acid metabolism, and chromatin modifications in glioblastoma. Tang *et al.* now add a distinct PTEN-loss-associated, phosphorylation-dependent scaffolding mechanism to this emerging non-canonical PI3Kβ landscape. Together, these studies argue that PI3Kβ should no longer be viewed solely through the lens of lipid kinase output. Nevertheless, several important questions remain before this framework can be fully translated.

(1) Most evidence in the current study comes from TNBC and prostate cancer models. It remains unclear whether the p-PI3Kβ^{Y962} axis is equally operative across other PTEN-deficient tumor types or across distinct modes of PTEN inactivation, including mutation, deletion, or transcriptional silencing.

(2) The landscape of acquired resistance: Although the study identifies p-PI3Kβ^{Y962} as a therapeutic vulnerability, the adaptive routes that could bypass SRC/EPHA2 blockade remain undefined. Chronic inhibition may select for alternative tyrosine kinases, rewired interactomes, or compensatory mechanisms that preserve PI3Kβ membrane localization and c-MYC stabilization.

(3) The newly generated p-PI3Kβ^{Y962} antibody is an important enabling reagent, but phospho-specific immunohistochemistry is highly sensitive to pre-analytical variables. Further work will be needed to convert this research-grade assay into a standardized clinical companion diagnostic with reproducible cutoffs across centers.

(4) Dasatinib provides an attractive proof-of-concept, but its systemic toxicities in solid tumors are well recognized. More broadly, the PI3K field has repeatedly shown that narrow therapeutic windows and insufficient biomarker selection can undermine otherwise compelling biology, underscoring the need for rigorous pharmacodynamic monitoring and biomarker-guided trial design.

In summary, Tang *et al.* redefine PTEN-deficient signaling by showing that loss of PTEN creates not only a lipid signaling imbalance but also a phospho-state-defined PI3Kβ dependency centered on Y962. By positioning p-PI3Kβ^{Y962} as a mechanistically important switch, a tractable therapeutic vulnerability, and a candidate biomarker for patient stratification, this work opens a new conceptual route for targeting PTEN-deficient tumors. More broadly, it suggests that future PI3Kβ drug discovery may need to move beyond isoform selectivity alone and toward state selectivity—targeting the disease-specific phospho-interactome rather than catalytic activity in isolation (Figure 1).

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FUNDING AND ACKNOWLEDGMENTS

This work was supported by Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (2024-RC350-01), Young Elite Scientists Sponsorship Program by CAST (No. 2024-2026QNRC001), CAMS Innovation Fund for Medical Sciences (2025-I2M-XHXX-148), State Key Laboratory of Drug Research (SKLDR-2025-KF-08), State Key Laboratory of Advanced Medical Materials and Devices Research Grant (YGSKL-JYY-2024-JK01, JYY25QZZZ0002). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.