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# Chemical Biology Approaches to Modulate Protein–protein Interactions in Cancer Therapy

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## Introduction

Cancer arises from a complex interplay of genetic mutations, dysregulated signaling pathways, and aberrant protein networks that disrupt normal cellular homeostasis. Among these molecular drivers, protein–protein interactions (PPIs) play a pivotal role in controlling critical processes such as signal transduction, transcriptional regulation, and apoptosis. In many cancers, PPIs involving oncogenes or tumor suppressors are hijacked to promote uncontrolled proliferation, resistance to cell death, and metastatic spread. For example, interactions between p53 and MDM2, BCL-2 and pro-apoptotic proteins, or receptor tyrosine kinases and downstream signaling molecules exemplify how dysregulated PPIs contribute to tumorigenesis. Targeting these interactions offers a compelling therapeutic avenue, but traditional drug discovery has often struggled to address PPIs due to their large, shallow, and dynamic binding interfaces. Chemical biology approaches have emerged as powerful strategies to overcome these challenges, enabling the design of small molecules, peptides, and chemical probes that can specifically modulate PPIs in cancer cells [1].

## Description

One of the earliest successes in targeting PPIs is the disruption of the MDM2–p53 interaction, which normally inhibits the tumor-suppressor activity of p53. Chemical biology tools, particularly structure-based drug design and fragment-based screening, enabled the development of small-molecule inhibitors like Nutlin-3 that mimic key p53 residues and block the interaction with MDM2. This reactivates p53 signaling, promoting cell cycle arrest and apoptosis in tumor cells. Small-molecule inhibitors such as Venetoclax, developed through chemical biology-guided screening and optimization, disrupt the interaction between BCL-2 and pro-apoptotic proteins, restoring the apoptotic pathway in chronic lymphocytic leukemia. These landmark cases highlight how chemical biology approaches can translate complex PPI modulation into clinically effective cancer therapies [2].

Peptide and peptidomimetic-based strategies have also gained traction in modulating PPIs due to their ability to mimic the extended binding surfaces of natural protein partners. Advances in peptide stapling and chemical modifications have improved stability, membrane permeability, and bioavailability of therapeutic peptides, making them more suitable for clinical use. Stapled peptides that mimic α-helical motifs, for instance, have been designed to disrupt interactions between transcription factors or block oncogenic signaling complexes. For example, stapled peptides targeting the NOTCH transcriptional complex or the BCL-XL interaction network have shown promising anti-cancer effects in preclinical models. Peptidomimetics, which combine structural elements of peptides with the stability of small molecules, further expand the toolbox for targeting previously undruggable PPIs [3].

In addition to direct inhibitors, chemical biology has facilitated the development of molecular glues and proteolysis-targeting chimeras, which exploit PPIs to degrade oncogenic proteins rather than merely inhibit them. Molecular glues, such as thalidomide derivatives, induce or stabilize novel PPIs between E3 ubiquitin ligases and target proteins, leading to ubiquitination and proteasomal degradation. PROTACs take this concept further by linking ligands for target proteins and E3 ligases, bringing them into proximity to trigger selective degradation. These approaches offer distinct advantages, including the ability to eliminate proteins that lack enzymatic activity and to overcome resistance mechanisms associated with traditional inhibitors [4].

High-throughput screening, chemical genetics, and advanced structural biology techniques are integral to chemical biology approaches for PPI modulation. Fragment-based drug discovery, combined enables precise mapping of PPI interfaces and identification of druggable hot spots. Meanwhile, chemoproteomics and activity-based probes facilitate global profiling of PPI networks and off-target effects, improving specificity and minimizing toxicity. Moreover, advances in computational modeling, artificial intelligence, and machine learning have accelerated the identification of PPI modulators by predicting binding affinities, dynamic conformations, and resistance mutations [5].

## Conclusion

Chemical biology has transformed the landscape of cancer drug discovery by enabling the rational modulation of protein–protein interactions once considered intractable. From small-molecule inhibitors and stapled peptides to molecular glues and PROTACs, a diverse arsenal of chemical biology tools is now available to rewire oncogenic signaling networks and restore tumor-suppressive functions. While challenges remain, such as improving pharmacokinetics, achieving tissue-specific delivery, and minimizing resistance, ongoing advances in synthetic chemistry, structural biology, and systems pharmacology hold immense promise. As cancer therapy continues to evolve toward precision medicine, chemical biology approaches to PPI modulation are poised to deliver next-generation therapeutics that exploit the vulnerabilities of malignant cells while sparing normal tissues. This convergence of chemistry and biology not only addresses one of the most formidable challenges in drug discovery but also offers renewed hope for developing durable and effective cancer treatments.

## Acknowledgement

None.

## Conflict of Interest

None.

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