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# Dual Targeting Approaches in Antiangiogenesis: Synergistic Pathways in Tumor Starvation

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## Introduction

Cancer remains one of the leading causes of mortality worldwide, with tumor growth and metastasis heavily dependent on angiogenesis-the formation of new blood vessels from existing vasculature. Tumor angiogenesis provides cancer cells with oxygen, nutrients, and a route for metastasis, making it a critical therapeutic target. Over the past two decades, antiangiogenic therapies have emerged as a cornerstone of targeted cancer treatment. However, monotherapies that focus solely on single angiogenic factors, such as Vascular Endothelial Growth Factor (VEGF), often result in limited efficacy due to resistance mechanisms and pathway redundancies. In response, dual targeting strategies have been developed to simultaneously inhibit multiple angiogenic and pro-tumoral signaling pathways. These approaches aim to enhance therapeutic efficacy by inducing synergistic effects, increasing tumor starvation, and overcoming resistance [1].

Dual targeting in antiangiogenesis involves the inhibition of two or more pathways-either within the angiogenic cascade itself or by combining angiogenic blockade with other oncogenic or immunomodulatory mechanisms. This multidimensional strategy addresses the complex interplay between tumor cells and their microenvironment [2].

## Description

Angiogenesis in tumors is regulated by a complex network of signaling pathways involving VEGF, Fibroblast Growth Factors (FGFs), angiopoietins, Platelet-Derived Growth Factors (PDGFs), and Hypoxia-Inducible Factors (HIFs). Inhibiting a single component of this network can lead to compensatory upregulation of alternate pro-angiogenic pathways, resulting in therapeutic resistance. Additionally, tumors adapt to anti-angiogenic pressure by increasing invasiveness, metastasis, and co-opting existing vasculature. Simultaneous inhibition of VEGF and other pro-angiogenic pathways (e.g., PDGF, FGF) reduces the likelihood of resistance. Combining antiangiogenic agents with drugs targeting tumor cells or stromal components disrupts the mutual support system within the tumor microenvironment. VEGF is the most well-characterized mediator of angiogenesis. However, tumors can upregulate FGF or PDGF signaling in response to VEGF inhibition. Co-targeting these pathways has shown improved outcomes in preclinical and clinical studies [3].

Anti-VEGF therapies increase tumor hypoxia, which stabilizes HIF-1α and leads to upregulation of alternative angiogenic factors. Dual inhibition of VEGF and HIF-1α suppresses this feedback loop and enhances tumor starvation.

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Angiopoietins (Ang-1 and Ang-2) modulate vascular stability and permeability via the Tie2 receptor. Combining VEGF inhibitors with Ang-2 blockade disrupts vascular remodeling and increases vessel regression. VEGF contributes to immunosuppression by promoting regulatory T cells (Tregs) and Myeloid-Derived Suppressor Cells (MDSCs). Dual targeting with immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1) enhances T-cell infiltration and function, improving antitumor immunity and enhancing vascular disruption. The mammalian target of rapamycin (mTOR) pathway regulates cell proliferation, metabolism, and angiogenesis. mTOR inhibitors reduce HIF-1α levels, amplifying the effects of anti-VEGF therapy and leading to tumor nutrient deprivation [4].

Drugs such as nintedanib and sunitinib target both VEGF and PDGF receptors. Nintedanib, in particular, has shown efficacy in non-small cell lung cancer (NSCLC) and ovarian cancer when combined with chemotherapy. The dual inhibition reduces vascular integrity and promotes apoptosis in endothelial cells. Lucitanib, a multi-targeted tyrosine kinase inhibitor, acts on VEGFR1-3, FGFR1-3, and PDGFR. Clinical trials in breast and endometrial cancers have demonstrated promising anti-tumor activity, especially in patients with FGF pathway alterations. Vanucizumab, a bispecific antibody targeting VEGF-A and Ang-2, has been tested in colorectal and ovarian cancers. Early-phase studies have shown tumor growth inhibition, enhanced vessel regression, and improved immune cell infiltration [5].

## Conclusion

Dual targeting approaches in antiangiogenic therapy represent a promising evolution in the fight against cancer. By simultaneously disrupting multiple angiogenic and tumor-supporting pathways, these strategies enhance tumor starvation, mitigate resistance, and improve therapeutic efficacy. The synergistic potential of dual targeting lies in its ability to collapse the tumor's vascular lifeline while concurrently modulating the microenvironment to favor anti-tumor responses. While challenges remain-including toxicity, resistance, and biomarker identification-the future of antiangiogenic therapy is increasingly multidimensional. Advances in molecular profiling, targeted drug delivery, and immunotherapy integration will continue to refine dual targeting approaches. Ultimately, combining insights from tumor biology with innovative therapeutics offers a potent strategy to deprive tumors of their critical lifelines and improve outcomes for patients across diverse cancer types.

## Acknowledgement

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## Conflict of Interest

None.

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