

EDITORIAL

On (cell surface), in (intracellular), and out (extracellular/systemic): Are we targeting all that matters in cancer immunotherapy?

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Major advances in medicine and technology have substantially reduced mortality from infectious and cardiovascular diseases, making cancer one of the leading causes of death, particularly in middle- and high-income countries.¹ While the fight against cancer has been long-standing, therapeutic strategies have evolved: after decades of efforts to improve chemotherapy selectivity toward malignant over normal cells, immunology has enabled approaches that exploit the intrinsic discriminatory capacity of immune cells, receptors, and biomolecules, transforming the therapeutic landscape of cancer.²

Modern immunotherapy has evolved into a broad therapeutic paradigm encompassing multiple strategies—some already implemented in clinical practice—aimed at inducing, restoring, and redirecting anti-tumor immune responses across different biological dimensions often impaired or actively subverted by tumor mechanisms.^{2,3} These strategies include, for example, cell-based approaches employing engineered receptors, such as chimeric antigen receptors, capable of recognizing an increasing number of tumor-associated antigens or other molecular targets expressed by malignant cells; monoclonal antibodies, including immune checkpoint inhibitors and antibody–drug conjugates such as trastuzumab deruxtecan and sacituzumab govitecan, which have represented important advances in the treatment of HER2-positive breast cancer and metastatic triple-negative breast cancer, respectively.⁴ Additional immunomodulatory therapies include cytokines, such as interferon gamma, and small-molecule immune response modifiers, such as imiquimod.^{2,3,5}

Despite these advances, important limitations remain evident in clinical practice. A substantial proportion of patients do not respond or eventually develop resistance, highlighting persistent challenges in oncology—one of which is the limited ability to effectively translate and exploit the current therapeutic target landscape.²

Notably, most clinically successful immunotherapies to date primarily target cell-surface molecules or extracellular receptor–ligand interactions, as exemplified by trastuzumab and pembrolizumab. While these approaches have delivered clinical benefits, their predominance may reflect, at least in part, a bias toward what is more accessible rather than what is necessarily most critical to disease biology. It may be hypothesized that therapeutic efficacy depends on the modulation of multiple pathways, potentially requiring the simultaneous or sequential targeting of distinct molecular mechanisms.

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From this perspective, we propose a conceptual framework of targeting strategies encompassing three complementary dimensions—on (cell surface), in (intracellular), and out (extracellular/systemic)—to understand both current therapeutic achievements and existing limitations in cancer immunotherapy. Targeting “on” refers to molecules expressed on the surface of tumor cells, immune cells, or other cancer-associated cells within the tumor microenvironment and has been a primary focus of current immunotherapies, including checkpoint inhibitors, monoclonal antibodies, and antibody–drug conjugates.

However, essential oncogenic processes also reside “in” the intracellular space, including signaling pathways, transcriptional programs, and metabolic adaptations that distinguish malignant from normal cells. Accessing these targets remains challenging, particularly for conventional biologics. In this context, nanobodies and their derivatives represent a promising frontier in cancer immunotherapy, as their small size may eventually allow access to previously inaccessible epitopes, opening new possibilities for targeting intracellular components and regulatory networks.⁶

Beyond the cellular compartment, an additional dimension lies “out” of cancer cells—within the tumor microenvironment and the systemic milieu shaped by tumor derived factors. Tumors secrete a complex repertoire of biomolecules—collectively referred to as the tumor secretome—that reshapes the immune landscape, promoting immunosuppression, angiogenesis, and disease progression. This continuous remodeling raises the possibility that critical drivers of disease remain insufficiently explored, as current therapeutic strategies typically target a limited subset of these signals, such as bevacizumab, which inhibits soluble vascular endothelial growth factor.⁷ If disrupting specific tumor-derived signals can impair the supportive niche required for tumor survival, which components of the tumor secretome are essential?

Taken together, this framework highlights that relevant therapeutic targets may lie in biological dimensions not yet fully addressed by current strategies. In this context, the *Cancer Plus* special issue titled “Emerging Horizons in Cancer Mechanisms and Therapeutic

Innovation” was designed to showcase studies exploring emerging breakthroughs in experimental oncology, with the expectation that integrating these insights will refine therapeutic strategies, identify novel targets and biomarkers, and guide precision immunotherapy toward more durable and clinically meaningful outcomes.

Conflict of interest

Maicon Roberto Kwiecinski is the Guest Editor of this special issue, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. The author declared that he has no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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