Commentory

Rewiring Lung Cancer Immunotherapy: The PD-L1–EphA2 Axis in CAR-T Evolution

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How to cite this article: Birupaksha Biswas. Rewiring Lung Cancer Immunotherapy: The PD-L1–EphA2 Axis in CAR-T Evolution. International Journal of Contemporary Pathology / Vol 12 No. 1, January - June 2026

Abstract

Non-small cell lung carcinoma remains difficult to treat despite advances in immunotherapy targeting the PD-1/PD-L1 axis, with limited durability of response. Chimeric antigen receptor T cell therapy has emerged as a novel strategy, particularly with targets such as EphA2 and PD-L1. This commentary highlights the shift of CAR-T therapy from direct tumor cytotoxicity toward modulation of the tumor microenvironment.

EphA2 directed CAR-T cells demonstrate strong preclinical efficacy but are limited by antigen heterogeneity and potential off target effects. In contrast, PD-L1 targeted CAR-T cells provide dual activity by eliminating tumor cells and disrupting immunosuppressive signaling. Advances such as multi antigen targeting and cytokine engineered CAR-T cells further address resistance mechanisms.

Early clinical evidence supports feasibility, though challenges in persistence and safety remain. The integration of tumor targeting with microenvironmental reprogramming represents a critical evolution in CAR-T design. Future strategies must focus on enhancing durability and safety to improve outcomes in lung carcinoma.

Keywords: *Chimeric Antigen Receptor T-Cell Therapy, Lung Neoplasms, Programmed Cell Death 1 Ligand 1, Receptor EphA2, Tumor Microenvironment*

Introduction

Non-small cell lung carcinoma continues to impose a major global health burden, with limited long-term survival despite therapeutic advances. Immune checkpoint blockade targeting the PD-1/PD-L1 axis has transformed management paradigms, yet only a subset of patients derives durable benefit [1]. Resistance remains common and highlights the need for more effective strategies. Chimeric antigen receptor T cell therapy has emerged as a promising modality. Early translational work targeting EphA2 and PD-L1 suggests a shift in therapeutic thinking. The central premise of this commentary is that CAR-T therapy in lung cancer must evolve beyond direct tumor targeting toward active modulation of the tumor microenvironment.

Submission: Mar 23, 2026 **Revision:** June 22, 2026 **Published date: June 26,2026**

Critical Analysis and Opinion

Initial CAR-T strategies in solid tumors were modeled on hematologic success. EphA2 was identified as a compelling target due to its overexpression and role in oncogenic signaling. Preclinical studies demonstrated that EphA2 directed CAR-T cells could induce significant tumor cell lysis and suppress tumor growth [2]. These findings provided early proof of concept.

However, translation into clinical benefit remains limited. EphA2 is not entirely tumor specific, raising concerns regarding target toxicity, particularly given its basal expression in normal epithelial tissues. This physiologic distribution introduces the potential for unintended vascular and endothelial injury, especially in organs where EphA2 contributes to tissue homeostasis. Furthermore, the absence of robust clinical toxicity data limits accurate risk stratification and highlights a critical gap in translational evaluation. More importantly, tumor heterogeneity enables immune escape through antigen loss or downregulation [3]. These limitations underscore the inadequacy of single antigen targeting in complex solid tumors.

Targeting PD-L1 introduces a fundamentally different strategy. PD-L1 is a key mediator of immune evasion and is expressed on tumor cells as well as immunosuppressive components of the tumor microenvironment. CAR-T cells directed against PD-L1 can therefore exert dual effects by eliminating tumor cells and disrupting suppressive signaling pathways [4]. This dual functionality represents a conceptual shift from cytotoxic targeting to immunologic reprogramming.

From a critical standpoint, this transition reflects a deeper understanding of tumor biology. Lung carcinoma functions as an integrated ecosystem rather than a collection of malignant cells. Therapies that fail to address this ecosystem are unlikely to achieve durable success. PD-L1 directed CAR-T therapy begins to address this complexity, although safety concerns related to systemic immune activation remain.

Beyond this, a more granular appraisal of safety reveals important translational constraints supported by emerging evidence. Programmed death-ligand 1 is not tumor restricted and is constitutively expressed on normal endothelial and epithelial tissues, raising the risk of on-target, off-tumor toxicity with potential collateral tissue injury. Preclinical and early translational studies of CAR-T therapies have highlighted the possibility of widespread immune activation driven by disruption of physiologic immune checkpoints. In this context, cytokine release syndrome remains a central concern, characterized by rapid elevations in interleukin-6 and interferon-γ that can precipitate systemic inflammatory responses and hemodynamic instability, while immune effector cell–associated neurotoxicity syndrome represents a related manifestation of systemic immune dysregulation [5]. These risks underscore the necessity for next-generation safety strategies, including inducible suicide switches, tunable CAR constructs, and logic-gated designs to mitigate on-target, off-tumor effects [6] .

Argument and Extension

The evolution of CAR-T therapy in lung carcinoma requires a multi-dimensional approach. Antigen targeting must expand beyond single markers, as combining EphA2 with other tumor-related antigens such as mesothelin or MUC16 offers a rational strategy to reduce antigen escape. Tandem CAR-T constructs have demonstrated the ability to overcome tumor heterogeneity and improve tumor control by sequentially targeting multiple antigens [9]. At the same time, CAR-T cells must be engineered to function effectively within the tumor microenvironment, where factors such as hypoxia, stromal barriers, and immunosuppressive cytokines limit T cell activity. Armored CAR-T cells engineered to secrete cytokines can enhance local immune responses and modulate the tumor stroma [8], thereby extending their role beyond cytotoxicity to active environmental regulation.

Third, integration of immune checkpoint targeting within CAR design is essential. PD-L1 directed CAR-T cells provide a model for this approach

by combining tumor targeting with immune modulation [4] . This integrated strategy may reduce dependence on external checkpoint inhibitors and enhance therapeutic efficacy.

Together, these developments suggest that CAR-T therapy must evolve into a multifunctional platform capable of addressing both tumor cells and their surrounding microenvironment.

Context and Implications

Early clinical evidence supports the feasibility of this approach. A Phase I trial evaluating PD-L1–targeted CAR-T therapy in advanced lung cancer has demonstrated initial safety and biological activity, providing proof of concept for this strategy [10]. This first-in-human, dose-escalation study primarily enrolled heavily pretreated patients with advanced non–small-cell lung carcinoma and was designed to evaluate safety, maximum tolerated dose, and preliminary signals of efficacy. Early observations suggest limited but detectable in vivo persistence of infused CAR-T cells, with clinical responses largely confined to disease stabilization and occasional partial responses rather than durable remissions. Reported and anticipated toxicities include manageable cytokine release syndrome and immune-related adverse events, consistent with prior CAR-T experience in solid tumors [5,6]. These findings are further supported by early clinical observations [10] and are consistent with broader clinical and translational reports highlighting feasibility while underscoring challenges in persistence and efficacy in solid tumor settings [11,12].

TCR-engineered T cells offer the advantage of targeting intracellular antigens through peptide–HLA presentation, thereby expanding the repertoire beyond surface markers; however, their efficacy remains constrained by HLA restriction and interpatient variability. In contrast, bispecific antibodies, particularly T-cell engagers, provide an off-the-shelf immunotherapeutic approach capable of redirecting endogenous T cells toward tumor cells without the need for ex vivo manipulation. Although these agents enable rapid deployment and broader accessibility, their clinical utility is often limited by short half-life and reduced persistence, necessitating repeated administration and potentially affecting durability of response. However, larger studies are required to establish efficacy and long-term outcomes.

Evidence Based Support

Preclinical data provide strong support for CAR-T therapy targeting EphA2 and PD-L1. EphA2-directed CAR-T cells have shown effective tumor cell killing and tumor regression in experimental models [2]. PD-L1–targeted CAR-T cells have demonstrated the ability to suppress tumor growth while modulating the tumor microenvironment [4].

Clinical translation remains in early stages. Initial trials indicate that CAR-T therapy is feasible and can produce responses in patients with advanced disease [10]. However, these responses are often limited by short in vivo persistence of CAR-T cells within the hostile tumor microenvironment, restricting long-term efficacy. Emerging evidence also suggests that functional exhaustion of T cells, characterized by upregulation of inhibitory markers such as PD-1, LAG-3, and TIM-3, further compromises sustained antitumor activity. In addition, antigen escape through downregulation or loss of target expression contributes to disease relapse and therapeutic resistance [3].

These findings highlight the importance of integrating multiple strategies to enhance CAR-T performance in solid tumors.

Conclusion and Future Directions

CAR-T therapy in lung carcinoma is undergoing significant transformation. Early approaches based on single antigen targeting have revealed important limitations. Emerging strategies signal a transition from a single-antigen cytotoxic paradigm toward a multi-functional immune reprogramming platform with greater therapeutic scope.

The PD-L1 and EphA2 axis exemplifies this evolution. By combining tumor targeting with immune modulation, these strategies address both the malignant cells and their supporting environment. Future research should focus on multi

antigen targeting, enhanced T cell engineering, and combination therapies to improve outcomes.

Now, a critical researchquestion arises from this field of evolution. Can CAR-T cells be engineered to simultaneously target heterogeneous tumor populations and reprogram the tumor microenvironment whilemaintaining safety and long-term persistence? [3,5,7] .

Addressing this question will define the next phase of CAR-T therapy in lung cancer and may ultimately transform clinical outcomes.

Source of Funding: Nil

Conflict of Interest: Nil

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