



Peripheral helper T cells indicate tumor PD-L1 expression in NSCLC

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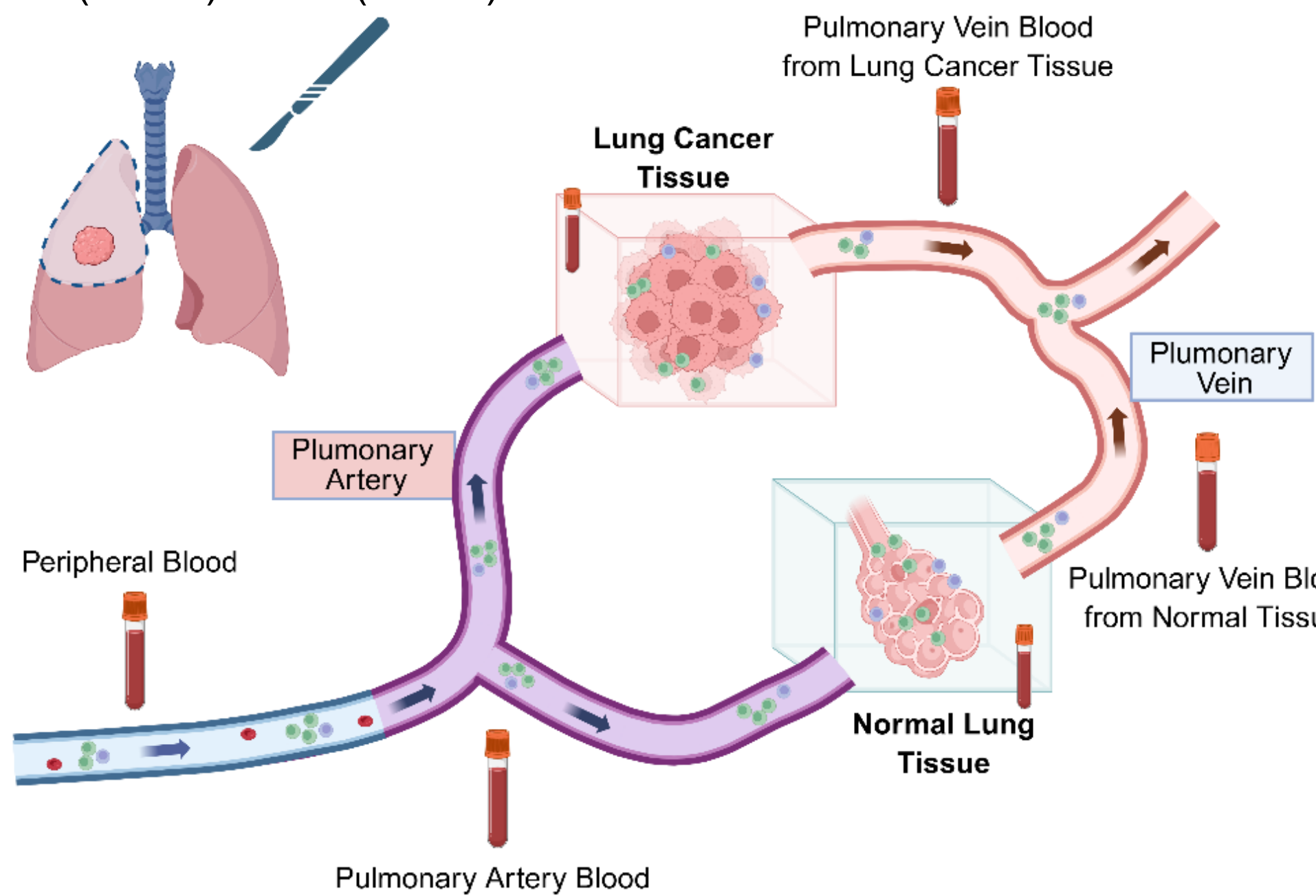
INTRODUCTION

The PD-L1 Tumor Proportion Score (TPS) is widely used as a predictive biomarker for immune checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC) and is useful for predicting response rates and prognosis. However, evaluating TPS requires invasive procedures such as tumor biopsies or surgery. Consequently, there is an unmet clinical need to develop non-invasive, blood-based surrogate markers for assessing the local tumor microenvironment (TME). To address this, we comprehensively evaluated paired lung cancer tissues and normal lung tissue, together with multi-compartment blood samples. By broadly profiling the immune cell dynamics across the local TME and the systemic circulation, we aimed to identify a circulating cell subset that can serve as a robust, non-invasive surrogate marker reflecting the intratumoral immune status in NSCLC.

METHODS

Study Cohort: 21 patients with NSCLC who underwent curative surgical resection without preoperative therapy (2022–2025).

Sample Collection: Matched compartments including lung cancer tissue (LCT), normal lung tissue (NT), peripheral blood (PB), and regional pulmonary vessels: pulmonary artery (PA) and pulmonary vein draining LCT (PVLC) or NT (PVNT).



Flow Cytometry: Isolated lymphocytes were broadly profiled for immune cell subsets, including peripheral helper T (Tph) cells.

Statistical Analysis: ANOVA, Spearman's rank correlation coefficient, and ROC curve analysis.

REFERENCES & ACKNOWLEDGEMENTS

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References



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DISCUSSION AND CONCLUSION

DISCUSSION

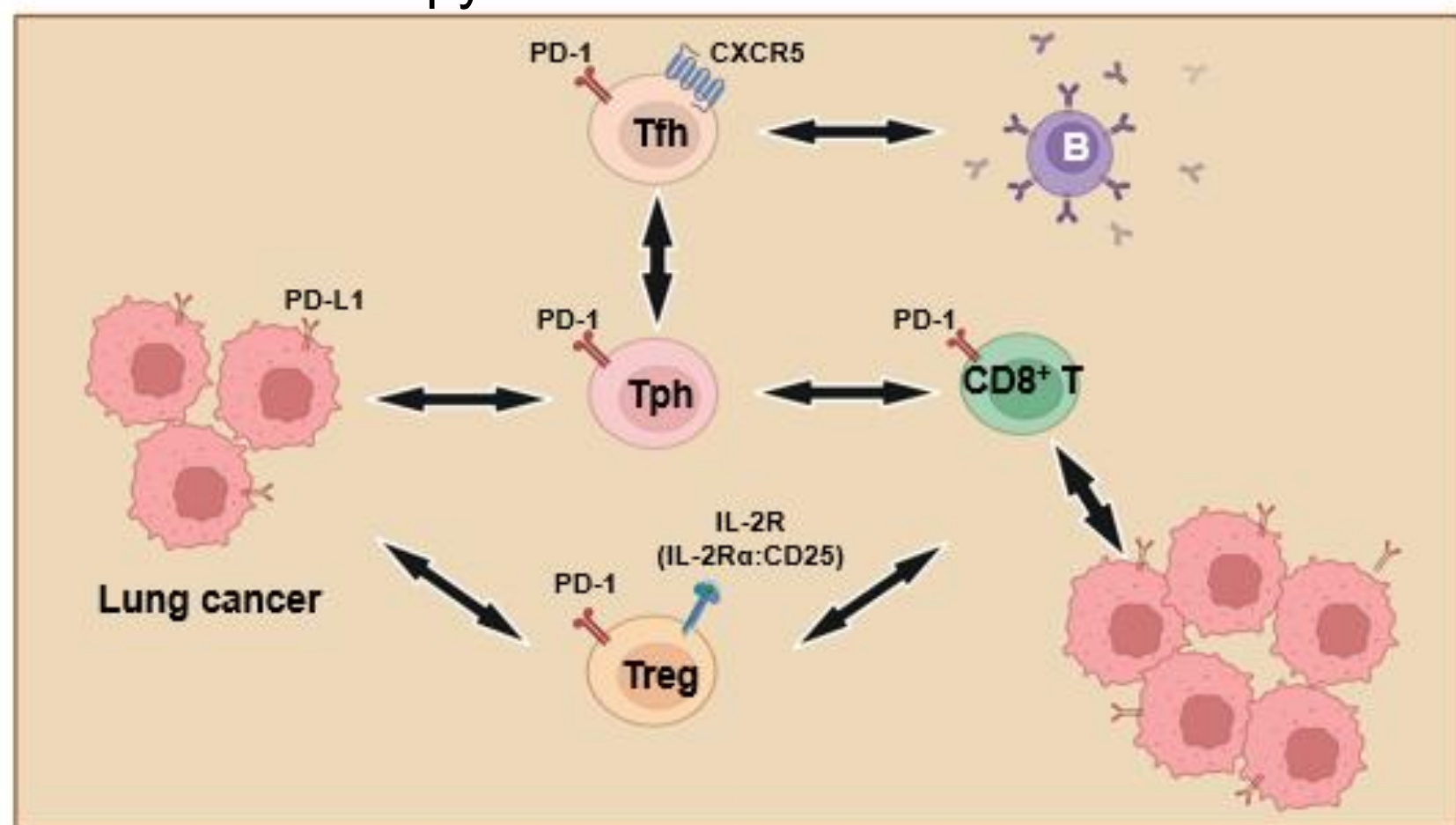
In the present study, the frequency and PD-1 MFI of Tph cells strongly synchronized with those of PD-1⁺CD8⁺ T cells in the lung cancer tissue, suggesting that they cooperatively exert potent anti-tumor activities. Indeed, CXCL13 produced by CD4⁺ T cells has been reported to play a crucial role in recruiting B cells and CD8⁺ T cells into the local tumor site.

By comprehensively analyzing six distinct compartments, we revealed that total Tph cells correlate with the arterial inflow but lose this correlation in the venous outflow. This suggests that Tph cells are either trapped within the tumor or undergo phenotypic changes during passage through the tumor bed. Because of this circulatory disconnect, evaluating total peripheral blood Tph cells fails to reflect local immunity. However, targeting the CD127⁻ effector-like Tph fraction within CD45RA⁺ activated cells successfully overcomes this barrier.

Limitations and Future Directions

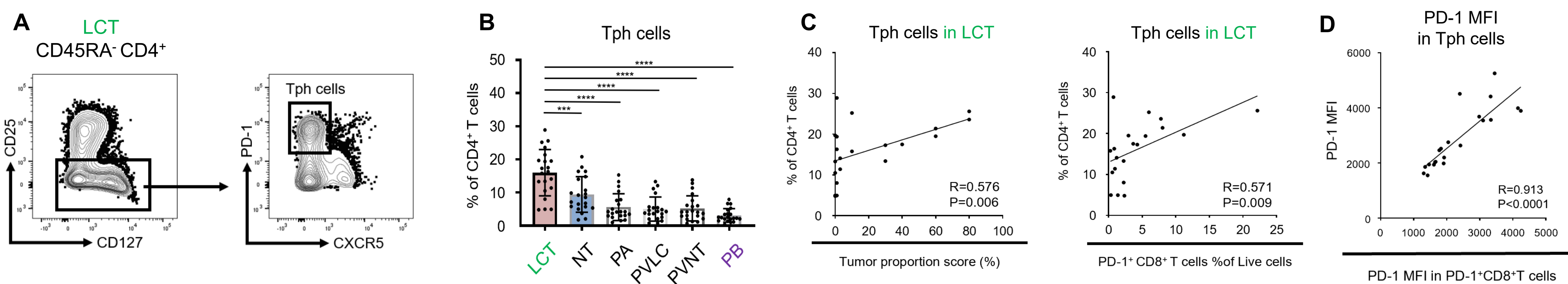
As a single-center study (n=21), these findings require validation in larger independent cohorts. Additionally, it remains unclear whether the interactions between Tph cells, PD-1⁺CD8⁺ T cells, and tumor cells are direct or indirect, necessitating further functional assays. Furthermore, while recent studies have identified distinct “stem-like” and “effector-like” Tph subsets in the inflamed synovium of rheumatoid arthritis, the precise phenotypic differences and behaviors of these subsets within the tumor microenvironment remain poorly understood. Despite these limitations, the clinical implications are highly significant.

In conclusion, evaluating circulating CD127⁻ effector-like Tph cells provides a robust, non-invasive liquid biopsy strategy to estimate intratumoral immune status in real-time, potentially optimizing patient stratification for ICI therapy in NSCLC.



RESULTS

Tph cells accumulate and synchronize with PD-1⁺CD8⁺ T Cells in LCT



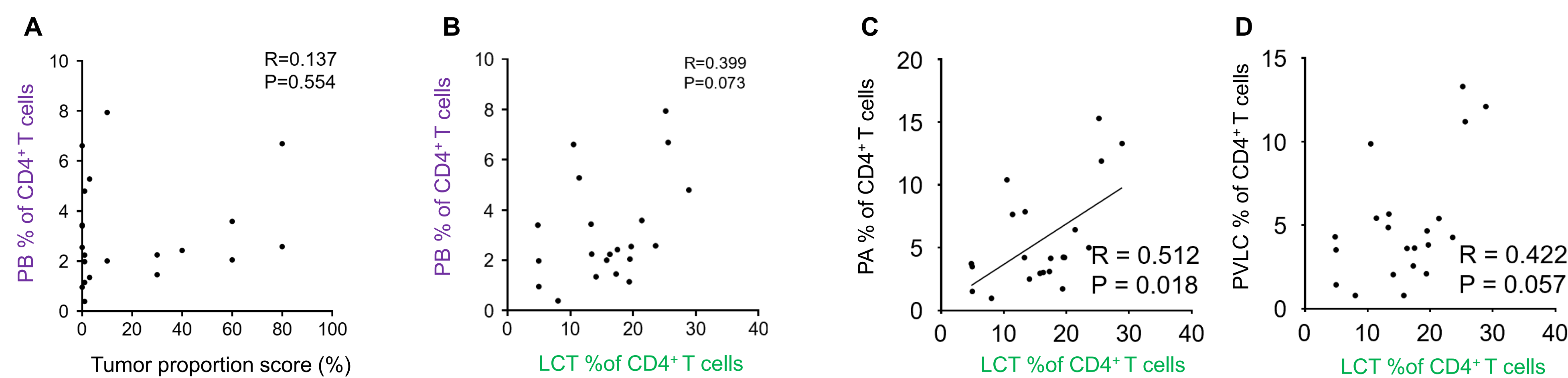
Tumor-Specific Accumulation: Various PD-1⁺CD4⁺ T cell subsets exist within the tumor, and among the six compartments, Tph cells are significantly enriched in the LCT (A, B).

Unique Coordination: Among CD4⁺ T cell subsets, Tph cells significantly correlate with both the PD-L1 TPS and intratumoral PD-1⁺CD8⁺ T cells .

Parallel Functional Adaptation: The PD-1 MFI of intratumoral Tph cells exhibits an exceptionally strong positive correlation with that of PD-1⁺CD8⁺ T cells (R=0.913, p<0.0001; D).

This suggests that in environments where PD-1⁺CD8⁺ T cells highly express PD-1, Tph cells synchronously exhibit strong PD-1 expression.

Loss of circulatory correlation during passage through the tumor

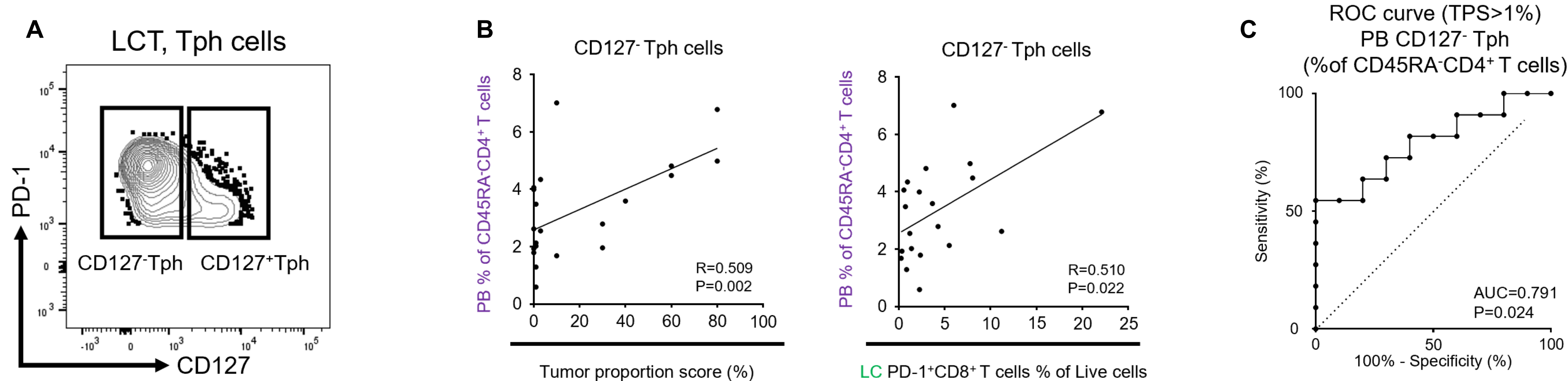


Failure of PB to Reflect Local Immunity: The frequency of Tph cells in the peripheral blood (PB) fails to reflect the local immune status, showing no significant correlation with either LCT Tph frequencies or the PD-L1 TPS (A, B).

Loss of Correlation upon Outflow: Crucially, LCT Tph frequencies correlate with the primary arterial inflow (PA; C) but lose this correlation with the venous outflow (PVLC; D).

This loss of correlation across the tumor bed explains why bulk PB analysis is insufficient.

Circulating CD127⁻ Tph Cells Serve as a Robust Liquid Biopsy



Focusing on Effector Phenotype: Since the peripheral blood contains abundant naive T cells, we first gated on CD45RA⁺ activated cells to exclude this background. Within this population, we targeted the CD127⁻ (IL-7R) effector-like Tph fraction to overcome the circulatory disconnect .

Robust Surrogate Marker: PB CD127⁻ Tph frequencies positively correlate with both the PD-L1 TPS and intratumoral PD-1⁺CD8⁺ T cells (B).

High Predictive Value: ROC analysis demonstrates that circulating CD127⁻ Tph cells effectively distinguish patients with TPS > 1% (AUC = 0.791, p=0.024; D).