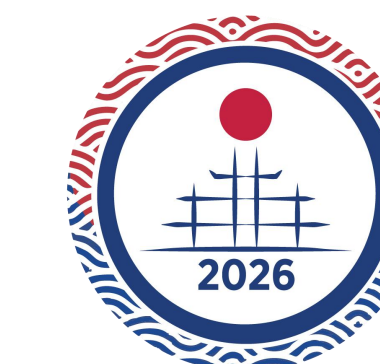




P2.100: CXCR4-positive circulating mucosa-associated invariant T cells can identify non-small cell lung cancer patients who respond to anti-PD1 immunotherapy



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INTRODUCTION

Brain metastases (BMs) are a devastating complication, particularly in NSCLC, conferring a poor prognosis and limited treatment options. Although immune checkpoint blockade (ICB), particularly targeting the programmed cell death-1 (PD-1)/PD-L1 axis, has revolutionized oncology, therapeutic responses within the CNS remain heterogeneous and are often less durable than systemic responses. The efficacy of anti-PD-1 therapy is intrinsically linked to the presence and functional state of tumor-infiltrating lymphocytes (TILs), especially cytotoxic CD8⁺ T cells. Therefore, identifying specific T cell subsets that retain robust cytotoxic potential and can be effectively reinvigorated by PD-1 blockade within the CNS niche is a paramount research focus.

METHODS

A total of 8 patients with confirmed NSCLC and newly diagnosed brain metastases were enrolled. Following anti-PD-1 monotherapy, patients were stratified into Responders ($n = 4$) and Non-Responders ($n = 4$) based on mRECIST criteria at week 9.

Baseline demographic parameters, including age, sex, smoking status, and intracranial tumor burden, were comparably distributed between the two cohorts (all $p > 0.05$).

We performed scRNA-seq on 16 samples of PB and CSF from 8 patients to characterize cellular and molecular of immune and stromal cells and dynamics during ICI treatment.

Dimensionality reduction and clustering were executed utilizing the *Seurat* R package.

Pseudotime trajectory inference was conducted using Monocle3 to model the transitional dynamics of MAIT cell states.

To map intercellular interactions, specifically the CXCR4-CXCL12 axis, CellChat (v1.6.0) was applied to the combined CSF single-cell dataset to infer ligand-receptor communications between the MAIT cell subset and other microenvironmental components.

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- The central finding of the present study is the identification of a distinct, clonally expanded subset of CXCR4-expressing CD8⁺ MAIT cells, which are preferentially recruited to the CSF and serve as a predictive biomarker for anti-PD-1 efficacy in lung cancer BM.

Future Direction for Research

- Combinatorial strategies designed to upregulate CXCR4 expression or augment CXCL12 gradients in the CNS could synergize with anti-PD-1 therapy in NSCLC brain metastasis patients.
- Future investigations should incorporate spatial biology to map the precise topological distribution of these cells relative to the BBB and the tumor core.

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RESULTS

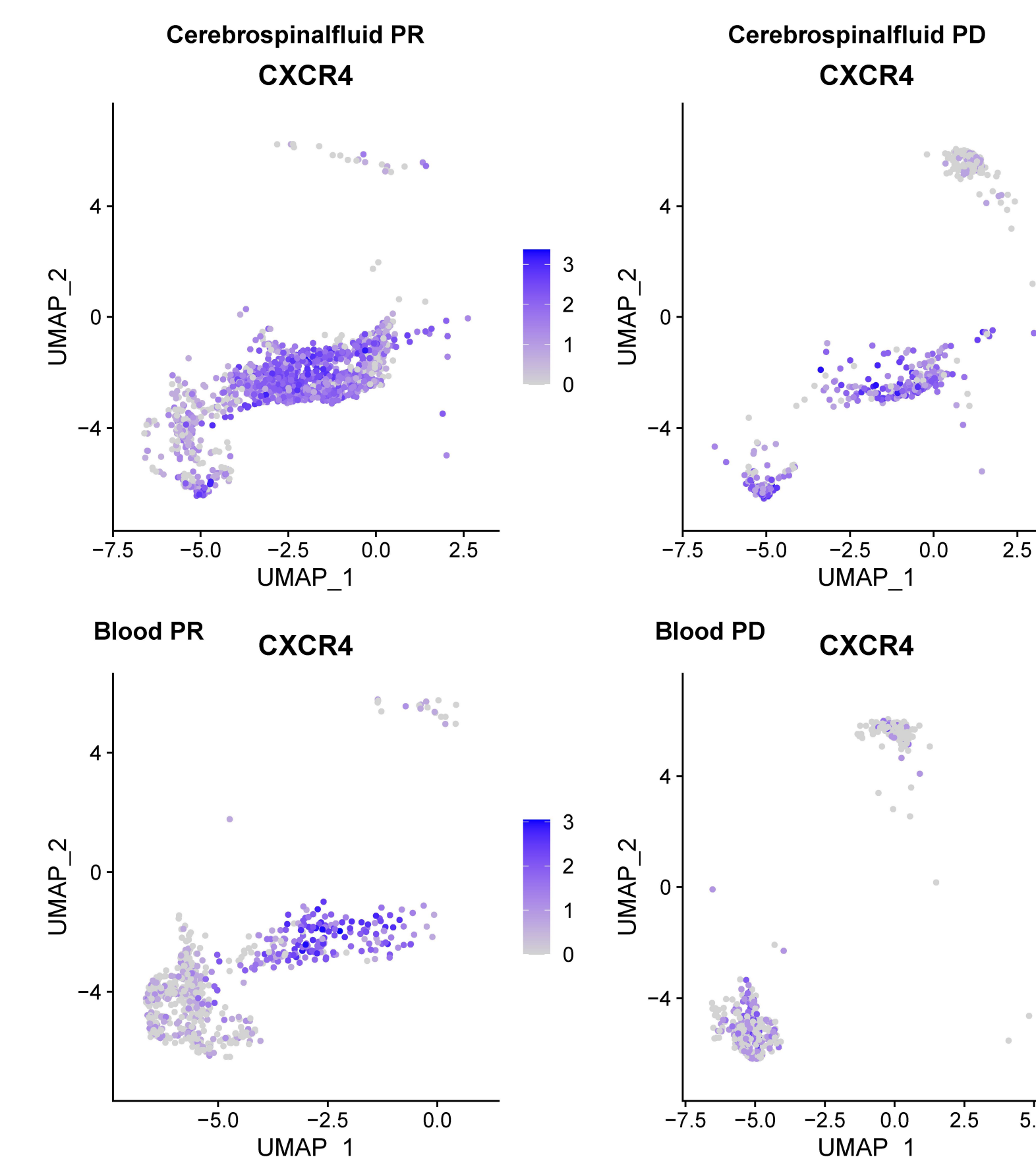


Figure 1: CXCR4+ CD8+ MAIT Cells are preferentially enriched in the CSF of ICB responders.

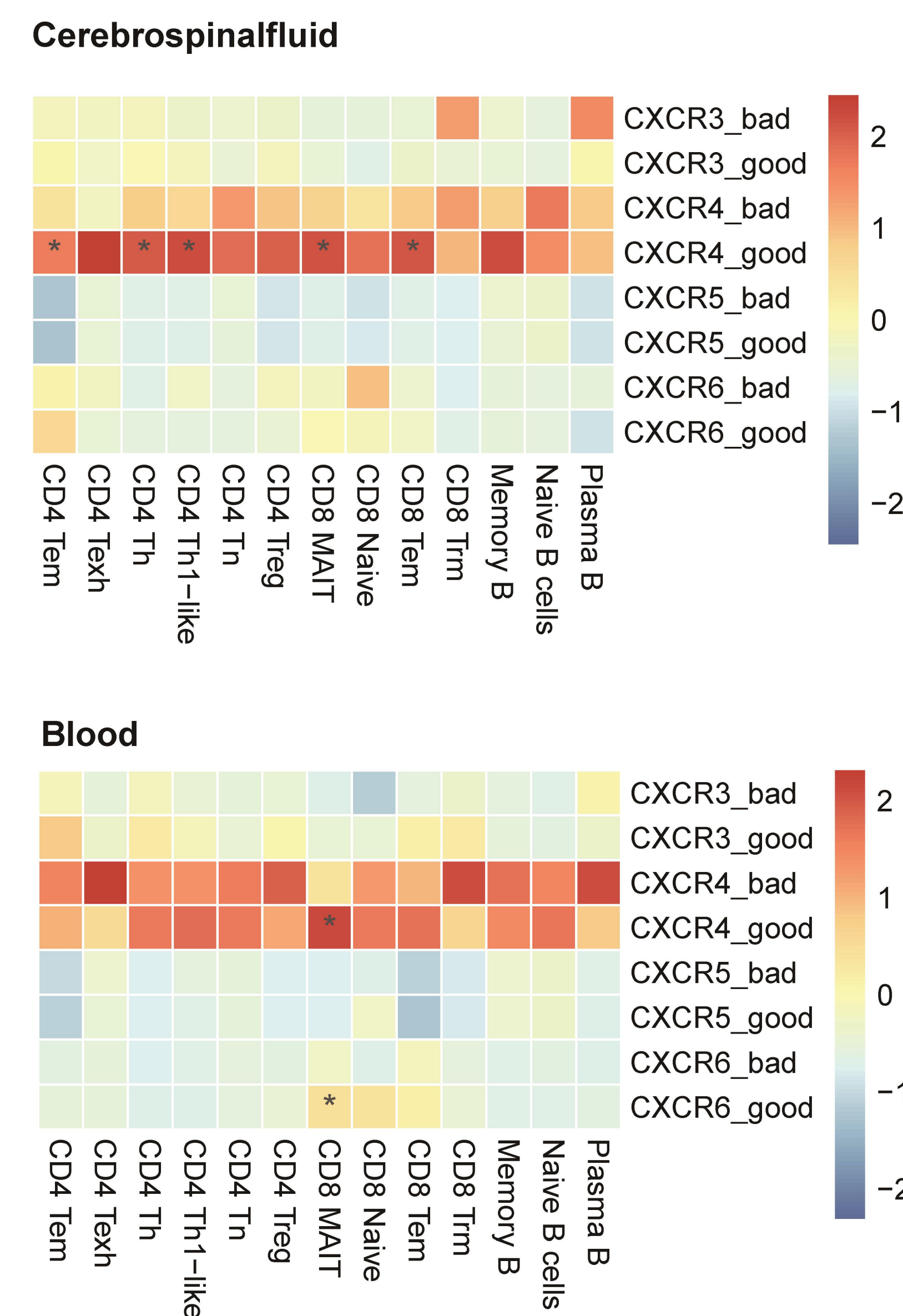


Figure 2: Baseline blood and CSF samples from Responders harbored a significantly greater proportion of CXCR4+ CD8+ MAIT cells compared to Non-Responders.

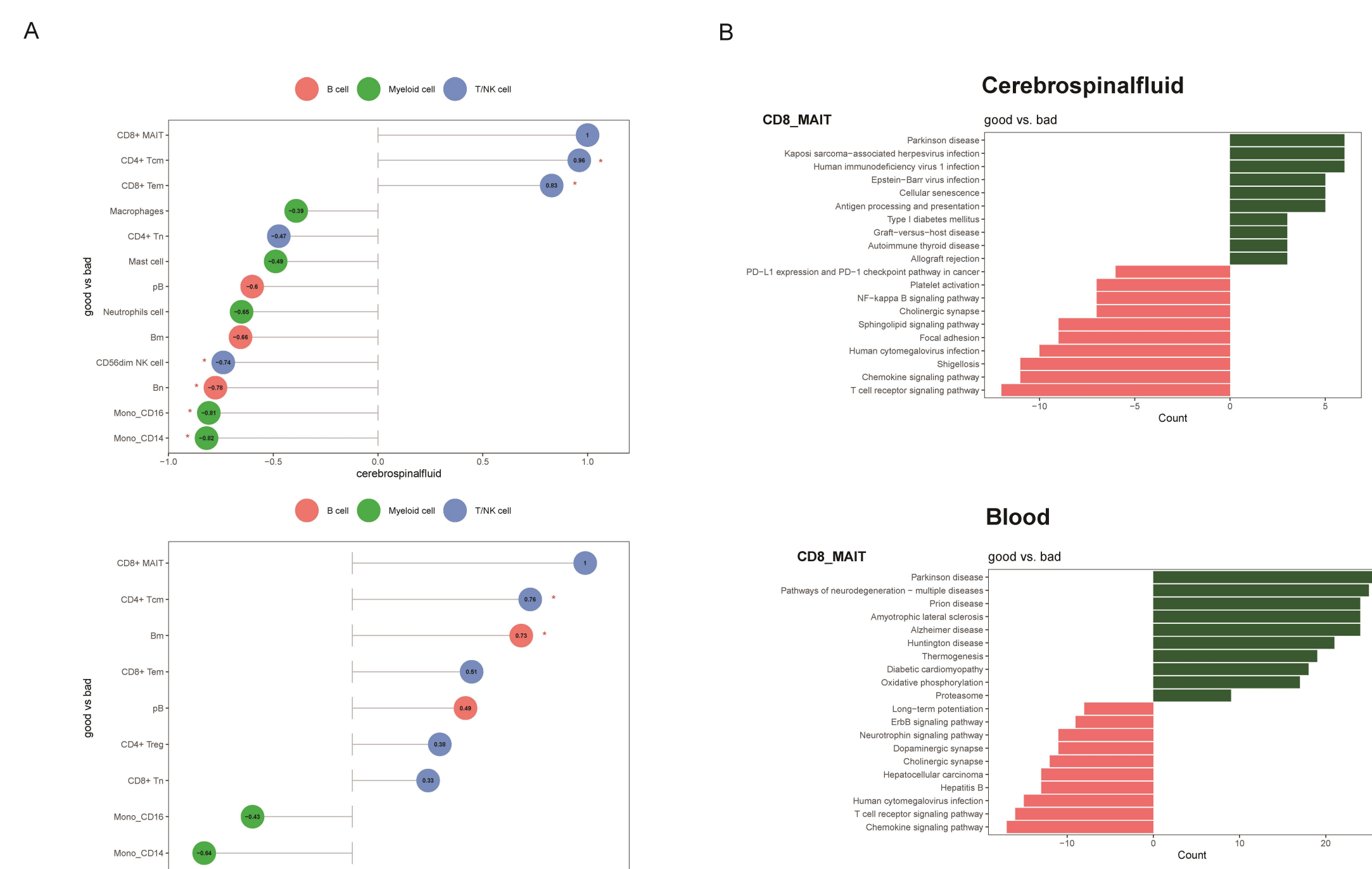


Figure 3: Correlation of CD8+ MAIT Cells and other immune cells and the significant enriched pathways between Responders and Non-Responders.

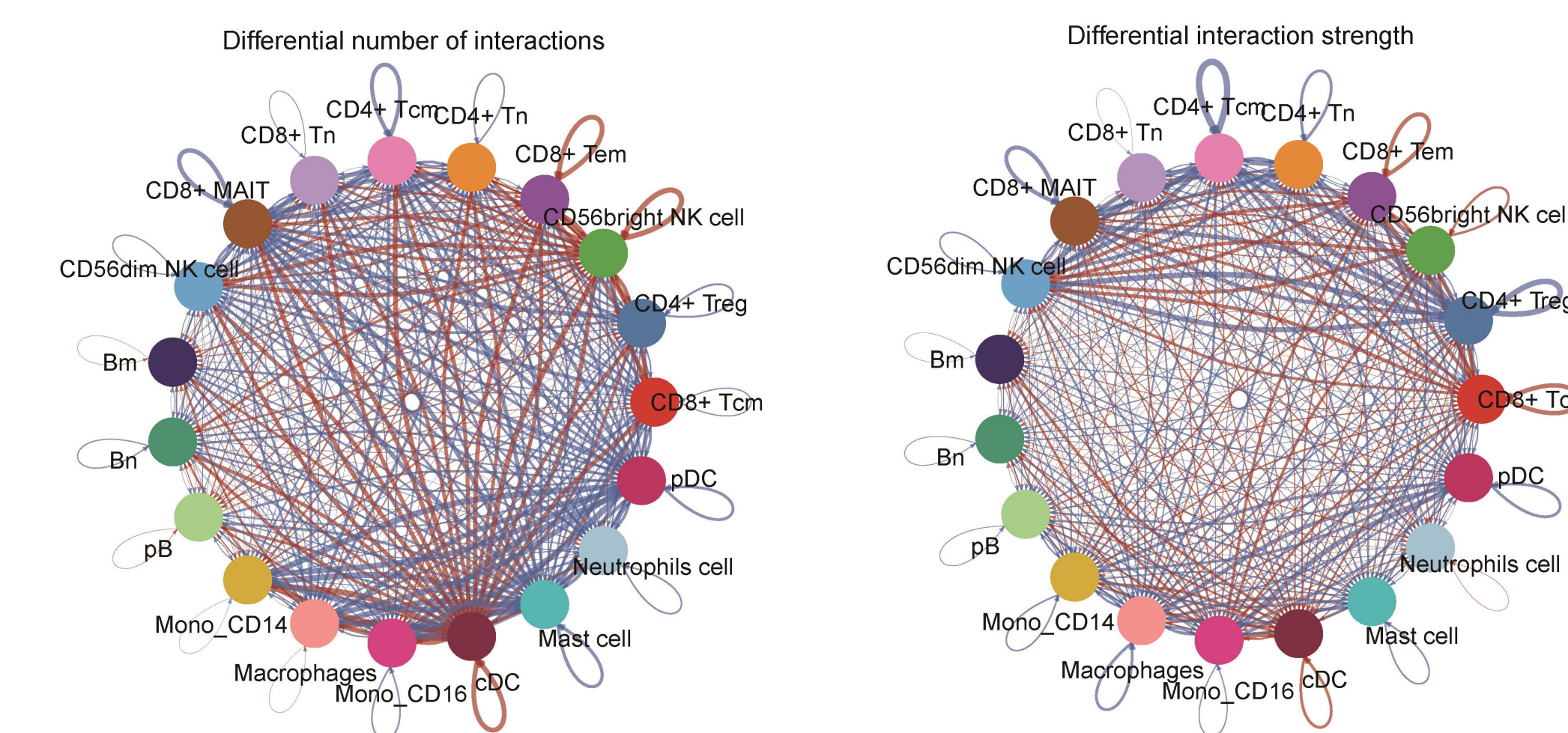


Figure 4: CellChat analysis of the CSF microenvironment revealed different interaction strength between Responders and Non-Responders.

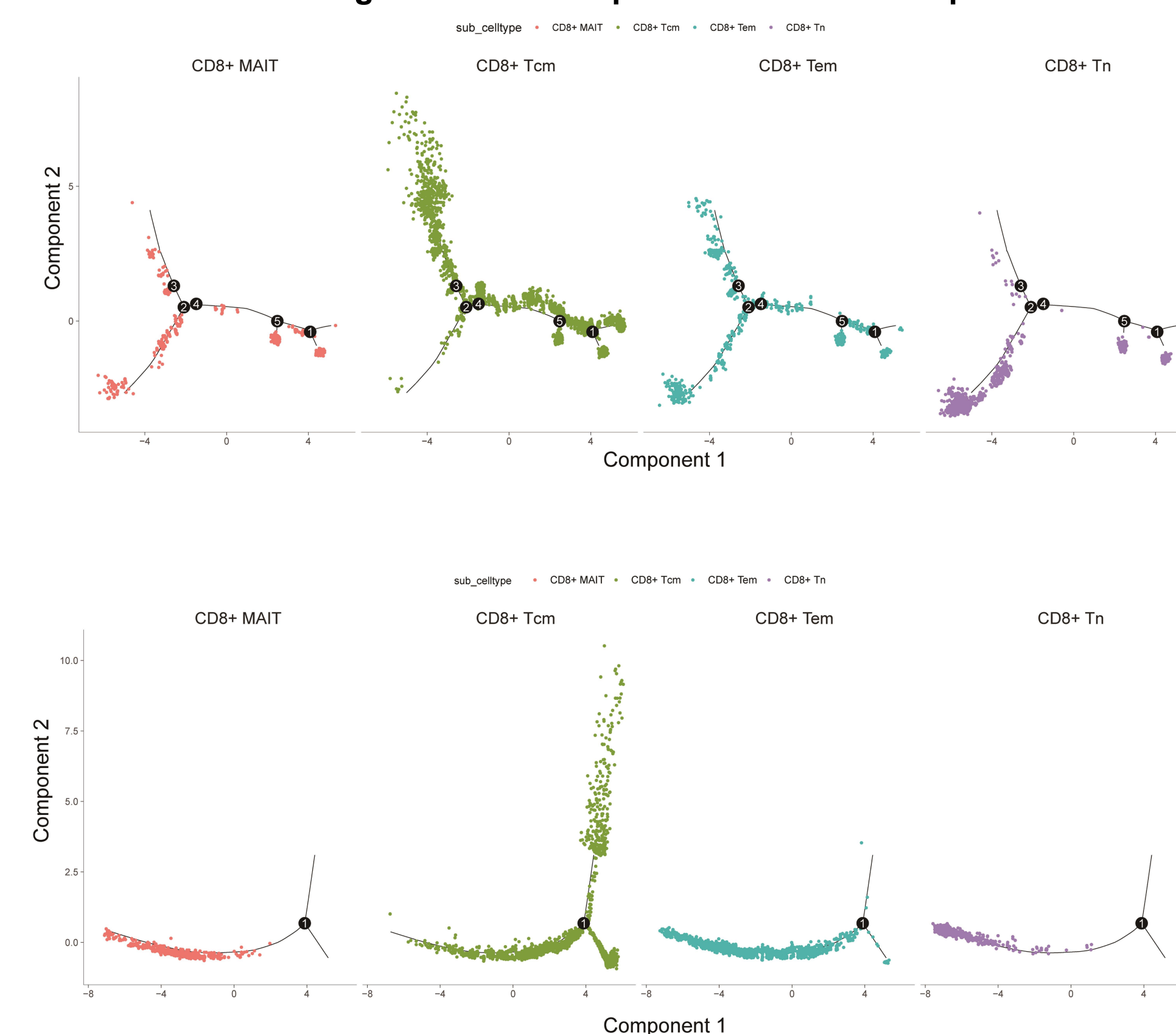


Figure 5: Monocle3 trajectory analysis mapped a different developmental continuum of CXCR4+ CD8 MAIT cells between Responders and Non-Responders.