Defining Effector and Memory-like Cell State In in-vivo CAR T Cells from Multi-center Clinical Trials

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Introduction

- Chimeric antigen receptor (CAR) T Cell immunotherapy has been shown to reduce the amount of non-solid tumor cancer cells.
- The first pediatric patient to receive CAR T cell immunotherapy (PT1) has been in complete remission for 12 years.
- Some patients relapse due to a lack of effector or memory T cell types.
- If CAR T cell states (effector/memory) can be defined and modulated, immunotherapy can be personalized to make patients cancer-free.

Research Questions

- Can we map groups against Persistent CAR T cells and see an overlap?
- Are the cell types of PT1 data expressing the same genes as their cell state counterpart?
- Are the phenotypes that are most expressed in the group representative of effector and memory cells?

Materials and Methods

- The Gaussian Mixture Model (GMM) defined the two cell states, and each group was proven to be effector/memory like:
- UMAP Joint-Embedding showed cellular correlation.
- Differential Expression analysis showed genetic correlation.
- Gene Set Enrichment Analysis showed phenotypic association.

Combined Clinical Data Cell State Map

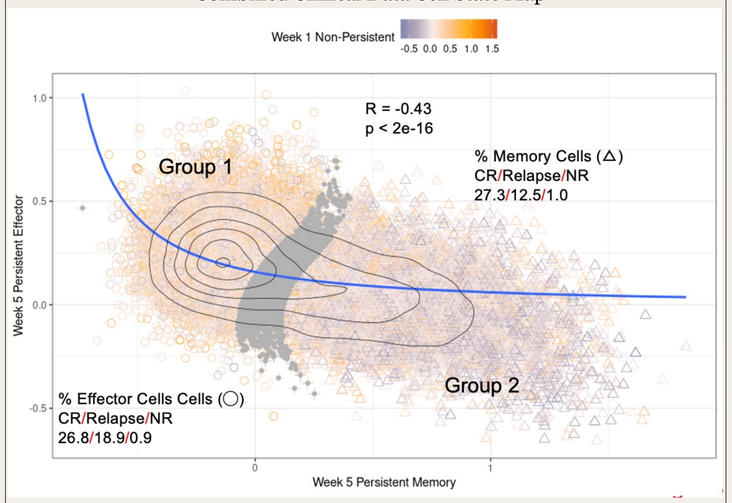
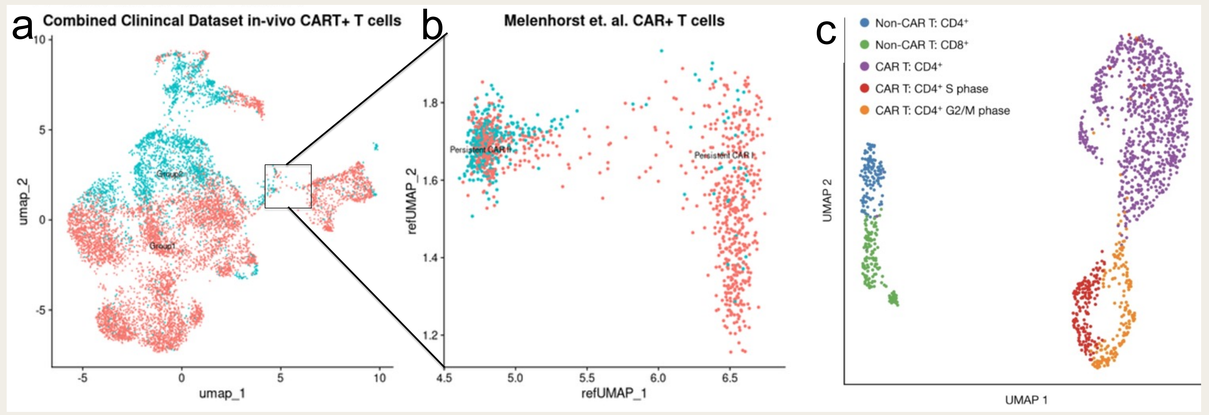
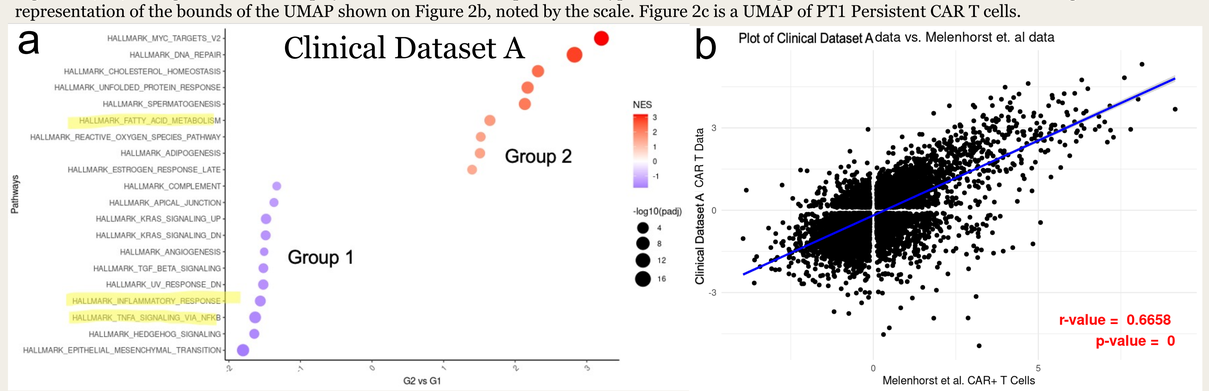


Figure 1. Cell state map derived from the GMM that defines Group 1 and Group 2 cells. Group 2 cells exhibit higher persistent memory concentrations, while Group 1 cells exhibit higher persistent effector concentrations, showing a negative correlation between effector and memory cells.

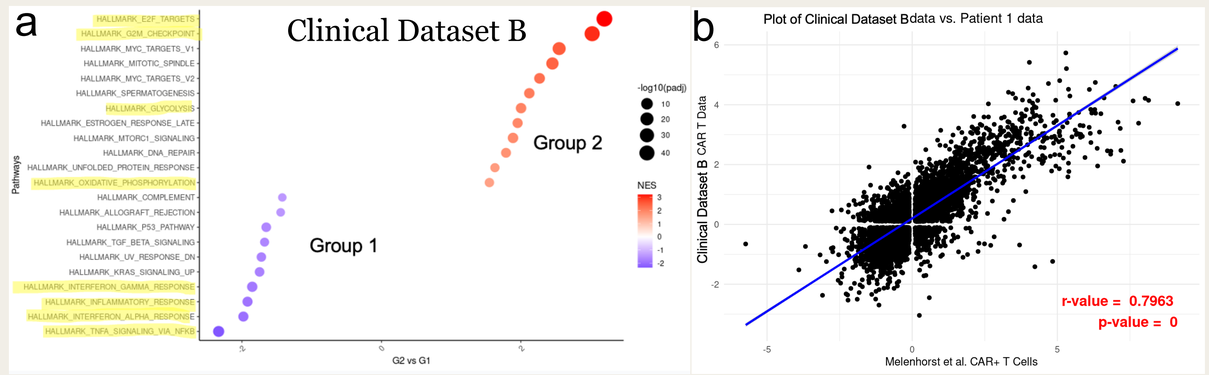
Results



Figures 2a, 2b, 2c. Figure 2a and 2b display the UMAP coordinate plots of cell types when anchored against each other. The box shown on Figure 2a is a representation of the bounds of the UMAP shown on Figure 2b, noted by the scale. Figure 2c is a UMAP of PT1 Persistent CAR T cells.



Figures 3a, 3b. The figures show the most expressed hallmark phenotypes of Group 1 and Group 2 cells (Figure 3a) and a correlation plot analysis of the fold change values of differentially-expressed genes of Group 2 v. Group 1 cells when comparing Clinical Dataset A to the PT1 cell types (Figure 3b).



Figures 4a, 4b. The figures show the most expressed hallmark phenotypes of Group 1 and Group 2 cells (Figure 4a) and a correlation plot analysis of the fold change values of differentially-expressed genes of Group 2 v. Group 1 cells when comparing Clinical Dataset B to the PT1 cell types (Figure 4b).

Conclusions

- Joint embedding shows an overlap of the data of cells by group compared against Patient 1 data, showing cellular correlation.
- Correlation of Log2FC (fold change) values show a strong correlation between differentially expressed genes.
- When comparing group 2 v. group 1, GSEA analysis shows that the top phenotypes expressed relate to those of effector (group 1) or memory (group 2) , showing phenotypic correlation.

Future Directions

- Collect more clinical datasets from different areas of the world to decrease bias.
- Build effector and memory types to build a network of genes.

Acknowledgements

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References

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Discussion

- Figure 2b appears to show the same color pattern (same groups) as Figure 2a based on the UMAP scale. This means that the clinical data maps directly the same way as PT1 persistent cell types.
- Figure 3a and 4a show that Group 2 cells tend to show phenotypes of fatty acid metabolism, oxidative phosphorylation, glycolysis, E2F Targets and G2-M checkpoints. These are commonly associated with memory cell phenotypes (Chapman, Chi et al.). Group 1 cells appear to express phenotypes of inflammatory response, TNF-signaling, and interferon gamma response, among others. These phenotypes are highly situated in the literature as effector cell type phenotypes.
- Figure 3b and 4b show a strong and positive correlation between Group 2 v. Group 1, showing that when comparing against persistent CAR T cell types, the differentially-expressed genes of effector-like cells and memory-like cells appear to map against their respective persistent counterpart.

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