
SITC
2017
November 8-12
NATIONAL HARBOR
MARYLAND
Gaylord National Hotel
& Convention Center
sitc
Society for Immunotherapy of Cancer

Concurrent Session 105: Building Personalized Vaccines and Technologies for Hematologic Malignancies and Solid Tumors

Co-Chairs:
Matthew M. Gubin, PhD – *Washington University of Medicine* Catherine J. Wu, MD – *Dana-Farber Cancer Institute*

2:05 – 2:25 p.m. **Cancer Neoantigens as Targets for Therapeutic Anti-Tumor Responses**
Matthew M. Gubin, PhD – *Washington University School of Medicine*

2:25 – 2:45 p.m. **Tumor Vaccines in AML**
David E. Avigan, MD – *Beth Israel Deaconess Medical Center*

2:45 – 3:05 p.m. **Improvement in Epitope Discovery**
Catherine J. Wu, MD – *Dana-Farber Cancer Institute*

3:05 – 3:20 p.m. **Predictive Biomarkers for Response to Anti-CTLA-4 and Anti-PD-1 Immunotherapy in Melanoma Patients**
Priyanka Subrahmanyam, PhD – *Stanford University*

SITC 2017

CANCER NEOANTIGENS AS TARGETS FOR THERAPEUTIC ANTI-TUMOR RESPONSES

Session 105: Building Personalized Vaccines and Technologies for Hematologic Malignancies and Solid Tumors

Matthew M. Gubin

Department of Pathology and Immunology

Washington University School of Medicine

CHiPs

The Andrew M. and Jane M. Bursky Center for Human Immunology & Immunotherapy Programs

Presenter Disclosure Information

Matthew M. Gubin

The following relationships exist related to this presentation:

No Relationships to Disclose

LETTER

doi:10.1038/nature13988

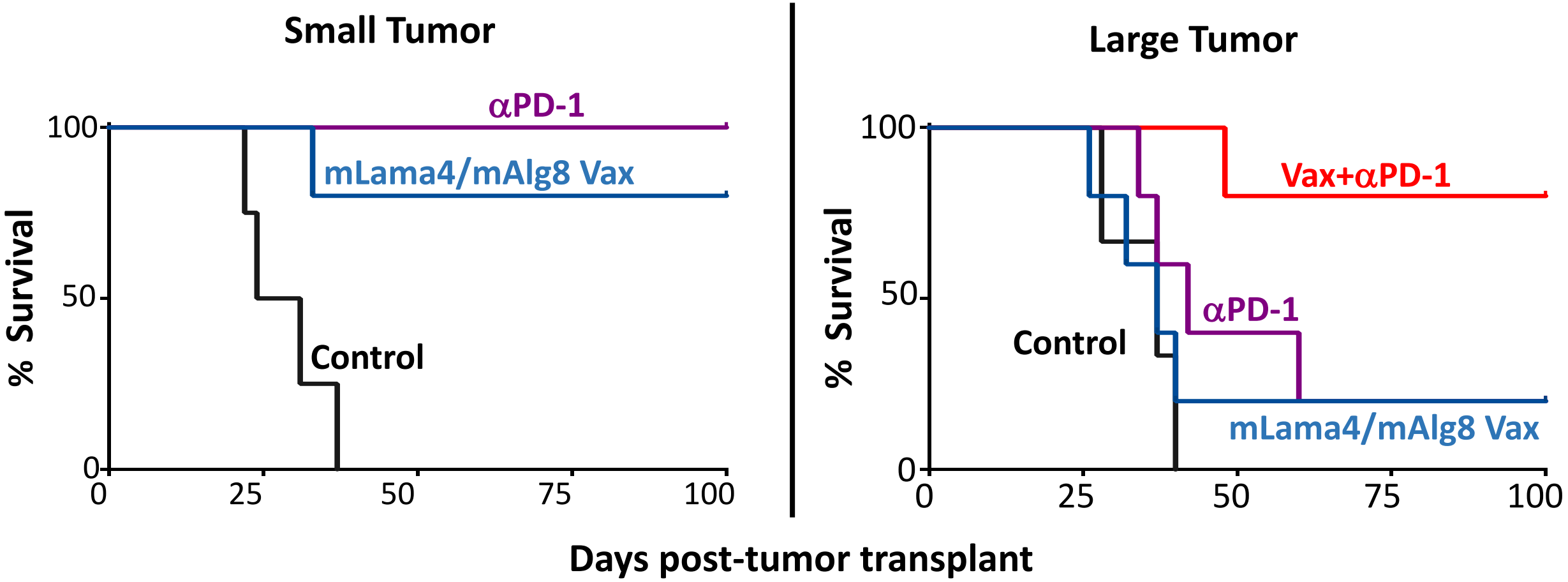
Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens

Matthew M. Gubin[1], Xiuli Zhang[2], Heiko Schuster[3], Etienne Caron[4], Jeffrey P. Ward[1,5], Takuro Noguchi[1], Yulia Ivanova[1], Jasreet Hundal[6], Cora D. Arthur[1], Willem-Jan Krebber[7], Gwenn E. Mulder[7], Mireille Toebes[8], Matthew D. Vesely[1], Samuel S. K. Lam[1], Alan J. Korman[9], James P. Allison[10], Gordon J. Freeman[11], Arlene H. Sharpe[12], Erika L. Pearce[1], Ton N. Schumacher[8], Ruedi Aebersold[4,13], Hans-Georg Rammensee[3], Cornelis J. M. Melief[7,14], Elaine R. Mardis[6,15], William E. Gillanders[2], Maxim N. Artyomov[1] & Robert D. Schreiber[1]

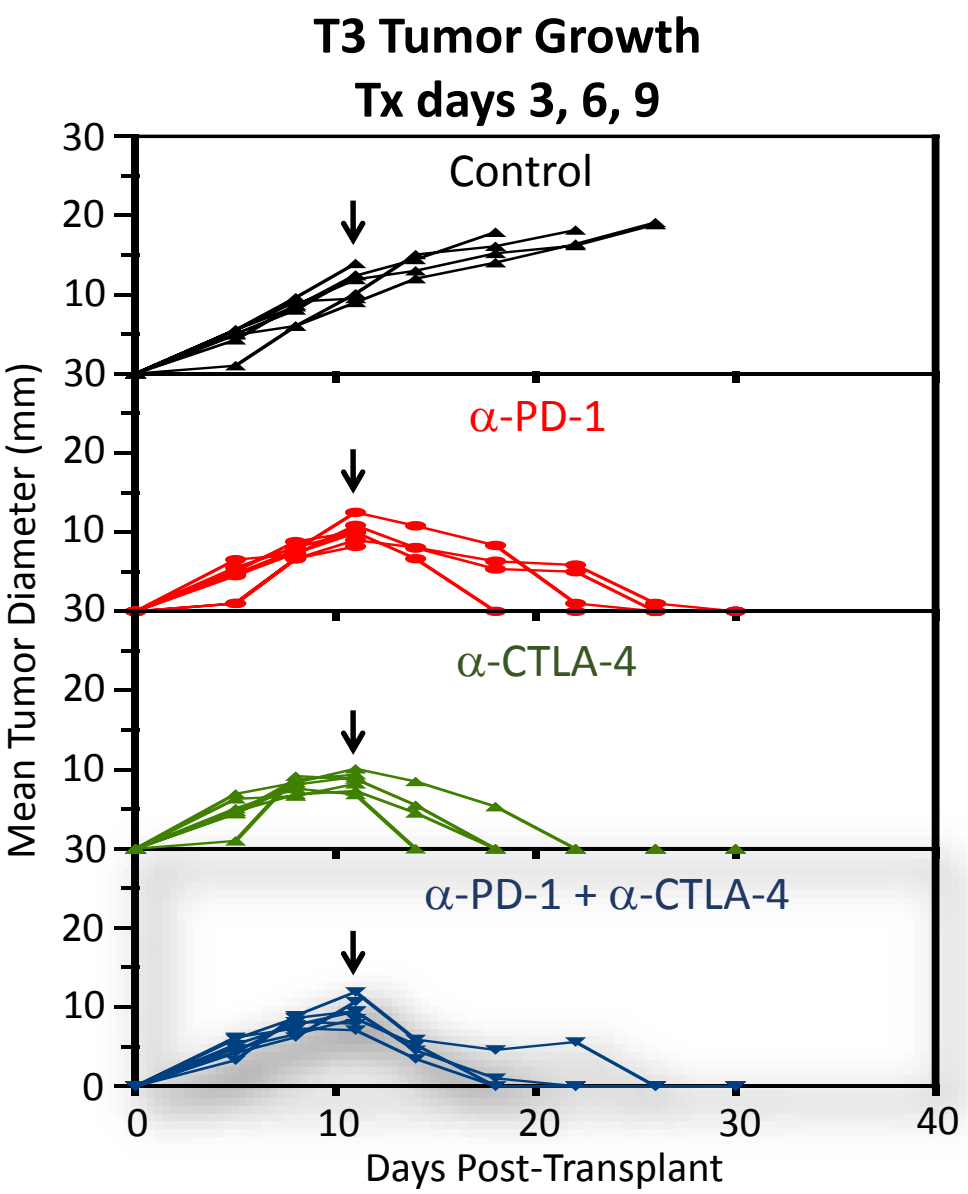
Nature ***515***:577-581 (2014)

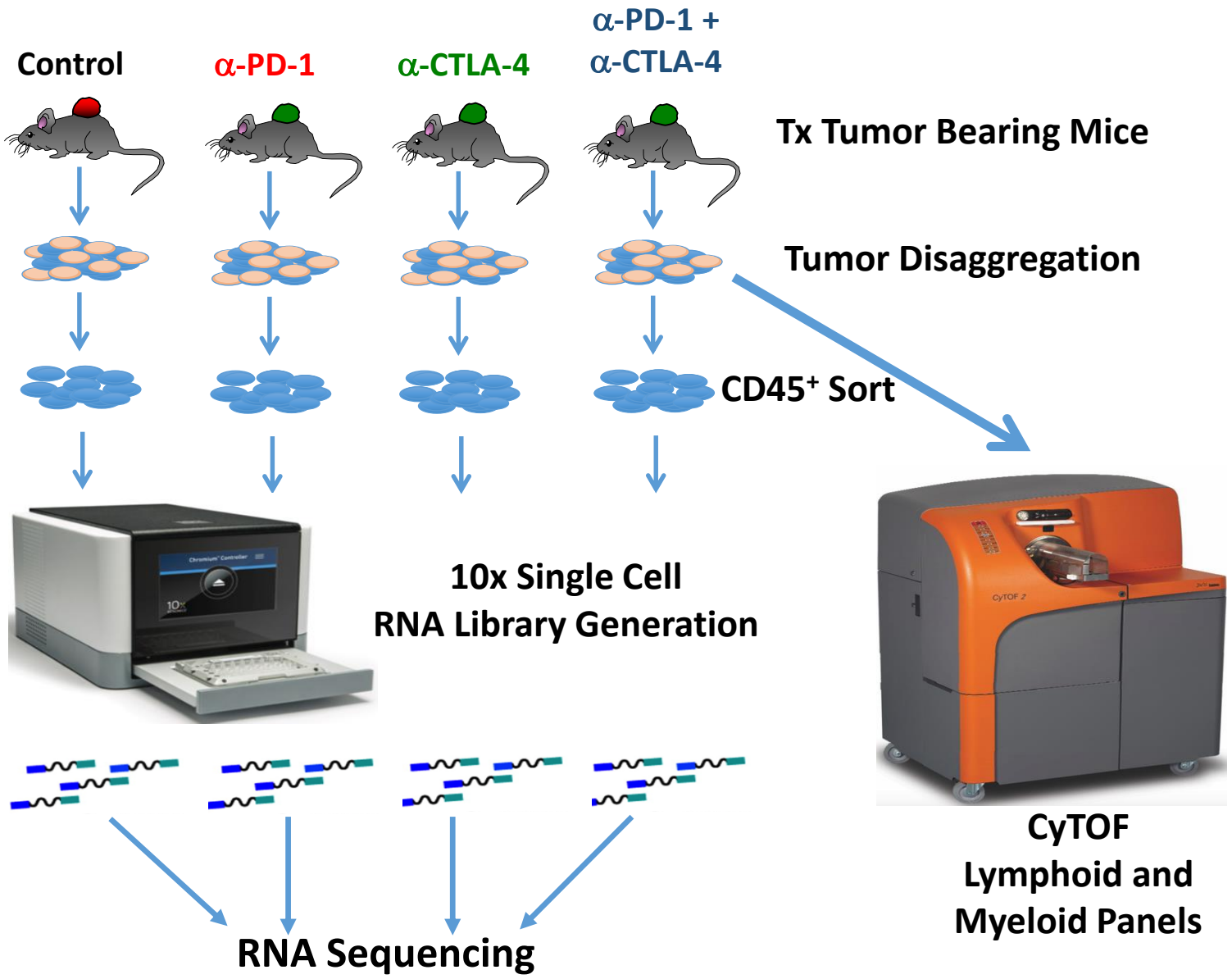
- Whole exome sequencing/RNA-Seq plus epitope prediction revealed that the T3 sarcoma cells express ~700 nonsynonymous mutations; 2 function as dominant neoantigens
- Tumor-specific mutant neoantigens are favored targets for T cells reinvigorated by immune checkpoint blockade
- Neoantigen-specific $CD8^+$ T cells display both overlapping and distinct changes upon either anti-CTLA-4 or anti-PD-1 immune checkpoint blockade therapy
- Tumor-specific mutant neoantigen personalized vaccines display therapeutic efficacy

Personalized Cancer Neoantigen Vaccine Extends the Immune Checkpoint Blockade Therapeutic Window for T3 Tumors



High Dimensional Analysis of Immune Checkpoint Blockade-Mediated T3 Sarcoma Rejection

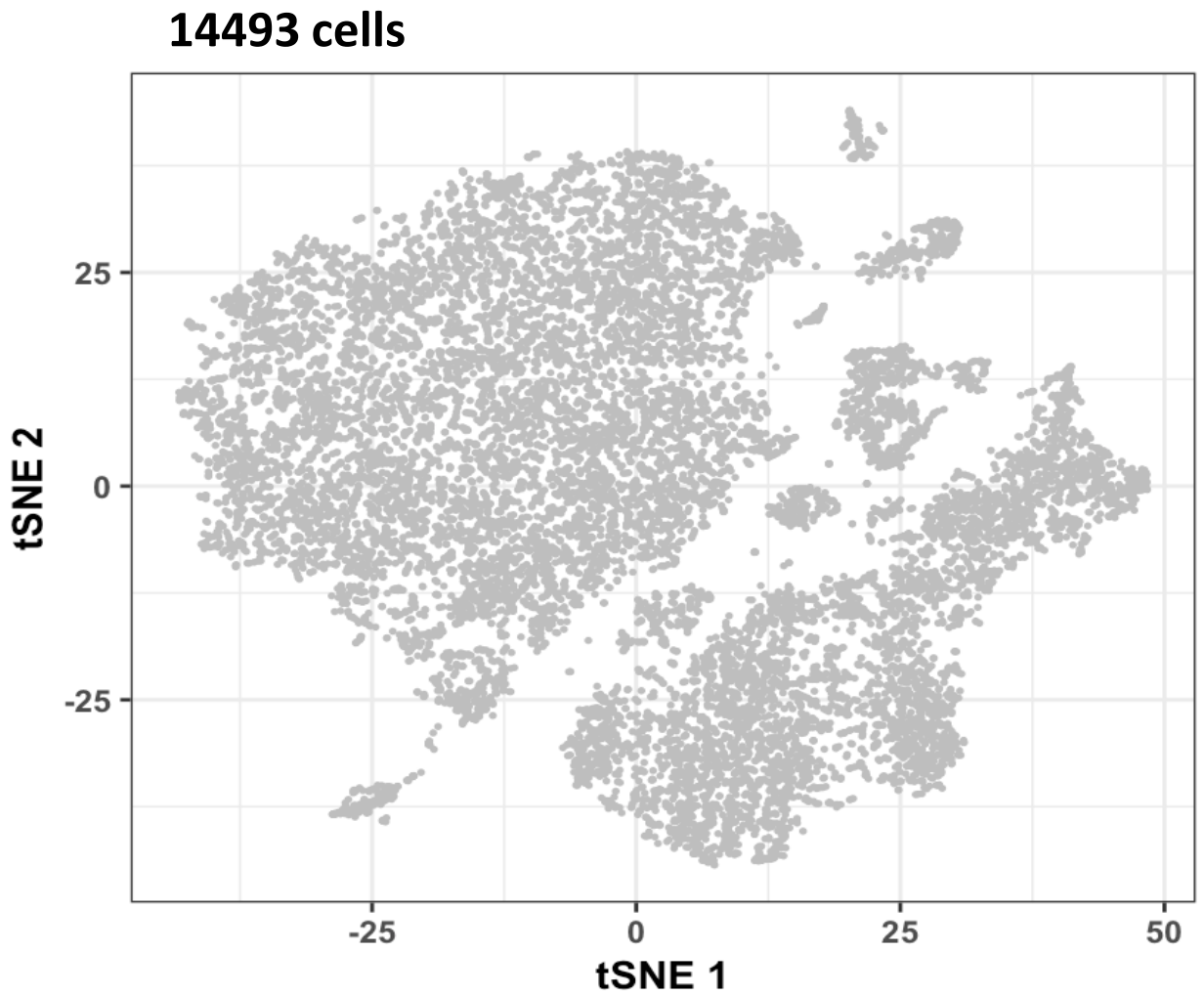




Visualization by tSNE: Fitting Data into 2 Dimensions

tSNE (t-distributed stochastic neighbor embedding):
Non-linear dimensionality reduction technique that aims to put data into 2 or 3 dimensional space and save the "distance" between each two dots.

Transcriptionally similar cells will be close to each other.

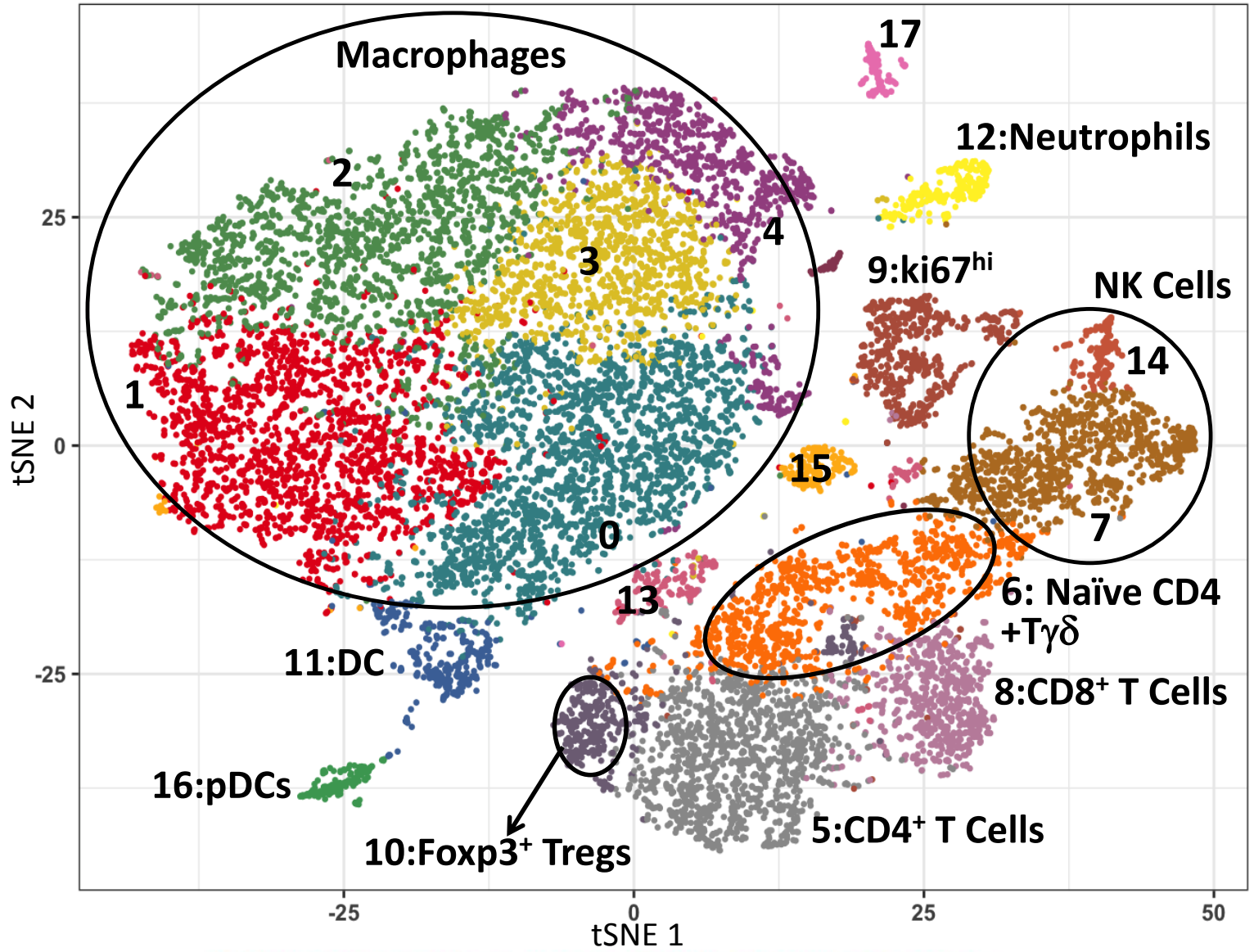


http://www.jmlr.org/papers/volume9/vandermaaten08a/vandermaaten08a.pdf

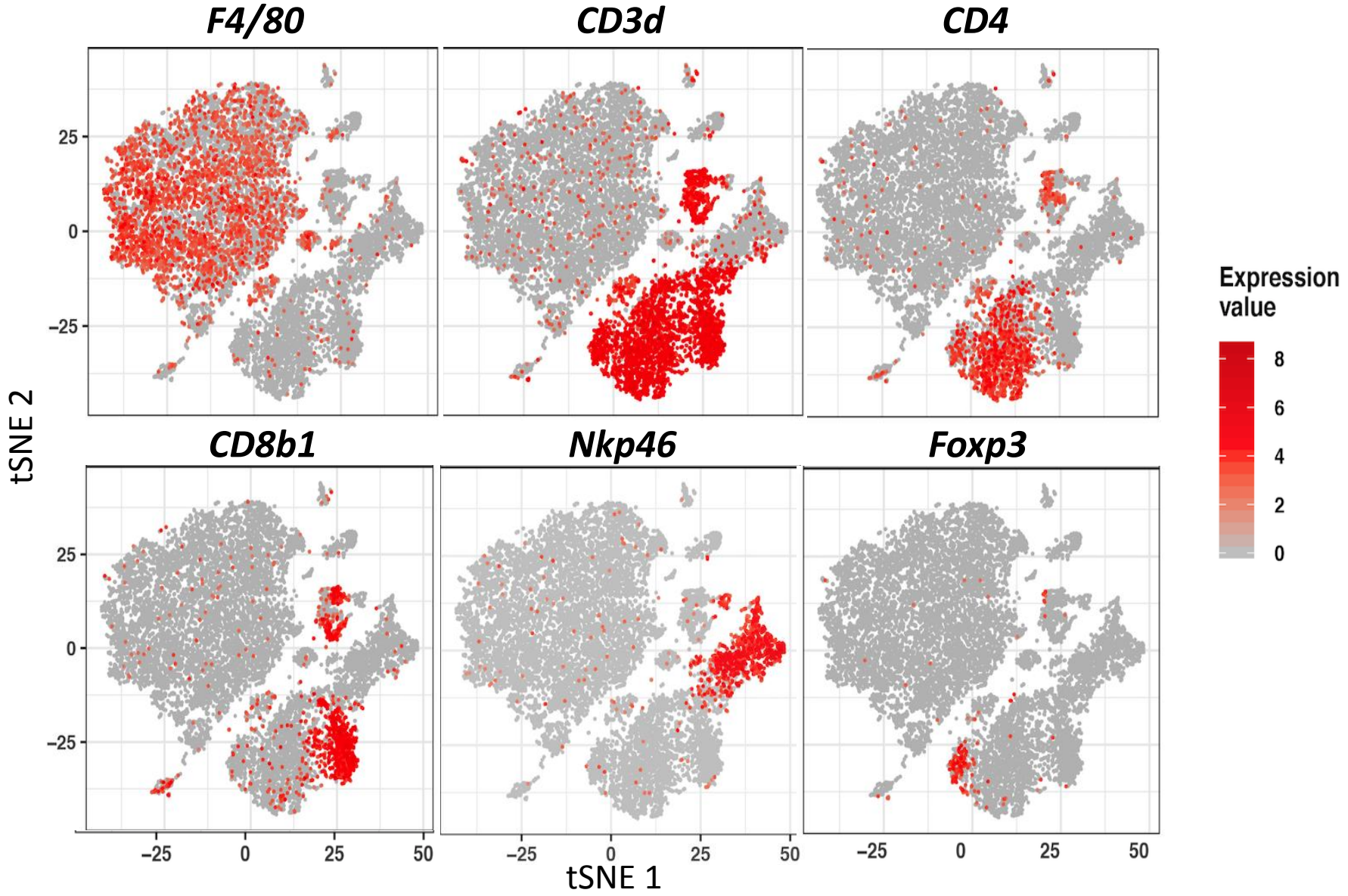
Annotation of Immune Cell Clusters Infiltrating Into T3 Sarcomas +/- Immune Checkpoint Blockade (scRNASeq)

14493 cells

Graph Based Clustering



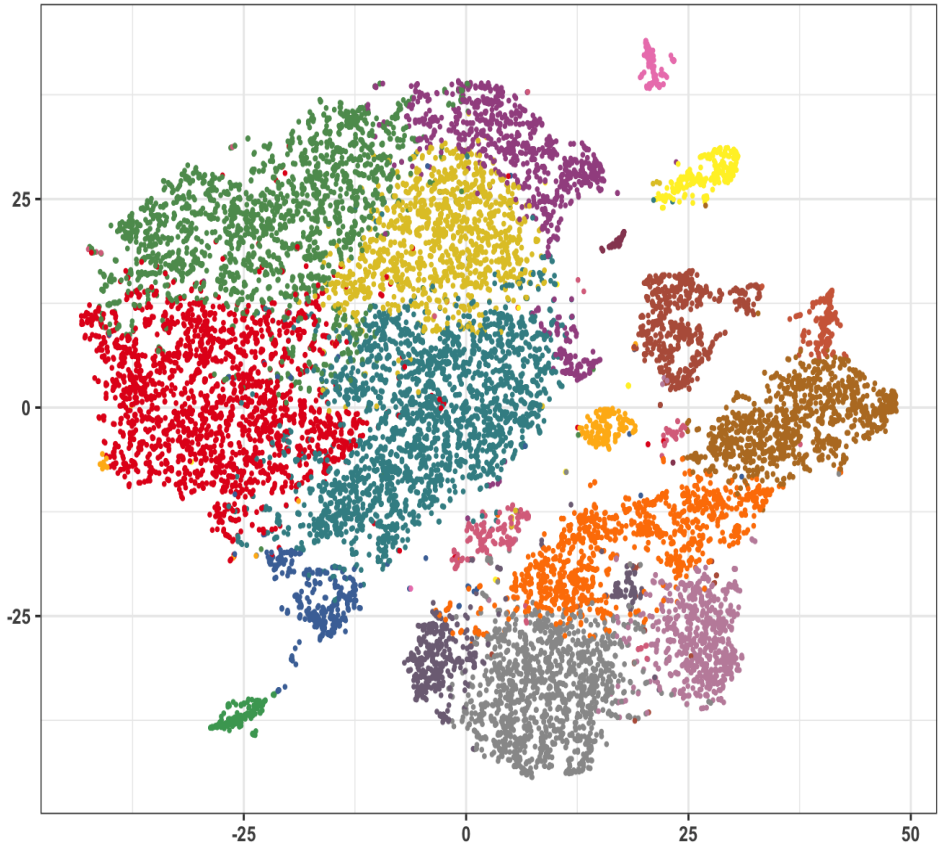
Using Known Markers to Test Whether Clustering Makes Sense

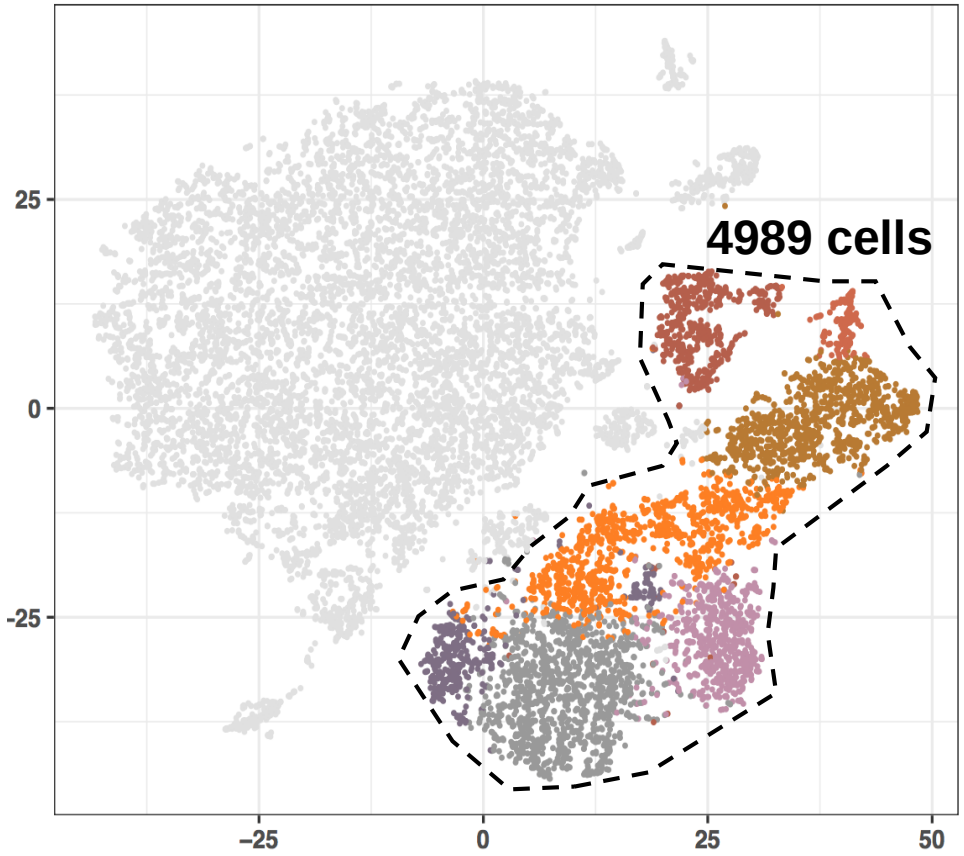


A glimpse into the complexity of the tumor infiltrating lymphoid compartment

Focus on Lymphoid Compartment (scRNASeq)

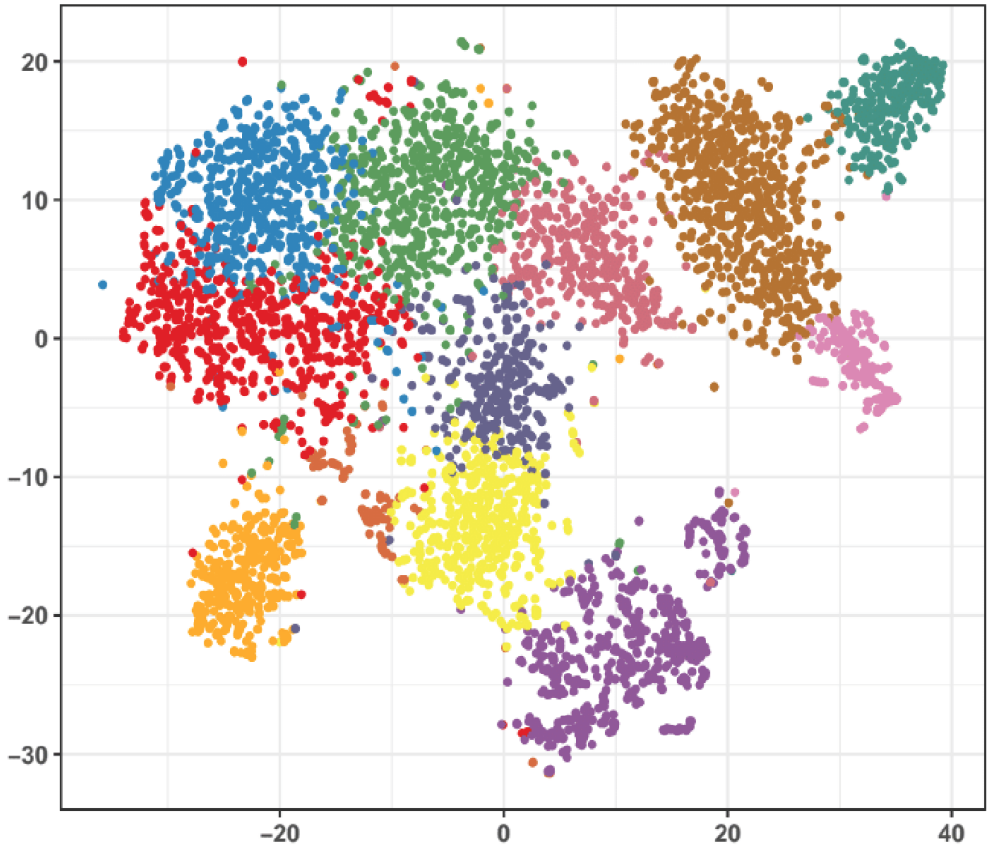
14493 cells

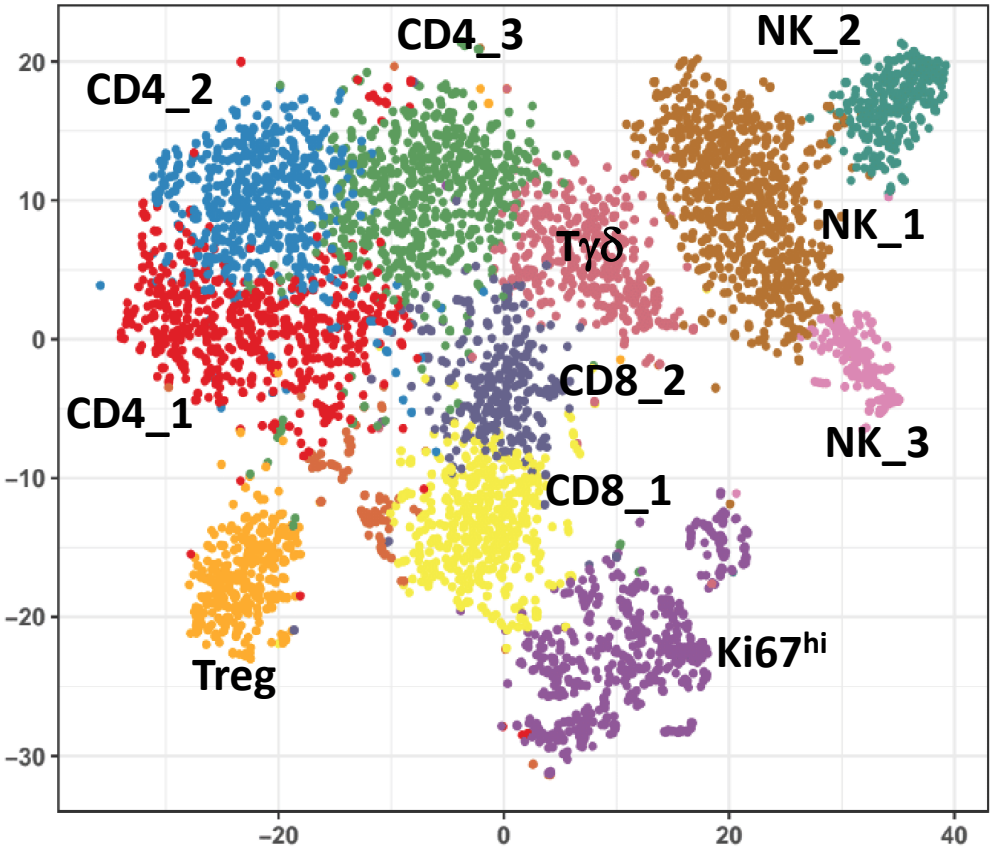




Lymphoid Compartment Annotation (scRNASeq)

Lymphoid: 4989 cells





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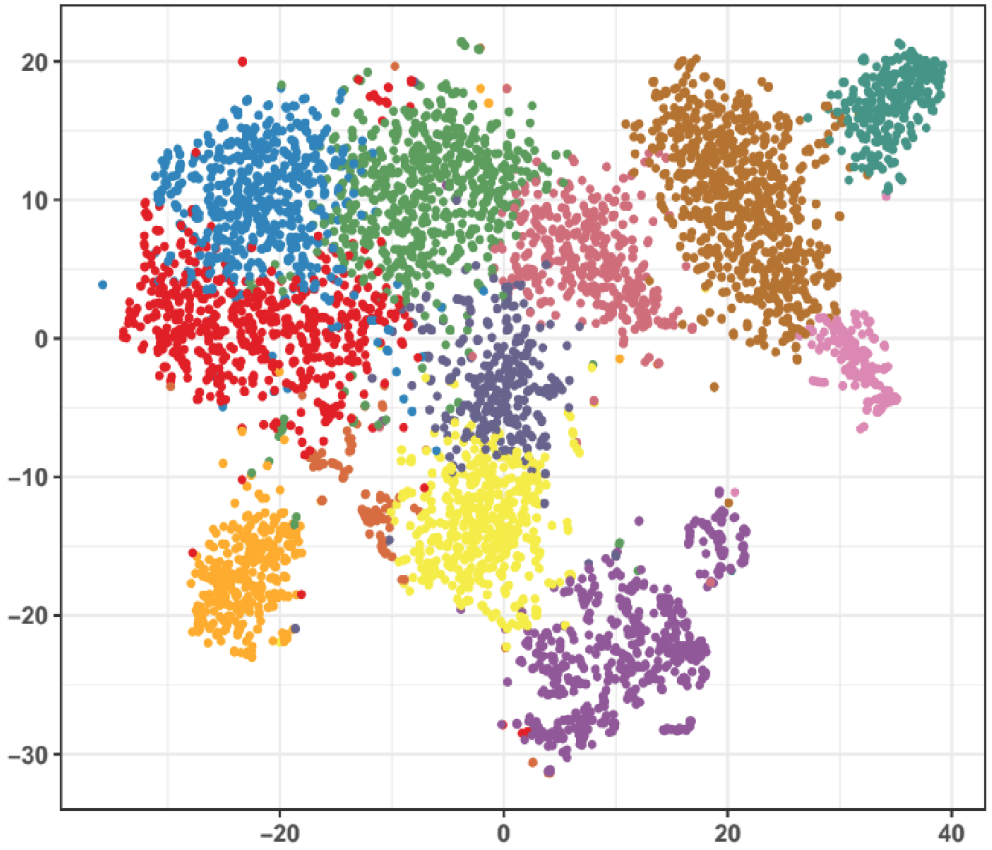
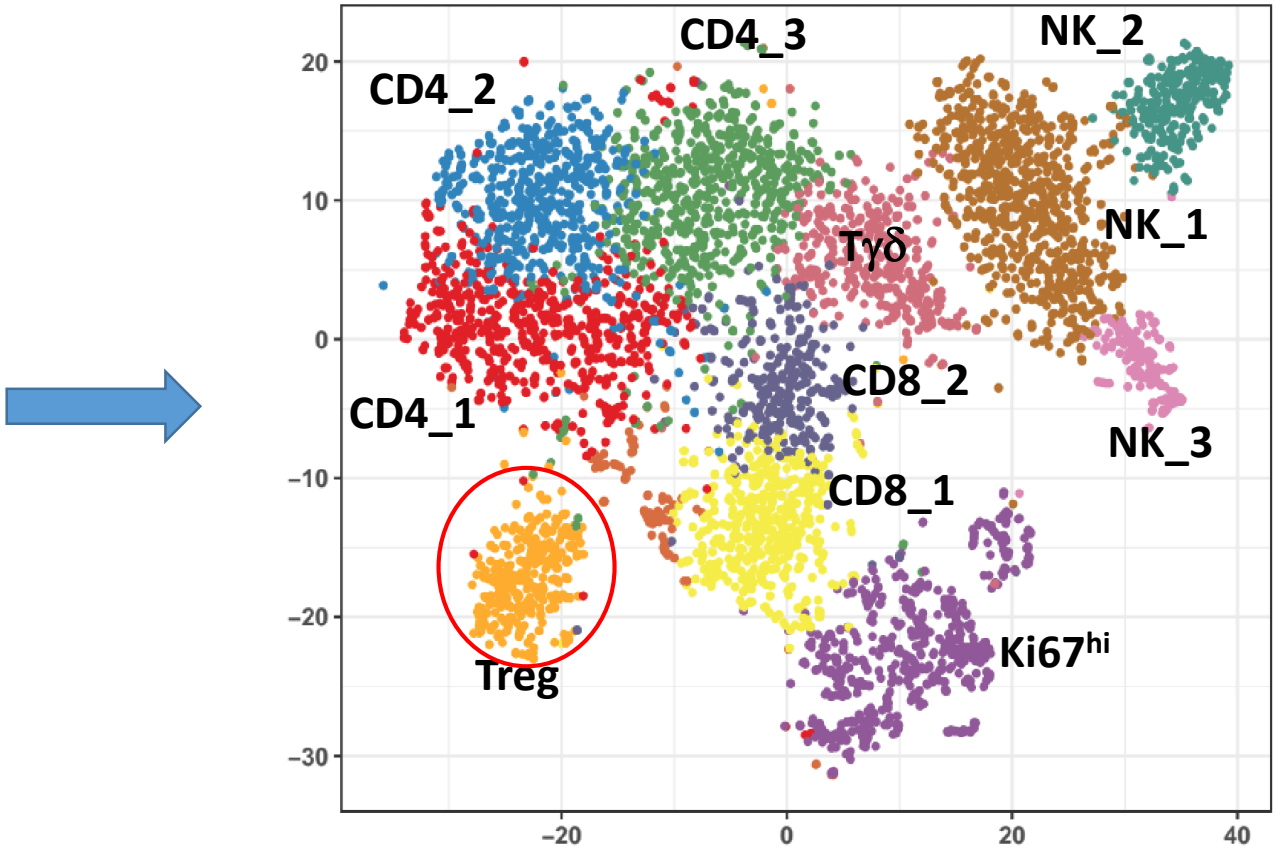
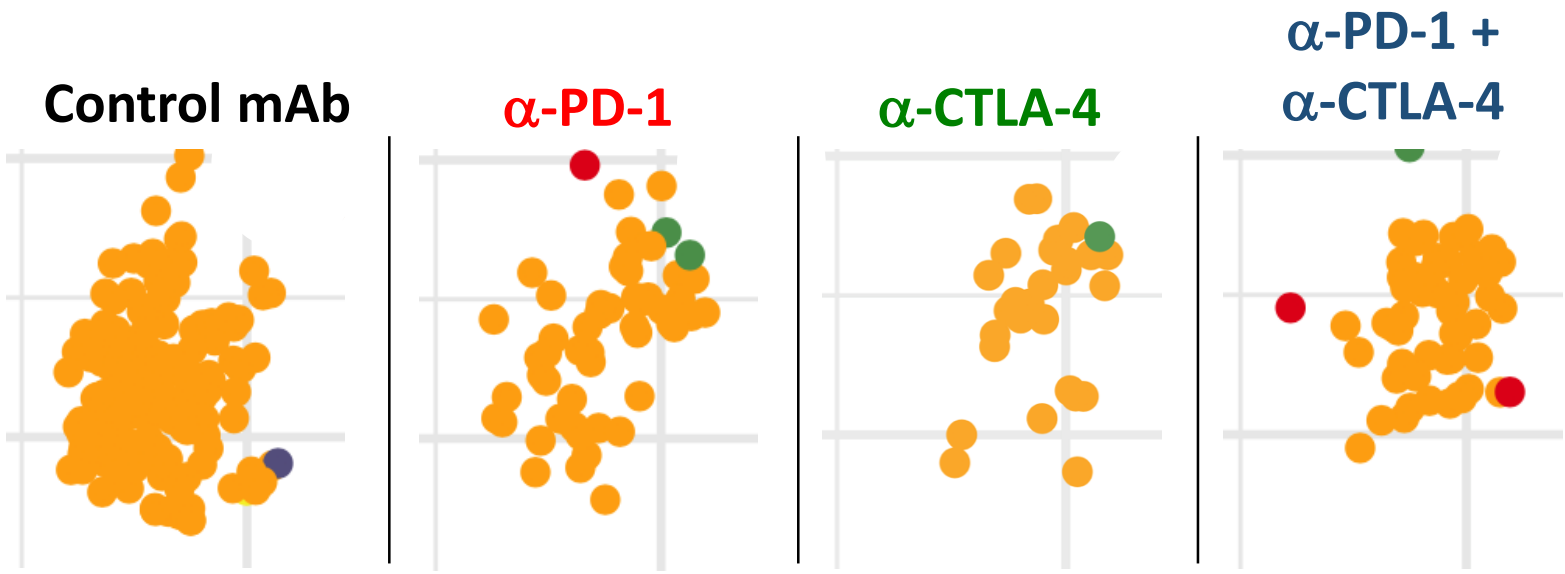
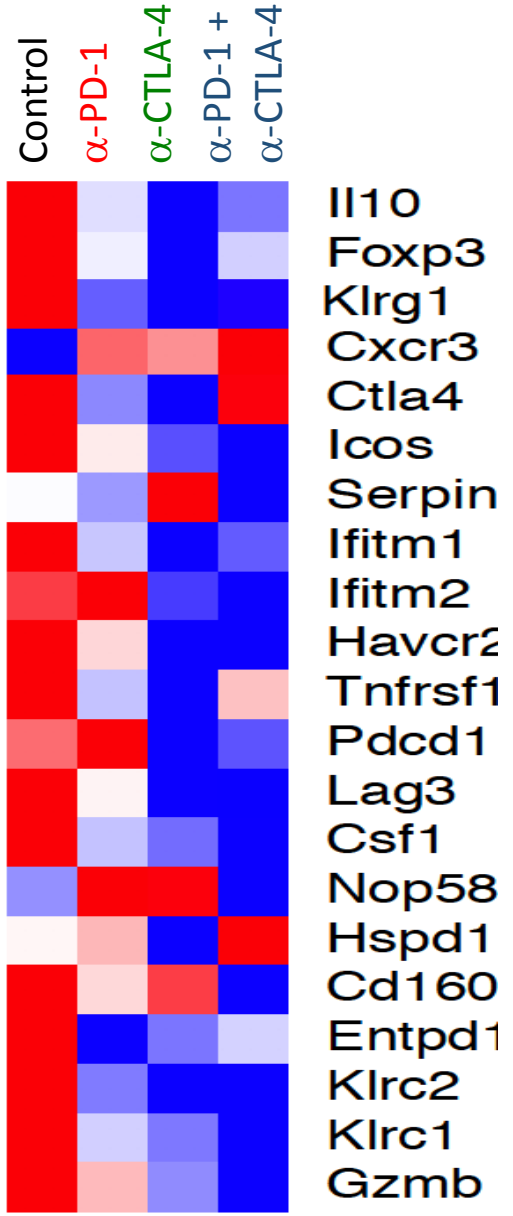


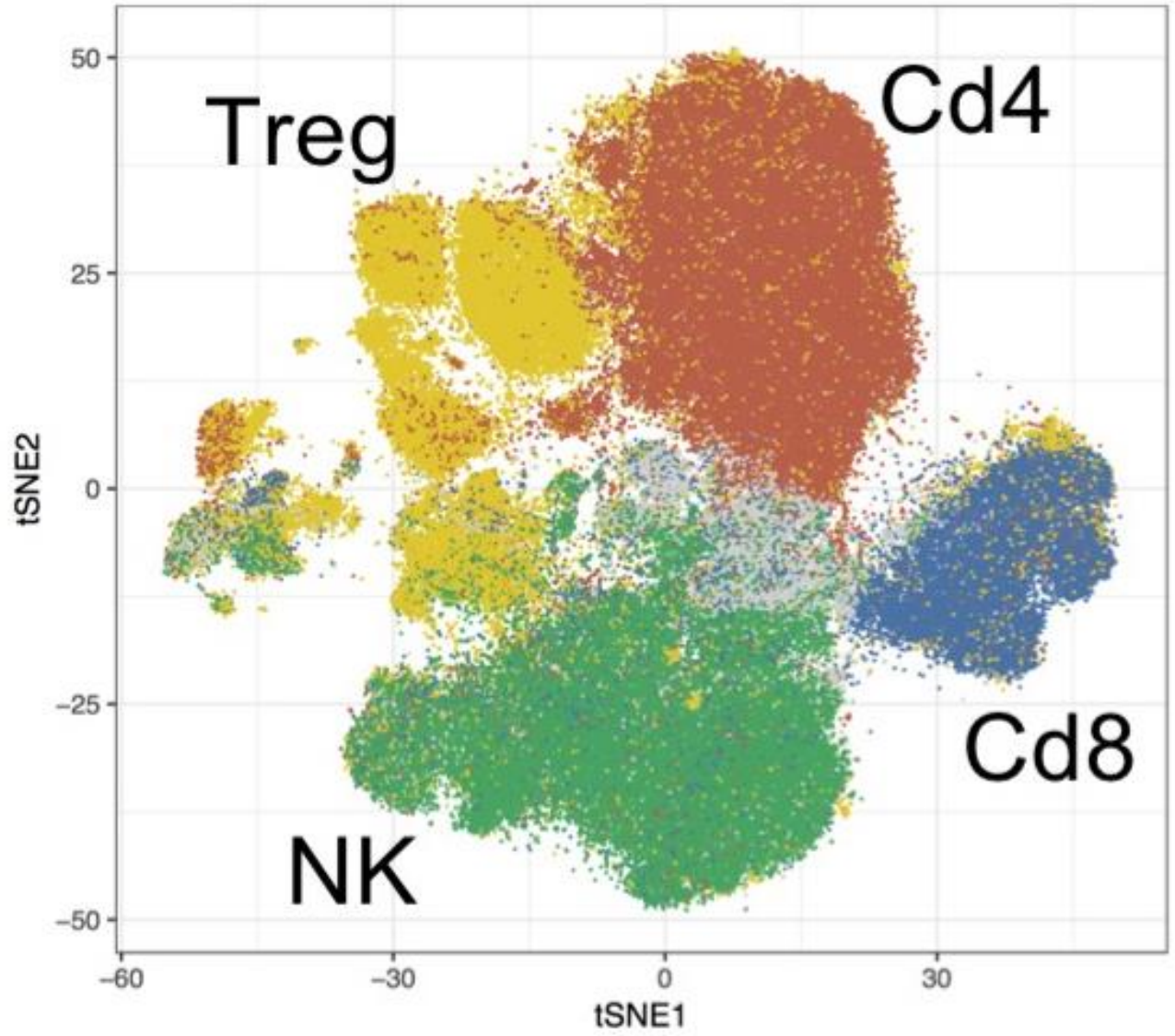


Immune Checkpoint Blockade Alters Intratumoral Tregs (scRNASeq)





CyTOF Analysis Identifies Defined Populations of Lymphoid Cells Infiltrating T3 Tumors (37 mAb markers)



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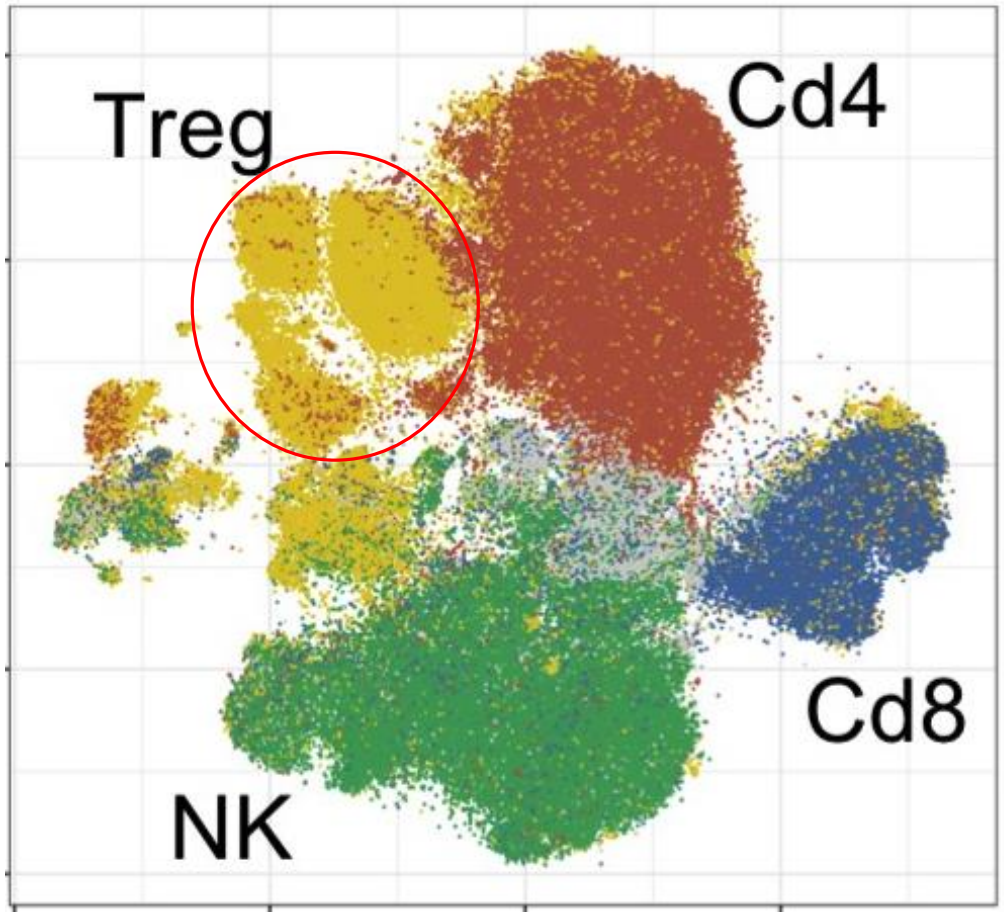
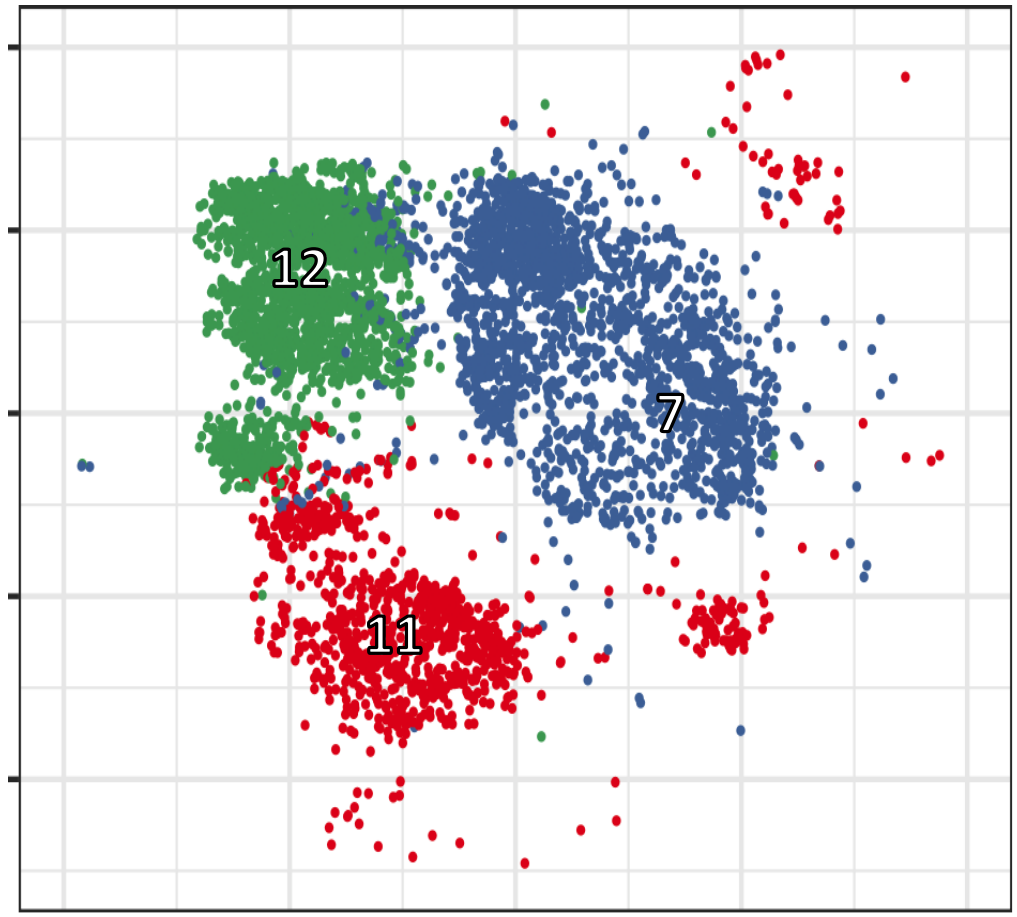
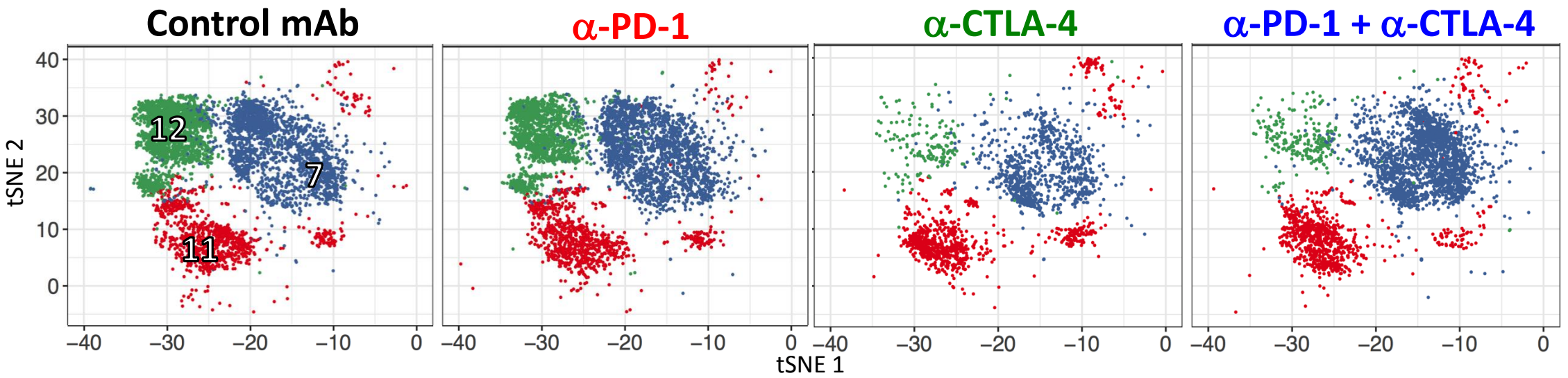
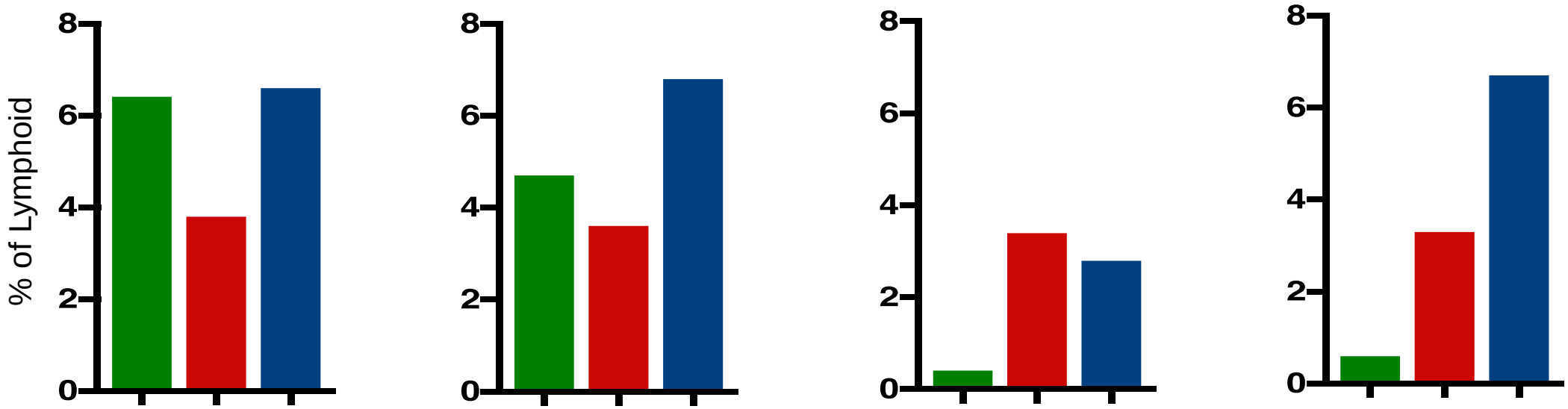


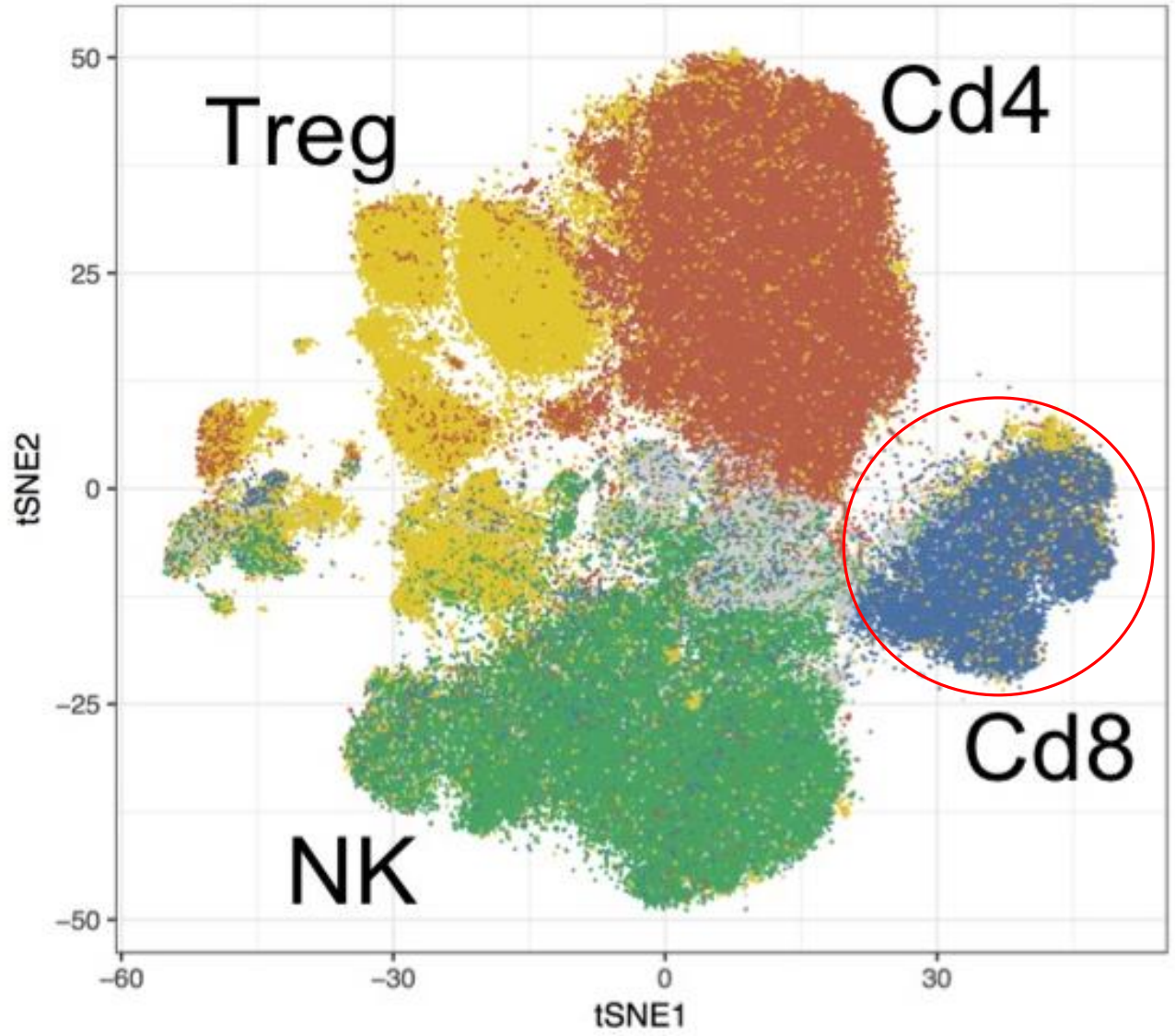


Specific Treg Subpopulations Are Depleted by Immune Checkpoint Blockade Immunotherapy (CyTOF)

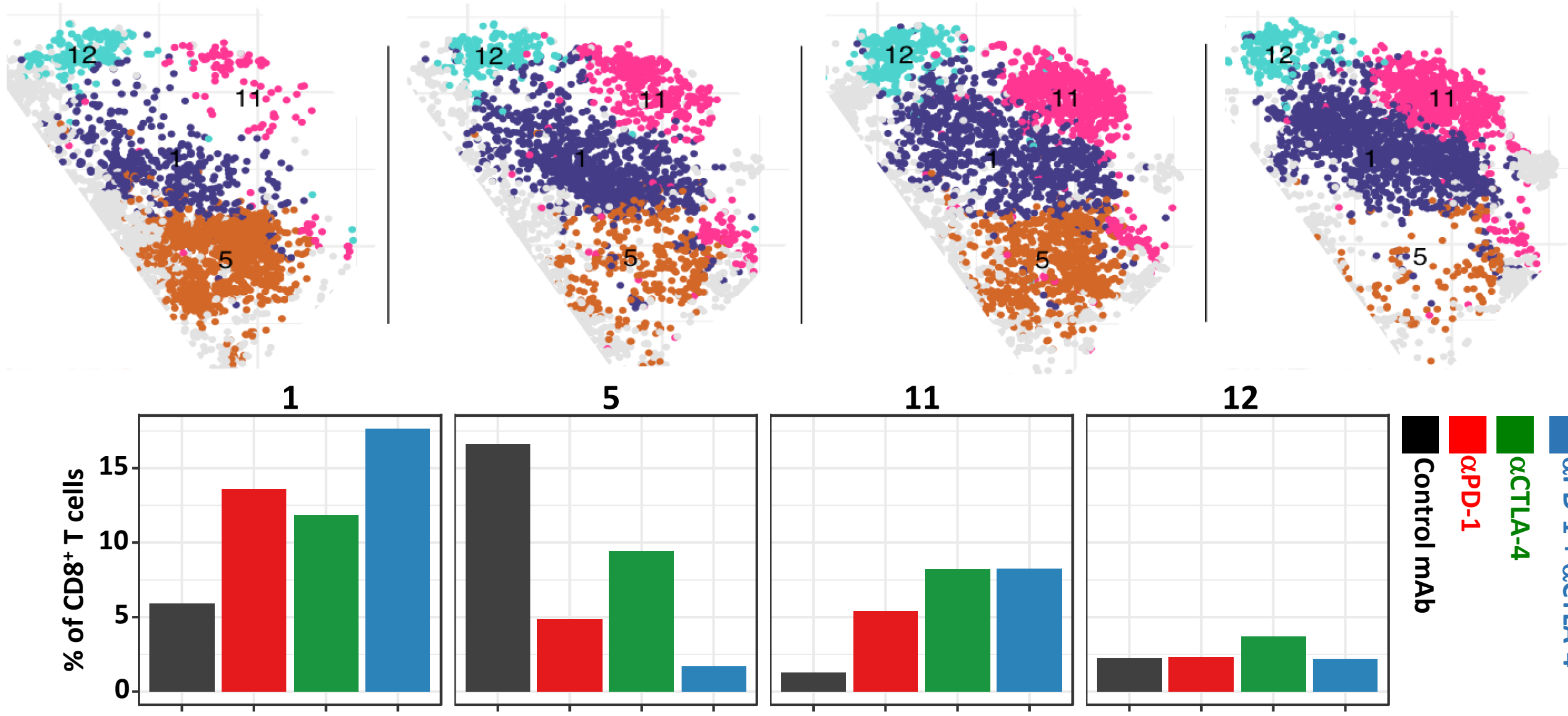




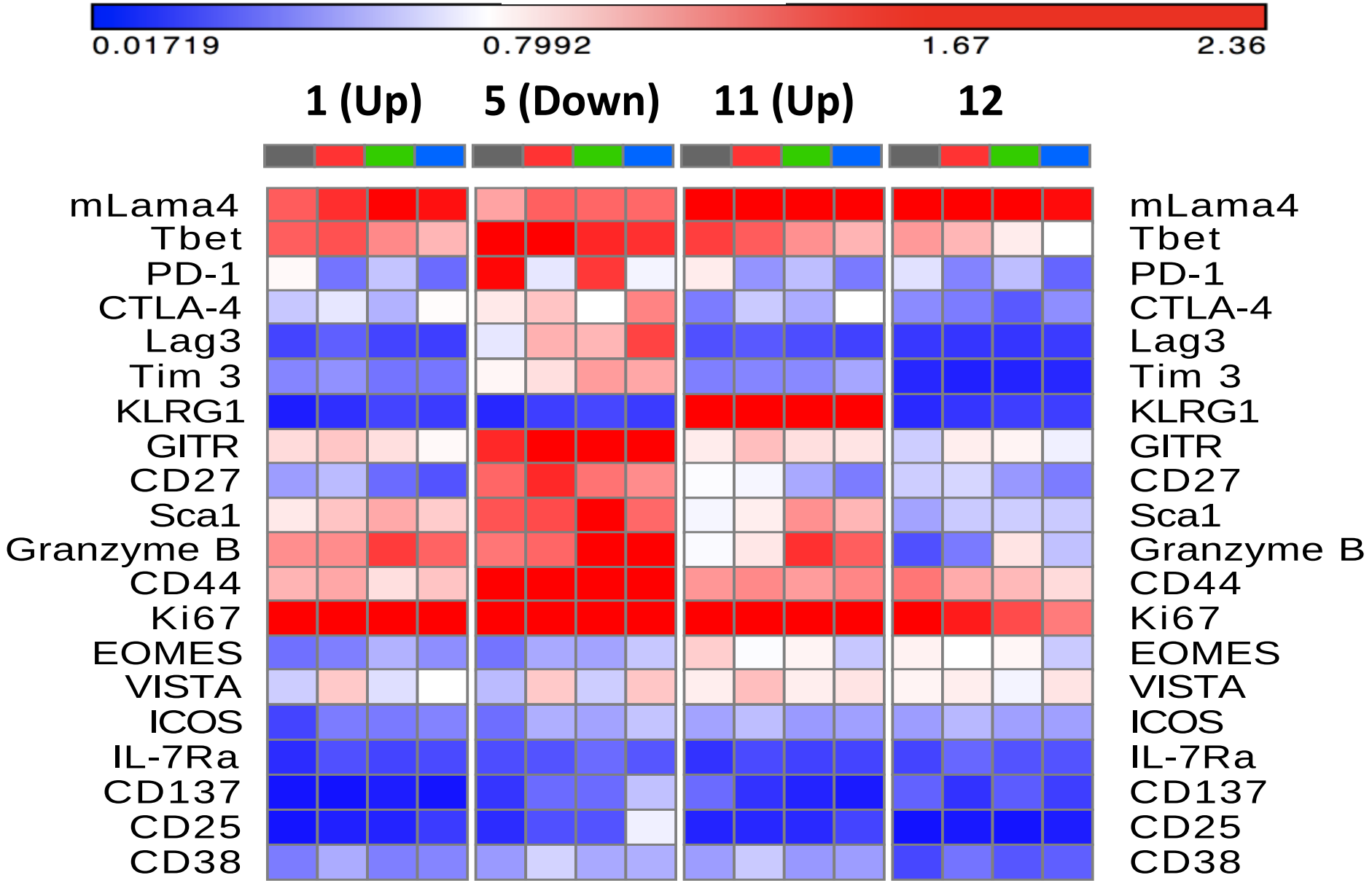
CyTOF Analysis Identifies Defined Populations of Lymphoid Cells Infiltrating T3 Tumors



Immune Checkpoint Blockade Therapy Remodels the Tumor Infiltrating CD8⁺ T Cell Compartment (CyTOF)

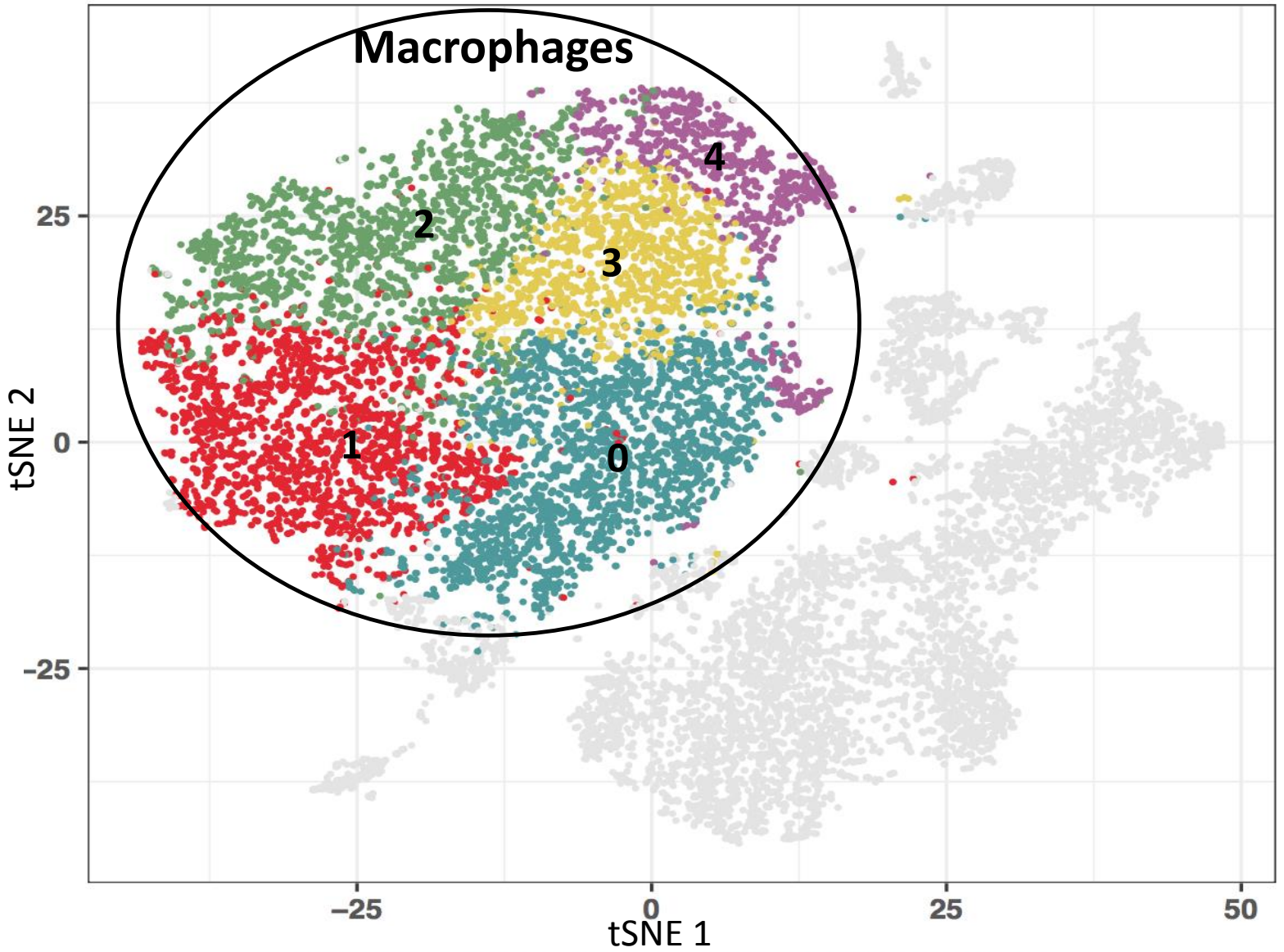


Immune Checkpoint Blockade Therapy Remodels the Tumor Infiltrating CD8^{+} T Cell Compartment (CyTOF)

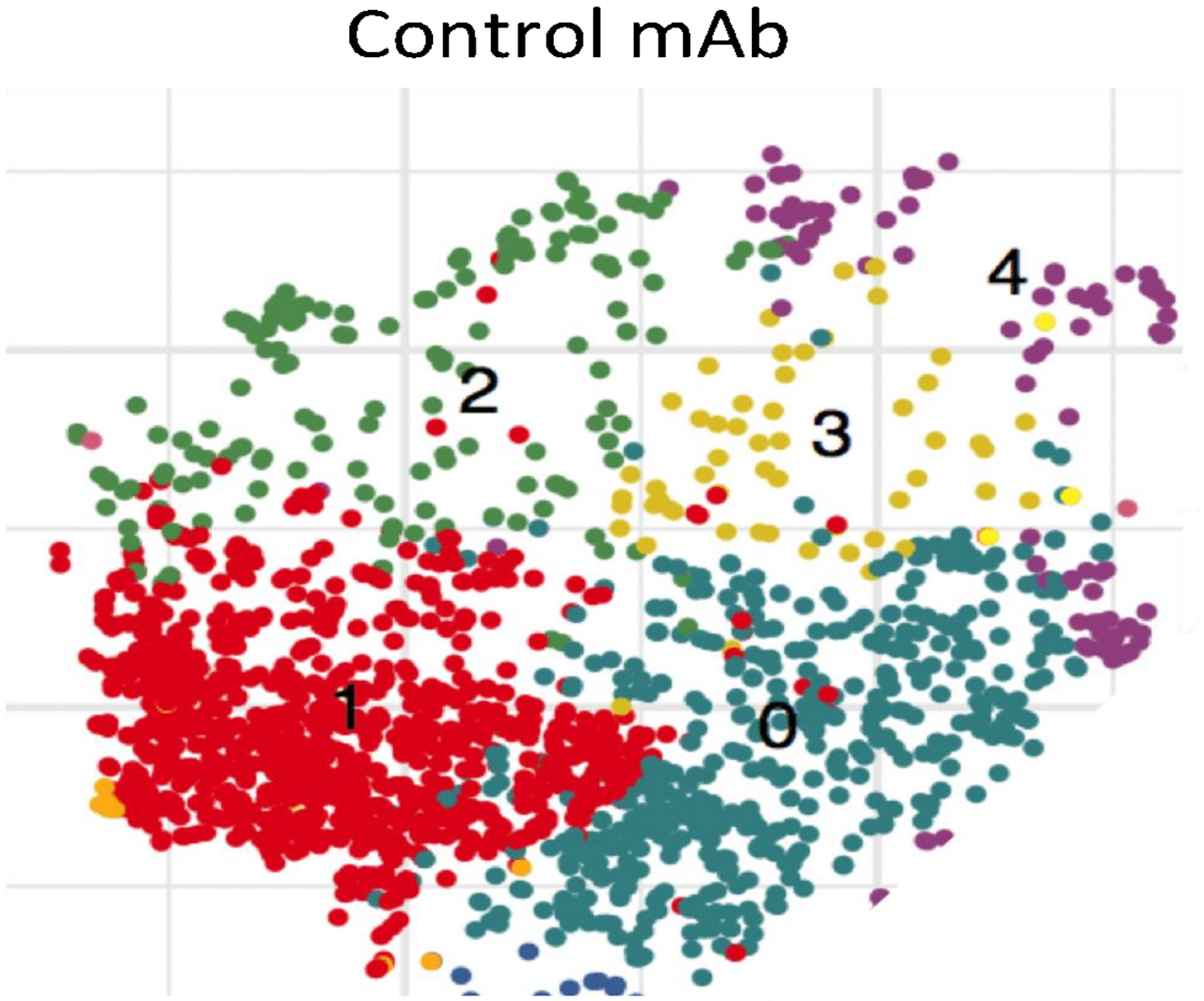


A glimpse into the complexity of the tumor infiltrating macrophage compartment

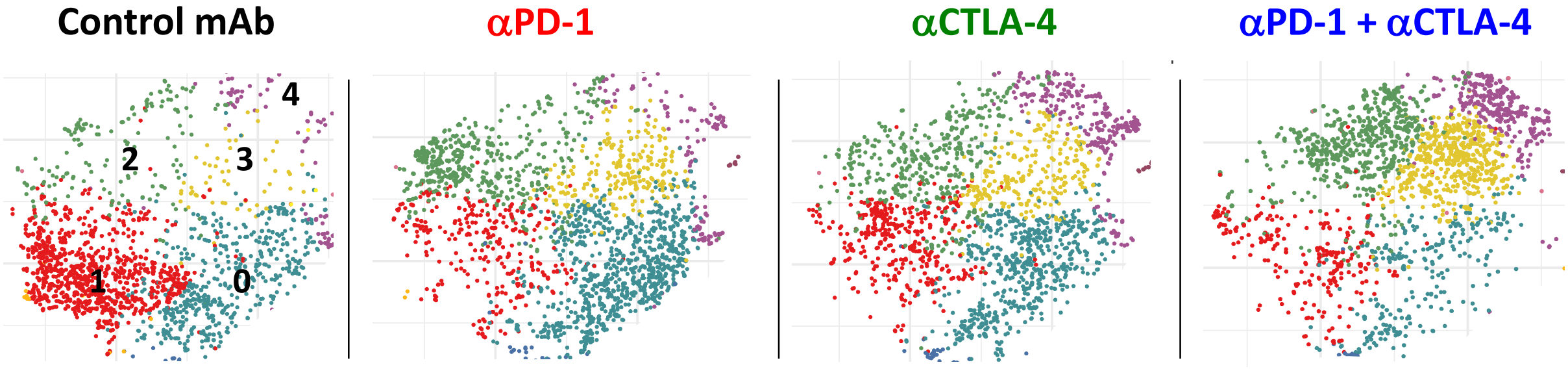
Five Macrophage Sub-Populations in T3 Tumors Tx With Immune Checkpoint Blockade Therapy (scRNAseq)



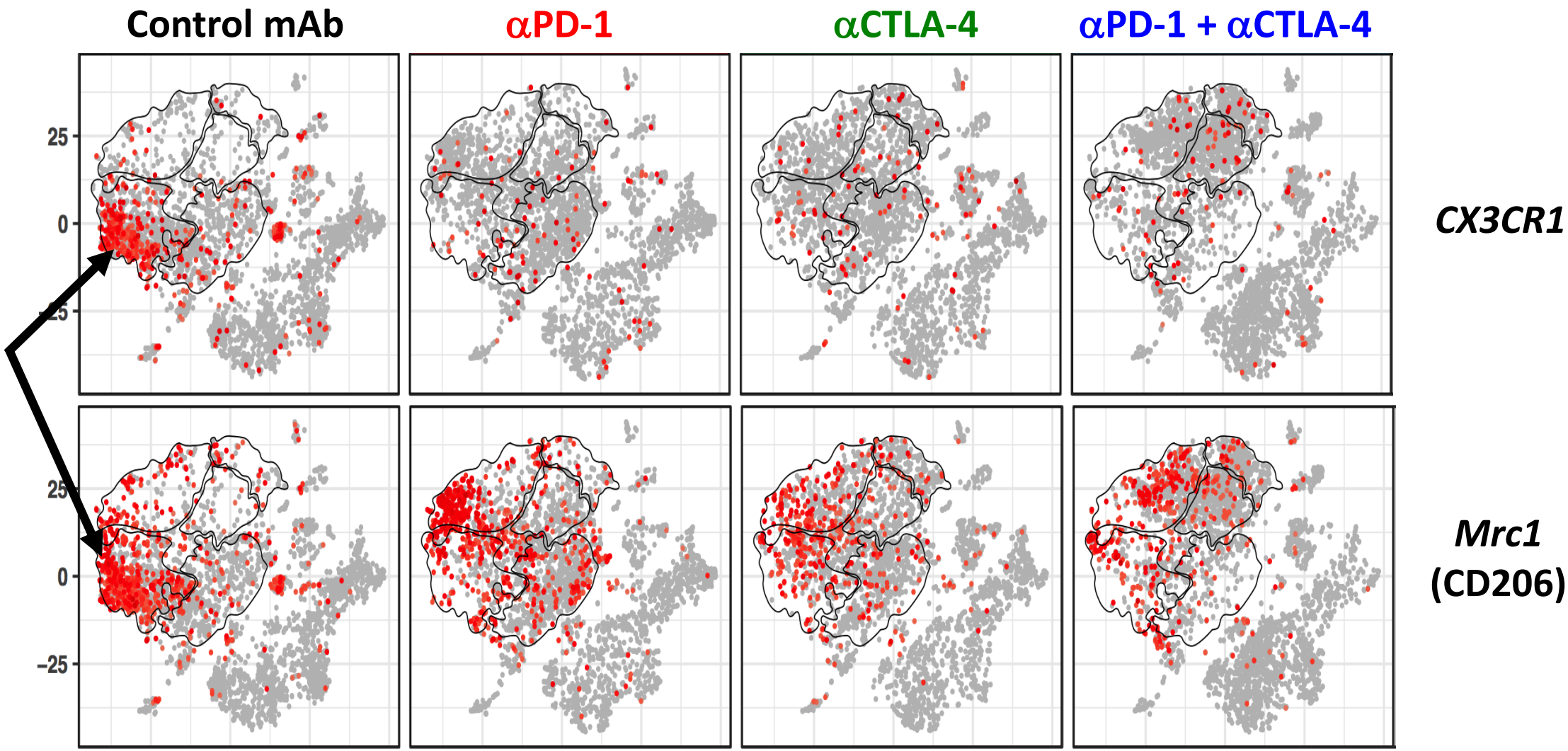
Shifts in Macrophage Subpopulations Upon Immune Checkpoint Blockade Treatment (scRNAseq)



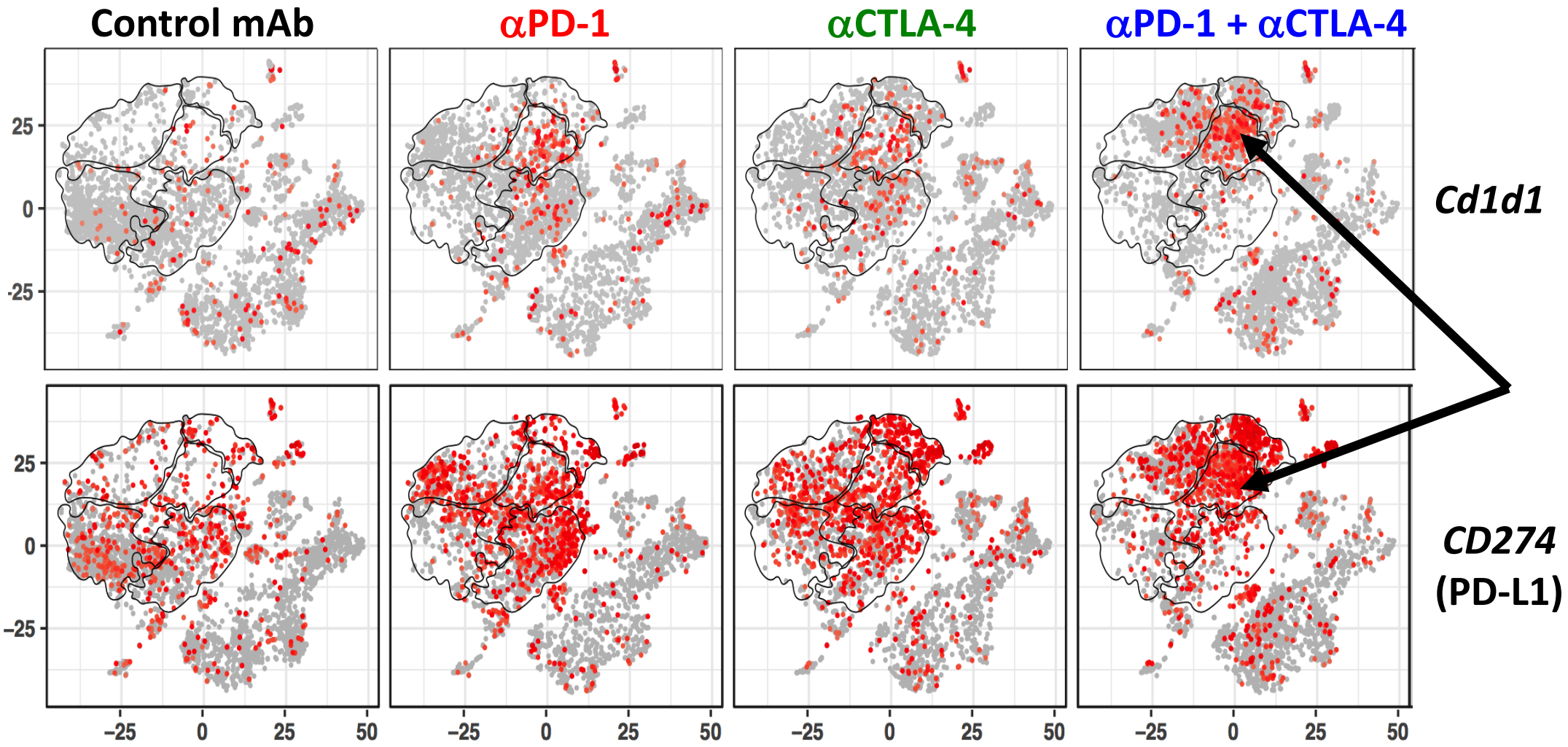
Distinct Remodeling Patterns of the Macrophage Compartment Post-Immune Checkpoint Blockade (scRNAseq)



Cluster 1: Expression of *Mrc1 (CD206)* and Exclusive Expression of *CX3CR1 (scRNAseq)*



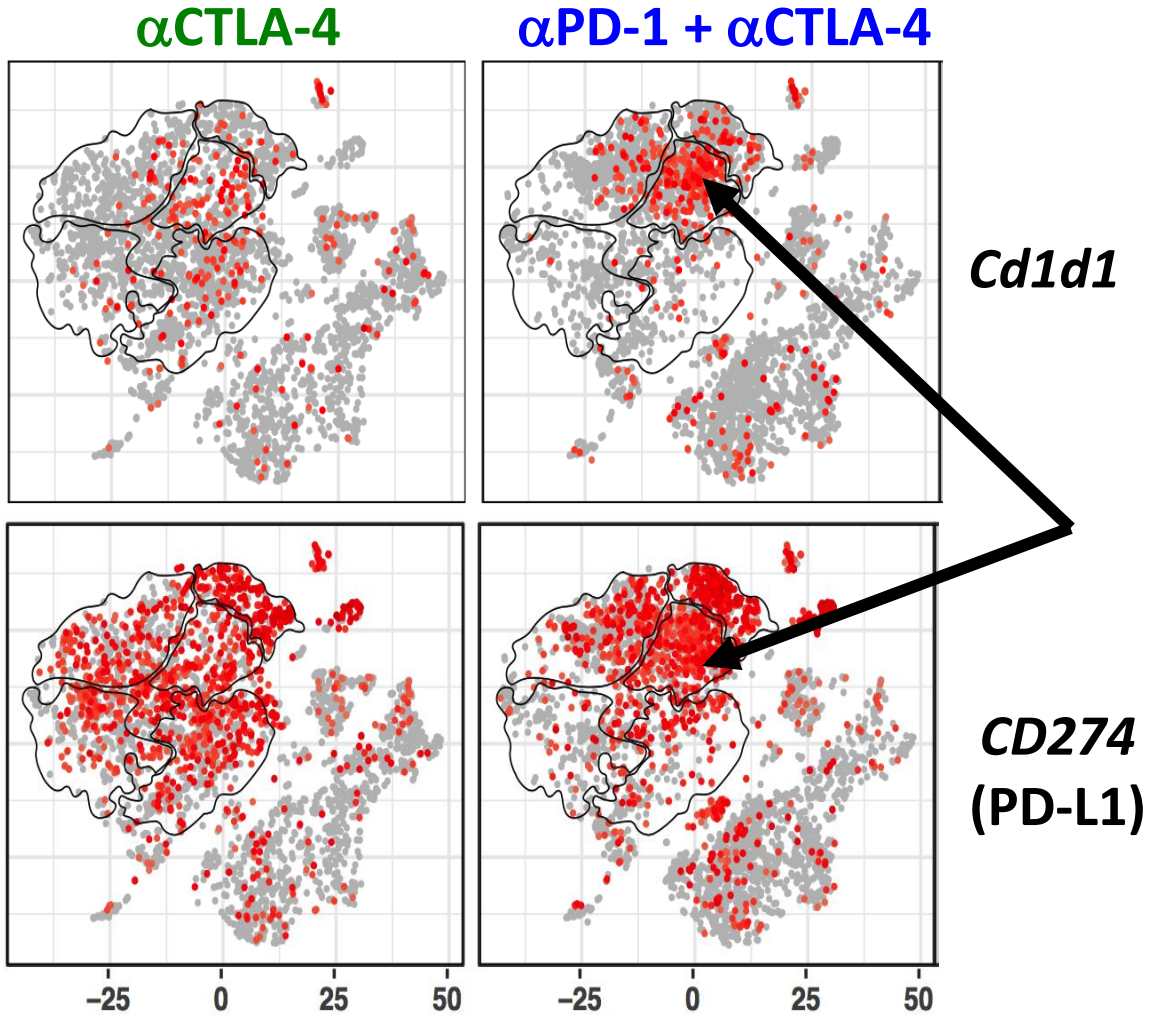
Cluster 3: Elevated Expression of *Nos2*, *PD-L1 (CD274)* and *CD1d1* (scRNAseq)



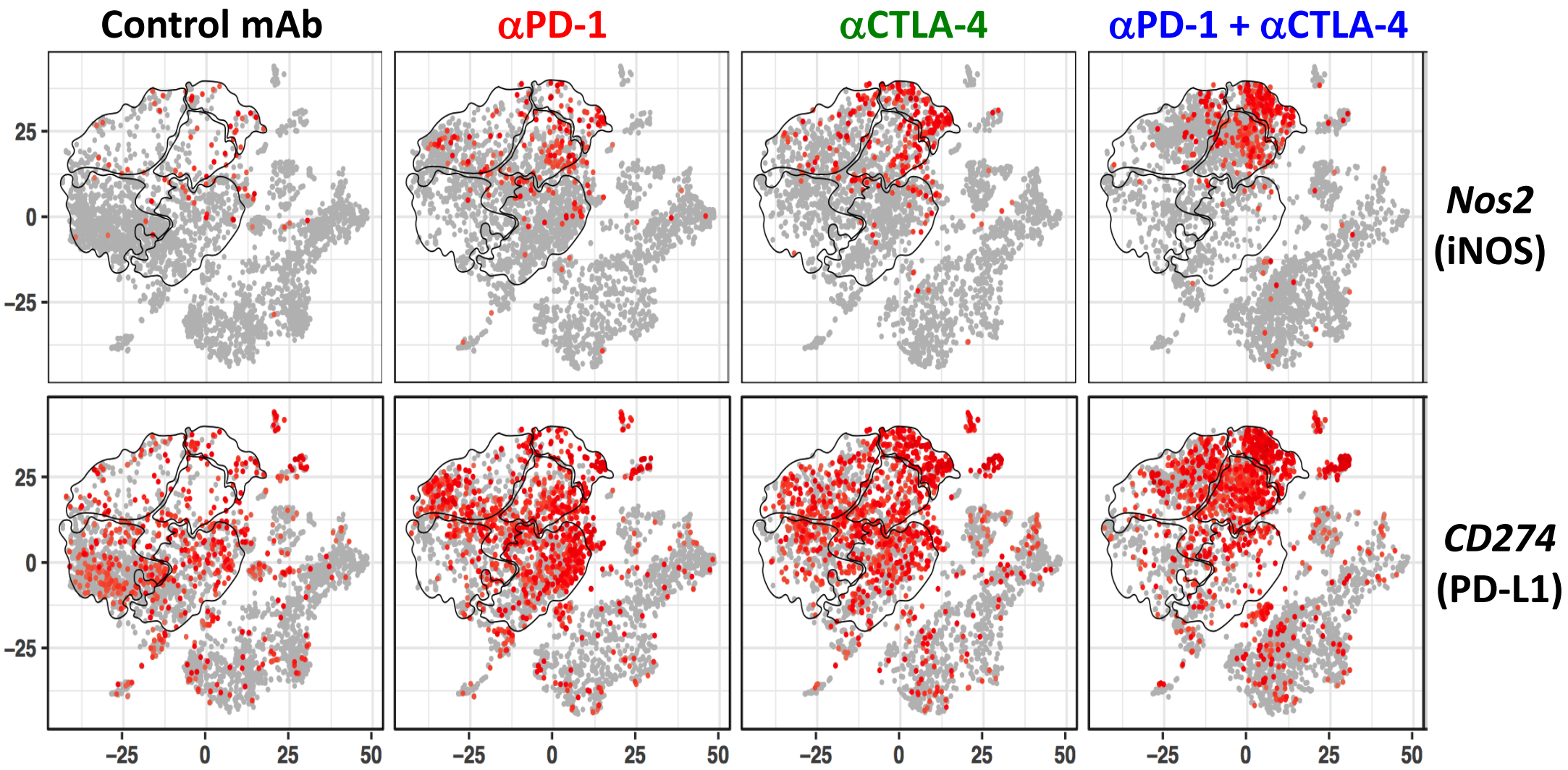
Cluster 3: Elevated Expression of *Nos2*, *PD-L1 (CD274)* and *CD1d1* (scRNAseq)

Cluster 3 has enrichment in pathways such as:

- **Hypoxia**
- **TNFα signaling of NF-κB**
- **Glycolysis**



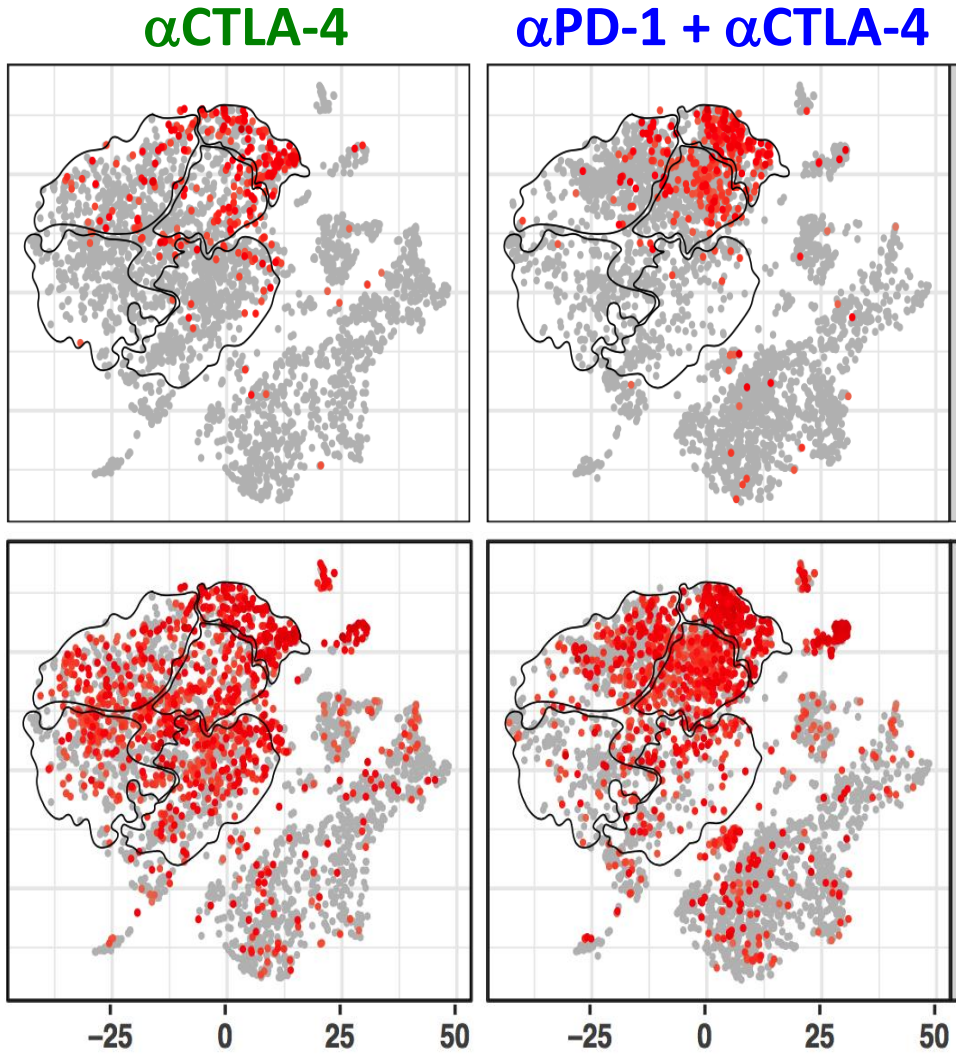
Cluster 4: Elevated Expression of Inflammation-Related Genes: *Nos2* (iNOS), *CD274* (PD-L1) (scRNAseq)



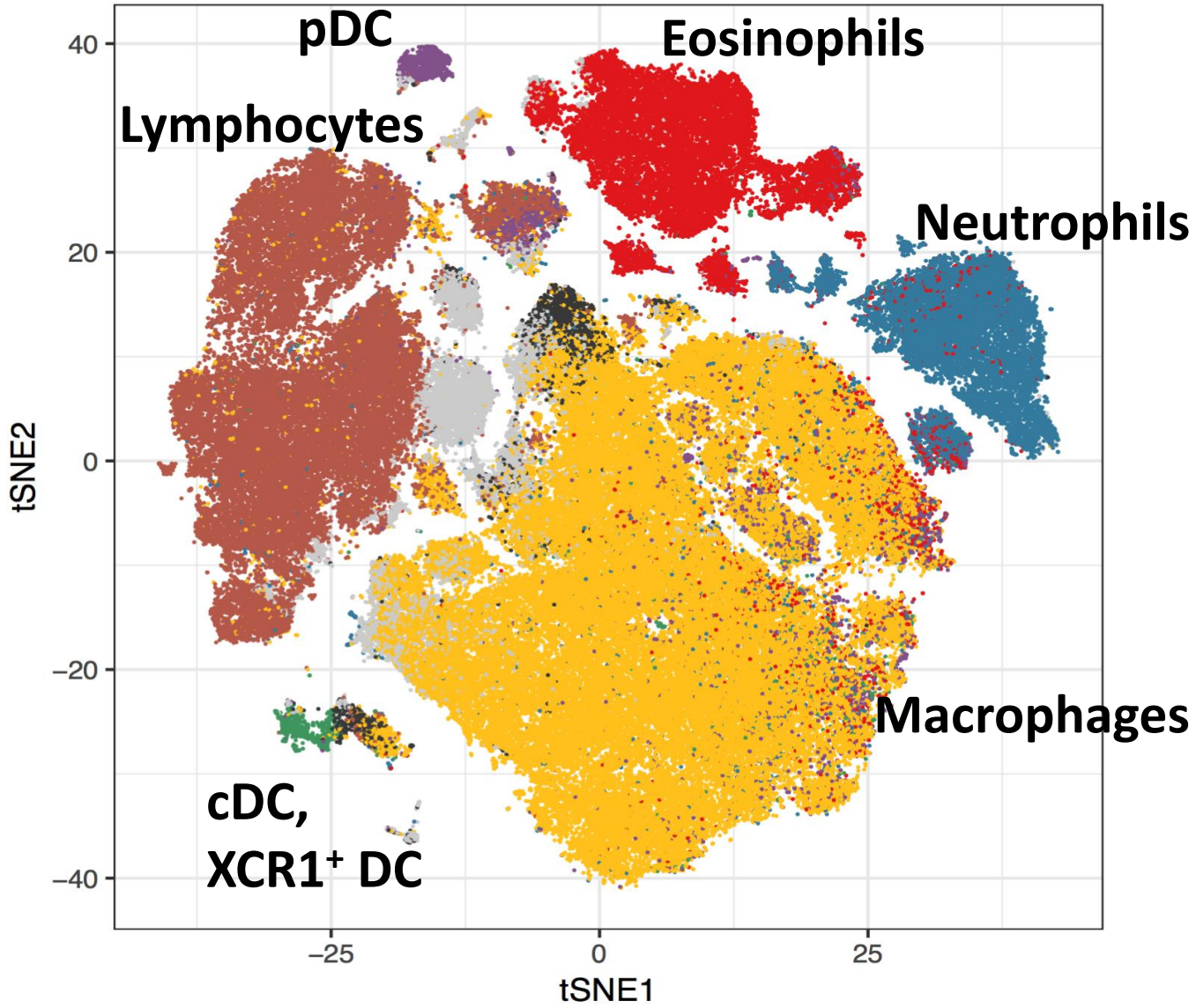
Cluster 4: Elevated Expression of Inflammation-Related Genes: *Nos2* (iNOS), *CD274* (PD-L1) (scRNAseq)

Cluster 4 has enrichment in pathways such as:

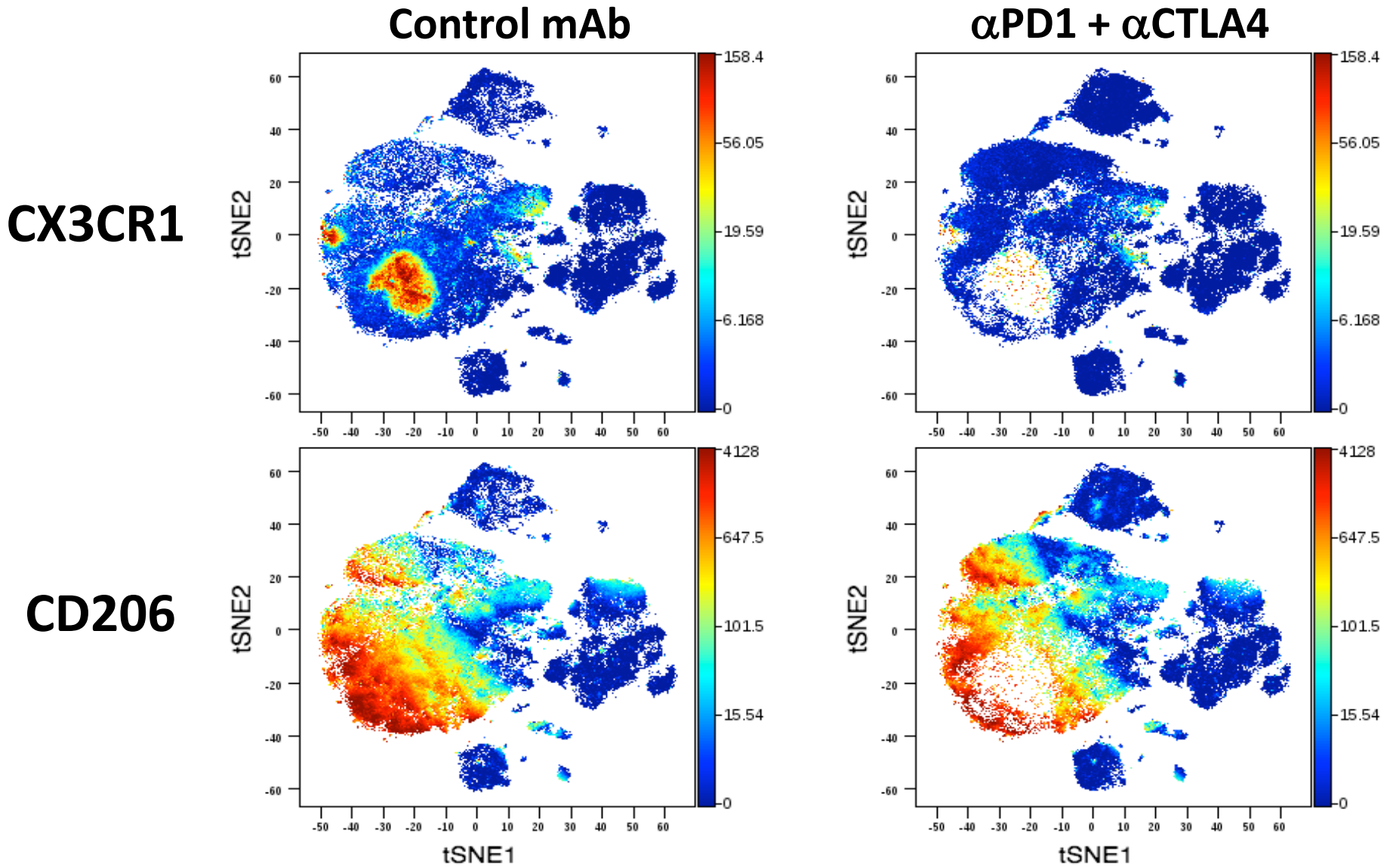
- **Hypoxia.**
- **TNFα signaling via NFκB**
- **Interferon–γ Response**
- **Inflammatory response**



CyTOF Clustering of T3 Tumor-Infiltrating Lymphoid and Myeloid Cell Populations (37 mAb Specificities)

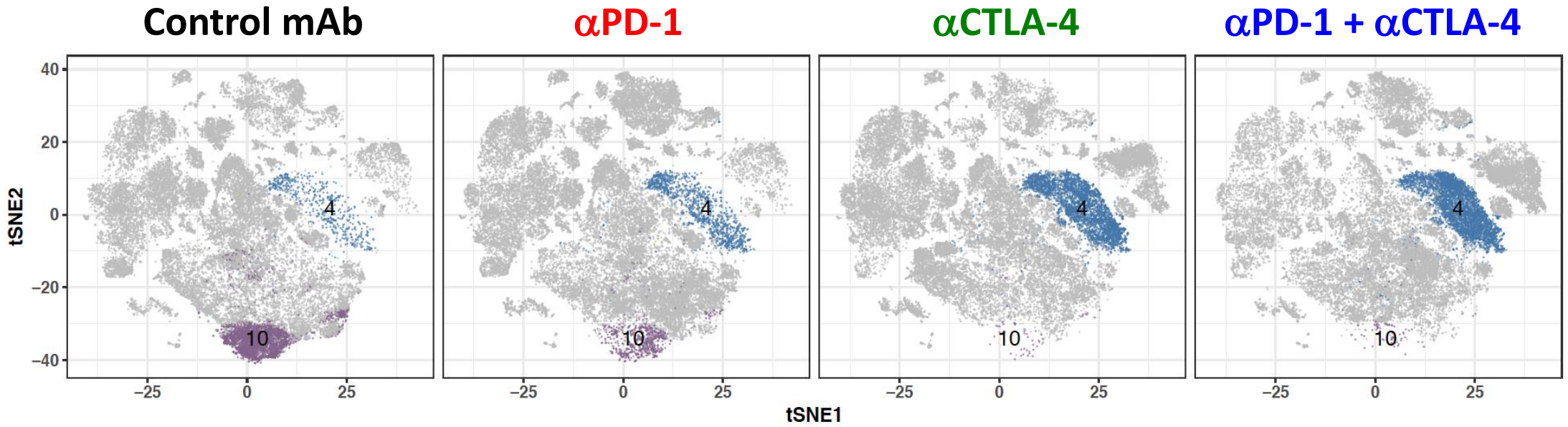


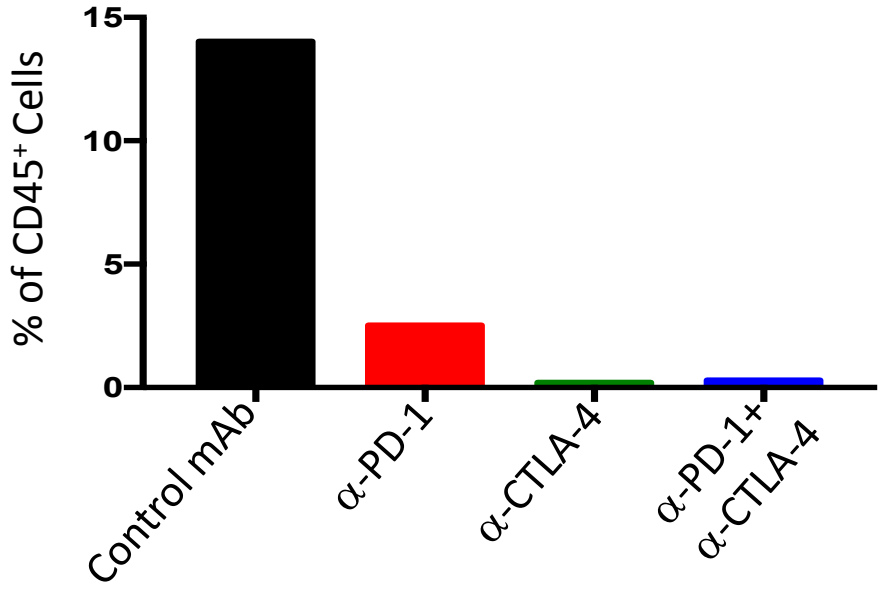
CyTOF Analysis Reveals Reordering of T3 Sarcoma Myeloid Populations During Immune Checkpoint Blockade Therapy

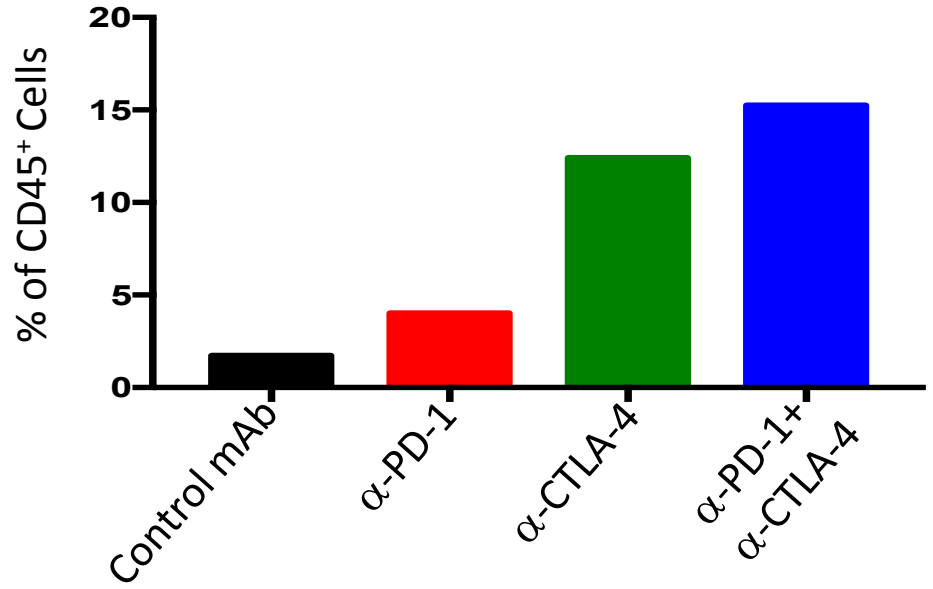


Macrophage Remodeling As Detected By CyTOF:

Cluster 10: (CX3CR1^{+}/CD206^{+}) vs Cluster 4: (iNOS^{+}/CD38^{hi})







Conclusions

- We have identified distinct subpopulations of lymphocytes and myeloid cells in progressively growing or therapeutically rejecting T3 sarcomas
- The subpopulations display distinct transcriptional profiles and functional markers
- The subpopulations display distinctive sensitivities to anti-PD-1 and anti-CTLA-4, when administered either alone or together
- Hypothesis to test: Do the subpopulations represent functional/dysfunctional or effector/inhibitory states of T cells (e.g., $CD4^+$ T cells or $CD8^+$ T cells or Treg) and macrophages
- Work is ongoing to isolate individual subpopulations and determine their positive or negative functional effects on the anti-tumor response

Lessons and Take Home Messages

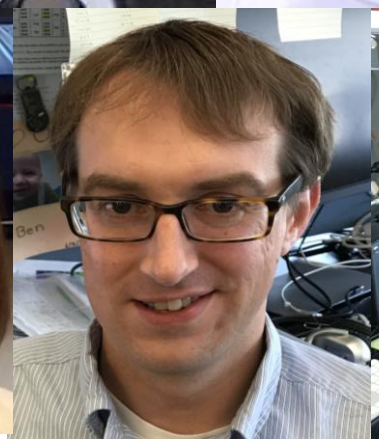
- scRNAseq and CyTOF each have unique advantages and their utility is maximized when used in concert

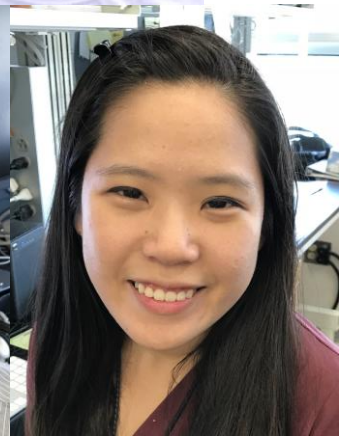
- Using high dimensional analysis approaches, we are identifying molecular and cellular changes that occur during successful cancer immunotherapy. We hope to apply what we learn from this work to human cancer immunotherapy thereby rendering it more effective

High Dimensional Analysis of Immune Checkpoint Blockade-Mediated T3 Sarcoma Rejection

Bob Schreiber

Max Artyomov





Katya Esaulova

Jeff Ward

Pamela Wong

ADVANCING CANCER IMMUNOTHERAPY WORLDWIDE

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Burksy Center for Human Immunology and Immunotherapy Programs
Immunomonitoring Core:
Olga Malkova
Likui Yang

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Ton Schumacher (Netherlands Cancer Institute)

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STAND UP TO CANCER · CURE PANCREATIC CANCER · LUSTGARTEN FOUNDATION ·
Pancreatic Cancer Convergence Dream Team

janssen

Lessons and Take Home Messages

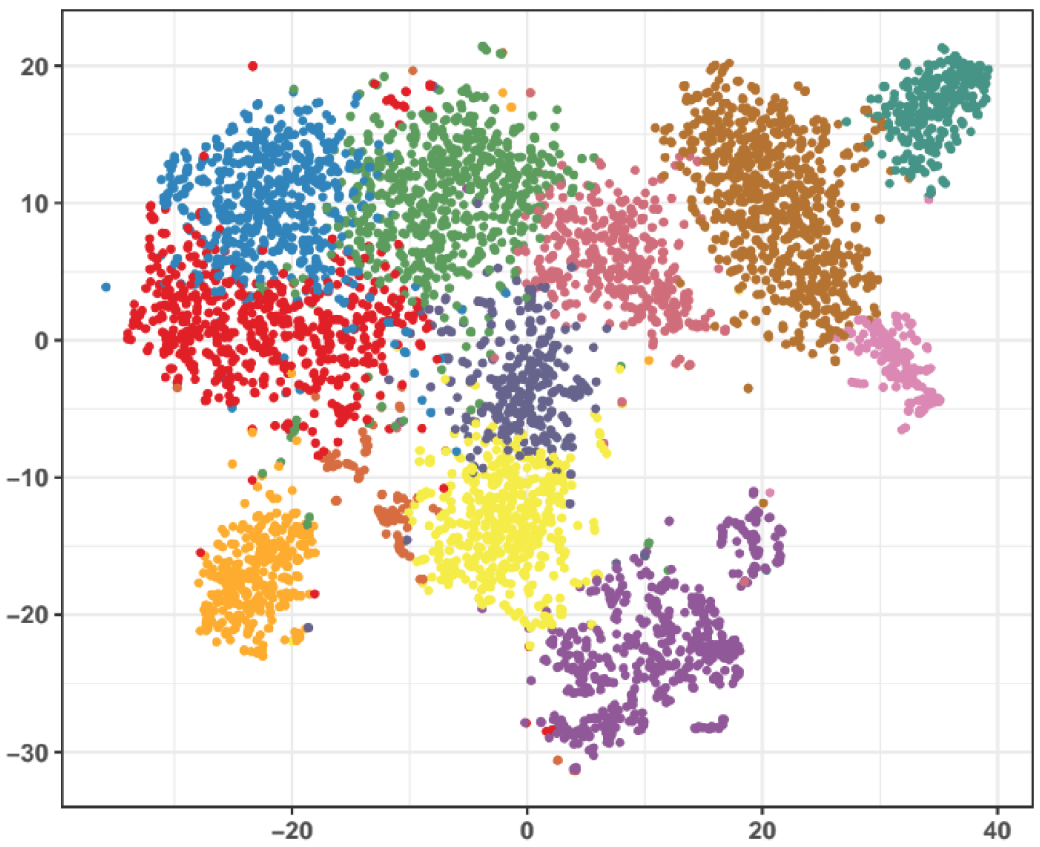
- Tumor neoantigen vaccines are safe, specific and effective in both preclinical tumor models and human cancer patients

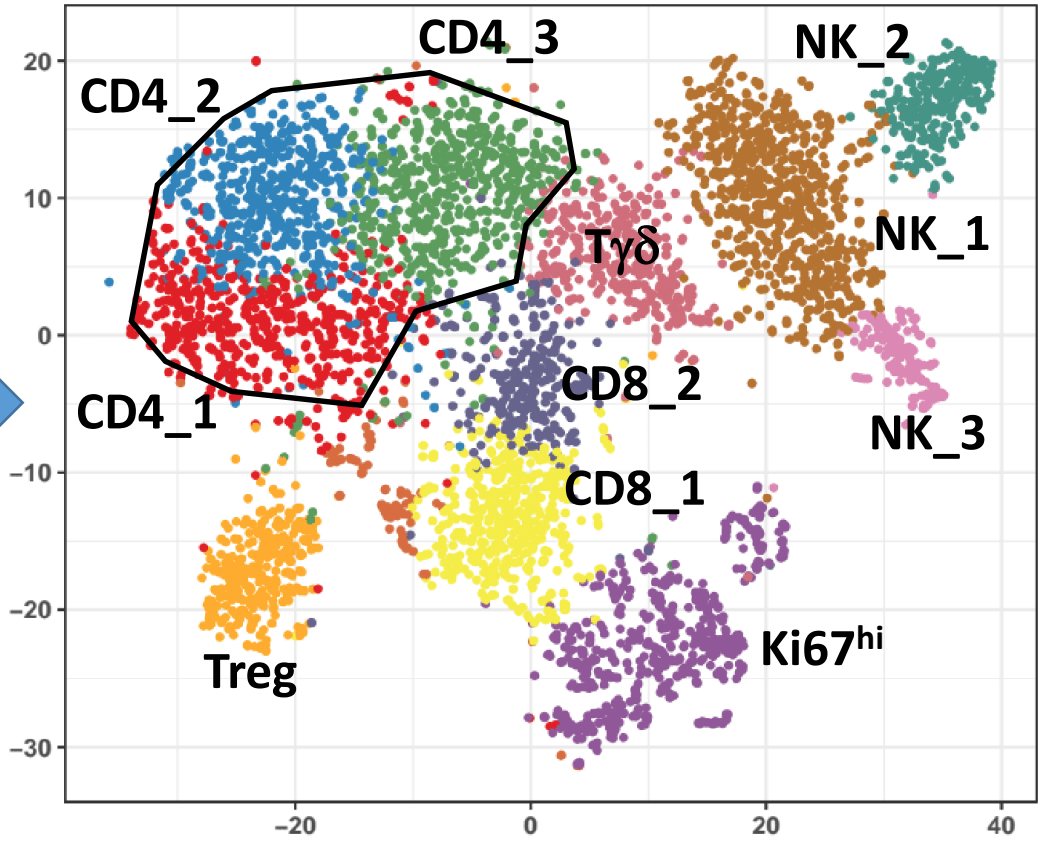
- Clinical trials have begun at WUSTL to test the safety, specificity and efficacy of personalized cancer vaccines in cancer patients

- scRNAseq and CyTOF
  Using high dimensional analysis approaches, we are identifying molecular and cellular changes that occur during successful cancer immunotherapy. We hope to apply what we learn from this work to human cancer immunotherapy thereby rendering it more effective

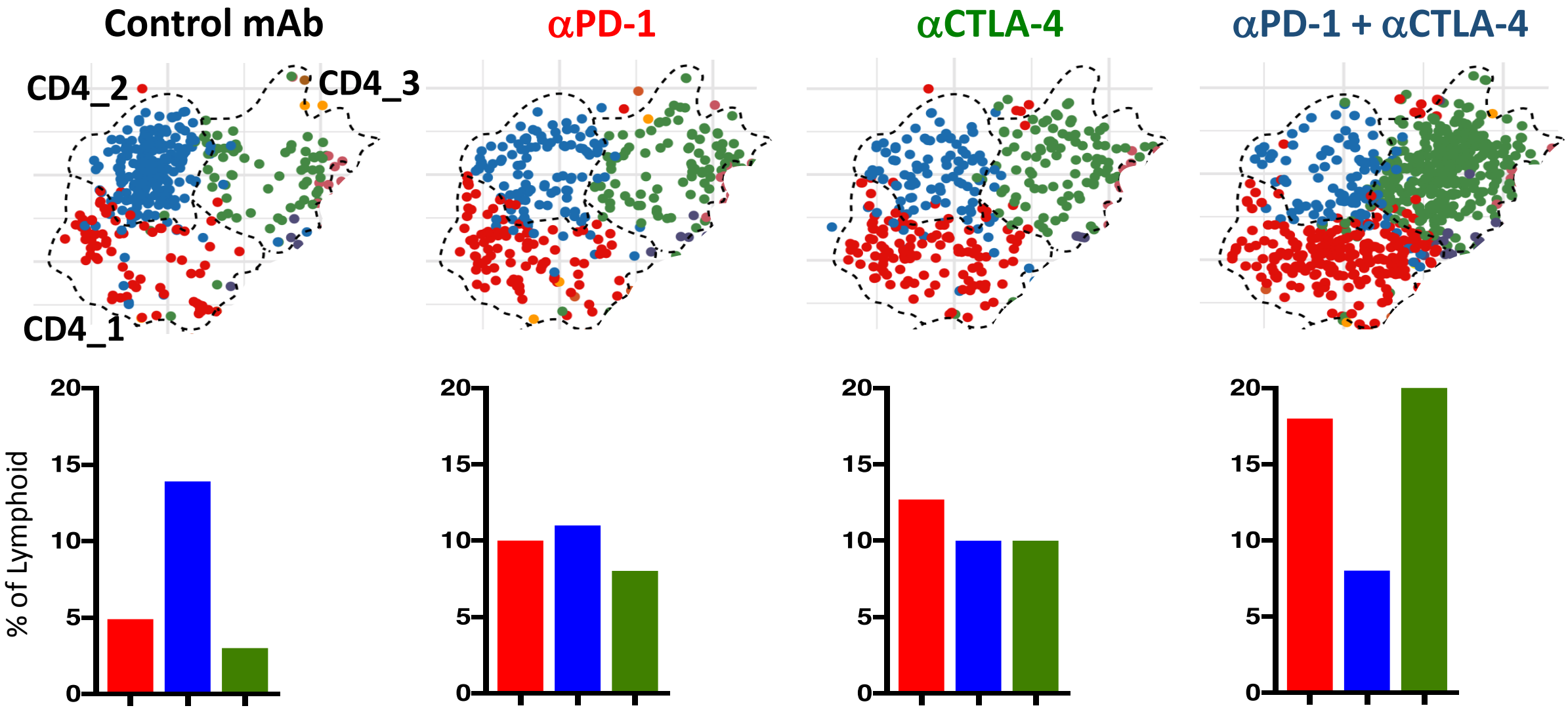
Identification of Three Major CD4^{+} T Cell Subpopulations (scRNAseq)

Lymphoid: 4989 cells

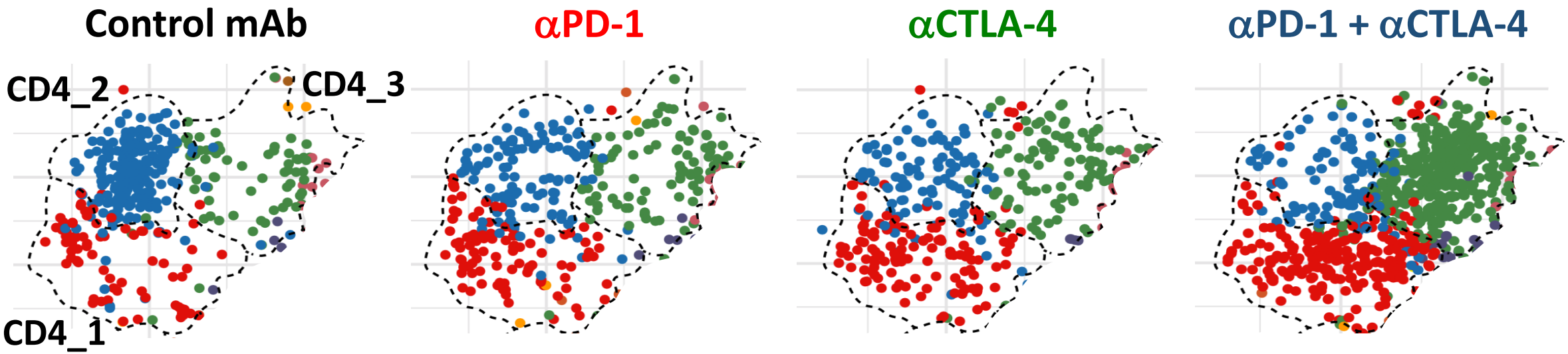




Remodeling of Intratumoral CD4+ T Cells Upon Immune Checkpoint Blockade Therapy (scRNAseq)



Remodeling of Intratumoral CD4$^+$ T Cells Upon Immune Checkpoint Blockade Therapy (scRNAseq)



CD4_1

Upregulated pathways:

- Hypoxia
- TNFα signaling via NF-κB
- MAPK signaling
- TCR Signaling

CD4_2

Upregulated pathways:

- Peptide chain elongation
- Ribosome pathway

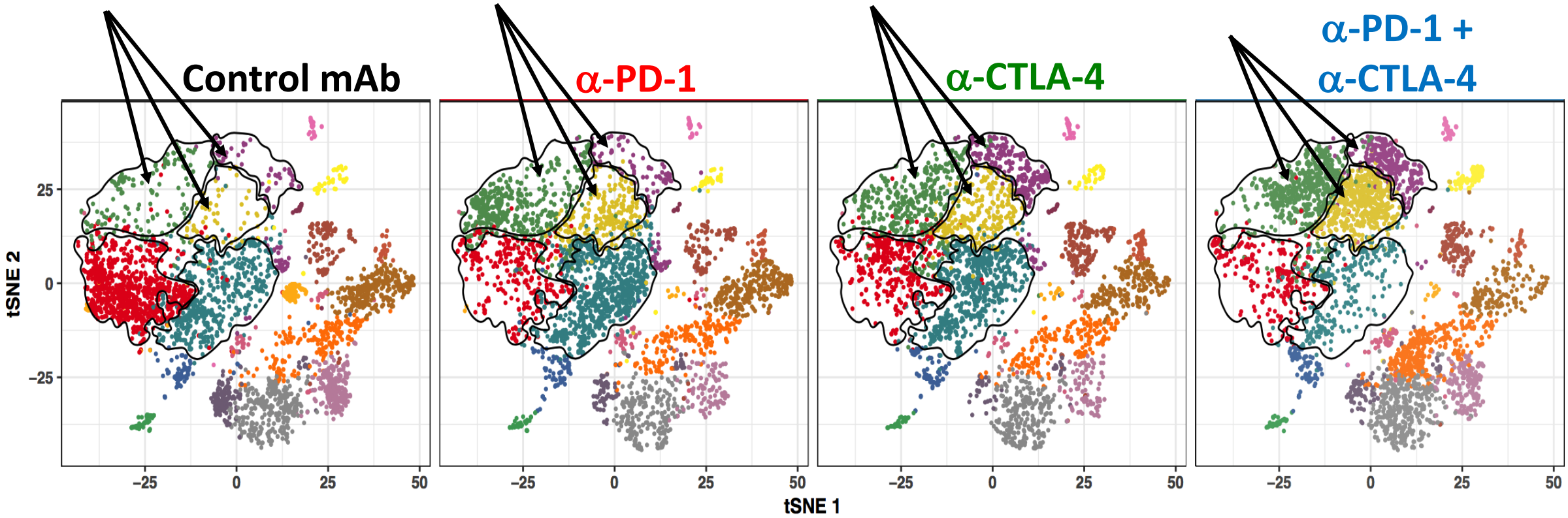
Downregulated pathways:

- Cell cycle
- G2M checkpoint

CD4_3

Less activated CD4$^+$ T Cells

Clusters 2, 3 & 4 Show the Strongest Increases Upon Immune Checkpoint Blockade Treatment (scRNAseq)



Immune Checkpoint Blockade Therapy Remodels the Tumor Infiltrating CD8$^+$ T Cell Compartment (CyTOF)