

# Spatiotemporal co-dependency between macrophages and exhausted CD8<sup>+</sup> T cells in cancer

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SITC Tumor Immune Microenvironment: A Holistic Approach

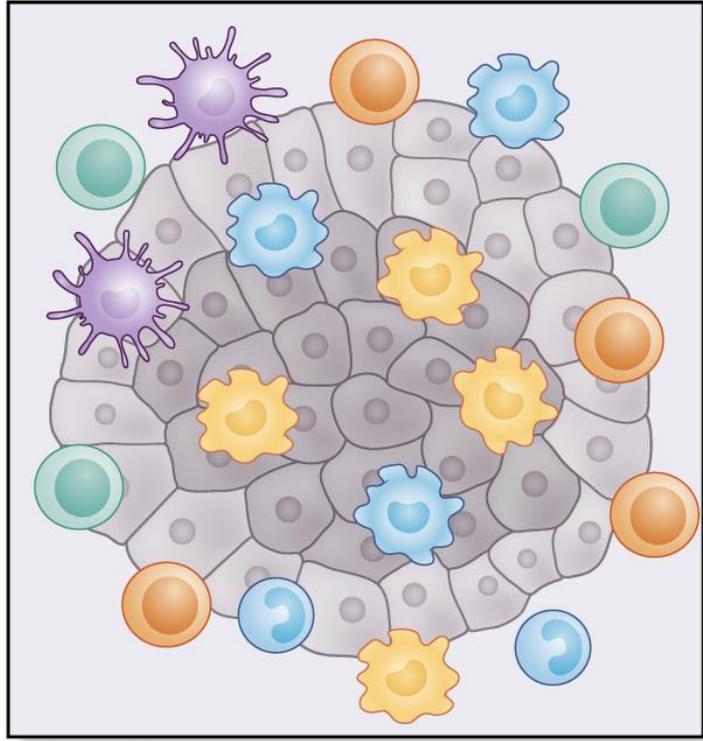
April 21-22, 2022 - San Diego, CA

## Disclosure information

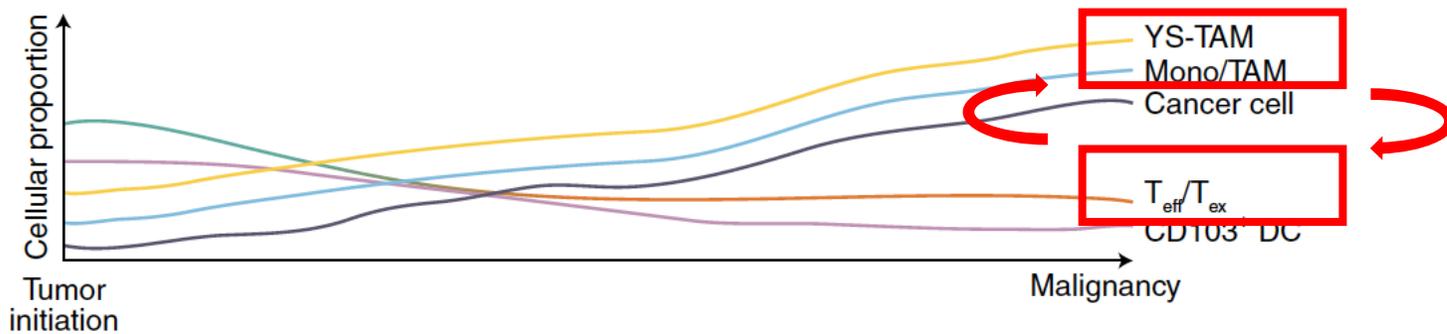
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I have no financial disclosures.

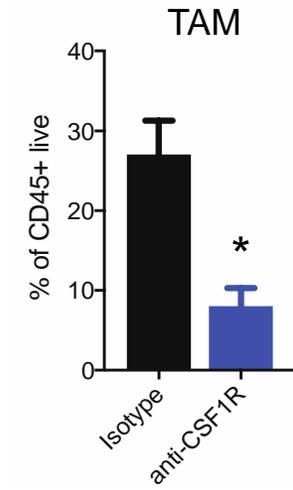
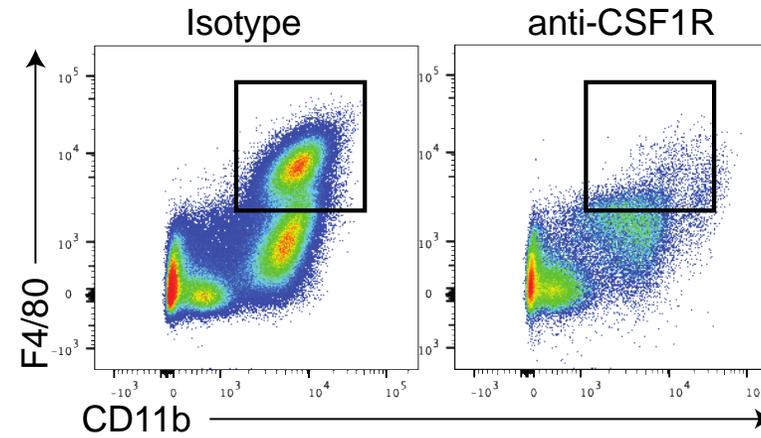
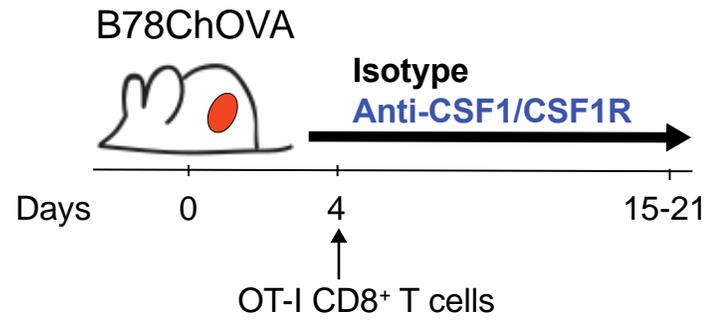
## A role for tumor-associated myeloid cells in CD8<sup>+</sup> T cell exhaustion?



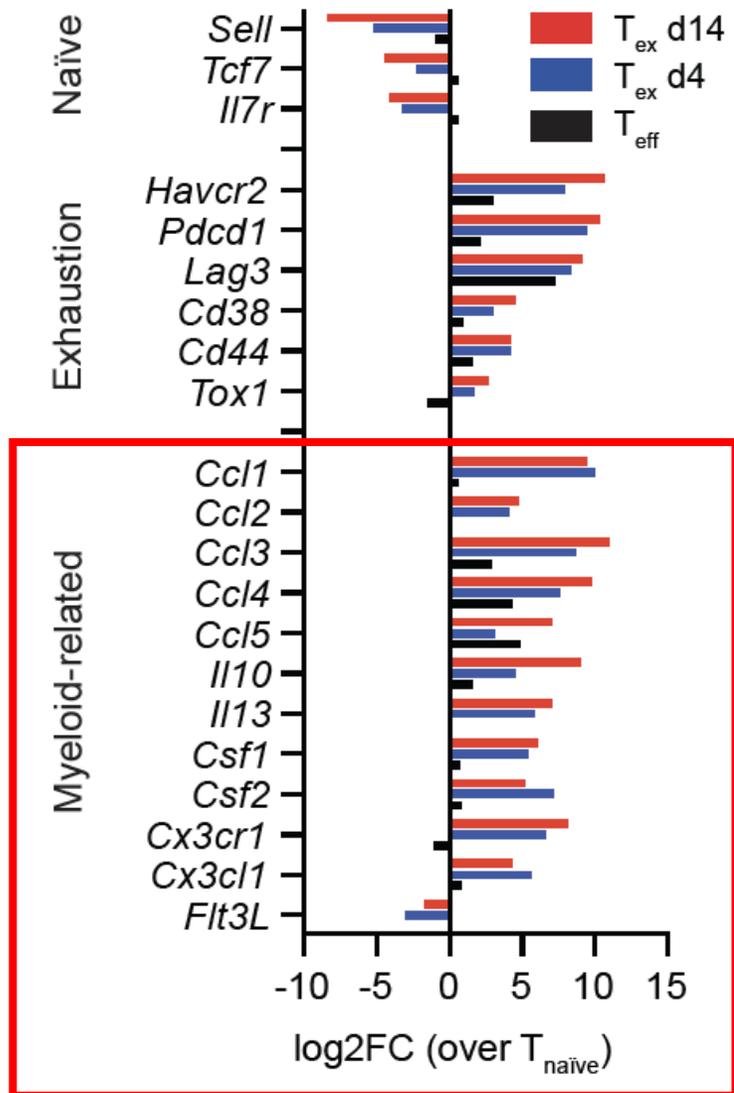
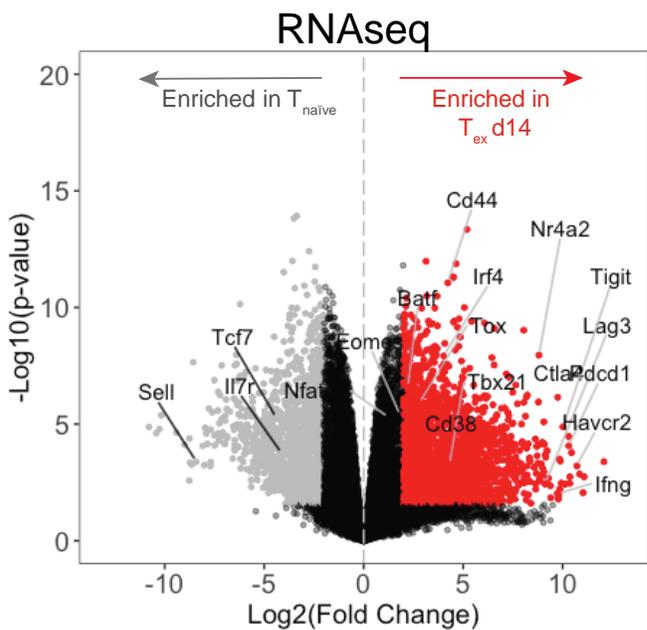
- T cell exhaustion is a major impediment to anti-tumor T cell responses
- Recent scRNAseq approaches have hinted towards a potential link between TAM and exhausted T cells in several cancer types
- However, the mechanisms remain unclear



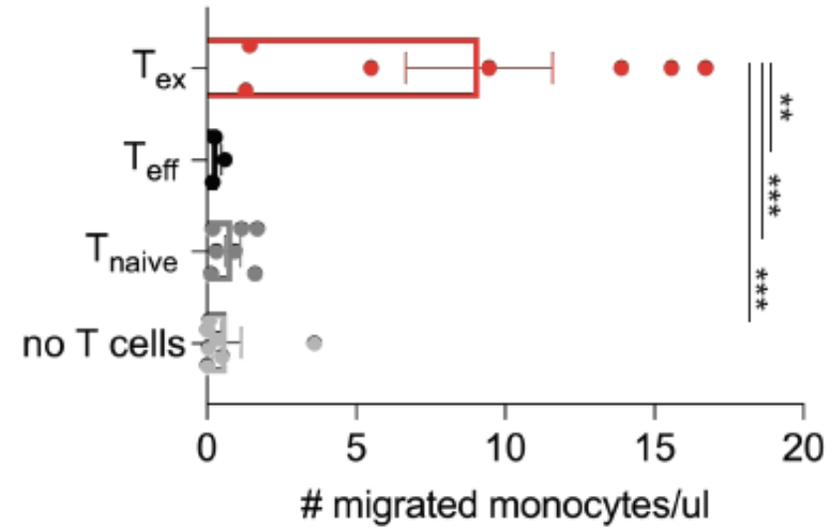
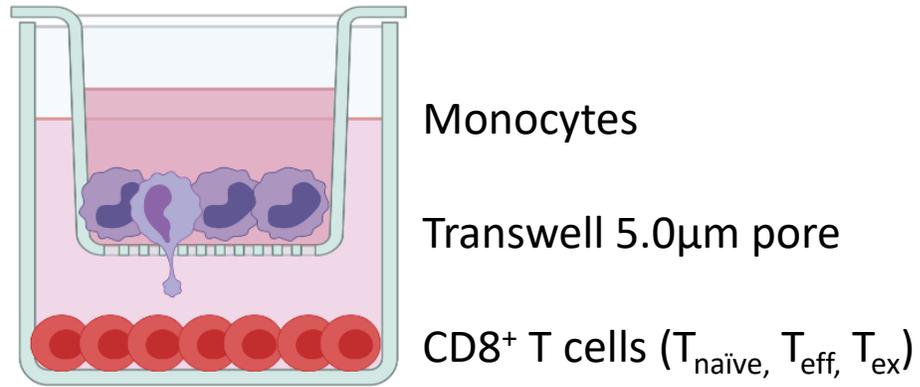
# TAM depletion reduces phenotypic markers of exhaustion on CD8<sup>+</sup> TIL, and restores effector function.



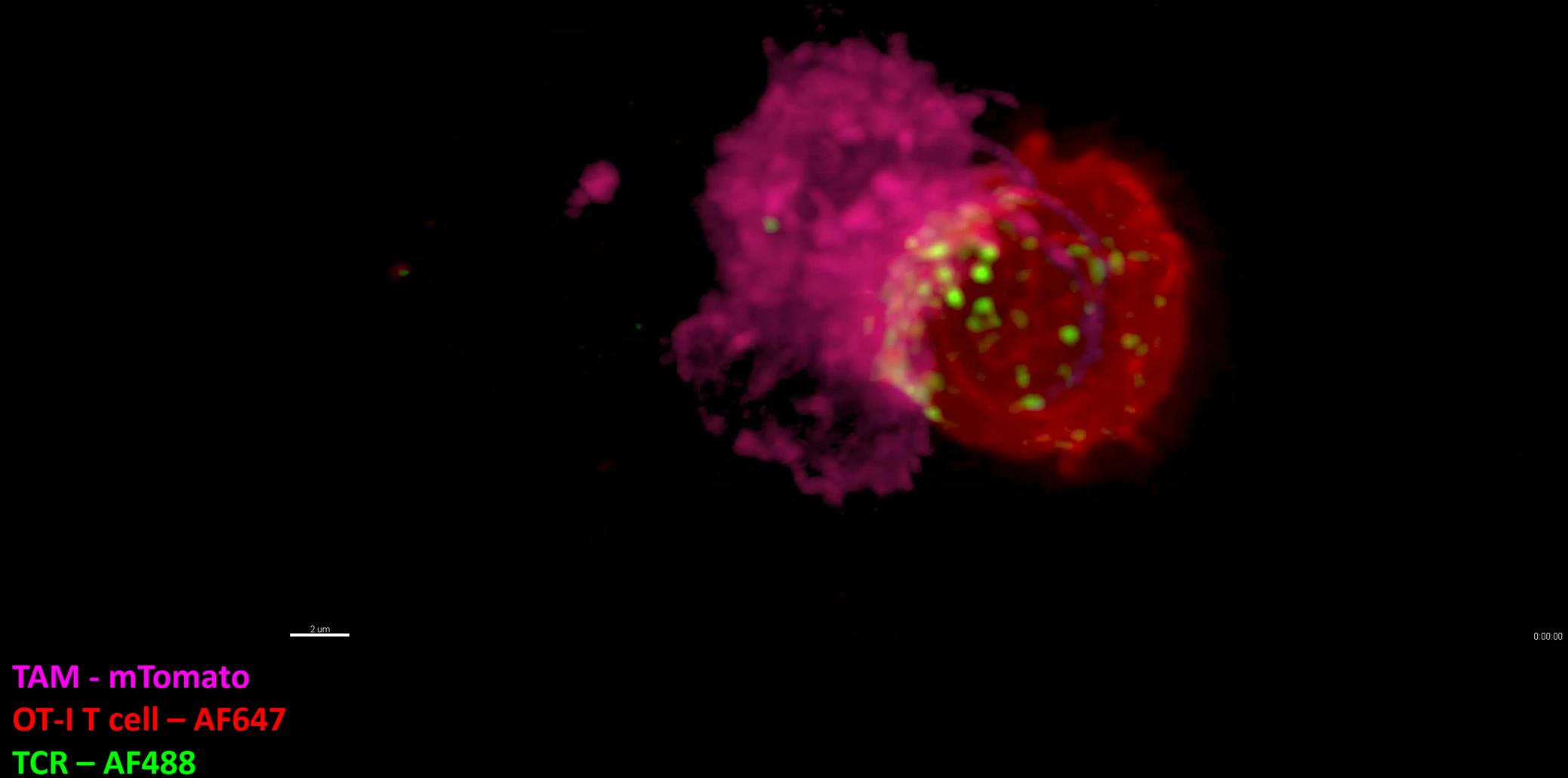
# T<sub>ex</sub> produce myeloid-related cytokines and chemokines in the TME



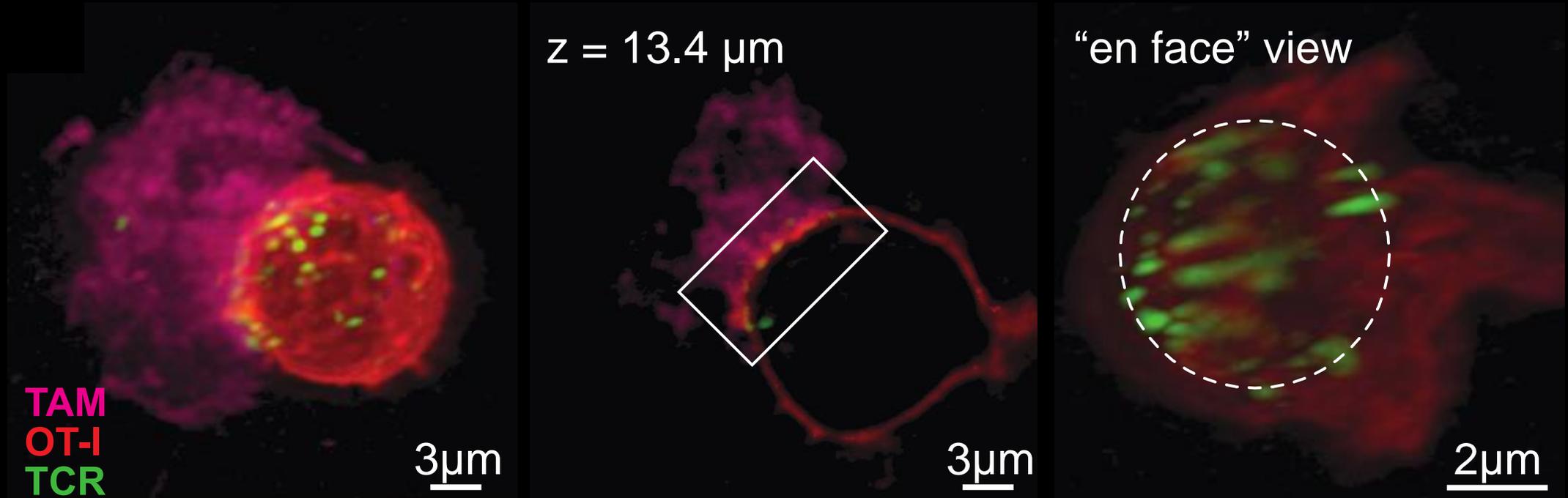
# What is the functional significance of $T_{ex}$ expressing myeloid-related genes?



# Formation of a stable immunological synapse between TAM and CD8<sup>+</sup> T cells



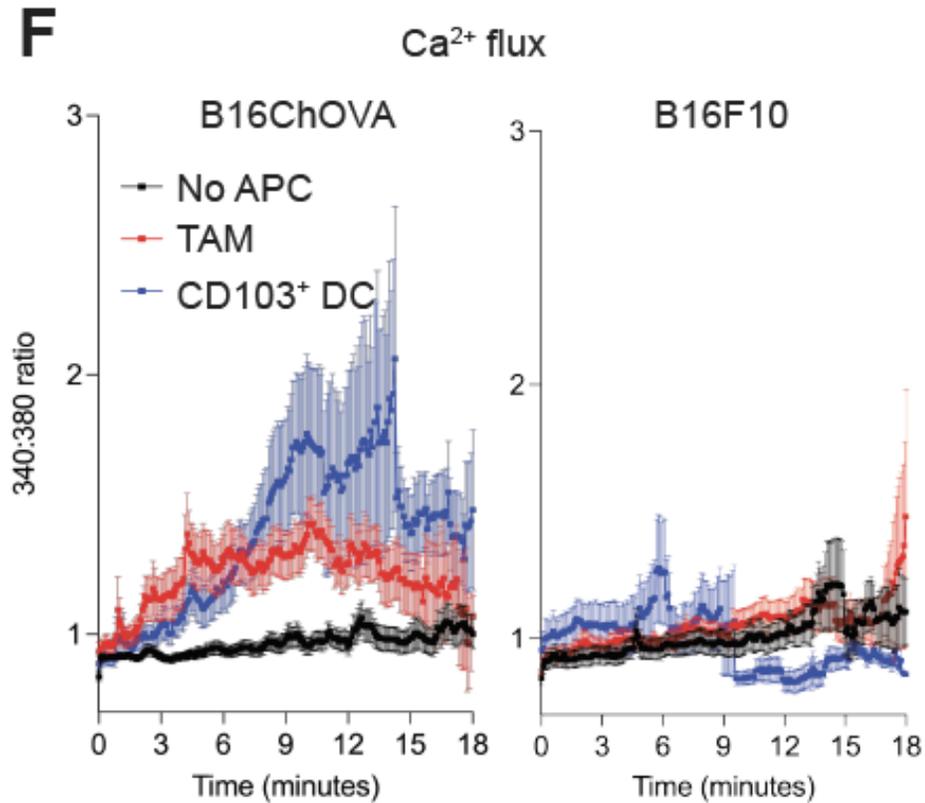
# TAM and CD8<sup>+</sup> T cells engage in unique long-lived synaptic interactions



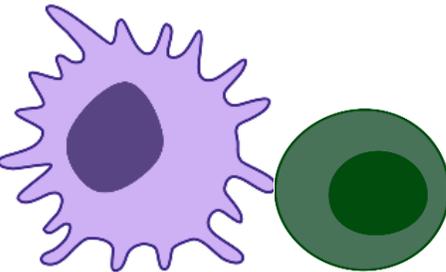
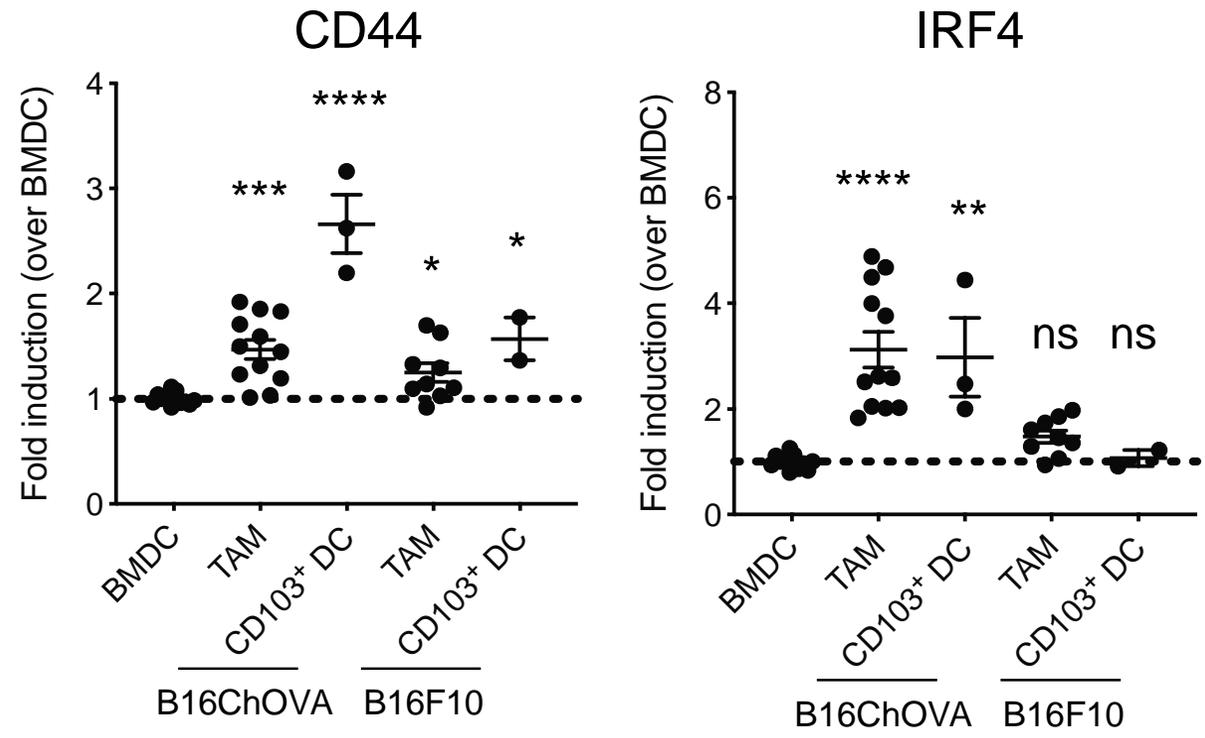
Do TAM provide a TCR trigger and does this lead to activation or exhaustion?

OT-I blasts – AF647  
TAM – mTomato  
TCR – AF488

**TAM derived from OVA<sup>+</sup> tumors induce Ca<sup>2+</sup> flux in OT-I blasts...**  
**... but fail to fully activate them, preventing proliferation**

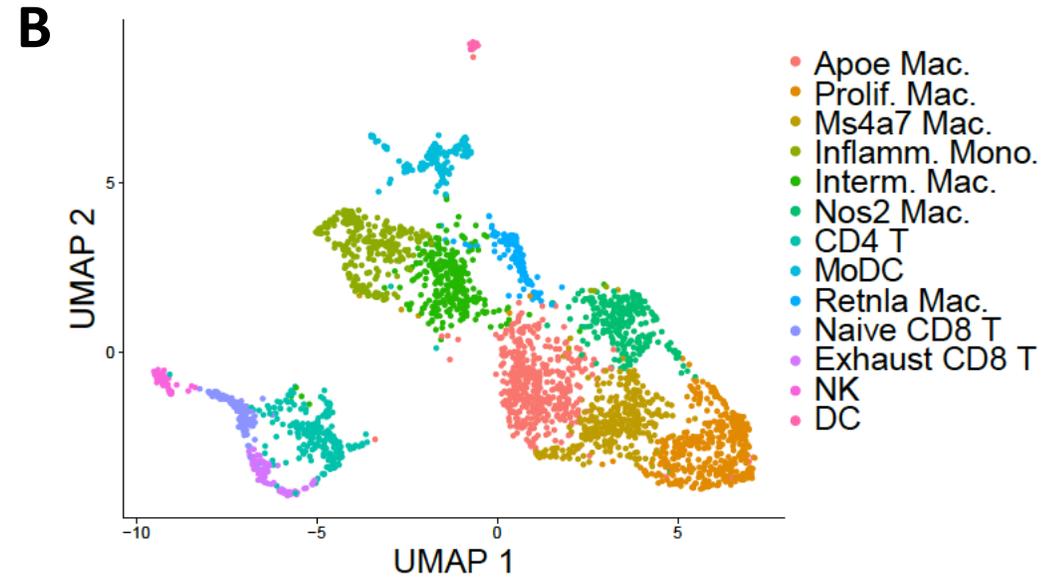
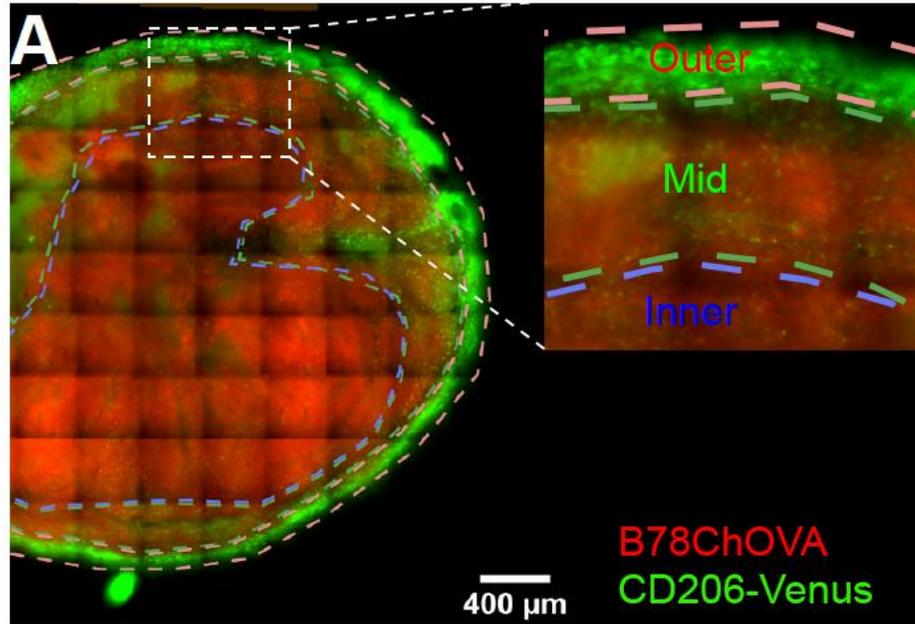


# Instead, TAM contribute to onset of exhaustion programs in an antigen-specific manner

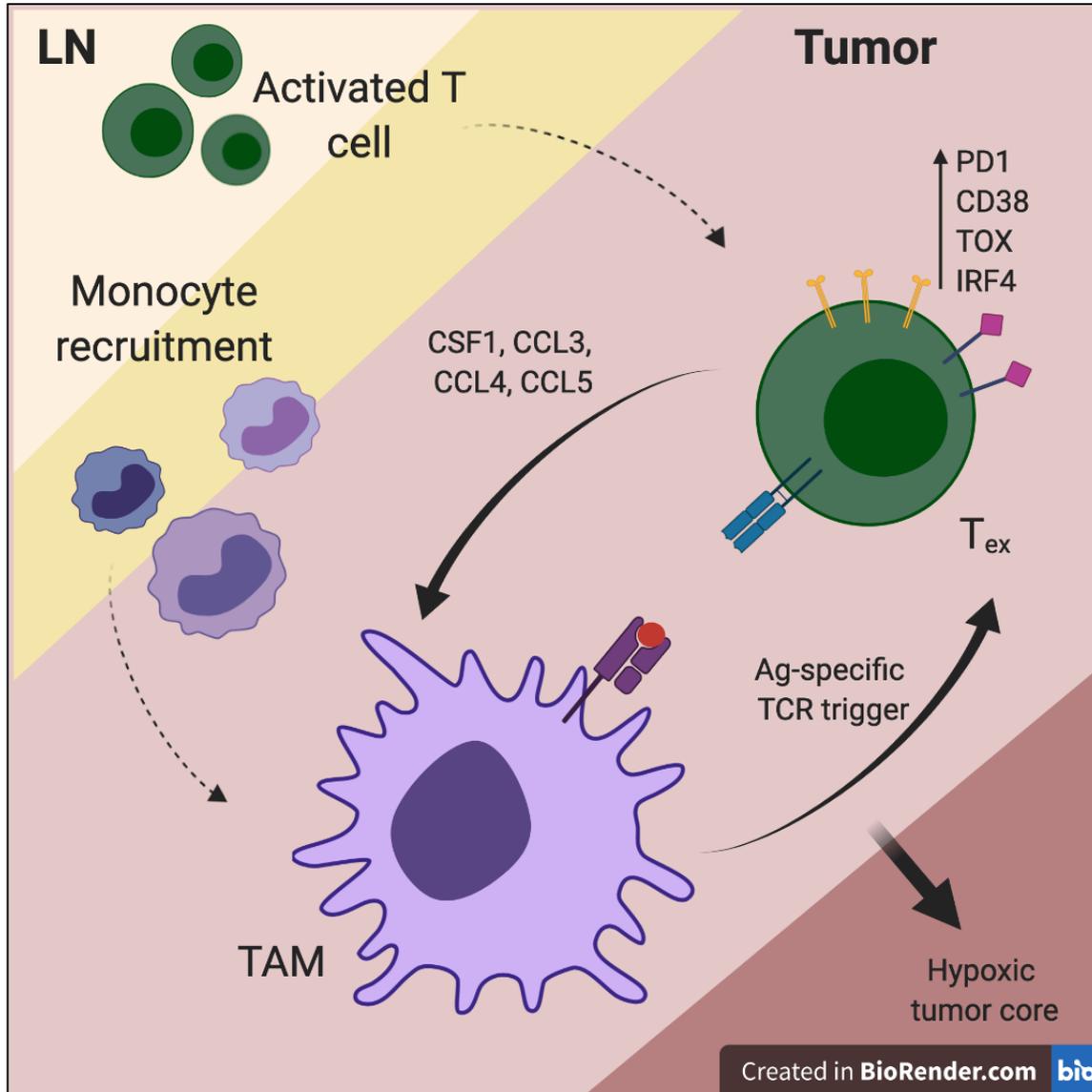


TAM-induced exhaustion programs are exacerbated in hypoxic conditions

# Zip-Seq spatial transcriptomics reveals TAM- $T_{ex}$ co-dependency in the inner TME



# Take home messages



- TAM and T<sub>ex</sub> in the TME are co-dependent through an antigen-driven positive feedback loop.
- ZipSeq spatial transcriptomics revealed a correlation between TAM and T<sub>ex</sub> in the inner regions of the TME

## Future directions

- What is the contribution of different TAM subtypes to T cell exhaustion?
- Dynamics of establishment of TAM-T<sub>ex</sub> axis early and late during carcinogenesis?
- Correlation TAM-T<sub>ex</sub> axis with ICB (non)responsiveness?

# Acknowledgements

## Krummel lab

Max Krummel  
Kenneth Hu  
Tristan Courau  
Arja Ray  
Nicholas Kuhn  
Casey Beppler  
Sophia Nelson  
Chris Im  
Nina Serwas  
Molly Bassette

## BIDC CoLab

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Quanming Shi

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Valerie Weaver @ UCSF  
Justin Eyquem @ UCSF  
Ansuman Satpathy @ Stanford

