Evasion of endogenous CD8 T cell-responses in murine osteosarcoma

Geoffrey Smith, MD, PhD | Jacks Lab / MIT

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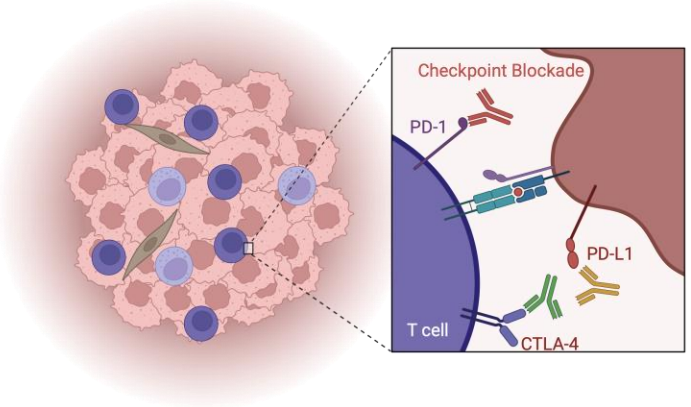
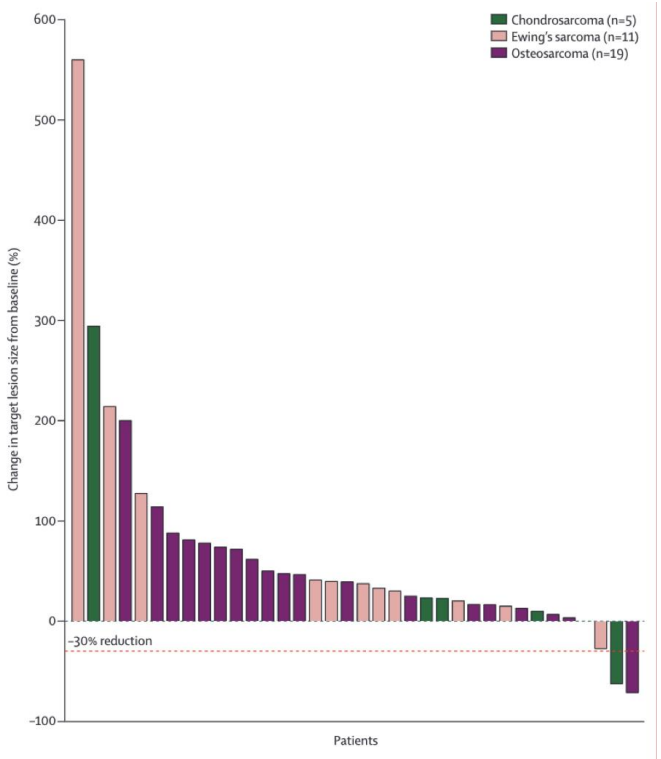
Dana-Farber/Boston Children's Cancer and Blood Disorders Center

Unleashing Endogenous T cell responses

Revolutionary in other cancers but not osteosarcoma



- Two studies of pembrolizumab (αPD-1) in recurrent or advanced osteosarcoma
  - Two partial responses across all studies
- No responses to nivolumab (αPD-1)
- No responses to ipilimumab (αCTLA-4)



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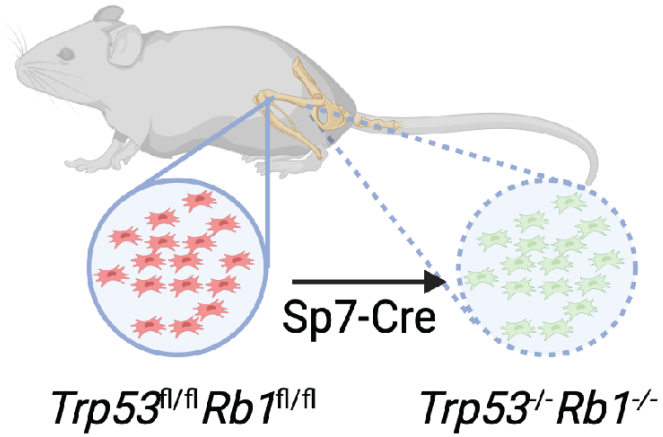
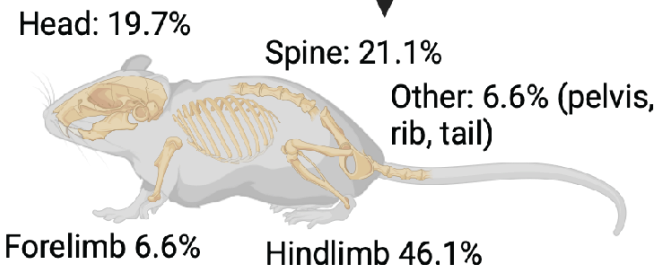
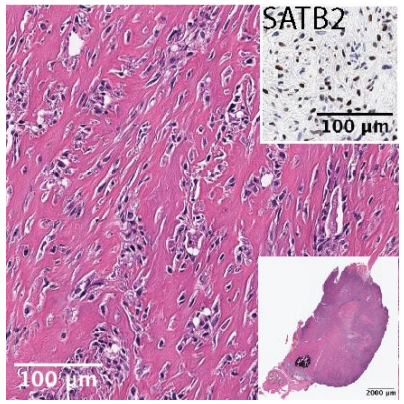
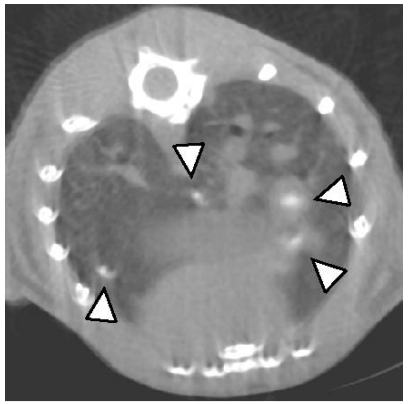
Murine Osteosarcoma

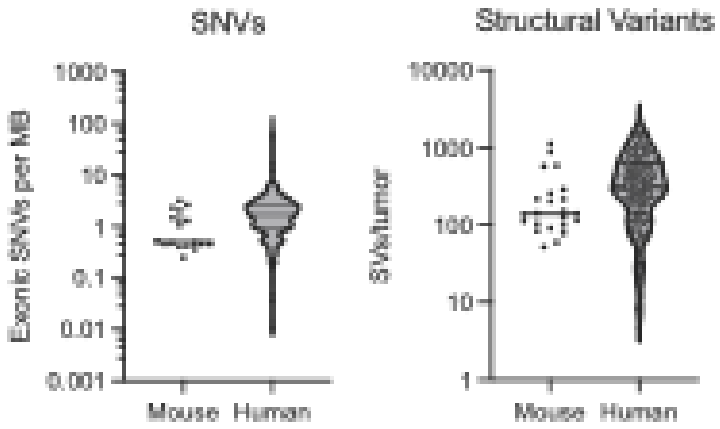
an immunocompetent model to study tumor-immune interactions



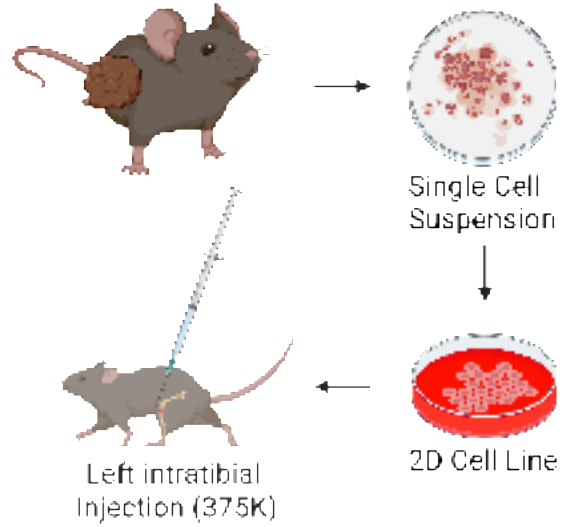








	mOS	Human (Valle-Inclan)
TMB (SNV/mb)	0.50 (0.25 - 1.61)	1.67 (0.93 - 2.54)
SVs (/tumor)	140 (98 - 256)	309 (146 - 621)

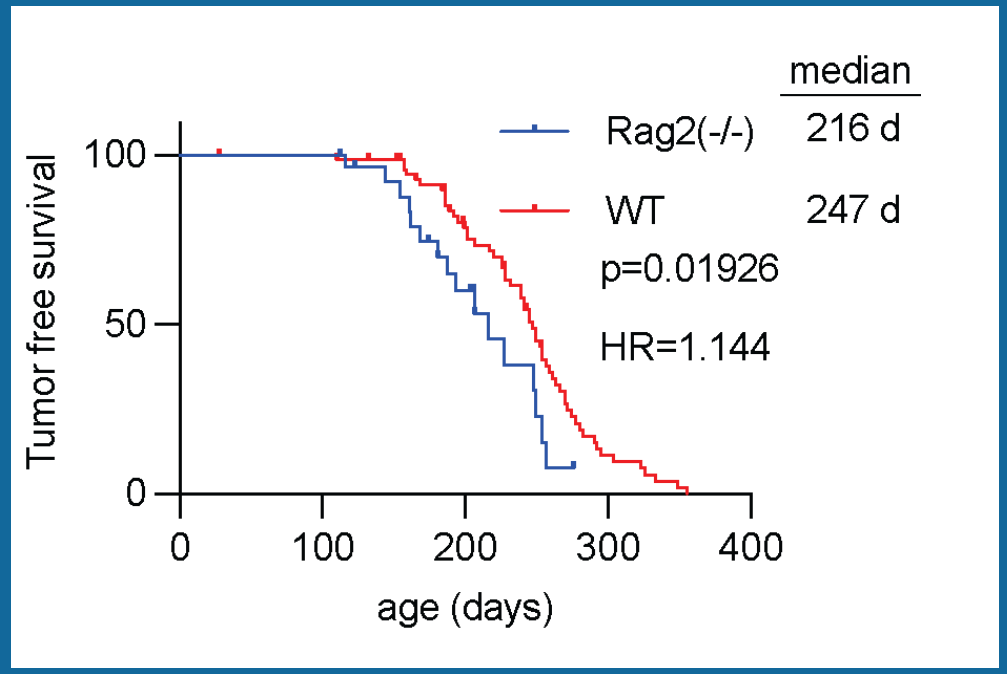


Walkley, C. R. …Orkin, S *Gene Dev* 22, 1662–1676 (2008).
Berman, S. D…. Lees, *Proc National Acad Sci* 105, 11851–11856 (2008).

Adaptive Immunity delays osteosarcoma outgrowth

Mice lacking B & T cells develop osteosarcoma sooner than immunocompetent mice

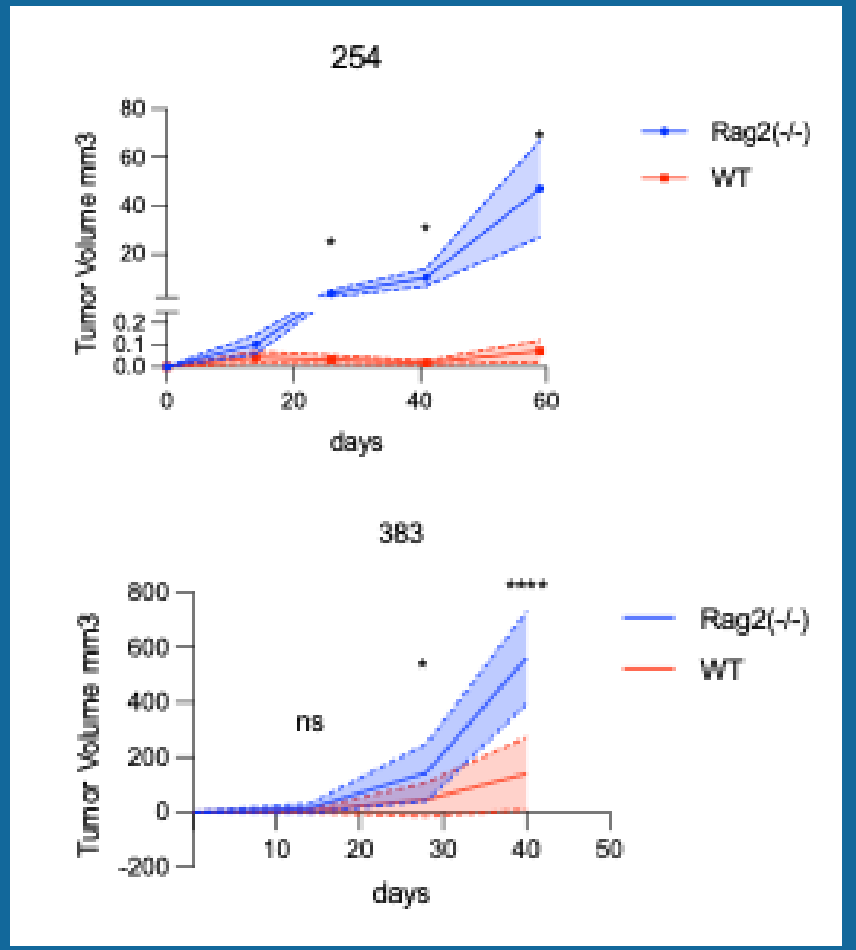
Spontaneous mOS



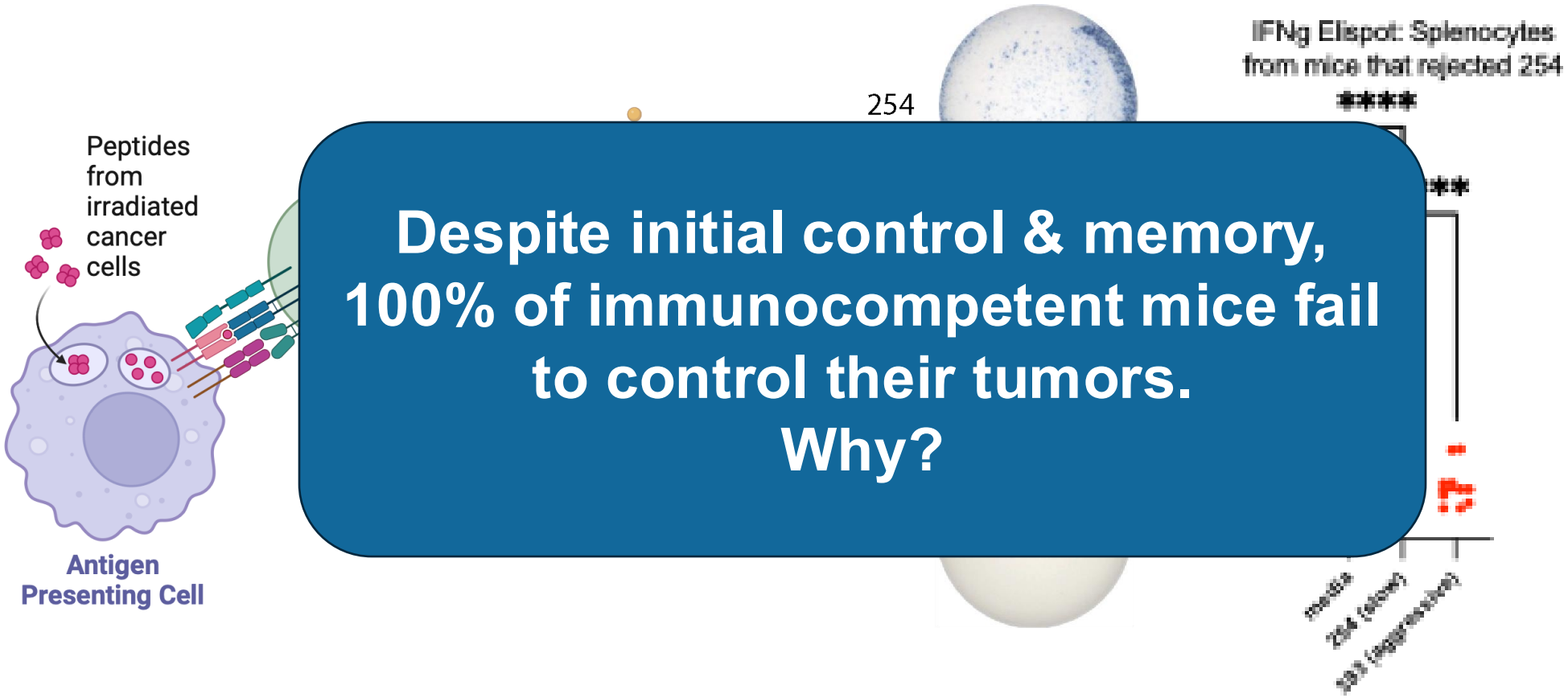
Orthotopic Transplant

Slow growing

Aggressive

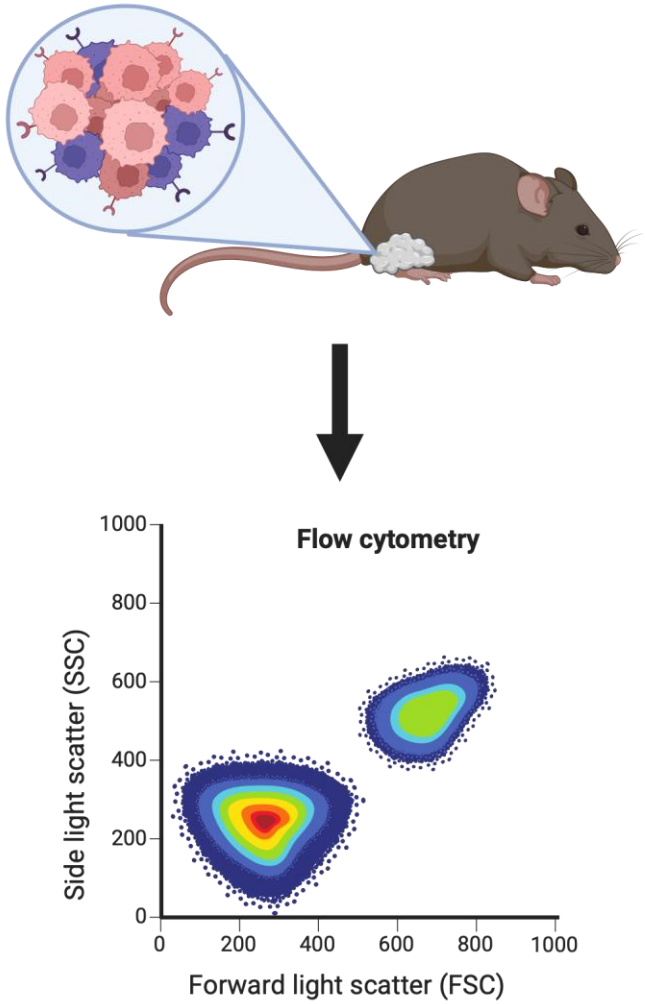


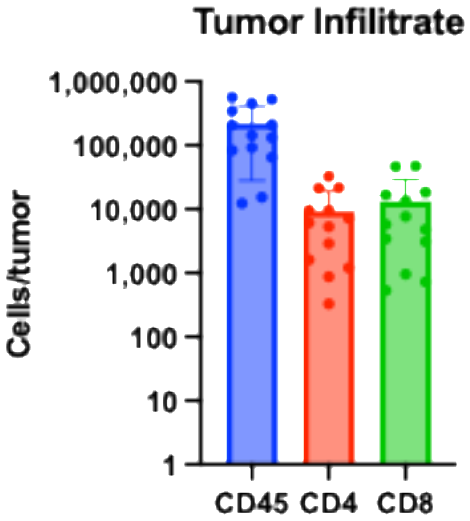
Immunological Memory to mOS



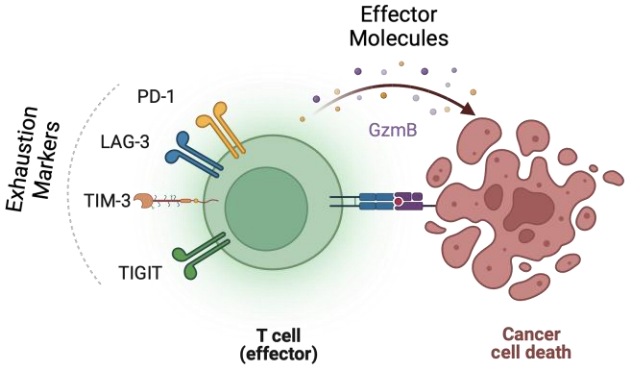
Recognition of rejected tumor and cross-recognition of other mOS lines

CD8+ T cells infiltrate mOS tumors

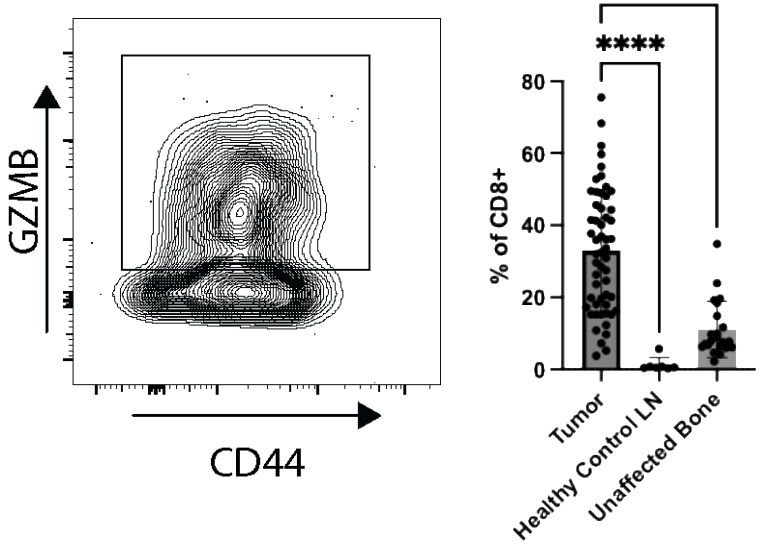




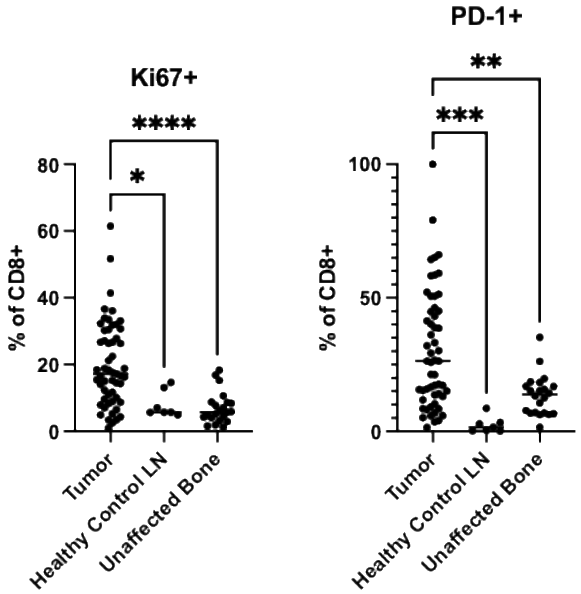
Tumor Infiltrating CD8+ T cells appear activated



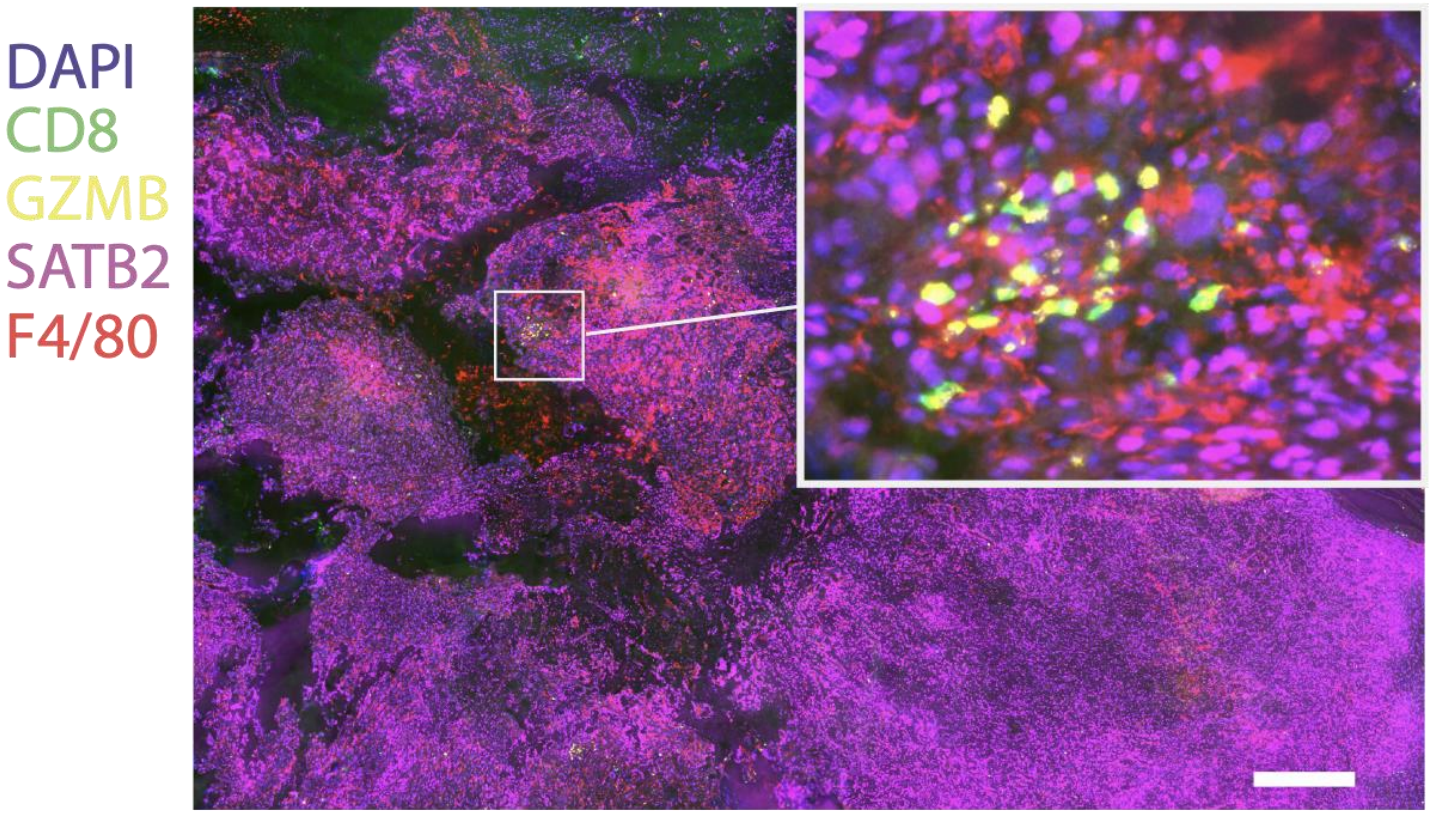
Upregulate Cytotoxic Granules



Express markers of antigen experience



Activated CD8+ T cells colocalize with osteosarcoma cells

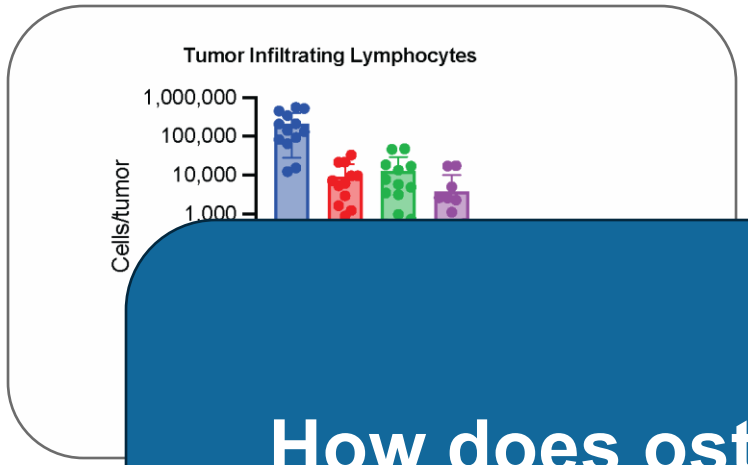


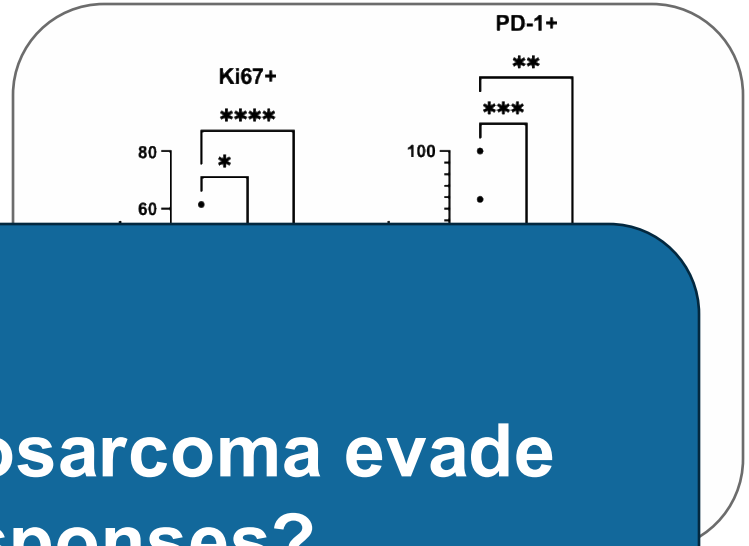
Jia-Yun Chen / Sandro Santagata (BWH/HMS)

CD8+ T cells

Infiltrate mOS tumors

Express markers of antigen experience

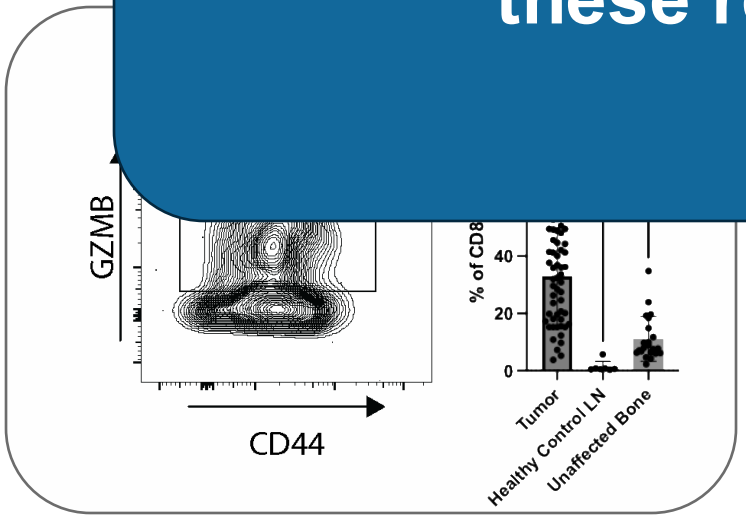


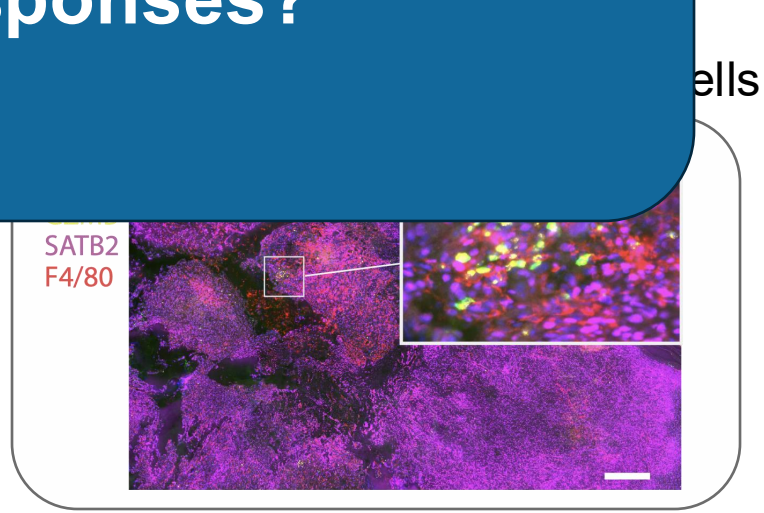


Upre

ells

How does osteosarcoma evade these responses?

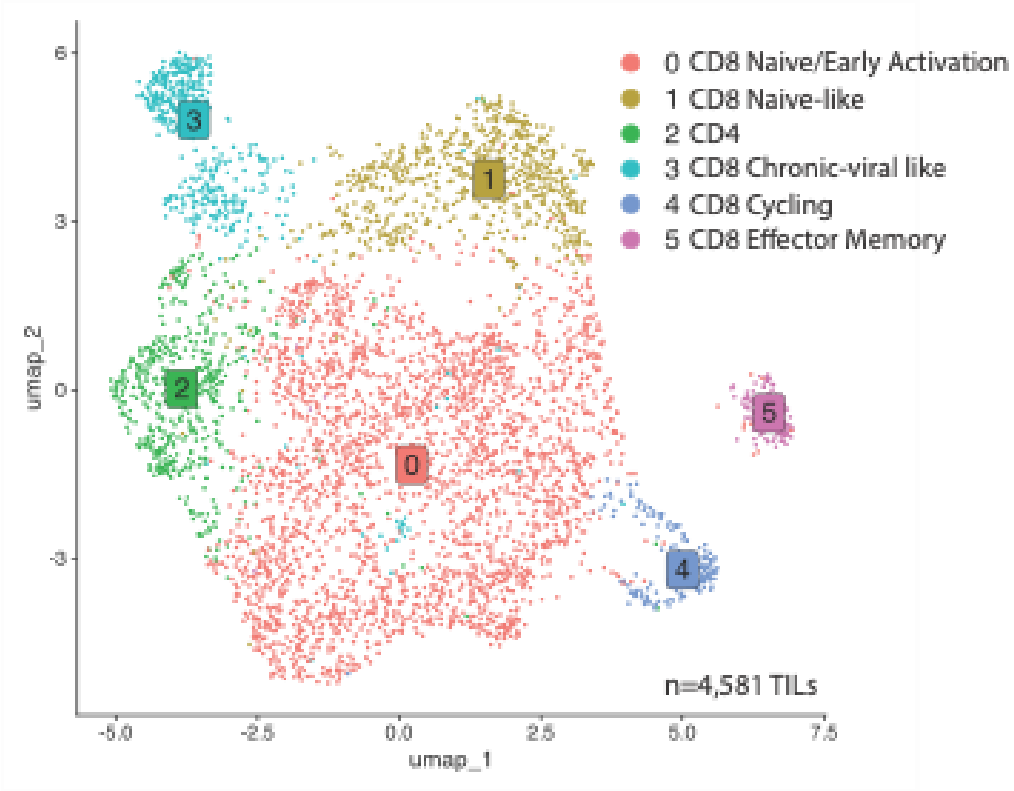


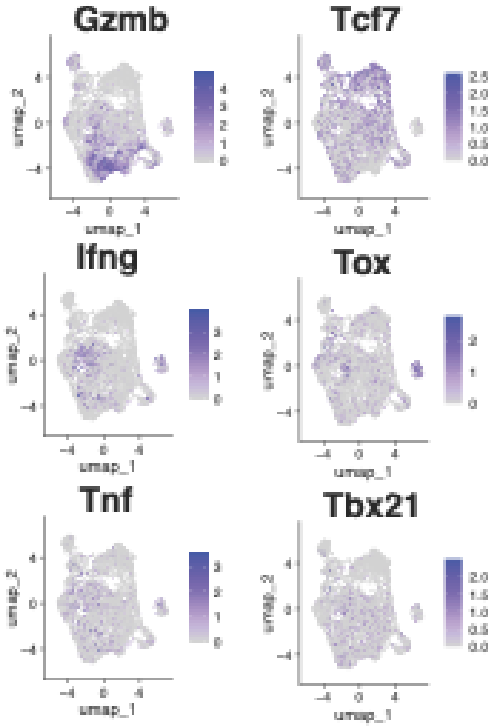


Poor T-cell Priming

Naïve-like population predominates

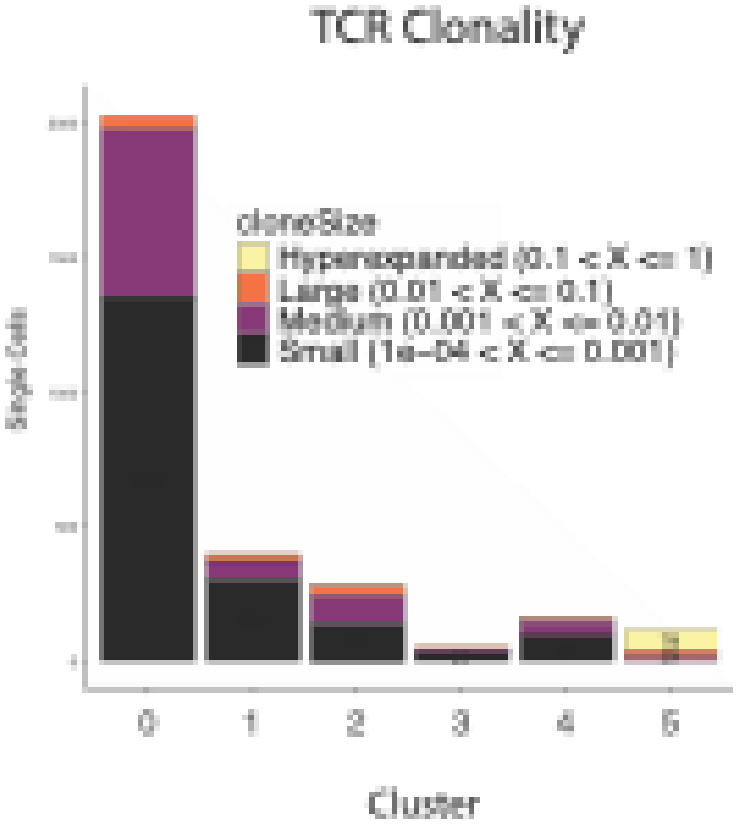
No Classically exhausted cells





Oligoclonal Expansion

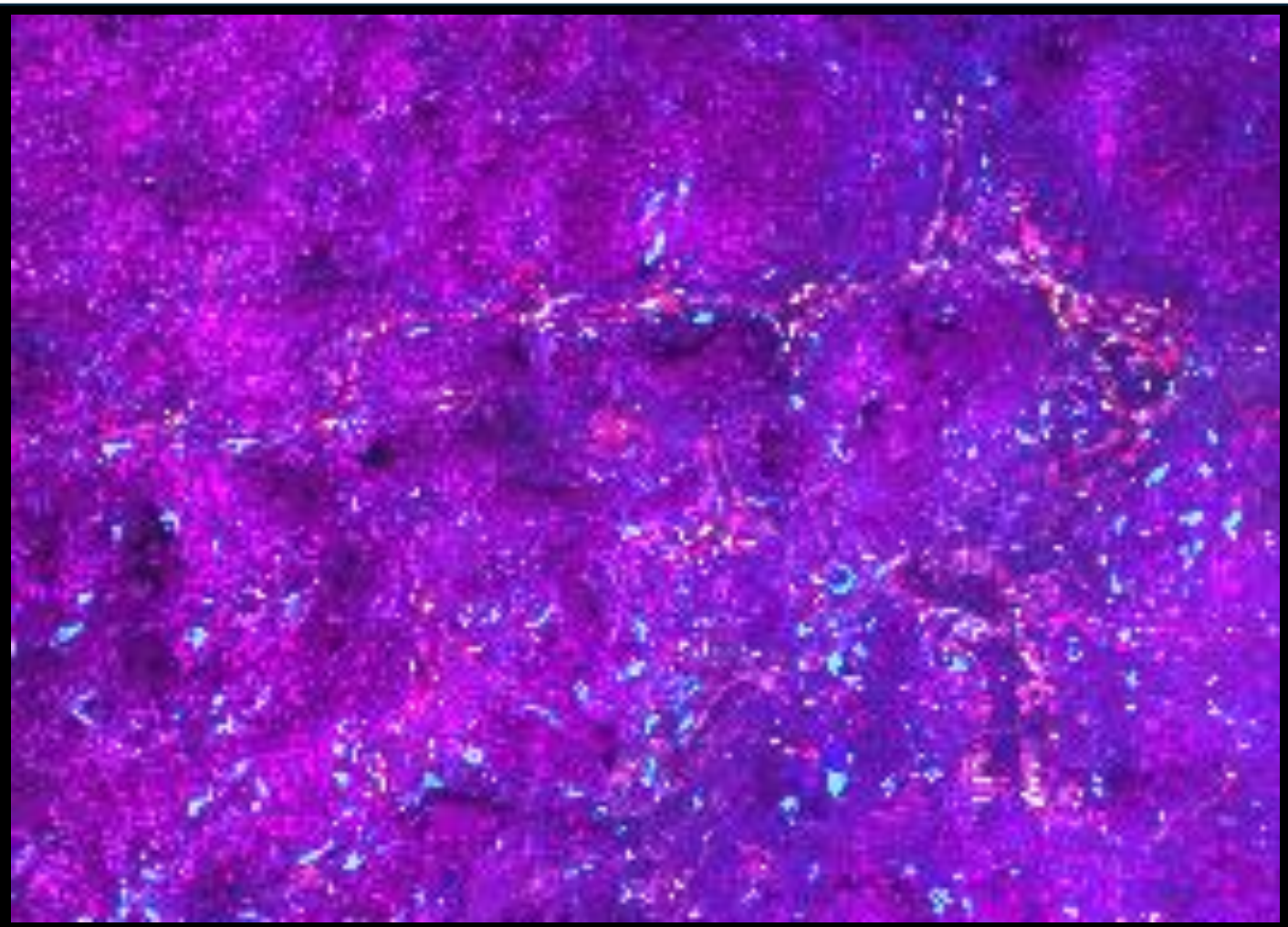
No dominant clones



Tumor Microenvironment

More than just osteosarcoma and effector T cells

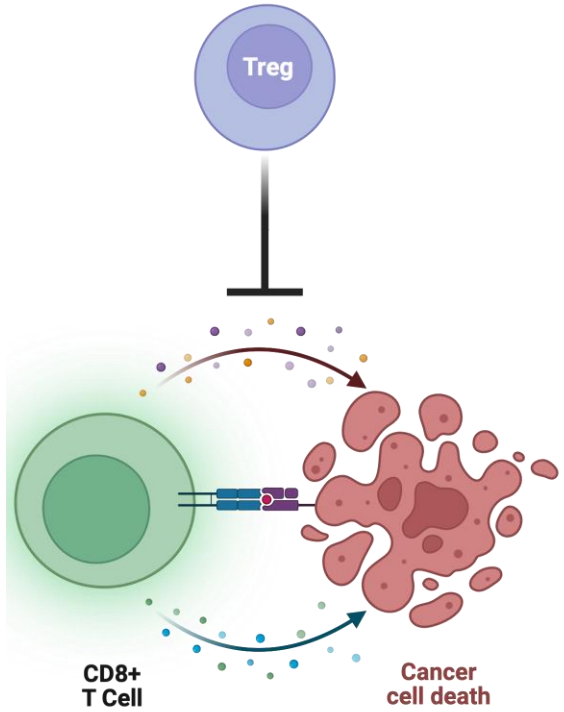
Cancer
T Cells
B Cells
Macrophages
Neutrophils

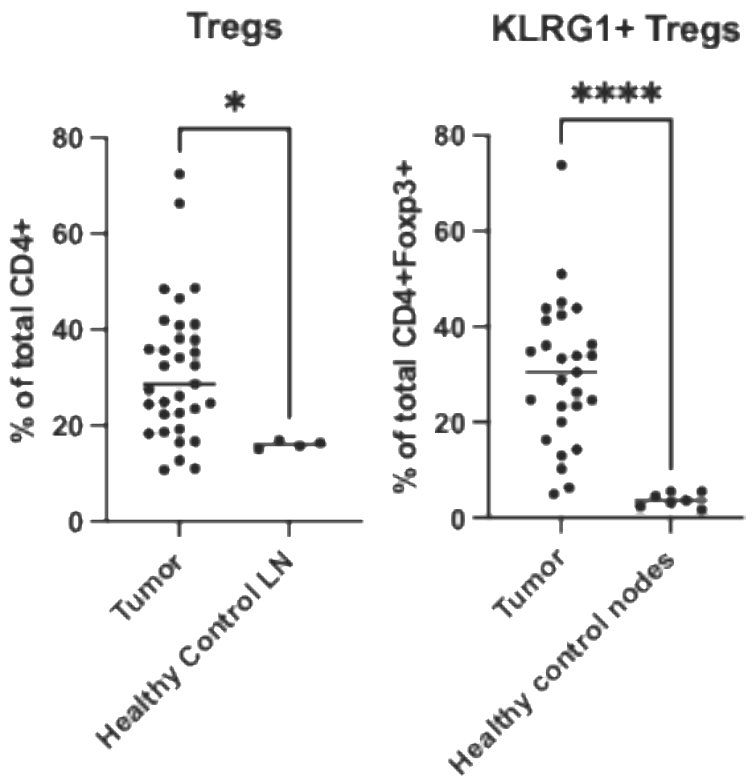


Immunosuppressive Microenvironment

Increased Regulatory T cells

Particularly Suppressive KLRG1+ population

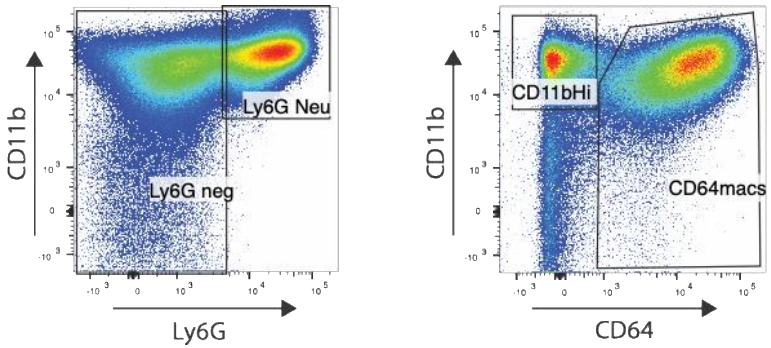


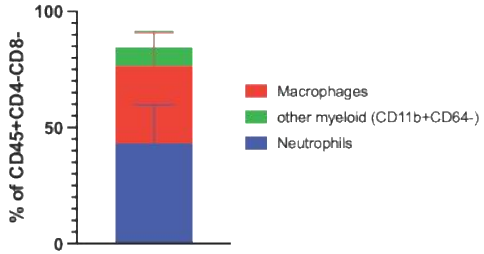


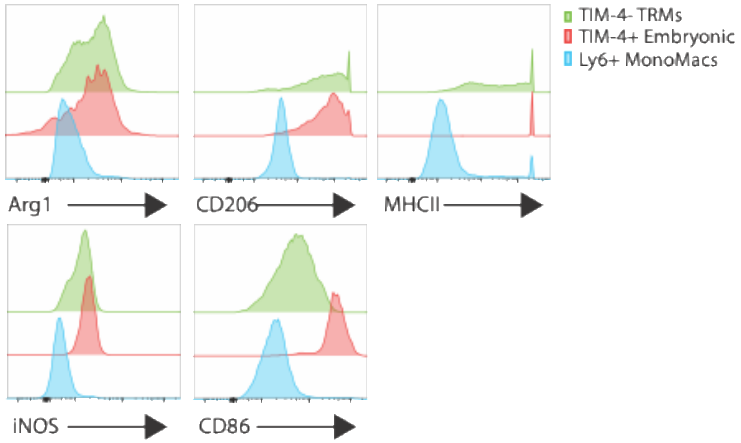
Immunosuppressive Microenvironment

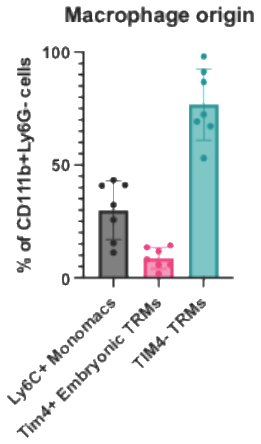
Suppressive Myeloid Compartment

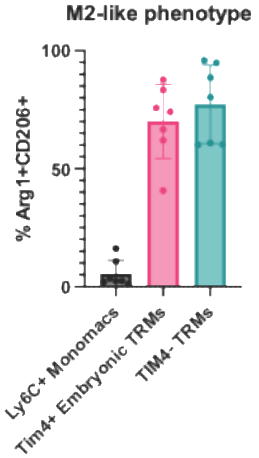
Neutrophils and M2-like macrophages











Barriers suggest potential therapies

1	2	3
Poor Priming of initial response	TME: Regulatory T cells	TME: Macrophages
• Vaccination: Expand initial response • Adoptive Cell Therapy / CAR-T: ex vivo expansion of large resposne	• Selective Depletion (aCCR8)	• CSF1R based depletion • Repolarization (cytokines, STING agonism)

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NIH National Cancer Institute

MIB Agents Osteosarcoma Alliance — Make It Better For Kids With Osteosarcoma

Because of Jayden