

Professional Advancement Virtual Engagement Series (PAVES)

January 26, 2022

Troy McEachron, PhD

Integrated Solid Tumor Biology Section

Pediatric Oncology Branch

National Cancer Institute



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IDAHO

MONTANA

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SOUTH DAKOTA

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WISCONSIN

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MARYLAND

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VIRGINIA

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OHIO

INDIANA

ILLINOIS

IOWA

NEBRASKA

KANSAS

MISSOURI

KENTUCKY

TENNESSEE

OKLAHOMA

ARKANSAS

MISSISSIPPI

ALABAMA

GEORGIA

LOUISIANA

NEW MEXICO

ARIZONA

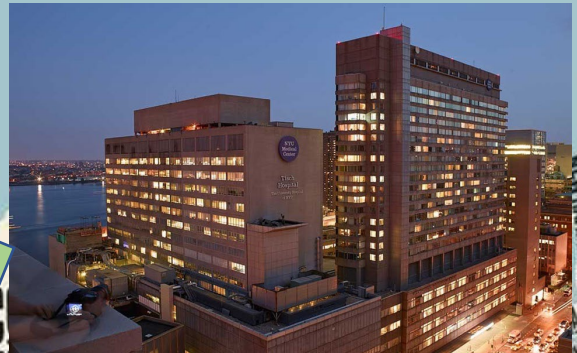
CALIFORNIA

TEXAS

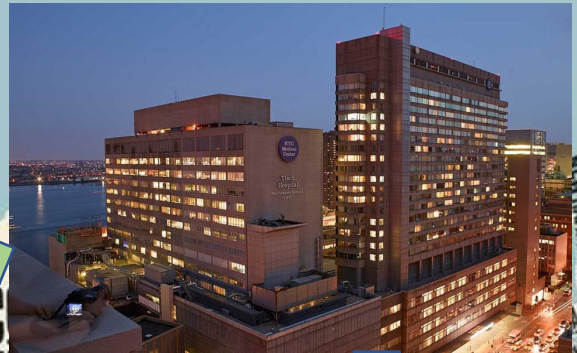
ALASKA

HAWAII

FLORIDA



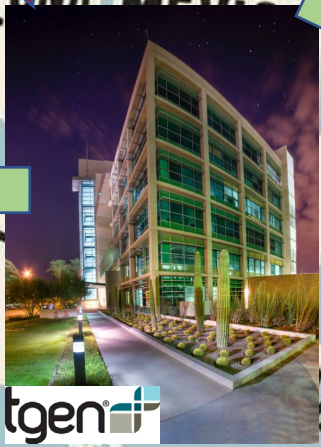
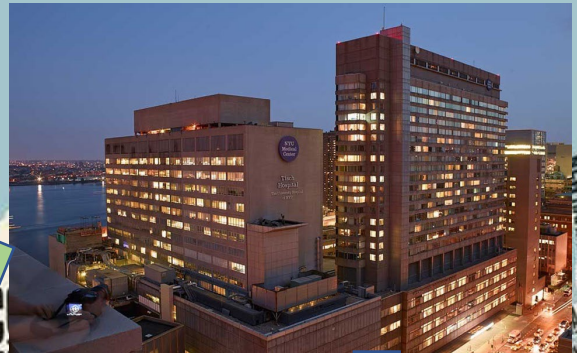








tgen



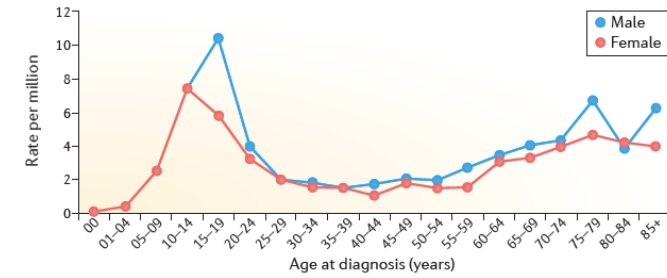
Focus of the Integrated Solid Tumor Biology Section

Functional characterization of high risk pediatric solid tumors to reveal the mechanisms by which tumor cells modulate the function and composition of their local tissue microenvironments to evade anti-tumor immune responses and promote disease progression



Introduction to osteosarcoma

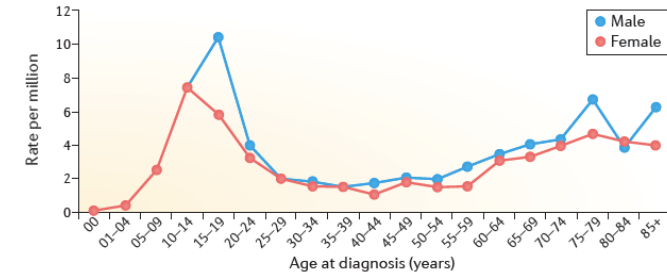
- Osteosarcoma (OS) is an aggressive malignant bone tumor typically arising in pediatric and adolescent/young adult patients



Gianferante DM, Mirabello L, Savage SA. *Nat Rev Endocrinology*. 2017

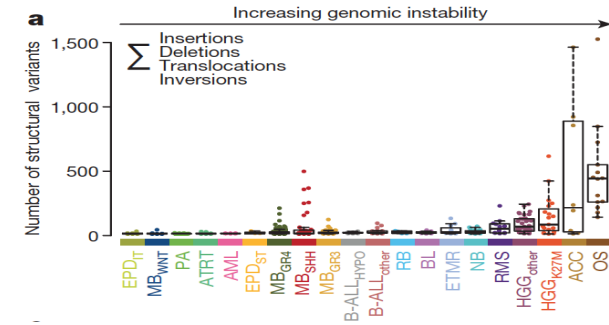
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Gianferante DM, Mirabello L, Savage SA. *Nat Rev Endocrinology*. 2017

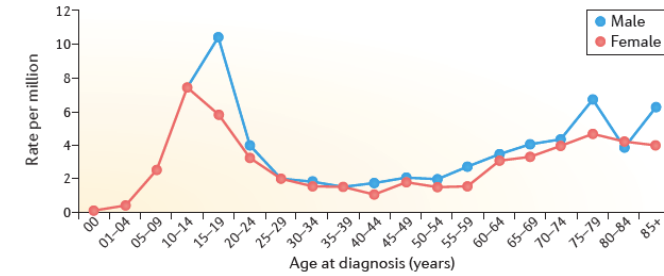
- OS is a genomically complex disease with numerous chromosomal structural aberrations and prevalent chromothripsis



Grobner SN, et al. *Nature*. 2018

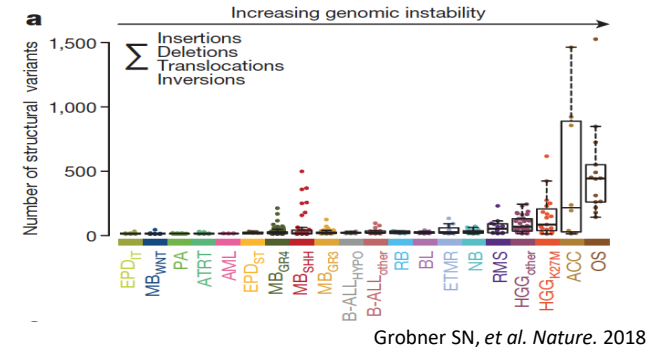
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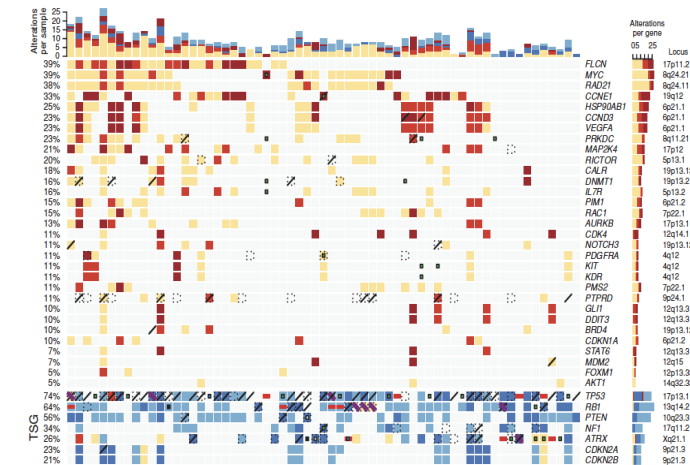
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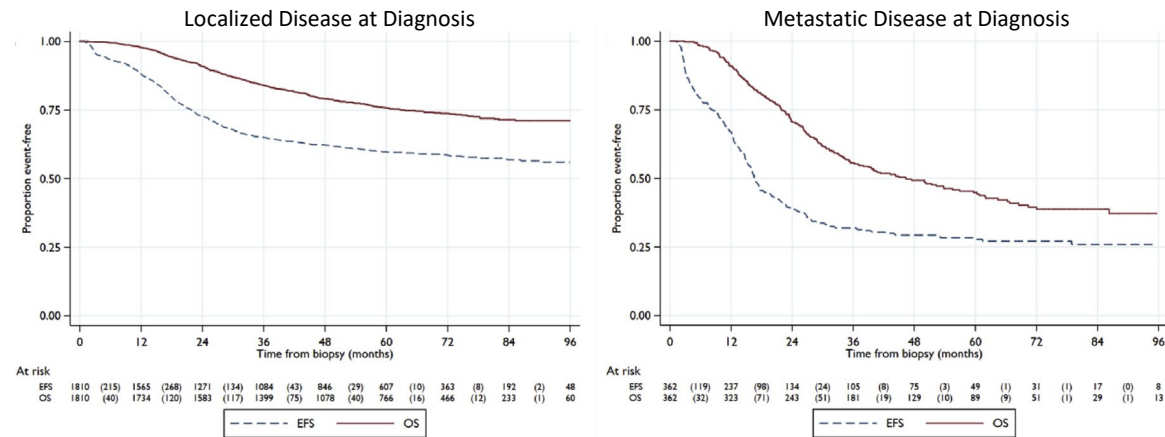
- Somatic copy number alterations > nonsynonymous point mutations



Sayles LC, et al. *Cancer Discovery*. 2018

The clinical dilemma in metastatic osteosarcoma

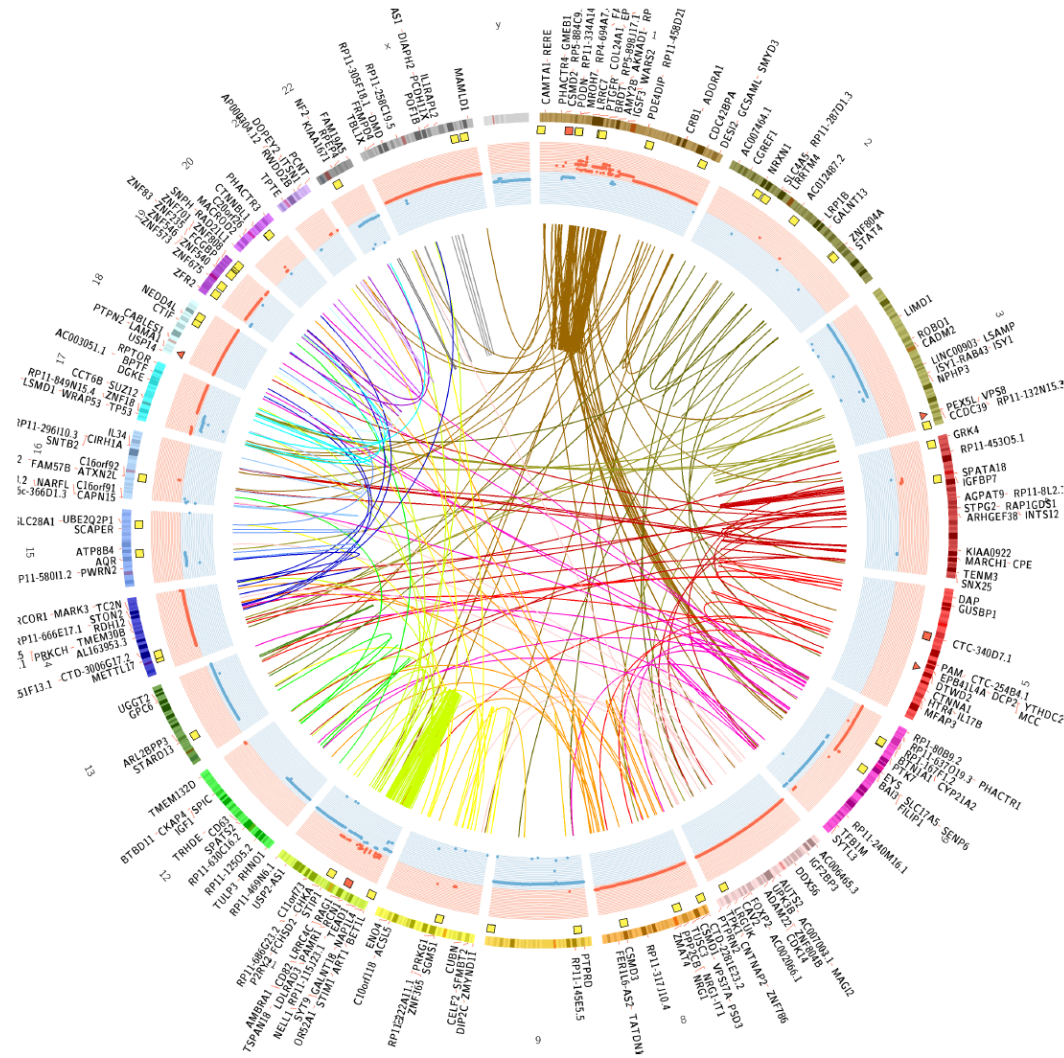
- Survival rates have not significantly improved in over 30 years
- Patients with metastatic disease demonstrate inferior outcome



Smeland S, et al. *European Journal of Cancer*. 2019

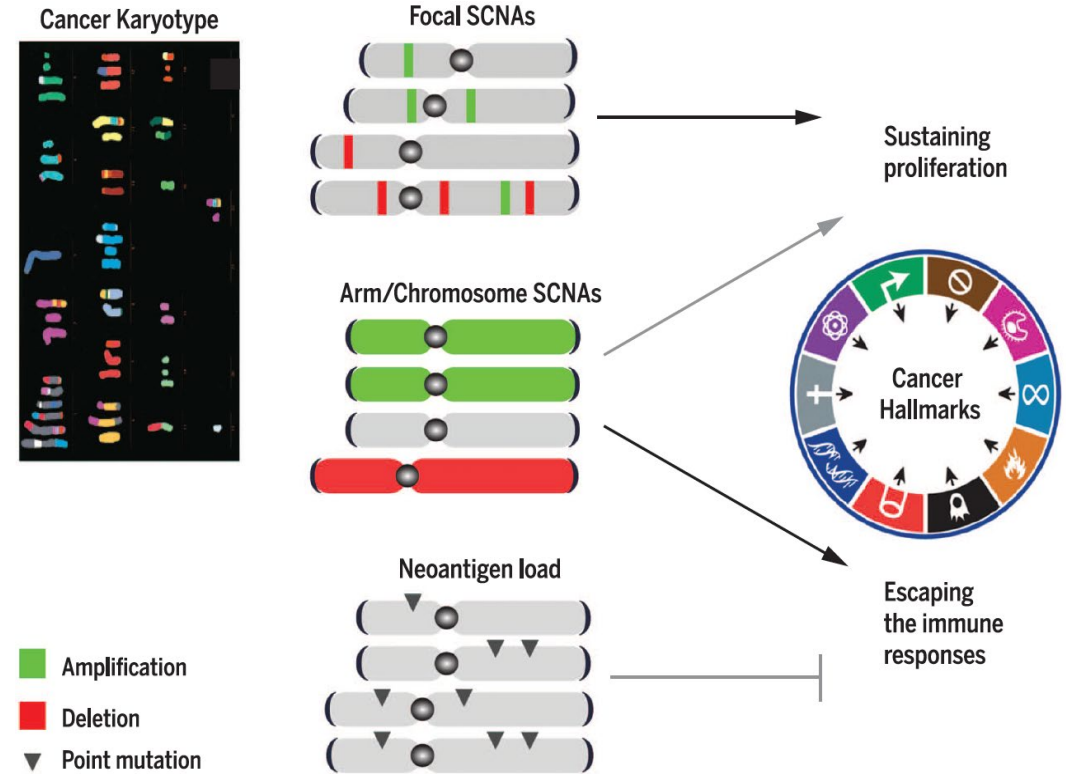
- Immune checkpoint blockade does not provide therapeutic benefit to patients diagnosed with OS

Does the genomic complexity of OS facilitate immune escape and resistance to immunotherapy?



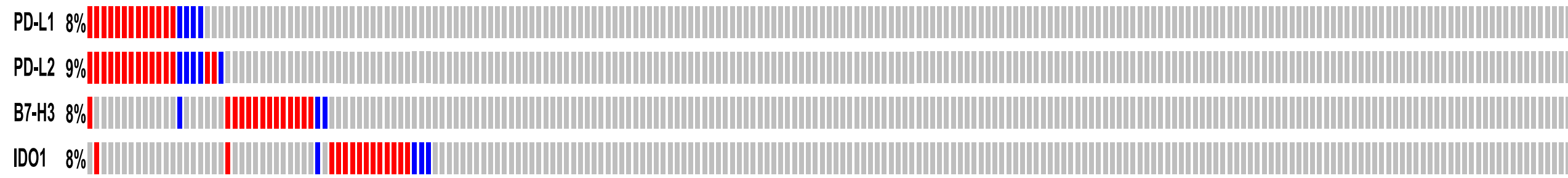
Tumor aneuploidy correlates with markers of immune evasion and with reduced response to immunotherapy

Teresa Davoli, Hajime Uno, Eric C. Wooten, Stephen J. Elledge*

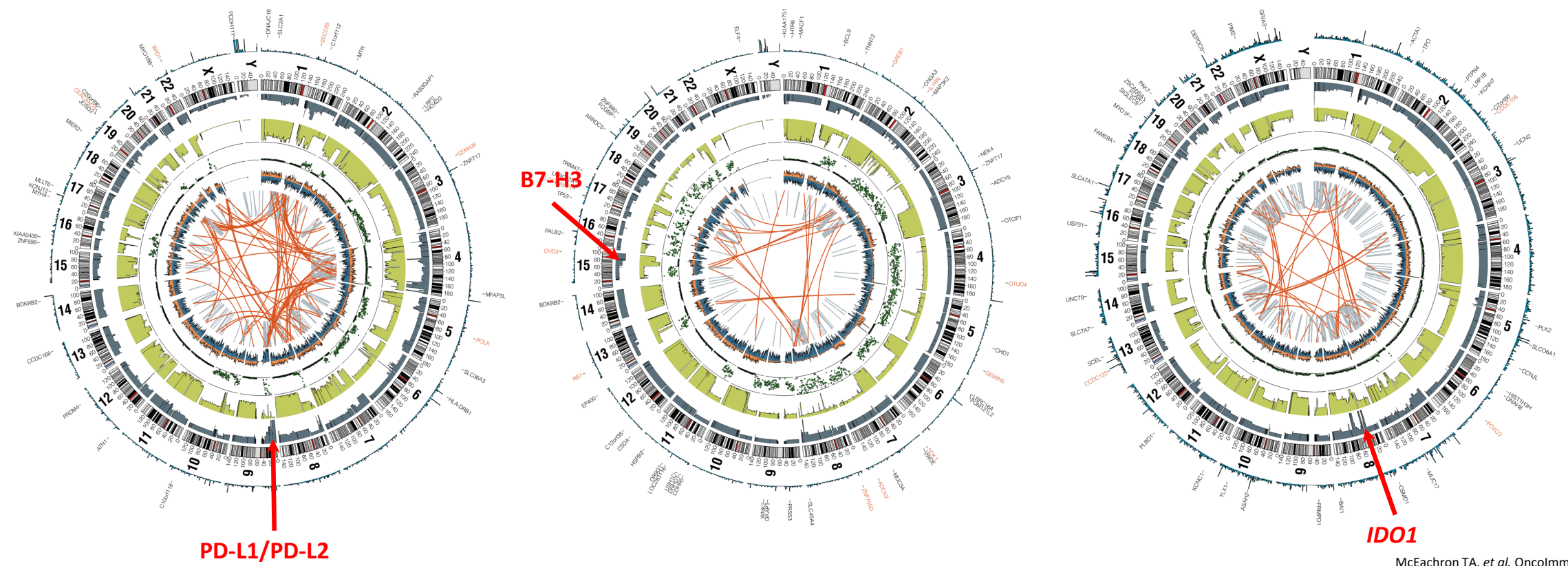


Davoli T, et al. Science 2017

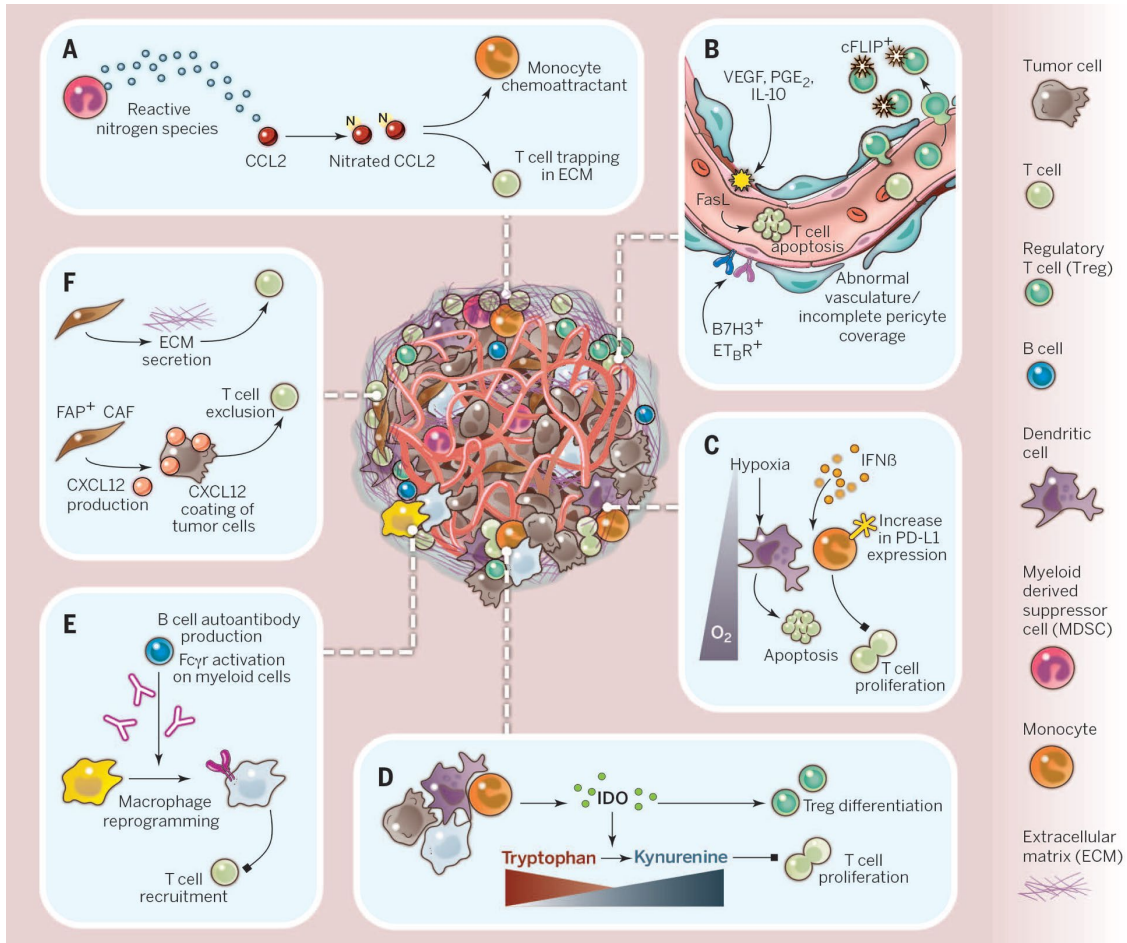
Copy number gains of immune checkpoints in OS



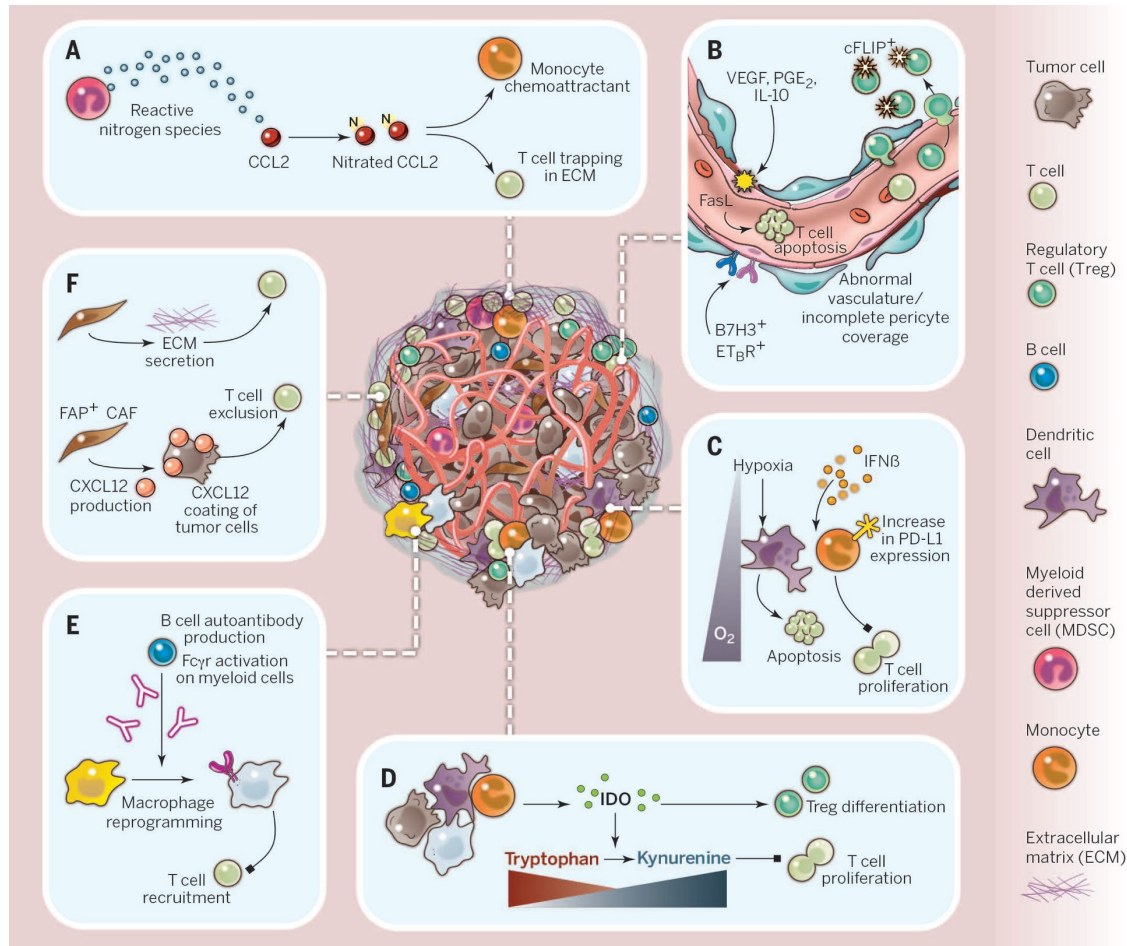
Copy Number Gain Determined by SNP6.0 Array
 Copy Number Gain Determined by WGS



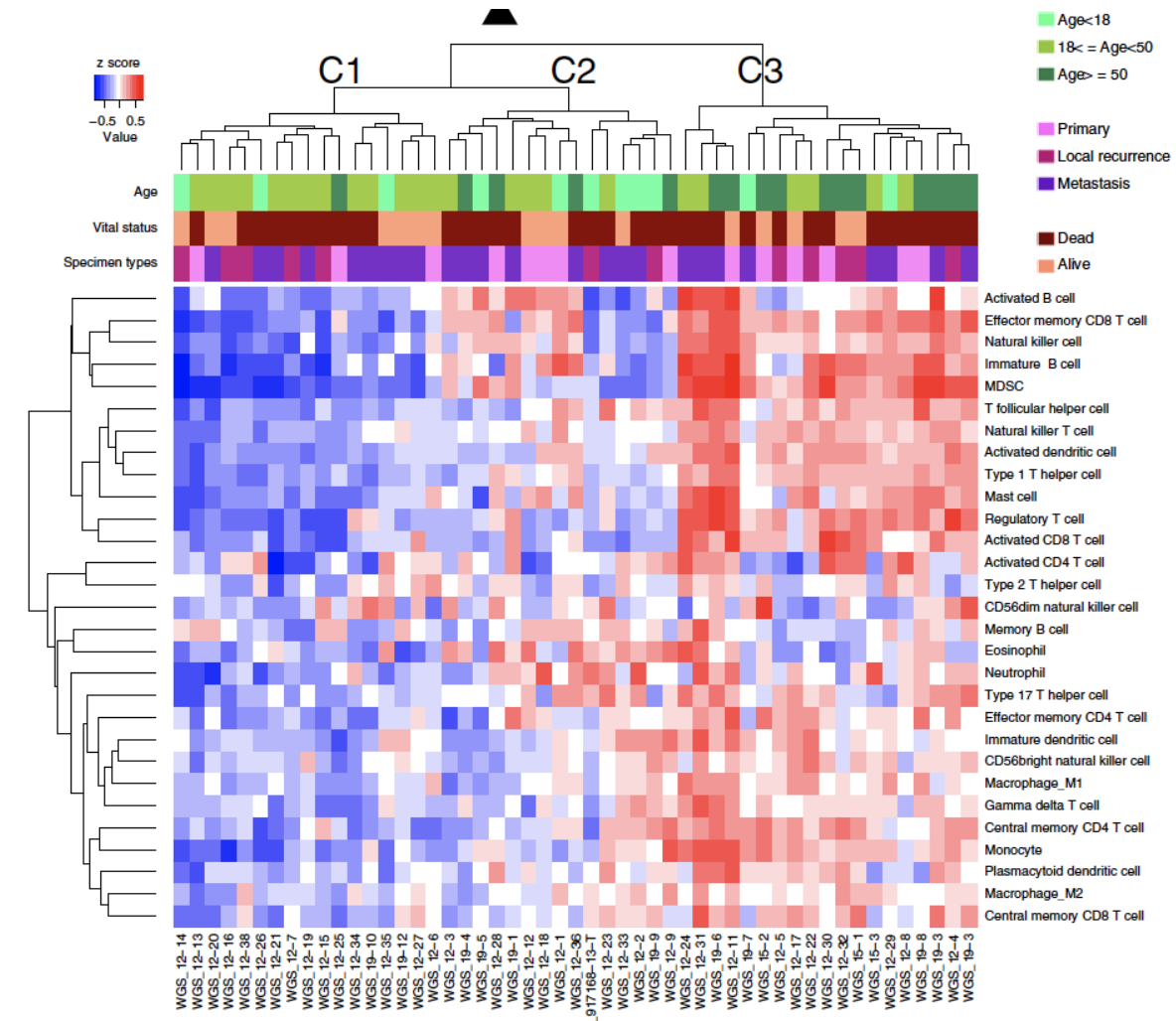
Complexity of the tumor microenvironment



Complexity of the tumor microenvironment

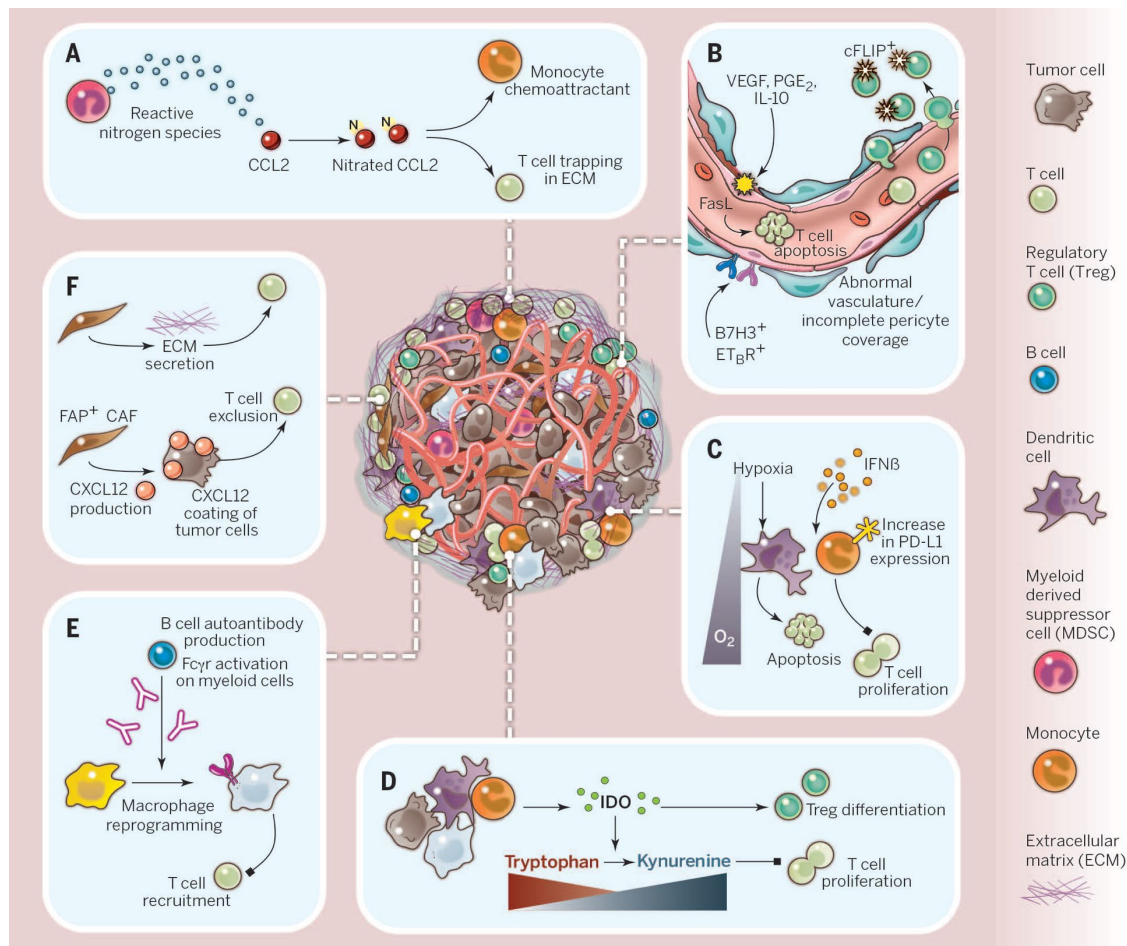


Joyce JA, et al. *Science*. 2015

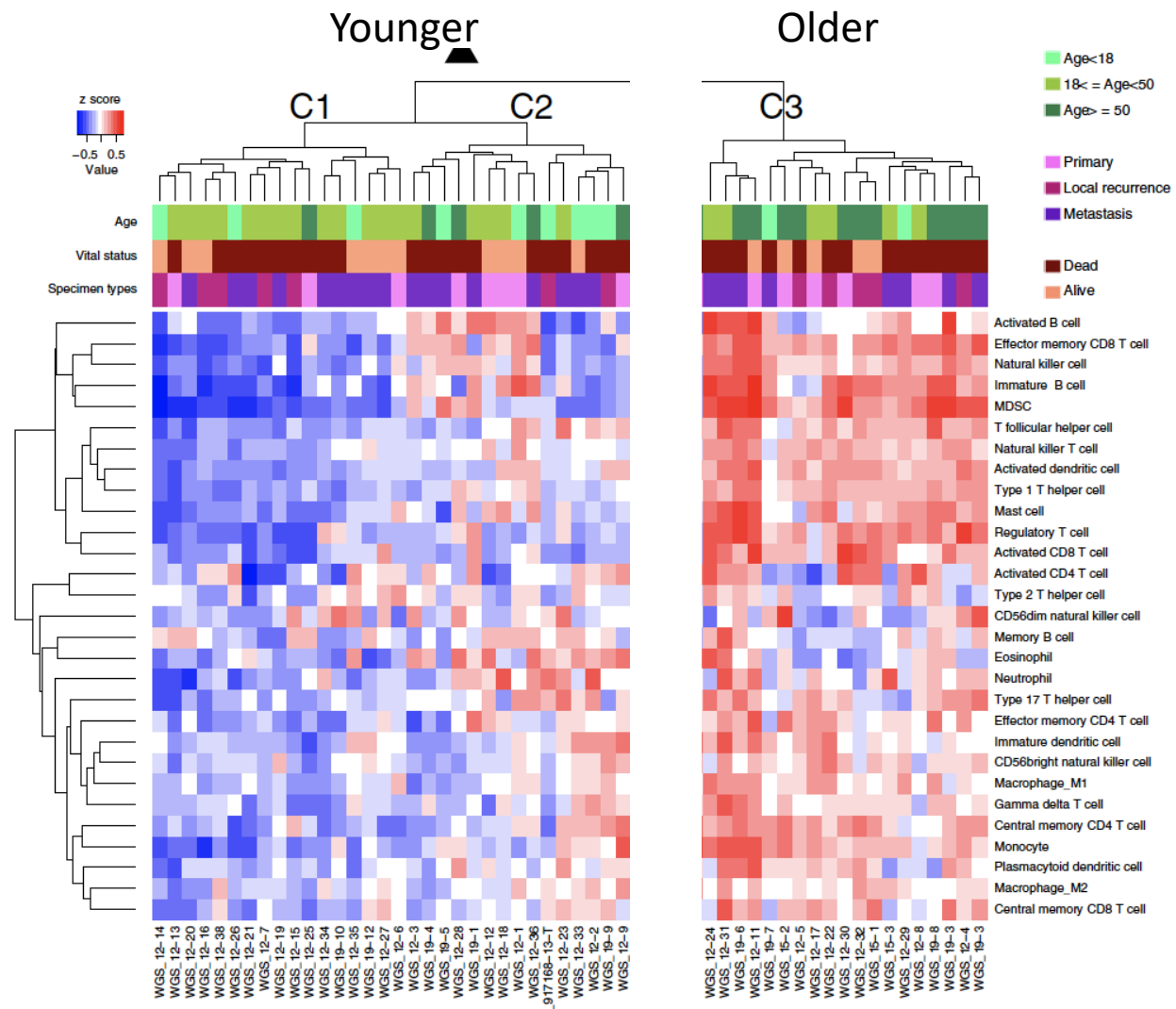


Wu CC, Beird HC, et al., et al. *Nat Com*. 2020

Complexity of the tumor microenvironment



Joyce JA, et al. *Science*. 2015



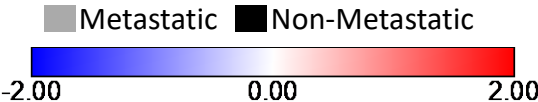
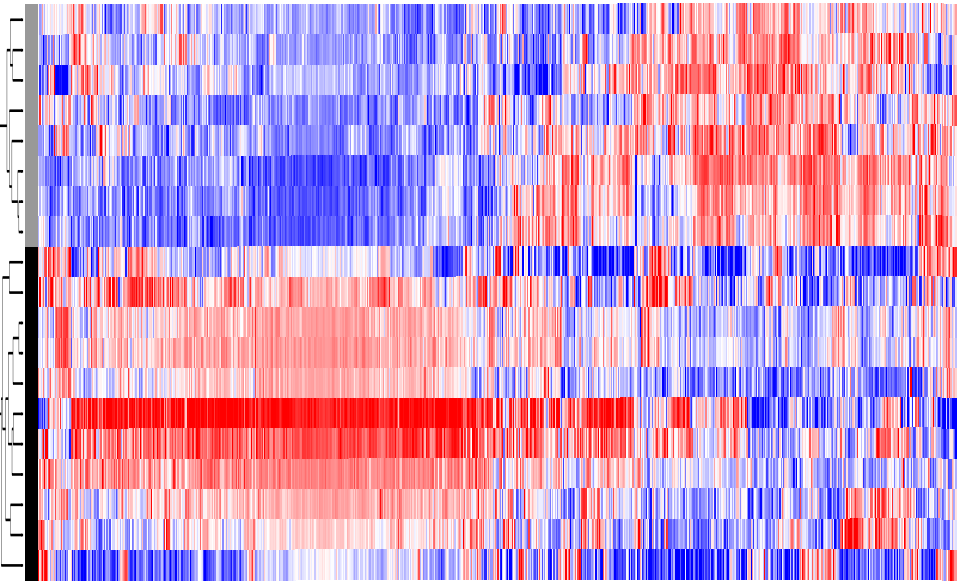
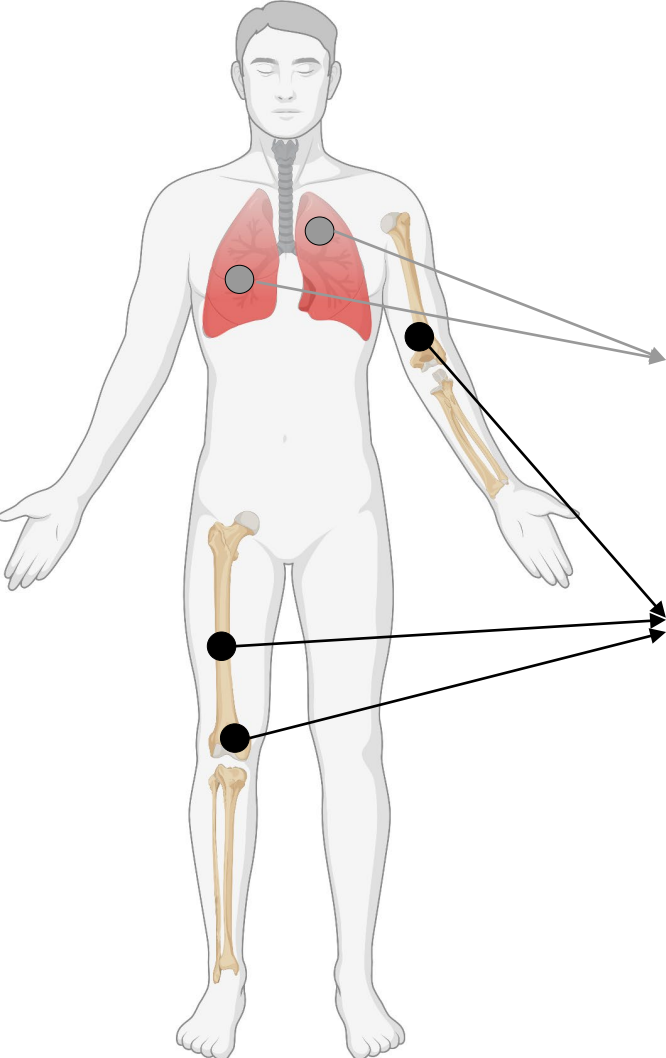
Wu CC, Beird HC, et al., et al. *Nat Com*. 2020

Gene expression profiling reveals distinct microenvironment and immuno-oncology landscapes in pediatric OS

Targeted transcriptional profiling of the tumor microenvironment reveals lymphocyte exclusion and vascular dysfunction in metastatic osteosarcoma

Laurie Sorenson^a, Yanfen Fu^b, Tressa Hood^b, Sarah Warren^b, and Troy A. McEachron^{c,d}

^aDepartment of Translational Genomics, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA; ^bNanoString Technologies, Inc., Seattle, WA, USA; ^cNorris Comprehensive Cancer Center, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA; ^dDepartment of Pediatrics, Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA

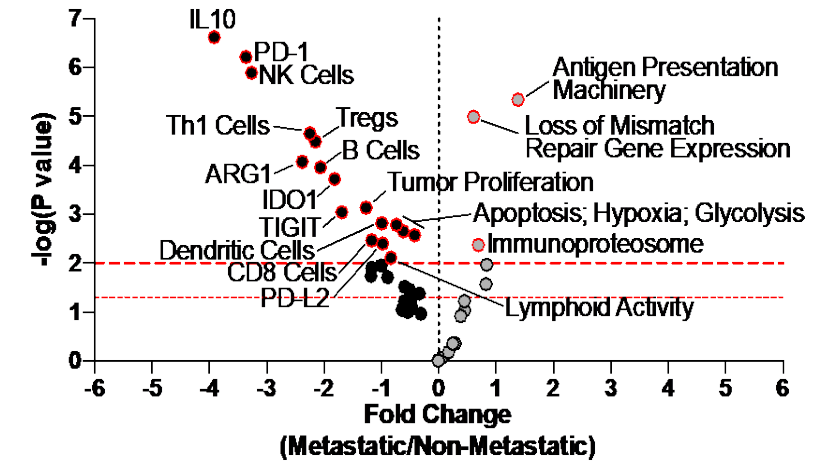
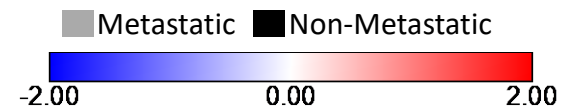
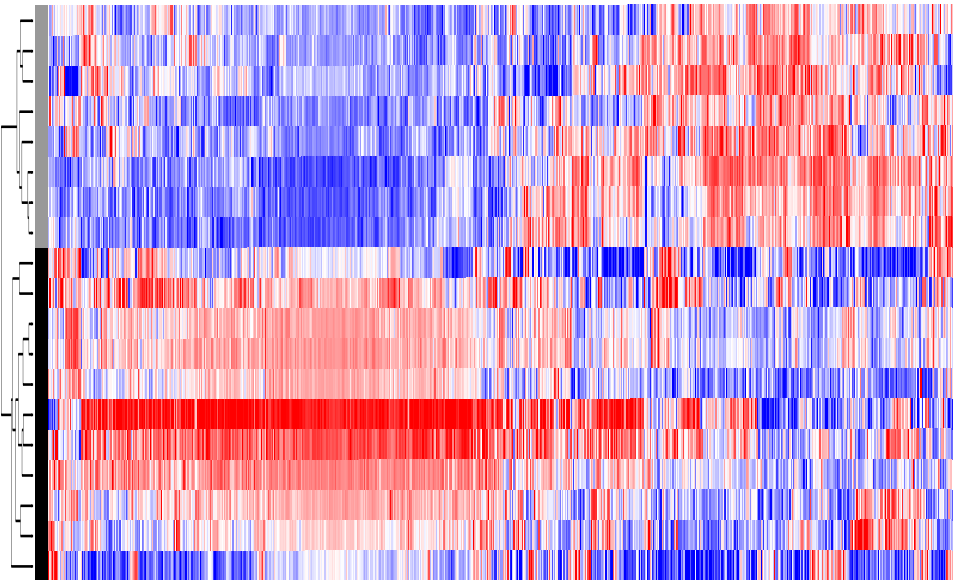
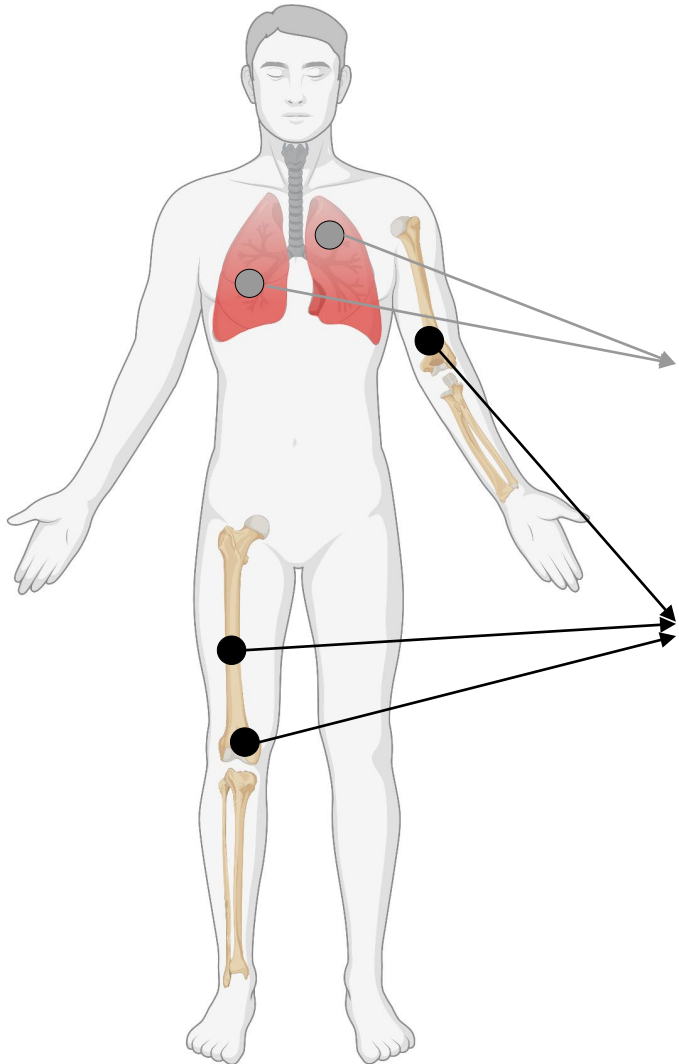


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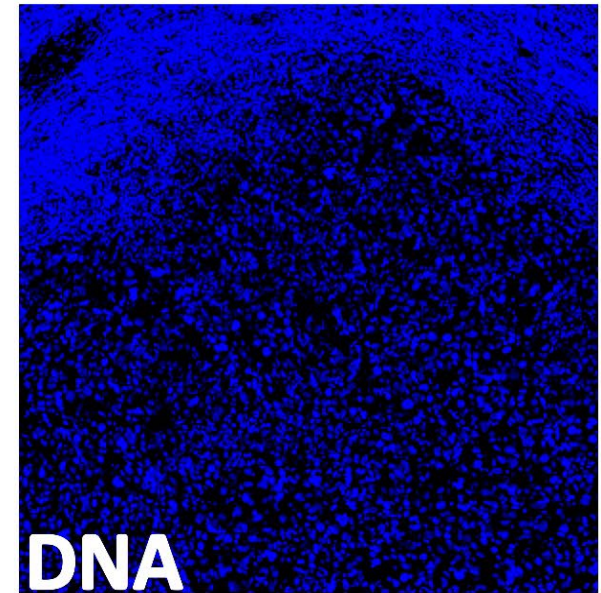
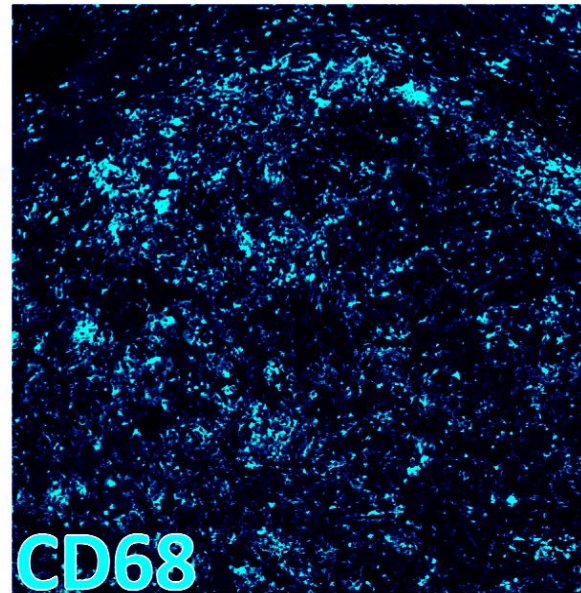
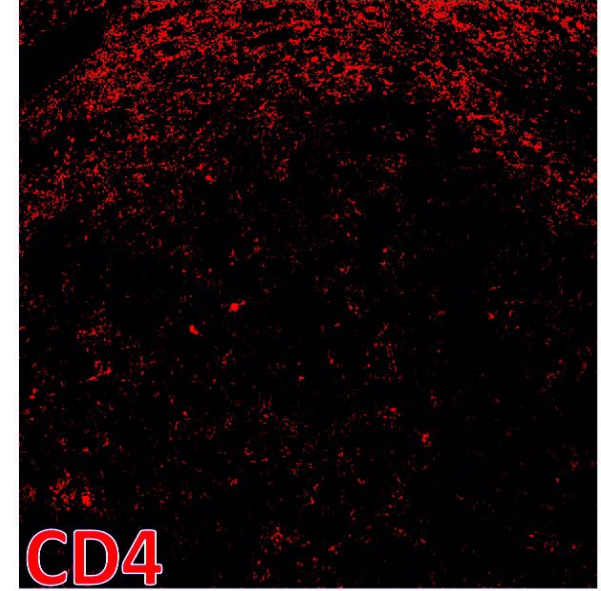
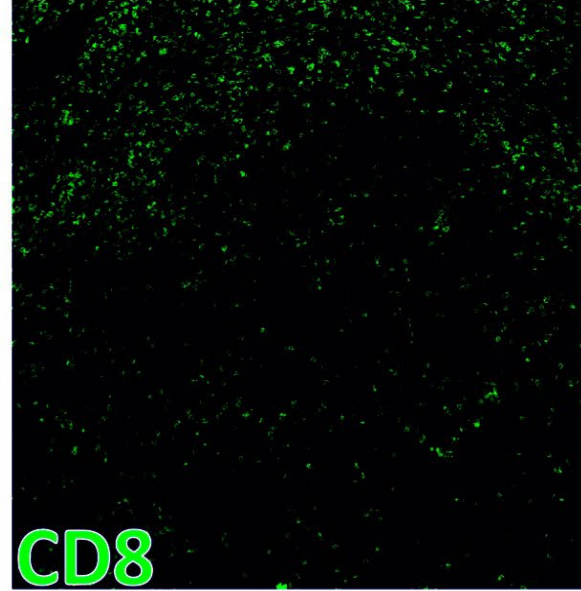
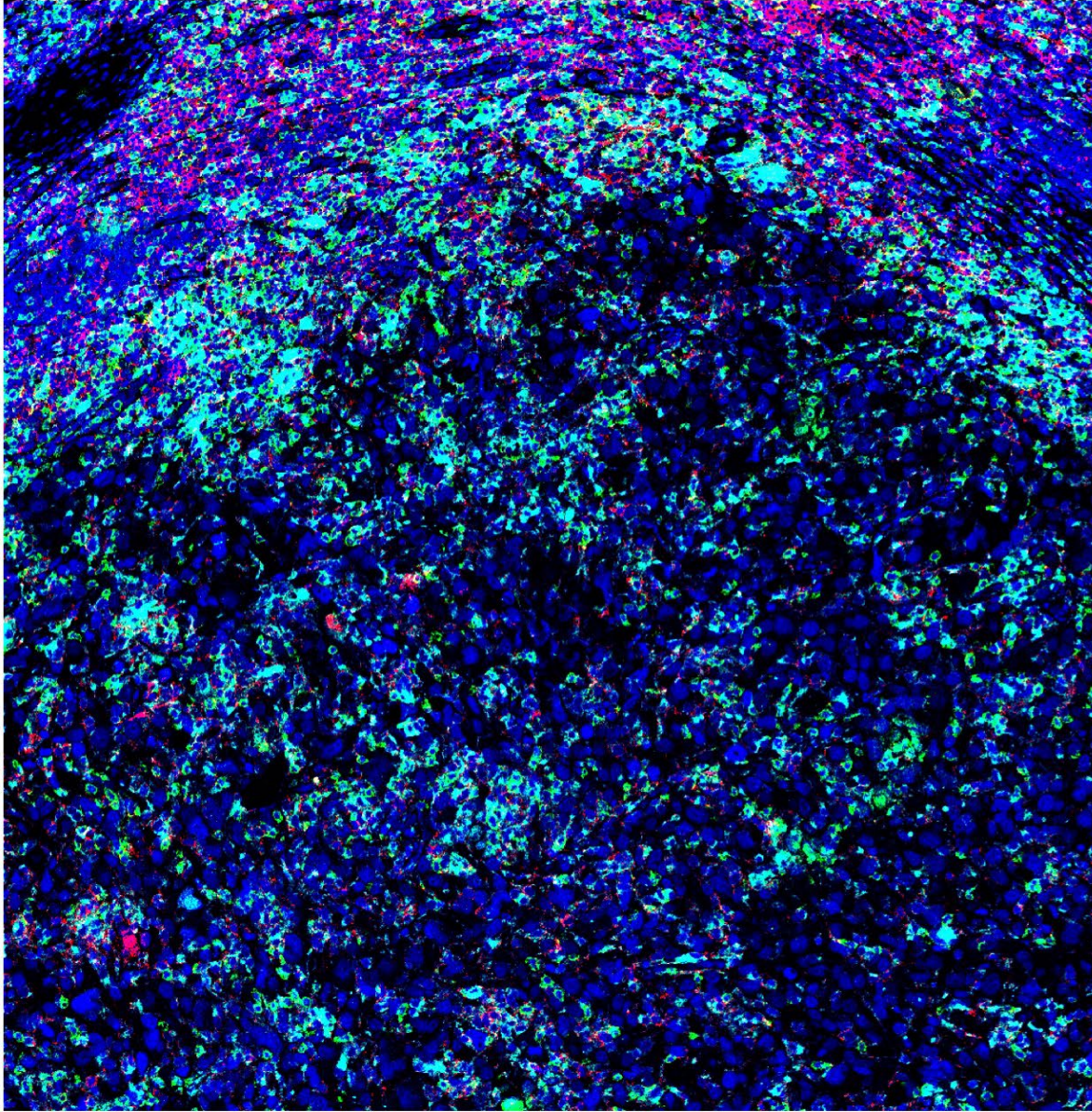
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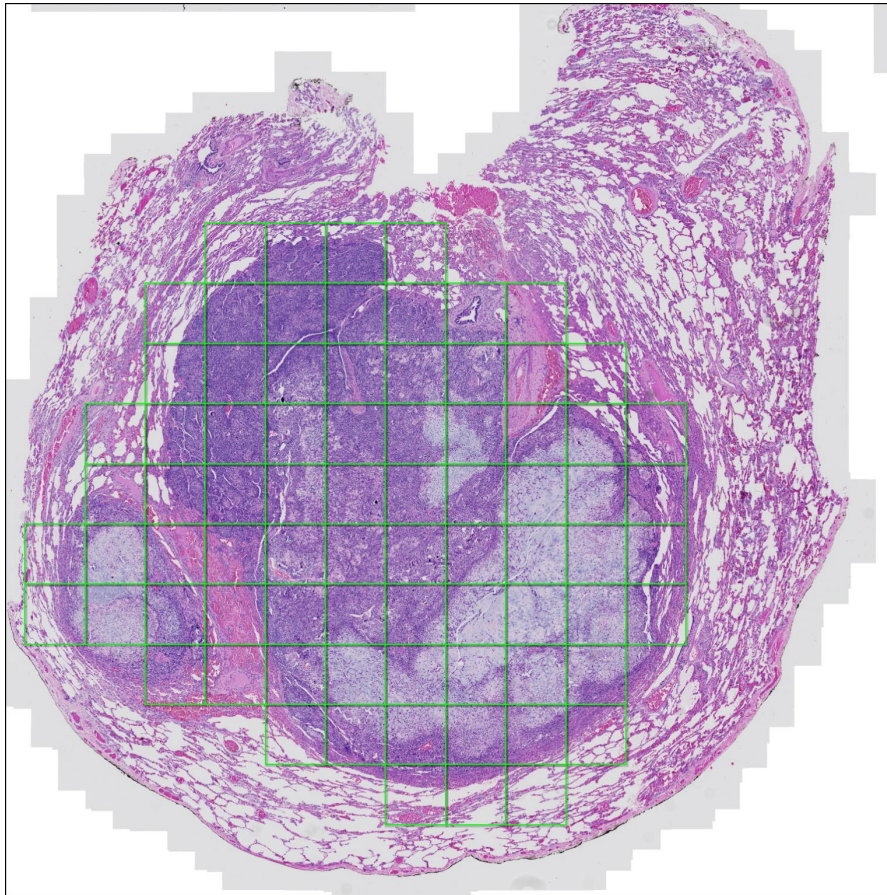


Lymphocyte exclusion in metastatic OS lesions



CD8 CD4 CD68 DNA

Spatial profiling of metastatic osteosarcoma specimens to reveal regional microenvironmental programs that promote lymphocyte exclusion



Whole Transcriptome Assay:
18,000 genes per ROI



GeoMx DSP

Imaging Mass Cytometry
36 antibody custom panel



In progress