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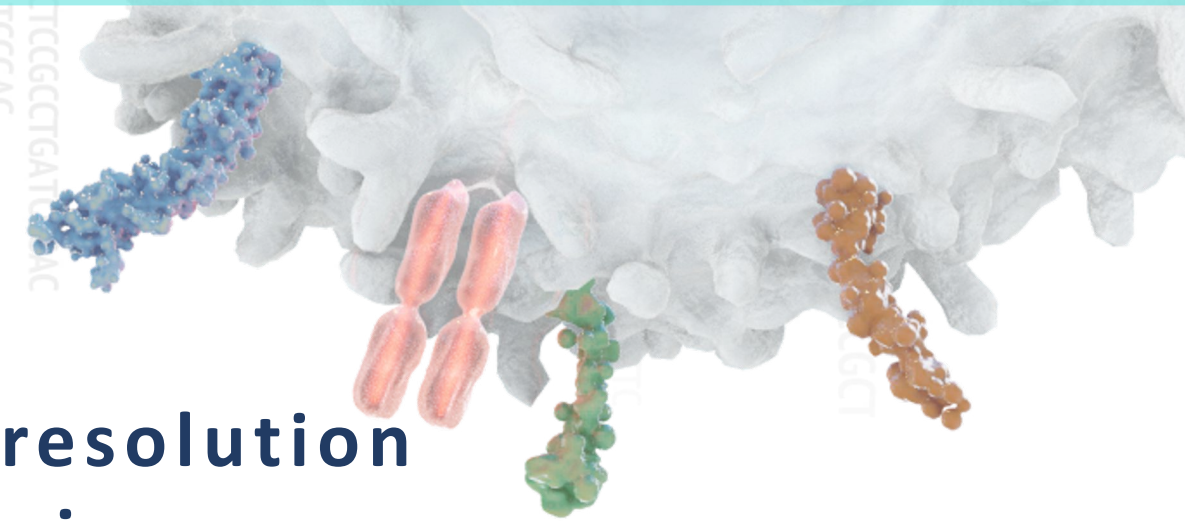

Exploring the immune-tumor microenvironment using high resolution single-cell spatial transcriptomics

Keystone Symposium, Decoding the Cancer Immunity Interactome. March 2022

Roy Granit, PhD

Senior Team Leader, Bioinformatics

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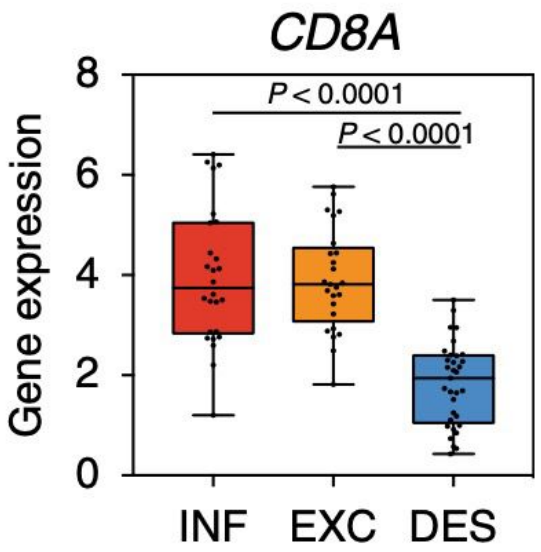
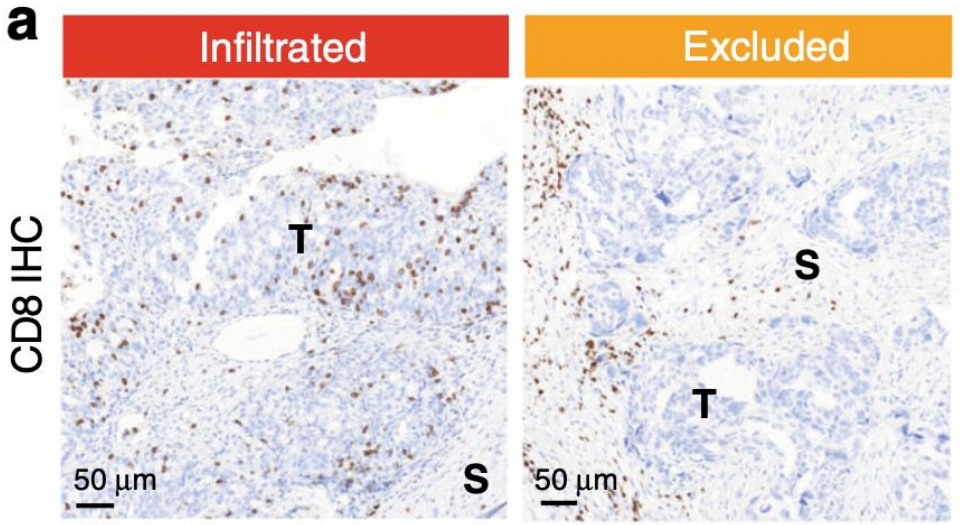
Spatial information provides critical insights in cancer research

The number of CD8 T-cells is not significantly changed between infiltrated and excluded – but their spatial localization is different





Desbois et al. 2020

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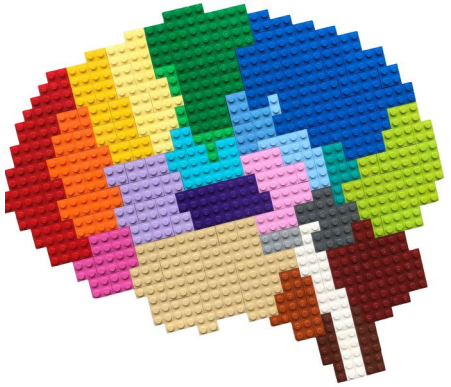
Spatial information provides critical insights in cancer research

New technologies enable probing the composition of the tumor microenvironment (TME) in high-resolution, spatially resolved manner

Bulk RNAseq

Single cell

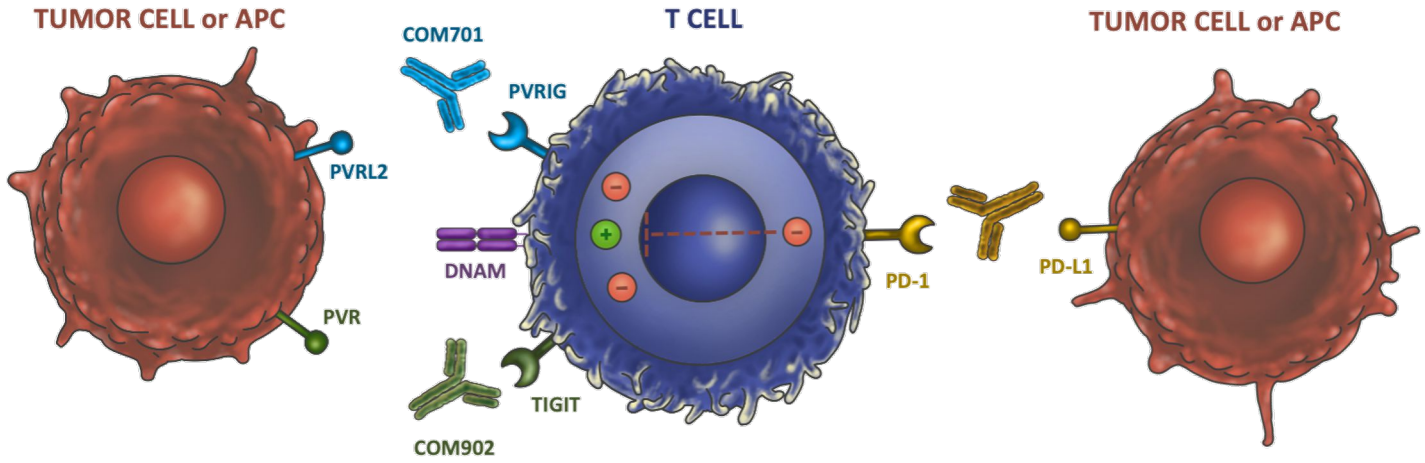
Spatial omics



Credit: Bo Xia

DNAM axis potential to be a game changer in the fight against cancer

PVRIG may be the missing piece when current checkpoint inhibitors fail



Alteber et al. 2021

Support combination approach to overcome immunotherapy resistance

- PVRIG and TIGIT discovered by Compugen's discovery platform
- DNAM axis – two parallel and complementary inhibitory pathways (PVRIG & TIGIT)
- Potential intersection between PVRIG/TIGIT and PD-1 pathway
- PVRIG is unique in generating new waves of T cells to infiltrate the TME
- PVRL2 broadly expressed in PD-L1 high and low tumors

Compugen is testing combinations of treatments targeting DNAM-1 axis members and PD-1 in the clinic

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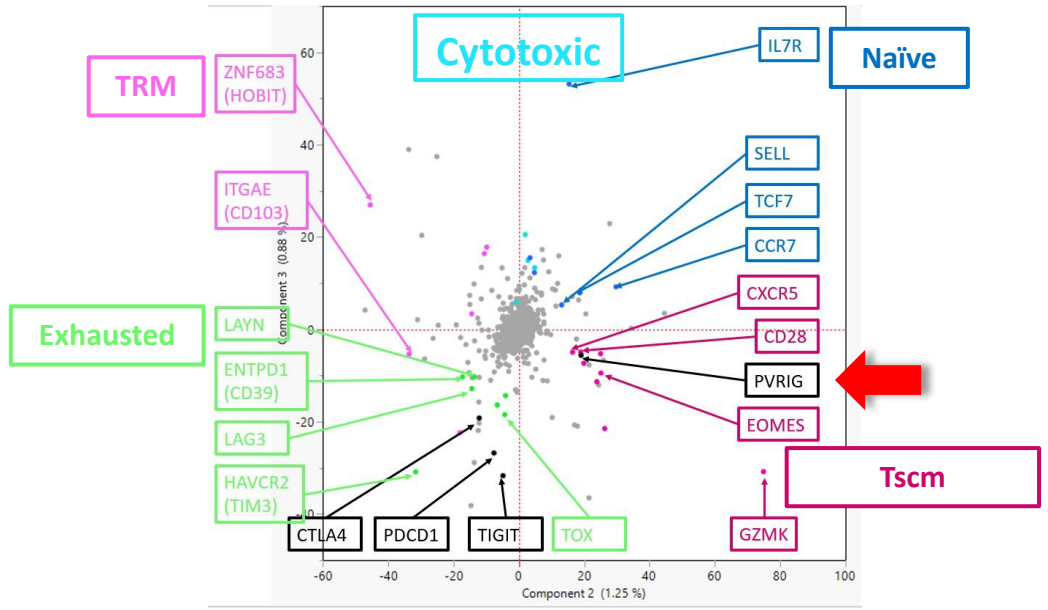
Expression pattern of PVRIG and PVRL2

PVRIG uniquely clusters with early differentiated/Tscm genes

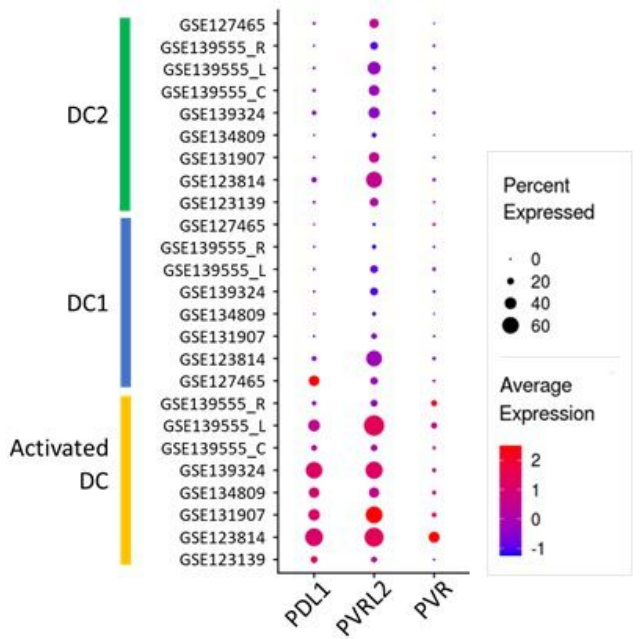
PCA Analysis of CD8+ T cell genes, NSCLC



GSE99254_NSCLC dataset internally analyzed

PVRL2 is dominant across DC subtypes

scRNA across cancer datasets



PVRIG blockage has potential for enhanced Tscm activation, expansion and generation of effector T cells

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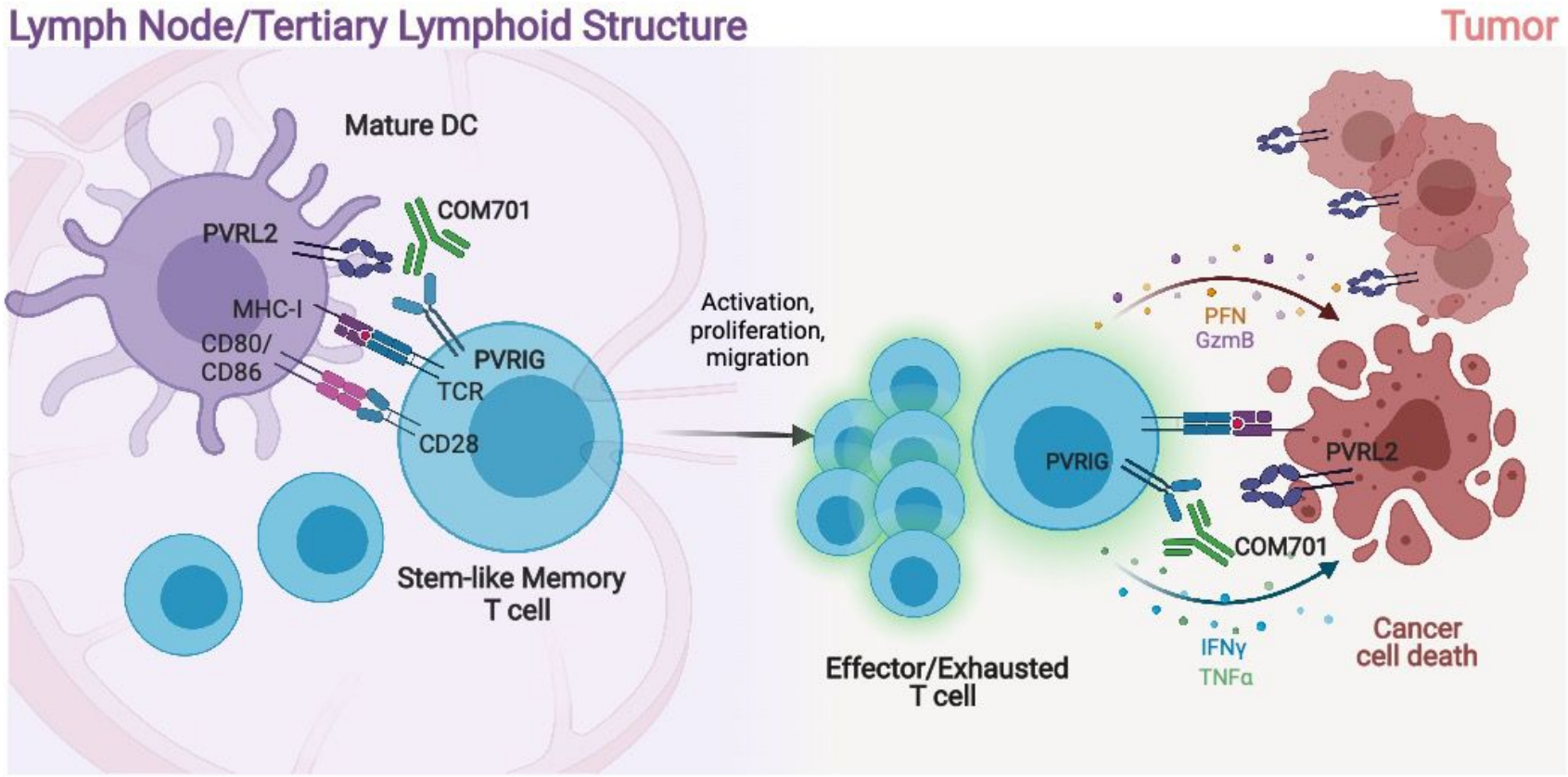
Hypothesis regarding DNAM-1 activity in the TME



Alteber et al. SITC 2021

PVRIG blockade may enhance interaction and activation of Tscm by DCs in PD-L1^{low} non-inflamed tumor types

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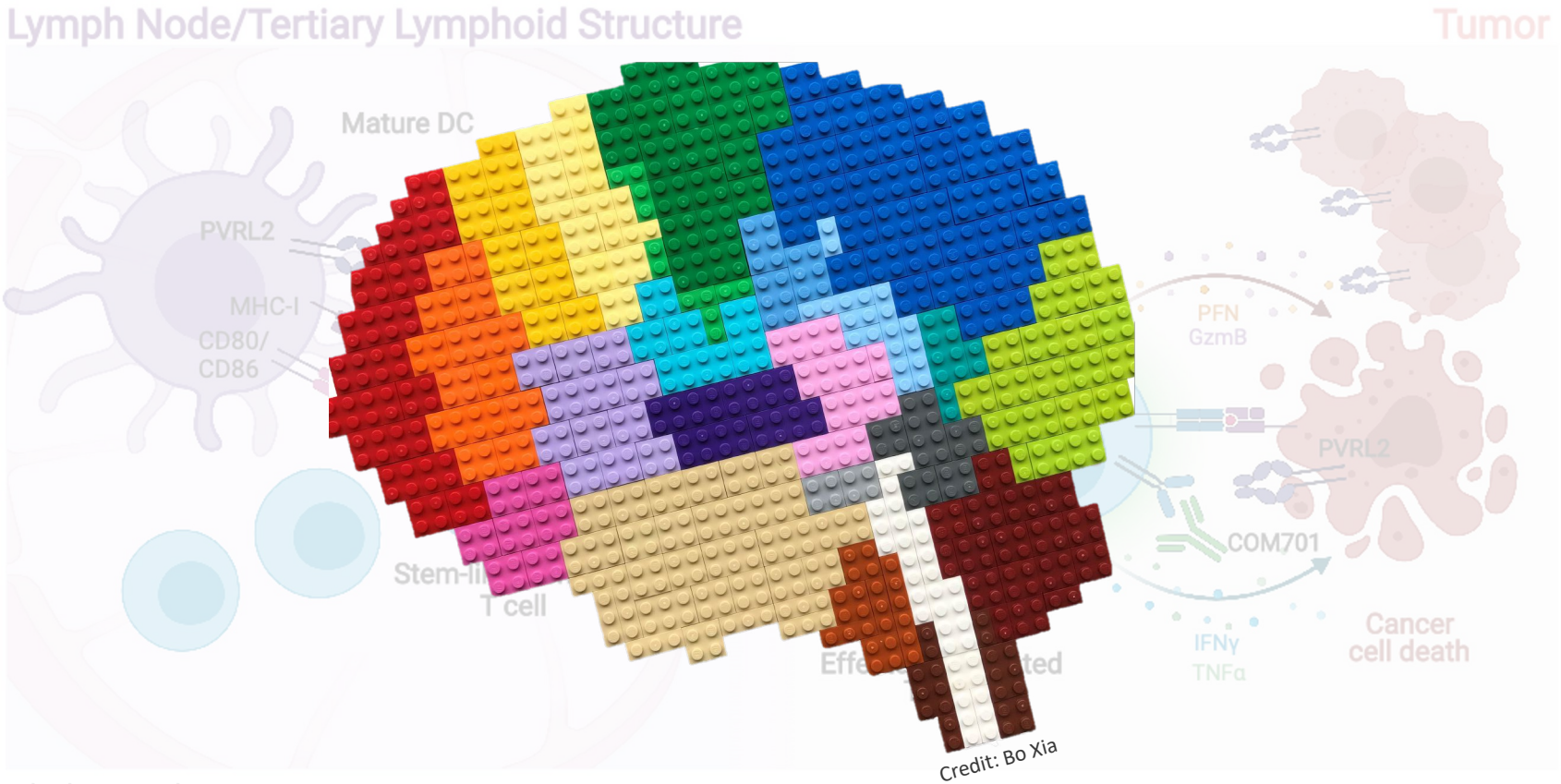
Hypothesis regarding DNAM-1 activity in the TME



To study this complexity in the TME we needed to adopt the latest innovations in spatial technologies

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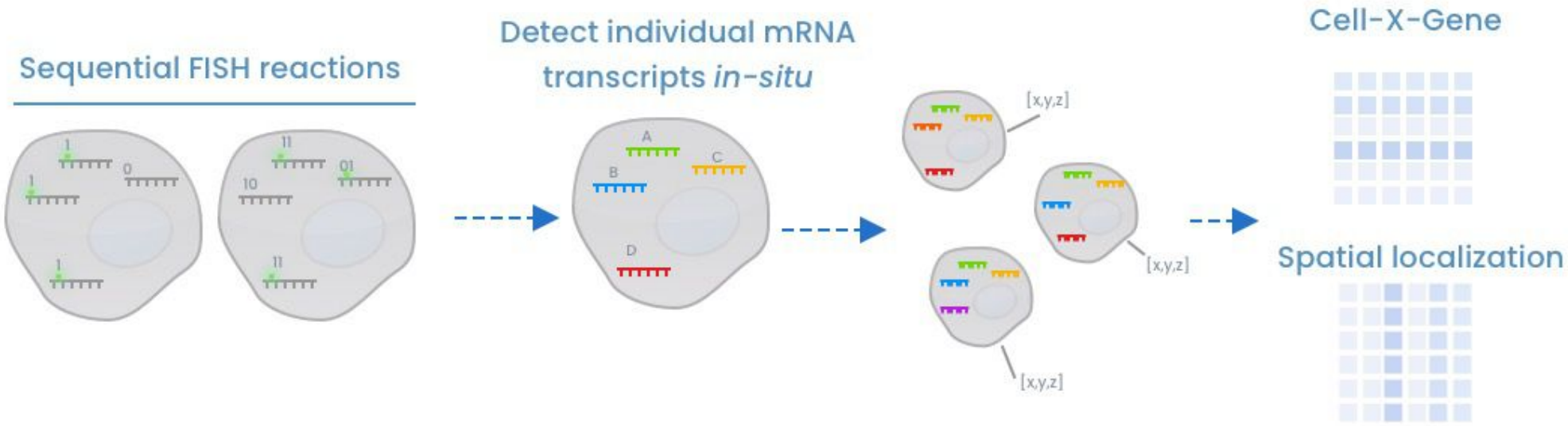
MERFISH (Multiplexed Error-Robust Fluorescent In Situ Hybridization)

vizgen



We employ this method with a panel consisting of 350 selected mRNAs in ovarian and colon cancer FFPE or frozen tissue samples

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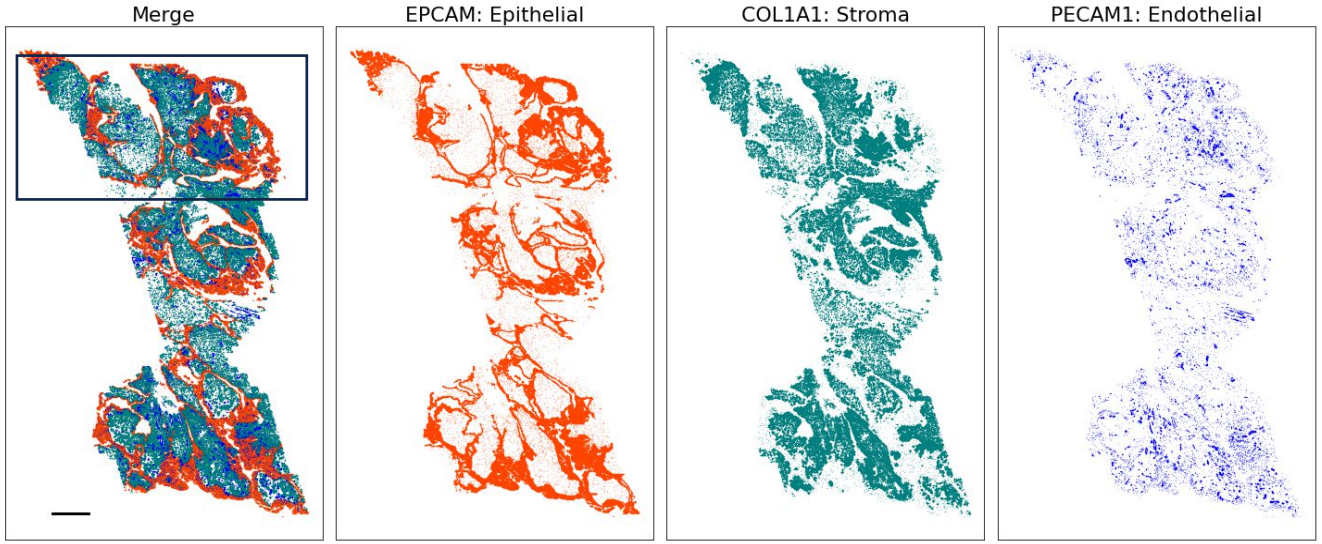
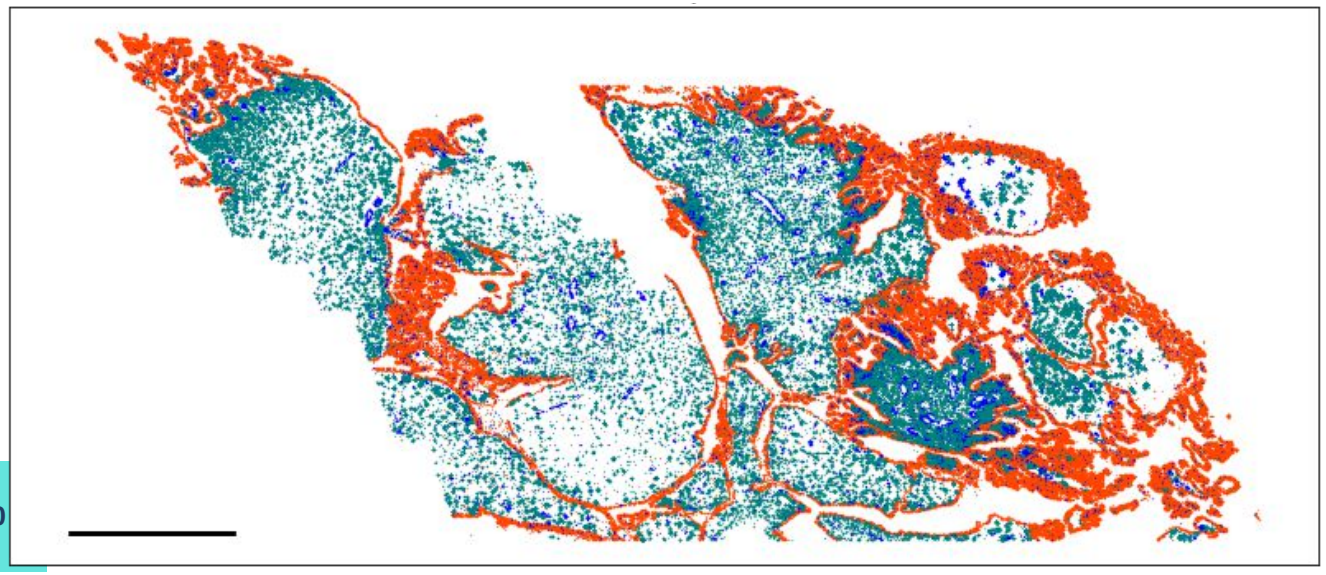
Spatial mRNA correlation provide means to study gene association

Ovarian Serous Carcinoma





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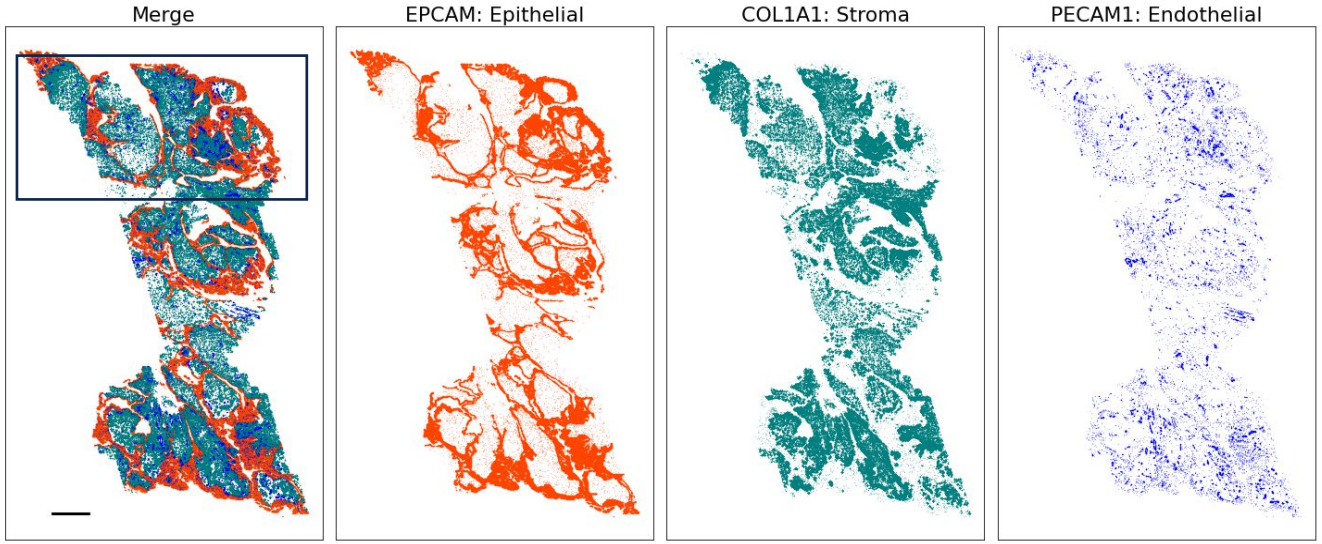
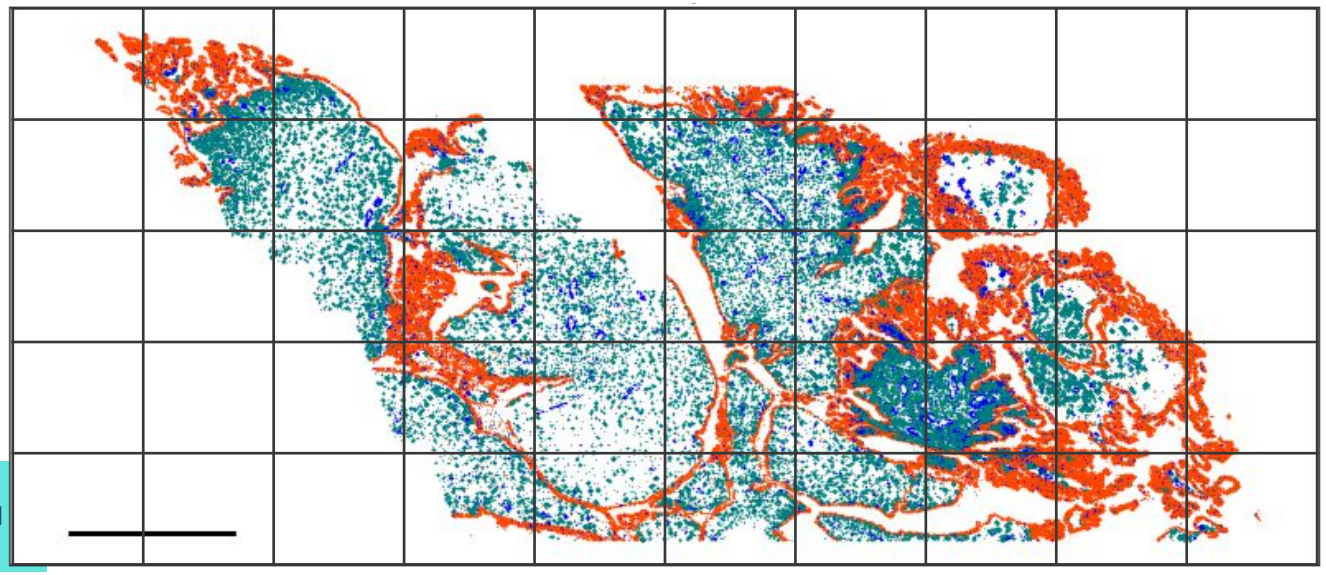
Spatial mRNA correlation provide means to study gene association

Ovarian Serous Carcinoma





Quantify probes per FOV

	Gene_1	Gene_2	Gene_3
FOV_1	12	0	9
FOV_2	1	22	5
FOV_3	123	23	247
FOV_4	65	17	72

Gene-gene spatial correlation

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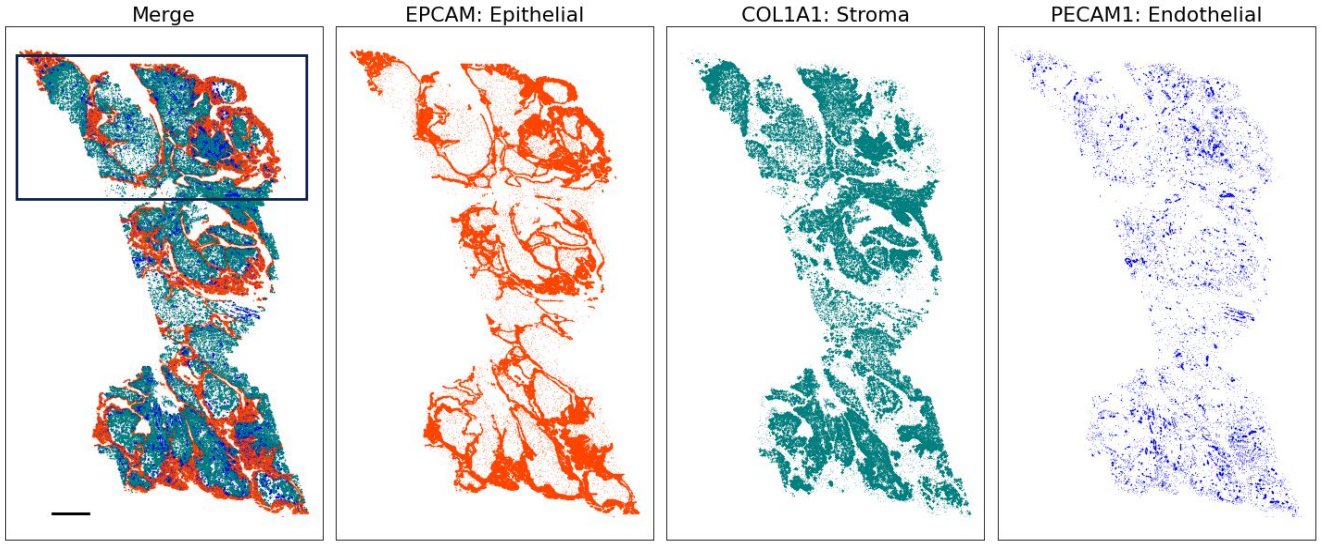
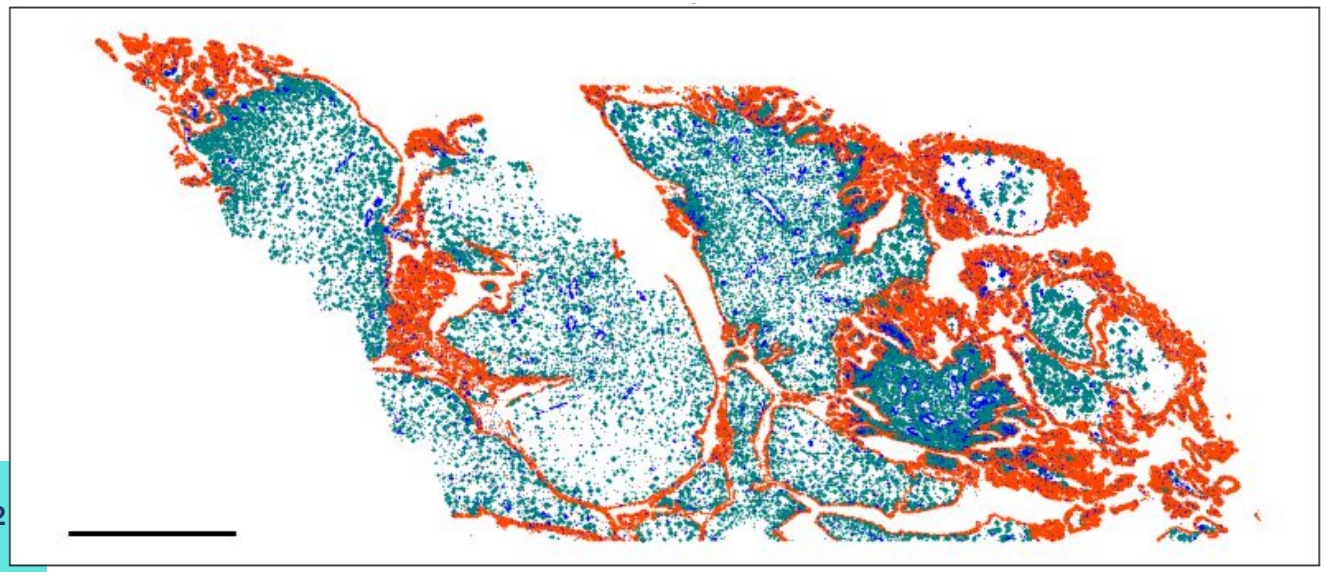
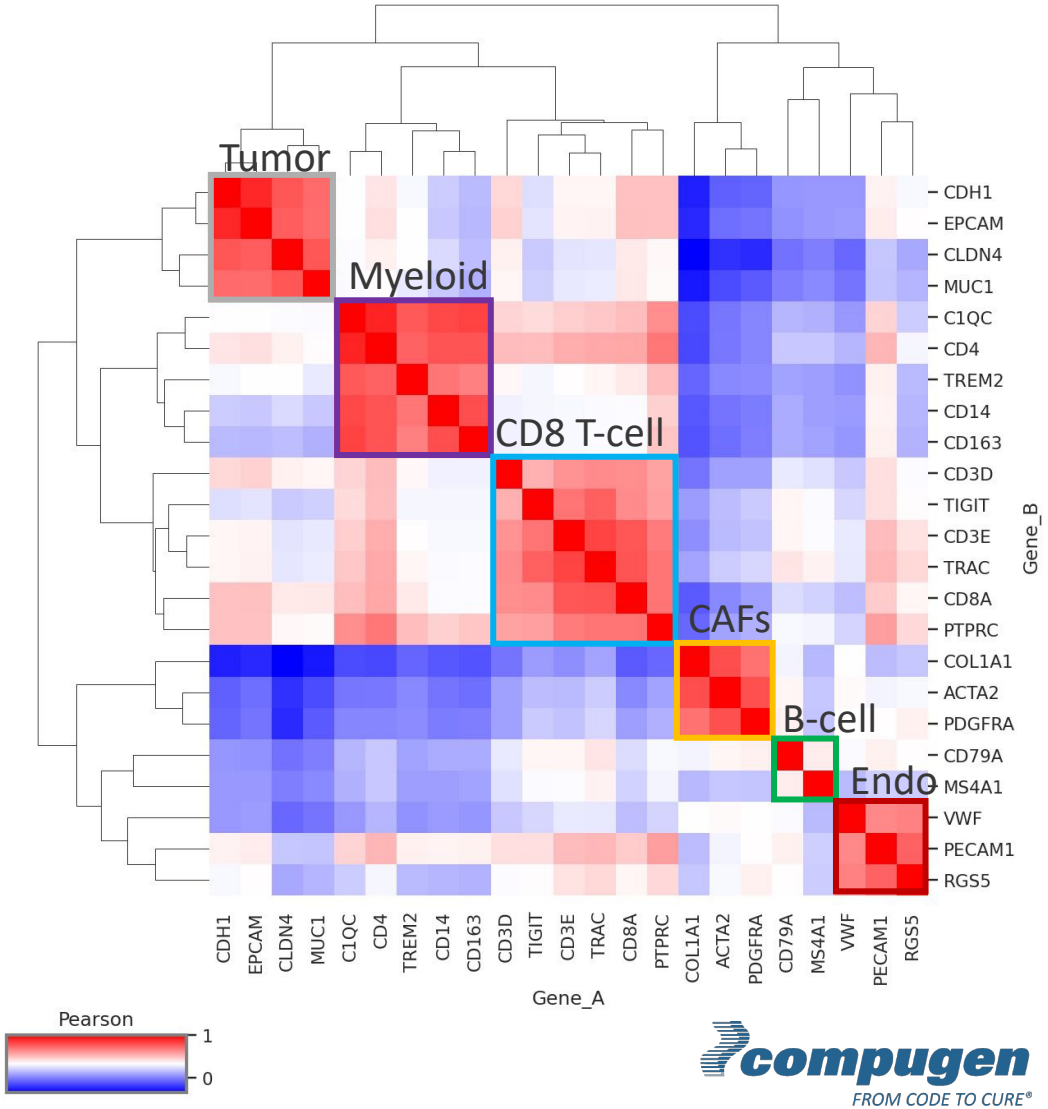
Spatial mRNA correlation provide means to study gene association

Ovarian Serous Carcinoma





Gene-gene spatial correlation (105 μm FOV)



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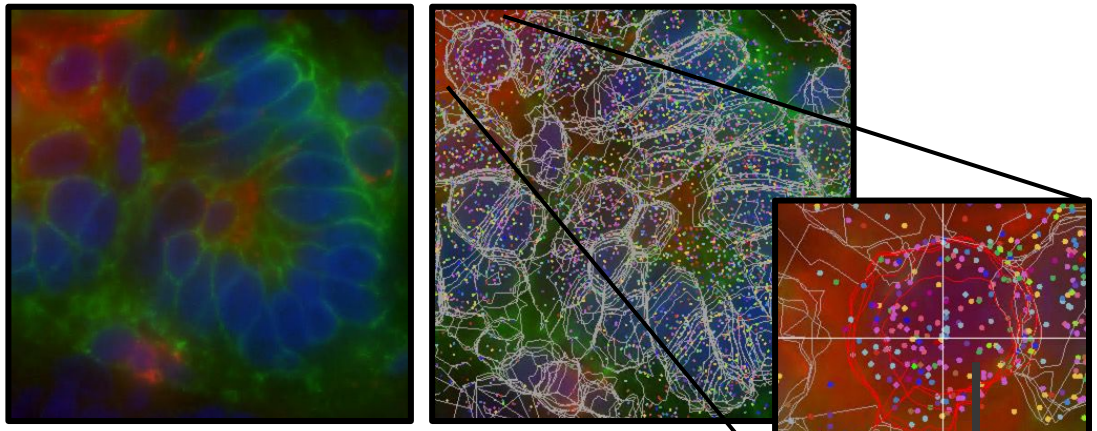
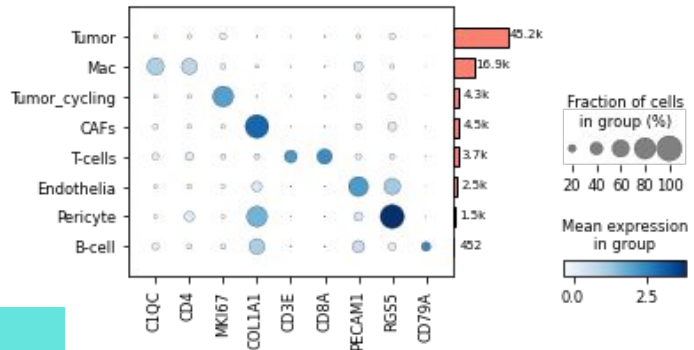
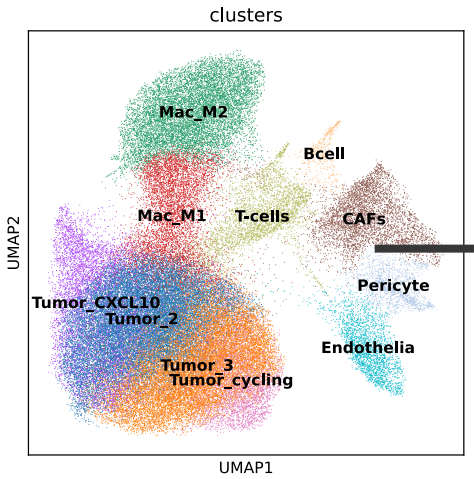
From probes to single cell spatial transcriptomics



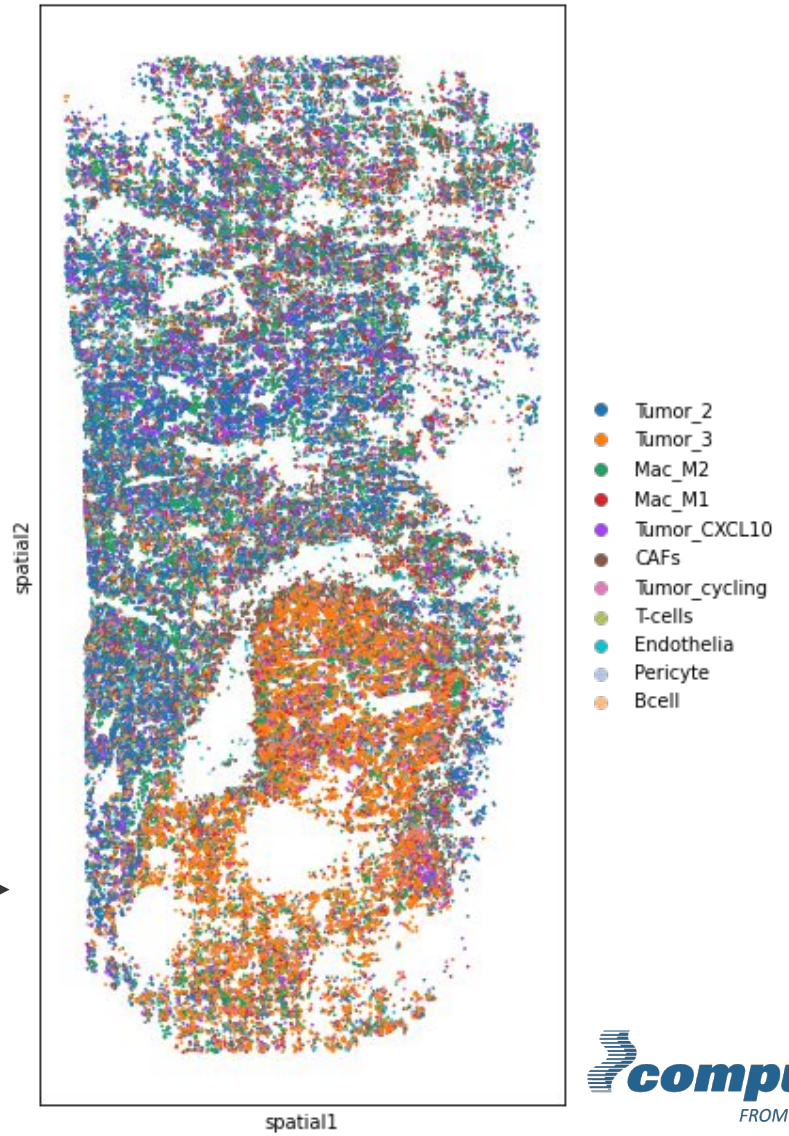
Single cell expression data





Project back to tissue

Single cell localization colored by cell-type



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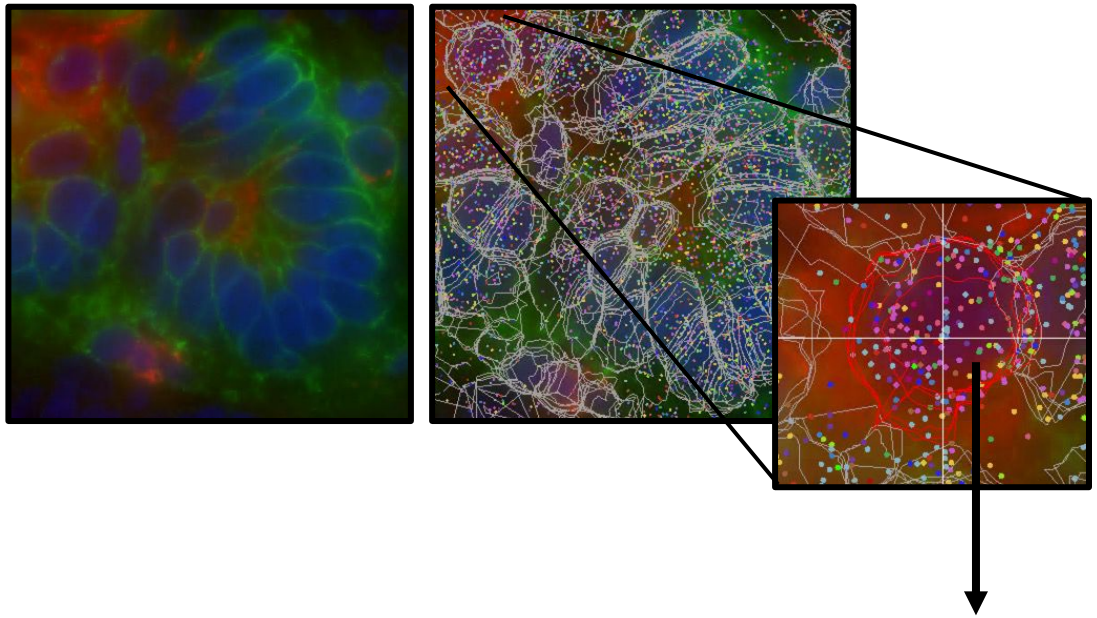
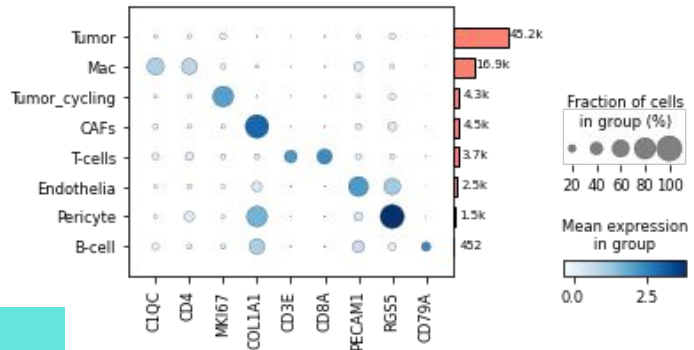
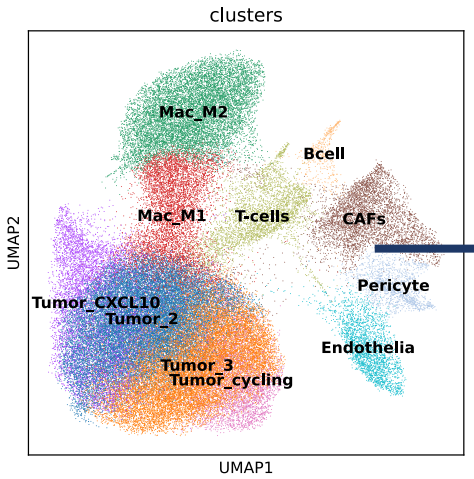
From probes to single cell spatial transcriptomics



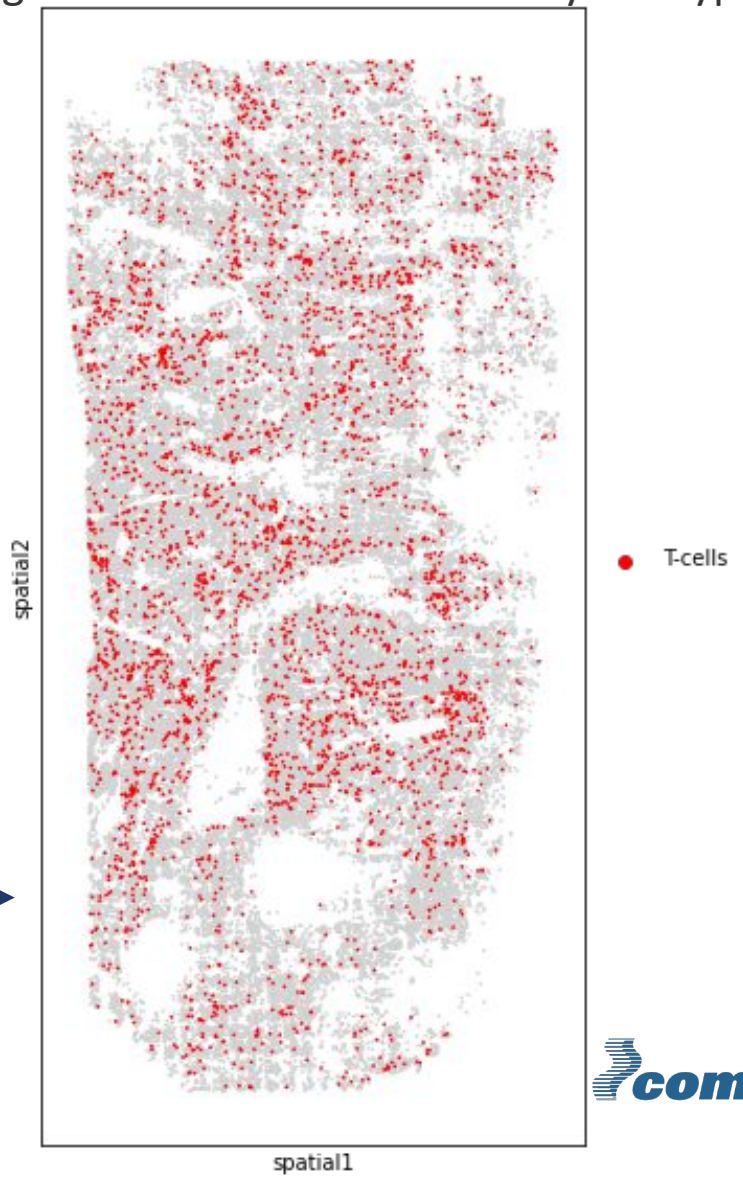
Single cell expression data





Project back to tissue

Single cell localization colored by cell-type



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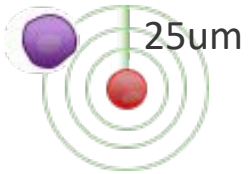
Profiling cellular neighborhood at the single cell level

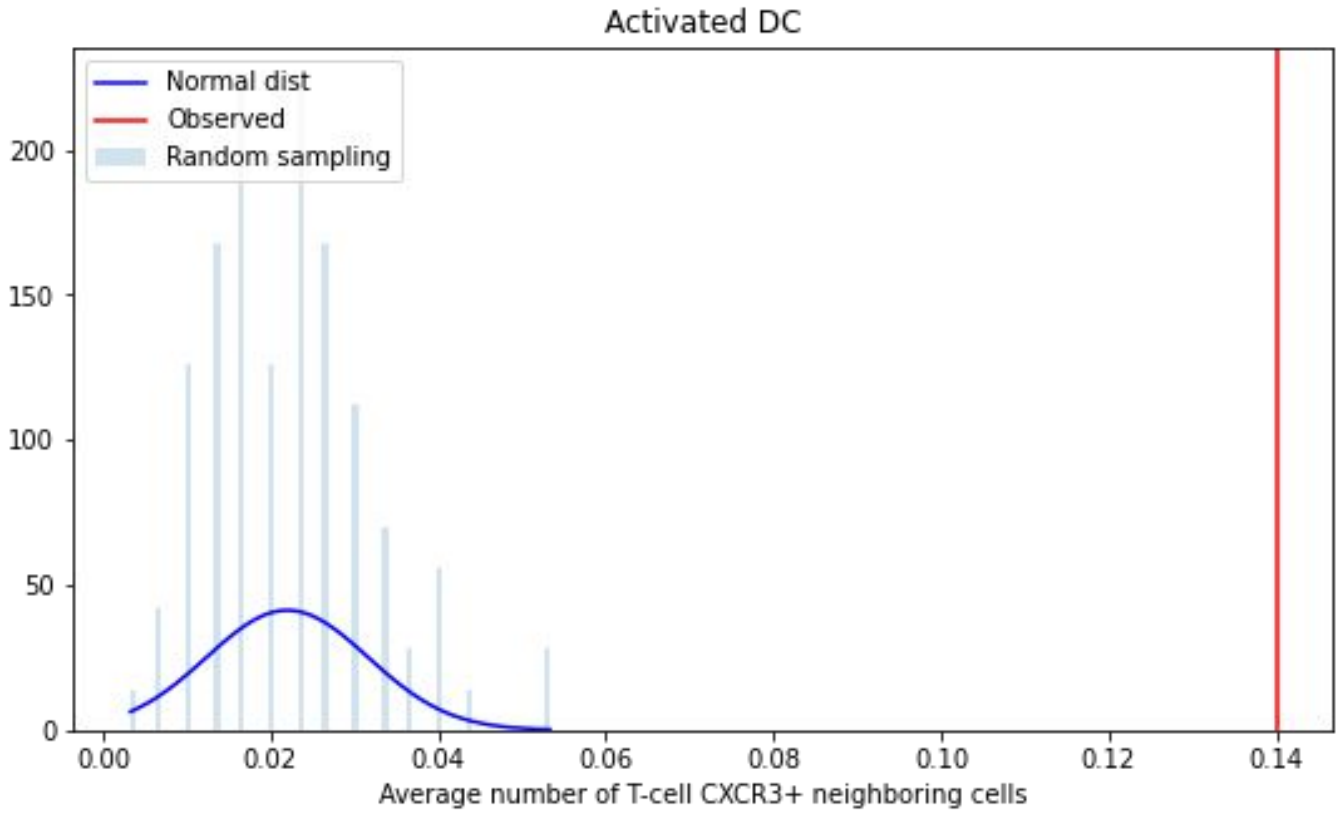
Ovarian tumor



Quantify neighboring cells to cell type of interest

↓

Compare to random sampling



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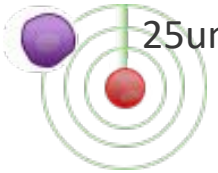
Profiling cellular neighborhood at the single cell level

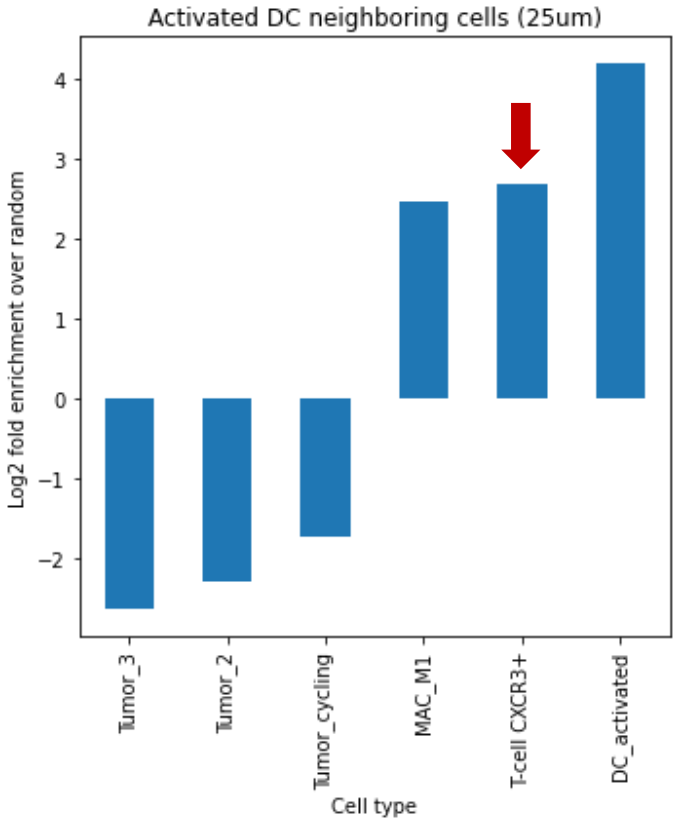
We confirm that Activated DCs that secrete CXCL10 are located next to T-cells that express the chemokine receptor CXCR3

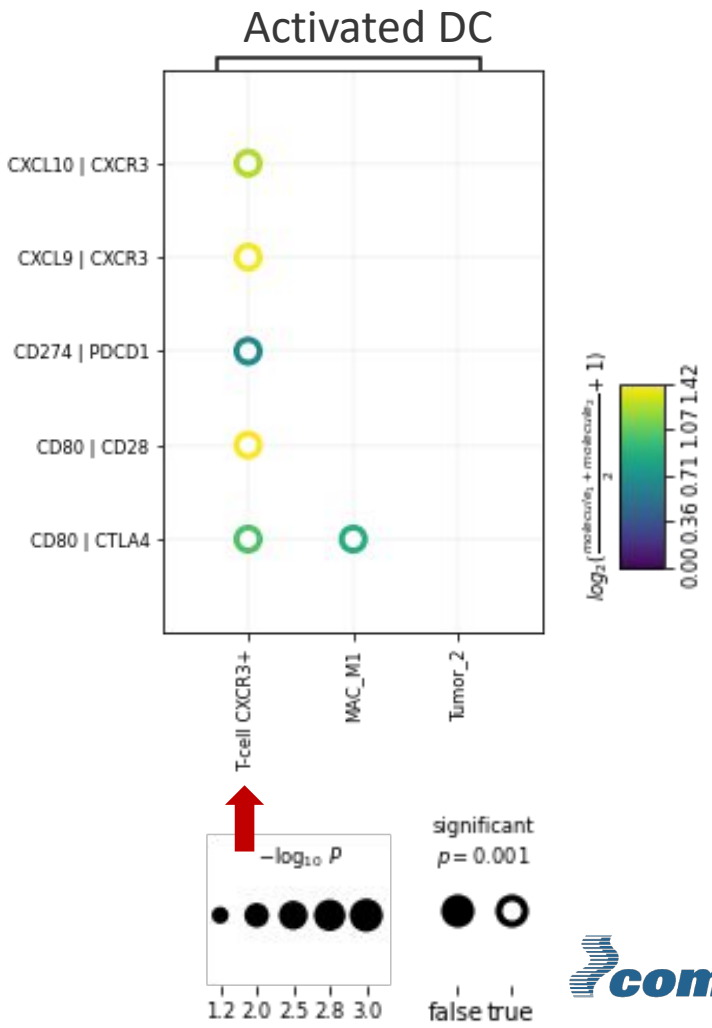
Ovarian tumor



Quantify neighboring cells to cell type of interest

Compare to random sampling





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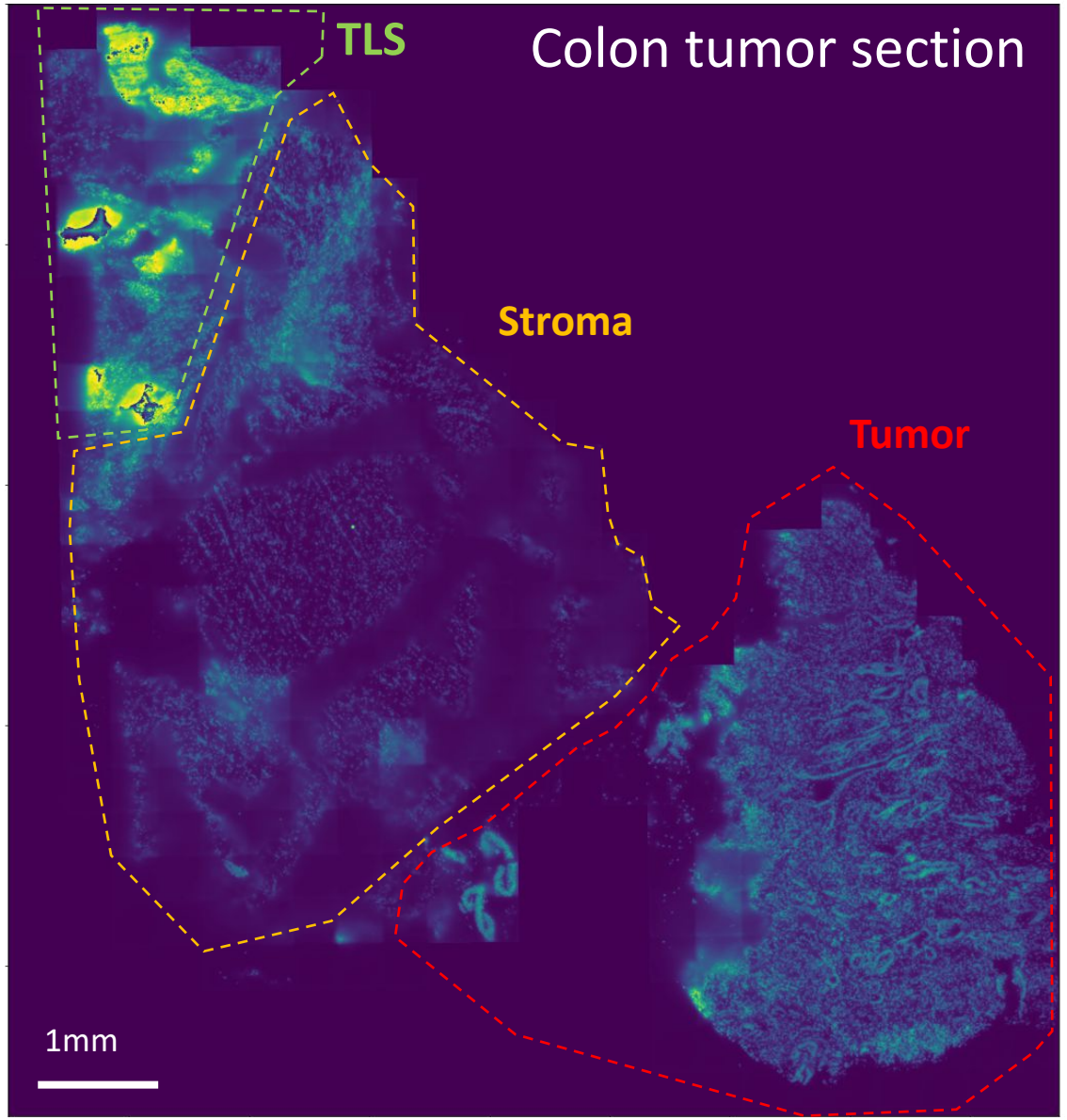
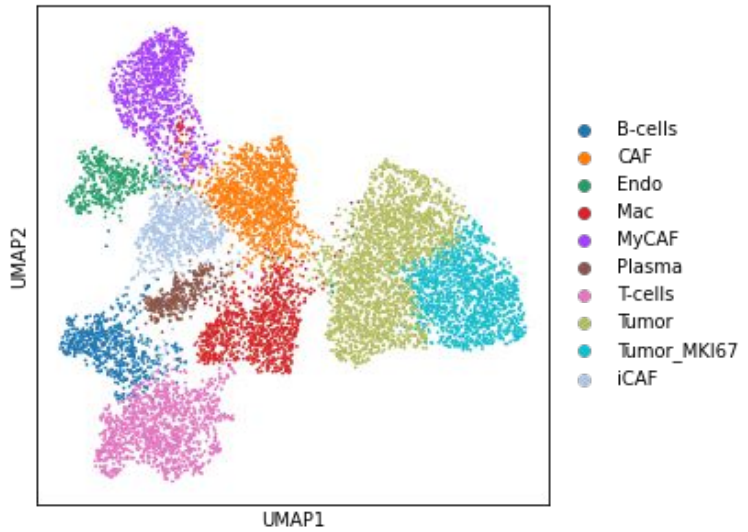
Analyzing Tertiary Lymphoid Structures(TLS) in CRC



Single cell clustering



Tertiary Lymphoid Structures are lymphoid structures in the tumor bed in which local T cell activation occur

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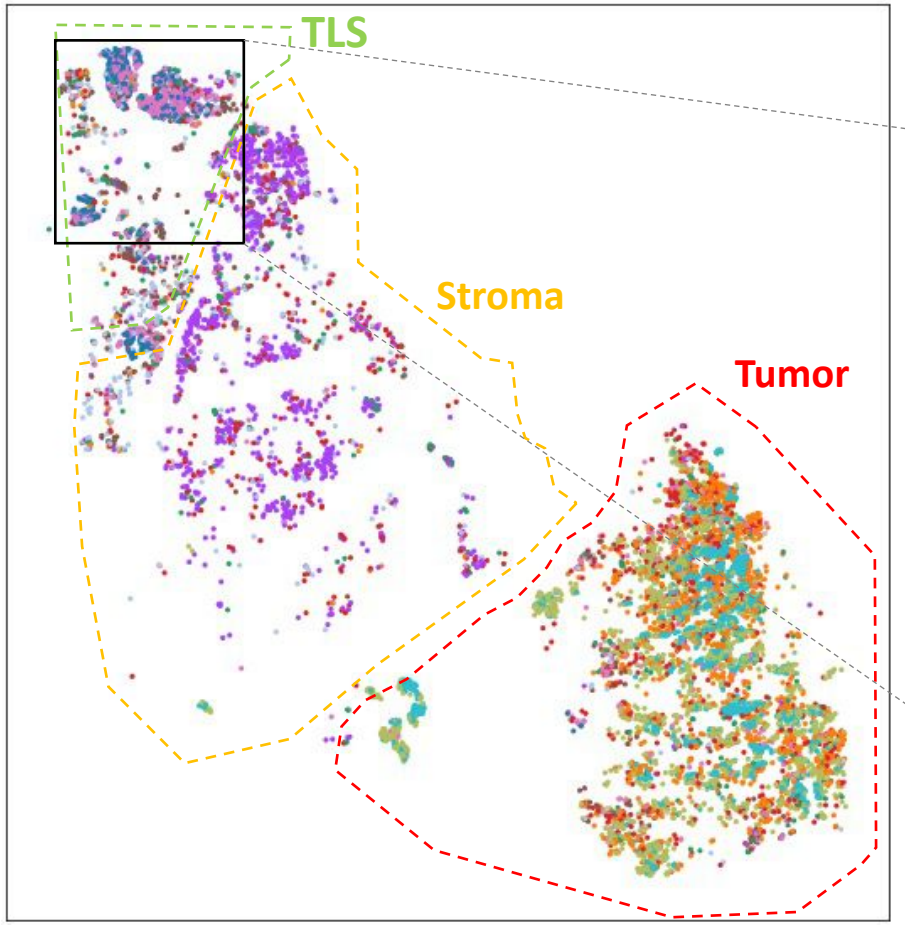
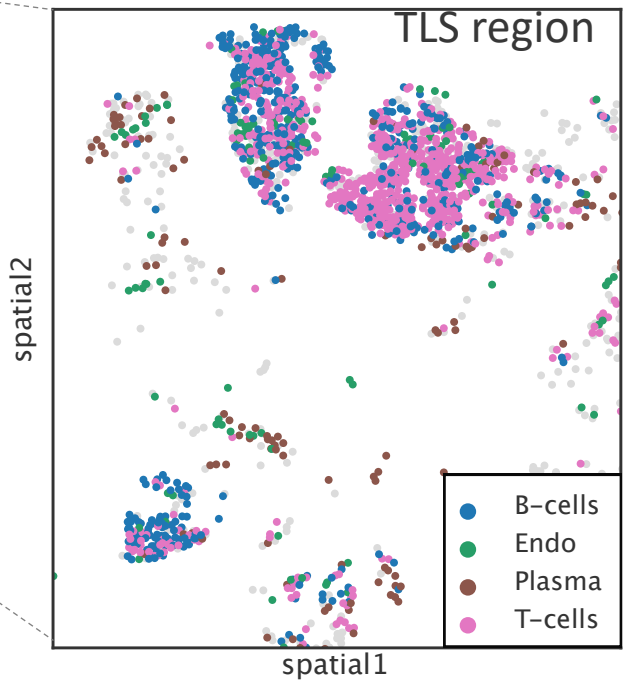
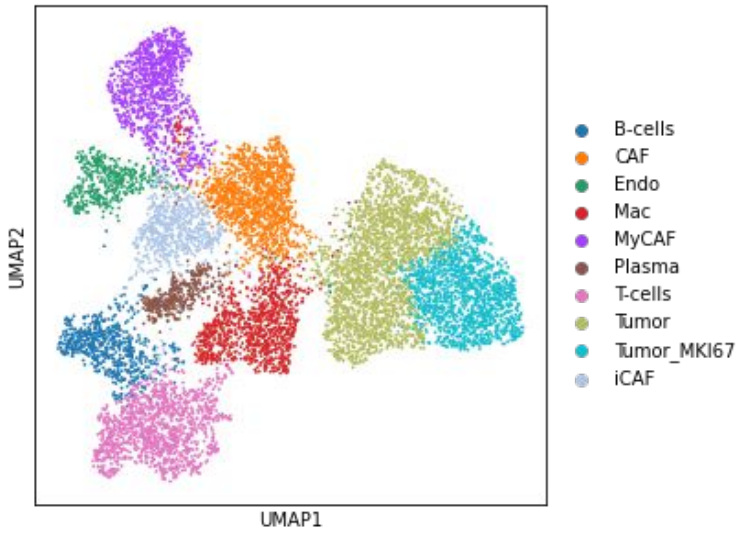
Analyzing Tertiary Lymphoid Structures(TLS) in CRC

Annotated cells *in-situ*





Single cell clustering



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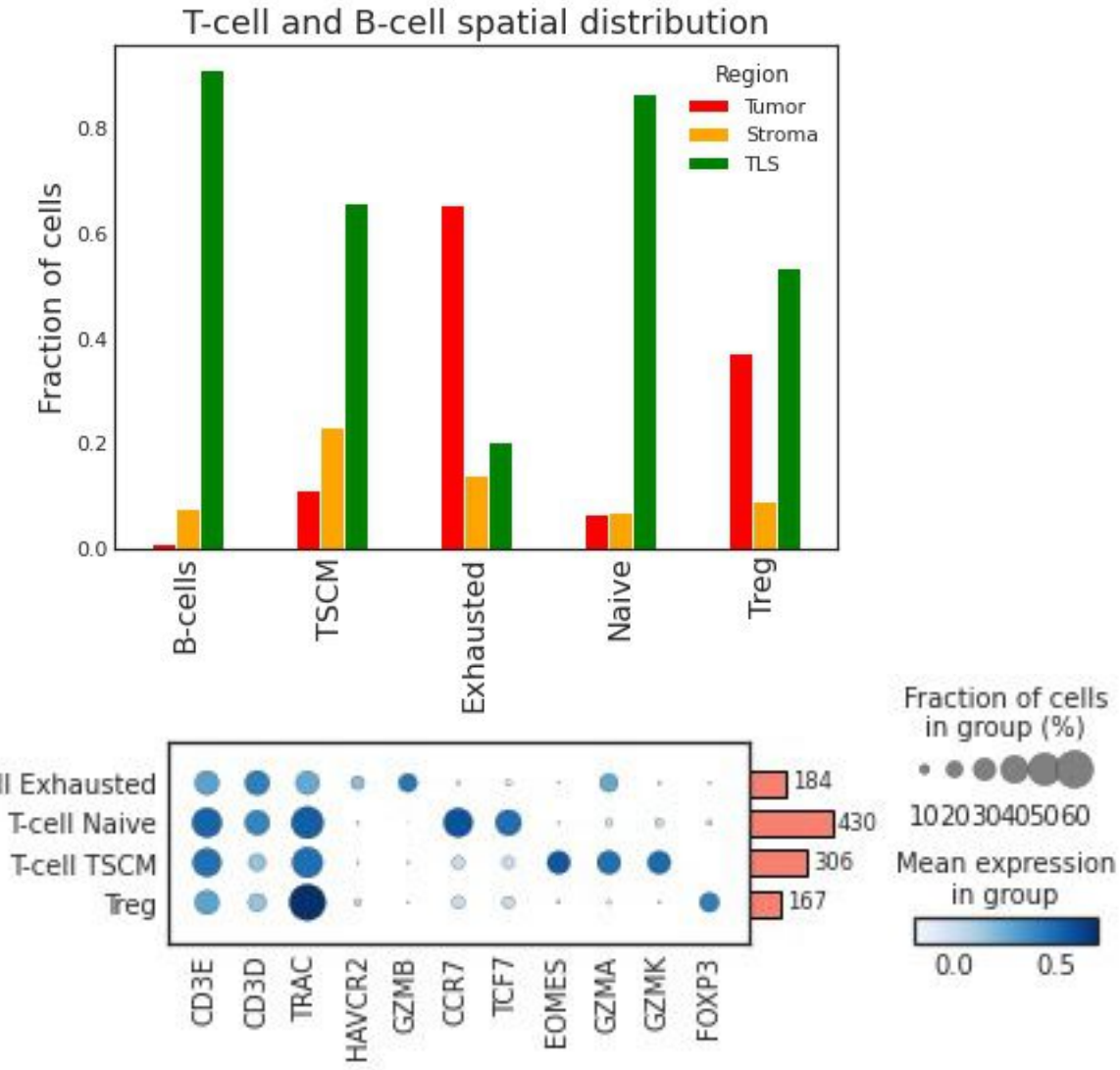
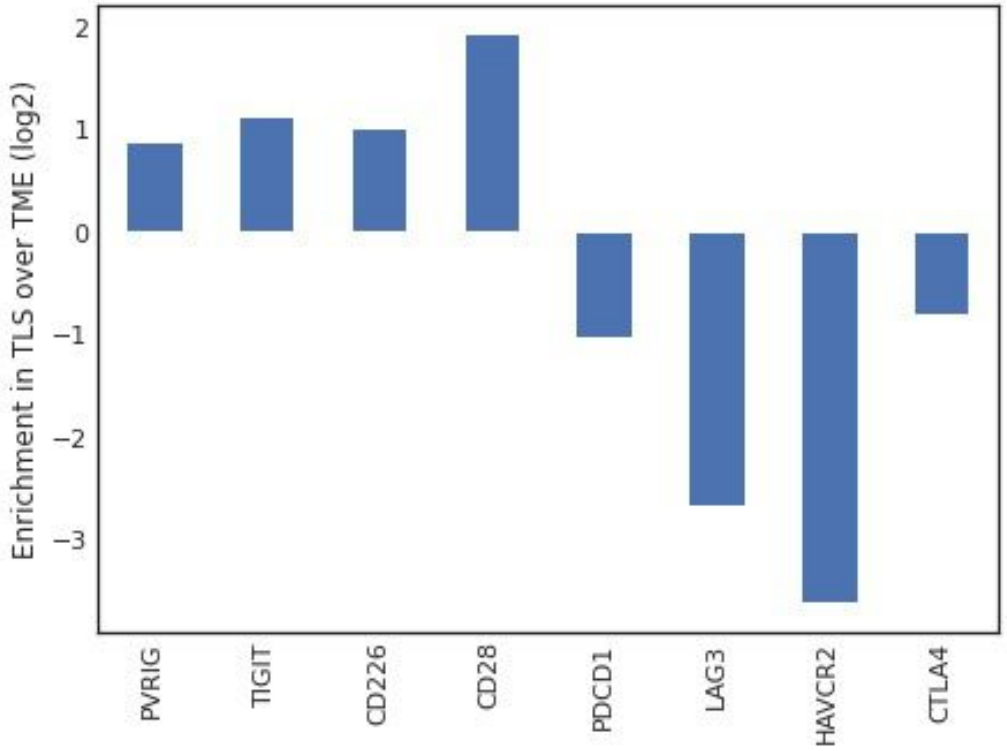
DNAM-1 axis show dominant presence in TLS region

TSCM cells localize to TLS while Exhausted localize to tumor region.





This data suggest that potential blocking of PVRIG and TIGIT might enhance T cells proliferation in the tumor

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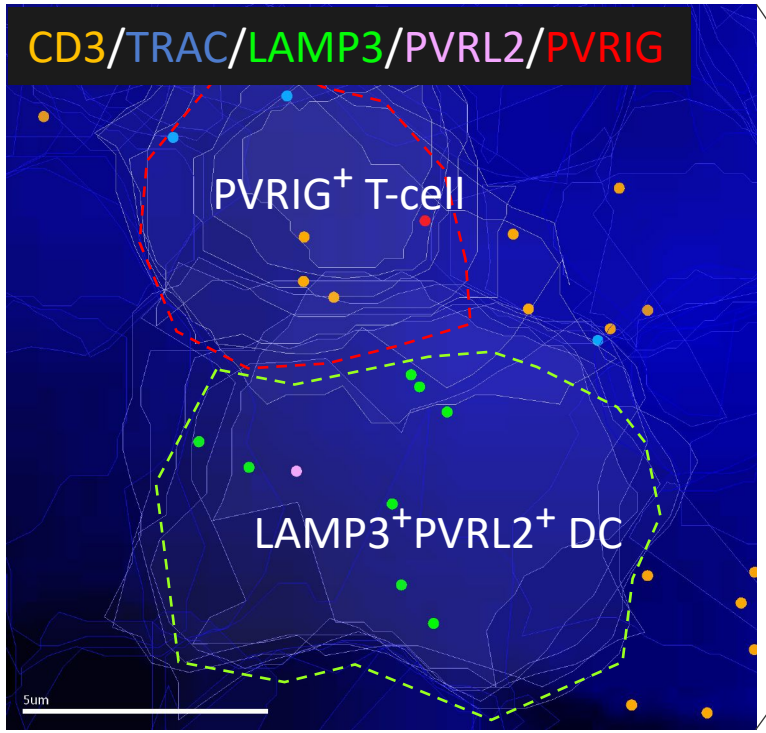
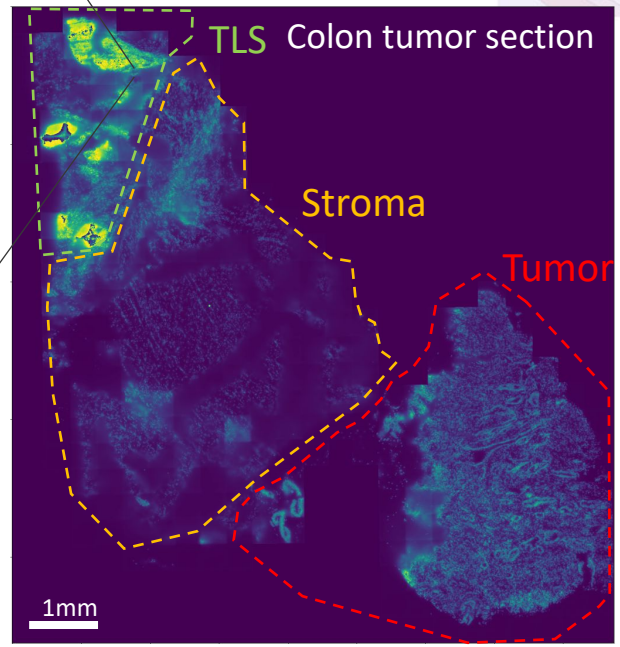
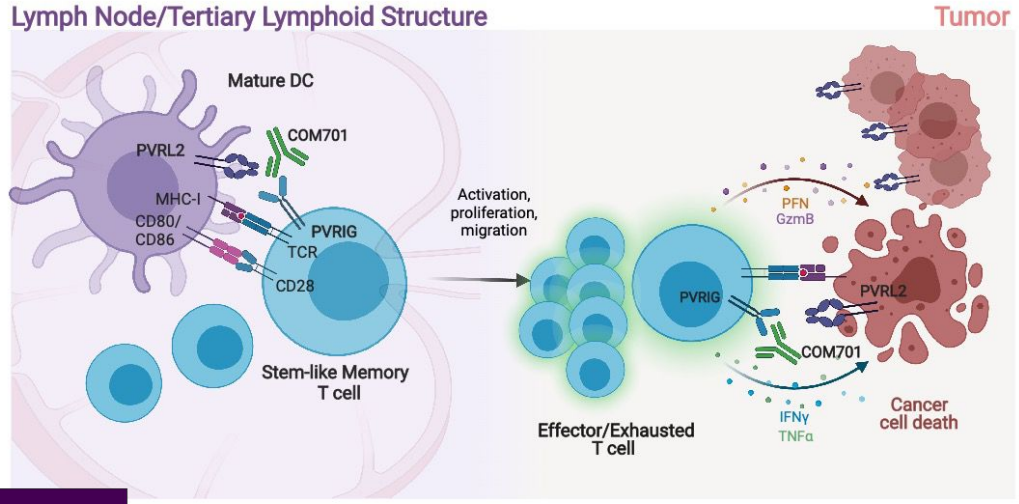
PVRIG+ T-cell interacting with PVRL2+ activated DC in the TLS







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Summary

- High-resolution Spatial Transcriptomics allows in-depth profiling of the TME at the single-cell level.
- We have used this method to reaffirm aspects of known biology of the TME, such as association of $CXCL10^{+}$ Activated DCs and $CXCR3^{+}$ T-cells.
- Tscm cells localize to TLS while Exhausted localize to tumor region.
- Preliminary data suggests that PVRIG & TIGIT show unique expression in TLS over other checkpoints.
- PVRIG blockade may enhance Tscm activation by DCs, resulting in their increased expansion and differentiation. A potential mechanism which could lead to increased T cell expansion and infiltration into less ‘inflamed’ tumors.

Thank you.

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Zurit Levine

Natalia Petrenko, Rob Foreman,

Jiang He, George Emanuel