

Insights into the progression of human colorectal cancer via spatial multiomic profiling

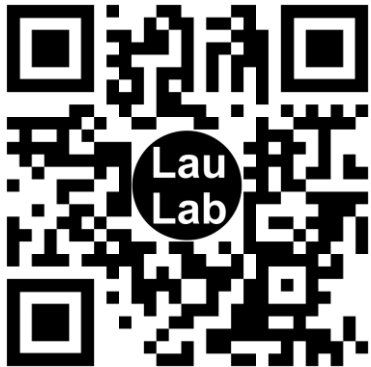
Ken S. Lau, PhD, Professor of Cell & Developmental Biology and Surgery
Vanderbilt University School of Medicine

SEASR Annual Meeting

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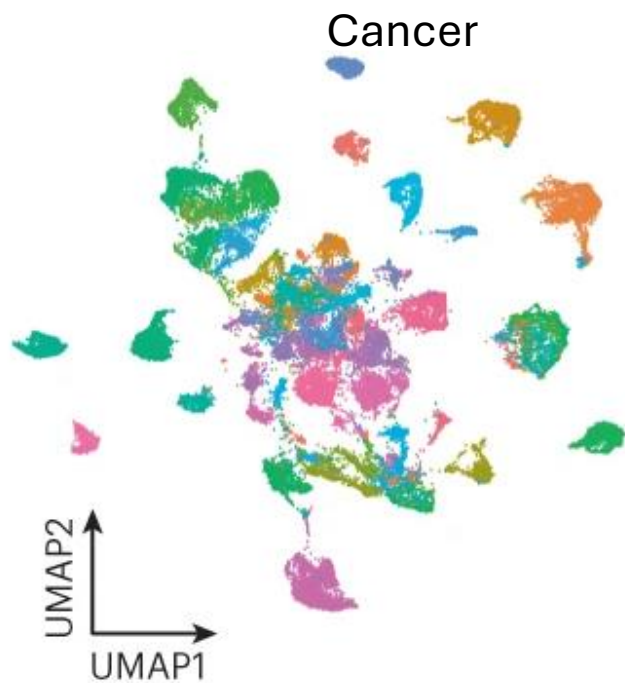


Understanding tumors by phenotypes

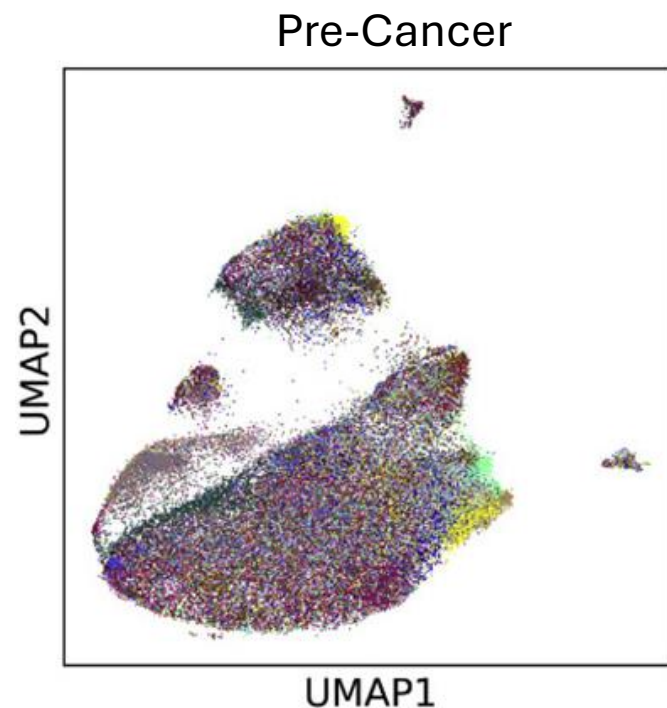
Cancers are genetically and evolutionarily heterogeneous at a per tumor level



(Nicos and Krawczyk, 2022)



(Malla et al., 2024)

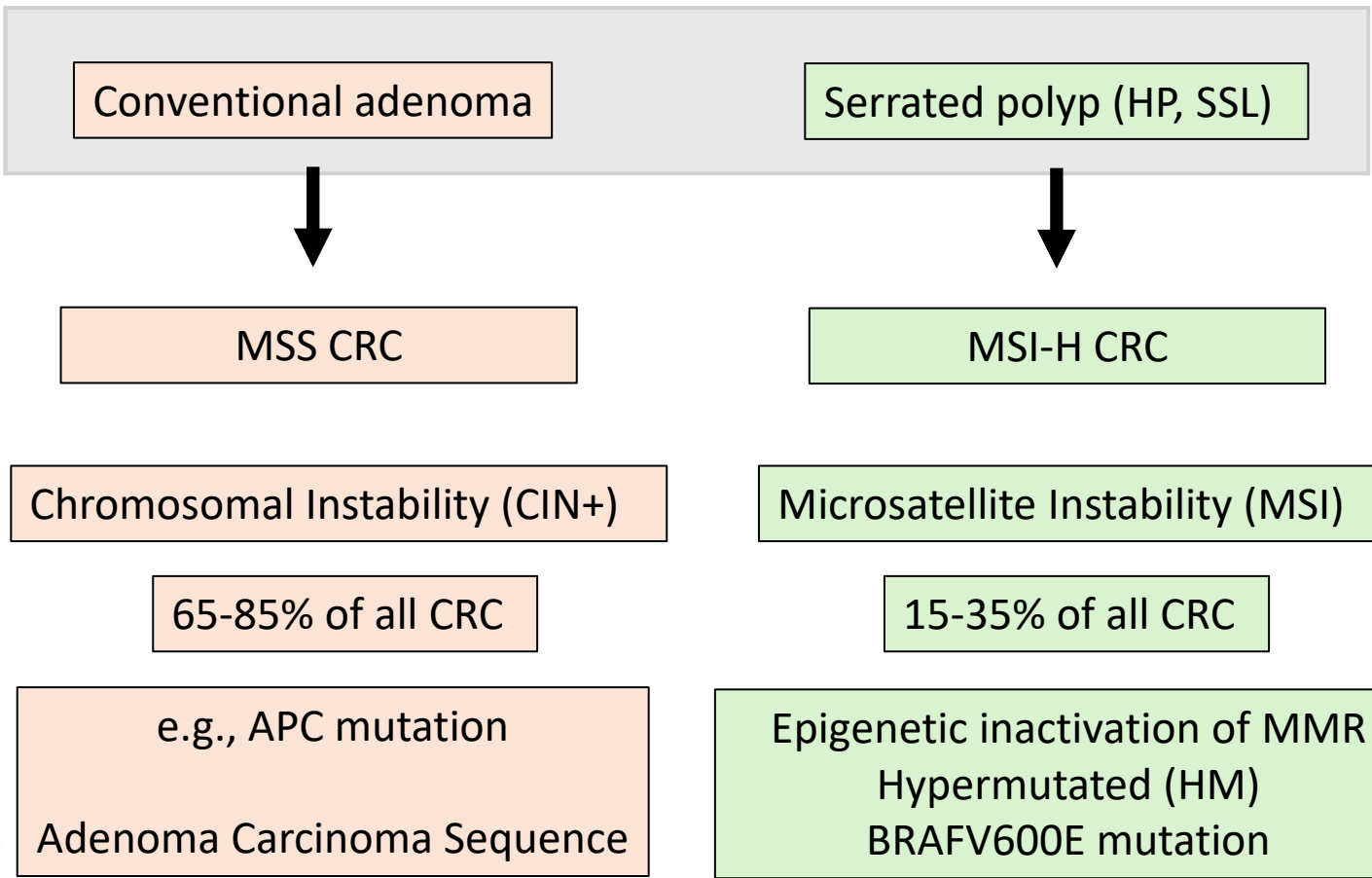


(Chen, Scurrah et al., 2021)

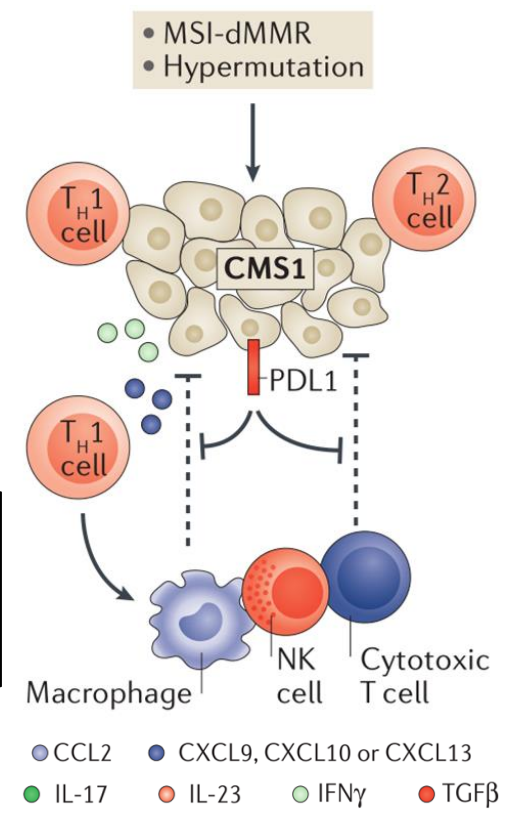
Cancer molecular subtypes are clinically important

Understanding how cancers arrive at certain states (from precursors) can reveal actionable opportunities.

Subtyping example:



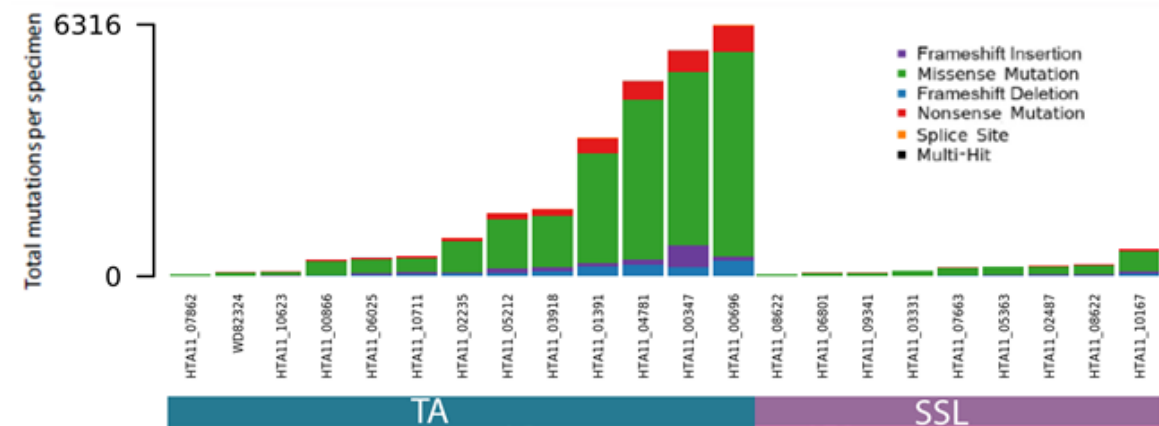
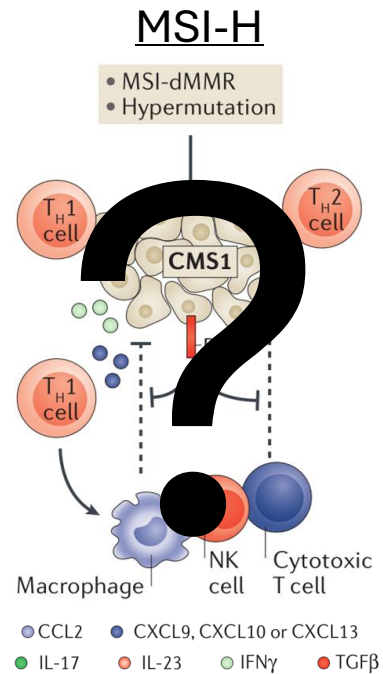
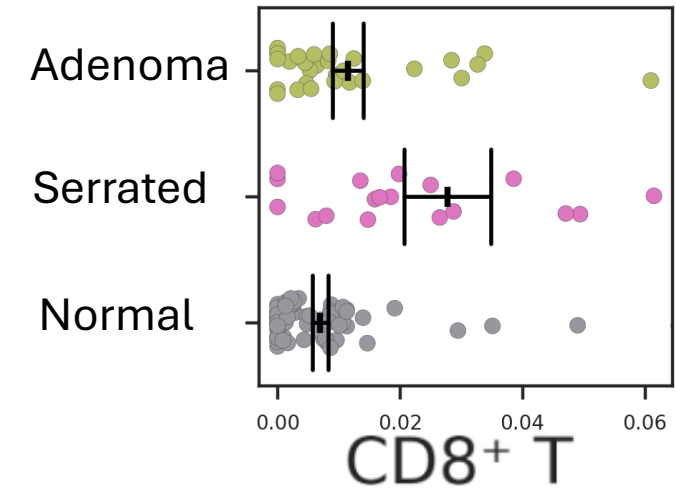
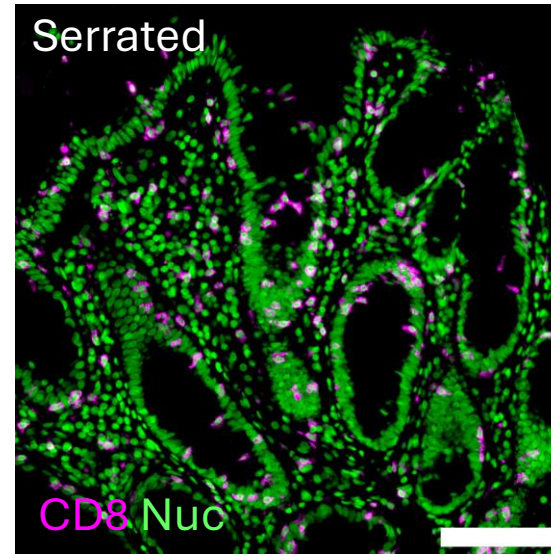
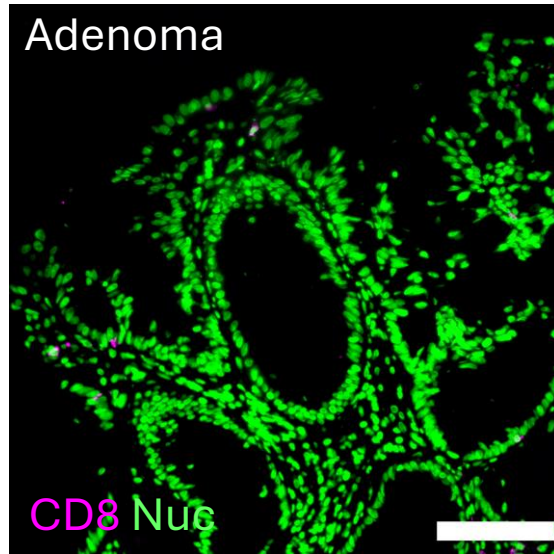
Precancerous lesions



CANCER
NYC Cancer Trial Delivers 'Unheard-of' Result: Complete Remission for Everyone
Patients with a particular kind of cancer and a particular kind of mutation received a new therapy called dostarlimab and had results not seen in a cancer trial before
Published June 6, 2022 • Updated on June 6, 2022 at 3:38 pm

ORIGINAL ARTICLE FREE PREVIEW
PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer
Andrea Cercek, M.D., Melissa Lumish, M.D., Jenna Sinopoli, N.P., Jill Weiss, B.A., Jinru Shia, M.D., Michelle Mendola-Essel, D.H.Sc., Imane H. El Dika, M.D., Neil Segal, M.D., Marina Shcherba, M.D., Ryan Sugarman, M.D., Ph.D., Zsolt Stadler, M.D., Rona Yaeger, M.D., et al.

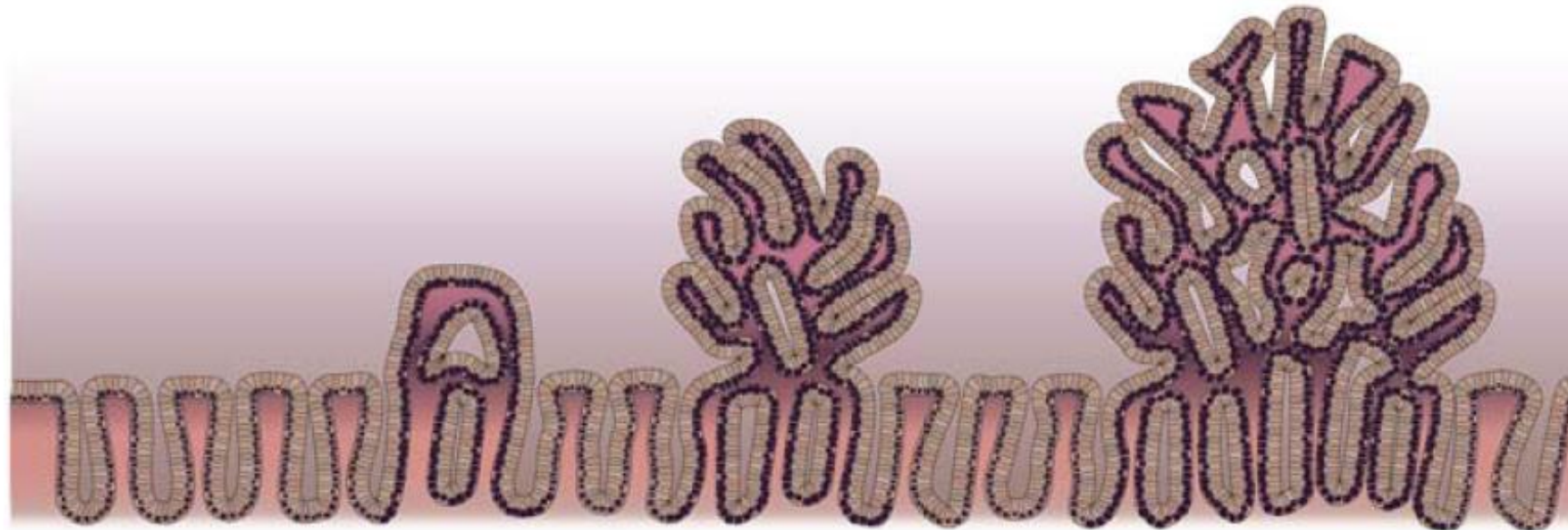
Cytotoxic cell infiltration into precancer is independent of mutation burden



Serrated polyps present a cytotoxic immune environment independent of hypermutation (and neoantigen expansion)

(Chen, Scurrah et al., *Cell*, 2021)

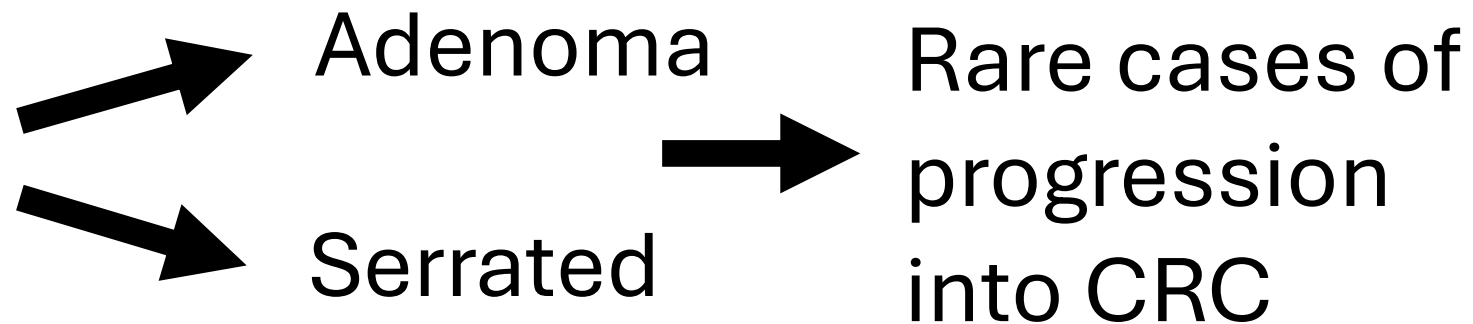
Transition from precancers to malignancy



Normal

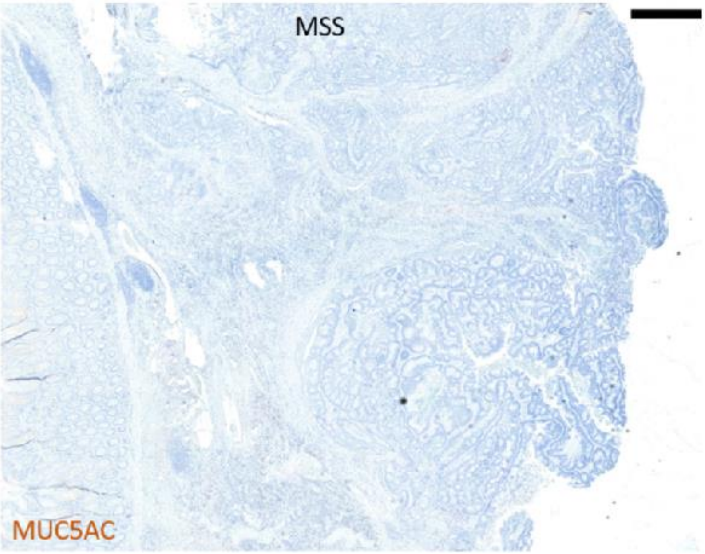
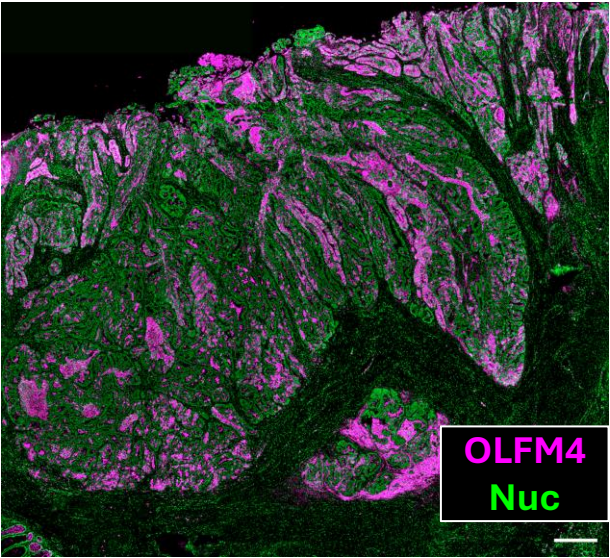
Polyp

Cancer

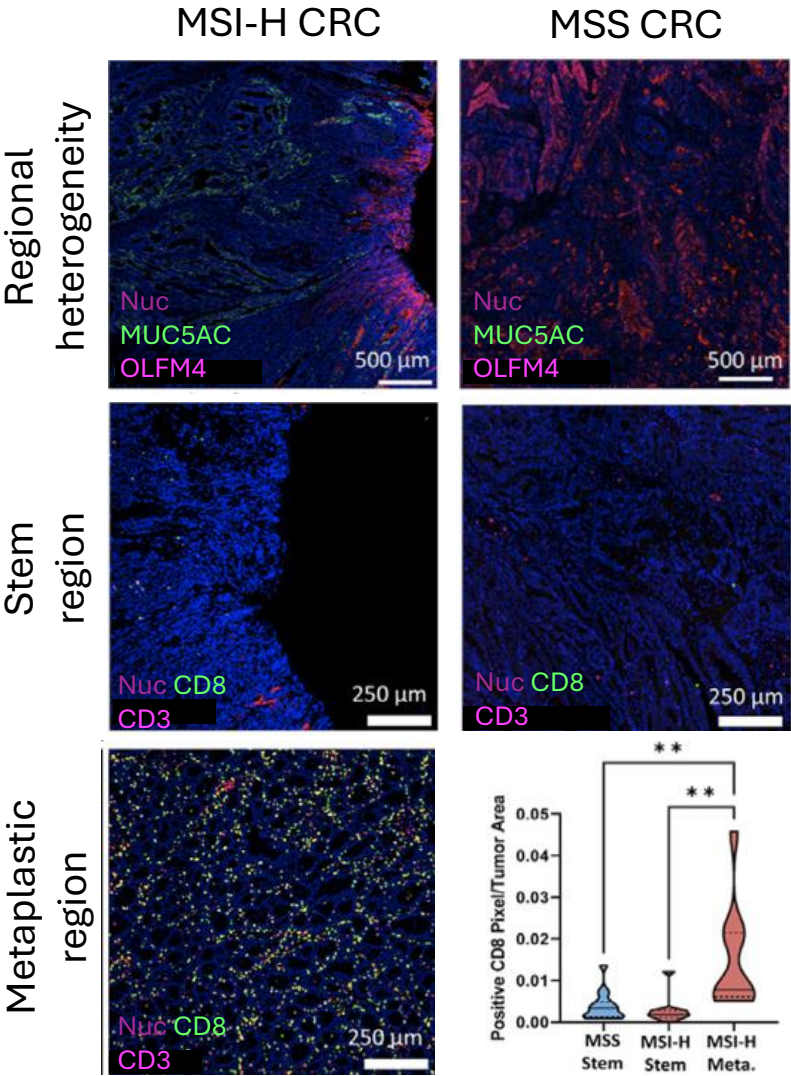
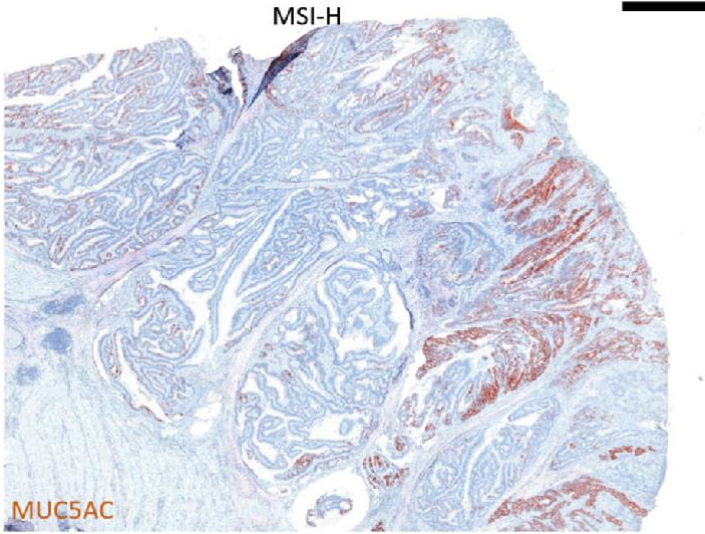
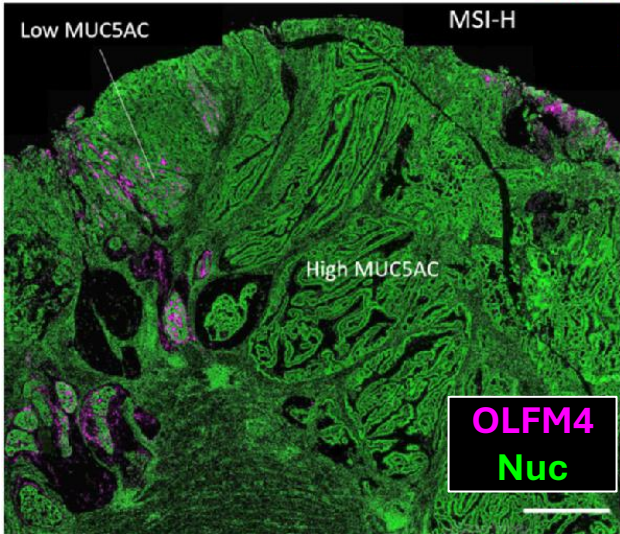


Heterogenous gains in stemness characterizes progression to malignancy

MSS



MSI-H



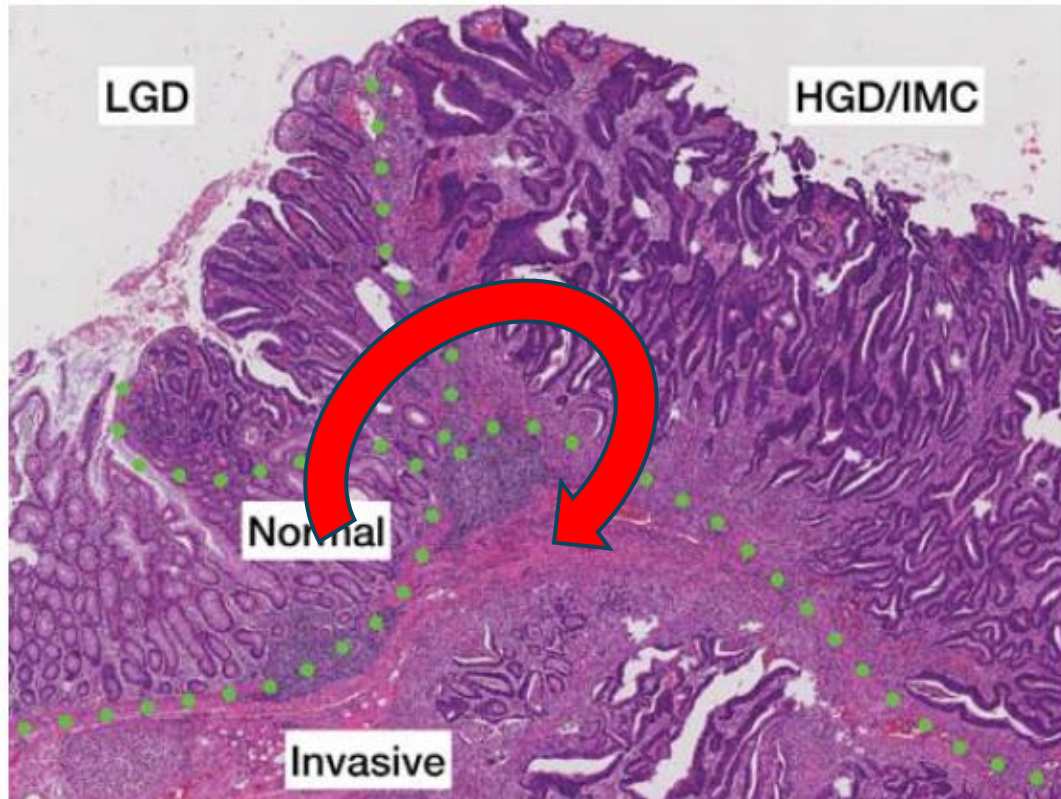
Spatial mapping of pre-cancer to cancer transitions within specimens

Goal: Leverage premalignant and malignant regions within colorectal cancers to map transitions

Molecular cartography uncovers evolutionary and microenvironmental dynamics in sporadic colorectal tumors

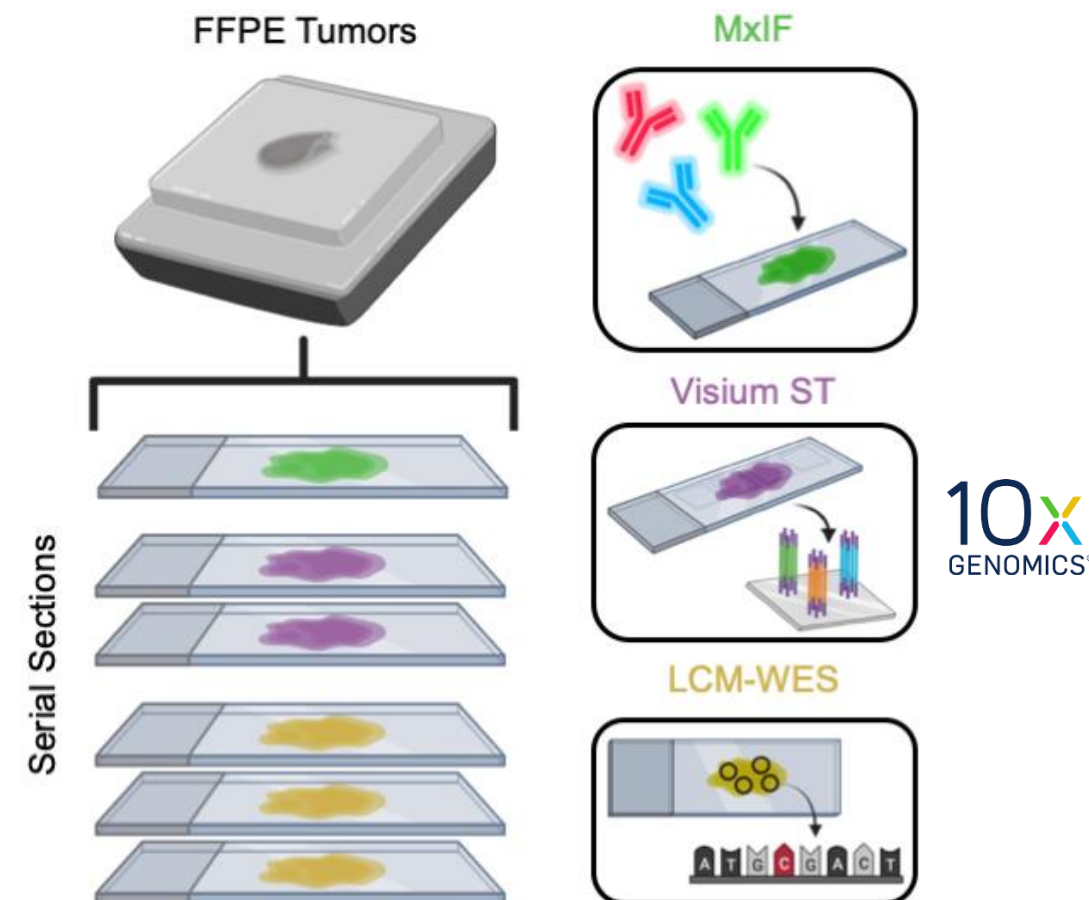
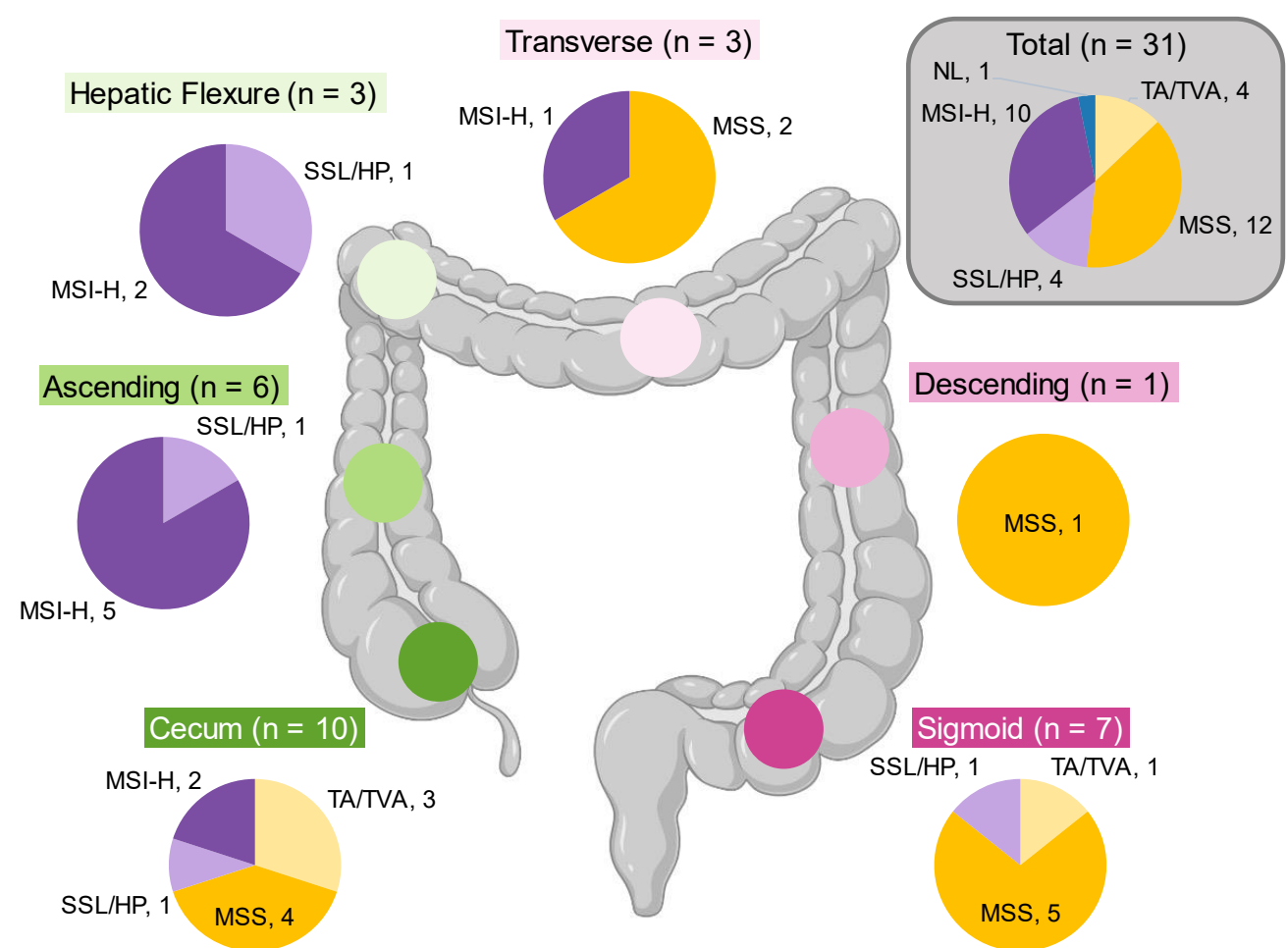
Cody N. Heiser,^{1,2} Alan J. Simmons,^{2,3} Frank Revetta,⁴ Eliot T. McKinley,^{2,3} Marisol A. Ramirez-Solano,⁵ Jiawei Wang,^{2,3} Harsimran Kaur,^{1,2} Justin Shao,^{2,6} Gregory D. Ayers,⁴ Yu Wang,⁵ Sarah E. Glass,^{2,3} Naila Tasneem,^{2,3} Zhengyi Chen,^{1,2} Yan Qin,⁷ William Kim,^{2,3} Andrea Rolong,^{2,3} Bob Chen,^{1,2,15} Paige N. Vega,^{2,3} Julia L. Drewes,⁸ Nicholas O. Markham,^{2,13} Nabil Saleh,^{2,3} Fotis Nikolos,⁹ Simon Vandekar,⁵ Angela L. Jones,¹⁰ M. Kay Washington,⁴ Joseph T. Roland,^{2,11} Keith S. Chan,⁹ Thomas Schürpf,⁷ Cynthia L. Sears,⁸ Qi Liu,⁵ Martha J. Shrubsole,¹² Robert J. Coffey,^{2,13,14,*} and Ken S. Lau^{1,2,3,11,14,16,*}

Heiser et al., **Cell**, 2023



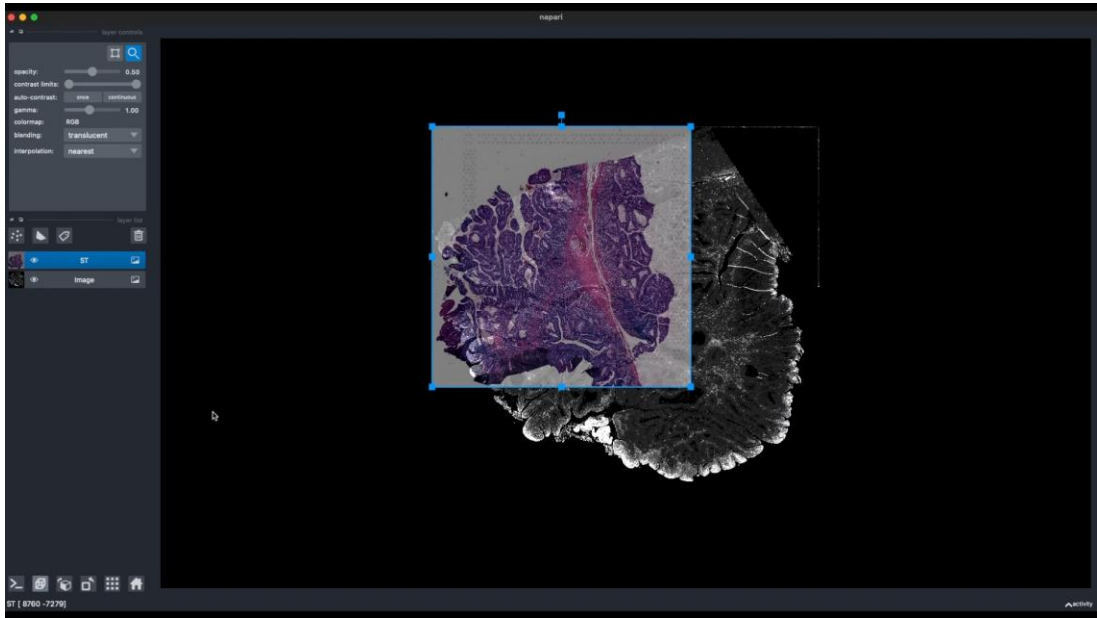
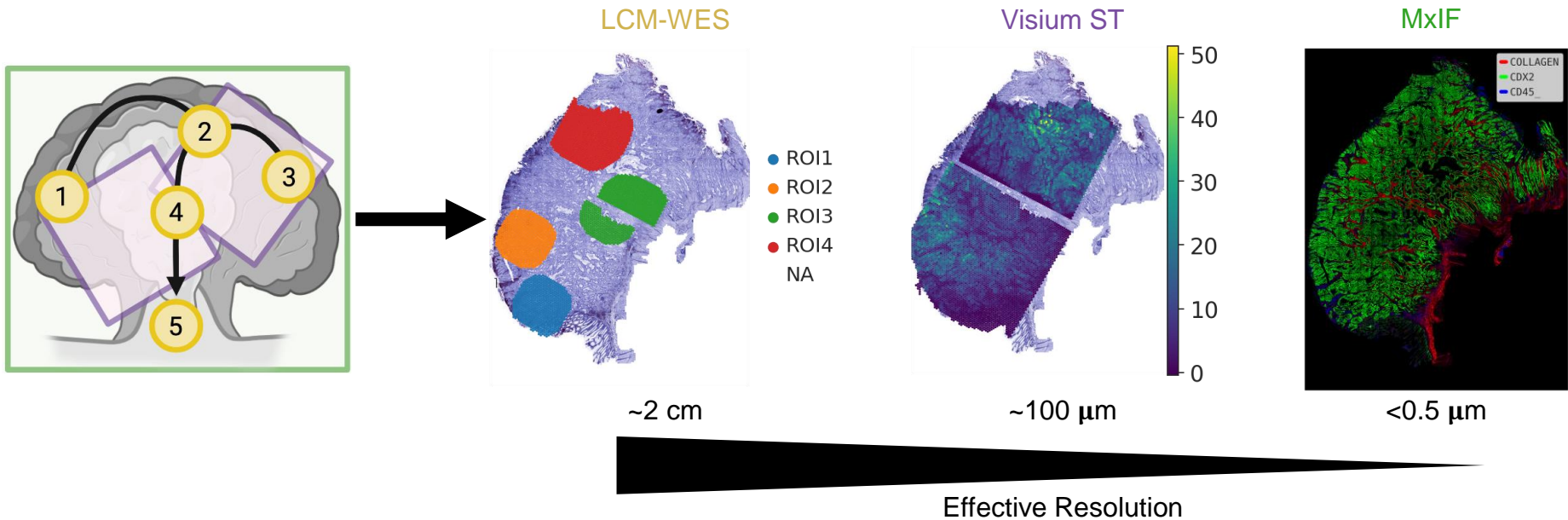
Cody Heiser
PhD Student

Multimodal data generated on the same specimens

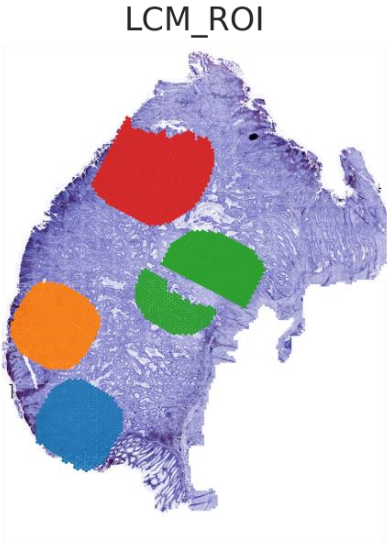


*Matching scRNA-seq of most samples and HCR-FISH also available

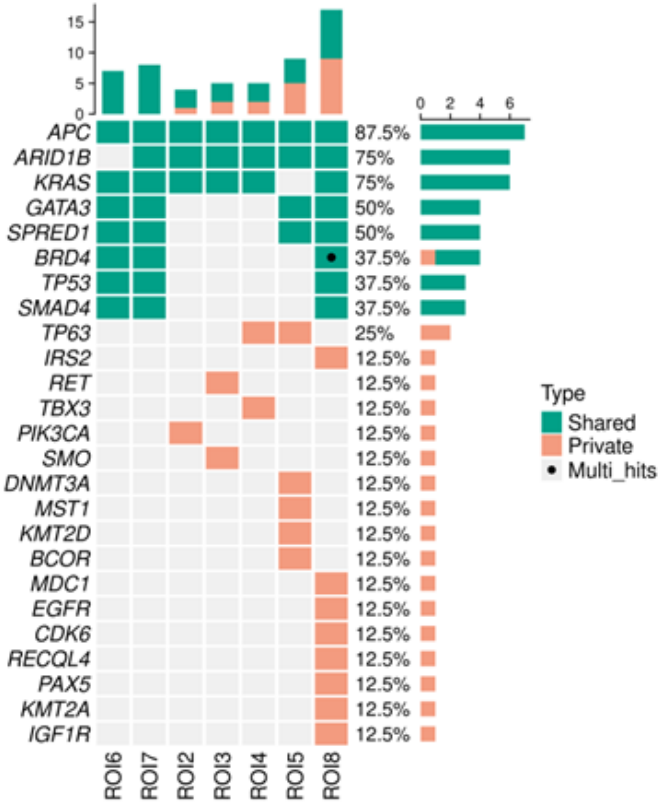
Partial registration to whole-slide serial sections allows for cross-modality analysis



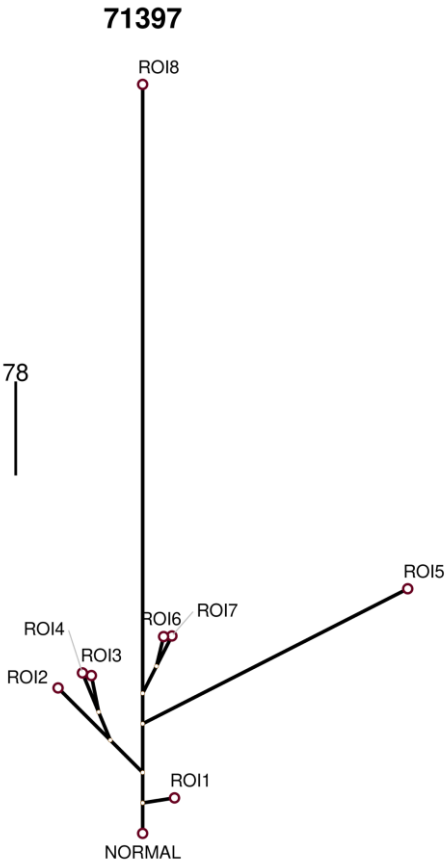
Spatial genetic information to determine phylogenetic relationship between clones



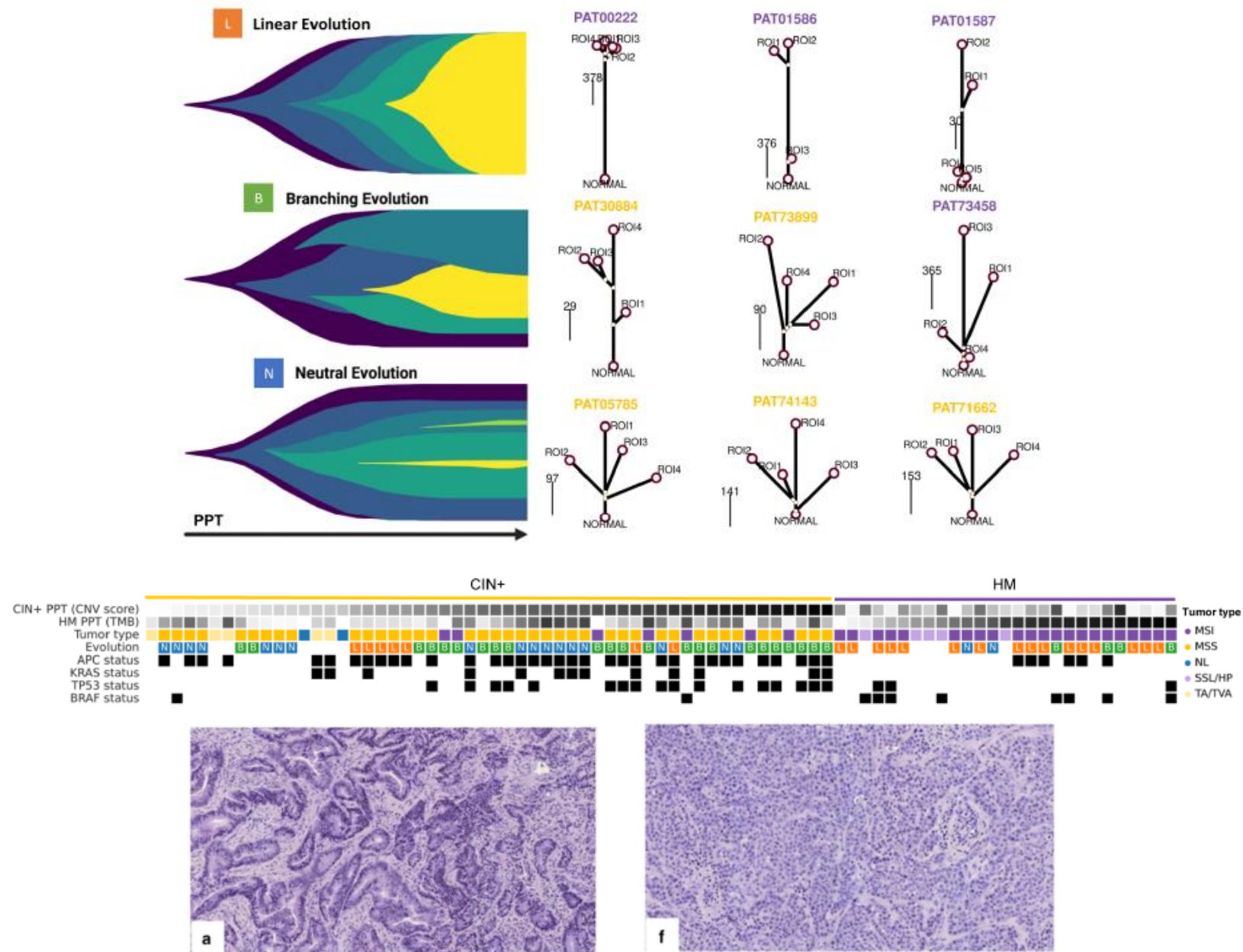
- ROI1
- ROI2
- ROI3
- ROI4
- NA



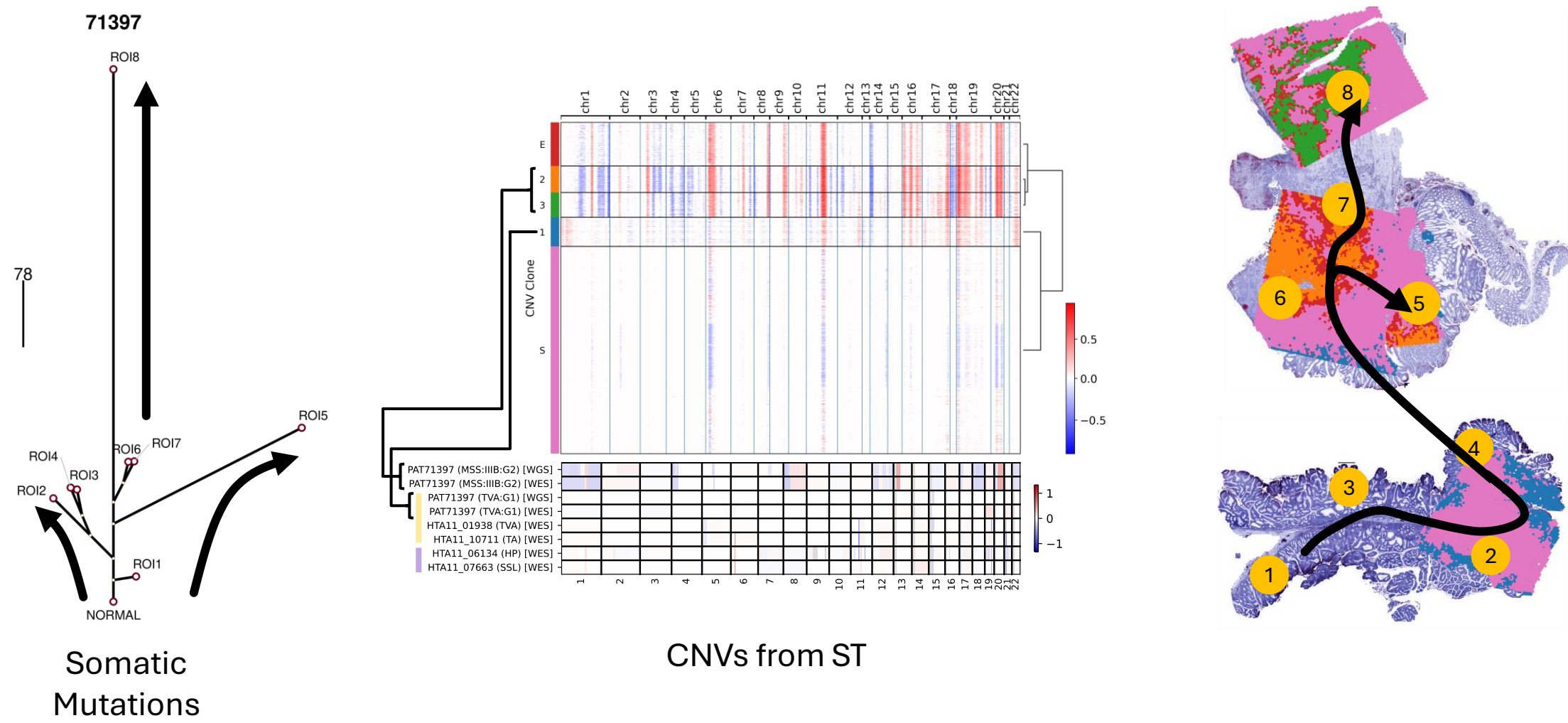
Somatic
Mutations



Tumor subtypes can be classified by evolutionary models

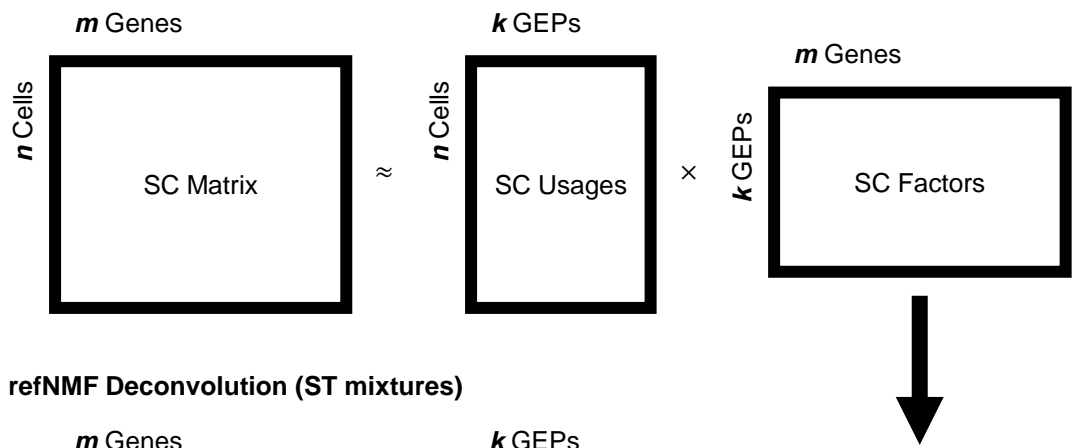


Spatially resolved genetic scaffold for ordering tumor regions on a progression axis

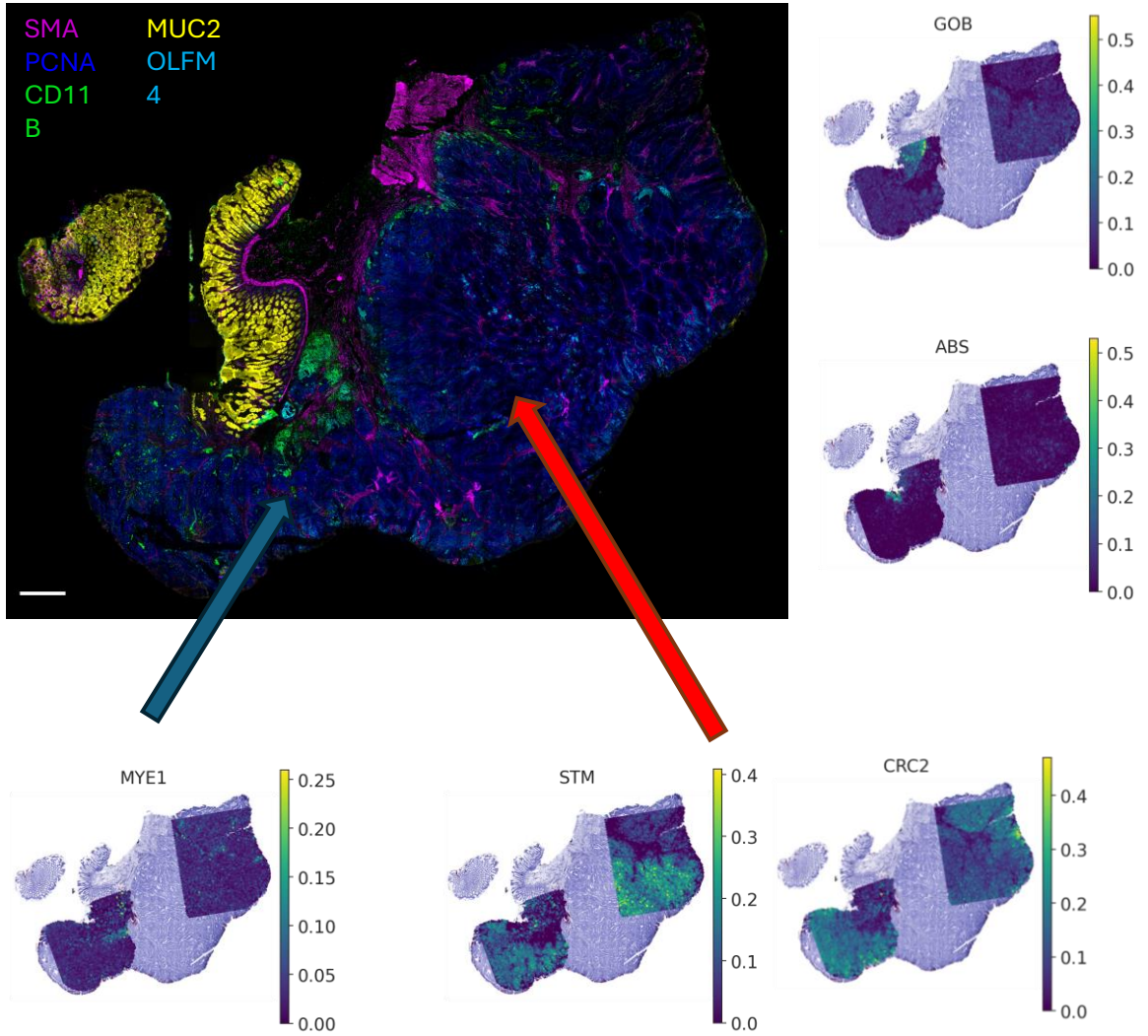
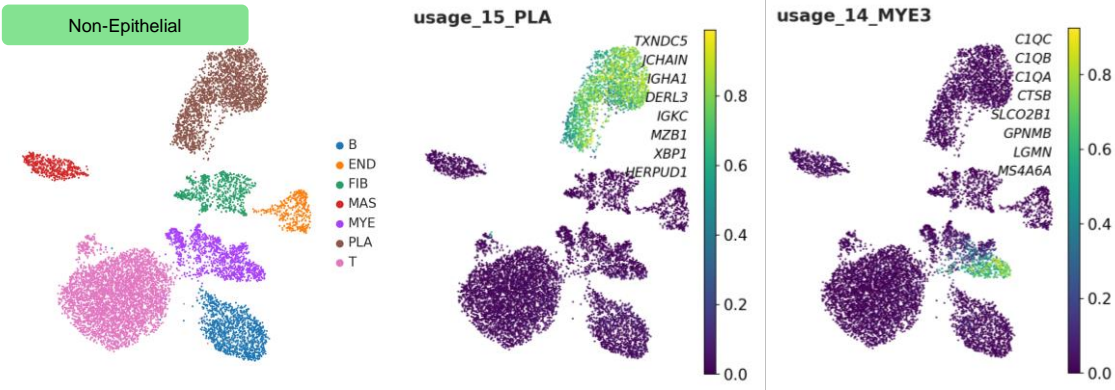
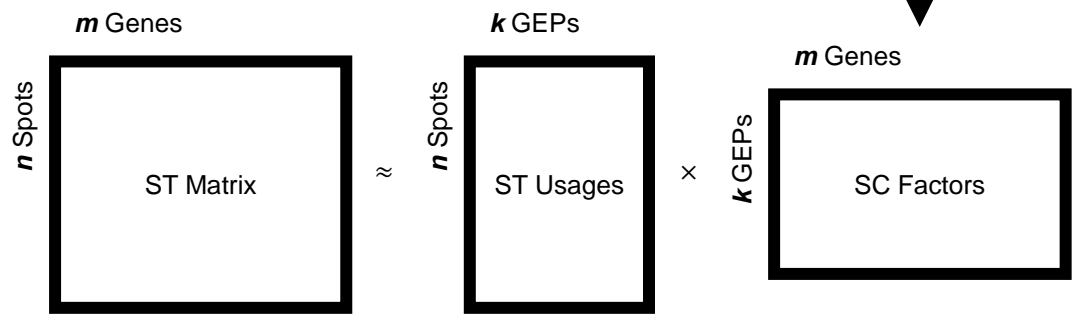


NMF-based cell state deconvolution

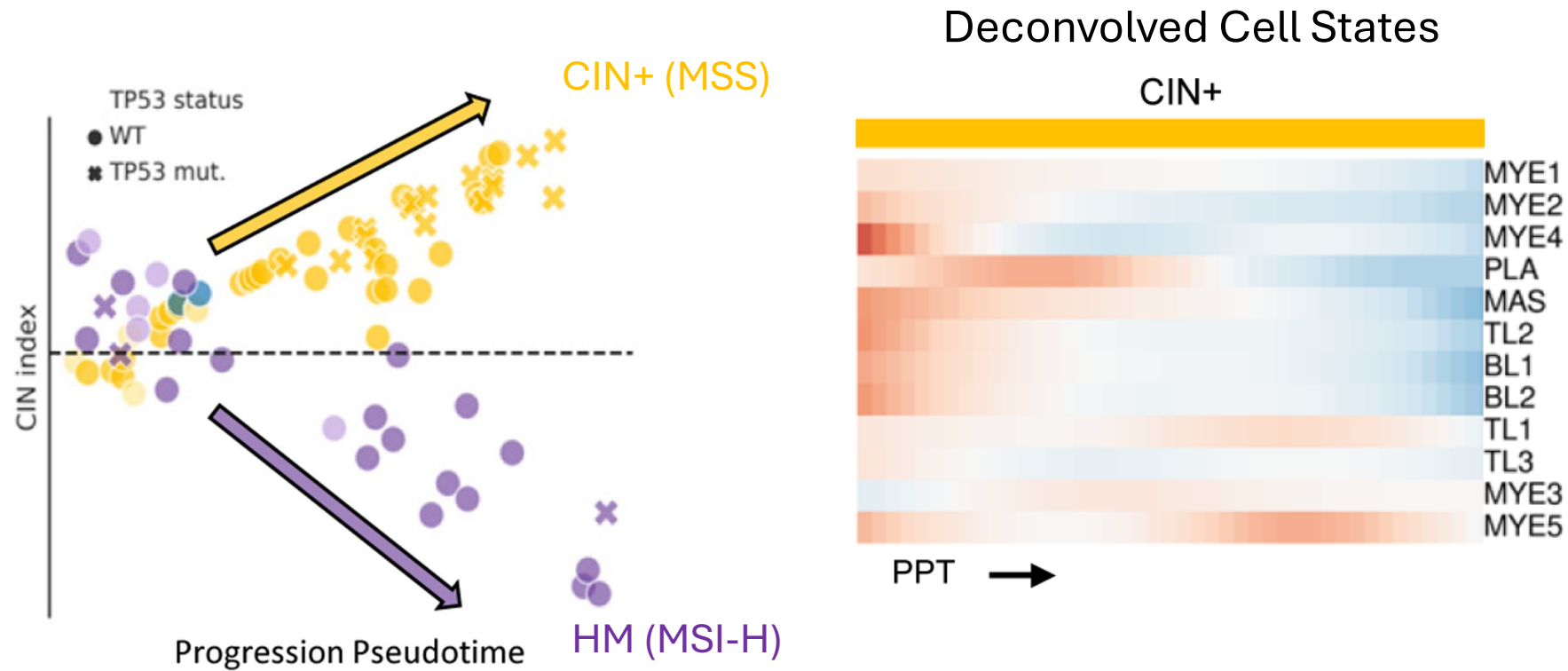
NMF State Discovery (scRNA-seq reference)



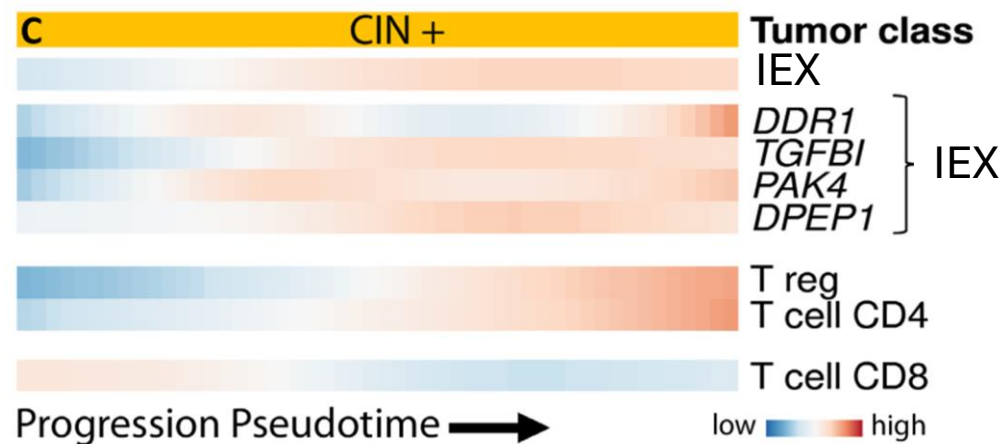
refNMF Deconvolution (ST mixtures)



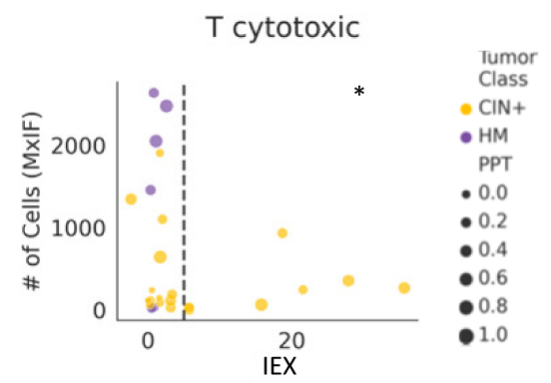
Integrating spatial genetic and transcriptomic information to reconstruct global progression pseudotime (PPT)



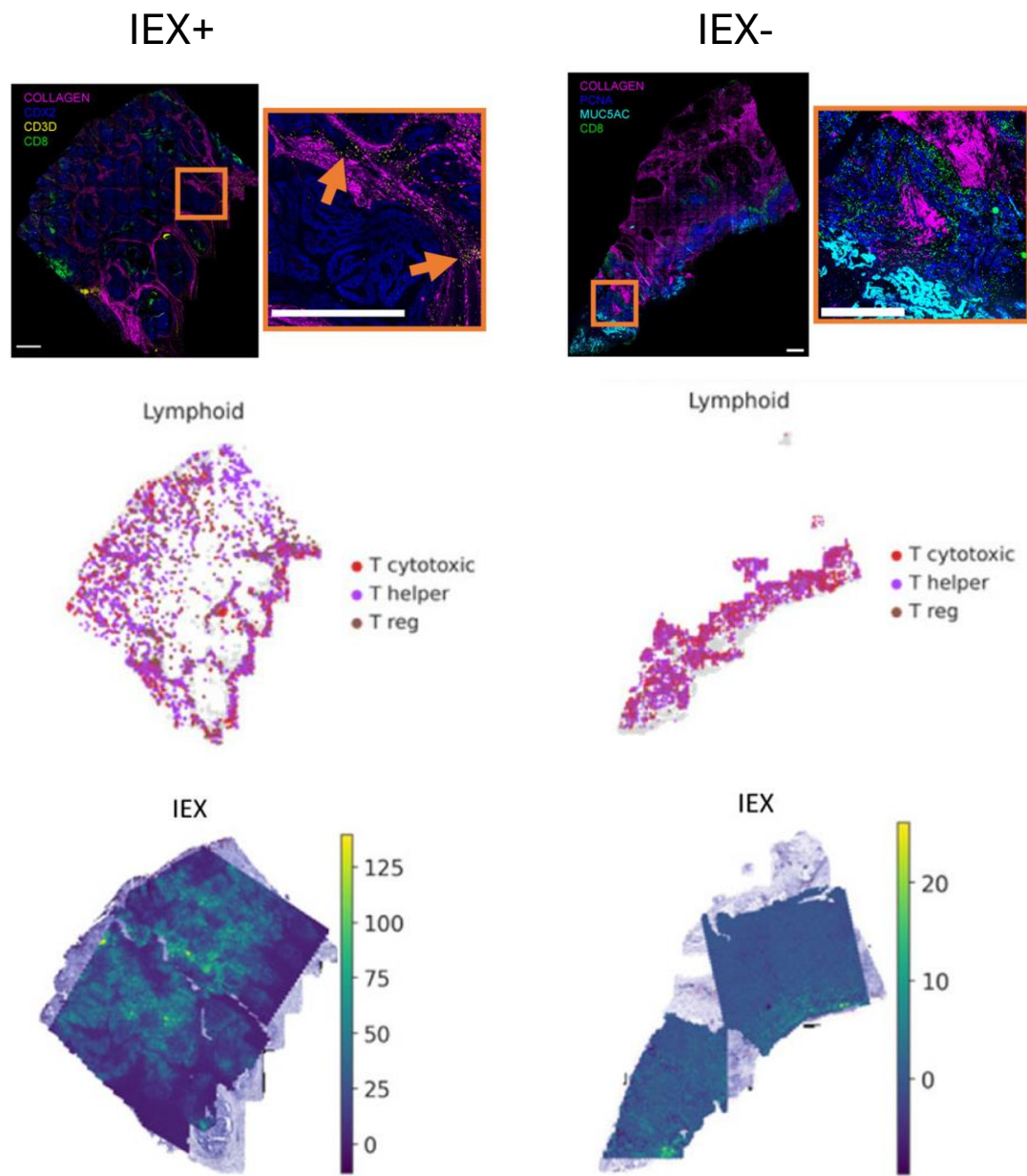
Integrating imaging with a transcriptional program that tracks with tumor progression



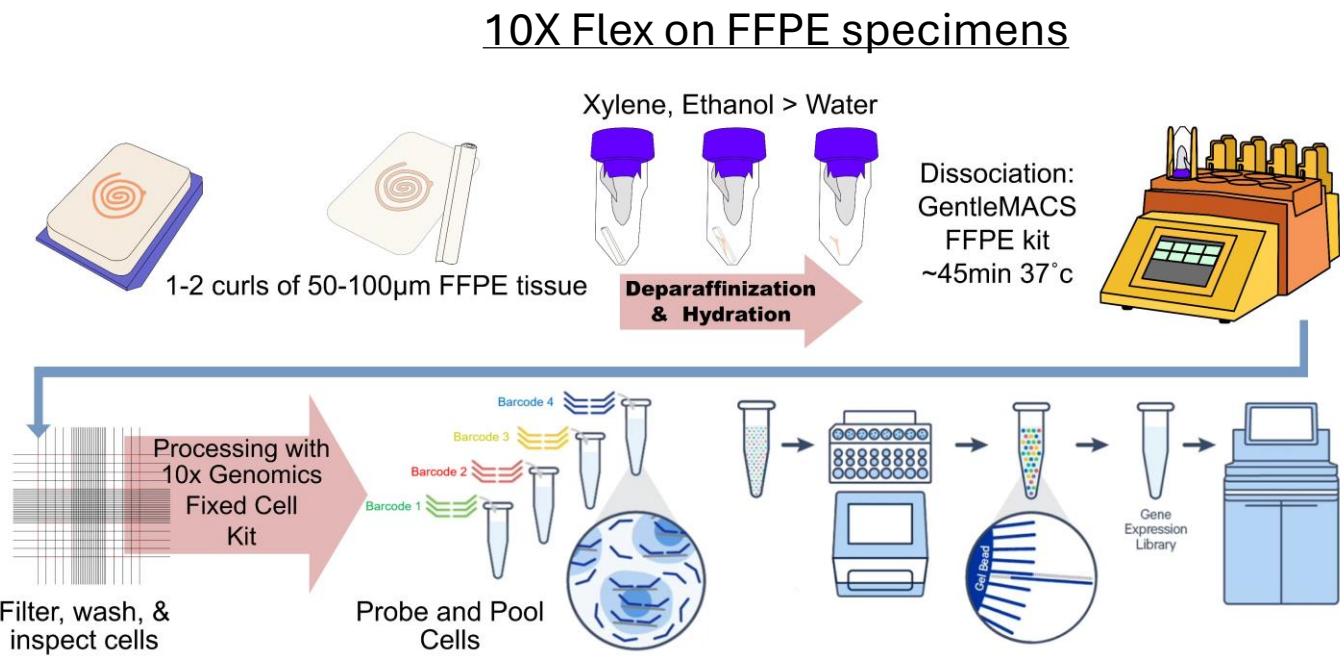
iCMS2, stemness, hypoxia



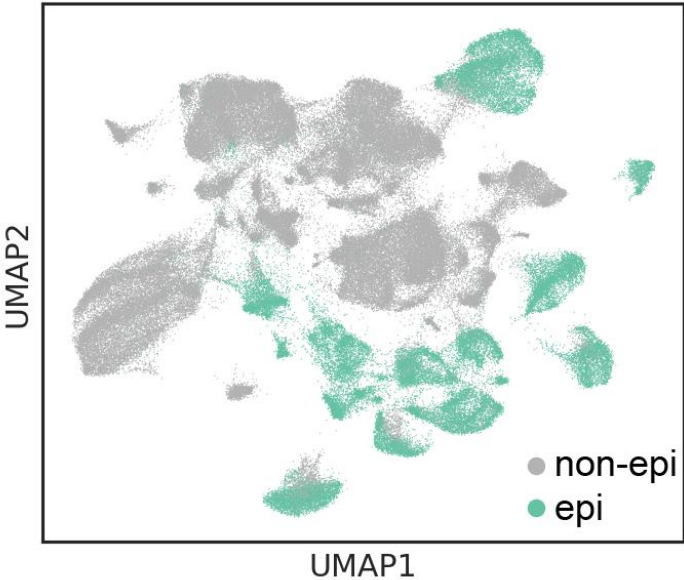
* same result shown in a separate scRNA-seq cohort



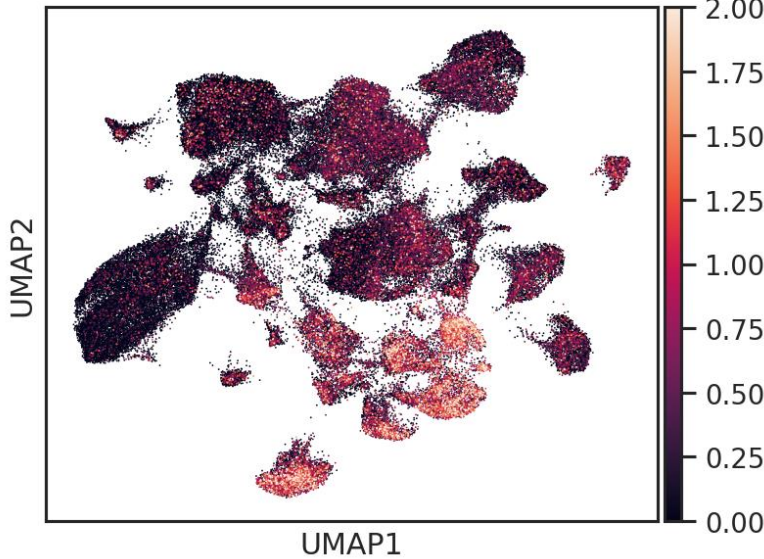
Immune exclusion signature is expressed by tumor cells



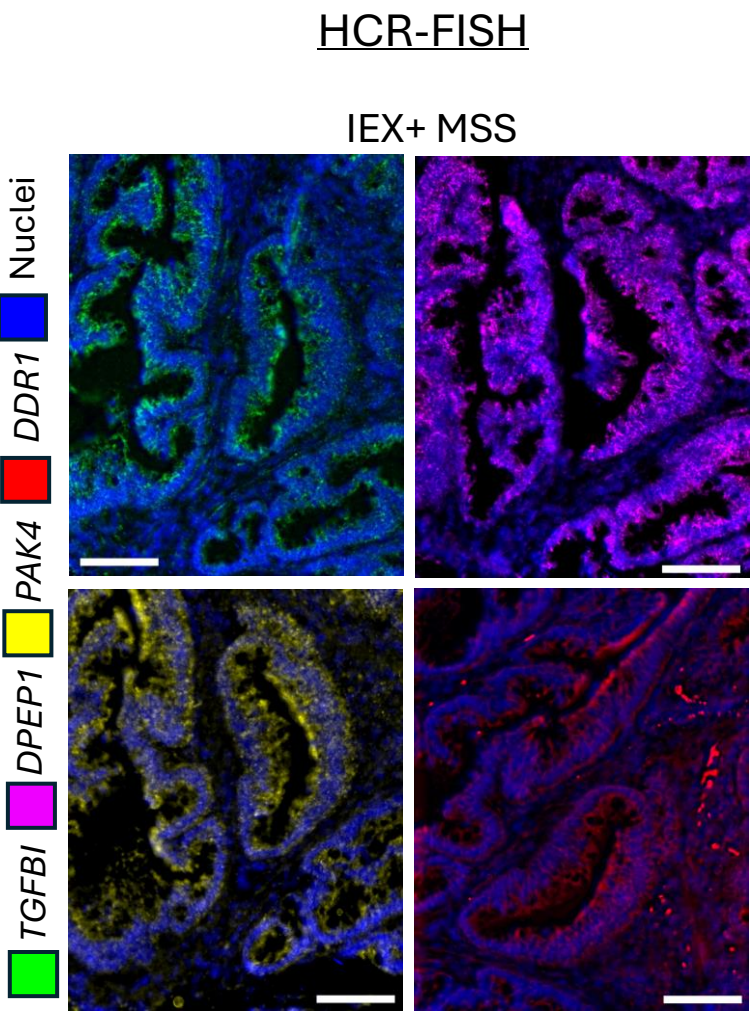
scRNA-seq



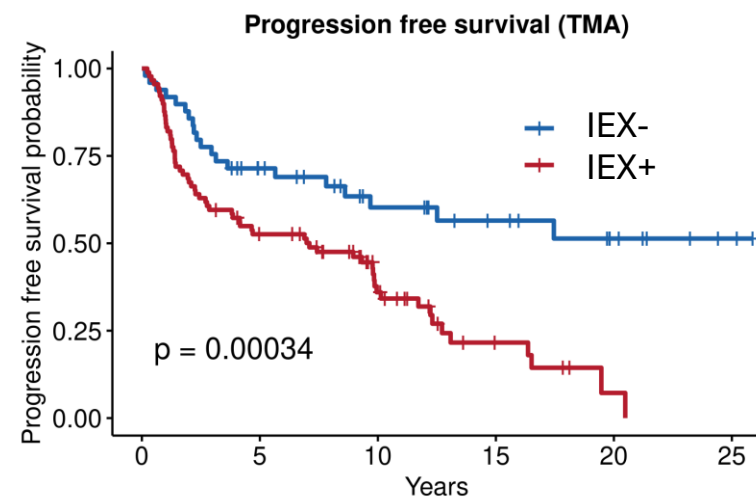
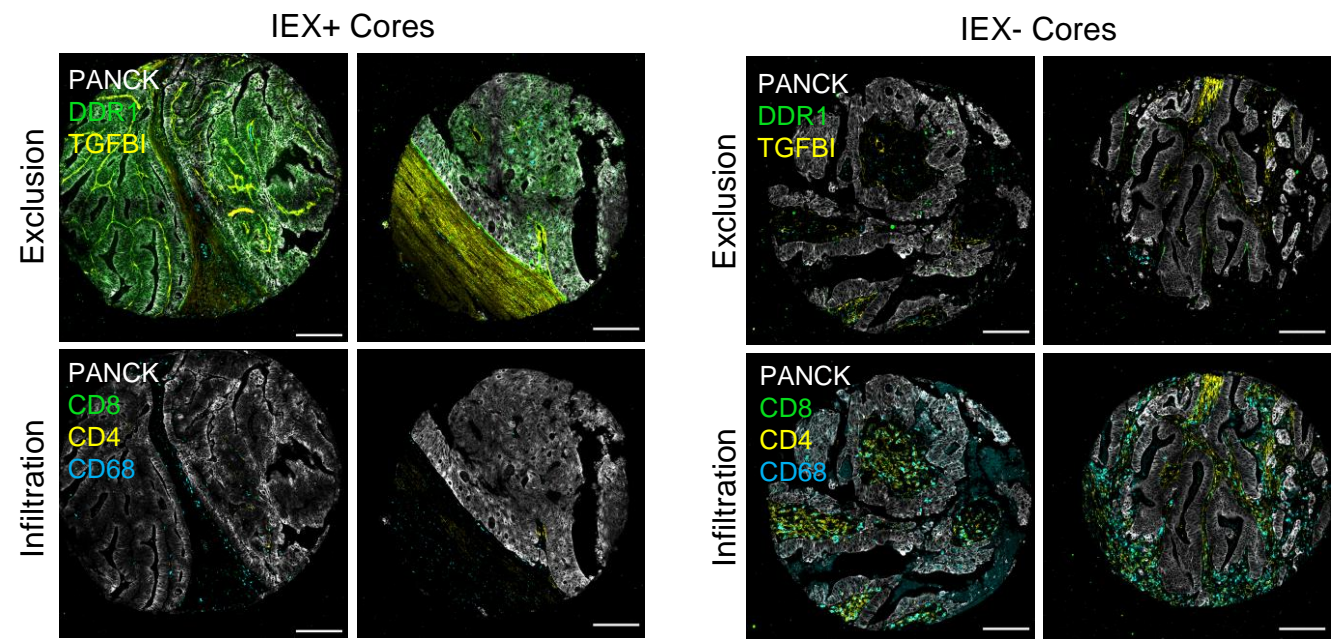
Normalized IEX



Immune exclusion signature is expressed by tumor cells

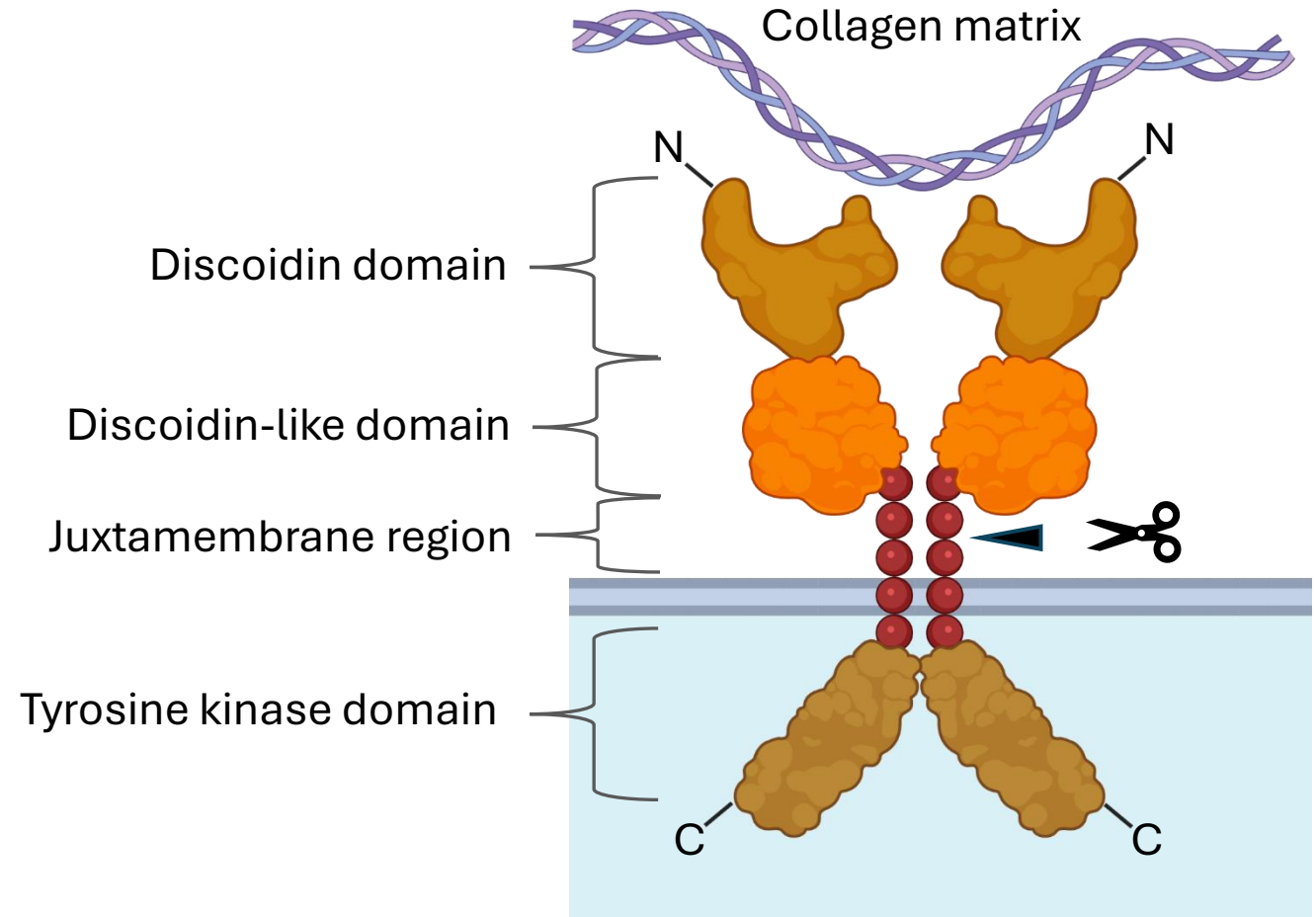


Immune Exclusion signature predicts poor progression-free survival in external cohorts

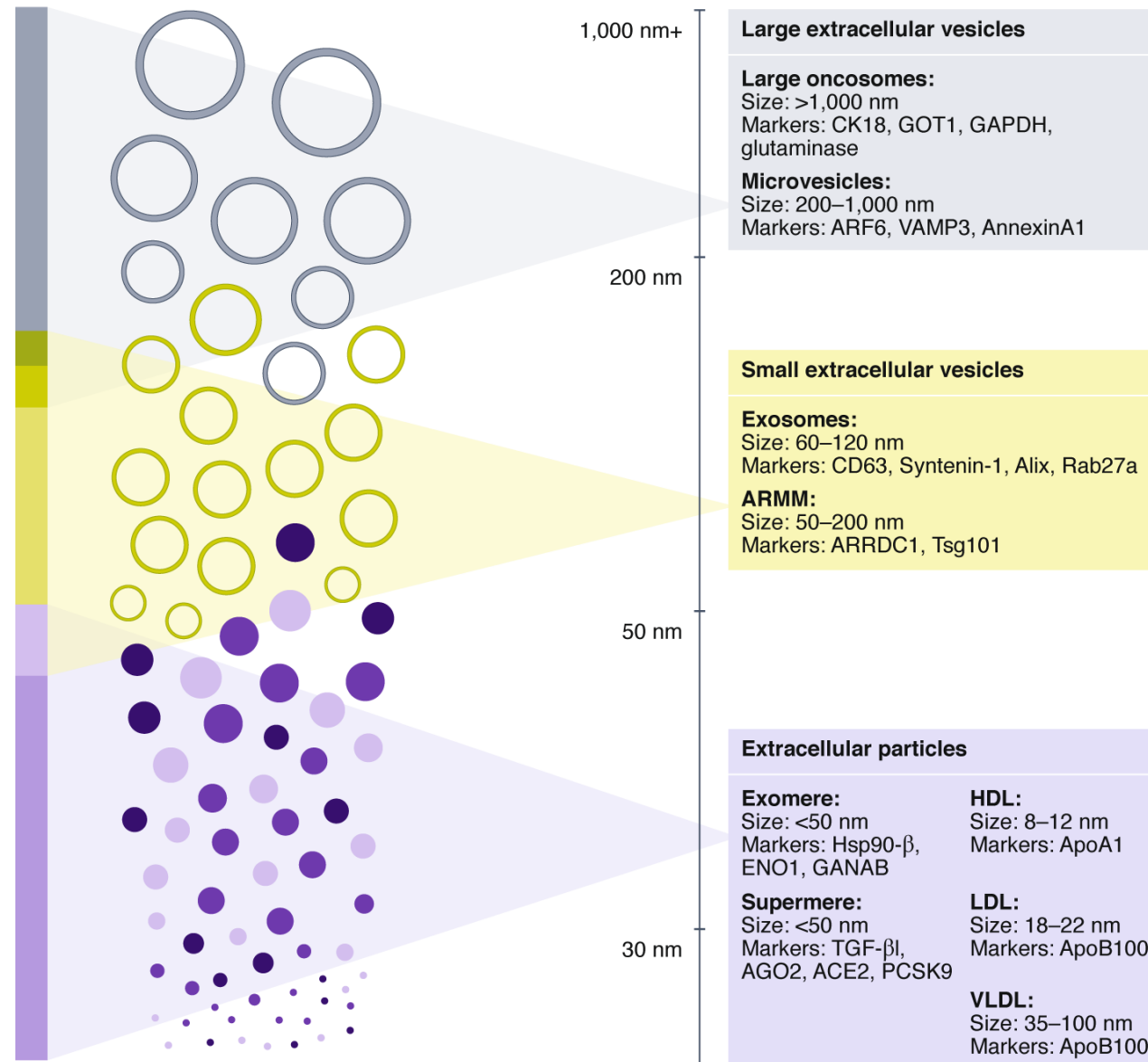


DDR1 is a collagen-interacting protein that has extra- and intra- cellular functions

- Discoidin-domain receptor tyrosine kinase 1
- Ligands are collagen I, II, III, IV, V and VIII
- Extracellular domain is cleaved by metalloproteases
- Is internalized following activation

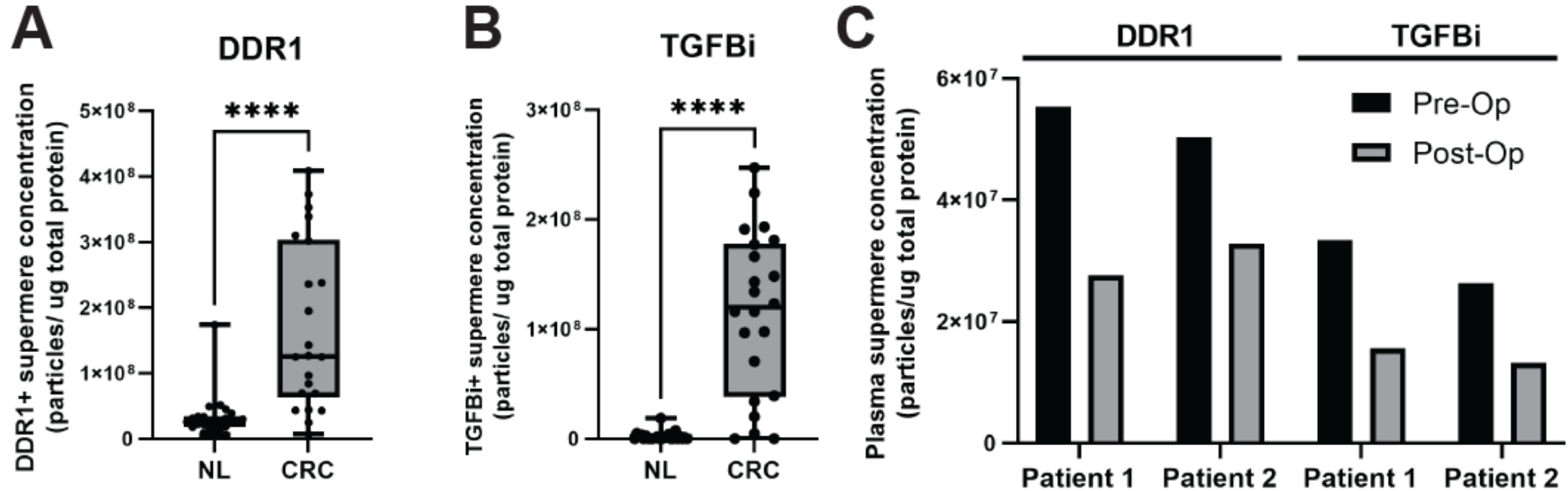


Extracellular nanoparticles are novel modes of cell-microenvironment communication



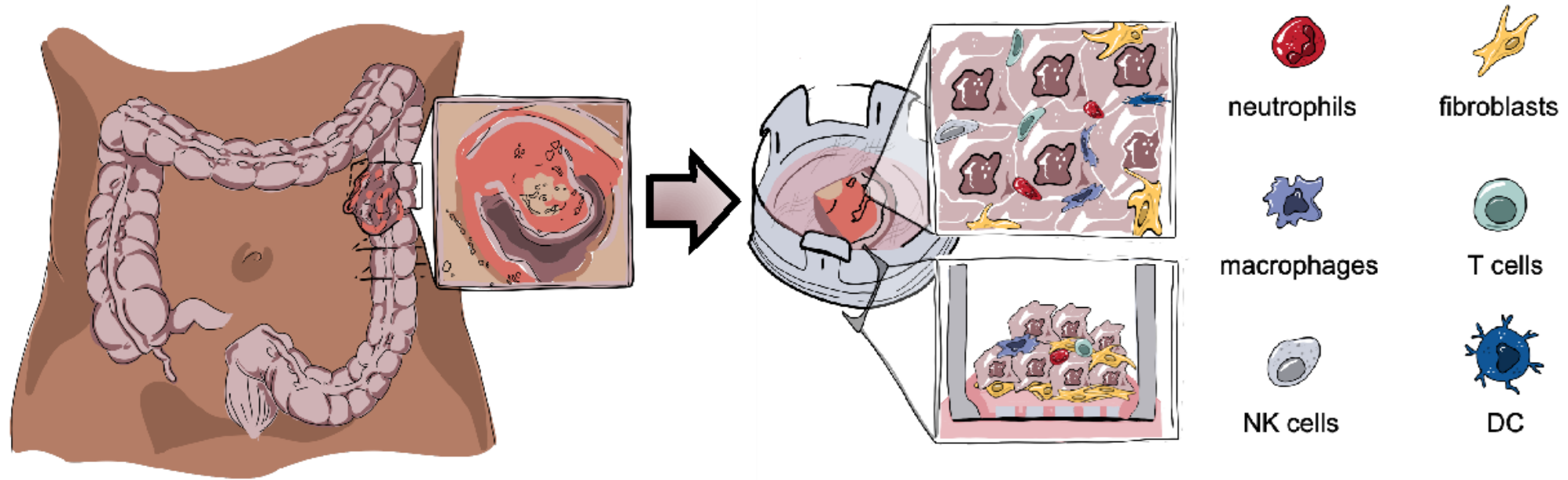
Qin Zhang, Bob Coffey

IEX proteins are packaged into a new secreted nanoparticle (the supermere) and can be detected in CRC patient plasma

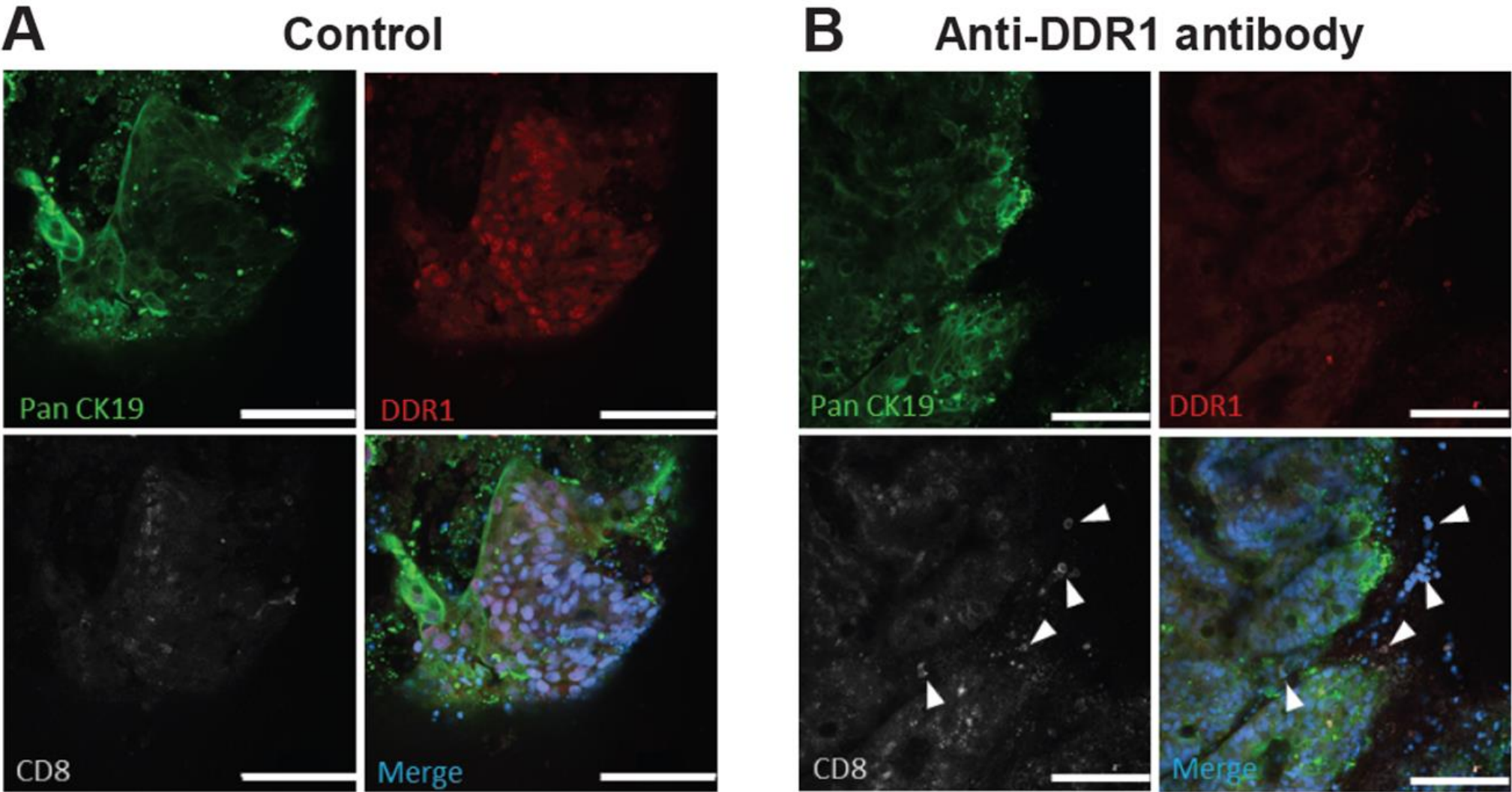


Patient-derived complex cultures for experiments on the tumor microenvironment

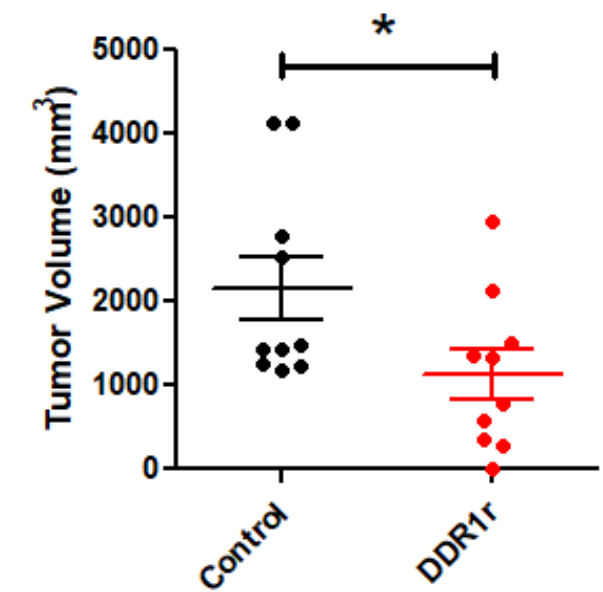
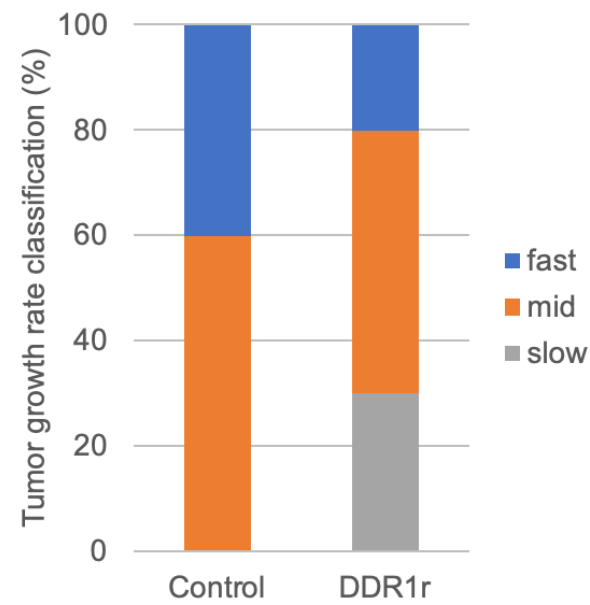
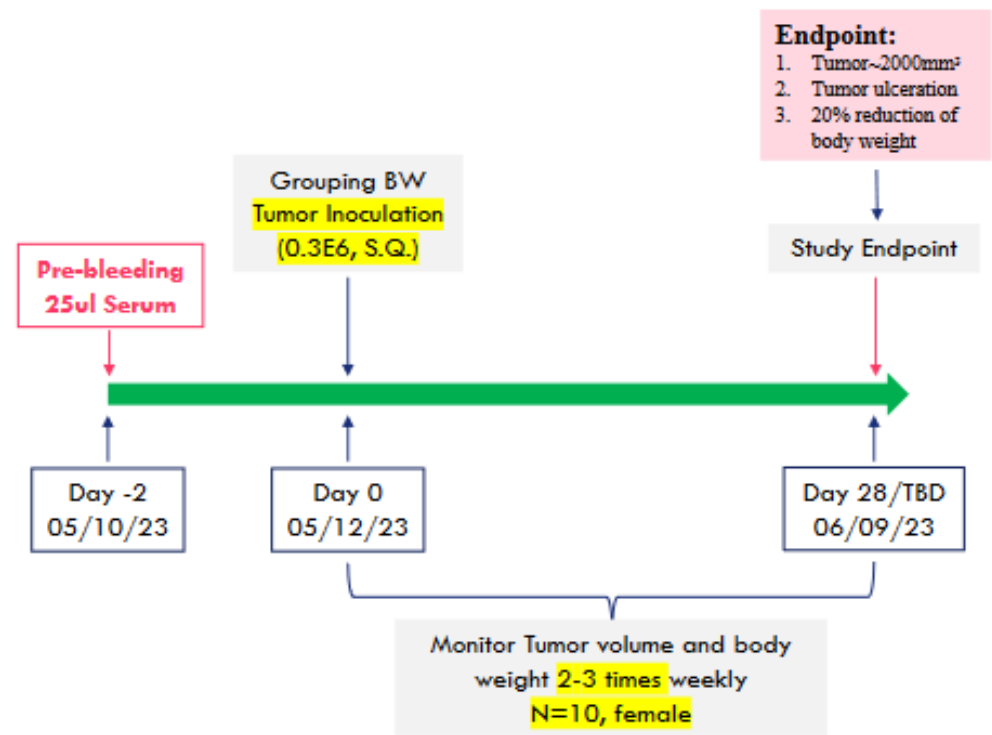
Air-Liquid Interface (ALI) Culture



DDR1 neutralization increases CD8+ T cell infiltration into the tumor proper



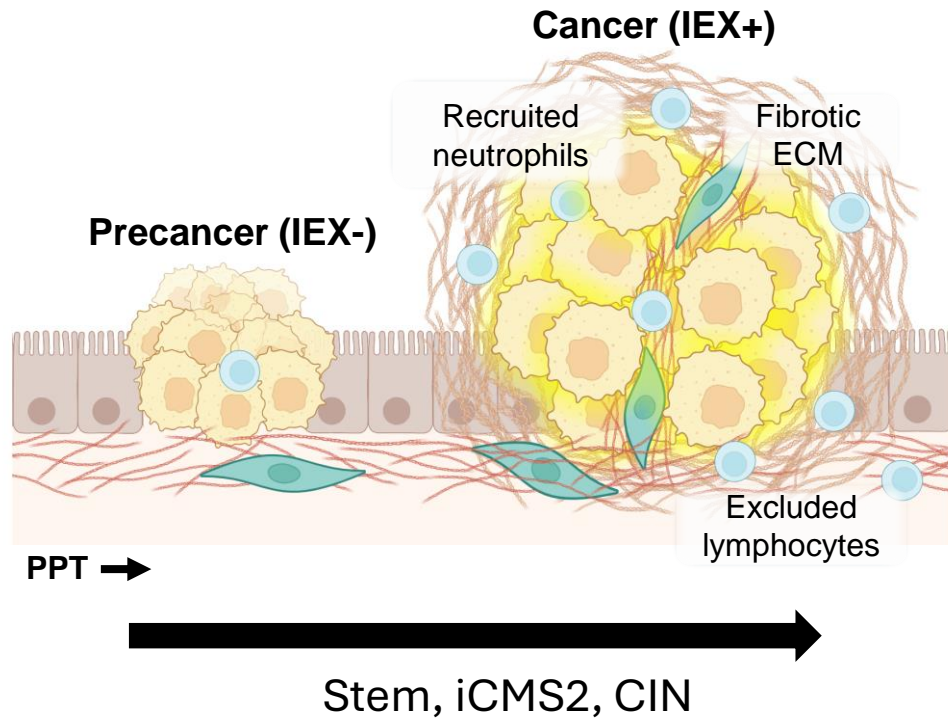
KO of DDR1 results in restraint of tumor progression in a CRC mouse model



* Accompanied by infiltration cytotoxic T cells and reduced suppressive cells (neutrophils)



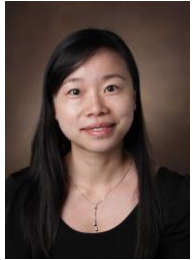
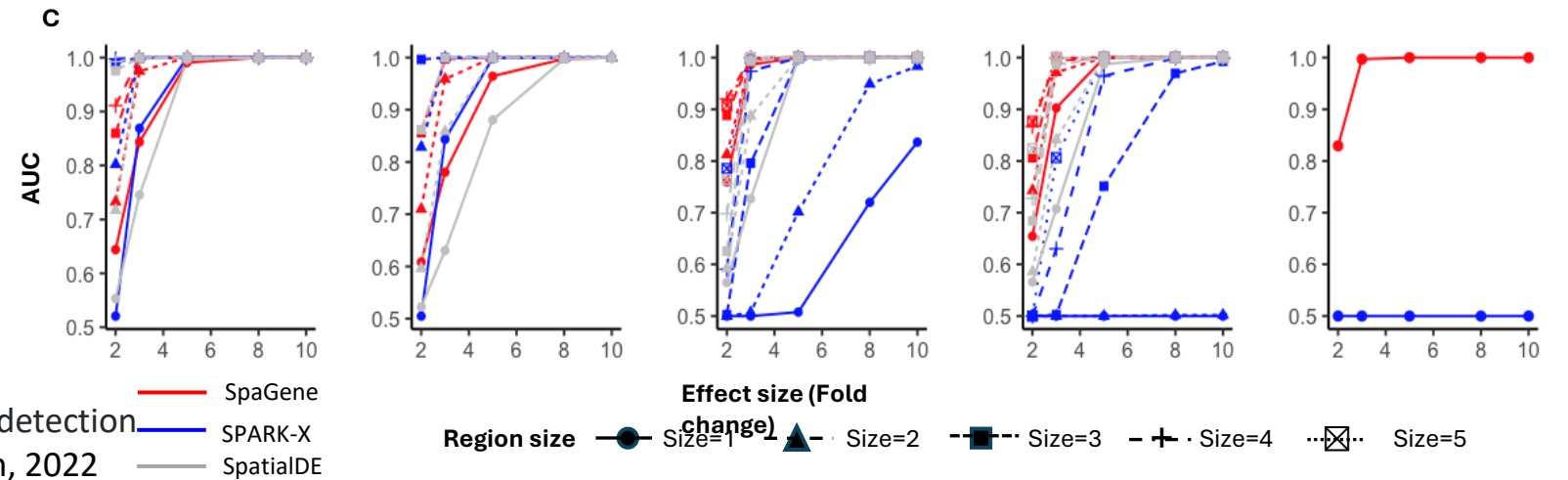
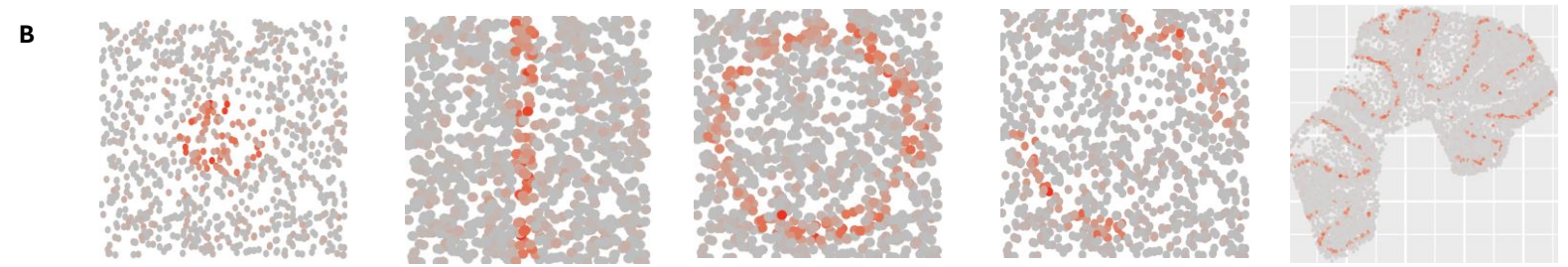
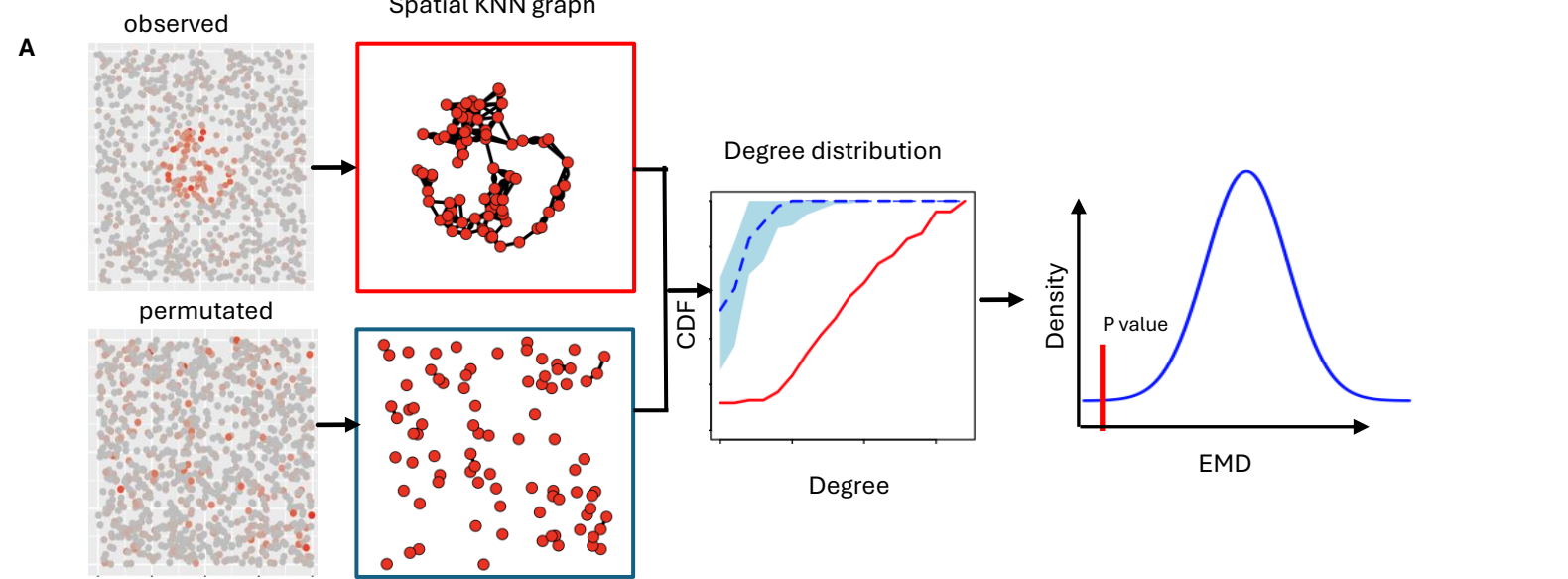
Summary



- Tumor subtypes constraint the mode of tumor evolution
- Stemness, hypoxia, immunosuppression are characteristics of transition from precancer to cancer
 - * TME - Neutrophils/ECM
- Tumor intrinsic immune exclusion program modulates the tumor microenvironment during progression

* Phase I clinical trial ongoing at VUMC target IEX with immune checkpoint blockade c/o Incendia

SpaGene: Identify spatial patterns and colocalization



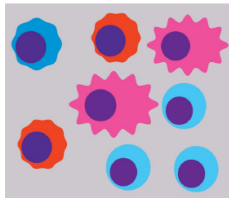
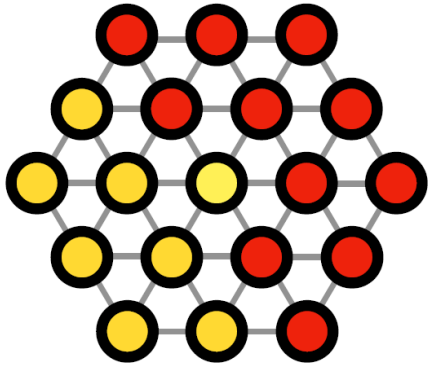
Dr. Qi Liu

<https://github.com/liuqivandy/SpaGene>

Liu Q, Hsu Chih-Yuan, Shyr Yu. Scalable and model-free detection of spatial patterns and colocalization, Genome Research, 2022

We are developing DeepEcoTyper, a geometric deep learning approach for embedding spatial transcriptomics data

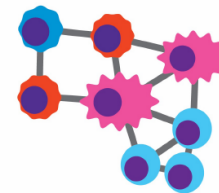
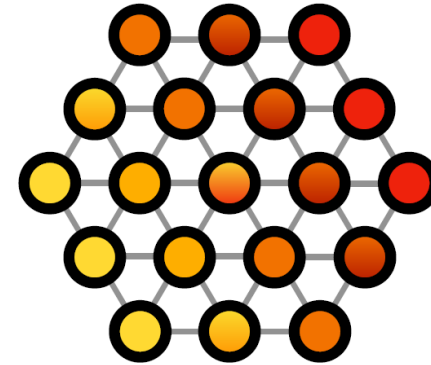
A neighborhood of
single cells or spots



DeepEcoTyper

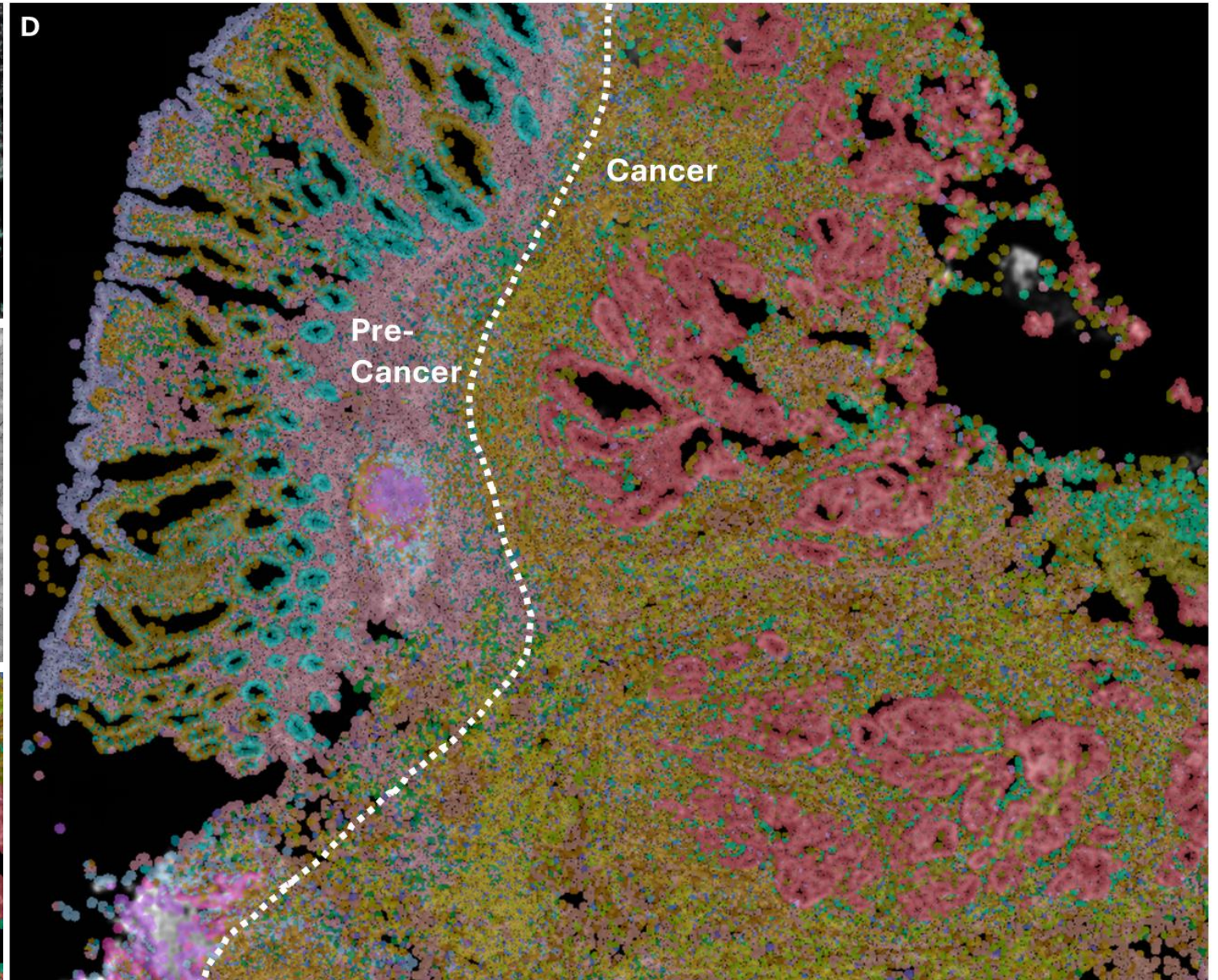
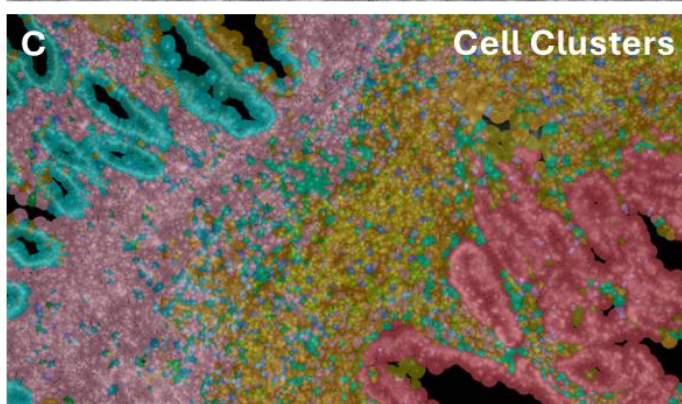
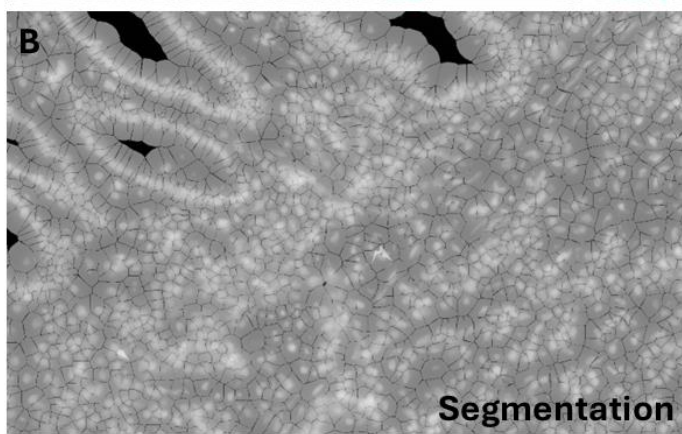
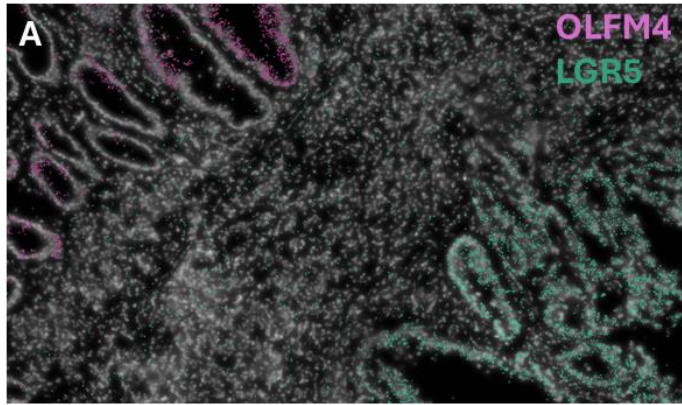


Geometric deep learning
creates spatially informed
representations



Newman lab

Xenium ST reveals distinct cellular microenvironments between precancer and cancer



Acknowledgements

Vanderbilt team

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Lucy Chen
Harsimran Kaur
Yilin Yang
Naila Tasneem

Alumni

Bob Chen
Cherie' Scurrah
Cody Heiser
Austin Southard-Smith
Janney Wang
Vishal Shah

Cores and Organizations

Cooperative Human Tissue
Network
Tissue Pathology Shared Resource
VANTAGE Sequencing Core
REDCap
Digital Histology Shared Resource
Molecular Epidemiology
Laboratory Shared Resource

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Dan Beauchamp
Memorial Fund

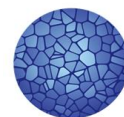


Heart felt thank you to all patient participants!

Join us for postdoc: ken.s.lau@vanderbilt.edu



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