Engineering High-Fidelity Early Cancer Models: Single-Cell Bioprinting in 2D and 3D to Mimic the Native Tumor Microenvironment

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INTERNATIONAL ALLIANCE FOR CANCER EARLY DETECTION

Image Source: Janesick et al. Nat Comms 202

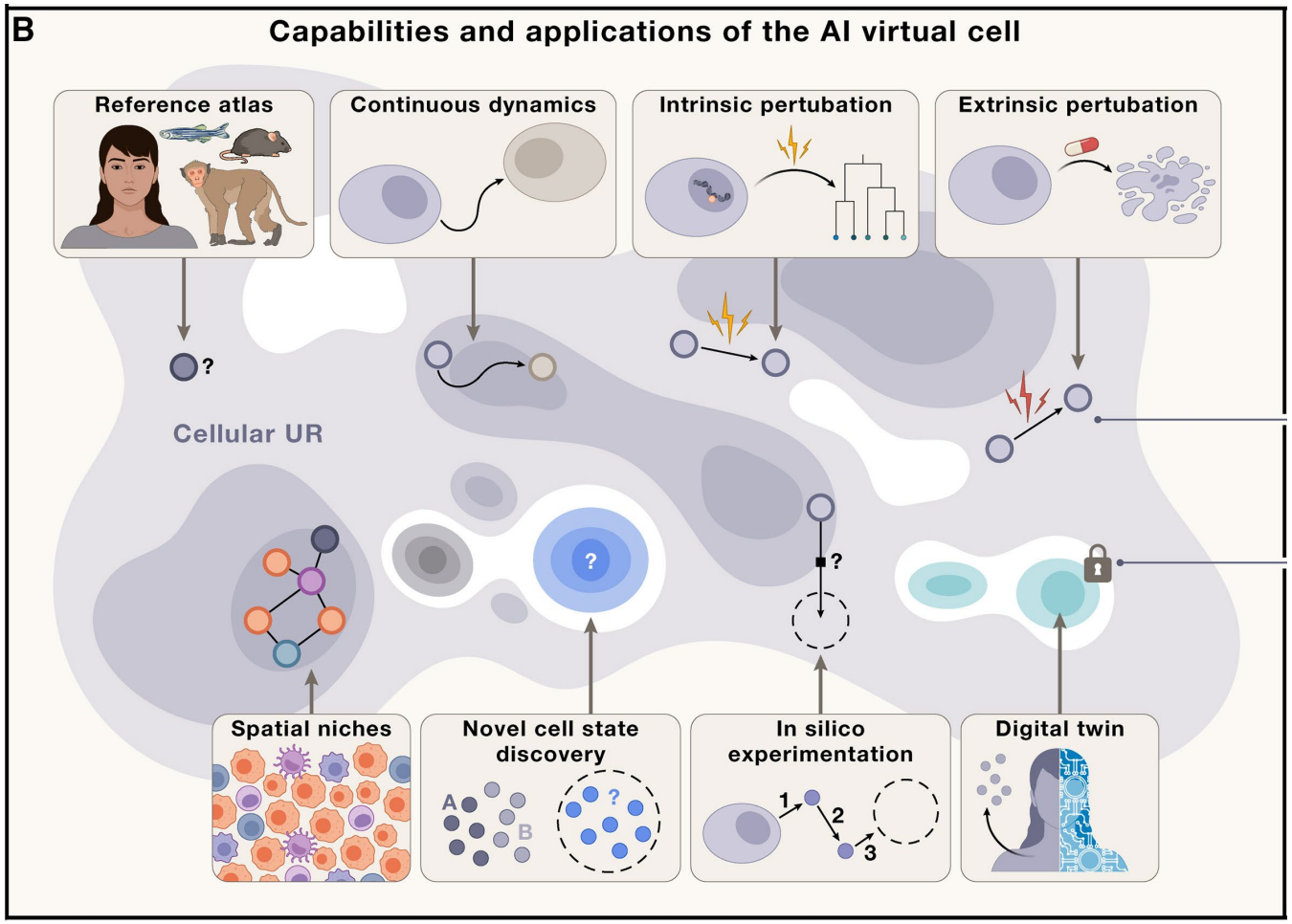
Deciphering the Complex TME

HTAN
HUMAN TUMOR ATLAS NETWORK

HUMAN CELL ATLAS

CZ CELL×GENE

HuBMAP
The Human BioMolecular Atlas Program

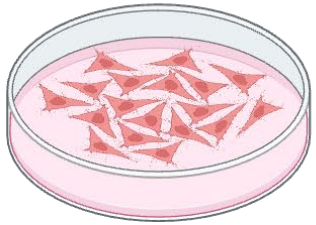


Bunne et al. Cell 2024

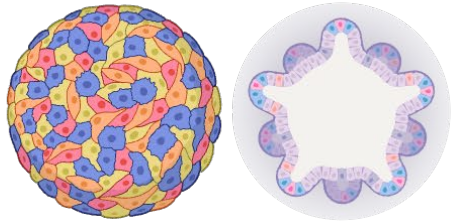
Spatial -omics, AI, and virtual cells are unlocking new insights,
yet much remains unknown about the mechanisms driving cancer evolution

Model Systems for Discovery

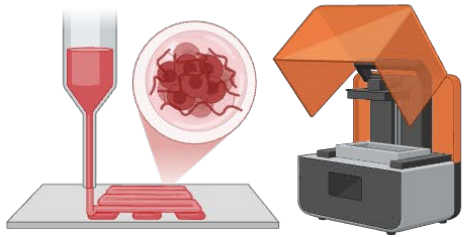
2D Cultures



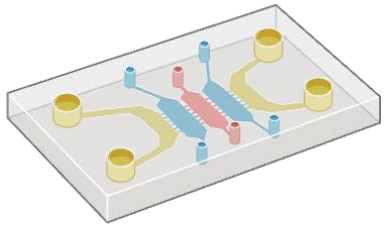
Spheroids & Organoids



3D Bioprinting



Organs-on-a-Chip



In Vivo

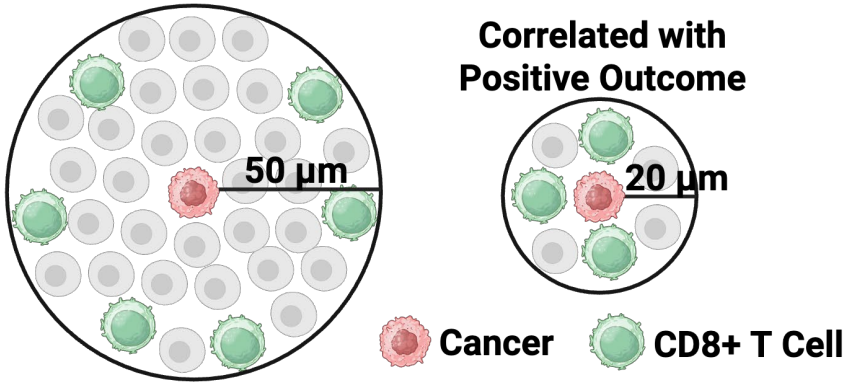
These approaches lack single-cell spatial resolution

npj | breast cancer Article

Published in partnership with the Breast Cancer Research Foundation

Spatial proximity of CD8$^+$ T cells to tumor cells predicts neoadjuvant therapy efficacy in breast cancer

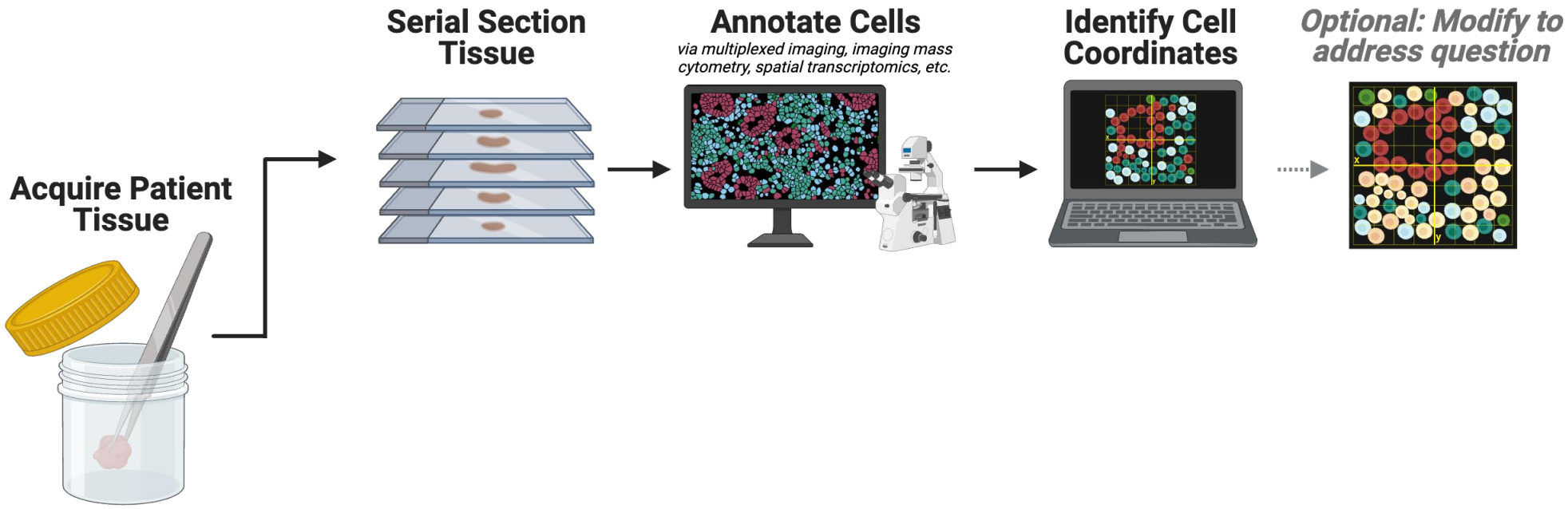
Hongling Liang[1], Jianqing Huang[1,2], Hongsheng Li[1], Weixing He[1], Xiang Ao[1], Zhi Xie[3,4], Yu Chen[3,4], Zhiyi Lv[3], Leyao zhang[1], Yanhua Zhong[1], Xiaojun Tan[5], Guodong Han[1], Jie Zhou[1], Ni Qiu[1], Ming Jiang[1], Haoming Xia[1], Yongtao Zhan[1], Lei Jiao[6], Jie Ma[6], Derek Radisky[7] ✉, Jia Huang[2] ✉ & Xuchao Zhang[3,4] ✉



Objective

Engineer tumor avatars that replicate the native cellular microenvironment to systematically dissect and understand the tumor microenvironment

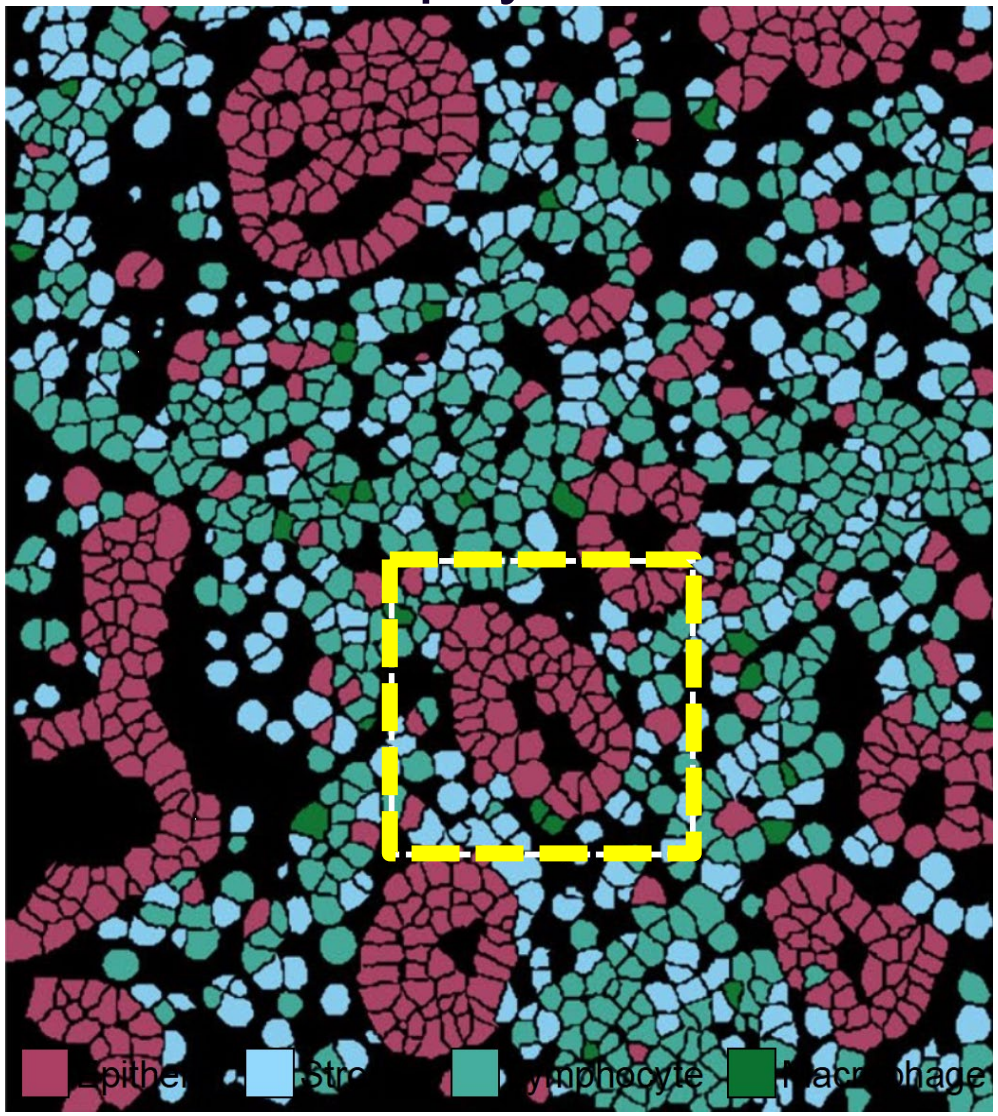
Approach



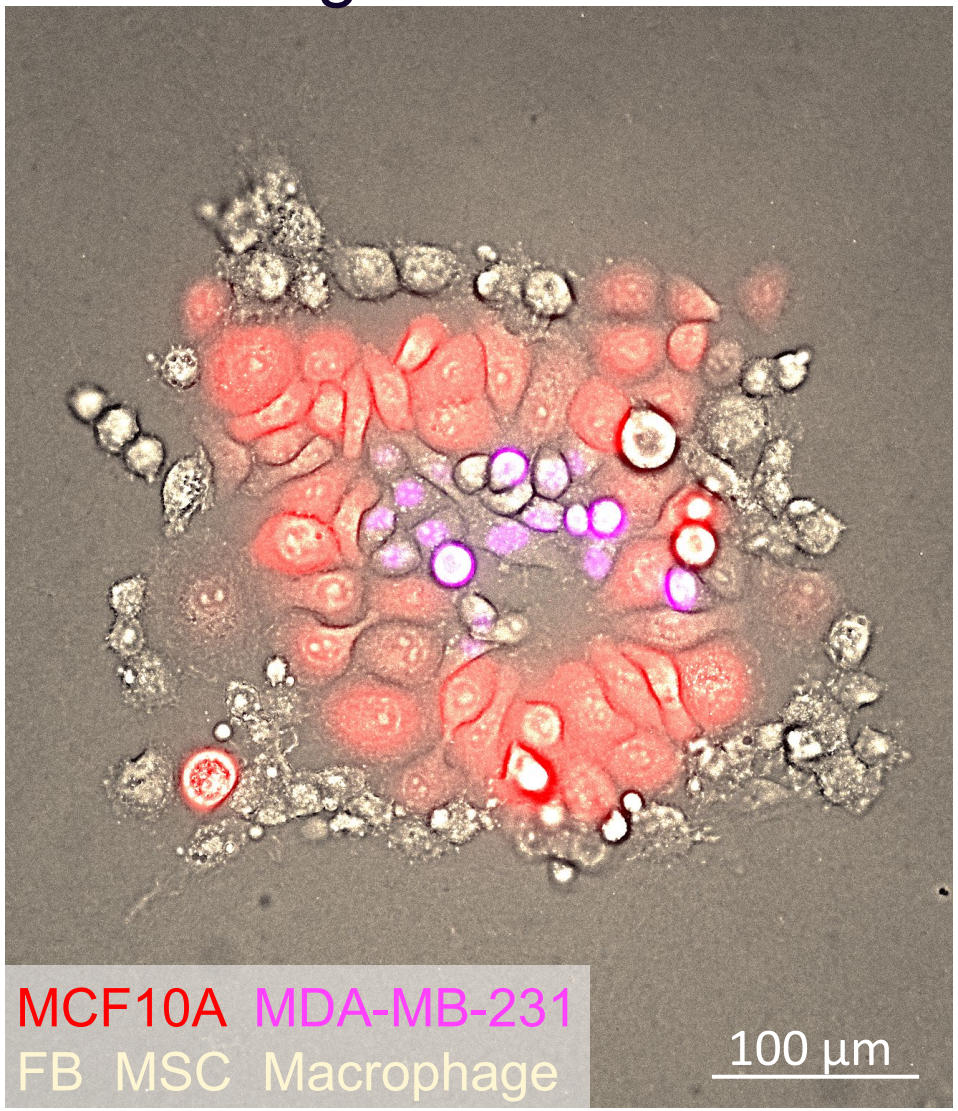
<u>Goal</u>: Fabricate patient derived tumor avatars with single-cell spatial resolution to 'replicate' the native tumor microenvironment

2D Single-Cell Spatial Patterning with Subcellular Resolution

Biopsy ROI



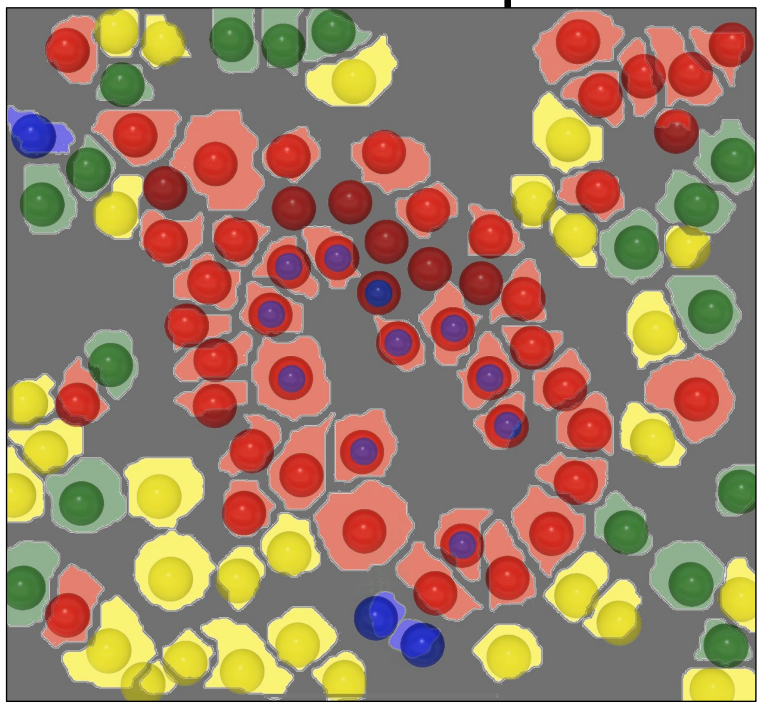
Single-Cell Print



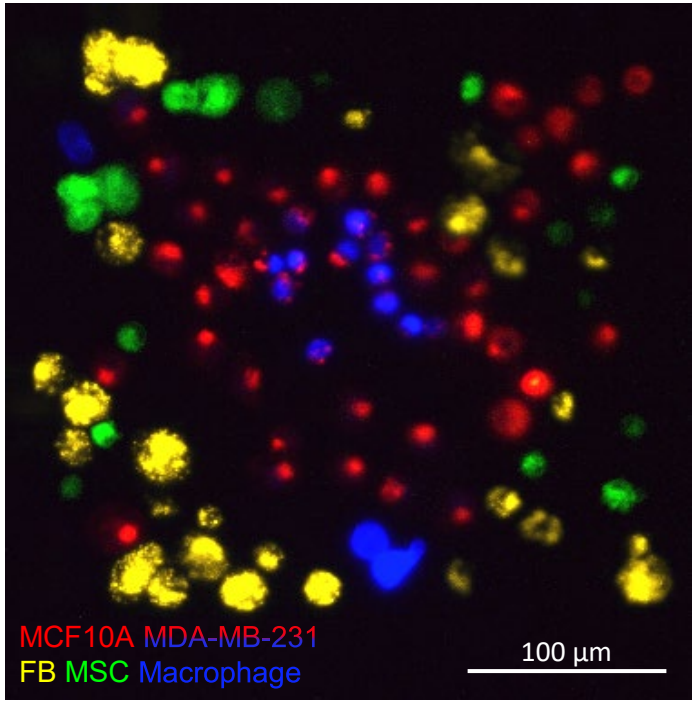
Annotated biopsy from Ali et al. Nature Cancer 2022

2D Single-Cell Spatial Patterning with Subcellular Resolution

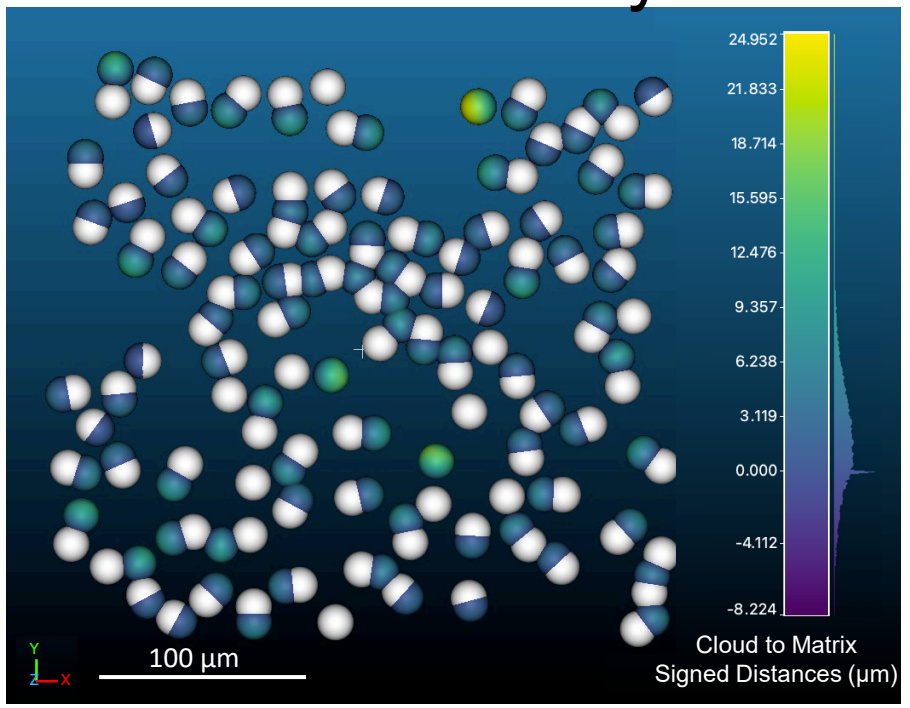
Print Map



Print Result

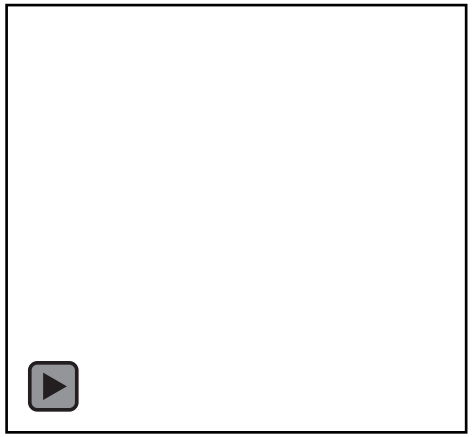


Print Fidelity



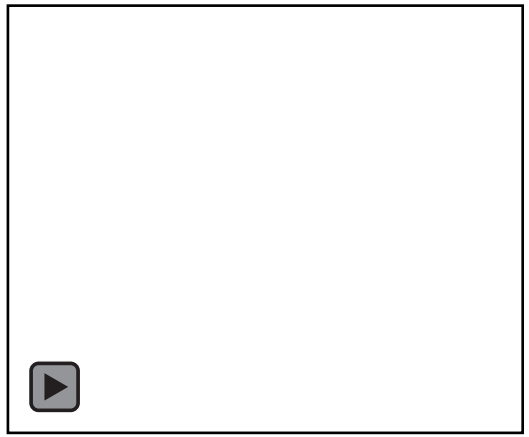
Prints Are Compatible With Spatial Tools

Live Cell Imaging



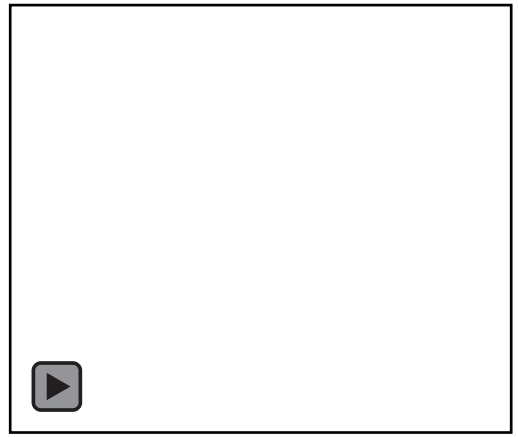
MDA-MB-231 Myoepithelial

Engineered Reporters

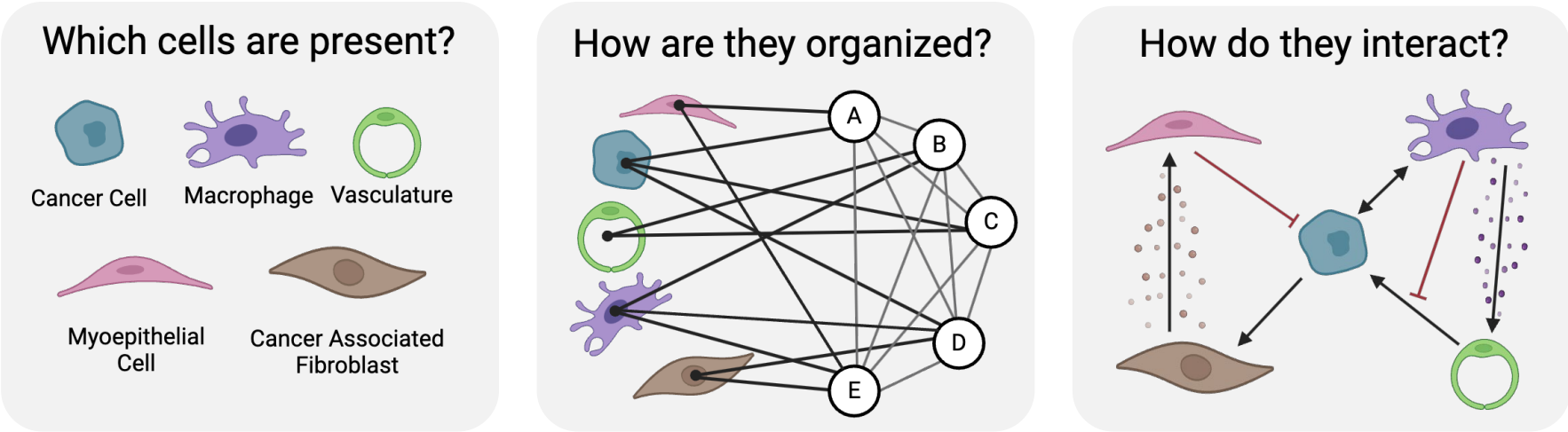


Davies et al. Cell Syst. 2020

Spatial Transcriptomics

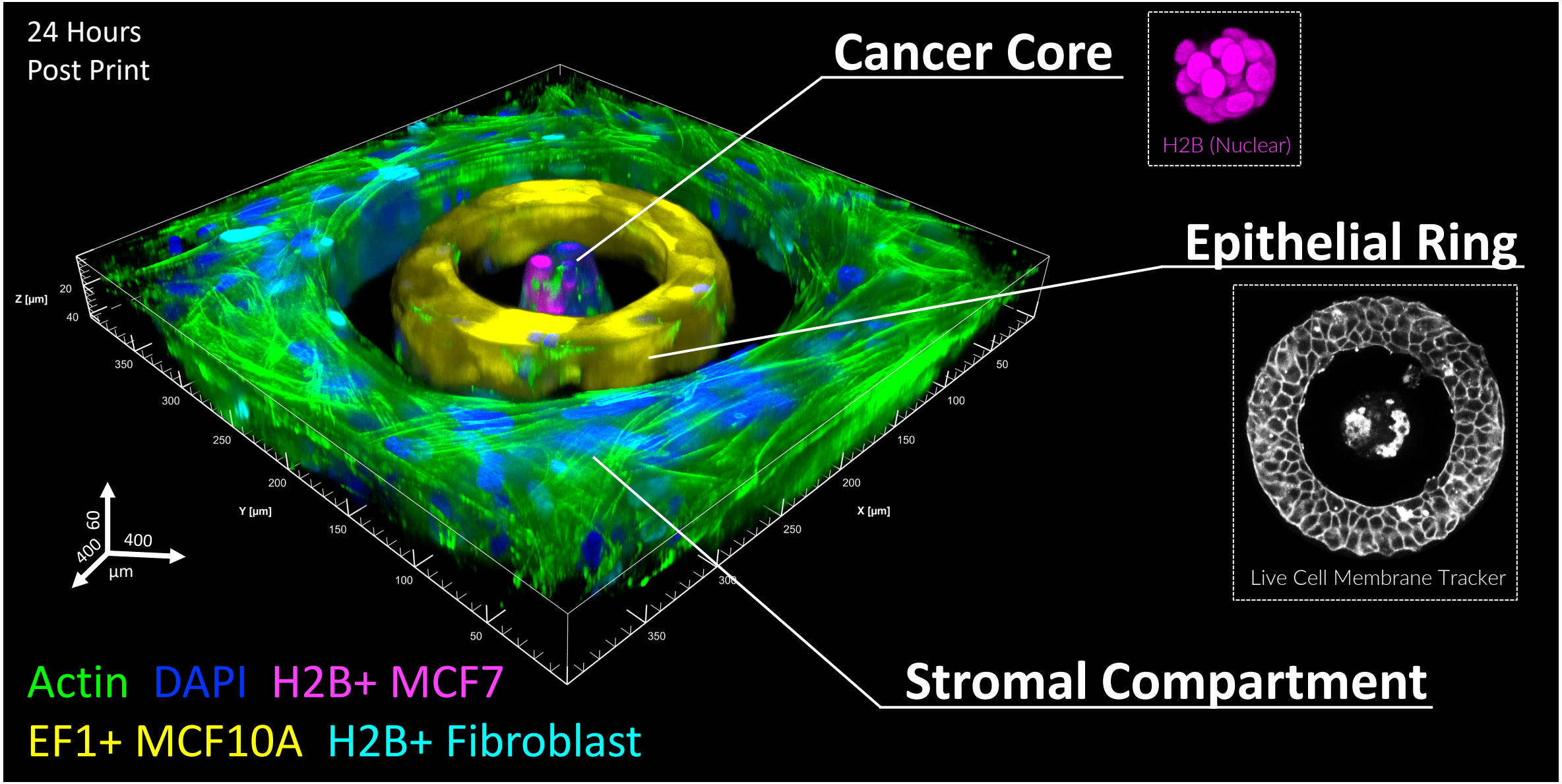


Visium HD Analysis

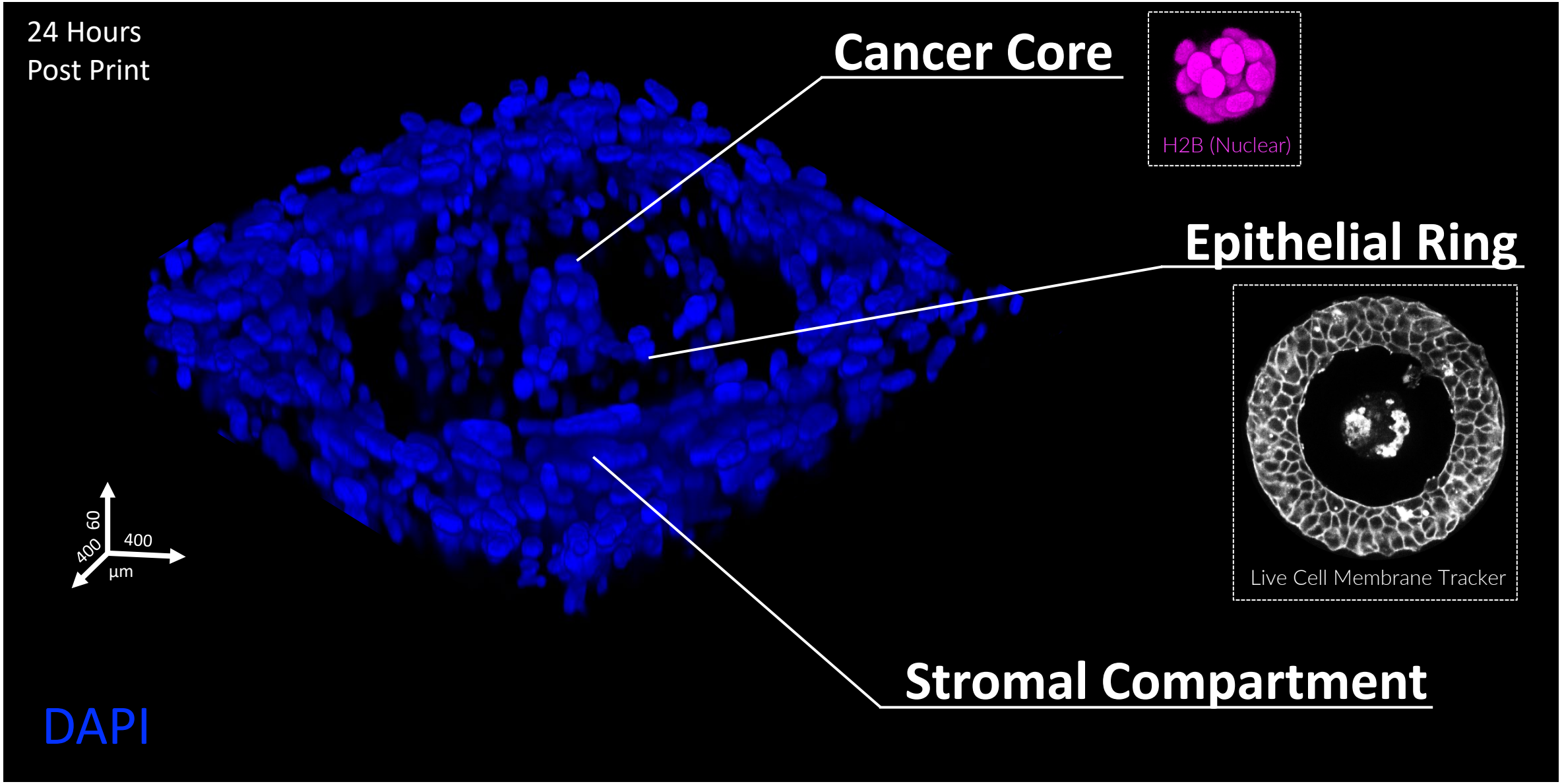


Adapted from Rozenblatt-Rosen et al. Cell 2020

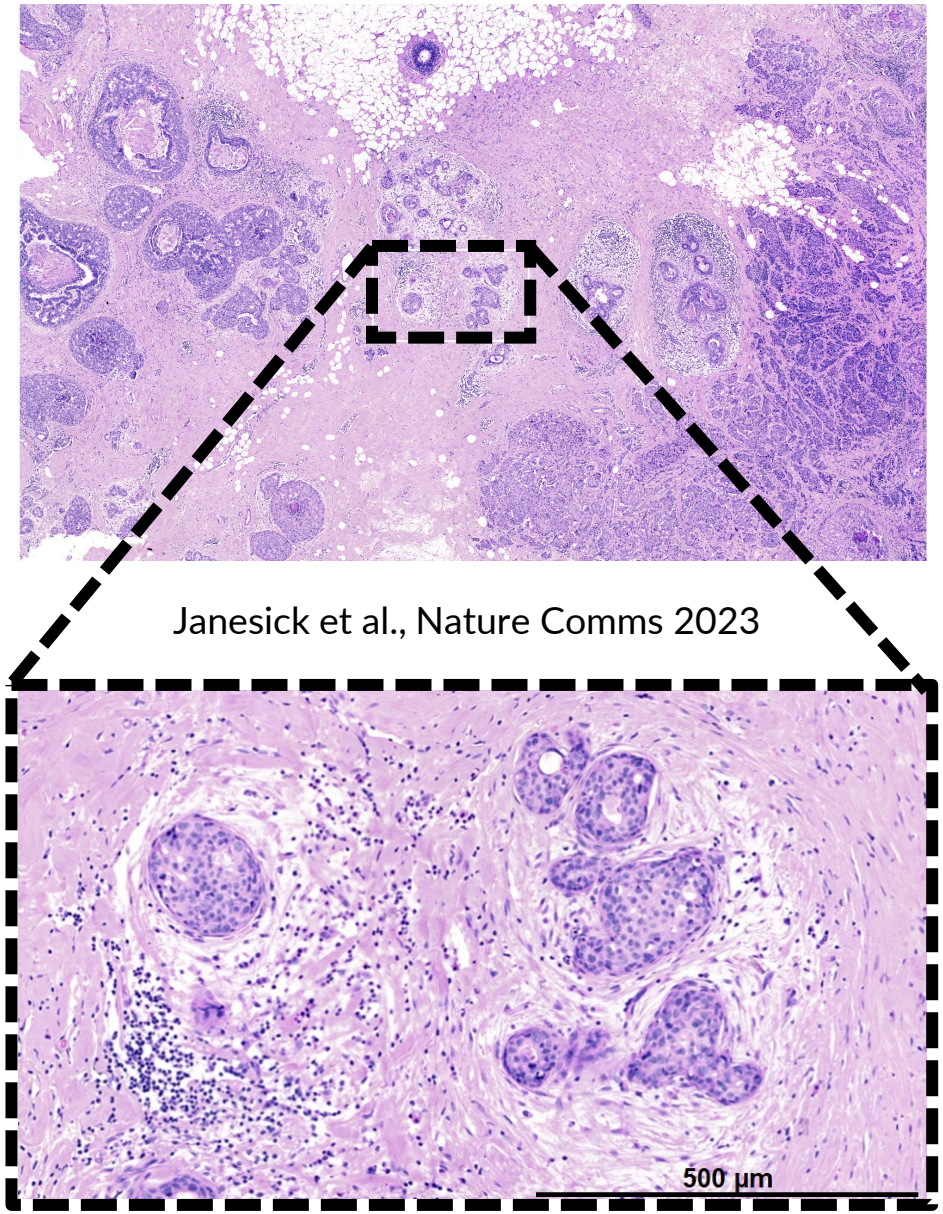
3D, Cell Dense, & Spatially Resolved TME Model

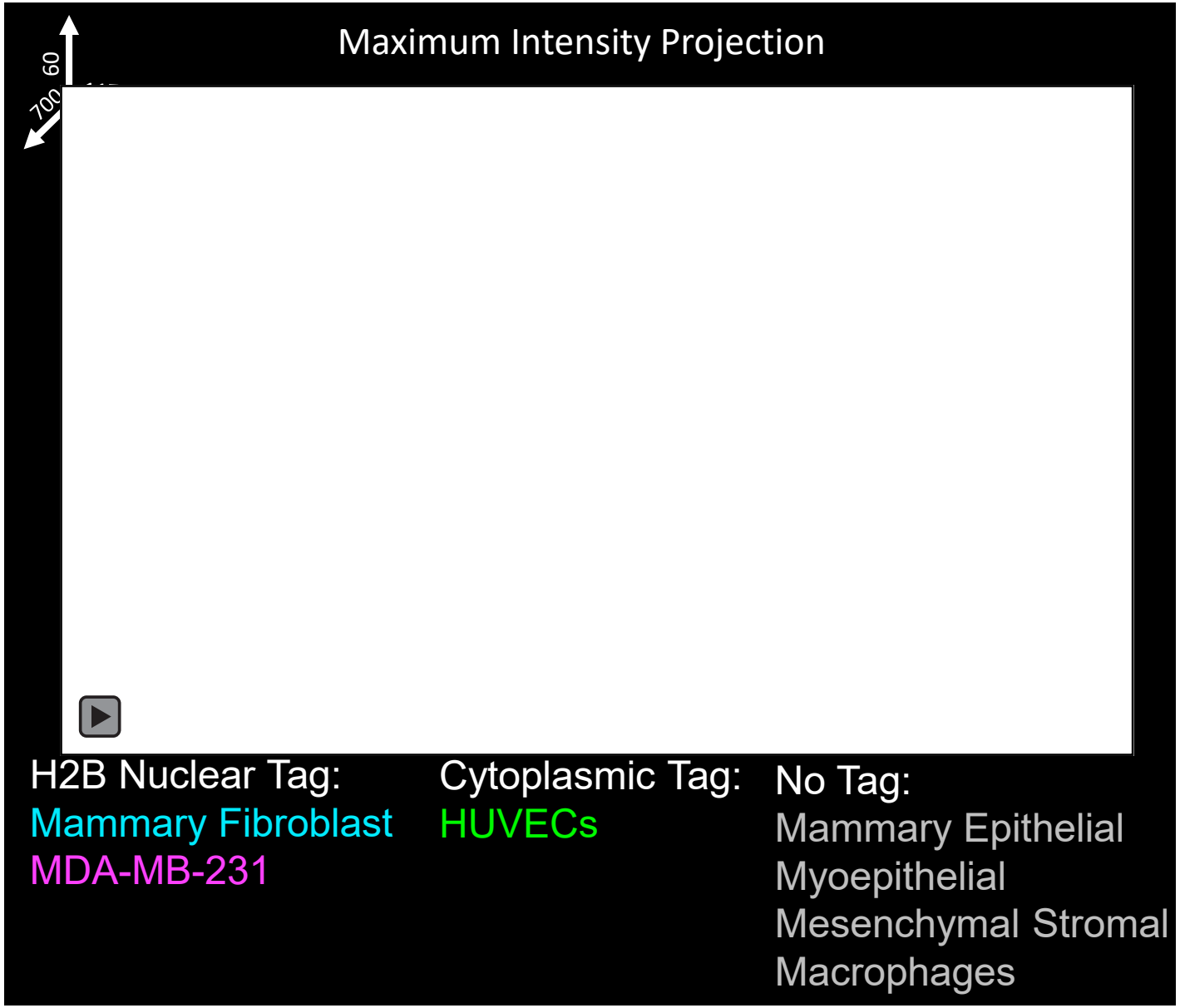


3D, Cell Dense, & Spatially Resolved TME Model



3D & Highly Heterogeneous Breast TME Model



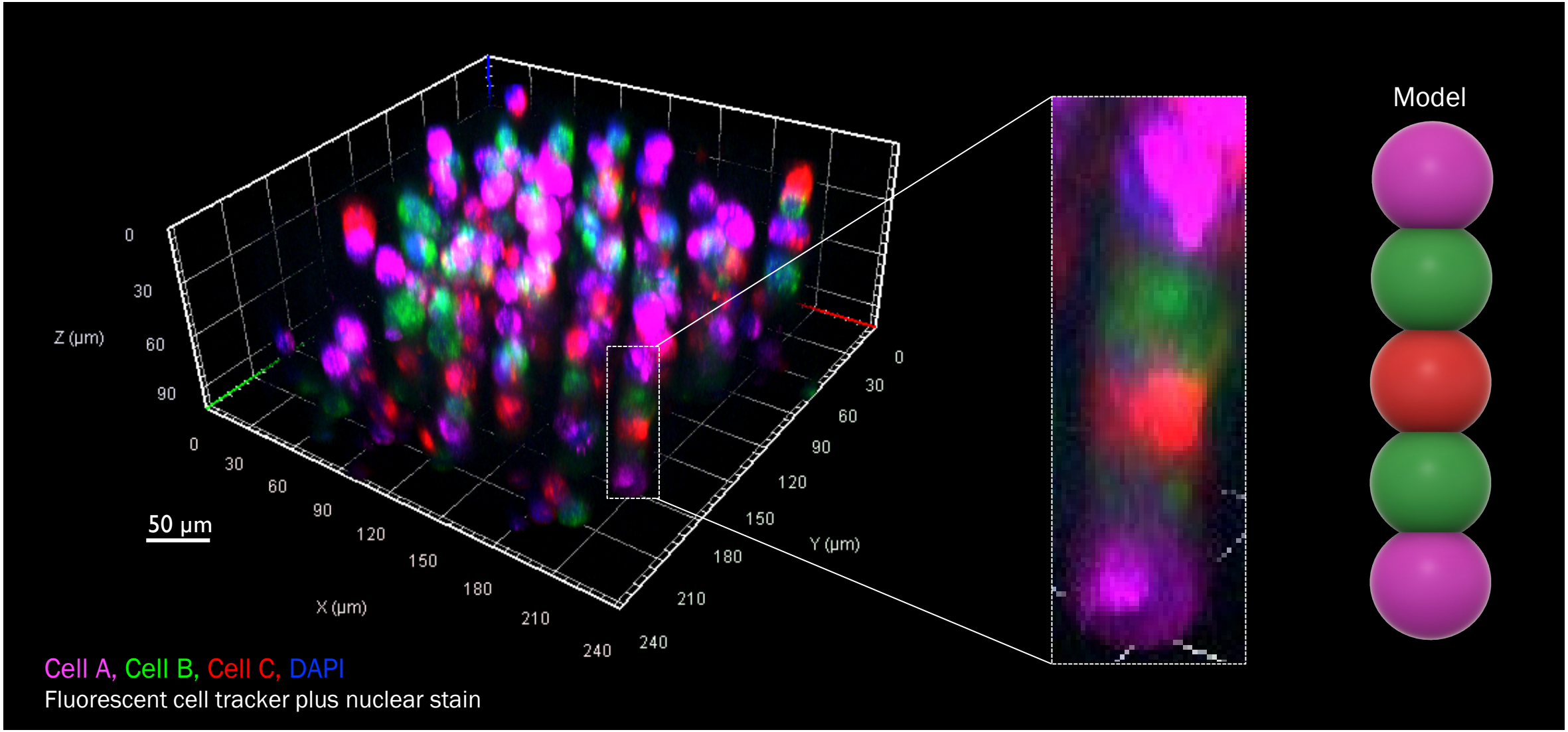


3D Model Mimics Gross Histological Features

Patient Biopsy H&E → Engineered Tissue

H&E from 10x Genomics public dataset. Janesick et al., Nature Comms 2023

In Development: 3D Single-Cell Resolution

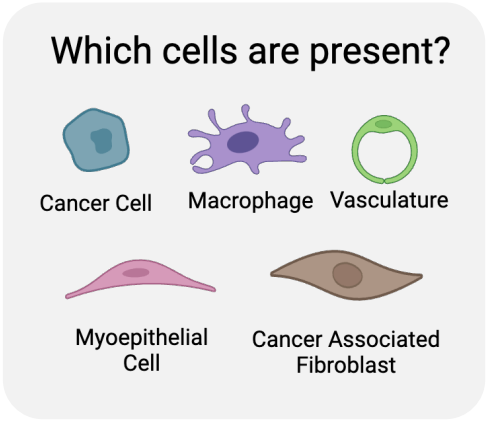


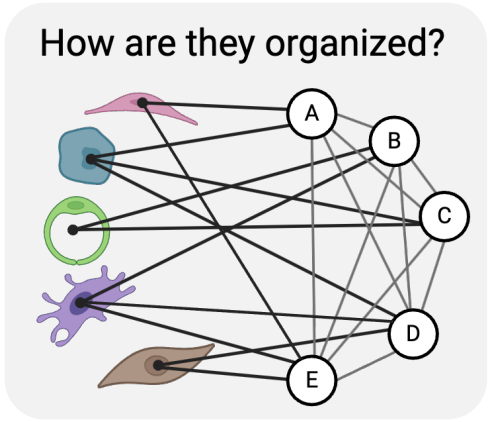
Summary of Platform Developments: Spatial Toolkit

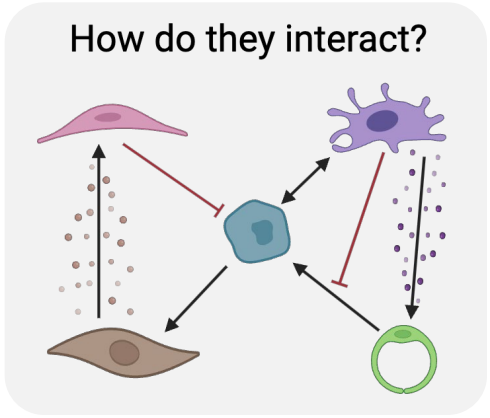
1. **Fabrication:** Heterogeneous, cell dense, tissue fabrication in 2D with subcellular resolution and 3D with 60 µm resolution
2. **Cell Sourcing:** Tissue dissociation and expansion for patient matched, immune competent models
3. **Live Cell Analysis:** Live cell imaging to observe evolution and cell-cell interactions in real time
4. **Spatial Transcriptomic Analysis**: Whole transcriptome with 2 µm resolution

Platform enables systematic testing of cause-and-effect relationships that drive cancer evolution

Summary of Platform Developments: Spatial Toolkit







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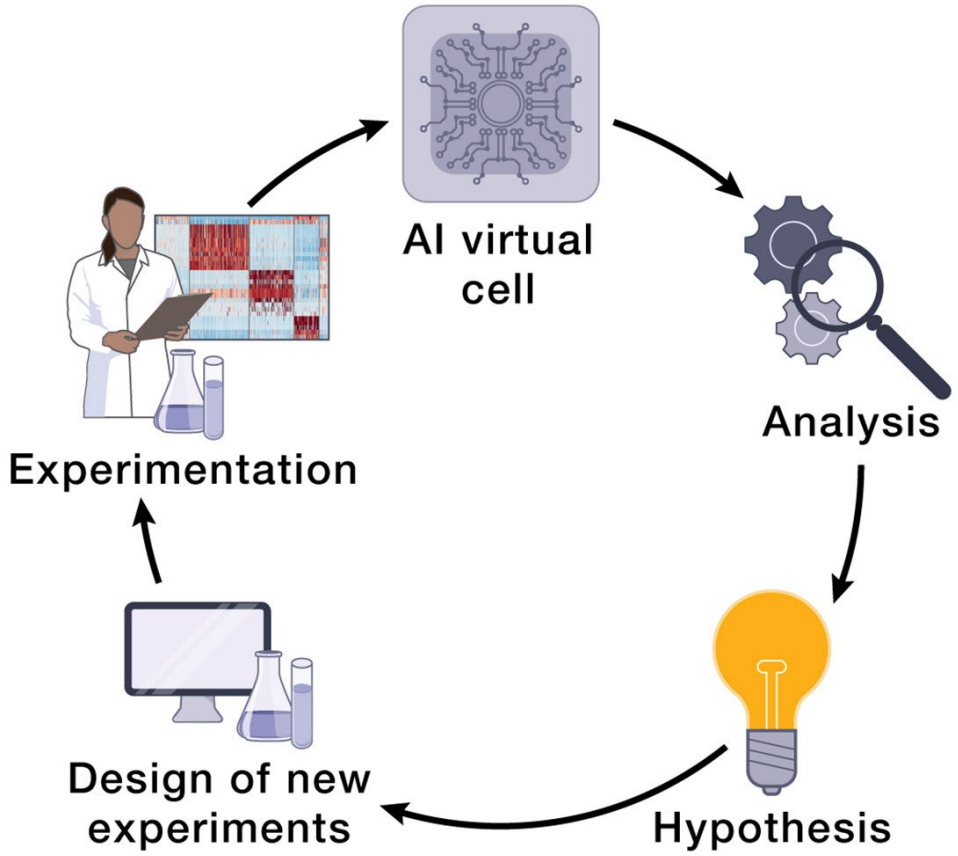

Bunne et al. Cell 2024

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