

Mount Sinai



The Tisch Cancer Institute

# AVANCES EN LA BIOLOGIA DEL CANCER DE MAMA

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## DISCLOSURES:

Consultant for Modern Meadow

# Tumor cell dissemination and metastasis in breast cancer

## Breast Primary Tumor



✓ About 13% (about 1 in 8) of U.S. women are going to develop invasive breast cancer in the course of their life.

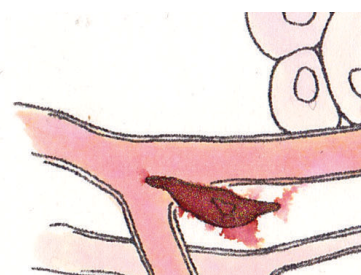
✓ 90% of BC deaths are from metastatic breast cancer.

**Intravasation/  
Extravasation**



By artist GB Kim

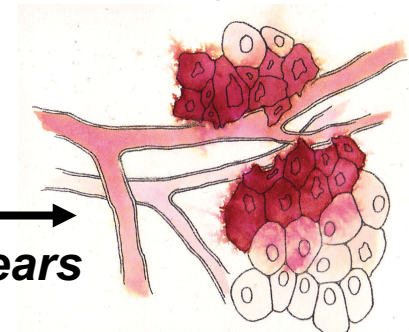
**Dormancy**



**Initial  
survival**

**Years**

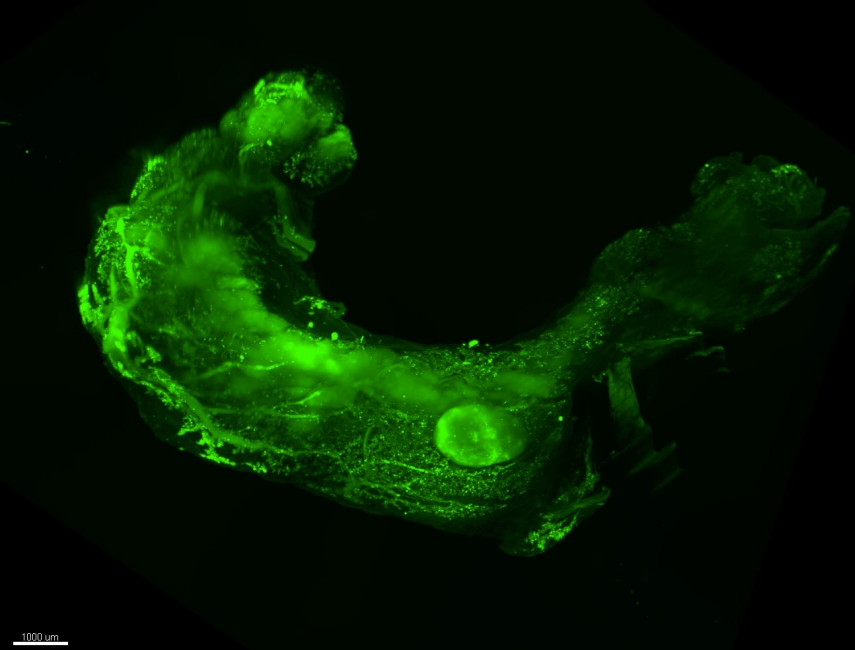
**Outgrowth**



*Di Martino et al., Essays in Bio. 2019*

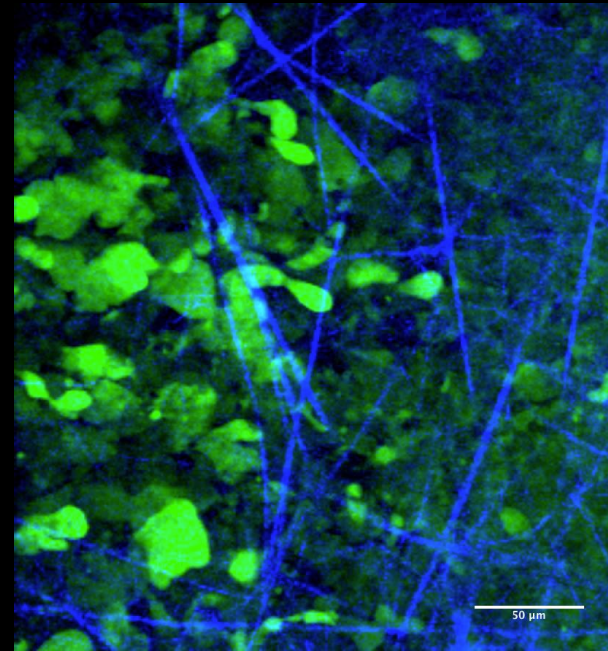
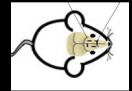
# Imaging technologies reveal new insights into breast tumor progression

Lattice Light-Sheet microscopy



Mammary Gland

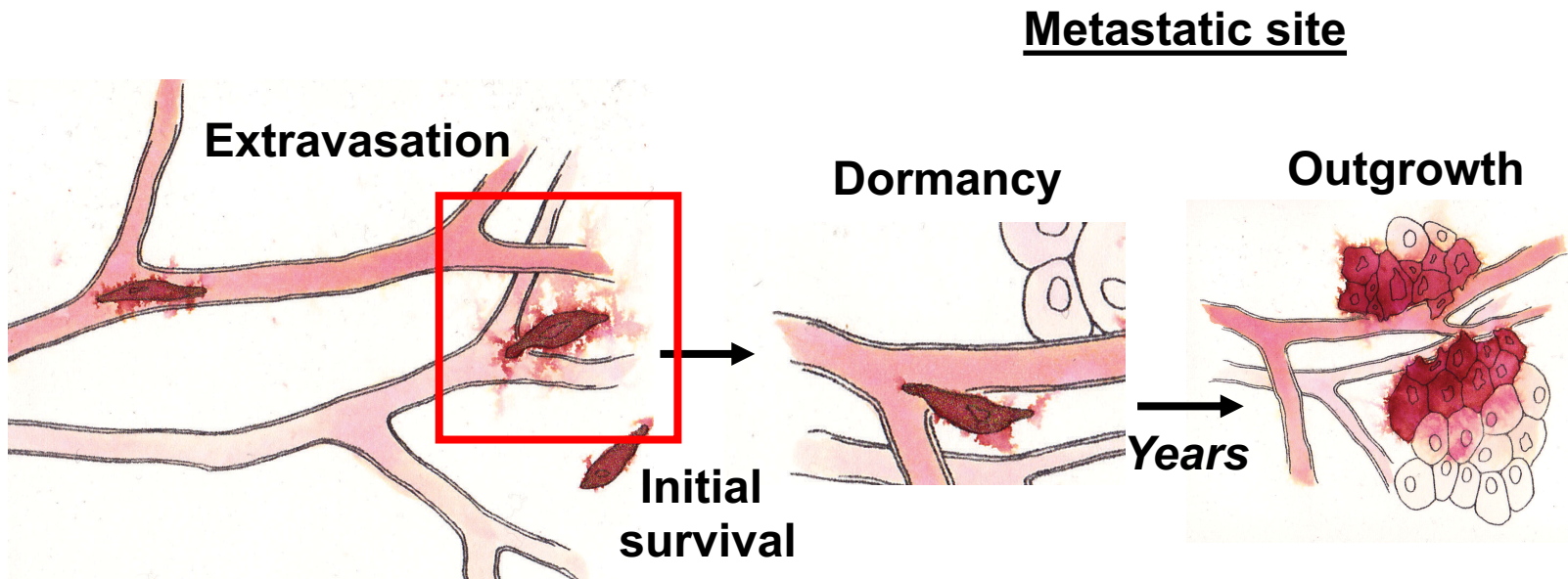
Intravital microscopy



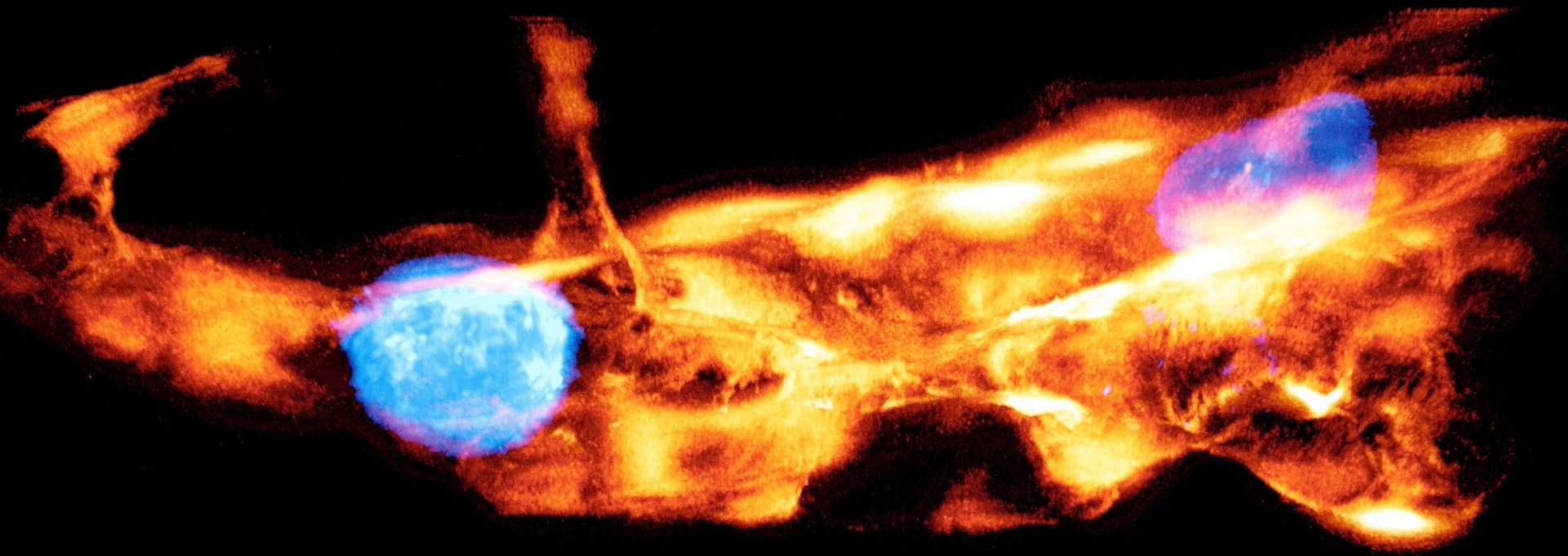
Tumor cell/SHG Collagen ECM

Priem et al., *Cell* 2020  
Mondal et al., *Cell Reports* 2022  
Di Martino et al., *EB* 2019  
Olmeda et al., *Nature* 2017  
Norbe et al., *Nature Cancer* 2021

# Tumor cell dissemination and metastasis

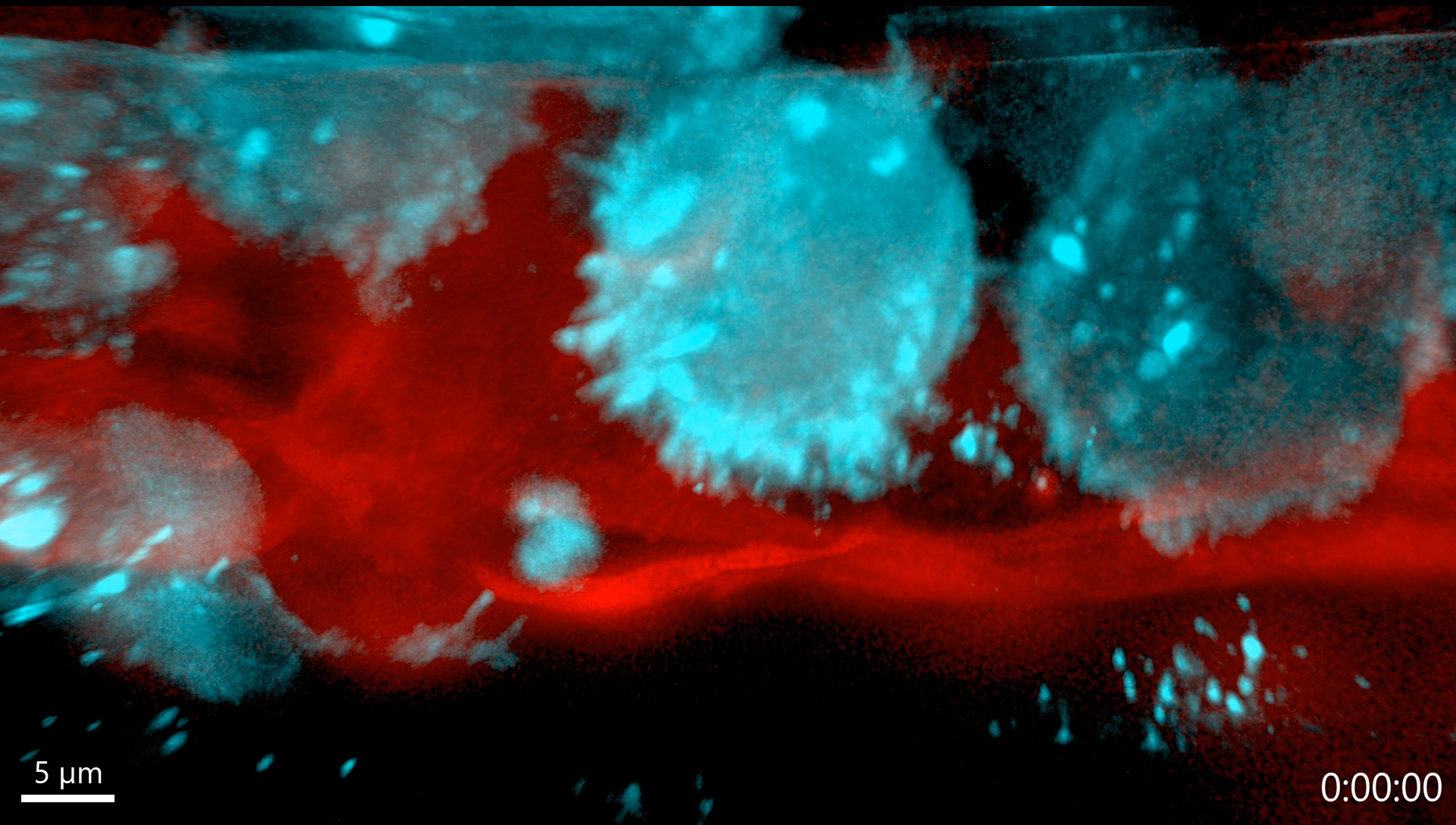


How do disseminated cancer cells extravasate?



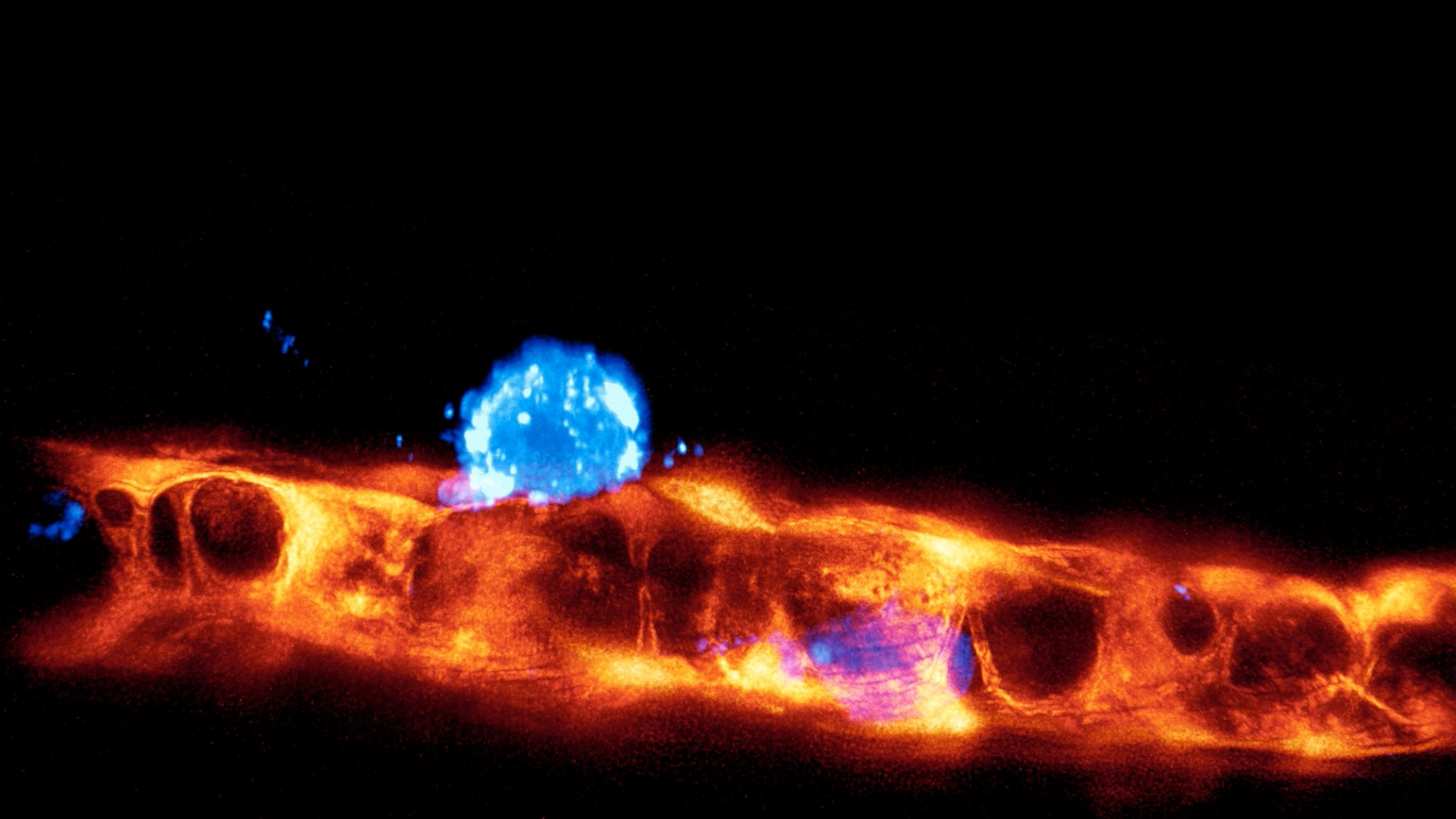
10  $\mu\text{m}$

0:01:13



5 μm

0:00:00

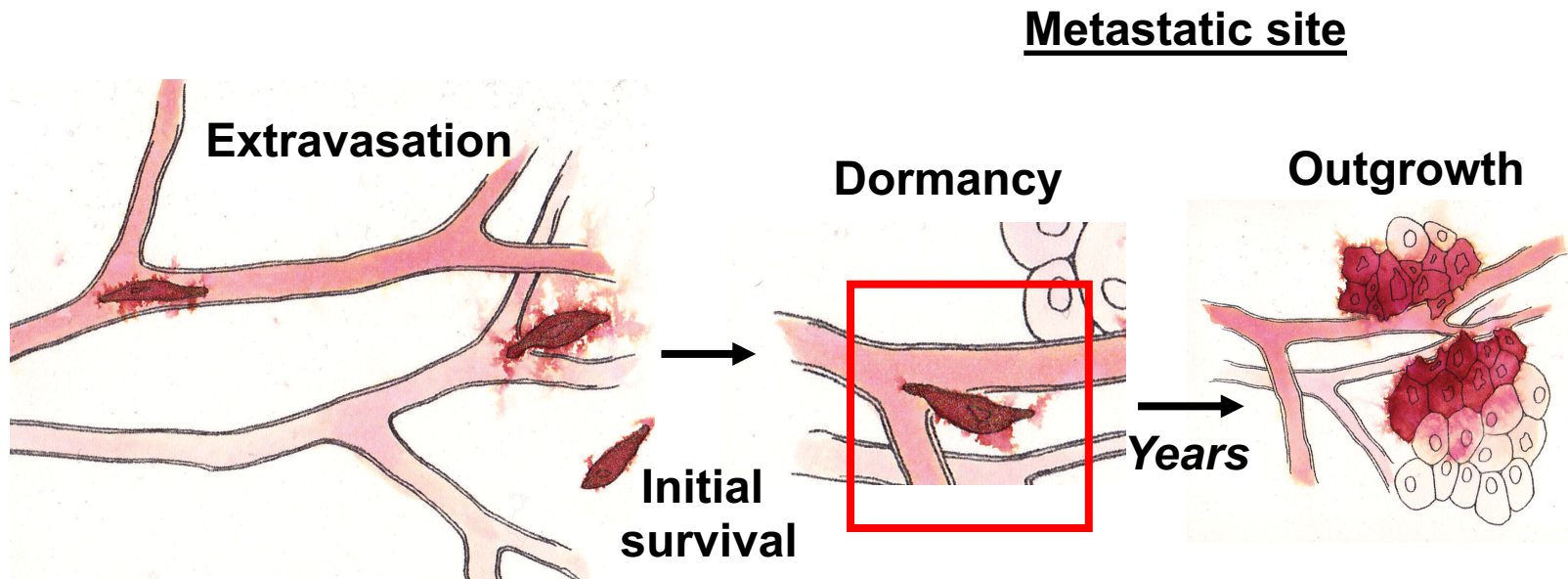


10  $\mu\text{m}$

0:00:00

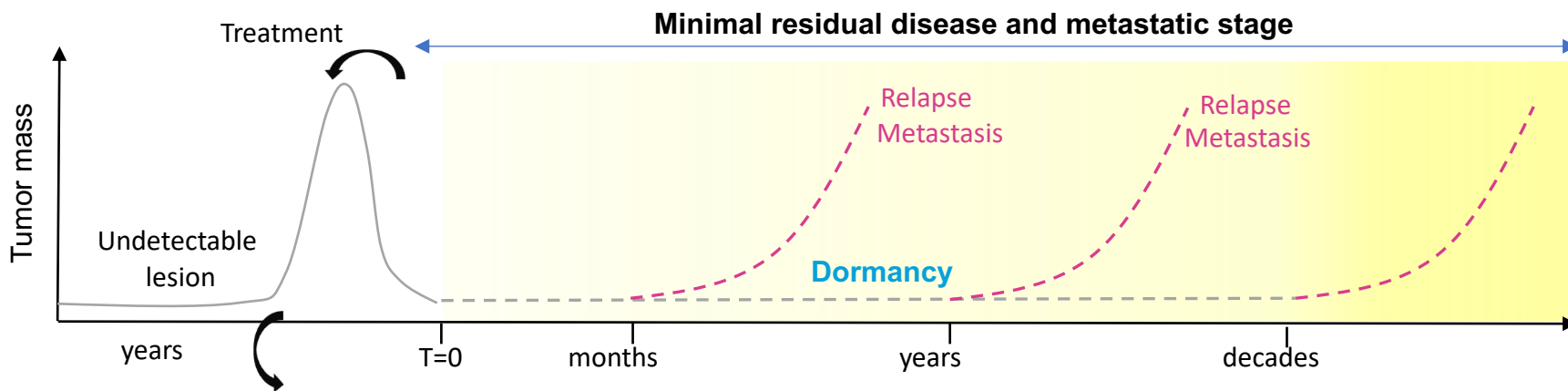


# Tumor cell dissemination and metastasis



**How do disseminated cancer cells remain dormant at metastatic sites?**

# Tumor dormancy and the time to metastasis in breast cancer



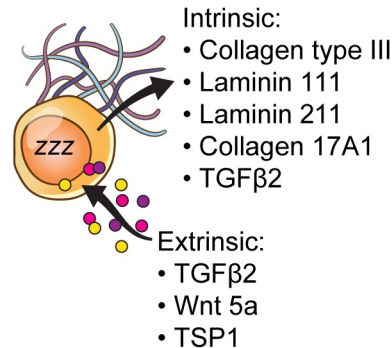
Early tumor cell dissemination

Adapted from Sosa et al., *Nature Rev. Cancer* 2014

## DORMANCY HALLMARKS

- ✓ QUIESCENCE (G0 Reversible growth arrest)
- ✓ SURVIVAL PATHWAYS
- ✓ LATENT PLURIPOTENCY
- ✓ PLASTIC STATE
- ✓ EPIGENETIC REPROGRAMMING

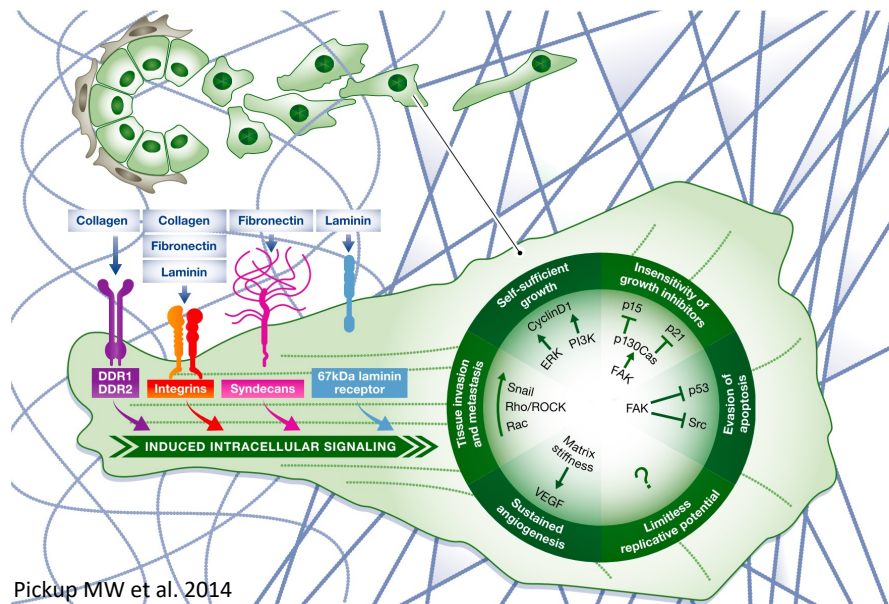
## Single Cell Dormancy



J Gregory ©2022 Mount Sinai Health System

# THE ECM IN CANCER PROGRESSION

## Influence of ECM on tumor progression



Pickup MW et al. 2014

- ✓ ECM Composition (tumor cells and stroma)
- ✓ ECM stiffness
- ✓ ECM organization
- ✓ Receptors available

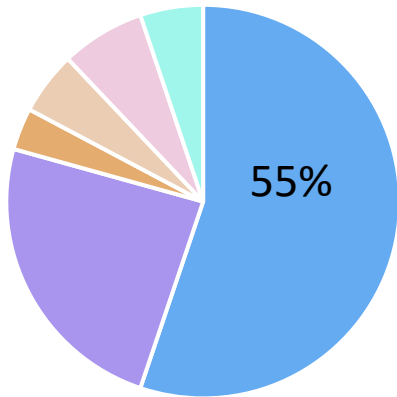
***Do tumor cells control their metastatic fate locally by regulating ECM composition and architecture?***

# Dormant matrixome is enriched in collagens

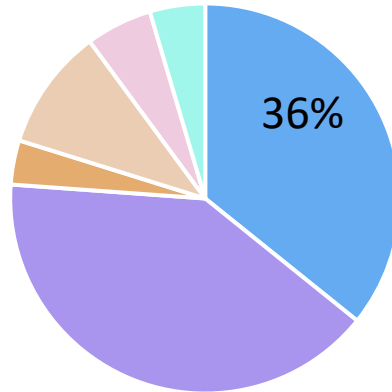
## ECM PROTEOMICS

### Matrixome subcategories

*Dormant*

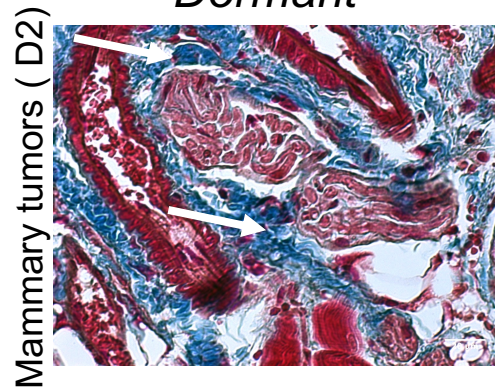


*Proliferative*

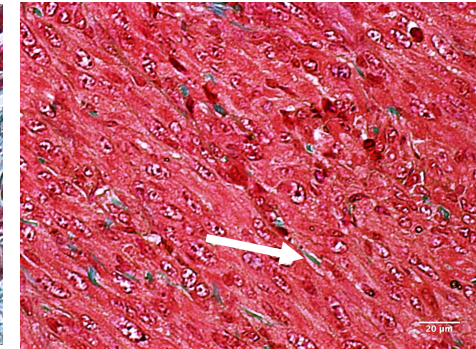


### Trichrome staining

*Dormant*



*Proliferative*



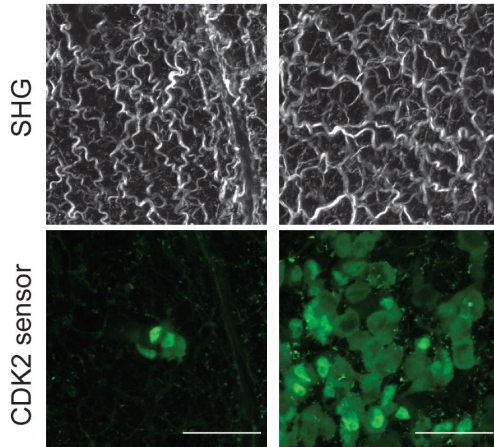
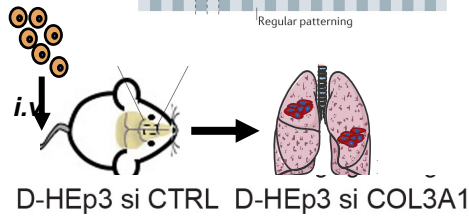
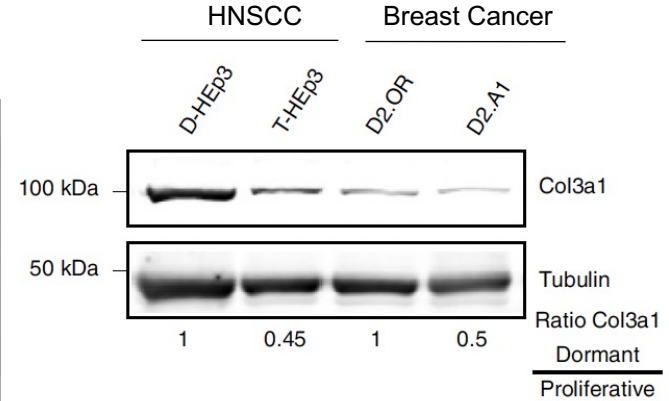
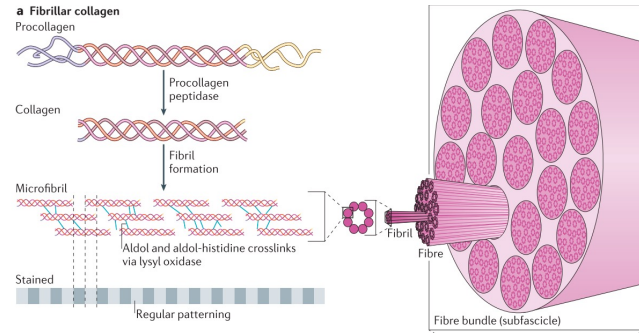
Mammary tumors ( D2)

# Tumor-derived COL III is required for dormancy

## Humana collagens peptide intensity in dormant tumors

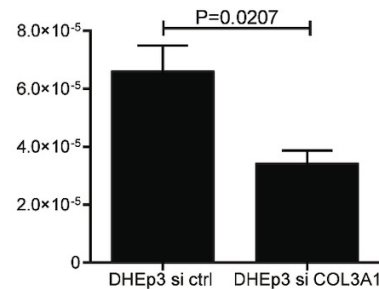
	Peptide Intensity
COL3A1	4.17E+08
COL6A3	1.98E+07
COL5A2	6.24E+06
COL1A1	2.63E+06
COL1A2	7.39E+05
COL5A1	7.24E+05
COL5A3	5.69E+05

## Fibrillar Collagens



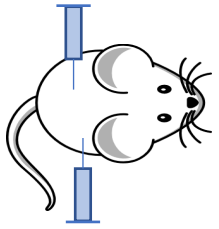
	single cells	clusters < 20 cells	micromets
si CTRL	7/7	5/7	0/7
si COL3A1 pool	0/7	3/7	6/7

## NR2F1 mRNA levels



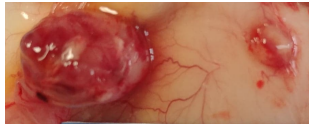
# COL III reprogram cancer cells into dormancy

Tumor cells  
+PBS



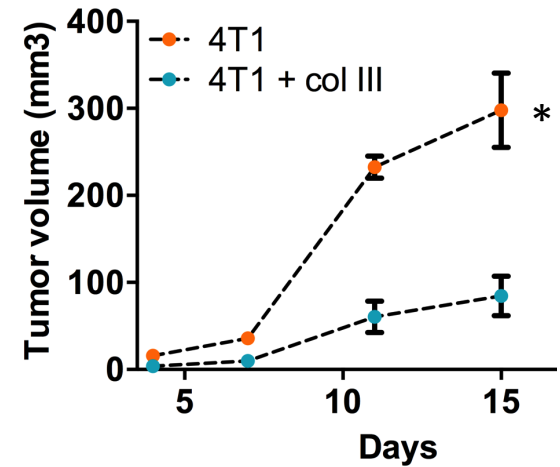
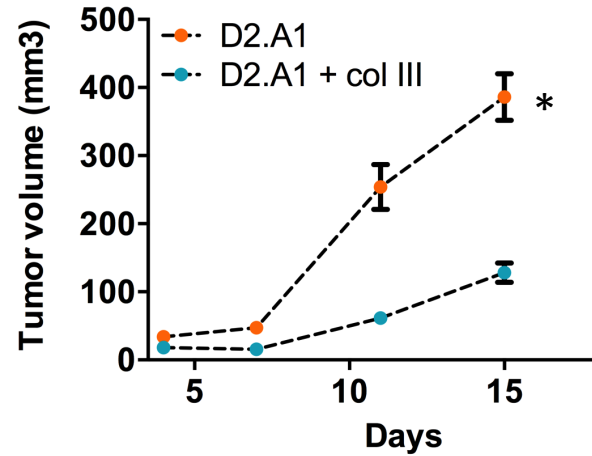
PBS

COL III

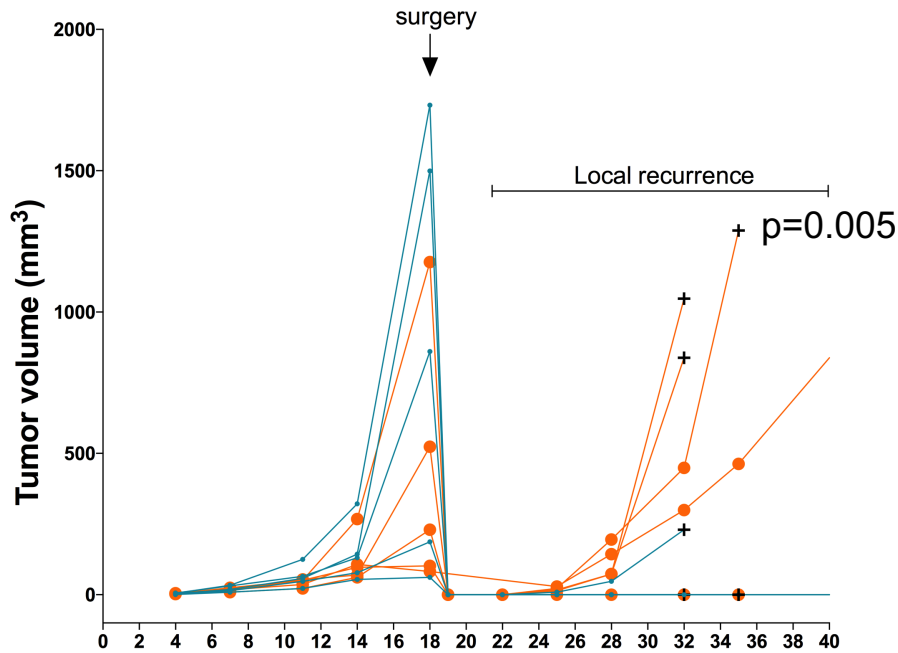
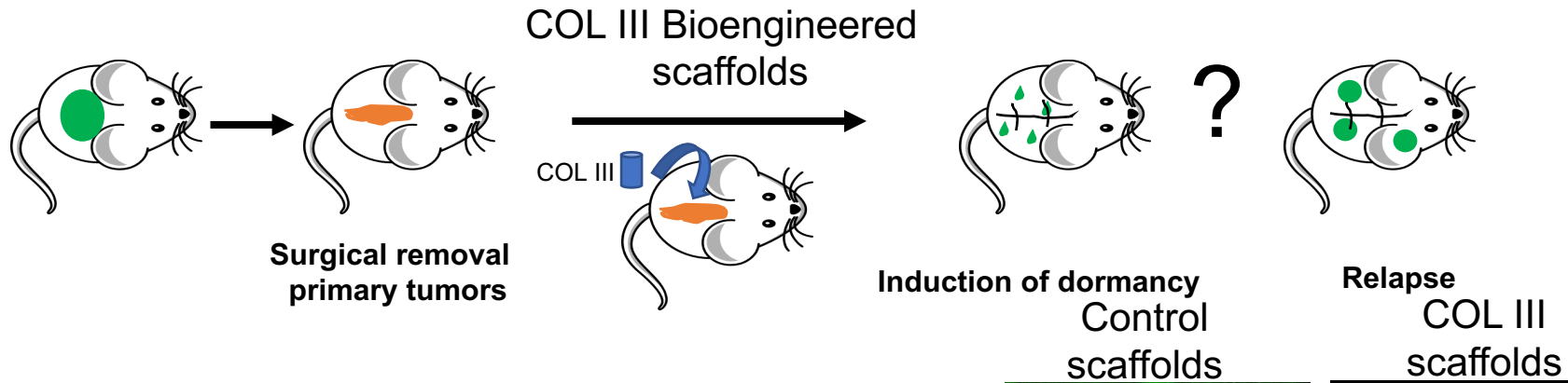


Tumor cells  
+ COL III

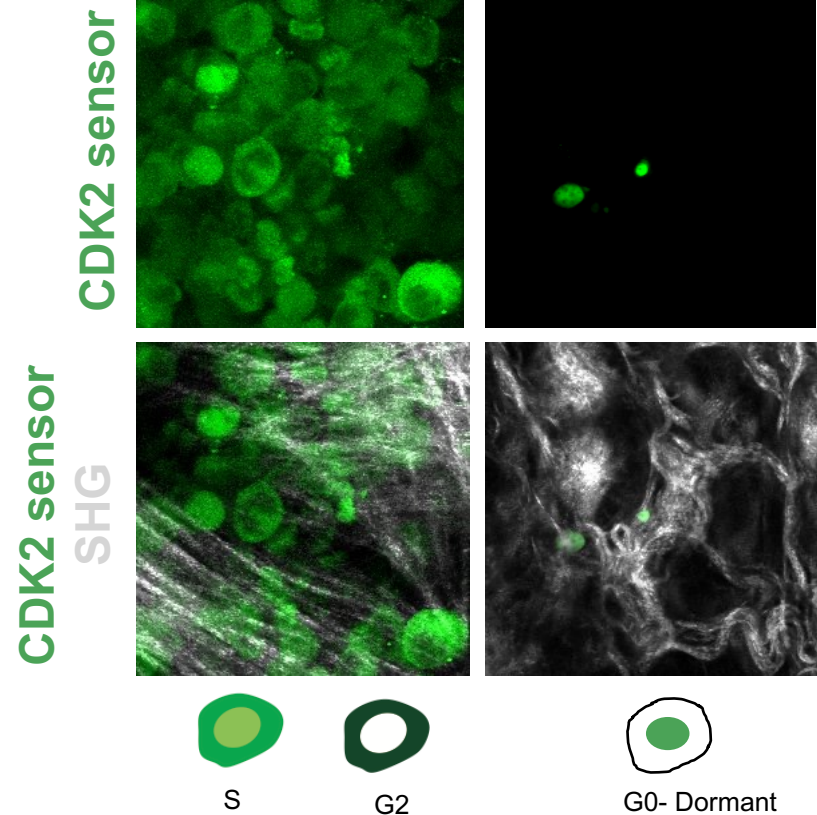
## Breast cancer cells



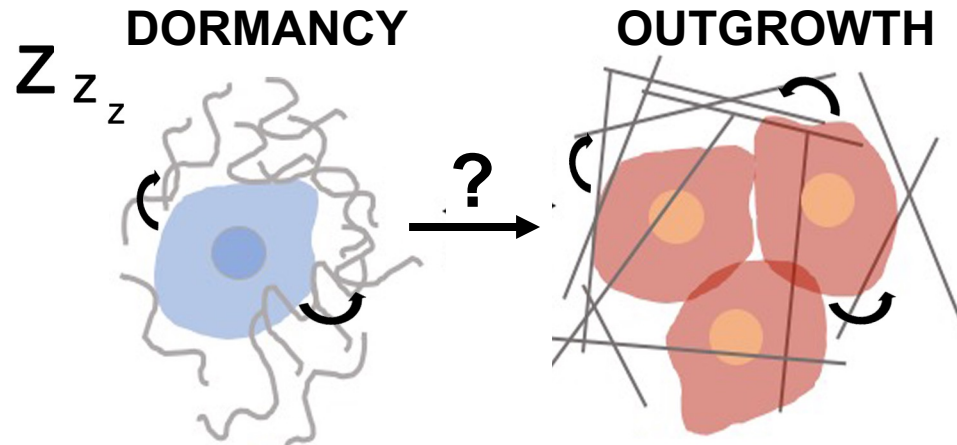
# COL III reprogram cancer cells into dormancy



recurrence at 40 days	%
empty sponge	80
Col III sponge	20

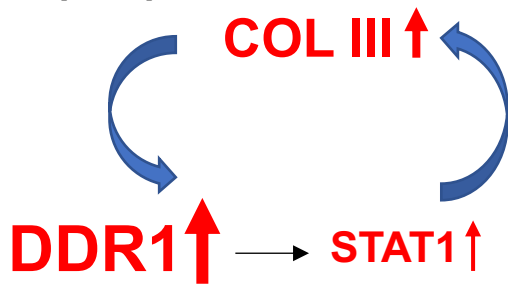


# Tumor cell-derived ECM Collagen III sustain tumor dormancy

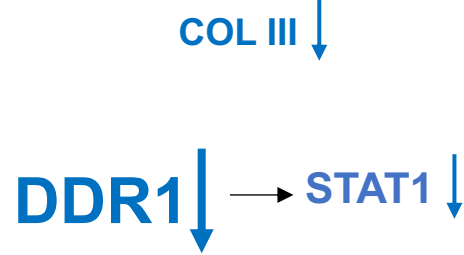


DORMANT DTC  
pro-quiescence ECM niche

PROLIFERATIVE DTCs  
pro-metastatic ECM niche



G0/G1 Arrest



Proliferation



Julie di Martino





# COL3A1, a novel regulator of tumor dormancy in breast cancer

nature  
cancer

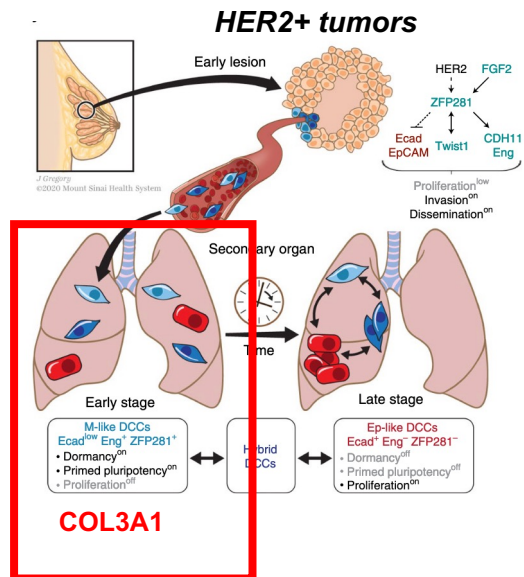
ARTICLES

<https://doi.org/10.1038/s43018-022-00424-8>

Check for updates

## ZFP281 drives a mesenchymal-like dormancy program in early disseminated breast cancer cells that prevents metastatic outgrowth in the lung

Ana Rita Nobre<sup>1,2,16</sup>, Erica Dalla<sup>1</sup>, Jihong Yang<sup>3,4</sup>, Xin Huang<sup>3</sup>, Lena Wullkopf<sup>1</sup>, Emma Risson<sup>1</sup>, Pedram Razghandi<sup>5,6</sup>, Melisa Lopez Anton<sup>1</sup>, Wei Zheng<sup>5,6</sup>, Jose A. Seoane<sup>7,8</sup>, Christina Curtis<sup>5</sup>, Ephraim Kenigsberg<sup>9,10,11</sup>, Jianlong Wang<sup>3</sup> and Julio A. Aguirre-Ghiso<sup>1,5,6,12,13,14,15</sup>✉



nature communications



Article

<https://doi.org/10.1038/s41467-022-32523-6>

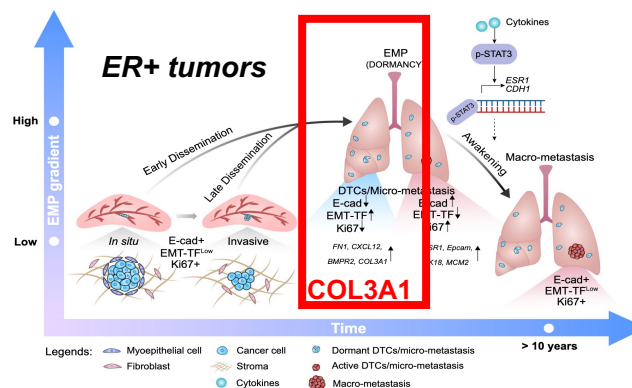
## Epithelial-mesenchymal plasticity determines estrogen receptor positive breast cancer dormancy and epithelial reversion drives recurrence

Received: 15 July 2021

Accepted: 2 August 2022

Published online: 25 August 2022

Patrick Aouad<sup>1</sup>, Yueyun Zhang<sup>1</sup>, Fabio De Martino<sup>1</sup>, Céline Stübölz<sup>1</sup>, Simak Ali<sup>2</sup>, Giovanna Ambrosini<sup>1</sup>, Sendurai A. Mani<sup>3</sup>, Kelly Maggs<sup>4</sup>, Hazel M. Quinn<sup>1</sup>, George Sfimos<sup>1</sup> & Cathrin Brisken<sup>1,5</sup>✉



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Dr. Tian Ming (Janelia)

Dr. Upadhyayula (Berkeley)

Drs. Matus and Martin (SB)

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Dr. Elana Fertig (JHU)

Dr. Ana Gomes (Moffitt)

Dr. Alana Welm (Univ. Utah)

Dr. Ji (Sinai)

Dr. Angel (MUSC)

Become a member!



Thanks!!!

# Funding:

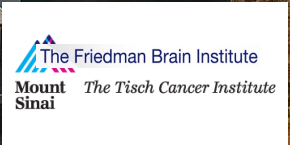
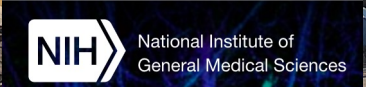
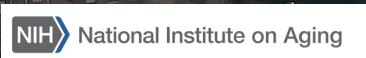
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Irma T. Hirschl/Monique Weill-Caulier Scientist Award