

Mathematical Methods for the Study of Self-organization in the Biological Science

ESI, University of Vienna

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Collective cancer cell invasion in 3D tissue: plasticity, interconversions *and jamming*

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Cell dynamics group Peter Friedl

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Cell movement in the body

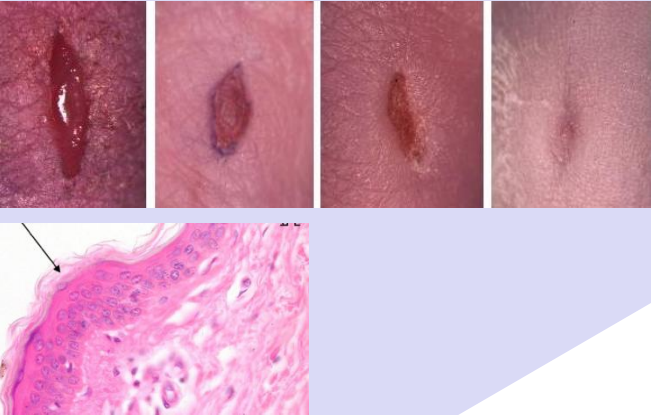
Morphogenesis/ embryogenesis



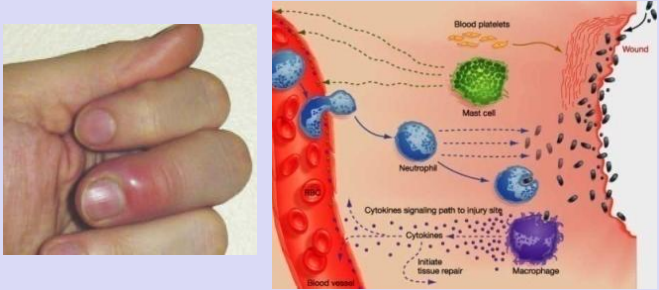
The adult body



Tissue repair and angiogenesis

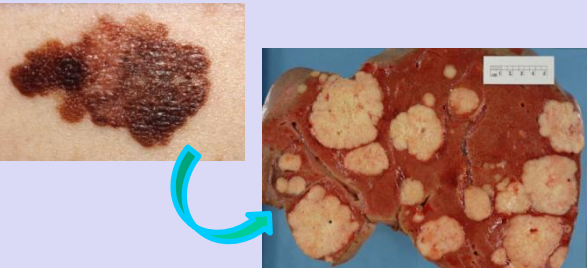


Immune surveillance and inflammation



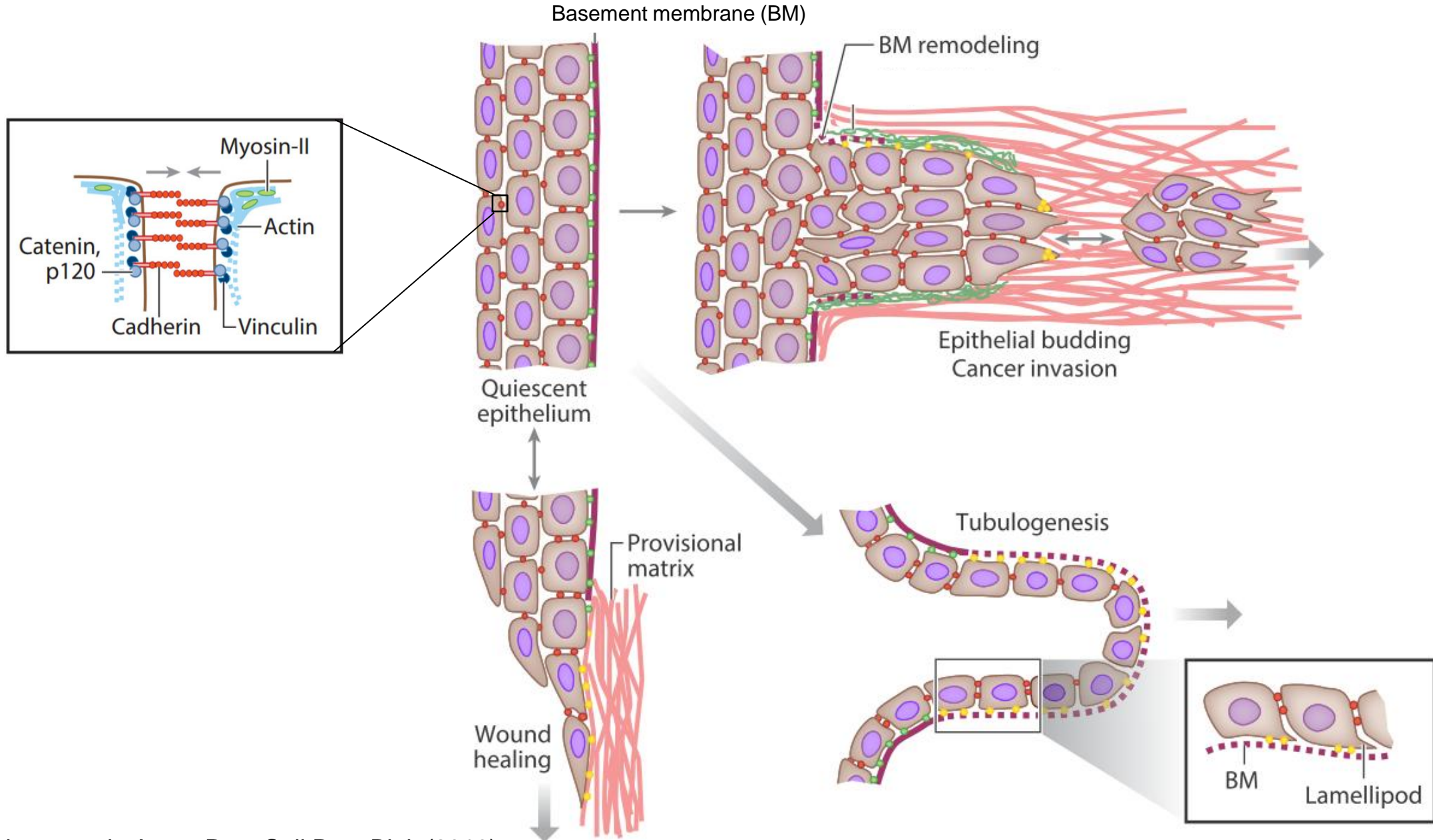
Immune system

Cancer

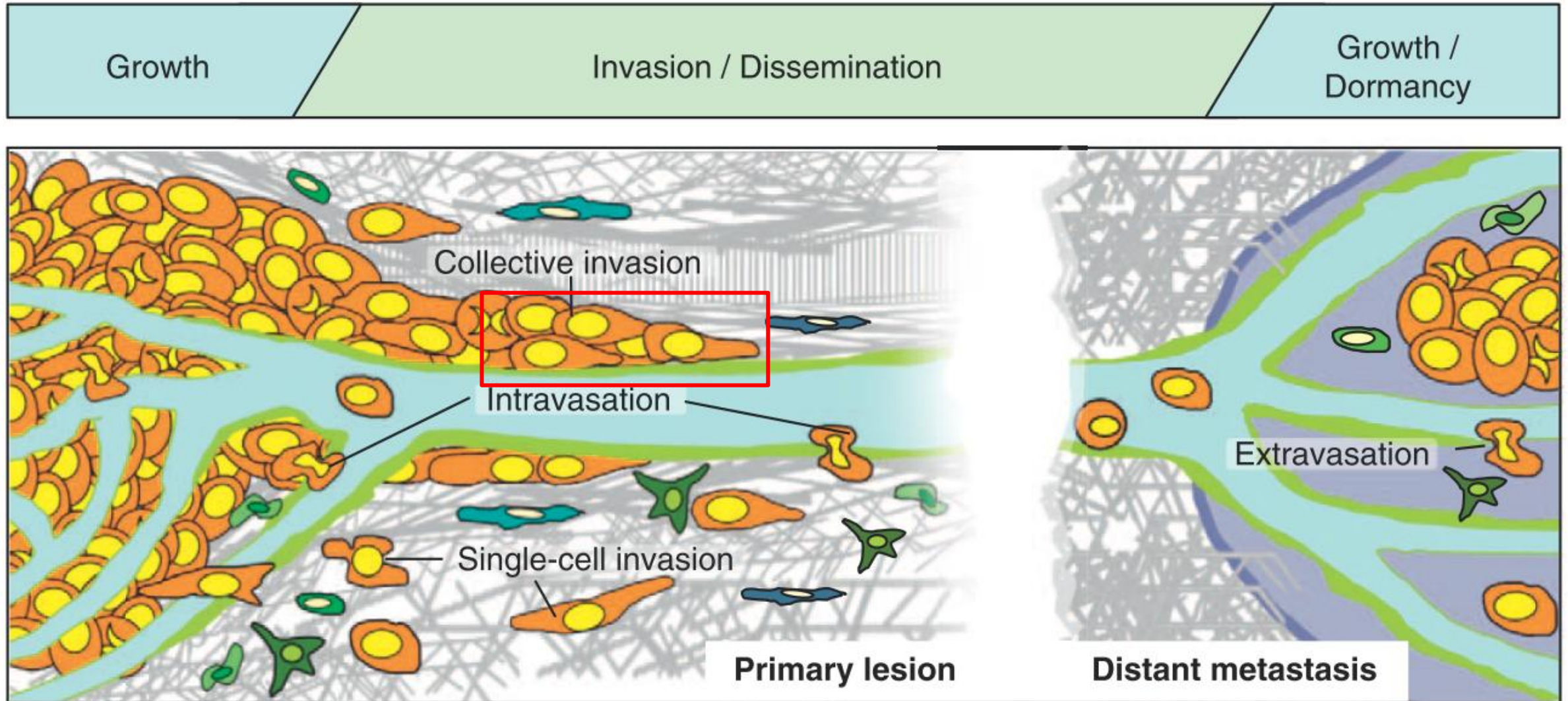


Metastasis

Transition programs from quiescent epithelium to collective migration



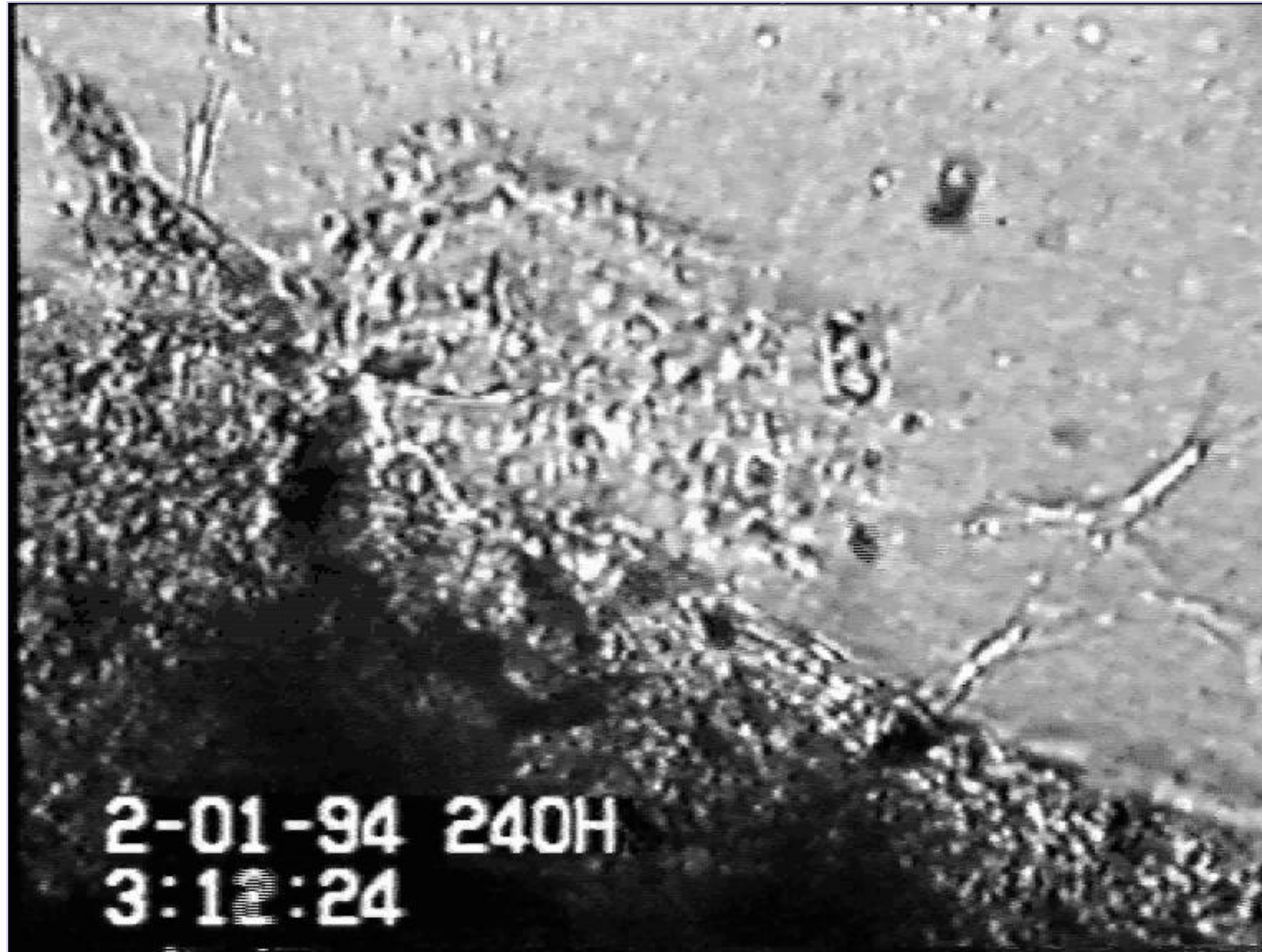
Collective tumor invasion into confined tissue regions



Collective cell migration

Collective movement: strongly connected cells

Expression of
N-, M-, R-cadherin
Charasse et al.,
Oncogene (2004)



→ Cohesive
mode of
collective cell
migration

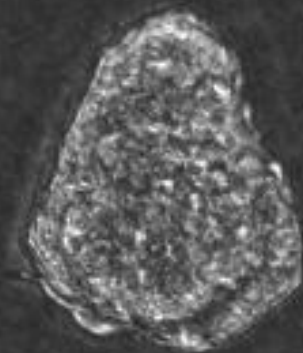
Primary rhabdomyosarcoma explant
(after 5 days of culture in 3-D collagen)

200 μ m

Friedl et al., Cancer Res. (1995)

Invasion culture

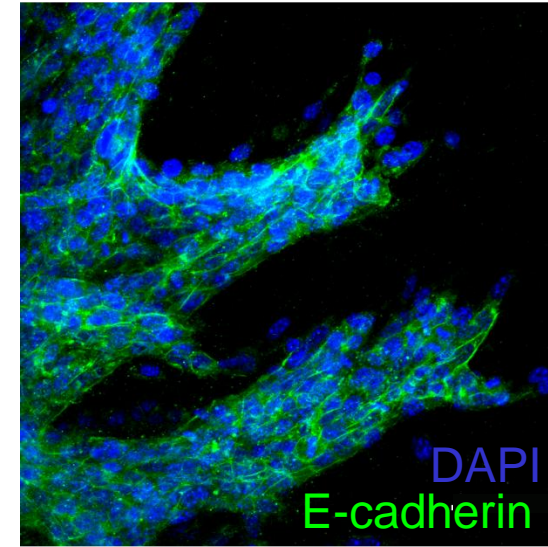
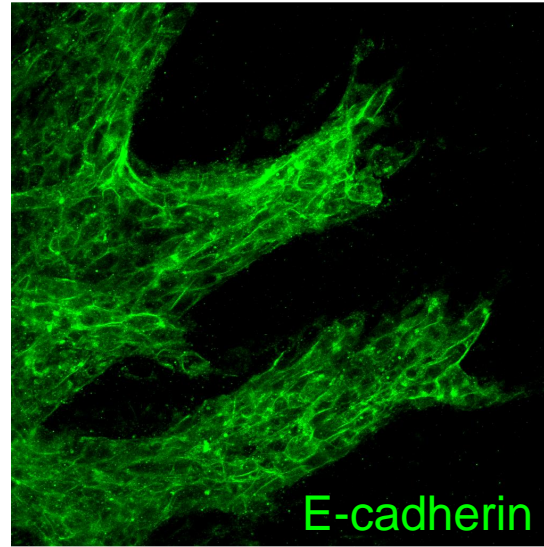
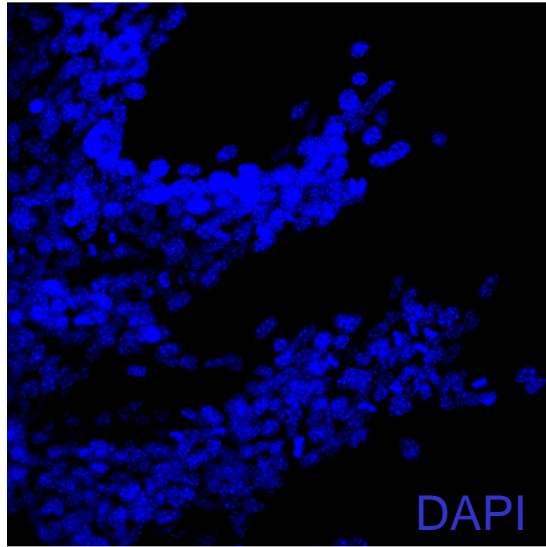
- Tumoroid
- 3D collagen matrix



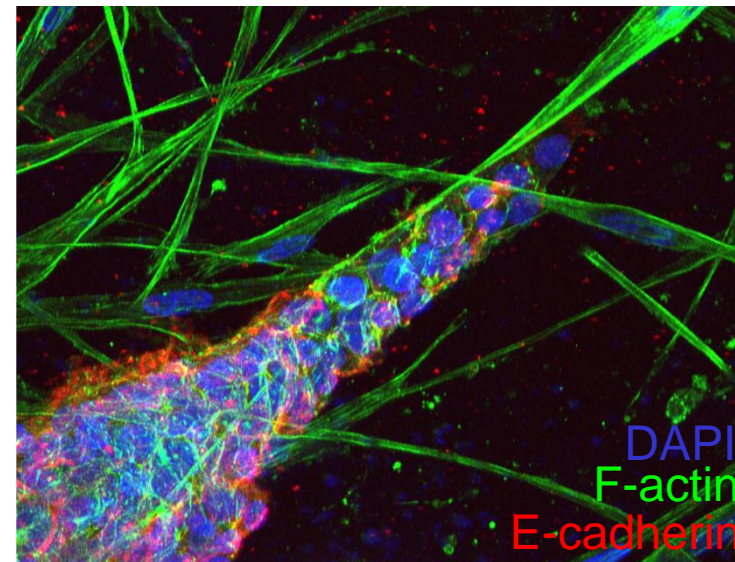
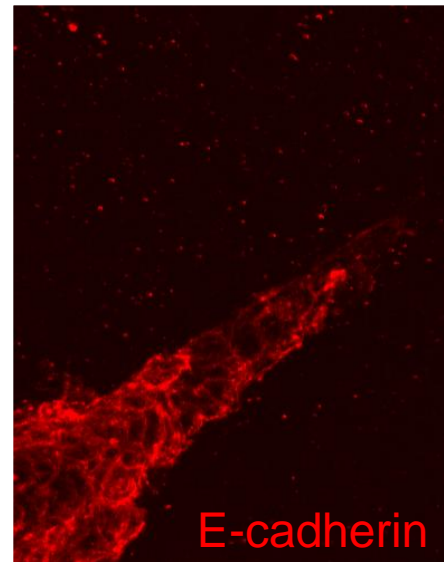
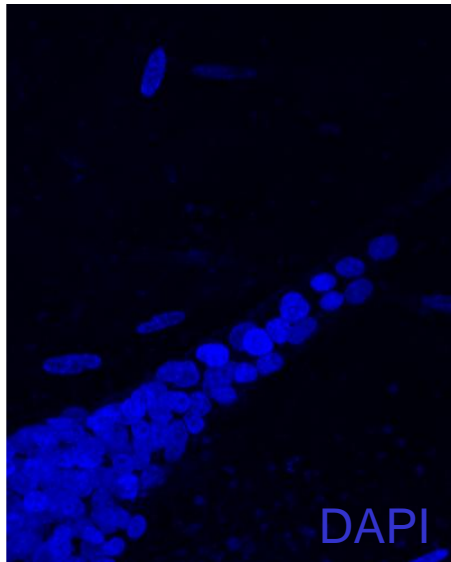
0.00 h

Collective invasion: cell-cell junctions retain cadherins

4T1



MCF-7 / fibrobl.



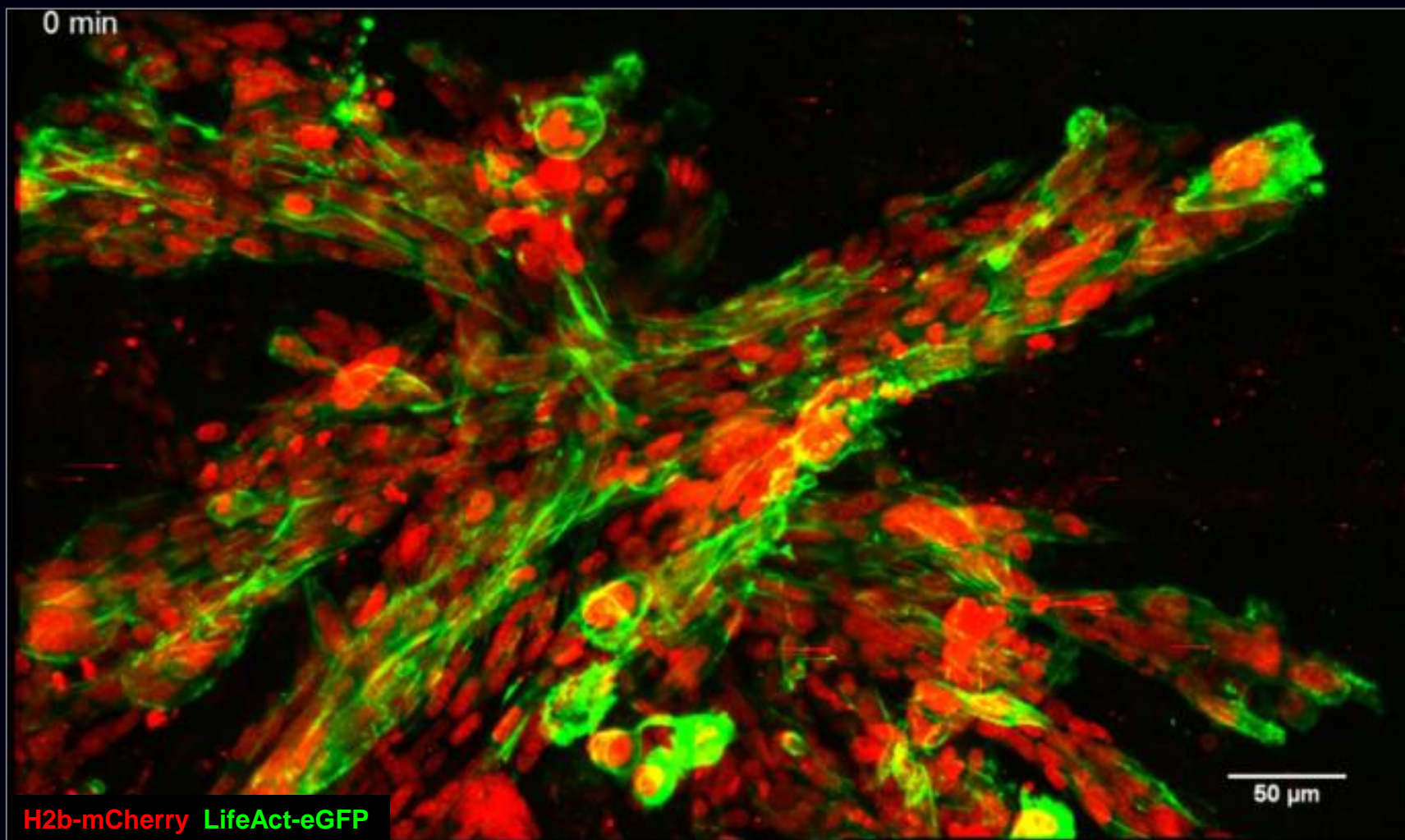
Monitoring breast cancer invasion modes in vivo



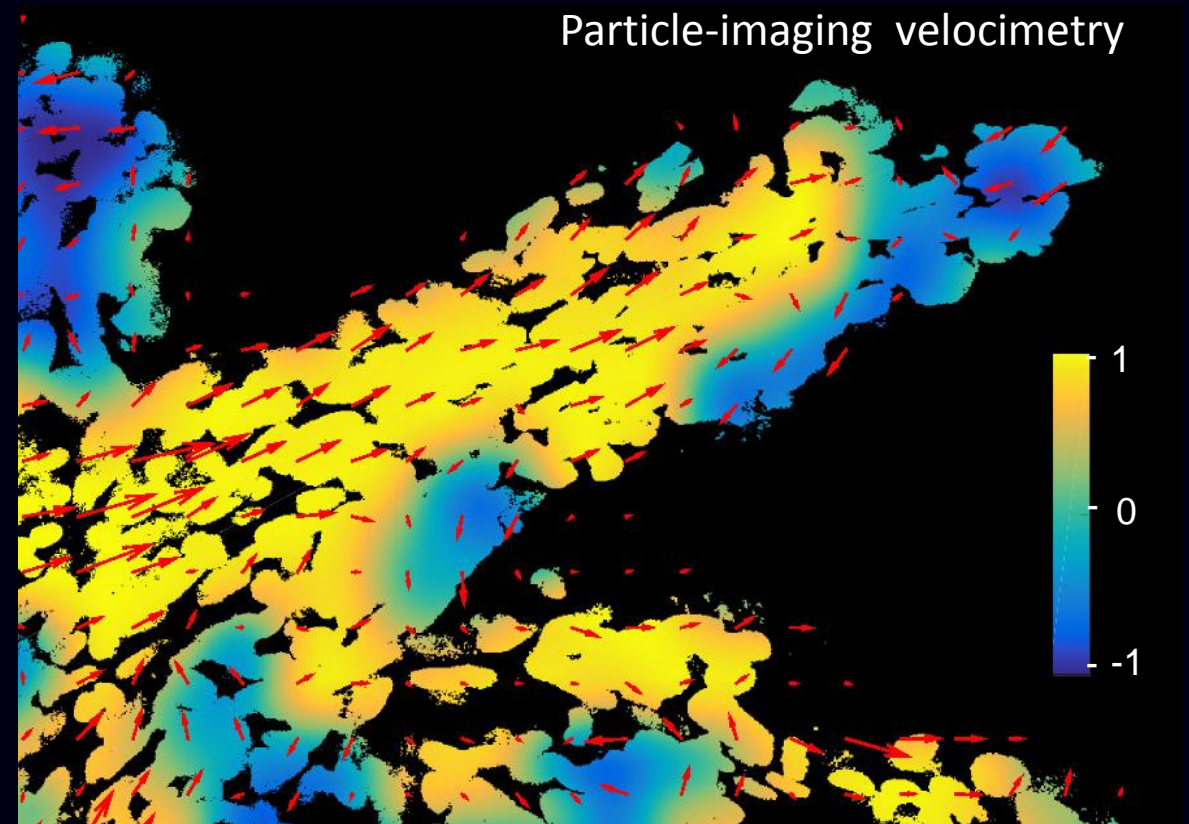
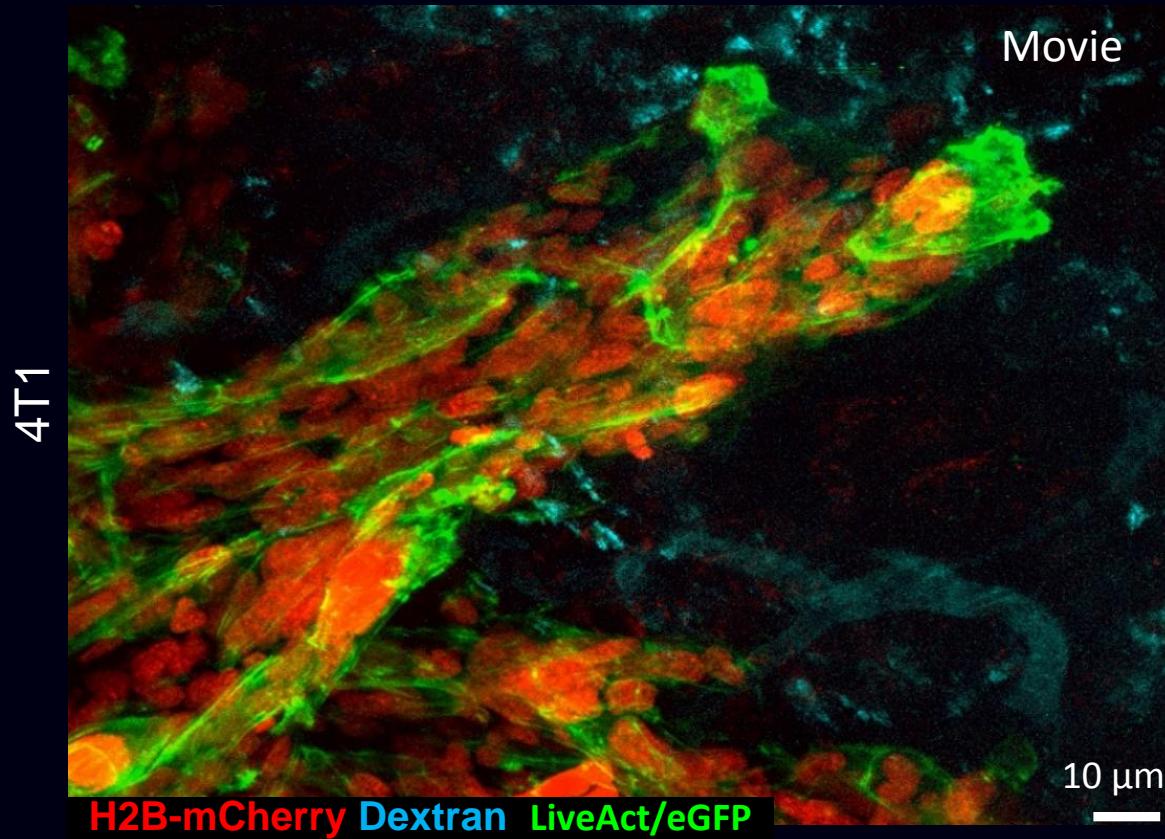
Ilina et al., Dis. Models Mechan. (2018)

Collective invasion in vivo

4T1

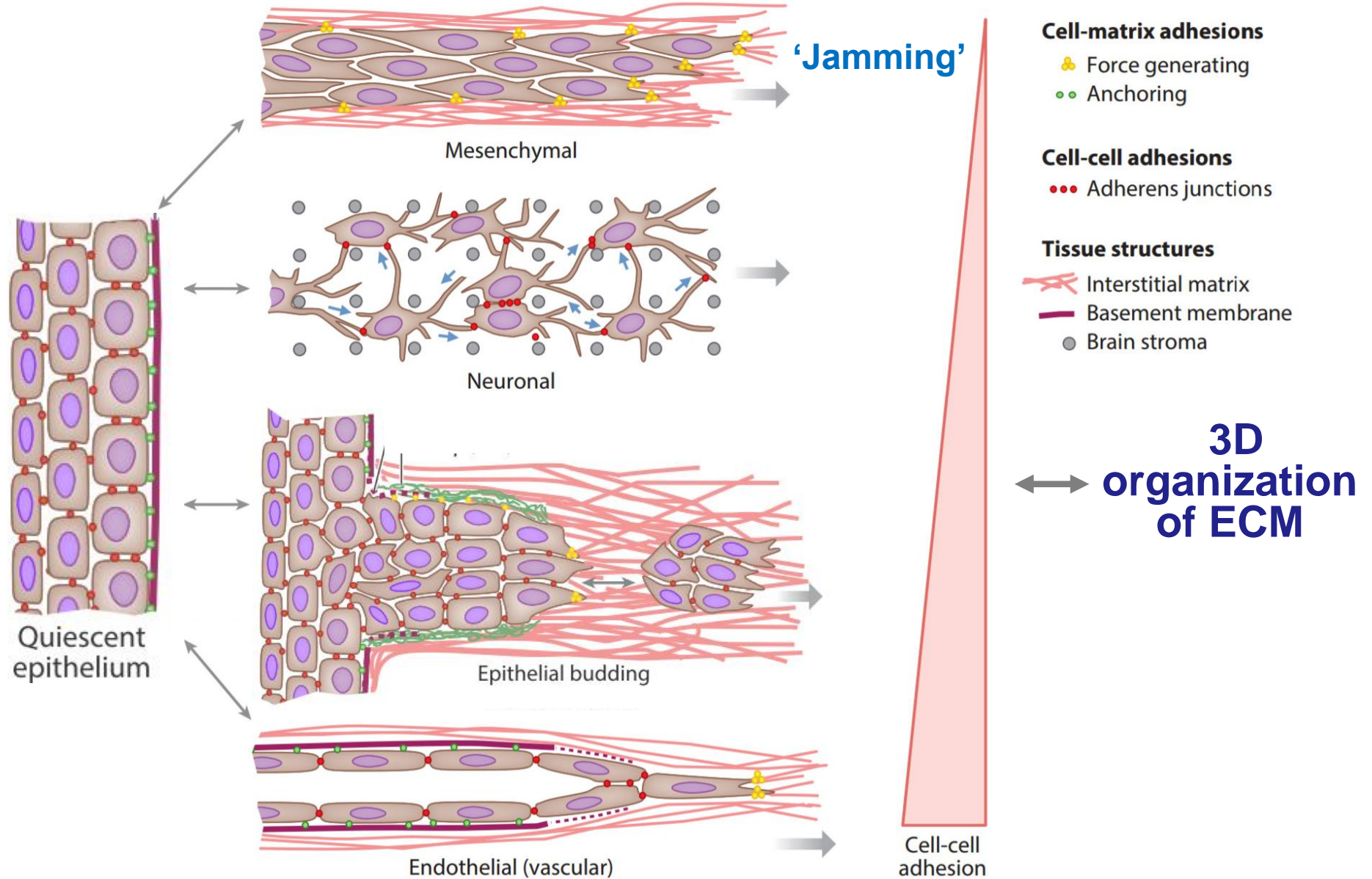


Collective invasion in vivo: flow-like behavior



Analysis by: Fabio Giavazzi, Giorgio Scita

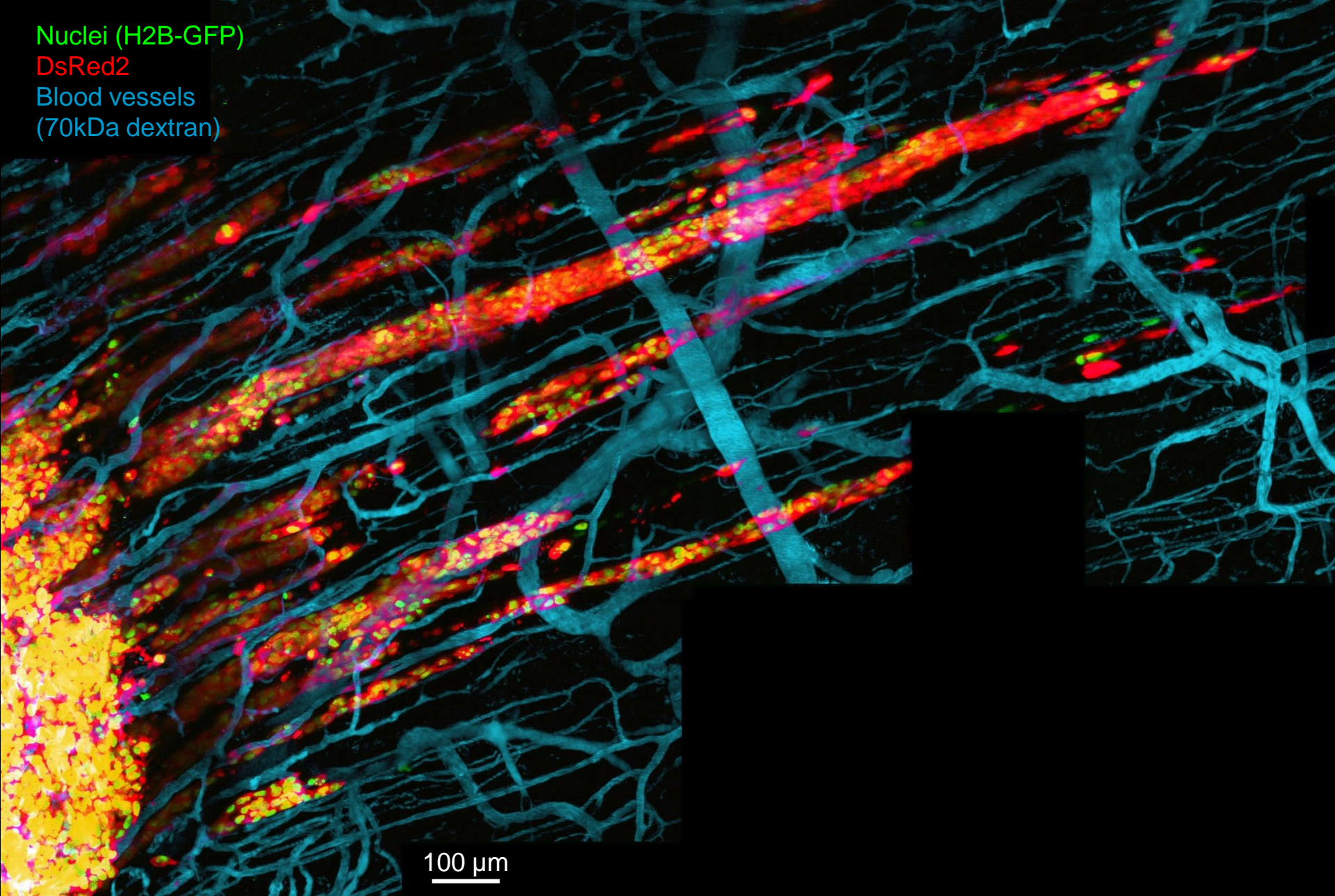
Diversity of collective migration modes



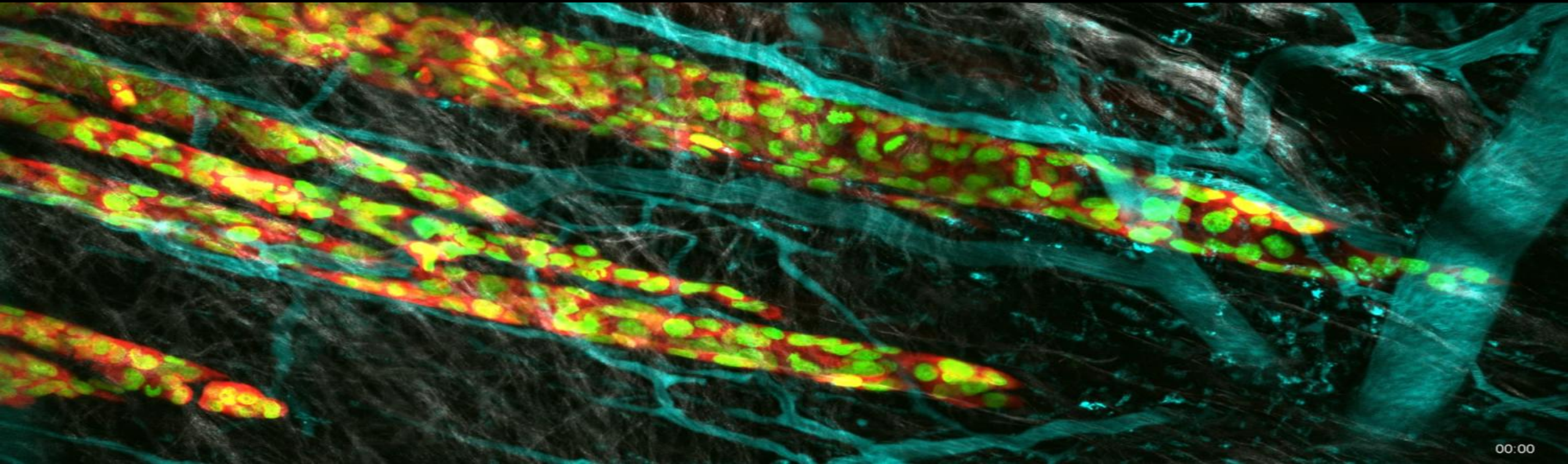
Jamming transition-

modulating tissue space

HT-1080 mesenchymal tumors in vivo: predominantly collective invasion



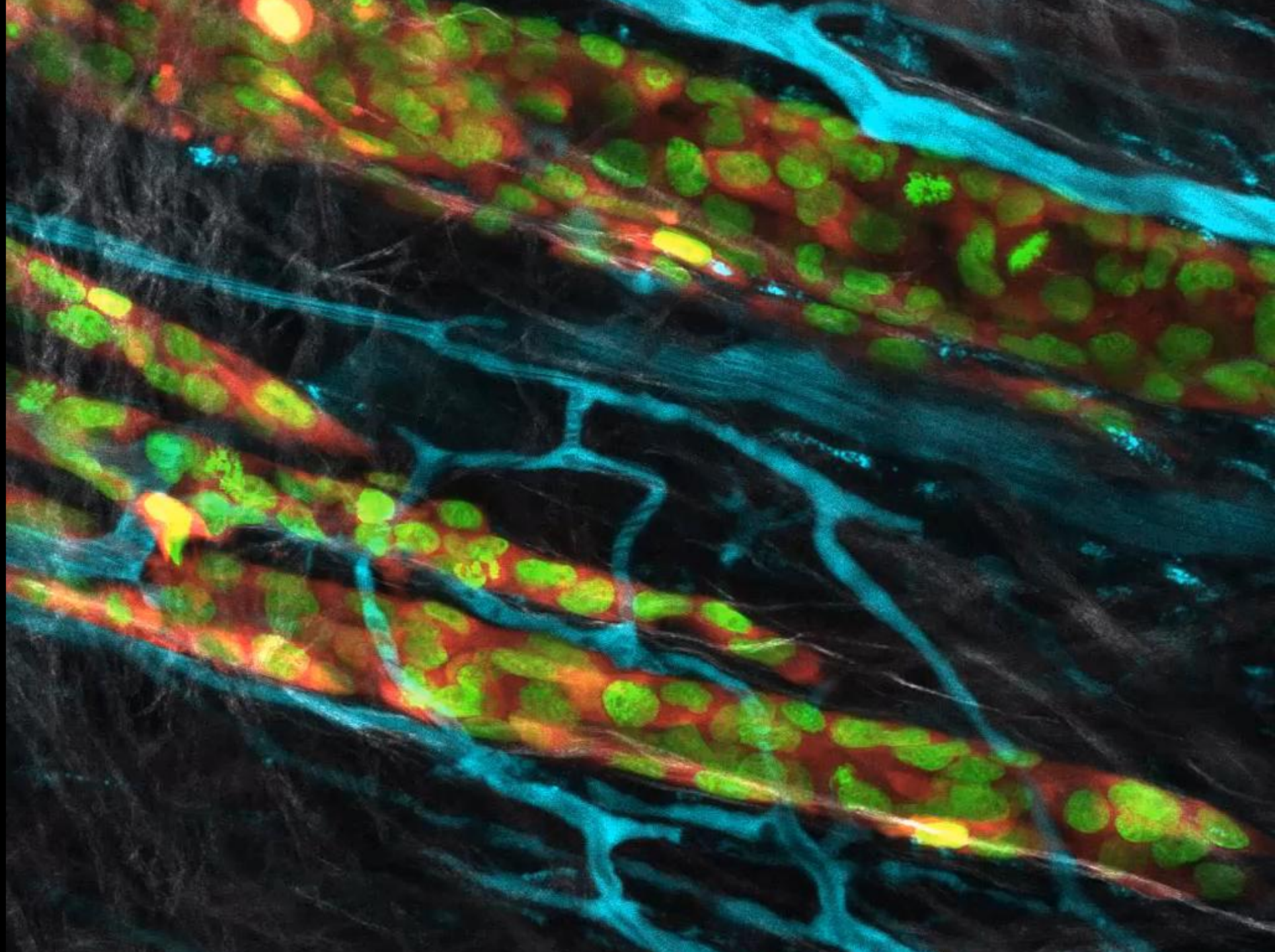
3 Tumor invasion: Leading edge follows pre-existing interfaces and adapts to tissue architecture



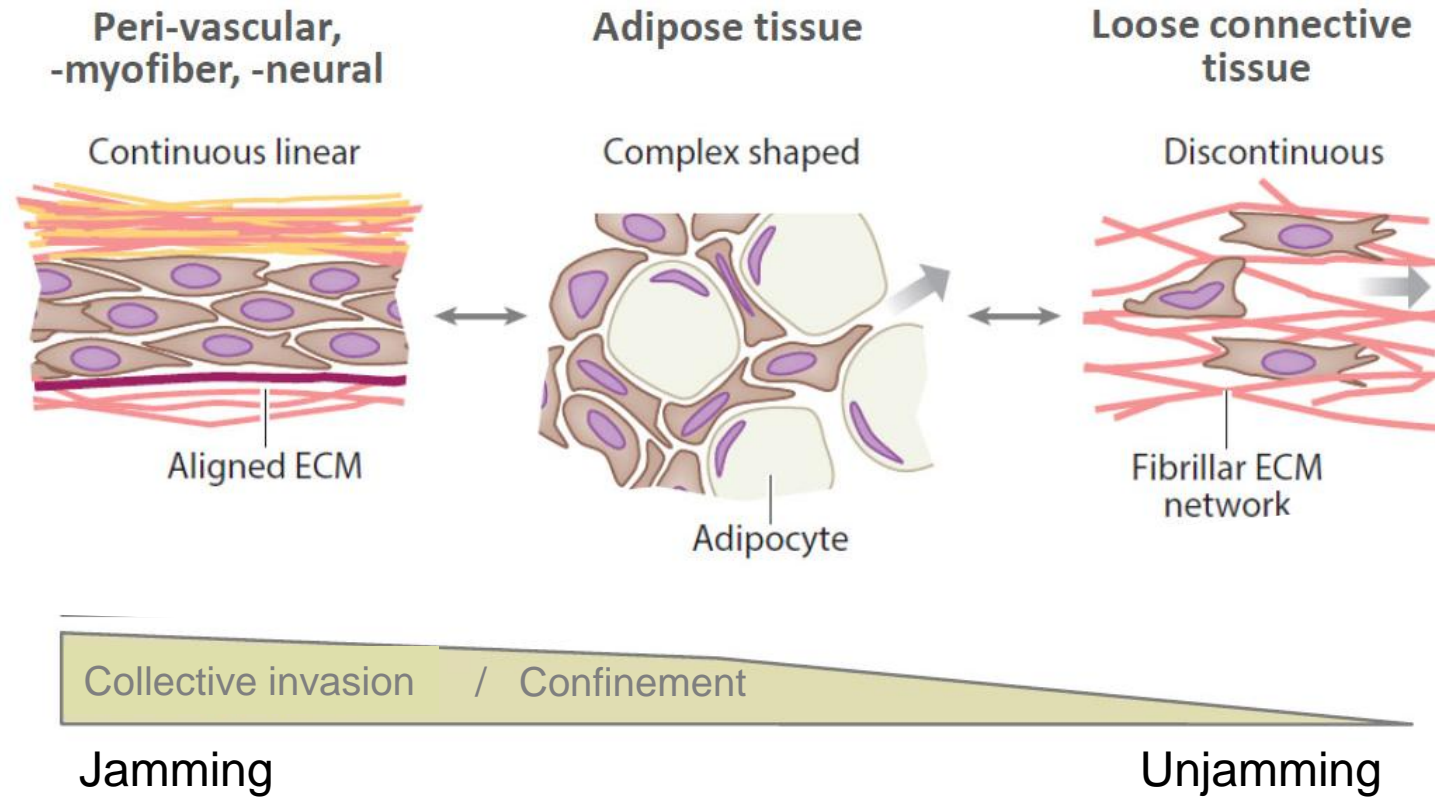
00:00

Myofibers, collagen (SHG)
Blood vessels (AlexaFluor 750)
Tumor cells Tumor nuclei

4 h

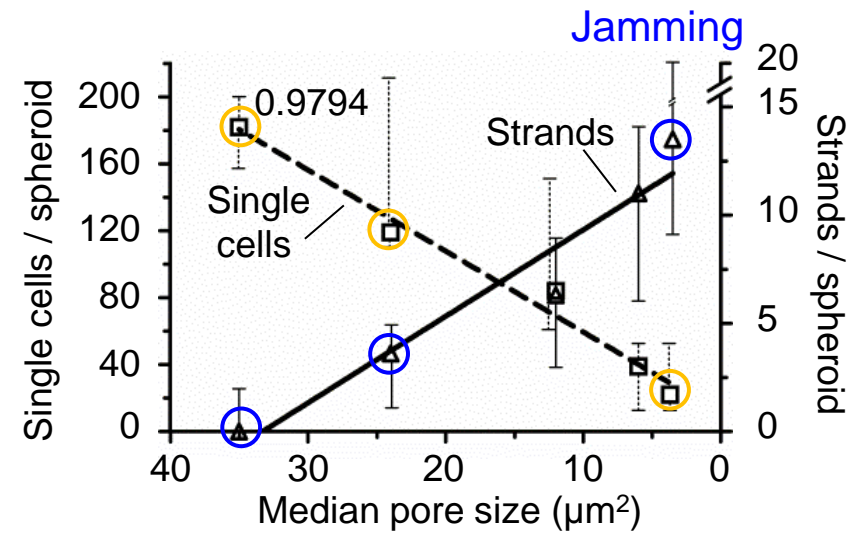
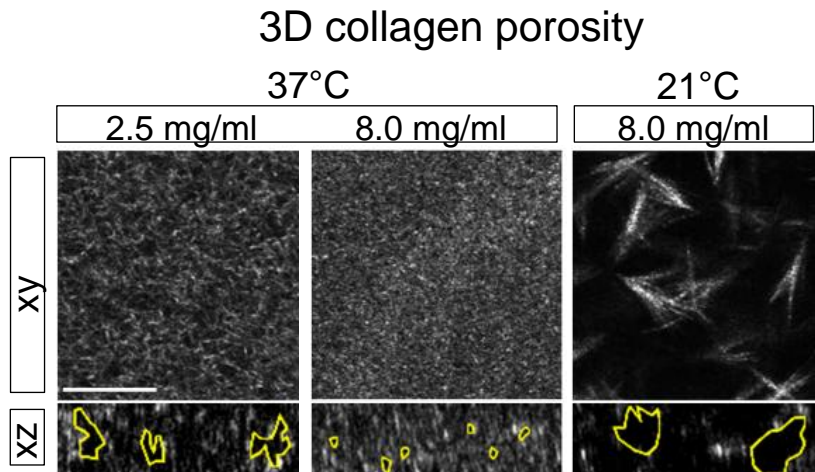
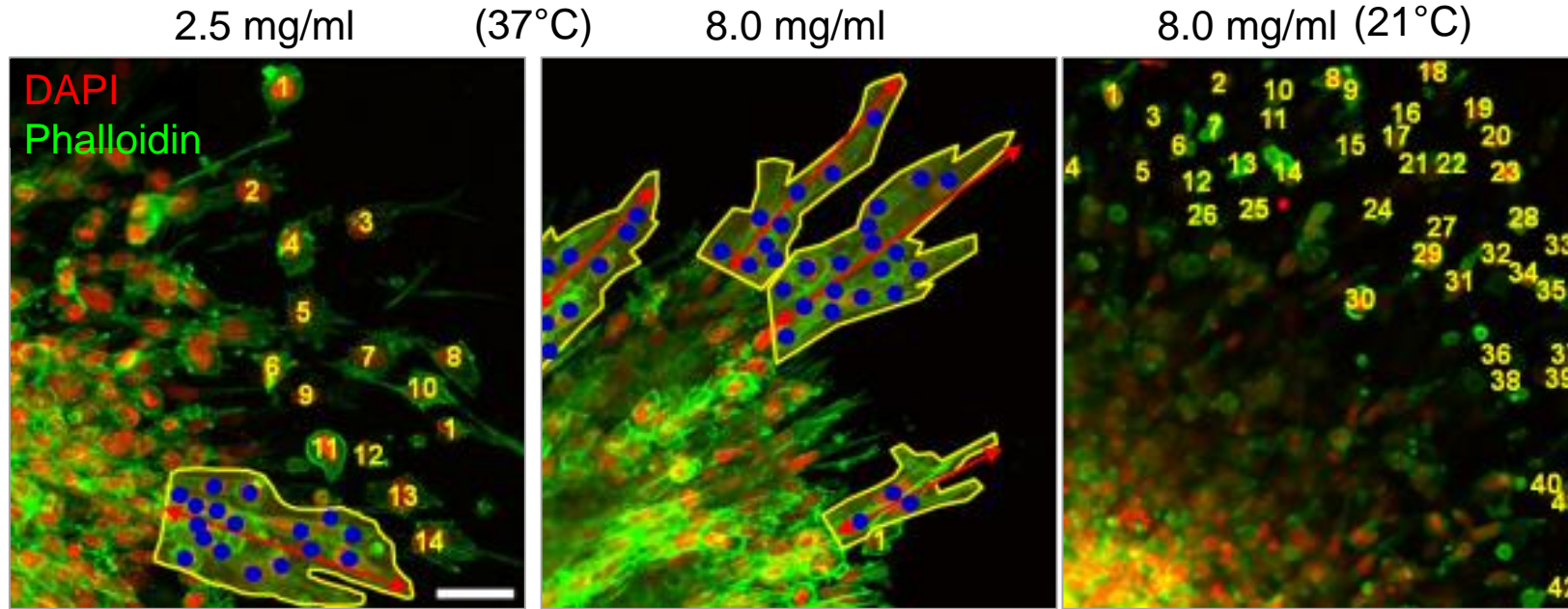


Adaptation of migration mode in response to tissue patterns

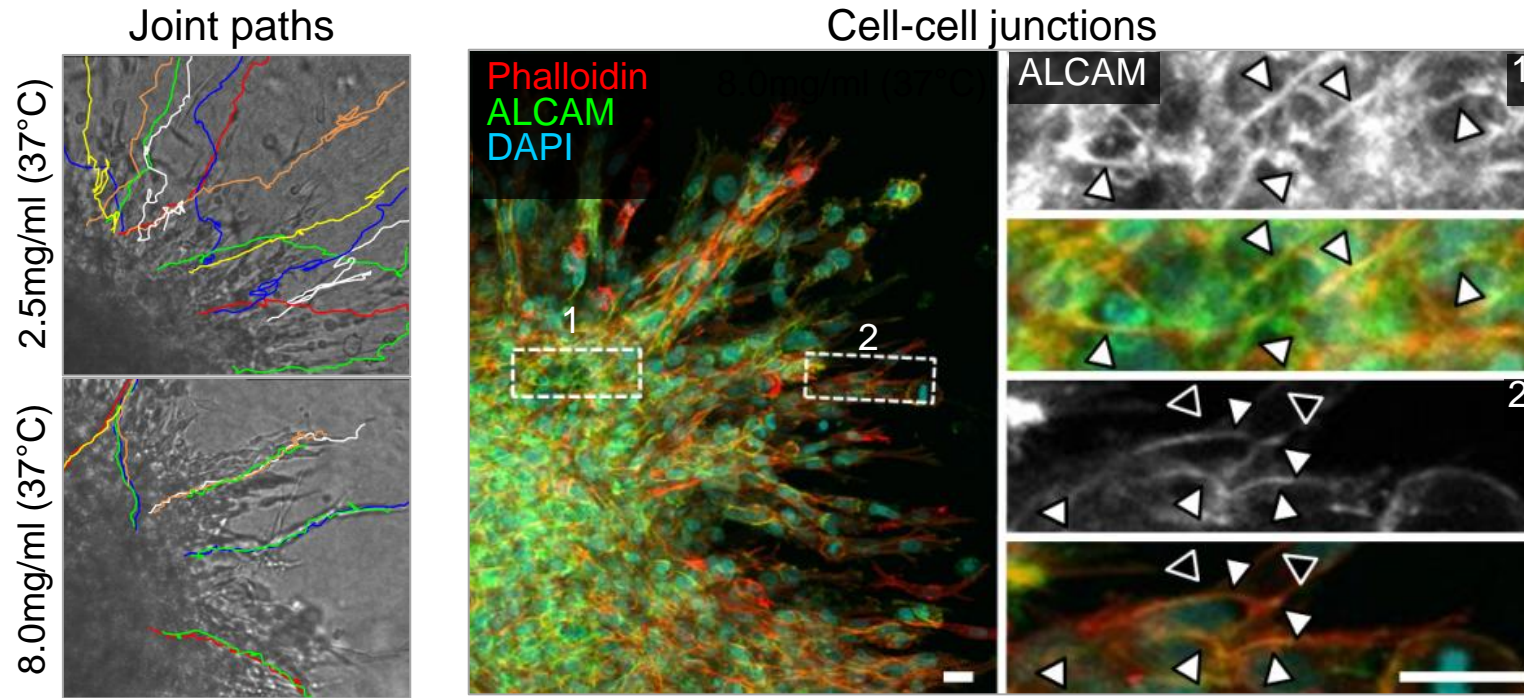


Weigelin et al., *Intravital* (2012)
Te Boekhorst, et al., *Annu. Rev. Cell Dev. Biol.* (2016)

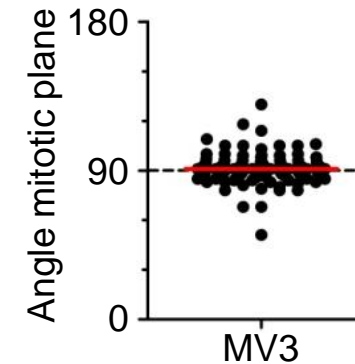
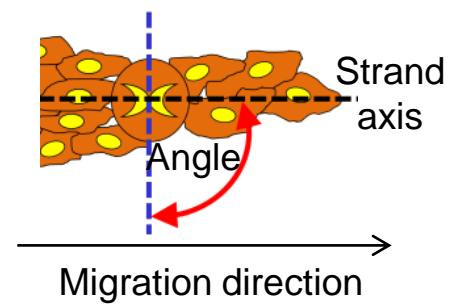
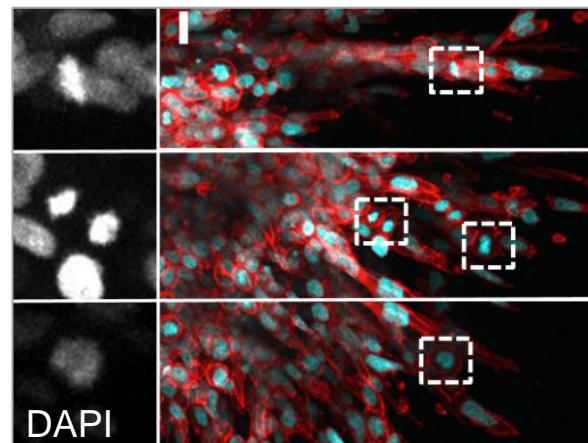
Plasticity of mesenchymal invasion: probing porosity



Confinement supports cell-cell junctions and alignment



Alignment of mitotic planes



Probing cell decision making in bimodal tissue in vitro: adjacent random and interphase-type 3D matrix

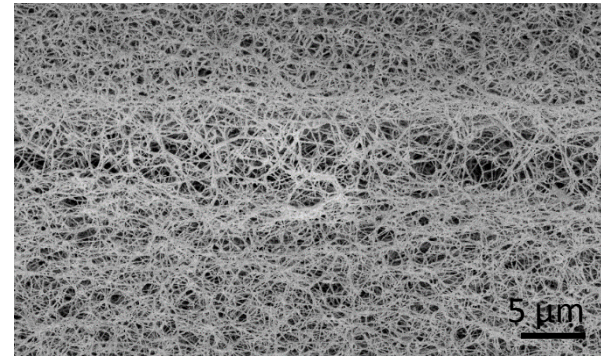
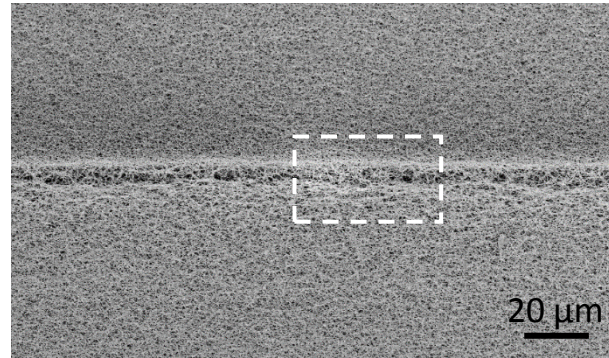
Two-layered
rat-tail collagen



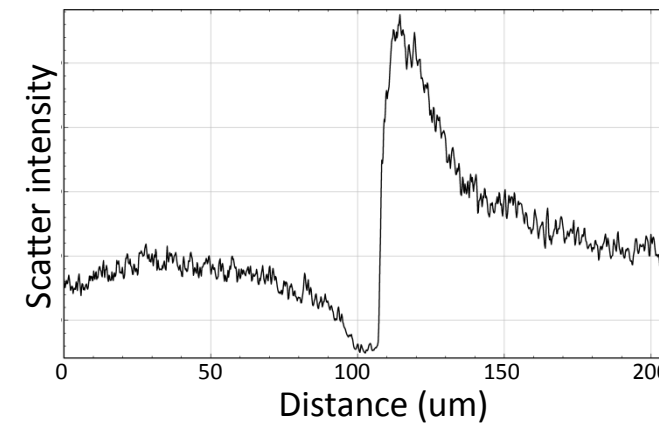
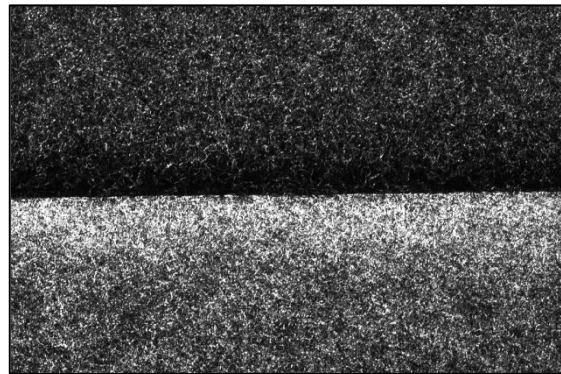
6.0 mg/ml

6.0 mg/ml

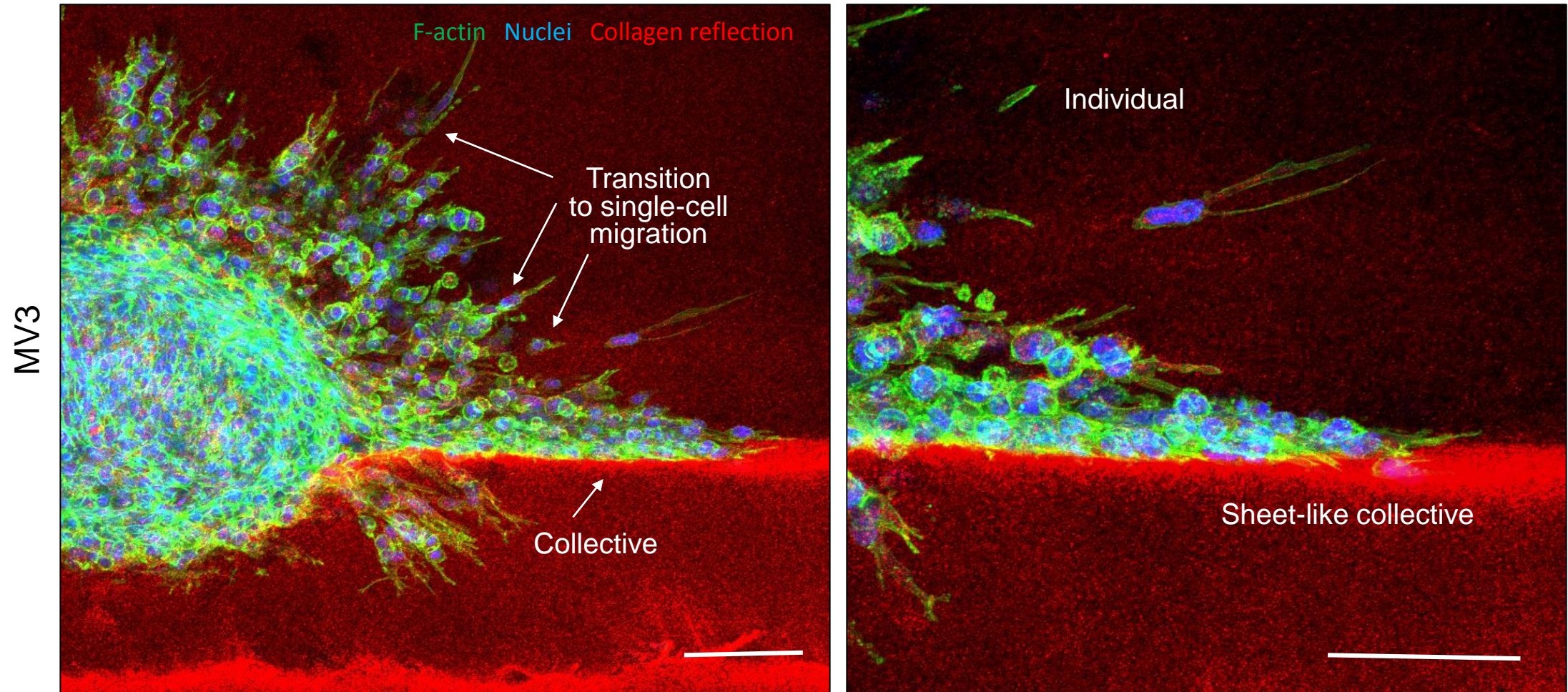
SEM



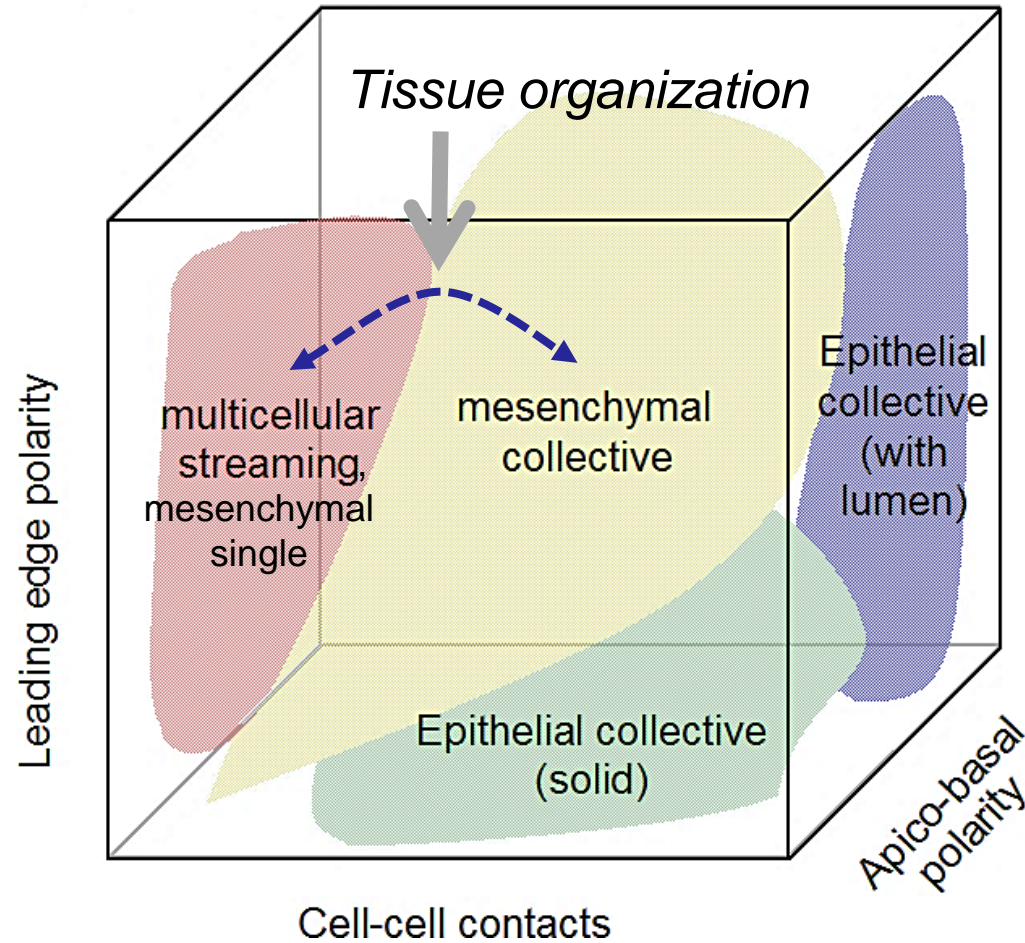
Confocal reflectance



Characterization of collagen-collagen interphase gels

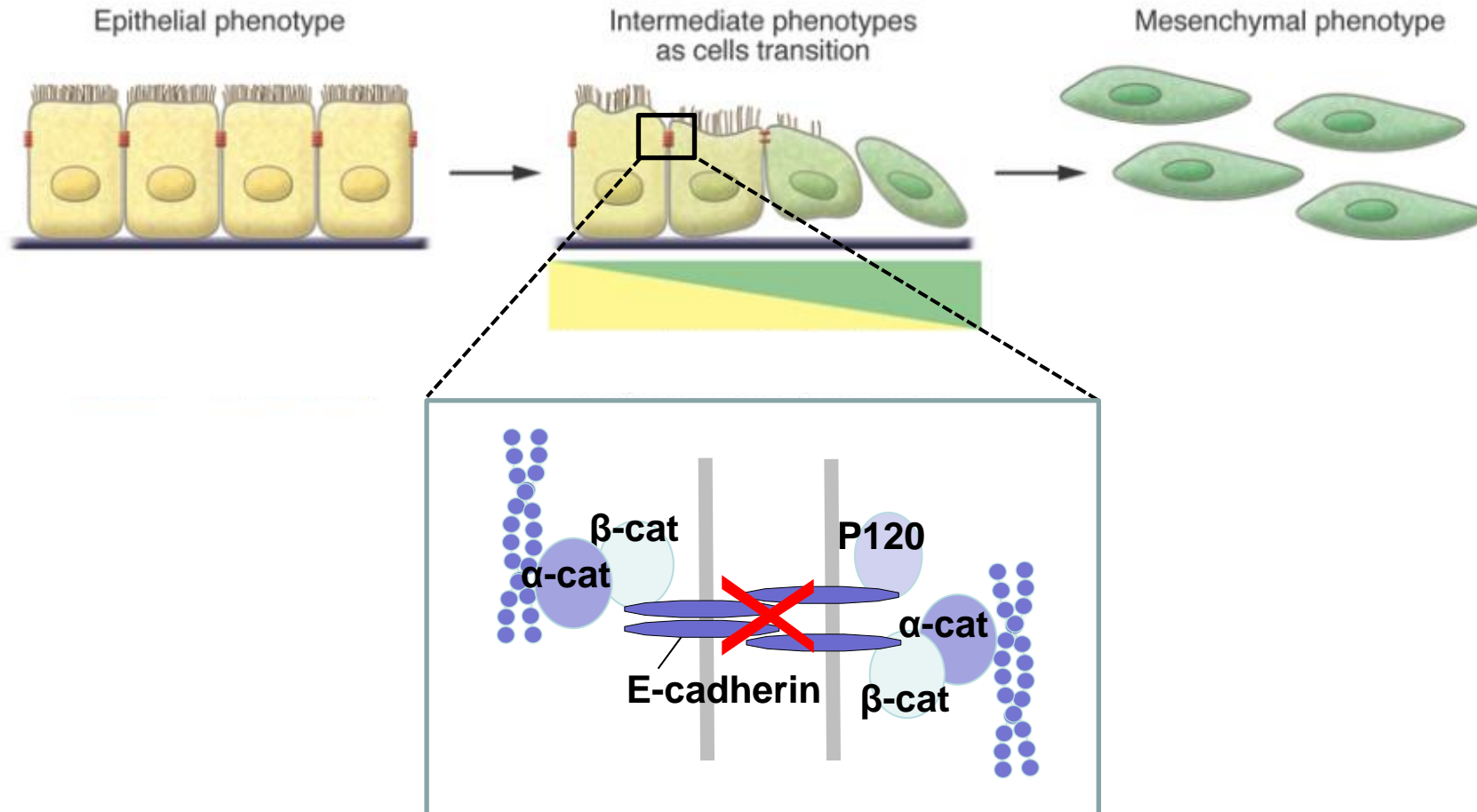


Diversity of multicellular invasion programs

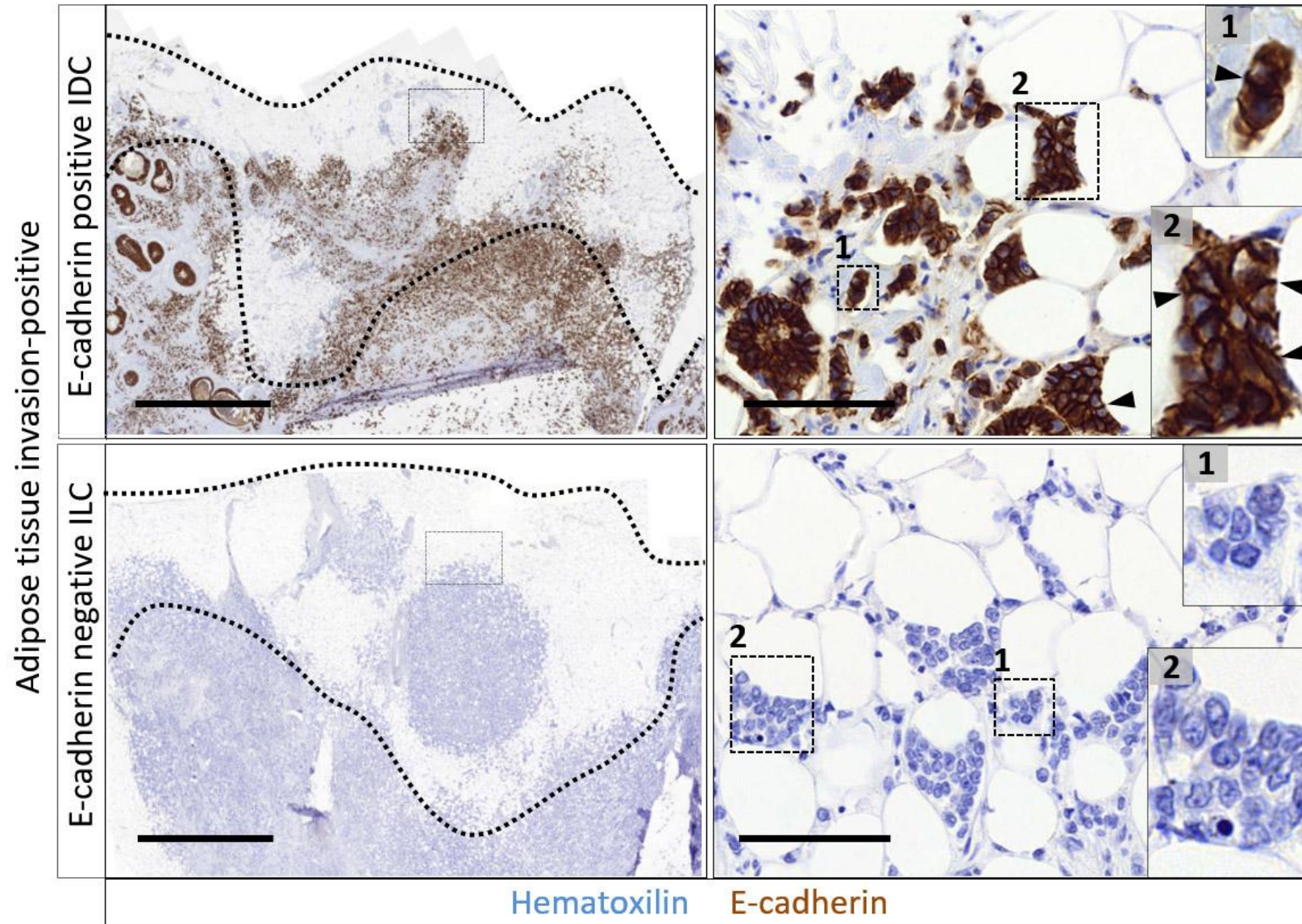


Loss of cadherin
expression

Epithelial-mesenchymal transition and cell individualization

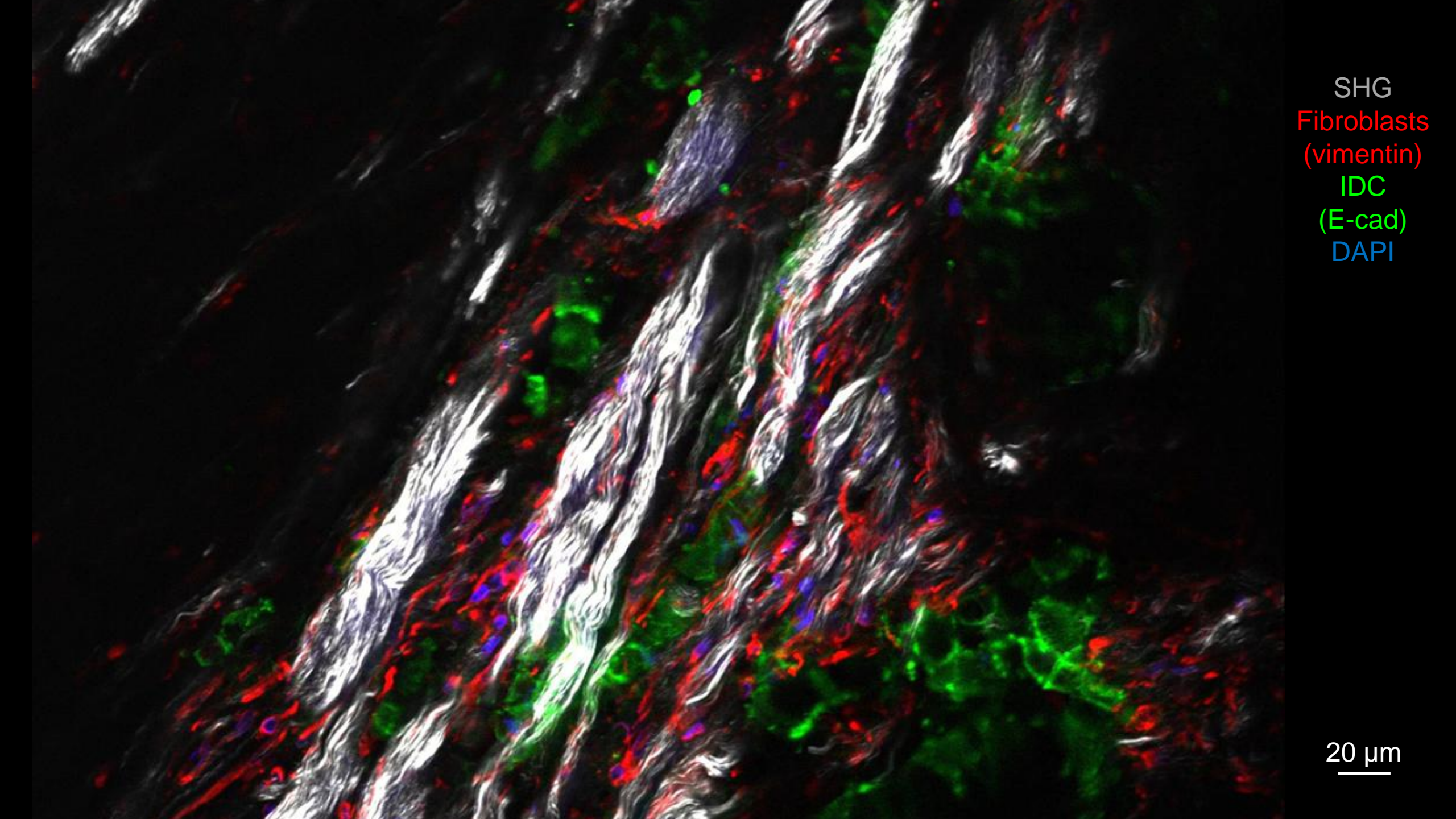


Collective patterns in human breast carcinoma irrespective of E-cadherin status

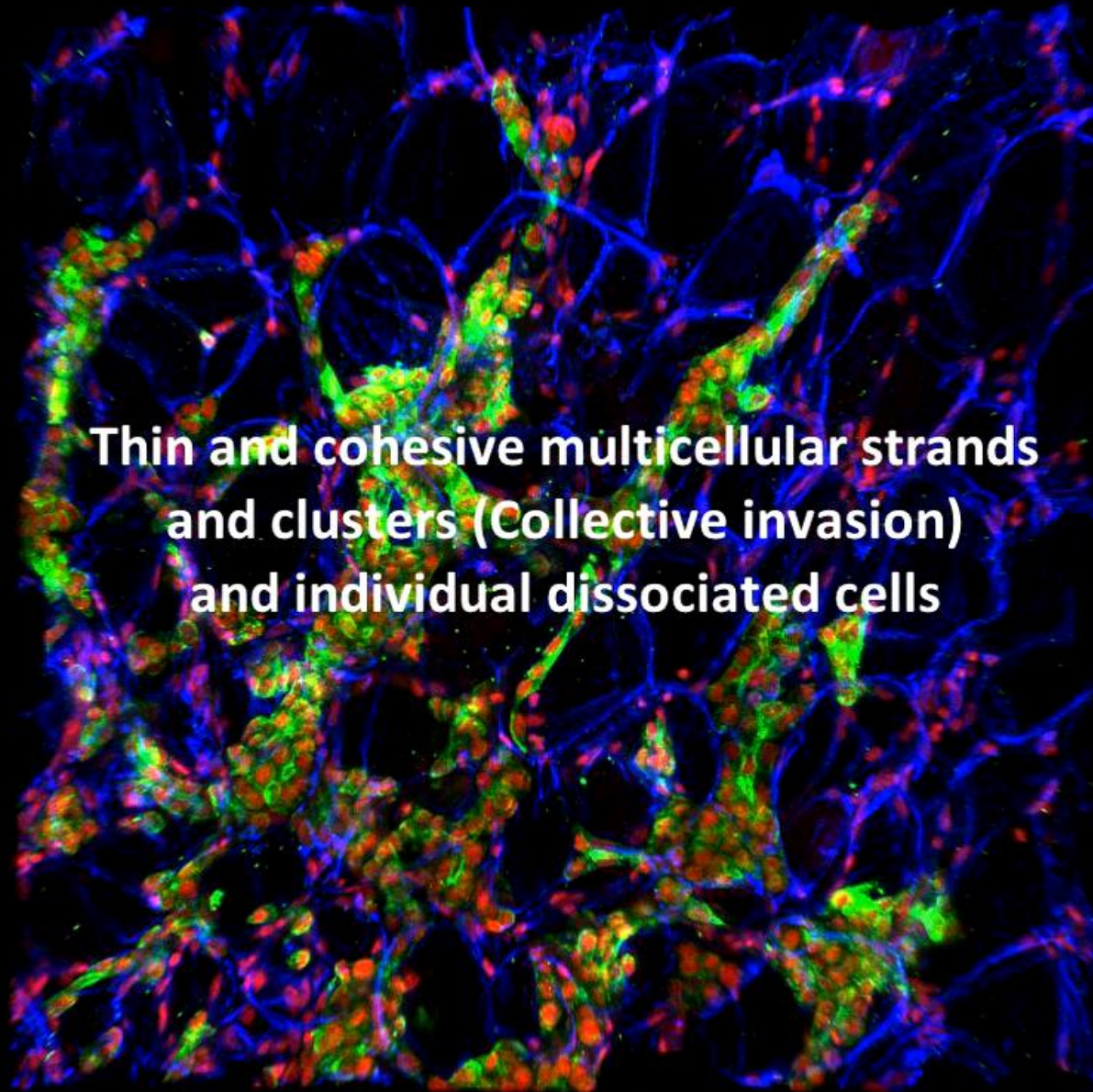


SHG
Fibroblasts
(vimentin)
IDC
(E-cad)
DAPI

20 μ m



Invasive lobular carcinoma



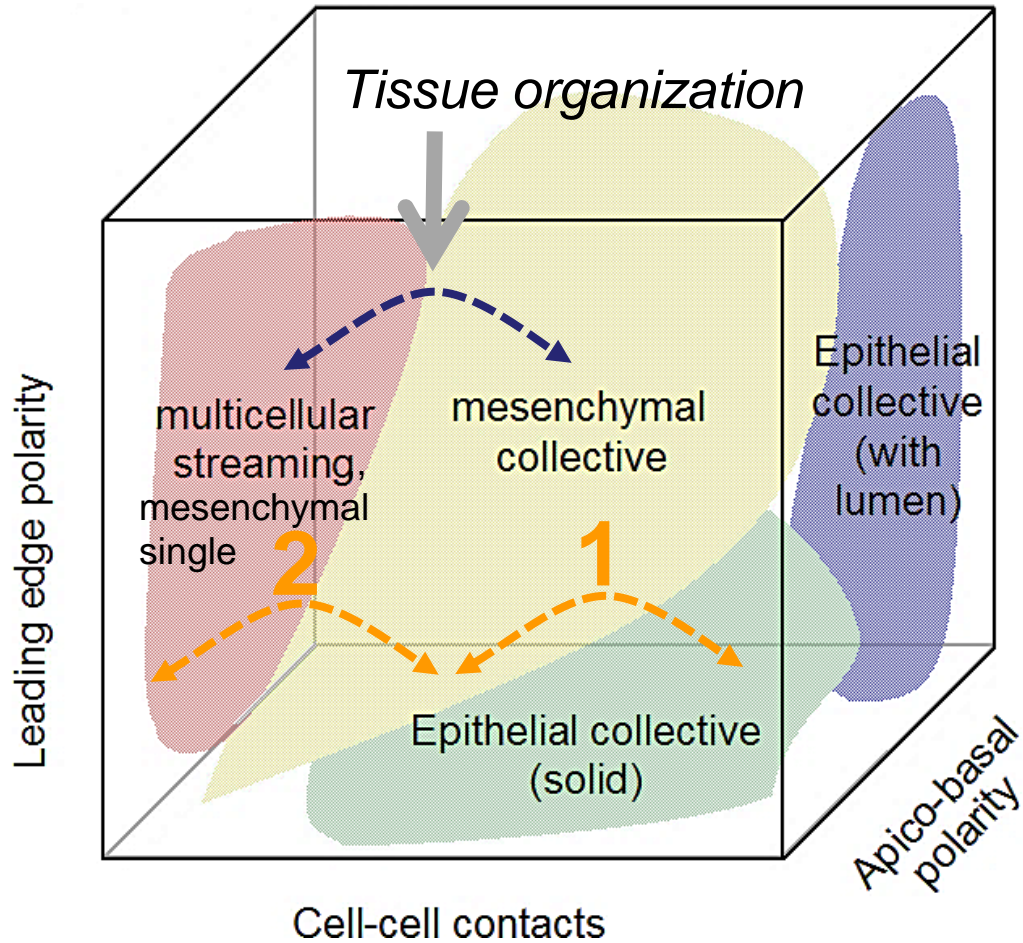
Thin and cohesive multicellular strands
and clusters (Collective invasion)
and individual dissociated cells

Khalil et al.,
Clin. Exp. Metast. (2017)

DAPI Vimentin Cytokeratin

100 um

Conclusion I

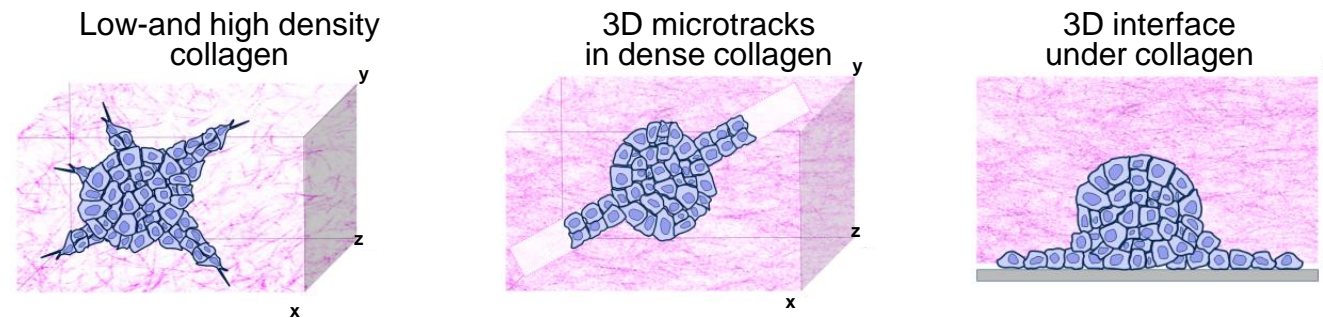


Two types of collective invasion:

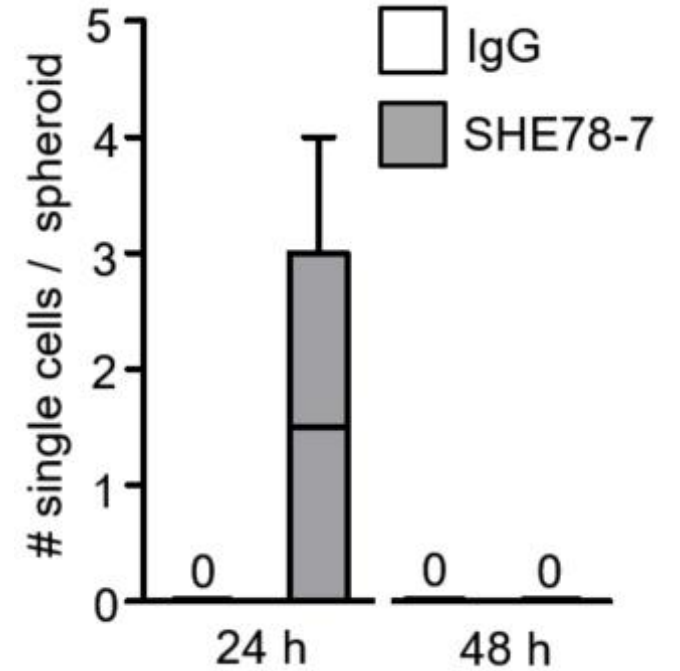
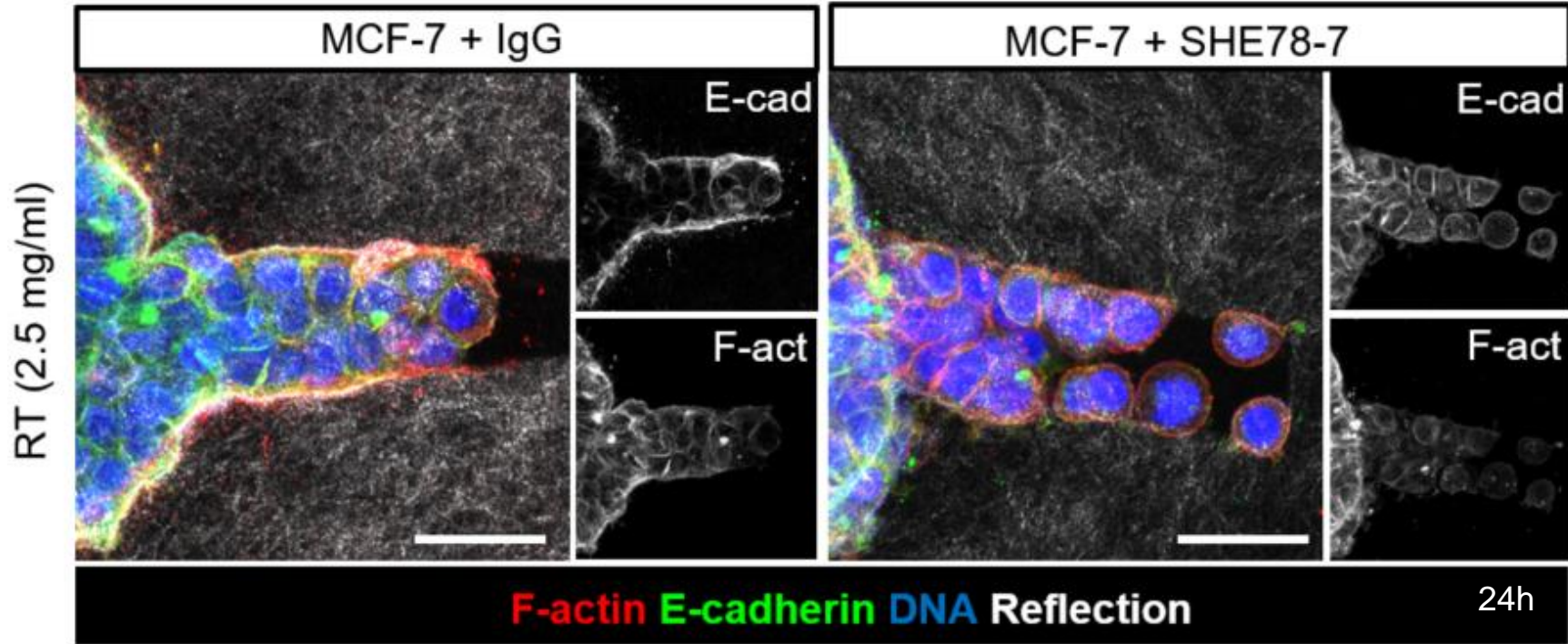
- 1) Cohesive: with stable cell-cell junctions
- 2) "Loose": weak cell-cell junctions, associated with tissue confinement

→ How do cell-cell junctions and confinement cooperate in regulating collective migration?

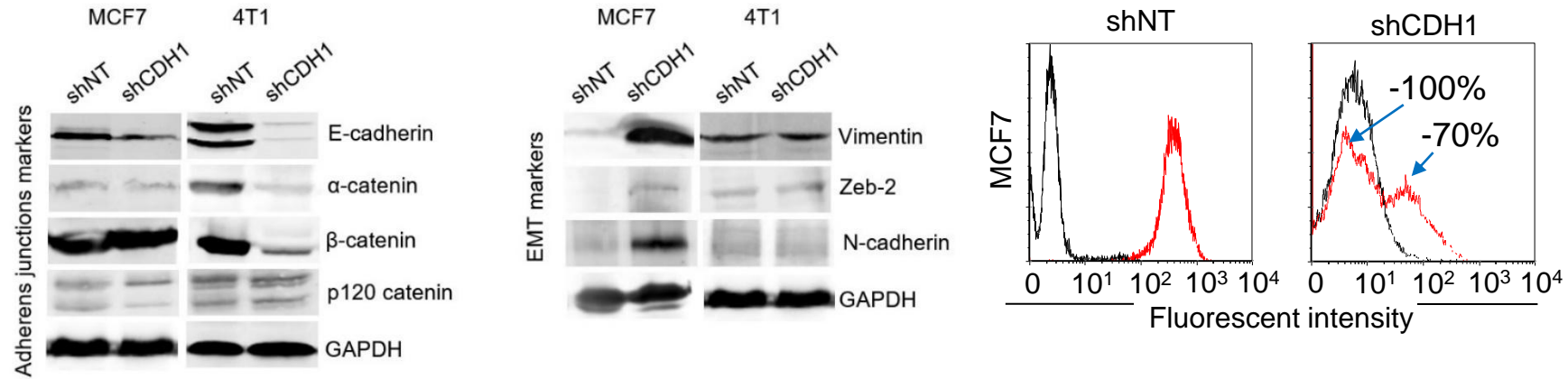
Modulating E-cadherin expression and tissue confinement



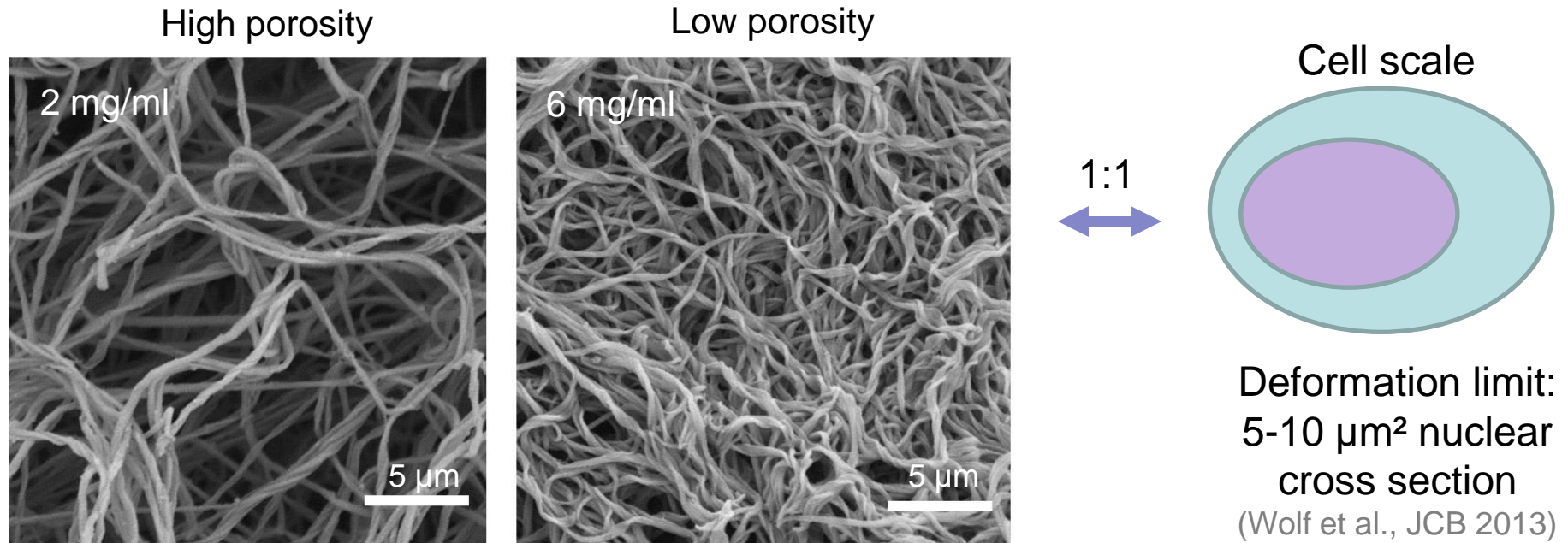
Low confinement regions enable single-cell detachment



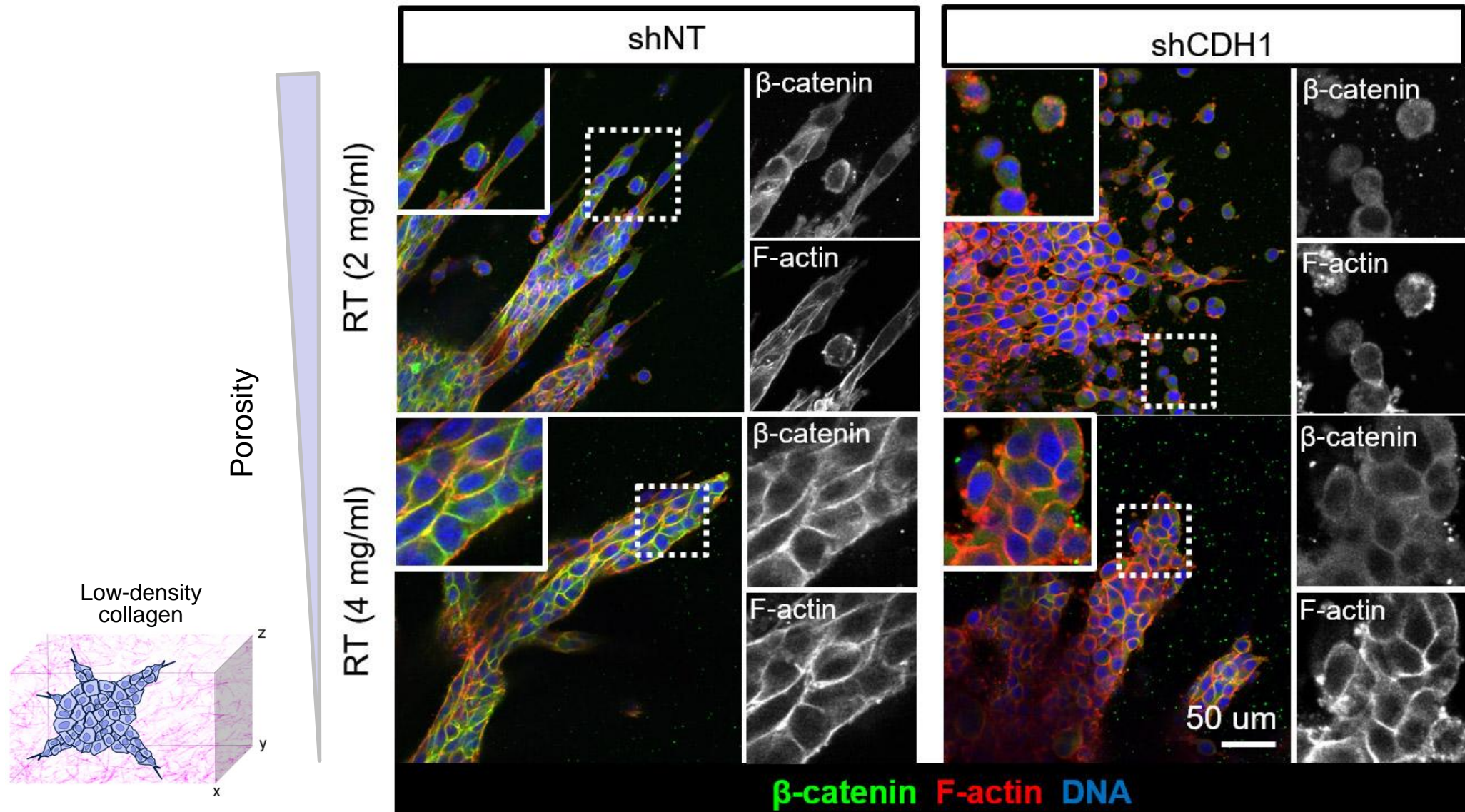
A: Downregulation of E-cadherin



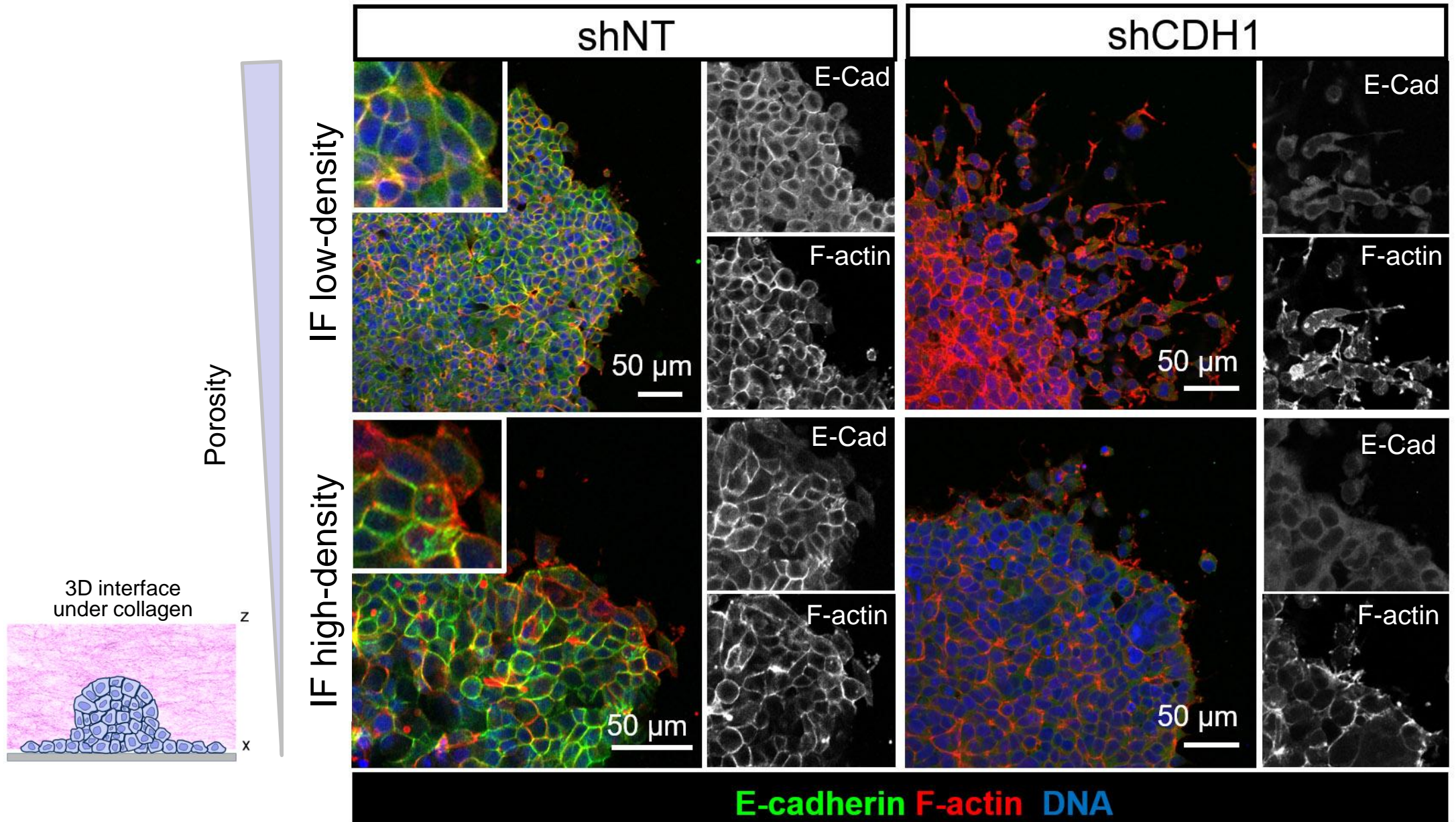
B: Modulation of tissue porosity (=confinement)



4T1 cells in low- vs mid-density 3D collagen



Persisting collective movement under confining conditions



1. Matrix confinement enforces multicellular patterns irrespective of E-cadherin levels in vitro and in vivo
2. Single-cell detachment is probabilistic and requires
 - (i) non-confining tissue niches and
 - (ii) weakened adherens junctions

Defining minimal components by *in silico* modeling



Andreas Deutsch

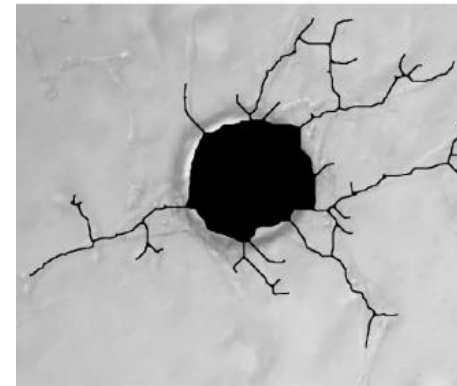
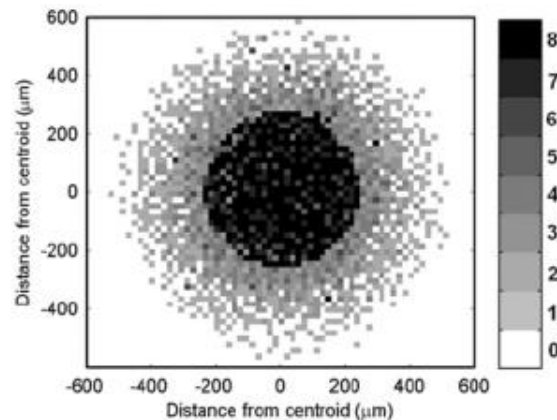
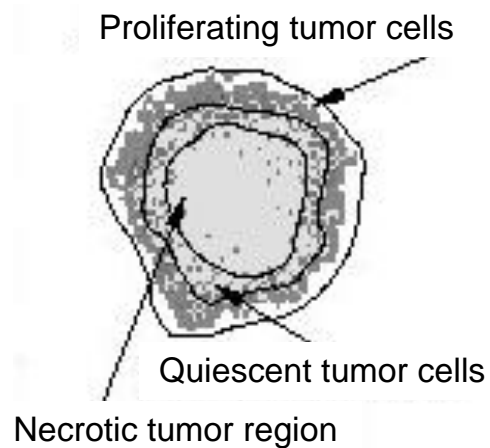


Simon Syga

TU Dresden

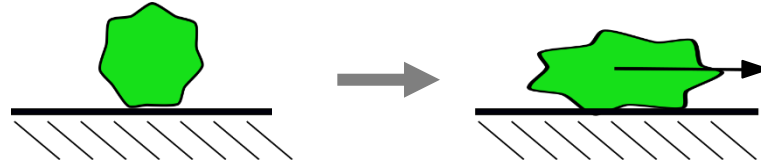
Lattice-Gas Cellular Automaton (LGCA)

- Origin: Simulation of fluid dynamics (Frisch, Hasslacher, Pomeau 1986; “FHP model”)
- Suitable for analyzing a range of biological systems:
 - Avascular tumor growth (Dormann, Deutsch 2002)
 - Glioma invasion (Tektonidis et al. 2011)
 - Angiogenesis (Mente et al. 2012)

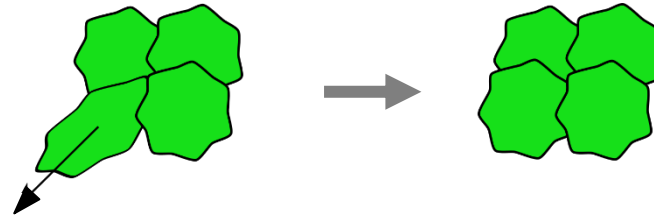


Modeling conditions

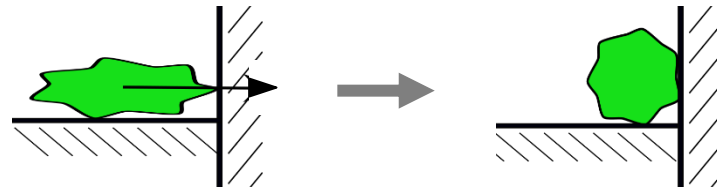
- General: cells proliferate and undergo apoptosis
- Cells move along ECM by cell-ECM adhesion



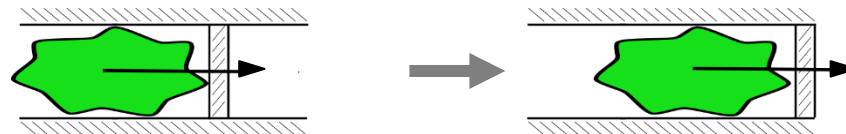
- Adhesion between cells reduces mobility of individual cells



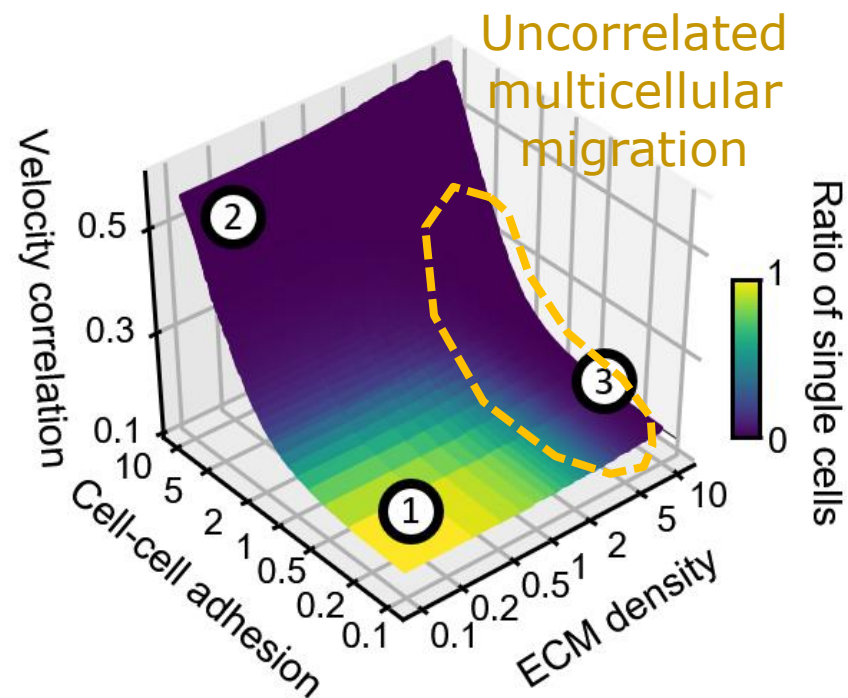
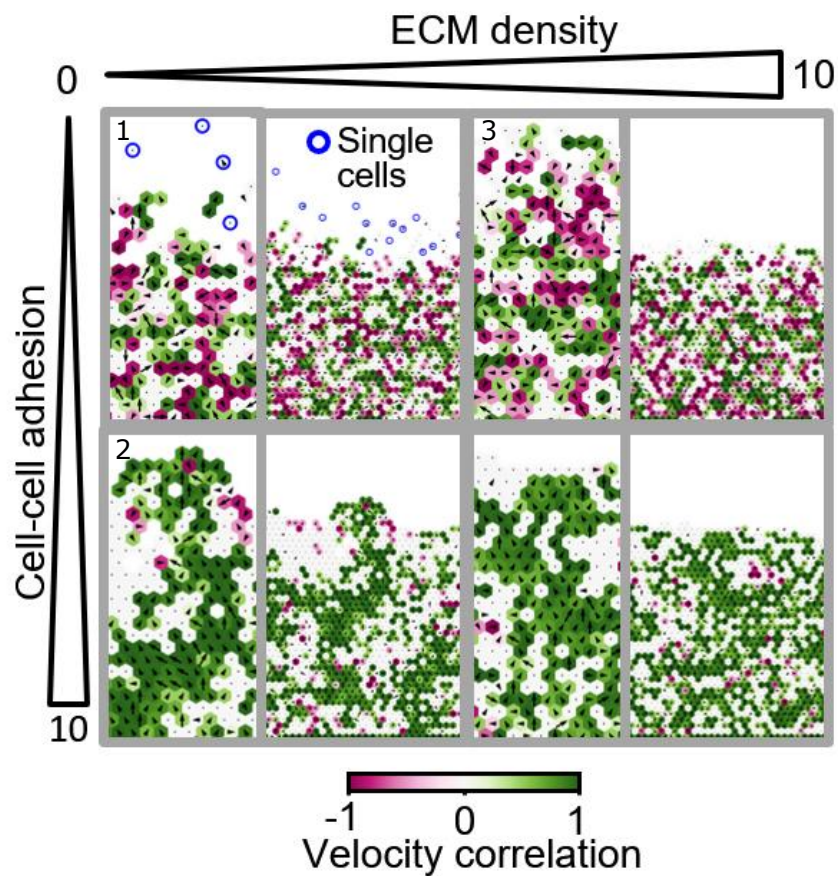
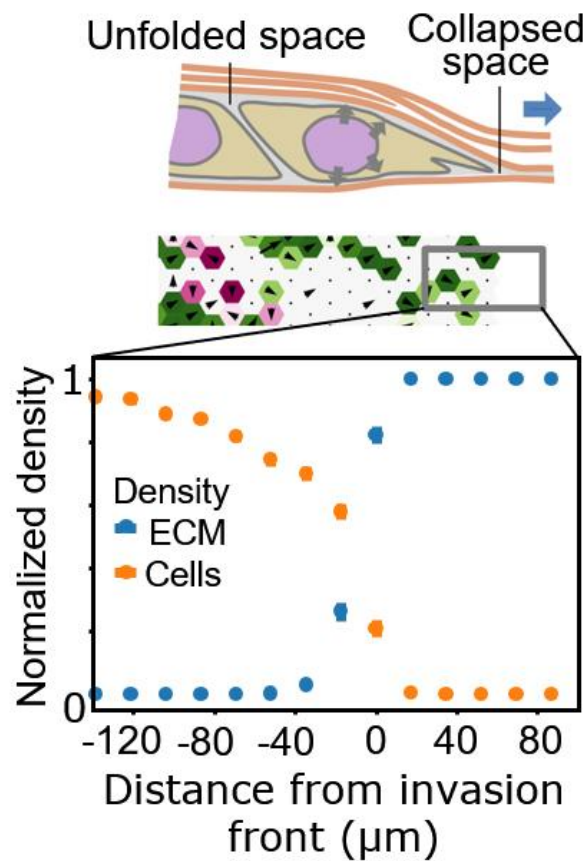
- Volume exclusion between cells and ECM



- ECM remodeling: cells can push ECM into free areas



Besides individualization: defective next-neighbor correlations



Differential „fluidity“ in collective patterning

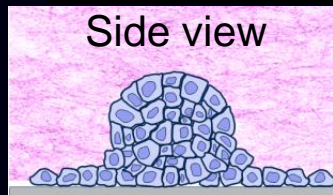
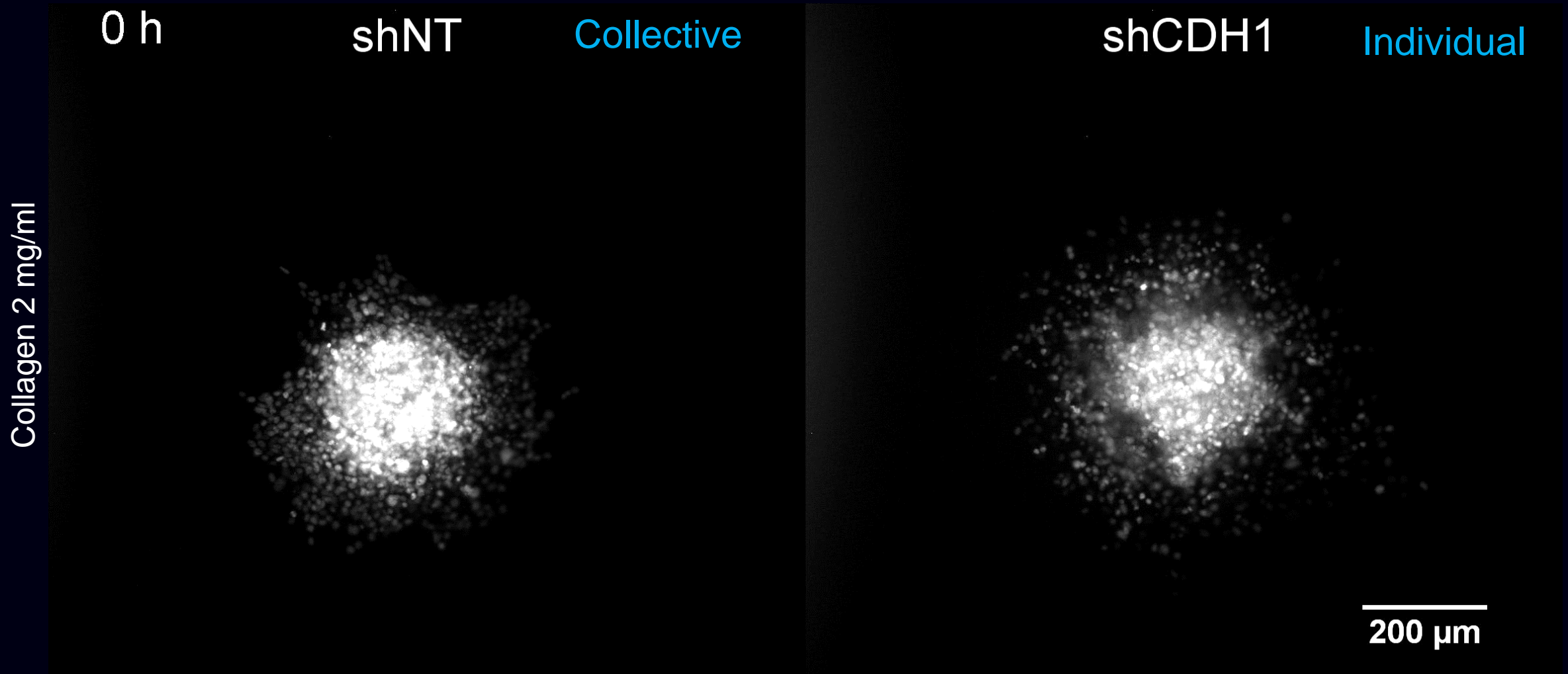


Caterina della Porta
Stefano Zapperi
U Milan



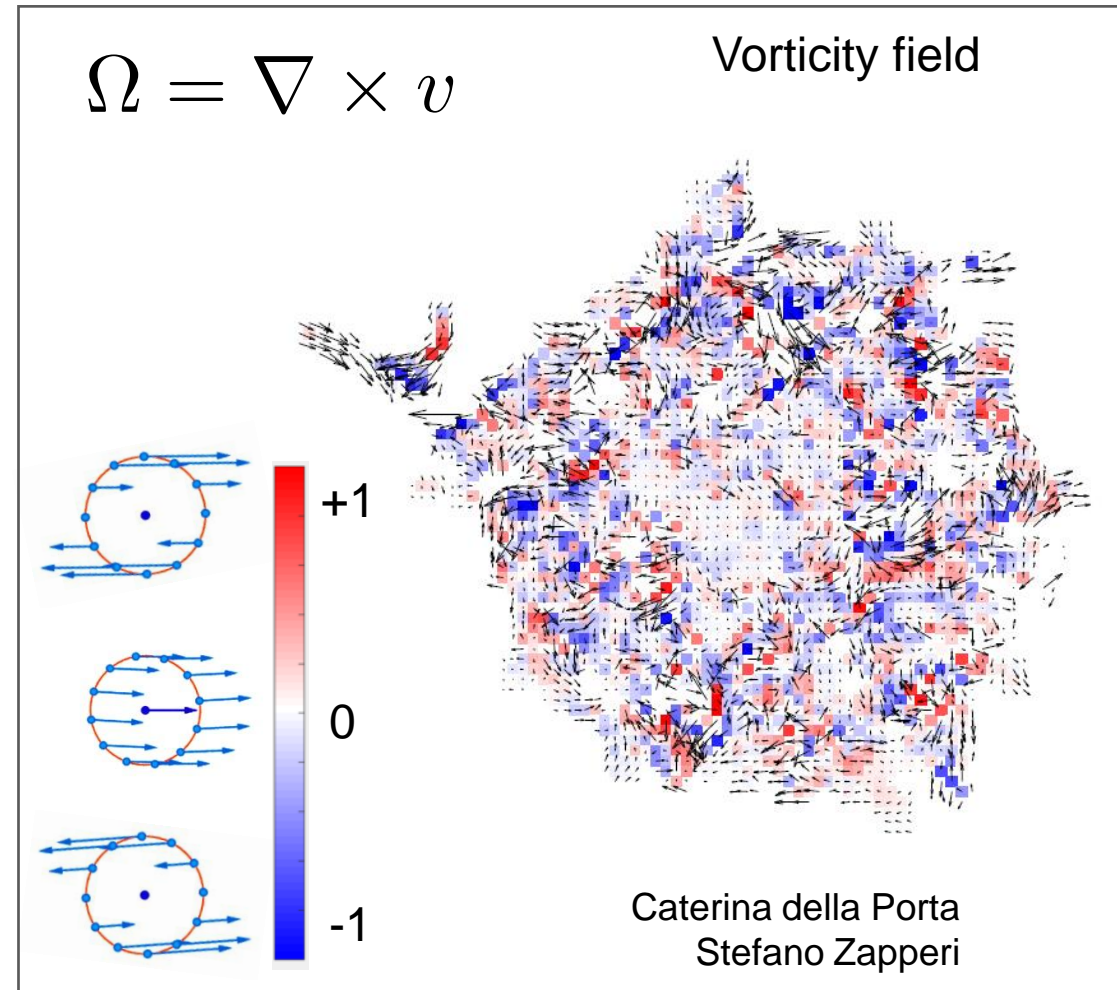
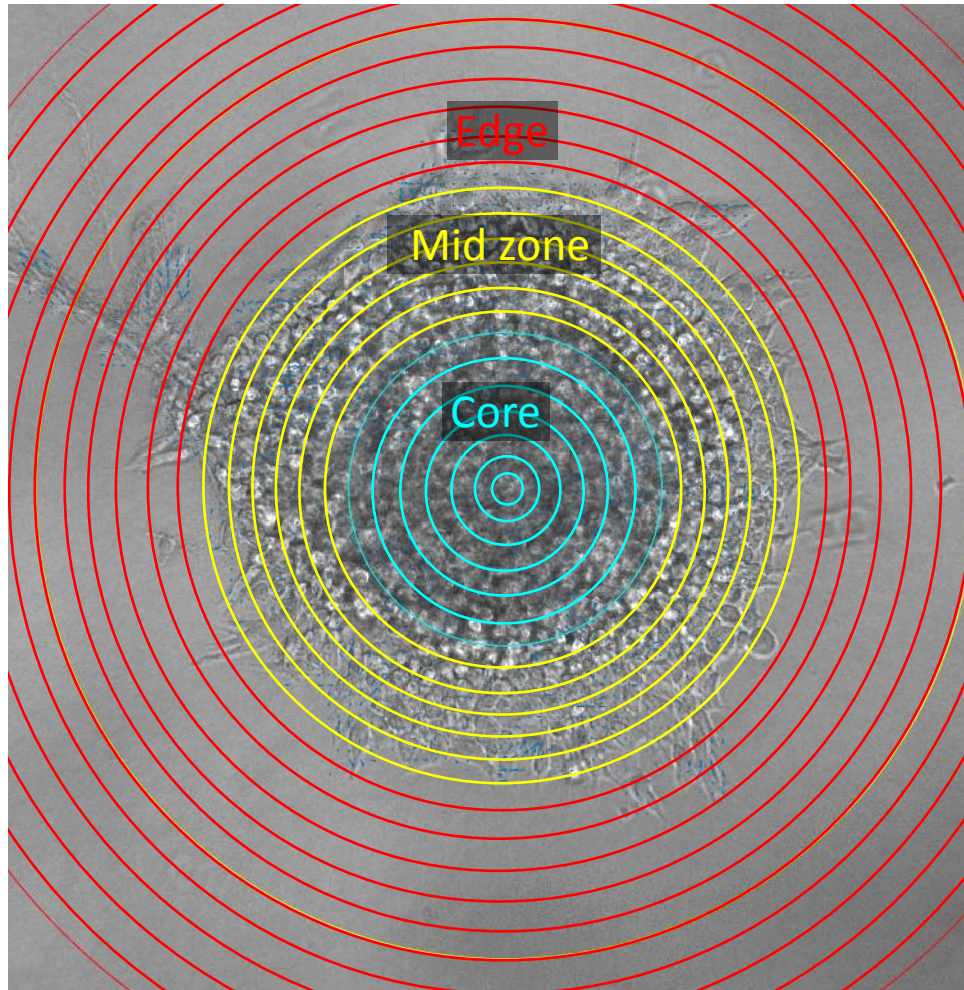
Jürgen Lippoldt
Josef Käs
U Leipzig

Probing jamming transitions under low and high ECM confinement

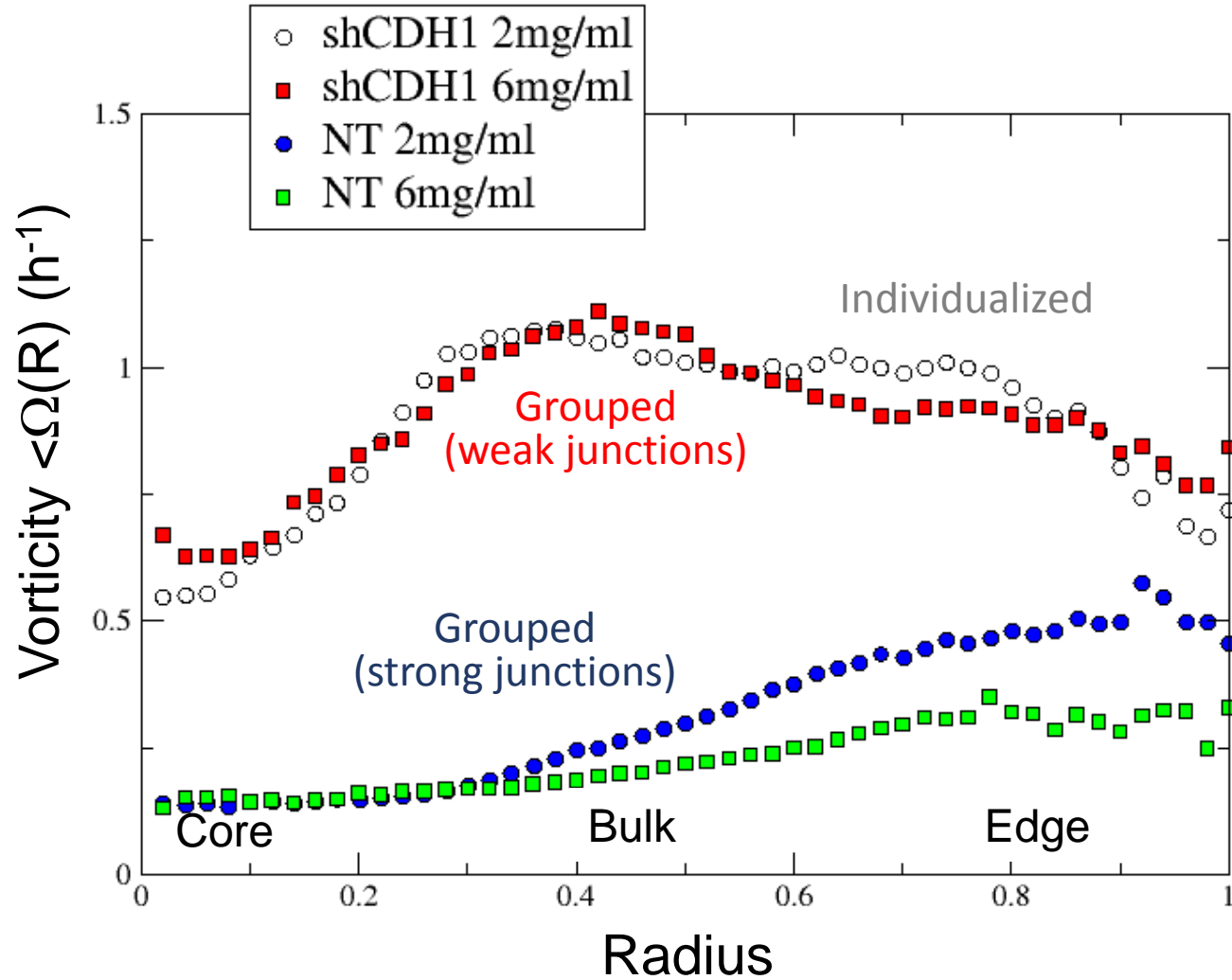
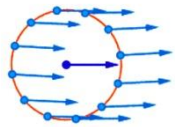
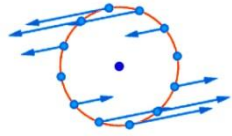


H2B/mCherry

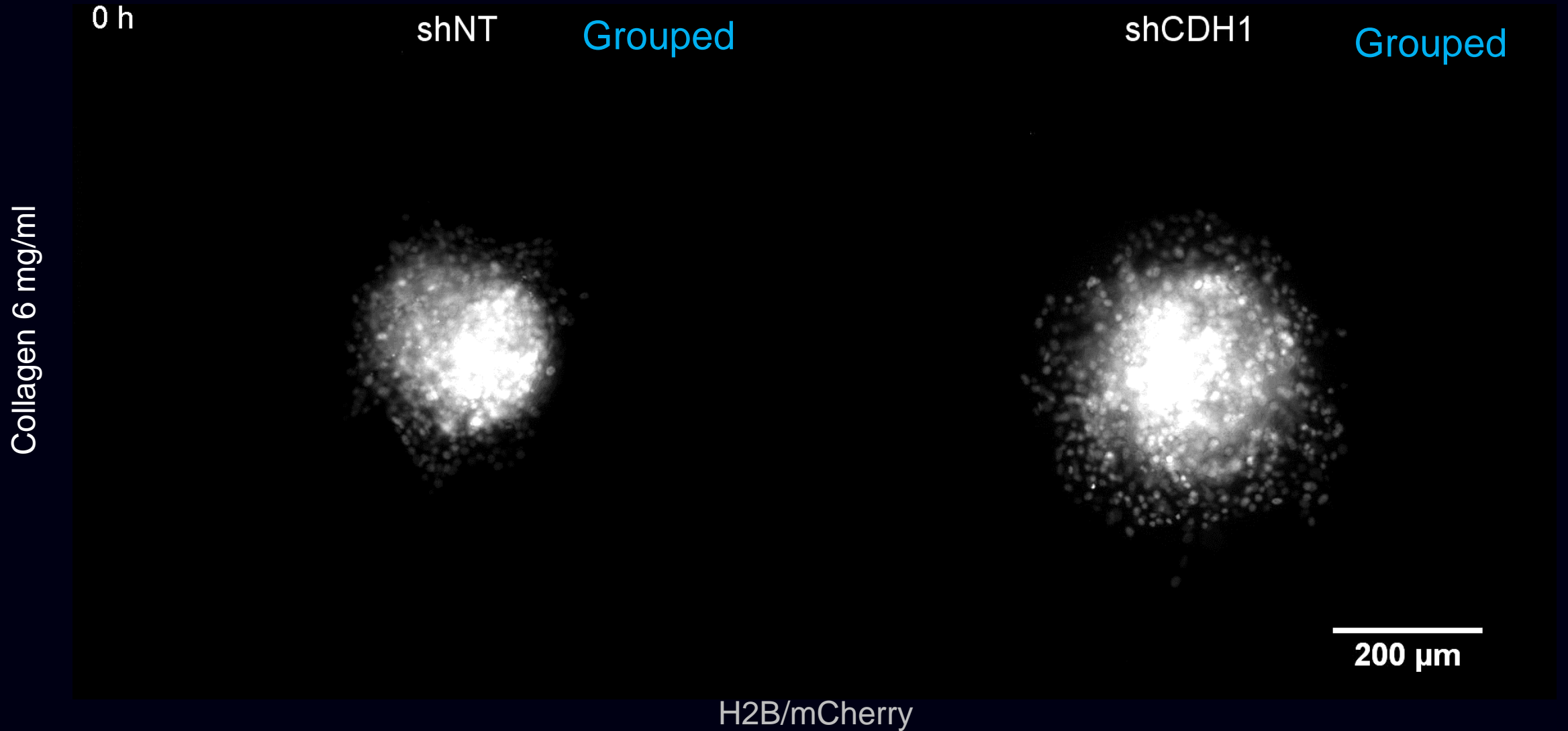
Particle imaging velocimetry: velocity and vorticity



Vorticity as a function of collagen density and junctional stability



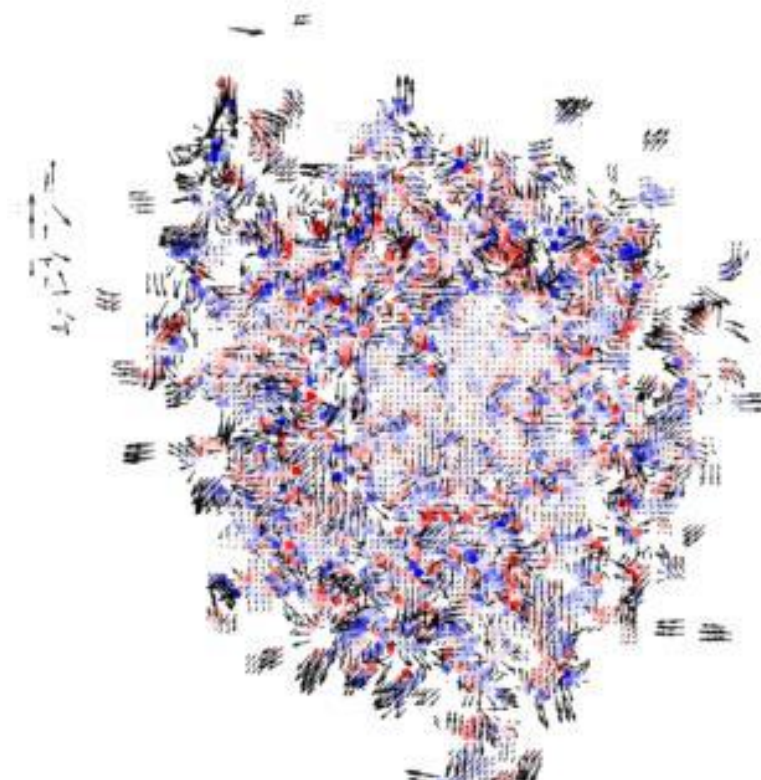
Probing jamming transitions under low and high ECM confinement



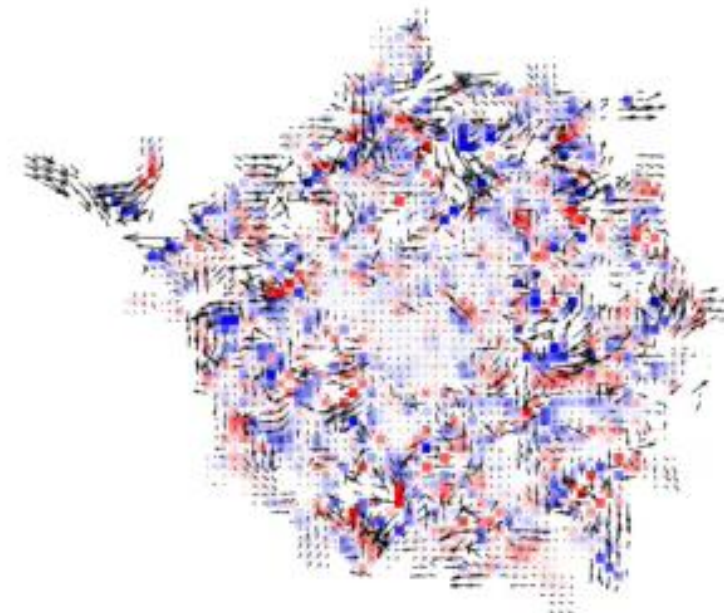
High vorticity during sheet migration under high-density collagen conditions

Individualized

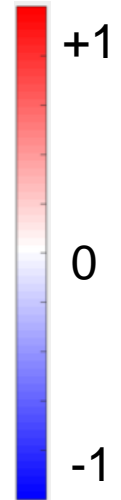
Grouped



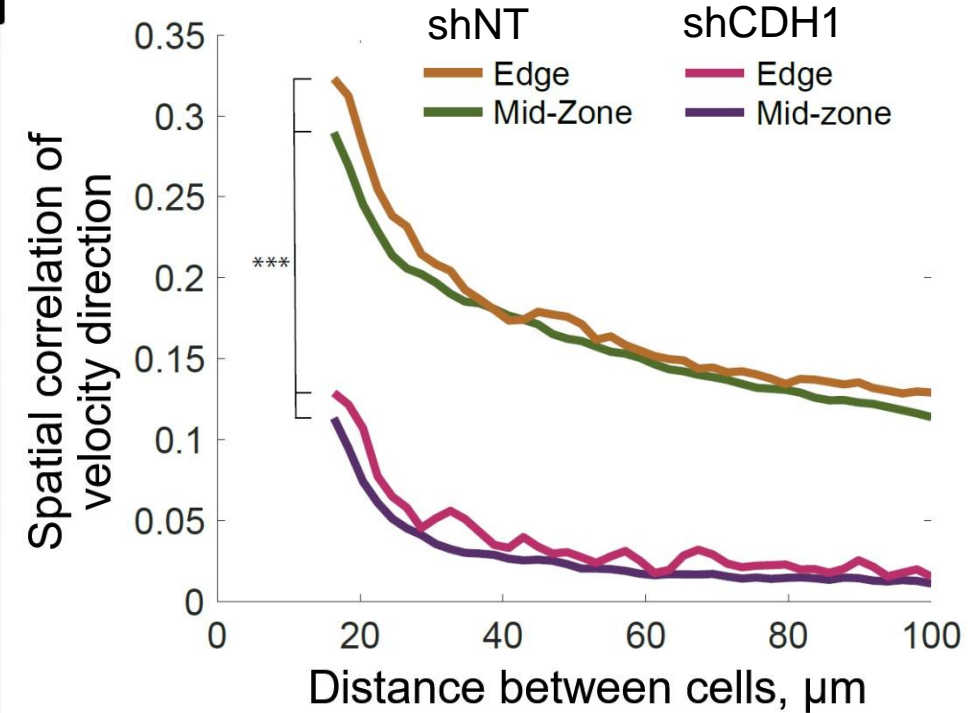
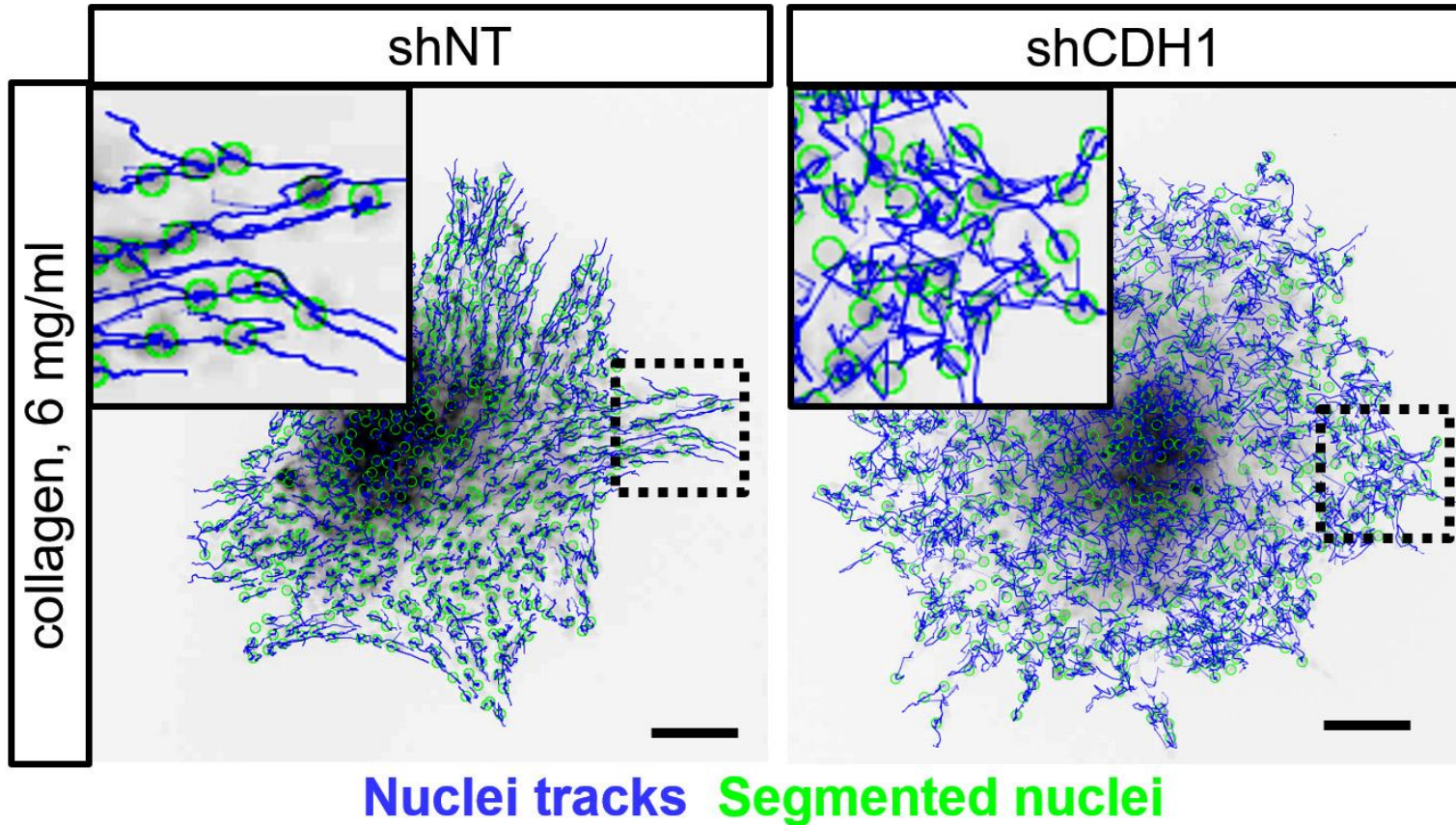
shCDH1 (2mg/ml)



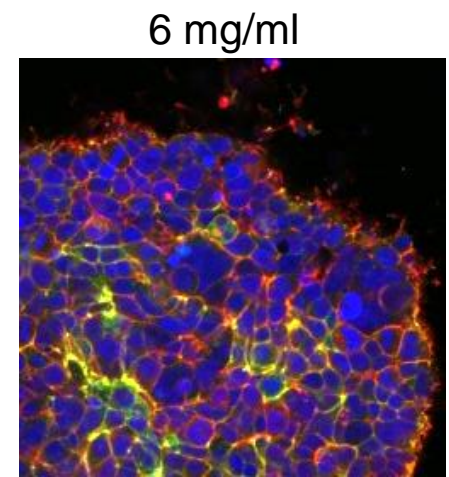
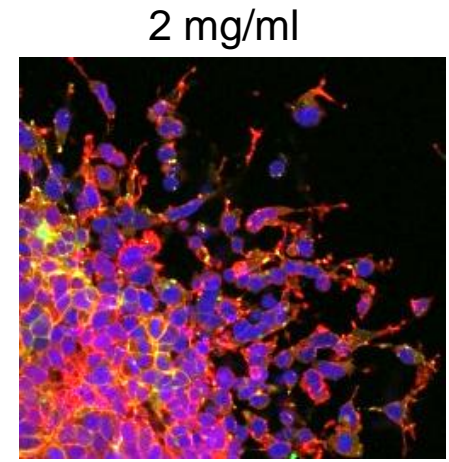
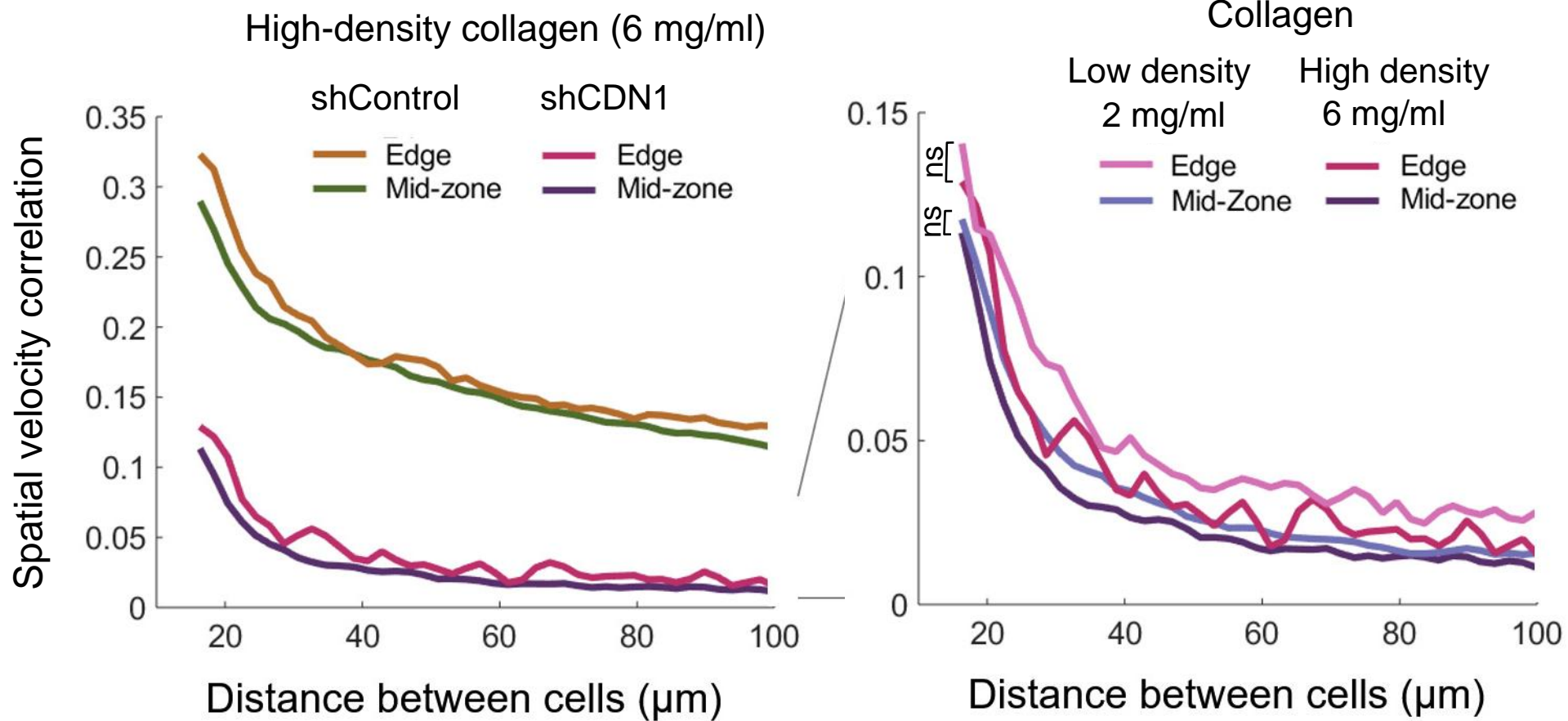
shCDH1 (6mg/ml)



E-cadherin is required for directional coordination between cells



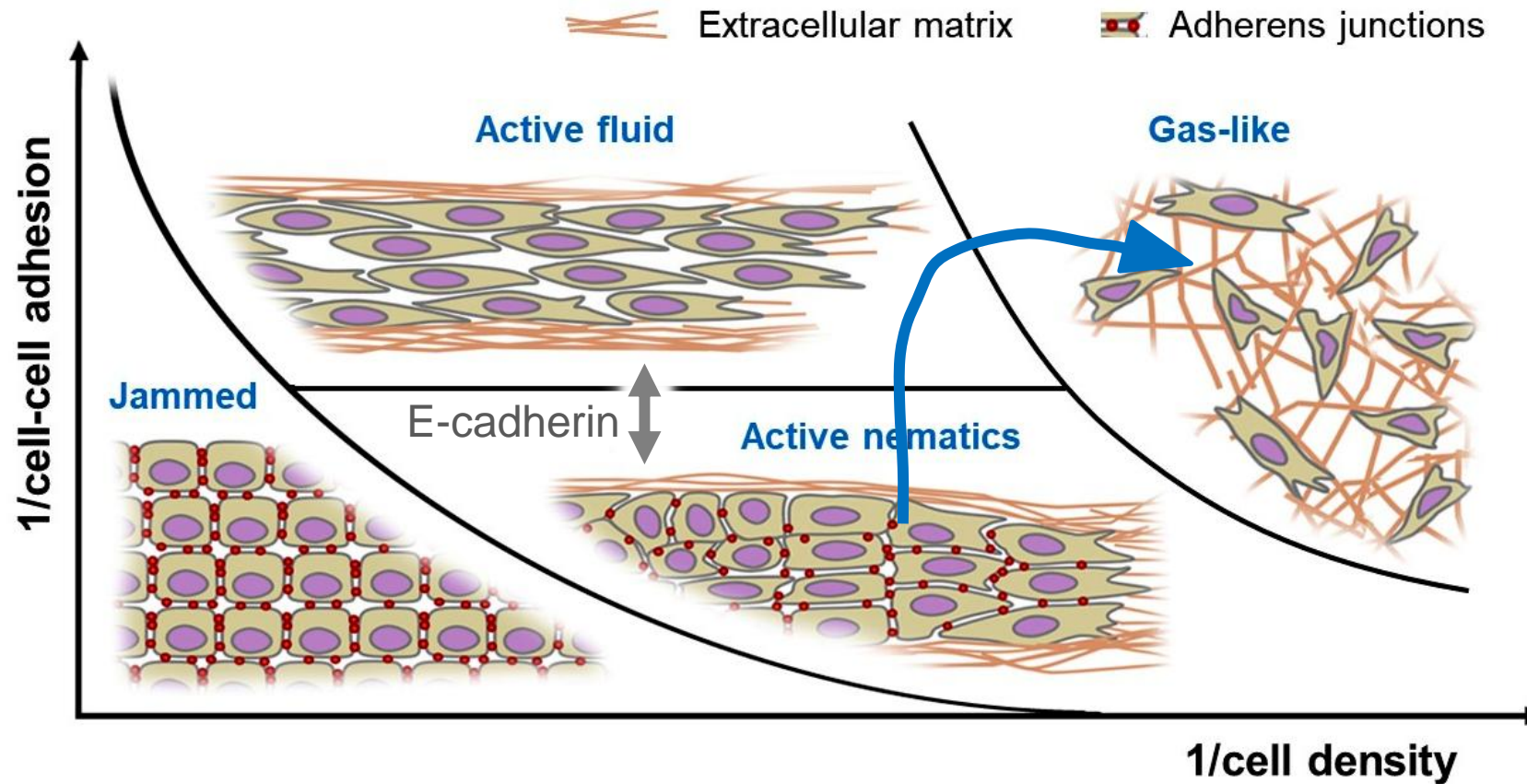
Collective cell pattern but lack of next-neighbor coordination



F-actin DAPI

→ Fully individualized kinetic behavior in the moving sheet

Plasticity of cancer invasion programs: partial and complete unjamming



Iliina et al.,
Nat. Cell Biol.
(2020)

Two types of multicellular migration

- 1) Active nematics: Collective migration with cadherin-based cell-cell junctions
- 2) Active fluid: Single-cell like movement with low-adhesive cell-cell interactions

Cell Dynamics Laboratory / MIC



Anna Häger



Antoine Khalil



Jack Fransen



Sjoerd van Helvert



Radboudumc
university medical center

NWO-*Vici*
ERC Consolidator
T3Net