Cell and tissue mechanics

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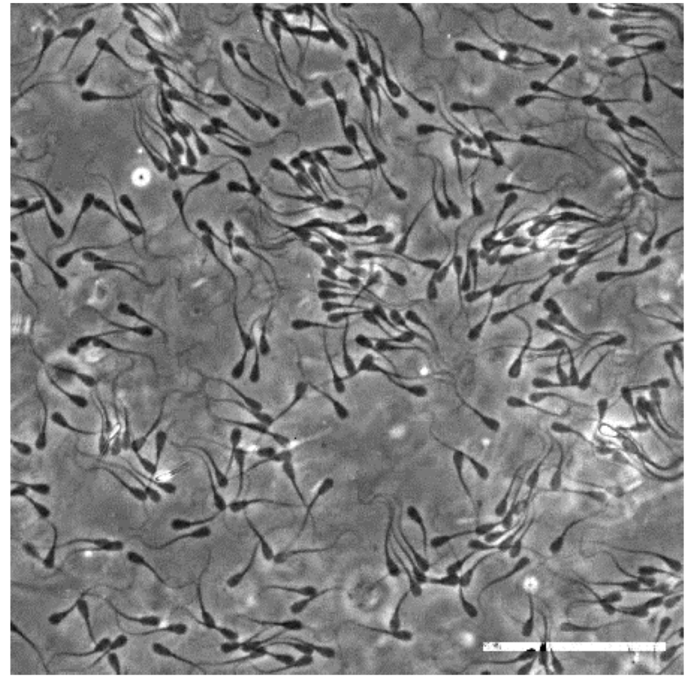
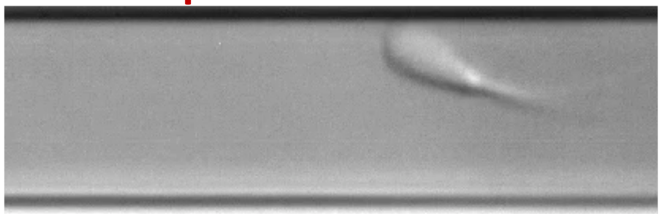
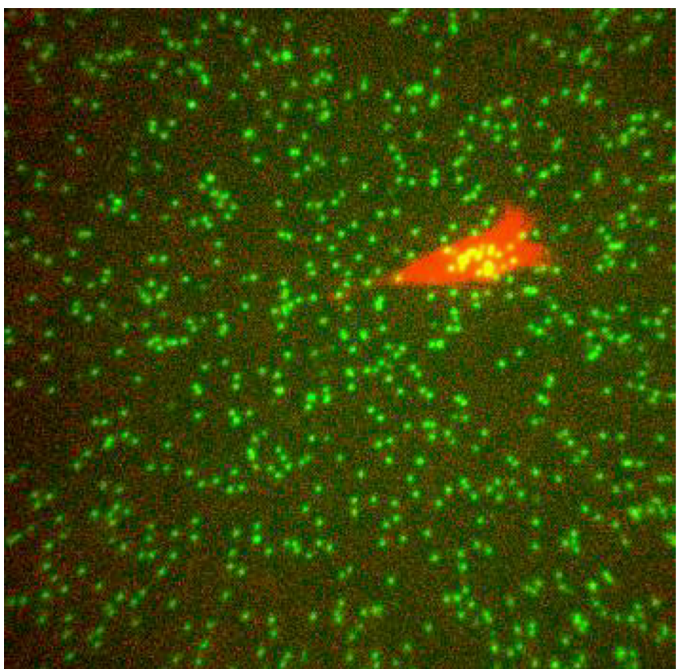
Cells in motion

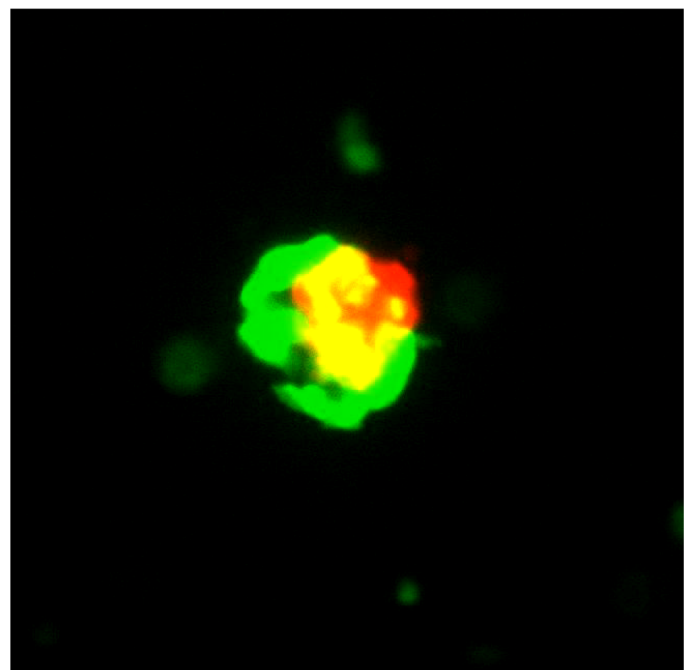


Bovine Sperm



Breast tumor cell

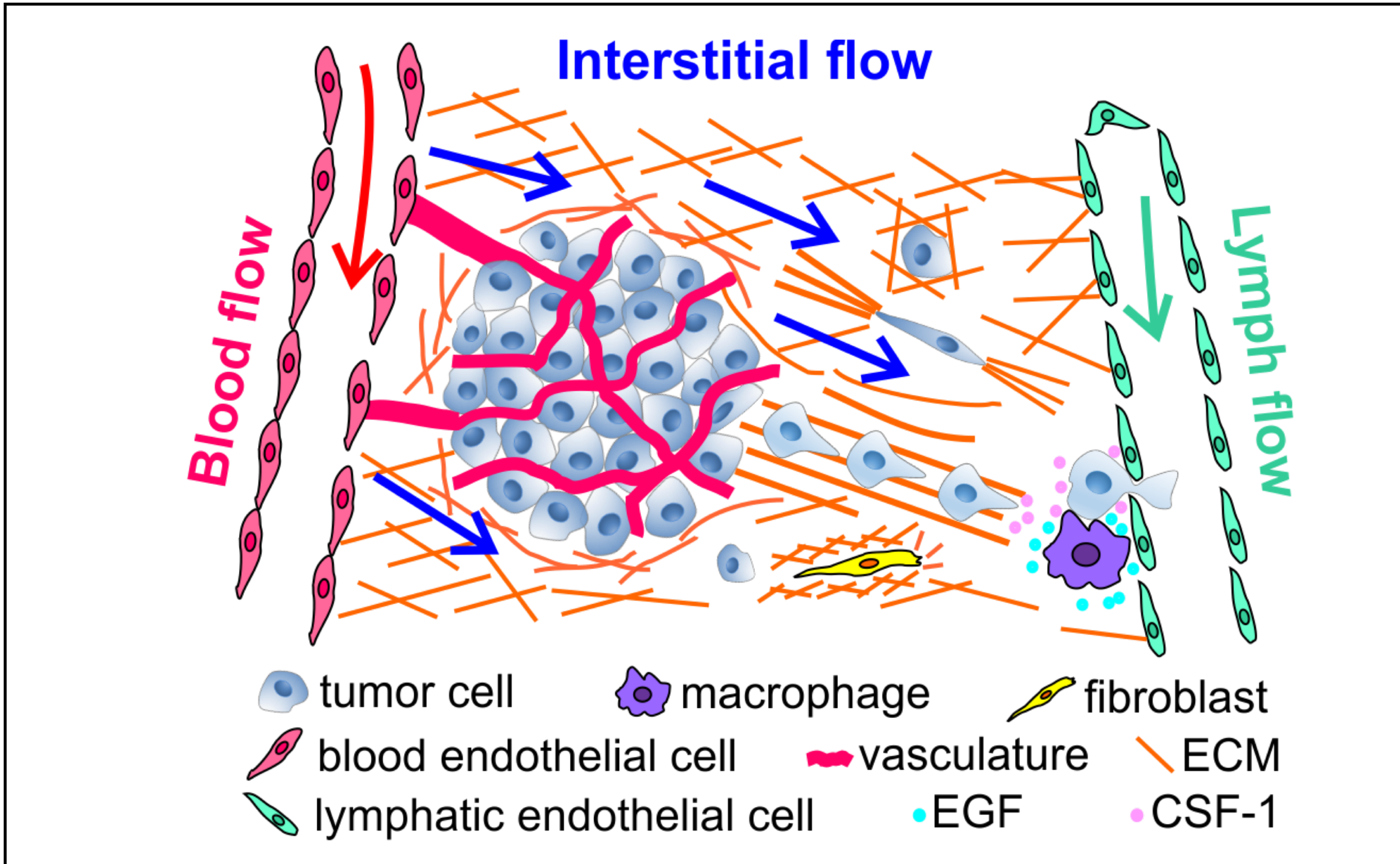




Satellite image of the earth at night

Population distribution is governed by the environment (temperature, proximity to water, landscape, …) and communications.

Problem of interest: Cancer metastasis - the leading cause of death of most cancer types



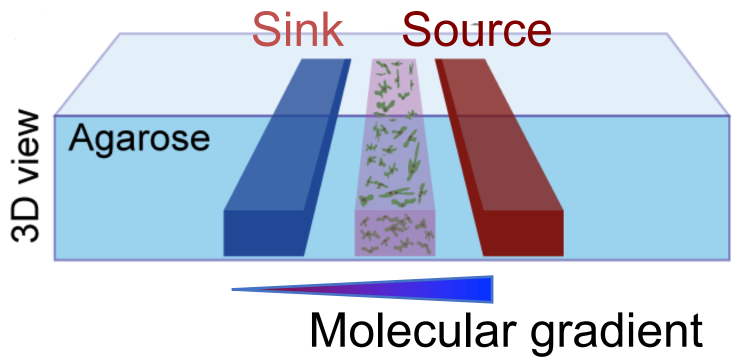
Cancer metastasis is a physical process where tumor cells need to generate enough force to invade

Cancer microenvironment critically regulates tumor cell invasiveness

Ref: Huang et al. Lab Chip, 2017; Wu and Swartz, J. Biomech. Eng, 2013; Kim and Wu, Ann Biomed Eng, 2012.

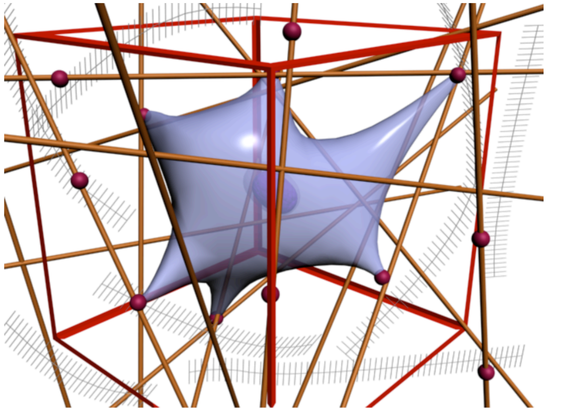
Key biophysical and biochemical parameters that drive cell migration

Chemical gradients



- Diao et al. Lab Chip, 2006,
- Cheng et al, Lab Chip, 2007,
- Haessler et al. Biomedical Microdevice, 2009.
- Haessler et al. PNAS, 2011.
- Kim et al. PlosOne 2013
- Geum et al. Euro. Phys. Journal, 2016.
- Huang et al. Lab Chip, 2017.
- Kim et al. Integrative Biology, 2020.

Mechanical stress



- Rong et al. Biophysical Journal, 2011
- Hall et al. Biophysical Journal, 2012
- Hall et al. Experimental cell research, 2013
- Hall et al. PNAS, 2016.
- Huang et al. Integrative Biology, 2017.
- Suh et al. Integrative Biology, 2019

OUTLINE:

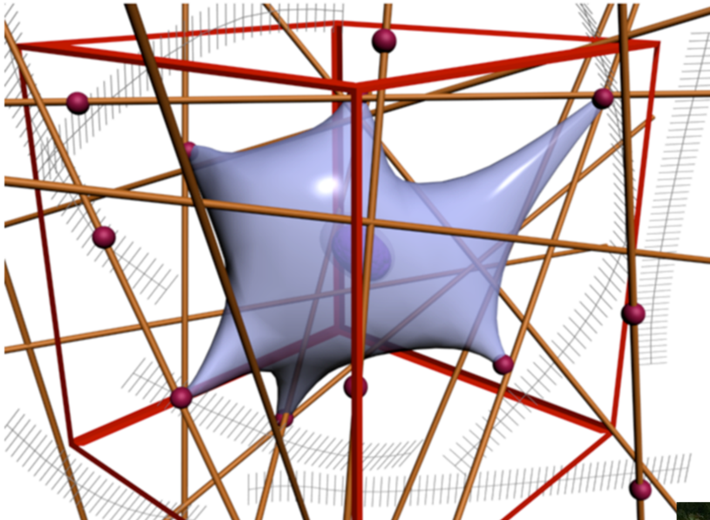
Single cell mechanics within a 3D biomatrix

- Single cell migration
- Mechanical driver
- Chemical gradient driver

Tumor spheroid invasion

- Tumor spheroid formation
- Tumor spheroid invasion (chemical and mechanical driver)

Single cell migration in 3D



Integrin

Collagen fiber

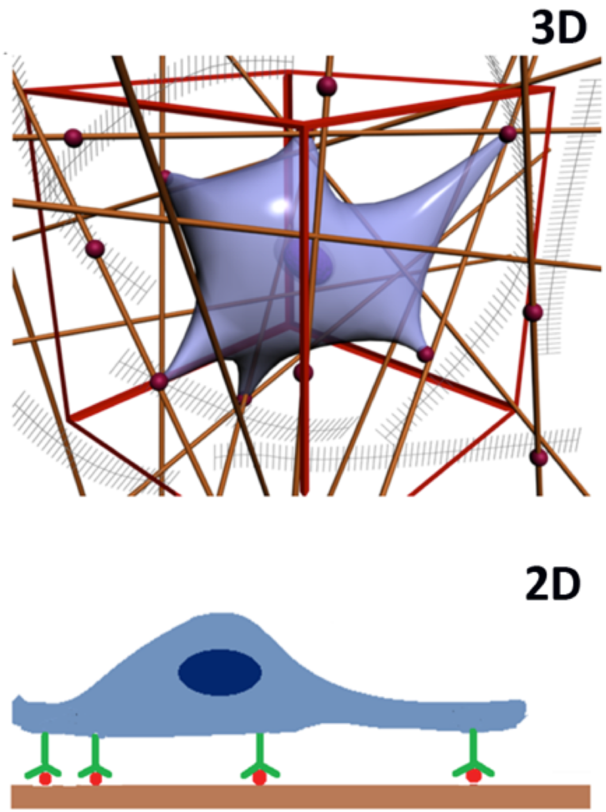
Cells are supported by a 3D fiber network

Differ from 2D cell migration

Cell-ECM tensional balance is regulated by cell traction force.

Wu and Swartz, J. Biomech. Eng. 2014.

Cell migration in two dimensional space (2D) versus 3D

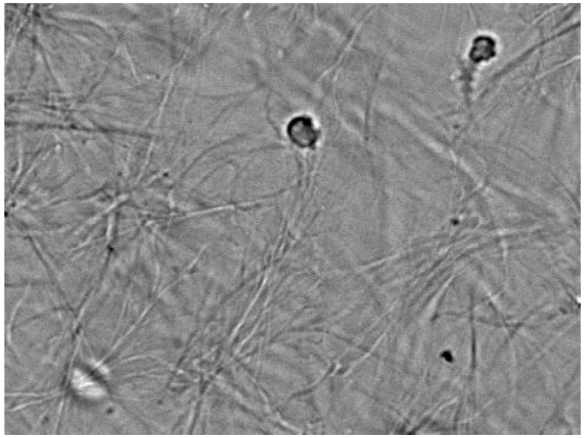


Many cell types requires the 3D environment to exhibit physiologically realistic phenotypes

Figure adapted from: Wu and Swartz, Journal of biomechanical engineering, 2014.

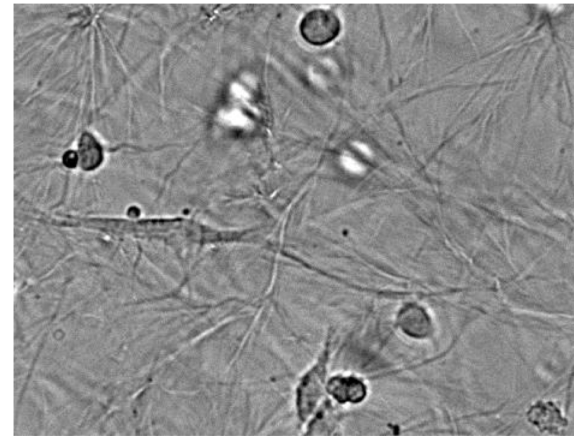
Amoeboid and mesenchymal cell migration

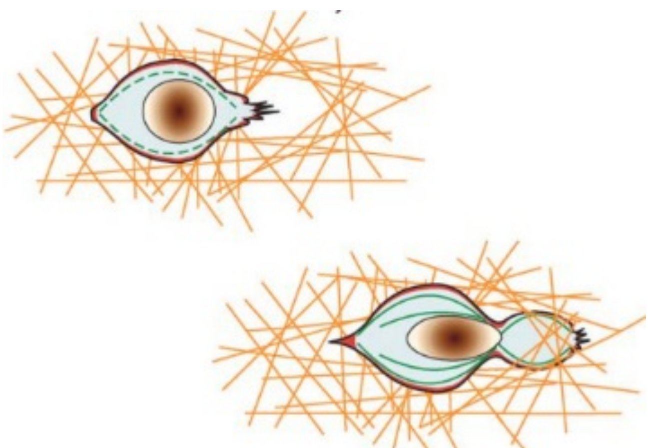
Amoeboid cells

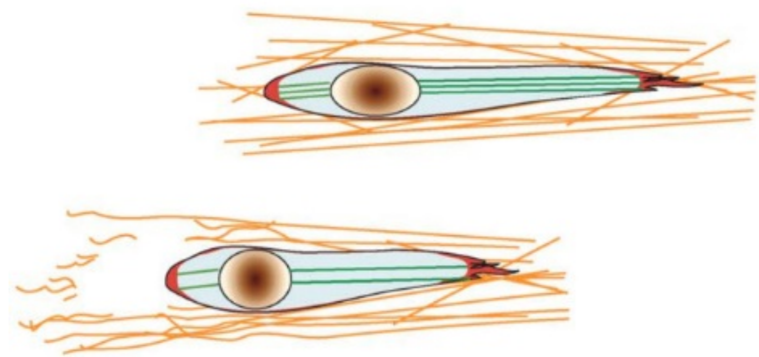


Amoeboid	Mesenchymal
Round	Elongated
Short-live adhesion	Long-live Adhesion
MMP independent	MMP dependent
Path finding	Path generating

Mesenchymal cells







[1] Turner et. al. (2011). [2] Paňková, K., et al. (2010).
[3] Sabeh, F., et al. (2009). [4] Pathak et al. (2011) Integr Biol

OUTLINE:

Single cell mechanics within a 3D biomatrix

- Single cell migration
- Chemical gradient driver
- Mechanical driver

Tumor spheroid invasion

- Tumor spheroid formation
- Tumor spheroid invasion (chemical and mechanical driver)

Cancer cell chemotaxis in 3D microfluidic model

In collaboration with Prof. Melody Swartz at Swiss Institute of Technology, now University of Chicago

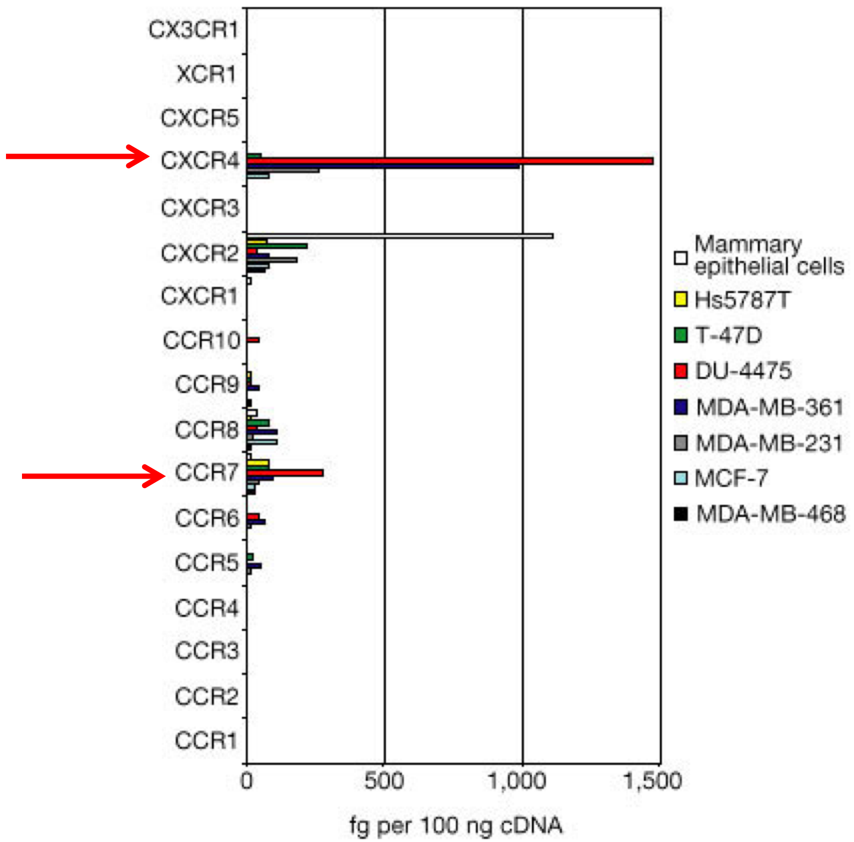
Roles of lymph node microenvironment in cancer cell migration

Clinical wisdom:
Lymph nodes --
first stops of metastatic cancer cells of many cancer types

Cancer cell types correlated with lymph nodes metastasis

- Breast (Cabioglu et al. 2005)
- Melanoma(Taakeuchi et al., 2004)
- Colorectal (Gunther et al. 2005)
- Head and neck (Wang et al. 2005)
- Prostate (Heresi et al. 2005)
- Non-small lung (Takanami, 2003)
- Gastric (Mashino et al. 2002)

Ref: Shields et al. Cancer Research, 2007



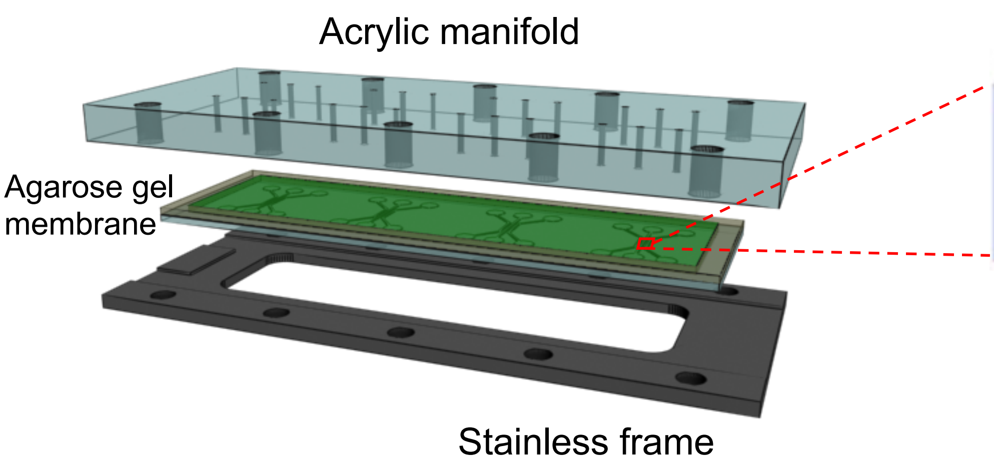
Gene profiling (breast cancer cells):
Chemokine receptors are implicated in metastatic breast cancer cells

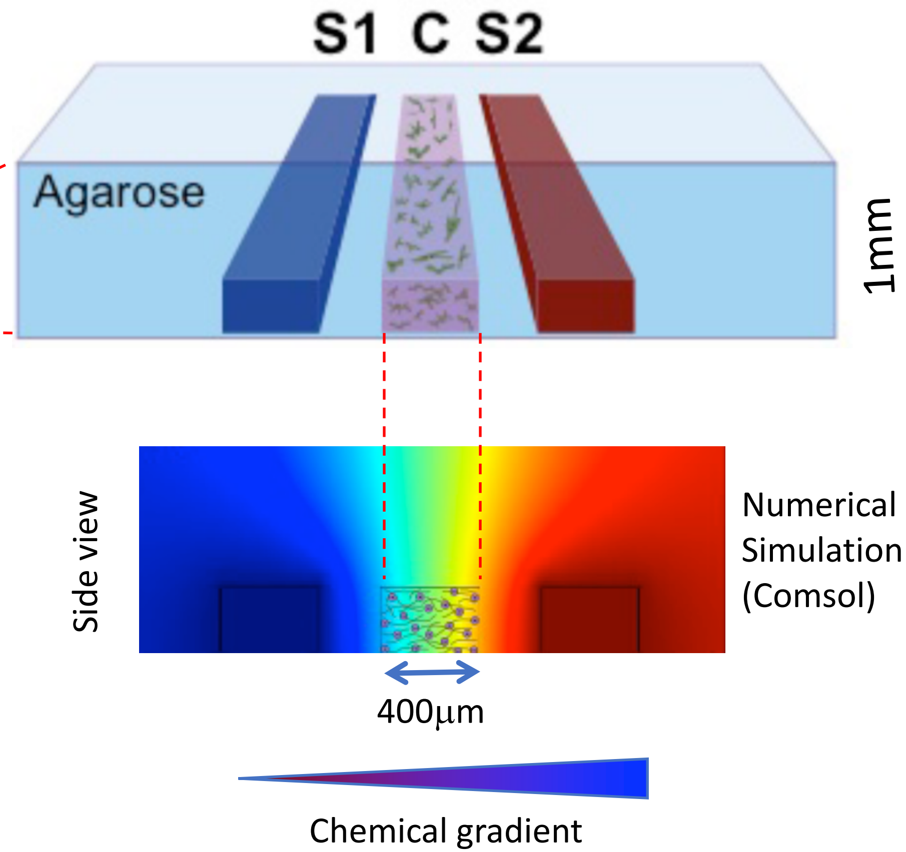
Muller et al. Nature, 2001

Hypotheses:

Breast tumor cells are chemotactic in SDF-1α (ligand to CXCR4) and CCL19 (ligand to CCR7) and gradients.

Creating chemokine gradients using a hydrogel-based microfluidic platform

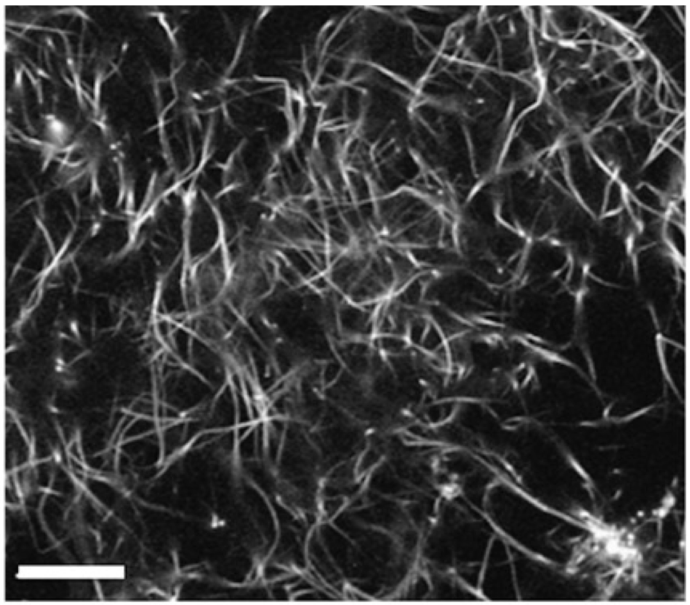




Diao et al. Lab on a Chip, 2006,
Cheng et al, Lab on a Chip, 2007,
Haessler et al. Biomedical Microdevice, 2009.
Haessler et al. PNAS, 2011.
Kim et al. PlosOne 2013
Geum et al. Euro. Phys. Journal, 2016.

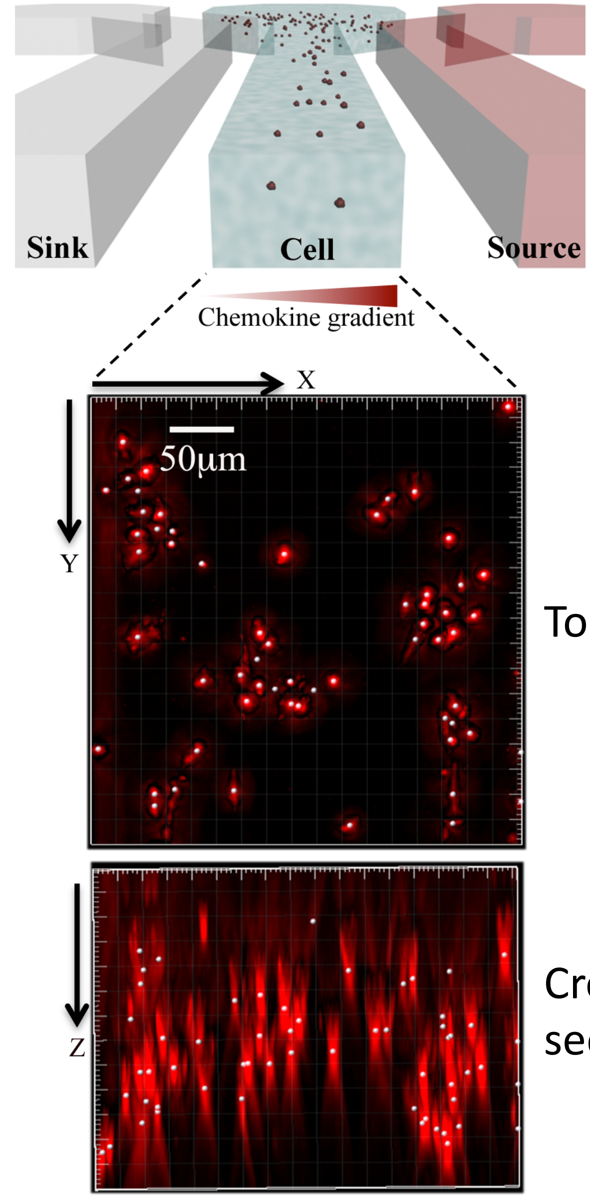
3D *in vitro* cell culture using type I collagen (derived from rat tails)

Type I collagen



20μm

Reflective confocal image of collagen Fibers (Cross and Stroock, Biomaterials, 2010).

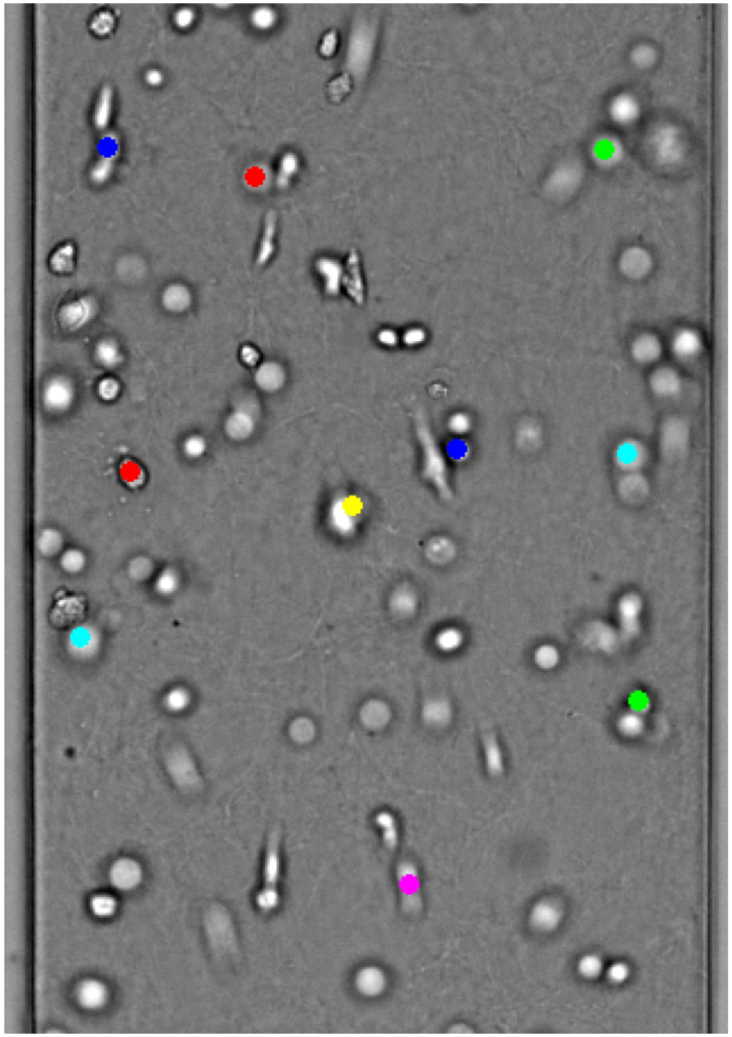


Top view

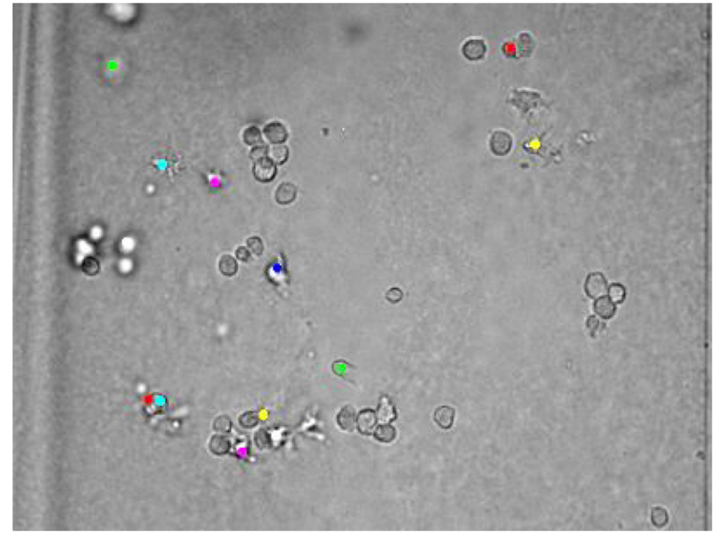
Cross section view

MDA-MB-231 cells embedded in collagen

Tumor cell versus immune cell chemotaxis



Breast tumor cells (MDA-MB-231)
SDF-1α gradient

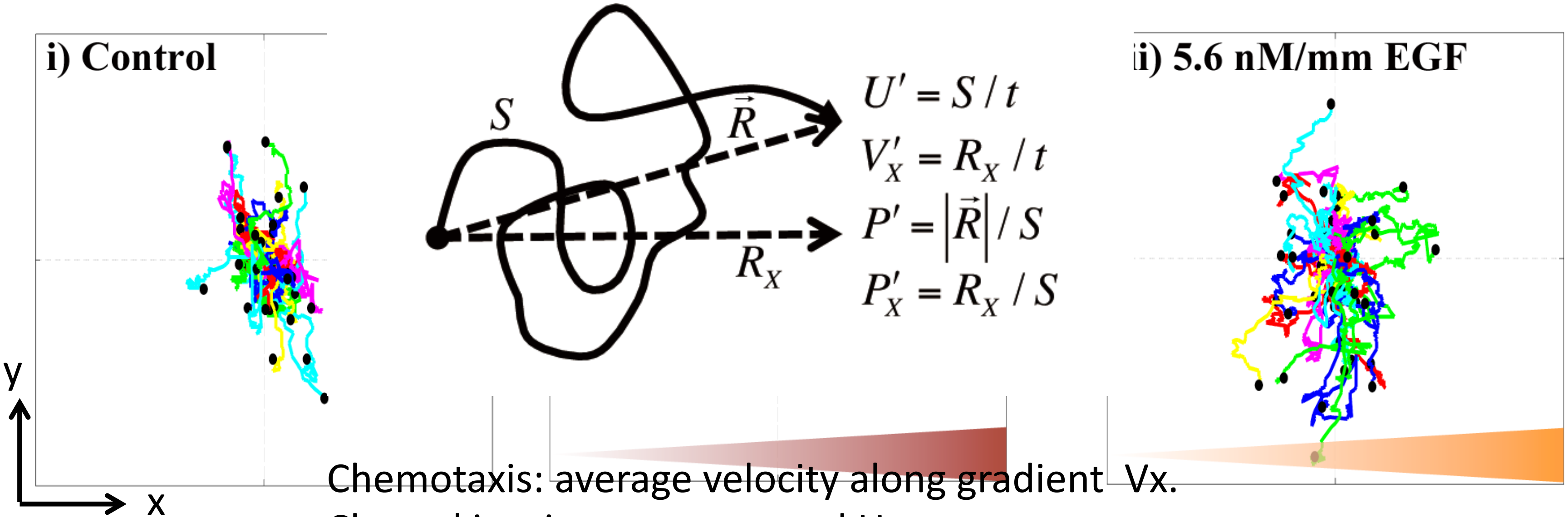


Dendritic cells
CCL19 gradient

Haessler et al. Biomedical Microdevice, 2009

Tumor cells are highly heterogenic in terms of morphology and motility

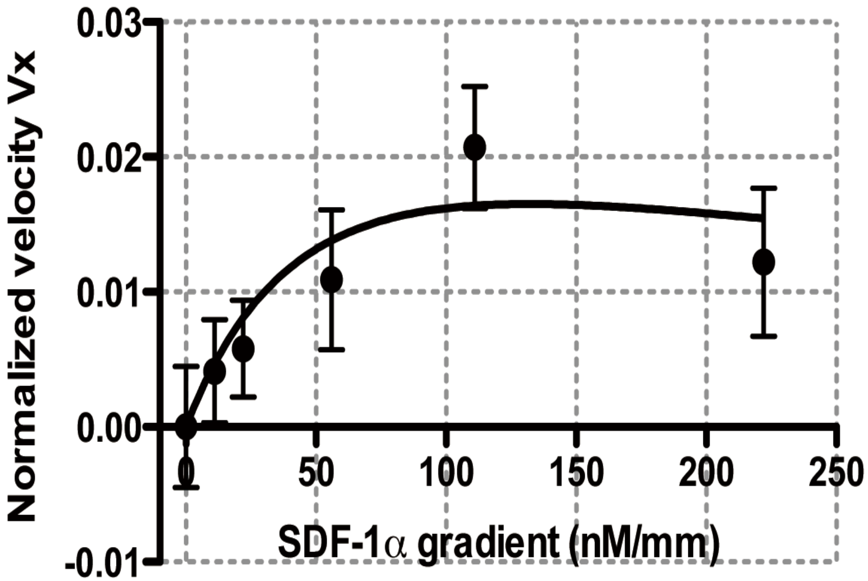
Quantifying tumor cell chemotaxis in cytokine gradients



Chemotaxis: average velocity along gradient Vx.
Chemokinesis: average speed U.
(Both scaled by average control cell speed.)

Both dendritic and tumor cell chemotaxis is governed by ligand receptor binding kinetics

Receptor/ligand: CXCR4/SDF-1alpha



Solid lines is a fit to:

$$V_x = A\frac{\nabla C}{(C_{Avg}+K_D)^2}$$

K_D : Ligand receptor association constant

A: constant

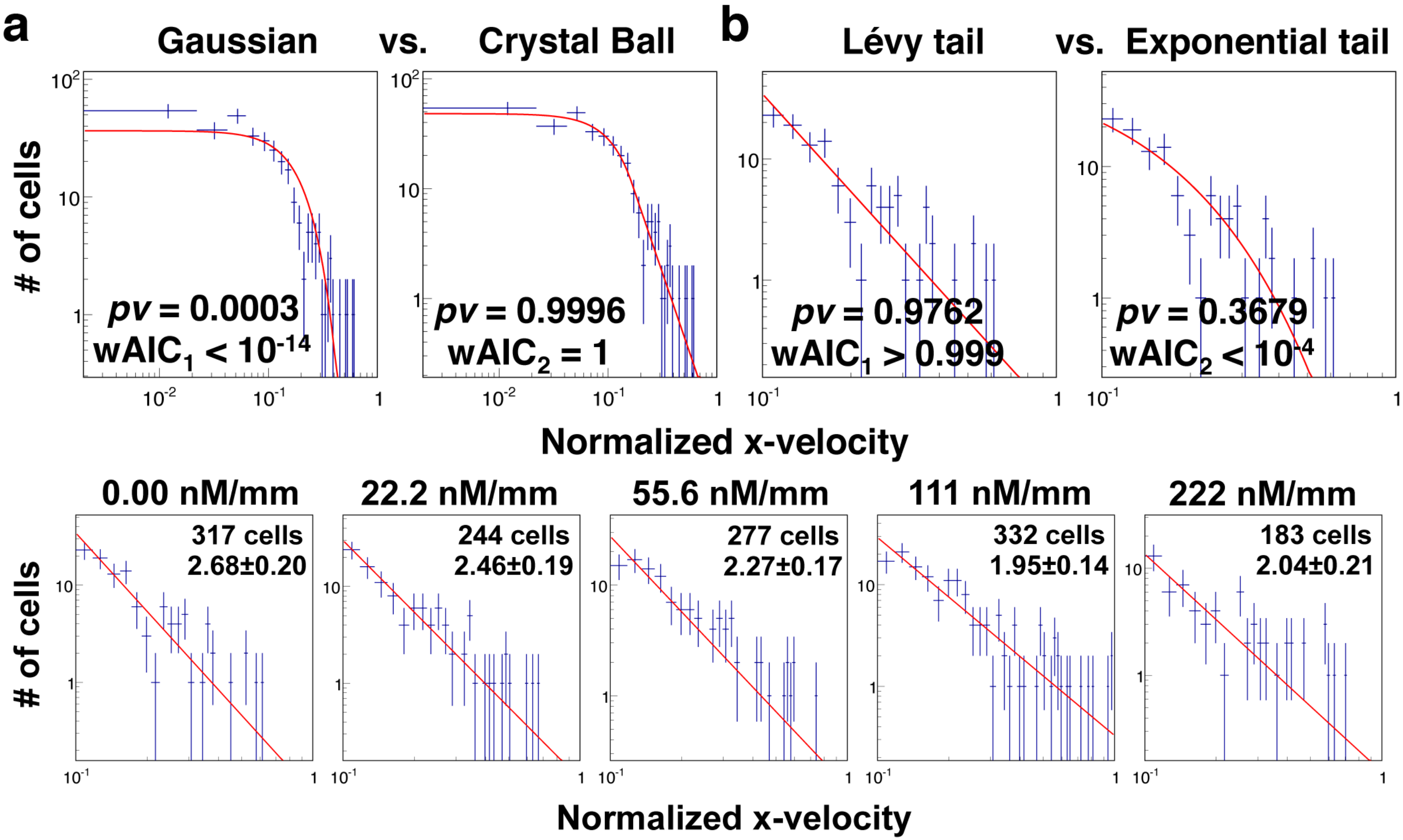
Fitted $K_D = 59.2$ nM

Reported $K_D = 55 \pm 15$ nM*

- **Tumor cell chemo-sensitivity is governed by the receptor – ligand binding kinetics.**
- **Fitted K_D agrees well with the reported value obtained using a FRET method.**

1. Hassler et al. PNAS, 2011
2. Kim et al. PlosOne, 2013
3. Valenzuela-Fernandez et al, I. Biol Chem, 2001 (using FRET)

Tumor cells execute Levy walks



Levy exponent reaches ~2.0 when CCL 19 concentration is close to its kinetic constant.

Kim et al. Integrative Biology, 2020.

What did we learn?

Tumor cell migration is governed by ligand receptor binding kinetics via either chemotaxis and/or chemokinesis.

Question:

Which is more effective for reaching a distant target, chemokinesis or chemotaxis?

OUTLINE:

Single cell mechanics within a 3D biomatrix

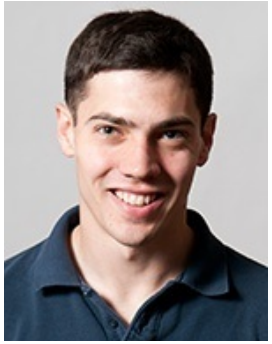
- Single cell migration
- Chemical gradient driver
- **Mechanical driver**

Tumor spheroid invasion

- **Tumor spheroid formation**
- **Tumor spheroid invasion (chemical and mechanical driver)**

Single cell mechanics

In collaboration with Vivek Shenoy at U Penn and Herbert Hui at Cornell

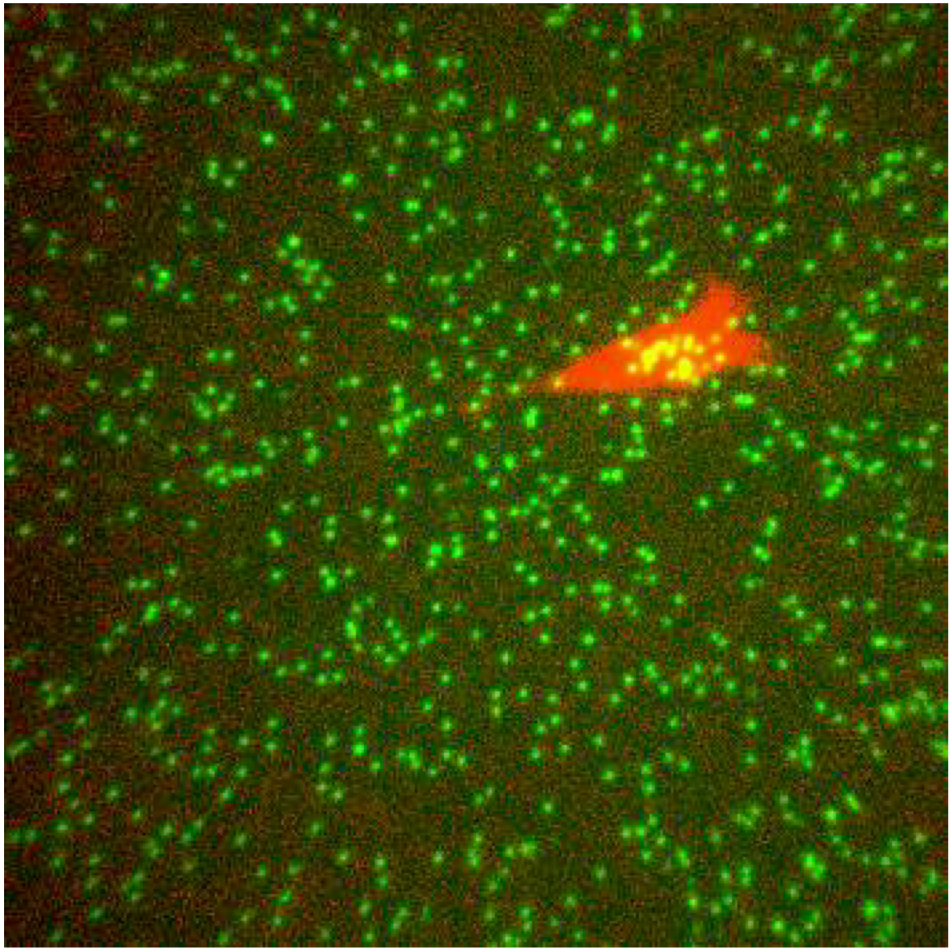


Matt Hall

Xingzhen Feng

Farid Alisafaei

A 3D traction force microscopy for single cell force generation in collagen gel

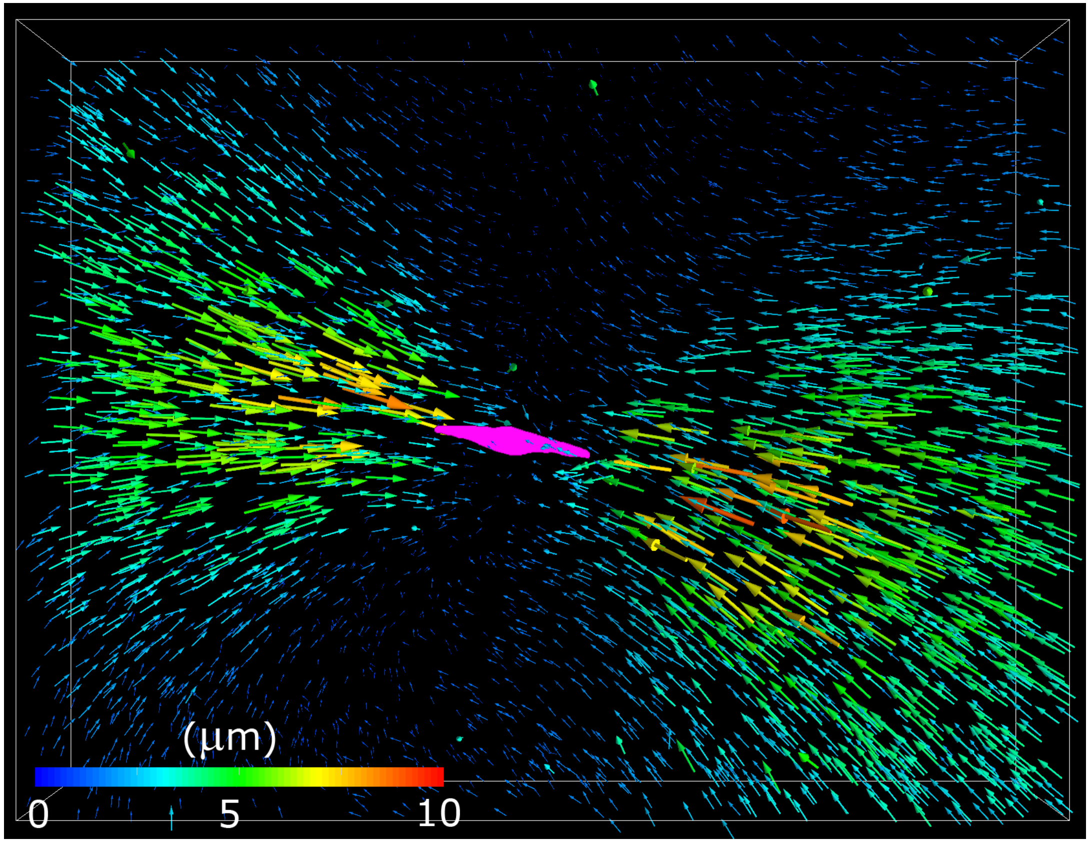


Cell-matrix cross talk revealed by the deformation of surrounding matrix

Breast tumor cell (MDA-MB-231) migrating within collagen matrix embedded with fluorescent beads

Rong et al. Biophysical Journal, 2011
Hall et al. Biophysical Journal, 2012
Hall et al. Experimental cell research, 2013
Hall et al. PNAS, 2016.

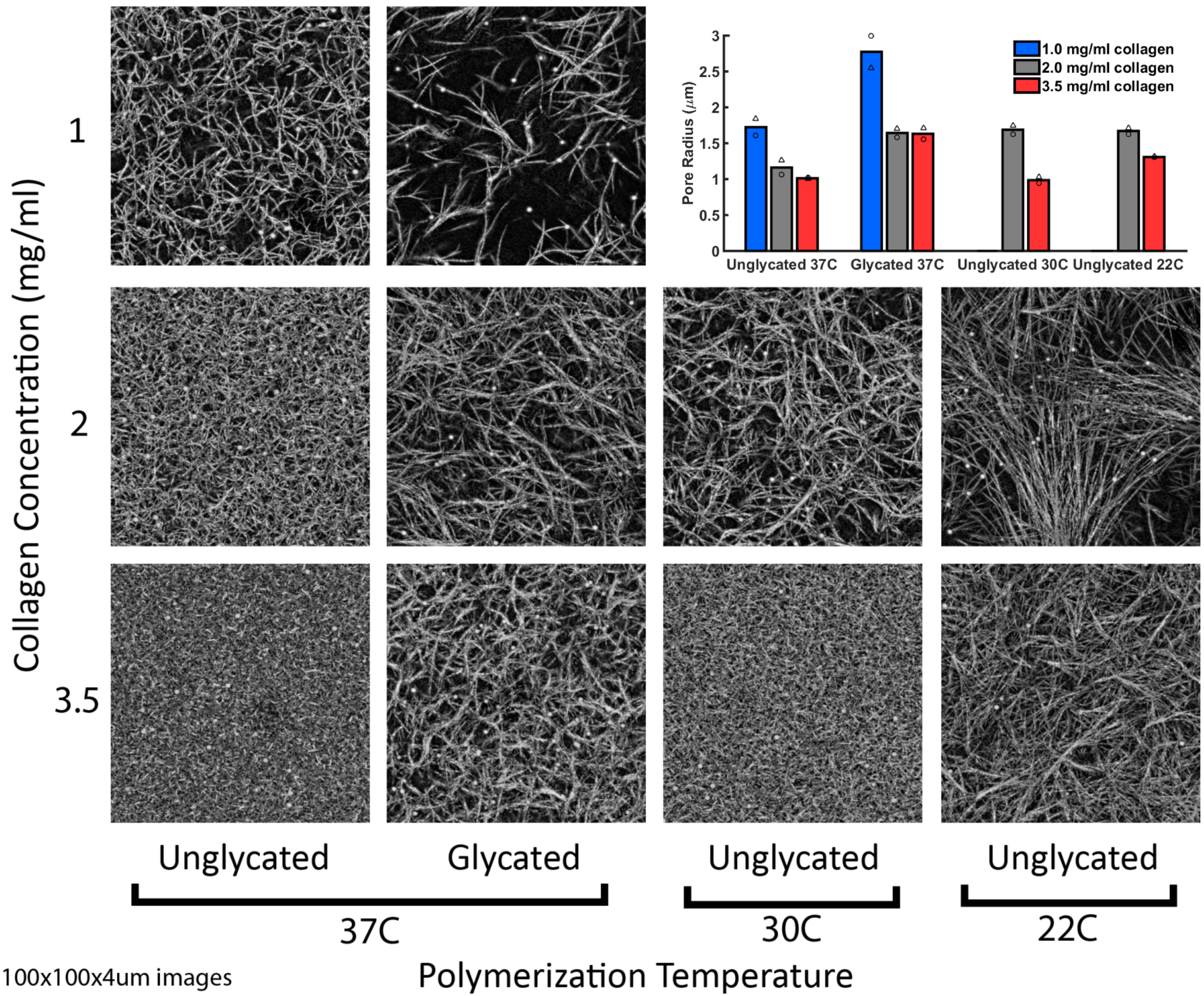
Mapping 3D fiber network deformation field



Bead displacement field around a breast tumor cell embedded in type I collagen

Ref: Hall, PNAS, 2016; Wang H, et al. 2014, Biophys. J. 107(11):2592-2603.

Engineering collagen microstructure and mechanical properties through fibril cross linking and gel density

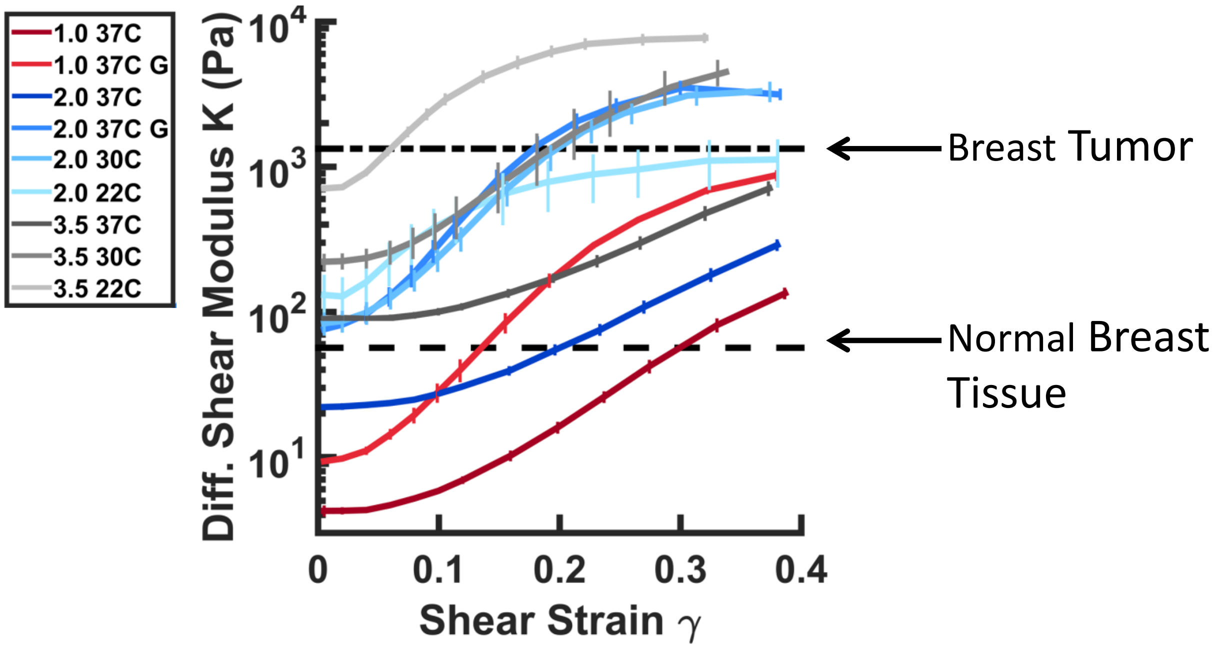


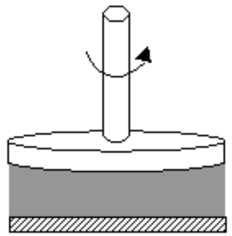
100x100x4um images

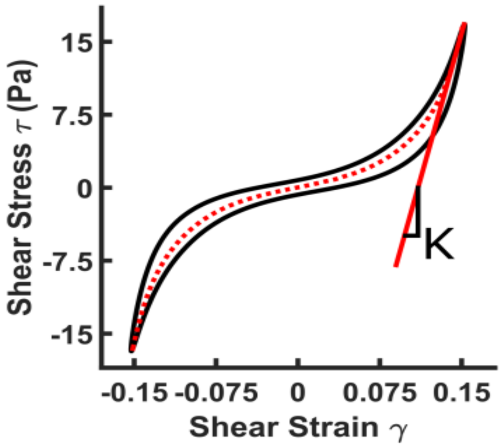
Methods

- Gel density
- Ribose glycation
- Polymerization temperature

A set of collagen gel representative of tumor microenvironment







Collagen matrices span the physiological range of stiffness for normal and malignant breast tissue

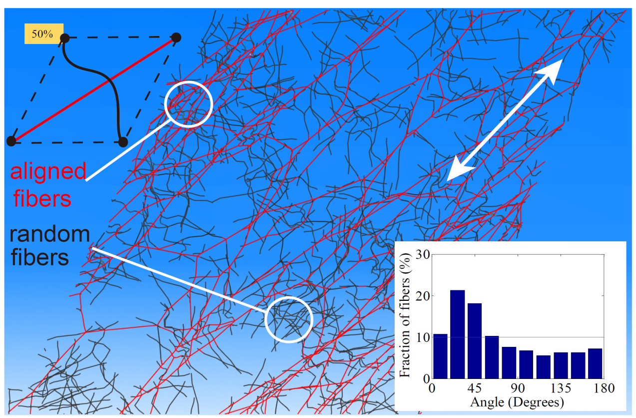
Material model with fiber alignment (slide from Shenoy)

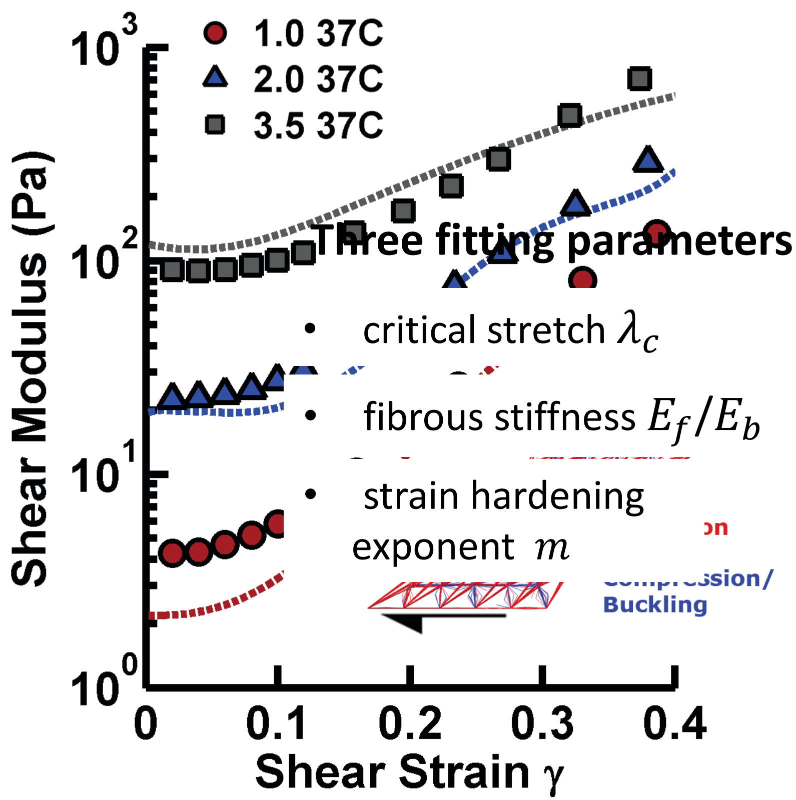
- The overall elastic energy consists the isotropic and fibrous contributions

$$W = W_b + W_f \qquad W_f = \sum_{a=1}^{3} f(\lambda_a)$$

- Fibers are aligned along principle stretch (λ_a) orientations $\boldsymbol{n_a}$

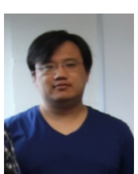
$$\boldsymbol{\sigma} = \boldsymbol{\sigma}^b + \boldsymbol{\sigma}^f \qquad \boldsymbol{\sigma}^b = \kappa(J-1)\boldsymbol{I} + \mu \mathrm{dev}(\bar{\boldsymbol{B}})/J \qquad \boldsymbol{\sigma}^f = \frac{1}{J}\sum_{a=1}^{3} \frac{\partial f(\lambda_a)}{\partial \lambda_a} \lambda_a (\boldsymbol{n_a} \otimes \boldsymbol{n_a})$$





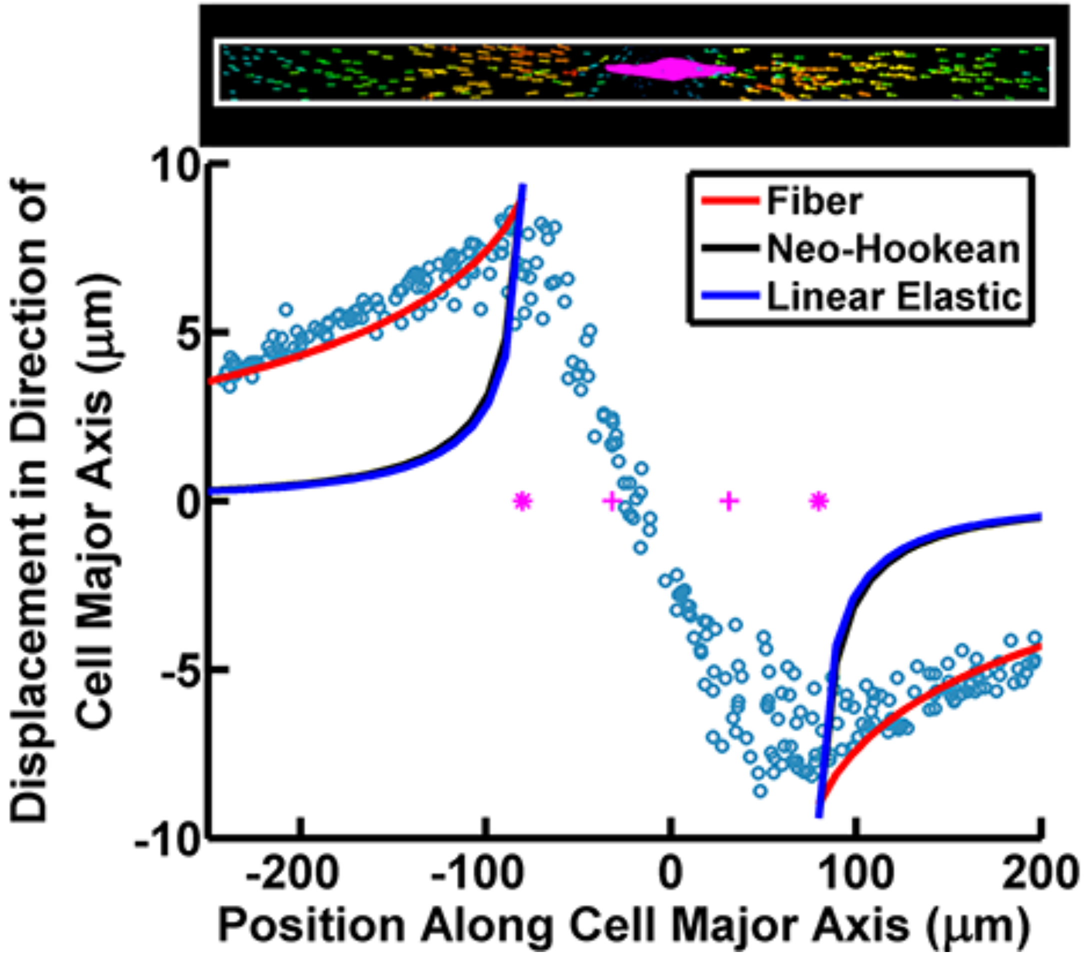
Three fitting parameters

- critical stretch λ_c
- fibrous stiffness E_f/E_b
- strain hardening exponent m




Ban et al., PNAS (2019)
Wang et al., Bio. Phys. J (2014)

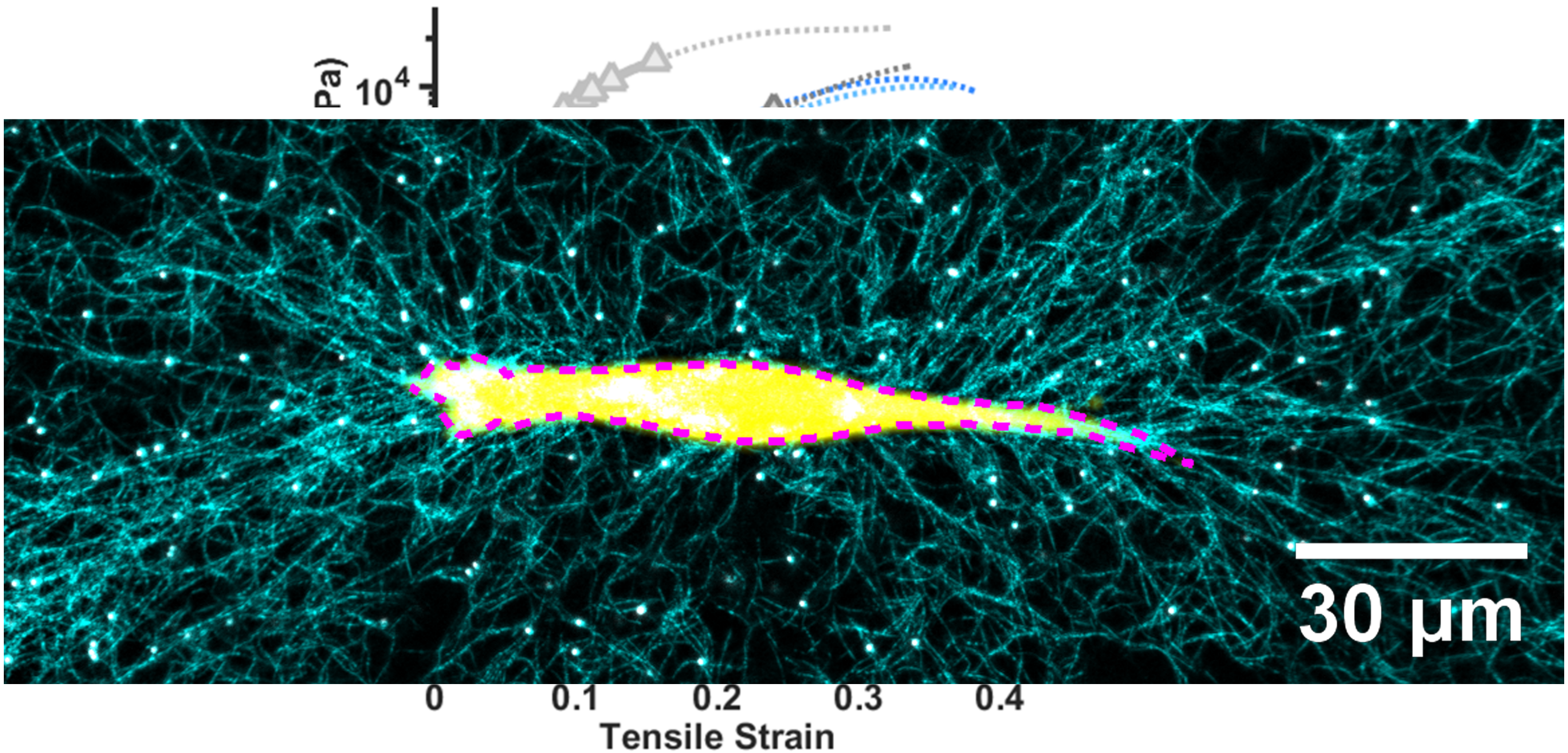
Mapping 3D gel deformation field using a 3D force microscopy and a network-inspired material model



Only the fiber network material model worked!

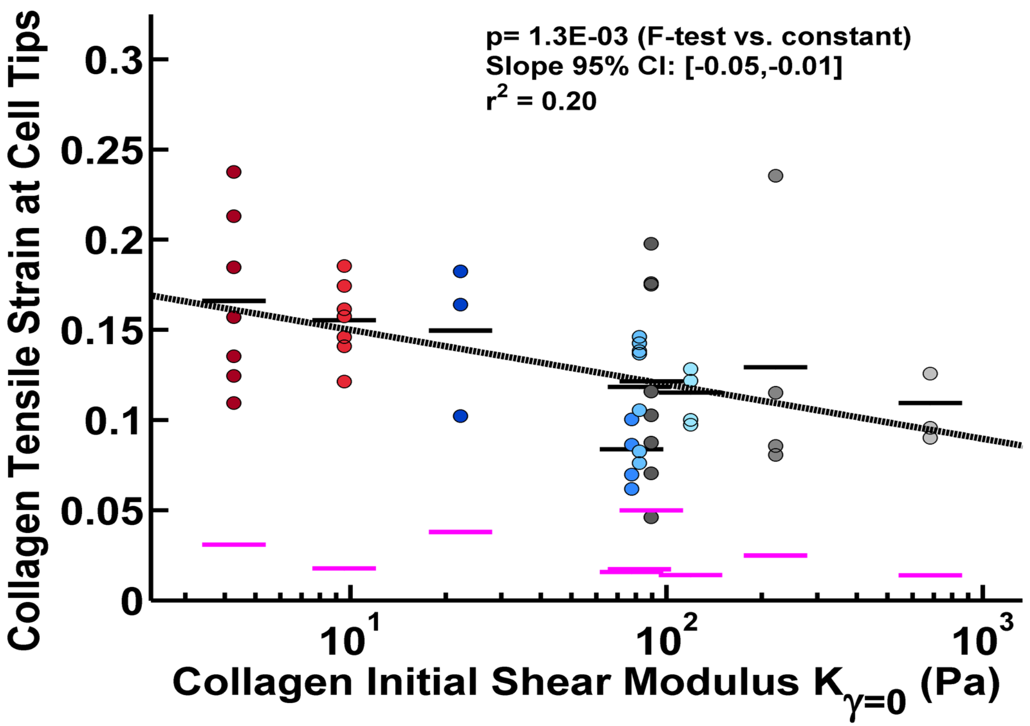
Ref: Hall, PNAS, 2016; Wang H, et al. 2014, Biophys. J. 107(11):2592-2603.

Cancer cells exert sufficient strain to locally stiffen collagen matrices



Fibrous nonlinear elasticity is critical for cell- ECM interaction

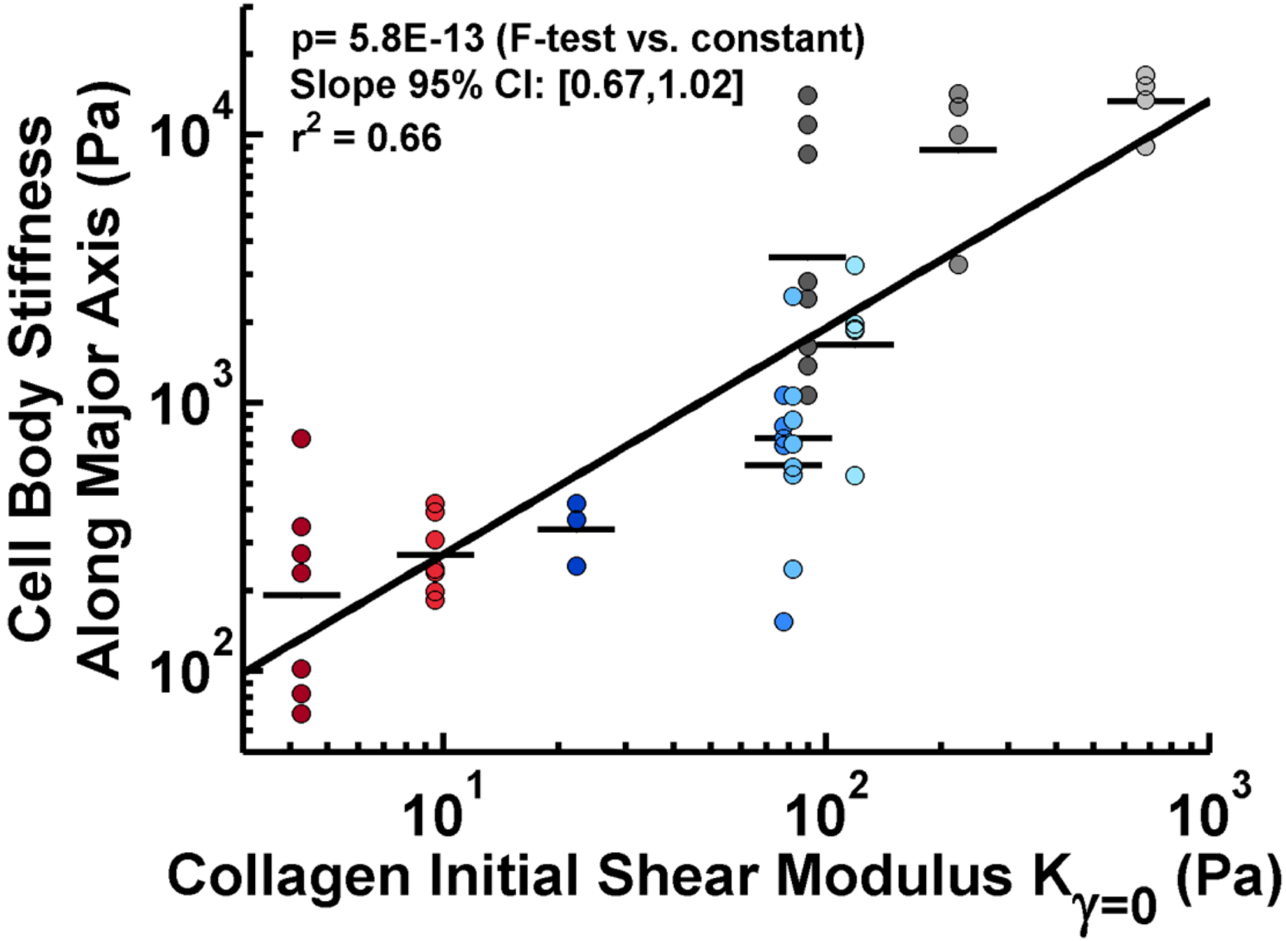
A mechanical feedback between cells and ECM



— Onset for strain stiffening of the gel

Cell to ECM:
Cells exert forces sufficiently to stiffen and align ECM

A mechanical feedback loop between cells and ECM



ECM to cell:
Stiffer gel promotes larger cell force generation and stiffer cell body

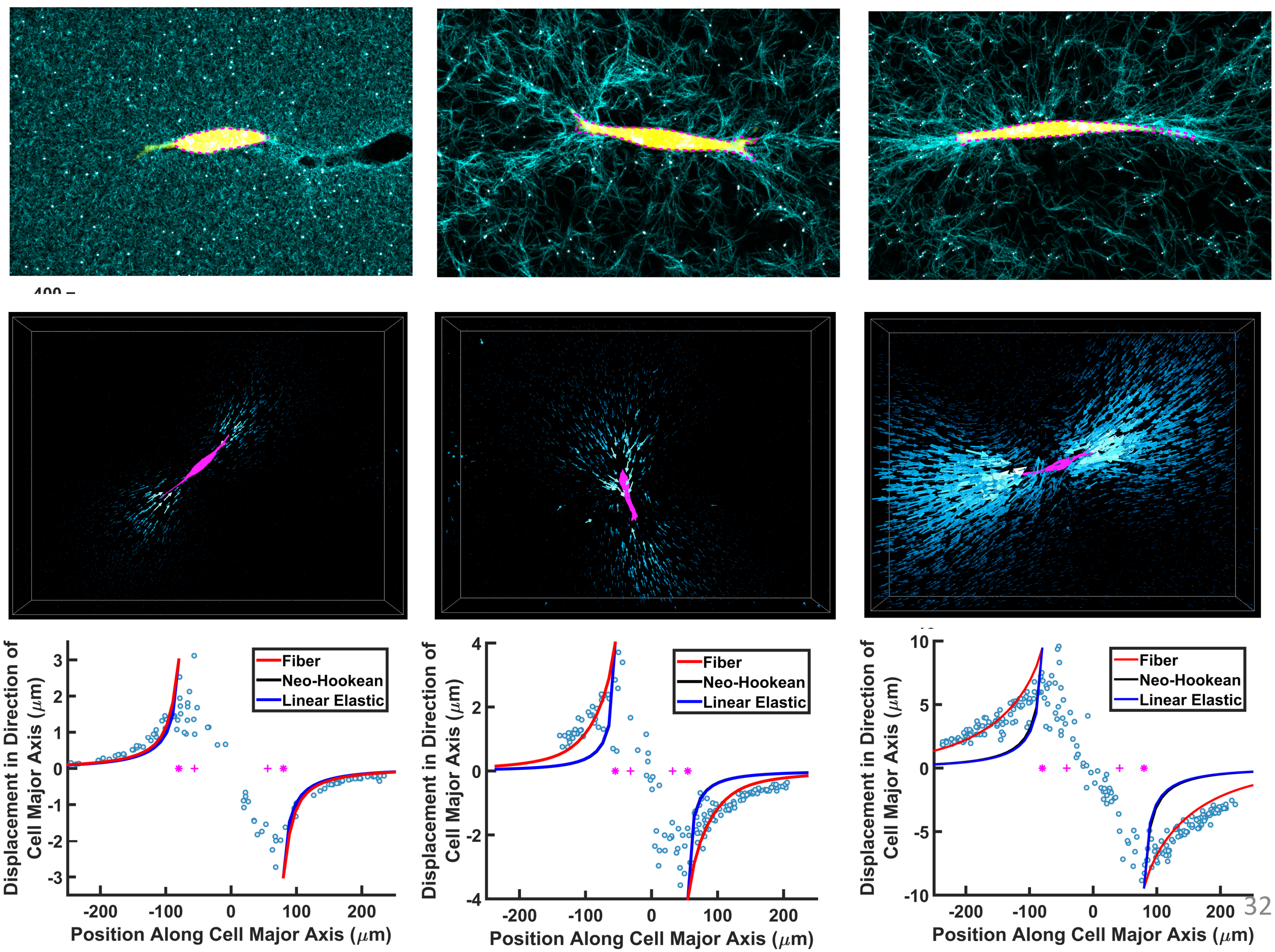
Fibrous nonlinear elasticity promotes cell force transmission distance

Increasing fibrous nonlinear elasticity

MDA-MB-231 Cell within Type I collagen

Bead displacement

Axial bead displacement



What did we learn?

Nonlinear anisotropy of the
material model is critical for cell function

Biological convergence
Biological materials promote cell-cell communication

OUTLINE:

How does single cell move within a 3D biomatrix ?

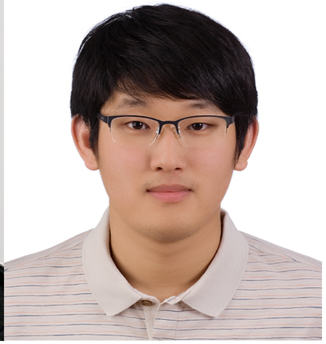
- Single cell migration
- Chemical gradient driver
- Mechanical driver

How does tumor spheroid invade ?

- **Tumor spheroid formation**
- **Tumor spheroid invasion (chemical and mechanical driver)**

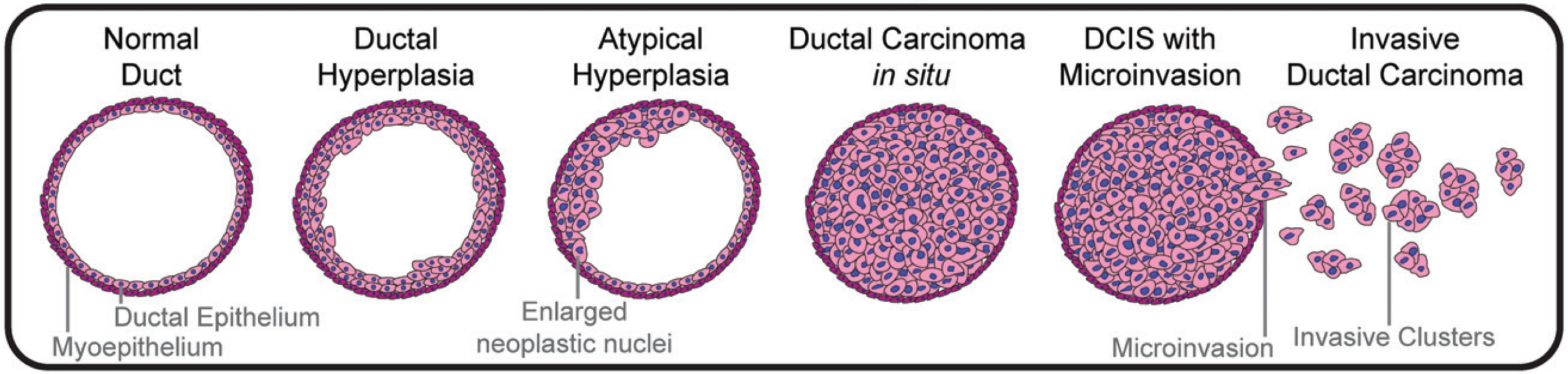
Tumor spheroid formation and invasion

In collaboration with Jeffrey Segall

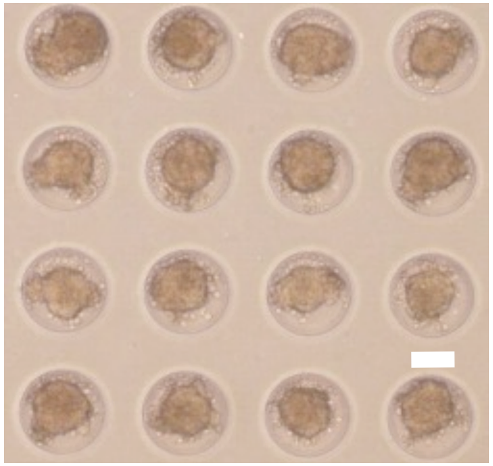


Why spheroid?

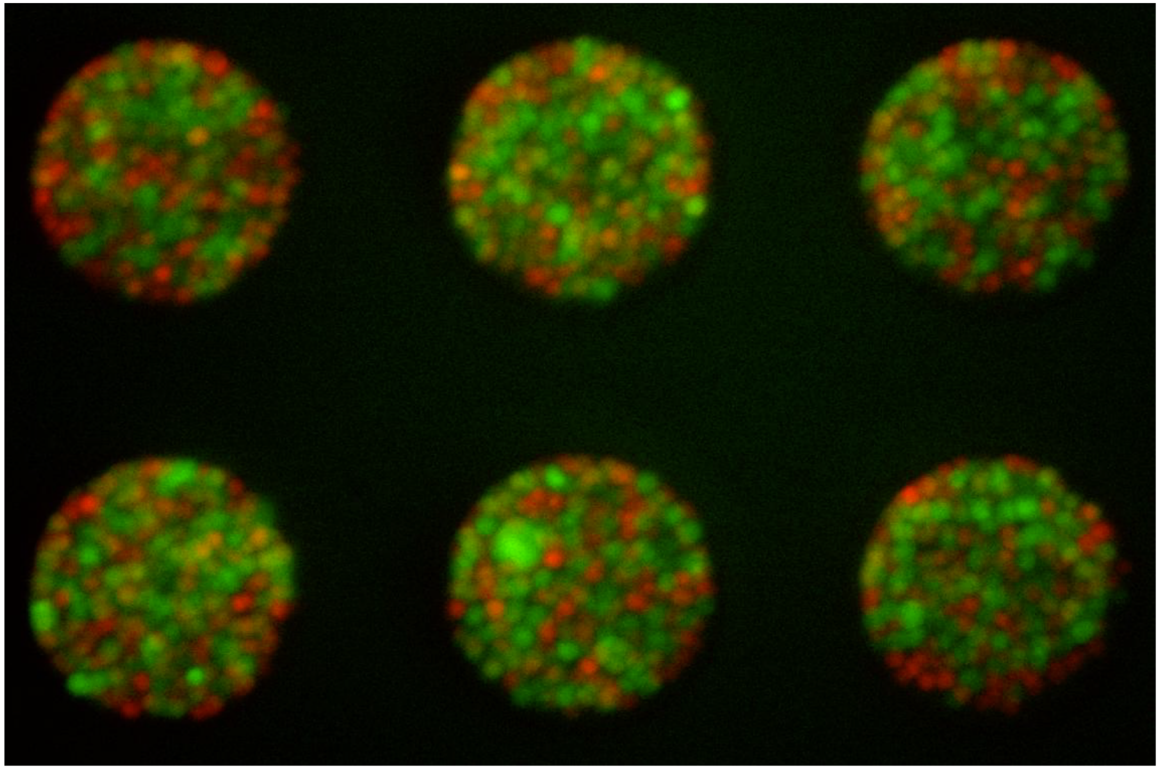
Breast Carcinoma Progression



Making tumor spheroids



Well diameter 200 μm



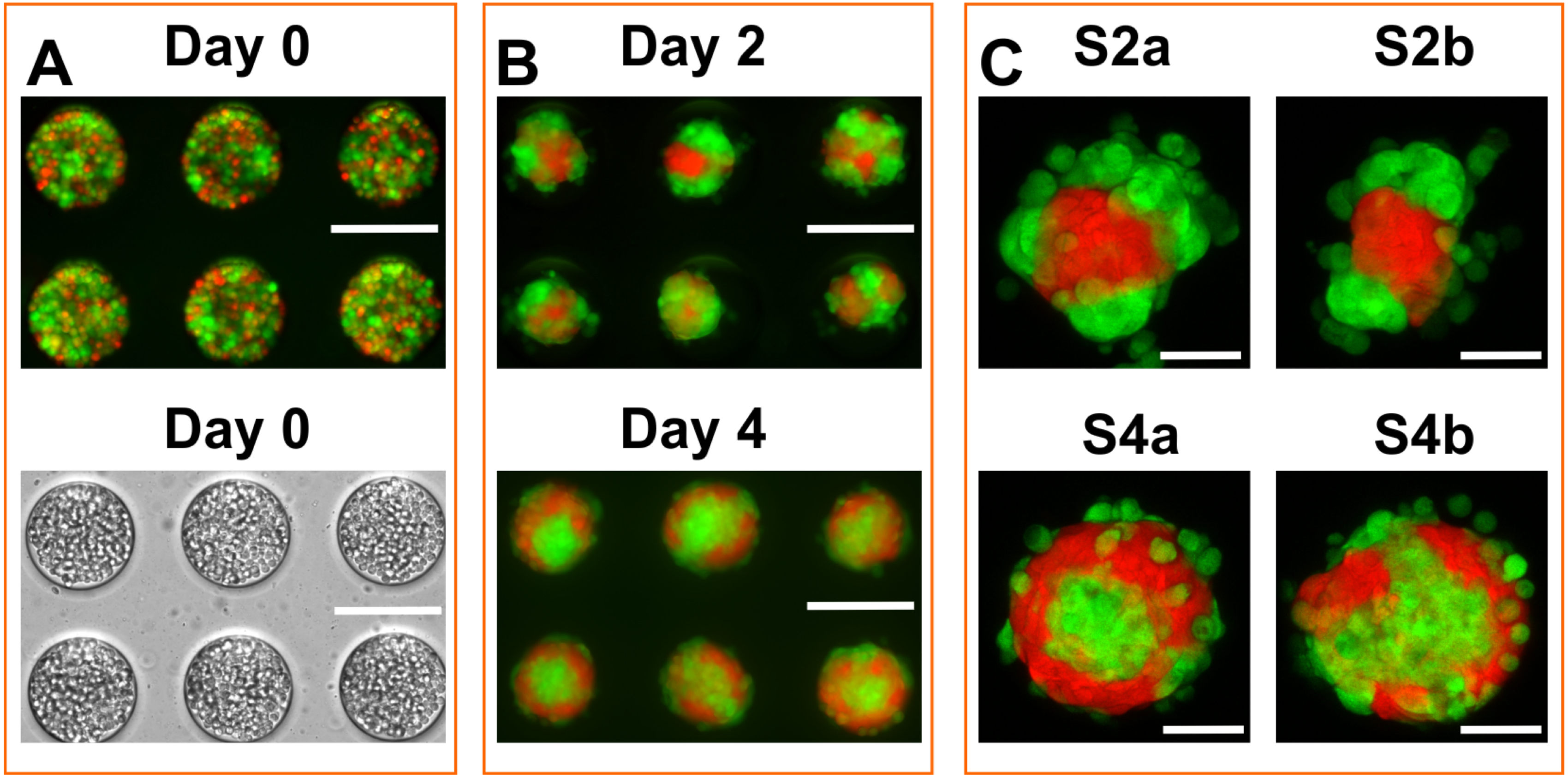
Green: malignant MDA-MB-231 cells

Red: non-tumorigenic epithelial MCF-10A cells

Song *et al.* (2016) *Soft Matter*

In collaboration with
Minglin Ma and Momita Das

Tumor spheroids inversion



Huang et al. Q-bio arXiv, 2020.

What did we learn?

Cells of different types segregate.
Shell – core inversion occurs due to differential growth.

Question?

Can the idea of phase transition be applied here?

OUTLINE:

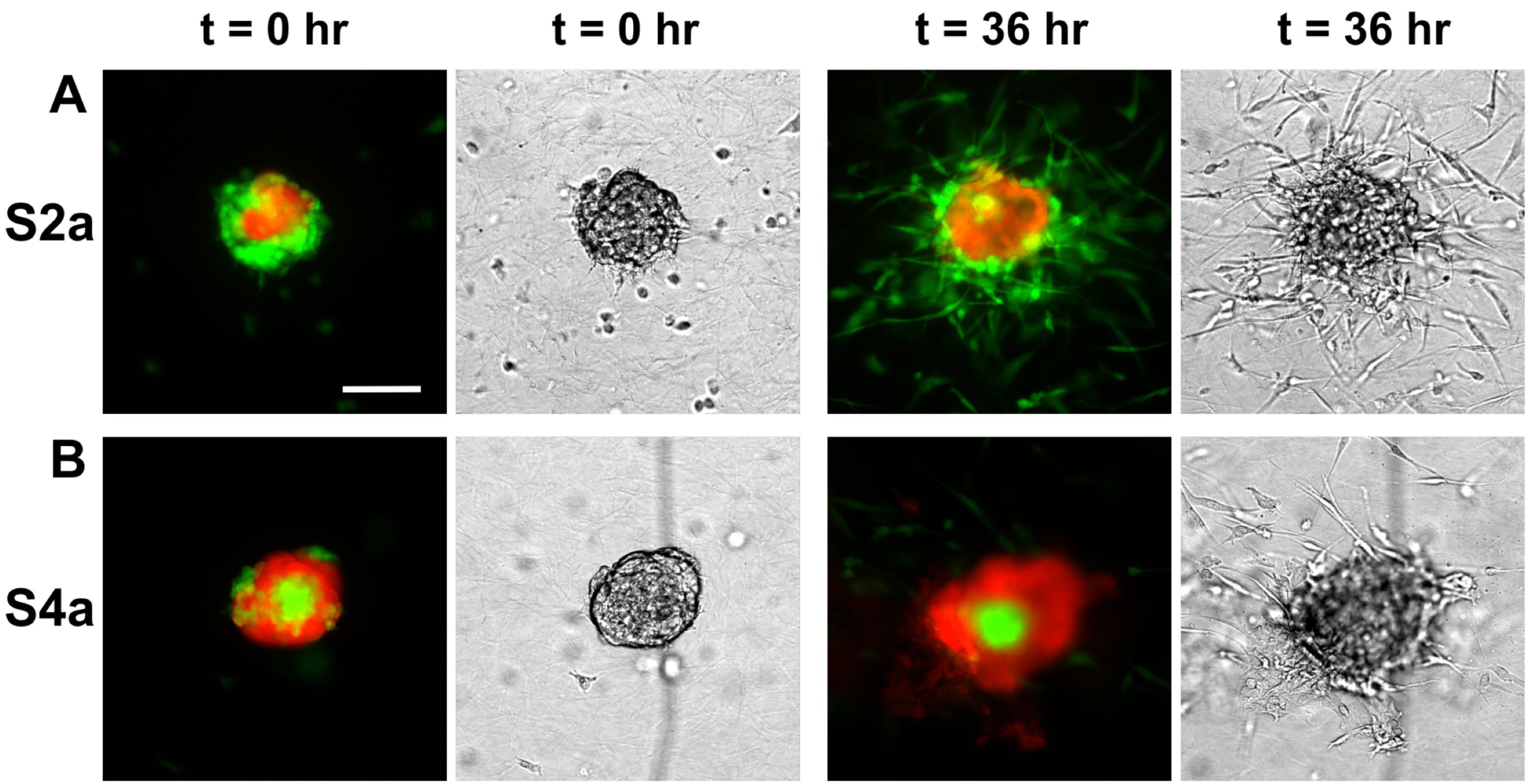
How does single cell move within a 3D biomatrix ?

- Single cell migration
- Chemical gradient driver
- Mechanical driver

How does tumor spheroid invade ?

- Tumor spheroid formation
- **Tumor spheroid invasion (chemical and mechanical driver)**

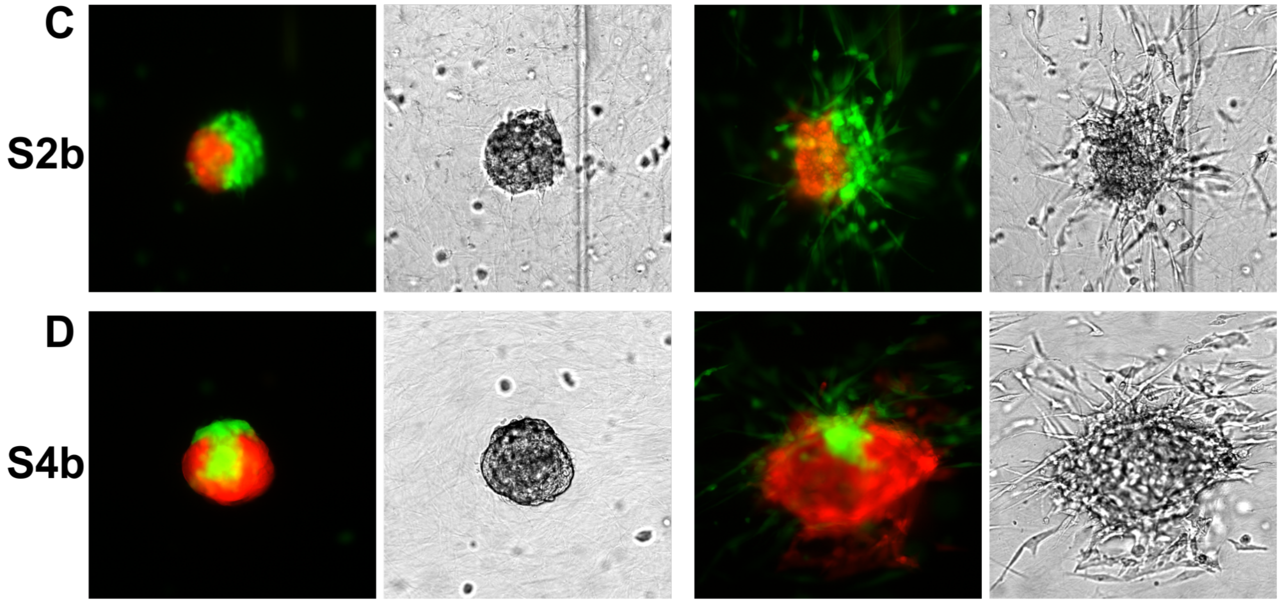
Tumor architecture critically regulates tumor invasion



Green: Metastatic cancer cells MDA-MB-231

Red: Non-tumorigenic cells MCF10A

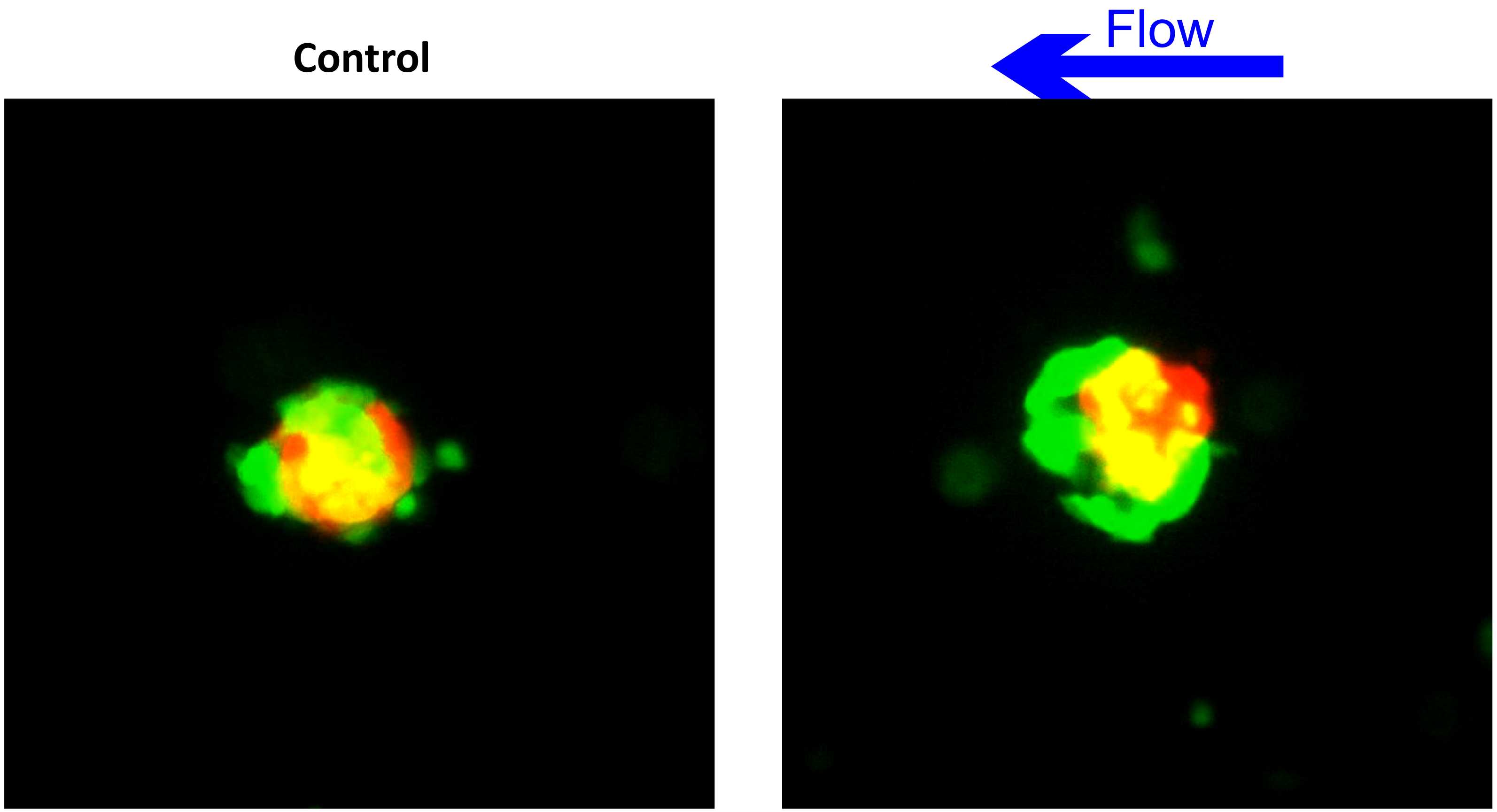
Tumor architecture critically regulates tumor invasion



Green: Metastatic cancer cells MDA-MB-231

Red: Non-tumorigenic cells MCF10A

Interstitial flow promotes tumor spheroid invasion via down-regulation of E-cadherin

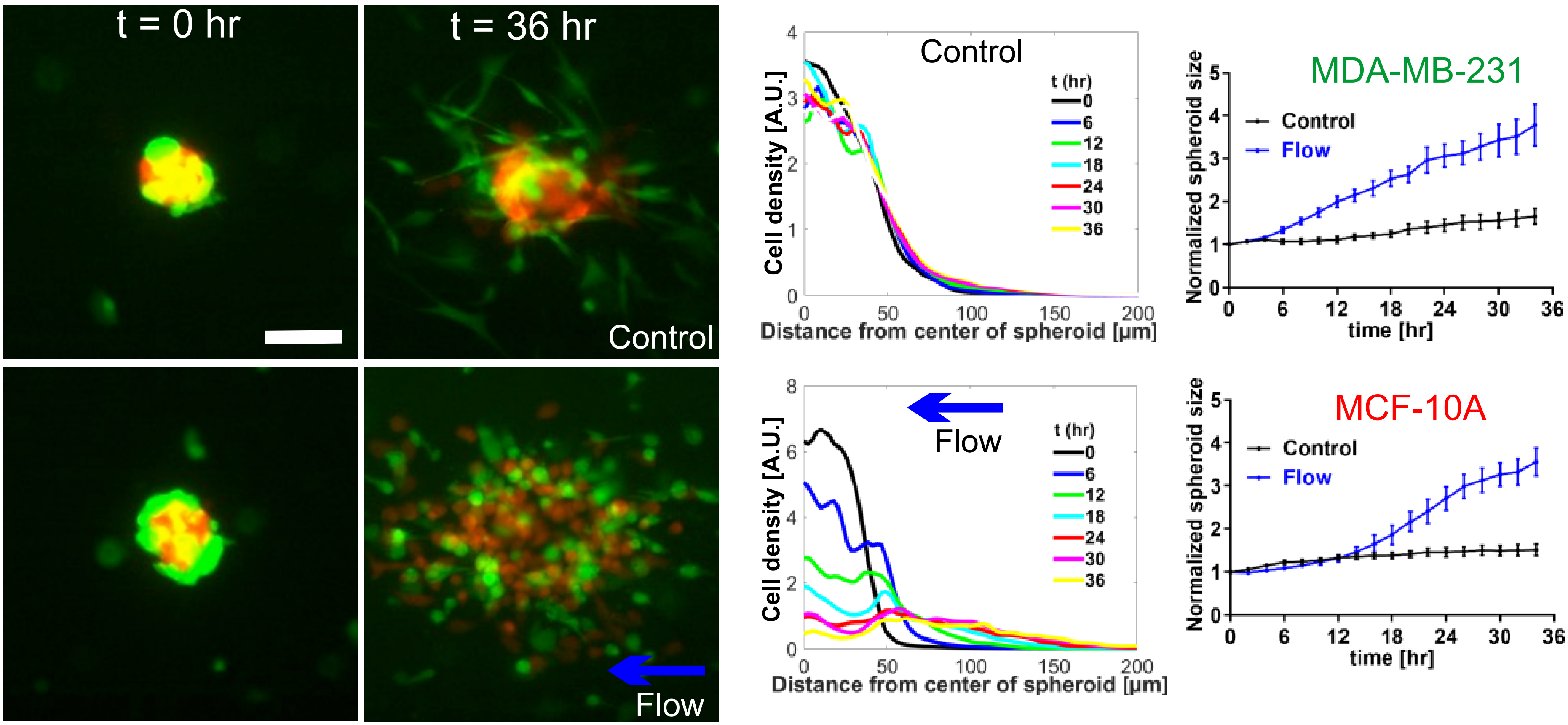


Green: malignant MDA-MB-231 cells

Red: non-tumorigenic epithelial MCF-10A cells

Huang et al. Unpublished.

Interstitial flows enable co-culture tumor spheroid explosion

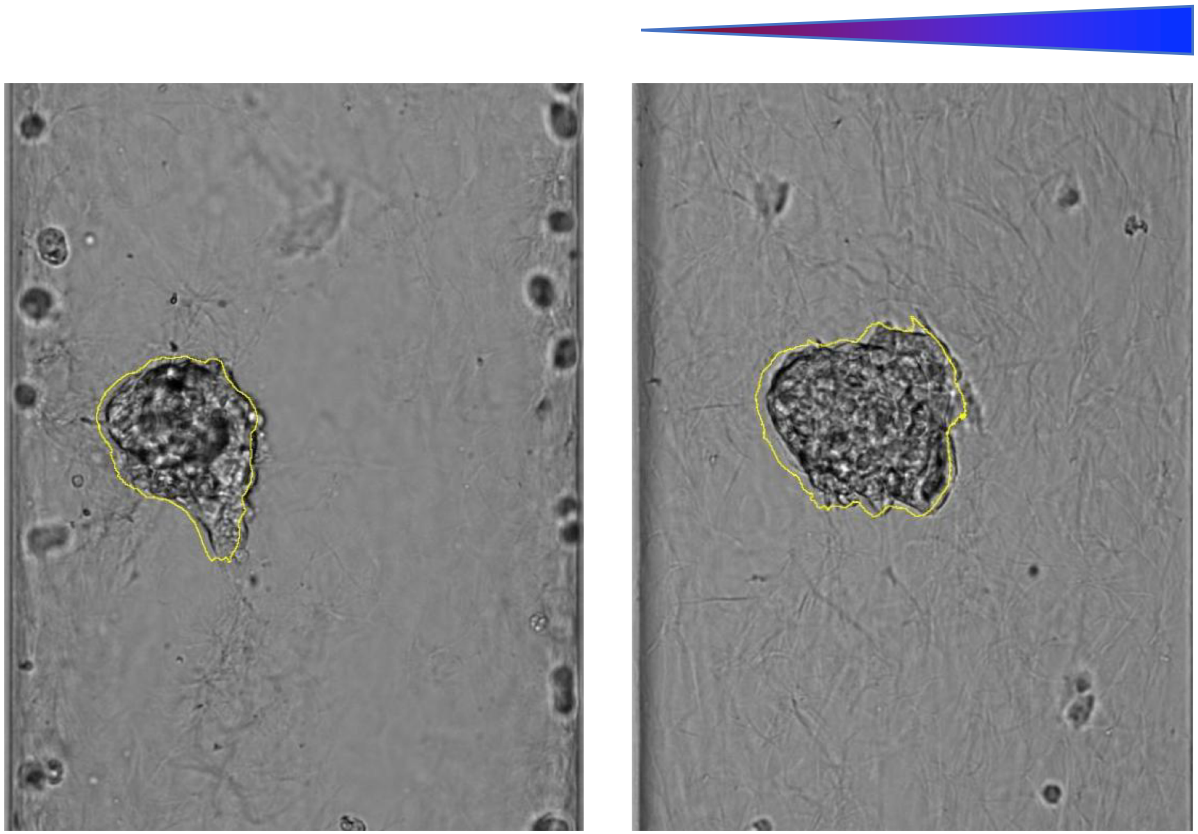


Green: malignant cells

Red: non-tumorigenic cells

- **Interstitial flows increase the spheroid sizes**
- **Greater impact on the non-tumorigenic cells.**

Tumor spheroid chemotaxis in EGF gradients



No EGF gradients **With EGF gradients**

Suh et al, Unpublished, 2020.

What did we learn?

Tumor architecture regulates tumor invasion.
Cell-cell adhesion regulates tumor invasion.

Question:

Can we predict tumor invasion knowing single cell characteristics and dynamics?

Acknowledgement

Collaborators

Jeffrey E. Segall
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Prof. Vivek Shenoy (U Penn)

Farid Alisafaei (U Penn)

Dr. Wei Song (Cornell)
Dr. Minglin Ma (Cornell)
Dr. Rikki Haessler (EPFL)
Dr. Melody Swartz (EPFL)
Herbert Hui (Cornell)
Don Koch (Cornell)
Susan Suarez(Cornell)

Students and postdoc.

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