Week 14: Mechanobiology of Cancer

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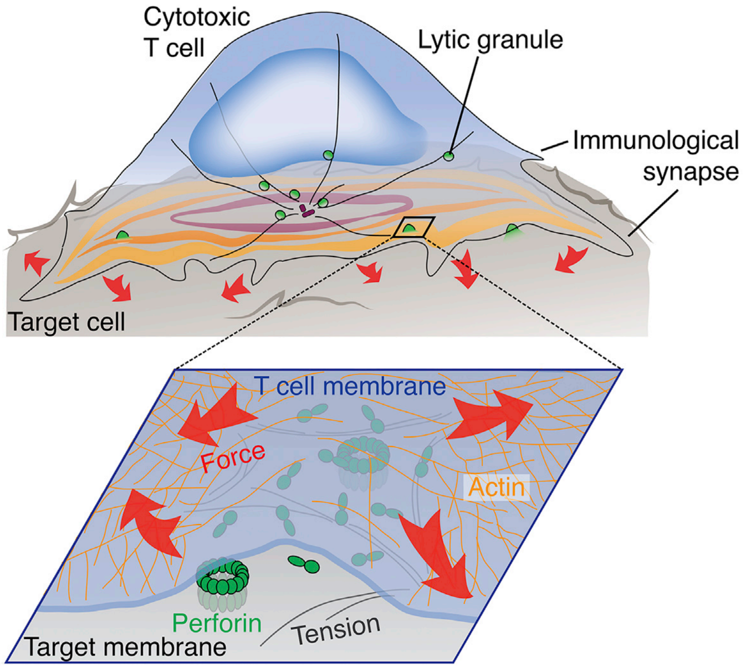
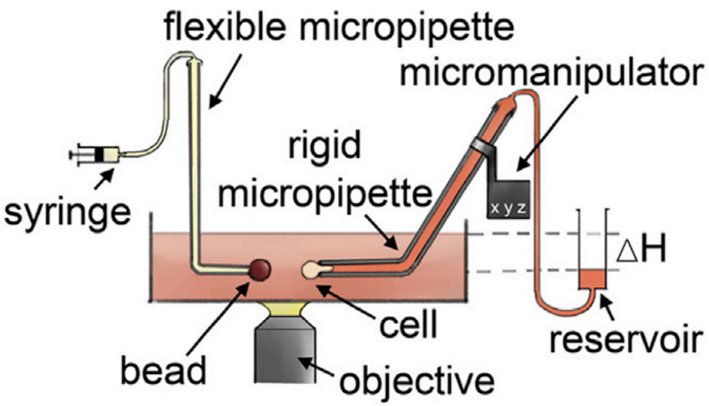
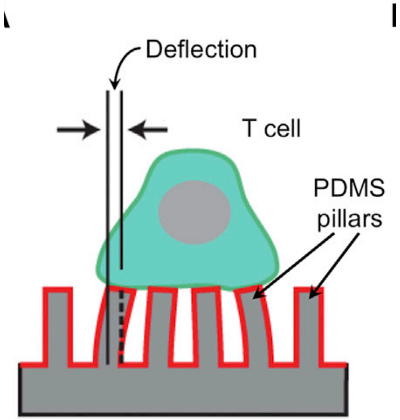
T cells use force for target cell killing

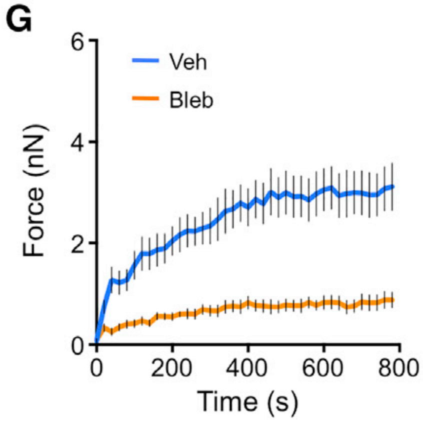
- T cell cytotoxicity correlates with the exertion of mechanical force
- Force exertion is associated with enhanced perforin pore formation on the target cell
- Cell tension promotes perforin pore formation

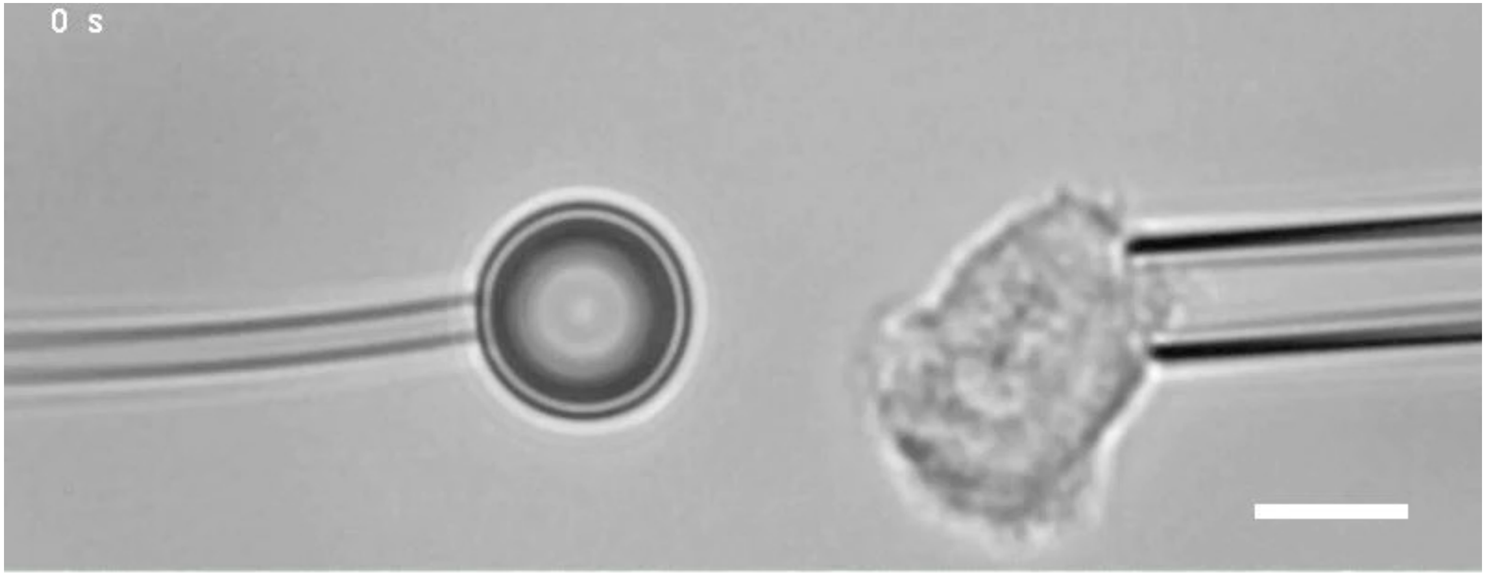


T cells use force for target cell killing

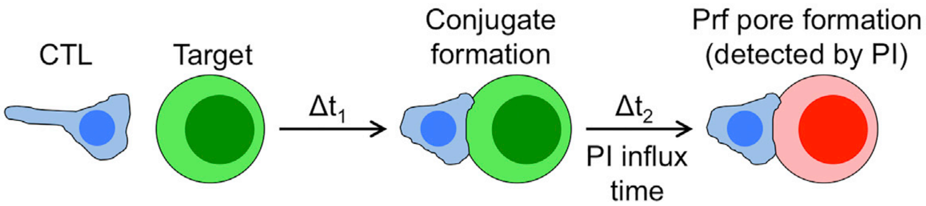


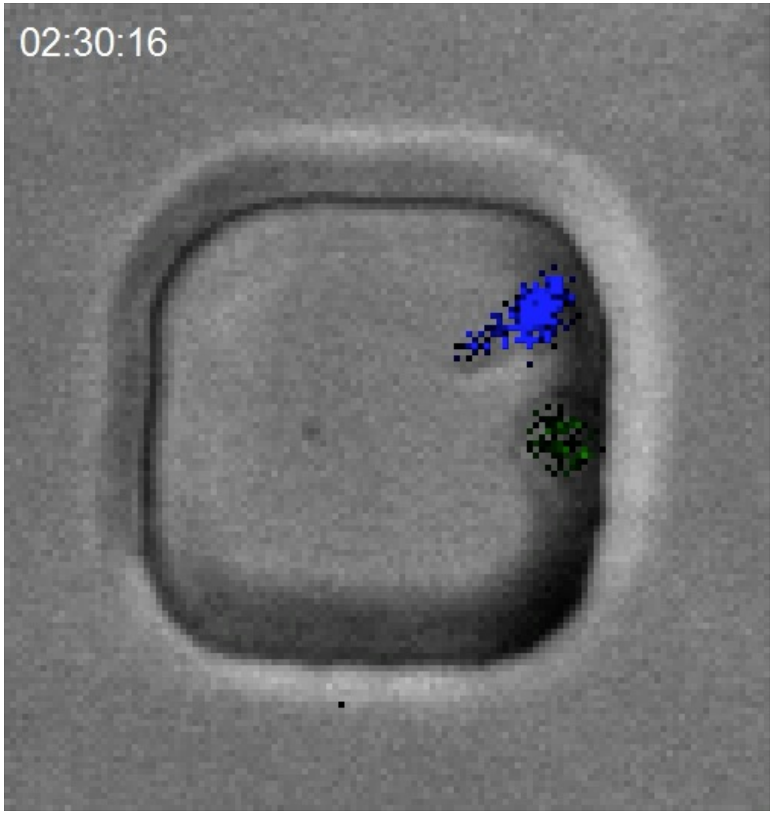




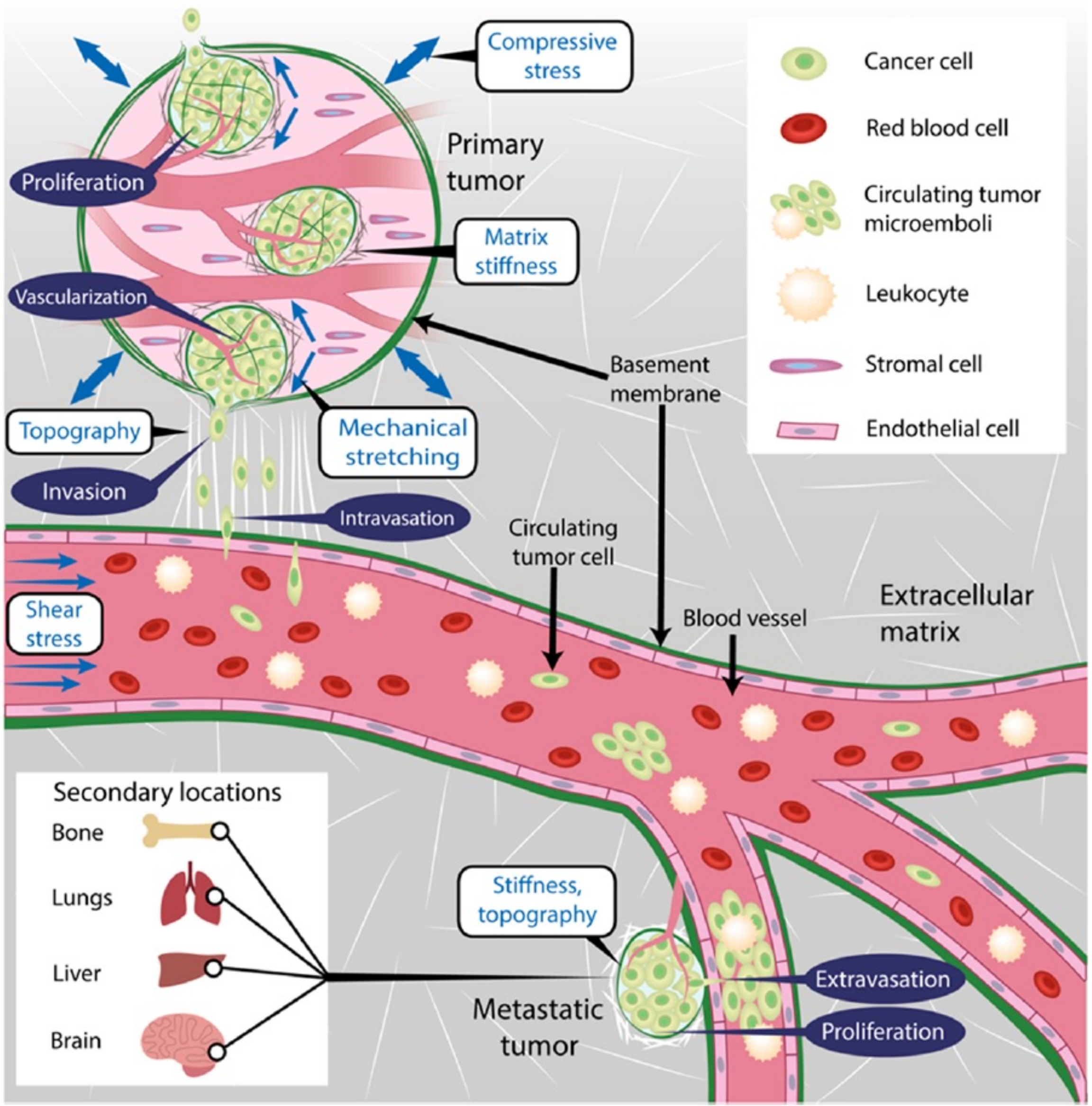


T cells use force for target cell killing

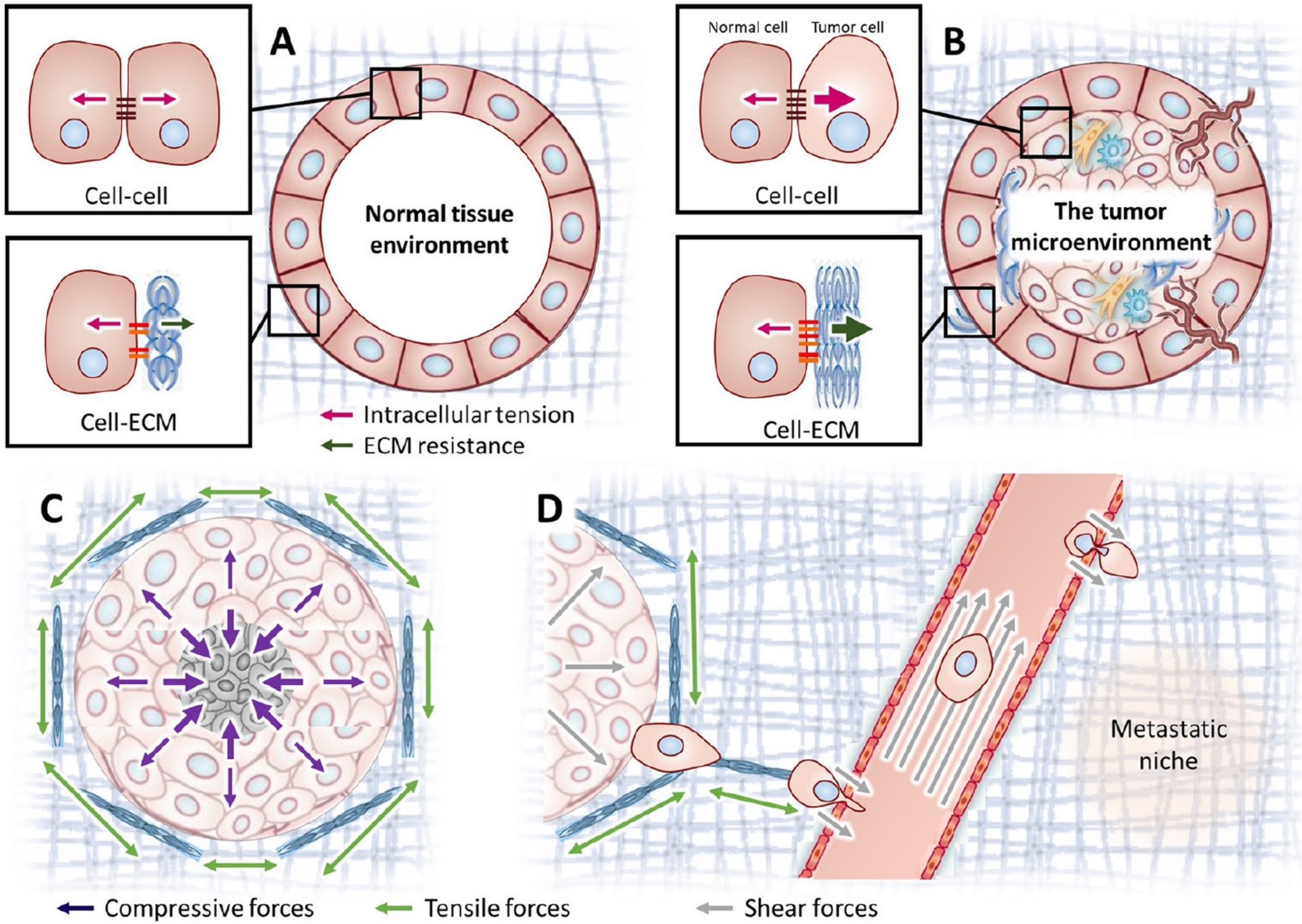




Mechanical landscape of cancer

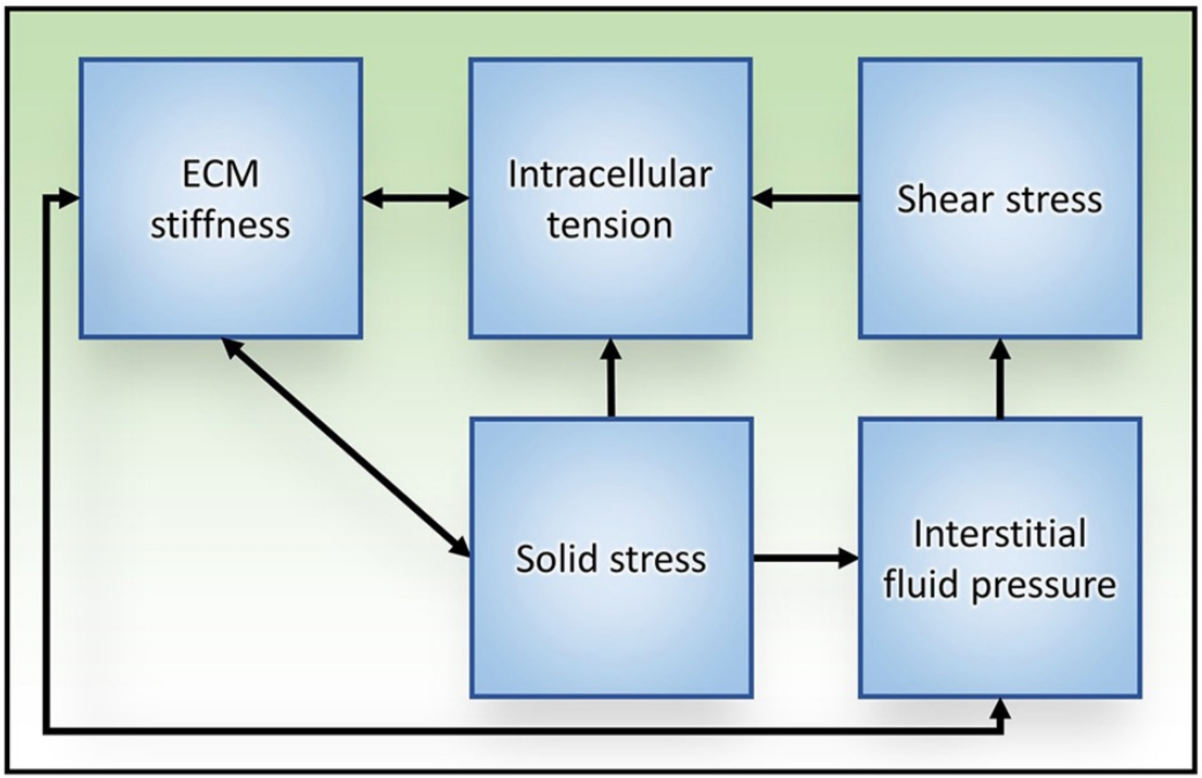


Mechanical forces and cancer progression

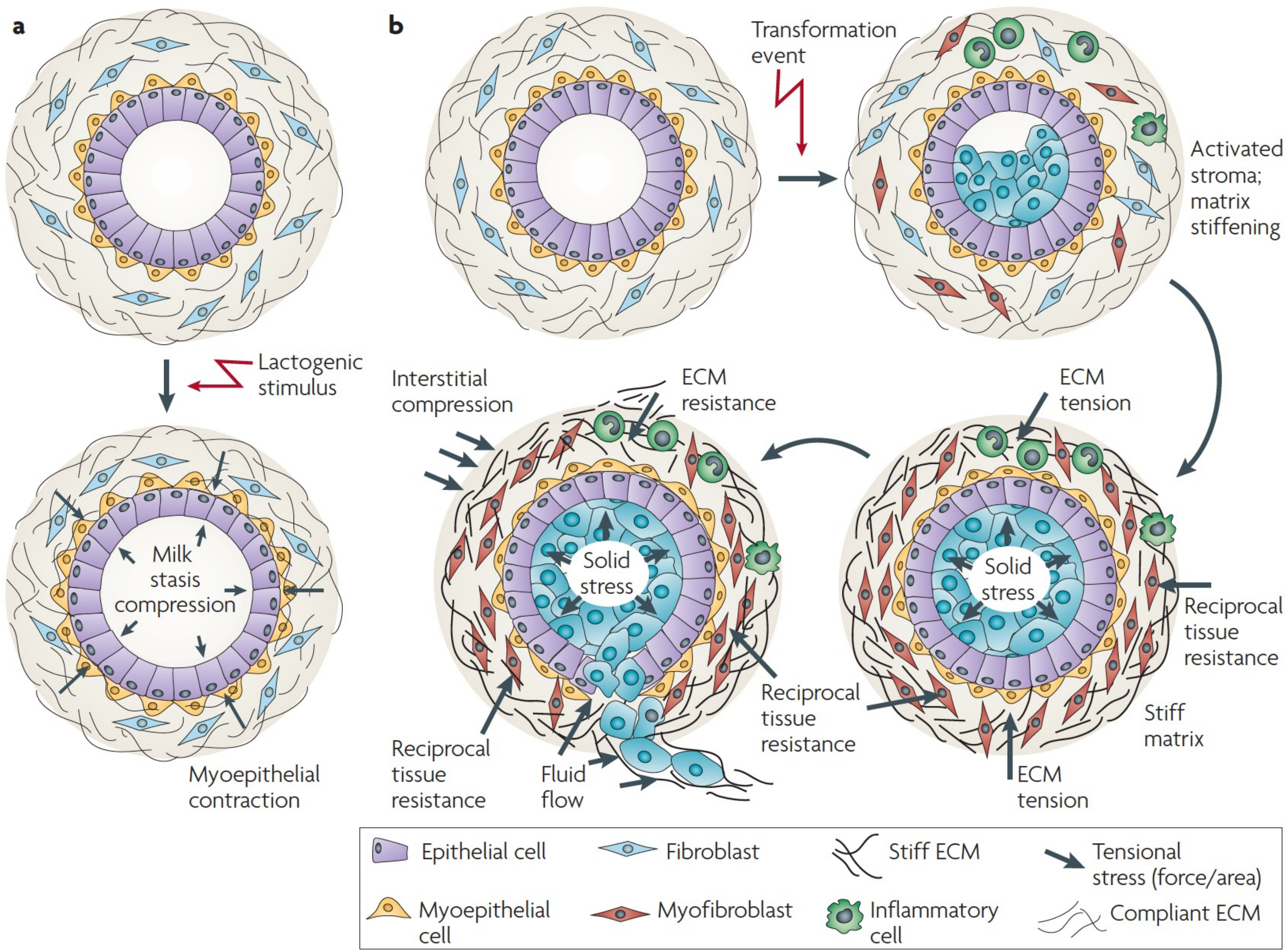


Viscous cycle of the cancer

- ECM stiffening → higher cellular tension and solid stress
- Tumor expansion → ECM stiffening and vascular malfunctioning
- Vascular issues → shear stress and interstitial pressure



Mammary gland



Mechanoreciprocity

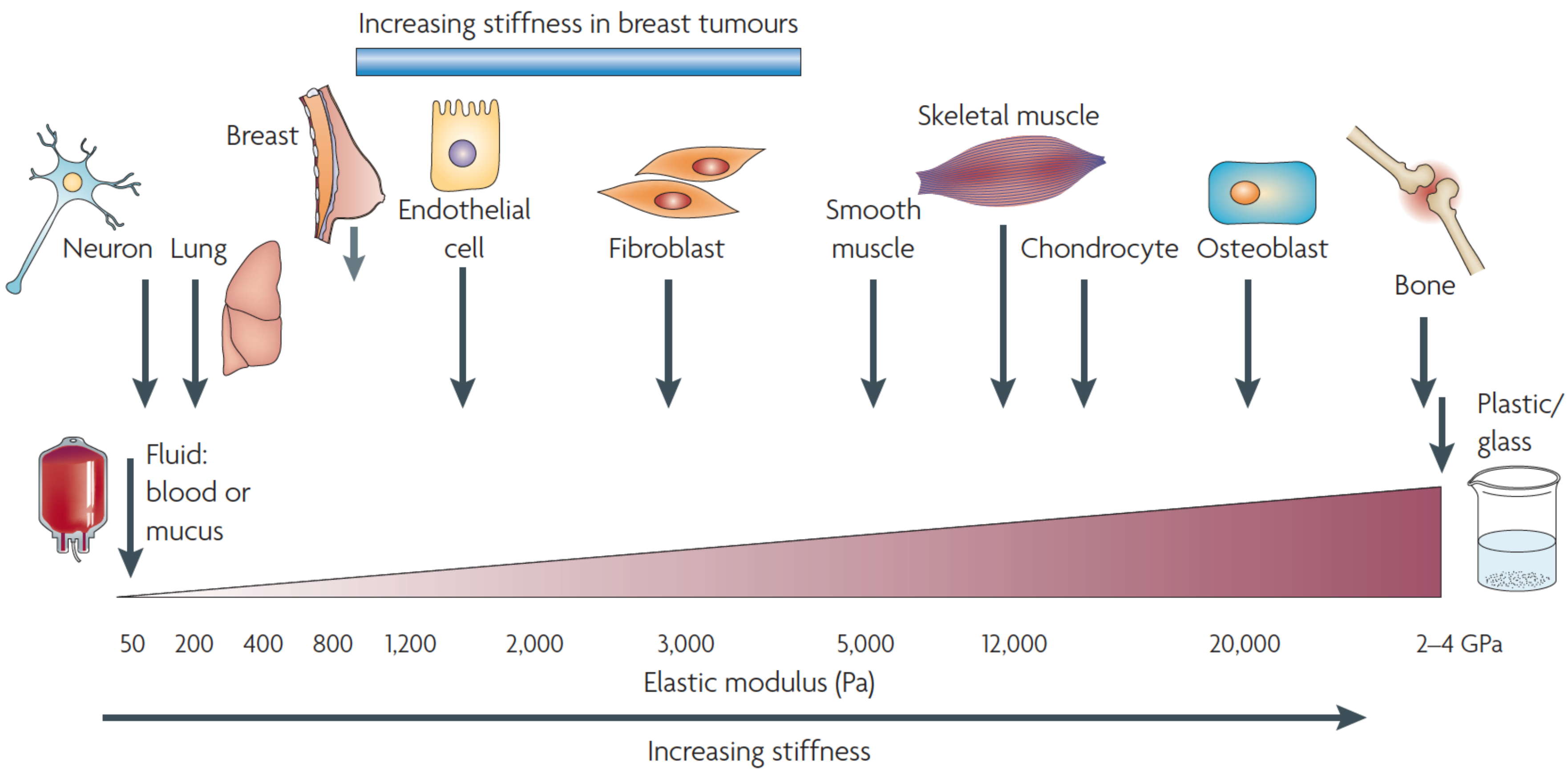
- Cells are continuously exposed to physical forces
  - Hydrostatic pressure, shear stress, compression, tension
- Cells dynamically adapt to force
  - Modifying behavior and remodelling the microenvironment
  - Sense forces and adjust contractility

- Loss of mechanoreciprocity → cancer

- Abnormal mechanics of tissues → cancer

Mechano-adaptation

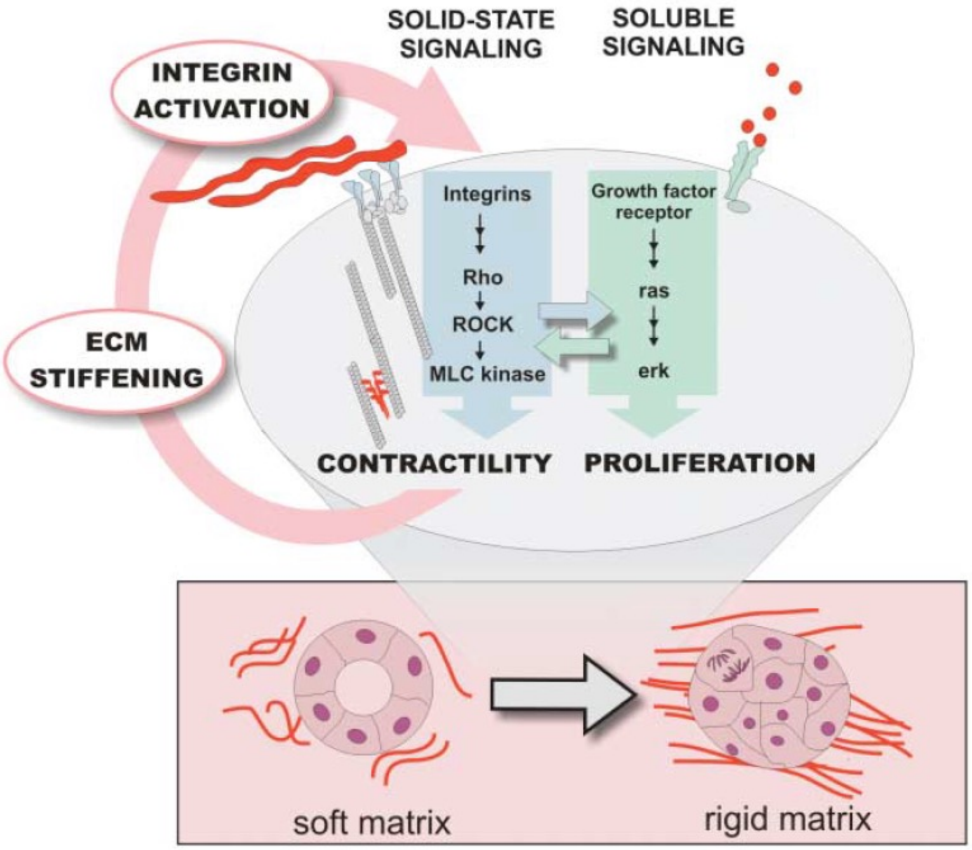
- Cells are tuned to the materials properties of their matrix



Mechano-adaptation

- Tumors are often detected as a palpable stiffness of the tissue
    - Magnetic resonance imaging and ultrasound elastography

- Preventing tissue stiffening may impede cancer progression
- Genetically susceptible individuals predisposed to matrix stiffening may be at greater risk



Elastography

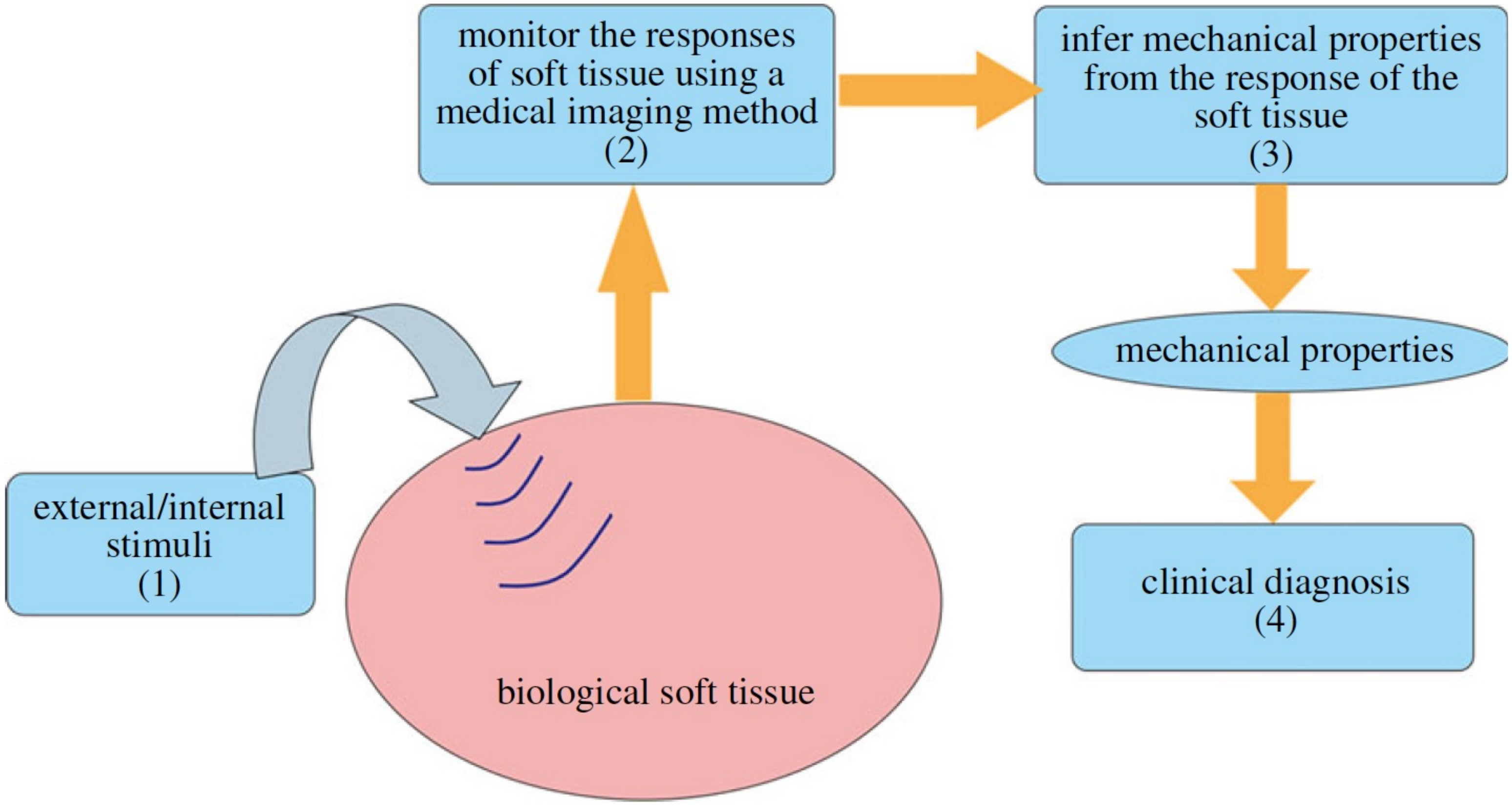
- Static and dynamic methods
  - Manual compression and ultrasound imaging

- Acoustic radiation force with focused ultrasound

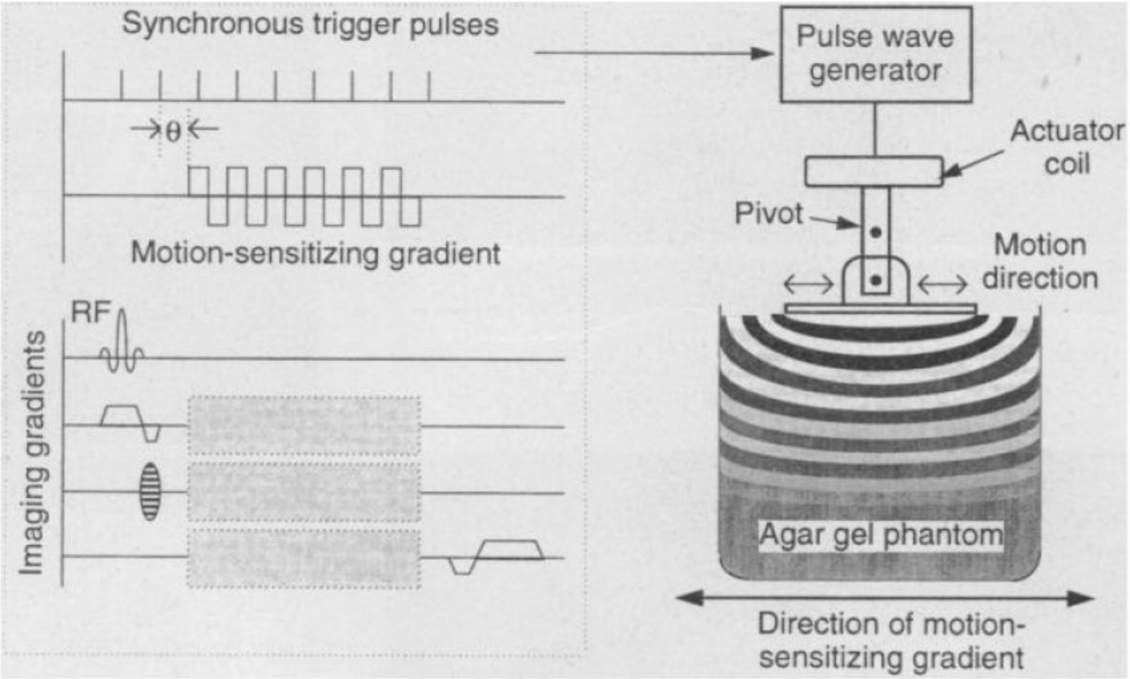
- Shear-wave elasticity imaging (shear modulus)
  - Acoustic radiation force creates the push
  - How fast the resulting shear wave travels through the tissue

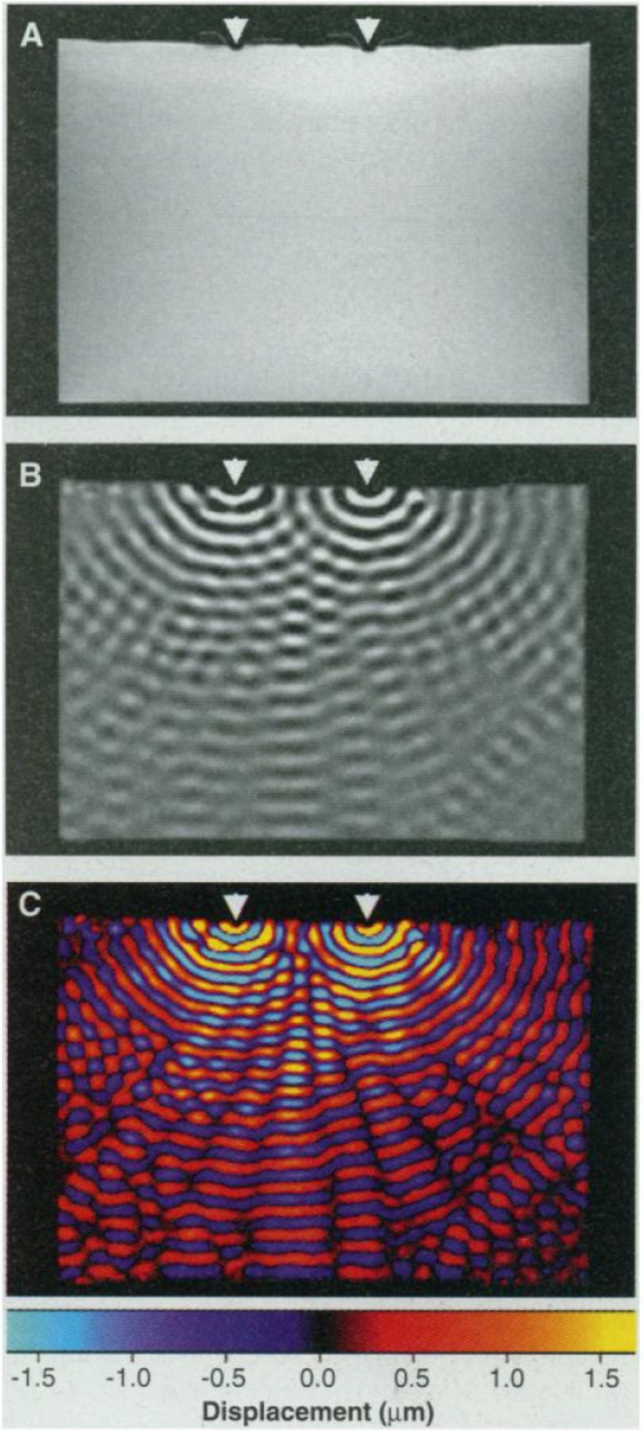
- Mechanical vibrator creates a shear wave and MRI imaging measured the velocity of the wave

Elastography

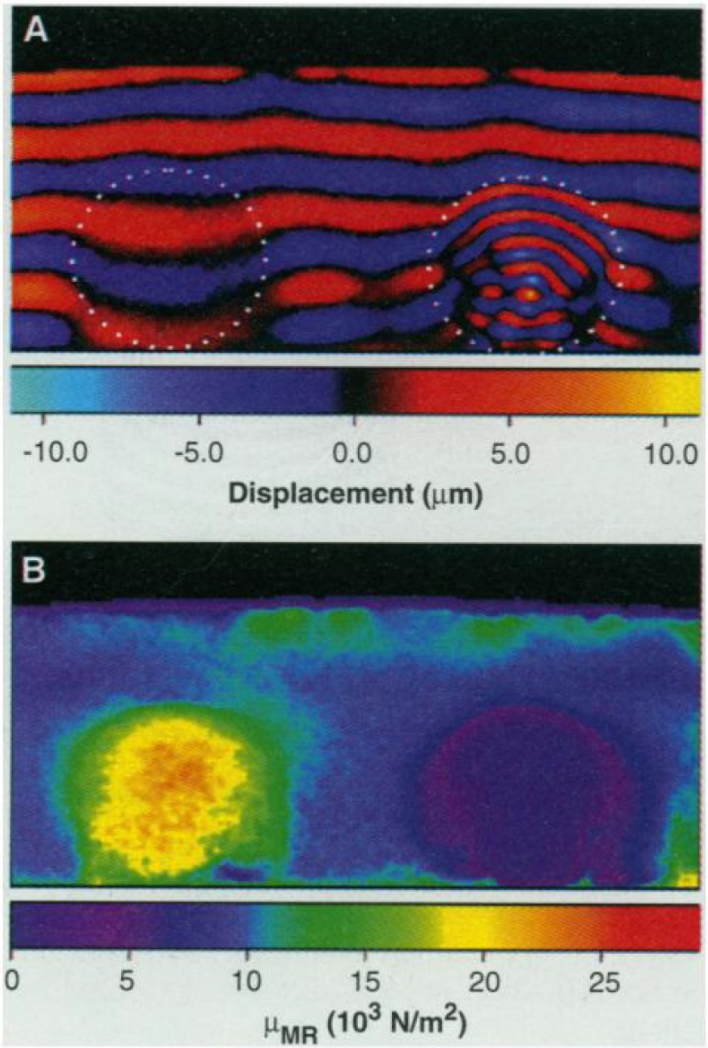


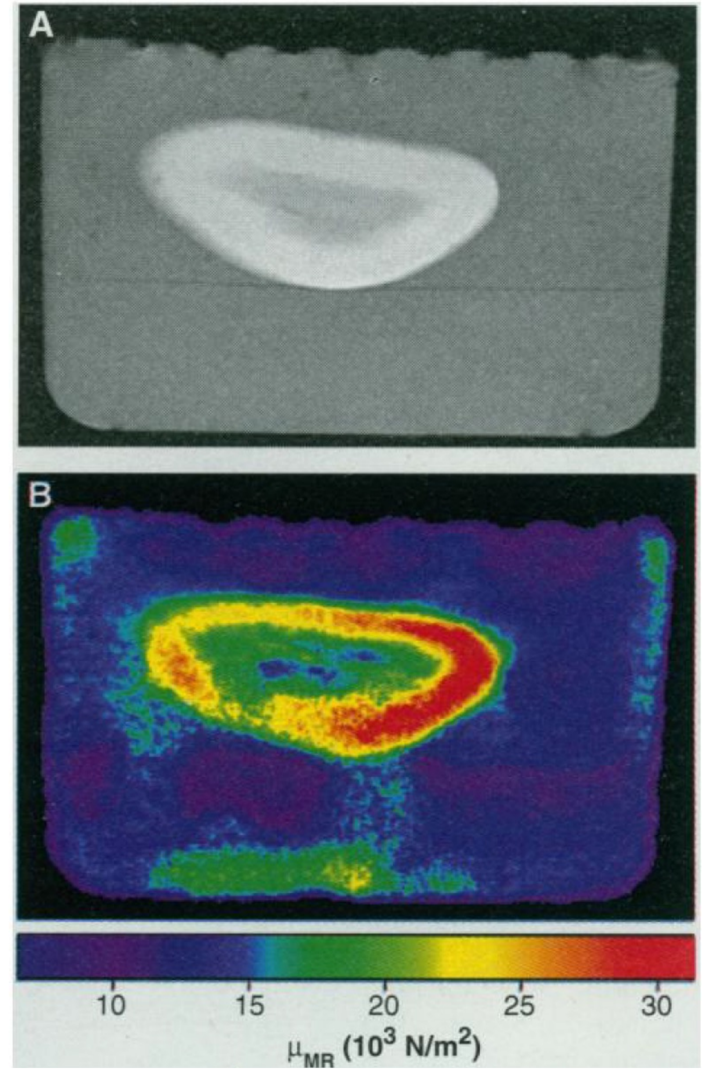
MRI Elastography



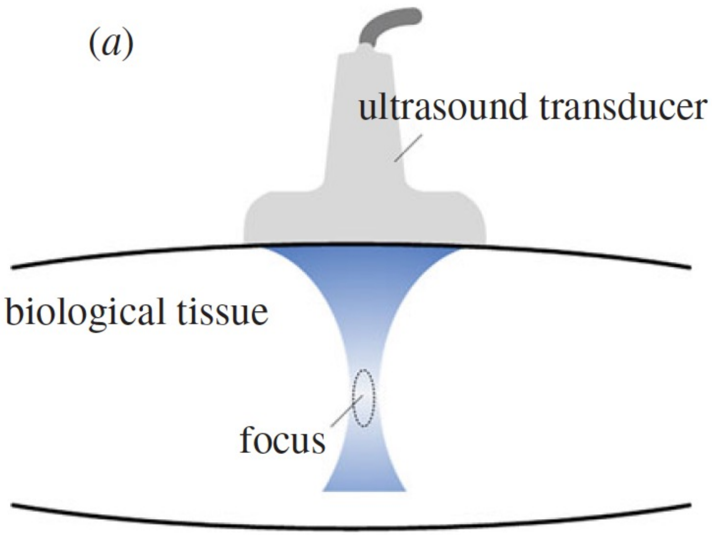


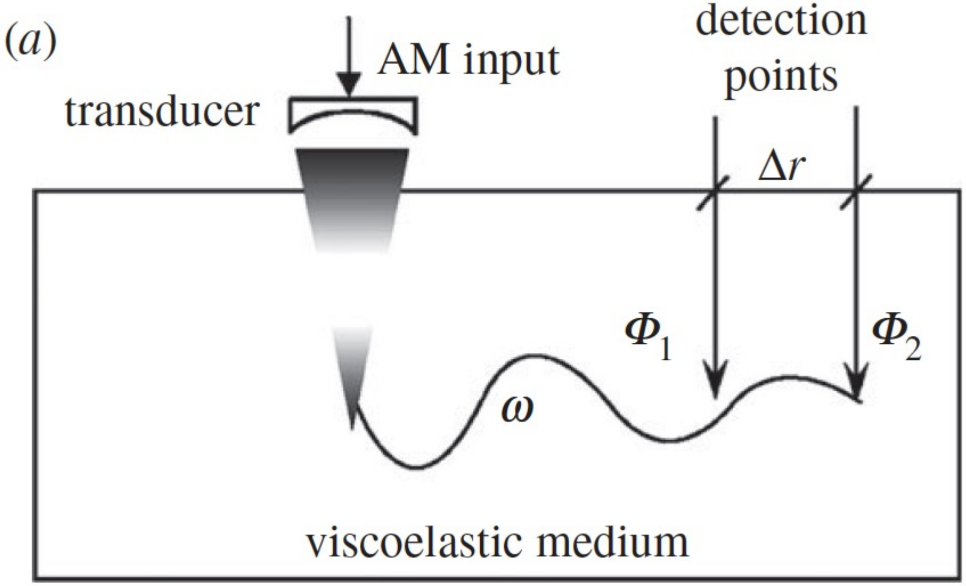
MRI Elastography



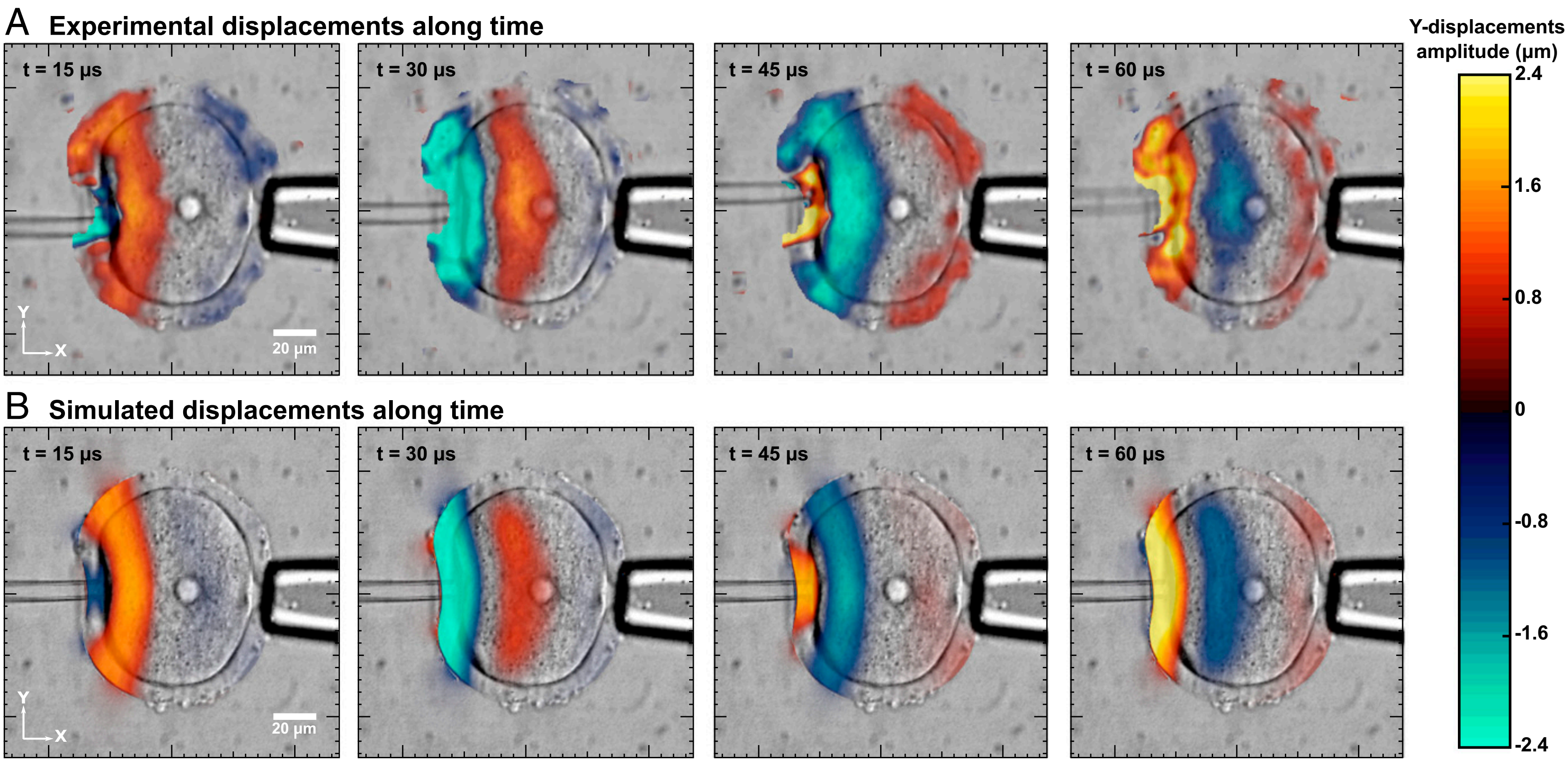


Ultrasound Elastography



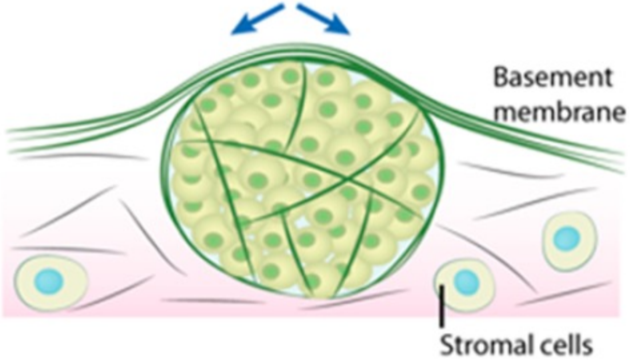


Optical Microelastography



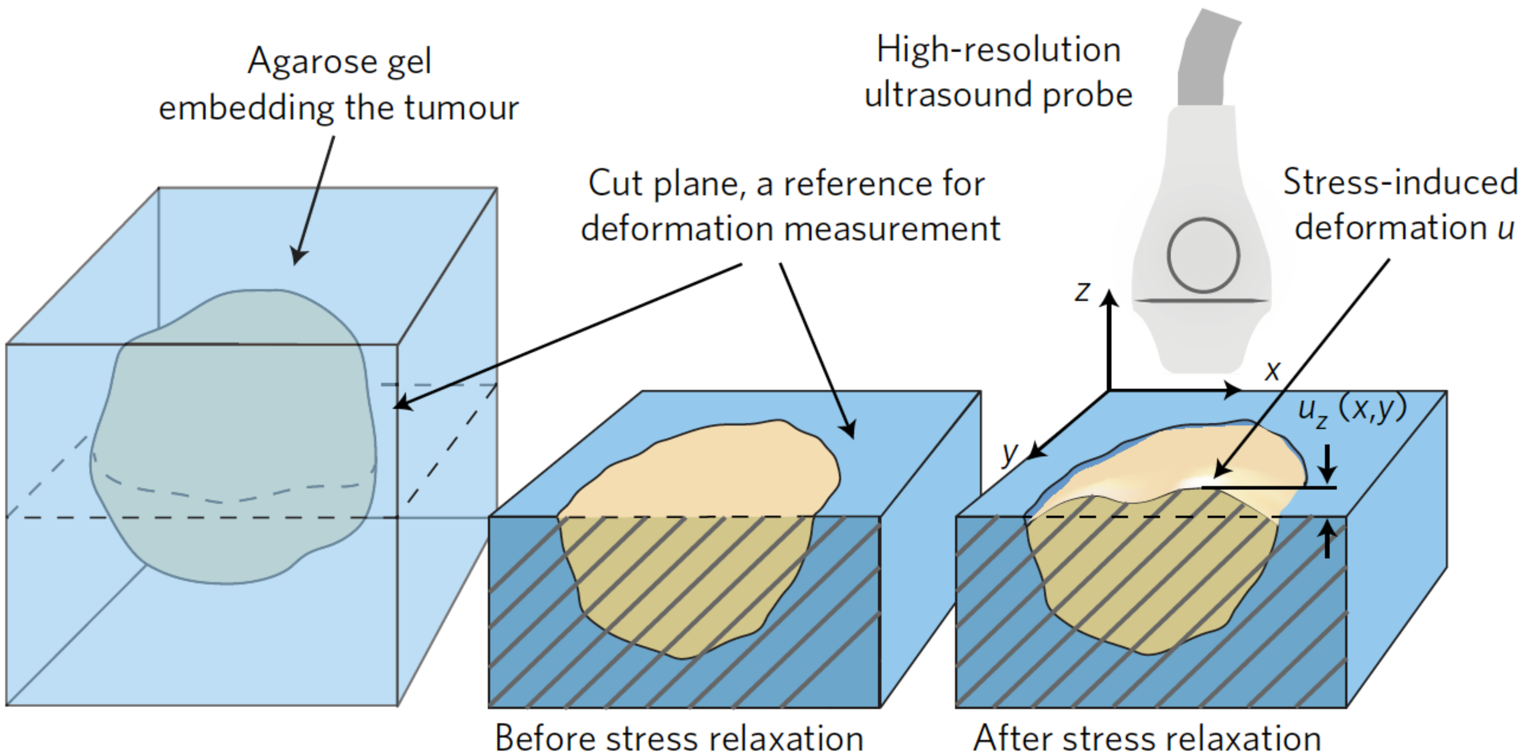
Mechano-adaptation

- Epithelial cancers are characterized by an altered tissue tensional homeostasis
  - Differences in rheology
  - Increased cell-generated force in the transformed cells
  - Increased compressive stress due to the solid state pressure generated by the expanding mass (i.e. uncontrolled proliferation)
  - Matrix stiffening due to the desmoplastic response (growth of fibrous or connective tissue)
  - Increased interstitial pressure due to leaky vasculature and poor lymphatic drainage



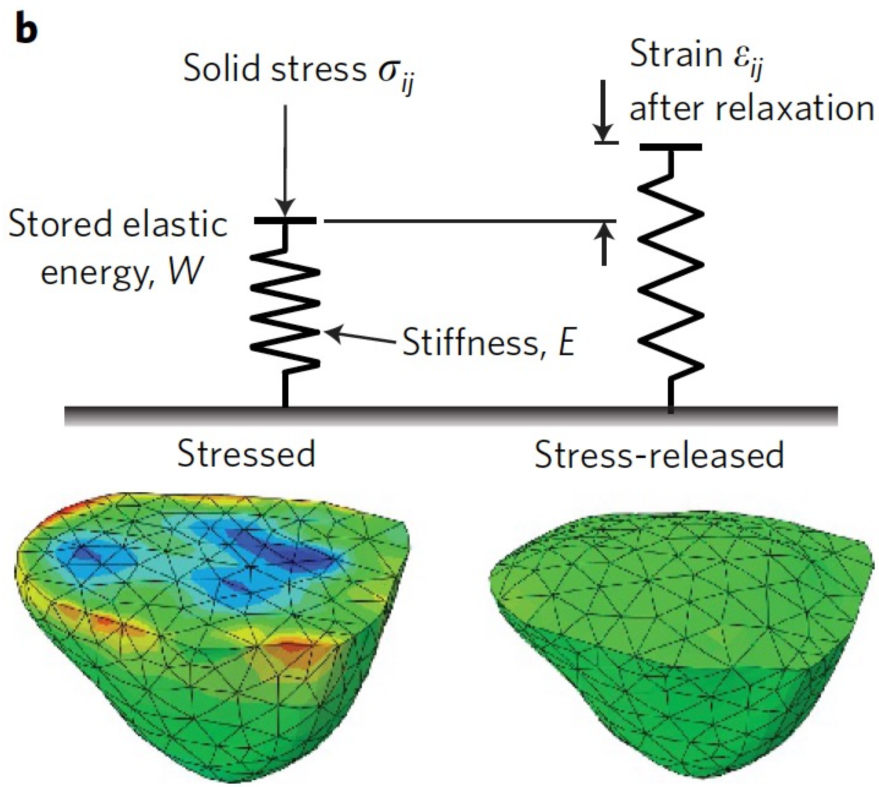
Solid stress and elastic energy

- Deformation is a measure of the stored elastic energy
- Deformation is mapped by 3D HD ultrasound



Solid stress and elastic energy

- 3D finite element model
  - Convert 2D map of deformation into strain tensor $\boldsymbol{\varepsilon}_{ij}$
  - Use strain tensor to calculate stress tensor σ_{ij} (Hooke's law)

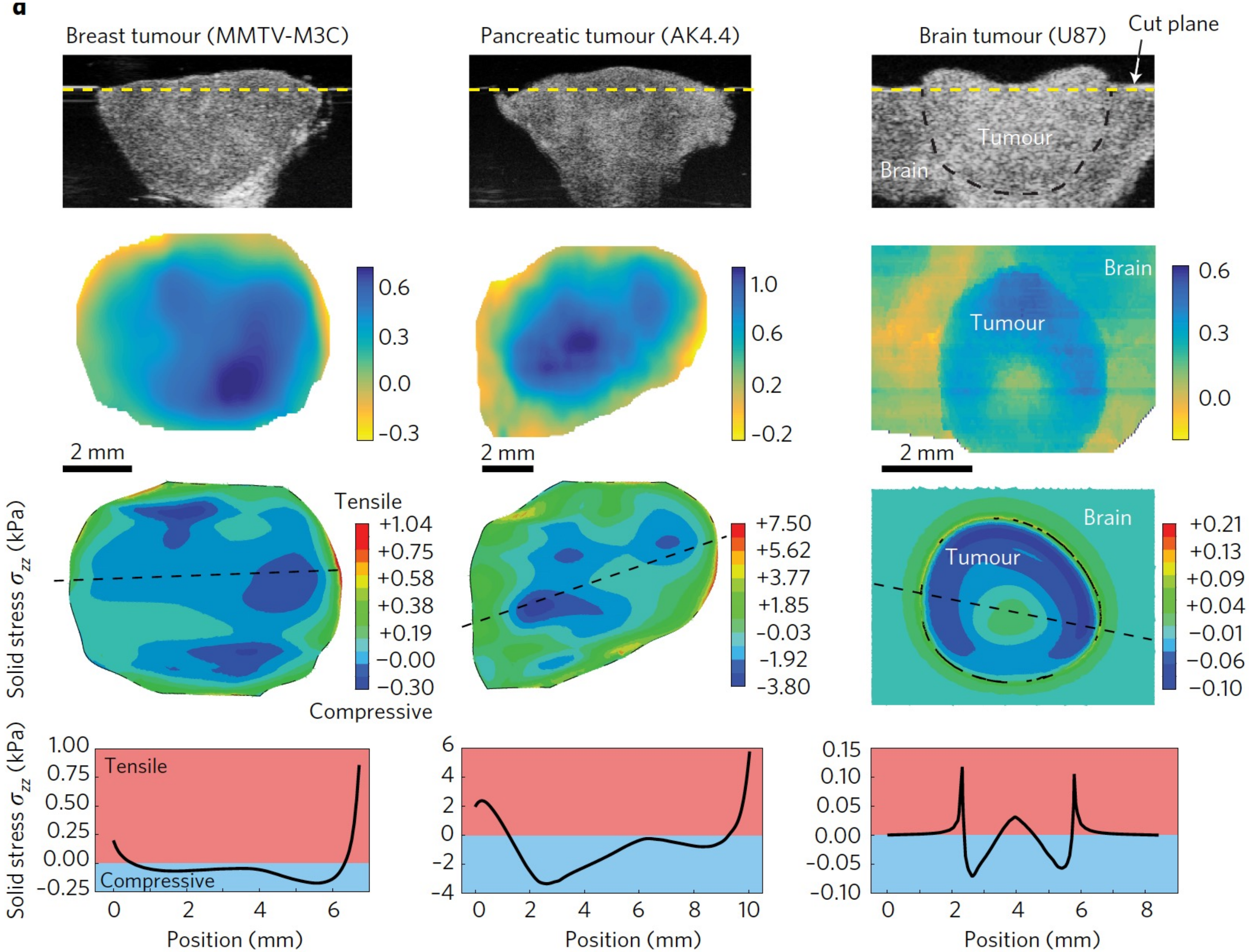


$$\sigma_{ij} = \frac{E}{(1+\nu)}\left(\varepsilon_{ij} + \frac{\nu}{(1+2\nu)}\varepsilon_{kk}\delta_{ij}\right)$$

Elastic energy density

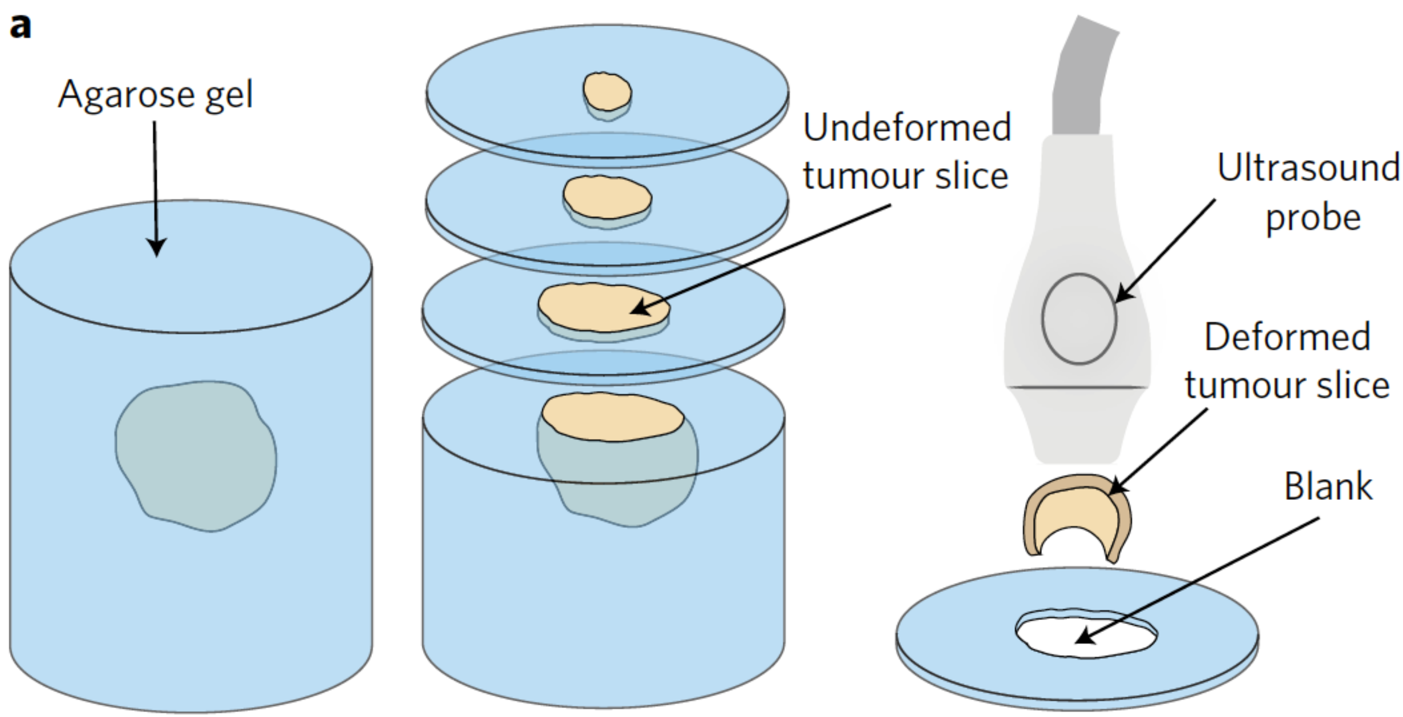
$$W = \frac{1}{2V}\int_V \sigma_{ij}\varepsilon_{ij}\,\mathrm{d}V$$

Solid stress and elastic energy



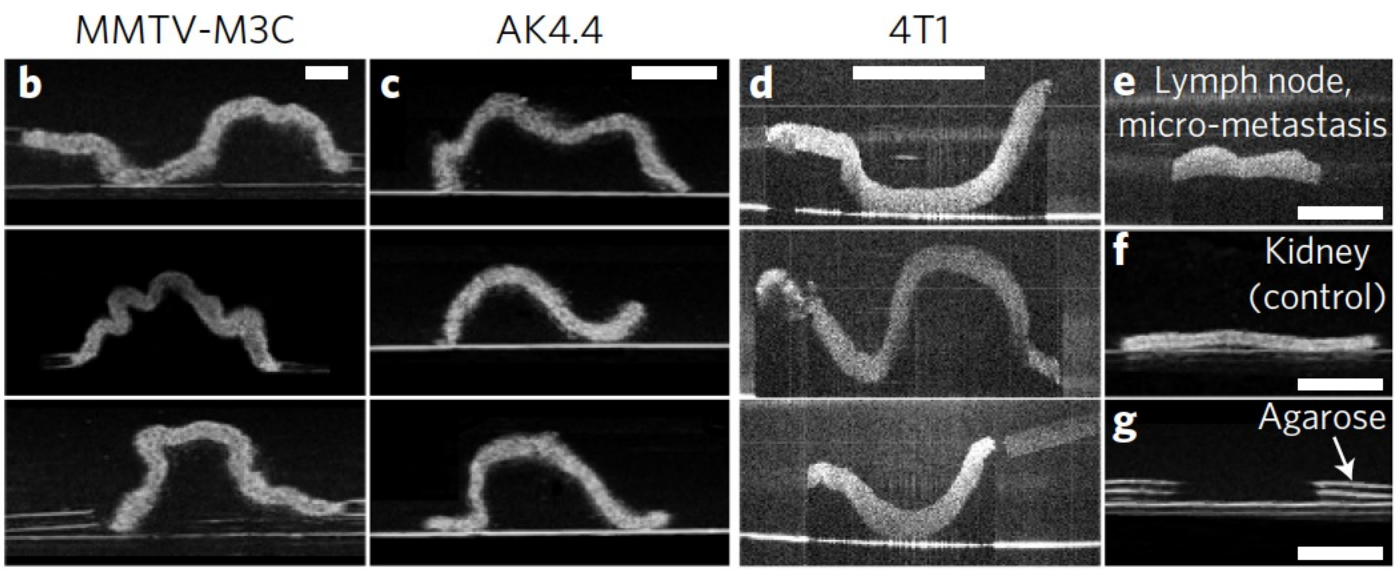
Solid stress and elastic energy

- Smaller tumors
  - Tumor slices: a more sensitive method

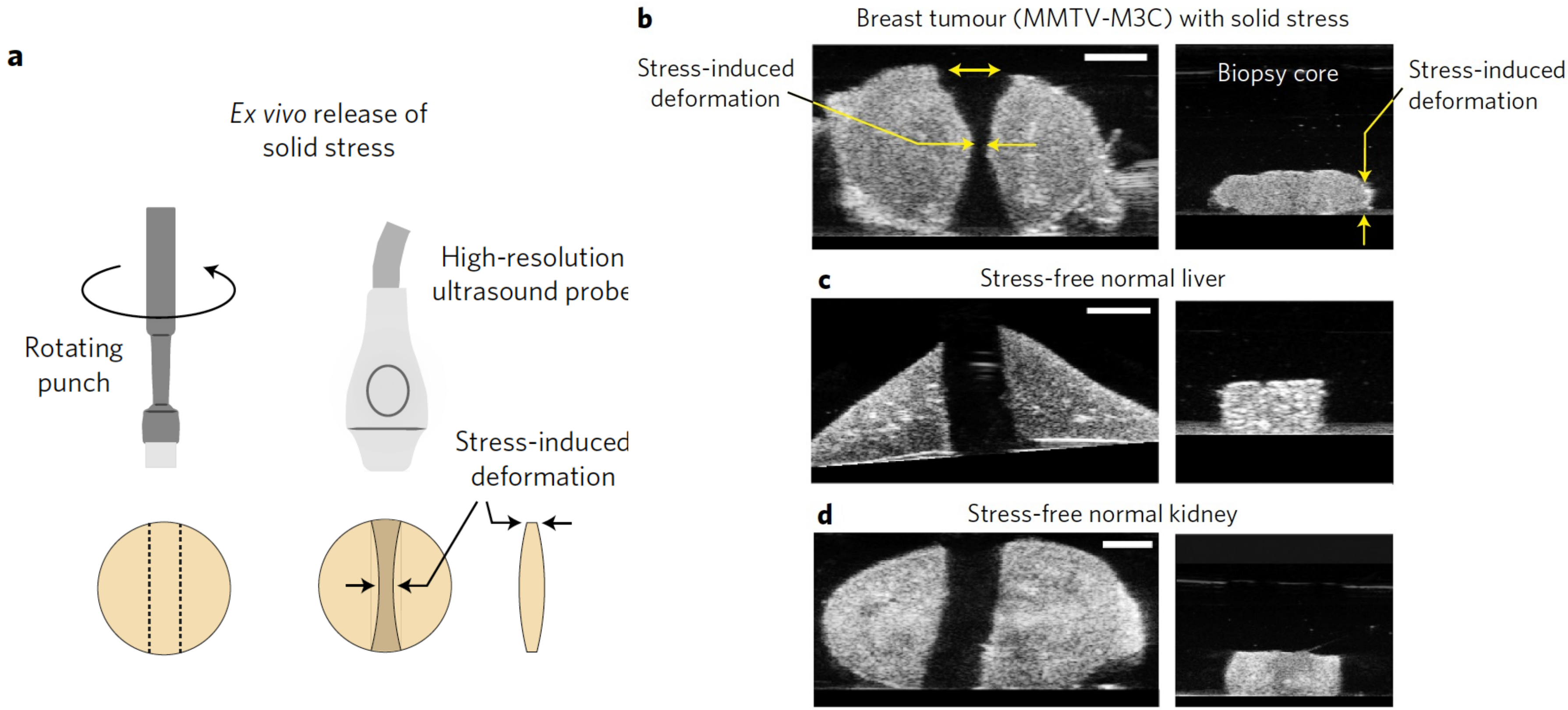


Solid stress and elastic energy

- Inhomogeneities in the in-plane stresses
  - Out-of-plane bending and buckling
- Complex shape → non-uniformity and residual compression and tension



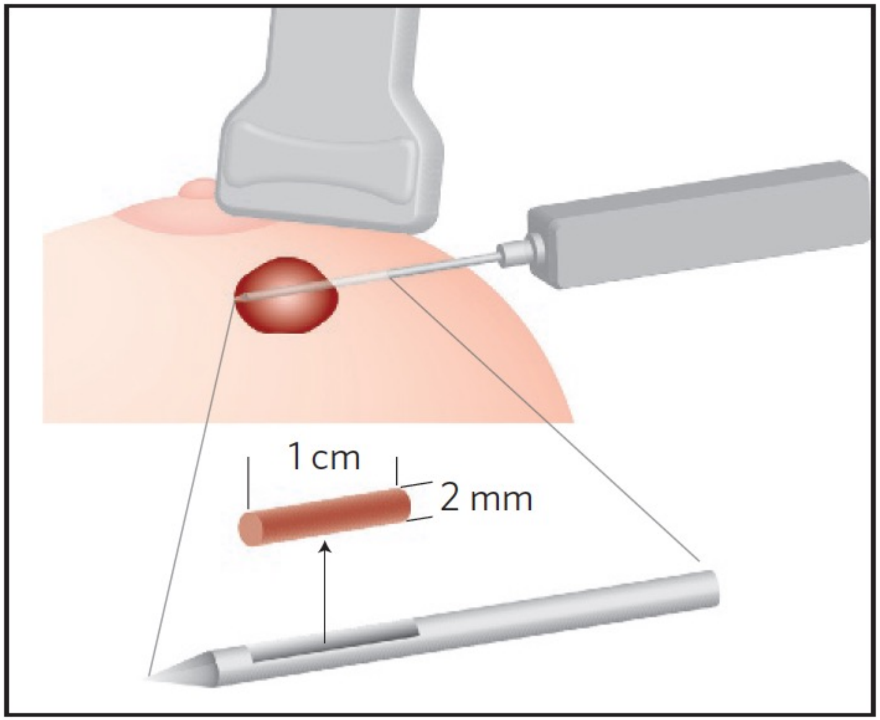
In situ measurements of solid stress

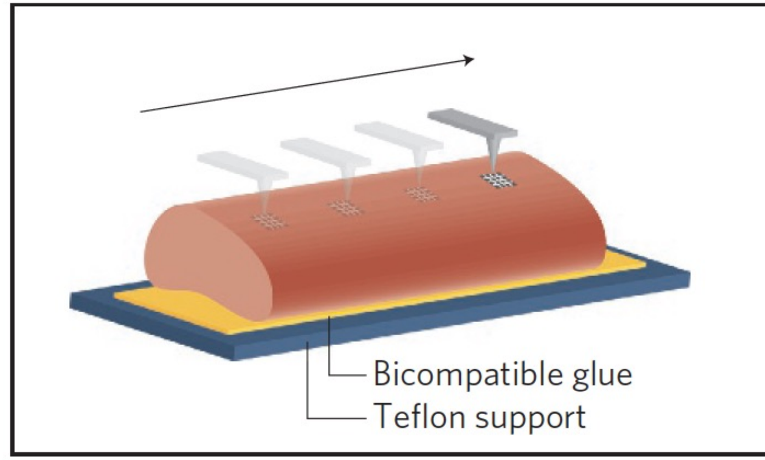


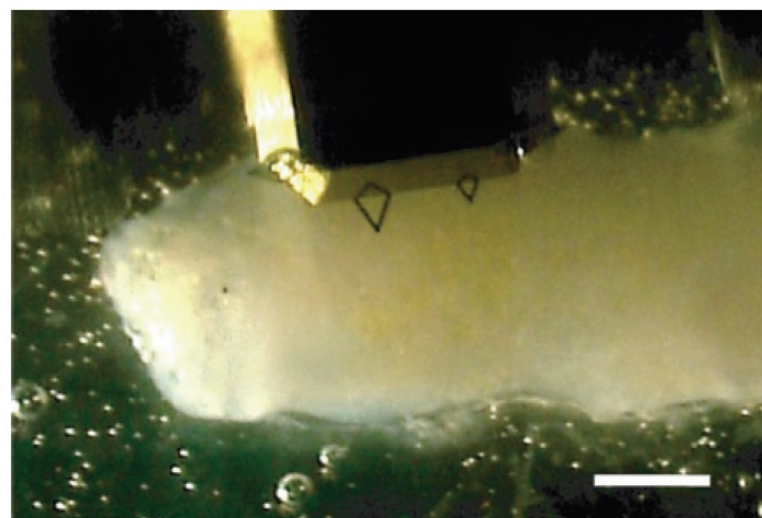
Nanomechanical signature of breast cancer

- AFM measurements on biopsies

Testing human breast biopsies by IT-AFM







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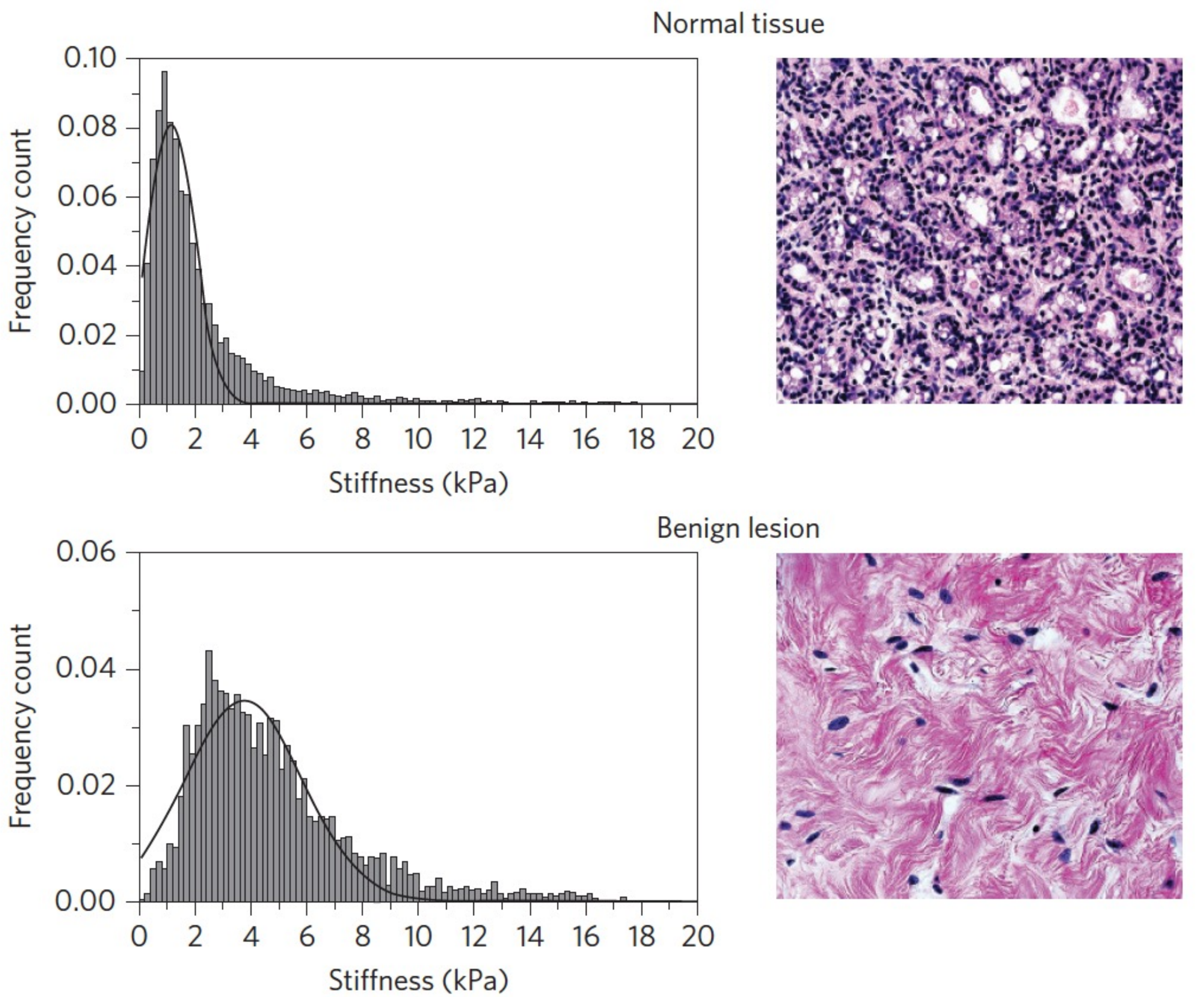
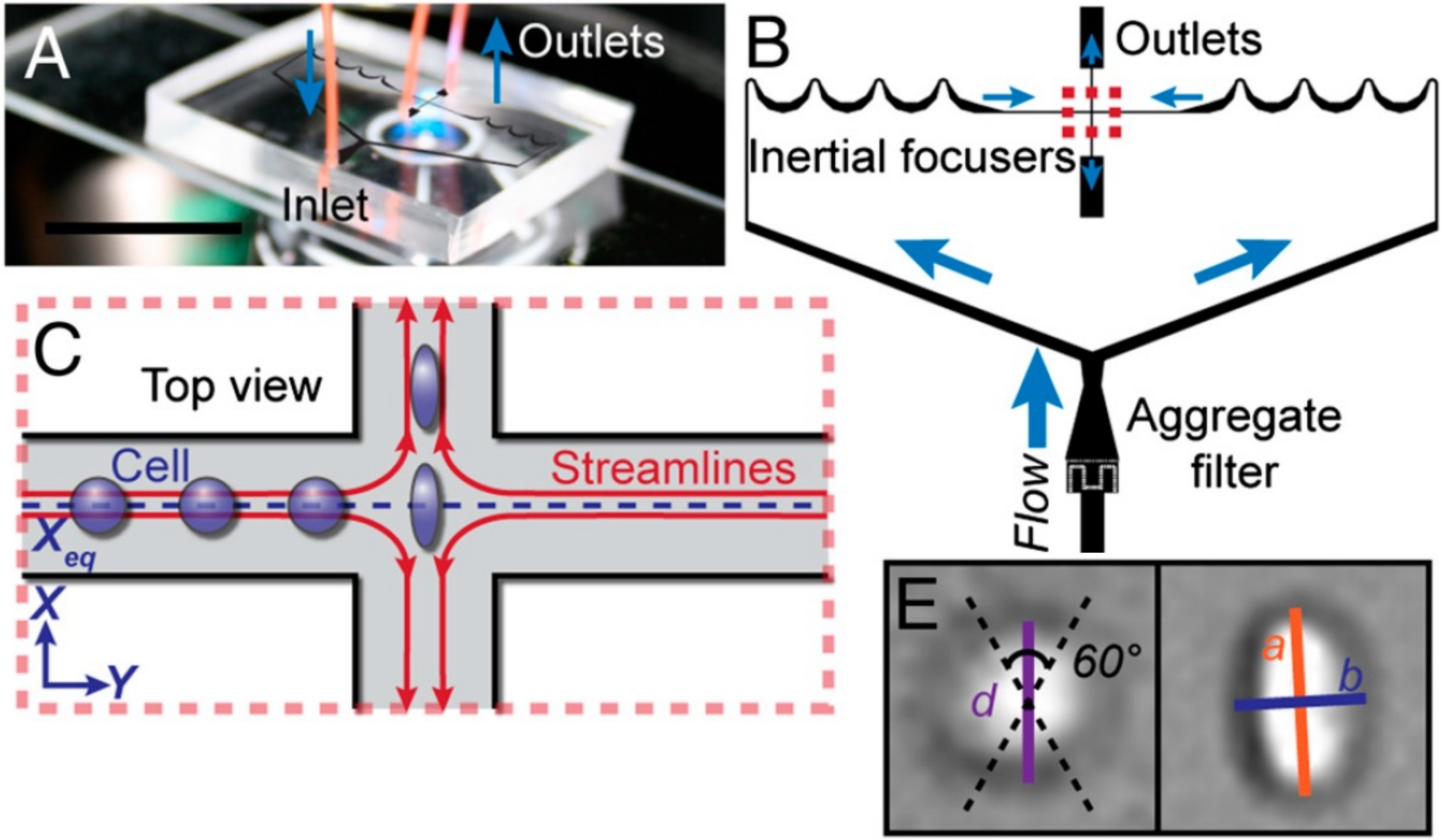


Hydrodynamic stretching

- Probing single cell deformability at 2,000 cells/s
- Inertial focusing and extensional flow



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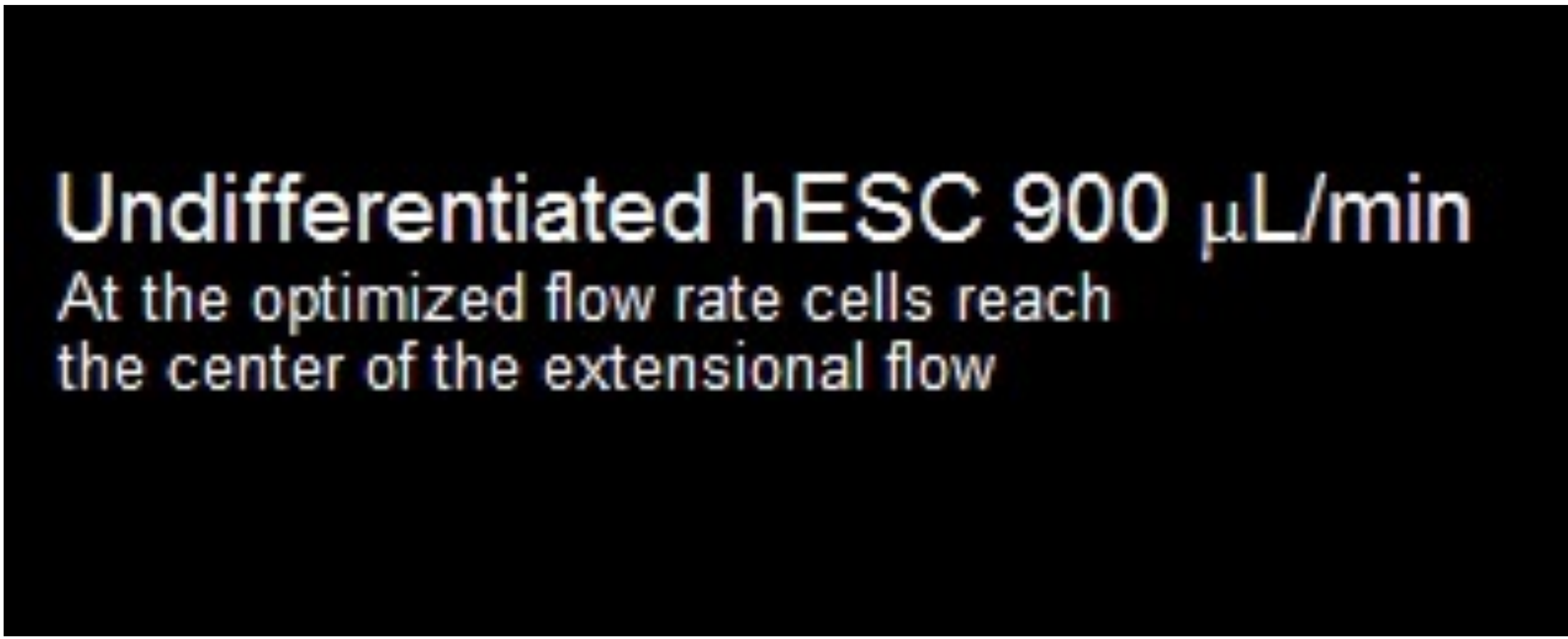
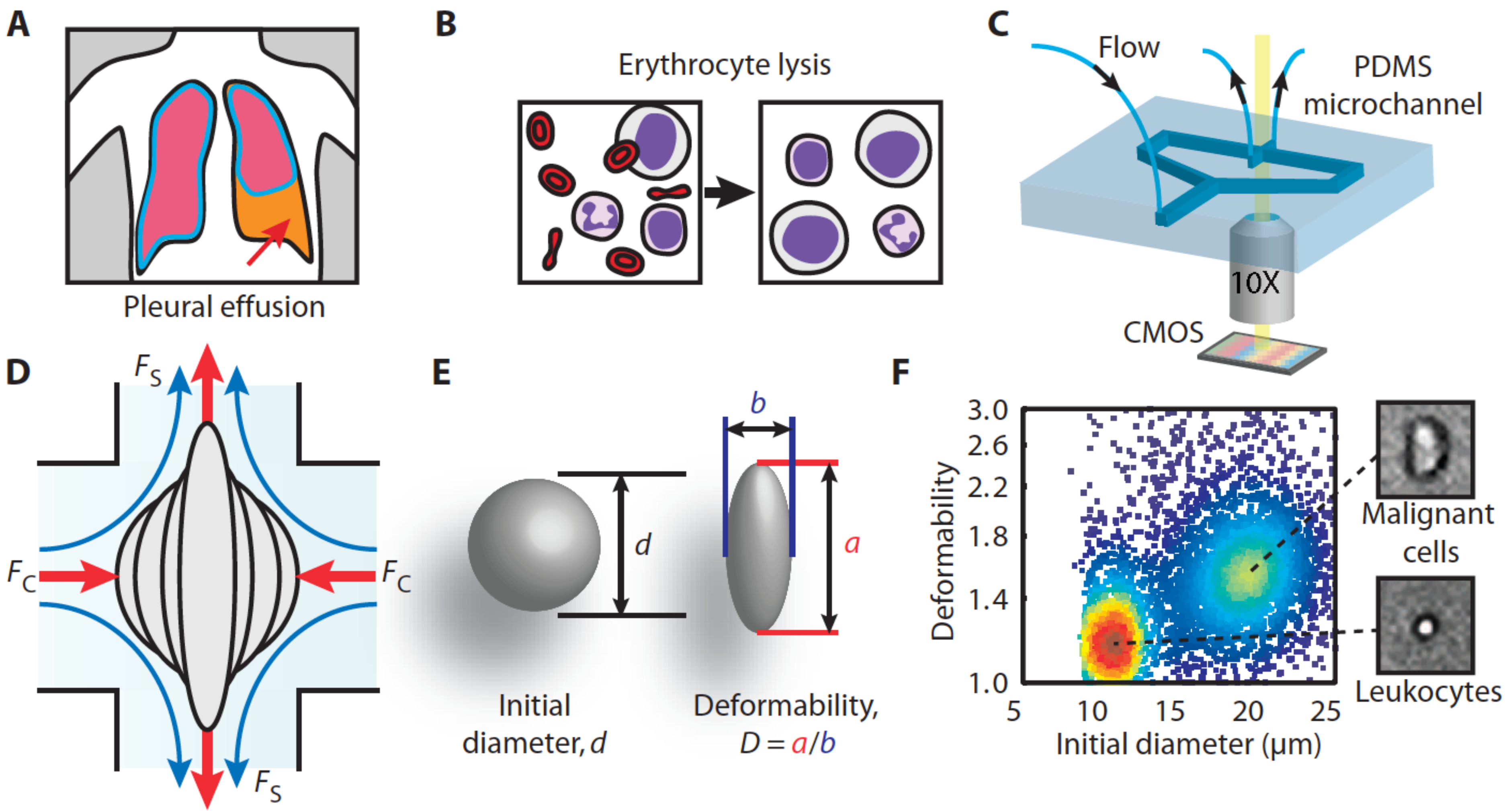
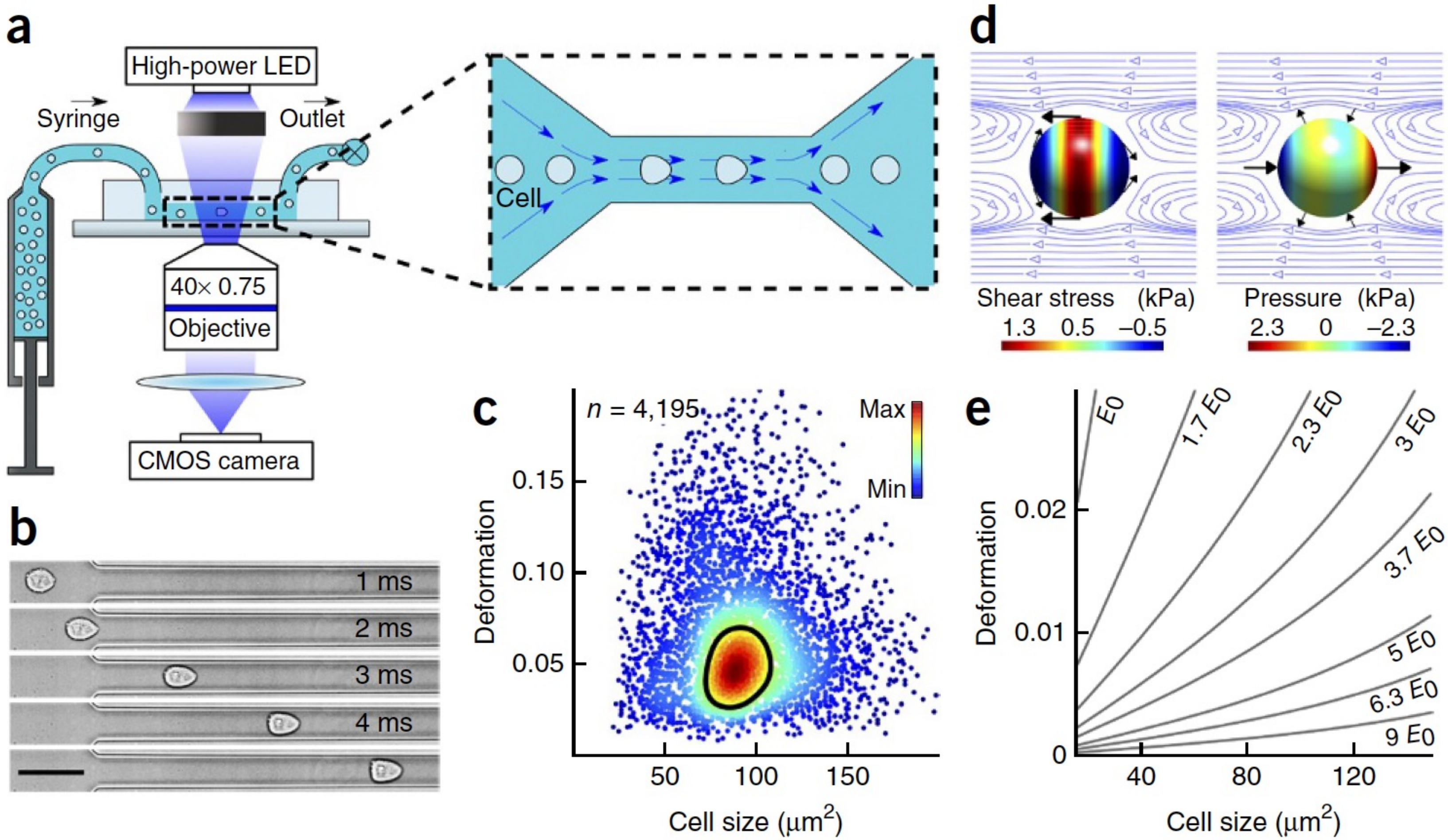


Mechanical profiling of pleural effusions for cancer diagnosis



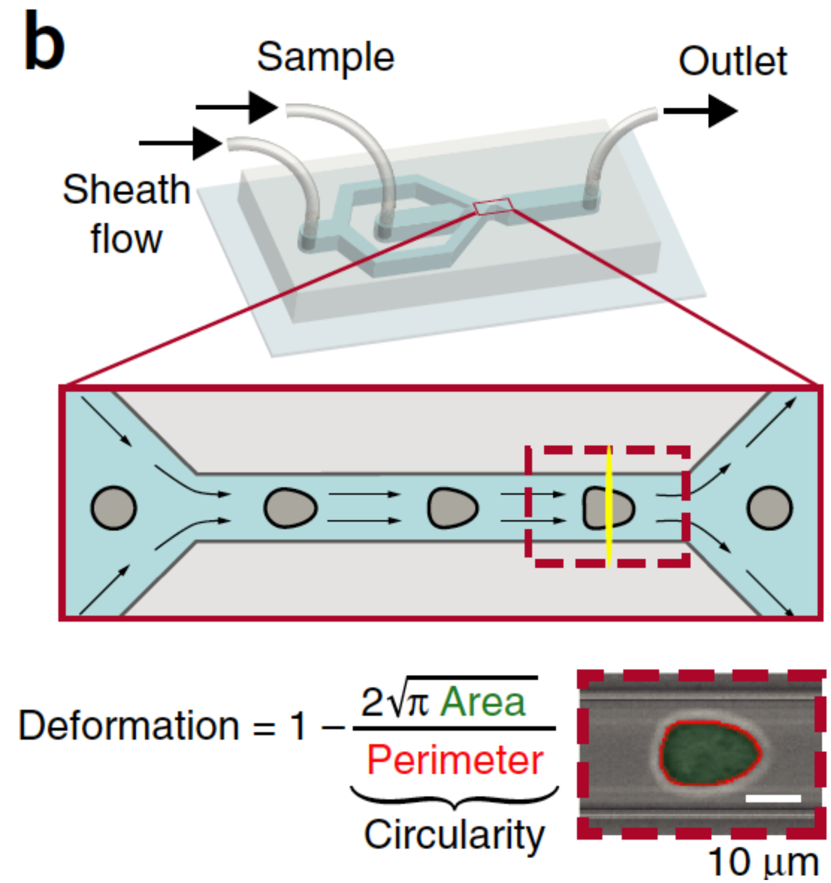
Real-time deformability cytometry

- Probing single cell deformability of >100,000 cells at 100 cells/s



Real-time deformability cytometry

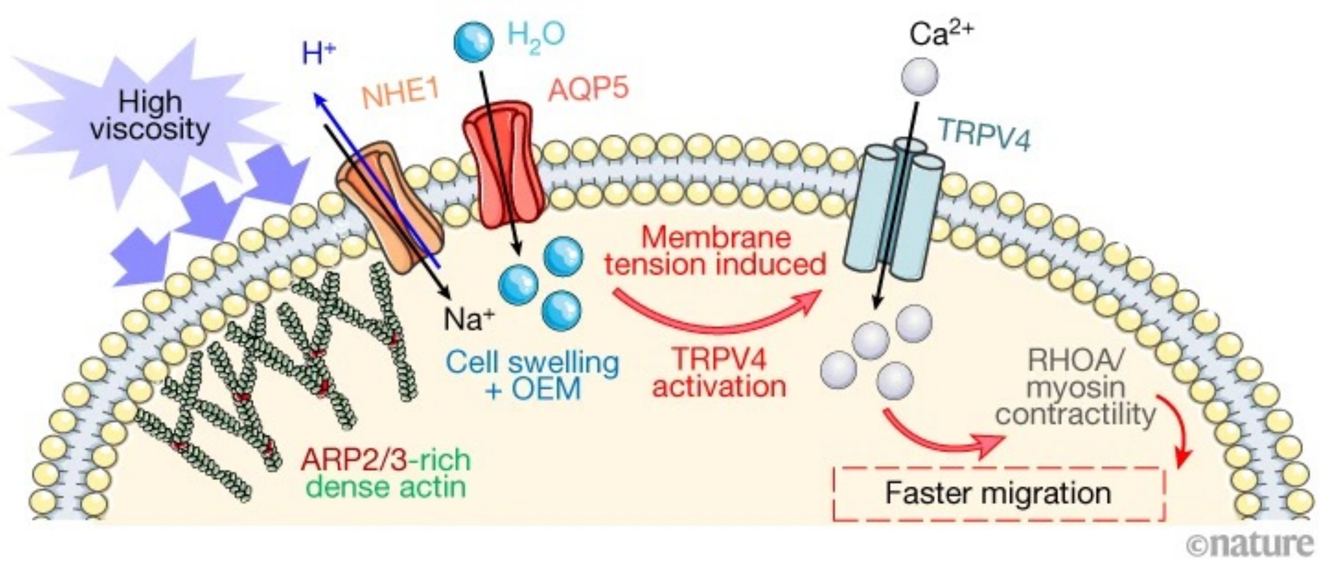
- 2,000 to 4,000 fps
- 1 µs LED pulses
- Flow rate: 10 cm/s
- Real-time measurement
    - Image processing
- Cell deformation is dependent on cell size
- Hydrodynamic model to calculate the shear stress and pressure
    - Decouples size and deformation
    - Isoelasticity lines with identical stiffness



Viscosity

- Cancer cells move and spread faster in thicker extracellular fluids

- Breast cancer cells pre-exposed to elevated viscosity acquire TRPV4 dependent mechanical memory through transcriptional control of the Hippo pathway, leading to increased migration in zebrafish, extravasation in chick embryos and lung colonization in mice.



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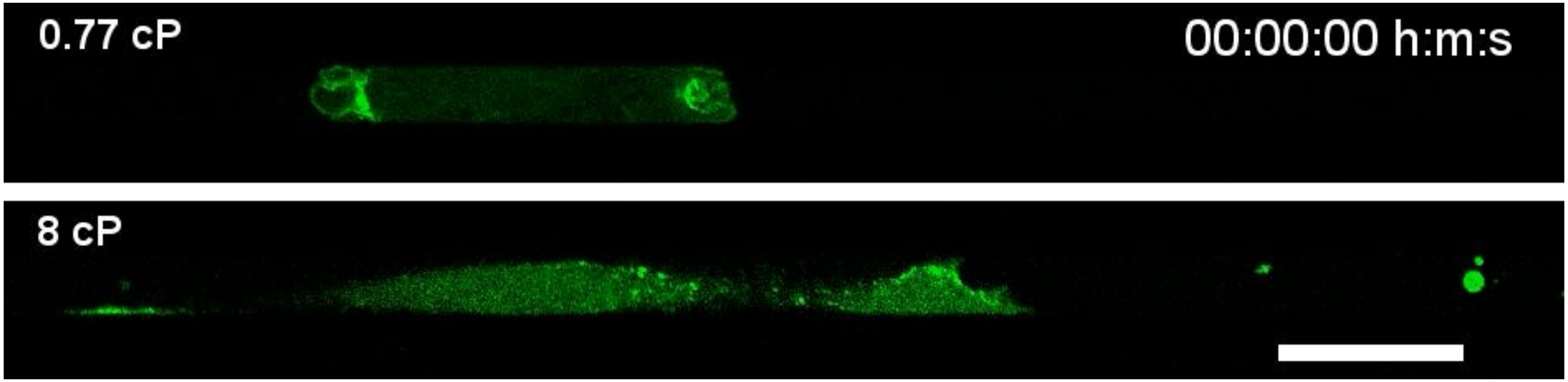
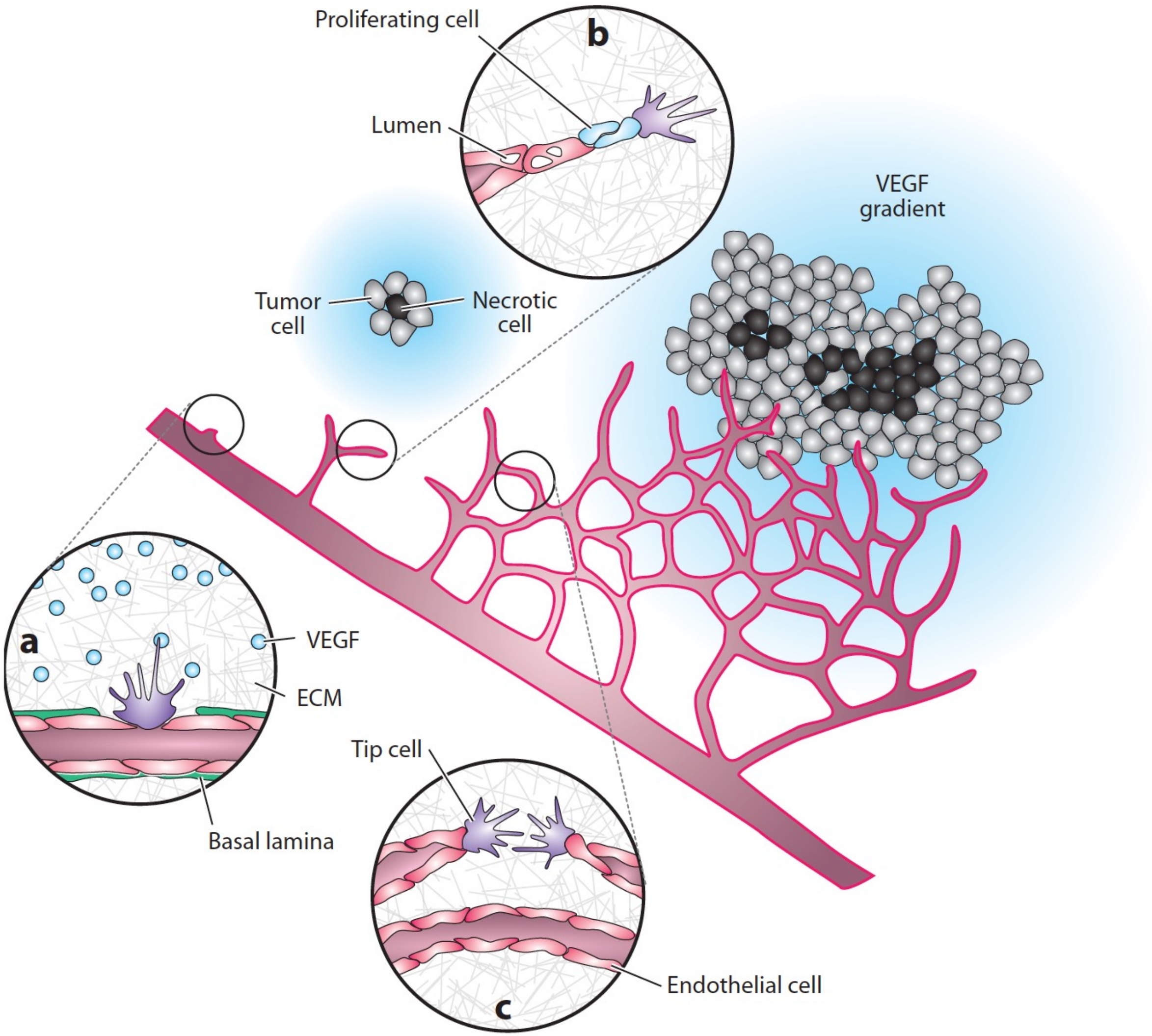
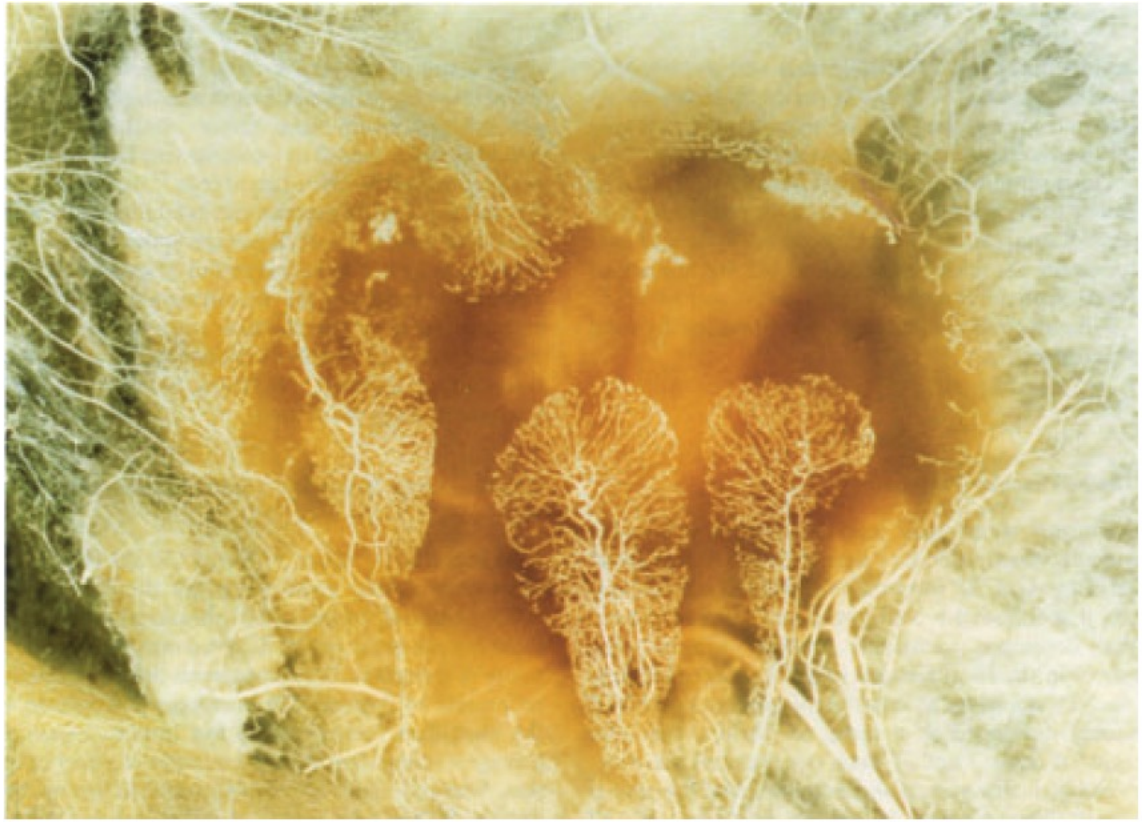


Tumor-induced angiogenesis

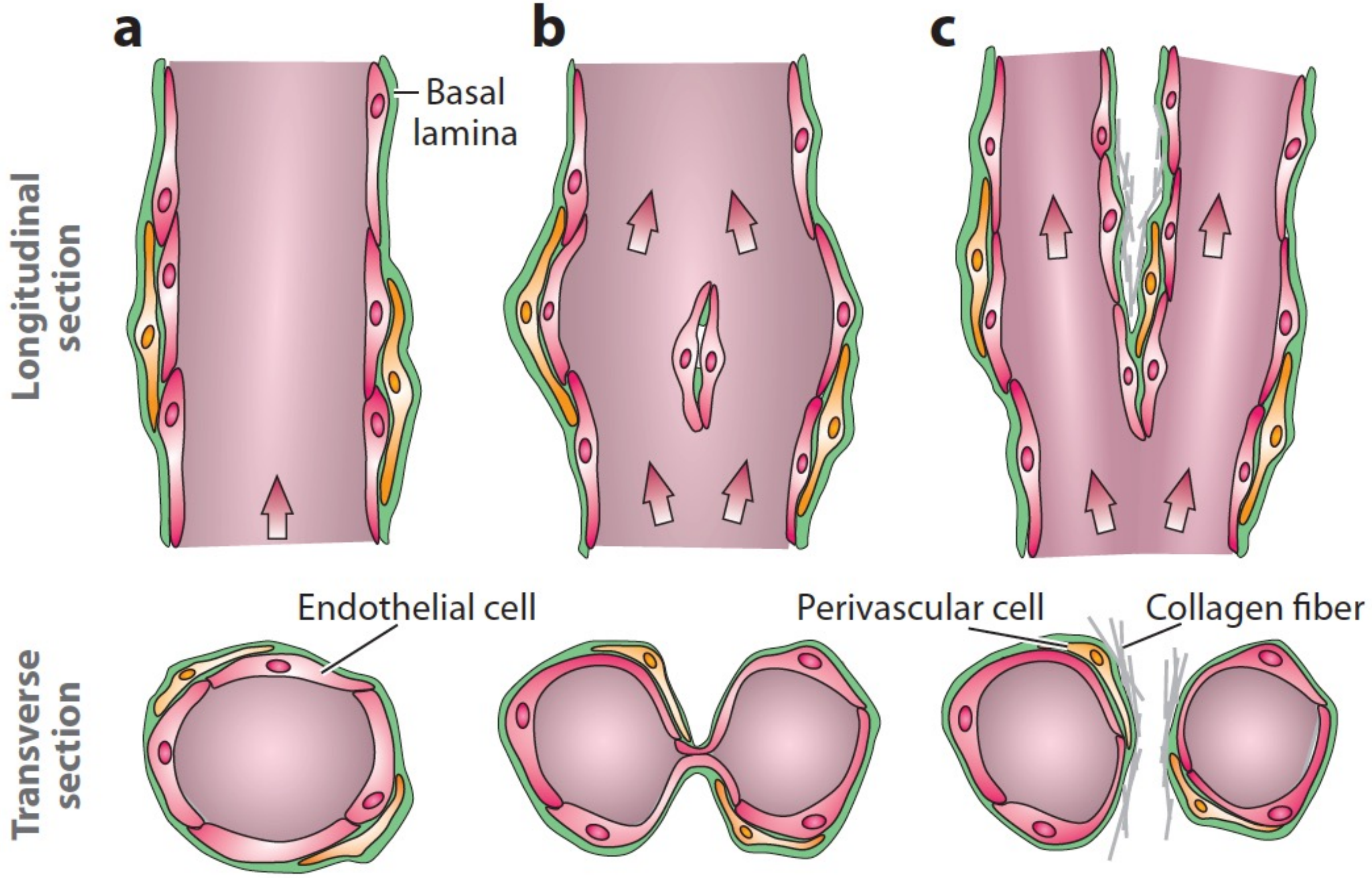


Tumor-induced angiogenesis



- Vasculature induced by a tumor (central brownish-yellow area) in the thigh muscle. The fanlike appearance of newly induced vessels.

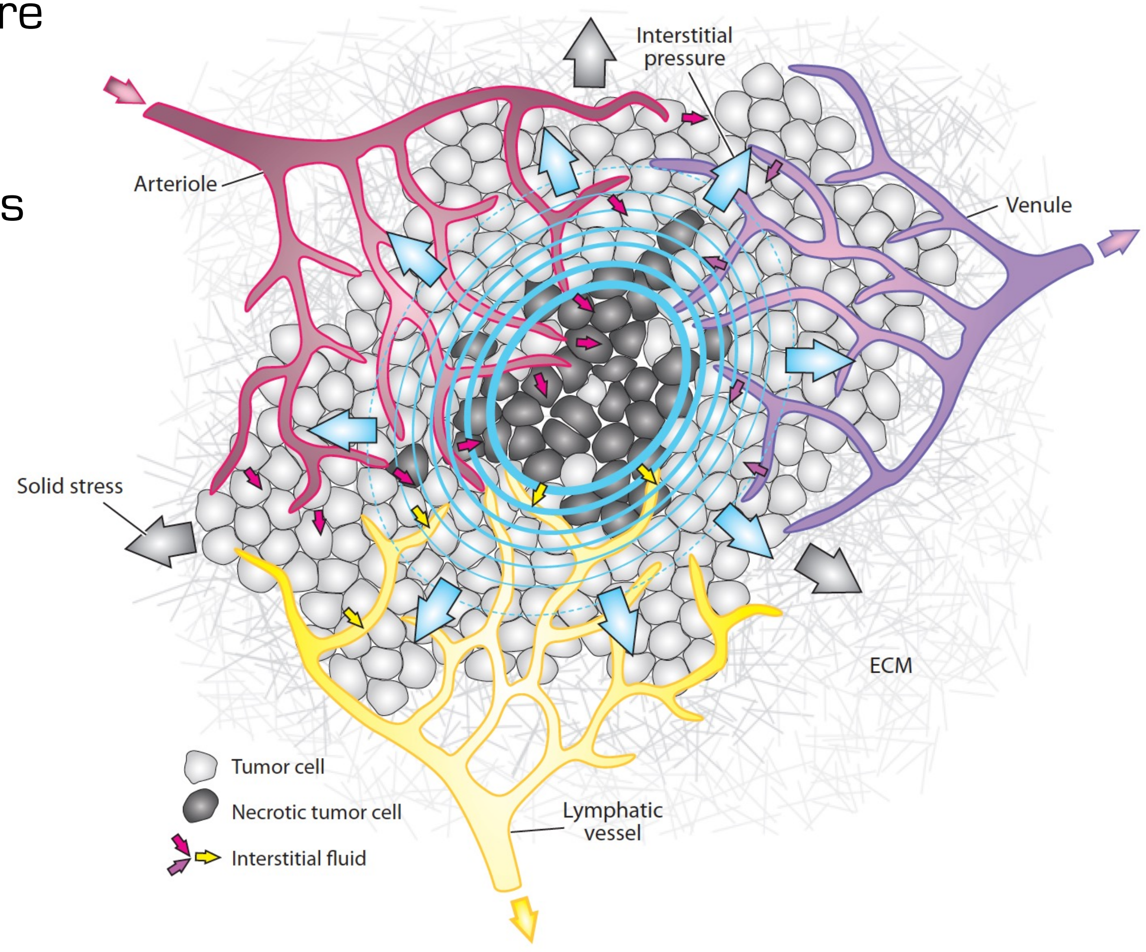
Intussusceptive (splitting) angiogenesis



- Insertion of tissue pillars into the vessels leads to formation of new vessels

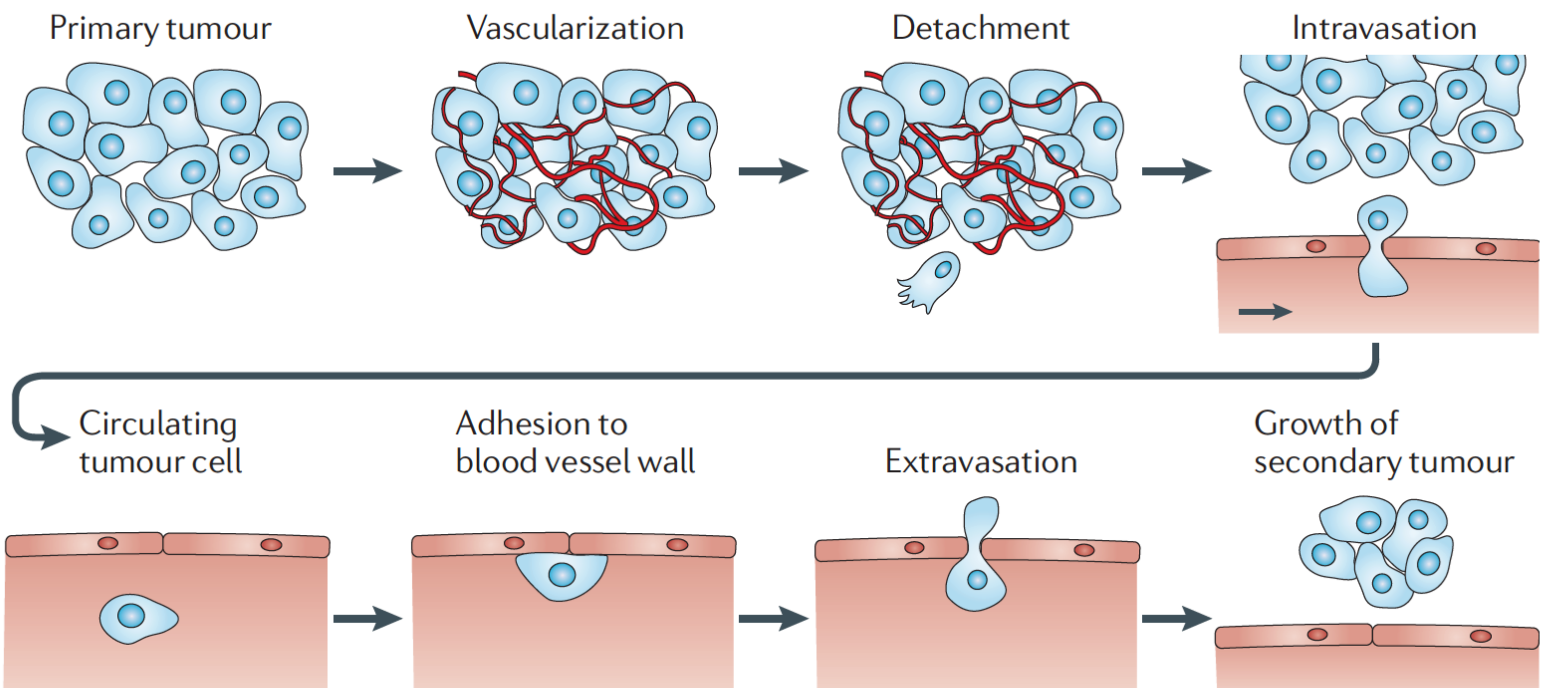
Tumor-induced angiogenesis

- Elevated interstitial pressure
- Increased interstitial flow
    - Activation of fibroblasts
    - ECM stiffening
    - Chemical diffusion
- Leaky vasculature
    - Drug delivery issues

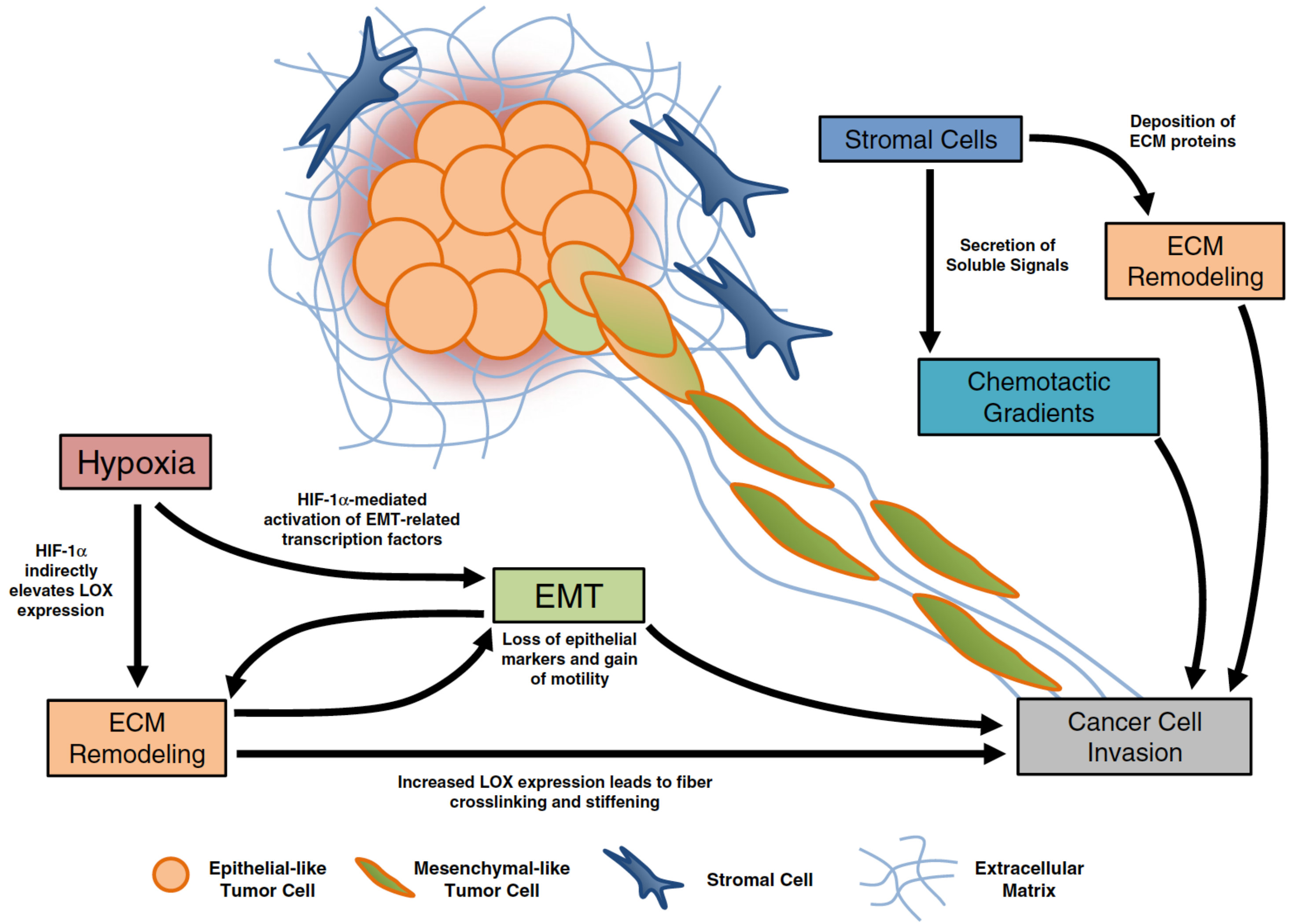


Metastasis

- Responsible for >90% of cancer-related deaths
- Physical and mechanical interactions
    - Migration through collagen-rich scaffold
    - Penetrating endothelial cell-cell junctions
    - Interplay between cell velocity and adhesion in the vessel

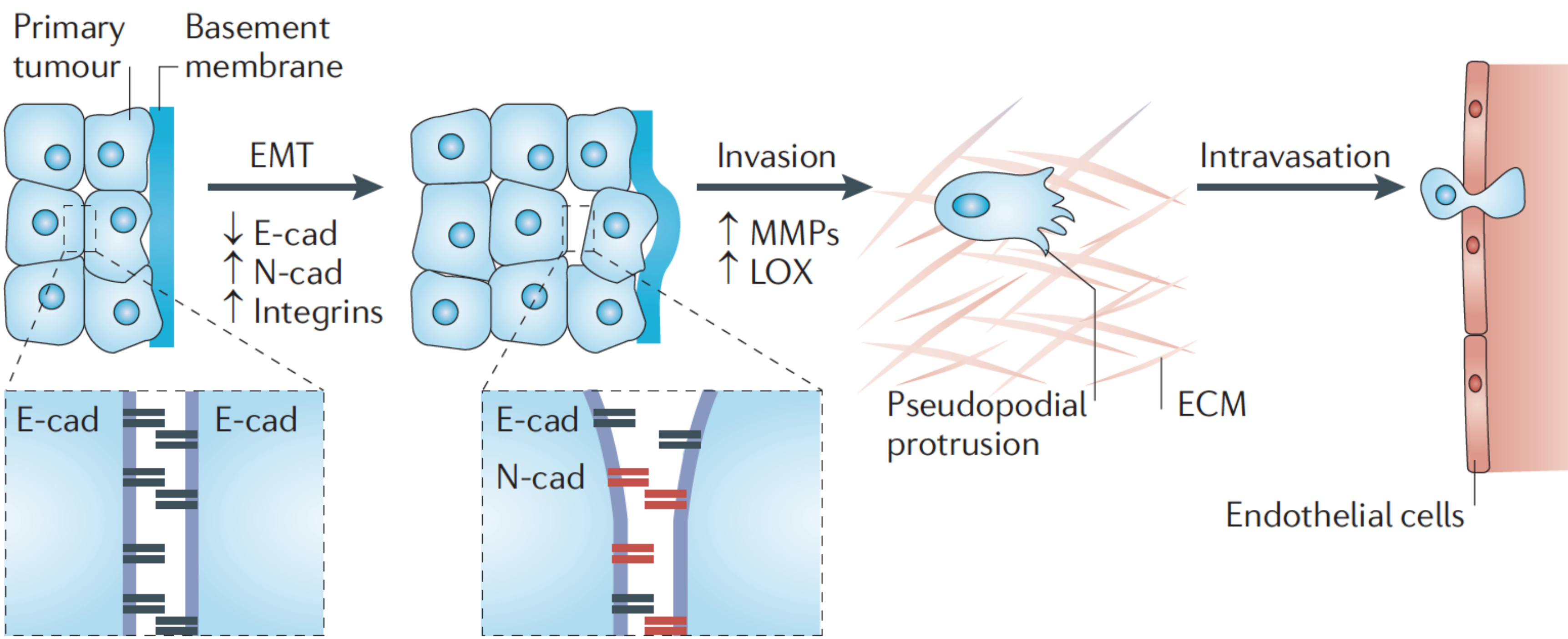


Metastasis


Stromal Cells
Deposition of ECM proteins
ECM Remodeling
Secretion of Soluble Signals
Chemotactic Gradients
Hypoxia
HIF-1α-mediated activation of EMT-related transcription factors
HIF-1α indirectly elevates LOX expression
EMT
Loss of epithelial markers and gain of motility
ECM Remodeling
Cancer Cell Invasion
Increased LOX expression leads to fiber crosslinking and stiffening
Epithelial-like Tumor Cell
Mesenchymal-like Tumor Cell
Stromal Cell
Extracellular Matrix

Invasion and intravasation

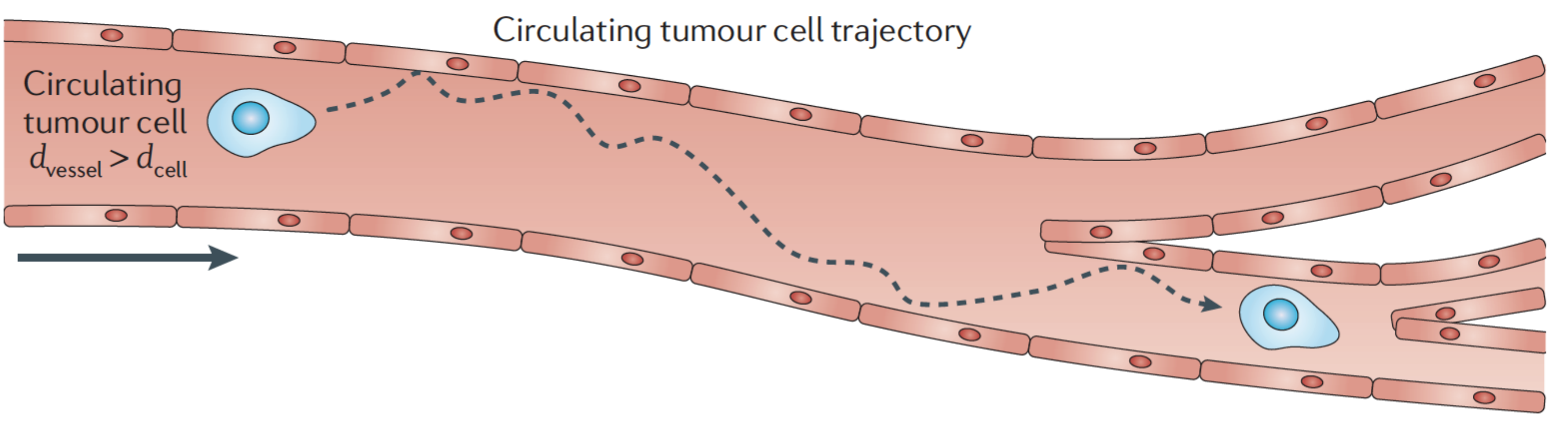
- Epithelial to mesenchymal transition
  - Loss of adhesion through downregulation of E-cadherin
  - Change in morphology
- Squeezing between blood vessels



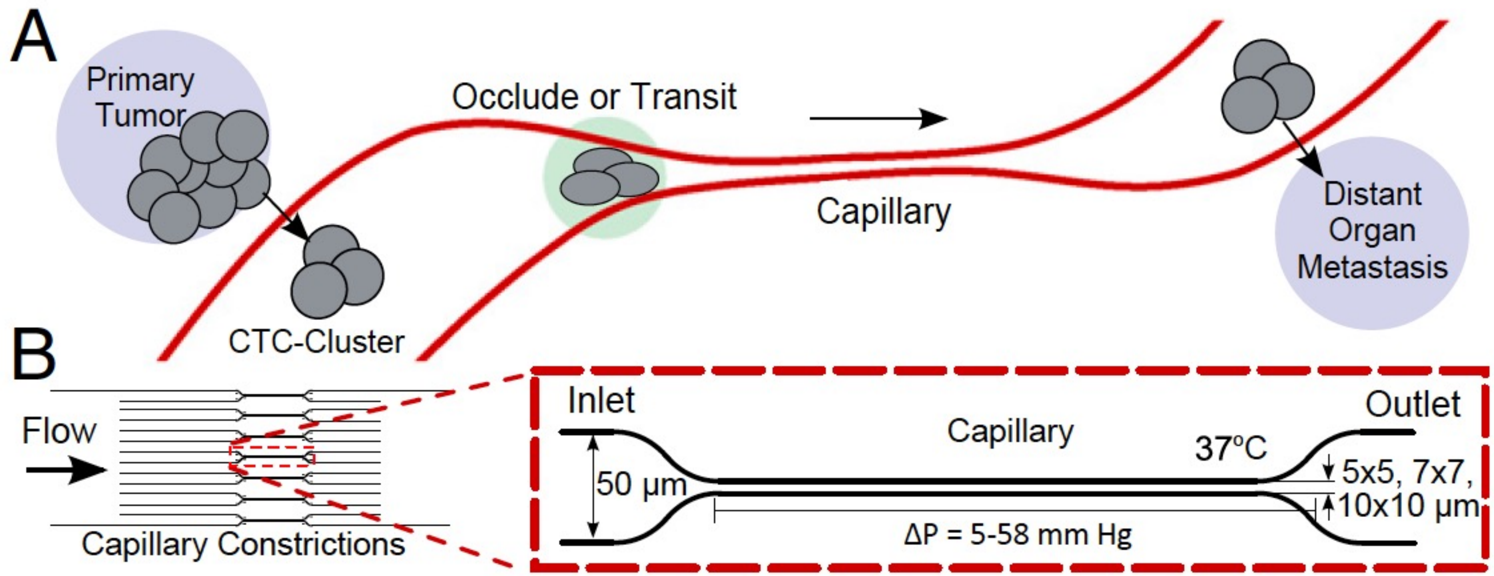
Arrest of circulating tumor cells

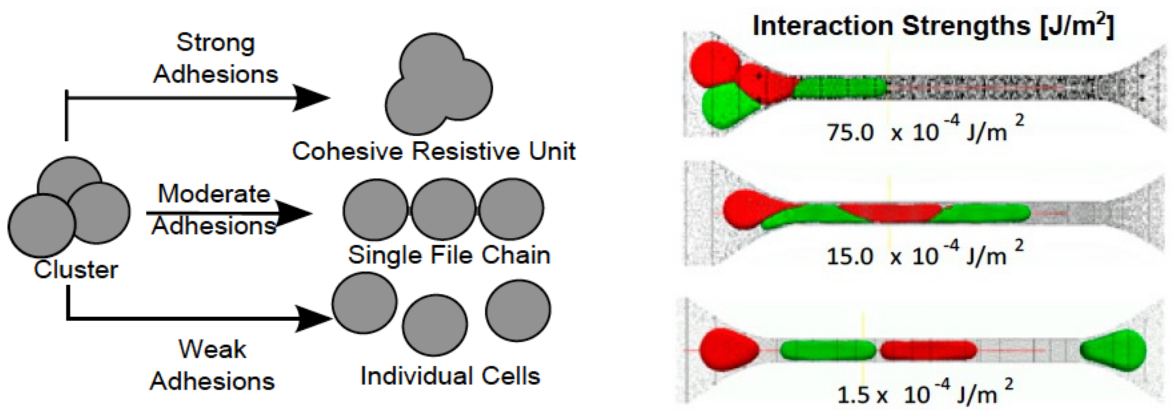
- Tumor cells smaller than the diameter of the blood vessel
  - Local flow pattern
  - Collisions with host cells and vessel walls
  - Arrest: attachment to the vessel wall

- Tumor cells larger than the diameter of the blood vessel
  - Mechanical trapping



Circulating tumor cells





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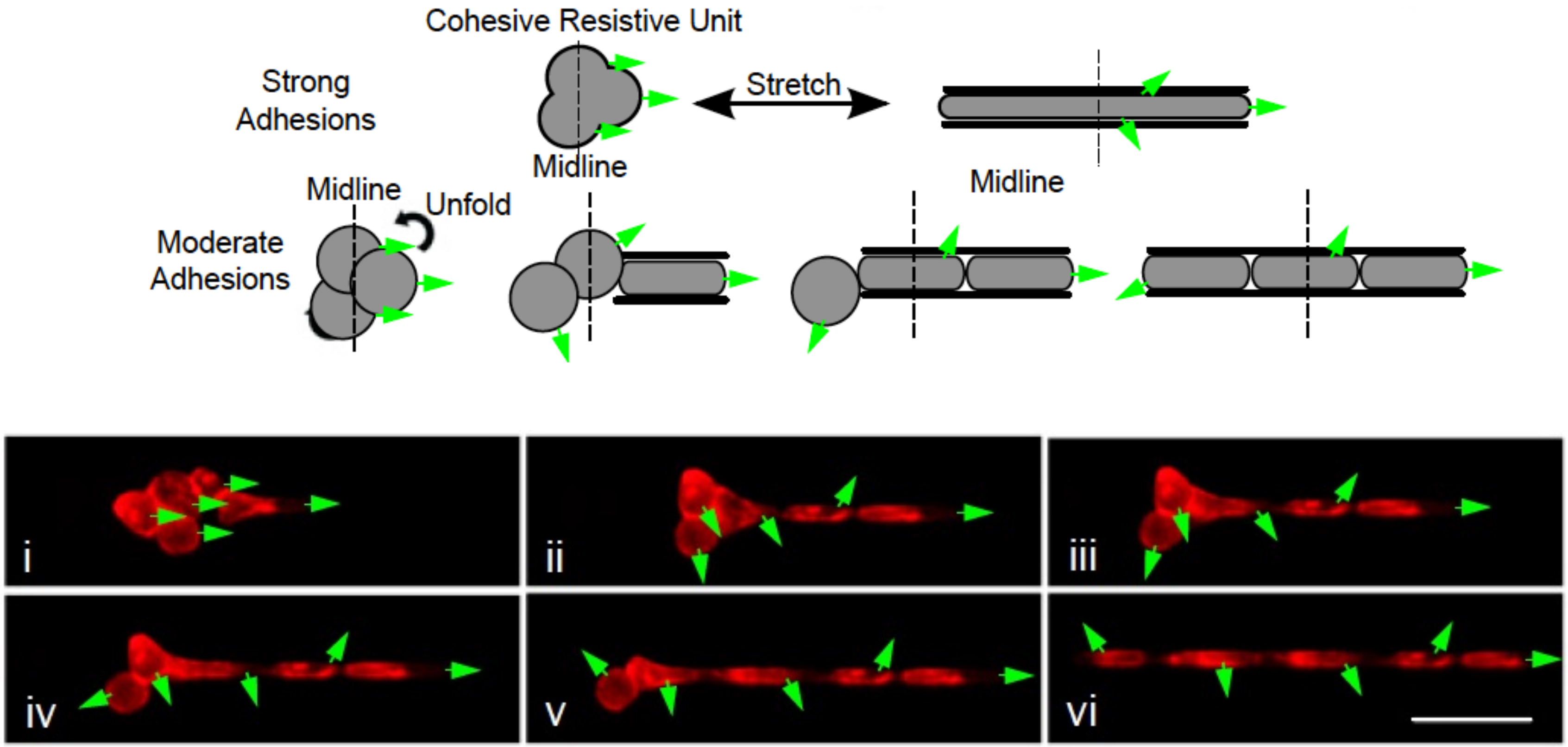

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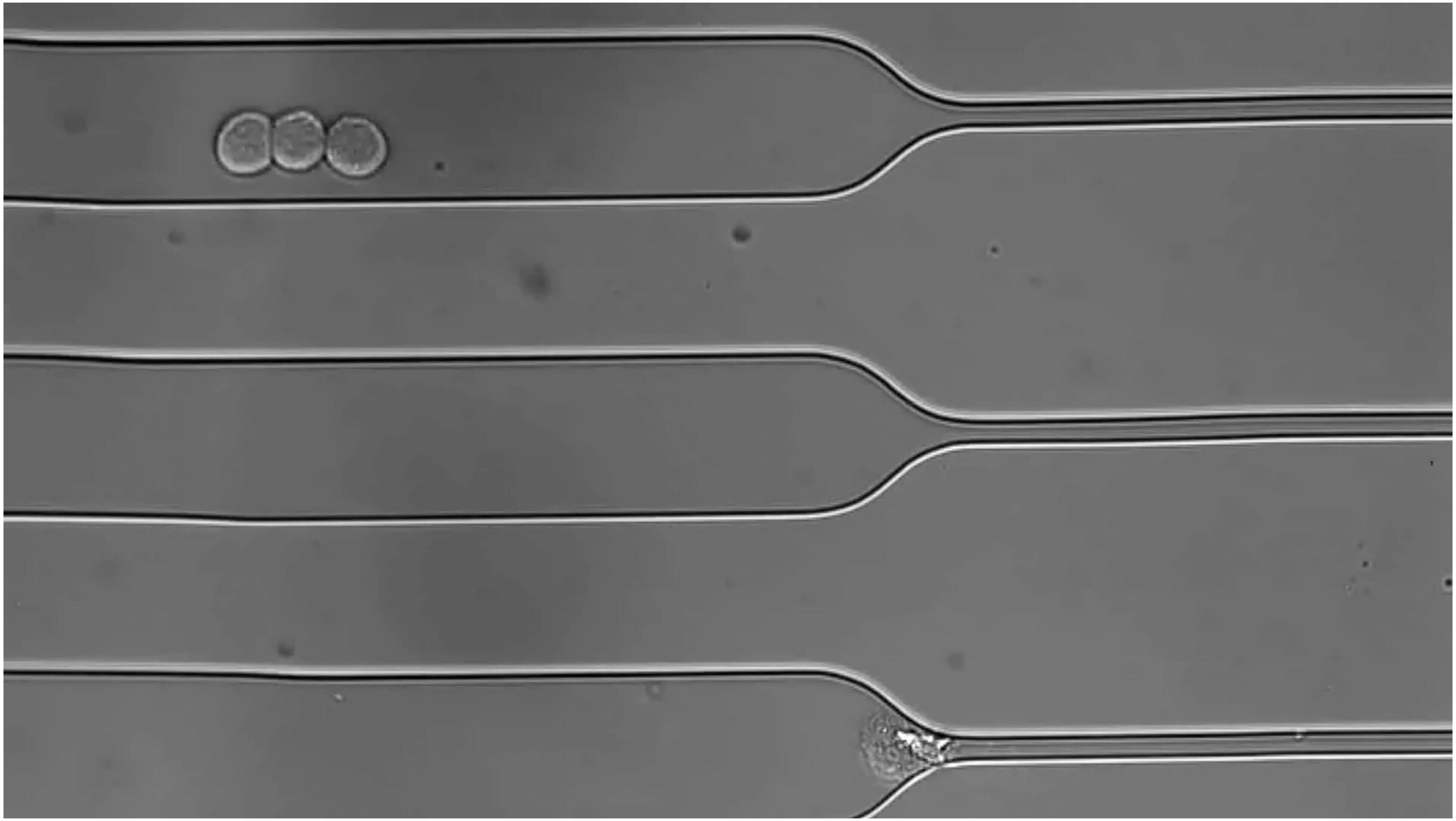

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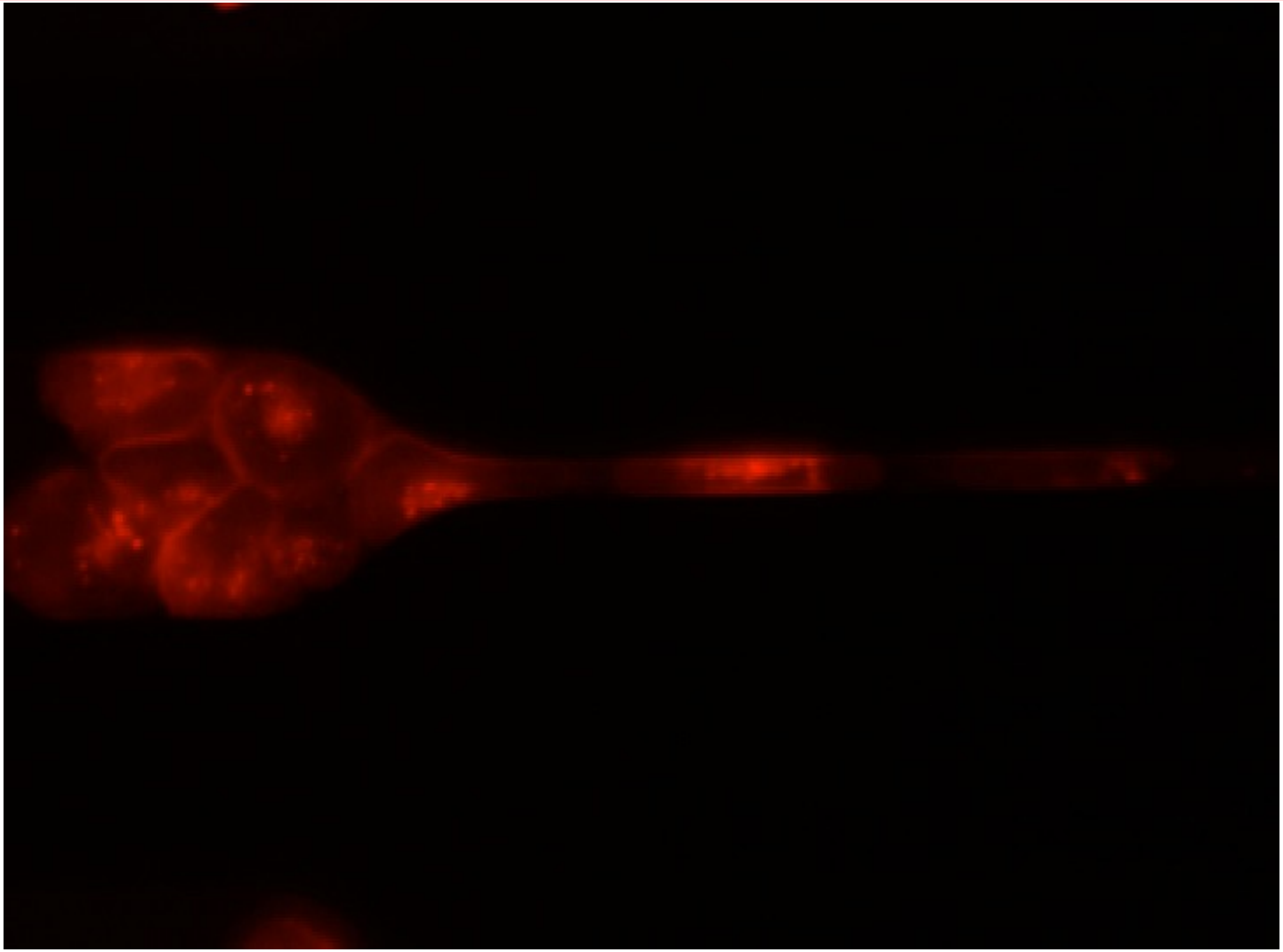
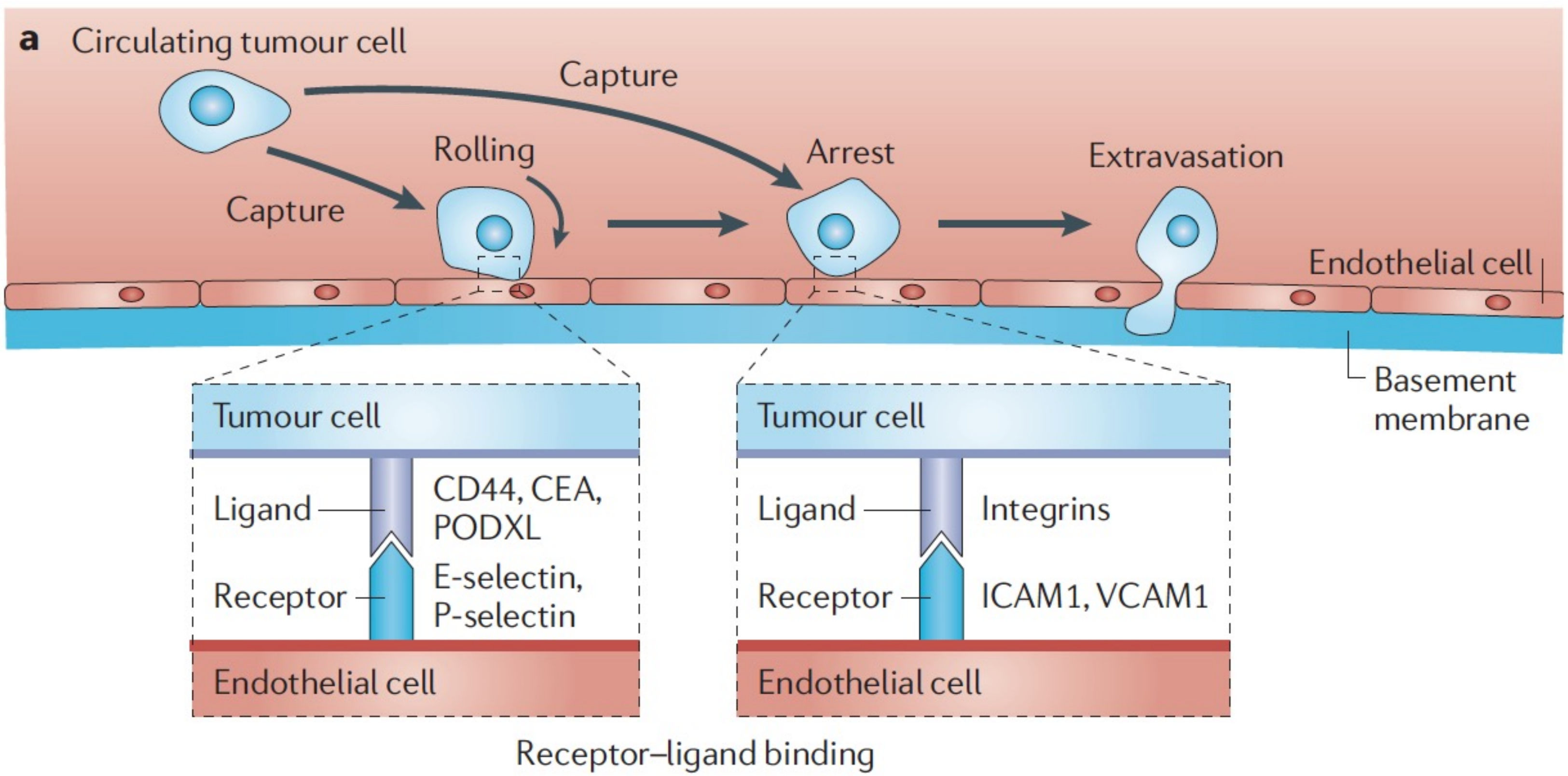
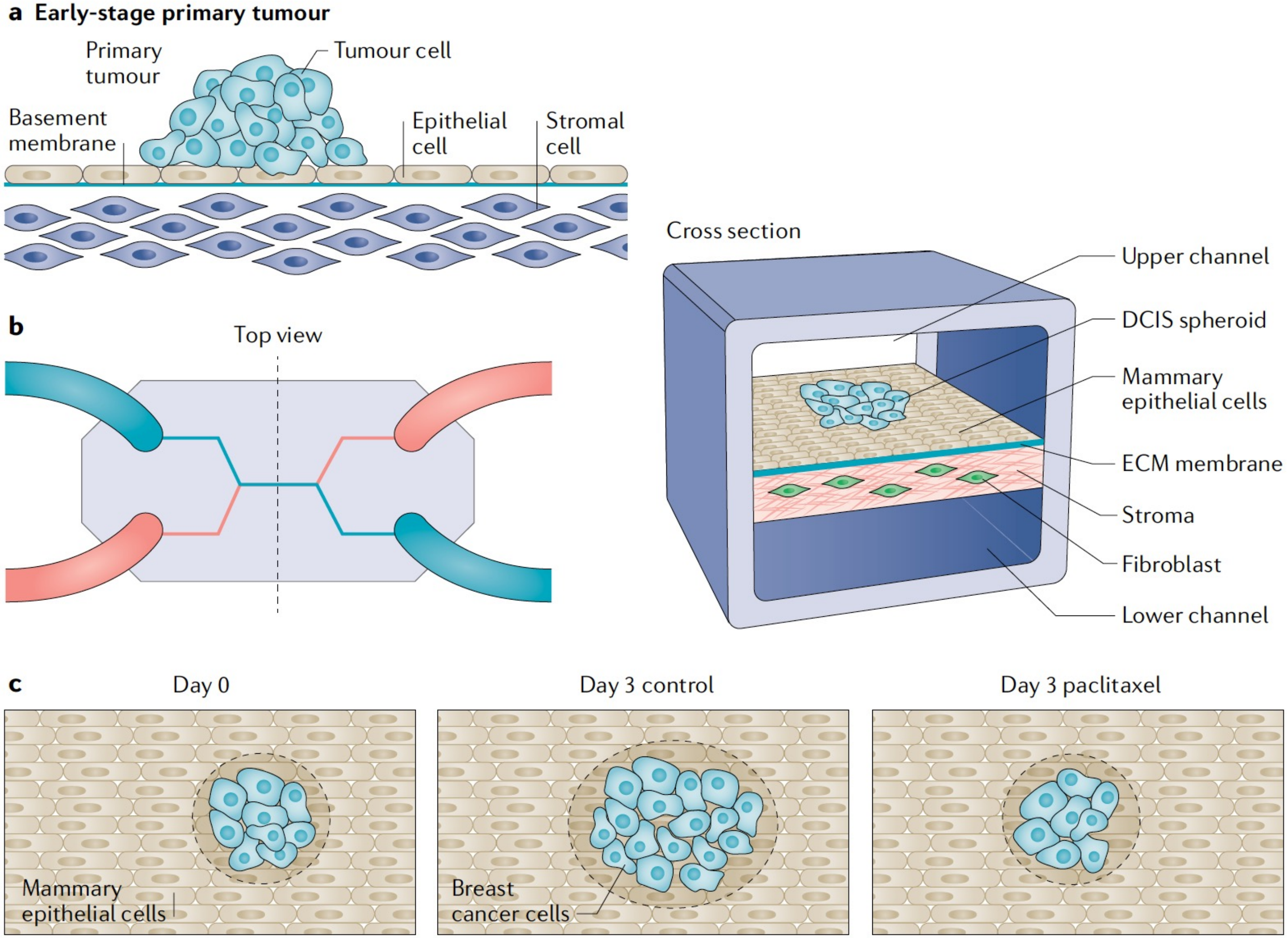


Capture and extravasation

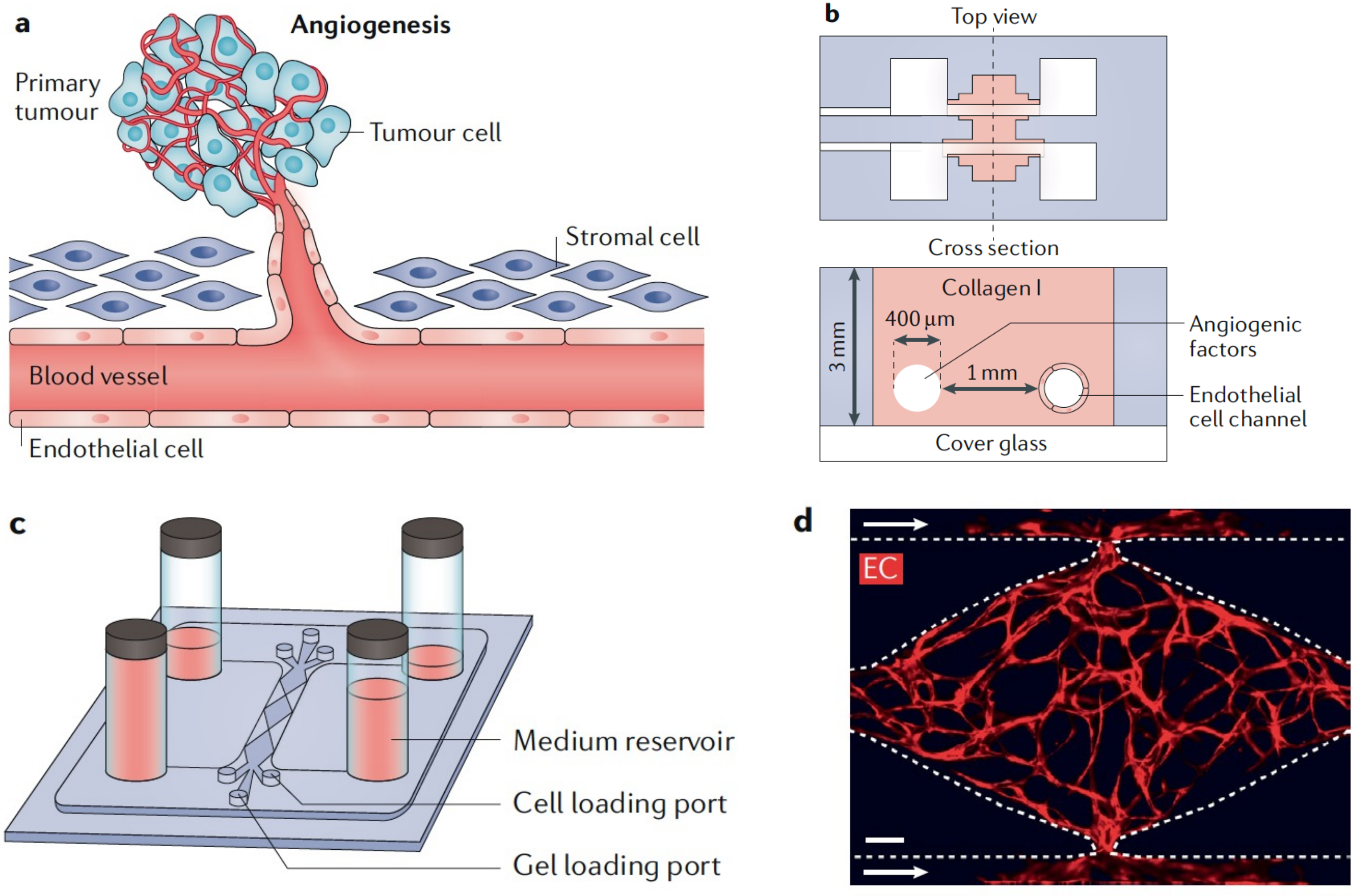
- Rolling with and without slipping
- Transient vs persistent (firm) adhesion
- Shear stress and bond lifetime



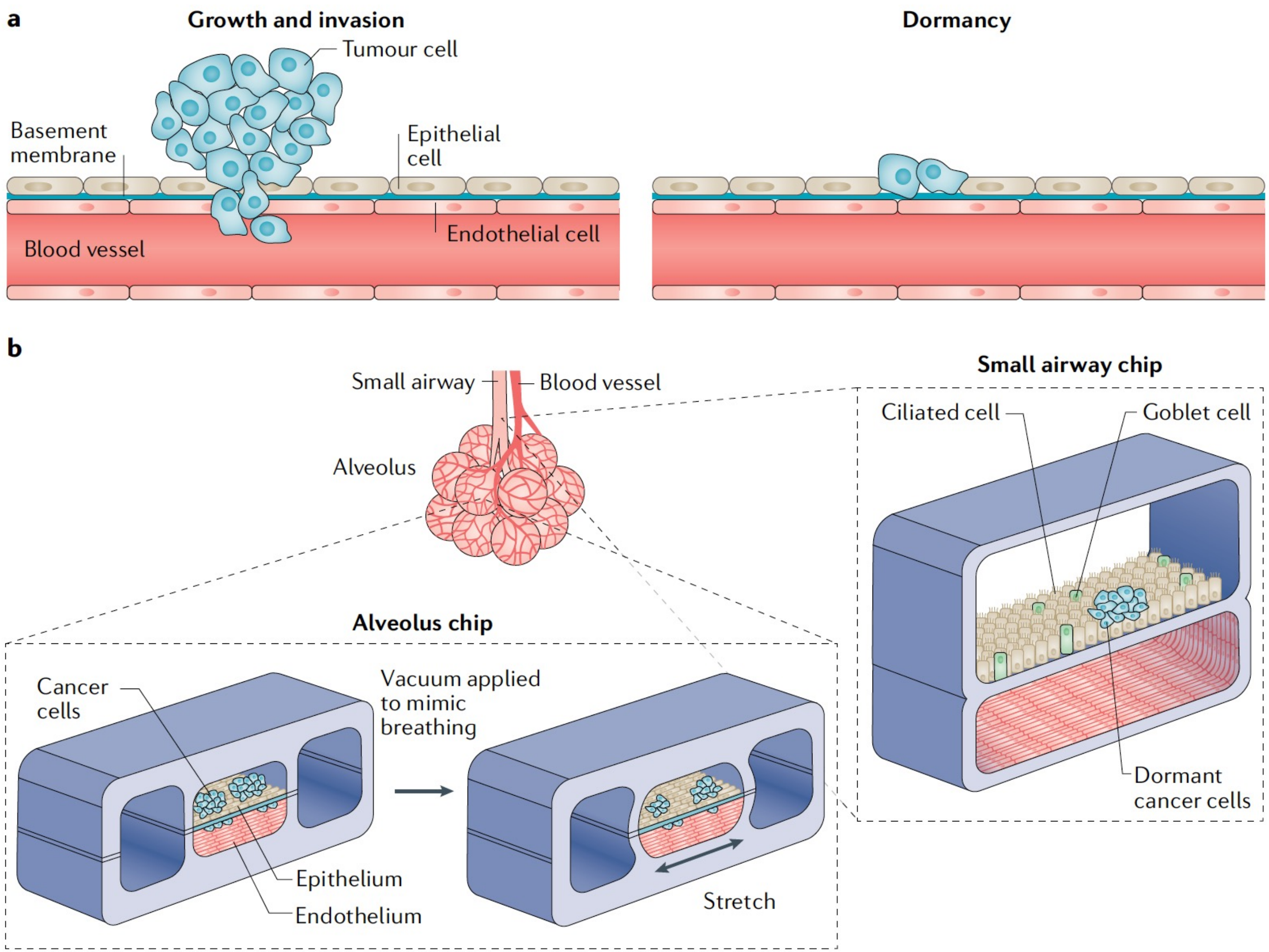
Breast cancer on a chip



Neovascularization on a chip



Lung cancer on a chip



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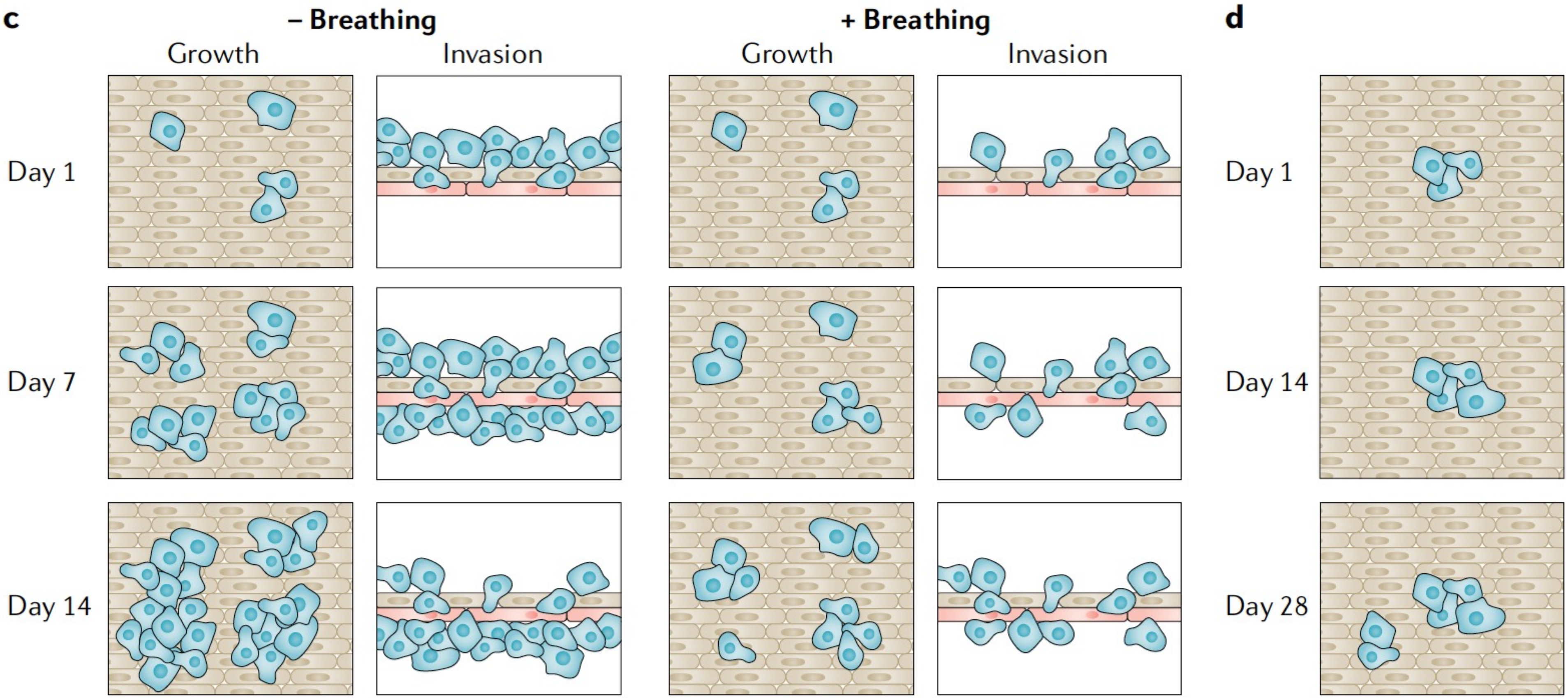
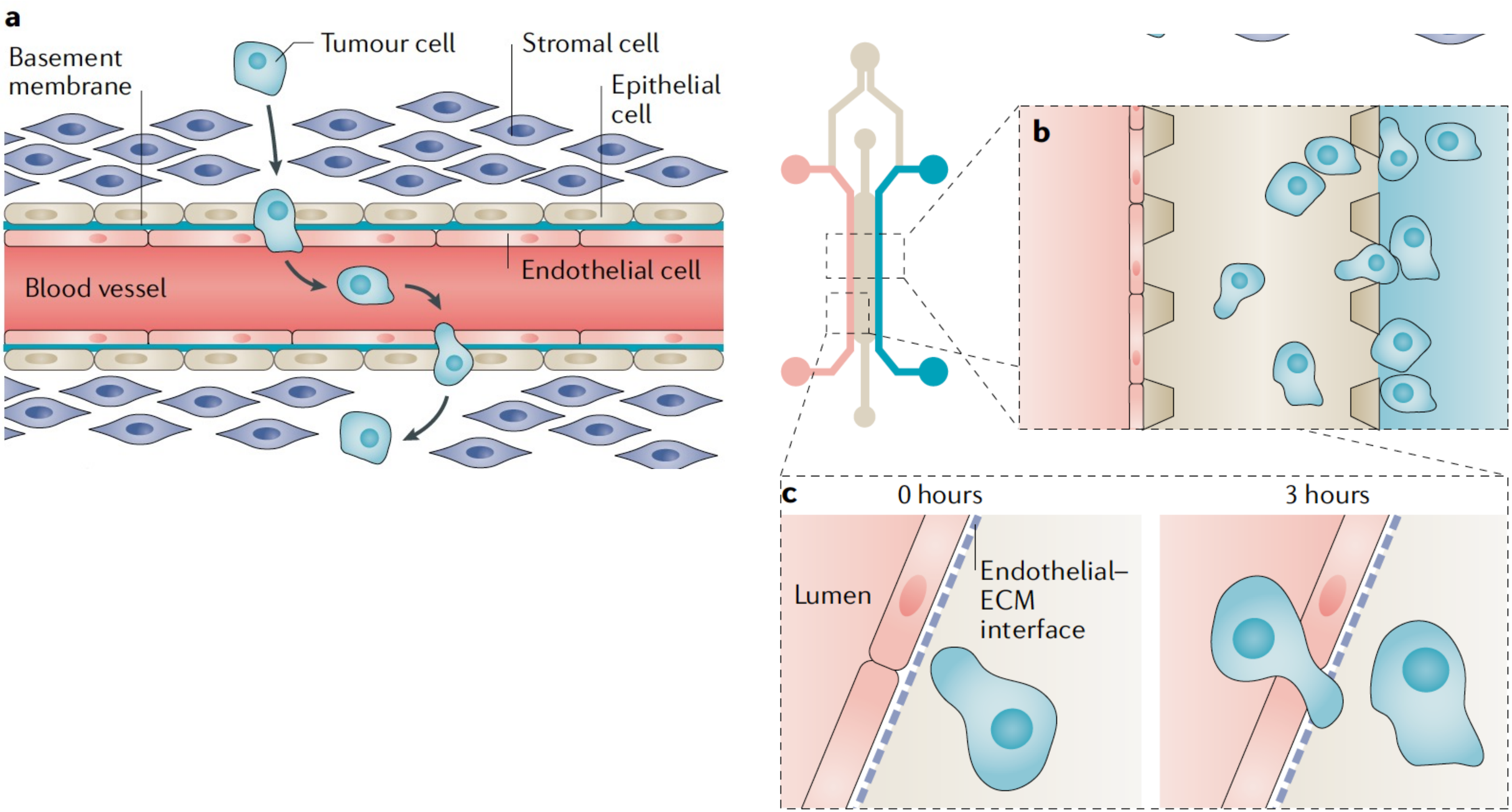


Metastatic cancer on a chip



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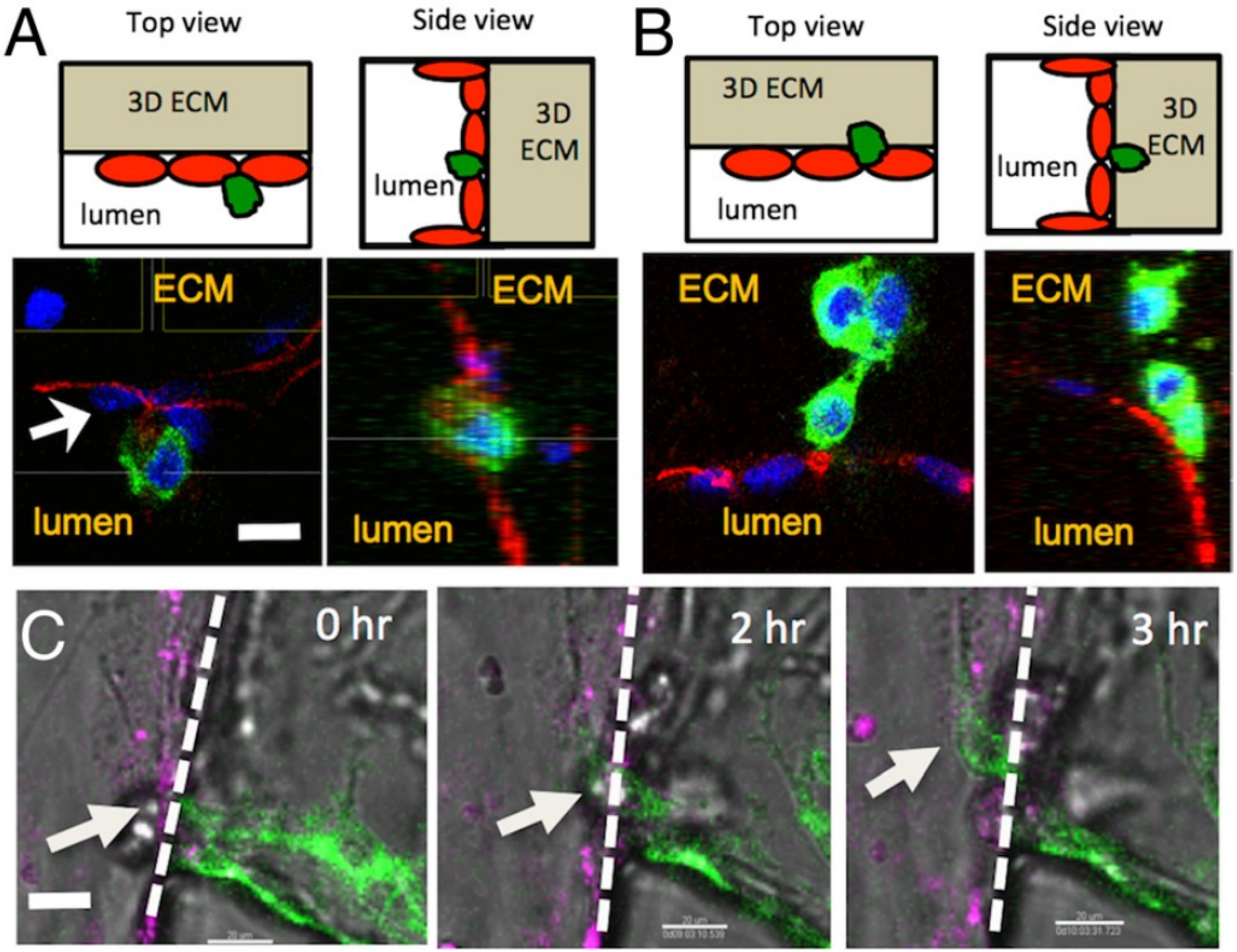

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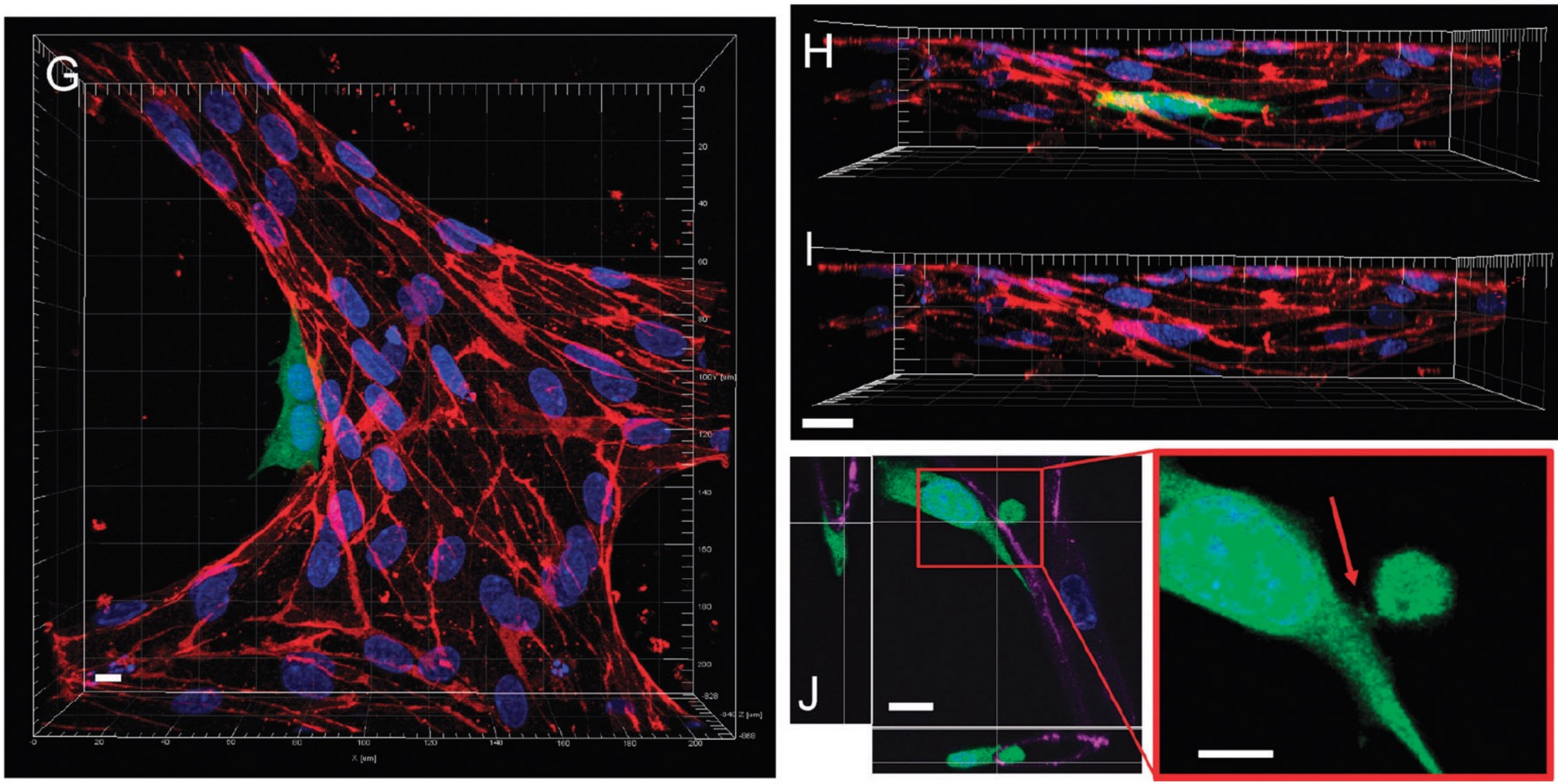

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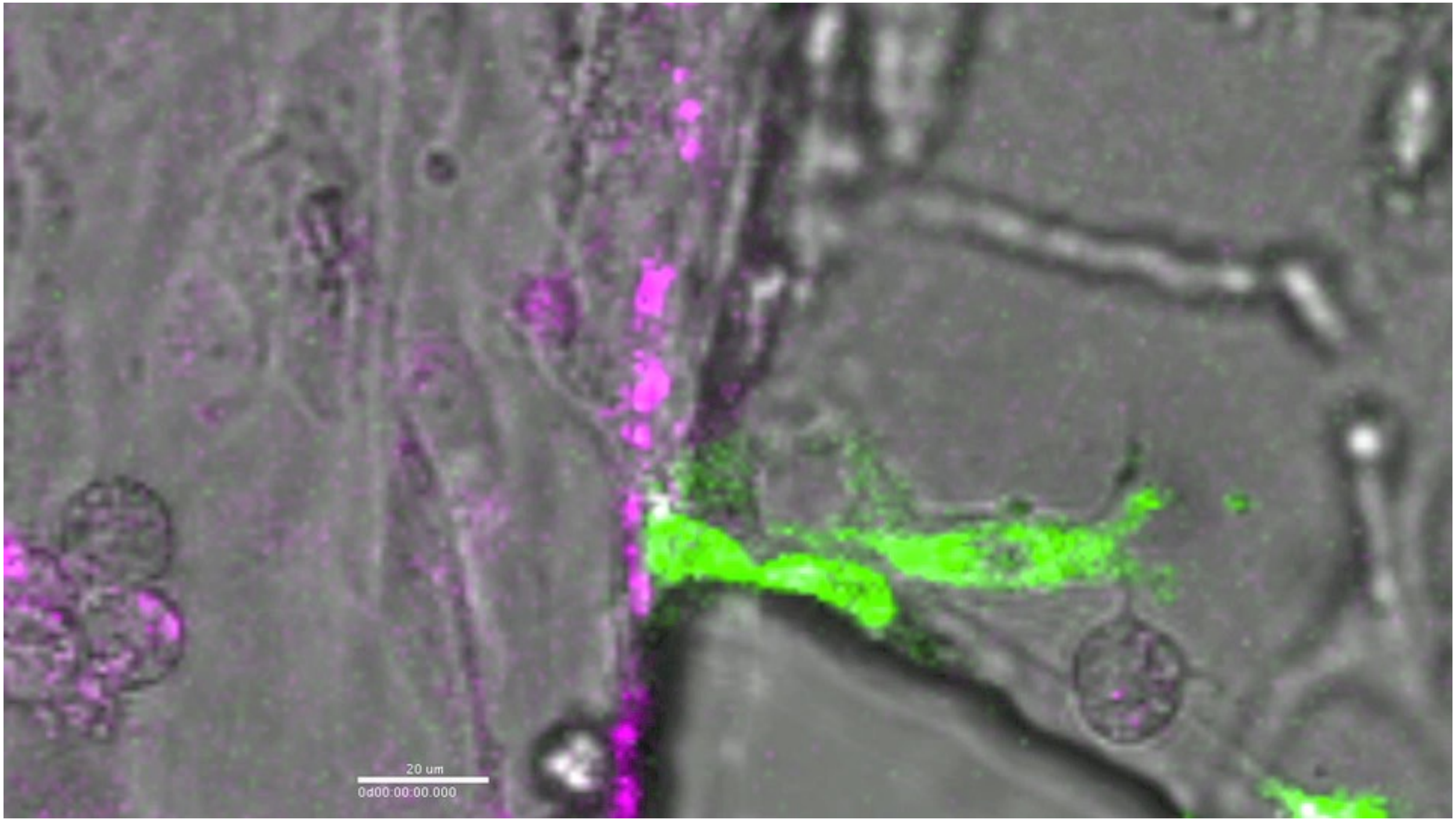
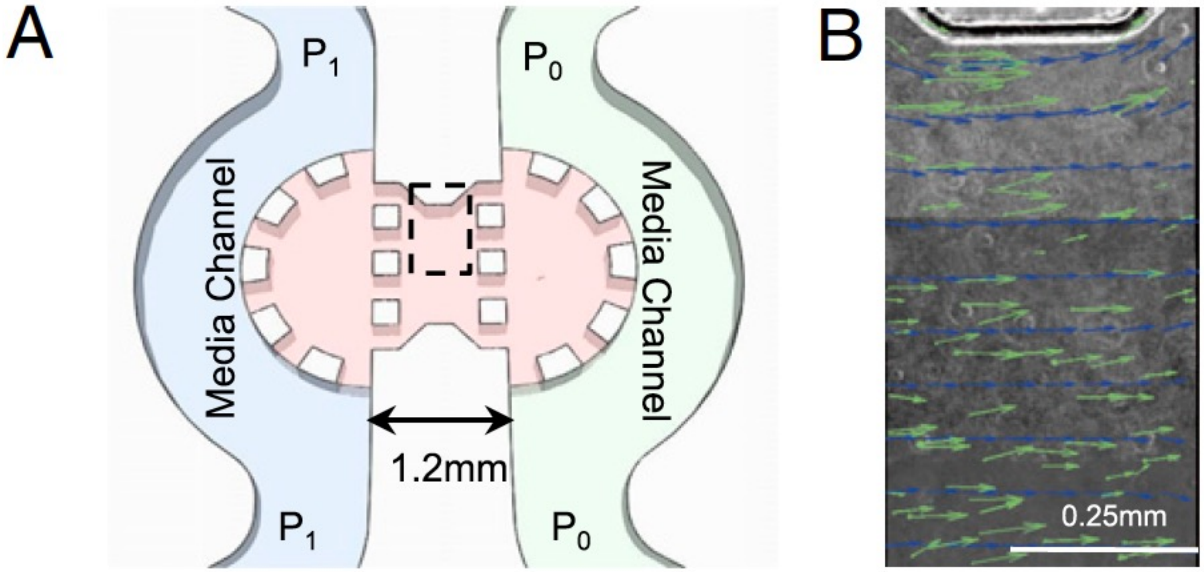
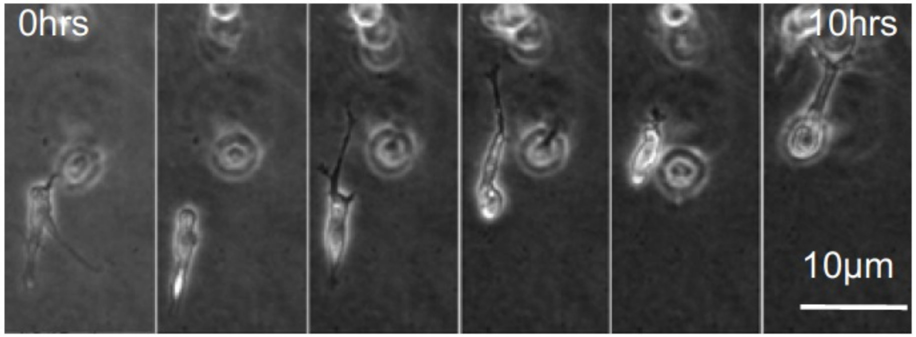
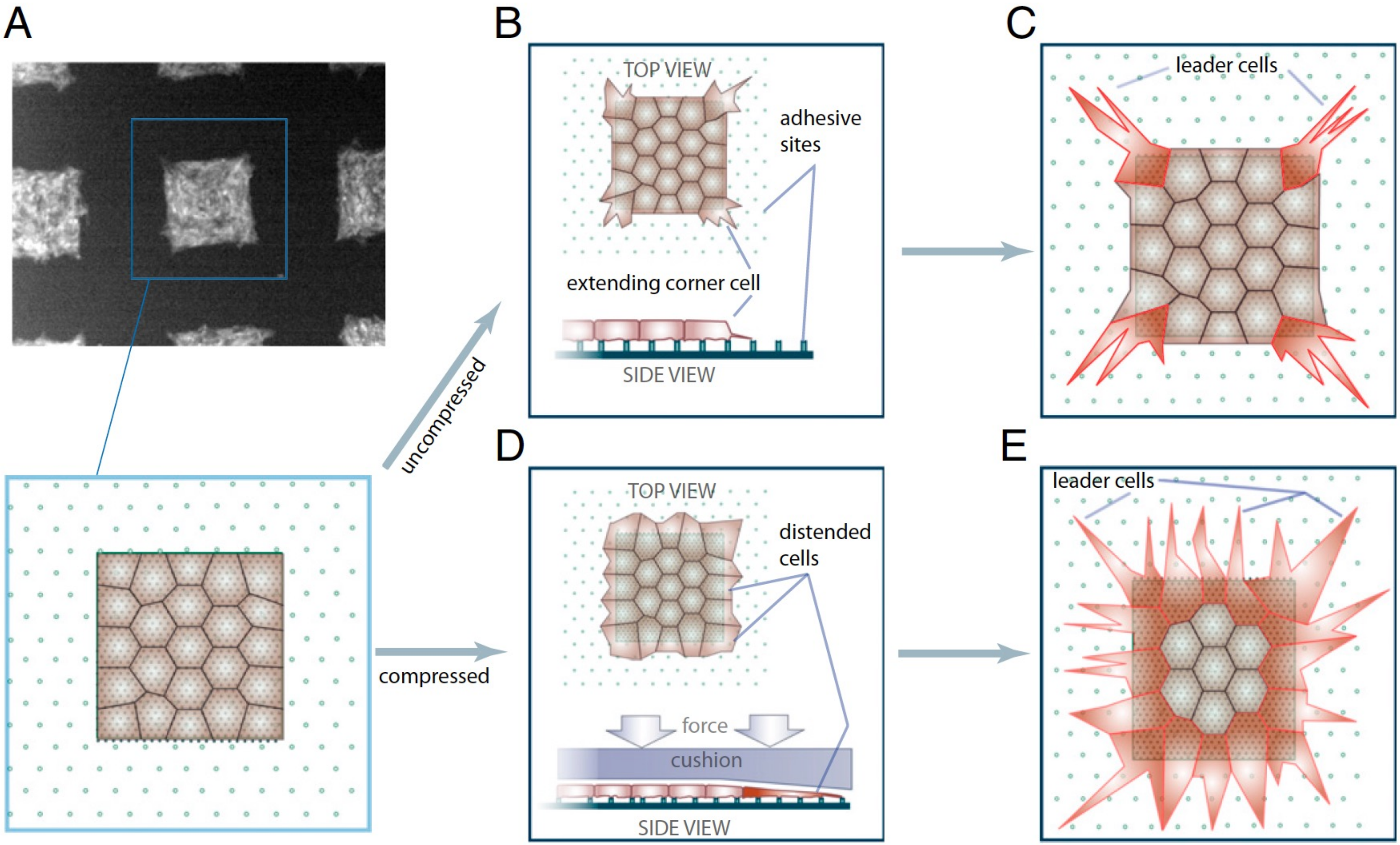


Interstitial flow

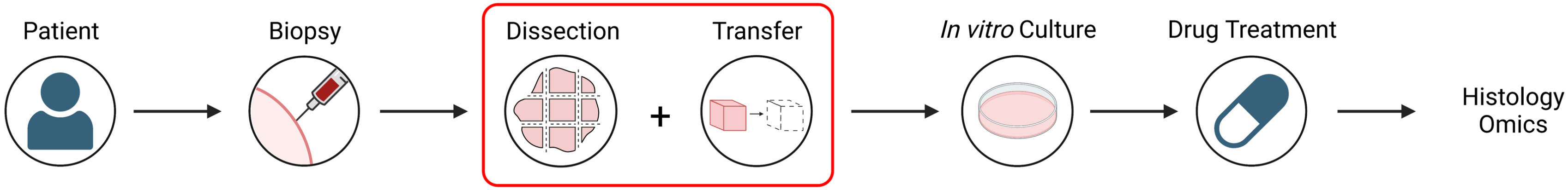




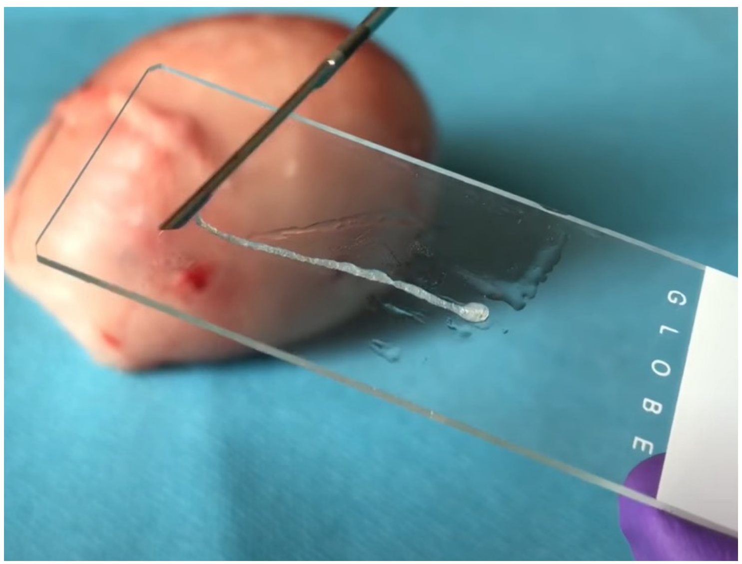
Compression-induced invasion



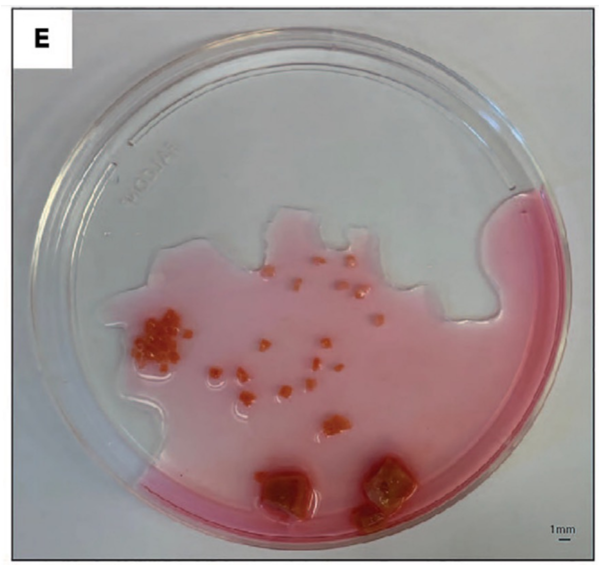
Cuboids



Patient
Biopsy
Dissection
+
Transfer
In vitro Culture
Drug Treatment
Histology
Omics

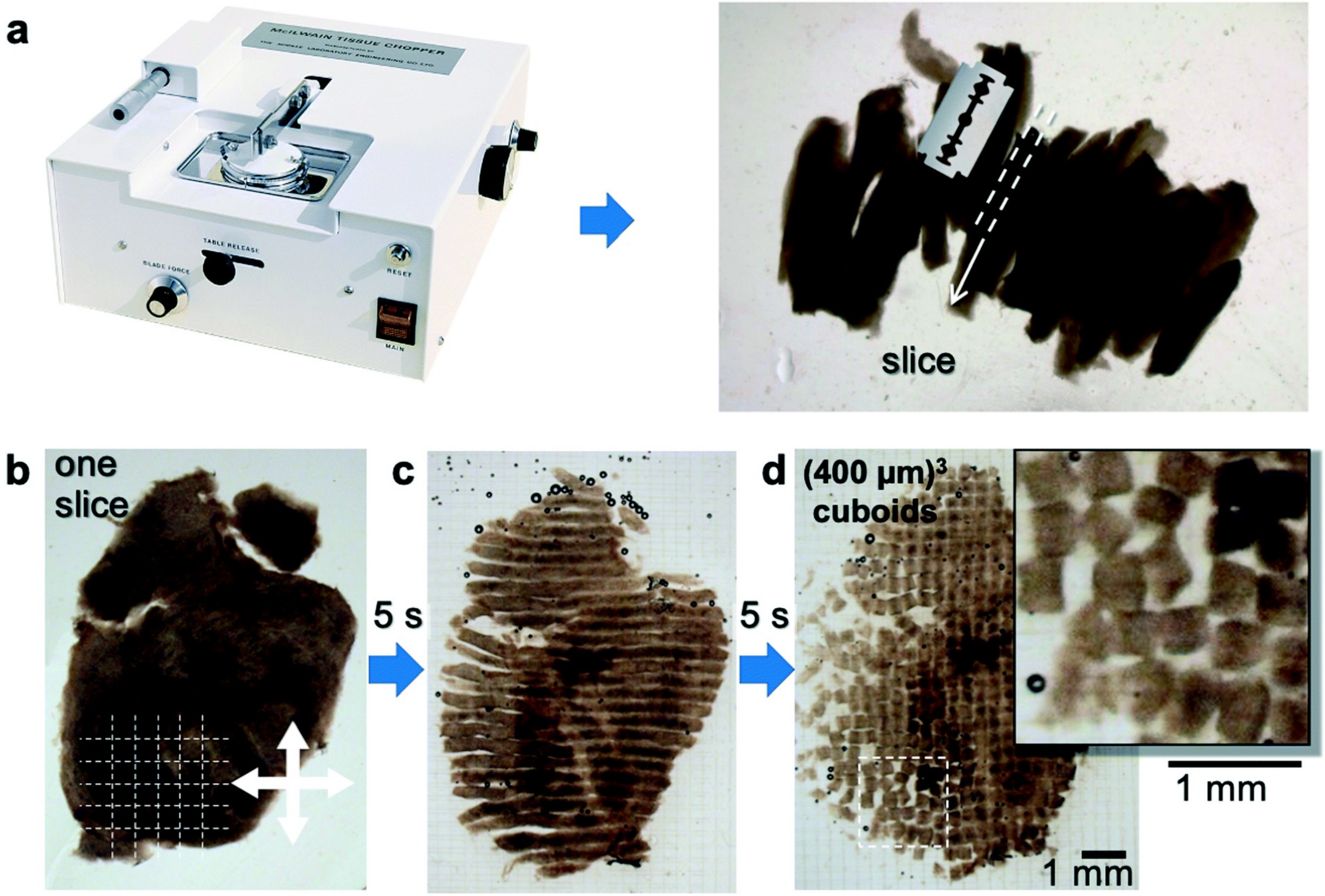


GLOBE



E
1mm

Cuboids


a
McILWAIN TISSUE CHOPPER
TABLE RELEASE
BLADE FORCE
RESET
MAIN
slice
b
one
slice
5 s
c
5 s
d
(400 µm)³
cuboids
1 mm
1 mm

Vibratome sectioning