Biomechanics in Organ-on-Chip Systems

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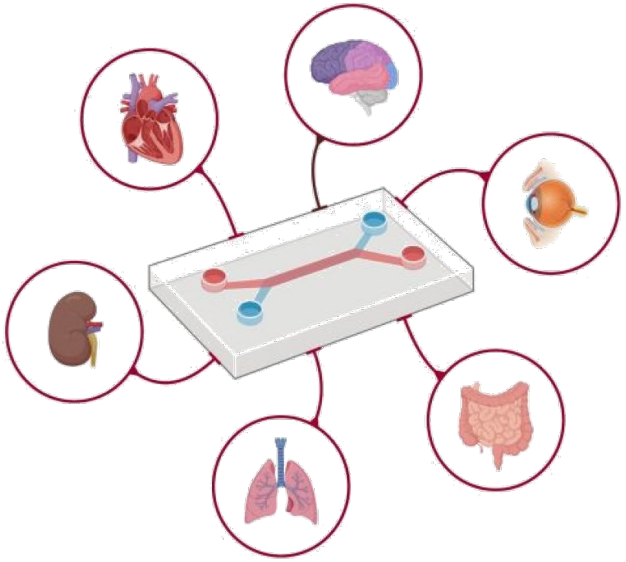
PART 2

OOCs are useful tools for preclinical experimentation



Pharmacology & Toxicology

Alternative to animal testing

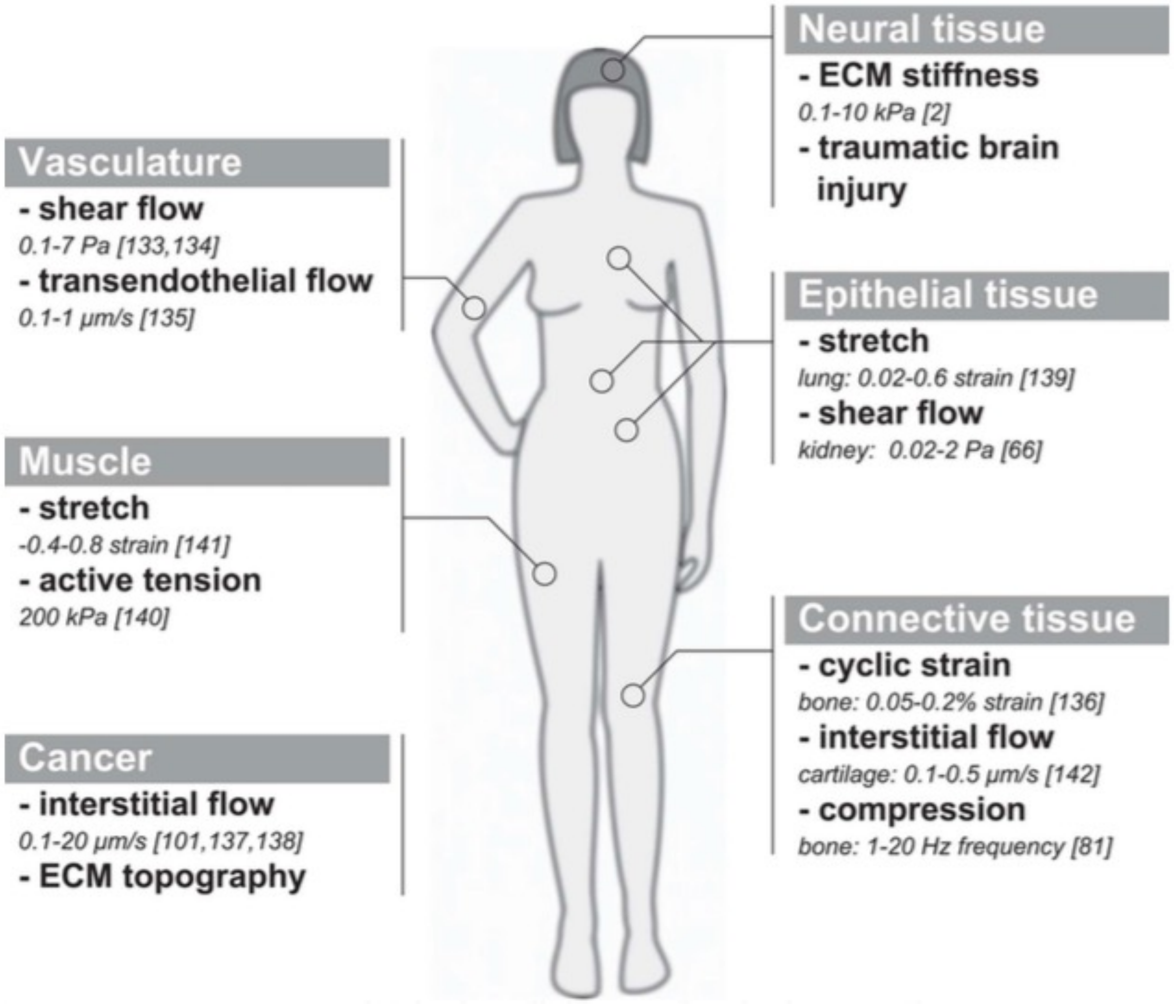
Biomechanics

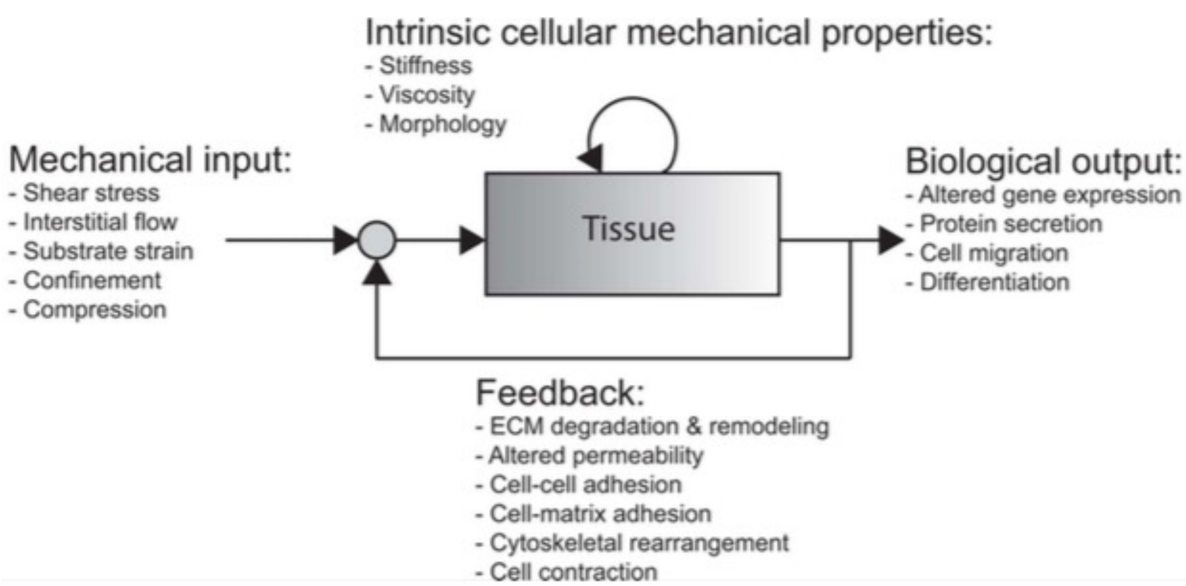
Controlled cell responses

Personalized medicine

Disease modeling

Biomechanics: from tissue level to cell level





→ Mechanobiology

Polacheck WJ et al. (*Lab Chip*, 2013)

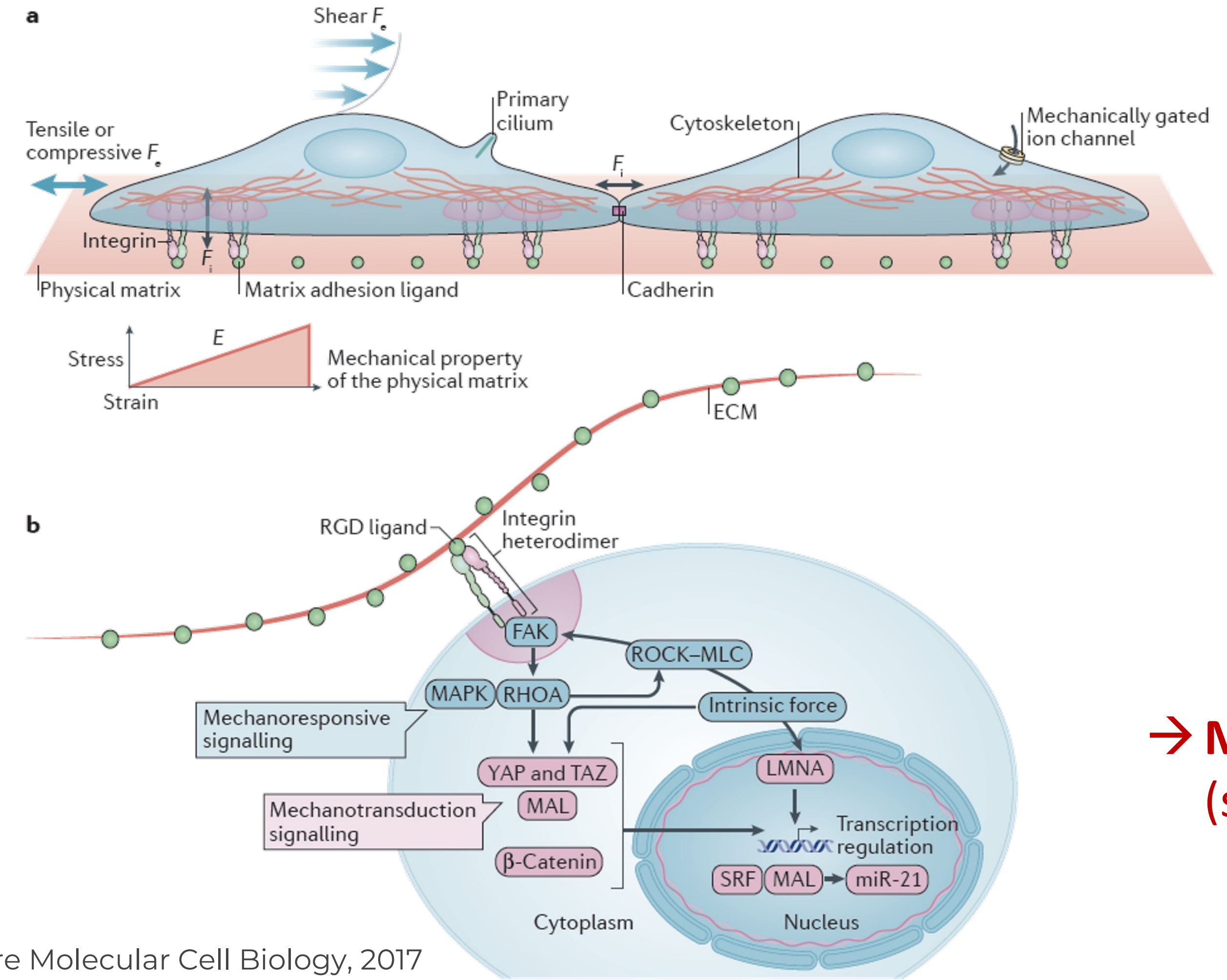
Mechanobiology

- Explains how cells sense and respond to their environment.

- **Critical for understanding development, disease progression, and tissue engineering.**

- Applications:
    - Regenerative medicine (mechanical cues direct stem cell differentiation)
    - Cancer (understanding tumor stiffness and metastasis)
    - Cardiovascular disease (remodeling of blood vessels)
    - Etc.

How does a cell sense a mechanical cue?



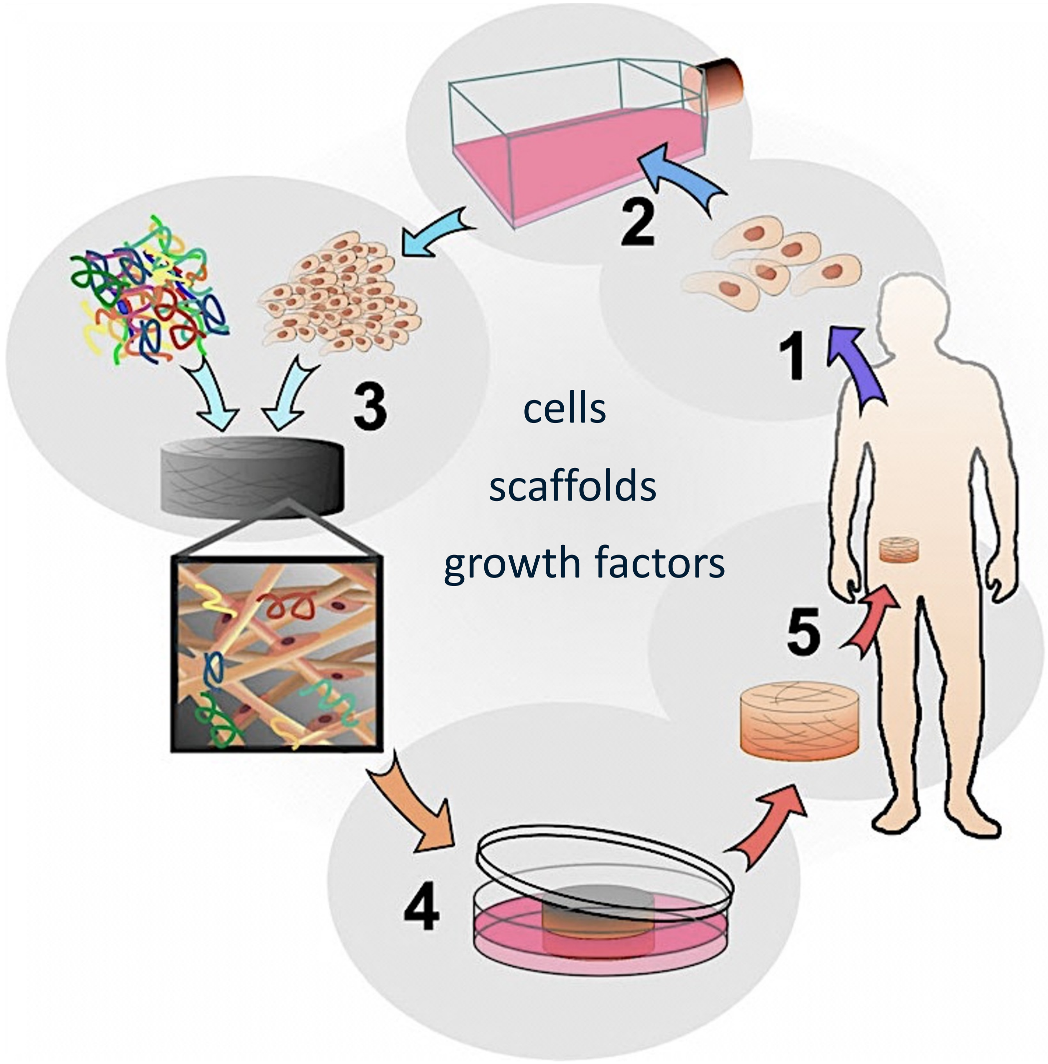
Vining, KH et al., Nature Molecular Cell Biology, 2017

→ Mechanosensing structures:

- Integrins
- Ion channels
- Focal adhesions
- Cadherins
- Etc.

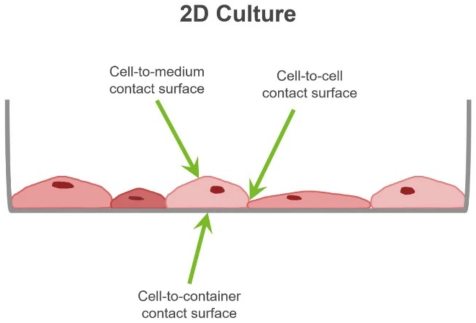
→ Mechanotransduction
(signaling pathway)

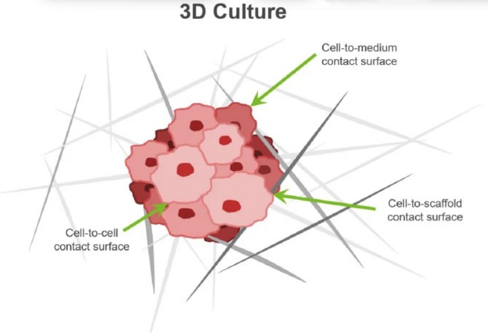
Tissue engineering concepts

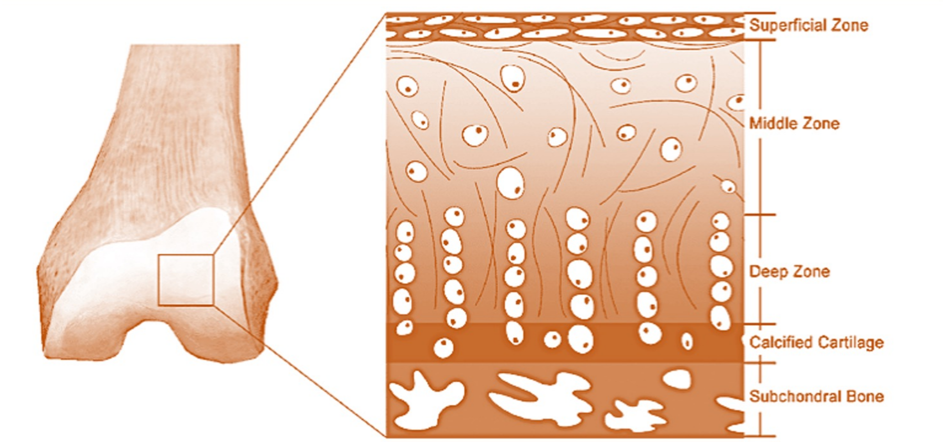


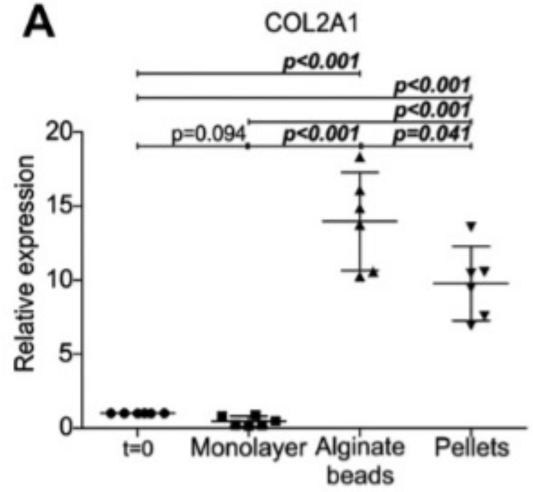
The goal is to restore, maintain, or improve damaged tissue or organs

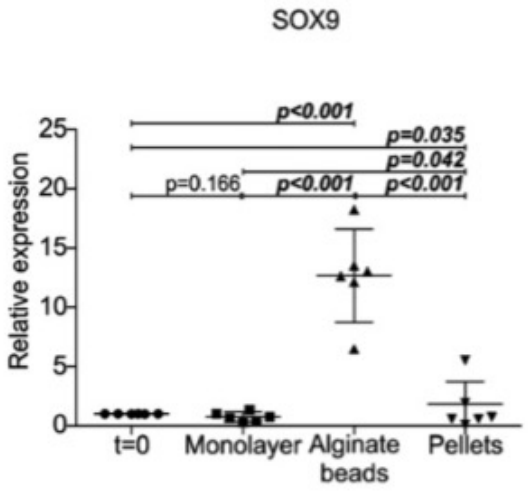
Chondrocytes culture:
3D encapsulation vs 2D monolayers

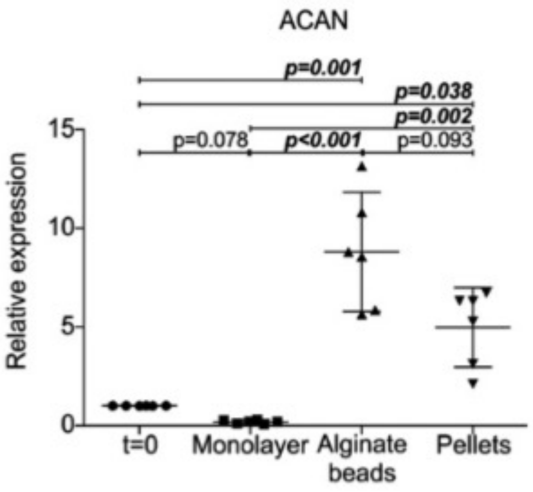






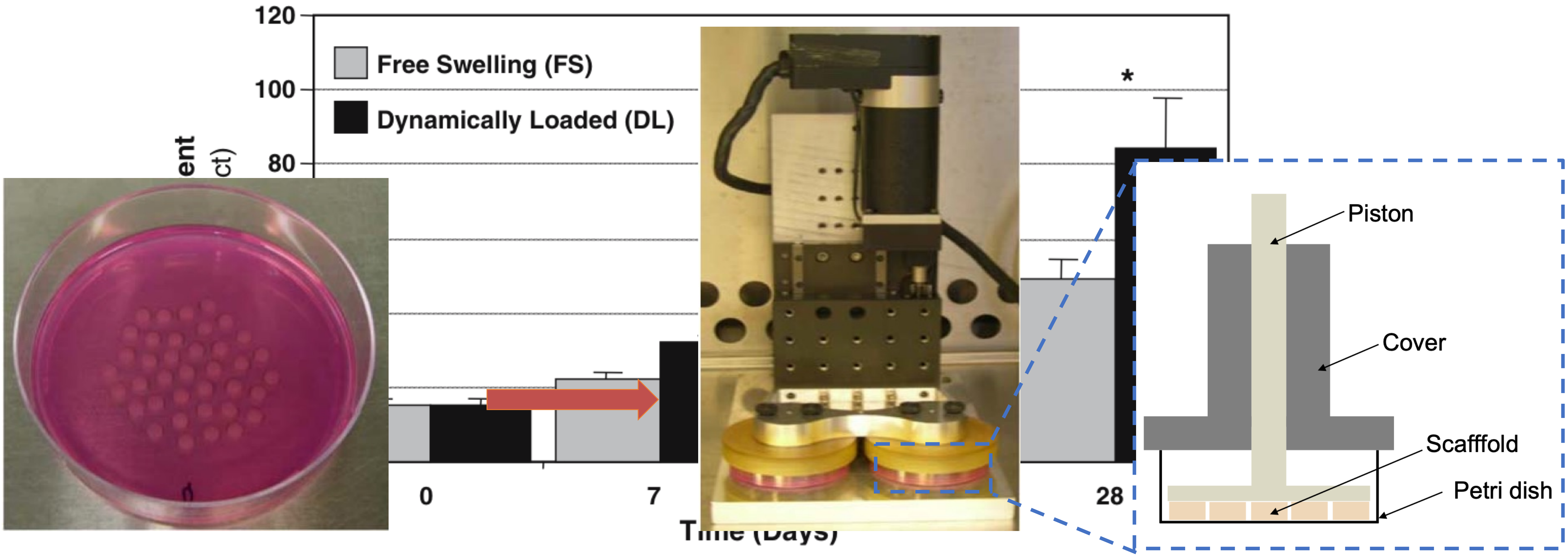






Hooi YN et al. (2017), Caron et al. (*Osteoarthritis and cartilage*, 2012)

Engineered Tissue Improvements by Mechanics



Mauck et al. Biomechanics and Modeling in Mechanobiology, 2007

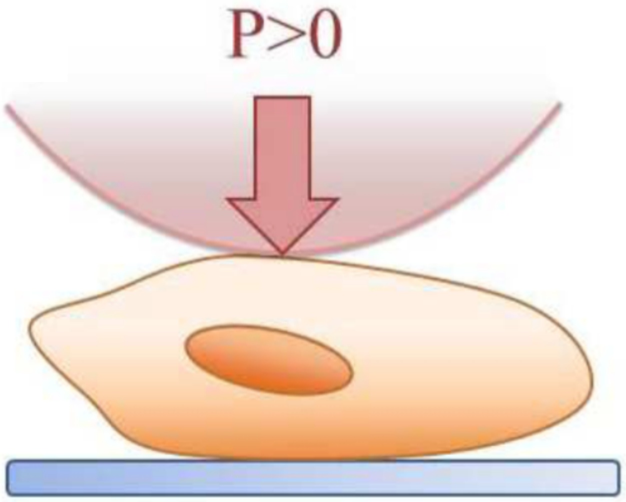
Main advantages of organ-on-chip systems

- Control over **spatiotemporal organization** of *in vivo*-like tissue architectures
- Ability to precisely control the **amount**, **duration** and **intensity** of the biomechanical stimuli
- Capability of **monitoring in real time** the effects of applied mechanical forces on cell, tissue and organ functions.

Biomechanics in microsystems

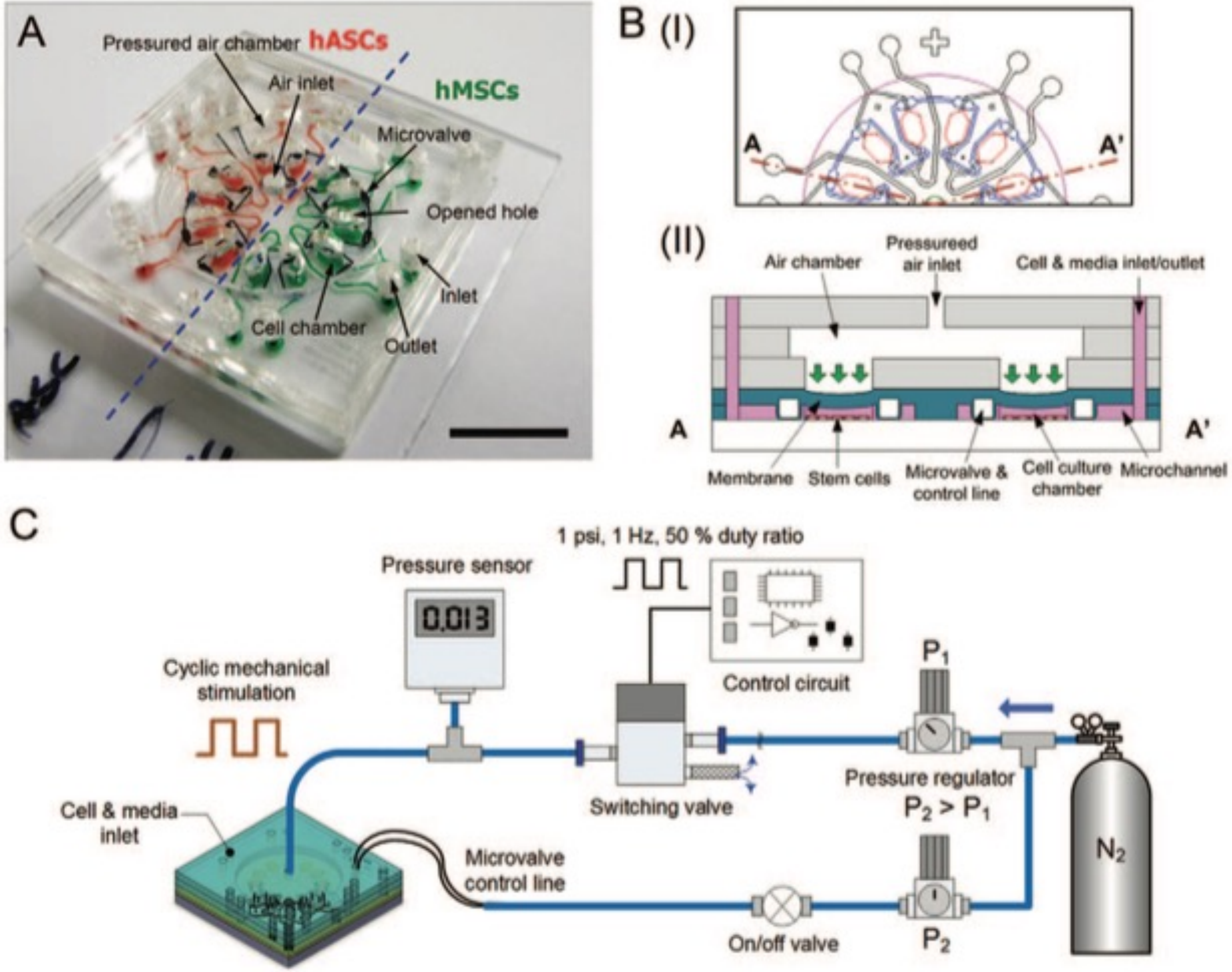
1. Compression

- Mechanical loading is a positive stimulus for **bone formation** and is an essential factor in **bone metabolism**



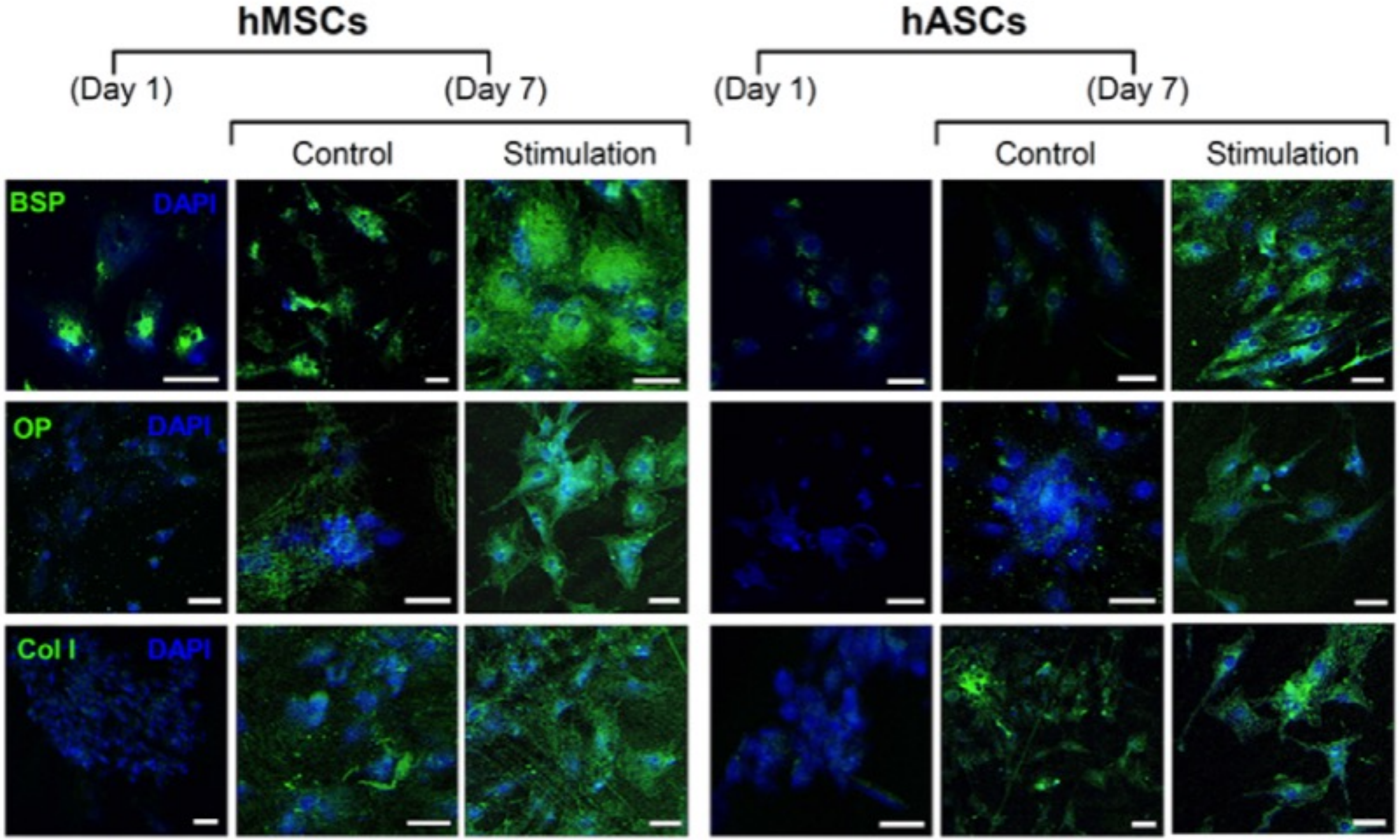
Compression
(Pneumatic)

Microchip to apply compression on stem cells



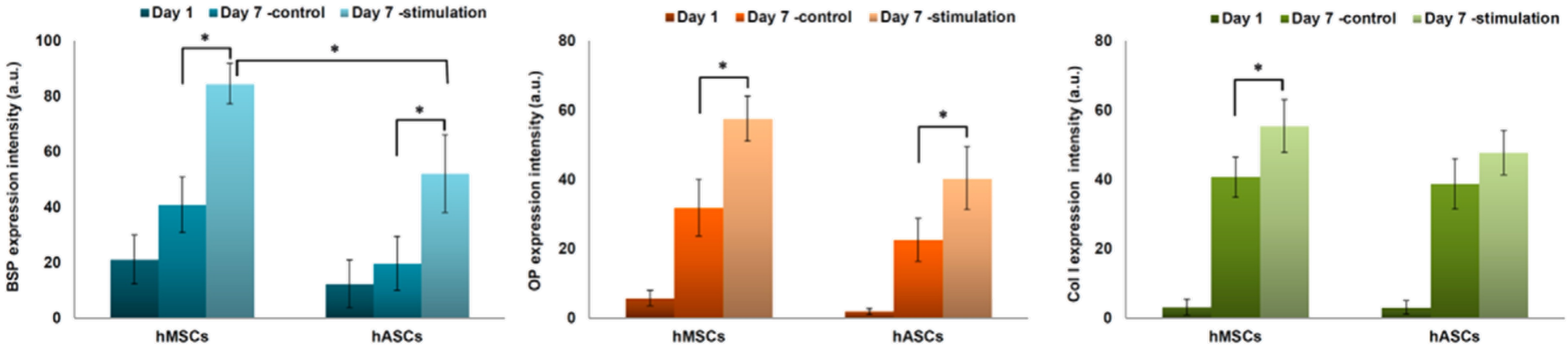
Sang-Hyug Park et al. (*PLOS one*, 2012)

Osteogenic induction by compression



Sang-Hyug Park et al. (*PLOS one*, 2012)

Osteogenic induction by compression



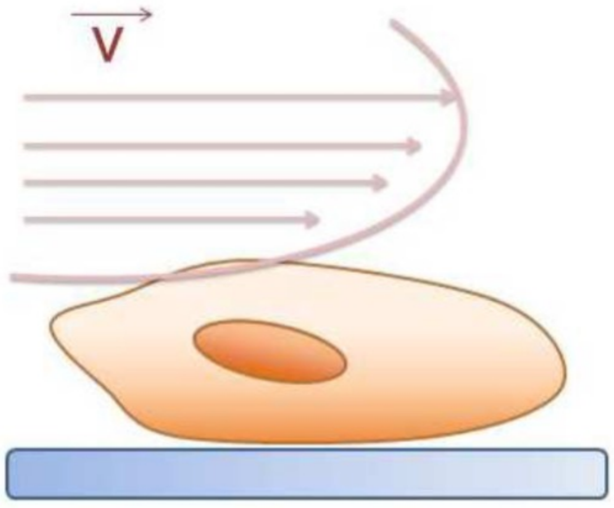
<u>Conclusions:</u>

- stimulated hMSCs and hASCs showed increased osteogenic gene expression compared to non-stimulated groups.
- The hMSCs were more sensitive to mechanical stimulation and more effective towards osteogenic differentiation than the hASCs under these modes of mechanical stimulation

Sang-Hyug Park et al. (*PLOS one*, 2012)

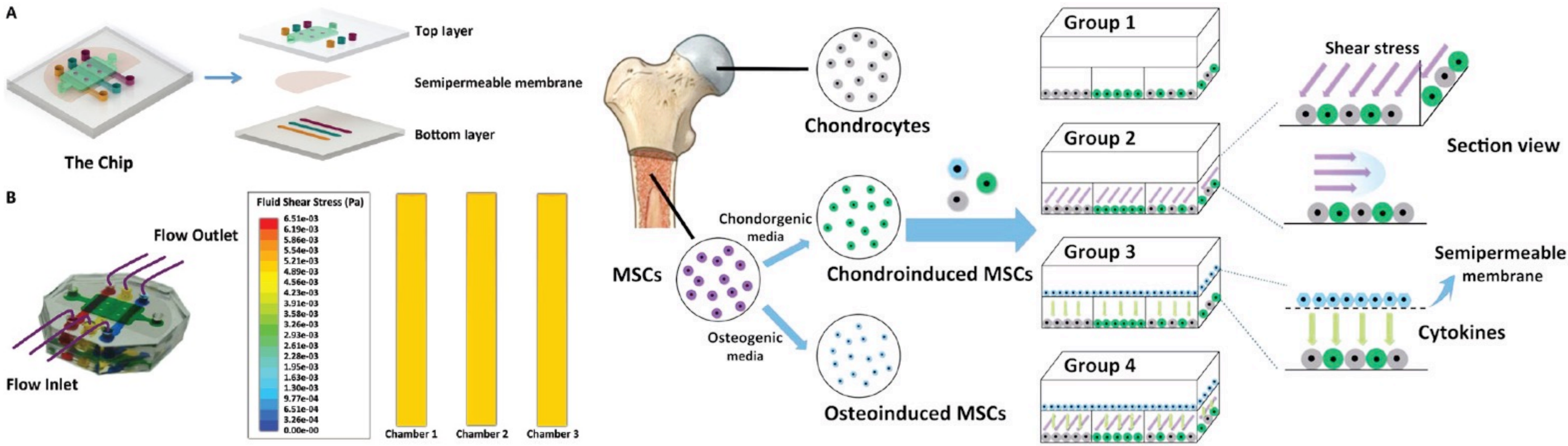
2. Shear stress

- How shear stress can alter the formation of **cartilage** in combination with signaling from of osteoinduced MSCs



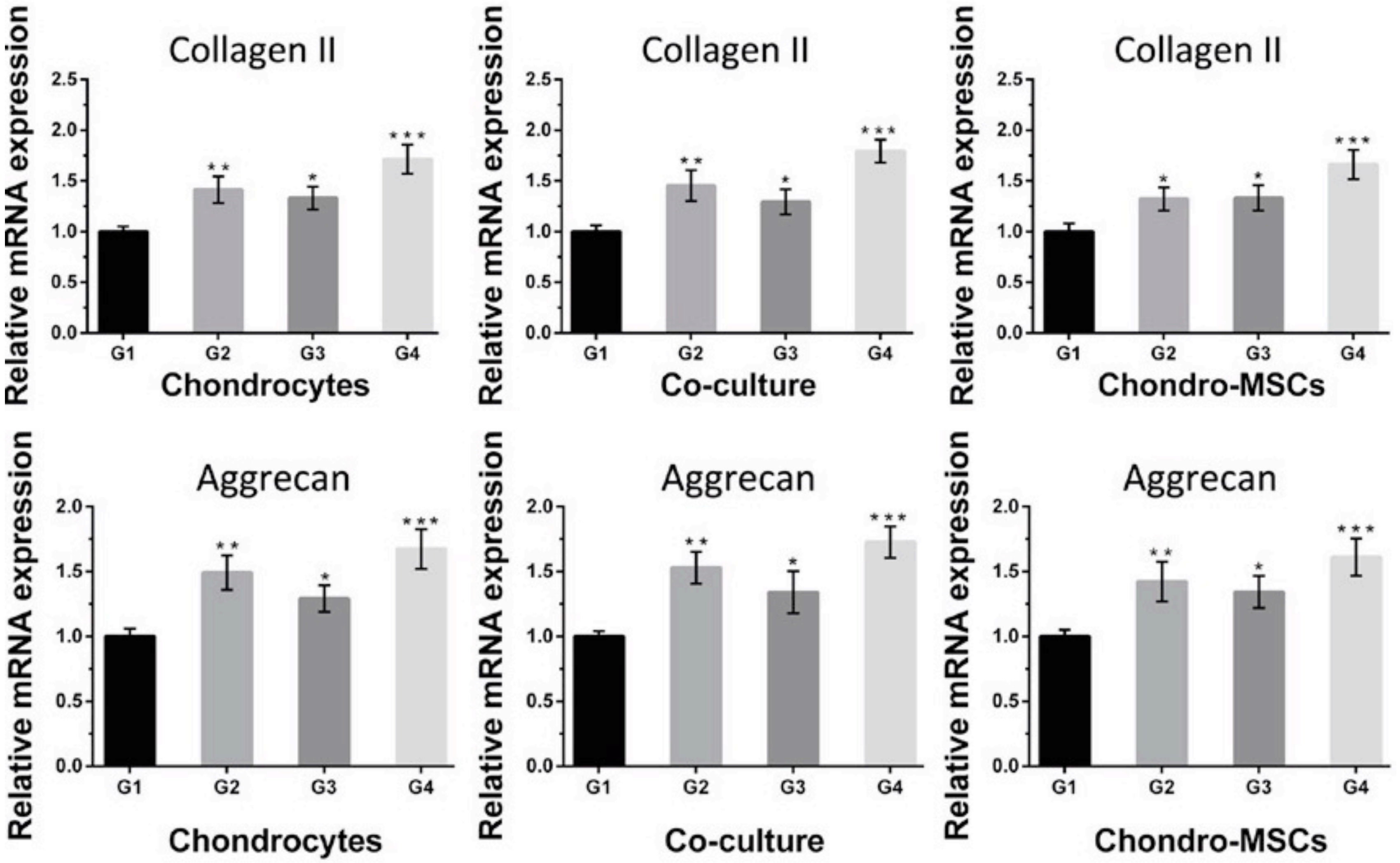
Shear stress

Two-layer device mimicking intersitital flow shear stress in articular cartilage



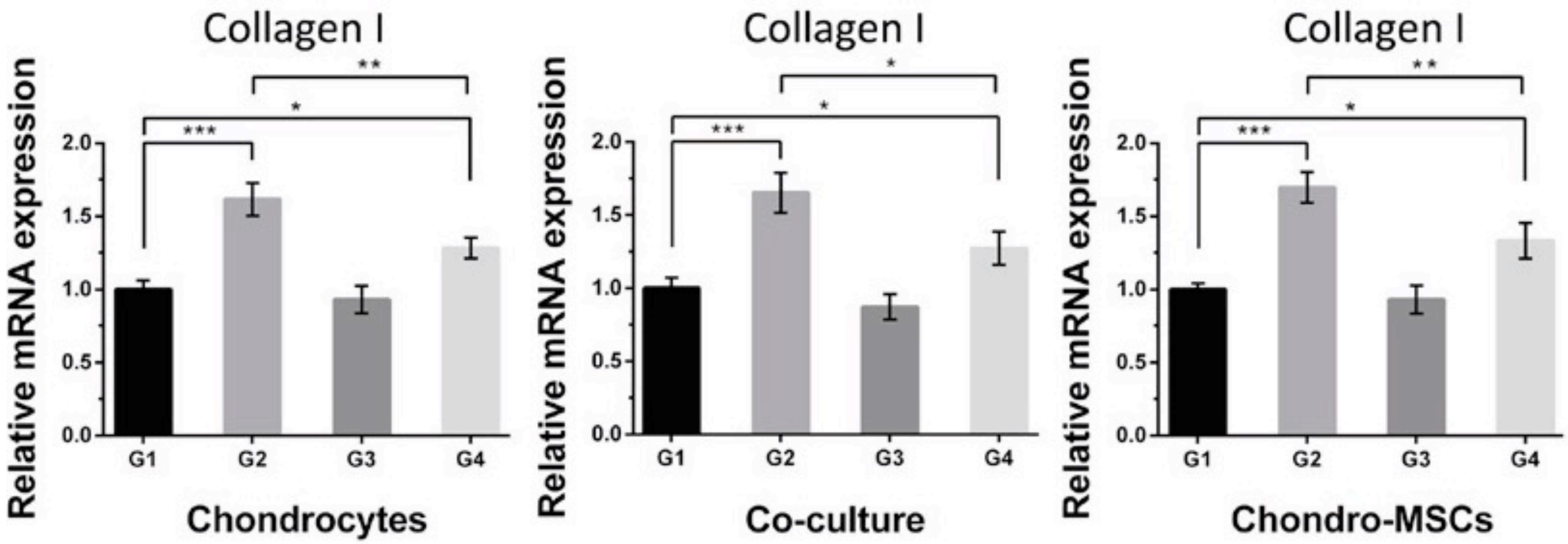
Xuanwen Bao et al. (*Molecular Medicine Reports*, 2018)

Synergy of shear stress and osteoinduced MSCs on chondrogenic expressions



G1: control
G2: shear stress
G3: cytokines release from ostoinduced cells
G4: synergy mechanics (shear stress) + biochemical cues

Synergy of shear stress and osteoinduced MSCs on chondrogenic expressions



G1: control
G2: shear stress
G3: cytokines release from ostoinduced cells
G4: synergy mechanics (shear stress) + biochemical cues

Conclusions:

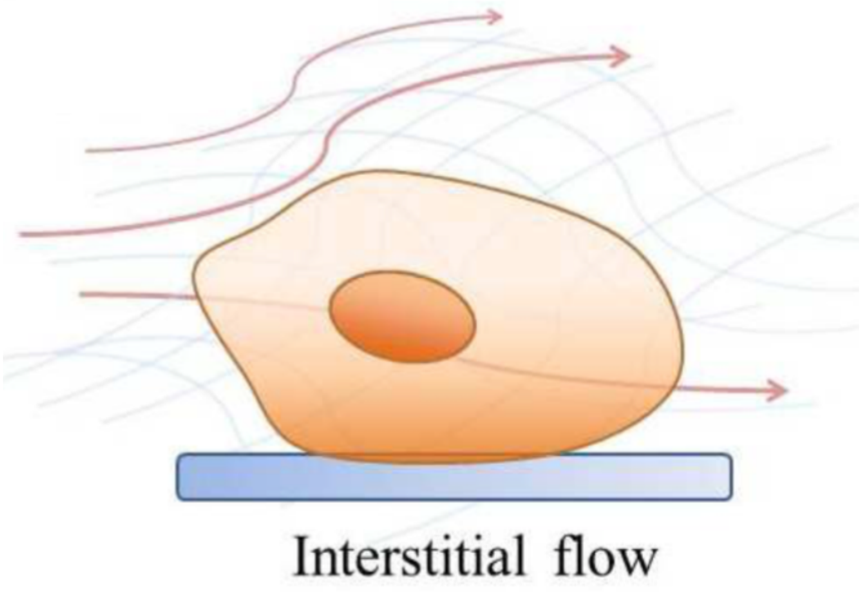
- Higher up-regulation of chrondrgenic markers in groupe with mechanical and biochemical cues
- Lower risk to hypertrophic differentation

Xuanwen Bao et al. (*Molecular Medicine Reports*, 2018)

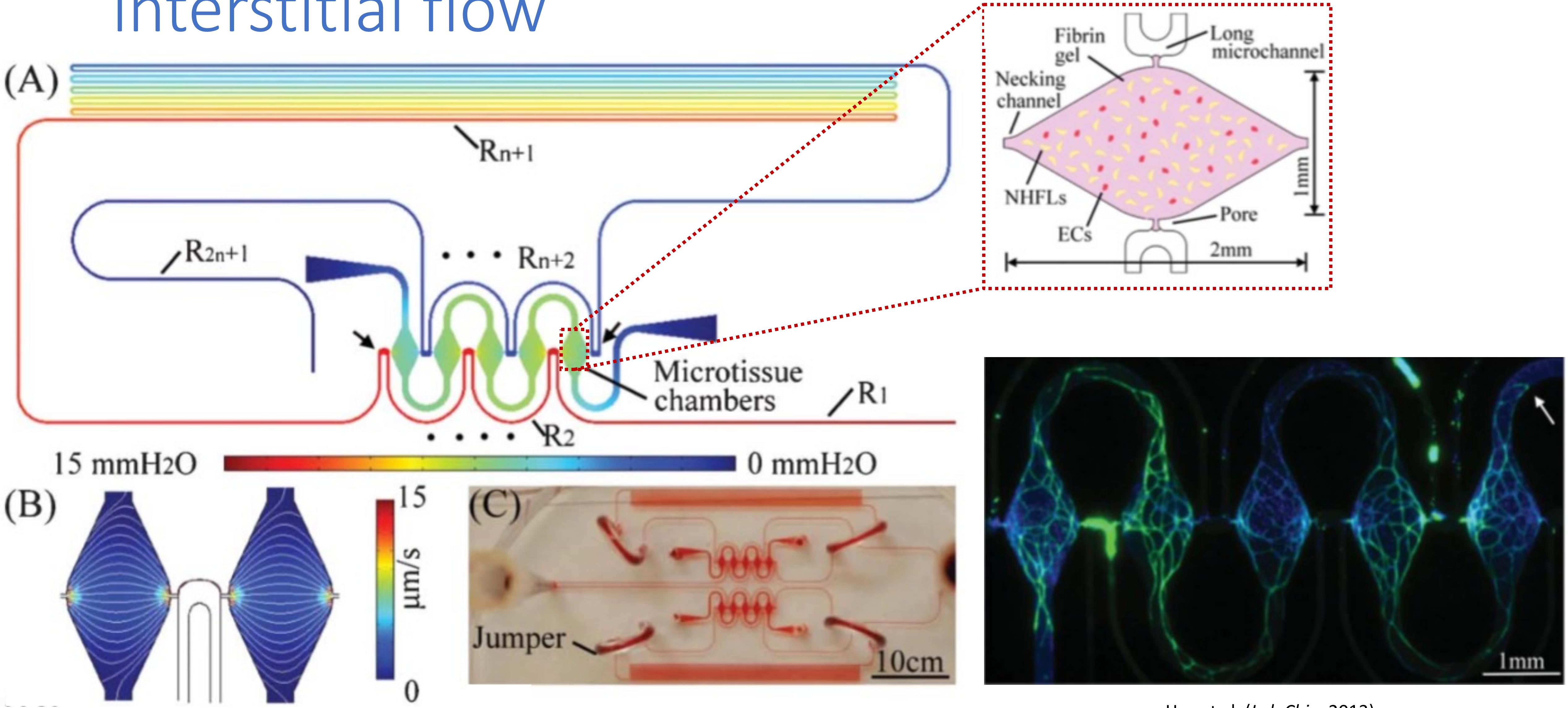
3. Interstitial flow

Interstitial fluid flow enhances:

- **Vessel-like** structure formation, blood **angiogenesis** and **lymphangiogenesis**
- More complex **neural networks** in neurospheroids cultures



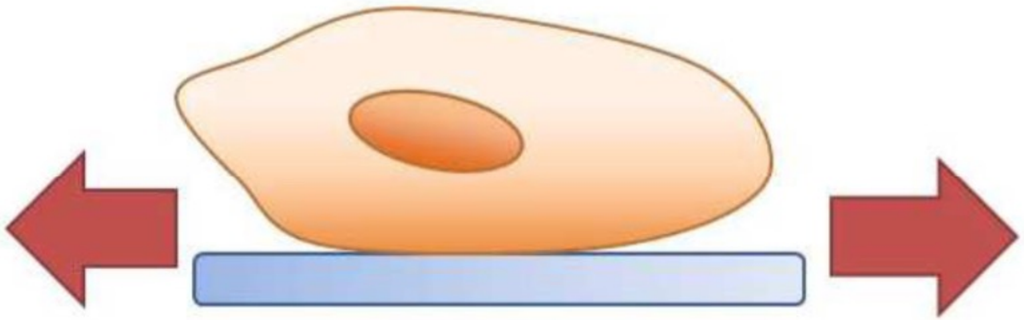
Induced self-organization of cells by interstitial flow



Hsu et al. (*Lab Chip*, 2013)

4. Stretching

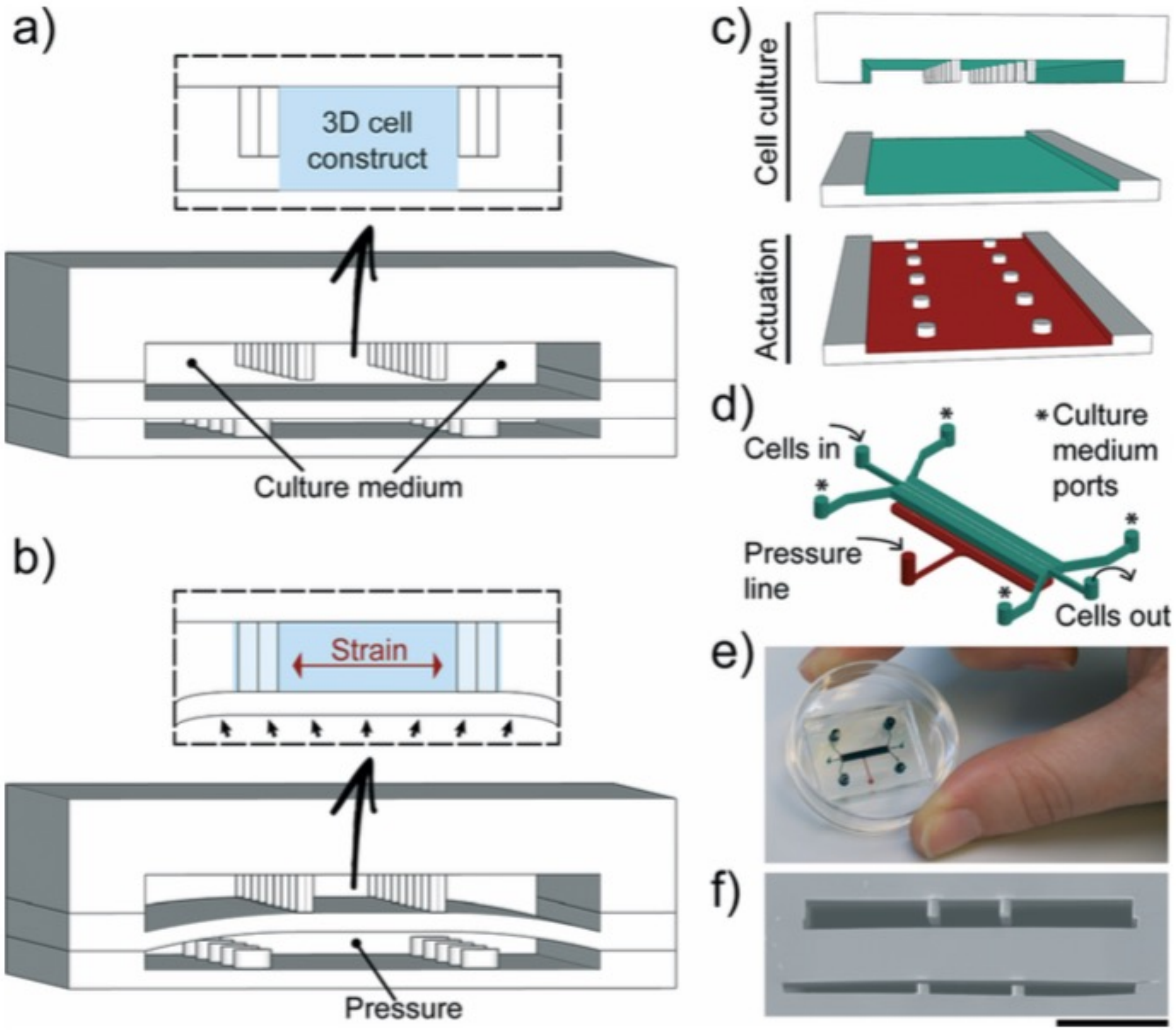
- microdevice containing a flexible membrane that is stretched by applying vacuum to two air channels on either side of the cultivation chamber
- Recapitulation of different pathological scenarios:
  - pulmonary edema (Huh et al., 2012),
  - small-airway inflammation (Benam et al., 2016), orthotopic lung cancer extravasation,
  - intravascular thrombosis assessment (Jain et al., 2018).



Stretching
(Flexible membrane)

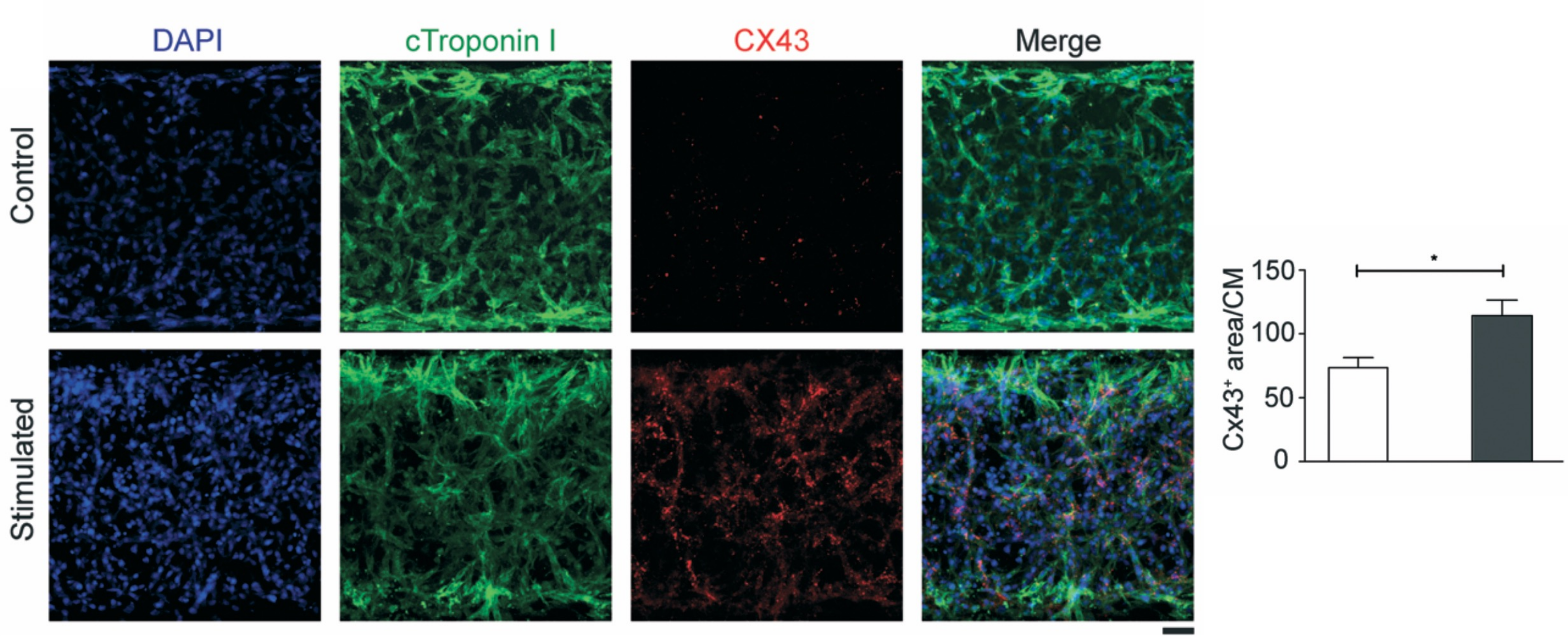
Beating heart on a chip

- A microfluidic platform to generate functional 3D cardiac microtissues



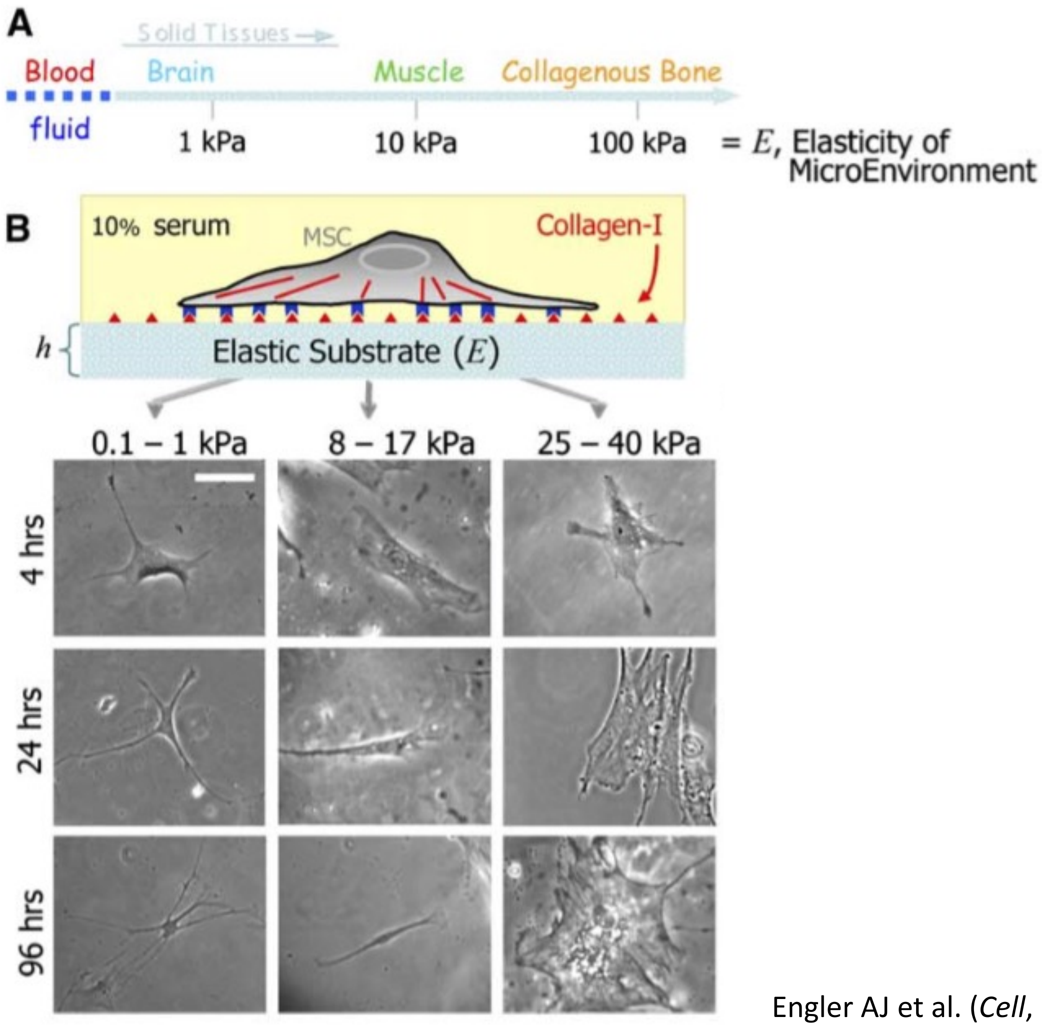
Marsano A et al. (*Lab Chip*, 2016)

Effect of uniaxial cyclic mechanical strain on micro-cardiac constructs maturation (Day 5)

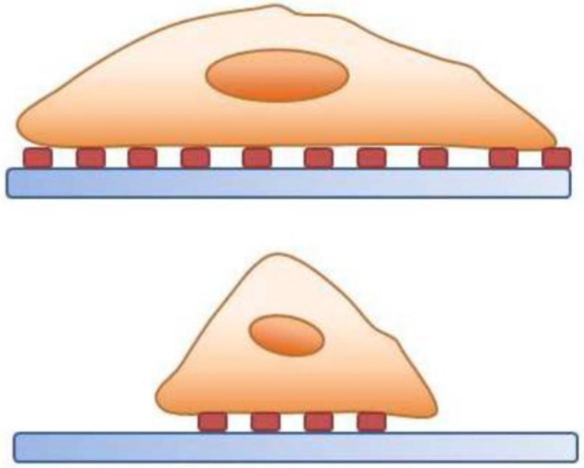


Marsano A et al. (*Lab Chip*, 2016)

5. Micropatterning and substrate stiffness

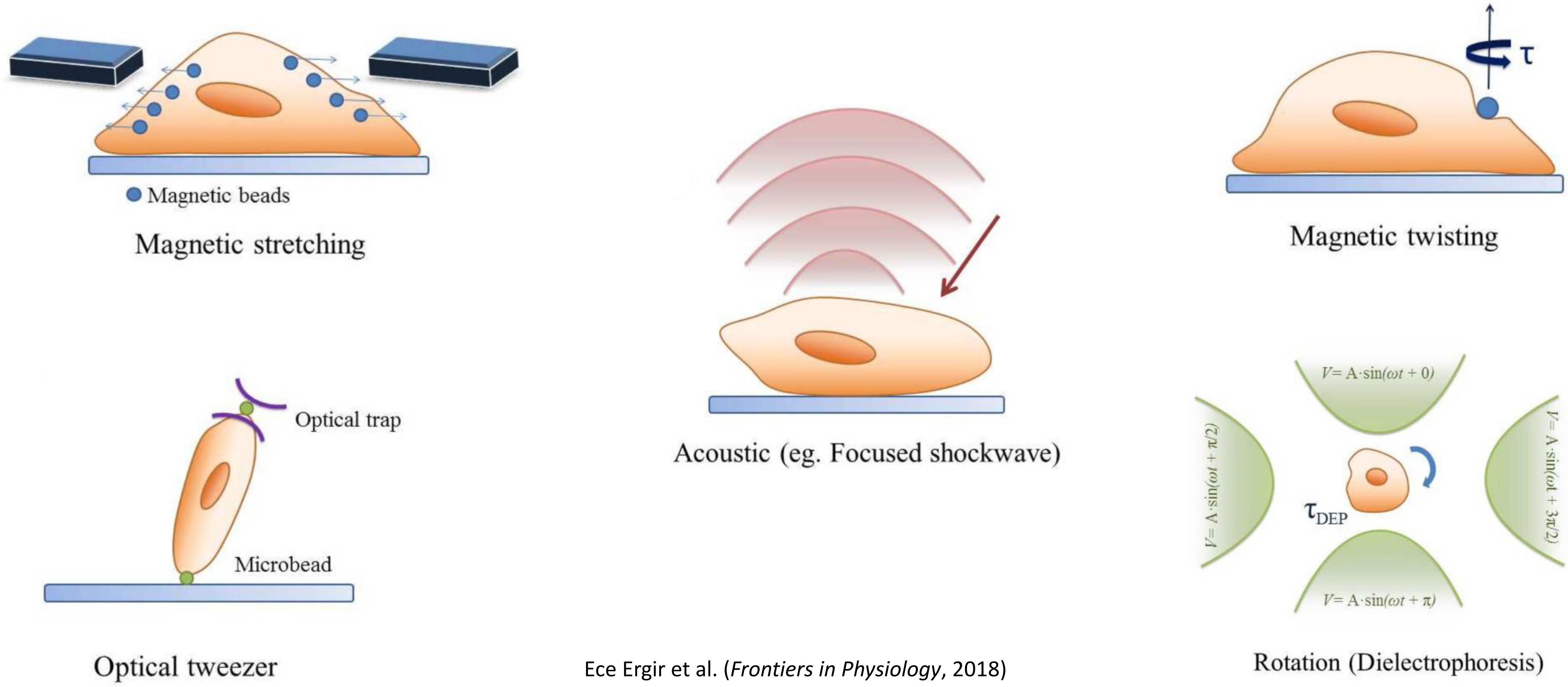


Engler AJ et al. (*Cell*, 2006)



Micropatterning

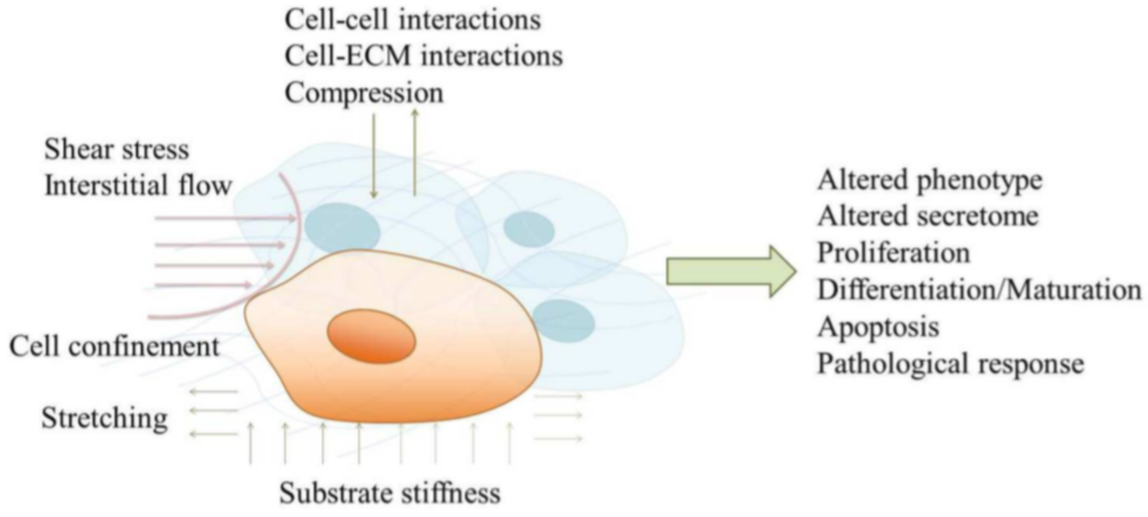
Other mechanical stimuli



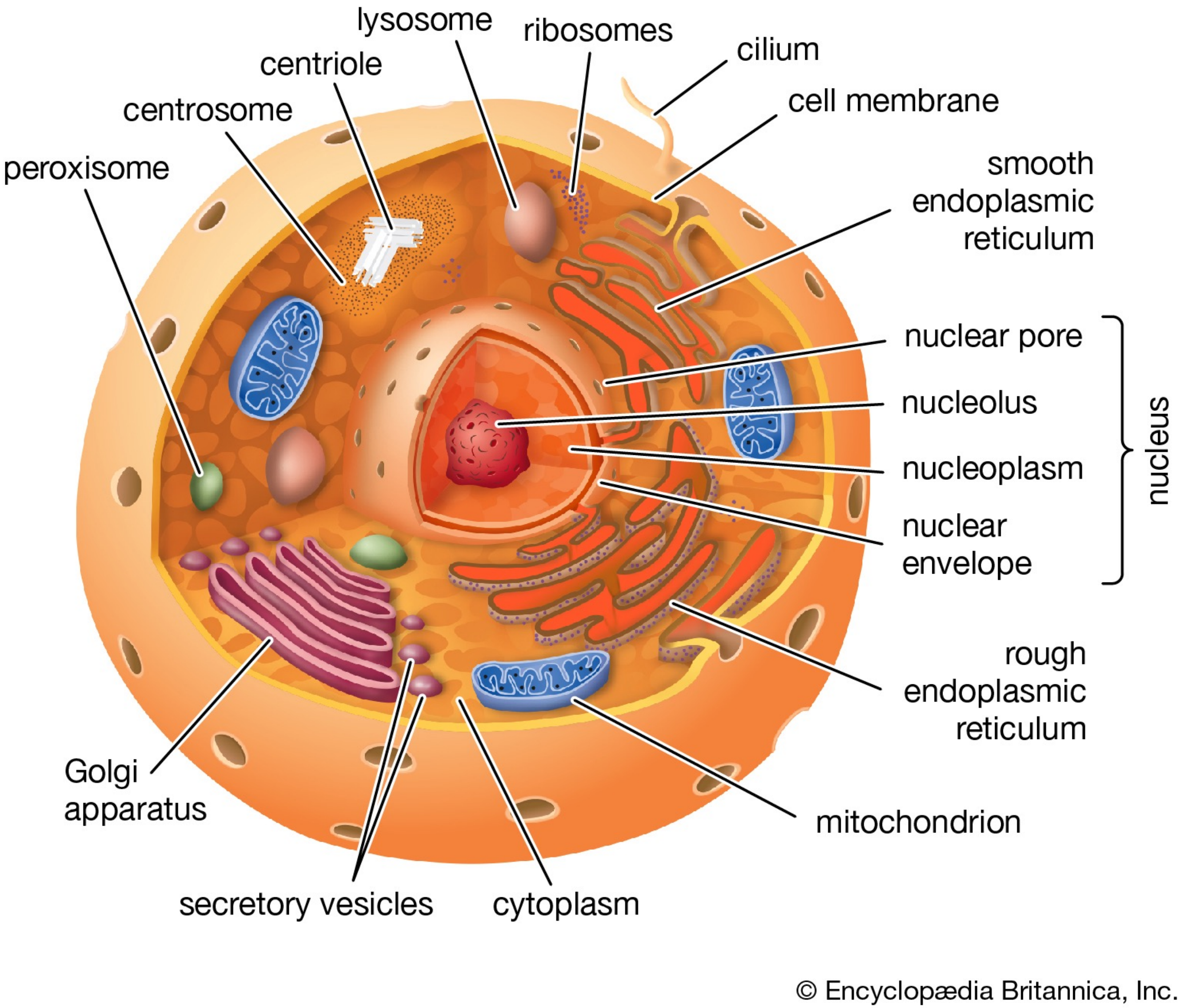
Ece Ergir et al. (*Frontiers in Physiology*, 2018)

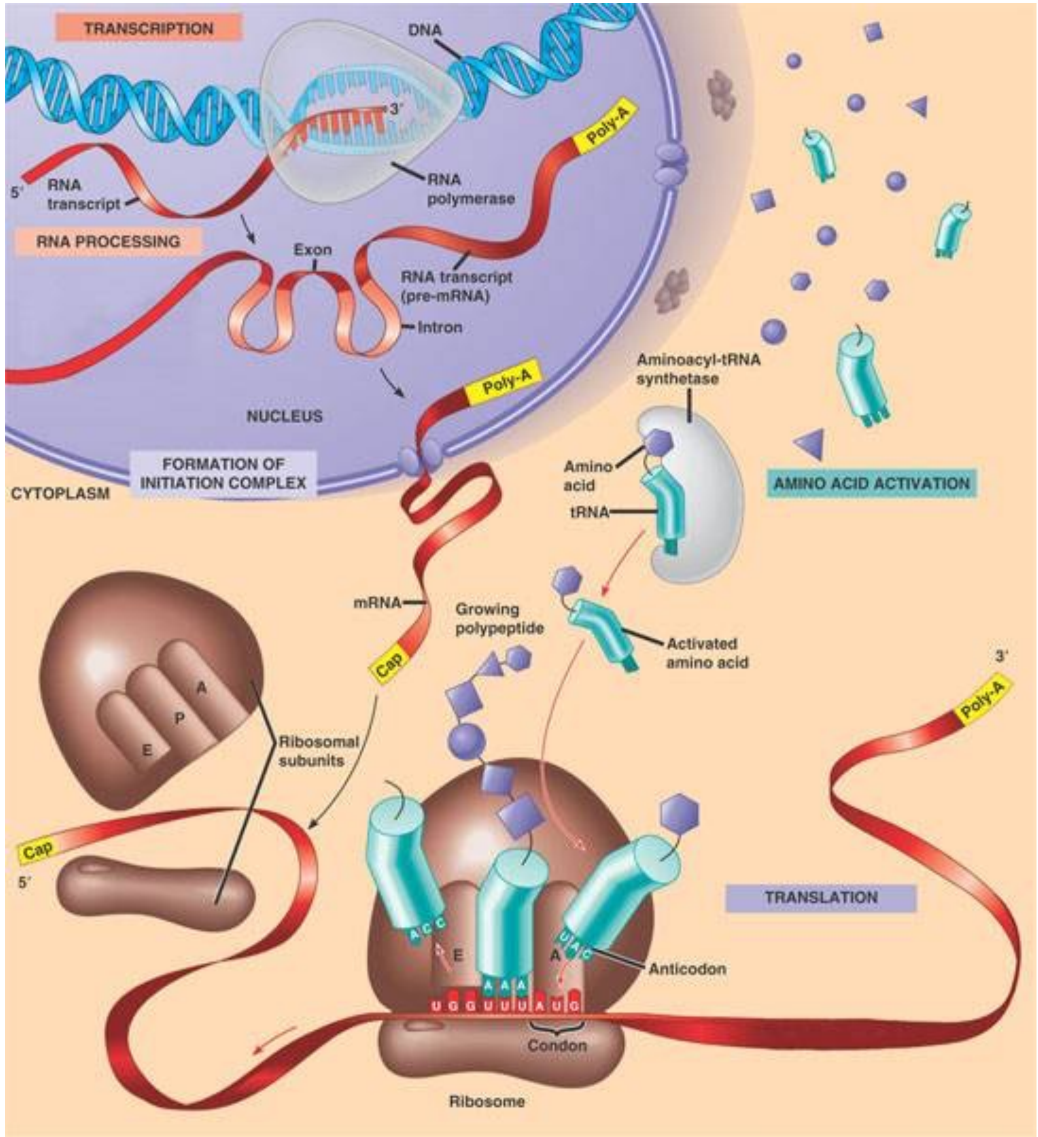
Cell response and analysis

Brief overview of cellular and molecular assays

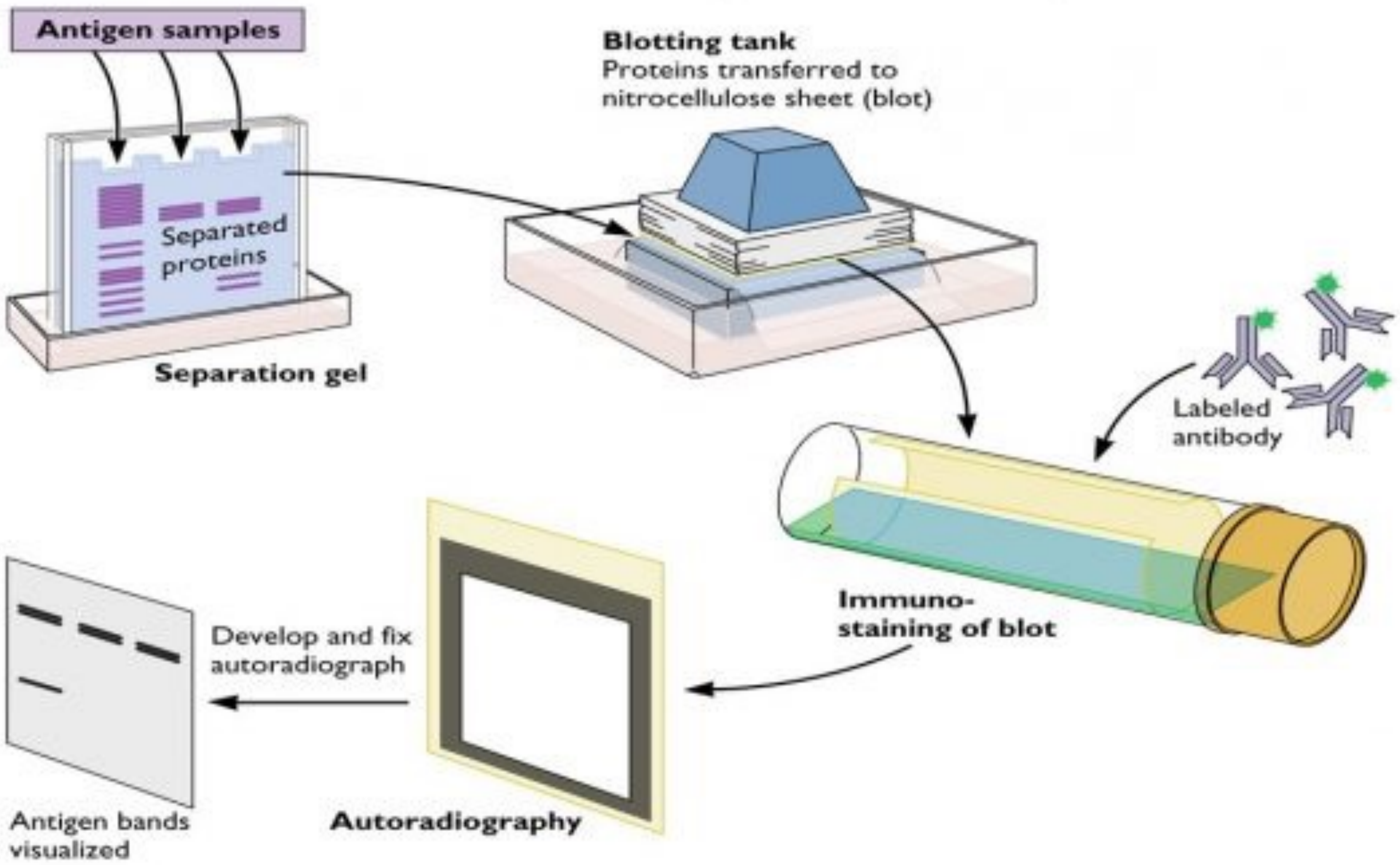


Basic cell biology: protein synthesis

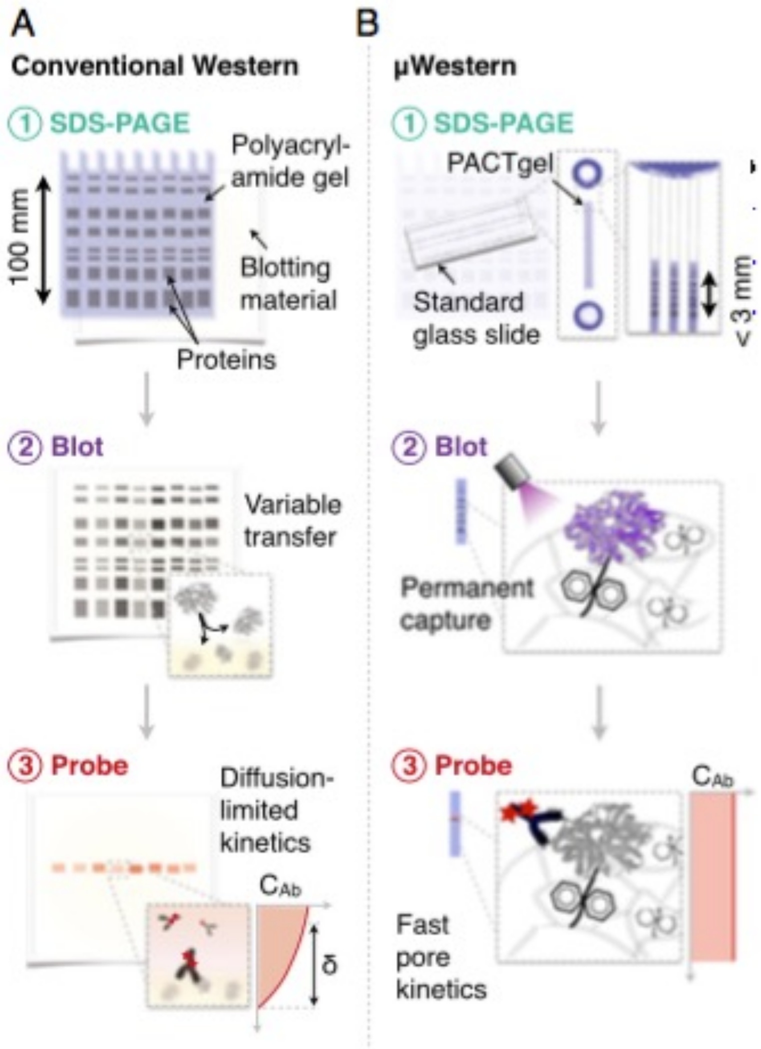


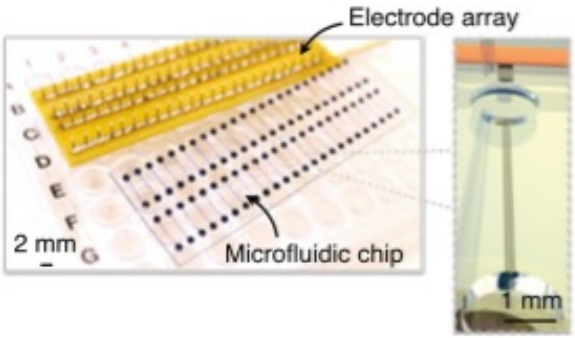


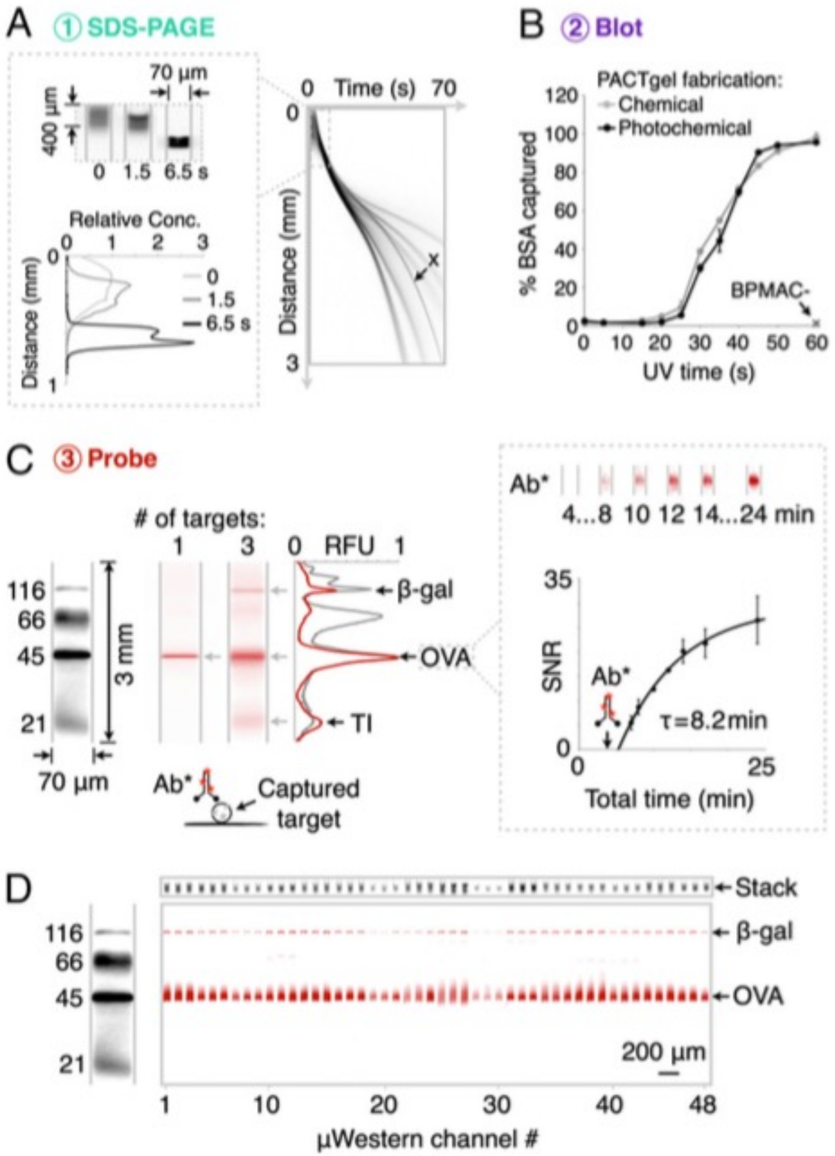
1. Protein detection: Western Blotting



Microfluidic Western Blotting

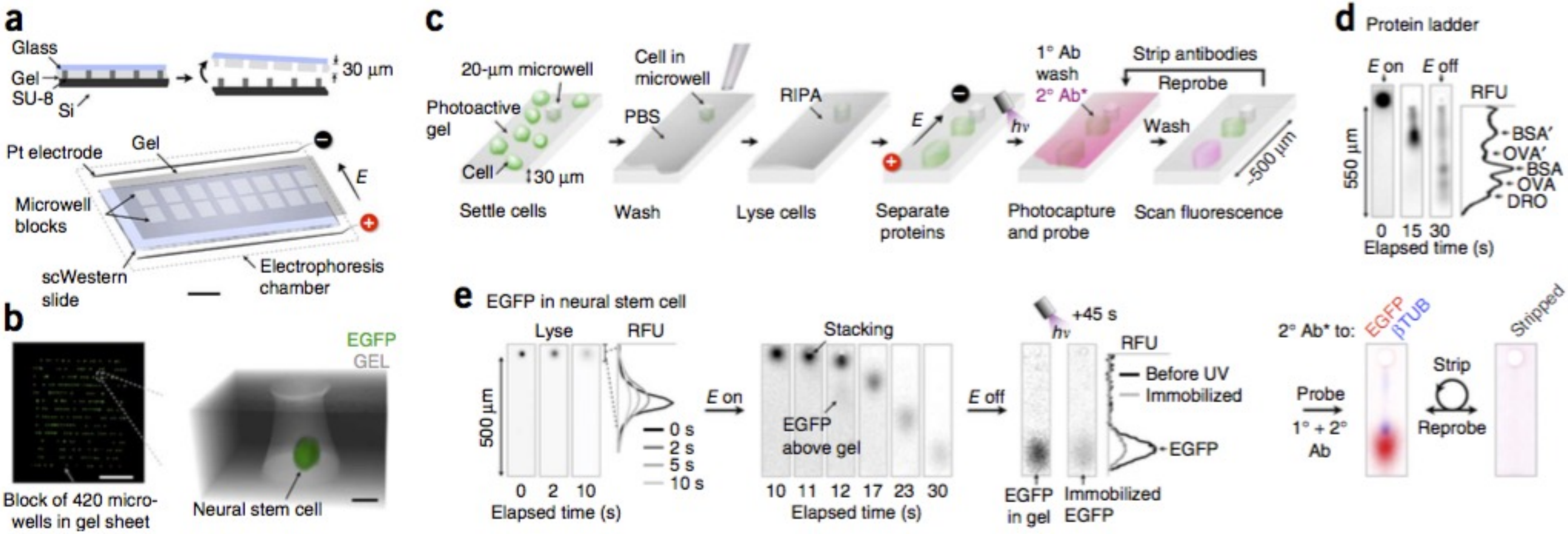






Hughes A et al. (PNAS, 2012)

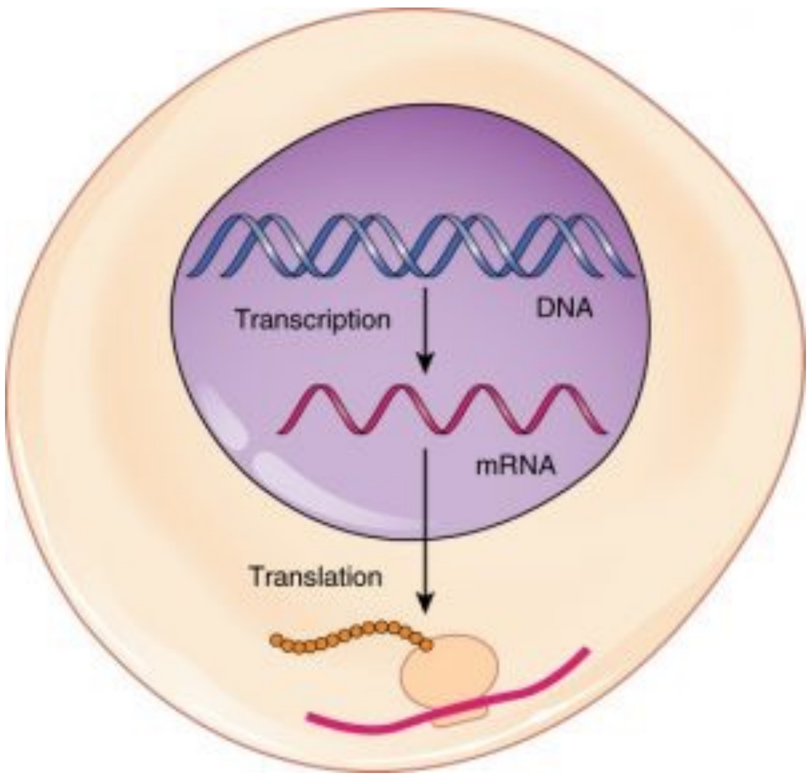
Single Cell Western Blotting

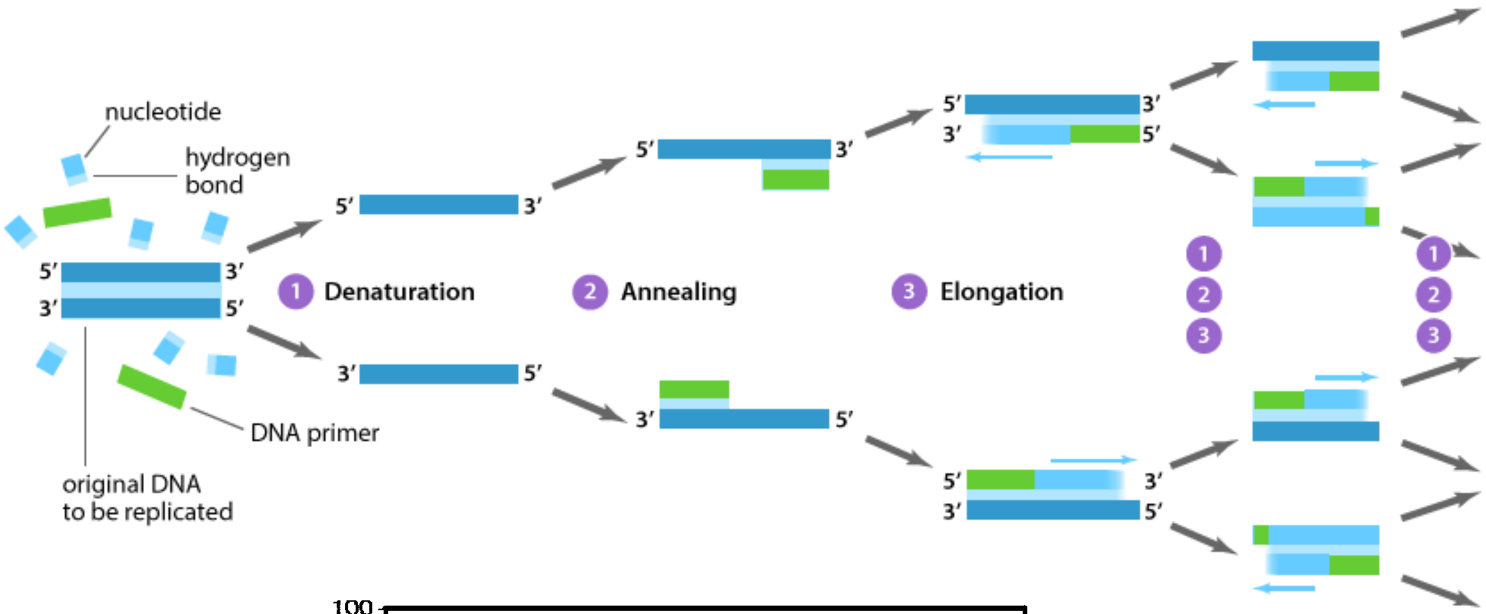


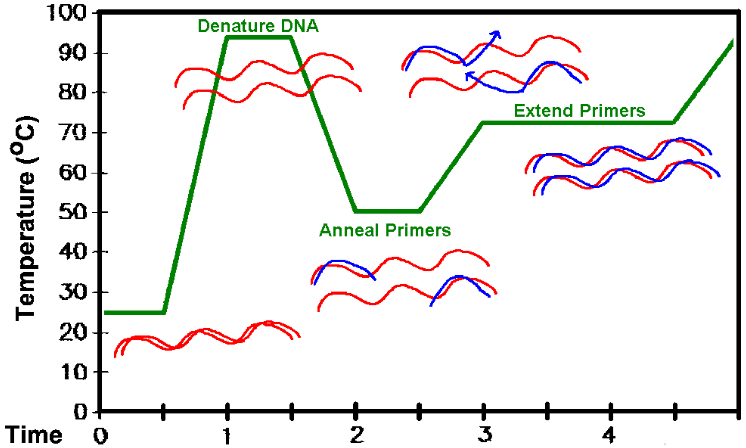
Example: Intra-tumor heterogeneity remains a major obstacle to effective cancer therapy and personalized medicine

Hughes et al. (*Nature Methods,* 2014)

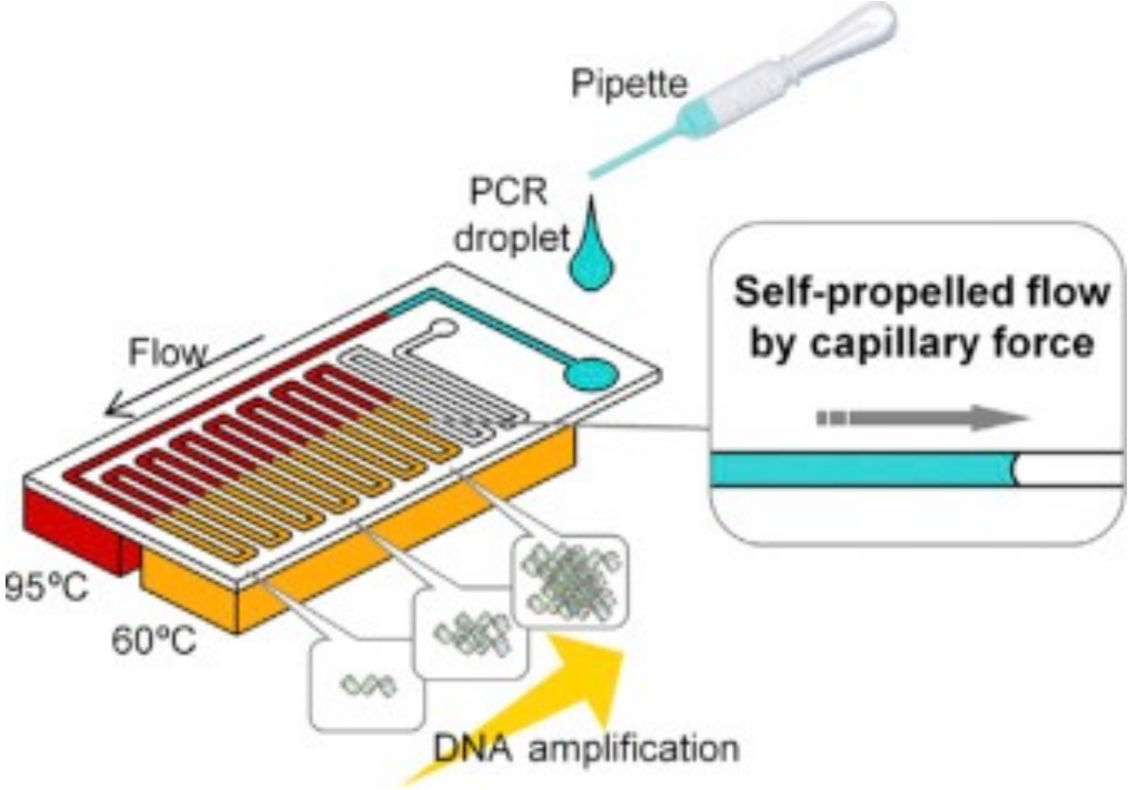
2. Gene expression: Polymerase Chain Reaction (PCR)





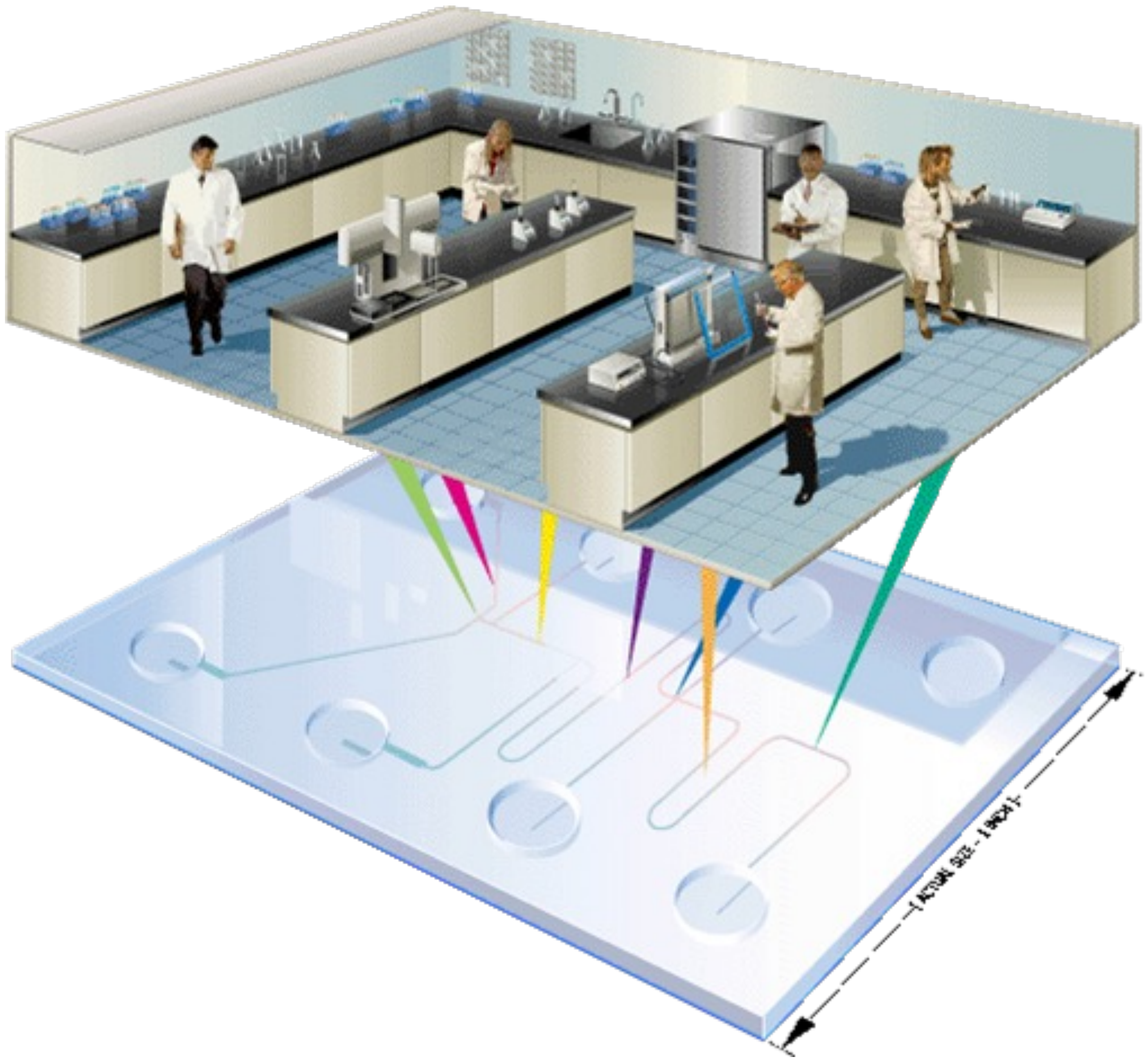


PCR at microfluidic scale



Ali Shahid et al. (Bioelectronics and Medical Devices, 2019)

From Organ on-a-chip to Lab on-a-chip



Questions?

Contact: Philippe.Abdel-Sayed@chuv.ch or philippe.abdel-sayed@epfl.ch