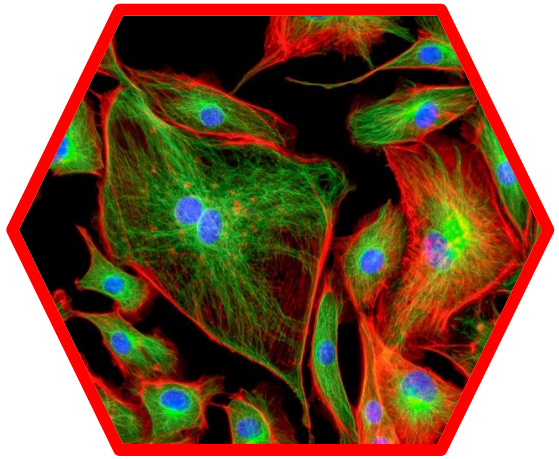
Biomaterials for MX

MSE – 471

Maartje Bastings

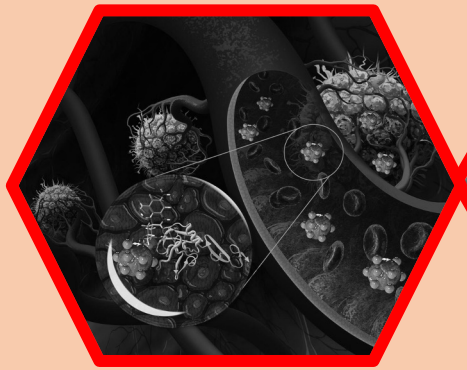


Materials for Tissue Engineering

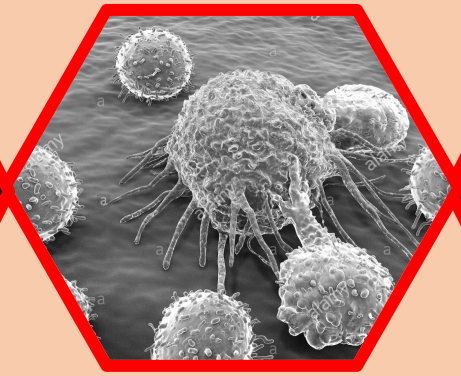
Today's Focus

BLOCK 2: Applications

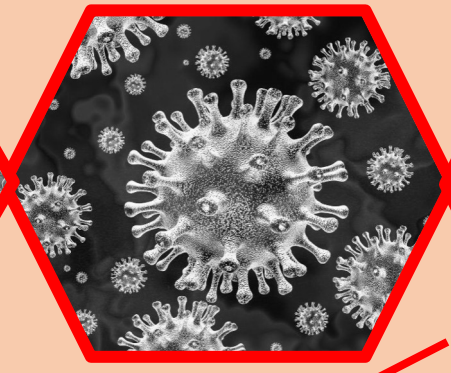
Drug delivery



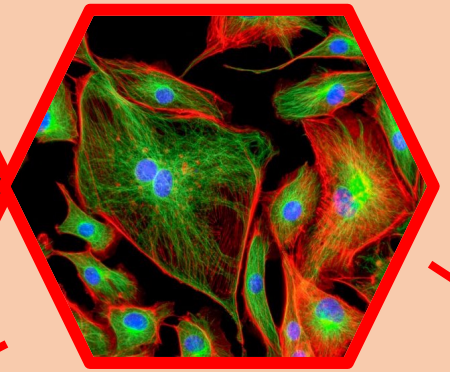
Cell adhesion



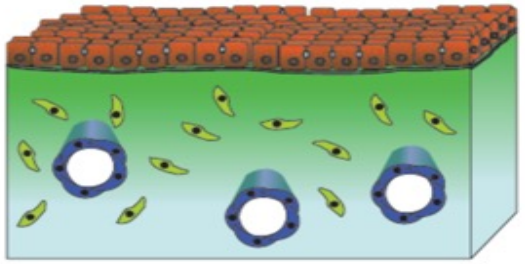
Immune engineering



Tissue engineering

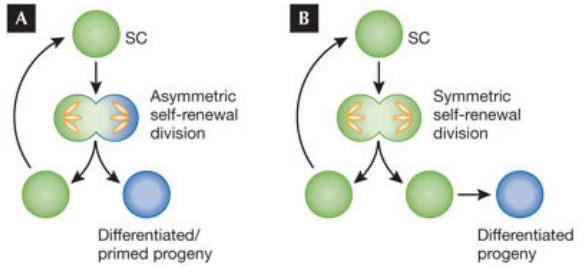


What is Tissue Engineering?

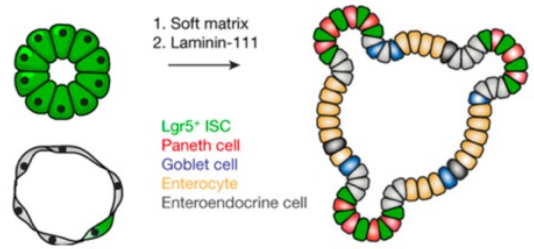


Organoids

Stem Cells



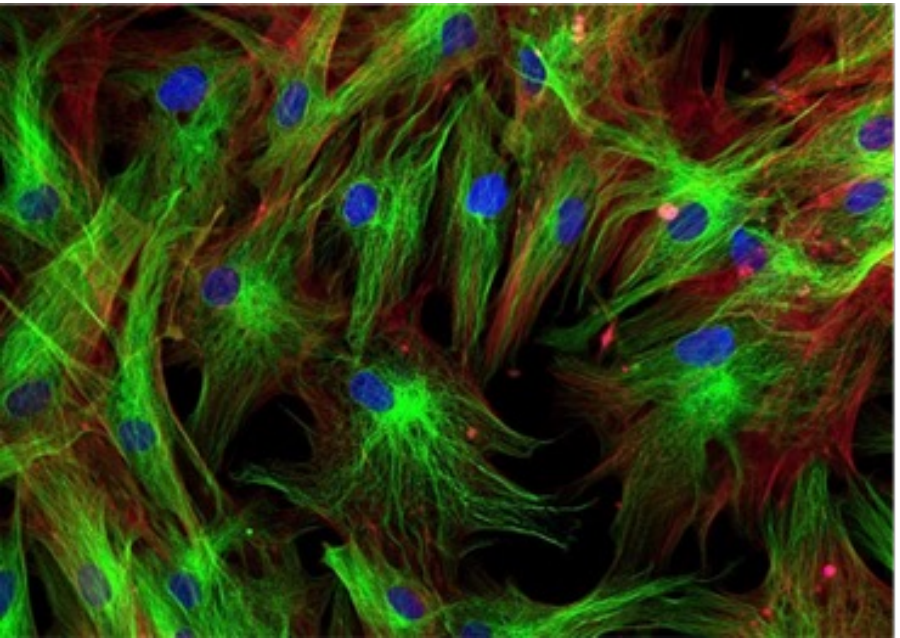
Current Research

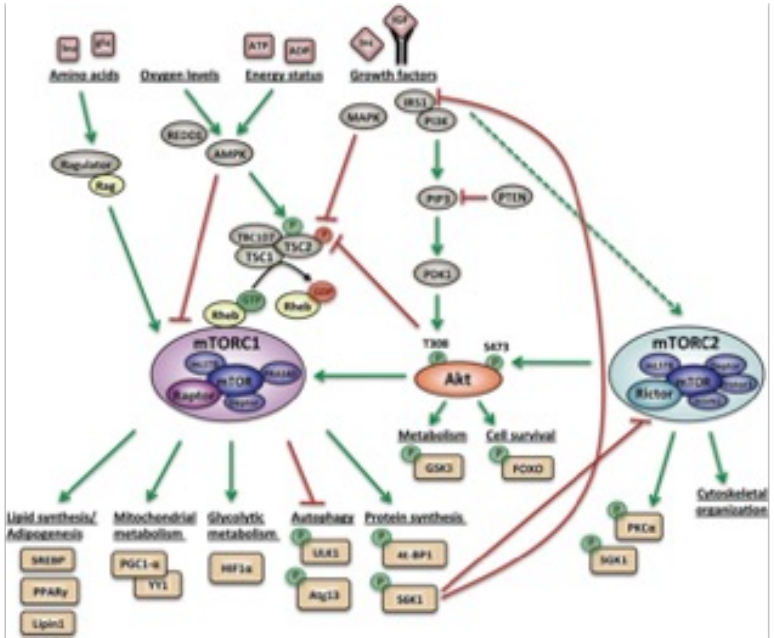


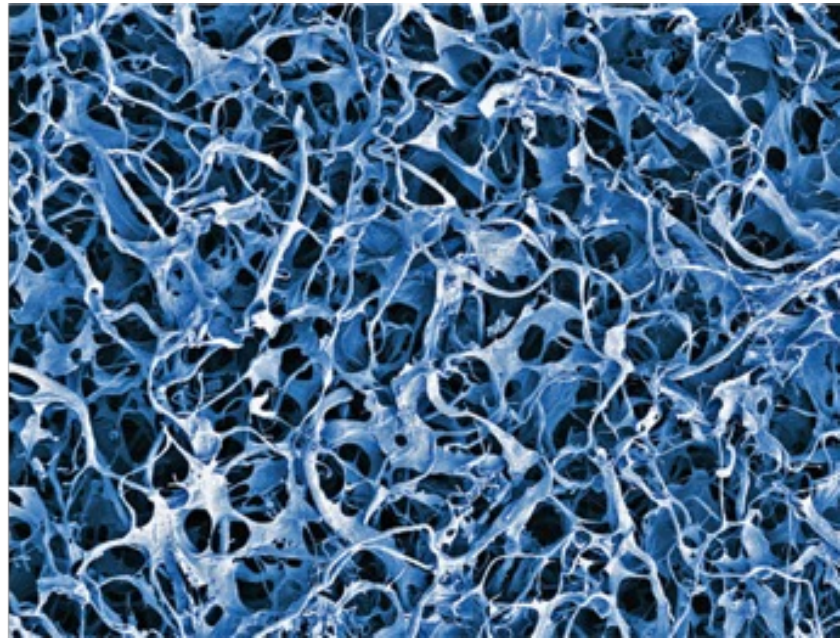
What is Tissue Engineering

Tissue engineering is the use of a combination of cells, engineering and materials methods, and suitable biochemical and physicochemical factors to **improve or replace biological tissues**.

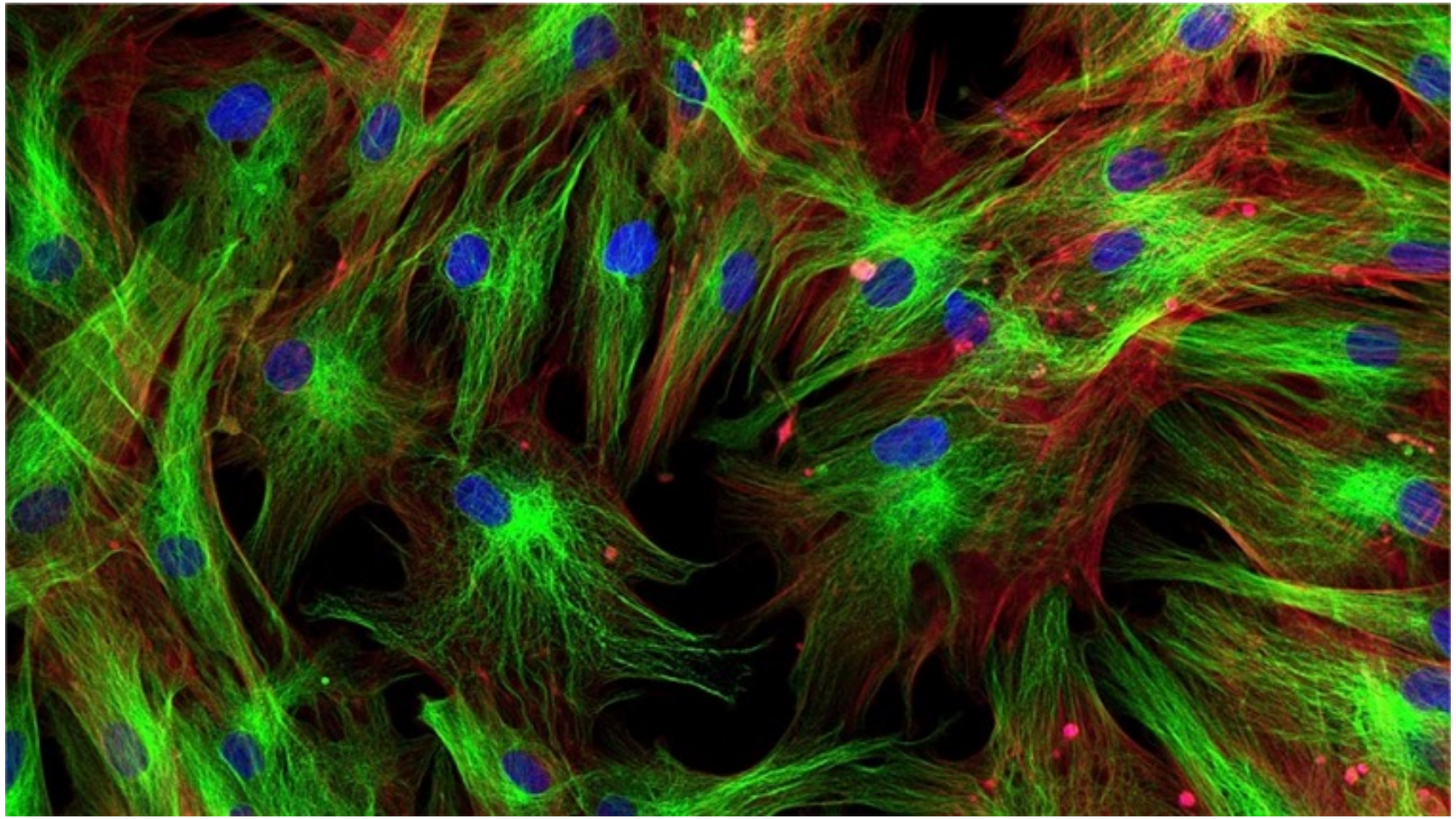
Tissue engineering involves the use of a **scaffold** for the formation of new viable tissue for a medical purpose. This scaffold can be either natural or synthetic, or a mix.







How many cells are in our body?



Tissue Engineering and Biomaterials

Proper tissue function and regeneration **rely on robust spatial and temporal control** of biophysical and biochemical micro-environmental cues through mechanisms that remain poorly understood.

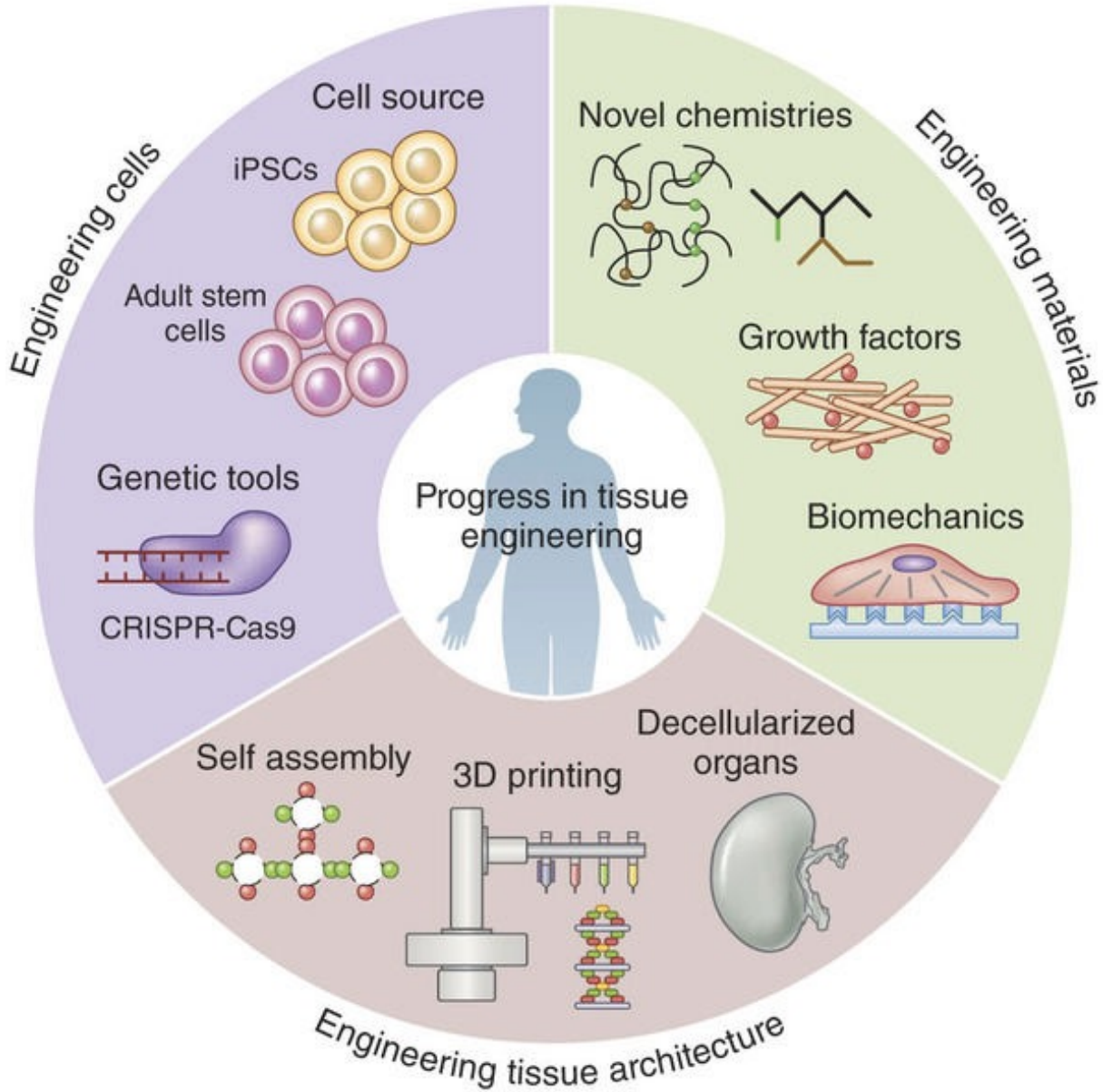
Biomaterials are rapidly being developed to display and deliver stem-cell-regulatory signals in a precise and near-physiological fashion, and serve as powerful **artificial micro-environments** in which to **study and instruct stem-cell fate** both in culture and in vivo.

Further synergism of cell biological and biomaterials technologies promises to have a profound impact on stem-cell biology and provide insights that will advance **stem-cell-based clinical approaches to tissue regeneration**

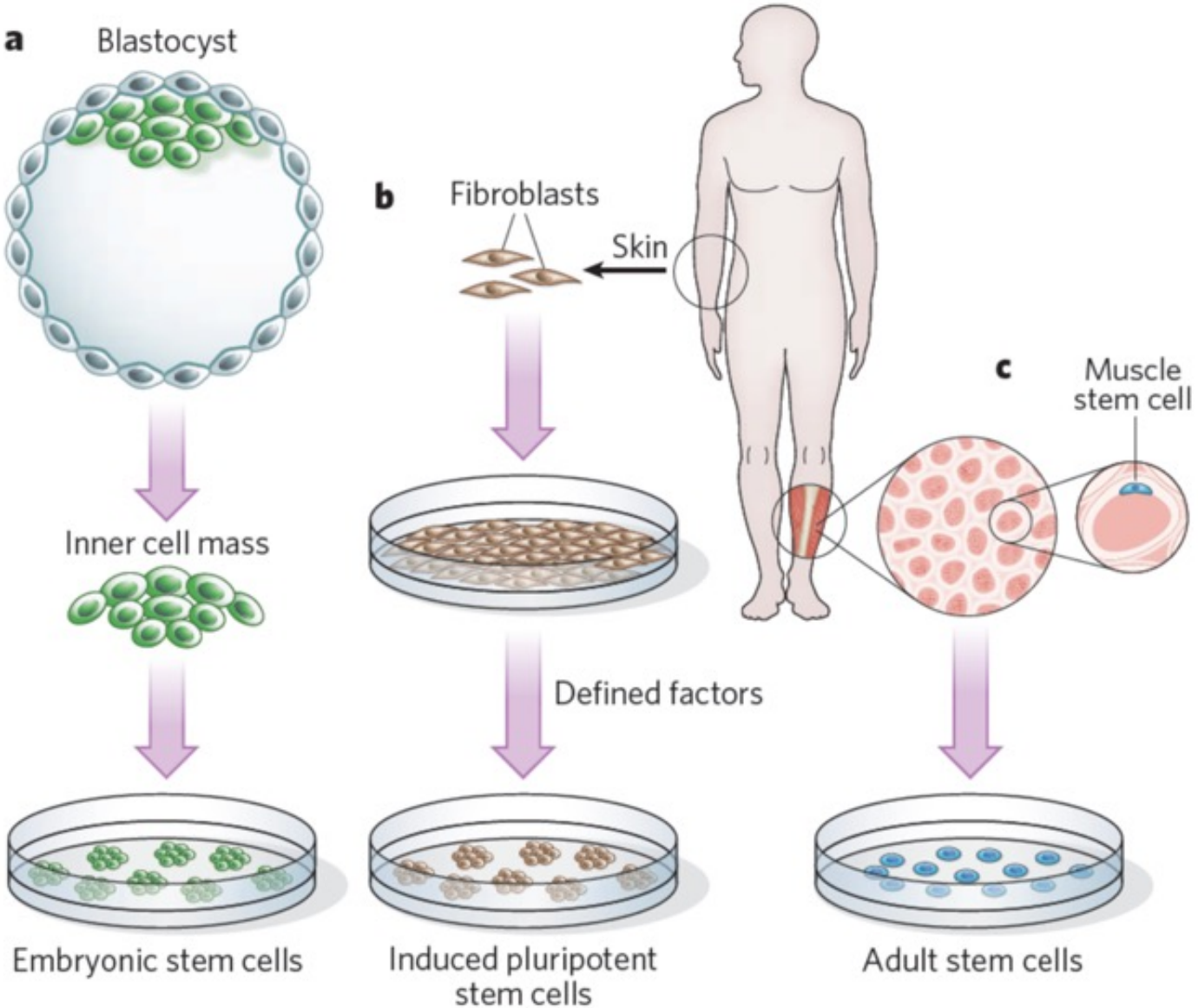
An increasing emphasis on **design principles** drawn from basic mechanisms of cell–matrix interactions and cell signaling has now set the stage for the successful **application of biomaterials to stem-cell biology**.

This application has the potential to **revolutionize our understanding of extrinsic regulators of cell fate,** as matrices can be made using technologies that are sufficiently versatile to allow recapitulation of features of **stem-cell micro-environments**, or **niches**, down almost to the molecular detail

What is needed for Tissue Engineering?



Stem Cells



Lutolf, Gilbert and Blau, Nature, 462, 433-441 (2009)

Stem Cells

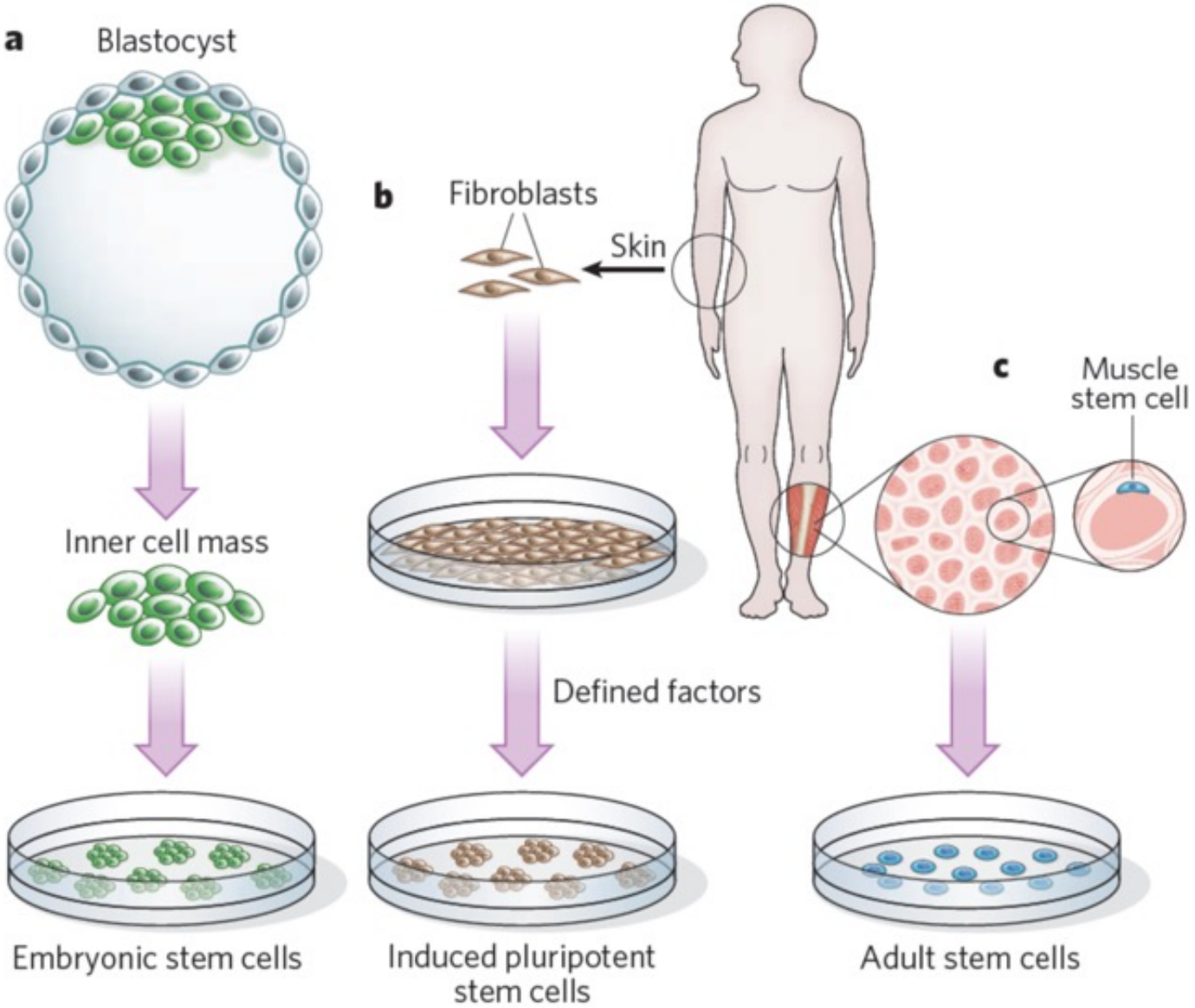
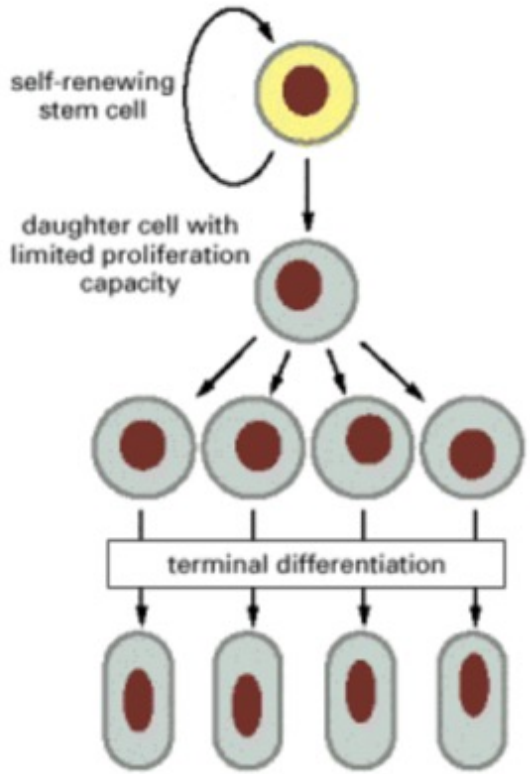


Table 1 | Current promises and limitations of stem-cell populations

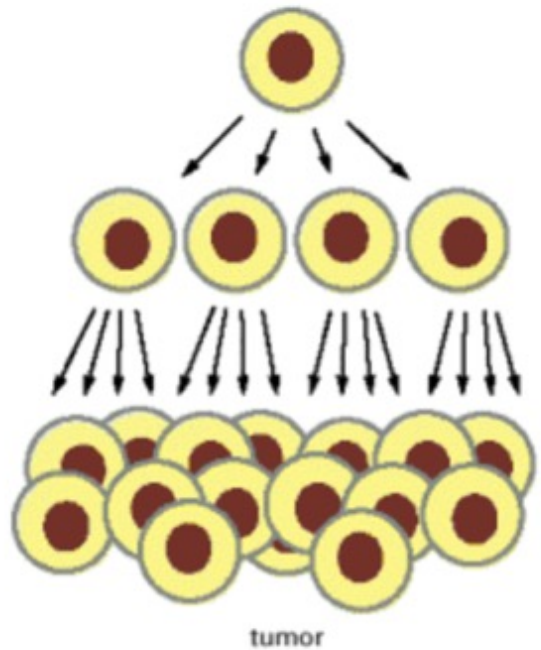
Feature	Embryonic stem cells	Adult stem cells	Induced pluripotent stem cells
Artificial system	Yes	No	Yes
Pluripotent	Yes	No	Yes
Efficient differentiation	No	Yes	No
Expansion in culture	Yes	No	Yes
Rare cell type	No	Yes	Yes
Immune compatible	No	No	Yes
Teratoma risk	Yes	No	Yes

Lutolf, Gilbert and Blau, Nature, 462, 433-441 (2009)

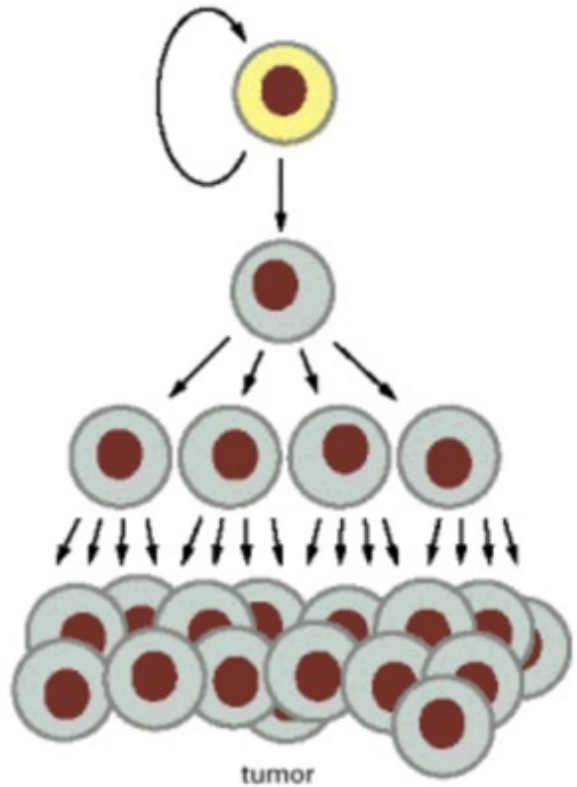
Balancing self-renewal and differentiation is crucial



(A) NORMAL PATHWAY

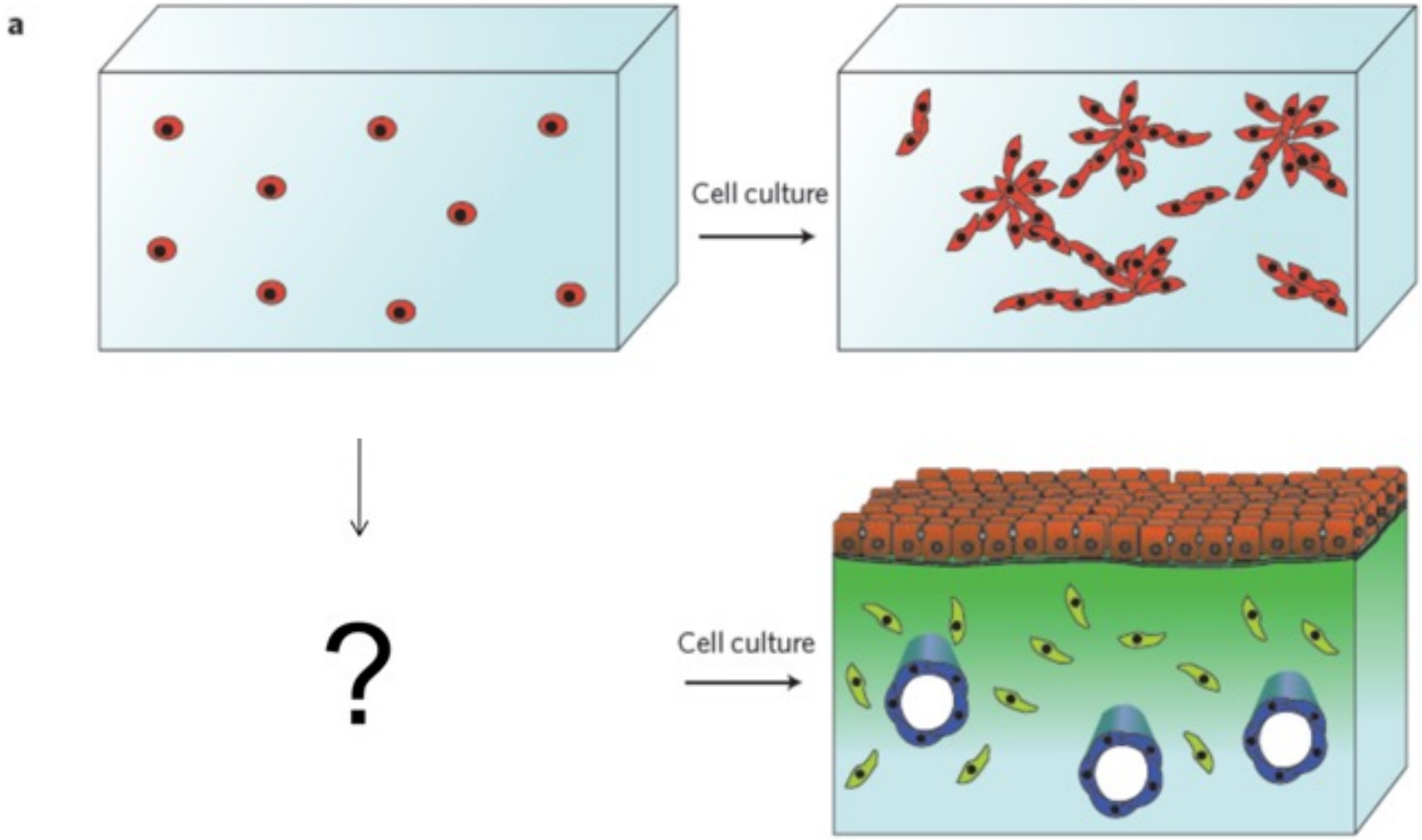


(B) STEM CELL FAILS TO PRODUCE ONE NON-STEM-CELL DAUGHTER IN EACH DIVISION AND THEREBY PROLIFERATES TO FORM A TUMOR



(C) DAUGHTER CELLS FAIL TO DIFFERENTIATE NORMALLY AND INSTEAD PROLIFERATE TO FORM A TUMOR

How does a stem cell know what to become?



What can materials tell the cell?

Stem cell fate decisions can be affected by properties inherent to materials near the cell/material interface:

- nanotopography,
- stiffness,
- chemical functionality,
- molecular flexibility,
- the adhesivity of cells to the material,
- its binding affinity for soluble factors,
- its cell-mediated degradability
- its degradation by-products.

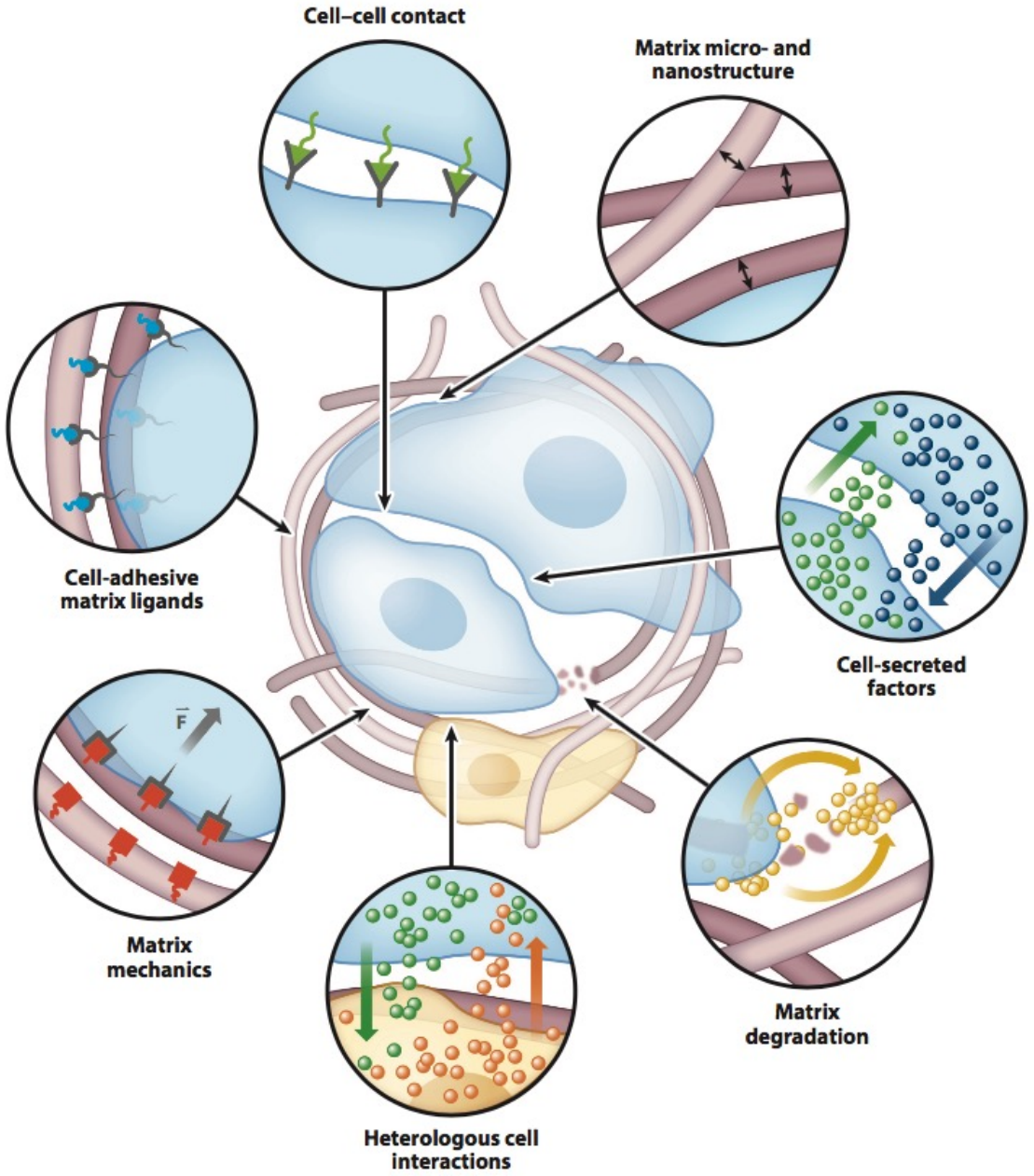


Figure 2

Niche interactions known to modulate stem cell phenotype.

Annu. Rev. Biomed. Eng. 2018. 20:21–47

What can materials tell the cell?

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- its degradation by-products.

Adult stem cells reside within instructive, tissue-specific niches that **physically localize** them and maintain their stem-cell fate

The key function of stem-cell niches is to **maintain a constant number of slowly dividing stem cells** during homeostasis by balancing the proportions of quiescent and activated cells.

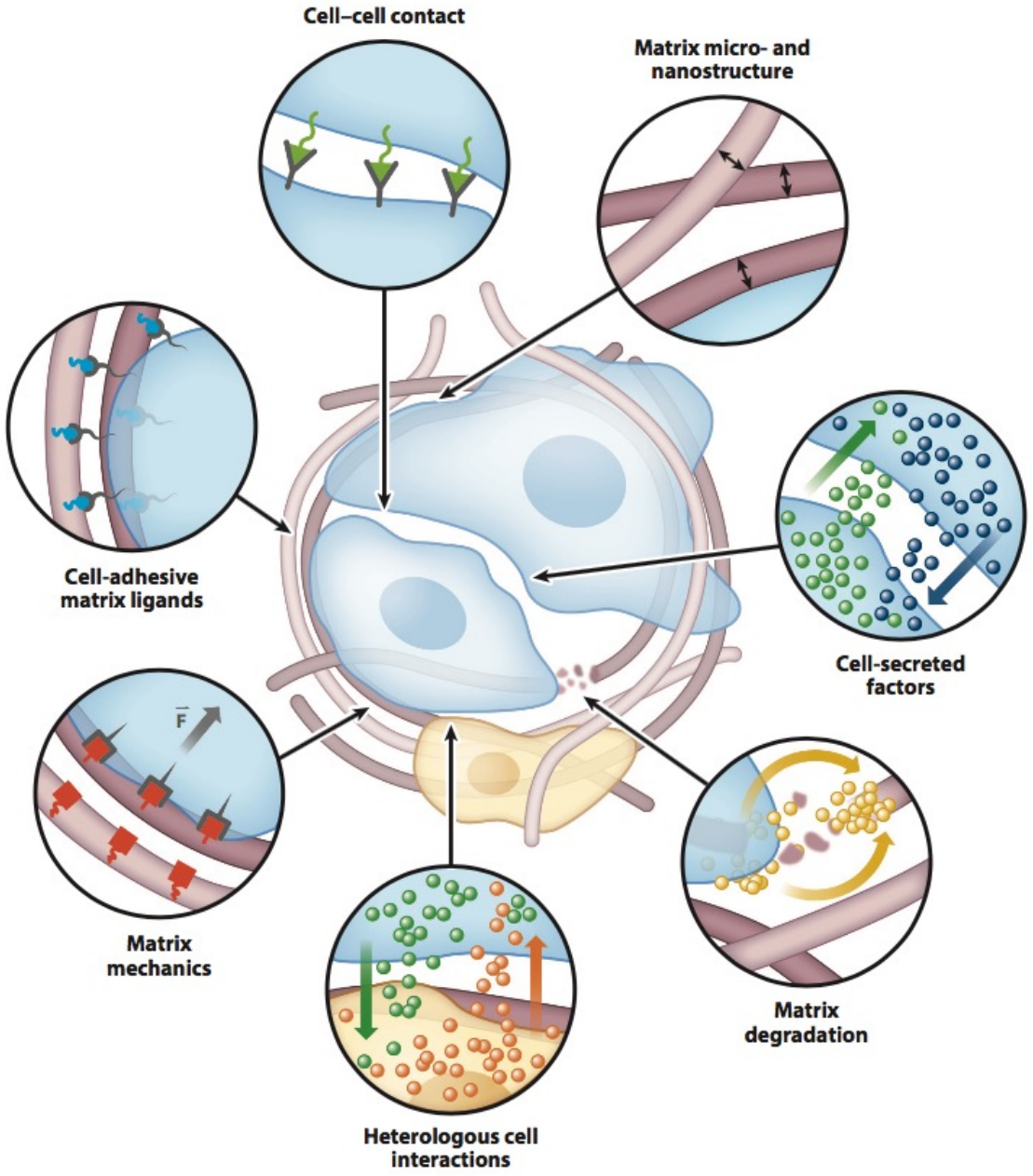


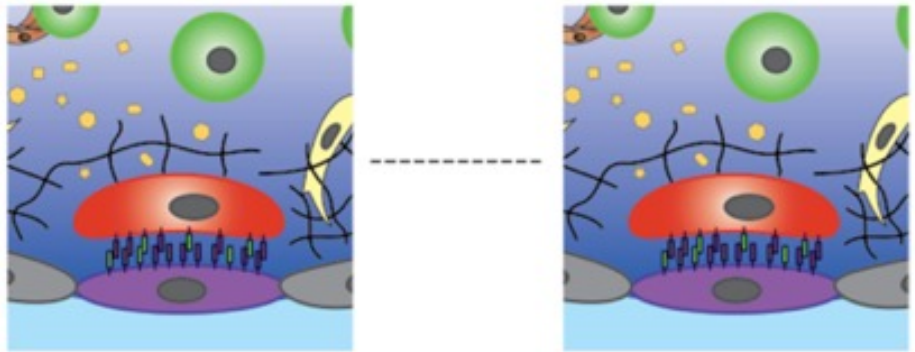
Figure 2

Niche interactions known to modulate stem cell phenotype.

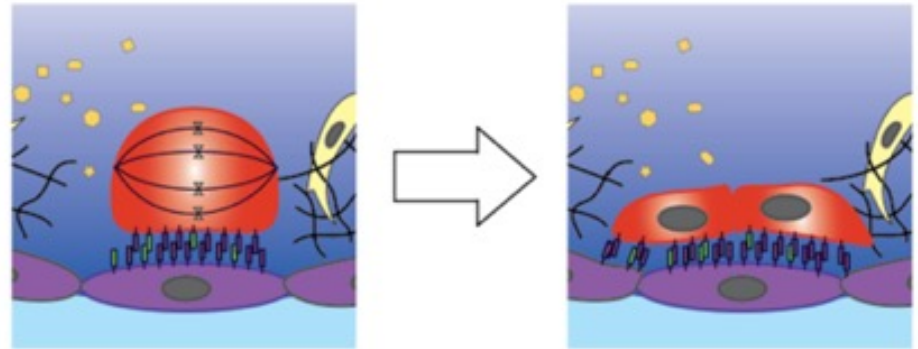
Annu. Rev. Biomed. Eng. 2018. 20:21–47

Possible single stem cell ‘fates’ in the niche

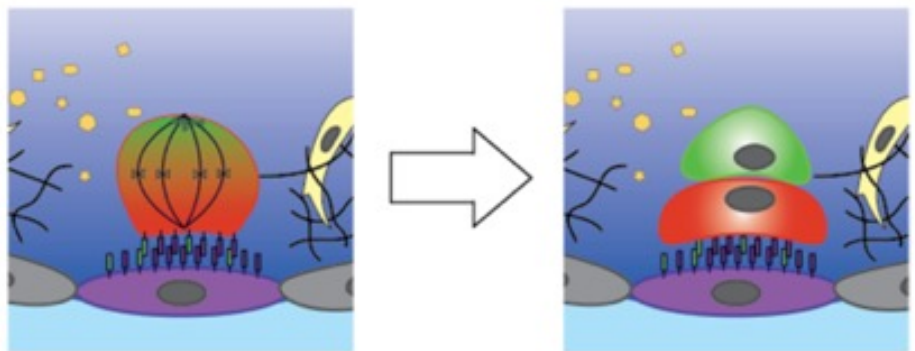
Quiescence



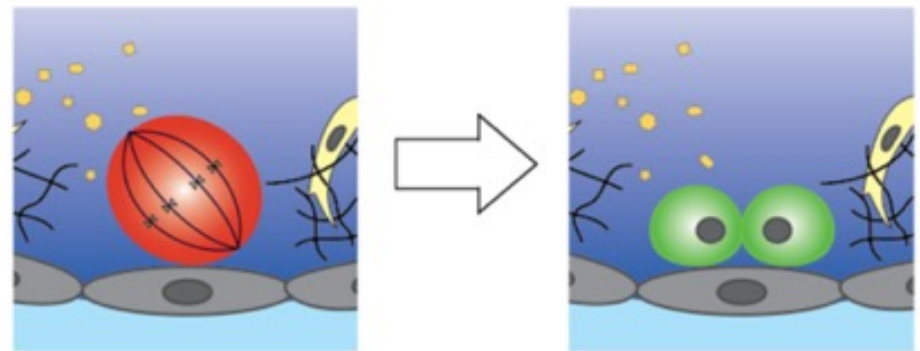
Symmetric self-renewal division



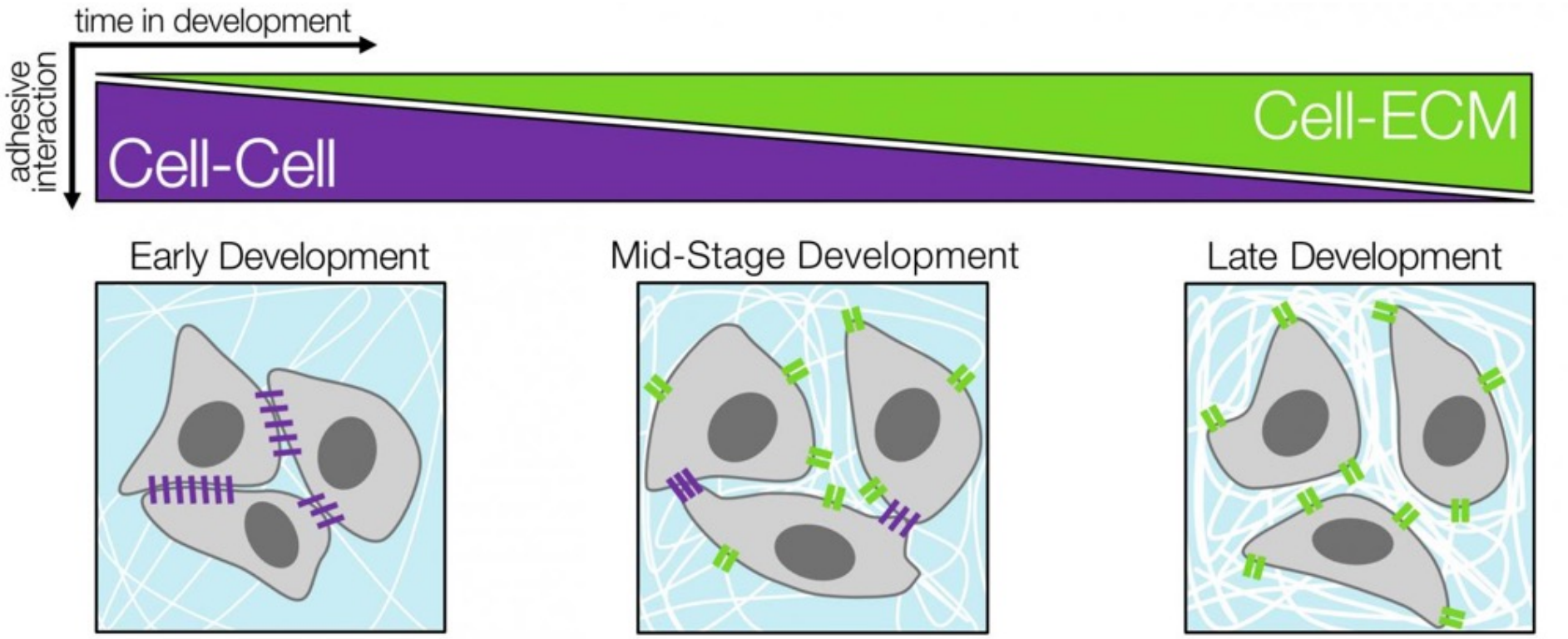
Asymmetric self-renewal division



Differentiation division



Time!



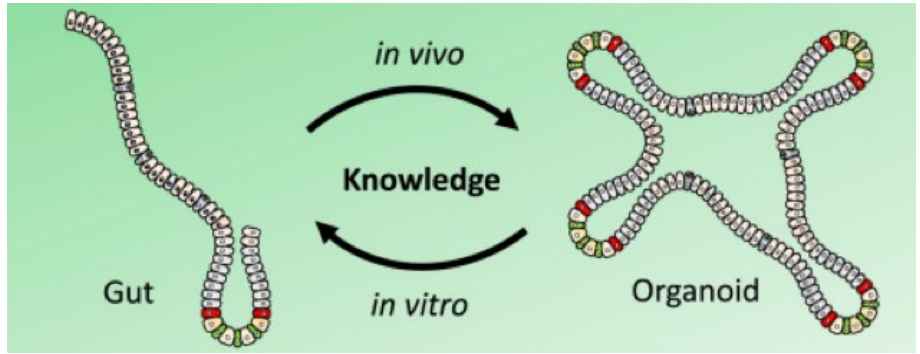
Thus, our material needs to be responsive in mechanical properties!

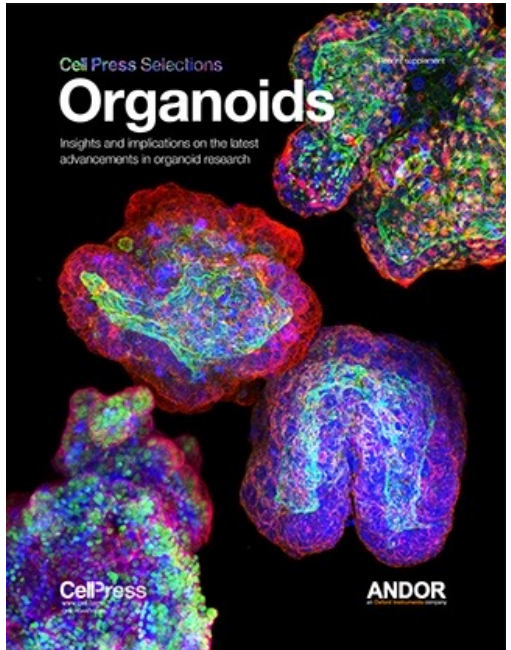
Organoids

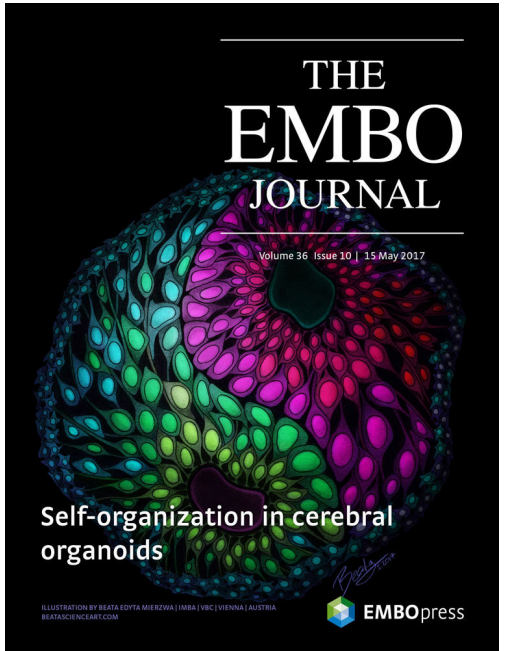
“mini” organs grown from stem cells

Recapitulate multiple aspects of real organs

Promising models of organ development, function and disease







Organoids

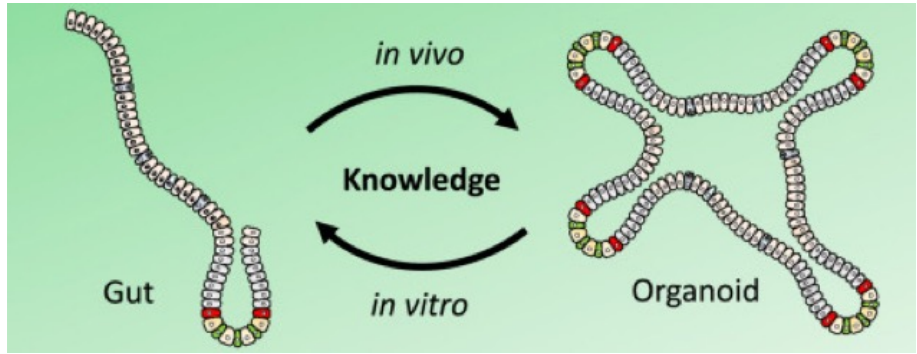
“mini” organs grown from stem cells

Recapitulate multiple aspects of real organs

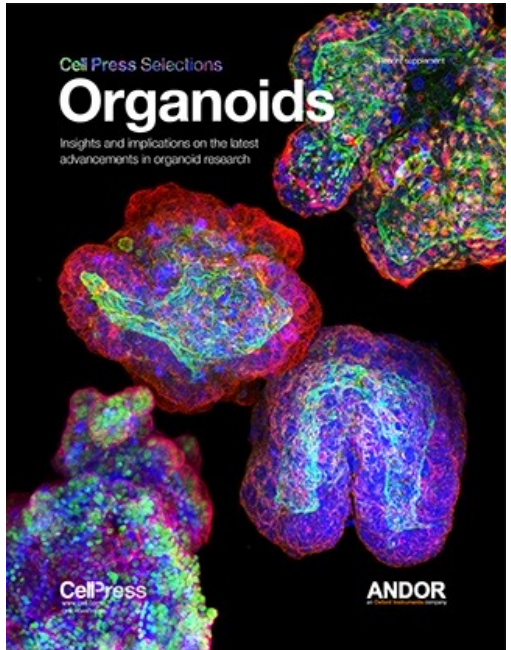
Promising models of organ development, function and disease

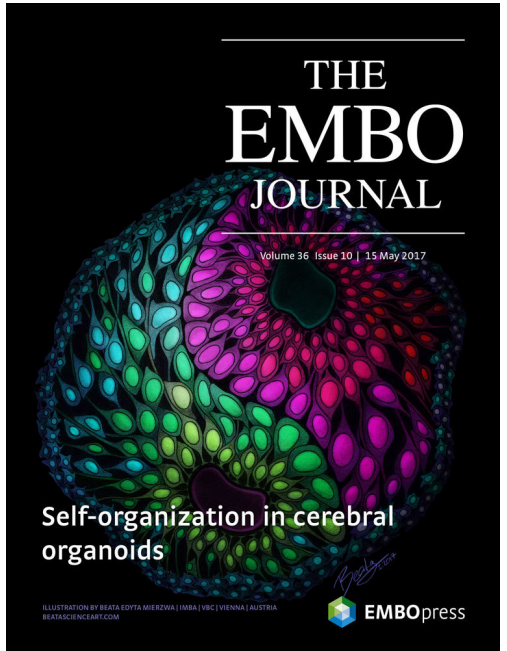
BUT: it turns out to be very difficult to find the key parameters that that govern stem cell expansion and organoid formation

Separate stages of development require different material properties and ECM components

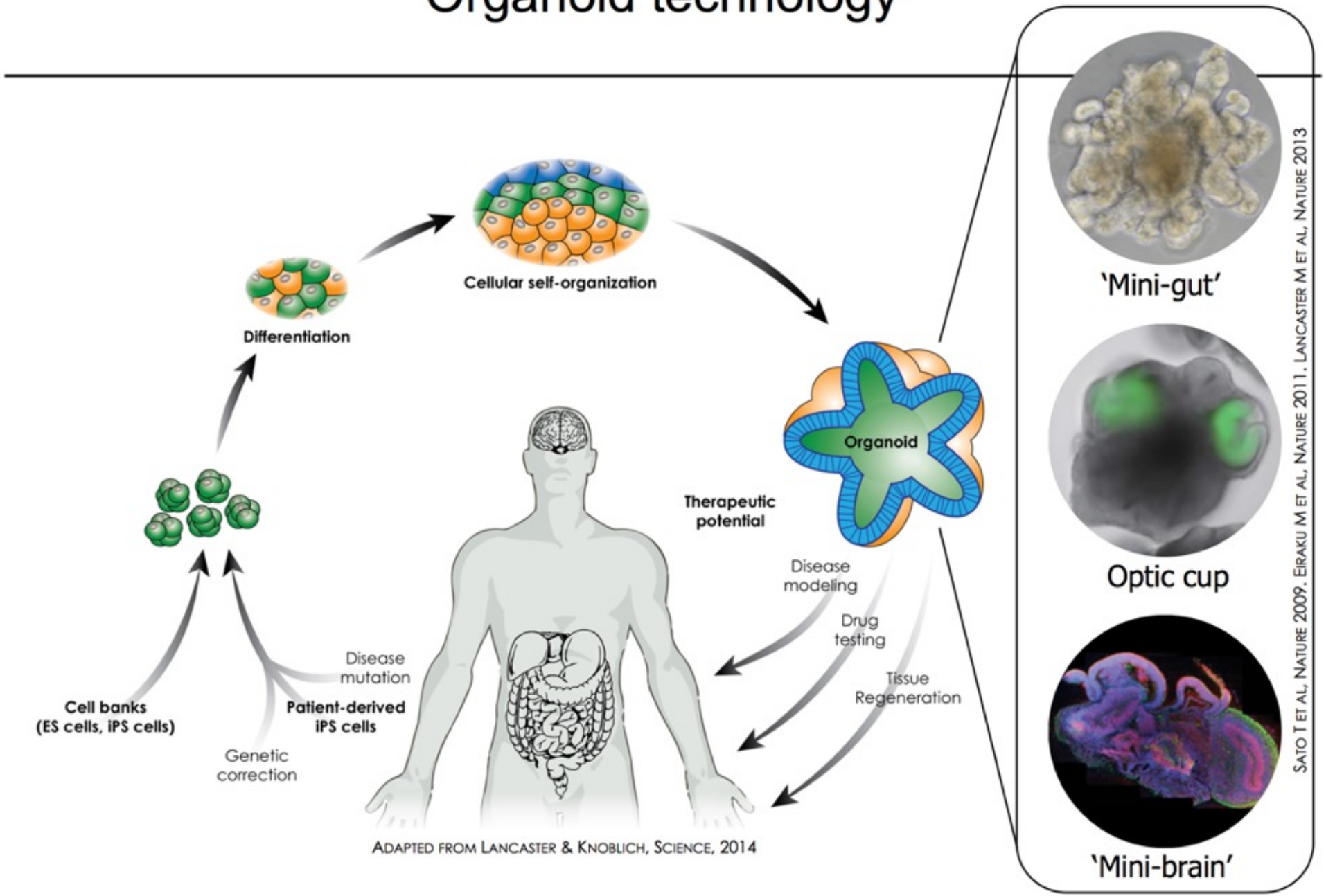


Synthetic (hydrogel) networks as instructive matrices are necessary!



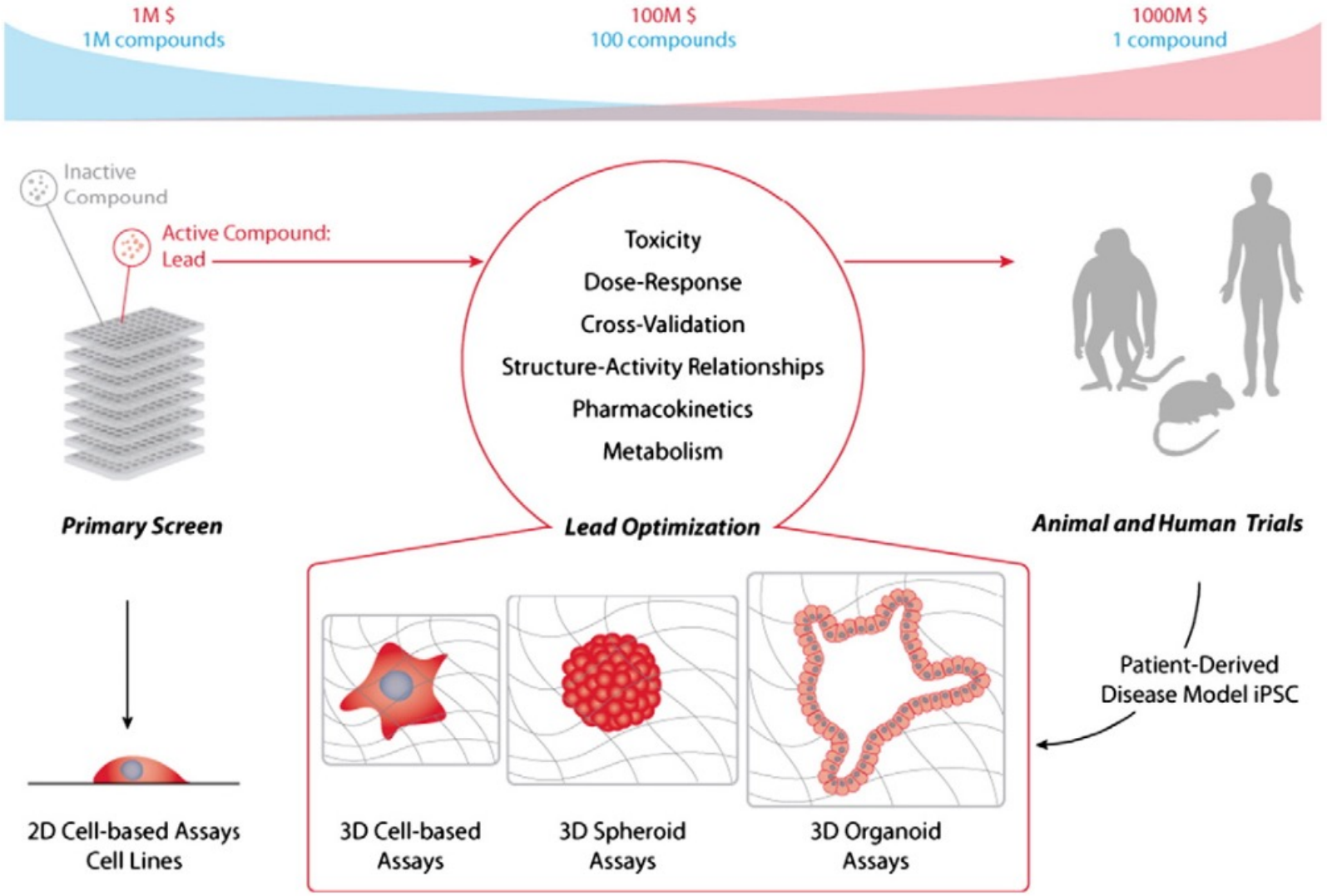


Organoid technology



ADAPTED FROM LANCASTER & KNOBLICH, SCIENCE, 2014

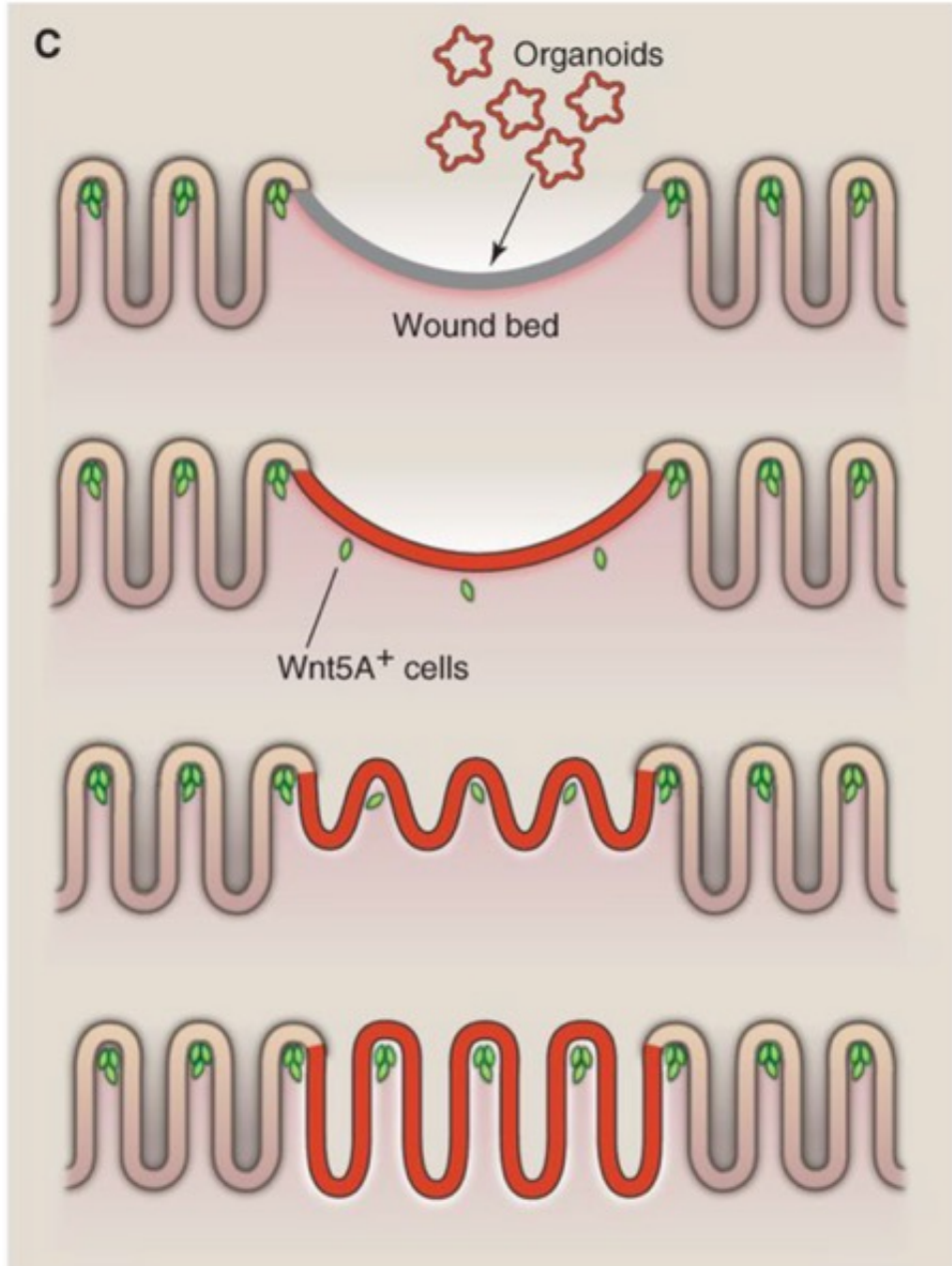
Organoids for better drug testing

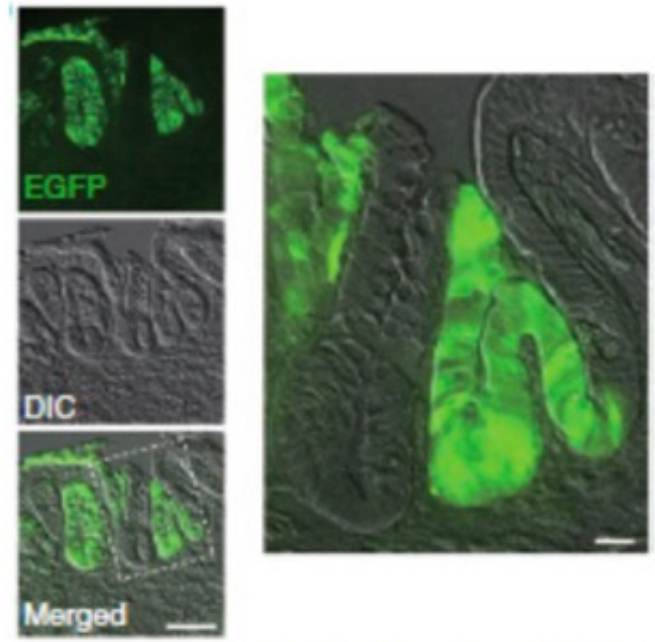


ig. 1. 3D assays could bridge the gap between primary screening and animal and human trials. Drug discovery pipeline typically proceeds from multiple compounds tested at relatively ow cost to few compounds in high-cost high-risk trials. The process of lead optimization and validation can benefit from increasingly representative in vitro technologies.

Advanced Drug Delivery Reviews 69–70 (2014) 19–28

Stem cell-based therapy of damaged intestinal tissue

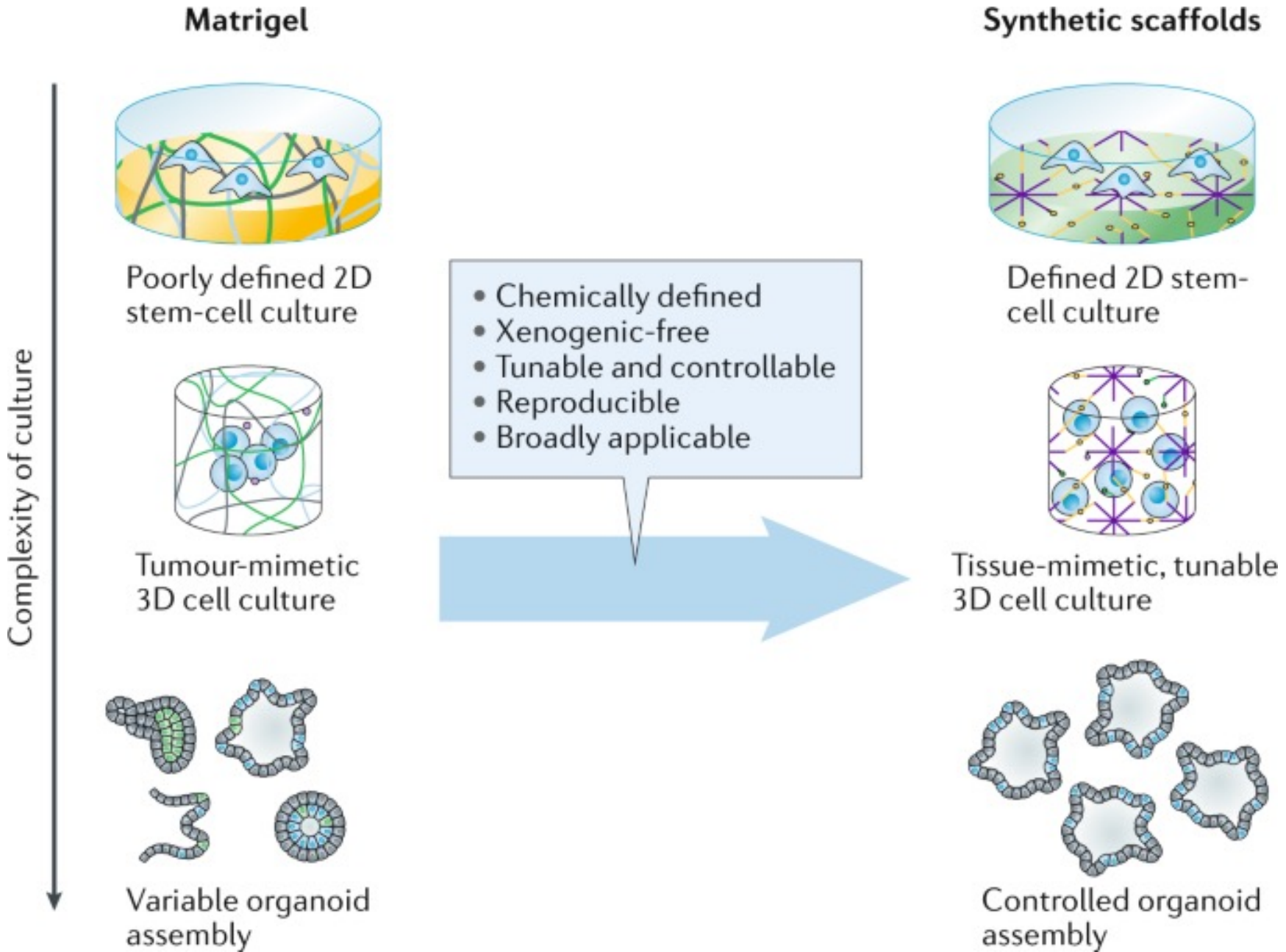




Yui et al (Nat Med, 2012)

Aisenbrey, E.A., Murphy, W.L.
Synthetic alternatives to Matrigel.
Nat Rev Mater **5,** 539–551 (2020).

Artificial ECM advantages

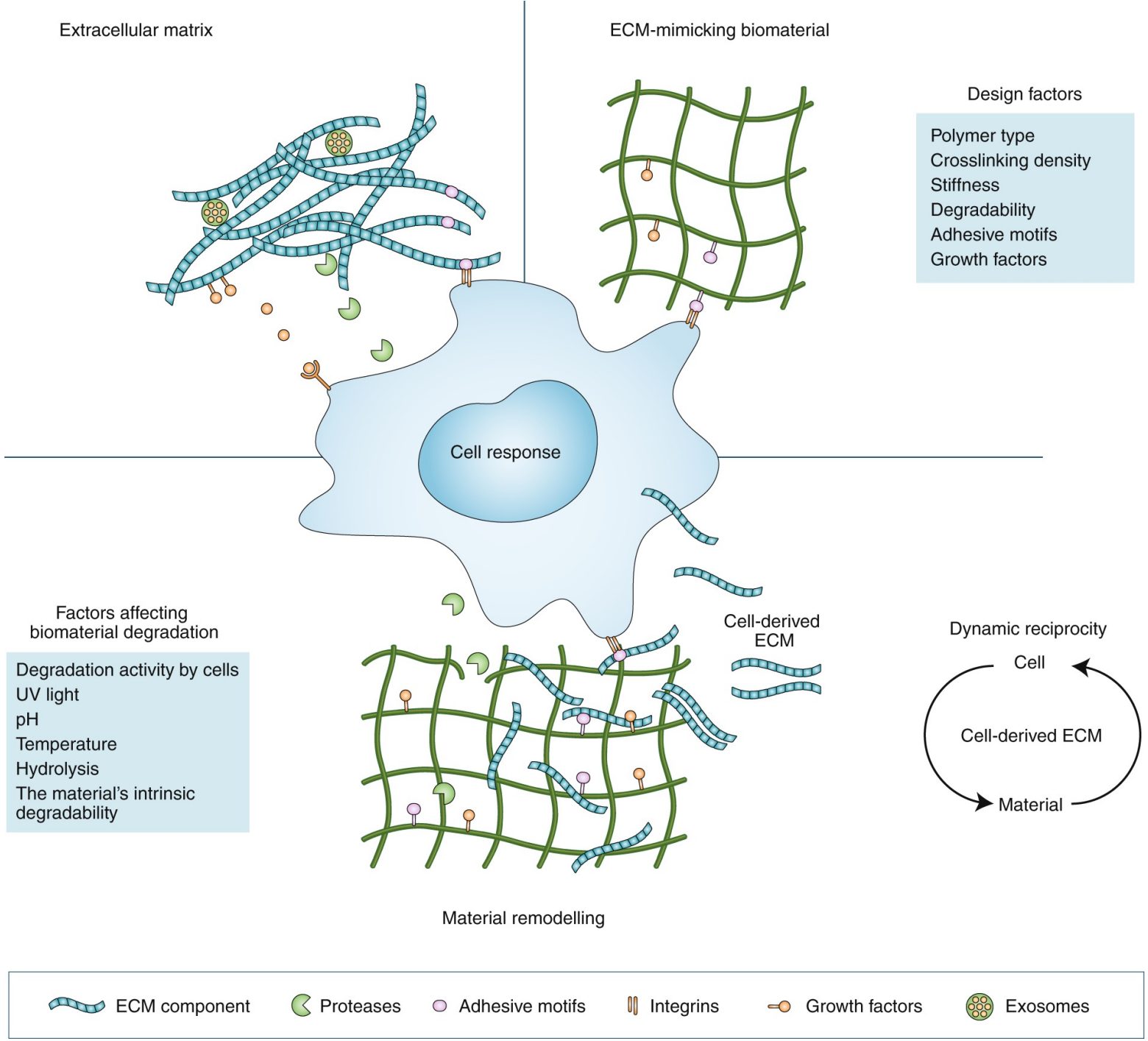


ECM-mimicking biomaterials can be rendered **cell-instructive** by incorporating protein-based or peptide-based motifs that recapitulate key features of the native ECM.

Cells encapsulated within hydrogels **remodel their surroundings** through a combination of matrix secretion and biomaterial degradation.

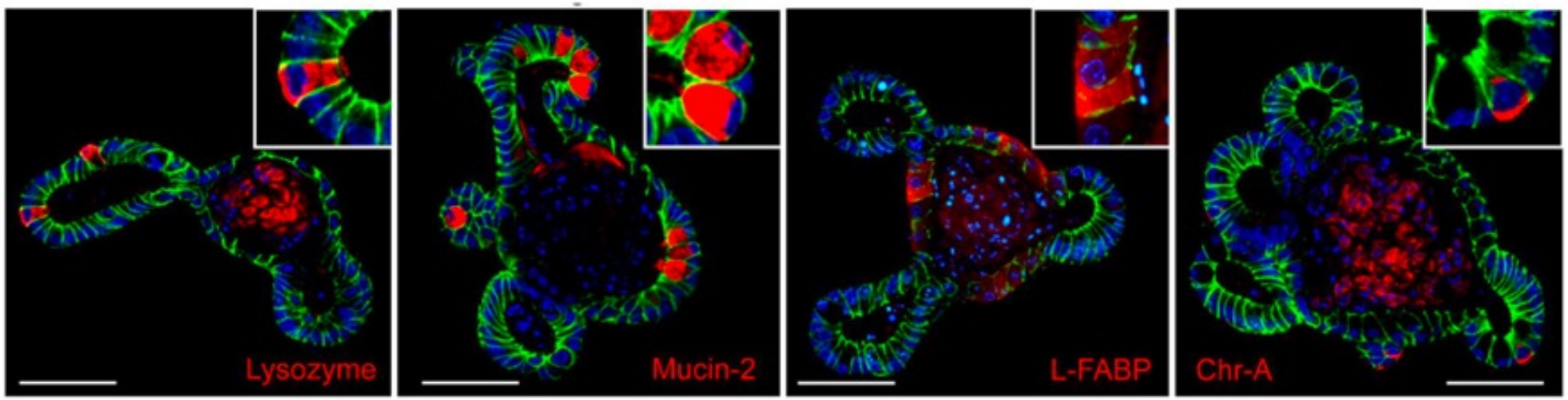
Over time, the **cell-secreted matrix can override cues provided by the hydrogel**.

This behaviour parallels the phenomenon of **dynamic reciprocity** observed in tissues, by which cells modulate their surroundings biochemically and mechanically, regulating intracellular signalling, gene expression and, ultimately, cell behaviour.

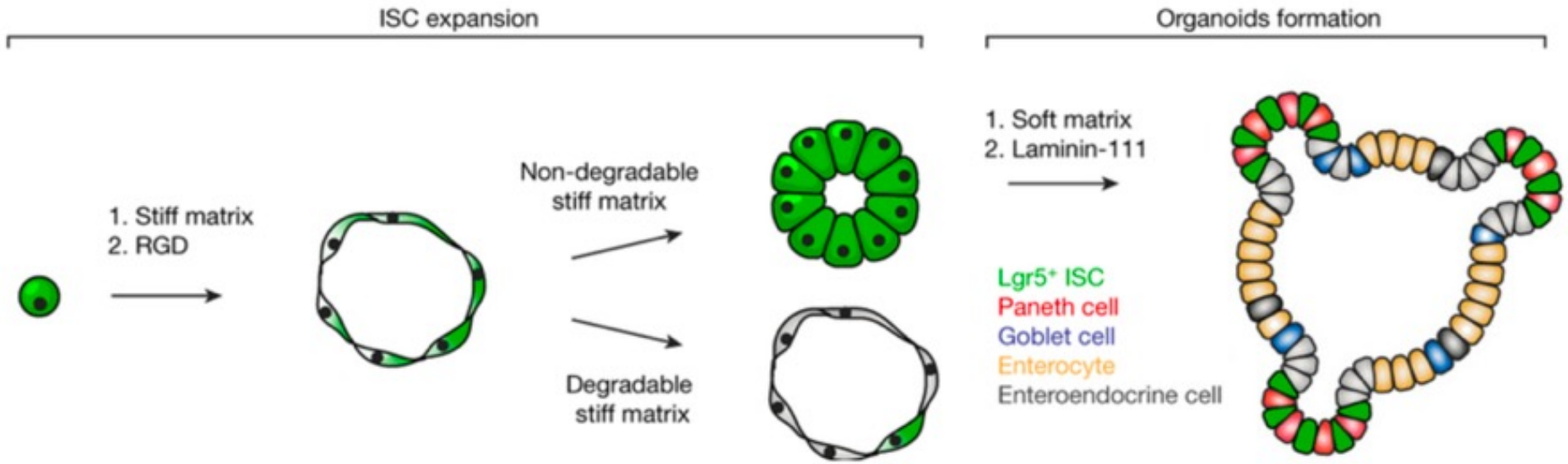


Blache, U., Stevens, M.M. & Gentleman, E. Harnessing the secreted extracellular matrix to engineer tissues. *Nat Biomed Eng* **4,** 357–363 (2020).

Intestinal organoids in a synthetic gel



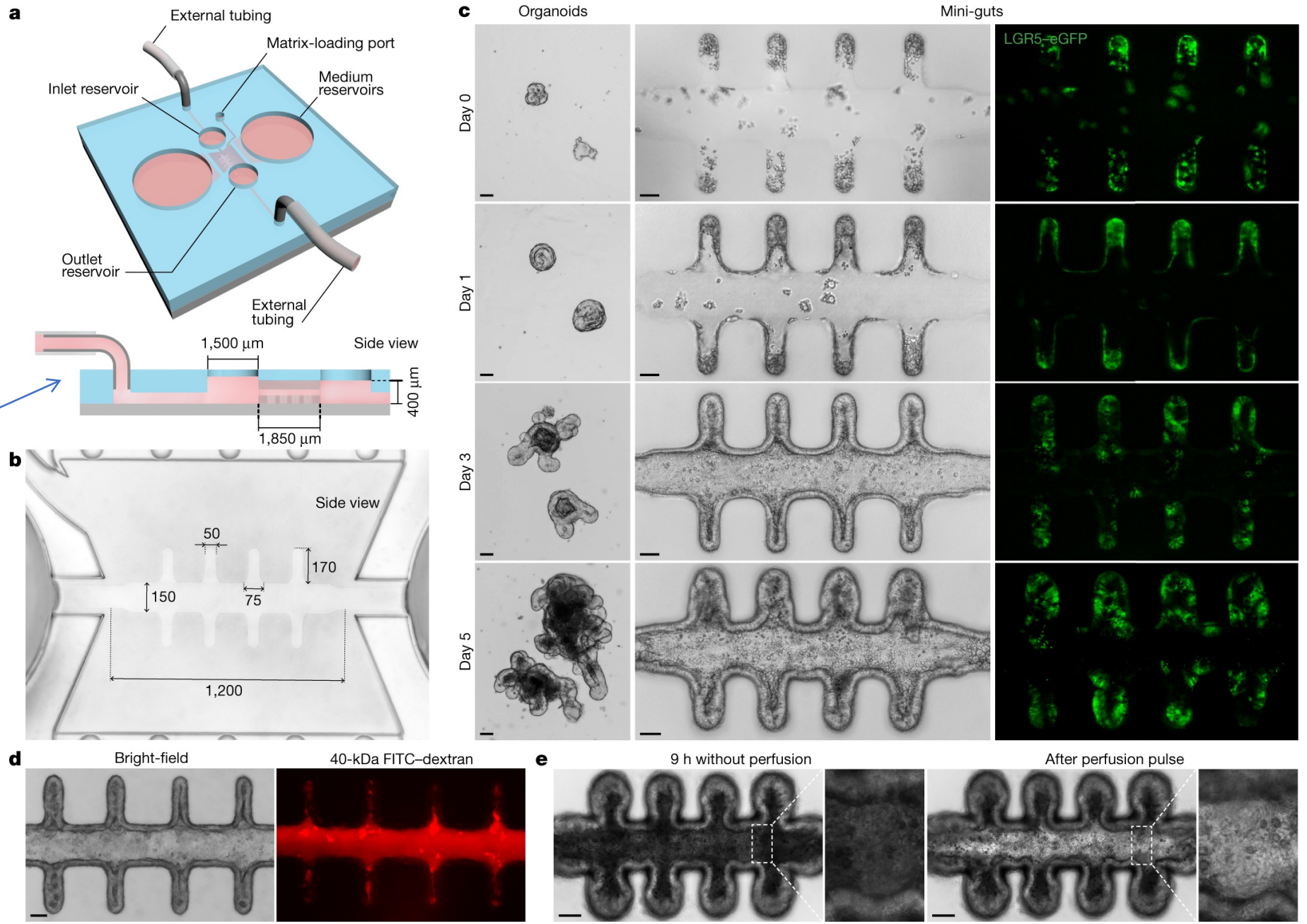
From intestinal stem cells to intestinal tissues



Lutolf, biomacromolecules 2007, science 2017

Mini Intestines: Current research

hybrid matrix composed of a mixture of type-I collagen, which provides a relatively stiff, adhesive substrate, and Matrigel, which contains the key constituents of the native basement membrane



Nikolaev, M., Mitrofanova, O., Broguiere, N. *et al.* Homeostatic mini-intestines through scaffold-guided organoid morphogenesis. *Nature* **585,** 574–578 (2020).

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LABORATORY OF STEM CELL BIOENGINEERING

Homeostatic mini-intestines through scaffold-guided organoid morphogenesis

Supplementary Video 1:

Mini-gut tube development

Time-lapse video of representative mini-gut tube development
during the first 72 hours

Lausanne, 2020

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Homeostatic mini-intestines through scaffold-guided organoid morphogenesis

Supplementary Video 2:

Tubular stem/progenitor cell epithelium

3D visualization of the coherent tightly-packed epithelium
composed of cells expressing high levels of E-cadherin at cell-cell junctions

Lausanne, 2020

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LABORATORY OF STEM CELL BIOENGINEERING

Homeostatic mini-intestines through scaffold-guided organoid morphogenesis

Supplementary Video 5:

Cell fate patterning in mini-gut tubes

Distribution of proliferative and differentiated cell types in spatially organized crypt and villus domains of a representative mini-gut tube

SOX9 (stem and progenitor cells)

Lysozyme (Paneth cells)

Mucin 2 (Goblet cells)

L-FABP (Enterocytes)

EdU pulse 12 hours (proliferative cells)

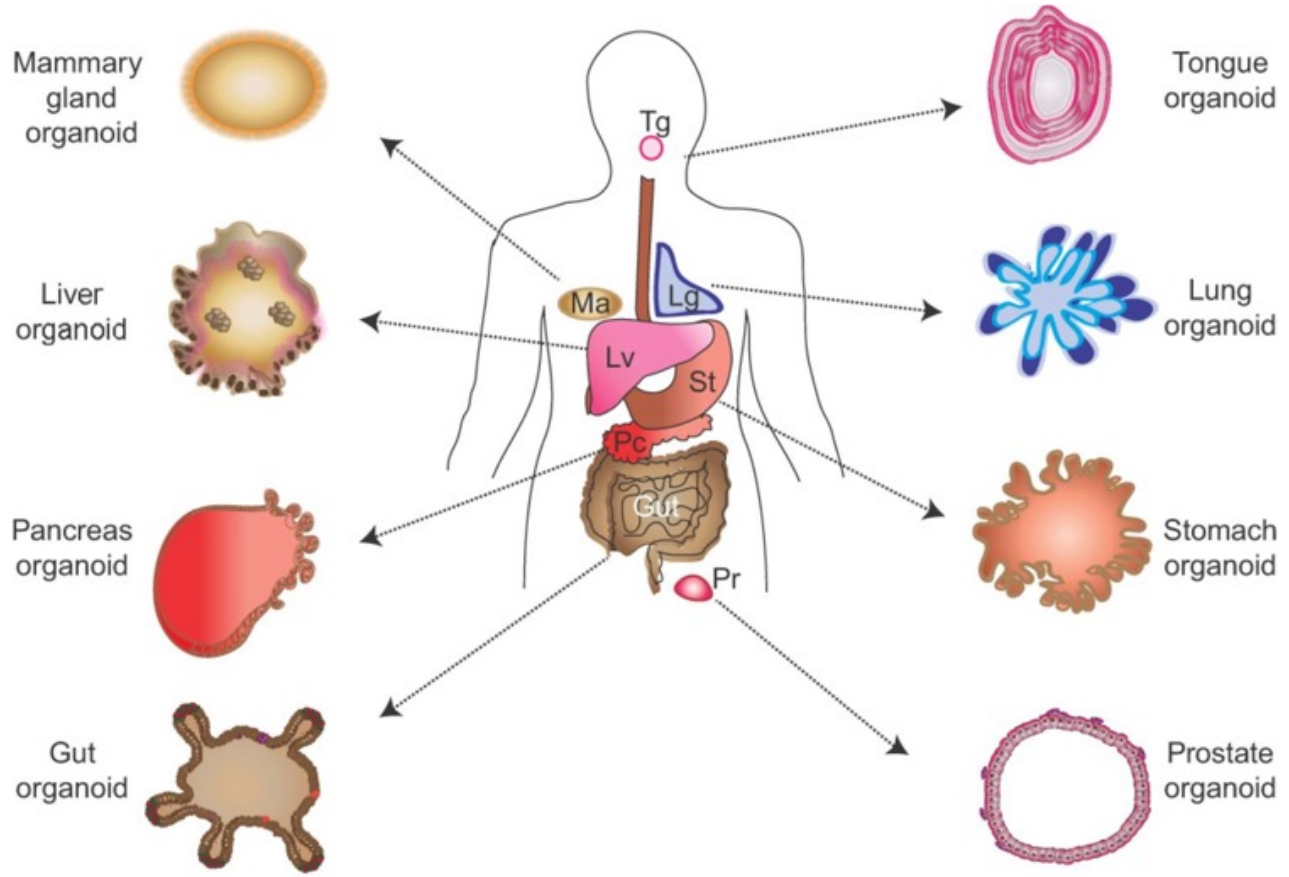
Lausanne, 2020

Clinical Applications: The Dream

Many medical problems arise from damage to differentiated cells

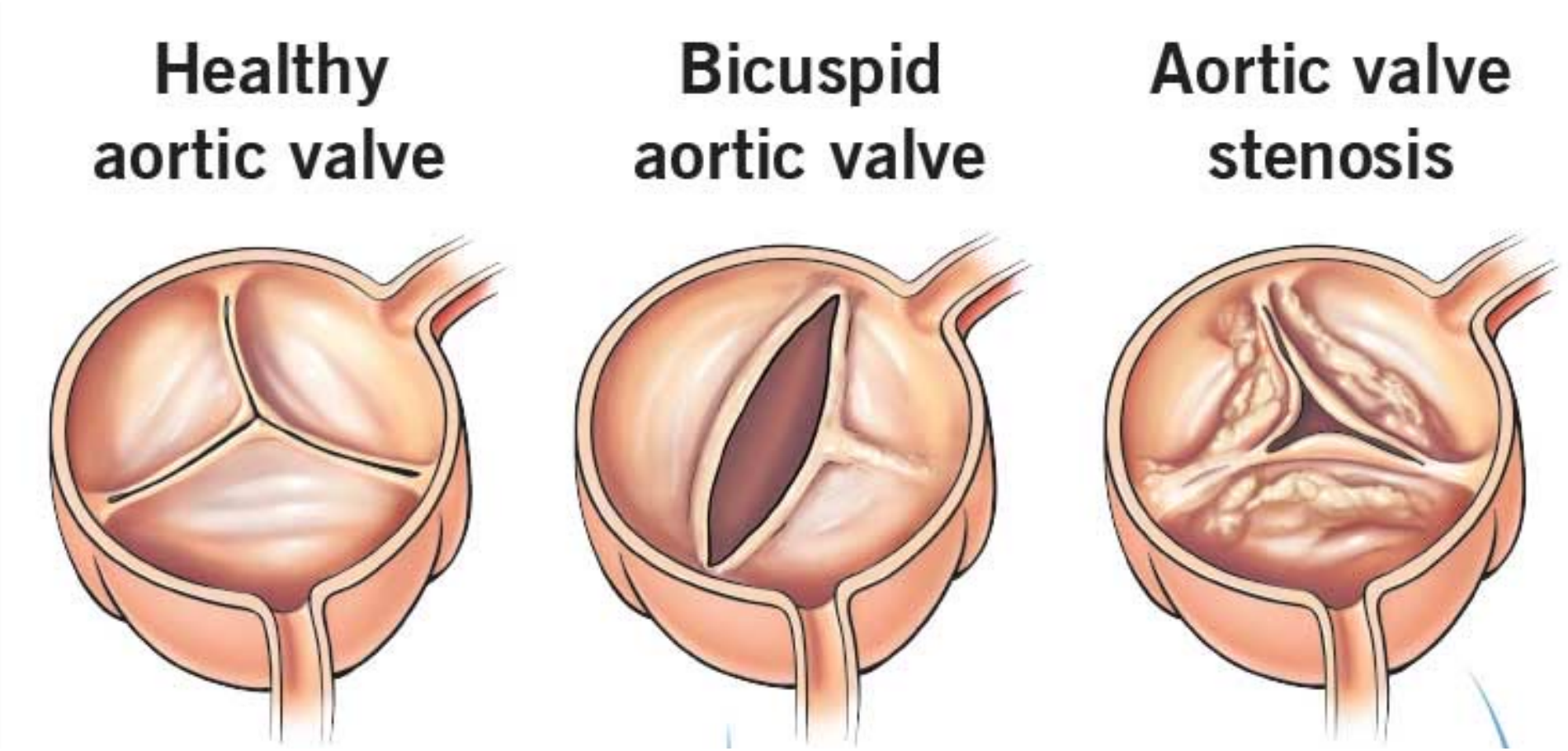
- Type 1 diabetes (destroyed Beta cells of the pancreas)
- Parkinson's disease (dopamine-secreting cells)
- Spinal cord injuries (loss of myelin sheath around axons)
- Ischemic stroke (blood clot in the brain → death of neurons)
- Multiple sclerosis (paralysis of skeletal muscles)
- Blindness (damage to the cornea)

Use **stem cells** to **REPLACE** lost cells of such disorders
Overcome **shortage** of **donor** organs for transplantation



Disclaimer: I am not a docter

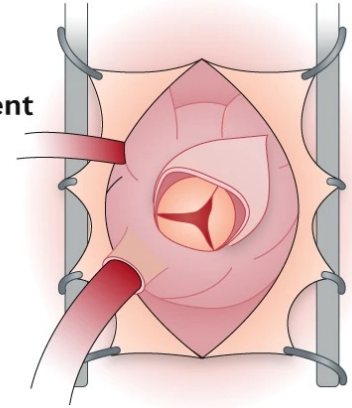
TE heart valves



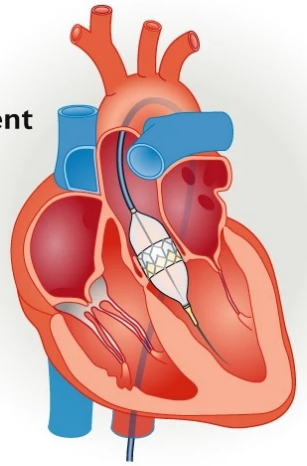
Disclaimer: I am not a docter

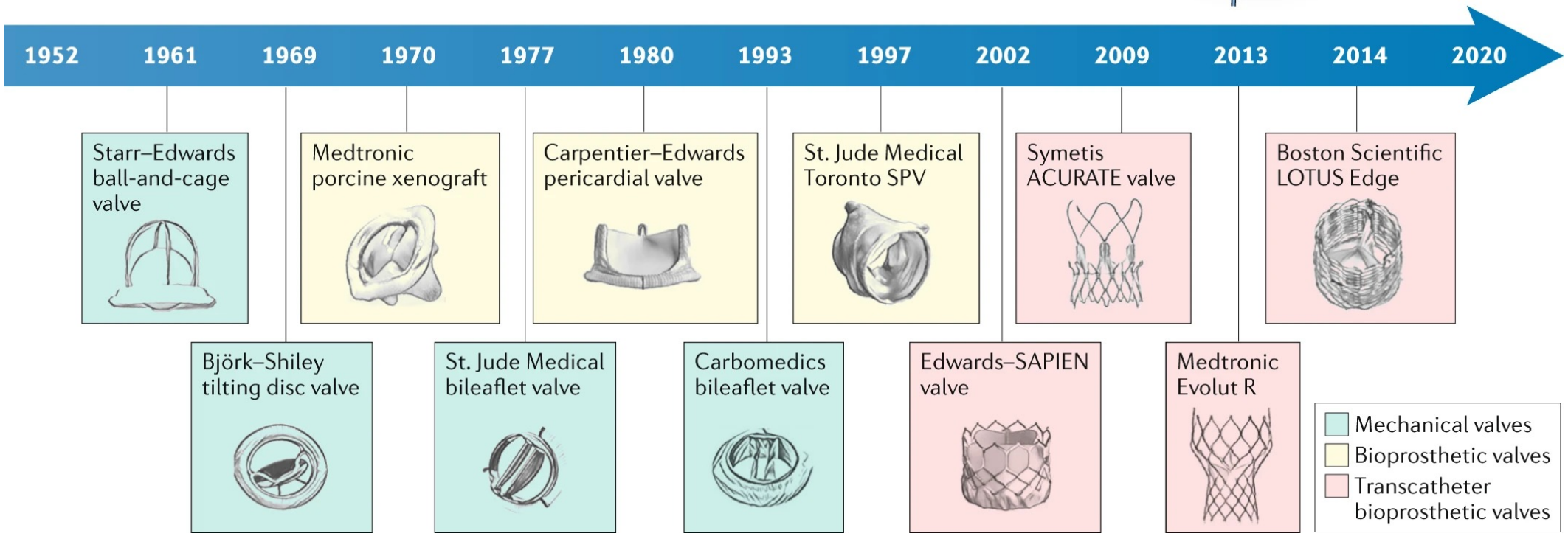
TE heart valves

Surgical aortic valve replacement
- Established in 1952
- Gold standard
- Requires open-heart surgery
- For mechanical and bioprosthetic valves



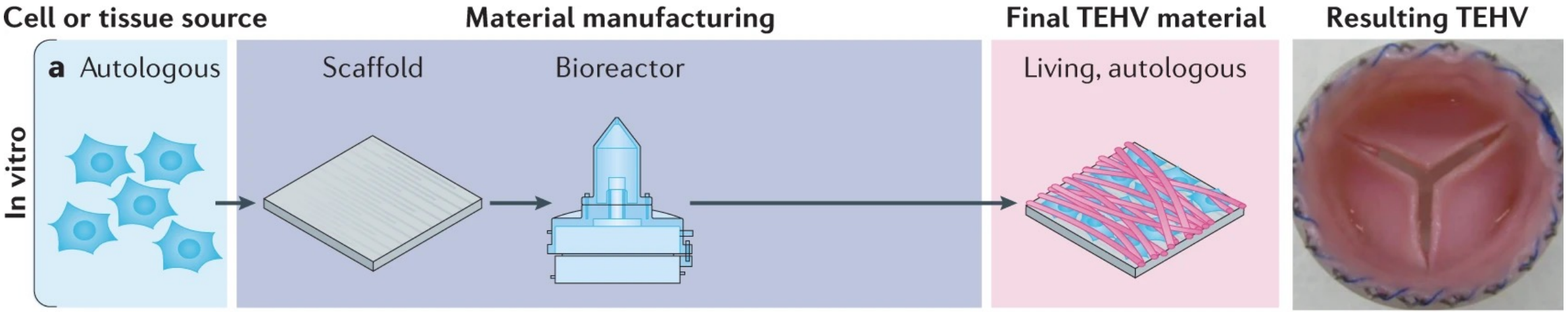
Transcatheter aortic valve replacement
- Established in 2002
- Minimally invasive
- Fast recovery
- For bioprosthetic valves





Fioretta, E.S., Motta, S.E., Lintas, V. *et al. Nat Rev Cardiol* **18**, 92–116 (2021). https://doi.org/10.1038/s41569-020-0422-8

TE heart valves



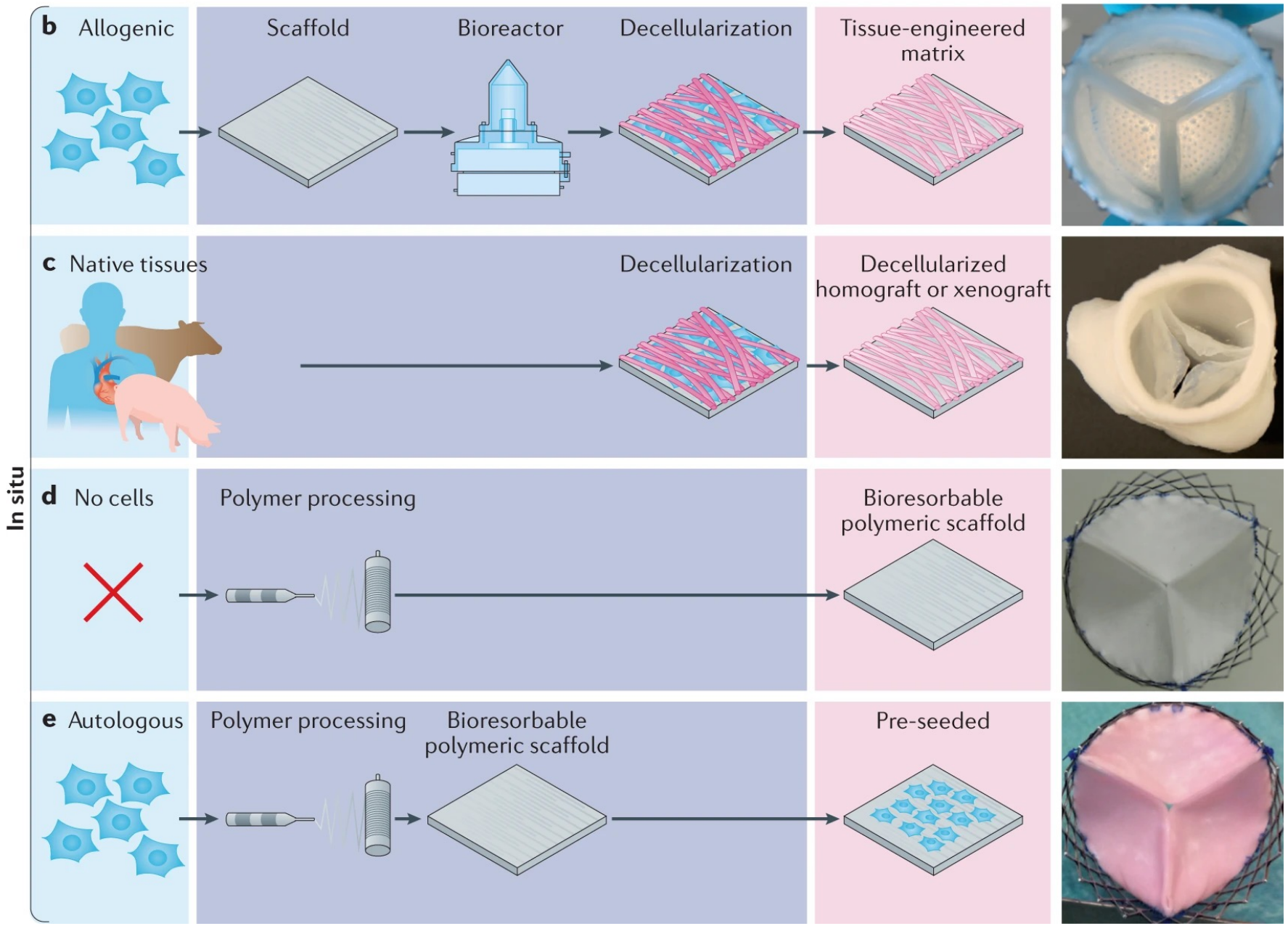
The paucity of homografts and the risk of xenograft immunogenicity have motivated researchers to find alternative materials in natural (such as collagen and fibrin) and synthetic (poly(glycolic acid) and polycaprolactone) polymers

challenges

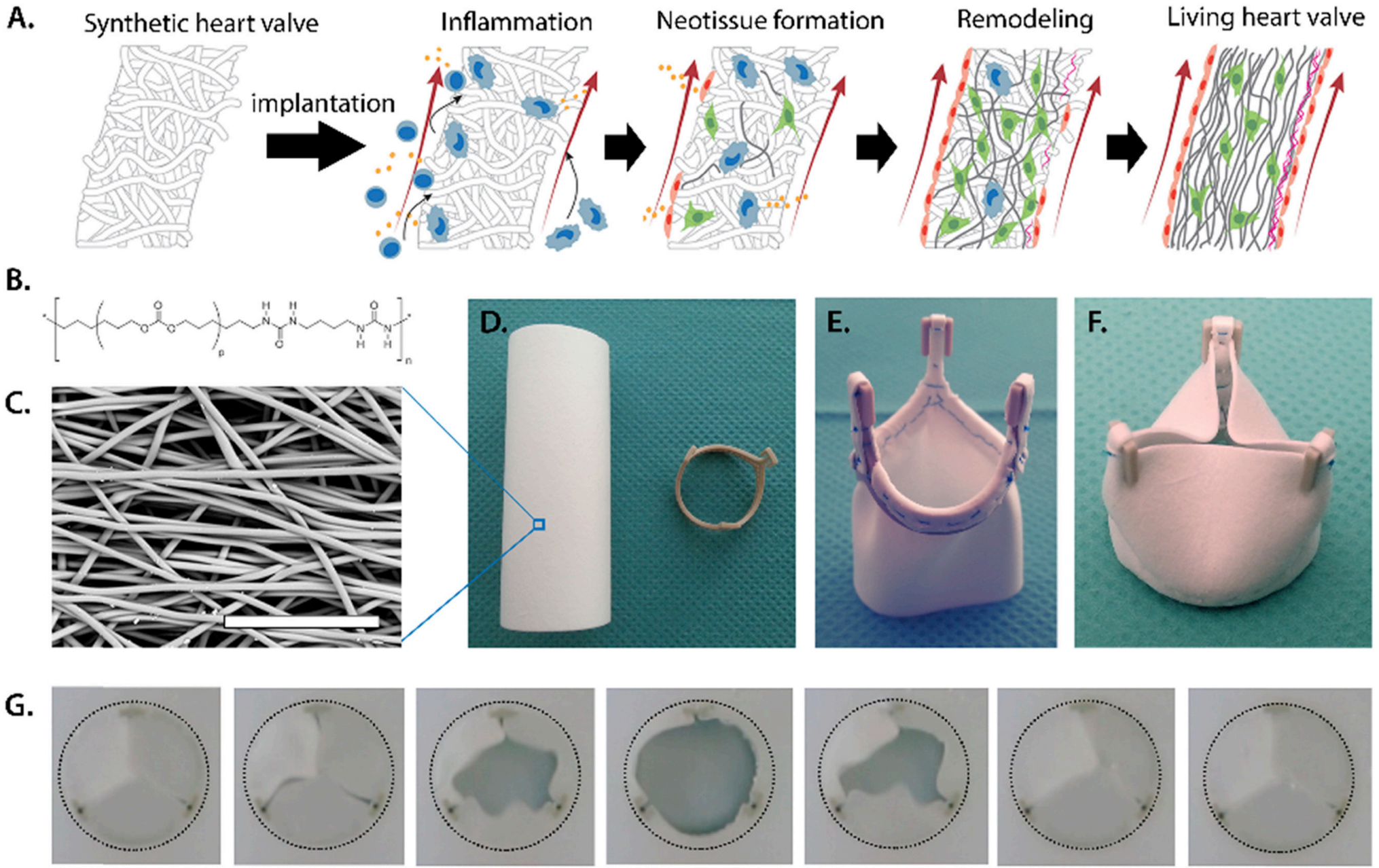
Technically and logistically complex (cells, expansion etc)
Donor-to-donor variation → inconsistencies in product
Uncontrolled thickening and shortening of the leaflets
Long-term safety and efficacy not yet established.

Fioretta, E.S., Motta, S.E., Lintas, V. *et al.* *Nat Rev Cardiol* **18**, 92–116 (2021). https://doi.org/10.1038/s41569-020-0422-8

TE heart valves

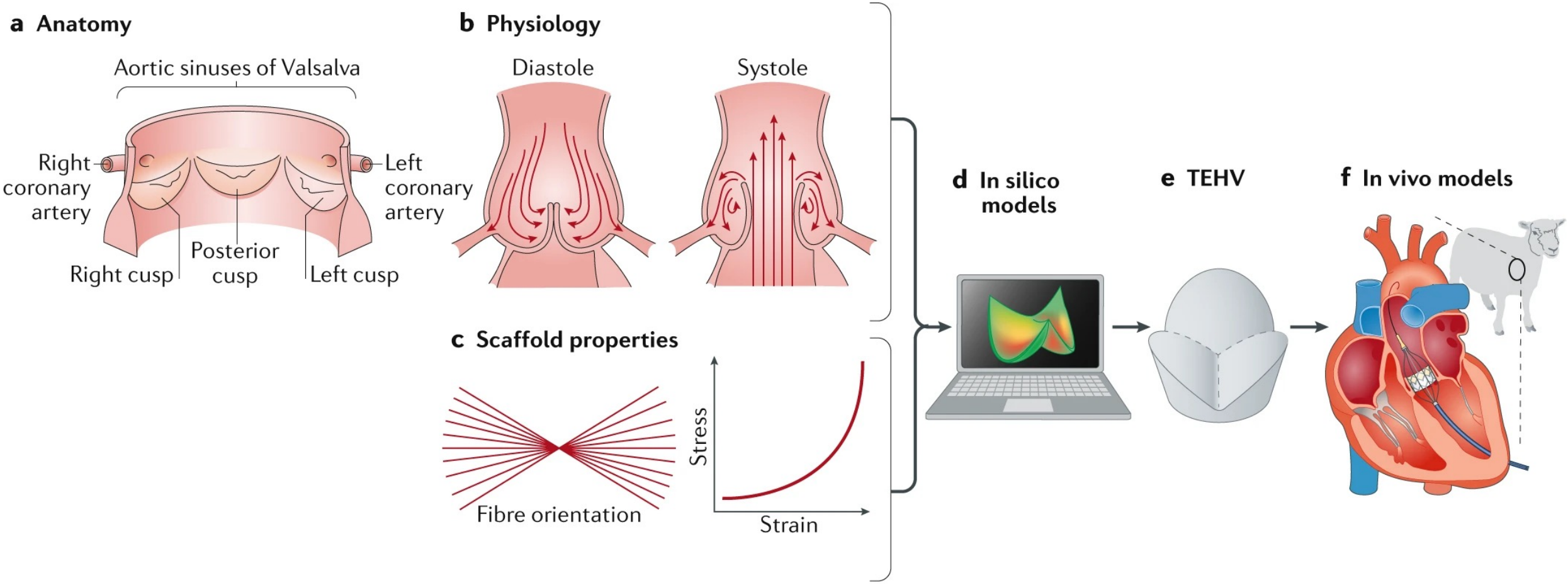


In situ valvular tissue engineering relies on the regenerative potential of the recipient's body to integrate and remodel an off-the-shelf implant that is designed to favour host cell adhesion and tissue formation and **provide valve functionality immediately upon implantation**



Biomaterials. Volume 125, May 2017, Pages 101-117

TE heart valves future steps and challenges



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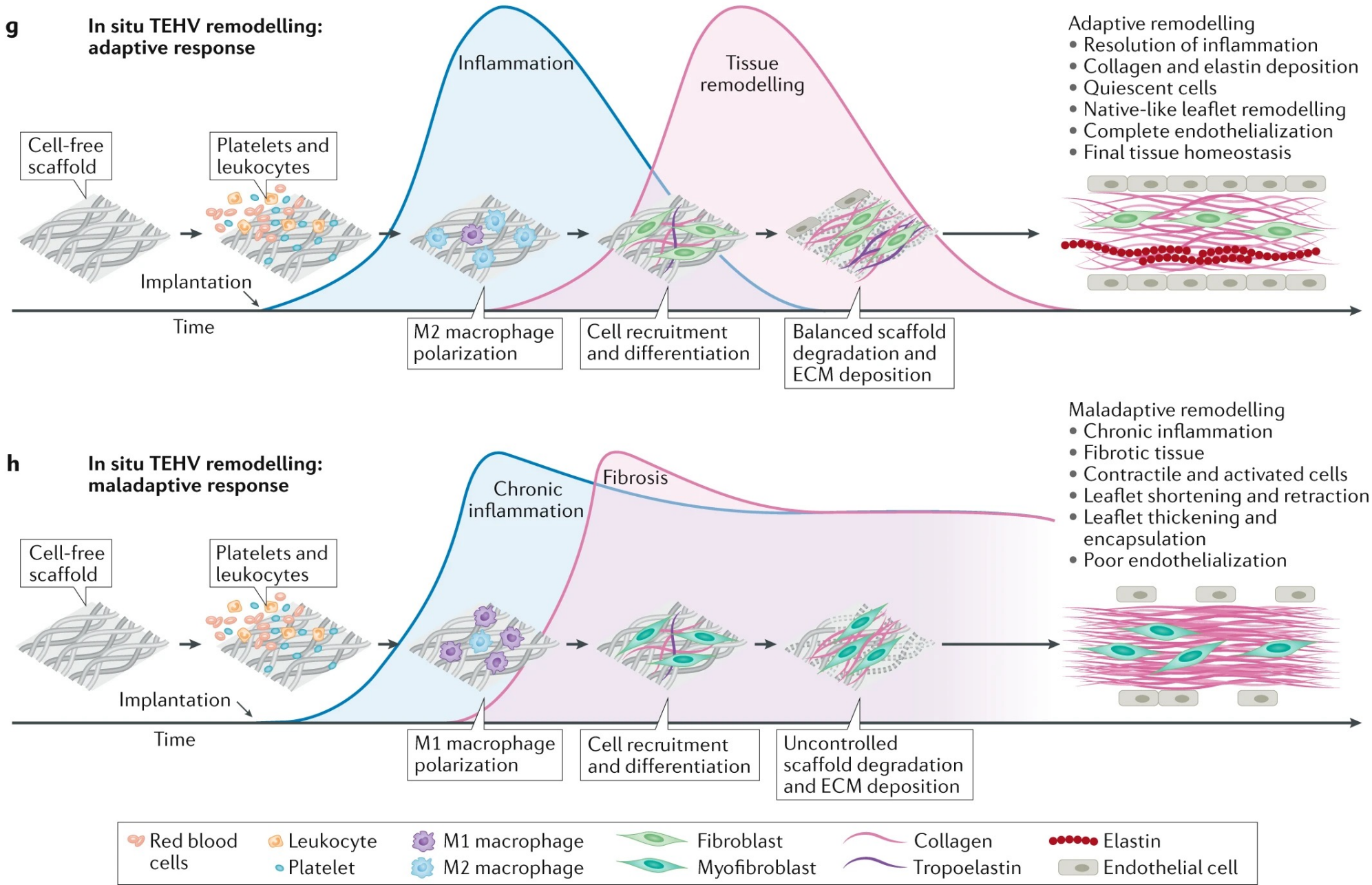
TE heart valves future steps and challenges



TE heart valves

•**Surgical heart valve replacement** is the **gold-standard treatment** for aortic valve disease, but **transcatheter valve implantation has revolutionized the field by providing a novel treatment option** for patients of all risk profiles.

•Despite rapid advances in the field of heart valve therapy, an **unmet clinical need remains for valve replacements with regenerative, remodelling and growth potential.**

•**In situ tissue engineering technologies** can be used to produce a heart valve replacement that is readily available, manufactured using decellularized extracellular matrix or bioresorbable polymers, and **transforms into a native-equivalent valve after implantation.**

•**Computational modelling is a powerful tool** that can be used to **improve and accelerate our understanding** of tissue-engineered heart valve growth and remodelling and should be used in concert with in vitro and in vivo tissue engineering technologies.

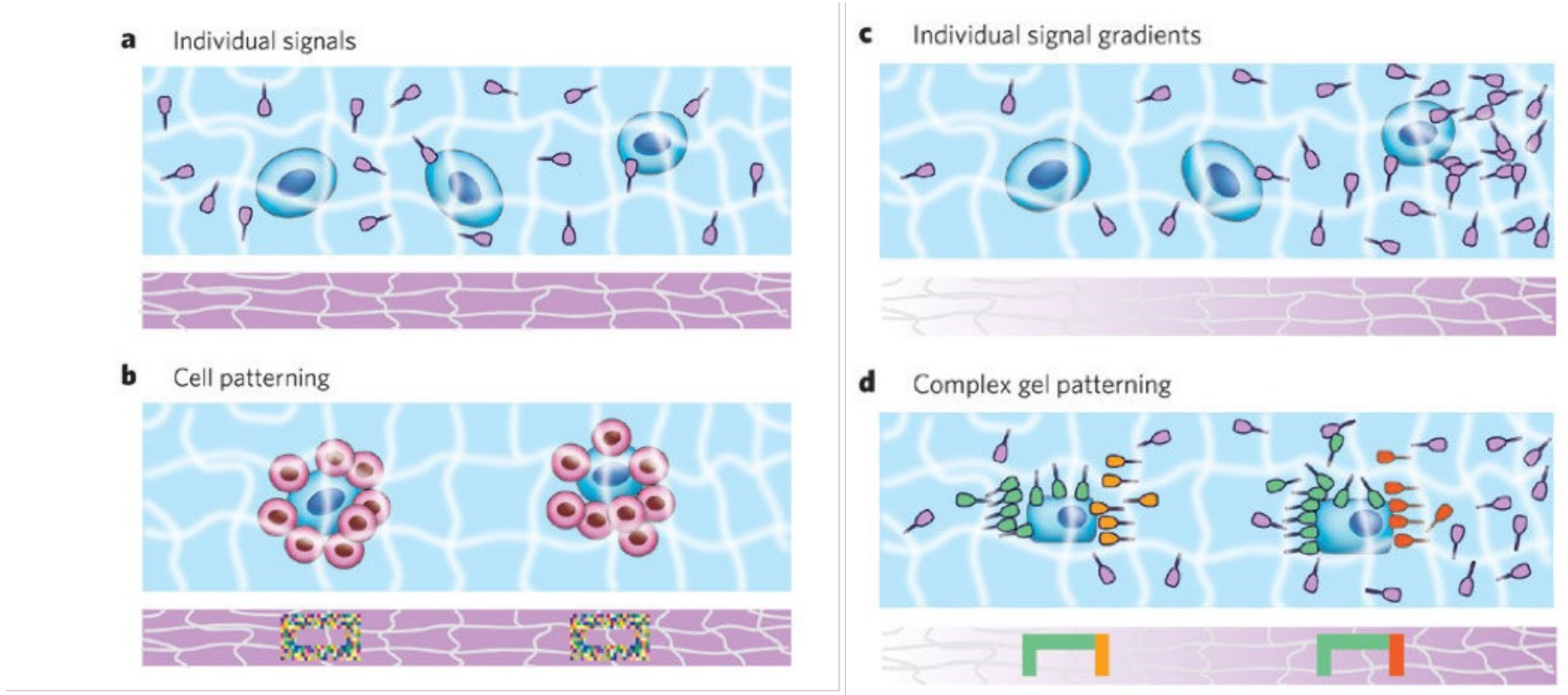
•To ensure the good clinical safety, feasibility and efficacy of the tissue-engineered heart valve, researchers and clinicians should work according to **Good Manufacturing Practices and Good Laboratory Practices** as well as to International Organization for Standardization requirements.

•The field of heart valve tissue engineering still faces **several challenges**, such as issues related to **immunocompatibility**, **haemocompatibility**, **remodelling and growth capacity**, which need to be further investigated before broad clinical adoption is possible.

Biomaterials Challenge

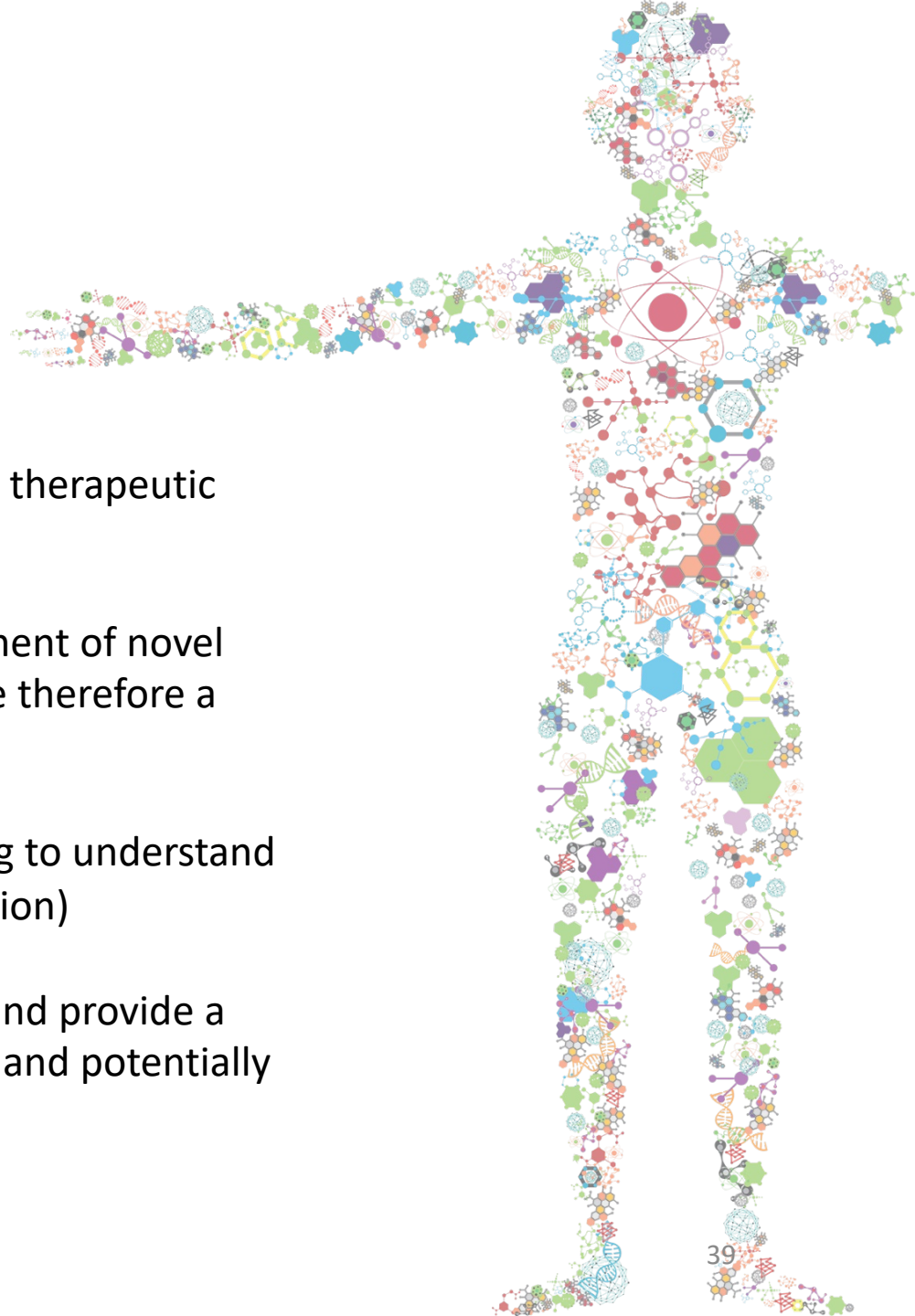
Biomaterials (surfaces, tissue engineering scaffolds), **biofabrication** (microfluidics, three-dimensional bioprinting) and **bioreactor** (physiological environment) **techniques** hold the potential to allow us to **construct, deconstruct and investigate the important components of cellular microenvironments.**

Such approaches could evolve the development of both **reductionist stem cell interfaces** allowing high throughput analysis and discovery and, perhaps more importantly, **non-animal technologies** (NATs) that recreate tissue complexity and reduce costly/inefficient animal experimentation.



Designing stem cell niches for differentiation and self-renewal, Hannah Donnelly , Manuel Salmeron-Sanchez and Matthew J. Dalby, 2018

Conclusion



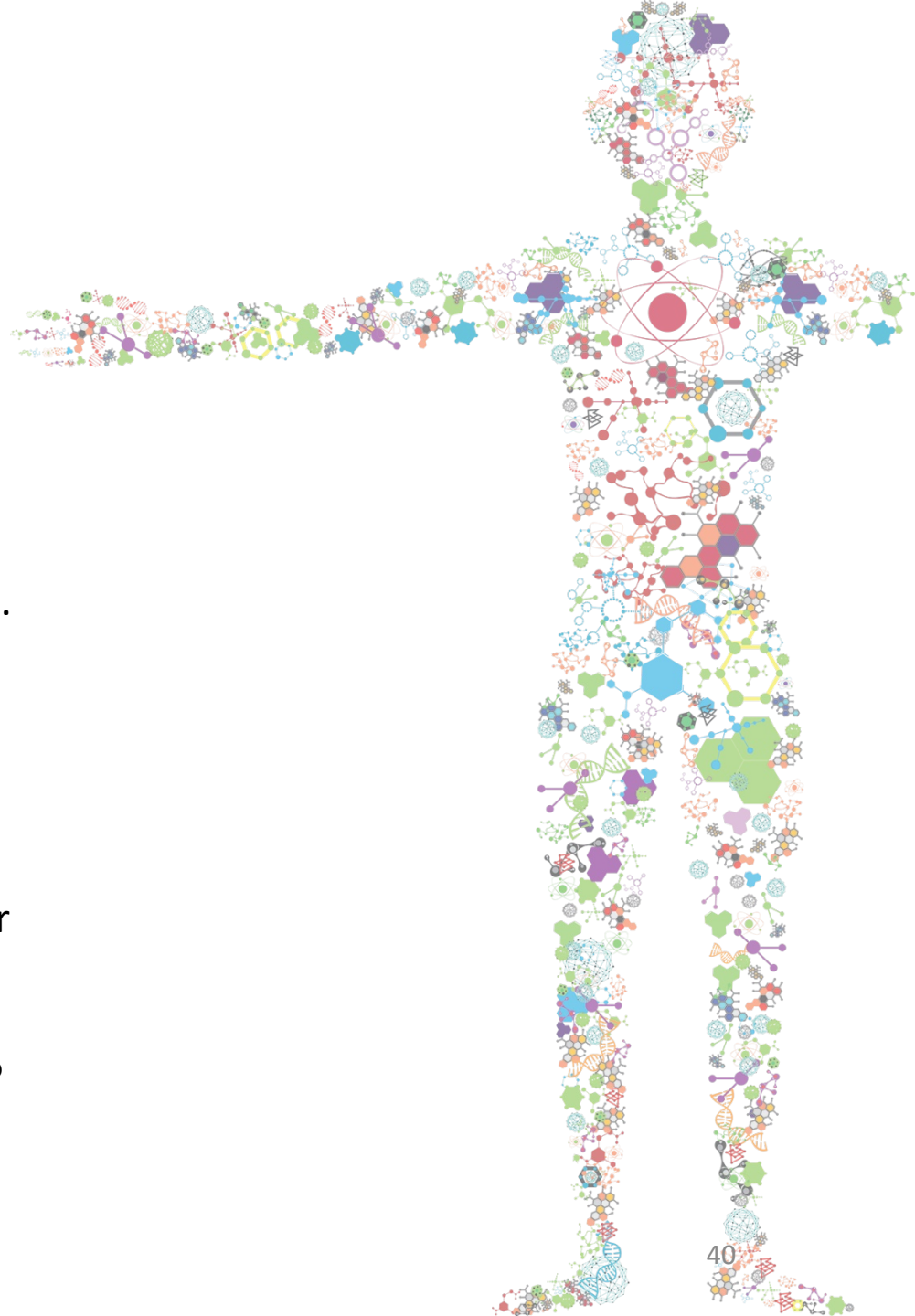
Tissue engineering is a very promising area in science where significant therapeutic advances will be made in the (near?) future

Biomaterials science and engineering plays a huge role in the development of novel tissue engineering therapies as they can control stem cell fate and have therefore a unique and powerful position within tissue engineering

However, the processes involved are complex and we are just beginning to understand the role of several parameters (stiffness, degradation, biofunctionalization)

Organoids are mini organs that are create by tissue specific stem cells and provide a patient specific system to study disease processes, organ development and potentially can become a novel treatment and transplant therapy

Test Questions



How is the ECM made?

Why is matrigel not suited for in vivo therapy?

Design an artificial material where cells can grow on in a circular pattern. Motivate your choice of scaffold material, functional adhesion sites, and indicate size / dimensions.

Which material parameters need to be screened in ECM engineering?

What are the 3 main types (populations) of stem cells and what are their limitations?

What are organoids and why are they interesting for tissue engineering?