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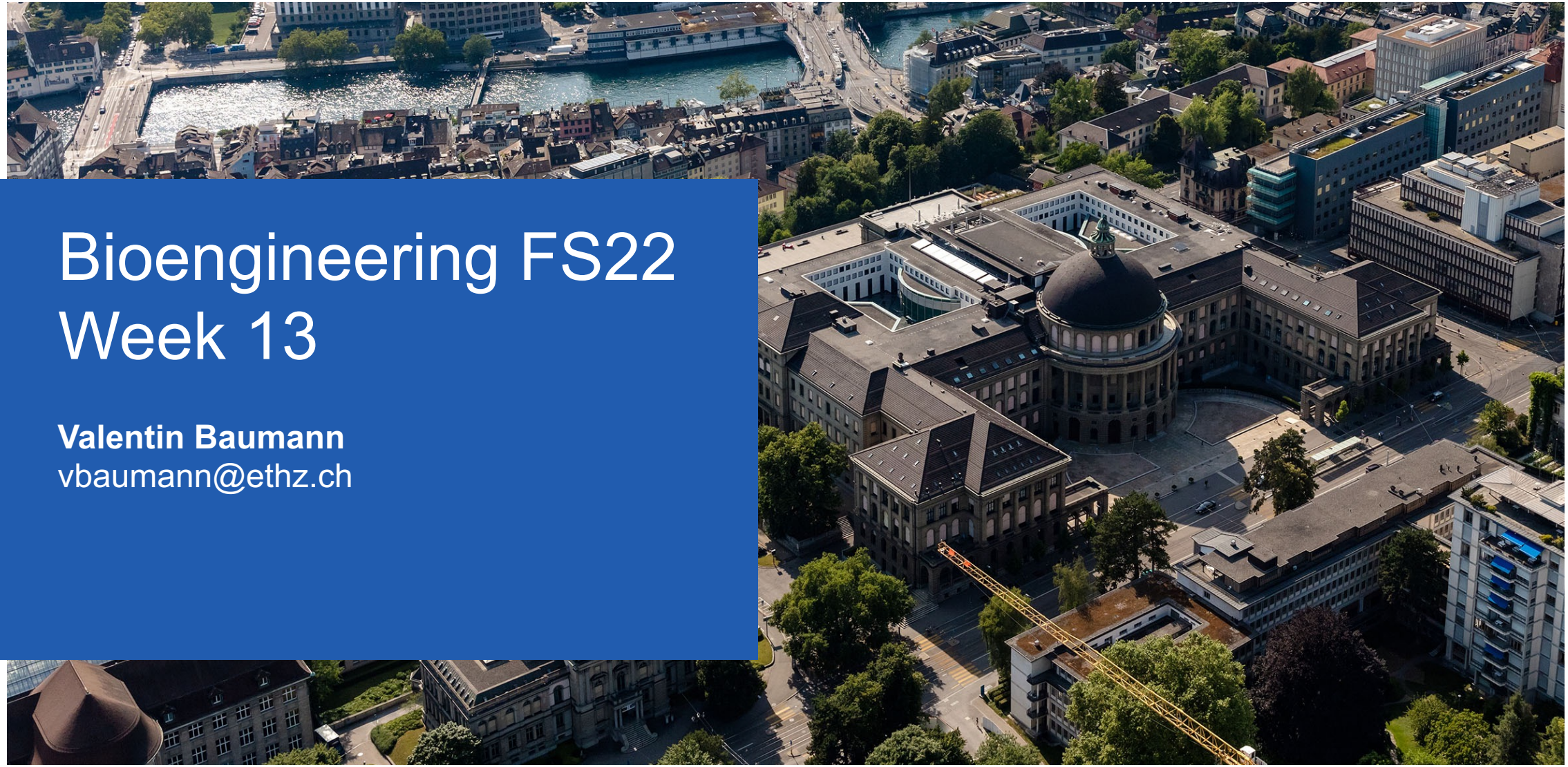

Bioengineering FS22
Week 13

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Agenda heute

1. Regenerative Medicine
2. Tissue Engineering
3. Clinical Translation & Legal Regulation
4. Clinical Applications
5. Paper

Regenerative Medicine


REVIEW

Stem cells and healthy aging

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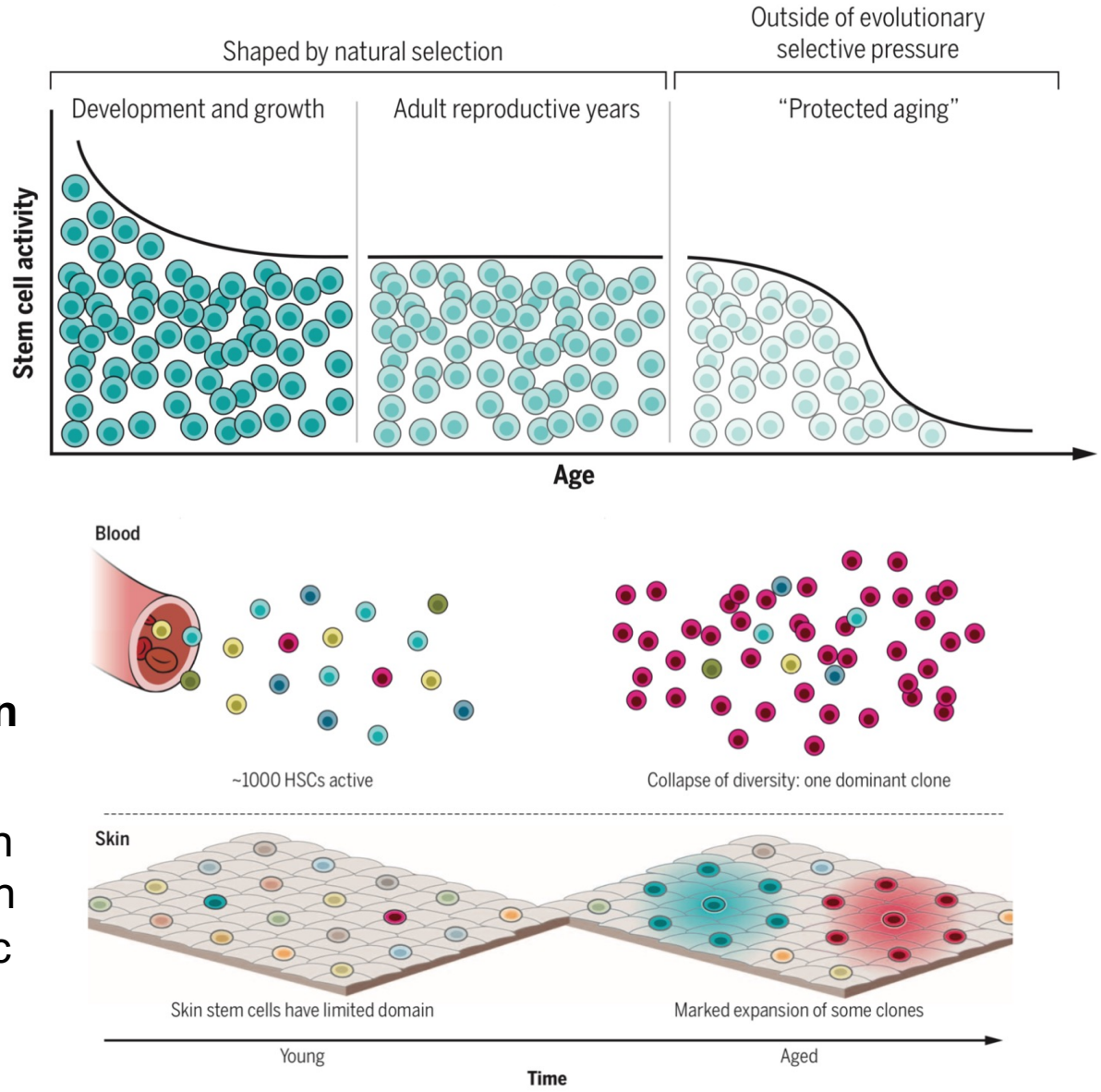
Regenerative Medicine

- The process of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal function
- Possibility of engineering damaged tissues and organs by stimulating the body's own repair mechanism to functionally heal previously irreparable tissues or organ
- → Especially important in aging individuals, as with age the ability of the body to heal significant injury without permanent damage to the tissue is lost.
- The decrease in regenerative potential is associated with a **decreasing stem cell activity** and a **decrease in stem cell diversity**
- Decrease in stem cell diversity might be explained by an erosion of epigenetic regulation in aging stem cells. With age, stem cells acquire somatic mutations and a genetic drift occurs, leading to attrition of some clones → expansion of some dominating clones



Regenerative Medicine

- Although stem cell activity is a key element of regenerative capacity, **environmental factors can strongly modify stem cell behaviour**

→ Extrinsic factors affect aging stem cells:

Extrinsic factors affect aging stem cells

The influence of the local and systemic environment on stem cell function during protected aging has been demonstrated by exposing young stem cells to an aged environment, and vice versa.

These studies have used strategies such as heterochronic transplantation, in which cells derived from a donor of one age are transplanted into a recipient of a different age, or heterochronic parabiosis, in which two mice of different ages are adjoined to create a shared circulatory system, thus exposing cells in one animal to the systemic environment of the other (Fig. 3).

When young stem cells were subjected to an aged systemic milieu by heterochronic parabiosis, they exhibited functional decline that resembled accelerated aging. On the other hand, the converse was also true: Aged cells placed in a young environment or exposed to a youthful systemic milieu exhibited more youthful characteristics, suggesting that it may be possible to ameliorate certain aging features.

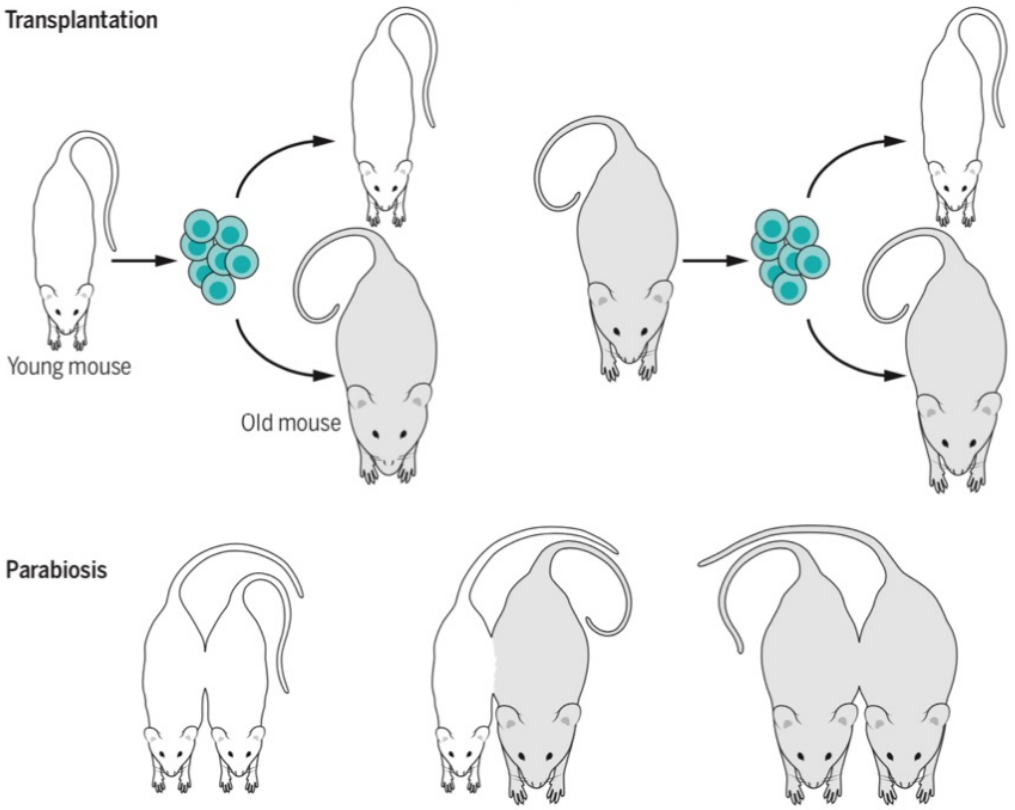


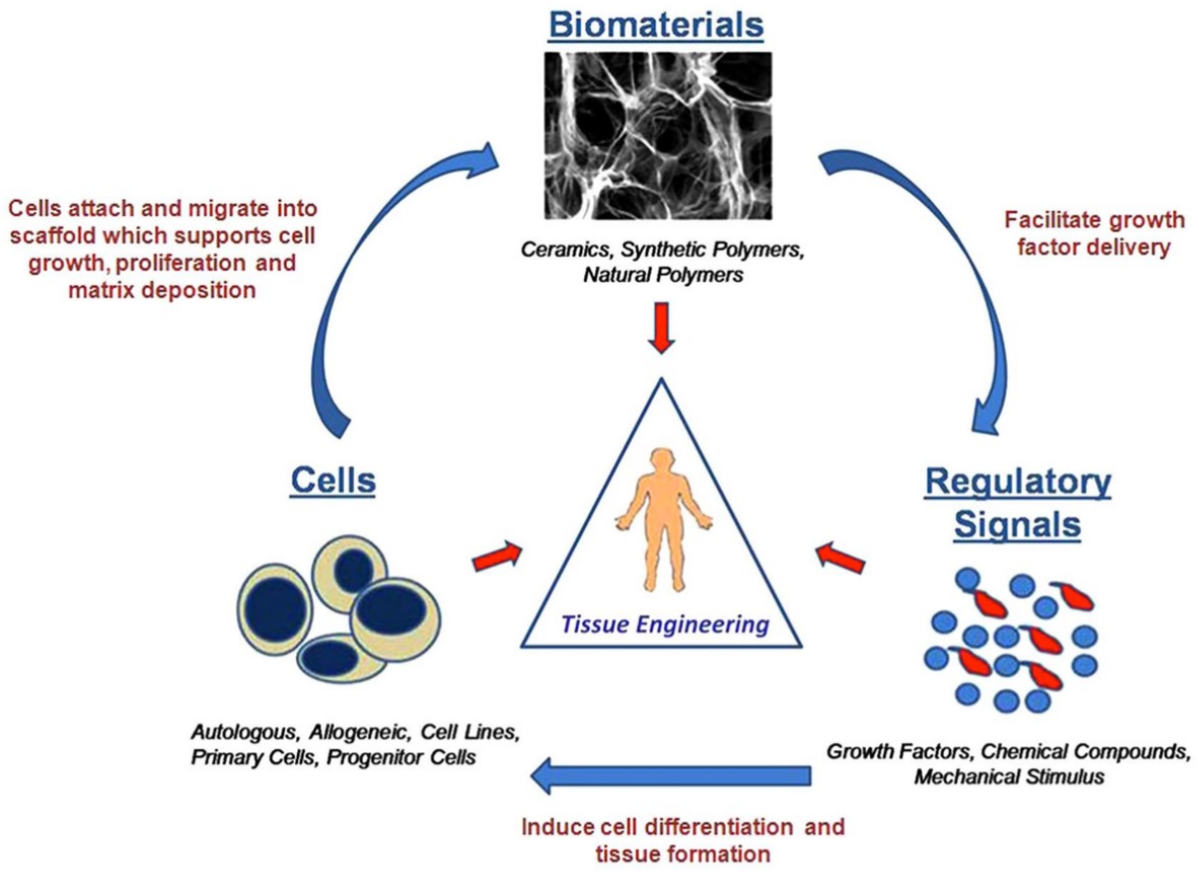
Fig. 3. Intrinsic and extrinsic factors influence age-related changes in stem cell function. Distinguishing cell-intrinsic changes from cell-extrinsic changes (e.g., arising from the cellular environment) in cell function has been aided by heterochronic studies. In heterochronic transplantation, stem cells isolated from either young or old donors are transplanted into young or old hosts, and cellular function is then analyzed in these four-way comparisons (young into young, young into old, old into young, old into old). In parabiosis, animals are joined to promote the development of a single, shared circulatory system, thus exposing cells in one animal to the systemic environment of the other animal. In this case, the cellular functions in young or old partners in the heterochronic pairs (young-to-old) are compared to those in isochronic pairs (young-to-young and old-to-old).

Tissue Engineering

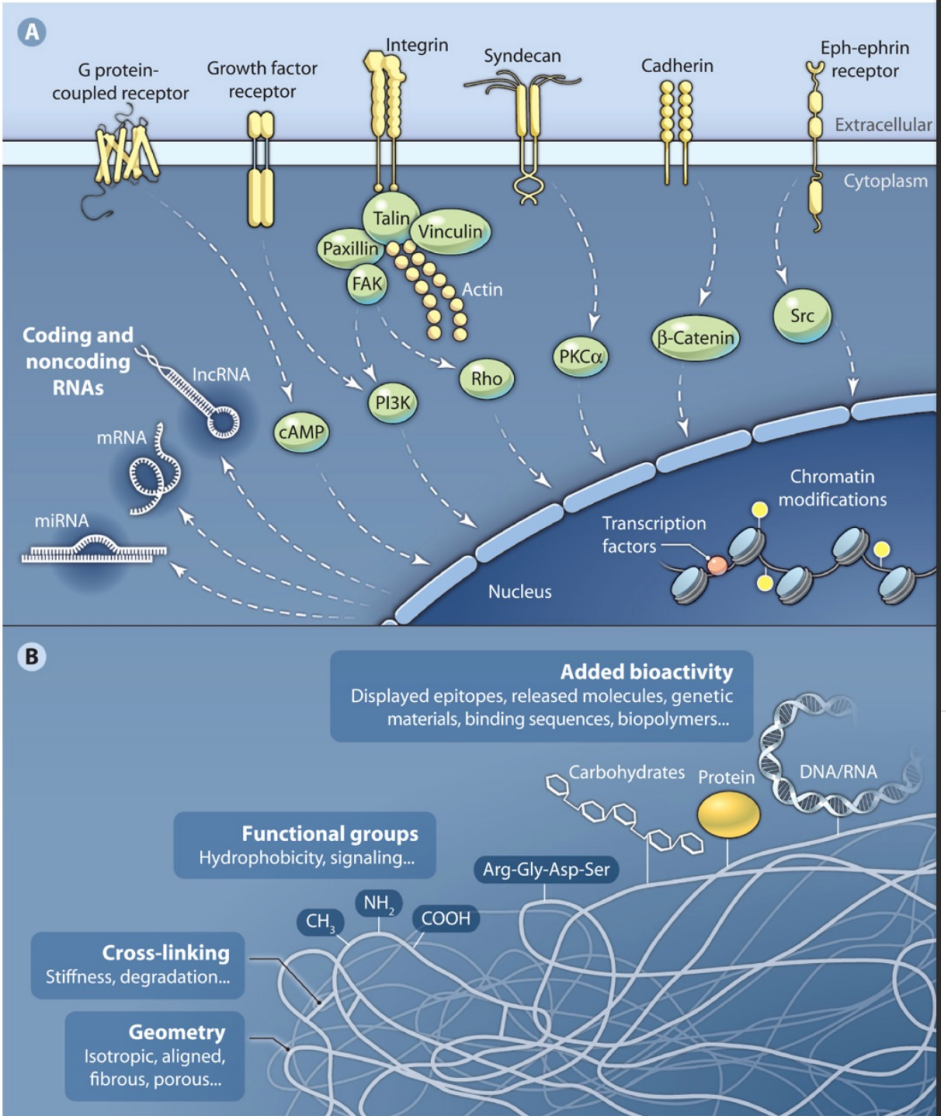
Tissue Engineering

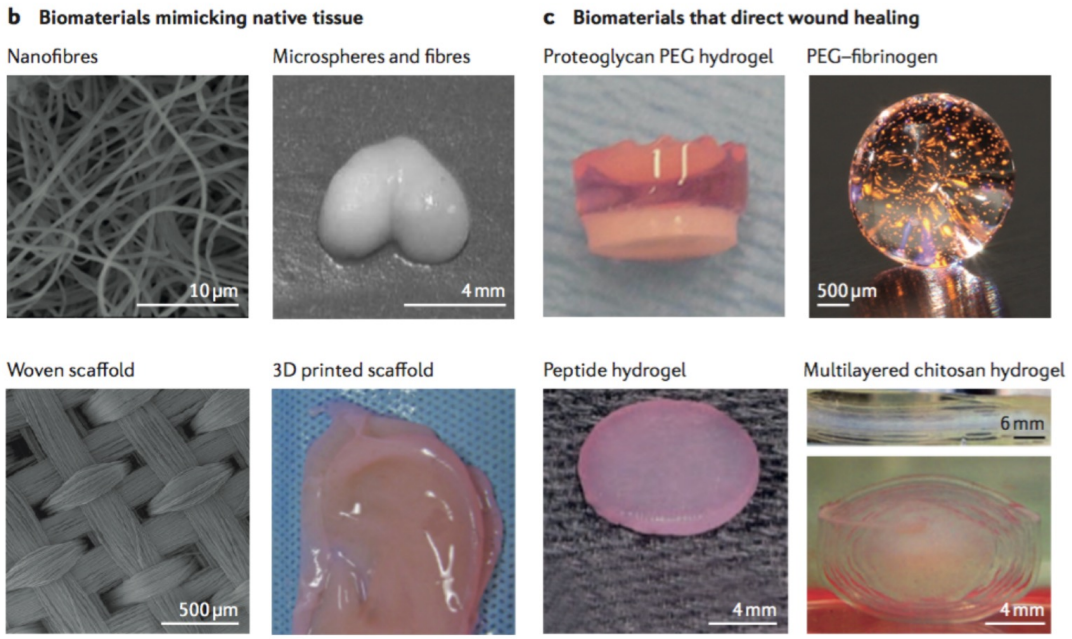
- **Key ingredients:**

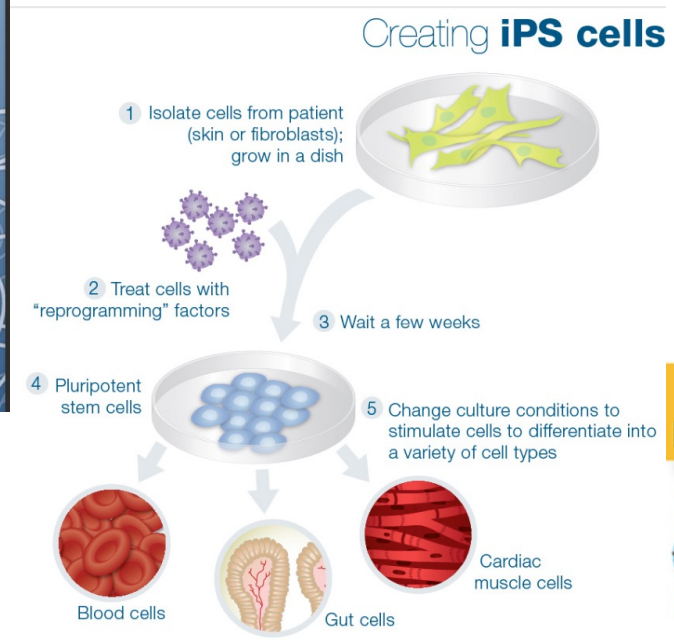
1. Cells
2. Scaffolds/Biomaterials
3. Bioactive factors/regulatory signals
4. Mechanics and physical cues (by correct scaffold and biomaterial properties

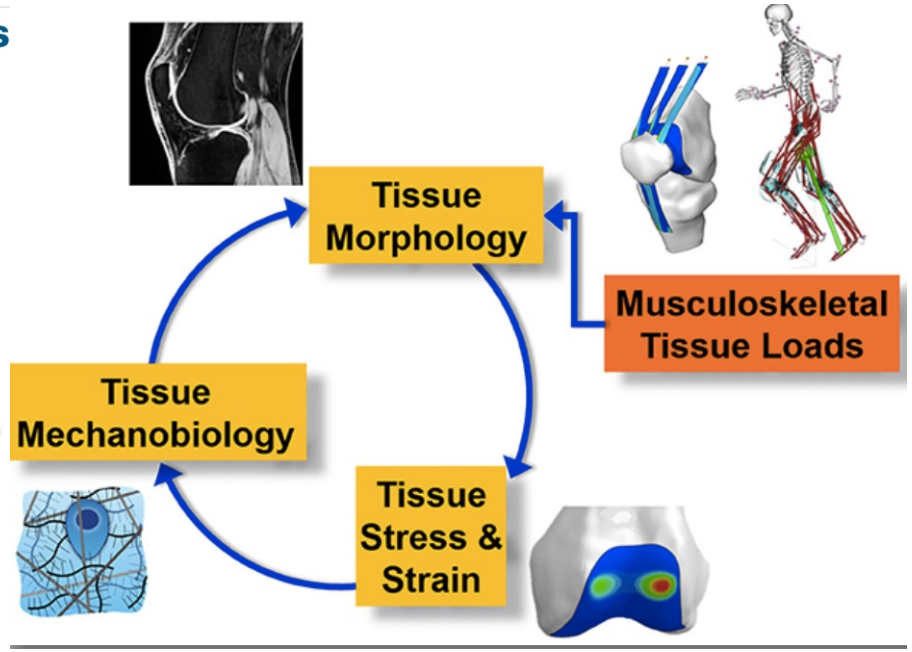


Tissue Engineering







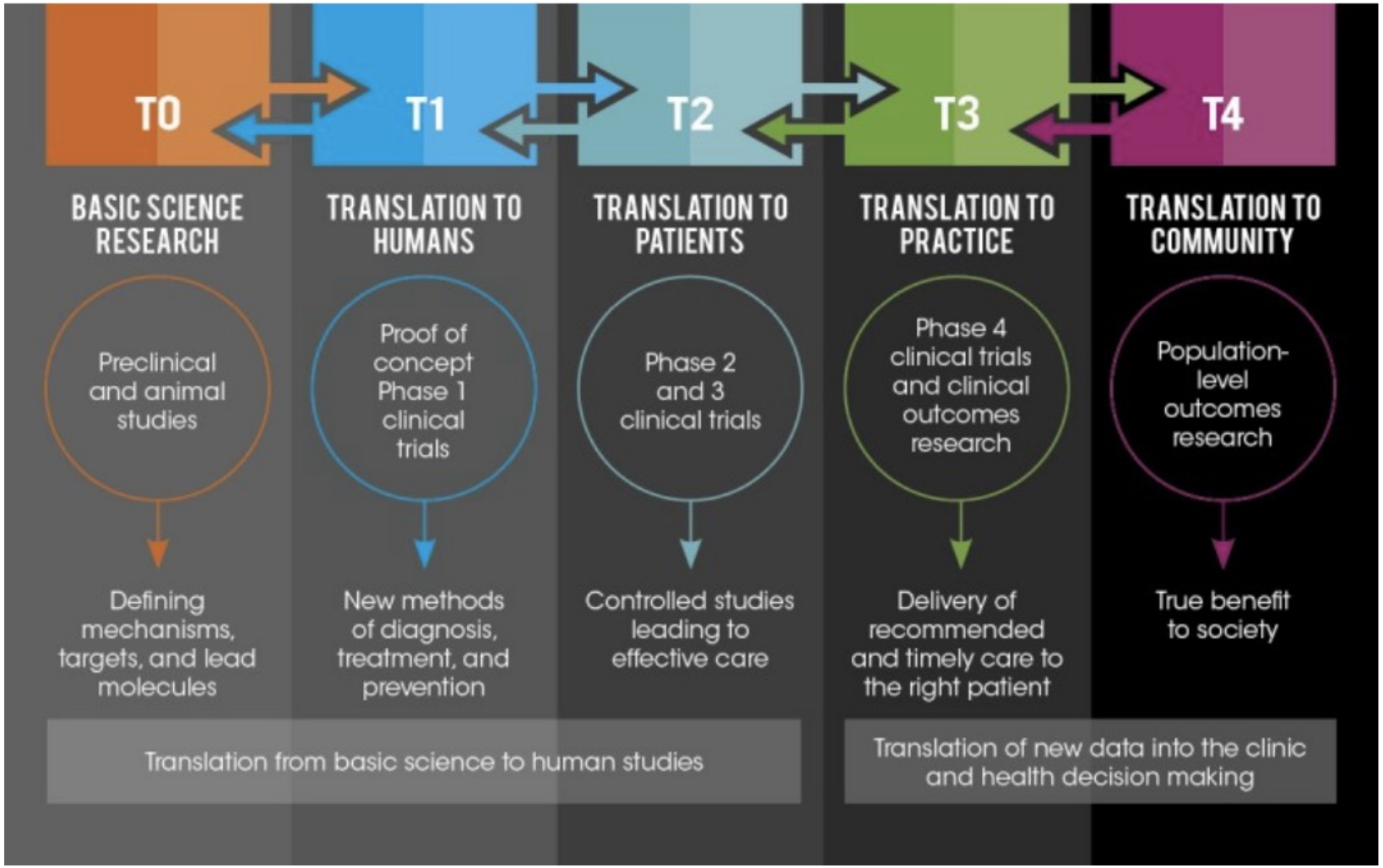


Clinical Translation & Legal Regulation

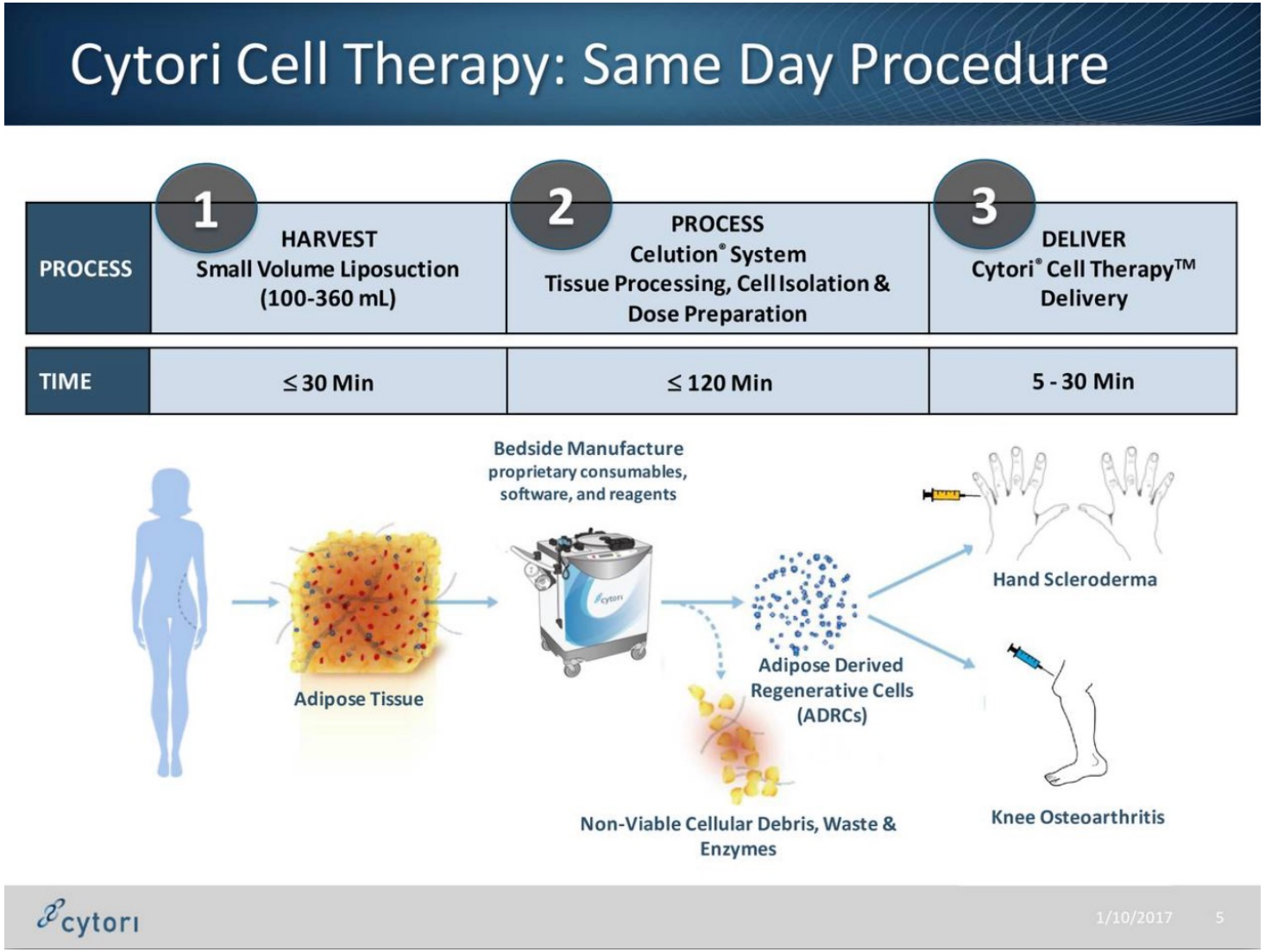
Clinical Translation

- Regulatory Obstacles for the use of cell based therapies, including any kind of modified cell (genetically or epigenetically modified) are extremely high (e.g. Due to cancer risk)
- There is increasing regulatory scrutiny for cell based therapy

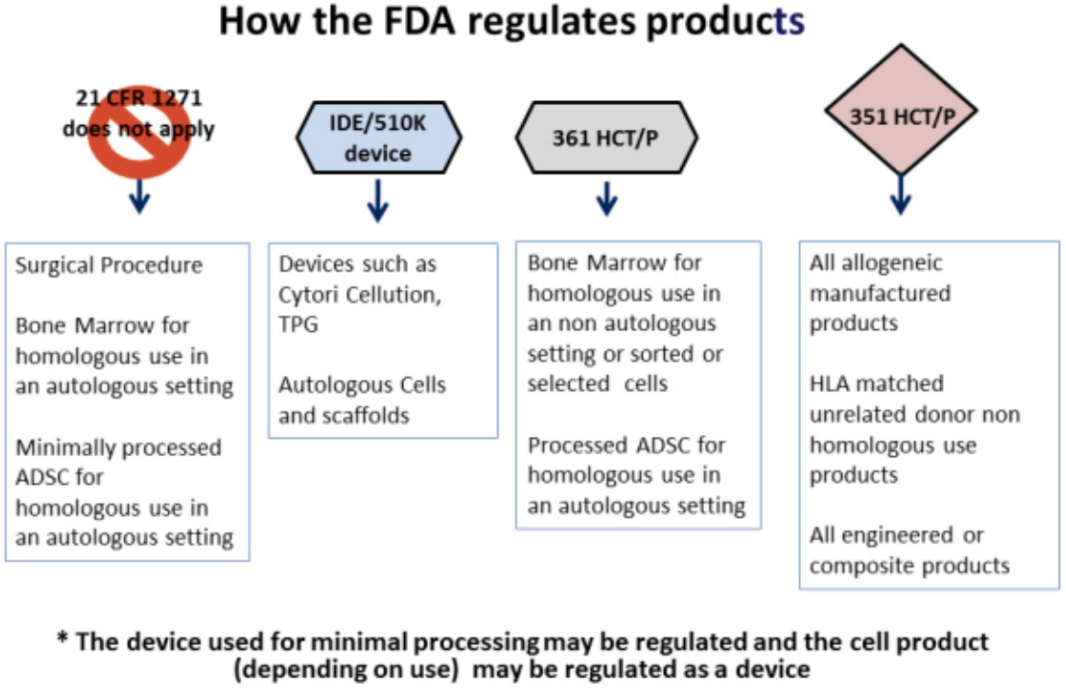
→ Relative benefit vs. safety is always in question

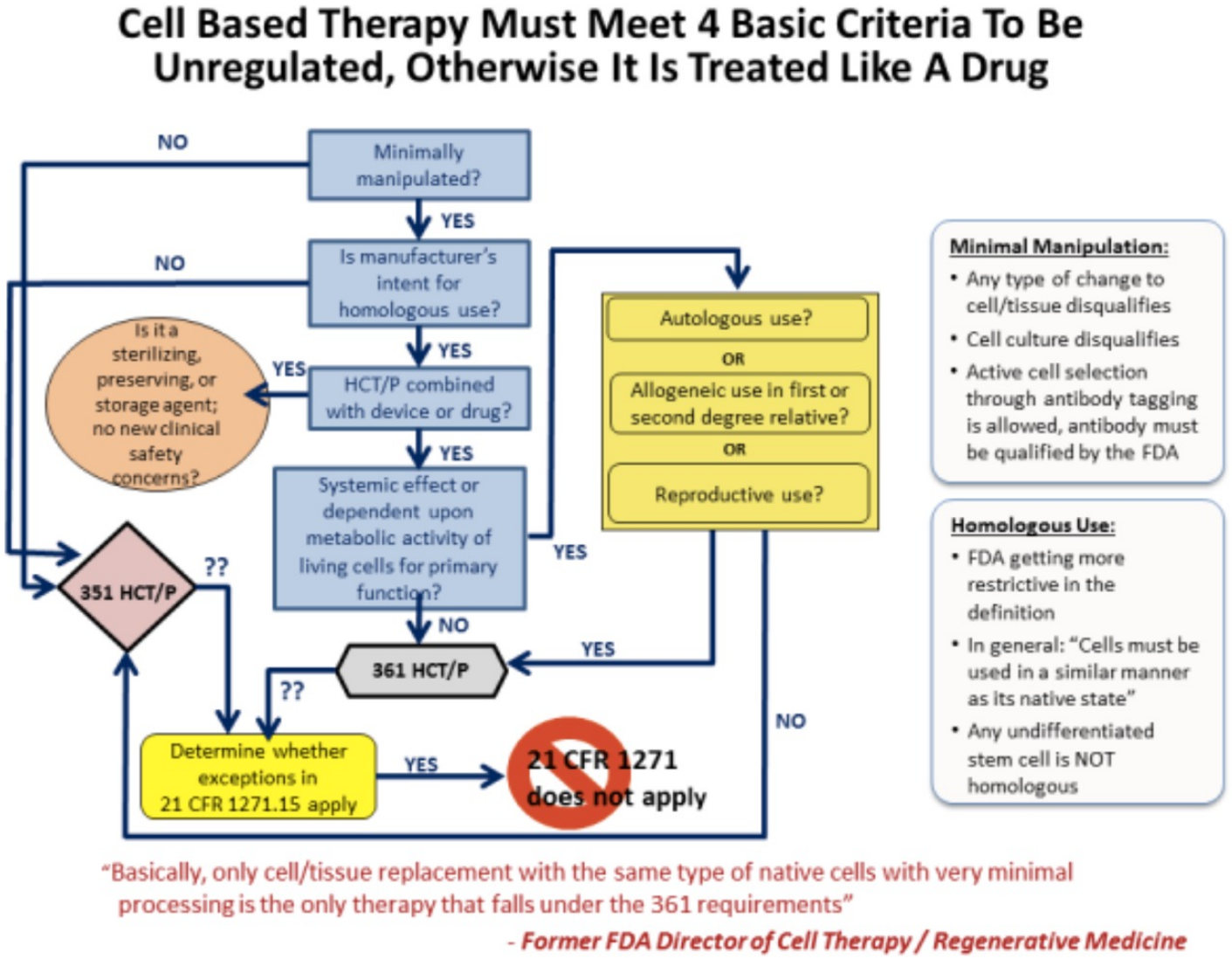


An early autologous cell-based therapy – an example



Legal Regulation





- **Autologous:** donor and recipient are the same person
- **Allogenic:** donor and recipient are different people

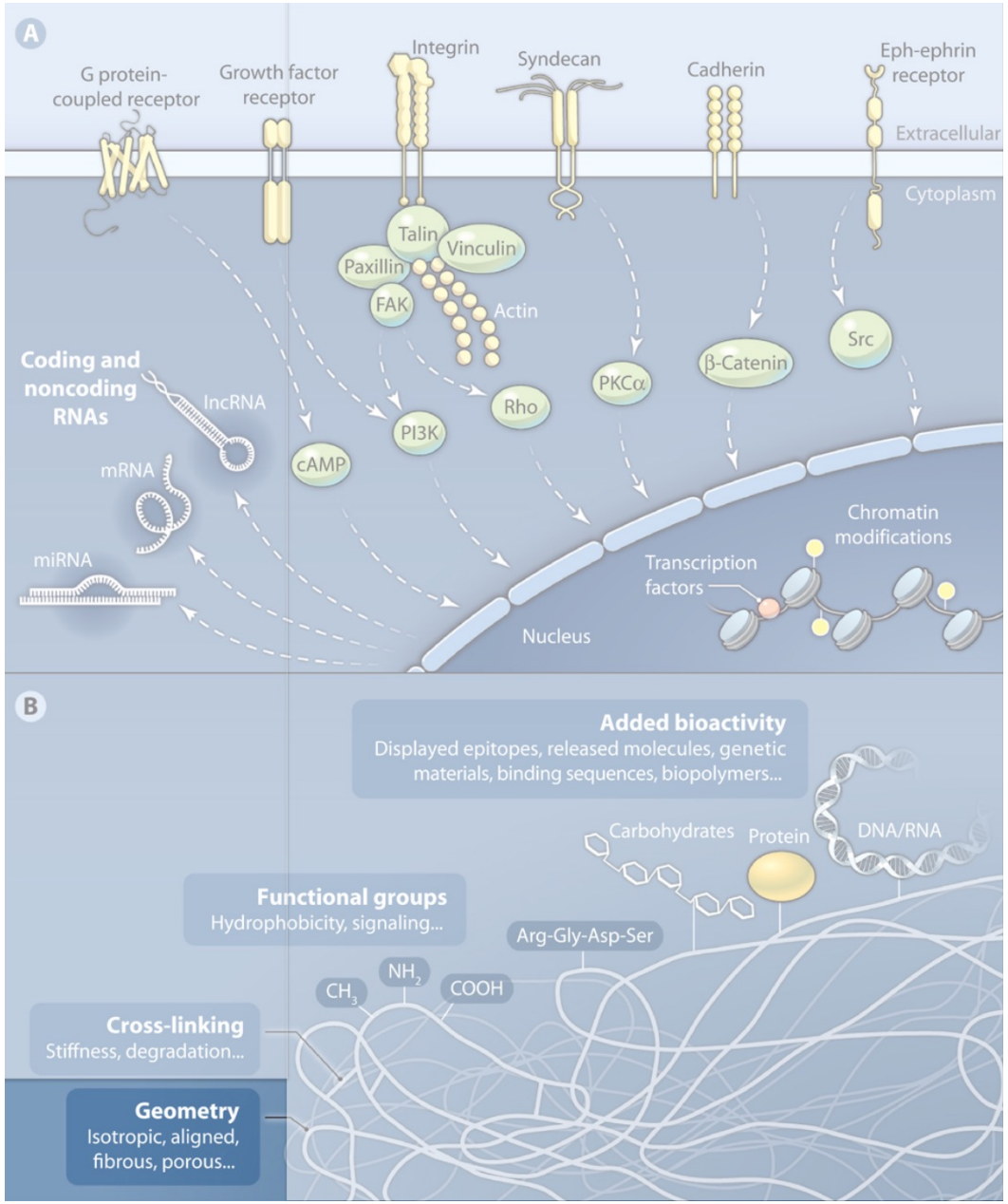
- Tissue Engineering far from clinics: any component or combination of cells, bioactive compound, or biomaterials have to be approved and regulated just like a drug

Legal Regulation

- Due to these many complex regulatory obstacles:

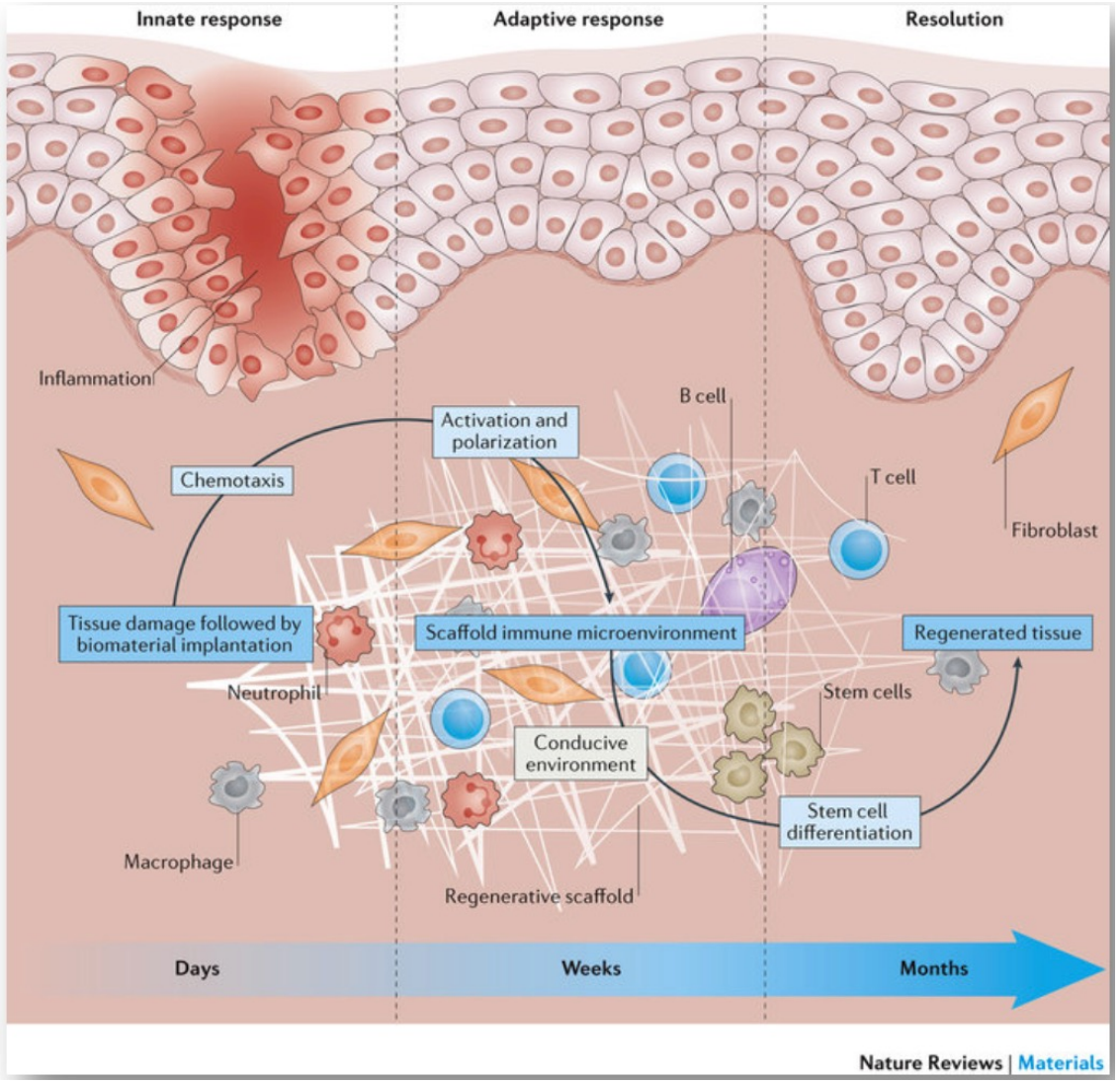
There is a lot of potential benefit to be gained exploiting only **geometry (mechanics)** of biomaterials established to be safe.

→ Because this approach brings minimal regulatory burden, it is cost effective and low risk

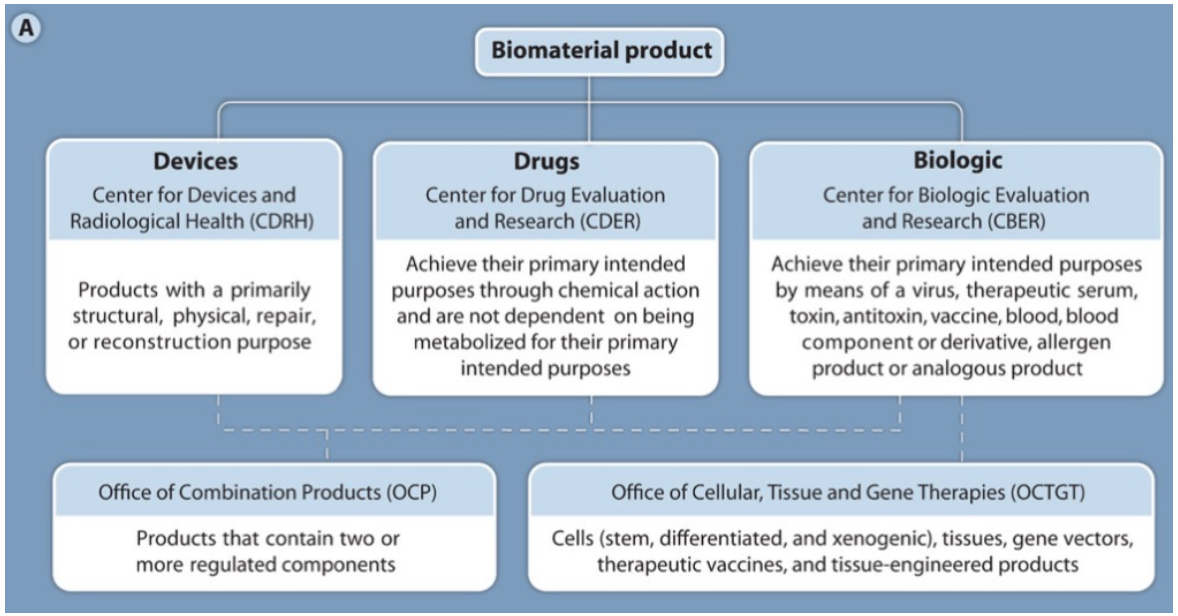


Therapeutic biomaterial (device) for scarless healing – an example

- Design of therapeutic biomaterials to help **control and guide cell behaviour** during regenerative processes such as wound healing
- **Cell recruitment** can cause improved healing outcomes
- **Steering recruited/injected and resident cells** in order to better control cell behaviour and consequently healing outcomes
- Guiding cell movement and behaviour can be achieved by creating biomaterials, which actively steer durotaxis (physical gradients) and chemotaxis (chemical gradients)



Legal Regulation – Devices vs. Drugs & Biologics



B

FDA approval: Drugs and biologics

	Preclinical	Phase I	Phase II	Phase III
Time (years)	4 - 6	1 - 2	1 - 2	2 - 3
Cost (millions)	$5 - 75	$50 - 150	$100 -200	$150 - 250
Aim	In vitro and in vivo animal tests to determine efficacy, safety, and formulations. One in 1000 to 2000 identified candidates go on to FDA trials.	Tested in a small number of (usually) healthy patients (<100), focused on safety of the intended dosing. Approximately 25% failure rate.	Tested in a slightly larger number of patients (100 - 300), focused on optimizing dosage range. Approximately 25% failure rate.	Tested in a large number of patients (1000 - 3000), focused on effectiveness and side effects. Approximately 35% failure rate.

C

FDA approval: Devices

	Premarket approval (PMA)		FDA - 510(k)
	Preclinical	Clinical trials	Preclinical
Time (years)	3 - 4	2 - 4	3 - 6
Cost (millions)	$5 - 50	$40 - 100	$1 - 50
Aim	Concept development; in vitro and in vivo testing to determine efficacy, safety, and proof of concept.	Device safety and effectiveness, conditions for using the device and its reliability.	Show substantial equivalence to previous 510(k) device.

Clinical Applications

(potentially viable) clinical applications in regernative medicine

(„viable“ means potential benefits may outweigh the inherent safety risks)

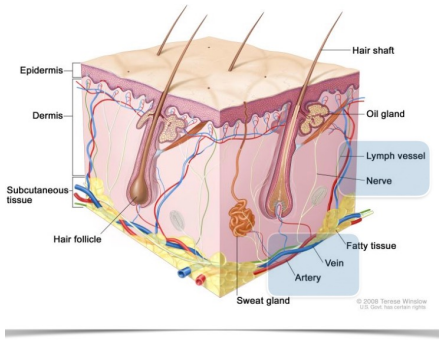
Cell Therapy:

- Biomineralization (bone)
- Blood substitutes
- Articular Cartilage
- Myoblast Transplantation in Skeletal Muscle
- Clinical Islet transplantation

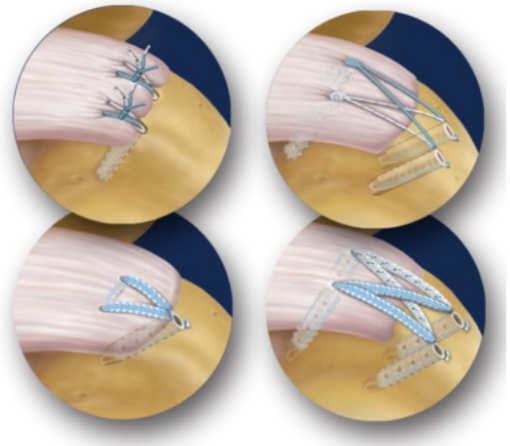
Tissue Therapy:

- Small diameter blood vessels
- Cardiac tissue & Valves
- Cornea
- Alimentary tract
- Extra- / Intra-corporeal renal tissue
- Reproductive system
- Cartilage, ligaments and tendons
- Nervous system (central and peripheral)
- Skin
- Respiratory tract

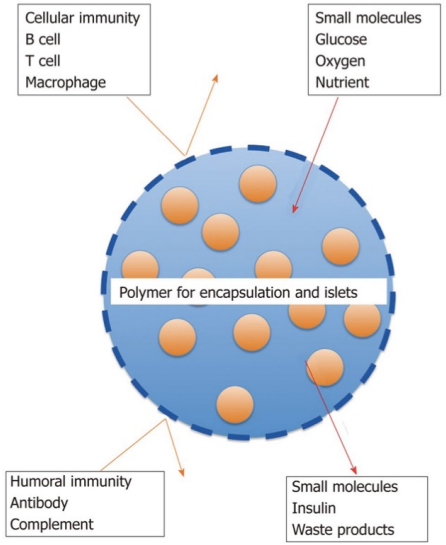
Unmet clinical needs in regenerative medicine



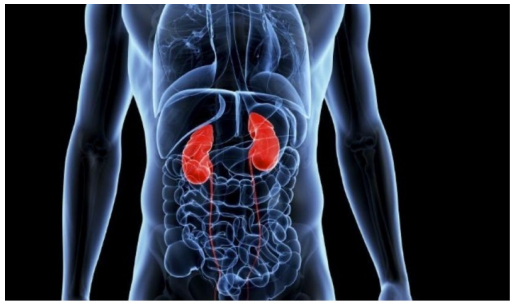
Skin grafts
(e.g. large area burns)



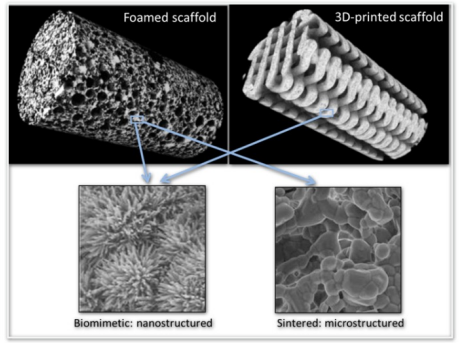
Soft tissue repair: soft-hard tissue transitions



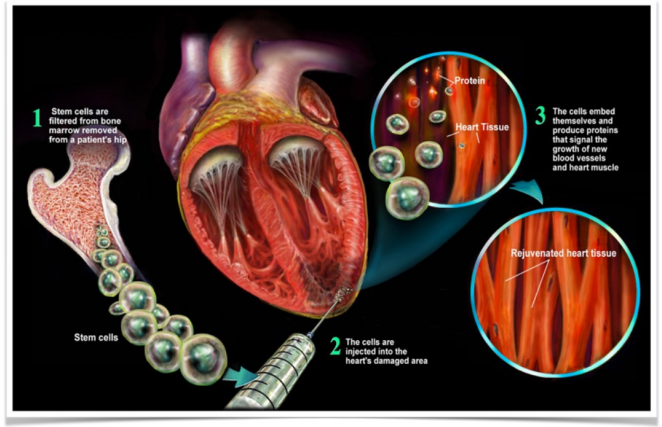
Diabetes
(encapsulated islet cells)



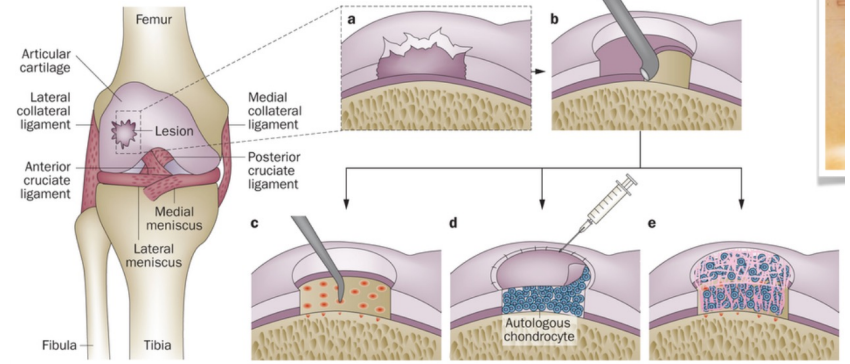
Kidney Disease
Cell therapy (short/middle term)
Replacement organs (very long term)



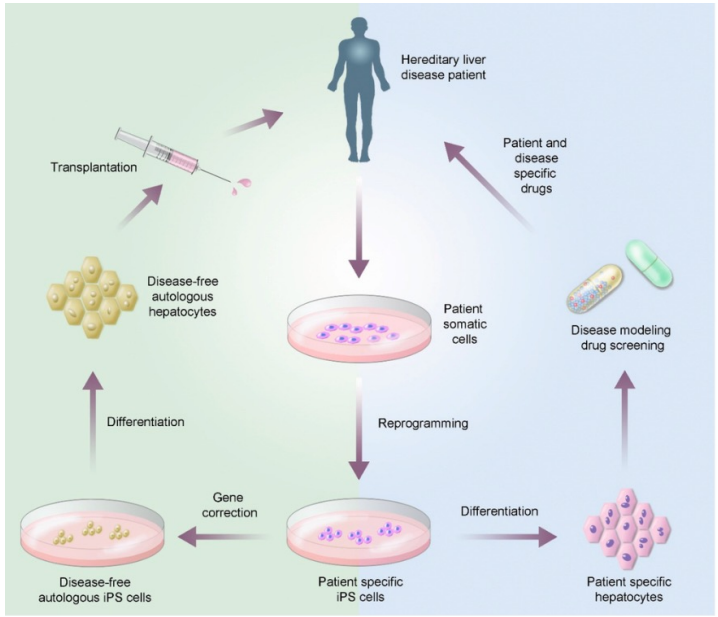
Bone Ingrowth &
Fortification (Osteoporosis)



Heart Disease
Cell therapy (short/middle term)
Replacement organs (very long term)



Focal Cartilage Defects, Meniscal Tears



Liver Disease
Cell therapy (short/middle term)
Replacement organs (middle/ long term)

Tissue Engineering: Clinical application is currently limited due to complexity and cost BUT there is quite useful pre-clinical potential

Currently, tissue engineering plays a relatively small role in patient treatment. Supplemental **bladders**, small **arteries**, **skin** grafts, **cartilage**, and even a **full trachea** have been implanted in patients, but the procedures are still **experimental** and **very costly**.

While more complex organ tissues like **heart**, **lung**, and **liver** tissue have been successfully recreated in the lab, they **are a long way from being fully reproducible** and ready to implant into a patient.

Using functioning human tissue to screen medication candidates can speed up development and provide key tools for facilitating personalized medicine (as cells and tissue from individual patients can be used), while saving money and reducing the number of animals used for research

Paper

Atherosclerosis

Aldons J. Lusis

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Atherosclerosis, a disease of the large arteries, is the primary cause of heart disease and stroke. In westernized societies, it is the underlying cause of about 50% of all deaths. Epidemiological studies have revealed several important environmental and genetic risk factors associated with atherosclerosis. Progress in defining the cellular and molecular interactions involved, however, has been hindered by the disease's aetiological complexity. Over the past decade, the availability of new investigative tools, including genetically modified mouse models of disease, has resulted in a clearer understanding of the molecular mechanisms that connect altered cholesterol metabolism and other risk factors to the development of atherosclerotic plaque. It is now clear that atherosclerosis is not simply an inevitable degenerative consequence of ageing, but rather a chronic inflammatory condition that can be converted into an acute clinical event by plaque rupture and thrombosis.