# Biomechanics of the musculoskeletal system

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EPFL

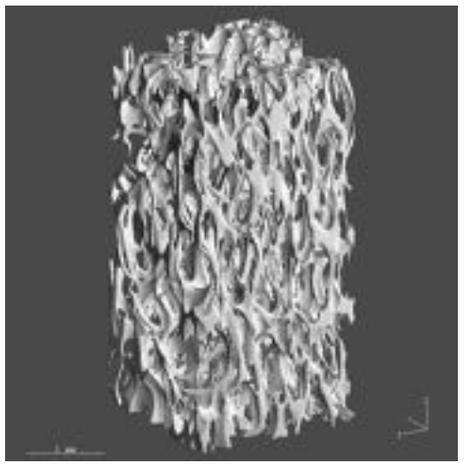
# Tissue engineering

i) General concepts

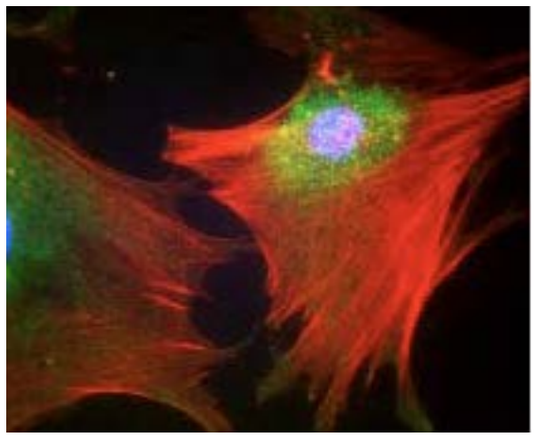
ii) Biomechanical considerations

iii) In vivo bioreactor

# The classical strategy in tissue engineering involved 3 different components



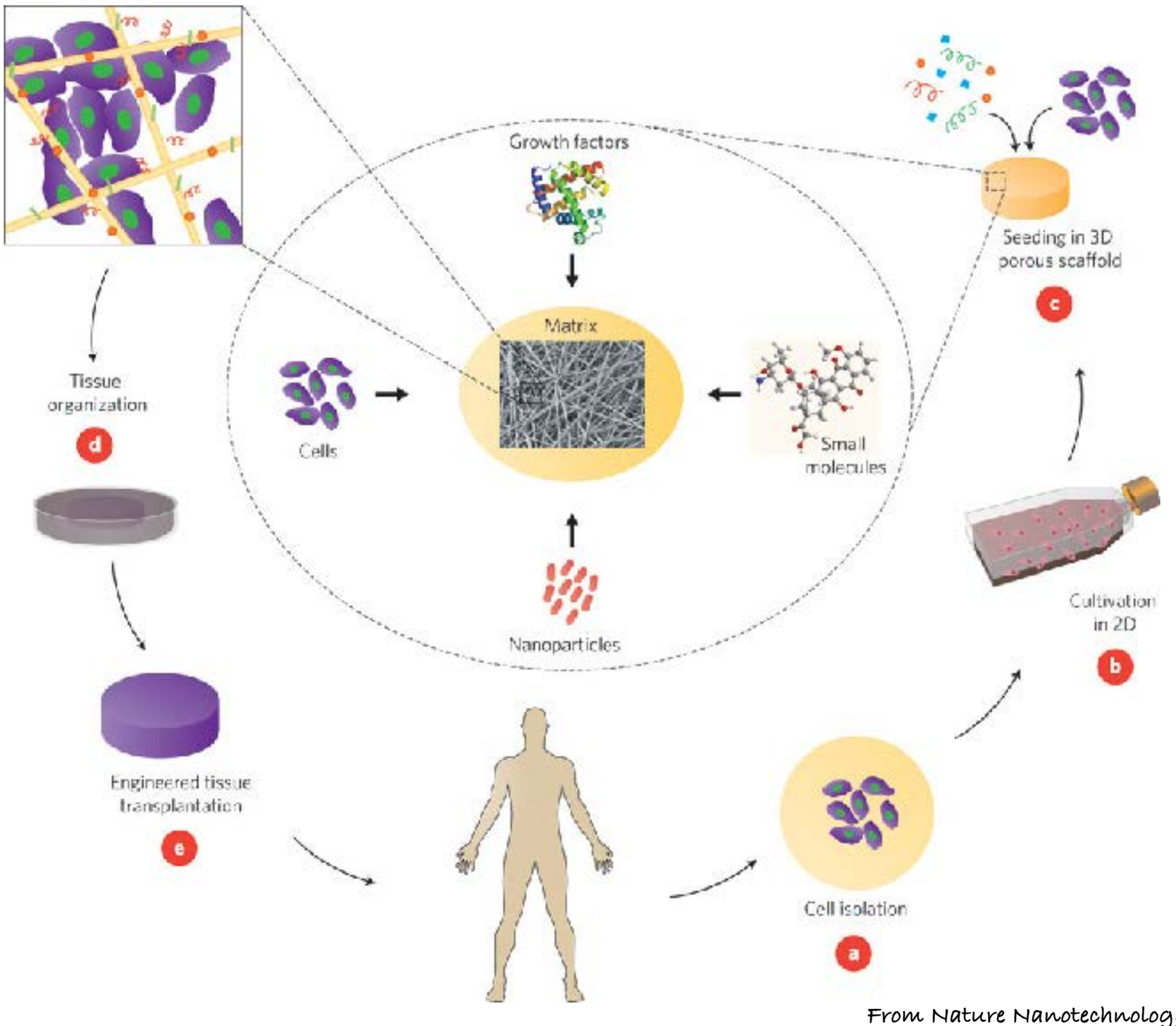
Scaffold



Cells

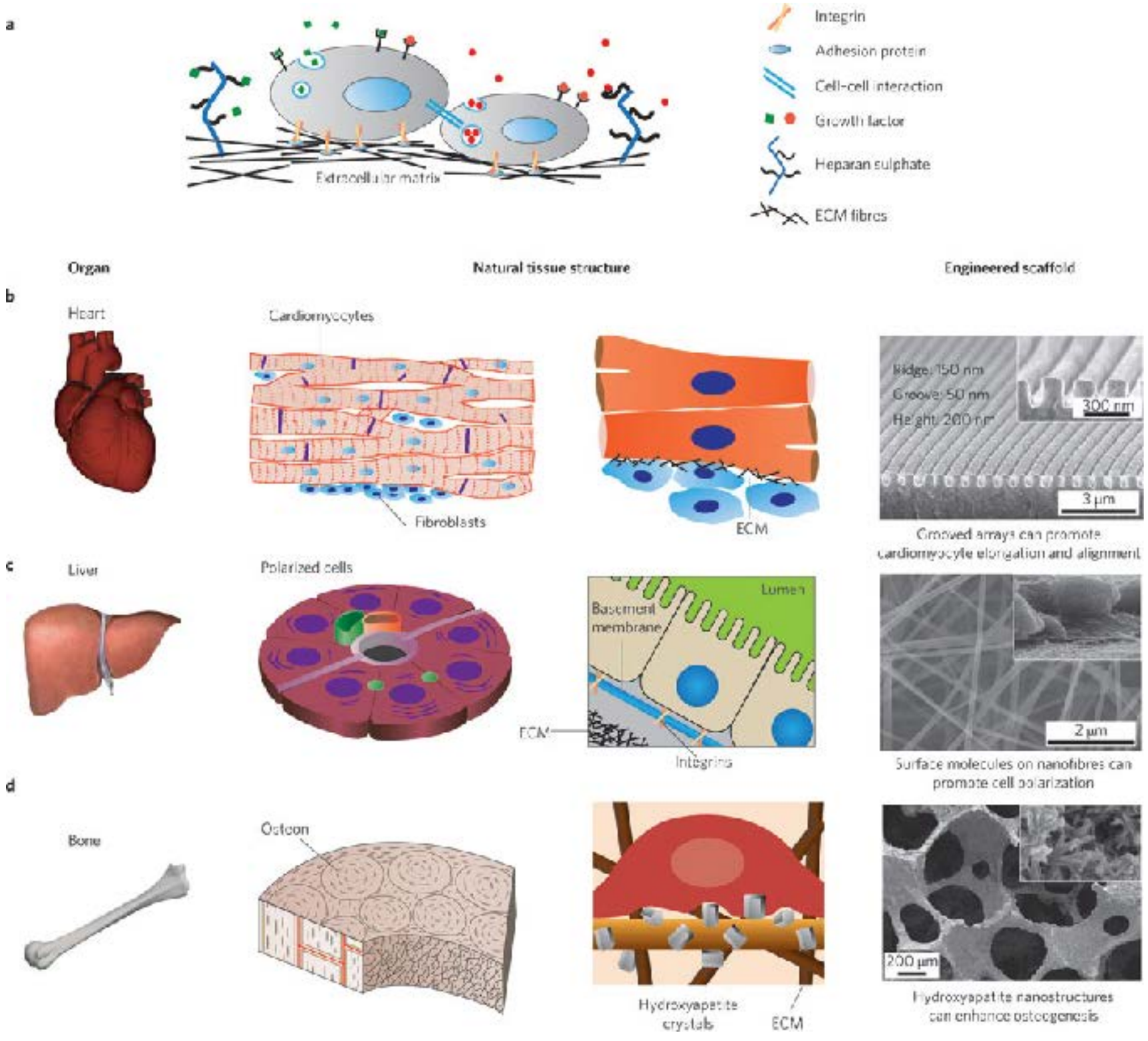
Growth factors

# Different processes are followed depending on the targeted clinical applications and cells source



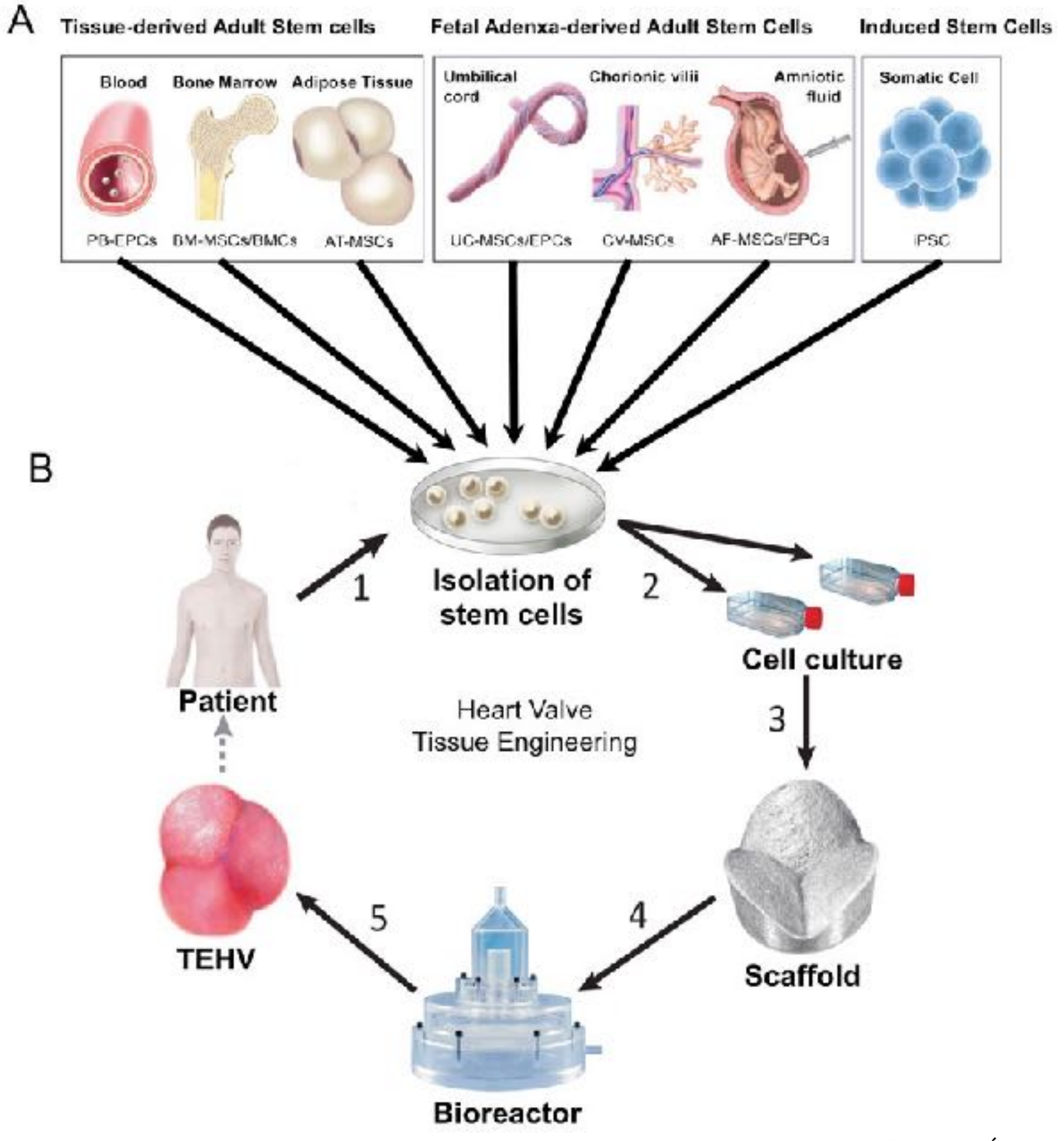

From Nature Nanotechnology 6, 13–22 (2011)

# Each component is important: scaffold



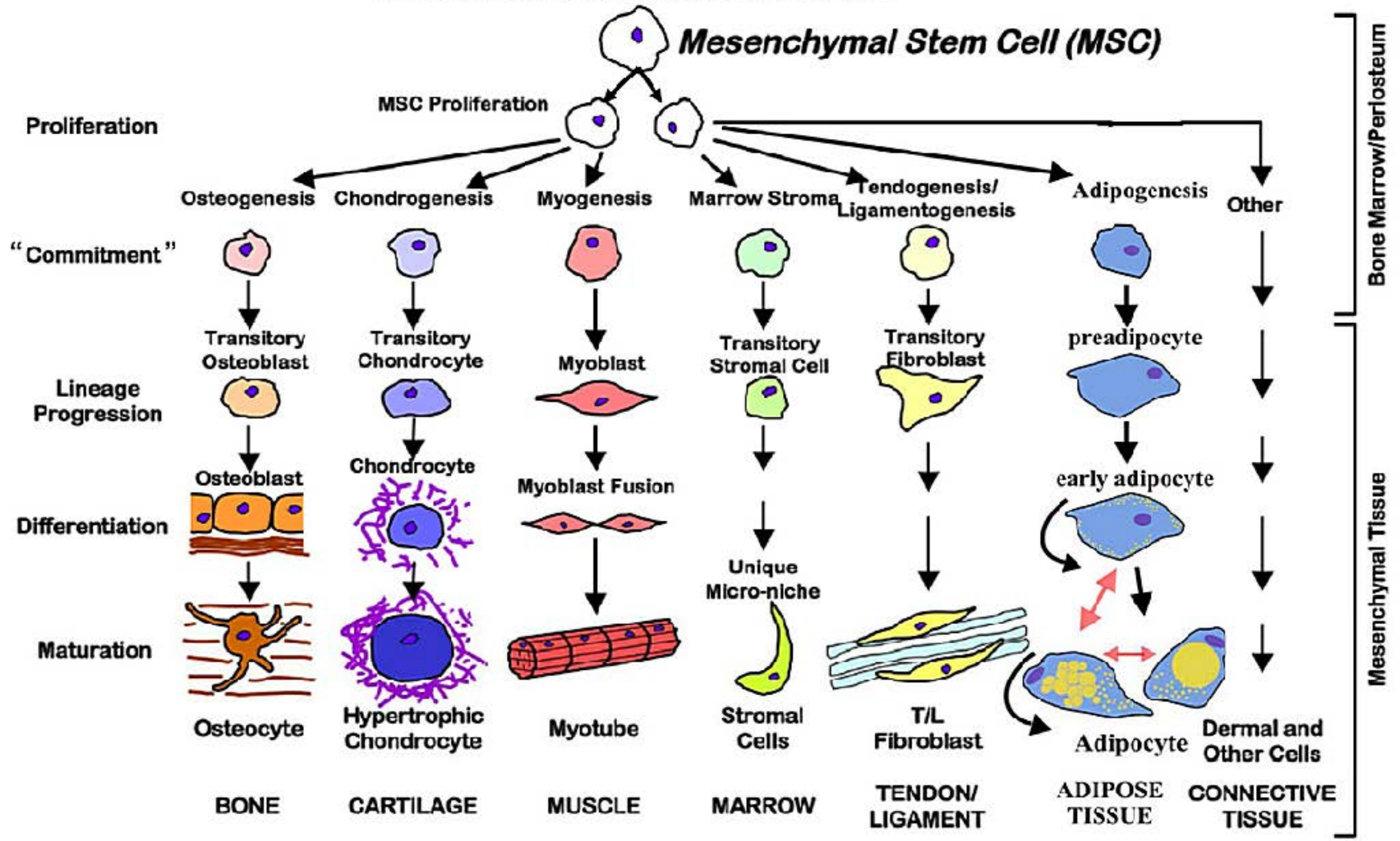

From Nature Nanotechnology 6, 13–22 (2011)

# Each component is important: cell source




From: Swiss Med Wkly. 2012;142:w13622

# THE MESENGENIC PROCESS



# Obviously, regulatory aspects are essential

## CHUV: BH05/516 : Validated Processing of "Clinical Progenitor Cell Banks"

Clean Rooms dedicated to Progenitor Cells: cGMP

# Example of a successful implementation

# How 3D Printing Could End The Deadly Shortage Of Donor Organs

**The Huffington Post | By Macrina Cooper-White**

Posted: 03/01/2015 9:51 am EST | Updated: 03/02/2015 2:59 pm EST

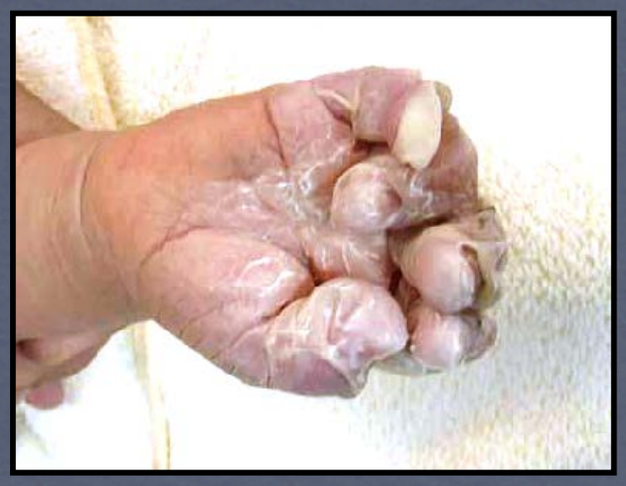
The Huffington post

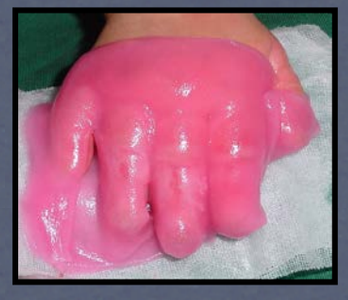
# Example of a successful implementation

# Example of a successful implementation

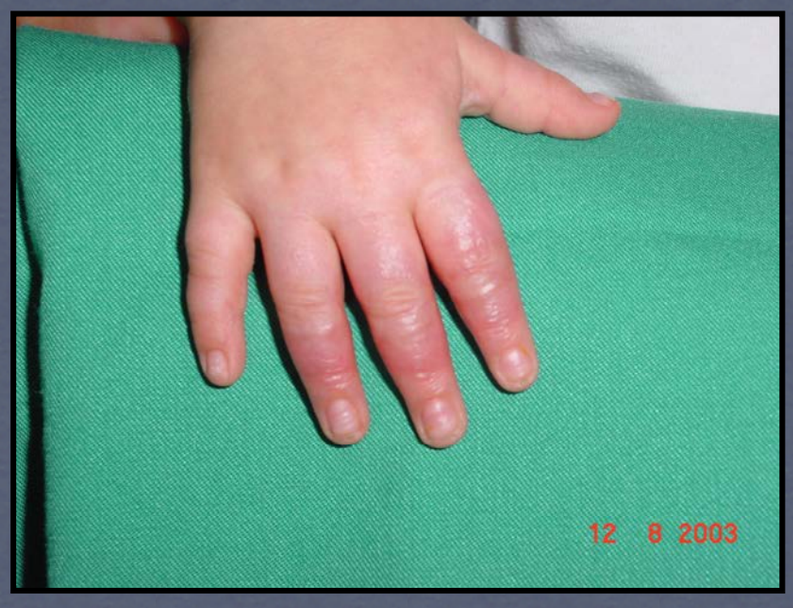
## Mlle A.P. 18 months old

2nd and 3rd degree Burns





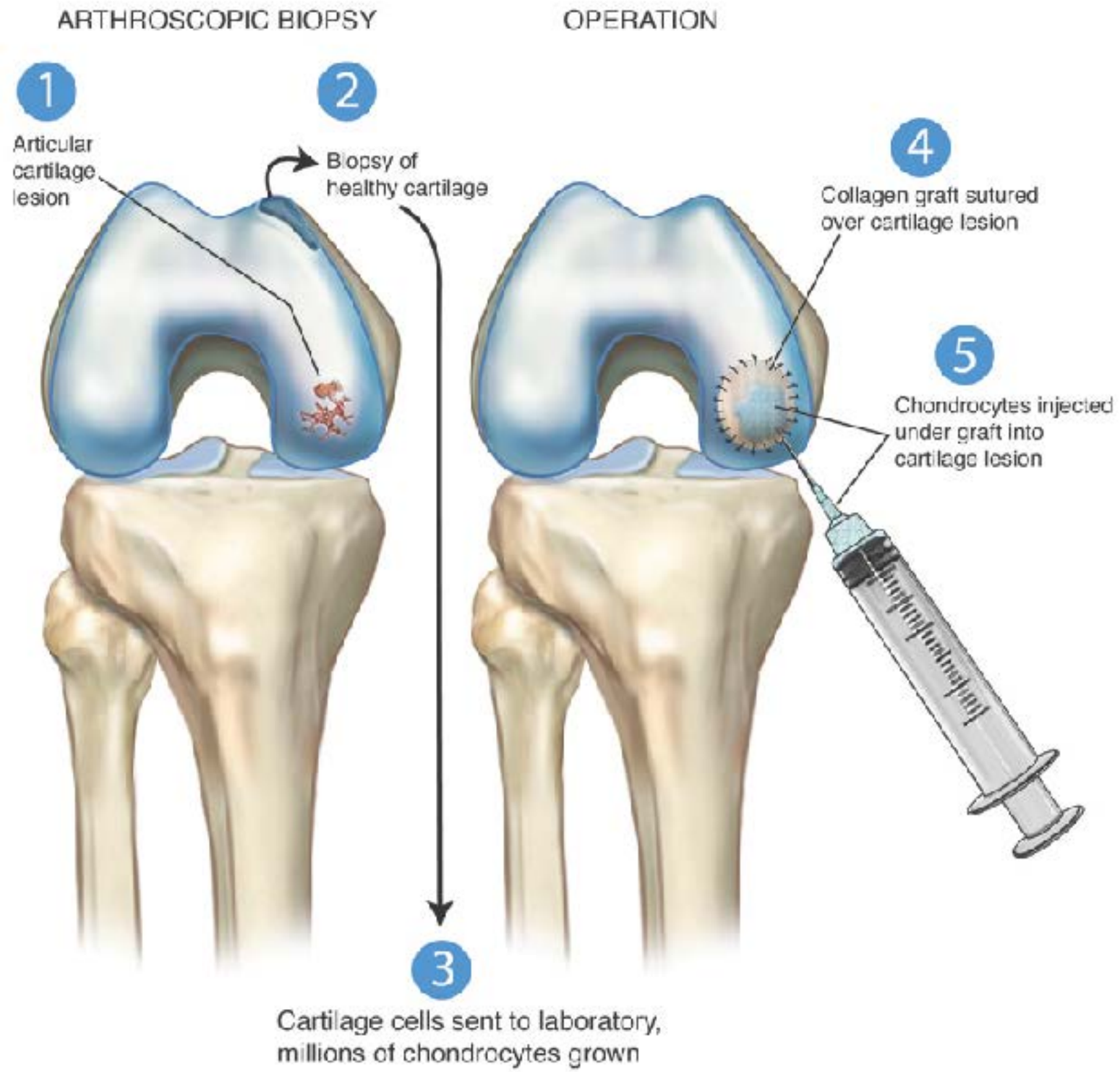
5 constructs




20 days later

From Lancet, 2005

# Example of a successful implementation




From http://noyeskneeinstitute.com/articular-cartilage-repair/

Anyway, tissue engineering is not (yet) the announced revolution in medicine, why?

- regulatory affairs
- cost
- business model
- logistic
- …
- inadequate mechanical properties of the scaffold (at least for musculoskeletal applications)

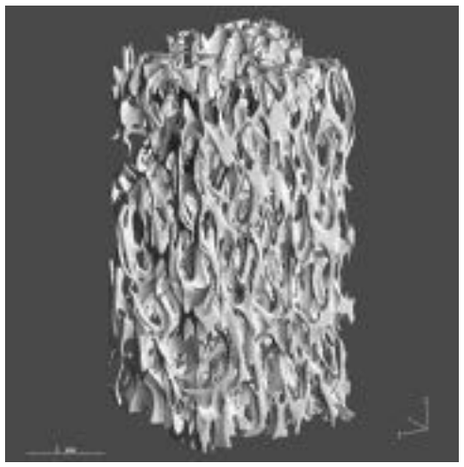
# Tissue engineering

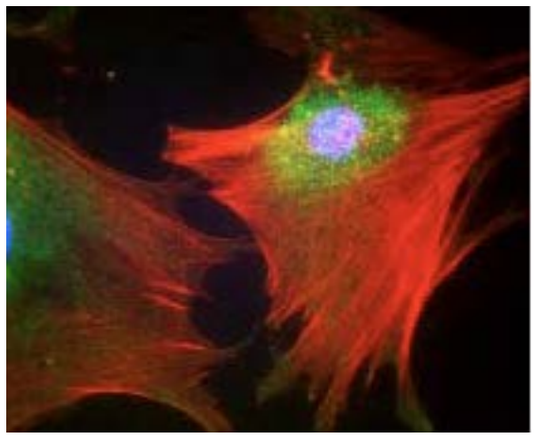
i) General concepts

ii) Biomechanical considerations (evaluation, bioreactor)

iii) In vivo loading bioreactor

# Evaluation of the mechanical loading situation to develop appropriate materials





Scaffold

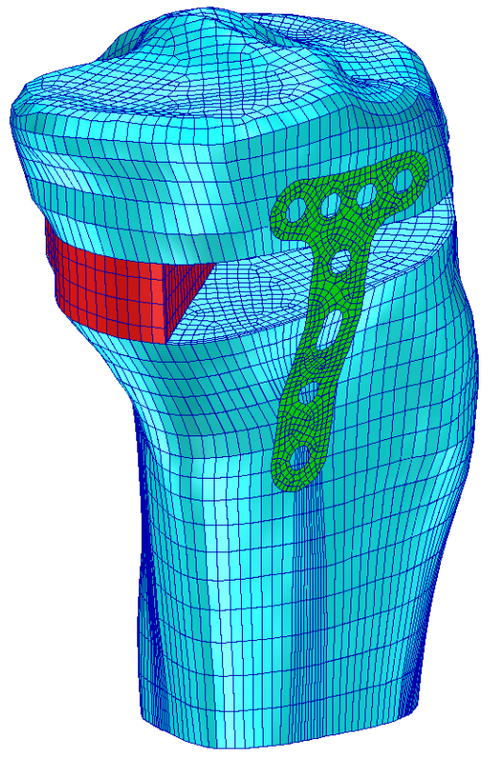
Cells

Growth factors

Load-bearing

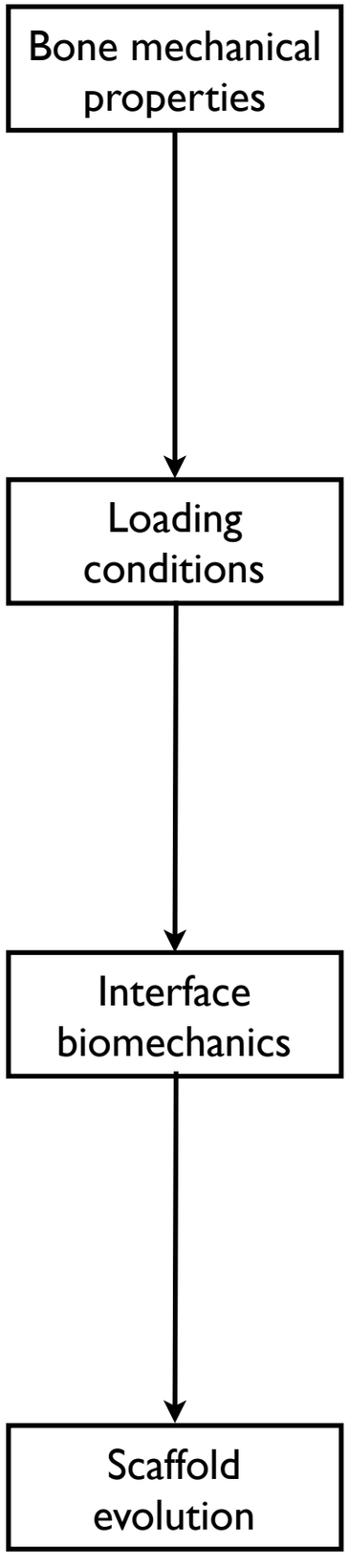
Biomechanics

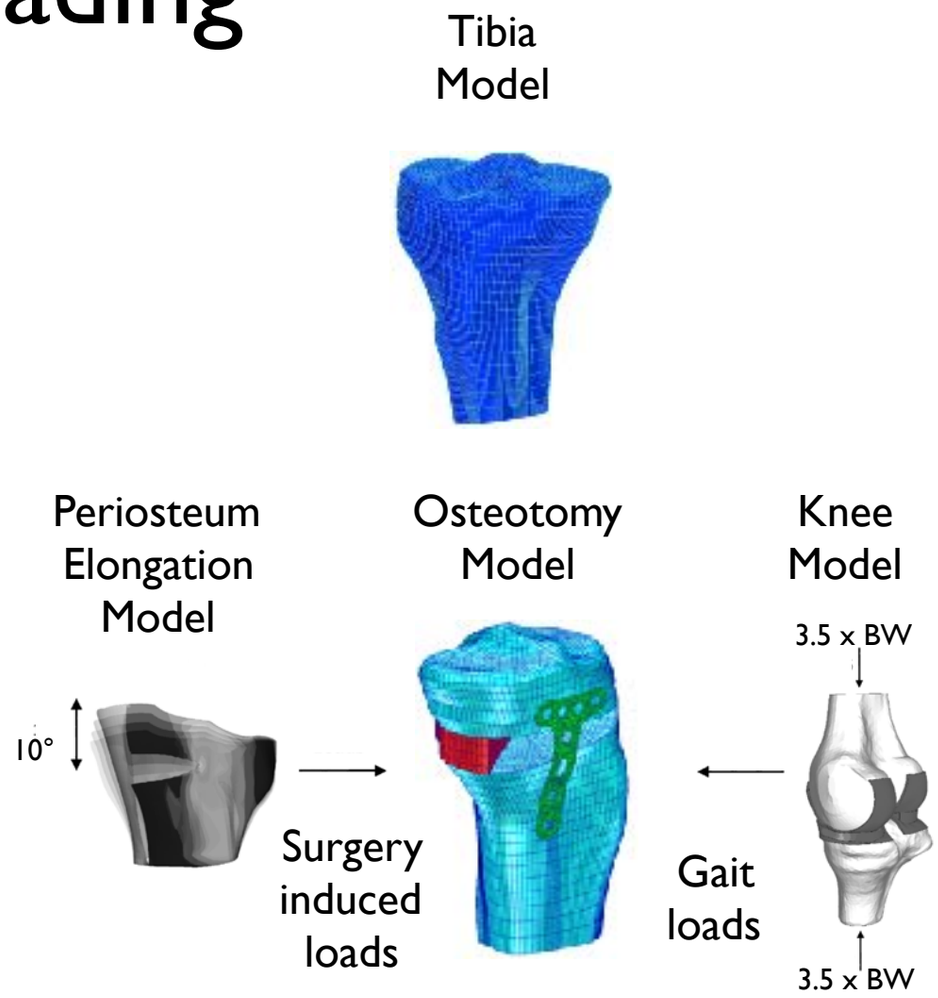
# The clinical application needs then to be clearly defined

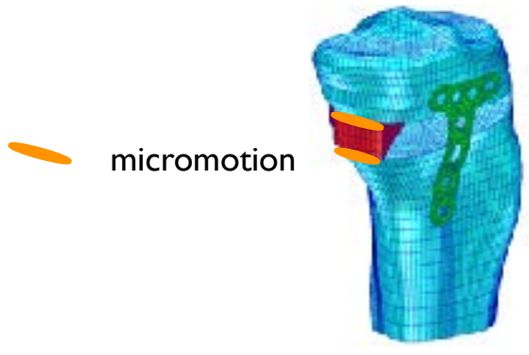


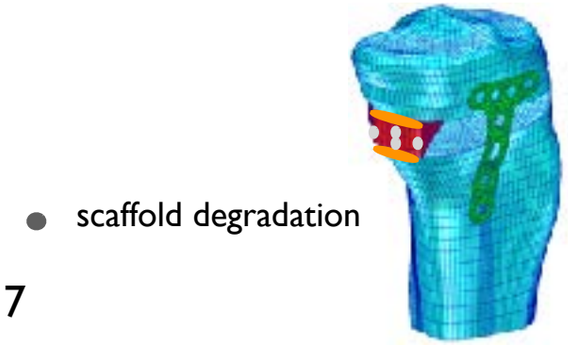
FEM

# … and corresponding loading evaluated



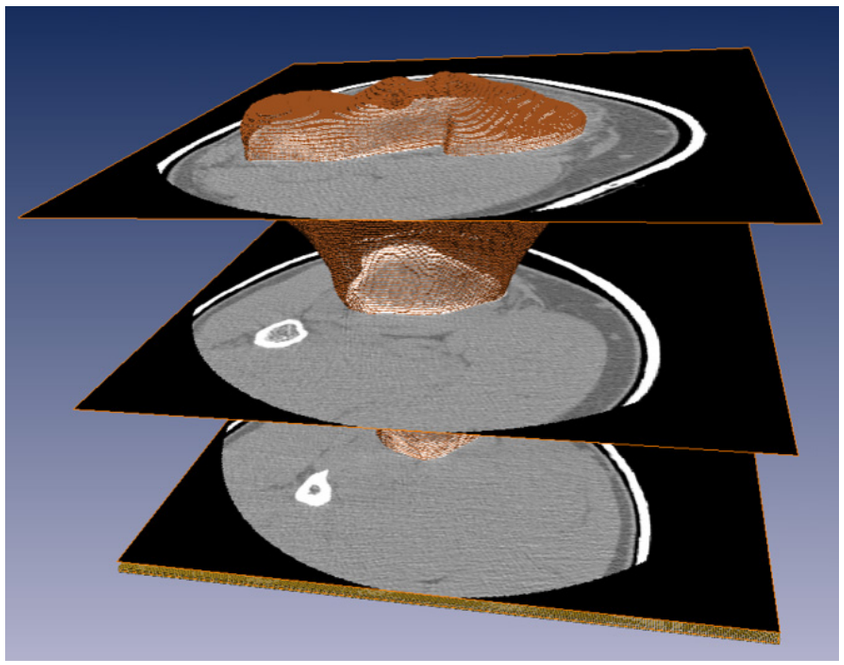



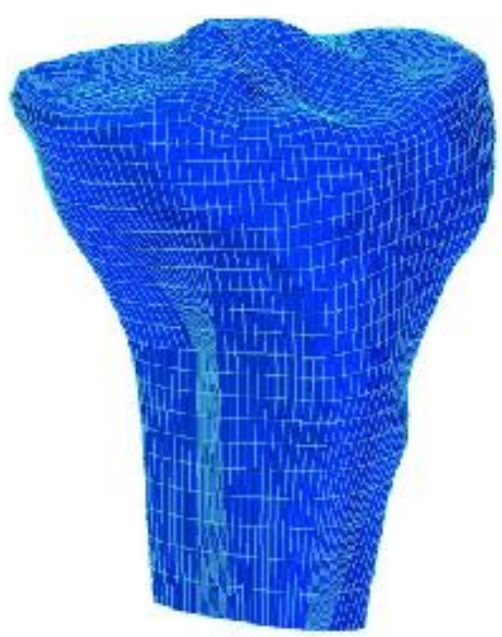



# Not only the geometry and density are needed, but also the osteotomy procedure

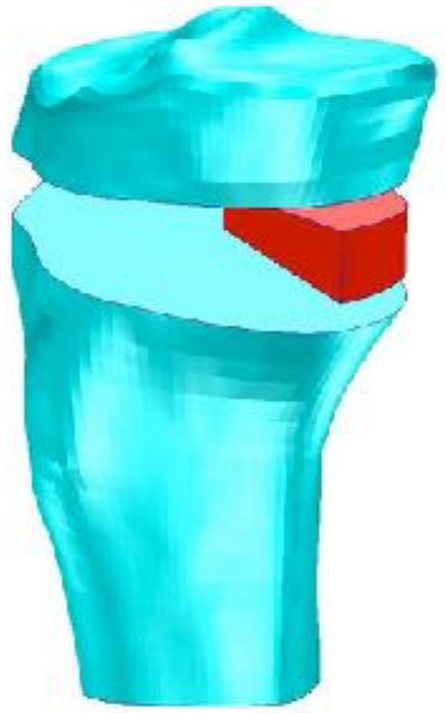
Geometry + bone density obtained by CT scan



Geometry transformed in FEM

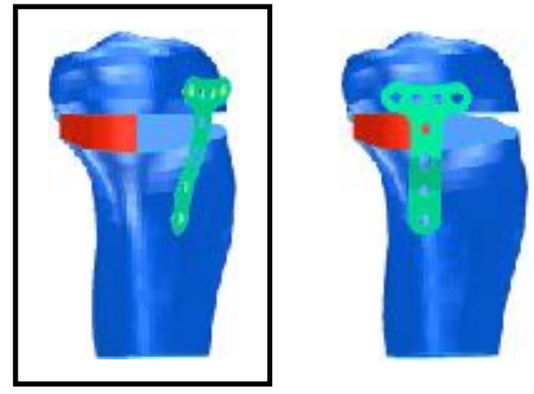


Tibial osteotomy simulated



# Mechanical information are then obtained for the scaffold

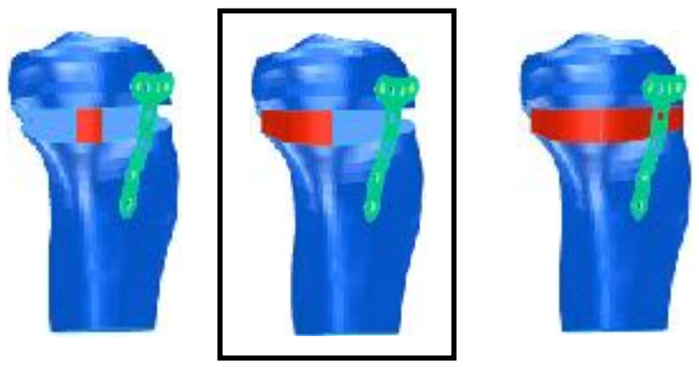
Evaluate the mechanical effect of the plate positioning



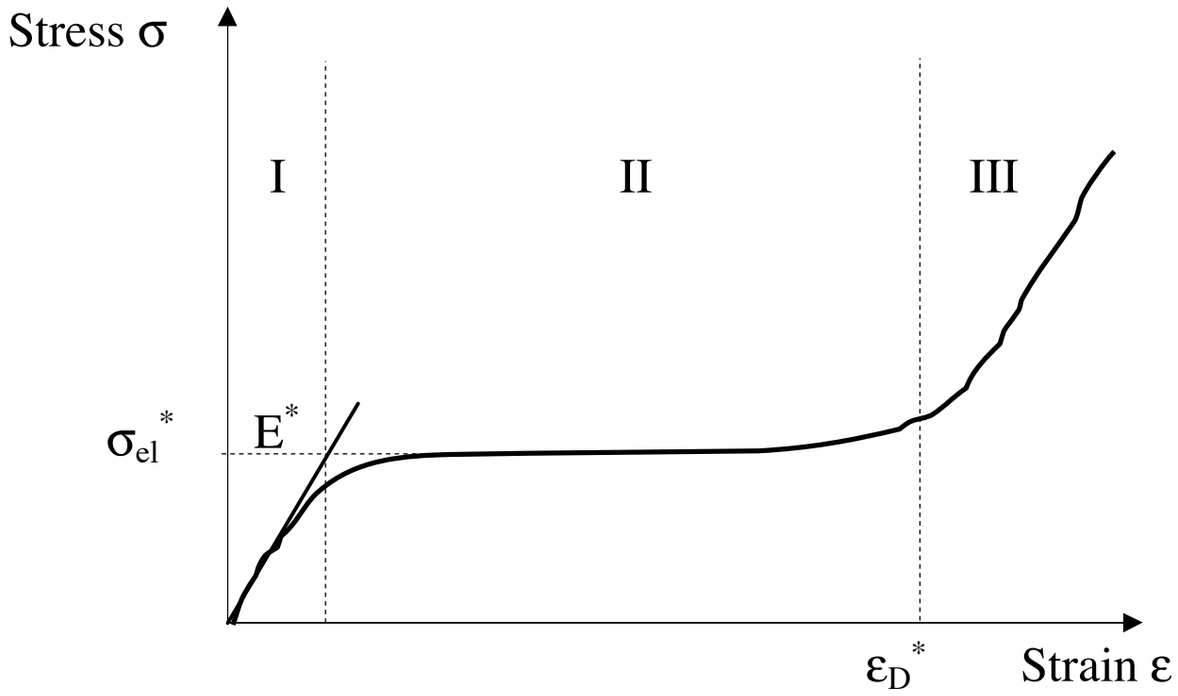
Optimisation of scaffold mechanical properties

Scaffold: flexible (E ≈ 300 MPa) but resistant ($\sigma$ > 50 MPa)

Numerical tests of different scaffold shapes



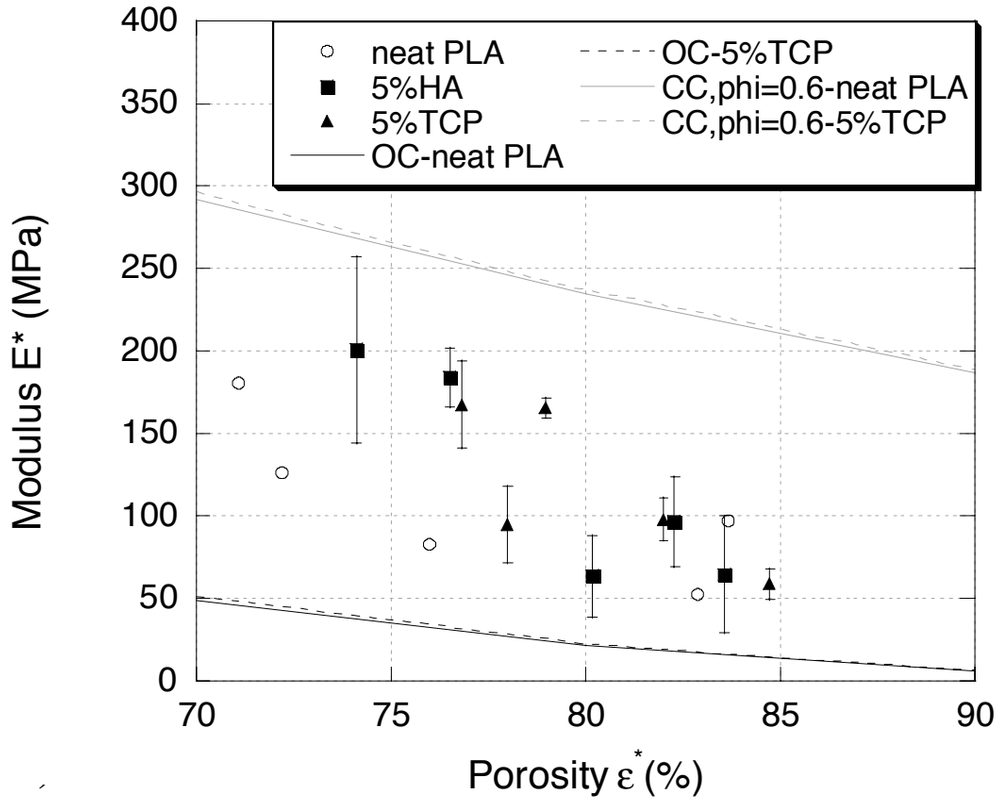
# Corresponding mechanical properties of the (porous) scaffold




Relationship between Young's modulus of porous scaffold and material (open cell)

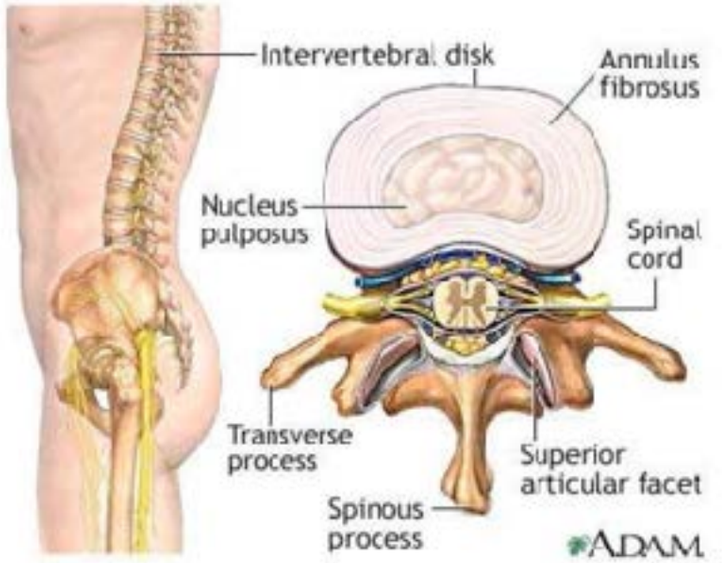
$$\frac{E^*}{E_s} = \left(\frac{\rho^*}{\rho_s}\right)^2$$

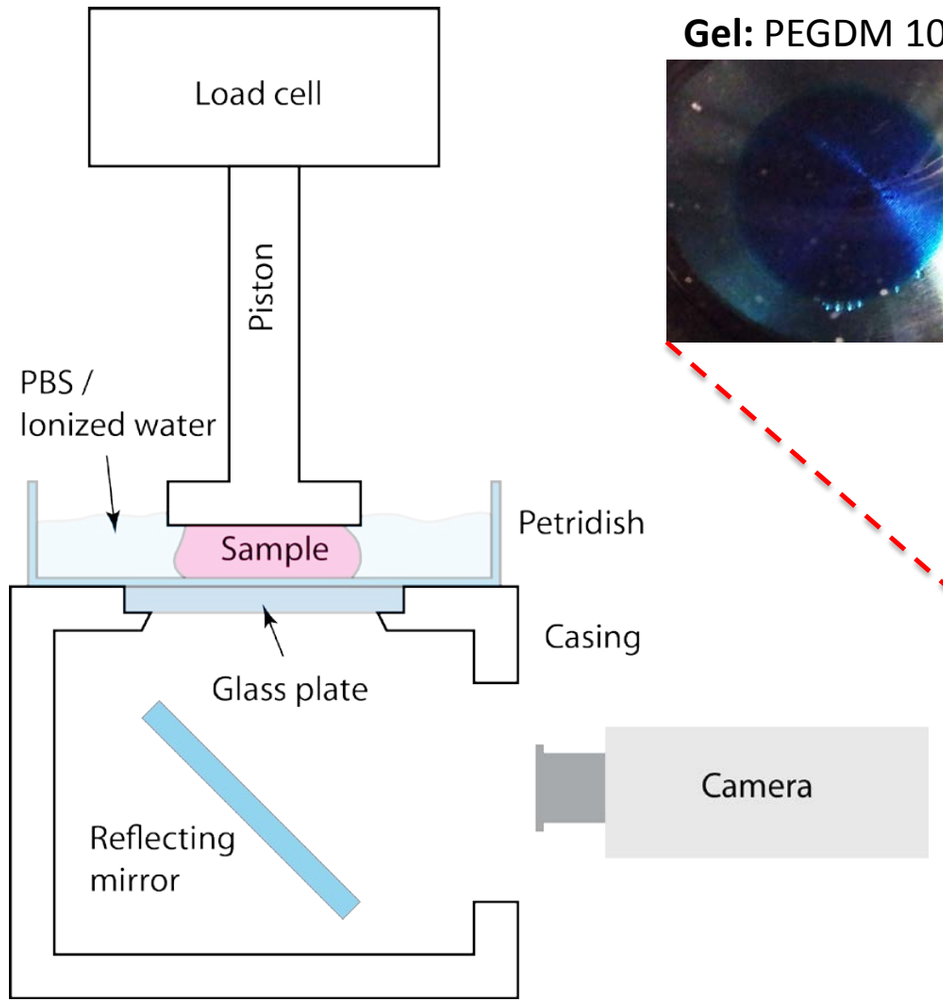
*: foam
s: solid

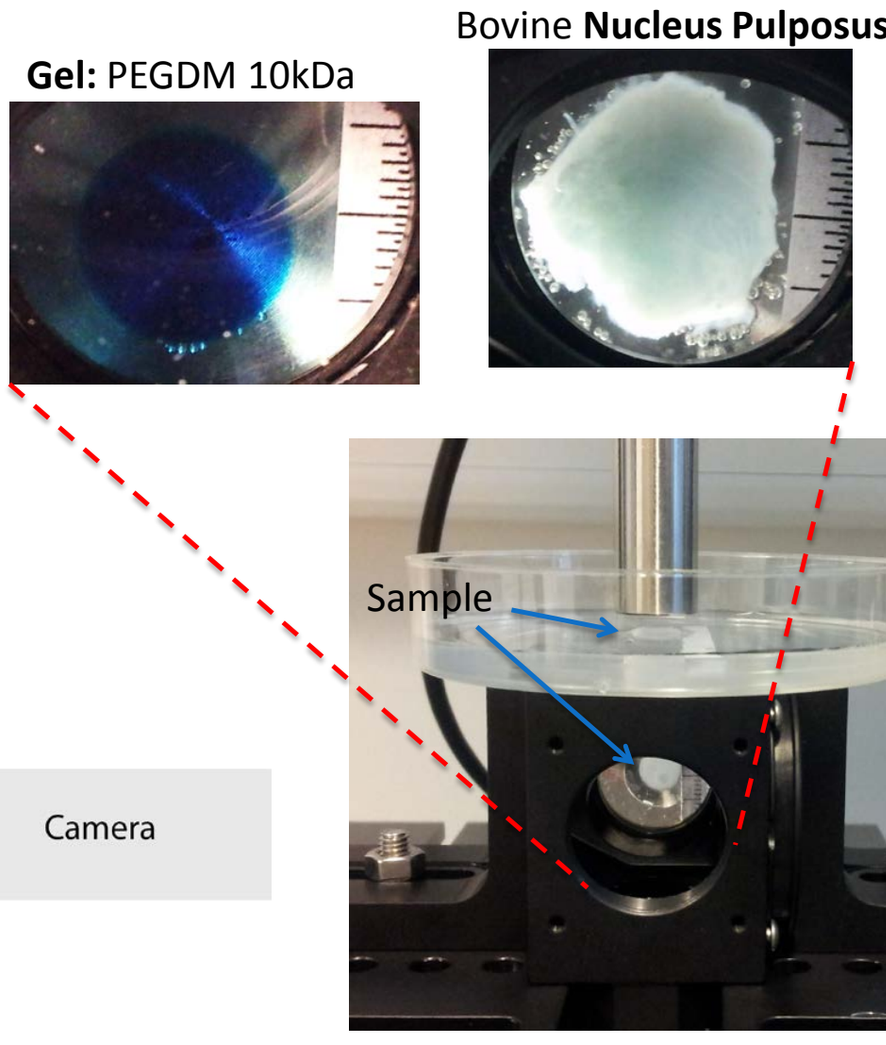



OC: open cell; CC: closed cell

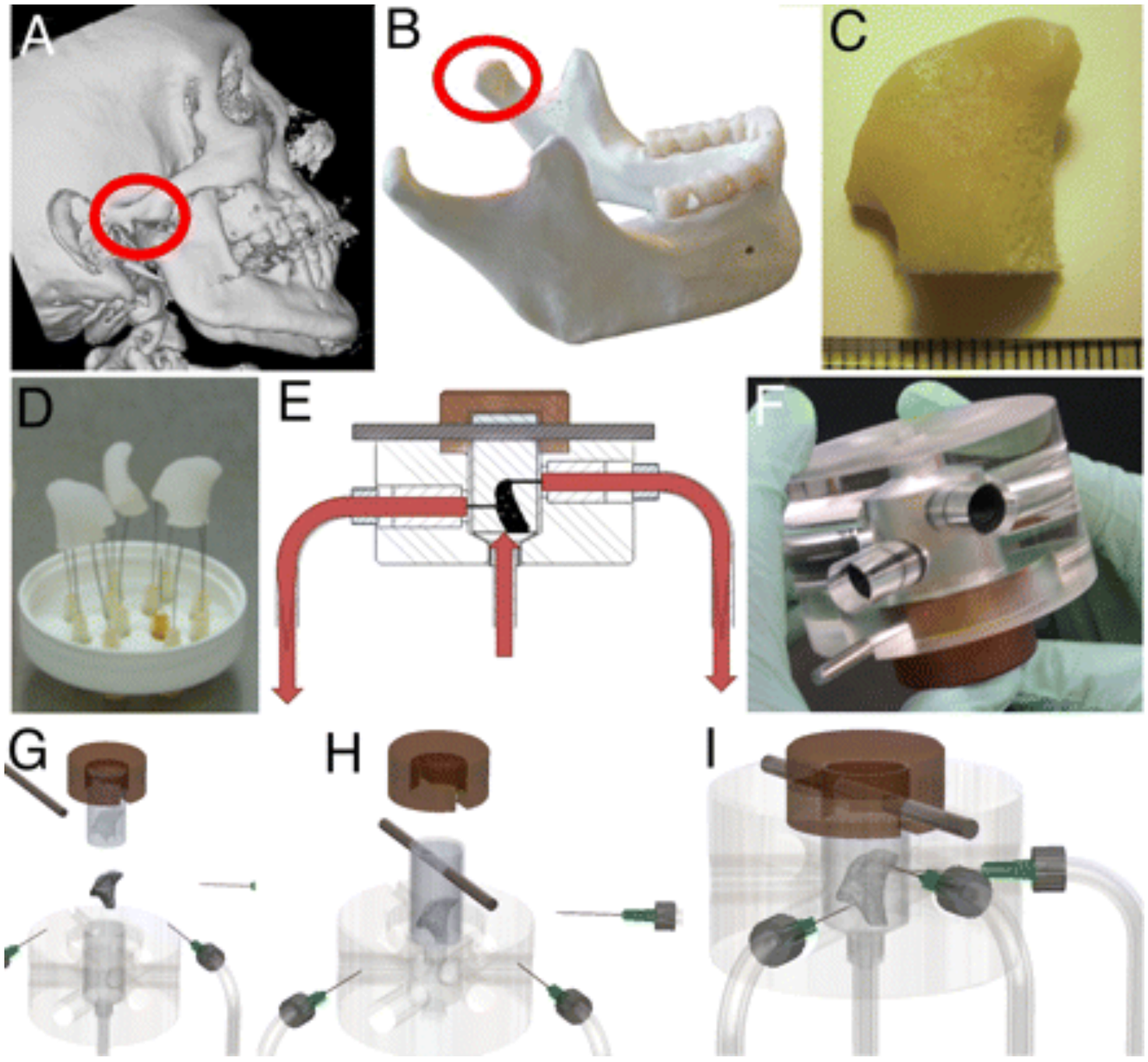
# The matching of mechanical properties for the native and artificial tissues is necessary for a functional tissue engineering approach



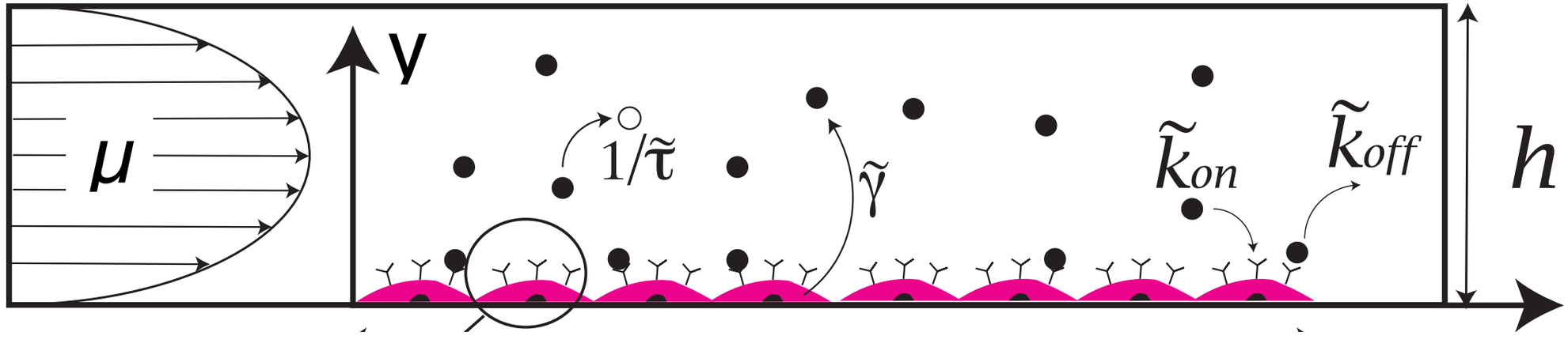



# Biomechanical consideration in bioreactors development: perfusion




From: PNAS, vol. 107 no. 8 3299-3304

# Biomechanical considerations in bioreactor development: perfusion




Fluid-induced shear stress

$$\tau = \mu \frac{du(y)}{dy}$$

u: fluid velocity; $\mu$: fluid viscosity

Laminar flow

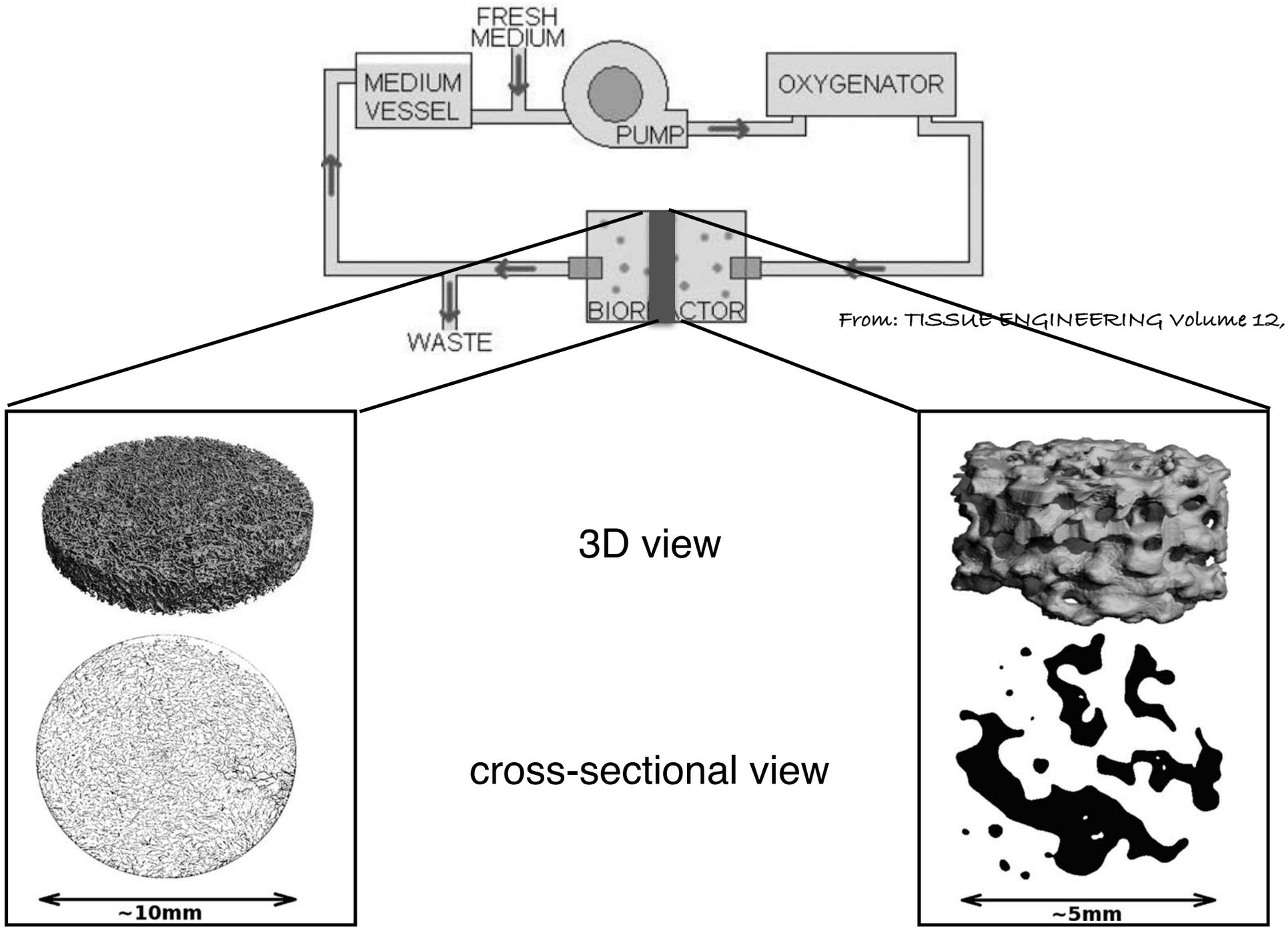
$$u(y) = u_{max}\left(1 - \frac{y^2}{\left(\frac{h}{2}\right)^2}\right) \qquad u_{max} = 2u_{av}$$

$u_{max}$: maximum fluid velocity; $u_{av}$: average fluid velocity

Shear stress on the cells

$$\boxed{\tau = \frac{8\mu u_{av}}{h}}$$

# The perfusion can then be tuned to favour tissue formation in scaffold placed inside bioreactor




From: TISSUE ENGINEERING Volume 12, Number 8, 2006

3D view

cross-sectional view

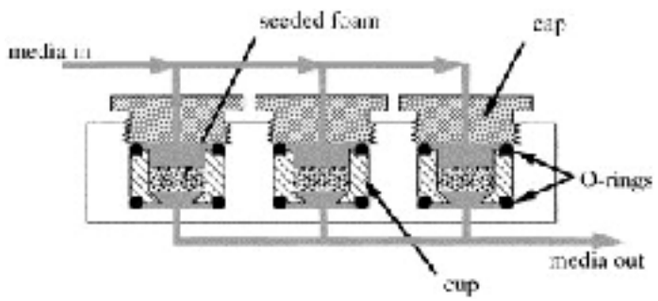
collagen-glycosaminoglycan scaffold

calcium-phosphate scaffold

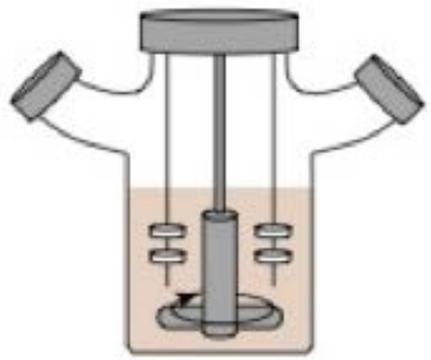


From: TISSUE ENGINEERING: Part A Volume 15, Number 5, 2009

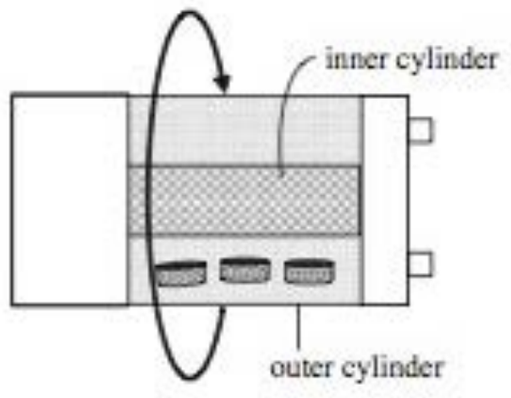
# The perfusion system seems then the best at least for tissue engineering of bone and cartilage tissues




Axial perfusion

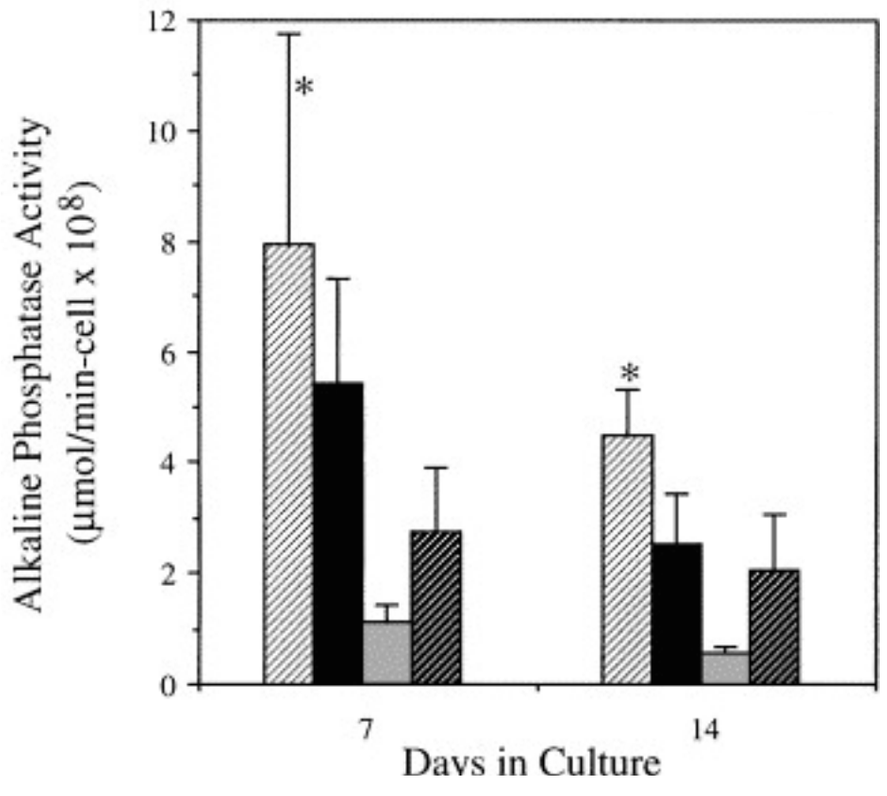


Spinner flask




Rotary vessel

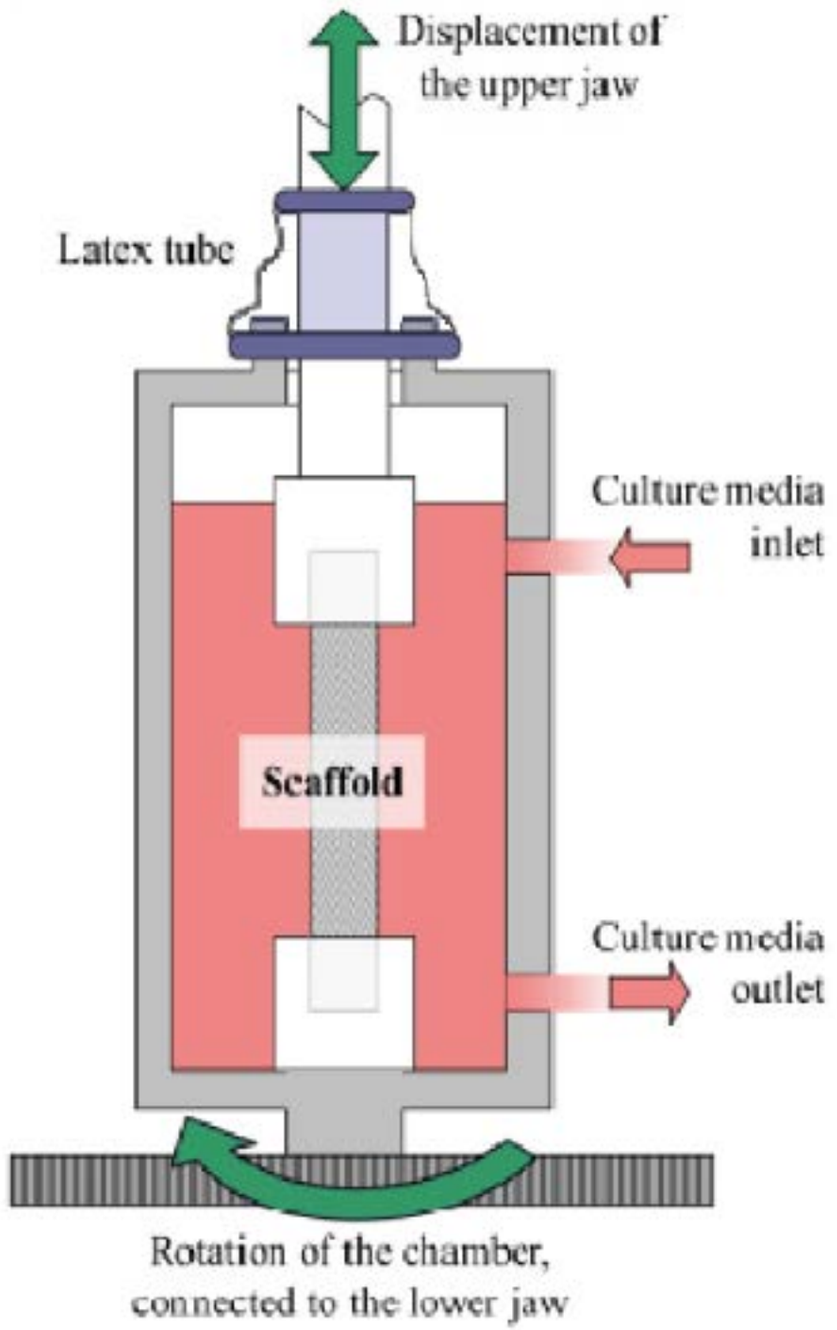
Static






From Biomaterials 22, 1279, 2001

# Obviously for tendon or ligament tissue engineering, bioreactor with traction mode are more adequate




From Processes 2014, 2(1), 167-179

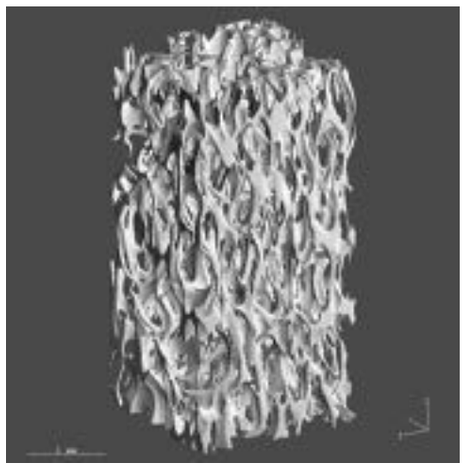
# Tissue engineering

i) General concepts

ii) Biomechanical considerations (evaluation, bioreactor)

iii) In vivo loading bioreactor

# The classical strategy in bone tissue engineering could be <u>modified</u>



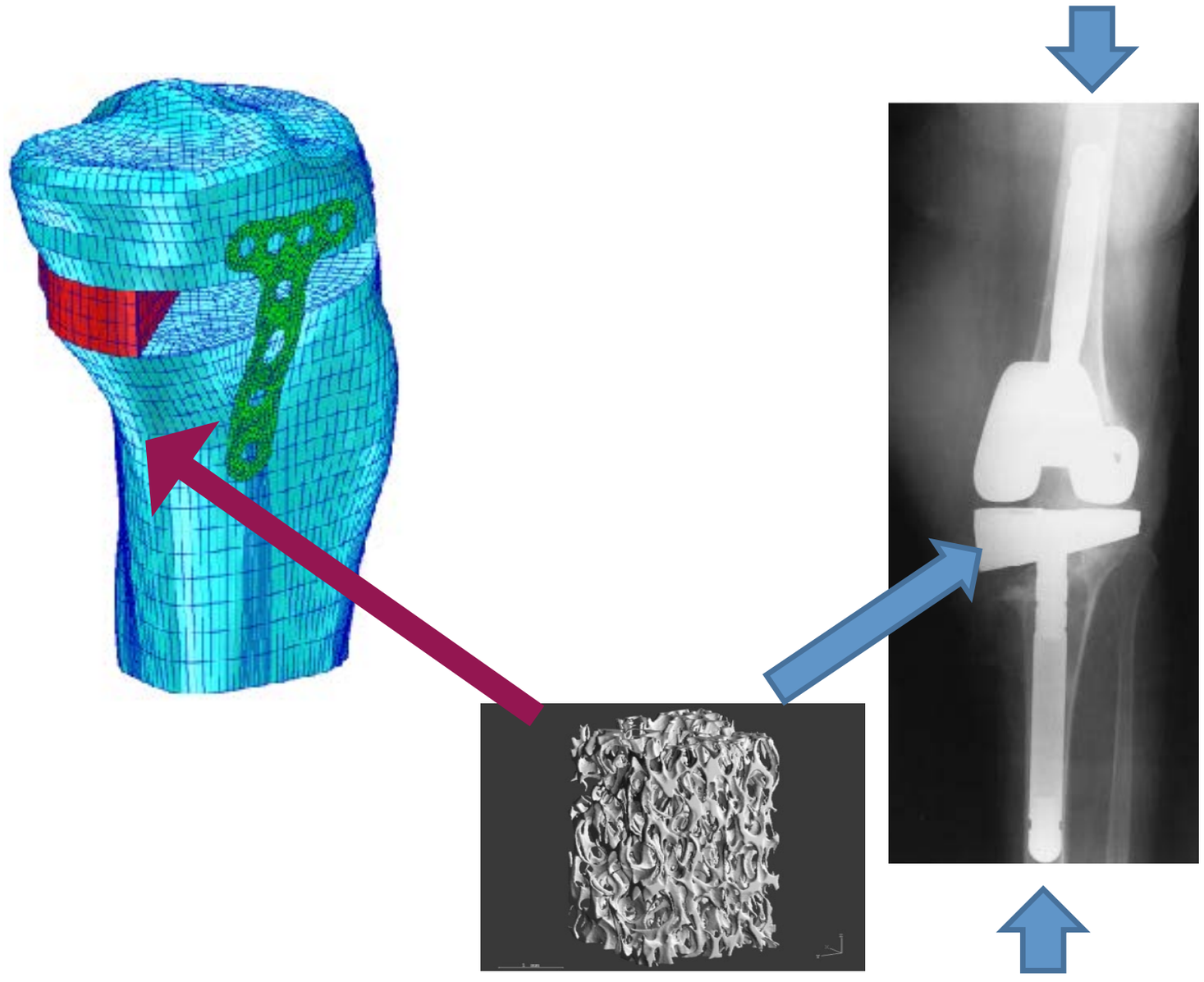
Scaffold

Cells

Growth factors

Biomechanics
(mechano-transduction)

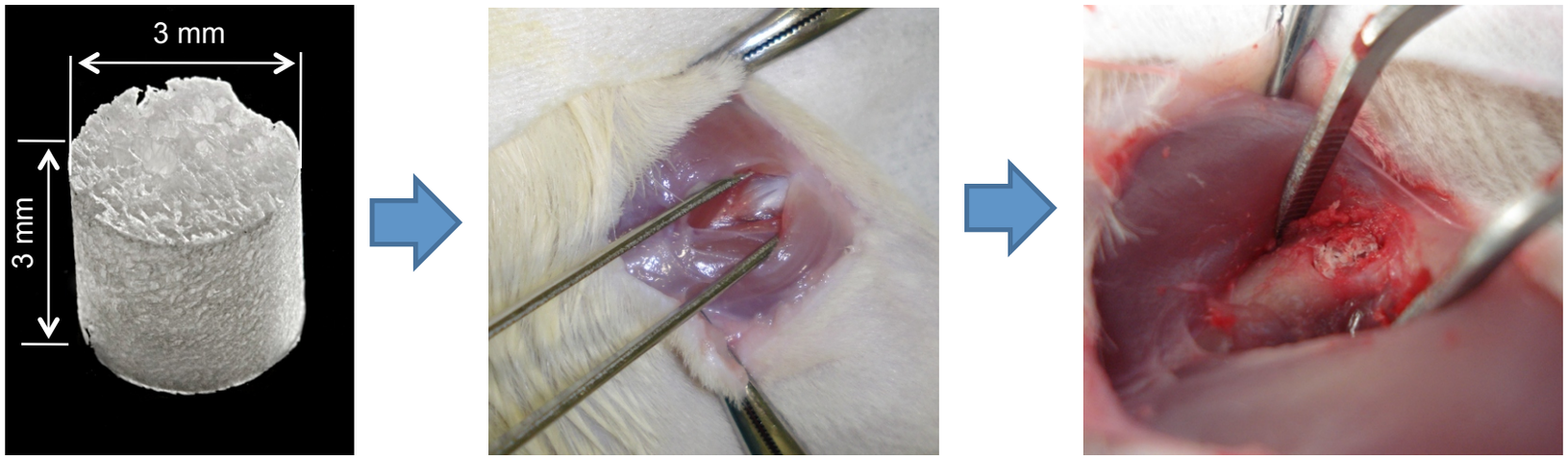
# Could we use the mechanical stimulation as an osteoinductor signal?



Mathieu *et al.* 2005

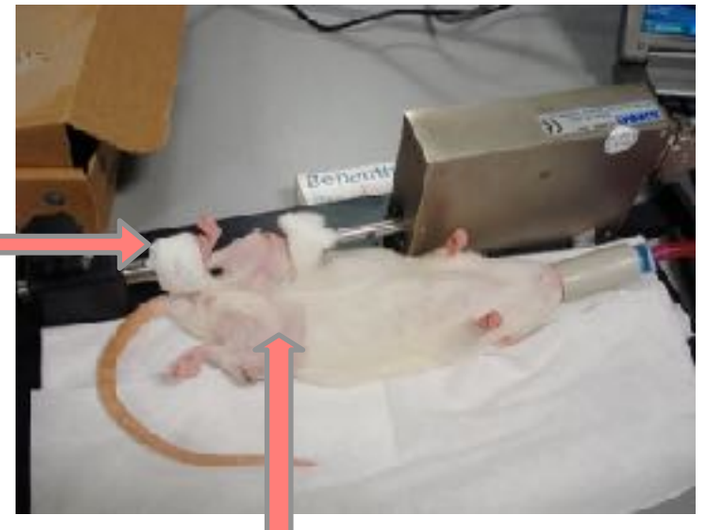
# A controlled in vivo mechanical loading system is developed

In vivo model




Design of the study

- 7 rats
- loading started 2 weeks after surgery



Loaded

10 N 4 Hz 5 min

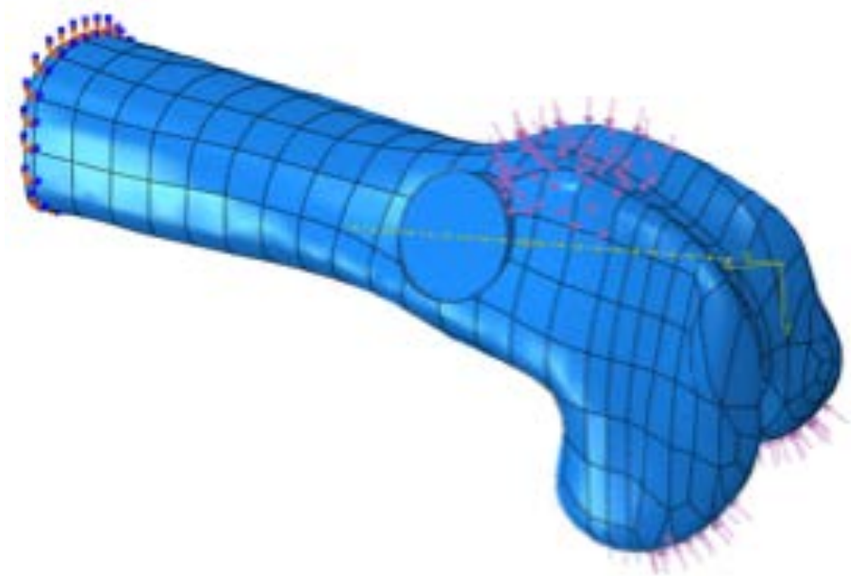
Control

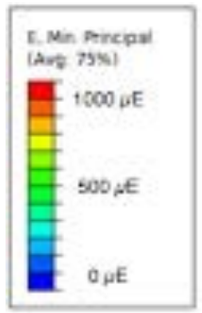
5 loadings total (1 loading every 2 days)

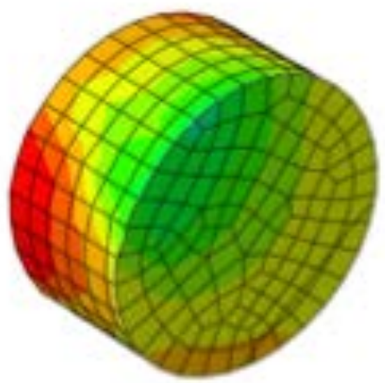


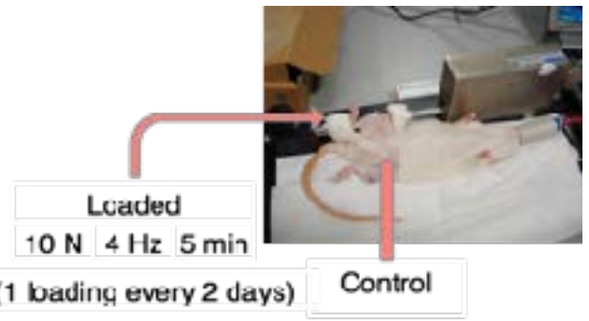
From European Cells and Materials Vol. 19 2010 (pages 41-49)

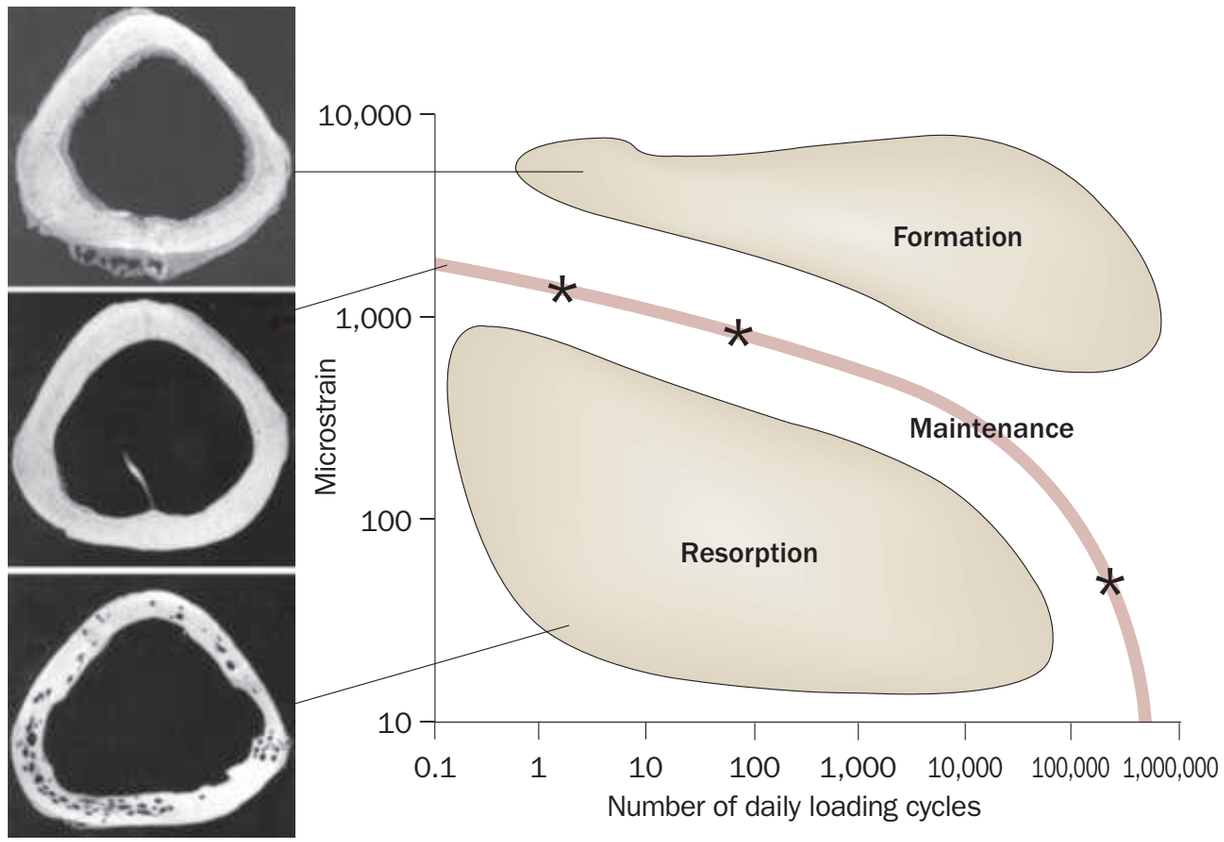
# A controlled in vivo mechanical loading system is developed








Ozcivici et al, Nat. Rev. Rheumatol., 2010

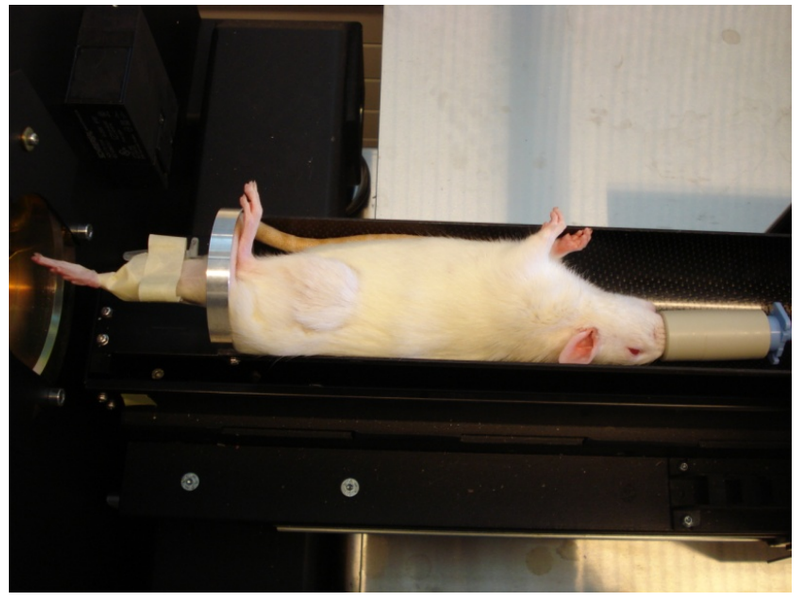
# A longitudinal in vivo μCT scanning is performed to evaluate bone formation in the scaffold

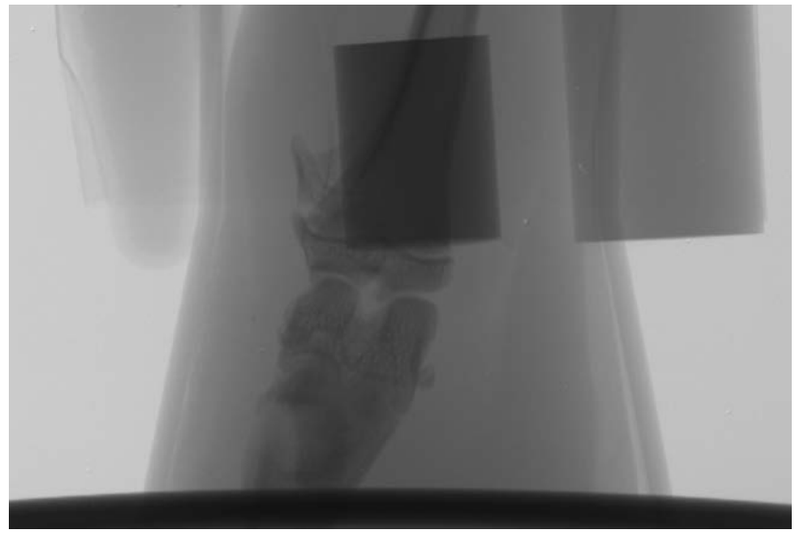
- Each leg is stretched and scanned separately

- CaHA fantoms and water tubes are used for calibration

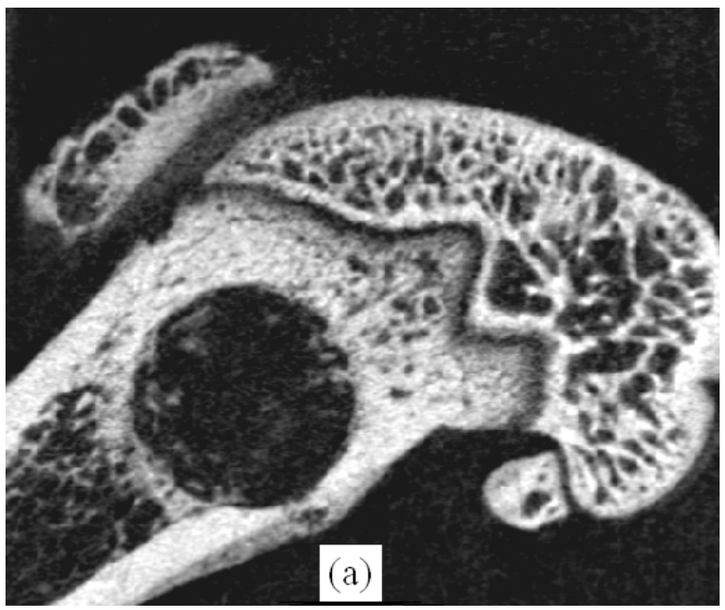
- 7 scans performed between 2 to 35 weeks following implantation

- Bone volume fraction (BVF) is measured

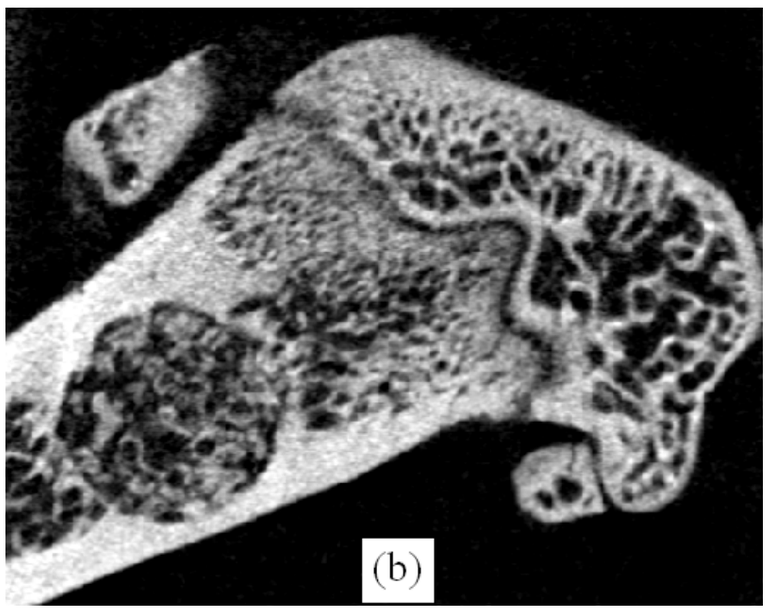




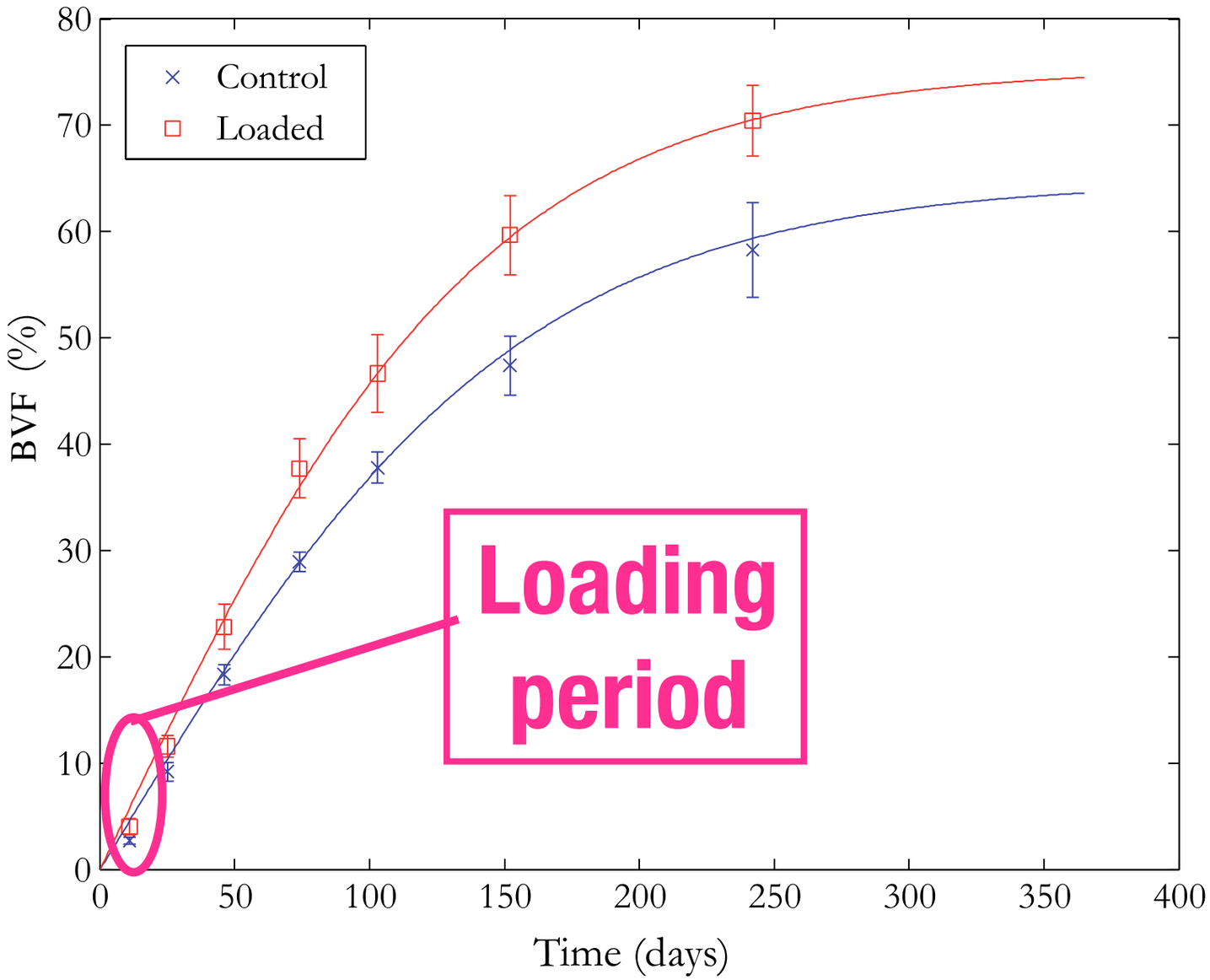
2 weeks




13 weeks

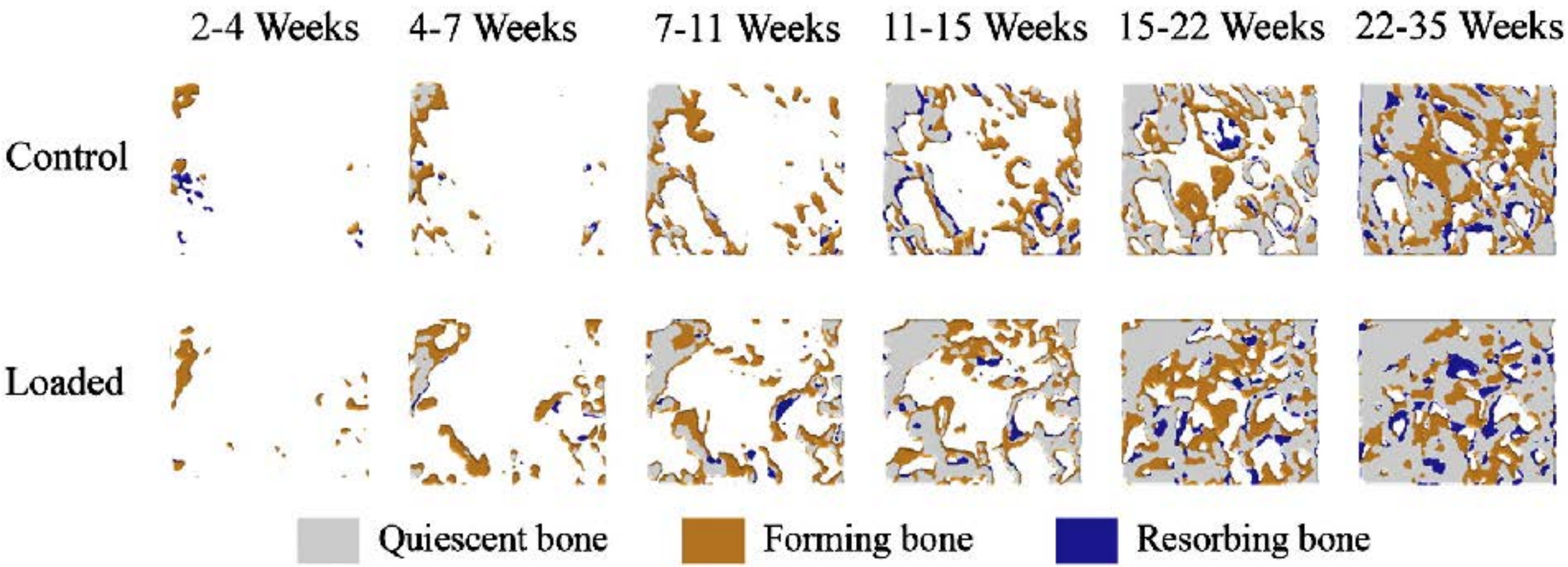


# Short periods of initial loading increase the long term bone formation in the scaffold




**18% increase** in final bone volume (P<0.05)

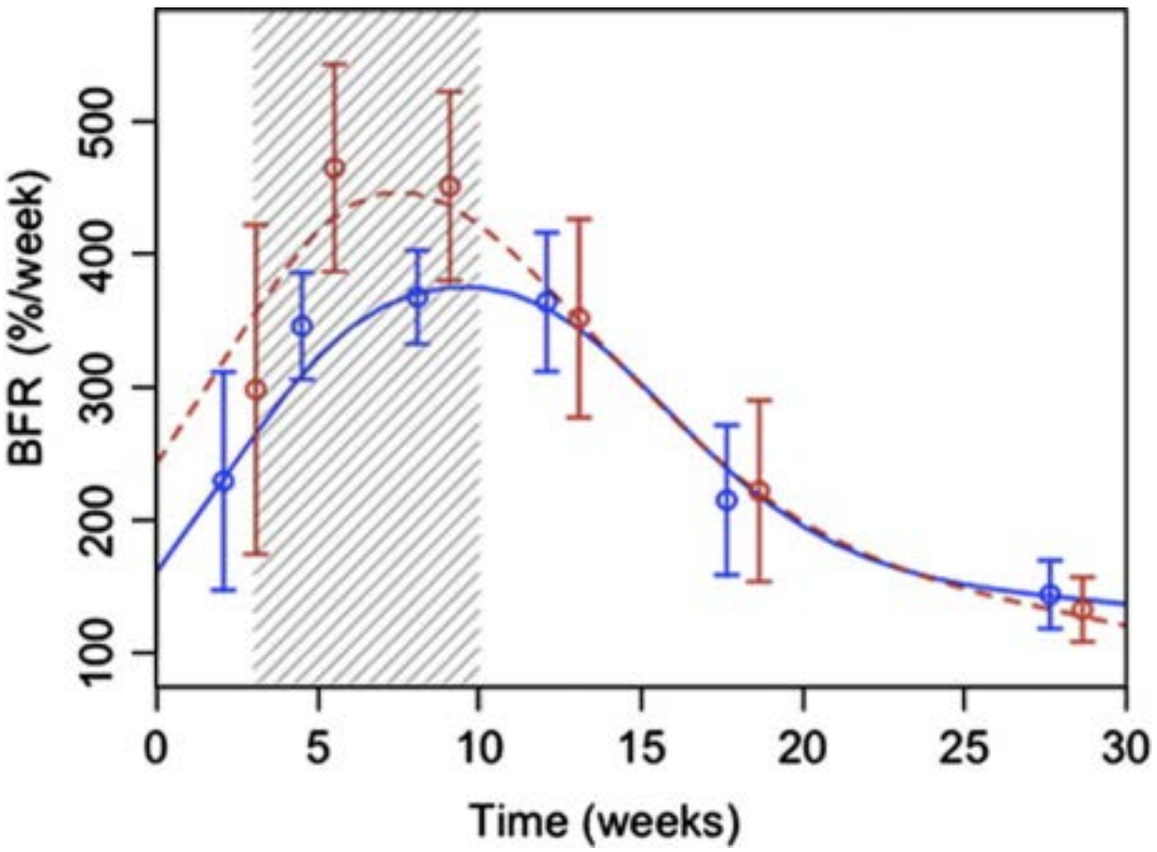
# Bone formation and resorption in the scaffold is a dynamic process

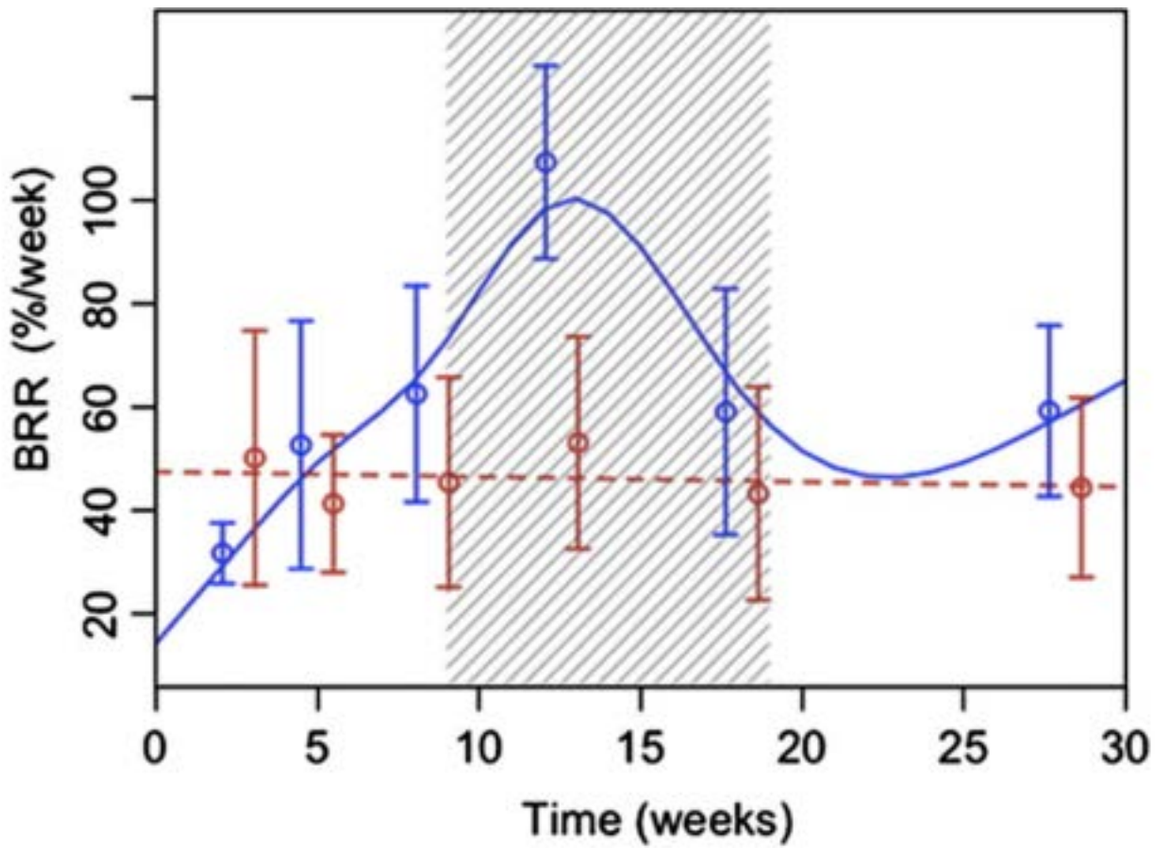



From Bone, vol. 49, p. 1357-1364, 2011

Mechanical stimulation not only increased bone formation rate, …

but also **decreased** bone **resorption** rate



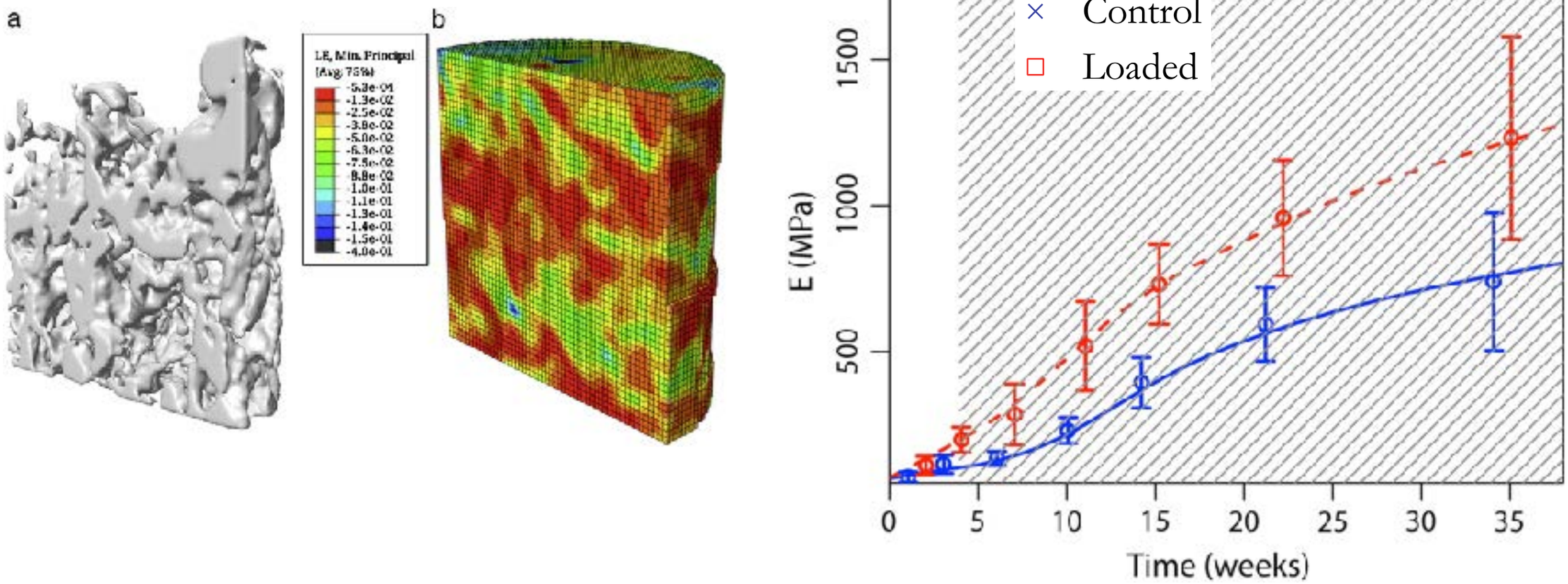




× Control

□ Loaded

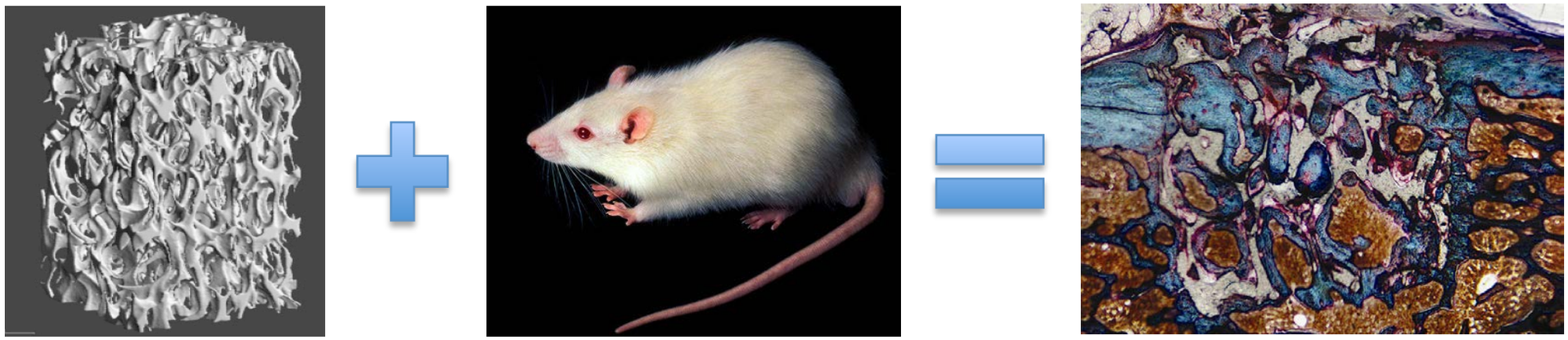
From Bone, vol. 49, p. 1357-1364, 2011

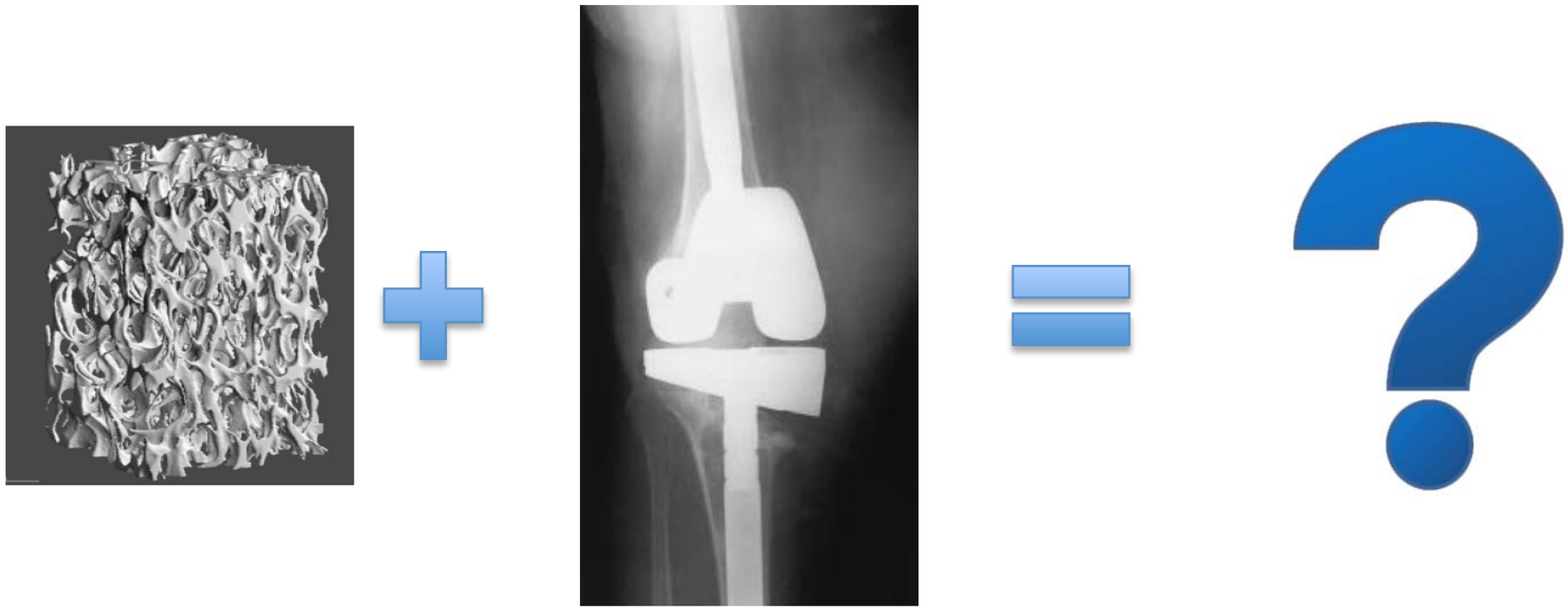
# The loading allowed to“functionalize” the “biological” competencies of the scaffold



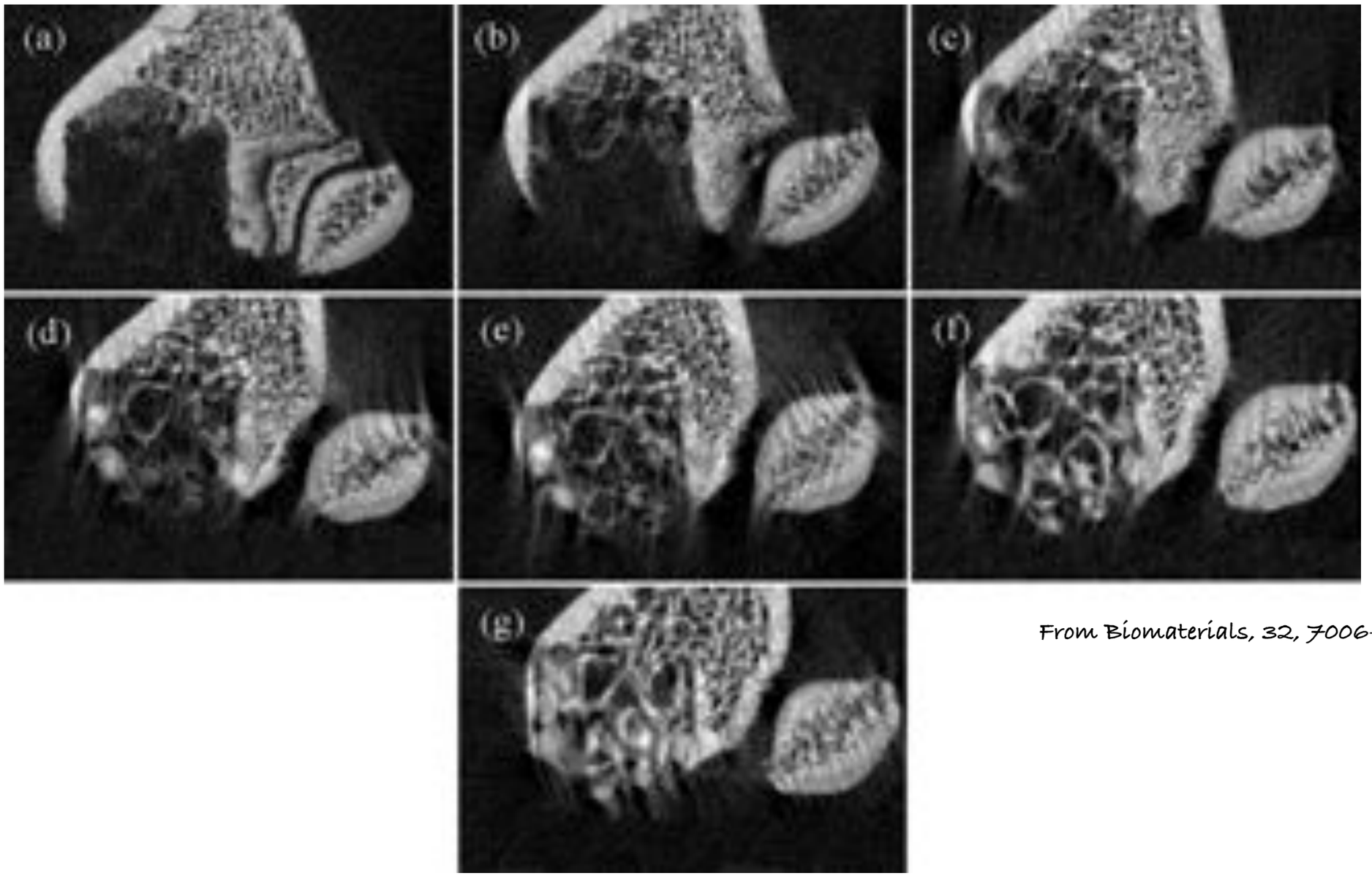

**Loading increases by 100% mech prop of scaffold**

# How can we translate the in vivo results into a clinical application?





# Bone formation is faster in regions closer to the bone-scaffold interface



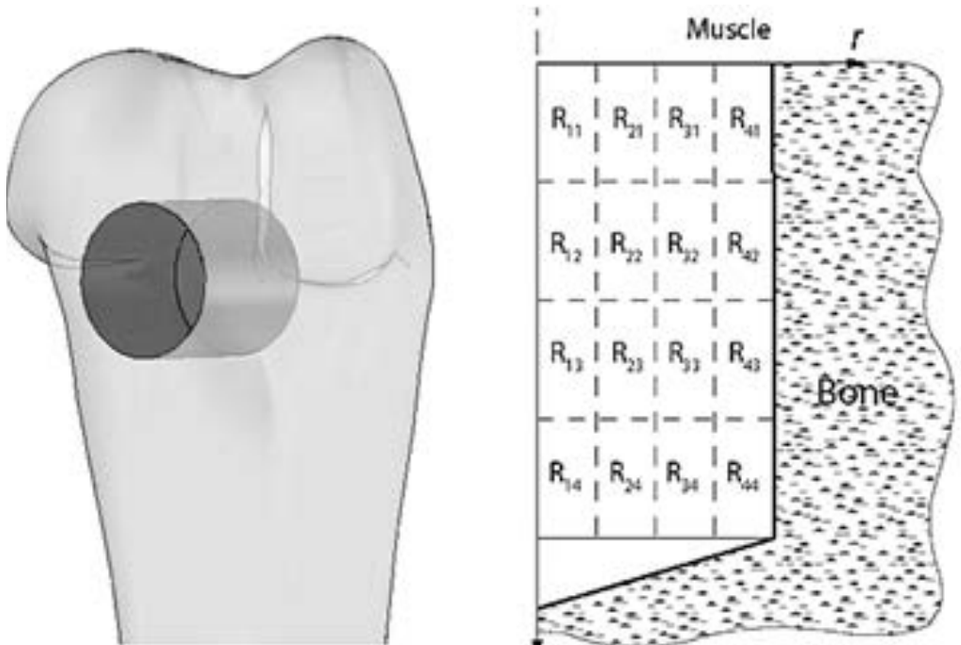

From Biomaterials, 32, 7006-7012, 2011

Hypothesis: bone formation in scaffold is governed by a diffusion phenomenon

# Bone formation in scaffold is described with a diffusion equation

$$\frac{\partial c}{\partial t} = \alpha\left[\frac{\partial^2 c}{\partial r^2} + \frac{1}{r}\frac{\partial c}{\partial r} + \frac{\partial^2 c}{\partial z^2}\right]$$

**α**: scaffold osteoconduction coefficient




Boundary conditions

$$-\alpha\left.\frac{\partial c}{\partial r}\right|_{r=R} = h[C - c(r,z,t)]_{r=R}$$

$$\left.\frac{\partial c}{\partial r}\right|_{r=0} = 0$$

$$-\alpha\left.\frac{\partial c}{\partial z}\right|_{z=H} = h[C - c(r,z,t)]_{z=H}$$

$$\left.\frac{\partial c}{\partial z}\right|_{z=0} = 0$$

**h**: peri-scaffold osteoinduction coefficient

**C**: final bone volume fraction

Initial condition

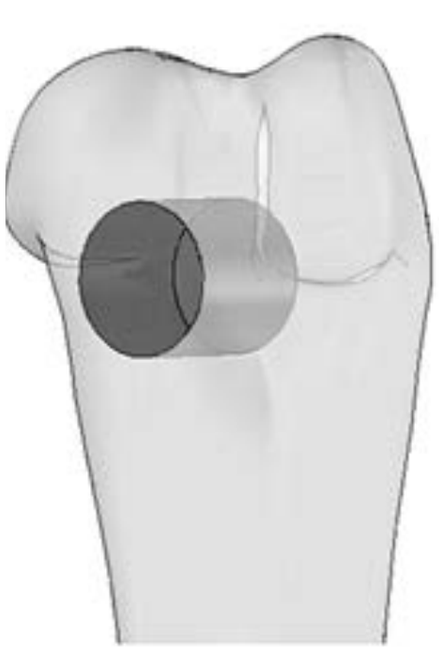
$$c(r,z,t)|_{t=0} = 0$$

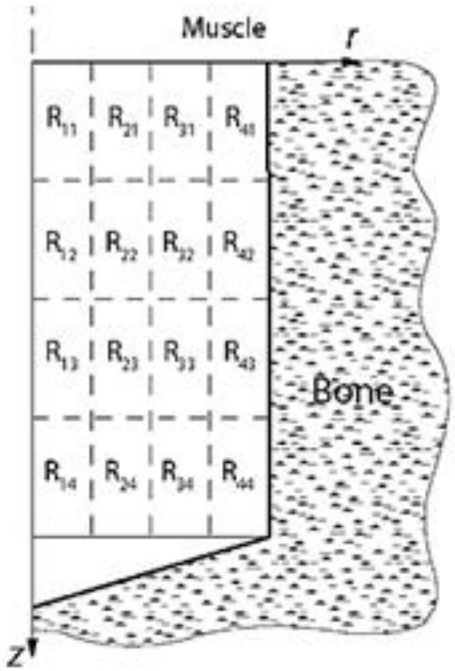
# An analytical solution to the bone diffusion can be found

$$\frac{\partial c}{\partial t} = \alpha\left[\frac{\partial^2 c}{\partial r^2} + \frac{1}{r}\frac{\partial c}{\partial r} + \frac{\partial^2 c}{\partial z^2}\right]$$

$$BVF(t)|_{R_{pq}} = C\left[V_{R_{pq}} - \sum_{i=1}^{\infty}\sum_{j=1}^{\infty} E_{ij} I_{ij} e^{-(\gamma_i{}^2+\beta^2\omega_j{}^2)Fo}\right]$$

$$E_{ij} = -\frac{4}{\gamma_i}\cdot\frac{Bi}{\gamma_i J_0(\gamma_i) + Bi.J_1(\gamma_i)}\cdot\frac{\beta sin(\omega_j)\tan(\omega_j)}{Bi + \beta sin^2(\omega_j)}$$





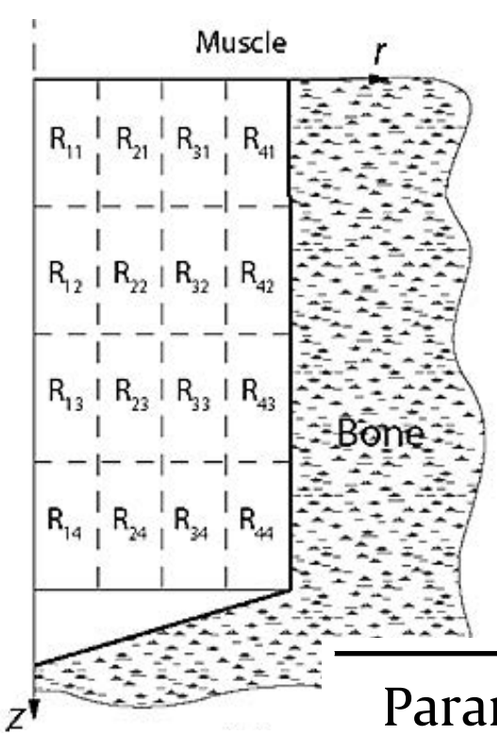

$$I_{ij} = \frac{2\pi RH}{\gamma_i\omega_j}\cdot\left[rJ_1\left(\frac{\gamma_i}{R}r\right)\right]_{r_p}^{r_{p+1}}\cdot\left[sin\left(\frac{\omega_j}{H}z\right)\right]_{z_q}^{z_{q+1}}$$

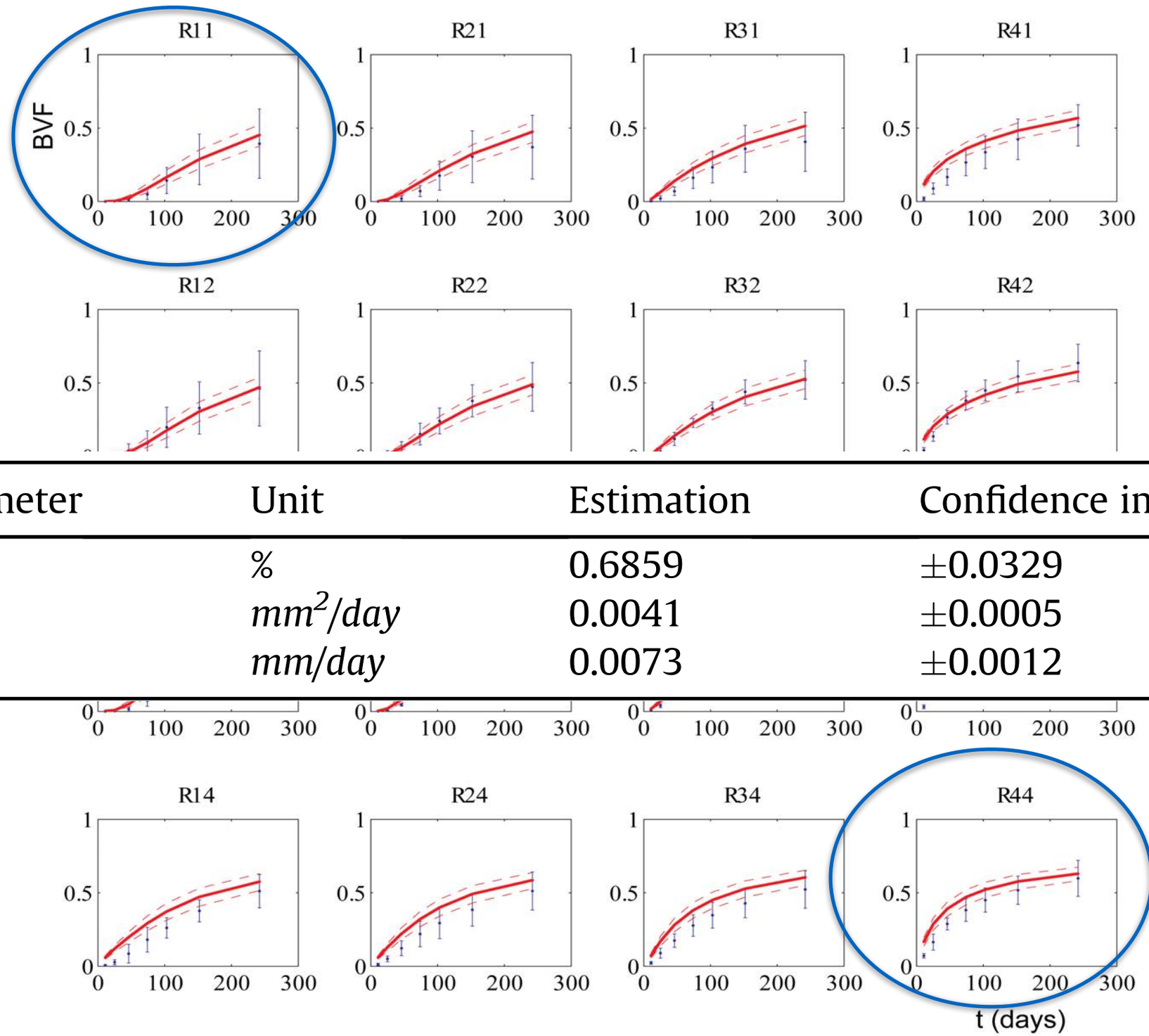
$$Bi = \frac{hr}{\alpha} \qquad Fo = \frac{\alpha t}{R^2}$$

Only 3 unknown:

$\alpha, C, h$

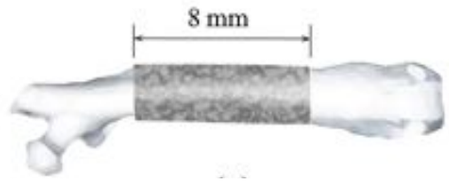
# Spatial and temporal experimental values of bone formation

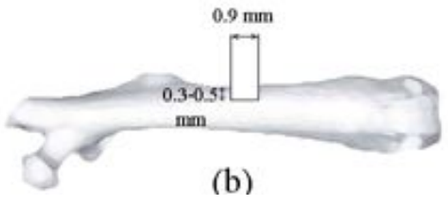



| Parameter | Unit | Estimation | Confidence interval |
|---|---|---|---|
| $C$ | % | 0.6859 | ±0.0329 |
| $\alpha$ | $mm^2/day$ | 0.0041 | ±0.0005 |
| $h$ | $mm/day$ | 0.0073 | ±0.0012 |

# Can the diffusion equation predict bone formation in tissue engineering scaffolds?

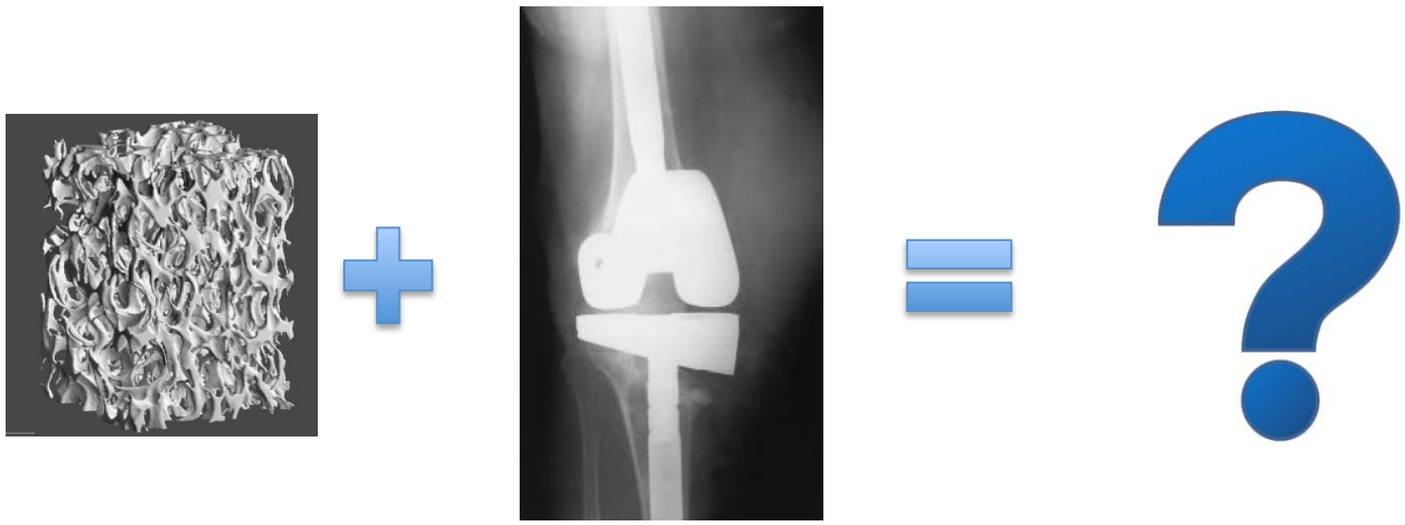


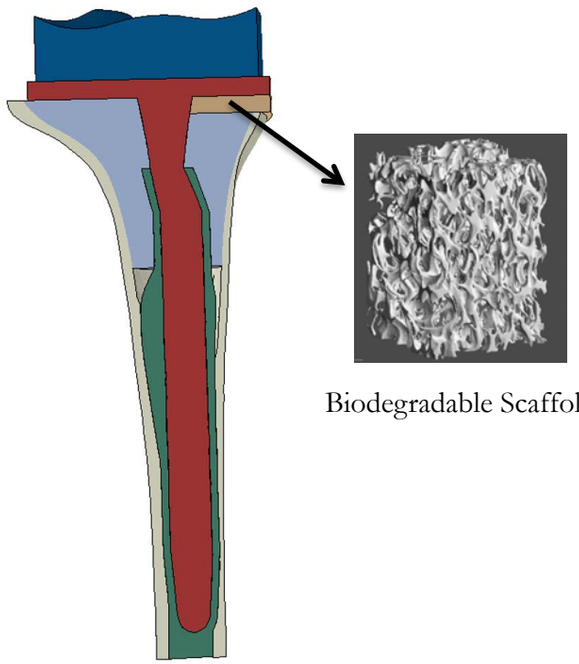




| In vivo experiment | Time points | Experimental BVF (%) | Predicted BVF (%) |
|---|---|---|---|
| Rat distal femur (this study) | 7 weeks | 19 ± 2 | 24 |
| | 22 weeks | 41 ± 7 | 47 |
| Segmental defect in rat[1] | 3 weeks | 1.4 ± 0.2 | 1.9 |
| | 12 weeks | 4.2 ± 1.0 | 5.7 |
| Cortical perforation in mice[2] | 14 days | 45 ± 13 | 36 |
| | 28 days | 58 ± 8 | 52 |

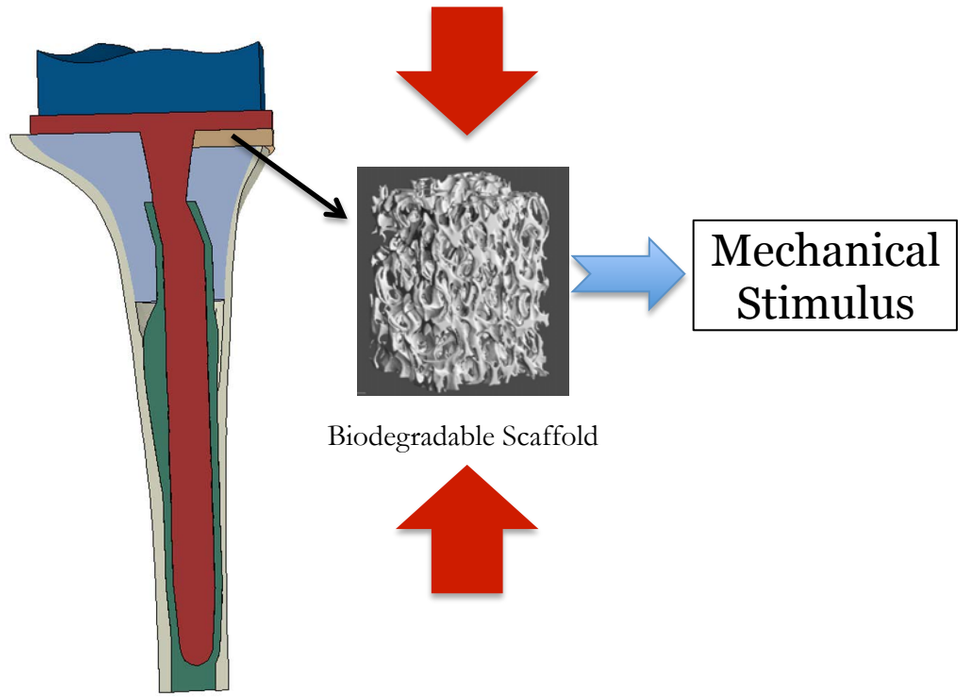
[1] Rai et al., J Biomed Mater Res A, 2007
[2] Monfoulet et al, Calc Tissue Int, 2010

# Based on the diffusion model, a translation of the rat in vivo results is proposed



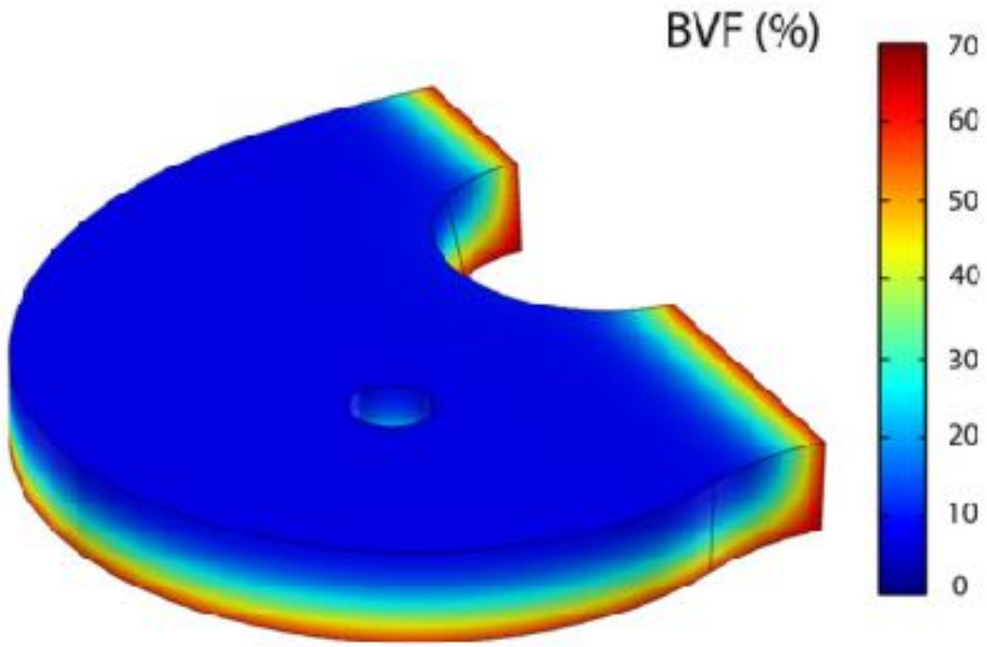


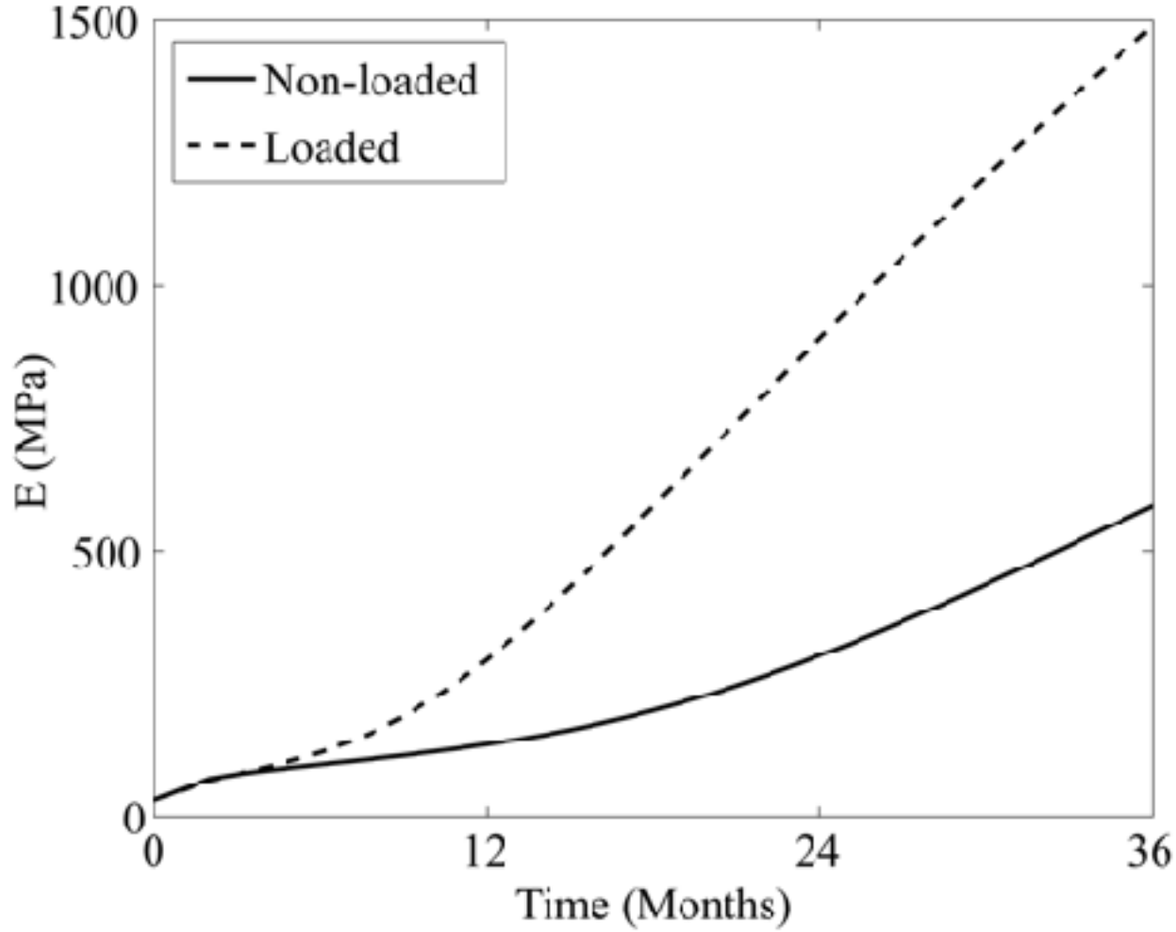
Biodegradable Scaffold




Biodegradable Scaffold

# The bone formation in and mechanical property of the scaffold are predicted (3 years post-implantation)



# Tissue engineering

i) General concepts

ii) Biomechanical considerations

iii) In vivo bioreactor