Βιοϋλικά και τρισδιάστατα μοντέλα συνθετικών οργάνων και ιστών

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School of Medicine, 11 April 2024

Biomaterial - Definition

In 1987, a group of experts defined the word biomaterial as "a non-viable material used in a medical device, intended to interact with biological systems" (**European Society of Biomaterials Conference (ESB)**, 1987).

This definition reflected the state of the field at the time, which was focused on developing materials and coatings to prevent the rejection of implantable medical devices. Since 1987, the field has advanced considerably with recent work resulting in the development of implantable scaffolds that consist entirely of specific biomaterials.

https://www.esbiomaterials.eu

European Society for Biomaterials

Biomaterial - Biocompatibility

Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application

(D. Williams, 1987)

Βιοσυμβατότητα είναι η ικανότητα ενός υλικού να προκαλεί μια κατάλληλη απόκριση στο σύστημα ξενιστή σε μια ειδική εφαρμογή

Overview

Biomaterials have many biomedical applications, eg as drug carriers for drug delivery, in therapeutics and diagnostics

Applications

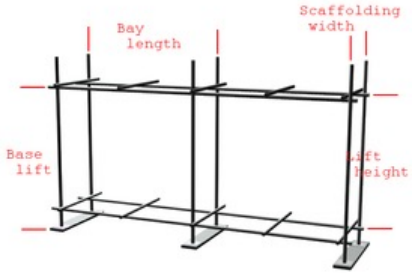
Tissue Engineering

Regenerative medicine

What is a biomaterial, a scaffold and a biomaterials-scaffold?

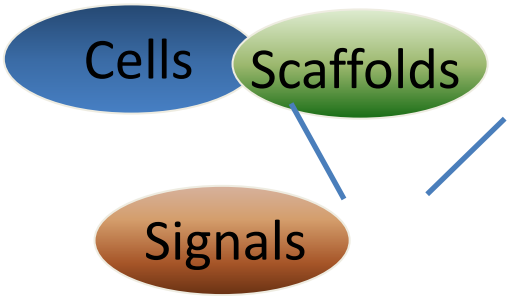
Scaffold

A scaffold (ικρίωμα) is a temporary structure used to support people and material in the construction or repair of buildings and other large structures

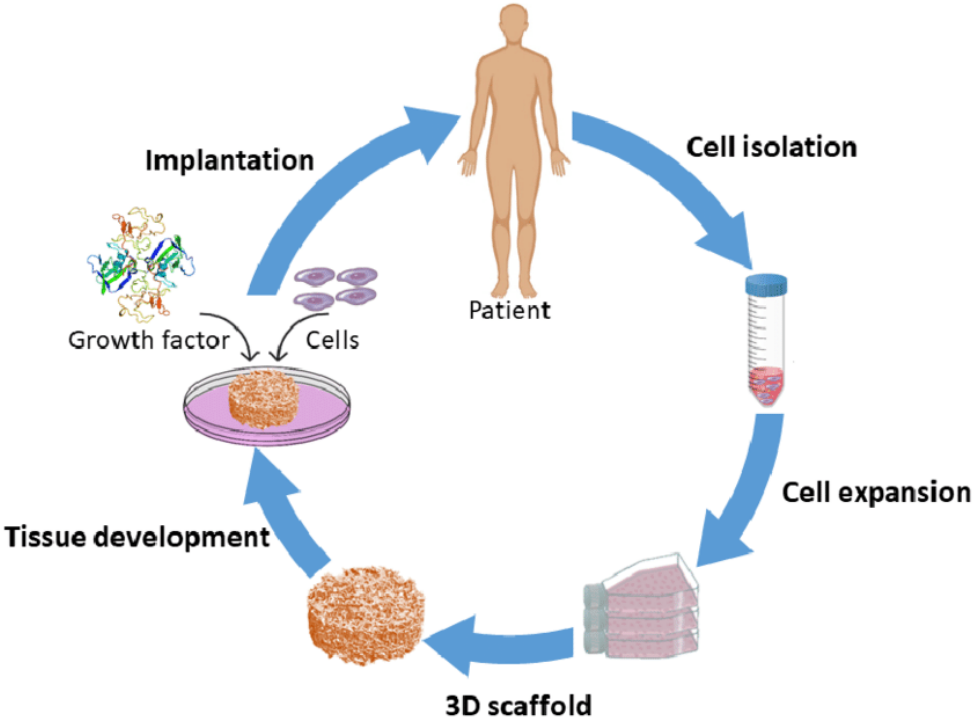


Tissue engineering
All protagonists in one schematic

Tissue engineering: a fascinating, multidisciplinary field



Coexistence, synergy,
harmonic orchestration



Fabrication and Plasma Modification of Nanofibrous Tissue Engineering Scaffolds, 2020, DOI: 10.3390/nano10010119

Μηχανική Ιστών - Tissue engineering

Tissue Engineering

Robert Langer; Joseph P. Vacanti

Science, New Series, Vol. 260, No. 5110. (May 14, 1993), pp. 920-926 *

Tissue engineering is an interdisciplinary field that applies the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function (7). Three general strategies have been adopted for the creation of new tissue:

1) Isolated cells or cell substitutes. This approach avoids the complications of surgery, allows replacement of only those cells that supply the needed function, and permits manipulation of cells before infusion. Its poten-

* Stable URL:
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Tissue Engineering
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http://links.jstor.org/sici?sici=0036-8075%2819930514%293%3A260%3A5110%3C920%3ATE%3E2.0.CO%3B2-G

tial limitations include failure of the infused cells to maintain their function in the recipient, and immunological rejection.

2) Tissue-inducing substances. The success of this approach depends on the purification and large-scale production of appropriate signal molecules, such as growth factors, and, in many cases, the development of methods to deliver these molecules to their targets.

3) Cells placed on or within matrices. In closed systems, the cells are isolated from the body by a membrane that allows permeation of nutrients and wastes but prevents large entities such as antibodies or immune cells from destroying the transplant. These systems can be implanted or used as extracorporeal devices (Fig. 1). In open systems, cells attached to matrices are implanted and become incorporated into the body (Fig. 2). The matrices are fashioned from natural materials such as collagen or from synthetic polymers. Immunological rejection may be prevented by immunosuppressive drugs or by using autologous cells.

Tissue engineering (TE) - Applications

Bioengineering of human skin substitutes
Nerve regeneration
Gene therapy and TE based on muscle derived stem cells
Bone TE / Bone marrow TE / Cartilage TE
TE of the temporomandibular joint
TE smooth muscle
Esophagus: A TE challenge
TE vascular grafts
Cardiac TE
TE of heart valves
TE for the regeneration of urologic organs
Hepatic TE for liver support
TE of renal replacement therapy
The bioengineering of dental tissues
Tracheal TE
Artificial pancreas

Biomaterial scaffolds

A biomaterial scaffold provides a **3D environment** for cells that is desirable for the production of the tissue

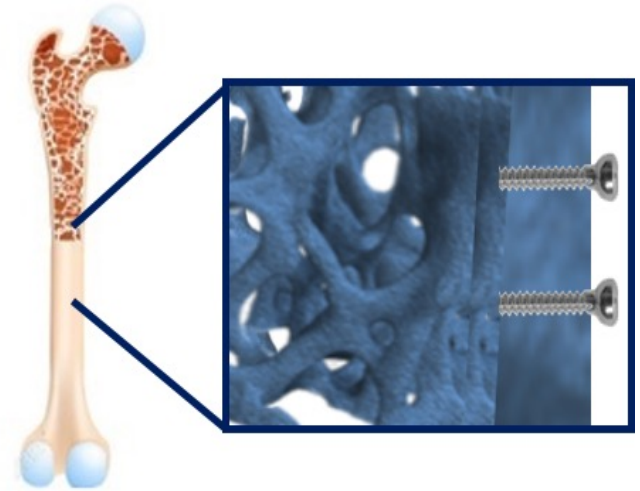
Ideally, a biomaterial scaffold should:

1. have directed and controlled degradation
2. promote cell viability, differentiation, and ECM production
3. allow for the diffusion of nutrients and waste products
4. adhere and integrate with the surrounding native tissue
5. span and assume the size of the defect
6. provide mechanical integrity depending on the defect location

Designing scaffolds for TE
What matters?

A biomaterial scaffold provides a **3D environment** for cells that is desirable for the production of the tissue

Considerations in designing a biomaterial scaffold:



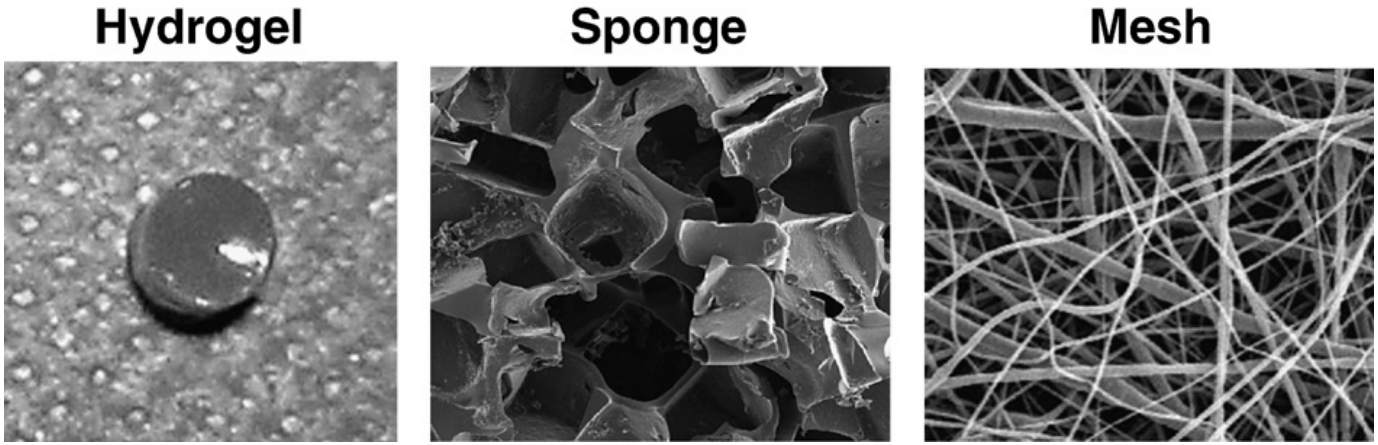
1. the chemistry (biochemical cues)
2. the architecture
3. mechanical properties (biophysical cues)
4. the stimulating factors
5. the functionality/multifunctionality

Designing a 3D scaffold

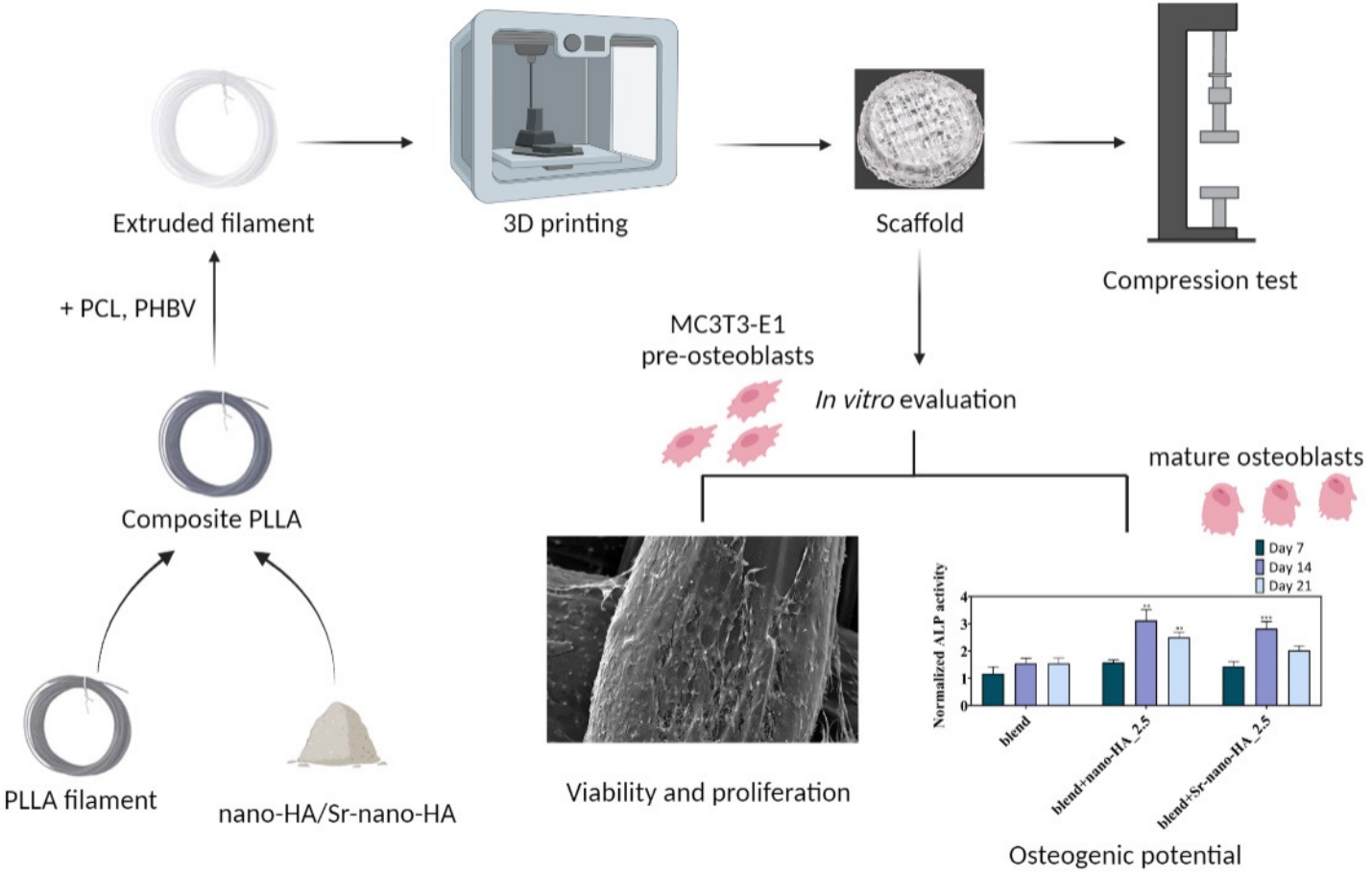
By designing a scaffold, cell seeding density and seeding method should be carefully considered since the appropriate numbers of cells must be used to ensure adequate cell–cell interactions.

Many approaches attempt to mimic the natural condensation of cells during embryonic development by seeding in aggregates or at high densities. Higher initial seeding densities tend to facilitate greater ECM synthesis and deposition, presumably due to cell–cell interactions. The method of seeding, statically or dynamically, can dictate cell distribution and infiltration into the scaffold. In sponge and mesh scaffolds, dynamic seeding can improve cellular distribution, whereas hydrogels typically support uniform cell distributions if cells are adequately suspended during gelation.

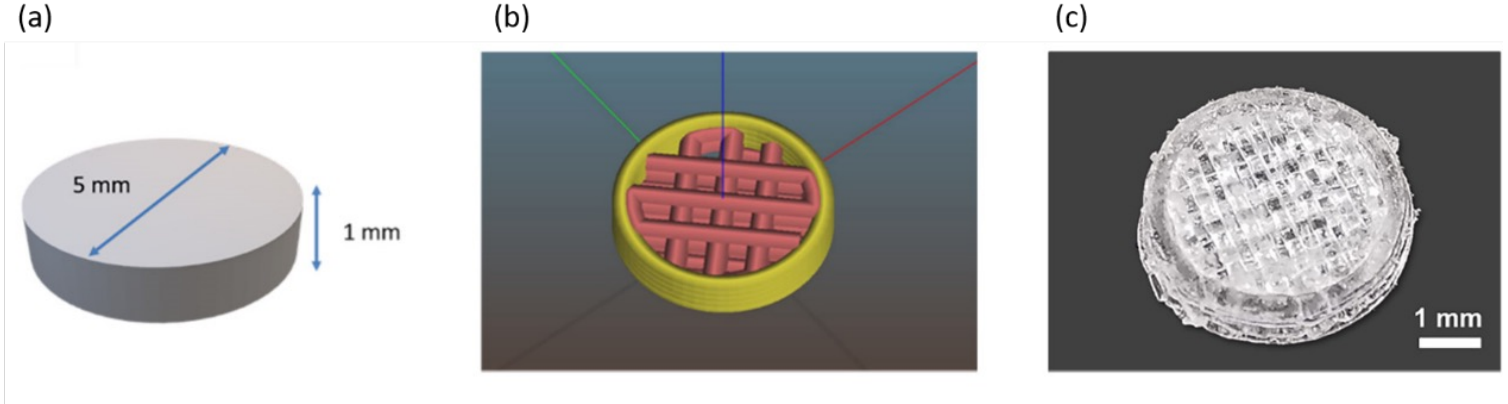
Examples of different scaffold architectures used in tissue engineering



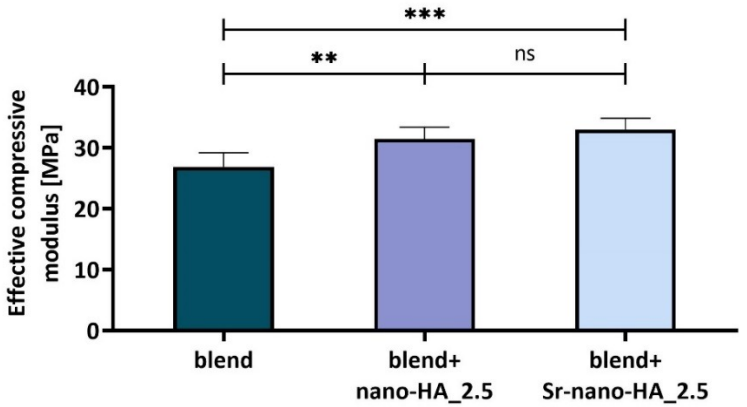
3D printed scaffolds – An example



Scaffold characteristics



Mean porosity: 40%
mean pore size: 800 µm
average compressive modulus: 32 MPa



Kontogianni et al., https://doi.org/10.3390/polym15041052

Scaffold degradation

Scaffold degradation can occur hydrolytically or enzymatically, and by controlling degradation temporally and spatially, scaffolds can enhance and direct new tissue growth. For example, scaffolds with degradable and non-degradable units show improved ECM distribution compared to completely non-degradable scaffolds.

However, a balance must be found since slow degradation may impede new ECM production, while fast degradation may compromise structural support and shape retention.

Example: Researchers showed that scaffolds with slower degradation rates yielded cartilage of greater thickness in an osteochondral defect model, but cracks and fissures were evident on the cartilage surface.

Components needed for success

Achieving success with tissue engineering depends on meeting a variety of critical experimental conditions. One is to have the necessary components, including both regeneration-competent cells and the carrier or support matrix. Another requirement is an environment conducive to cell growth, differentiation and eventually integration with the surrounding tissue. In many cases, the appropriate biological, physical and chemical cues are not yet completely understood. The differences between a regenerative or developmental environment and that of wound repair may be difficult to control. Obtaining the number and type of cells needed for tissue engineering is very important for treating damaged tissues, particularly in cases where either the tissue does not have the ability to regenerate, or the native reparative mechanisms are inadequate.

The mechanical properties

TABLE 1 Mechanical Properties of Cortical Bone, 316L Stainless Steel, Cobalt–Chromium Alloy, Titanium and Titanium-6-Aluminum-4-Vanadium

Material	Young's modulus (GPa)	Compressive strength (GPa)	Tensile strength (GPa)
Bone			
(wet at low strain rate)	15.2	0.15	0.090
(wet at high strain rate)	40.7	0.27–0.40	—
316L stainless steel	193	—	0.54
Co–Cr (cast)	214	—	0.48
Ti			
0% porosity	110	—	0.40
40% porosity	24[a]	—	0.076
Ti–6Al–4V			
0% porosity	124	—	0.94
40% porosity	27[a]	—	0.14

Biomaterials

Natural biomaterials

Agarose, alginate, cellulose, collagen, chitosan, chondroitin sulfate, fibrin glue, gelatin, hyaluronic acid, silk fibroin

Synthetic biomaterials

poly(α-hydroxy esters), poly(ε-caprolactone), poly(L,D- lactic acid), poly(ethylene glycol/oxide), poly(NiPAAm), poly(propylene fumarate), poly(urethane), poly(vinyl alcohol), Self-assembling peptides
Ceramic based biomaterials

Natural and synthetic biomaterials

To date, a wide range of natural and synthetic materials have been investigated as scaffolding materials. Natural polymers that have been explored as bioactive scaffolds and include: alginate, agarose, fibrin, HA, collagen, gelatin, chitosan, chondroitin sulfate, and cellulose.

Natural polymers can often interact with cells via cell surface receptors and regulate or direct cell function. However, due to this interaction, these polymers may also stimulate an immune system response; thus, antigenicity and disease transfer are of concern when using these biomaterials.

In addition, natural polymers may be inferior mechanically and subject to variable enzymatic host degradation.

Natural and synthetic biomaterials

On the other hand, synthetic polymers are more controllable and predictable, where chemical and physical properties of a polymer can be modified to alter mechanical and degradation characteristics. Synthetic polymers currently explored for cartilage repair include: poly (α-hydroxy esters), PEG, poly(NiPAAm), poly(propylene fumarates), and polyurethanes.

However, unless specifically incorporated, synthetic polymers do not benefit from direct cell-scaffold interactions, which can play a role in adhesion, cell signaling, directed degradation, and matrix remodeling. In addition, degradation byproducts may be toxic or elicit an inflammatory response.

Finally, scaffold architecture also plays a major role in dictating cellular behavior. Scaffolds can be categorized into hydrogels, sponges, and fibrous meshes.

Cell-biomaterial interactions

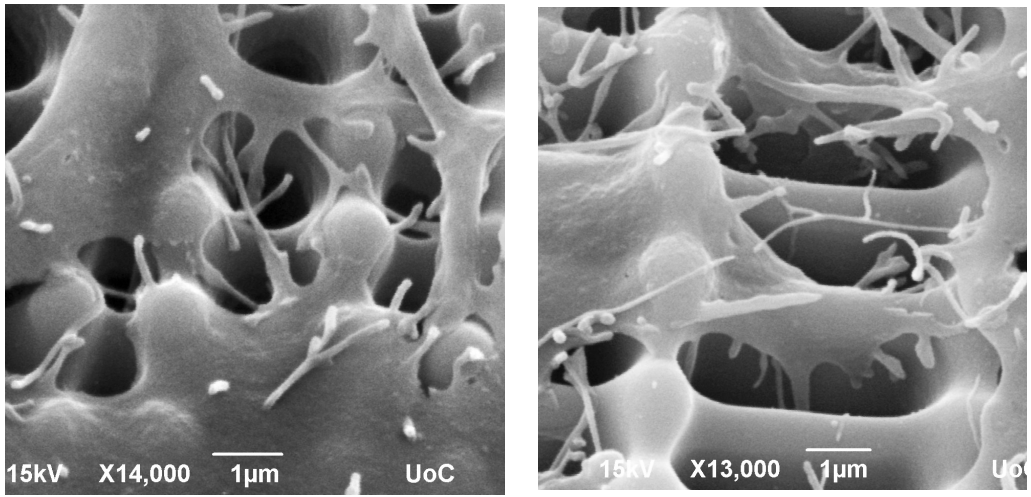
Evaluation of the biocompatibility and osteogenic capacity of developed scaffolds under conditions mimicking the in vivo situation →
Experimental design of *in vitro* studies under static and dynamic conditions, mono- and co-cultures

Initial cell adhesion in scaffolds

Cell source: MC3T3-E1 pre-osteoblastic cell line

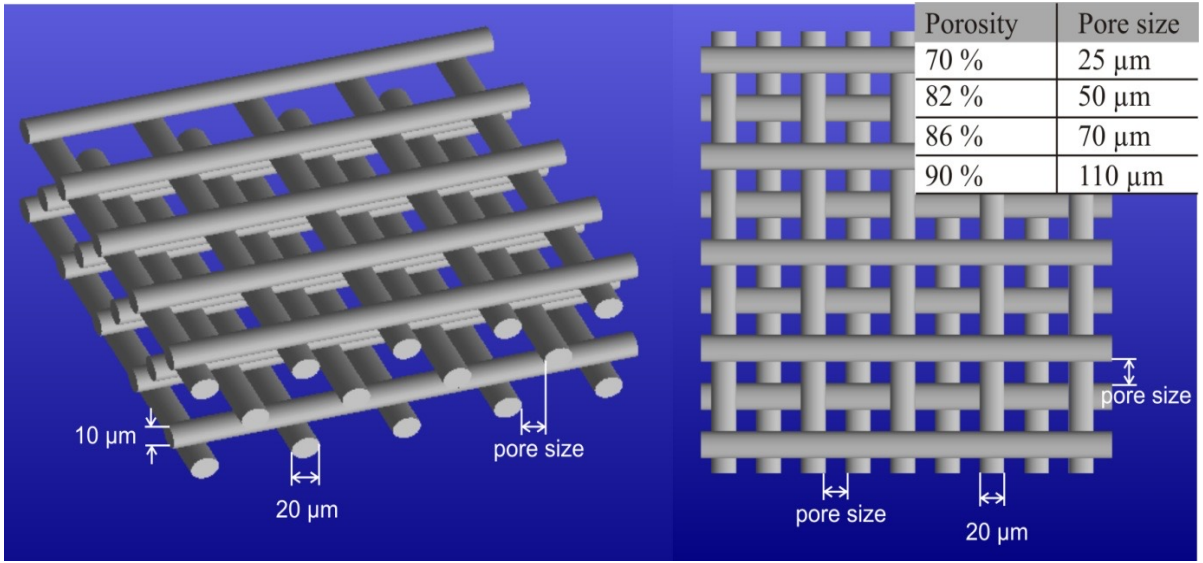
Biomaterial: organic-inorganic composite material – **mesh scaffolds** structured by two-photon polymerization (50% DMAEMA)

after 1 hour



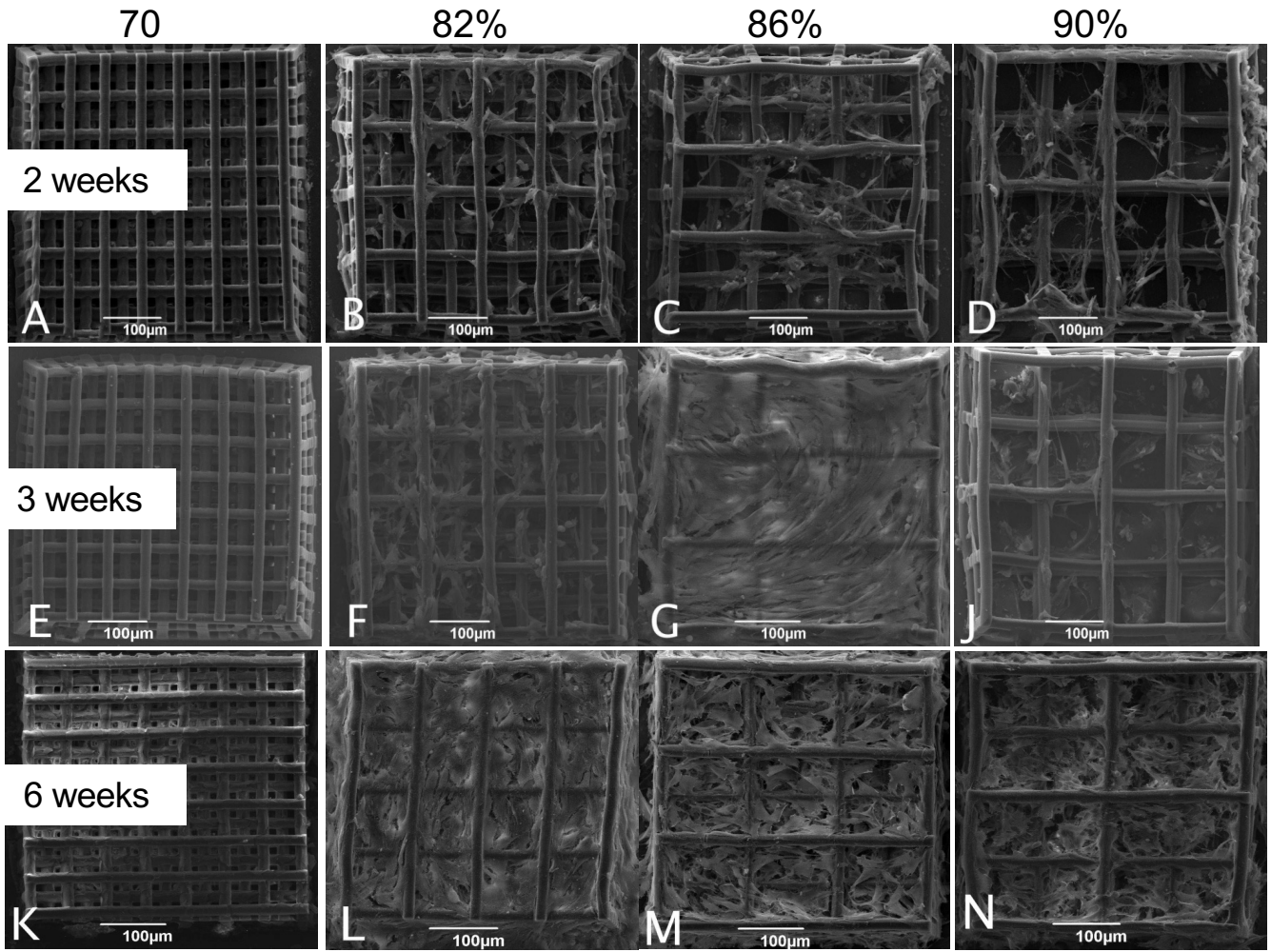
Terzaki K., et al. J Biomed Mater Res Part A 2013, https://doi.org/10.1002/jbm.a.34516

Architecture matters: Design of PLLA woodpile scaffolds

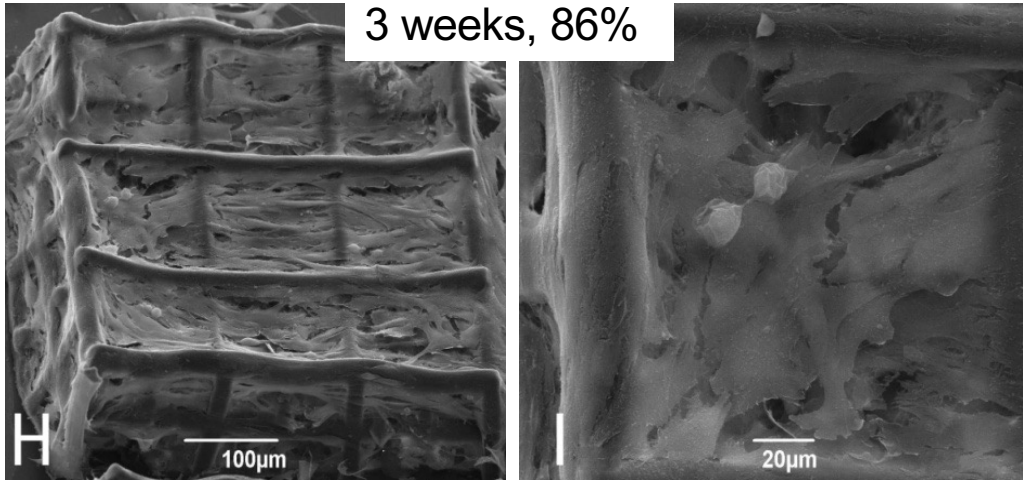


Porosity	Pore size
70 %	25 µm
82 %	50 µm
86 %	70 µm
90 %	110 µm

Danilevicius P., et al. The effect of porosity on cell ingrowth into 3D laser-fabricated biodegradable scaffolds for bone regeneration. Applied Surface Science 2015, http://dx.doi.org/10.1016/j.apsusc.2014.06.012


70
82%
86%
90%
2 weeks
3 weeks
6 weeks
A
B
C
D
E
F
G
J
K
L
M
N
100µm

Cell ingrowth within PLLA woodpile scaffolds

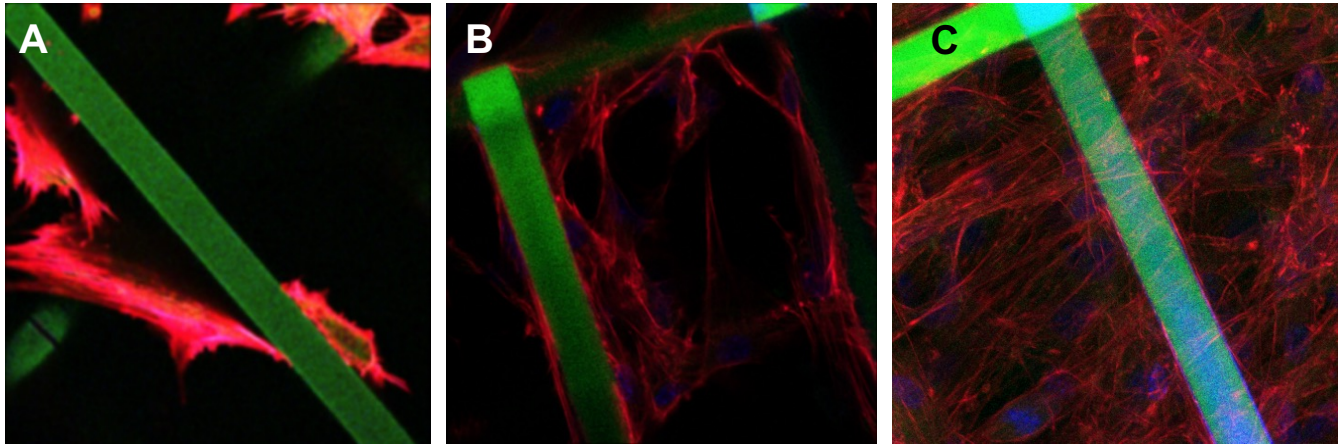


Danilevicius P., et al. Applied Surface Science 2015

Evolvement of tissue growth
Cell growth within PLLA woodpile scaffolds

Confocal microscopy
pre-osteoblastic cells' actin cytoskeleton stained with TRITC phalloidin

24 hours | 2 weeks | 3 weeks



Danilevicius P., et al. Applied Surface Science 2015

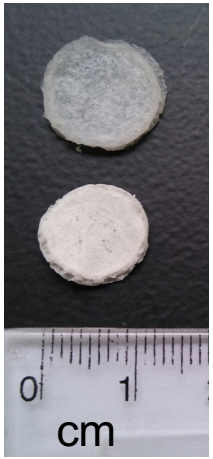
Example of a natural biomaterials scaffold: Chitosan/Gelatin scaffolds

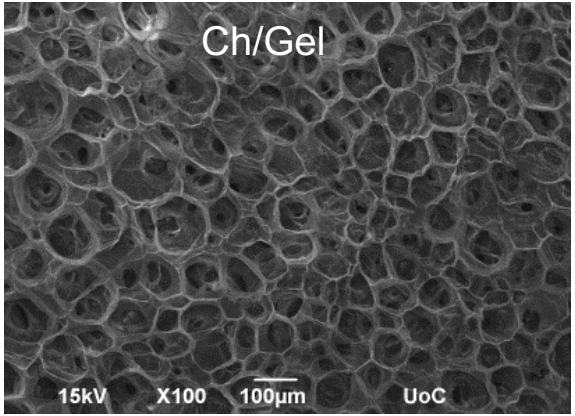
Chitosan/gelatin scaffolds crosslinked with glutaraldehyde

- Chitosan, a partially deacetylated chitin derivative present in anthropoid exoskeletons is a bioactive, biodegradable, non-toxic, non-antigenic and biocompatible cationic polymer. It interacts with GAGs
- Gelatin derives from collagen and is another natural biomaterial that promotes cell adhesion, proliferation, migration and differentiation as it retains the Arg-Gly-Asp (RGD) sequence from collagen

Wet state

Dry state

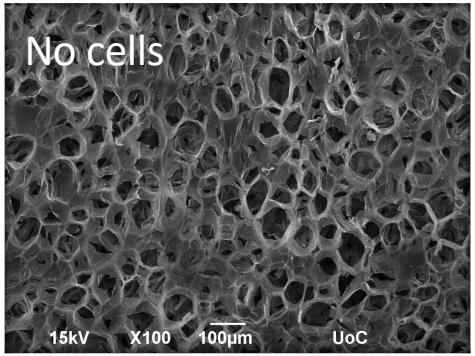


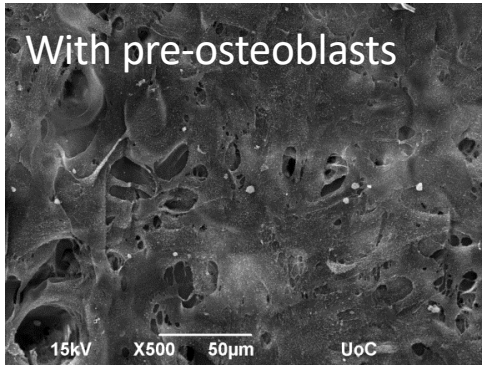


Georgopoulou et al, JMSM 2018, https://doi.org/10.1007/s10856-018-6064-2

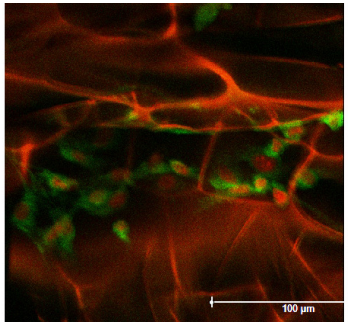
Pre-osteoblastic cell infiltration in chitosan/gelatin scaffolds

Scanning electron microscopy (SEM) images of pre-osteoblastic cells after 4 days in culture in chitosan/gelatin scaffolds crosslinked with 0.1% glutaraldehyde





Confocal fluorescence laser scanning image

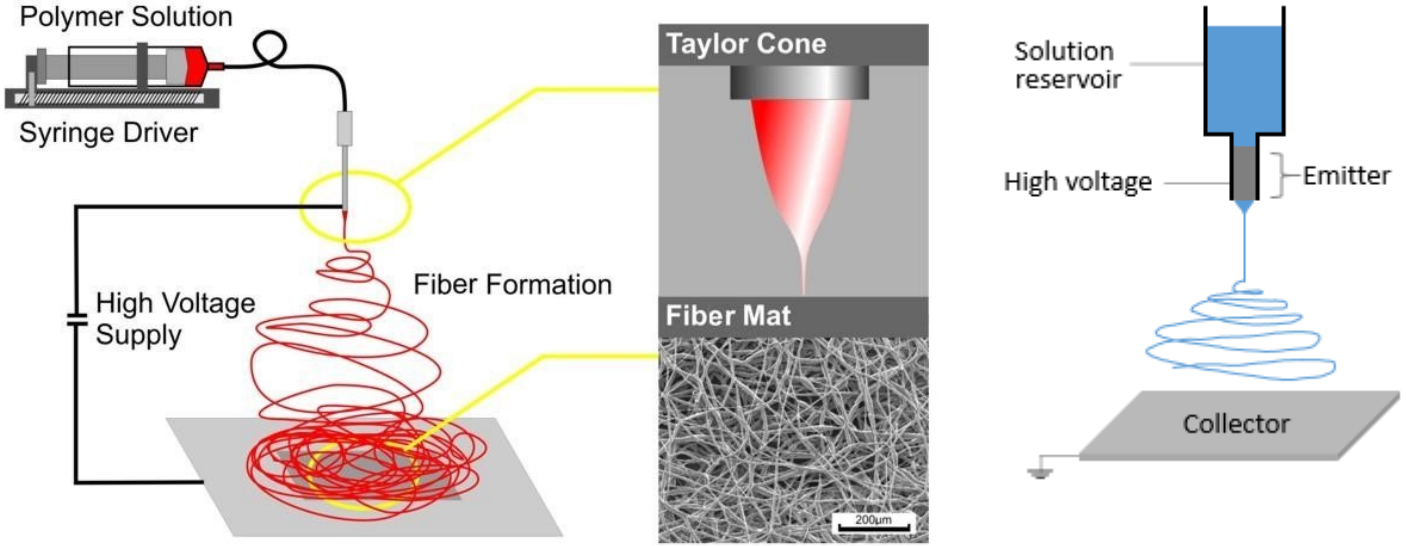


Actin cytoskeleton and cell nuclei

Georgopoulou et al, JMSM 2018, https://doi.org/10.1007/s10856-018-6064-2

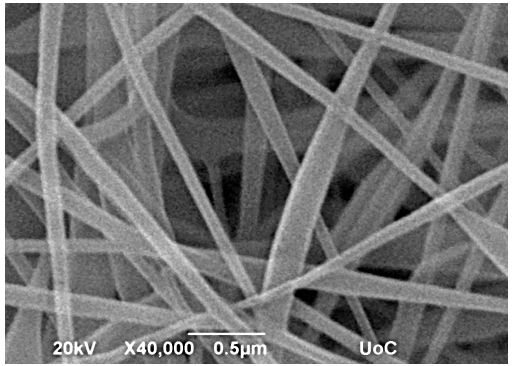
Biomaterials processing: micro- and nanofabrication

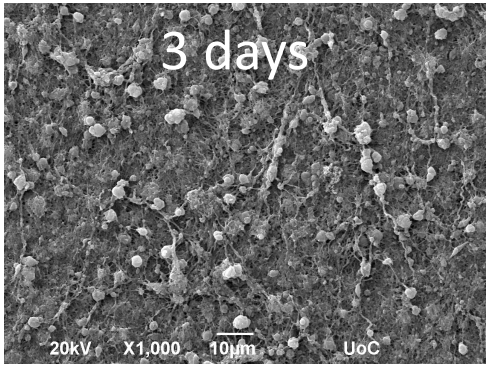
- 3D printing/prototyping - Stereolithography
- Electrospinning: A method for fiber production method using electric force to draw charged threads of polymer solutions or polymer melts up to fiber diameters in the order of some hundred nanometers

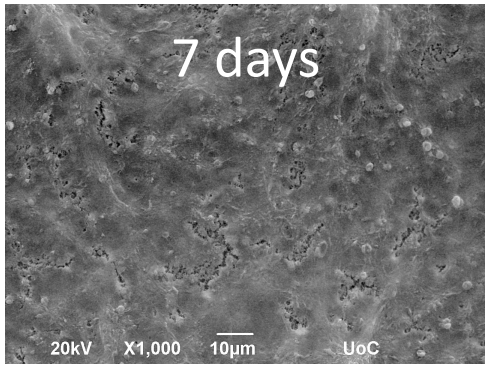


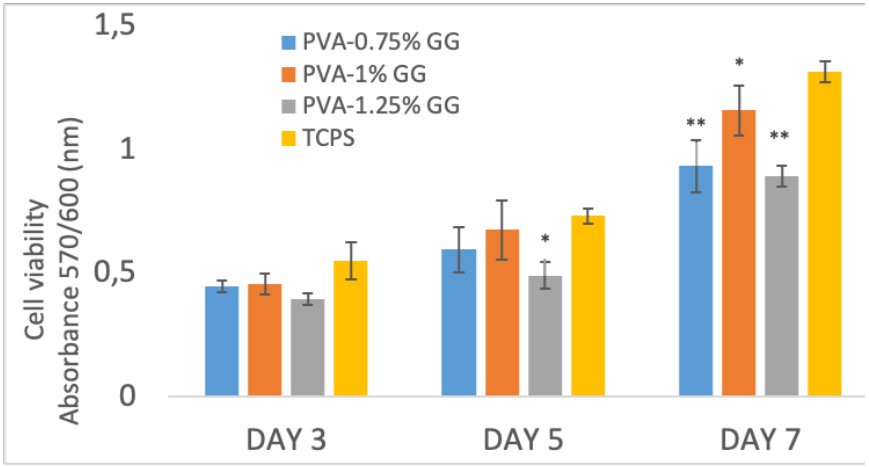
Electrospinning

Electrospun nanofibrous membranes for oral soft tissue regeneration
Poly vinyl alcohol (PVA) - 1% gellan gum (GG)



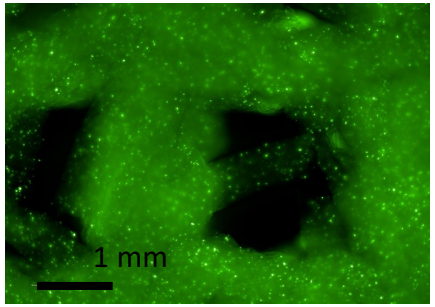




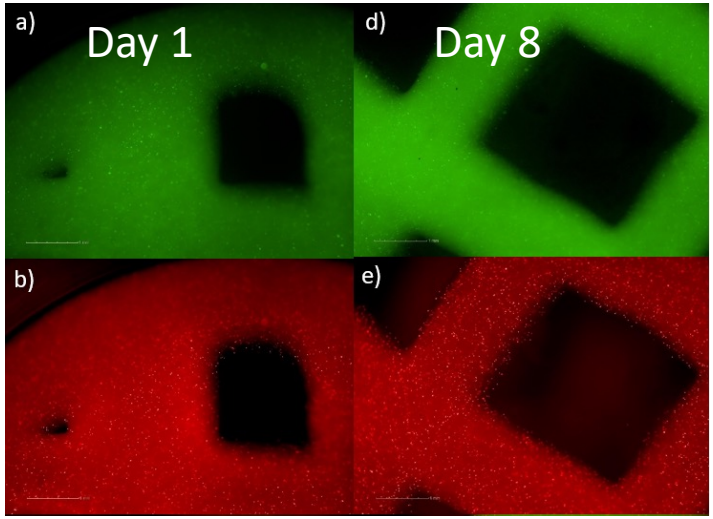


Loukelis et al, https://doi.org/10.1016/j.carpta.2024.100454

Bioprinting: printing encapsulated cells within a hydrogel



kappa carrageenan-gellan gum bioink
with L929 fibroblasts, day 7



7% Alg – 8% Gel – 3% nano-HAp bioink
with pre-osteoblasts

Koutsomarkos, Platania et al, unpublished data

International Societies

European Society for Biomaterials

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