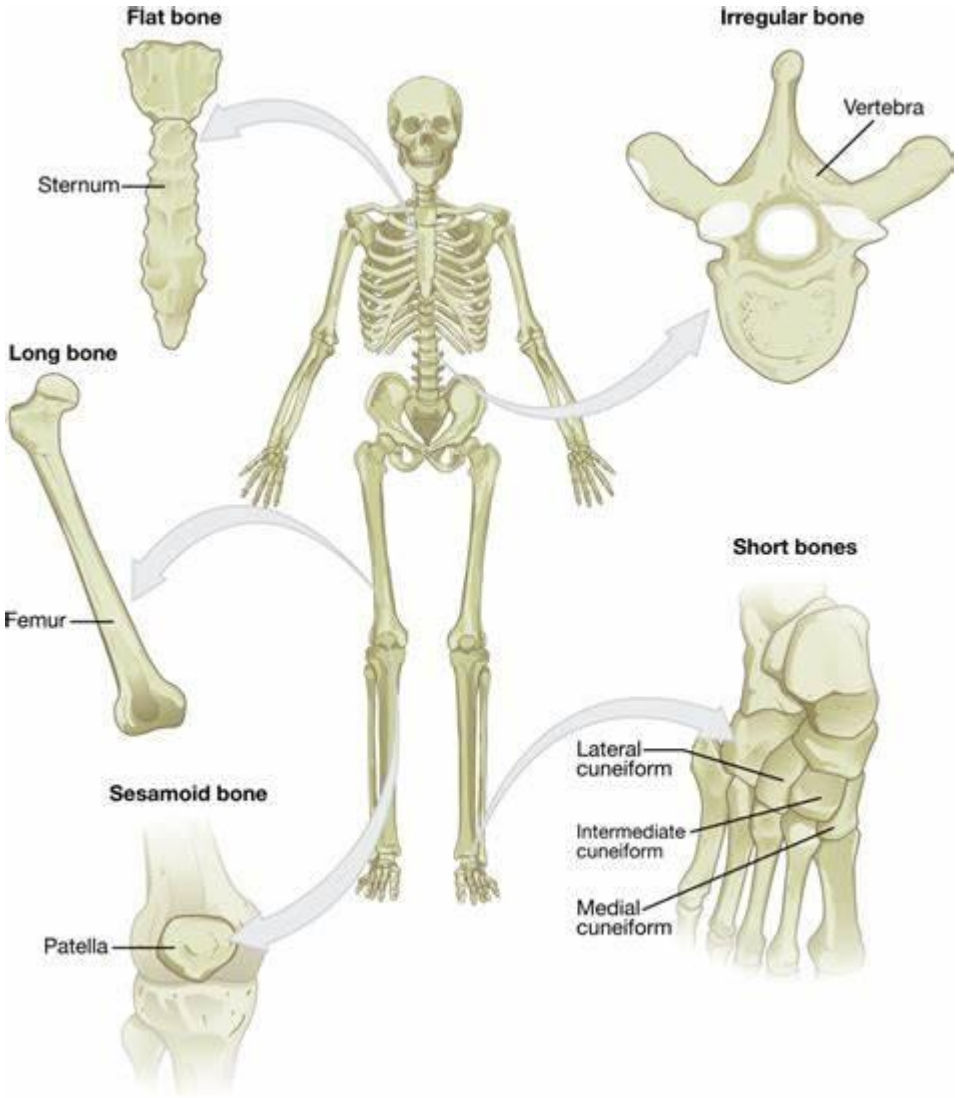
Biomaterials dedicated to bone regeneration

SNOSCELLS
Les Houches

Pierre Weiss
INSERM U 1229
RMES Regenerative medicine and skeleton,
University of Nantes, 1 place Alexis Ricordeau, 44042 Nantes, France.
E-mail : pierre.weiss@univ-nantes.fr

A : Introduction of bone and skeletal tissues
A reflexion on the 4R medicine

Skeletal Bones



Bone constitution

Specialized connective tissue

= Extracellular matrix (ECM) + cells

Extracellular matrix (ECM)

10 % H_2O

25% organic matrix

Collagen type I (>90%)

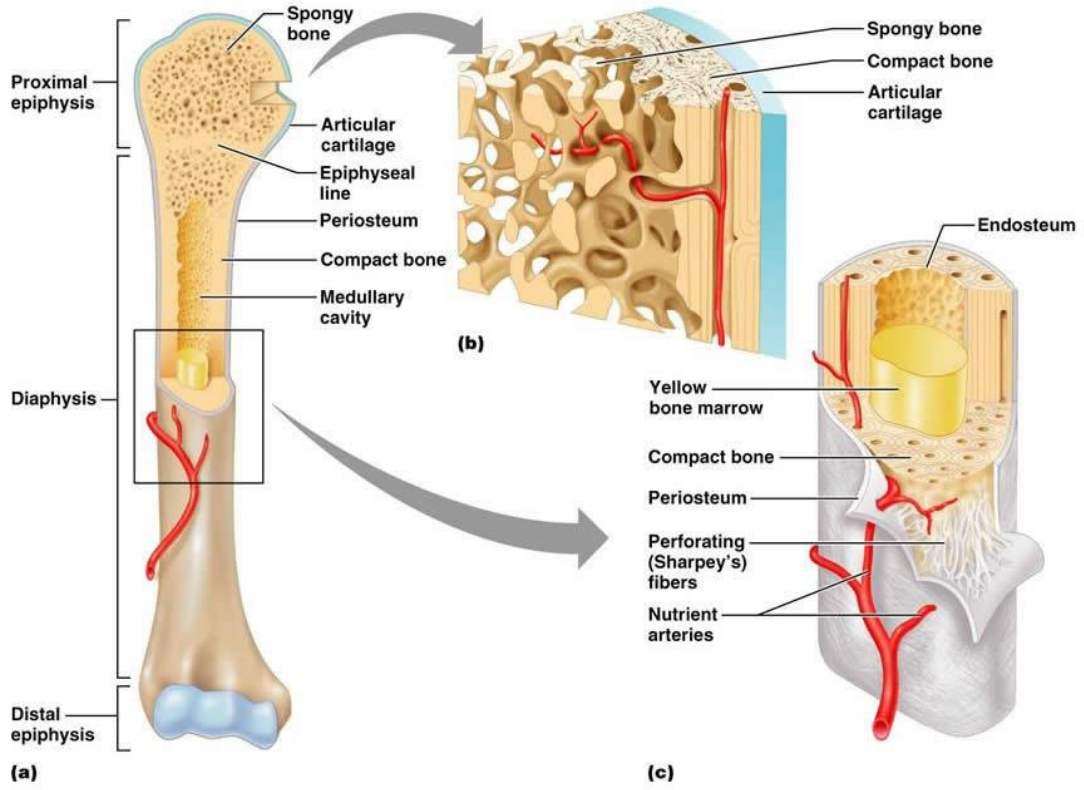
Biological factors – BMP2, TGF-β... (1%<)

65% inorganic matrix: calcium phosphate

(1) *Ehrlich H. et al, Journal of Membrane Science (2009), 326, p. 254-259*

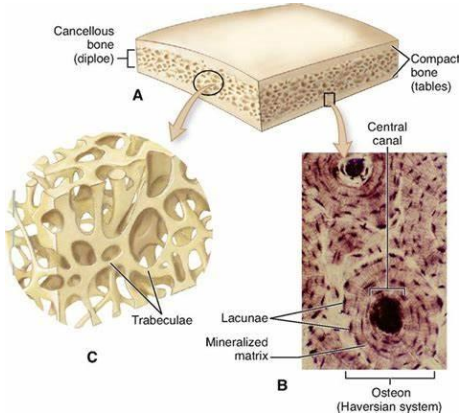
(2) *Legros R et al, Calcified Tissue Int (1987), 41, p.137-144*

Bone, a complex organe



- Functions :
  - Mechanicals
    - Structure
    - Protection
  - Metabolic
    - Storage: fat, heavy metals...
    - Ionic balance
    - Acid/base balance
    - Hormonal action
  - Synthesis
    - Blood cell production

Bone tissu organisation



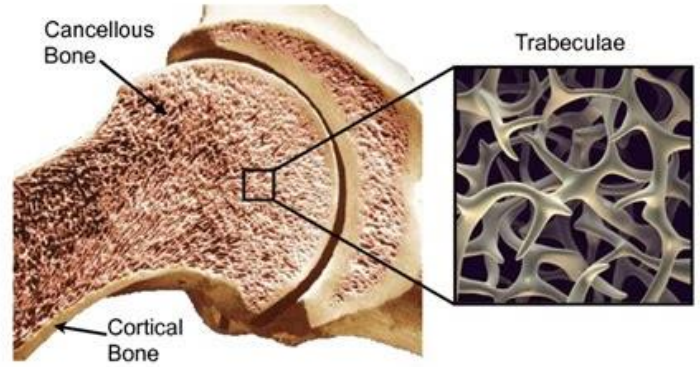
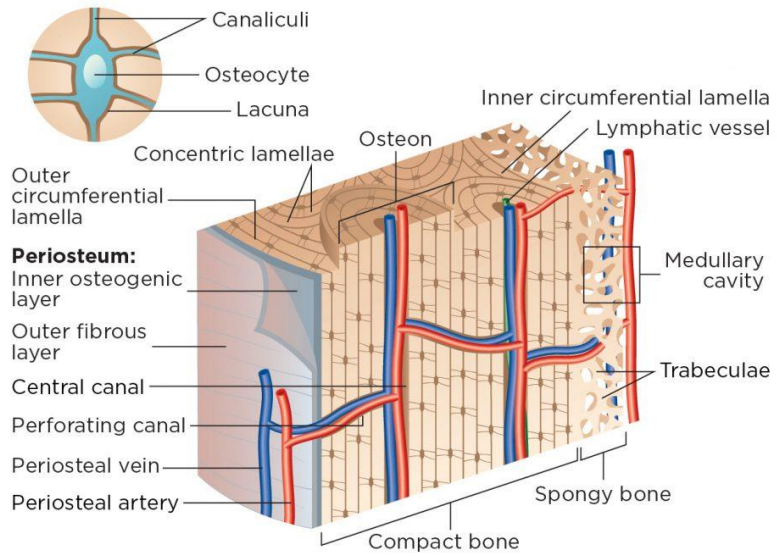
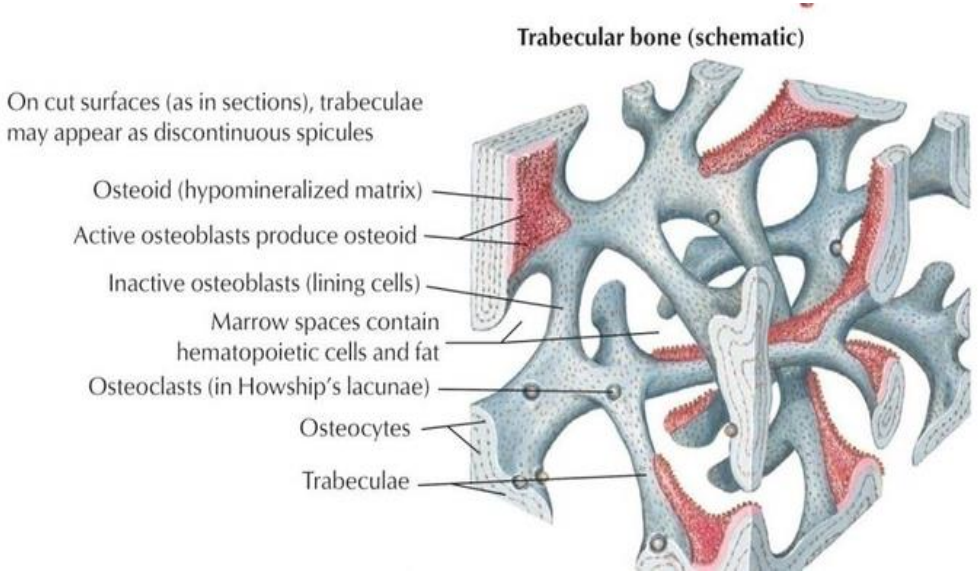
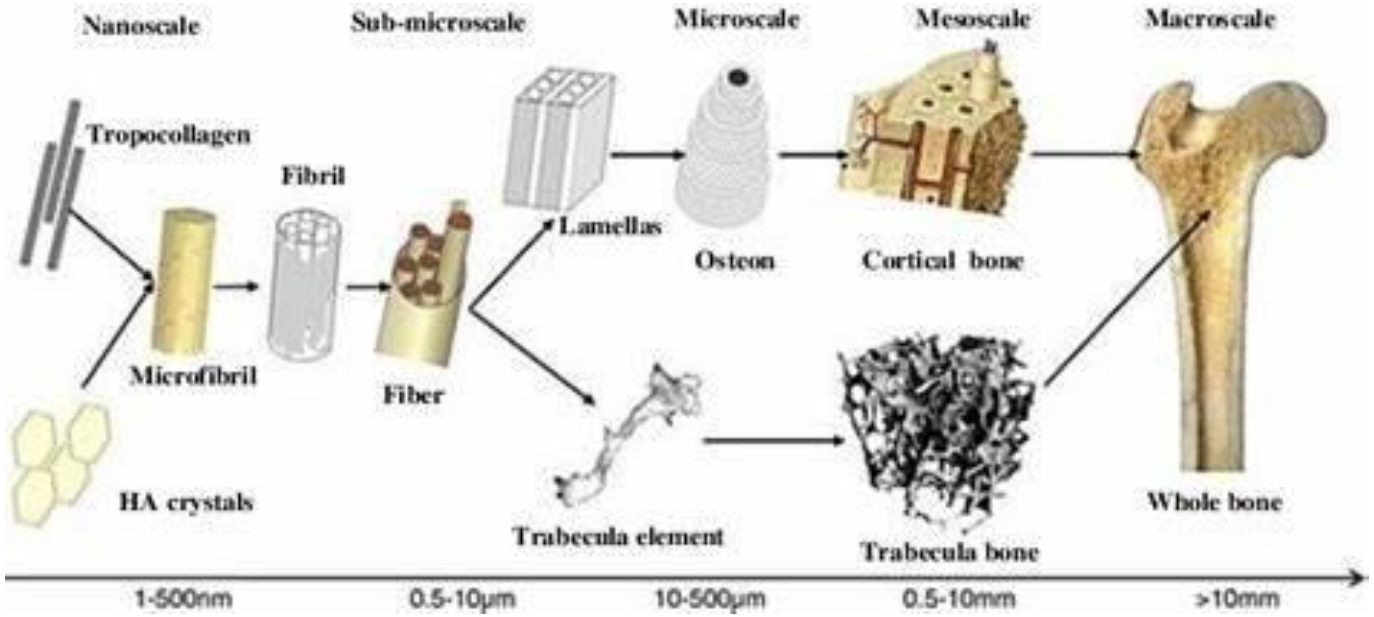


Fig 2. **Anatomy of cortical bone**

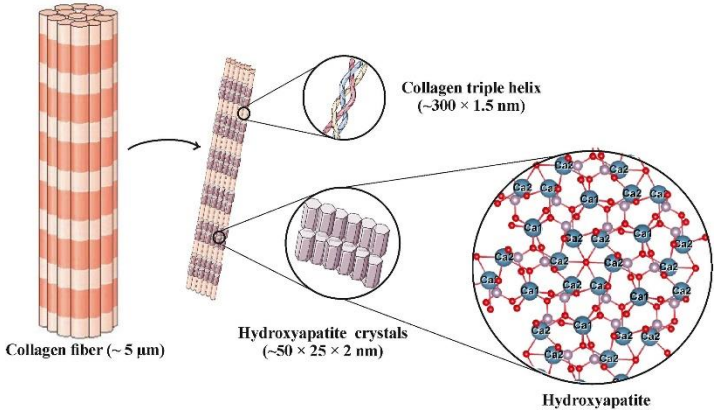




Multiscale bone structure



Barkaoui, A.,*Int J Numer Meth Bio* **30**, 318–338 (2014).



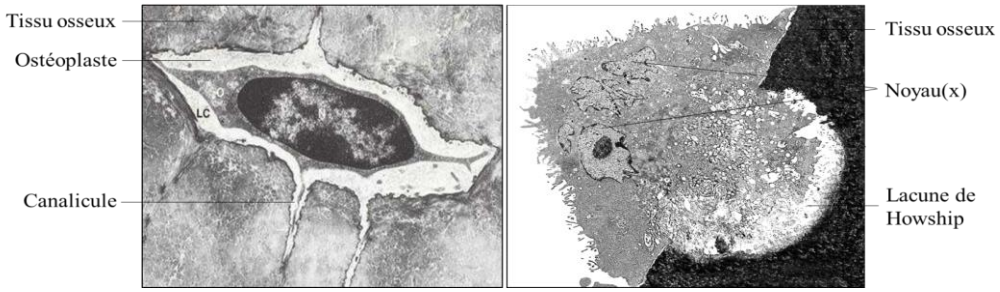
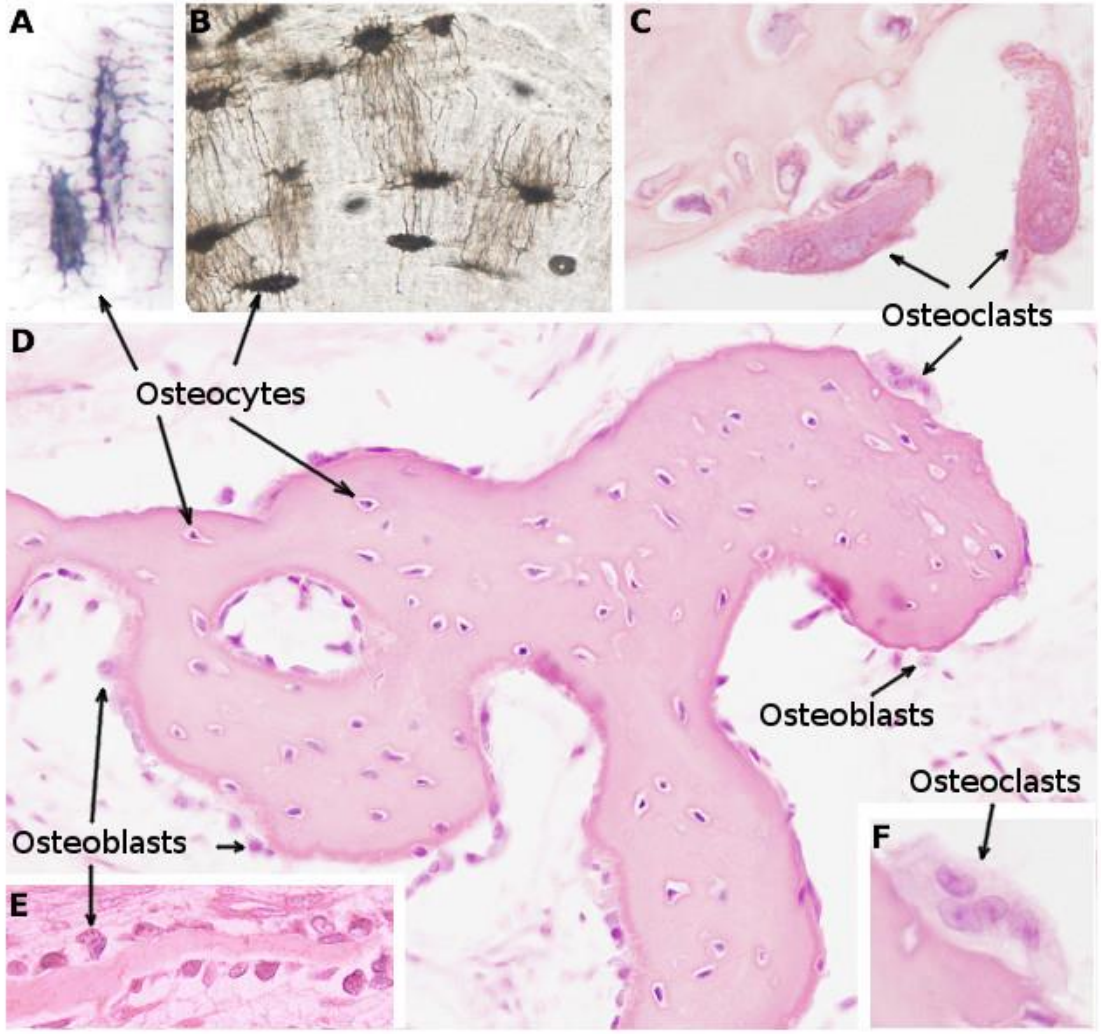
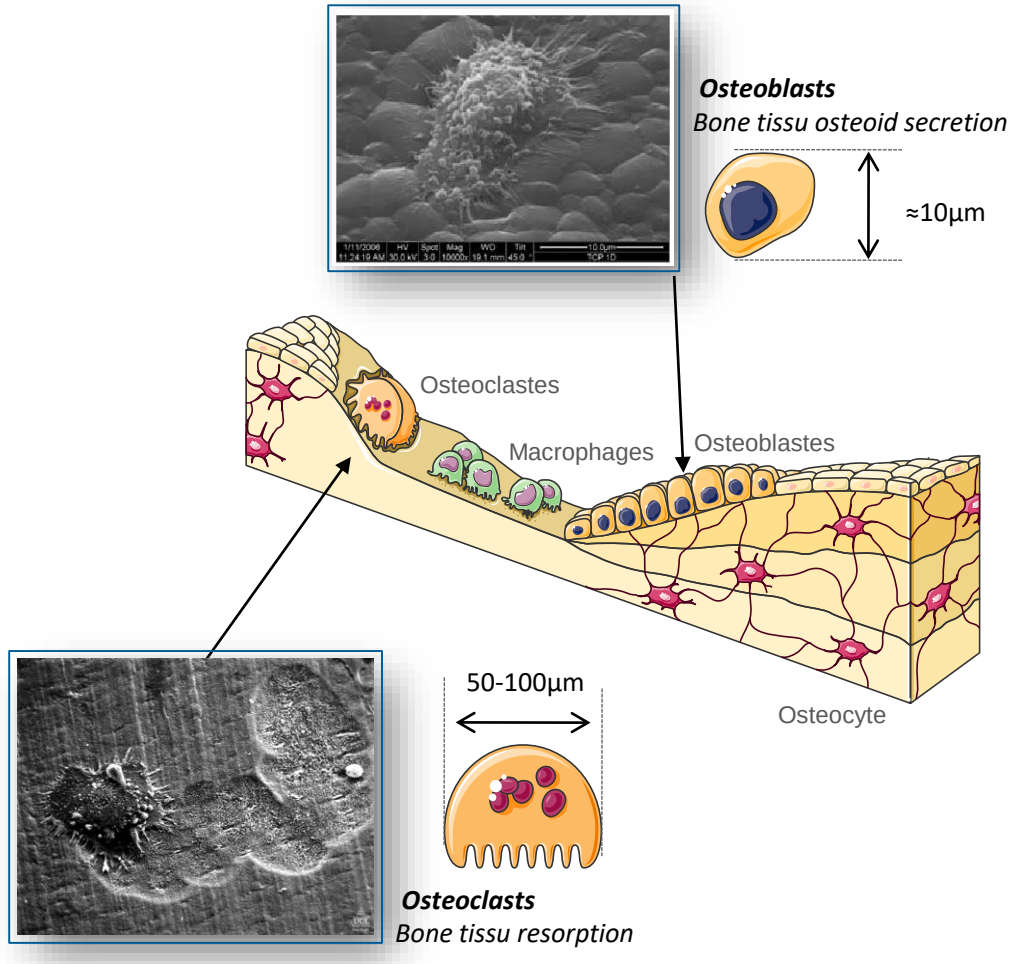


Figure 4 : (a) Observation d'un ostéocyte (généralement 15-30µm) dans son ostéoplaste et (b) un ostéoclaste (généralement 50-100µm) en activité (Pillet, P./Guicheux, J. non publié). Microscope électronique à transmission.

Histologie of Bone





https://mmegias.webs.uvigo.es/02-english/a-imagenes-grandes/oseo_osteocitos.php#n

Bone loss = function loss

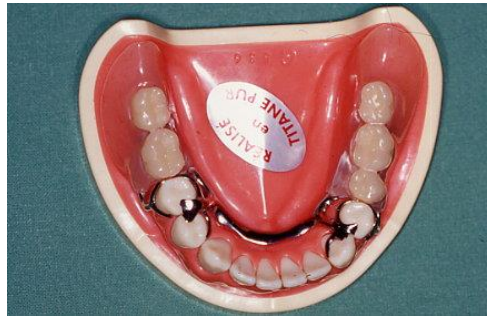
- Bone disease :
  - Osteoporosis
  - Genetic malformations : cleft palate / lip deformities
  - Bone infections
  - Bone tumors
- Bone traumatisms
  - Fractures
  - Ballistic
- Bone loss after teeth extraction

4 R medicine

- https://alliancerm.org/

4R

Replace

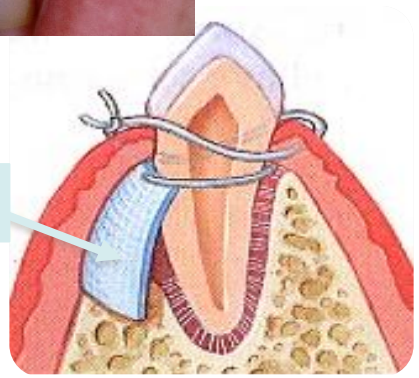


We replace an organ with an object that restores a function: Mechanical and Medical Device

Repair

We repair a part of an organ with a biomaterial to restore a mechanical and biological function

Regenerate

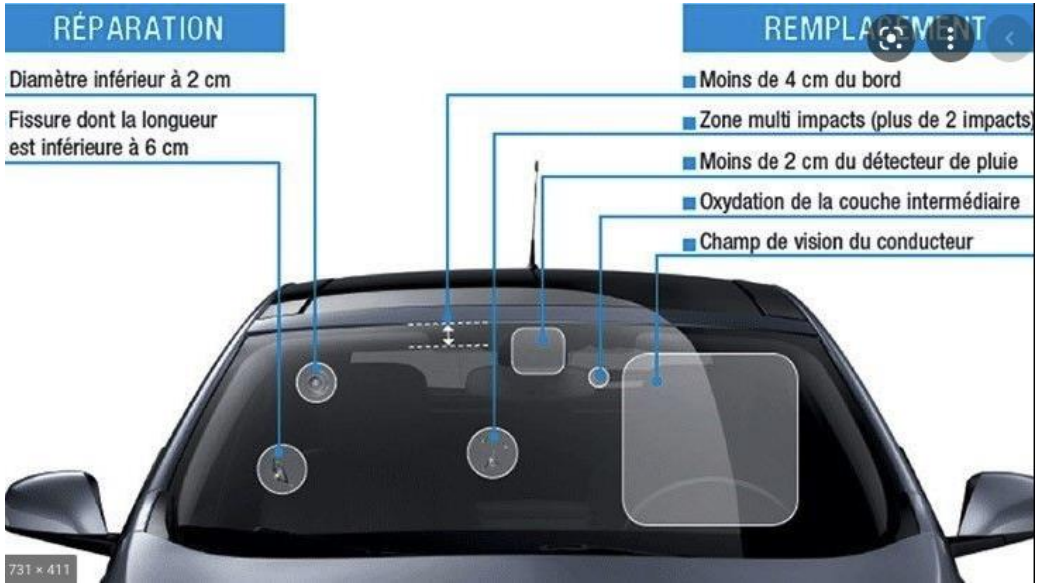


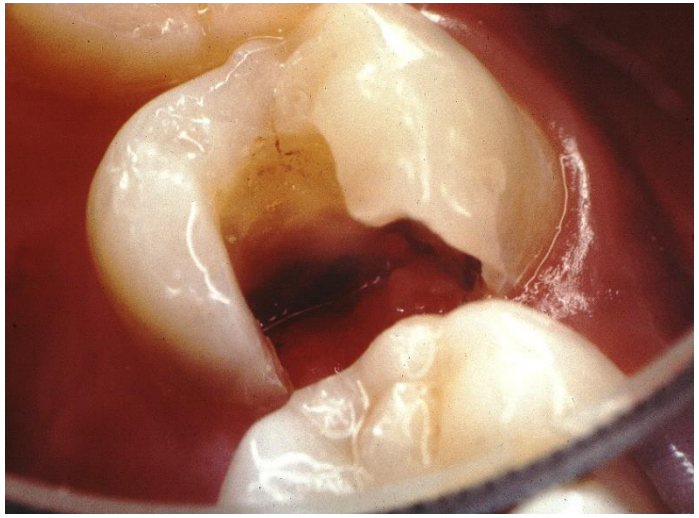
We regenerate *ad integrum* a part of an organ with a biomaterial, cells, growth factors...

Reprogram

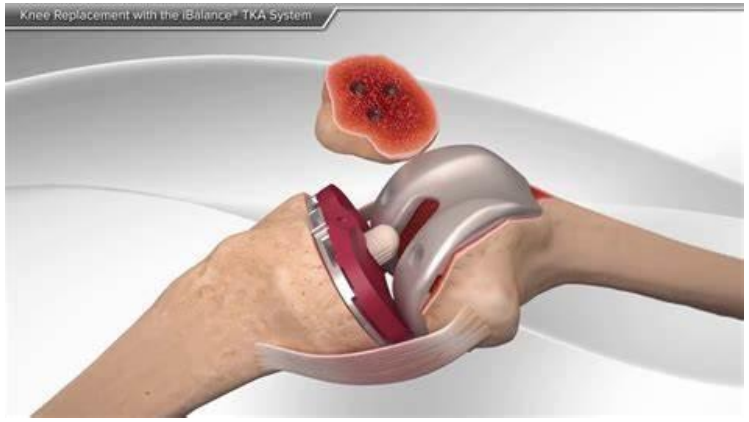
We reprogram cells to ask them to regenerate a tissue.(Production of GF, IPS (induced pluripotent stem cells...)

Replace ou repair ?





Replace



Repair

Acta Biomaterialia 121 (2021) 1–28

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actbio

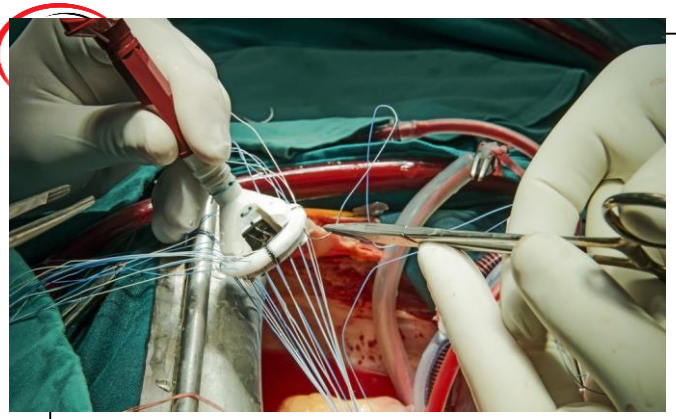
Review article

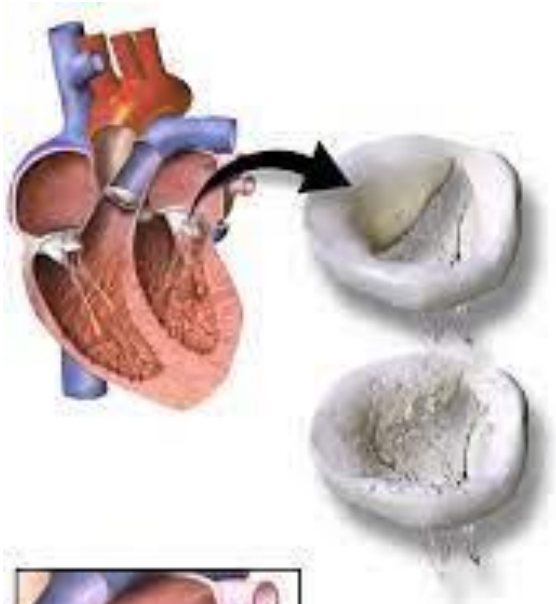
Additive manufacturing pertaining to bone: Hopes, reality and future challenges for clinical applications

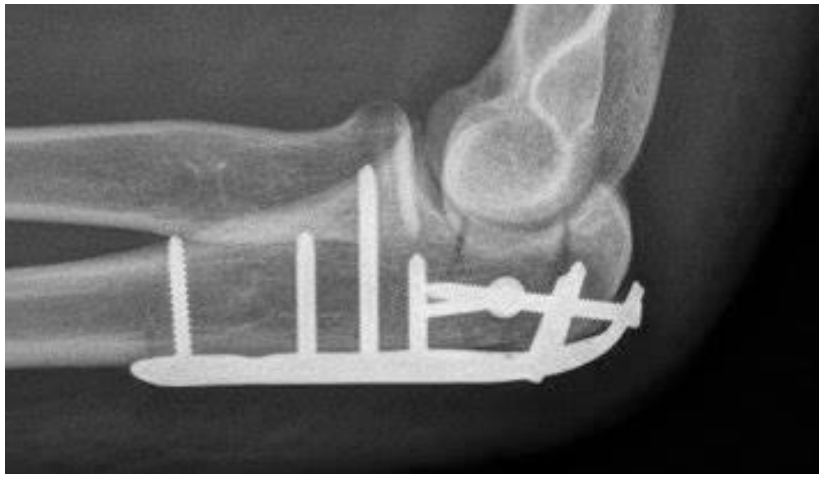
Baptiste Charbonnier*, Mikhael Hadida, David Marchat

Mines Saint-Etienne, Université de Lyon, Université Jean Monnet, INSERM, U 1059 Sainbiose, 158, cours Fauriel, CS 62362, 42023 Saint-Etienne Cedex 2, France

Repair



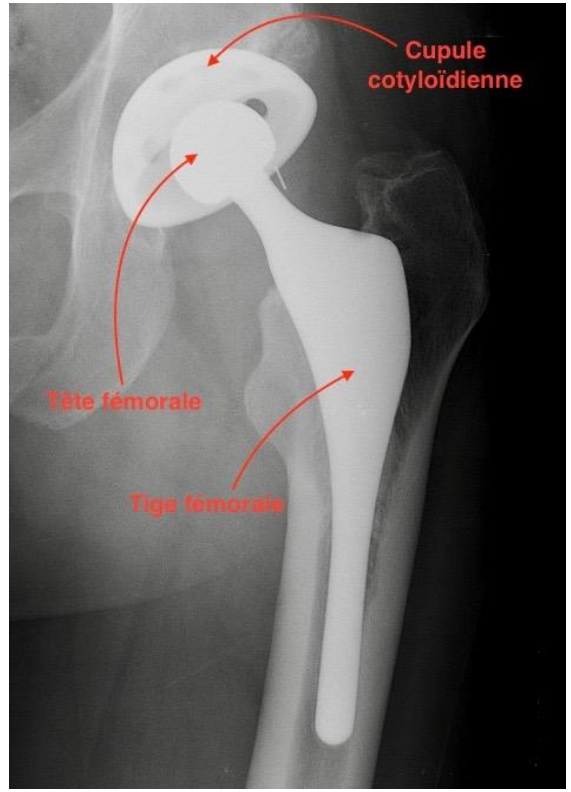




Replace ou repair ?

- We repair a part of an organ
- We replace an organ

→To recover a biological function



Medical Device

- ***medical device'*** *means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:*
  - diagnosis, prevention, monitoring,
  - treatment, or compensation for, an injury or disability,
  - replacement or modification of the anatomy or of a physiological or pathological process or state,
- *and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.*

Biomaterials

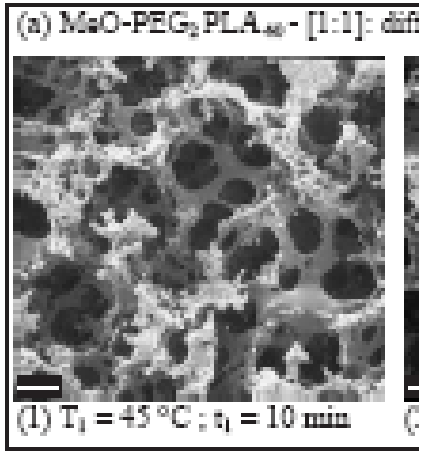
- A **biomaterial** is a substance that has been engineered to interact with biological systems for a medical purpose, either a therapeutic (treat, augment, repair, or replace a tissue function of the body) or a diagnostic one.
- The ability of an engineered biomaterial to induce a physiological response that is supportive of the biomaterial's function and performance is known as **bioactivity**.

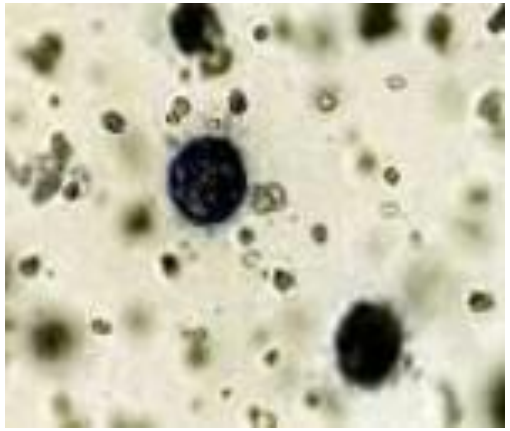
Material / Cells interactions

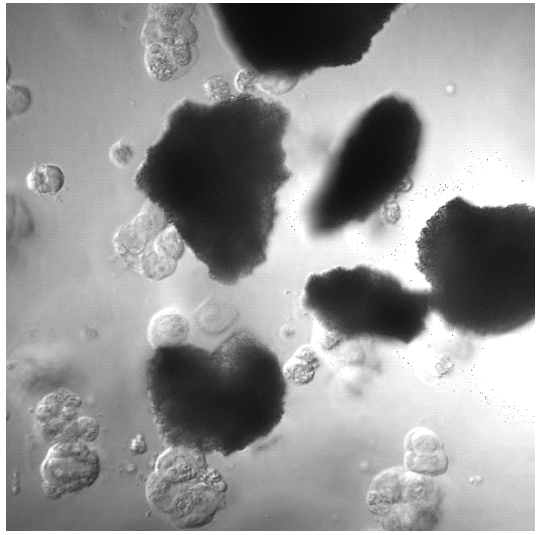
On hard materials

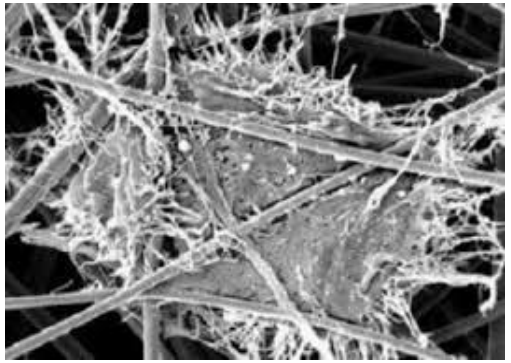
What is 2D and 3D ?

In what type of material

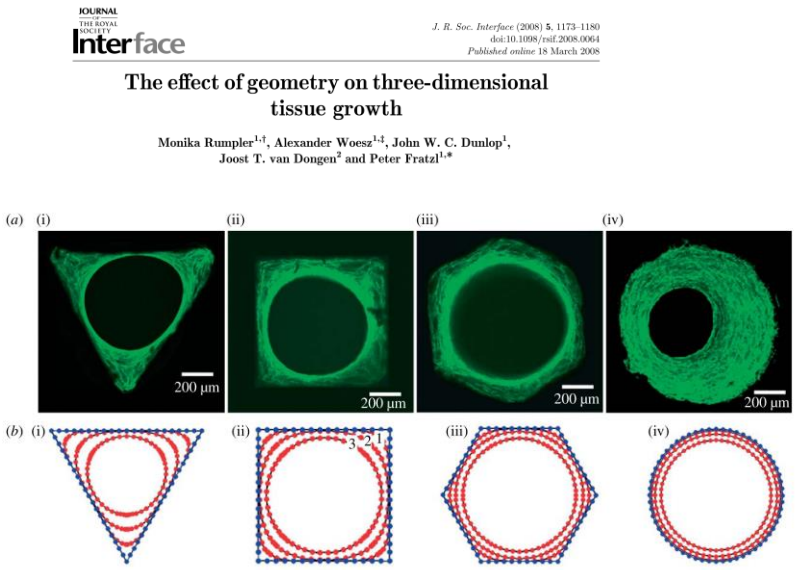








The shape of the macro-pores ?



JOURNAL OF THE ROYAL SOCIETY Interface

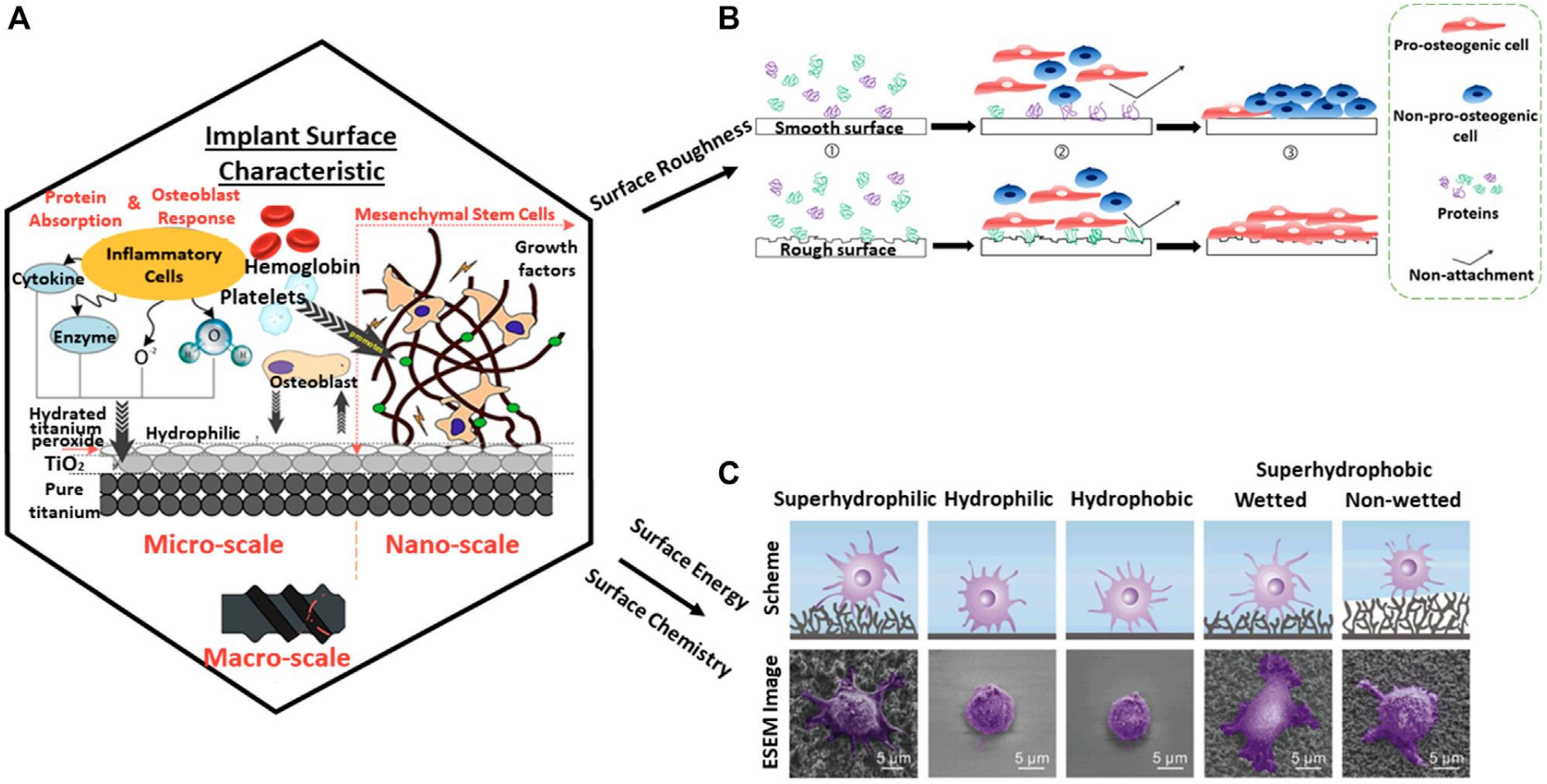
J. R. Soc. Interface (2008) 5, 1173–1180
doi:10.1098/rsif.2008.0064
Published online 18 March 2008

The effect of geometry on three-dimensional tissue growth

Monika Rumpler[1,†], Alexander Woesz[1,‡], John W. C. Dunlop[1], Joost T. van Dongen[2] and Peter Fratzl[1,*]

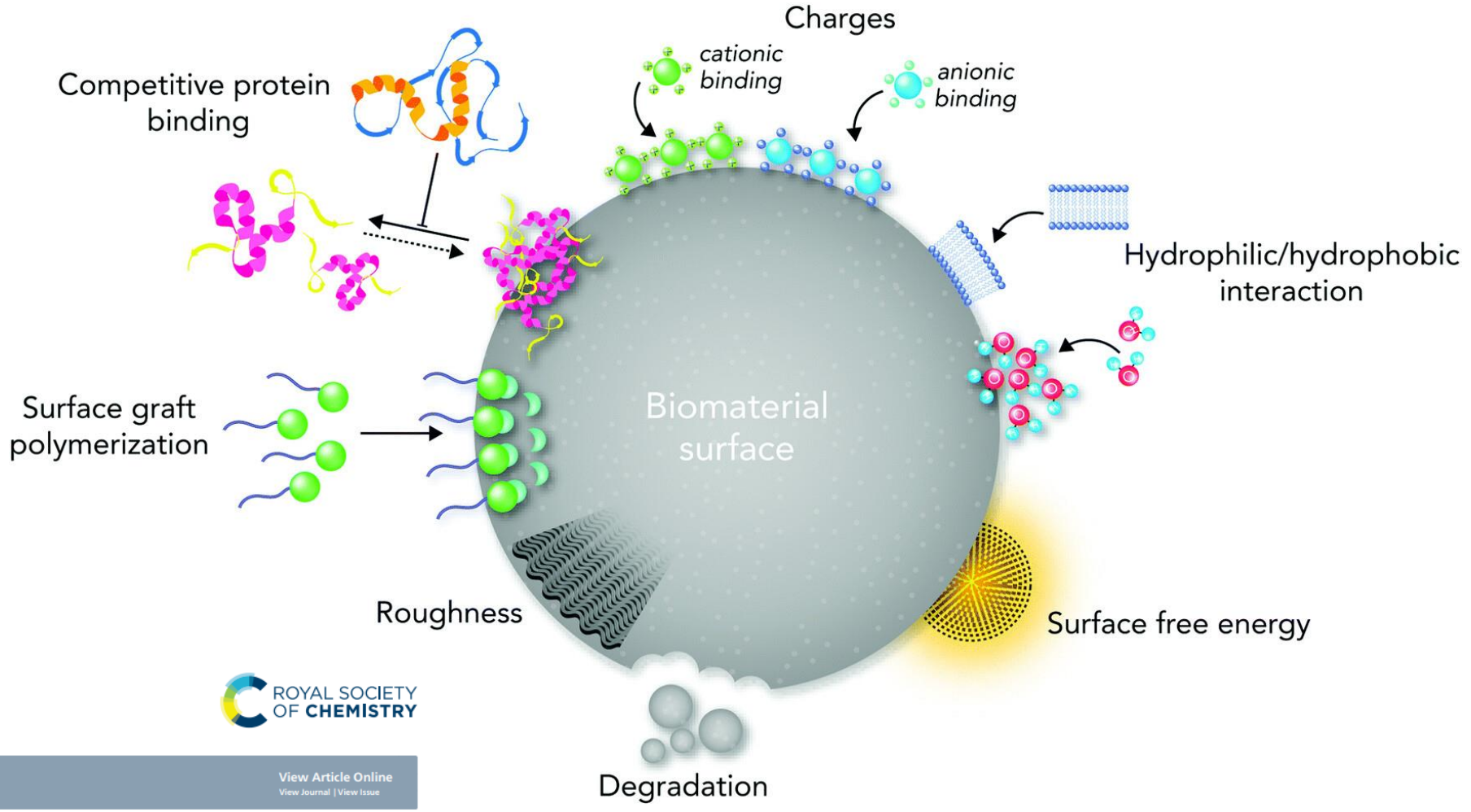
The amount of tissue deposited is proportional to the local curvature

Surface / Protein adsorption



Protein adsorption on the substrate from (A) nano-to-macro level which is dependent on several factors. (B) Surface roughness (Stich et al., 2021). (C) Surface chemistry and surface energy (Meng et al., 2017). Diagram adapted and adjusted from Alipal et al. (2021).

Key surface physicochemical properties



Chem Soc Rev

REVIEW ARTICLE

View Article Online
View Journal | View Issue

Check for updates

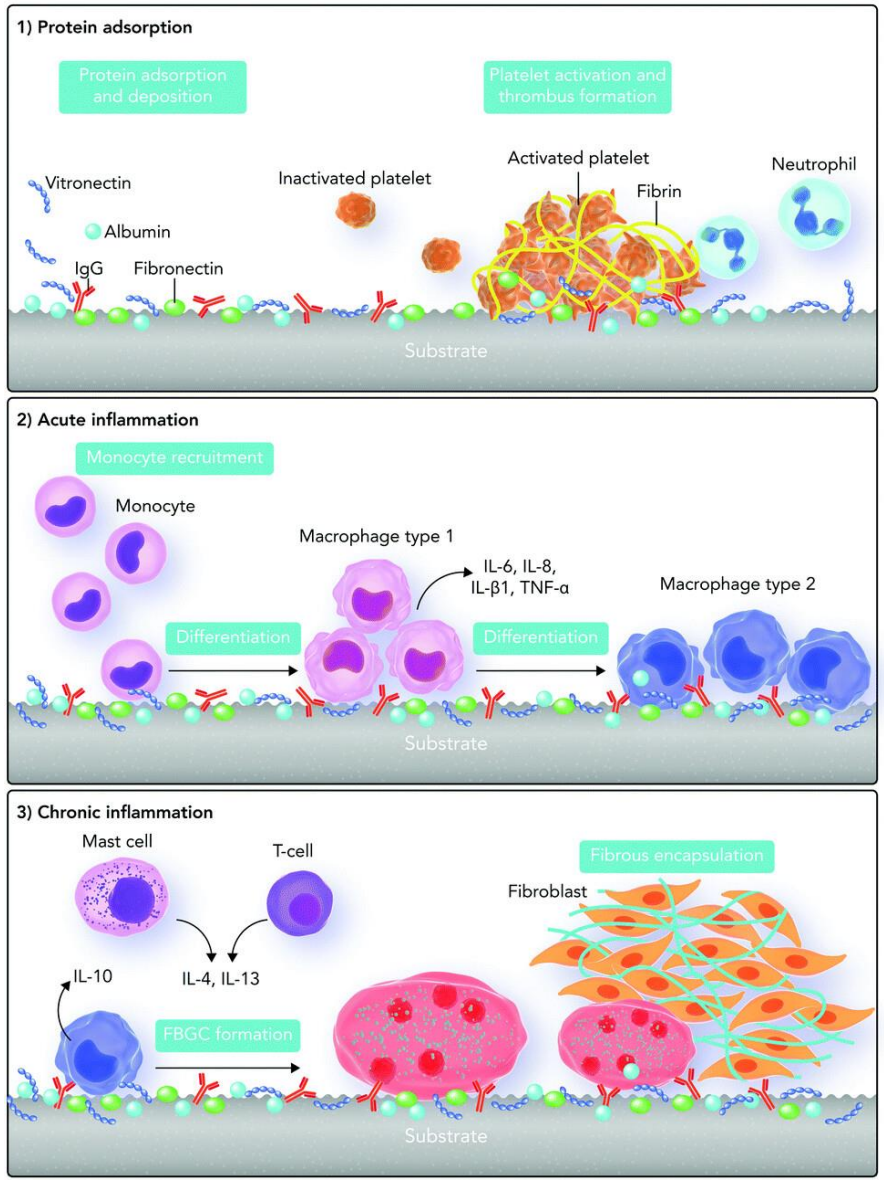
Cite this: *Chem. Soc. Rev.*, 2020, 49, 5178

Biological responses to physicochemical properties of biomaterial surface

Maryam Rahmati,[a] Eduardo A. Silva,[b] Janne E. Reseland,[a] Catherine A. Heyward[c] and Håvard J. Haugen*[a]

An illustration of the key surface physicochemical properties in directing biological responses to biomaterials. Biomaterials can manipulate molecular and cellular signaling pathways through their surface physicochemical properties (e.g. topography, stiffness, functional groups, biological moieties, ions, charges, and surface free energy).

regarding foreign body responses to the biomaterial surface.

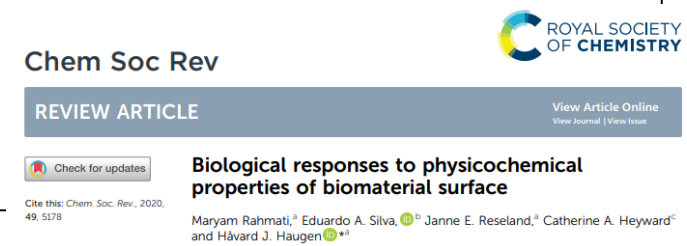


The foreign body responses are a combination of both acute and chronic phases of inflammation.
The mechanism starts with protein adsorption and desorption (Vroman binding) on the surface of the biomaterial after its implantation.

It continues with thrombin formation through activating platelets. After that, monocytes differentiate into type ‘‘1’’ macrophages which are responsible for the acute phase of inflammation.

After some days, type ‘‘1’’ macrophages differentiate into type ‘‘2’’ macrophages which are responsible for chronic inflammation.

T cells and mast cells also express cytokines that increase foreign body giant cell (FBGC) creation. In addition, FBGCs express fibroblast-recruiting factors and consequently by collagen deposition, a capsule starts forming around the biomaterial.


Chem Soc Rev

REVIEW ARTICLE

View Article Online

Check for updates

Biological responses to physicochemical properties of biomaterial surface

Maryam Rahmati, Eduardo A. Silva, Janne E. Reseland, Catherine A. Heyward and Håvard J. Haugen

Regenerate

- We regenerate *ad integrum* a part of an organ with a biomaterial, cells, growth factors...

Bone Remodeling

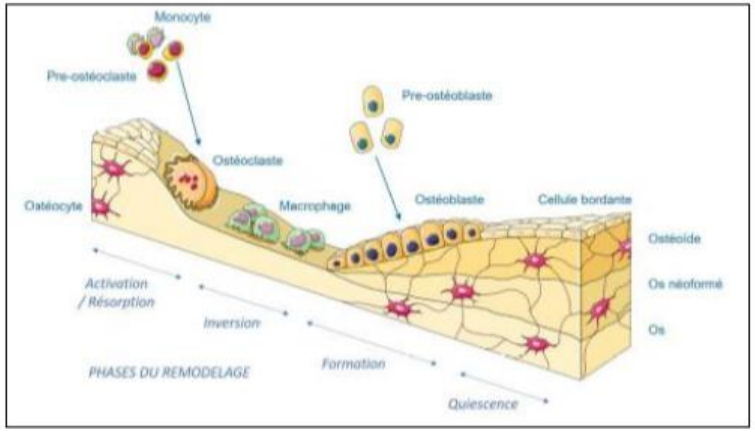


Figure 8 : Cycle du remodelage osseux (adaptée de la banque d'image SERVIER)

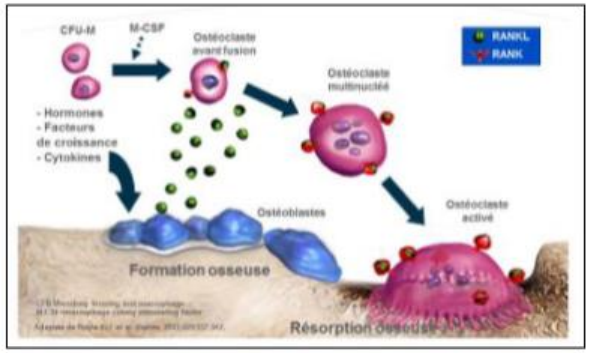


Figure 7 : Activation des ostéoclastes par les ostéoblastes par la sécrétion de différents facteurs solubles (M-CSF et RANK) (44).

Lebret T, Progres en Urologie.
2011.

Spontaneous Bone regeneration

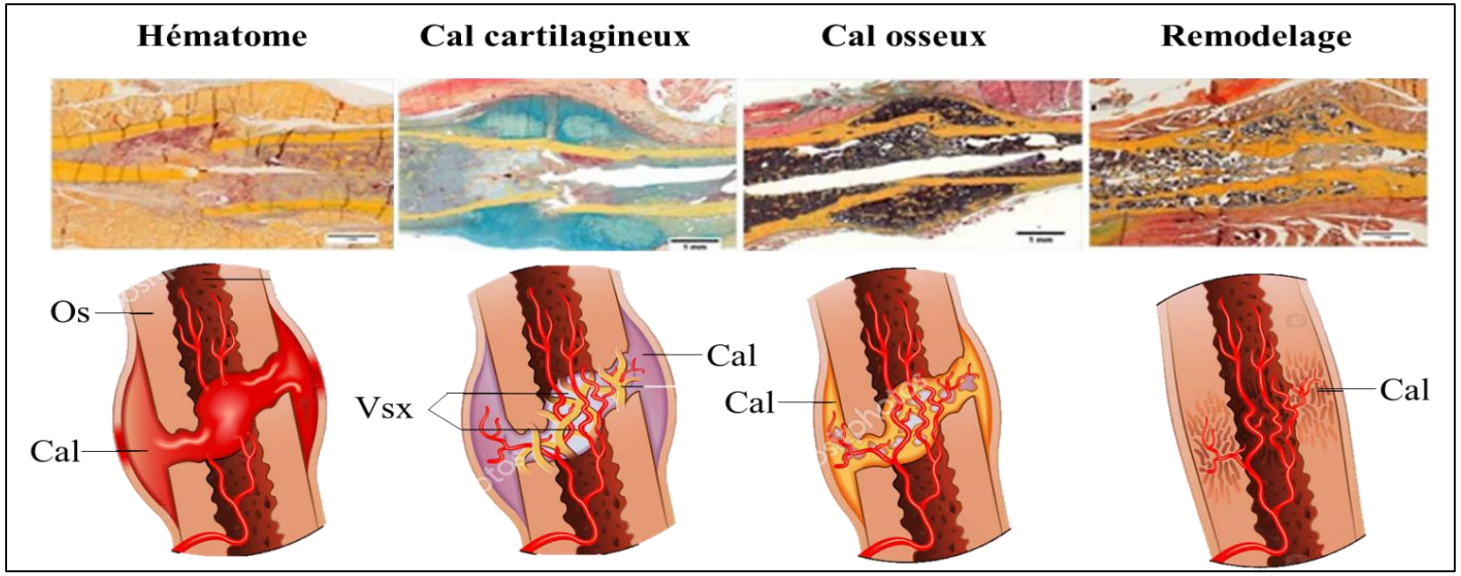
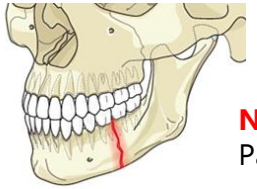


Figure 6 : Les grandes étapes de la régénération osseuse endochondrale. Vsx : vaisseaux sanguins. Modifié d'après Eweida AM, Arch Orthop Trauma Surg. 2012

General context of Biomaterials for Bone regeneration



Large bone defects

No spontaneous recovery
Pain, impairment of performance

2,2 million
Bone grafts/year
(Worldwide, 2011)

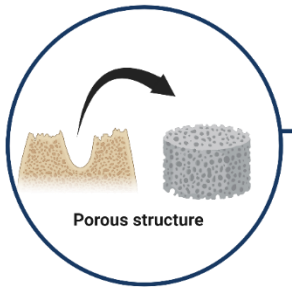
Gold standard :
AUTOGRAFTS

Additional surgery
Donor site morbidity
Limited disponibility
Risks of excessive bleeding
Anatomical mismatch and pain

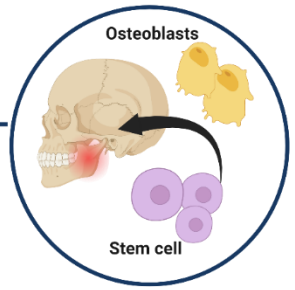
Reported cases with complications : 20,6%
(USA, 2019)

NEW ALTERNATIVES

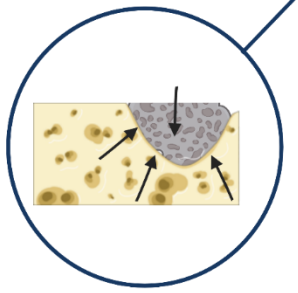
Synthetic biomaterials



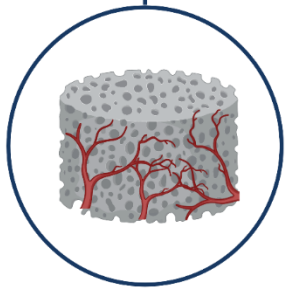
Biomimetic



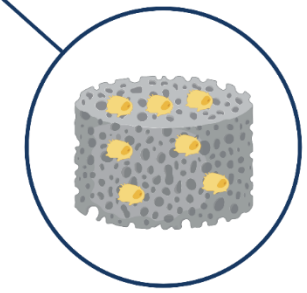
Osteoinductive



Osteointegrative

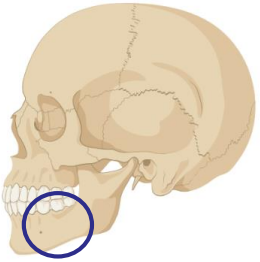


Angiogenic



Osteoconductive

= **Bone regeneration**



Fox, S. et al. , Sports Health (2009)
Lopa, S. et al., Tissue Engineering (2014)
Sohn, HS., Oh, JK., Biomaterials Research (2019)
Archunan, M. W., & Petronis, S. Cureus (2021)

General context of Biomaterials for Bone regeneration

Calcium phosphates (CaP)

Ceramics

H_2O

Cements

-Clinical use -Stable with living tissues -Resorbable -High stiffness and strength	-Low bioactivity -Low biodegradation -Brittle behavior
-Biocompatibles -Osteoconductives -Self-hardening -Minimally invasive applications -Better biodegradation than ceramics	-Lower mechanical properties -Inadequate biodegradation rate -No interconnected macroporosity

Schröter, L. et al. Acta Biomaterialia (2020)
Tavoni, M. et al., Journal of Composites Science (2021)
Zhao. R. et al., Molecules (2021)

General context of Biomaterials for Bone regeneration

Calcium phosphates (CaP)

Ceramics

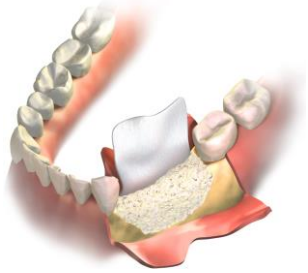
H_2O

Cements

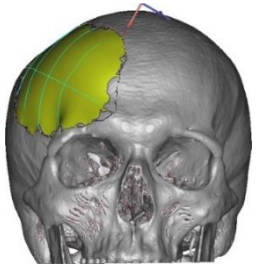
-Clinical use -Stable with living tissues -Resorbable -High stiffness and strength	-Low bioactivity -Low biodegradation -Brittle behavior
-Biocompatibles -Osteoconductives -Self-hardening -Minimally invasive applications -Better biodegradation than ceramics	-Lower mechanical properties -Inadequate biodegradation rate -No interconnected macroporosity

Need of optimisation and modulation of properties

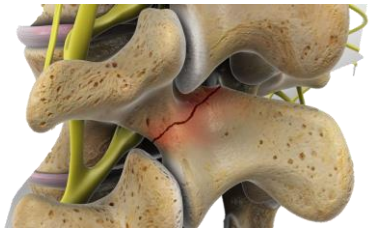
Maxillofacial and dental defects



Craniofacial defects



Spinal bone repair



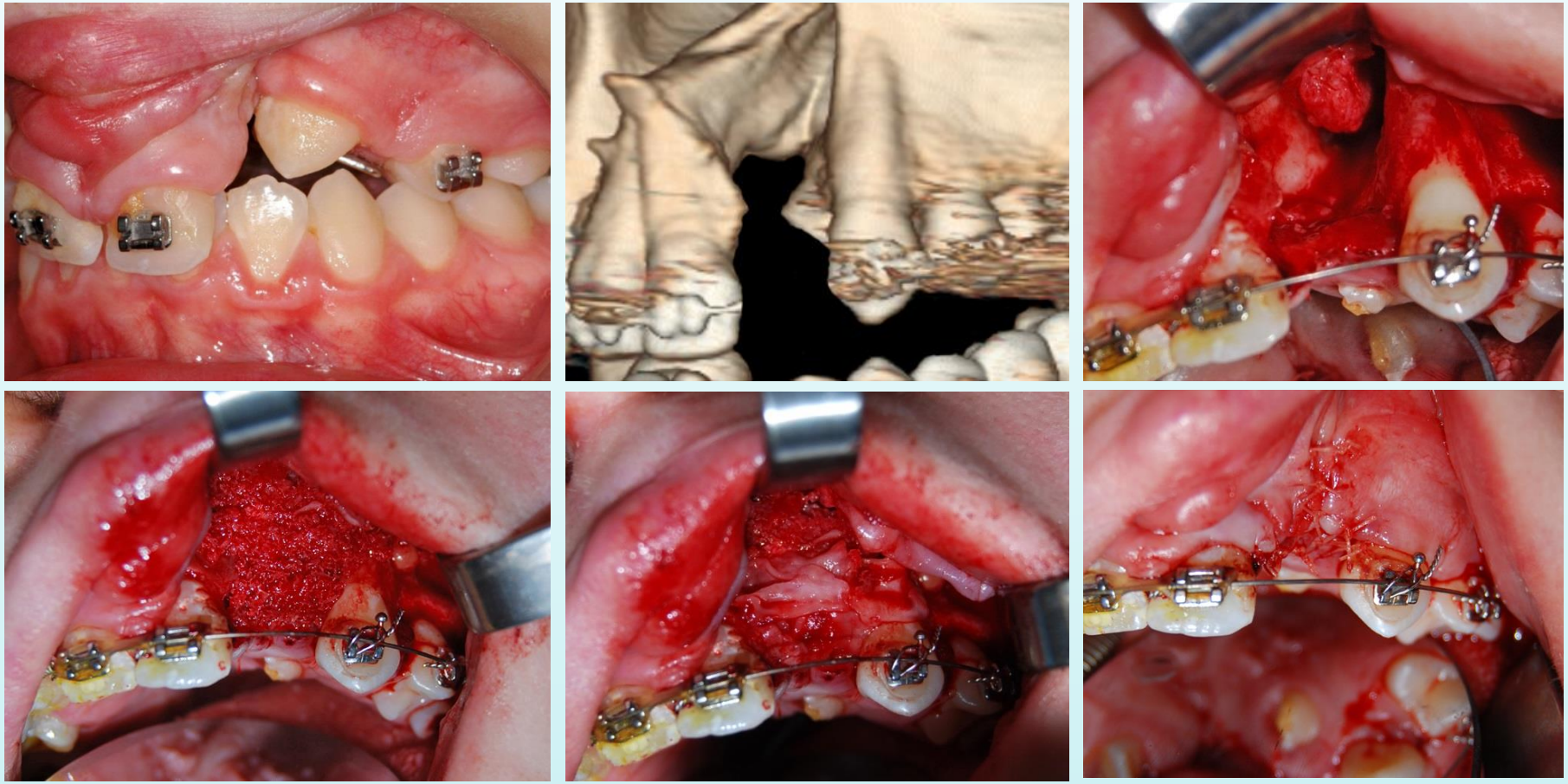
Schröter, L. et al. Acta Biomaterialia (2020)
Tavoni, M. et al., Journal of Composites Science (2021)
Zhao. R. et al., Molecules (2021)

Genetic disease exemple :
Cleft lip and palate
AND Calcium phosphate particles

Cleft lip and palate

Photos : Pr. Pierre Corre

Gingivoperiosteoplasty with bone graft



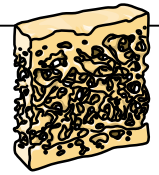
Photos : Pr. Pierre Corre

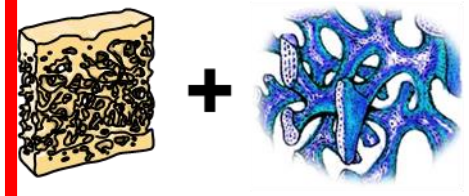
Current limitations of autologous transplantation

- BG failure rate
  - Child: 0%.
  - Adult: 10
- Tibial morbidity
  - Pain: 5 days
  - Lameness: 10 days
  - Visible scarring: 13 %

Corre P *et al*. Intérêt du site de prélèvement tibial médio-proximal dans l'alvéoloplastie secondaire: expérience de 55 cas chez l'enfant. Rev Stomatol Chir Maxillofac. 2011 Nov;112(5):280-5

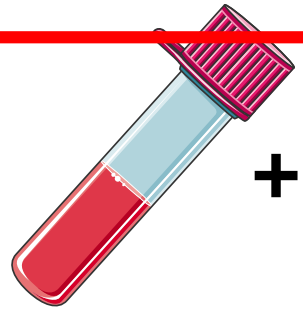
Bone Graft = Gold standard

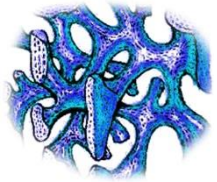




Bone Expansion =

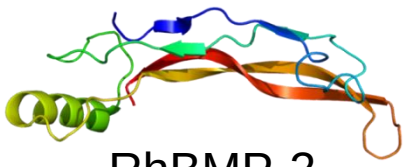
Bone Graft +
Biomaterial



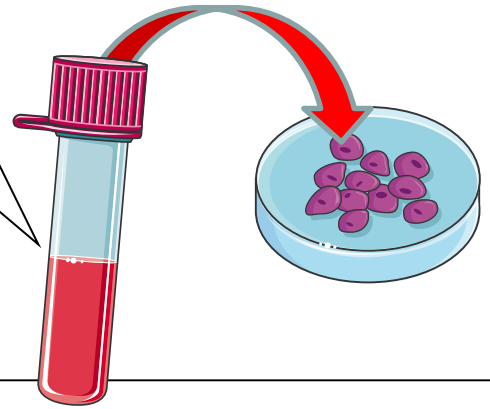


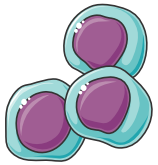
Total bone marrow +
Biomaterial

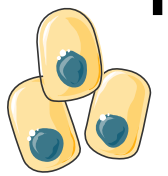
Pr. Pierre Corre



RhBMP-2

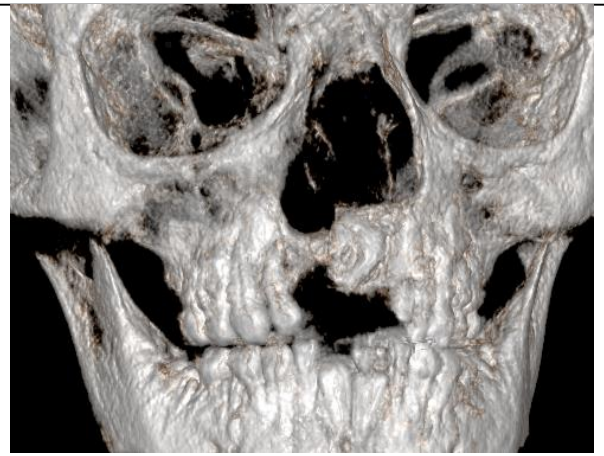


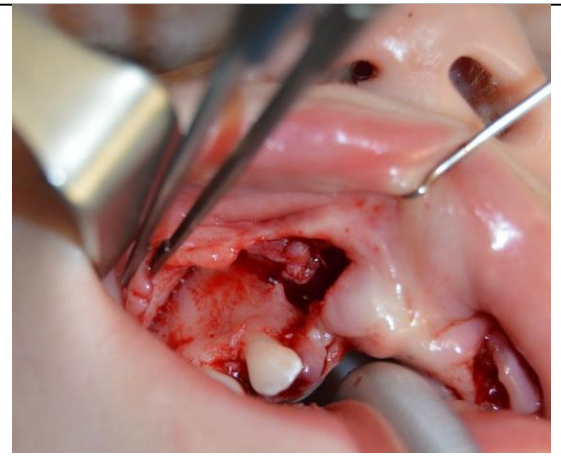




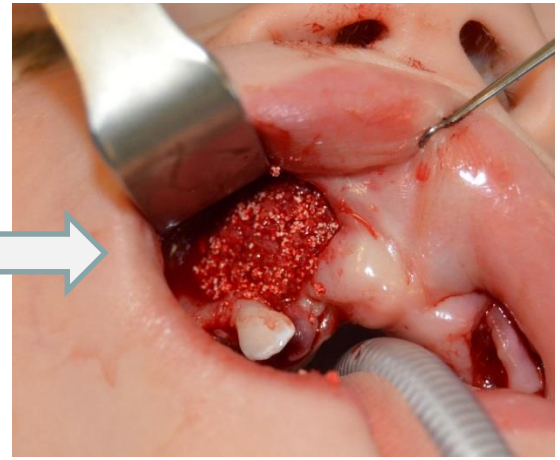
+/-

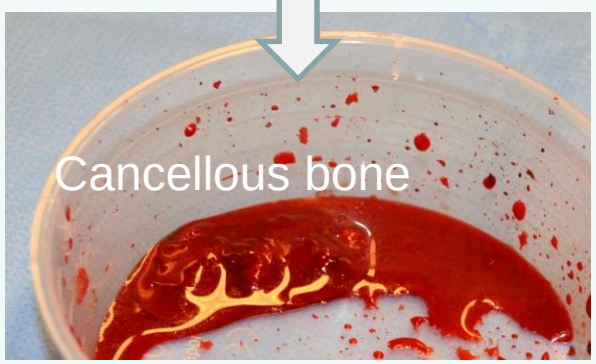
Thérapie cellulaire / ITO

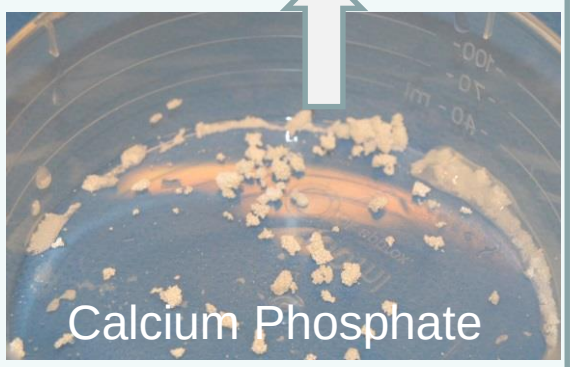


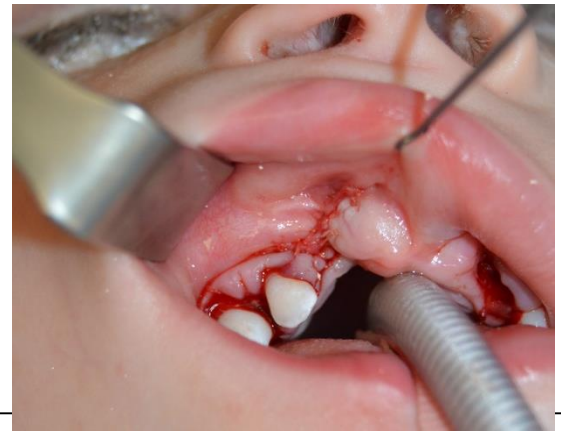


Tibial bone graft + bone expansion









First patient in Nantes

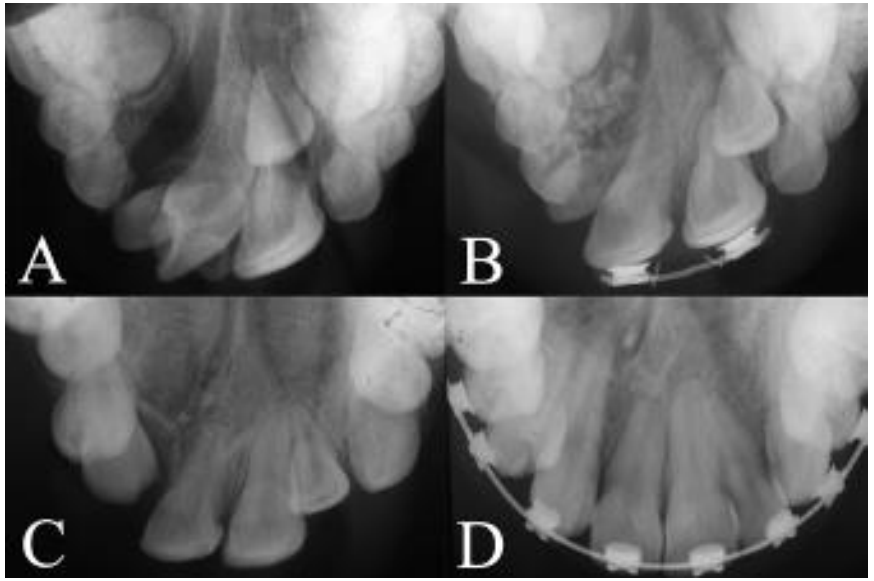


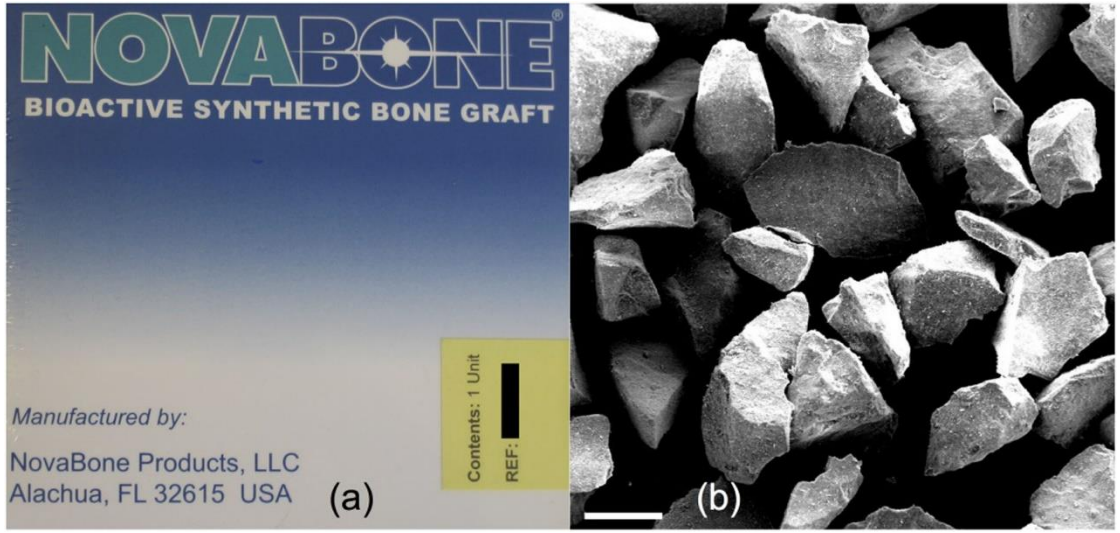
Image Pr. Pierre CORRE

Bioglass

Granules

NOVABONE

Proven to Signal, Recruit, Proliferate, and Differentiate.



A) Packaging of NovaBone (45S5 Bioglass) powder for orthopedic applications and (B) scanning electron micrograph of NovaBone particles. Modified with permission from Jones (2013).

NORAKER®
THE BIOGLASS® COMPANY

IBS

NovaBone Putty is a versatile bone graft substitute that is ready to use out of the package with exceptional handling characteristics that will save time and improve placement.

Glassbone injectable putty is composed of 45S5 bioactive glass and a polymer. This composite technology allows it to be very easily malleable and applicable in complex defects. It is sold directly in the syringe, ready to use.

Utilisation clinique

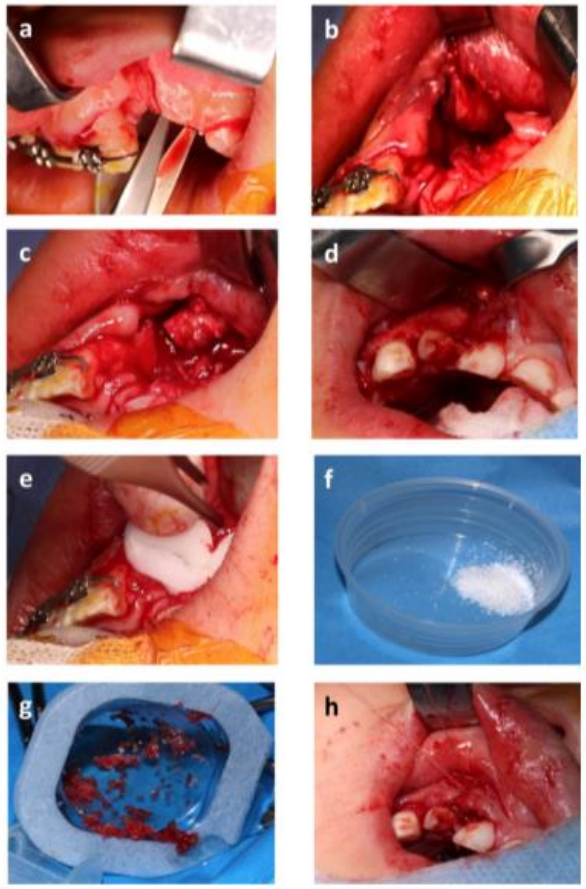
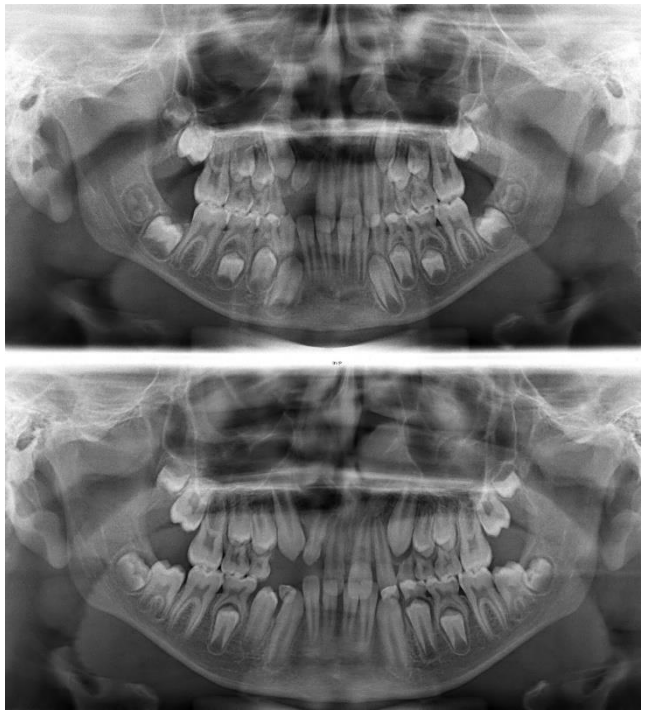


Figure 9: Photographies des étapes de la GOA (d'après la collection personnelle des Drs Audrey Gallucci et Nathalie Degardin, Hôpital La Timone Enfant, AP-HM). (a) Incision de la muqueuse. (b) Lambeau muco-périosté, visualisation du défaut osseux. (c,d) Dissection de la muqueuse nasale. (e) Mise en place du Pangen®. (f) GlassBONE™ pur. (g) GlassBONE™ mélangé au sang du patient. (h) Sutures finales du lambeau muco-périosté après mise en place du GlassBONE™.



Dental panoramic view-preoperative (A) and at 1 year (B) showing the evolution of the lateral incisor and the canine through the right alveolar bone graft with GlassBONE™.

Journal of Cranio-Maxillo-Facial Surgery 46 (2018) 1772–1776

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Bioactive glass 45S5 ceramic for alveolar cleft reconstruction, about 58 cases☆

Nicolas Graillon [a,*], Nathalie Degardin [b], Jean Marc Foletti [c,d], Magali Seiler [e], Marine Alessandrini [f], Audrey Gallucci [a]

5. Conclusion

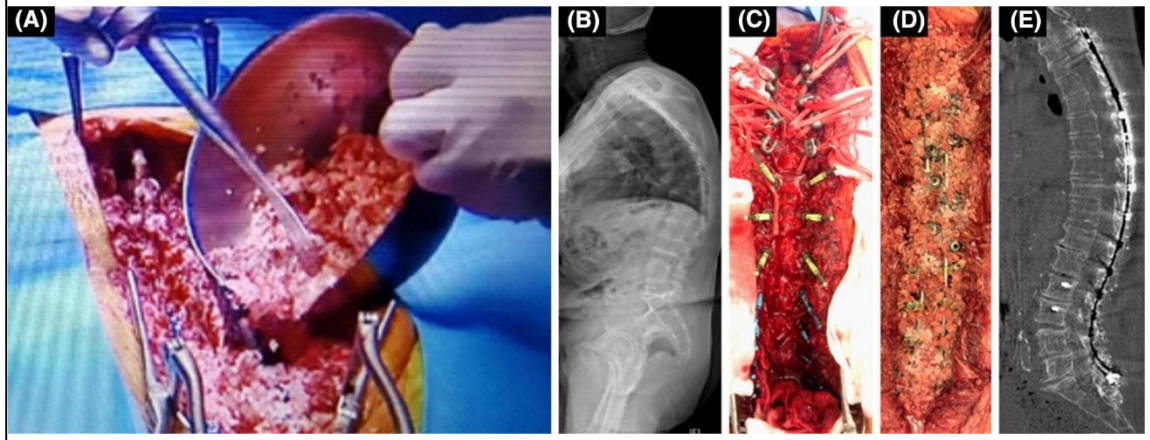
Alveolar bone grafting using a synthetic bioactive glass bone substitute can be an alternative to iliac crest bone grafting. It simplifies the surgical procedure and outcomes, allows satisfactory mucosal and bone healing, supports tooth eruption, authorizes the performance of the grafting at an earlier stage, and facilitates the acceptability of a late pre-implant transplant because of its simplicity. In case of failure, it does not contraindicate a new grafting using a bone substitute or autologous bone.

European Journal of Orthopaedic Surgery & Traumatology (2019) 29:1623–1629
https://doi.org/10.1007/s00590-019-02477-5

ORIGINAL ARTICLE • SPINE - BIOMATERIALS

Clinical and radiographic evaluation of bioactive glass in posterior cervical and lumbar spinal fusion

Cédric Barrey[1] · Théo Broussolle[1]



Mix of GlassBone with local autologous bone and saline serum place on the decorticated posterior elements of the spine;

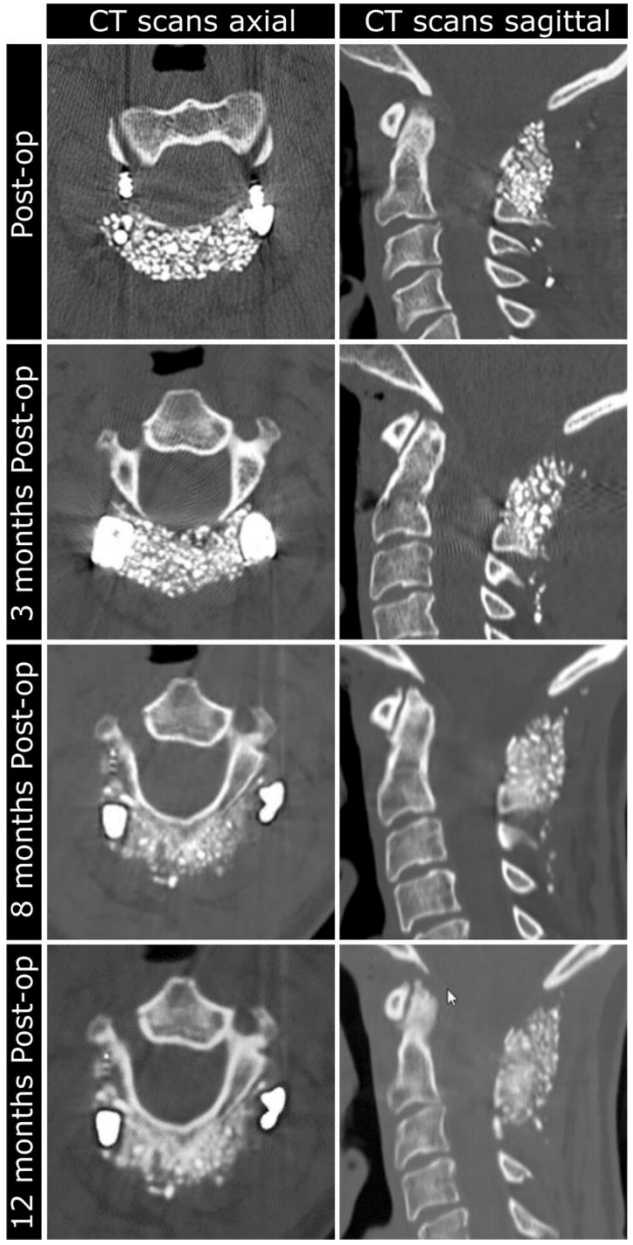


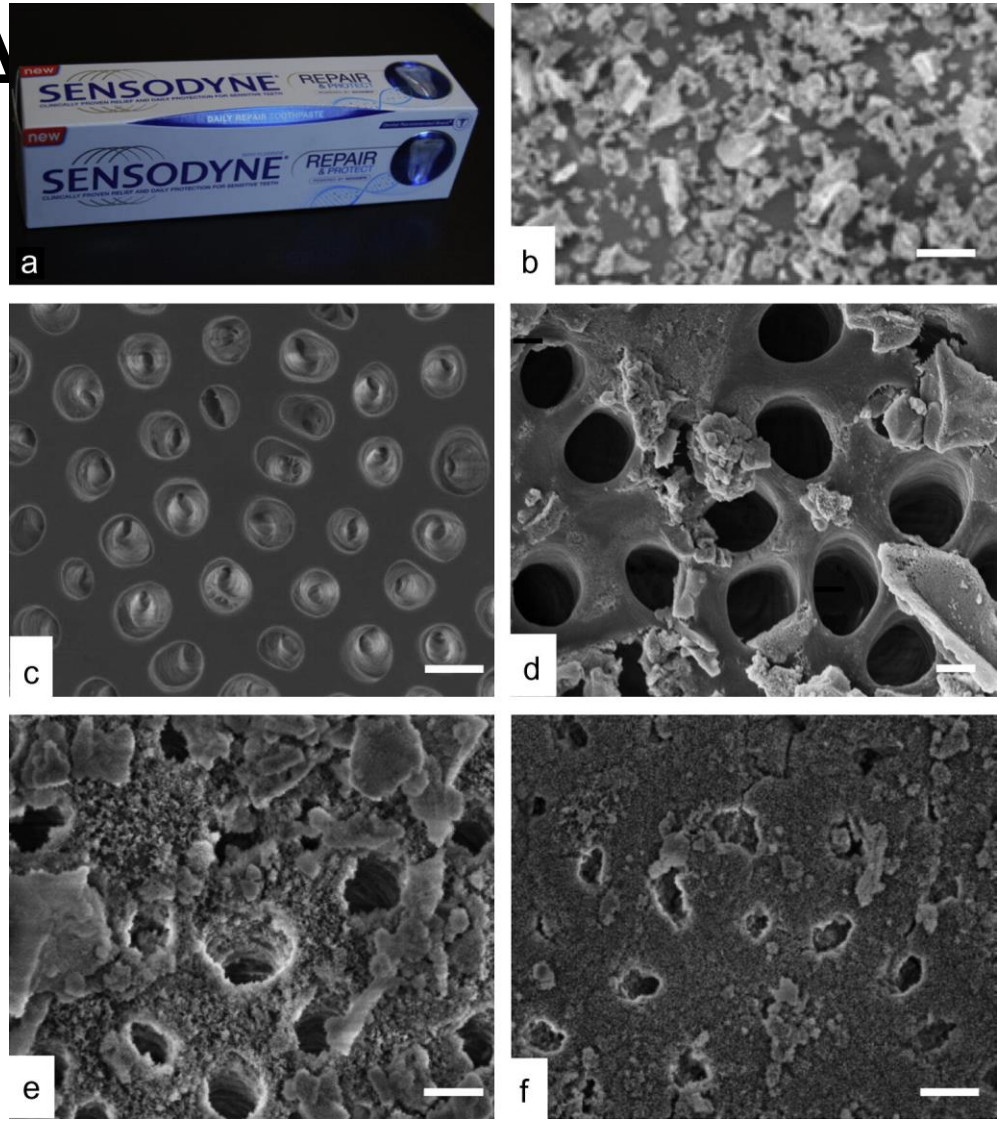
Table 4 Graft consolidation for 29 patients. One patient was excluded for this study (see Table 3)

Graft consolidation	12 m post-op cervical (*n*)	1 y post-op for T-L-S (*n*)
Acquired	2 (100%)	22 (82%)
In progress	0	3 (11%)
Pseudarthrosis	0	2 (7%)
Mediocre	0	0

T-L-S thoraco-lumbar-sacral

- Dentifrices

Photograph of Sensodyne Repair and Protect toothpaste, which contains NovaMin®, a fine particulate of Bioglass 45S5®. (b) SEM image of NovaMin particles (bar=20µm). (c–f) SEM micrographs of human dentine (bar=1µm): (c) untreated, (d) immediately after application of NovaMin in artificial saliva (AS); (e) 24h after application of NovaMin in AS; (f) 5days after application. SEM images modified from Earl et al.



Reprogram

We reprogram cells to ask them to regenerate a tissue :

- Gen therapy : Production of Growth Factors by DNA transfection
- Induced pluripotent stem cells : IPS...before re-differentiation
- ARN cell programming

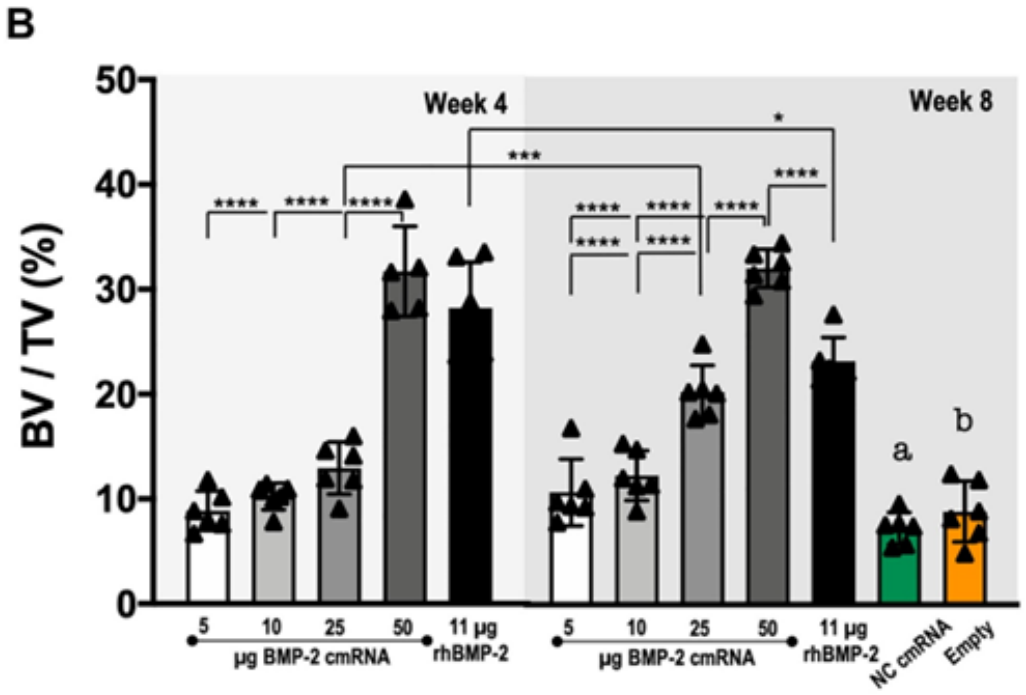
Reprogram

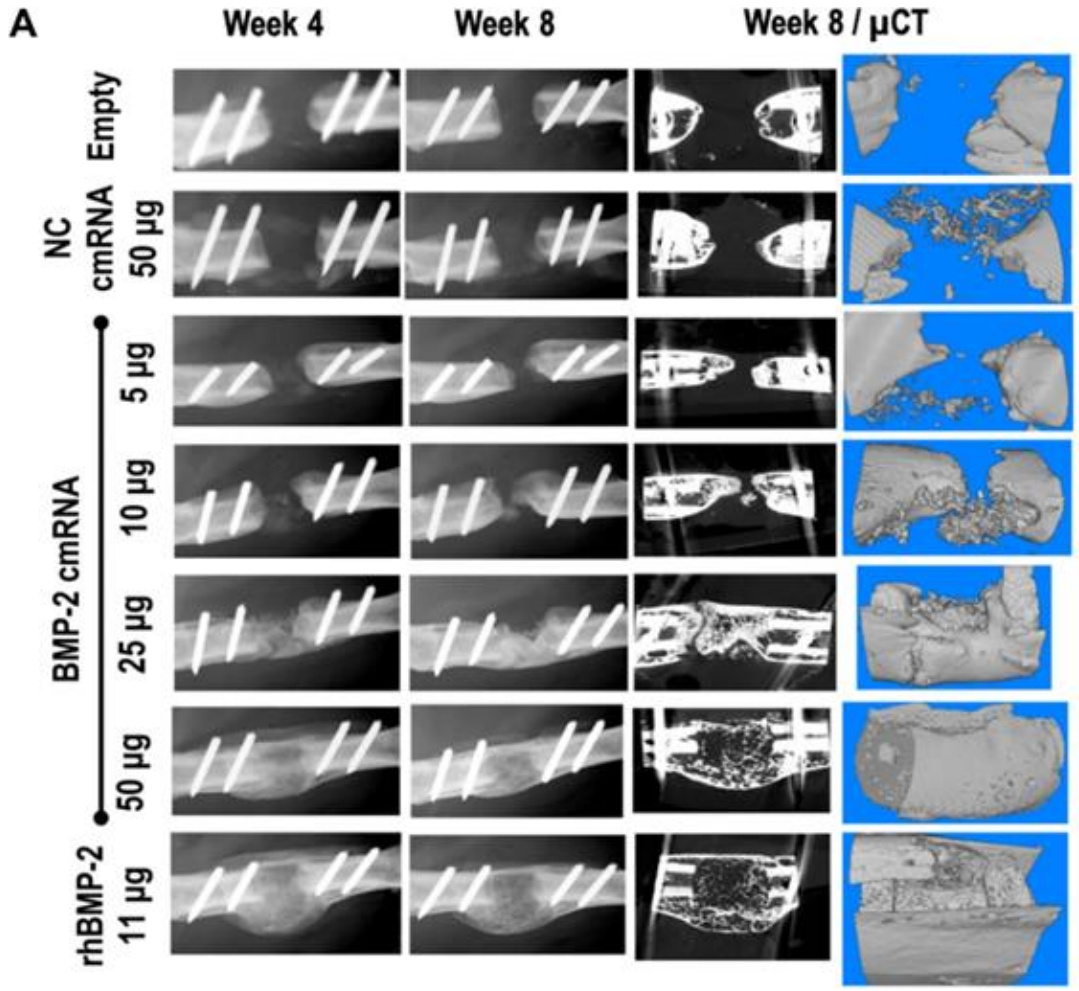
SCIENCE ADVANCES | RESEARCH ARTICLE

BIOCHEMISTRY

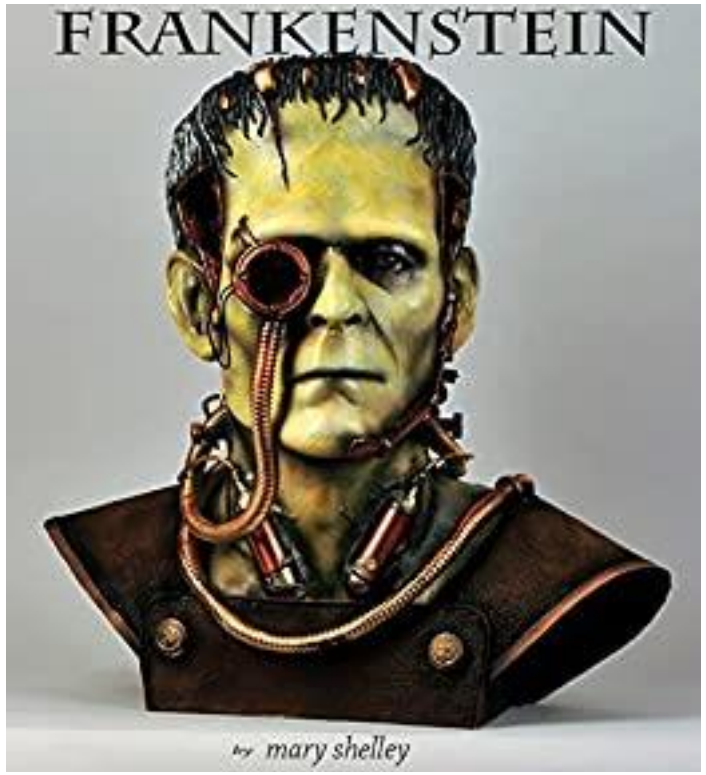
Efficient healing of large osseous segmental defects using optimized chemically modified messenger RNA encoding BMP-2

Rodolfo E. De La Vega[1,2], Martijn van Griensven[1,2], Wen Zhang[3], Michael J. Coenen[1], Christopher V. Nagelli[1], Joseph A. Panos[1], Carlos J. Peniche Silva[2], Johannes Geiger[3], Christian Plank[3], Christopher H. Evans[1], Elizabeth R. Balmayor[1,4]*





Replace ou repair ?

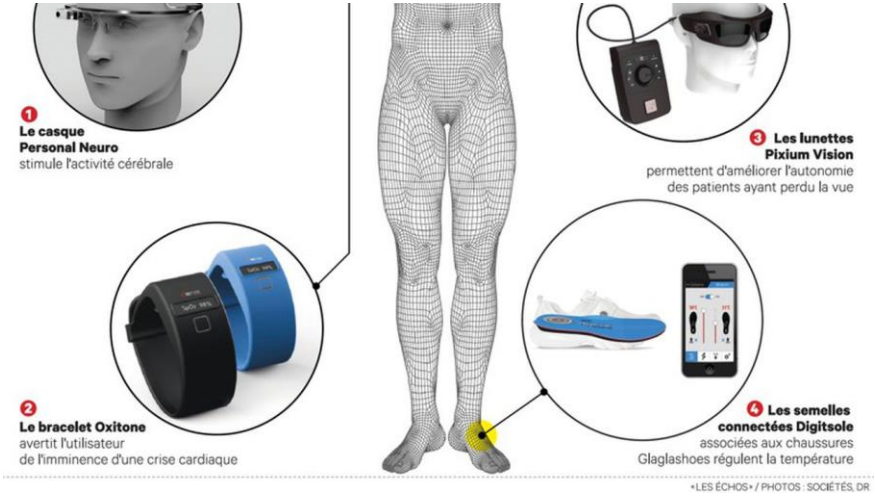


Self-image ?

The augmented human being

The augmented human being and Ethic ?

Transhumanism



Transhumanism is a philosophical and intellectual movement which advocates the enhancement of the human condition by developing and making widely available sophisticated technologies that can greatly enhance longevity and cognition