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

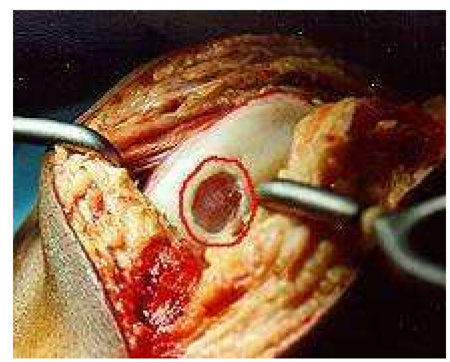
Day 3

Biomaterial for regeneration in Tissue engineering strategies before to move to personalized medicine with specific construct adapted to one patient

Inserm
La science pour la santé
From science to health

Why Tissue engineering?

- 2 THERAPEUTIC AXES
  - Large bone losses.
  - Articular and IV Cartilage Lesions



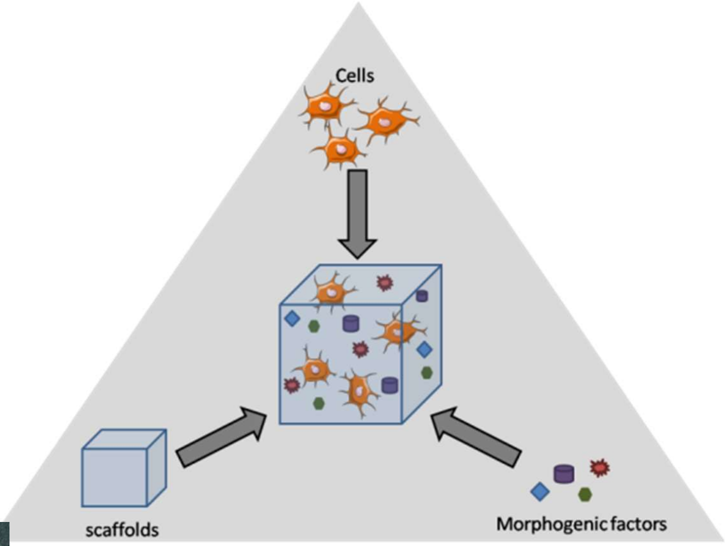
Tissue engineering

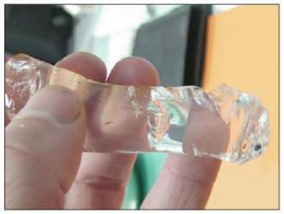
« The application of the principles and methods of engineering and life sciences toward the development of biological substitutes that restore, maintain or improve tissue function » (Woodfield, 2001).

cells like seeds

Biomaterials like Soil

GFs like fertilizer

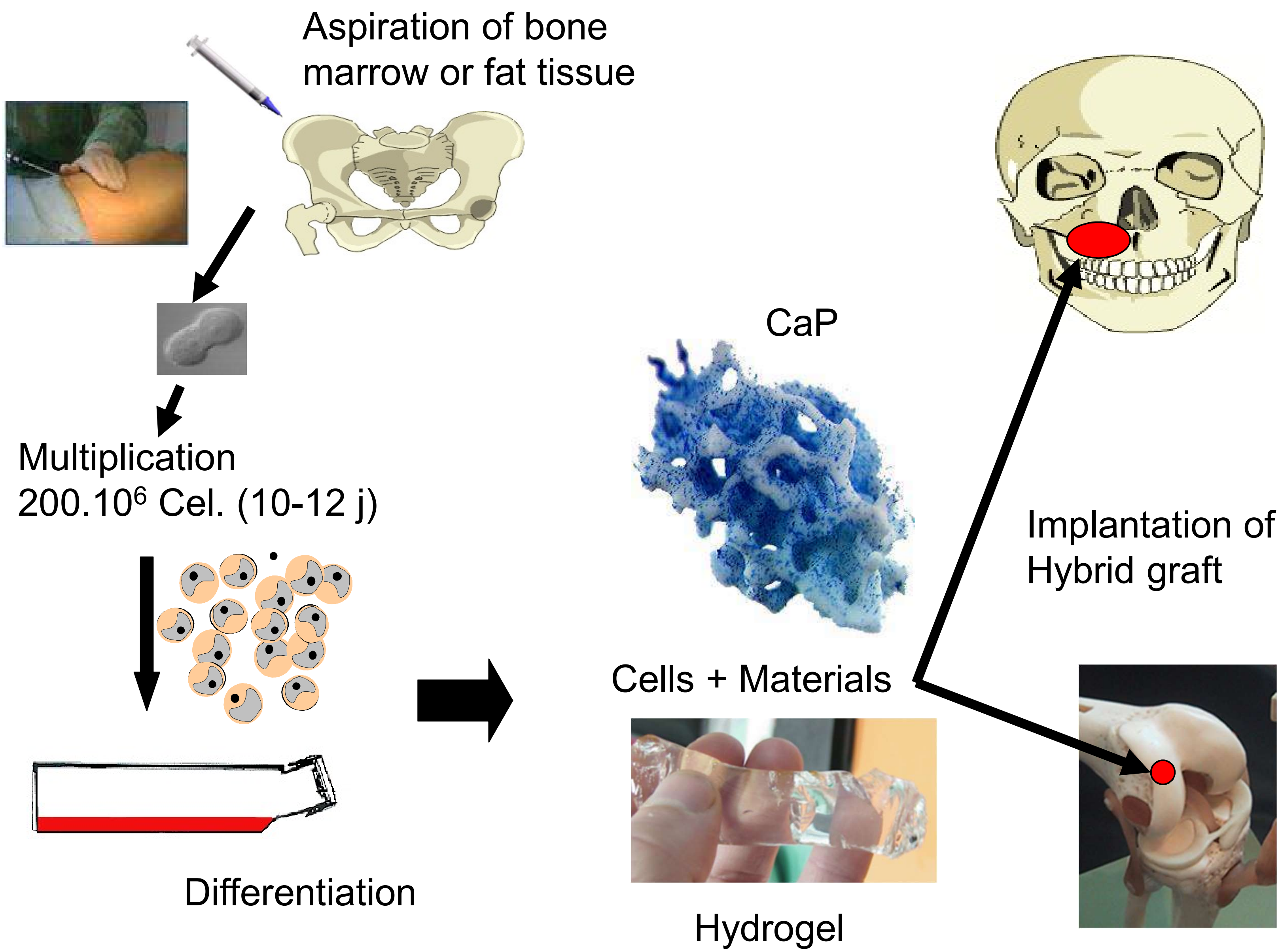




Merceron, Vinatier, Guicheux. Joint Bone Spine 2008

Inserm
La science pour la santé
From science to health

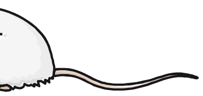
How do we do TE:



Cells ?
and Cells interactions ?

Bone Tissue Engineering ?

ny,S et Al.
esearch 2010



e (n= 2x30)
weeks

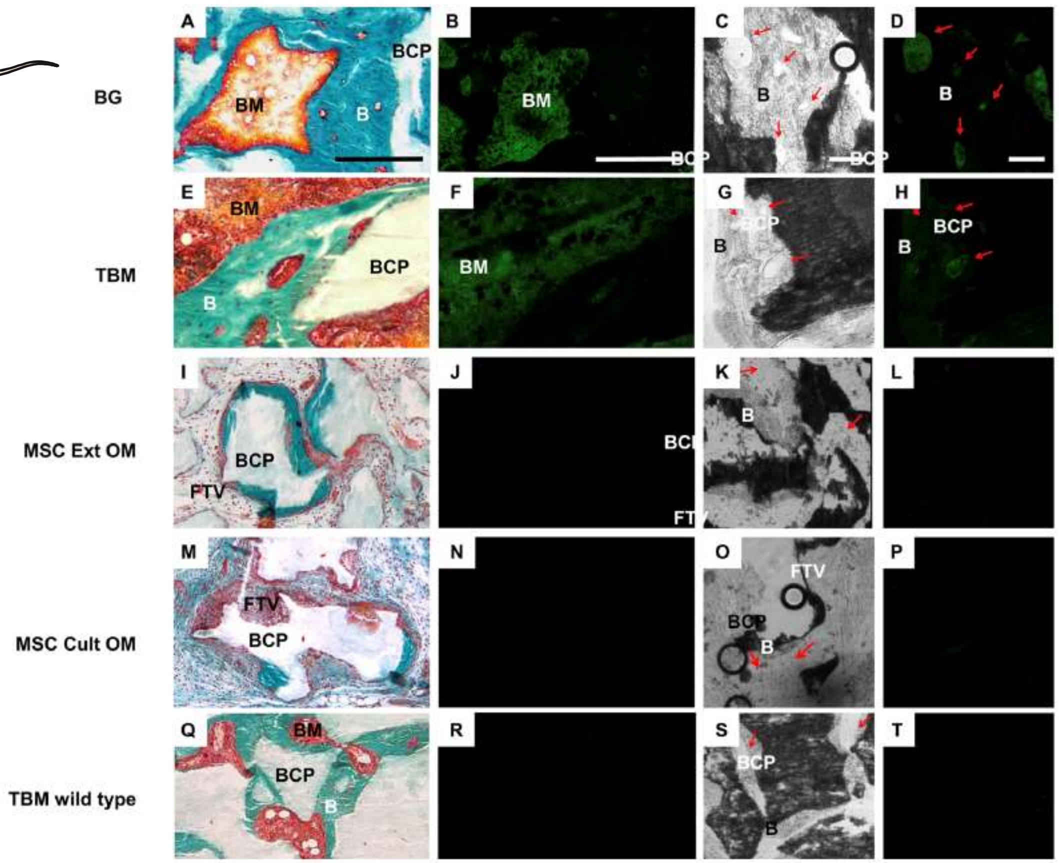


Figure 7. "*In vivo*" tracking of donor cells. Goldner trichrome staining (A, E, I, M and Q). B: bone, BCP: biphasic calcium phosphate, BM: bone marrow, FVT: fibrovascular tissue. Bar: 250 µm. Green fluorescence of GFP retrieved in subcutaneous implants (B, F, J, N and R). Nude mice implanted with non-GFP BM were used as negative controls (TBM wild type). Bar: 250 µm. Transmitted light showing vessels in connective tissues surrounding the BCP granules or in newly formed bone (red arrow) (C, G, K, O and S) Bar: 100 µm. Fluorescent light showing vessels only in TBM and BG groups (red arrow) (D, H, L, P and T) Bar: 100 µm.
doi:10.1371/journal.pone.0081599.g007

OPEN ACCESS Freely available online PLOS ONE

Determining a Clinically Relevant Strategy for Bone Tissue Engineering: An "All-in-One" Study in Nude Mice

Pierre Corre[1,2,5]*, Christophe Merceron[1,5], Caroline Vignes[1,5], Sophie Sourice[1,5], Martial Masson[1,5], Nicolas Durand[1,3,5], Florent Espitalier[1,3,5], Paul Pilet[1,5], Thomas Cordonnier[1,5], Jacques Mercier[2,5], Séverine Remy[4], Ignacio Anegon[4], Pierre Weiss[1,5], Jérôme Guicheux[1,5]

MSCs fate ?

→ Cells die after 4 weeks of implantation in bone

J. Cell. Mol. Med. Vol 15, No 7, 2011 pp.

Survival and function of mesenchymal stem cells (MSC depend on glucose to overcome exposure to long-term severe and continuous hypoxia

M. Deschepper[a], K. Oudina[a], B. David[a, b], V. Myrtil[a], C. Collet[c], M. Bensidhoum D. Logeart-Avramoglou[a], H. Petite[a,*]

⇨ Hypoxia with Glucose didn't kill MSC : Ischemia is problem

nature medicine

Mesenchymal stem cell–based tissue regeneratio governed by recipient T lymphocytes via IFN-γ a TNF-α

Yi Liu[1,2], Lei Wang[1,3], Takashi Kikuiri[1], Kentaro Akiyama[1], Chider Chen[1], Xingtian Xu[1,4], Ru WanJun Chen[5], Songlin Wang[2] & Songtao Shi[1]

⇨ T cells regulate autologous MSC

Why an Hydrogel better than liquid viscous solution ?

- Against flow and leakage of the injectable biomaterials
- To do injectable foam cements
- To protect cells from Immune system in Bone TE

For Bone -> Calcium phosphate + Hydrogel

Hydrogels

What is an Hydrogel ?»

"Water swollen networks of polymers."
"Hydrogels are hydrated polymeric networks […]"

(**Burdick**; Nat Methods. 2016 April 28; 13(5): 405–414.;
Current Opinion in Biotechnology 2016, 40:35–40)

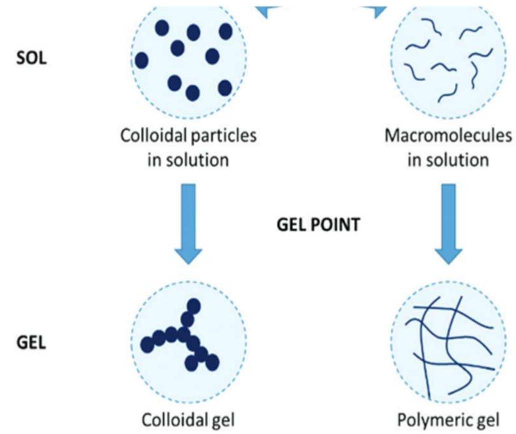
"They swell spontaneously in water to high levels without being water soluble, and provide readily chemically modified, cross-linked, hydrated, elastic networks."

(**David Grainger**; Biomaterials 141 (2017) 96e115)

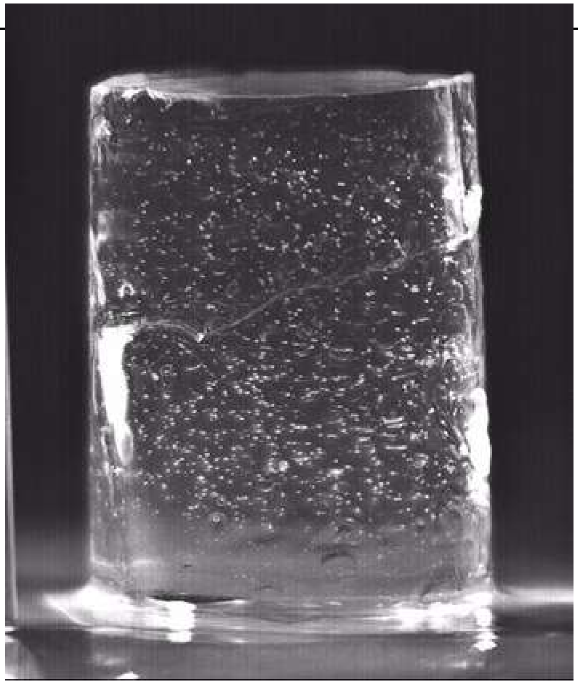
"hydrogels are networks of polymer chains that are sometimes found as colloidal gels in which water is the dispersion medium."
(**Ahmed**; Journal of Advanced Research (2015) 6, 105–121)

<u>International Union of Pure and Applied Chemistry (IUPAC) :</u>

"Non-fluid colloidal network or polymer network that is expanded throughout its whole volume by a fluid.“

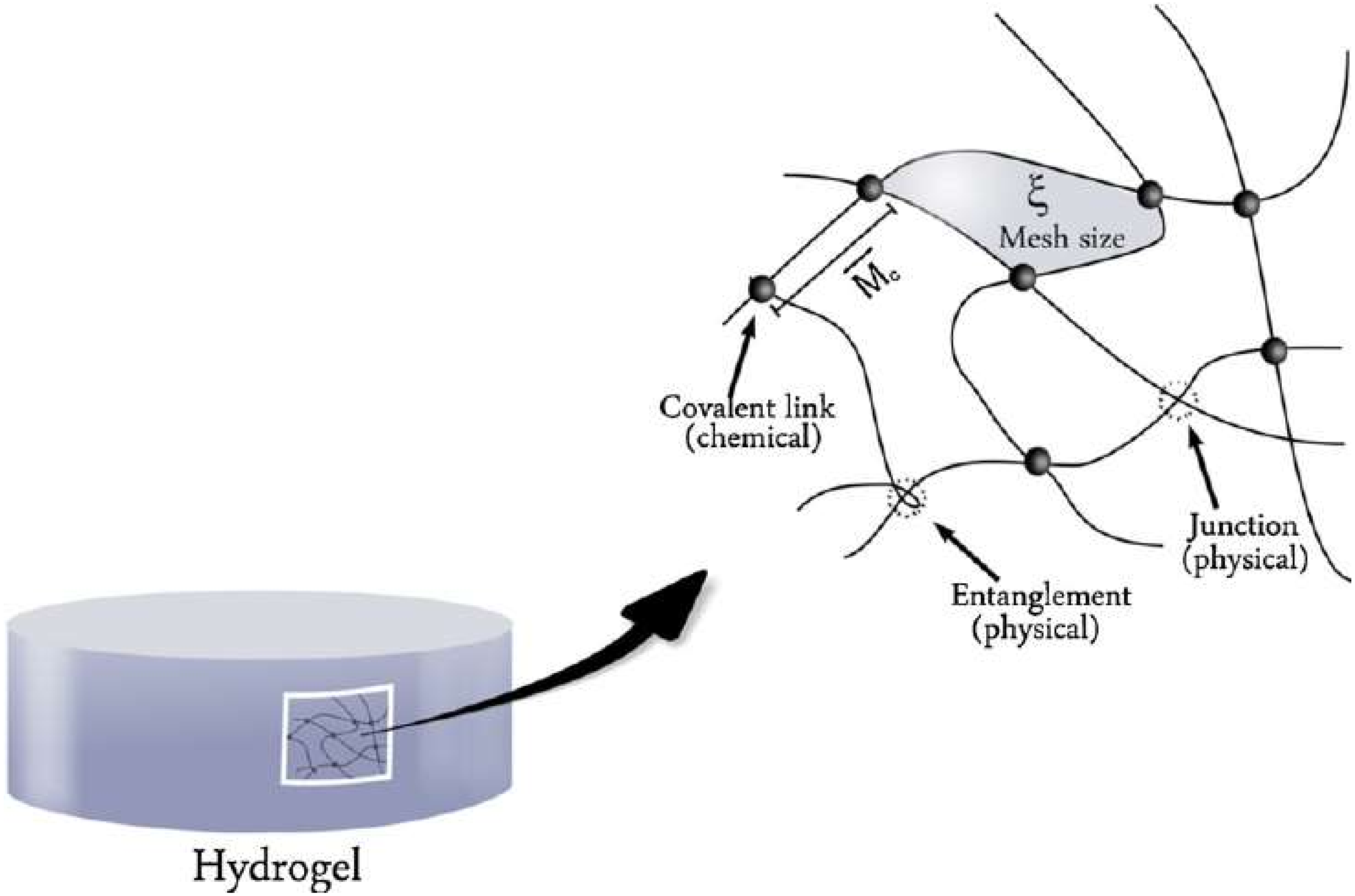


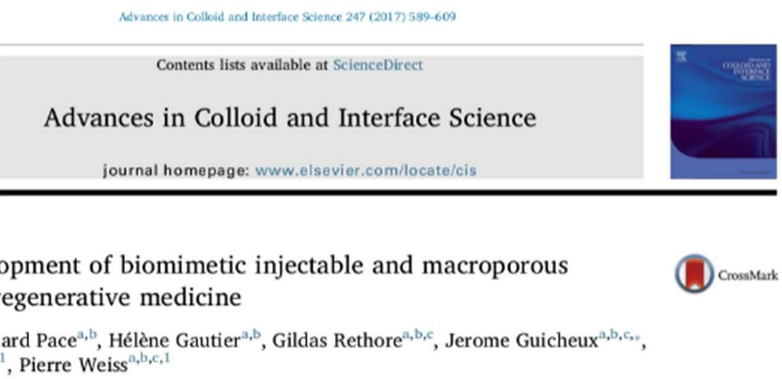
Montheil TJournal of Materials Chemistry B 2018



Hydrogel of a superabsorbent polymer

Viscous liquid or elaslic solide ?


ξ
Mesh size
$\overline{M}_c$
Covalent link
(chemical)
Junction
(physical)
Entanglement
(physical)
Hydrogel


Advances in Colloid and Interface Science 247 (2017) 589–609

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

opment of biomimetic injectable and macroporous
regenerative medicine

ard Pace[a,b], Hélène Gautier[a,b], Gildas Rethore[a,b,c], Jerome Guicheux[a,b,c,*],
[1], Pierre Weiss[a,b,c,1]

- Hydrogels in Tissue Engineering:
  - 90%+ Water
  - Hydrophilic polymer
  - Biocompatible
  - Biodegradable
  - Weak mechanical properties

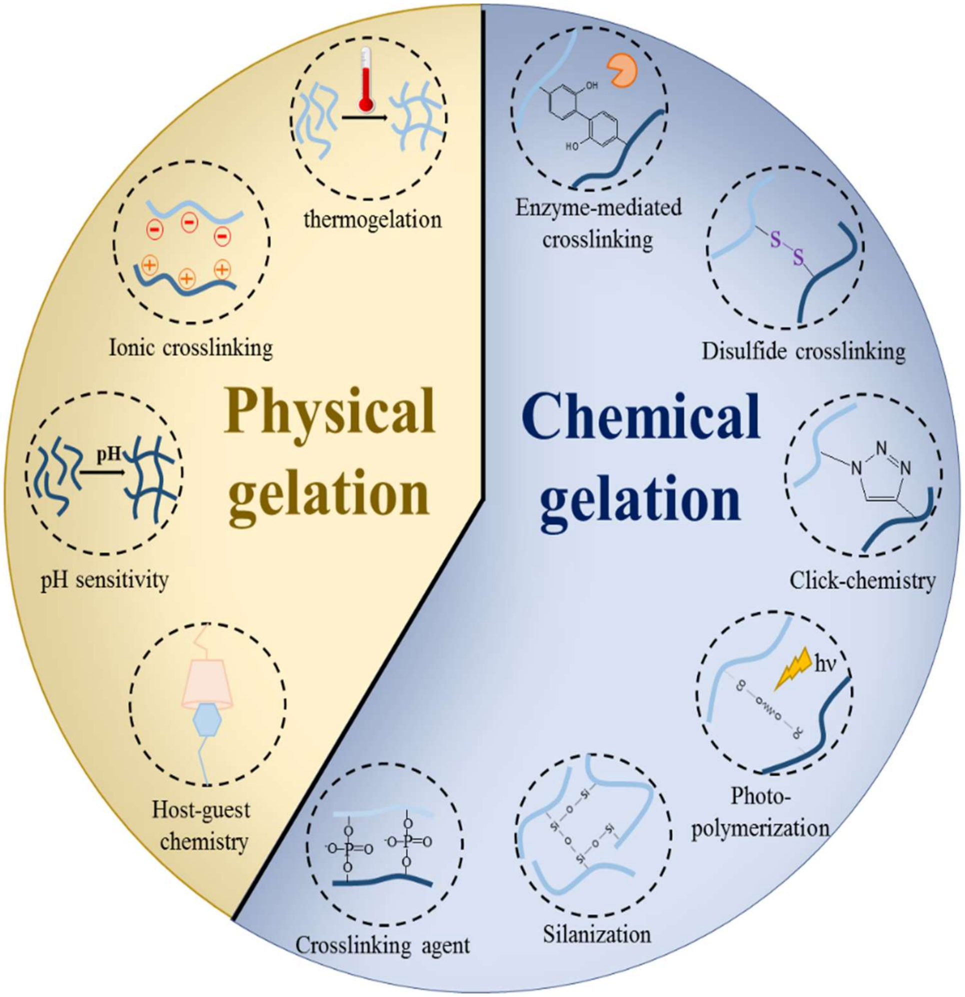
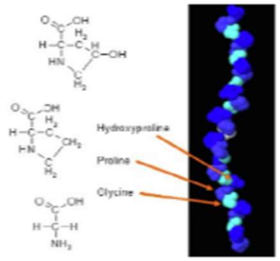
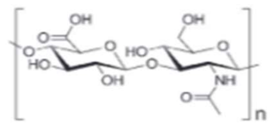
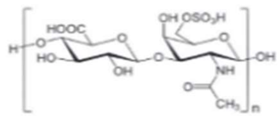
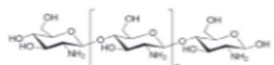
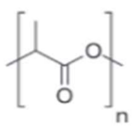
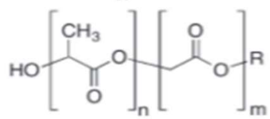
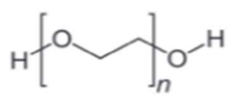
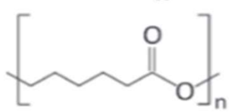


Table 1

Common polymer types (natural and synthetic) used as drug-delivering carriers and drug-releasing scaffolds. Chemical structure, advantages, drawbacks, and cartilage applications provided.

	Polymer name	Chemical structure	Advantages	Drawbacks	Uses
Natural	Collagen (type I/II)		Excellent biocompatibility, bioresorbable, natural component of ECM, already used clinically	Type II collagen (cartilage-specific) can be immunogenic, relatively low biomechanics	Tissue engineering scaffolds and gels, used for MACI and other clinical cartilage restoration techniques
	Hyaluronic Acid [HA]		Chemically modifiable, natural GAG in cartilage matrix	Requires modification to form 3D structures	Tissue engineering hydrogels/ scaffolds, drug depots, intra-articular injection
	Chondroitin Sulfate [CS]		Chemically modifiable, native to cartilage tissue	Low molecular weight	Hydrogels for tissue engineering, nanoparticle carriers
	Chitosan		Biocompatible, non-cytotoxic, contains cartilage components	Slow gelation for in situ applications	Microsphere carrier, tissue engineering scaffold
Synthetic	Polylactic acid [PLA]		Easily processed, elongated degradation, high strength	Acidic byproducts, auto-catalytic degradation	Tissue engineering scaffolds, drug carriers
	Poly(lactic-co-glycolic acid) [PLGA]		Selectable degradation based on copolymer ratio	Acidic byproducts, poor long-term stability	Nano-carriers (e.g. FX006), micro-carriers, tissue engineering scaffolds
	Polyethylene glycol [PEG]		Easily functionalized	Non-degradability, no inherent biologic impact	Microcapsules, drug depots, hydrogels, liposomal fortification
	Polycaprolactone [PCL]		Easily processed and manufactured	Slow degradation, intracellular resorption	manufactured scaffolds (e.g. 3D-printing), drug delivery

J. M. Patel, K. S. Saleh, J. A. Burdick et al., Bioactive factors for cartilage repair and regeneration: Improving deliver y, retention, and activity, Acta Biomaterialia,https://doi.org/10.1016/j.actbio.2019.01.06

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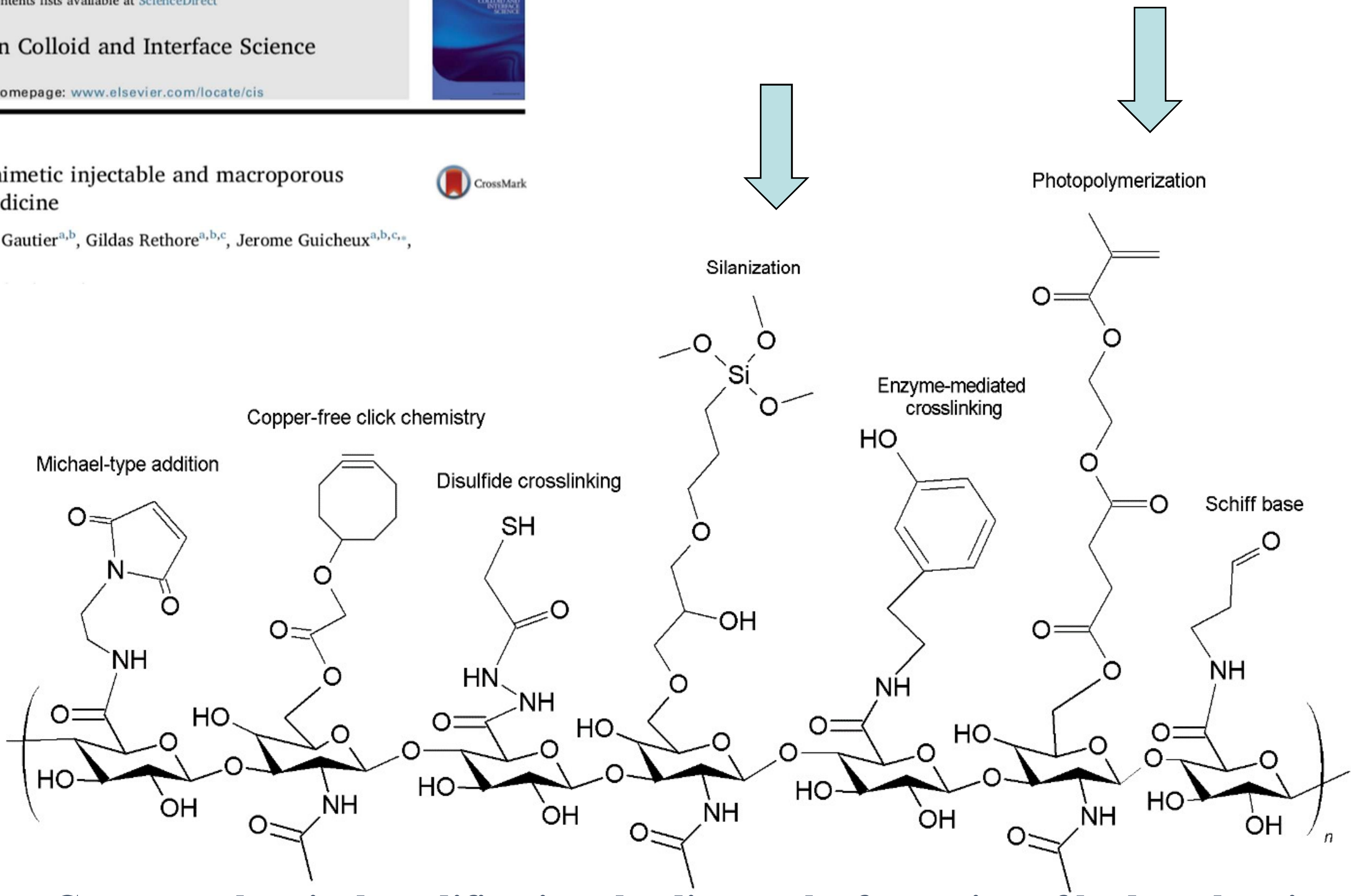
lopment of biomimetic injectable and macroporous
regenerative medicine

hard Pace[a,b], Hélène Gautier[a,b], Gildas Rethore[a,b,c], Jerome Guicheux[a,b,c,*],
b,1, Pierre Weiss[a,b,c,1]



Common chemical modifications leading to the formation of hydrogels using the example of the hyaluronic acid polysaccharide.

Dehydrated hydrogel: porous structures

Pierre-Olivier Bagnaninchi, *Biotechnol Bioeng*, 2003.

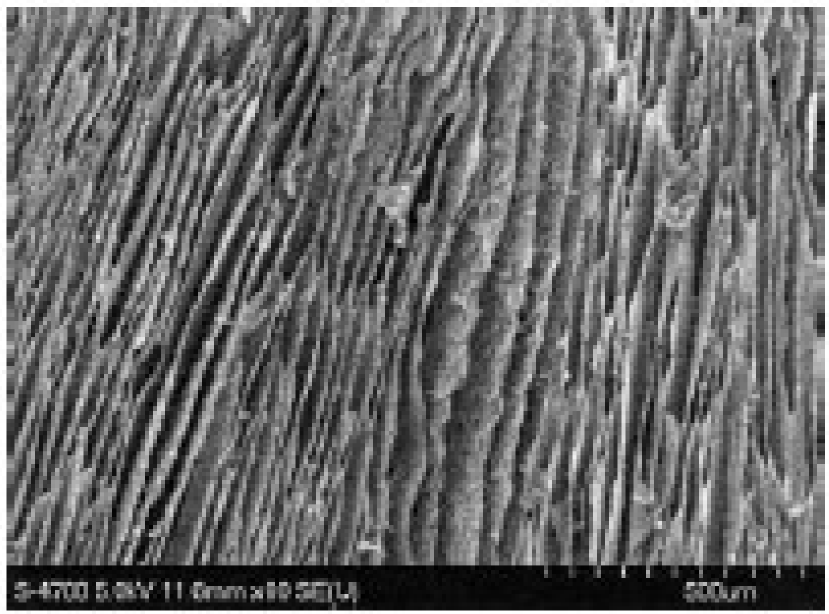


Figure 1. SEM picture of a radially oriented microporous scaffold obtained from the casting and freeze-drying of 3.0% (w/w) LMCS gels (batch Ib).

Rapid prototyping of scaffolds

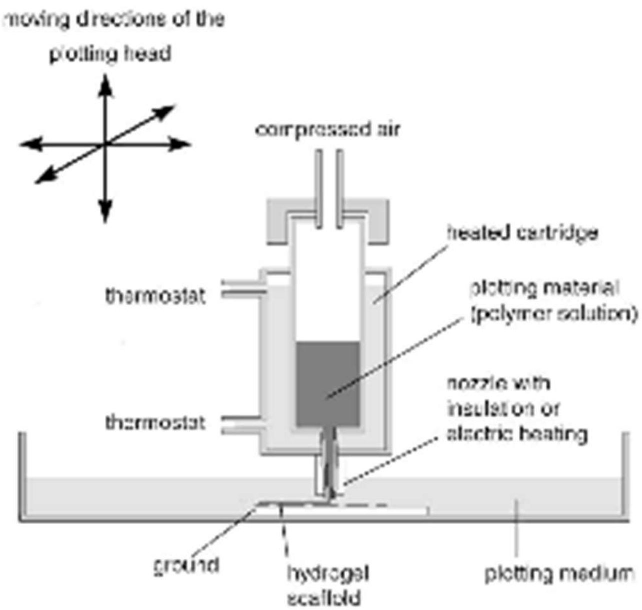


Fig. 2. Technical arrangement of the 3D plotter for the processing of thermoreversible hydrogels.

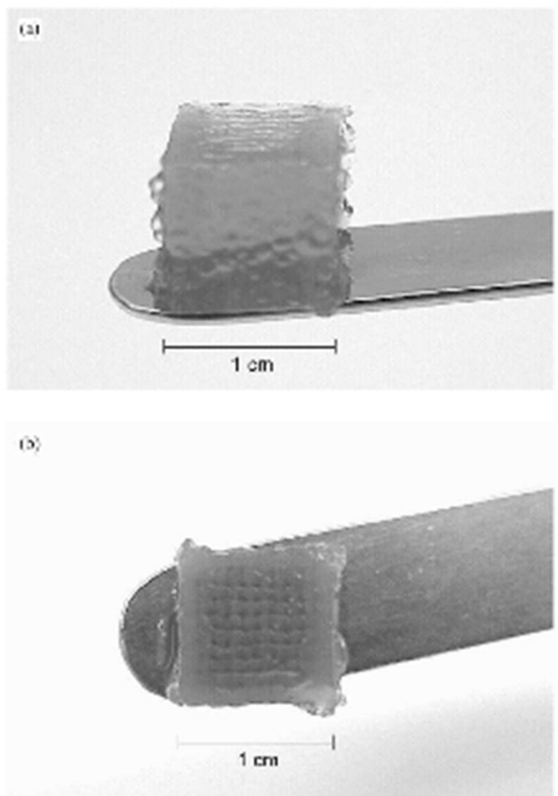


Fig. 6. Images of an agar scaffold: (a) side view of the porous scaffold, (b) top view of the same sample. The elastic scaffold is placed on air for acquiring the images. Gravity forces deform it to some extent, but the strand structure is still visible.

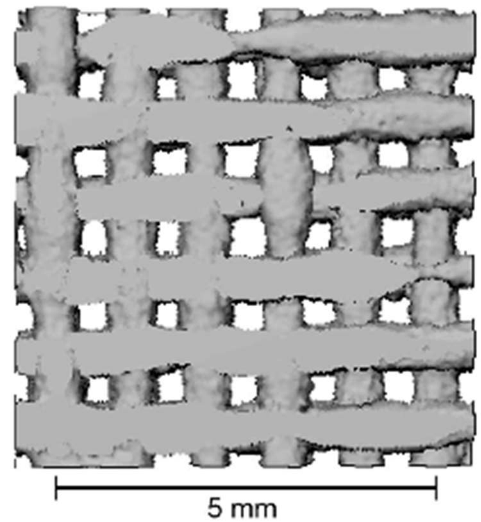
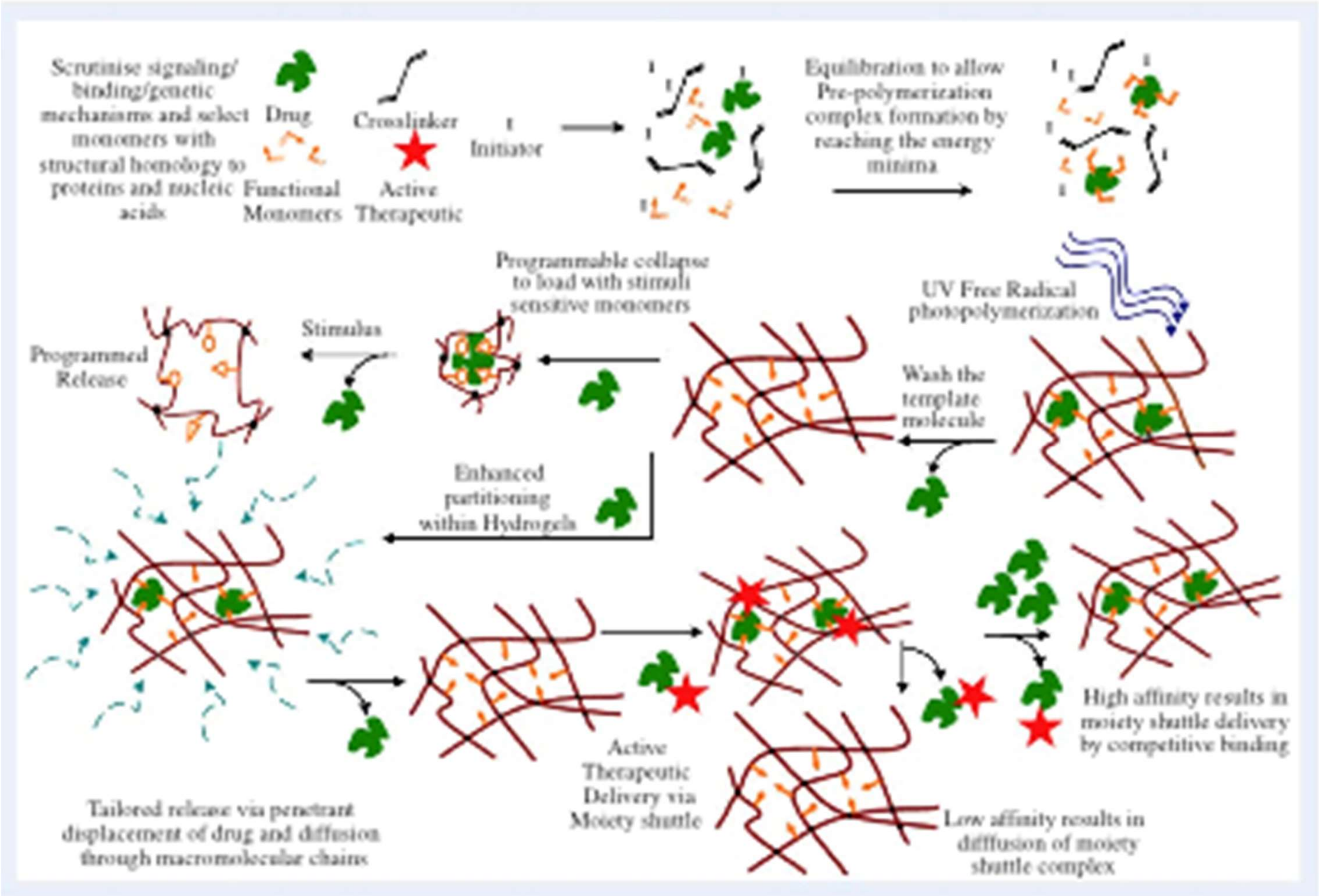


Fig. 7. Microtomographical analysis of a frozen agar scaffold. The pixel size is 5 µm. The virtual cut of the 3D reconstruction is not exact in plain and the freezing causes smaller irregularities. The image indicates the porous structure inside the agar scaffold.

Landers et al. Rapid prototyping of scaffolds derived from thermoreversible hydrogels and tailored for applications in tissue engineering. Biomaterials (2002) vol. 23 (23) pp. 4437-47

« Smart » hydrogels



Venkatesh et al. Biomimetic hydrogels for enhanced loading and extended release of ocular therapeutics. Biomaterials (2007) vol. 28 (4) pp. 717-24

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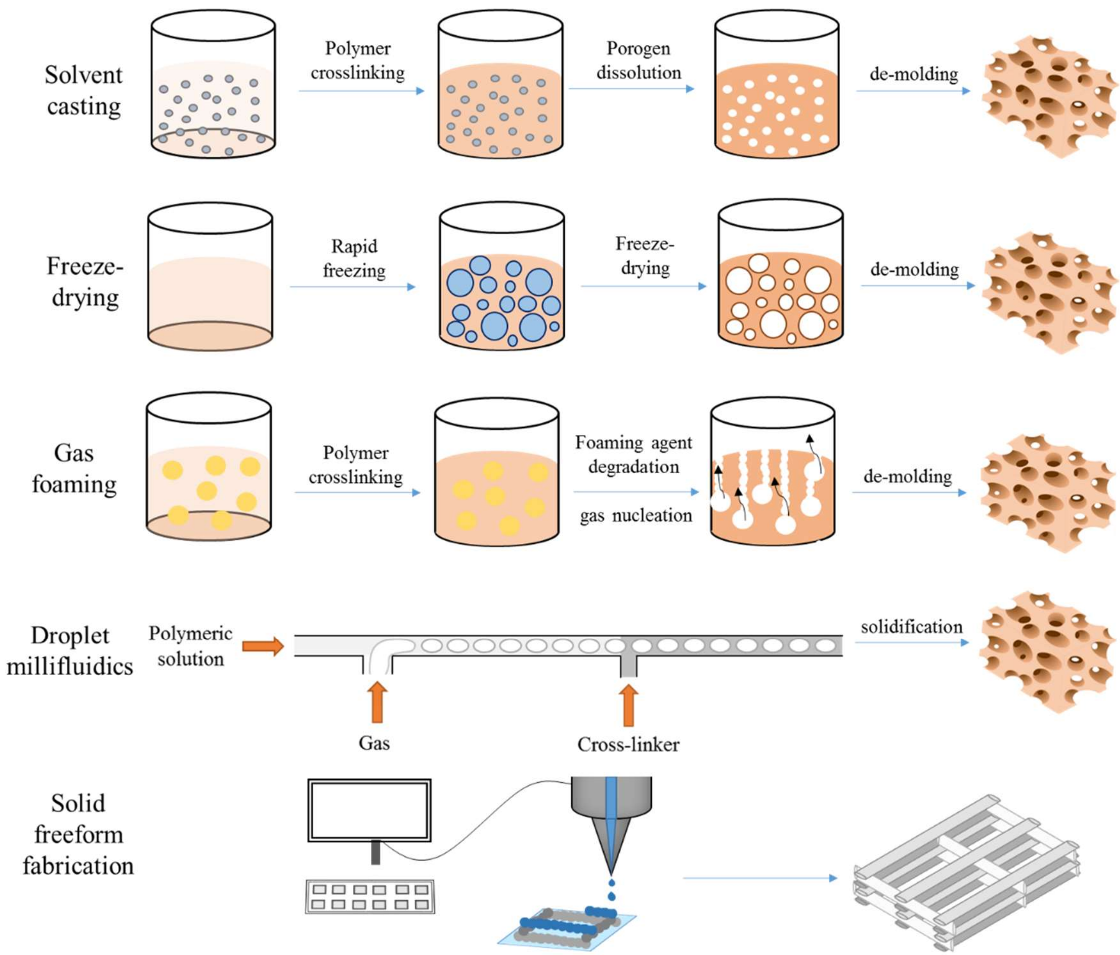
Common manufacturing processes used to develop macroporous biohydrogels



Pierre-Olivier Bagnaninchi, *Biotechnol Bioeng*, 2003.

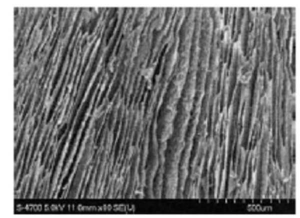


Figure 1. SEM picture of a radially oriented microporous scaffold obtained from the casting and freeze-drying of 3.0% (w/w) LMCS gels (batch Ib).

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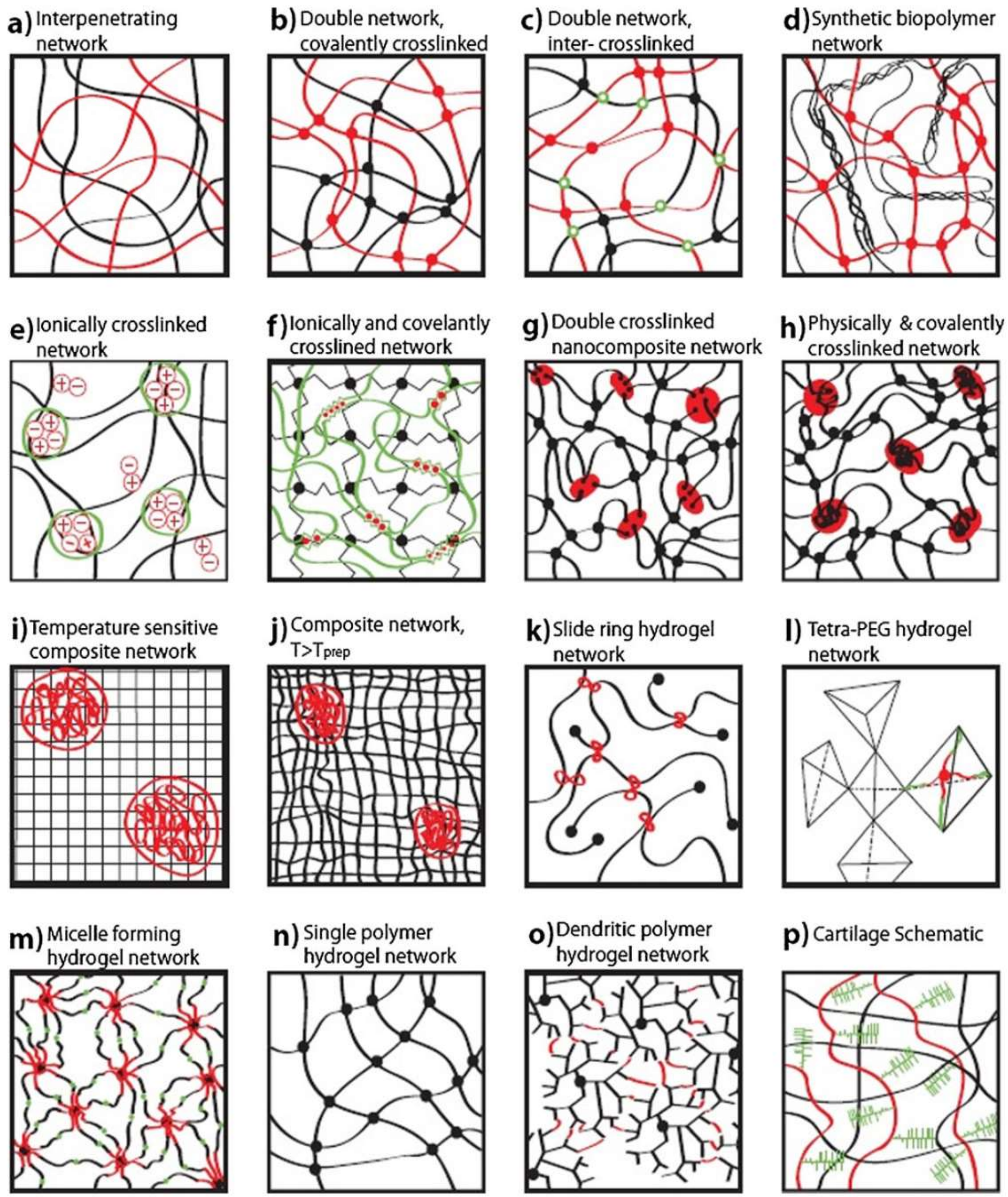
journal homepage: www.elsevier.com/locate/cis

Historical perspective

Toward the development of biomimetic injectable and macroporou
biohydrogels for regenerative medicine

Killian Flégeau[a,b], Richard Pace[a,b], Hélène Gautier[a,b], Gildas Rethore[a,b,c], Jerome Guich
Catherine Le Visage[a,b,1], Pierre Weiss[a,b,c,1]

Gel toughening?



From Peak, Wilker, et al.,
Colloid and Polymer Science, 2013

2 formulations : hydrogels or composites

Molding and
injectable material

Hydrogel alone

Or blend with Calcium phosphate ceramics

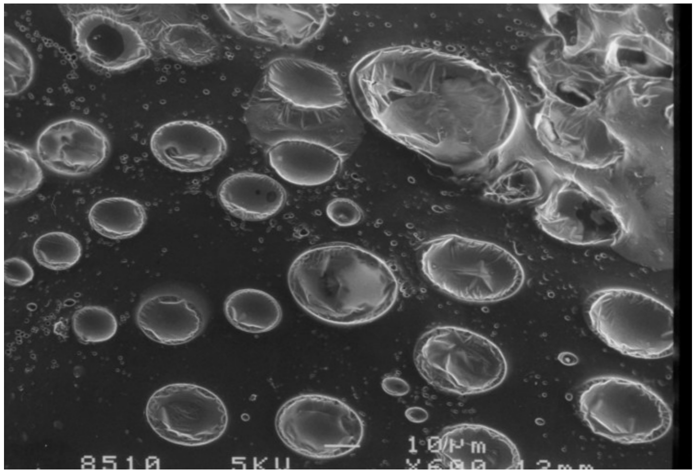
55- 80% of Hydrogel (1.5% of dry polymer in water solution (w/w)) + 20-45 % Calcium Phosphate BCP granules (40-80 µm) for Bone Tissue engineering.

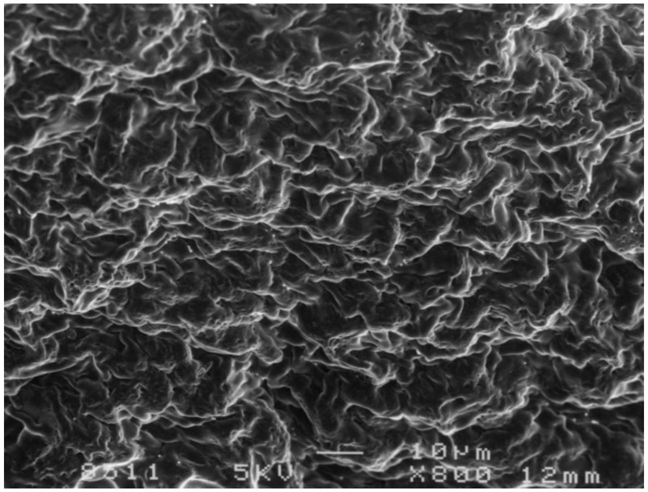
Inserm
La science pour la santé
From science to health

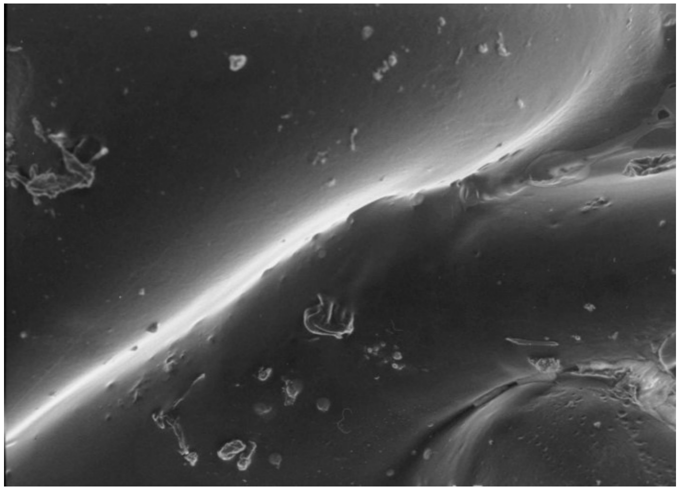
Hydrogel caracterization

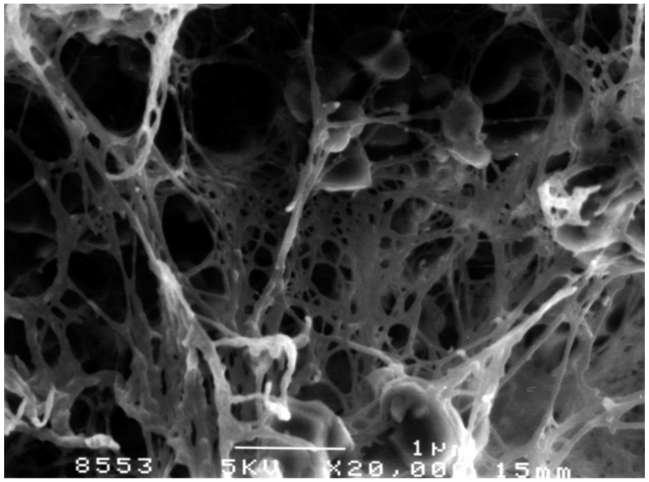
µ-characterization Platform

Same dry hydrogel by SEM

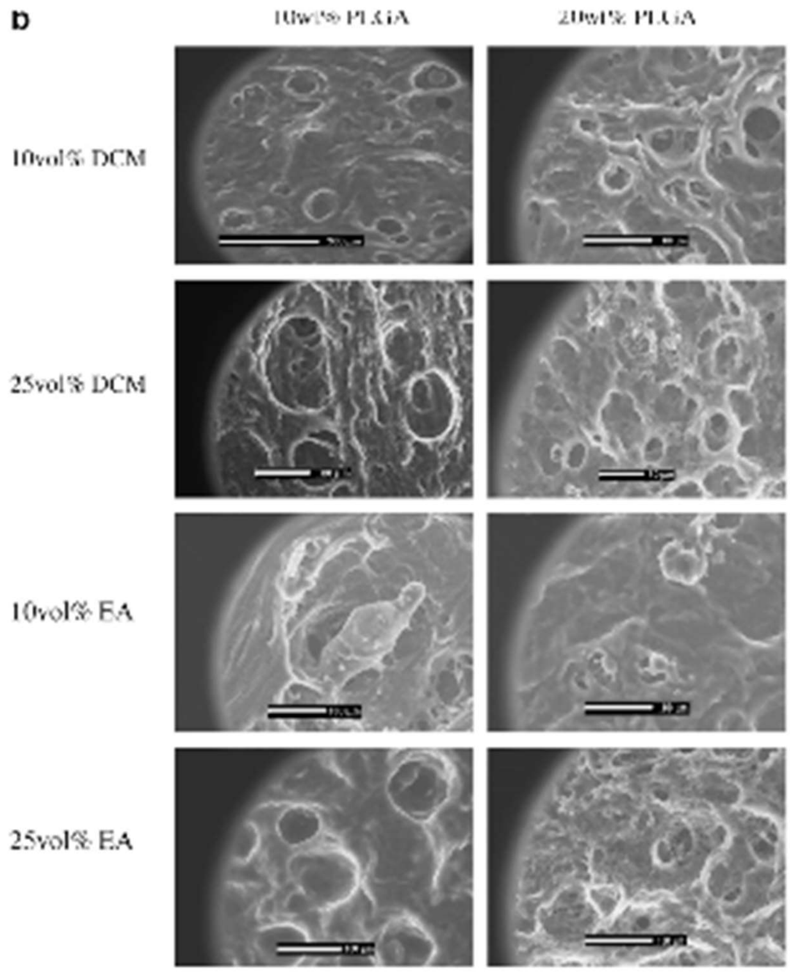






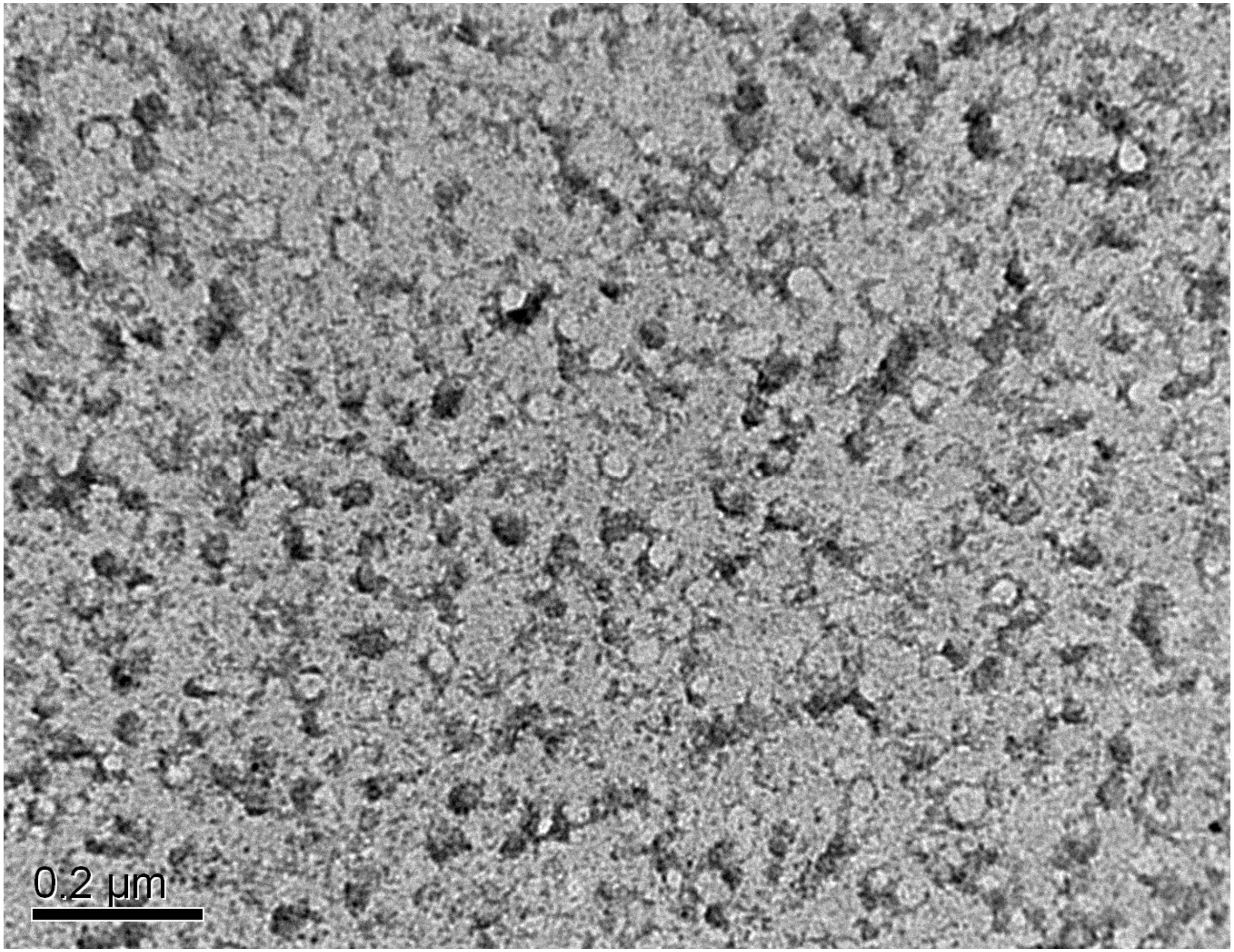


ESEM



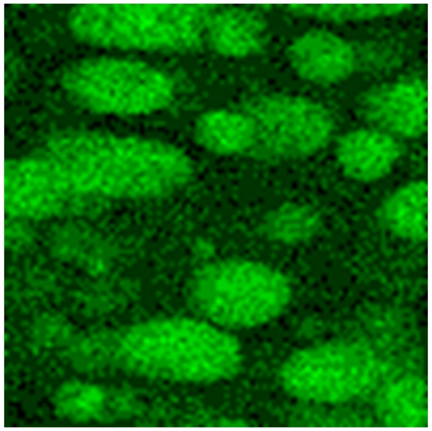
Spiller et al. Superporous hydrogels for cartilage repair: Evaluation of the morphological and mechanical properties. Acta Biomaterialia (2008) vol. 4 (1) pp. 17-25

Cryo-TEM

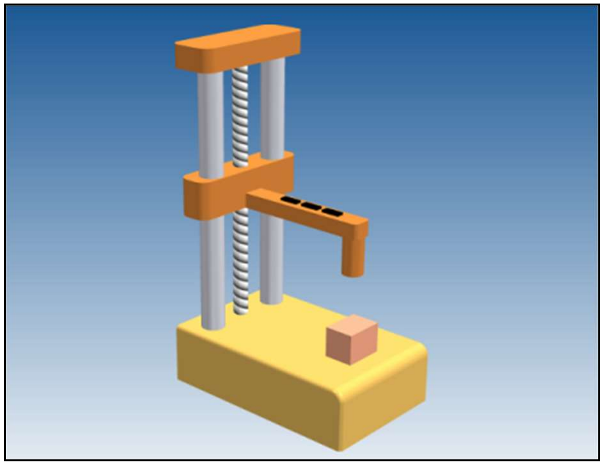


Physico-chemistry : DRX, MFTIR, Rheology, Mechanics

Methods of analysis



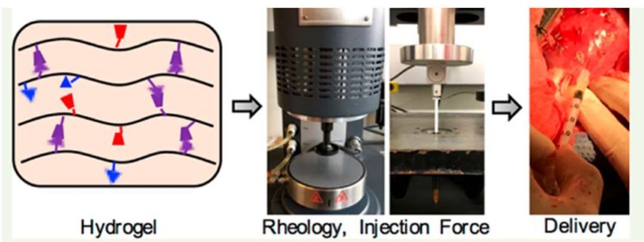
- Rheometry
  - Flow (injectability)
  - Oscillation (network)
- Mechanical measurements in compression
  - Resistance, creep, relaxation



ACS Biomaterials SCIENCE & ENGINEERING
Methods/Protocols
pubs.acs.org/journal/abseba

Methods To Assess Shear-Thinning Hydrogels for Application As Injectable Biomaterials

Minna H. Chen,[†,‡] Leo L. Wang,[†,‡] Jennifer J. Chung,[§] Young-Hun Kim,[‡] Pavan Atluri,[§] and Jason A. Burdick*,[‡]



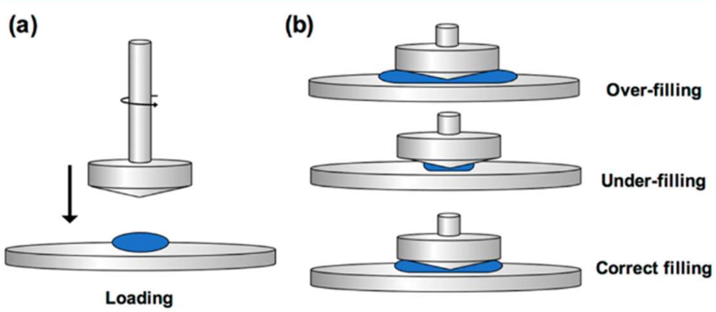


Figure 1. Hydrogel loading onto the rheometer stage. (a) When lowering the geometry onto the hydrogel, spin the geometry slightly for more even hydrogel loading. (b) Over-filling and under-filling of the sample results in increased and decreased forces, respectively. The hydrogel sample must fill the space between the geometry and the rheometer stage correctly for accurate measurements.

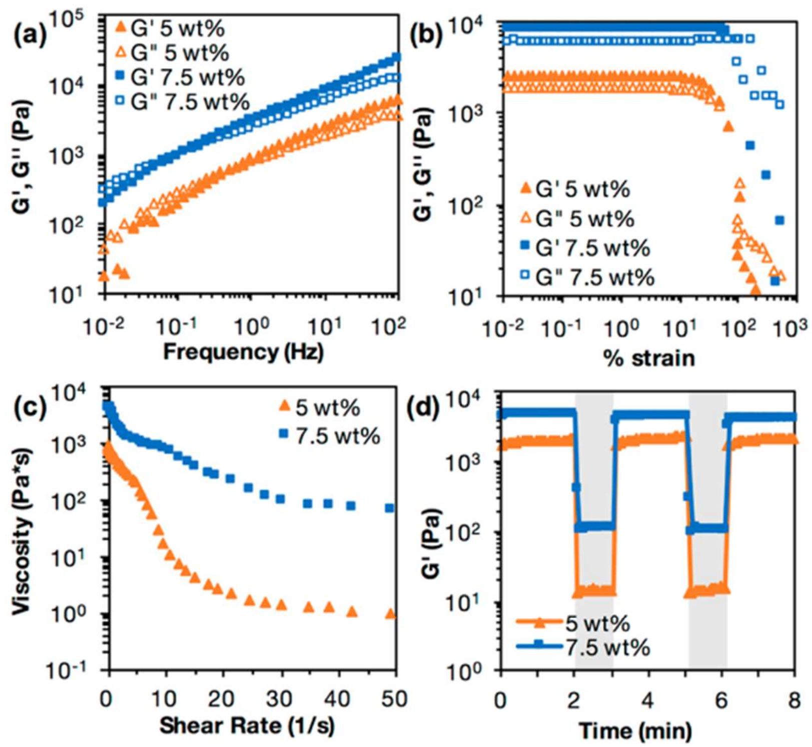


Figure 2. Results of (a) frequency sweep, (b) strain sweep, (c) continuous flow, and (d) cyclic strain time sweep rheology experiments for hydrogels of 5 and 7.5 wt % material concentration, using the described method and rheological parameters. For cyclic strain, shaded regions are high strain (500%) and unshaded regions are low strain (0.2%).

Sweling

Creep or relaxation

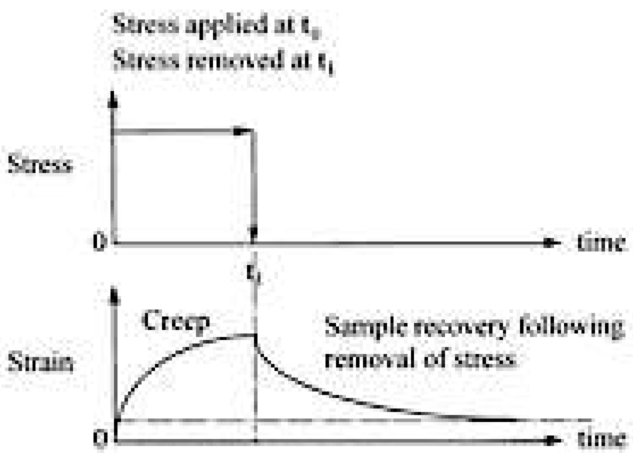


Fig. 2. Characteristic deformation (creep) of viscoelastic solids as a function of time.

Jones. International Journal of Pharmaceutics (1999) vol. 179 (2)

The equilibrium water content (EWC)

$$\mathrm{EWC} = \frac{W_s - W_d}{W_s} \times 100\%$$

Wd and Ws are, respectively, the mass of dried and swollen hydrogel

$$q = \frac{W_s}{W_d}$$

q is the equilibrium swelling ratio.

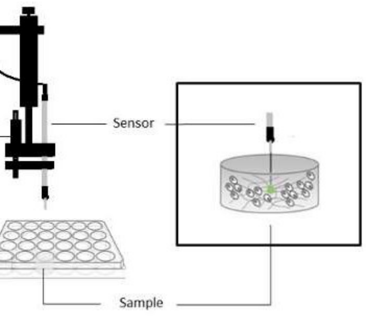
ing and Regenerative Medicine

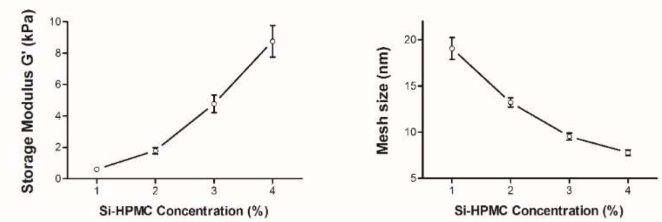
e and oxygen diffusion in hydrogels for the
f 3D stem cell scaffolds in regenerative

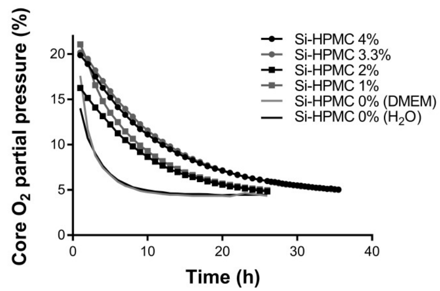
'Arros, G. Réthoré, J. Guicheux, C. Le Visage, P. Weiss

y 2018 | https://doi.org/10.1002/term.2656

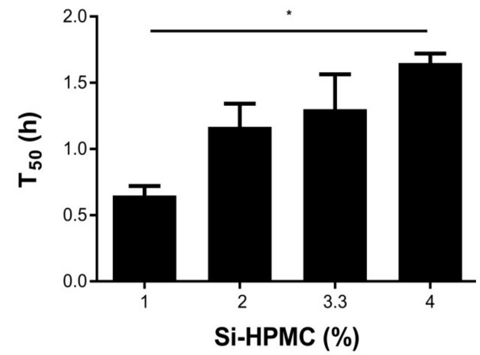
Ischemia in Hydrogels



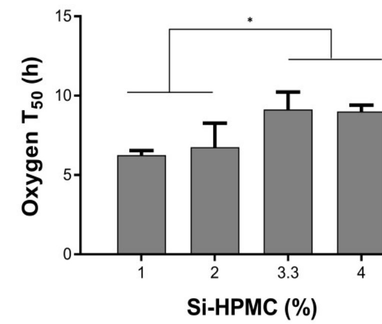




Glucose

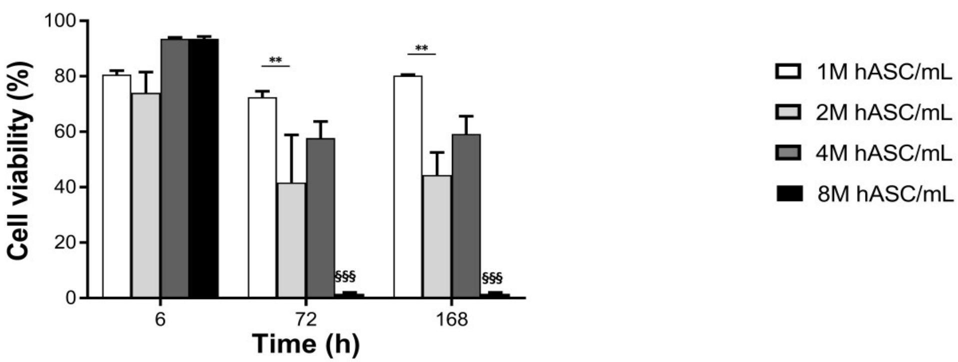


Oxygen

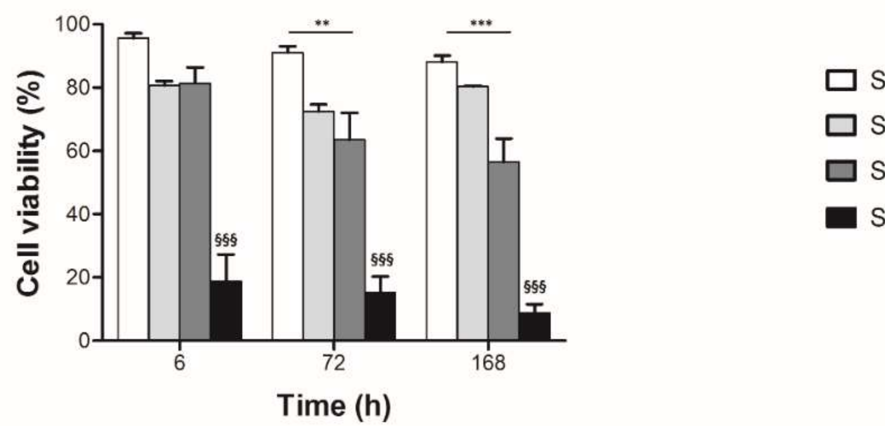


+ human adipose stem cells

2% Si-HPMC



1 M hASC/ml



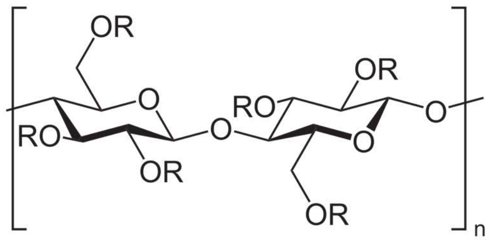
What is important ?

- No cytotoxicity
- Stiffness (G’, E’)
- Adhesion to cells
- Degradation
- Visco-elasticity (Relaxation) / Stability
- Nutrients diffusion
- Formulation and design

→Each Hydrogel construct is specific with a specific answer to cells

Silanized HPMC

➢ Hydroxypropylmethylcellulose



R = –H, –CH_3, –CH_2–CHOH–CH_3

Cellulose ether, cheap

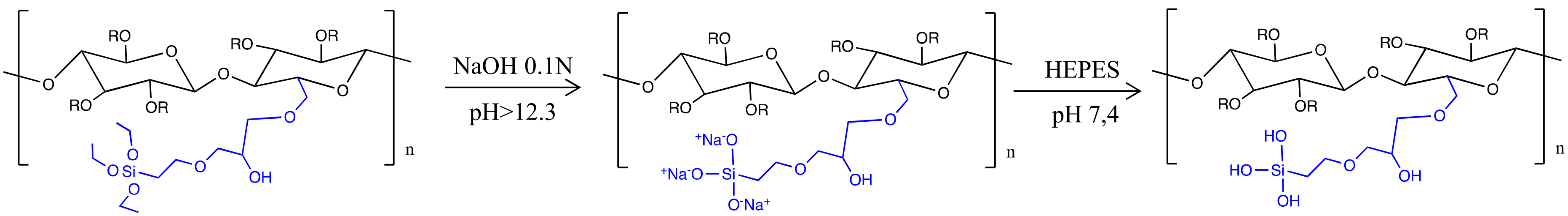
Inert

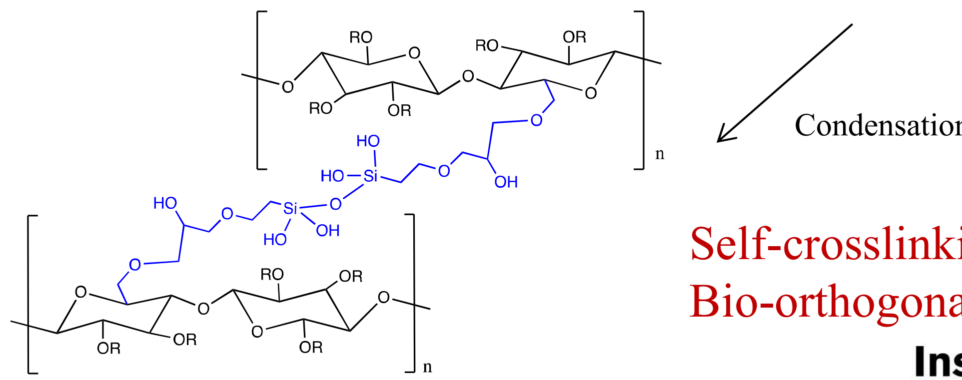
Non toxic

Common excipient,
European Pharmacopoeia grade

➢ Silanized hydroxypropylmethylcellulose

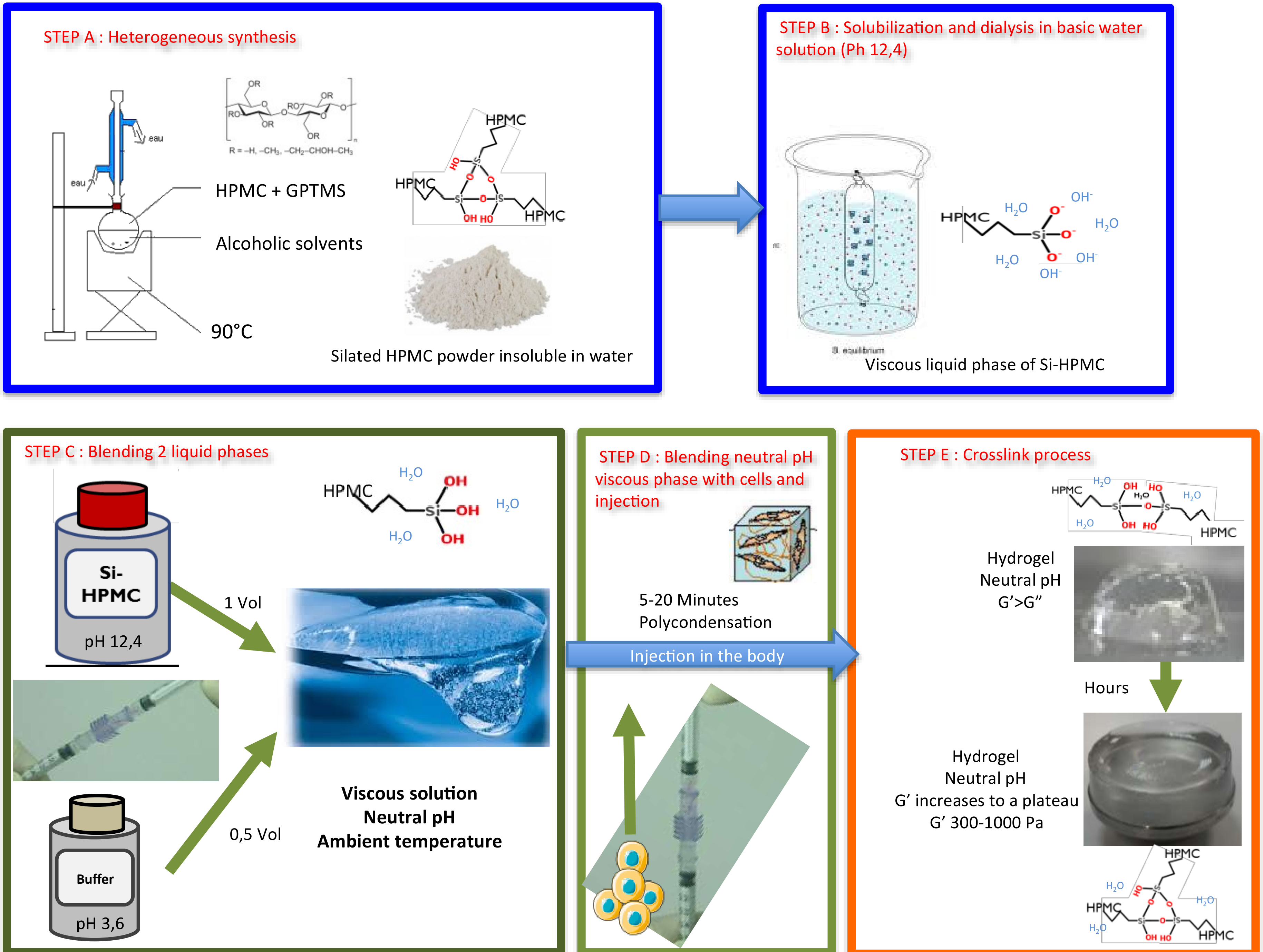
Injectable





Self-crosslinking
Bio-orthogonal

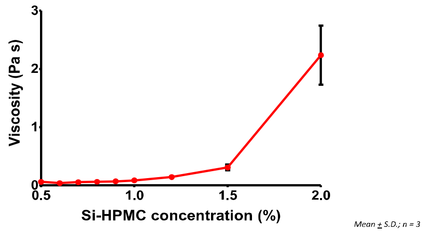
Bourges *et al.* ACIS 2002



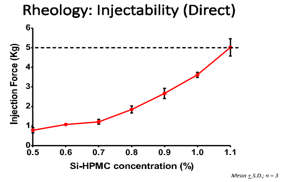
STEP A : Heterogeneous synthesis
eau
eau
R = -H, -CH3, -CH2-CHOH-CH3
HPMC + GPTMS
Alcoholic solvents
90°C
HPMC
HPMC
HPMC
Silated HPMC powder insoluble in water
STEP B : Solubilization and dialysis in basic water solution (Ph 12,4)
HPMC
H2O
OH-
H2O
H2O
OH-
OH-
Viscous liquid phase of Si-HPMC
STEP C : Blending 2 liquid phases
Si-HPMC
pH 12,4
1 Vol
HPMC
H2O
OH
OH
OH
H2O
H2O
Buffer
pH 3,6
0,5 Vol
Viscous solution
Neutral pH
Ambient temperature
STEP D : Blending neutral pH viscous phase with cells and injection
5-20 Minutes
Polycondensation
Injection in the body
STEP E : Crosslink process
HPMC
HPMC
Hydrogel
Neutral pH
G'>G"
Hours
Hydrogel
Neutral pH
G' increases to a plateau
G' 300-1000 Pa
HPMC
HPMC
HPMC

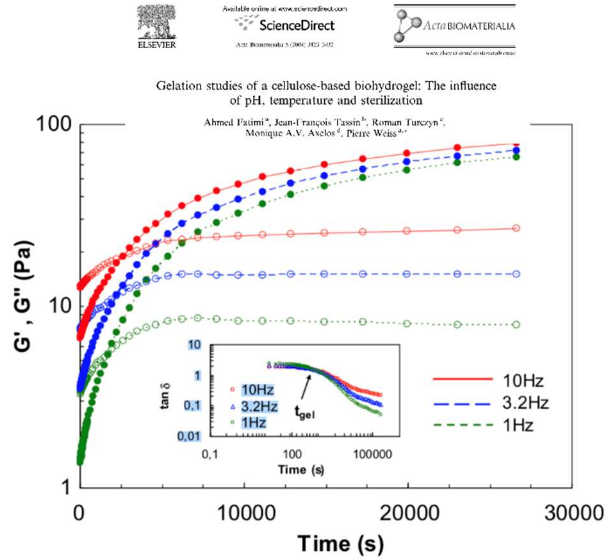
- Nantes

Rheology: Viscosity

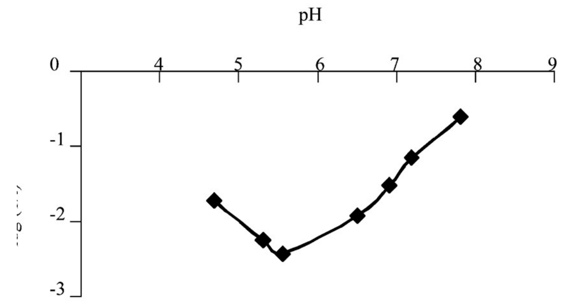


Rheology: Injectability (Direct)



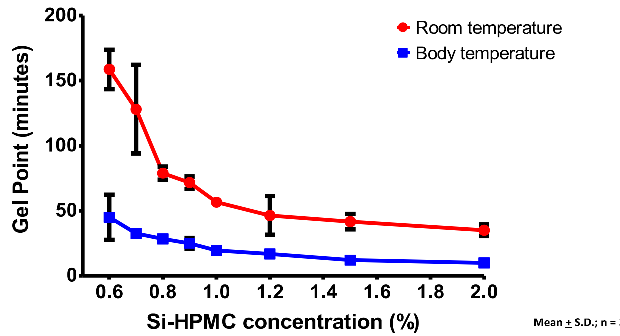


Time evolution of G'(closed symbols) andG''(open symbols) at25°C for Si-HPMC (3%) hydrogel at pH 7.4. Three frequencies wereapplied (1, 3.2 and 10 Hz) at a fixed total shear stress (1 Pa). The tandisshown in the inset vs. the frequency for Si-HPMC hydrogel where gel time(tgel) is indicated.

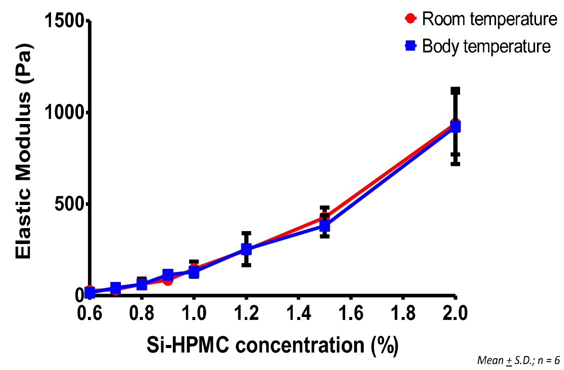


Representation of the self-hardening kinetics of P(6)3% 0.05 M in function of the pH.
X. Bourges et al. / Advances in Colloid and Interface Science 99 (2002) 215–228

Rheology: Gel-Point



Rheology: G'



G.Pattapa, ANR Anthos

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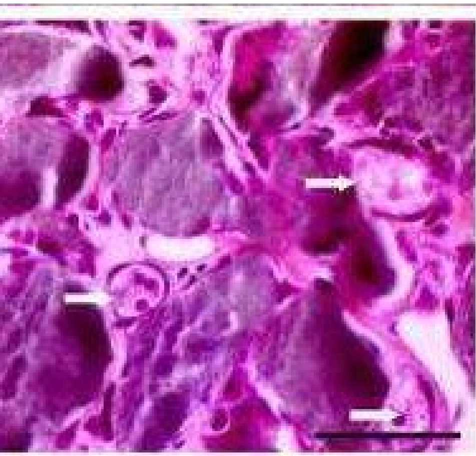
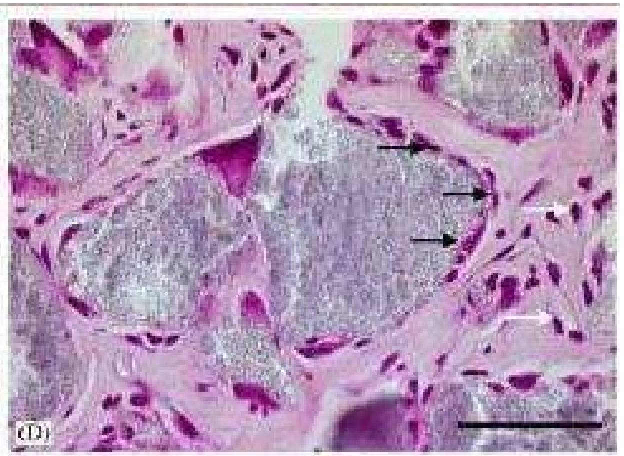
Bone Tissue reconstruction *in vivo*

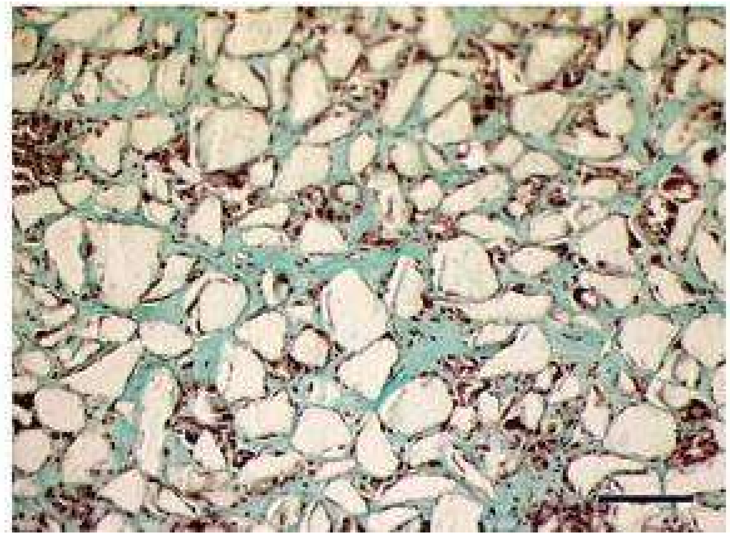
BMSC with Si-HPMC / BCP formulation implanted under skin of mice for 4 weeks



Blood vessels



Osteoblasts and osteocytes



Goldner staining paraffin sections

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Biomaterials 27 (2006) 3256–3264

Biomaterials

www.elsevier.com/locate/biomaterials

bone formation using an injectable biphasic calcium
sphate/Si-HPMC hydrogel composite loaded with
undifferentiated bone marrow stromal cells

jani[a,b], Florian Boukhechba[a], Jean-Claude Scimeca[a], Fanny Vandenbos[c],
François Michiels[c], Guy Daculsi[d], Pascal Boileau[b], Pierre Weiss[d],
Georges F. Carle[a], Nathalie Rochet[a,*]

Ectopic bone formation
was available in mice model using TE strateg
With Si HPMC and BCP granules and MSC

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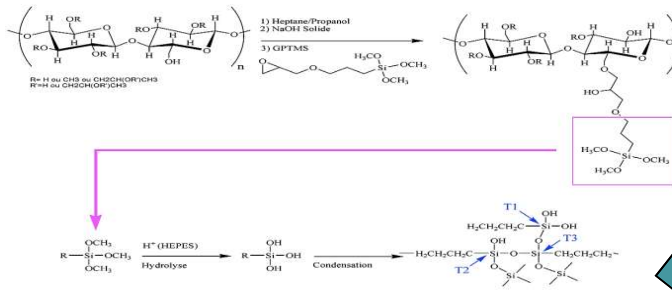
How to reinforce hydrogels?

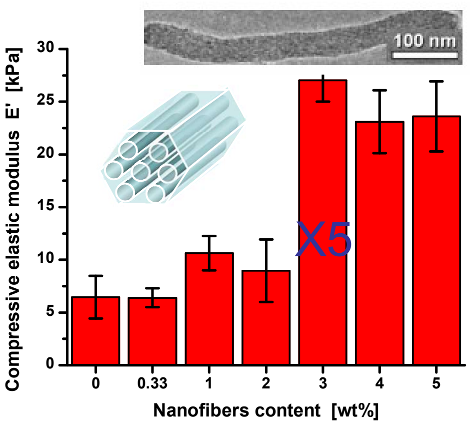
Characterization



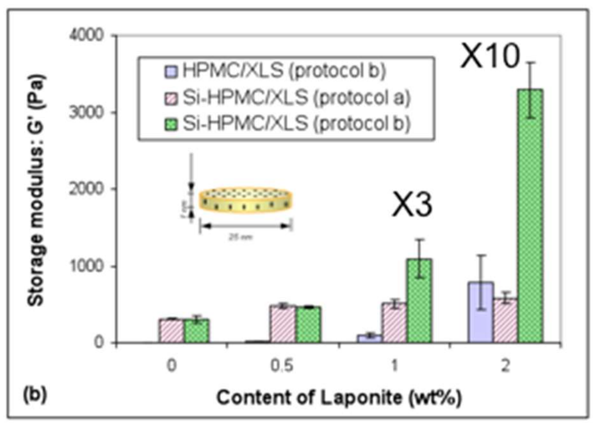
Nano reinforcement

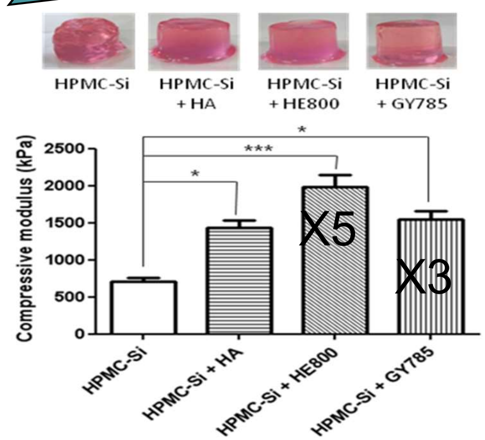
Marine macromolecules blended with SiHPMC

silica nanofibers (NFs)



Laponite (silicate clays)





N. Buchtová,

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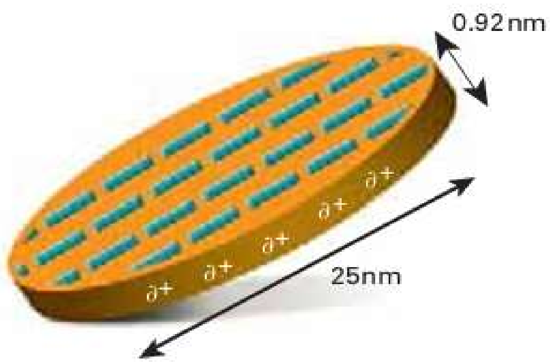
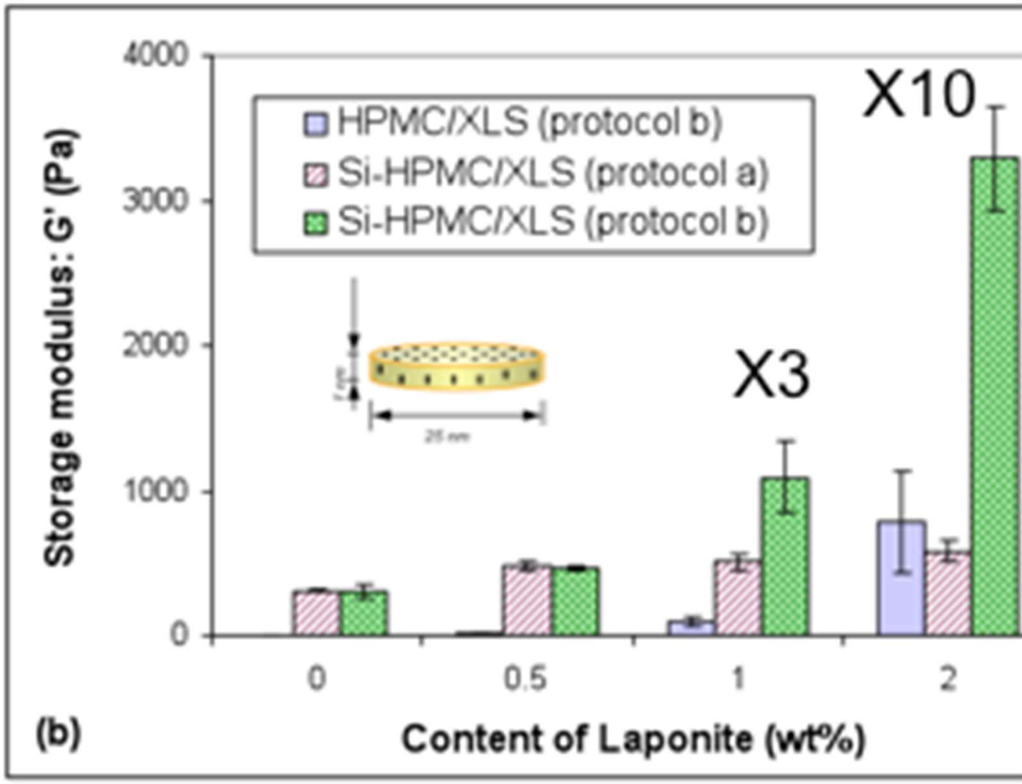
Laponites (XLS et XLG)

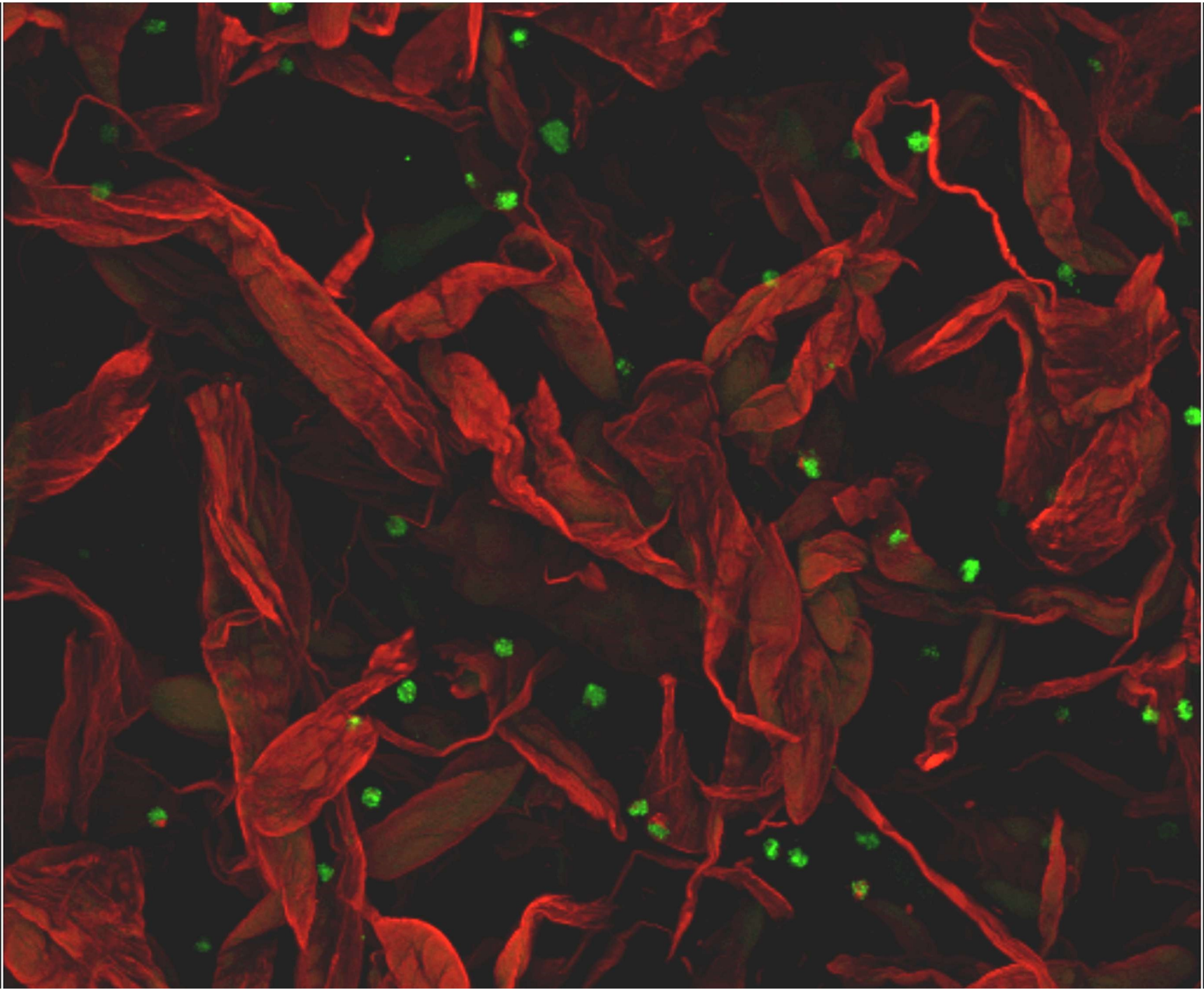
Clay nano disc
Silicate based
Diameter : 25 nm
Thickness : 1 nm



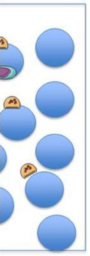
XLS 55% silicate, 26% MgO, 1% LiO, 3% Na_2O, 4% H_3I
XLG 60% silicate, 28% MgO, 1% LiO, 3% Na_2O.

Laponite (silicate clays)

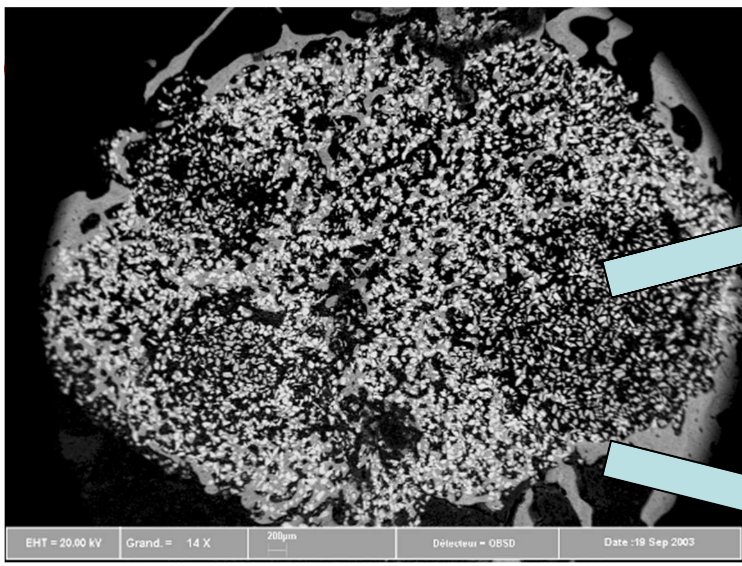


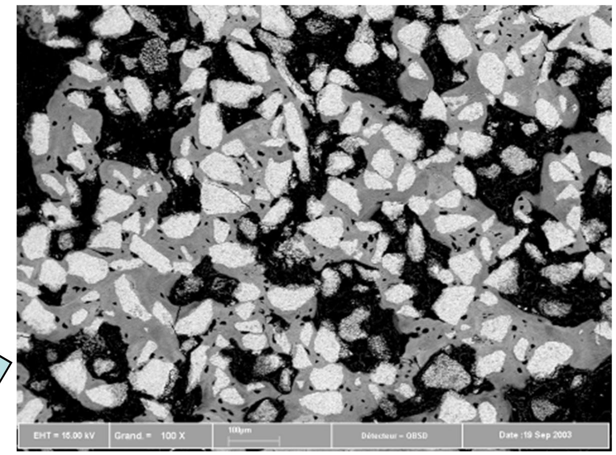


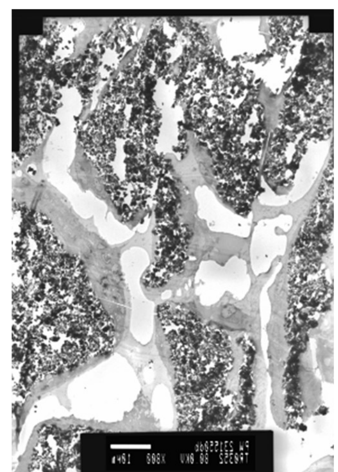
Granule suspension in a self setting hydrogel matrix

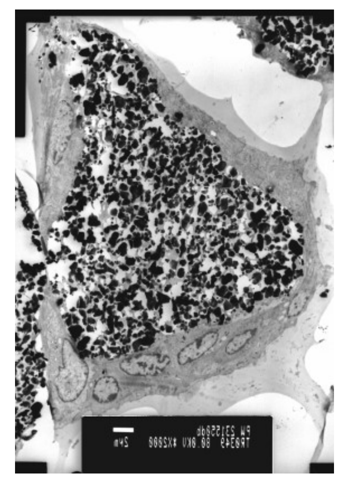


BCP ceramic granules are the scaffold
→ Like CPS : against leakage







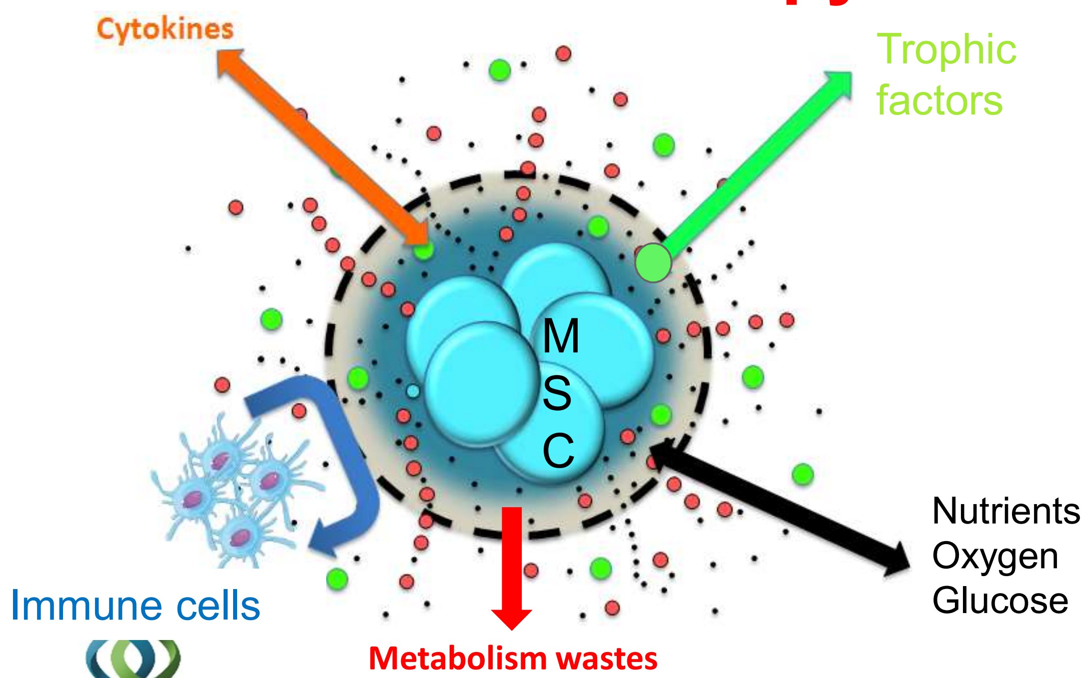


Fellah BH, Weiss P, Gauthier O, Rouillon T, Pilet P, Daculsi G, et al. Bone repair using a injectable self-crosslinkable bone substitute. J Orthop Res. 2006 Apr;24(4):628-35.

→ Cross-linked Hydrogel can decrease the bone ingrowth kinetic → To control network degradation
→ NEW SILATED MACROMOLECULES…..

NEW WAYS OF RESEARCH

Embedded MSC in hydrogel for
assisted cell therapy



« IXBONE »
ANR Program

Hindawi

, 11 pages
3598

le

e Hydrogels Support the Long-Term Viability of
Human Mesenchymal Stem Cells and Their Ability to
nomodulatory Factors

,[1,2] Claire Vinatier,[1,3] Pierre-Gabriel Pinta,[1,4] Philippe Hulin,[5]
Visage,[1,3] Pierre Weiss,[1,3,6] Jérôme Guicheux,[1,3,6]
-Chabaud,[1,2] and Gaël Grimandi[1,2,4]

Assisted cell therapies use hydrogels to fix cells in the tissue and act as a shield to protect MSC from immune system and allowing them to feel the environment and secrete growth factors.

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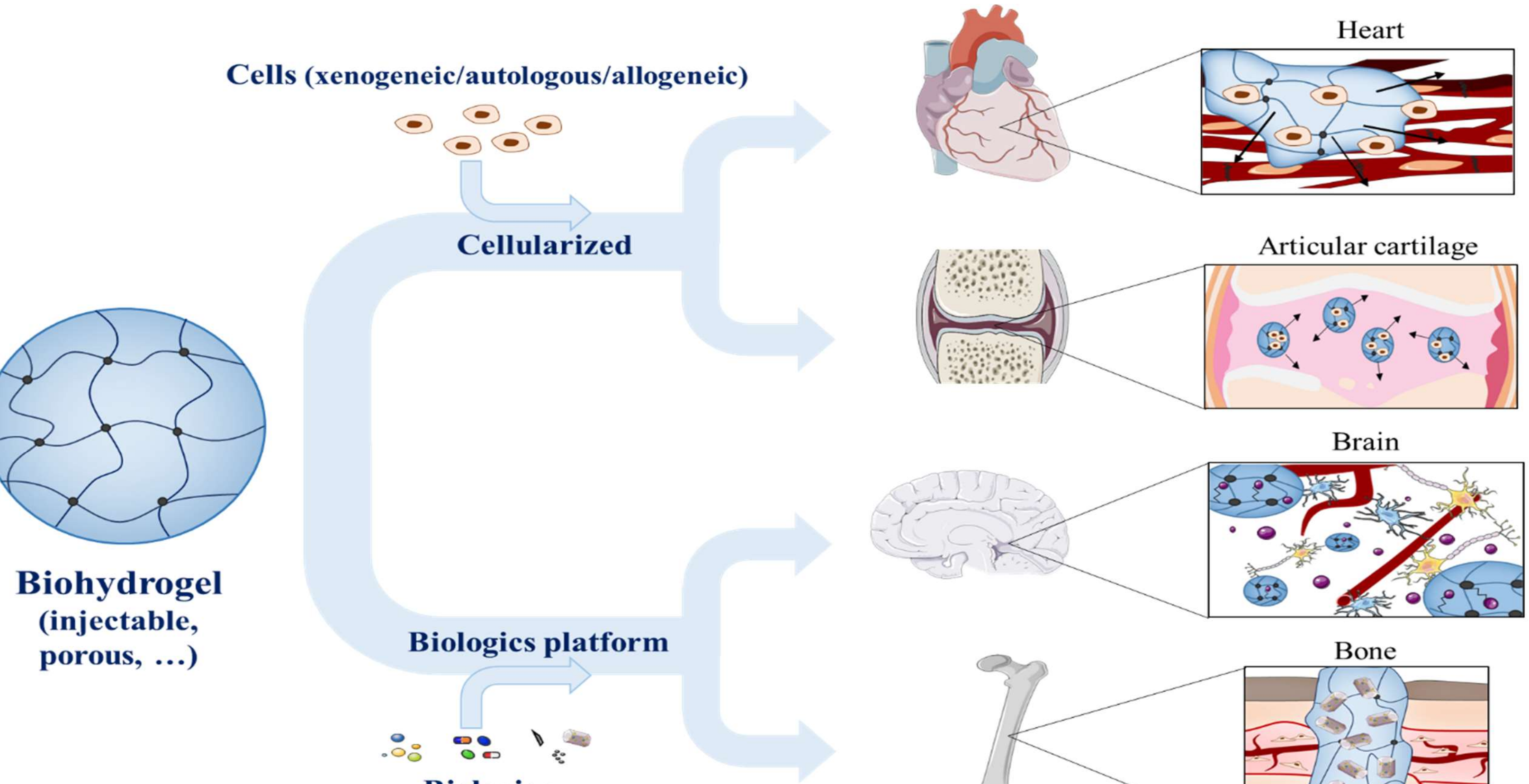
S
- Nantes

Na
Ur

ain strategies used in regenerative medicine using cells and/or biologics to drive local tissu regeneration.



Cell T-E

Assisted
cell therapy

DDS

DDS
Hydrogels
+ BMP2

Advances in Colloid and Interface Science 247 (2017) 589–609

Contents lists available at ScienceDirect

Advances in Colloid and Interface Science

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

ment of biomimetic injectable and macroporous
enerative medicine

Pace[a,b], Hélène Gautier[a,b], Gildas Rethore[a,b,c], Jerome Guicheux[a,b,c,*],
ierre Weiss[a,b,c,1]

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RÉPUBLI
FRANÇA

Hydrogel/cement Composites

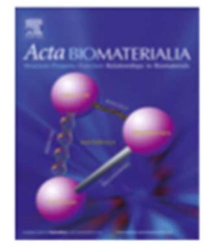
Hydrogel with calcium phosphate cements

Acta Biomaterialia 31 (2016) 326–338

Contents lists available at ScienceDirect

Acta Biomaterialia

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



Full length article

A simple and effective approach to prepare injectable macroporous calcium phosphate cement for bone repair: Syringe-foaming using a viscous hydrophilic polymeric solution

Jingtao Zhang [a,b,1], Weizhen Liu [a,b,1], Olivier Gauthier [c], Sophie Sourice [a], Paul Pilet [a,e], Gildas Rethore [a,e], Khalid Khairoun [a], Jean-Michel Bouler [d], Franck Tancret [b], Pierre Weiss [a,e,*]

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Making Foam CPC

Acta Biomaterialia 31 (2016) 326–338

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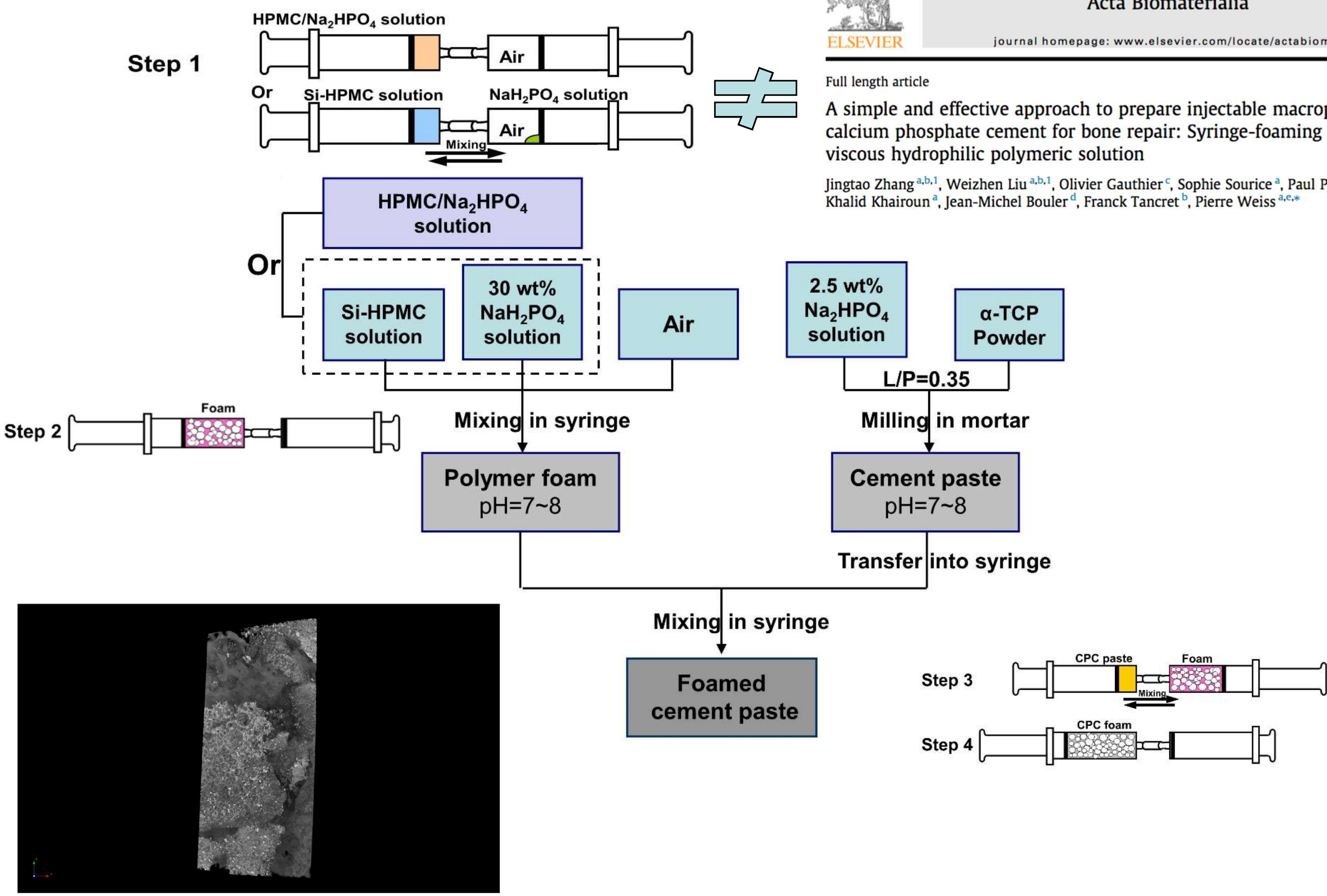
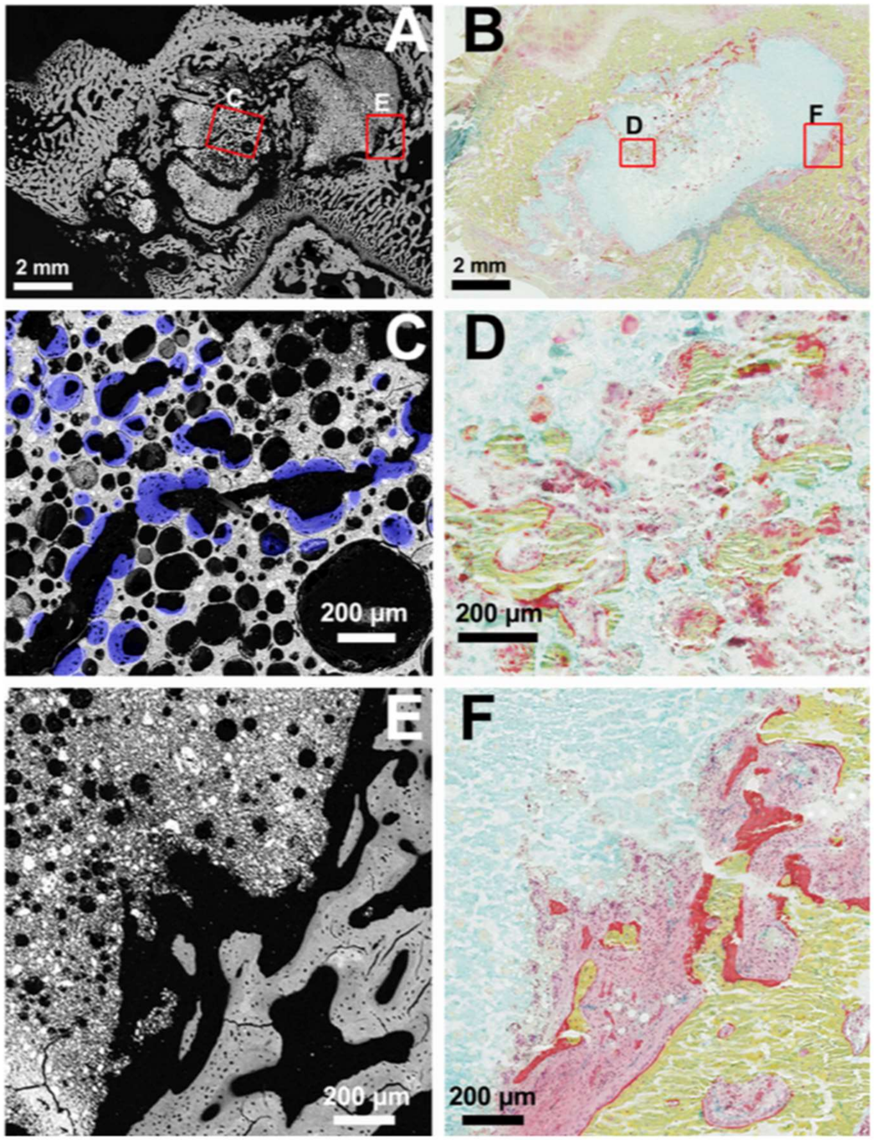
Full length article

A simple and effective approach to prepare injectable macroporous calcium phosphate cement for bone repair: Syringe-foaming using a viscous hydrophilic polymeric solution

Jingtao Zhang[a,b,1], Weizhen Liu[a,b,1], Olivier Gauthier[c], Sophie Sourice[a], Paul Pilet[a,e], Gildas Rethore[a,e], Khalid Khairoun[a], Jean-Michel Bouler[d], Franck Tancret[b], Pierre Weiss[a,e,*]



First biological behavior



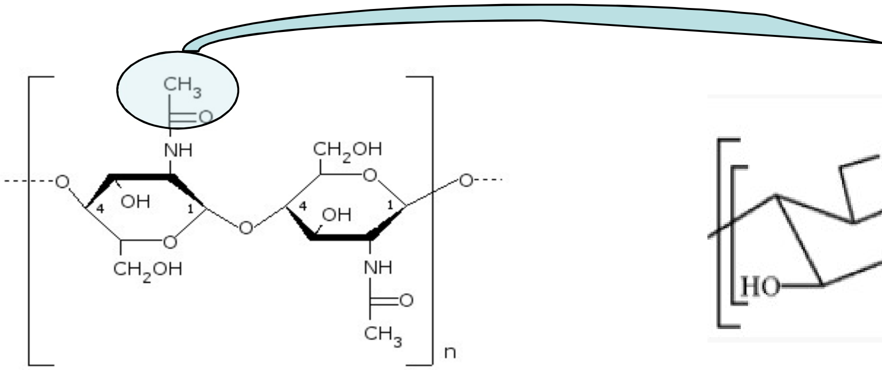
SI-HPMC Foamed CPC implanted
in distal end of rabbit femur
Six weeks of implantation

Good osteo condution
in some areas C D

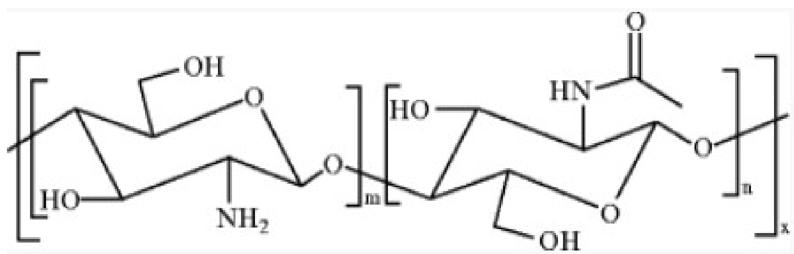
But not always (E,F)

Silated HPMC is low degradable
→ We need to develop higher degradable Silated polysaccharides

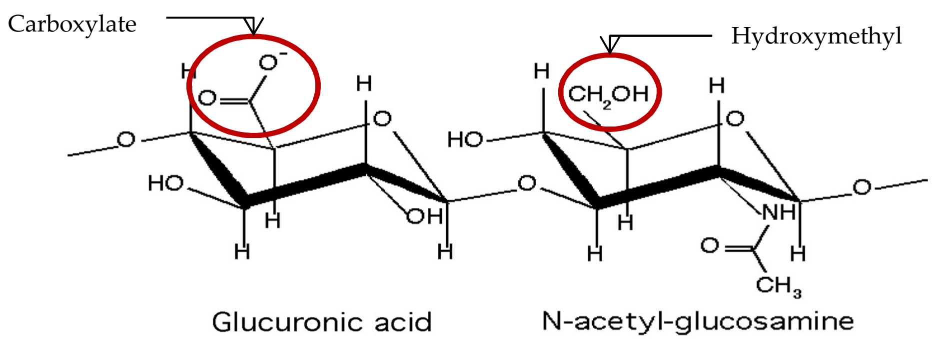
Move to other silated polysacharides



Chitine

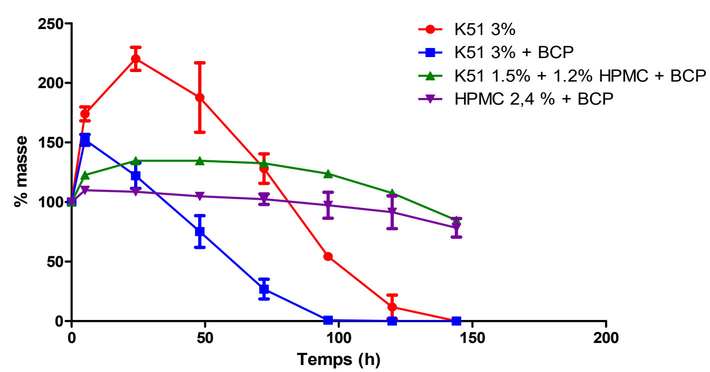


Chitosan



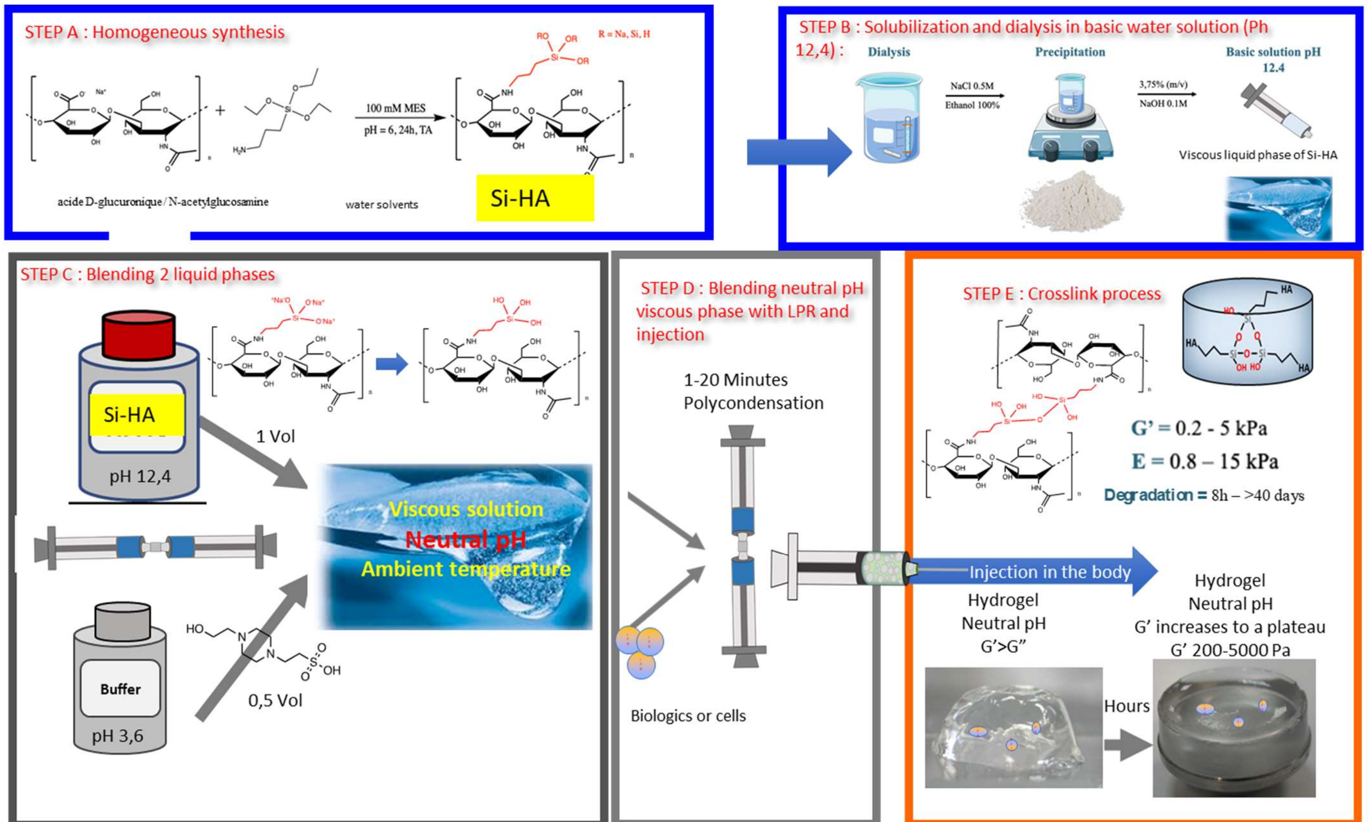
Hyaluronic acide

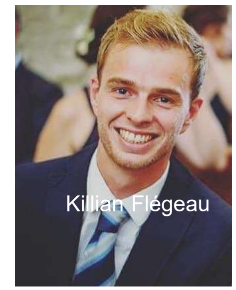
Degradation profile



Killian Flégeau

Silated Hyaluronic acid : a versatil self-cross linking hydrogel platform for regenerative medicine





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ng, Silanized Hyaluronic Acid Hydrogels with Over Mechanical Properties and In Vivo for Tissue Engineering Applications

*re Toquet, Gildas Rethore, Cyril d'Arros, Léa Messager, Boris Halgand, nt Autrusseau, Julie Lesoeur, Joëlle Veziers, Pascal Bordat, ôme Guicheux, Vianney Delplace, Hélène Gautier, and Pierre Weiss**

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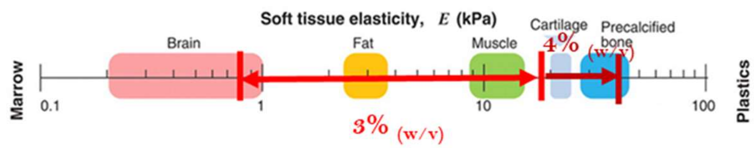
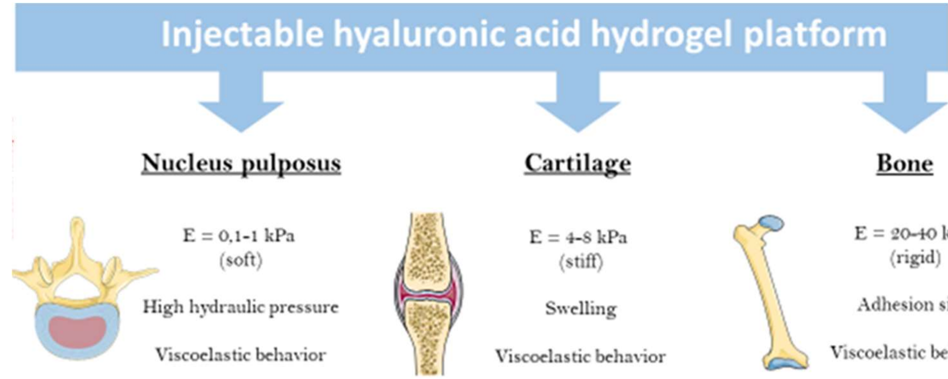
Silated Hyaluronic acid : a versatil self-cross linking hydrogel platform for regenerative medicine

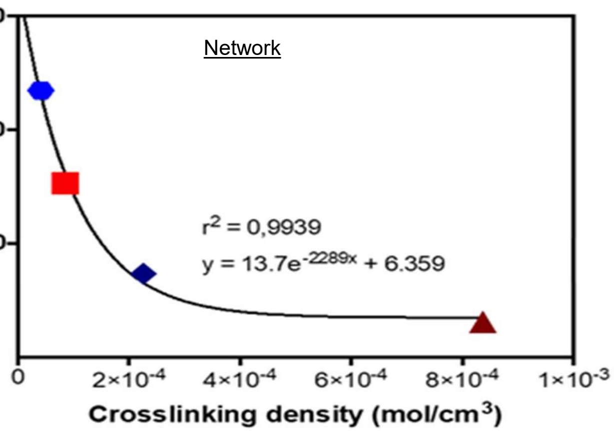


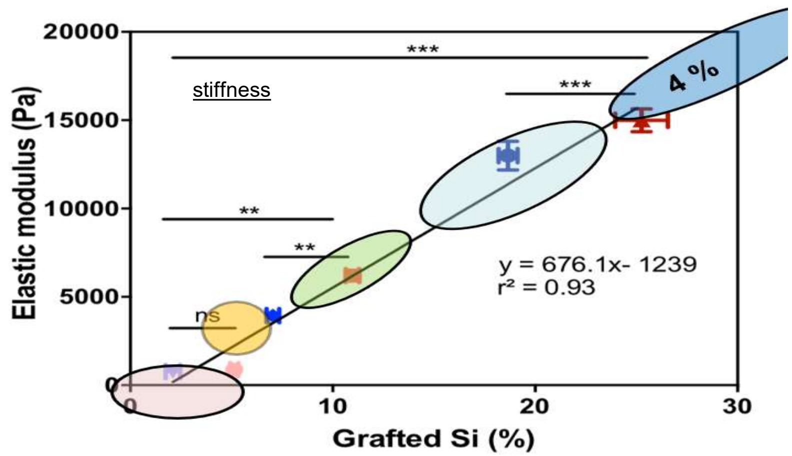
Discher *et al.* Science, 2009

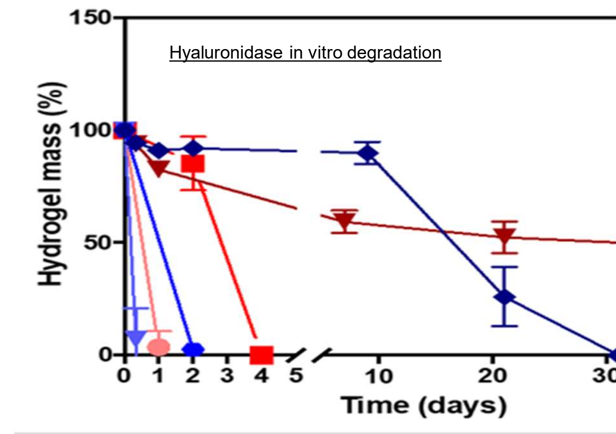


420 kDa

2.88 MDa

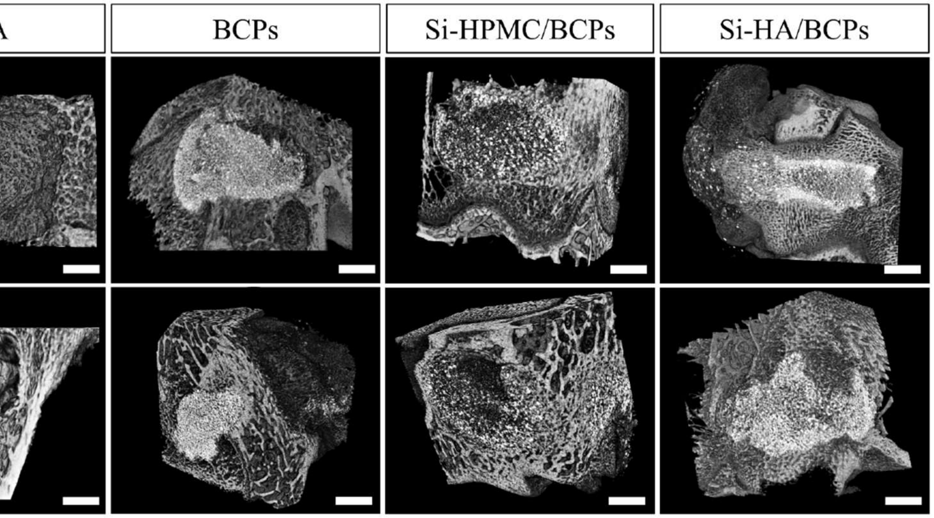


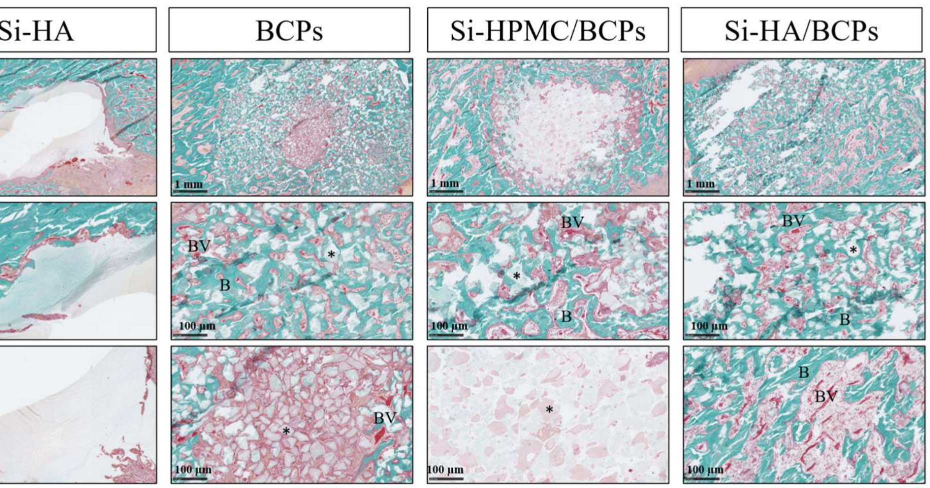




Tunable properties for each targeted tissues

Silated Hyaluronic acid with Biphasic Calcium Phosphate granules in a rabbit bone defect





ARTICLE

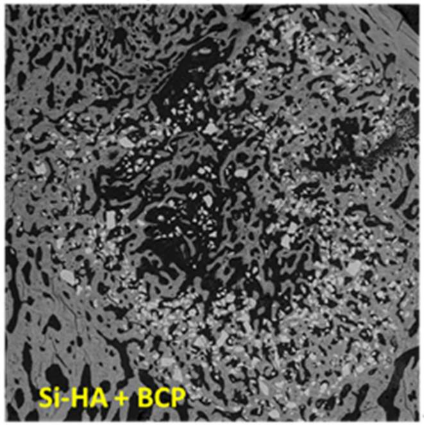
Received 00th January 20xx,
Accepted 00th January 20xx

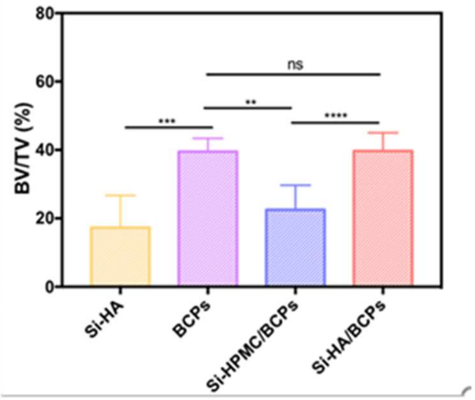
DOI: 10.1039/x0xx00000x

Injectable Silanized Hyaluronic Acid Hydrogel/Biphasic Calcium Phosphate Granule Composites with Improved Handling and Biodegradability Promote Bone Regeneration in Rabbits

Killian Flegeau[1,2,6], Olivier Gauthier[1,2,8], Gildas Rethore[1,2,3], Florent Autrusseau[1,2,7], Aurélie Schaefer[1,2,5], Julie Lesoeur[1,2,5], Joëlle Veziers[1,3,5], Anthony Brésin[6], Hélène Gautier[1,2,4], Pierre Weiss*[1,2,3].

SEM : Not published data





- Bone ingrowth
  - Si-HA + BCPs ≃ BCP alone
  - > Si-HPMC that is low degradable

Move to CaP Foam and **BioInks**

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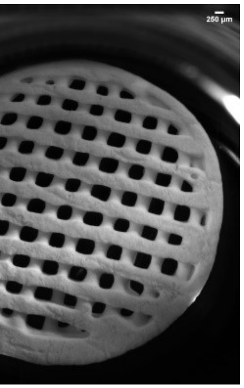
DEVELOPMENT OF A PRINTABLE COMPOSITE FORMULATION OF PHOSPHOCALCIC CEMENT AND HYALURONIC ACID FOR CLEFT LIP AND PALATE REPAIR

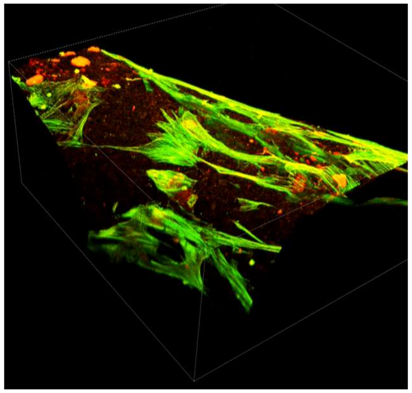
3D refentine

Marie-Michèle Germaini [1]; Pierre Weiss[1]; Sofiane Belhabib[2]; Sofiane Guessasma[3]; Remi Deterre[2]; Helene Gautier[1];
Steven Nedellec[1]; Boris Halgand[1]; Joëlle Veziers[1]; Thierry Rouillon[1]; Pierre Corre[1] and Valérie Geoffroy[1]

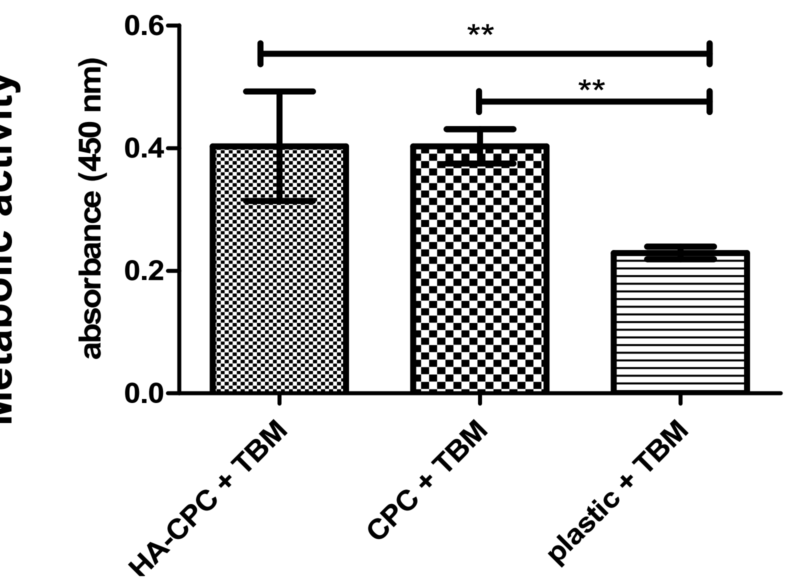
[1] Inserm, UMR 1229, RMeS, Regenerative Medicine and Skeleton, Université de Nantes, ONIRIS, Nantes, F-44042, France
[2] Laboratoire GEPEA, UMR CNRS 6144, Université - IUT de Nantes, avenue du Professeur Jean Rouxel, 44475 Carquefou Cédex, France.
[3] INRAE, laboratoire BIA, rue de la Géraudière 44316 Nantes

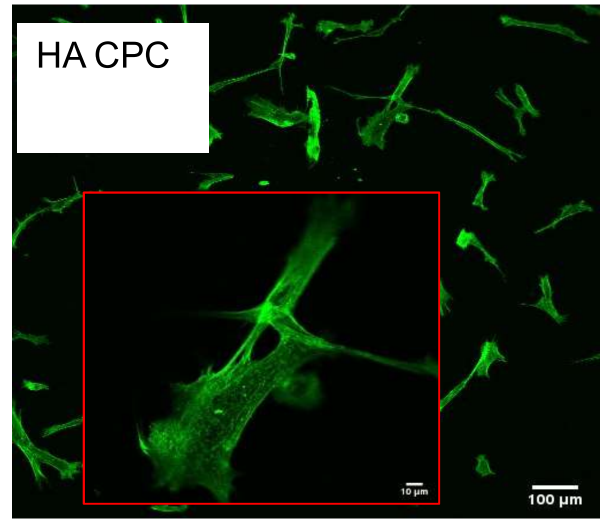
Mesenchymal Stem Cells adhesion

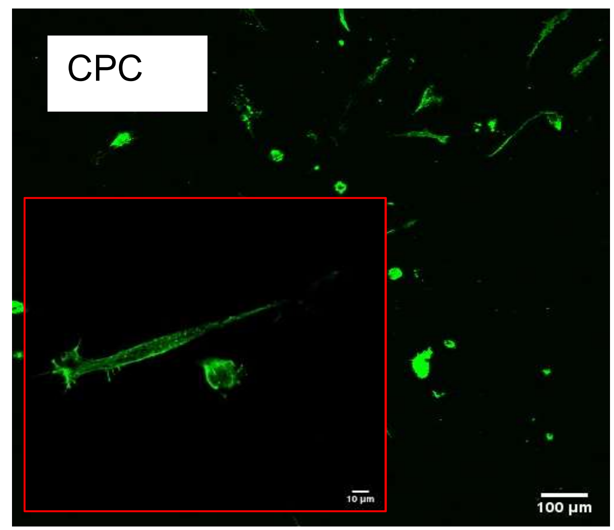




ation of cells inside the 3D model since 48h of culture

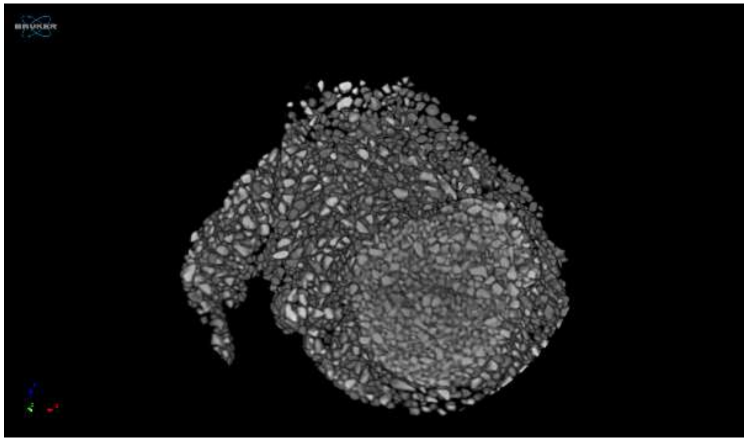




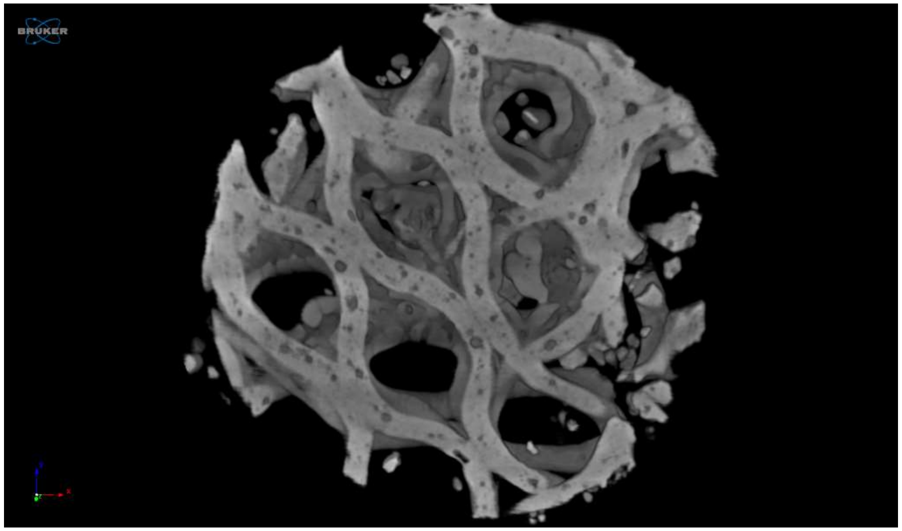


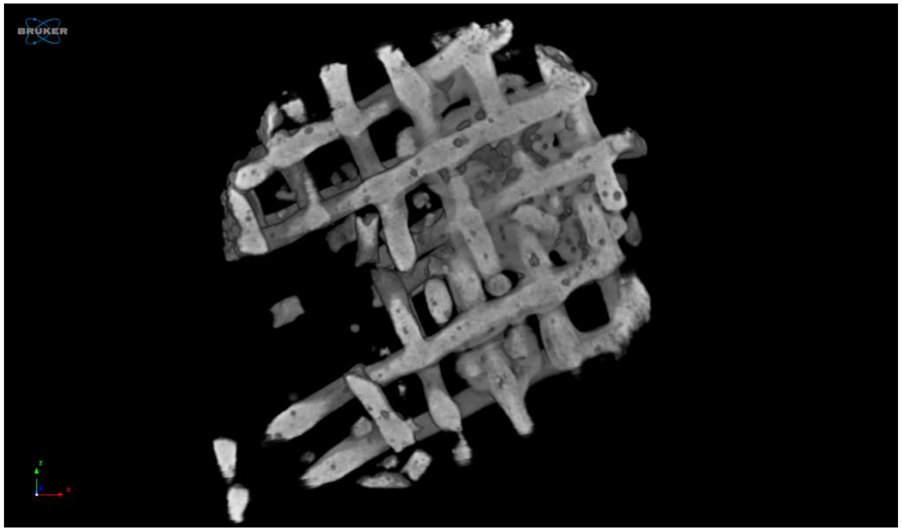
Better spreading of cells on HA-CPC after 48h of culture

HA TCP cement+ Total Bone Marrow



Nude mice : subcutaneous implantation 4 months



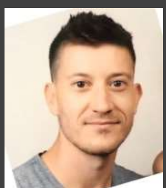


New Bone formation with TBM but the construct is still fragile

We move to Silated covalent hydrogels in the cements : GI JAW program

er

m



Arnaud

Pierre

Maéva

Pierre

Léna

hierry

and more…!

ANR GI-JAW

Bench to bedside translational research

→ Innovative solutions for personallized care of cleft deformities

But… what are cleft palate / lip deformities?

- Congenital deformity: 2nd most common malformation after clubfoot
- Occurrence : 1/700 birth

Is alveolar cleft reconstruction still controversial? (Review of literature) 10.1016/j.sdentj.2015.01.006

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GI-JAW Timeline

Feedback loop

Formulation
- Inorganic phase
  - *CaP*
  - *MgP*
- Hydrogel
  - *Physical*
  - *Chemical*

Ink characterization
- Rheology
- Printability
- Cohesivity
- Setting time
- Inorganic phases evolution
- …

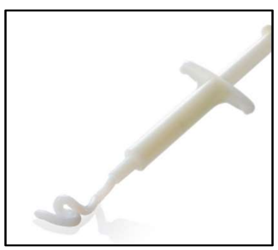
***In vitro* assays**
- Cytotoxicity
- Cell adhesion
- Proliferation
- Differentiation

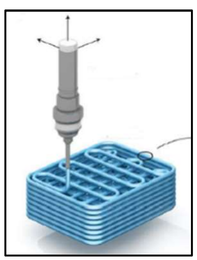
***In vivo* assays: small animal**
- Bone regeneration
- Angiogenesis
- Scaffold biodegradation
- …

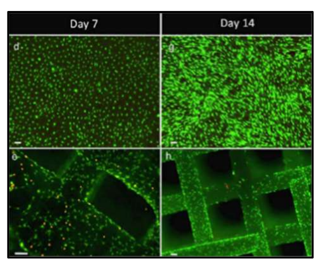
2022

Dogs as PATIENTS
- Repair of alveolar cleft in ''dogs''

2022-2023







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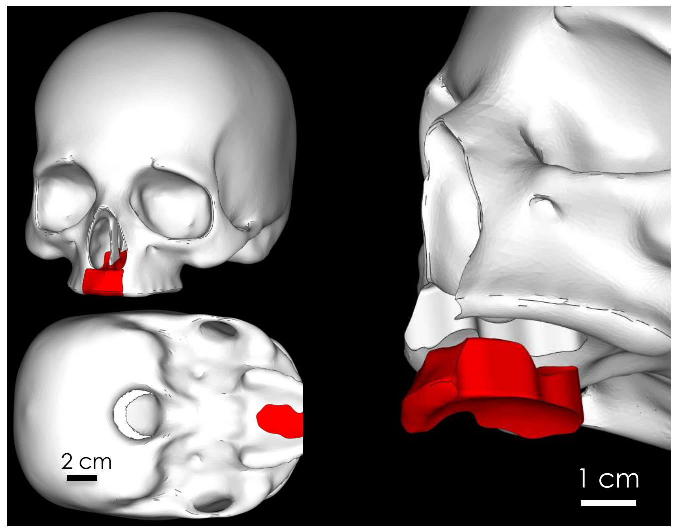
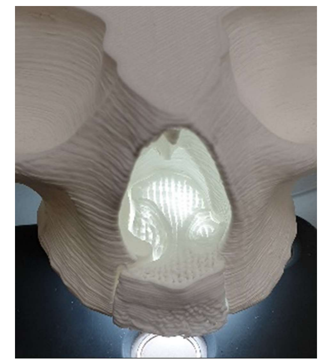
GI-JAW: Starting point

Scaffolds

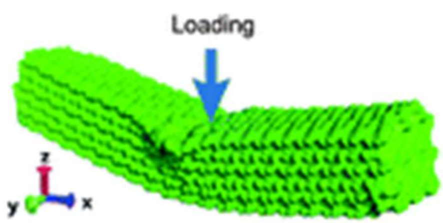
- Tailorable (compositon, shape) ☑
- Biologically relevant scaffolds ☑
- Ductile until drying☑
- Cell/substance friendly process ☑
- Large scaffolds ☑





Insertion of implants 15% larger

Deformable (<u>plastic</u>) scaffolds for a few days @ ambient temperature / hygrometry after AM



Summary

- Hydrophilic polymer with Calcium phosphate was the beginning of injectable bone substitutes
- We moved to hydrogels for the control of the leakage, make macroporosity i... cements
- Hydrogel allows us to embedded cells and we moved to tissue engineering
- Now, most of our applications are focus on assisted cell therapies using hydrogels to fix cells in the tissue and act as a shield to protect MSC from immune system and allowing them to feel the environment and secrete grow... factors.
- ...lrogels / cells interactions in 3D is multifactorial →Each Hydrogel chemistry design is specific with a specific answer to cells and a specific application
- Now we move to personalysed medicine using Additing manufacturing of ...ride bio ink for bone reconstructions and TE

ACKNOWLEDGEMENTS

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Accélérateur de progrès médical

agence de la biomédecine

BIOREGATE
EUROPEAN REGENERATIVE MEDICINE

l'esprit grand ouvert
Région PAYS DE LA LOIRE

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

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A. SOUEIDAN, A. GAUDIN, G RETHORE)

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O. GAUTHIER

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Union des Blessés de la Face et de la Tête
Fondation des "Gueules Cassées"

THANK YOU

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

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