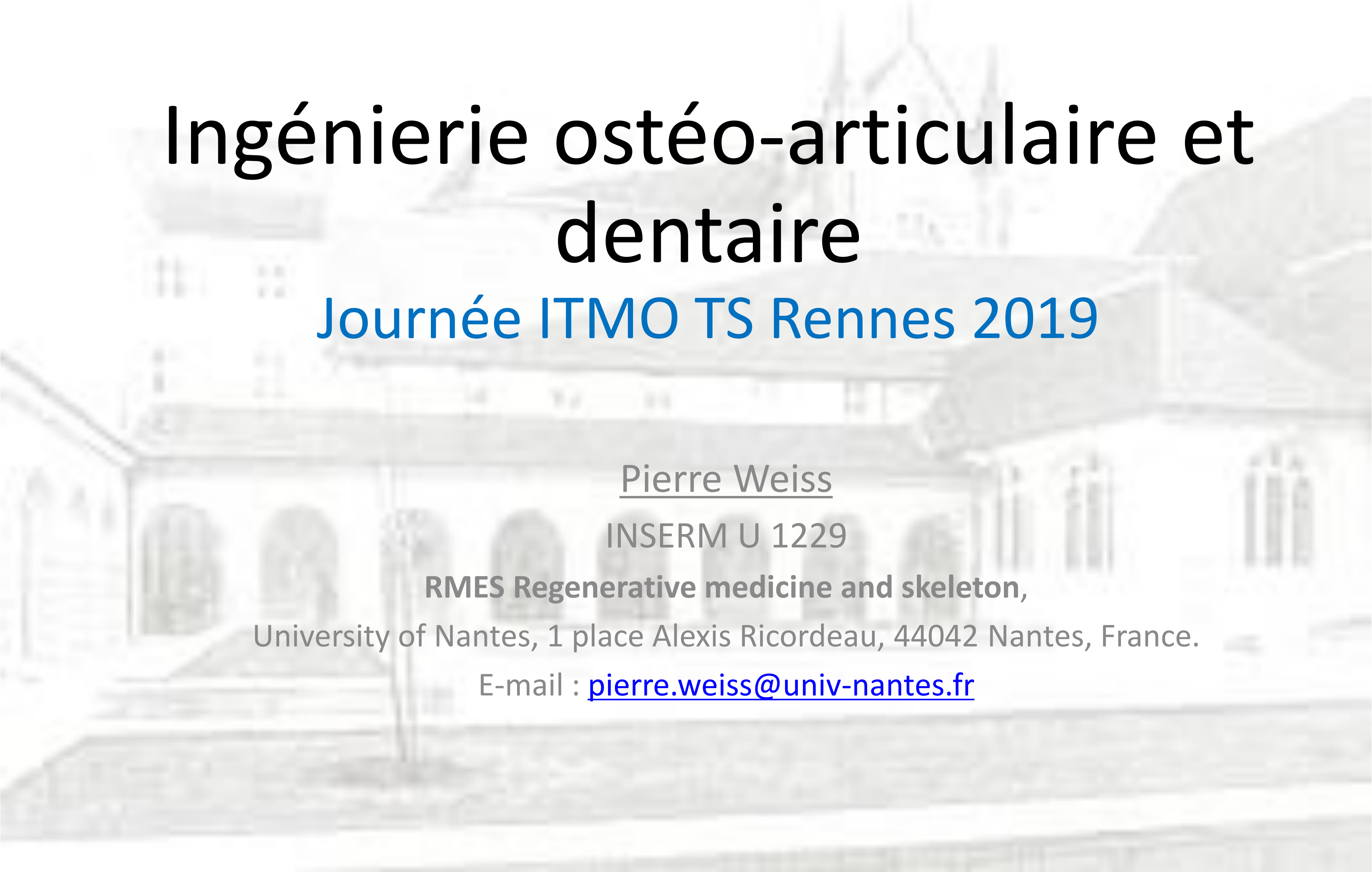


Ingénierie ostéo-articulaire et dentaire

Journée ITMO TS Rennes 2019

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

Regenerative Medicine and Skeleton research centre (RMeS)

INSERM/UN/ONIRIS UMR 1229

Director Jerome Guicheux
Deputy-director Catherine Le Visage
INSERM CSS 6/CSS 3 - ITMO TECSAN/PMN

Nantes University Hospital Campus

Nantes university school of dental medicine
&
Nantes National Veterinary School-ONIRIS

INSERM UMR 1229-RMeS

1700 m^2-110 people
60 holding a PhD
27 clinicians (DVM, MD, DDS, PharmD)
± 20 PhD students, ± 5 post-docs
20 technical staffs
4 technological Platforms

Regenerative Medicine & Skeleton Research Centre
INSERM-UN-ONIRIS UMR 1229-RMeS

Director J. Guicheux / Deputy-Director C. Le Visage

International Scientific Advisory Board

Scientific communication committee

Steering committee

Lab council

Emerging project initiative

Shared services

Administrative, HR, Communication & Logistics division
(V. Pecqueret)
*Valérie **Pecqueret**, Tec INSERM*
Aurore Vanpoucke, Tec INSERM
Gilles Souhiard, Ass-Tec Univ

Budget & Financial division
(F. Seynaeve)
Fabienne Seynaeve, Ass-Eng Univ
Carole Gauthier, Tec Univ
Sophie Salle, Tec Univ

C. Vignes, Safety & prevention officer
T. Rouillon, Radioactivity Competent officer

STEP TEAM

Skeletal Physiopathology and Joint Regenerative Medicine

Coord. J. Guicheux / L. Beck (dep.)

40 PP
27.5 FTE

- **5 Senior** scientists
- 10 Univ/hosp Researchers
- **3 Post-docs**
- 4 Techn. Staff
- 11 PhD students
- 7 Master 2

Skeletal integrative physiology
Laurent Beck, CR INSERM

Stem cells and axial skeleton development
Anne Camus, CR CNRS

Functionalized hydrogels as joint microenvironments
Catherine Le Visage, DR INSERM

Translational research in joint regeneration
Jerome Guicheux, DR INSERM

REGOS TEAM

Regenerative Medicine of Bone Tissues

Coord. P. Weiss / V. Geoffroy (dep.)

39 PP
20.3 FTE

- **3 Senior scientists**
- **19** Univ/hosp Researchers
- 2 Post-docs
- 2 Techn. Staff
- 5 PhD students
- 6 Master 2

Molecular control of bone aging and regeneration
Valérie Geoffroy, DR INSERM

Hybrid Biomaterials for bone scaffolds
Pierre Weiss, PU-PH

Translational research in bone regeneration
Florent Espitalier, PU-PH

Translational research in parodontal **regeneration**
Philippe Lesclous, PU-PH

Technical Platforms And Translational Unit

SC3M* (J. Guicheux, C. Vinatier)
*Joëlle **Véziers** , Eng CHU*
*Julie **Lesoeur** , Ass-Eng INSERM*

Florent Autrusseau, Eng Univ
Caroline Vignes, Eng INSERM
Martial Masson, Eng INSERM
Aurélie Schaefer, Tec INSERM

Cell Culture (S. Beck-Cormier)
Boris Halgand, Eng CHU

Molecular biology (F. Jehan)
Sophie Source, Tec Univ

BIO^{3*} (P. Weiss, C. Le Visage)
Thierry Rouillon, Eng Univ
François Loll, Eng INSERM

Preclinical and clinical Transfer unit
1 Tec, 17 Univ/hosp researchers 9 associated clinicians

*SC3M: Electron Microscopy, Microcharacterization and Functional Morphohistology-imaging Core Facility

*BIO^3: Biomaterials, Biohydrogels, Biomechanics

110 people, 65 full-time equivalent ; HCERES Wave B; Pluri-team INSERM - UNIVERSITE NANTES - ONIRIS created on January 1st 2017

Bioregate, a centre of expertise in regenerative medicine

pour les sciences de la vie et de la santé

- About 200 researchers working on regenerative medicine developments in Pays de la Loire region

BIOREGATE
PÔLE DE MÉDECINE RÉGÉNÉRATRICE

Operational partners

Inserm
Institut national de la santé et de la recherche médicale

INRA
SCIENCE & IMPACT

Ifremer

Project holder
UNIVERSITÉ DE NANTES

Centre Hospitalier Universitaire d'Angers

Centre Hospitalier Universitaire de Nantes

université angers

Université du Maine

Oniris

Atlanpole biothérapies

Financial partners

Région PAYS DE LA LOIRE

Nantes Métropole

UNION EUROPÉENNE

angers loire métropole

Le Mans Métropole
Communauté urbaine

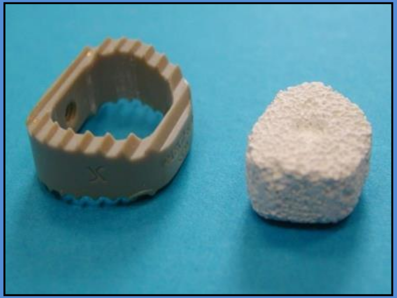
http://www.bioregate.com/en/

What is regenerative medicine ?

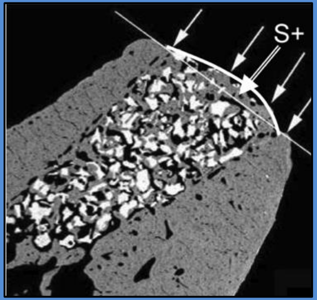
- **Regenerative medicine** is the "process of replacing or regenerating human cells, tissues or organs to restore or establish normal function »

……. to 4R medicine

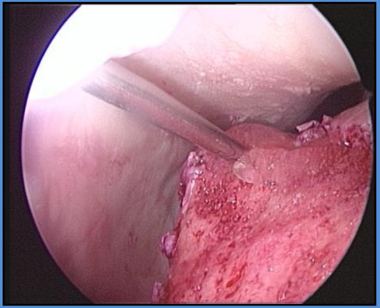
Replace



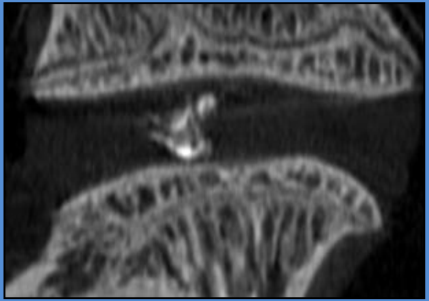
Repair



Regenerate

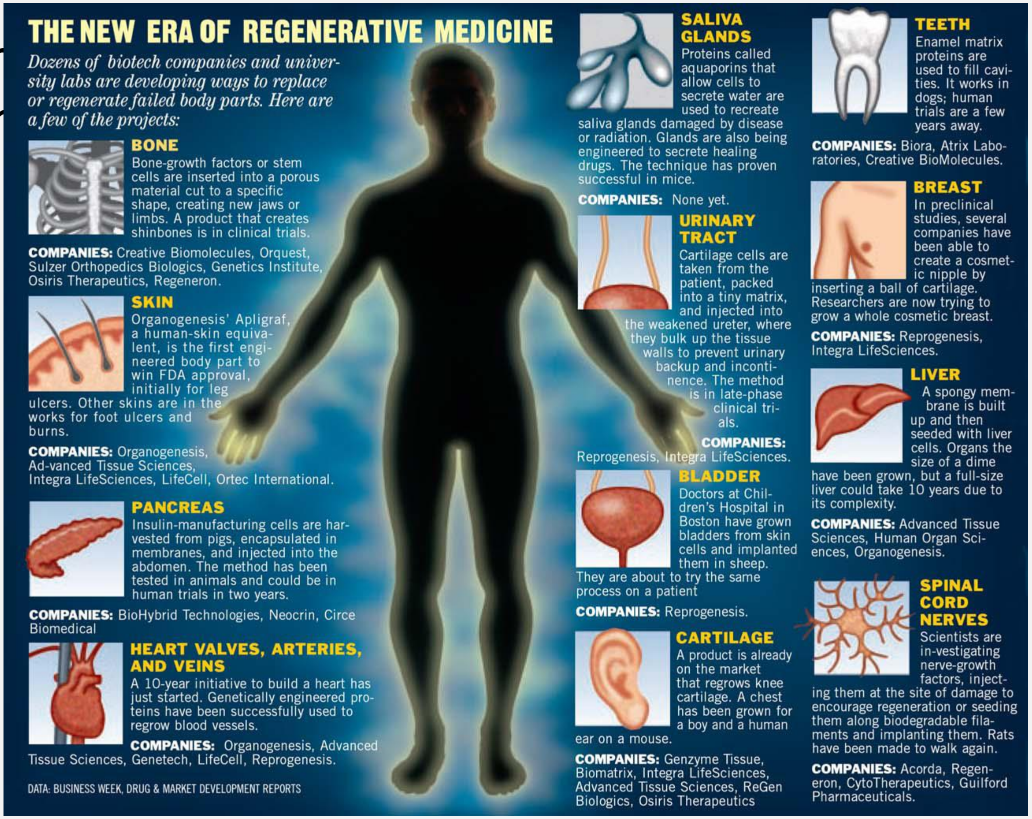


Reprogram



What is regenerative medicine ?

- Biomaterials
  - Tissue substitutes
  - Scaffold for cells attachm
    proliferation and differen
    - Calcium phosphate
    - Polymers
    - Hydrogels
- Cellular Therapy
  - Stem cells
  - IPS
- Gene Therapy
- Tissue engineering



THE NEW ERA OF REGENERATIVE MEDICINE

Dozens of biotech companies and university labs are developing ways to replace or regenerate failed body parts. Here are a few of the projects:

BONE
Bone-growth factors or stem cells are inserted into a porous material cut to a specific shape, creating new jaws or limbs. A product that creates shinbones is in clinical trials.
COMPANIES: Creative Biomolecules, Orquest, Sulzer Orthopedics Biologics, Genetics Institute, Osiris Therapeutics, Regeneron.

SKIN
Organogenesis' Apligraf, a human-skin equivalent, is the first engineered body part to win FDA approval, initially for leg ulcers. Other skins are in the works for foot ulcers and burns.
COMPANIES: Organogenesis, Ad-vanced Tissue Sciences, Integra LifeSciences, LifeCell, Ortec International.

PANCREAS
Insulin-manufacturing cells are harvested from pigs, encapsulated in membranes, and injected into the abdomen. The method has been tested in animals and could be in human trials in two years.
COMPANIES: BioHybrid Technologies, Neocrin, Circe Biomedical

HEART VALVES, ARTERIES, AND VEINS
A 10-year initiative to build a heart has just started. Genetically engineered proteins have been successfully used to regrow blood vessels.
COMPANIES: Organogenesis, Advanced Tissue Sciences, Genetech, LifeCell, Reprogenesis.

DATA: BUSINESS WEEK, DRUG & MARKET DEVELOPMENT REPORTS

SALIVA GLANDS
Proteins called aquaporins that allow cells to secrete water are used to recreate saliva glands damaged by disease or radiation. Glands are also being engineered to secrete healing drugs. The technique has proven successful in mice.
COMPANIES: None yet.

URINARY TRACT
Cartilage cells are taken from the patient, packed into a tiny matrix, and injected into the weakened ureter, where they bulk up the tissue walls to prevent urinary backup and incontinence. The method is in late-phase clinical trials.
COMPANIES: Reprogenesis, Integra LifeSciences.

BLADDER
Doctors at Children's Hospital in Boston have grown bladders from skin cells and implanted them in sheep. They are about to try the same process on a patient
COMPANIES: Reprogenesis.

CARTILAGE
A product is already on the market that regrows knee cartilage. A chest has been grown for a boy and a human ear on a mouse.
COMPANIES: Genzyme Tissue, Biomatrix, Integra LifeSciences, Advanced Tissue Sciences, ReGen Biologics, Osiris Therapeutics

TEETH
Enamel matrix proteins are used to fill cavities. It works in dogs; human trials are a few years away.
COMPANIES: Biora, Atrix Laboratories, Creative BioMolecules.

BREAST
In preclinical studies, several companies have been able to create a cosmetic nipple by inserting a ball of cartilage. Researchers are now trying to grow a whole cosmetic breast.
COMPANIES: Reprogenesis, Integra LifeSciences.

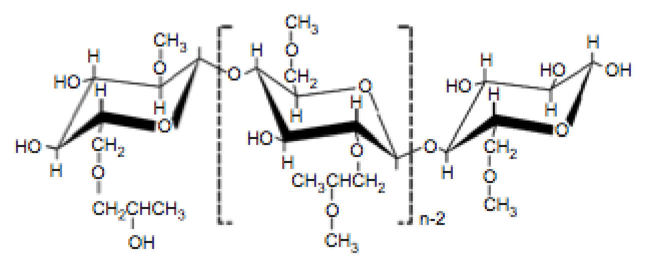
LIVER
A spongy membrane is built up and then seeded with liver cells. Organs the size of a dime have been grown, but a full-size liver could take 10 years due to its complexity.
COMPANIES: Advanced Tissue Sciences, Human Organ Sciences, Organogenesis.

SPINAL CORD NERVES
Scientists are in-vestigating nerve-growth factors, injecting them at the site of damage to encourage regeneration or seeding them along biodegradable filaments and implanting them. Rats have been made to walk again.
COMPANIES: Acorda, Regeneron, CytoTherapeutics, Guilford Pharmaceuticals.

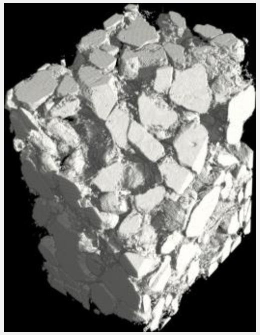
Williams 1987

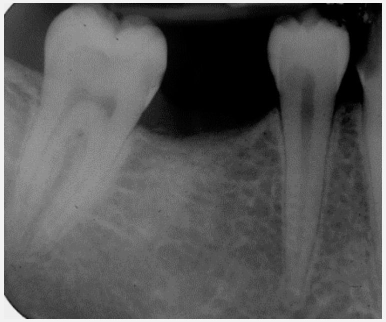
- Biomatériau :
  - – Matériau non vivant utilisé dans un dispositif médical,
  - – destiné à interagir avec les systèmes biologiques
  - – (attention ≠ matériau naturel)

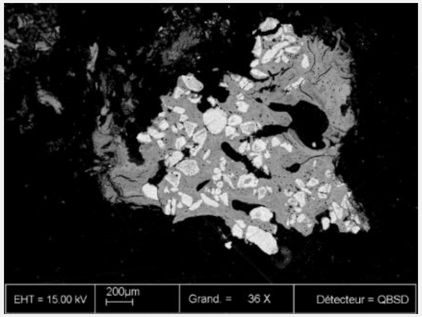
1992:Calcium Phosphate Suspensions in HPMC viscous water solution



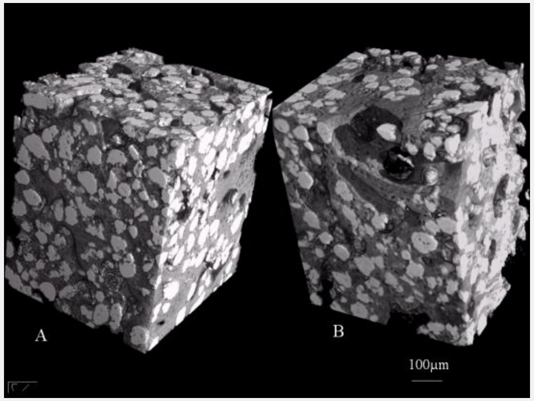
2% HPMC in water + BCP granules

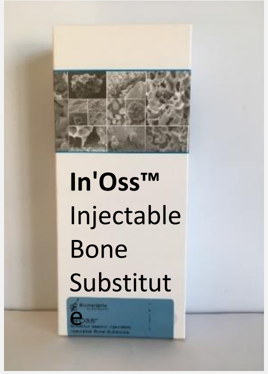






WO 9521634 (A1) Injectable Bone Substitute : WEISS P, DACULSI G,, DELECRIN J, GRIMANDI G ET PASSUTI N





In'Oss™
Injectable
Bone
Substitute

Without hardening properties

po

Substituts osseux injectables commercialisés

Propriétés biologiques

Propriétés mécaniques

In'Oss™MBCP™

Suspension Injectable

MBCP™ Putty - In'Oss™

Hydroxyapatite + Phosphate Tricalcique Béta (BTCP)
+ viscous liquid

+ Biocompatible
+ Injectable
+ Osteoconduction

- Pas de propriété mécanique

WO 9521634 (A1)

Biomatlante
Biological Solutions

Matériau solide

Graftys® QuickSet

+ Biocompatible
+ Injectable
+ Propriétés mécaniques

- Porosité plus faible
- Osteoconduction

calcium phosphate salts + HydroxyPropylMethylCellulose (HPMC)) + Na_2HPO_4

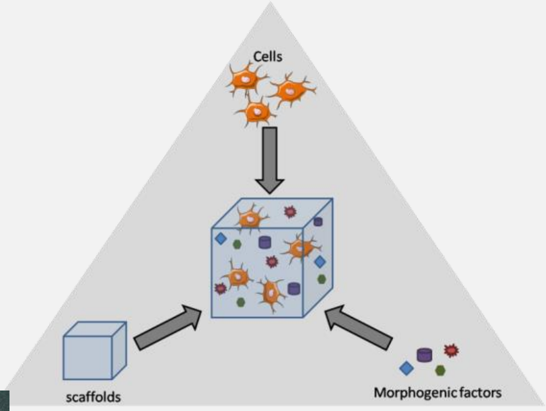
Graftys®

WO2008023254 A1 (2008)

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



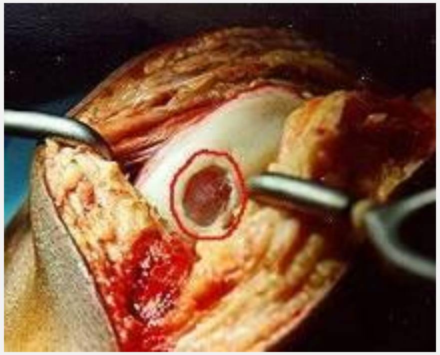
Biomaterials like Soil

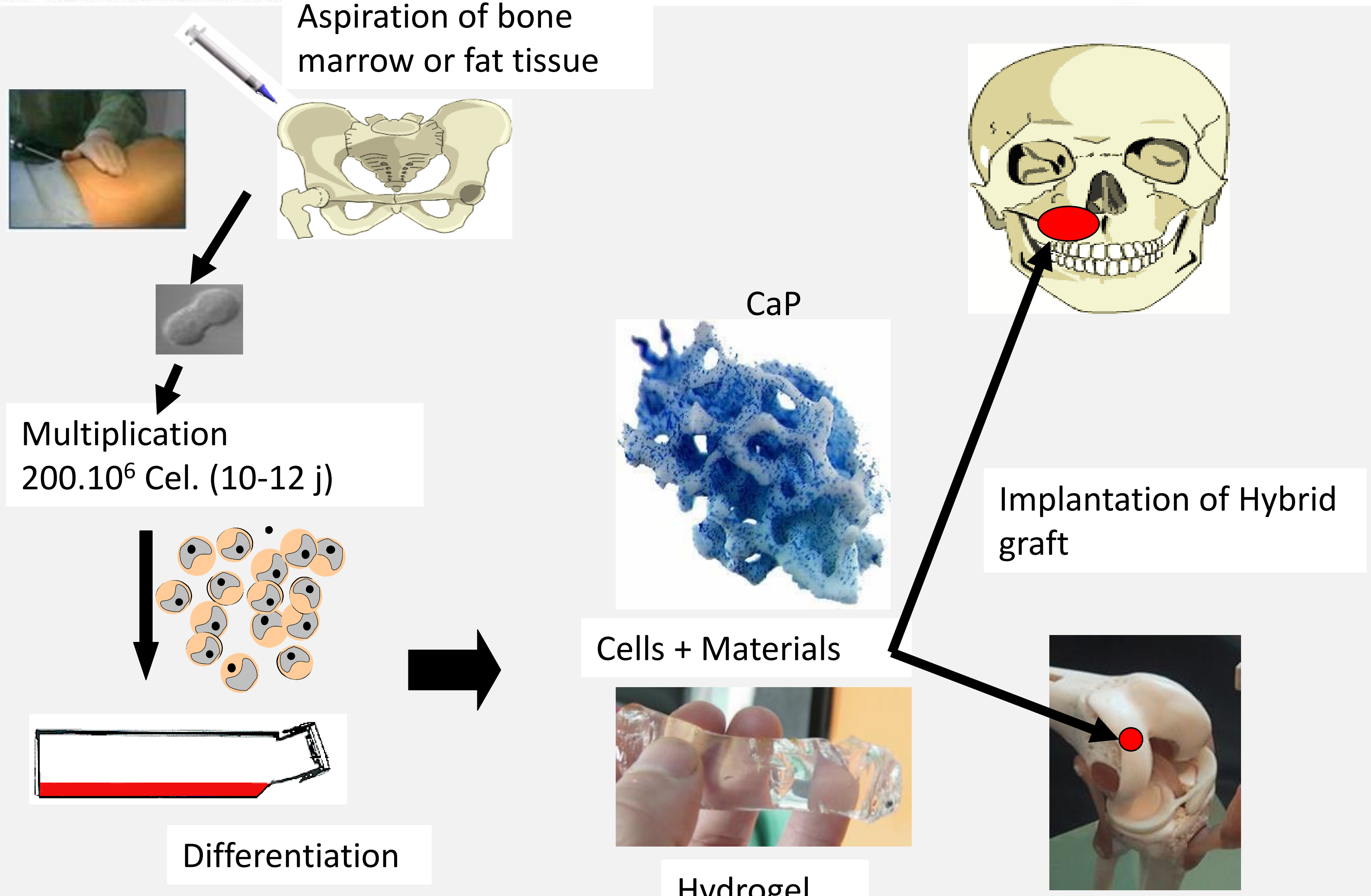
GFs like fertilizer

Merceron, Vinatier, Guicheux. Joint Bone Spine 2008

Why Tissue engineering?

- 2 THERAPEUTIC AXES
  - Large bone losses.
  - some affections of the cartilage





Aspiration of bone marrow or fat tissue

Multiplication
200.10^6 Cel. (10-12 j)

Differentiation

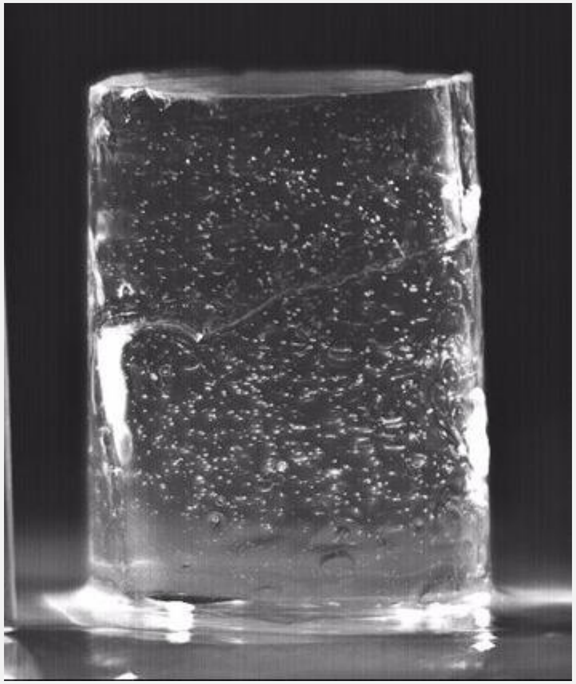
CaP

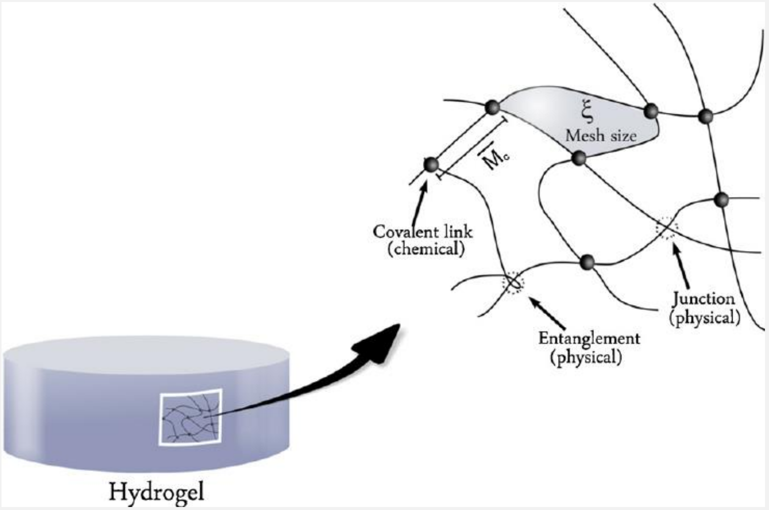
Cells + Materials

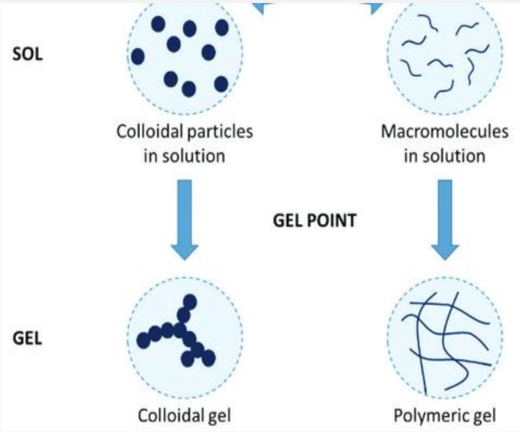
Hydrogel

Implantation of Hybrid graft

What is an Hydrogel ?»



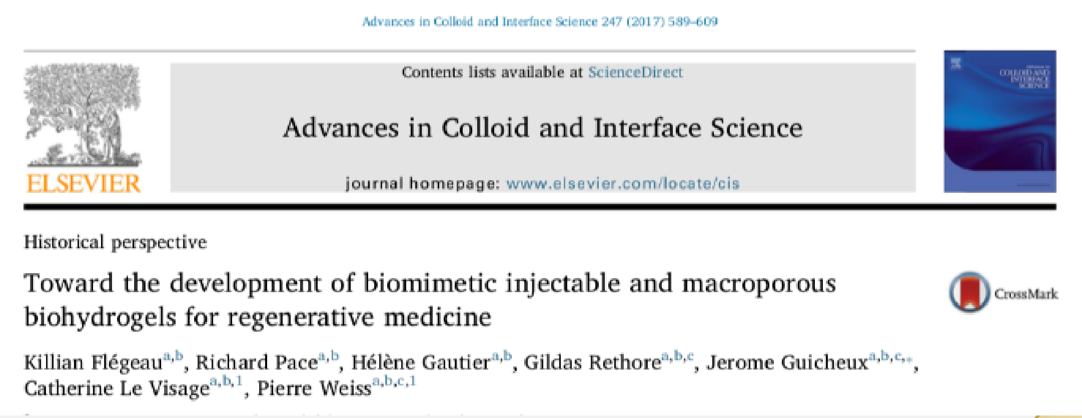




Montheil TJournal of Materials Chemistry B 2018

<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.“



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

Contents lists available at ScienceDirect

Advances in Colloid and Interface Science

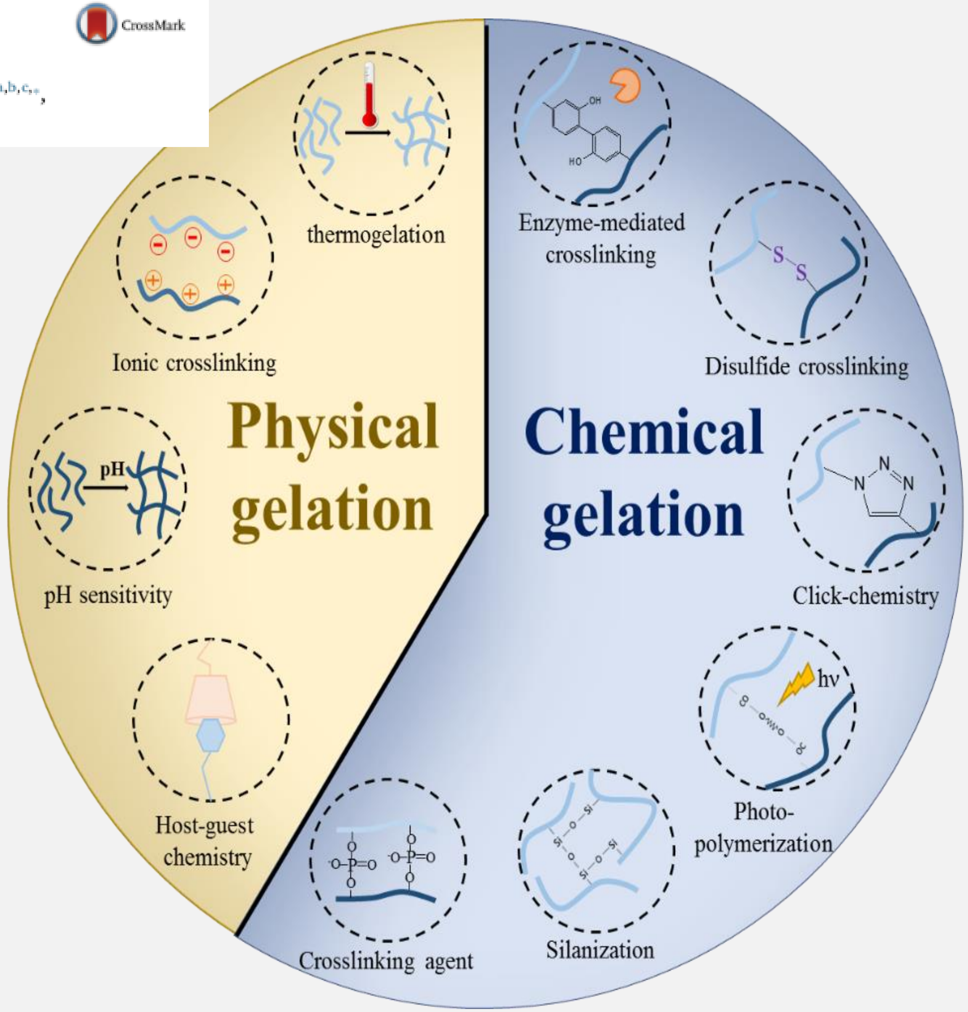
journal homepage: www.elsevier.com/locate/cis

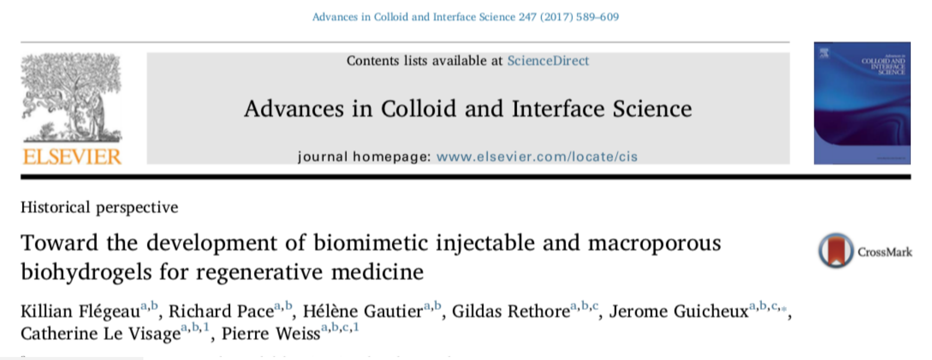
Historical perspective

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

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

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

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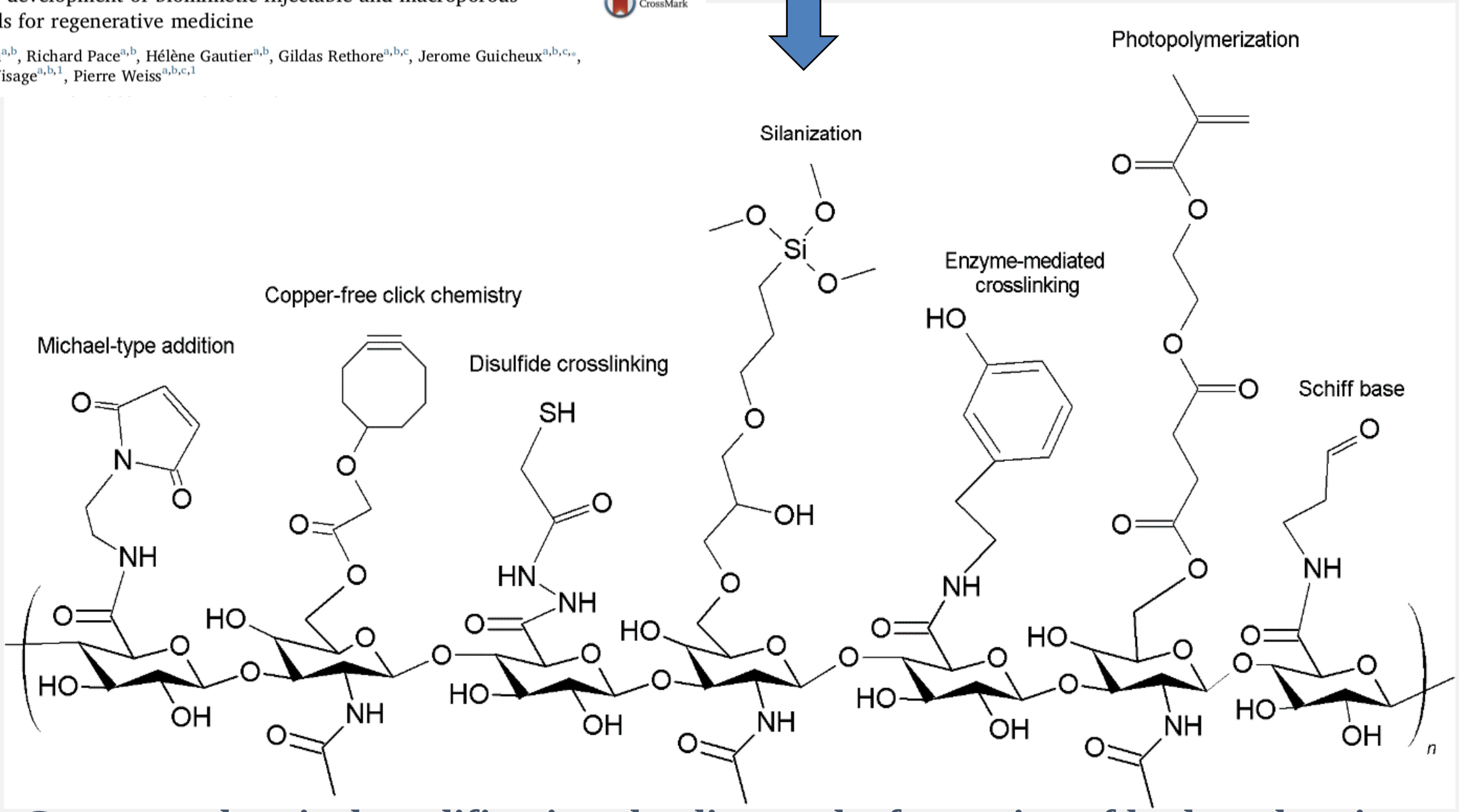
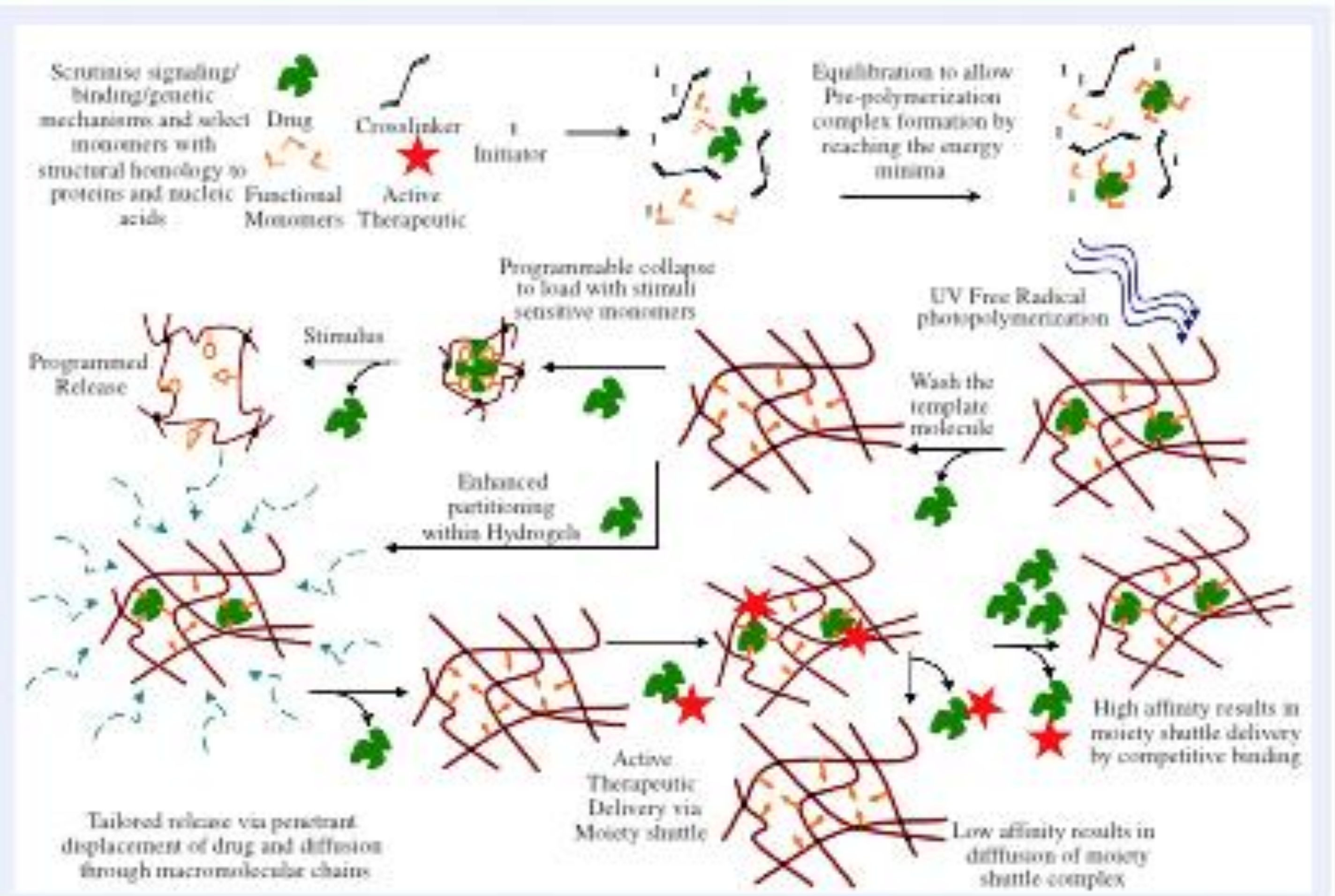
stitut Thématique Multi-Organismes
echnologies pour la santé



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

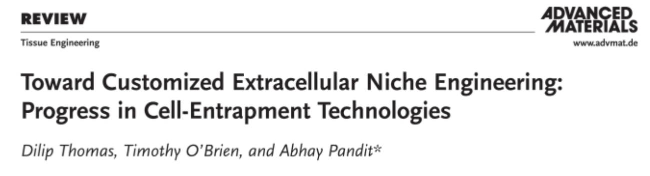
« Smart » hydrogels



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

Cells ?
and Cells interactions ?

Hydrogels and cells



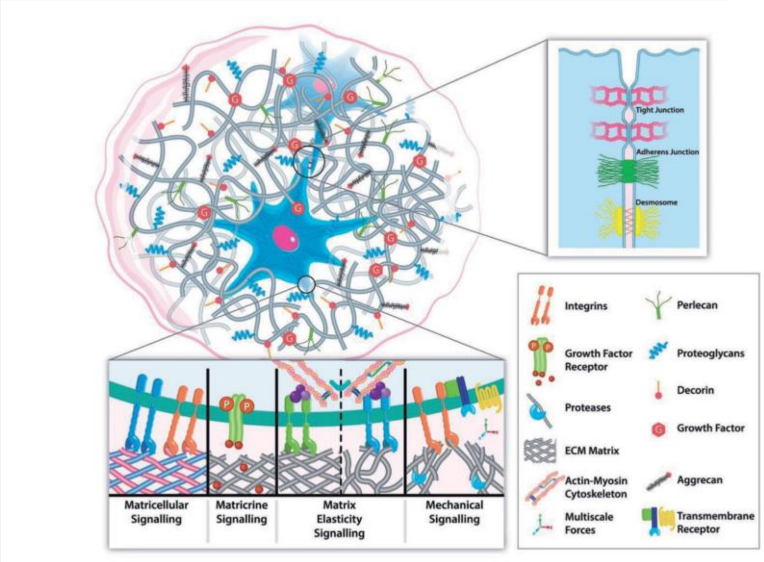
REVIEW

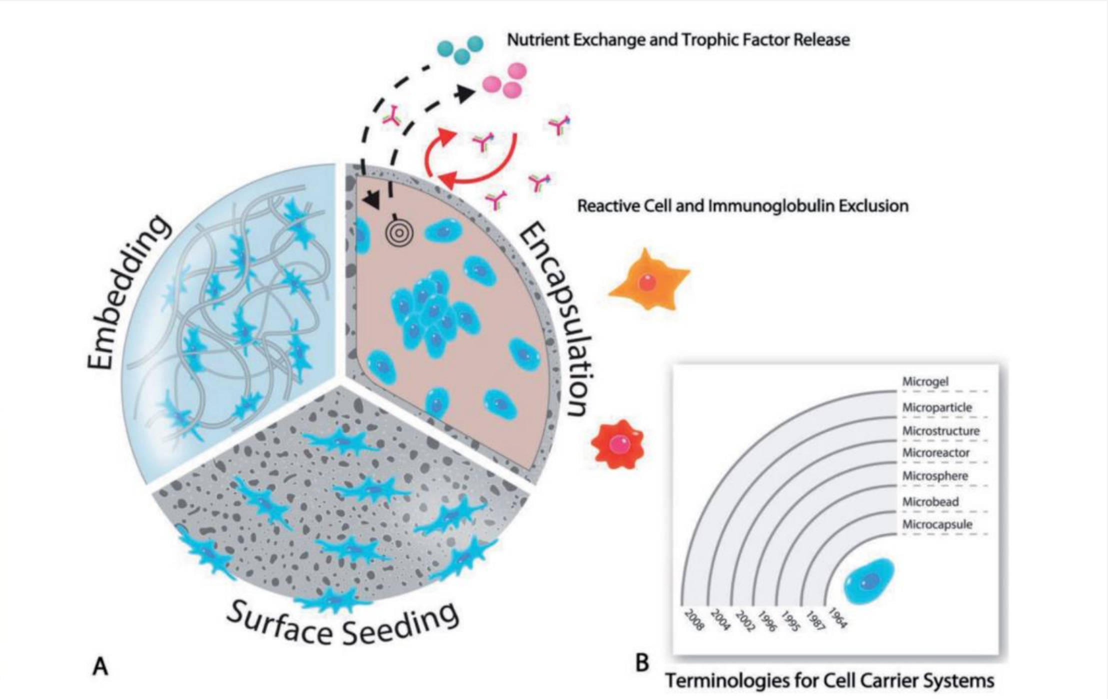
Tissue Engineering

ADVANCED MATERIALS
www.advmat.de

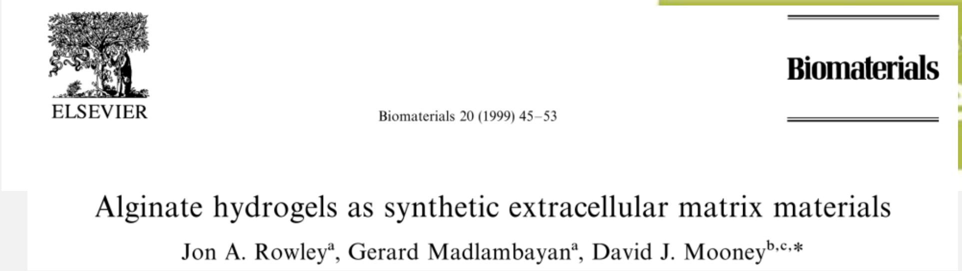
Toward Customized Extracellular Niche Engineering: Progress in Cell-Entrapment Technologies

*Dilip Thomas, Timothy O'Brien, and Abhay Pandit**





Hydrogel / Cell interactions in 2D : Surface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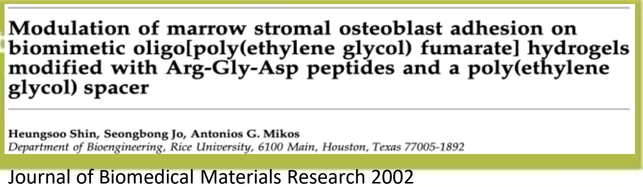
Biomaterials 20 (1999) 45–53

Biomaterials

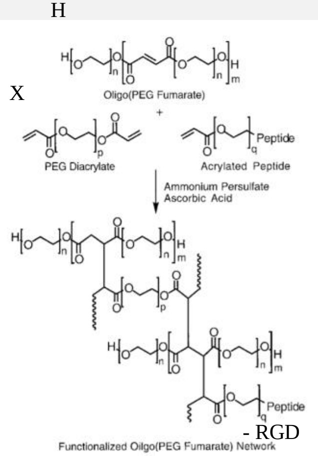
Alginate hydrogels as synthetic extracellular matrix materials

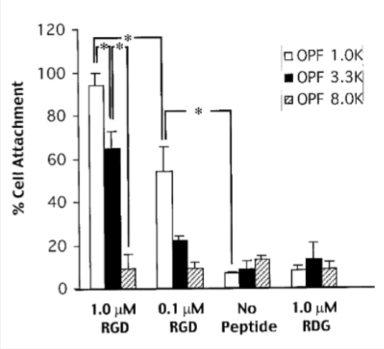
Jon A. Rowley[a], Gerard Madlambayan[a], David J. Mooney[b,c,*]

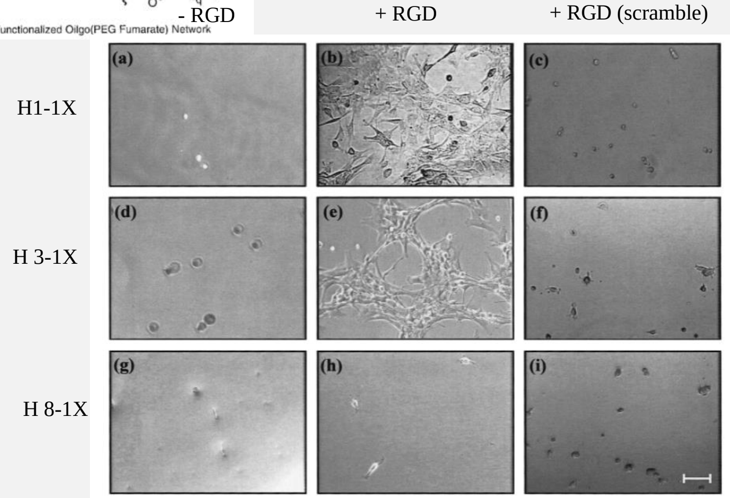

Modulation of marrow stromal osteoblast adhesion on biomimetic oligo[poly(ethylene glycol) fumarate] hydrogels modified with Arg-Gly-Asp peptides and a poly(ethylene glycol) spacer

Heungsoo Shin, Seongbong Jo, Antonios G. Mikos
Department of Bioengineering, Rice University, 6100 Main, Houston, Texas 77005-1892

Journal of Biomedical Materials Research 2002







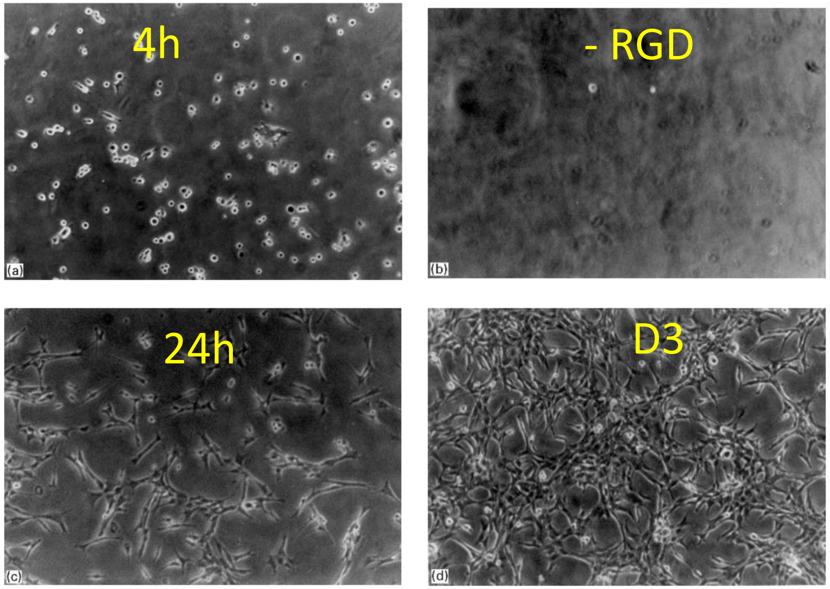


Fig. 4. Photomicrographs of myoblasts adherent to alginate hydrogel surfaces after medium changing at 4 h post-seeding on GRGDY-modified surfaces (a), and control alginate surfaces (b).The myoblasts on GRGDY-modified alginate spread extensively after 24 h of culture (c), and proliferated greatly between days one and three (d).

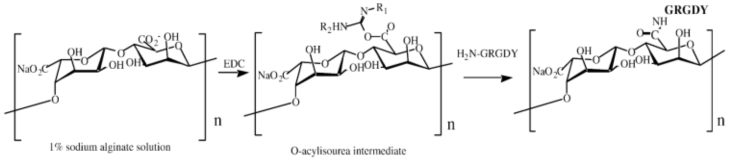
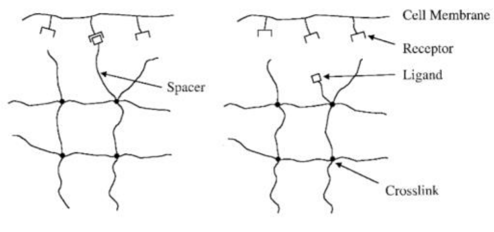
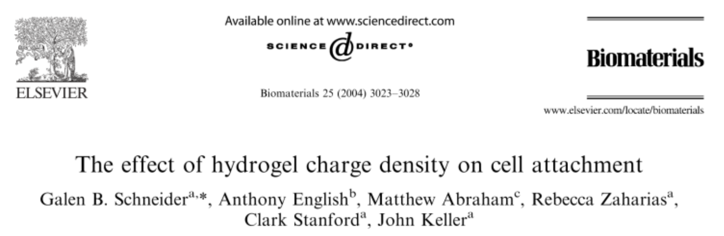


Fig. 1. Reaction scheme of peptide coupling to alginate molecules. Amide bond formation is mediated by the carbodiimide through the carboxyl group of the alginate and the N-terminal amine of the GRGDY pentapeptide.



The tripeptide Arg-Gly-Asp (**RGD**) consists of Arginine, Glycine, and Aspartate



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Available online at www.sciencedirect.com
SCIENCE DIRECT®

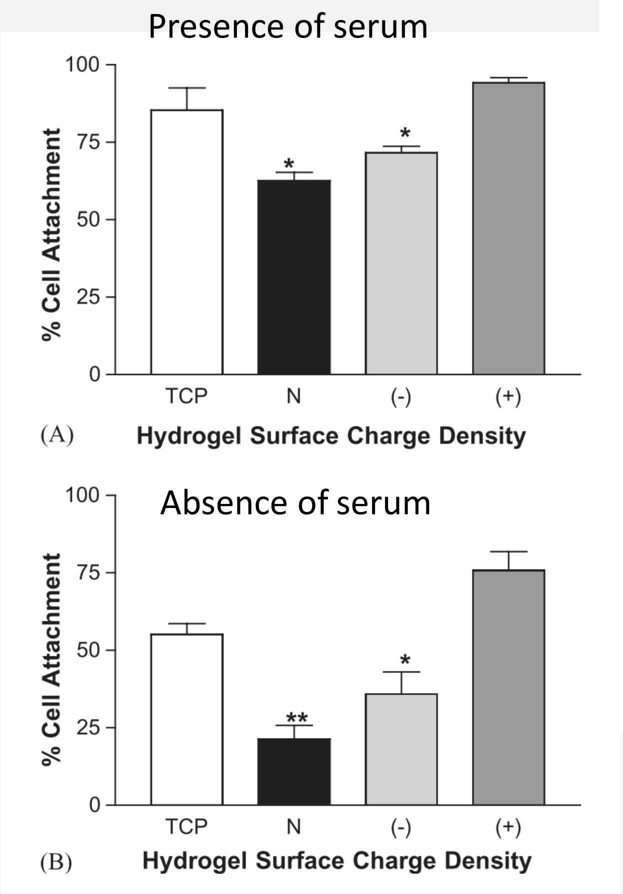
Biomaterials 25 (2004) 3023–3028

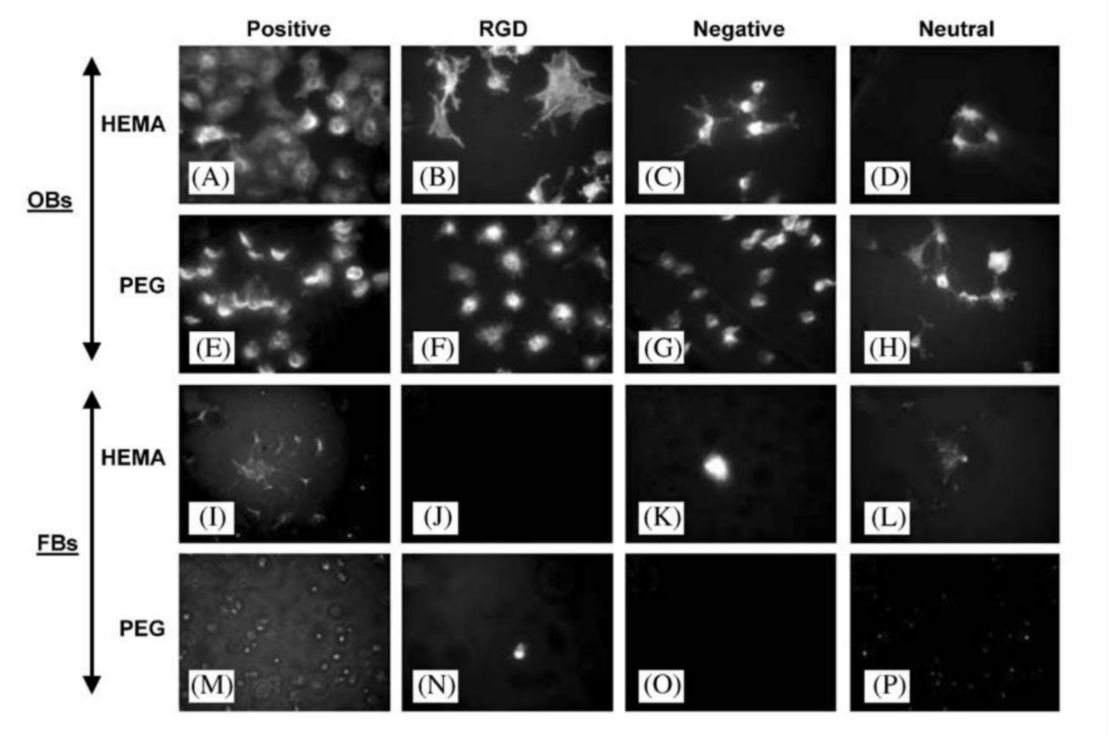
Biomaterials

www.elsevier.com/locate/biomaterials

The effect of hydrogel charge density on cell attachment

Galen B. Schneider[a,*], Anthony English[b], Matthew Abraham[c], Rebecca Zaharias[a], Clark Stanford[a], John Keller[a]





Better cell attachment and spreading was seen in osteoblasts (A–H) as compared to fibroblasts (I–P) on HEMA and PEG hydrogels with positive, negative, and neutral charge densities. Grafted RGD ligand supported cell attachment and spreading in a similar fashion as that seen on positive charge densities. Magnification, 630 ⍰ .

Schneider et al. The effect of hydrogel charge density on cell attachment. Biomaterials (2004) vol. 25 (15) pp. 3023-8

Cell

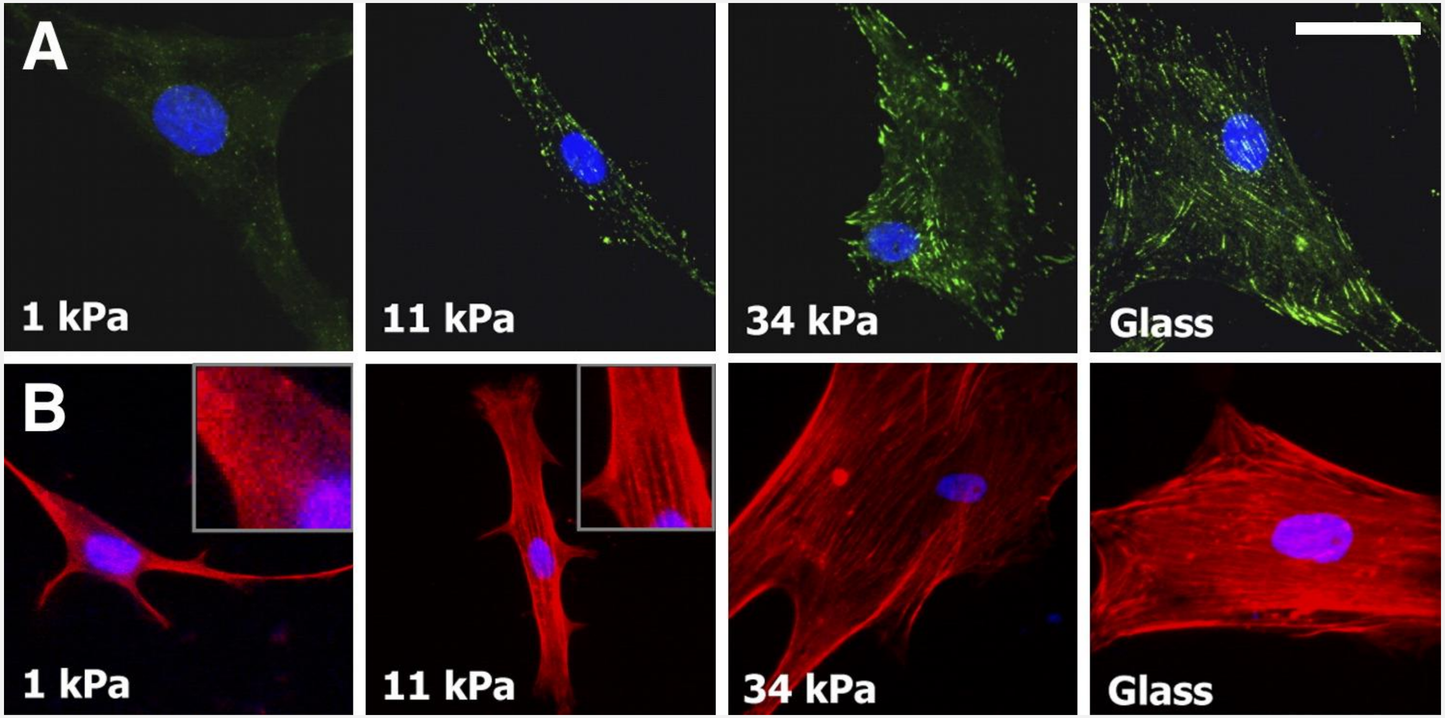
Volume 126, Issue 4, 25 August 2006, Pages 677-689

Article

Matrix Elasticity Directs Stem Cell Lineage Specification

Adam J. Engler [1, 2], Shamik Sen [1, 2], H. Lee Sweeney [1], Dennis E. Discher [1, 2, 3, 4]

Cell adhesion



Adhesions Grow and Cytoskeletal Organization Increases with Substrate Stiffness :

- (A) Paxillin-labeled adhesions grow from undetectable diffuse “contacts” on neurogenic, soft gels (1 kPa) to punctate adhesions on stiffer, myogenic gels (11 kPa). On the stiffest, osteogenic gels (34 kPa), the adhesions are long and thin and slightly more peripheral than they appear on glass.
- (B) F-actin organization shows a similar trend, from diffuse on soft gels to progressively organized on stiffer substrates (as stress fibers). Scale bar is 20 µm.

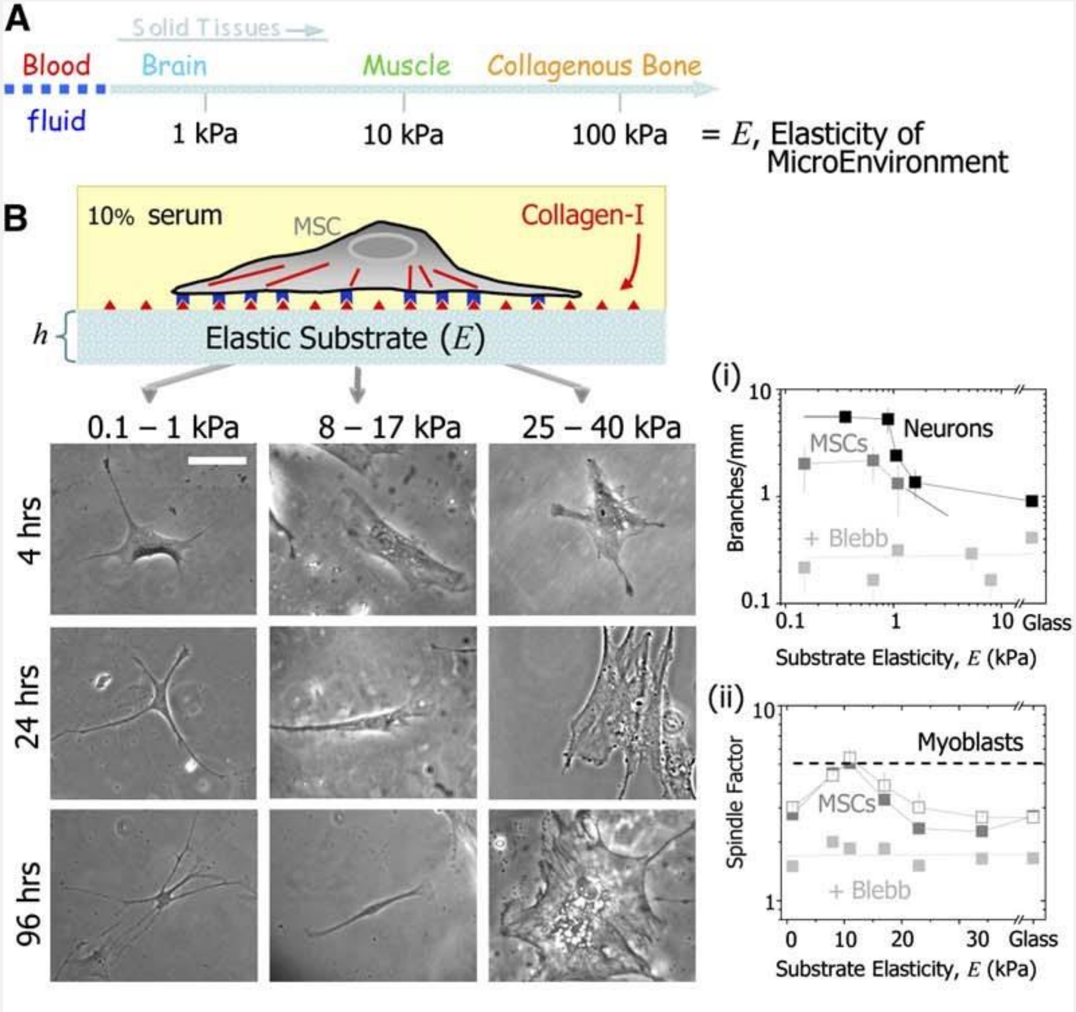
Cell
Volume 126, Issue 4, 25 August 2006, Pages 677-689

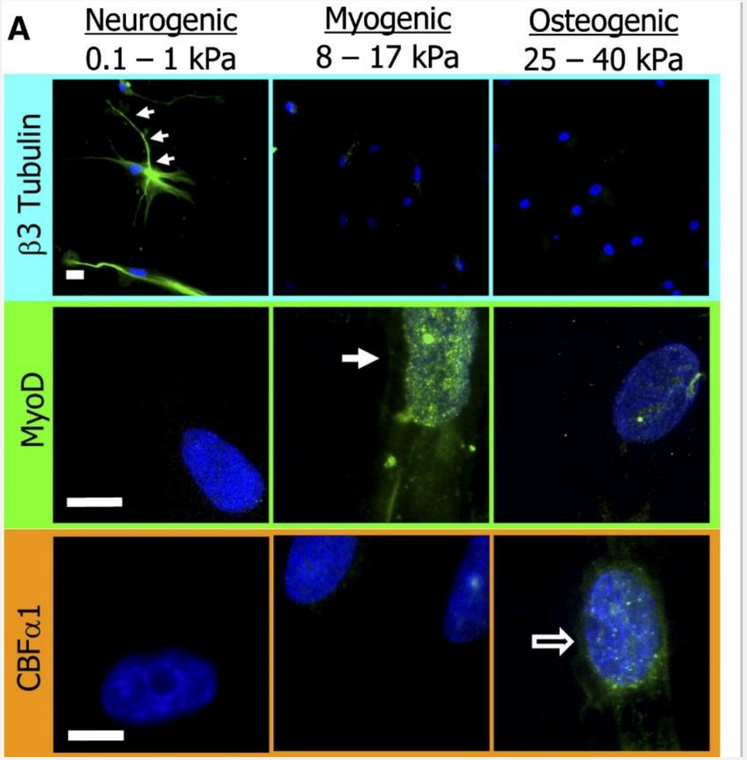
Article

Matrix Elasticity Directs Stem Cell Lineage Specification

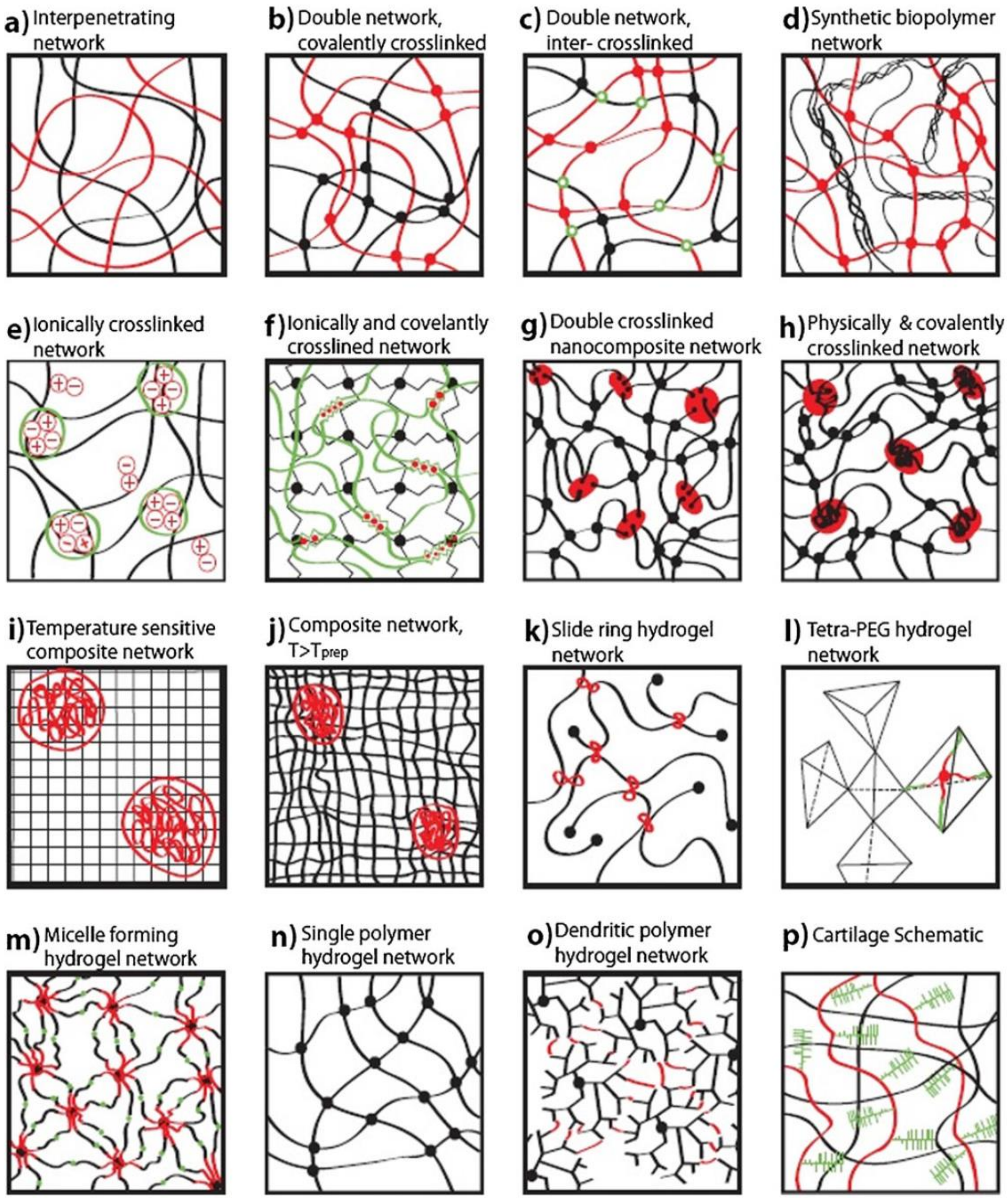
Adam J. Engler [1, 2], Shamik Sen [1, 2], H. Lee Sweeney [1], Dennis E. Discher [1, 2, 3, 4]

Cell differentiation





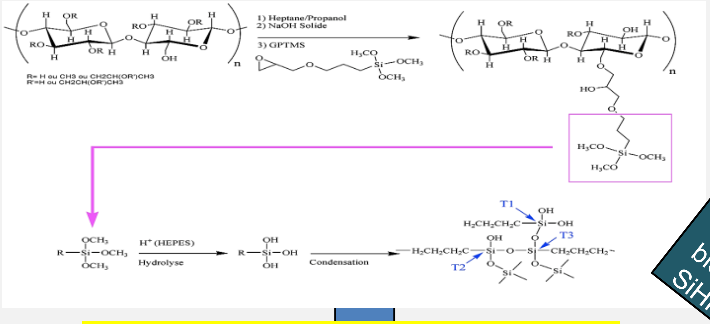
Gel toughening?



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

How to reinforce hydrogels?

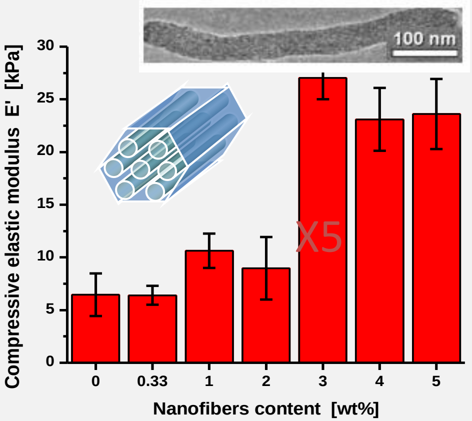
Characterization

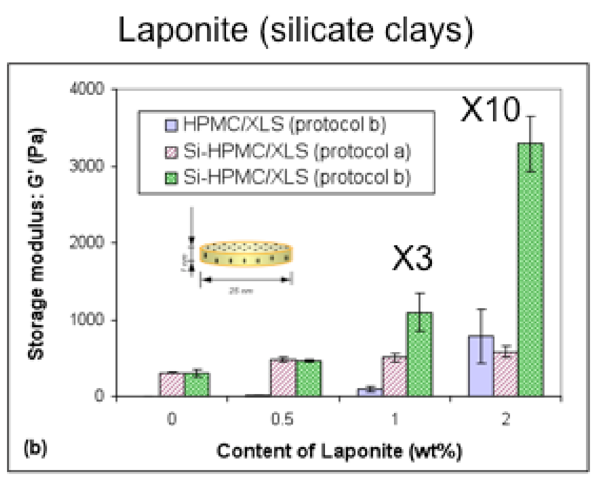


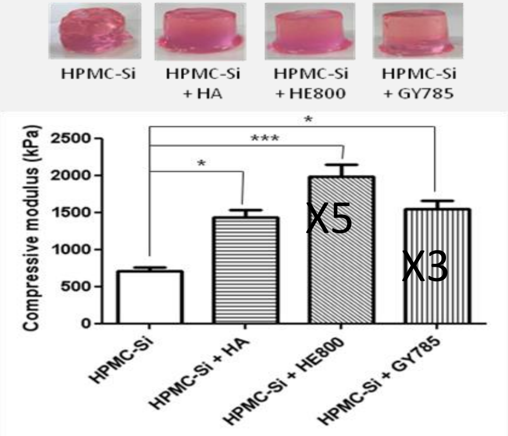
Marine macromolecules blended with SiHPMC

Nano reinforcement

silica nanofibers (NFs)



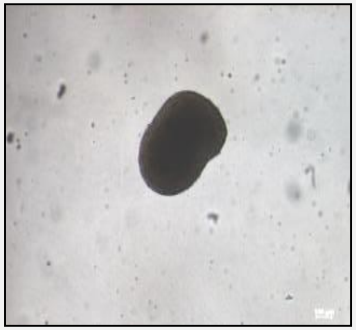




N. Buchtová,

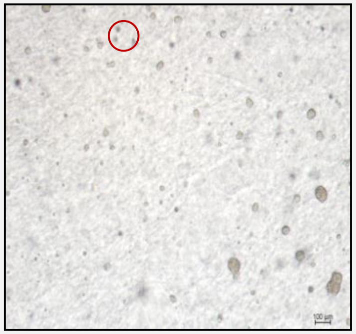
Cell attachment

- **Cell attachment at** t=48h

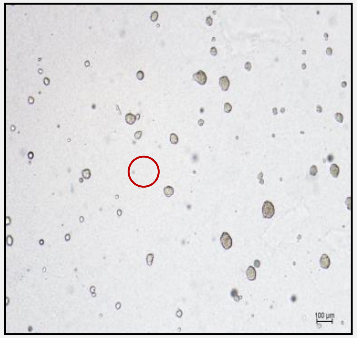


Si-HPMC

Si-HPMC+**HE800**



Si-HPMC+**HA**

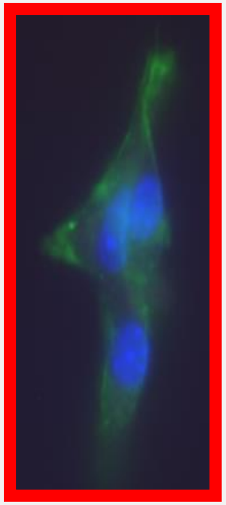


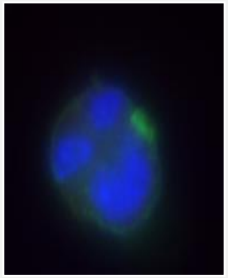
Si-HPMC+**GY785**

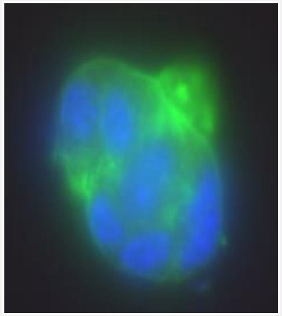
Stainings

● Actin fibers

● Nucleus







HE800 promotes cell spreading

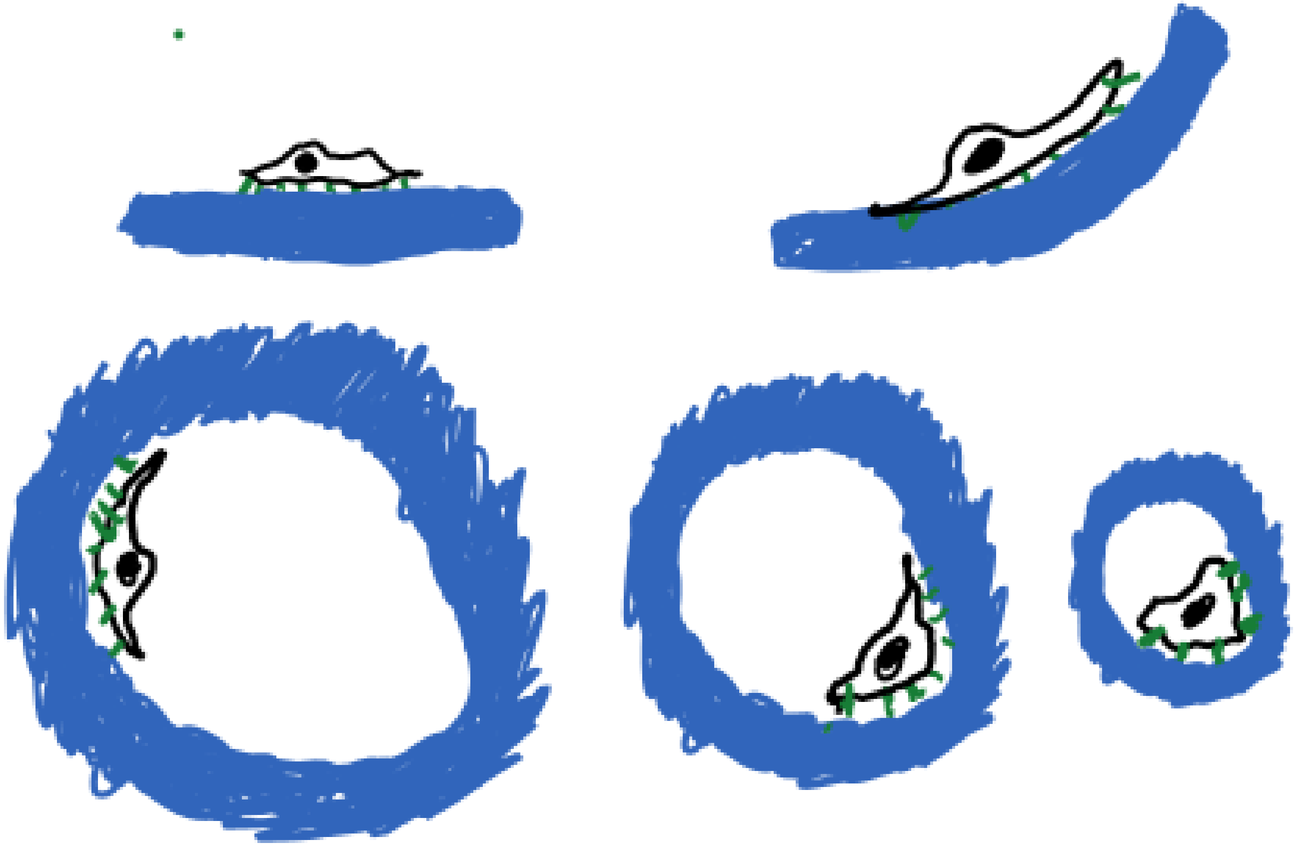
Rederstorff, E.. (2011). An in vitro study of two GAG-like marine polysaccharides incorporated into injectable hydrogels for bone and cartilage tissue engineering. *Acta Biomaterialia*.

Rederstorff, E.. (2017). Enriching a cellulose hydrogel with a biologically active marine exopolysaccharide for cell-based cartilage engineering. *Journal of Tissue Engineering and Regenerative Medicine*.

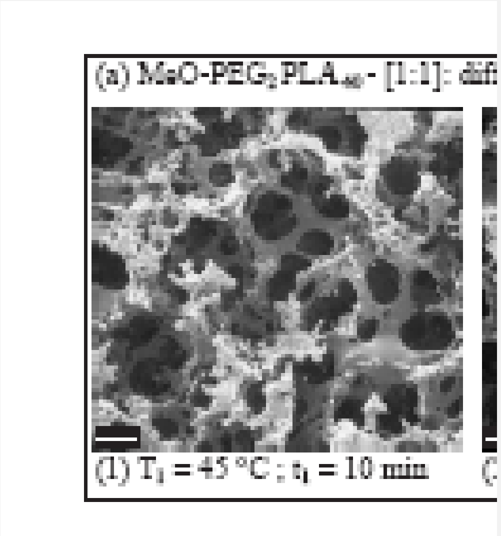
Magnification X63

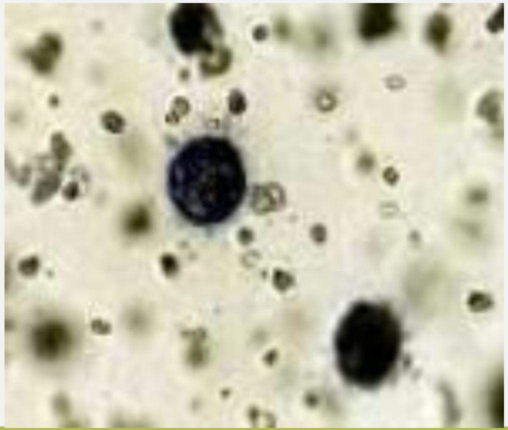
Hydrogels / Cells Interaction in 3D

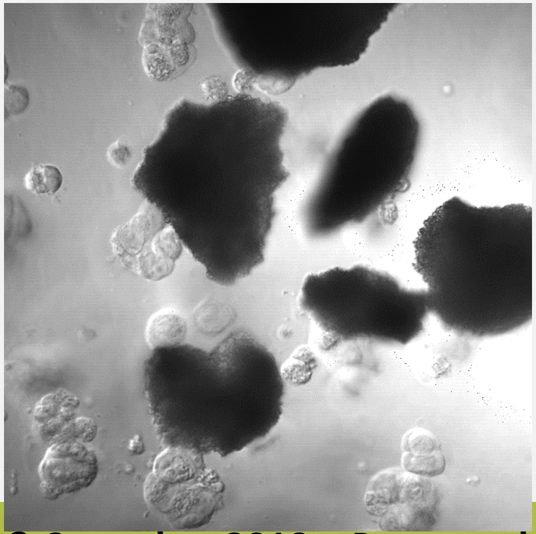
What is 3D ?

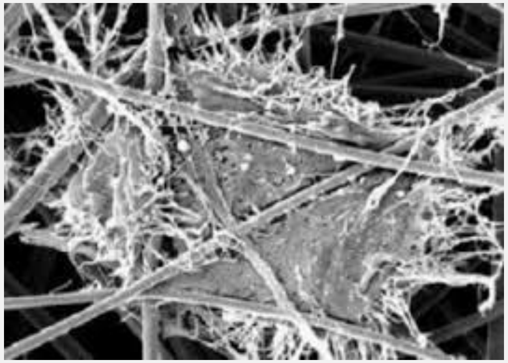


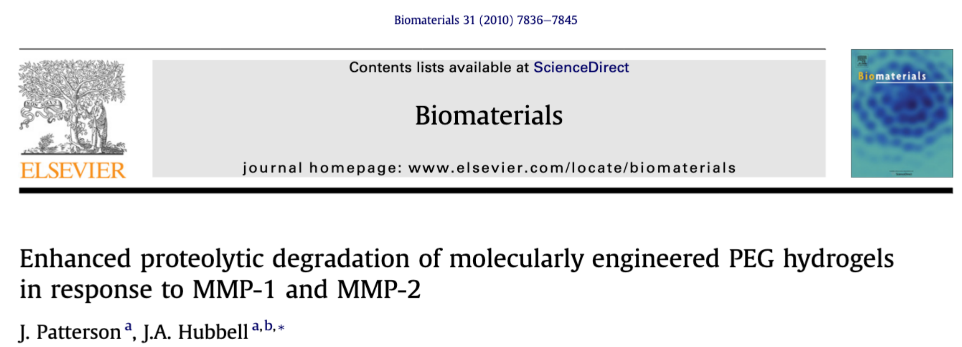
In what type of material ?











Biomaterials 31 (2010) 7836–7845

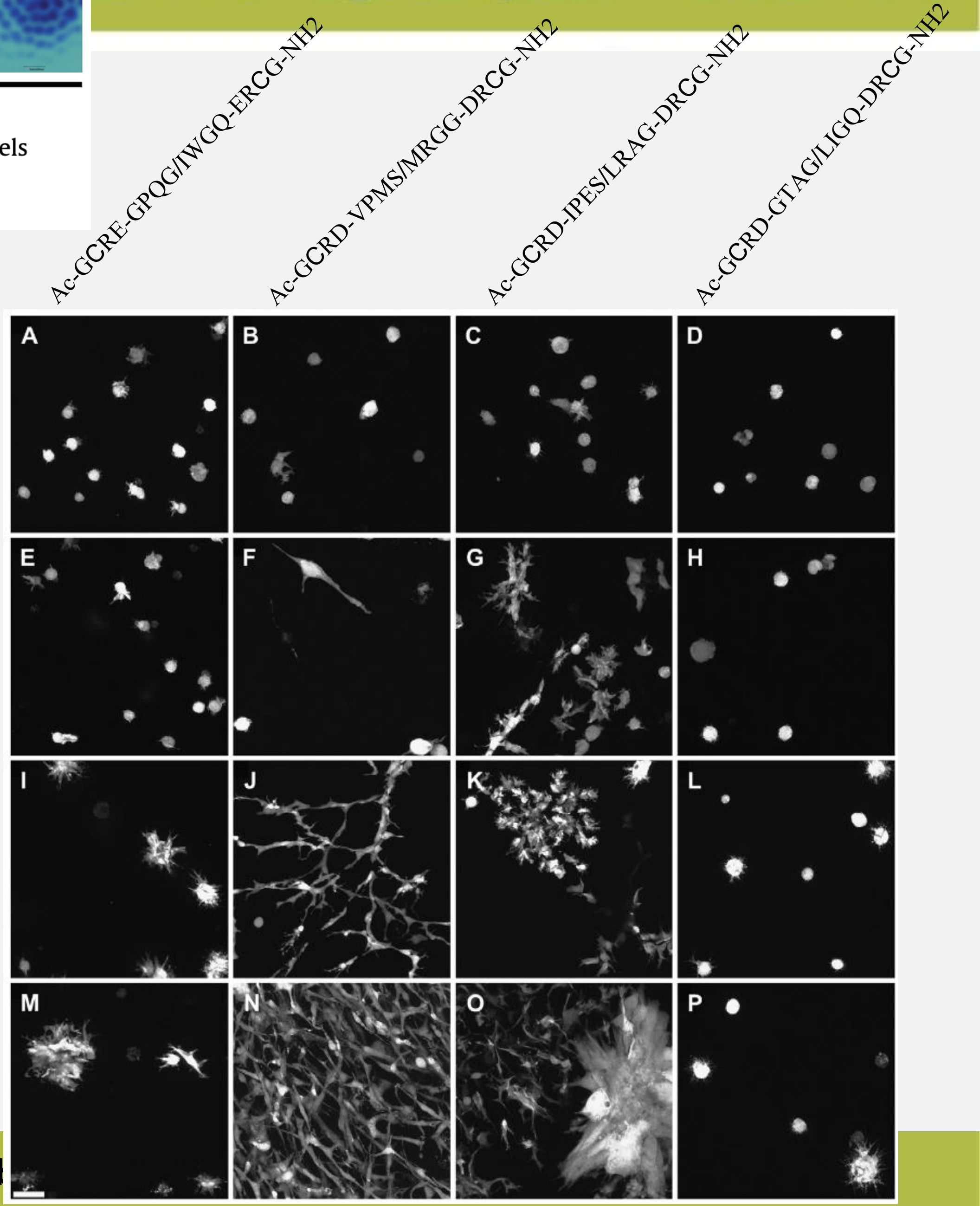
Contents lists available at ScienceDirect

Biomaterials

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

Enhanced proteolytic degradation of molecularly engineered PEG hydrogels in response to MMP-1 and MMP-2

J. Patterson[a], J.A. Hubbell[a,b,*]



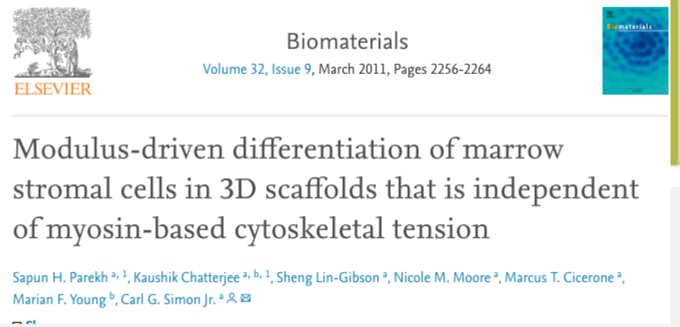
3 Days

7 days

13 Days

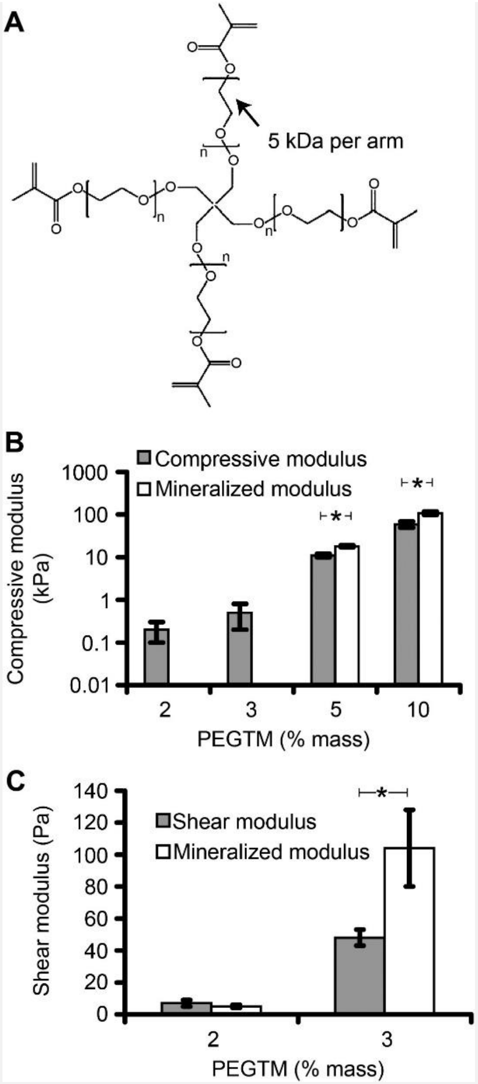
21 Days

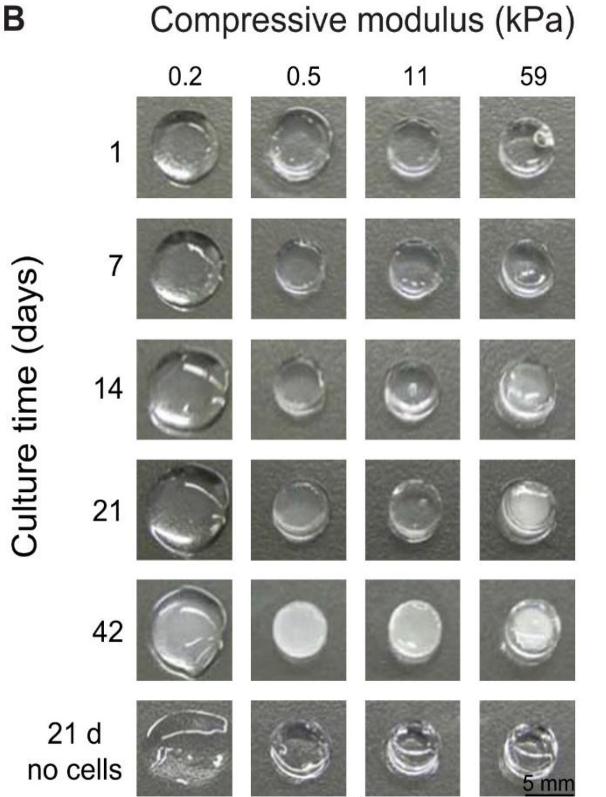
Visualization of mouse myofibroblast spreading and proliferation in 3D PEG hydrogels using confocal microscopy **with sensible peptide crosslinkers.**

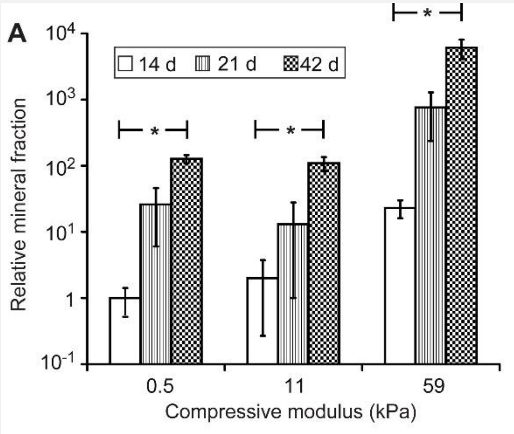

Biomaterials
Volume 32, Issue 9, March 2011, Pages 2256-2264

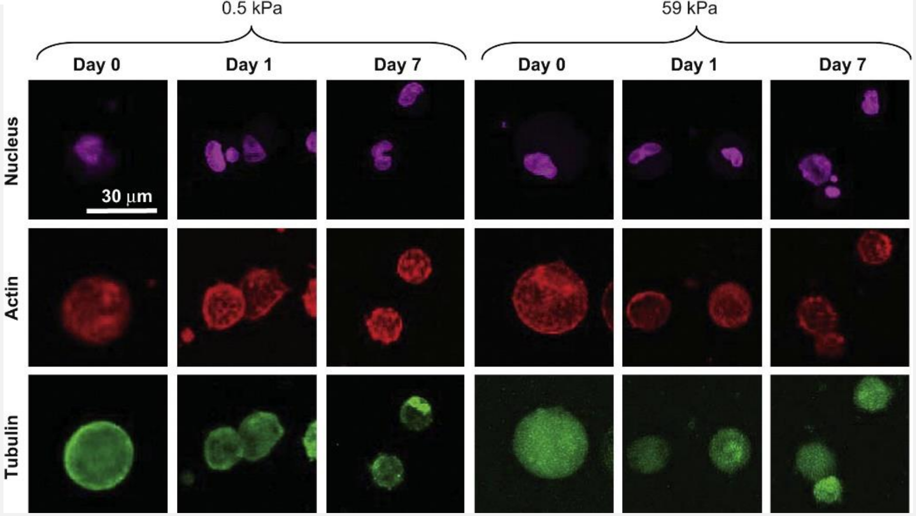
Modulus-driven differentiation of marrow stromal cells in 3D scaffolds that is independent of myosin-based cytoskeletal tension

Sapun H. Parekh [a, 1], Kaushik Chatterjee [a, 1], Sheng Lin-Gibson [a], Nicole M. Moore [a], Marcus T. Cicerone [a], Marian F. Young [b], Carl G. Simon Jr. [a]










ARTICLES
PUBLISHED ONLINE: 30 NOVEMBER 2015 | DOI: 10.1038/NMAT4489
nature materials

Hydrogels with tunable stress relaxation regulate stem cell fate and activity

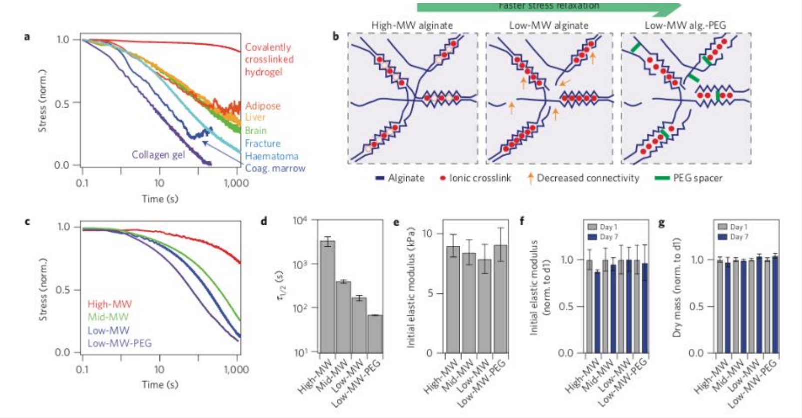
Ovijit Chaudhuri[1,2,3†], Luo Gu[1,2†], Darinka Klumpers[1,2,4], Max Darnell[1,2], Sidi A. Bencherif[1,2], James C. Weaver[2], Nathaniel Huebsch[1,5], Hong-pyo Lee[3], Evi Lippens[2,6], Georg N. Duda[6] and David J. Mooney[1,2*]

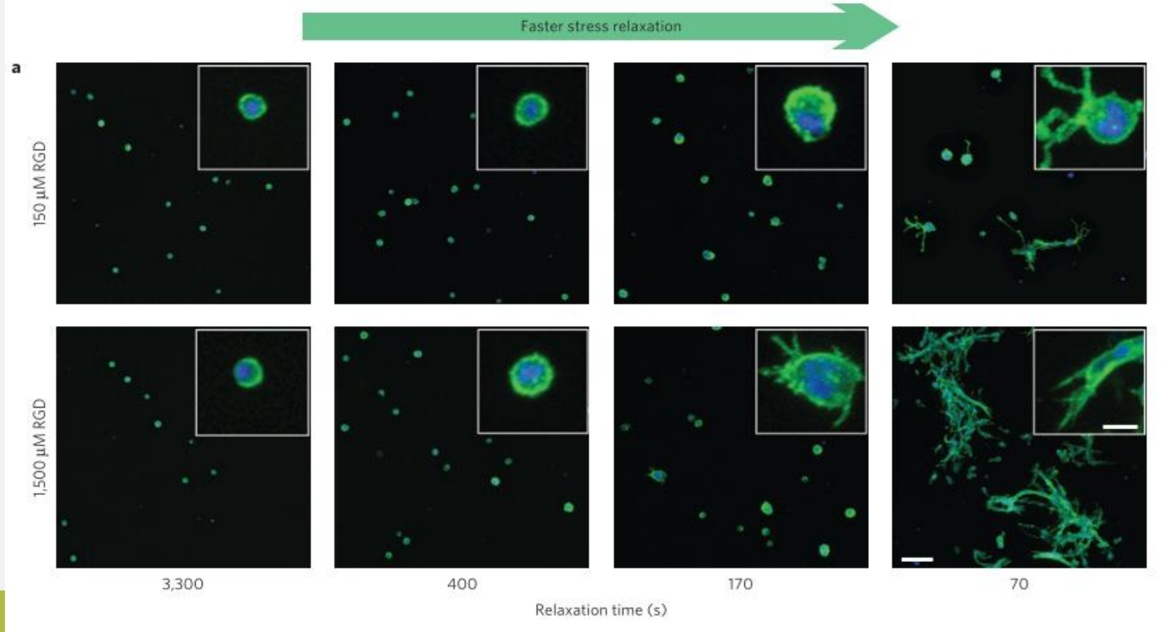
NATURE MATERIALS | VOL 15 | MARCH 2016 | www.nature.com/naturematerials

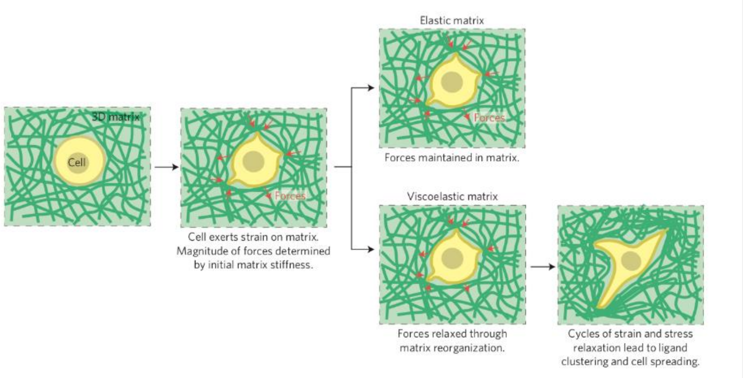
Cell differentiation

In 3D

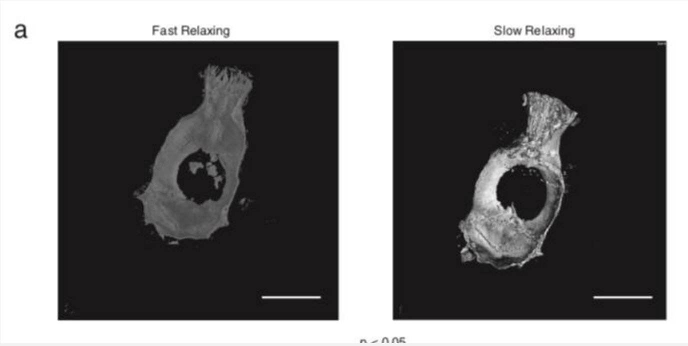
Modulating the nanoscale architecture of alginate hydrogels to modulate stress relaxation properties independent of initial elastic modulus and matrix degradation to capture the viscoelastic behaviours of living tissues







Relaxation in vivo



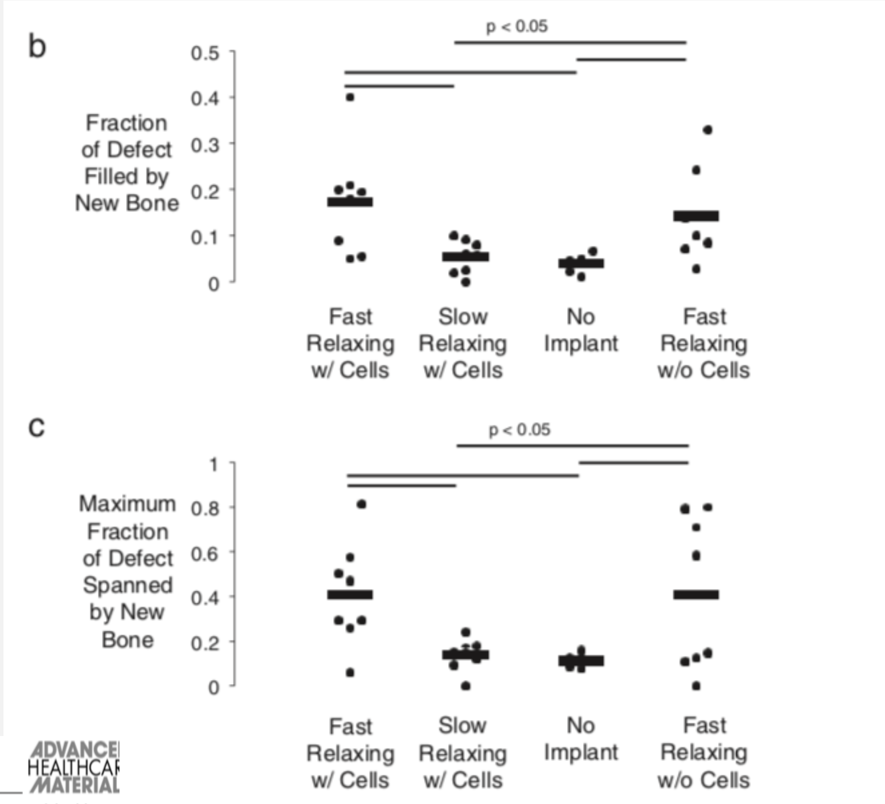


Figure 2. Microcomputed tomography analysis of new bone formation after implantation of hydrogels in rat calvarial defect model. A) Representative µCT renderings of rat calvaria three months postinjury. Scale bar, 1 cm. B) Maximum fraction of wound spanned after three months calculated by taking the maximum fraction of bone occupying any line drawn through the center of the defect. (One-way analysis of variance (ANOVA), Tukey's posthoc test, $n = 3–4$) C) Fraction of the original wound area inhabited by new bone after three months. (One-way ANOVA, Tukey's posthoc test, $n = 5–8$).

ADVANCED SCIENCE NEWS
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ADVANCE
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www.advhealthmat.

Substrate Stress-Relaxation Regulates Scaffold Remodeling and Bone Formation In Vivo

Max Darnell, Simon Young, Luo Gu, Nisarg Shah, Evi Lippens, James Weaver, Georg Duda, and David Mooney*

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Institut Thé
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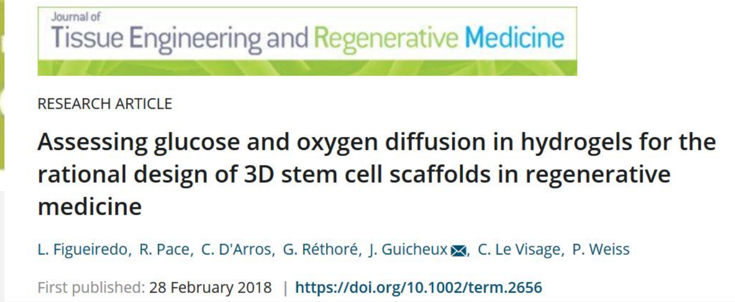

Journal of Tissue Engineering and Regenerative Medicine

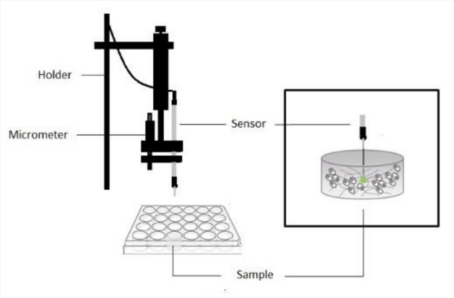
RESEARCH ARTICLE

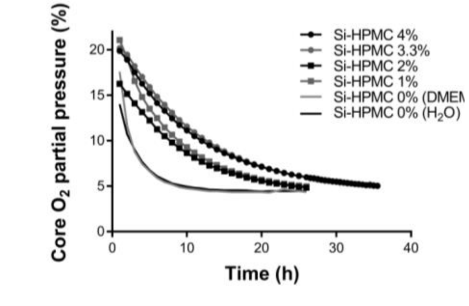
Assessing glucose and oxygen diffusion in hydrogels for the rational design of 3D stem cell scaffolds in regenerative medicine

L. Figueiredo, R. Pace, C. D'Arros, G. Réthoré, J. Guicheux, C. Le Visage, P. Weiss

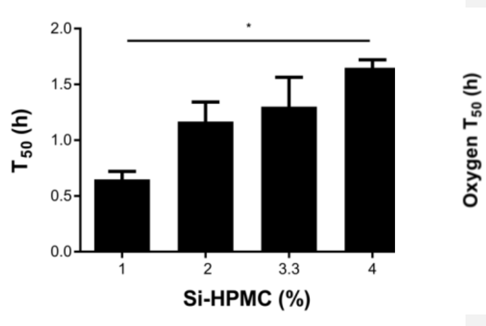
First published: 28 February 2018 | https://doi.org/10.1002/term.2656

Ischemia in Hydrogels

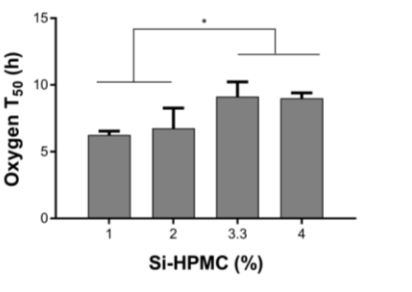


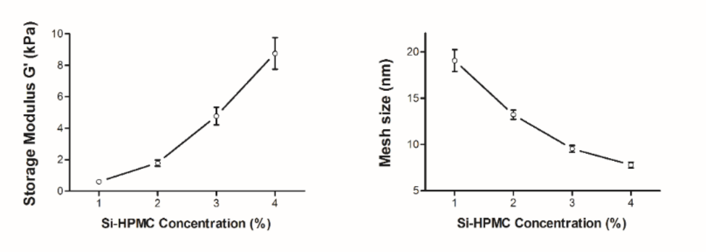


Glucose



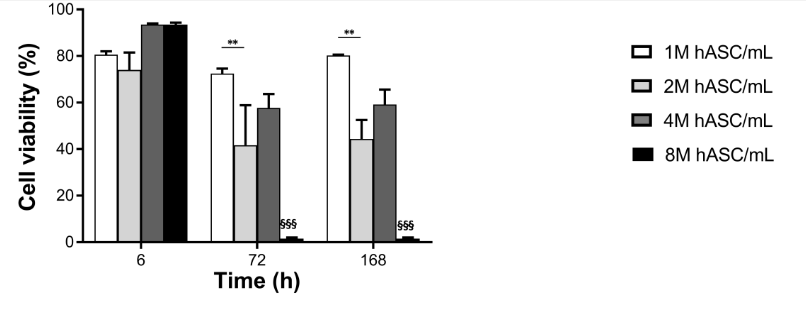
Oxygen

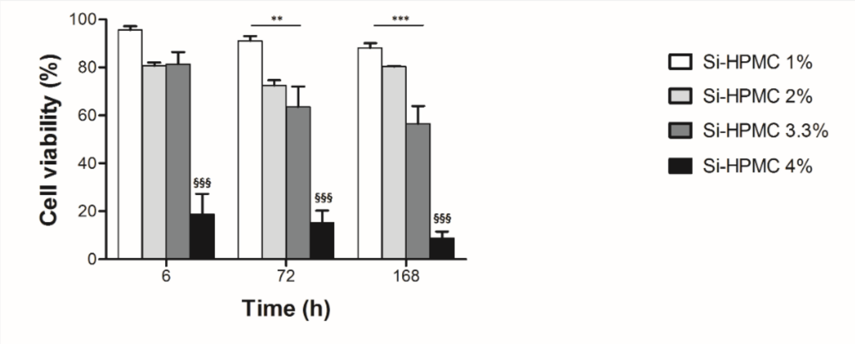




2% Si-HPMC

1 M hASC/ml





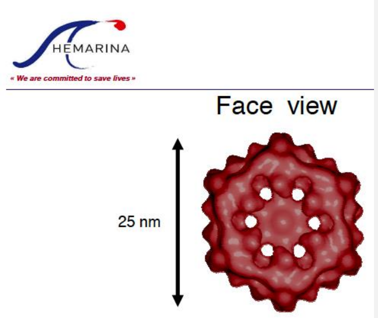
O2 and glucose in Biomaterials

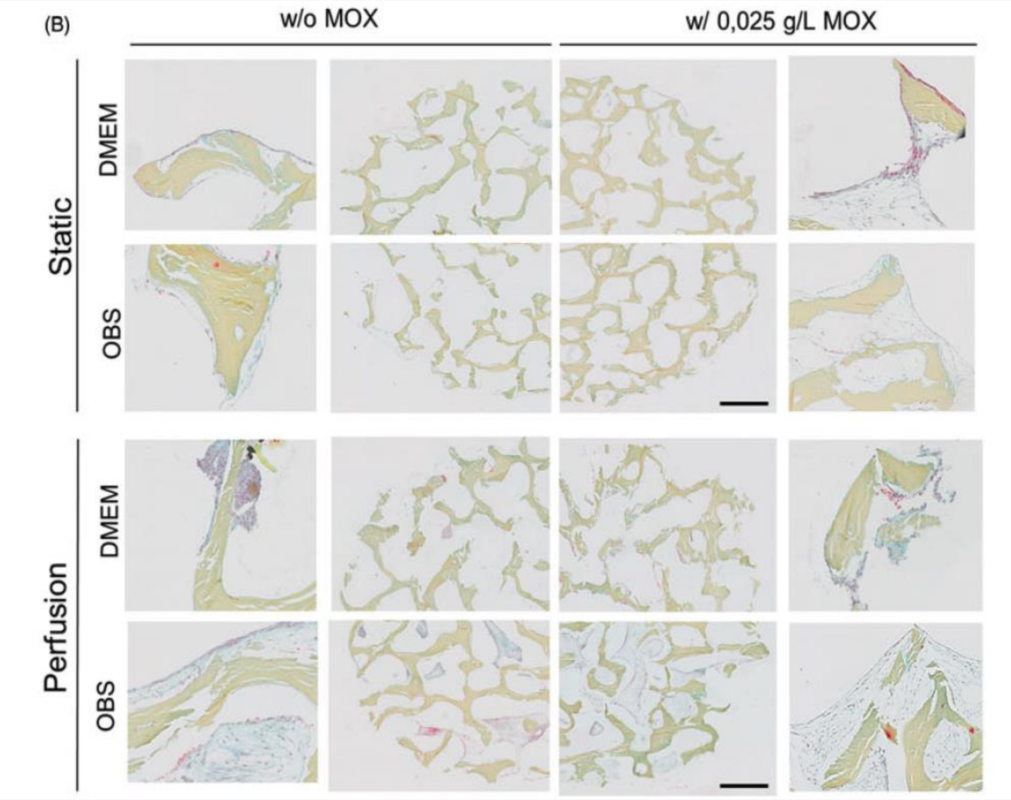
ARTIFICIAL CELLS, NANOMEDICINE, AND BIOTECHNOLOGY, 2017
https://doi.org/10.1080/21691401.2017.1365724

Taylor & Francis
Taylor & Francis Group

Adhesion, proliferation and osteogenic differentiation of human MSCs cultured under perfusion with a marine oxygen carrier on an allogenic bone substitute

Fiona Le Pape[a,b], Gaëlle Richard[a,c], Emmanuelle Porchet[a], Sophie Source[d,e], Frédéric Dubrana[f], Claude Férec[a,c,f], Valérie Polard[b], Richard Pace[d], Pierre Weiss[d], Franck Zal[b], Pascal Delépine[a,c*] and Elisabeth Leize[a,g*]

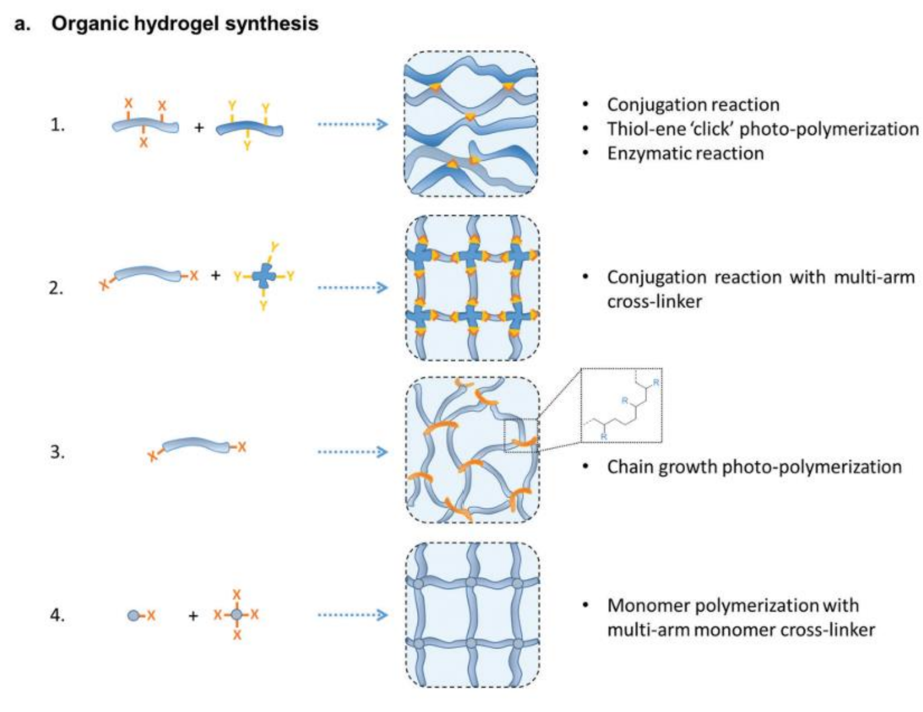




Cell hydrogel interactions

- Adhesion
- Stiffness
- Electrostatic Charges
- Degradation
- Visco-elasticity
- Molecule diffusion
- Cell-cell contact
- → In 3D : you change 1 parameter all the overs can change

Hybrid Hydrogels

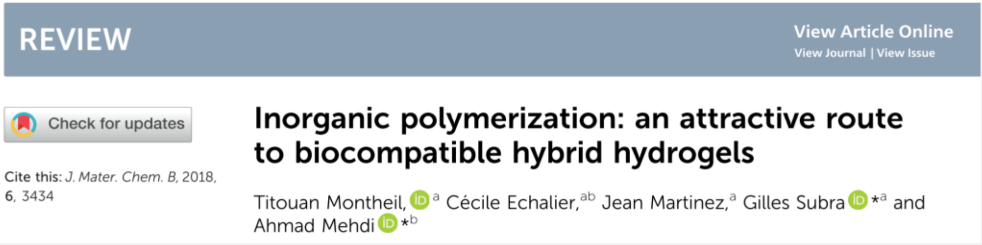

a. Organic hydrogel synthesis

1.
- Conjugation reaction
- Thiol-ene 'click' photo-polymerization
- Enzymatic reaction

2.
- Conjugation reaction with multi-arm cross-linker

3.
- Chain growth photo-polymerization

4.
- Monomer polymerization with multi-arm monomer cross-linker


REVIEW

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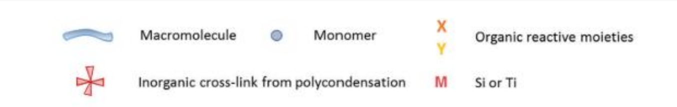
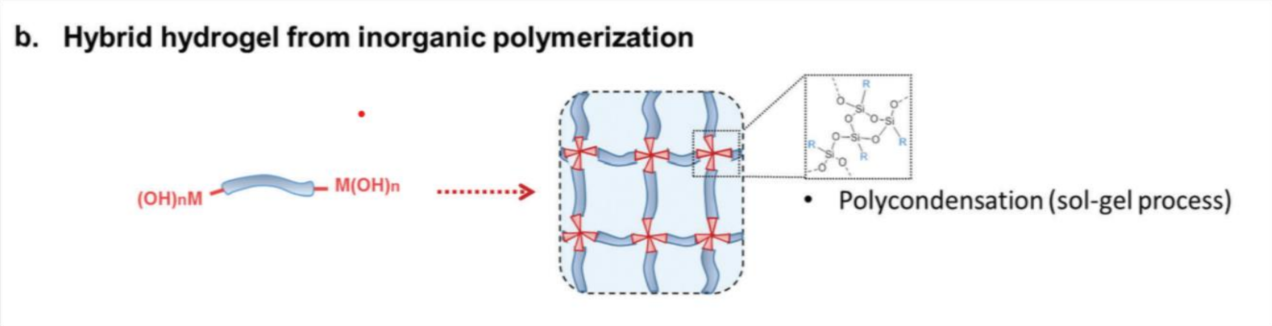
Cite this: *J. Mater. Chem. B*, 2018, 6, 3434

Inorganic polymerization: an attractive route to biocompatible hybrid hydrogels

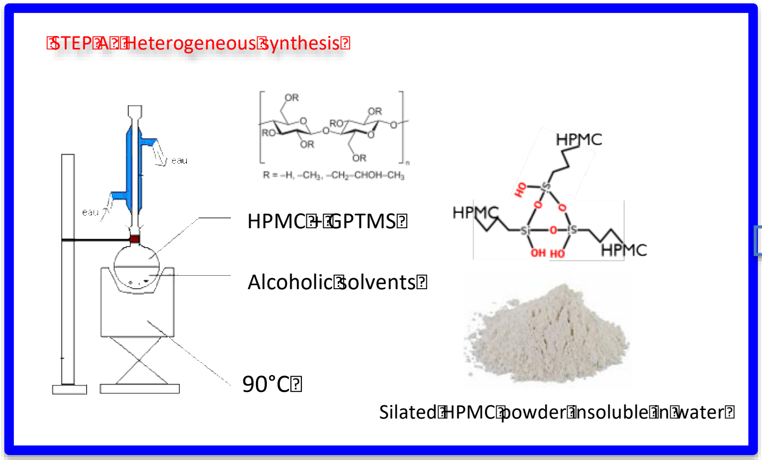
Titouan Montheil,[a] Cécile Echalier,[ab] Jean Martinez,[a] Gilles Subra*[a] and Ahmad Mehdi*[b]




b. Hybrid hydrogel from inorganic polymerization

- Polycondensation (sol-gel process)

Silated HPMC



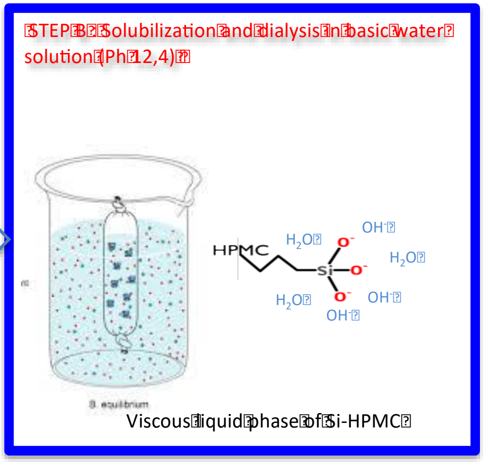
STEP A : Heterogeneous synthesis

HPMC + GPTMS

Alcoholic solvents

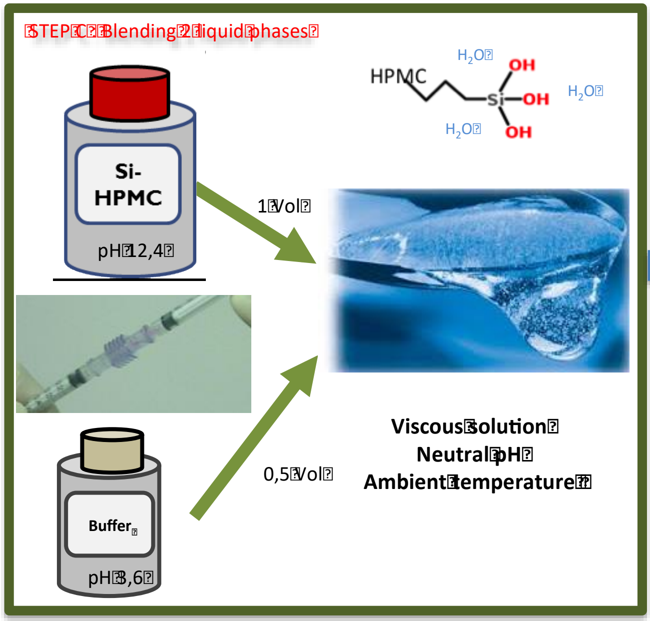
90°C

Silated HPMC powder insoluble in water



STEP B : Solubilization and dialysis in basic water solution (Ph 12,4)

Viscous liquid phase of Si-HPMC

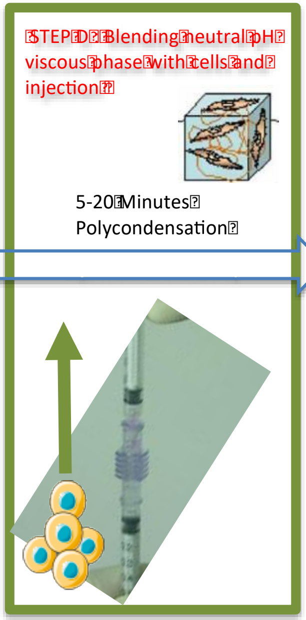


STEP C : Blending 2 liquid phases

1 Vol

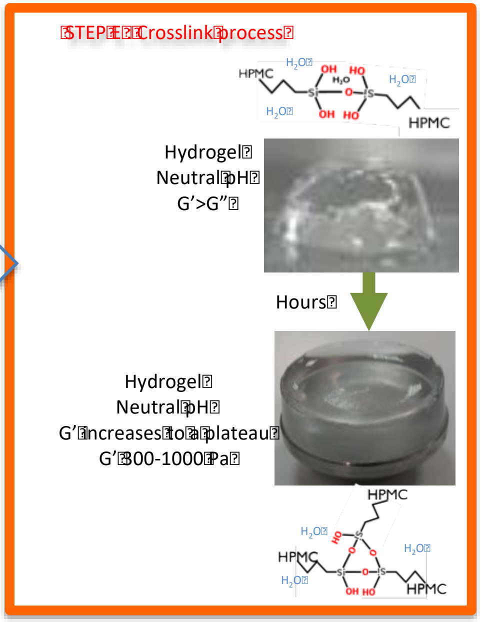
0,5 Vol

Viscous solution
Neutral pH
Ambient temperature



STEP D : Blending neutral pH viscous phase with cells and injection

5-20 Minutes
Polycondensation

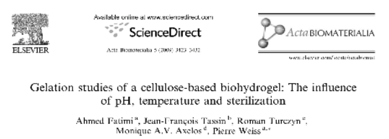


STEP E : Crosslink process

Hydrogel
Neutral pH
G'>G"

Hours

Hydrogel
Neutral pH
G' increases to a plateau
G' 300-1000 Pa



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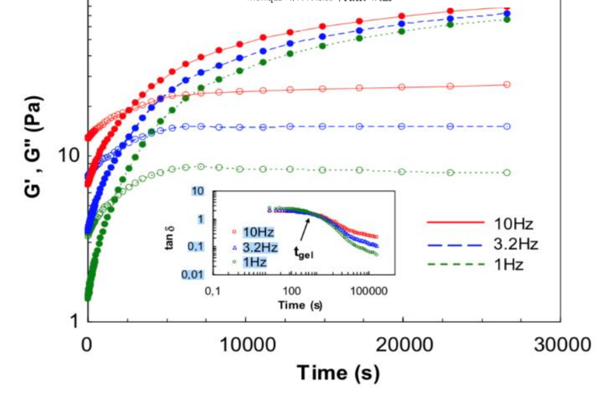
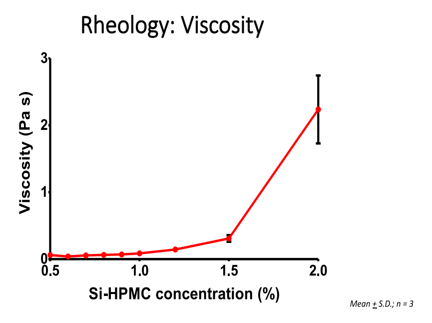
Acta BIOMATERIALIA

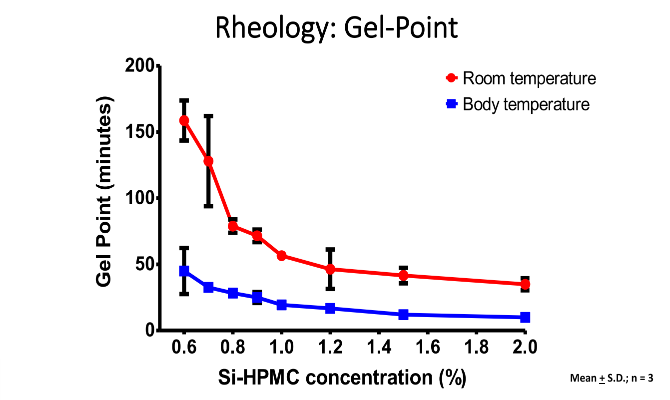
Gelation studies of a cellulose-based biohydrogel: The influence of pH, temperature and sterilization

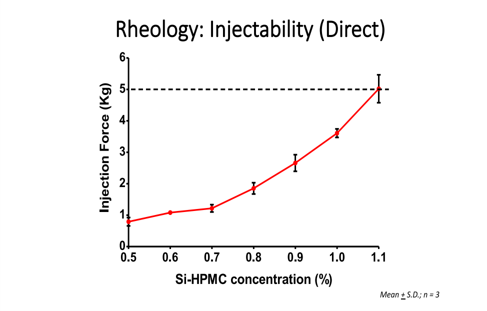
Ahmed Fatimi[a], Jean-François Tassin[b], Roman Turczyn[c], Monique A.V. Axelos[d], Pierre Weiss[a,*]



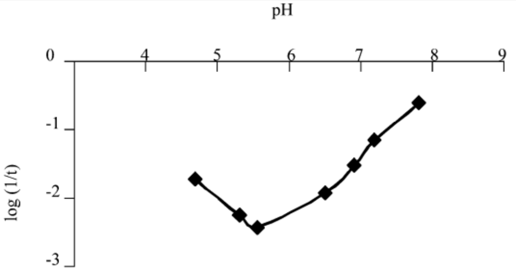
Time evolution of G'(closed symbols) andG"(open symbols) at25°C for Si-HPMC (3%) hydrogel at pH 7.4. Three frequencies wereapplied (1, 3.2 and 10 Hz) at a fixed total shear stress (1 Pa). The tandisshown in the inset vs. the frequency for Si-HPMC hydrogel where gel time(tgel) is indicated.



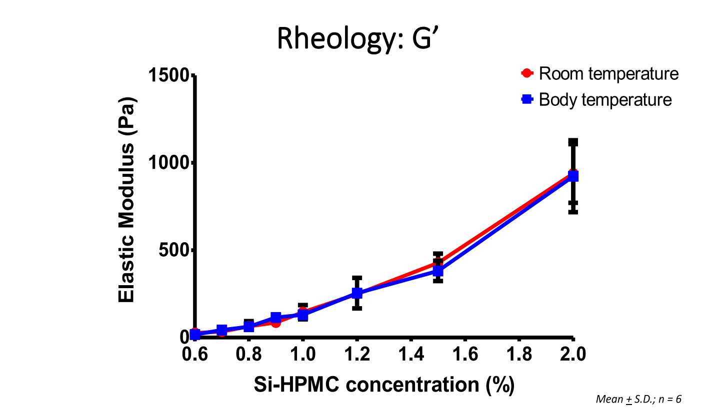


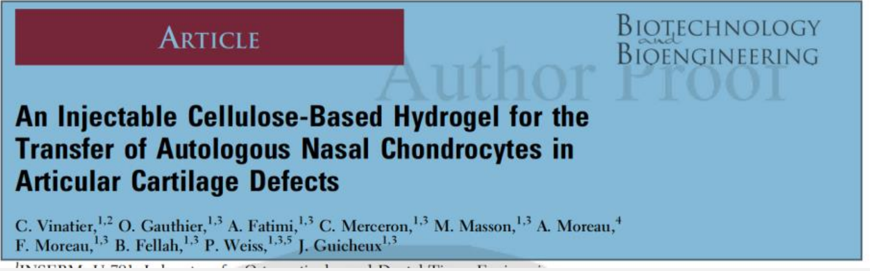


G.Pattapa, ANR Anthos



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





ARTICLE

BIOTECHNOLOGY and BIOENGINEERING

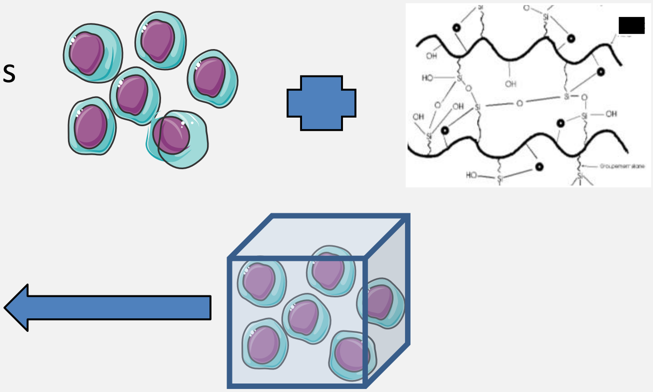
Author Proof

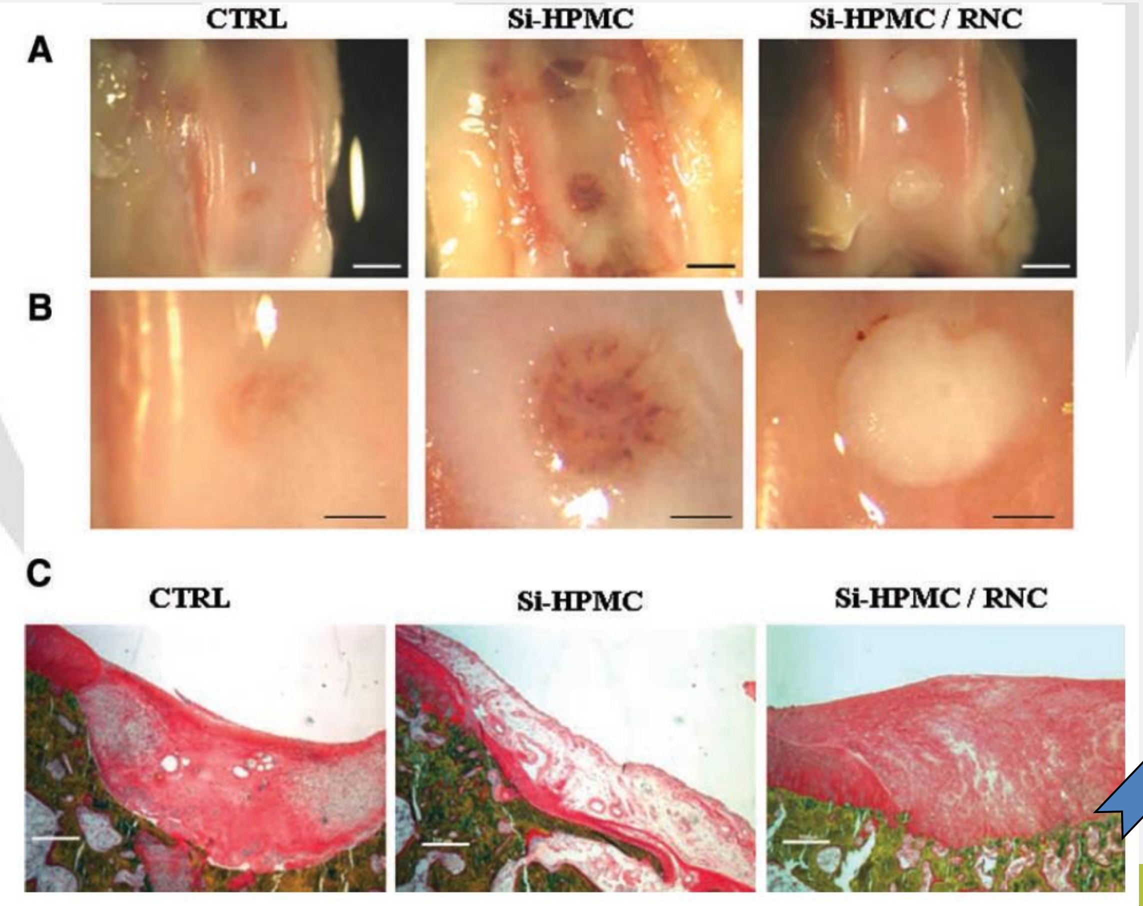
An Injectable Cellulose-Based Hydrogel for the Transfer of Autologous Nasal Chondrocytes in Articular Cartilage Defects

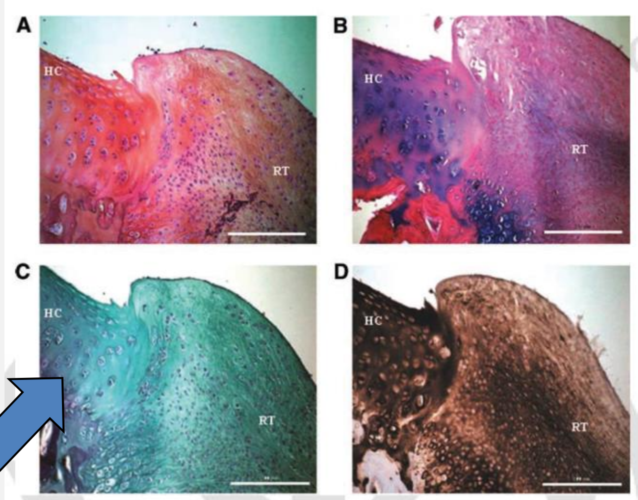
C. Vinatier,[1,2] O. Gauthier,[1,3] A. Fatimi,[1,3] C. Merceron,[1,3] M. Masson,[1,3] A. Moreau,[4] F. Moreau,[1,3] B. Fellah,[1,3] P. Weiss,[1,3,5] J. Guicheux[1,3]

For cartilage

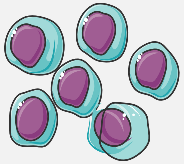
Autologous
Nasal chondrocytes



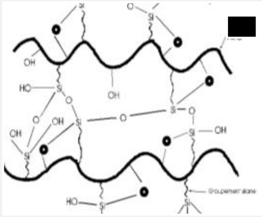


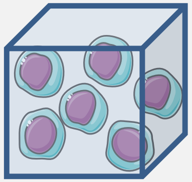


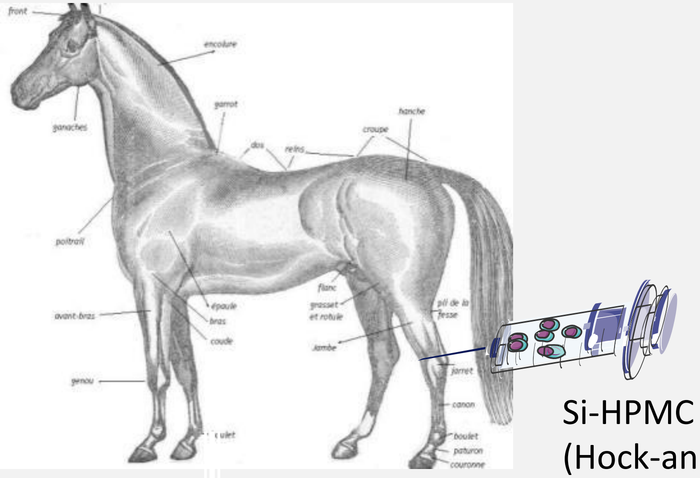
Cartilage engineering « Proof of concept in large animal and in full-thickness cartilage defect»



Autologous
Nasal chondrocytes







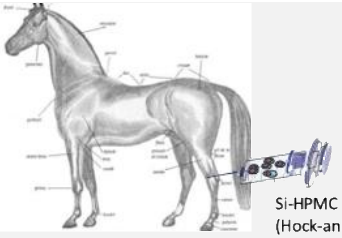
Si-HPMC 3%
(Hock-ankle)

Arthroscopic injection
(cartilage defect)

O. Geffroy, Equine clinics, National veterinary school of Nantes.

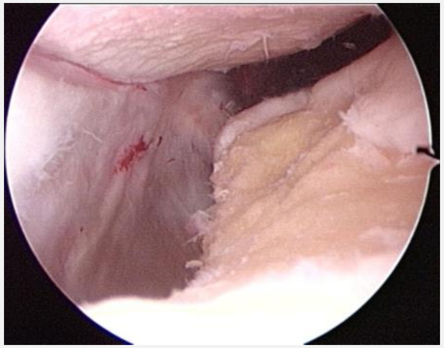
Equine clinical case

stifle (Knee)

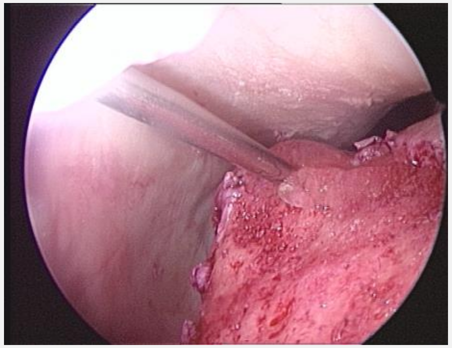


Si-HPMC 3%
(Hock-ankle)

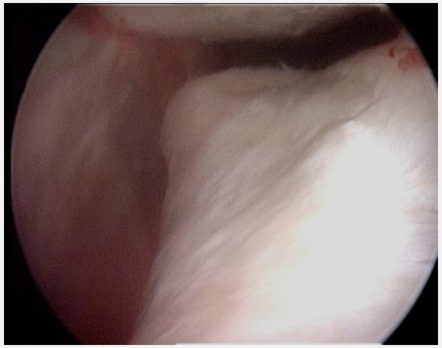
Arthroscopic injection
(cartilage defect)



Cartilage defect

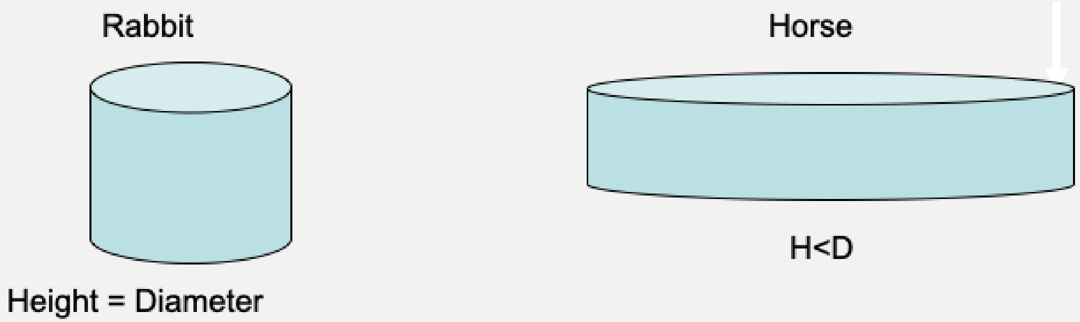


Injection ENC/Si-HPMC



13 weeks

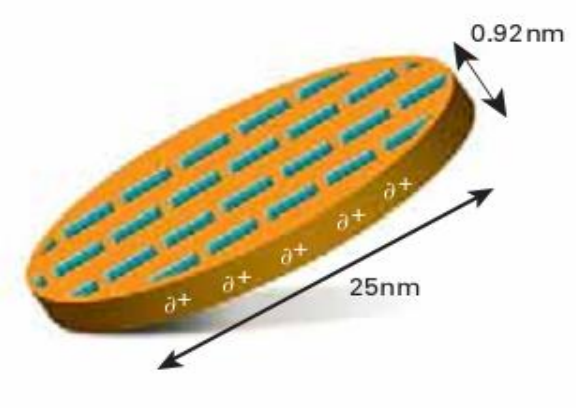
☞ Cartilaginous tissue formation with smooth surface

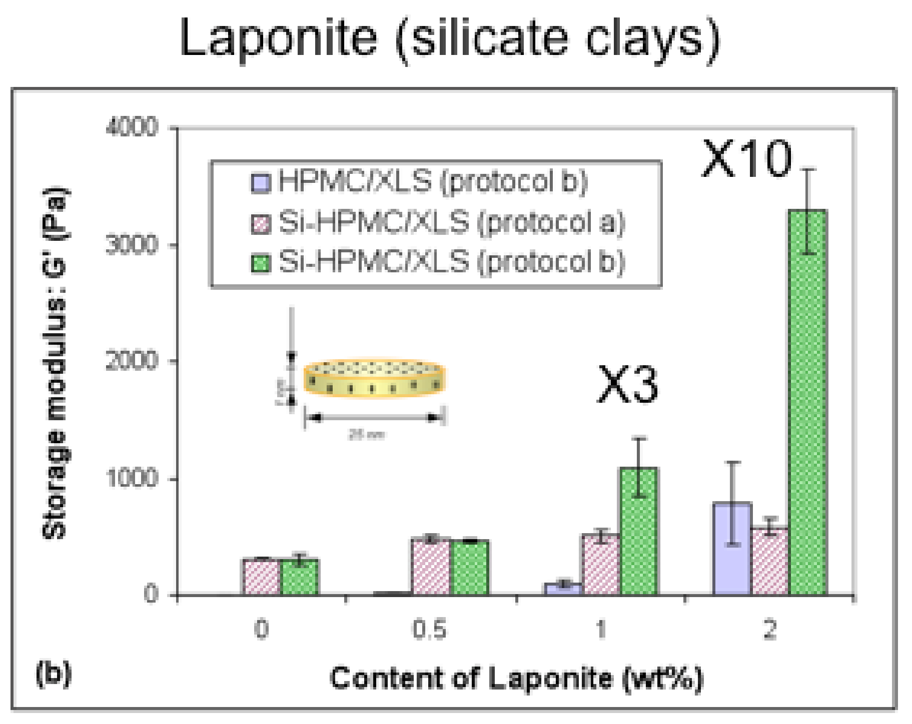


- Hydrogel is weak and does not support unfavourable cavity design
- This Si-HPMC seems bond to the cartilage surface

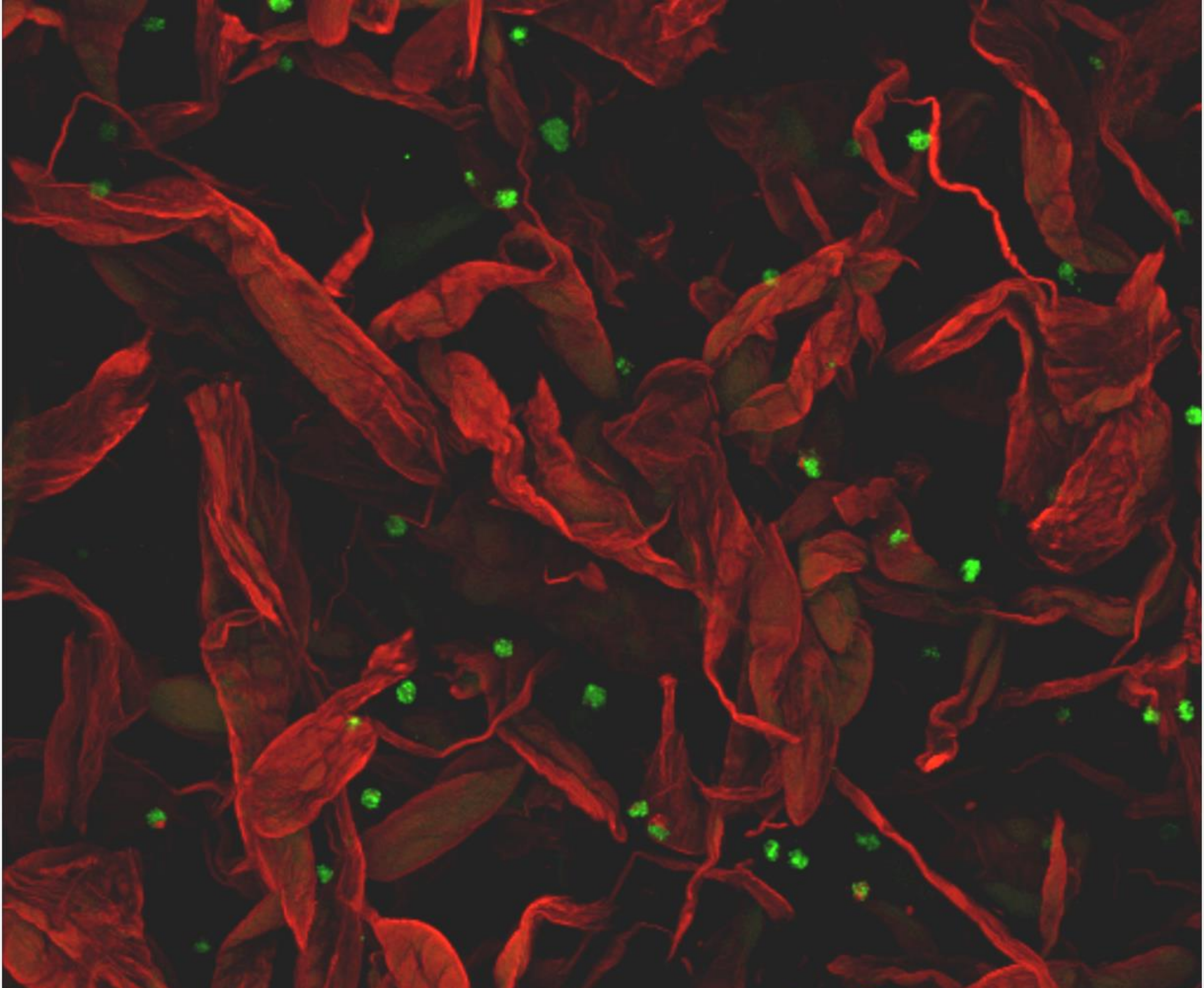
Laponites (XLS et XLG)

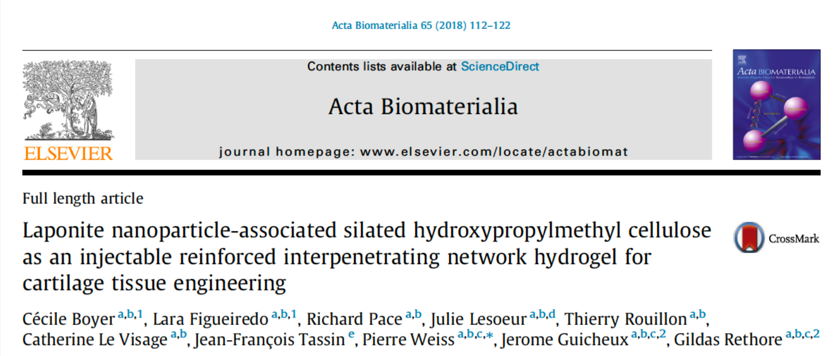
Clay nano disc
Silicate based
Diameter : 25 nm
Thickness : 1 nm





XLS 55% silicate, 26% MgO, 1% LiO, 3% Na_2O, 4% H_3 O_4.
XLG 60% silicate, 28% MgO, 1% LiO, 3% Na_2O.





Acta Biomaterialia 65 (2018) 112–122

Contents lists available at ScienceDirect

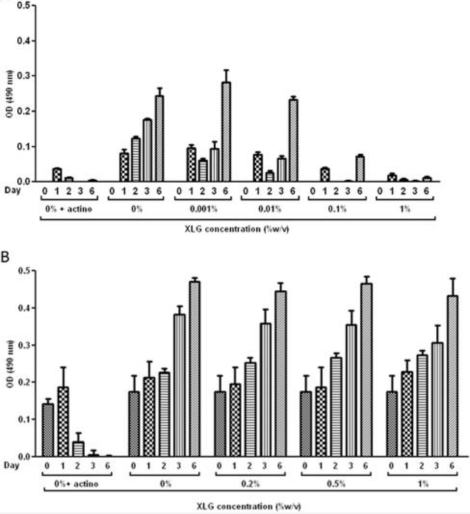
Acta Biomaterialia

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

Full length article

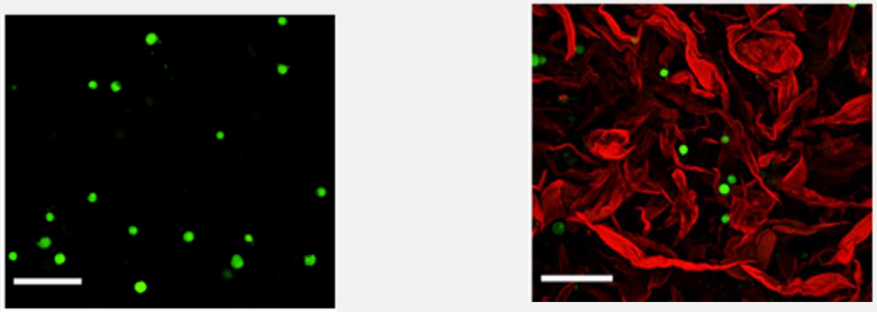
Laponite nanoparticle-associated silated hydroxypropylmethyl cellulose as an injectable reinforced interpenetrating network hydrogel for cartilage tissue engineering

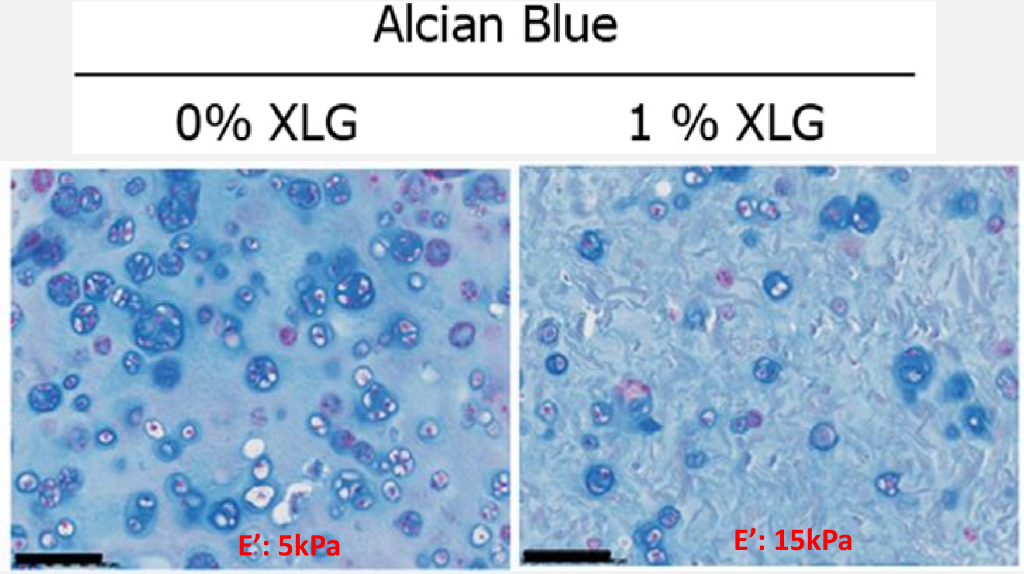
Cécile Boyer [a,b,1], Lara Figueiredo [a,b,1], Richard Pace [a,b], Julie Lesoeur [a,b,d], Thierry Rouillon [a,b], Catherine Le Visage [a,b], Jean-François Tassin [e], Pierre Weiss [a,b,c,*], Jerome Guicheux [a,b,c,2], Gildas Rethore [a,b,c,2]



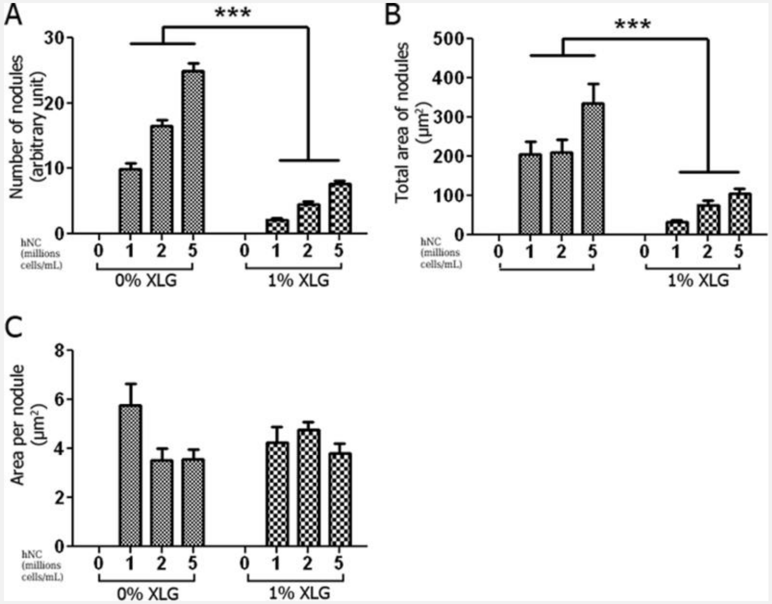
2D free laponites

2D with laponite in the hydrogel on the top of the cells



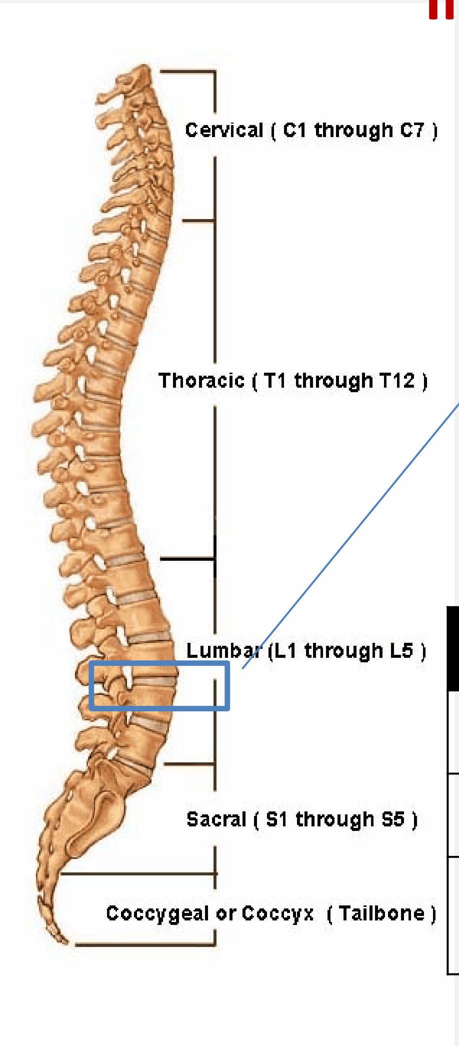


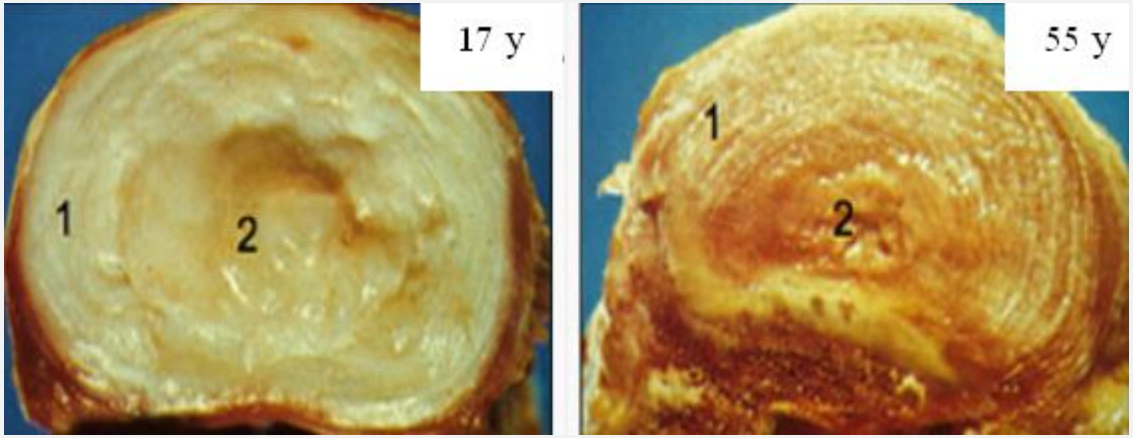
Subcutaneous implantation of hNC with Si-HPMC/XLG hydrogels in a nude mice model



Multi parameters

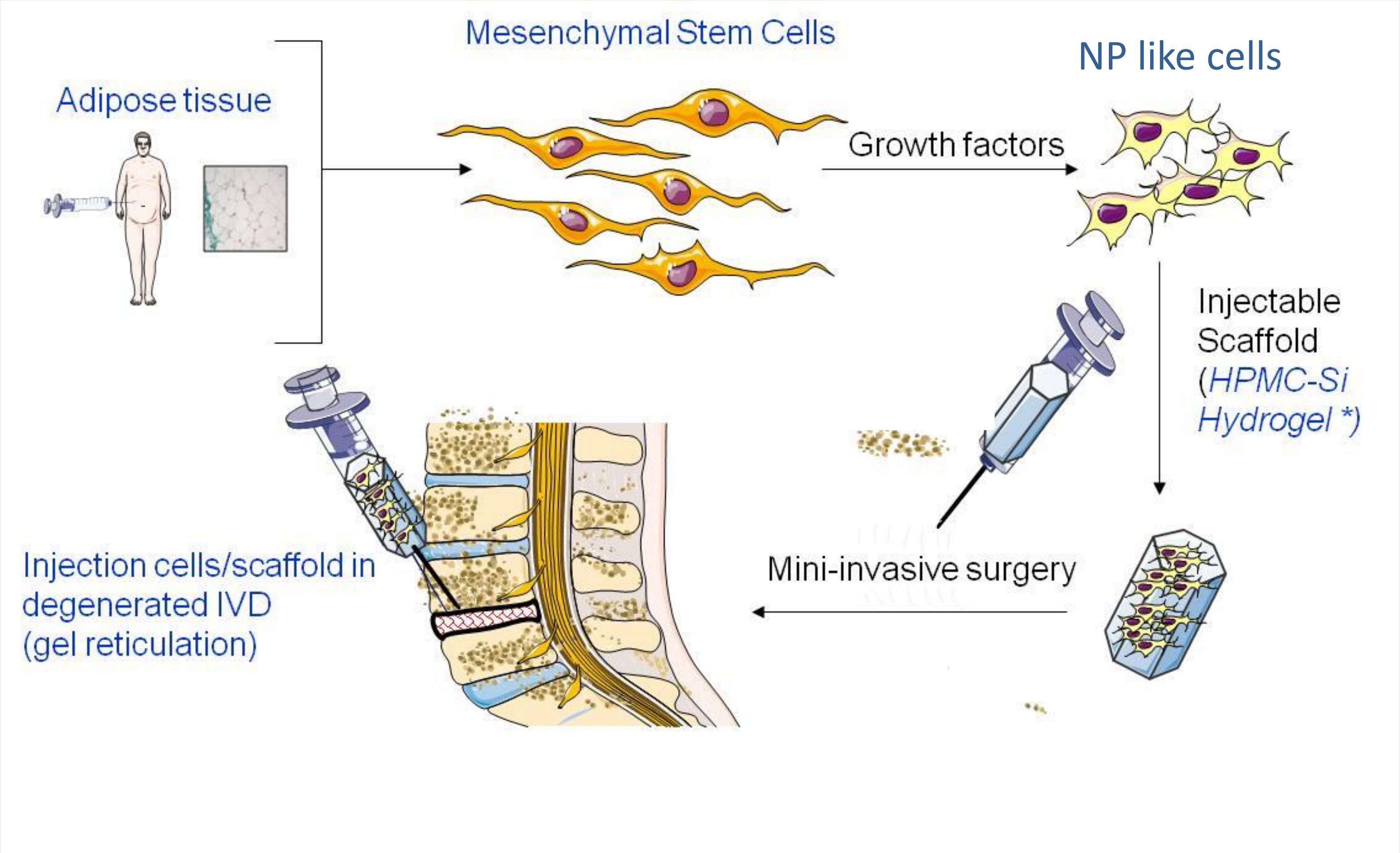
Intervertebral disc degeneration : IVD





	Healthy	Degenerated
Cell density	+	-
PG amount	+++	+
Hydration	+++	+

IVD Tissue engineering strategy

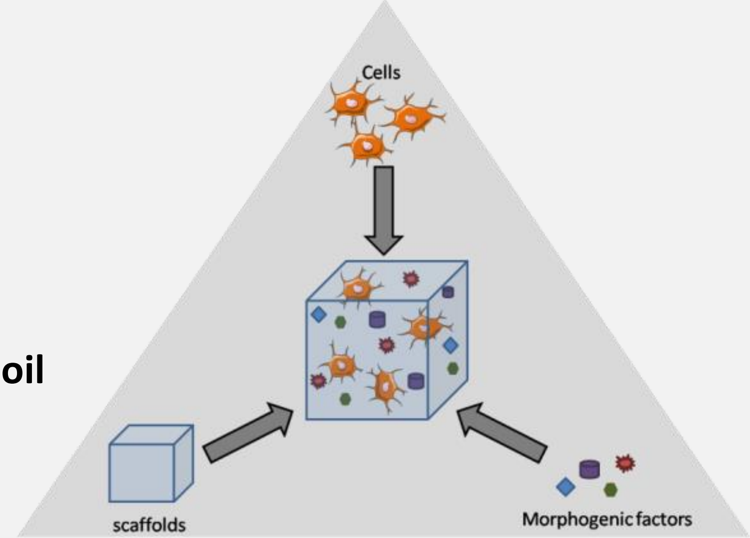


(Clouet *et al*, Joint Bone Spine, 2009

Bone Tissue engineering

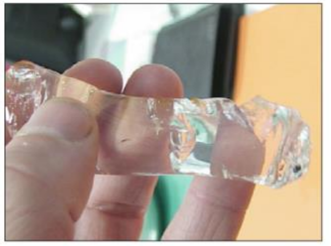
1) CaP

cells like seeds



Biomaterials like Soil

GFs like fertilizer



2) Hydrogels ?

Merceron, Vinatier, Guicheux. Joint Bone Spine 2008

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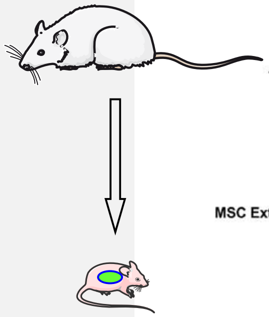
PLOS ONE

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¶]

Bone Tissue Engineering using CaP ceramics and BMSC ?

GFP Rats Remy,S et Al.
Transgenic Research 2010



Nude mice (n= 2x30)
Sacrifice 8 weeks

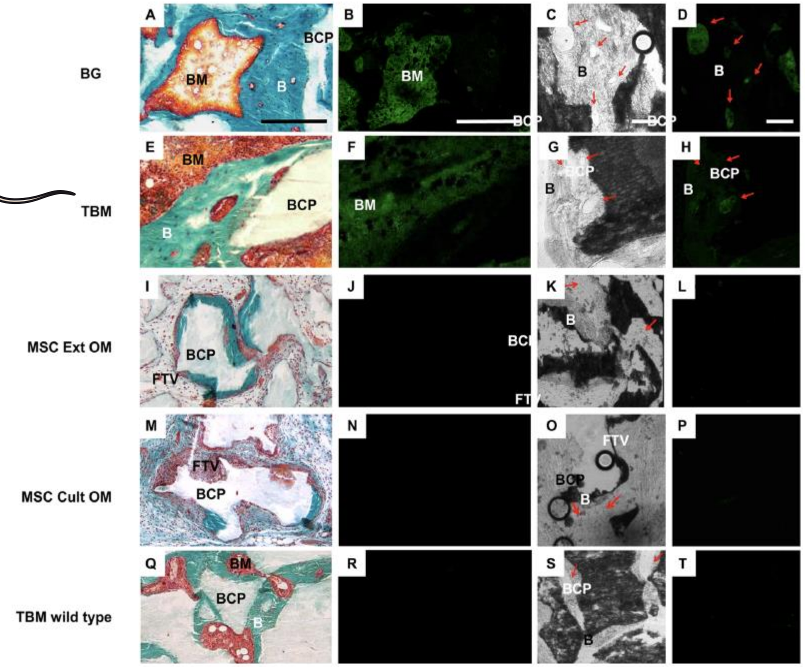
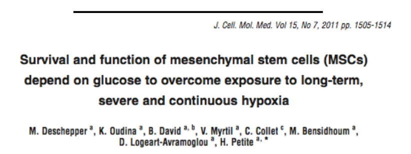


Figure 7. ''*In vivo*'' tracking of donor cells. Goldner trichrome staining (A, E, I, M and Q). B: bone, BCP: biphasic calcium phosphate, BM: bone marrow, FVT: fibrovascular tissue. Bar: 250 µm. Green fluorescence of GFP retrieved in subcutaneous implants (B, F, J, N and R). Nude mice implanted with 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

MSCs fate ?

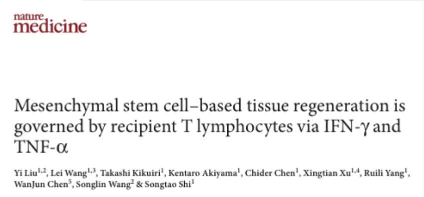
→ Cells die after 4 weeks of implantation in bone


J. Cell. Mol. Med. Vol 15, No 7, 2011 pp. 1505-1514

Survival and function of mesenchymal stem cells (MSCs) 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 [a], D. Logeart-Avramoglou [a], H. Petite [a, *]

➡ Hypoxia with Glucose doesn't kill MSC : Ischemia is the problem


nature medicine

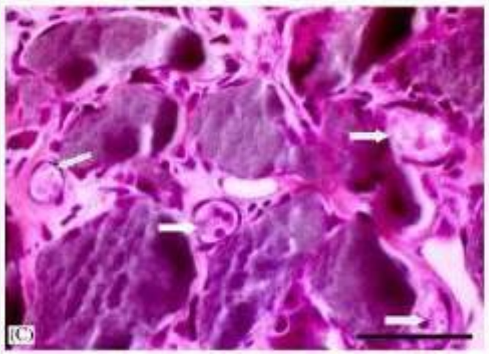
Mesenchymal stem cell–based tissue regeneration is governed by recipient T lymphocytes via IFN-γ and TNF-α

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

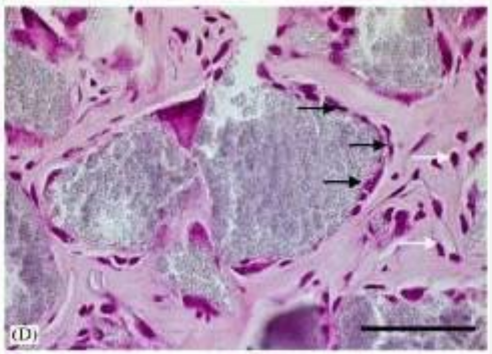
➡ T cells regulate autologous MSC

Bone Tissue reconstruction *in vivo* with an hydrogel

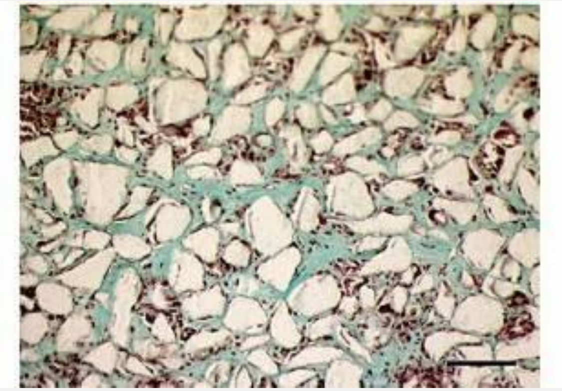
BMSC with Si-HPMC / BCP formulation implanted under skin of mice for 4 weeks



Blood vessels



Osteoblasts and osteocytes



Goldner staining paraffin sections

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SCIENCE DIRECT

Biomaterials 27 (2006) 3256–3264

Biomaterials

www.elsevier.com/locate/biomaterials

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

Christophe Trojani[a,b], Florian Boukhechba[a], Jean-Claude Scimeca[a], Fanny Vandenbos[c], Jean-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 MSC in Hydrogel

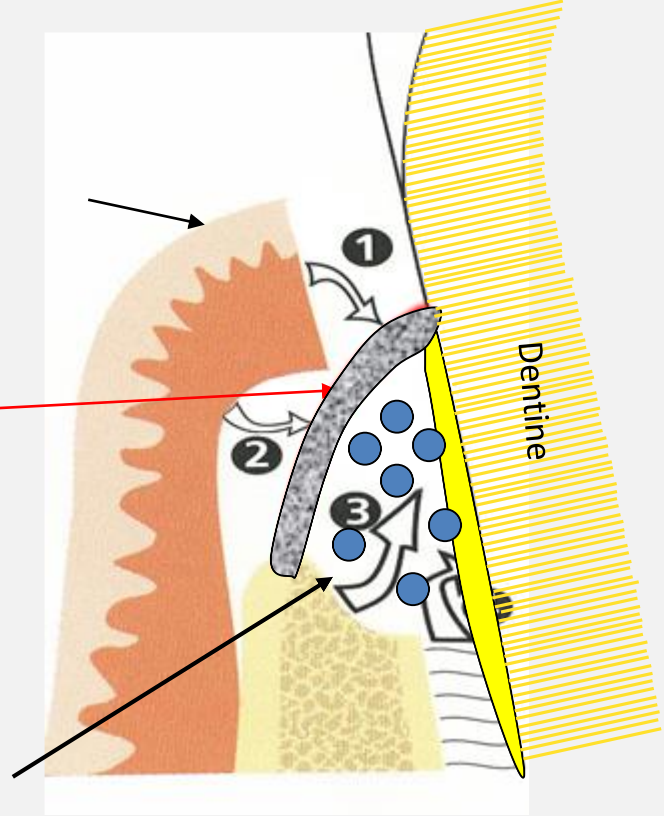
→ enough nutrients diffusion

→Hydrogel is a shield against immune system ?

The futur

GTR using stratification

Periodontal disease



Injectable Hydrogel Membrane

IBS : Injectable bone substitute = fast bone ingrowth

- Easy and quick protocol
- Spatial control of tissue differentiation

Dental Materials
Volume 34, Issue 12, December 2018, Pages 1769-1782

In situ photochemical crosslinking of hydrogel membrane for Guided Tissue Regeneration

Pauline Marie Chichirico [a, b], Raphael Riva [a], Jean-Michel Thomassin [a], Julie Lesoeur [b, c, d], Xavier Struillou [b, c, e], Catherine Le Visage [b, c], Christine Jérôme [a, 1], Pierre Weiss [b, c, e] [1]

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https://doi.org/10.1016/j.dental.2018.09.017

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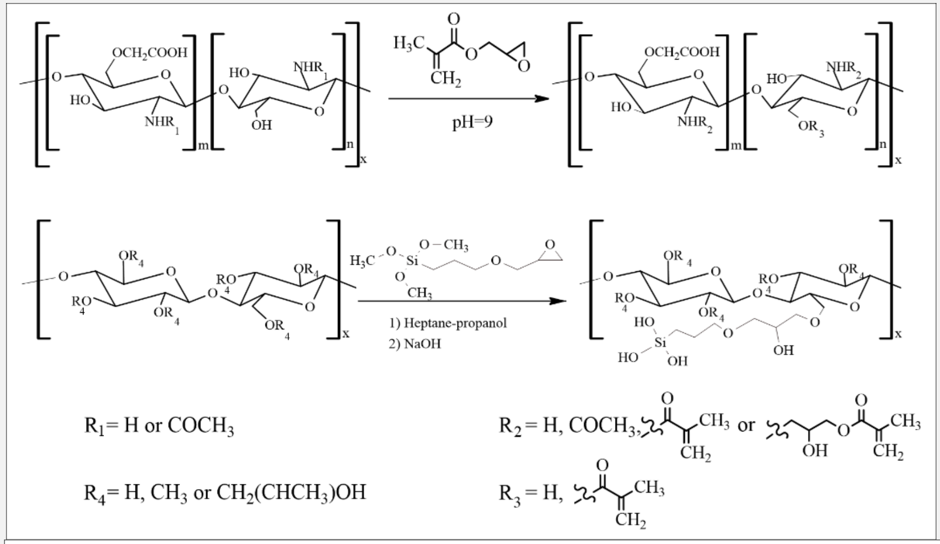
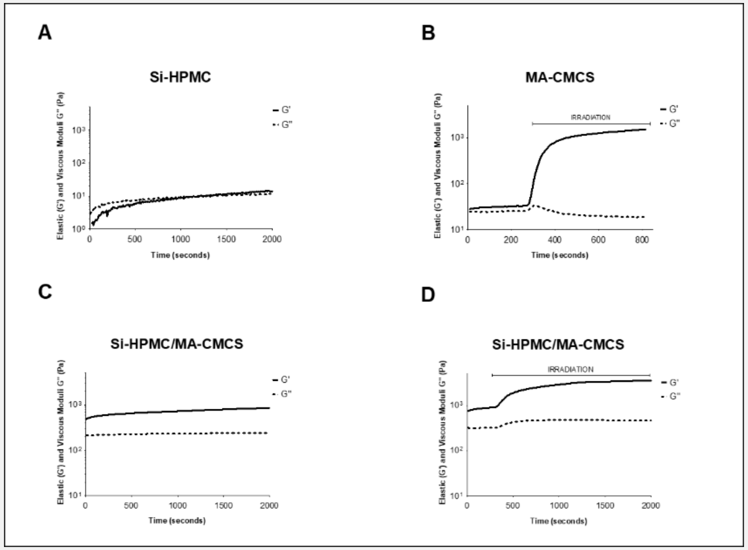
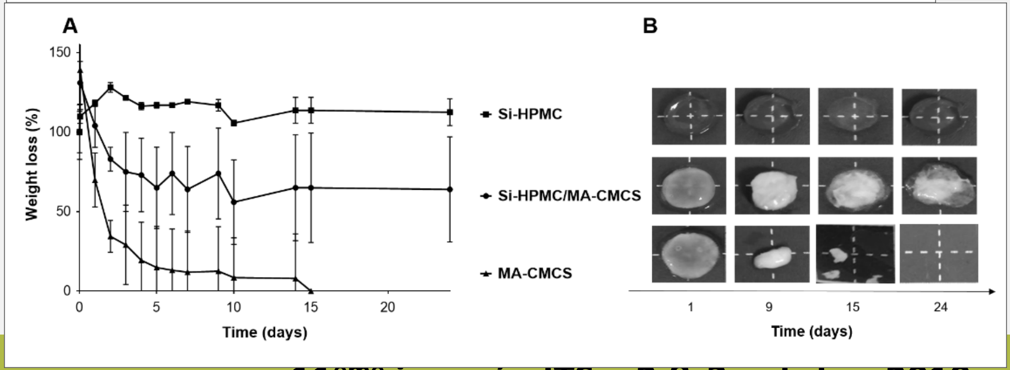
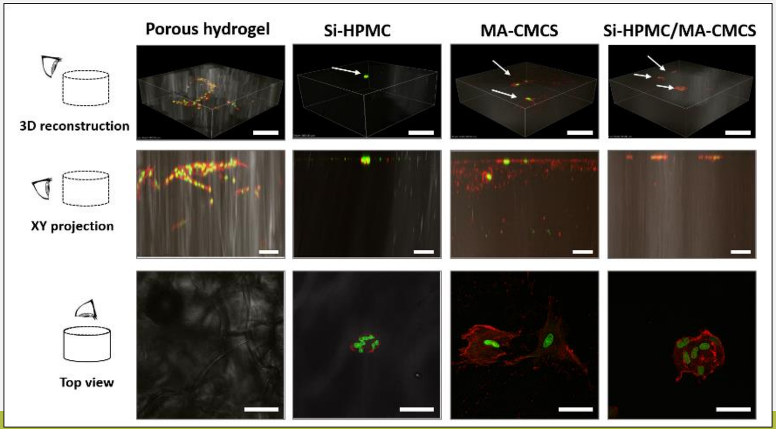
GTR membrane

Pauline Chichirico
(Posture program)



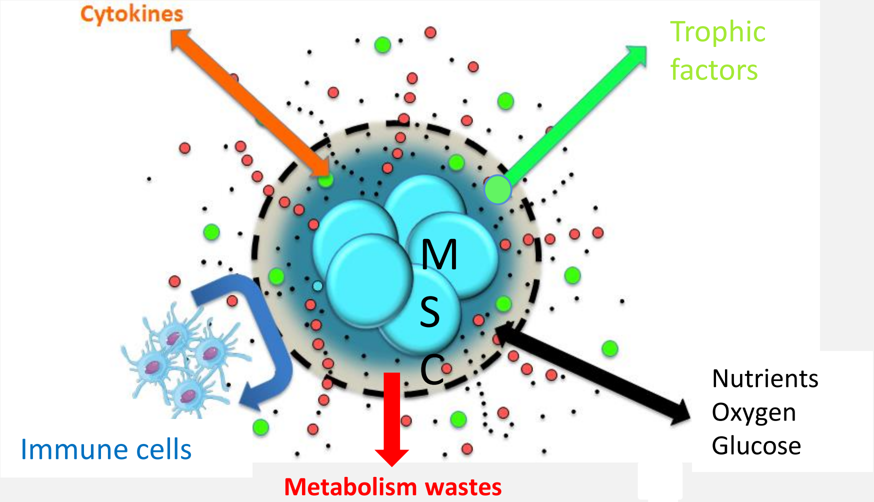


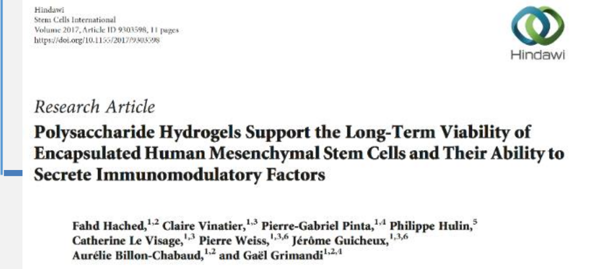




Assisted cell therapy

Embedded MSC in hydrogel




Hindawi
Stem Cells International
Volume 2017, Article ID 9303598, 11 pages
https://doi.org/10.1155/2017/9303598

Research Article

Polysaccharide Hydrogels Support the Long-Term Viability of Encapsulated Human Mesenchymal Stem Cells and Their Ability to Secrete Immunomodulatory Factors

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

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From science to health

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REGENERATIVE MEDICINE CLUSTER

Agence Nationale de la Recherche
ANR

Conclusion

- Regenerative medicine / Innovation
  - >10 SMEs
  - >10 Medical applications
- New biomaterials / Closer to ECM
- 3D printing and Bio printing
  - ART Bordeaux, ECN...
  - Personalized medicine
  - Bio-Ink
- Assisted cell therapy
- Extra cellular vesicles

THANK YOU

- 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

Resercher ID : P-1372-2014