

L'impression 3D appliquée à l'ingénierie tissulaire

Concept, applications potentielles, évaluation de la biocompatibilité des matrices

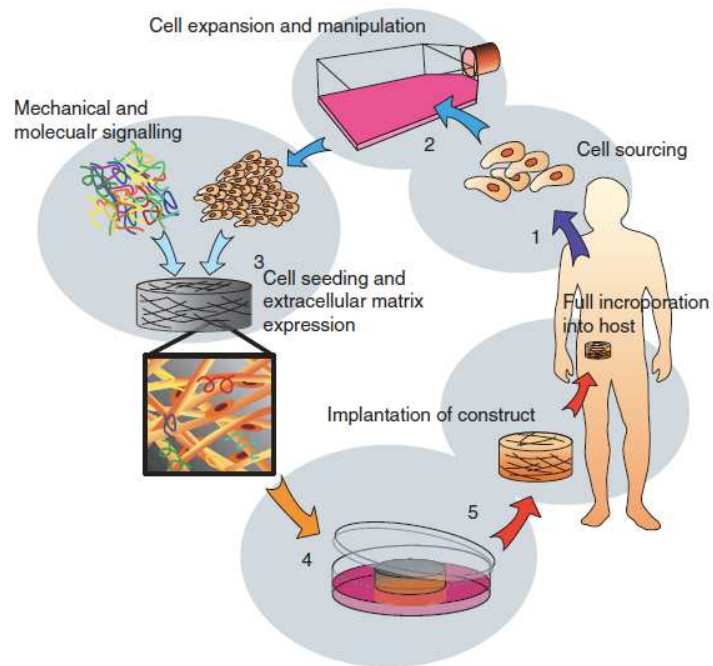
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UFR d'Odontologie et Inserm U1026
Université de Bordeaux

DÉCLARATION DE LIENS D'INTÉRÊT

Pas de Conflit d'intérêt



Ingénierie Tissulaire ?

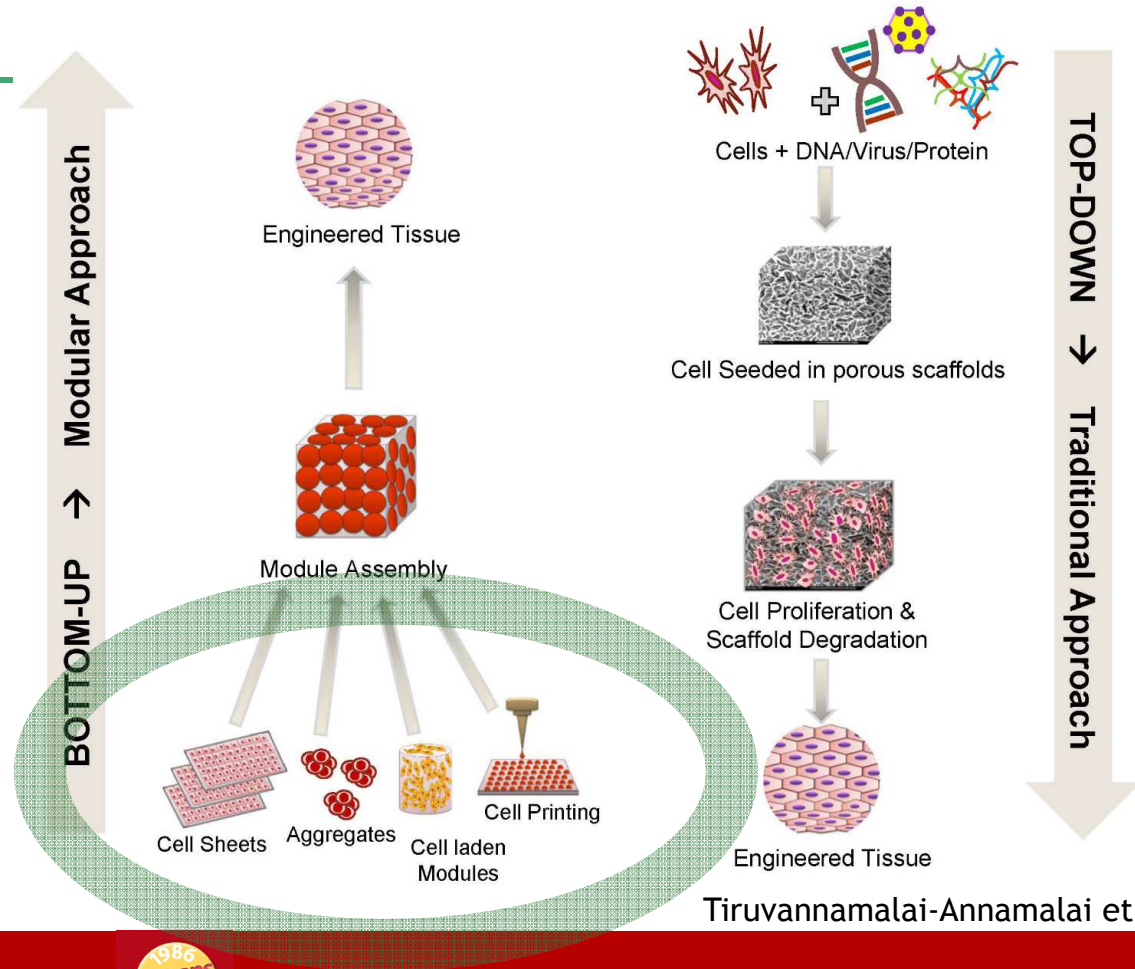


Clemens Van Blitterswijk, 2008

“**Tissue Engineering** is the application of the principles and methods of **engineering** and **life sciences** toward the fundamental understanding of structure-function relationships in normal and pathologic mammalian tissue and the development of biological substitutes to **restore, maintain, or improve function.**”

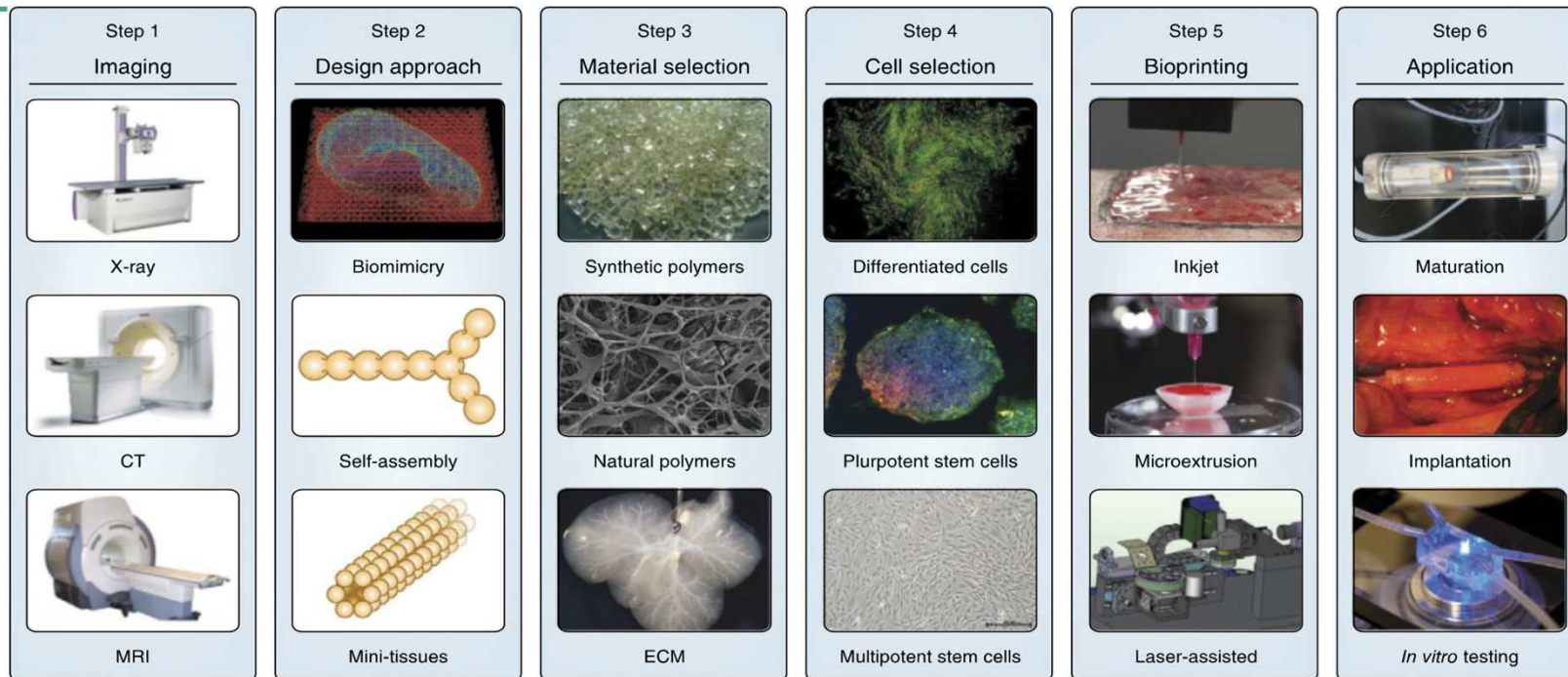
Langer, R., and Vacanti, J. (1993).
Tissue engineering. *Science* 260, 920–926.

Deux Approches en Ingénierie Tissulaire



Tiruvannamalai-Annamalai et al. PlosOne 2014

Quelles Etapes ?



Murphy SV, Atala A. Nat Biotechnol 2014

Imprimantes 3D ?

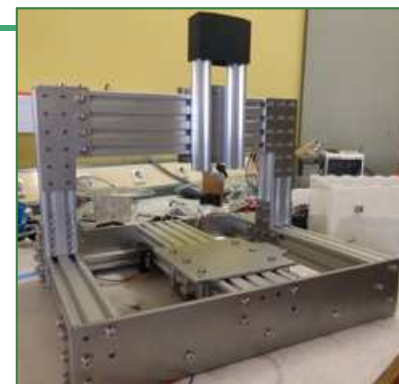
Technology

- 1993 - Selective laser sintering (SLS)**
Lee and Barlow, to assist the regeneration of bone defects and injuries
- 1997 - Stereolithography (SLA)**
Level et al. to fabricate a porous hydroxyapatite orbital floor prosthesis for 3D bioimplant
- 1998 - Three-dimensional printing (3DP)**
Kim et al. to evaluate the survival and function of hepatocytes on a biodegradable polymer scaffold
- 2000 - 3D fiber deposition (3DF)**
Landers and mulhaupt to built scaffold from hydrogels for soft tissue engineering
- 2000 - Fused deposition modeling (FDM)**
Hutmacher et al. to process bioresorbable scaffolds for TE applications
- early 2000s - Precision extrusion deposition (PED)**
Wang et al. to avoid the time consuming precursor step of filament preparation and frequent filament buckling failure in FDM
- 2002 - Pressure assisted micro syringe (PAM)**
Pozzi et al. employing a 3D micropositioning system with a pressure controlled micro syringe to produce 3D polymer scaffolds
- 2002 - Low-temperature deposition manufacturing**
Xiong et al. to fabricate porous scaffold for bone tissue engineering by freeze-drying solvents
- 2004 - Robocasting**
Cesarano patented as a method to form 3D biocompatible porous scaffold
- 2004 - Biological laser printing (BioLP)**
Barron et al. to create 3 dimensional cell patterns with multiple cell types
- 2004 - Inkjet printing**
Boiland et al. to create cellular patterns of multiple cell types with high throughput
- 2006 - Electrohydrodynamic jetting (EHDJ)**
Jayasinghe et al. to deposit living cells

Impression 3D, Médecine et Chirurgie

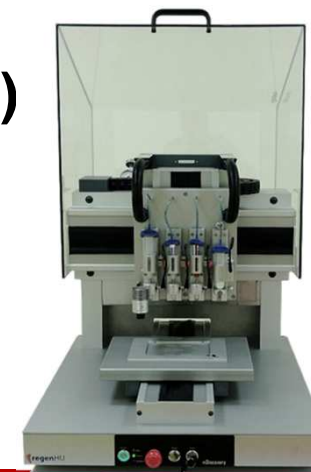
- **Imprimantes 3D « Conventionnelles »**

- Aide à la chirurgie
- Biomatériaux sur mesure



- **Bio-imprimantes (impression d'éléments biologiques)**

- Modèles Cellulaires
- Modèles Tissulaires
- Médecine Régénératrice



Planification – Guides Chirurgicaux

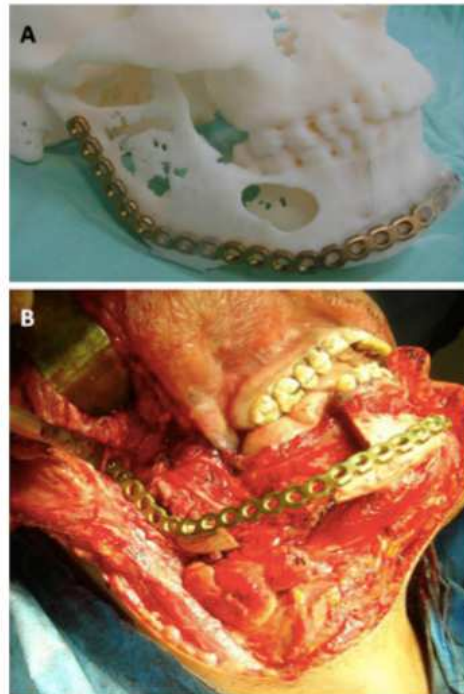
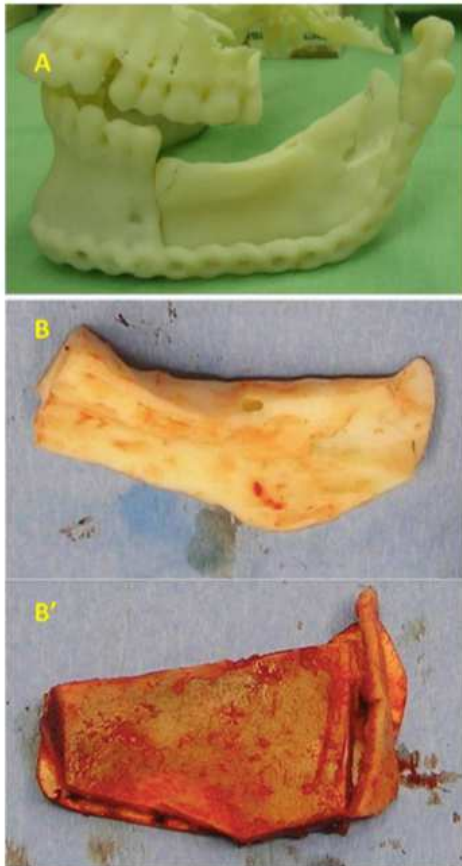


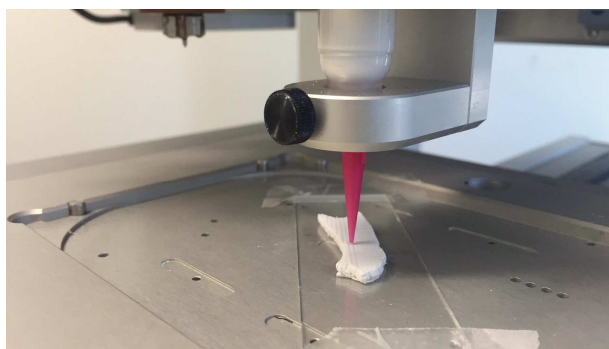
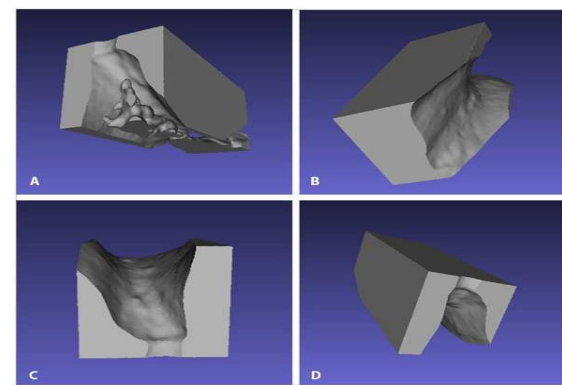
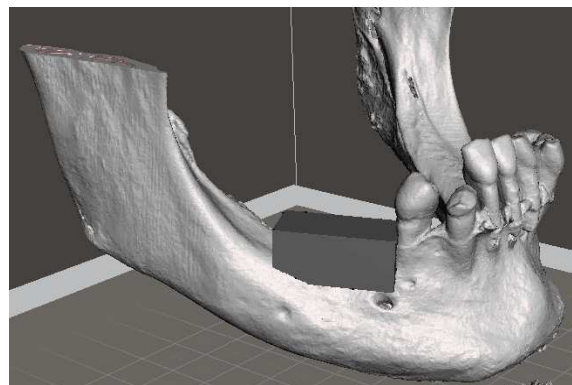
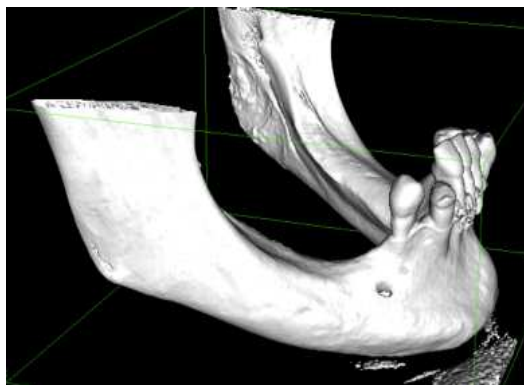
Fig. 3. A, Precontoured mandibular reconstruction plate placed over the right mandible consisting the ameloblastoma B, Reconstruction plate bridges the gap following tumour resection.

Cohen A. et al. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:661-666



résine biocompatible de Classe 1
(EN-ISO 10993-1:2009/AC:2010, USP Class VI)

Substituts Osseux sur mesure Collaboration RegenHU®



DEFINITION ET INTERET DE LA BIOIMPRESSION ?

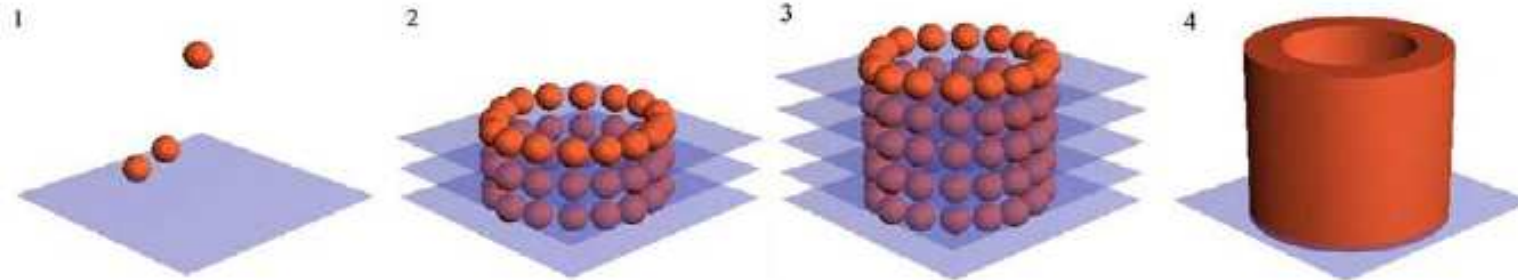
« Utilisation de procédés de **fabrication numérique** pour organiser et assembler en 3D les constituants des **tissus biologiques** dans le but de produire des greffons pour la **médecine régénératrice** ou des **modèles** pour la recherche biomédicale »

F. Guillemot, V. Mironov & M. Nakamura,

Biofabrication (2010)

Techniques	Plus value
Conception assistée par ordinateur	Tissus reproductibles à la demande
Fichier numérique	Partage ou externalisation de la conception
Résolution à l'échelle cellulaire	Tissus 3D complexes avec microarchitectures définies

« Bioprinting? » « Micro-impression d'éléments biologiques »



(Mironov et al. Biomaterials 2009)

Technologies CAD-CAM
Eléments vivants ou non
Organisation 2D – 3D

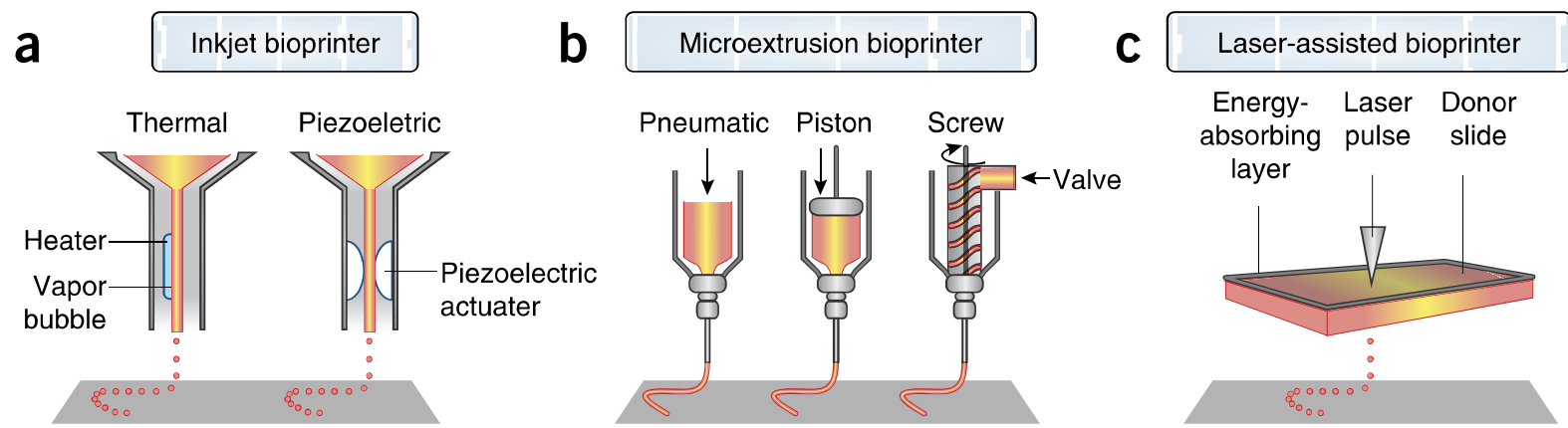


- **Biologie Cellulaire**
- **Modèles pharmacologiques**
- **Médecine régénératrice**

Guillemot et al. Biofabrication
2010

Objectif: organiser les éléments biologiques au coeur du matériau

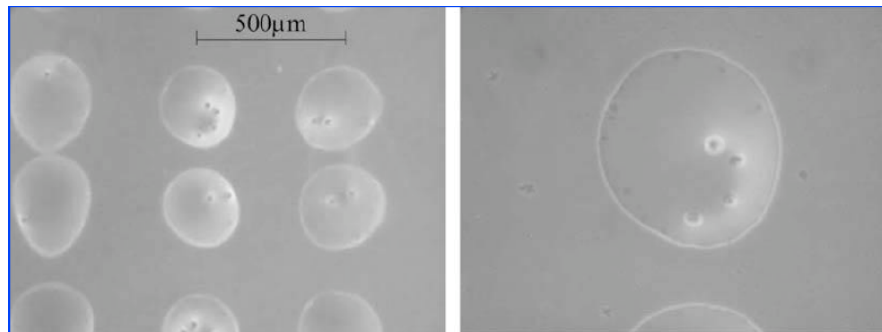
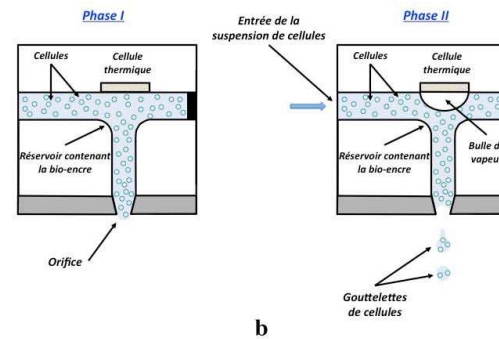
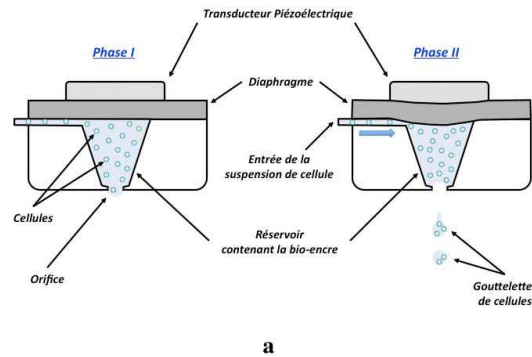
Bioimpression: Quelles Technologies?



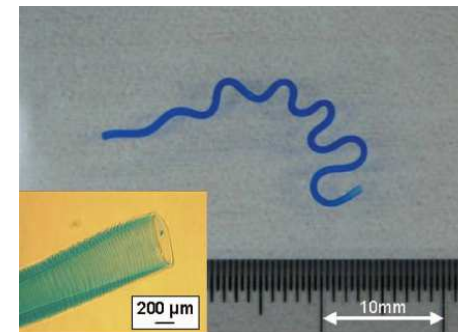
Katie Vicari/
Nature Publishing Group

Murphy SV, Atala A. Nat Biotechnol 2014

Bioimpression par Jet d'encre



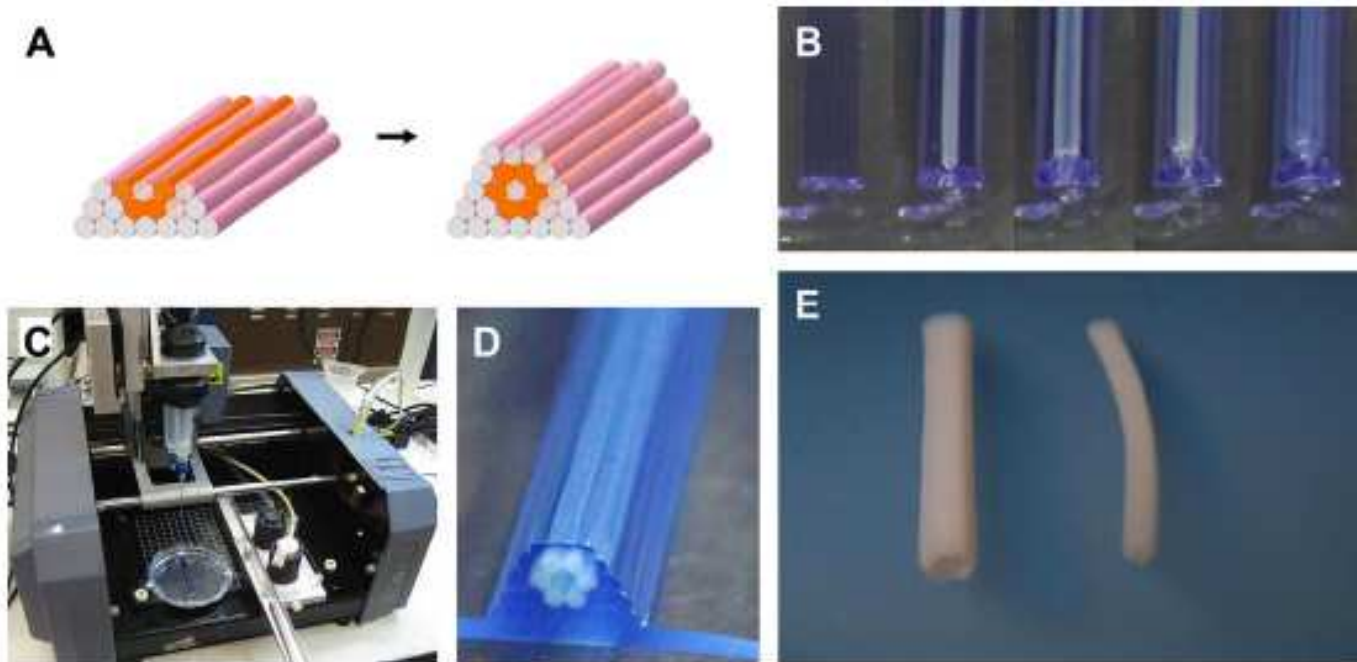
Nakamura, Tissue Eng 2005



Nishiyama, J Biomech Eng 2009

- Viabilité importante après impression
- Résolution maximale 150 μm
- Encres: 10^5 Cellules/ml : peu de cellules par goutte
- Obstruction des buses d'impression

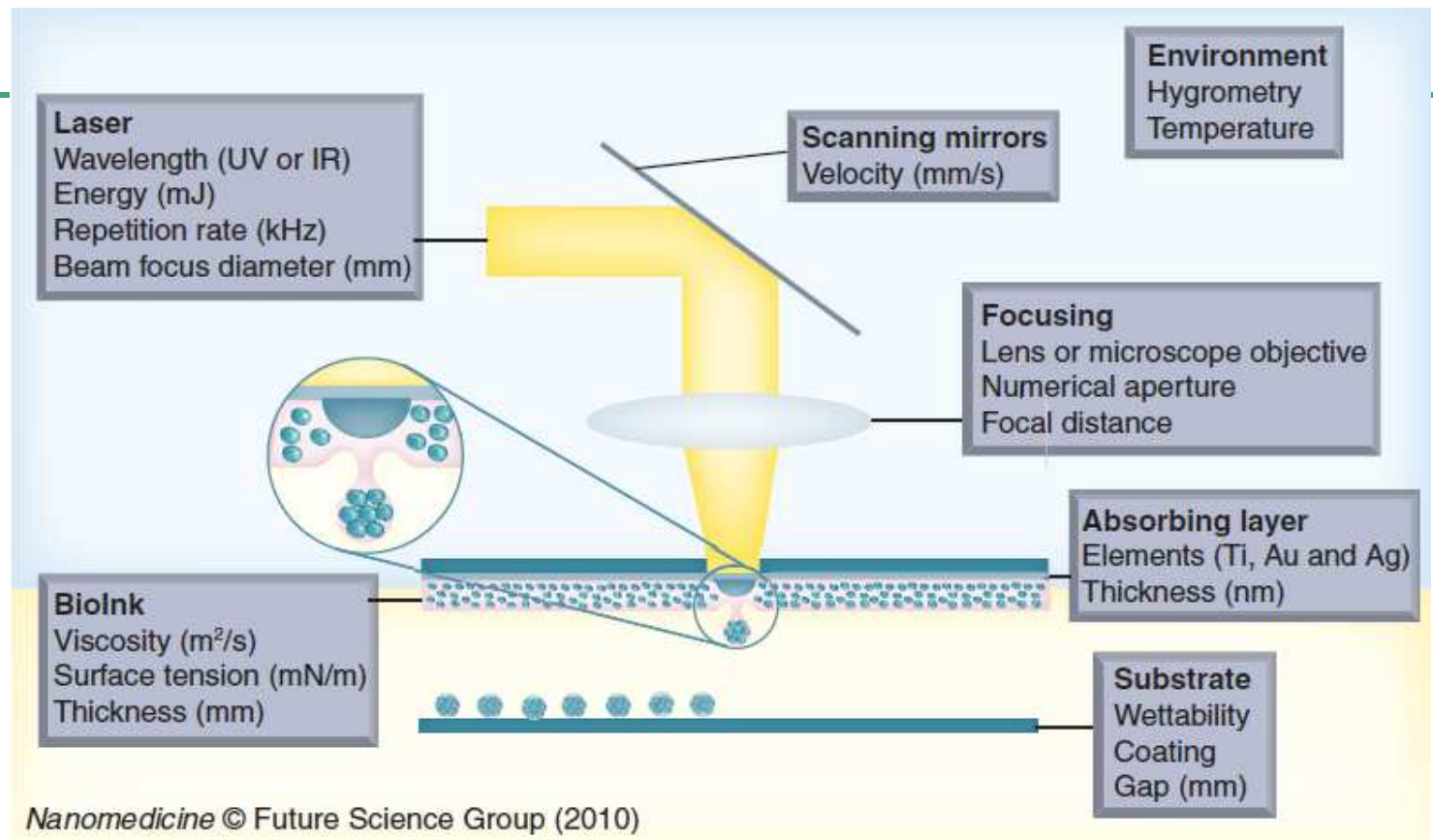
Bioimpression par Extrusion



C. Norotte et al. / Biomaterials 30 (2009) 5910–5917

- Encres: Hydrogels / Sphéroïdes cellulaires
- Viabilité importante après impression
- Faible résolution / volumes importants

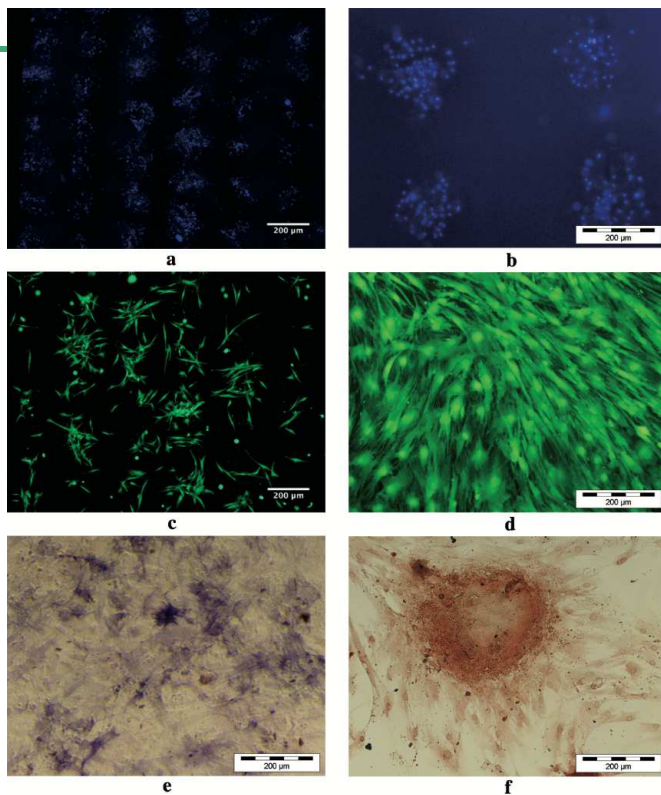
Bioimpression assistée par laser



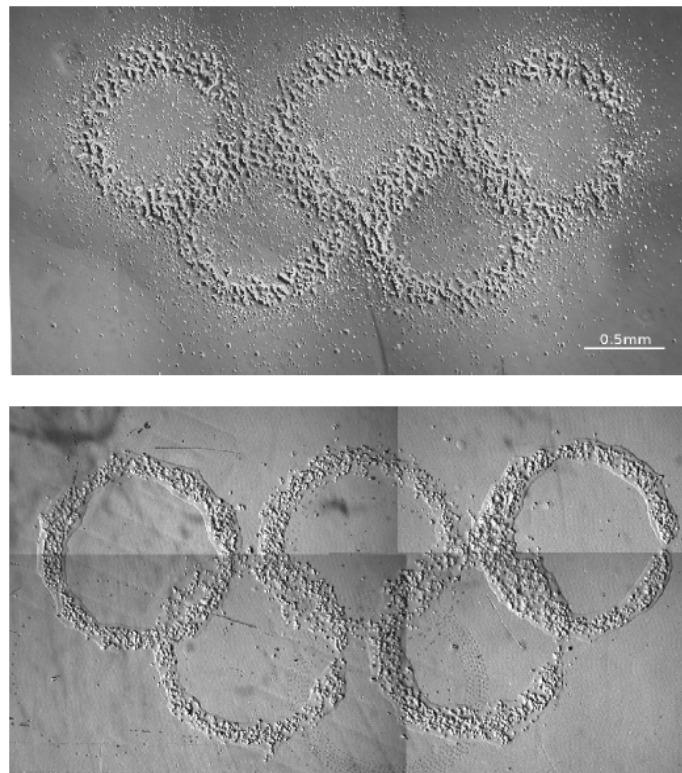
Guillemot et al. *Nanomedicine* 2010

Impression de cellules par laser

Viabilité et phénotype (HBMSCs)



Effet de la viscosité



Catros et al. Biofabrication 2011

Encres Biologiques (Bioinks)

Encre	Composés biologiques
<ul style="list-style-type: none"> ➤ Milieu de Culture ➤ Collagène type 1 ➤ Alginate ➤ Gélatine ➤ PEG ➤ Fibrine ➤ Matrigel® ➤ Agarose ➤ Chitosan ➤ ... 	<ul style="list-style-type: none"> ➤ Cellules ➤ Sphéroïdes ➤ Protéines ➤ Médicaments ➤ ...

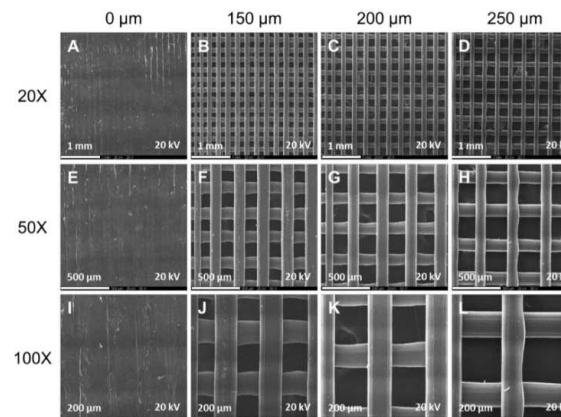
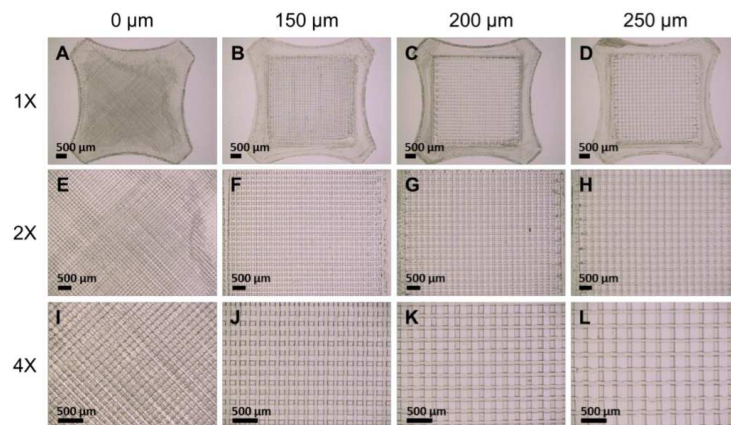
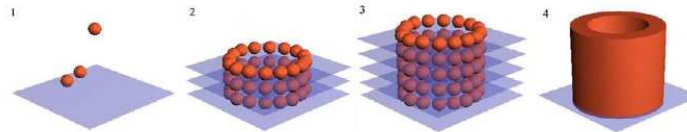
Paramètres à Contrôler

- Composition
- Rhéologie
- Densité Cellulaire
- Réticulation



Maintien des propriétés post-impession?

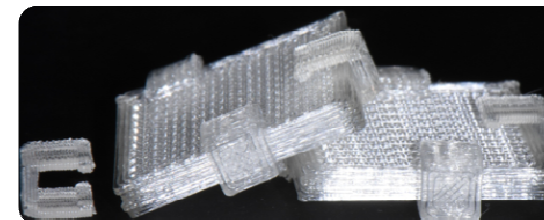
Papiers Biologiques (Biopapers)



Cuvelas Carrées
Sourire Quand Même
Union des Bravés de la Poce et de la Tête
Fondation des "Gueules-Carrées"

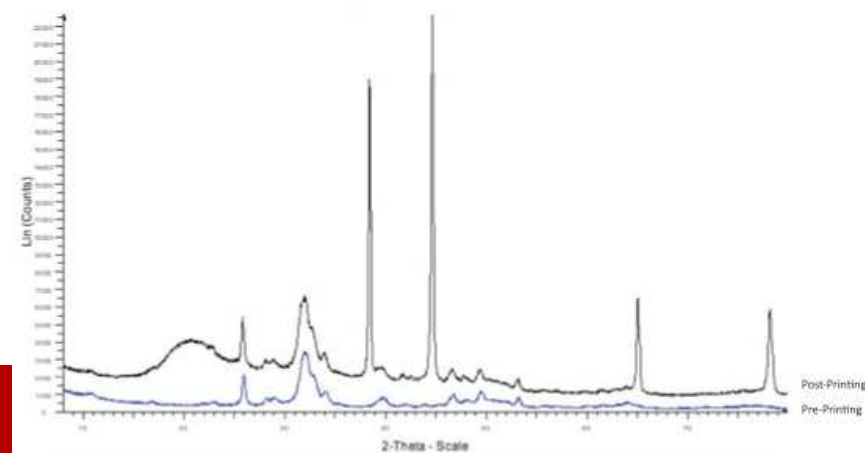
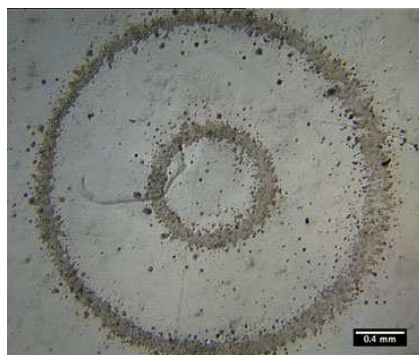
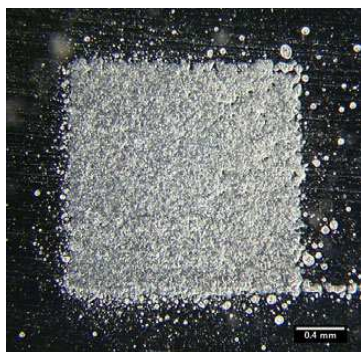
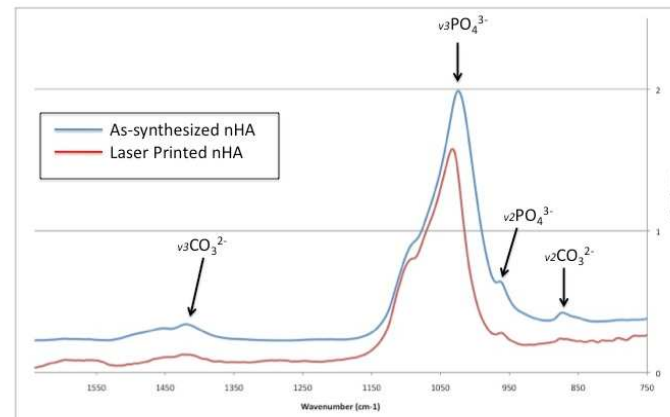
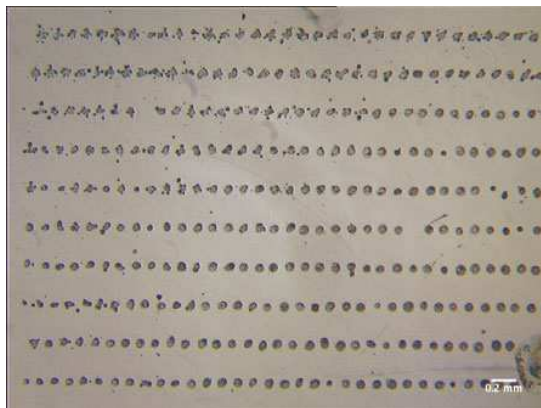
A Gremare, V Guduric

Polymères: PCL, PLA, PLGA...
Fabriqués par FDM, Electrospinning...
Biocompatibilité? Manipulation? Fixation?



Impression d'hydroxyapatite par Laser

Caractérisation pré / post impression



Applications

Impression 3D en médecine régénératrice

Modèle Cellulaire

- **Biologie Cellulaire fondamentale**
- Interaction Cellules-Cellules et Cellules-Matrice
- Patterning et Organisation 2D/3D

Modèle Tissulaire

- **Modèles d'étude Physiologiques / Pathologiques**
- Etudes Pharmacologiques *in vitro*
- Arrangements 3D complexes

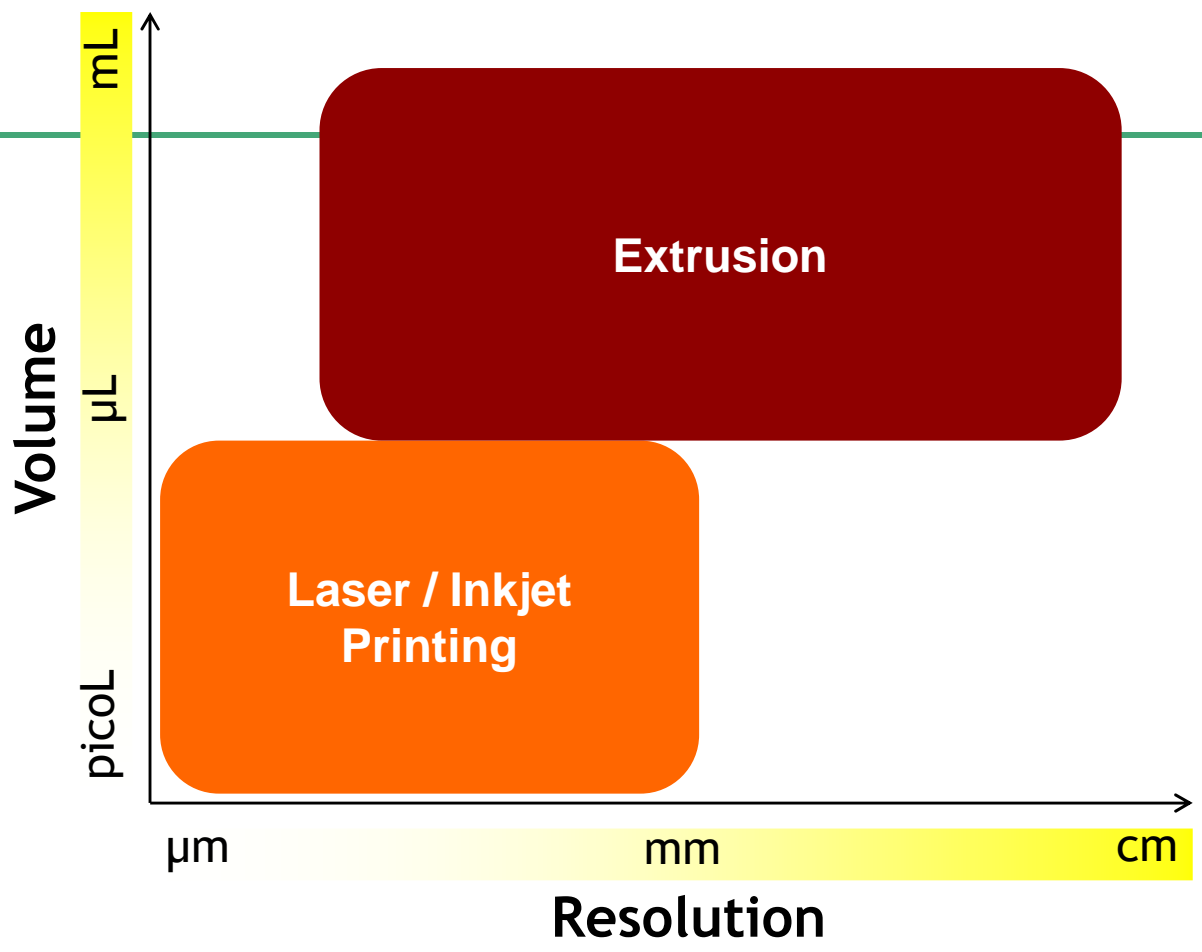
Thérapeutique

- **Substituts Tissulaires sur mesure**
- Recherche Translationnelle
- Chirurgie Personnalisée et minimalement invasive

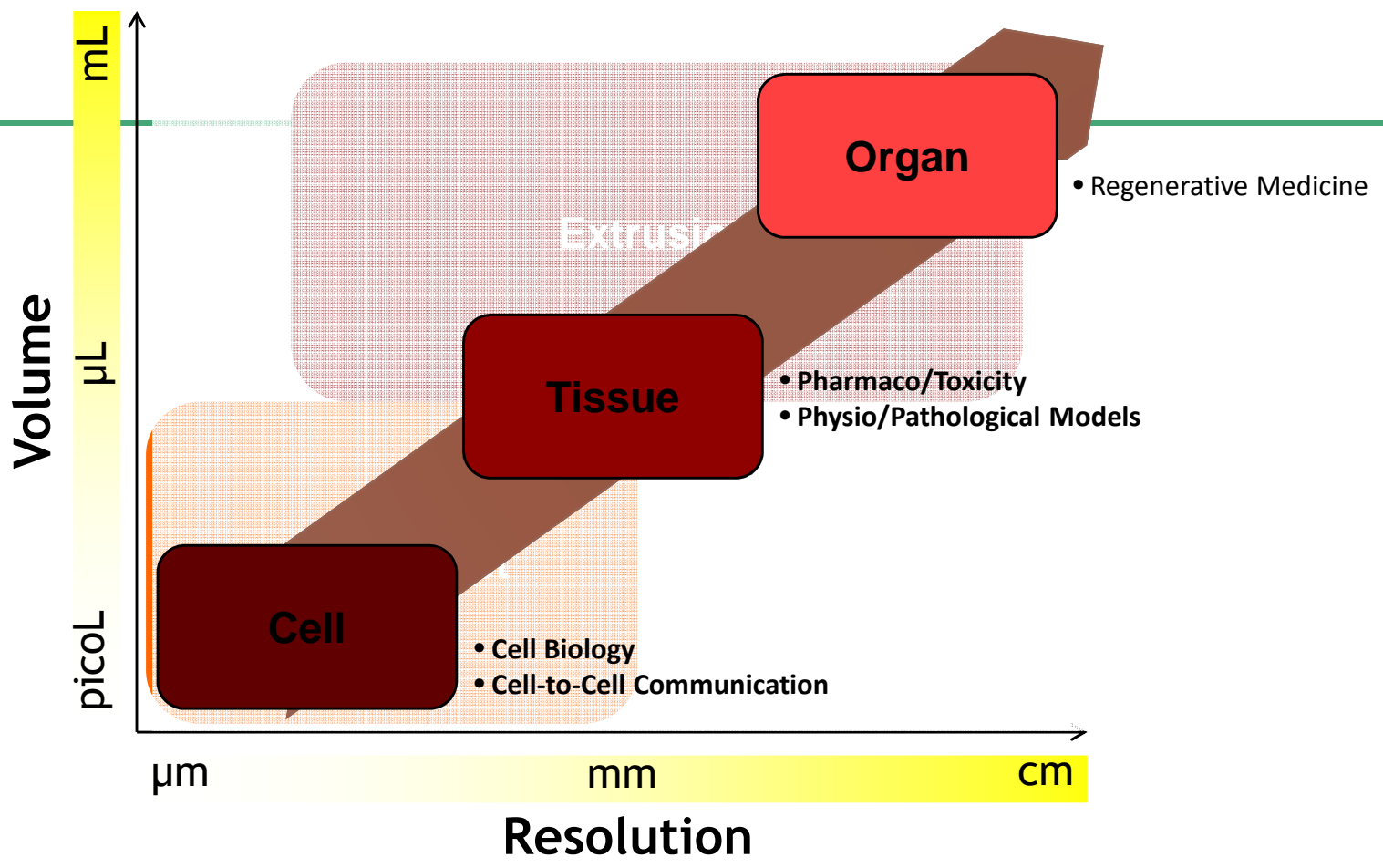


Moyens Technologiques Spécifiques

Technologie selon l'application!

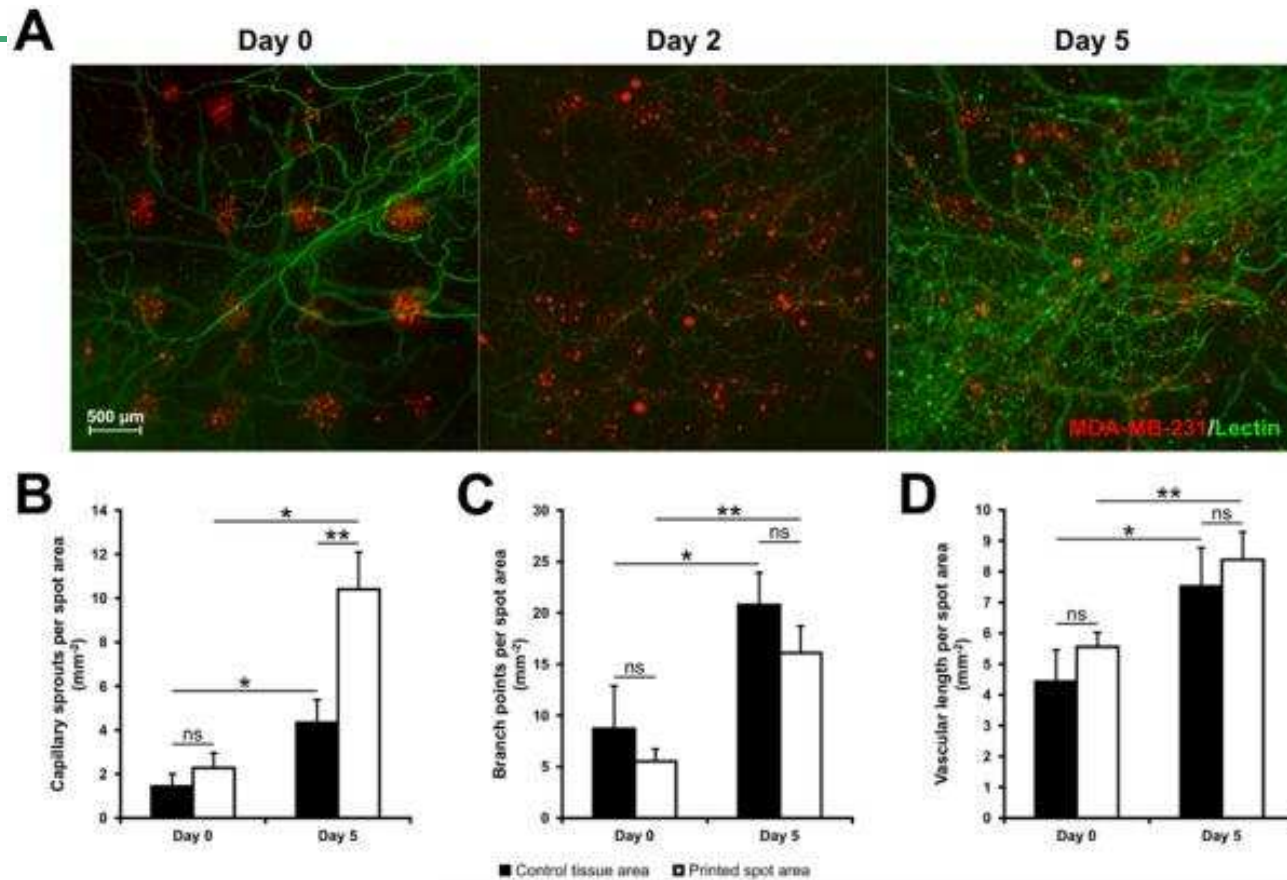


Technologie selon l'application!

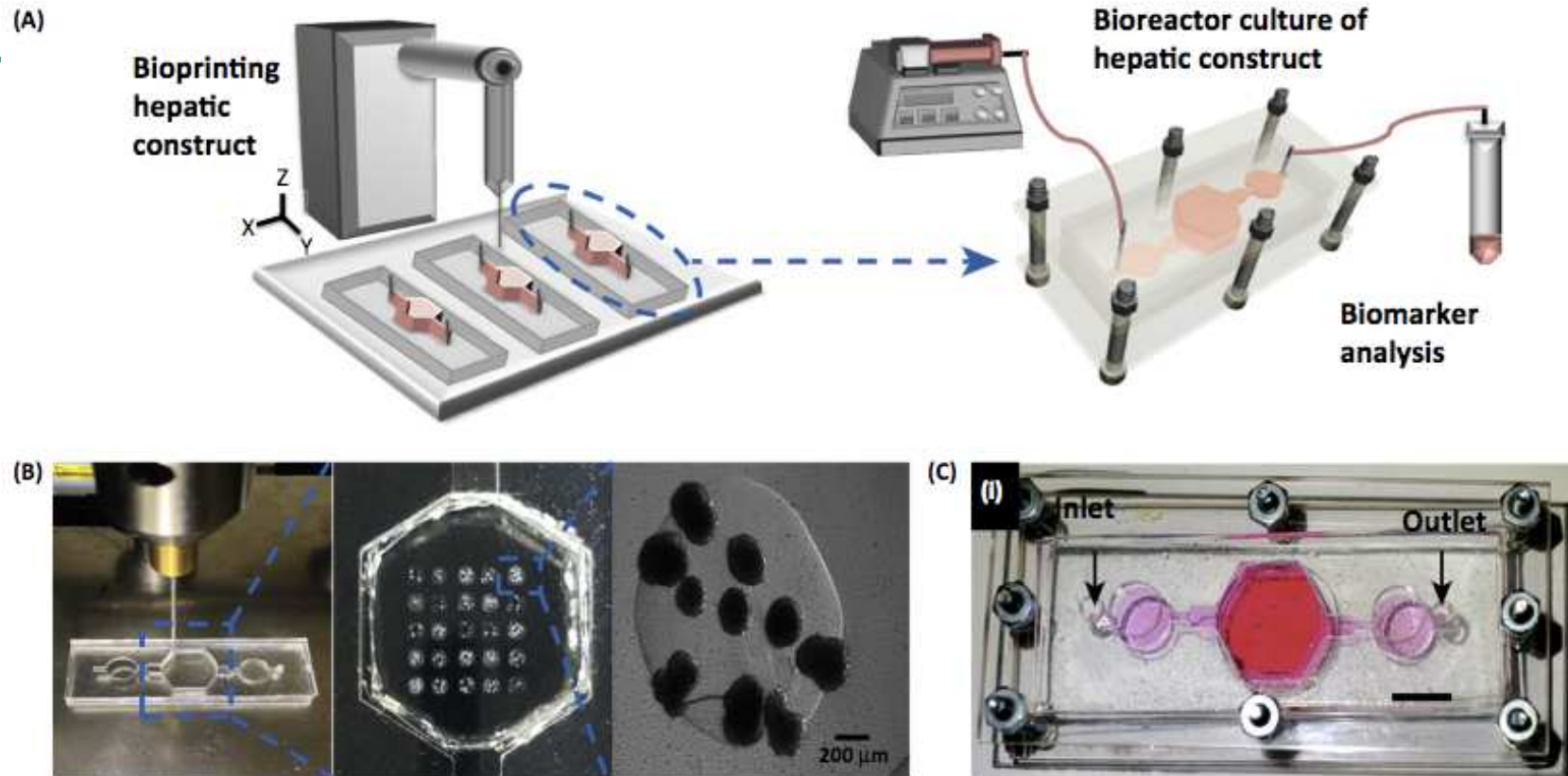


Applications: modèle cellulaire

Printing Cancer Cells into Intact Microvascular Networks: A Model for Investigating Cancer Cell Dynamics during Angiogenesis. Phamduy et al. Integr Biol (Cambr) 2015;7(9):1068-1078



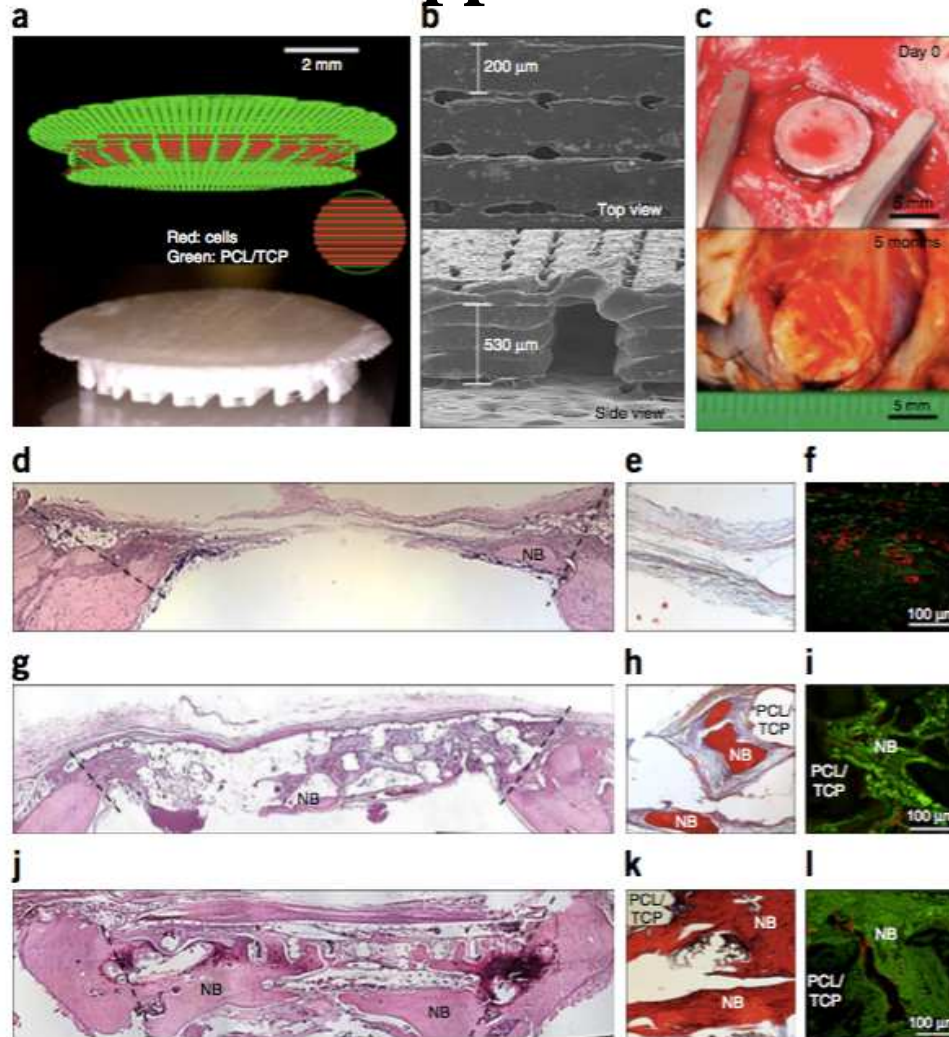
Applications: modèle Tissulaire



Bhise, N.S. et al. (2016) A liver-on-a-chip platform with bioprinted hepatic spheroids. *Biofabrication* 8, 014101

Trends in Biotechnology

Applications: médecine régénératrice



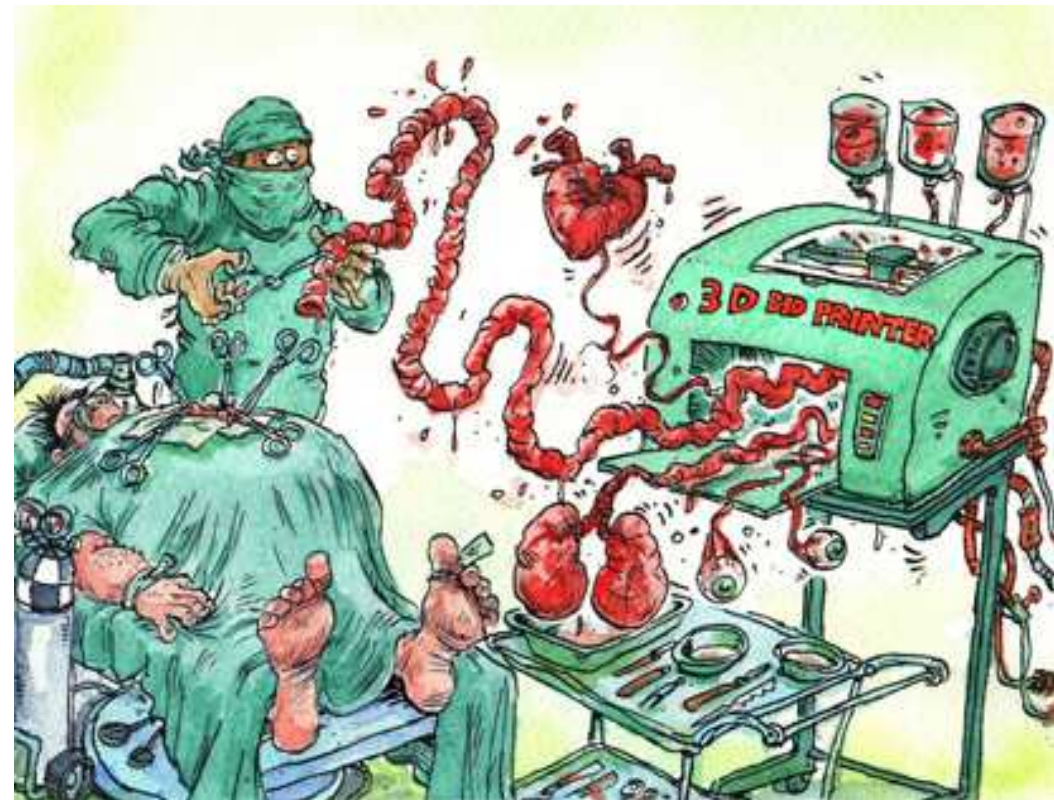
VOLUME 34 NUMBER 3 MARCH 2016 NATURE BIOTECHNOLOGY

A 3D bioprinting system to produce human-scale tissue constructs with structural integrity

Hyun-Wook Kang, Sang Jin Lee, In Kap Ko, Carlos Kengla, James J Yoo & Anthony Atala

CONCLUSIONS

- Nouveaux outils en Ingénierie Tissulaire
- Développement de BioEncres
- Evaluation du maintien de la Biocompatibilité après impression
- Applications principalement en recherche
- Applications cliniques à venir



Merci!

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