L’impression 3D appliquée à l’ingénierie tissulaire
Concept, applications potentielles, évaluation de la biocompatibilité des matrices

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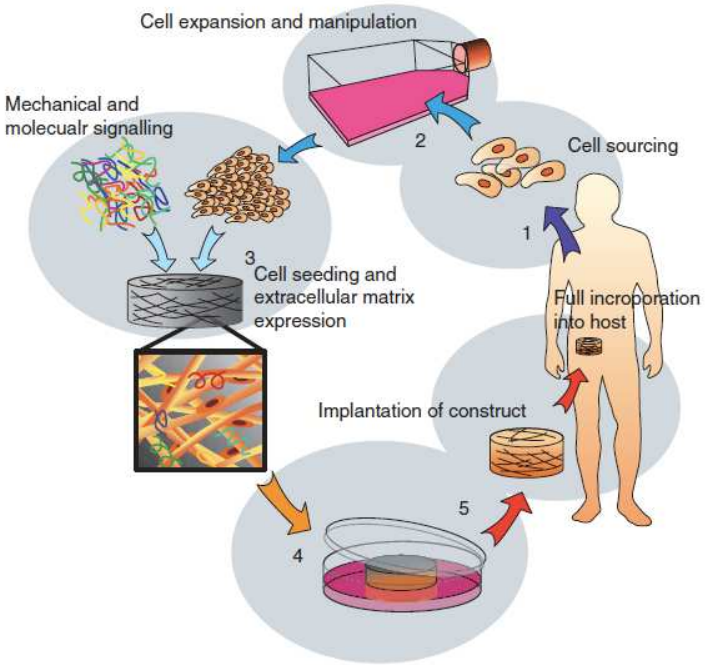
DÉCLARATION DE LIENS D'INTÉRÊT

Pas de Conflit d'intérêt

Ingénierie Tissulaire ?

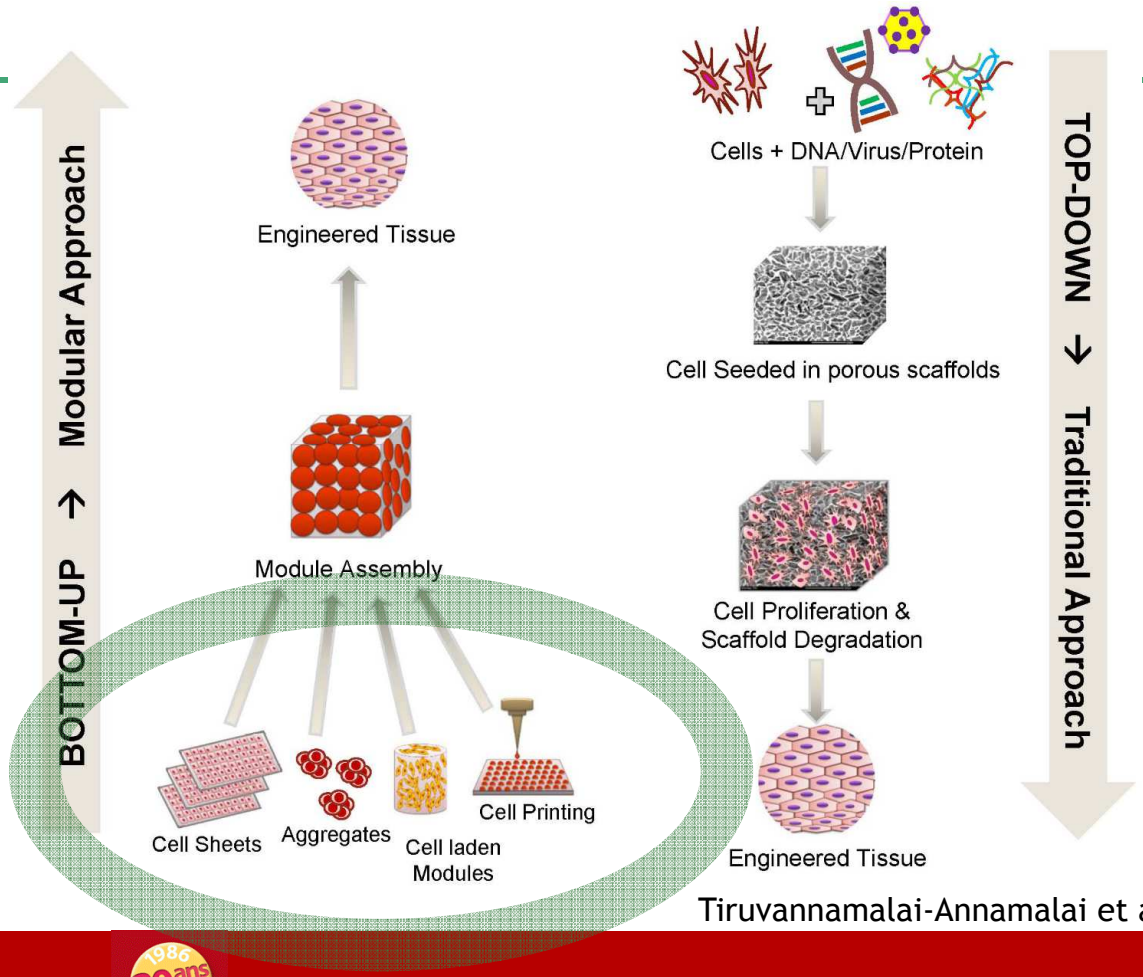


Clemens Van Blitterswijk, 2008

"**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.**"

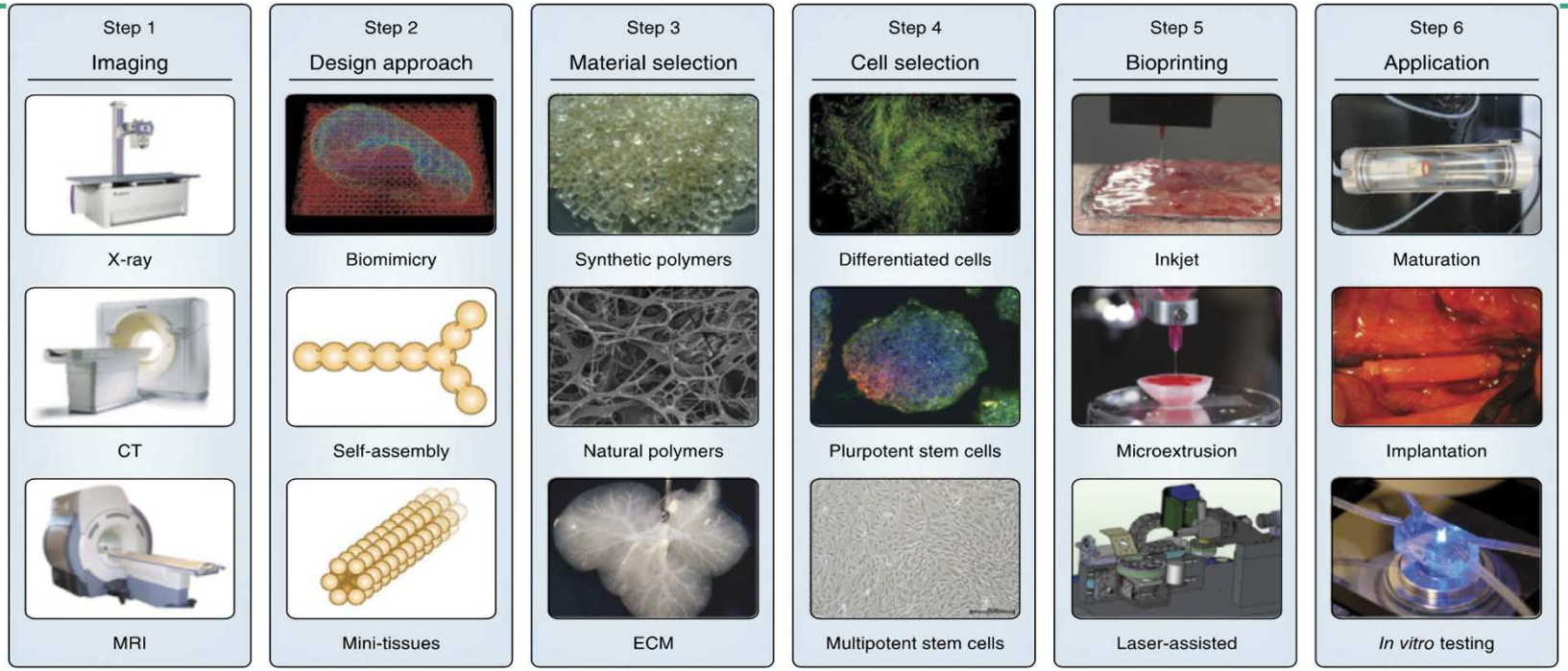
Langer, R., and Vacanti, J. (1993).
Tissue engineering. Science 260, 920–926.

Deux Approches en Ingénierie Tissulaire



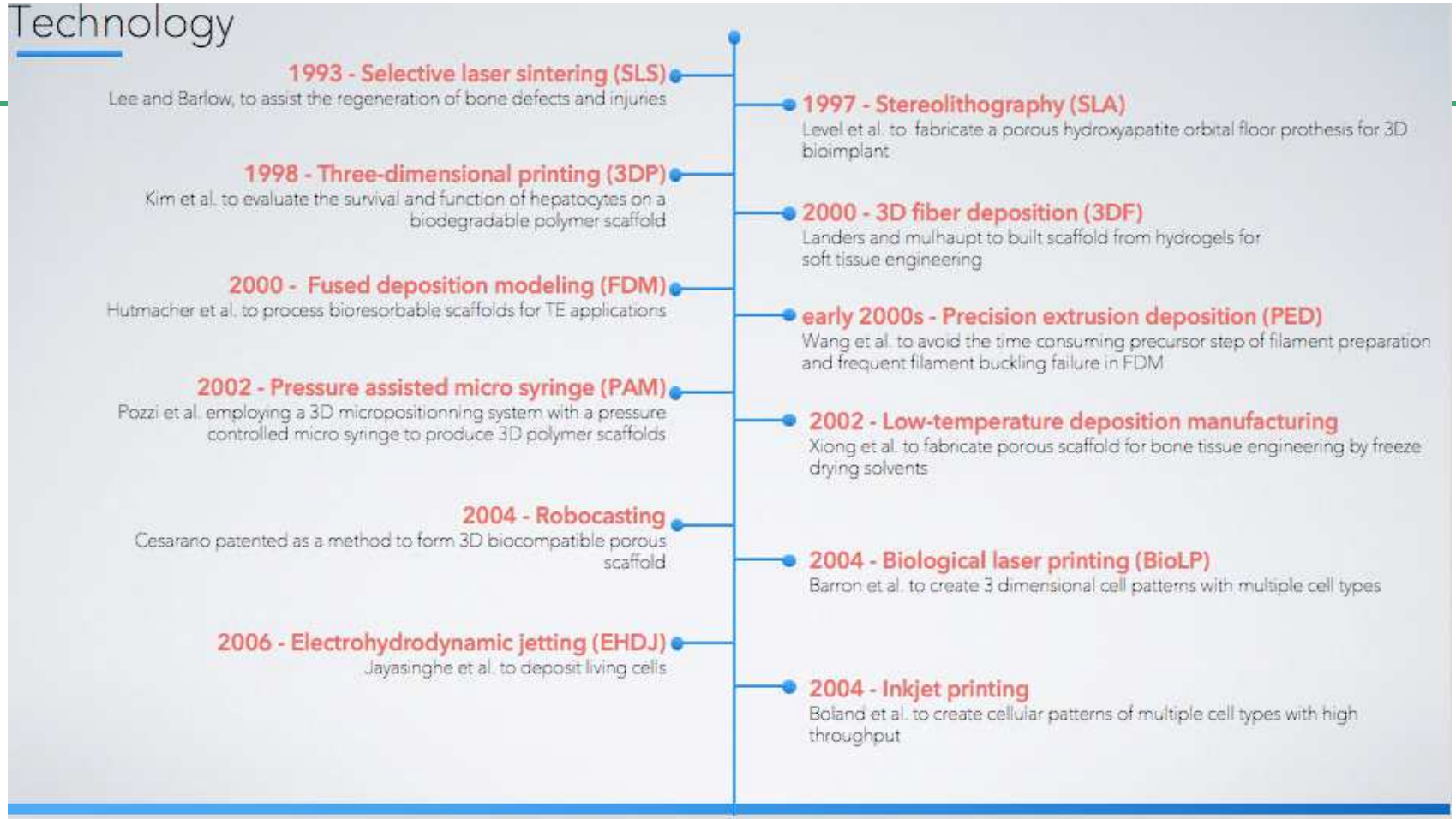
Tiruvannamalai-Annamalai et al. PlosOne 2014

Quelles Etapes ?



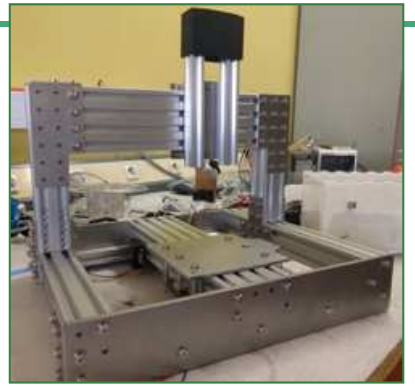
Murphy SV, Atala A. Nat Biotechnol 2014

Imprimantes 3D ?



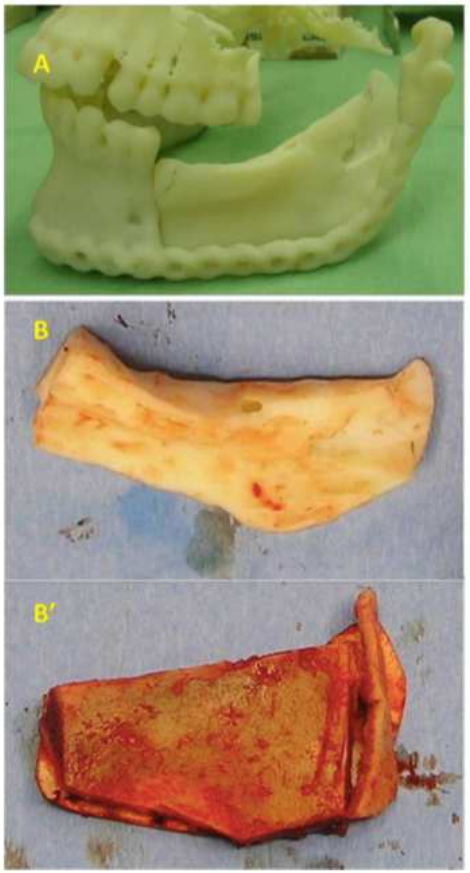
Impression 3D, Médecine et Chirurgie

- **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



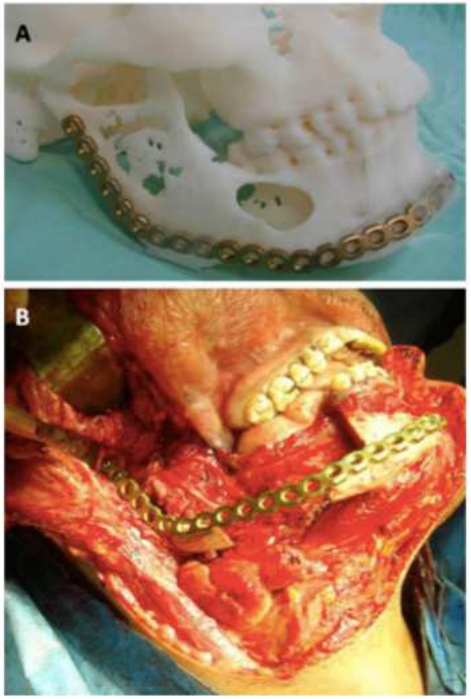
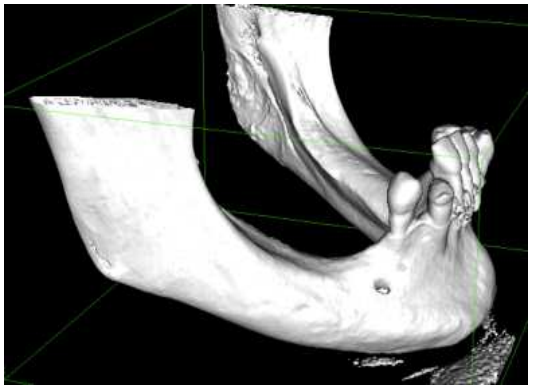


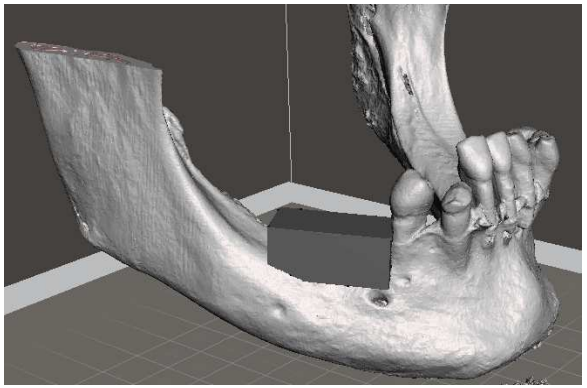
Fig. 3. **A,** Precontoured mandibular reconstruction plate placed over the right mandible consisting the ameloblastoma **B,** Reconstruction plate bridges the gap following tumour resection.

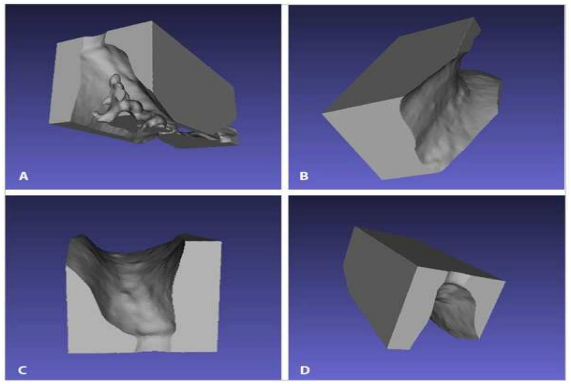
Cohen A. et al. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:661-666

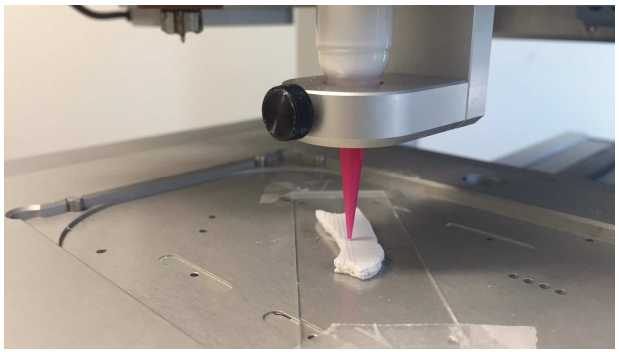
résine biocompatible de Classe 1
(EN-ISO 10993-1:2009/AC:2010, USP Class VI)

Substituts Osseux sur mesure
Collaboration RegenHU®









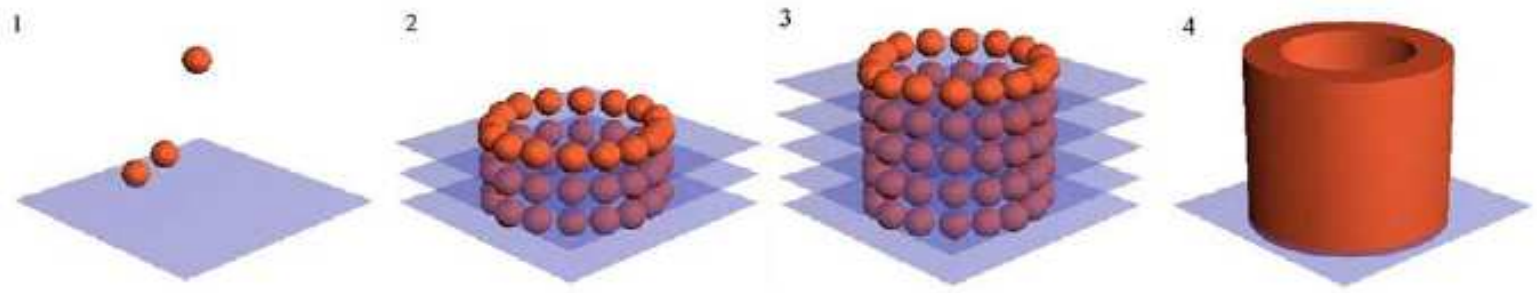
DEFINITION ET INTERET DE LA BIOIMPRESSION ?

« 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)

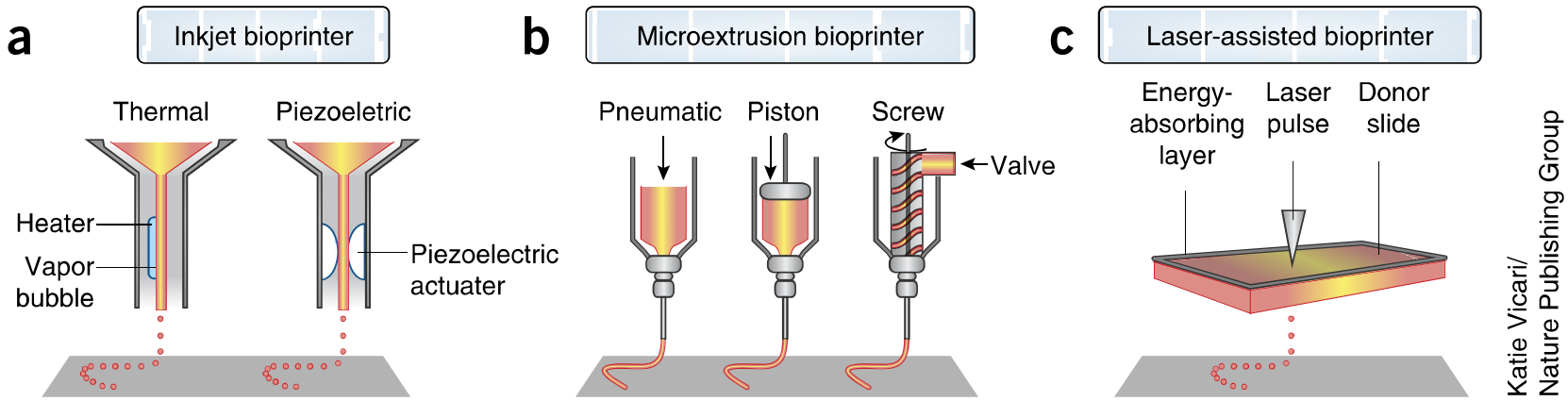
Technologies CAD-CAM
Eléments vivants ou non
Organisation 2D – 3D

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

Guillemot et al. Biofabrication 2010

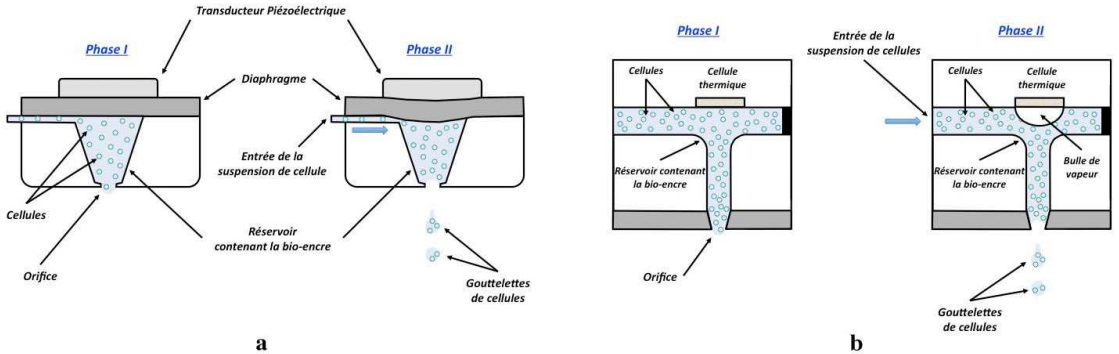
Objectif: organiser les éléments biologiques au coeur du matériau

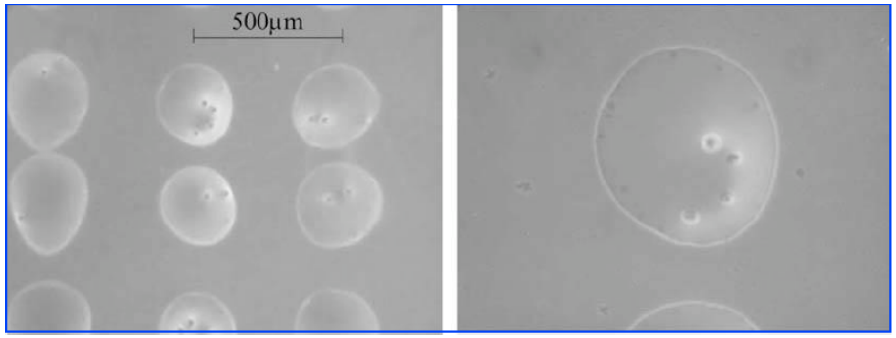
Bioimpression:
Quelles Technologies?



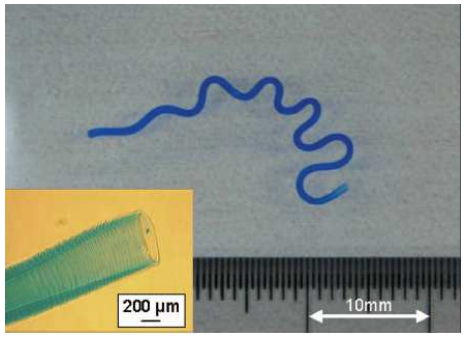
Murphy SV, Atala A. Nat Biotechnol 2014

Bioimpression par Jet d'encre





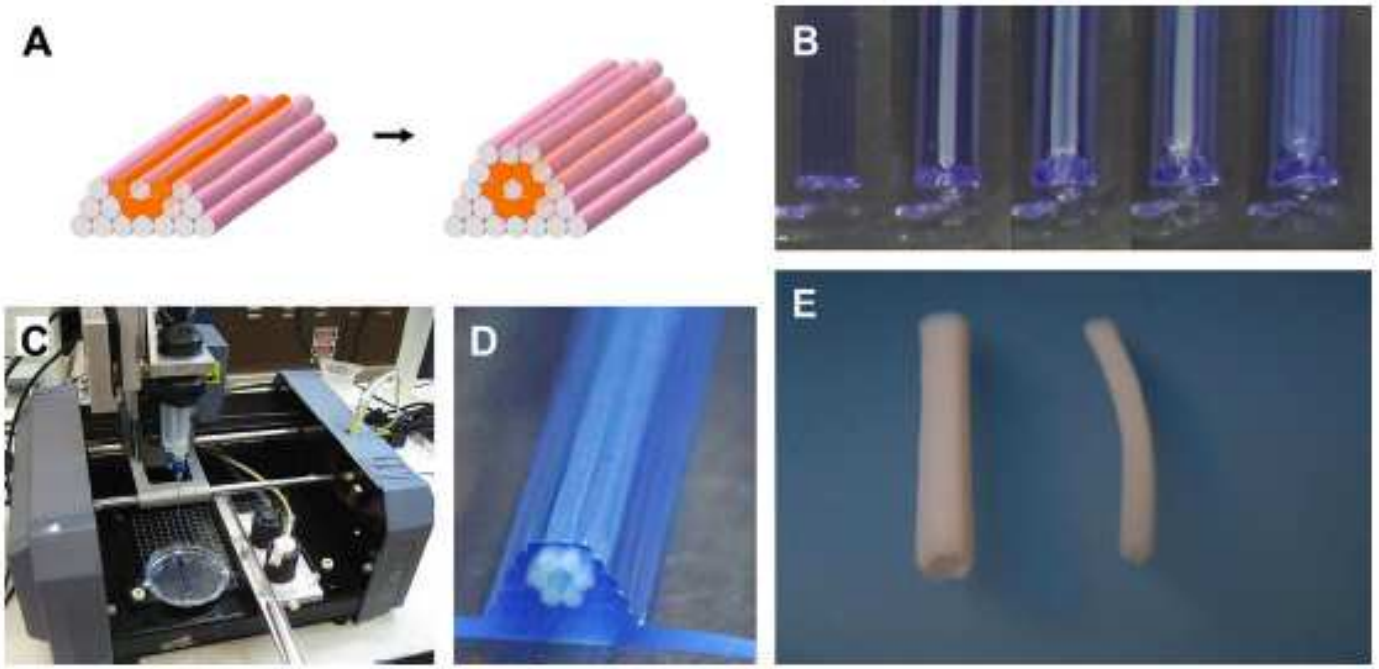
Nakamura, Tissue Eng 2005



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

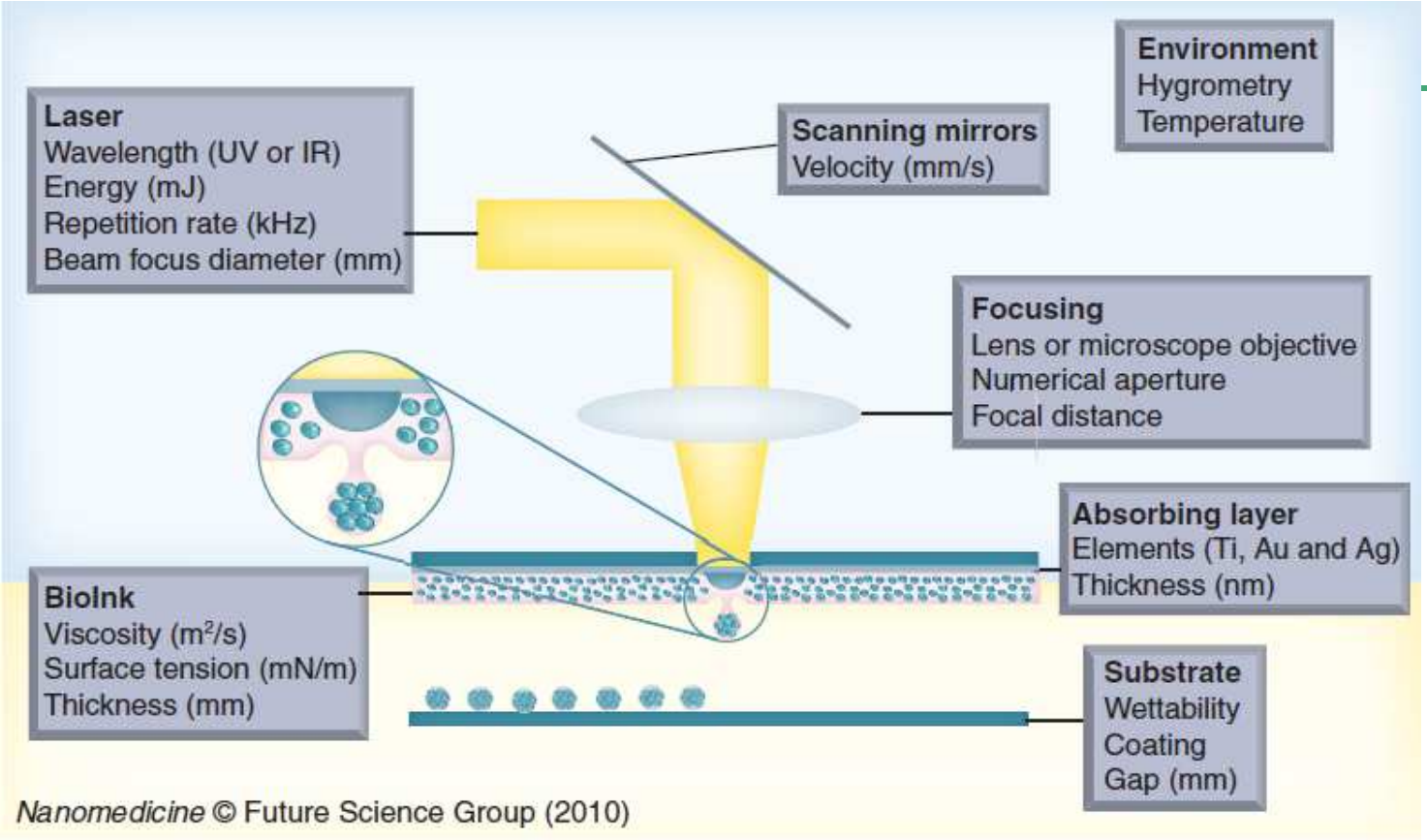
Bioimpression par Extrusion



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

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

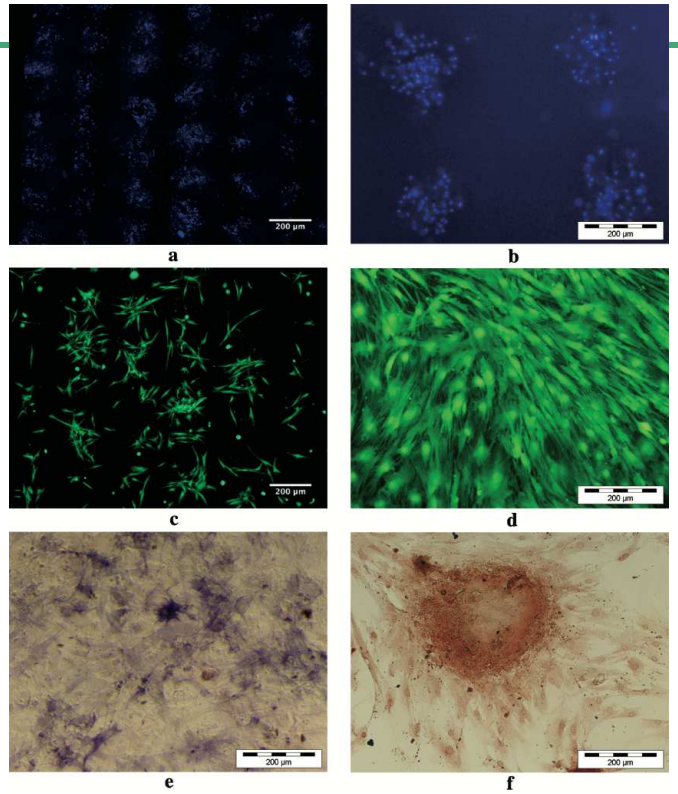
Bioimpression assistée par laser



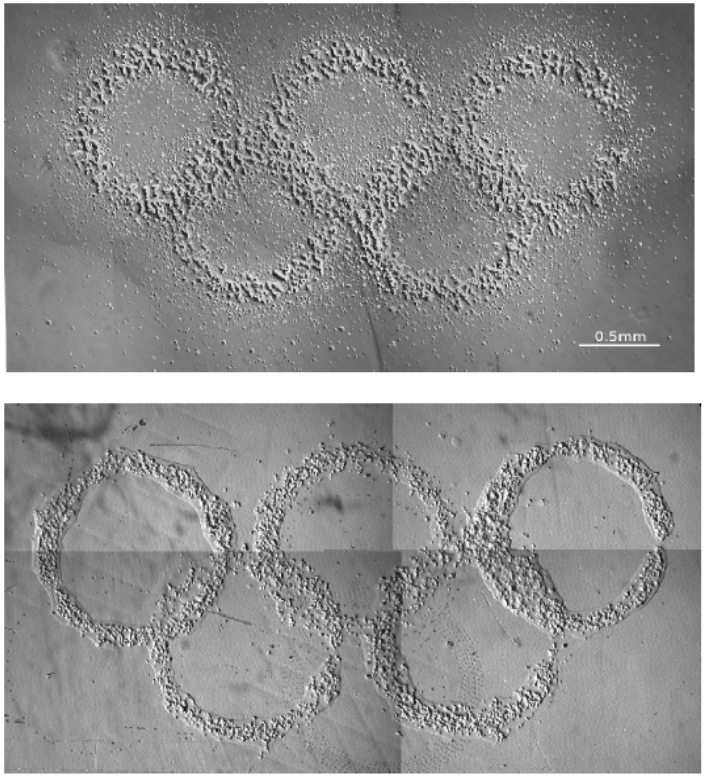
Guillemot et al. Nanomedicine 2010

Impression de cellules par laser

Viabilité et phénotype (HBMScs)



Effet de la viscosité



Catros et al. Biofabrication 2011

30.10^6 Cellules / ml

Encres Biologiques (Bioinks)

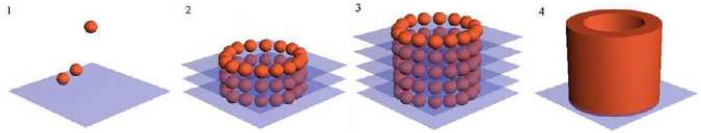
Encre	Composés biologiques
➢ Milieu de Culture ➢ Collagène type 1 ➢ Alginate ➢ Gélatine ➢ PEG ➢ Fibrine ➢ Matrigel® ➢ Agarose ➢ Chitosan ➢ …	➢ Cellules ➢ Sphéroïdes ➢ Protéines ➢ Médicaments ➢ …

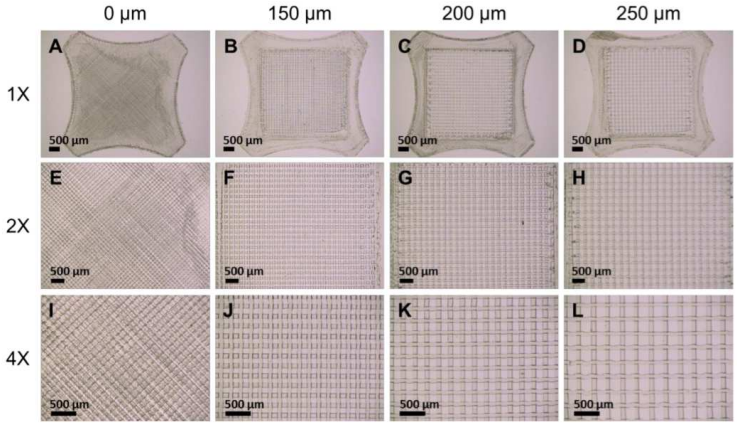
Paramètres à Contrôler

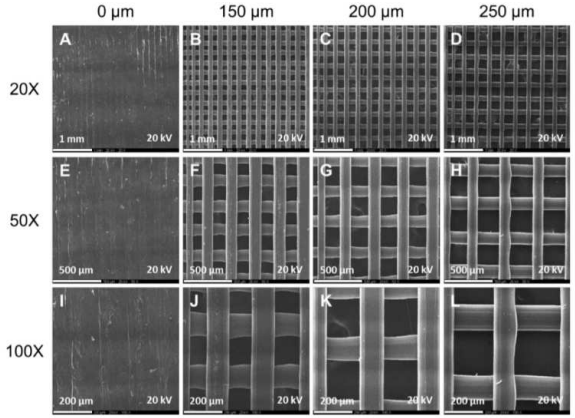
- Composition
- Rhéologie
- Densité Cellulaire
- Réticulation

Maintien des propriétés post-impression?

Papiers Biologiques (Biopapers)

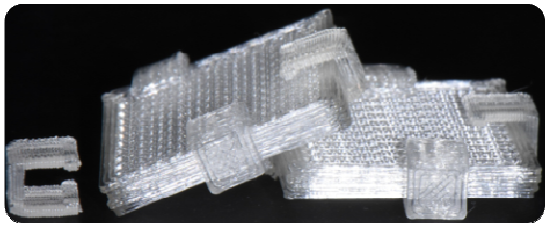




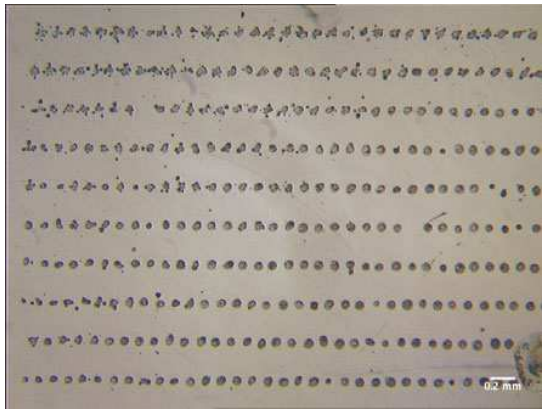


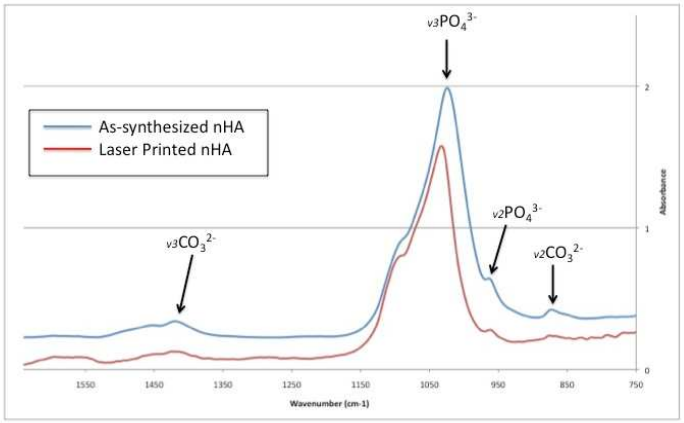
A Gremare, V Guduric

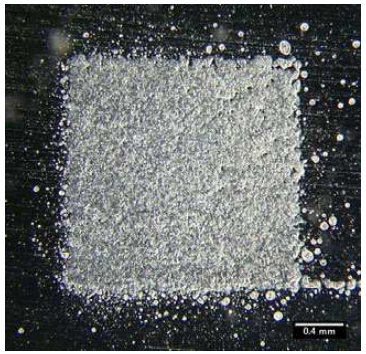
Polymères: PCL, PLA, PLGA…
Fabriqués par FDM, Electrospinning…
Biocompatibilité? Manipulation? Fixation?

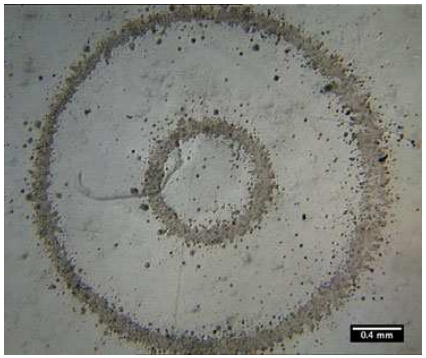


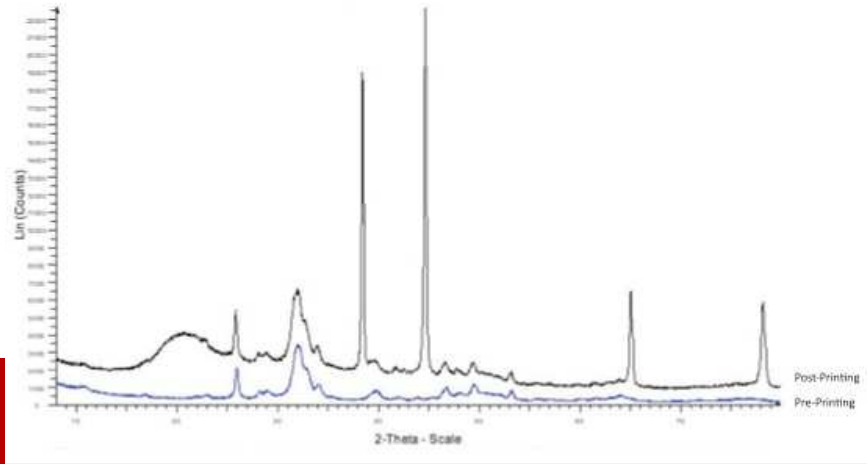
Impression d'hydroxyapatite par Laser
Caractérisation pré / post impression











Applications
Impression 3D en médecine régénératrice

Modèle Cellulaire

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

Modèle Tissulaire

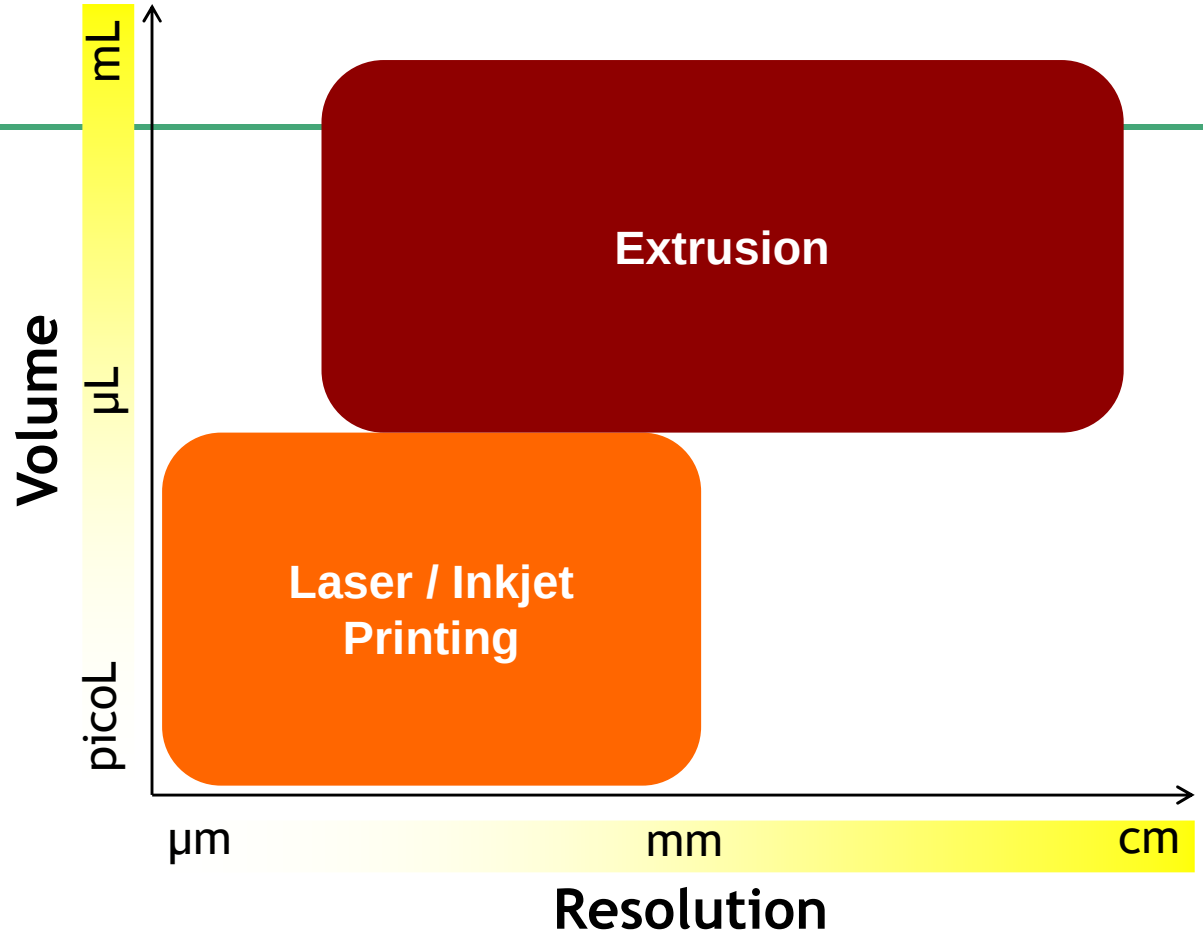
- **Modèles d'étude Physiologiques / Pathologiques**
- Etudes Pharmacologiques *in vitro*
- Arrangements 3D complexes

Thérapeutique

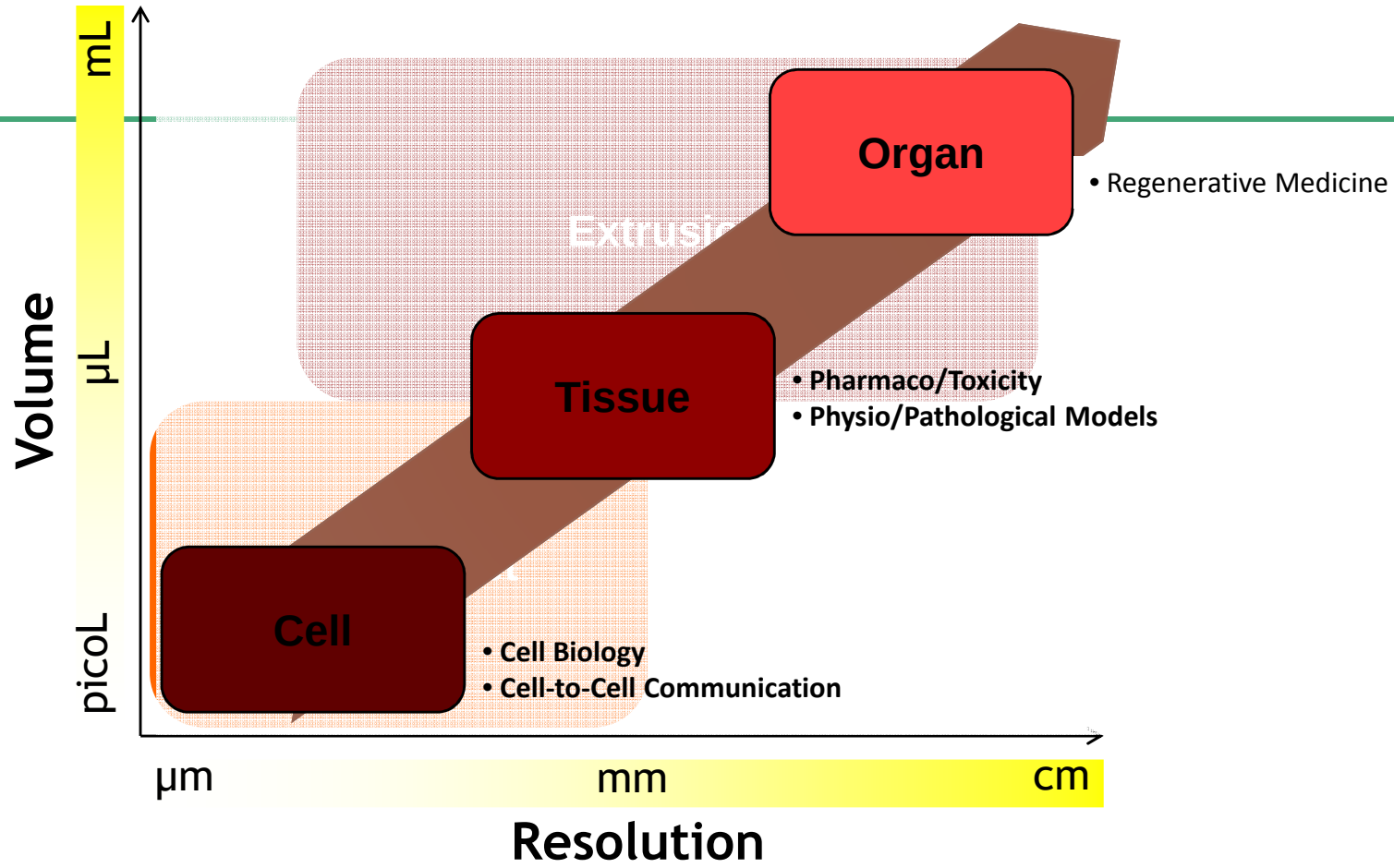
- **Substituts Tissulaires sur mesure**
- Recherche Translationnelle
- Chirurgie Personnalisée et minimalement invasive

→ **Moyens Technologiques Spécifiques**

Technologie selon l'application!

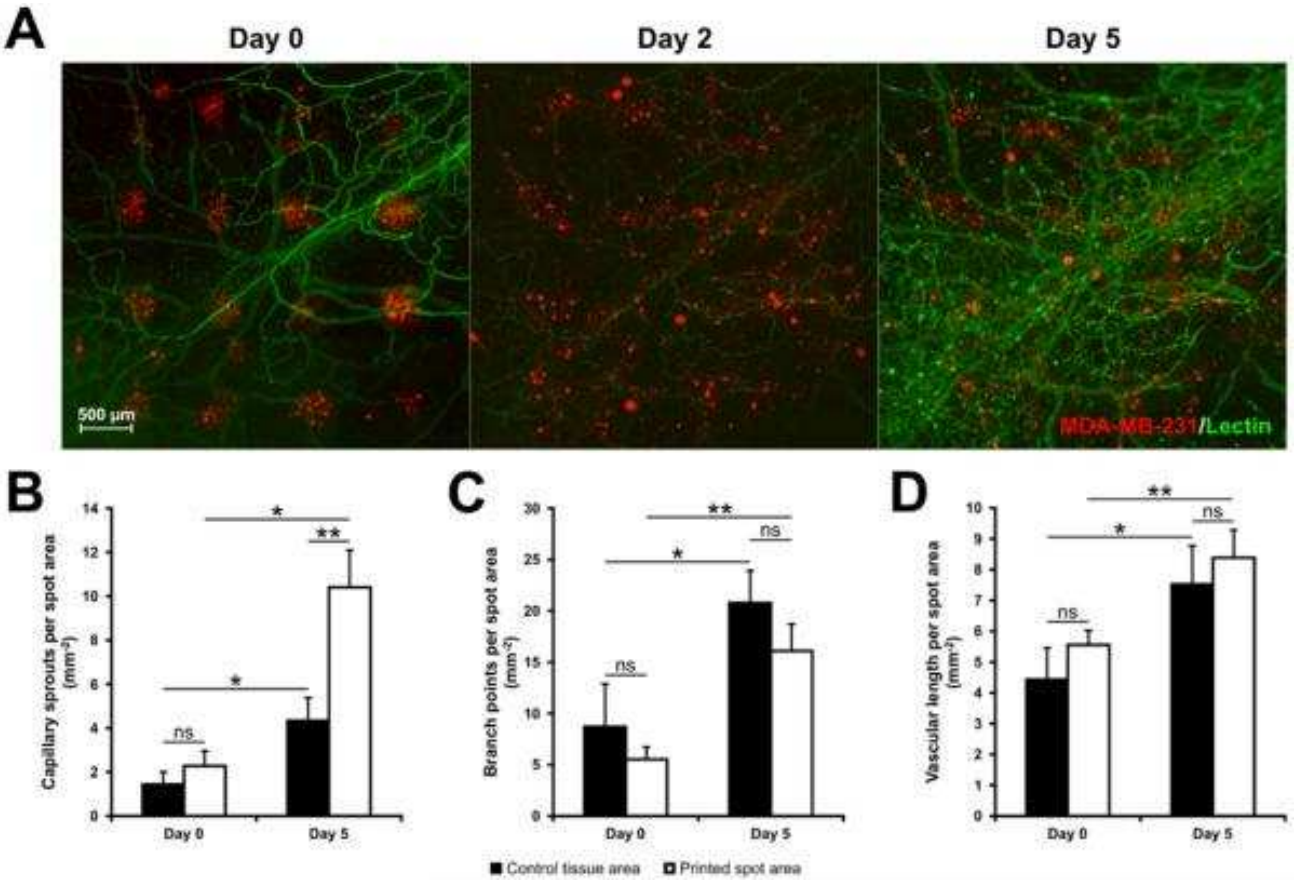


Technologie selon l'application!

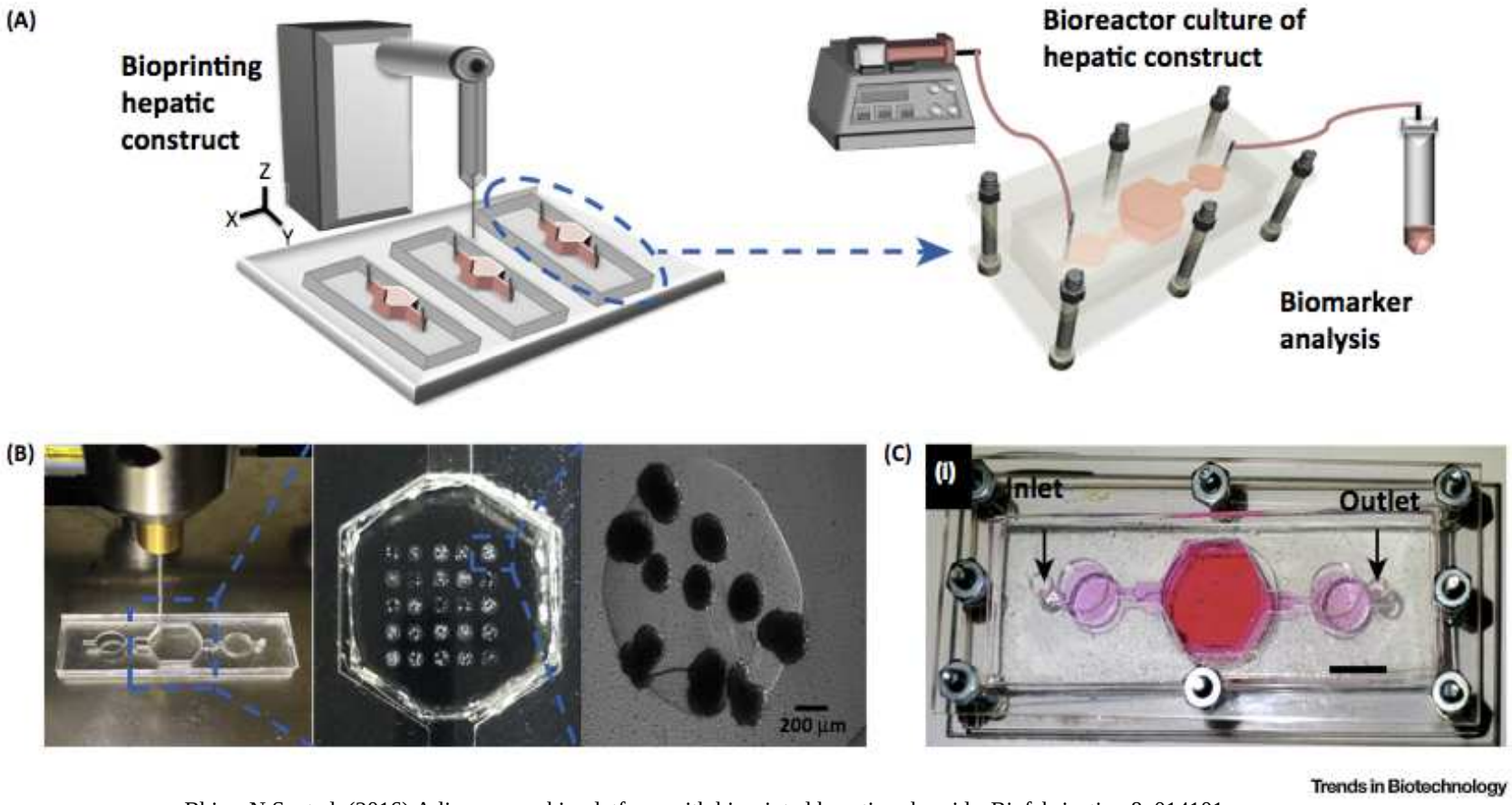


Applications: modèle cellulaire

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

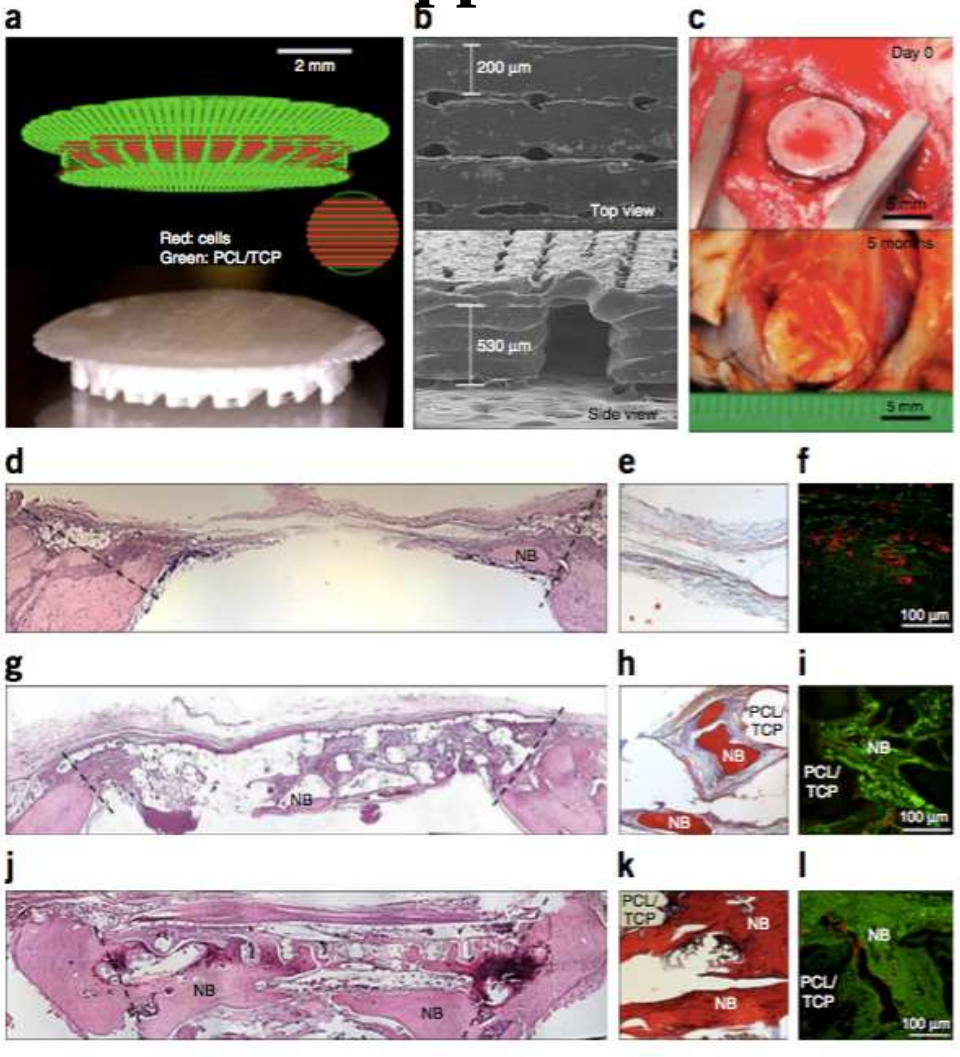


Applications: modèle Tissulaire



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

Applications: médecine régénératrice



VOLUME 34 NUMBER 3 MARCH 2016 NATURE BIOTECHNOLOGY

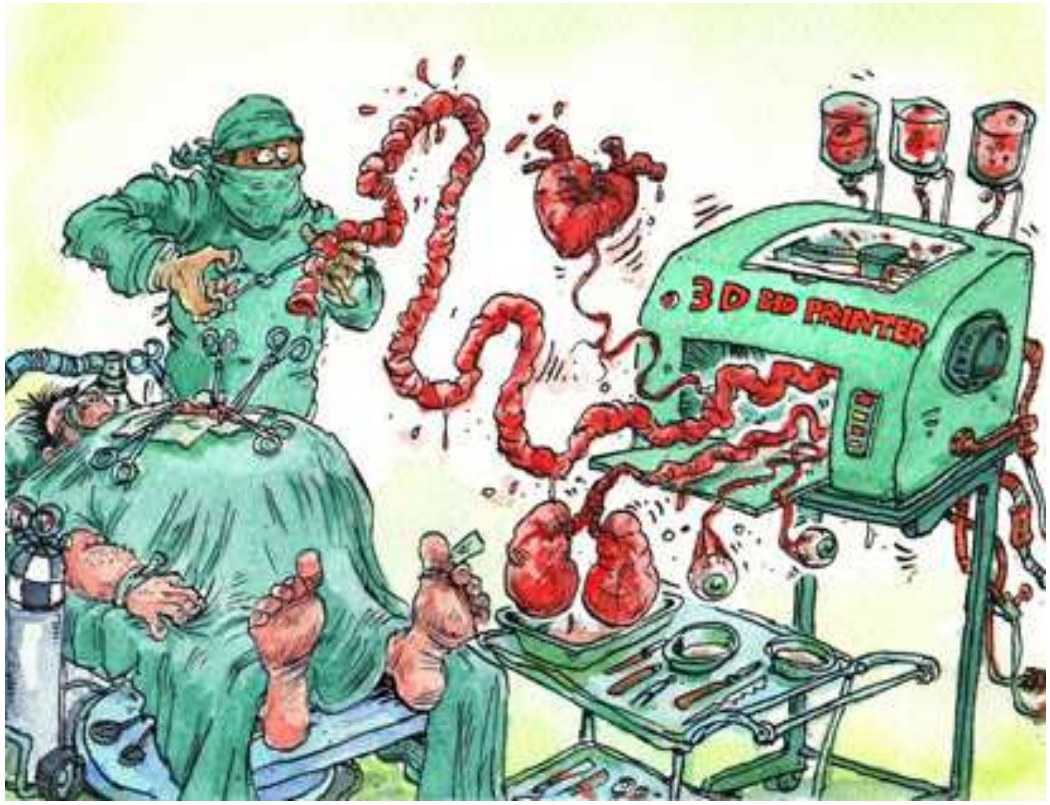
A 3D bioprinting system to produce human-scale tissue constructs with structural integrity

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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