Prothèses diaphragmatiques pédiatriques

ULR 2694

État de l'art

Synthetic versus Biological Patches for CDH: A Comparison of Recurrence Rates and Adverse Events, Systematic Review, and Meta-Analysis
Kamal, Tasnim Rowshan ; **EUROPEAN JOURNAL OF PEDIATRIC SURGERY**
AUG 2022

- A total of 47 studies with 986 patients (226 biological, 760 synthetic) : synthetic patch seem to be preferred but biological ones are more recent
- The most commonly used patch types-PTFE (polytetrafluoroethylene) and SIS (small intestinal submucosa)
- Biological patches appear to have higher recurrence rates than synthetic patches,
- while skeletal deformities are associated more commonly with synthetic patches

État de l’art

Porcine dermal patches as a risk factor for recurrence after congenital diaphragmatic hernia repair
Irene de Haro Jorge, *Pediatric Surgery International* **volume 37**, pages59–65 (2021)

50 patients entered the study

25 Gore-Tex® and 8 porcine dermis patches were used. Seven patients presented recurrence (14%). Median follow-up time was 3.5 years (1.2–6.2). Univariate analysis revealed that the use of a porcine dermis patch (75%) increased the risk of recurrence.

État de l’art

Recurrence of Congenital Diaphragmatic Hernia : Risk factors, Mamangement and future perspectives. ***In Frontiers in pediatrcs. 2022***. *Francesco Macchini and al.*

Surgical-related PFs seem to have a major role in recurrence among postnatal variables, especially the use of patches.

Patients who require a diaphragmatic patch repair are reported to have a risk 2.83 times higher of developing a recurrence

The inability of the synthetic patch to grow with the patient is the mechanism underlying this strong association

Based on current evidence, major international study groups recommend using non-absorbable prosthetic patches, mainly PTFE, aiming at an oversized/dome shape

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Waiting for better

Cher utilisateur du biomatériau GORE® DUALMESH® et/ou du patch de renforcement des tissus mous GORE-TEX® :

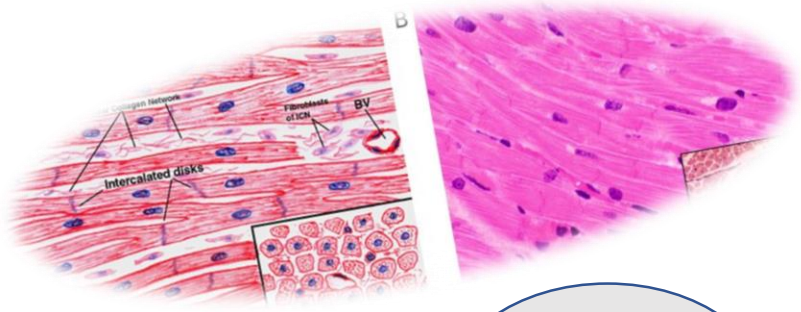
Nous souhaitons, par la présente, vous informer que W. L. Gore & Associates, Inc. (Gore) ne poursuivra pas sa demande d'obtention des futures certifications réglementaires de l'Union européenne (marquage CE de l'UE) dans le contexte du nouveau Règlement relatif aux dispositifs médicaux (RDM) concernant le biomatériau GORE® DUALMESH® et le patch de renforcement des tissus mous GORE-TEX®. Nous avons pris cette difficile décision dans un objectif stratégique commercial

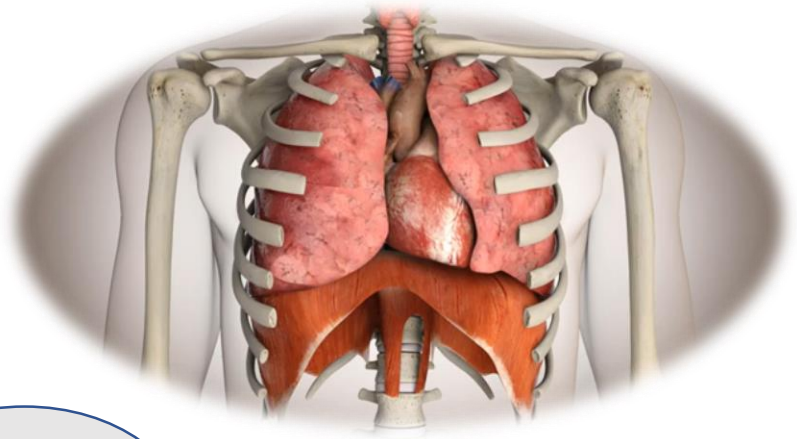
Nos projets

BIOMATÉRIAUX BIOINGÉNIERIE

Problématique croissante de la hernie à large défect

Analyses d'explants, littérature





Propriétés biologiques

Propriétés mécaniques

DIAPID and Biomekid projects

“Functional prosthesis for the repair of congenital diaphragmatic hernia”

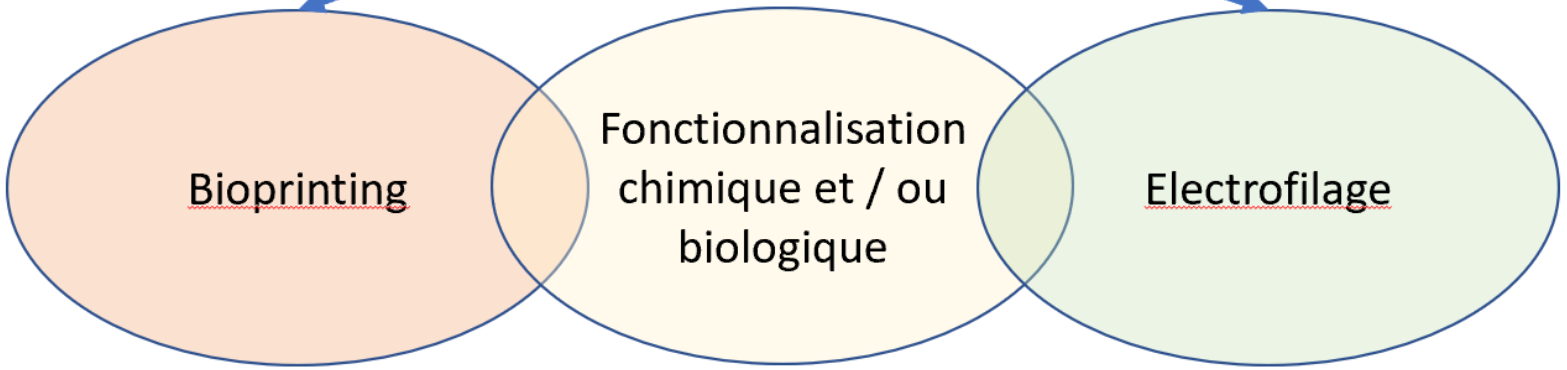
Quelle serait la prothèse idéale ?

- Résorbable ?... Études encore insuffisantes
- Etirable ? … Oui, pour suivre la croissance et la ventilation
- Mais plastique également (rigide) !
- Double face ?... Oui, intérêt d’une réponse cellulaire différente
- Hydrophile ? … Oui, attractive pour les cellules !
- Fonctionnalisée ? … Oui, guide la colonisation cellulaire

BIOMATÉRIAUX
BIOINGÉNIERIE

Problématique croissante de la hernie à large défect

Analyses d'explants, littérature



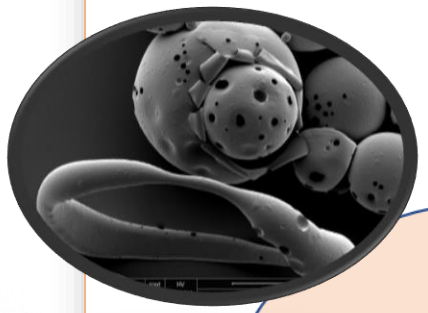
- Analyses biologiques in vitro, in vivo
  - Cytotoxicité
  - Inflammation
  - Colonisation

- Analyse mécanique
  - Uniaxiale
  - Multiaxiale
  - Gonflement

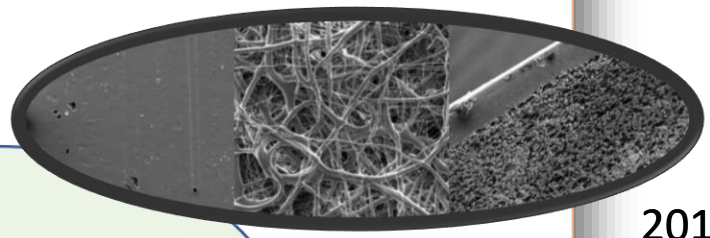
Problématique croissante de la hernie à large défect

Analyses d'explants, littérature

Biomekid



Diapid



Bioprinting

Fonctionnalisation chimique et / ou biologique

Electrofilage

- Analyses biologiques in vitro, in vivo
  - Cytotoxicité
  - Inflammation
  - Colonisation
- Analyse mécanique
  - Uniaxiale
  - Multiaxiale
  - Gonflement

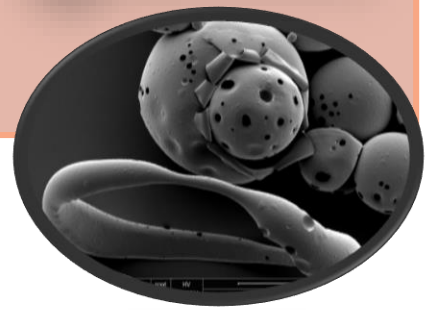
2022

2018

2019

2022

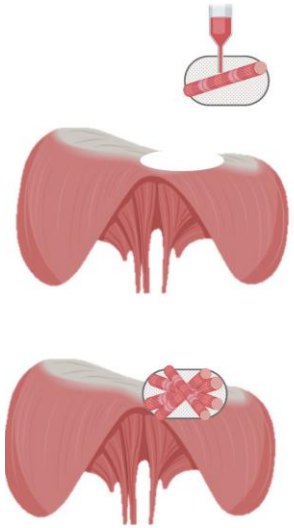
Biomekid

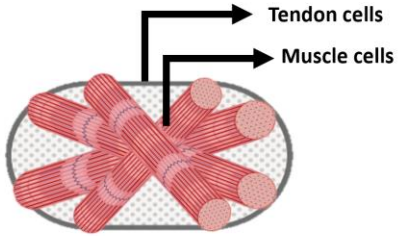


Répondre aux faiblesses des prothèses résorbables :

- Récidives
- Tissu conjonctif non fonctionnel
- Adhérences (processus inflammatoire de résorption)

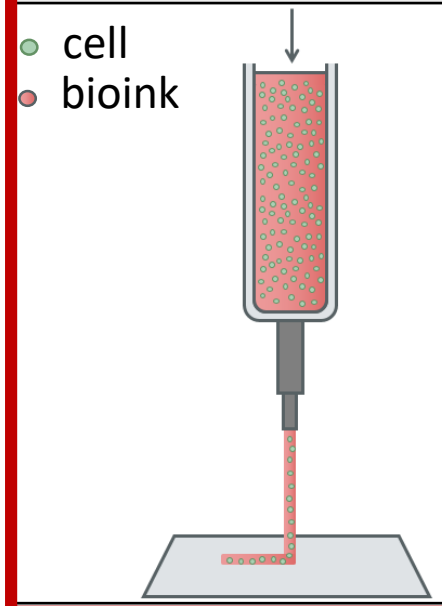
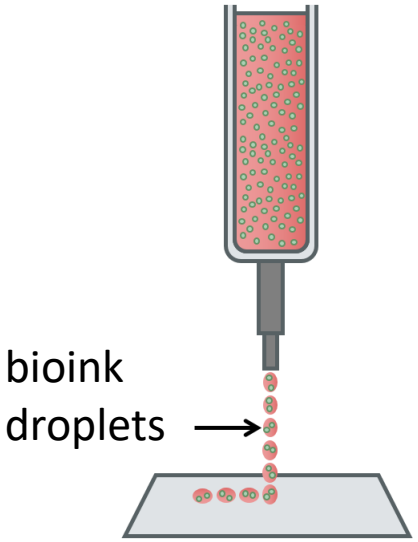
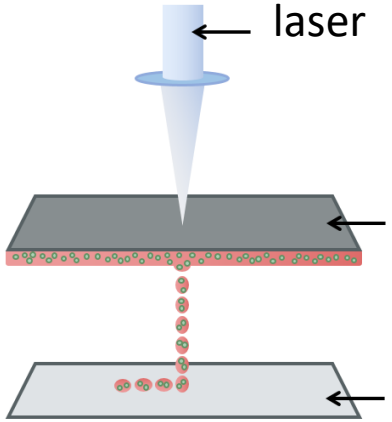
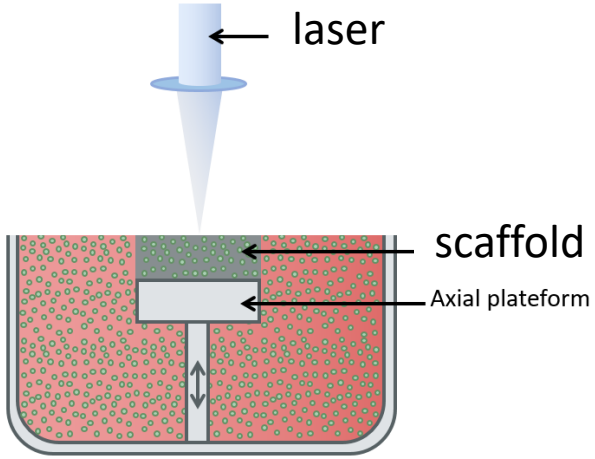
- Favoriser la régénération diaphragmatique
- Et donc une fonction diaphragmatique



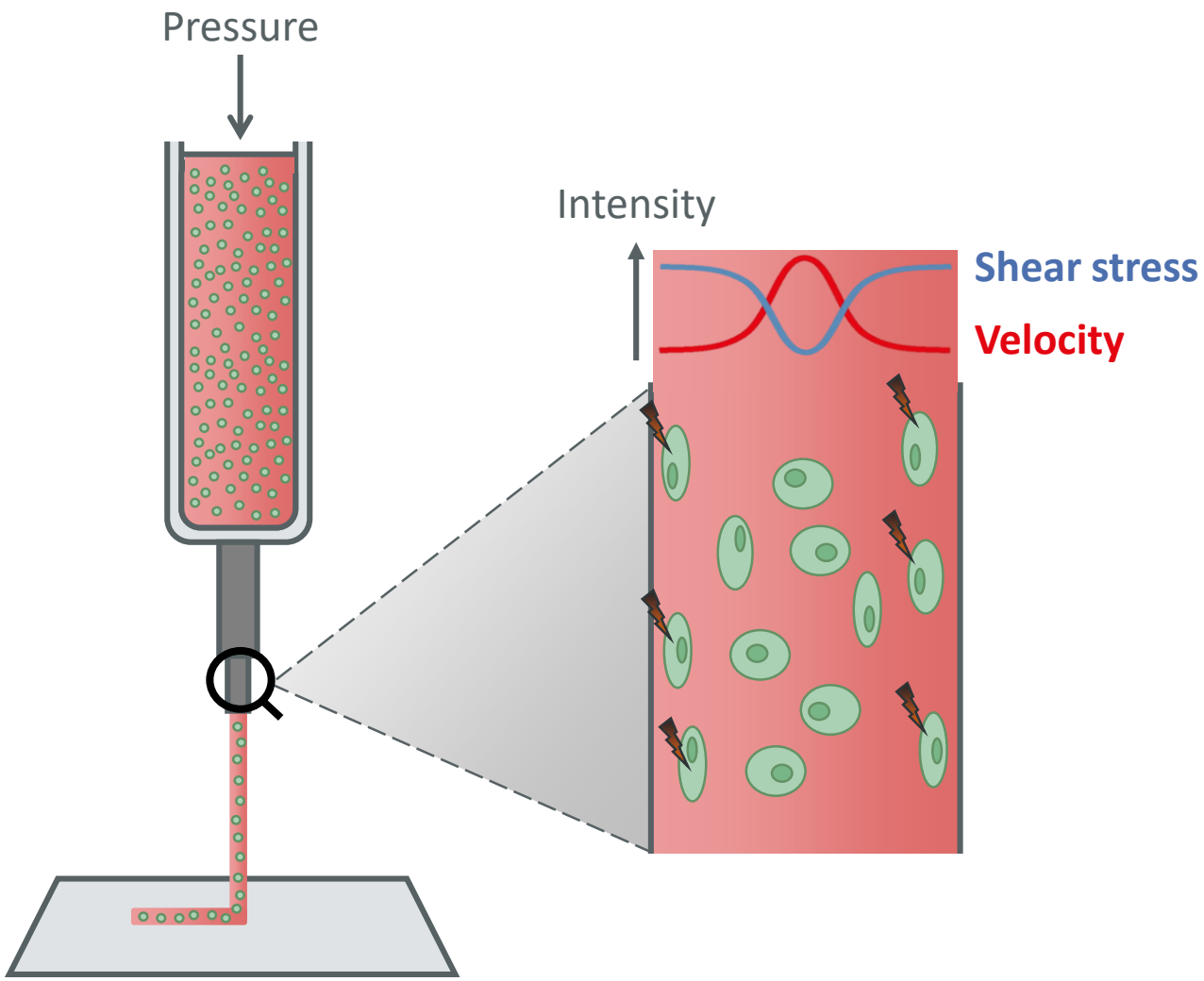


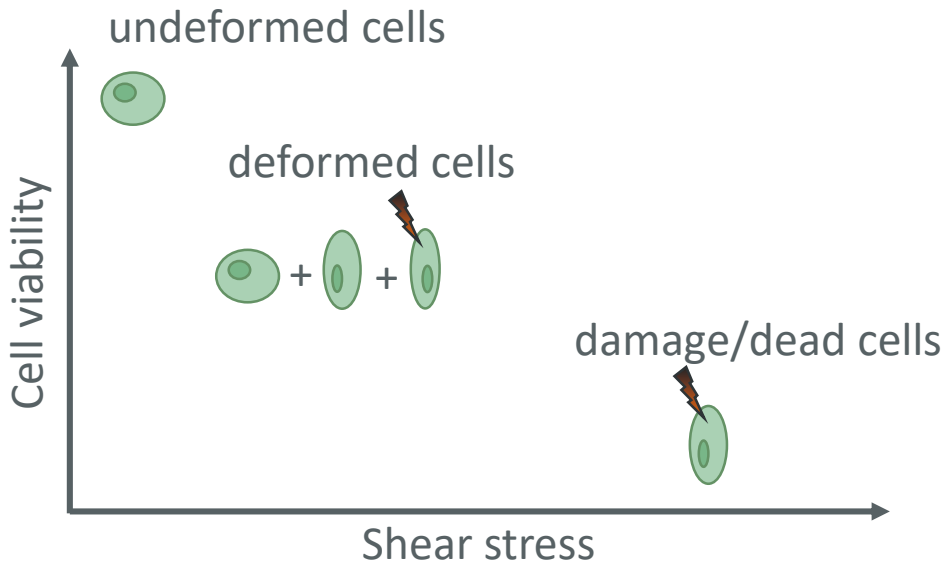
…Bioimpression cellulaire

Les différents modes de bioimpression

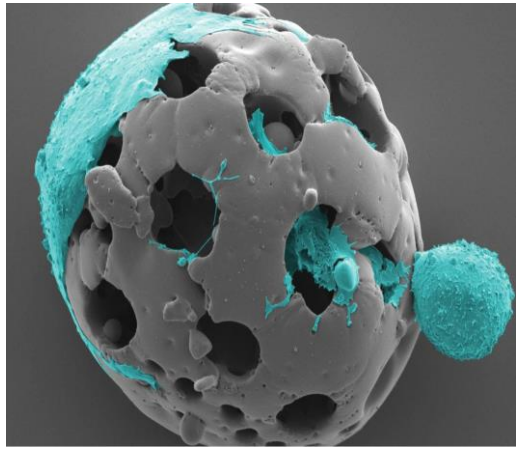
EXTRUSION	INKJET	LASER	STEREOLITHOGRAPHY
			
Advantages and limitations			
• High cell density • Cost effective • High versatility	• Fast printing speed • High cell viability • High resolution	• High cell viability • High-variability • High resolution	• High cell viability • High resolution
• Shear-stress inducing low cell viability • Low resolution	• Low cell density • High-viscosity bioinks • Clogging of nozzle	• Low fabrication speed • Low cell density • High cost	• UV polymerization • Amount of material • Low cell density • Lack of multi-material

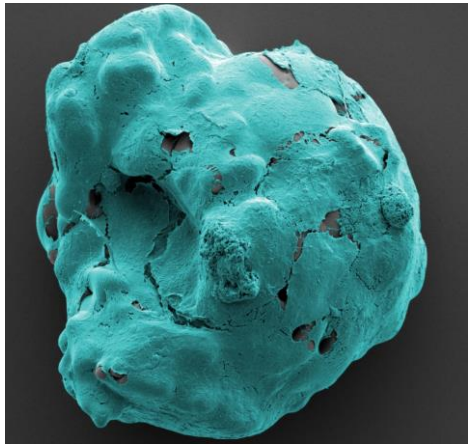
Les inconvénients de la bioimpression par extrusion

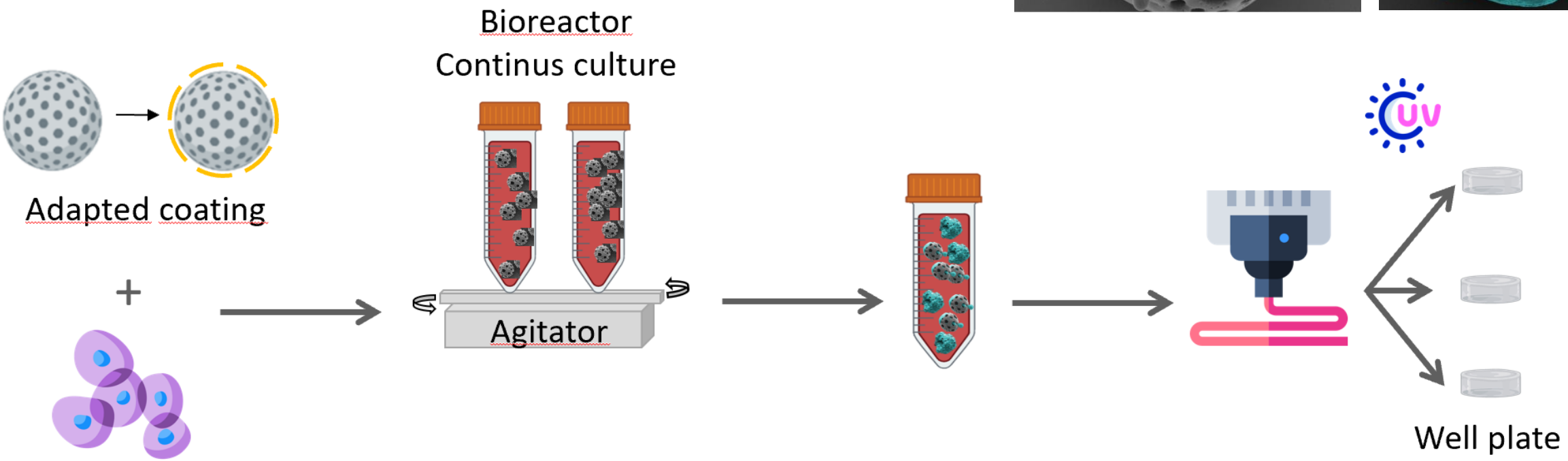




Mise au point de microparticules « protégeant les cellules »







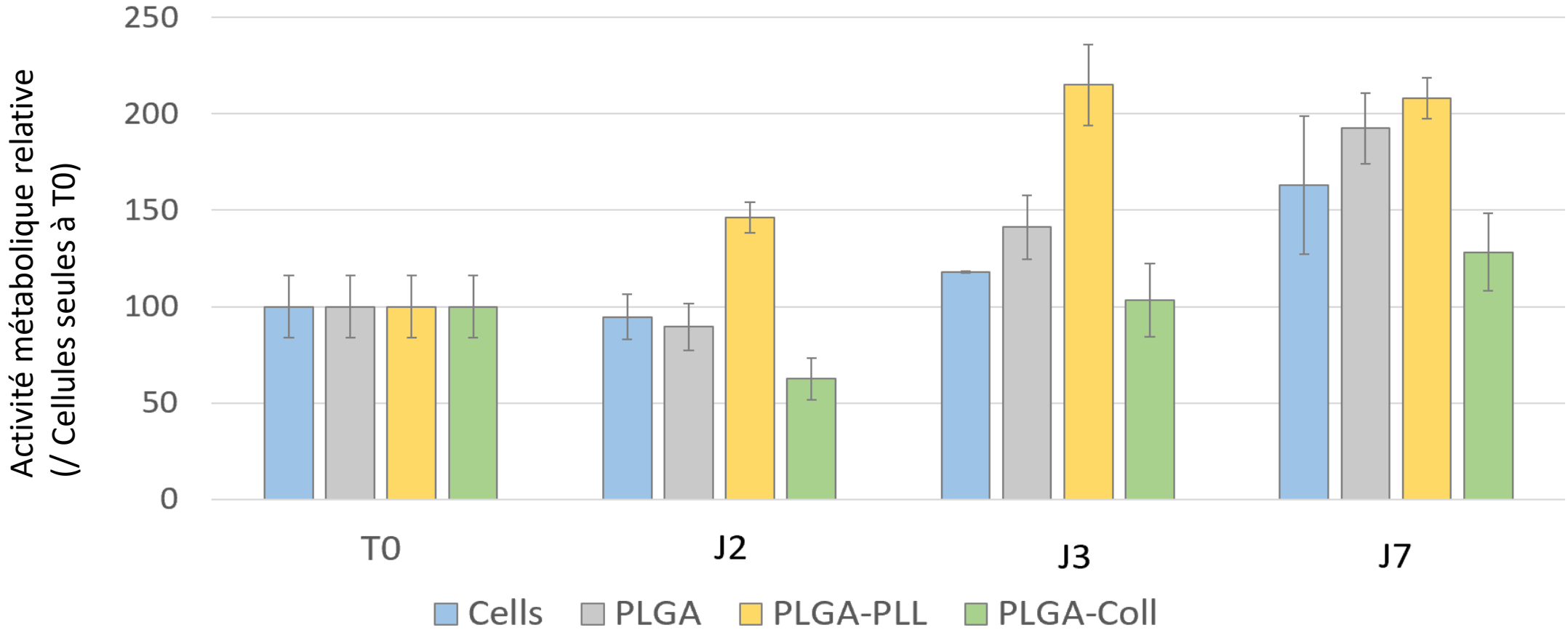
MICROSCAFFOLDS + CELLS

PRE-CELLULARIZED MICROSCAFFOLDS

MICROSCAFFOLDS + CELLS + BIOINK

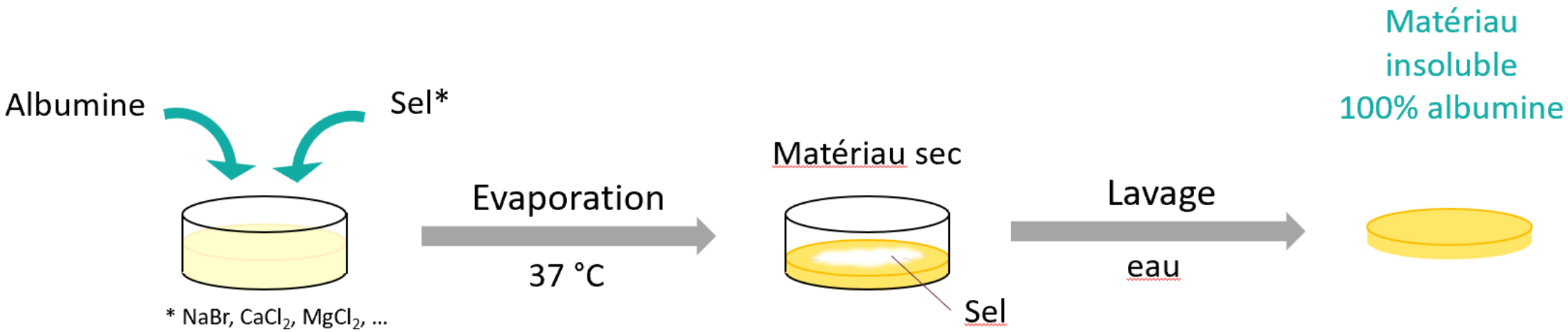
BIOPRINTING

Prolifération cellulaire selon les microparticules

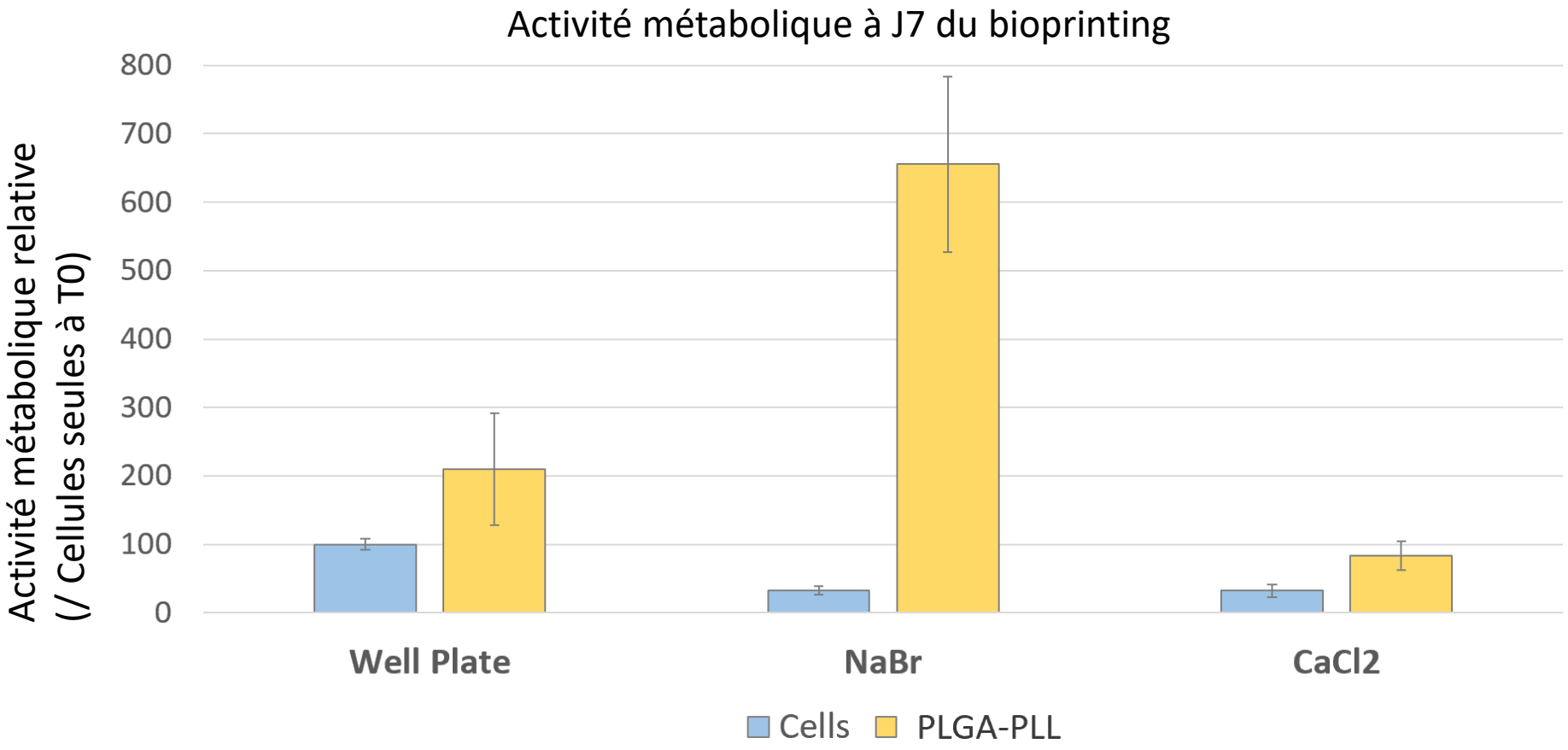


Time/Condition	Cells	PLGA	PLGA-PLL	PLGA-Coll
2 days	94.7 %	89.5 %	146.2 %	62.5 %
3 days	117.9 %	141.2 %	**215.1 %**	103.3 %
7 days	162.9 %	192.5 %	208.0 %	128.3 %

Scaffold de support pour impression : ALBUPAD, innovation du laboratoire



Viabilité cellulaire selon la nature du scaffold *(bromure de sodium ou chlorure de calcium)*



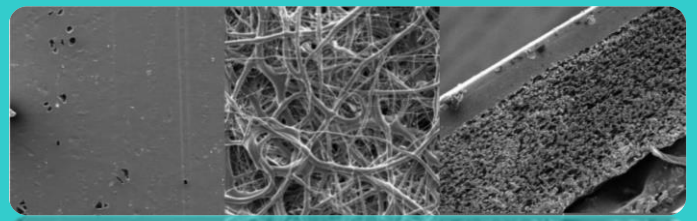
	Well Plate	NaBr	CaCl2
Cells Alone	100 %	32.7 %	32.4 %
PLGA-PLL	210.4 %	**655.5 %**	83.5 %

Next steps

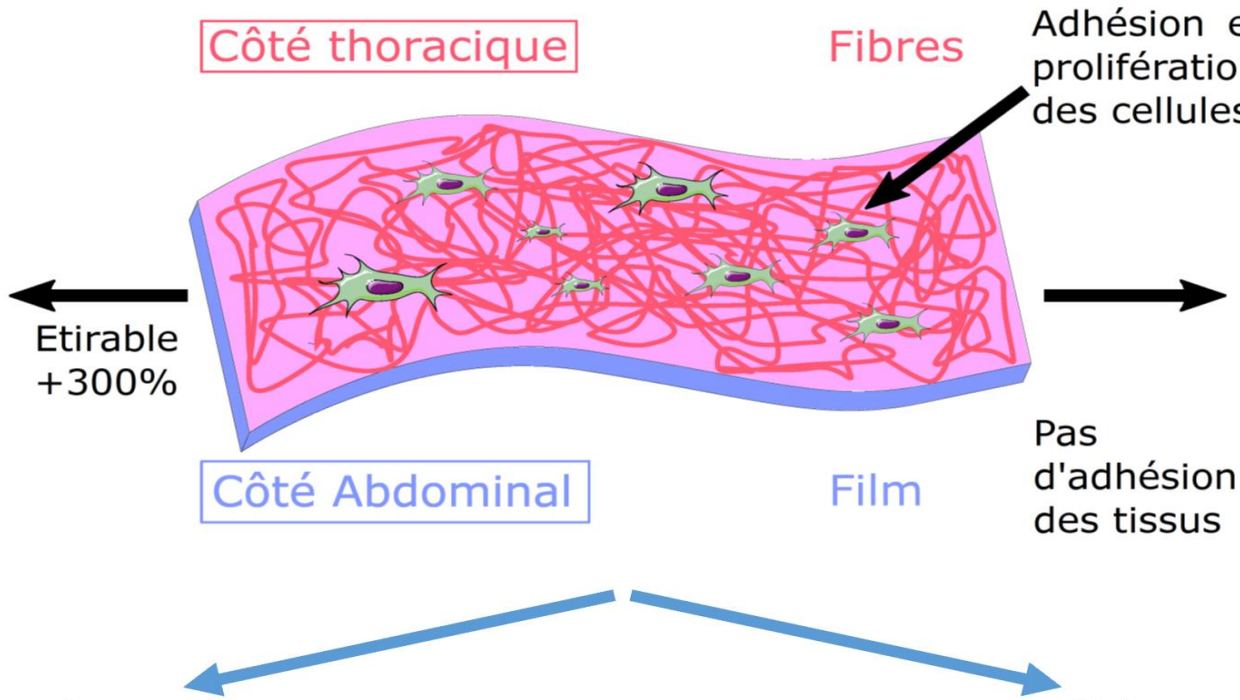
- Coculture tendinocytes et cellules musculaires
- Architecture de bioimpression
- In Vivo

Equipe biomekid :

Diapid



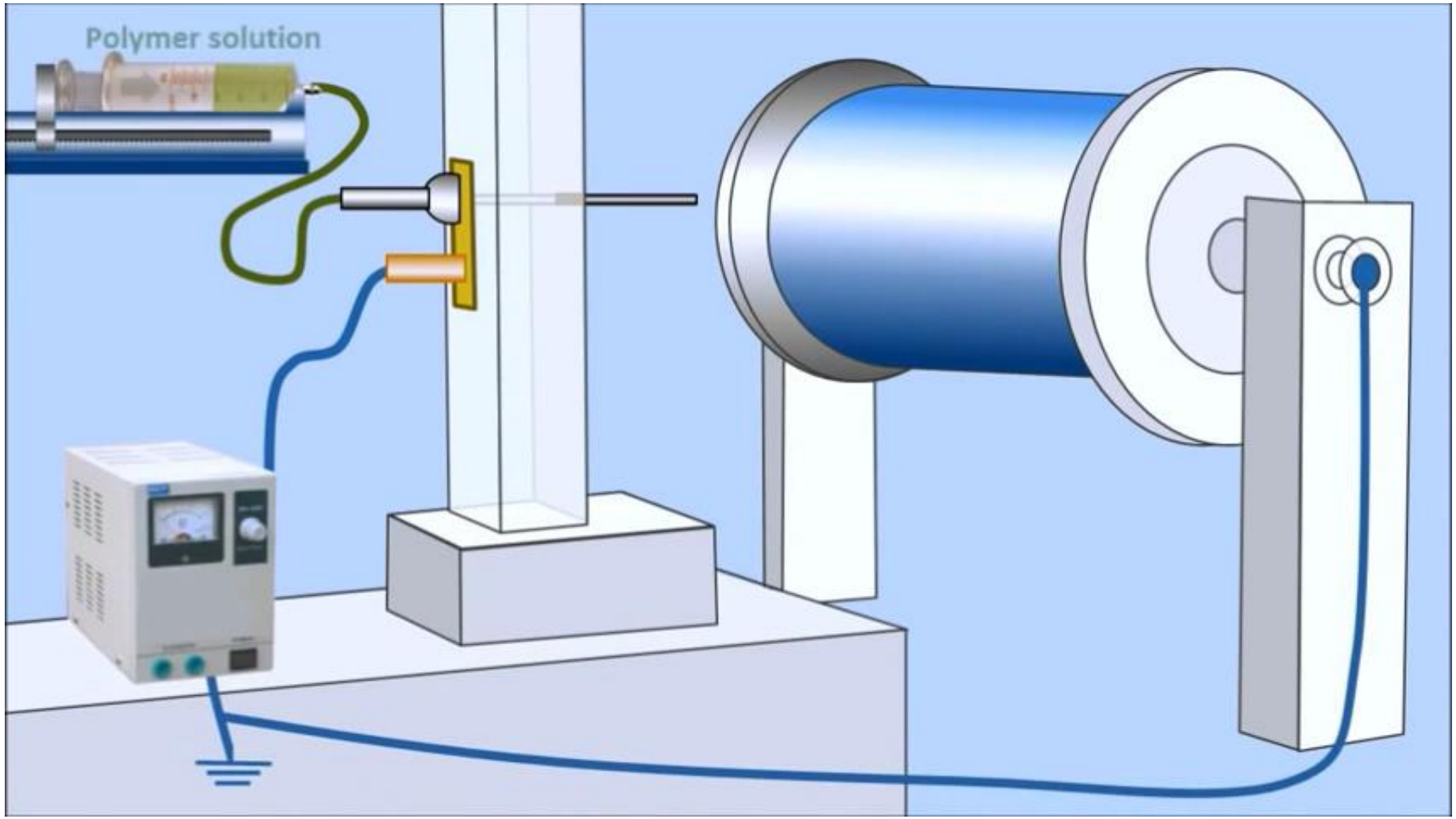
Electrofilage de polyuréthane de grade médical

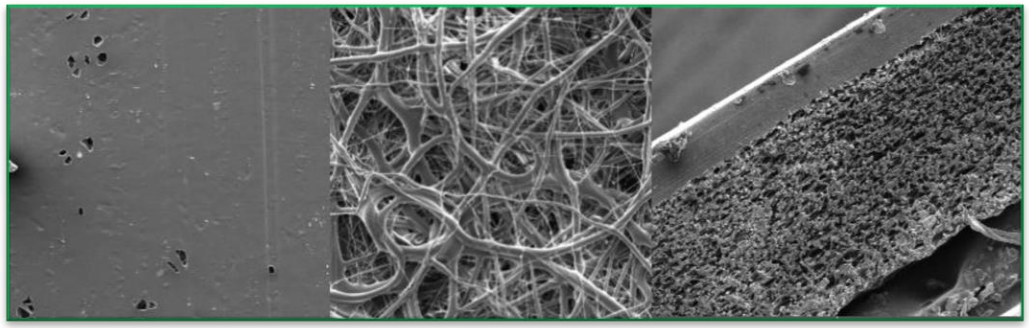


≠

Voie solvant organique
TPU en granulé
→Chronoflex AL 75A
→Tecothane 1074A

Voie aqueuse
TPU en suspension aqueuse
→Luphen 700





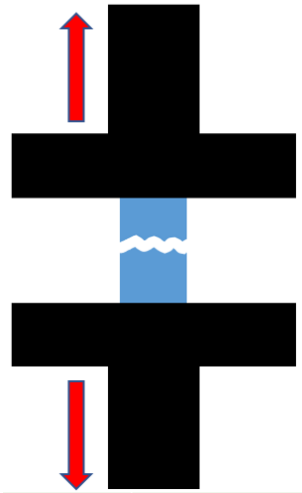
From I Garcia Alvarez

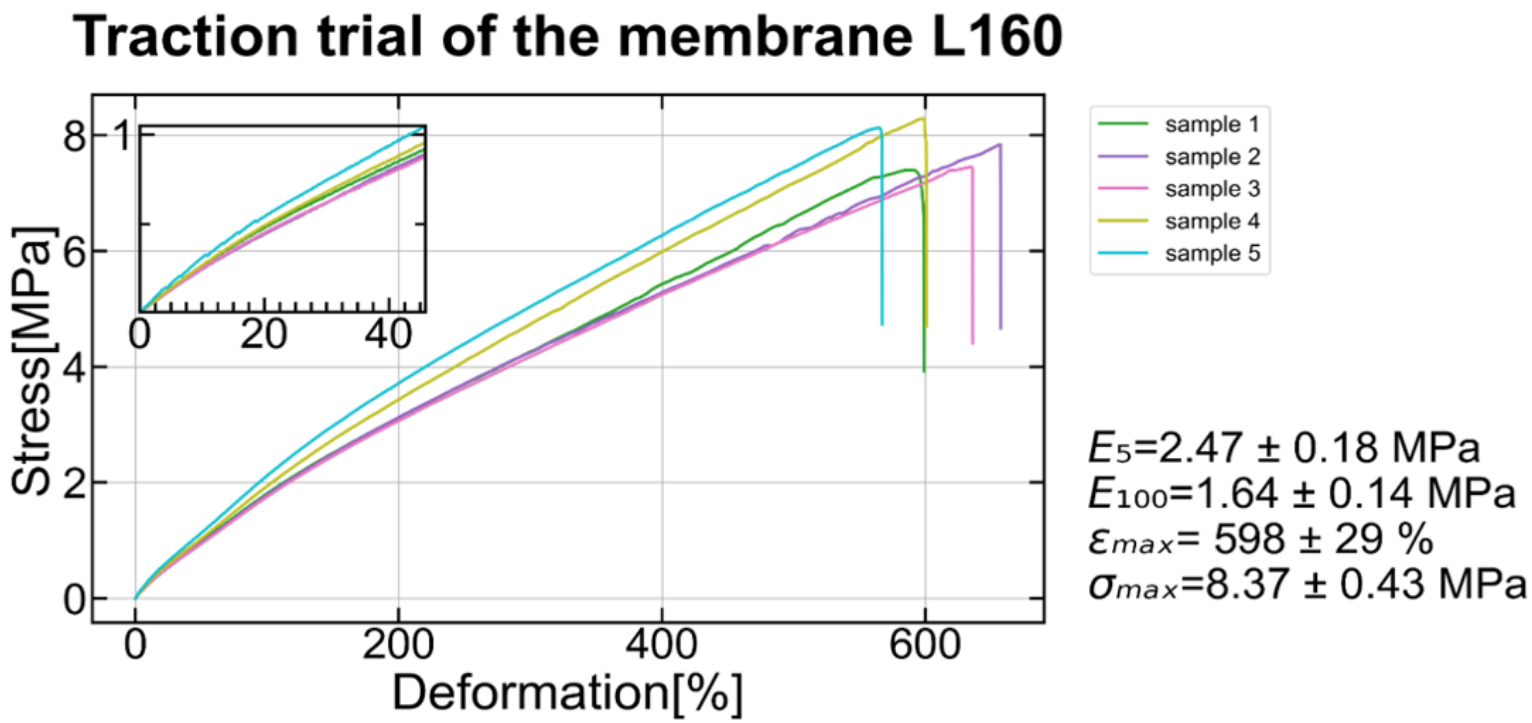
Tests mécaniques

Pour chaque membrane :

- Quelle déformation maximale (%)
- Quelle est la valeur de stress maximal (MPa)
- Quel module de young (rigidité) (MPa)

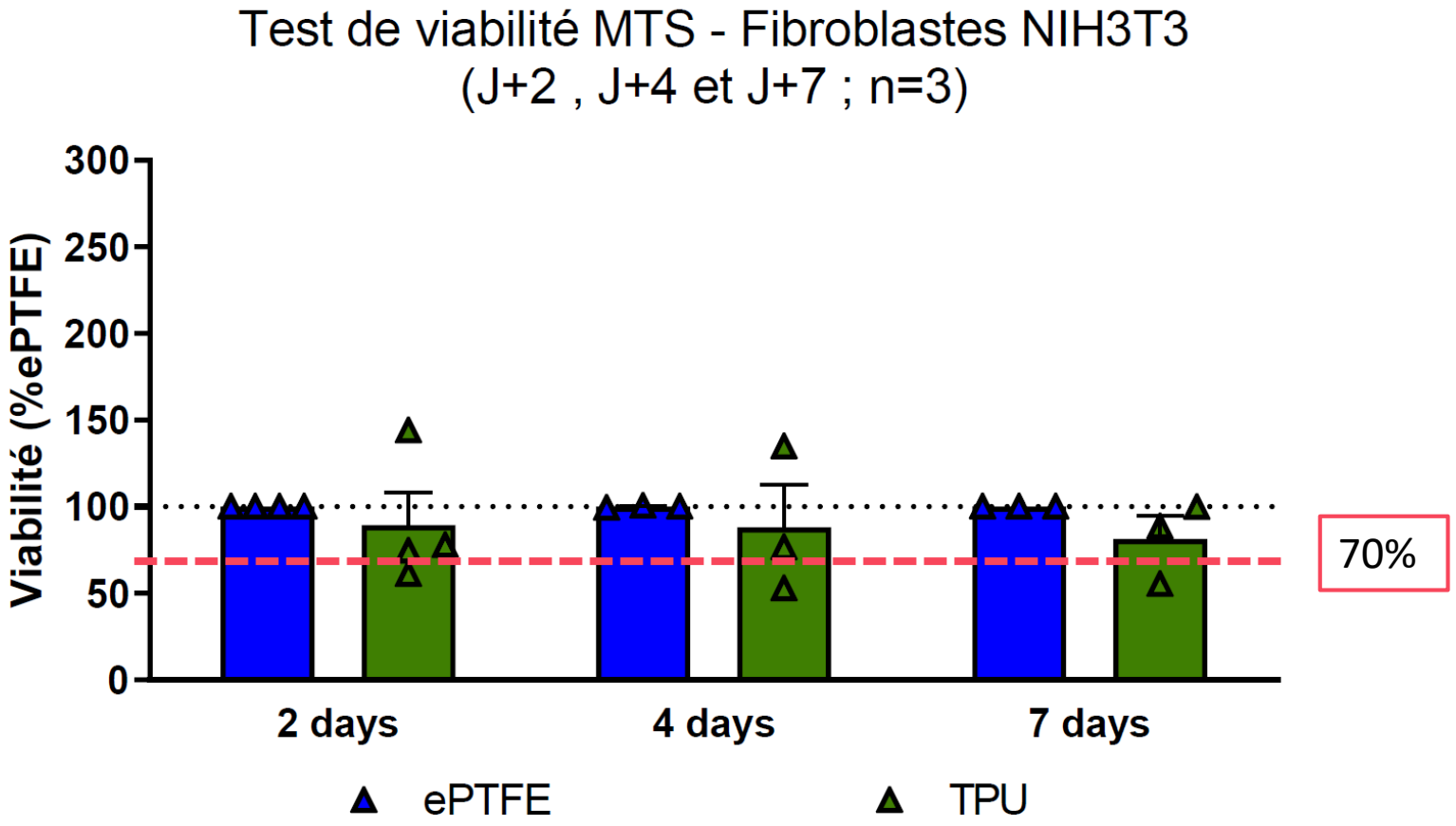
Membrane	Young Modulus (MPa)	Max deformation(%)	Max Stress(MPa)
One of our membrane (L160)	2.5±0.2	600±30	8.4±0.3
Gortex (current prosthesis)	8.0±1,4	285±60	12.7±3,2





E_5=2.47 ± 0.18 MPa
E_{100}=1.64 ± 0.14 MPa
ε_{max}= 598 ± 29 %
σ_{max}=8.37 ± 0.43 MPa

Tests biologiques : viabilité cellulaire

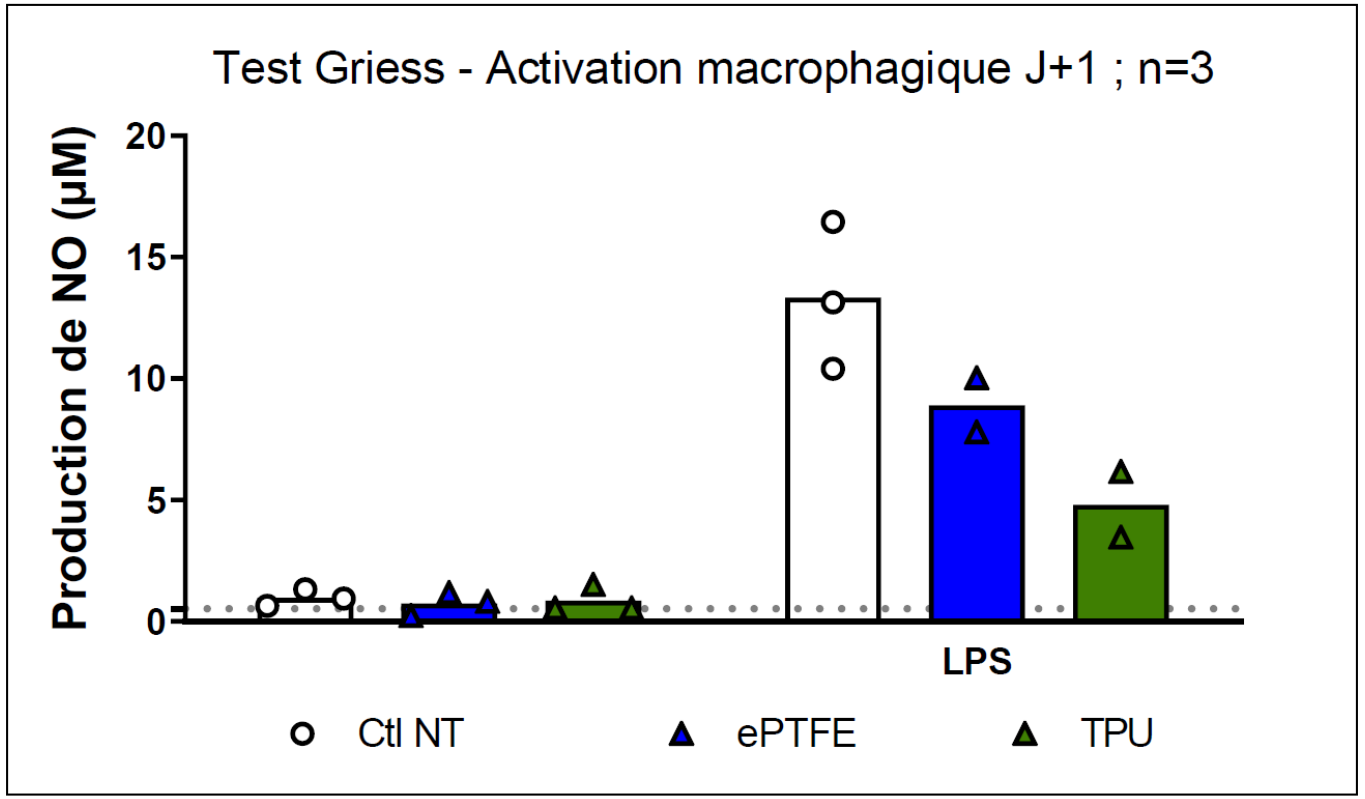


Absence de cytotoxicité, conditions Normes ISO 10993-5

Tests biologiques : inflammation

Lignée cellulaire de macrophages RAW 264.7

Activation par du LPS (50ng/mL)



Pas d'indicateur de réponse pro-inflammatoire

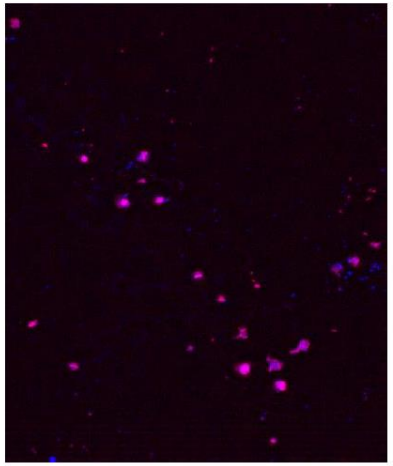
Tests biologiques : colonisation NIH3T3

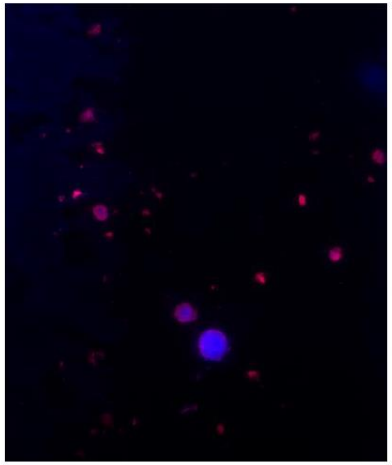
Efficacité de notre nouveau matériau TPU : Comparaison avec e-PTFE

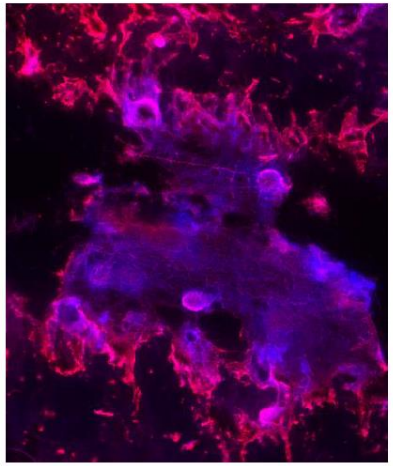
Actine
Noyaux

Observation au x4 des membranes

e-PTFE

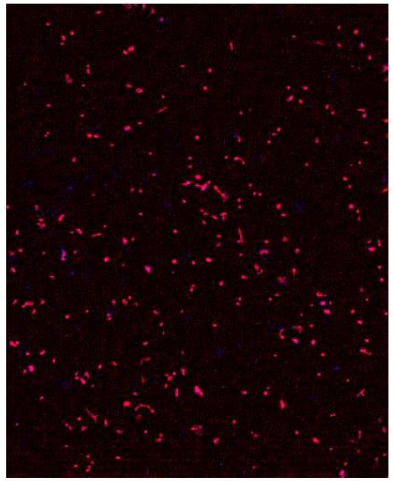


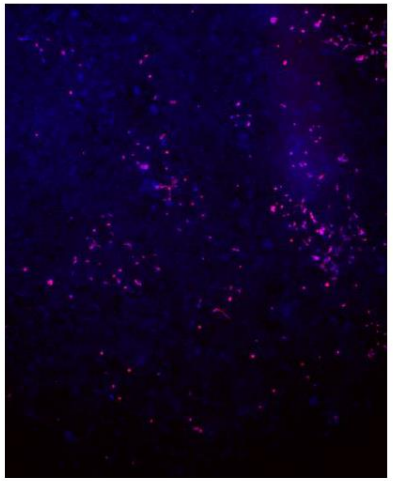


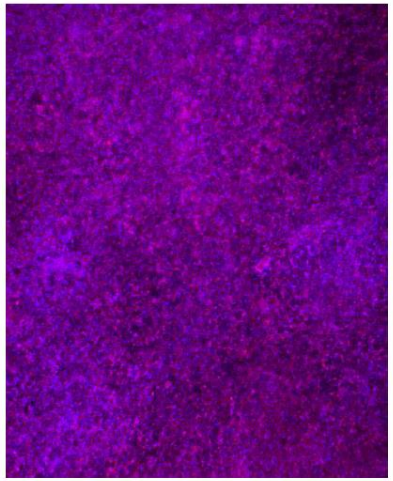


J+2 **J+4** **J+7**

TPU





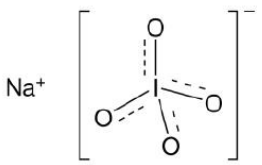


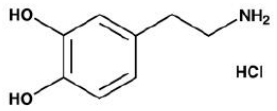
Colonisation hétérogène en amas à la surface de l'e-PTFE

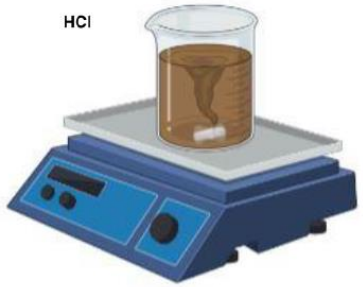
Colonisation homogène à la surface du TPU à J+7

Intérêt d’une fonctionnalisation

Coating de Polydopamine + Collagène I par immersion

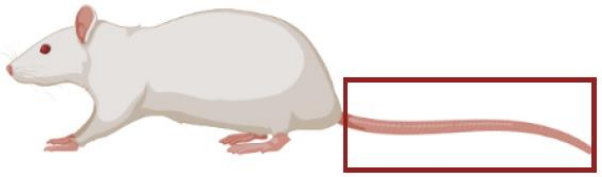






Immersion 3h

Découper membranes



Collagène de type I (Coll1) du tendon de queue de rat

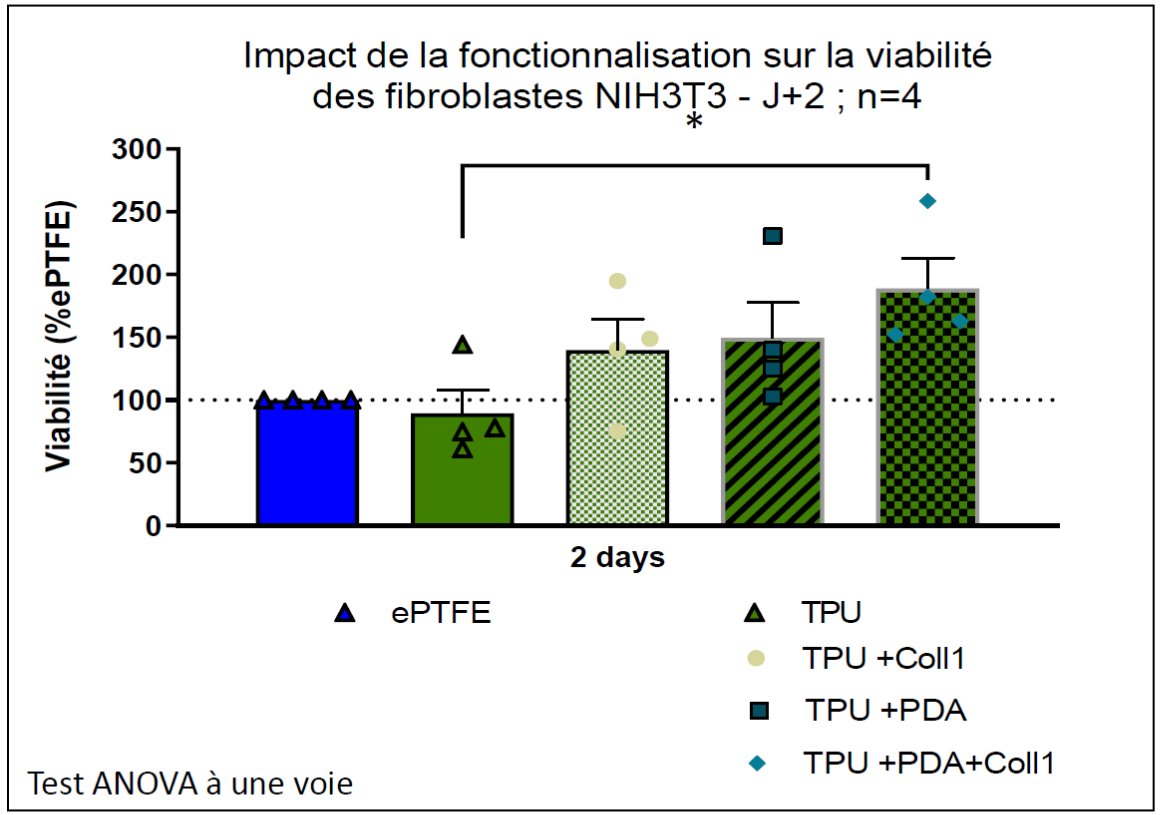
Immersion 3h à rt

(5µg/cm²) (10µg/mL)

Intérêt d'une fonctionnalisation

Viabilité à 2 jours

J+2



En comparaison avec l'e-PTFE :

- **Coll1** a tendance à augmenter l'activité métabolique sur le TPU
- **PDA** présente également cette tendance
- **PDA+Coll1** semble améliorer davantage l'activité sur le TPU

En comparaison avec le TPU :

- **PDA+Coll1** augmente significativement la viabilité cellulaire par rapport au TPU nu

PDA+Coll1 augmente de façon significative la viabilité

Next steps

- Coculture tendinocytes et cellules musculaires
- Tests mécaniques Biaxiaux et gonflement
- In Vivo

Equipe Diapid :











Merci pour votre attention

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