

# **Thérapies cellulaires en urologie**

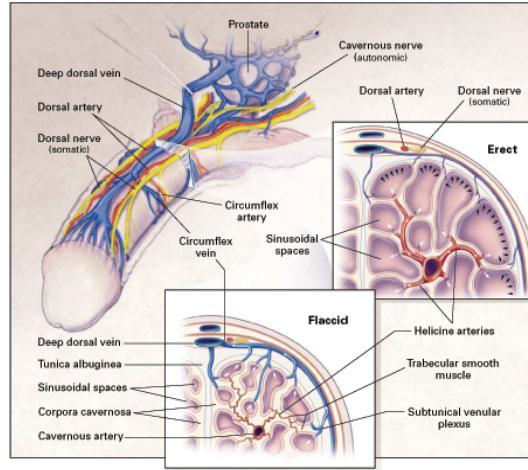
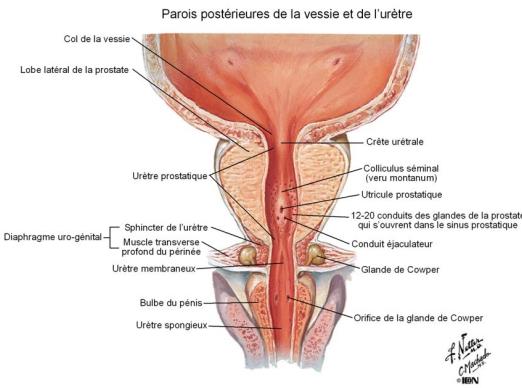
**Pr. René Yiou**  
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# Contexte

## Développement des biothérapies pour les séquelles de la chirurgie du cancer de prostate:

### 1. Incontinence urinaire par insuffisance sphinctérienne urétrale

### 2. Troubles de l'érection (dysfonction érectile)



1 cm

# Traitements actuels

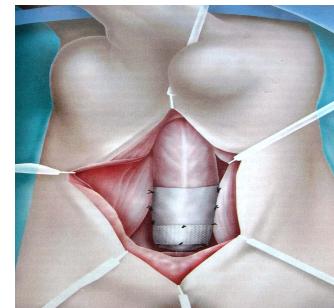
## Traitements actuels de l'incontinence urinaire



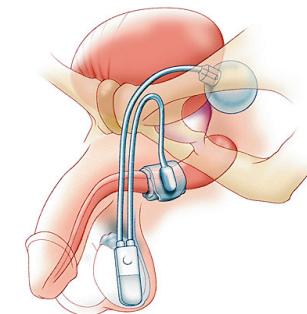
Injection  
comblement



Ballons compressifs

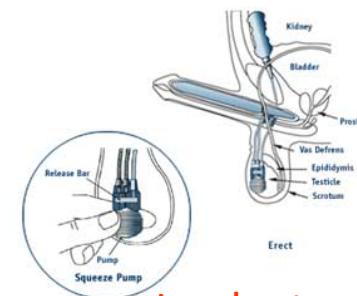


Bandelettes



Sphincter artificiel

## Traitements actuels des troubles de l'érection



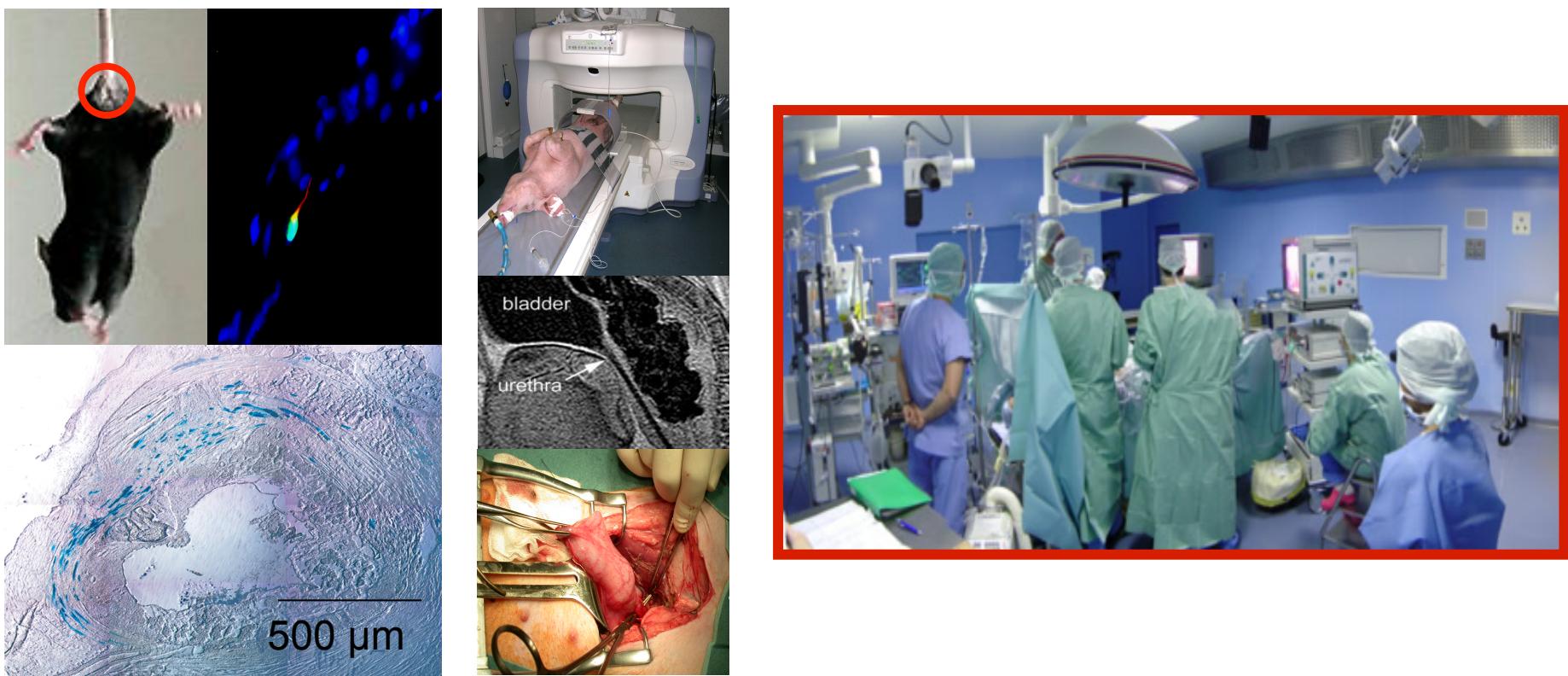
Implants péniens

# Principales sources de cellules souches utilisées en urologie et applications

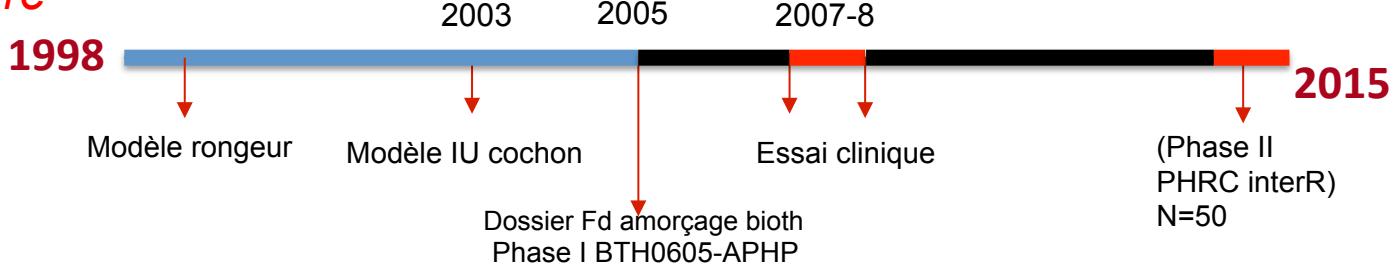
- **Cellules précurseurs de muscle strié (incontinence U)**
  - Cellules satellites + fibres musculaires
  - Myoblastes
  - Cellules souches musculaires
- **Cellules souches médullaires**
  - Cellules souches mésenchymateuses
  - Cellules souches hématopoïétiques
  - Cellules progénitrices endothéliales
- **Cellules souches adipeuses et cellules hMADS**
- **(Cellules souches embryonnaires, amniotiques)**



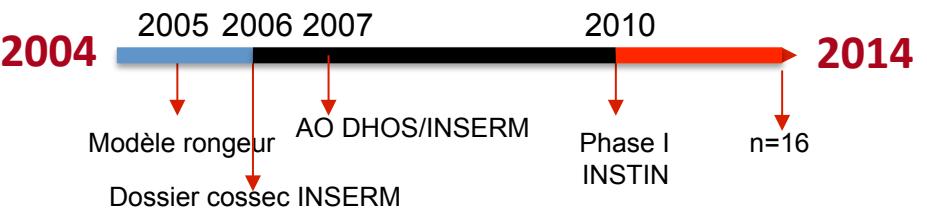
- **Incontinence urinaire**
- **Dysfonction érectile**
- **Dysfonction vésicale**
- **Sténose urétrale**
- **Insuffisance rénale**



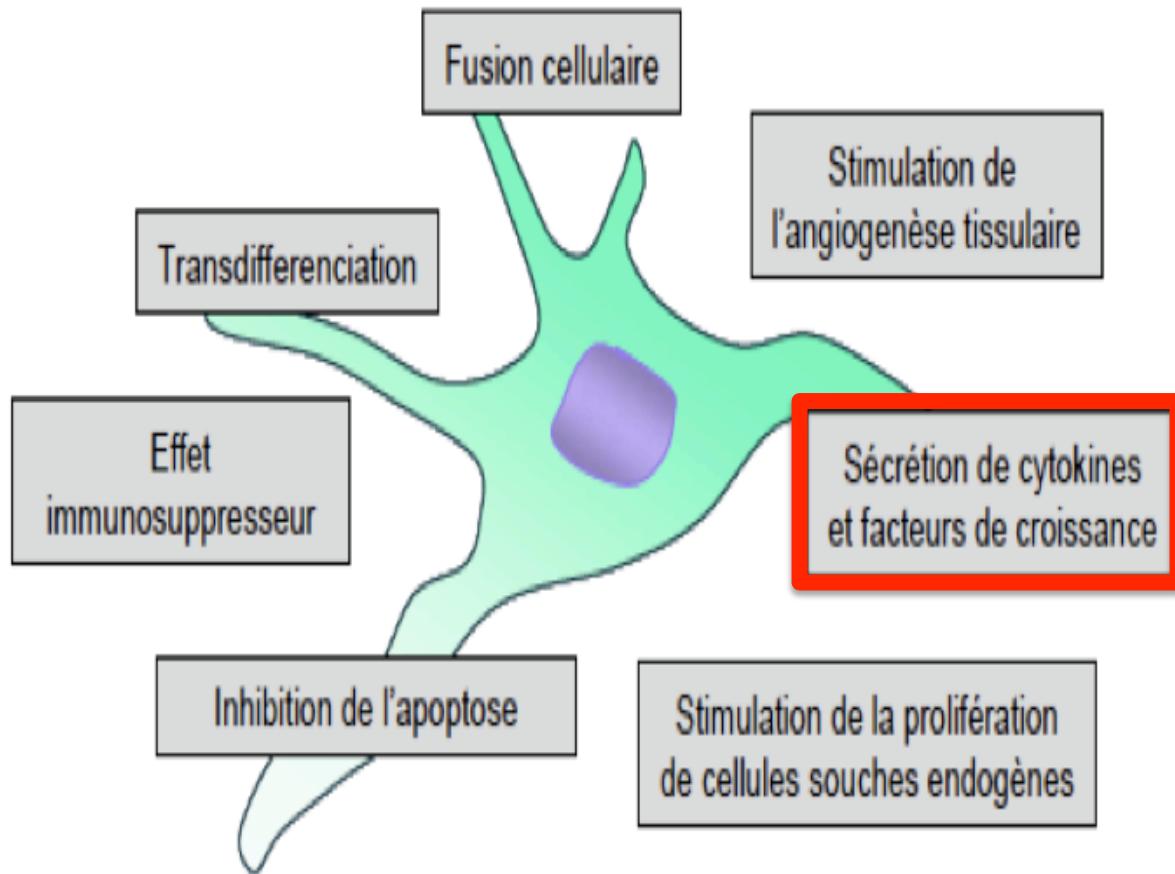
### Incontinence urinaire



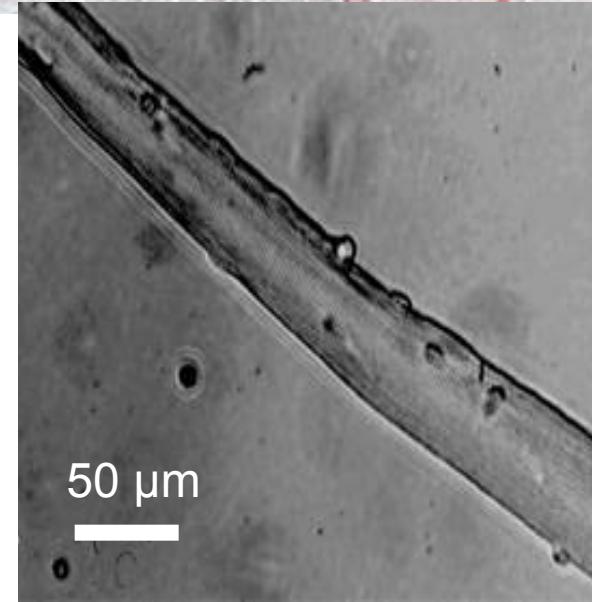
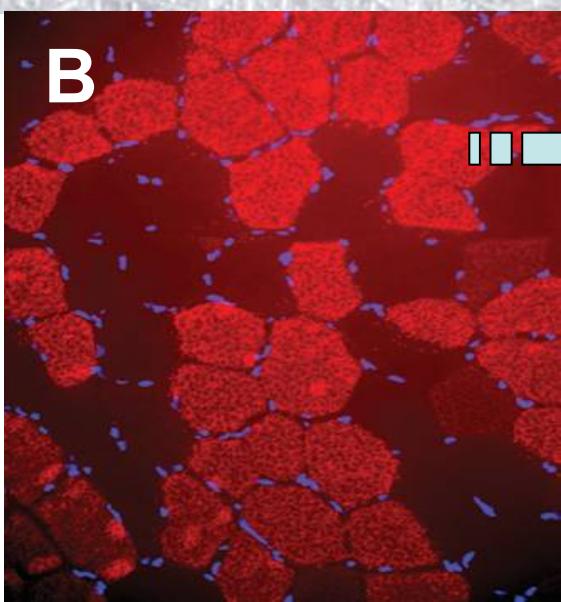
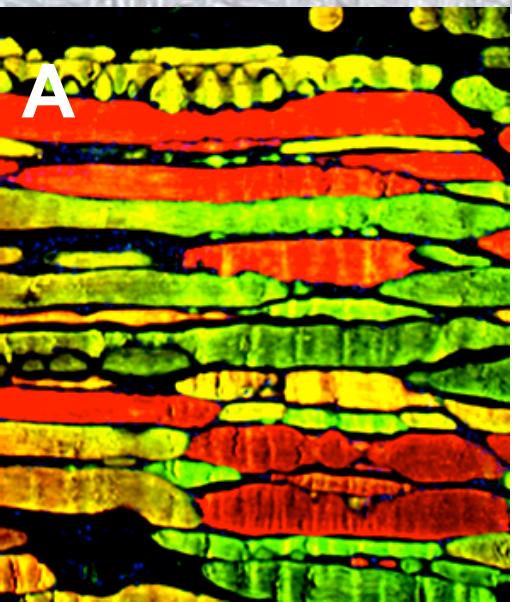
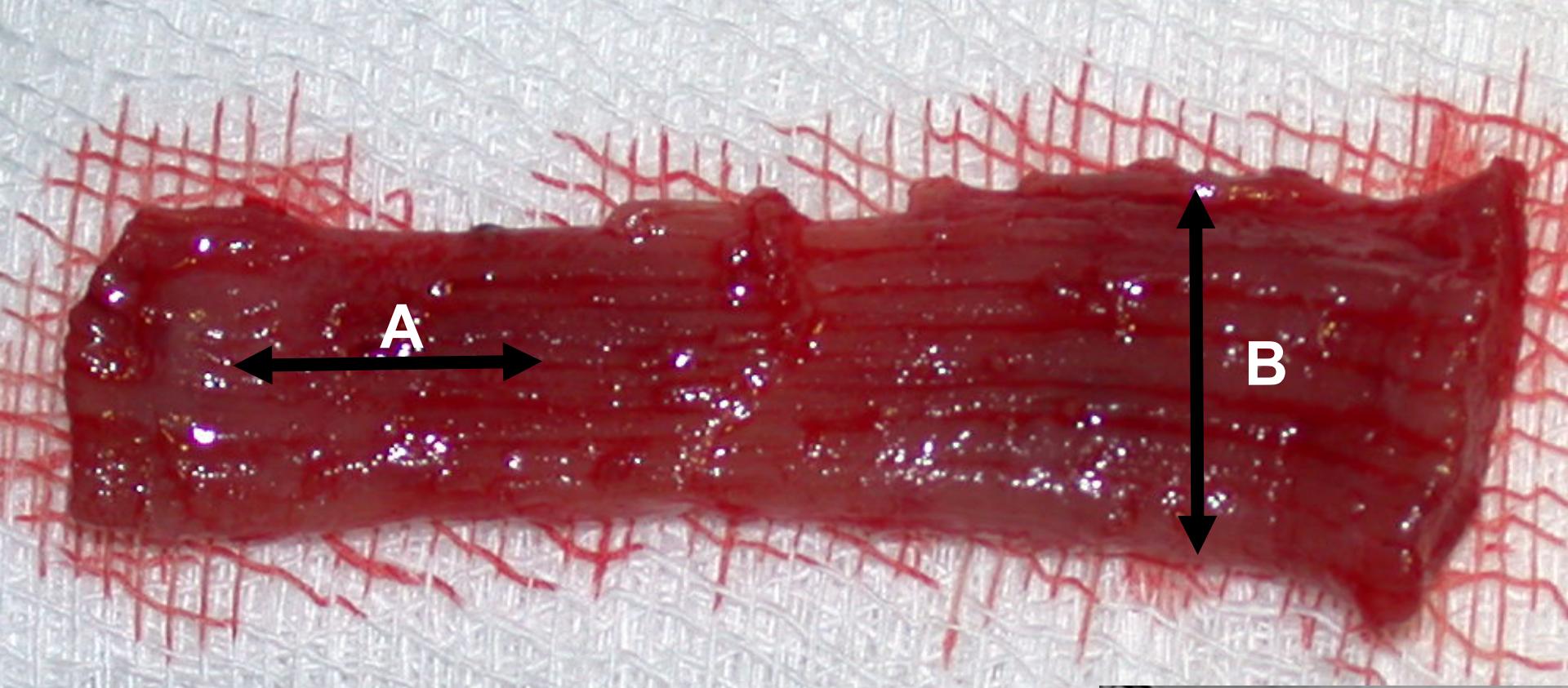
### Dysfonction érectile



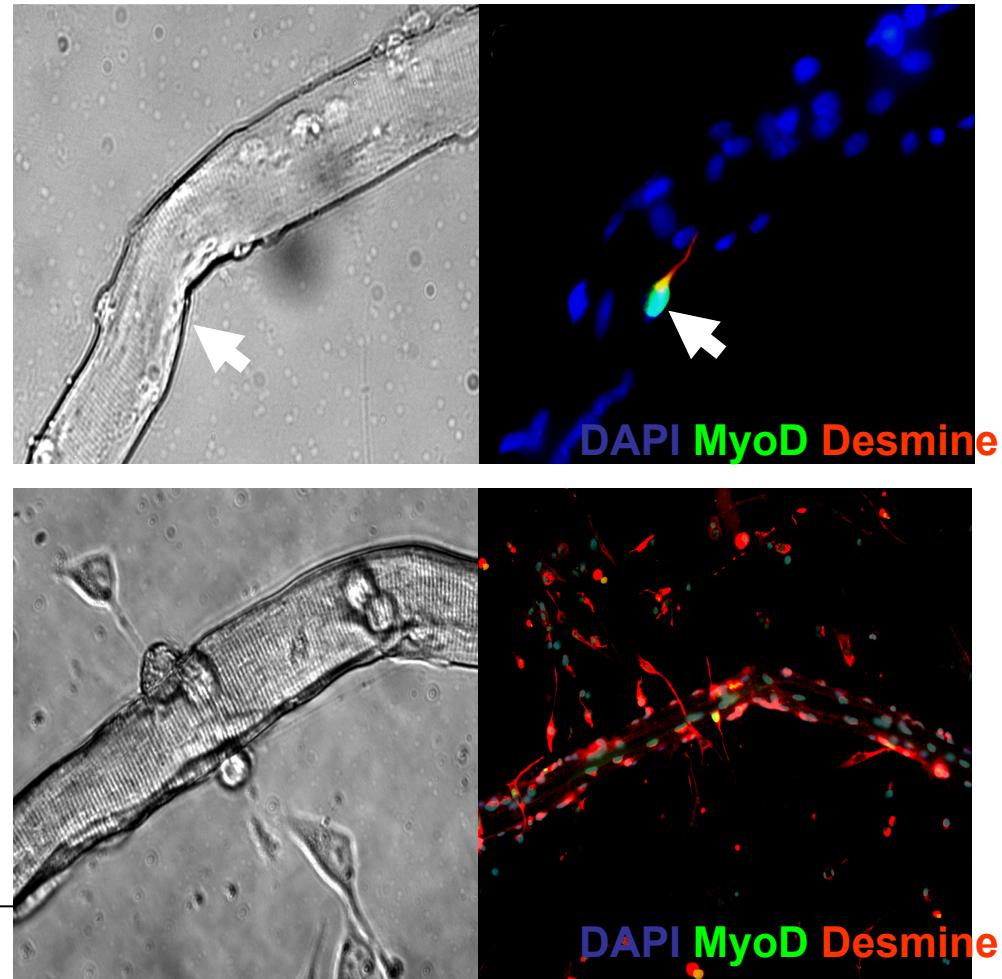
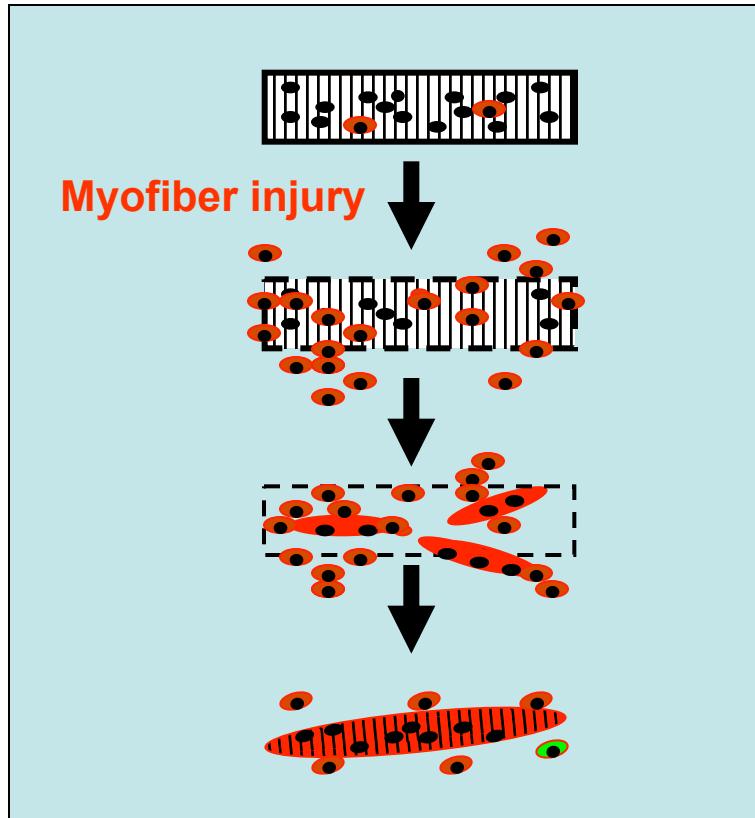
# Mécanismes de régénération des cellules souches



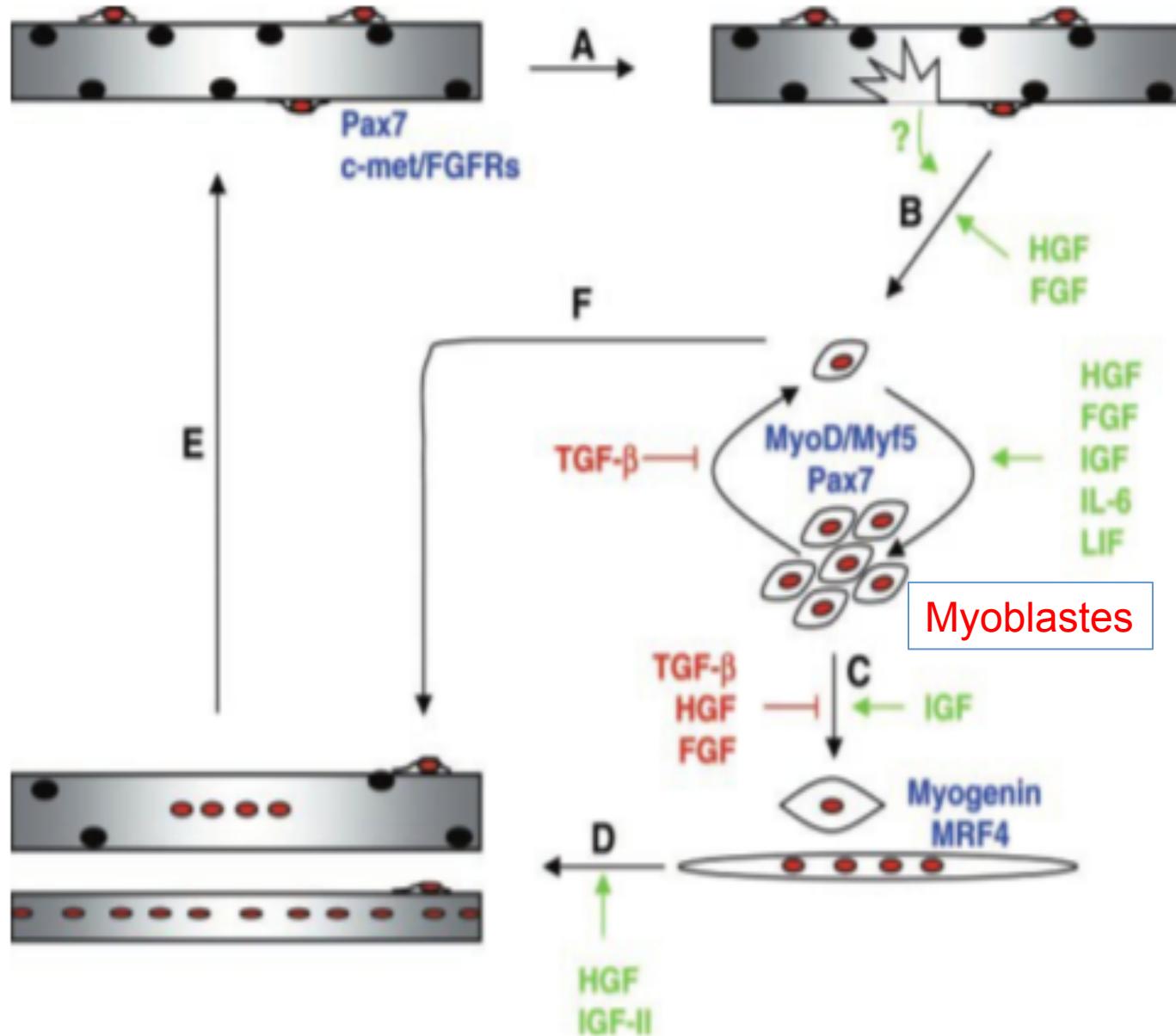
## **Les cellules précurseurs de muscle strié**

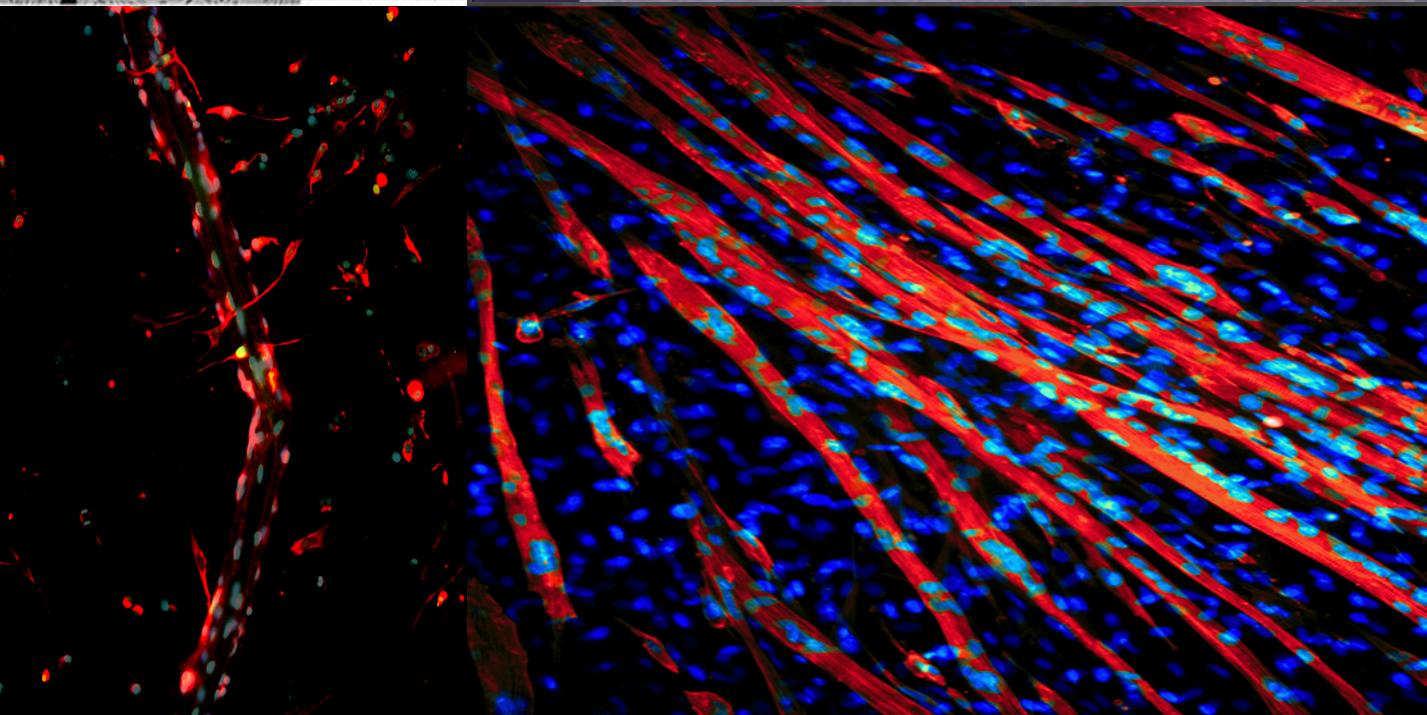
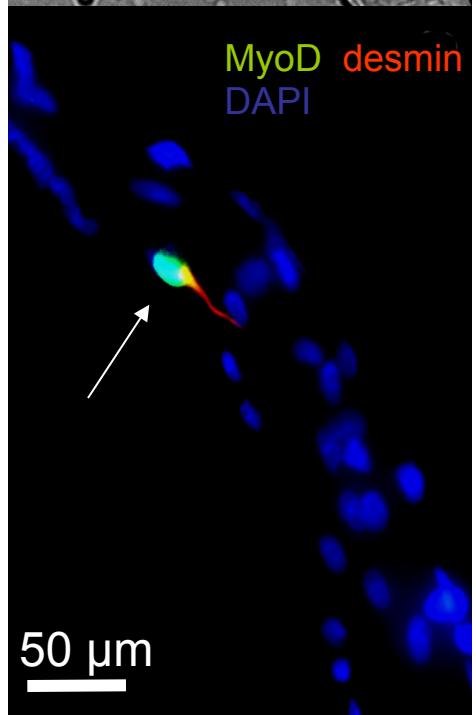
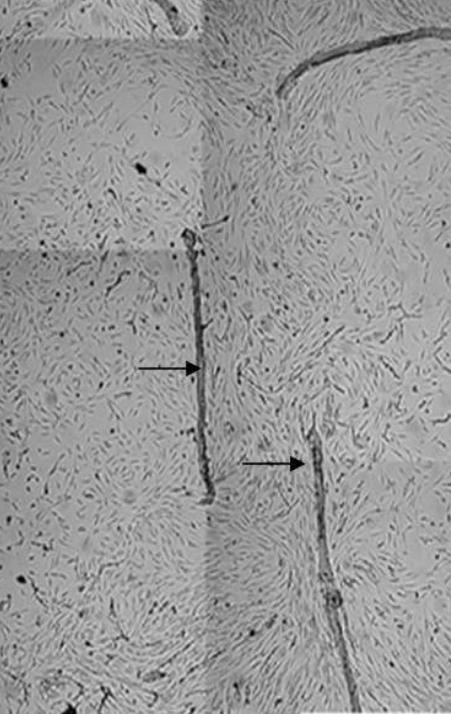
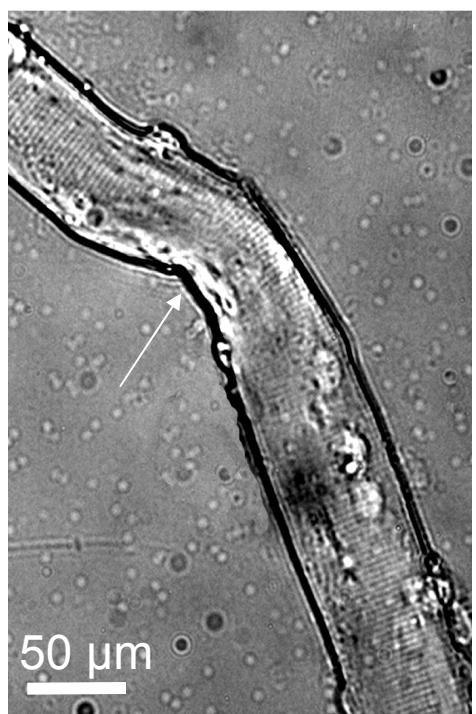


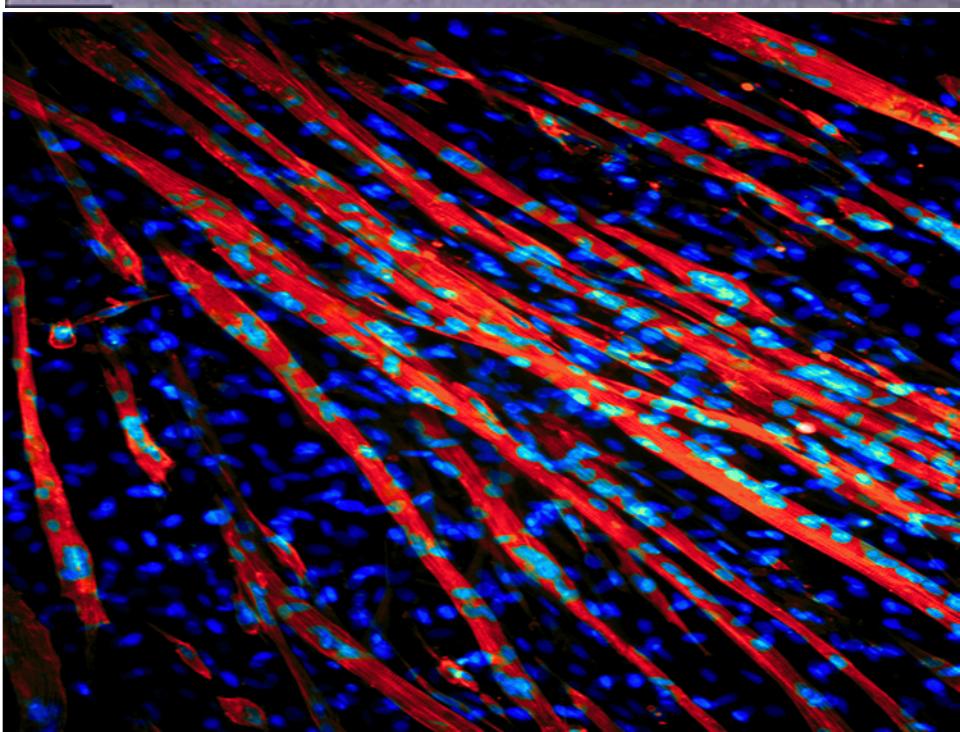
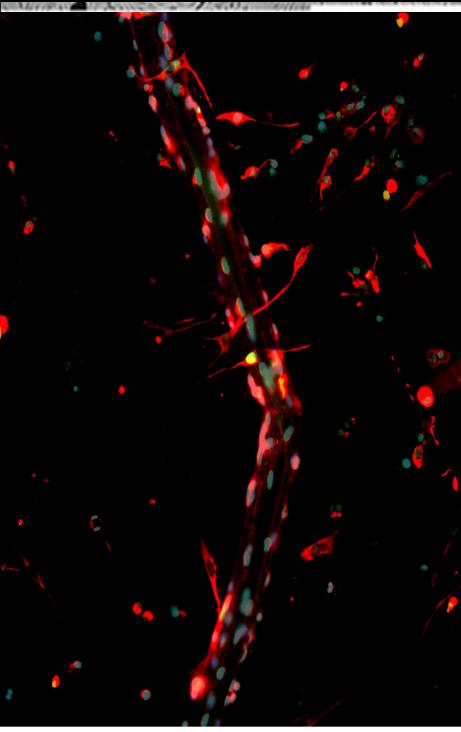
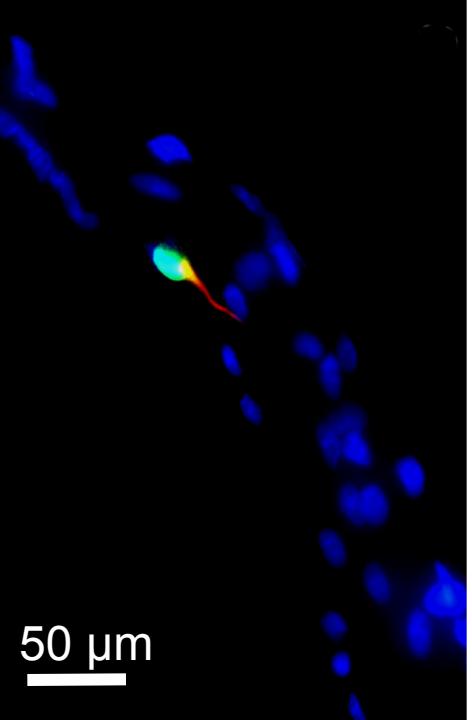
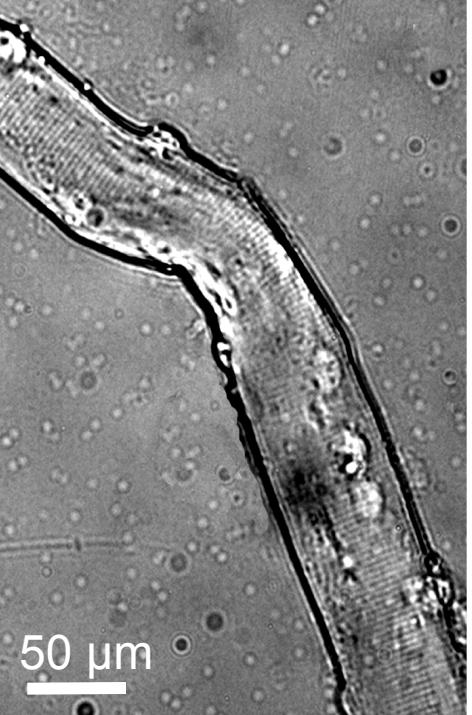
# SKELETAL MUSCLE REGENERATION: ACTIVATION OF MUSCLE PRECURSOR CELLS (satellite cells>myoblasts)

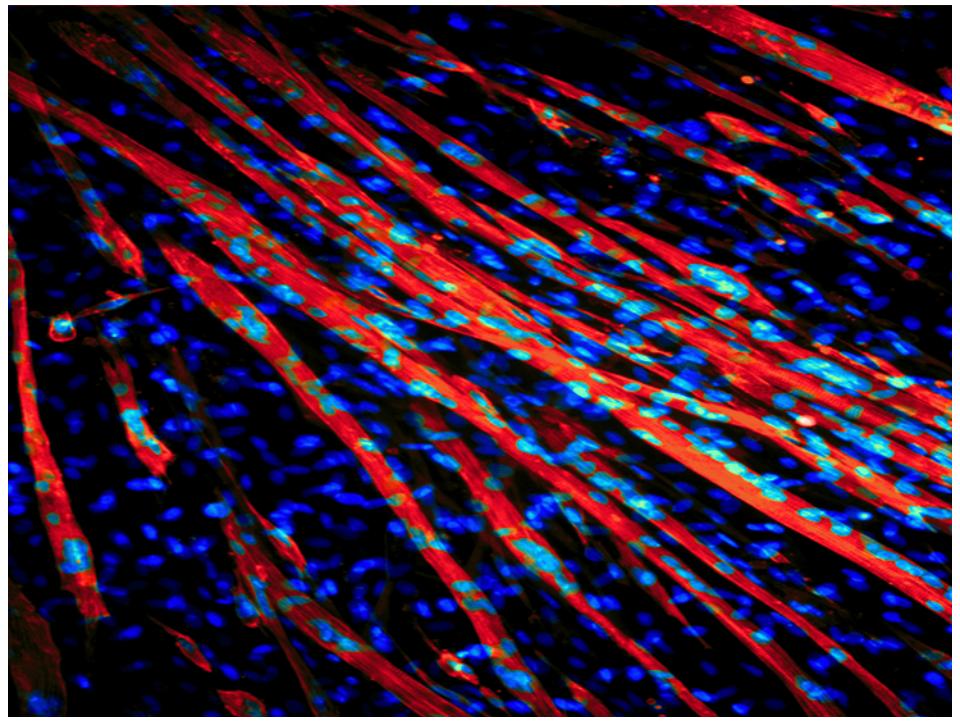
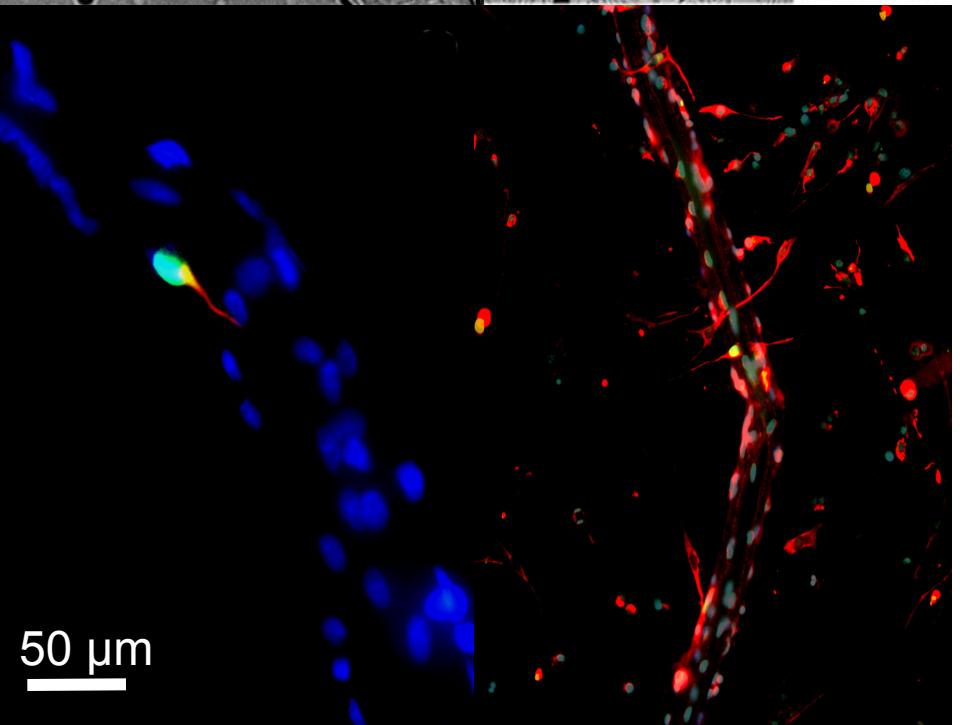
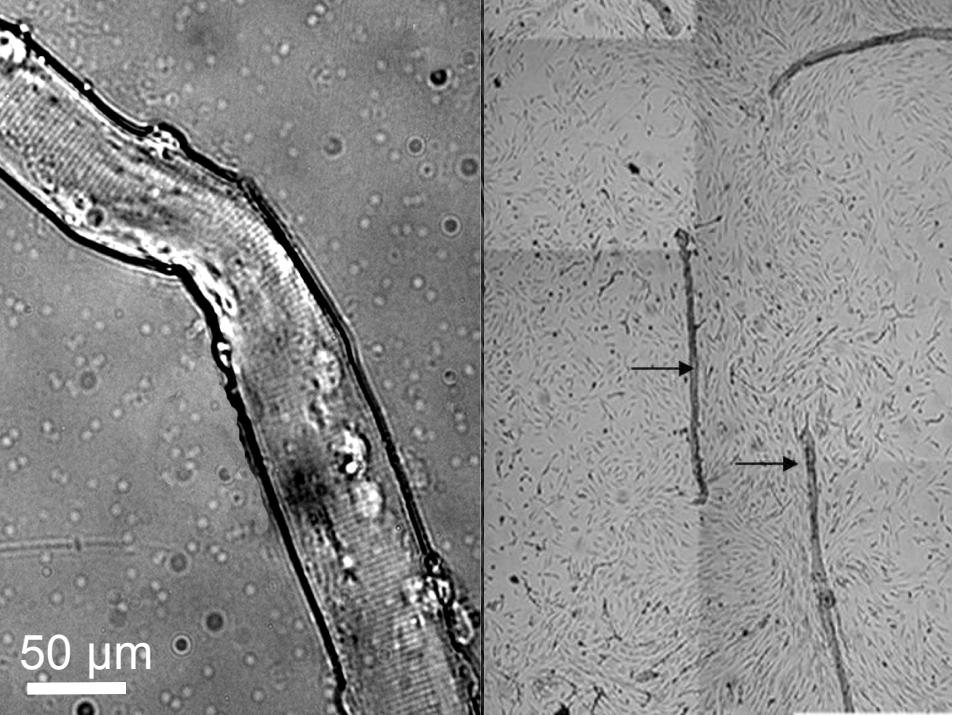


## Les cellules satellites

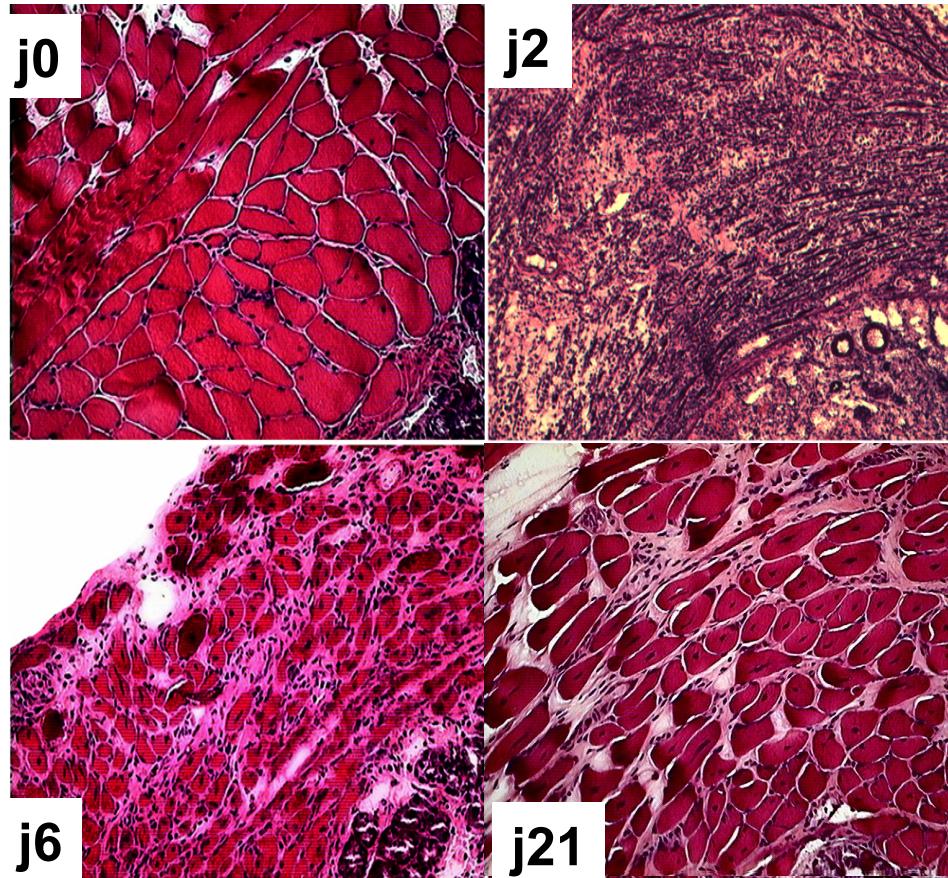




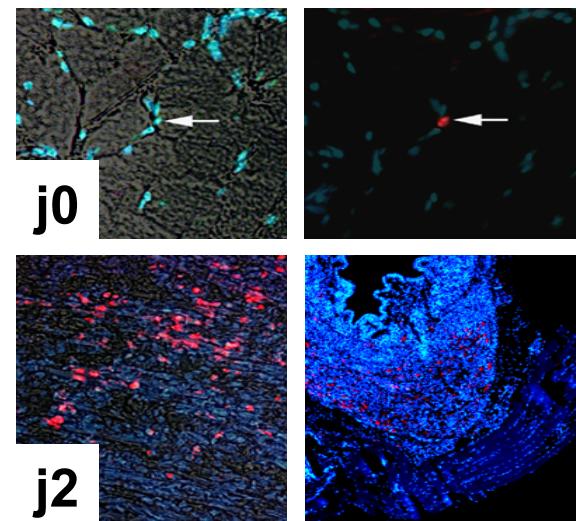




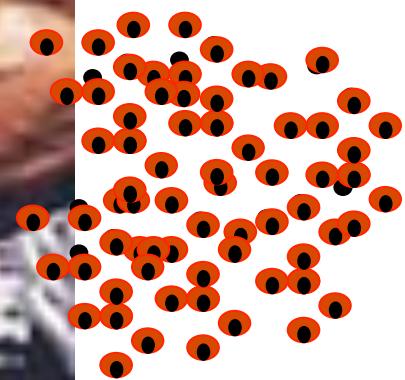
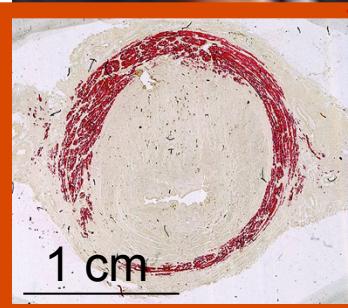
# Exemple de régénération musculaire: le sphincter strié de la souris après injection de notexine

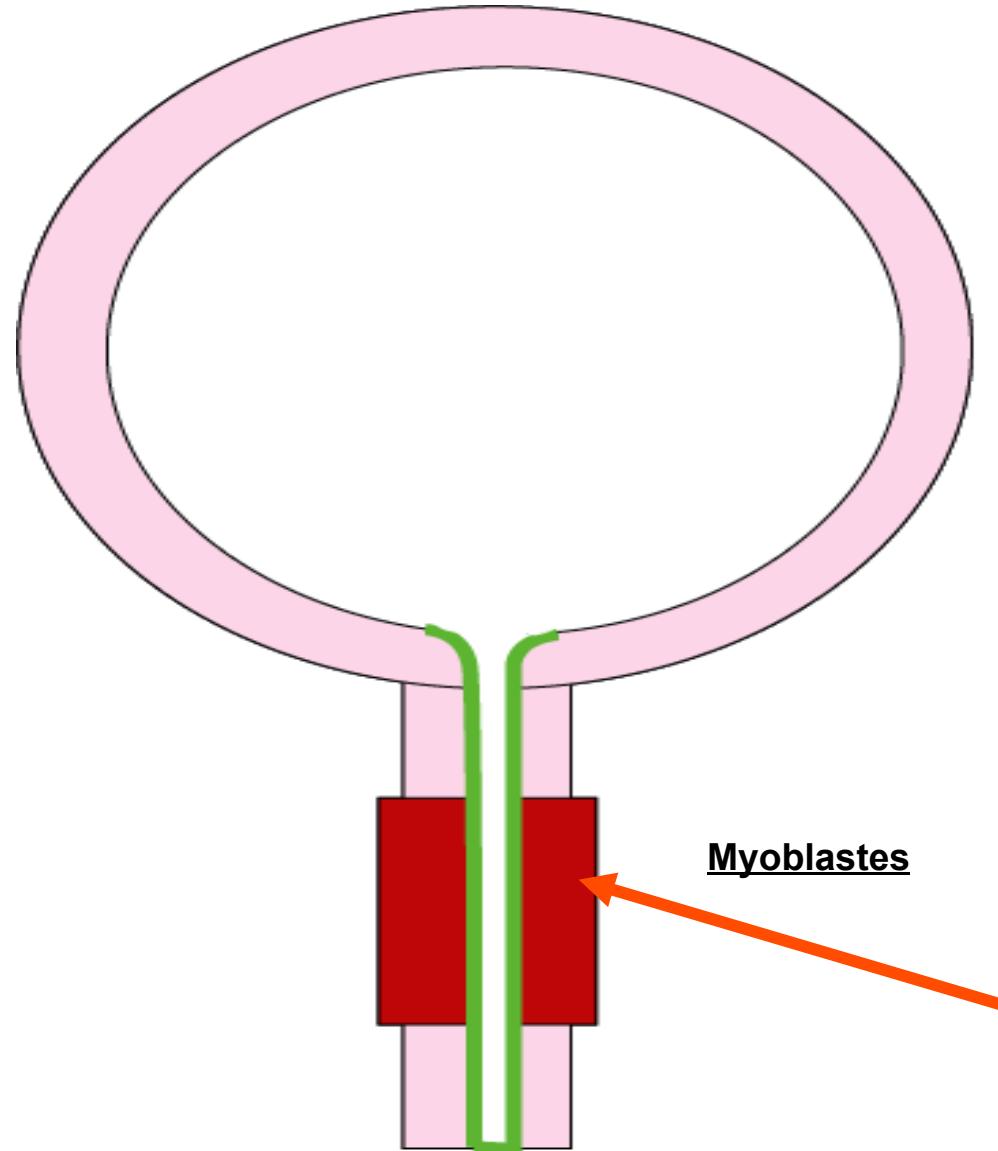


	<i>twitch (mg)</i>	<i>tetanic (mg)</i>	<i>number o f myofiber s</i>	<i>diameter myofibers (<math>\mu</math>m)</i>
Day 2	0	0	$607 \pm 7$	$9 \pm 0.3$
Day 6	$405 \pm 41$	$1750 \pm 193$	$372 \pm 22$	$13 \pm 0.8$
Day 21	$504 \pm 34$	$4500 \pm 649$	$362 \pm 35$	$23 \pm 0.8$
<b>Normal controls</b>	$498 \pm 14$	$5030 \pm 340$	$390 \pm 24$	$22 \pm 0.5$

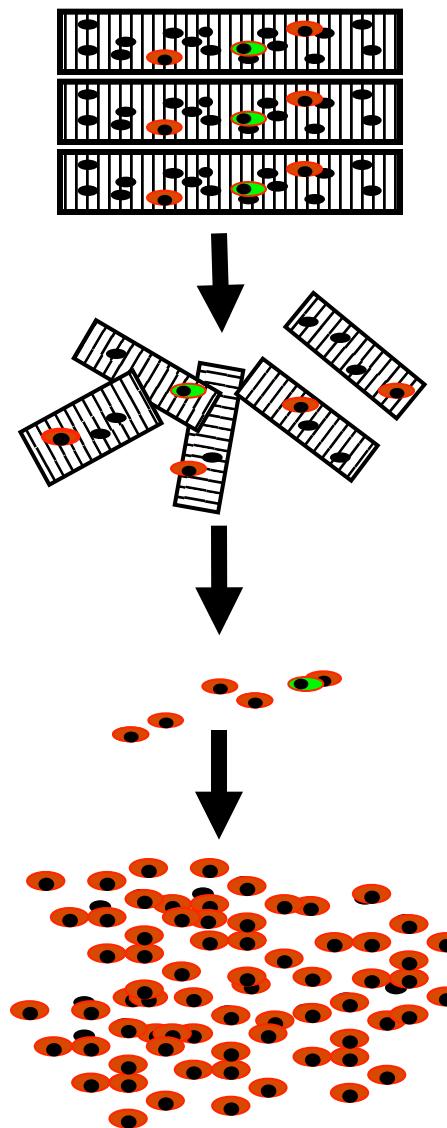


C'est quoi la thérapie cellulaire ???





Myoblastes



Muscle biopsy

Mincing

Enzymatic digestion

Cell culture

Thérapie cellulaire selon un procédé “classique”

# Résultats de la greffe de myoblastes pour les pathologies musculaires chez l'homme

**La thérapie cellulaire pour les maladies musculaires a été conçue il y a plus de 25 ans**

- Partridge, Nature, 1989: *Conversion of mdx myofibres from dystrophin-negative to -positive by injection of normal myoblasts*

**L'injection de myoblastes n'augmente pas (ou très peu) la force contractile d'un muscle dystrophique:**

- Mendell, New England J Med 1995: Myoblast transfer in the treatment of duchenne's muscular dystrophy  
« *There was no significant difference in muscle strength between arms injected with myoblasts (110 million cells) and sham-injected arms.* »
- Menasche C R Biol, 2007  
« *The potential benefits of cardiac cell therapy are mediated by alternate mechanisms such as limitation of left ventricular remodelling or paracrine activation of signalling pathways involved in angiogenesis.* »

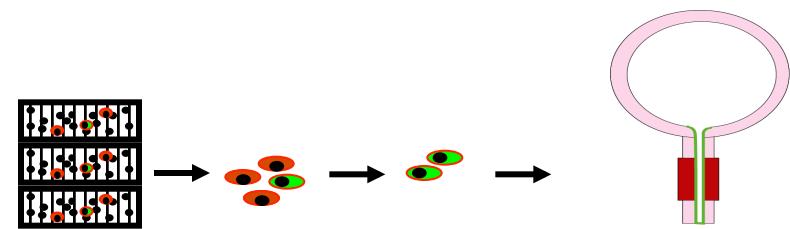
# Les raisons de l'échec de la greffe de myoblastes

- Forte mortalité cellulaire++++
  - >97% 1 heure après injection (1)
- Faible migration
- (Réaction immunitaire)

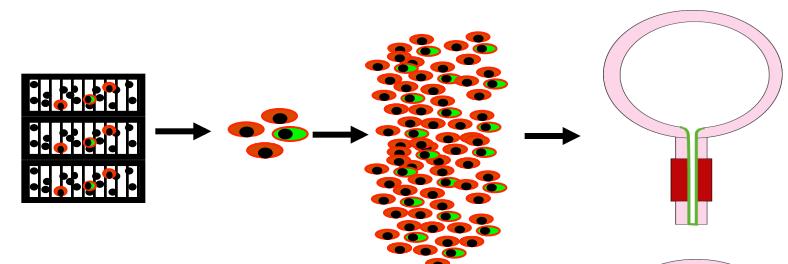
1. Beauchamps JR. Dynamics of myoblast transplantation reveal a discrete minority of precursors with stem cell-like properties as the myogenic source. *J Cell Biol.* 1999

# Approches du problème de la survie cellulaire dans les essais cliniques

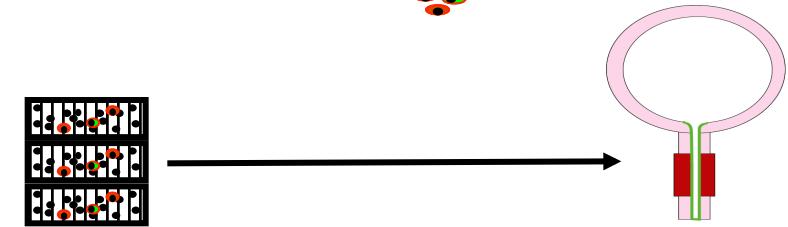
1. Injection de myoblastes avec caractéristiques de cellules souches (1)



2. Augmentation du nb de myoblastes injectés (effet-dose?) (2)



3. Suppression des phases de préparation cellulaire altérant le potentiel myogénique : implantation de cellules satellites (3)

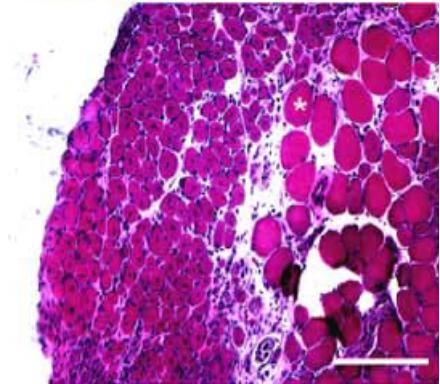
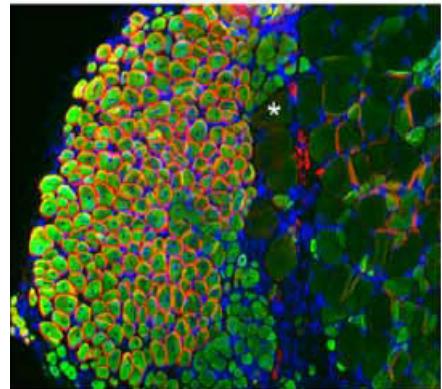
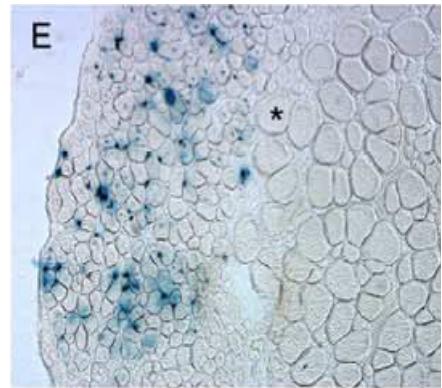
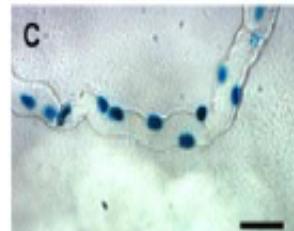
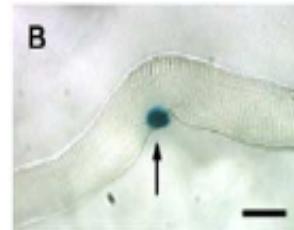
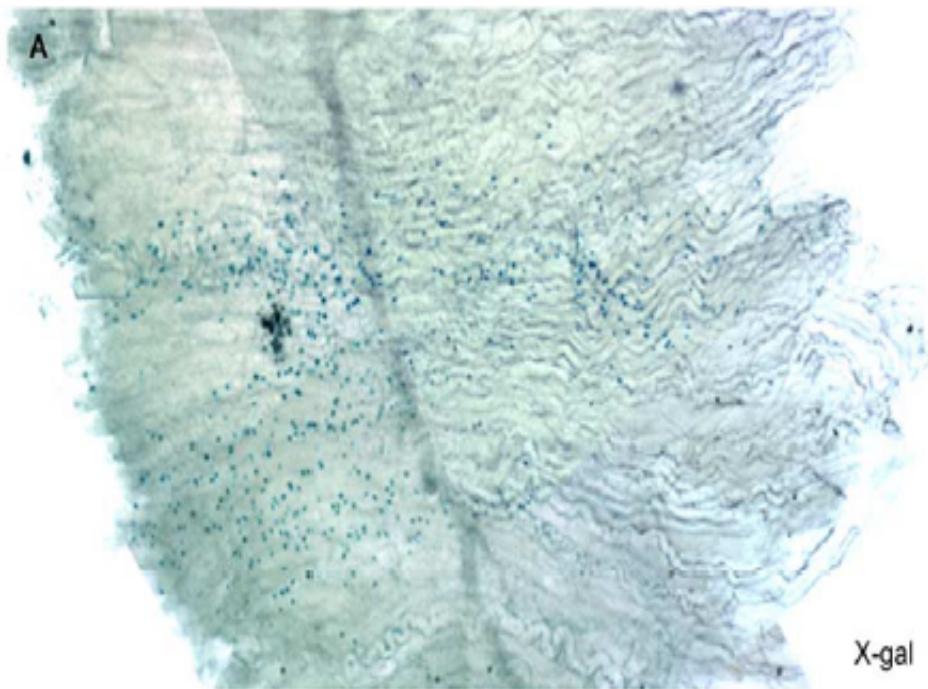


1. Beauchamps JR. Dynamics of myoblast transplantation reveal a discrete minority of precursors with stem cell-like properties as the myogenic source. *J Cell Biol.* 1999
2. Mitterberger et al. *Europ Urol* 2007; Strasser et al. *Lancet* 2007
3. Smythe et al.; *Cell Transplant*, 2000. Exposure to tissue culture conditions can adversely affect myoblast behavior in vivo in whole muscle grafts: implications for myoblast transfer therapy  
Collins et al. *Cell* 2005

- Collins et al. *Cell*, Août 2005

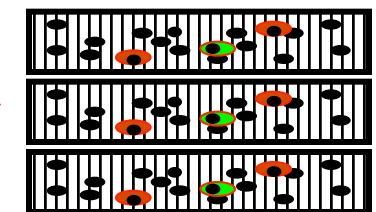
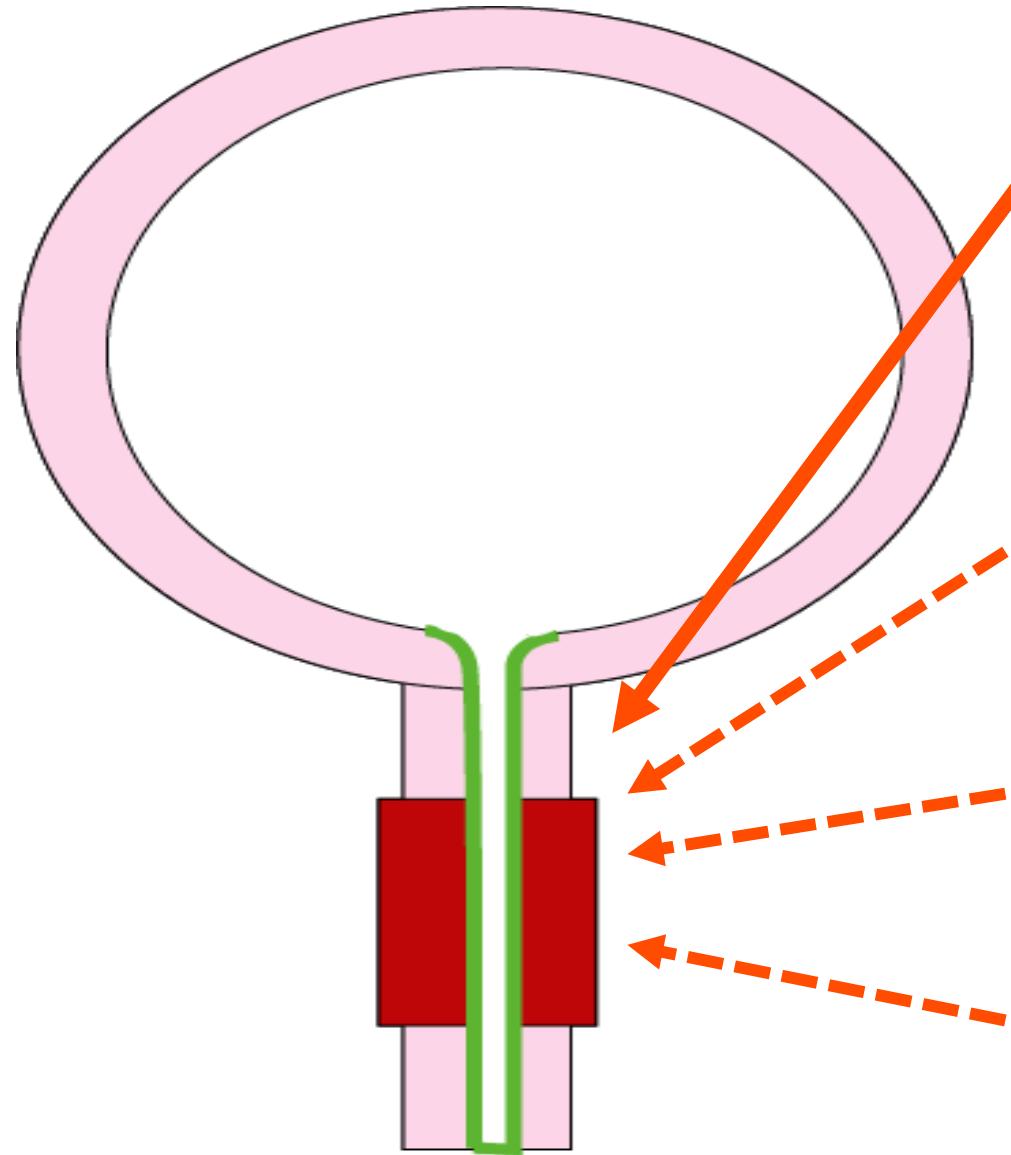
« As few as seven satellite cells associated with one transplanted myofiber can generate over 100 new myofibers containing thousands of myonuclei. »

*Altération du potentiel myogénique/ digestion enzymatique+++*

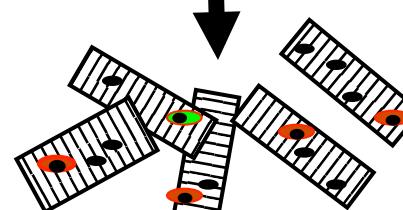


- **Montarras et al., Science, September 2005**

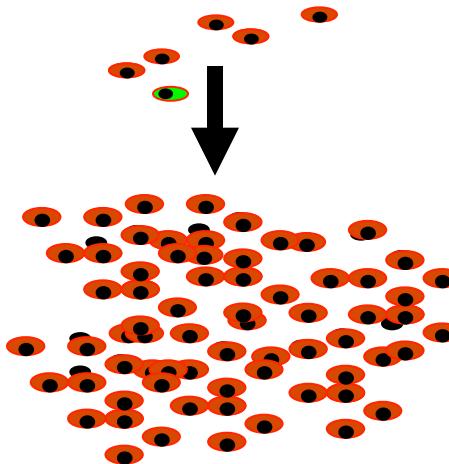
« *The culture of muscle progenitor cells prior to grafting markedly reduces their regenerative efficiency, such that the culture expansion itself is an “empty” process, yielding the same amount of muscle as the number of cells from which the culture was initiated.*»



Muscle biopsy

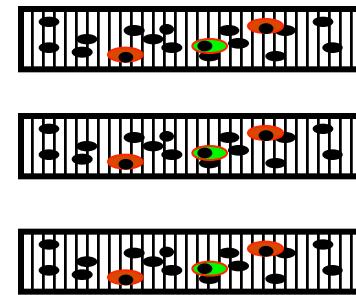
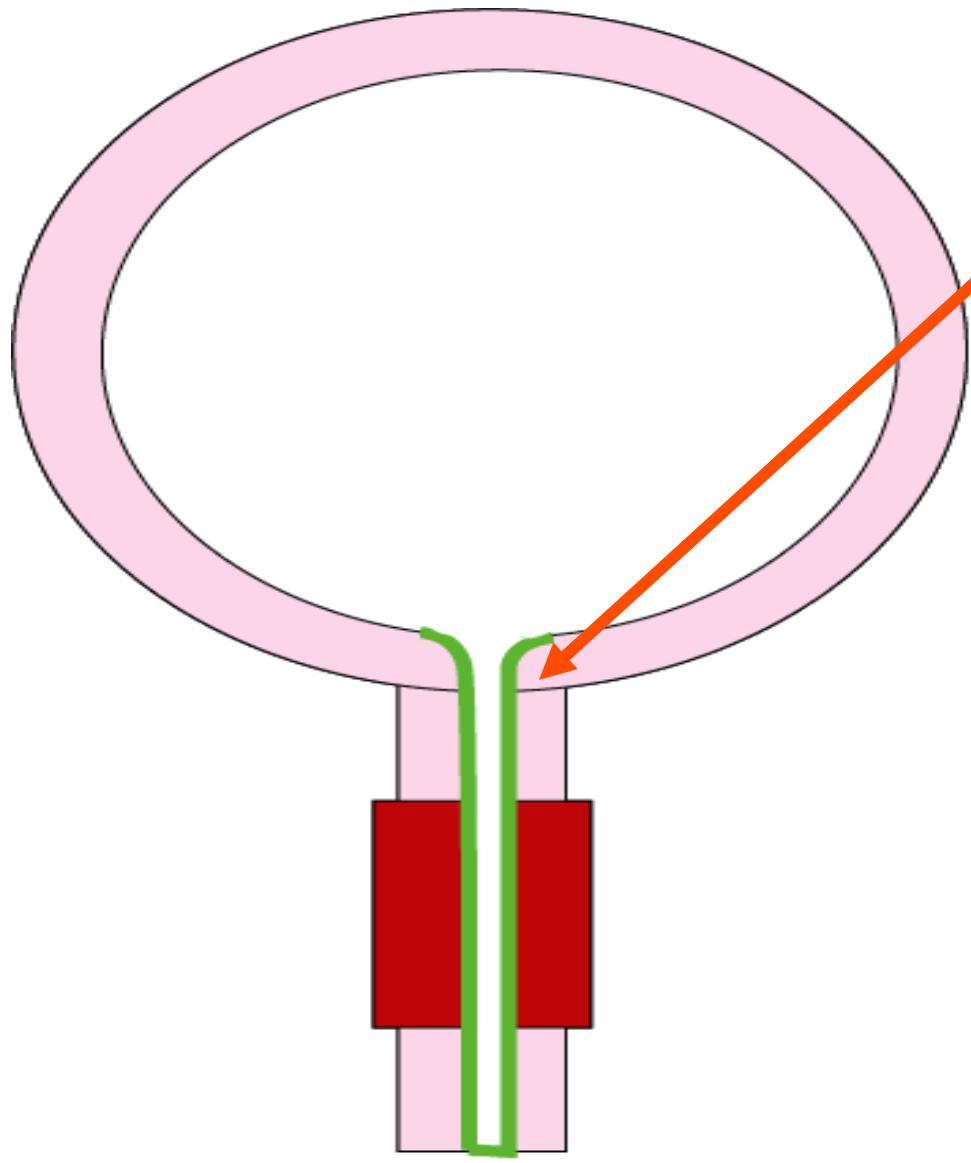


Mincing

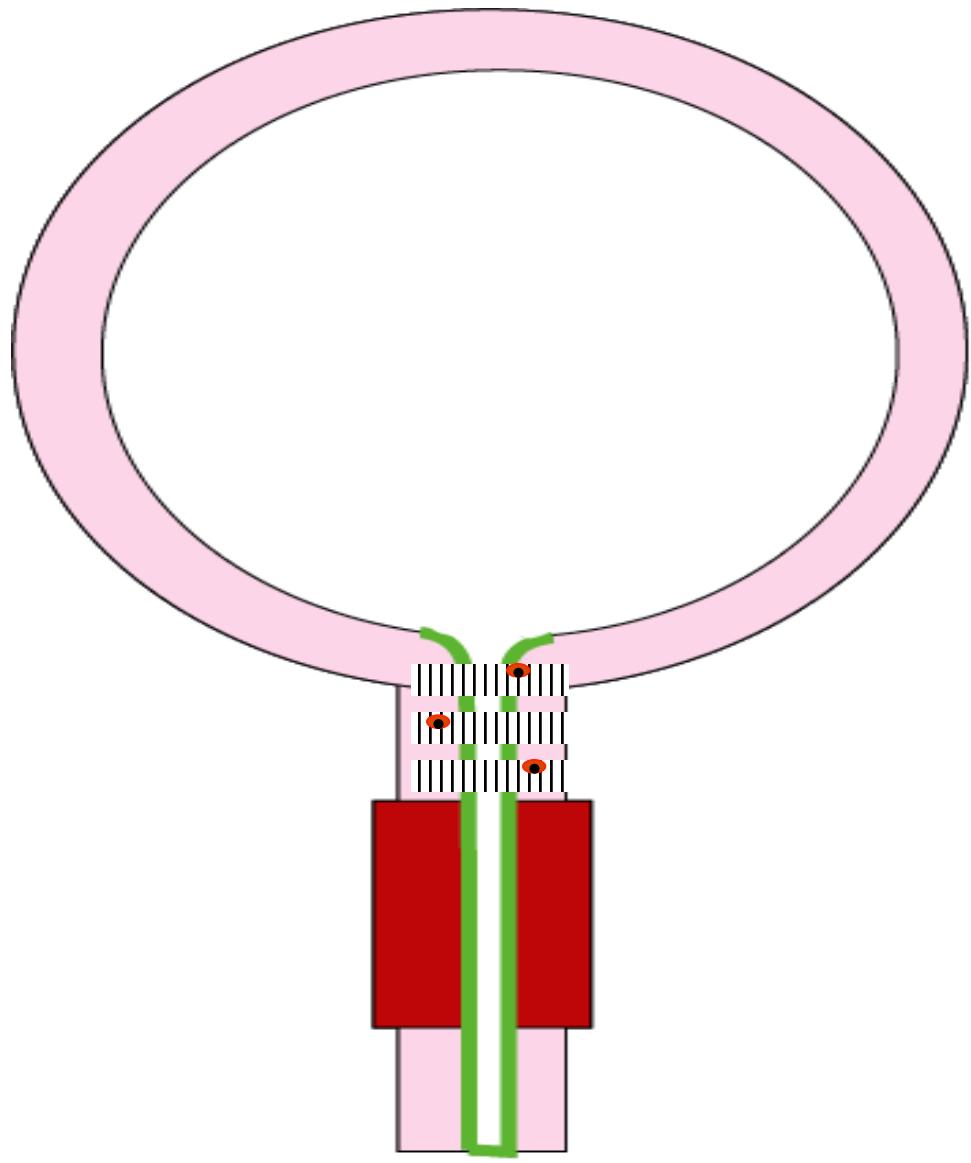


Enzymatic digestion

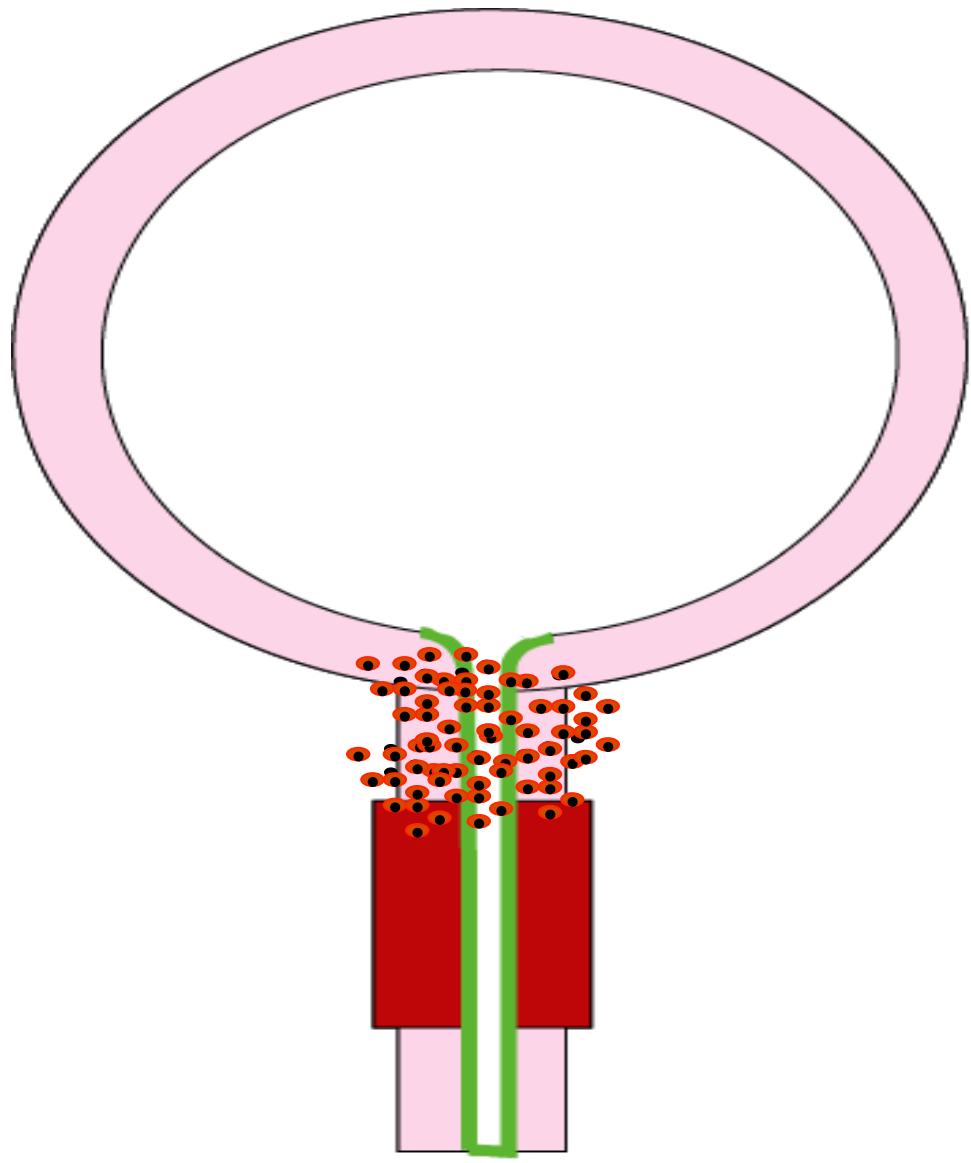
Cell culture



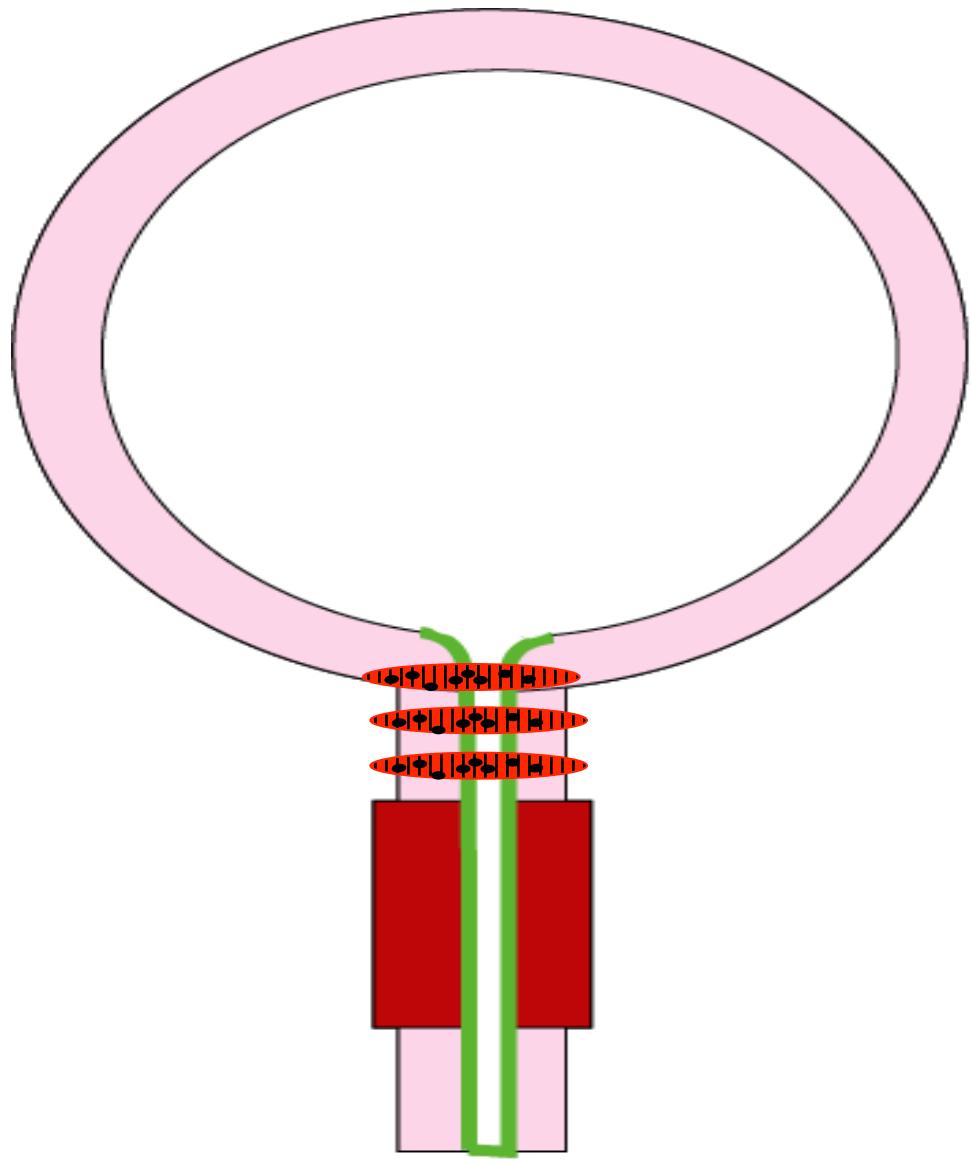
Myofibres porteuses de cellules satellites



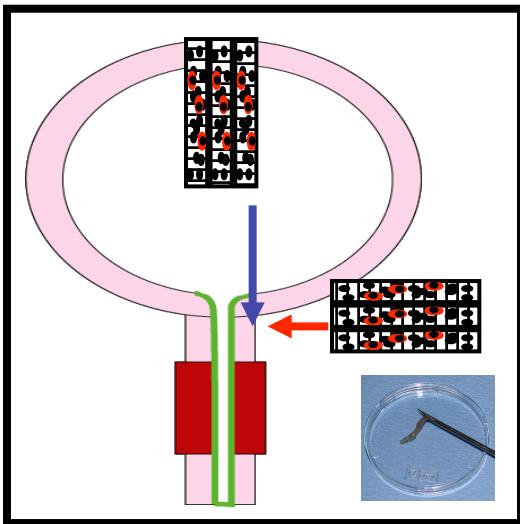
Dégénérescence rapide  
des myofibres



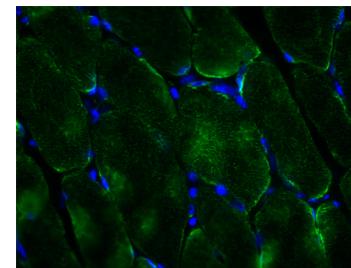
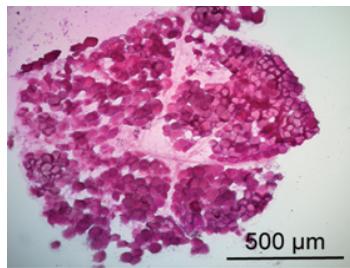
La dégénérescence des myofibres déclenche la prolifération *in vivo* des cellules satellites en myoblastes



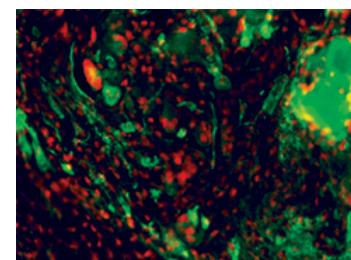
Fusion des myoblastes  
en myotubes remplaçant  
les myofibres parentales



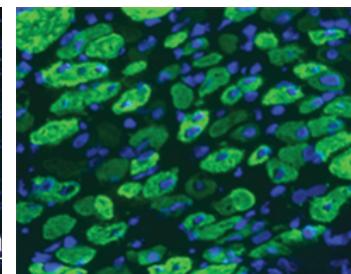
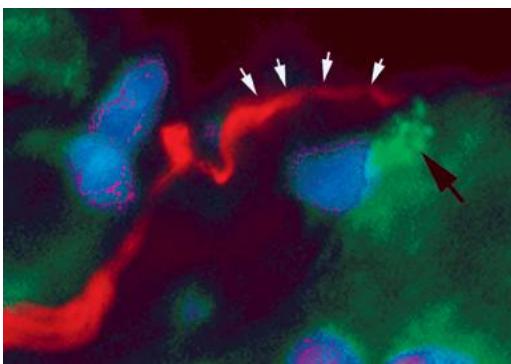
## Preuve de concept chez la truie



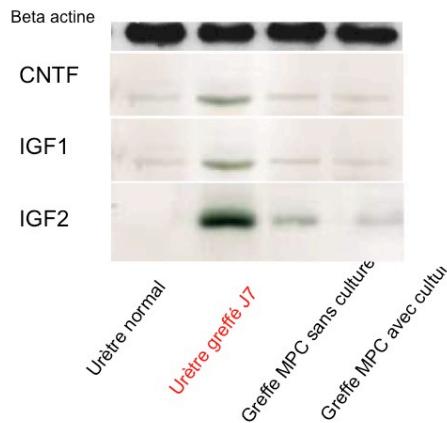
Myofibres avant  
implantation



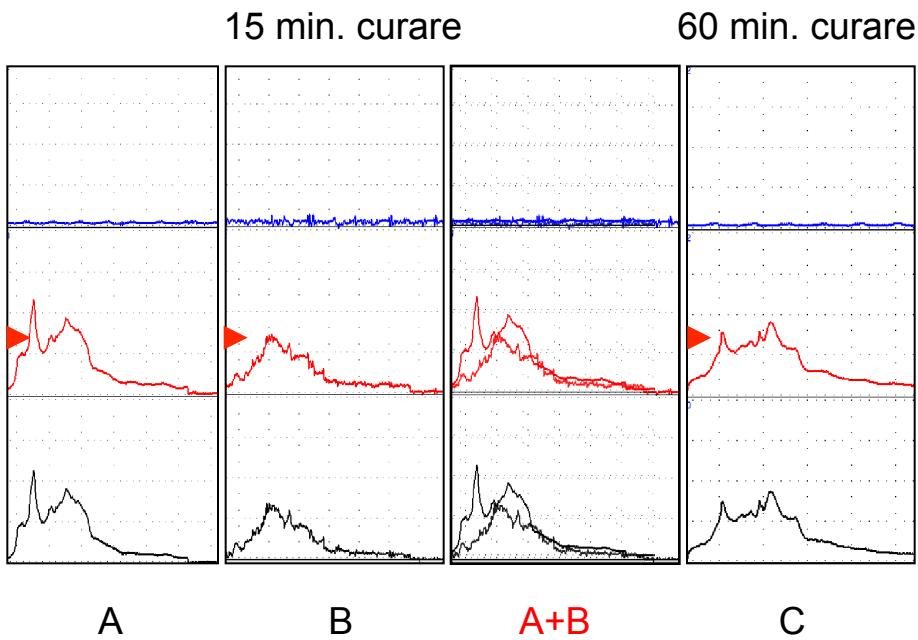
J7 implantation  
Dégénérescence des myofb  
Activation myoblastes



J30 implantation  
Myotubes innervés

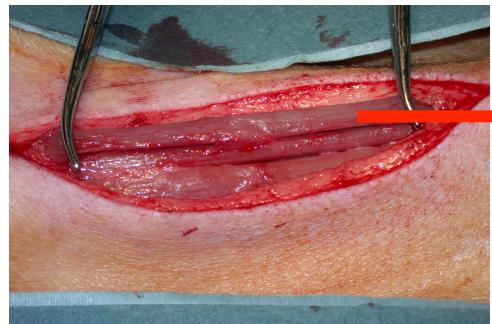


# Bilan Urodynamique (implantation de myofibres)

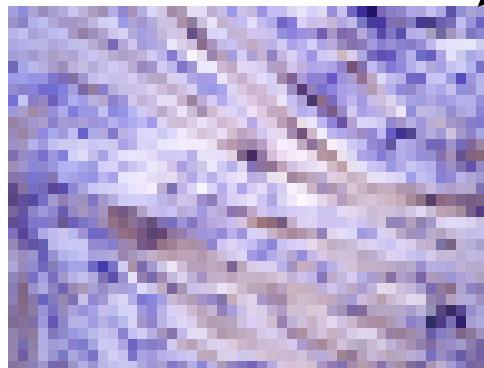


	Adipocyte implantation	Myofiber implantation	P values
<b>mUCP<sub>prox</sub></b>			
Baseline	15+/-6	16.6+/-3.8	NS
Day 30 without curare	16.2+/-7.3	71.5+/-17.8	0.037
Day 30 after curare	16.5+/-10	33.5+/-14.8	NS
<b>mUCP<sub>dist</sub></b>			
Baseline	64.2+/-11.5	62.3+/-8	NS
Day 30 without curare	22+/-4.9	35.1+/-18.5	NS
<b>Day 30 after curare</b>	21.7+/-4	25.6+/-8.6	NS

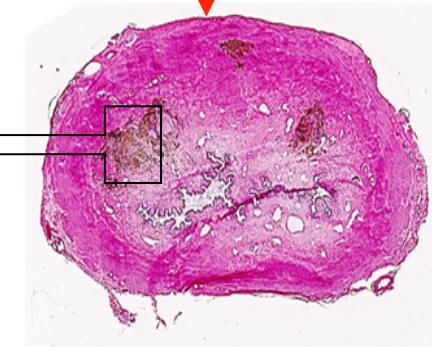
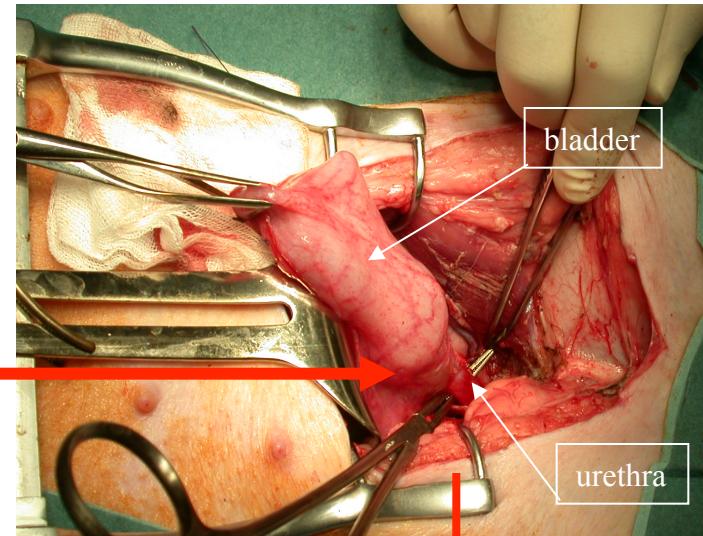
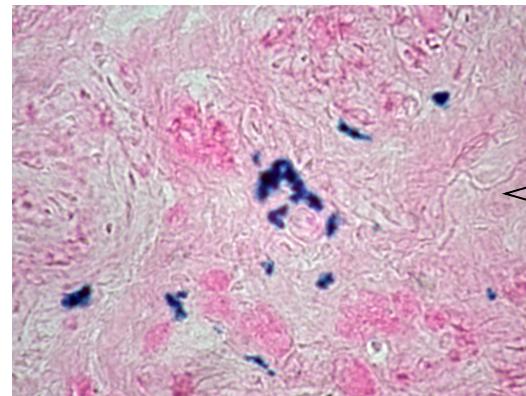
## Myoblasts obtained by enzymatic digestion form myotubes in vitro but fail to form myotubes when injected into the urethra of the pig

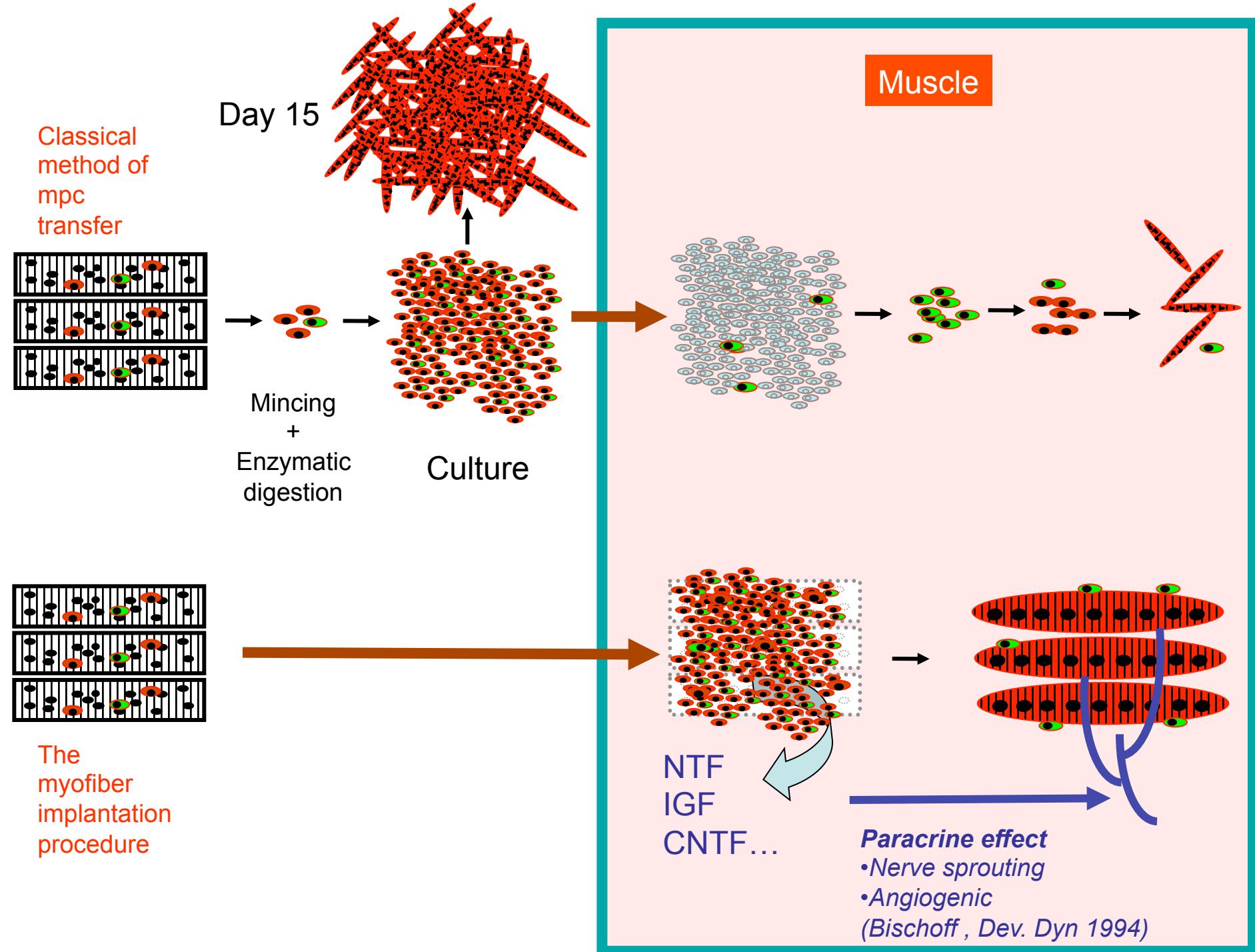


day 5



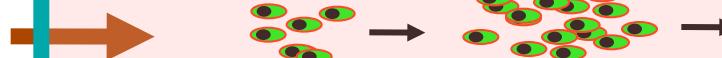
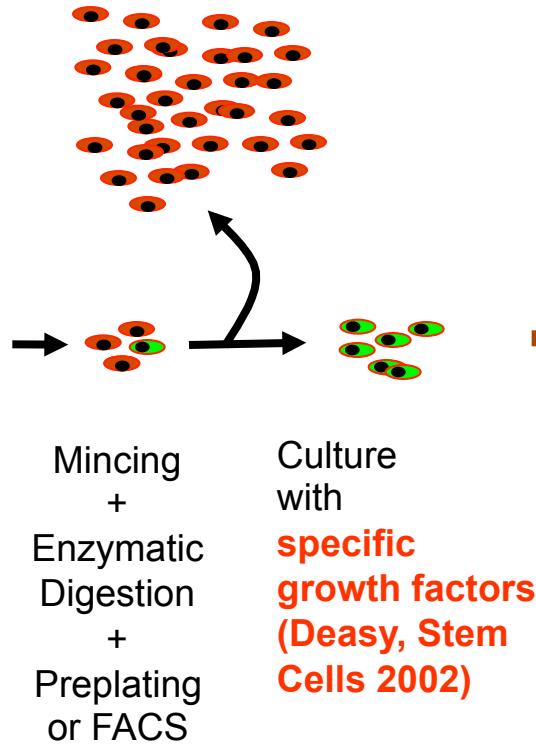
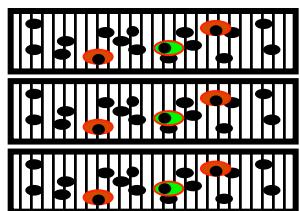
day 15 in vitro





Muscle

Muscle  
derived  
stem cells



Myogenic  
differentiation  
relies on the  
environmental  
cues

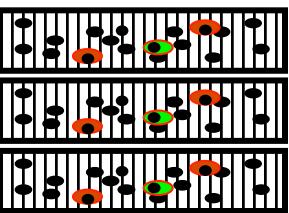


Yiou et al., Transplantation 2003, 2005

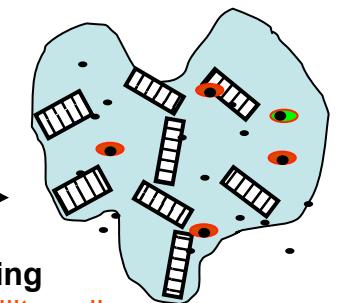
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Cannon et al. Urology, 2003

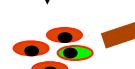
Minced muscle



- Mincing
- Satellite cells
  - Myofibers debris
  - Growth factors



Enzymatic digestion

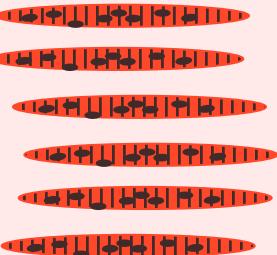


Paracrine effect  
sufficient  
for self innervation?



submucosa

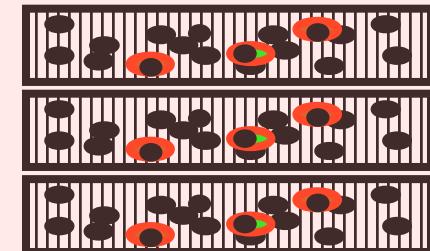
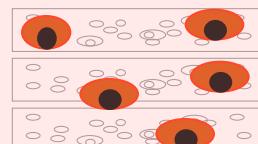
Muscle



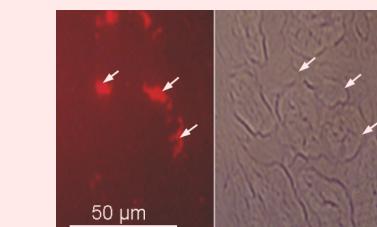
Plasticity?

Paracrine effect

- Nerve sprouting
- Angiogenic
- Inflammation+++ (?)  
(Pouzet et al. Circulation 2000)



Fusion with  
preexisting myofibers  
≠ myogenic process +++



Hypertrophy of preexisting  
myofibers resulting in  
increased force contraction ?

Yiou R, BJU int. 2002

**Table 2** Study characteristics

References	Stem cells	Quality score (0–20)	Primary endpoint	Study design	N	Population	Follow-up (M)
Blagajne et al. [22]	Autologous MDSC	12.5	Urinary incontinence episodes, number of voids, patient satisfaction, and QoL	Prospective intervention study. Injection into urethral sphincter with electrical stimulation.	38	Women, mean age 52 years, parity 2, BMI 26.6.	1.5
Surcel et al. [23]	Autologous MDSC	2	Not stated	Prospective intervention study. Injection of stem cells into mid-urethral sphincter.	8	SUI, mean age 54.9 years	12
Sèbe et al. [27]	Autologous MDSC	11.5	Presence of dysuria. Safety at 3 months (flow rate, post-void residual and urine culture)	Randomized prospective intervention study. 3 doses MDSCs.	12	SUI due to ISD, mean age 58, mean BMI 27.6. Female. Failed surgical treatment.	3
Lee et al. [28]	UCSC	10.5	Patients' voiding diaries, and satisfaction	Prospective intervention study. Injection of fibroblast and myoblast into rhabdosphincter and submucosa.	39	SUI; all failed conservative, 1 failed surgical treatment; mean age 51.5 years; para 2.3	Mean 13
Carr et al. [29]	Autologous MDSC	4.5	Voiding diary, pad test, QoL.	Prospective intervention study. Myoblast and fibroblast injection.	8	SUI, mean age 54 years, BMI <30, failed conservative treatment.	Med. 17
Mitterberger et al. [30]	Autologous MDSC	9.5	Incontinence score (voiding diary, pad test, self-report)	Prospective intervention study. Injection of fibroblast and myoblast into rhabdosphincter and submucosa.	63	Men, post-prostatectomy, mean age 68 years	12
Mitterberger et al. [31]	Autologous MDSC	11.5	Incontinence score (voiding diary, pad test, self-report)	Prospective intervention study. Injection of fibroblast and myoblast into rhabdosphincter and submucosa.	20	Women with intrinsic sphincter insufficiency, mean age 49.8	24
Mitterberger et al. [32]	Autologous MDSC	11	Incontinence score (voiding diary, pad test, self-report)	Prospective case series. Injection of fibroblast and myoblast into rhabdosphincter	123	All SUI, failed PFE, 68 previous surgery	12

QoL Quality of life

*Prospective evaluation of intrasphincteric injections of autologous muscular cells in patients with stress urinary incontinence following radical prostatectomy*

Cornu et al. Prog Urol 2011.

- 12 patients IU post PR. Myoblastes cultivés (Deltoïde)
  - Q(max) variation
  - Effets secondaires
  - Pad test, catalogue mictionnel
  - Qualité de vie
- RESULTATS
  - Pas de complications
  - Résultats fonctionnels hétérogènes:
    - 4/12 patients diminution du nb de fuite
    - **1/12 patient augmentation de la pression de clôture**
    - 8/12 patients amélioration du pad-test.

## *1-year follow-up of autologous muscle-derived stem cell injection pilot study to treat stress urinary incontinence.*

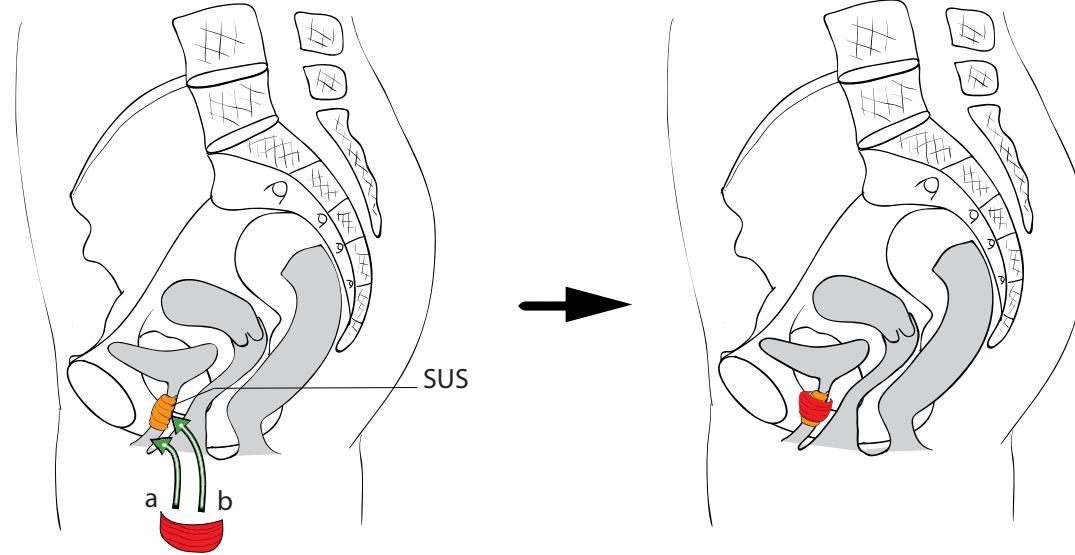
Int Urogynecol J Pelvic Floor Dysfunct. 2008 Jun;19(6):881-3

Chancellor M et al.

- Injection de cellules souches musculaires
- Amélioration 5/8 femmes dont une guérison
- Début de l'amélioration: **5-8 months** après l'injection

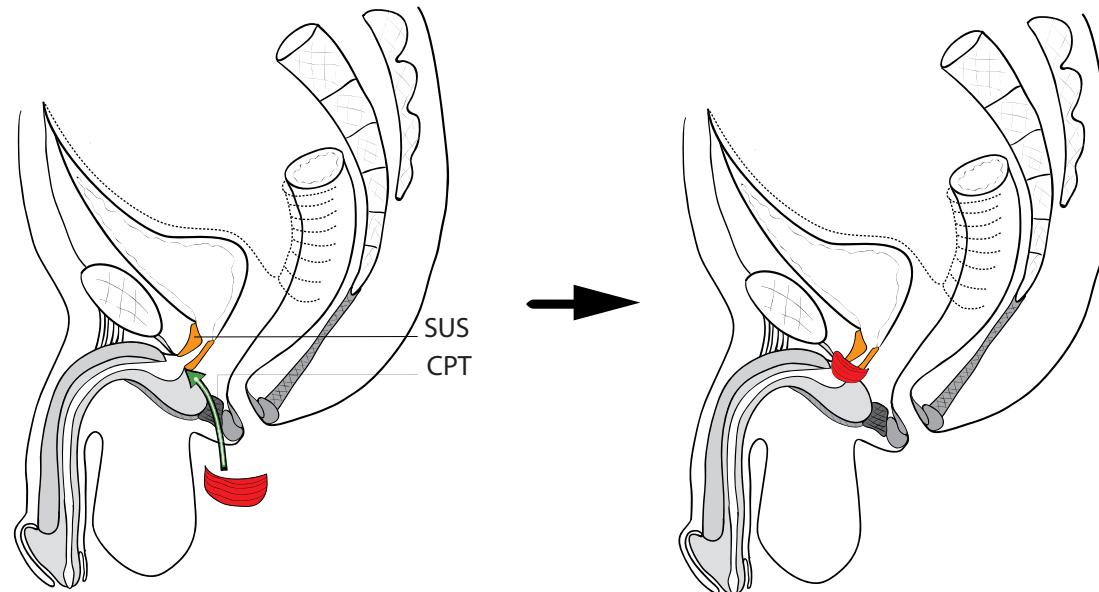
ESSAI CLINIQUE BTH05006: implantation directe de myofibres+cellules souches sans phase de culture

A



5 femmes

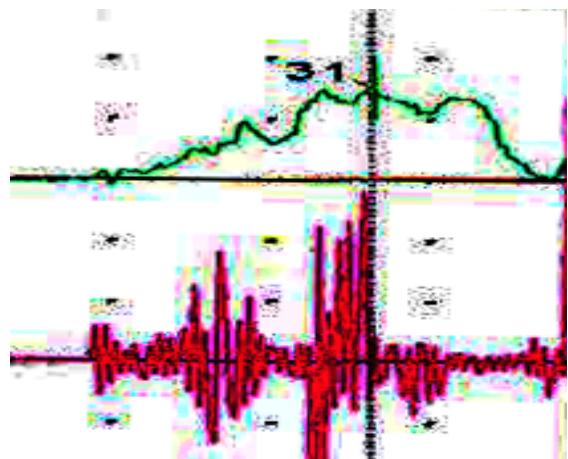
B



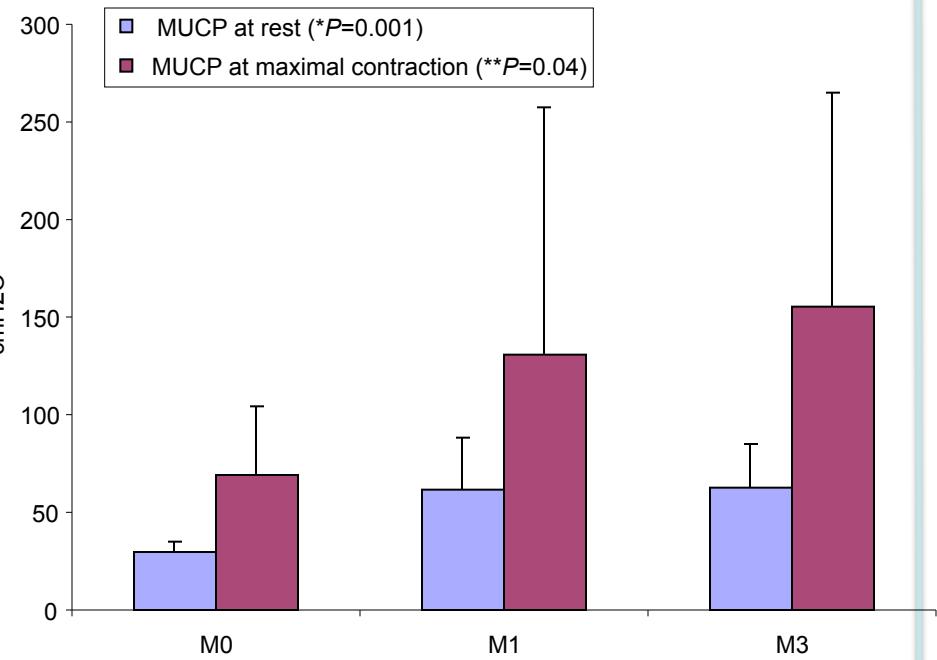
5 hommes

## AVANT INTERVENTION

Pression  
urétrale

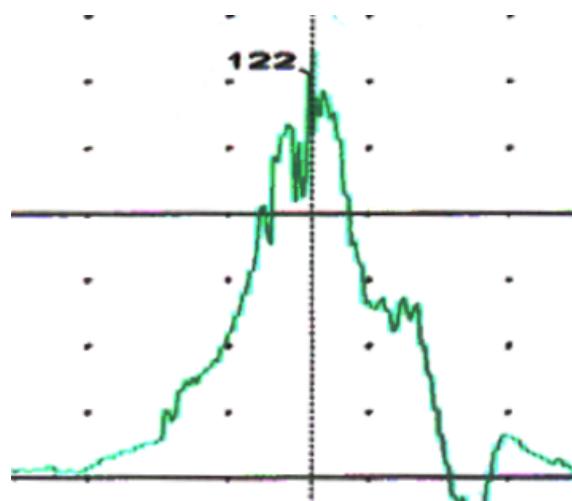


Activité  
électrique

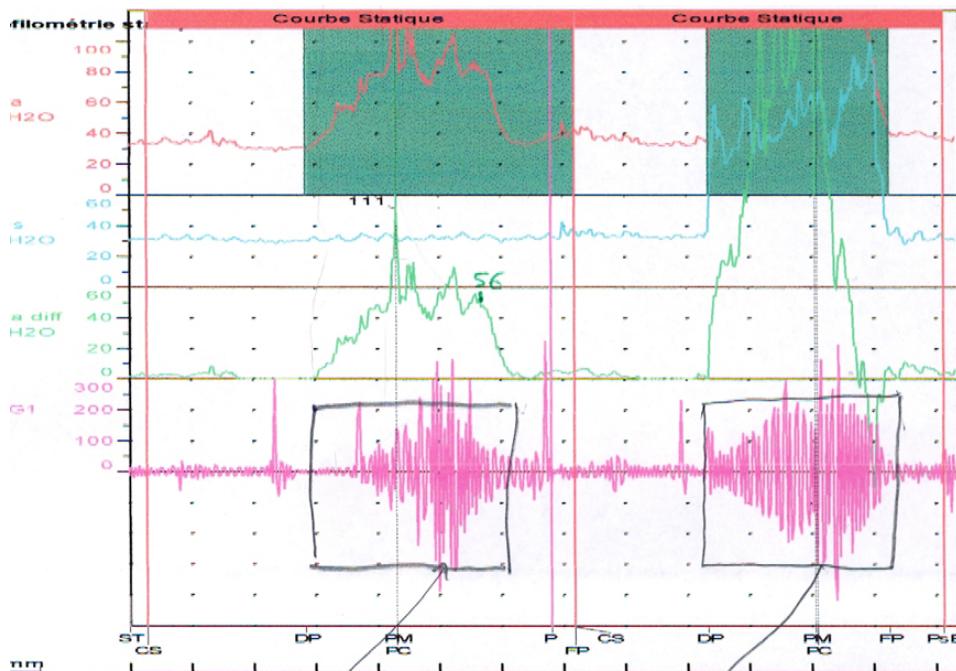
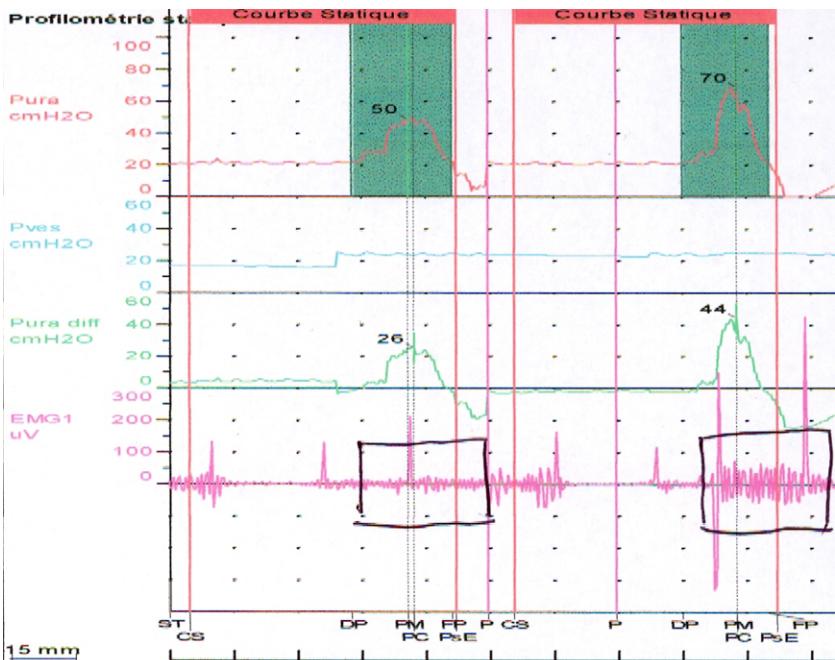


## APRÈS INTERVENTION

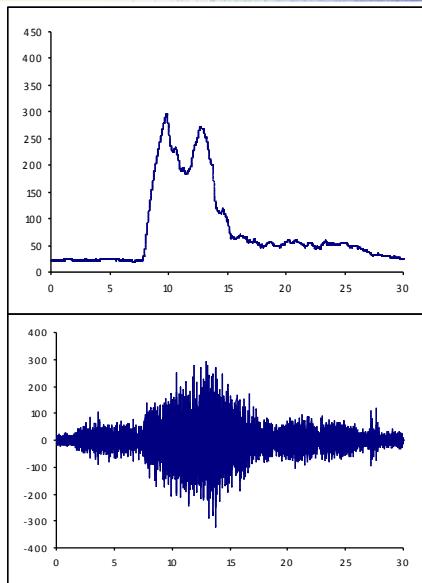
Pression  
urétrale



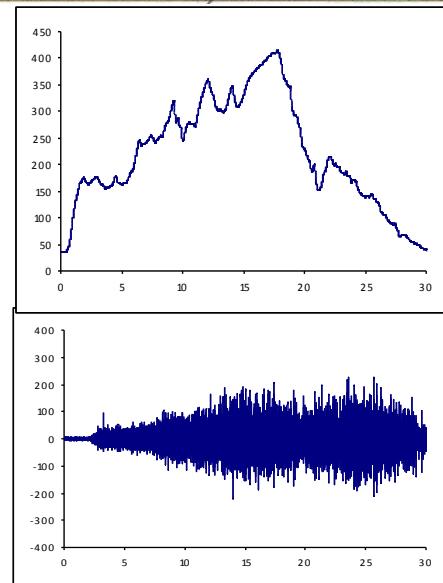
Activité  
électrique

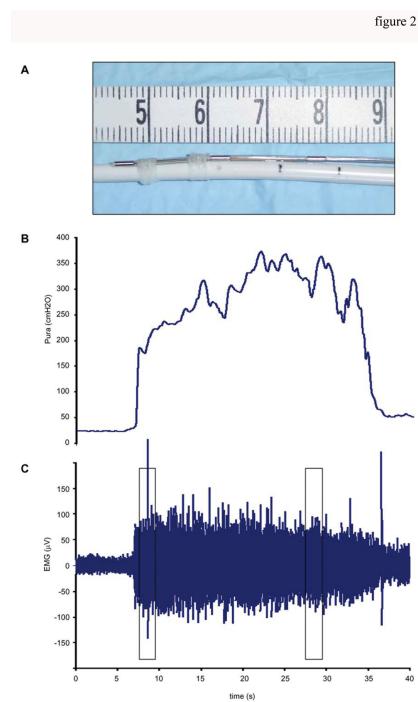
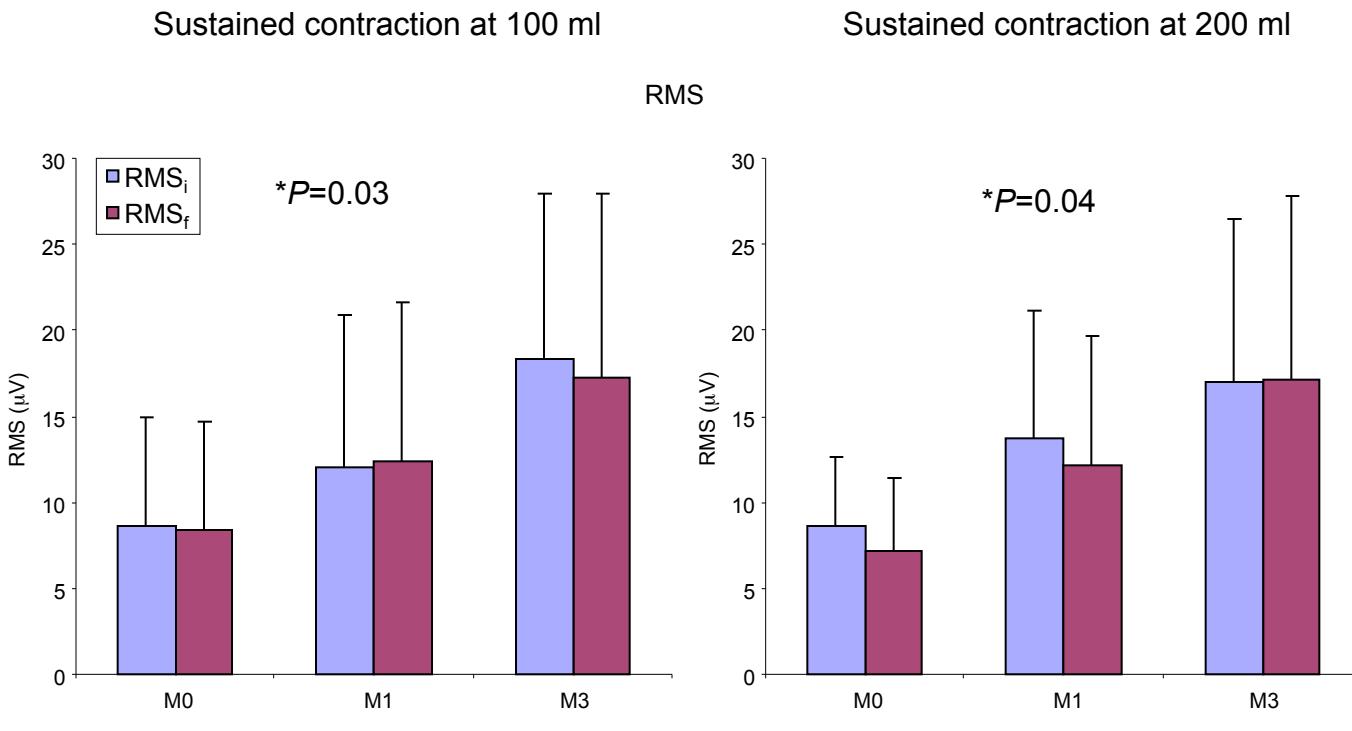


preop

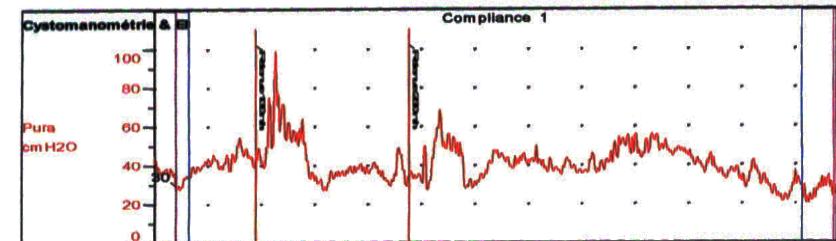
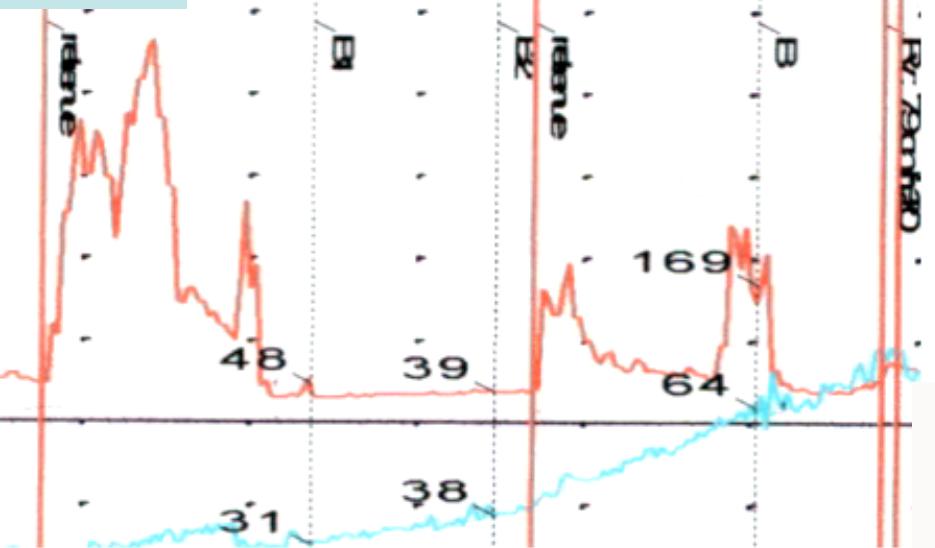


M3 post-op



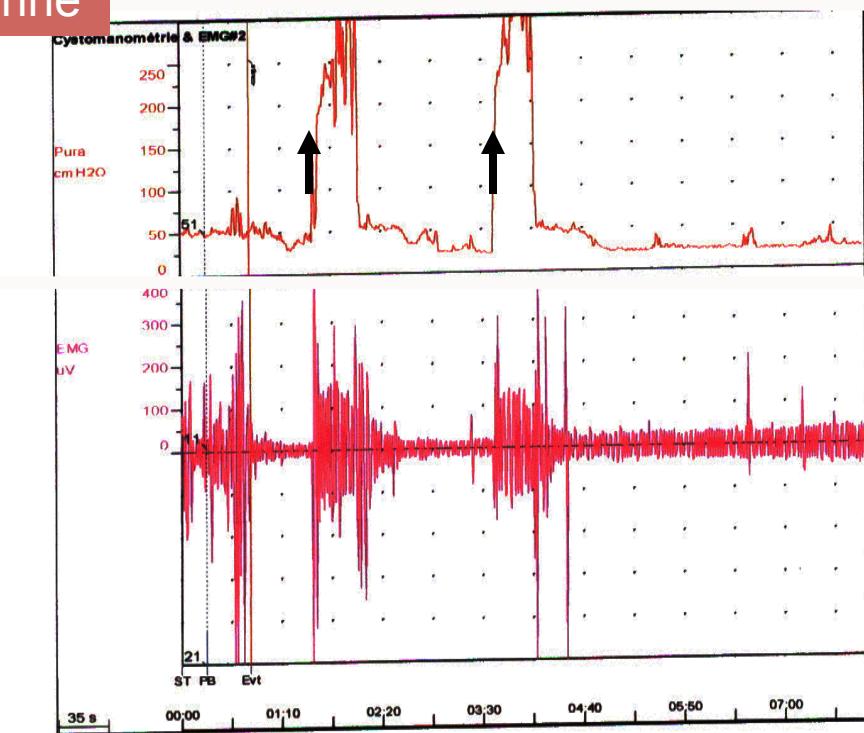
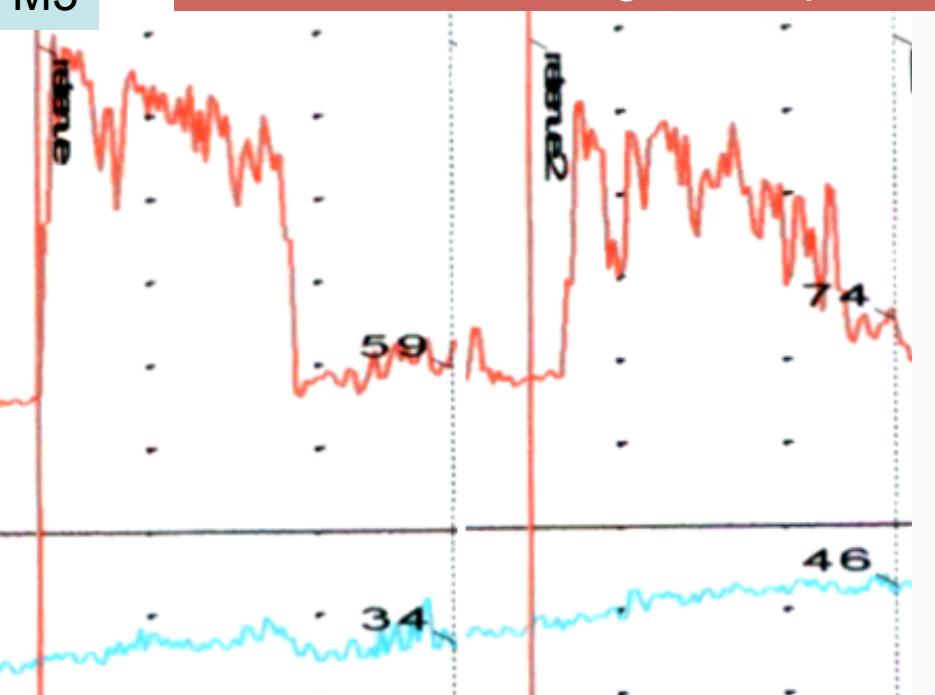


PREOP

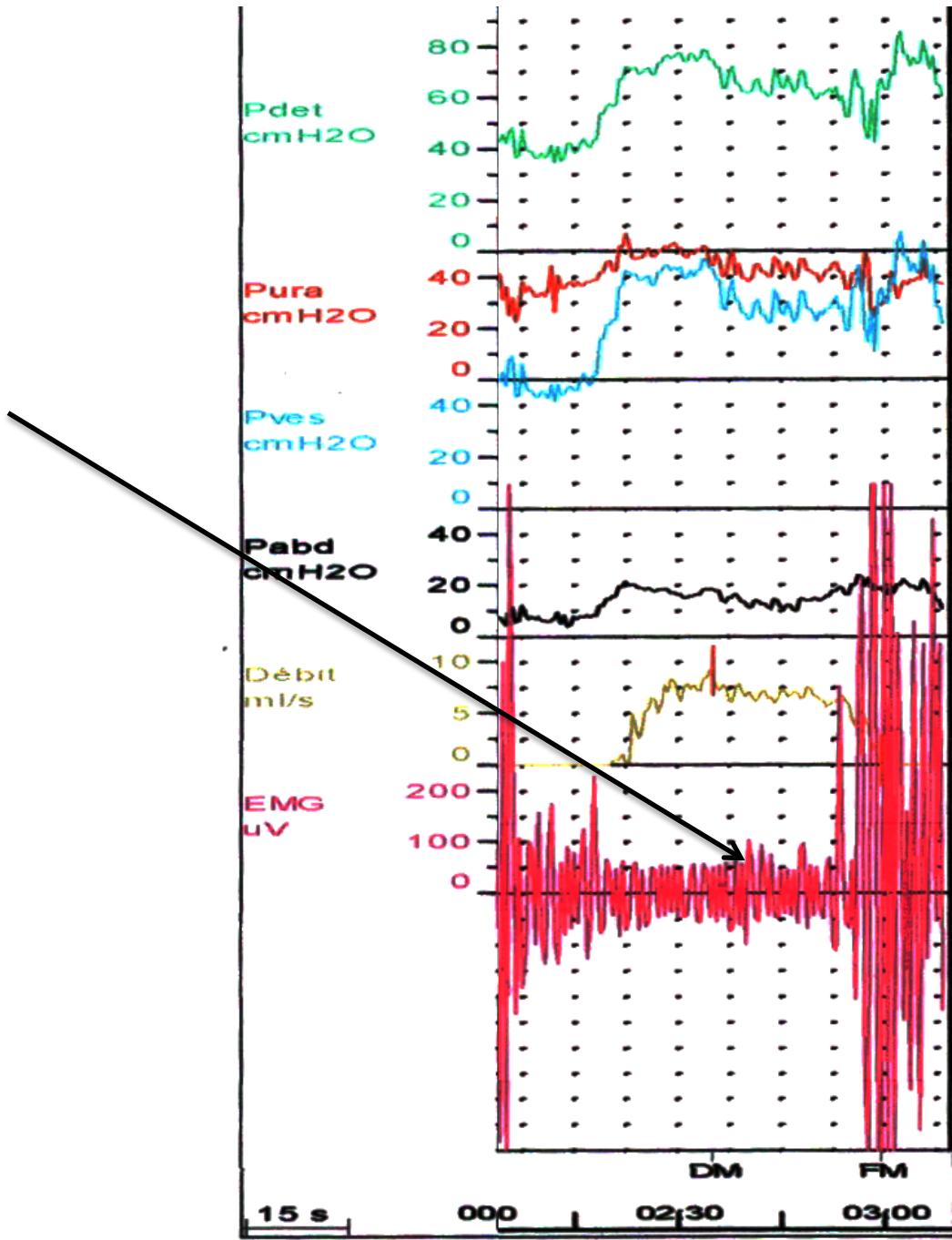


M3

Diminution de la fatigabilité sphinctérienne



Synergie vésico-**néosphincterienne**  
respectée

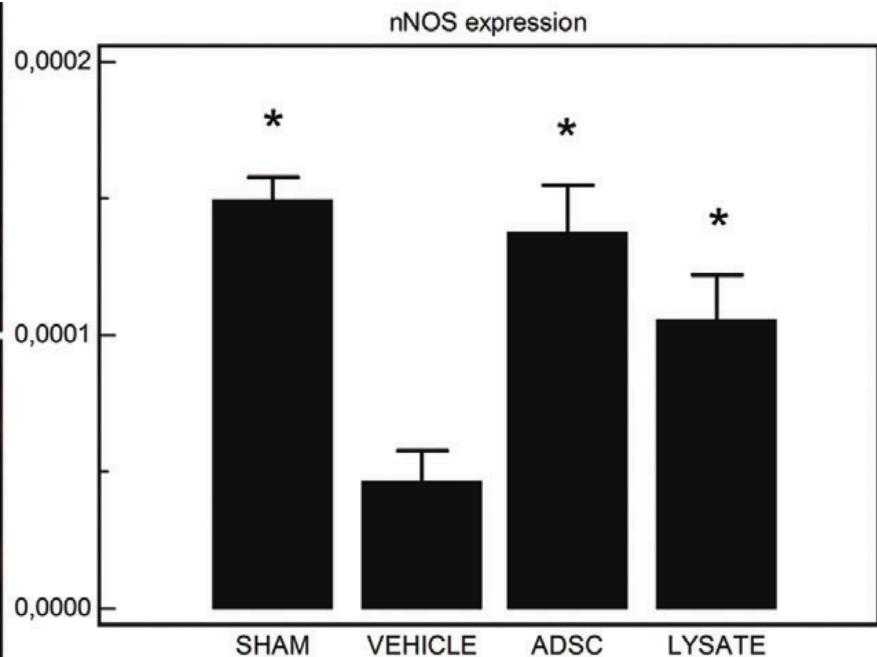
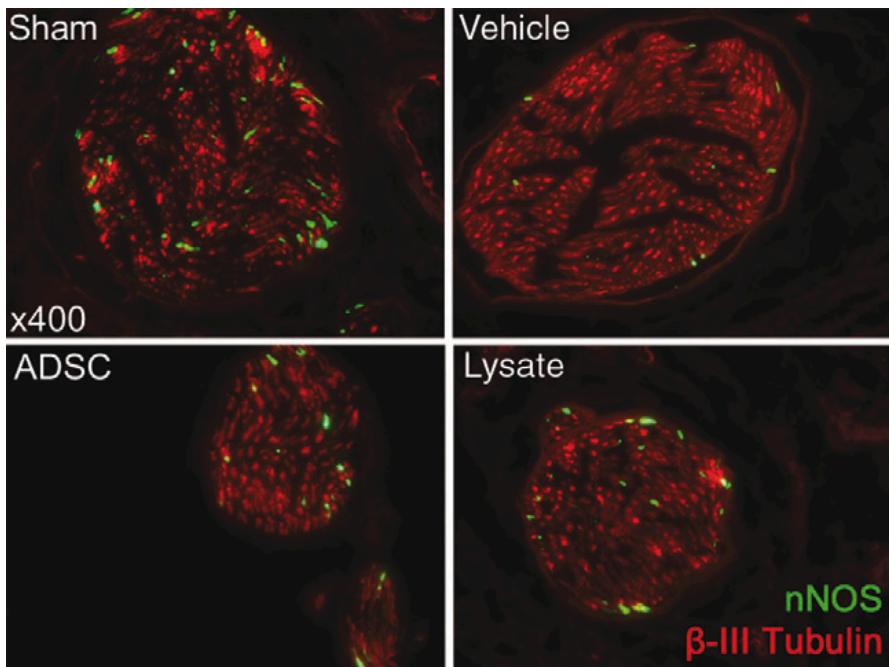


# Essai clinique IPSMA

- PHRC inter-régional
- Injection **Péri-Sphinctérienne de Myofibres Autologues** pour le traitement de l'incontinence urinaire par insuffisance sphinctérienne (phase II)
  - Insuffisance sphinctérienne. Soutènement -
  - 11 puis 39 patients
  - Prélèvement, dissociation de myofibres, injection directe

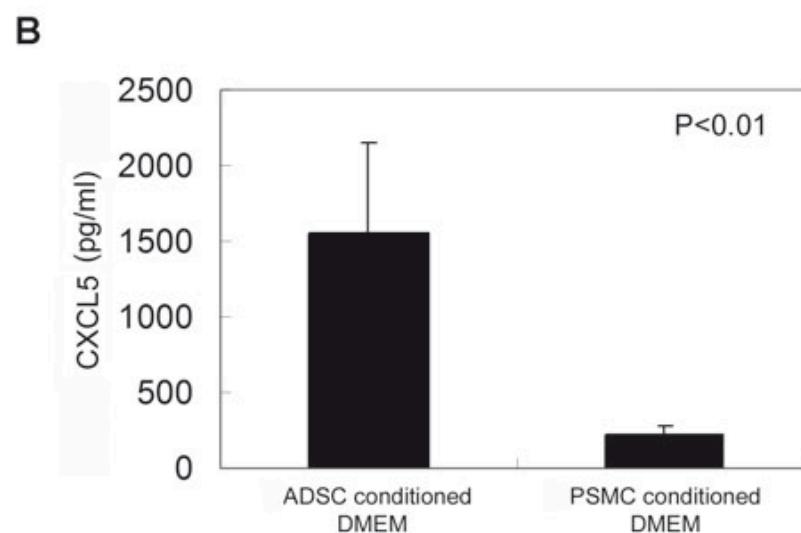
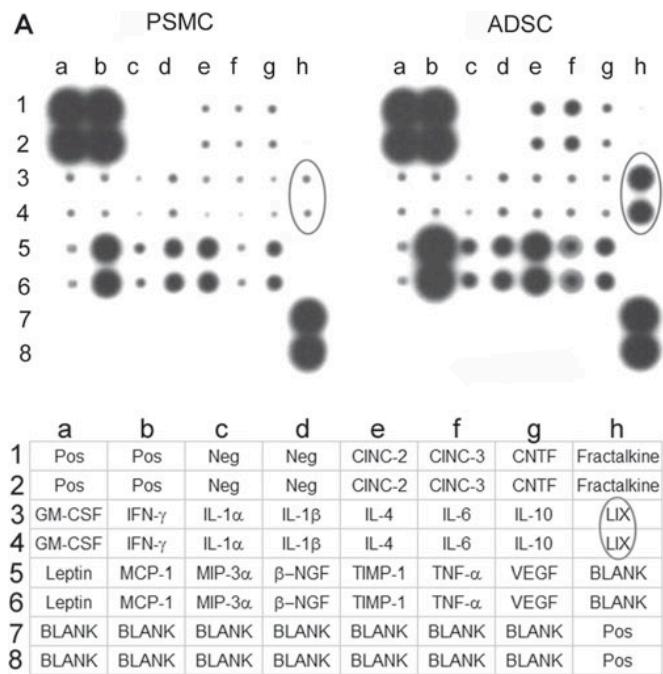
## **Les cellules souches issues du tissu adipeux**

# Les cellules souches issues du tissu adipeux produisent des facteurs neurotrophiques



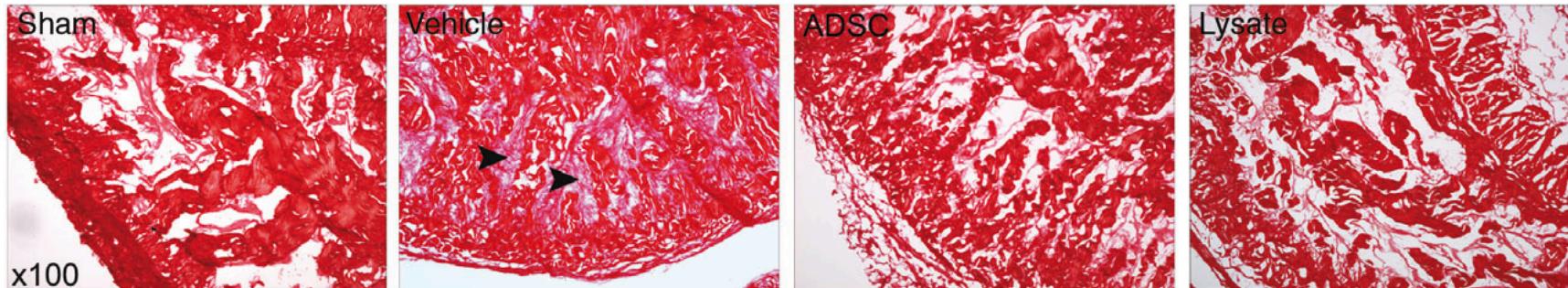
# **Adipose Tissue-Derived Stem Cells Secrete CXCL5 Cytokine with Neurotrophic Effects on Cavernous Nerve Regeneration**

J Sex Med 2011;8:437–446

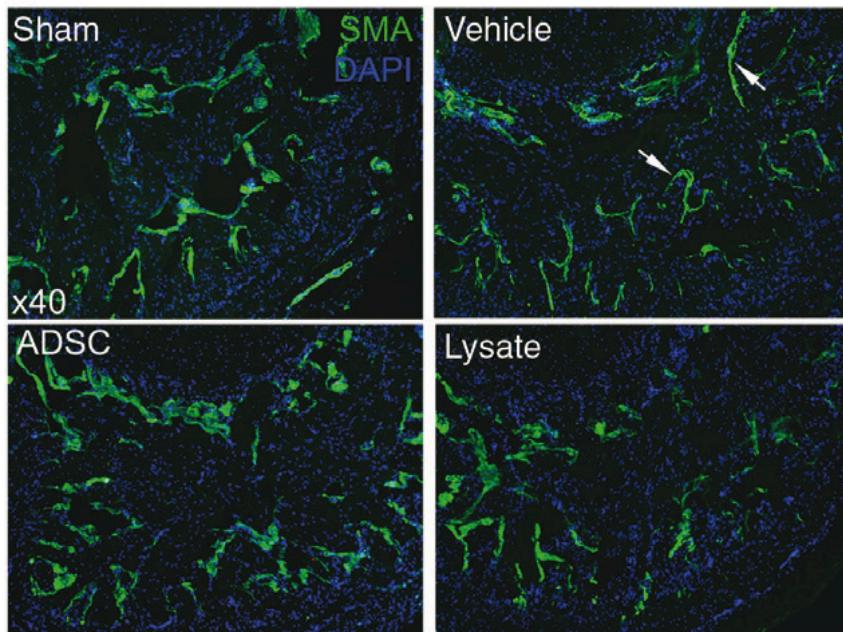


# L'injection de cellules souches adipeuses peut faire régresser la fibrose

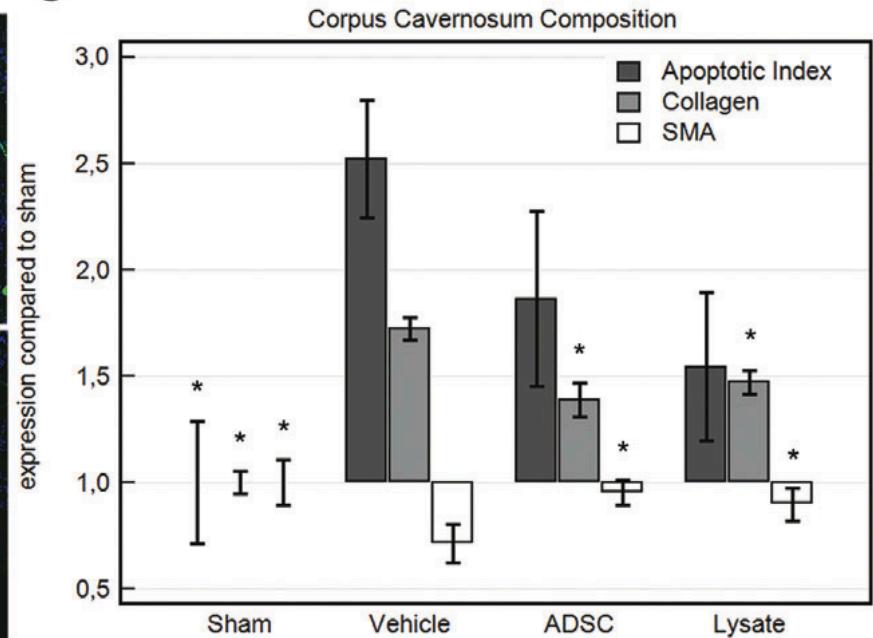
A



B

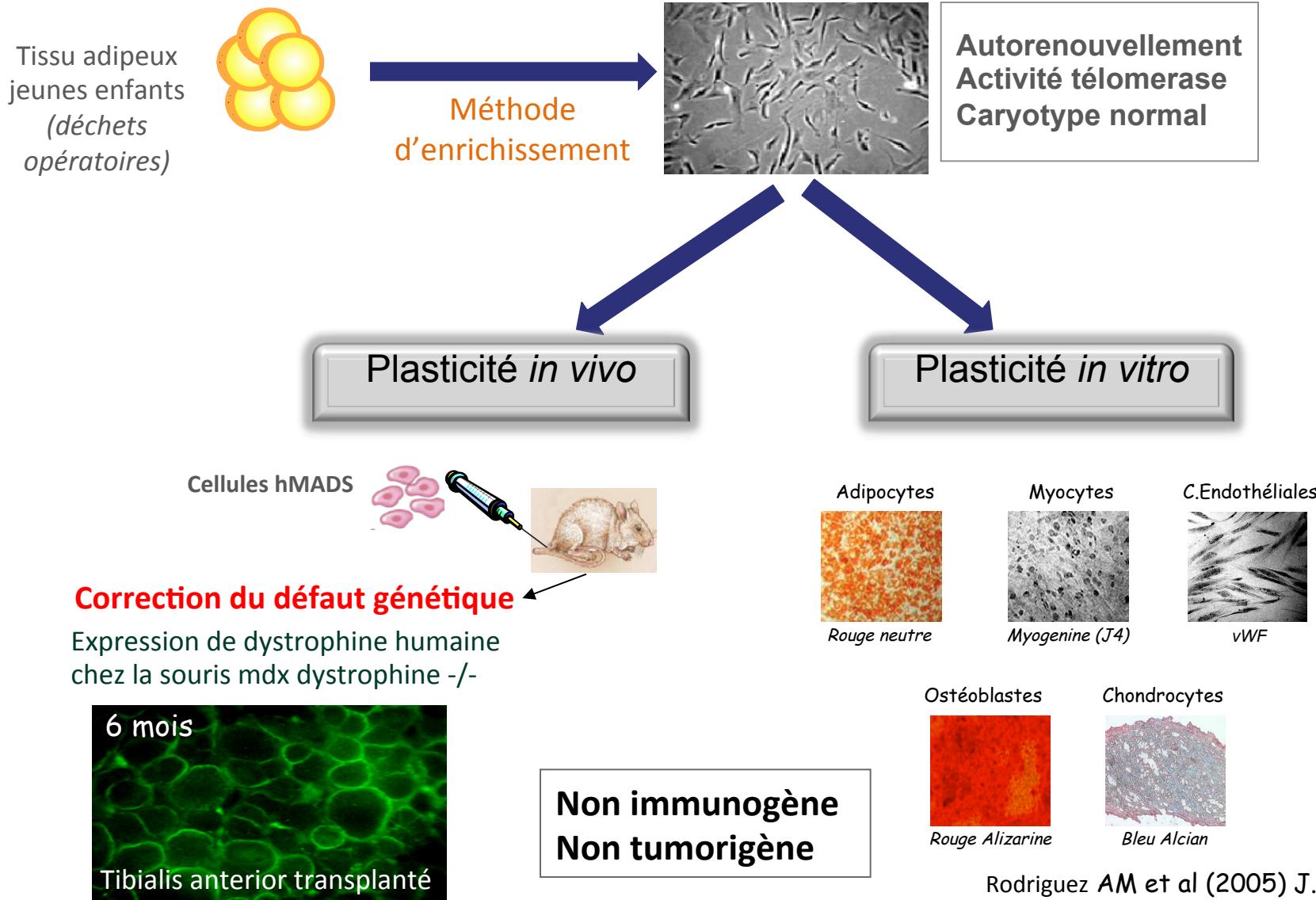


C

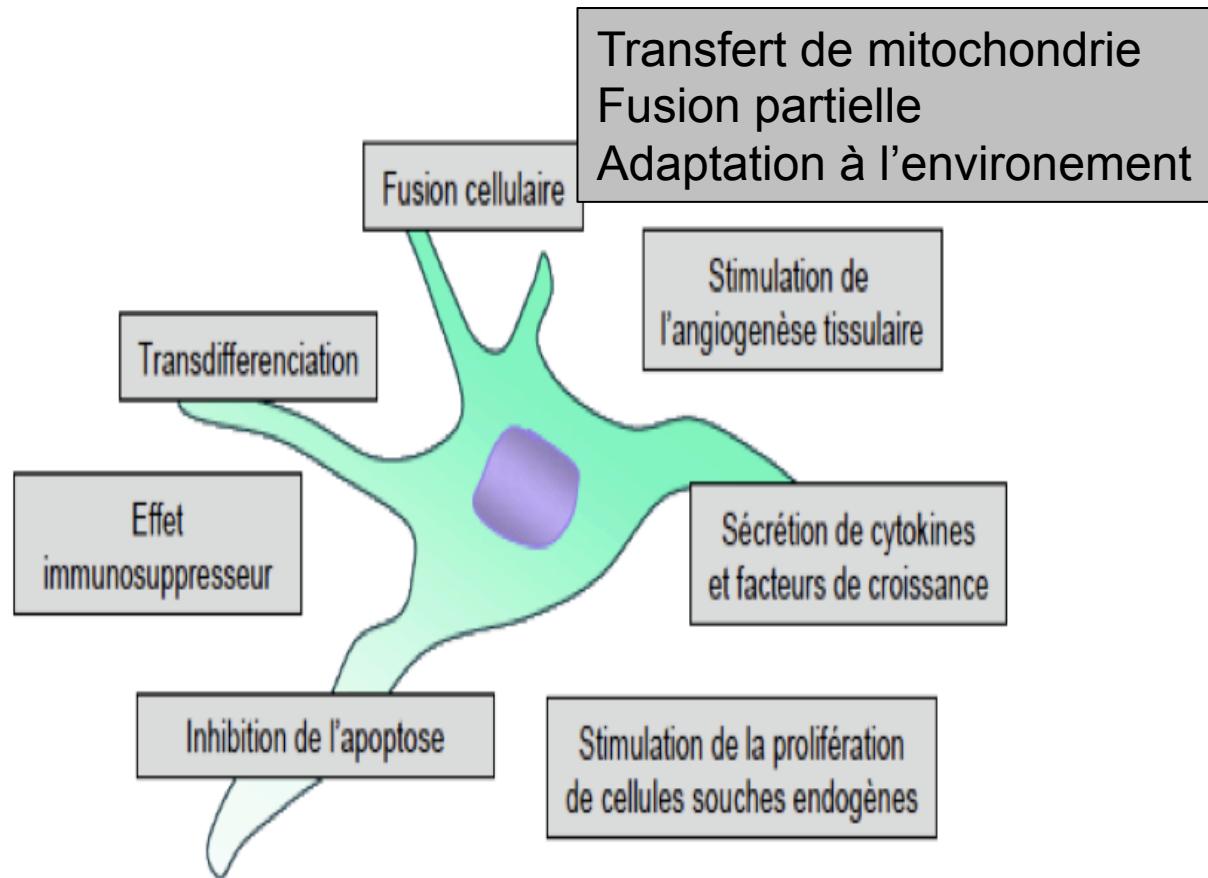


# Les cellules hMADS

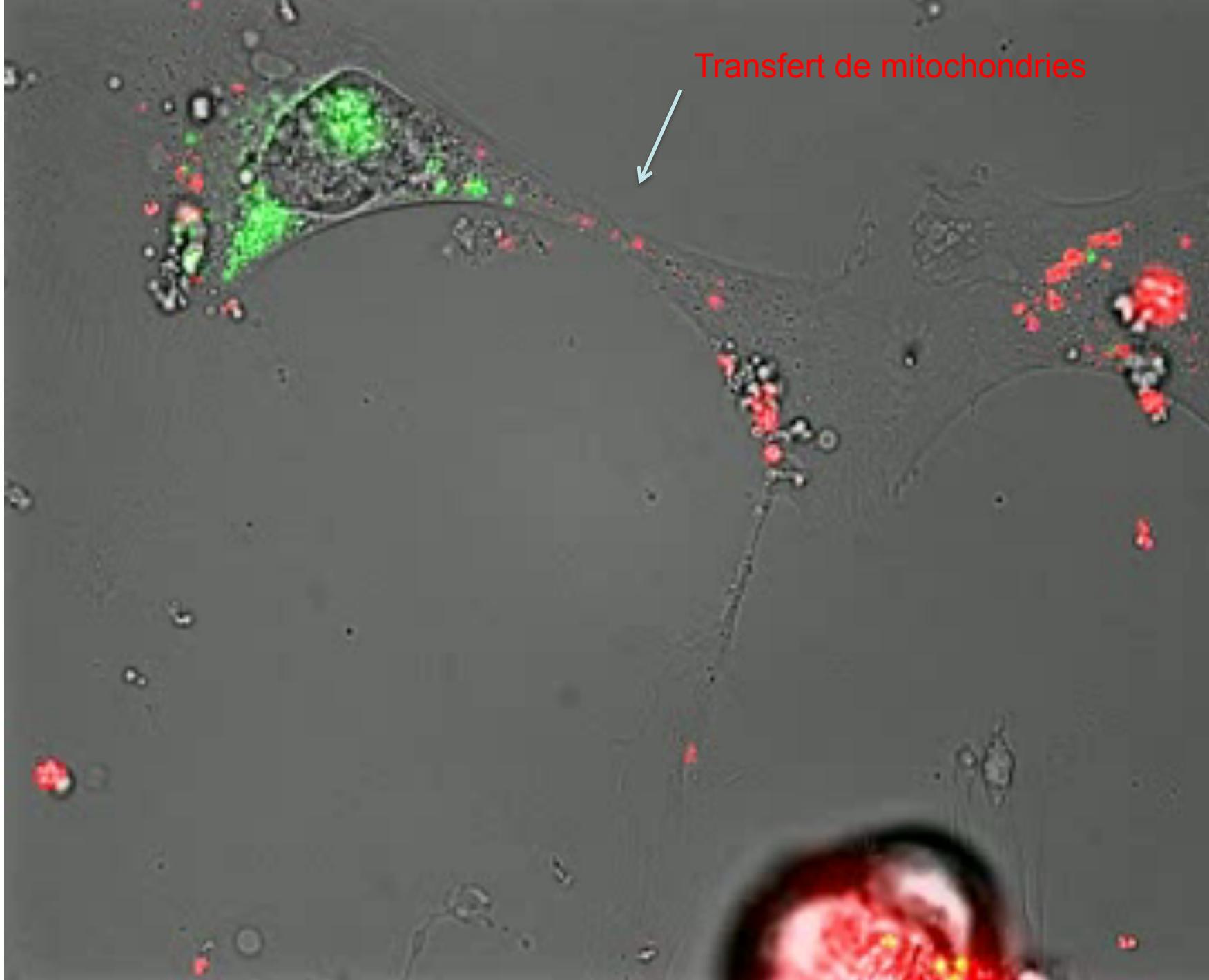
(mesenchymal adipose derived stem cell)



# Mécanismes de régénération médiés par les cellules souches

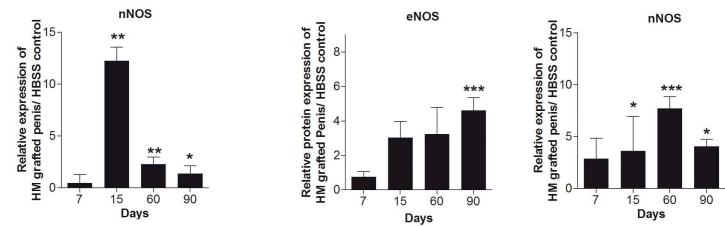
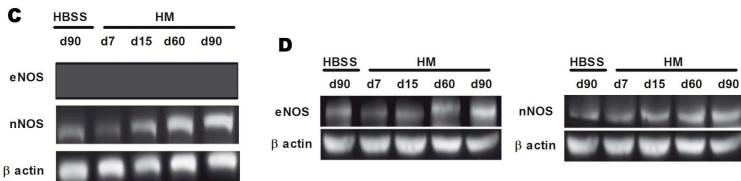
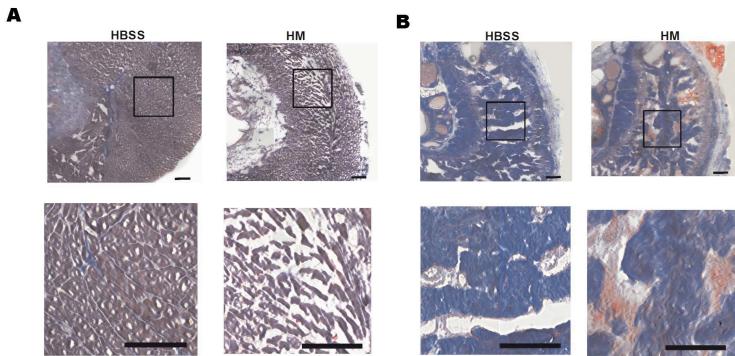


Transfert de mitochondries

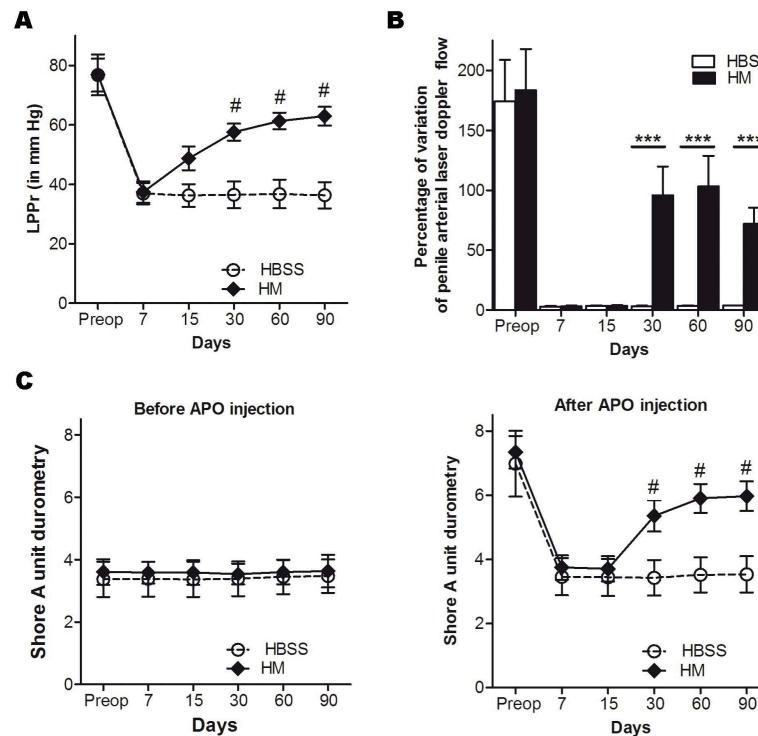


# Delivery of human Mesenchymal Adipose-Derived Stem Cells restore multiple urological dysfunctions in a rat model mimicking radical prostatectomy damages through Tissue-Specific Paracrine Mechanisms

Yiou et al. Stem Cells 2015

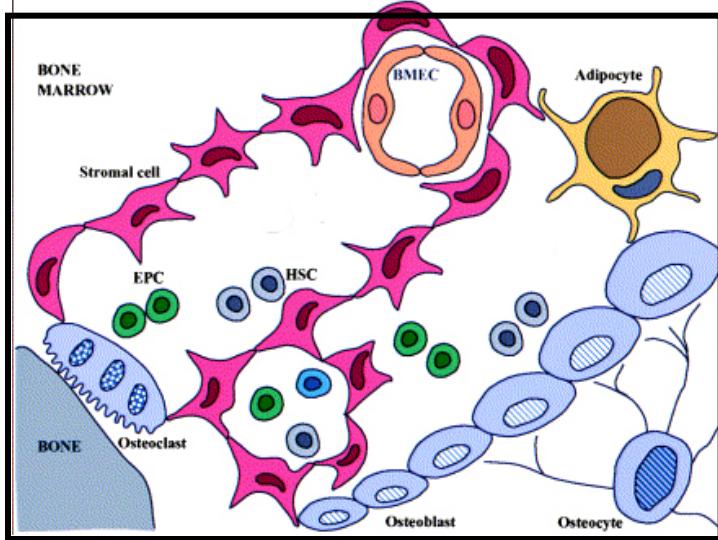


Activation du secretome de l'hôte  
Tissu dépendant

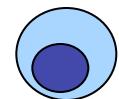


# **Mise au point de la thérapie cellulaire pour la dysfonction érectile après prostatectomie radicale**

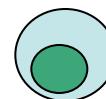
# Les cellules souches médullaires



Non adhérente

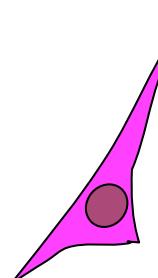


cellules souches  
hématopoïétiques

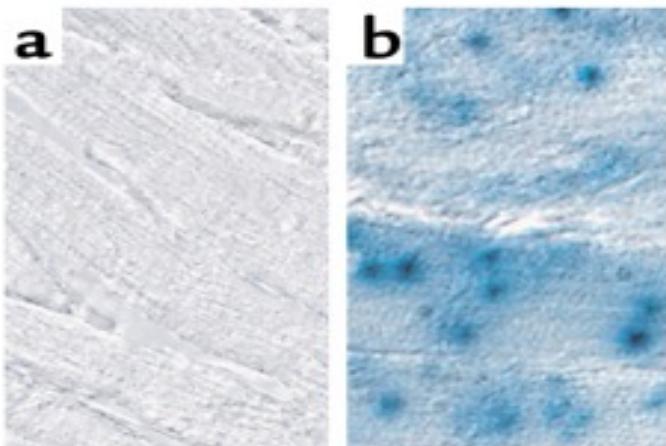
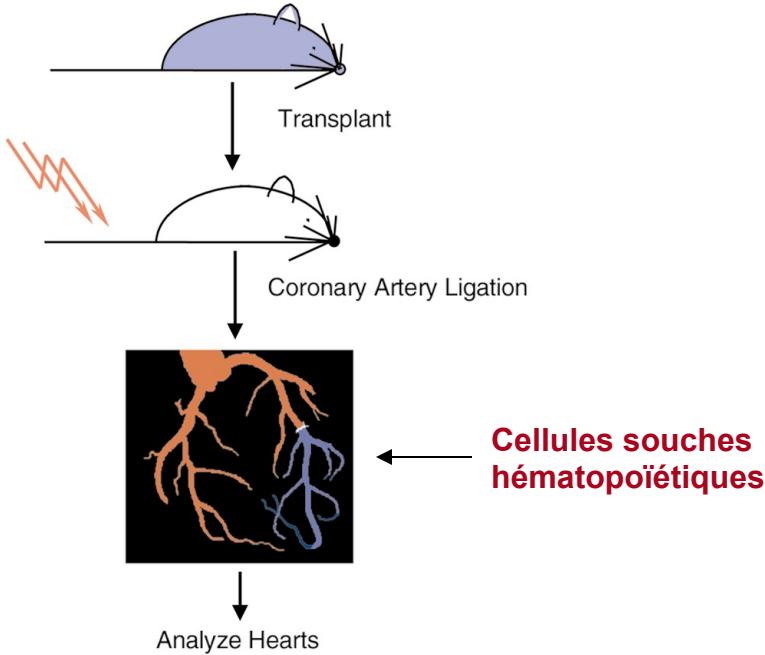


cellules progénitrices  
endothéliales (EPC)

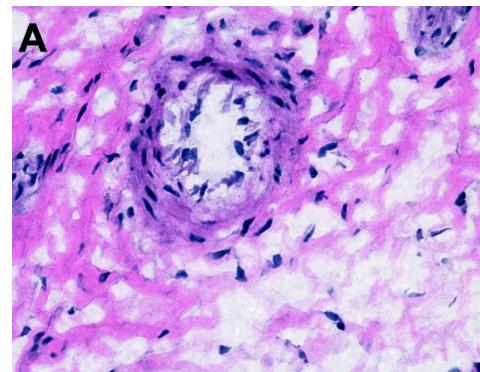
Adhérente



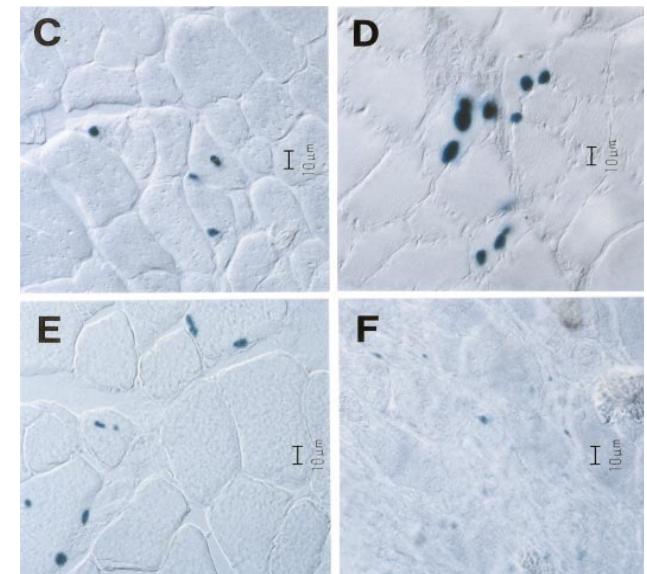
cellules souches  
mésenchymateuses



Jackson et al. J Clin Invest 2001

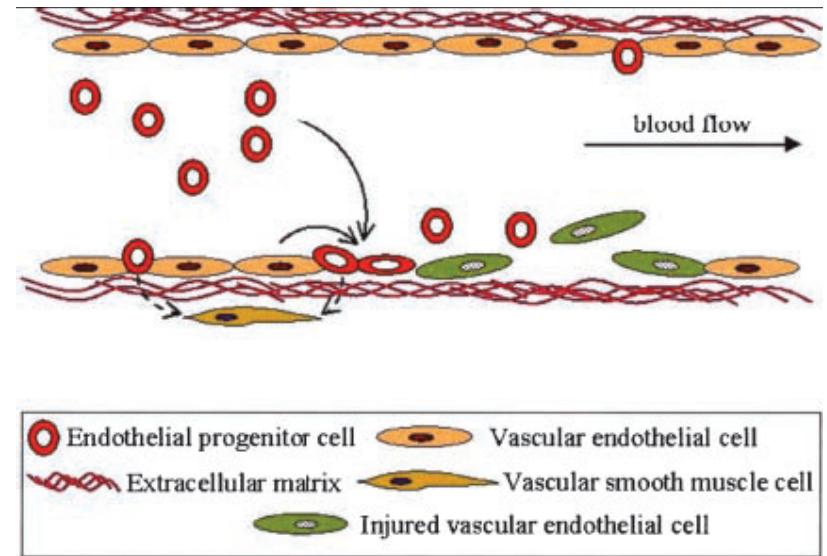
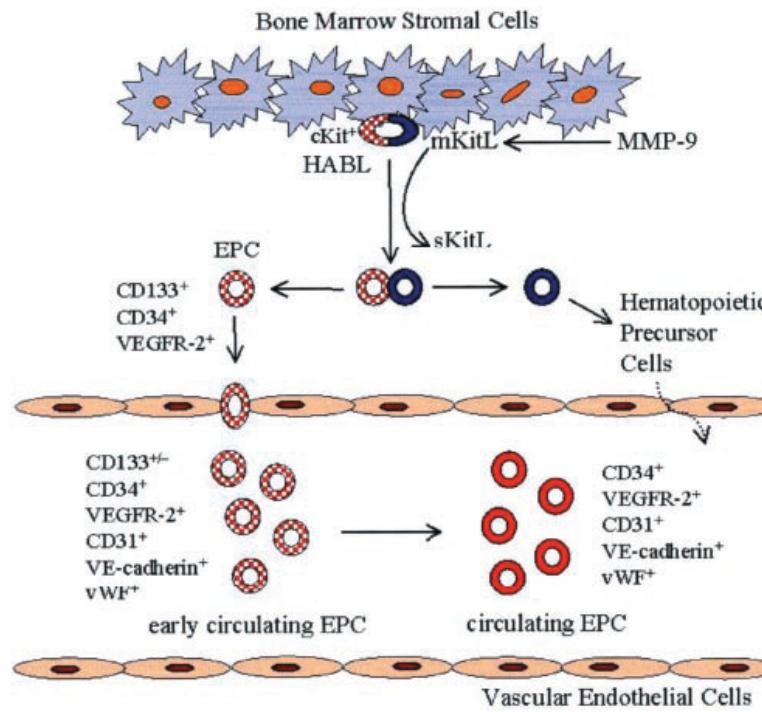


Modèle porc  
8 semaines après inj endocardique **CSM**  
dans une région de nécrose  
CSM marquée au DAPI  
Association avec la paroi vasculaire  
(Pittenger Circ Res 2004;95:9)



Modèle de lésion musculaire chronique  
**Moelle non fractionnée**  
Ferrari et al. Science 2001

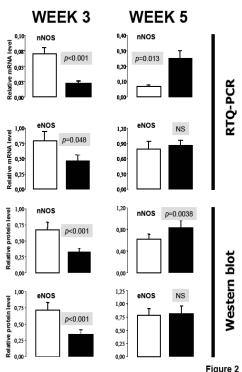
# Cellules progénitrices endothéliales



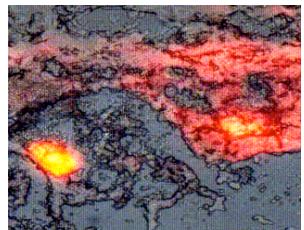
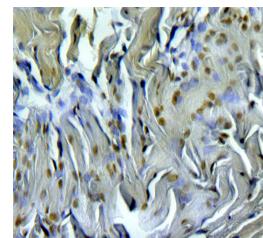
Diminution du nombre de progéniteurs endothéliaux circulants chez les patients ne récupérant pas une fonction érectile après PR?

Baumhakel M, Werner N, Bohm M, Nickenig G. Circulating endothelial progenitor cells correlate with erectile function in patients with coronary heart disease. Eur Heart J. 2006 Aug 22

- Dysfonction Erectile post Prostatectomie
    - perte de CML
    - cellules conjonctives
    - altération endothélium
    - Insuffisance veineuse et artérielle
    - Déficit NOSe NOSn
    - Ischémie chronique, fibrose
    - Insuffisance de cellules prog. endoth. circulantes (1)
  - Cellules médullaires mononucléées:
    - cellules souches hématopoïétiques
    - cellules progénitrices endothéliales
    - cellules stromales
- 
- Multipotentialité (2):
    - CML
    - cellules conjonctives
    - cellules endothéliales
  - Secrétions de facteurs pro-angiogéniques neurotrophique (3)
- (1) Baumhakel. Circulating endothelial progenitor cells correlate with erectile function in patients with coronary heart disease. Eur Heart J. 2006
- (2) Jackson et al. J Clin Invest, 2001
- (3) Kinnaird Circ Res 2004



**Dr Edhahibi Pr Adnot  
Equipe 8- U955  
Evaluation biologique  
de la greffe de CM (NOS)**



**Pr Yiou  
Dr Fall (Master)  
Service d'urologie  
Equipe 10- U841**

available at [www.sciencedirect.com/journal/europeanurology.com](http://www.sciencedirect.com/journal/europeanurology)



**eu**  
European Association of Urology

**Andrology**

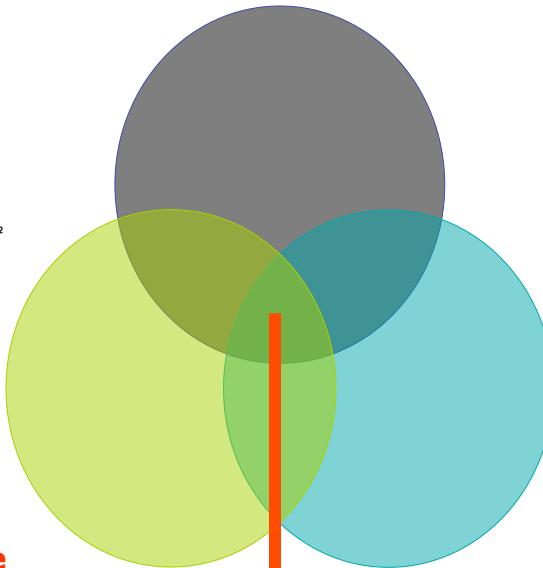
**Apoptosis and Effects of Intracavernous Bone Marrow Cell Injection in a Rat Model of Postprostatectomy Erectile Dysfunction**

Papa Ahmed Fall<sup>a,b</sup>, Mohamed Izikki<sup>b</sup>, Li Tu<sup>b</sup>, Salem Swieb<sup>a,b</sup>, Francois Giuliano<sup>c</sup>, Jacques Bernabe<sup>c</sup>, Rachid Souktani<sup>b</sup>, Claude Abbou<sup>a</sup>, Serge Adnot<sup>b</sup>, Saadia Eddahibi<sup>b</sup>, René Yiou<sup>a,b,\*</sup>

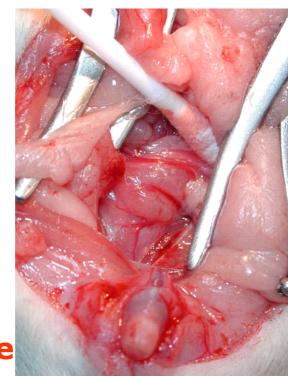
<sup>a</sup>Urology Department, Henri Mondor Teaching Hospital, Créteil, France

<sup>b</sup>INSERM Unit 841, Teams 8 and 10, plateforme du petit animal, School of Medicine, Henri Mondor Teaching Hospital, Créteil, France

<sup>c</sup>Pelvipharm Laboratories, Orsay Parc Bâtiment Cèdre, 86 Rue de Paris, 91400 Orsay, France



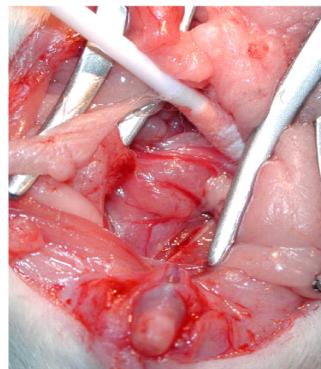
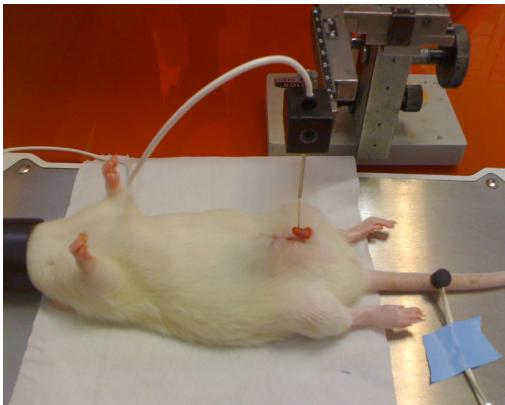
**Pr Giuliano  
Pelvipharm  
Gif sur Yvette  
Modèle de  
dysfonction érectile  
chez le rat**



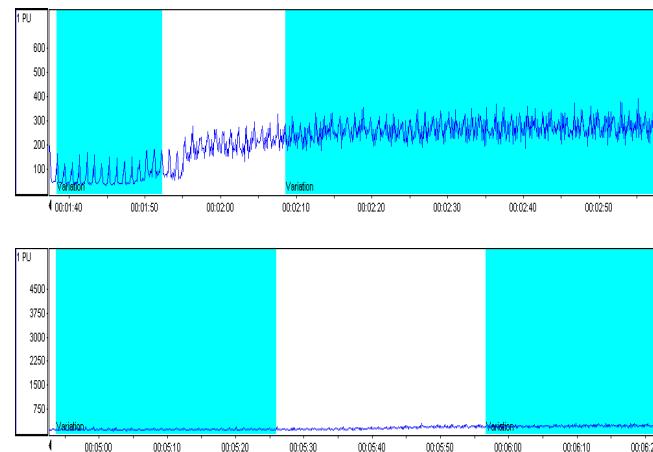
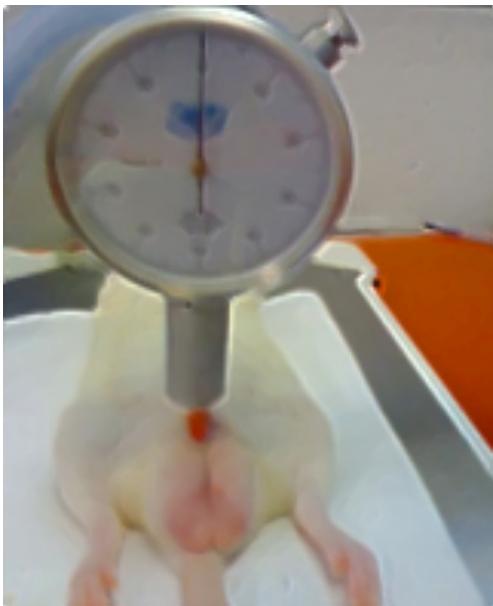
**COSSEC INSERM  
CIC biothérapie  
URC  
EFS**

**RECHERCHE TRANSLATIONNELLE INSERM/DHOS  
Avis favorable le juin 2007**

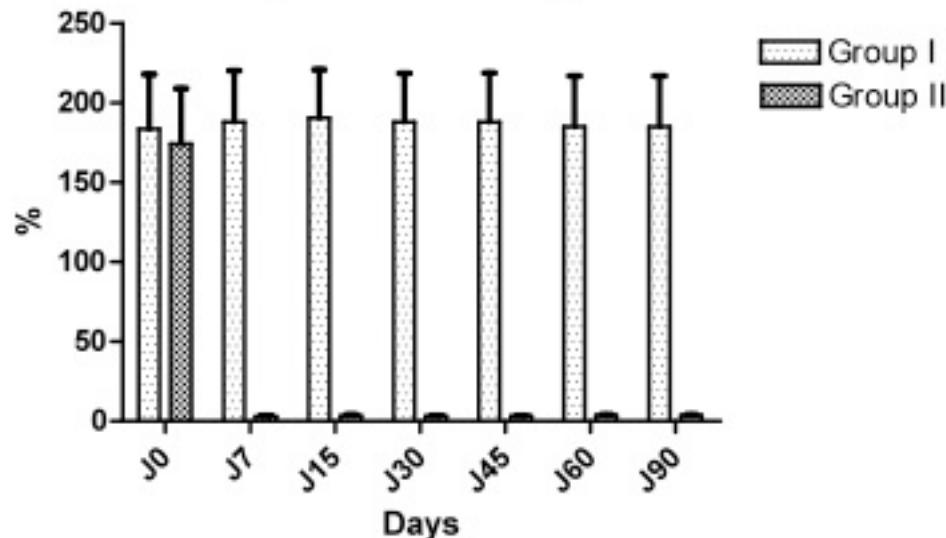
# Mise au point d'un modèle de dysfonction érectile non invasif chez le rat



Lésion des pédicules neurovasculaires péniens

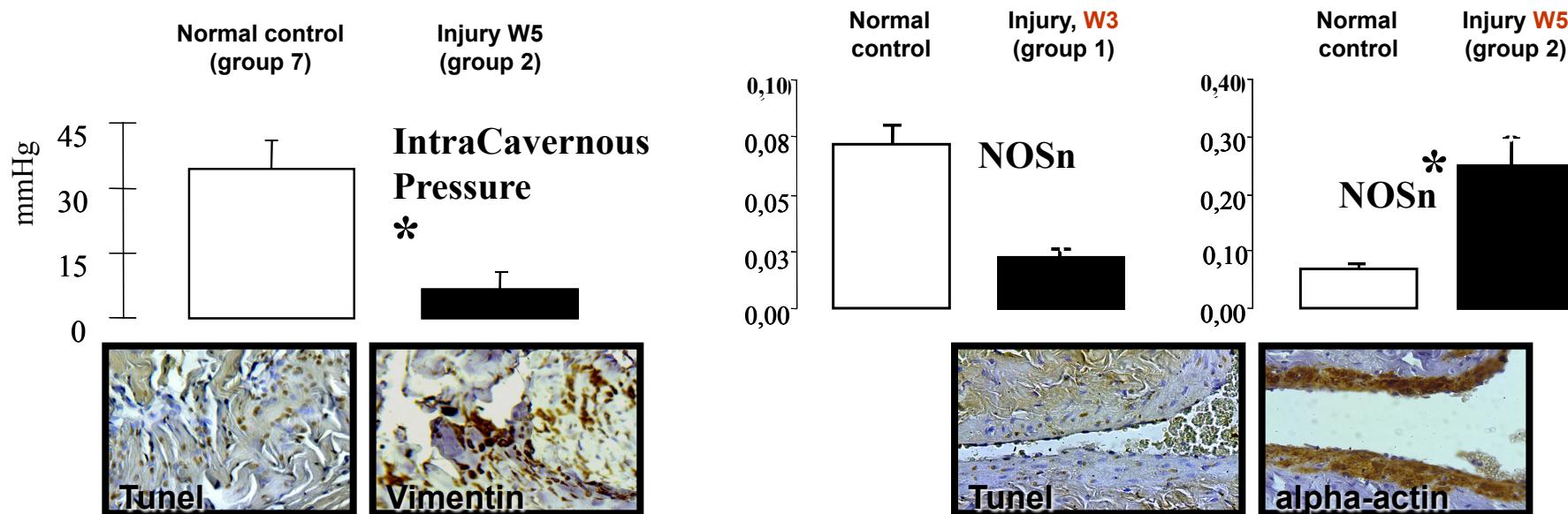


Percentage of variation of arterial penile laser Doppler flow

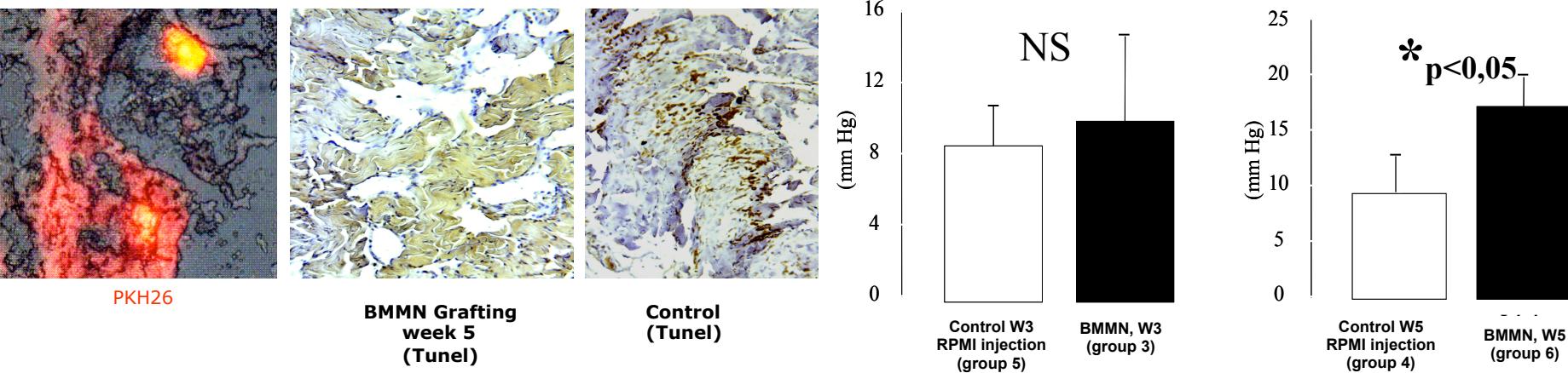


Erectile dysfunction persisted over 5 weeks although both RT-PCR and Western blot analysis showed recovery of NOSn at 5 weeks, suggesting 1) a spontaneous nerve regeneration process occurred; 2) decrease of NOS may not be the preponderant mechanism of pPDE at the long term.

The main abnormality that can be incriminated in the persistence of erectile dysfunction was the **diffuse apoptosis** (Tunel, brown) affecting **mesenchymal** (vimentin+, brown), endothelial and smooth muscle cells (alpha-actin, brown) of the corpus cavernosus that persisted over five weeks



Intra-cavernous injection of BMMN decreases the number of apoptotic cells (Tunel, brown) in the penis and partially recovers intracavernous pressure. Taken together, it can be considered that diffuse apoptosis of mesenchymal, smooth muscle cells and endothelial cells has a preponderant role in the persistence of pPED.



**BT06-07**

**« Evaluation de la tolérance et de l' efficacité de l' injection intra-caverneuse de cellules médullaires mononucléées autologues pour le traitement de la dysfonction érectile après prostatectomie radicale »**

***INSTIN***

**« Intracavernous STem-cell INjection for post prostatectomy erectile dysfunction »**

Hôpital Henri Mondor – Créteil

**Investigateur Coordonnateur: Pr René Yiou**  
**Responsable scientifique: Dr Hélène Rouard**  
**Promoteur : Inserm – ISP - PRC**  
**N° Clinical trial: NCT01089387**

# OBJECTIF PRINCIPAL

Tester la **faisabilité et la tolérance** de  
l' injection de cellules médullaires  
mononucléées dans les corps caverneux  
pour le traitement de la dysfonction érectile  
(DE) chez des patients opérés de  
prostatectomie radicale (PR) pour cancer de  
prostate localisé

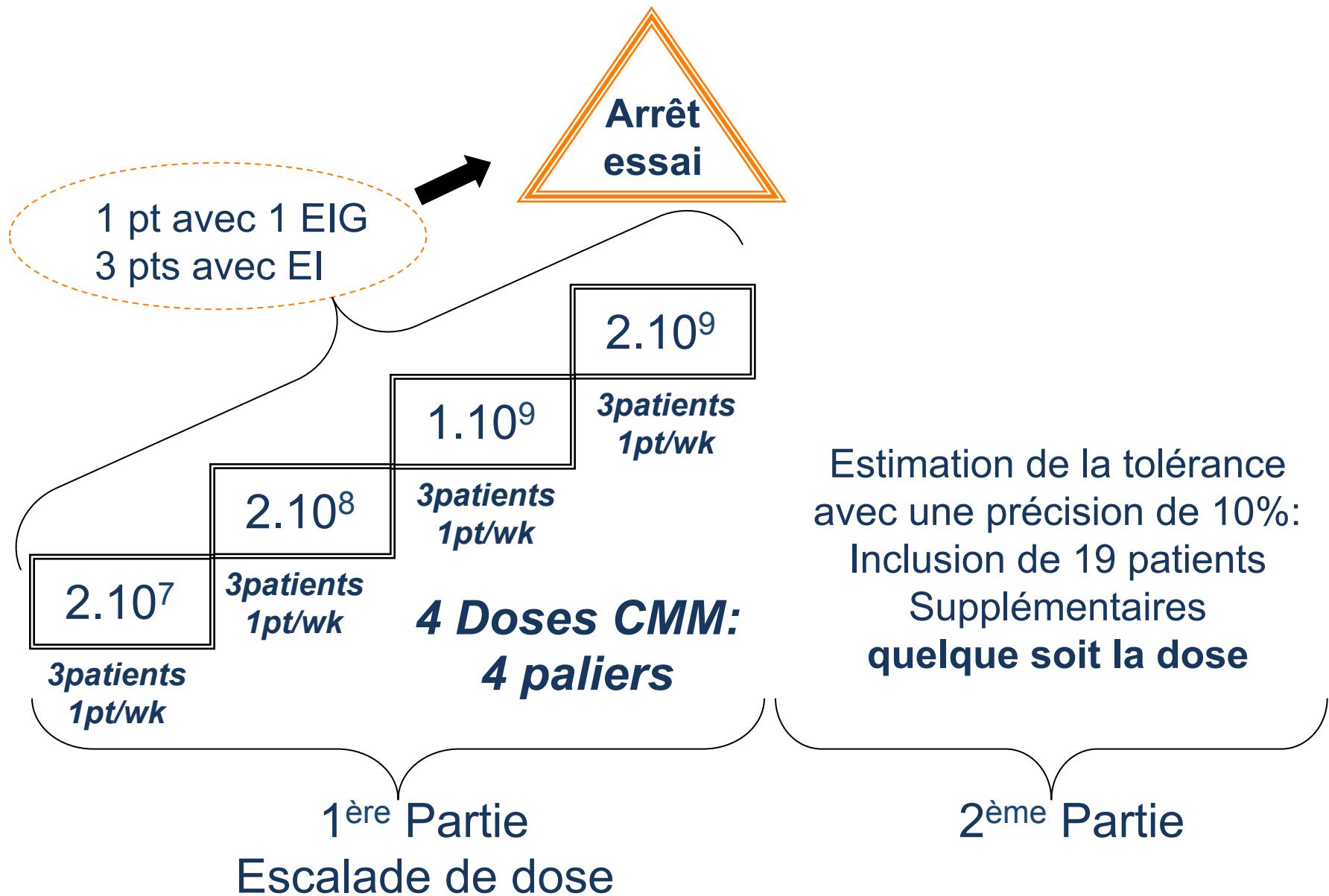
# OBJECTIFS SECONDAIRES

- La récupération de la fonction érectile évaluée à l'aide de questionnaires validés (scores IIEF15, EHS) remplis avant et après l'injection cellulaire
- L'amélioration des critères écho-doppler péniens ( $20\mu$  Edex) : PSV basale, 20 min, EDV, RI, *Penile Nitric Oxide Release Test (PNORT)*.
  - Insuffisance artérielle: PSV <25 cm/sec
  - Dysfonction caverno-veineuse:
    - PSV >25 cm/sec
    - EDV>5cm/sec s'accompagnant d'une rapide détumescence
    - RI<0,75

# PLAN EXPERIMENTAL (1/2)

Phase	Sélection	Hospitalisation (5 jours) et intervention (injection CMM)	Période d' observation dans l' essai <b>INSTIN</b>		
			M1 : Mois 1	M 3 : Mois 3	M6 : Mois 6
Consentement informé	•				
Critères d' inclusion	•				
Critères d' exclusion	•				
Questionnaires (Scores IIEF15, ISL, UCLA- PCI)*	•		•	•	•
Echo-doppler pénien avec injection de 10µg de PGE1**	•		•	•	•
Reprise des injections intracaverneuses ou IPDE5 si absence d' érection suffisante pour un rapport			•		

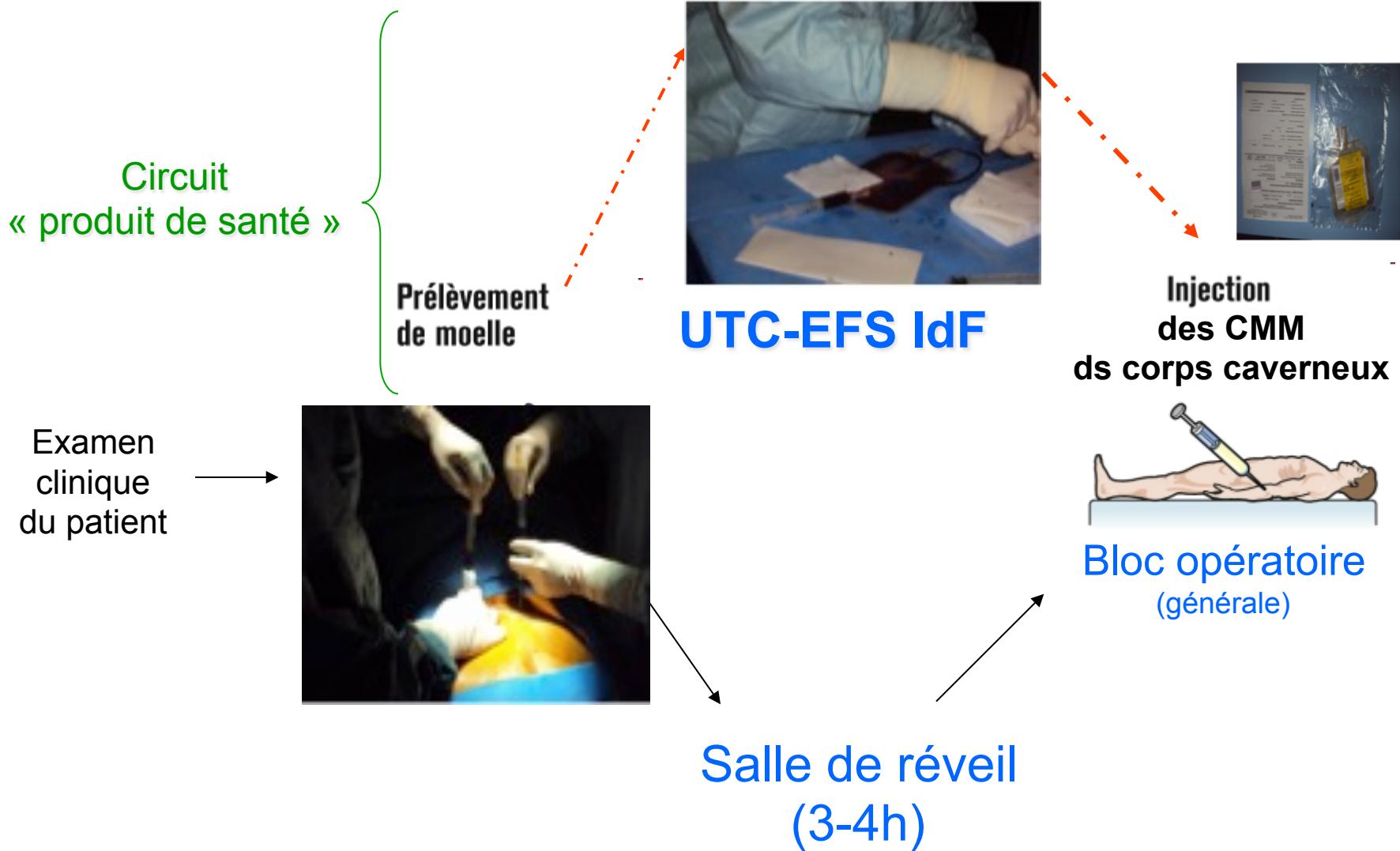
# PLAN EXPERIMENTAL (2/2)



# CRITERES D' INCLUSION

- Hommes de 45 ans à 70 ans opérés d'une PR datant d' au moins 6 mois et de moins de 3 ans
- Cancer de prostate sans extension extra-prostatique et peu agressif (pT2, Gleason 7, PSA préop <10 ng/ml)
- Fonction érectile pré-opératoire normale (fonction érectile  $25 \leq \text{IIEF} \leq 30$ ) et absence prise de traitement pro-érectile avant la PR
- Fuite veineuse, Insuffisance artérielle constatée à l'écho doppler pénien
- Echec traitements médicaux habituels
  - 10 essais Viagra 100
  - Vacuum
  - Edex 20

# Déroulement du J0



# Résultats

- Aucun EIG
- 3 Contaminations du prélèvement (>J10) *Propioni bactéri* sans conséquences → modification procédure de prélèvement
- Douleurs moyenne post op: 2/10
- Diminution du tx d'HB de 3 g/dl pour les doses 4 sans conséquences
- Pas de modifications du PSA
- 1 patient a eu une prothèse pénienne sans difficulté per-opératoire

**Table 1. Changes in sexual function scores and penile length after intracavernous injection of bone marrow mononuclear cells**

Sexual function with pharmacotherapy was assessed based on IIEF-15 questionnaire subscores for intercourse satisfaction (IS), sexual drive (SD), overall satisfaction (OS), erectile function (EF), and orgasmic function (OF); and on the Erection Hardness Score (EHS). The patients were also asked to determine their EHS without pharmacotherapy, to evaluate spontaneous erections. Significant differences compared to baseline are in bold type. The data are mean±SD.

	<b>Baseline</b>	<b>Month 1</b>	<b>Month 3</b>	<b>Month 6</b>		
			<i>P</i> value	<i>P</i> value	<i>P</i> value	
IIEF-IS	3.9±2.5	4.9±2.7	<i>0.35</i>	6.7±4.2	<b>0.026</b>	6.8±3.6
IIEF-SD	6.7±2.6	6.4±2.1	<i>0.67</i>	7.3±1.7	<i>0.23</i>	7.5±1.5
IIEF-OS	3.9±2.2	3.2±2.3	<i>0.35</i>	5.1±2.9	<i>0.12</i>	5.5±2.4
IIEF-EF (with pharmacotherapy)	7.3±4.5	9.8±8.8	<i>0.51</i>	14.6±10.1	<b>0.04</b>	17.4±8.9
IIEF-OF	3.5±3	4±3.8	<i>0.80</i>	6±3.8	<b>0.035</b>	6.3±3.3
EHS with pharmacotherapy	1.3±0.8	1.7±1.2	<i>0.37</i>	2.3±1.4	<i>0.07</i>	2.6±1.1
EHS without pharmacotherapy	0.4±0.7	0.9±1	<i>0.09</i>	0.9±1.2	<i>0.12</i>	1.1±1.2
Penile length, cm	12.4±2.2	13.5±2.1	<b>0.031</b>	13.3±2.2	<b>0.040</b>	12.9±2.4
					0.29	

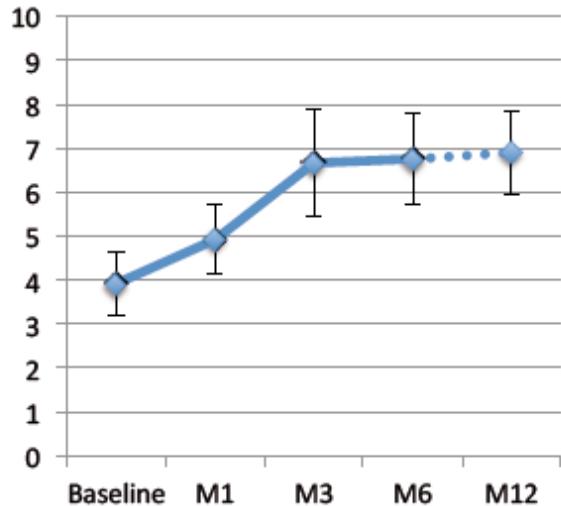
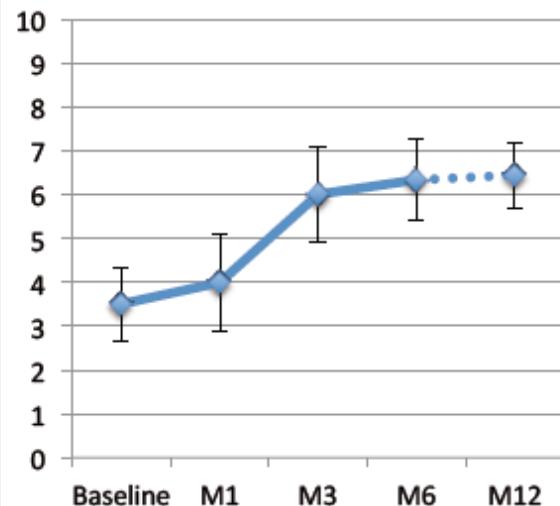
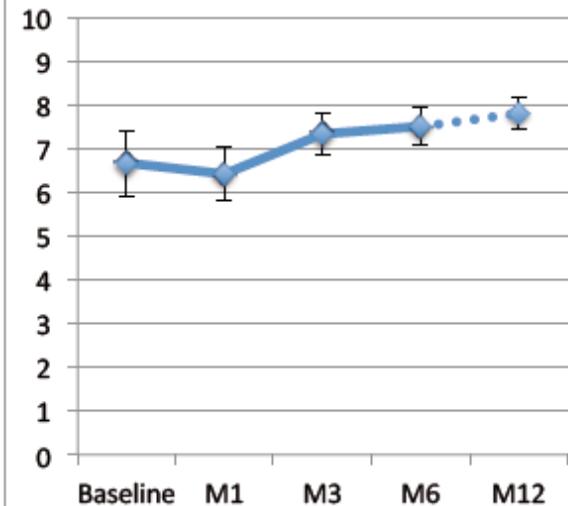
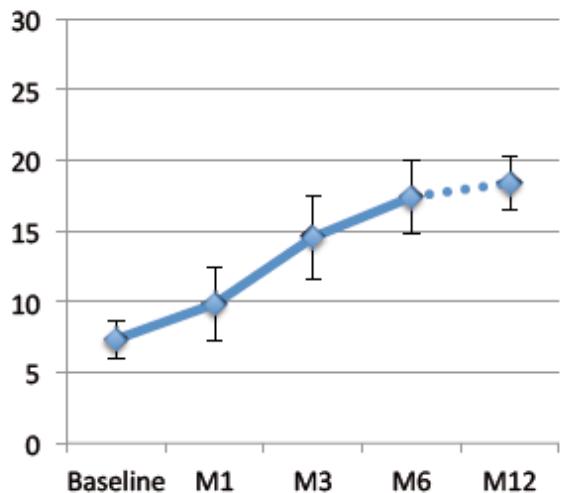
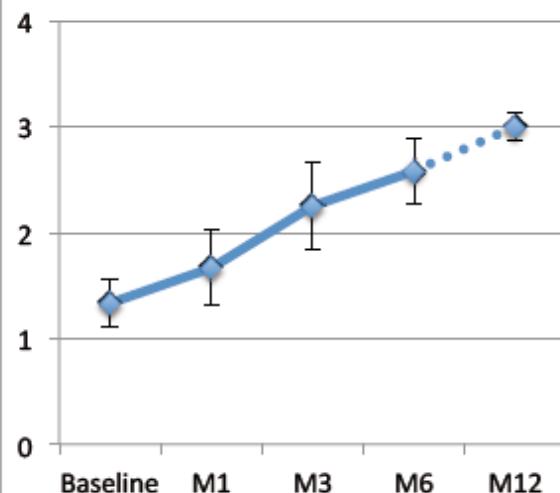
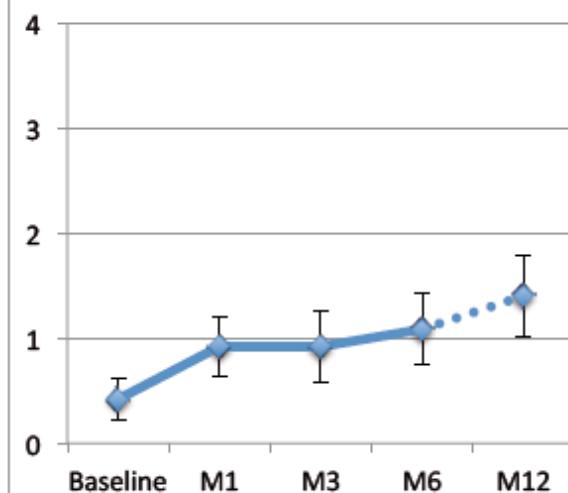
**Table 2. Changes in color duplex Doppler ultrasound parameters after the intracavernous injection of bone marrow mononuclear cells**

We assessed penile vascularization by measuring peak systolic velocity (PSV), end-diastolic velocity (EDV), and the resistive index (RI) in both cavernosal arteries before (basal PSV) and 20 minutes after an intracavernous injection of 20 mg of alprostadil (20-min PSV).

Endothelial function was assessed using the penile nitric oxide release test (PNORT), i.e., by measuring the percentage postocclusive change in cavernosal artery diameter. Significant and near-significant differences versus baseline are in bold type.

PSV, peak systolic velocity; EDV, end-diastolic velocity; PNORT, penile nitric oxide release test; RI, resistive index. The data are mean $\pm$ SD.

	Baseline	Month 1	Month 3	Month 6		
				P value	P value	P value
<b>Basal PSV (cm/s)</b>	9.2 $\pm$ 6.5	10.9 $\pm$ 6.6	<b>0.056</b>	14.3 $\pm$ 7.6	<b>0.004</b>	12.8 $\pm$ 9.2
<b>%PNORT</b>	22.5 $\pm$ 25.5	42 $\pm$ 27.6	<b>0.074</b>	38.9 $\pm$ 18.1	<b>0.083</b>	55.3 $\pm$ 51
<b>20-min PSV (cm/s)</b>	21.6 $\pm$ 7.2	33.5 $\pm$ 13	<b>0.003</b>	34.5 $\pm$ 11.7	<b>0.003</b>	32.1 $\pm$ 13.2
<b>20-min EDV (cm/s)</b>	7.9 $\pm$ 4.4	9.1 $\pm$ 3.8	0.32	9.4 $\pm$ 4.8	0.19	8.5 $\pm$ 5.2
<b>RI</b>	0.7 $\pm$ 0.2	0.7 $\pm$ 0.1	0.41	0.7 $\pm$ 0.1	0.31	0.7 $\pm$ 0.1

**IIEF-Intercourse satisfaction****IIEF-Orgasmic function****IIEF-Sexual drive****On-medication IIEF-EF****On-medication EHS****Off-medication EHS**

EHS: Erection Hardness Score

- Effets bénéfiques à court terme avec reprise d'une activité sexuelle chez 9/12 patients initialement candidats à une prothèse pénienne. Activité sexuelle possible sans traitement: 2 patients
- Possibilité de mettre une PP
- Augmentation du PNORT suggérant une amélioration de la fonction endothéliale
- Bonne tolérance mais diminution taux d'HB pour doses élevées

- Effets à long terme? Réinjection?
- Place de la thérapie cellulaire: Traitement curatif, adjuvant?
- Autres formes de DE?
- Discussion des différentes sources de cellules mésenchymateuses: tissu adipeux ou médullaire?
  - Adipeux: richesse en progéniteurs > moelle mais nécessité d'une digestion enzymatique
- Qualification du procédé (réglementation européenne)+++
  - MTI
  - MTI-PP
  - Préparation non-MTI

→ Contraintes **radicalement** différentes

# La réglementation

- Préparation de thérapie cellulaire
- MTI
- MTI-PP
- (intervention chirurgicale simple)
- **PTC vs MTI : Critères fondamentaux:**
  1. Pas de modification substantielle
  2. Usage homologue/non homologue
  3. Association avec un DM

- **Manipulations non substantielles**

(liste non exhaustive)

- Découpage
- Broyage
- Centrifugation
- Séparation, concentration
- Irradiation
- Filtration
- Lyophilisation
- Congélation
- Cryoconservation
- vitrification

- **Manipulations considérées comme substantielles**

- Culture
- Transfert de gènes
- Modification du génome
- Altération du phénotype