Stem cells for ED and incontinence post-prostatectomy

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Main sources of cells for functional urological disorders

- **Muscle precursor cells**
  - Satellite cells, myofiber
  - Myoblasts
  - Muscle derived stem cells
- **Bone marrow**
  - Mesenchymal stem cells
  - Hematopoiétic stem cells
  - Endothelial progenitors

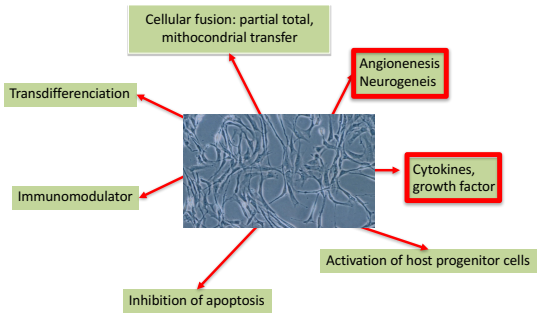
  -> Whole bone marrow, mononucleated cells, selected +/- cultured cells
- **Adipose derived cells**
  - Mesenchymal stem cells
  - Endothelial progenitors

  -> stromal vascular fraction, Endothelial progenitors
- **Embryonnic, amniotic cells, Wharton**

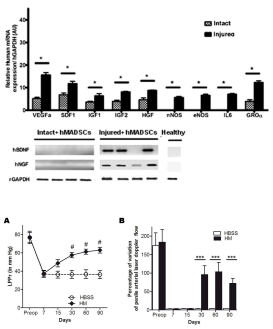
→

- **Urinary incontinence**
- **Erectile dysfunction**
- **Bladder dysfunction**
- **Urethral stricture**

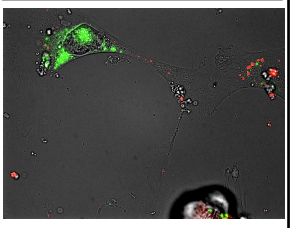
Mecanisms of action of stem cells



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
Stem Cells 2015



- No hMADS > day 7
- Improvement of erectile & urinary function
- Activation of secretome+++
- Adaptation to environment and injury



REGULATION ASPECTS

Definitions of Advanced Therapy Medicinal Products (ATMP)

Cell-based products **Somatic cell therapy** medicinal products:
-**substantially manipulation** cells or tissues **or not intended** to be used for **the same essential function**(s);
-administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action.

Tissue engineered product:
-**engineered** cells or tissues, and administered to human beings with a view to regenerating, repairing or replacing a human tissue.

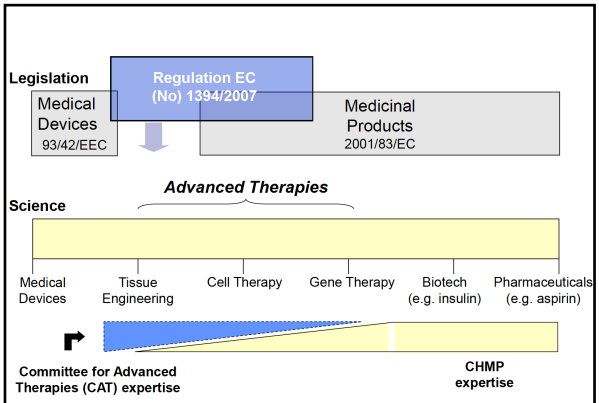
Gene therapy medicinal product:
-recombinant nucleic acid →to regulating, repairing, replacing, adding or deleting a genetic sequence

Non-substantial Manipulations

What is a non substantial manipulation?

- cutting
- grinding
- shaping
- centrifugation
- soaking in antibiotic or antimicrobial solutions
- sterilization
- irradiation
- cell separation, concentration or purification
- filtering
- lyophilization
- freezing
- cryopreservation
- vitrification

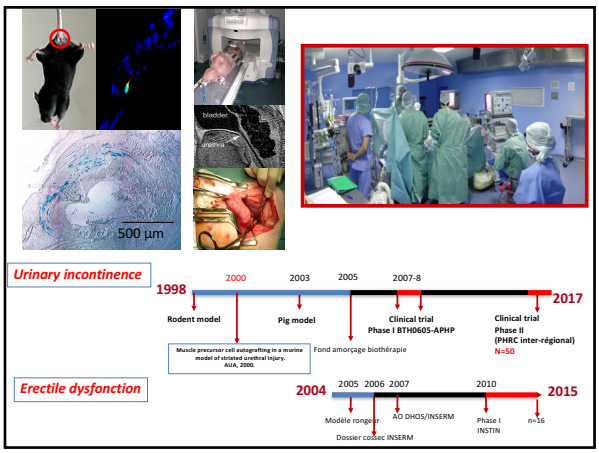
Everything else (ex: cell culture, enzymatic digestion) is considered as substantial



ATMP

- Tracability: **link** between donor and donation, between donation and product, between product and recipient
- **anonymous coding systems**.
- Material tested/documented **for viral**, TSE safety?
- **Tumourigenicity & chromosomal stability**
- **Demonstrate genotypic / phenotypic stability during process**
- **Non-homologous model (immunocompromised?) to test human product**
- Biologically relevant animal model available (concomitant treatment immunogenicity, delivery)?
- **Large animal model *necessary***
- **Methods for tracking cells *in vivo* to be developed/employed**
- **Study differentiation process / migration *in vivo***
- Manipulated/extensively cultured cell products
- T**esting dependent on route** of administration, intended clinical use.

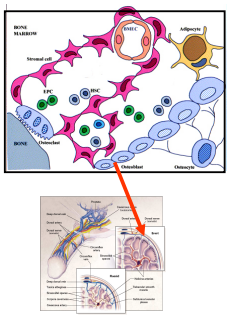
etc.....



CLINICAL TRIALS FOR ERECTILE DYSFUNCTION

Published clinical trials	**n=2**
Ongoing clinical trial	**12 (clinical.trials.gov)**
Source of cells	*Adipose tissue (Sromal vascular fraction): 6* *Bone marrow: 3* *Fetal/ placenta/ cord blood: 4* *Matrices: 2*
Evaluation of functional results	Neurophysiology: 1 Vascular (doppler): 8 Endothelial function: 2
Localization	Arabie Saoudite:1, Jordania:2, Egypt: 1, Corea: 1, Denmark: 1, USA: 3, China; 2, Russia: 1
Cell expansion-specific lab	no: 5, yes: 5, not known: 2
Nb f cells	?: 8 yes with dose escalation: 1 (30.10^6,60.10^6,90.10^6) yes one dose: 3
Phase	Phases I ou II **Control groups: 2**
Status	Closed:3, Recruiting: 9
Nb patients:	4-100 (overall: 293)
Inclusion	All ED: 5, Diabetes: 4, Post-radical prostatectomy: 1, ED+ Peyronie: 1 Rectal cancer: 1

BONE MARROW MONONUCLEATED CELLS IN THE TREATMENT OF pRP-ED



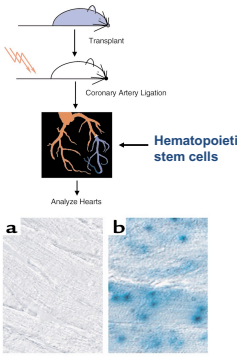
Non adherent cells

hematopoietic stem cell

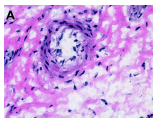
endothelial progenitors

Adherent cells

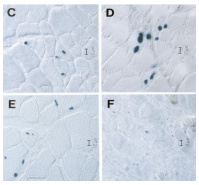
Mesenchymal stem cells



Jackson et al. J Clin Invest 2001



Mesenchymal stem cell participate to vessel formation (Pittenger Circ Res 2004;95:9)



BMMNCs form muscle in dystrophic muscle Ferrari et al. Science 2001

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

BT06-07

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

INSTIN

« INtracavernous STem-cell INjection for post prostatectomy erectile dysfunction »

Investigateur Coordonnateur: Pr René Yiou
Responsable scientifique: Dr Hélène Rouard

Promoteur : Inserm – ISP - PRC

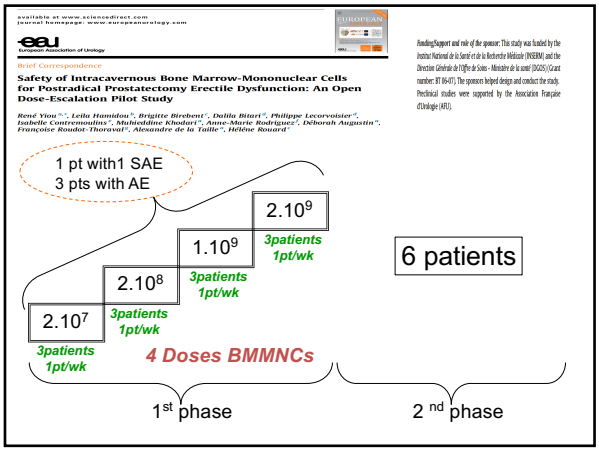
STUDY DESING

- Nonrandomized, **dose-escalation**, phase 1/2 pilot clinical trial investigating intra-cavernous injection of BM-MNCs in patients with severe post-radical prostatectomy ED (NCT01089387).
- **Inclusion criteria**
  - 45–70 yr
  - RP 6 mo to 3 yr earlier
  - **failure of pharmacotherapy** defined as an Erection Hardness Score (EHS) <3 after at least 10 intracavernous alprostadil injections (20 mg) combined with sildenafil (100 mg) and the use of a vacuum device.

Study design

Phase 1/2 clinical trial investigating intracavernous injection of autologous BM-MNCs to treat pRP-ED (NCT01089387)

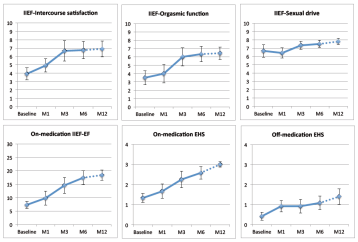
- primary endpoint: **tolerance**
- secondary endpoints effects of BM-MNC injection on **erectile function** measured using validated scores and on penile vascularization assessed using color duplex Doppler ultrasound (CDDU).



RESULTS

Changes in sexual function scores after intracavernous injection of bone marrow mononuclear cells

Mean time from RP to BM-MNC injection was 22.9 months



	Baseline	Month 1	*P* value	Month 3	*P* value	Month 6	*P* value
IIEF-IS	3.9±2.5	4.9±2.7	*0.35*	6.7±4.2	***0.026***	6.8±3.6	***0.044***
IIEF-SD	6.7±2.6	6.4±2.1	*0.67*	7.3±1.7	*0.23*	7.5±1.5	*0.17*
IIEF-OS	3.9±2.2	3.2±2.3	*0.35*	5.1±2.9	*0.12*	5.5±2.4	*0.11*
IIEF-EF (with pharmacotherapy)	7.3±4.5	9.8±8.8	*0.51*	14.6±10.1	***0.04***	17.4±8.9	***0.006***
IIEF-OF	3.5±3	4±3.8	*0.80*	6±3.8	***0.035***	6.3±3.3	***0.014***
EHS with pharmacotherapy	1.3±0.8	1.7±1.2	*0.37*	2.3±1.4	*0.07*	2.6±1.1	***0.008***
EHS without pharmacotherapy	0.4±0.7	0.9±1	*0.09*	0.9±1.2	*0.12*	1.1±1.2	***0.054***
Penile length, cm	12.4±2.2	13.5±2.1	***0.031***	13.3±2.2	***0.040***	12.9±2.4	*0.29*

	Baseline	Month 1	*P* value	Month 3	*P* value	Month 6	*P* value
Basal PSV (cm/s)	9.2±6.5	10.9±6.6	***0.056***	14.3±7.6	***0.004***	12.8±9.2	*0.18*
%PNORT	22.5±25.5	42±27.6	***0.074***	38.9±18.1	***0.083***	55.3±51	***0.084***
20-min PSV (cm/s)	21.6±7.2	33.5±13	***0.003***	34.5±11.7	***0.003***	32.1±13.2	***0.003***
20-min EDV (cm/s)	7.9±4.4	9.1±3.8	*0.32*	9.4±4.8	*0.19*	8.5±5.2	*0.74*
RI	0.7±0.2	0.7±0.1	*0.41*	0.7±0.1	*0.31*	0.7±0.1	*0.57*

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±SD.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com/eufocus

Brief Correspondence

Intracavernous Injections of Bone Marrow Mononucleated Cells for Postradical Prostatectomy Erectile Dysfunction: Final Results of the INSTIN Clinical Trial

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Table 1 – Changes in sexual function scores after intracavernous injection of bone marrow mononuclear cells.

	Baseline[b]	Month 1	*p* value	Month 3	*p* value	Month 6	*p* value	Month 12	Last follow-up	*p* value[c]
Stage I (n = 9)[a]										
IIEF-IS	4.6 ± 2	4.9 ± 3.1	0.81	7 ± 4.4	0.078	7.2 ± 3.6	**0.035**	6.9 ± 3.4	6 ± 3.5	0.44
IIEF-SD	6.4 ± 2.7	6.2 ± 2.4	0.87	7.3 ± 1.6	0.23	7.6 ± 1.6	0.16	7.6 ± 1.1	7 ± 1.5	0.85
IIEF-OS	3.9 ± 2.3	2.9 ± 2	0.41	5 ± 3.1	0.36	5.8 ± 2.3	0.15	5.8 ± 2.7	4.4 ± 3.2	0.14
IIEF-EF (with pharmacotherapy)	7.1 ± 3.1	10 ± 9.8	0.64	14.8 ± 10.3	0.092	18.4 ± 8.2	**0.0091**	18.1 ± 7	15.3 ± 8.1	0.22
IIEF-OF	3.8 ± 3.1	4 ± 3.6	0.93	5.9 ± 3.4	0.44	6.3 ± 2.6	**0.024**	6 ± 2.4	5.9 ± 3.8	1
EHS with pharmacotherapy	1.4 ± 0.7	1.4 ± 0.9	1	2.4 ± 1.4	0.11	2.9 ± 0.8	**0.02**	3 ± 0.5	2.5 ± 0.9	0.11
EHS without pharmacotherapy	0.6 ± 0.7	0.8 ± 0.8	0.34	0.9 ± 1.3	0.37	1.2 ± 1.2	0.09	1.6 ± 1.3	1.3 ± 1	0.5
Stage II (n = 6)										
IIEF-IS	2.2 ± 3.4	5.7 ± 4.5	**0.058**	8.5 ± 3.6	**0.031**	7.8 ± 3.1	**0.033**	–	–	–
IIEF-SD	6.2 ± 1.8	6.2 ± 2.3	**0.058**	7 ± 0.9	0.17	6.7 ± 1	0.34	–	–	–
IIEF-OS	3.3 ± 2.4	3.5 ± 2	0.88	5.5 ± 2.9	0.41	6.8 ± 2.5	**0.035**	–	–	–
IIEF-EF (with pharmacotherapy)	3.7 ± 4.1	11.8 ± 11.6	0.062	18.2 ± 10.3	**0.031**	18 ± 8.3	**0.035**	–	–	–
IIEF-OF	3.3 ± 3.2	6 ± 3.1	0.073	8.2 ± 2.9	0.062	7.3 ± 2.3	**0.034**	–	–	–
EHS with pharmacotherapy	1.8 ± 0.8	2.2 ± 1.5	0.85	2.7 ± 1.2	0.41	3.3 ± 0.8	**0.053**	–	–	–
EHS without pharmacotherapy	0.8 ± 0.8	1.5 ± 1	0.46	1.3 ± 1	0.5	1.2 ± 0.4	0.58	–	–	–

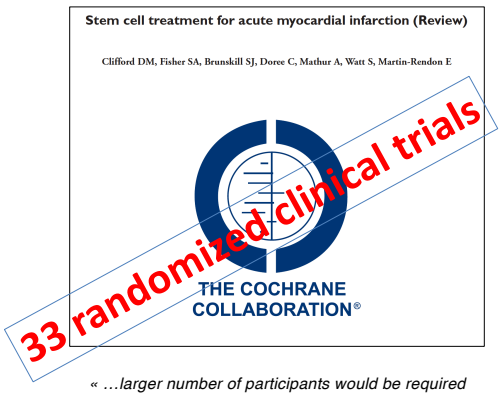
Safety and Potential Effect of a Single Intracavernous Injection of Autologous Adipose-Derived Regenerative Cells in Patients with Erectile Dysfunction Following Radical Prostatectomy: An Open-Label Phase I Clinical Trial

Haahr et al. EbioMedicine 2016

- Autologous adipose-derived cells (ADRCs) freshly isolated / liposuction (Cytori Therapeutics)
- The men received between 8.4–37.2 million ADRCs
- 17 men with post RP ED, with no recovery using conventional therapy
- **IIEF=7** at baseline
- 8/11men recovered erectile function (**IIEF=17**) at M6
- No efficient if urinary incontinence

CONCLUSIONS

- What is next in research/clinical trial?
- Does it work? Magnitude of improvement?
- When/how can we do it?



« …larger number of participants would be required to assess the full clinical effect of this treatment »

P-shot

= injection of PRP into the penis

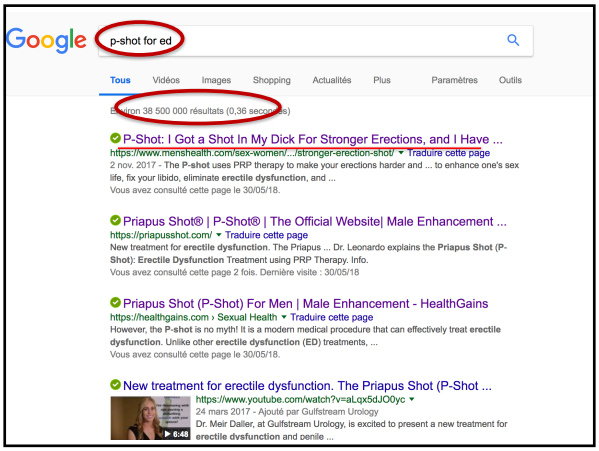
Qu'est-ce que le PRP?

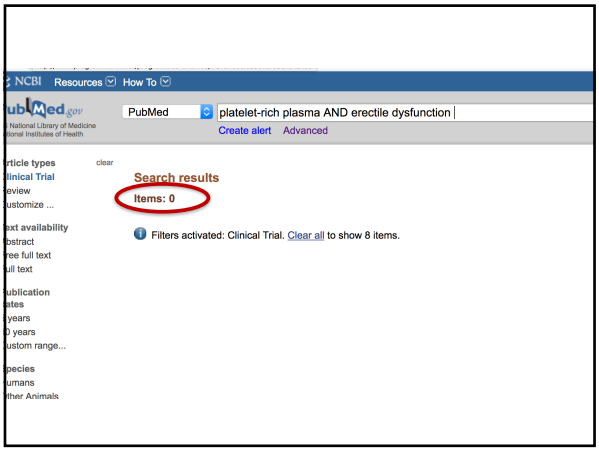
Platelet-rich plasma: platelet concentrate **5 X** > blood concentration. **Centrifugation of blood sample.**

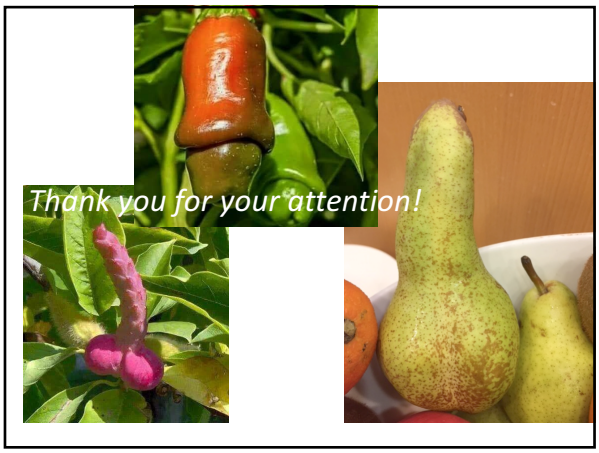
≠ cell therapy because platelet have no nucleus !

After injection into injured tissue: release of cytokines & growth factor responsibles for tissue regeneration.

Advantages:
- Biocompatibility, disponibility
- Easy to use, less expensive than cell therapy
- **flimsy regulatory framework**






Thank you for your attention!