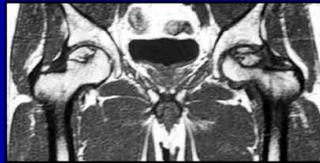


**THERAPY WITH STEM CELLS IN THE TREATMENT OF ISCHEMIC NECROSIS IN FEMORAL HEAD**  
 Osteonecrosis repair with stem cells: 30 years of experience with bone marrow concentration

> 200 patients with osteonecrosis treated / year



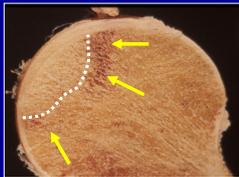
Ph. HERNIGOU

Hospital Henri Mondor; University of Paris ; France  
 philippe.hernigou@wanadoo.fr

**PLAN**

- Rationale of the technique
- Technique
- Clinical results
- Repair of osteonecrosis
- How many cells are necessary ?
- Other techniques of graft improvement  
 Work in progress – Tissue Engineering
- Conclusion and indications

**Autologous Bone Marrow Grafting before Collapse**



At its first stages, before collapse, osteonecrosis is characterized by presence of dead bone and absence of mechanical failure.

Presence of a vascular demarcating line

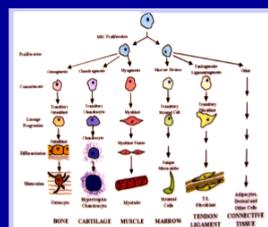
So, injection of osteogenic cells in the dead area should improve the repair process

**There is a decrease of MSCs in the femoral head of patient with osteonecrosis**

- Hernigou P, Decrease in the mesenchymal stem-cell pool in osteonecrosis. *J Bone Joint Surg Br* 1999;81:349–55
- Calder JD, The extent of osteocyte death in the proximal femur of patients with osteonecrosis. *J Bone Joint Surg Br* 2001;83:419–22.
- Gangji V, Abnormalities in the replicative capacity of osteoblastic cells in osteonecrosis of the femoral head. *J Rheumatol*
- Suh KT, Kim SW, Roh HL, Youn MS, Jung JS Decreased osteogenic differentiation of MSCs. *Clin Orthop Relat Res* 2005;431:220–225
- Chang JK, Ho ML, Yeh CH, Chen CH, Wang GJ Osteogenic gene expression decreases in stromal cells of patients with osteonecrosis. *Clin Orthop Relat Res* 2006 453:286–292

**Autologous Concentrated Bone Marrow Grafting 1986 – 2017 (30 years)**

> 3000 hips



**PLAN**

- Rationale of the technique
- **Technique: how to get stem cells**
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**Bone marrow can be collected from either the anterior or posterior part of the iliac crest**

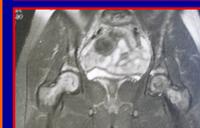


Supine position the patient permits the access to the anterior iliac crest (IC).

The trocard should remain well within the tables of the crest .

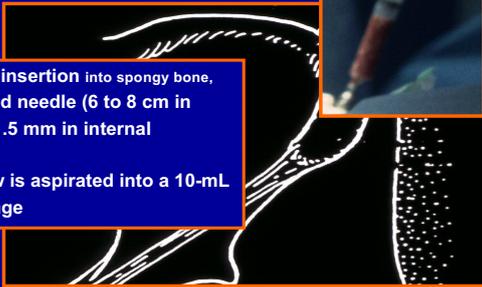


### Anatomy of the ilium



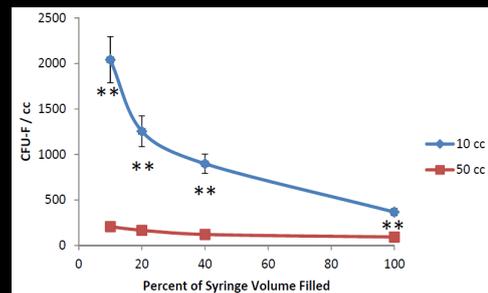
### Bone Marrow Aspiration Red marrow of the Iliac Crest

- After deep insertion into spongy bone,
- of a beveled needle (6 to 8 cm in length and 1.5 mm in internal diameter)
- the marrow is aspirated into a 10-mL plastic syringe



### MSCs obtained by aspiration.

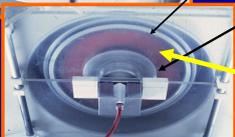
Hernigou; International Orthop 2014



### Concentration of Bone Marrow

After a 5 minutes centrifugation at 1200 g :

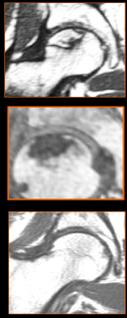
- The centrifugation forces the polynuclear cells (with the heavier nuclei) to be in the periphery where they can be removed
- The lighter anuclear red cells are found in the center and can also be removed
- Only mononuclear cells (with Stem Cells) are kept and useful for grafting



### PLAN

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**Qualitative Repair on MRI : Total Resolution**

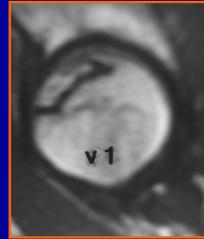


**Resolution of osteonecrosis may be observed at stage I**

- These osteonecroses had a normal fat intensity area with a marginal band like-pattern.
- During the resolution of disease, intra lesional area with low intensity on T1 images were observed before a return to a normal fat intensity area with disappearance of the marginal band like-pattern.
- Time for resolution may be as long as 10 years

**Qualitative Repair on MRI : Sub-total Resolution**

Stage I :  
Good functional result and spherical head without collapse  
But a small intra lesional area with low intensity on T1 remained on the MRI at the most recent follow-up at 15 years



**Qualitative Repair : Condensation on radiograph and CT-scan**

Stage II :  
Good functional result and spherical head without collapse at the most recent follow-up at **20 years**



**Anatomical evaluation of revascularization**  
Qualitative evaluation : macroscopic aspect

Same patient with bilateral osteonecrosis



Core decompression alone



Autologous bone marrow injection

**Anatomical evaluation of revascularization**  
Quantitative evaluation : microangiography



Stage II osteonecrosis treated without stem cells therapy

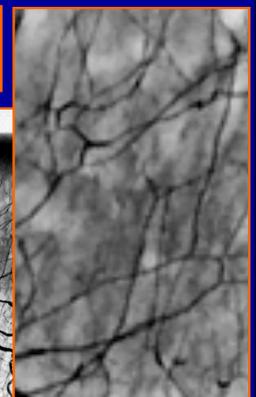
Injection of the circumflex artery on anatomical specimen after section of the neck during total hip arthroplasty :

No revascularization of the necrotic area

**Anatomical evaluation of revascularization**

Stage II osteonecrosis treated with MSCs

microangiography shows revascularization of the necrotic area



## 3-D microangiography of the femoral head

### Core decompression alone



### Autologous bone marrow injection



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International Orthopaedics (2018) 42:1639–1649  
<https://doi.org/10.1007/s00264-018-3941-8>

ORIGINAL PAPER



Cell therapy versus simultaneous contralateral decompression in symptomatic corticosteroid osteonecrosis: a thirty year follow-up prospective randomized study of one hundred and twenty five adult patients

Philippe Hemigou<sup>1</sup> · Arnaud Dubory<sup>1</sup> · Yasuhiro Homma<sup>1</sup> · Isaac Guissou<sup>1</sup> · Charles Henri Flouzat Lachaniette<sup>1</sup> · Nathalie Chevallier<sup>1</sup> · Hélène Rouard<sup>1</sup>

- ON related to corticosteroids during the period time from 1988 to 1998
- Bilateral osteonecrosis
- Both hips symptomatic and at the same stage on each side (I or II)
- Randomization by volume of ON
- Cell therapy on the size with larger volume
- Ministry Health Program

## Conditions for corticosteroids

- lupus erythematosus, uveitis, eosinophilic granuloma, multiple sclerosis, Crohn's disease, pemphigus vulgaris, nephrotic syndrome, liver transplantation, renal transplantation, aplastic anaemia, cardiac transplantation.....
- 65 patients cumulative **glucocorticoid dose > 4g**
- 35 patients glucocorticoid use **between 2g and 4g**
- 25 patients received < 2g.

## Hips

- stage I, 138 hips (69 patients);
- stage II 112 hips (56 patients).
- Same trocar; same technique
- core decompression one one side
- BM injection same day: The average total number of MSCs (counted as CFU-F) injected in hip was  $90,000 \pm 25,000$  cells (range 45,000 to 180,000 cells).
- Follow-up: 20 to 30 years; mean 25 years

## Bone marrow implantation decreased the number of hips that progressed to collapse:

- 250 hips included in the study (125x2)
- 35 hips had collapsed at the most recent follow-up after bone marrow grafting **28%**
- 90 after core decompression **72%**
- (28%, 35 among 125 versus 72%, 90 among 125; odds ratio 0.1512, 95% confidence interval [CI] 0.0871 - 0.2627; **P < 0.0001**).

### Bone marrow implantation decreased the need for primary total hip replacement.

- 95 THA (76%) in the CD group
- 30 THA (24%) with bone marrow graft ( $p < 0.0001$ ).

### Bone marrow decreased the need for revision and re-revision of total hip replacement

- CD: 45 of 95 THA required one revision (second THA) and 5 of these 45 hips a re-re-revision (at 18, 22, 26, 29 years FU after core decompression).
- BM: 2 of 30 THA had a revision

### Bone marrow injection improved the repair process on MRI

- There was a significant difference ( $p < 0.0001$ ) in the number of hips with repair between hips with core decompression alone and hips with BM.
- For hips with repair, there was a significant difference in the volume of repair between hips with core decompression and hips with bone marrow injection:
- For hips treated with BM injection, volume decrease from 45% to 17%, as percentage of the volume of the femoral head,
- With CD decrease moved from 35.8 % to 27.6 %.

### Discussion

- Better results for stage I and II
- Better results for small volume
- This rough estimate of effect size and effect stage in the same patient in a series with the cause of ON is the same may explain various odds for conversion to THA in the literature when the cell therapy is compared to the core decompression in different patients with different causes of ON, and when volume and stage of ON are not matched

### PLAN

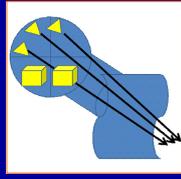
- History
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### NORMAL FEMORAL HEAD

Hernigou – JBJS A 1997 – JBJS B 1999  
Homma Y, Kaneko K, Hernigou Int Orthop. 2013

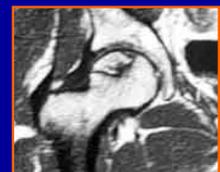
- Average  $700 \pm 264$  MSCs per  $\text{cm}^3$  with average volume of  $50 \text{ cm}^3$ ,
- 35 000 MSCs may be considered as a useful approximation of the number of MSCs present in a femoral head.

This number may be considered as the target number to load in a femoral head with osteonecrosis to have the same number of MSCs than in a normal femoral head.



### Femoral Head with Osteonecrosis

- Necrosis area : no MSCs
- Outside : decreased to 200 MSCs per  $\text{cm}^3$



**Total < 3000 MSCs**

## Theoretical Assessment of MSC Levels in Treating ONFH

- A normal 50 cm<sup>3</sup> femoral head contains approximately 36 000 MSCs
  - In a 30% Osteonecrosis : 12 000 MSCs are missing in the femoral head
  - **Only 30% to 50% of the injected stem cells remain in the femoral head** (studied by Hernigou and Gangji)
  - That means that it is necessary to inject at least 12 000 x3 = 36 000 MSCs
- Depending of the volume, of the cause of osteonecrosis, unilaterality or bilaterality.....

## Other techniques of graft improvement Work in progress – Tissue Engineering

### CELLS PRODUCTION

Expansion of the number of Autologous Cells by culture :  
- with or without scaffold  
- +/- growth factors

Allogenic stem cells grafts

Genetic Therapy

### WAY OF ADMINISTRATION

Directly in bone with scaffold

Intra-arterial circumflex injection

Intravenous injection for multifocal osteonecrosis

International Orthopaedics  
https://doi.org/10.1007/s00264-018-3953-4

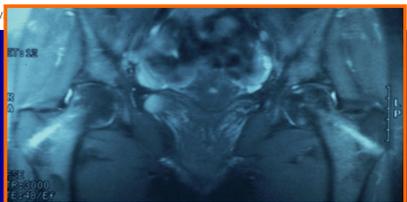
ORIGINAL PAPER

CaseMark

### Stem cell therapy in bilateral osteonecrosis: computer-assisted surgery versus conventional fluoroscopic technique on the contralateral side

Philippe Hernigou<sup>1</sup> · Benjamin Thiebaut<sup>1</sup> · Victor Housset<sup>1</sup> · Claire Bastard<sup>1</sup> · Yasuhiro Homma<sup>1</sup> · Younes Chaib<sup>1</sup> · Charles Henri Flouzat Lachaniette<sup>1</sup>

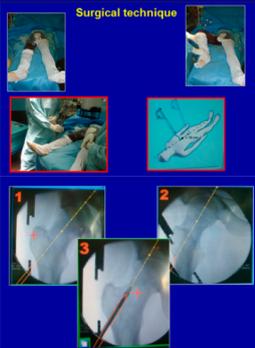
Received: 11 April 2018 /  
© SSOOT 2018



### Computer-Assisted Navigation Instrumentation



### Surgical technique




## Results

- Each side: same volume of concentrated bone marrow and number of cells.
- The average total number of MSCs counted as CFU-F injected in each hip, was 110,000 ± 27,000 cells (range 50,000 to 190,000 cells).
- Using computer navigation tool
  - fewer attempts to position the trocar,
  - used less fluoroscopy time,
  - and decreased the radiation exposure
- Increasing the precision with computer navigation resulted
  - in less collapse (7 versus 1)
  - and better volume of repair (13.4 versus 8.2 cm<sup>3</sup>) for hips treated with the computer-assisted technique.

## Expansion of the number of Autologous Cells by culture for osteonecrosis (Reborn study)

- **Gangji V, Hauzeur JP**  
Cellular-based therapy for osteonecrosis.  
*Orthop Clin N Am* 2009; 40:213–221
- **Liu L, Sun Z, Chen B, Han Q, Liao L, Jia M, et al.**  
Ex vivo expansion and in vivo infusion of bone marrow-derived Fik-1 + CD31-CD34- mesenchymal stem cells: feasibility and safety from monkey to human.  
*Stem Cells Dev* 2006;15:349–57.
- **Rackwitz et al.**  
Stem cell- and growth factor-based regenerative therapies for avascular necrosis of the femoral head  
*Stem Cell Research & Therapy* 2012; 3:7
- **Zhao D, Cui D, Wang B, Tian F, Guo L, Yang L, et al.**  
Treatment of early stage osteonecrosis of the femoral head with autologous implantation of bone marrow derived and cultured mesenchymal stem cells.  
*Bone* 2012;50:325–30.

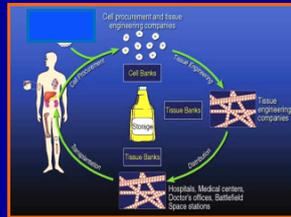
## Allogenic Stem Cells Grafts

### Indication :

Patients with impossibility to get enough autologous stem cells even after expansion

**Intravenously** delivery of **allogenic** bone marrow-derived stem cells

Hernigou P, Bernaudin F, Reinert P, Kuentz M., Vernant J.P.  
Bone marrow Transplantation in Sickle Cell Disease: effect on osteonecrosis.  
J. Bone and Joint Surgery 1997, 79-A, 1726-1730.



## First Conclusion

**Autologous concentrate Bone Marrow : safety and efficiency**

### • Efficiency :

– A 25 years experience with more than 2000 hip osteonecroses

### • Indications:

– Stage I and II  
– Stage III with crescent line or collapse < 2mm

### • Etiologies:

– Sickle cell disease; alcohol abuse; corticosteroids, idiopathic...

### • Safety :

– Very few complications (per-operative hypotension : 2 cases)  
– No fractures when using a small diameter trocar (4 mm)  
– Patients treated with cell therapy do not have a greater incidence of cancer than the rest of the population \*

\*Hernigou P, Homma Y, Flouzat-Lachaniette CH, Pognard A, Chevallier N, Rouard H.  
Cancer risk is not increased in patients treated for orthopaedic diseases with autologous bone marrow cell concentrate.  
J Bone Joint Surg Am. 2013 Dec 18;95(24):2215-21.

## Second Conclusion

**Work is in progress**

### • Expansion or allogenic stem cells could be necessary in some indications :

– Patients with stem cells deficiency such as post-chemotherapy...  
– Patients with multifocal osteonecrosis (Sickle cell disease)

### • Allogenic grafts are already possible :

– but total immunological safety is not proved

### • Expansion is promising but

– Still in experimentation  
– Cost is very high as compared with concentration  
– Safety is not proved

**THANK YOU FOR YOUR ATTENTION**