

**MiSOT V**

5<sup>th</sup> Expert Meeting



# MSC in clinics: Liver transplantation

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Bergamo, Italy



# **INFUSION OF THIRD-PARTY MESENCHYMAL STEM CELLS (MSC) AFTER KIDNEY AND LIVER TRANSPLANTATION: A PHASE I-II, OPEN-LABEL, CLINICAL STUDY**

**(EudraCT 2011-001822-81 & NCT01429038)**

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**LGCT**

# LCGT

- Hematology department (Pr Yves Beguin)
- best clinical practice to GMP
- Clinical grade, ready to use, third-party MSC
- Several clinical trials
  
- Clinical grade Tregs for future trials



# Active MSC Clinical Trials

## HSCT

1. **TJB0703:** Infusion of MSC as treatment for steroid resistant grade II to IV acute GVHD or poor graft function
2. **TJB0603:** Randomized double-blind study of mesenchymal stem cells (MSC) in patients undergoing matched unrelated allogeneic bone marrow or peripheral blood stem cell transplantation - A European multicentre study
3. **TJB0909:** Co-transplantation of MSC and HLA-mismatched allogeneic hematopoietic cell after nonmyeloablative conditioning: a phase II randomized double-blind study.
4. **TJB0905:** A pilot study to assess the feasibility of unrelated UCB transplantation with coinfusion of third-party MSC after myeloablative or non-myeloablative conditioning in adult patients with hematological malignancies

# Active MSC Clinical Trials

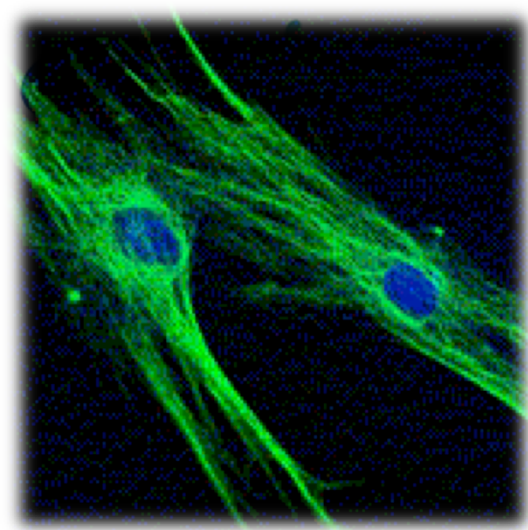
## Non-HSCT

1. **TJT1106**: Infusion of third-party mesenchymal stem cells after renal or liver transplantation: a phase I-II, open-label, clinical study
2. **TJT1123**: Mesenchymal stem cell therapy for the treatment of severe or refractory inflammatory and/or autoimmune disorders



<b>1</b>	<b>Recruiting</b>	<u><a href="#">MSC and HSC Coinfusion in Mismatched Minitransplants</a></u> <b>Conditions:</b> Leukemia, Myeloid, Acute; Leukemia, Lymphoblastic, Acute; Leukemia, Myelocytic, Chronic; Myeloproliferative Disorders; Myelodysplastic Syndromes; Multiple Myeloma; Leukemia, Lymphocytic, Chronic; Hodgkin's Disease; Lymphoma, Non-Hodgkin <b>Interventions:</b> Biological: Mesenchymal stem cells; Other: Isotonic solution
<b>2</b>	<b>Recruiting</b>	<u><a href="#">Mesenchymal Stem Cells After Renal or Liver Transplantation</a></u> <b>Conditions:</b> Liver Failure; Kidney Failure <b>Intervention:</b> Biological: Mesenchymal Stem Cells
<b>3</b>	<b>Recruiting</b>	<u><a href="#">Mesenchymal Stem Cell Infusion as Treatment for Steroid-Resistant Acute Graft Versus Host Disease (GVHD) or Poor Graft Function</a></u> <b>Conditions:</b> Graft-versus-host Disease; Poor Graft Function <b>Intervention:</b> Biological: Mesenchymal stem cells
<b>4</b>	<b>Not yet recruiting</b>	<u><a href="#">Treatment of Atrophic Nonunion Fractures by Autologous Mesenchymal Stem Cell Percutaneous Grafting</a></u> <b>Condition:</b> Nonunion Fracture <b>Interventions:</b> Biological: Mesenchymal Stem Cells; Other: Culture medium without MSC.
<b>5</b>	<b>Recruiting</b>	<u><a href="#">Mesenchymal Stem Cell Therapy for the Treatment of Severe or Refractory Inflammatory and/or Autoimmune Disorders</a></u> <b>Condition:</b> Crohn's Disease <b>Intervention:</b> Biological: Mesenchymal Stem Cells (MSC)
<b>6</b>	<b>Completed</b>	<u><a href="#">Mesenchymal Stem Cell Infusion as Prevention for Graft Rejection and Graft-versus-host Disease</a></u> <b>Condition:</b> Hematological Malignancies <b>Intervention:</b> Procedure: Mesenchymal stem cell infusion





# Mesenchymal Stem Cells

MSC: technical aspects

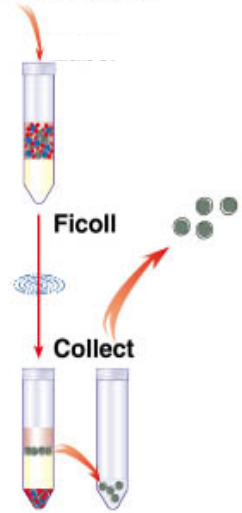
# MSC production

- Collect 30-60 ml BM healthy allogeneic volunteers
- Day 0: culture initiation (MNC obtained by ficoll isolation):  
DMEM-Glu + 10% FBS + 1% Pen/Strep
- 2X/week: medium exchange
- Day 14: 1st passage (trypsinisation et replating)
- Day 21: 2<sup>nd</sup> passage
- Day 28: Harvest and freezing

# MSC Production

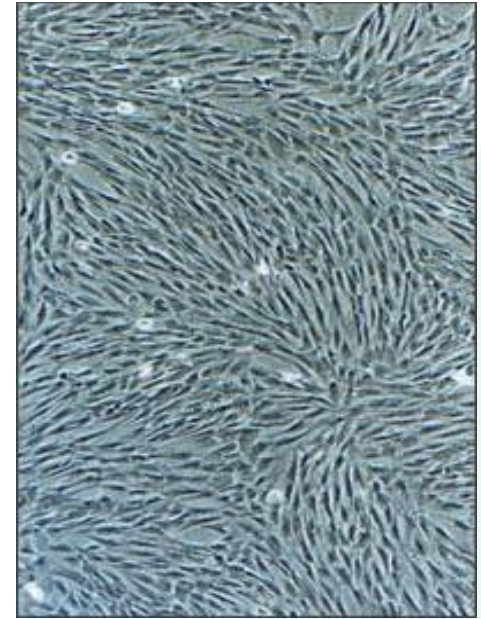
Enrichment

Unprocessed Bone Marrow



EBMT procedure

MNC culture initiation  
(DMEM + FBS + Pen/Strep)



MSC

Day 0

Day 14 P1

Day 21 P2

Day 28 harvest and  
freezing in aliquots

Cell feeding 2x/week

Quality Controls

# MSC Production

Enrichment



EBMT procedure

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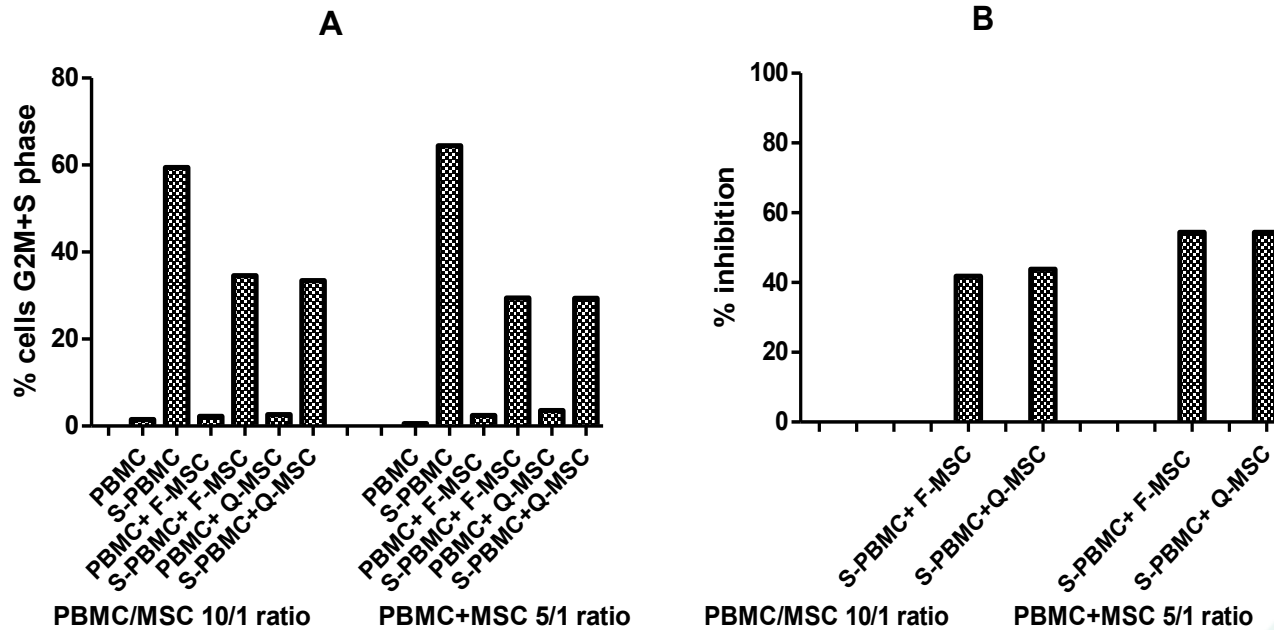
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Quality Controls

# Release Criteria

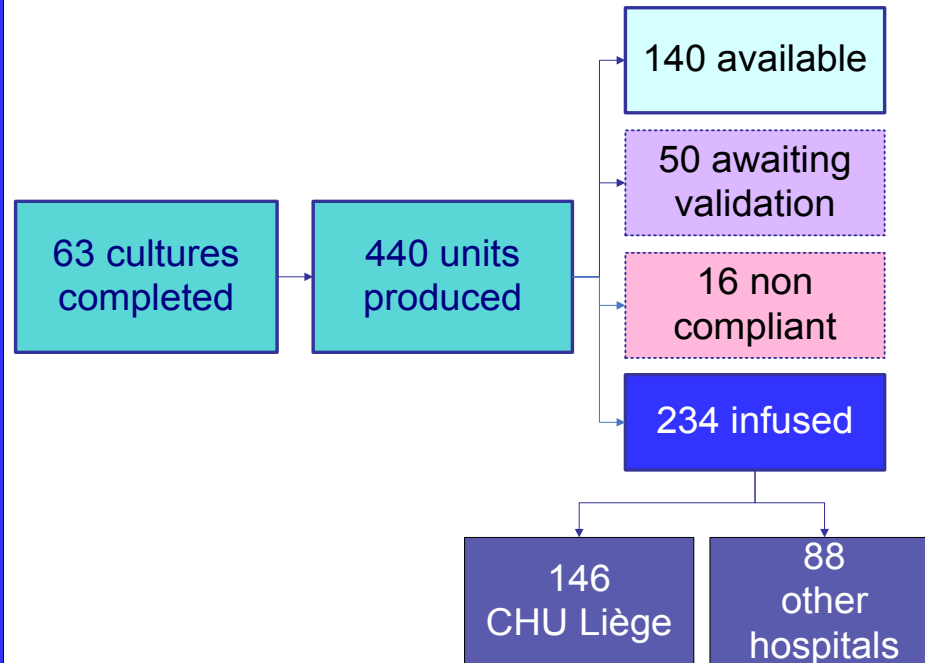
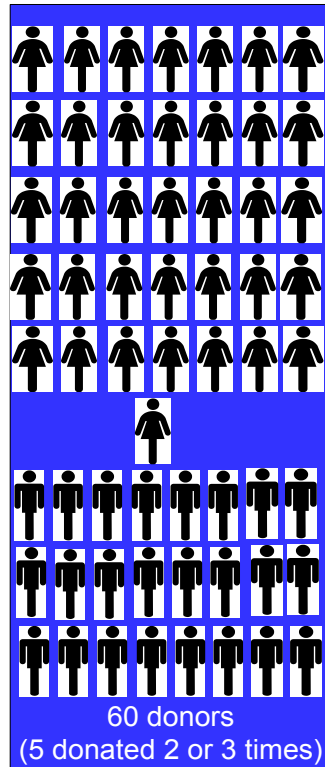
- Donor:
  - Serology, clinical examination and consent
- MSC Product :
  - Sterility
  - Endotoxins and mycoplasma free
  - Phenotype :
    - **CD105+, CD90+, CD73+**
    - **CD34-, CD45-, CD14- CD3-**
  - Fibroblastic morphology
  - No aggregates
  - Normal karyotypes
  - Immunosuppressive *in vitro*

## Inhibition of PBMC proliferation by third party MSC

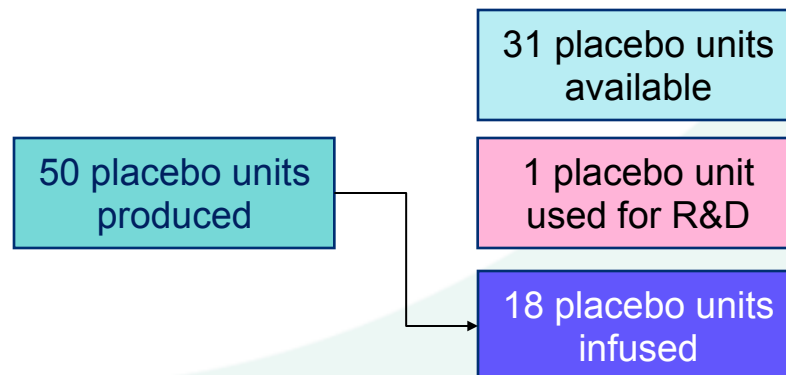


PBMC (100,000 or 50,000) were stimulated (S-PBMC) with anti- $\alpha$ CD3/CD28 microbeads during 4 days with or without irradiated (25 Gy) MSC (10/1 or 5/1 PBMC/MSC ratios) added at the beginning of the culture. Proliferation was assessed by analysis of the cell cycle by flow cytometry. Results are expressed as the percentage of cells present in S+G2M phases (A) and as the percentage of inhibition compared to the stimulated PBMC condition alone (B).

# MSC Bank in Liège (12-2006 to 03-2014)



- UCL St Luc Brussel
- UZ Brussel
- KUL Leuven
- UZG Gent
- UZA Antwerpen
- ZNA Stuivenberg
- AZ St Jan Brugge
- UZ Gasthuisberg
- Mont-Godinne Yvoir
- ...





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# Background

- MSC may have an immunosuppressive effect
- MSC may be used in GVHD after SCTx
- MSC may have an effect in organ regeneration

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- MSC may be used in GVHD after SCTx
- MSC may have an effect in organ regeneration
  
- Role after organ transplantation ???
  - safety?
  - efficacy?

# Objectives

- Primary endpoint: safety for LT & KT recipients
  - tolerability of infusion
  - infections (bacterial, viral, fungi)
  - cancers (PTLD, others)
  - patient and graft survivals

# Objectives

- Primary endpoint: safety for LT & KT recipients
  - tolerability of infusion
  - infections (bacterial, viral, fungi)
  - cancers (PTLD, others)
  - patient and graft survivals
- Secondary endpoint 1: immunosuppression
  - rejection rate
  - biopsy
  - blood immune profile
- Secondary endpoint 2: graft function & biopsy

# M&M

- Cadaveric liver & kidney recipients
- Classical immunosuppressive management
- Dose: 1.5 to  $3 \times 10^6$ /kg MSC
- Central IV injection at day 3 +/-2 post Tx

# M&M: liver 1

- Liver transplantation
  - 2 groups: -10 MSC +  
-10 MSC -
  - no randomisation, no double-blind
  - regular immunosuppression (Tac-MMF-steroids)
  - protocol biopsy at month 6 in both groups
- MSC group:
  - tapering of Tac from month 6 to 9, then biopsy
  - tapering MMF from month 9 to 12

# M&M: liver 2

- Inclusions:
  - liver candidates between 18 to 75y
- Exclusions:
  - history of K except HCC within Milan
  - active infection (D and R), including HCV, HIV
  - EBV negative
  - reTx, combined Tx, LRLTx
  - autoimmune
  - intubation
  - clinical problem at the time of injection

# M&M: liver 3

- Tacrolimus: 8-12 for one month, 5-8 after one month
- MMF: 2x500mg/d
- Steroids:
  - Solumedrol: 500 mg d0, 125 mg d1, 80 mg d2, 40 mg d3
  - Medrol:
    - 32mg d4 to 6, 16mg d7 to 9,
    - 8mg d10 to 12, then 4 mg until day 30
- Antibiotics:
  - cefuroxime 3x1.5g or piperacillin-tazobactam for 5 days
  - co-trimoxazole 500 mg po 1/d for three months
  - CMV prophylaxis if D+/R-



# M&M: kidney 1

- Kidney transplantation
  - 2 groups:    -10 MSC +  
                         -10 MSC –
- - regular immunosuppression (antiIL2-Tac-MMF-steroids)
  - biopsy at month 3 in both groups
  - weaning of steroids

# M&M: kidney 2

- Inclusions:
  - kidney candidates between 18 to 75y
- Exclusions:
  - history of K
  - active infection (D and R), including HCV, HIV
  - EBV negative
  - reTx, combined Tx, LRLTx
  - presumed impossibility to wean steroids
  - intubation
  - clinical problem at the time of injection
  - PRA >50%

# M&M: kidney 3

- Anti-IL2 day 0 & 4
- Tac: 12-15 for one week, 8-12 for three months
- MMF: 2x1000mg/d
- Steroids:
  - Solumedrol: 500 mg d0, 125 mg d1
  - Medrol:
    - 16mg d2 to d21
    - 12mg d22 to d42
    - 8mg d43 to 63
    - 6 mg d64 to 84
    - 4mg d85 to 90
- Antibiotics:
  - cefuroxime 3x1.5g or piperacillin-tazobactam for 1 day
  - co-trimoxazole 500 mg po 1/d for three months
  - CMV if D+/R-

# M&M

- Blood: FACS, Tregs, Ig, anti-HLA
- Biopsies:
  - Histology
  - Immunohistology: C4d, CD3, CD4, CD8, CD20, CD138, CD68, CD1a, FoxP3, CMV, EBV, Hbs
- Banking of serum & biopsies

# Update

- Started in early 2012
- Liver Transplantation
  - 10 MSC treated, 10 controls  
(last February 2014)
- Kidney transplantation
  - 4 MSC treated, 4 controls

# Liver recipients

		MSC+ (n=10)	MSC- (n=10)	<i>P</i>
<b>Age (years)</b>		62.5 (47-74)	58 (52-69)	0.516
<b>Male/Female</b>		8/2	7/3	1
<b>Lab MELD</b>		16.5 (6-29)	15 (8-38)	0.491
<b>BMI</b>		25.7 (20.9-38.2)	25.6 (22.2-33.0)	0.541
<b>Liver disease</b>				
	Post alcoholic cirrhosis	5	5	
	NASH	3	0	
	HCC	2	5	

Median (Ranges) or *n* (Mann Whitney or Fischer test)

# Liver donors & Transplantations

	MSC+ group (n=10)	Control group (n=10)	<i>P</i>
Age (years)	57 (17-77)	54 (18-79)	0.985
Male/Female	4/6	6/4	0.656
CPR (Y/N)	4/6	3/7	1
Donor type (DBD/DCD)	4/6	5/5	1
BMI (kg/m <sup>2</sup> )	24 (21-31)	25 (22-29)	0.510
Intensive care stay (days)	4 (1-75)	6.5 (2-29)	0.401
Urinary output (mL/h)	82 (7-160)	127.5 (47-357)	0.096
Pressors (Y/N)	5/5	6/4	1
Na (mmol/L)	144 (133-155)	144.5 (141-160)	0.445
Total bilirubin (mg/dL)	0.35 (0.30-1.59)	0.32 (0.15-0.85)	0.668
AST (U/L)	38 (23-190)	48.5 (26-91)	0.615
GGT (U/L)	59.5 (14-256)	68 (12-144)	0.888
CIT (min)	229 (149-800)	345 (181-713)	0.386
TIT (min)	317.5 (186-831)	402.5 (216-754)	0.519

Median (Ranges) or *n* (Mann Whitney or Fischer test)

# MSC injection in LT recipients

	Per protocol	Study (Median) (IQR; Ranges)
MSC Injection day	day 3 +/- 2	3 (3-3.25; 2-5)
Dose MSC ( $10^6$ /kg)	1.5-3	2.1 (2.0-2.4; 1.9-2.7)
Injection volume (ml)		342 (322-469; 306-614)
Injection duration (min)		25 (16.2-40; 11-60)

Median (IQR; Ranges)

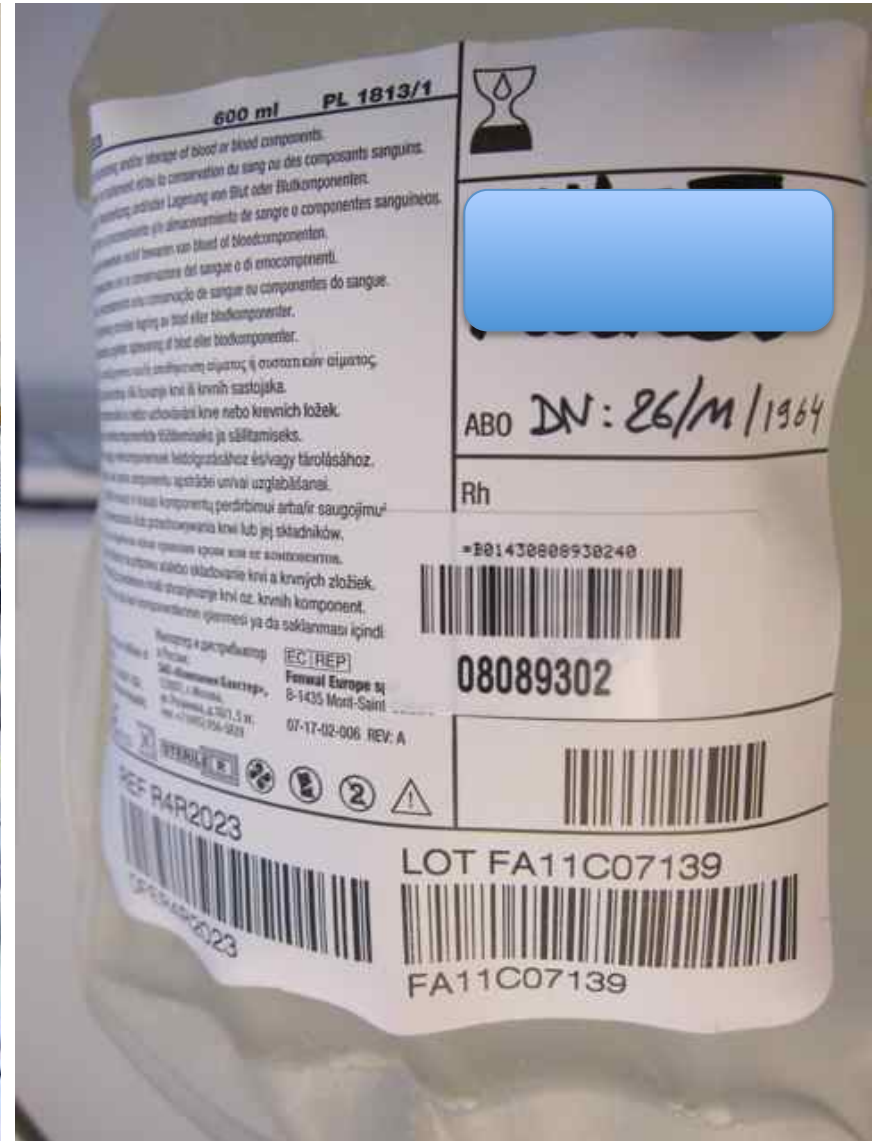


# Infusional toxicity

	Pre Infusion	15 min	End of infusion	<i>P</i>
Body temperature (°C)	36.0 (35.4-37.7)	36.3 (35-36.9)	36.2 (35.5-37)	0.869
Mean PA (mmHg)	103.3 (87-124)	107 (84-119.5)	106 (94-115)	0.830
NI O2 saturation	99 (93-100)	100 (92-100)	97.5 (93-100)	0.670

Median (Ranges) (Friedman test & ANOVA)

- No hepatic artery or portal vein thrombosis
- No sign of pulmonary embolism
- No post infusional intubation
- No anaphylactic reaction, no skin reaction
- No increase of 30 days mortality
- No increase in opportunistic infection rate



# Issues

- MSC have to be thawed and infused within one hour
  - problems for intra operative infusion
  - 24/7 open GMP lab
- Next step?
  - 2 injections ?
- Multicenter blinded phase 3 study ?
- Any idea or collaboration is welcome
- Active MISOT participation?

# Thanks to:

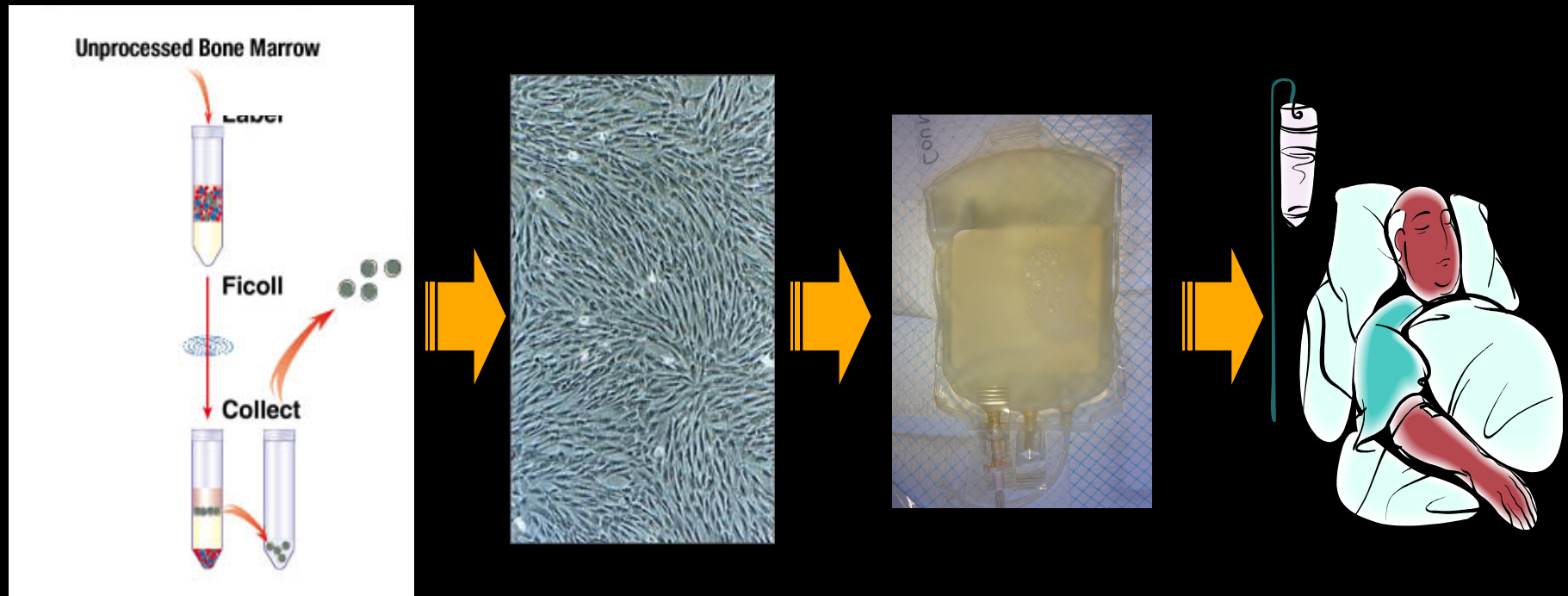
- **Hematology & LTCG**
  - Pr Y Beguin, Pr F Baron, Dr E Baudoux, Mrs C Lechanteur
- **Surgery & Transplantation**
  - Pr O Detry, Pr A Deroover, Dr N Meurisse, Mrs MH Delbouille, Dr Vandermeulen
- **Nephrology**
  - Dr L Weekers, Dr C Bonvoisin, Dr F Jouret, Dr P Erpicum
- **Pathology**
  - Pr P Delvenne, Dr J Somja Dr N Blethard

# Sponsors



# ALLOGENEIC MSC

## Immunosuppressive therapy



Bone marrow  
collection  
(volunteer)

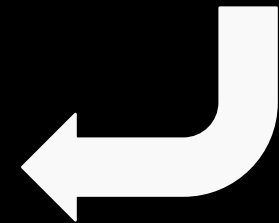
Culture  
(3-4 weeks)

Freezing &  
banking

Thawing &  
infusion

### 6 clinical trials

- 4 in bone marrow transplantation
- 1 in liver/kidney transplantation
- 1 in auto-immune diseases



# ALLOGENEIC MSC

## BHS transplant clinical network

