Les cellules souches du cordon ombilical dans le traitement du sepsis :

exemples d'applications dans le choc septique et les formes graves de COVID19

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UMR CNRS 7365 IMoPA

U1116 INSERM DCAC (collaboration)

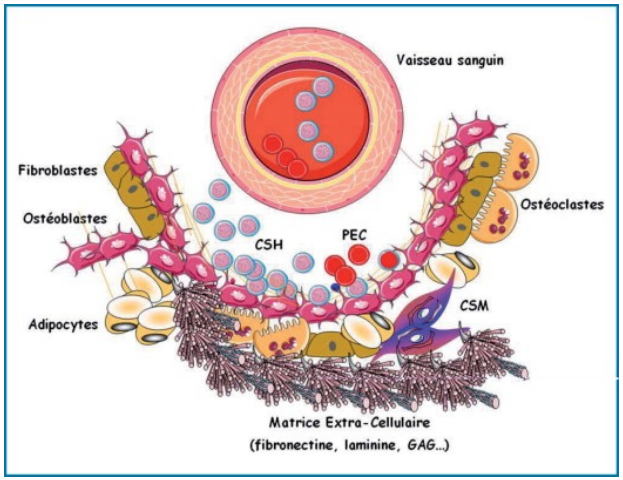
StemInov

12 Octobre 2022

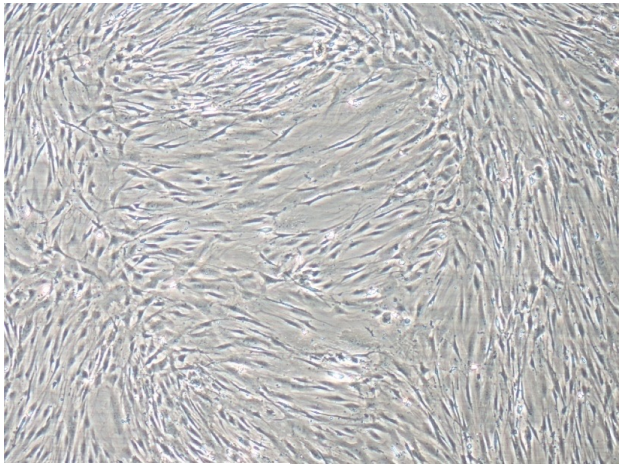
Académie Lorraine des Sciences

Mesenchymal Stromal Cells (MSCs)

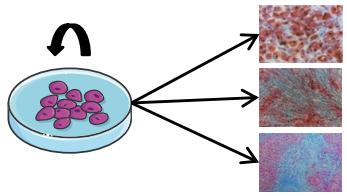
Characteristics



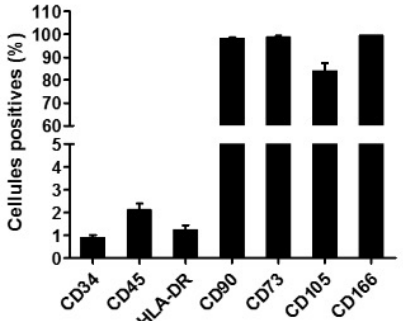
Lataillade et al. 2010

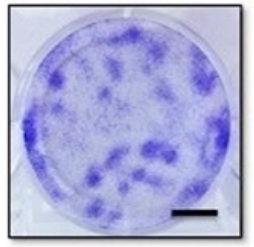


ISCT



Phénotype membranaire	
Positif	Négatif
CD73	HLA-DR
CD90	CD34
CD105	CD45





Clonogenic capacity

- **No HLA class II molecules**
- **Low expression of HLA class I molecules**
- **No CD80 CD86**

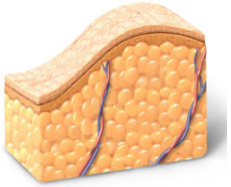
ALLOGENEIC USE

Sources

MSC Sources

Adult

Bone Marrow



Adipose tissue

Dental pulp

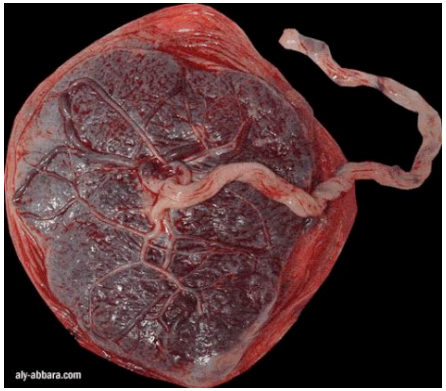
Synovial membrane,

Periost,

Menstrual blood…

Fetal

- **Placenta**
- **Amniotic bag**
  - ✓**Amniotic Membrane**
  - ✓**Chorionic membrane**
- **Amniotic fluid**
- **Umbilical cord**
  - ✓**Cord blood**
  - ✓**Wharton Jelly**



WJ-MSCs

Wharton's Jelly

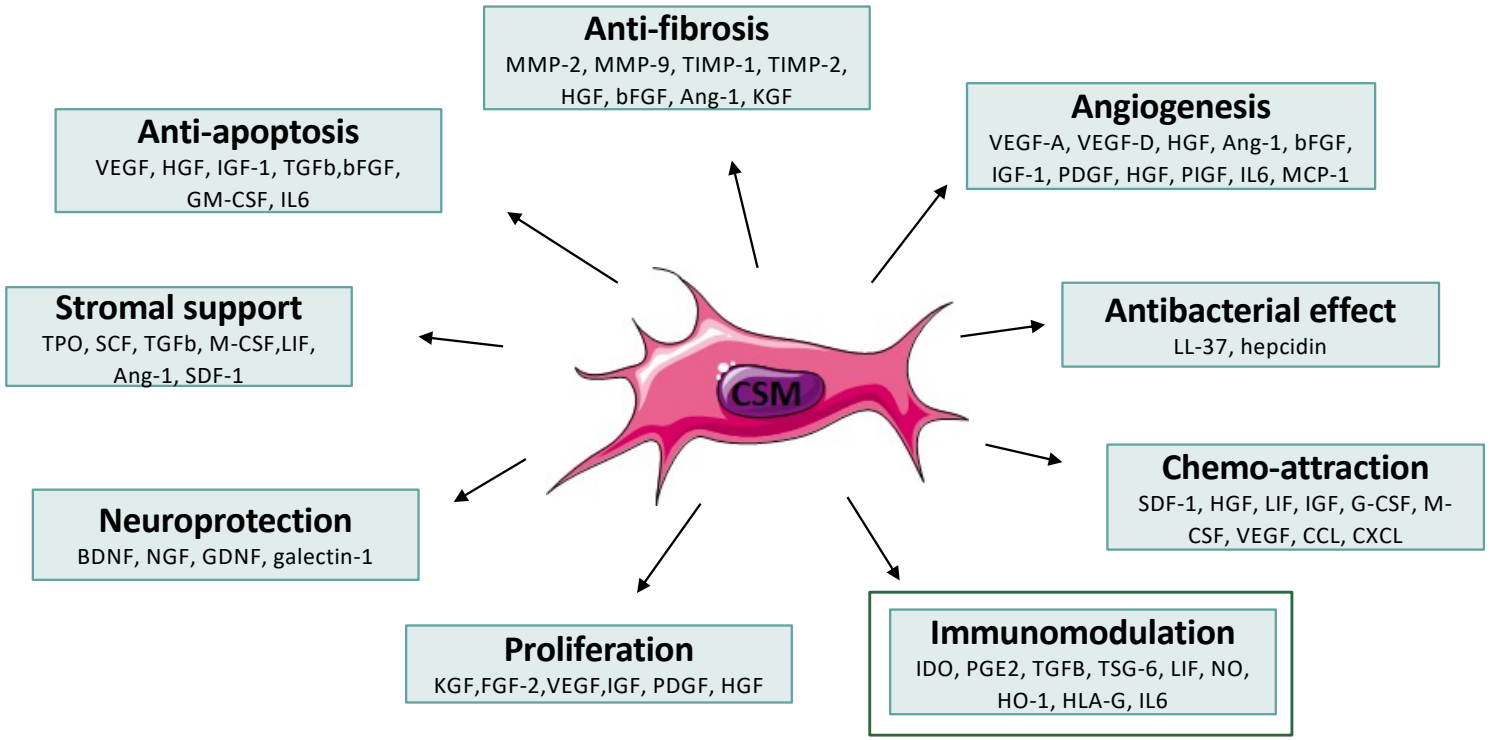
- **Immaturity**
- **Increased plasticity**
- **Easy collection**
- **Few ethical problem**

Donor variations

Main properties

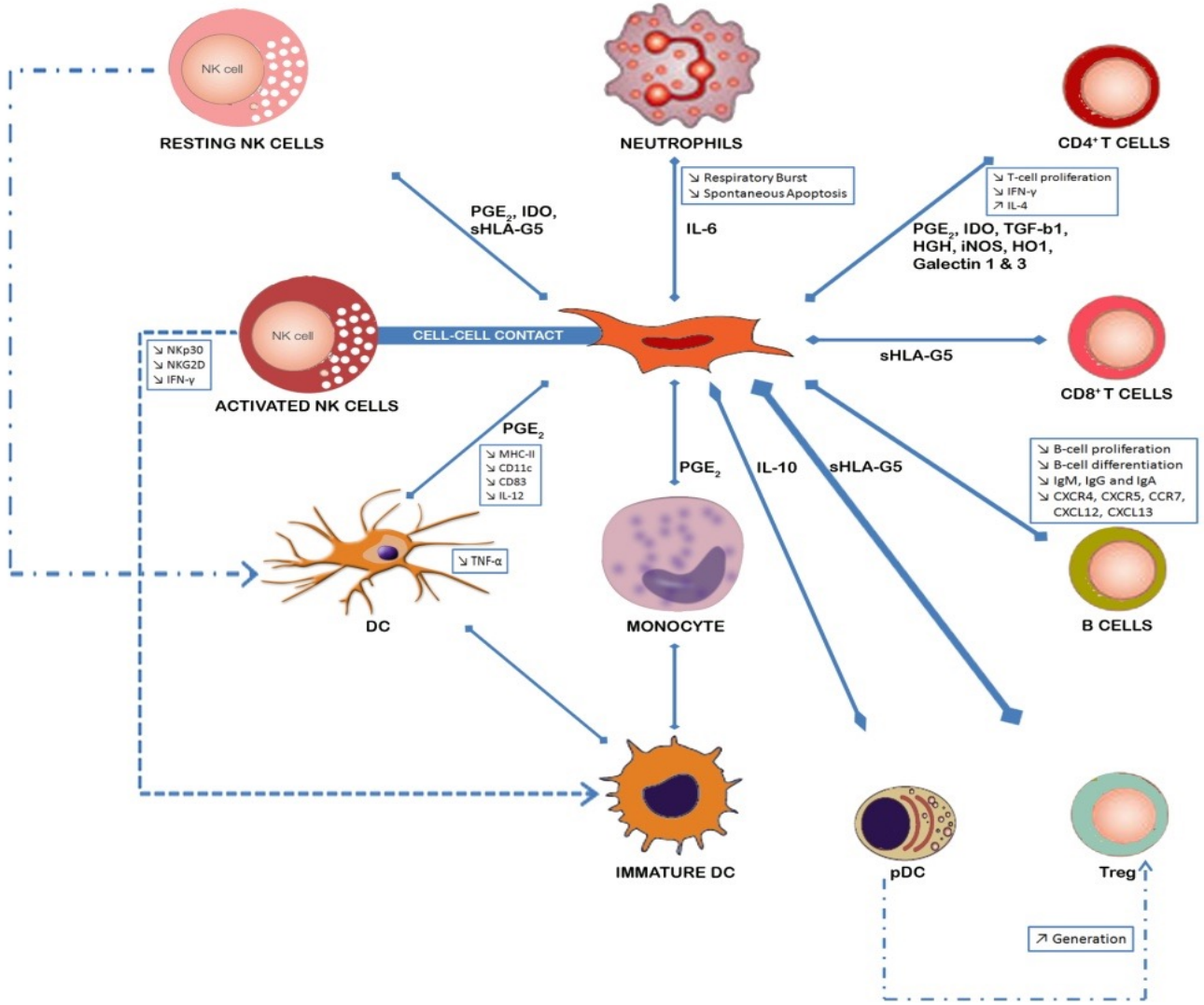
Soluble factors, Extracellular vesicules

cytokines, chemokines, Growth factors, miRNA….

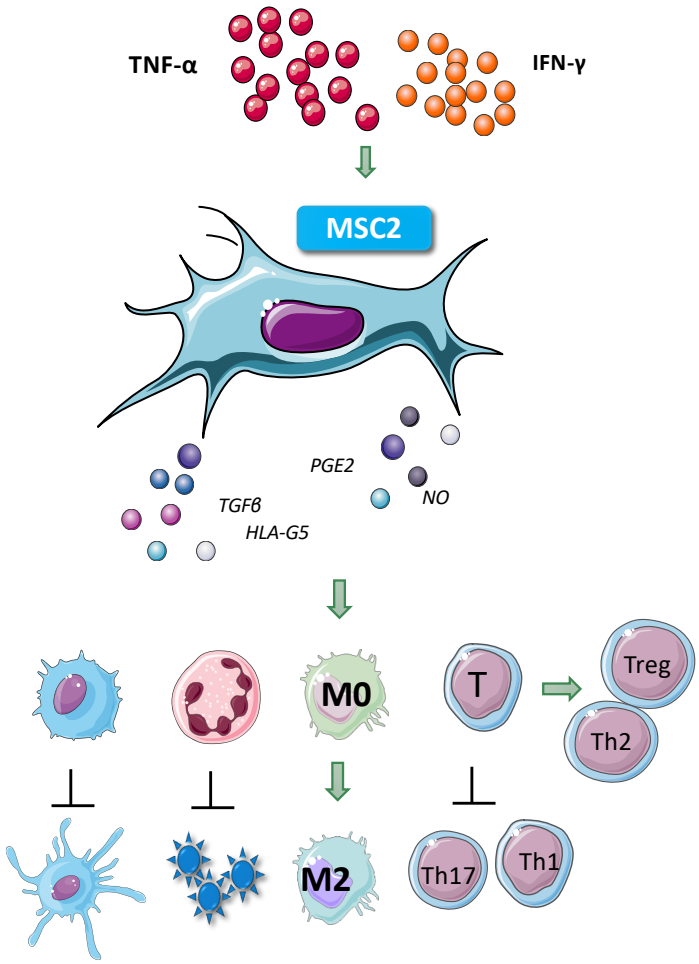


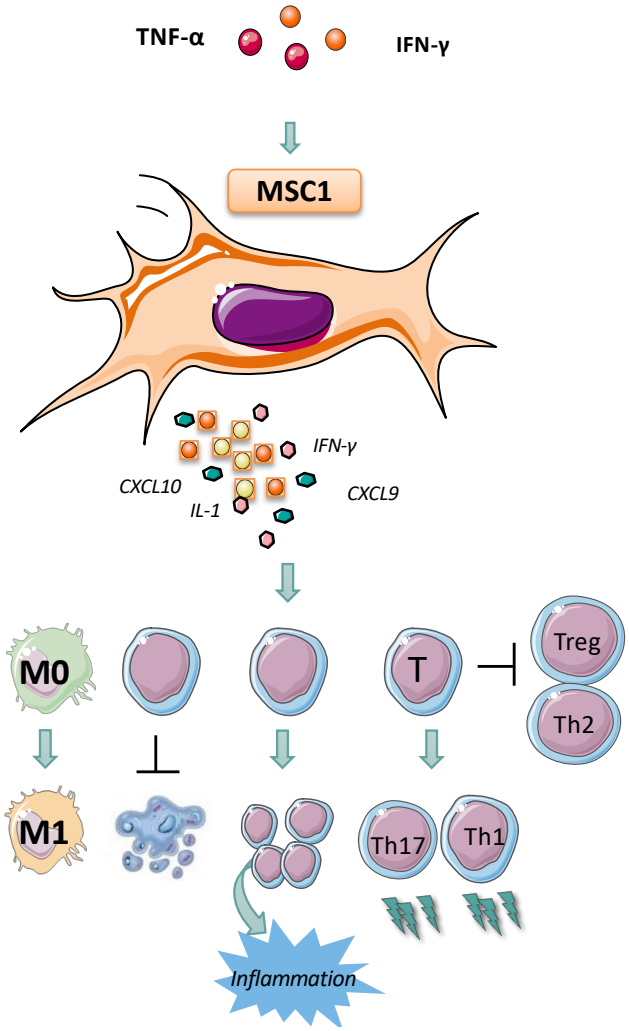
D'après Maumus et al 2013

Immunomodulatory properties



Mesenchymal Stromal Cells: double phenotype





Sepsis and Septic Shock

Sepsis and septic shock

Pathogen Infection

↓

Dysfonction of host response to the infection

↓

Organ Failure → life-threatening

↓

Major public health issues: - death rate : 46,7%
- 11th cause of death

Consensus conference 2016

Suspected infection

↓ Yes

SOFA Score > or = 2

↓ Yes

SEPSIS

↓

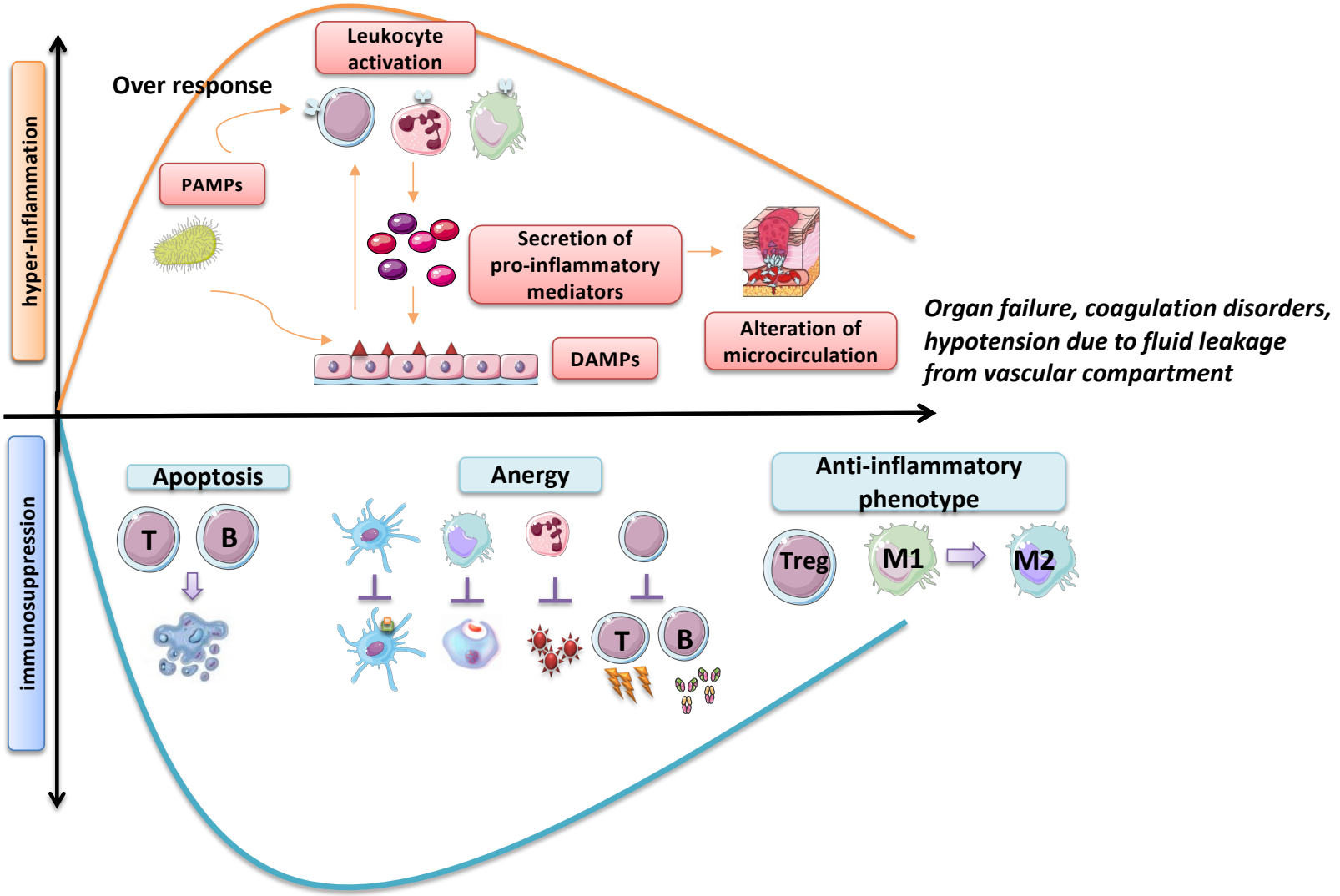
- *PAM<65 mmHg despite vascular filling*
- *Lactatemia > 2mmol/L*

↓ Yes

SEPTIC SHOCK

Septic shock Pathophysiology

Dynamic model with concomitant inflammatory and anti-inflammatory states



Treatment of Septic shock

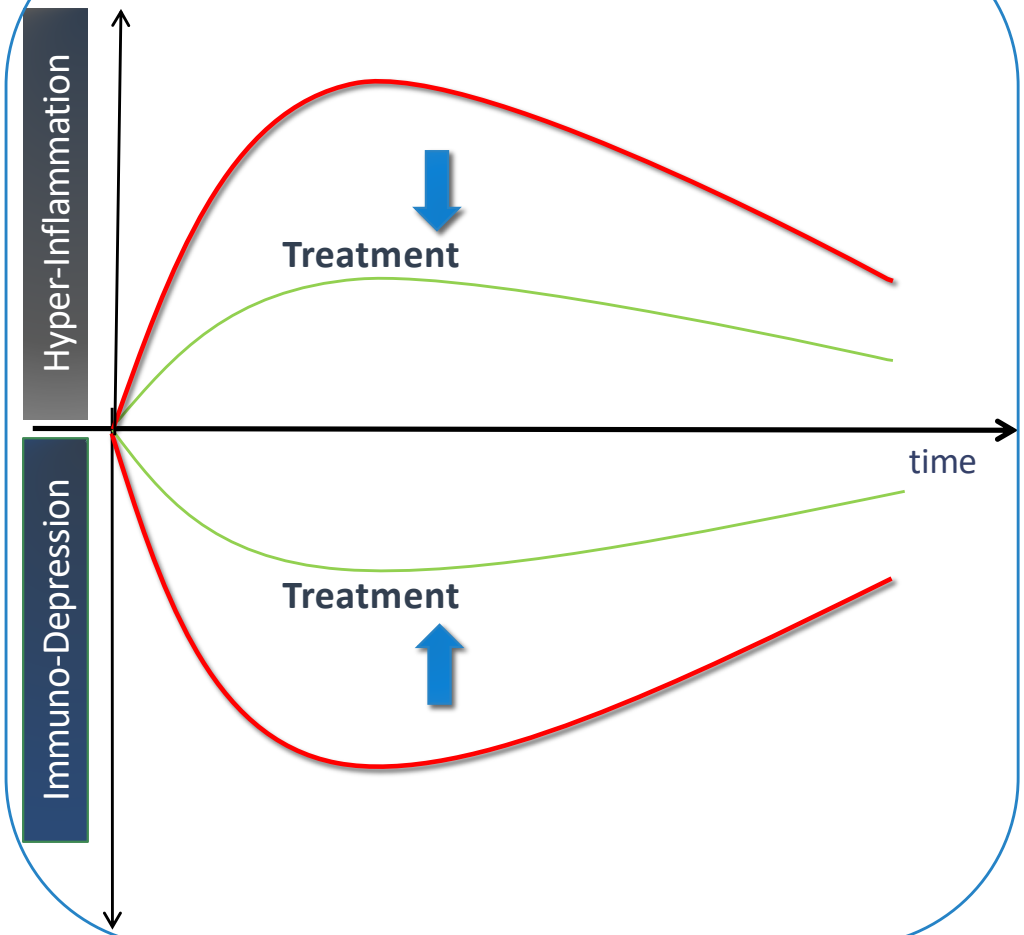
Current Therapeutic care

No specific treatment available
Management is only symptomatic and consists in resuscitation, antibiotic and catecholamine infusions.

1- Antibiotics
2- Vascular filling and maintaining of arterial pressure
3- Preservation of organs (hemodialysis)

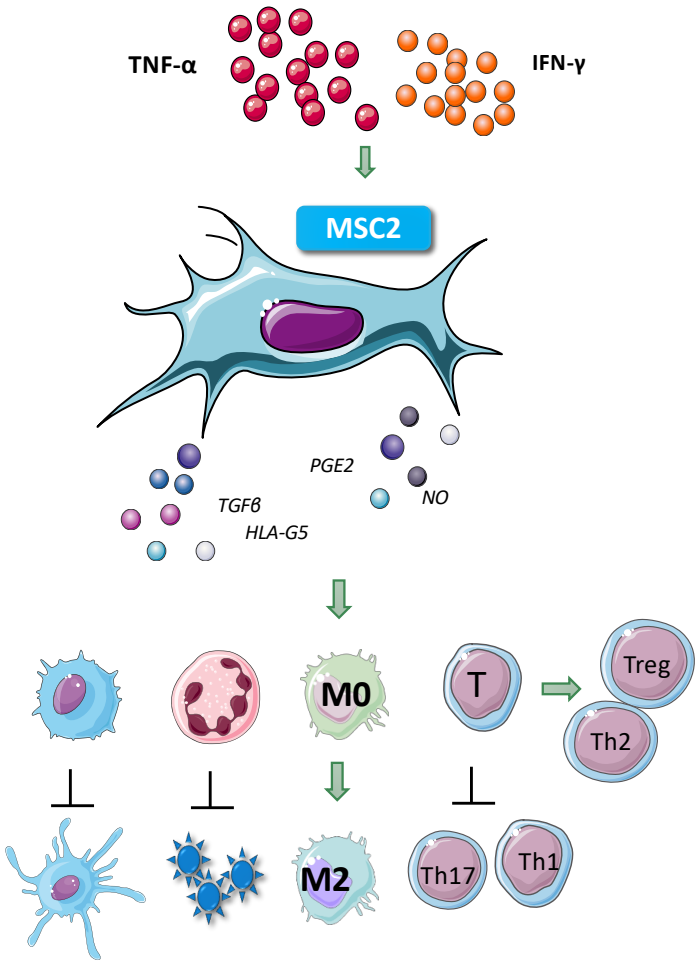
Failure of exclusively anti-inflammatory treatments
(anti-TNFα, etc…)

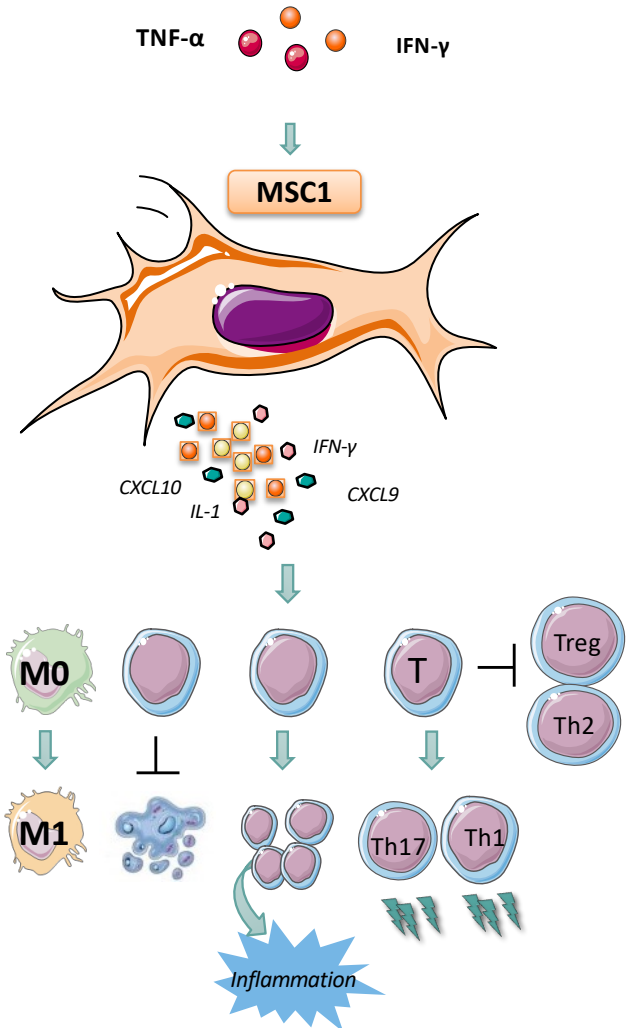
Optimal treatment

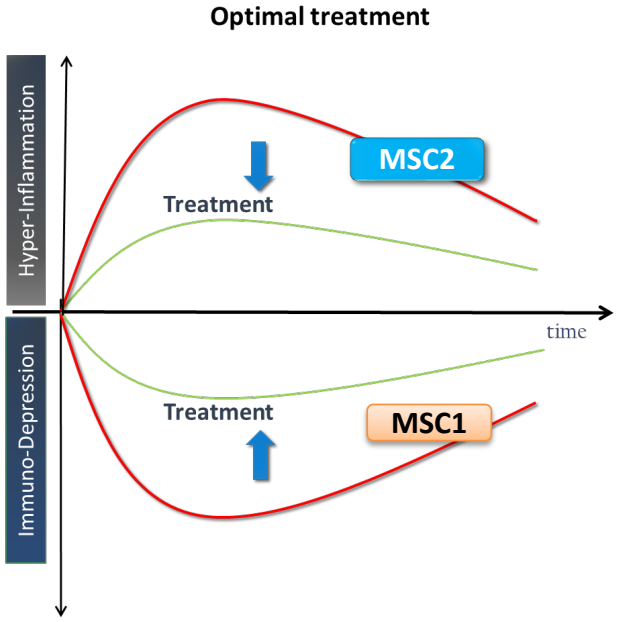


MSC and Septic shock

Mesenchymal Stromal cells: double phenotype



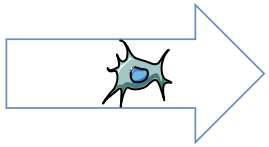




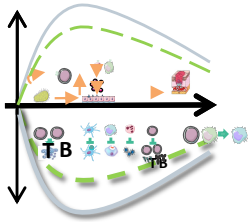
MSC action during septic shock

Septic Shock

Uncontrolled Inflammatory Body Response

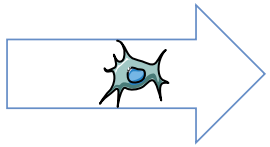


Infusion of MSCs

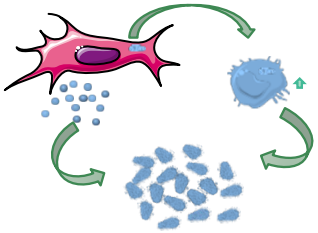


MSCs modulate Inflammation and Immune-response

High level of Infection

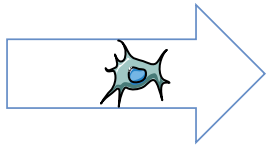


Infusion of MSCs

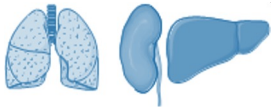


MSCs have direct and Indirect Anti-bacterial Effect

High heterogeneity of injuries for patients

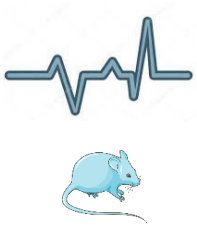


Infusion of MSCs



MSCs Target and Migrate to Injured Sites – Tropism for lungs

Increased survival



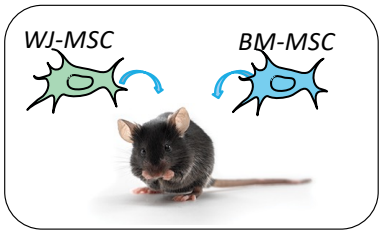
(Laroye C, Stem Cells. 2017)

Caroline Laroye
PhD student

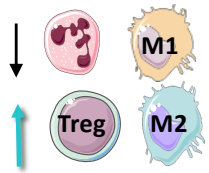
Experimental results

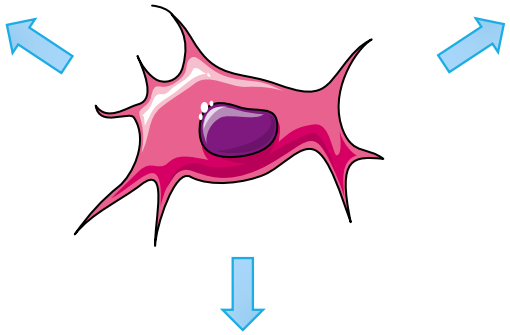
WJ-MSC infusion improve leukocyte trafficking, bacterial clearance and survival

SEPTIC SHOCK MURINE MODEL

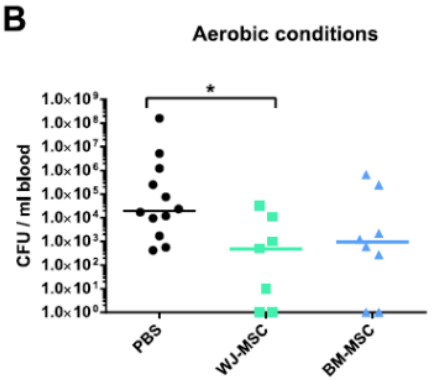


Leukocyte trafficking

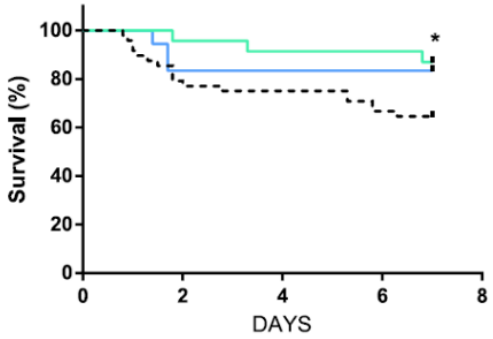




Bacterial clearance



Survival



WJ-MSC : Mesenchymal stromal cells from Wharton Jelly
BM-MSC : Mesenchymal stromal cells from Bone Marrow

Laroye *et al. Stem Cell Research & Therapy* (2019) 10:192

WJ-MSC = BM-MSC:
But difference with PBS only significant with WJ-MSCs

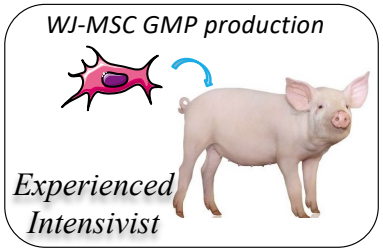
✓ **WJ-MSC source**

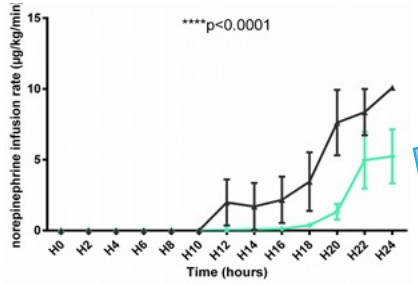
WJ-MSC infusion maintains arterial pressure, protects against organ dysfunction and improves survival

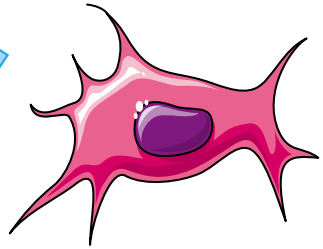
Norepinephrine infusion

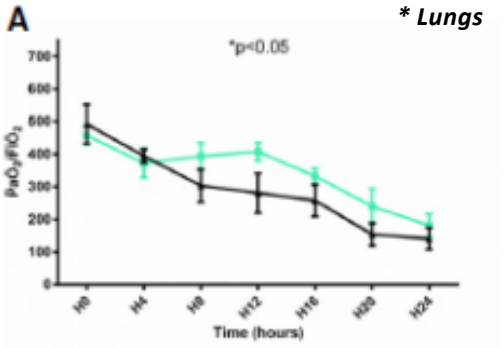
Organ dysfunction

SEPSIS PORCINE MODEL



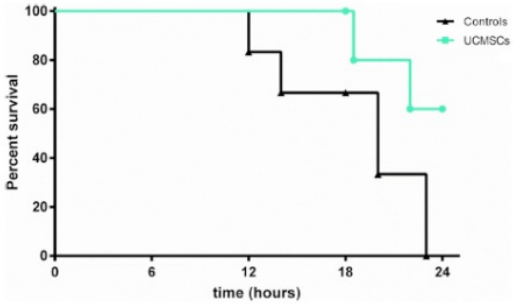


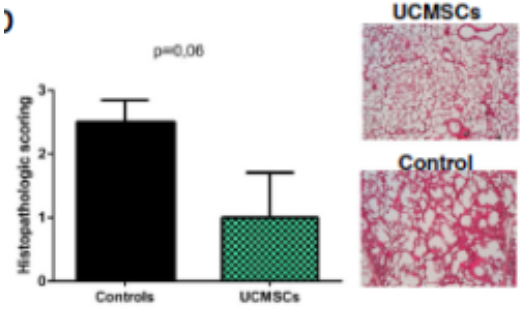




**** Lungs***

Survival





Controls
WJ-MSC

WJ-MSC : Mesenchymal stromal cells from Wharton Jelly

Laroye *et al. Intensive Care Medicine Experimental* (2018) 6:24

Valorisation

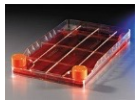
Clinical Transfer

CHRU NANCY

UTCT
ATMP dpt

ansm

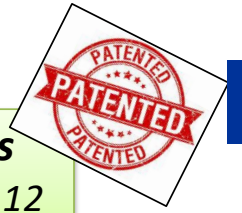
CHOC-MSC: *2017-004123-67*
MSC-COVID19: *2020-002772-12*



Maturation and Spin Off creation

SAYENS SATT

Incubateur Lorrain



WJ-MSC in sepsis
EP 18 712 945.7 - 1112

i-Lab
bpifrance
FINOVAM GESTION

STEMINOV

CEO:
J HUTIN

Valorisation

Clinical transfer

UTCT
ATMP dpt

CHOC-MSC: ***2017-004123-67***
MSC-COVID19: ***2020-002772-12***

CLINICAL TRIAL: *CHOC-MSC*

3 clinical trials with adult MSCs :

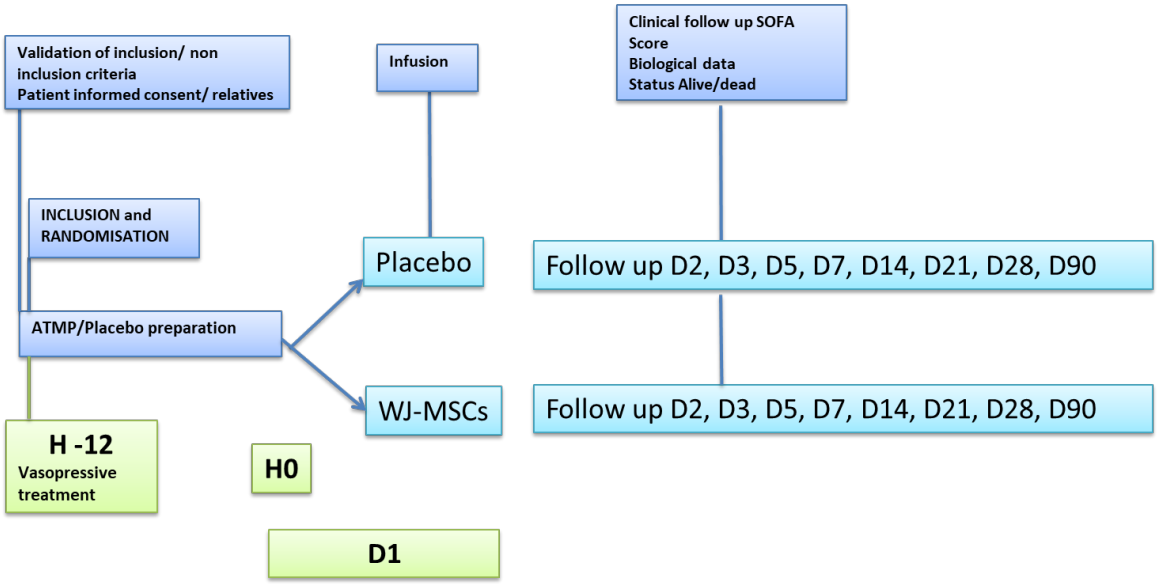
Phase I (Tigenix), Phase I/II (escalating dose) with few patients (one Russian, one canadian)

Phase IIa, comparative, double blind clinical trial with 60 patients :

30 treated with WJ-MSCs / 30 with placebo (vehicule of cells)

CLINICAL TRIAL: *CHOC-MSC*

Efficacy Endpoint : SOFA score *(Sepsis Organ Failure Assessment score)* improvement (D7)



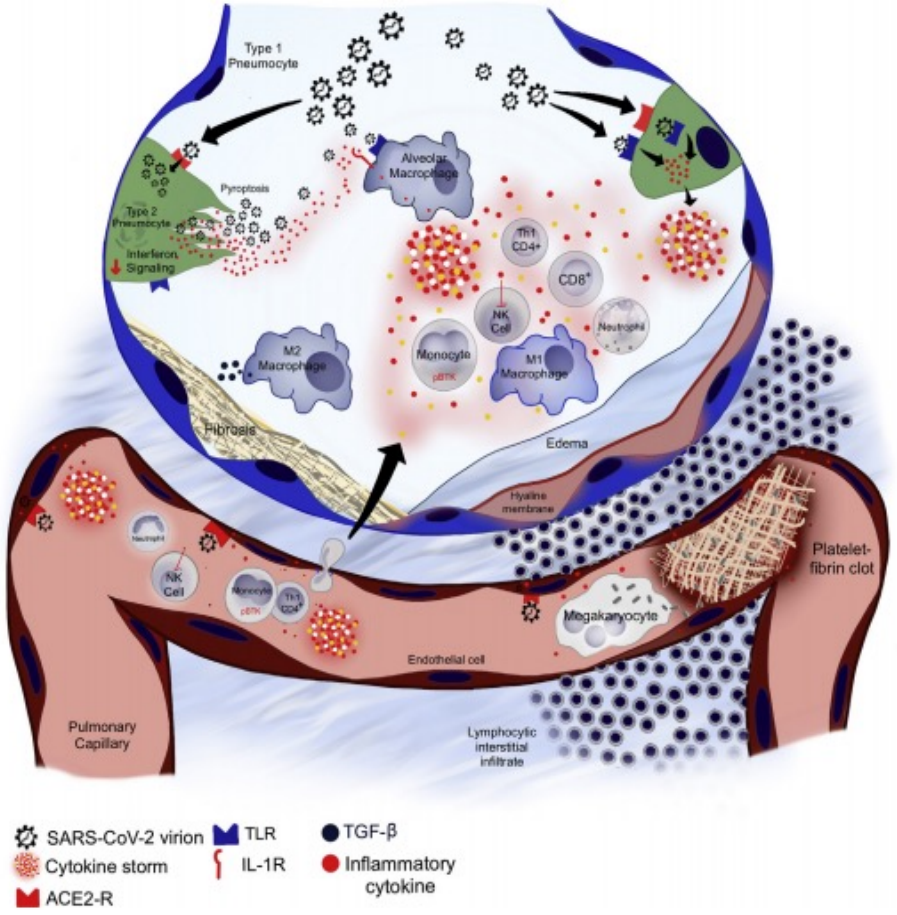
Main inclusion criteria

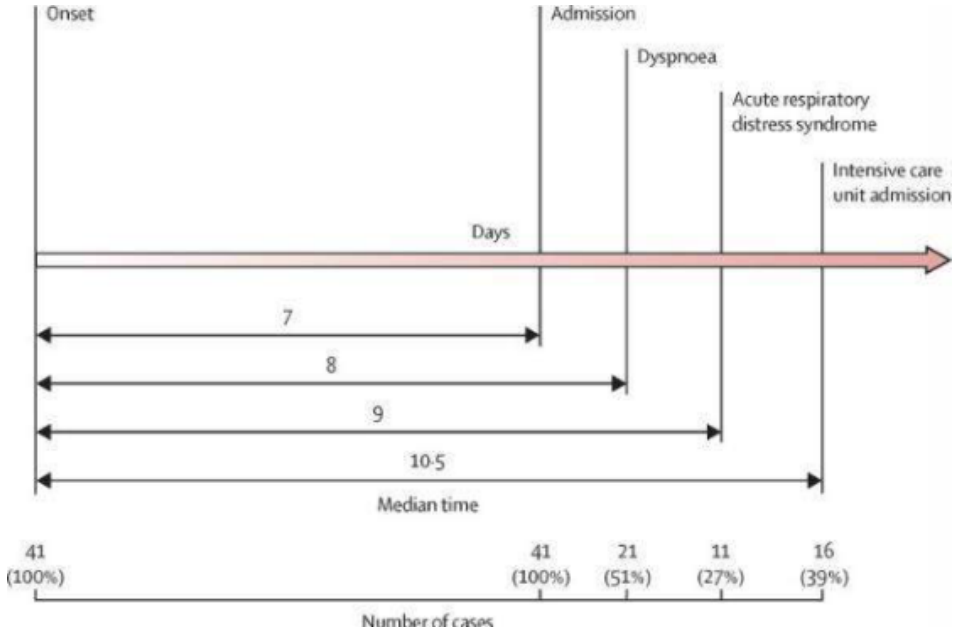
- Septic shock for less than 12 hours
- Men >18 or women > 65 years old
- Informed consent signed

Status:

- 1 patient included
- Stop inclusion during COVID 19
- Restart inclusions in October 2022

CLINICAL TRIAL: *MSC-COVID19*
COVID 19 Pathophysiology and clinic





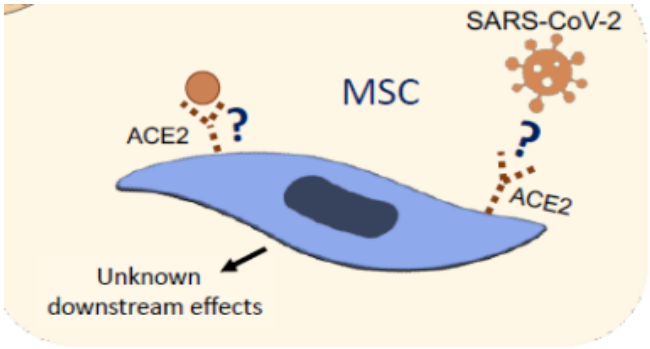
Huang C, *et al. Lancet*. Feb 2020

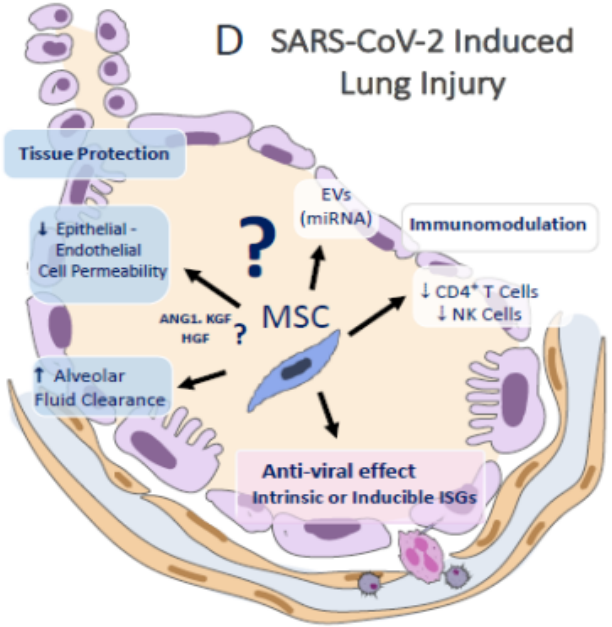
CLINICAL TRIAL: *MSC-COVID19*
MSC rational in COVID 19 ARDS

- **MSC trapped in lungs : major concentration during the first 24hrs in lungs**

- **MSC and ARDS (non viral/viral) models**

- **MSC and ARDS clinical trials**





ARDS : Syndrome de détresse respiratoire aiguë

Khoury M, *et al. Eur Respir J,* 2020

CLINICAL TRIAL: *MSC-COVID19*

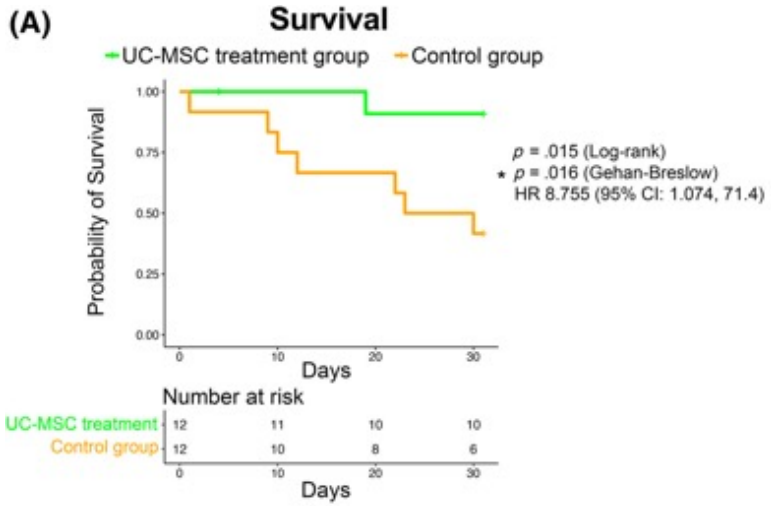
- **Around 80 trials around the world using WJ-MSC in severe forms of Covid-19**
  Phase I, I/II, II
- **Encouraging results**

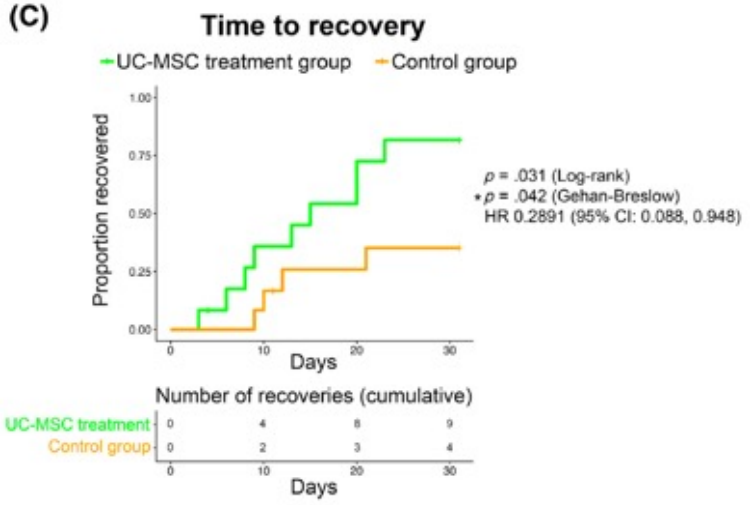
HUMAN CLINICAL ARTICLES

STEM CELLS TRANSLATIONAL MEDICINE

Umbilical cord mesenchymal stem cells for COVID-19 acute respiratory distress syndrome: A double-blind, phase 1/2a, randomized controlled trial

Giacomo Lanzoni[1,2] | Elina Linetsky[1,3] | Diego Correa[1,4] | Shari Messinger Cayetano[5] | Roger A. Alvarez[6,7] | Dimitrios Kouroupis[1] | Ana Alvarez Gil[1] | Raffaella Poggioli[1] | Phillip Ruiz[3] | Antonio C. Marttos[6,7,8] | Khemraj Hirani[1,6] | Crystal A. Bell[6] | Halina Kusack[6] | Lisa Rafkin[1] | David Baidal[1,6,7] | Andrew Pastewski[8] | Kunal Gawri[6,7] | Clarissa Leñero[1] | Alejandro M. A. Mantero[5] | Sarah W. Metalonis[5] | Xiaojing Wang[1] | Luis Roque[1] | Burlett Masters[1] | Norma S. Kenyon[1] | Enrique Ginzburg[3,7,8] | Xiumin Xu[1] | Jianming Tan[9] | Arnold I. Caplan[10] | Marilyn K. Glassberg[11] | Rodolfo Alejandro[1,6,7] | Camillo Ricordi[1,3]

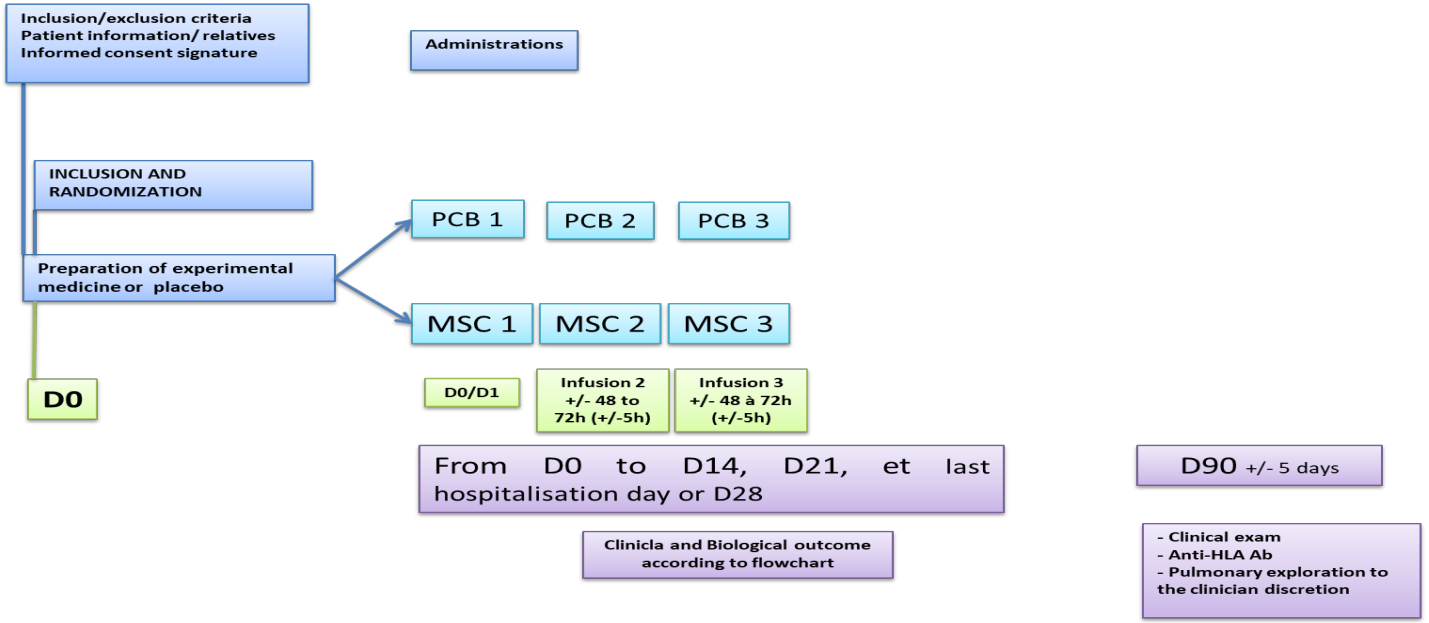




2 infusions of 100 ± 20 × 10^6 UC-MSCs each

CLINICAL TRIAL: *MSC-COVID19*

- **Nancy Trial MSC-COVID: N=30 (15/15)**
  - **Phase II efficacy trial : Infusion of WJ-MSCs to patients with moderate to severe Covid-19 ARDS**
  - **Randomized double blind study vs placebo**
  - **WJ-MSC 1× 10^6/kg, 0,5 × 10^6/kg and 0,5 × 10^6/kg**
  - **Lung function : number of patients with PaO2/FiO2 > 200, 10 days after treatment initiation**
  - **Results in analysis**



Valorisation

Spin-off creation

StemInov

SAYENS SATT

Incubateur Lorrain

PATENTED

WJ-MSC in sepsis

EP 18 712 945.7 - 1112

i-Lab

bpifrance

FINOVAM GESTION

StemInov

CEO:
J HUTIN

MATURATION AND SPIN-OFF CREATION

Incubateur Lorrain

SAYENS SATT

- Incubation process began in 2015
- Emergence grant allowing the pig study
- Connexion with SATT SAYENS
- Presentation of Julie HUTIN as a CEO

- Many contacts (ex: ICOSA for the patent)

ICOSA

- i-Lab coaching

i-Lab bpifrance

- Frenchtech/Deeptechn grant

bpifrance

- Bourse anté-création
  help in StemInov creation

Grand Est
ALSACE CHAMPAGNE-ARDENNE LORRAINE

- Connexion with FINOVAM Gestion

FINOVAM GESTION

- Maturation process in 2016 allowing
  - Pre-clinical study (help to clinical transfer)
  - Production Runs
- Patentability study
- Licensing negociation with StemInov

Julie Hutin,
CEO

Ecole Centrale Lyon Master EM Lyon
HEC Challenge + 2020-2
5y experience in Eurofins Genomics

Danièle Bensoussan,
Scientific founder

PU-PH - Head of Cellular Therapy Unit and Tissue Banking, Cord Blood Banking (UTCT)
Head of a CNRS Team
Lead to the patent operated by StemInov
Scientific advice

CONSULTANTS

Eric HALIOUA
STRATEGY

Eric is a serial entrepreneur who combines strong strategic, technological and managerial experience with proven track record of deal-making and fund-raising. He is the CEO of PDC line Pharma

PE Charles
CLINICAL STRATEGY

Prof. in an Intensive Care Unit of a University Hospital. In charge of designing and conducting experimental and translational research towards sepsis

Claude DEDRY
CMC

Industrial Pharmacist
Cell Production GMP Unit Expert
CMC expert in cell and gene therapy
Several GMP accreditations

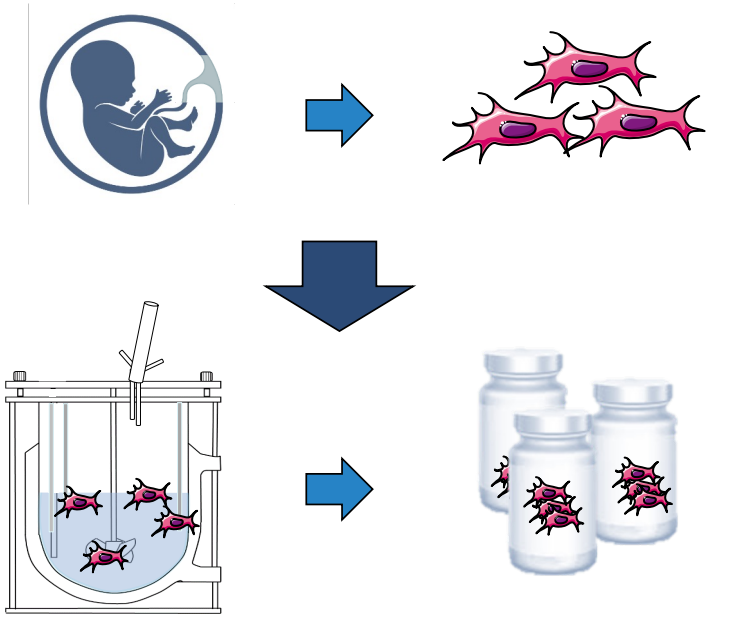
Roland GORDON
BERESFORD
REGULATORY

Expert in regulatory affair with experience in ATMP
Intellectual Property management

*MSC: Mesenchymal Stromal Cells

MATURATION AND LICENSING

INDUSTRIAL PRODUCTION OF CRYOPRESERVED WJ-MSC



3D Production

Cryopreserved
Off-the-shelf product

Phase I escalating dose trial
Phase II efficacy trial

Phase I/II in ARDS / Septic shock

- End points:
  - Safety,
  - Reduced mechanical ventilation duration
  - Reduced death
  - Reduced hospital stay
  - Dose regimen validation
  - Pharmacodynamic assessment

Clinical trial preparation

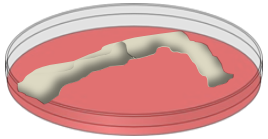
- Design & CTA approval
- Validate sites and PI

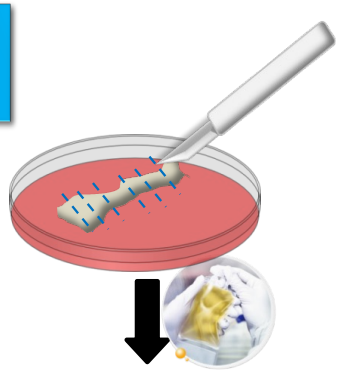
FUND RAISING ON GOING

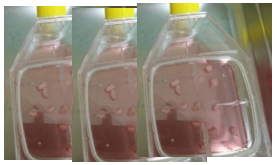
WJ-MSC production

2D expansion

Umbilical cord

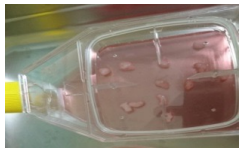






10-15 pieces/flask
3 Flasks

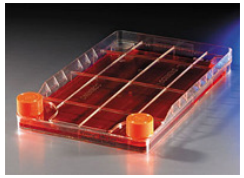
37°C, 5% CO_2,
5% O_2,
3-4 weeks



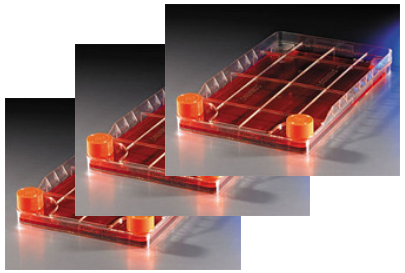
3 .10^6 MSC/flask
9.10^6 MSC

Passage 0

QC : -30
10^6 MSC



37°C, 5% CO_2,
5% O_2,
1 week



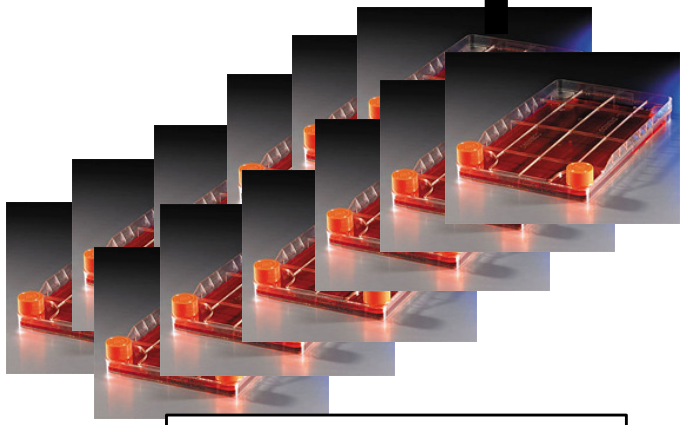
CellSTACKs
1000 MSC/cm²; 1,27 .10^6/Cell STACK
1 Cell STACK

Passage 1

37°C, 5% CO_2,
5% O_2,
1 week

CellSTACK
1000 MSC/cm²; 1,27 .10^6/Cell STACK
3 Cell STACKs

Passage 2



CellSTACK
1000 MSC/cm²; 1,27 .10^6/Cell STACK
12-14 Cell STACKs

Passage 3

Adapted from Capelli *et al*, 2011

3D expansion in Bioreactor on micro carriers

WJ-MSC expansion in 2D

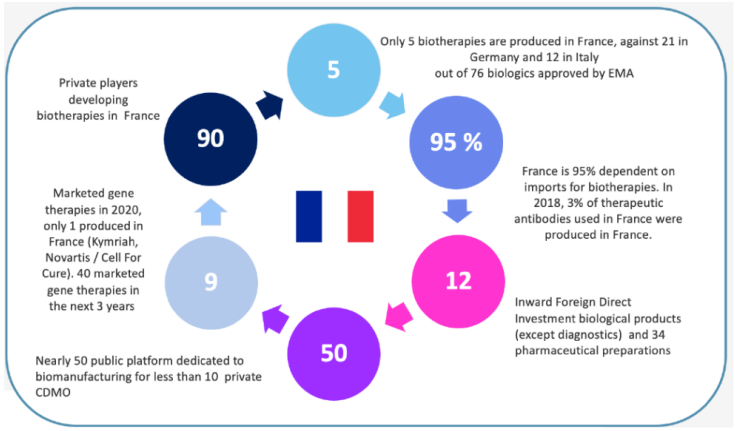
WJ-MSC in 3D

PRODUCTION SCALE UP PRODUCTION GMP

RA COVID 2021 (150k€)

Industrial Integrator

Biotherapies: State of the art



40 marketed ATMPs

25 cell therapies **15** gene therapies

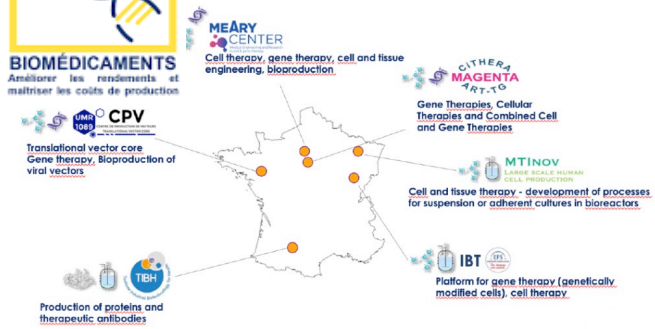
Top 3 of countries developing ATMPs

2020 → 2022

GRAND DÉFI BIOMÉDICAMENTS

Améliorer les rendements et maîtriser les coûts de production

BioT ⇔ BioP



FRANCE 2030

Innovation Santé 2030

Un objectif : produire **20 biomédicaments** sur le sol français.

MTInov LARGE SCALE HUMAN CELL PRODUCTION

Grand Est ALSACE CHAMPAGNE-ARDENNE LORRAINE

GE Start-ups

- StemInov
- Core Biogenesis
- CellProthera

EASE European Aseptic and Sterile Environment TRAINING CENTER

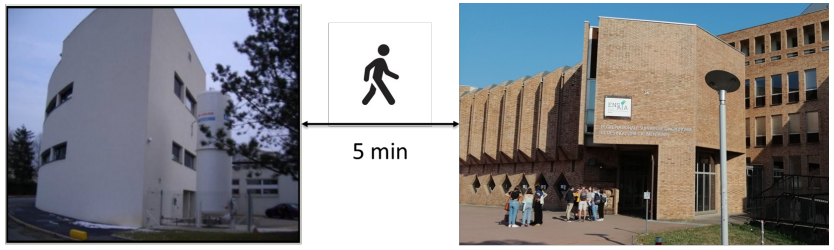
france BIOVALLEY l'innovation santé

Industrial Integrator: MTInov

Aug 2020, Grand Défi Biomédicament

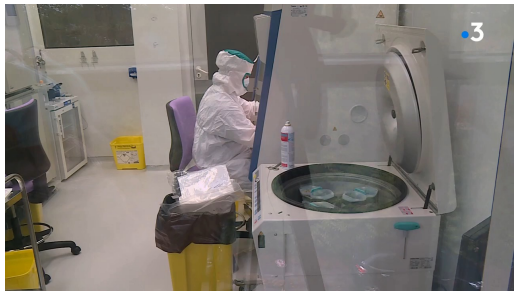
MTINOV
LARGE SCALE HUMAN CELL PRODUCTION

Pr. Danièle Bensoussan (UTCT – CHRU – Nancy)
Pr. Eric OLMOS (LRGP – Université de Lorraine – CNRS)



UTCT, CHRU, Vandoeuvre les Nancy

LRGP / ENSAIA, Vandoeuvre les Nancy



MTInov: projects since labelling of MTInov

« Grand défi Biomédicaments : améliorer les rendements et maitriser les coûts de production »

- **ACCESS** (2,8 M€): optimization of the MSC production through the development of an in-line clinical grade production control system.
- **SELPHi** (2,8 M€): development and industrialization of a new generation of sensors based on holographic imaging via monitoring of cells states.
- **IT'SME** (670 k€): development of a tool for the purification of biodrugs in continuous flow of reduced size and very low cost use (modular factory).

« Nouvelles biothérapies et outils de production (AMI Biothérapies) »

- **SEQRET** (1,3 M€): development of an on-line quality control system based on the real-time analysis of the secretome of MSC cells.
- **CLIMBIN** (2,2 M€): development of an innovative solution for process analytical control for optimization and automation of cell cultures.
- **OPTI-STEM2** (7 M€): optimization of the MSC production in order to democratize their availability and allow the diversification of therapeutic applications.

- ***12 persons recruited in fixed term contracts (or planned to be) in addition to permanent staff.***
- ***National partnerships (Nancy, Montpellier, Marseille, Paris, Toulouse, Tours…).***
- ***Academic and industrial collaborations (from start-up to large pharmaceutical groups).***

Conclusion

WJ-MSCs in the Sepsis model

1st:

Best source of MSCs between WJ-MSC and BM-MSCs in a murine CLP model

WJ-MSCs seem to present a better profile in this murine model

WJ-MSC source

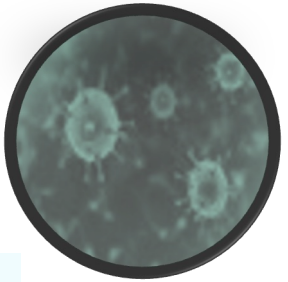
2nd :

Efficacy of GMP WJ-MSCs in a pig model of septic shock

WJ-MSCs present efficiency in this animal model very close from clinical context

ansm
Agence nationale de sécurité du médicament et des produits de santé

ANSM authorization



MTInov
LARGE SCALE HUMAN CELL PRODUCTION

Production Scale-up

PATENTED

StemInov

Industrial Production
Phase II Clinical trial

UMR-CNRS-UL 7365

- D. Bensoussan, PU-PH
- **C. Laroye, PhD student, AHU**
- C. Huselstein, PU
- L. Reppel, MCU-PH

UMR-INSERM-UL 1116

- S Gibot, PU-PH, Intensive care physician
- **C. Laroye, PhD student, AHU**

CHRU Nancy

- **UTCT**
  - D. Bensoussan, PU-PH
  - **C. Laroye, AHU**
  - L. Reppel, MCU-PH
- **Réanimation**
  - S Gibot, PU-PH
  - A Kimmoun, PU-PH
- **Maternité Régionale**

Start up StemInov

- Julie Hutin (CEO)

Intégrateur Industriel MTInov

- Pr Eric OLMOS (PU)

StemInov

MTInov
Large scale human cell production