

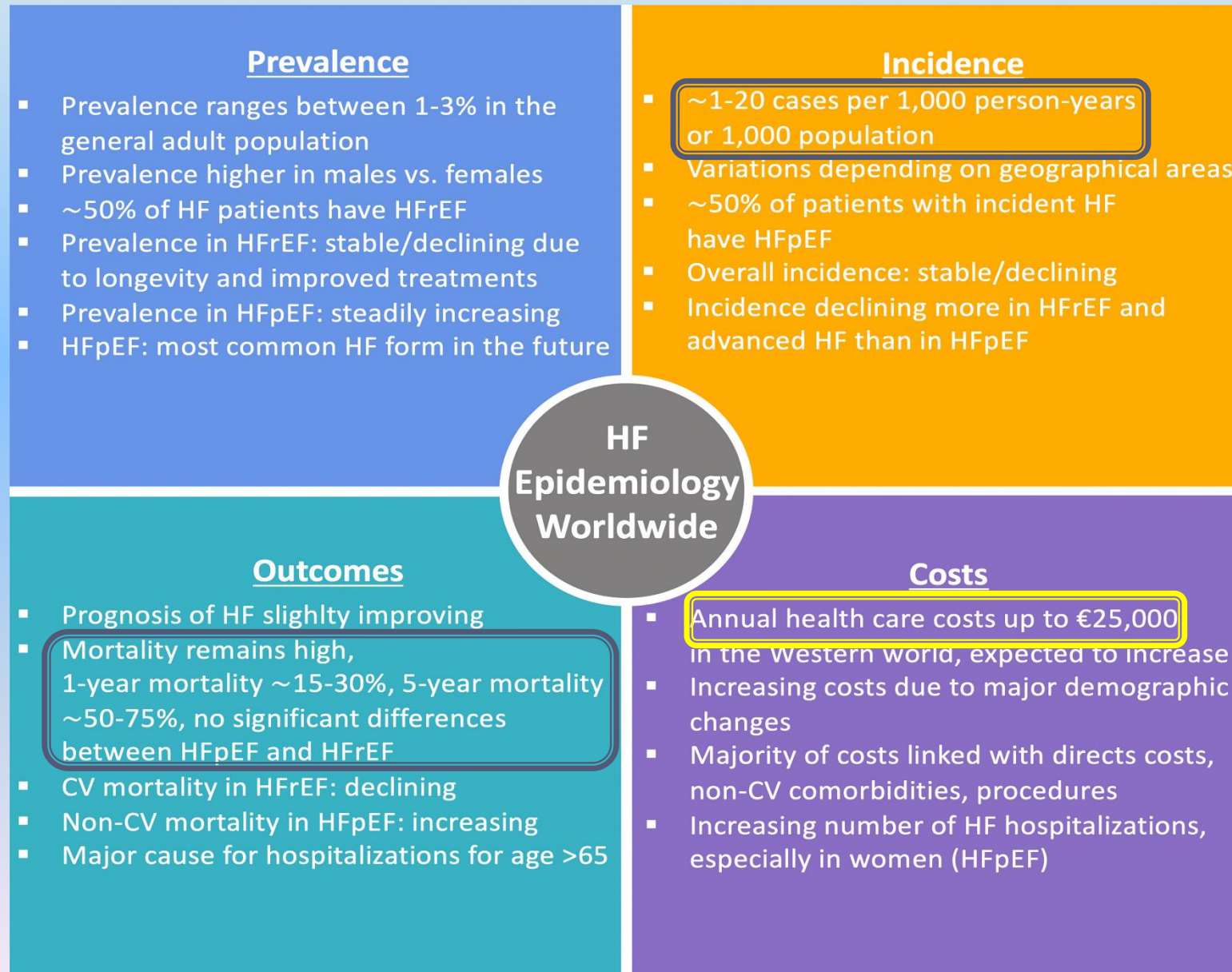
# Biothérapies et Pathologies Cardiaques : Quelle Biothérapie pour quel Effet ?

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Dpt of Cardiovascular Surgery & INSERM U 970  
Hôpital Européen Georges Pompidou  
Université Paris-Cité

Disclosures  
Consultancy for Help Therapeutics



# An Update on Global Epidemiology in Heart Failure




# Biothérapies et Pathologies Cardiaques : Quelle Biothérapie pour quel Effet ?

## Outline


- **Repair vs. regeneration**
- Delivery issues
- Remaining challenges

# Biothérapies et Pathologies Cardiaques : Quelle Biothérapie pour quel Effet ?

Target effect	Mechanism of action	Biotherapy
Repair	Paracrine signaling	<ul style="list-style-type: none"><li>■ Mesenchymal stromal cells</li><li>■ Extracellular vesicles</li></ul>
Regeneration	<p>Increase of the contractile cell pool from:</p> <ul style="list-style-type: none"><li>■ Exogenous sources</li><li>■ Endogenous sources</li></ul>	 <ul style="list-style-type: none"><li>■ Cardiomyocytes</li><li>■ RNA triggers</li></ul>

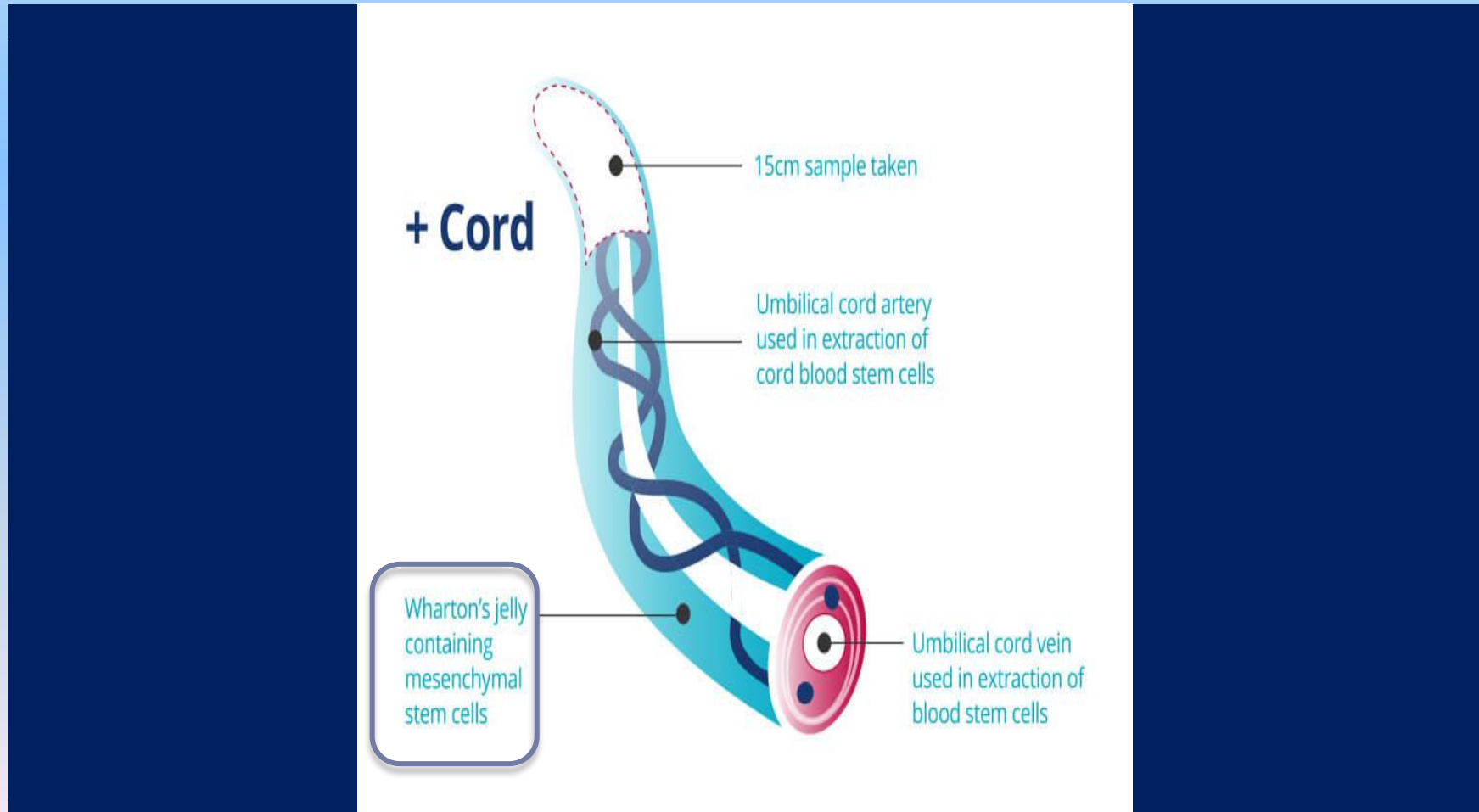


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# 20 years of treating ischemic cardiomyopathy with mesenchymal stromal cells: a meta-analysis and systematic review

16 randomized controlled studies (excluding those with high risk of bias and including 4 for AMI)  
**LVEF**



# Key Translational Challenges

## MSC

- Tissue source
- Scalability
- Batch-to-batch reproducibility

# Key Translational Challenges

Inter- and Intra-donor variability in bone marrow–derived mesenchymal stromal cells: implications for clinical applications


Analyte	Donor 1	Donor 2	Donor 3	Donor 3W
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## Potential Solutions

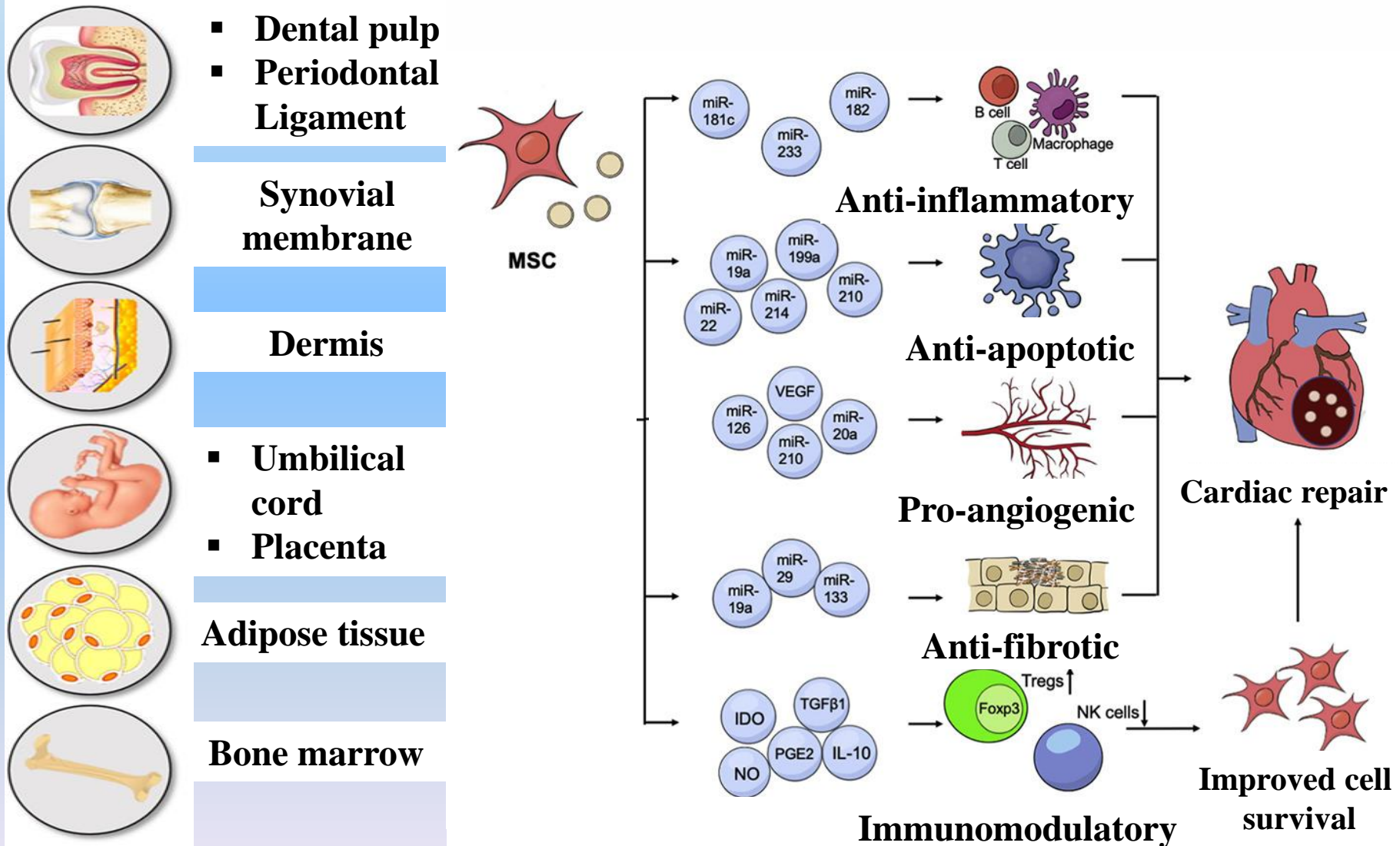
- Immortalized cell lines
- Differentiation of MSC from iPSC

CXCL12	ND <sup>a,b</sup>	291.22 ± 23.4 <sup>d,e</sup>	103.4 ± 20.46 <sup>f</sup>	ND
ANG-1	1482 ± 46.89 <sup>a,b,c</sup>	1014 ± 85.42 <sup>e</sup>	896.6 ± 162.4	827.8 ± 103.6
HGF	48.45 ± 3.37 <sup>a,b</sup>	70.5 ± 10.47 <sup>d,e</sup>	59.98 ± 5.99	57.9 ± 3.39
CXCL1	82.56 ± 10.88 <sup>a</sup>	41.48 ± 0.96 <sup>d,e</sup>	70.60 ± 6.79	78.83 ± 9.99

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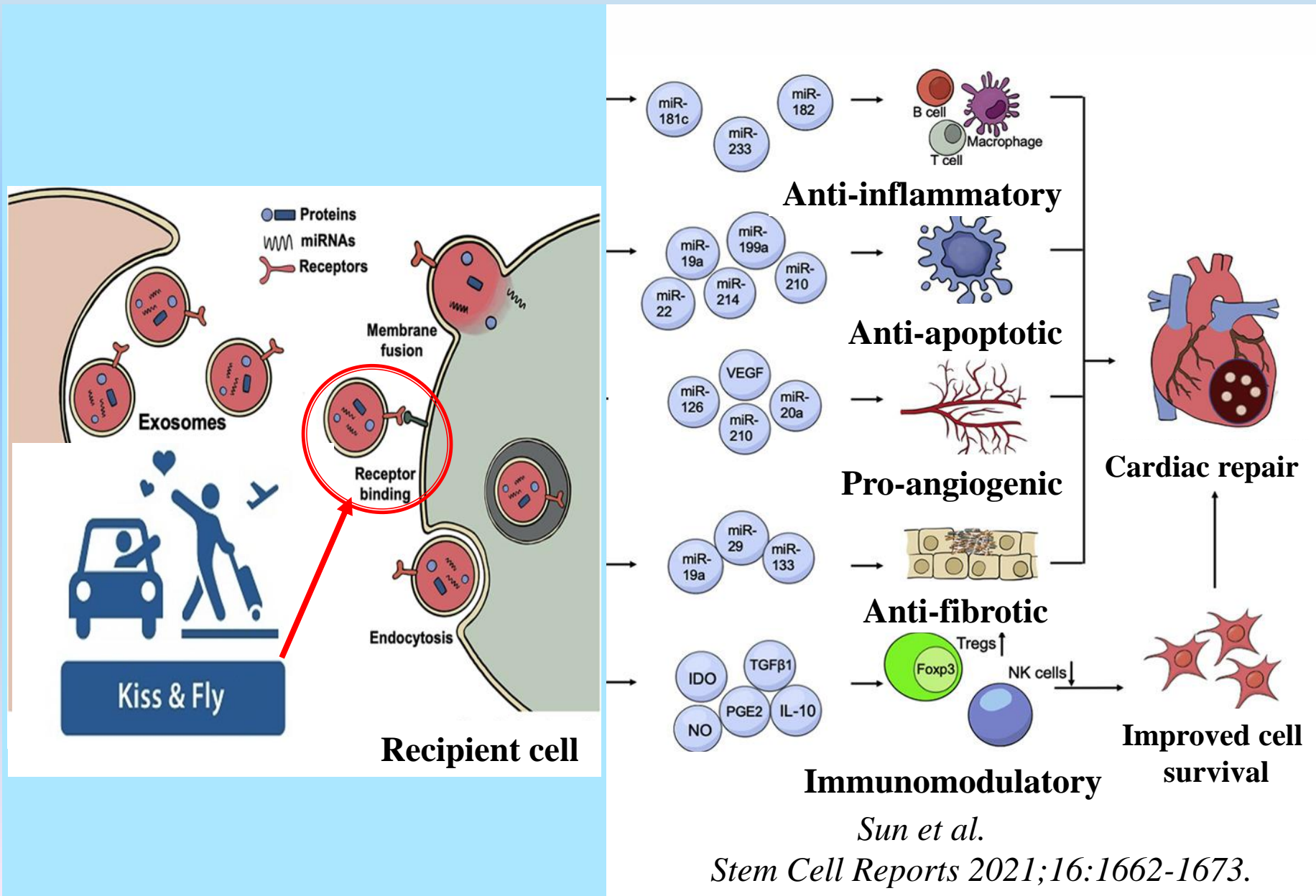
# Paracrine Effects of MSC



Lee and Kang. *Stem Cell Research & Therapy* 2020;11:397.

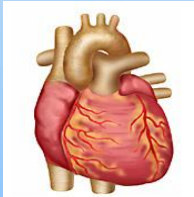

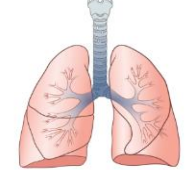
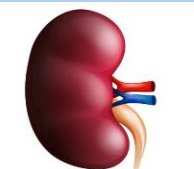

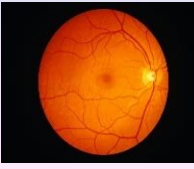
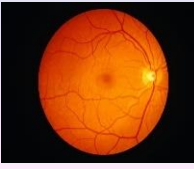
Sun et al. *Stem Cell Reports* 2021;16:1662-1673.

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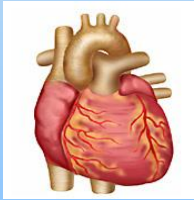

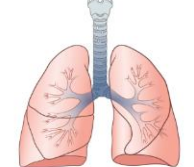
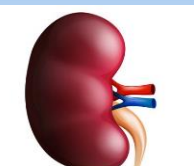





# Equivalence of Outcomes Between Cells and Their Secretome

Organ	Model	Comparator	Reference
	Ischemia	<p>If EV Duplicate the Effects of Their Parental Cells, Why Choosing EV?</p> <ul style="list-style-type: none"> <li>Absence of potential cell-induced adverse events (<i>arrhythmias, uncontrolled proliferation</i>)</li> <li><b>Better « druggability »</b></li> <li>Lack of immunogenicity</li> </ul>	795-807.
	Duchenne		942-55.
	Limb		66-1476.
	Pulmo		:1121-8.
	Acute		:1053-7.
	Stroke Traum		1131-43. 3:170-5.
	Retina		6:34562.




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# Clinical Trials of EV-Based Therapies

## Treatment of Non-ischemic Cardiomyopathies by Intravenous Extracellular Vesicles of Cardiovascular Progenitor Cells (SECRET-HF)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated  by the U.S. Federal Government. [Know the risks and potential benefits](#) of clinical studies and talk to your health care provider before participating. Read our [disclaimer](#) for details.

ClinicalTrials.gov Identifier: NCT05774509

[Recruitment Status](#) ⓘ : Not yet recruiting

[First Posted](#) ⓘ : March 17, 2023

[Last Update Posted](#) ⓘ : March 17, 2023

See [Contacts and Locations](#)

[View this study on Beta.ClinicalTrials.gov](#)

### Sponsor:

Assistance Publique - Hôpitaux de Paris

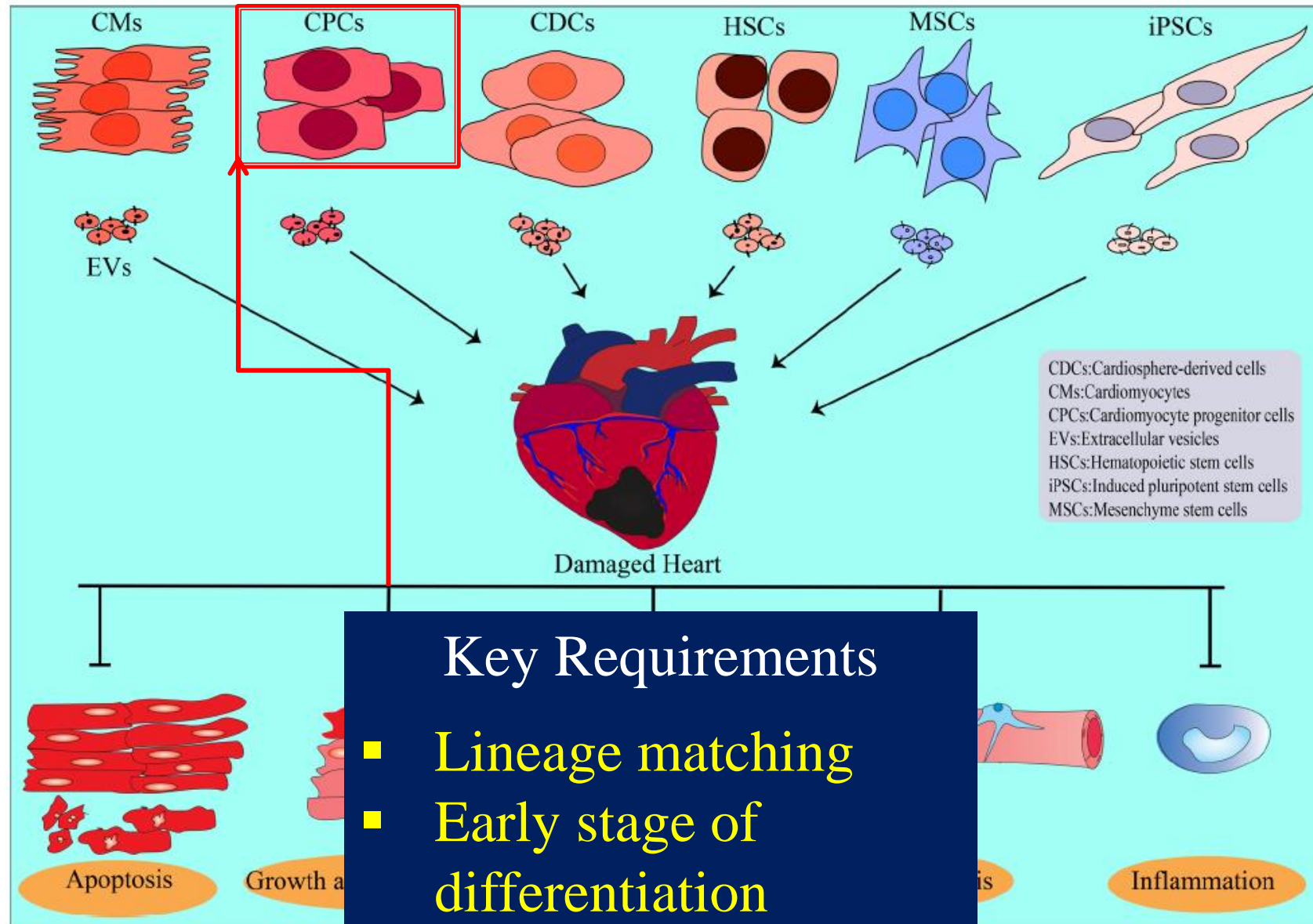
### Collaborator:

Ministry of Health, France

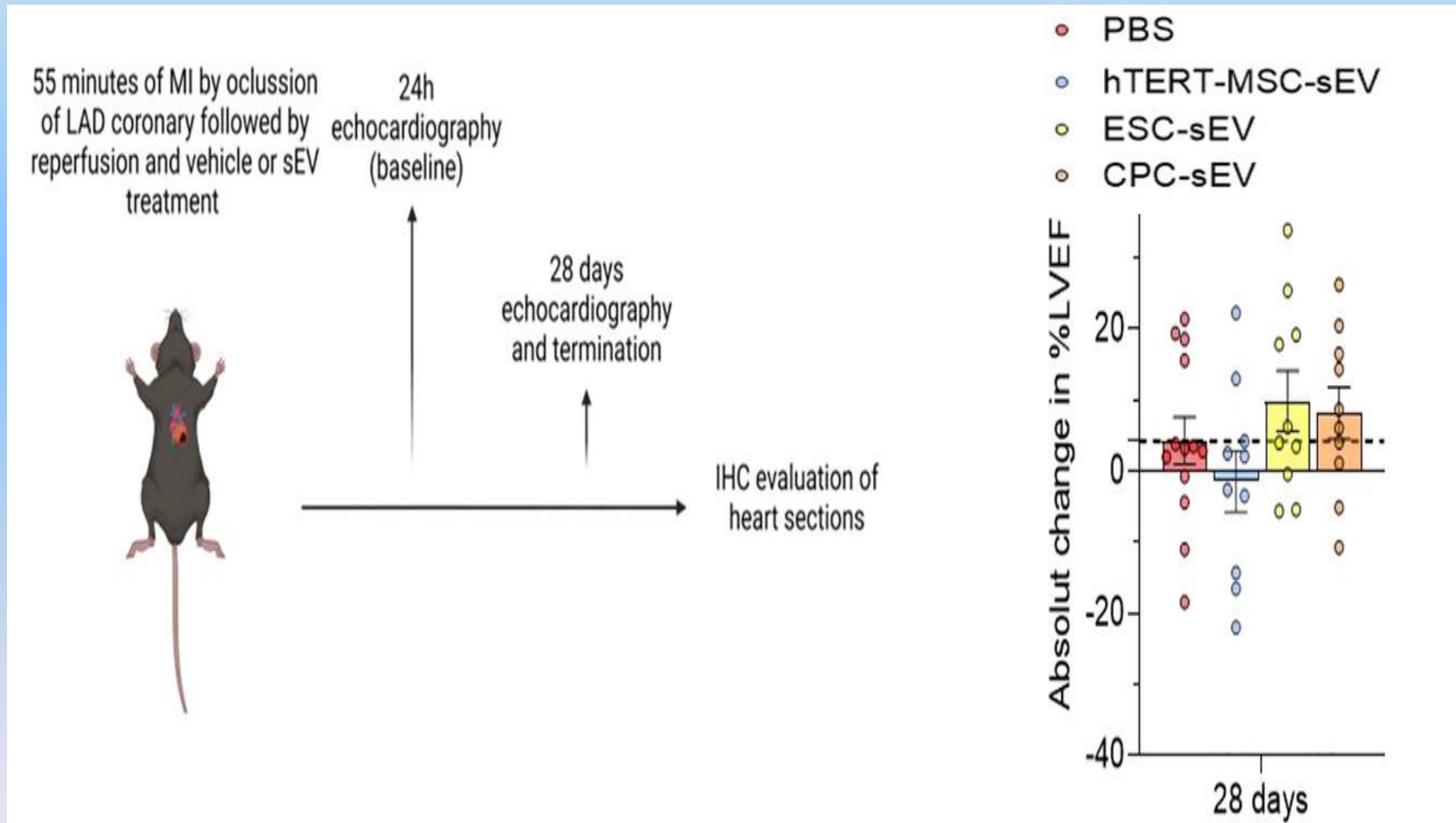
The goal of this clinical trial is to assess the safety and efficacy of three intravenous injections of the extracellular vesicle-enriched secretome of cardiovascular progenitor cells in severely symptomatic patients with drug-refractory left ventricular (LV) dysfunction secondary to non-ischemic dilated cardiomyopathy. The main questions it aims to answer are:

- Are these repeated injections safe and well tolerated?
- Do they improve cardiac function and, if yes, to what extent?

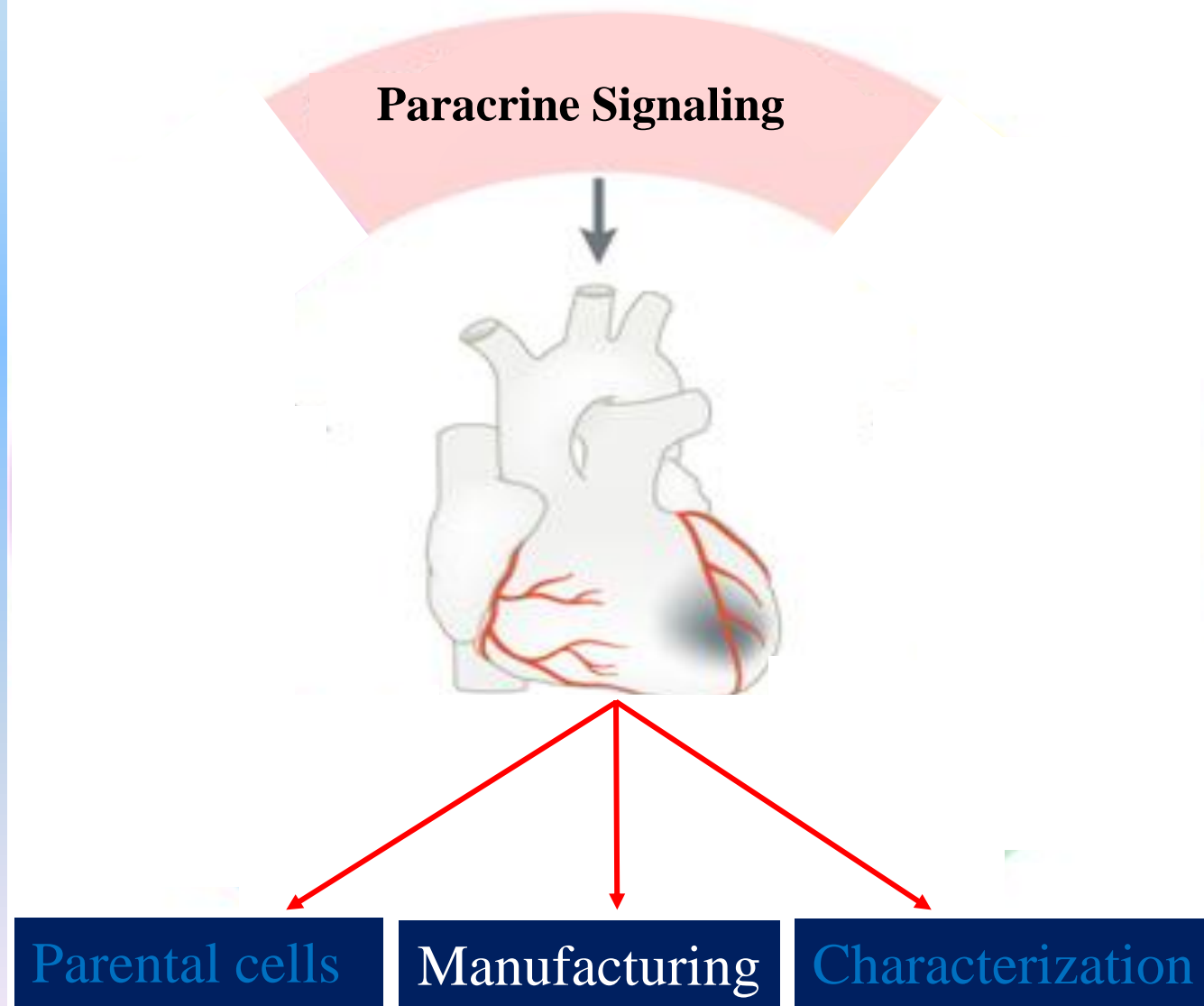
# Use of Secretome for Heart Failure: Translational Issues



# Selection of EV Parental Cells: Early Differentiation & Lineage Matching

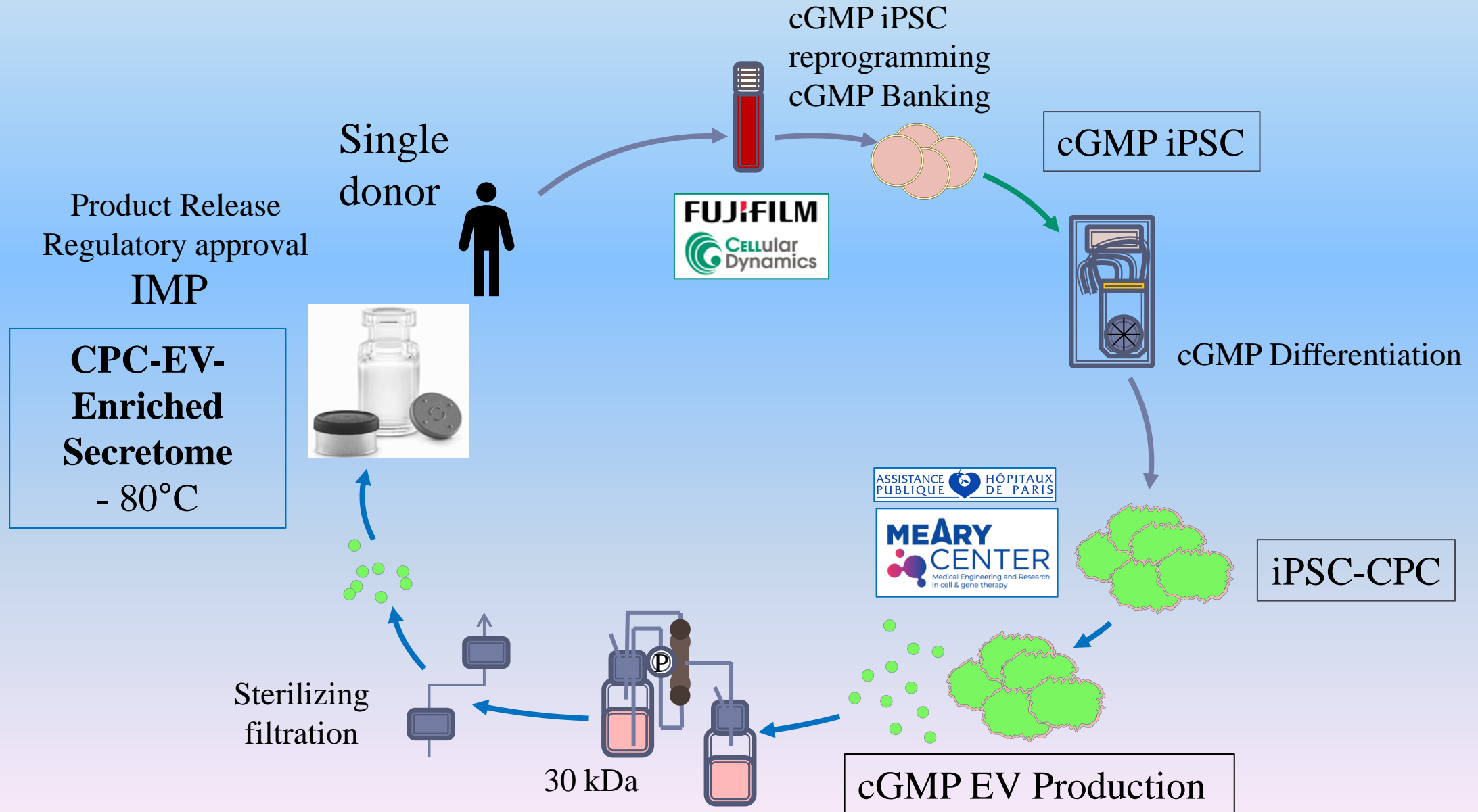


# Translational Issues



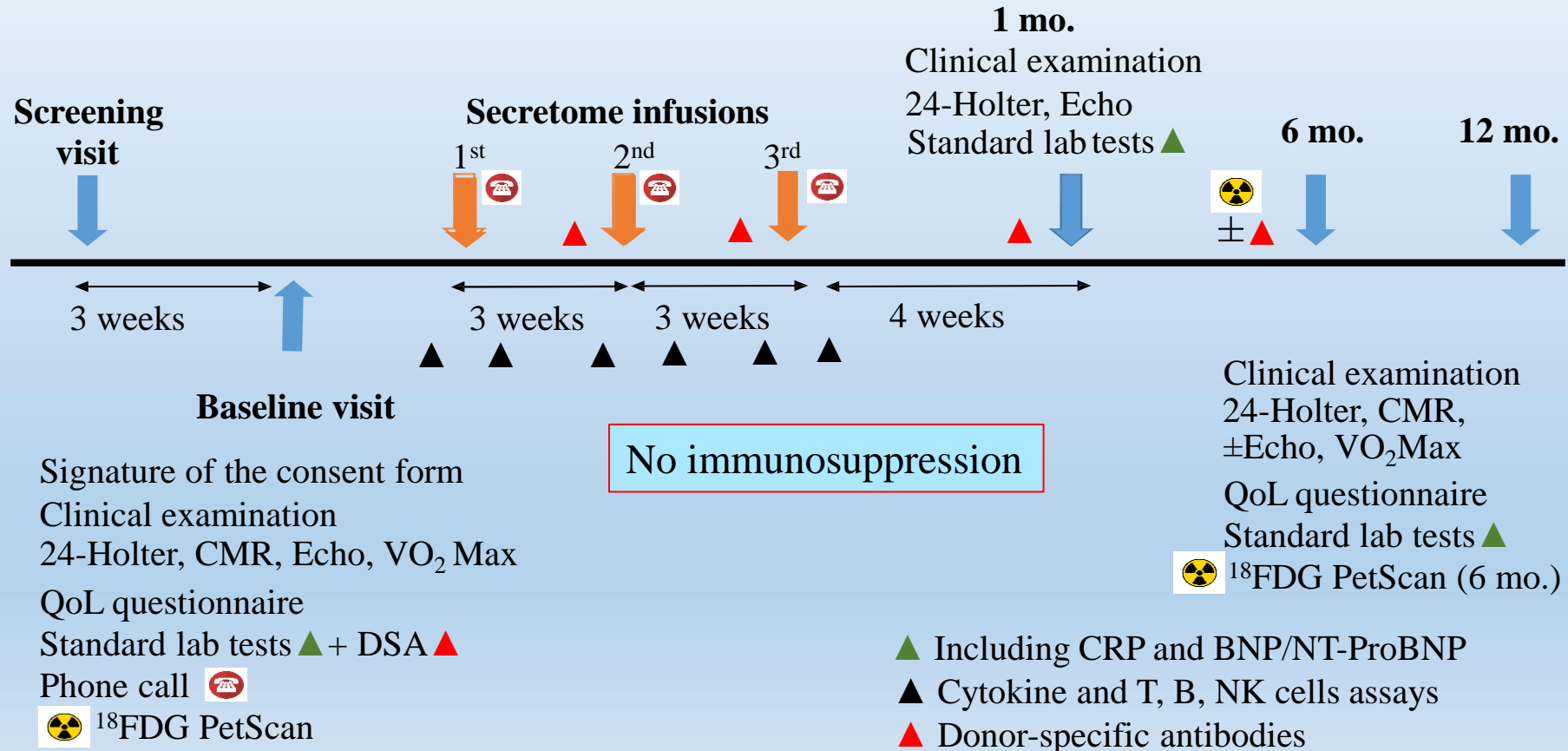
*Adapted from Bertero & Murry Nature Rev Cardiol 2018;15:579–80.*

# First-in-Man Treatment of Heart Failure by a Cardiovascular Cell-Derived Secretome



## Treatment of Non-ischemic Cardiomyopathies by Intravenous Extracellular Vesicles of Cardiovascular Progenitor Cells (SECRET-HF)

- Cohort 1: 4 patients:  $20 \times 10^9$  particles/kg per infusion (cumulated dose:  $60 \times 10^9$  particles/kg per treatment)
- Cohort 2: 8 patients (if no SAE in cohort 1):  $40 \times 10^9$  particles/kg (cumulated dose:  $120 \times 10^9$  particles/kg per treatment)





# Characterization of the Final Product: EV-Enriched Secretome

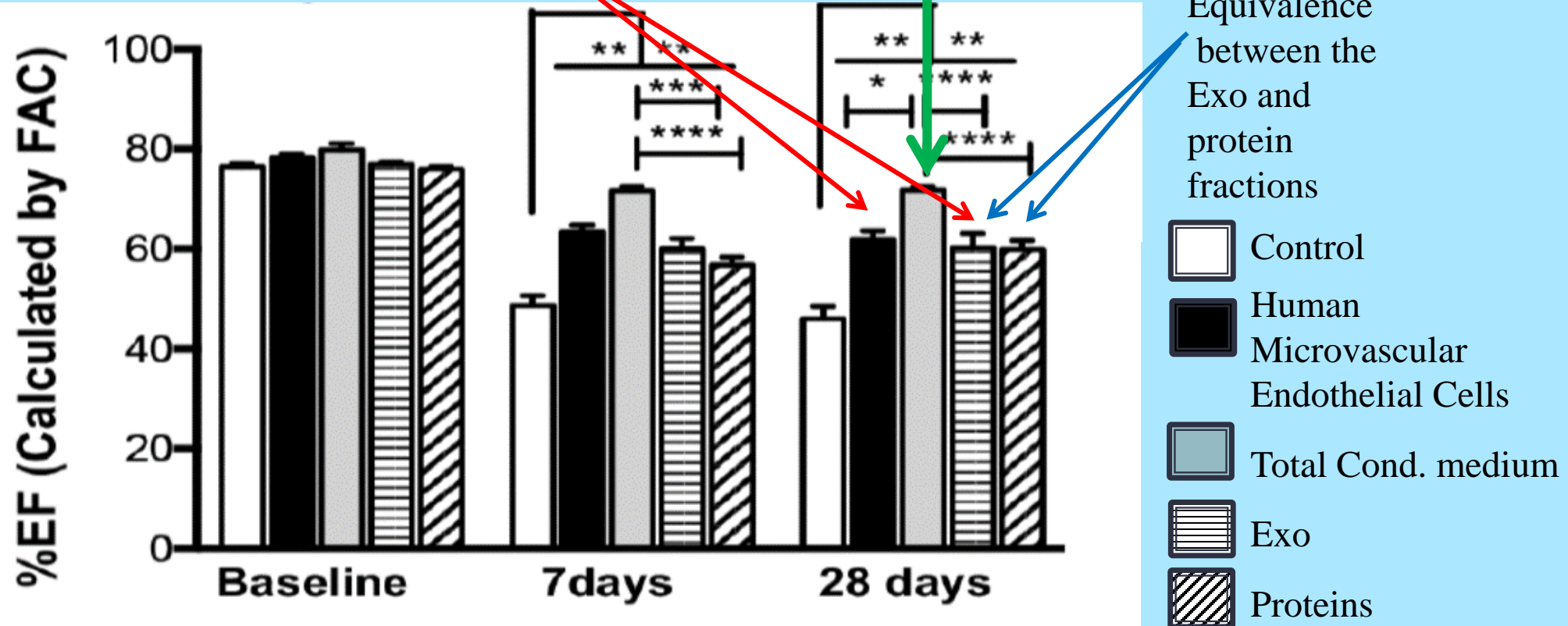
## Comparison of Total Conditioned Medium (TCM) Exosomes (EXO) and Exosome-Free Protein-Enriched Fraction (EF)

### Changes in LVEF in a Rat Model of MI

Equivalence between cells  
and the Exo fraction

CM better than each fraction separately

Equivalence  
between the  
Exo and  
protein  
fractions

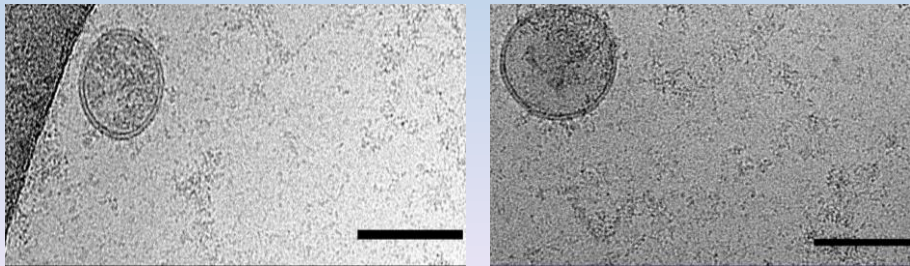
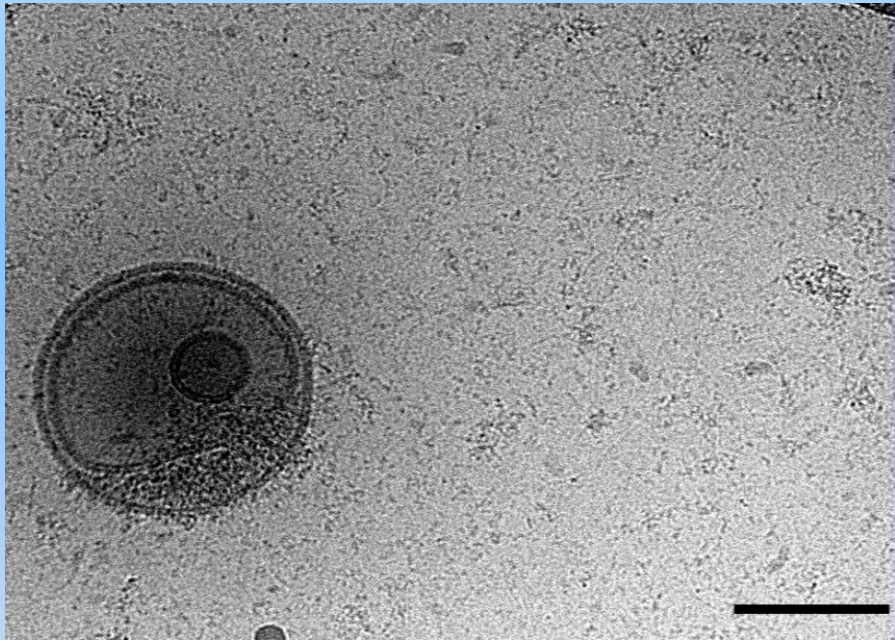


*Sharma et al. Circ Res 2017;120:816-34.*

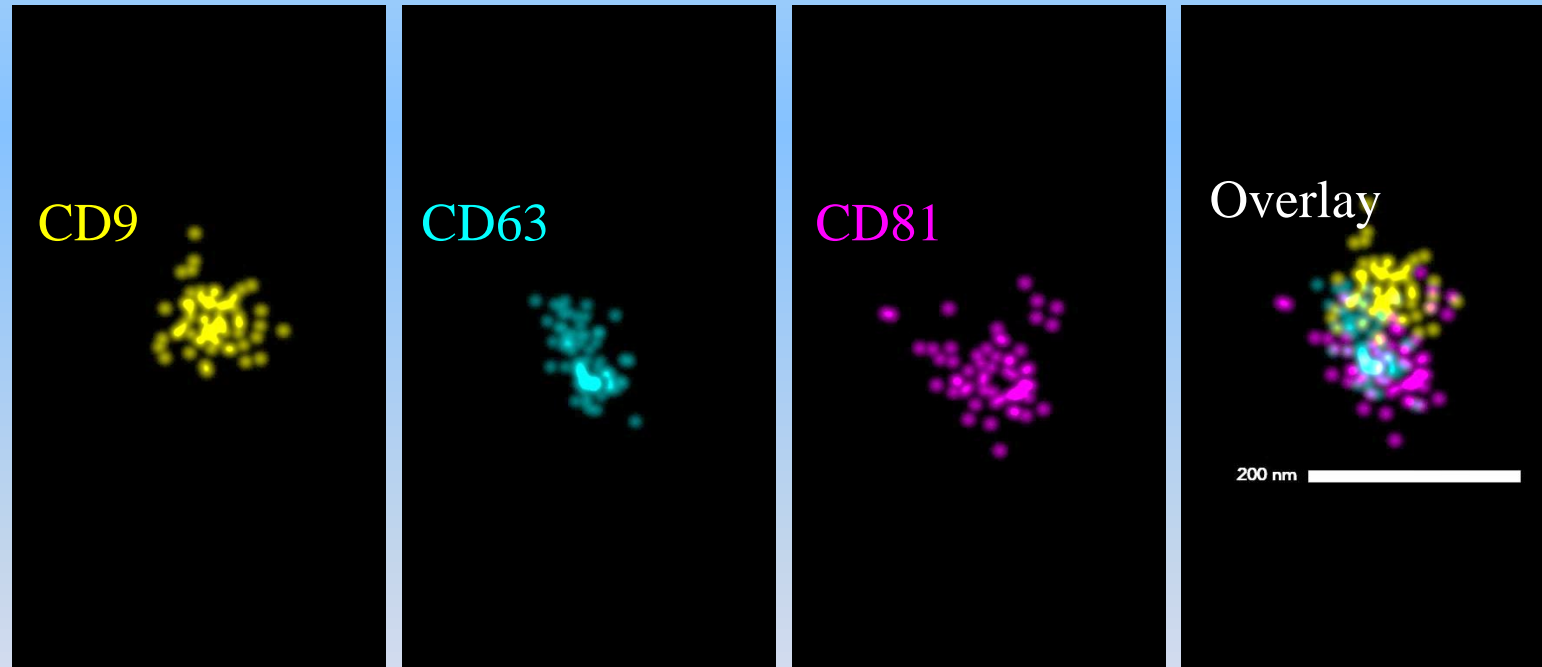


# Characterization of the Final Product: Identity

Cryo-TEM images of single particles from a sample of the final product

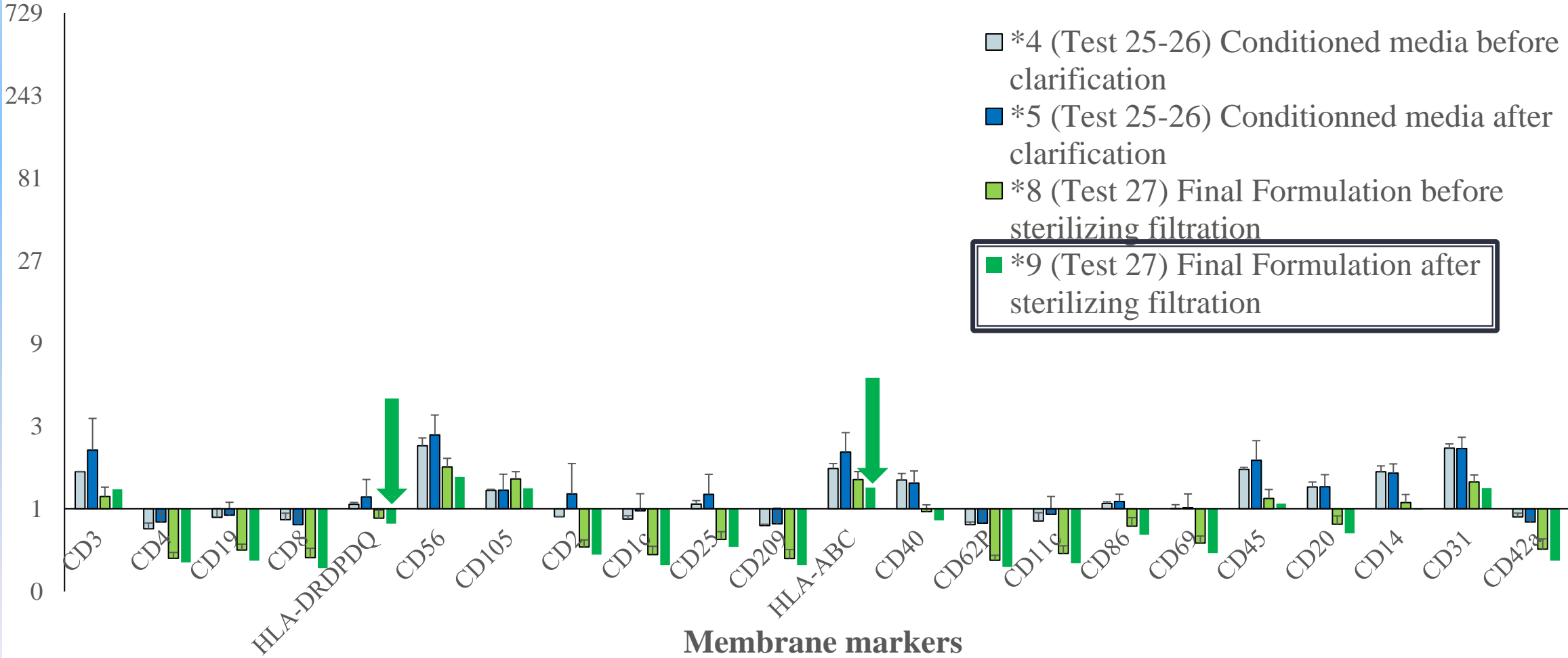


Super-resolution microscopy (ONi) images of a single particle from a sample of the final product



# Characterization of the Final Product: Lack of Immunogenicity

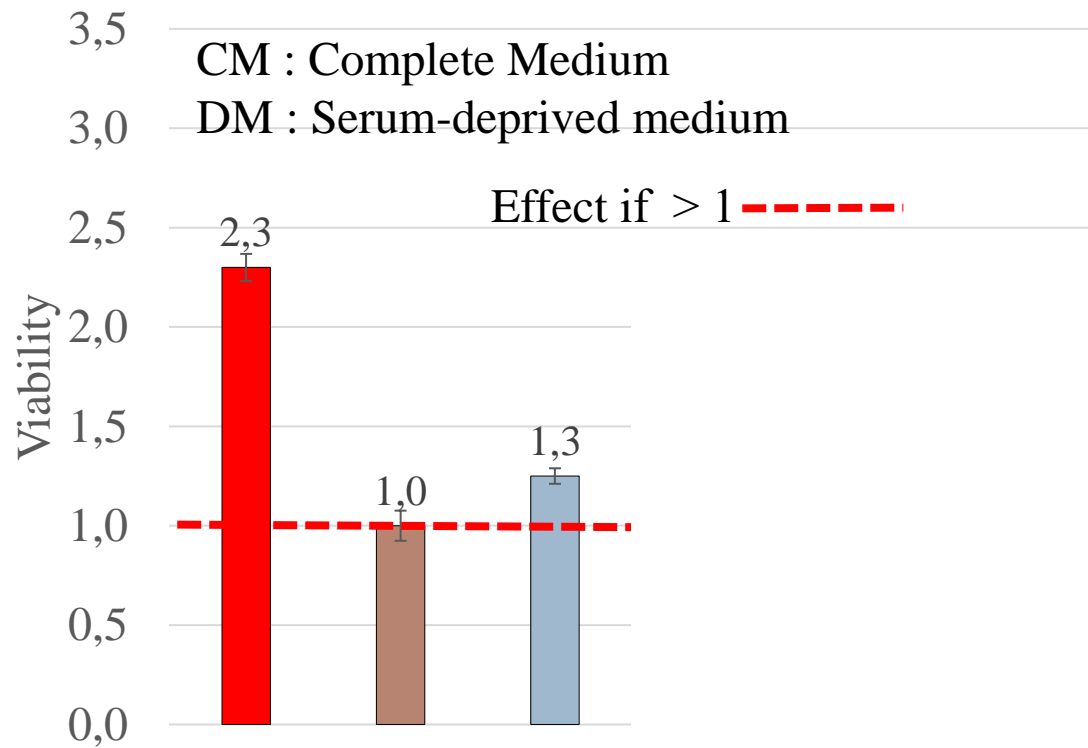
Mean fluorescence intensity (MFI)



# Characterization of the Final Product: Potency

## Patient #4: Cell Viability Tests

### Deprivation Test



CM

DM

EV-FBS  
 $10^E+09$

1<sup>st</sup>

2<sup>nd</sup>

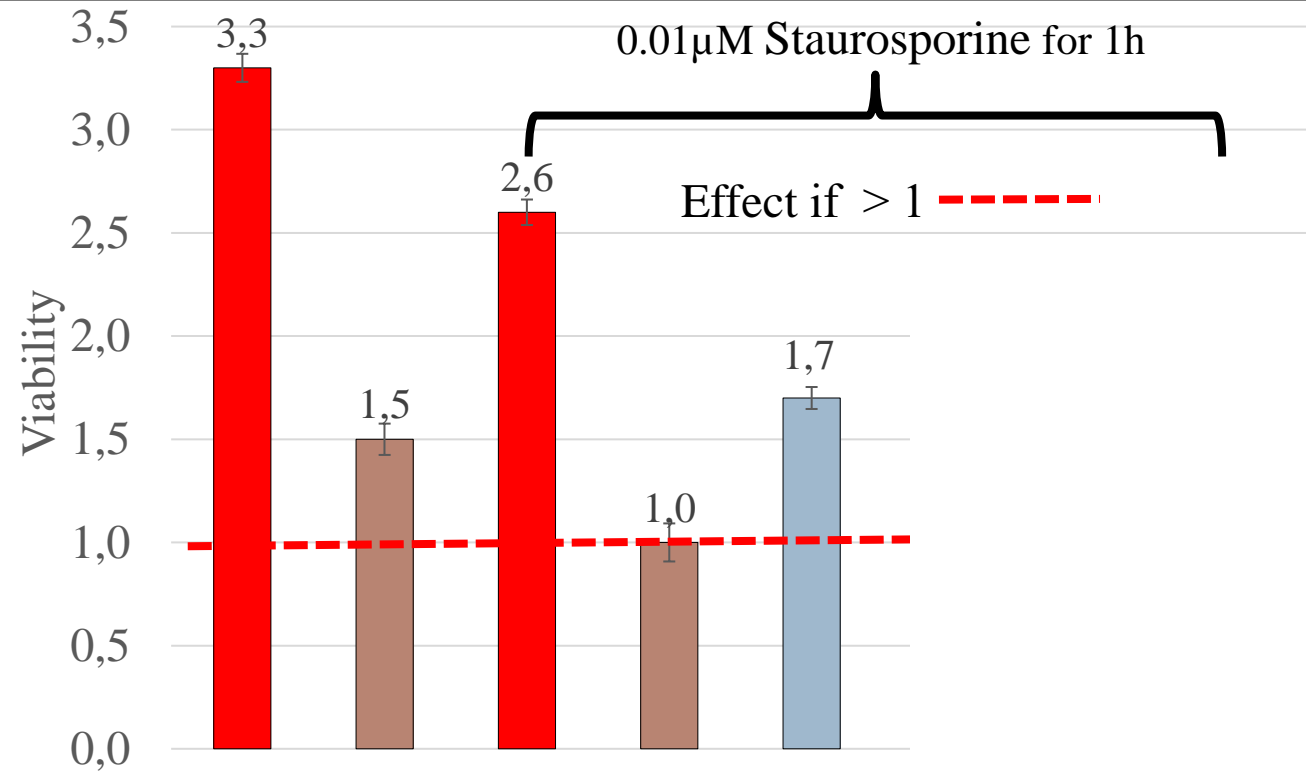
3<sup>rd</sup>

$5^E+09$

CONTROLS

SECRET-HF

### Staurosporine Test



CM

DM

CM

DM

EV-FBS  
 $10^E+0$

1<sup>st</sup>

2<sup>st</sup>

3<sup>rd</sup>

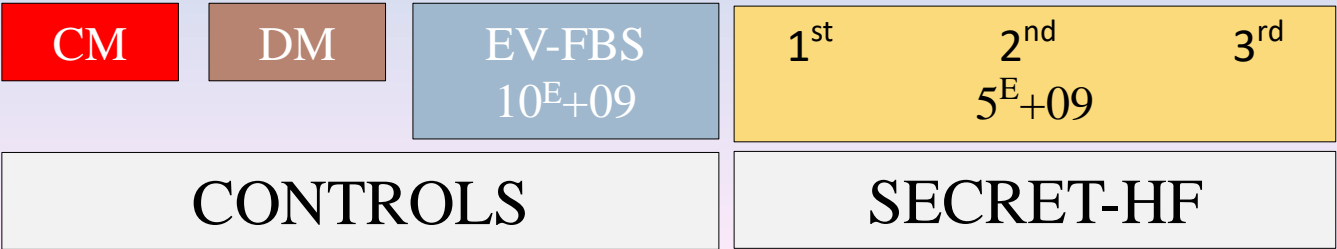
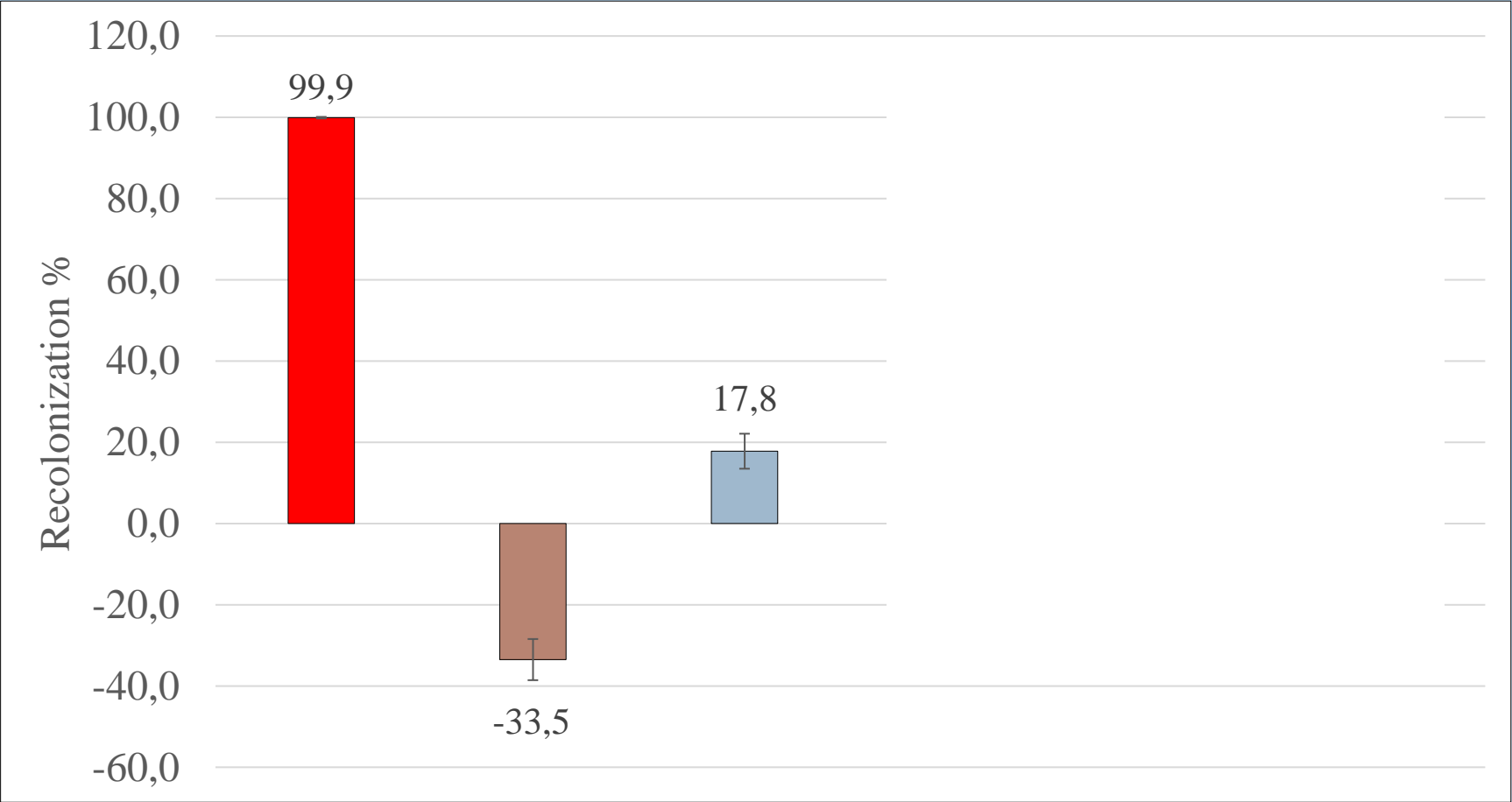
$5^E+09$

CONTROLS

SECRET  
-HF

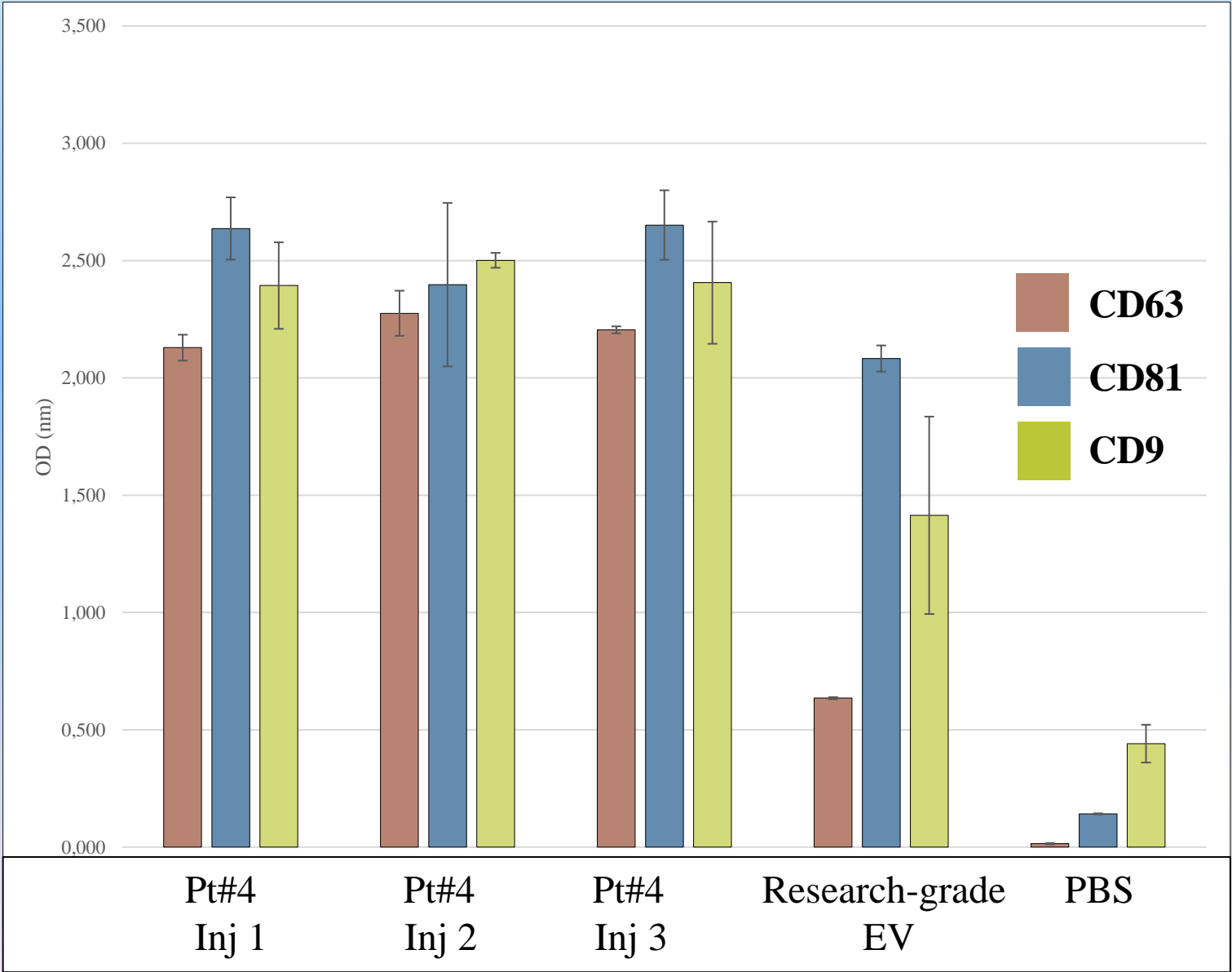
# Characterization of the Final Product: Potency

## Patient #4: Angiogenesis Test

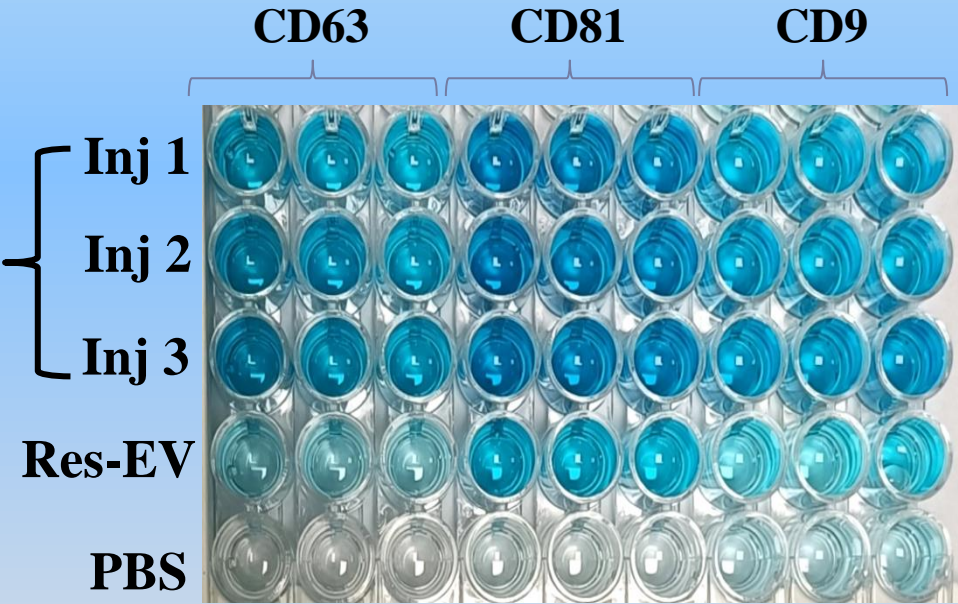


CM : Complete Medium  
DM : Serum-deprived medium

# Characterization of EV by ELISA Test for CD63, CD81 and CD9 (EV markers)



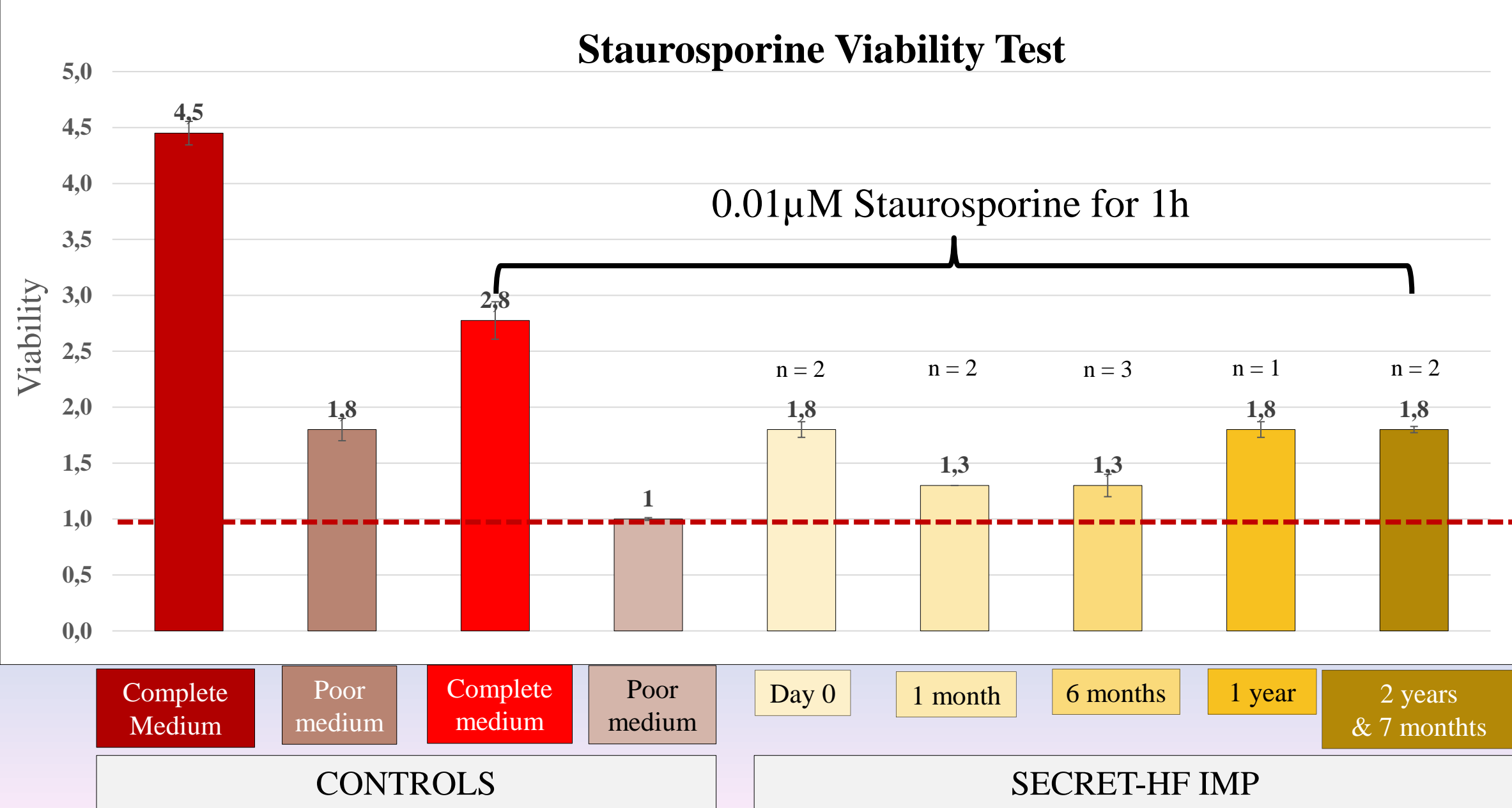
Patient # 4 : EV of CTC-1



Blue = Positive markers

# Characterization of the Final Product: Stability

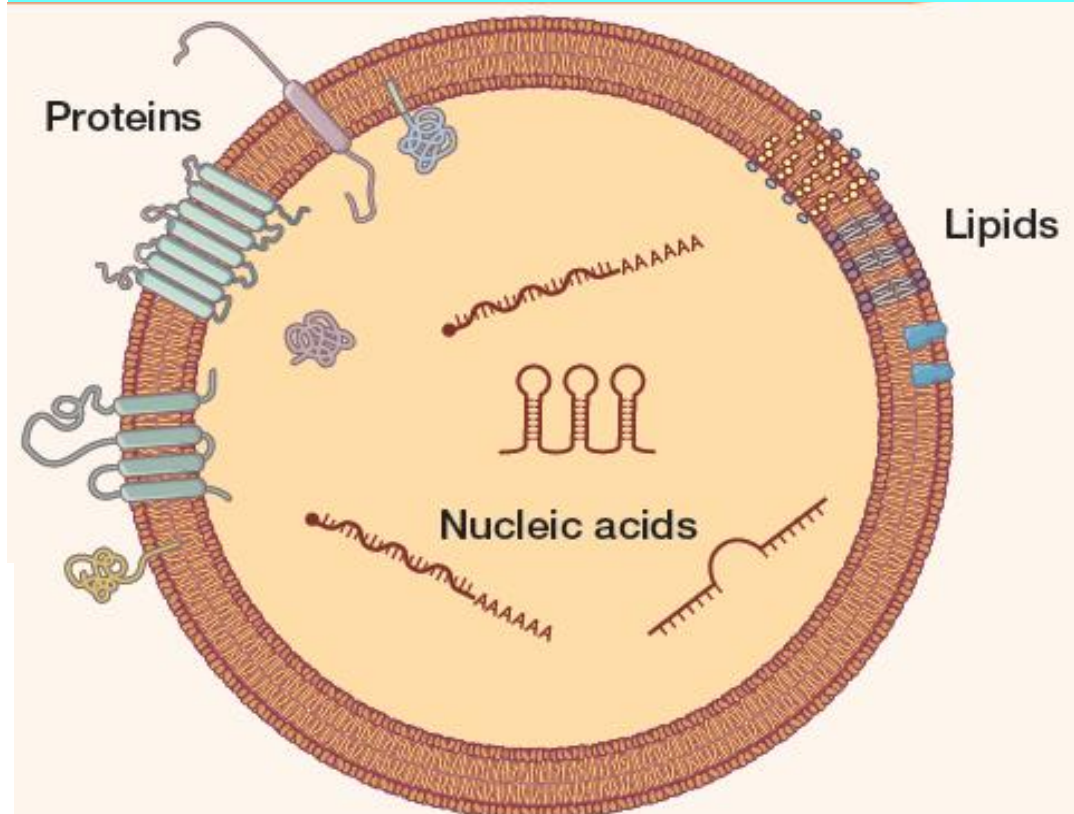
Effect  
if > 1






# Use of Secretome for Heart Failure: Translational Issues

- Mapping of the cargo content by omics
- Bioinformatics-based prediction of targets



SECRET-HF: Quality Controls


FCDI-CTC1	In-process	Final clinical-grade product
Viability		
Identity	Number and size of particles	
Purity	EV marker identity	
Sterility	Protein concentration	
Genomic integrity		
Adventitious agent screening	Sterility	Toxicity
		Tumorigenicity



# Final Product Preparation and Delivery



# Biothérapies et Pathologies Cardiaques : Quelle Biothérapie pour quel Effet ?

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# Cardiac Cell Therapy Clinical Trials

## Pluripotent stem cells

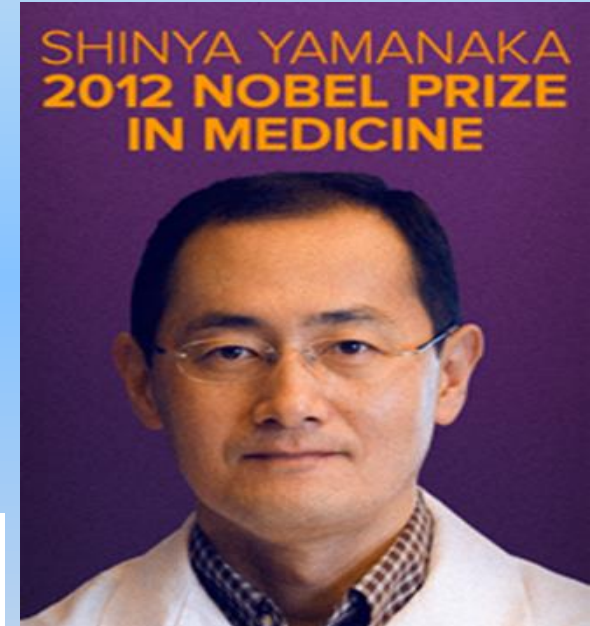


ESC

Cardiomyocytes



iPSC

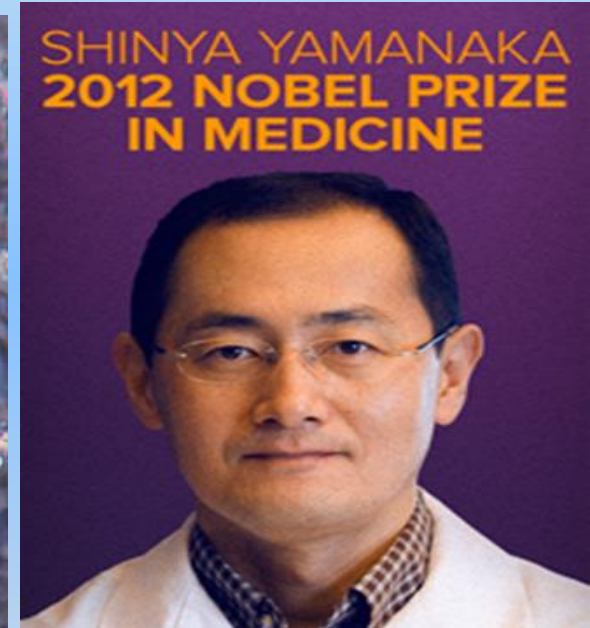
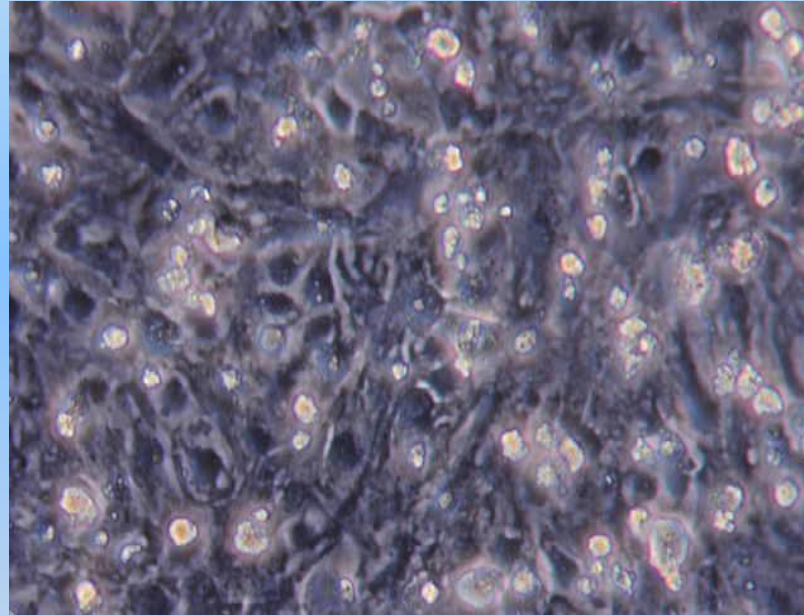


- Cardiovascular differentiation potential in response to specific cues
- Possibility of controlling the maturation stage
- Scalability



# Cardiac Cell Therapy Clinical Trials

## Pluripotent stem cells



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- Scalability

# Cardiac Cell Therapy Clinical Trials



JACC 2018;71:429-38.

## ESCORT Trial

- 6 patients with severe LV dysfunction ( $EF \leq 35\%$ )
- SSEA-1 *Isl*-1<sup>+</sup> cardiac progenitors embedded in a surgically delivered fibrin patch
- Outcome measures:
  - ✓ **Feasibility**: Scale-up, cardiac specification, purification

➡ Established

- ✓ **Safety**: Arrhythmias (ICD recordings), tumor (whole-body CT & PET scans), allo-immunization (donor-specific antibodies)

➡ No safety issues (FU: 7 yrs and 6 mo-10 yrs)

# PSC Clinical Trials

## Surgical Delivery

Study ID	Nb Pts	Cell source	Dosing X 10 <sup>6</sup>	Indication	Delivery	Status
jRCT2053190081	10	iPSC	33/patch (3 patches)	Ischemic	Cell sheet/Stand-alone	Not recruiting
NCT04696328	10	iPSC		Ischemic	Cell sheet/Stand-alone	Unknown
jRCTa032200189	3	iPSC	50	Ischemic	+ CABG	Completed
LAPIS NCT04945018	10	iPSC	50/150	Ischemic	+ CABG	Active
Bio-VAT NCT 04396899	53	iPSC	200/800 (5-20 patches)	Ischemic & non ischemic	Collagen patch/ Stand alone	Active
HEAL NCT03763136	20	iPSC	200	Ischemic	+ CABG	Active
NCT05566600	32	iPSC	100/200/400	Ischemic	+ CABG	Active
NCT05223894	20	iPSC	100	Ischemic	+ CABG	Active
NCT05647213	50	iPSC Autologous skin cells to cardiac lineage	? (dose- escalating)	CHD	?	Active

## Catheter-based Delivery

HECTOR NCT05068674	18	ESC	50/150/300	Ischemic	Endoventricular	Suspended
NCT04982081	20	iPSC	100/400	Ischemic	Endoventricular	Not yet recruiting

# Key Translational Challenges

## Strategies

- Patch delivery
- Anti-arrhythmic drugs
- **Optimization of cell maturation**
- Gene editing ?

## PSC

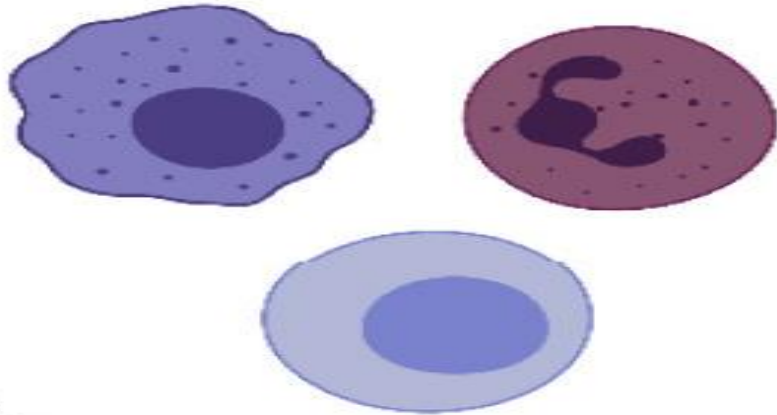
**Challenge:**  
Ventricular arrhythmias  
due to automaticity of  
PSC-CMs





# Key Translational Challenges

## Challenge: Immune rejection

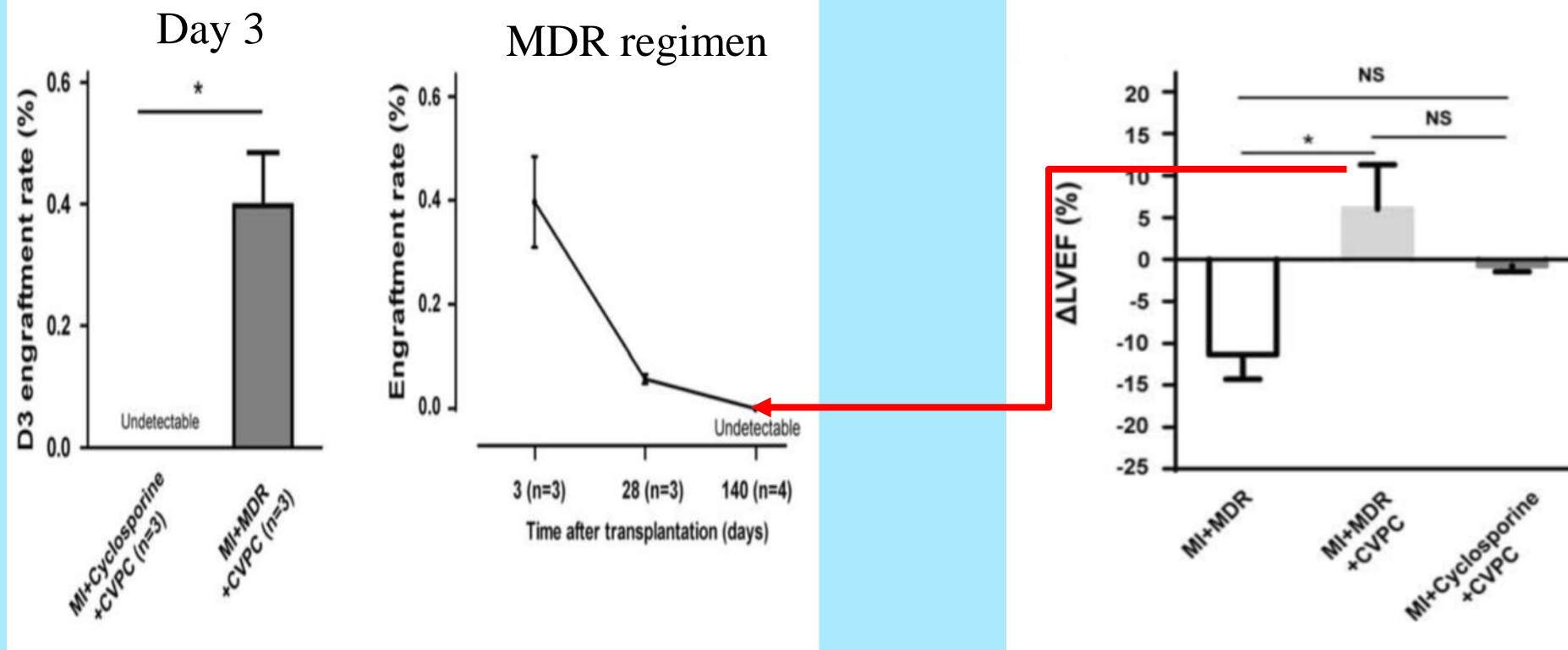


## PSC



- Completeness of differentiation
- Extent of differentiation (CPC *vs.* Mature CM; optimal CM/EC/Fb ratio)
- Arrhythmias
- Immune response
- Persistence of engraftment

# Key Translational Challenges

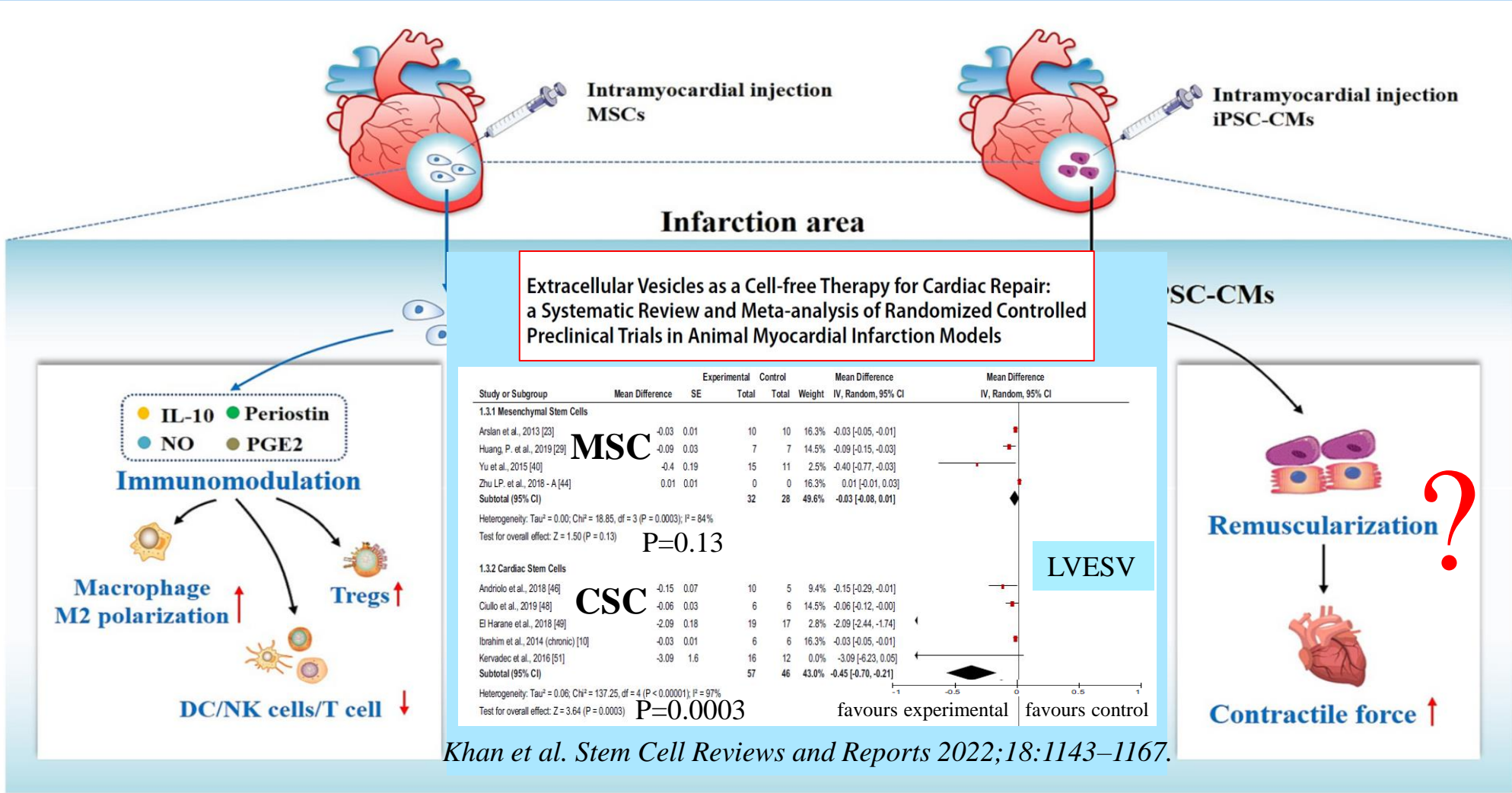
« Our observations clearly exclude remuscularization as an important mechanism whereby hPSC-CVPCs (cardiovascular progenitors) improve LV function after MI in primates »



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# Common and Distinct Mechanisms of Action of the Most Investigated Stem Cells for Cardiac Repair



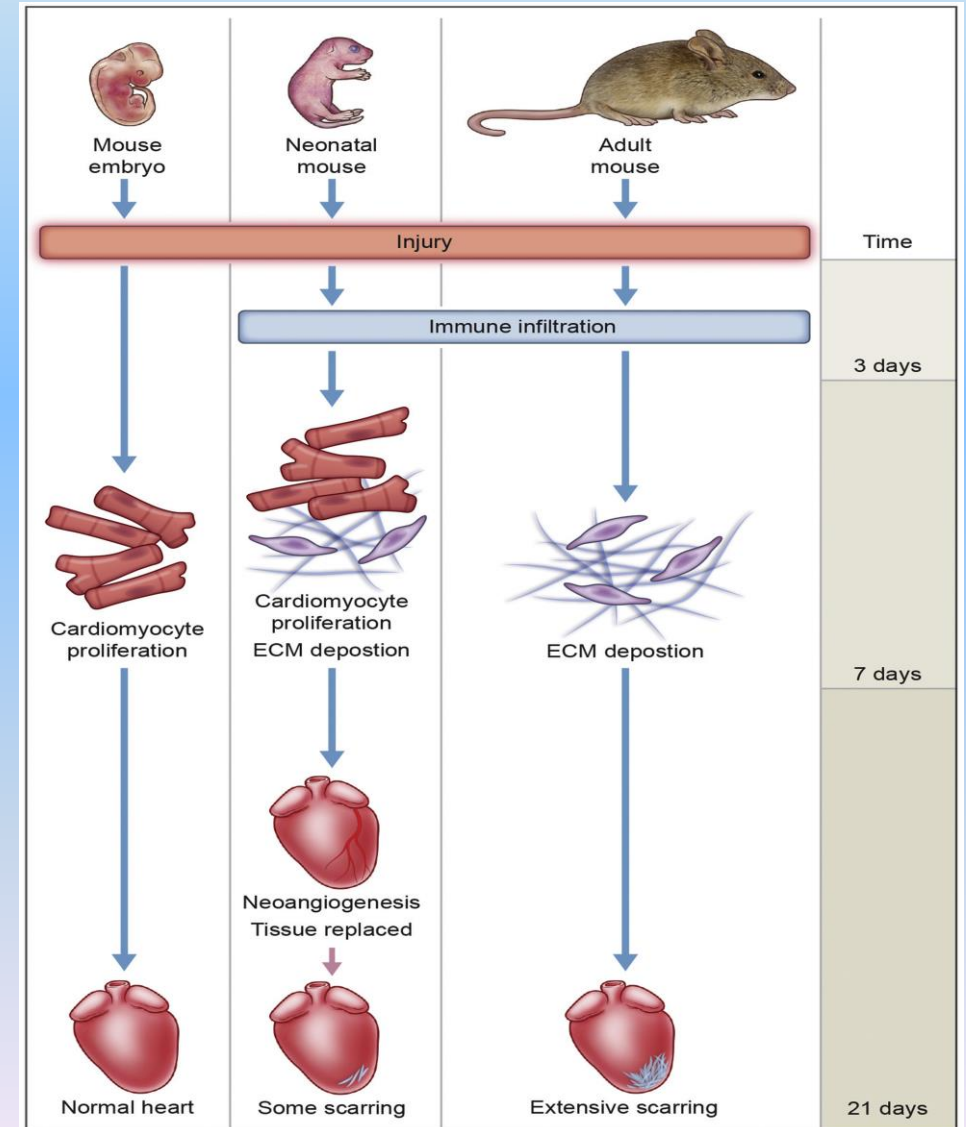
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# Biothérapies et Pathologies Cardiaques : Quelle Biothérapie pour quel Effet ?

## Cardiac Regeneration

- In the mammalian heart, cardiomyocyte proliferation is turned off shortly after birth
- However, the mechanisms of cell cycling are still in place
- Their reactivation might improve pump function



# Biothérapies et Pathologies Cardiaques : Quelle Biothérapie pour quel Effet ?

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## Functional Recovery of a Human Neonatal Heart After Severe Myocardial Infarction

Rationale: Cardiac remodeling and subsequent heart failure remain critical issues after myocardial infarction despite improved treatment and reperfusion strategies. Recently, cardiac regeneration has been demonstrated in fish and newborn mice after apex resection or cardiac infarctions. Two key issues remain to translate findings in model organisms to future therapies in humans: what is the mechanism and can cardiac regeneration indeed occur in newborn humans?

Objective: To assess whether human neonatal hearts can functionally recover after myocardial infarction.

Methods and Results: Here, we report the case of a newborn child having a severe myocardial infarction due to coronary artery occlusion. The child developed massive cardiac damage as defined by serum markers for cardiomyocyte cell death, electrocardiograms, echocardiography, and cardiac angiography. Remarkably, within weeks after the initial ischemic insult, we observed functional cardiac recovery, which translated into long-term normal heart function.

Conclusions: These data indicate that, similar to neonatal rodents, newborn humans might have the intrinsic capacity to repair myocardial damage and completely recover cardiac function.

*Haubner et al. Circ Res 2016;118:216-221.*



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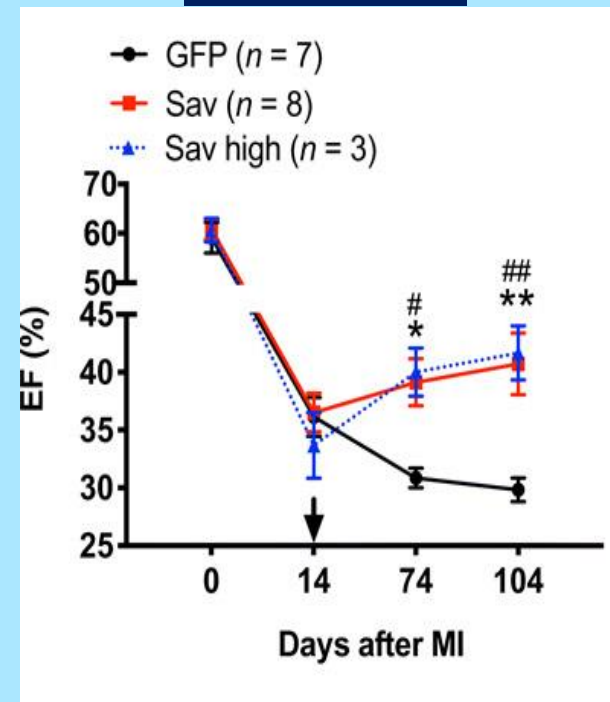
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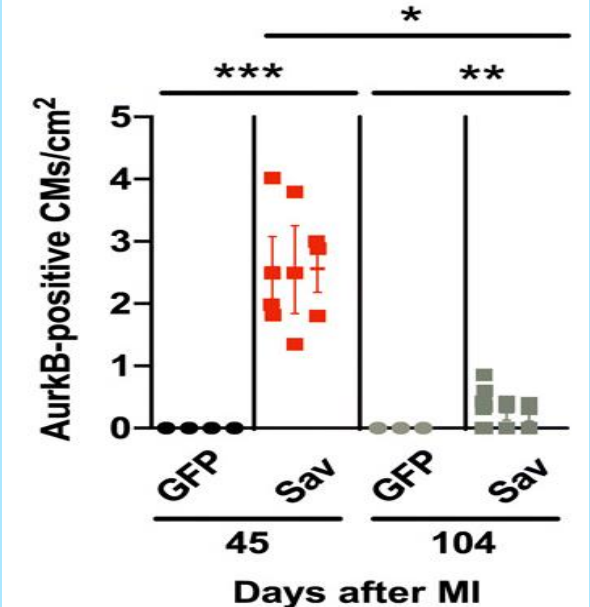
Gene therapy knockdown of Hippo signaling induces cardiomyocyte renewal in pigs after myocardial infarction

(AAV9)–based gene therapy to locally **knock down the Hippo pathway gene Salvador (Sav)** in a pig model of ischemia/reperfusion

### LV Function



### Cardiomyocyte proliferation

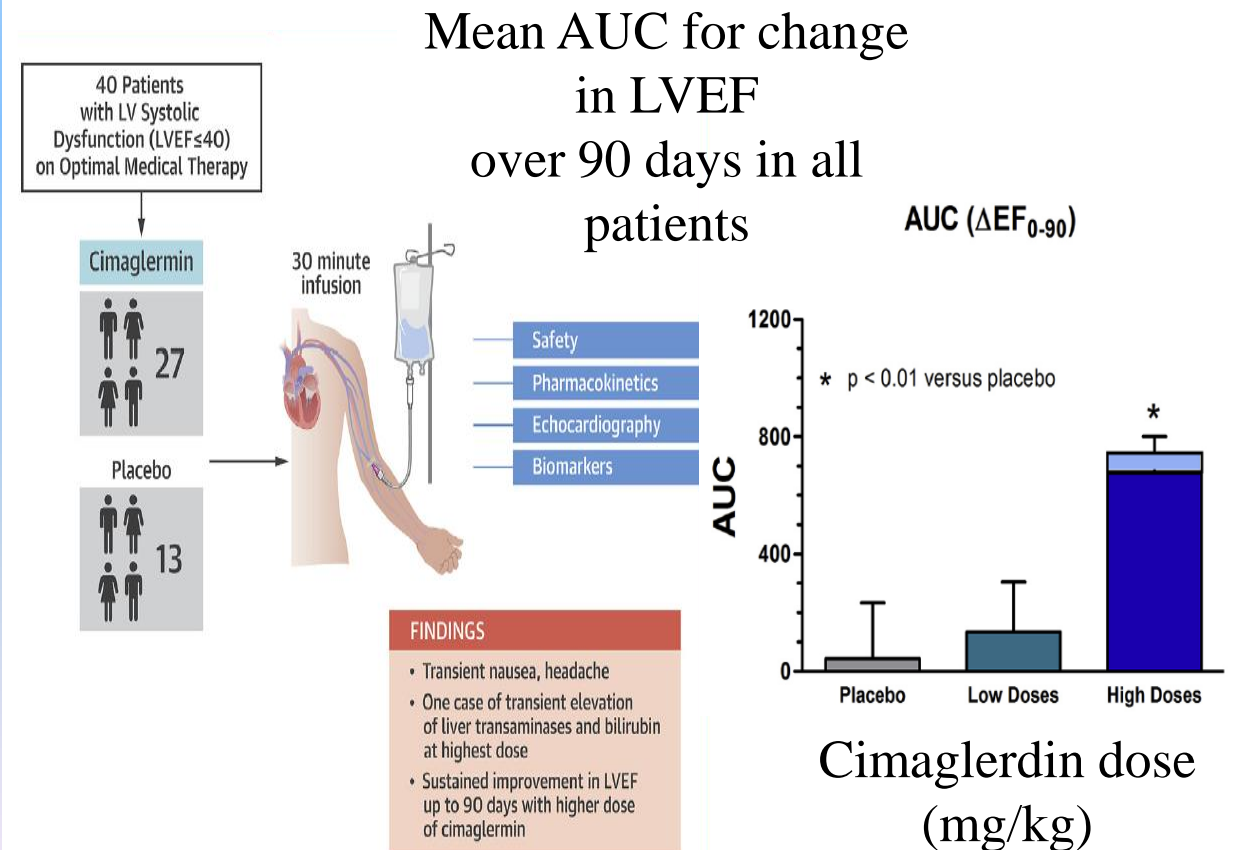


# Biothérapies et Pathologies Cardiaques : Quelle Biothérapie pour quel Effet ?

## Factors Inducing Cardiac Regeneration

- Small molecules
- Non coding RNAs
- Gene therapy
- mRNAs

### A Phase I, Single Ascending Dose Study of Cimaglermin Alfa (Neuregulin 1 $\beta$ 3) in Patients With Systolic Dysfunction and Heart Failure



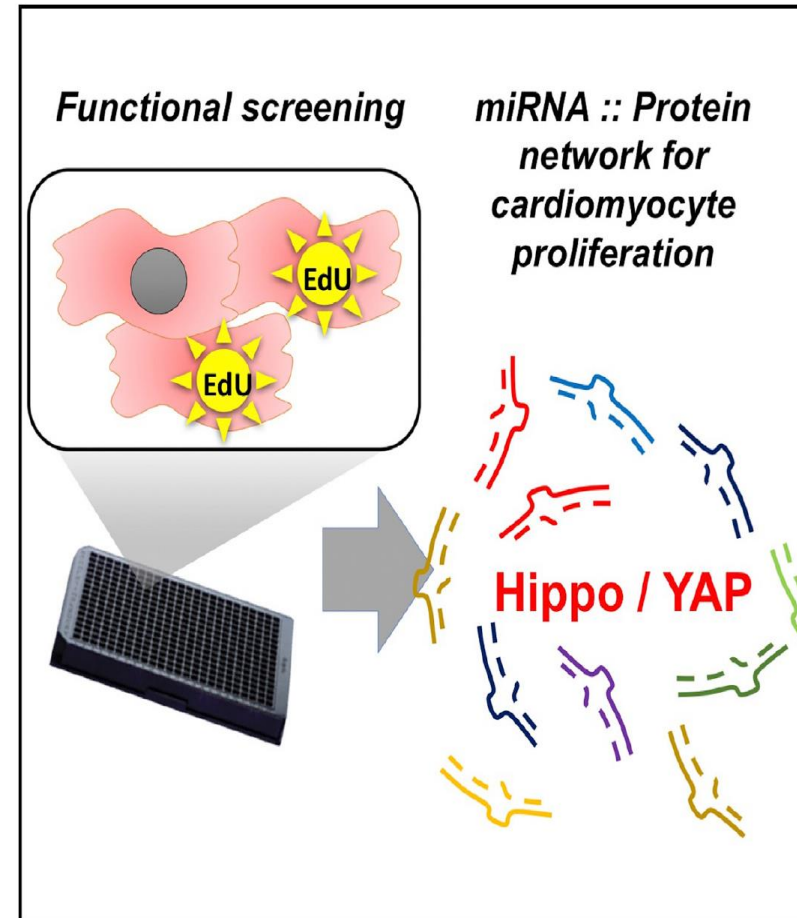
Lenihan et al. *J Am Coll Cardiol Basic Trans Science* 2016;1:576–86.

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- Gene therapy
- mRNAs

### miRNAs that Induce Human Cardiomyocyte Proliferation Converge on the Hippo Pathway



miR'ome screens reveals that 96 miRNAs promote human iPSC-derived cardiomyocyte replication

Most of the miRNAs act by inhibiting Hippo signaling

The data suggest highly redundant regulation of Hippo components by many miRNAs

# Biothérapies et Pathologies Cardiaques : Quelle Biothérapie pour quel Effet ?

## Factors Inducing Cardiac Regeneration

- Small molecules
- Non coding RNAs
- Gene therapy
- mRNAs

## Challenges Associated With Gene Therapy

### AAV:

- Immune response limiting to a single dose
- Liver toxicity
- Thrombotic microangiopathy (at high AAV doses in a subset of patients with pre-existing antibodies or rapid antibody responses)

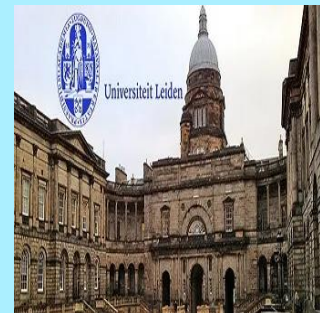
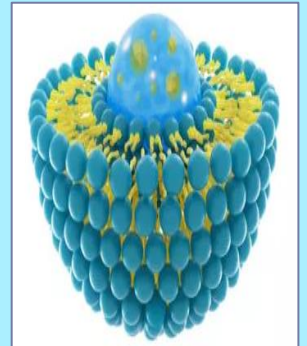
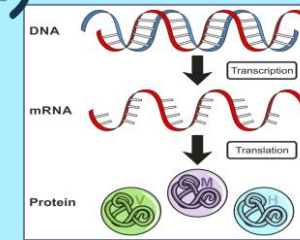
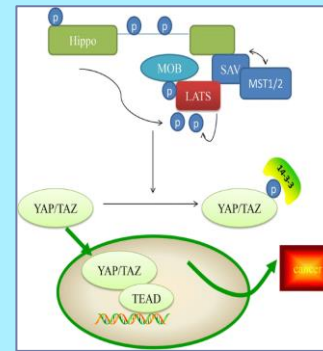
**Lentiviruses:** Genotoxicity

**All:** Manufacturing, scale-up and costs

# Biothérapies et Pathologies Cardiaques : Quelle Biothérapie pour quel Effet ?

## Factors Inducing Cardiac Regeneration

- Small molecules
- Non coding RNAs
- Gene therapy
- mRNAs



Horizon Europe  
Programme





## Issues Associated With mRNAs for Cardiac Regeneration

- Efficiency of the LNP-mediated transfection of the target cardiomyocytes
- Cardiomyocyte-specific expression of the pro-proliferation factors(s)
- Achievement of therapeutically active levels of the translated factor(s)
- Arrhythmia-free coupling of the newly formed cardiomyocytes with the resident ones

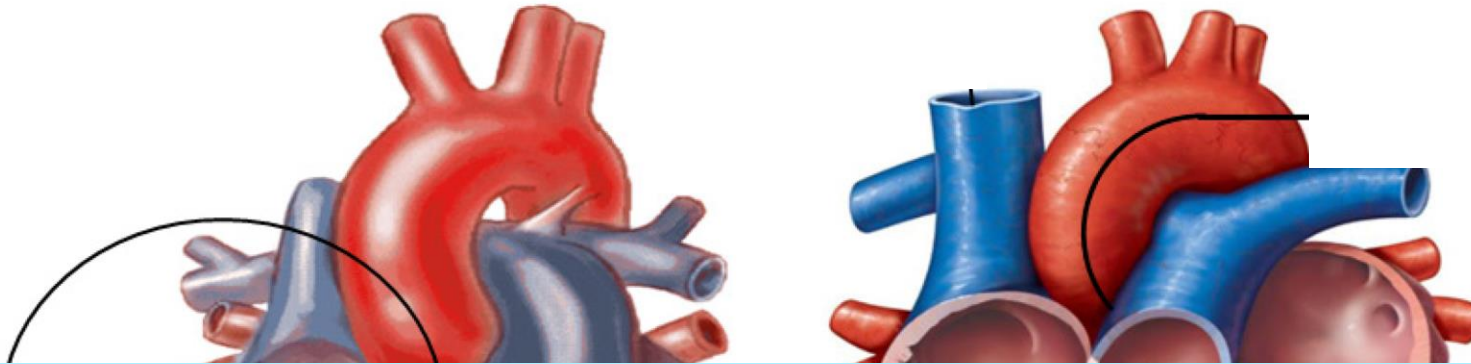


# Biothérapies et Pathologies Cardiaques : Quelle Biothérapie pour quel Effet ?

## Outline

- Repair vs. regeneration
- **Delivery issues**
- Remaining challenges

# The Issue of Delivery



Interest of the IV route for the delivery of a cellular secretome

- Absence of invasiveness
- Ease/low cost of implementation expanding potential indications
- **Possibility of repeated administrations**

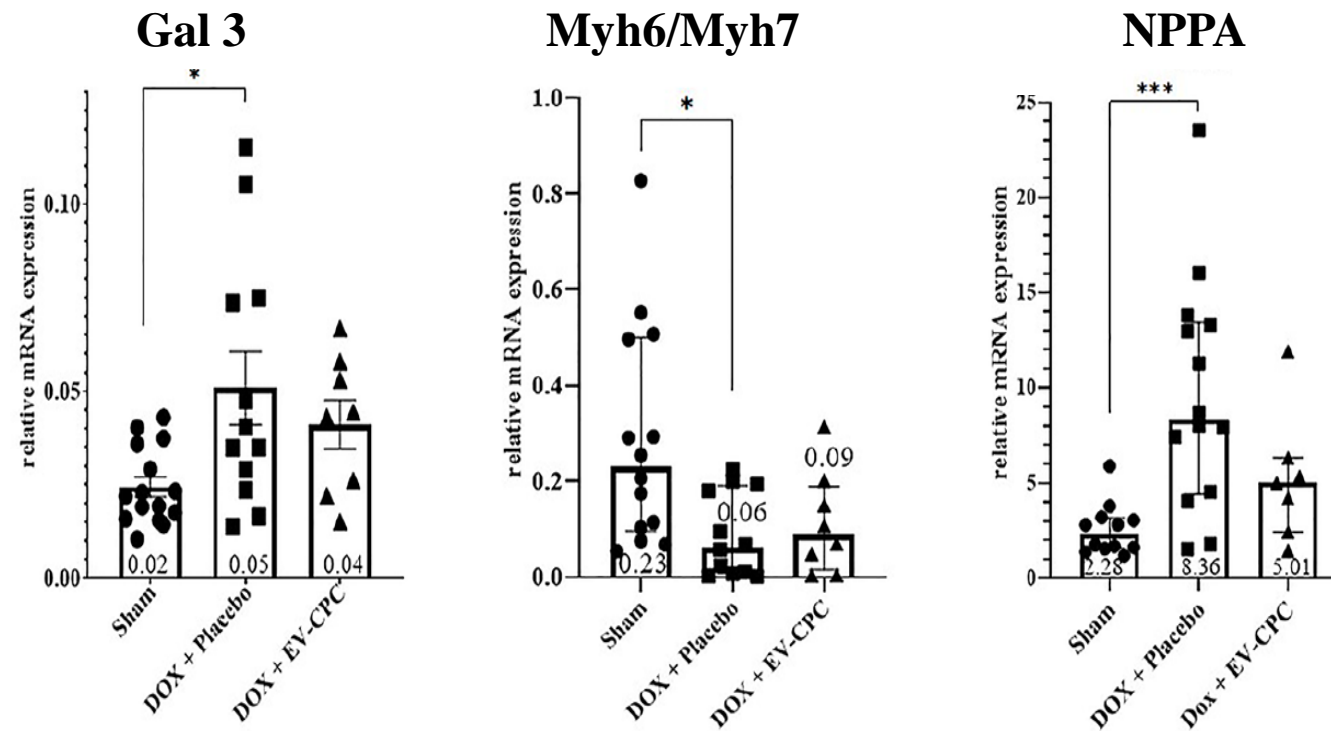
# The Paradox of IV Delivery of Cells

## Clinical Trials of Randomized Placebo-Controlled Intravenous Cell Therapy

Author	Patient Population	Trial Design	FU	Outcome
<b>Hare</b> <i>J Am Coll Cardiol.</i> 2009;54:2277-86.	Acute MI LVEF ~ 50% Placebo:21; MSC:39	Allogeneic BM-MSC Double-blind Dose-ranging 0.5, 1.6 and 5 x 10 <sup>6</sup> cells/kg	6 mo.	↑ LVEF ↓ Remodeling ↓ VT
<b>Butler</b> <i>Circ Res</i> 2017;120:332-40.	Nonischemic cardiomyopathy LVEF ≤40% Placebo: 12; MSC:10	Allogeneic BM-MSC Single-blind 1.5×10 <sup>6</sup> cells/kg	3 mo.	↑ 6 min WT ↑ Functional scores
<b>Bartolucci</b> <i>Circ Res</i> 2017;121: 1192-1204.	Ischemic & nonischemic cardiomyopathy LVEF ≤40% Placebo:15; MSC:15	Allogeneic UC-MSC Double-blind 1×10 <sup>6</sup> cells/kg	1 yr	↑ LVEF ↑ Functional scores

# The Paradox of IV Delivery of Cell Products

Therapeutic potential of extracellular vesicles derived from cardiac progenitor cells in rodent models of chemotherapy-induced cardiomyopathy



# Extracellular Vesicles as a Cell-free Therapy for Cardiac Repair: a Systematic Review and Meta-analysis of Randomized Controlled Preclinical Trials in Animal Myocardial Infarction Models

37 studies, 703 animals

## Impact of the Route for Delivery (Meta-regression Analysis)

Criteria	Subgroups	Mean difference [95%CI]	P-value
EF	Local (N=31)	7.97% [3.55, 12.39]	0.001
	Peripheral (N=7)	12.10% [9.54, 14.66]	<0.001
LVESV	Local (N=3)	-0.07mL [-0.10, 0.87]	0.878
	Peripheral (N=8)	-0.45mL [-1.06, 0.16]	0.131
LVEDV	Local (N=3)	-0.78mL [-1.48, -0.09]	0.030
	Peripheral (N=6)	-0.51mL [-0.91, -0.11]	0.016
Infarct size	Local (N=5)	-7.57% [-13.67, -1.46]	0.018
	Peripheral (N=18)	-10.60% [-14.35, -6.86]	<0.001

*Khan et al. Stem Cell Reviews and Reports 2022;18:1143–1167.*

# Cells/EV for the Treatment of Heart Failure

## Clarifying the Efficacy and MoA of Possible Delivery Routes

Requirement for the therapeutics  
to be present in the heart

Delivery  
route

No

IV

Yes

✓ IV

- Bypass of the MPS hepatic uptake
- Engineering of EV with heart-specific ligands

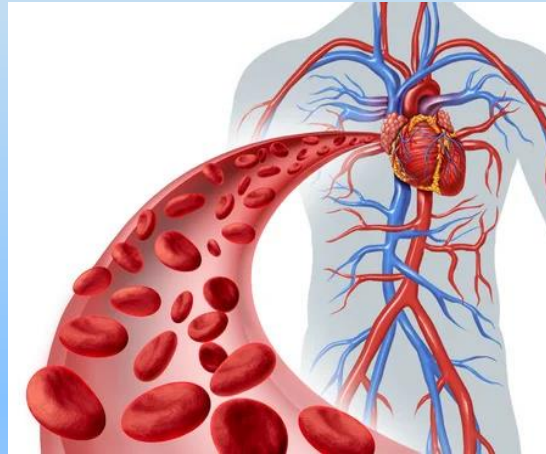
✓ Local



# The “Bioreactor” Hypothesis

Cardiac tissue repair

Blood trafficking

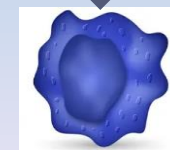
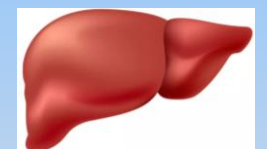
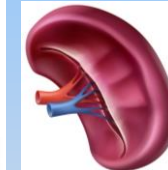
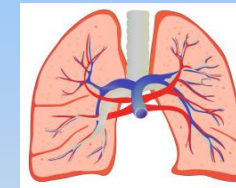
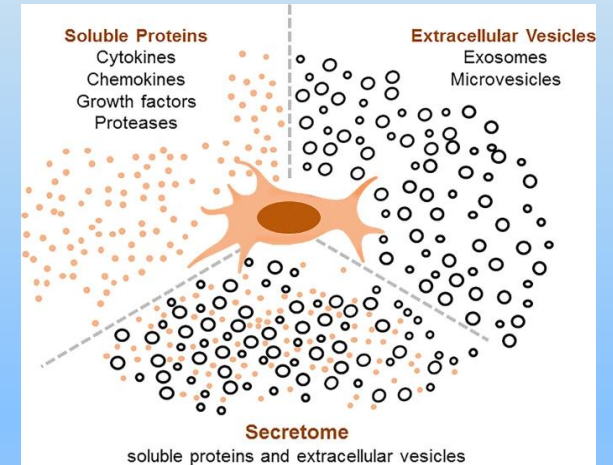
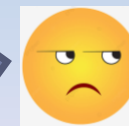


Reprogrammed  
host immune cell



Modulation of the immune response

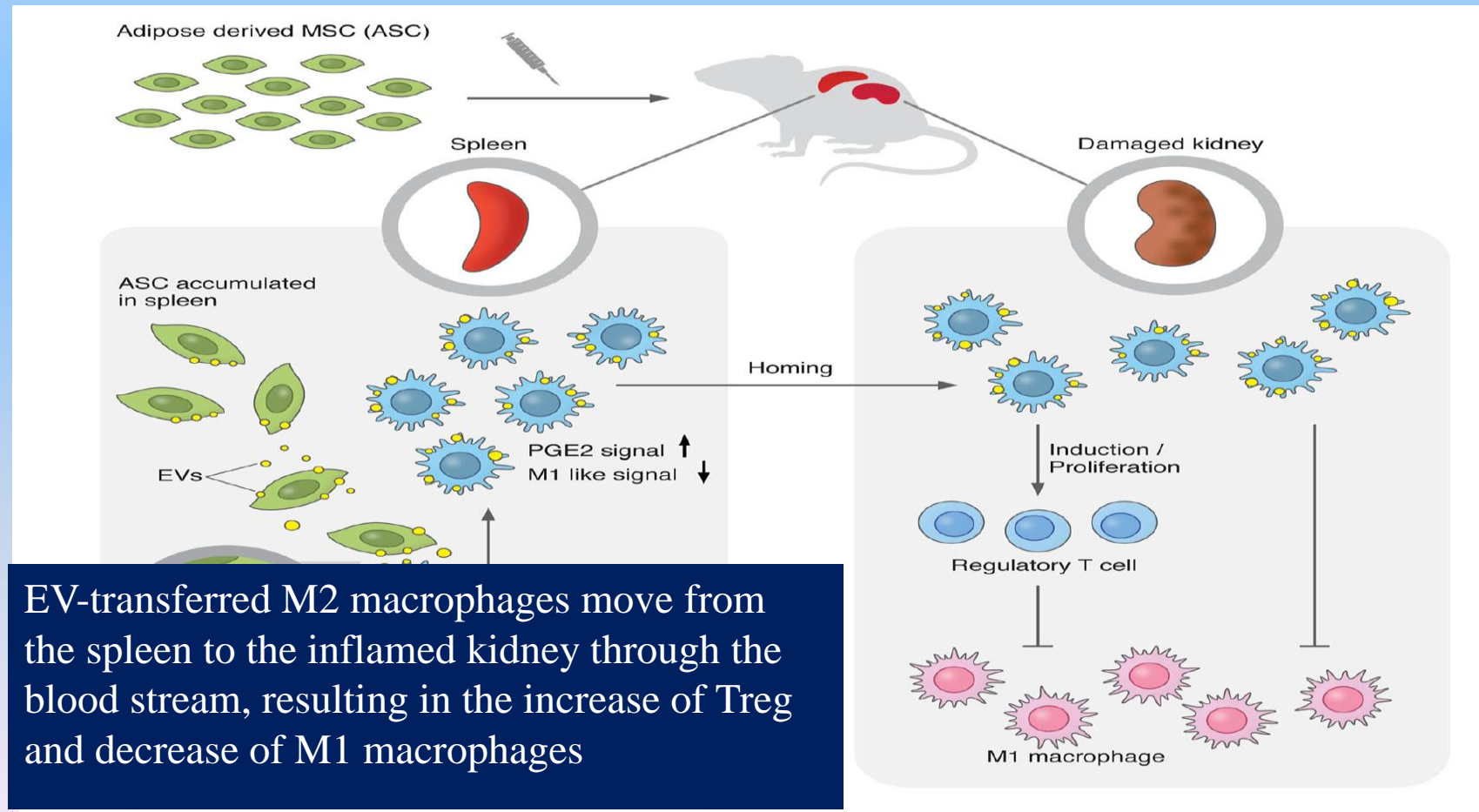
- Down-regulation of pro-inflammatory signals
- Up-regulation of anti-inflammatory signals (↗ M2 macrophages, ↗ Treg)



Macrophage

# Mesenchymal stem cells exert renoprotection via extracellular vesicle-mediated modulation of M2 macrophages and spleen-kidney network

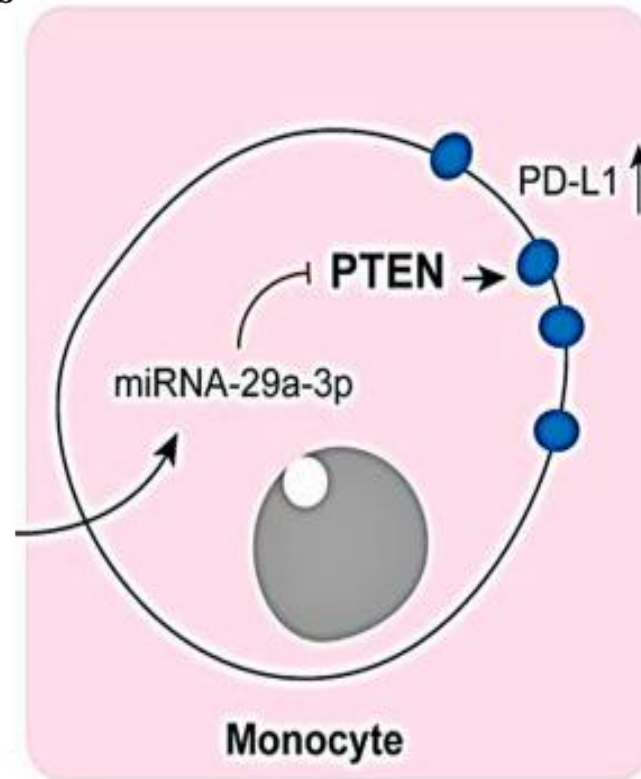
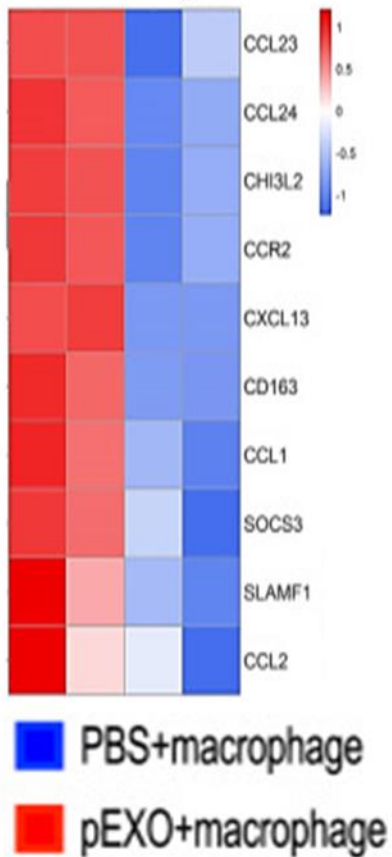
## Rat model of glomerulonephritis



EV-transferred M2 macrophages move from the spleen to the inflamed kidney through the blood stream, resulting in the increase of Treg and decrease of M1 macrophages

# Human Placental Exosomes Induce Maternal Systemic Immune Tolerance by Reprogramming Circulating Monocytes

Heatmap of 10 M2 markers



CD4<sup>+</sup> and CD8<sup>+</sup>T cell proliferation  
Treg differentiation

M2 macrophages  
MDSC-like

# Cells/EV for the Treatment of Heart Failure

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---

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Delivery  
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---

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✓ IV

- Bypass of the MPS hepatic uptake
- Engineering of EV with heart-specific ligands

✓ Local

# Cells/EV for the Treatment of Heart Failure

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Requirement for the therapeutics  
to be present in the heart

---

No

Yes

Delivery  
route

---

IV

✓ IV

- Bypass of the MPS hepatic uptake
- Engineering of EV with heart-specific ligands

✓ Local (mandatory for intended regeneration)

# Biothérapies et Pathologies Cardiaques : Quelle Biothérapie pour quel Effet ?

## Outline

- Repair vs. regeneration
- Delivery issues
- **Remaining challenges**



## Key Remaining Challenges

- Should we pursue the quest for regeneration or shift to a paracrinally-mediated repair?
- If the paracrine paradigm is privileged:
  - ✓ Can the therapeutic effects of the secretome be duplicated by just a few of its components?
  - ✓ What are the optimal dosing metrics?
  - ✓ Does its presumed mechanism of action (resetting of the immune system) validate a systemic delivery?
- How can we leverage the capabilities of AI for making CMC more cost-effective (enhancement of process efficiency, product quality, regulatory compliance) and prospectively identify responders vs. non responders to improve positive outcomes of clinical trials?

# Those Who Did the Work



# Those Who Did the Work

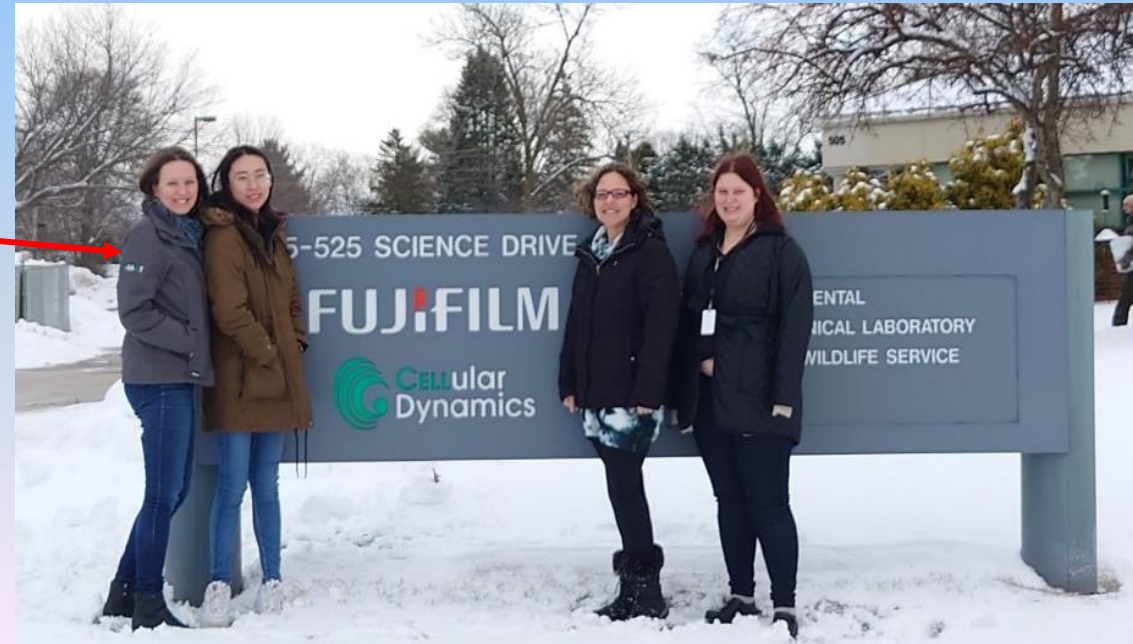


FCDI Innovation Facility  
for Advanced Cell Therapy  
(iFACT)



Nisa Renault

FUJIFILM  
Cellular Dynamics, Inc.  
(FCDI)  
EV team





# Those Who Did the Work



Centre MEARY de Thérapie Cellulaire et Génique  
de l'Assistance Publique – Hôpitaux de Paris  
(Centre MEARY – AP-HP)

Jérôme Larghero



# Funding Sources

