Thérapie Cellulaire. Coeur

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Société Francophone de Greffe de Moelle et de Thérapie Cellulaire
Montpellier, Novembre 23 2018

ESC Transplantation for Severe Heart Failure

Outline

- **Rationale**
- Protocol & Results
- Perspectives

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Evolution of Cardiac Cell Therapy Trials

Ongoing MSC Clinical Trials for Ischemic Heart Disease

Study	*n*	Cell source	Condition	Design	Delivery	ClinicalTrials ID
Chronic ischemic heart disease						
Jerome et al.	NYD	Autologous BM	Ischemic CM (LVAD)	Phase I	IM	NCT02460770
MESAMI2	90	Autologous BM	Chronic ischemic CM	Phase II	IM	NCT02462330
Dai et al.	45	Autologous BM	Chronic ischemic CM	Phase I/II	Collagen scaffold	NCT02635464
CONCERT-HF	144	Autologous BM	Ischemic CM	Phase II	IM	NCT02501811
Antonitsis et al.	30	Allogeneic BM	Ischemic CM needing CABG	Phase I	IM	NCT01753440
Antonitisis et al.	5	Allogeneic BM	Ischemic CM with LVAD	Phase I	IM	NCT01759212
Kastrup et al.	10	Allogeneic adipose tissue	Ischemic CM	Phase I	IM	NCT02387723
Kastrup et al.	81	Allogeneic adipose tissue	Ischemic CM	Phase II	IM	NCT03092284
SCIENCE	138	Allogeneic adipose tissue	Ischemic CM	Phase II	IM	NCT02673164
UCMSC-Heart	40	Allogeneic UC	Ischemic CM	Phase I/II	IC	NCT02439541
TRIDENT	60	Allogeneic BM	Ischemic CM	Phase II	IM	NCT02013674
DREAM HF-1	600	Allogeneic BM (rexlemestrocel-L)	Ischemic CM	Phase III	IM	NCT02032004
SEESUPIHD	64	Allogeneic UC	Ischemic CM	Phase I/II	IC	NCT02666391
TPAABPIHD	200	Autologous BM	Ischemic CM	Phase I/II	NYD	NCT02504437
Maskon et al.	80	Autologous BM	Ischemic dilated CM	Phase II	IC	NCT01720888
Harjula et al.	60	Autologous BM	Ischemic CM needing CABG	Phase II	IM	NCT00418418
TAC-HFT-II	55	Autologous BM + CSC	Ischemic CM	Phase I/II	IM	NCT02503280
TEAM-AMI	124	Autologous BM	Ischemic CM	Phase II	IC	NCT03047772
Nonischemic cardiomyopathy						
Hu et al.	30	Umbilical cord	Idiopathic dilated CM	Phase I	IM	NCT01219452
Olson et al.	45	Allogeneic BM	Anthracycline-mediated CM	Phase I	IV	NCT02408432
Fernandez-Avilez et al.	70	Autologous BM	Idiopathic dilated CM	Phase I/II	IM	NCT01957826
Bartolucci et al.	30	Allogeneic UC	Dilated CM	Phase I/II	IV	NCT01739777

Ward et al. Stem Cells Transl Med 2018;7:543-50.

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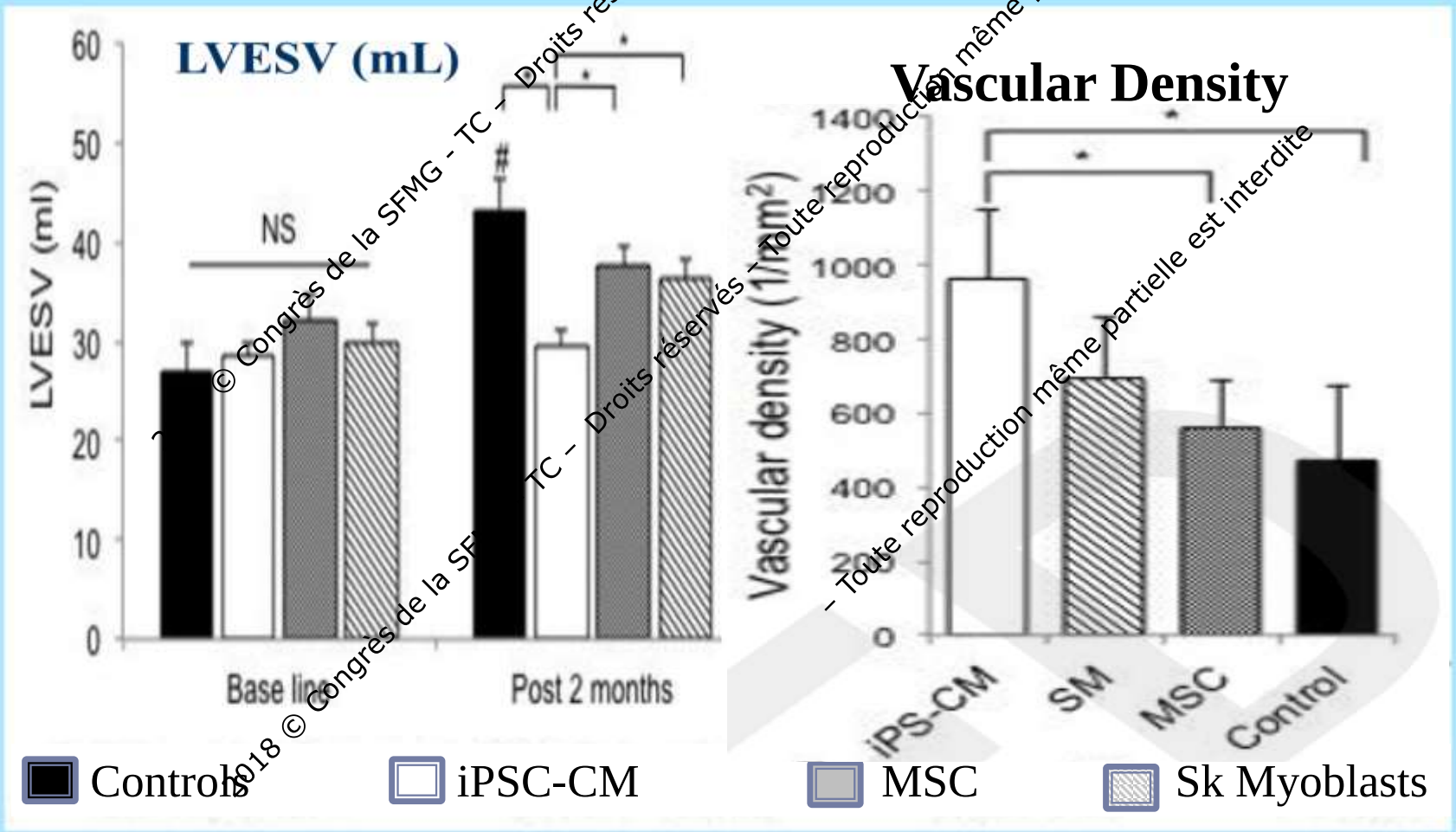
Adapted from Banerjee et al. Circ Res 2018;123:266-287.

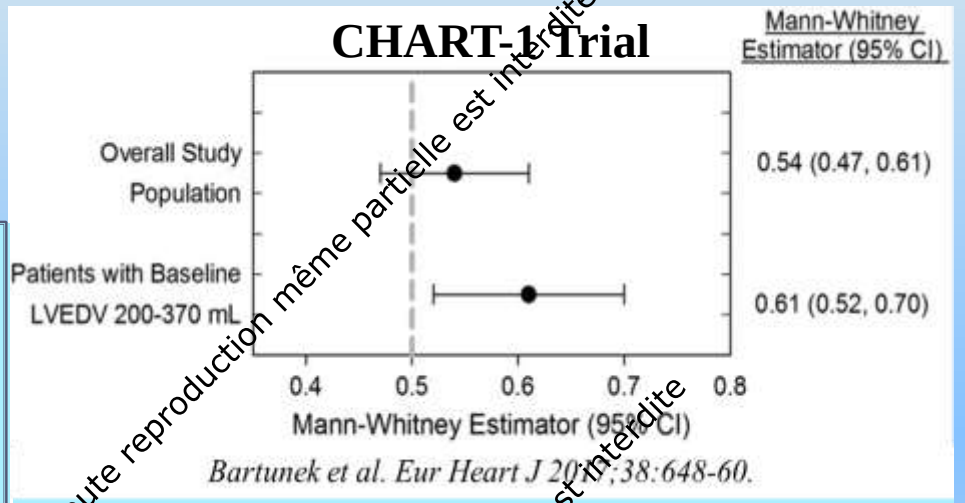
Transplantation of human induced pluripotent stem cell-derived cardiomyocytes is superior to somatic stem cell therapy for restoring cardiac function and oxygen consumption in a porcine model of myocardial



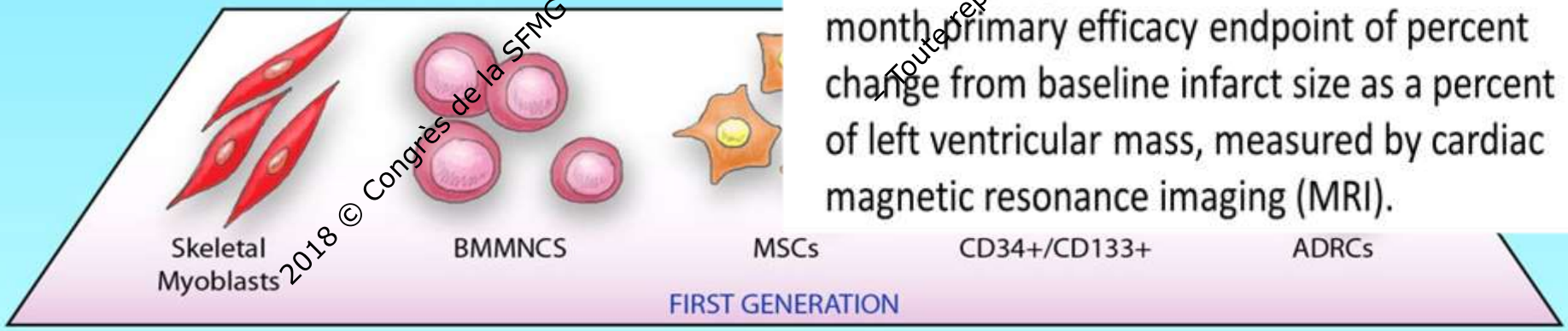
Ishida et al. Transplantation (on-line, August 5, 2018)

Evolution of Cardiac Cell Therapy Trials

Harvard Medical School and Brigham and Women's Hospital have recommended that 31 papers from a former lab director be retracted from medical journals.
October 14, 2018



- **Capricor Therapeutics Provides Update on ALLSTAR Trial (May 12, 2017)**
- Low probability (futility) of achieving a statistically significant difference in the 12-month primary efficacy endpoint of percent change from baseline infarct size as a percent of left ventricular mass, measured by cardiac magnetic resonance imaging (MRI).



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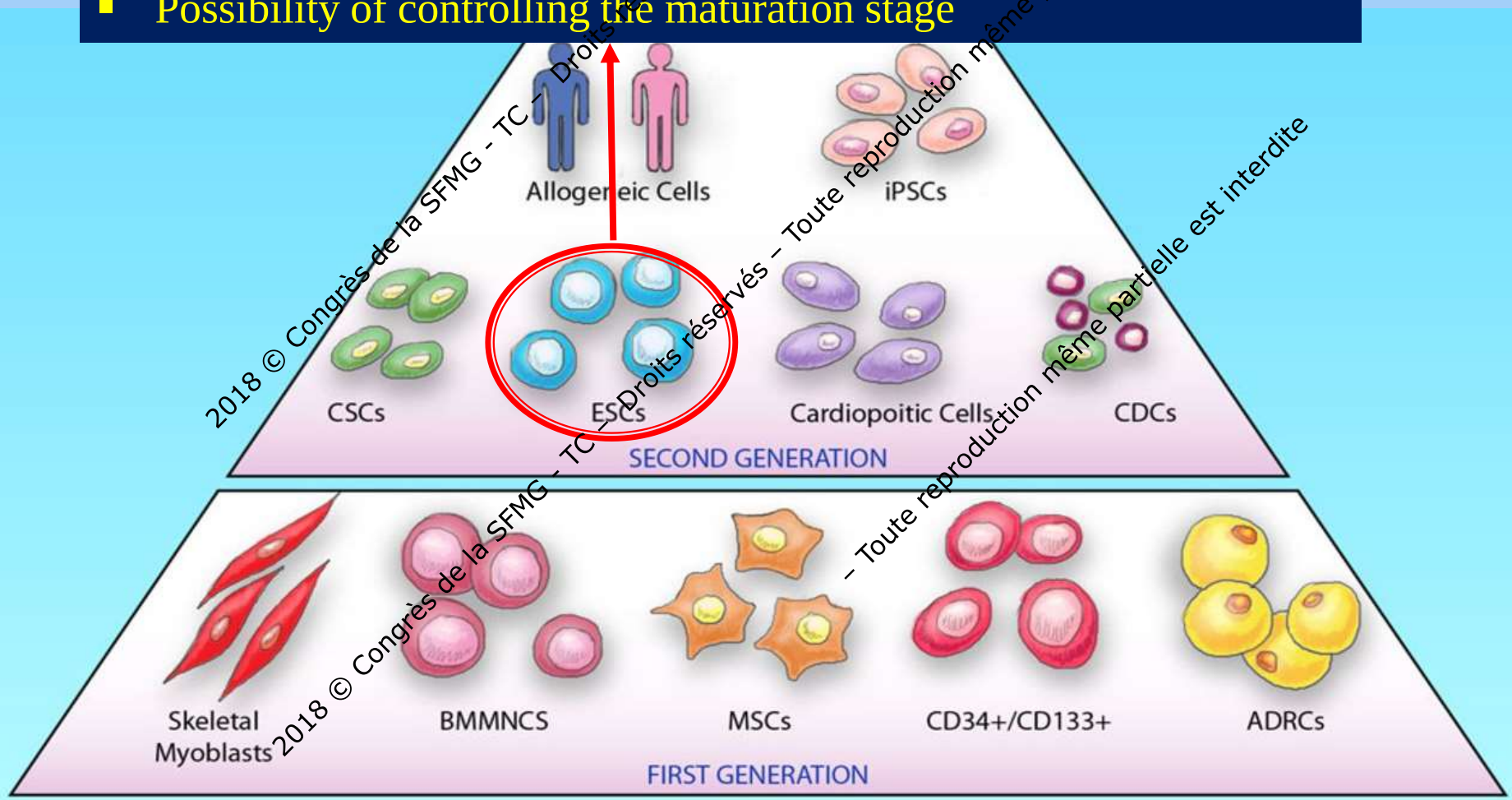
Evolution of Cardiac Cell Therapy Trials

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



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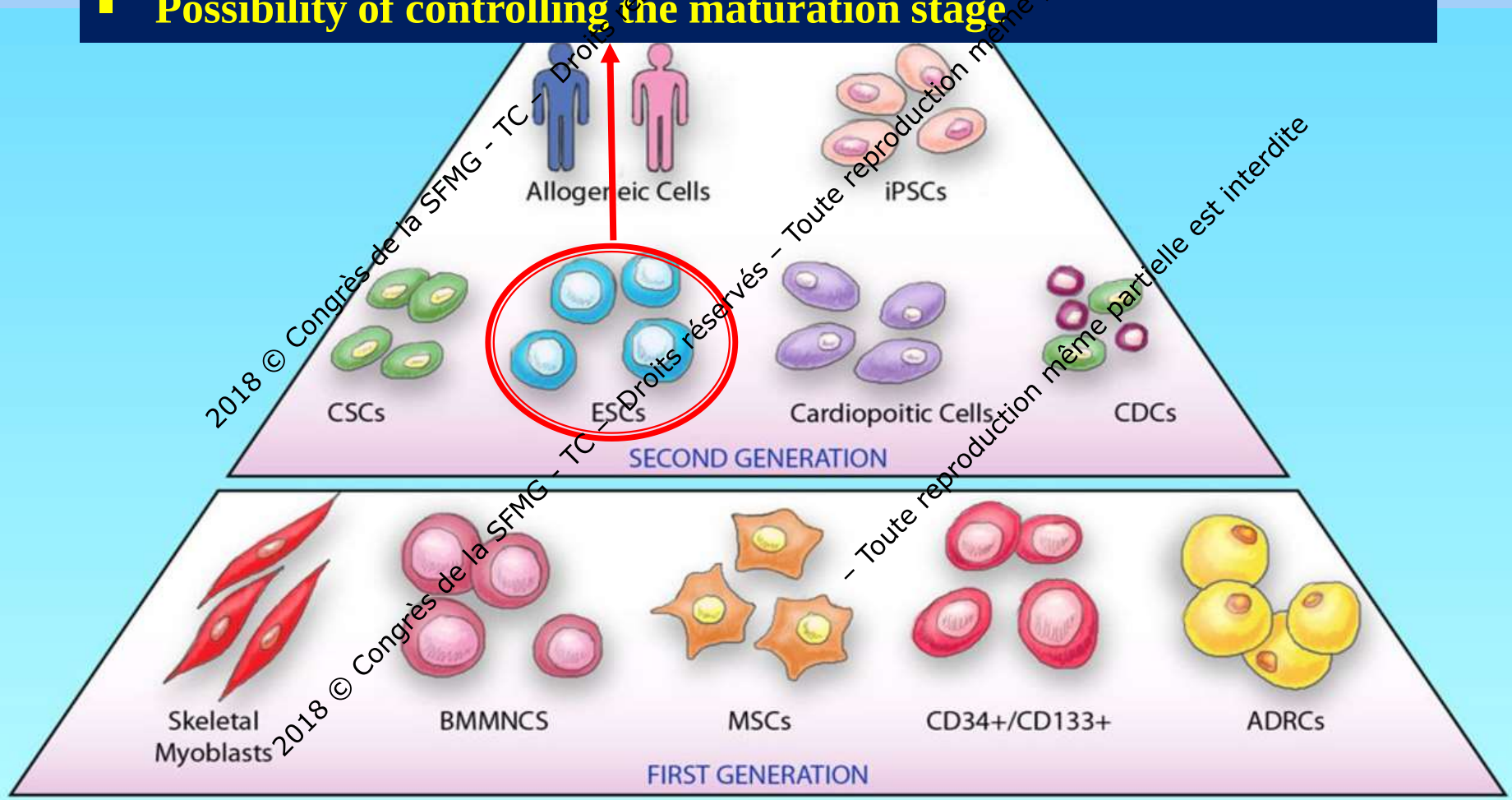

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Evolution of Cardiac Cell Therapy Trials

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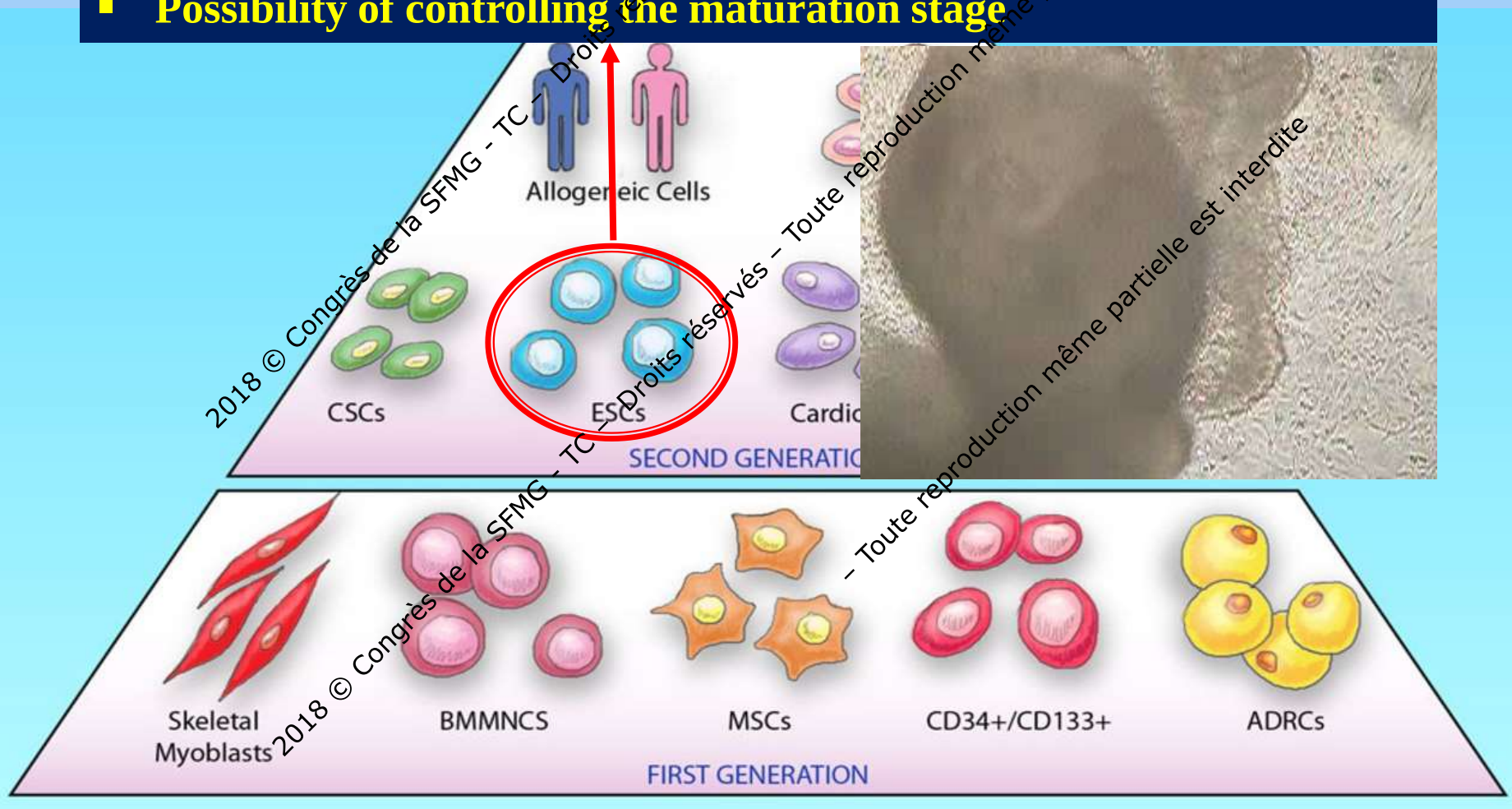


Adapted from Banerjee et al. Circ Res 2018;123:266-287.

ESC Transplantation for Severe Heart Failure

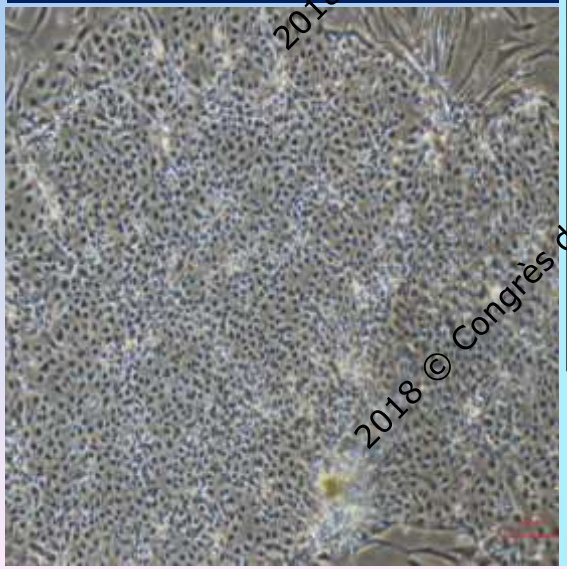
Outline

- Rationale
- **Protocol & Results**
- Perspectives

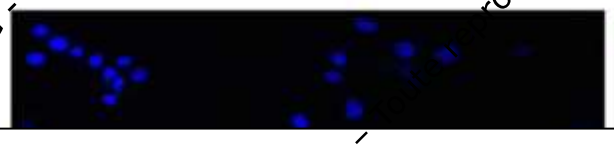
ESC Transplantation for Severe Heart Failure

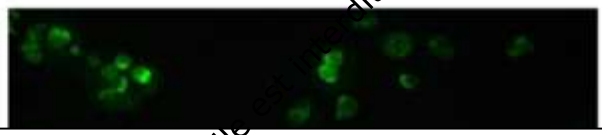
The Three Pillars of the ESCORT Trial

1- Human embryonic stem cell-derived cardiovascular progenitors



Expression of *Isl-1* immediately after sorting (cytospin)

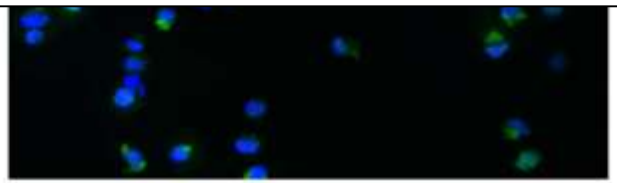




STEM CELLS AND DEVELOPMENT
Volume 19, Number 10, 2010
© Mary Ann Liebert, Inc.
DOI: 10.1089/scd.2009.0483

Islet-1 Cells Are Cardiac Progenitors Present During the Entire Lifespan: From the Embryonic Stage to Adulthood

Rami Genead,[1] Christian Danielsson,[1] Agneta B. Andersson,[1] Matthias Corbascio,[2] Anders Franco-Cereceda,[2] Christer Sylvén,[1] and Karl-Henrik Grinnemo[2]



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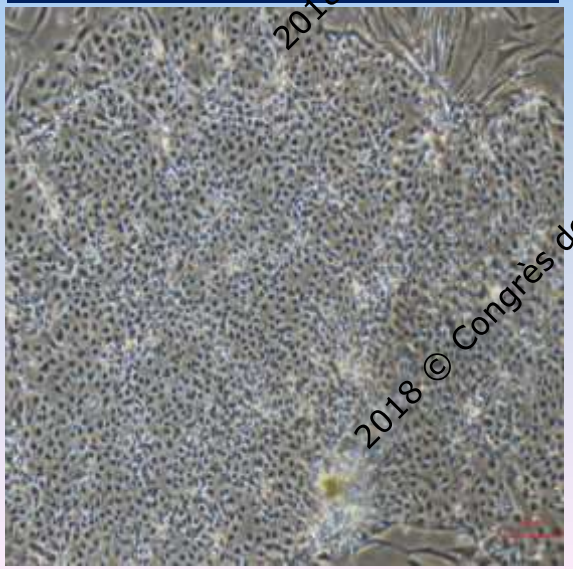
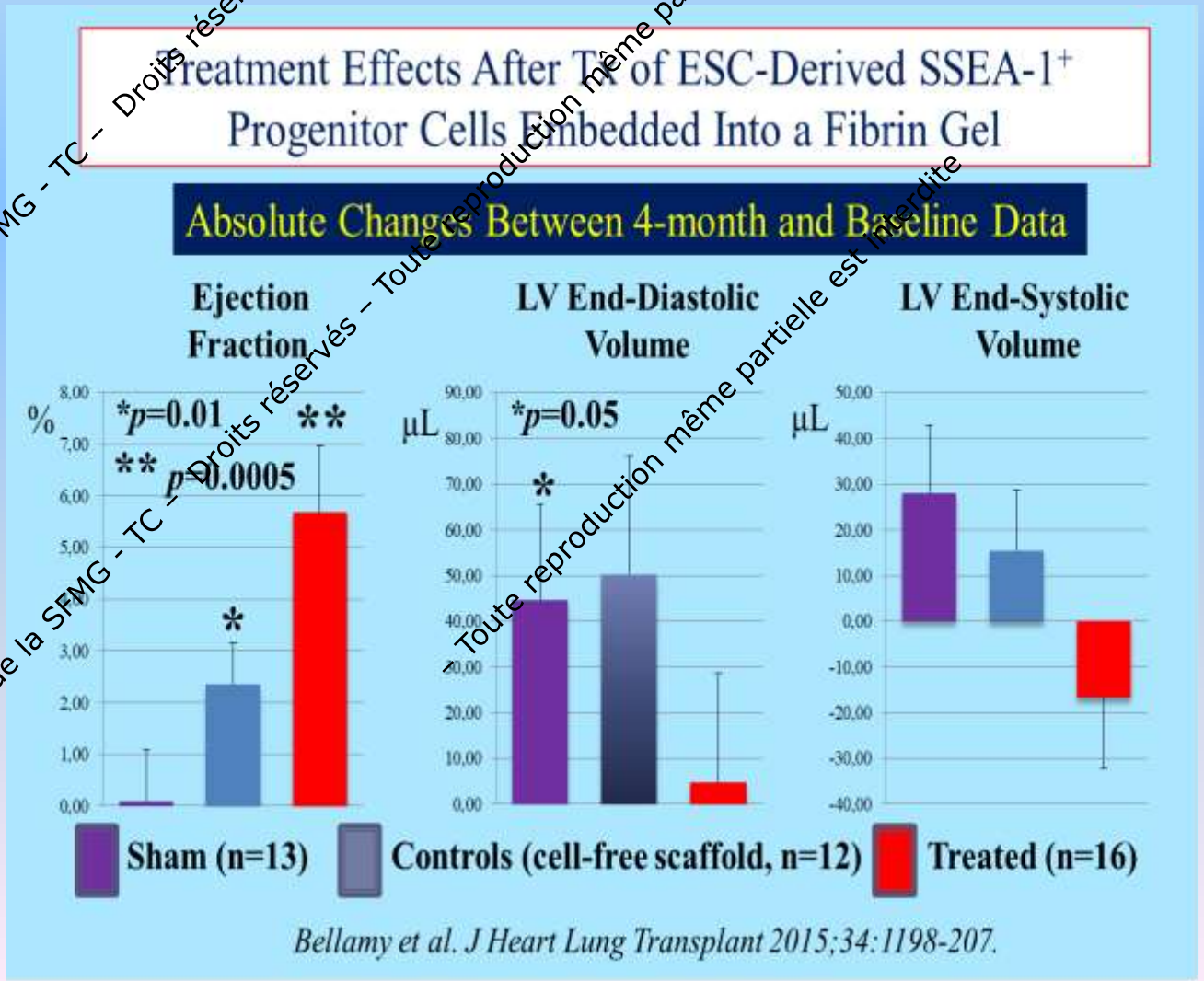
ESC Transplantation for Severe Heart Failure

The Three Pillars of the ESCORT Trial

1- Human embryonic stem cell-derived cardiovascular progenitors





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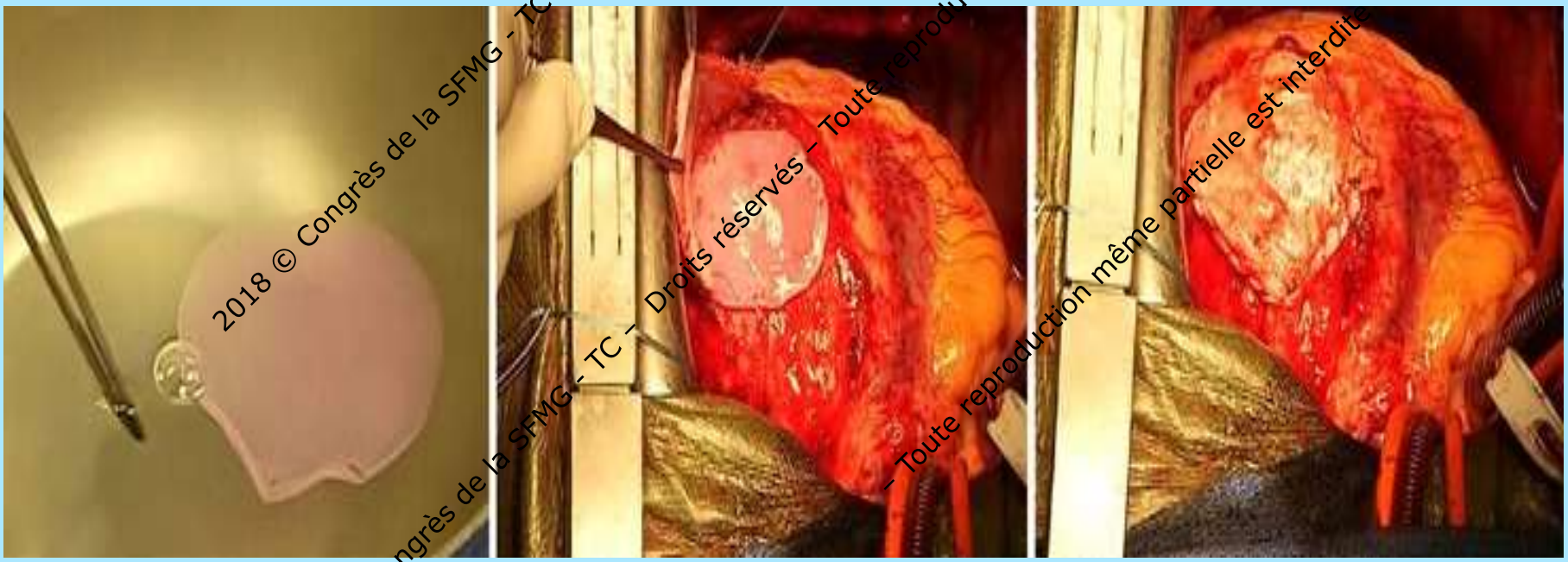
ESC Transplantation for Severe Heart Failure

The Three Pillars of the ESCORT Trial

The « Kangaroo » Operation



Fibrin patch embedding human ESC-derived cardio-vascular progenitors

Delivery of the patch onto the epicardium of the infarct area

Coverage of the cell-loaded fibrin patch by the patient's pericardium used as a bioreactor

Roadmap of Preclinical Studies

Model

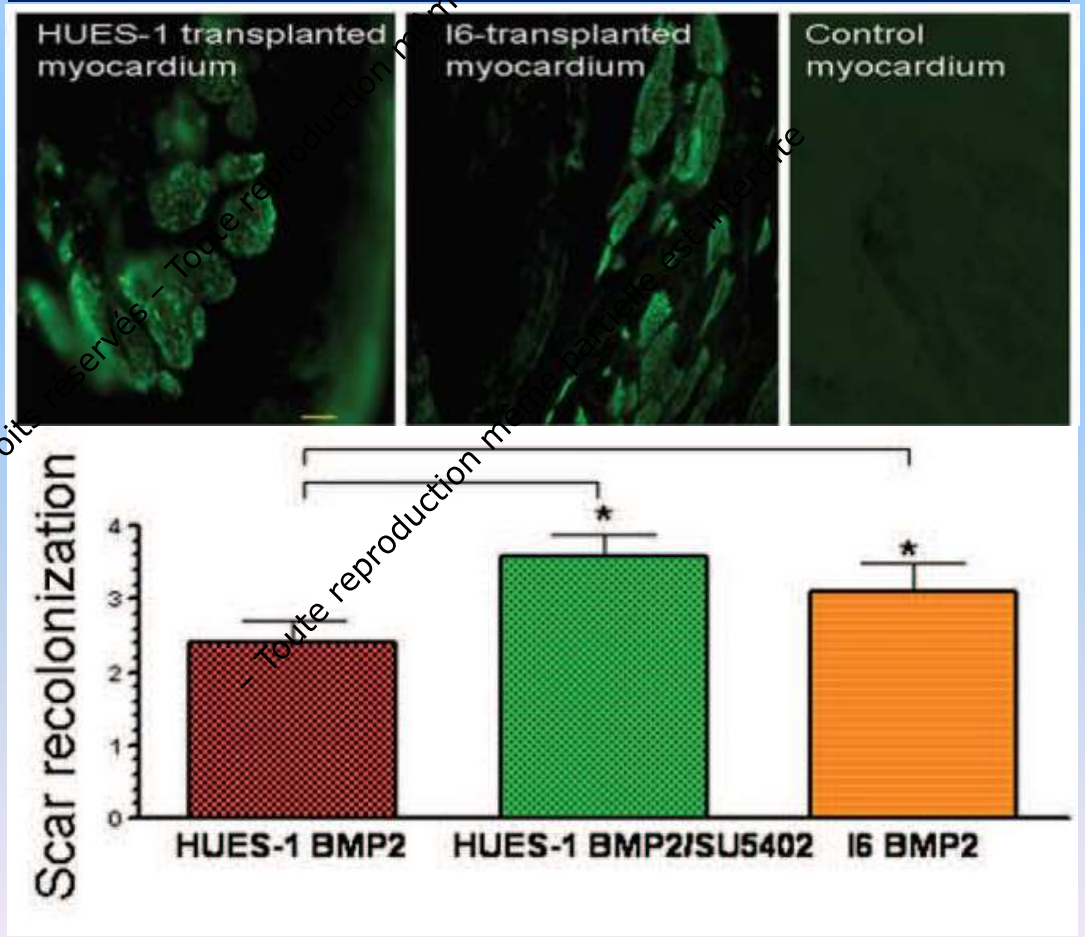
Number

⩾300

Primary End point

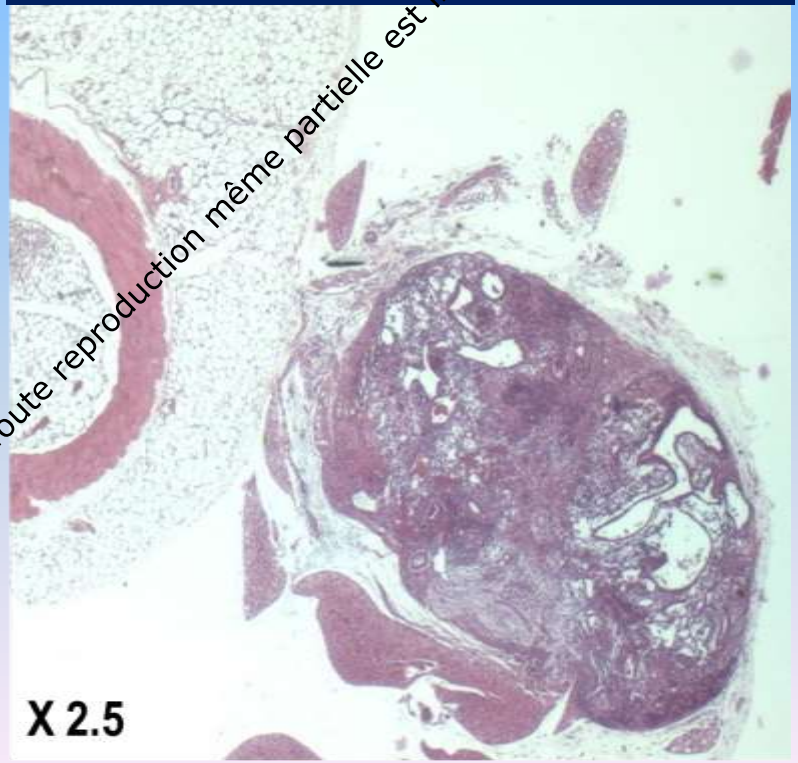
- Cardiac differentiation
- Assessment of scaffolds
- Functional outcome
- Absence of teratoma

Engraftment of hESC-derived cardiac-committed cells in the infarcted rat myocardium (Immunostaining against anti-human myosin)



Tomescot et al. Stem Cells 2007;25:2200-5.

Roadmap of Preclinical Studies

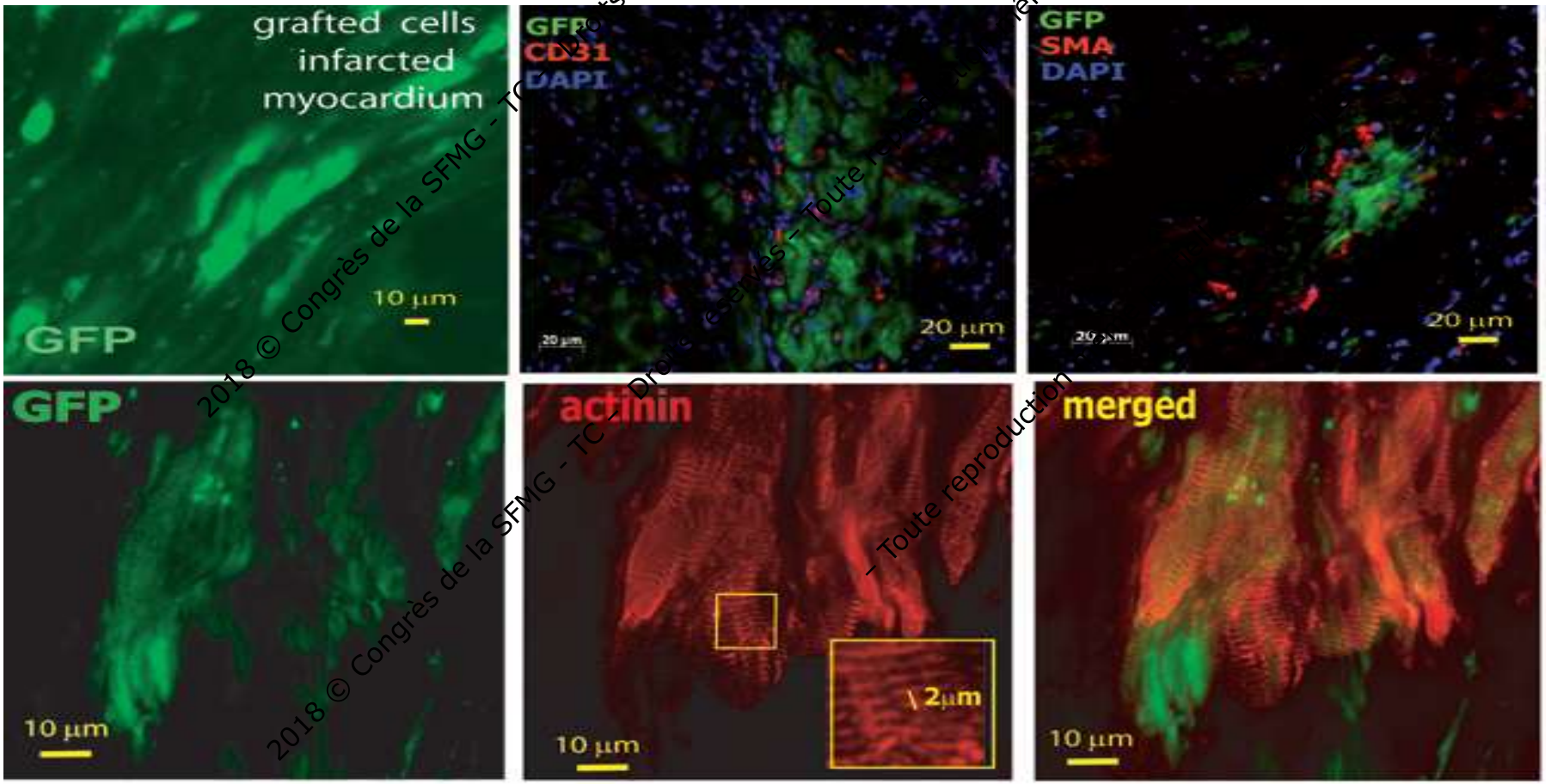
Model			Teratoma formation 7 weeks after Tx of undifferentiated hESC in a mouse model of immunodeficiency (RAG2-/- γc-/- C5-/-)
Number	⩾300	54	
Primary End point	▪ Cardiac differentiation ▪ Assessment of scaffolds ▪ Functional outcome ▪ Absence of teratoma	Absence of teratoma	

Roadmap of Preclinical Studies

Allogeneic Tx of Rhesus ESC-Derived SSEA1^{+} CV Progenitor Cells in Infarcted Rhesus

Cell transfection with GFP driven by a cardiac promoter

Assessment at 2 months



Blin et al. J Clin Invest 2010;120:1125-39.

X 40

ESC Transplantation for Severe Heart Failure

Safety Testing

Virology

- Cell banks (MCB/WCB, LPCB)
- Antibody
- SSEA-1^{+} progenitors

No contamination

ESCORT Trial: Viral Testing

Cell line "I6"

Mouse antibody production test with LCMV challenge
Evaluation by real-time quantitative P
type 1 (HIV-1) RNA sequences
Evaluation by real-time quantitative P
type 2 (HIV-2) RNA sequences
Evaluation by real-time quantitative P
RNA sequences
Evaluation by real-time quantitative P
sequences
Evaluation by real-time quantitative P
and II (HTLV-1 and 2) DNA sequenc
Evaluation by real-time quantitative P
DNA sequences
Evaluation by real-time quantitative P
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DNA sequences
Evaluation by real-time quantitative P
DNA sequences
Evaluation by real-time quantitative P
sequences using Taqman technology
Evaluation by real-time quantitative P
DNA sequences
Evaluation by real-time quantitative P
DNA sequences
Detection of viral contaminants using
In vitro assay for the detection of bovi

Supernatant from I6 cell culture

Cultivable and non cultivable mycoplasma detection according to European Pharmacopeia

into cells (Stade I)
leno-Associated Viruses
ythrovirus B19 DNA
patitis A virus (HAV)
ation method (2 media)
ation method (2 media)
European Pharmacopeia
ce according to European
nated eggs according to
R
Retrovirus detection
ce according to European
nated eggs according to
R

CD15⁺ progenitors (P41)

Cultivable and non cultivable mycoplasma detection according to European Pharmacopeia
Determination of viral contaminants using MRC-5 and Vero cell lines
Detection of viral contaminants using human cells (HEK293)
Evaluation by F-PERT of the presence of reverse transcriptase activity
In vitro assay for the detection of bovine viruses according to 9CFR

CD15⁺ progenitors (P47)

Cultivable and non cultivable mycoplasma detection according to European Pharmacopeia
Determination of viral contaminants using MRC-5 and Vero cell lines
Detection of viral contaminants using human cells (HEK293)
Evaluation by F-PERT of the presence of reverse transcriptase activity
In vitro assay for the detection of bovine viruses according to 9CFR

Anti-SSEA-1 antibody : Lysate of cells, clone VIM C6 Batch 5110705246

Extended assay for murine Xenotropic/Amphotropic/MCF Retrovirus detection
Detection of viral contaminants using mouse cells (NIH/3T3)
Determination of viral contaminants using MRC-5 and Vero cell lines
Transmission electron microscopy for detection of adventitious agents into cells (Stade I)

Anti-SSEA-1 antibody : 530 Anti-SSEA 1 (CD15)-Microbeads batch 5110824021

Detection of viral contaminants using mouse cells (NIH/3T3)
Determination of viral contaminants using MRC-5 and Vero cell lines
Analysis by negative stain electron microscopy

Concise Review: Assessing the Genome Integrity of Human Induced Pluripotent Stem Cells: What Quality Control Metrics?

Minimal DNA integrity testing in hiPSCs

	Karyotyping	FISH, PCR or ddPCR on selected chromosomes	aCGH	*P53* mutation screen	Exome seq	Whole genome seq
Initial hiPSC line quality assessment for research, or quality assessment after CRISPR/Cas9-mediated modification	Yes	Optional	Optimal if done	Optimal if done, and essential for research on aging, cell cycle, apoptosis, cancer	On a case by case basis	In the future?
Routine screening (culture-induced abnormalities) for research	Karyotyping, FISH, PCR, or ddPCR analysis of selected chromosomes (every 3 months)		No	Optimal if done, and essential for research on aging, cell cycle, apoptosis, cancer		In the future?
For clinical use	Yes	Optional (to monitor cells during amplification or for rapid control before releasing the cell line)	Alternative to exome sequencing	Yes	Yes	In the future?

Abbreviations: aCGH, array comparative genomic hybridization; ddPCR, digital droplet PCR; FISH, fluorescent in situ hybridization; hiPSCs, human induced pluripotent stem cells; PCR, polymerase chain reaction.

Assous et al. Stem Cells 2018;36-814-21.

ESC Transplantation for Severe Heart Failure

Safety Testing

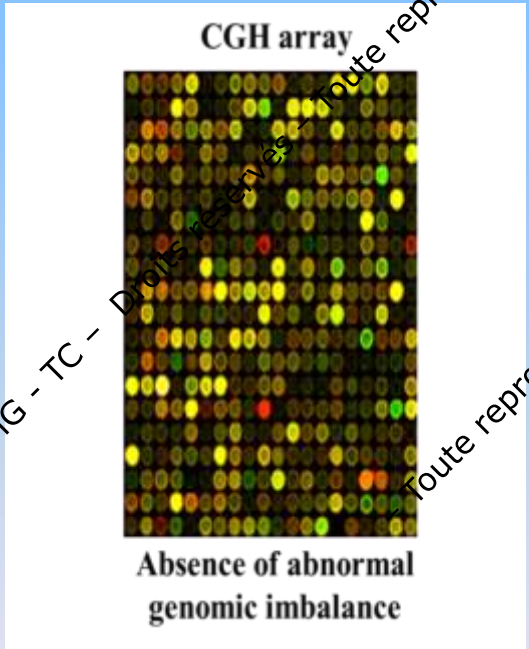
Virology

- Cell banks (MCB/WCB, LPCB)
- Antibody
- SSEA-1$^+$ progenitors

No contamination

Cytogenetics

- Cell banks
- SSEA1$^+$progenitors



No genetic abnormalities

Tumorigenicity

- Pluripotent ESC
- SSEA1$^+$ progenitors
- **SSEA-1$^-$ cells**

- Spiking experiments
- Injections in immunodeficient mice (RAG2 -/- γc-/- C5-/-)

No tumor if appropriate purification

Embryonic **S**tem **C**ell f**O**r **R**egenerative **T**herapy (ESCORT)
NCT02057900

Inclusion Criteria

- Severe LV dysfunction (LVEF ≤ 35%)
- History of MI (≥ 6 mo.)
- Disabling functional limitation (angina and/or NYHA Class III/IV heart failure) despite optimal medical therapy
- Previous implantation of an ICD ± CRT
- Indication for a conventional coronary and/or valve procedure

interdite.

2010

ESCORT Trial

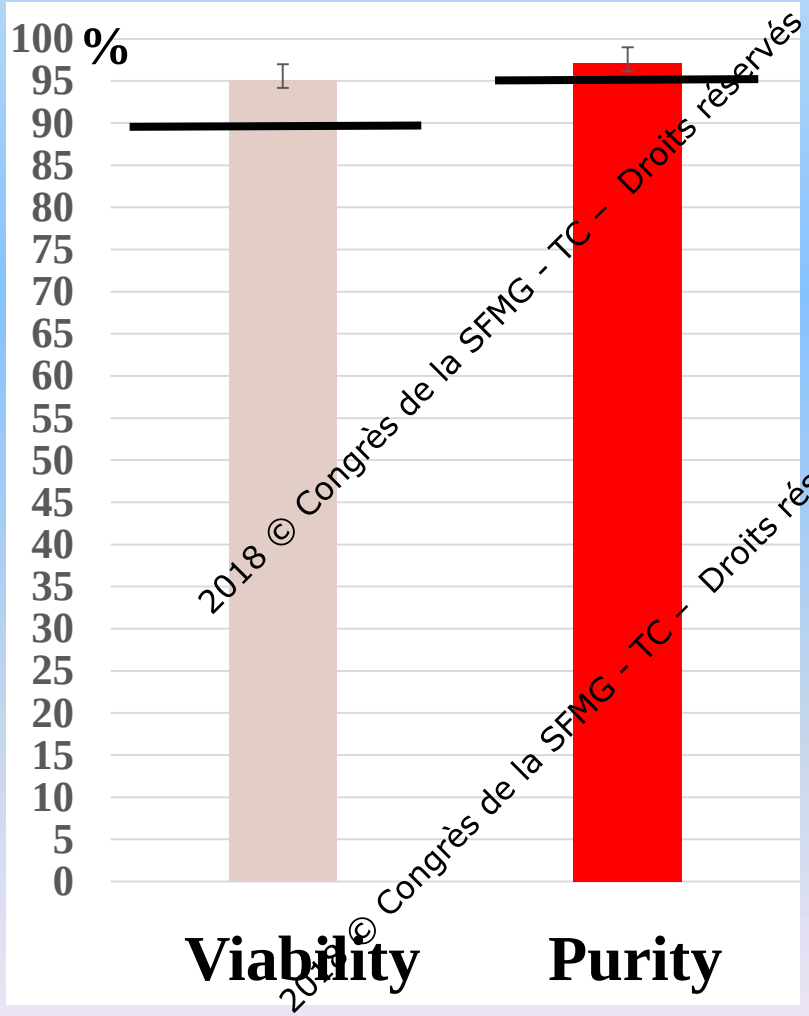
Patient Data

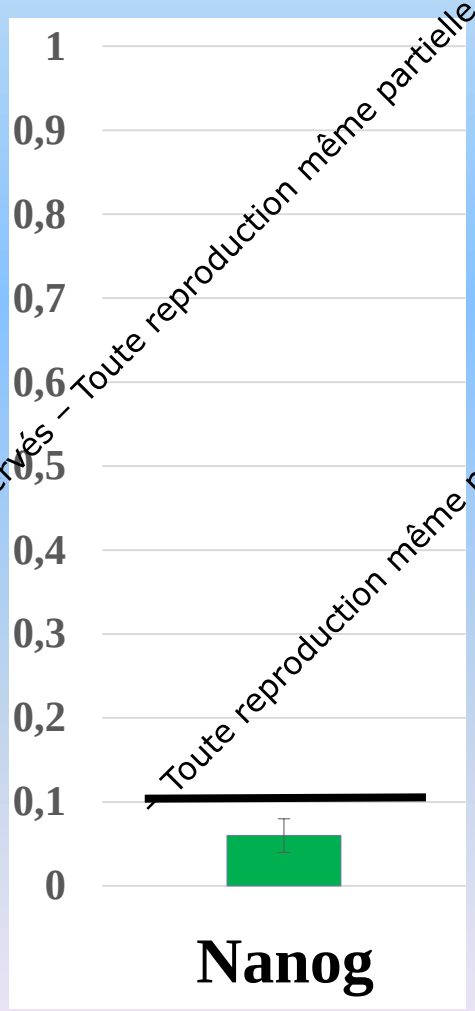
Pt #	Sex/Age (yrs)	LVEF (%)	Myocardial infarction	
			Age	Location
1*	M/77	20	30 yrs	AS
2	F/68	26	?	Lat
3	M/81	19	10 yrs	Ant
			9 yrs	Inf
4	M/60	32	6 mo.	Ant
5	M/65	34	17 mo.	Ant
6	M/57	19	10 mo.	Inf

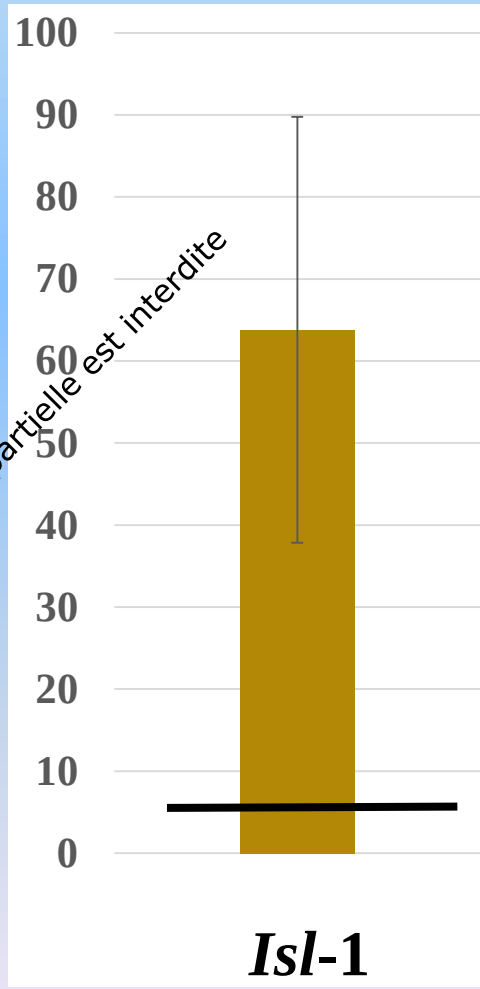
*Early post-op death; Multiple co-morbidities (EF:17%; 2 previous MIs; respiratory failure; Afib; obesity; peripheral arterial disease); **no relationship with treatment**

Cell Characteristics

Mean dose of delivered cells: 7.5 ± 1.2 million







PCR measurements expressed as fold changes relative to undifferentiated I6 ESC

ESCORT Trial: Safety

Current follow-up: 17 months-4 years

Outcome Measurements

Potential complication	Assessment	Timing
Arrhythmias	ICD interrogations	Pre-op, 2 wks 1, 3 & 6 mo., 1 yr.
Tumour	PET scan CT scan	Pre-op, 6 mo. Pre-op, 1 yr.
Alloimmunization	Donor cell-specific antibodies	Pre-op, 2 wks, 3 & 6 mo., 1 yr.
Side-effects of immunotherapy	Clinical evaluation Renal function	Regular routine checks

ESCORT Trial: Assessment of Arrhythmias

Interrogation of ICD	Pt #2	Pt #3	Pt #4	Pt #5	Pt #6
2 weeks	None	None	None	None	None
1 month	None	None	None	None	None
3 months	None	None	None	None	None
6 months	None	None	None	None	None
1 year	None	None	None	None	None

ESCORT Trial: Assessment of Tumorigenicity

^{18}FDG Pet Scan
Pre-op & 6 months

Whole-body CT Scan
Preop & 1 year

Method of Assessment	Pt #2	Pt #3	Pt #4	Pt #5	Pt #6
PET Scan (6 months)	Normal	Normal	Normal	Normal	Normal
CT Scan (1 year)	Normal	Normal	Normal	Normal	Normal

ESCORT Trial: Assessment of Tumorigenicity

Detection of donor cell DNA in patients' blood

The ESC line was sequenced on the 22-gene NGS panel validated for rare variant detection

Sample Name	CCI Dat.ab	Localisation	Pathogenic Class	Polymorphisme	Interprétable	Mutation sur Alamut	Gene_Symbol	Protein_Change	Exon	Variant_Fr	Position_Cov	RefSeq_Id	cDNA_Change	Codon	Chr
17SG160	ERBB4 (NM_	Intron 3	Benign intro	#N/A	OUI		ERBB4	/	3	67,7	551	NM_005235.2	c.421+58A>G	/	2
17SG160	FGFR3 (NM_	Exon 14	Benign Silen	#N/A	OUI		FGFR3	p.Ser451Thr	14	100	3129	NM_000142.4	c.1953G>A	651	chr4
17SG160	EGFR (NM_0	Exon 20	Benign Silen	Polymor	OUI		EGFR	p.Gln787Gln	20	50,3	1861	NM_005228.3	c.2361G>A	787	chr7
17SG160	MET (NM_00	Exon 2	Benign Silen	Polymor	OUI		MET	p.Ile377Ile	2	46,65	1895	NM_001127500.1	c.1131C>T	377	chr7
17SG160	TP53 (NM_0	Exon 4	Benign	Polymor	OUI		TP53	p.Pro72Arg	4	50,19	3921	NM_000546.5	c.215C>G	72	chr17
17SG160	SMAD4 (NM	Exon 9	Benign Silen	Polymor	OUI		SMAD4	p.Phe362Phe	9	49,59	3394	NM_005359.5	c.1086T>C	362	chr18

Among the 6 polymorphic loci, one is a rare alteration: **SMAD4 p.Phe362Phe; c.1086T>C**

- This polymorphism was not present in any of the patients' constitutive DNAs
- Its presence at an allelic fraction > 0.005 was not detected either in any patient's plasma postoperatively

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ESCORT Trial: Assessment of Tumorigenicity

Detection of donor cell DNA in patients' blood

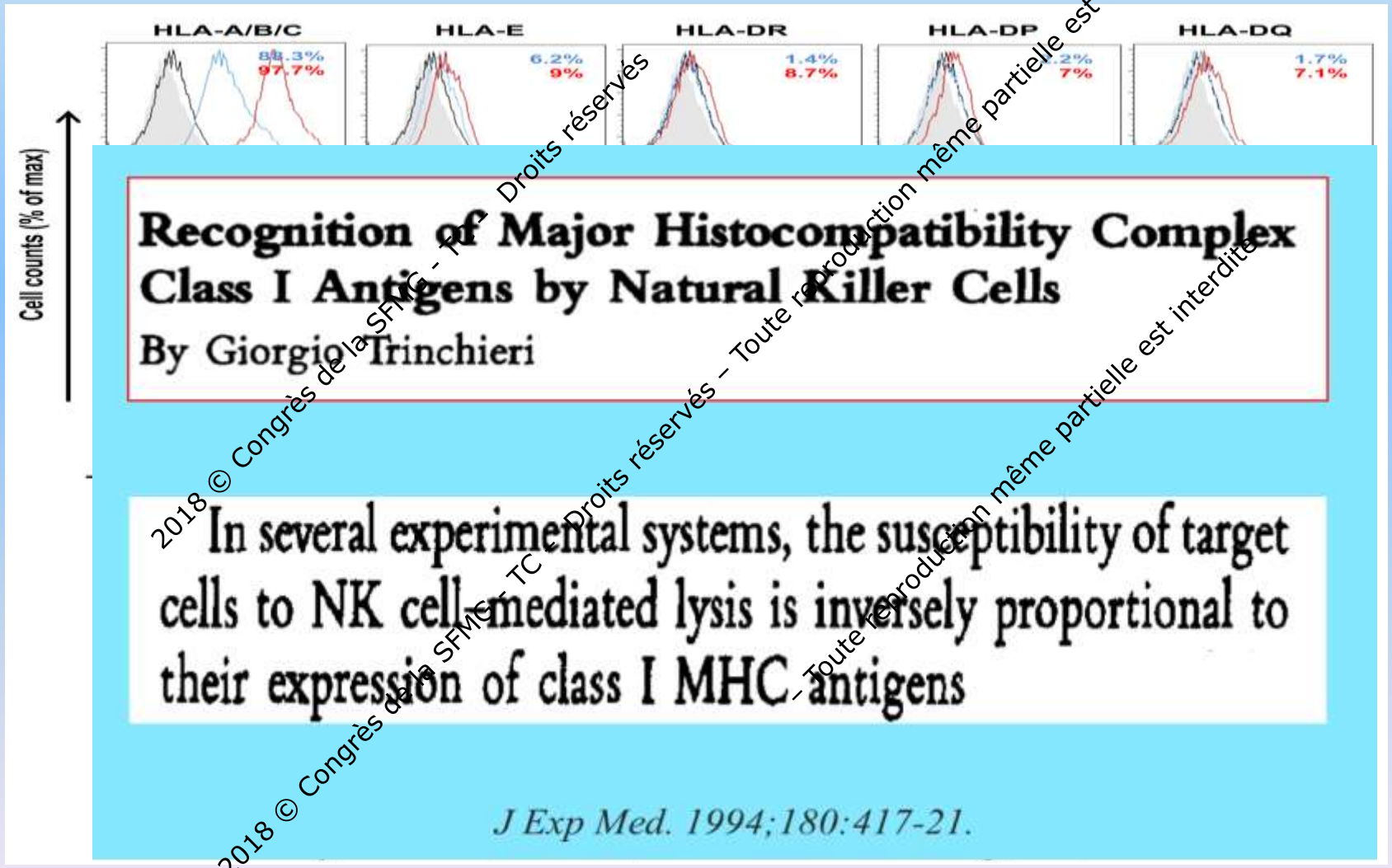
Cell line sequence for the SMAD4 Polymorphism

3394 sequences: **1683 C & 1711 T**

- No signicant variation found in plasma sample for the same genomic position
- 7245 sequences: **3 C & 7242 T**
- No cell line DNA in the circulation (cut-off of 0.5%)

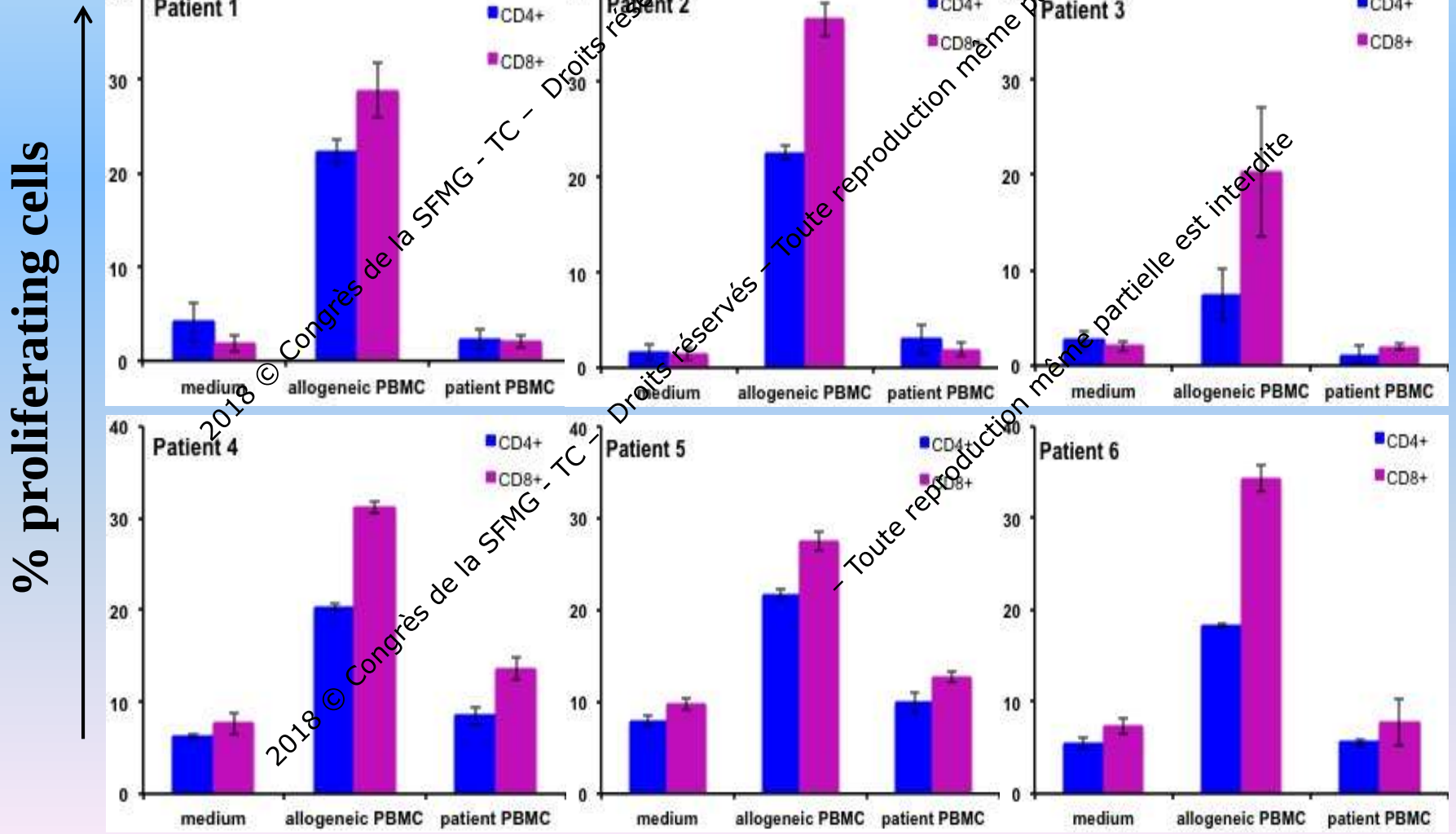
ESCORT Trial: Assessment of Alloimmunization

Immunophenotyping of SSEA-1^{+} Cardiovascular Progenitors

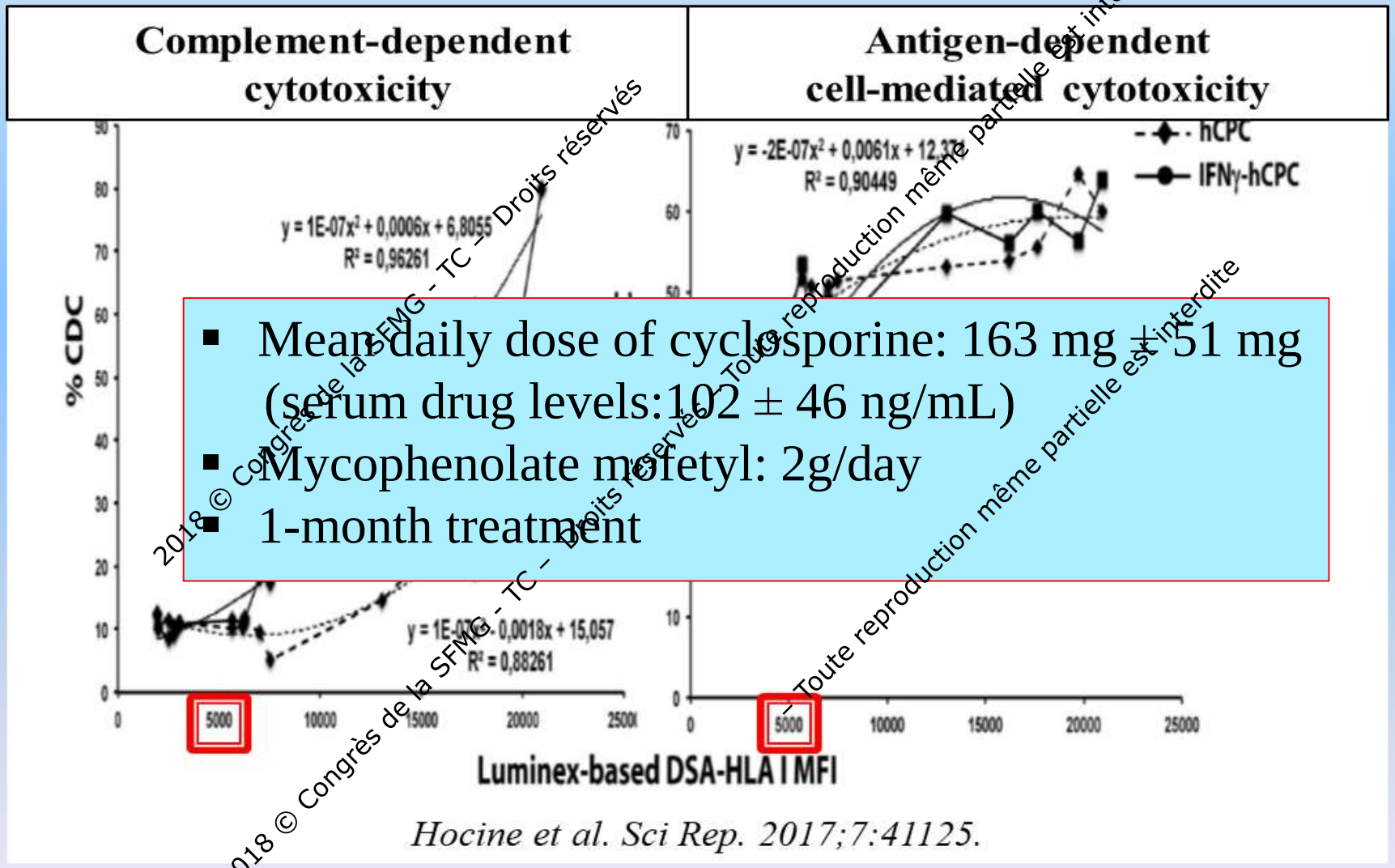


ESCORT Trial: Assessment of Alloimmunization

Mixed Lymphocyte Reactions

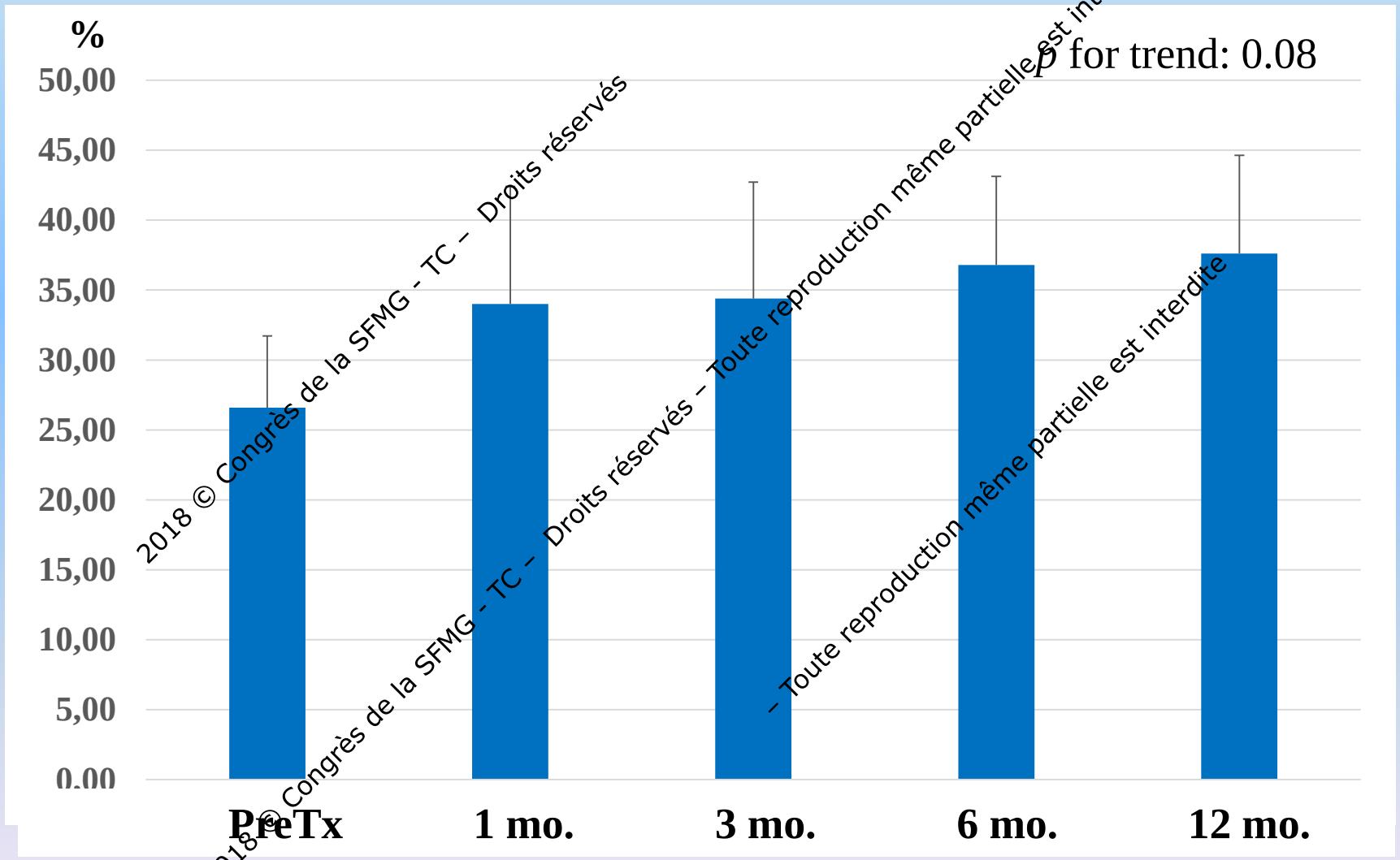


ESCORT Trial: Assessment of Alloimmunization



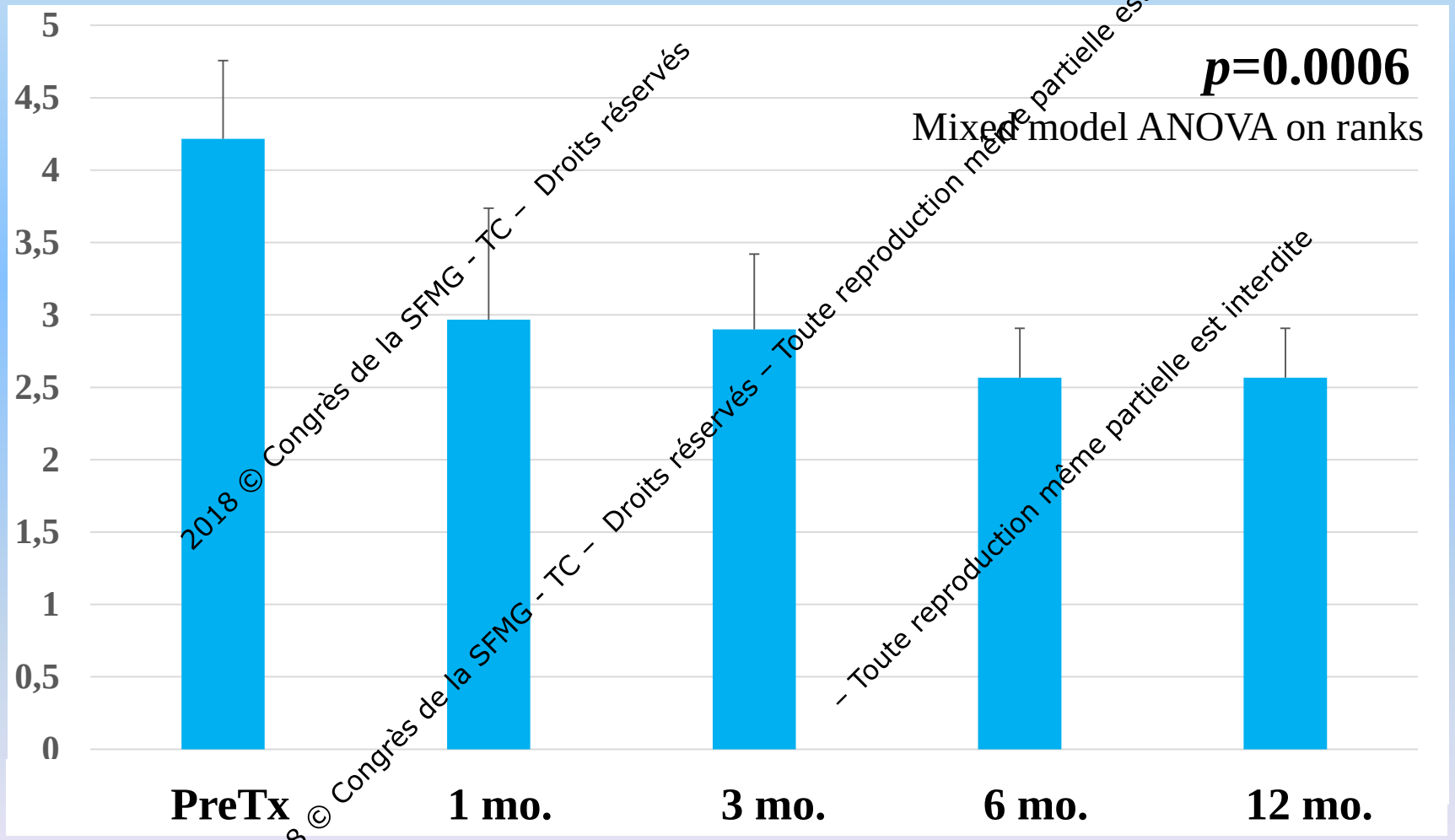
- Mean daily dose of cyclosporine: 163 mg ± 51 mg (serum drug levels:102 ± 46 ng/mL)
- Mycophenolate mofetyl: 2g/day
- 1-month treatment

Changes in LV Ejection Fraction



Changes in the Regional Function of the Cell/Patch-Treated Segments (Score Tx segments/Nb segments)

Normal : 1; Mild hypokinesia : 2; Severe hypokinesia : 3; Akinesia : 4; Dyskinesia: 5



4 of the 5 patients who contributed the 1-year data had no revascularization of the treated segments

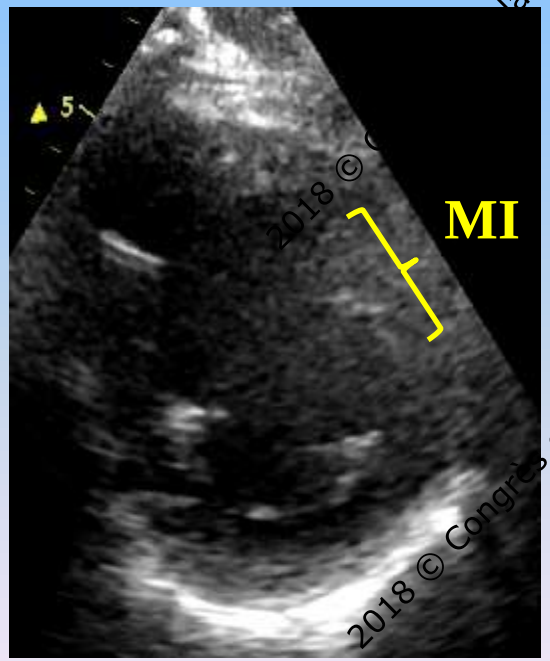
Case Report

Infarcted Non-viable **Non-revascularized** Cell/Patch Transplanted Area

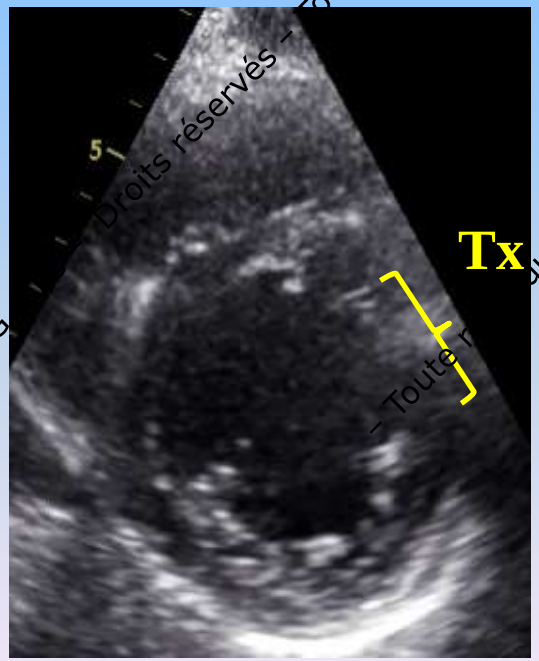
(2-D Echo, Parasternal short-axis view)

Antero-lateral MI; LAD CABG (mammary graft)

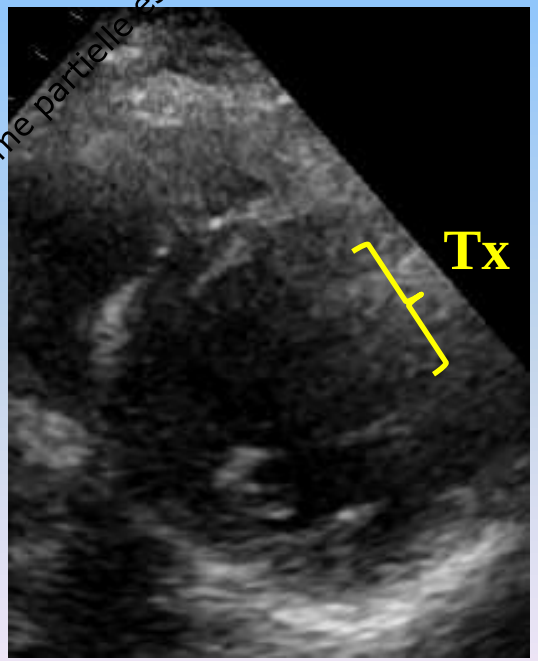
+ cell/patch delivery on the lateral wall (4 x 10^6 cells)



Pre-op



3 months



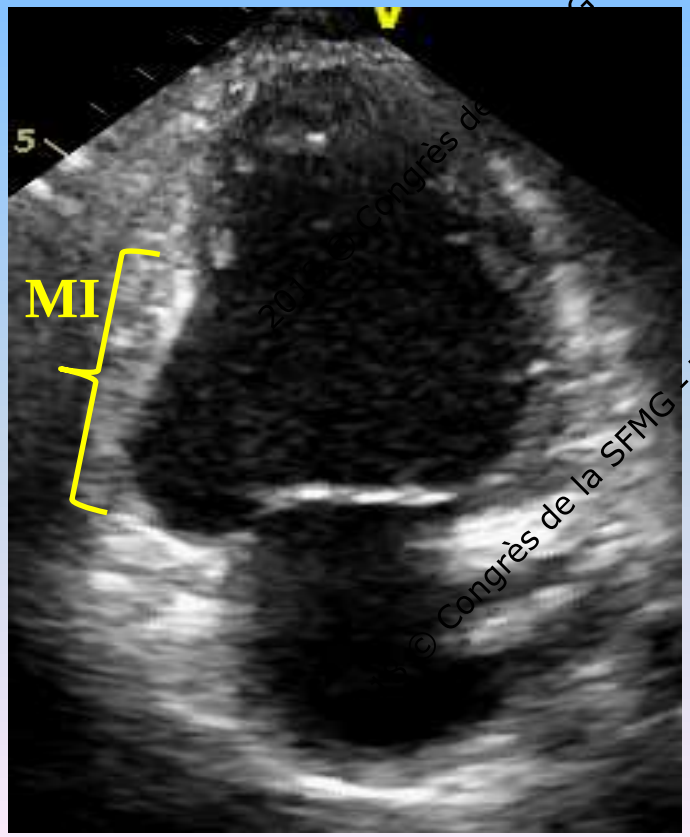
12 months

Case Report

Infarcted Non-viable **Non-revascularized** Cell/Patch Transplanted Area *(2-D Echo, 2-chamber views)*

Infero-lateral MI; LAD + obtuse marginal CABG (2 mammary grafts)
+ cell/patch delivery on the infero-lateral wall (6,5 x 10^6 cells)

Pre-Op



Case Report

Infarcted Non-viable **Non-revascularized** Cell/Patch Transplanted Area

(2-D Echo, 2-chamber views)

Infero-lateral MI; LAD + obtuse marginal CABG (2 mammary grafts)
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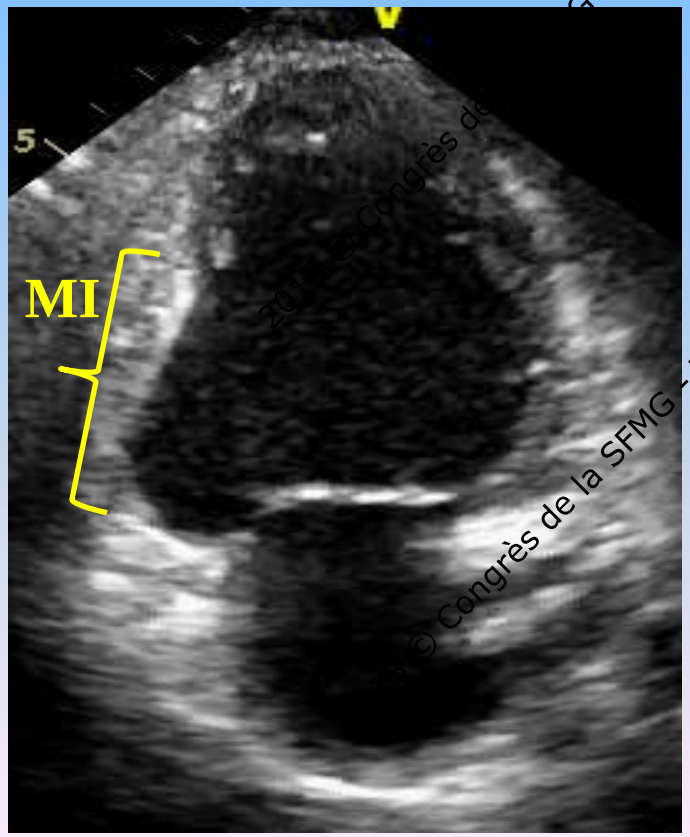
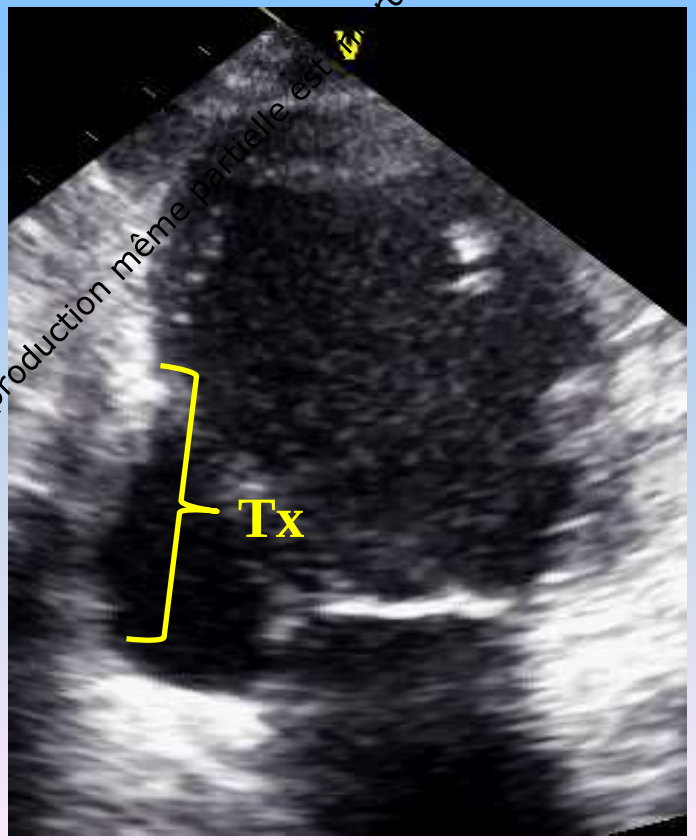
Pre-Op



1 year



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EDITORIAL COMMENT

Trial of Embryonic Stem Cell–Derived Cardiac Progenitor Cells

An Encouraging Start*

Leslie W. Miller, MD

ESC Transplantation for Severe Heart Failure

Outline

- Rationale
- Protocol & Results
- **Perspectives**

ESCORT in Perspective

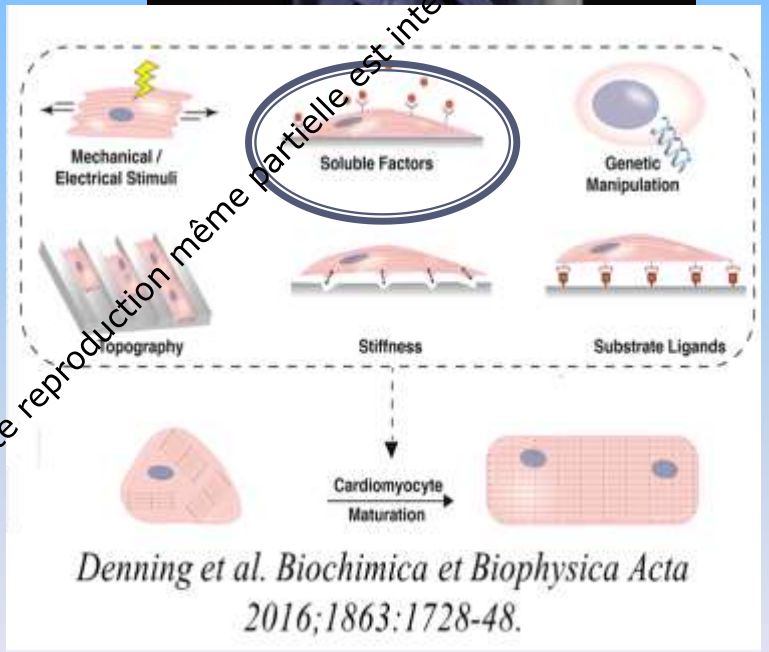
- An encourag… …ed clinical trials with re…
- A platform s… …future improvemen… …ardiac differentiatio… …on with tissue engineering
- A mechanist… …way for a-cellular thera… …ivery of the cellular secre…

ESCORT in Perspective

- An encouraging signal for future PSC-based clinical trials with regard to safety
- A platform serving as a building block for future improvements in cell scale-up, controlled cardiac differentiation, purification and combinaison with tissue engineering
- A mechanistic insight possibly paving the way for a-cellular therapy based on the exclusive delivery of the cellular secretome

ESCORT Trial : The Feedback Experience

Step	Objective	Method
▪ Expansion	Feeder-free automated cultures	Bioreactor
▪ Differentiation	Improvement of the CV cell yield	
▪ Purification		



Denning et al. Biochimica et Biophysica Acta 2016;1863:1728-48.

ESCORT Trial : The Feedback Experience

Step	Objective	Method
▪ Expansion	Feeder-free automated cultures	Bioreactor
▪ Differentiation	Improvement of the CV cell yield	Small molecules
▪ Purification	✓ Negative selection targeting pluripotency markers ✓ Microfluidics-based selection	

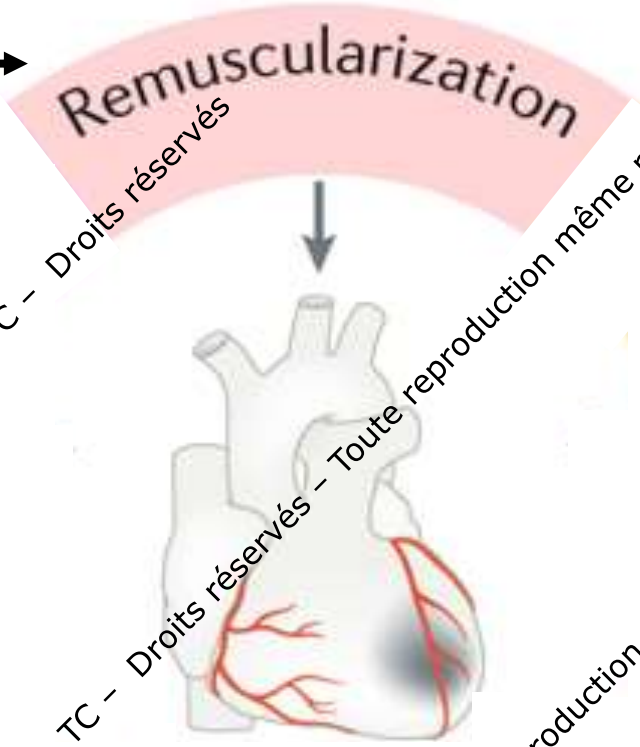
ESCORT in Perspective

- An encouraging signal for future PSC-based clinical trials with regard to safety
- A platform serving as a building block for future improvements in cell scale-up, controlled cardiac differentiation, purification and combinaison with tissue engineering
- A mechanistic insight possibly paving the way for a-cellular therapy based on the exclusive delivery of the cellular secretome

Hallmarks of Cardiac Regeneration

Methods

- Transplantation of exogenous PSC-derived cardiomyocytes
- Stimulation of endogenous cardiomyocyte division
- Reprogramming of endogenous fibroblasts



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

Hallmarks of Cardiac Regeneration

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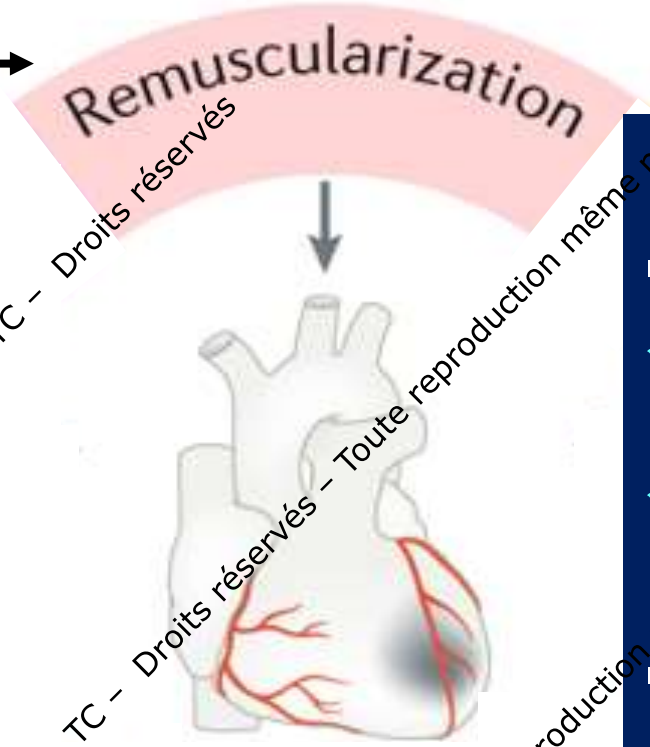


Challenges

- Exogenous sources:
  - ✓ Large-scale production
  - ✓ Maintenance of long-term cell survival
- Endogenous sources:
  - ✓ Control of cell cycling
- Avoidance of life-threatening arrhythmias

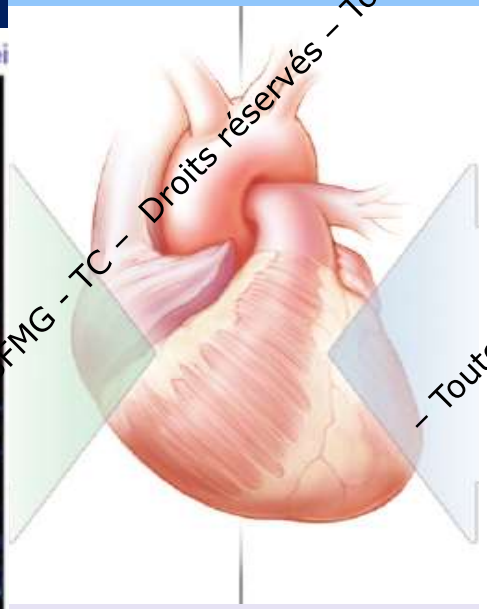
Adapted from Bertero & Murry Nature Rev Cardiol 2018;15:579–80.

Cell Therapy : A Changing Paradigm

Remuscularization

Transplantation of high numbers of cells for regenerating the diseased myocardium

Chong et al. Nature2014;510:273–7.



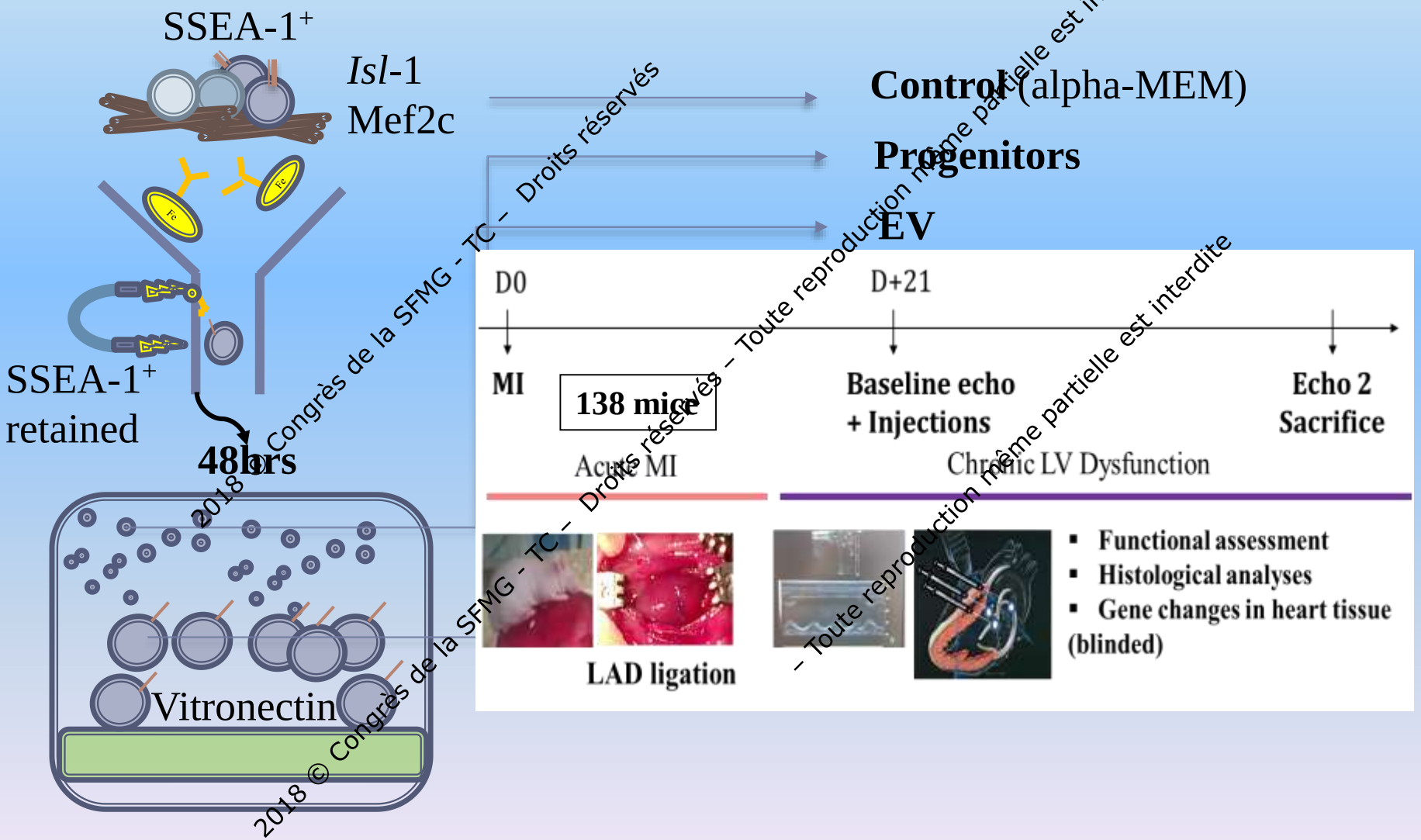
Paracrine signaling

Cellular graft-induced harnessing of endogenous repair pathways

Lines of Evidence

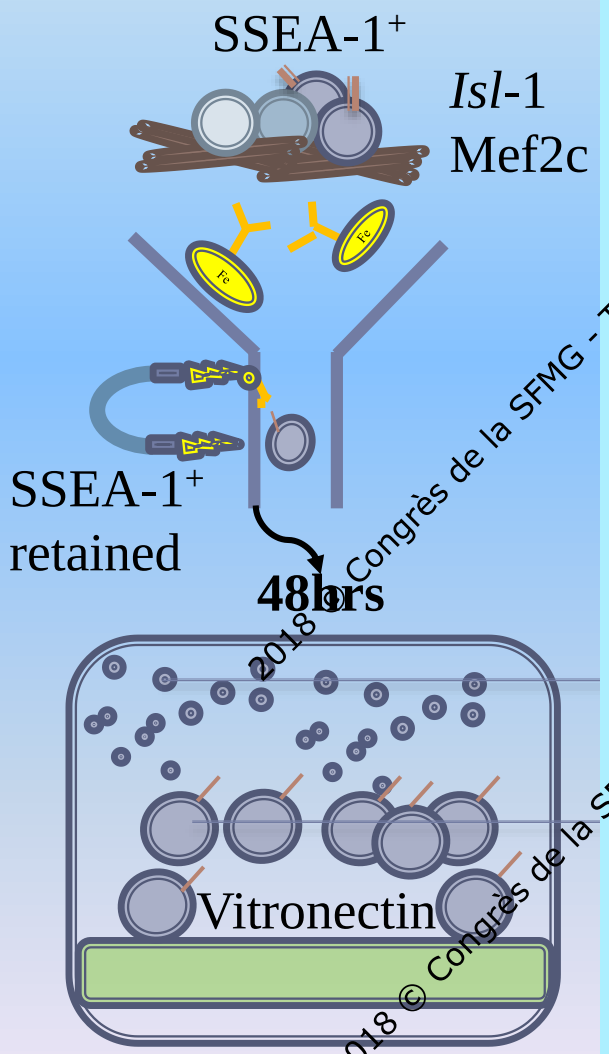
- The therapeutic efficacy of transplanted cells is disconnected from their sustained engraftment
- Cells secrete a wide blend of bioactive factors
- The functional benefits of the transplanted cells can be recapitulated by their secretome

Head-to-Head Comparison of ESC-Derived SSEA-1$^+$ Cardiac Progenitors *vs.* Cell-Derived Extracellular Vesicles

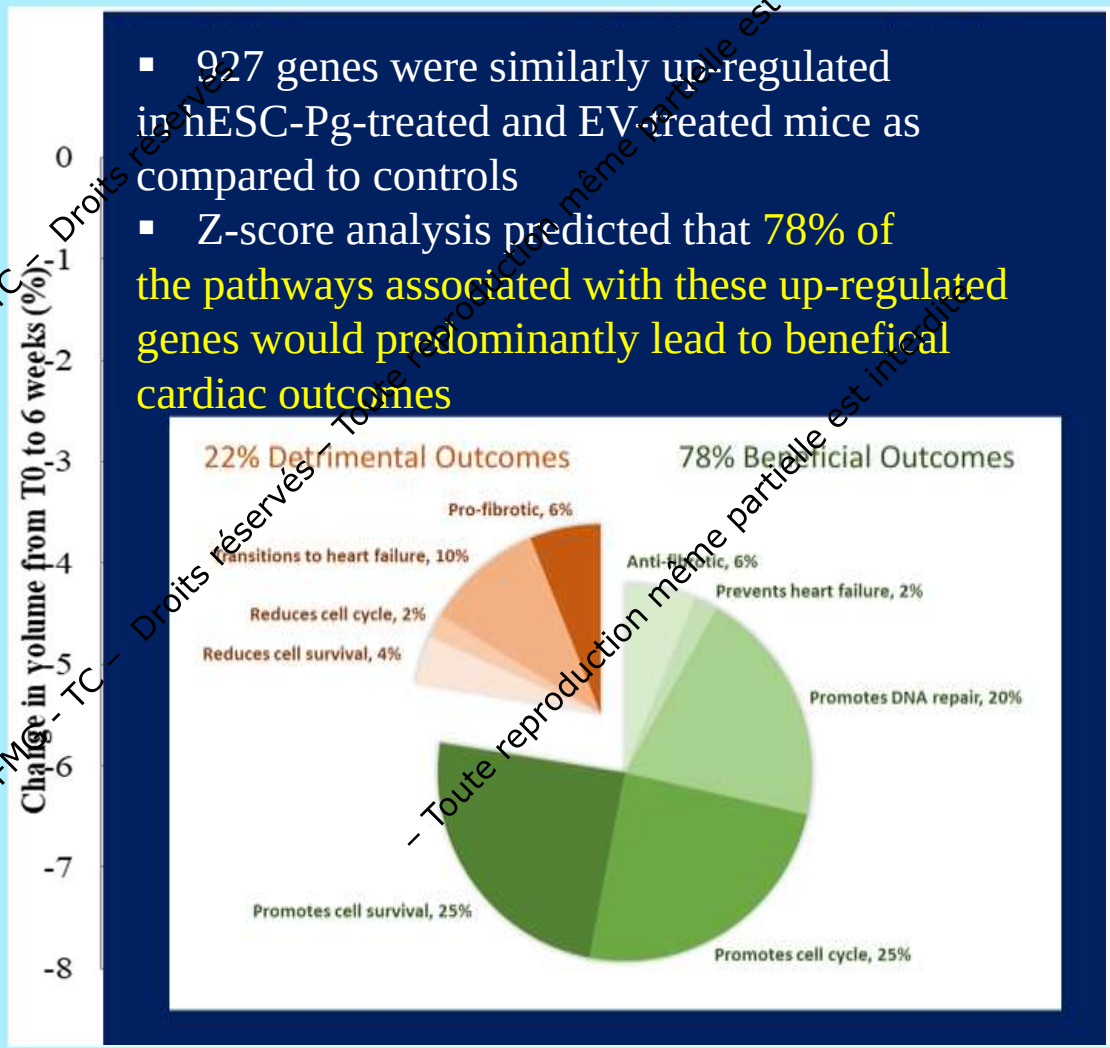


Kervadec et al. J Heart Lung Transplant 2016;35:795-807.

Head-to-Head Comparison of ESC-Derived SSEA-1$^+$ Cardio-Vascular Progenitors *vs.* Cell-Derived Extracellular Vesicles

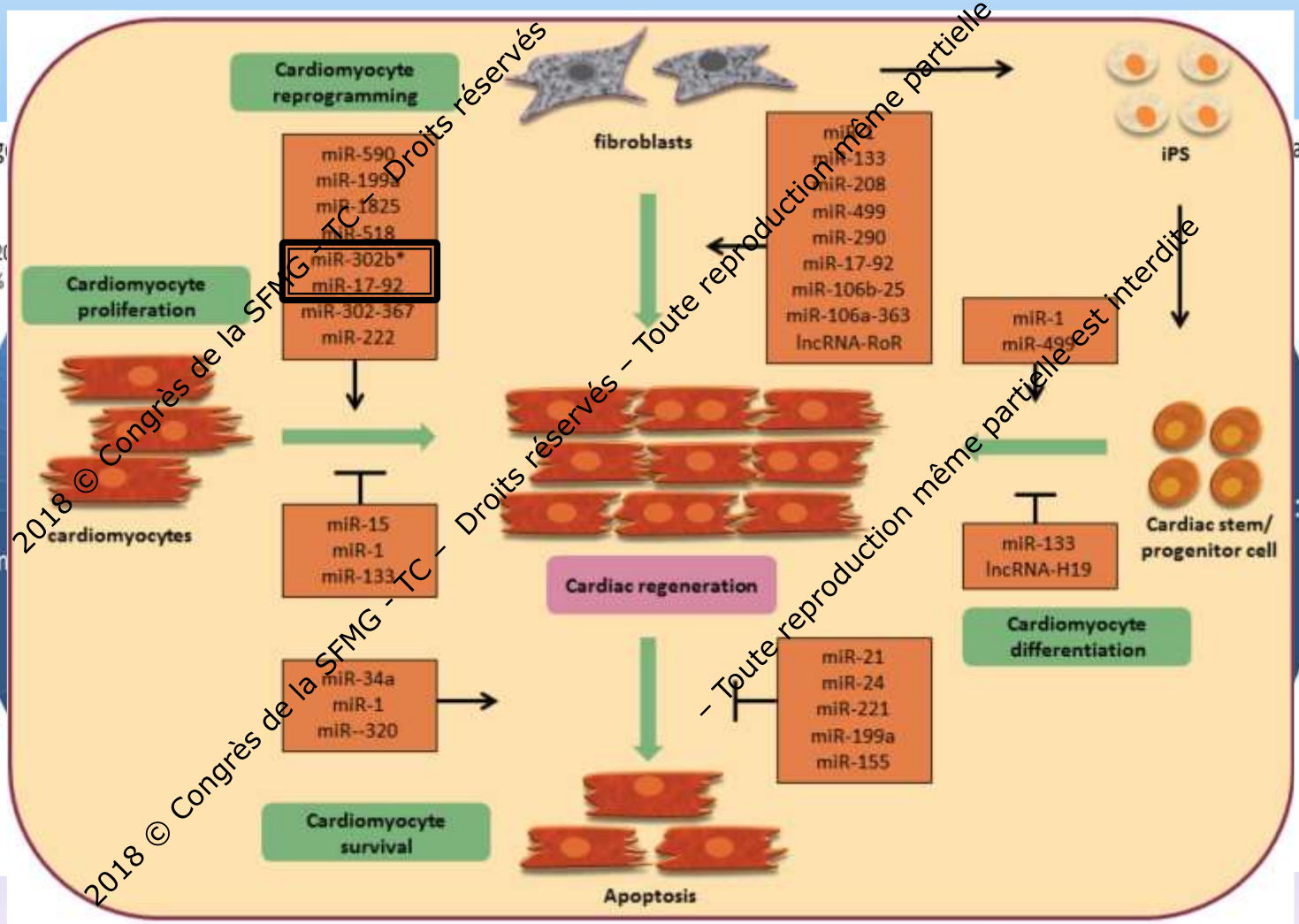


- 927 genes were similarly up-regulated in hESC-Pg-treated and EV-treated mice as compared to controls
- Z-score analysis predicted that 78% of the pathways associated with these up-regulated genes would predominantly lead to benefical cardiac outcomes



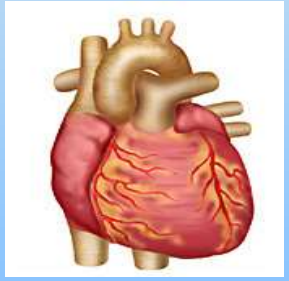
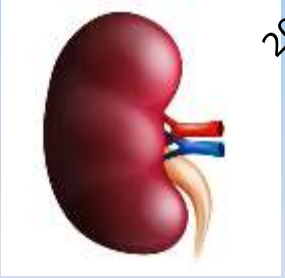
Kervadec et al. J Heart Lung Transplant 2016;35:795-807.

Paracrine Mechanism of Action of hESC-Derived SSEA-1^{+} Cardiac Progenitors

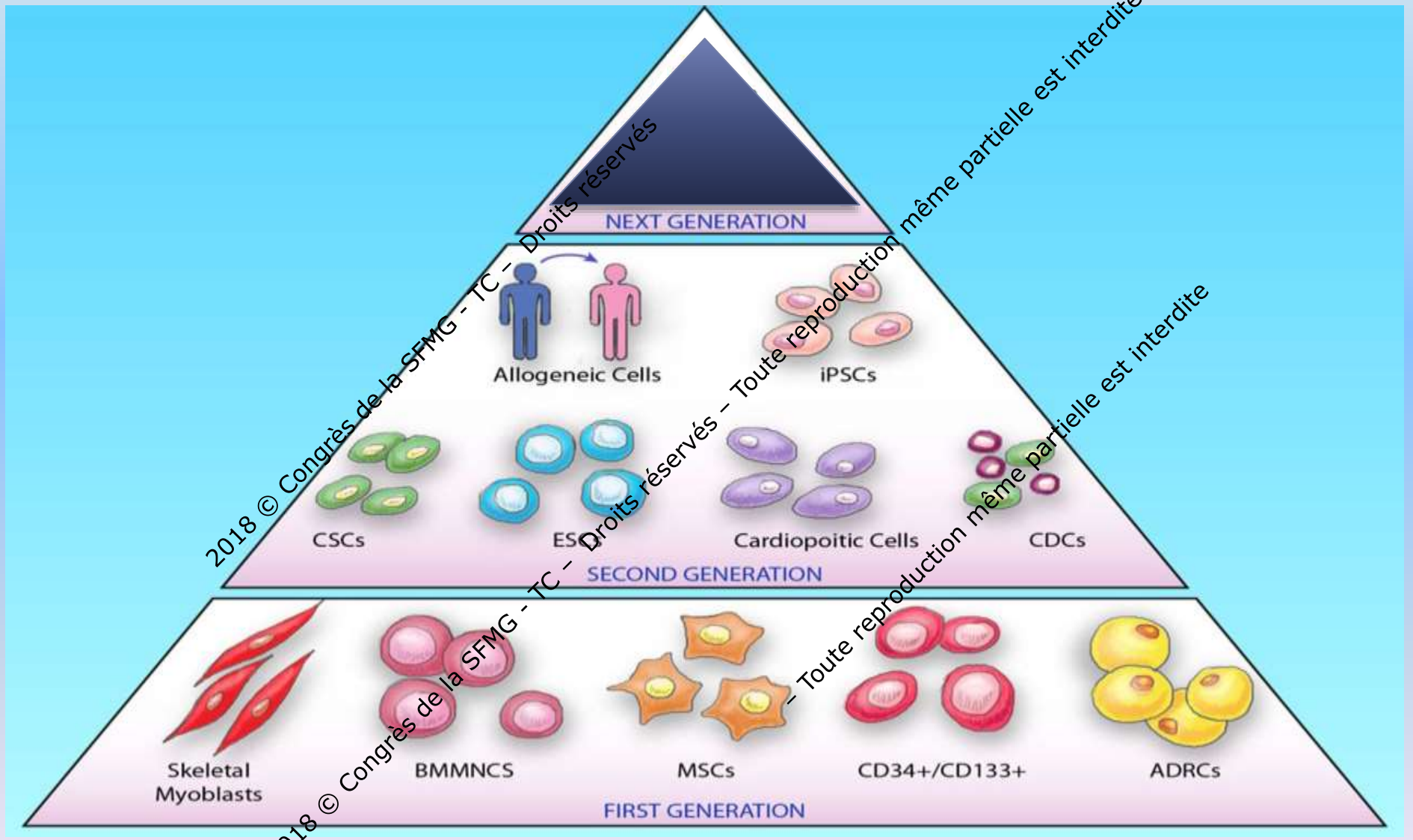


Tao et al. Oncotarget 2015;6:42613-22.

Functional Equivalence Between the EV-Enriched Secretome and the « Mother » Cells

Organ	Model	Comparator	End Points	Outcome	Reference
	Chronic ischemic Heart failure	ESC-derived CV progenitors	LV function	⟷	Kervadec et al. J Heart Lung Tx 2016;35:795-807.
	Duchenne DCM	Cardiosphere-derived cells	LV function	⟷	Aminzadeh et al. Stem Cell Reports 2018;10:942-55.
	Pulmonary hypertension	MSC	Pulmonary hemodynamics RV hypertrophy Pulmonary arteriole remodeling	⟷	Chen et al. Acta Pharmacol Sin 2014;35:1121-8.
	Acute kidney injury	MSC	Recovery of tubular lesions Renal function (BUN & creatinine levels)	⟷	Bruno et al. J Am Soc Nephrol 2009;20:1053-7.
	Stroke	MSC	Motor coordination deficits Neuronal survival Angio-neurogenesis	⟷	Doeppner et al., Stem Cells Translational Medicine 2015;4:1131-43.

Evolution of Cardiac Cell Therapy Trials



Adapted from Banerjee et al. Circ Res 2018;123:266-287.

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