VARIABILITY IN THE USE OF MESENCHYMAL STEM CELLS FOR TREATING CARDIOMYOPATHY

New Frontiers of Tissue Regeneration: Culture Expanded Cell Products in Clinical Trials

Ivonne Hernandez Schulman, MD

Interdisciplinary Stem Cell Institute

The Miller School of Medicine, University of Miami

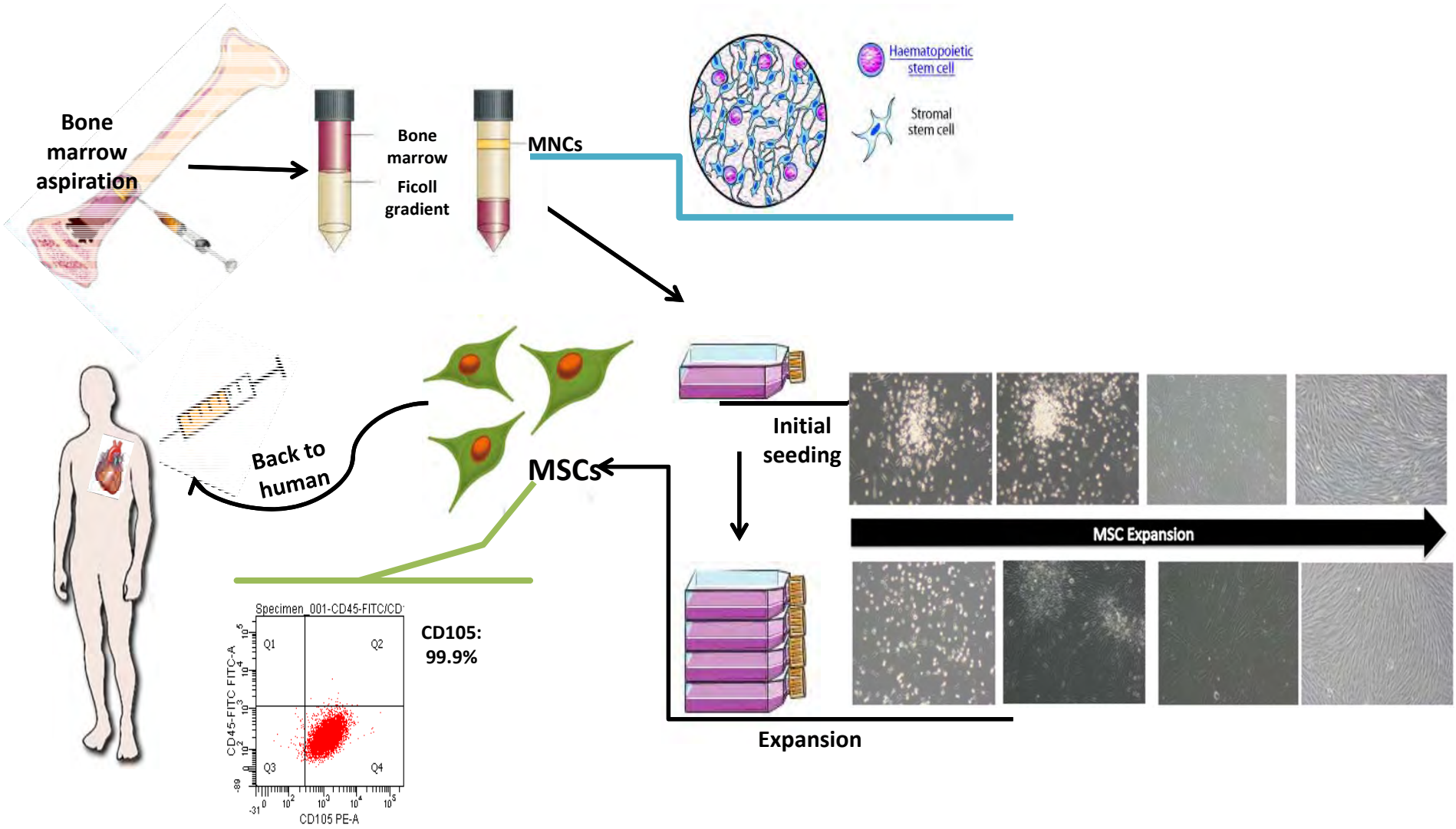
October 18, 2018

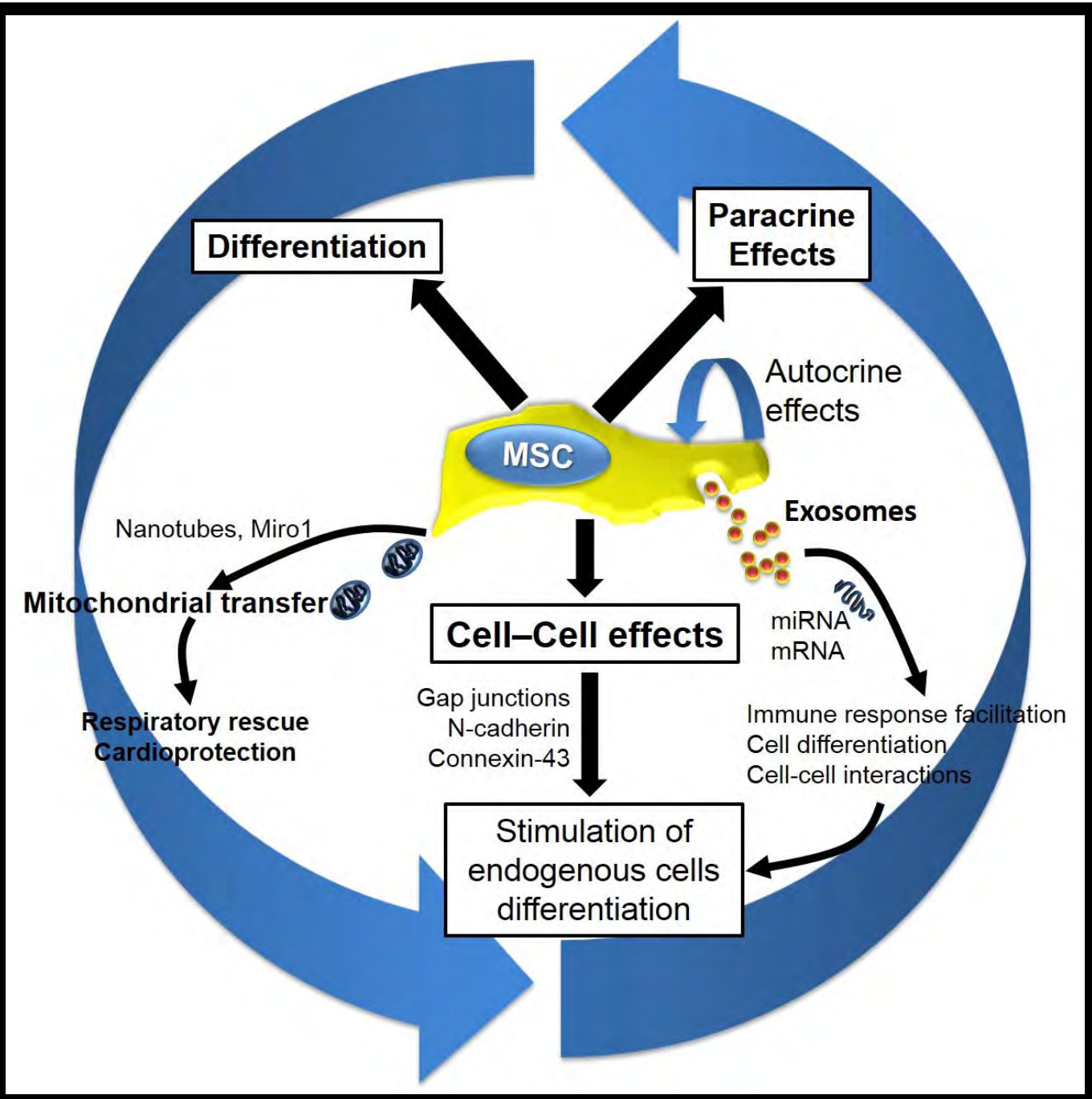
Disclosures

- Research Grants – NIH, Marcus Foundation
- Philanthropic support from the Soffer Family, Lipson Family, and Starr Foundations

- **Cell Products:**
  - Bone Marrow Derived CD105+ Cells
  - Umbilical Cord Derived CD105+ Cells
  - Cell Combination Therapy
- **Sources of variability:**
  - Donor sex, age, health status.
  - Manufacturing process (isolation, expansion, and characterization).
  - In vitro and in vivo assays of viability and efficacy (differentiation, anti fibrotic, pro angiogenic, anti inflammatory) to choose most potent cell product.

Manufacturing Steps of MSCs





Karantalis and Hare. *Circ Res* 2015

Circulation Research

American Heart Association

Brief UltraRapid Communication

Intramyocardial Stem Cell Injection in Patients With Ischemic Cardiomyopathy

Functional Recovery and Reverse Remodeling

Adam R. Williams, Barry Trachtenberg, Darcy L. Velazquez, Ian McNiece, Peter Altman, Didier Rouy, Adam M. Mendizabal, Pradip M. Pattany, Gustavo A. Lopera, Joel Fishman, Juan P. Zambrano, Alan W. Heldman, Joshua M. Hare

Circ Res. **2011;108:792-796.**

To Promote the Science and Art of Medicine and the Betterment of the Public Health

December 12, 2012, Vol 308, No. 22 Pages 2297-2420

JAMA

The Journal of the American Medical Association

Comparison of Allogeneic vs Autologous Bone Marrow–Derived Mesenchymal Stem Cells Delivered by Transendocardial Injection in Patients With Ischemic Cardiomyopathy: The POSEIDON Randomized Trial 2369

J. M. Hare, J. E. Fishman, G. Gerstenblith, and Coauthors

Circulation

American Heart Association

Molecular Cardiology

Enhanced Effect of Combining Human Cardiac Stem Cells and Bone Marrow Mesenchymal Stem Cells to Reduce Infarct Size and to Restore Cardiac Function After Myocardial Infarction

Adam R. Williams, MD; Konstantinos E. Hatzistergos, PhD; Benjamin Addicott, MD; Fred McCall, BS; Decio Carvalho, MD; Viky Suncion, MD; Azorides R. Morales, MD; Jose Da Silva, PhD; Mark A. Sussman, PhD; Alan W. Heldman, MD; Joshua M. Hare, MD

Circulation. 2013 Jan 15; 127(2): 213–223.

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jama.com

January 1, 2014

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JAMA

Journal of the American Medical Association

Research

Original Investigation

Transendocardial Mesenchymal Stem Cells and Mononuclear Bone Marrow Cells for Ischemic Cardiomyopathy

The TAC-HFT Randomized Trial

Alan W. Heldman, MD; Darcy L. DiFede, RN, BSN; Joel E. Fishman, MD, PhD; Juan P. Zambrano, MD; Barry H. Trachtenberg, MD; Vasileios Karantalis, MD; Muzammil Mushtaq, MD; Adam R. Williams, MD; Viky Y. Suncion, MD; Ian K. McNiece, PhD; Eduard Ghersin, MD; Victor Soto, MD; Gustavo Lopera, MD; Roberto Miki, MD; Howard Willens, MD; Robert Hendel, MD; Raul Mitrani, MD; Pradip Pattany, PhD; Gary Feigenbaum, MD; Behzad Oskouei, MD; John Byrnes, MD; Maureen H. Lowery, MD; Julio Sierra, MD; Marlesty V. Pujol, MBA; Cindy Delgado, MA; Phillip J. Gonzalez, CRC; Jose E. Rodriguez, RTMR; Luiza Lima Bagno, PhD; Didier Rouy, MD, PhD; Peter Altman, PhD; Cheryl Wong Po Foo, PhD; Joseda Silva, PhD; Erica Anderson, MA; Richard Schwarz, PhD; Adam Mendizabal, PhDc; Joshua M. Hare, MD

Circulation Research

American Heart Association

Clinical Track

Does Transendocardial Injection of Mesenchymal Stem Cells Improve Myocardial Function Locally or Globally?

An Analysis From the Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis (POSEIDON) Randomized Trial

Viky Y. Suncion, Eduard Ghersin, Joel E. Fishman, Juan Pablo Zambrano, Vasileios Karantalis, Nicole Mandel, Katarina H. Nelson, Gary Gerstenblith, Darcy L. DiFede Velazquez, Elayne Breton, Kranthi Sitammagari, Ivonne H. Schulman, Sabrina N. Taldone, Adam R. Williams, Cristina Sanina, Peter V. Johnston, Jeffrey Brinker, Peter Altman, Muzammil Mushtaq, Barry Trachtenberg, Adam M. Mendizabal, Melissa Tracy, Jose Da Silva, Ian K. McNiece, Alberto C. Lardo, Richard T. George, Joshua M. Hare, Alan W. Heldman

Circ Res. 2014 Apr 11; 114(8): 1292–1301.

Published online 2014 Jan 21. doi: 10.1161/CIRCRESAHA.114.302854

Circulation Research

American Heart Association

Editorial

PROMETHEUS and POSEIDON

Harnessing the Power of Advanced Cardiac Imaging

Atul R. Chugh, Joao A.C. Lima

Circulation Research. 2014;114:1222-1224,
doi:10.1161/CIRCRESAHA.114.303792

J. of Cardiovasc. Trans. Res. (2014) 7:769–780
DOI 10.1007/s12265-014-9594-0

Rationale and Design of the Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis in Dilated Cardiomyopathy (The POSEIDON-DCM Study)

A phase I/II, Randomized Pilot Study of the Comparative Safety and Efficacy of Transendocardial Injection of Autologous Mesenchymal Stem Cell vs. Allogeneic Mesenchymal Stem Cells in Patients with Non-ischemic Dilated Cardiomyopathy

Muzammil Mushtaq · Darcy L. DiFede · Samuel Golpanian · Aisha Khan · Samirah A. Gomes · Adam Mendizabal · Alan W. Heldman · Joshua M. Hare

EBioMedicine 2 (2015) 467–475

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Original Article

Allogeneic Mesenchymal Stem Cells Restore Endothelial Function in Heart Failure by Stimulating Endothelial Progenitor Cells

Courtney Premer [a,1], Arnon Blum [b,1], Michael A. Bellio [a], Ivonne Hernandez Schulman [a], Barry E. Hurwitz [c], Meela Parker [c], Christopher R. Dermarkarian [a], Darcy L. DiFede [a], Wayne Balkan [d], Aisha Khan [a], Joshua M. Hare [a,*]

The Translational Pipeline
Phase I/II Clinical Trials

- **PROMETHEUS** – Surgical delivery of autologous MSCs (Karantalis et al, Circ Res, 2014)
- **TAC-HFT** – Catheter delivery. Autologous MSCs vs. Whole Bone Marrow vs. Placebo. 65 patients. (Heldman et al, JAMA, 2014)
- **POSEIDON** and **POSEIDON-DCM** – Catheter delivery. Autologous vs. Allogeneic MSCs. (Hare et al, JAMA, 2012; Hare et al, JACC, 2017)
- **TRIDENT** – Catheter delivery. 20 vs. 100 million Allogeneic MSCs. (Florea and Rieger et al, Circ Res, 2017)

Clinical Trial Results of MSCs Applied to Human Heart Failure

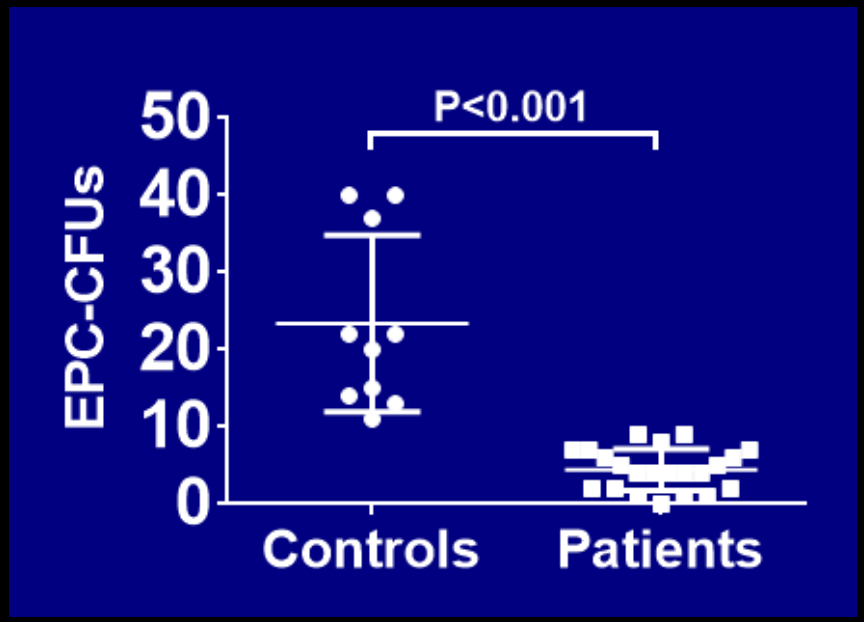
- Intra-cardiac autologous and allogeneic MSC injections are safe (4 phase I/II successful)
- Absence of significant alloimmune reactions with allo MSCs
- Moderate but consistent improvements in 6 min walk distance and Minnesota Living with HF questionnaire scores
- Scar size reduced by 30 to 50%; Reverse remodeling
- EF improvement in the dilated cardiomyopathy patients (allo>auto)
- Improved endothelial function (FMD and EPCs) with allo MSCs
- Decrease in TNF alpha in dilated cardiomyopathy patients

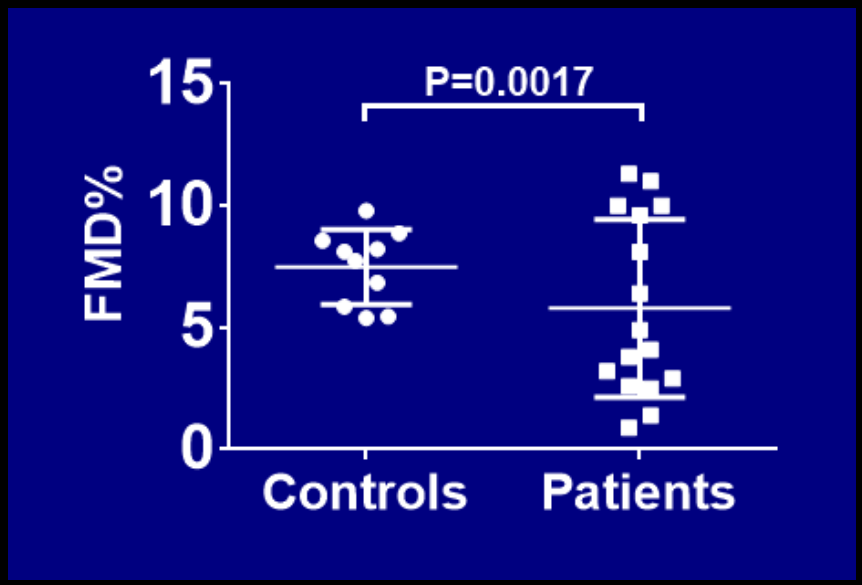
Hare et al, *JAMA* 2012; Heldman et al, *JAMA* 2014; Hare et al, *JACC* 2017; Florea et al, *Circ Res* 2017

Basic and Preclinical Studies Mechanisms of Action of Cardiac Repair with MSCs

- Anti-fibrotic effects (Berry at, AJP Heart Circ 2006)
- Anti-inflammatory effects
- Pro-angiogenic effects (Perin et al, Circ. 2005)
- Restoration of Contractile Function
  - Engraftment, differentiation and stimulation of endogenous cardiac stem cells to proliferate and differentiate (Quevedo et al, PNAS 2009; Hatzistergos et al, Circ Res 2010)

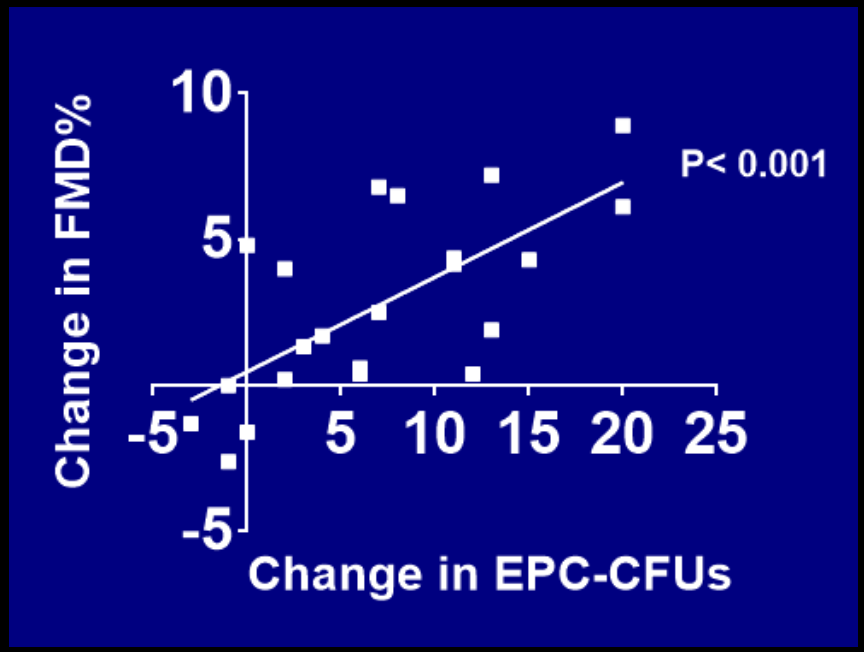
Patients with cardiomyopathy have impaired endothelial function compared to healthy controls at baseline

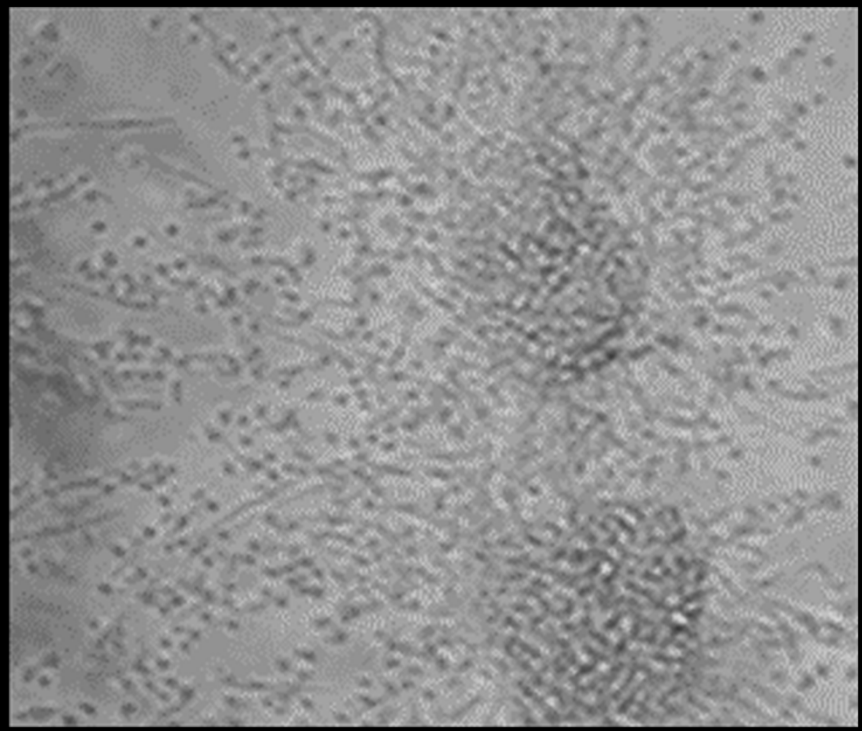




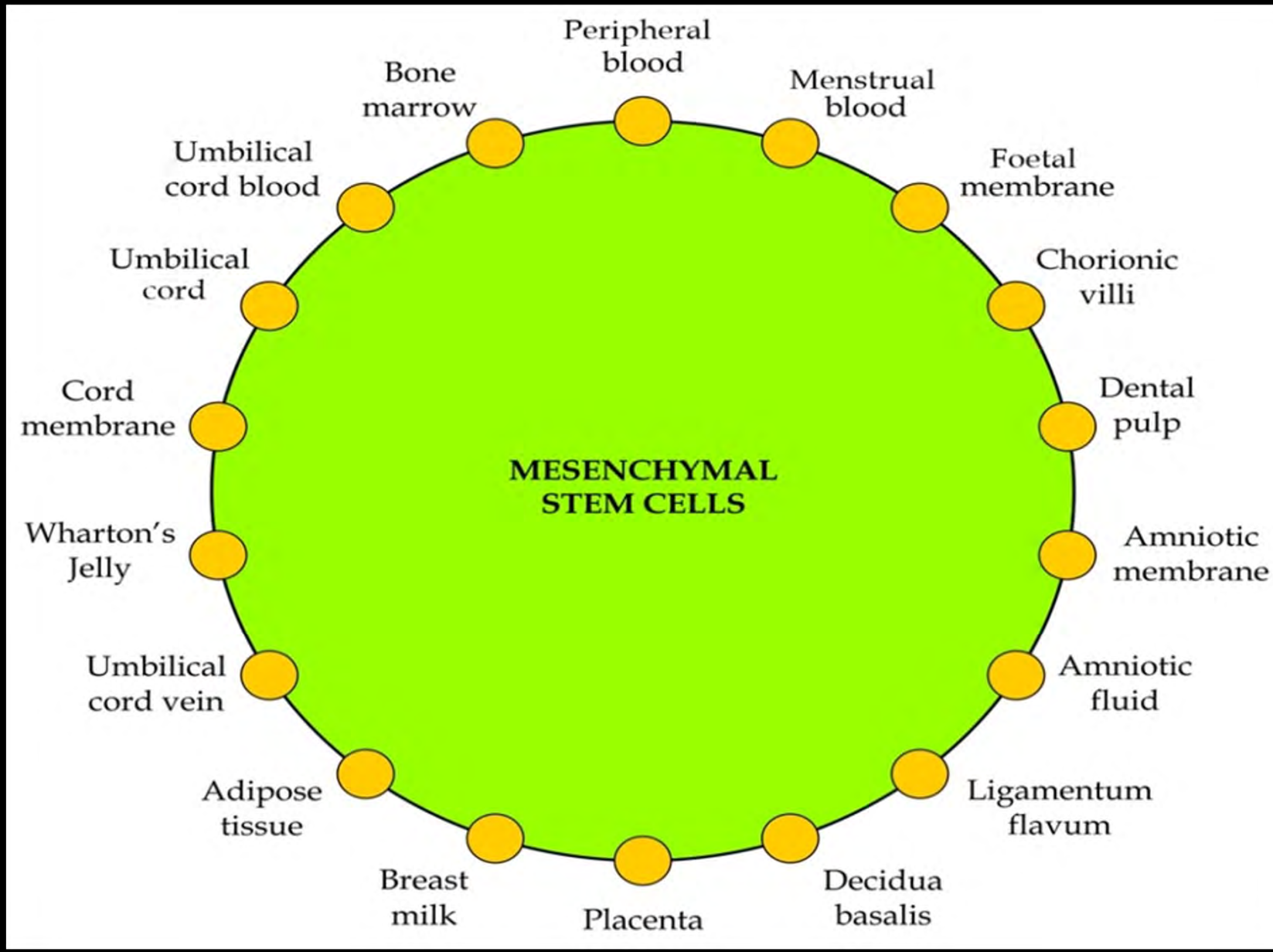
Premer et al. EBioMed 2015

MSCs increase circulating EPCs and augment brachial artery reactivity



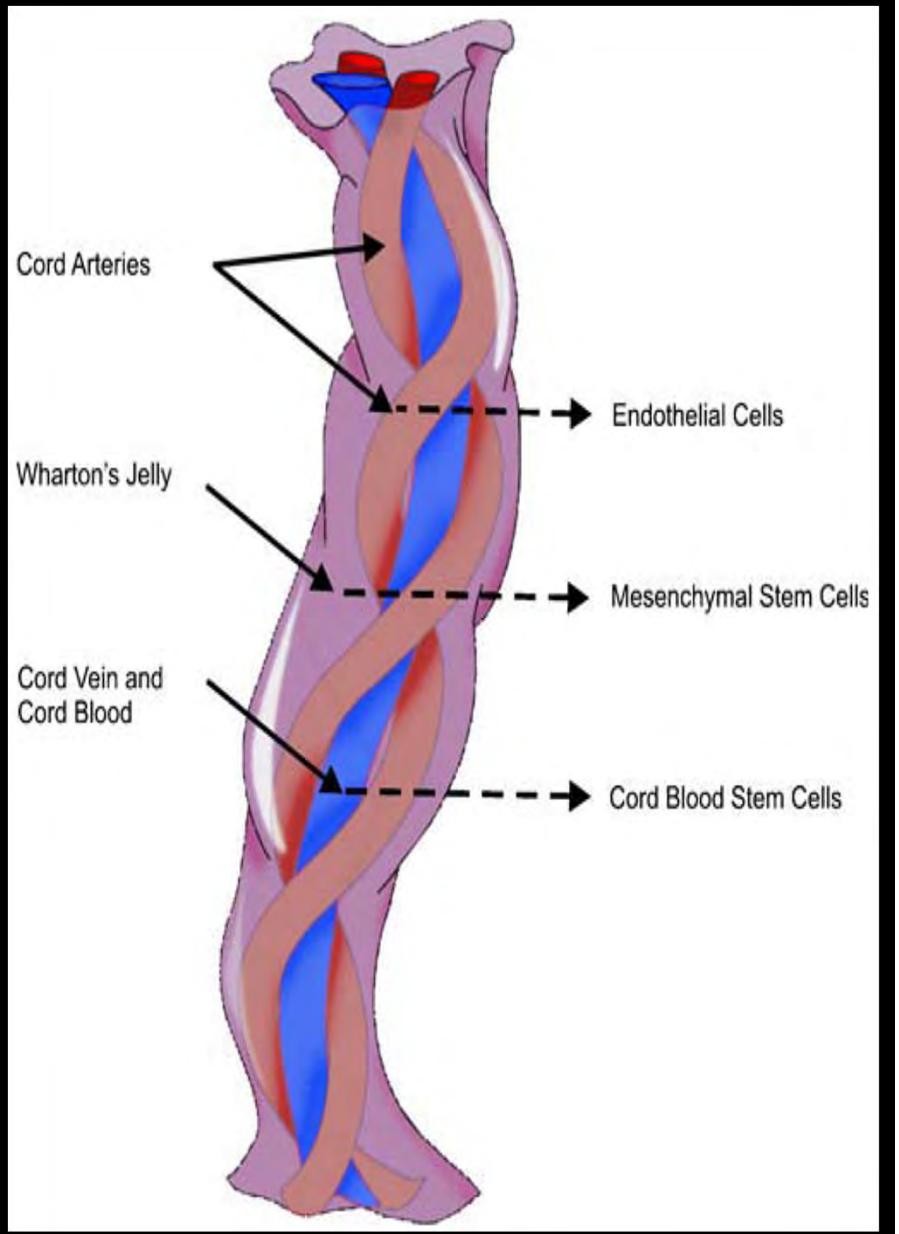


Premer et al. EBioMed 2015

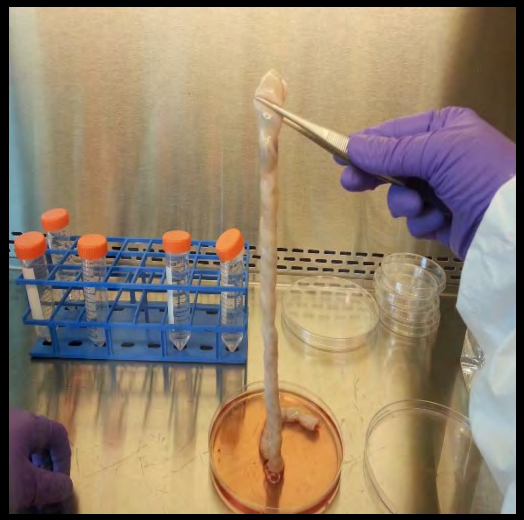

Peripheral blood
Bone marrow
Menstrual blood
Umbilical cord blood
Foetal membrane
Umbilical cord
Chorionic villi
Cord membrane
Dental pulp
MESENCHYMAL STEM CELLS
Wharton's Jelly
Amniotic membrane
Umbilical cord vein
Amniotic fluid
Adipose tissue
Ligamentum flavum
Breast milk
Placenta
Decidua basalis

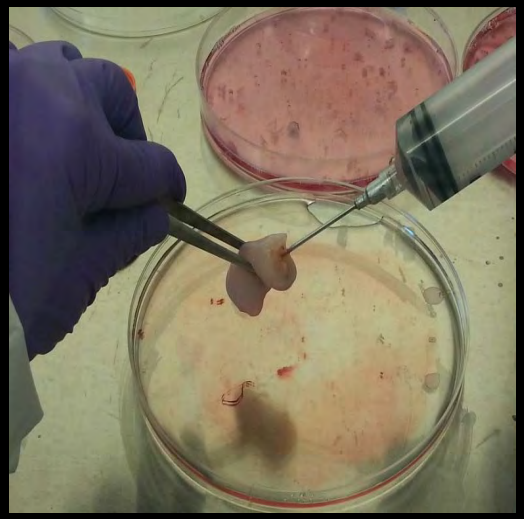
Umbilical Cord Mesenchymal Stem Cells

- Also Known as Wharton's Jelly
- Adult stem cells of infant origin
- Isolated immediately following birth
- Alternate to bone marrow stem cells

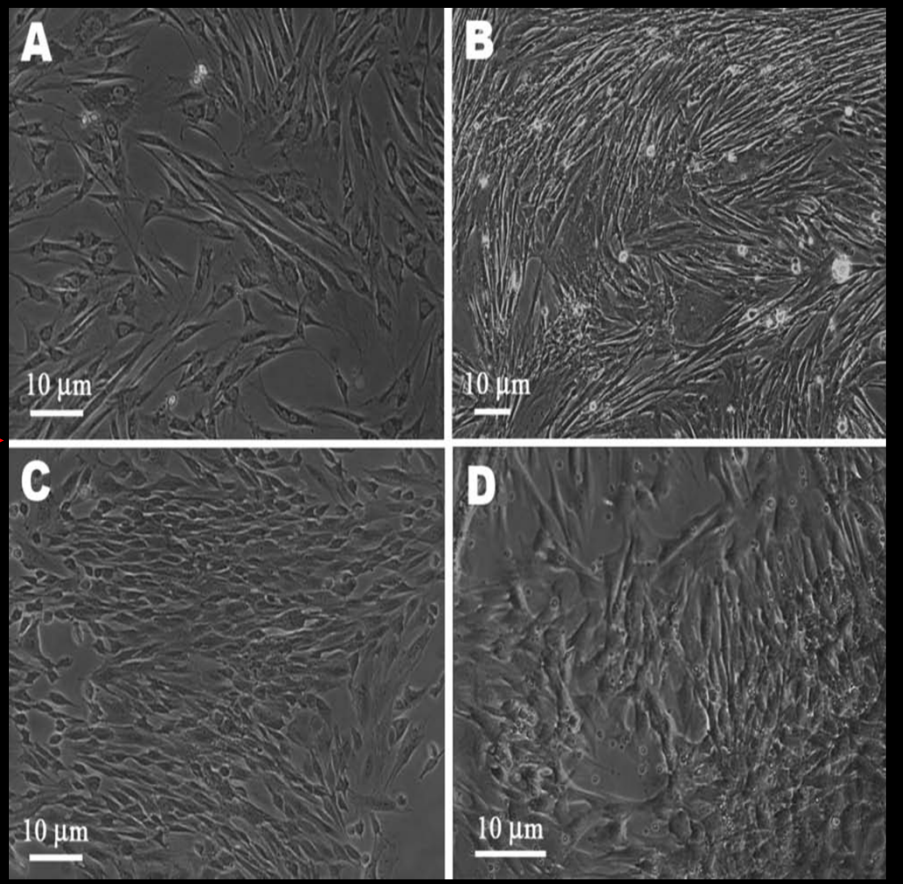


Umbilical Cord MSC Processing

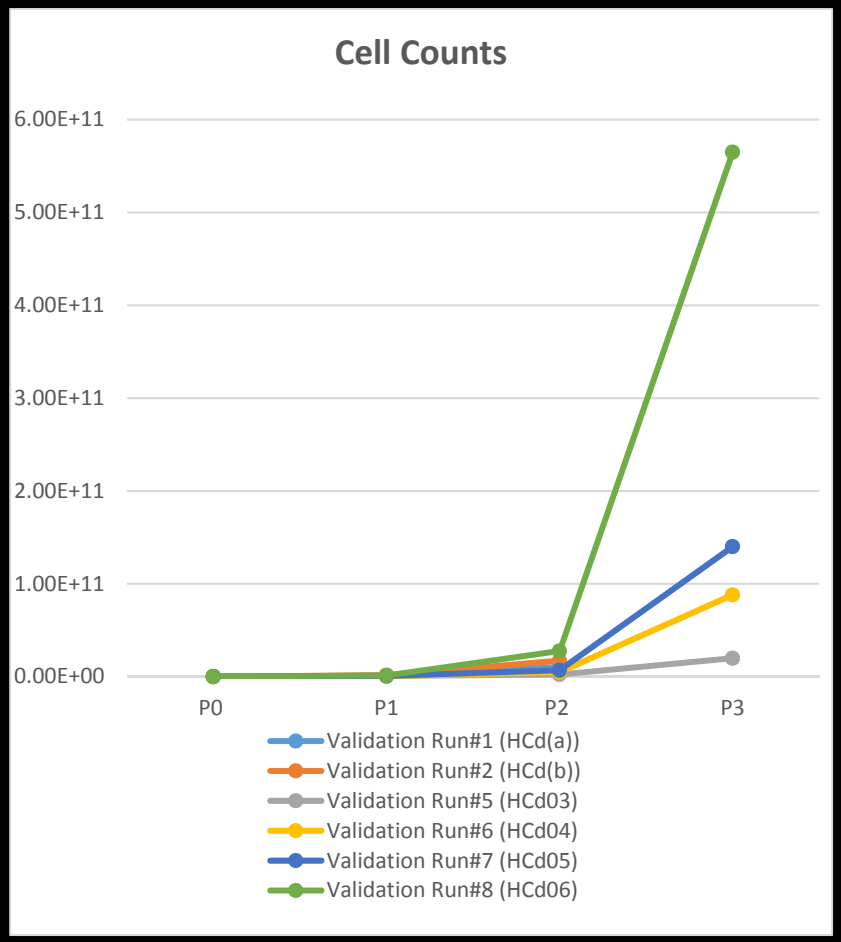


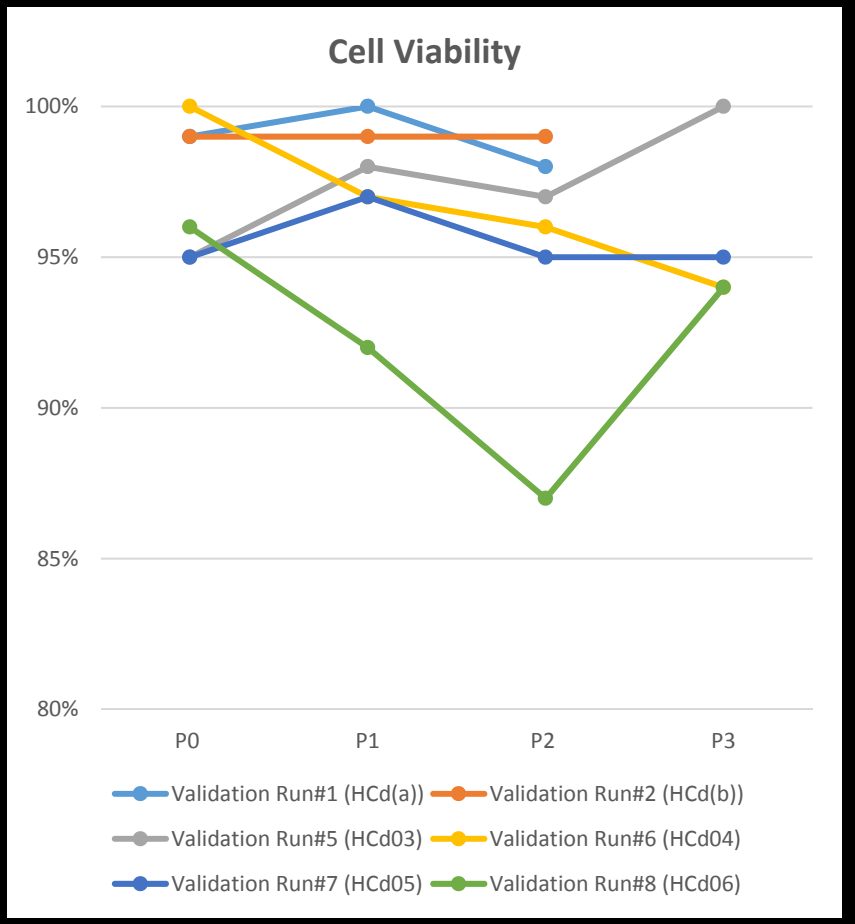


UC MSC Processing

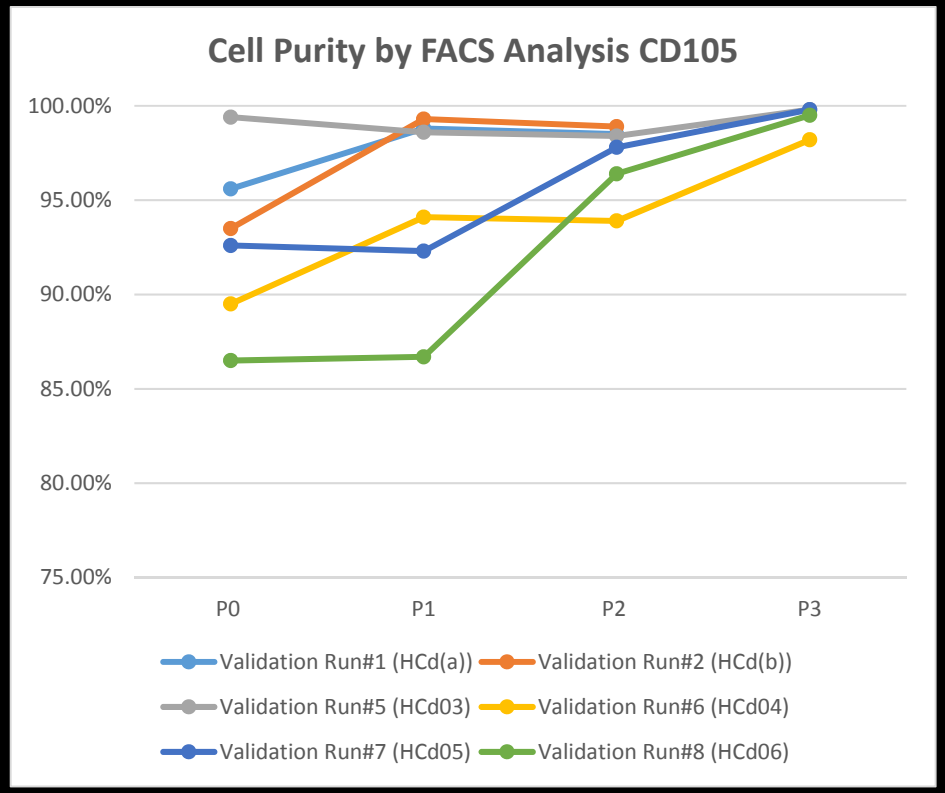


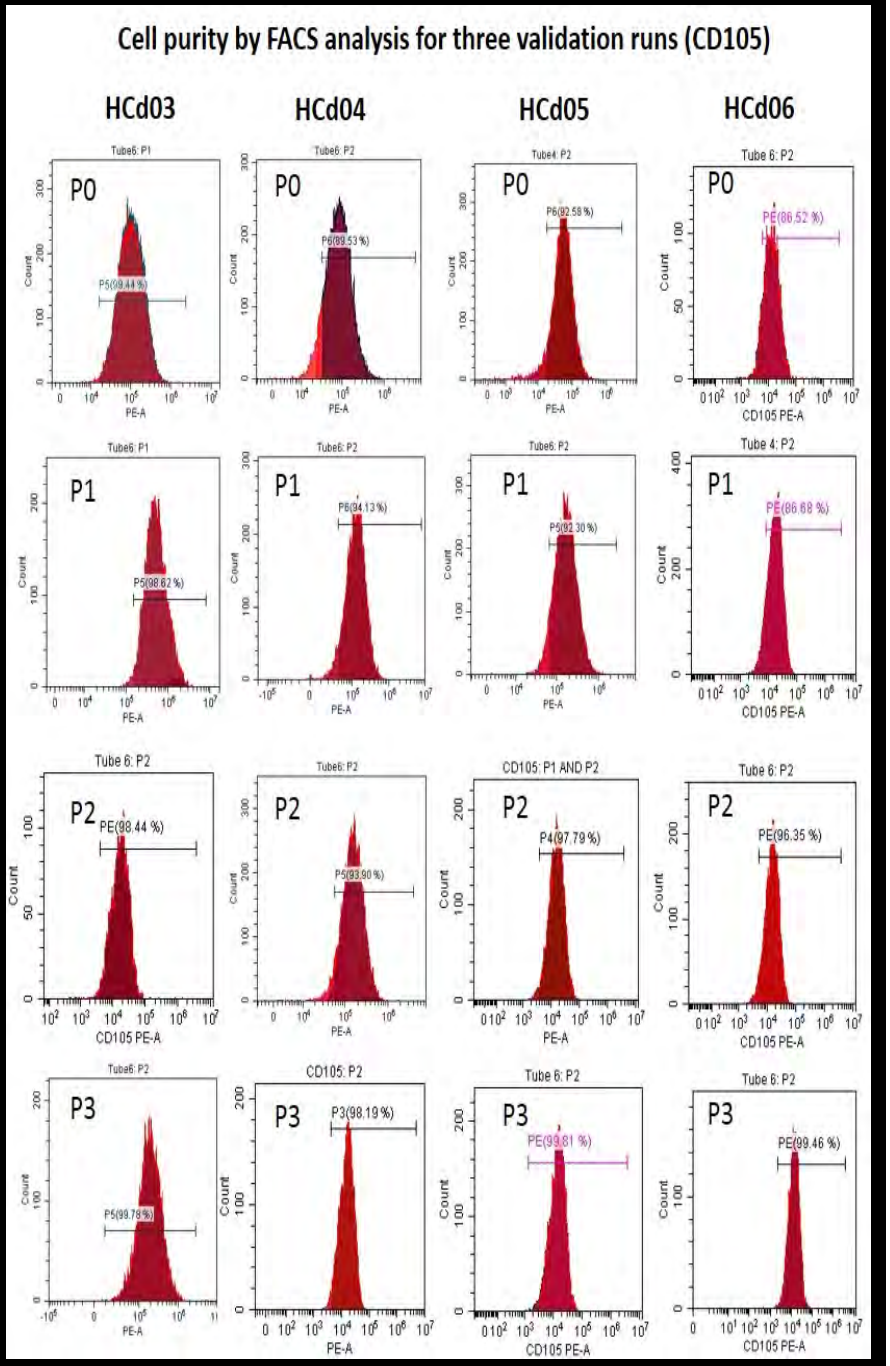
UC MSC Cell Counts and Viability



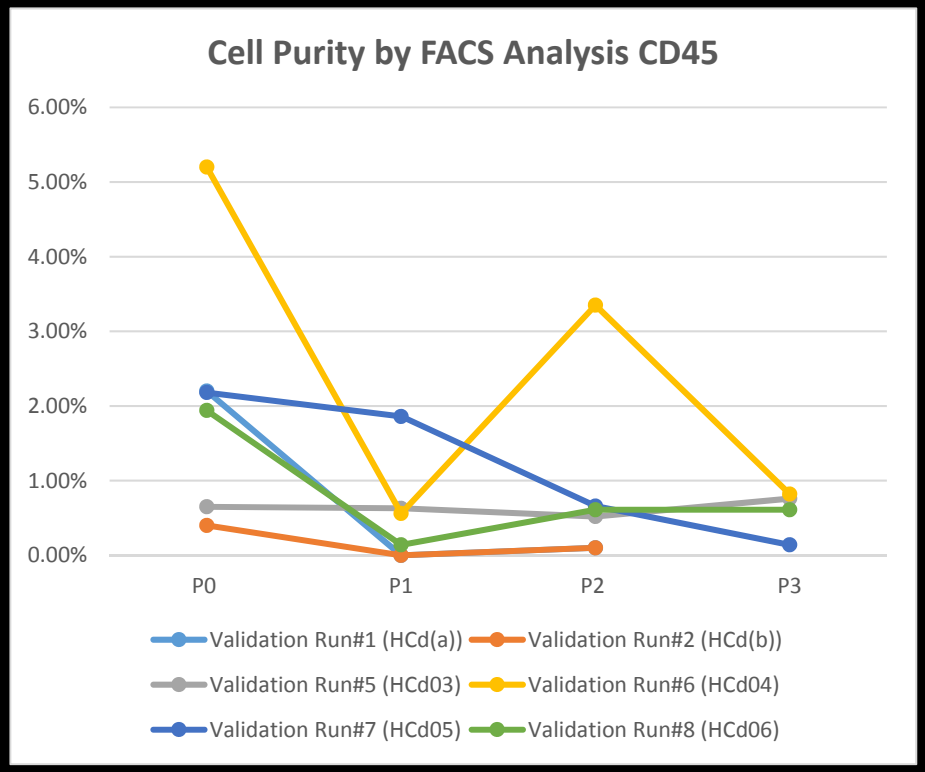


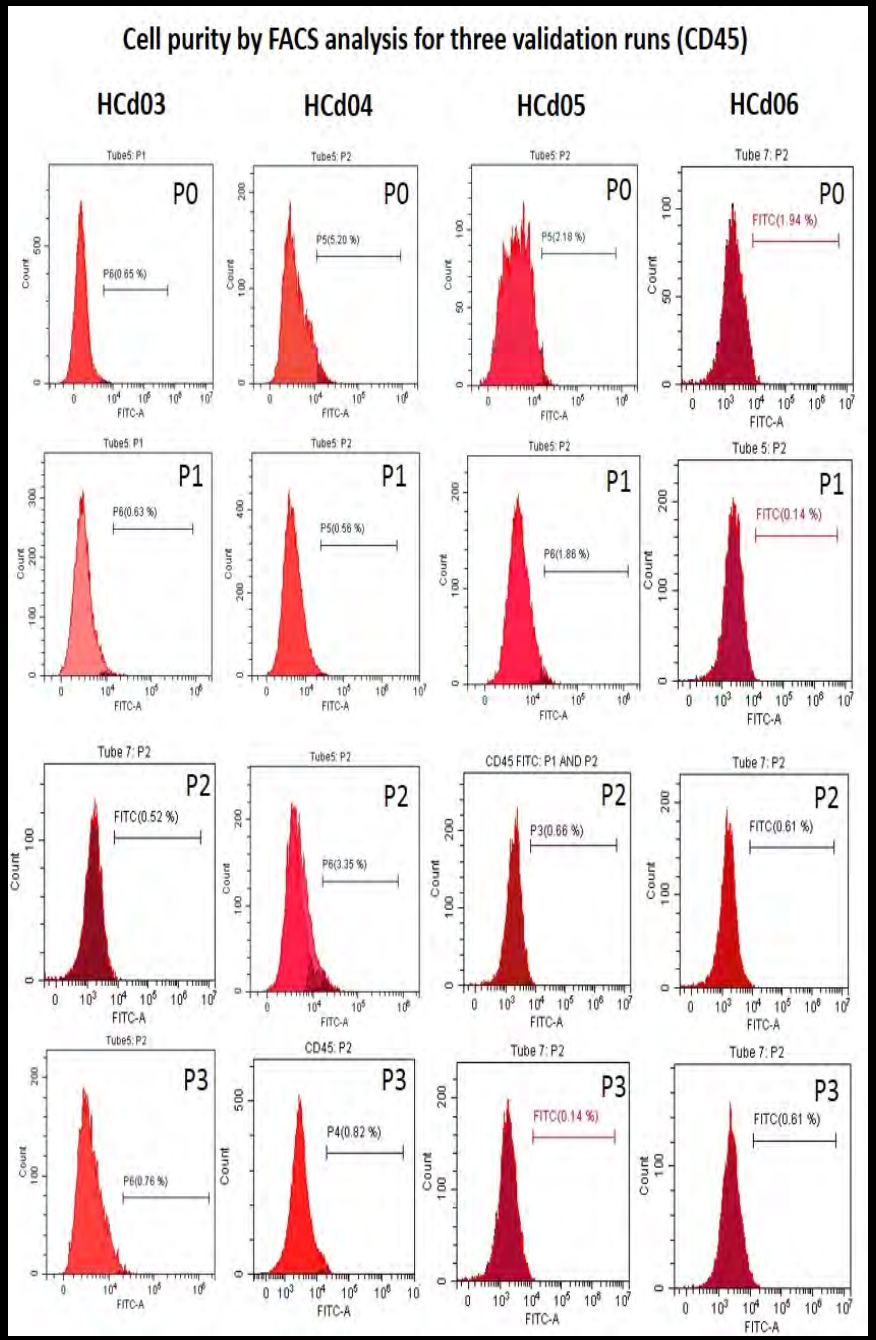
UC MSC Cell Purity CD105



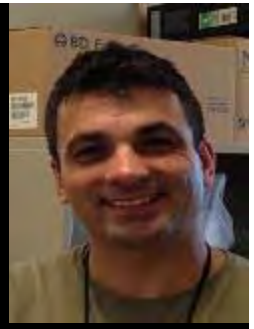


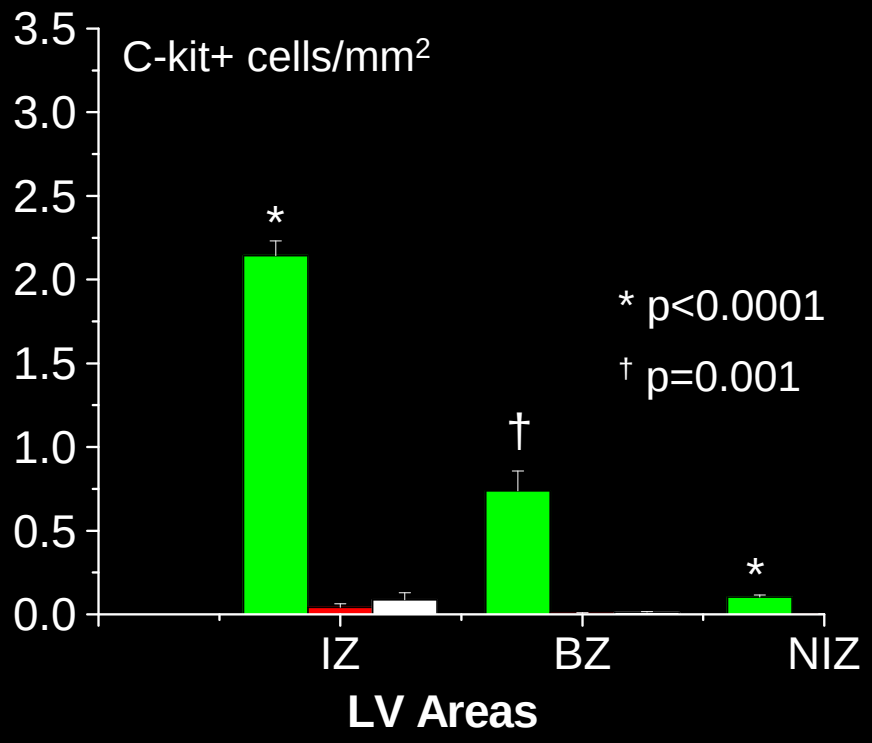
UC MSC Cell Purity CD45

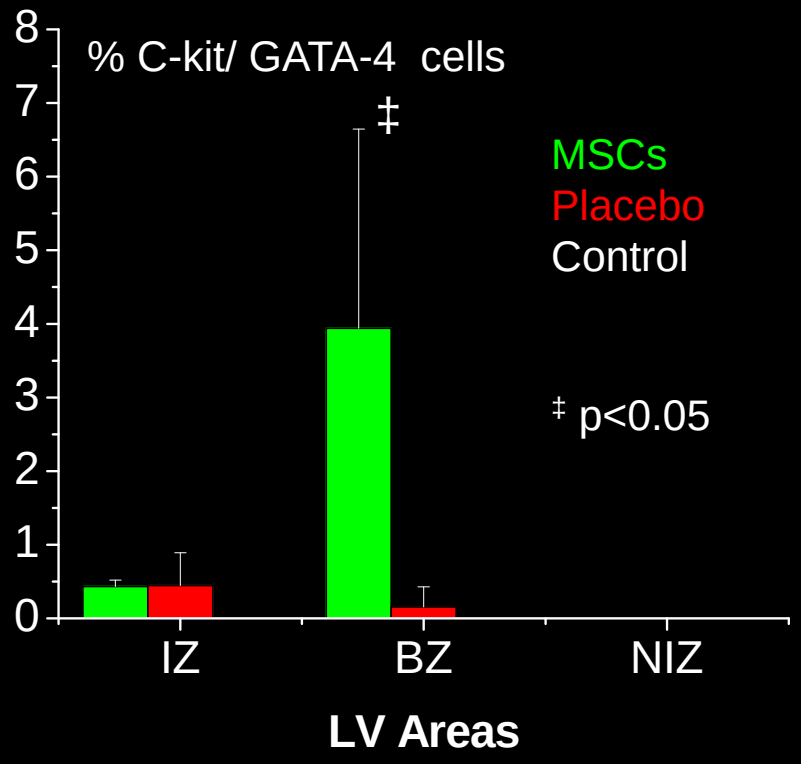




MSCs stimulate endogenous cardiac repair

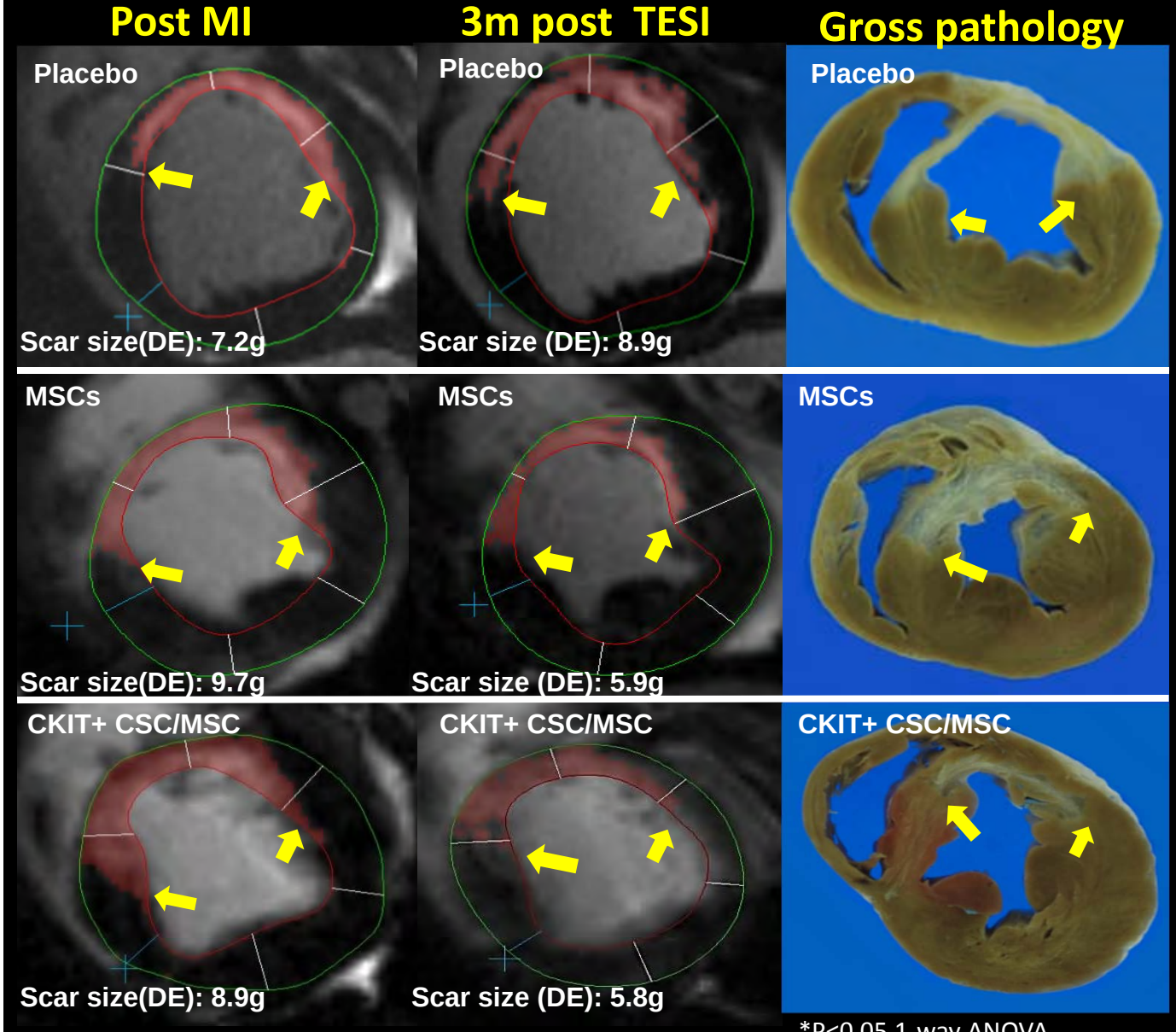


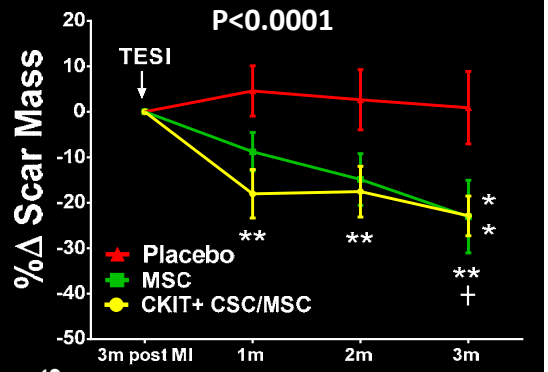


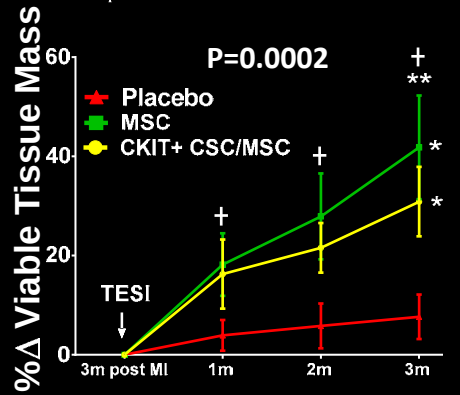


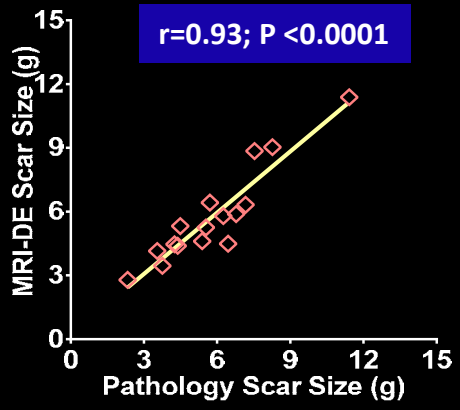
Hatzistergos et al. Circ Res 2010

Cell treated groups have similar antifibrotic effects









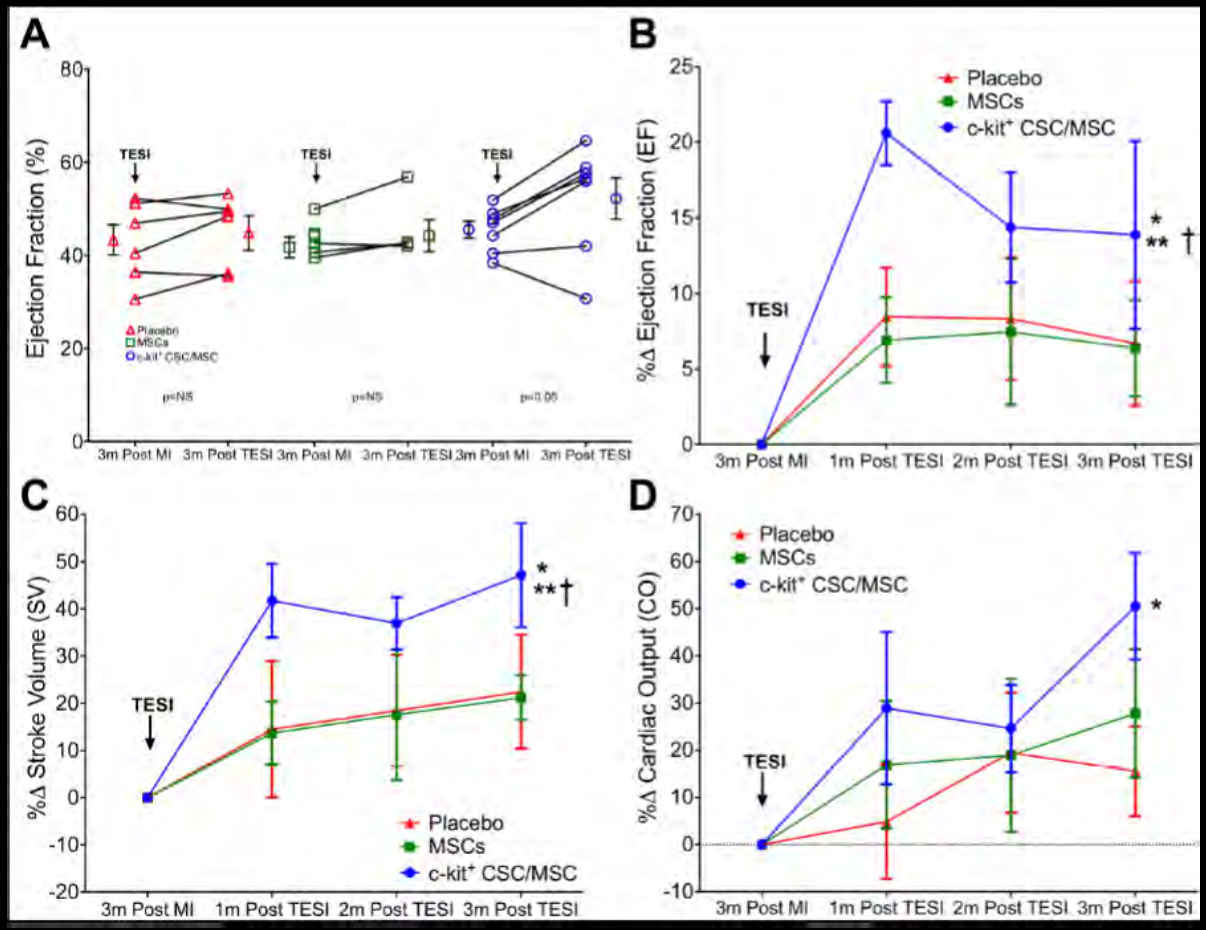
Qmass MR 7.2 (Medis Inc)

*P<0.05 1-way ANOVA

**P<0.05 2-way ANOVA posttest CKIT+CSC/MSC vs placebo

\+ P<0.05 2-way ANOVA posttest MSCs vs placebo

Combined engraftment enhances repair in an autologous model of chronic ischemic cardiomyopathy



Karantalis et al. JACC, 2015

The Cardiovascular Cell Therapy Research Network

The CONCERT -CHF Trial:

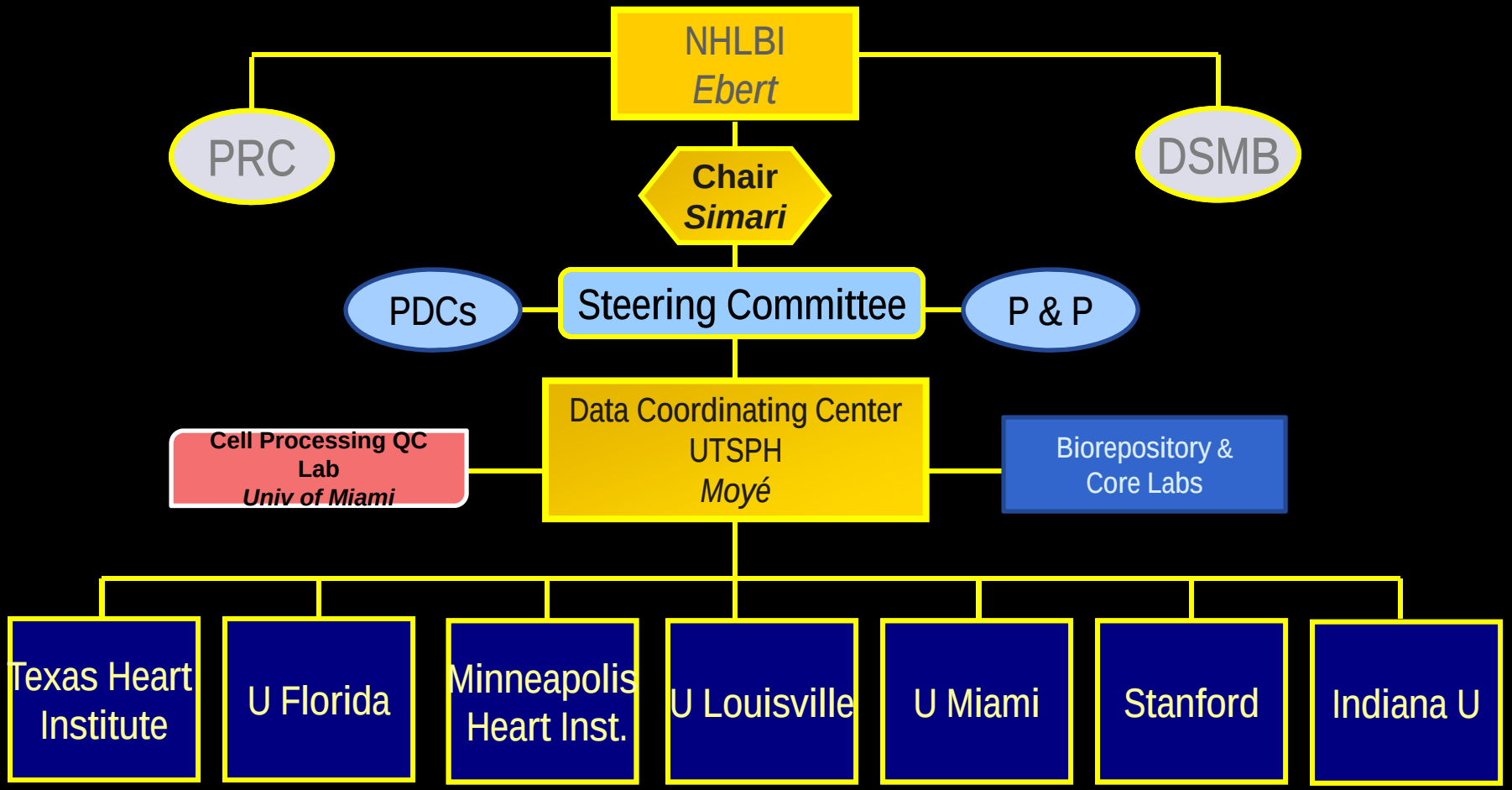
Combination **O**f c-kit cells and mesenchymal cells: a **N**ovel, dual **C**ell study **E**valuating **R**egenerative properties for **T**reatment in **C**hronic **H**eart **F**ailure

Study Chair: Atul R. Chugh, MD

Asst. Professor, Director-Advanced Cardiac Imaging and Preventive Cardiology

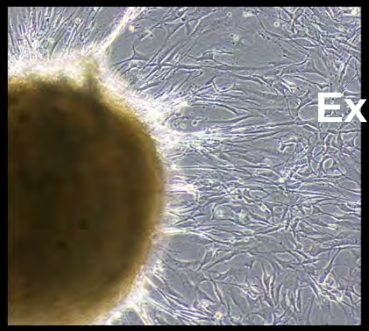
University of Louisville, Louisville, KY

Organizational Structure: NHLBI
Cardiovascular Cell Therapy Research Network (CCTRN)

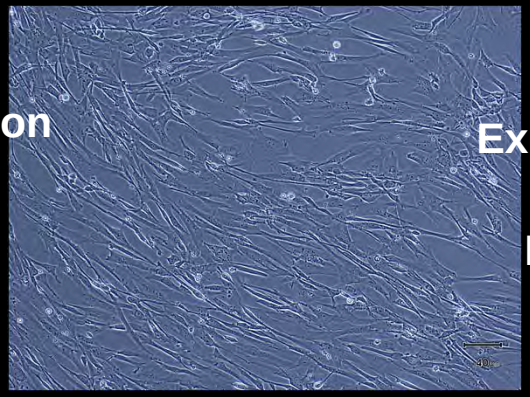


C-Kit Cell Expansion

- Endomyocardial Biopsy Digestion
- Cell Expansion
- CD117+ Cell Sorting
- Further Cell Expansion

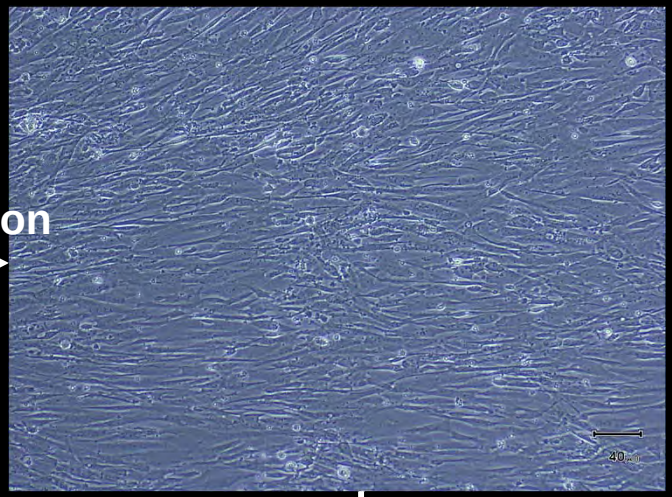


Expansion



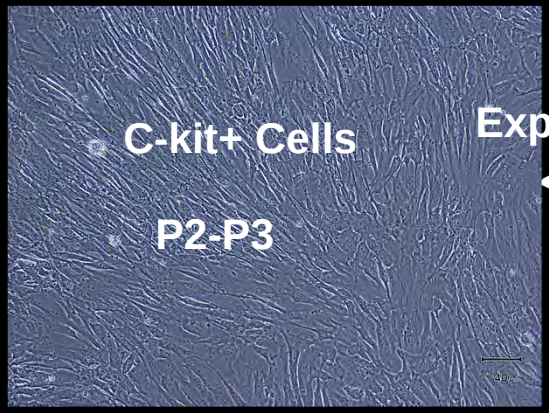
Expansion

P0

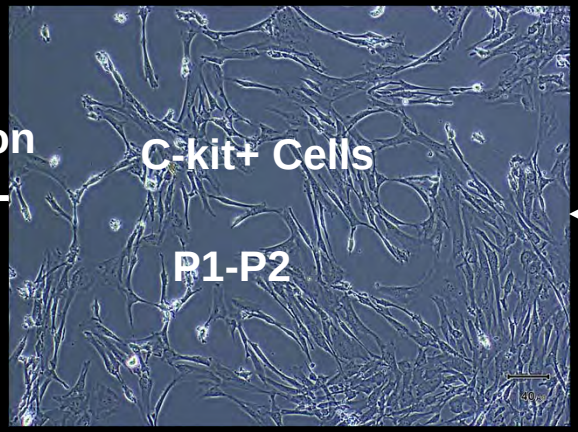


Sorting

Adherence to surface of cell culture



Expansion

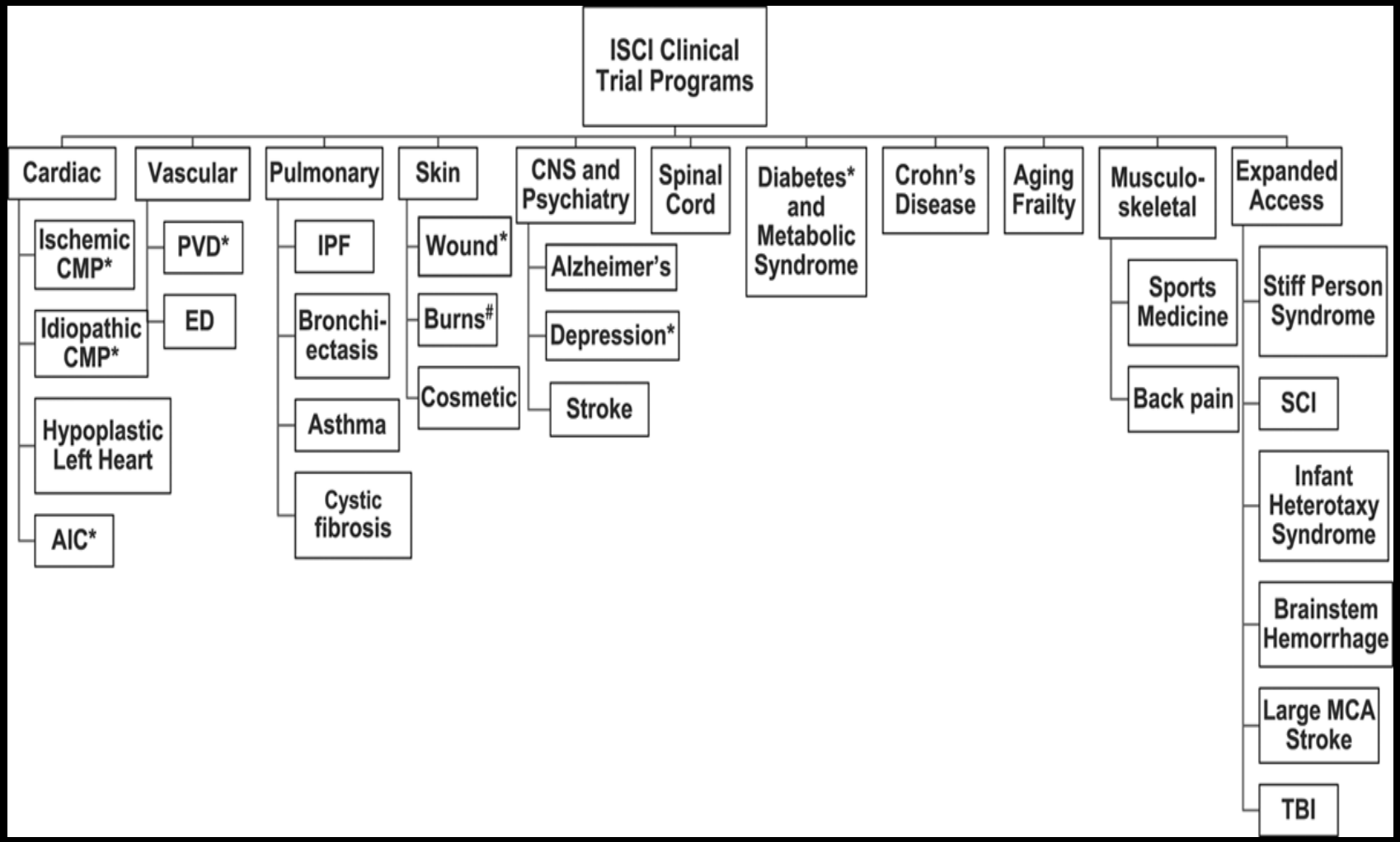


Sample Size and Treatment Groups

- 144 subjects will be randomized 1:1:1:1
- 36 subjects/group to 1 of 4 treatment groups:
  1. **Combo:** Target dose is a mixture of 150 million MSCs and 5 million CSCs
  2. **MSCs:** Target dose is 150 million MSCs
  3. **CSCs:** Target dose is 5 million CSCs
  4. **Placebo:** Cell-free PlasmaLyte-A medium
- Run in phase (n=16)
- Each subject will receive 15 injections, each of 0.4 ml volume (cells or placebo)

Conclusions and Implications

- MSCs are powerful antifibrotic, anti-inflammatory, and immunomodulatory cells that stimulate neoangiogenesis and cell proliferation
- MSCs activate regenerative pathways in the human heart
- Trials are underway using MSCs, CPCs, and combinations of MSCs-CPCs (cell combination therapy)
- We are performing comparison studies of CD105 cell effects derived from different sources (bone marrow and umbilical cord) in human subjects
- Cell Combination Therapy may enhance cell-based cardiac repair
- Exosomes are being evaluated and compared to MSCs
- Future research: Impact of Sex of donor and patient; Age of donor and patient; underlying health status of donor; disease process/genetics of patient on efficacy of MSCs.



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SCCT
Specialized Centers for Cell-Based Therapy
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

CCTRN
Cardiovascular Cell Therapy Research Network

PACT
Production Assistance for Cellular Therapies
National Heart Lung and Blood Program

Soffer Family Foundation,
Starr, Marcus