Outcome Variability in Cardiovascular Stem Cell Trials

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Director, Stanford Cardiovascular Institute
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Forum on Regenerative Medicine
October 18, 2018

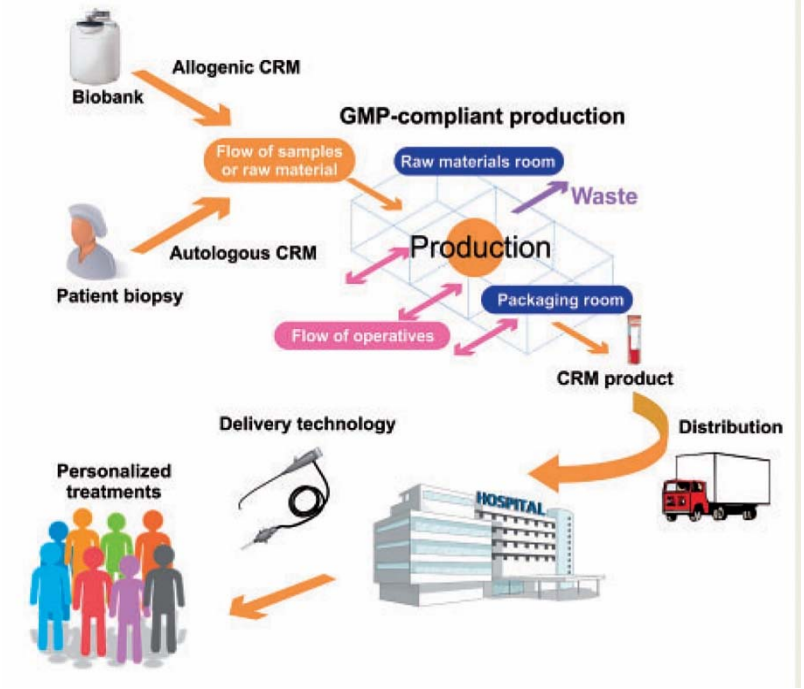
Stanford | Cardiovascular Institute

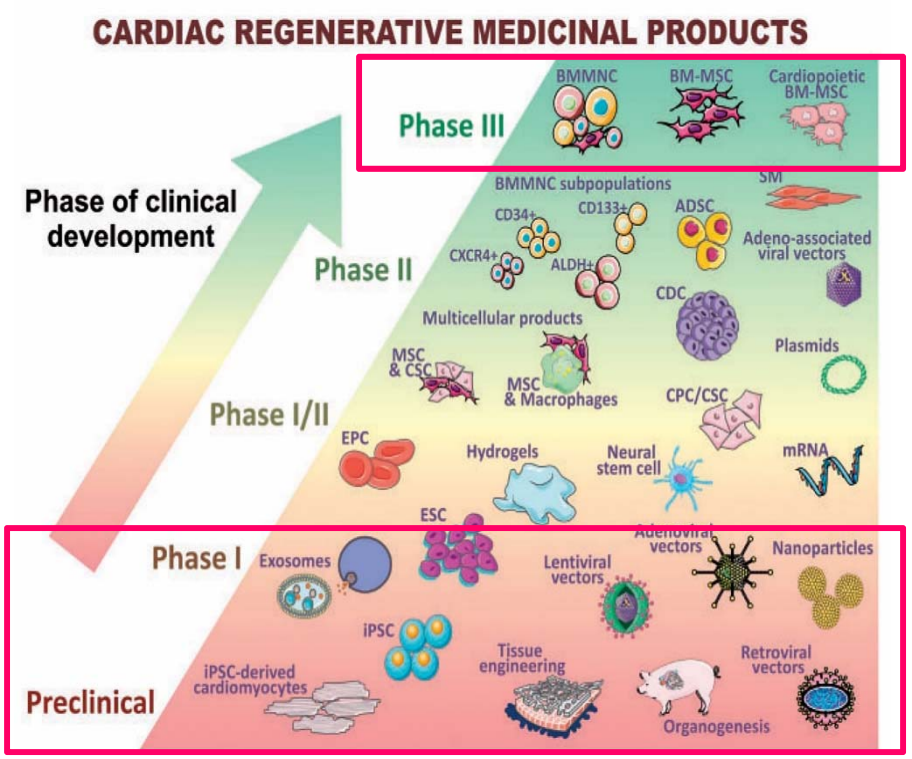
STANFORD SCHOOL OF MEDICINE

Global position paper on cardiovascular regenerative medicine

Scientific statement of the transnational alliance for regenerative therapies in cardiovascular syndromes (TACTICS) international group for the comprehensive cardiovascular application of regenerative medicinal products

Francisco Fernández-Avilés[1,2], Ricardo Sanz-Ruiz[1,2], Andreu M. Climent[1,2], Lina Badimon[2,3], Roberto Bolli[4], Dominique Charron[5], Valentin Fuster[2,6,7], Stefan Janssens[8], Jens Kastrup[9], Hyo-Soo Kim[10], Thomas F. Lüscher[11], John F. Martin[12], Philippe Menasché[13], Robert D. Simari[14], Gregg W. Stone[15], Andre Terzic[16], James T. Willerson[17], and Joseph C. Wu[18]; the TACTICS (Transnational Alliance for Regenerative Therapies in Cardiovascular Syndromes) Writing Group





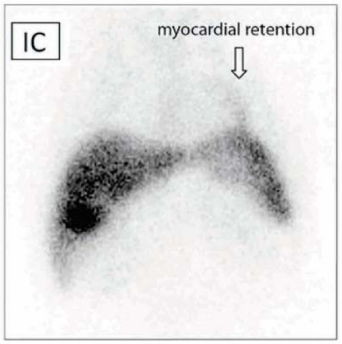
Eur Heart J 2017

Our Experience with Adult Stem Cell Trials

Comparison of Transendocardial and Intracoronary CD34+ Cell Transplantation in Patients With Nonischemic Dilated Cardiomyopathy

Bojan Vrtovec, MD, PhD; Gregor Poglajen, MD, PhD; Luka Lezaic, MD, PhD; Matjaz Sever, MD; Aljaz Socan, MPharm; Dragoslav Domanovic, MD, PhD; Peter Cernelc, MD, PhD; Guillermo Torre-Amione, MD, PhD; François Haddad, MD; Joseph C. Wu, MD, PhD

Circulation 2013



Effects of Intracoronary CD34+ Stem Cell Transplantation in Nonischemic Dilated Cardiomyopathy Patients

5-Year Follow-Up

Bojan Vrtovec, Gregor Poglajen, Luka Lezaic, Matjaz Sever, Dragoslav Domanovic, Peter Cernelc, Aljaz Socan, Sonja Schrepfer, Guillermo Torre-Amione, François Haddad, Joseph C. Wu

Circ Res 2013

Effects of Repetitive Transendocardial CD34+ Cell Transplantation in Patients With Nonischemic Dilated Cardiomyopathy

Bojan Vrtovec, Gregor Poglajen, Matjaz Sever, Gregor Zemljic, Sabina Frljak, Andraz Cerar, Marko Cukjati, Martina Jaklic, Peter Cernelc, François Haddad, Joseph C. Wu

Circ Res 2018

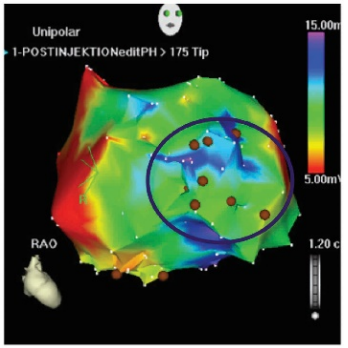


Table 1 Summary of randomized clinical trials in cardiovascular diseases with regenerative products

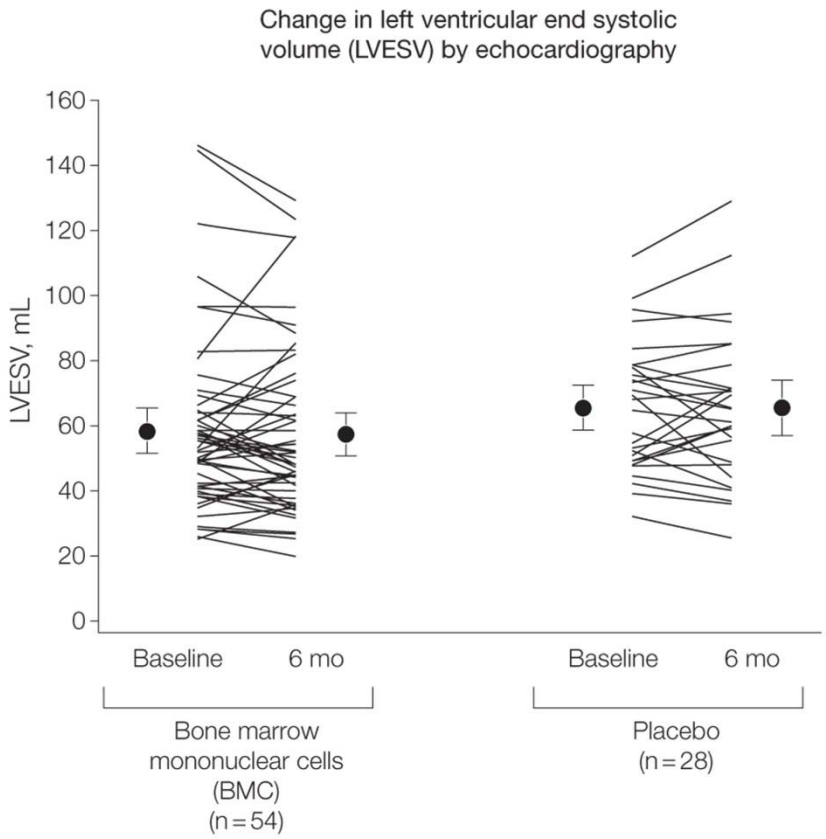
Disease (patients treated)	Regenerative product	Safety	Overall efficacy[a] (surrogate endpoints)
Acute myocardial infarction (n = 2732)	BMMNC[48–63]	Favourable	Inconsistent
	BM-MSC[64]	Favourable	Inconsistent
	Specific BM cells[65–69]	Favourable	Inconsistent
	ADSC[70]	Favourable	Inconsistent
	CDC[71]	Favourable	Positive
	Growth factors[72–77]	Favourable	Inconsistent
Ischaemic heart failure (n = 2035)	SM[78–81]	Favourable[b]	Inconsistent
	BMMNC[82–85]	Favourable	Inconsistent
	BM-MSC[86–88]	Favourable	Positive
	Specific BM cells[89–96]	Favourable	Positive
	CSC[97]	Favourable	Positive
	Gene therapy[37,98–101]	Favourable	Inconsistent
Refractory angina (n = 353)	BMMNC[102–106]	Favourable	Positive
	Specific BM cells[107–109]	Favourable	Positive
	ADSC[110]	Favourable	Positive
Non-ischaemic heart failure (n = 166)	BMMNC[111,112]	Favourable	Inconsistent
	Specific BM cells[113,114]	Favourable	Inconsistent
	BM-MSC[115]	Favourable	Inconsistent
Peripheral artery disease (n = 1217)	BMMNC[116]	Favourable	Positive
	Specific BM cells[117–119]	Favourable	Positive
	Gene therapy[120–124]	Favourable	Inconsistent
Stroke (n = 95)	Neural stem cells[125]	Favourable	Inconsistent
	BMMNC[125]	Favourable	Inconsistent
	Specific BM cells[125]	Favourable	Inconsistent

To date, more than **7,000** cardio-vascular patients injected with different adult stem cells in randomized clinical trials. However, overall data show neutral or minimal benefits.

Fernandez-Aviles F. *Eur Heart J* 2017

How Do We Design Trials Better?

Why Significant Variability Among Different Trials and Even Patients Within the Same Trials?



1) Bad delivery?

FOCUS-CCTRN (JAMA 2012): *"Among patients with chronic ischemic heart failure, transendocardial injection of autologous BMCs compared with placebo did* ***not*** *improve LVESV, maximal oxygen consumption, or reversibility on SPECT."*

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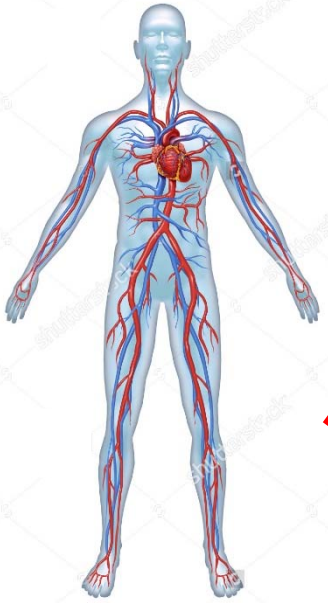
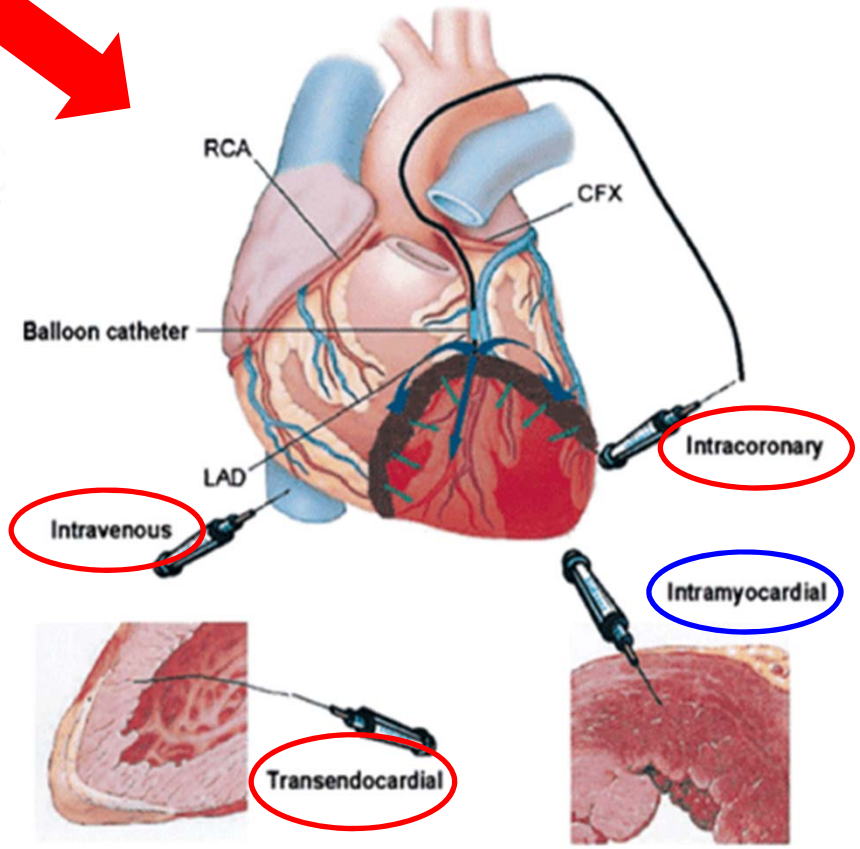
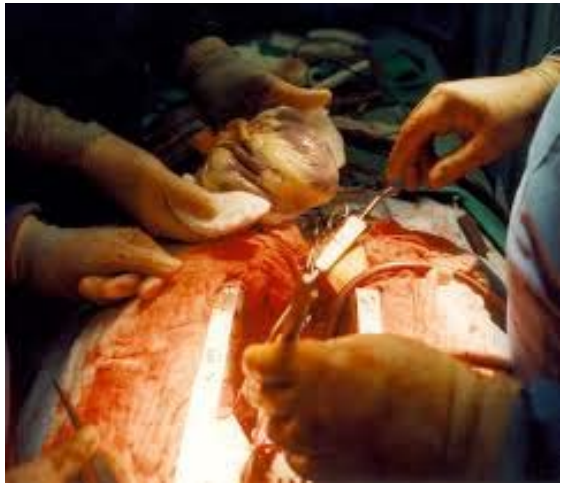
Stem Cell Delivery to the Heart





Cardiologists



Cardiac surgeons

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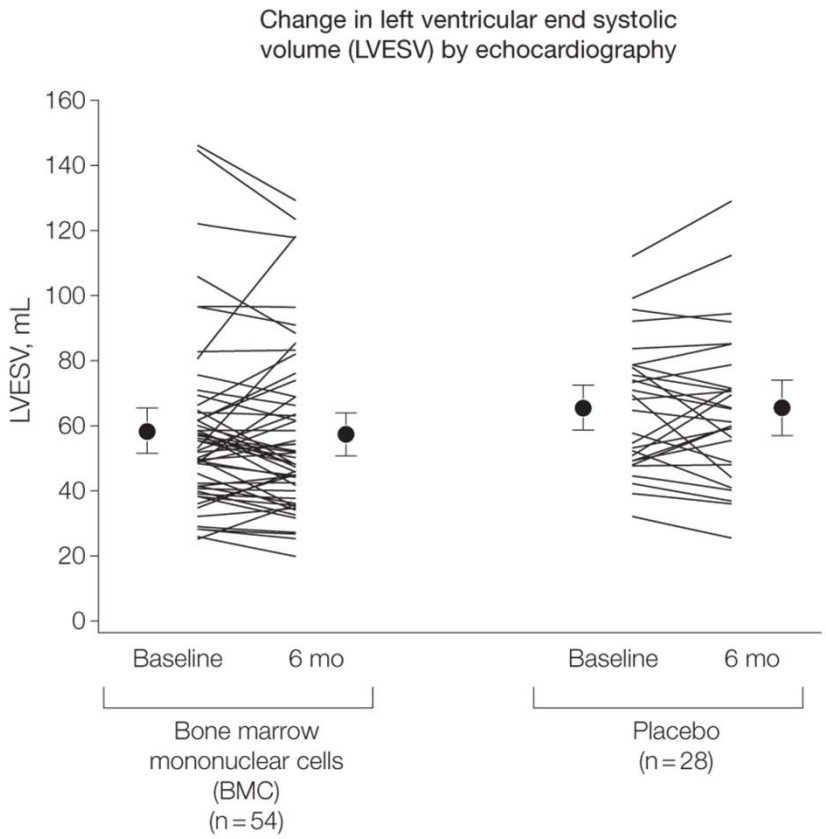
Why Significant Variability Among Different Trials and Even Patients Within the Same Trials?



1) Bad delivery?

2) Bad cellular engraftment?

FOCUS-CCTRN (JAMA 2012): *"Among patients with chronic ischemic heart failure, transendocardial injection of autologous BMCs compared with placebo did **not** improve LVESV, maximal oxygen consumption, or reversibility on SPECT."*

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Comparison of Transendocardial and Intracoronary CD34+ Cell Transplantation in Patients With Nonischemic Dilated Cardiomyopathy

Bojan Vrtovec, MD, PhD; Gregor Poglajen, MD, PhD; Luka Lezaic, MD, PhD; Matjaz Sever, MD; Aljaz Socan, MPharm; Dragoslav Domanovic, MD, PhD; Peter Cernelc, MD, PhD; Guillermo Torre-Amione, MD, PhD; François Haddad, MD; Joseph C. Wu, MD, PhD

Circulation 2013

Background—In an open-label blinded study, we compared intracoronary (IC) and transendocardial (TE) CD34+ cell transplantation in patients with nonischemic dilated cardiomyopathy.

Methods and Results—Of the 40 patients with dilated cardiomyopathy, 20 were randomized to receive IC injection and 20 received TE CD34+ cell delivery. In both groups, CD34+ cells were mobilized by filgrastim, collected via apheresis, and labeled with technetium-99m radioisotope for single-photon emission computed tomographic imaging. In the IC group, cells were injected intracoronarily in the artery supplying segments of greater perfusion defect on myocardial perfusion scintigraphy. In the TE group, electroanatomic mapping was used to identify viable but dysfunctional myocardium, and transendocardial cell injections were performed. Nuclear single-photon emission computed tomographic imaging for quantification of myocardial retention was performed 18 hours thereafter. At baseline, groups did not differ in age, sex, left ventricular ejection fraction, or N-terminal pro-brain natriuretic peptide levels. The number of CD34+ cells was also comparable ($105\pm31\times10^6$ in the TE group versus $103\pm27\times10^6$ in the IC group, $P=0.62$). At 18 hours after procedure, myocardial retention was higher in the TE group (19.2±4.8%) than in the IC group (4.4±1.2%, $P<0.01$). At 6 months, left ventricular ejection fraction improved more in the TE group (+8.1±4.3%) than in the IC group (+4.2±2.3%, $P=0.03$). The same pattern was observed for the 6-minute walk test distance (+125±33 m in the TE group versus +86±13 m in the IC group, $P=0.03$) and N-terminal pro-brain natriuretic peptide (−628±211 versus −315±133 pg/mL, $P=0.04$).

Conclusions—In patients with dilated cardiomyopathy, transendocardial CD34+ cell transplantation is associated with higher myocardial retention rates and greater improvement in ventricular function, N-terminal pro-brain natriuretic peptide, and exercise capacity compared with intracoronary route.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01350310. (***Circulation*. 2013;128:00-00.**)

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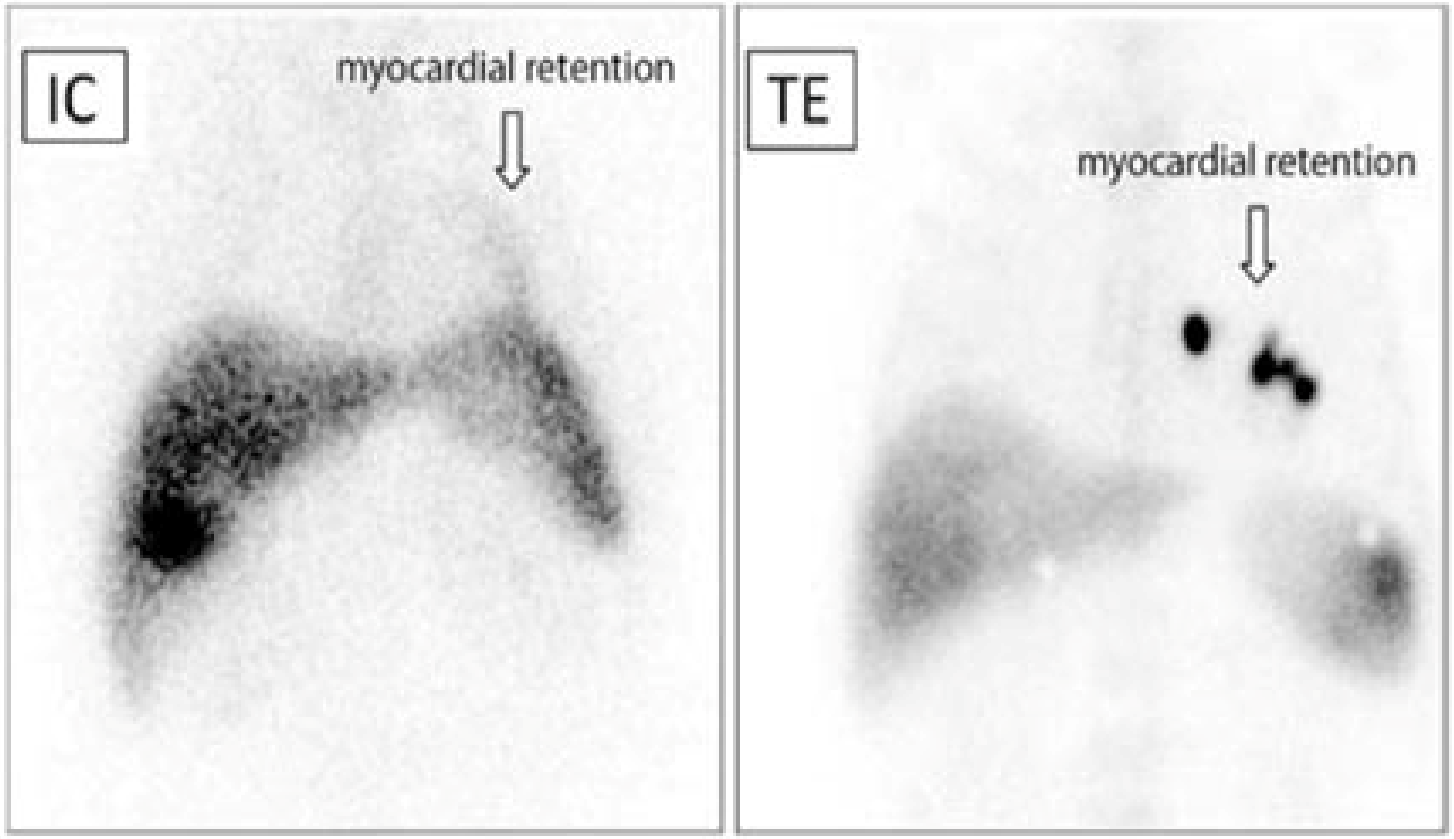
Biodistribution of CD34^{+} Stem Cells 18 Hours After Intracoronary vs. Transendocardial Delivery in Patients

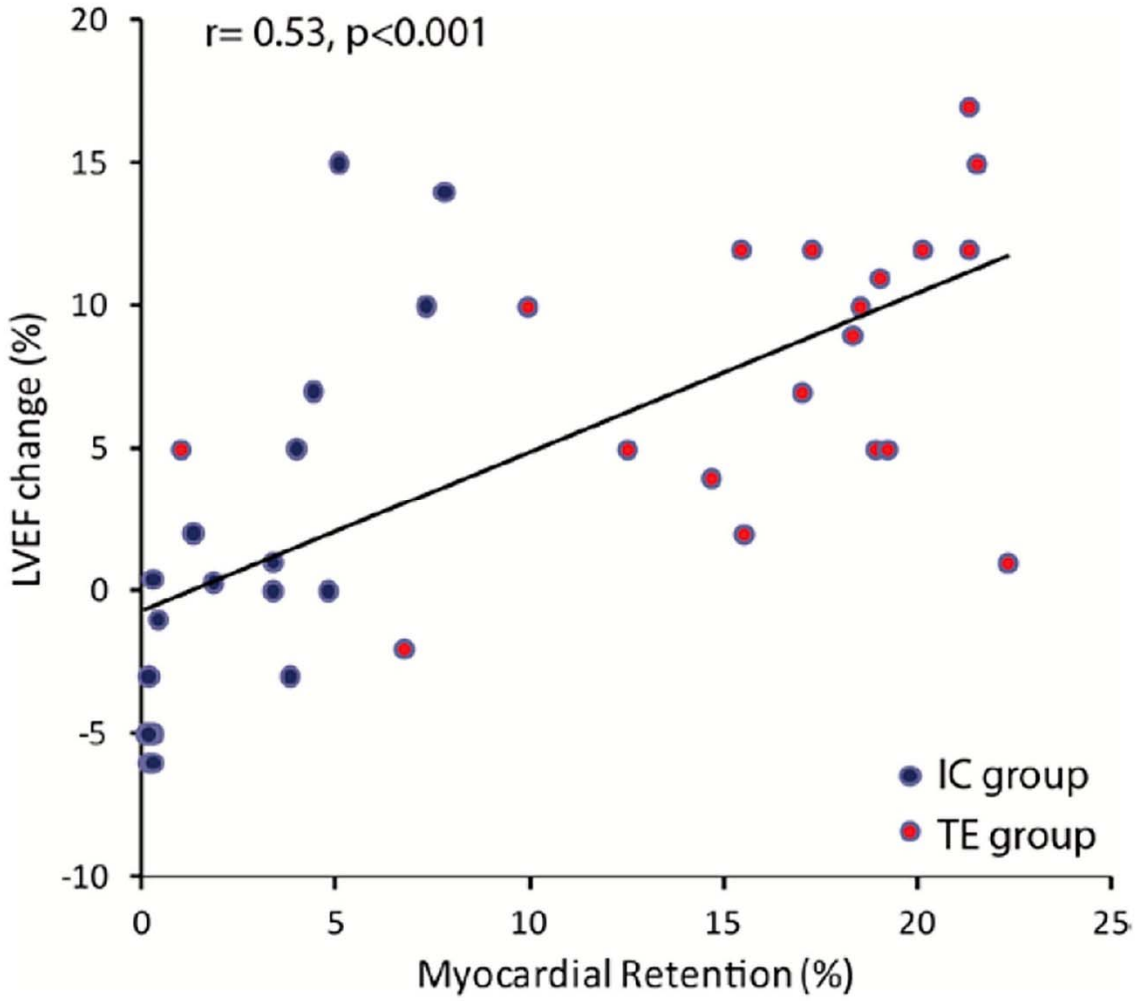


4.4±1.2%

19.2±4.8%

Vrtovec et al, *Circulation* 2013

Functional Outcomes 6 Months After Delivery
(↑ Early Engraftment = ↑ Late LVEF)



Vrtovec et al, *Circulation* 2013

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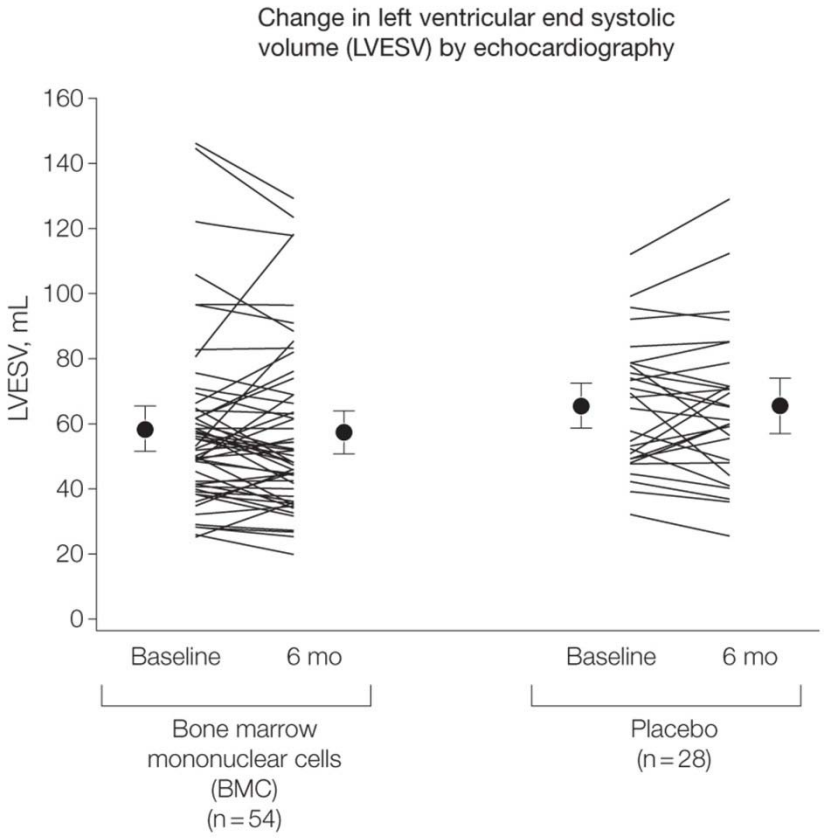
Why Significant Variability Among Different Trials and Even Patients Within the Same Trials?



1) Bad delivery?

2) Bad cellular engraftment?

3) Bad dosing?

FOCUS-CCTRN (JAMA 2012): *"Among patients with chronic ischemic heart failure, transendocardial injection of autologous BMCs compared with placebo did **not** improve LVESV, maximal oxygen consumption, or reversibility on SPECT."*

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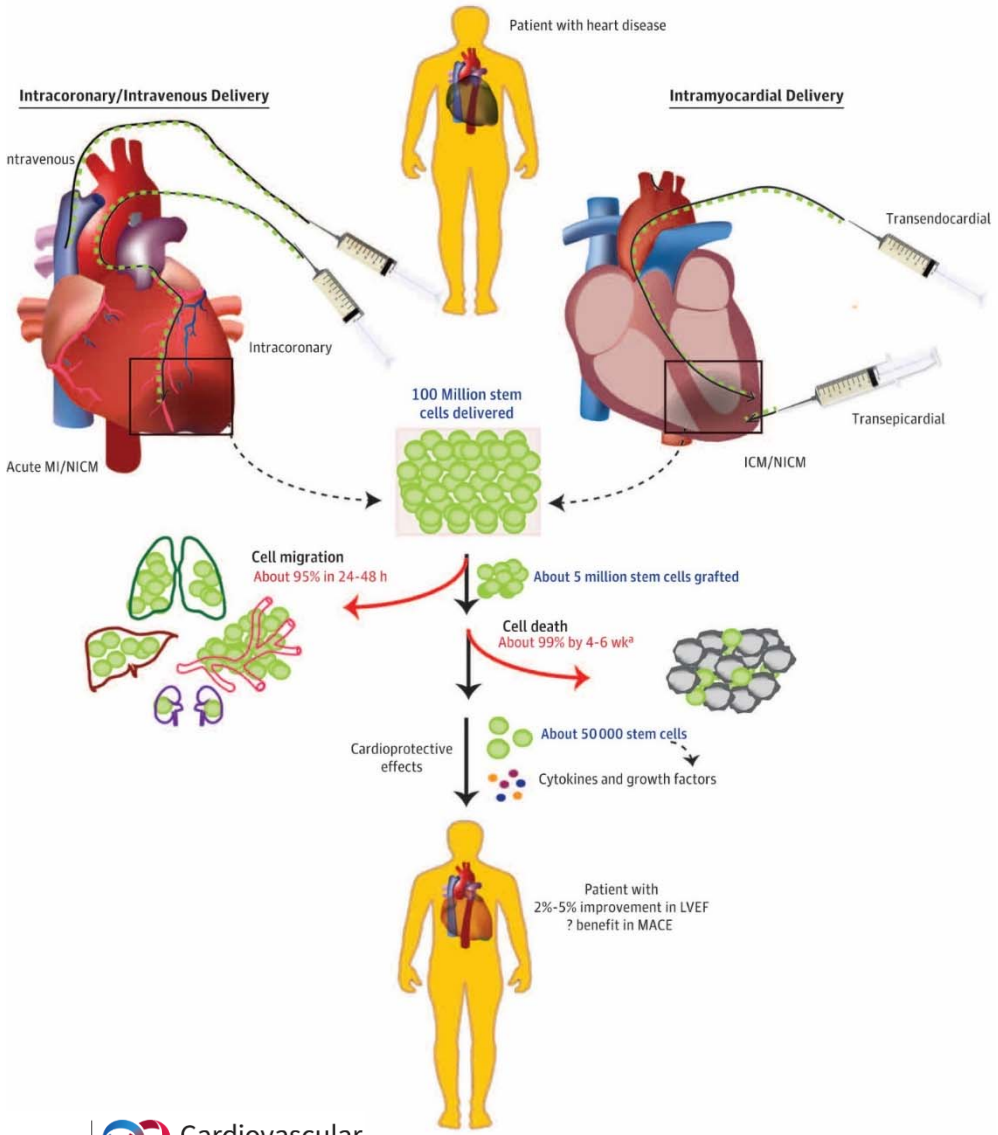
Dosing for Cardiac Stem Cell Therapy



--Most adult cardiac stem cell therapy is one time dosing at ~20M to 200M cells.

--Assuming 100M cell dosing, 95% gone in 24-48 hours due to cell migration.

--Among 5M cells engrafted, another 99% dead by 4-6 weeks.

--Left with 50k cells that home/engraft in the heart (vs. human heart has 2-3 billion cardiac cells and 4-5 billion fibroblasts).

Nguyen PK et al, *JAMA Cardiol* 2016

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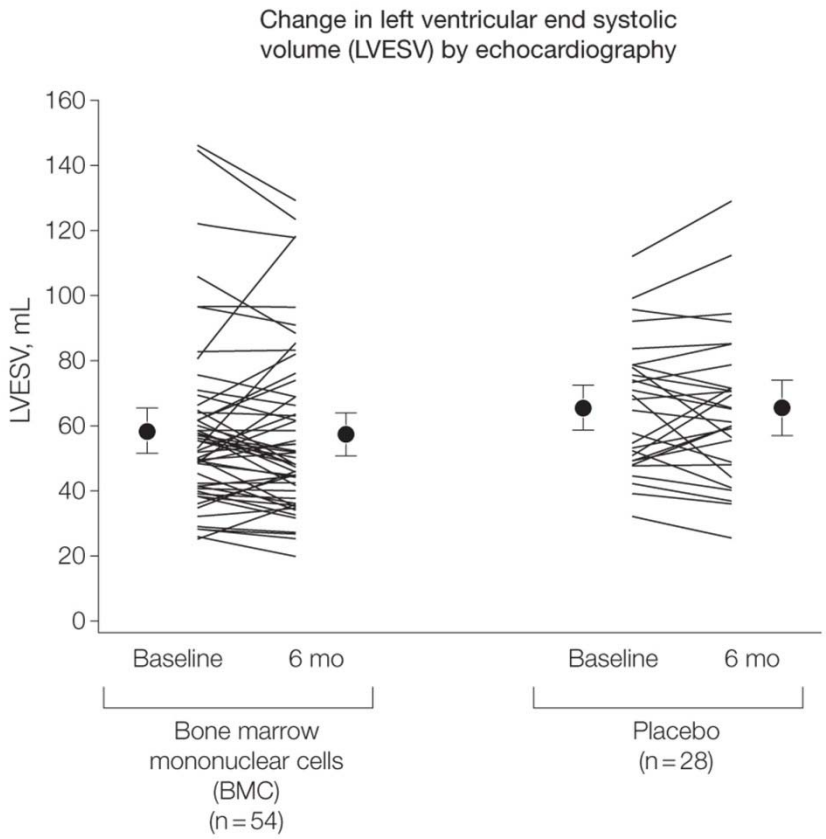

1) Bad delivery?

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4) Bad patient population?

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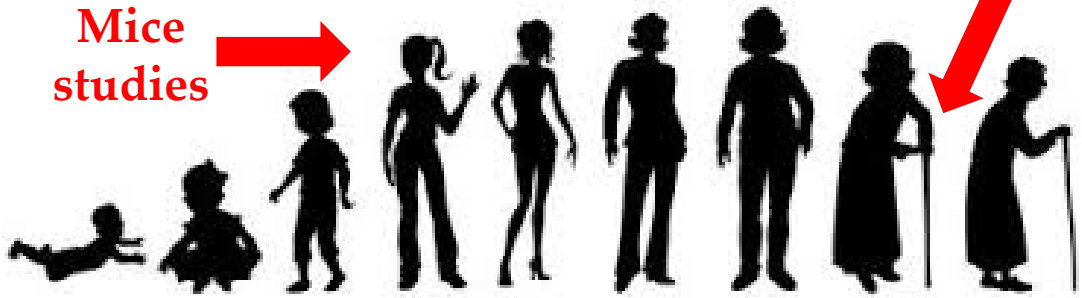
Bad Patient Population

Your typical 70 yo patient with HTN, DM, CAD s/p stents, and prior EtOh or smoking hx.

Mice studies

Human studies



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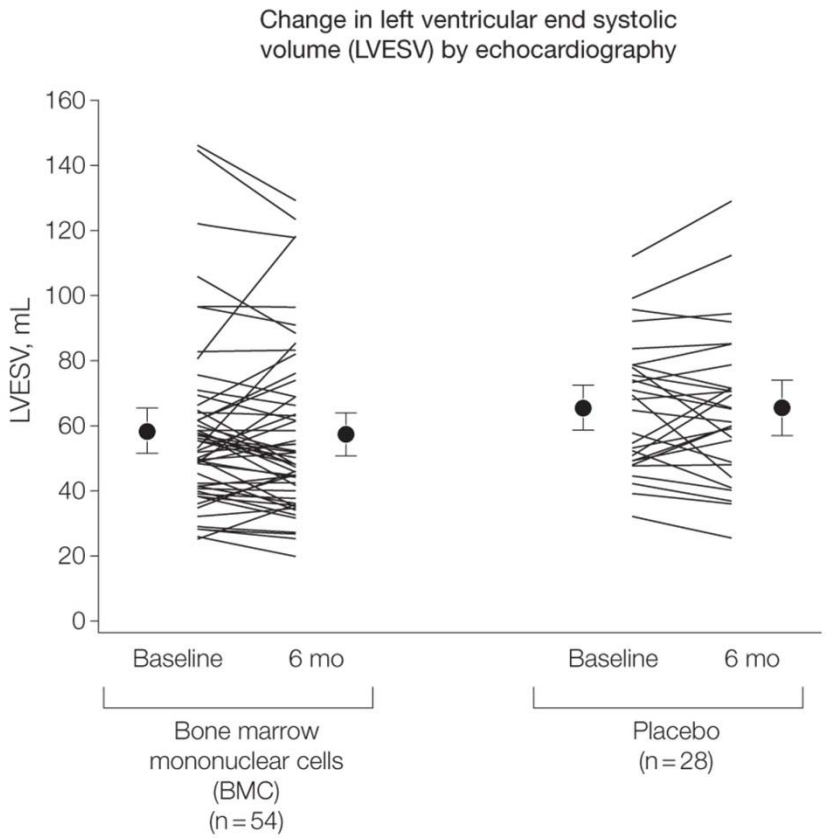

1) Bad delivery?

2) Bad cellular engraftment?

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4) Bad patient population?

5) Bad cell type?

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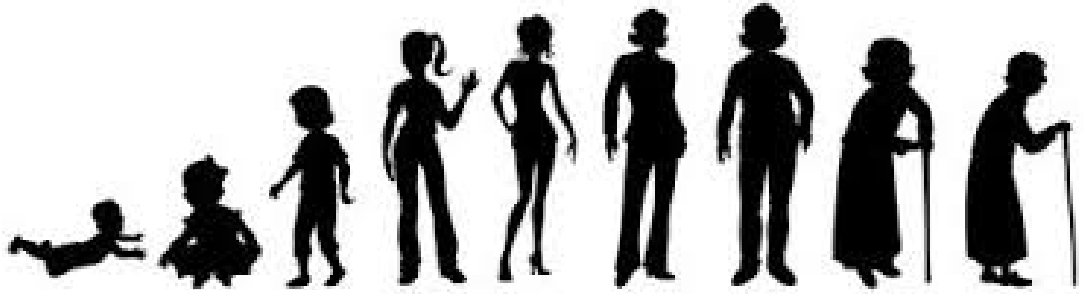
Bad Patient Population

Your typical 70 yo patient with HTN, DM, CAD s/p stents, and prior EtOh or smoking hx.

Autologous adult stem cells

Pluripotent stem cells (iPSC/ESC)



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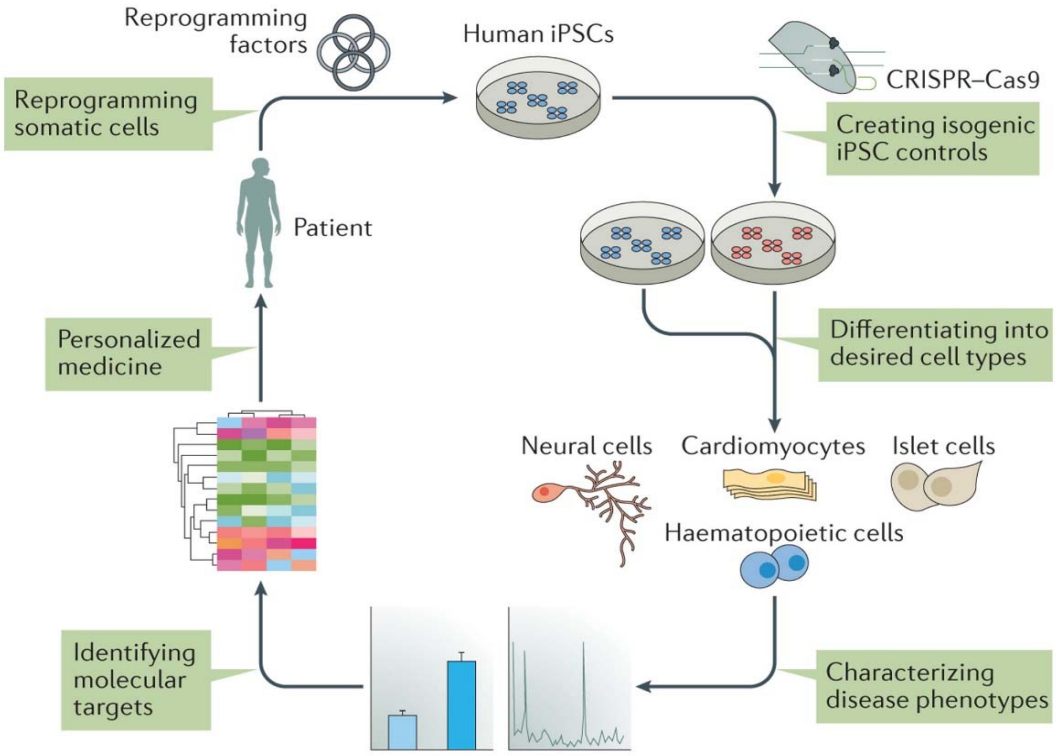
Human Induced Pluripotent Stem Cells

Shinya Yamanaka at the Kyoto University in Japan created the first iPSCs from mouse in **2006 and from human in **2007**. He shared the Nobel Prize in Medicine & Physiology in **2012** with Sir John Gurdon.

**iPSCs can be generated from the patient's blood, skin, hair, or fat and then reprogrammed.

**Human iPSCs are essentially the same as human ESCs or SCNT and can "*self-renew*" and are "*pluripotent*".



Wilson, Wu. *JAMA* 2015
Shi, Inoue, Wu, Yamanaka. *Nat Rev Drug Discov* 2016

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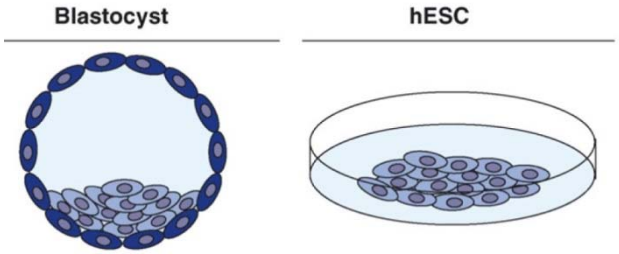
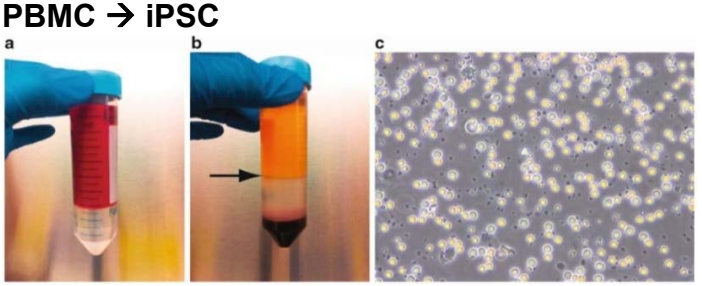
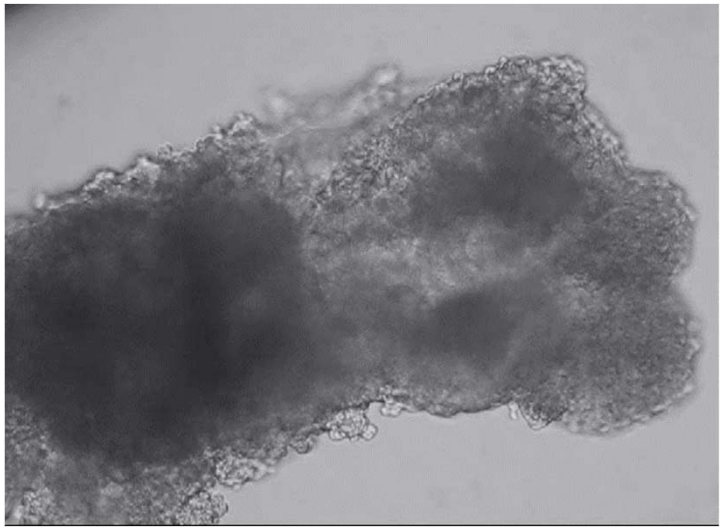
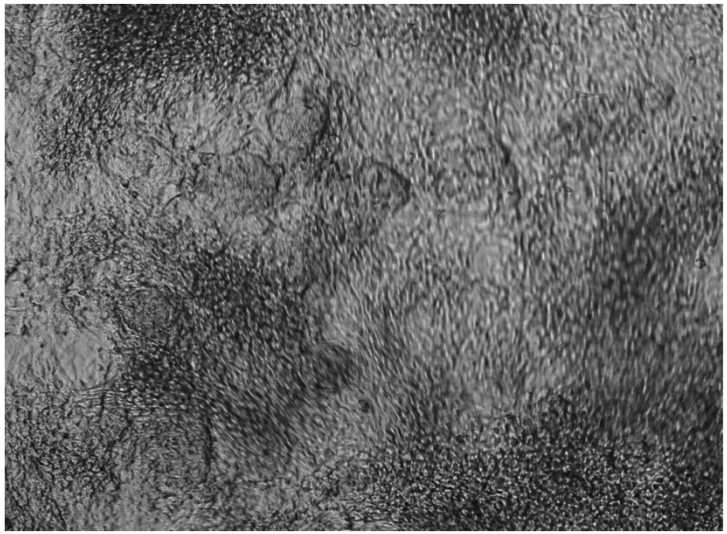
Differentiation of Human Cardiomyocytes







2004 (5% efficiency)



2018 (90%+ efficiency)

PNAS 2008, *PNAS* 2009, *Nature Methods* 2010, *Cell Stem Cell* 2011, *JCI* 2011, *Nature Biotech* 2011, *Cell Stem Cell* 2012, *Science Transl Med* 2012, *Nature Medicine* 2013, *Science* 2013, *Science Transl Med* 2013, *JAMA* 2013, *Nature Materials* 2014, *Nature Methods* 2014, *Science Transl Med* 2014, *Cell Stem Cell* 2015, *JAMA* 2015, *Science Translational Med* 2016, *Nature Medicine* 2016, *Cell Stem Cell* 2016, *Cell* 2016, *Cell Report* 2017, *PNAS* 2017, *Science Transl Med* 2017, *Cell Stem Cell* 2018, *Nature Biomed Eng* 2018

One Size Does Not Fit All: Genetic vs. Acquired vs. Multifactorial Causes of Heart Diseases

Primary

- Genetic
  - Arrhythmogenic right ventricular cardiomyopathy
  - Hypertrophic cardiomyopathy
- Mixed (genetic and nongenetic)
  - Dilated cardiomyopathy
  - Restrictive cardiomyopathy
- Acquired
  - Myocarditis (inflammatory cardiomyopathy)
  - Peripartum (or postpartum) cardiomyopathy
  - Stress cardiomyopathy

Secondary

- Autoimmune (systemic lupus)
- Electrolyte imbalance
- Endocrine (diabetes, hypothyroidism)
- Endomyocardial (fibrosis)
- Infiltrative (amyloidosis, Gaucher disease)
- Inflammatory (sarcoidosis)
- Neurologic (neurofibromatosis)
- Nutritional (beriberi)
- Radiation
- Storage (hemochromatosis)
- Toxic (medications)
- Velocardiofacial syndrome

Stanford Cardiovascular Institute Cardiac iPSC Biobank: Creating 1,000 iPSC Lines to Accelerate Drug Discovery

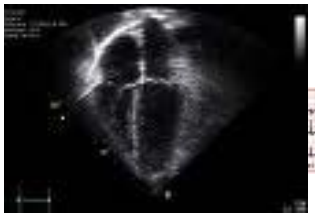
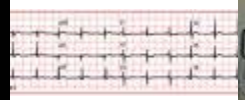
1) Create a biorepository of 1,000 iPSC lines from patients with different CV history, ethnicity, sex, and also isogenic lines using CRISPR genome editing.

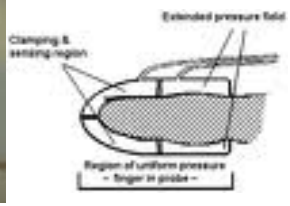
2) Perform DNA-seq of iPSCs and RNA-seq on iPSC-CMs and iPSC-ECs.

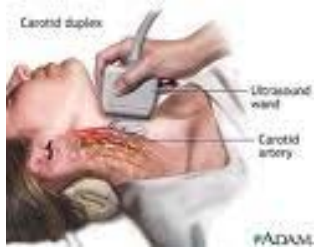
3) Use PharmGK (http://www.pharmgkb.org) to create a database on how human genetic variation impacts drug response phenotypes.

4) Link to medical information using clinical database *(STRIDE: Stanford Translational Research Integrated Database Environment)*

5) Working with NHLBI and CIRM on iPSC biobanking and FDA on drug safety testing. Established sharing resource plan with many investigators.





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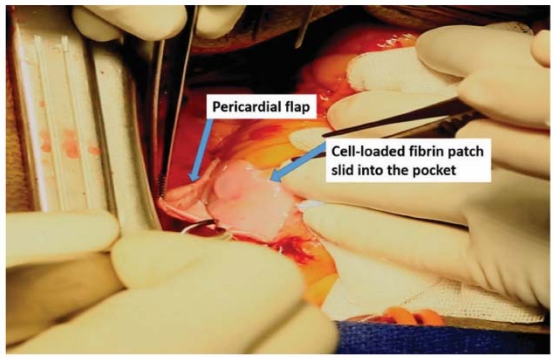
Human embryonic stem cell-derived cardiac progenitors for severe heart failure treatment: first clinical case report



Philippe Menasché[1,2,3]*, Valérie Vanneaux[4,5], Albert Hagège[2,3,6], Alain Bel[1], Bernard Cholley[2,7], Isabelle Cacciapuoti[4,5], Alexandre Parouchev[4,5], Nadine Benhamouda[8], Gérard Tachdjian[9], Lucie Tosca[9], Jean-Hugues Trouvin[10], Jean-Roch Fabreguettes[12], Valérie Bellamy[3], Romain Guillemain[8], Caroline Suberbielle Boissel[13], Eric Tartour[2,3,8], Michel Desnos[2,3,6], and Jérôme Larghero[4,5,14]

Eur Heart Journal 2015

Aims Comparative studies suggest that stem cells committed to a cardiac lineage are more effective for improving heart function than those featuring an extra-cardiac phenotype. We have therefore developed a population of human embryonic stem cell (ESC)-derived cardiac progenitor cells.

Methods and results Undifferentiated human ESCs (I6 line) were amplified and cardiac-committed by exposure to bone morphogenetic protein-2 and a fibroblast growth factor receptor inhibitor. Cells responding to these cardio-instructive cues express the cardiac transcription factor *Isl-1* and the stage-specific embryonic antigen SSEA-1 which was then used to purify them by immunomagnetic sorting. The *Isl-1*$^+$ SSEA-1$^+$ cells were then embedded into a fibrin scaffold which was surgically delivered onto the infarct area in a 68-year-old patient suffering from severe heart failure [New York Heart Association [NYHA] functional Class III; left ventricular ejection fraction (LVEF): 26%]. A coronary artery bypass was performed concomitantly in a non-infarcted area. The implanted cells featured a high degree of purity (99% were SSEA-1$^+$), had lost the expression of *Sox-2* and *Nanog*, taken as markers for pluripotency, and strongly expressed *Isl-1*. The intraoperative delivery of the patch was expeditious. The post-operative course was uncomplicated either. After 3 months, the patient is symptomatically improved (NYHA functional Class I; LVEF: 36%) and a new-onset contractility is echocardiographically evident in the previously akinetic cell/patch-treated, non-revascularized area. There have been no complications such as arrhythmias, tumour formation, or immunosuppression-related adverse events.

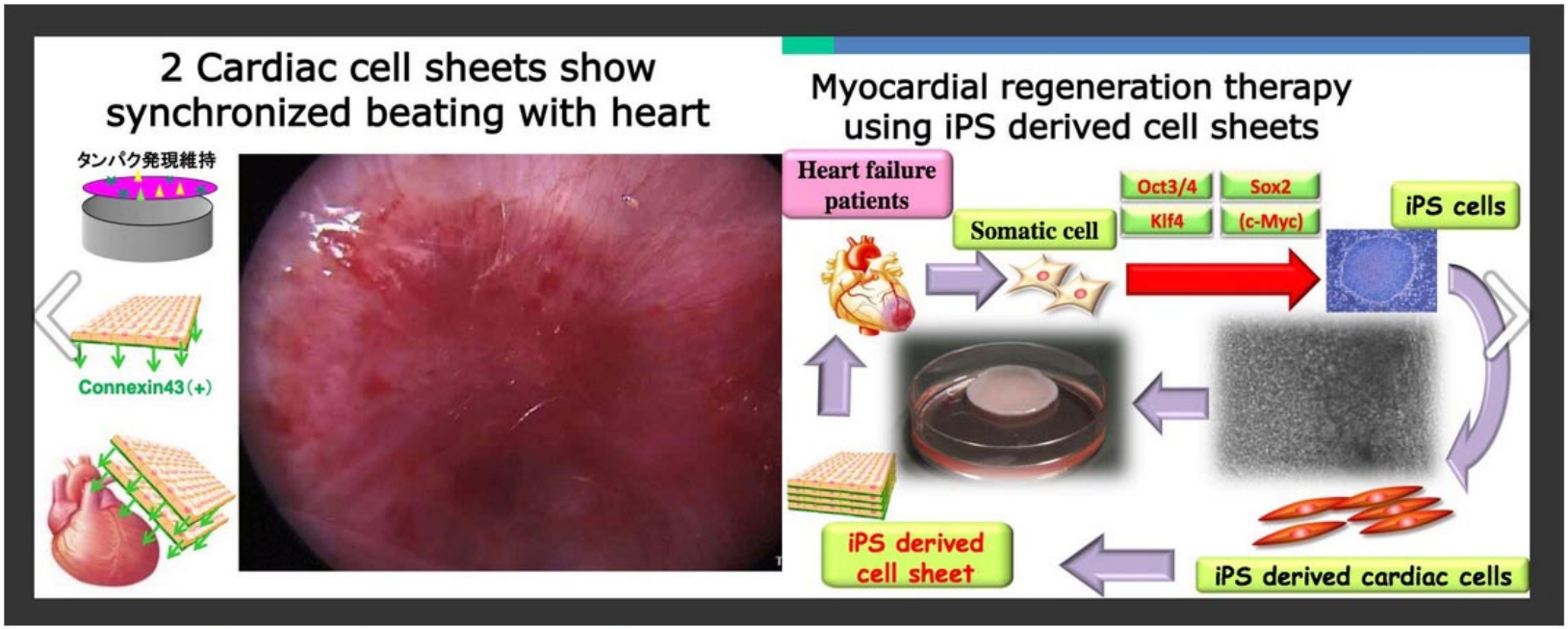
Conclusion This observation demonstrates the feasibility of generating a clinical-grade population of human ESC-derived cardiac progenitors and combining it within a tissue-engineered construct. While any conclusion pertaining to efficacy would be meaningless, the patient's functional outcome yet provides an encouraging hint. Beyond this case, the platform that has been set could be useful for generating different ESC-derived lineage-specific progenies.

Keywords Heart failure • Embryonic stem cells • Cell therapy

World's First Clinical Application of iPS Cells for Cardiac Disease

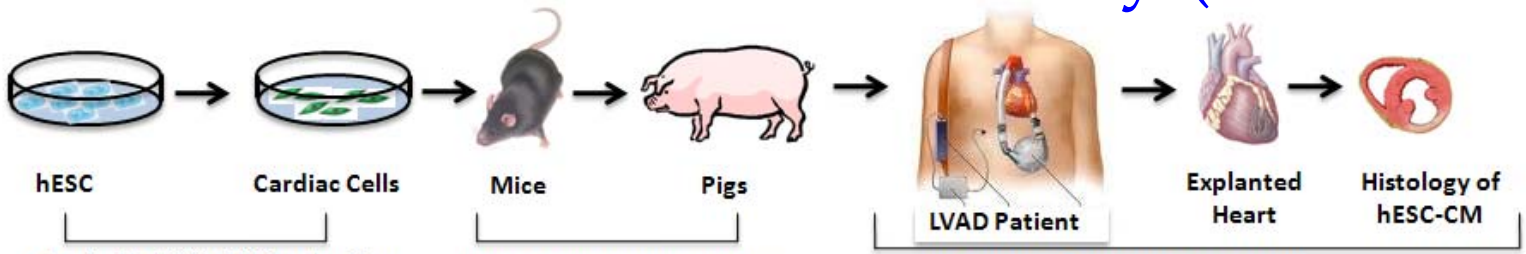
June 2, 2018 By Cade Hildreth (CEO) — Leave a Comment

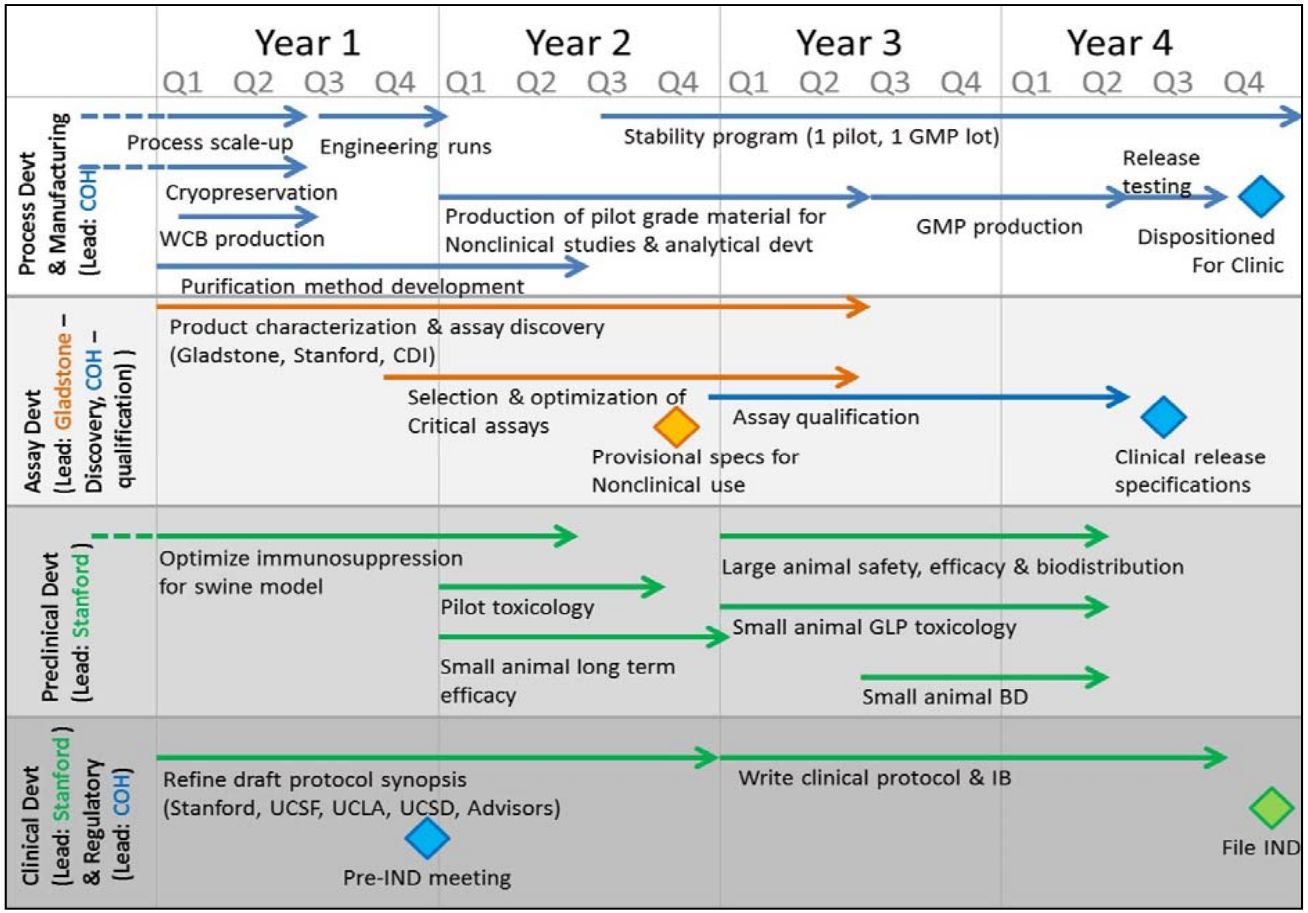
On 16 May, Nature News reported that "Japan's health ministry gave doctors at Osaka University permission to take sheets of tissue derived from iPS cells and graft them onto diseased human hearts." The team of Japanese doctors, led by cardiac surgeon Yoshiki Sawa at Osaka University, will use iPS cells to "create a sheet of 100 million heart-muscle cells."



Screenshot of Yoshiki Sawa slide on IPS cell approach for heart failure, which is similar to approach for ischemic heart disease.

Stanford ESC-CM Preclinical Study (2013-2018)





Challenges: *Tumorigenicity*

**How do you make sure no undifferentiated cells within 50M -1B (?) cells that you plan to inject into patients?

**No data on long-term follow-up in small and large animal models (ie, years not months)

**Low risk, but needs to be absolutely 0% risk, o/w entire field is doomed.

**Because of significant improvement in cardiac differentiation protocol, we are actually *less* worried about this issue.

In Vivo Visualization of Embryonic Stem Cell Survival, Proliferation, and Migration After Cardiac Delivery

Feng Cao, MD, PhD; Shuan Lin, BS; Xiaoyan Xie, PhD; Pritha Ray, PhD; Manishkumar Patel, BS; Xianzhong Zhang, PhD; Micha Drukker, PhD; Scott J. Dylla, PhD; Andrew J. Connolly, MD, PhD; Xiaoyuan Chen, PhD; Irving L. Weissman, MD; Sanjiv S. Gambhir, MD, PhD; Joseph C. Wu, MD, PhD

Circulation 2006

An antibody against SSEA-5 glycan on human pluripotent stem cells enables removal of teratoma-forming cells

Nat Biotech 2011

Chad Tang[1], Andrew S Lee[2], Jens-Peter Volkmer[1,3], Debashis Sahoo[1], Divya Nag[2], Adriane R Mosley[1], Matthew A Inlay[1], Reza Ardehali[1], Shawn L Chavez[1], Renee Reijo Pera[1], Barry Behr[4], Joseph C Wu[2], Irving L Weissman[1] & Micha Drukker[1]

Tumorigenicity as a clinical hurdle for pluripotent stem cell therapies

Nature Med 2013

Andrew S Lee[1–3,6], Chad Tang[1,4,6], Mahendra S Rao[5], Irving L Weissman[1] & Joseph C Wu[1–3]

Comparison of Magnetic Resonance Imaging and Serum Biomarkers for Detection of Human Pluripotent Stem Cell-Derived Teratomas

Stem Cell Report 2016

Johannes Riegler,[1,2,5] Antje Ebert,[1,2,5] Xulei Qin,[1,2] Qi Shen,[1] Mouer Wang,[1] Mohamed Ameen,[1] Kazuki Kodo,[1,2] Sang-Ging Ong,[1,2] Won Hee Lee,[1,2] Grace Lee,[1] Evgenios Neofytou,[1,2] Joseph D. Gold, Andrew J. Connolly,[3] and Joseph C. Wu[1,2,4,*]

Challenges: *Immunogenicity*

**ESC-based therapy is allogeneic and will require immunotolerance, which is *not* what our patients want b/c the whole point of stem cell therapy is to avoid immunosuppressive drugs from heart transplant.

**For many iPSC-based therapies, most likely will also be *allogeneic* therapy (*not autologous*) b/c of biotech company's focus on "return on investment".

**Possibility of using universal iPSC lines that lack HLA I and II to avoid immune rejection?

Immunosuppressive therapy mitigates immunological rejection of human embryonic stem cell xenografts

Rutger-Jan Swijnenburg*†‡, Sonja Schrepfer*‡, Johannes A. Govaert*†, Feng Cao§, Katie Ransohoff*, Ahmad Y. Sheikh*, Munif Haddad¶, Andrew J. Connolly‖, Mark M. Davis**††, Robert C. Robbins*, and Joseph C. Wu§‡‡§§

PNAS 2008

Short-Term Immunosuppression Promotes Engraftment of Embryonic and Induced Pluripotent Stem Cells

Cell Stem Cell 2011

Jeremy I. Pearl,[1,2,3] Andrew S. Lee,[1,2] Dennis B. Leveson-Gower,[4] Ning Sun,[1,2] Zhumur Ghosh,[1,2] Feng Lan,[1,2] Julia Ransohoff,[1,2] Robert S. Negrin,[4] Mark M. Davis,[5,*] and Joseph C. Wu[1,2,3,*]

Transplanted terminally differentiated induced pluripotent stem cells are accepted by immune mechanisms similar to self-tolerance

Patricia E. de Almeida[1,2,3,*], Everett H. Meyer[4,*], Nigel G. Kooreman[1,2,3,*], Sebastian Diecke[1,2,3], Devaveena Dey[1,2,3], Veronica Sanchez-Freire[1,2,3], Shijun Hu[1,2,3], Antje Ebert[1,2,3], Justin Odegaard[5], Nicholas M. Mordwinkin[1,2,3], Thomas P. Brouwer[1,2,3], David Lo[3,6], Daniel T. Montoro[3,6], Michael T. Longaker[3,6], Robert S. Negrin[4] & Joseph C. Wu[1,2,3]

Nature Comm 2014

Alloimmune Responses of Humanized Mice to Human Pluripotent Stem Cell Therapeutics

Nigel G. Kooreman,[1,2,3,6,9] Patricia E. de Almeida,[1,2,3,9] Jonathan P. Stack,[1,2,3,4,9] Raman V. Nelakanti,[1,2,3] Sebastian Diecke,[1,2,3] Ning-Yi Shao,[1,2,3] Rutger-Jan Swijnenburg,[6] Veronica Sanchez-Freire,[1,2,3] Elena Matsa,[1,2,3] Chun Liu,[1,2,3] Andrew J. Connolly,[5] Jaap F. Hamming,[6] Paul H.A. Quax,[6] Michael A. Brehm,[7] Dale L. Greiner,[7,*] Leonard D. Shultz,[8,*] and Joseph C. Wu[1,2,3,10,*]

Cell Report 2017

Challenges: *Costs of Product Development*

**Expensive to do large animal studies (>$100/day housing), and difficult to get NIH funding b/c not "*mechanistic enough*" by most reviewers.

**Showing efficacy in randomized double-blinded study requires large patient # size, so difficult to get funding.

**What is the competitive advantage of ESC/iPSC-based therapy vs. adult stem cell therapy vs. standard medical therapy or surgical mechanical devices?

Preclinical Derivation and Imaging of Autologously Transplanted Canine Induced Pluripotent Stem Cells*

Received for publication, February 28, 2011, and in revised form, June 17, 2011 Published, JBC Papers in Press, June 30, 2011, DOI 10.1074/jbc.M111.235739

Andrew S. Lee[‡§1], Dan Xu[‡§1], Jordan R. Plews[‡§], Patricia K. Nguyen[§], Divya Nag[‡§], Jennifer K. Lyons[¶], Leng Han[‡§], Shijun Hu[‡§], Feng Lan[‡§], Junwei Liu[‡§], Mei Huang[‡§], Kazim H. Narsinh[‡§], Charles T. Long[¶], Patricia de Almeida[‡§], Benjamin Levi[‖], Nigel Kooreman[‡], Charles Bangs**, Cholawat Pacharinsak[¶], Fumiaki Ikeno[§], Alan C. Yeung[§], Sanjiv S. Gambhir[‡], Robert Robbins[‡‡], Michael T. Longaker[‖§§2], and Joseph C. Wu[‡§ §§3]

J Biol Chem 2011

Microfluidic Single-Cell Analysis Shows That Porcine Induced Pluripotent Stem Cell–Derived Endothelial Cells Improve Myocardial Function by Paracrine Activation

Mingxia Gu,* Patricia K. Nguyen,* Andrew S. Lee, Dan Xu, Shijun Hu, Jordan R. Plews, Leng Han, Bruno C. Huber, Won Hee Lee, Yongquan Gong, Patricia E. de Almeida, Jennifer Lyons, Fumi Ikeno, Cholawat Pacharinsak, Andrew J. Connolly, Sanjiv S. Gambhir, Robert C. Robbins, Michael T. Longaker, Joseph C. Wu

Circ Res 2012

Stem Cell Imaging: From Bench to Bedside

Patricia K. Nguyen,[1,2,3] Johannes Riegler,[1,2,3] and Joseph C. Wu[1,2,3,4,*]

Cell Stem Cell 2014

Hurdles to clinical translation of human induced pluripotent stem cells

Evgenios Neofytou,[1,2,3] Connor Galen O'Brien,[1,3] Larry A. Couture,[4] and Joseph C. Wu[1,2,3]

J Clin Invest 2016

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