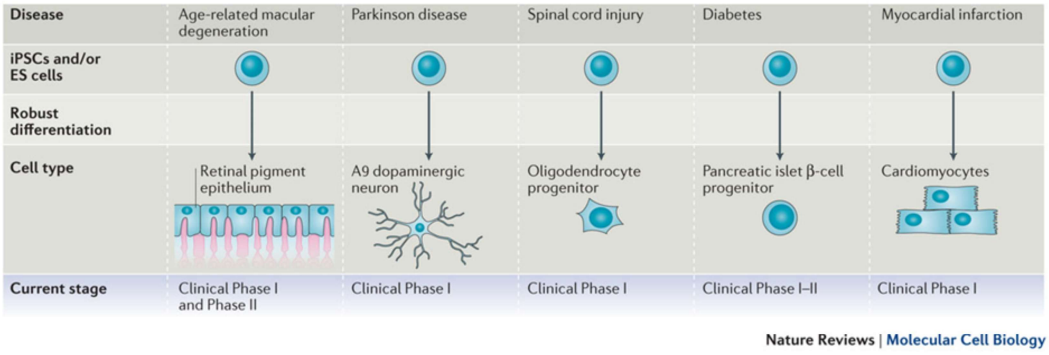
Progress in clinical applications of PSCs

Up Date2019 -Theoretical Bases of Clinical Medicine



Nature Reviews | Molecular Cell Biology

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Trounson A. et al. *Nature Reviews Molecular Cell Biology* 17, 194–200 (2016) doi:10.1038/nrm.2016.10

Robust strategies have been developed to differentiate pluripotent stem cells into retinal pigment epithelium, A9 dopaminergic neurons, oligodendrocyte, pancreatic β-islet cells and cardiomyocytes. Clinical trials are underway for embryonic stem cell (ES cell) derivatives for age-related macular degeneration (AMD), type I diabetes, spinal cord injury, myocardial infarct and Parkinson disease (using parthenogenetic embryonic stem cells (pES cells)).

Induced pluripotent stem cells (iPSCs) are in a clinical trial for AMD. Rigorously tested, abundant sources of these cell types are needed for preclinical research to generate data for regulatory approval for human studies. The cells also need to be manufactured in large quantities for clinical trials.

These clinical studies in humans begin with regulatory approval for Phase I trials, which demonstrate safety. They are followed by Phase II studies showing proof of concept for cell therapy in human patients. Sometimes, Phase I–II studies are designed to demonstrate both safety and efficacy. Larger-scale Phase III clinical trials aim to demonstrate the statistical significance of the therapeutic benefit.

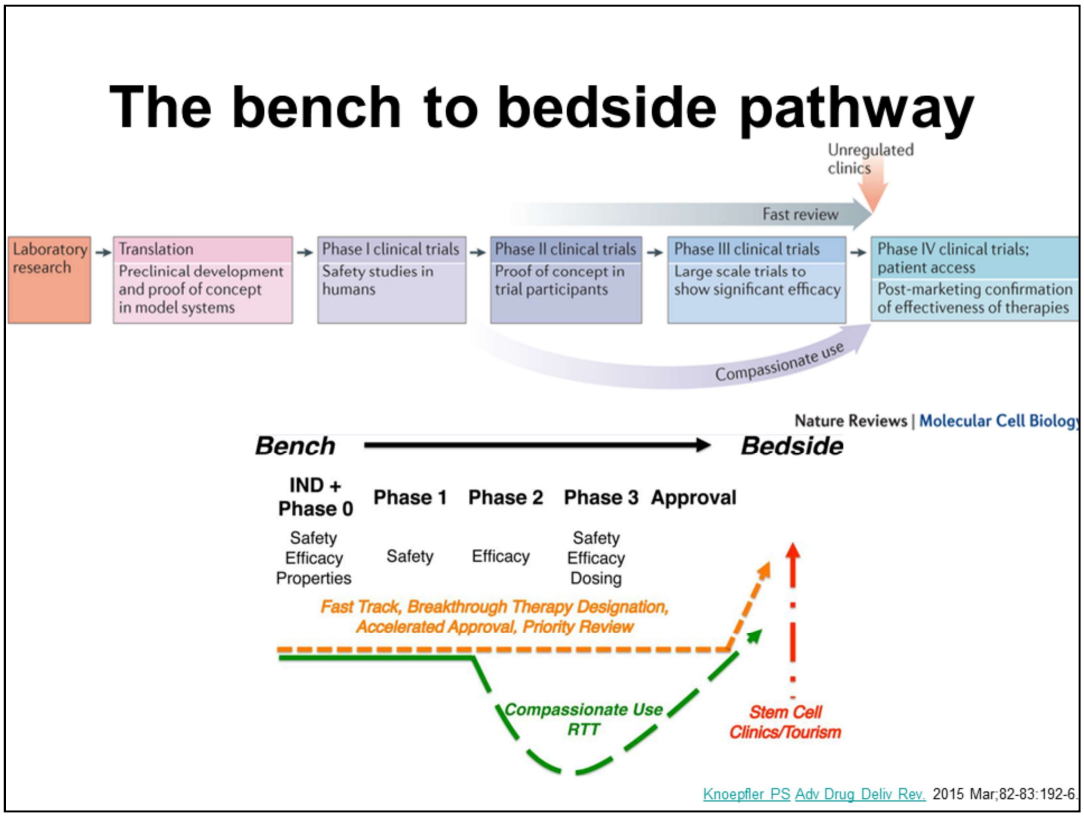
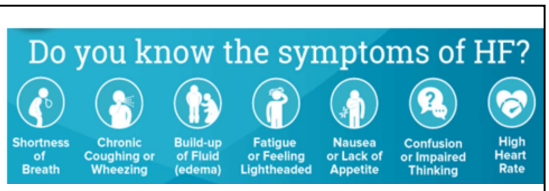


Diagram of the evolving clinical trials process and other mechanisms of therapy translation to the bedside. The traditional, multi-phasic FDA clinical trials process is shown in black with a black arrow from bench to bedside. Evolving FDA mechanisms for accelerating the clinical trial process are shown in orange. Compassionate Use (also known as “Expanded Access”) and Right To Try (RTT) are shown in green with a loop reflecting the bypassing of Phase 2 and Phase 3. It is notable that the requirements for Compasionate Use are evolving and there are diverse stakeholder views. The precise pre-requisites (e.g. Phase 1 versus Phase 2 data) obtainable from FDA guidance are not completely clear and may vary on a case-by-case basis. The common stem cell clinic approach of entirely avoiding the clinical trials approval process is shown in red. Note that for some non-more than minimally manipulated stem cell products used in a homologous manner, direct use by stem cell clinics or other physicians may be appropriate with only a relatively minor role for the FDA.

ClinicalTrials.gov



- 213040 ⇨ 297984 Clinical studies (total)

- 12126 ⇨ 18312 heart, cardiac, coronary
- 3520 ⇨ 7435 heart failure
- 237 ⇨ 736 heart stem cell

- **4 studies**: heart human embryonic
  Escort 2018, Poseidon 2015, TAC-HFT 2015,
- **2 studes**: heart human induced pluripotent
  - in vitro phenotyping
- **1 study (China)**: heart human induced pluripotent HEAL-CHF

Updated data from 23/2/2018 – compared to 22/2/2019

https://clinicaltrials.gov/ct2/results?term=heart+failure+human+embryonic

https://clinicaltrials.gov/ct2/show/NCT02057900?term=heart+failure+human+embryonic&rank=1 PATCH – ESCORT study est JUNE 2018

http://www.onlinejacc.org/highwire/markup/28281/expansion?width=1000&height=500&iframe=true&postprocessors=highwire_figures%2Chighwire_math%2Chighwire_inline_linked_media%2Chighwire_embed

https://clinicaltrials.gov/ct2/results?term=heart+human+induced+pluripotent&type=&rslt=&recr=&age_v=&gndr=&cond=&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=&rcv_e=&lup_s=&lup_e=

Why?

- human heart has limited potential for regeneration (0,01%/y in healthy adult)
- the loss of cardiomyocytes during course of cardio-myopathy and ischaemic injury can result in heart failure and death
- some patients recover very well from myocardial infarction and myokarditis episodes, others do not…

What to do?

- **Prevention** – non smoking, education, lifestyle, lipids…
- **Pharmacology**
  - **AC Inhibitor** – lowering blood pressure, reverse remodeling
  - **Betablocker** – reducing adrenergic stimulation = lower oxygen need and consumption
  - **Diuretics** – reduces volume overload

  etc… symptomatic treatment
- **Bypass / Angioplasty / Transplantation… in time?**

- **4th strategy?**
  - cardiac repair to regenerate functionally viable myocardium after insult as myocardial infarction to prevent or heal heart failure…

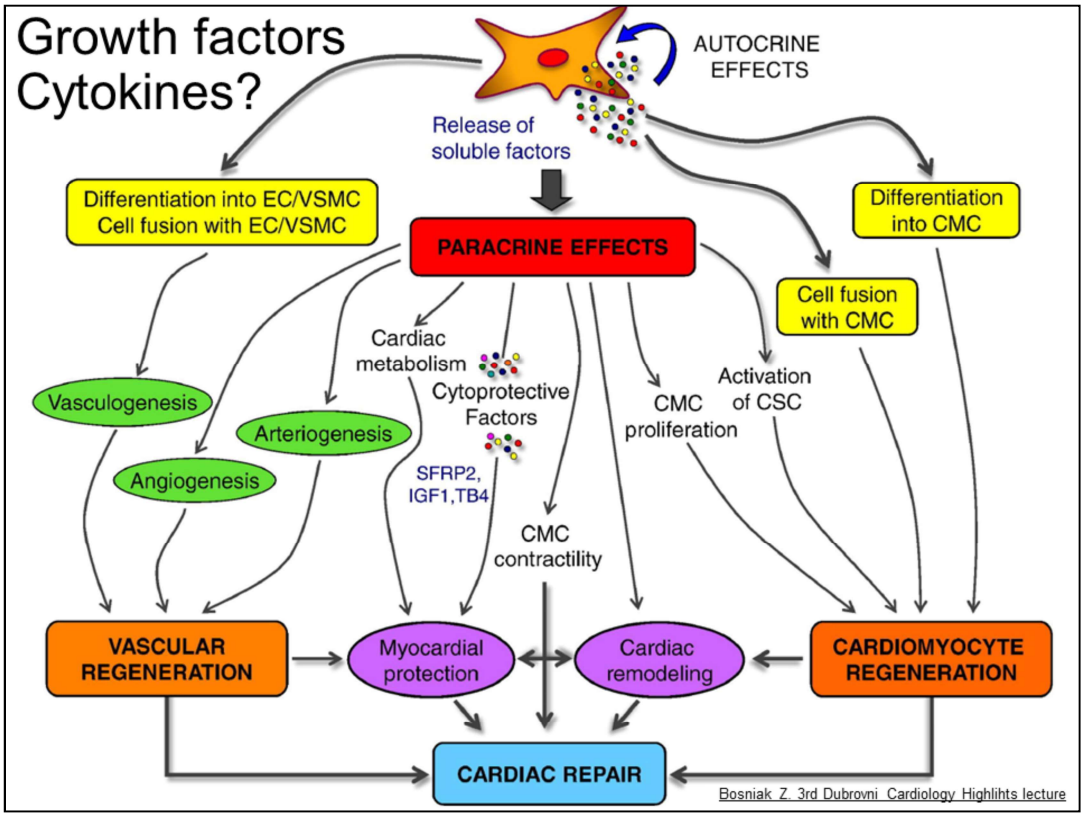
How?

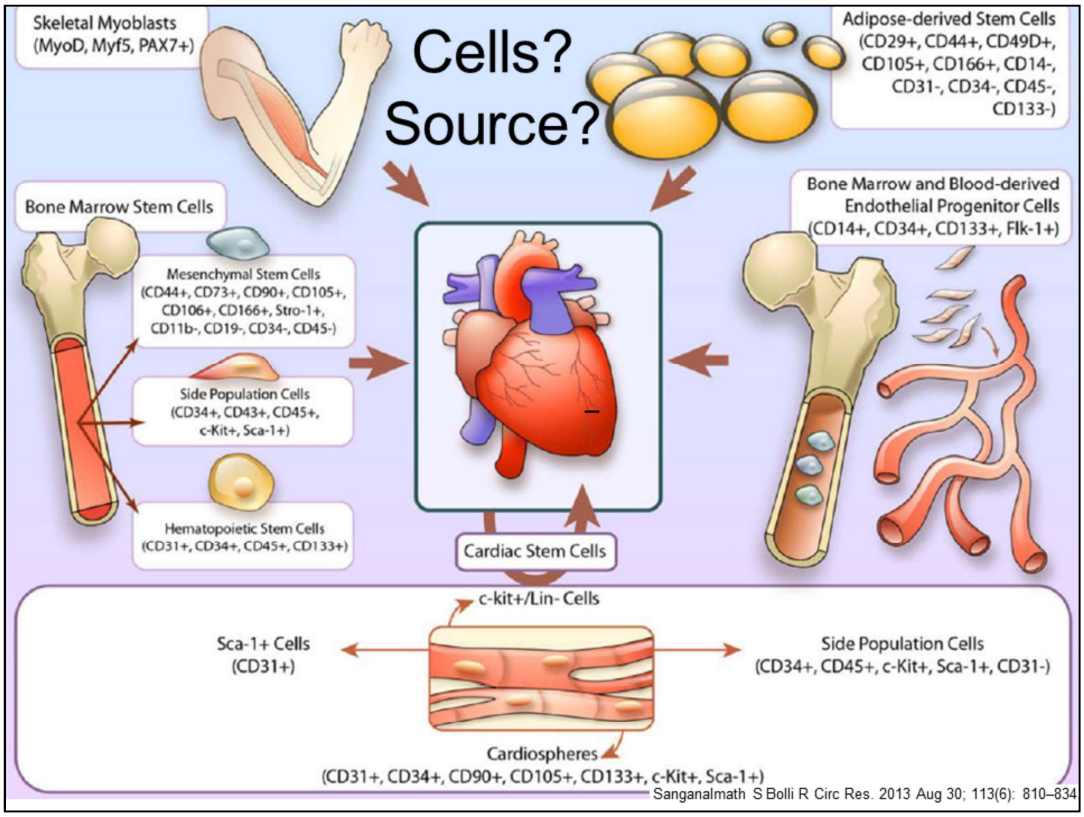
- cells/ tissues / vessels
- growth factors / cytokines

- origin:

endogenous repair	– original tissue
autologous	– other organs
allogenic	– other human(s)
xenogenic	– other species

- number of different strategies…


Growth factors
Cytokines?
AUTOCRINE
EFFECTS
Release of
soluble factors
Differentiation into EC/VSMC
Cell fusion with EC/VSMC
PARACRINE EFFECTS
Differentiation
into CMC
Cell fusion
with CMC
Cardiac
metabolism
Cytoprotective
Factors
SFRP2,
IGF1,TB4
CMC
proliferation
Activation
of CSC
Vasculogenesis
Arteriogenesis
Angiogenesis
CMC
contractility
VASCULAR
REGENERATION
Myocardial
protection
Cardiac
remodeling
CARDIOMYOCYTE
REGENERATION
CARDIAC REPAIR
Bosniak Z. 3rd Dubrovni Cardiology Highlihts lecture



Sanganalmath S Bolli R Circ Res. 2013 Aug 30; 113(6): 810–834

Skeletal Myoblasts (SKMs)?

- precursors of satellite cells
- found in muscle biopsies,
- proliferative + resistant to ischaemia/hypoxia
-
- no functional coupling of SKMs with the myocardium in vivo = fail to contract synchronously with the native myocardium
- the MAGIC trial - no significant improvement in LV function = discontinued

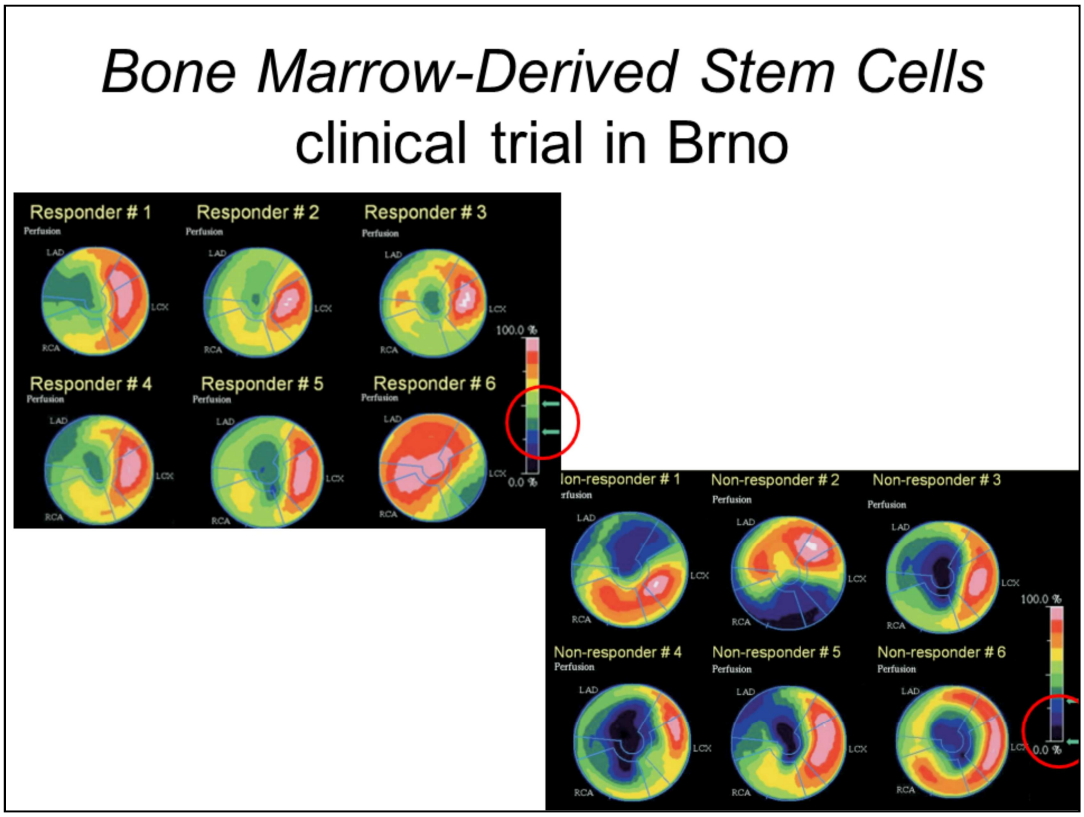
P. Menasch´e, O. Alfieri, S. Janssens et al., "The myoblast autologous grafting in ischemic cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation," *Circulation*, vol. 117, no. 9, pp. 1189–1200, 2008.
[41] H. Reinecke, V. Poppa, and C. E. Murry, "Skeletal muscle stem cells do not transdifferentiate into cardiomyocytes after cardiac grafting," *Journal of Molecular and Cellular Cardiology*, vol. 34, no. 2, pp. 241–249, 2002.

Bone Marrow-Derived Stem Cells (BMCs) *unselected ?*

- in circulation
  - contribute to myocytes renewal
  - (cell fusion and transdifferentiation)
- haematopoietic stem cells (HSCs)
- mesenchymal stem cells (MSCs)
- endothelial progenitor cells (EPCs)
- optimal the mixture of stem-like cells
- harvested from pelvic bones of patients
- TOPCARE-AMI and BALANCE trial
  - intracoronary BMCs 10-11% increase LVEF (5Y)
- meta- analysis: over 3000 patients have been treated with BMCs
  - overall LVEF (+3.96%)
  - smaller infarct size (~−4.03%)
  - clinical significance?
  - limited data on mortality, recurrence of MI, and rehospitalization for heart failure
  - no of carcinogenesis, arrhythmias, or any other adverse effects

D. M. Leistner, U. Fischer-Rasokat, J. Honold et al., "Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI): final 5-year results suggest long-term safety and efficacy," *Clinical Research in Cardiology*, vol. 100, no. 10, pp. 925–934, 2011.

M. Yousef, C.M. Schannwell, M. K¨ostering, T. Zeus, M. Brehm, and B. E. Strauer, "The BALANCE Study: clinical benefit and long-term outcome after intracoronary autologous bone marrow cell transplantation in patients with acute myocardial infarction," *Journal of the American College of Cardiology*, vol. 53, no. 24, pp. 2262–2269, 2009.



Long-term results of intracoronary bone marrow cell transplantation: the potential of gated sestamibi SPECT/FDG PET imaging to select patients with maximum benefit from cell therapy. **Kaminek M**, **Meluzin** J, Panovský R, Metelkova I, Budikova M, Richter M. Clin Nucl Med. 2010 Oct;35(10):780-7. doi: 10.1097/RLU.0b013e3181e4d9c5.

Autologous transplantation of mononuclear bone marrow cells in patients with acute myocardial infarction: the effect of the dose of transplanted cells on myocardial function.

Meluzín J, Mayer J, Groch L, Janousek S, Hornácek I, Hlinomaz O, Kala P, Panovský R, Prásek J, Kamínek M, Stanícek J, Klabusay M, Korístek Z, Navrátil M, Dusek L, Vinklárková J. Am Heart J. 2006 Nov;152(5):975.e9-15.

Mesenchymal Stem Cells (MSCs) selected?

- *Bone Marrow* - LVEF was increased by approximately 6.7% at 6 months, an inverse dose response, 20 million better than 200 million cells, - the POSEIDON-pilot
- *Umbilical cord matrix* in 18-month follow-up, global LVEF improved by 5% no arrhythmias or immuno side effects
- *Adipose-Derived Mesenchymal Stem Cells.*
  harvested and expanded
  o MHC class II antigens,
  differentiate in to cardiomyocytes and endothelial cells upon induction
  the PRECISE study cells stabilized the scar size in patients with advanced ischaemic heart disease (not reduction of scar size or increase LVEF)

J. M. Hare, J. E. Fishman, G. Gerstenblith et al., "Comparison of allogeneic vs autologous bonemarrow-derivedmesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: the POSEIDON randomized trial," *JAMA*, vol. 308, no. 22, pp. 2369–2379, 2012.

The TRansendocardial Stem Cell Injection Delivery Effects on Neomyogenesis STudy (The TRIDENT Study) (Trident) (NCT02013674)

E. C. Perin, R. Sanz-Ruiz, P. L. S´anchez et al., "Adipose-derived regenerative cells in patients with ischemic cardiomyopathy: the PRECISE Trial," *American Heart Journal*, vol. 168, no. 1, pp. 88.e2–95.e2, 2014.

Cardiac Stem Cells (CSCs)?

- resident stem-like cells, self-renewing cells able to differentiate into a 3 cell lineages
- low proportion (0.01%) of native cardiomyocytes = low turnover rate
- meta-analysis 1970 animals improvement in LVEF by approximately 12%
- SCIPIO study phase I, c-kit+ CSCs - ischaemic MI, CSCs from right atrial appendage Coronary Artery Bypass Graft (CABG)
  - 1 million of cells administered to 16 patients intracoronary 4 months after CABG increase in LVEF 12.3% at 12 months injection / no tumour formation
  - **4–8%** of transplanted CSCs colonized / persisted in the myocardium 1y
  - **effect of paracrine factors released by injected cells modulating the proliferation of the host cardiac cells?**

R. Bolli, A. R. Chugh, D. D'Amario et al., "Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial," *The Lancet*, vol. 378, no. 9806, pp. 1847–1857, 2011.

Cardiosphere-Derived Cells (CSps)?

- in vitro cultured myocardial biopsies form spheroids
- self-renewal, positive for progenitor cell markers (c-kit, CD-34, Sca-1, and Nkx2.5)
- heterogeneous mixture of cardiac stem cells, differentiating progenitors and differentiated cardiomyocytes
- enhance cardiac function, angiogenic formation, and paracrine factor secretion (supporting cells)
- the CADUCEUS - decreased scar size of 12.3% at 12 months - no improvement in global LVEF
- large size may embolize capillary
- lack MHC II antigen = allogeneic CDCs trials

R. R. Makkar, R. R. Smith, K. Cheng et al., "Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial," *The Lancet*, vol. 379, no. 9819, pp. 895–904, 2012.

Embryonic Stem Cells (ESCs)?

- derived from the inner cell mass of the early embryo in the blastocyst stage
- self-renewing, clonogenic, and capable of differentiating into any type of cell in the adult
- atrial-like, ventricular-like, sinus nodal-like, Purkinje-like cells
- beat spontaneously and synchronously
- teratomas after transplantation because of the unlimited differentiation potential of ESCs - need for selection
- ethical concerns, potential genetic instability, risk of immune rejection - the ESCORT study

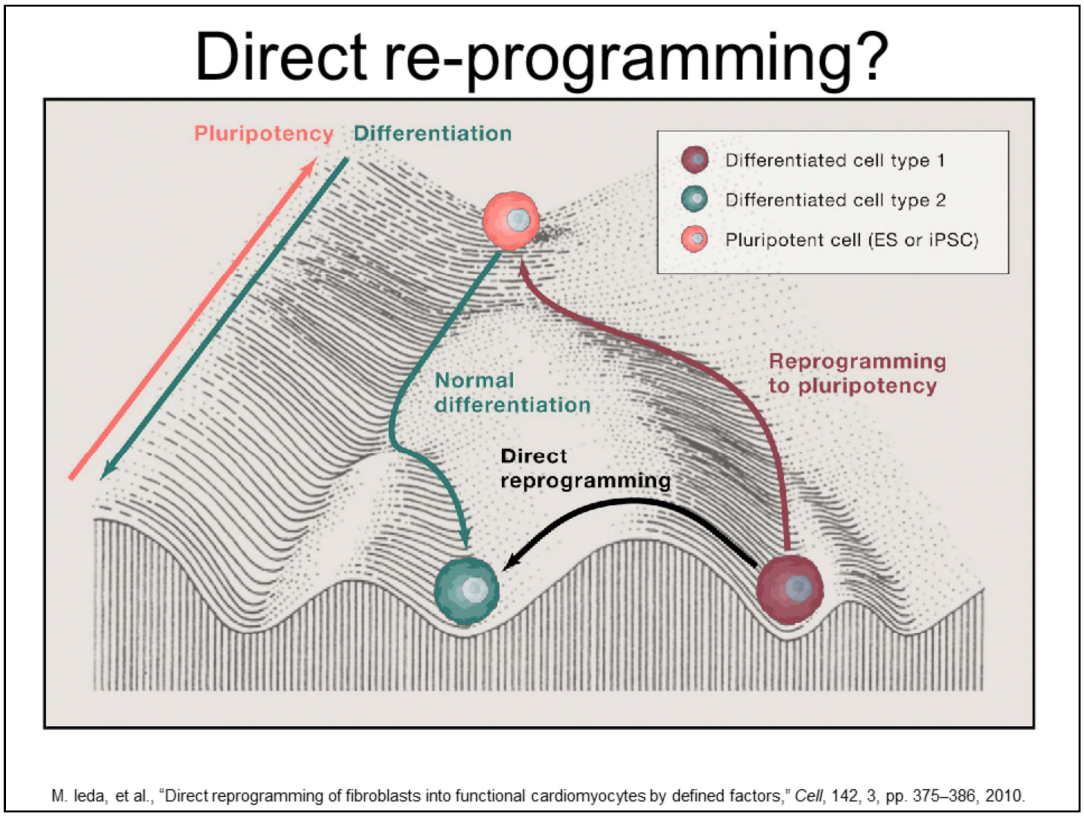
Transplantation of Human Embryonic Stem Cell-derived Progenitors in Severe Heart Failure (ESCORT) (NCT02057900)

induced Pluripotent Stem Cells (iPSCs)

- forced expression of OCT4, SOX2, KLF4, and c-MYC transcription factors reprogram terminally differentiated
- cells - resemble embryonic stem cells
- iPSCs can be derived from individual patients for autologous transplantation
- teratoma formation in swine model, the low efficiency of cardiogenic differentiation, high costs, and time-consuming methods
- diagnostic methods – phenotype analyses and on demand patient specific drugs testing

Derivation of Human Induced Pluripotent Stem (iPS) Cells to Heritable Cardiac Arrhythmias (NCT02413450),

"Blood Collection From Healthy Volunteers and Patients forthe Production of ClinicalGrade Induced Pluripotent StemCell (iPSC) Products (NCT02056613),"



M. Ieda, J.-D. Fu, P. Delgado-Olguin et al., "Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors," *Cell*, 142, 3, pp. 375–386, 2010.

Medicine paradigm shift!

Gillray J. Bloodletting 1804, World History Archive