




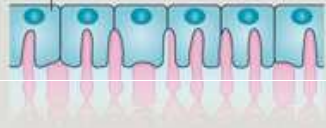






Progress in clinical applications of PSCs

Up Date 2020 Theoretical Bases of Clinical Medicine

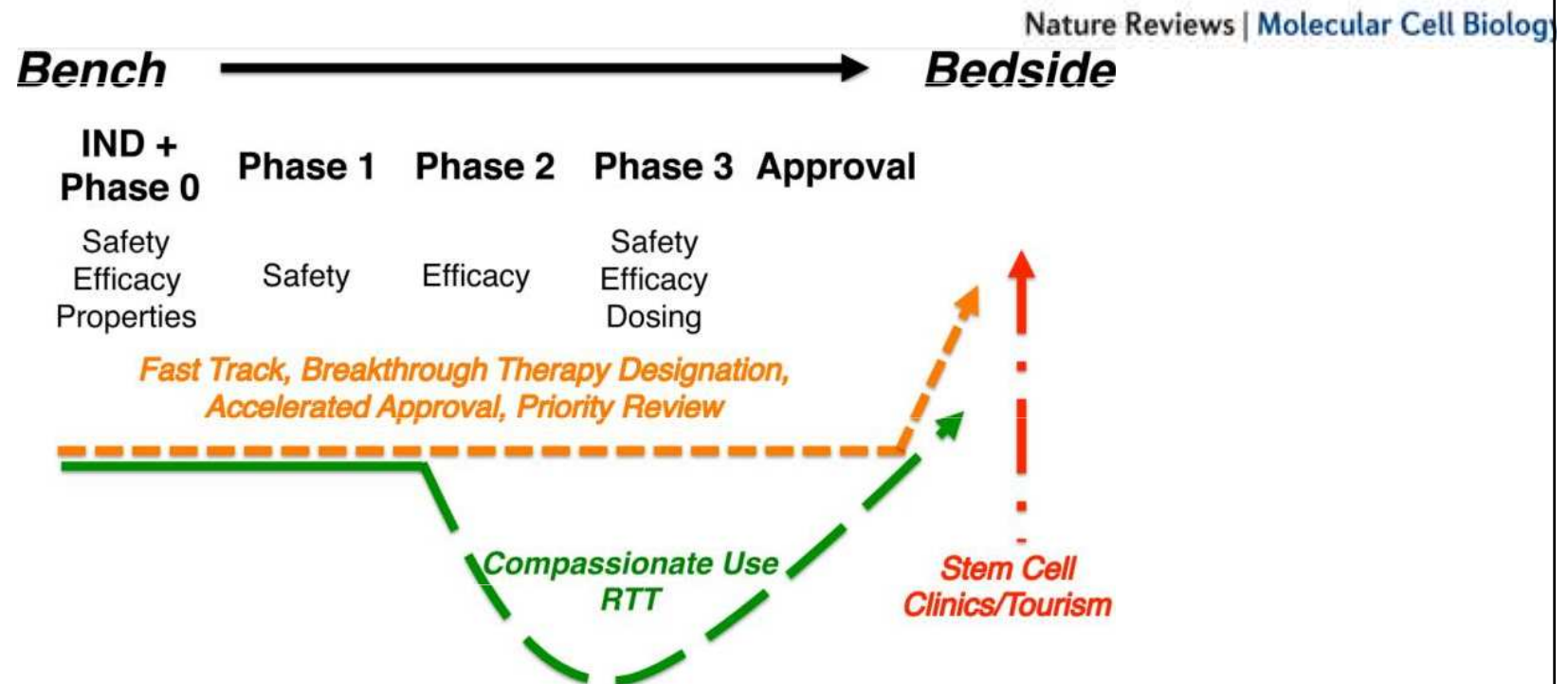
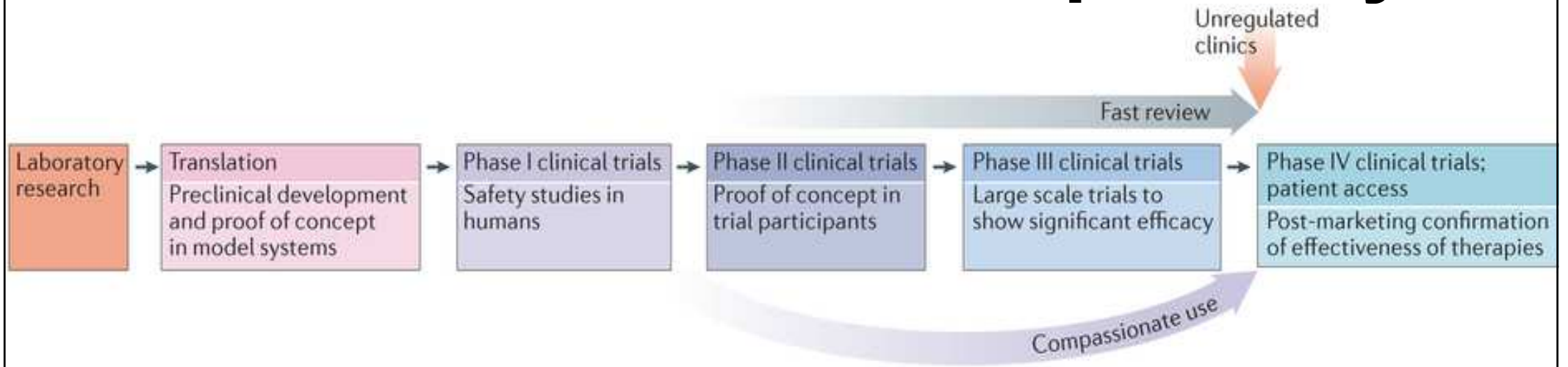
Disease	Age-related macular degeneration	Parkinson disease	Spinal cord injury	Diabetes	Myocardial infarction
iPSCs and/or ES cells					
Robust differentiation	↓	↓	↓	↓	↓
Cell type	Retinal pigment epithelium 	A9 dopaminergic neuron 	Oligodendrocyte progenitor 	Pancreatic islet β -cell progenitor 	Cardiomyocytes 
Current stage	Clinical Phase I and Phase II	Clinical Phase I	Clinical Phase I	Clinical Phase I–II	Clinical Phase I

Nature Reviews | [Molecular Cell Biology](#)

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The bench to bedside pathway





Shortness
of
Breath



Chronic
Coughing or
Wheezing



Build-up
of Fluid
(edema)



Fatigue
or Feeling
Lightheaded



Nausea
or Lack of
Appetite



Confusion
or Impaired
Thinking



High
Heart
Rate

- 213040 → 297984 → 331536 Clinical studies
- 12126 → 18312 → 20267 heart, cardiac, coronary
- 3520 → 7435 → 8054 heart failure
- 237 → 736 → 782 heart stem cell
- **4 studies:** heart human embryonic
Escort 2018, Poseidon 2015, TAC-HFT 2015,
- **3 studies:** heart human induced pluripotent
- in vitro phenotyping
 - **1 study (China):** heart human induced pluripotent HEAL-CHF (5 pts.)

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 myocarditis 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

– **Intervention: Bypass / Angioplasty / Transplantation**

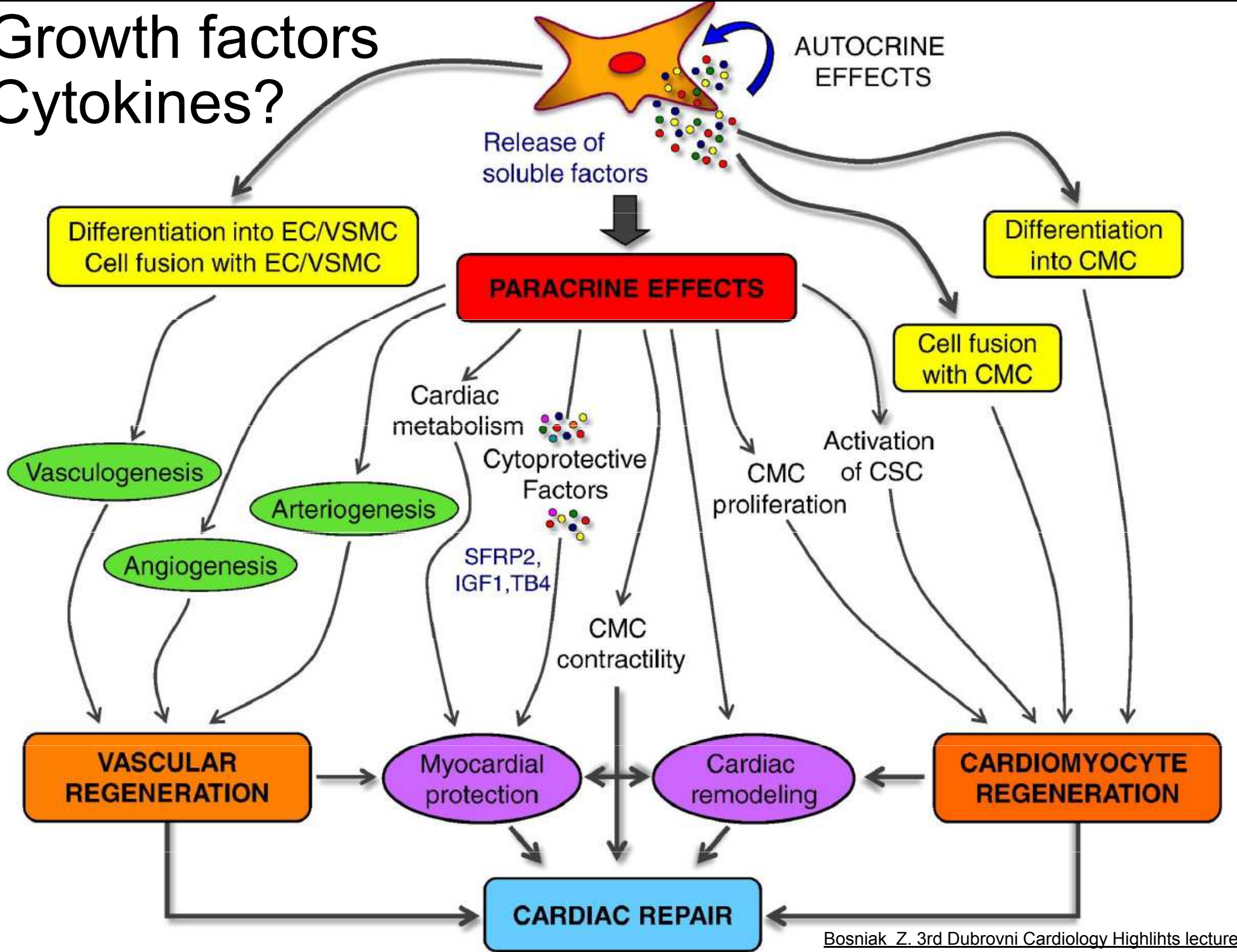
• **4th strategy?**

– cardiac repair to regenerate functionally viable myocardium after insult as eg. myocardial infarction to prevent its progression or heal failing heart...

How?

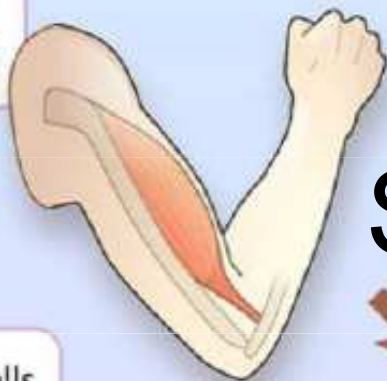
- cells/ tissues / vessels / organs
- growth factors / cytokines
- nucleic acid interventions (gene therapies)
- origin/source:
 - endogenous repair – original tissue of individual
 - autologous – other organs of individual
 - allogenic – other human(s)
 - xenogenic – other species
- number of different strategies...

Growth factors Cytokines?

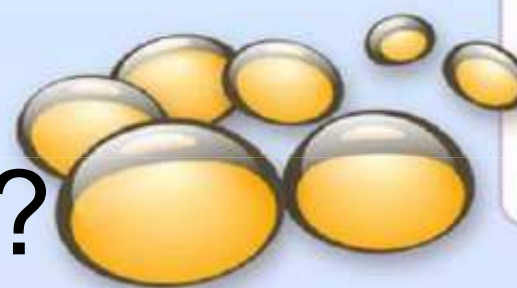


Cells? Source?

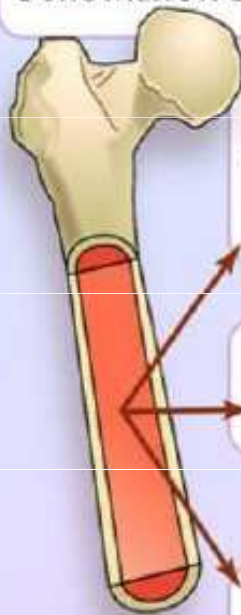
Skeletal Myoblasts
(MyoD, Myf5, PAX7+)



Adipose-derived Stem Cells
(CD29+, CD44+, CD49D+,
CD105+, CD166+, CD14-,
CD31-, CD34-, CD45-,
CD133-)



Bone Marrow Stem Cells

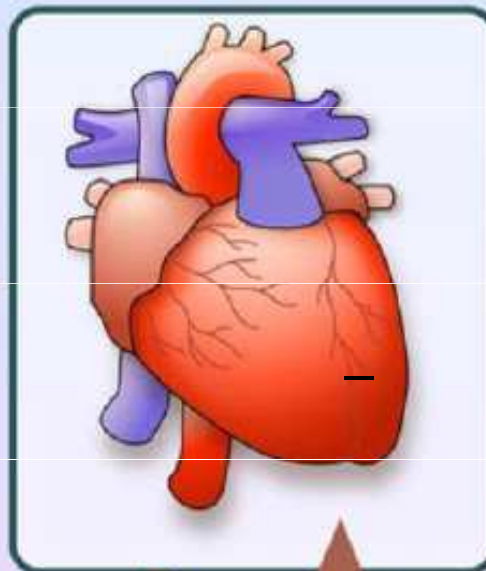
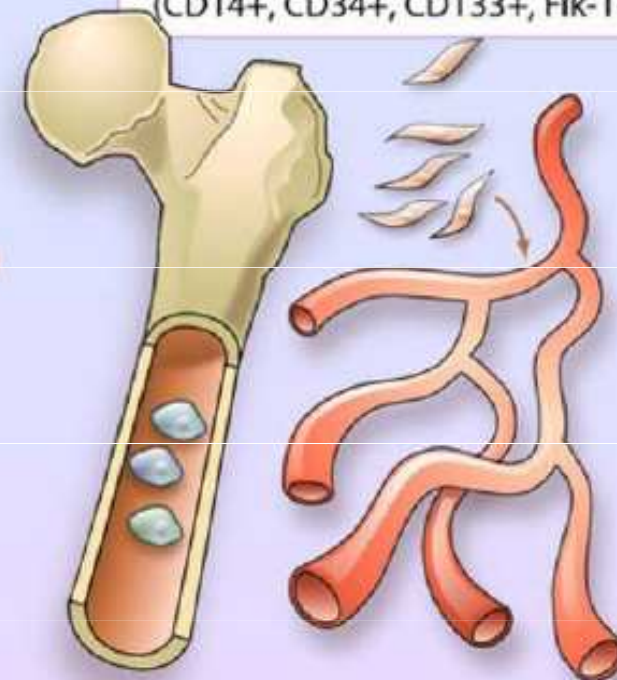


Mesenchymal Stem Cells
(CD44+, CD73+, CD90+, CD105+,
CD106+, CD166+, Stro-1+,
CD11b-, CD19-, CD34-, CD45-)

Side Population Cells
(CD34+, CD43+, CD45+,
c-Kit+, Sca-1+)

Hematopoietic Stem Cells
(CD31+, CD34+, CD45+, CD133+)

Bone Marrow and Blood-derived
Endothelial Progenitor Cells
(CD14+, CD34+, CD133+, Flk-1+)

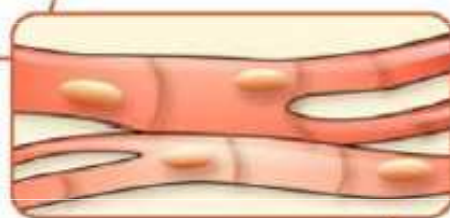


Cardiac Stem Cells

c-kit+/Lin- Cells

Sca-1+ Cells
(CD31+)

Side Population Cells
(CD34+, CD45+, c-Kit+, Sca-1+, CD31-)



Cardiospheres

(CD31+, CD34+, CD90+, CD105+, CD133+, c-Kit+, Sca-1+)

Skeletal Myoblasts (SKMs)?

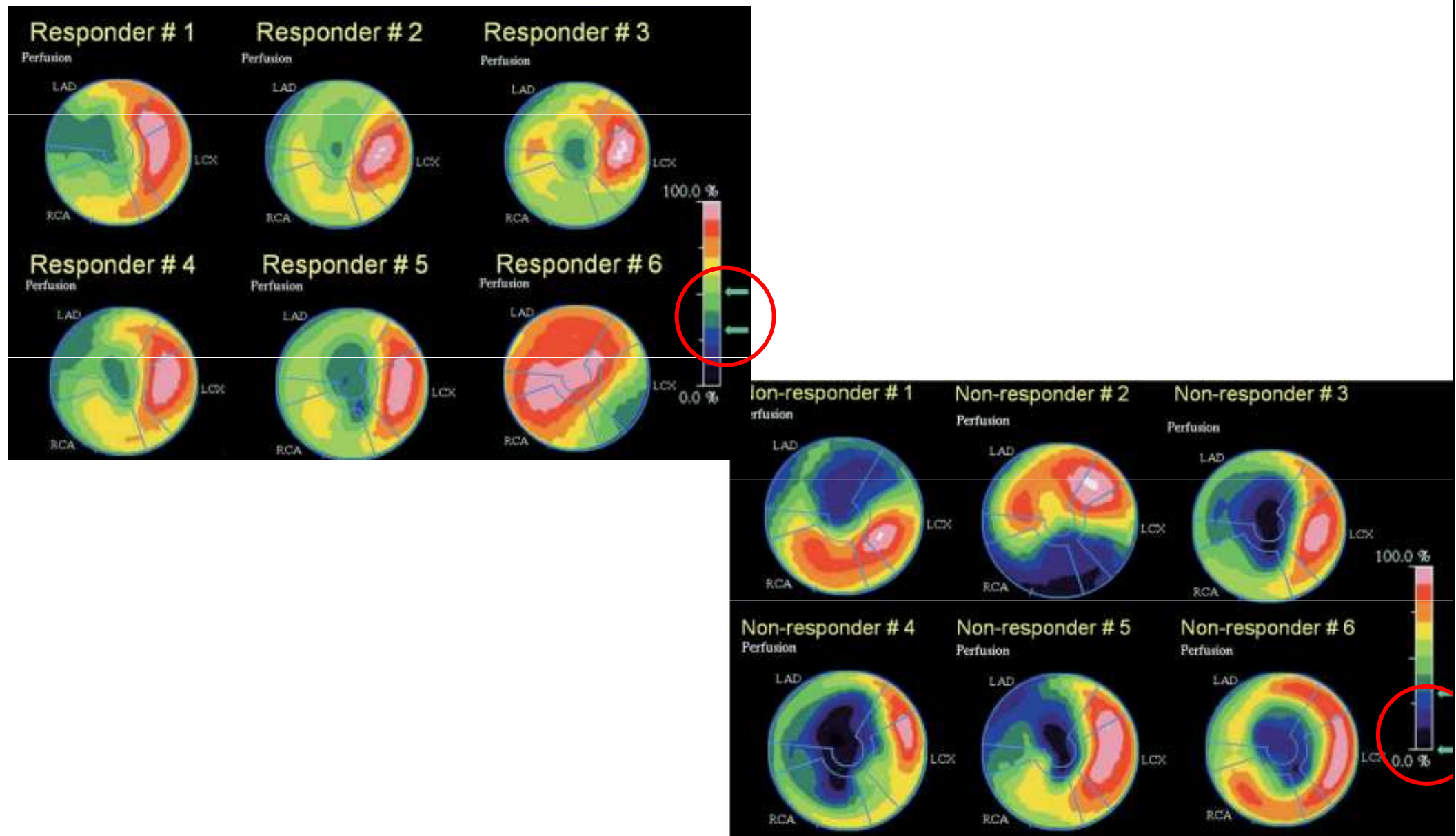
- precursors of satellite cells
- found in muscle biopsies,
- proliferative + resistant to ischaemia/hypoxia

- 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

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 re-hospitalization for heart failure
 - no of carcinogenesis, arrhythmias, or any other adverse effects

Bone Marrow-Derived Stem Cells clinical trial in Brno (2010)



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 inductionthe PRECISE study cells stabilized the scar size in patients with advanced ischaemic heart disease (not reduction of scar size or increase LVEF)

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%
- SCIPPIO 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?**

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

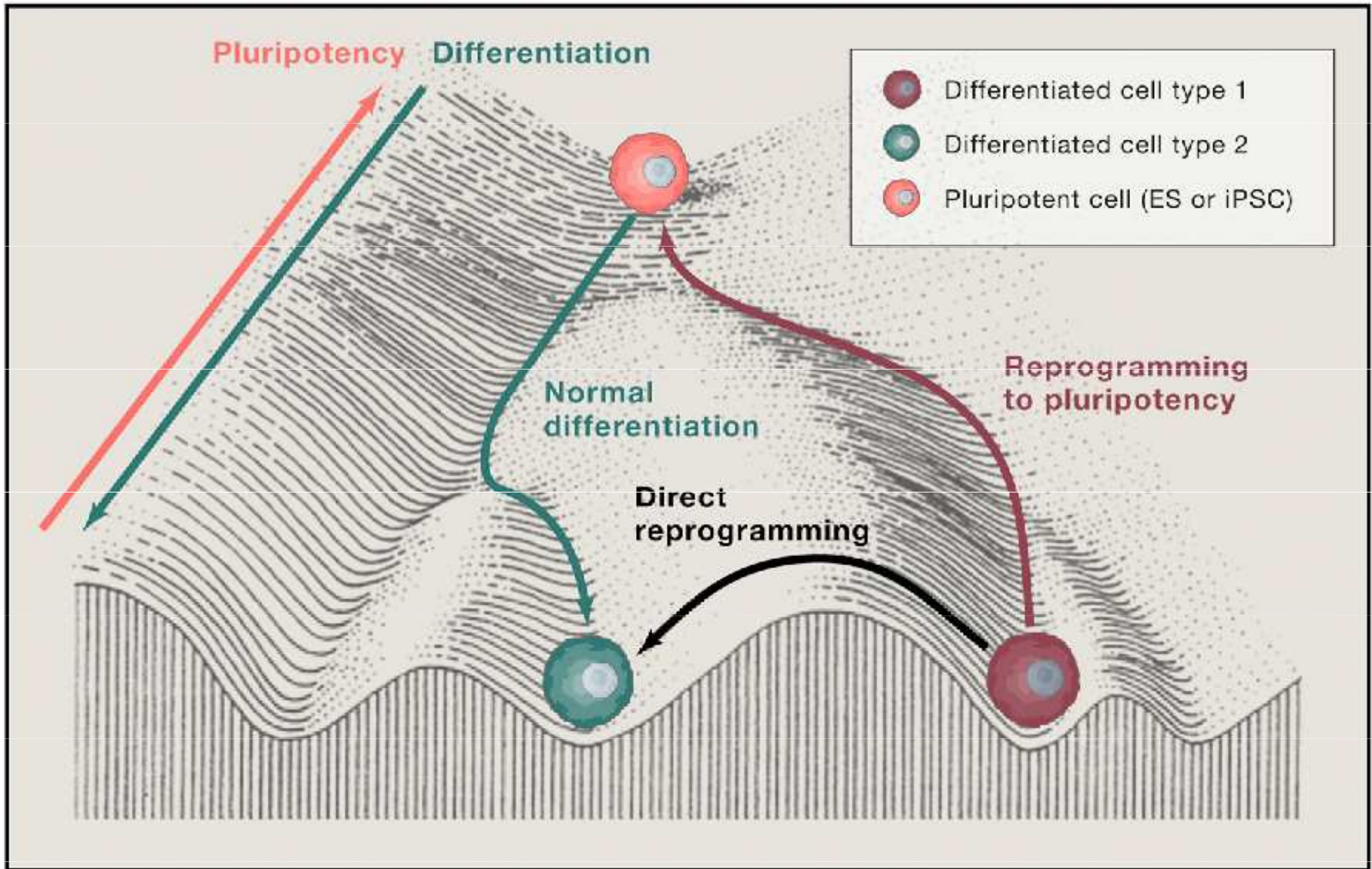
Embryonic Stem Cells (ESCs)?

- 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

induced Pluripotent Stem Cells (iPSCs)

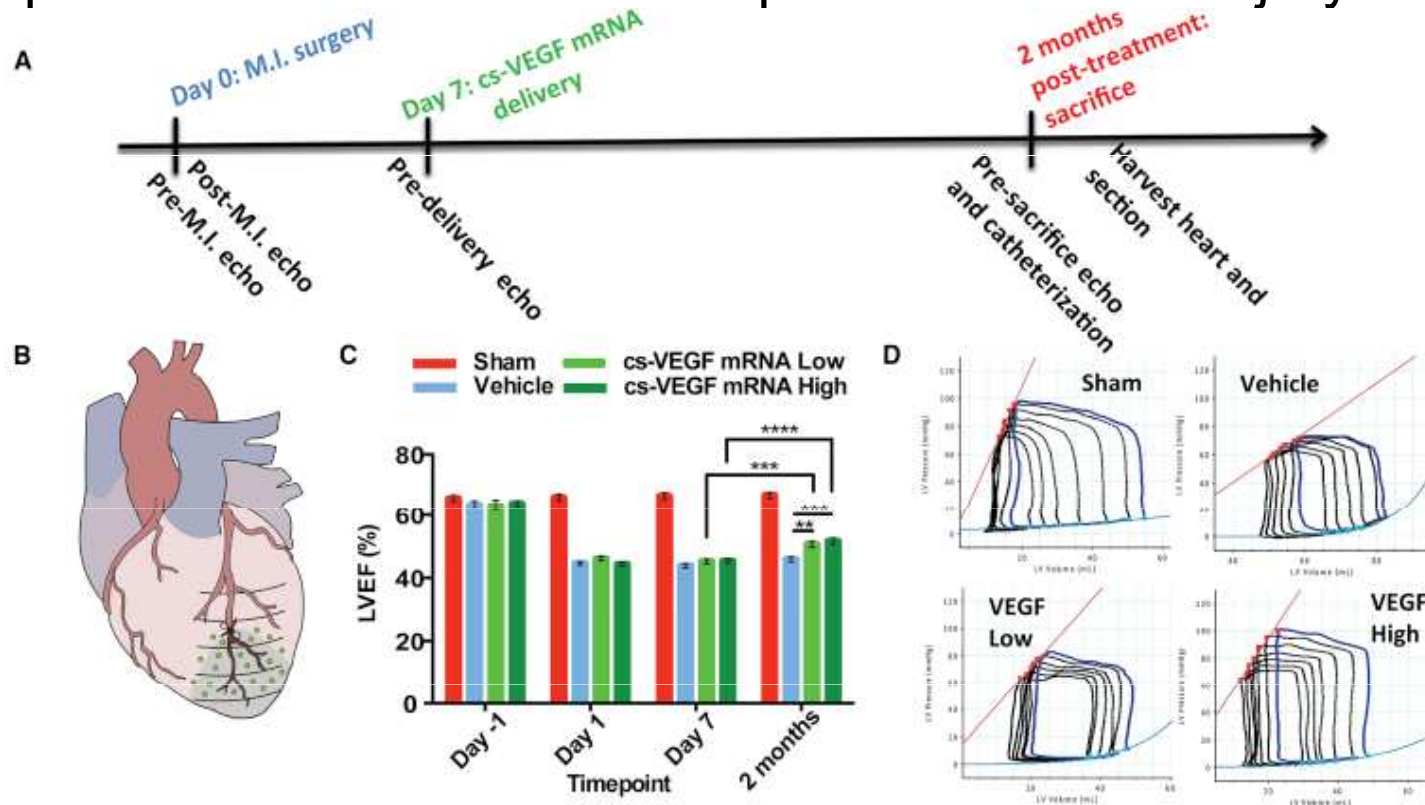
- forced expression of OCT4, SOX2, KLF4, and c-MYC transcription factors reprogram terminally differentiated
- cells - resemble embryonic stem cells
- iPSCs can be derived from individual patients for autologous transplantation
- teratoma formation in swine model, the low efficiency of cardiogenic differentiation,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

Direct re-programming?



Nucleic acid strategies

- Genome – CRISPR/Cas9, prime editing, AAV (MYDICAR)
- mRNA regulation of protein expression in cardiac muscle without genome integration
 - Purified *VEGF-A* mRNA establishes the feasibility of improving cardiac function in the sub-acute therapeutic window and may represent a new class of therapies for ischemic injury.



Medicine paradigm shift!



Gillray J. Bloodletting 1804, World History Archive



2009 Cover KIT RODOLFA/HARVARD STEM CELL INSTITUTE.