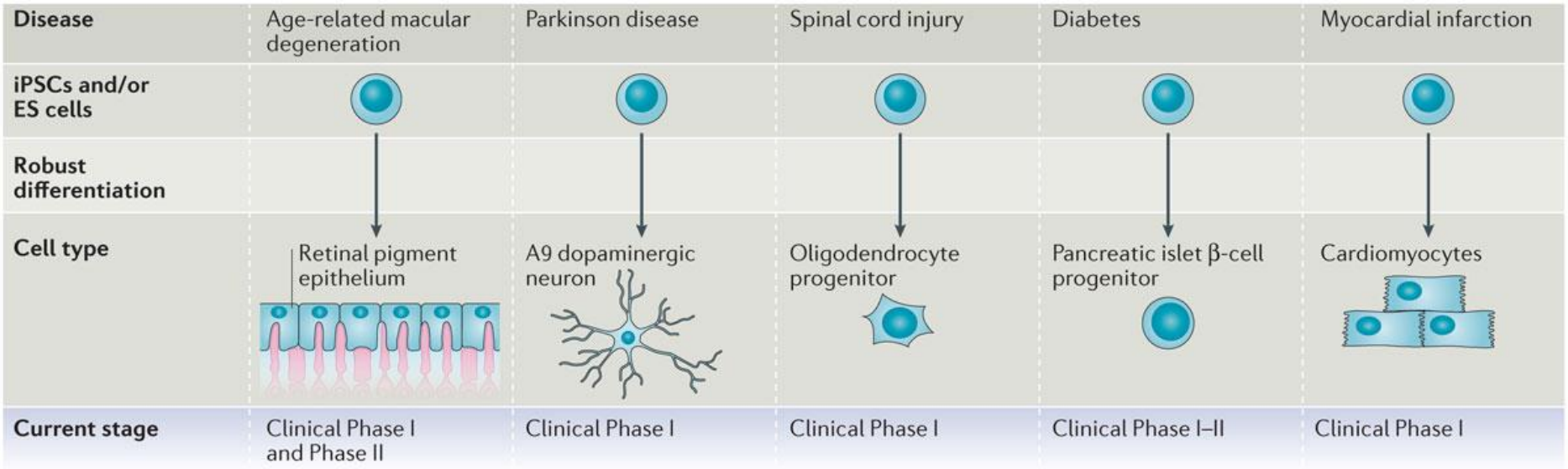
Progress in clinical applications of PSCs in 2018



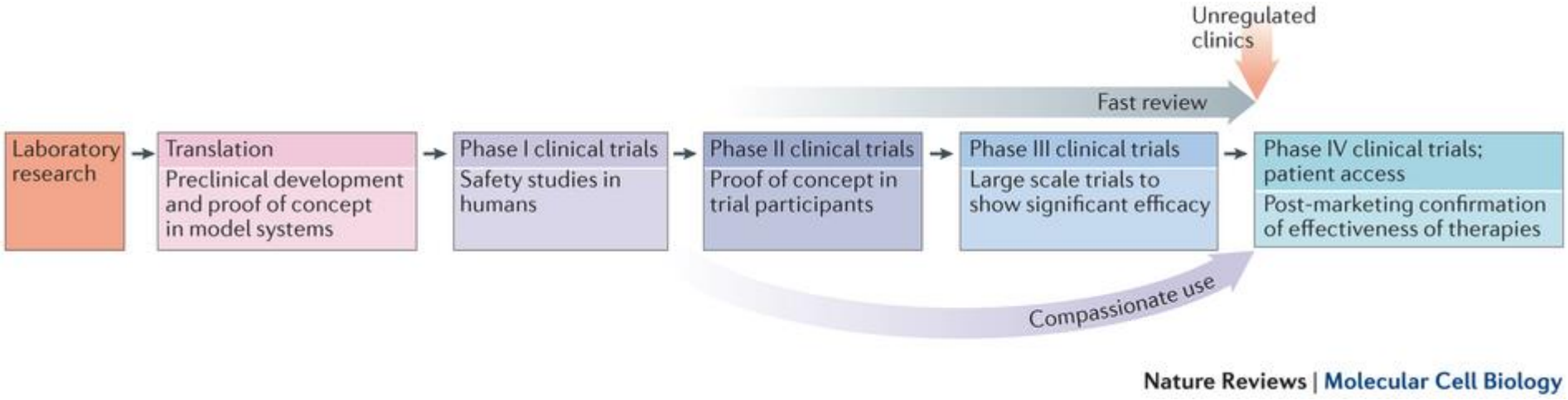
Nature Reviews | Molecular Cell Biology

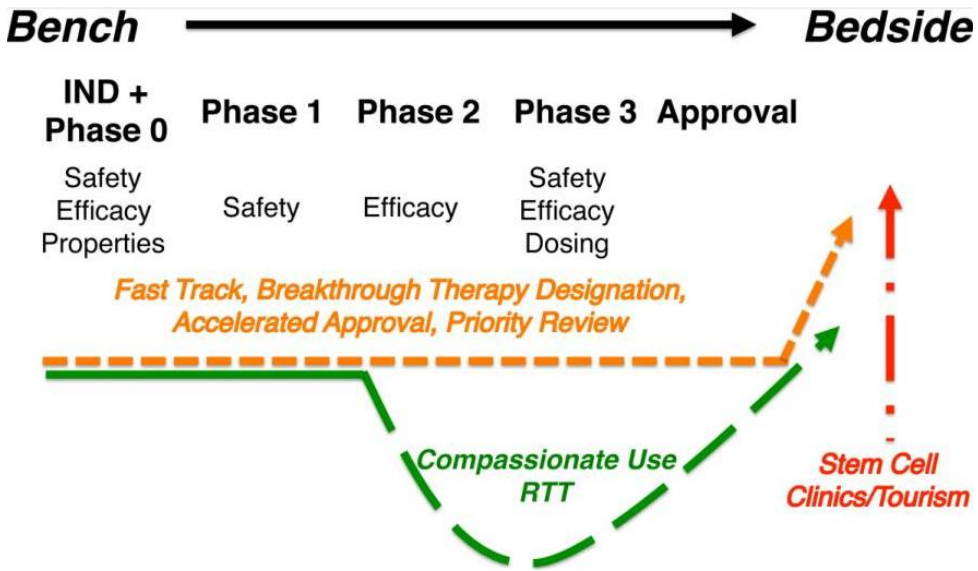
Martin Pešl

TZKM – Dep. of Biology and 1st IKAK LFMU

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

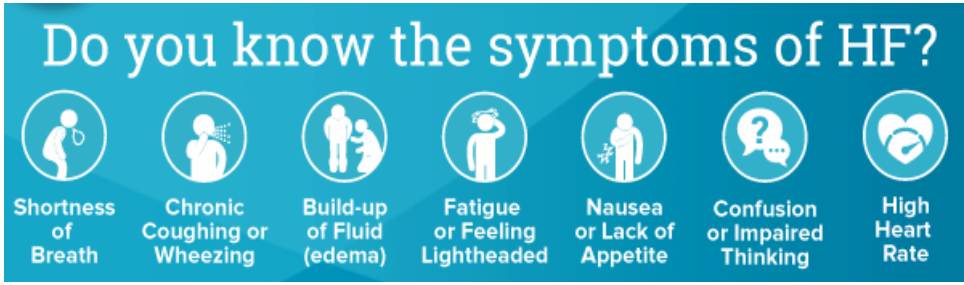
The bench to bedside pathway





Knoepfler PS Adv Drug Deliv Rev. 2015 Mar;82-83:192-6

ClinicalTrials.gov



- 213040 Clinical Intervenentional studies (total)

- 12126 studies: heart, cardiac, coronary
- 3520 studies : heart failure
- 237 studies: heart stem cell

- **1 study**: heart human embryonic (ESCORT)
  transplantation of cardiac progenitor, feasibility/safety
- **2 studies**: heart human induced pluripotent
  - SOLELY in vitro phenotyping

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

What to do?

- **current status**
  - **prevention** – non smoking, education, lifestyle, lipids…
  - **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?**

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

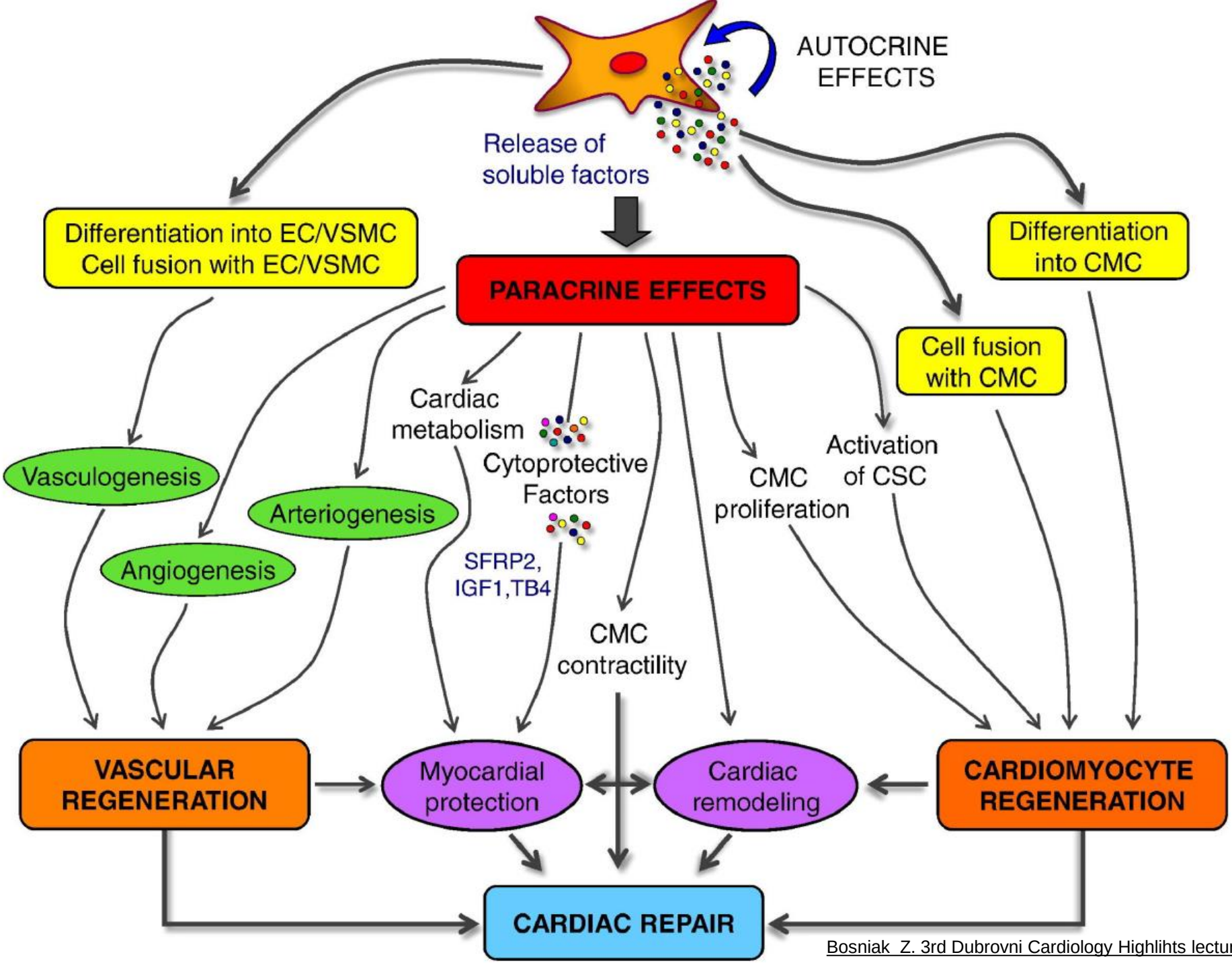
How?

- cells/ tissues / vessels
- growth factors / cytokines

- origin:

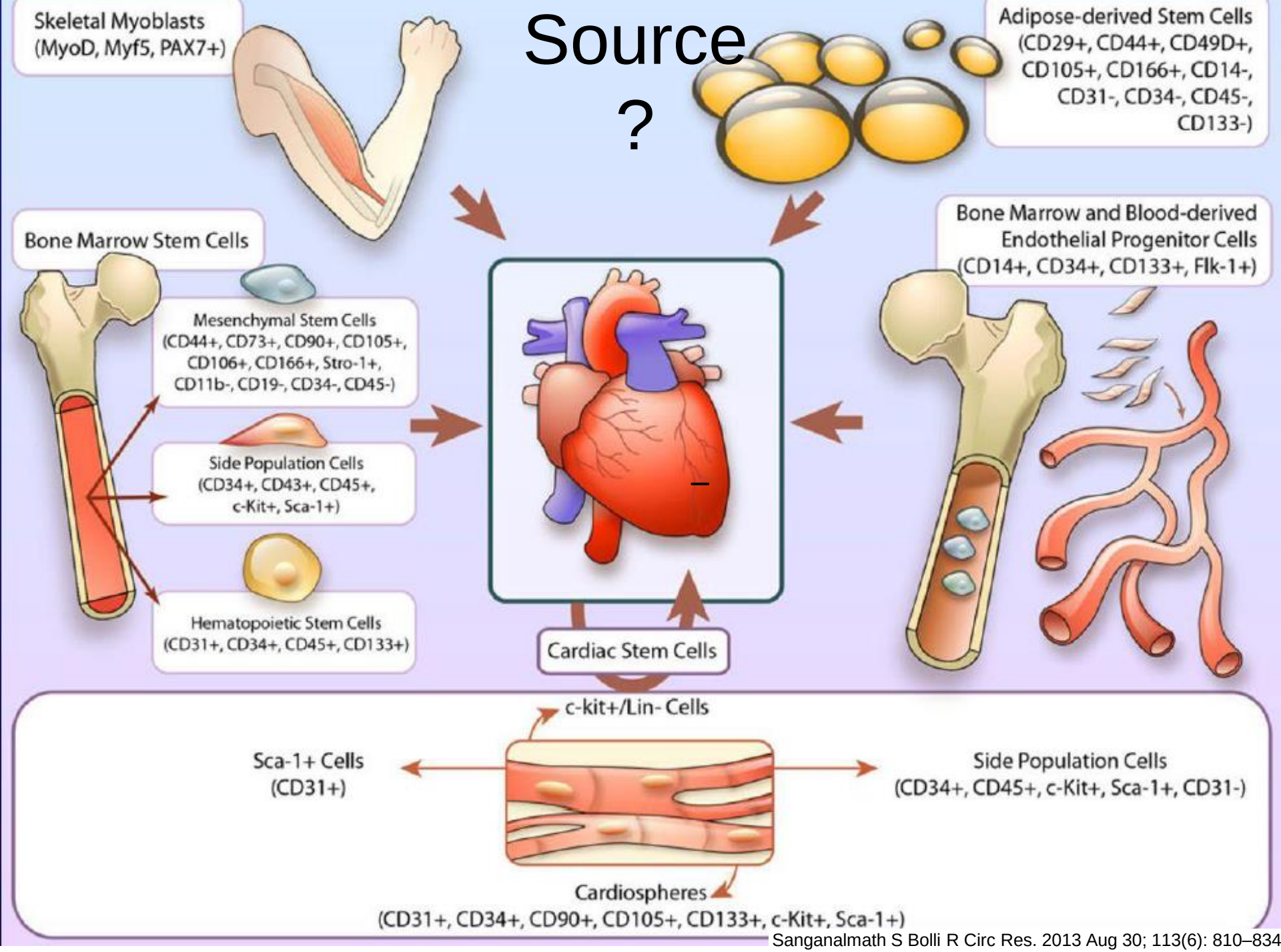
  endogenouse repair – original tissue
  autologouse – other organs
  allogenic – other human(s)
  xenogenic – other species

- number of different strategies…



Bosniak Z. 3rd Dubrovni Cardiology Highlihts lecture

Source ?



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

Skeletal Myoblasts?

- precursors of satellite cells (SKMs)
- muscle biopsies, proliferative + resistant to ischaemia and 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)

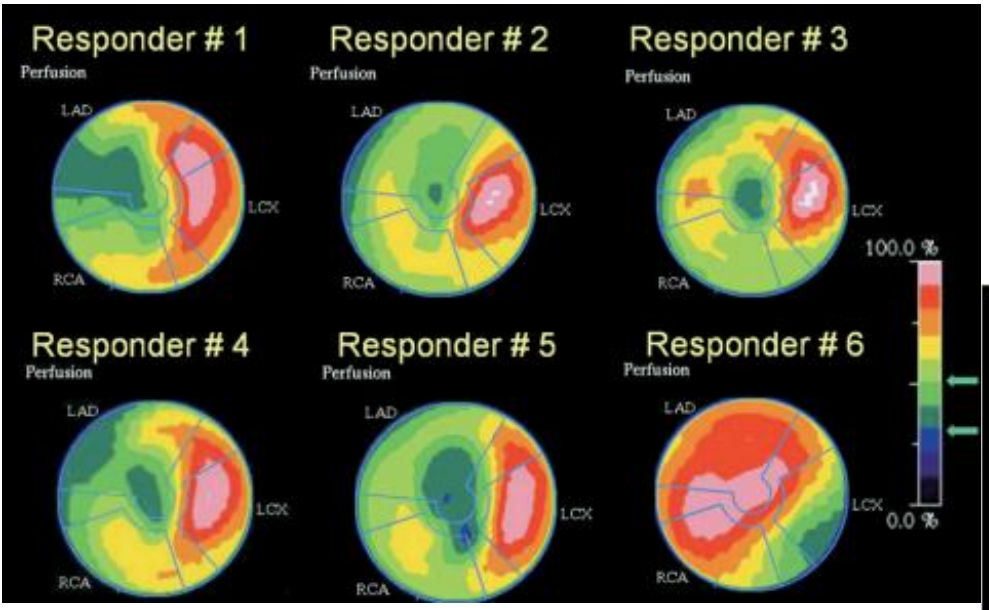
- harvested from pelvic bones of patients

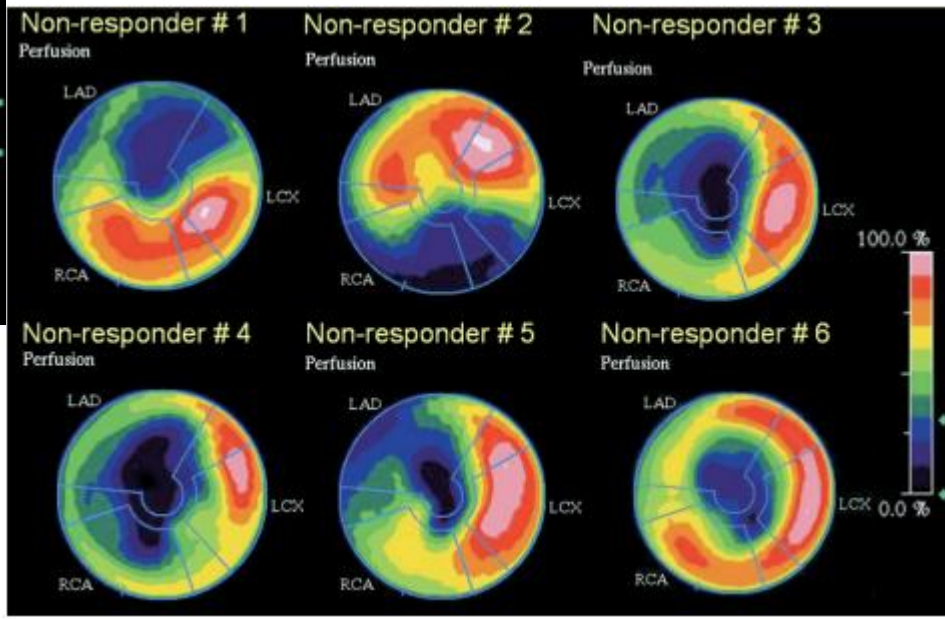
- haematopoietic stem cells (HSCs)
- mesenchymal stem cells (MSCs)
- endothelial progenitor cells (EPCs)
- optimal the mixture of stem-like cells

- 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

Bone Marrow-Derived Stem Cells clinical trial in Brno





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)

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 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

- risk of teratoma formation, the low efficiency of cardiogenic differentiation, high costs, and time-consuming methods

- diagnostic methods – phenotype analyses and on demand patient specific drugs testing

Direct reprogramming?

- additional slide according to question :-)

- M. Ieda, J.-D. Fu, P. Delgado-Olguin et al., “Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors,” *Cell*, vol. 142, no. 3, pp. 375–386, 2010.

Medicine paradigm shift!

Gillray J. Bloodletting 1804, World History Archive