NEW ADVANCES IN MYOCARDIAL INFARCTION THERAPY: THE REGENERATION APPROACH

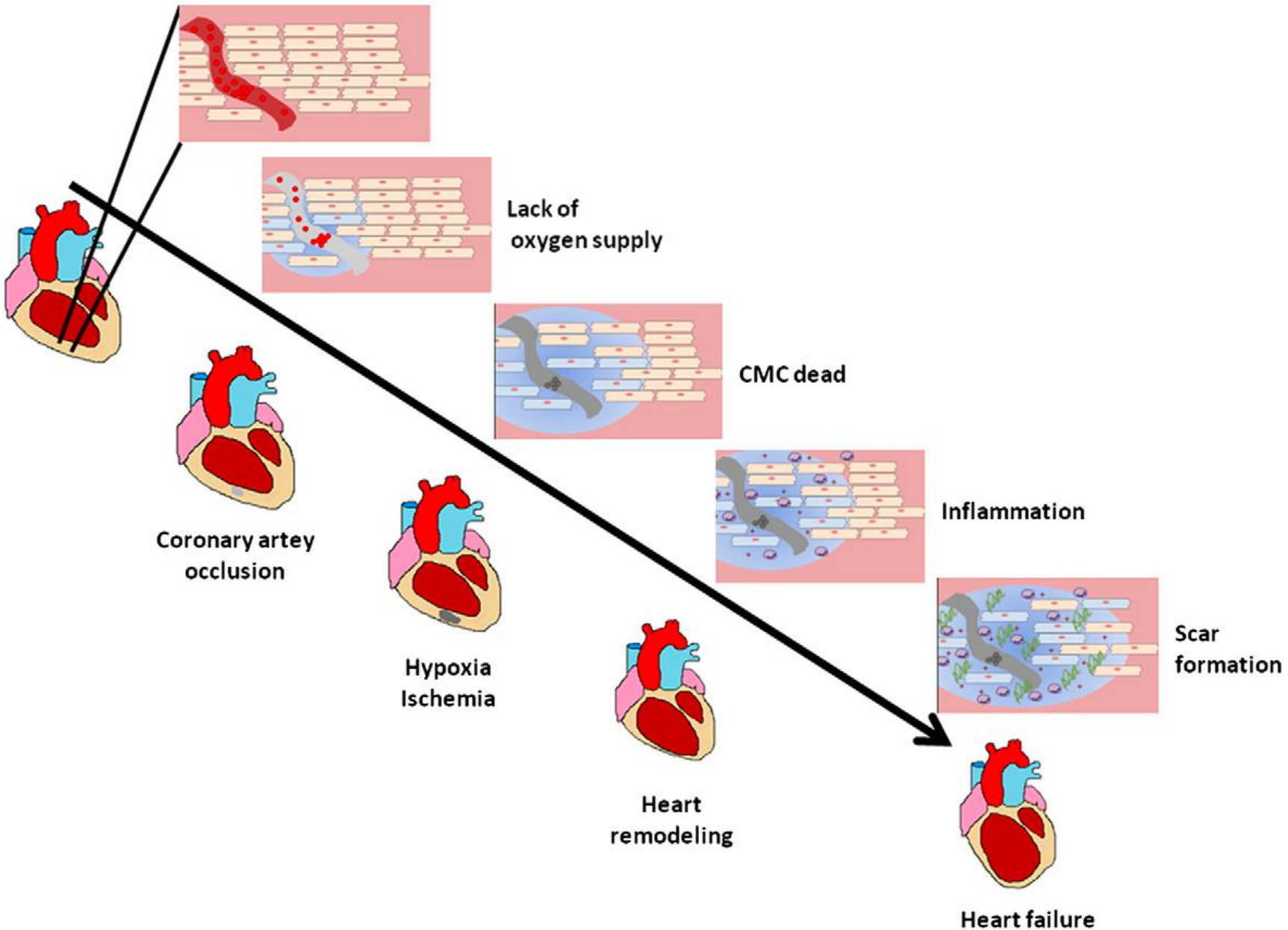
Giovanni Esposito, MD, PhD

Dipartimento di Cardiologia, Cardiochirurgia ed Emergenze Cardiovascolari
Laboratorio di Emodinamica ed Interventistica
Cardiovascolare "Massimo Chiariello"
Università degli studi di Napoli Federico II

NEW ADVANCES IN MYOCARDIAL INFARCTION THERAPY: THE REGENERATION APPROACH

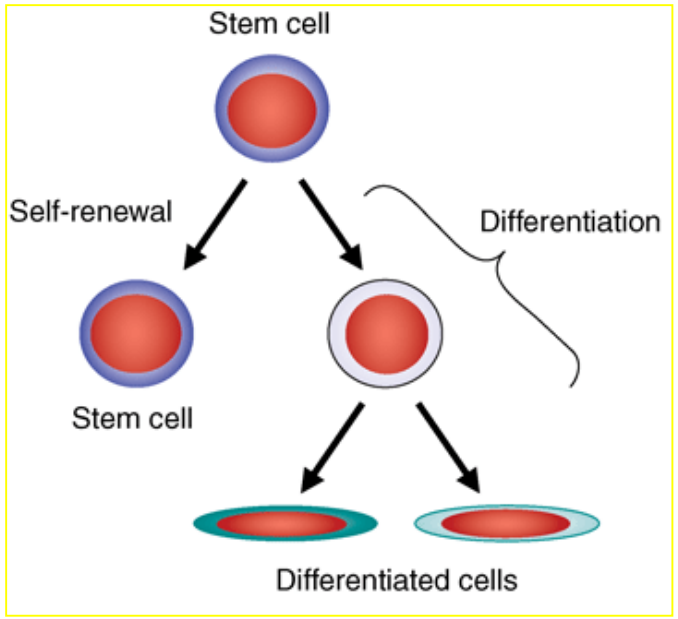
- Cardiovascular disease ➔ leading cause of morbidity and mortality worldwide
- Over 7 million deaths each year for AMI
- Despite advances in medical and cath-based therapy for AMI
    - 1-year mortality: 13%
    - 5-year prognosis for patients with HF: 50%
- LV systolic dysfunction:
    - major determinant of prognosis
    - associated with significant loss of cardiomyocytes

MYOCARDIAL INFARCTION



STEM CELL THERAPY

SC have a unique capacity to produce unaltered daughter cells (**self-renewal**) and to generate specialized cell types (**potency**)



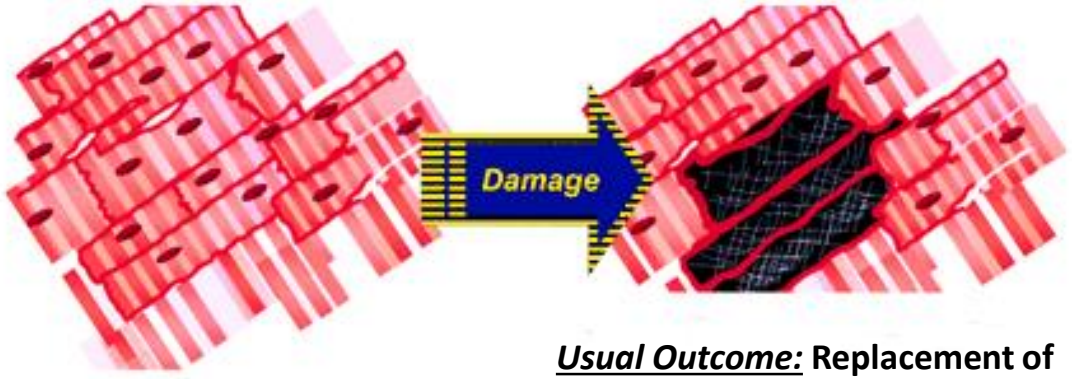
Self-renewal:

Symmetric division:

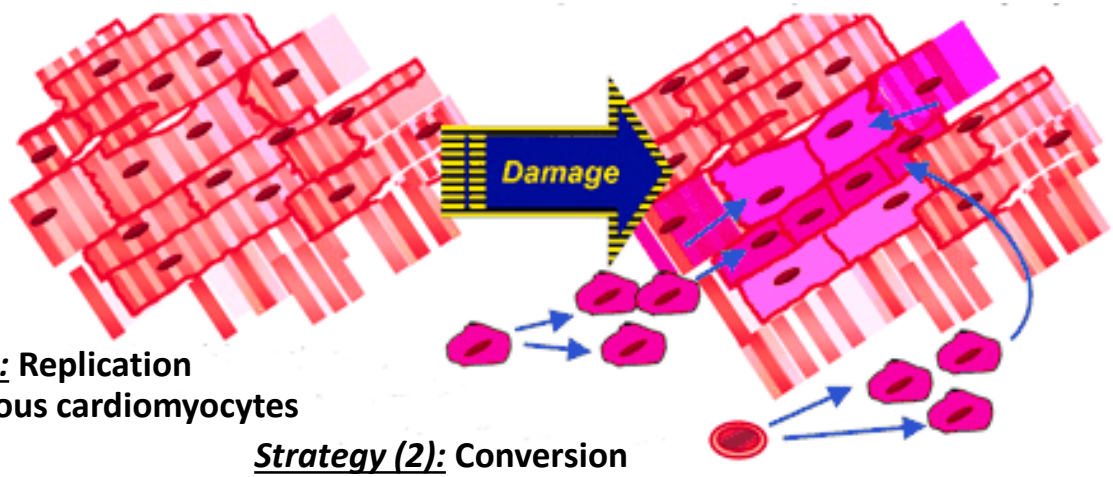
- two stem cells
- two cells destined for differentiation

Asymmetric division:

- one stem cell and one differentiating cell



Usual Outcome: **Replacement of heart muscle with SCAR TISSUE**



Strategy (1): **Replication of endogenous cardiomyocytes**

Strategy (2): **Conversion of stem cells into new cardiomyocytes**

Grounds MD et al. *J Histochem Cytochem.* 2002;50:589-610.

STEM CELL THERAPY

- Clinical trials focused on 3 main situations:
  - Acute MI (with the hope of preventing LVSD)
  - Chronic heart failure secondary to previous MI
  - DCM (non ischemic cardiomyopthy)

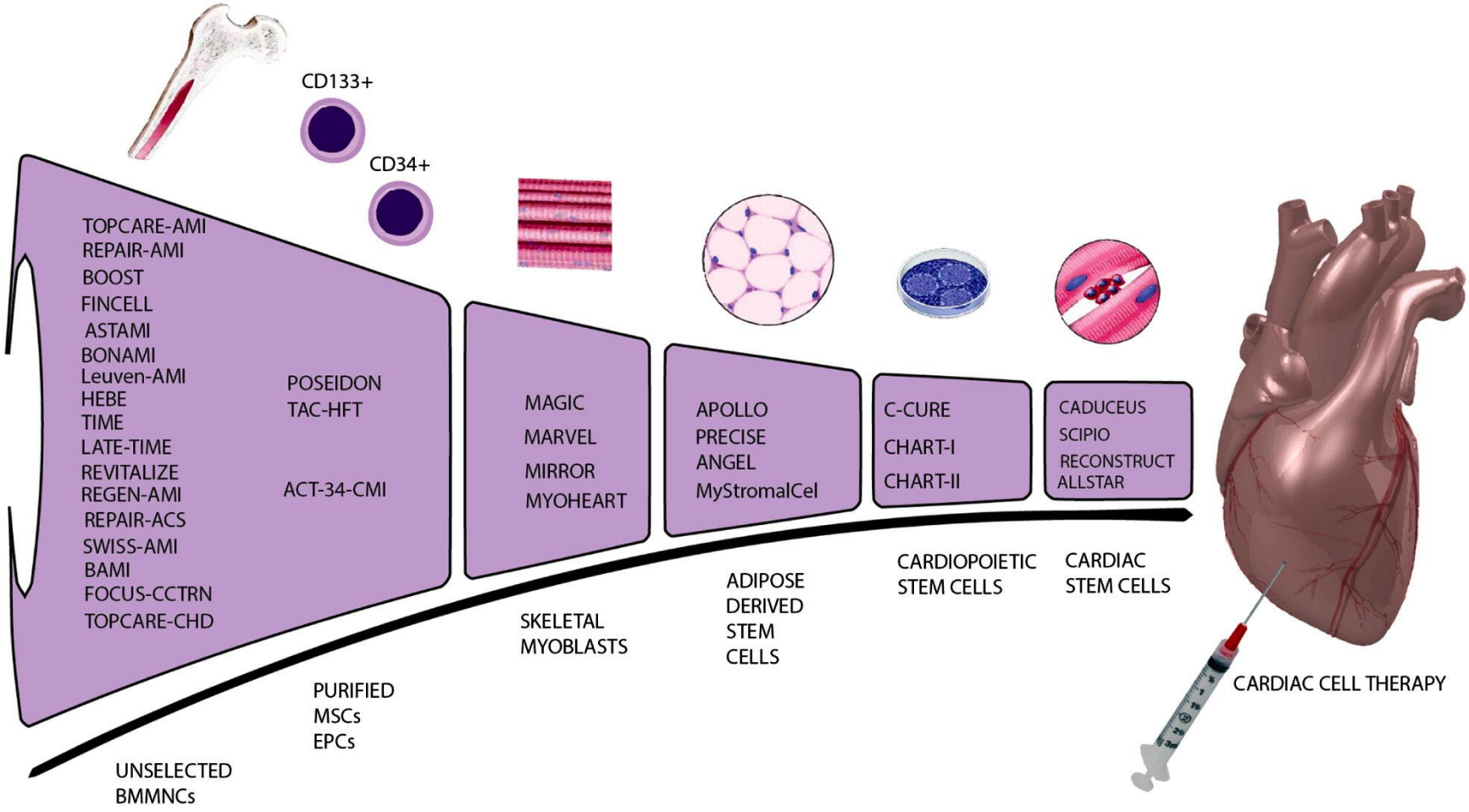
- Main areas of discussion:

1. Stem cell types used in cardiac repair

2. Methods of cell delivery in clinical practice

3. Clinical trial evidence to date

CLINICAL TRIALS AND CELL THERAPY



Cell therapy in acute myocardial infarction

- Most of the trials used intracoronary delivery of BMSCs following successful stenting of the infarct-related artery

- Surrogate markers used to assess efficacy of cell therapy:
  - Improvements in the LVEF
  - Reduction in size of scar tissue
  - Reduction in cardiac volume

- Post infarction heart failure:
  - results from ventricular remodeling processes
  - characterized by progressive expansion of the infarct area and dilation of the LV cavity

STEM CELL THERAPY IN ACUTE MI

- Major goal to reverse LV remodeling:
  - enhancement of regeneration of cardiac myocytes
  - stimulation of neovascul. within the infarct area

- Main randomized controlled trials (RCTs) published with positive findings:

1. TOPCARE-AMI (Circulation - 2002)
2. BOOST trial (Lancet - 2004)
3. REPAIR-AMI trial (EJM - 2006)
4. FINCELL (Eur Heart J - 2008)

CELL THERAPY IN ACUTE MI

RCTs with neutral findings:

- LEUVEN-AMI study[1]:
  - No changes in global LVEF after BMSC infusion

- ASTAMI trial[2] :
  - No significant effect on the LVEF, LV volumes, or infarct size

- HEBE trial[3] :
  - No changes in global or regional LV systolic function after BMSC therapy

[1]Janssens et al. Lancet 2006;367:113–21

[2] Lunde K et al. N Eng J Med 2006;355:1199–209

[3]Alexander Hirsch et al. Eur Heart J 2010

RCTs OF INTRACORONARY BMSC THERAPY AFTER ACUTE MI

Study name (ref)	Date published	*n*	Days after AMI	Primary outcome
TOPCARE-AMI[41]	2002	59	4.3 ± 1.5	Improvement in global LVEF from 51.6 ± 9.6% to 60.1 ± 8.6% ($P = 0.003$) at 4 months
BOOST[42]	2004	60	5.1 ± 1.3	Improvement in global LVEF at 6 months but effect was only maintained in large infarcts at long-term follow-up
REPAIR-AMI[43]	2006	187	3–6	Improvement in the LVEF at 4 months by 2.5% above baseline
ASTAMI[46]	2006	97	6 ± 1	No change in the LVEF at 6 months
LEUVEN-AMI[45]	2006	66	1	No change in global LVEF at 4 months but there was improvement in regional contractility and infarct size in patients with the largest infarcts
FINCELL[44]	2008	77	3	Improvement in the LVEF at 6 months by 5% above baseline
HEBE[47]	2010	200	3–8	No change in global LVEF at 4-month follow-up

AMI, acute myocardial infarction; BMSC, bone marrow stem cells; *n*, number of patients; LVEF, left ventricular ejection fraction.

STEM CELL THERAPY IN ACUTE MI

Reasons for the inconsistent findings:

1. Variations in the number of cells delivered
2. Timing of delivery after AMI
3. Differences in the cell isolation protocol
4. Others

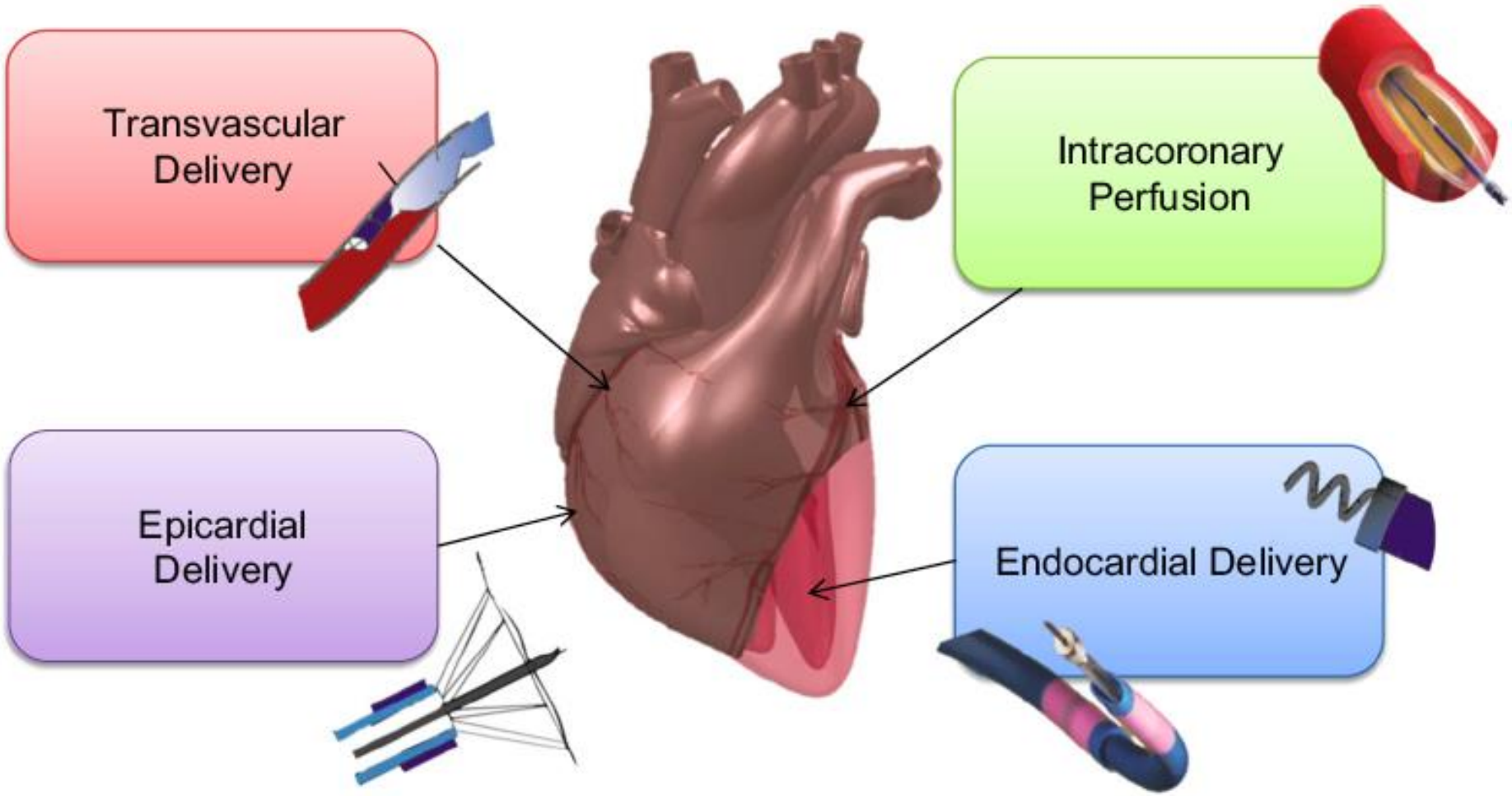
SECOND GENERATION STEM CELL THERAPY

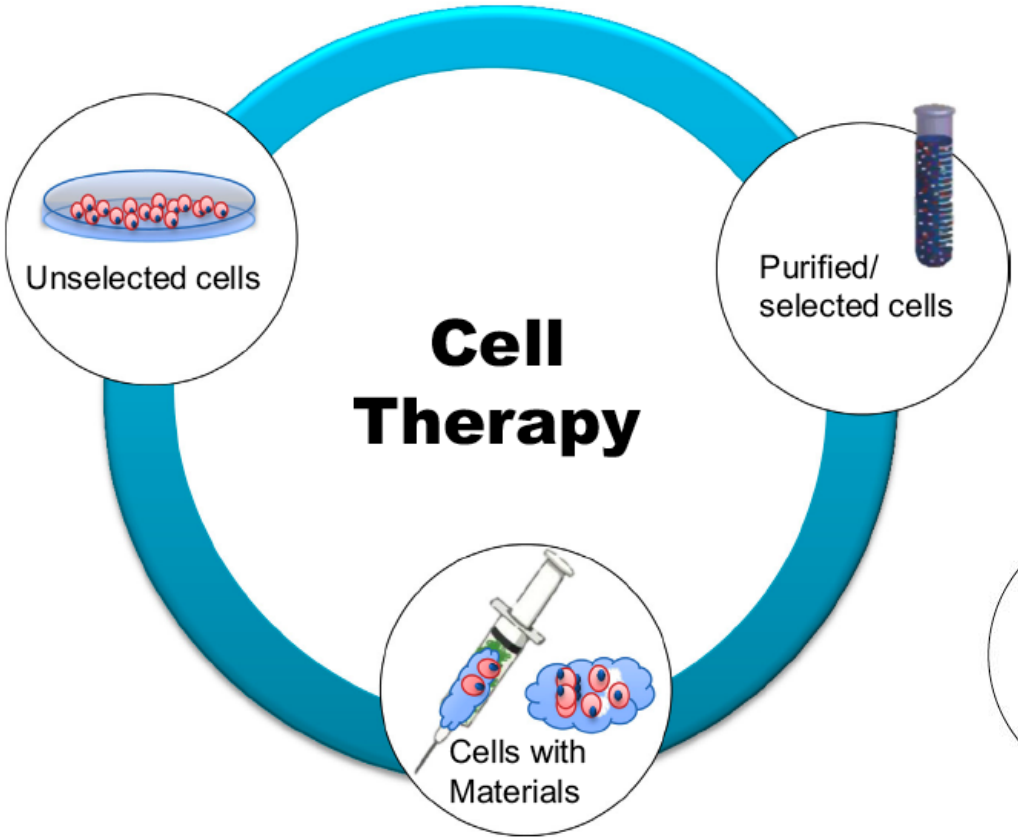
Table 1 Clinical trials evaluating new stem cells for cardiac repair following myocardial infarction

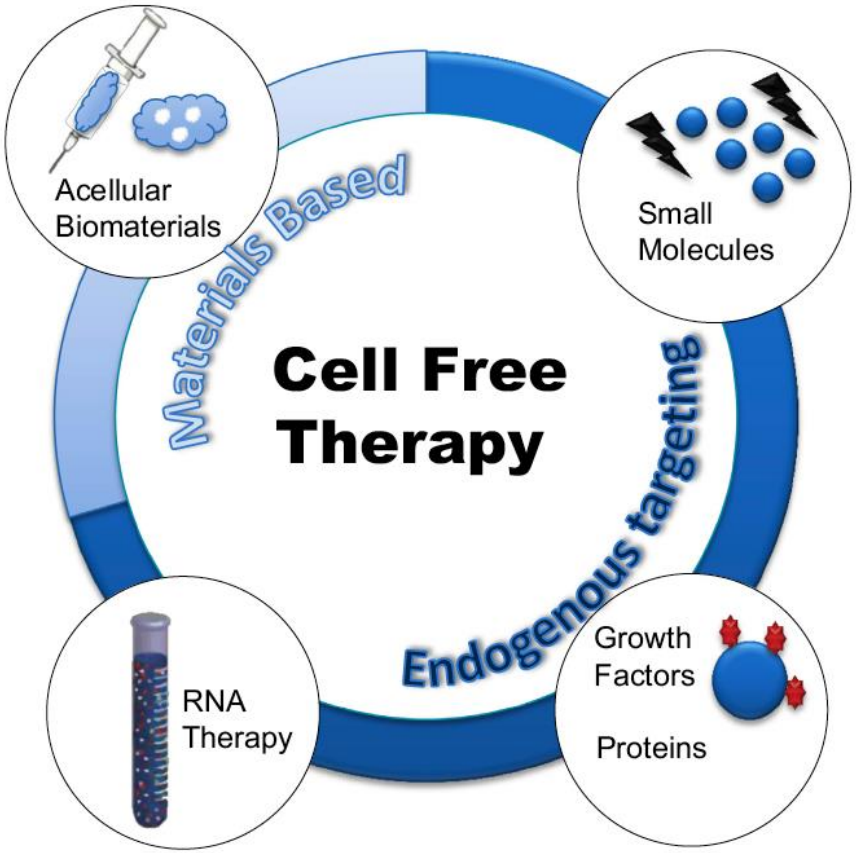
Study	*n*	Design	Type of cells	Delivery route	Clinical setting	Follow-up	Outcomes
Bartunek *et al*[95] (C-CURE)	47	Multicenter, randomized 2:1 (cells *vs* standard of care)	Autolo-gous bone marrow derived cardiopoietic MSCs	Endo-myocardial injection	Chronic ischemic heart failure (LVEF 15%-40%)	Safety 2 yr Efficacy 6 mo	Feasible and safe ↑ LVEF ↓ LVESV ↑ 6-min walk distance and improvements in QoL and NYHA
Bolli *et al*[113] (SCIPIO)	23	Unicenter, randomized 2:1 (cells *vs* standard of care)	Autolo-gous c-kit+/lin- CSCs	Intra-coronary infusion	Chronic ischemic heart failure (LVEF ⩽ 40% four months post CABG)	12 mo	Feasible and safe ↑ LVEF ↓ Infarct size
Malliaras *et al*[122] (CADUCEUS)	25	Two centers, randomized 2:1 (cells *vs* standard of care)	Autolo-gous CDCs	Intra-coronary infusion	Chronic ischemic heart failure (1.5-3 mo after MI)	12 mo	Feasible and safe ↓ Infarct size ↑ Viable myocardium and regional contractility ≈ LVEF and ventricular volumes
Hare *et al*[144] (POSEIDON)	30	Multicenter, randomized 1:1 (autologous *vs* allogeneic cells)	Three different doses of autologous or allogeneic bone marrow derived MSCs	Endo-myocardial injection	Chronic ischemic heart failure (LVEF ⩽ 50%)	12 mo	Feasible and safe ≈ LVEF Autologous ↑ 6-min walk distance and QoL Allogeneic ↓ LVEDV

↑: Indicates increased; ↓: Indicates decreased; ≈: Indicates no change; MI: Myocardial infarction; MSCs: Mesenchymal stem cells; LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end-systolic volume; QoL: Quality of life; CSCs: Cardiac stem cells; CABG: Coronary artery by-pass graft; CDCs: Cardiosphere-derived cells; LVEDV: Left ventricular end-systolic volume.

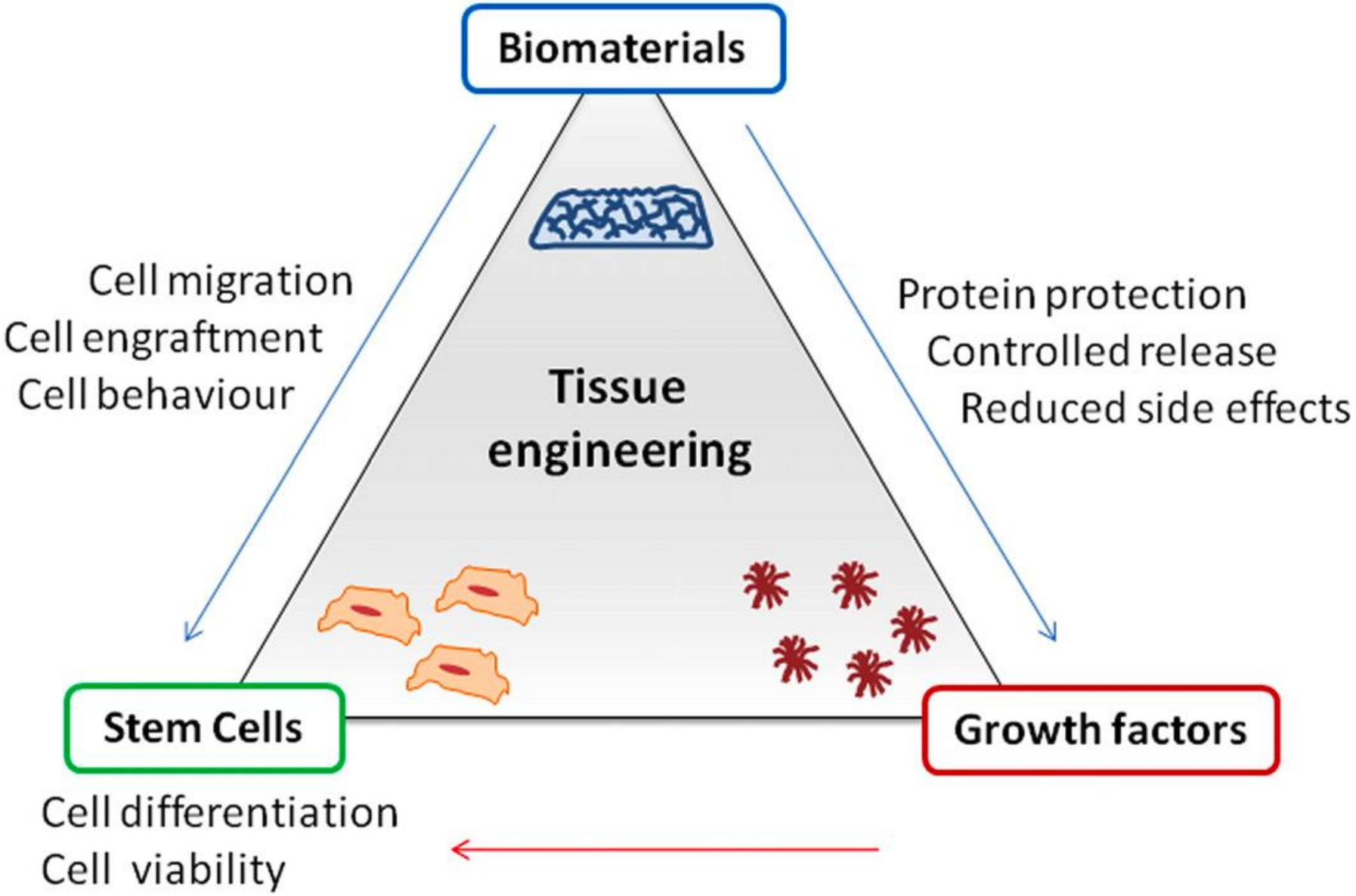
CURRENT ACCESS ROUTES FOR CELL THERAPY



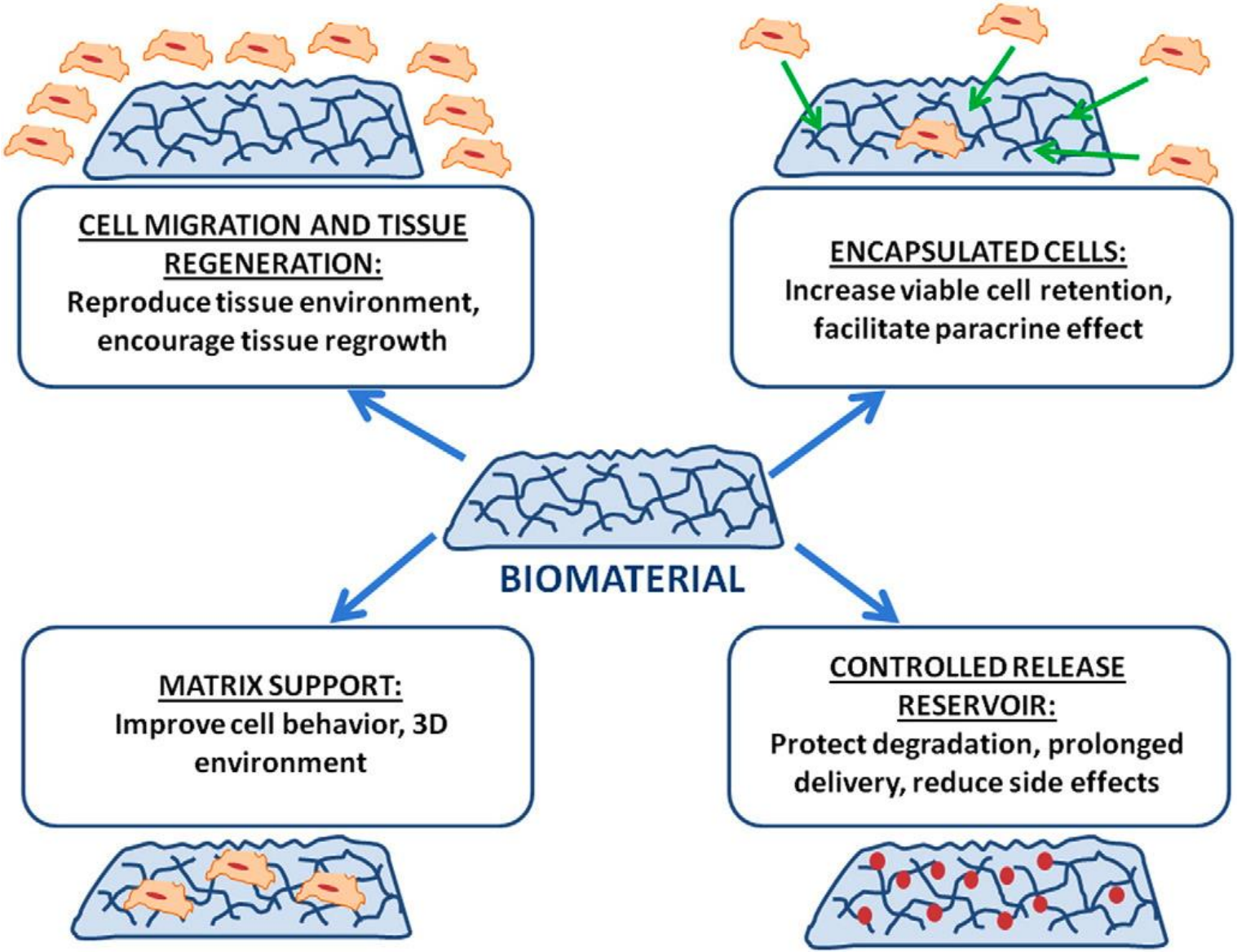

Unselected cells
Purified/
selected cells
Cell
Therapy
Cells with
Materials


Acellular
Biomaterials
Small
Molecules
Materials Based
Cell Free
Therapy
Endogenous targeting
RNA
Therapy
Growth
Factors
Proteins

THE TISSUE ENGINEERING TRIAD

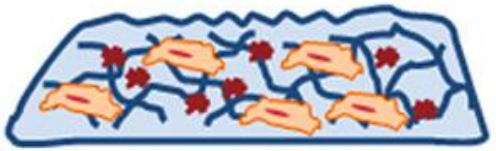


PRINCIPAL BENEFITS OF BIOMATERIALS

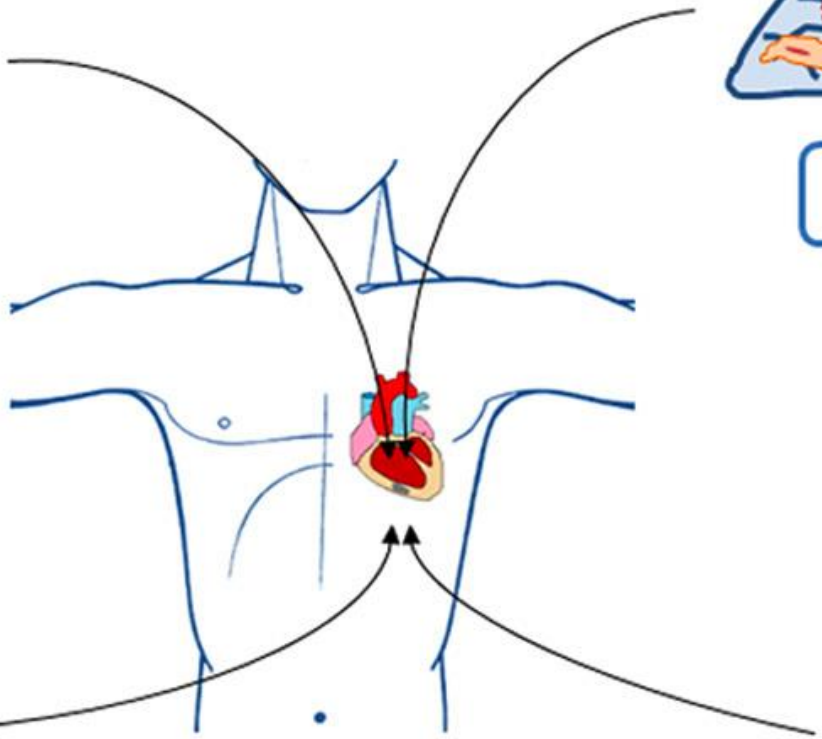


TYPES OF DRUG DELIVERY SYSTEMS MADE OF BIOMATERIALS

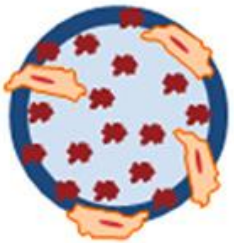
NANOFIBERS



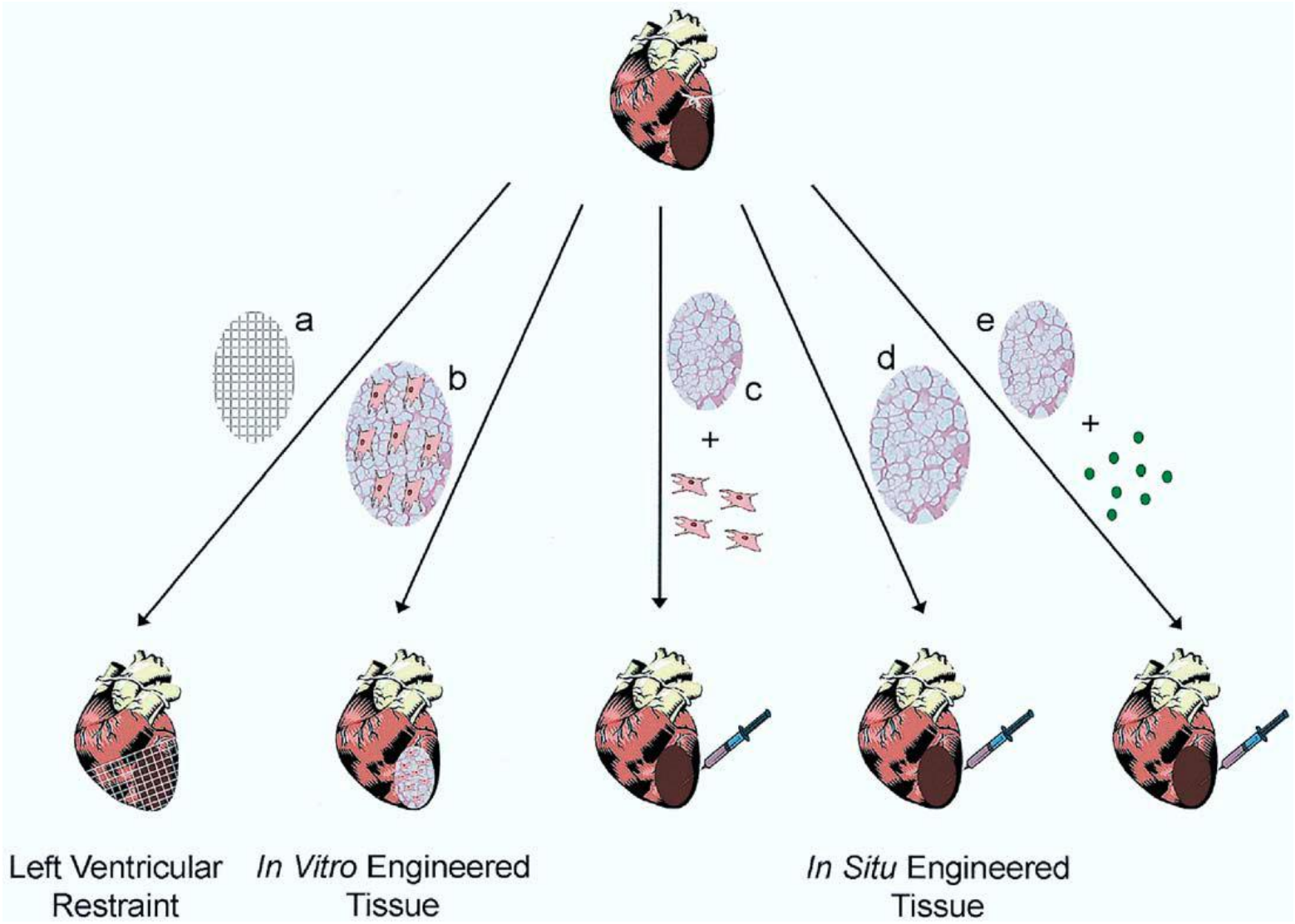
HYDROGELS



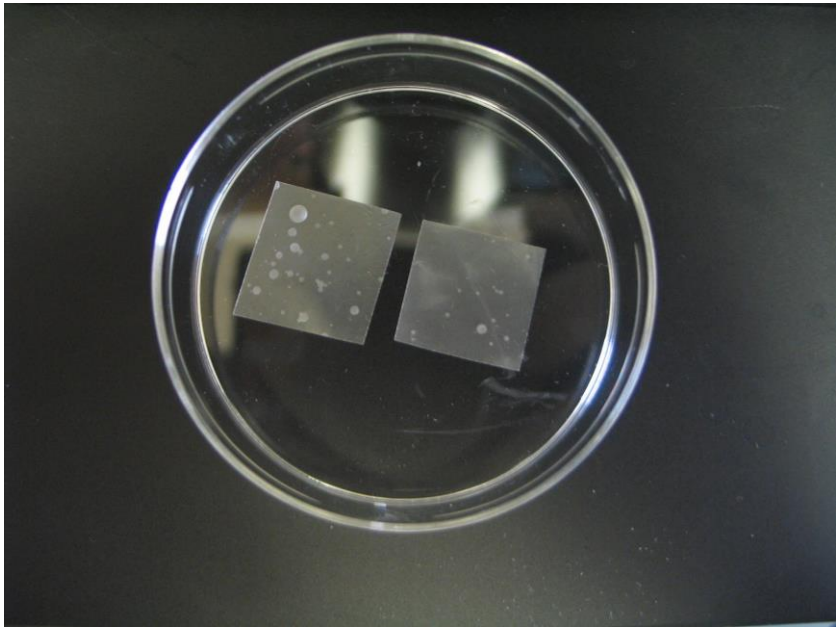
LIPOSOMES

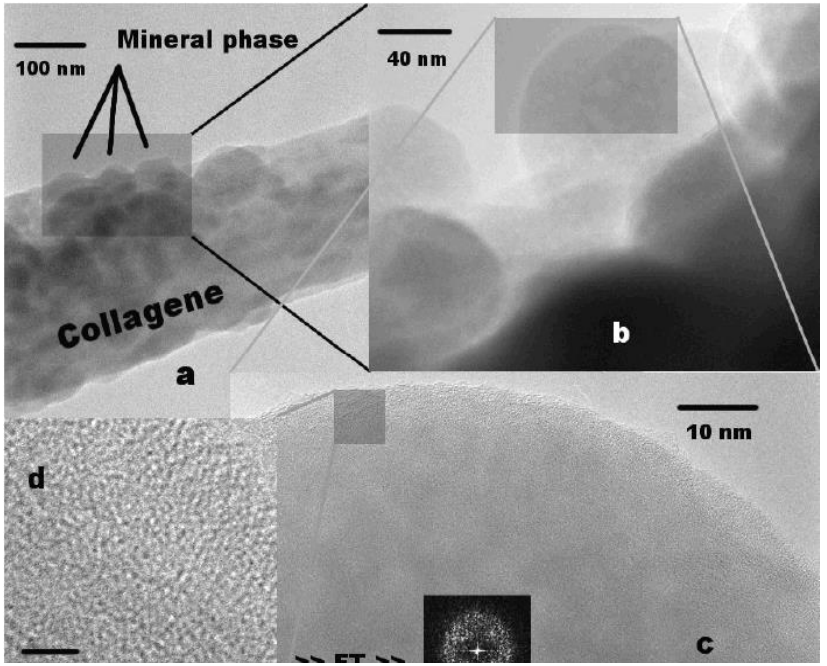


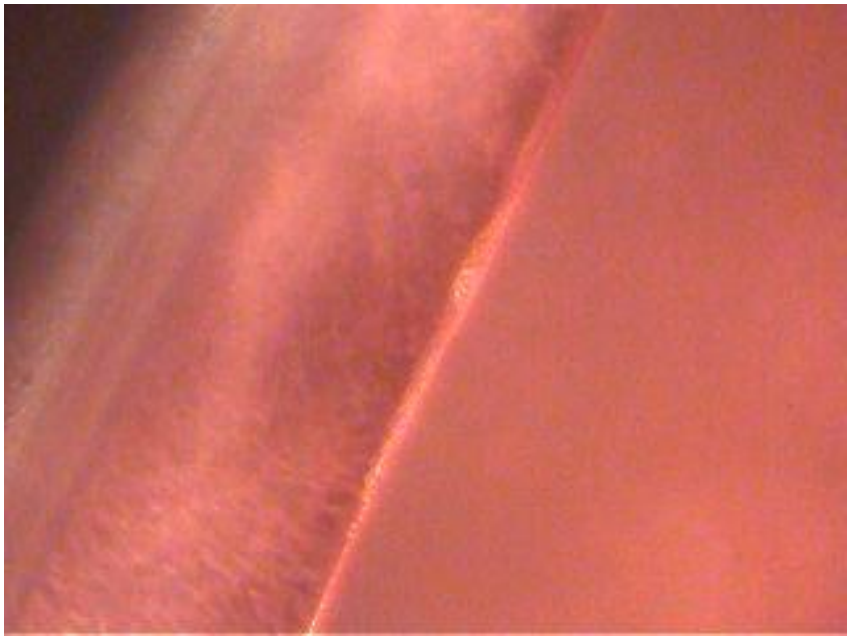
NANO AND MICRO-PARTICLES



***Christman KL. et al*, JACC 2006**



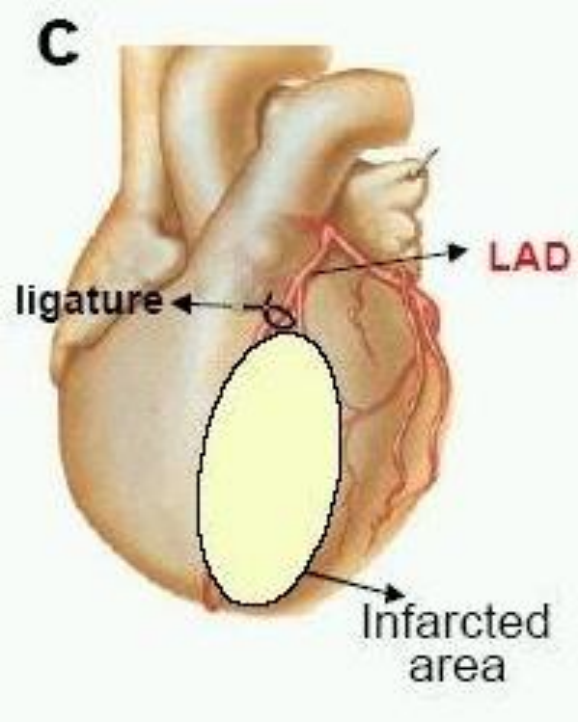


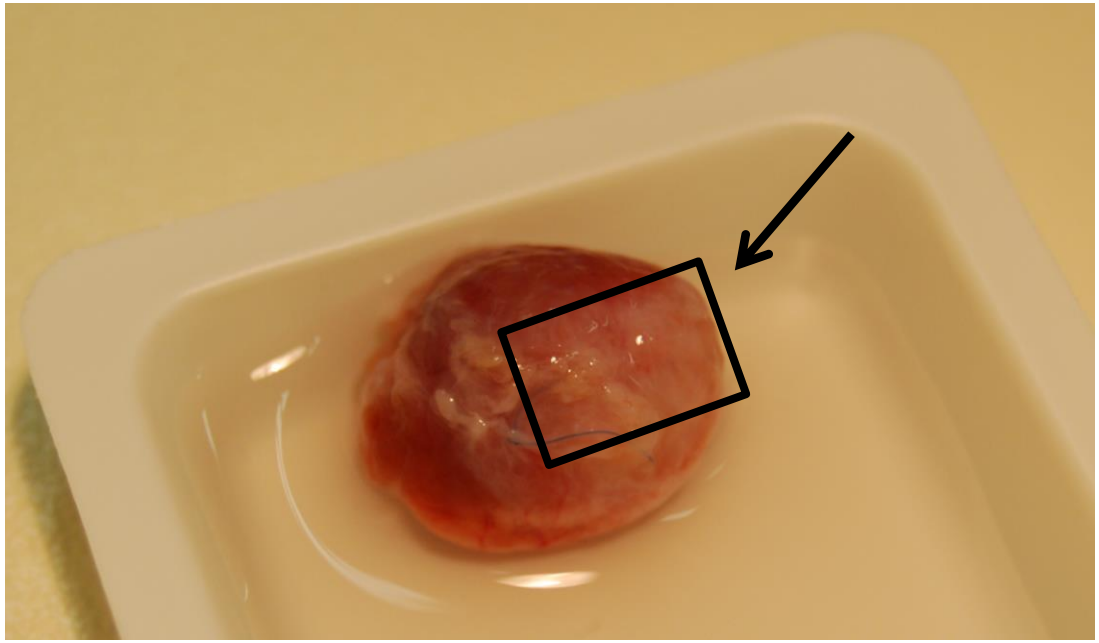


D4

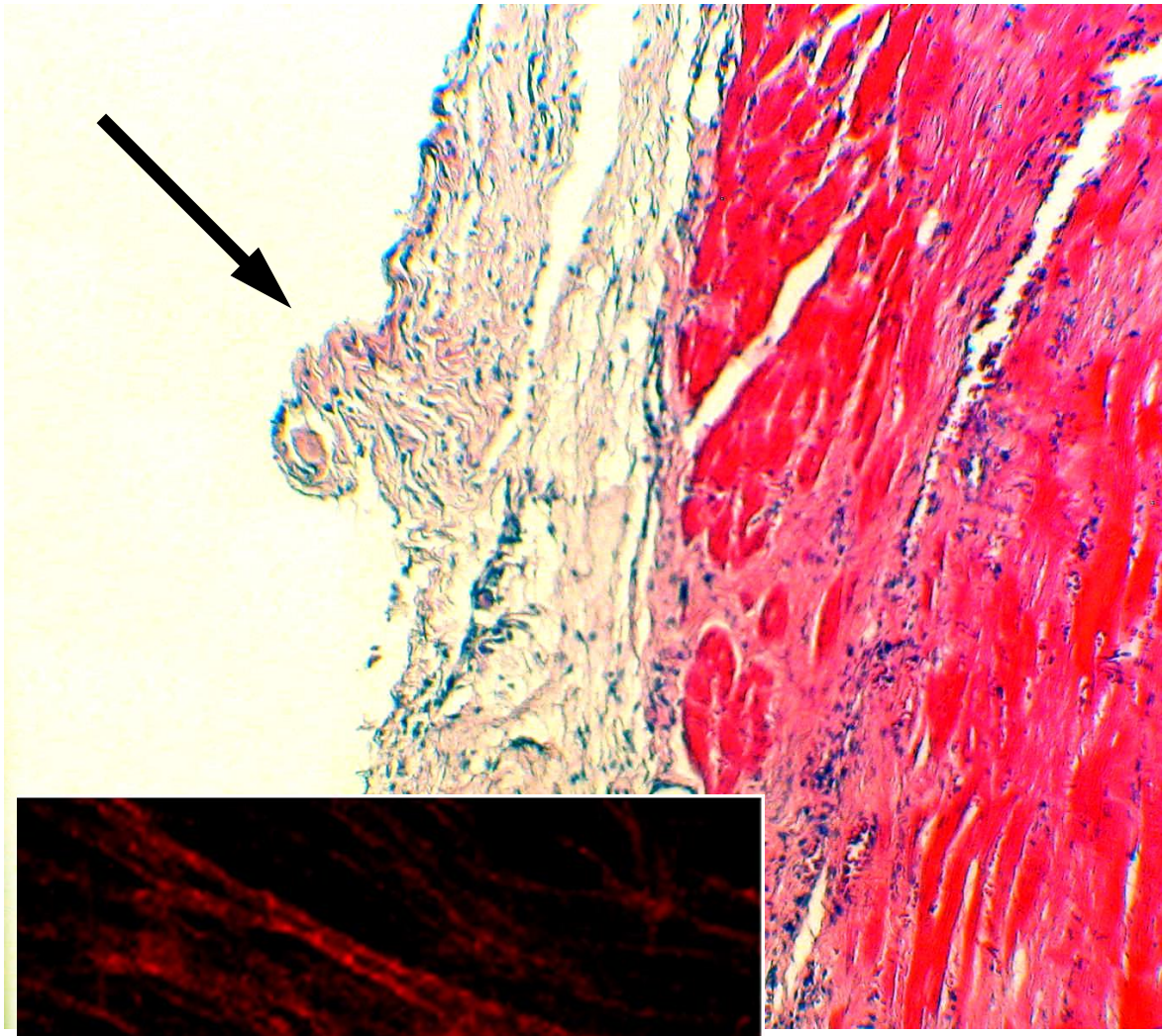
D8

Rat model of myocardial infarction (WKY, N=20)



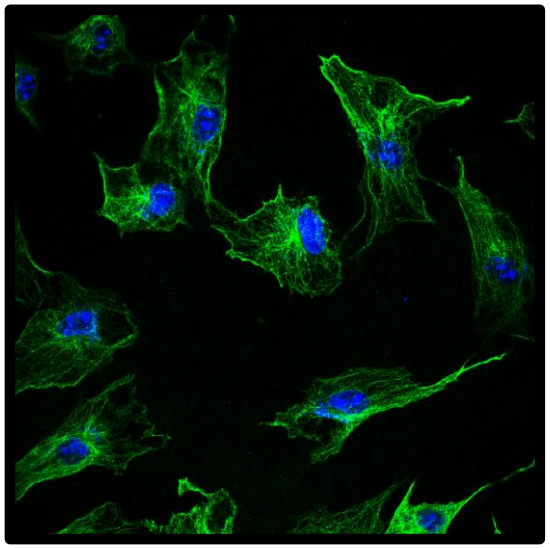


Membranes 8 weeks following AMI

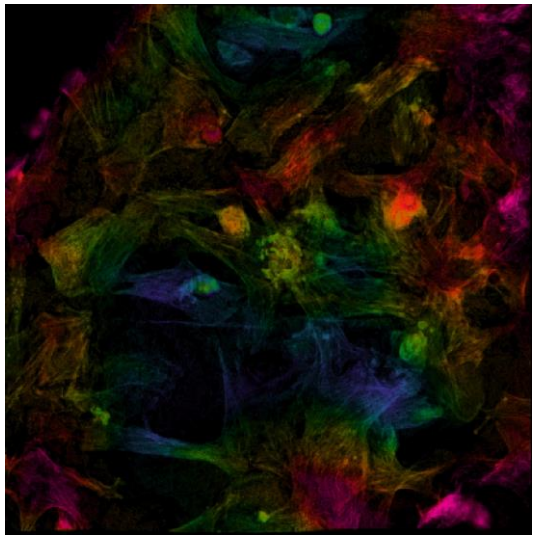


H&E

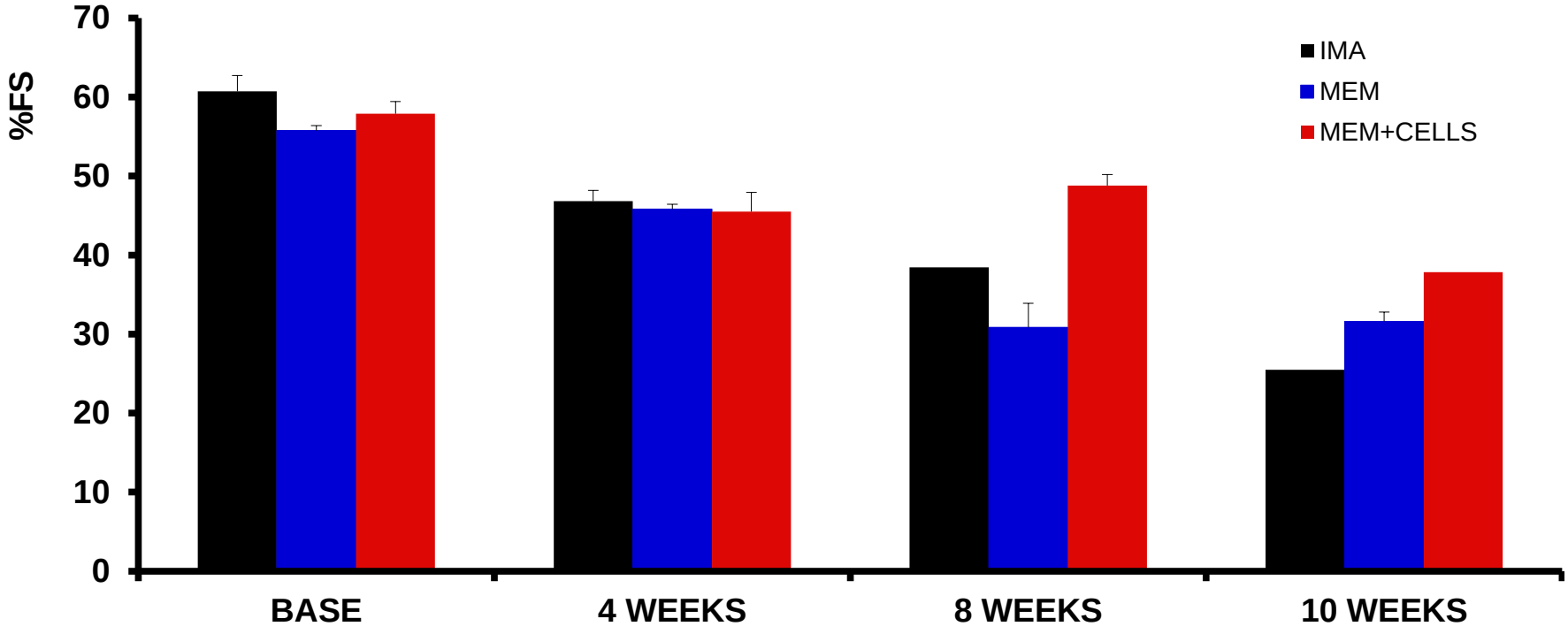
(Phalloidin, 20×)

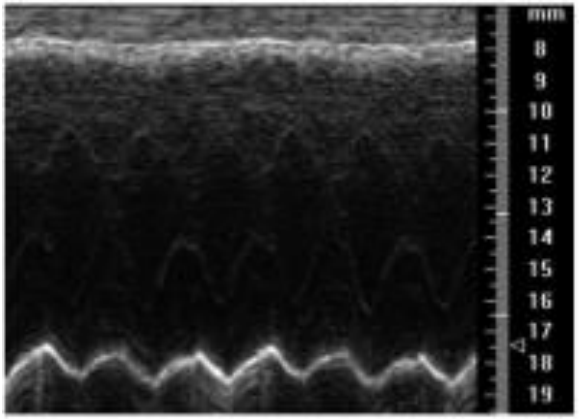


(C-Troponin, 40x)

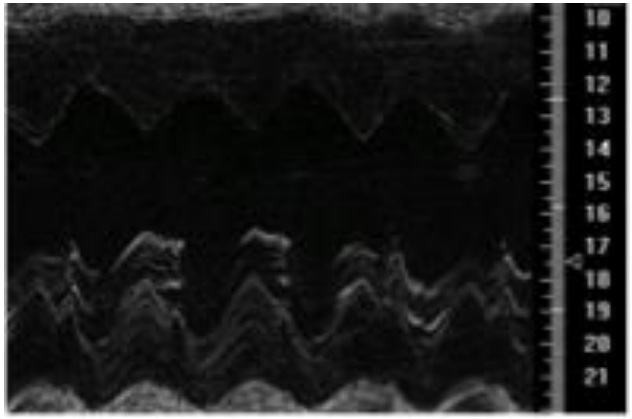


(Phalloidin, 20x)

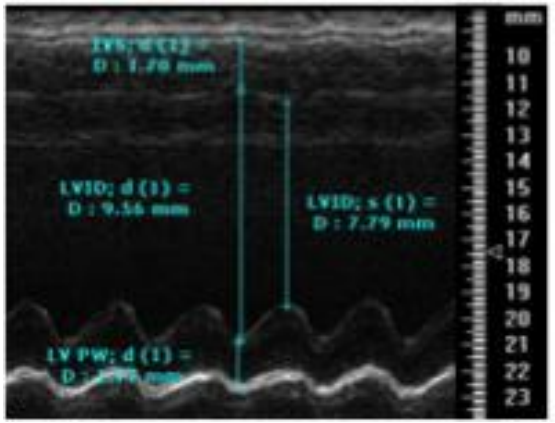




IMA

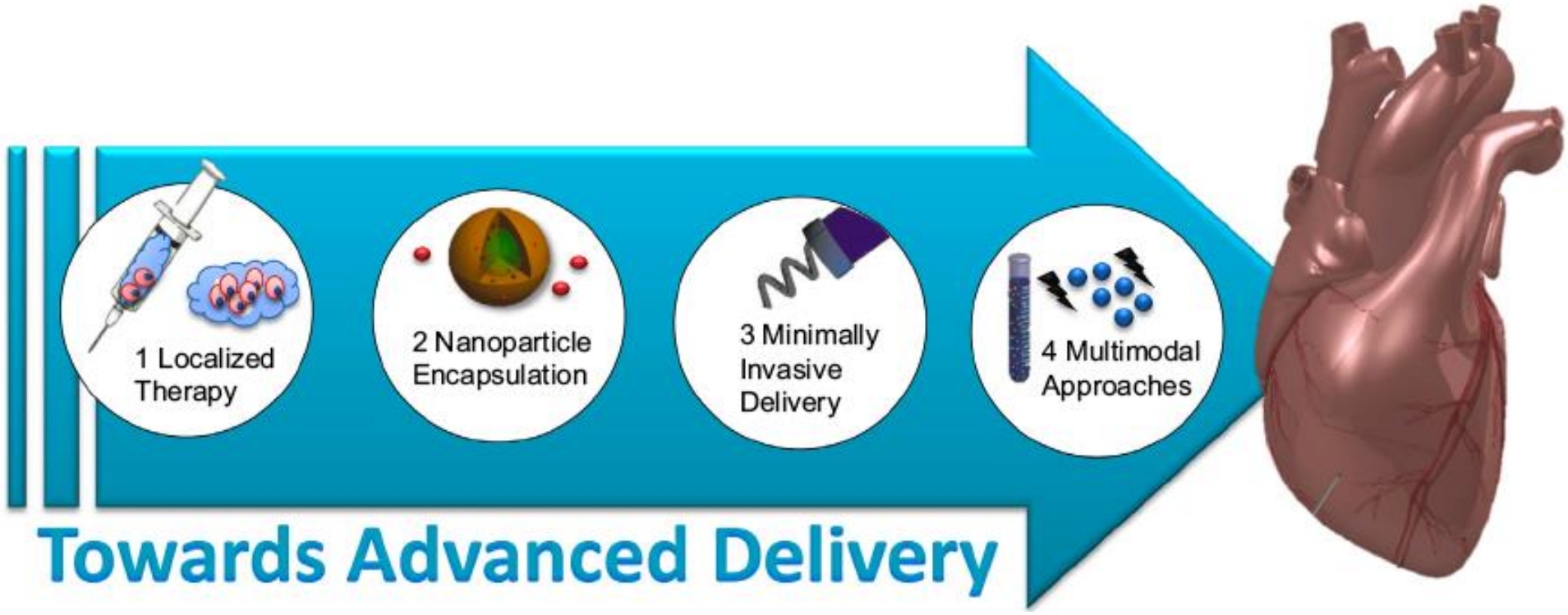


MEM

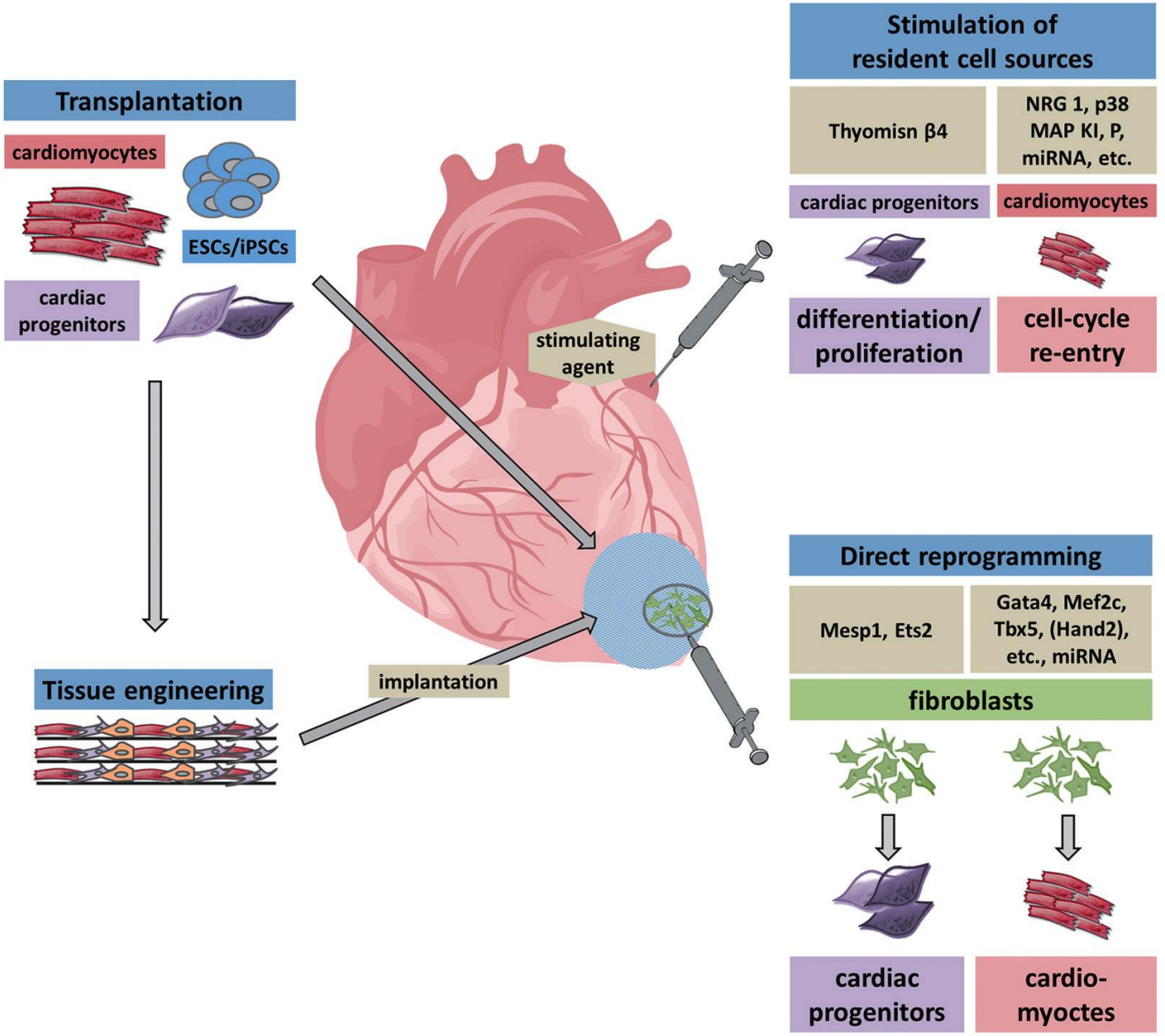


MEM + CELLS

ADVANCED DELIVERY



FUTURE CONCEPTS FOR REGENERATIVE THERAPIES



CONCLUSIONS

- Past decade has seen an explosion in clinical studies investigating the safety and efficacy of Cell therapy for heart diseases.
- Safety of SC therapy has been demonstrated uniformly in the vast majority of the studies.
- Beneficial effects of cell therapy have been not fully demonstrated: AMI, chronic ischemic HF and DCM.
- New technologies and advances also led to ”Second Generation SC”, Protein (Growth factors) and Biomaterials therapy showing promising effects.
- Need for larger RCTs with longer term follow-up assessing morbidity and mortality as primary outcome measures.