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Cell therapy for the treatment of coronary heart disease: a critical appraisal

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Nature Reviews Cardiology 2010; 7: 204-215

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Introduction(1)

- AMI is a leading cause of death worldwide
- Improvement of therapy leads to decreased early mortality
- BUT results in higher incidence of HF among survivors[1]

1 Velagelati et al.; Circulation 2008; 118: 2057-2062

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Introduction(2)

Problems for regenerative cell therapy

- Cardiomyocyte deficit could be in the order of 1 billion cells[2]
- Diversity of cell types
- Homing and survival of the infused cells

2 Rabey et al.; J. Mol. Cell. Card. 2008; 45: 567-581

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Trials

Table 1 | Randomized trials in patients with acute myocardial infarction or ischemic heart failure

Trial name	Number of patients	Cell type	Dose	Route of delivery	Timing of delivery	Primary end point	Comments
Acute myocardial infarction							
BOOST	60	nBMC	128 ml	i.c.	Day 6±1	LVEF ↑	Effect diminished after 18 and 61 months
REPAIR-AMI	187	mnBMC	50 ml	i.c.	Day 3–6	LVEF ↑	NA
Leuven-AMI	66	mnBMC	130 ml	i.c.	Day 1	LVEF ↔	Regional contractility ↑ Infarct size ↓
ASTAMI	97	mnBMC	50 ml	i.c.	Day 6±1	LVEF ↔	NA
FINCELL	77	mnBMC	80 ml	i.c.	Day 3	LVEF ↑	NA
REGENT	117	mnBMC (unselected vs $CD34^+$/ $CXCR4^+$)	50–70 ml (unselected) 100–120 ml (selected)	i.c.	Day 3–12	LVEF ↑ with both cell types	NA
HEBE	189	mnBMC vs mnPBC	60 ml (mnBMC) 150 ml (mnPBC)	i.c.	Day 3–8	Regional contractility ↔	NA
Ischemic heart failure							
MAGIC	97	SkM	400 or 800×10^6	i.m.	>Week 4	LVEF ↔	LVEDV ↓ LVESV ↓
TOPCARE-CHD	58	mnBMC vs CPC	50 ml	i.c.	Month 81±72	LVEF ↑ (mnBMC) LVEF ↔ (CPC)	NA

Only patients with complete imaging studies are considered here. Dose refers to the average amount of bone marrow or peripheral blood that was harvested, or the number of transplanted skeletal myoblasts. Abbreviations: ↓, decreased; ↑, increased; ↔, no significant change; CPC, circulating blood-derived progenitor cells; i.c., intracoronary; i.m., intramuscular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; mnBMC, mononucleated bone marrow cells; mnPBC, mononucleated peripheral blood cells; NA, not applicable; nBMC, nucleated bone marrow cells; SkM, skeletal myoblasts.

Wollert and Drexler; Nat. Rev. Cardiol. 2010; 7: 204-215

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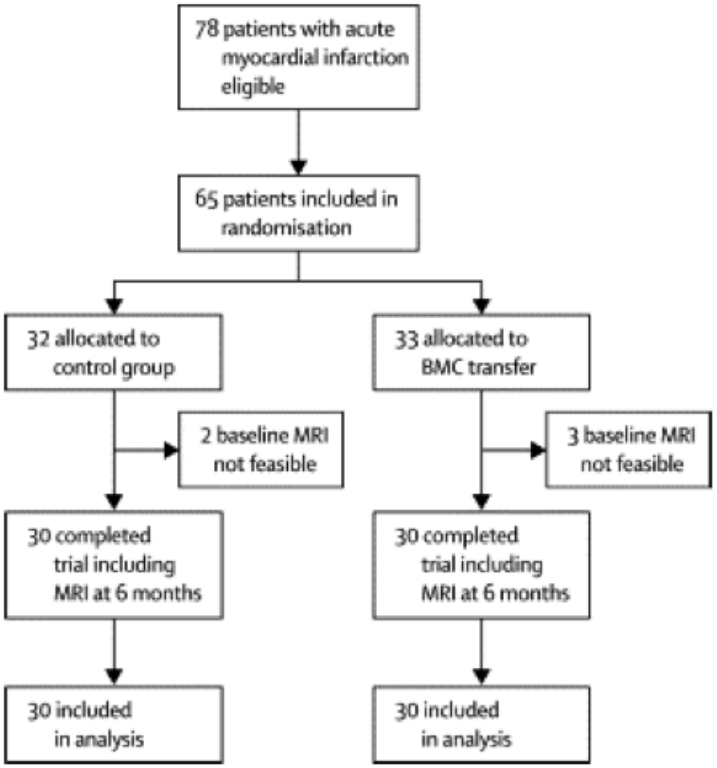
BOOST-Trial(1)

Methods



PCI after acute STEMI

↓

Baseline MRI after 3.5 d

↓

Standard therapy +/- BMC i.c. after 4.8 d

↓

Cardiac MRI and CA after 6 months

Video

Wollert et al.; Lancet 2004; 364: 141-148

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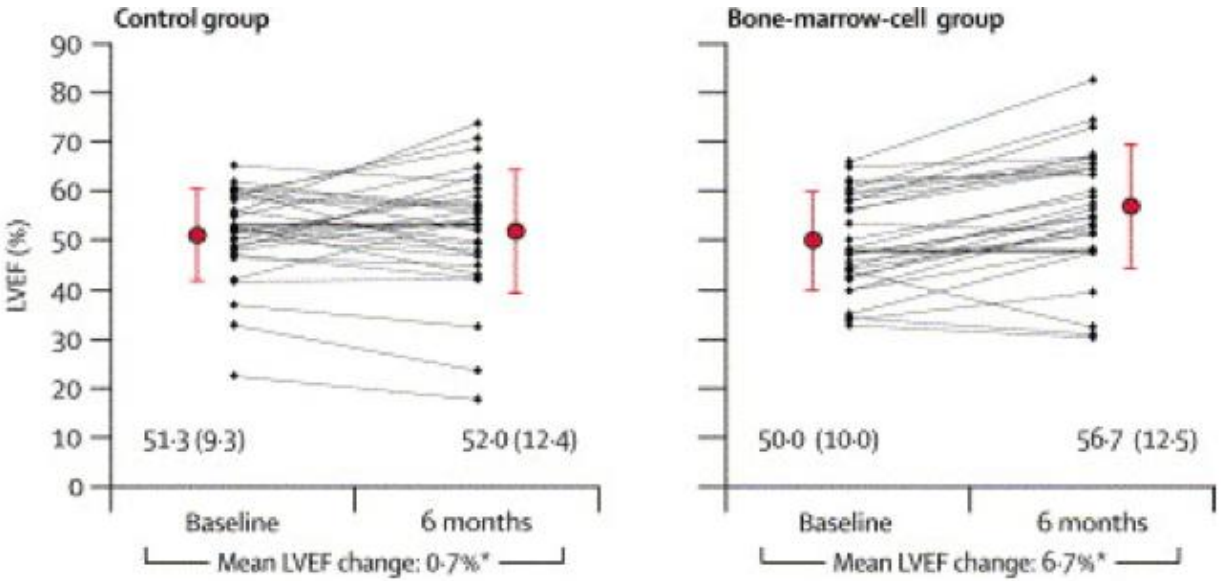
BOOST-Trial(2)

Results



Wollert et al.; Lancet 2004; 364: 141-148

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BOOST-Trial(3)

Results

	Baseline		6 months		Change		BMC treatment effect†	p
	Controls	BMC group	Controls	BMC group	Controls	BMC group		
Regional LVEF (%)	47·8 (9·7)	46·3 (10·6)	48·9 (15·2)	53·0 (15·5)	1·1 (11·8)	6·7 (9·5)	5·7 (0·2 to 11·3)	0·04
Systolic wall motion (mm), infarct region	3·9 (1·8)	4·4 (1·9)	4·9 (2·9)	5·9 (2·5)	1·0 (2·5)	1·5 (2·1)	0·6 (-0·6 to 1·8)	0·32
Systolic wall motion (mm), border zone	6·8 (1·6)	7·0 (1·7)	6·8 (2·1)	8·0 (2·1)	–0·1 (2·2)	1·0 (1·9)	1·1 (0·1 to 2·1)	0·03

BMC=bone-marrow cell. Data are mean (SD). Treatment effects are expressed as differences in least-squares means (ANCOVA model) and 95% CI· There were no differences between groups at baseline·

***Table 3*: Regional LVEF and systolic wall motion as determined by contrast-enhanced MRI at baseline and 6 months' follow-up**

Wollert et al.; Lancet 2004; 364: 141-148

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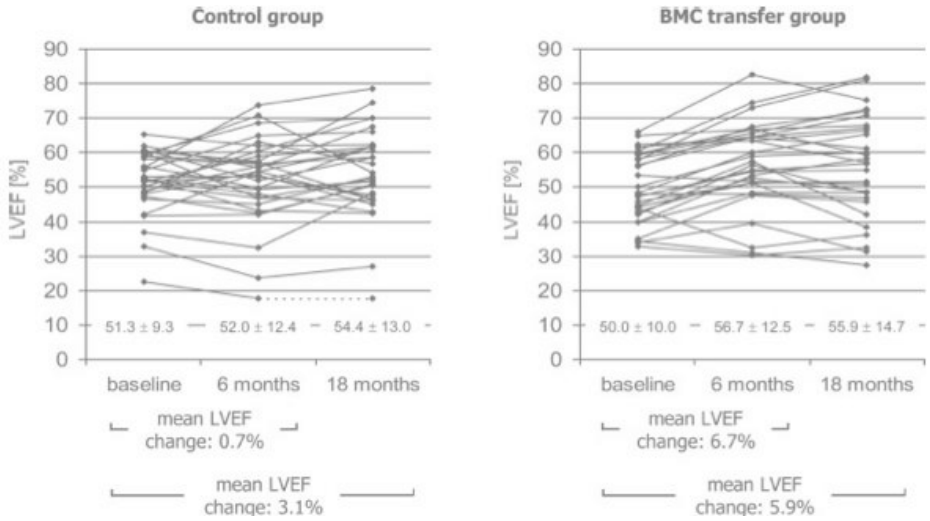
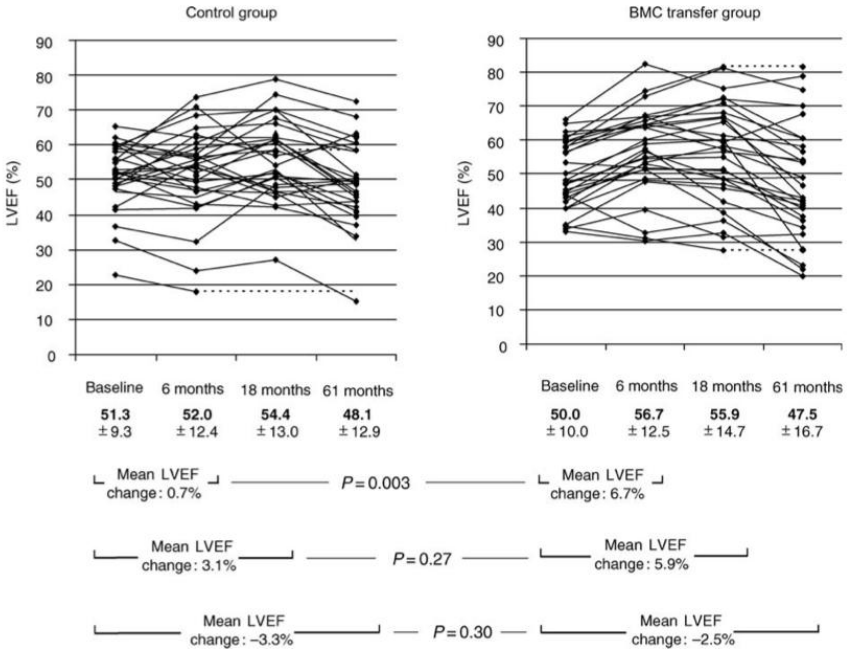
BOOST-Trial(4)

Further Results



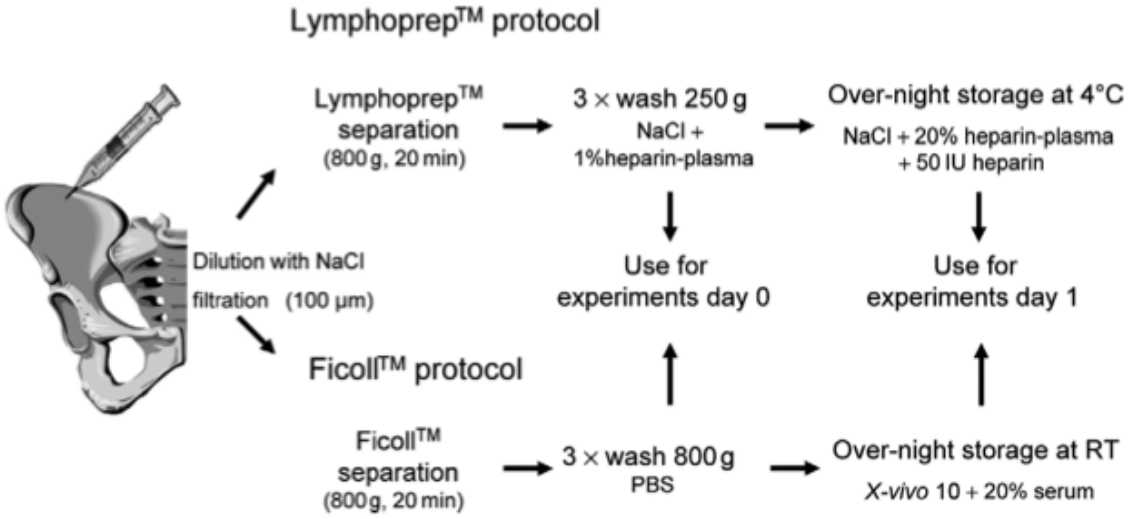


Meyer et al.; Circulation 2006; 113: 1287-1294

Meyer et al.; Eur. Heart J. 2009; 30: 2978-2984

Considerations

- Heterogeneity of methods / procedural details
- Patier
- Curre

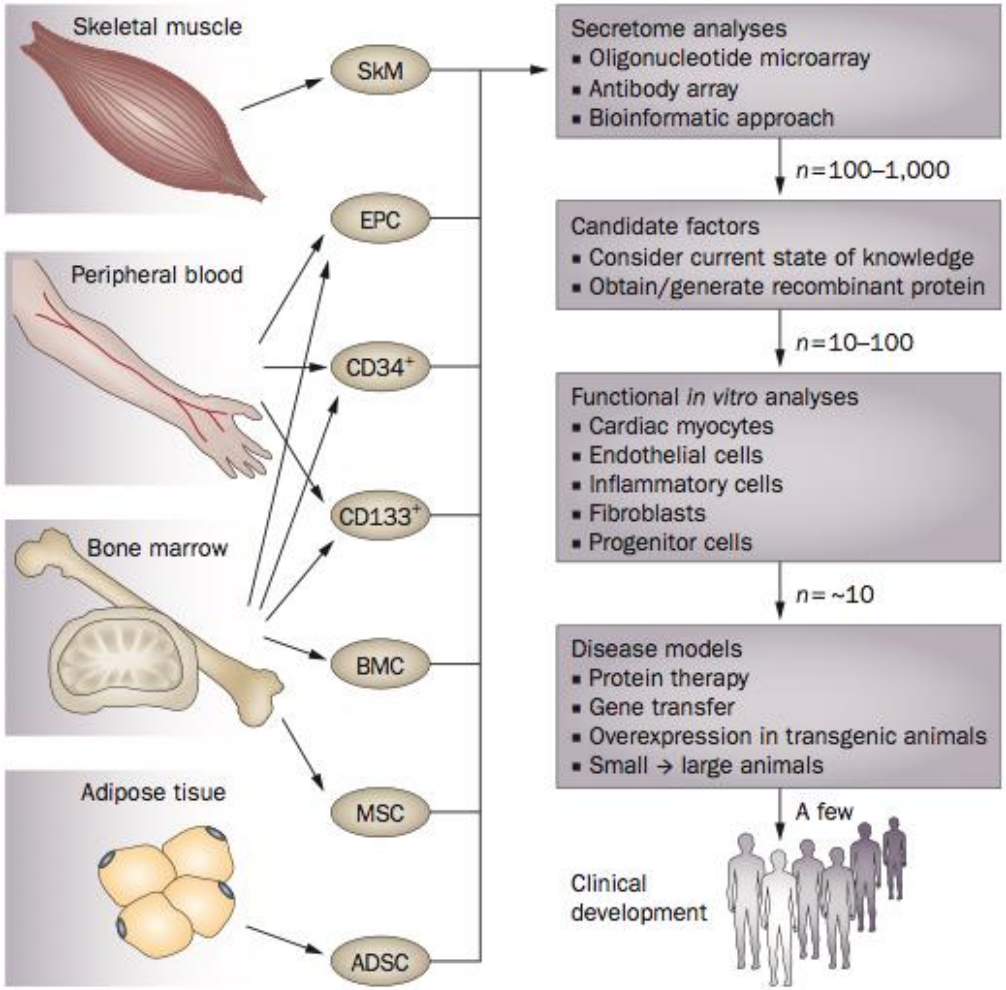


Seeger et al.; Eur Heart J. 2007; 28: 766-772

Wollert and Drexler; Nat. Rev. Cardiol. 2010; 7: 204-215

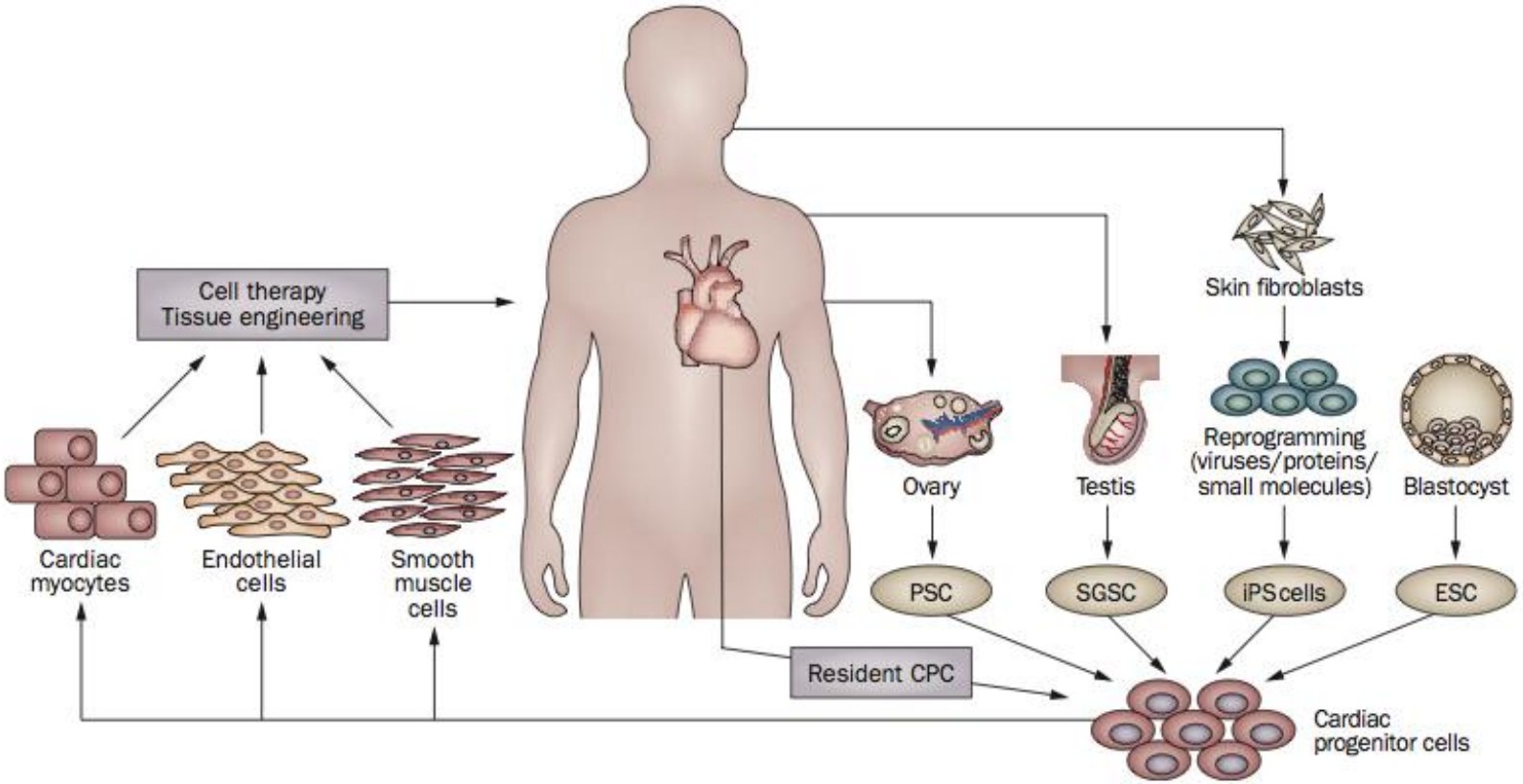
Future of cell therapy

- Paracrine effects
- Pluripotent stem cells



Wollert and Drexler; Nat. Rev. Cardiol. 2010; 7: 204-215

Sources of CPCs



Wollert and Drexler; Nat. Rev. Cardiol. 2010; 7: 204-215

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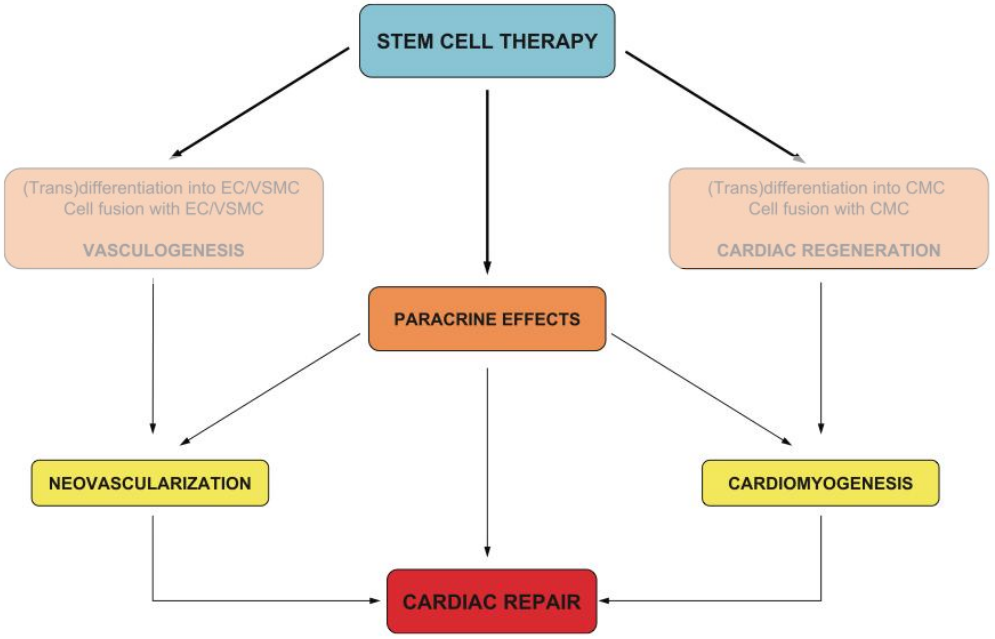
Conclusion

- Inconsistent trial results

- Paracrine factors



Gnecchi et al.; Circ. Res. 2008; 103: 1204-1219

Wollert and Drexler; Nat. Rev. Cardiol. 2010; 7: 204-215

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Thank you for your attention!