The Future of Regenerative Medicine in Cardiac surgery

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Professor of Cardiovascular Surgery

Rajaei cardiovascular Medical & Research Center

Tir 1397 July 2018

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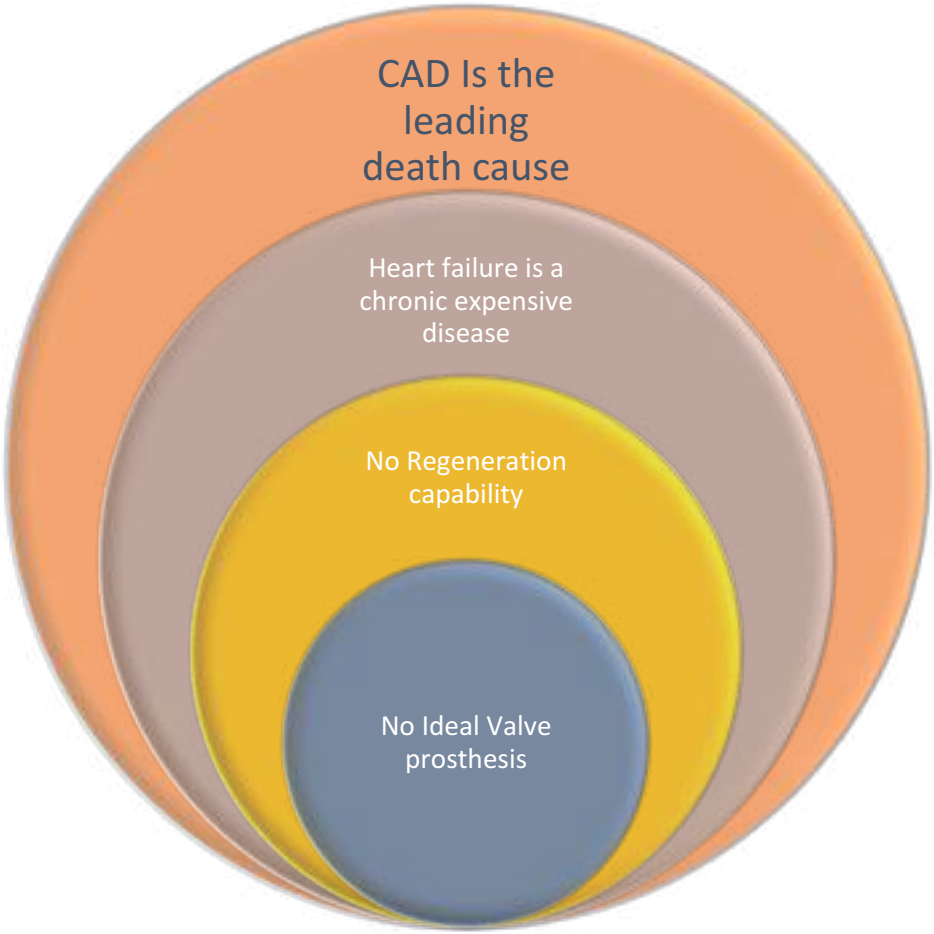
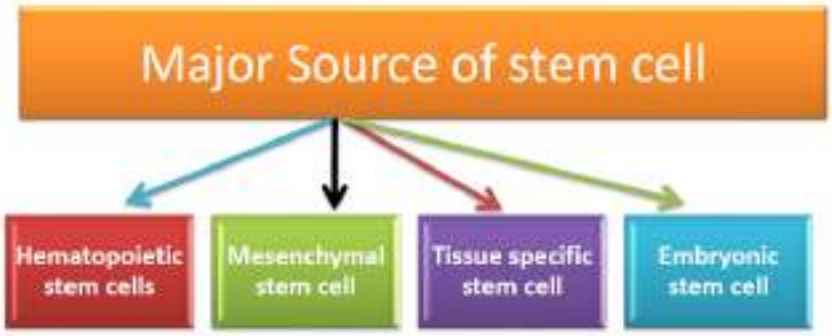

CAD Is the leading death cause
Heart failure is a chronic expensive disease
No Regeneration capability
No Ideal Valve prosthesis


Major Source of stem cell
Hematopoietic stem cells
Mesenchymal stem cell
Tissue specific stem cell
Embryonic stem cell

Original papers

Med Ultrason 2015, Vol. 17, no. 2, 160-166
DOI: 10.11152/mu.2013.2066.172.effbm

Effectiveness of bone marrow mononuclear cells delivered through a graft vessel for patients with previous myocardial infarction and chronic heart failure: an echocardiographic study of left ventricular remodeling.

Fujian Duan*[1], Zhi Qi*[1], Sheng Liu[2], Xiuzhang Lv[1], Hao Wang[1], Yiming Gao[1], Jianpeng Wang[1]

[1]Department of Echocardiography, [2]Department of Cardiovascular Surgery, Fuwai Hospital & Cardiovascular Institute, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Tsinghua University, Peking Union Medical College, Beijing, China.

Table I. Baseline Characteristics

Clinical date	CABG+BMMNC group (n=24)	CABG group (n=18)	P value
Age,y	57.88±8.52	56.56±9.09	0.881
Man,%	95.8	94.4	0.679
BSA,m2	1.81±0.12	1.78±0.13	0.723
NYHA function class	3 (2,3)	2 (2,3)	0.239
No.of grafts	4 (4,5)	4 (4,5)	0.331
CPB time,min	90(61,103)	89(78,116)	0.198
Clamping time,min	60(50,67)	55(48,70)	0.868
Ventilation time,h	16(13,20)	17(14,20)	0.332
ICU stay,days	3(3,5)	3(3,4)	0.221
6-min walking test	452(408,495)	433(382,497)	0.206
BNP,ng/L	1302(714,1676)	890(680,1646)	0.431
Hypertension,%	16.7	11.1	0.481

Table III. Echocardiographic parameters in CABG group

	pre-surgen (mean±SD)	1 year later (mean±SD)	P value
LVEDD (mm)	56.66±6.76	54.61±6.64	0.364
LVESD (mm)	45.67±6.27	41.66±8.05	0.105
LVEDV (ml)	167.61±42.10	156.78±36.30	0.414
LVESV (ml)	106.94±27.68	95.56±28.92	0.236
LVEDVI (ml/m^2)	93.76±23.65	87.17±15.36	0.285
LVESVI (ml/m^2)	59.84±13.59	53.02±13.48	0.140
LV-mass (g)	242.11±60.56	233.50±60.51	0.672
LV-massI (g/m^2)	135.41±28.56	129.95±27.43	0.562
MR score	1.28±0.75	1.17±1.29	0.755

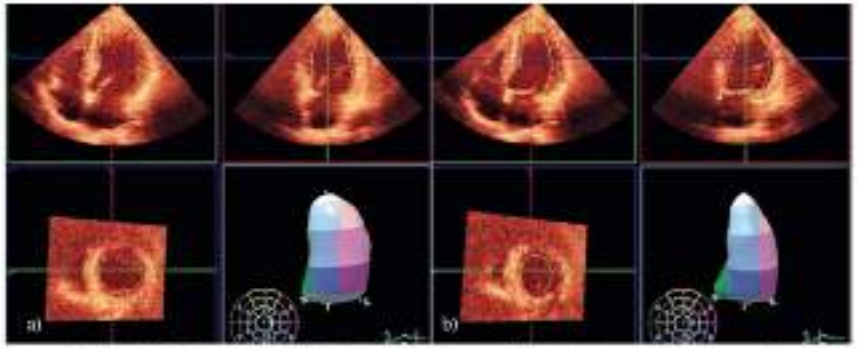


Fig 1. a) Apical 3D full-volume data set. Triplane is displayed. Para-sternal short-axis views are shown for completeness and to indicate the image plane position in the 3D images. End-diastolic volume of left ventricle is calculated and shown in the 3D imagings; b) Apical 3D full-volume data set. Triplane is displayed. Para-sternal short-axis views are shown for completeness and to indicate the image plane position in the 3D images. LVESV is calculated and shown in the 3D imagings.

Table II. Echocardiographic parameters in CABG+BMMNC group

	pre-surgen (mean±SD)	**1 year later (mean±SD)**	**P value**
LVEDD (mm)	60.96±5.26	52.29±5.94	0.000
LVESD (mm)	46.70±5.77	37.86±6.47	0.000
LVEDV (ml)	196.17±41.26	145.38±40.81	0.000
LVESV (ml)	126.04±28.22	82.04±34.02	0.000
LVEDVI (ml/m2)	108.14±20.94	80.72±22.59	0.000
LVESVI (ml/m2)	69.47±14.52	45.62±19.13	0.000
LV-mass (g)	267.25±67.97	222.88±60.44	0.021
LV-massI (g/m2)	147.37±35.33	123.53±32.45	0.019
MR score	1.42±0.65	1.04±0.71	0.061

European Heart Journal (2009) **30**, 662–670
doi:10.1093/eurheartj/ehn532

Improved regional function after autologous bone marrow-derived stem cell transfer in patients with acute myocardial infarction: a randomized, double-blind strain rate imaging study

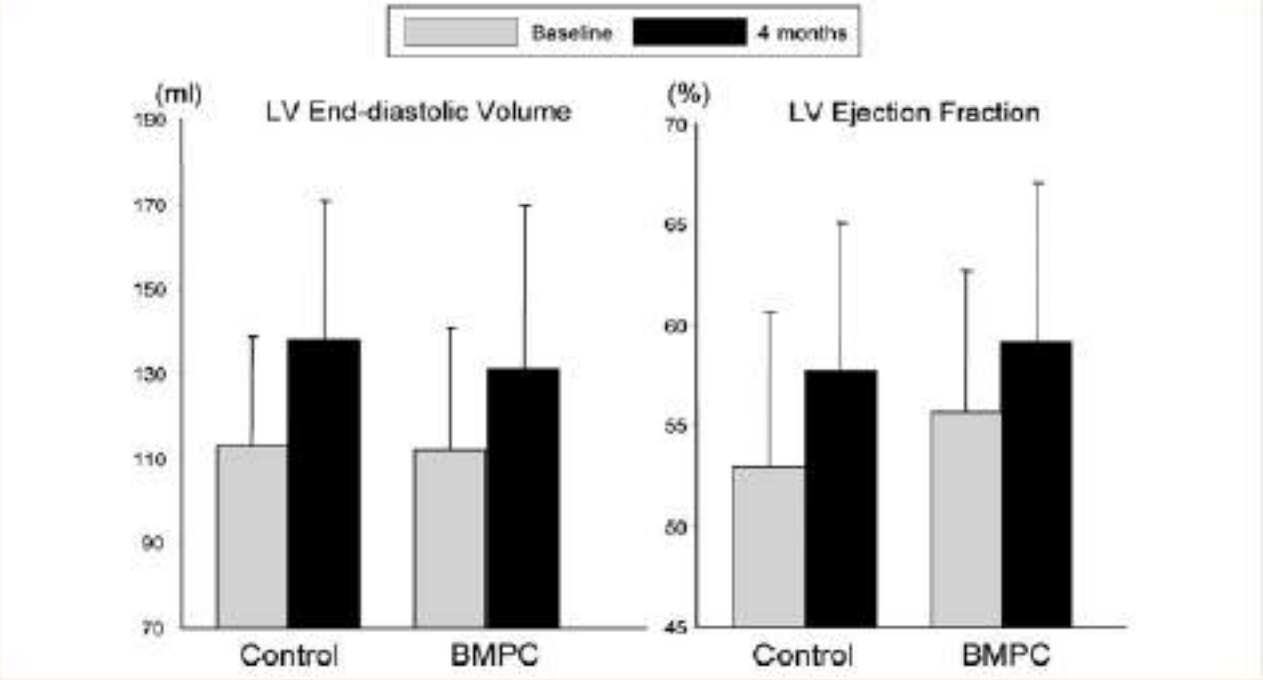


Figure 3 LV end-diastolic volume (mL) and LV ejection fraction (%) by ultrasound modified Simpson's method at baseline and at 4 months' follow-up in patients treated with bone-marrow progenitor cells (BMPCs) and in controls. Data are mean ± SD.

Clinical Track

Autologous Mesenchymal Stem Cells Produce Concordant Improvements in Regional Function, Tissue Perfusion, and Fibrotic Burden When Administered to Patients Undergoing Coronary Artery Bypass Grafting

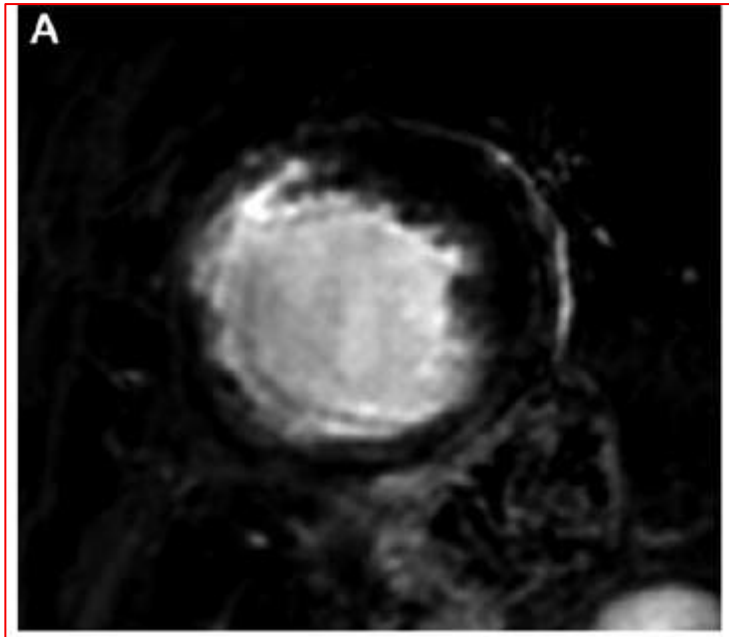
The Prospective Randomized Study of Mesenchymal Stem Cell Therapy in Patients Undergoing Cardiac Surgery (PROMETHEUS) Trial

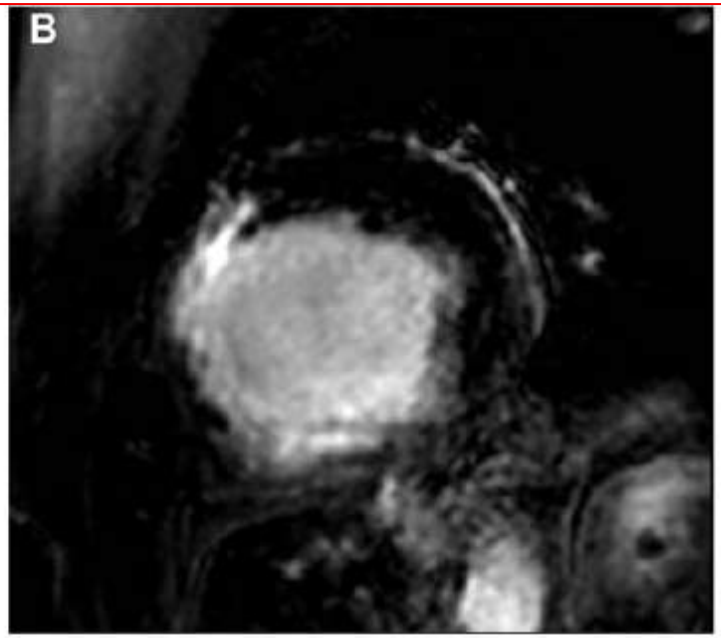
Vasileios Karantalis, Darcy L. DiFede, Gary Gerstenblith, Si Pham, James Symes,

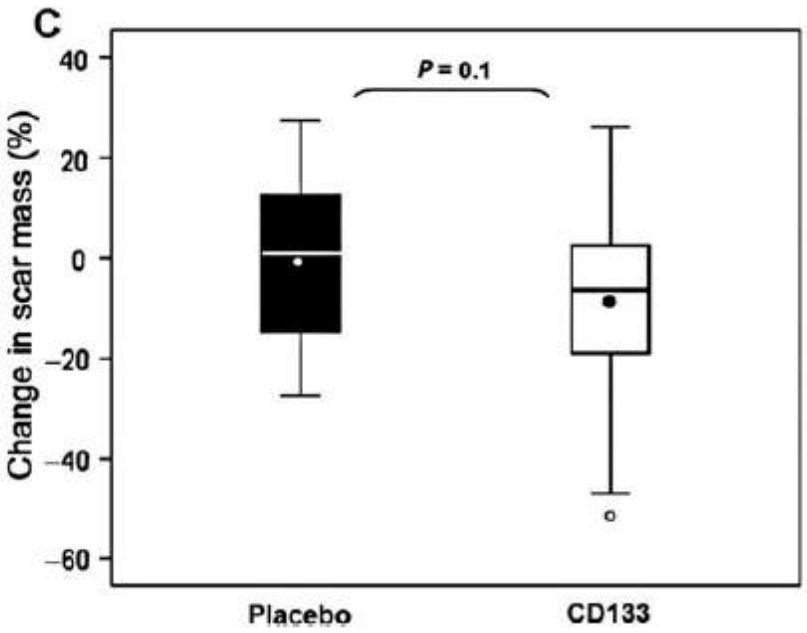
Here, we test the hypothesis that intramyocardial injections of autologous MSCs delivered to segments of myocardium not receiving surgical revascularization improve regional cardiac structure and function

- ***Methods and Results:*** **patients were injected with autologous MSCs into akinetic/hypokinetic myocardial territories not receiving bypass graft for clinical reasons.**

After 18 months, subjects receiving MSCs exhibited increased LV ejection fraction (+9.4±1.7%, *P*=0.0002) and decreased scar mass (−47.5±8.1%; *P*<0.0001) compared with baseline.


A


B


C
P = 0.1
Change in scar mass (%)
40
20
0
−20
−40
−60
Placebo
CD133

European Heart Journal (2014) **35**, 1263–1274
doi:10.1093/eurheartj/ehu007

CLINICAL RESEARCH
Stem cells

Autologous CD133$^+$ bone marrow cells and bypass grafting for regeneration of ischaemic myocardium: the Cardio133 trial†

[5]Berlin-Brandenburg Center for Regenerative Therapies, Berlin 13353, Germany

Conclusion Although there may be some improvements in scar size and regional perfusion, intra-myocardial injection of CD133$^+$ BMC has no effect on global LV function and clinical symptoms. Improvements in regional myocardial function are only detectable in patients with posterior infarction, probably because the interventricular septum after anterior infarction is not accessible by trans-epicardial injection.

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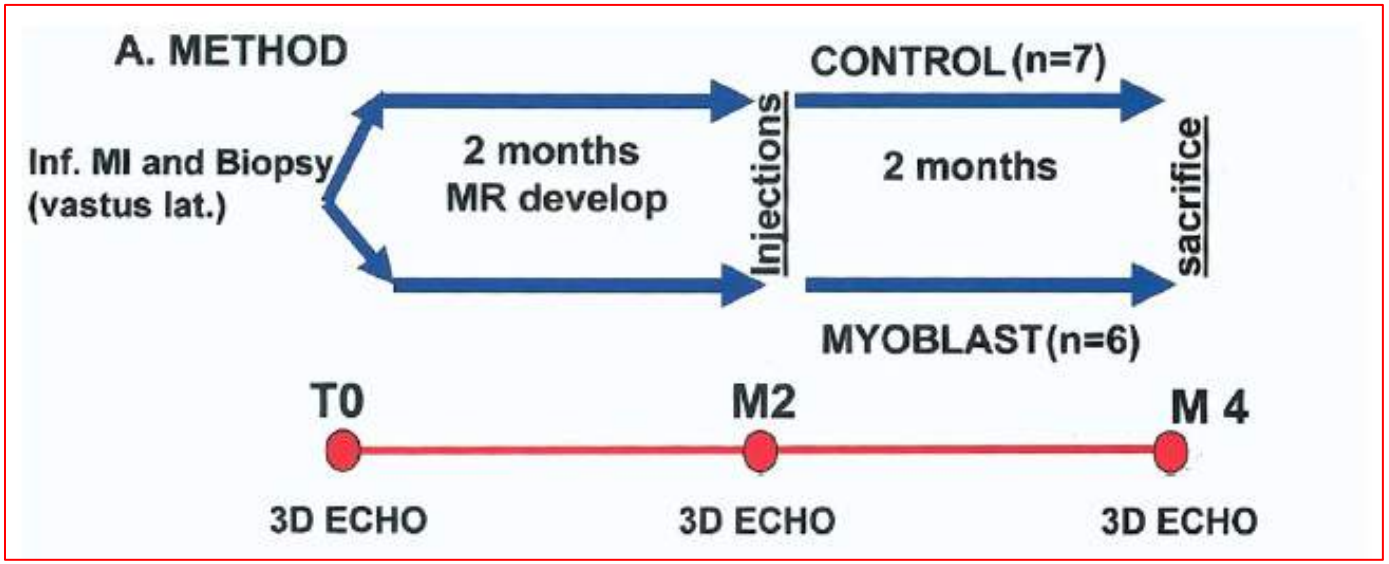
Autologous Myoblast Transplantation for Chronic Ischemic Mitral Regurgitation

Emmanuel Messas, MD, MSc,*†‡§ Alain Bel, MD,*†‡§ Miguel Cortes Morichetti, MD,†‡§ Claire Carrion, PhD,‖ Marc D. Handschumacher, BS,¶ Séverine Peyrard, BS,# Jean Thomas Vilquin, PhD,‖ Michel Desnos, MD,*†‡§ Patrice Bruneval, MD,*§** Alain Carpentier, MD, PhD, FACC,*†‡§ Philippe Menasché, MD, PhD,*†‡§ Robert A. Levine, MD,¶ Albert A. Hagège, MD, PhD†‡§

Paris, France; and Boston, Massachusetts



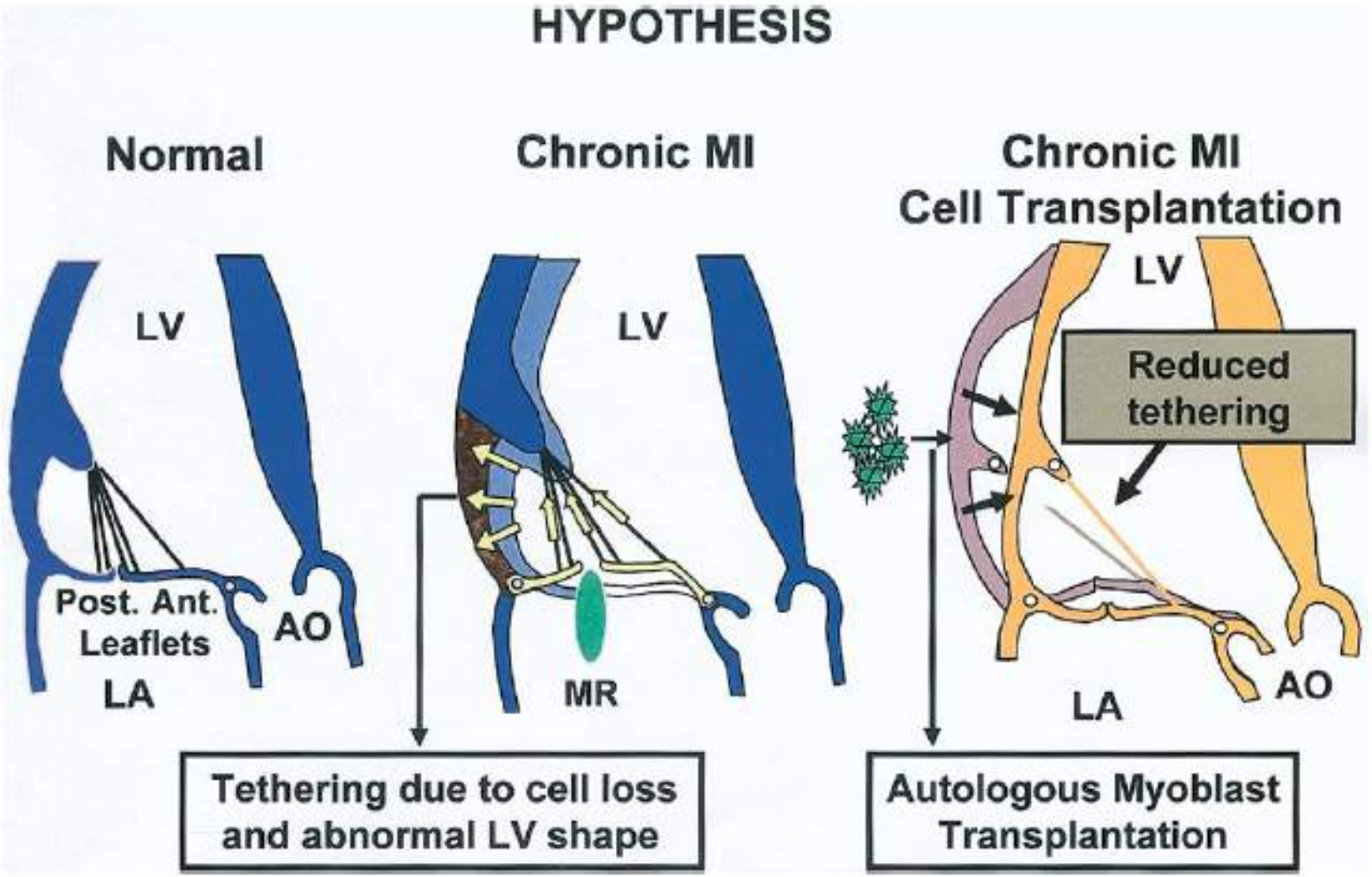

HYPOTHESIS
Normal
Chronic MI
Chronic MI
Cell Transplantation
LV
LV
LV
Post. Ant.
Leaflets
AO
LA
MR
Reduced
tethering
LA
AO
Tethering due to cell loss
and abnormal LV shape
Autologous Myoblast
Transplantation

Table 1. Echocardiographic Measurements

	Baseline		Chronic MI		Sacrifice	
	Control	Cell Transplantation	Control	Cell Transplantation	Control	Cell Transplantation
HR	99.5 ± 1.6	99.1 ± 2.7	103.1 ± 3.4	100.6 ± 3.6	109.7 ± 2.9	100.8 ± 4.9
EDV(ml)	32.01 ± 0.5	32.2 ± 1.6	63.4 ± 3.1*	62.6 ± 5.1*	111.0 ± 3.8†	102.3 ± 5.1†
ESV(ml)	10.5 ± 0.33	11.8 ± 0.5	39.1 ± 1.7*	39.7 ± 3.1*	75.4 ± 4.1†	63 ± 2.9†
EF	0.67 ± 0.01	0.63 ± 0.02	.38 ± 0.02*	.36 ± 0.02*	.33 ± 0.01	.38 ± 0.01
WMS indexed	0.0 ± 0.0	0.0 ± 0.0	1.25 ± 0.08*	1.19 ± 0.05*	1.39 ± 0.11†	.94 ± 0.13†
Tethering dist (cm)	2.48 ± 0.03	2.5 ± 0.05	3.07 ± 0.05*	2.9 ± 0.06*	3.5 ± 1.1†	2.51 ± 0.04†
MAA (cm^2)	5.8 ± 0.04	5.8 ± 0.19	6.8 ± 0.19*	6.3 ± 0.12*	7.2 ± 0.12†	6.6 ± 0.18†
MRSV (ml)	1.14 ± 0.2	1.33 ± 0.41	7.2 ± 0.59*	5.8 ± 0.59*	13.1 ± 0.77†	4 ± 0.51†
RF%	5.4 ± 0.9	6.3 ± 1.8	30 ± 0.5*	27.4 ± 4.8*	36 ± 1	10.5 ± 1.6†

All two-way ANOVAs but one (heart rate) were significant $p < 0.05$. Significant changes $p < 0.025$ (Bonferroni corrected) are indicated for the two-way comparisons: *Baseline

doi:10.1510/icvts.2010.245936

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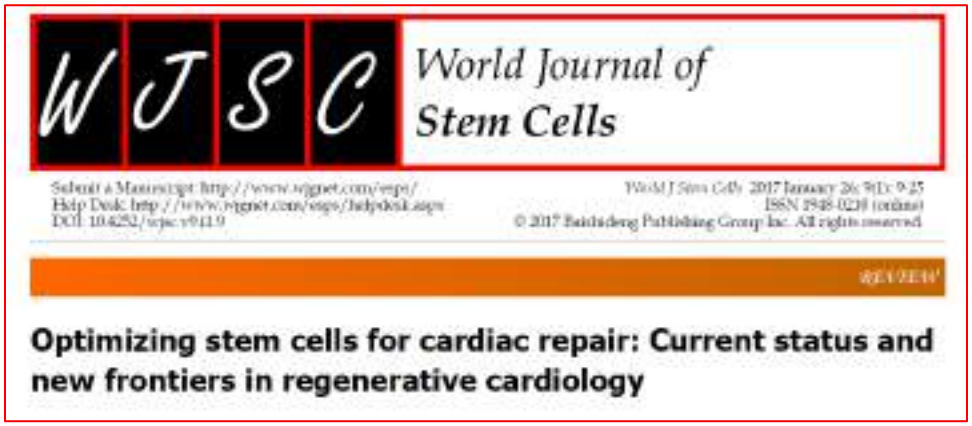
Tra ...ation

retrospective studies showed no effect on long-term mortality in patients affected by severe MR and considerable left ventricular dysfunction undergoing mitral valve repair [5]. These results reflect the etiology of ischemic MR which is secondary to ventricular dysfunction and indicate that myocardial factors form fundamental determinants regarding the outcomes of patients with cardiomyopathy undergoing mitral valve surgery. Mitral valve repair without addressing myocardial remodelling processes most likely results only in a temporary reduction of the MR grade [4]. Therefore, patients with ischemic MR offering no option to address the underlying pathology by revascularisation pro-



Poor retention and survival of transplanted cells in the heart which

can decrease to 39% at 1 h following injection as seen in human studies

The
increased cell death is swayed by various inflammatory response mediators, mechanical injury, hypoxia and ischemia-reperfusion stressors, and influenced as well by the donor cell source and quality[69]

In 2001, Orlic *et al.* reported that bone marrow stem cells injected into the infarcted myocardium

Unfortunately, although some randomized clinical trials disclosed a functional improvement due to bone marrow-derived stem cells, the initial enthusiasm for heart regeneration by stem cell transplantation has since been dampened by the modest clinical benefits observed to date

injected stem cells do not persist for long in the myocardium and do not work through a transdifferentiation process into new cardiomyocytes but rather through paracrine effectors

BMJ

BMJ 2014;348:g2688 doi: 10.1136/bmj.g2688 (Published 29 April 2014)

RESEARCH

Discrepancies in autologous bone marrow stem cell trials and enhancement of ejection fraction (DAMASCENE): weighted regression and meta-analysis

Conclusions Avoiding discrepancies is difficult but is important because discrepancy count is related to effect size. The mechanism is unknown but should be explored in the design of future trials because in the five trials without discrepancies the effect of bone marrow stem cell therapy on ejection fraction is zero.

Austin Journal of Clinical Cardiology

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Editorial

Cardiovascular Surgery Contributing to Regenerative Medicine

Acute ischemic injury and chronic cardiomyopathies lead to permanent loss of cardiac tissue and, consequently, heart failure. Cell transplantation is thought to be an ideal therapeutic method for replacing lost myocardium

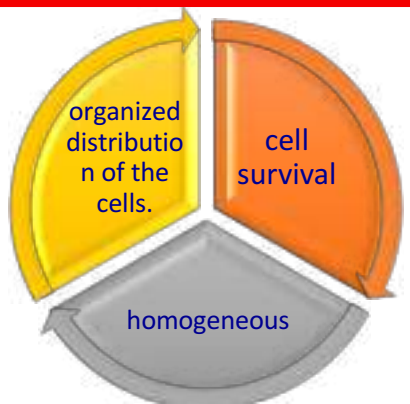
Death Valley

Many clinical studies have conducted using these somatic stem cells so far: TOPCARE-AMI, BOOST, REPAIR-AMI, LateTime (Bone marrow hematopoietic stem cells), REGENT (endothelial progenitor cells), POSEIDON (mesenchymal stem cells), MAGIC CAuSMIC (skeletal myoblasts), CADUCEUS, SCIPIO (cardiac stem/ progenitor cells) and so on

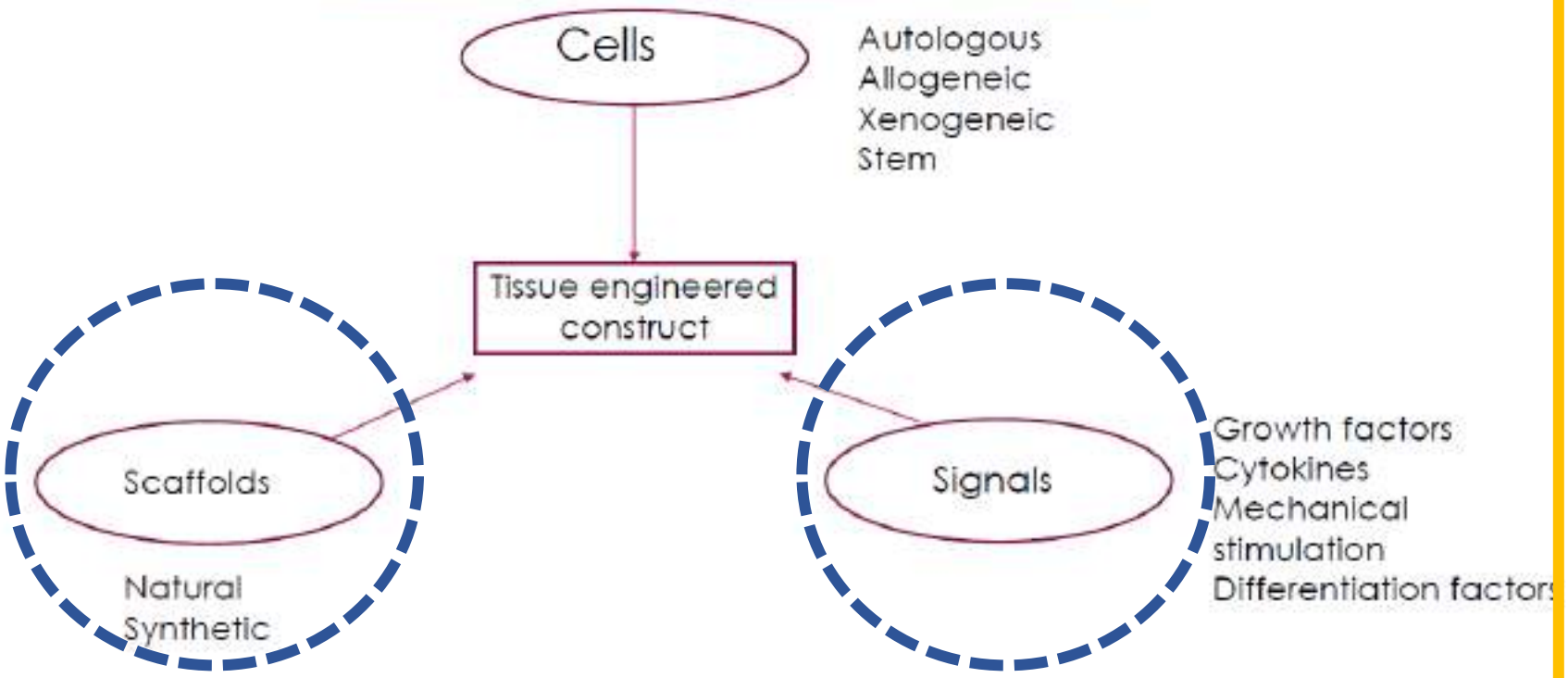
Over 70% of injected cells have been reported to die progressively during the first 48 hours after needle injection due to the hypoxic, inflammatory, and/or fibrotic environment.

New strategies such as combining the cells with bioengineering techniques have been developed and shown improvement of the efficiency of stem cell therapies

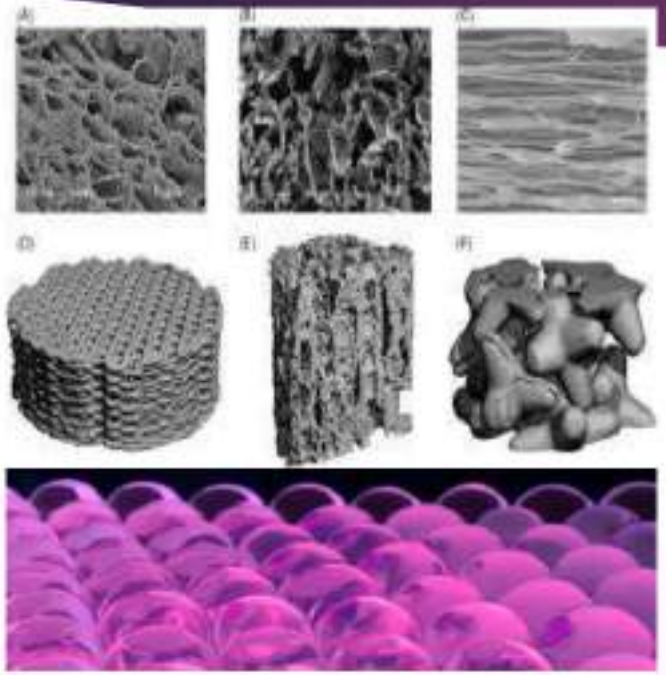
injectable biomaterials (collagen, fibrin, gelatin or Matrigel),
new techniques such as the creation of microtissues (cell sheets, patches engineered cardiac tissue)



Overview


Cells
Autologous
Allogeneic
Xenogeneic
Stem
Tissue engineered construct
Scaffolds
Natural
Synthetic
Signals
Growth factors
Cytokines
Mechanical stimulation
Differentiation factors

Biomaterials



Most commonly used biomaterials for cardiovascular tissue engineering are

- **Biodegradable Polymeric scaffolds** (Polyglycolic acid PGA)
- **Hydrogels** (seeded with collagen, fibrin, alginate)
- **Decellularized tissue** (composed of natural ECM proteins: collagen, fibronectin etc.)

TE Product Requirements

- **Biocompatible**

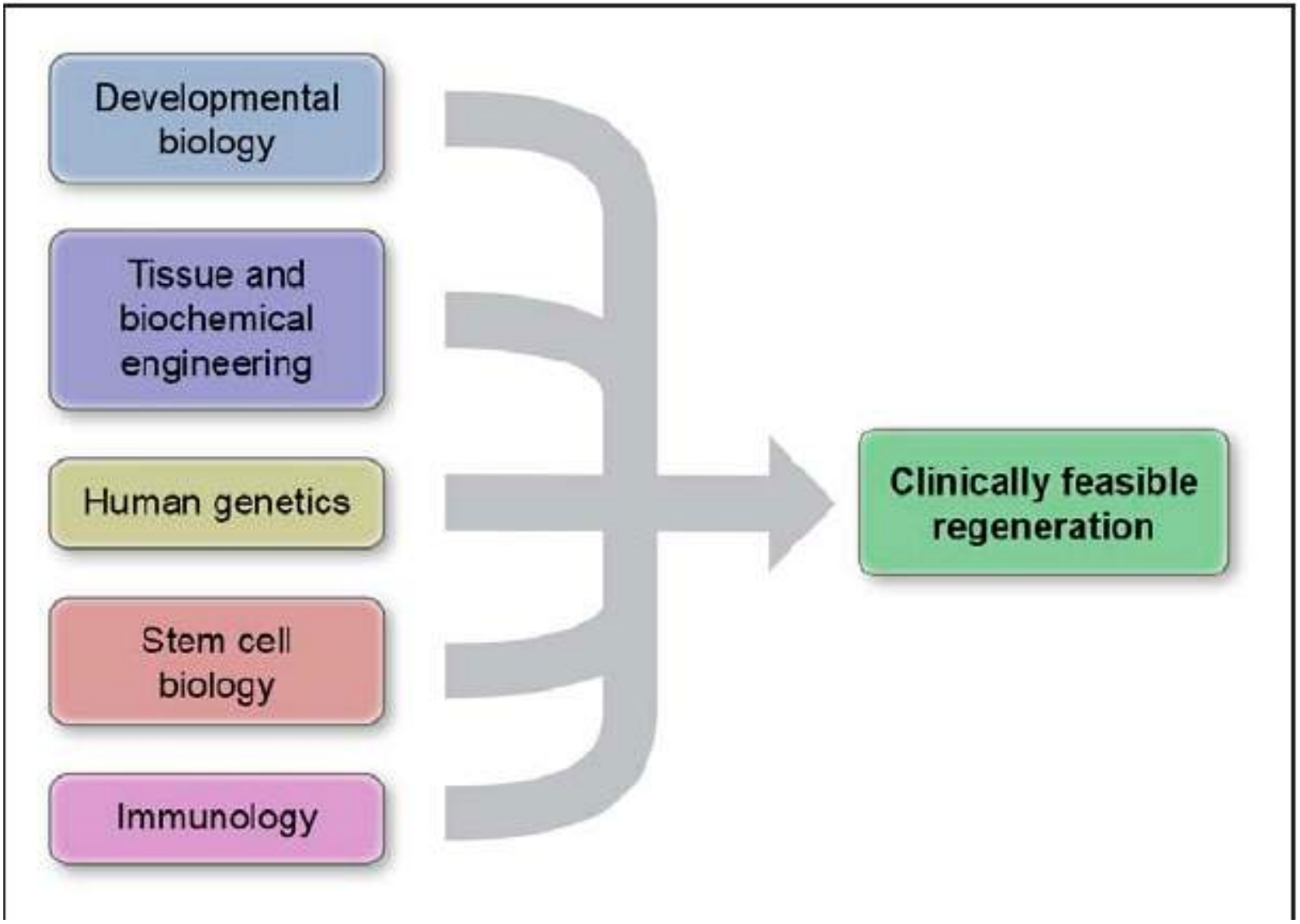
  Should not elicit immune or inflammatory response

- **Functional**

  Adequate mechanical and hemodynamic function, mature ECM, durability

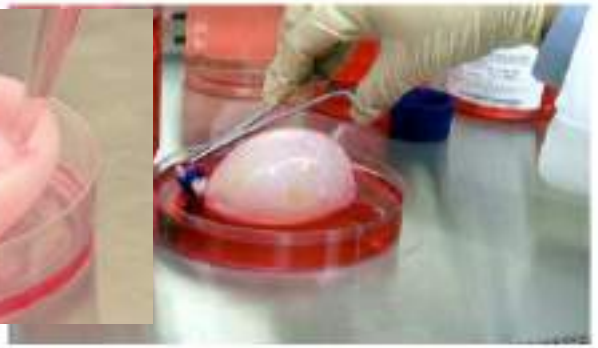
- **Living**

  Growth and remodelling capabilities of the construct should mimic the native heart valve, blood vessel or myocardium structure

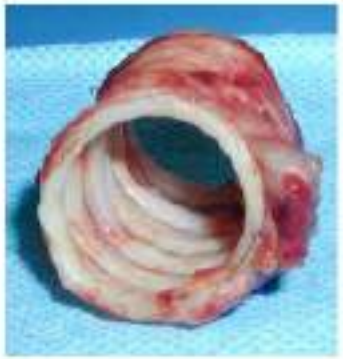

Developmental biology
Tissue and biochemical engineering
Human genetics
Stem cell biology
Immunology
Clinically feasible regeneration

Areas of Regenerative Medicine

1. Artificial Organs: Medical Devices

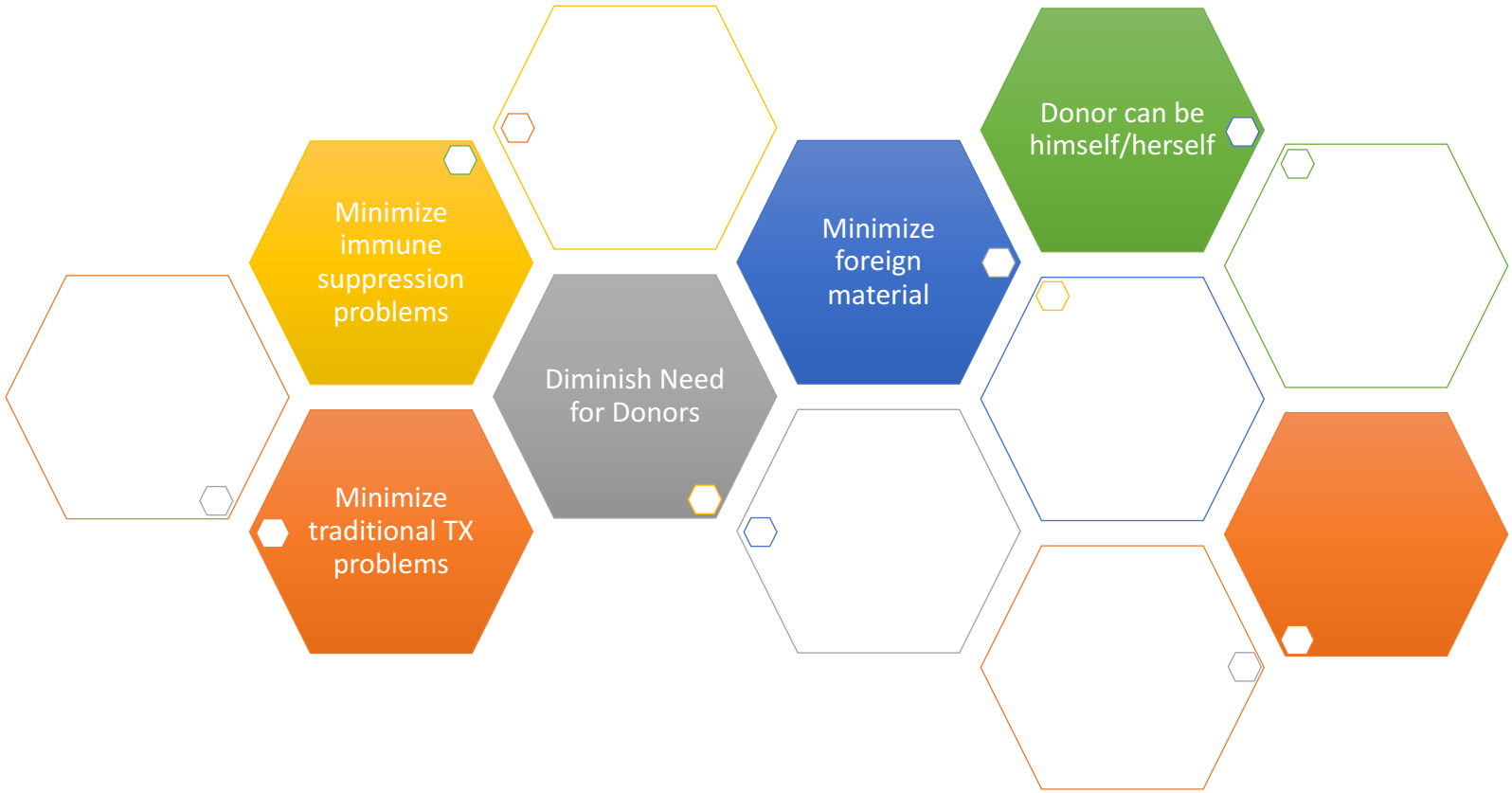


2.Tissue Engineering & Biomaterials

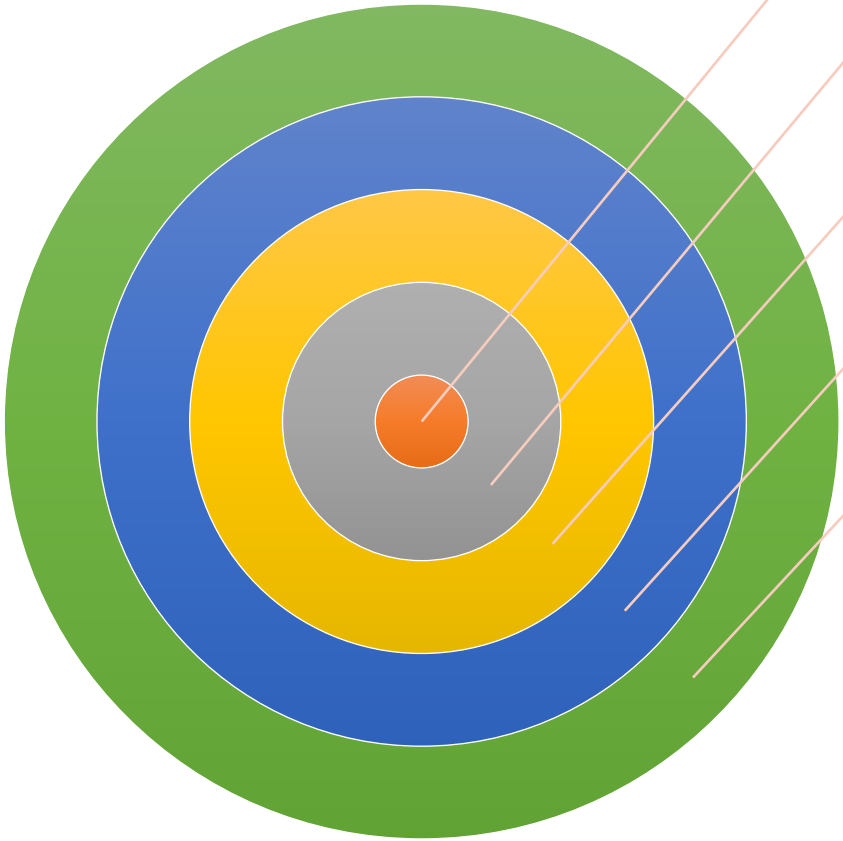


Scaffolds

Advantages of tissue engineering



Disadvantages?



Cell preparation is very complex

Cell differentiation into desired cell is difficult

Cell nutrient supply is challenging

Possible lack of function at donor site

Cost and time

Utilized a scaffold-free cell sheet technology using culture dishes

showed that mouse embryonic stem cell (ESC)-derived cell rat myocardial infarction model

However, no evidence of the reinforcement of contraction by the physical integration of the cell sheet and host myocardium was reported to date.

supplemental strategies together with current cell sheet transplantation, such as

vascularization of cell sheet, might be promising.

Review

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Regenerative Medicine

Regulation of the microenvironment for cardiac tissue engineering

Regen. Med. (2017) 12(2), 187–201

Engineering cardiac tissue that mimics native myocardium tissue depends on modulating several microenvironmental cues, including biochemical, electrical, spatial and biomechanical factors, along with intercellular interactions. The implementation of these different microenviromental cues can influence CM differentiation, maturation, organization and electrophysiology, in order to improve the engineered cardiac tissue's functionality and ultimately myocardial function.

Review Article

The Rapidly Evolving Concept of Whole Heart Engineering

Laura Iop,[1,2] Eleonora Dal Sasso,[1,2] Roberta Menabò,[3] Fabio Di Lisa,[3,4] and Gino Gerosa[1,2]

Stem Cells International
Volume 2017, Article ID 8920940, 18 pages
https://doi.org/10.1155/2017/8920940

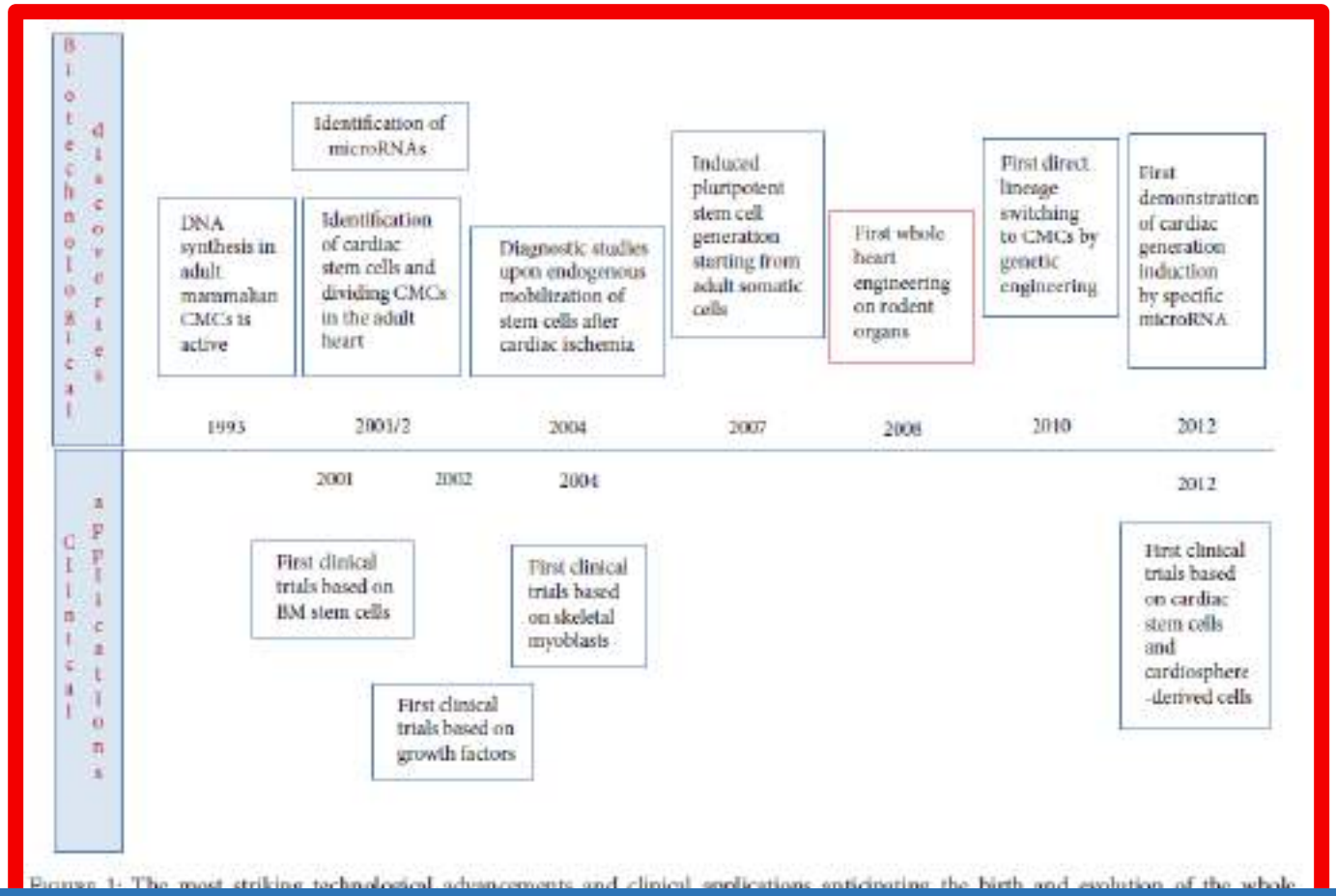
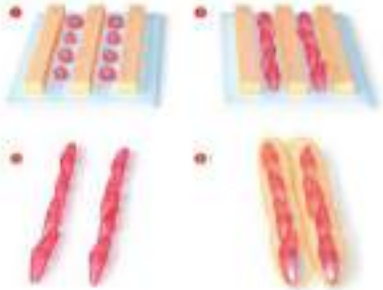


Figure 1: The most striking technological advancements and clinical applications anticipating the birth and evolution of the whole

Regenerative Medicine Pioneers

Dr. Ali Khademhosseini (Wyss Institute at Harvard)



[MIT Technology Review: www2.technologyreview.com/tr35/profile.aspx?TRID=610]

- 2007: Creating living tissues
- Organs in the lab

Regenerative Medicine Pioneers

Dr. Paolo Macchiarini (Karolinska Institute)

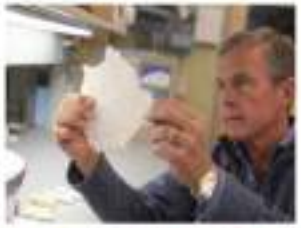
- 2008: Implanted World's First Donor Trachea
- Recipient: Claudio Castillo
- Survived Procedure — Now Has Normal Respiratory Function

Regenerative Medicine Pioneers

McGowan Institute of Regenerative Medicine (University of Pittsburg)

Dr. Stephen Badylak

- Removed Cells from Pig Bladder Extra Cellular Matrix (ECM)
- Re-grows Severed Digits and
- New Muscle Tissue Development of 3-D bioscaffolds for liver and heart regeneration



Regenerative Medicine Pioneers

1993: Dr. Robet Langer (Langer Lab, MIT)

Tissue engineering, controlled release systems and transdermal delivery systems

Nobel research on Stem cell biology

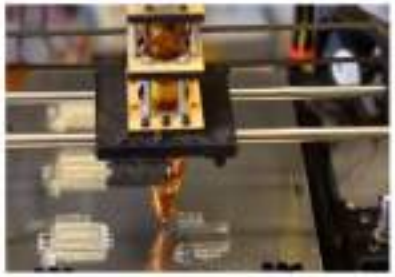
Sir John B. Gurdon **Shinya Yamanaka**

The Nobel Prize in Physiology or Medicine 2012 was awarded jointly to Sir John B. Gurdon and Shinya Yamanaka "for the discovery that mature cells can be reprogrammed to become pluripotent"

Regenerative Medicine Innovators

Dr. Jordan Miller (Rice University)

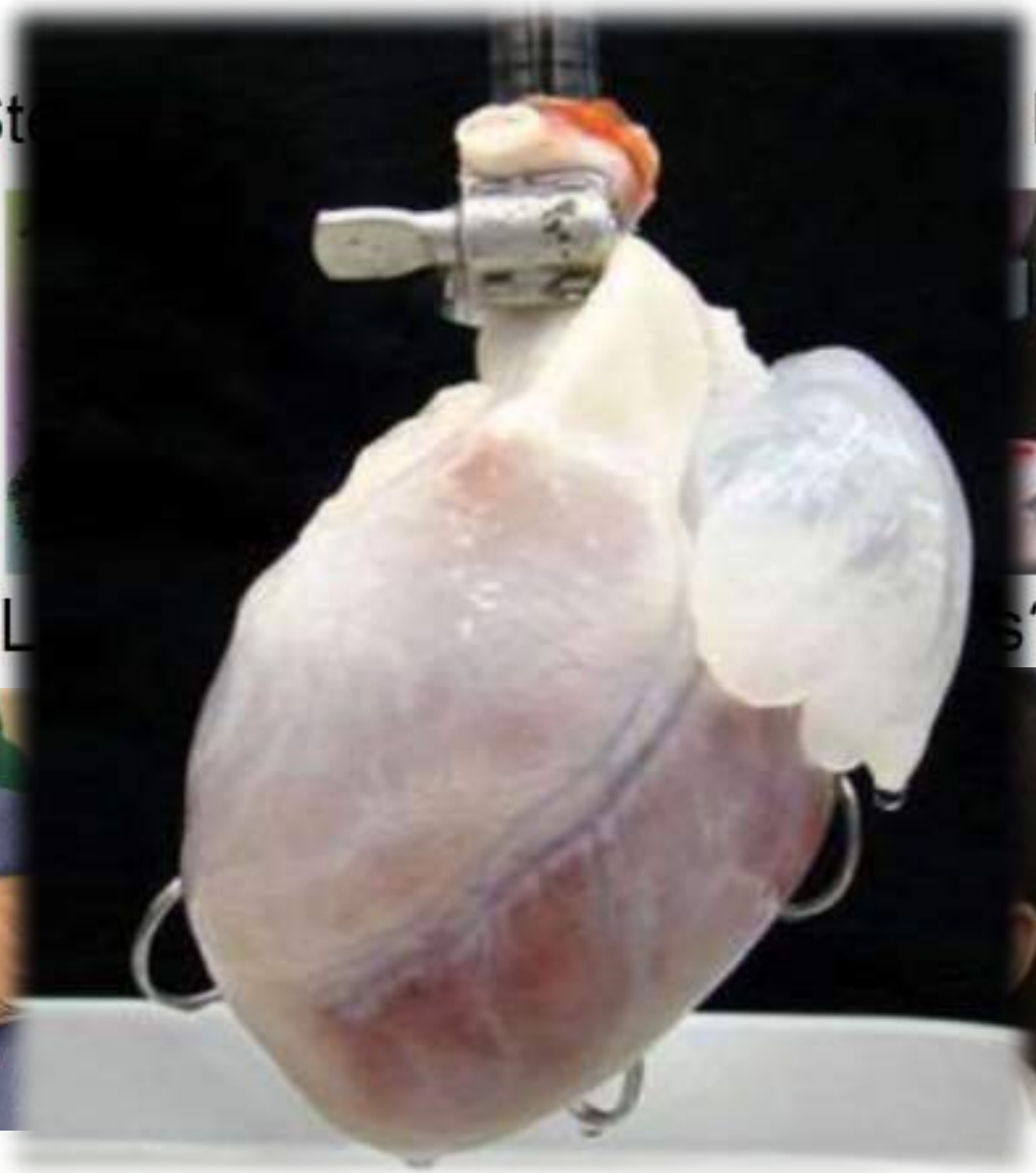
- 2013: Uses 3-D Print Technology
- Engineers Blood Vessels Using Sugar



Futuristic!

St Printer

= L s?



Advanced Drug Delivery Reviews 120 (2017) 3–24

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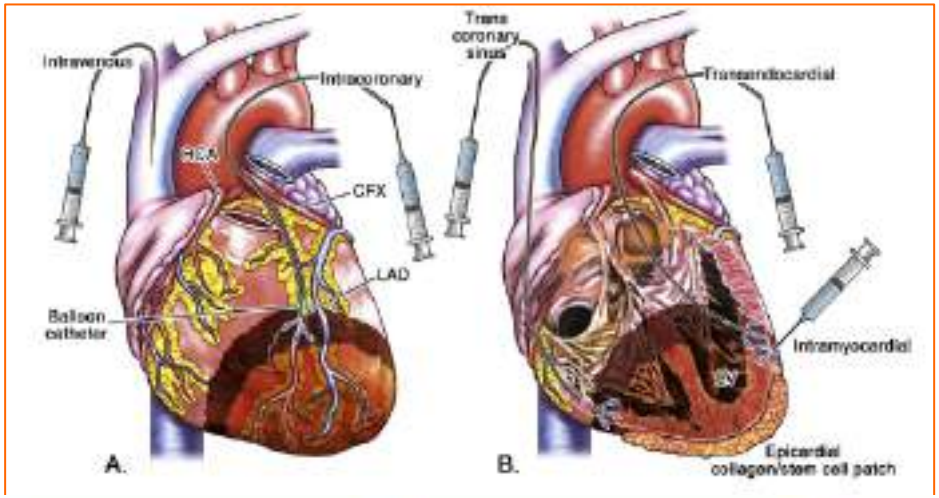
journal homepage: www.elsevier.com/locate/addr

Stem cells and heart disease - Brake or accelerator?☆

Gustav Steinhoff [a,*], Julia Nesteruk [a], Markus Wolfien [b], Jana Große [a], Ulrike Ruch [a], Praveen Vasudevan [a], Paula Möller [a]

[a] University Medicine Rostock, Department of Cardiac Surgery, Reference and Translation Center for Cardiac Stem Cell Therapy, University Medical Center Rostock, Schillingallee 35, 18055 Rostock, Germany

[b] University Rostock, Institute of Computer Science, Department of Systems Biology and Bioinformatics, Ulmenstraße 69, 18057 Rostock, Germany



Basic Research (GSP) → Preclinical Research (GLP; GMP) → Clinical Research (GMP; GCP) → MA / Market (GMP; GVP) → ?

European Heart Journal (2011) **32**, 2830–2840
doi:10.1093/eurheartj/ehr059

BASIC SCIENCE

Injectable living marrow stromal cell-based autologous tissue engineered heart valves: *first experiences with a one-step intervention in primates*

Aims A living heart valve with regeneration capacity based on autologous cells and minimally invasive implantation technology would represent a substantial improvement upon contemporary heart valve prostheses. This study investigates the feasibility of injectable, marrow stromal cell-based, autologous, living tissue engineered heart valves (TEHV) generated and implanted in a one-step intervention in non-human primates.

Methods

Scaffold fabrication

Isolation of primate bone marrow-derived mononuclear cells

Phenotyping of bone marrow-derived mononuclear cells

Bone marrow-derived mononuclear cell seeding and characterization

Tissue engineered heart valves implantation and *in vivo* functionality

Minimally invasive delivery: the transapical implantation of tissue engineered heart valves

The transapical implantations were successful in all animals. Of all six animals five valves were deployed in the orthotopic valvular

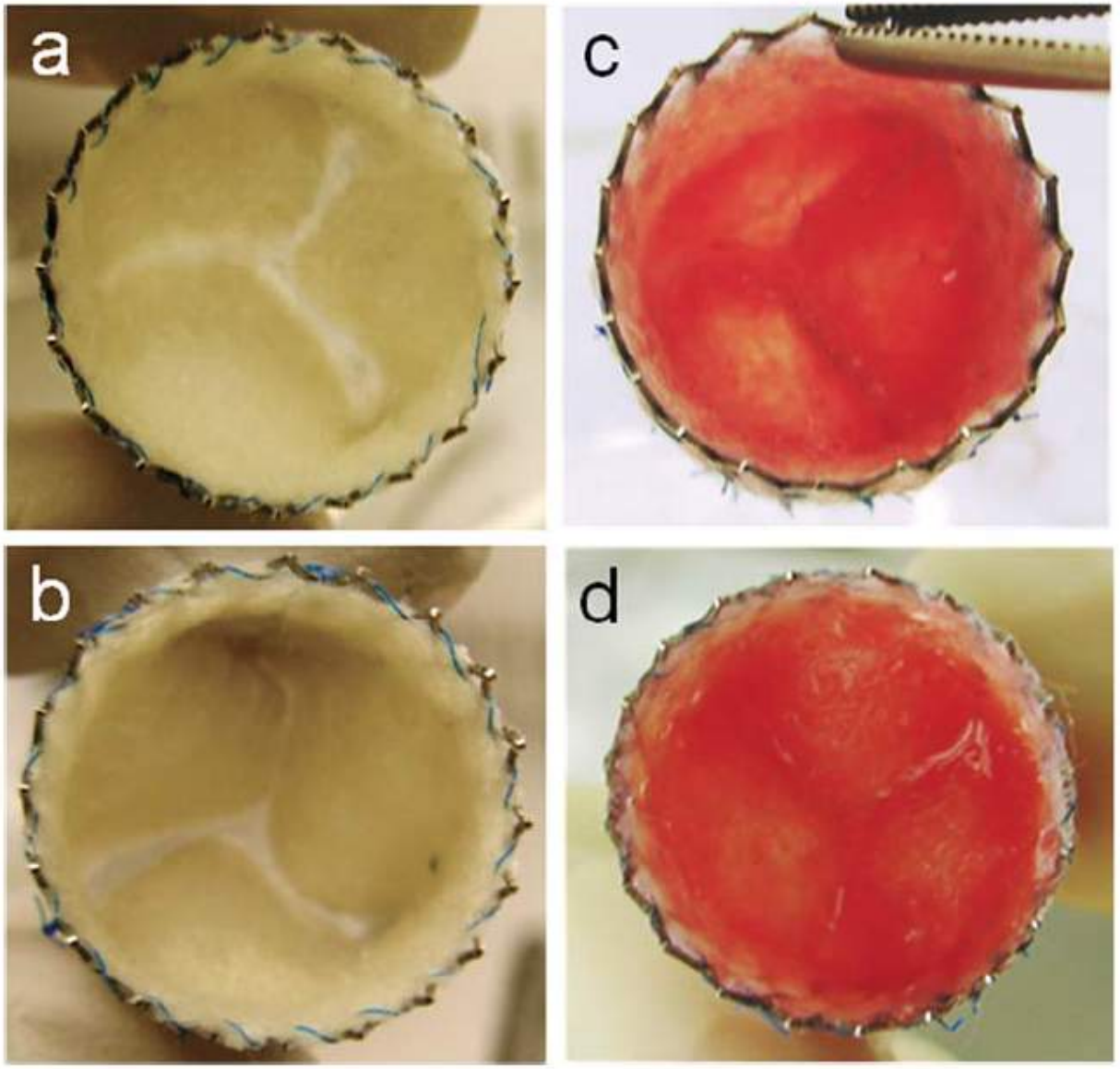
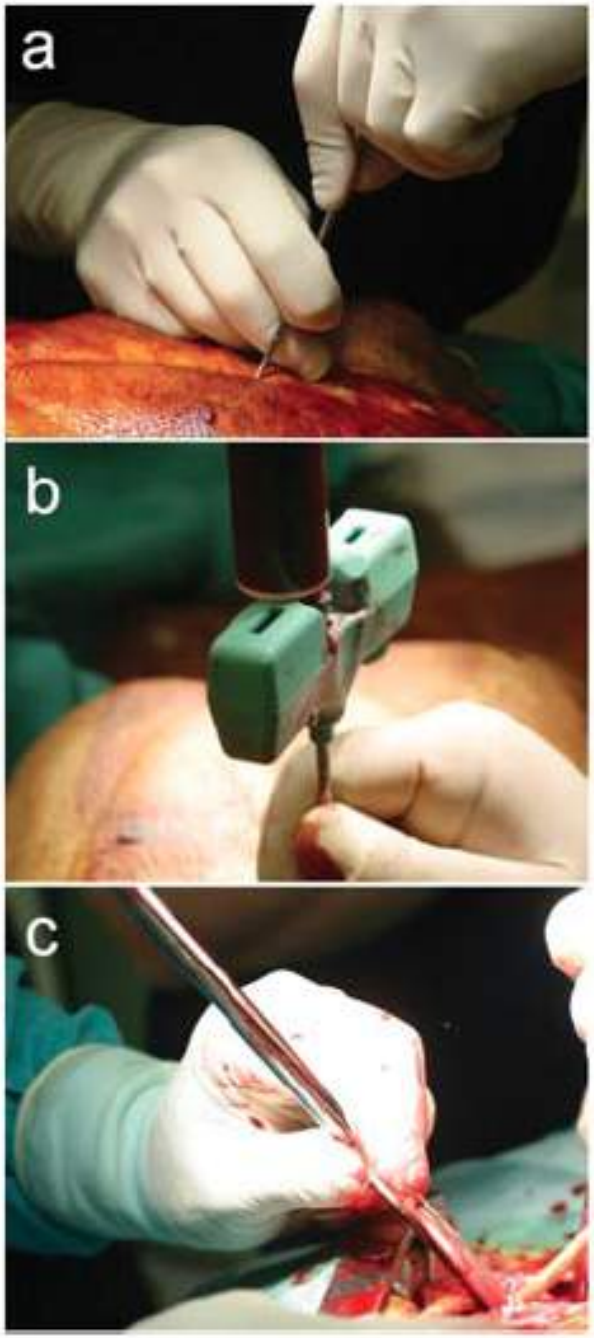


Figure 2 Bone marrow-derived tissue engineered heart valves. After isolation of bone marrow-derived mononuclear cells, stented polyglycolic acid scaffold matrices (*A* and *B*) were seeded with cells using fibrin as a cell carrier (*C* and *D*).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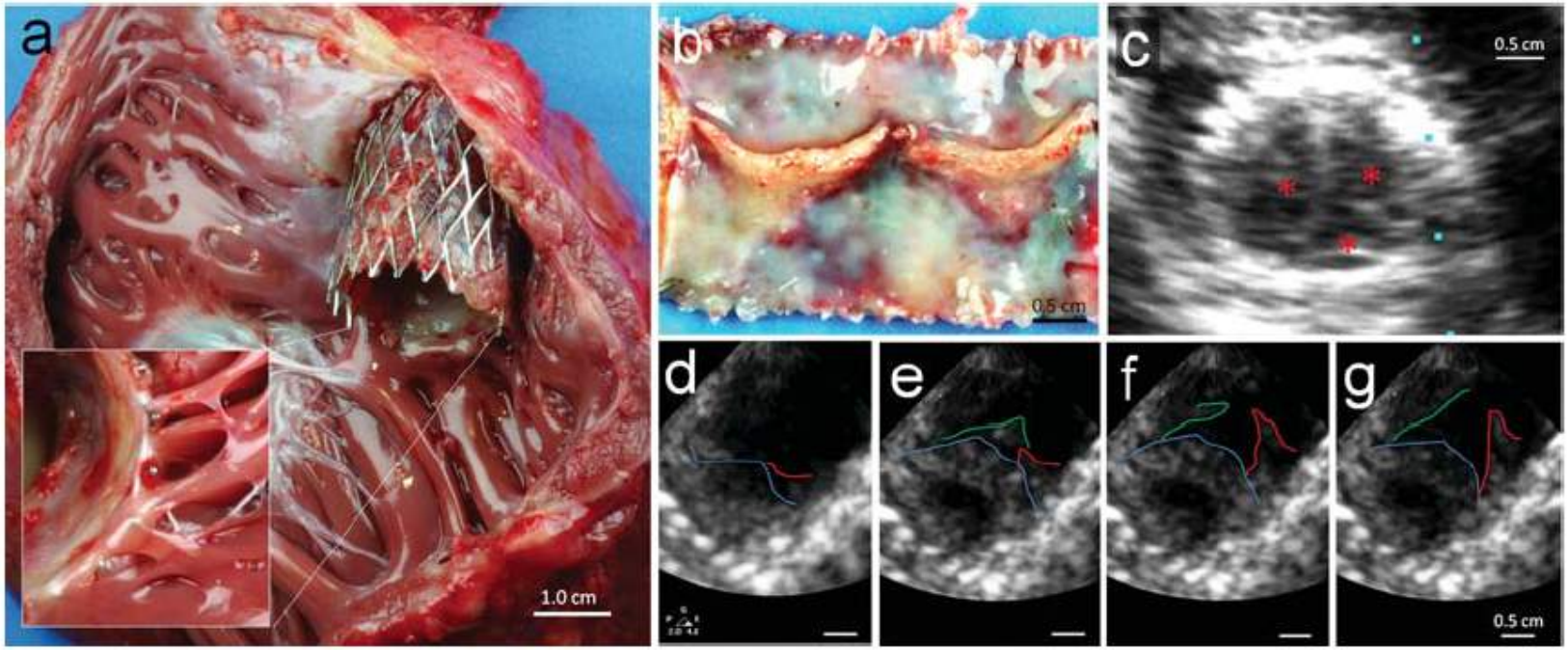

Figure 4 Explant analysis of tissue engineered heart valves. After 4 weeks *in vivo* the stented constructs were well integrated into the adjacent tissue (*A*). Orthotopical tissue engineered heart valves (*B*) presented with a cusp-like leaflet structure, with shorter leaflets than native controls. In a final transoesophageal echocardiography-assessment the leaflet co-aptation (*C*; asterisk indicates leaflets) as well as opening movements of all three leaflets could be visualized (*D*–*G*).

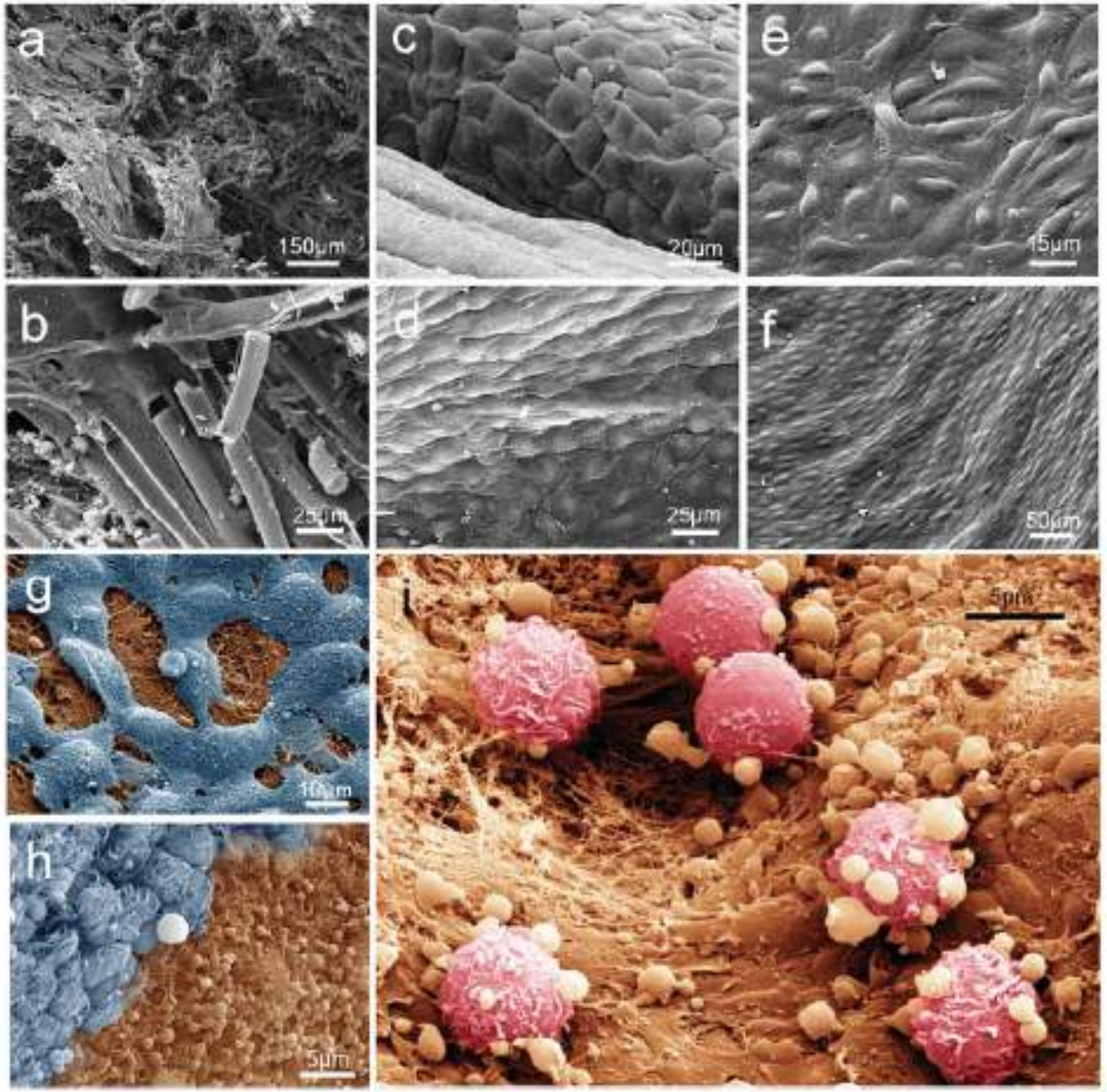

Figure 5 Scanning electron microscopy of the polyglycolic acid–poly-4-hydroxybutyrate scaffold (*A* and *B*), primate (*C*), and human (*D*) control leaflets. In most areas the surface of the 4 week explants showed confluent (*E* and *F*) or initial (*G*) endothelial coverage. In some areas the surface remodelling was still evident involving thrombocyte attachment (*H*) and leucocyte attraction (*I*).

Conclusions

These first results of combining minimally invasive valve replacement procedures with heart valve tissue engineering in a single intervention in a preclinical primate model are promising and demonstrate the feasibility of using BMCs for the fabrication of TEHV. Moreover, utilizing the body's natural abilities to regenerate TEHV *in vivo*, may greatly simplify, and improve the clinical feasibility of the autologous cell-based TEHV approach. Such autologous and living heart valves with repair and regeneration capacities may represent the next generation of transcatheter and transapical heart valves overcoming the time limitations of the currently used bioprosthetic valves suggesting their future clinical application also beyond elderly patients.

One of regenerative medicine supported by cardiovascular surgery is the **combination** of stem cell therapy and conventional surgical procedures

CABG and stem cell

results were too marginal to justify full-scale therapeutic implementation

Stem Cell + left ventricular assist device implantation,
left ventricular reconstruction
mitral repair for ischemic mitral insufficiency.

There are many promising approaches to cardiac regeneration besides cell therapies discussed above.

The generation of human hearts from other animals by using interspecific chimera technology with blastocyst complementation is one such approach

Another avenue of regenerative medicine is **gene therapy**, which is emerging as a potential treatment option in patients suffering from a wide spectrum of cardiovascular diseases

Ieda M, Fu JD, Delgado-Olguin P, Vedantham V, Hayashi Y, Bruneau BG, et al. Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors. Cell. 2010; 142: 375-386.

MicroRNAs (miRNAs), which are small, non-coding RNAs that regulate gene expression in a sequence-dependent manner, are also being investigated as a new modality of gene therapy for ischemic heart disease or vascular diseases.

In 2010, Ieda et al. reported that a combination of three developmental transcription factors (Gata4, Mef2c, and Tbx5) directly reprogrammed postnatal cardiac or dermal fibroblasts into differentiated cardiomyocyte-like cells in vitro (direct reprogramming)

This technology was recently applied to an *in-vivo* mouse MI model

Therefore, despite concerns over the ethics and safety of gene therapy, it is a promising segment of the broad field of cardiovascular disease research.

J Tissue Eng Regen Med. 2016 Jan 22. doi: 10.1002/term.2127. [Epub ahead of print]

Engineering natural heart valves: possibilities and challenges.

Namiri M1,2, Ashtiani MK1, Mashinchian O1, Hasani-Sadrabadi MM1,3, Mahmoudi M4,5,6, Aghdami N1, Baharvand H1,2.

During the past three decades, tissue engineering-based approaches have shown tremendous potential to overcome these limitations by the development of a **biodegradable scaffold**, which provides biomechanical and biochemical properties of the native tissue. Among various scaffolds employed for tissue engineering, the decellularized heart valve (DHV) has attracted much attention, due to its native structure as well as comparable haemodynamic characteristics. Although the human DHV has shown optimal properties for valve replacement, the limitation of valve donors in terms of time and size is their main clinical issue. In this regard, xenogenic DHV can be a promising candidate for heart valve replacement. Xenogenic DHVs have similar composition to human valves, which will overcome the need for human DHVs. **The main concern regarding xenogeneic DHV replacement is the immunological reaction and calcification following implantation, weak mechanical properties and insufficient recellularization capacity**.

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Review

Accelerating *in Situ* Endothelialisation of Cardiovascular Bypass Grafts

Ee Teng Goh [1,2], Eleanor Wong [1,2], Yasmin Farhatnia [1], Aaron Tan [1,2,3] and Alexander M. Seifalian [1,4,*]

REVIEW

Luminal Surface Engineering, 'Micro and Nanopatterning': Potential for Self Endothelialising Vascular Grafts?

D.S.T. Chong [a,b], B. Lindsey [a], M.J. Dalby [c], N. Gadegaard [d], A.M. Seifalian [b], G. Hamilton [a,b,*]

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[b] Centre for Nanotechnology and Regenerative Medicine, Division of Surgery and Interventional Science, University College London, London, UK
[c] Centre for Cell Engineering, University of Glasgow, Glasgow, UK
[d] Division of Biomedical Engineering, School of Engineering, University of Glasgow, Glasgow, UK

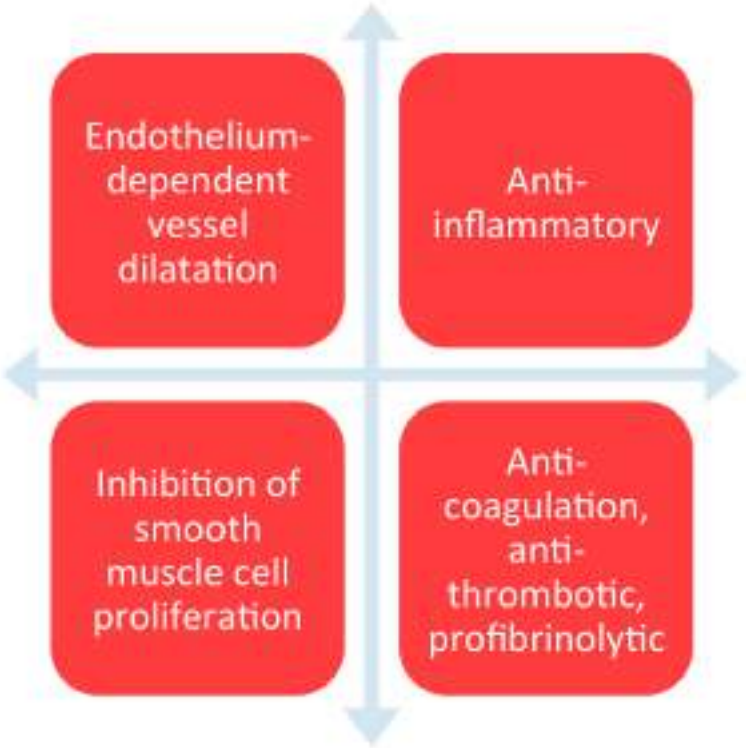

Figure 1. Shows the different functions of endothelium.

Biointerphases
A Journal of Biomaterials and Biological Interfaces

Novel heart valve prosthesis with self-endothelialization potential made of modified polyhedral oligomeric silsesquioxane-nanocomposite material

Hossein Ghanbari, Dina Radenkovic, Sayed Mahdi Marashi, Shirin Parsno, Nima Roohpour, Gaetano Burriesci, and Alexander M. Seifalian

(Received 1 October 2015; accepted 11 December 2015; published 13 January 2016)

In the cardiovascular system, the endothelial layer provides a natural antithrombogenic surface on the inner portion of the heart and associated vessels. For a synthetic material therefore, the ability to attract and retain endothelial or endothelial progenitor cells (EPCs), ultimately creating a single endothelial layer on its surface, is of prime importance. The authors have developed a nanocomposite polymer, based on a combination of polyhedral oligomeric silsesquioxane nanoparticles and polycarbonate urea urethane (POSS-PCU), which is biocompatible and has been used in human for the world's first synthetic trachea, tear duct, and bypass graft. In this study, the authors modified the surface of this casted nanocomposite by grafting fibronectin derived bioactive peptides [glycine-arginine-glycine-aspartic acid-glycine (GRGDG) and lauric acid conjugated GRGDG (GRGDG-LA)] to enhance the endothelialization for using heart valves leaflets from circulating EPCs. Human peripheral blood mononuclear cells were separated using Ficoll–Paque centrifugation, with harvested EPCs purified using CD34 microbead labeling and magnetic-activated cell sorting. Cells were seeded onto 96 well plates coated with POSS-PCU, GRGDG/GRGDG-LA modified POSS-PCU and PCU polymers, for a period of 21 days. Cells

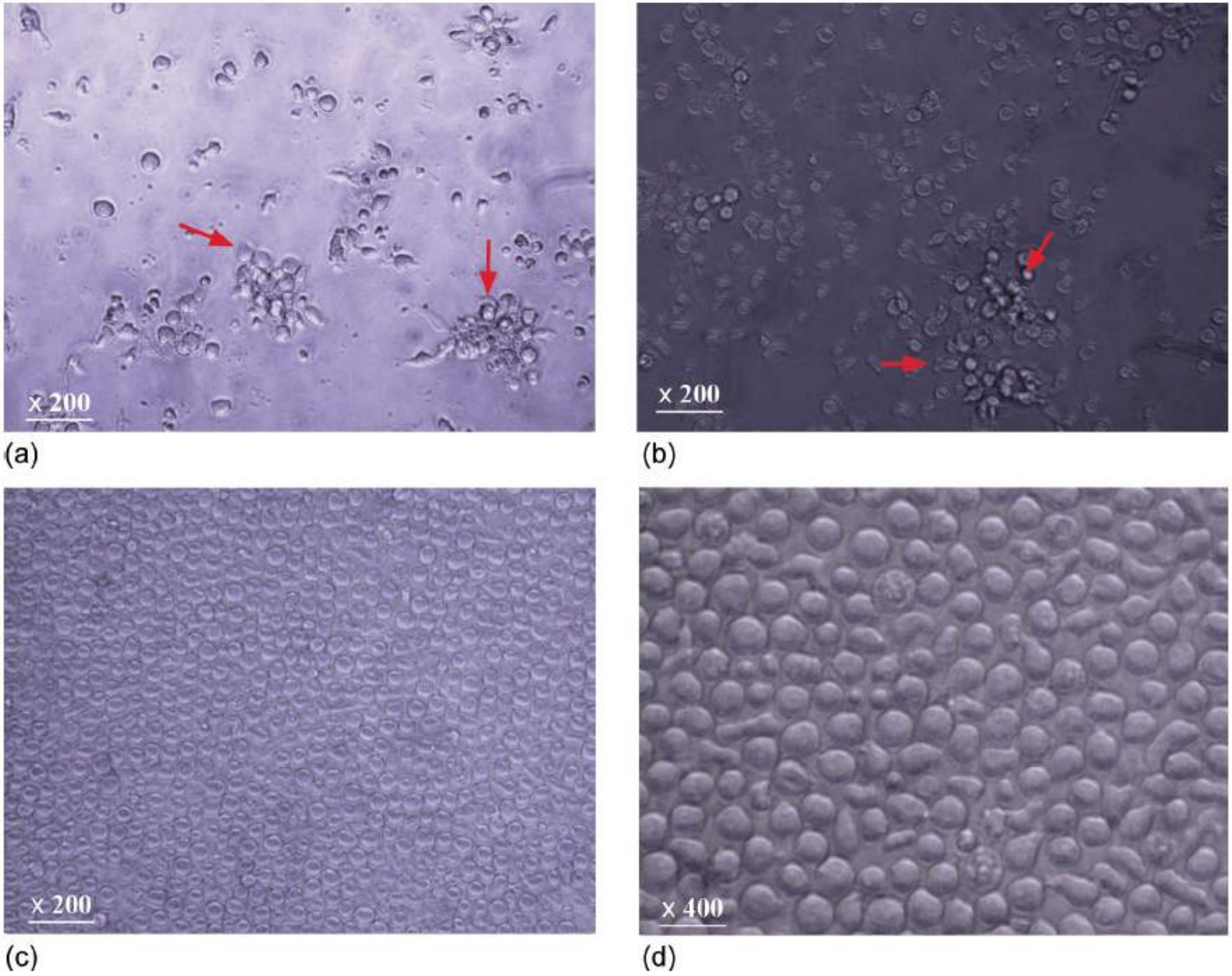

FIG. 6. Live microscopy images of the isolated cells cultured on POSS-PCU nanocomposite samples. Colonies of EPC (marked with arrows) undergoing proliferation resulted in an increased cell population over time of culture as shown on day 7 (a) and day 14 (b). The cells underwent morphological changes during the culture and spindle-shaped morphology of early EPCs on day 7 (a) was dominated by cobble stone-shaped confluent layer at day 21 (c), characteristic morphology of the endothelial cells. (d) Higher magnification of confluent layer of EC on day 21.

AVS Biointerphases
A Journal of Biomaterials and Biological Interfaces

Novel heart valve prosthesis with self-endothelialization potential made of modified polyhedral oligomeric silsesquioxane-nanocomposite material

Hossein Ghanbari, Dina Radenkovic, Sayed Mahdi Marashi, Shirin Parsno, Nima Roohpour, Gaetano Burriesci, and Alexander M. Seifalian

V. CONCLUSIONS

In an *in vitro* setting, EPCs were extracted from adult peripheral blood and umbilical cord blood and cultured on the POSS-PCU nanocomposite in comparison with PCU, GRGDG, and GRGDG-LA modified polymers. EPCs' proliferation and differentiation was noticed over the time of culture. The POSS-PCU nanocomposite revealed an enhanced cell affinity and capability to provide a cell friendly environment for EPC proliferation and differentiation. According to the results, this nanocomposite material can be used for the development of synthetic leaflet heart valves, but modification with suitable peptides could result in superior in-situ endothelialization capability.

Ann Thorac Surg. 2012 May ; 93(5): 1524–1533. doi:10.1016/j.athoracsur.2012.01.063.

Stem Cells in Thoracic Aortic Aneurysms and Dissections: Potential Contributors to Aortic Repair

Ying H. Shen, MD, PhD[1,2], **Xiaoqing Hu, MD**[1,2], **Sili Zou, MD**[1,2], **Darrell Wu, MD**[1,2,3], **Joseph S. Coselli, MD**[1,3], and **Scott A. LeMaire, MD**[1,2,3]

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Comment

Multipotent SCs are known to play an important role in arterial remodeling after injury. The presence of circulating endothelial progenitor cells has been previously reported in a murine model of abdominal aortic aneurysms [15], in patients with abdominal aortic aneurysms [16], and, recently, in patients with ascending aortic aneurysms [17]. In this study, we have shown that SCs are abundant in two other forms of aortic disease: descending TAA and chronic TAD. Specifically, we found that there were significantly more STRO-1+ cells, c-kit+ cells, and CD34+ cells and in the media and adventitia of aortic tissue from TAA and TAD patients than in control aortic tissue. Furthermore, subsets of STRO-1+ cells, c-kit+ cells, and CD34+ cells appeared to differentiate into SMCs and fibroblasts, and a large number of STRO-1+ cells exhibited differentiation into macrophages. The presence of multipotent SCs at sites of aneurysm and dissection formation that can further differentiate into SMCs suggests the existence of an active repair process involving SCs.

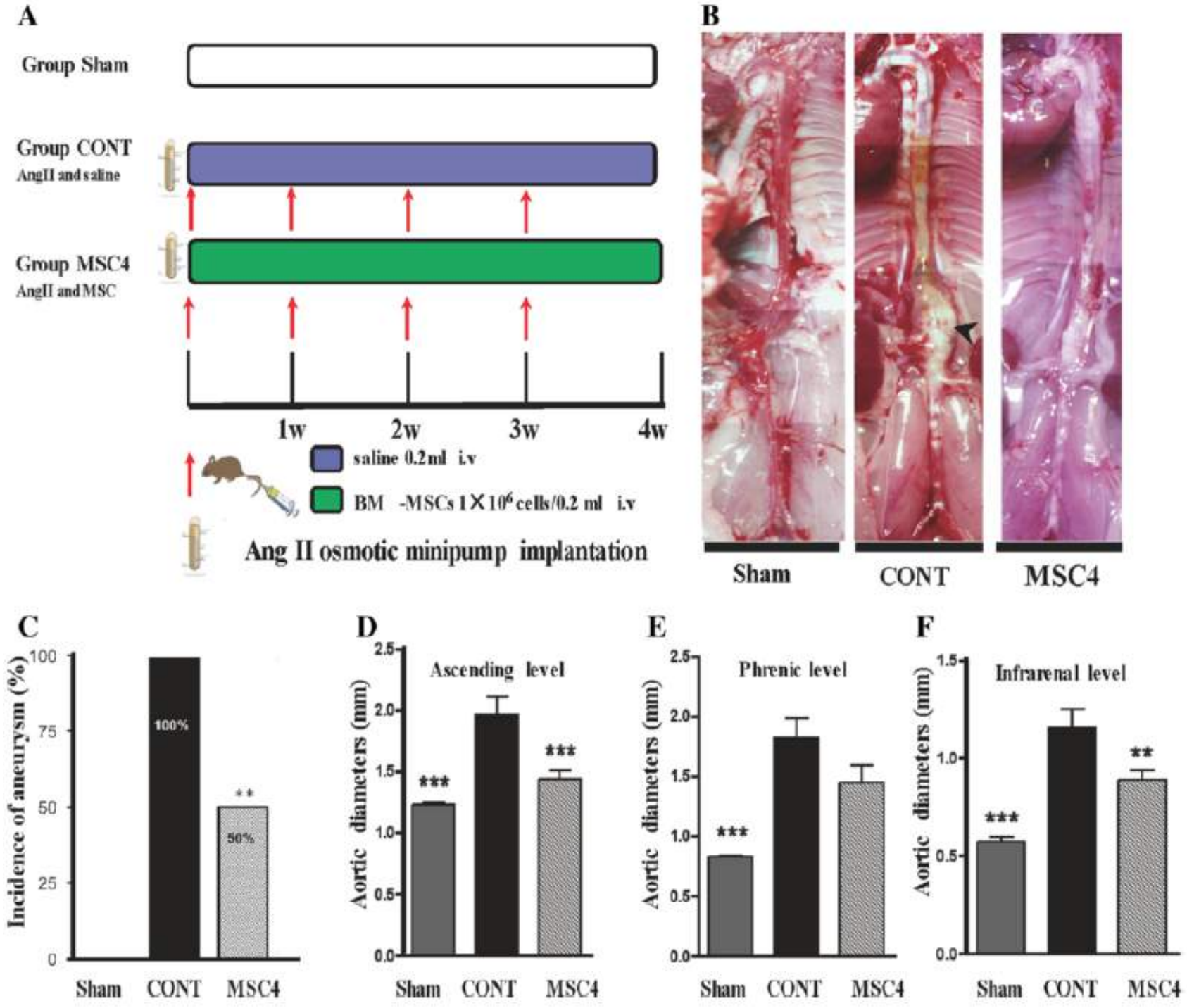
Fu et al. Journal of Translational Medicine 2013, 11:175
http://www.translational-medicine.com/content/11/1/175

JOURNAL OF TRANSLATIONAL MEDICINE

RESEARCH Open Access

Intravenous administration of mesenchymal stem cells prevents angiotensin II-induced aortic aneurysm formation in apolipoprotein E-deficient mouse

Xian-ming Fu†, Aika Yamawaki-Ogata†, Hideki Oshima, Yuichi Ueda, Akihiko Usui and Yuji Narita*


A
Group Sham
Group CONT
AngII and saline
Group MSC4
AngII and MSC
1w
2w
3w
4w
saline 0.2ml i.v
BM -MSCs 1×10^6 cells/0.2 ml i.v
Ang II osmotic minipump implantation
B
Sham
CONT
MSC4
C
Incidence of aneurysm (%)
100
75
50
25
0
100%
**
50%
Sham
CONT
MSC4
D
Ascending level
Aortic diameters (mm)
2.5
2.0
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1.0
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2.5
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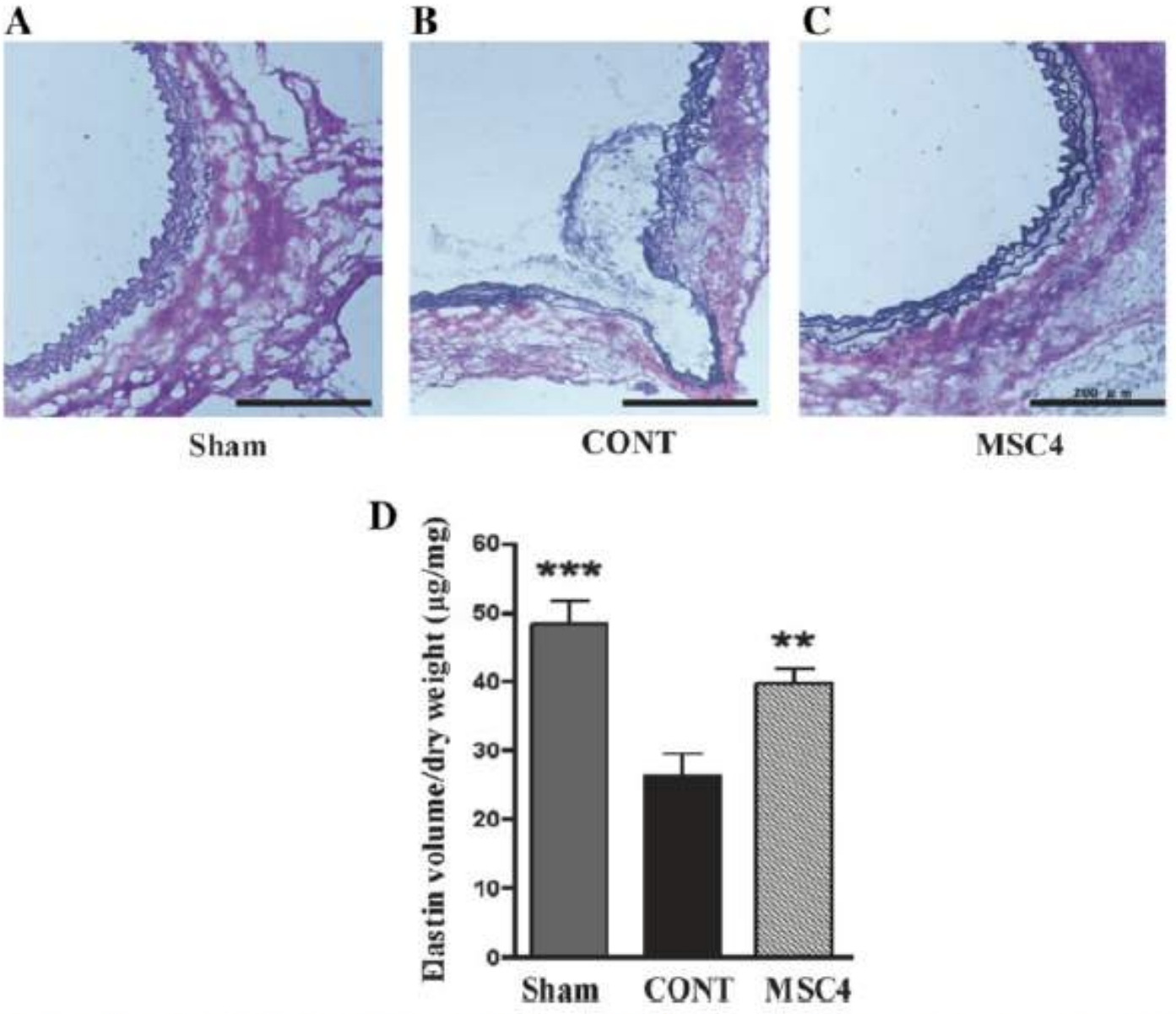


Figure 2 Multiple intravenous administrations of BM-MSCs attenuated aortic elastin degradation in apoE$^{-/-}$ mice. A) EVG staining shows normal wavy elastic lamina structure in group Sham, and **B)** disruption of elastic lamina and aneurysm formation in group CONT. **C)** Administration of BM-MSCs maintained wavy structure of the elastic lamellae. Scale bar = 200 µm. **D)** Measurement of elastin volume of aortic tissues showed a significant decrease in group CONT compared with group Sham, but preservation in group MSC4. Data are presented as means ± SEM (n =10-12) $^{**}P<0.01$, $^{***}P<0.001$ vs. group CONT, assessed by one-way ANOVA.

JOURNAL OF TRANSLATIONAL MEDICINE

Conclusions

Multiple intravenous administrations of BM-MSCs were effective to suppress inflammatory reactions in Ang II-infused apoE$^{-/-}$ mice, and inhibit the development of AAs. It may therefore serve as a new therapeutic strategy for patients with AA.

European Heart Journal Advance Access published May 19, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv189

EHJ BRIEF COMMUNICATION
Heart failure/cardiomyopathy

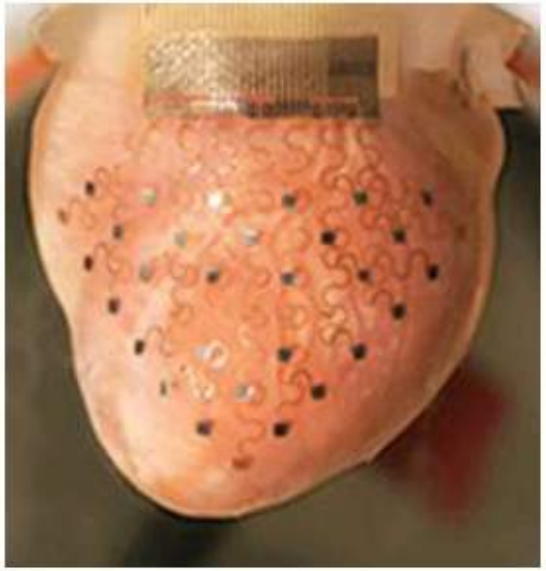
Human embryonic stem cell-derived cardiac progenitors for severe heart failure treatment: first clinical case report

tive applications, and based on the epicardial delivery of a cell-loaded patch. Several studies have documented the superiority of this patch-based approach over intramyocardial injections with regard to cell retention, survival,[22] and, ultimately, preservation of heart function.[21] Our choice of encaging the *Isl-1*$^{+}$ cardiac

Figure 1 Intraoperative view of the progenitor cell-loaded fibrin patch that has been slid into the pocket between an autologous pericardial flap and the epicardial surface of the infarct area.

Promise of Regenerative Medicine

3-D Printer Creates Heart Membrane



[Prof. Igor Efimov, Washington University in St. Louish: ttps://news.wustl.edu/news/Pages/26554.aspx]

Lizhi Xu and al., Nature Communications, 2014, 3329, doi:10.1038/ncomms4329

3-D Elastic Membrane Fits Heart's Epicardium

Current Interventional and Surgical Management of Congenital Heart Disease

Specific Focus on Valvular Disease and Cardiac Arrhythmias

Kimberly A. Holst, Sameh M. Said, Timothy J. Nelson, Bryan C. Cannon, Joseph A. Dearani

Circulation Research March 17, 2017

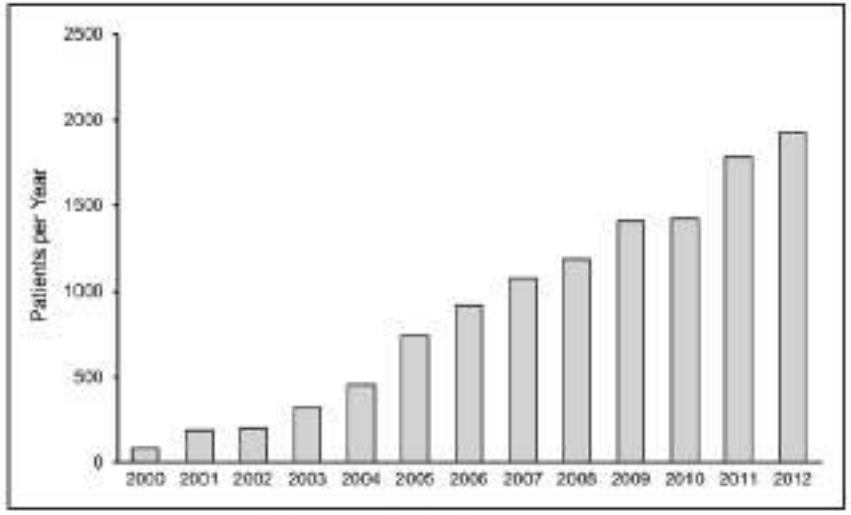
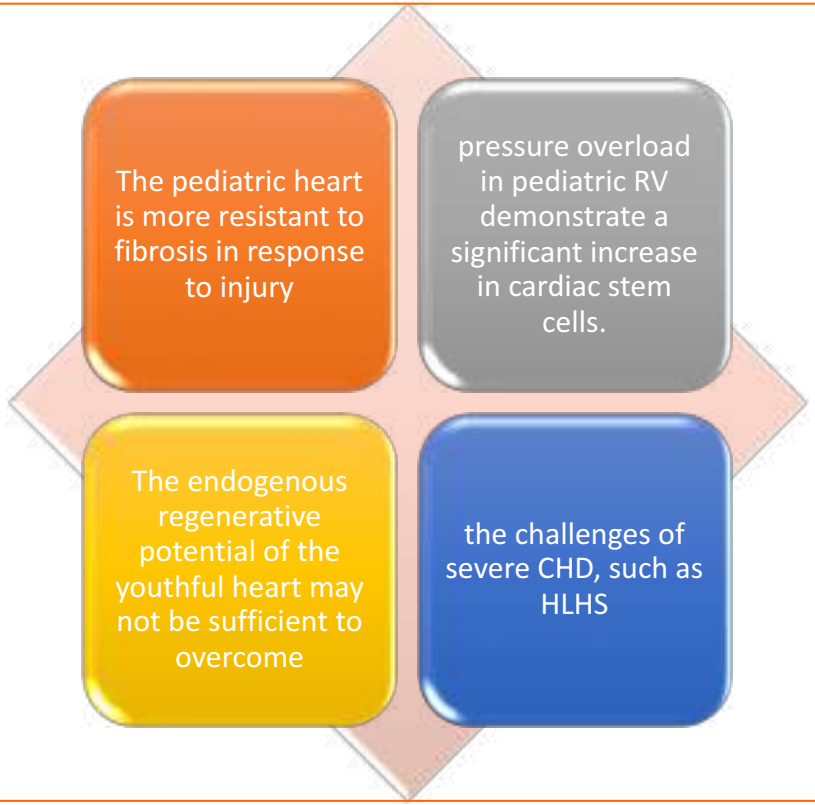


Figure 1. Adult congenital volume through time. Adult patients with congenital heart disease continue to increase through time. Adult patient volumes as reported to The Society of Thoracic Surgeons Congenital Heart Surgery Database from 2000 to 2012 from 116 congenital heart surgery centers. Reproduced from Fuller et al[9] with permission of the publisher. Copyright ©2015, The Society of Thoracic Surgeons.



The surgical repair of CHD is continuously challenged by a growing heart with increased physiological demands.

Therefore, customized regenerative products that can meet the emerging gaps of yesterday's treatments

Autologous cardiosphere derived cells and intracoronary delivery of $3.0\times10_5$ cells/kgmonths after either stage 2 or stage 3 palliation

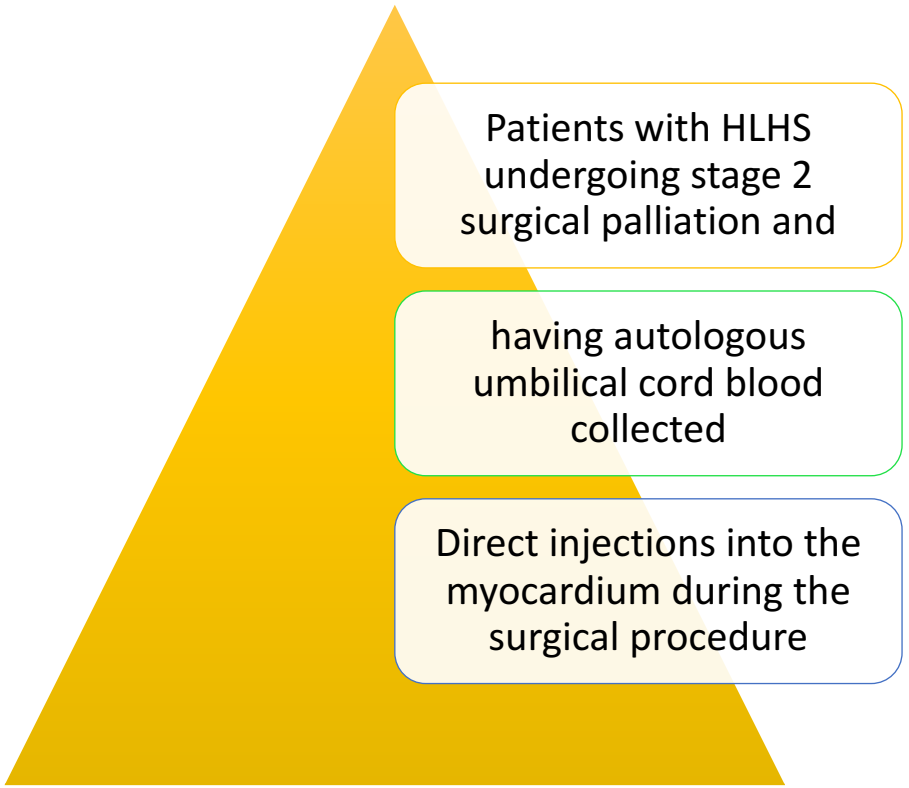
≈6% increase of ejection fraction of the single ventricle by 3 independent measures

PERSEUS trial;

(Cardiac Progenitor Cell Infusion to Treat Univentricular Heart Disease)

TICAP trial

(Transcoronary Infusion of Cardiac Progenitor Cells in Patients With Single Ventricle Physiology)



Kardiologia Polska 2013; 71, 5: 485–492; DOI: 10.5603/KP.2013.0095 ISSN 0022–9032

ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

The combined use of transmyocardial laser revascularisation and intramyocardial injection of bone-marrow derived stem cells in patients with end-stage coronary artery disease: one year follow-up

Methods: Five male patients (age 49–78 years) with end-stage diffuse CAD, severe angina (CCS III/IV) despite intensive medical therapy and disqualified from prior coronary artery bypass grafting (CABG) or percutaneous coronary intervention were included. After heart exposure, at sites where CABG was impossible, TMLR was performed with the Holmium: YAG laser combined with injection of 1 mL of bone marrow concentrate into the border zone of a laser channel using a Phoenix handpiece.

Results: No deaths in the follow-up period were observed. All patients were in I CCS Class. One year after the procedure, left ventricular (LV) segments treated by BMLR tended to demonstrate stronger myocardial thickening compared to baseline ($53.0 \pm 7.5\%$ vs. $45.0 \pm 9.5\%$; $p = 0.06$). Using late gadolinium-enhanced imaging, new myocardial infarction was found after one year only in one LV segment treated by BMLR. The BMLR treated regions in the remaining subjects, as well as regions subtended by left internal thoracic artery in two subjects, did not show new myocardial infarction areas. In contrast, all subjects who underwent only BMLR procedure revealed new and/or more extensive myocardial infarct in regions not treated by BMLR.

Conclusions: Intramyocardial delivery of bone marrow stem-cells together with laser therapy is a safe procedure, with improvement in quality of life during follow-up. One year after the procedure, myocardial regions where BMLR was performed tended to demonstrate stronger myocardial thickening observed in cardiac magnetic resonance imaging.

Thank You