Heart to Heart Luncheon

Presenting

Dr. Ramin Beygui
Director Cardiac, Thoracic, and Vascular Surgery
Novel Technology in Cardiovascular Surgery

Presented by
Dr. Ramin Beygui
Director Cardiac, Thoracic, and Vascular Surgery
Coronary Artery Bypass Graft

- 1946, Vineberg, Implanted bypass to myocardium
- 1953, Gibbon Jr., Developed Heart-Lung Machine
- 1954, Murray: Systemic Artery to Coronary anastomosis
- 1958, Longmire: Coronary endarterectomy IMA to RCA bypass
- 1962, Sones & Shirey: Cine Coronary Arteriography
- 1967, Kolessov: IMA coronary anastomosis
Off-Pump CABG

Shumacker (1983) credits Longmire with the first internal mammary to coronary artery anastomosis. “It was almost surely Longmire, long-time chairman at U.C.L.A. and his associate, Jack Cannon, who first performed an anastomosis between the internal mammary artery and a coronary branch, probably in early 1958”
Off-Pump CABG

W. Dudley Johnson, one of the pioneers in the development of coronary artery surgery, wrote, “From 1962 to 1967, several sporadic instances of coronary grafting have subsequently been reported. All were isolated cases and, for uncertain reasons, were not reproduced. None had an impact on the development of coronary surgery”

- Green et al. advocated using cardiopulmonary bypass (CPB), fibrillating the vented heart, cross clamping the aorta, and washing all blood from the coronary system while performing the anastomosis.

- 1970s: CABG on CPB with cold cardioplegia: “GOLD STANDARD”
Coronary Artery Bypass Graft

99% blockage in LAD

90+% blockages in RCA
Coronary Artery Bypass Graft
Coronary Artery Bypass Graft
Cardiopulmonary Bypass

- Adsorbed Proteins from Heparinized Blood
- Activation of Blood Elements
  - Contact System: XII, XI, Prekallekrein, HMWK
  - Complement System: C3a, C5a
  - Intrinsic Coagulation pathway, Extrinsic Coagulation Pathway
  - Fibrinolysis
  - Platelets
Off-Pump CABG

• Minimally Invasive Direct Coronary Artery Bypass (MIDCAB) by Cardiothoracic Systems

• The Octopus System was devised by Medtronic
Off-Pump CABG
Coronary Shunting

- Reduces Coronary Occlusion Time
- May Avoid Ischemic Pre-conditioning
- Reduces the Risk of Dysrhythmias
- Allows More Time for Anastomosis
Off-Pump CABG
Shunt Insertion
Off-Pump CABG
Shunts

Single Limb
Double Limb
Triple Limb
Indications for Off-Pump CABG

• Feasibility of Optimal Revascularization*

• Reason to Avoid CPB:
  - Cerebrovascular disease
  - Diseased Ascending Aorta
  - Jehovah’s Witness ?

  *Circumflex Branches were initially deemed inaccessible for OPCABG
Conclusion:

• OPCABG can be done safely with significant morbidity <2% and mortality <1.5%

• With improved stabilization techniques and coronary shunting full revascularization, including circumflex Branches, is feasible

• It can be done safely in the elderly
Conclusion:

• It can be done safely in urgent cases
• It can be done safely in patients with low EF
• Early graft patency is comparable to CABG on CPB
• It may reduce hospital charge
• Long-term durability of OPCABG is yet to be determined
Application of Robotics

- Small incisions
- Significantly reduced patient pain
- Shorter hospital stays
- Applicable for beating-heart and stopped-heart approaches
- Improved surgeon precision and dexterity
- Improved visualization in 2-D or 3-D
- Minimized surgeon fatigue with an ergonomic operating environment
Atrial Fibrillation Surgery: Minimally Invasive

• If concomitant surgery is not needed, atrial fibrillation can be treated using minimally invasive techniques

• Ablation to eradicate atrial fibrillation

• Video Assisted Thoracoscopy, beating heart or hybrid procedures
  – Dual Epicardial Endocardial Persistent Atrial Fibrillation (AFib) Study (DEEP Trial)
Stent-Graft Repair of Aortic Aneurysms, A Review

• Single Piece Tapered Stent-Graft for AAA Repair
• Single Piece Stent-Graft for descending TAA Repair
• Bifurcated Modular Stent-Graft for AAA Repair
# Abdominal Aortic Aneurysm

## Incidence

- **Autopsy**: 1.5-3.0%
- **Unselected Ultrasound Screening**: 3.2%
- **Selected Patients with CAD**: 5.0%
- **Selected Patients with PVOD**: 10.0%
- **Femoral/Popliteal Aneurysms**: 50.0%
- **Men 80-85**: 6%
- **Men/Women >70, Hypertensive**: 11-12%
Aortic Aneurysm

Etiology

• Degenerative/Atherosclerotic
• Cystic Medial Necrosis
• Dissection
• Ehlers-Danlos Syndrome
• Collagen Vascular Disease
• Mycotic
Aortic Aneurysm

• Natural History of Thoracic and Abdominal Aortic Aneurysm: Increasing Diameter & Rupture

• 15000 deaths/ year in USA due to AAA rupture (13th leading cause of death)
## Abdominal Aortic Aneurysm

### Incidence of Ruptured Aneurysms at Autopsy

<table>
<thead>
<tr>
<th>Aneurysm Size</th>
<th>% Ruptured</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4cm</td>
<td>10</td>
</tr>
<tr>
<td>4.1-5cm</td>
<td>23.4</td>
</tr>
</tbody>
</table>
## Operative Mortality and Late Survival of Elective AAA Repair

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (n)</th>
<th>Mortality (%)</th>
<th>5-yr. Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whittemore</td>
<td>110</td>
<td>68</td>
<td>0</td>
</tr>
<tr>
<td>Crawford</td>
<td>860</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td>Reigel</td>
<td>499</td>
<td>76</td>
<td>3</td>
</tr>
<tr>
<td>Bernstein</td>
<td>123</td>
<td>71</td>
<td>1</td>
</tr>
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</table>
## Operative Morbidity of Elective AAA Repair

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>*Major Morbidity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnston et al, 202</td>
<td>30%</td>
</tr>
<tr>
<td>1989 (multicenter)</td>
<td></td>
</tr>
<tr>
<td>Cambria et al, 666</td>
<td>15%</td>
</tr>
<tr>
<td>1992 (single institution)</td>
<td></td>
</tr>
</tbody>
</table>

*Cumulative*
• In good-risk patients, aneurysms > 5 cm in diameter are best treated by replacement with a prosthetic graft.
  - Operative mortality should be < 5% 1-year survival > 90%.
  - Aortic endograft techniques must meet or exceed these standards if they are to supplant standard surgical repair”
    • Aneurysms 4-5cm documented 0.5cm increase in diameter in 6 months
    • Aneurysms 2 x the diameter of infrarenal neck or saccular

AAA Repair

with

Single Piece Tapered Stent-Graft
Stent-Graft Repair of Thoracic Aortic Aneurysms
Bifurcated Modular Stent-Graft Repair of AAA
New Developments

in the

Treatment of Heart Failure
Heart Failure Demographics

• Over 4.8 million Americans with heart failure
• Over 400,000 new cases per year
• Most common of all Medicare admission DRG’s
• Over 240,000 deaths per year
• Most common cause is Coronary Artery Disease
  *about 2 / 3
• Severe heart failure - Heart Transplants
  ± 5,000 listed  ± 2,500 tx’d per year
• Candidates for mechanical devices as destination
  40,000 to 80,000
End Stage Heart Disease
Therapeutic Options

- Medical Management
- Conventional Surgical Procedures
- Innovative Surgical Procedures
- Heart Transplantation
- LV Assist Devices
- Artificial Heart
## Cumulative Impact of Heart Failure Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Relative Risk</th>
<th>2yr Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td>35%</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>↓ 23%</td>
<td>27%</td>
</tr>
<tr>
<td>Aldosterone Antagonist</td>
<td>↓ 30%</td>
<td>19%</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>↓ 35%</td>
<td>12%</td>
</tr>
<tr>
<td>ICD (CAD, EF&lt;30%)</td>
<td>↓ 31%</td>
<td>8.5%</td>
</tr>
</tbody>
</table>

Cumulative risk reduction if all four therapies are used: 75%
Absolute risk reduction: 26.5%

Moss et al.  NEJM 2002
Ischemic Cardiomyopathy

Treatment Alternatives

Medical Therapy
  Angiogenesis

Transplantation
  Tissue Regeneration/Tissue Engineering

Revascularization
  Stem Cell Therapy
ETIOLOGY OF END-STAGE CARDIAC FAILURE

- ischemic heart disease
- idiopathic dilated cardiomyopathy.
- infectious (viral), inflammatory, toxic, metabolic, postpartum and familial
- valvular heart disease
- congenital heart disease
- Intractable angina, refractory malignant ventricular arrhythmias, allograft occlusive coronary artery disease
Heart Failure

- Over 4000 patients awaiting heart transplant in USA
- Over 700 people die while on transplant list annually
- Over 40,000 patients with heart failure die or never listed for transplantation
Ventricular Assist Devices

• To prevent or reverse end-organ dysfunction due to heart failure
• Used as bridge to recovery (example myocarditis)
• Used as bridge to transplantation
• Used as target
Thoratec Ventricular Assist Device
Thoratec Ventricular Assist Device
Abiocor Total Artificial Heart
Abiocor Total Artificial Heart

This artificial heart system uses a hydraulic motor, powered by batteries.
SynCardia Temporary Total Artificial Heart

Total Artificial Heart

Human Heart
Jarvik Ventricular Assist Device
Left Ventricular Assist Devices for Heart Failure

- Bridge to Recovery
- Bridge to Transplant
- Bridge to Eligibility

HeartMate II
Left Ventricular Assist Device

HeartWare Left Ventricular Assist Device
Cardiovascular Tissue Engineering and Tissue Regeneration
Cleavage stage embryo

Cultured blastocyst

Isolated inner cell mass

Irradiated mouse fibroblast feeder cells

Cells dissociated and replated

New feeder cells

Established ES cell cultures
Mouse adult stem cells are injected into the muscle of the damaged left ventricular wall of the mouse heart.

Human adult bone marrow stem cells are injected into the tail vasculature of a rat.

The stem cells induce new blood vessel formation in the damaged heart muscle and proliferation of existing vasculature.

Stem cells help regenerate damaged heart muscle.

New blood vessels
Delivery Options for Stem Cell Transfer Modalities to the Heart

The red colored area represents apical lesion of the left ventricle by myocardial infarction. Blue and green arrows suggest the possible route of cell infusion and migration into the infarct.

ASCs Home to Heart After Injury

MI induced (LAD occl or cryo) + Stem cells injected intraventricular

β-Gal positive ADCs isolated + Stem cells injected into circulation

β-Gal positive myocytes identified

Assessment of LV Function

4 weeks Post-MI

<table>
<thead>
<tr>
<th></th>
<th>LVEF (%)</th>
<th>LVEDD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>70 ± 5</td>
<td>4.5 ± 0.5</td>
</tr>
<tr>
<td>Saline</td>
<td>75 ± 3</td>
<td>4.0 ± 0.3</td>
</tr>
<tr>
<td>ADCs</td>
<td>80 ± 2</td>
<td>3.5 ± 0.2</td>
</tr>
</tbody>
</table>

* p < 0.05 vs Control
** p < 0.01 vs Control
Cell transplantation improves LV Function Post-MI

Autologous Atrial Appendage, Cryolesion, Tx 3W, $2 \times 10^6$ cells, $n = 12$ rats
How does cell transplantation work?

Direct

• Regenerate contractile muscle

Indirect

• Cell transplantation leads to stabilization of the scar preventing infarct expansion and subsequent LV remodeling → matrix secretion
• Induction of angiogenesis
• Paracrine action of transplanted cells → Anti-apoptotic
• Many cell types which do not contract improve function
• Skeletal myocytes are not coupled electrically by gap junctions
Cell Types Utilized for Cell Transplantation

- Skeletal Myoblasts
- Adult Stem/Progenitor Cells
  - Bone Marrow Stem Cells
  - Endothelial Progenitor Cells (EPCs)
  - Adipose Tissue-derived Stem Cells (ASCs)
  - (Embryonic Stem Cells → Ethical Issues)
- Induce Pluripotent Stem Cell
Myoblast Transplantation

CABG and Cell Transplantation
• 24 subjects total
• 10 million cells
• 30 million cells
• 100 million cells
• 300 million cells

LVAD and Cell Transplantation
• 6 subjects total
• 300 million cells

3 to 30 sites are injected. Each 0.1 ml injection has 10 million cells per injection
### Serious Adverse Events

**DSMB determined unrelated to Cell Injections**

<table>
<thead>
<tr>
<th>Condition</th>
<th>CABG</th>
<th>LVAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1*</td>
<td>3*</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>4*</td>
<td>2*</td>
</tr>
<tr>
<td>AICD ACTIVATION</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1*</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>1*</td>
<td>3*</td>
</tr>
<tr>
<td>Infarction</td>
<td>1*</td>
<td>0</td>
</tr>
<tr>
<td>CVA</td>
<td>2*</td>
<td>1</td>
</tr>
</tbody>
</table>
Adverse Events
Possibly related to Cell Injection

Non-sustained Ventricular Tachycardia

• 3 patient \((100 \times 10^6 \text{ dose group})\) 1 week post transplant.

• ICD implantation performed

• No further Arrhythmias detected during interrogation of ICD at 6-months follow-up.
Myoblast Stably Engraft in Human Myocardium

Trichrome

Skeletal MHC (MY-32)

Baseline

6 mo f/u

Anterior

Apex

Inferior

3 months Post-Tx

Pagani et al, JACC 41-2003

Myoblast + with LV AD → listed for OHTX
Engrafted Myoblast Induce Angiogenesis

CD31 Staining

Scar  Graft

* P<0.0001

# CD-31 + vessels

<table>
<thead>
<tr>
<th>Scar</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>226</td>
</tr>
</tbody>
</table>

Baseline

6 month follow-up

Perfusion
Effect of CABG + Myoblast Transplantation on EF

Associated with a decrease in NYHA Classification from an average of 2.1 Pre-CABG to 0.8 Post-CABG

Menasche P, J Am Coll Cardiol 2003 Apr 2;41(7):1078-83
## Published Clinical Trials of Myoblast Transplantation

<table>
<thead>
<tr>
<th>Control Group</th>
<th># of pts</th>
<th>Delivery Method</th>
<th>Dose</th>
<th>Revasc</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dib et al.</td>
<td>None</td>
<td>30 Transepicardial (during CABG)</td>
<td>0.1-3X10^8</td>
<td>Yes</td>
<td>Global EF ↑&lt;br&gt;Perfusion/Viability in Infarct Area ↑</td>
</tr>
<tr>
<td>Menasche et al.</td>
<td>None</td>
<td>10 Transepicardial (during CABG)</td>
<td>9X10^8</td>
<td>Yes</td>
<td>Global EF ↑&lt;br&gt;Regional Wall Motion Global EF ↑&lt;br&gt;Increased VT</td>
</tr>
<tr>
<td>Herros et al.</td>
<td>None</td>
<td>11 Transepicardial (during CABG)</td>
<td>1.9X10^8</td>
<td>Yes</td>
<td>Global EF ↑&lt;br&gt;Regional Wall Motion Global EF ↑&lt;br&gt;Viability in Infarct Area ↑</td>
</tr>
<tr>
<td>Chacques et al.</td>
<td>None</td>
<td>20 Transepicardial (during CABG)</td>
<td>34X10^8</td>
<td>Yes</td>
<td>Global EF ↑&lt;br&gt;Regional Wall Motion Global EF ↑&lt;br&gt;Viability in Infarct Area ↑</td>
</tr>
<tr>
<td>Smits et al.</td>
<td>None</td>
<td>5 Transendocardial* (NOGA catheter)</td>
<td>3X10^8</td>
<td>No</td>
<td>Global EF ↑&lt;br&gt;Regional Wall Motion Global EF ↑&lt;br&gt;1 pt developed VT</td>
</tr>
<tr>
<td>Siminiak et al.</td>
<td>None</td>
<td>10 Catheter Base (Coronary Sinus)</td>
<td>0.004-0.5X10^8</td>
<td>Yes</td>
<td>Global EF ↑&lt;br&gt;Regional Wall Motion Global EF ↑&lt;br&gt;4 pts developed sustained VT</td>
</tr>
</tbody>
</table>
Adult Stem Cells are an Alternative Source of Cells

Bone Marrow Cells Improve LV Function Post-MI

18 pigs underwent permanent coronary artery occlusion
Received ~8x10^7 BMC or vehicle IC 1 month post-MI

Rates of differentiation to cardiac myocytes range from 0% to 60-80% in the infarcted region

Differentiation vs. Fusion of Stem Cells

**Fusion:**

- Stem Cell
- Myocyte

**Differentiation:**

- Stem Cell
- Liver
- Myocyte
- Nerve

Rates of fusion of delivered stem cells to endogenous cardiac myocytes range from 0% to ~50% in the infarcted region.
<table>
<thead>
<tr>
<th>Study</th>
<th>Cells transplanted</th>
<th>Route of delivery</th>
<th>Results</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menasche et al⁸</td>
<td>Skeletal myoblasts</td>
<td>IM during CABG</td>
<td>improved LVEF, wall thickness, symptoms</td>
<td>4 sustained VT</td>
</tr>
<tr>
<td>Herreros et al⁶</td>
<td>Skeletal myoblasts</td>
<td>IM during CABG</td>
<td>improved LVEF, regional wall motion, viability in infarct zone</td>
<td>None</td>
</tr>
<tr>
<td>Dib et al⁷</td>
<td>Skeletal myoblasts</td>
<td>IM during CABG/</td>
<td>increased LVEF, viability, symptoms</td>
<td>3 non-sustained VT</td>
</tr>
<tr>
<td>Pagani et al¹¹</td>
<td>Skeletal myoblasts</td>
<td>IM during LVAD</td>
<td>neovascularization at engrafted cells</td>
<td>None</td>
</tr>
<tr>
<td>Smits et al⁹</td>
<td>Skeletal myoblasts</td>
<td>IM via NOGA</td>
<td>improved LVEF, wall motion, wall thickness</td>
<td>5 non-sustained VT</td>
</tr>
<tr>
<td>Siniak et al¹⁰</td>
<td>Skeletal myoblasts</td>
<td>IM via coronary sinus</td>
<td>improved LVEF</td>
<td>1 sustained VT</td>
</tr>
<tr>
<td>Strauer et al¹³</td>
<td>Mononuclear BMCs</td>
<td>CI during PCI</td>
<td>improved wall motion, cardiac geometry and function</td>
<td>None</td>
</tr>
<tr>
<td>Tse et al²¹</td>
<td>Mononuclear BMCs</td>
<td>IM via NOGA</td>
<td>unchanged LVEF; improved wall motion, thickness, angina symptoms</td>
<td>None</td>
</tr>
<tr>
<td>Stamm et al²⁴</td>
<td>AC133+ BMCs</td>
<td>IM during CABG</td>
<td>improved LVEF, cardiac geometry, perfusion</td>
<td>None</td>
</tr>
<tr>
<td>Fuchs et al¹²</td>
<td>Mononuclear BMCs</td>
<td>IM via NOGA</td>
<td>improved perfusion, exercise tolerance, angina symptoms, quality of life</td>
<td>None</td>
</tr>
<tr>
<td>Perin et al¹²</td>
<td>Mononuclear BMCs</td>
<td>IM via NOGA</td>
<td>improved LVEF, cardiac geometry, perfusion, symptoms, exercise tolerance</td>
<td>None</td>
</tr>
<tr>
<td>Assmus et al¹⁶</td>
<td>Mononuclear BMCs or circulating</td>
<td>CI</td>
<td>improved LVEF, cardiac geometry; migratory capacity more important than cell type</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>blood-derived progenitor cells</td>
<td></td>
<td></td>
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<tr>
<td>Aviles et al¹⁷</td>
<td>Mononuclear BMCs</td>
<td>CI</td>
<td>improved LVEF, cardiac geometry</td>
<td>None</td>
</tr>
<tr>
<td>Galinanes et al²⁹</td>
<td>Mononuclear BMCs</td>
<td>IM during CABG</td>
<td>improved wall motion only in areas injected with BMC and received CABG;</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>improved angina heart failure symptoms</td>
<td></td>
</tr>
<tr>
<td>Kang et al¹⁹</td>
<td>PBSCs</td>
<td>CI during PCI</td>
<td>improved LVEF, perfusion, exercise tolerance</td>
<td>70% in-stent restenosis in G-CSF groups</td>
</tr>
<tr>
<td>Engelmann et al²⁰</td>
<td>PBSCs</td>
<td>G-CSF mobilization of PBSC (no actual infusion)</td>
<td>improved cardiac geometry</td>
<td>None</td>
</tr>
<tr>
<td>Wollert et al³⁰</td>
<td>Mononuclear BMCs</td>
<td>CI</td>
<td>improved LVEF</td>
<td>None</td>
</tr>
</tbody>
</table>

BMC = bone marrow cell; PBSC = peripheral blood stem cell; IM = intramyocardial; CI = coronary infusion; CABG = coronary artery bypass grafting; LVAD = left ventricular assistive device; PCI = percutaneous coronary intervention; G-CSF = granulocyte-colony stimulating factor; LVEF = left ventricular ejection factor; VT = ventricular tachycardia
# Human Trials of Stem/Progenitor Cells Post-MI

<table>
<thead>
<tr>
<th>Control Group</th>
<th>End point</th>
<th>Length of F/U (mon)</th>
<th>Time to cell infusion</th>
<th>N</th>
<th>LVEF Baseline</th>
<th>LVEF Endpoint</th>
<th>% LVEF Increase</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schächinger et al.</td>
<td>None</td>
<td>LVEF</td>
<td>4</td>
<td>4.3 dy</td>
<td>CPC</td>
<td>30</td>
<td>51</td>
<td>59</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BMC</td>
<td>29</td>
<td>49</td>
<td>57</td>
</tr>
<tr>
<td>Strauer et al.</td>
<td>PCI alone</td>
<td>LVEF</td>
<td>3</td>
<td>5.9 dy</td>
<td>Control</td>
<td>10</td>
<td>60</td>
<td>64</td>
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<td>BMC</td>
<td>10</td>
<td>57</td>
<td>62</td>
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<tr>
<td>Wollert et al.</td>
<td>PCI alone</td>
<td>LVEF</td>
<td>6</td>
<td>4.8 dy</td>
<td>Control</td>
<td>30</td>
<td>51.3</td>
<td>52</td>
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<td>50</td>
<td>56.7</td>
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<tr>
<td>Chen et al.</td>
<td>PCI alone</td>
<td>LVEF</td>
<td>6</td>
<td>18 dy</td>
<td>Control</td>
<td>35</td>
<td>49</td>
<td>54</td>
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<tr>
<td></td>
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<td>BMC</td>
<td>34</td>
<td>48</td>
<td>67</td>
</tr>
<tr>
<td>Assmus et al (TOPCARE-AMI)</td>
<td>PCI alone</td>
<td>LVEF</td>
<td>48</td>
<td>4.5 dy</td>
<td>Control</td>
<td>20</td>
<td>51</td>
<td>53</td>
</tr>
</tbody>
</table>
STEM CELL Tx Post-MI

Inclusion criteria
Acute myocardial infarction, cumulative ST-segment elevation of 6 mm or more, time after symptom onset longer than 2 h, successful reperfusion after percutaneous coronary intervention, and documented LV dysfunction

Within 24 h of enrolment
Informed consent obtained, acetate PET scan done, transthoracic echocardiography examination undertaken, bone marrow aspiration, randomisation

In-hospital monitoring (7 days)
Rhythm monitoring
CineMRI with late enhancement
Echocardiography and tissue doppler imaging

Follow-up
Acetate PET scan (4 months)
CineMRI with late enhancement (4 months)
Echocardiography and tissue doppler imaging (2–4 months)

Stefan Janssens et al The Lancet, Volume 367, Issue 9505, 14 January 2006-20 January 2006,
STEM CELL Tx Post-MI

152 patients assessed for eligibility
- 83 ineligible

69 enrolled
- 2 excluded
  - 1 no bone marrow access
  - 1 emergency coronary artery bypass graft

67 randomised

34 assigned placebo
- 4 no MRI
  - 1 claustrophobia
  - 1 intracochlear implant
  - 1 technical failure
  - 1 patient refusal

34 assessed at 7 days

33 assigned BMSC transfer
- 2 no MRI
  - 1 claustrophobia
  - 1 patient refusal

33 assessed at 7 days
- 1 death from haemorrhagic shock at 2 months

34 completed
- 4 month follow-up
- 30 assessed with MRI

32 completed
- 4 month follow-up
- 30 assessed with MRI

Stefan Janssens et al The Lancet, Volume 367, Issue 9505, 14 January 2006-20 January 2006,
Stable Ischemic Heart Disease, Transcoronary Infusion, No cell (23 patients) CPC (24 patients) BMC (28 patients) Assmus B, NEJM, 2006, Sept 21, 355(12)

<table>
<thead>
<tr>
<th>Table 2: Quantitative Variables Pertaining to Left Ventricular Function, as Assessed by Left Ventricular Angiography.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Global LVEF (%)</td>
</tr>
<tr>
<td>Control group</td>
</tr>
<tr>
<td>CPC group</td>
</tr>
<tr>
<td>BMC group</td>
</tr>
<tr>
<td>P value for all 3 groups</td>
</tr>
<tr>
<td>Regional contractility in central target area (SD from normal/chord)</td>
</tr>
<tr>
<td>Control group</td>
</tr>
<tr>
<td>CPC group</td>
</tr>
<tr>
<td>BMC group</td>
</tr>
<tr>
<td>P value for all 3 groups</td>
</tr>
<tr>
<td>Extent of regional left ventricular dysfunction (% circumference)</td>
</tr>
<tr>
<td>Control group</td>
</tr>
<tr>
<td>CPC group</td>
</tr>
<tr>
<td>BMC group</td>
</tr>
<tr>
<td>P value for all 3 groups</td>
</tr>
<tr>
<td>End-diastolic volume (ml/m² of BSA)</td>
</tr>
<tr>
<td>Control group</td>
</tr>
<tr>
<td>CPC group</td>
</tr>
<tr>
<td>BMC group</td>
</tr>
<tr>
<td>P value for all 3 groups</td>
</tr>
<tr>
<td>End-systolic volume (ml/m² of BSA)</td>
</tr>
<tr>
<td>Control group</td>
</tr>
<tr>
<td>CPC group</td>
</tr>
<tr>
<td>BMC group</td>
</tr>
<tr>
<td>P value for all 3 groups</td>
</tr>
<tr>
<td>Stroke volume (ml/m² of BSA)</td>
</tr>
<tr>
<td>Control group</td>
</tr>
<tr>
<td>CPC group</td>
</tr>
<tr>
<td>BMC group</td>
</tr>
<tr>
<td>P value for all 3 groups</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
</tr>
<tr>
<td>Control group</td>
</tr>
<tr>
<td>CPC group</td>
</tr>
<tr>
<td>BMC group</td>
</tr>
<tr>
<td>P value for all 3 groups</td>
</tr>
</tbody>
</table>

* Plus-minus values are means ±SD. BSA denotes body-surface area.
Unanswered Questions

• Issues of dose, timing, delivery route and optimal cell type remain unresolved?

• Optimal source of donor stem cells is unknown and clinical utility of Skeletal Myoblasts vs. BMCs vs. “off the shelf” MSCs?

• What is the risk of ventricular arrhythmias?

• Mechanism of action of transplanted cells?
Adipose Tissue Contains a Stem Cell

A. Stem Cell Markers

- Sca1+, cKit−, Stro-1lo
- Similar to BM-MSC
  - CD13+, CD29+, CD44+
  - CD11c−, CD45−
- Distinct from BM-MSC
  - CD106−, CD54+, CD34lo

B. Clonal Analysis

<table>
<thead>
<tr>
<th></th>
<th>Adipogenic</th>
<th>Osteogenic</th>
<th>Chondrogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tri:</td>
<td>(A, O, C)</td>
<td>7 of 33</td>
<td></td>
</tr>
<tr>
<td>Dual:</td>
<td>(O, C)</td>
<td>10 of 33</td>
<td></td>
</tr>
<tr>
<td>Dual:</td>
<td>(A, O)</td>
<td>10 of 33</td>
<td></td>
</tr>
<tr>
<td>Dual:</td>
<td>(A, C)</td>
<td>3 of 33</td>
<td></td>
</tr>
<tr>
<td>Single:</td>
<td>A only</td>
<td>6 of 33</td>
<td></td>
</tr>
</tbody>
</table>
Human Adipose Tissue Contains a Multipotent Stem Cell
Conclusion

• Heart Failure Treatment is Mainly Symptom Management

• Heart Transplantation is the ONLY curative option

• Heart Txp is limited by organ shortage, immunologic rejection, and immunosuppression

• Evidence for Autologous Cell Therapy & Tissue Regeneration is Promising
Tissue Engineering’s Most Popular Approach is Based on the Premise that Preparation of Cells, Extracellular Matrix, and Growth Factors Leads to Tissue Reconstruction, and that 3-dimensional Biodegradable Scaffolds are Useful Alternatives for Extracellular Matrix.
SCAFFOLDS

Polymers
Gels
Fibers
Membranes

Cultivated Adult Stem Cells
Embryonic stem cells
Autogenous Mobilized Allogenic Engineered

PROSTHESIS

CELLS

SIGNALS

TGFβ FGF Hemo-dynamic
Three Areas of Cardiovascular Tissue Engineering

1. Vascular grafts
2. Heart valve prostheses
3. Cardiac muscle grafts
Campbell JH et al., 1999

Diagram showing the transition from myofibroblast wall and mesothelium in silastic tubing.
Hoestrup SP, et al 2000

Pulse Duplicator Bioreactor
Figure 3. TE heart valve after 14 days of conditioning in bioreactor.