CARDIAC STEM CELL THERAPY – Update 2008

Yerem Yeghiazarians, MD
Assistant Professor of Medicine
Director, Cardiac Translational Stem Cell Program
Co-Director, Cardiac Catheterization Laboratory
Director, Cardiac Peripheral Interventions

University of California, San Francisco

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Today’s Topics

• Scope of the problem and brief background
• Recent developments in the stem cell field as related to cardiology
  – Human clinical trial data in cardiology
• UCSF Translational Cardiac Stem Cell Program
• Speculate about the future
Epidemiology of Myocardial Infarction and Angina in the U.S.

- Single Largest Cause of Death
  - >500,000 deaths in the U.S./year
  - 1 in every 4.8 deaths

- Incidence
  - 1,500,000 Americans will have a new or recurrent MI each year

- Prevalence
  - ~14,000,000 with a history of MI, angina, or both
  - ~5,000,000 Americans with Heart Failure

* Based on data from the Atherosclerotic Risk in Communities study (ARIC) of the National Heart, Lung, and Blood Institute, 1987-94. Includes Americans hospitalized with definite or probable MI or fatal CHD, not including silent MIs.

American Heart Association, 1998 Heart and Stroke Statistical Update
Myocardial Infarction and Heart Failure

Myocardial Infarction

Death of cardiomyocytes

Scar tissue formation

Aneurysmal thinning

Left ventricular remodeling

Decreased pumping capacity

Courtesy of Randall Lee and Karen Christman
Current Therapeutic Options For Patients with Large MI and Severe Heart Dysfunction

• Revascularization therapy
• Medications --- aspirin, plavix, statin, ace-inhibitor, beta-blocker, aldactone
• Prophylactic ICD to decrease risk of sudden death
• Cardiac resynchronization therapy
• Biventricular assist devices
• Heart Transplantation

None of these therapies lead to myocyte generation
Novel Therapies Are Much Needed

- Concept of “regenerative medicine” is clearly very attractive

- 1990’s → Gene therapy was the novel therapy

- 2000’s → Use of Stem Cells for cell-based therapies has become a very active area of research

- But, what do we really know about this mode of therapy?

   FACT vs. FICTION
Stem Cell -- “Fountain of Youth?”
Potential Beneficial Mechanisms of Stem Cell Therapy after MI

Classification of Stem Cells

- The classification of stem cells is still in evolution based on a large number of cell markers

  Primary distinction is between:

  1) Embryonic stem cells
  2) Non-embryonic stem cells
     - adult stem cell
     - cord blood
  3) Induced Pluripotent Stem cells
  4) Somatic Cell Nuclear Transfer
In the 3-5 day old embryo, called a blastocyst, a group of about 30 cells called the **inner cell mass** gives rise to specialized cells that make up an adult organism.

Adapted from UCSF Program in Development and Stem Cell Biology
Embryonic Stem Cell Differentiation

Körbling and Estrov NEJM 349;6, 2003
Induced Pluripotent Stem Cell Lines (iPS)

Four factors (Oct 4, NANOG, Sox 2, LIN28) sufficient to reprogram a human somatic stem cell (fibroblast) to a pluripotent cell with all the characteristics of hES (Yu J, et al., Thomson J, Science 2007)

Patient-Specific Somatic Cell Nuclear Transfer

Perry ACF, NEJM 2005
Adult Stem Cells

• In distinction with human embryonic stem cells, these cells are undifferentiated cells found in mature tissues.

• They appear to remain quiescent for many years but they can generate and replace terminally differentiated cells once activated by tissue injury or disease.

• Some of the tissues that contain stem cells include the bone marrow (hematopoietic and mesenchymal stem cells), brain, peripheral blood, blood vessels, skeletal muscle (myoblasts), skin (keratinocytes), liver, lung, pancreas, and heart.
Which Stem Cells to use?

Somatic Cell Nuclear Transfer Cells

Embryonic Stem Cells

Induced Pluripotent Cells

Adult Stem Cells

How many cells to use?
Which patients will benefit?
How to deliver the cells?
What is the fate of the cells?
What are the risks/benefits?
How are the benefits achieved?
Can we make the cells work better?
Many other questions ….
Human Embryonic Stem Cells

Advantages
- Highly Expandable
- Pluripotent

Disadvantages
- Ethical objections
- Difficult to isolate
- Risk of rejection
- Immune-suppressive Rx required
- Arrhythmogenic potential
- Risk of teratocarcinomas
- Lack of specific markers

Strauer BE and Kornowski R 2003;107: 929-934
Somatic Cell Nuclear Transfer

**Advantages**
- Highly Expandable
- Pluripotent

**Disadvantages**
- ? Ethical objections
- **Difficulty in obtaining oocytes**
- ? Risk of rejection
- ? Immune-suppressive Rx required
- ? Arrhythmogenic potential
- ? Risk of teratocarcinomas
- ? Lack of specific markers
Adult Stem Cells

**Advantages**
- Likely more easily obtainable
- No ethical objections
- Highly compatible
- Autologous transplantation
- No need for immunosuppressive Rx
- Clinical application already realized

**Disadvantages**
- Lack of specific markers
- ? arrhythmogenic

Strauer BE and Kornowski R 2003;107: 929-934
Adult Stem Cell Therapy and the Heart

**Bone Marrow**
- Mesenchymal stem cells (CD 34⁻)
- Hematopoietic stem cells (CD 34⁺)
- Multipotent stem cells

**Skeletal Muscle**
- Satellite cells (myoblast)

**Blood Vessel**
- Endothelial Progenitor Cells (Hemangioblasts)

**Heart**
- Side Population cells/
  Cardiac specific progenitor

**Other (Adipose)**

Adapted from M. Schneider MD
Skeletal Myoblast

• Cell based cardiac therapies began with skeletal myoblast because of their availability from autologous sources, ability to proliferate, and withstand ischemia.

• Skeletal muscle does not normally express gap junction proteins and hence do not form electromechanical coupling between engrafted cells and host cardiomyocytes → this can lead to dangerous heart arrhythmias.

• Numerous Phase I and II studies reported.

• Dr. Menasche conducted a large scale, randomized, multicenter, double-blind, placebo-controlled trial in bypass patients. All patients had to have a defibrillator implanted.

The study was stopped without much benefit ..... But another trial (MARVEL Trial) is underway .....
Autologous Bone Marrow

• Second wave of trials were fueled in part by hopes for cardiac transdifferentiation as well as angiogenic activity
• Large number of unfractionated cells could be obtained
• Little processing required
• Reduced cost and less regulatory burden
• BM however contains many different type of cells (hematopoietic, MSC and others)
Procedure of Intracoronary Cell Transplantation into Infarcted Myocardium in Humans
Transendocardial Targeted Injection Technique

NOGA Myostar injection catheter

Injection catheter Advanced into LV

Perin EC et al Circulation 2003;107: 2294-2302
Adult Stem Cell Trials in Cardiac Patients

• Acute Myocardial Infarction

• Myocardial ischemia and no revascularization options

• Ischemic and non-ischemic cardiomyopathy

Majority of these trials have delivered bone marrow cells to the heart by intra-coronary infusion
# Meta-analysis of intra-coronary cell therapy clinical trials

## Table 1  Main Features of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Patients Enrolled (Patients at Follow-Up)</th>
<th>Cell Type</th>
<th>Follow-Up (Months)</th>
<th>Primary End Point</th>
<th>Imaging Modality for LVEF Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strouwer et al. (10)</td>
<td>2002</td>
<td>Non-RCT</td>
<td>20 (20)</td>
<td>BMC</td>
<td>3</td>
<td>LVEF</td>
<td>LV angiography</td>
</tr>
<tr>
<td>Bertrand et al. (11)</td>
<td>2005</td>
<td>Non-RCT</td>
<td>35 (35)</td>
<td>BMC</td>
<td>4</td>
<td>Safety, LVEF</td>
<td>LV angiography, SPECT</td>
</tr>
<tr>
<td>Jannsens et al. (8)</td>
<td>2006</td>
<td>RCT</td>
<td>67 (66)</td>
<td>BMC</td>
<td>4</td>
<td>LVEF</td>
<td>Cardiac MRI</td>
</tr>
<tr>
<td>BOOST (7)</td>
<td>2006</td>
<td>RCT</td>
<td>60 (60)</td>
<td>BMC</td>
<td>18</td>
<td>LVEF, safety</td>
<td>Cardiac MRI</td>
</tr>
<tr>
<td>Zhan-Qun et al. (13)</td>
<td>2006</td>
<td>Non-RCT</td>
<td>70 (58)</td>
<td>PMC</td>
<td>6</td>
<td>LVEF, LV volumes, WMSI</td>
<td>Echocardiography</td>
</tr>
<tr>
<td>MAGIC-CELL-3-DES (12)</td>
<td>2006</td>
<td>RCT</td>
<td>56 (50)</td>
<td>PMC</td>
<td>6</td>
<td>LVEF</td>
<td>Cardiac MRI</td>
</tr>
<tr>
<td>TCT-STAMI (15)</td>
<td>2006</td>
<td>RCT</td>
<td>20 (20)</td>
<td>BMC</td>
<td>6</td>
<td>LVEF</td>
<td>Echocardiography, SPECT</td>
</tr>
<tr>
<td>ASTAMI (2,4)</td>
<td>2006</td>
<td>RCT</td>
<td>100 (87)</td>
<td>BMC</td>
<td>6</td>
<td>LVEF, EDV, infarct size</td>
<td>SPECT, MRI, echo</td>
</tr>
<tr>
<td>REPAIR-AMI (5)</td>
<td>2006</td>
<td>RCT</td>
<td>204 (187)</td>
<td>BMC</td>
<td>12</td>
<td>LVEF</td>
<td>LV angiography</td>
</tr>
<tr>
<td>Meluzin et al. (16)</td>
<td>2006</td>
<td>RCT</td>
<td>66 (66)</td>
<td>BMC</td>
<td>3</td>
<td>Infarct zone systolic function</td>
<td>SPECT</td>
</tr>
</tbody>
</table>

BMC = bone marrow cells; EDV = end-diastolic volume; LV = left ventricular; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PMG = peripheral mononuclear cells; RCT = randomized controlled trial; SPECT = single-photon-emission computed tomography; WMSI = wall motion score index.
Meta-analysis of intra-coronary cell therapy clinical trials

Table 2  Patients and Procedural Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean Age (yrs)</th>
<th>Men (%)</th>
<th>Anterior AMI (%)</th>
<th>Hours to PCI</th>
<th>DES Use (%)</th>
<th>Days to ICT</th>
<th>Average Number of Injected Cells (10⁶)</th>
<th>CD34⁺ Cells (10⁹)</th>
<th>Injected Volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strauer et al. (10)</td>
<td>50</td>
<td>92.5</td>
<td>37.5</td>
<td>11.5</td>
<td>0</td>
<td>8</td>
<td>46</td>
<td>NP</td>
<td>20</td>
</tr>
<tr>
<td>Bartunek et al. (11)</td>
<td>54</td>
<td>91</td>
<td>94</td>
<td>10</td>
<td>8.6</td>
<td>11.6</td>
<td>NP</td>
<td>15.4</td>
<td>15-20</td>
</tr>
<tr>
<td>Janssens et al. (8)</td>
<td>57</td>
<td>82</td>
<td>63</td>
<td>3.9</td>
<td>NP</td>
<td>1</td>
<td>304</td>
<td>2.8</td>
<td>10</td>
</tr>
<tr>
<td>BOOST (7)</td>
<td>56</td>
<td>70</td>
<td>77</td>
<td>8.9</td>
<td>NP</td>
<td>4.8</td>
<td>2,460</td>
<td>9.5</td>
<td>26</td>
</tr>
<tr>
<td>Zhang-Quan et al. (13)</td>
<td>60</td>
<td>80</td>
<td>60</td>
<td>24</td>
<td>NP</td>
<td>6</td>
<td>72.5</td>
<td>NP</td>
<td>57</td>
</tr>
<tr>
<td>MAGIC CELL-3-DES (12)</td>
<td>60</td>
<td>80</td>
<td>54</td>
<td>9.1</td>
<td>100</td>
<td>4</td>
<td>1,500</td>
<td>NP</td>
<td>7</td>
</tr>
<tr>
<td>TCT-STEMI (15)</td>
<td>58</td>
<td>90</td>
<td>70</td>
<td>7.5</td>
<td>NP</td>
<td>0.5</td>
<td>58.7</td>
<td>1.8</td>
<td>16</td>
</tr>
<tr>
<td>ASTAMI (2,4)</td>
<td>57</td>
<td>84</td>
<td>100</td>
<td>3.5</td>
<td>5</td>
<td>6</td>
<td>68</td>
<td>0.7</td>
<td>NP</td>
</tr>
<tr>
<td>REPAIR-AMI (5)</td>
<td>56</td>
<td>82</td>
<td>78</td>
<td>7.2</td>
<td>14.5</td>
<td>4.4</td>
<td>236</td>
<td>3.6</td>
<td>10</td>
</tr>
<tr>
<td>Meluzin et al. (16)</td>
<td>55</td>
<td>92.4</td>
<td>85</td>
<td>7.7</td>
<td>NP</td>
<td>7</td>
<td>55</td>
<td>0.55</td>
<td>21</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; DES = drug-eluting stent; ICT = intracoronary cell therapy; NP = not provided; PCI = percutaneous coronary intervention.

Lipinski MJ et al, JACC 2007;50: 1761-7
Meta-analysis of intra-coronary cell therapy clinical trials – Impact on LV Ejection Fraction

- 3% ↑EF with cell therapy (p<0.001)
- 5.6% reduction in infarct size (p<0.001)
- 7.4 ml reduction in LV ESV (p=0.002)
- Non-significant trend towards LV EDV reduction (4.6 ml) (p=0.11)

Lipinski MJ et al, JACC 2007;50: 1761-7
Meta-analysis of intra-coronary cell therapy clinical trials – SAFETY

Table 4  Clinical Events at the Longest Available Follow-Up as Reported by Included Studies and Pooled With Peto Method*

<table>
<thead>
<tr>
<th>Study</th>
<th>Death</th>
<th>Recurrent Myocardial Infarction</th>
<th>Target Vessel Revascularization</th>
<th>Rehospitalization for Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strauer et al. (10)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bartunek et al. (11)</td>
<td>0/19 vs. 0/16</td>
<td>0/33 vs. 0/34</td>
<td>11/19 vs. 4/16</td>
<td>—</td>
</tr>
<tr>
<td>Jannsens et al. (8)</td>
<td>1/34 vs. 0/34</td>
<td>0/33 vs. 0/34</td>
<td>2/33 vs. 2/34</td>
<td>—</td>
</tr>
<tr>
<td>BOOST (7)</td>
<td>0/30 vs. 1/30</td>
<td>1/30 vs. 0/30</td>
<td>5/30 vs. 4/30</td>
<td>1/30 vs. 3/30</td>
</tr>
<tr>
<td>Zhan-Quan et al. (13)</td>
<td>0/35 vs. 0/23</td>
<td>0/35 vs. 0/23</td>
<td>0/35 vs. 0/23</td>
<td>0/35 vs. 0/23</td>
</tr>
<tr>
<td>MAGIC-CELL-3-DES (12)</td>
<td>1/27 vs. 1/29</td>
<td>0/27 vs. 1/29</td>
<td>0/27 vs. 1/29</td>
<td>—</td>
</tr>
<tr>
<td>TCT-STAMI (15)</td>
<td>0/10 vs. 0/10</td>
<td>0/10 vs. 0/10</td>
<td>0/10 vs. 0/10</td>
<td>0/10 vs. 0/10</td>
</tr>
<tr>
<td>ASTAMI (2,4)</td>
<td>0/50 vs. 0/50</td>
<td>—</td>
<td>11/50 vs. 11/50</td>
<td>1/50 vs. 1/50</td>
</tr>
<tr>
<td>REPAIR-AMI (5)</td>
<td>2/101 vs. 6/103</td>
<td>0/101 vs. 6/103</td>
<td>16/101 vs. 26/103</td>
<td>0/101 vs. 3/103</td>
</tr>
<tr>
<td>Meluzin et al. (16)</td>
<td>0/44 vs. 0/22</td>
<td>0/44 vs. 0/22</td>
<td>6/44 vs. 1/22</td>
<td>0/44 vs. 0/22</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.52 (0.16-1.63)</td>
<td>0.22 (0.05-0.90)</td>
<td>0.97 (0.62-1.52)</td>
<td>0.32 (0.09-1.21)</td>
</tr>
<tr>
<td>p value</td>
<td>0.26</td>
<td><strong>0.04</strong></td>
<td>0.90</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*Comparing intracoronary cell therapy versus control event rates (n/N).

CI = confidence interval; OR = odds ratio.
REPAIR-AMI Trial (Schachinger V. et al)

- ST-elevation MI (Rx’ed <24 hrs)
- Bone Marrow Aspiration (days 3-5)
  - Placebo #103
  - B.M. treated #101
- Intracoronary Infusion (236 million cells; 98% viable)
  - Baseline and F/U LV-angiogram at 4 months

AHA 2005
## Improvement in ejection fraction (%) from baseline (3-6 days post MI) to four months

<table>
<thead>
<tr>
<th>Group</th>
<th>Stem cells</th>
<th>Placebo</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>5.5</td>
<td>3</td>
<td>0.014</td>
</tr>
<tr>
<td>Patients with baseline EF&lt;49%</td>
<td>7.5</td>
<td>2.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Patients with baseline EF&gt;49%</td>
<td>4.0</td>
<td>3.7</td>
<td>0.81</td>
</tr>
<tr>
<td>Patients treated within 5 days of MI</td>
<td>4.5</td>
<td>3.9</td>
<td>0.62</td>
</tr>
<tr>
<td>Patients treated after 5 days</td>
<td>7.0</td>
<td>1.9</td>
<td>0.004</td>
</tr>
</tbody>
</table>
### Clinical events at four months

<table>
<thead>
<tr>
<th>Event</th>
<th>Events in stem-cell group, n</th>
<th>Events in placebo group, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Recurrent MI</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Hospitalization for CHF</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Revascularization</td>
<td>19</td>
<td>28</td>
</tr>
</tbody>
</table>

Schachinger V. American Heart Association Scientific Sessions 2005; Nov 13-16, 2005;
Is cardiovascular cell therapy at a “crossroads?”

“That we have only a partial understanding of many of the small-molecule pharmacologic therapeutic agents commonly used in clinical practice is a humbling thought. One must remember that only after decades of clinical use was aspirin recognized as an aid in reducing fatalities after myocardial infarction and a more precise understanding of aspirin’s mechanism of action was established. We believe it would be naive to assume that we will understand cells as therapeutic agents completely from the onset of their use; however, it is also naive to believe that preclinical studies could determine precisely the effects of cell delivery in our complex patients. Acceptance of the current limitations of our knowledge should not halt efforts to harness this knowledge and to ascertain how it can be used in patients with unmet clinical needs.”

CCTRN Steering Committee -- NHLBI
NHLBI Cardiovascular Cell Therapy Research Network (CCTRN)

The uncertainty surrounding this growing field
The compelling clinical need
The supportive preclinical data
The promising early clinical experience

prompted the NHLBI to create CCTRN with the goals of:

• Accelerating research into the use of cell-based therapies in the management of cardiovascular diseases
• Performing early phase I and II clinical investigations that will help to identify optimum cell-therapy techniques
• Established in January 2007, with the clinical trials beginning in 2008 (both acute infarct and chronic left ventricular dysfunction conditions)
Potential Mechanisms for the Observed Benefits with Stem Cell Therapy?

- Progenitor Cells
- Cell transdifferentiation
- Cell fusion
- Soluble factors
- Cell-to-cell contact
- ? other

- ? Improved cardiac function
- ? New muscle
- ? Less apoptosis
- ? New blood vessels
UCSF Translational Cardiac Stem Cell Program

- Human Clinical Trials
  - Small Animal Model
  - Large Animal Model
  - Observational Human Trials
  - Embryonic Stem Cell
The problem – inaccuracy of cell delivery

Need to be able to inject into myocardial wall without piercing the LV cavity (heart rate 400-600 beats/min)
Closed chest injection technique guided by high-resolution echocardiography

VisualSonics Vevo 660 system

Amer. J. Physiol. Heart Circ. Physiol. 2005;289:1307-1314
Ultrasound-guided injection to LV wall

Fluor. microspheres

LacZ myoblasts
Example post-MI
Bone marrow cells injection 3 days after MI improves cardiac function

Mechanism?
Less left ventricular dilatation with cell therapy

Mechanism?

In detailed histologic analysis, we see no new cardiomyocytes forming and in fact, very rare GFP+ cells are even identified in the hearts!

Infarct size smaller with cell therapy
Multiple levels of GFP detection (+ control)

- GFP direct fluor: green filter
- GFP direct fluor: red filter
- GFP direct fluor: merged
- GFP immunoperoxidase
- Direct GFP green/red merged
- Immunofluor. far red (alexa660)
- Immunofluor. green (alexa488)

Scale bar: 50 μm
Additional controls are enlightening…

![Graph showing LVEF% over time with different treatments: saline, live mBMCs, and mBMC lysate.]

- **Baseline**
  - Saline: P=NS
  - Live mBMCs: P=0.048
  - mBMC lysate: P=0.048
Summary so far ..... 

- In our hands, and many other labs now, we see:
  - No transdifferentiation or fusion
  - Poor survival and retention
  - Functional improvement exceeds apparent regeneration
- These findings could be consistent with paracrine involvement of secreted growth factors and cytokines.
- Paracrine mechanisms, but how?
  - Changes in blood vessel counts early after MI?
  - Decreasing apoptosis early after MI?
  - Stimulating native cardiac progenitor cells?
Increased Vessel Density with both BMC and Lysate Therapy at Day 6

Vessel Density at Border Zone

* P=0.001 vs. HBSS
Decreased Apoptosis at Border Zone with Therapy at Day 6

Border Zone Day 6 Post-MI

- No injection
- HBSS injection
- BMC injection
- Lysate injection

Mean ±SD
Native Cardiac Progenitor Cells

• **Traditional View**
  The adult heart is a terminally differentiated organ without regenerative capacity after injury.

• **Current View**
  The adult heart has some regenerative capacity after injury and several stem/progenitor cells have been identified.
Background -- Cardiospheres

Cells isolated from the heart which can form self-adherent clusters in *in-vitro* culture. These cells have the following characteristics:

1. express stem cell markers
2. are clonogenic
3. self renew for long term
4. are able to differentiate into cardiomyocytes, smooth muscle cells and endothelial cells in vitro and in vivo.

Messina and Giacomello 2004; Smith and Marban 2007
**Method of Isolating CSs**

Cut heart to small piece (2 mm³) and digest by enzymes

Culture the small piece (explants) for 1 to 7 weeks

Fibroblast-like cells grow out from adherent explants first

Small, phase-bright cells (putative CS forming cells) appeared on top of the fibroblast-like cells

Harvest putative CS forming cells and transfer them to Poly-D-lysine coated plate

Cardiospheres

![Images of explants and CSs at different stages]

An Explant cultured 1st day, 40x

CSs forming cells around an explant 30th day, 40x

CSs 40x
Cardiospheres from Adult Mice
Will induction of myocardial infarction have an effect on the cardiospheres?

YES
Increased numbers of CSs detected in a time-dependent manner following MI.

The results suggest that MI may induce the proliferation of cardiac stem/progenitor cells (CSCs) in the shorter term post-infarct.

The mechanisms for the increase in CSs post-MI need further investigation, which may lead to novel therapeutic strategies post-infarct.
What is in the lysate??
ANTIBODY ARRAY TECHNOLOGY

• Principle:
  - similar to any ELISA
  - (= 2 primary antibodies are used, the second primary being linked to avidine)

• Modification to make it quantifiable:
  - radioactive streptavidine

• Output:
  - detection of multiple proteins at the same time

Courtesy JP Coppe; Campisi Lab (LBNL)
Proteomics of the lysate underway

VEGF, HGH, FGF, IGF-1, Adrenomedullin, SFRP-2, TB4, … (V. Dzau)

Myocardial protection
Cardiac metabolism
Contractility
Regeneration
Neovascularization
Remodeling
UCSF Translational Cardiac Stem Cell Program

Human Clinical Trials

Small Animal Model
Large Animal Model
Observational Human Trials
Embryonic Stem Cell
Human Embryonic Stem Cells

- To efficiently and reproducibly differentiate and isolate cardiomyocytes using human embryonic stem cell lines
- Use these cells for transplantation studies in the established animal models
- With Dr. Harold Bernstein, we have been awarded a Comprehensive California Institute for Regenerative Medicine (CIRM) Award
Conclusion

• We are in the early days of our understanding of stem cell therapy for cardiac therapies
• Therapy with some of the cells appears safe but more research is certainly required to address the many unanswered questions
• Further understanding of the components of the lysate derived from bone marrow cells is a must
• Studying the role of hESC and iPS cells in cardiac regeneration is critical
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