State of the Art:

Cardiac Stem Cell Therapeutics from the Outside, Looking In

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No conflicts or disclosures
Those who can do;

those who can’t give “State of the Art” lectures.
Myocardial infarction can kill ~1 billion cardiac myocytes.
Acute intervention for MI is unlikely to get measurably faster or better.
Heart failure is increasing in prevalence.

Medical therapy is not curative.

Heart transplants are for only a few.

Regenerative therapies offer a CURE.
Some hearts can regenerate lost myocardium:

Adult zebrafish
Some hearts can regenerate lost myocardium:

Neonatal mouse

Porrello ER et al. Science 2011;331:1078-80
Developing cardiomyocytes can generate new cardiomyocytes:

Neonatal mouse

Porrello ER et al. Science 2011;331:1078-80
Even adult mammalian hearts have (limited) regenerative potential.

Regenerating myocardium in scarred infarct

Endogenous myocardial c-Kit+ stem cells

Cultured human “cardiosphere”

Barile L et al. Prog Cardiovasc Dis 2007;50:31-48

What is the source of regenerative cardiac stem cells?
Bone marrow mesenchymal stem cells are multipotent
Bone marrow mesenchymal stem cells are angiogenic

Bone marrow mesenchymal stem cells are useful for occlusive arterial disease
## What is the optimal source of therapeutic cardiac stem cells?

<table>
<thead>
<tr>
<th><strong>Myocardium</strong></th>
<th><strong>Bone marrow</strong></th>
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<tbody>
<tr>
<td><strong>Pros:</strong></td>
<td><strong>Pros:</strong></td>
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<tr>
<td>Cardiomyocyte progenitors (or not?)</td>
<td>Ready availability in large amounts</td>
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<tr>
<td>Potential clinical utility</td>
<td>Possibly more angiogenic</td>
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<td>SCIPIO (atrial explants)</td>
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<td>CADUCEUS (RV biopsy)</td>
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<tr>
<td><strong>Cons:</strong></td>
<td><strong>Cons:</strong></td>
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<tr>
<td>Limited availability</td>
<td>Stem cell content low</td>
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<tr>
<td>Not likely transdifferentiation and engraftment</td>
<td>Variable reported benefits</td>
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<tr>
<td></td>
<td>REPAIR-MI</td>
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<td></td>
<td>POSEIDON</td>
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<td>TIME</td>
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<td>MultiStem</td>
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What is the optimal *cardiac disease* for stem cell treatment?

**Chronic heart failure**

**Pros:**
- HUGE clinical need
- Ample opportunity for ex vivo cell expansion

**Cons:**
- Endogenous repair mechanisms are inactive

**Acute myocardial infarction**

**Pros:**
- Endogenous repair mechanisms are active
- Prevent heart failure easier than cure

**Cons:**
- Limited time for ex vivo cell expansion
- Progress has been better than for heart failure
- Cell engraftment/survival diminished in ischemic tissue

What is the optimal *method to deliver* regenerative cardiac cells?

Trans-coronary infusion

Intra-myocardial injection

Strauer and Steinhoff. *JACC* 2011 58:1095-1104
Once delivered, what is the fate of regenerative cardiac cells?
Stem cell administration can provide clinical benefit

BUT

Stem cells do not survive to regenerate damaged myocardium
The clinical benefits accruing from stem cell therapy are not because they engraft, differentiate into, and replace cardiac tissue.

In theory,
Direct regeneration

In practice,
Paracrine stimulation of endogenous repair

Lionetti V et al Heart Failure Rev 2010 15:531-542
Maybe cells will ultimately prove dispensable for cell-mediated regeneration?