The goal of molecular medicine is to find treatments for human diseases by clever and effective application of tools of molecular and cellular biology.

Set of animal models of the disease is devised, investigated and characterized. Novel therapies are conceived and tested on the animal models until a rescue from the pathology is achieved. The strategy is then developed for human trial.

Not simple… The level of complexity of most diseases is great and our present knowledge of physiology and pathology is inadequate to undertake comprehensive repair.

DEFINE UNMET CLINICAL PROBLEMS

• ACUTE CORONARY SYNDROMES
• HEART FAILURE
• ARRHYTHMIAS

DEFINE CLINICAL PROBLEMS

• ACUTE CORONARY SYNDROMES-
  – UNSTABLE ANGINA
  – MYOCARDIAL INFARCTION
• TREATMENTS DESIGNED BASED UPON MOLECULAR UNDERSTANDING OF PATHOPHYSIOLOGY
  – DRUG ELUTING STENTS- IDENTIFICATION OF ANTI-PROLIFERATIVE AGENTS.
    • POTENTIAL UNMET NEED- REQUIREMENT FOR CONTINUED ANTI-PLATELET THERAPY FOR 1 YEAR. RISK-BLEEDING, IN ELDERLY
    • ENDOTHELIAL PROGENITOR CELL CAPTURE MECHANISM
  – BETTER ANTI-THROMBOTICS/ANTI-PLATELET AGENTS
DEFINE CLINICAL PROBLEMS

- Angioplasty of coronary arteries for angina
  Clinical problem- recoil of arteries after balloon injury
  Solution: develop scaffold to prevent recoil- STENT
- Stent
  Clinical problem- abnormal smooth muscle proliferation. Occurred in ~30% of cases.
  Solution: use of anti-proliferative agent to inhibit smooth muscle proliferation
Clinical problem- late thrombosis after DES placement

Molecular Regulators of the Cell Cycle

Cyclins
Cyclin-dependent kinases-CDK
CDK-inhibitors
  INK4 family
  KIP/CIP family
Major regulators of VSMC proliferation
pRb phosphorylation
p27KIP1
Rapamycin (Sirolimus)
Paclitaxel (Taxol)
Numerous trials have demonstrated that the sirolimus (rapamycin)-eluting and the paclitaxel-eluting stents are much more effective than bare-metal stents in preventing restenosis.

A meta-analysis has compared rapamycin and paclitaxel-eluting stents. Target lesion revascularization was needed in 95 of 1845 (5.1%) patients assigned to sirolimus-eluting stent group and 142 (7.8%) of the 1824 patients assigned to the paclitaxel-eluting stent group.

**Figure 1. Odds Ratios of Target Lesion Revascularization Associated With Sirolimus-Eluting Stent vs Paclitaxel-Eluting Stent**

<table>
<thead>
<tr>
<th>Source</th>
<th>SES Group (n)</th>
<th>SES Group (95% CI)</th>
<th>Odds Ratio (SES vs PES) (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CORAL 2005</td>
<td>1959</td>
<td>861</td>
<td>0.81 (0.71-0.91)</td>
<td>0.002</td>
</tr>
<tr>
<td>SAPHIRE 2005</td>
<td>1959</td>
<td>861</td>
<td>0.81 (0.71-0.91)</td>
<td>0.002</td>
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<tr>
<td>SAVANNAH 2005</td>
<td>1959</td>
<td>861</td>
<td>0.81 (0.71-0.91)</td>
<td>0.002</td>
</tr>
<tr>
<td>SYNTAX 2005</td>
<td>1959</td>
<td>861</td>
<td>0.81 (0.71-0.91)</td>
<td>0.002</td>
</tr>
<tr>
<td>VIVA 2005</td>
<td>1959</td>
<td>861</td>
<td>0.81 (0.71-0.91)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

SES indicates sirolimus-eluting stent; PES, paclitaxel-eluting stent; CI, confidence interval. The size of the data marker is proportional to the weight of the individual studies, measured as the inverse of the variance in the trial by the Mantel-Haenszel procedure.
Tobin figures for every 1,000 patients who get a bare–metal stent to clear clogged arteries, 200 will need to repeat the procedure, and 20 will have serious heart attacks. Using a Taxus stent appears to cut that number in half by addressing the reclogging problem—called restenosis.

Long–term results now suggest 5 out of 1,000 Taxus patients will eventually suffer a heart attack triggered by a blood clot. But that's still just 15 heart attacks for Taxus vs. 20 for bare metal, so "you're better off with Taxus," he says.

OCTOBER 9, 2006

SCIENCE & TECHNOLOGY

"No One Wanted To Hear"

Renu Virmani warned that, over time, some drug–coated stents could lead to fatal clots

Two years ago, at a meeting of top heart doctors in Paris, Dr. Renu Virmani tried to dampen the raging enthusiasm for drug–eluting stents—new devices that prop open narrowed blood vessels and exude chemicals to keep them open. The stents were having a glorious sunrise, she said, because they prevented blood vessels from renarrowing. But inevitably "the sun would set," she warned, as patients with the stents ran into deadly problems.

At this time, FDA believes that coronary drug–eluting stents remain safe and effective when used for the FDA–approved indications. These devices have significantly reduced the need for a second surgery to treat restenosis for thousands of patients each year.

Advisory panel meeting-- there appears to be a numerical excess of late stent thrombosis with DES, but the magnitude is uncertain; and the off–label use of DES, as with bare–metal stents, is associated with increased risk when compared with on–label use.

New DES studies should have longer follow–up, enroll greater number of patients and include stent thrombosis as a study end–point.

Advisory panel concurred with joint clinical practice guideline recommendations for 12 months of dual antiplatelet therapy after placement of DES in patients who are not at high risk of bleeding.
(1) Before implantation of a stent, the physician should discuss need for dual antiplatelet therapy.
(2) In patients likely to require invasive or surgical procedures within the next 12 months, consideration should be given to implantation of bare-metal stent or balloon angioplasty.
(3) Ensure patient education about risks associated with prematurely stopping therapy.
(4) Instruct patients to contact cardiologist before stopping antiplatelet therapy.
(5) Healthcare professionals should be instructed about risks of stopping antiplatelet therapy.
(6) Elective procedures should be deferred until appropriate course of antiplatelet therapy (12 months for DES).
(7) If Plavix needs to be discontinued, ASA should be continued.

**Other uses of rapamycin in cardiology**
- Transplant arteriopathy--

![Graph showing the effect of rapamycin and control on outcome over time](graph.png)

46 patients--treatment with rapamycin slowed disease progression

FUTURE USES OF A STENT, AS A DELIVERY PLATFORM:

The Conor drug eluting stent design.

Endothelial progenitor cell technology.
Heart failure: Deficiency in ventricular pump function

Results from numerous initial causes

Causes of heart failure:
(1) defects intrinsic to cardiac muscle contractility due to altered expression or operation of Ca$^{2+}$-cycling proteins, components of the sarcomere and enzymes for cardiac energy production.

(2) defects extrinsic to cardiac muscle cells, such as interstitial fibrosis (compliance), myocyte loss.

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Ca$^{2+}$ is the link in excitation-contraction (EC) coupling. Ca$^{2+}$ influx is required for contraction in cardiac muscle, which requires Ca$^{2+}$ entry with each beat and triggers Ca$^{2+}$ release from the sarcoplasmic reticulum (SR) via Ca$^{2+}$-release channels - ryanodine receptor 2 (RyR2). Rapid increase in intracellular Ca$^{2+}$ concentration from 100 nM to 1 μM-a level required for optimal binding of Ca$^{2+}$ to troponin C. Contraction is followed by Ca$^{2+}$ release from troponin C and its reuptake by the SR via activation of the SR Ca$^{2+}$-ATPase 2a (SERCA2a) Ca$^{2+}$ pump in addition to extrusion across the sarcolemma via the Na$^+$/Ca$^{2+}$ exchanger (NCX).

In the human heart under resting conditions, the time required for cardiac myocyte depolarization, Ca2+-induced Ca2+ release, contraction, relaxation, and recovery is 600 ms. This process occurs approximately 70 times a minute or over 2 billion times in the average lifespan. Ca2+ is also required for maintenance of cell integrity and gene expression relevant to the growth and development of the embryonic heart.

Heart failure:
Phosphorylation of RyR2 by PKA-- release of regulatory protein FKBP12.6, leads to RyR leakiness, especially during diastole.
Hypophosphorylation of phospholamban, the regulator of SERCA. Leads to decreased Ca2+ uptake.
Proposed therapy: Enhancing SR Ca2+ loading

Increasing reuptake of Ca\(^{2+}\) into the SR by stimulating SERCA2a has been proposed as an approach to improving systolic and diastolic function.

Proof of principle experiments have been performed using adenovirus-mediated gene transfer of SERCA2a, which normalized Ca2+ handling and cardiac contractility in a rat model of heart failure. Overexpression of SERCA2a was shown to improve myocardial performance in the senescent heart, to prevent heart failure due to aortic banding and to improve the contractile performance of human heart cells taken from the explanted hearts of patients with heart failure.

SERCA-activating drugs not yet available.

Enhancing SR Ca2+ loading- knockout of PLB leads to normalization of heart function

Mechanistically, not clear why the problems caused by breaking one thing (genetic ablation of the muscle LIM protein), a structural protein involved in muscle development) could be completely repaired by knocking out another protein, phospholamban.
Increase SR Ca2+ reuptake by increasing levels of phospholamban phosphorylation, because PLB inhibits SERCA2a function in its unphosphorylated form.

Antisense PLB gene transfer into cardiomyocytes isolated from failing human hearts could normalize contractile function.

Gene therapy using adenoviral transfer of pseudo-phosphorylated PLB after MI in rat

Serial changes of echocardiographic variables before and after S16EPLN gene transfer

These studies provided hope that a relatively simple solution could overcome the complexity inherent in heart failure.

However…

PLN ablation failed to rescue two mouse models of hypertrophic cardiomyopathy caused by either overexpression of Gαq or expression of a mutant myosin binding protein C. At the cellular level, crossing of these mice with PLN -/- mice appeared to rescue heart failure phenotype in that contraction strength was increased and Ca2+ signaling defects were reversed. However, the molecular therapy of PLN ablation did not reverse the hypertrophy or prevent cardiac dysfunction at the organ level.

Studies on PLN -/- mice indicated that these mice are super-healthy with improved cardiac function relative to control mice and no apparent deleterious effects. Surprising, given important role of PLN in regulating Ca2+ signaling.

Two families carrying a point mutation in PLN that produces a stop codon at Leu39. Heterozygous individuals develop hypertrophy without reduced contractility. Homozygous individuals develop dilated cardiomyopathy and heart failure.

Are there differences between human and mice?
Is the truncation mutant a true null or has other consequences?

These findings challenges conventional wisdom and suggest that simple molecular therapeutic strategies may not be optimal in heart failure.
RyR2/calcium release channel is PKA hyperphosphorylated in failing hearts: reversal with Left Ventricular Assist Device
PKA phosphorylation of RyR2 dissociates FKBP12.6 from the complex
β-adrenergic receptor blocker restores stoichiometry of the RyR2 macromolecular complex

β-adrenergic receptor blocker restores normal single channel activity in heart failure
Catecholaminergic Ventricular Tachycardia: Mutations in RyR2
The Long QT Syndrome: Dysfunction in Ventricular Repolarization

R. Kass (Jan 6)- discussed gene-targeted therapies


Voltage at the cellular level
Table 2
Molecular and cellular mechanisms of cardiac arrhythmias

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene (alternate name)</th>
<th>Protein</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT-1</td>
<td>KVLQ1T1 (KCNQ1)</td>
<td>I&lt;sub&gt;Ks&lt;/sub&gt; K&lt;sup&gt;+&lt;/sup&gt; channel α subunit</td>
<td>28</td>
</tr>
<tr>
<td>LQT-2</td>
<td>HERG (KCNH2)</td>
<td>I&lt;sub&gt;Kr&lt;/sub&gt; K&lt;sup&gt;+&lt;/sup&gt; channel α subunit</td>
<td>29</td>
</tr>
<tr>
<td>LQT-3</td>
<td>SCN5A</td>
<td>I&lt;sub&gt;Na&lt;/sub&gt; K&lt;sup&gt;+&lt;/sup&gt; channel α subunit</td>
<td>30</td>
</tr>
<tr>
<td>LQT-4</td>
<td>ANKB</td>
<td>ANKRIN-β</td>
<td>31</td>
</tr>
<tr>
<td>LQT-5</td>
<td>minK (KCNE1)</td>
<td>I&lt;sub&gt;Ks&lt;/sub&gt; K&lt;sup&gt;+&lt;/sup&gt; channel β subunit</td>
<td>32</td>
</tr>
<tr>
<td>LQT-6</td>
<td>MiRP1 (KCNE2)</td>
<td>I&lt;sub&gt;Kr&lt;/sub&gt; K&lt;sup&gt;+&lt;/sup&gt; channel β subunit</td>
<td>33</td>
</tr>
<tr>
<td>LQT-7</td>
<td>KCNJ2</td>
<td>I&lt;sub&gt;Kr&lt;/sub&gt; K&lt;sup&gt;+&lt;/sup&gt; channel α subunit</td>
<td>34</td>
</tr>
</tbody>
</table>

Triggering Events for Syncope or SCD

- 3 main factors contributing to syncope or SCD
  - Exercise, especially swimming
  - Emotions or emotional stress
  - Events occurring during sleep or at rest, with or without arousal

Circ 2001;103:89-95
Occurrence of Gene-Specific Triggers

![Bar Chart]

Beta Blocker Therapy is Effective

![Bar Chart]

SCN5A Mutations: Invalid Targets for Beta Blockers:

Bradycardia and excessive AP prolongation

Lidocaine Controls LQT-3 Prolongation

Control: QTc=524 ms

Lidocaine: QTc=442 ms

Figure 5. Lidocaine shortens Qtc interval in patient carrying KPQ deletion mutation of SCN5A gene. Note minimal effects on QRS interval. Courtesy Dr. A. Moss.
Timothy syndrome; loss of voltage dependent inactivation of Cav1.2
Conclusions for Inherited LQTS

- Inherited structural defects in ion channel architecture can cause arrhythmias;
- Triggers for arrhythmias are gene (mutation)-specific
- Therapeutic strategy is gene-specific

Cardiac regeneration

Cardiac injury in mammals and amphibians typically leads to scarring, with minimal regeneration of heart muscle. Cardiac regeneration is robust for certain organisms such as newt and zebrafish. Regeneration occurs through robust proliferation of cardiomyocytes localized at the leading epicardial edge of the new myocardium.

Poss et al Science 298:2188
Cardiac regeneration

Restorative growth dependent upon the retention of proliferative potential in a subset of adult cardiomyocytes and is impossible in mammals under normal, unassisted biological circumstances.

Strategies to overcome restrictions:

1. Overriding cell cycle checkpoints
2. Supplementing cytoprotective mechanisms or inhibiting pro-death pathways
3. Supplementing angiogenic mechanisms that occur naturally using defined growth factors or vessel-forming cells.
4. Providing exogenous cells as a surrogate or precursor for cardiac muscle.

First strategy to be translated from bench to bedside: Cell implantation

Variety of adult progenitor cells, all autologous to avoid tissue rejection.
First clinically relevant cells proposed were skeletal muscle myoblasts- undifferentiated, proliferation-competent cells that serve as precursors to skeletal muscle.
Isolated from muscle biopsies, propagated and expanded ex vivo for a few days or weeks and then injected directly into the ventricular wall.

Cell implantation

Bone marrow, at present, is the most frequent source of cells used for clinical cardiac repair. Consists of complex assortment of progenitor cells, including HSCs; side population (SP) cells, defined by their ability to expel a Hoescht dye, mesenchymal stem cells (MSC) or stromal cells and multipotential adult progenitor cells (MAPCs), a subset of MSC.

Bone marrow aspirated under local or general anesthesia, the entire mononuclear cell fraction or specific subpopulation purified and isolated cells are injected into the heart without need for further ex vivo expansion.

Peripheral blood-derived progenitor cells are used for clinical cardiac repair and neovascularization in peripheral arterial occlusive disease. These circulating cells (endothelial progenitor cells; EPC) are bone marrow derived. EPCs are isolated from mononuclear blood cells and selected ex vivo by culturing in endothelium specific medium for 3 days, prior to reinjection into the heart. Hypothesis is that these cells might transdifferentiate to create new cardiomyocytes.
Delivered three ways:
intracoronary arterial route
injection into ventricular wall via percutaneous endocardial or surgical epicardial approach.

Intracoronary infusion- cells travel directly into myocardial regions in which nutrient blood flow and oxygen are preserved, ensuring a favorable environment for cells’ survival. Unperfused areas are targeted far less efficiently.
Whereas bone marrow- and blood-derived progenitors cells are known to extravasate and migrate to ischemic areas, skeletal myoblasts do not and may even obstruct the microcirculation leading to embolic myocardial damage.

Direct delivery of progenitor cells into scar tissue or areas of hibernating myocardium by catheter-based needle injection, direct injection during open-heart surgery, and minimally invasive thorascopic procedures are not limited by cell uptake from the circulation or embolic risk.
Offsetting consideration is risk of ventricular perforation, which may limit use of direct needle injection into freshly infarcted hearts.
Regions may lack syncytium of live muscle cells that may furnish instructive signals and lack blood flow for delivery of oxygen and nutrients.
Electromechanical mapping of viable but hibernating myocardium may be useful.
Diffuse disease- focal areas of injected cells might be poorly matched to underlying anatomy.
Patient’s individual pathobiology will influence the source and route chosen. Not yet possible to assert an optimal cell type or best mode of delivery.
Clinical trials:
Distinguish between patients with acute myocardial infarction and chronic heart failure due to prior myocardial infarction.

In patients with acute myocardial infarction, progenitor cell transplantation is predicted to modify postinfarction LV remodeling through enhanced neovascularization and reduced cardiomyocyte apoptosis, irrespective of long-term engraftment and transdifferentiation.

Enhanced neovascularization and reduced cardiomyocyte apoptosis may have little effect in long-established scars.

Myocardial ischemia acutely and potently upregulates the chemoattractants for neoangiogenesis—logical to test intracoronary infusion of bone marrow- or blood-derived progenitor cells in patients with acute MI.

Table 1
Clinical trials of intracoronary progenitor cells for acute MI

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Days after MI</th>
<th>Cell type</th>
<th>Cell preparation (volume/purification/culture)</th>
<th>Mean cell no. (×10⁶)</th>
<th>Safety</th>
<th>Myocardial function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strauer et al. (12)</td>
<td>10</td>
<td>8</td>
<td>BMCs</td>
<td>40 ml/Ficol/overnight (Teflon)</td>
<td>28</td>
<td>+</td>
<td>Regional contractility ↑ (LVA); end-systolic volume ↓ (LVA); perfusion ↑ (angiography)</td>
</tr>
<tr>
<td>TOPCARE-AWI (13, 17, 129)</td>
<td>59</td>
<td>4.9</td>
<td>CPCs</td>
<td>250 ml/blood/3 days</td>
<td>16</td>
<td>+</td>
<td>Global contractility ↑ (LVAMRI); and systolic volume ↓ (LVAMRI); viability ↑ (MRI); flow reserve ↑ (Doppler); similar results for both cell types</td>
</tr>
<tr>
<td>BMCs</td>
<td>56 ml/Ficol/hone</td>
<td>213</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOOST (16)</td>
<td>30 vs. 30 randomized controls</td>
<td>4.8</td>
<td>BMCs</td>
<td>150 ml/bleomycin-polyacrylate sedimentation/hone</td>
<td>2,400</td>
<td>+</td>
<td>Global contractility ↑ (MRI)</td>
</tr>
<tr>
<td>Fernández-Aviles et al. (129)</td>
<td>20</td>
<td>13.5</td>
<td>BMCs</td>
<td>50 ml/Ficol/overnight (Teflon)</td>
<td>78</td>
<td>+</td>
<td>Global contractility ↑ (MRI); and systolic volume ↓ (MRI)</td>
</tr>
</tbody>
</table>

*Indicates increases; ↓ indicates decreases; + denotes lack of adverse events. BMC, bone marrow–derived cell; CPC, circulating progenitor cell (EPCs); LVA, LV cineangiography; MI, myocardial infarction.

All published trials reported nearly identical results; 7-9% improvement in global LV ejection fraction, significantly reduced end-systolic LV volumes and improved perfusion in the infarcted area, 4-6 months after cell transplantation.
Clinical trials of intracoronary progenitor cells for acute MI

In BOOST study (prospectively randomized), global LV function was significantly improved compared to nontreated control group.

In TOPCARE-AMI, magnetic resonance showed improvement of LV function and absence of reactive hypertrophy preserved after 1 year.

In all 4 trials- totaling >100 patients- observed complications did not exceed controls. No arrhythmic complications.
Clinical trials of intracoronary progenitor cells for acute MI

Single dose of intracoronary bone marrow cells did not provide long-term benefit on LV systolic function after AMI; however study suggests an acceleration of LV EF recovery after AMI by BMC therapy.

First trial used skeletal muscle-derived progenitor cells directly injected in LV during open heart surgery for CABG. Global and regional LV function were improved, but may be due concomitant revascularization, complicating the assessment of benefit.

Transcatheter injection of myoblasts in myocardial scar reduced symptoms of heart failure but without objective evidence of improved global LV function.

Patients experienced life-threatening arrhythmias; lack of electrical coupling of skeletal muscle to neighboring cardiomyocytes, or coupling by the few hybrid cells formed by fusion with adjacent cardiomyocytes, which generate spatially heterogeneous calcium transients. Requires implantation of an cardioverter/defibrillator.
Clinical trials of catheter-based progenitor cell delivery for chronic coronary heart disease

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Delivery technique</th>
<th>Cell type</th>
<th>Cell preparation (volume/purification/culture)</th>
<th>Mean cell no. (x10^3)</th>
<th>Safety</th>
<th>Myocardial function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tee et al.</td>
<td>8</td>
<td>Endocardial injection, guided by electromechanical mapping</td>
<td>BMGs</td>
<td>40 x10^3/Ficol/noone</td>
<td>Not reported</td>
<td>+ Wall motion and thickening ↑; hypoperfusion ↓</td>
<td>Global contractility ↓; endystolic volumes ↓; reversible perfusion defects ↓; exercise capacity ↑</td>
</tr>
<tr>
<td>Fuchs et al.</td>
<td>10</td>
<td>Endocardial injection, guided by electromechanical mapping</td>
<td>BMGs</td>
<td>Filtered/noone</td>
<td>78.3</td>
<td>+ Angina score ↓; stress-induced ischemia ↓</td>
<td></td>
</tr>
<tr>
<td>Perin et al.</td>
<td>14</td>
<td>Endocardial injection, guided by electromechanical mapping</td>
<td>BMGs</td>
<td>50 x10^3/Ficol/noone</td>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Initial attempts in patients with chronic ischemic heart disease and old MI more heterogeneous in outcome. Patient population more heterogeneous.

Summary:
For acute MI patients, the safety and suggestive efficacy of intracoronary progenitor cell transplantations provide rationale for randomized double blinded trials--- ongoing in USA and Europe.

For chronic ischemic heart failure--- is identification of hibernating myocardium to direct cell therapy essential for effective outcome? Is delivery of skeletal myoblasts safe?

Does cellular therapy improve morbidity and mortality?

Do marrow derived cells implanted in the heart form cardiomyocytes? To date there is no direct clinical evidence that cellular cardiomyogenesis occurs in the human heart after transplantation of progenitor cells.

Cardiac myogenesis by noncardiac cells—human embryonic stem cells, if politically acceptable, pose the clinical challenge of immunological barriers.

In culture, embryonic stem cells form nodes of pulsing cells, presumably immature heart muscle cells, that beat in unison. But might these stem cells differentiate into different tissue (i.e. bone)?

G-CSF—a number of investigators are using to force bone marrow to release stem cells, which are then collected from the blood and reinfused—could it promote cardiac inflammation? Boost blood vessel development in undetected tumors? 7/10 people receiving G-CSF in a trial in South Korea experienced a renarrowing of the previously blocked artery, requiring treatment.

Cardiac myogenesis by adult cardiac progenitor cells

Several rationales: inability of skeletal myocytes to transdifferentiate; challenges to the claims of bone marrow-derived cells’ far-ranging plasticity and findings of tissue-resident progenitor cells, showing some evidence for stemness, yet predisposed to differentiate into lineages of the organ in which they reside.

? persistence as undifferentiated remnants of heart-forming tissue in the early embryo;

? Hematogenous origin

? Ingrowth of the developing coronary vasculature

How many new cardiomyocytes, if any, are generated in the normal heart after birth? Do they replace dead or dying cells?
Conclusions:
Molecular cardiology: lessons learned
(1) Novel approaches to treat coronary artery disease- the identification of smooth muscle proliferation after stent implantation-- targeted approaches using anti-proliferative drugs
(2) Heart failure-- SERCA2a/PLB; are cellular studies equivalent to whole animal studies? Animal models vs. man?
(3) Ryanodine receptor phosphorylation-- potential use of novel pharmaceuticals such as JTV519
(4) Cell transplantation-- potential uses for acute MI; chronic use unclear
(5) Identifying genetic abnormalities for arrhythmias.