1. Disease Prevalence
   a. AHA estimates 16.8 million Americans suffer from CAD
   b. 5.7 million with heart failure
   c. Expected to increase
      i. Advancing age
      ii. Sedentary lifestyle
      iii. Obesity
      iv. DM

2. Current Therapy
   a. Risk factor modification
   b. Medical therapy
      i. Beta-blocker
      ii. Afterload reduction
   c. Interventional Therapy
      i. Percutaneous coronary interventions
      ii. Coronary artery bypass grafting
      iii. Surgical restraints (ie. ACORN jacket)
      iv. Surgical ventricular restoration
   d. Limitations of current therapy
      i. Does not address microcirculation
      ii. Only revascularize 63-80% of all patients
      iii. Greatly increased survival following acute MI, no difference in progression to heart failure
      iv. Insufficient microvascular perfusion produces derangements in cardiomyocyte metabolic state. Myocardial ischemia induces altered cardiomyocyte metabolism, apoptosis, and mitochondrial damage resulting a deleterious cycle of cell slippage, ventricular dilatation, and ischemic heart failure.
   e. Cell Based Therapy – a means to restore perfusion and microcirculation to ischemic myocardium
i. Concept of post-natal angiogenesis using pluripotent bone marrow derived progenitor cells capable of endothelial lineage differentiation

ii. Highly promising in numerous basic science trials – small animal and large animal preclinical studies
   1. Direct cell mediated angiogenesis
   2. Paracrine – secretion of proangiogenic cytokines

iii. Limited efficacy in clinical trials
   1. Statistical significance has been demonstrated, but clinically significant improvements have not been seen
   2. Key historical clinical trials


g. Dozens of subsequent trials with limited efficacy - varying cell phenotype has not altered benefit
   i. Ongoing Penn trial – CD133+ cell injection at the time of CABG in the setting of LV dysfunction

iv. Limitations to current cell based therapies
   1. Techniques are purely myocardial cell injection – direct endocardial NOGA mapped injection, epicardial injection, intracoronary
   2. A lack of cell retention (<1%)
   3. Limited cell engraftment

v. Alternative therapeutic strategies for cell delivery
   1. Cell sheet – Yoshiki Sawa, Osaka University
   2. Alternative cell delivery strategies
   3. Tissue Engineering
      a. EPC encapsulated constructs
      b. Penn – vascularized constructs
3. Cytokine based therapy
   a. Numerous pro-angiogenic cytokines capable of inducing EPC recruitment to ischemic myocardium and stimulating angiogenesis
      i. Vascular endothelial growth factor (VEGF)
      ii. Basic Fibroblast growth factor (bFGF)
      iii. Hepatocyte growth factor (HGF)
      iv. Stromal cell derived factor (SDF)
      v. Placental growth factor (PIGF)
   b. Promise in small animal and pre-clinical studies
   c. Lack of clinically translatable efficacy
   d. Key initial studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>PAD vs. CAD</th>
<th>Therapeutic Strategy</th>
<th>Delivery Route</th>
<th>Phase I/II</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td>AGENT</td>
<td>CAD</td>
<td>adeno-FGF-4</td>
<td>Intracoronary</td>
<td>I</td>
<td>Safe</td>
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<tr>
<td>Latham et al.</td>
<td>CAD</td>
<td>Sustained release FGF-2 protein</td>
<td>Intramuscular</td>
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<td>Safe</td>
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<td>Comerota et al.</td>
<td>PAD</td>
<td>phFGF-1</td>
<td>Intramuscular</td>
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<td>FIRST</td>
<td>CAD</td>
<td>Recombinant FGF-2 protein</td>
<td>Intracoronary</td>
<td>II</td>
<td>No improvement in exercise tolerance or perfusion</td>
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<td>AGENT-2</td>
<td>CAD</td>
<td>adeno-FGF-4</td>
<td>Intracoronary</td>
<td>II</td>
<td>Trend toward improved myocardial perfusion</td>
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<tr>
<td>Ruel et al.</td>
<td>CAD</td>
<td>Sustained release FGF-2 protein</td>
<td>Intramuscular</td>
<td>II</td>
<td>Decreased residual myocardial ischemia</td>
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<tr>
<td>TALISMAN 201</td>
<td>PAD</td>
<td>phFGF-1</td>
<td>Intramuscular</td>
<td>II</td>
<td>Reduced amputation rate</td>
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<td>Baumgartner et al.</td>
<td>PAD</td>
<td>phVEGF&lt;sub&gt;165&lt;/sub&gt;</td>
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<td>I</td>
<td>Safe</td>
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<tr>
<td>Rosengart et al.</td>
<td>CAD</td>
<td>adenoVEGF&lt;sub&gt;121&lt;/sub&gt;</td>
<td>Intramuscular</td>
<td>I</td>
<td>Safe</td>
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<tr>
<td>Fuchs et al.</td>
<td>CAD</td>
<td>adenoVEGF&lt;sub&gt;121&lt;/sub&gt;</td>
<td>Intramuscular</td>
<td>I</td>
<td>Safe</td>
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<tr>
<td>Symes et al.</td>
<td>CAD</td>
<td>phVEGF&lt;sub&gt;165&lt;/sub&gt;</td>
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<td>I</td>
<td>Safe</td>
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<tr>
<td>Makinen et al.</td>
<td>PAD</td>
<td>phVEGF&lt;sub&gt;165&lt;/sub&gt;/ adenoVEGF&lt;sub&gt;165&lt;/sub&gt;</td>
<td>Intravascular</td>
<td>II</td>
<td>Improved perfusion</td>
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<tr>
<td>RAVE</td>
<td>PAD</td>
<td>adenoVEGF&lt;sub&gt;121&lt;/sub&gt;</td>
<td>Intramuscular</td>
<td>II</td>
<td>Single intramuscular injection not associated with improved exercise performance or QOL</td>
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<tr>
<td>Groningen</td>
<td>PAD</td>
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<td>Intramuscular</td>
<td>II</td>
<td>No reduction in amputation rate</td>
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<tr>
<td>REVASC</td>
<td>CAD</td>
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<td>Intramuscular</td>
<td>II</td>
<td>Improved exercise tolerance</td>
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<td>Ripa et al.</td>
<td>CAD</td>
<td>phVEGF&lt;sub&gt;165&lt;/sub&gt; + G-CSF</td>
<td>Intramuscular</td>
<td>II</td>
<td>Increased CD34&lt;sup&gt;+&lt;/sup&gt; stem cells, no change in perfusion</td>
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<tr>
<td>EUROINJECT ONE</td>
<td>CAD</td>
<td>phVEGF&lt;sub&gt;165&lt;/sub&gt;</td>
<td>Intramuscular</td>
<td>II</td>
<td>No change in perfusion, enhanced regional contractility</td>
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<tr>
<td>KAT</td>
<td>CAD</td>
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<td>Intravascular</td>
<td>II</td>
<td>Enhanced myocardial perfusion following adenoVEGF&lt;sub&gt;165&lt;/sub&gt; therapy</td>
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<tr>
<td>TREAT-HGF</td>
<td>PAD</td>
<td>phHGF</td>
<td>Intramuscular</td>
<td>I/II</td>
<td>Improved rest pain, ankle brachial index, and ischemic ulcer reduction</td>
</tr>
</tbody>
</table>

e. Novel Approaches
   i. Hydrogel encapsulation
   ii. Slow release cytokines