Clinical Trials of Cardiac Gene Therapy

Roger J. Hajjar MD
Mount Sinai School of Medicine
New York, NY

Disclosures:
Celladon: Scientific Founder
Nanocor: Scientific Founder
Why Gene Therapy for Heart Failure?

• Unmet needs using current therapies
• Advances in the understanding of the molecular basis of heart failure
• Cardiomyocyte-specific targets have emerged that are difficult to manipulate pharmacologically
• Increasingly efficient gene transfer technology
The Challenges

• Safe vectors
• Homogeneous transduction of the cardiomyocytes
• Long-term expression
• Cardiac specificity
• Effective and minimally invasive techniques of delivery
Over 100 new isolates of AAV
Ca^{2+} Cycling Targets
<table>
<thead>
<tr>
<th></th>
<th>Pharmacological Inotropy (cAMP Dependent)</th>
<th>Targeting SERCA2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energetics</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Arrhythmogenecity</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>cAMP</td>
<td>↑</td>
<td>↔</td>
</tr>
<tr>
<td>Diastolic Calcium</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Survival</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>
Modes of Delivery

• **Surgical Technique**
  - Gene Transfer During Bypass

• **Catheter Based Techniques**
  - Extracoporeal Re-Circulating System (V-Focus™)
  - Retrograde Perfusion
  - Antegrade Epicardial Coronary Artery Infusion (AECAI)
Immune Response following AAV Gene Transfer

- Neutralizing Antibodies to specific AAV serotype
- T cell (CD8+) response
These Patients Would Need to be Excluded in Clinical Trials of Gene Therapy Especially at Low Doses of AAV
CLINICAL TRIALS

SERCA2a

Enrollment completed:
• **CUPID Trial:** Class III/IV patients with heart failure received different doses of AAV1.SERCA2a by percutaneous delivery. Phase 1 completed (12 patients), Phase 2 enrollment completed (37 patients)

Enrollment to start:
• Patients undergoing LVAD insertion as destination-therapy or bridge to transplant will receive AAV6.SERCA2a one month after VAD placement $5 \times 10^{12}$ drp (8 patients) and saline (8 patients). *(Harefield/Papworth, UK)*
• Class III/IV heart failure patients will receive AAV6.SERCA2a vs saline and LV function will be followed by multi-imaging modalities *(Pitie-Salpetriere, France)*

Adenylyl Cyclase Type 6
• Class III/IV heart failure patients will receive intra-coronary delivery of Ad5.hAC6 or PBS in 3:1 randomization with dose escalation: $3.2 \times 10^9$ vp to $3.2 \times 10^{12}$ vp in 6 dose groups *(UCSD & VA Hospital, K.H. Hammond)*
Calcium Up-Regulation by Percutaneous Administration of Gene Therapy In Cardiac Disease (CUPID Trial)

Phase 1 & 2 Trial of Intracoronary Administration of AAV1.SERCA2a in Class III/IV Heart Failure

Phase 1: Open-Label, Sequential Dose Escalation
1.4x10^{11}, 6x10^{11}, 3x10^{12}, 1x10^{13} drp N=12 (3:3:3:3)

Phase 2: Randomized, Double-Blind, Placebo Controlled.
6x10^{11}, 3x10^{12}, 1x10^{13} drp, & saline N=37 (8:8:9:14)
Methods: Main Inclusion Criteria

- Age 18-75 years old
- NYHA Class III/IV
- Ischemic (vessel patency) or non-ischemic cardiomyopathy
- Maximal oxygen consumption ($V_{O_2}^{max}$) of $\leq 20$ mL/kg/min
- Left ventricular ejection fraction $\leq 35$
- ICD implanted
- If indicated, resynchronization pacemaker implanted for $>6$ months
- Anti-AAV1 neutralizing antibody titer (NAb):
  - Phase 1: 1:2 or $<1:2$;     Phase 2: $<1:2$
  - Using pre-screening protocol; $\sim 50\%$ population is eligible
- Stable, optimized HF regimen for 30 days, except for diuretics
Methods: Main Exclusion Criteria

- Clinically significant MI within 6 months
- Likely need for HF-related surgery within next 6 months
- Expected survival <1 years
  - Based on investigator's clinical judgment of HF and co-morbid conditions
## Phase 1: Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Very Low Dose</th>
<th>Low Dose</th>
<th>Mid Dose</th>
<th>High Dose</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>53 (7.0)</td>
<td>55 (4.6)</td>
<td>47.7 (9.0)</td>
<td>58 (19.5)</td>
<td>53.5 (10.6)</td>
</tr>
<tr>
<td>Male, n</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Race, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>African-American</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NYHA Status, number (%)</th>
<th>Very Low Dose</th>
<th>Low Dose</th>
<th>Mid Dose</th>
<th>High Dose</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA classification</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>3 (100)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac, Mean (SD)</th>
<th>Very Low Dose</th>
<th>Low Dose</th>
<th>Mid Dose</th>
<th>High Dose</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLWHFQ (points)</td>
<td>46.0 (31.8)</td>
<td>46.3 (20.5)</td>
<td>40.7 (20.2)</td>
<td>32.3 (23.3)</td>
<td>41.8 (21.5)</td>
</tr>
<tr>
<td>6-Minute Walk (meters)</td>
<td>376.7 (29.3)</td>
<td>421.7 (129.3)</td>
<td>386.3 (115.2)</td>
<td>349.3 (66.7)</td>
<td>383.5 (84.6)</td>
</tr>
<tr>
<td>VO₂ max (mL/kg/min)</td>
<td>14.6 (2.5)</td>
<td>13.0 (2.8)</td>
<td>14.9 (2.9)</td>
<td>13.2 (2.2)</td>
<td>13.9 (2.4)</td>
</tr>
<tr>
<td>LVESV (mL)</td>
<td>213.3 (44.9)</td>
<td>252.0 (86.6)</td>
<td>210.7 (47.4)</td>
<td>351 (158.9)</td>
<td>261.1 (98.6)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>24.3 (6.0)</td>
<td>20.3 (4.5)</td>
<td>22 (3.6)</td>
<td>18.7 (8.3)</td>
<td>21.3 (5.8)</td>
</tr>
<tr>
<td>NT-Pro BNP (pg/mL)</td>
<td>1857 (1369)</td>
<td>3084 (1954)</td>
<td>10644 (17373)</td>
<td>5735 (2719)</td>
<td>5330 (8346)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heart Failure Etiology, number</th>
<th>Very Low Dose</th>
<th>Low Dose</th>
<th>Mid Dose</th>
<th>High Dose</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Inflammatory</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ischemic</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Pregnancy-related</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Toxic</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical Findings, Mean (SD)</th>
<th>Very Low Dose</th>
<th>Low Dose</th>
<th>Mid Dose</th>
<th>High Dose</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>105.3 (20)</td>
<td>98.0 (5.3)</td>
<td>105.3 (4.2)</td>
<td>98 (8.7)</td>
<td>102.3 (10.6)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>69.3 (1.2)</td>
<td>68.3 (10.4)</td>
<td>79.0 (1.7)</td>
<td>61.7 (4.9)</td>
<td>71.3 (10.8)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>94.0 (17.7)</td>
<td>85.0 (13.6)</td>
<td>94.7 (21.1)</td>
<td>81.1 (23.9)</td>
<td>88.3 (17.5)</td>
</tr>
</tbody>
</table>
Administration via Percutaneous Intracoronary Artery Infusion

- Gene delivery to viable myocardium
  - Dominance and coronary artery anatomy from angiography determines infusion scenario

- Antegrade epicardial coronary artery infusion over 10 minutes
  - 60 mL divided into 1, 2 or 3 infusions depending on anatomy
  - Delivered via commercially available angiographic injection system & guide or diagnostic catheters
# Safety & Efficacy Measurements

## Safety
- Physical Examination
- Adverse Events
- CBC, Serum Chemistries, Urinalysis
- Creatine Kinase MB, Troponin T
- ELISPOT (cellular immune response against viral proteins)
- Echocardiogram
- Interrogation of ICD
- ECG

## Efficacy Domains
- Symptomatic
  - NYHA Class
  - MLWHFQ
- Functional
  - 6MWT
  - VO$_{2}$max
- Biomarker
  - NT-proBNP
- Remodeling
  - Ejection Fraction
  - End Systolic Volume
Clinically Meaningful Changes Within Patient Individual Analysis: Improvement +1, Worsening -1, NC 0

<table>
<thead>
<tr>
<th>DOMAIN</th>
<th>PARAMETER</th>
<th>CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>NYHA</td>
<td>1 Class</td>
</tr>
<tr>
<td></td>
<td>MLWHFQ</td>
<td>10 points</td>
</tr>
<tr>
<td>Functional</td>
<td>6MWT</td>
<td>50 meters</td>
</tr>
<tr>
<td></td>
<td>VO₂max</td>
<td>1.5 mL/kg/min</td>
</tr>
<tr>
<td>Biomarker</td>
<td>NT-proBNP</td>
<td>35% or 300 pg/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(whichever is greater)</td>
</tr>
<tr>
<td>Remodeling</td>
<td>EF</td>
<td>5% absolute</td>
</tr>
<tr>
<td></td>
<td>ESV</td>
<td>20 mL or 10%, (whichever is greater)</td>
</tr>
</tbody>
</table>
Majority of NAb Negative Patients Improved Composite Score at 6 months

NC = Increase, decrease, or no change in HF medications (Beta-blocker, diuretic, or aldosterone antagonist)
CUPID Trial: Phase 2

- Randomized, Double-Blind, Placebo-Controlled
  - Low, Mid and High Doses of AAV1.SERCA2a vs. Placebo
  - N=39 (8:8:9:14)
CUPID Time to First SAE: Phase 1 & Phase 2 Combined

Post AAV1.SERCA2a infusion 266 Patient Months of Follow-up

During Screening 83 Patient Months of Follow-up
New Directions

New Vectors

New Targets
# Acknowledgment

<table>
<thead>
<tr>
<th>Cardiovascular Research Center</th>
<th>Mount Sinai</th>
<th>Celladon Co.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antoine Chaanine MD</td>
<td>Valentin Fuster MD. PhD</td>
<td>Krisztina Zsebo PhD</td>
</tr>
<tr>
<td>Elie Chemaly MD</td>
<td>Fadi Akar PhD</td>
<td></td>
</tr>
<tr>
<td>Jiqiu Chen MD PhD</td>
<td>Hongwei Jin PhD</td>
<td></td>
</tr>
<tr>
<td>Elisa Y’aniz Galende PhD</td>
<td>Alex Lyon MD, PhD</td>
<td></td>
</tr>
<tr>
<td>Lahouaria Hadri PhD</td>
<td>Yoshiaki Kawase MD</td>
<td></td>
</tr>
<tr>
<td>Jean-Sebastien Hulot MD</td>
<td>Kitiyoke Ishikawa PhD</td>
<td></td>
</tr>
<tr>
<td>Dongtak Jeong PhD</td>
<td>Dennis Ladage PhD</td>
<td></td>
</tr>
<tr>
<td>Ioannis Karakikes PhD</td>
<td>Jimmy Lough</td>
<td></td>
</tr>
<tr>
<td>Chang Won Kho PhD</td>
<td>Catherine McMahon</td>
<td></td>
</tr>
<tr>
<td>Erik Kohlbrenner PhD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thomas Larocca PhD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ah Young Lee PhD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifan Liang MD</td>
<td>Dhamele Lebeche PhD</td>
<td></td>
</tr>
<tr>
<td>Larissa Lipskaia PhD</td>
<td>Joe Dobrin BS</td>
<td></td>
</tr>
<tr>
<td>Marta Miguel-Turu PhD</td>
<td>Soonjeong Kang PhD</td>
<td></td>
</tr>
<tr>
<td>Charlotte Morel BS</td>
<td>Jaewon Kim PhD</td>
<td></td>
</tr>
<tr>
<td>Manuel Ramos-Kuri MD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kleopatra Rapti PhD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gwangju Institute for Science &amp; Technology</th>
<th>INSERM, Pitie-Salpetriere</th>
<th>University of Cincinnati</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woojin Park PhD</td>
<td>Anne-Marie Lompre PhD</td>
<td>Litsa Kranias PhD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>University of North Carolina</th>
<th>Imperial College</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. Jude Samulski PhD</td>
<td>Sian E. Harding PhD</td>
</tr>
</tbody>
</table>