Choosing a Research Project/Mentor

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Choosing a Project:  
First Rule

FOCUS

FOCUS

FOCUS

FOCUS

FOCUS

FOCUS
The Project as a Post-Doc Fellow

- **DOs**
  - Focus on a theme
  - Logical progression of work in the laboratory of the PI
  - High likelihood of meaningful results
  - Do all the experiments yourself even if you have to learn many techniques

- **DONTs**
  - Spend your energy on work that is tangential to the core of the laboratory’s expertise
  - Involve yourself in multiple projects
Choosing a Laboratory:
*Size Counts*

- **Established Mentor with Large Laboratory**
  - More personnel to interact with and learn from
  - More resources
  - Less one-on-one time with the PI

- **Junior Mentor with small laboratory**
  - More one-on-one time with the PI who most likely will be doing bench work
  - Less resources
  - More pressure to produce as PI will be under tenure/promotion stress
Mentors

Ideal Attributes

• Advocate: Works closely with you until your goal is attained and remains a resource and part of your network for life.
• Coach: Addresses specific issues or questions posed and sends you on your way to implement.
• Advisor: Provides choices for your career and may refer you to other specialists who might better help.
Personal Experience with Fellowship to Faculty Transition
Physiological Observation of Abnormal Calcium Handling in Failing Myocardium

Trabeculae
*Aequorin*

Isolated Cardiac Myocytes
*Fura-2*

Control

Dilated Cardiomyopathy

1 mM

5g

100 msec

300 nM

300 msec

Judith K. Gwathmey VMD, PhD
Increase β₂ receptors
βARKct overexpression

Increase SERCA2a
Ablate phospholamban
Increase phospholamban mutated proteins
Increase Inhibitor 1
Identification of SERCA2a Downregulation as a Major Cause of Calcium Handling Abnormalities

SERCA2a Phospho-lamban

Non-Failing  Failing

p<0.005

Non-Failing  Failing

ATPase Activity (mmol/mg.min)

SR ATPase Activity

ATPase Activity (nmol/mg.min)

Diastolic [Ca^{2+}] (µmol/l)

[Ca^{2+}] (µmol/l)
Pharmacological Targeting of SERCA2a/Phospholamban Has Failed

• Search for small molecules targeting SERCA2a has not yielded specific, non-toxic compounds
  – Multiple significant efforts abandoned by large pharma
• Antibodies to phospholamban have been tried but have had no effect in vivo: intracellular protein

Gene Transfer Methodologies

Anthony Rosenzweig
Choosing a Vector for Cardiovascular Applications--Many Choices
Validating the Target in Human Cardiomyocytes

Cell Shortening and Ca$^{2+}$ Transient

- Failing Myocyte + Ad.GFP
- Non-Failing Myocyte + Ad.GFP
- Failing Myocyte + Ad.SERCA2a

Cell shortening (%)

Fura-2 Ratio (360/380)
Gene Transfer of SERCA2a in a Model of Pressure-Overload Hypertrophy in Transition to Heart Failure

Aortic Banding \rightarrow POH \rightarrow Heart Failure

Ad.\beta gal

Ad.SERCA2a

Transition from Compensated Hypertrophy to Failure

<table>
<thead>
<tr>
<th>Weeks Post Banding</th>
<th>Fractional Shortening (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.45±0.02</td>
</tr>
<tr>
<td>6</td>
<td>0.45±0.02</td>
</tr>
<tr>
<td>12</td>
<td>0.50±0.03</td>
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<tr>
<td>18</td>
<td>0.48±0.02</td>
</tr>
<tr>
<td>20-24</td>
<td>0.30±0.01</td>
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</table>
Effect of SERCA2a Gene Transfer on Survival in Rats with Pressure-Overload Hypertrophy in Transition to Heart Failure

Graph showing survival rates over days with different groups: Sham, Failing + Ad.SERCA2a, Failing + Ad.GFP, and Failing + Dobutamine. The y-axis represents % Survival, and the x-axis represents DAYS. Gene Transfer is marked by an arrow at the bottom.
Pre-Clinical Efficacy and Safety Studies

• Porcine Mitral Regurgitation Model of Heart Failure
  – Delivered into LCA through 10 minute infusion
  – $1 \times 10^{12}$ DRP

• Porcine Myocardial Infarction Model
  – Delivered into LCA through 10 minute infusion
  – $5 \times 10^{12}$ DRP

• Ovine Pacing Model of Heart Failure
  – Delivered into LCA using either direct infusion or V-Kardia device over 10 minutes
  – $10^{10} - 2.5 \times 10^{13}$ DRP
1. Patients with non-ischemic cardiomyopathy undergoing Left Ventricular assist device insertion as destination-therapy or bridge to transplant. Randomization: 8 patients will receive AAV6.SERCA2a (2 different doses in ant. & lat walls) and 8 subjects will receive saline injection. Weaning protocol 3 months after VAD placement (NIH Trial: R. Hajjar/B. London).

2. Patients with ischemic and non-ischemic cardiomyopathy undergoing LVAD insertion as destination-therapy or bridge to transplant will receive AAV6.SERCA2a one month after VAD placement by percutaneous gene transfer at 3 different doses. Weaning protocol 3 months after VAD placement. 25 patients. (Harefield/Papworth, UK, R. Hajjar/S. Harding). CAERUS.

3. Randomized, double-blind, placebo-controlled, sequential dose escalation trial in patients with NYHA Class III/IV HF due to ischemic/non-ischemic cardiomyopathy. Evaluate safety and feasibility of a single antegrade epicardial coronary artery infusion of 3 dose levels of AAV1.SERCA2a in 45 patients. (Celladon Corp., M. Jessup). CUPID.
New Directions

New Vectors

New Targets
Training Grants from NIH for M.D. Careers

- **T35** - Short-term training grant for health professional students
- **T32** - Institutional training grant (NRSA) – has pre- and post doc slots
- **F32** - Individual postdoctoral fellowship (NRSA)
- **K08** - Mentored clinical scientist development award
- **K23** - Mentored patient-oriented research career development award
- **R01, R03, R21** - Research grant
- **K02** - Independent scientist award
- **F33** - Senior fellowship (NRSA)
- **K24** - Mid-Career investigator in patient-oriented research
Keys for Success in Pursuing Your Topic

- Passion
- Persistence
- Energy
- Creativity/Innovation
- Adaptation
- Self-confidence
- Independence/Self Reliance
- Intuition