Real-life examples: Successes and Challenges from an OAIC-supported Pilot Study

Aerobic exercise to improve regulation of EPCs and the vasculature in T2DM

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1. Forming a Hypothesis

- Initial, "general" Hypothesis
- Consultation with mentors, OAIC Core leaders
- Conceptual Model
- Combine to form directional/testable hypotheses

Lessons Learned

- How to get started
- Establishing goals for the pilot study
- Developing Hypotheses, Aims, and Conceptual Model
- Subjects and Sample Size
- Timing, feasibility, and efficiency

- Flexibility
- Perseverence

Example: Hypotheses

We hypothesize that in older adults with T2DM:

1) Reduced skeletal muscle capillarization and endothelial dysfunction are associated with reduced EPC number and function due to a) reduced EPC mobilization, and b) impaired EPC function.

2) Aerobic exercise training will increase EPC number and function, and this will be associated with increases in skeletal muscle capillarization and endothelial function.

How I started

- Identify an important question and knowledge gap
- "Nugget" of data & general hypothesis
- Establish Goals
  - Study novel mechanisms underlying EPC and vascular dysfunction in T2DM
  - Establish methods new to my lab
  - Generate convincing preliminary data
  - Submit for K23, VA Merit, and R01 funding

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2. Writing Specific Aims

- Must be focused, yet comprehensive
  - Need to acquire key preliminary data for larger grant
    - Major outcomes and mechanisms

- Feasible
  - Must be able to conduct and complete project within budget and time frame

3. Writing the application

- Don't over-simplify in early stages of pilot development
  - Write the pilot application as if submitting to your target funding agency
    - Need to identify:
      - All of the methods you need to establish
      - All of the data you need

- Try to establish feasibility of the study

- Can scale back later to fit pilot guidelines

5. Sample Size

- Attempt power analysis for all key variables
  - Can't assess everything in a pilot study
  - Helps to identify all data you need
  - Can focus on "holes"

- Determine a realistic number of subjects
  - Must be feasible
  - Must provide compelling data (proof of concept)
  - Then used to generate sample size for grant

4. Subject Selection

- What is the target population?

- Will my pilot sample be representative of this population?

- Need a sample that will yield interpretable data
  - Understand what might confound your data/interpretation
  - Consult with mentors and other experts

Example: Sample Size

- What's missing?
  - EPC function
  - EPC mobilization
  - Endothelial function

- How many subjects are feasible in pilot?
  - Our goal was n=10 to establish proof of concept and acquire data for full power analysis

Example: Subject Selection

- Inclusion Criteria:
  - T2DM controlled by lifestyle or oral medications (HbA1c < 9.0%)
  - - or - NGT
  - Age 50-80 years; BMI = 25-40 kg/m^2
  - No regular, vigorous physical activity (<20min exercise, 2x/week)
  - Non-smoking (>2 years)
  - For women, >1yr past menopause, FSH >30 mIU/ml, and not on hormone replacement therapy
  - An asymptomatic screening Bruce treadmill exercise test to exclude those with symptomatic cardiovascular disease
- Exclusion criteria:
  - History of CVD (CAD or PAD)
  - Microalbuminuria, or liver, pulmonary or renal disease
  - History of cancer
  - Chronic anemia
  - Any orthopedic or other condition limiting the ability to exercise for 6 months

6. Conducting the Pilot

- Need to capture meaningful and interpretable data
  - Establish and validate methods first!

- Continual review of data

- Continue to seek input (internal and external)

- Ongoing challenges…

Challenges

- Timeline
  - IRB approval
  - Regulatory
  - Recruitment

  - My pilot: 6-month AEX training study
    - Tough with 1-yr pilot = needed 2nd continuation year

Example: Flexibility

- Feedback on complexities of T2DM

  - K23 – expand training in clinical management of subjects with T2DM to control/account for confounders

  - R01 – focus on IGT (less complex than T2DM)

Challenges

- Support and Mentoring
  - OAICs provide great environment
    - Senior scientists
    - Core support

  - Consistent interaction with pilot mentors

  - Ongoing review of data

7. Getting to the next level

- When to Submit for external funding
  - Depends on mechanism (K-award, R21/R03, VA Merit, R01)

- Establish all methods

- Accumulate enough data to:
  - Provide proof of concept
  - Estimate sample size

- Review your data
  - Unanticipated outcomes

Challenges

- Remain Flexible
  - Seek internal and external review
    - Even as pilot is ongoing

  - Submit grant to funding agencies with some data
    - Get feedback on concept, what's lacking, etc.

  - Add new experiments when appropriate
    - Look for unanticipated results in data
    - Science evolves continuously
      - 1-3 years from application – completion

Summary / Keys for success

- Starts with a good idea

- Remain flexible and continue to re-evaluate your pilot

- Need plasticity, support, and continued input

- Perseverence!
  - Be ready for challenges