Mentored Career Development
UC Irvine K-Club

UC Irvine K-Club Faculty

Vince Caiozzo, Ph.D.
Professor, Departments of
Orthopedics and Physiology &
Biophysics
Institute for Clinical and Translational
Sciences

Diana Vigil-Stephens, MBA
Institute for Clinical and Translational
Sciences

Brooke Piercy, MA
Research Program Manager
UC Irvine K-Club Faculty

Connie Rhee, M.D., M.S.
Assistant Professor, Department of Medicine
Division of Nephrology

Kam Kalantar, M.D., Ph.D., MPH
Professor and Chief, Division of Nephrology, Department of Medicine
How To Develop a Competitive “K Award”

Importantly, You Have to Clearly and Convincingly Answer Three Important Questions:

Where Are We Going? (Biological Issue/Hypothesis)

Who’s Driving? (Principal Investigator)

How Are We Getting There? (Specific Aims/Experimental Design)
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How To Develop a Competitive “K Award”

Importantly, You Have to Clearly and Convincingly Answer Three Important Questions:

Where Are We Going? (Biological Issue/Hypothesis)

Common sense argues that funding would revolve around the most important biological problems
Importantly, You Have to Clearly and Convincingly Answer Three Important Questions:

Who’s Driving? (Principal Investigator)

Common sense argues that those individuals who publish the most and with the greatest impact will more frequently be funded.
How To Develop a Competitive “K Award”

Importantly, You Have to Clearly and Convincingly Answer Three Important Questions:

Who’s Driving? (Principal Investigator)
How To Develop a Competitive “K Award”

Importantly, You Have to Clearly and Convincingly Answer Three Important Questions:

How Are We Getting There? (Specific Aims/Experimental Design)

Common sense argues that the well-thought-out design (experimental) will have the highest probability of funding.
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What Is The Magical Formula?
What Reviewers Evaluate

- Overall Impact
- Core Criteria

Candidate
Research Plan
Career Development Plan (Tracking/Evaluation)
Mentors
- RCR
- Environment

- Additional considerations (Human subjects, Animal Welfare)
- Contact NIH IC PO for guidance once you have a plan in place
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**SUBSTRATE IS EVERYTHING!!**

**Goal(s) of K-Club**

- There is no science without science. In other words, candidates must be viewed as exceptional scientists and the science that they pursue must be important.
- “Nothing is worth doing well if it isn’t worth doing.”
Research Plan and Specific Aims

Goals for today

1. Working draft of your NIH biosketch
2. Working draft of Specific Aims section
3. The Specific Aims tells the reviewer
   a. Why and where are we going (the problem)
   b. How are we getting there (hypothesis and specific aims).
4. Talk about different approaches to Specific Aims section
   a. Reductionist approach versus holistic/systems biology
   b. Organizing cartoon?
5. One-on-one meetings - need to schedule - 2nd draft (1-2 wks)
Specific Aims – Why and Where Are We Going

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Specific Aims - Why and Where Are We Going
Specific Aims - Why and Where Are We Going

Some issues are obvious and others may not be.

No matter, your job is to convince the reviewer that you are studying an important problem.
Specific Aims - Structural Suggestions

- First paragraph - provide succinct background of problem and identify the current gaps of knowledge
- Second paragraph - provide succinct discussion of how your previous work addresses this important problem
- Third paragraph - what is the general hypothesis that you will be testing? Give it a name. This will help the reviewer and is a good way to succinctly reinforce the fundamental basis of your proposal
- Fourth paragraph - Specific aim 1
- Fifth paragraph - Specific aim 2
Specific Aims – How Are We Getting There?
Scientific Method - Hypothesis

- The research component driven by strong hypotheses rather than advances in technology.
- Hypothesis is the foundation.
- Research component should focus on proving or disproving a hypothesis.
- Doesn't necessarily exclude applied research but need to be careful.
- Focused hypothesis that increases understanding of an important biologic process.
Specific Aims - How Are We Getting There?
Scientific Method - Hypothesis

- Limit Specific Aims (1, 2, 3)
- Do not include Sub Aims in this section. Not appropriate place. You can do this under Research Strategy
Specific Aims - How Are We Getting There?
Scientific Method - Hypothesis

A few Tips:

- Construct hypothesis and specific aims so that they can be accomplished during 3-5 years.
- Scientific focus of application should be consistent with NIH priorities.
- Show reviewers how your project fits in your field. Make this explicit.
- Remember, methods are the means for performing your experiments. Your experimental results will prove or disprove your hypothesis.
- Have one general hypothesis rather than multiple general hypotheses.
Specific Aims - How Are We Getting There?

Scientific Method - Hypothesis

- Make sure your hypothesis will generate aims and methods you can accomplish within the 3-5 years time and with the resources available.
- After you have chosen your hypothesis, outline your specific aims:
  - Experiments support specific aims, specific aims support testing hypothesis..
- Use graphics to plan experiments.
  - Simple graphics/decision trees describing approach to testing hypothesis demonstrate thoughtfulness.
Specific Aims – How Are We Getting There?
Scientific Method - Hypothesis

- **Examples of a poor research hypothesis:**
  - Analogs to chemokine receptors can be biologically useful.
    *Problem: Too broad! Searching for a potential biological application.*
  - A wide range of molecules can inhibit HIV infection.
    *Problem: Fishing expedition! Searching for a solution to a biological problem by throwing darts.*

- **Example of a good research hypothesis:**
  - Analogs to chemokine receptors can inhibit HIV infection.
Given the paucity of data related to the radioresponse of satellite cells, the primary objective of this grant proposal is to expand on our preliminary data and to perform a series of baseline studies that address the following hypothesis: *irradiation of satellite cells compromises muscle growth via pathways mediated by oxidative stress (i.e., oxidative stress hypothesis)*. To test this hypothesis, we are proposing two complimentary specific aims, that will employ genetically modified animals designed to maximize (SOD) and minimize (MCAT) oxidative stress induced by g-irradiation.

1. **Specific Aim 1** will test the “oxidative stress” hypothesis by using a SOD2 knockout model. Specifically, we hypothesize that satellite cells with compromised oxidative stress defense mechanisms will dramatically accentuate the impact of g-irradiation on the proliferative capacity of satellite cells.

2. **Specific Aim 2** will test the “oxidative stress” hypothesis by using a genetically modified animal with enhanced oxidative defense mechanisms. In particular, we will use animals where human catalase has been targeted to the mitochondria. We hypothesize that satellite cells in these MCAT animals will have enhanced oxidative defense mechanisms that make them less susceptible to the oxidative stress induced by g-irradiation.
Given the paucity of data related to the radioresponse of satellite cells, the primary objective of this grant proposal is to expand on our preliminary data and to perform a series of baseline studies that address the following hypothesis: **irradiation of satellite cells compromises muscle growth via pathways mediated by oxidative stress (i.e., oxidative stress hypothesis)**. To test this hypothesis, we are proposing two complimentary specific aims, that will employ genetically modified animals designed to maximize (SOD) and minimize (MCAT) oxidative stress induced by g-irradiation.

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Specific Aims - How Are We Getting There?
Scientific Method - Do You Have A Unifying Hypothesis?

Hence, the overall goals of the proposed 5-year project are to elucidate the temporal dynamics of distal segment lengths during postnatal muscle development and after injury, and to use nanometer-resolution imaging to create an ultrastructural “map” of the distal segment pointed end that will elucidate the molecular rearrangements required for actin subunit association and dissociation from the pointed end. Addressing both of these goals will allow me to investigate the hypothesis that sarcomeric Tmods regulate distal segment lengths and remodeling by controlling the molecular architecture of the pointed end. This proposal is divided into two Aims, which can be performed independently from one another:
AIM 1 (SUPERVISED K99 RESEARCH). INVESTIGATE THE BIOLOGICAL ROLES OF SARCOMERIC TMODS IN DISTAL SEGMENT REMODELING DURING SKELETAL MUSCLE MATURATION, INJURY, AND PATHOLOGY. The extent of pointed end capping by sarcomeric Tmod is inversely related to thin filament lengths in both cardiac myocytes and Drosophila muscle (19, 28, 38, 40, 66). Here, I will test the hypothesis that sarcomeric Tmods (Tmod1 and Tmod4) regulate distal segment remodeling during postnatal muscle development and after muscle damage by comparing the skeletal muscle phenotypes of wild-type (WT), Tmod1-/-, and Tmod4-/- mice under a variety of experimental conditions. Confocal fluorescence microscopy and Distributed Deconvolution (DDecon) analysis will be used to measure distal segment lengths at different postnatal ages, after acute mechanical injury (eccentric exercise), and after chemical injury (cardiotoxin injection). To study distal segment remodeling in pathologically chronic muscle injury, I will use two mouse models of Duchenne muscular dystrophy (DMD), the mdx model of mild DMD and the mdx/mTR model of severe DMD. Both mdx and mdx/mTR muscles exhibit calpain-mediated proteolysis of Tmod1 and Tmod4 that vary in a muscle-specific manner, providing novel and clinically relevant models of Tmod depletion leading to distal segment remodeling in vivo.
AIM 2 (INDEPENDENT R00 RESEARCH). CHARACTERIZE THE LENGTH VARIABILITY AND MOLECULAR ARCHITECTURE OF THE DISTAL SEGMENT AT NANOMETER-SCALE RESOLUTION. To develop a mechanistic understanding of the molecular events involved in distal segment length variability and remodeling, the molecular architecture of the distal segment needs to be described. However, the short length and tight lattice spacing of the distal segments within a sarcomere preclude investigation of the molecular architecture of the distal segment using conventional diffraction-limited optical microscopy methods. Thus, I will use cutting-edge nanometer-resolution imaging and computational techniques to circumvent these obstacles and examine the hypothesis that the molecular architecture of the distal segment provides a structural basis for distal segment length variability and remodeling. I will use stochastic optical reconstruction microscopy (STORM) and electron tomography to quantify distal segment length variability in WT, Tmod1 /-/, and Tmod4 /-/- mice. Finally, I will perform singleparticle cryoEM of isolated thin filaments to solve the 3D structure of the Tmod/tropomyosin/actin complex at the pointed end and ascertain a structural mechanism for actin subunit dynamics at the pointed end.
Specific Aims – Reductionist Approach Versus Systems Biology Approach/Holistic Approach/ Other

Bad Information Flow:

A → K

Nice flow of one specific aim to another to provide a rigorous test of your hypothesis.
Specific Aims - Reverse Engineering
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How cool it is to be a scientist who helps improve human health!!!!

Enjoy the Magical Mystery Tour!