Navigating a Successful Path to the Mentored Research Scientist Development Award (K01)

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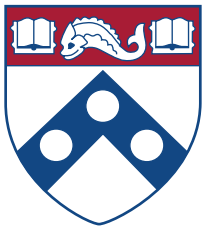

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Overview

- Purpose
- The Key Components of K01 Application
- Application Timeline
- Research Strategy
- Strengths & Weaknesses

What is the K01 Mentored Research Scientist Career Development Award for?

- Purpose
  - Provide support and “protected time” (3-5 years) for an intensive, supervised (ie. mentored) career development experience in the biomedical, behavioral, or clinical sciences leading to research independence.
  - Typically funds Ph.D. researches
  - Typically supports individuals 3 to 5 years post terminal degree (ie. outside eligibility for K99/R00)
  - ****NCI Specific**:** The overarching goal of this FOA is to enhance the pool of independent cancer research investigators from backgrounds underrepresented in the biomedical, clinical, behavioral, and social sciences such as:
    - Individuals from underrepresented and underserved populations: African Americans, Hispanic Americans, American Indians, Alaska Natives, Native Hawaiians, and other Pacific Islanders.
    - Individuals with disabilities, who are defined as those with a physical or mental impairment that substantially limits one or more major life activities.

The Key Components of K01 Application

- Candidate's Background
- Career Goals & Objectives
- Career Development/ Training Activities
- Training in RCR
- Statements of Support (ie. Letter of Support from Mentor)
- Description of Institutional Environment
- Institutional Commitment to Candidate (ie. Letter from Chair of Department)
- Research Strategy

Candidate's Background

- Where and in what field have you trained thus far?
  - Undergraduate Research Fellowship- UNC-CH Pharmacology (Channing Der, Ph.D.)
  - Graduate Student- UNC-CH Pharmacology (Adrienne Cox, Ph.D.)
  - Postdoctoral Fellow- Duke University Pharmacology & Cancer Biology (Chris Counter, Ph.D.)
  - Highlight relevant cancer biology training
- What did you accomplish during these training opportunities?
  - Technical Skills (ie. molecular and cellular biology)
  - Grants (ie. F31 or predoctoral fellowship)
  - Awards (ie. Posters or Talks)
  - Publications
- Why did you choose your postdoctoral fellowship?
  - Gain new skills (ie. screens or animal models)
  - Explore new scientific field (ie. New to cancer biology or basic vs. translational)
- What will you gain from the mentored phase of K01?
  - Protected time to develop independent research program
  - Networking
  - Improve presentation skills
  - Highlight commitment to cancer biology research

Career Goals & Objectives

- Previous Research History
  - Where did you train?
  - With whom did you train?
  - What skills did you learn?
  - Highlight foundation in cancer biology research if applicable

- Justification for Future Research and Career Development
  - Why do you need protected time to achieve independence?
    - Additional Skills/Training
    - Networking/presenting
    - Develop independent research program
  - Highlight commitment to cancer biology research
  - Highlight why you're an ideal candidate

- Research, Training, and Transition Plan
  - Use a bullet point list of what you aim to accomplish each year
    - Research, Additional Training, & Presentation of Research
    - Preparation for Transition (ie. Application package & job talk)
    - Future as an Independent Investigator (ie. Setting up lab & applying for RO1)

Career Development/ Training Activities

- New Research Skills and Knowledge
  - Highlight the new skills gained within the proposed research project (ie. animals models, pharmacological interventions, translational research)

- Formal Training Activities
  - Responsible Conduct of Research (26 hours/4%)
  - Presentations (543 hours/90%)- (ie. Lab meetings, journal clubs, works in progress meetings, retreats, annual meetings)
  - Running an Academic Research Lab (10 hours/2%)- (ie. Courses and/or seminars at your University that will be applicable)
  - Effective Strategies for the Academic Job Search (22 hours/4%)-(ie. Courses and/or seminars at your University that will be applicable)

Statements of Support

- Mentoring Plan
  - General Strategy (ie. meetings, seminars, conferences, & mentorship committee)
  - Trainee Specific Strategy (ie. around the strengths & career goals of applicant)
  - Research Project Design

- Source of Support
  - Is the project funded?
  - If not what's the plan for funding?

- Nature and Extent of Supervision and Mentoring
  - Experimental Design
  - Career Planning
  - Manuscript & Grant Preparation
  - Job Application & Talk Preparation

- Teaching Load
  - Mentorship of Undergraduates, Graduate Students, & Research Technicians

- Transition Plan from Mentored to Independent Investigator
  - Research Qualifications and Previous Experience as a Mentor
  - 6 Component Transition Plan (Mentoring, Exposure, Job Application Prep, Job Talk/ Interview Prep, RO1/Future Direction Prep, & Networking)

Description of Institutional Environment

- Relevant Key Faculty Members
  - Who makes up your mentorship committee and why?

- Facilities and Other Resources
  - What is available at your institution that will make your research plan feasible?

- Intellectual Interactions with Other Investigators.
  - What networking opportunities are available at your institution that are relevant to your proposal?

When to Apply for the K01 Mentored Research Scientist Career Development Award ?

- Have you established yourself in the research area?
  - Your previously published work is the background for the specific aims
  - ie. The discovery that MEK requires Cu for kinase activity. (published in MCB)

- Do you have adequate preliminary data?
  - Is the preliminary data published and/or under review?
  - ie. The discovery that Cu influx is specifically required for $BRAF^{V600E}$ oncogenesis. (under review at Nature)

- Will completion of these aims lead to a fundable RO1/independent research program?
  - Will the completed project serves as preliminary data for an RO1?
  - Will the proposed work differentiate the applicant from mentor?

Research Strategy

- Significance/Relevance
  - Is there a need? (ie. Intrinsic and acquired resistance to the standard of care)
- Innovation
  - What's unique about your proposed research? (ie. Novel mechanism of inhibition)
  - What's novel about your approach? (ie. Repurposing existing drugs & physiologically relevant animals models)
- Approach (Preliminary Data)
  - Grounded in published work and work under review
- Aim 1. Determine the efficacy of combining Cu chelation and BRAF inhibition to reduce *Braf*^{V600E}-driven malignant melanoma.
  - Use a novel GEMM of metastatic melanoma
  - Leverage Cu chelators as a novel strategy to inhibit MEK1/2 function
  - Combine Cu chelators with the current standard of care
  - Leverage Cu chelators in settings of resistance to standard of care
- Aim 2. Determine whether Cu ablation either genetically or pharmacologically reduces tumorigenesis of other BRAF^{V600E}-mutant cancers.
  - Leverage Cu chelators in additional BRAF mutant cancer settings

Review Process

- Candidate
- Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring
- Research Plan
- Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s)
- Environment and Institutional Commitment to the Candidate

Overall Impact

- “This K01 application is **based upon prior work** from this group showing that copper (Cu) influx enhanced MEK1 phosphorylation through a Cu-MEK1 interaction. The applicant proposes to determine the efficacy of combining Cu chelation and BRAF inhibition **using GEMM models**. In Aim 2, she will determine whether Cu ablation either **genetically or pharmacologically** reduces tumorigenesis of other BRAFV600E-mutant cancers. **Overall, the work is a logical extension of prior studies** but **lacks innovation and mechanistic depth**. The applicant has had a good record of accomplishments but a modest publication record. **The input from the mentorship committee beyond Dr. Counter was inadequately described**.”

Overall Impact

- “This **proposal builds on a solid track record** of the applicant’s achievement in graduate school and first post-doctoral appointment in most recently defining intracellular Cu as an important contributor to MEK activation. The strengths include the **intrinsic diligence of and clarity of experimental designs** by the applicant; **a superb proposed mentor and consultative team**, and **the significance and innovation** of the Aims. All these increase enthusiasm that this applicant has the potential to transition to an independent researcher on the strengths of output from this proposal’s successful completion.”

Overall Impact

- "The PI of this proposal is a postdoctoral fellow at the Duke Cancer Institute. She has a BS degree in chemistry and a PhD degree in Pharmacology. She **has published 7 original articles in high level journals and two book chapters and is the recipient of multiple awards**. **The mentor and referees provide extremely strong letters**, all supporting that the PI is well suited for this funding mechanism and future success. **A comprehensive career development and training plan** is provided and the mentor provides a **detailed plan to support the PI's training**. The PI has made the novel observation that Cu is required for MEK activity and that tumors driven by BRAF mutations are dependent on Cu. She proposes a series of genetic and pharmacologic studies to determine the effects of Cu chelation in multiple Braf driven cancers. **The research is a logical growth from** her previous work and will provide training in more translational science, different cancers, and pharmacology. The candidate is ideally suited for this award mechanism. Given the strength of the candidate, mentor, and research plan, this proposal is likely to have significant impact scientifically and provide a path for the PI to become successful and independent."

Strengths

- “Productivity during previous training.”
- “Logical research direction & systematic approach.”
- “Exceptionally strong mentoring plan with general and specific mentoring tasks, including mentoring committee.”
- “Continuing input from experts in kinase signaling and in Cu cellular biochemistry.”
- “Grounded in a highly productive laboratory and institutional environment.”
- “Appropriately makes space for organizing findings and preparing additional grant proposals during the latter part of the funding period.”
- “The PI has strong recommendation letters from four referees.”

Weaknesses

- “Not clear how the applicant will differentiate from the mentor as he has a pending R01 on the proposed topic.”
- “The studies, particularly Aim 2, are incremental and lack significant innovation.”
- “The studies are primarily descriptive and lack mechanistic depth.”
- “The letter from the mentorship committee lacked sufficient detail.”
- “The grants to specifically support the research proposed in this application are not yet funded.”

Response to Critiques

- Acknowledge
  - Concern: “The studies, particularly Aim 2, are incremental and lack significant innovation.”
    - “As requested, I **acknowledge** here that while the goal of Aim2 to expand Cu chelation therapy to other cancers is not innovative, it is a pressing and clinically relevant problem that many of the other BRAF mutation-positive cancers are less responsive to current targeted therapies due to intrinsic resistance. However, **I did not overlook** this concern and have **begun experimental approaches to better understand the mechanism** by which Cu impacts MEK1/2 kinases on the atomic level that involve investigation of protein-protein interactions, binding affinities for ATP, and structural changes mediated by Cu binding. Elucidation of this mechanism could result in the creation of novel MEK1/2 inhibitors that specifically interfere with Cu binding and may reveal Cu binding to other kinases **as a novel, general mechanism to modulate activity.**
- Be concise
  - Concern #1: “The letter from the mentorship committee lacked sufficient detail.”
    - “As requested, I have **met with my mentorship committee** to set up a **regular meeting schedule** and now have an agenda for these meetings to serve as a **more detailed guide**.”
- Be respectful
  - Concern #1: “The entire proposal is in the wrong font. Should be Arial 11pt, not Times. The proposal would have likely been over in length had the appropriate font been used.”
    - “As requested, **I thank the reviewers for their close attention to my K01 application** and indicate here that the font used throughout the proposal was Georgia 11pt and point the reviewer to Section 2.6 Format Specifications for Text (PDF) Attachments in the SF424 (R&R) Application Guide for NIH and Other PHS Agencies that states “Use an Arial, Helvetica, Palatino Linotype, or Georgia typeface, a black font color, and a font size of 11 points or larger.”

Acknowledgements

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