Sample Application for Research Training and Career Development Funding

Through the K99/R00 Pathway to Independence Awards, NIA supports exceptional postdoctoral researchers in completing the final years of their postdoctoral work and transitioning to a role as an independent scientist. Each award has two phases, the K99 phase supporting postdoctoral training, and the R00 phase supporting an independent research career.

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https://www.nia.nih.gov/research/training/k99-r00-sample-applications
SUMMARY STATEMENT

PROGRAM CONTACT: (Privileged Communication)
Jose Velazquez

Release Date: 06/14/2019

Privileged Communication

Application Number: 1 K99 AG065200-01

Principal Investigator
HIGUCHI-SANABRIA, RYO

Applicant Organization: UNIVERSITY OF CALIFORNIA BERKELEY

Review Group: NIA-B
Biological Aging Review Committee
NIA-B

Meeting Date: 06/04/2019
Council: OCT 2019
Requested Start: 09/01/2019

RFA/PA: PA19-130
PCC: 1ACBYJV

Project Title: More than just a load control: cytoskeletal form and function during aging

SRG Action: Impact Score:32
Next Steps: Visit https://grants.nih.gov/grants,next_steps.htm

Human Subjects: 10-No human subjects involved
Animal Subjects: 10-No live vertebrate animals involved for competing appl.

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ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.
RESUME AND SUMMARY OF DISCUSSION: This application for a Pathway to Independence Award (K99/R00) is submitted by the University of California (UC), Berkeley, CA, on behalf of the candidate Dr. Ryo Higuchi-Sanabria, to study novel genes that are found to alter the chromatin state and lipid homeostasis in regulating the actin cytoskeleton. The application will also examine the influence of neurons overexpressing the heat-shock factor 1 (hsf-1) on actin in peripheral tissues in addition to searching for differences in genes involved in actin changes among three peripheral tissues. The candidate is a talented postdoctoral researcher with an exceptional track record of productivity as a graduate student in Dr. Liza Pon’s laboratory at Columbia University, and has already published 2 manuscripts as first author with his current mentor and has a potential to become an independent investigator. The area of study is significant, and the application is well written. There is little knowledge regarding the actin changes with increasing age and across tissues and the candidate proposes experiments using in vivo imaging of the actin using novel tools. There are additional assays and tools planned to test and uncover novel regulators of actin across different tissues that are dependent and independent of the influence of neurons expressing hsf-1. Thus, the study may provide significant and new information associated with the actin cytoskeleton during aging. The mentor (Dr. Dillin), the advisory committee, and the research environment are outstanding. While the candidate and the proposed research are very strong, the panel noted several weaknesses. The career development training is primarily on what the candidate has already learned and there are no future courses, or workshops to attend and the suggested meetings primarily focus on anatomy, cellular and molecular biology and neuroscience, a concern given the candidate’s primary background is on yeast. The lack of formal training on aging is another concern since the candidate is relatively new to this field and the plan for supervision and mentoring of the candidate by the mentoring team is insufficient. Overall, this outstanding candidate has planned an innovative approach to tackle an important biological question and uncover modulators of the actin cytoskeleton. However, the weaknesses in the research plan (lack of detail, mechanistic insight to better link candidate modifiers with changes in actin and overly ambitious research plan) alongside insufficient background in the career development plan on aging biology and of complex cellular systems tempered enthusiasm for the proposed study.

TRAINING IN THE RESPONSIBLE CONDUCT OF RESEARCH: Acceptable. The training in the responsible conduct of research is adequately addressed.

DESCRIPTION (provided by applicant): Although the cytoskeleton has historically been understood as the structural framework of the cell, the proper function of actin is also required for a diverse array of cellular pathways. The collapse of these cellular processes manifests during aging and exposure to a myriad of stresses, which is in part due to the breakdown of the cytoskeleton under these conditions. Interestingly, the breakdown of the cytoskeleton throughout age has been adopted as common knowledge in the field of aging biology, despite the lack of clear and direct evidence. A major contributor to the lack of these essential studies is the lack of tools available for in vivo, live-cell imaging of the actin cytoskeleton in multi-cellular organisms. Early in my postdoctoral career, I developed a system for robust, tissue-specific, live-cell imaging of the cytoskeleton in the muscle, intestine, and hypodermis of C. elegans, utilizing LifeAct fused to a fluorescent molecule. LifeAct-mRuby reliably binds to F-actin, allowing visualization of functional, filamentous actin in the cells it is expressed. Using this system, I performed an exhaustive characterization of the decline of actin cytoskeletal integrity during aging. This work laid the foundation of my currently ongoing work in identification of novel regulators of the actin cytoskeleton. Having set up a system to interrogate cytoskeletal quality, I can now interrogate novel genes in their potential role for actin regulation. Using this and other platforms, I performed a multi-pronged screening approach to identify novel genetic regulators of actin. These studies combined in vivo live cell imaging of actin filaments, synthetic lethality screening with known regulators of the actin cytoskeleton, and both transcriptome analysis and whole genome CRISPR-Cas9 screening of organisms experiencing actin stress. Cross-referencing these rich datasets has revealed two critical nodes of genes: 1) modifiers of chromatin state and their downstream transcriptional regulators and 2) genes involved in lipid storage and global lipid homeostasis. In Aim 1, I propose to
characterize these major molecular pathways and how they contribute to cytoskeletal integrity. I hypothesize that a general chromatin state exists to promote a healthy transcriptome for proper cytoskeletal form and function, and that this breaks down as a function of age. Moreover, a healthy metabolic state can work either upstream of – or independent of – chromatin remodeling to also promote cytoskeletal health. In Aim 2, I propose to study whether any of the identified processes can function in a cell non-autonomous manner, by answering two questions: 1) does non-autonomous hsf-1 signaling occurs through changes in chromatin or metabolic state in peripheral tissue? and 2) does overexpression of major genes involved in chromatin remodeling or lipid homeostasis in neurons alone drive non-autonomous protection of the actin cytoskeleton in peripheral tissue, similar to HSF-1? Finally, Aim 3 uses a molecular approach to characterize protein interactors of actin important for its proper form and function. This study will open exciting avenues of research in understanding the role of cytoskeletal form and function on physiological aging.

PUBLIC HEALTH RELEVANCE: Many cellular functions, such as autophagy, organelle dynamics, and endocytosis/exocytosis, as well as their dedicated quality control machineries, such as the ubiquitin-proteasome system and the heat-shock response, decline in efficiency and function during the aging process. The actin cytoskeleton is no exception, and exhibits marked decline in structural integrity and function at old age. I propose a multipronged approach to understand how the regulatory network involved in cytoskeletal maintenance deteriorates during aging, and how this contributes to the physiological consequences of aging.

DISCLAIMER: Please note that the following critiques were prepared by the reviewers prior to the Study Section meeting and are provided in an essentially unedited form. While there is opportunity for the reviewers to update or revise their written evaluation, based upon the group’s discussion, there is no guarantee that individual critiques have been updated subsequent to the discussion at the meeting. Therefore, the critiques may not fully reflect the final opinions of the individual reviewers at the close of group discussion or the final majority opinion of the group. Thus, the Resume and Summary of Discussion is the final word on what the reviewers actually considered critical at the meeting.

CRITIQUE 1:

Candidate: 1
Career Development Plan/Career Goals/Plan to Provide Mentoring: 5
Research Plan: 6
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 1
Environment, Commitment to the Candidate: 1

Overall Impact:
In this K99 application, network of molecules involved in maintaining the cytoskeleton, and specifically actin, will be examined with the goal of understanding why the cytoskeleton deteriorates with advancing age in peripheral tissues. The application will also seek to identify molecular mechanisms responsible for the disparate rates of actin deterioration across different tissues during aging. Three aims are proposed and in Aim1, several assays will be deployed to determine how chromatin remodeling and altered lipid homeostasis affect actin organization and function. In Aim 2, the manner by which neuronal hsf-1 regulates the cytoskeletal of innervating tissues will be sought. In Aim 3, experiments will be undertaken to seek out novel tissue-specific cytoskeletal interactors altered in wild type and overexpressing hsf-1 specifically in neurons in c. elegans during aging. While further understanding how and why the cytoskeletal changes with advancing age is significant and this study may provide new insights, there are few concerns with this application. The application is overly ambitious, fails to go deep enough in most experiments to establish causality, lacks important details and additional alternative explanations/future directions. There is also concern with the applicants’ career
development and training plan. Given the applicant's background in yeast and recent entry into more complex cellular systems, the applicant would be expected to take courses and participate in workshops and meetings with content about tissue, cellular, molecular, physiological aspects of peripheral and nervous tissues in multi-cellular organisms.

1. Candidate:
   Strengths
   • BA from Hunter College, MA and PhD with 2015 graduation from Columbia, and postdoctoral fellowship at UC Berkeley all on the biological sciences. Participated in research at all stages demonstrating commitment.
   • Has published 8 manuscripts to date and all as first author. One manuscript is a review and two are method-based papers.
   Weaknesses
   • None noted.

2. Career Development Plan/Career Goals & Objectives:
   Strengths
   • Instructional courses on Mass Spectrometry at the Proteomic core at UC Davis and Databases and Tools of Bioinformatics at UC Berkeley.
   • Strong team of mentors, starting with primary mentor Dr. Andrew Dillin having the expertise, track record and clear devotion to help advance the candidate’s career. The mentoring team - consisting of Drs. Eisen who is an expert geneticist and on computational approaches, Drubin expert on the cytoskeleton, and Ting who has developed novel methods for protein labeling and purification - also has the prerequisite expertise and knowledge to help the candidate to navigate all aspects of the dependent and independent phases of the application.
   Weaknesses
   • The candidate is new to studying tissues having obtained a PhD in yeast. It would therefore benefit the candidate to take courses, attend workshops and meetings primarily focus on anatomy, cellular and molecular biology and neuroscience.
   • Lack of proposed formal training on aging.
   • Plan for supervision and mentoring of candidates by mentor and mentoring team.

3. Research Plan:
   Strengths
   • Using a variety of cellular, molecular and biochemical tools to uncover new interactors and modulators of actin.
   Weaknesses
   • Lack of details in most proposed experiments – ex.: number of animals needed in each experiment (see Aim1.1a, Aim1.1b, Aim1.2 for lifespan studies following bet-1 overexpression and knockdown or dod-21 overexpression). Statistical assessments are generally lacking. Thus, there is concern about rigor.
   • Overly ambitious as each aim on its own would require all of the resources and time allotted for this application during the dependent phase. Aim 1 has multiple large studies and each could be expanded to gain more detailed biological analysis, including tinkering with levels of bet-1 rather than blunt overexpression or knockdown. Aim1.2b is a fishing expedition that could be its own study given all the other data accrued on actin modifiers. Along this line, the applicant has an excellent opportunity to dive into the role of chromatin modifiers and their effect on actin in different tissues and cells, and thus the additional studies on lipid homeostasis and going after the neuronal nature of hsf-1 effect on the cytoskeletal of peripheral tissue make this application quite massive and disjointed.
   • Since this application is about the impact of aging on actin modifiers/novel interactors, there was expectation that experiments aimed at assessing levels, distribution and function of candidate
modifiers (ex.: bet-1) would be described and carried out first. This would make the a rather dense, yet well-written application has a better logical flow.

- Caveats/pitfalls, alternative explanations and future directions are not sufficiently flushed out. For example, it is plausible that overexpressing bet-1 in a specific peripheral tissue is more protective during aging. This and other alternative possibilities are not explored, an important component of the Research Plan as the candidate moves onto the independent phase of the study.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Strengths
- Dr. Andrew Dillin is the primary mentor. He is a world-renowned expert on aberrant molecular changes that contribute to the normal aging process, particularly assessing basic yet critical mechanisms. He is very supportive of the applicant, application and path to independency. The co-mentors and collaborators bring expertise in all other areas necessary for this candidate and are very supportive of the applicant and application. Altogether, this team of mentors and collaborators have vast experiences and expertise and importantly the desire to support this applicant during the K and R portions of this application.

Weaknesses
- None noted.

5. Environment and Institutional Commitment to the Candidate:

Strengths
- The MCB department at the University of California, Berkeley is an excellent environment and very supportive of and committed to the applicant's career development.

Weaknesses
- None noted.

Training in the Responsible Conduct of Research:
Acceptable.

Format:
- Appropriately described for both formal and informal training.

Subject Matter:
- Appropriate.

Faculty Participation:
- A plan is in place for the primary mentor and co-mentors to advise on best practices on research and teaching.

Duration:
- Appropriate.

Frequency:
- Weekly meetings.

Resource Sharing Plans:
Acceptable.

Authentication of Key Biological and/or Chemical Resources:
Acceptable.

Budget and Period of Support:
Recommend as Requested.
CRITIQUE 2:

Candidate: 1
Career Development Plan/Career Goals/Plan to Provide Mentoring: 4
Research Plan: 3
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 2
Environment, Commitment to the Candidate: 2

Overall Impact:
Dr. Higuchi-Sanabria is a 4th year post-doc at UC Berkley. He is finishing his third year on an NIA-F32 award in which he has been studying the cytoskeletal biology of C. elegans in cell stress and aging. This application extends that work to explore gene regulation of the cytoskeleton specifically in identified areas of chromatic state and lipid homeostasis. The candidate is well-rounded with many experiences to support his research career independence. An excellent advisory team for mentoring the candidate, along with the superb primary mentor, will likely facilitate success in this area. These are the strengths of the application. The training plan is largely to gain expertise in big data science to address research questions. The concerns with the application include modest connections in actin/cytoskeletal questions to aging, lack of detail in the Research Plan (e.g., no statistical analyses and few alternative plans provided should hypotheses not hold true), and the missed opportunities to engage in UCB Glenn Foundation to foster further engagement of the candidate in aging research.

1. Candidate:
   **Strengths**
   • PhD work in cell biology at Columbia provided strong foundation for post-doc work in stress and proteostasis in aging and now K99 phase toward big data science and analytics.
   • Current F32 through NIA aims to determine cell stress responses that protect the cytoskeleton during aging with goal to provide information toward therapies against diseases of aging.
   • Solid productivity in terms of publications with 7 first author publications from PhD work, and 2 sole and 4 co-first authored papers in high profile journals from his post-doc work, with several more in progress.
   • Broad academic and professional experiences, such as lab management, mentoring and leadership opportunities, and teaching in both laboratory and lectures, provide strong base for future success in academic research.
   • The candidate’s dedication to increasing URM in science is commendable.

   **Weaknesses**
   • None noted.

2. Career Development Plan/Career Goals & Objectives:
   **Strengths**
   • The candidate’s K99 goal is to further his research program on actin cytoskeleton in health and aging and in particular is seeking development in large data science and has assembled an advisory team to assist in meeting that goal.
   • The candidate is interested in academic research.
   • Many technologies will be learned during the training period.

   **Weaknesses**
   • There is no mention of aging biology in the candidate’s long-term career/research goal statement, rather the statement highlights broadening his research program further to lipid homeostasis, ER, and mitochondria interacting with cytoskeletal biology and regulation.
   • Advanced training in fundamentals of biology of aging are lacking.
   • The career development training is largely what the candidate is already doing.

3. Research Plan:
Strengths
• The conceptual significance of cytoskeletal biology under conditions of stress including aging is well described.
• Better understanding how actin cytoskeleton breaks down differently across tissues/cells with aging in Aim 3 will be informative for the biological field of aging.

Weaknesses
• “Caveats” for some but not all subaims are provided as back up plans should results not go as predicted; more are needed.
• Details are lacking for experimental designs (e.g., replicate numbers, statistical outcomes, etc.) and procedures.
• Despite the conceptual links to aging, it is difficult to ascertain how Aims 1 and 2 and two of the three ‘goals’ in Aim 3 provide insight to aging of the cytoskeleton and related consequences.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):
Strengths
• The primary mentor, Dr. Dillin, has the experience in successfully mentoring junior researchers to independence in academia and biomedical companies and has a strong track record in proteostasis and mitochondrial stress as it relates to aging and is supported through the HHMI to understand aging and age-related disease; all relevant to the candidate’s research and career development.
• Advisory committee adds strengths in ATAC- and ChIP-seq (Eisen), proteomics (Ting and Phinney) and cytoskeletal biology (Drubin) techniques.

Weaknesses
• Engagement from a biology of aging faculty on the advisory committee (from Glenn Foundation at UCB or UCSF, for example) in addition to the primary mentor, would benefit the candidate and his commitment to future biology of aging research.

5. Environment and Institutional Commitment to the Candidate:
Strengths
• UC Berkeley has the infrastructure and technologies to support the research proposed by the candidate such as imaging, computational, and mass-spec facilities and equipment.

Weaknesses
• Would be ideal for the candidate to interface at some level with Glenn Foundation Center for Biology of Aging at UC Berkeley to take full advantage of opportunities available at the institution and more immerse himself in broader aging environment, particularly given Dillin is one of the Directors.

Training in the Responsible Conduct of Research:
Acceptable.

Format:
• formal and informal training; in person and online.

Subject Matter:
• 8 topics listed.

Faculty Participation:
• Dr. Dillin (sponsor) directly for informal training; formal by Sharma the RCR program manager at Berkeley and faculty.

Duration:
• 5 x 2 hr meetings.

Frequency:
• 5 x 2 hr meetings.
Resource Sharing Plans:
Acceptable.
  • Very detailed including sharing of data and model organisms.

Authentication of Key Biological and/or Chemical Resources:
Acceptable.
  • thorough descriptions provided.

Budget and Period of Support:
Recommend as Requested.

CRITIQUE 3:

Candidate: 1

Career Development Plan/Career Goals/Plan to Provide Mentoring: 2
Research Plan: 1
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 1
Environment, Commitment to the Candidate: 1

Overall Impact:
This is a K99 application by a very talented postdoc, Dr. Ryo Higuchi-Sanabria, to study actin and the cytoskeleton in the nematode worm during aging. Strengths of the application are the scientific excellence of both the applicant and the proposed mentor, Dr. Andrew Dillin, and the exciting and very well written Research Plan. A minor weakness is a rather thin Career Development Plan with few details on evaluation, metrics and course work.

1. Candidate:
Strengths
• Dr. Ryo Higuchi-Sanabria received his PhD from Columbia University in 2015 on yeast mitochondrial dynamics in the lab of Dr. Liza Pon. Since 2016 he is a postdoctoral fellow in the lab of Dr. Andrew Dillin, University of California, Berkeley, the primary mentor of the proposed study.
• Dr. Higuchi has been extraordinary productive with 7 first-author papers since 2014, one with his current mentor, Dr. Dillin, in 2018, and a review article in Developmental Cell also in 2018.
• Dr. Higuchi is the PI on an F32.
• Reference letters are exceptionally good.

Weaknesses
• None noted.

2. Career Development Plan/Career Goals & Objectives:
Strengths
• Dr. Higuchi is committed to a career in studying cytoskeletal homeostasis in relation to aging. Both his background at Columbia and his research plans are very well described. The same is true for his planned interactions with committee members, Drs. Eisen, Ting and Drubin, and his plans for training students.

Weaknesses
• The Career Development Plan is rather thin, with no attention to planned course work, conferences, evaluation, metrics, etc. However, the mentor's statement is detailed and covers essentially everything.

3. Research Plan:
Strengths

- Actin as a critical part of the cytoskeleton and associated proteins is generally assumed to breakdown with age, but this is understudied, in part due to a lack of tools for in vivo, live-cell imaging of the actin cytoskeleton in multi-cellular organisms. The candidate developed a system for tissue-specific, live-cell imaging of the cytoskeleton in C. elegans, based on a peptide, termed LifeAct, that binds specifically to F-actin. This has been fused to mRuby, a fluorophore allowing visualization of functional, filamentous actin. This and other tools allow the proposed studies of HSF-1 dependent and independent regulation of actin organization and the identification of novel regulators of the actin cytoskeleton. The proposed study is significant and, based on the tools developed, likely to increase our understanding of actin and cytoskeleton breakdown during aging of the worm.

- In preparation for Aim 1 the candidate performed a set of screening experiments resulting in the identification of novel genetic regulators of actin modifiers of chromatin state and their downstream transcriptional regulators, as well as genes involved in lipid storage and global lipid homeostasis. These are important preliminary data. In Aim 1 the applicant proposes to characterize the molecular pathways associated with these genes and how they contribute to cytoskeletal integrity.

- Using his LifeAct probe the candidate provide evidence that HSF-1 is critical for cytoskeletal maintenance, with knockdown resulting in premature decline and overexpression in protection. These are important preliminary data for Aim 2, which is focused on non-autonomous mechanisms of protection based on the identified pathways in Aim 1.

- Aim 3 makes use of available expertise in proximity-based protein labeling in the lab of Dr. Ting, a member of the advisory committee. The proposed combined application of the improved miniTurbo system and the LifeAct probe to characterize protein interactors of actin important for its proper form and function is innovative and could yield important novel insight.

Weaknesses

- The Research Plan is very ambitious for a K99 with a lot of information that necessitates ultra-small type in the figure legends, which are almost unreadable. But it should be mentioned that the application is impressive and a good read with critical preliminary data provided, suggesting it could actually be carried out as planned.

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Strengths

- Dr. Andrew Dillin, the proposed mentor is a Professor in the Department of Molecular and Cell Biology, University of California at Berkeley, since 2012. His research focus is on ER proteostasis and aging. Dr. Dillin is renowned in the field of aging, extremely well published and very well-funded through the NIH. He is the best possible mentor for the proposed project.

- The advisers, Drs. Eisen, Drubin, Phinney and Ting are all very good and provide unique and critical technical support.

Weaknesses

- It would have been good to see biosketches of the advisers because their contributions are critical to the success of the application.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- The Dillin lab in the Li Ka Shing Center on the University of California, Berkeley campus is a great environment for the proposed project.

- Institutional support is testified by the letter from Dr. Rio, co-chair of the Department of Molecular and Cell Biology.

Weaknesses

- None noted.
Training in the Responsible Conduct of Research:  
Acceptable.

Resource Sharing Plans:  
Acceptable.

Authentication of Key Biological and/or Chemical Resources:  
Acceptable.

Budget and Period of Support:  
Recommend as Requested.

THE FOLLOWING SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO  
SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE, OR REVIEWERS’  
WRITTEN CRITIQUES, ON THE FOLLOWING ISSUES:

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Footnotes for 1 K99 AG065200-01; PI Name: Higuchi-Sanabria, Ryo

NIH has modified its policy regarding the receipt of resubmissions (amended applications).  
The impact/priority score is calculated after discussion of an application by  
averaging the overall scores (1-9) given by all voting reviewers on the committee and  
multiplying by 10. The criterion scores are submitted prior to the meeting by the individual  
reviewers assigned to an application, and are not discussed specifically at the review meeting  
or calculated into the overall impact score. Some applications also receive a percentile  
ranking. For details on the review process, see  
http://grants.nih.gov/grants/peer_review_process.htm#scoring.