NIH Grant Writing and Peer Review

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Career Path for a Ph.D. (or equivalent)

Graduate student → Ph.D. → Faculty Position → Independent PI

Diversity Supplements

T32 - Institutional training grant (NRSA) - has pre- & postdoc slots
F30 and F31 - Individual predoc fellowship (NRSA)
(some ICs only support Diversity F30/31s)
F32 - Individual postdoc fellowship (NRSA)
F33 - Sr. postdoc fellowship (NRSA)
R03 - Small Grant
R21 - Exploratory/Developmental Research Grant
R01 - Research grant

K02 - Independent Scientist Award
K22 - Research Scholar Development Award
K99/R00 - Pathway to Independence Award
R37 - Merit award
P01 - Program Project Grant
U01 - Cooperative Agreement

From nih.gov
Advice for Mapping Your Career With NIH

• **Review** Institute/Center (IC) priorities and goals. Each IC has a research training and career development program.

• **Learn** the NIH application and review process

• **Identify** the grant programs offered by each IC

• **Make** early contact with program officers

• **Find** innovative, well-respected mentors and collaborators

• **Study** successful grant applications - talk to your mentor

• **Propose** your best and most creative ideas

**Apply and persevere!**
Questions that Reviewers Ask About a Grant?

• What do you want to do? -> Objective

• Should you do it? -> Significance: scientific premise and gap in knowledge; Innovation
  • Phrase it in another way: will the accomplishment of your objectives significantly advance your field?

• How do you want to do it? -> Aims and Approaches
  • Feasibility: literature support and preliminary data
  • Experimental strategies sound and rigorous? Controls, replicates, statistical analysis
  • Are potential variables considered?

• Can you do it? -> Expertise, past record, future training (for fellowship and K grants)

Hold the reviewers’ hands and walk them through your proposal because more likely they are not experts in your field!
How do you identify a gap in knowledge or a need?

• Read! Read! Read!
  • Determine what is already known
  • Critically examine whether the known knowledge is reliable
  • Who are actively working in this area? (literature and NIH REPORTER)

• Identify a problem or gap in knowledge that is preventing the field from making a leap, not a problem that would only result in incremental advance
How to Write the Specific Aims Page?

• **Current knowledge**
  • Not all reviewers are expert of your field (they need some handholding to get up to speed)
  • Include key references only

• **Gap in knowledge**
  • Gap in knowledge that’s preventing the field from making a leap
  • What problems need to be solved to fill this gap? If not solved, what are the consequences?

• **Overall objective**
  • Your proposed solution to the problem(s)
How to Write the Specific Aims Page? – Cont’d

• Hypothesis and how your hypothesis is formulated
  • Based on your preliminary studies and critically evaluated literature

• Aims
  • What is the hypothesis for each aim?
  • Try to focus on “why” you want to pursue each Aim
  • Later aims not completely dependent on earlier aims (what if the earlier aim completely failed?)

• Expected outcomes
  • What will become possible after you accomplishing your aims that is not possible now: relate back to your objective
Significance

• NIH Grant Review Criteria:
  • Does the project address an important problem or a critical barrier to progress in the field?
  • Is there a strong **scientific premise** for the project?
  • If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?
  • How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?
Significance – Cont’d

• How to write about Scientific Premise?
  • Discuss scientific foundation that your proposal is built on
  • Critically evaluate strength and weakness of key literature (original work, not reviews) that would support your hypothesis
  • Present key preliminary data that would support your scientific foundation, not those that support technical feasibility

• Statement of significance
  • Link back to your objective
  • Contribution to your immediate field
  • Broader contribution to other fields or problems that are important to NIH
An example of reviewers’ comments on Significance:

For a grant that proposes to study the effect of environmental molecules, quaternary ammonium compounds (QACs), on neurodevelopment through disruption of cholesterol homeostasis.

**Strengths**

- Strong premise supports role of cholesterol homeostasis in neurodevelopment, and the effect of a specific subset of QACs on inhibiting DHCR7 activity (key enzyme in the cholesterol biosynthetic pathway) whereas other QACs appear to impact lipid homeostasis.

- Strong potential significance given the ubiquitous presence of QACs in consumer and industrial disinfectants and clear human exposure.
An example of reviewers’ comments on Significance:

• Weaknesses
  • The PI does not provide clear consideration of exposure specifics in presentation of the published and preliminary data supporting the scientific premise of a link between QAC exposure and neurodevelopmental toxicity and associated alterations in cholesterol and lipid homeostasis. Ref 66 is referred to as a dose for a mixture of QACs, examination of this reference reveals multiple exposure levels were used - it is wholly unclear which exposures were tested for the data in Figs 6, 10 and 11). These levels, and how they relate to levels in human populations is critical to determine whether the proposal will provide information that has high or low significance to human health. Further, given the differences in potential toxicity of different QACs, reporting total QACs in human plasma is incomplete.
  • The C10 form of QAC was reported as most potent, followed by C12, for inhibition of DHCR7; but there is no discussion of what forms of QACs are found in products and relative exposure levels in people.
Innovation

• Review criteria:
  • Does the application **challenge** and seek to **shift current research or clinical practice paradigms** by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions?
  • Are the concepts, approaches or methodologies, instrumentation, or interventions **novel to one field of research or novel in a broad sense**?
  • Is a **refinement, improvement, or new application** of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?
Innovation – Cont’d

• Conceptual Innovation
  • Departure from the status quo: what, why, and how

• Technical Innovation
  • Application of a novel technology or instrument in a broad sense
  • Application of an old technology or instrument to a new field
Approaches

Recent NIH emphasis:
• Rigorous experimental design that will produce robust and unbiased results
• Consideration of relevant biological variables

• Review criteria:
  • Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?
  • Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?
  • Are potential problems, alternative strategies, and benchmarks for success presented?
  • If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed? (for exploratory grant such as R21)
  • Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?
Development of Approach for Each Aim

• Introduction section
  • Objective for this aim
  • Hypothesis for this aim
  • Rationale: emphasize why you do the work in this aim

• Detailed research design
  • Divide into a list of interconnected experiments
  • Overview of the methods: only meaningful detail, not those in the experimental section of a paper
  • Rigor: controls, replicates, biological variables, statistical analysis
  • Expectations for each experiment and interpretation of results

• Expected outcomes
  • How the experiments contribute to the attainment of the objectives?

• Potential problems and alternative strategies
  • Discuss problems could arise, but probably less likely
  • If they do, what is your backup plan?
  • If your hypothesis proved invalid, what is your next best bet?
An example of reviewers’ comments on Approach:

• **Strengths**
  
  • The research strategy is comprehensive and utilizes a combination of cell culture (Aim 1) and whole animal cellular (Aim 2) and behavioral (Aim 3) models to assess the toxicity of QACs in the fetus. The progression from cell culture to whole animal models is appropriate. Based on concordance with the SLOS syndrome, the proposed behavioral analyses are reasonable as an initial approach. All proposed cell biological approaches are standard and the experimental outcomes likely to be interpretable. **Preliminary data supports the feasibility of the proposed studies.**
An example of reviewers’ comments on Approach – Cont’d:

• Weaknesses
  • **Issues of experimental rigor** (e.g., randomized block designs, blinded analysis) are not adequately addressed. Sex as a biological variable is not considered in the analyses. Statistical design constraints for the use of parametric vs nonparametric tests are not addressed. Sample size calculations are not provided.
  
  • Co-I, Dr. Hrubec has identified fetal toxicity associated with maternal QAC exposure. However, direct vaginal application of QAC may result in reproductive system toxicity without direct QAC toxicity in the fetus. Similarly, the preliminary data (e.g., Figure 14) may represent an outcome due to reproductive system toxicity of QACs. Even if QACs cross the adult blood brain barrier, it would be necessary to document that they cross the placenta and accumulate in fetal brain.
  
  • The interpretative value of the DHCR7-het model is questionable. Moreover, the mouse model was created on a mixed genetic background. Genetic background should be controlled for as a significant **biological variable**.
  
  • Aim 1 focuses on cell death. It is not clear how this is more relevant to Autism/SLOS as compared to, for example, synaptogenesis and synapse elimination.
  
  • The Shh-Light2/NIH3T3 cells have not been shown by the PI as a relevant model for Shh signaling in neural cells.
Prepare for This Class

Expect a little bit more time commitment for everyone!
For the Written Proposal

• Include sections of Specific Aims, Significance, and Approaches, with guidelines discussed above

• OK to use data from your thesis project to support your scientific premise and hypothesis

• Recommend two aims due to the page limit (use margins of 0.5; OK with longer than 2 pages, but be concise on your writing)

• Prepare a figure/scheme that illustrates the aims

• Seek your mentor’s feedback

• Revise your proposal after in-class discussion
For In-Class Presentation and Discussion

• Reviewers discuss their comments first

• Authors’ presentation focuses on these topics (you can use whiteboard drawing, slides, and handouts):
  • What the problem/gap is and why it should be studied?
  • How do you propose to solve it and your hypothesis?
  • Aim 1 and experimental design
  • Aim 2 and experimental design
Peer Review of Each Proposal

• 3-4 primary reviewers
• Score on Significance, Approaches, and Overall impact on a scale of 1-9 before class meets (keep it anonymous unless you want to reveal your identity)
• Provide objective comments on the strengths and weaknesses of each section (justify your score)
• After the in-class presentation and discussion, re-consider your score and provide feedback on which additional information or change in writing would have changed your scoring
• For all other student, read the proposal before hand, think about the same review criteria, and contribute to the discussion in class.
• For all students, submit your score and typed comments to me after the class.
NIH Grant Review Process

1-3 mo: Referral: Assign Institute and Study Section

Center for Scientific Review

4-5 mo: Peer Review: Study Section

Scientific Review Officer (SRO)

5-6 mo: Score and Summary Statement

Program Officer (PO)

6-8 mo: Council Meeting

Grant Management Specialist (GMS)

9-10 mo: Award
What Happens in a Study Section?

https://www.youtube.com/watch?v=fBDxI6l4dOA
Additional Considerations for Fellowships and K Grants
Candidate

• Sell yourself as the candidate that would worth their investment!

• You academic background, productivity, contribution to science, and awards. Relates your past achievement to your future goals and make them coherent.

• Your short-term and long-term career goals and how additional training in specific areas will help you achieve these goals
Training and Career Development Plan

- Mentors: primary mentors (current mentor) and additional mentors for additional skill sets (could be mixed senior and junior investigators)
- Make your training plan concrete: lab training, additional courses or workshops, conferences, evaluation plan by mentors, regular mentor committee meeting, etc.
- Transition to independence plan: attending career development workshops, teaching experience, conference networking, plan for next step of grant application (for K only)
- Describe how you will distinct yourself from the research programs of your mentors (for K only)
Research Plan

• Like a regular research plan: need specific aims, hypothesis, significance, innovation, research strategies, etc.

• Take advantage of the new skills you WILL obtain during your training and incorporate them into the research plan (reviewers will not criticize you that you lack such skills at the moment, they will like such element instead).

• Show preliminary data if possible and show that you’ve started working with your mentors

• Plan for both the Mentored Phase and the Independent Phase: the whole picture (for K only)
Institutional and Mentor Support

• Institutional Environment and Commitment are very important in training grants: detailed description of institution resources/environment relevant to your training and a strong commitment letter from your department chair.

• Detailed mentorship plan from mentors are very important: convince the reviewers that you’ve discussed with your mentors and come up with a concrete plan.

• Make sure your mentors state in his letter that they can supplement the cost of your project with his funds.