

The K99/R00 and the NIH Grant Process

Pointers on writing a K99/R00 grant and an overview of the NIH review process

Pamela Mellon
2012

Pathway to Independence Award K99/R00

- The PI award provides up to 5 years of support consisting of 2 phases
- The initial phase provides 1-2 years of mentored support for senior postdoctoral research scientists
- This phase is followed by up to 3 years of independent support contingent on securing an independent tenure-track or equivalent research position
- Eligibility: Application must be submitted prior to reaching five years as a postdoc. Thus, best to apply during year 4 so can have time to resubmit application after first try (which usually wouldn't get funded)
- Qualifications: impressive record of research productivity and publications, and will have identified a unique research direction to pursue after the mentored phase of the award
- New applications are due February 12, June 12, and October 12
Resubmissions are due March 12, July 12, and November 12

Before you start

- Get an eCommons login and fill in personal profile as a PI
- Download the K99/R00 instructions and 424 forms
- Talk over your aims and approaches with colleagues
- RFA is at <http://grants.nih.gov/grants/guide/pa-files/PA-11-197.html>
- READ THE INSTRUCTIONS including the section labeled: Supplemental Instructions to the SF 424(R&R) for Preparing an Individual Research Career Development Award (CDA) Application ("K" Series)
- Lay out a plan of attack to get all of the components you need: make a checklist of all the PDF files you will need to generate (see next slide)
- Get help from the right people: collaborators and mentors
- Accumulate preliminary data
- Talk to the Institute Grants Administrator in your topic area for pointers - they love young investigators
- Make sure your Chair and references are willing to write letters of support
- Talk over your plan with your Dept. administrative staff and send them copies of the specific RFA and grant forms/package for them to help you
- Plan ahead to be able to give a draft of the science to colleagues with enough time (at least 2-3 weeks) to incorporate their feedback (2 weeks)

Components for K99/R00:

Narrative (3 sentences max)

Summary (30 lines max)

Specific Aims (1 page limit)

These four within 12 pages total:

1. Candidate's Background
2. Career Goals and Objectives
3. Career Development/Training Activities During Award Period
4. Research Strategy (try to save 8 pages for this)

Training in the Responsible Conduct of Research (1 page limit)

Environment: Include colleagues and interactions (1 page limit)

Facilities: Include your mentor's space allocation and Core facilities you may use

Equipment: Include your equipment and shared equipment access

Human and/or Animal Subjects

Literature Cited

List of Referees

Cover Letter: to direct grant to best Institute at NIH

Resource Sharing Plan (use UCSD set language)

Budget Justification

Biosketches for Candidate and Mentor

Other support for Mentor

Institutional Commitment

Mentor's section

Collaborators and Chair's letters

Best to write 12 page section as one Word document, so you can format references with Endnote, then split it up to make the PDFs after it is final, creating Literature cited pages

Each is a separate PDF

To be attached to the Adobe forms

Early Stage Investigator Cheat Sheet for a K99/R00

- Download latest forms from NIH web site (they change often)
- Make sure PI exception is done by your Department/mentor
- Request reference and collaborator letters
 - Contact references and collaborators
 - Send the referee's instructions and your CV
 - Letters are required to be uploaded by them right after submission
- Get internal UCSD forms such as RES form, 9510 form, PI form, salary backup, etc. from your department's grants person
- Prepare NIH format Biosketches, facilities, equipment lists, budget justification, etc.
- Write the candidate's sections
- Write the science and abstract drafts
- Sign RES, PI, and 9510 forms and to get other required signatures on the RES form and any needed worksheets to grants office at least 2 weeks before deadline
- Get Mentor's materials
- Create a draft version of every PDF for the Adobe online package
 - Include all forms in their final format
 - Include draft of the science parts
- Work with your Department grants person to get it uploaded for Grants office by >2 weeks before deadline
- Have some folks read the science section for suggestions
- Polish and finalize the science section
- After the main grants office calls with their corrections, fix up final version of science and send PDF to Departmental Grants person to insert into Adobe package
 - This version is only the material that actually goes to NIH
 - You do not need the RES, 9510, PI form, salary projection backup in this version, they will have that from before.
 - They will upload it to Grants.gov for you
 - They need 2-3 working days for this
- Download application from eCommons and make sure it is OK

Cheat Sheets for a K award

- Mentor
 - Write the PI exception
 - More than 30 days prior to deadline
 - First year: remain a postdoc for Phase I - first year
 - Second year - can advance to Assistant Project Scientist if past the UC 5-year limit
 - Write a draft of the Chair's Letter and send it to the Chair to edit and sign
 - Write Institutional Commitment section
 - Write the Mentor's section
 - plan for transitioning candidate from mentored phase to independent phase
 - Specifically justify further training under the same mentor (if applicable)
 - Commit to protected time and supplies/expenses
 - Provide your Biosketch to Candidate
 - Provide your Current and Pending Support pages
 - Read the draft of the science
 - Review the paperwork

Budget

- **Mentored phase (K99):** As a Postdoc
 - Salary: up to \$75,000 plus fringe benefits per year
 - Must commit at least 75% effort, 100% is OK
 - Mentor is “0%” effort
 - Research Support: up to \$25,000 per year
 - Overhead will be provided at 8% of modified direct
- **Independent investigator phase (R00):**
 - Total cost may not exceed \$249,000 per year. This amount includes salary, fringe benefits, research support allowance and full overhead (also called indirect costs or F&A costs).
 - UCSD Overhead is about 54% so that leaves ~\$160,000 for direct costs in Phase II

Page limits

For **Individual Career Development Award (K)** Applications

Section of Application	Page Limits * (if different from FOA, FOA supersedes)
Introduction to Resubmission or Revision Application (when applicable)	1
Specific Aims	1
First three items of Candidate Information (Candidate's Background, Career Goals and Objectives, and Career Development/Training Activities During Award Period and Research Strategy)	12 pages (for all sections combined)
Training in the Responsible Conduct of Research	1
Mentoring Plan (Include only when required by the specific FOA, e.g., K24 and K05)	6
Statements by Mentor, Co-Mentors, Consultants, Contributors	6
Description of Institutional Environment	1
Institutional Commitment to Candidate's Research Career Development	1
Biographical Sketch	4

Title, Abstract and Key Personnel

Title should steer application to right institute, study section and reviewers, and catch their attention

Key Personnel:
You are the PI,
Mentor is Key Personnel too

“Project Narrative” is really a Relevance section. Using 2-3 sentences, describe the relevance of the research to public health in language for a lay audience.

Abstract is 30 lines, sentences should be:

- 1-2 significance/background
- 1-2 on your prelim. findings
- 1-2 on model/approach viability
- 1-2 on each aim
- 1-2 on excitement of discovery

Follow directions on Biosketch.
Writing your paragraph to convince the reviewers that you know what you are doing and deserve to be P.I.
Limit of 15 publications
Show awards and national service

Specific Aims Page

Rules of thumb:

- Begin with explanatory intro of 4-5 sentences and overall hypothesis
- Two aims for Phase 1, two or three for Phase II
- First aim should be practical and doable, maybe even partly done already...
- Second phase I aim should have some aspects that can be done even if the prior aim fails (independent aims)
- Second phase aims can be more forward-looking, discuss how this direction separates from Mentor's program
- Final Aim should have spice, adventure, speculation, but not too wild...
- Title aims well and give a short paragraph of explanation with each
- Give several organized sub-aims for each

Text

- Use formal outlining techniques to keep organized. Keep numbering and lettering consistent throughout. Example: D.1.a.ii.
- Use many sub-topics and title breaks to ease the reading and show your logical organization. At least one or more on every page.
- Use many figures, tables, and diagrams to keep the interest, show your logic flow, to prove your findings, and to save on words.
- Minimize JARGON and provide definitions of abbreviations. If you have a lot of abbreviations and names, make a table or text box with the definitions so they can refer back to one place to find them all.
- READ the INSTRUCTIONS on Font size and page limits (Best font is Arial 11). They will reject it online.
- Reference your text points with literature, since the reference list does not count in the page limit. This makes you look scholarly.
- Remember that your reviewers are on noisy planes, spilling coffee, interrupted by phone calls and crying babies, and reading your grant among 10+ others, and probably as a pdf on a computer screen. Help them keep track of where they are and what your point is. Be clean and clear.
- Look up the members of your likely study section on the Web and if appropriate quote/credit them for their work in the text and "Literature Cited".
- Think about their experience and work. Let that flavor how thoroughly you explain your methods.

Use numbering, referencing, and Tables to make clear convincing arguments

Though the interaction of Dlxin with Msx and Dlx is well demonstrated *in vitro* and in differentiating muscle precursors,²¹⁵ the mechanism by which MAGE proteins relieve Msx repression is not known. Several hypotheses will be tested in GnRH neuronal cells: 1) MAGE proteins may sequester Msx away from the DNA since they are known to bind to Msx off of the DNA.²¹⁸ 2) MAGE proteins may recruit ubiquitin ligases²¹⁹ to degrade Msx. For example, the ubiquitin ligase, Praja1, a RING-finger protein,²¹⁹ is recruited by Dlxin through its MAGE domain to cause degradation of Dlx5 in osteoblasts.²¹⁸ 3) MAGE proteins may translocate Msx out of the nucleus. The subcellular distribution of MAGE proteins changes with the presence or activation of membrane receptors such as the tyrosine kinase orphan membrane receptor ROR2²²⁰ and p75.^{221,222} In fact, ROR2 is also highly expressed in GT1-7 cells (8 fold more than GN11), indicating that it may have a role in differentiation (Table 2). 4) MAGE proteins may act directly in transcriptional regulation since Necdin has been shown to bind GC-rich sequences like Sp1 sites *in vitro*.²¹⁷

The structure of an aim

- Hypothesis
- Rationale: Logic and justification for doing it
- Approach, including experimental design
- Include controls, be explicit but conceptual (not buffer conditions)
- Potential results and their interpretations
- Potential problems and alternatives approaches to solve them

Key issues for aims

For each Aim:

- Provide several logical sub-aims to separate out goals and approaches
- Be linear and organized
- Make it clear that each aim has aspects that do not depend on the prior aims working
- Focus on the overall experimental design and the strengths of the model system or approach
- Use flow charts, diagrams, tables, figures with examples to illustrate your experimental design or prove that you can do a technique
- Do not provide minute details on the methods. Don't list protocols. Just outline and reference them.
- If you have no experience with a technology, get a collaborator or use a core facility (include a letter of collaboration or for core support)
- If you do not have a key reagent, mouse, patient population, or drug you will need, include a letter from the source or say that it is available from a commercial source or collection, or a collaborator
- Talk about Statistics if you need them (power analysis when needed)

Ending the grant

- After the last experiment in the last aim:
 - Write a paragraph on the time line and priorities in which several aims are started and overlap in time. Draw a time line or show a table.
- | Year | 1 | 2 | 3 | 4 | 5 |
|-------|---|---|---|---|---|
| Aim 1 | X | X | | | |
| Aim 2 | | X | X | X | X |
| Aim 3 | | X | X | X | |
| Aim 4 | | | X | X | X |
- Point out that you have experience with the methods and have already obtained reagents, tested antibodies, collected human subjects, obtained transgenic animals, etc. OR that you have collaborators that know how.
 - Include a paragraph on speculative future directions that may come after the aims are completed or may branch from the stated aims. (long-term goals)
 - Summarize the significance of the potential discoveries again.
 - Check again that you have referenced and discussed any relevant publications of your likely reviewers on the Study section...
 - Rosters: <http://era.nih.gov/roster/index.cfm>

Revising the grant

Points about the “Introduction” to a revised grant application

- Begin by summarizing the positive points: The PI is deeply honored by the careful and enthusiastic reviews of this application. The reviewers found the proposed studies “highly innovative, combining state-of-the-art molecular approaches with innovative in vivo mouse models”, the goals “clearly highly significant”, and the experiments “hypothesis-based, well justified, and technically within the expertise of the PI and her strong group of investigators”. They found the preliminary data “elegant” and “abundant”. The environment was “outstanding”, the collaborators “superb”, and the budget “appropriate”.
- NICE, NICE, NICE: “We are most grateful to the reviewers for their thorough and thoughtful reviews and have taken their very helpful criticisms to heart in thoroughly revising our application to directly address...”
- Address the points one by one, even if they are not that organized in the reviews
- Whenever possible, find a way to DO WHAT THEY ASKED, even if it doesn’t seem logical to you. Or at least fully justify the reasons for not changing it
- Don’t get defensive or argumentative. Don’t rebut, explain
- NICE, NICE, NICE with Sugar On Top

What Happens after Your Application Arrives at NIH

CSR: Center for Scientific Review

- Assignment of Study Section
 - Based on Title and maybe Abstract or Aims
 - Can be influenced by your cover letter request
 - This may be determined by RFA choice you make
 - K awards usually reviewed by an Institute-based Study Section rather than a CSR-based study section
- Assignment of Institute
 - Based on Title and maybe Abstract or Aims
 - Based on RFA
 - Based on your cover letter with suggestion and contact person named
 - Dual Assignment can occur with one primary and one secondary institute
- Check assignment and status on eCommons using your log on

What Happens after Your Application Arrives at NIH

Study Section Review Process

- Scientific Review Administrator = NIH CSR or Institute employee
- Study section membership and ad hoc members = ~20 peer reviewers
- Primary, secondary, reader
- Expedited review: lower ~50% of grants “Not Discussed”
 - Still get full written review and a score
 - Just no oral discussion at Study Section meeting
- Scoring
 - Score will appear on eCommons
- Summary Statement {Reviews}
 - Summary paragraph is written by SRA or lead reviewer
 - Reviews are verbatim from reviewers
 - Will be available to you to download from eCommons a few weeks later

Review criteria

- **Candidate**
 - Record of research productivity
 - Quality of the candidate's pre- and postdoctoral research training experience
 - Potential
 - Evidence of the candidate's research creativity
 - Letters of reference
- **Career Development Plan**
 - Proposed didactic and research components of the career development plan
 - Additional proposed training needed and appropriate
 - Timeline reasonable
- **Research Plan**
 - Significance
 - Appropriate for training
 - Innovation and Creativity
- **Mentors**
 - Strong track record in training future independent researchers
 - Comprehensive plan to support the proposed K99 phase career development and research plans
 - Clear Path to Independence
- **Environment and Institutional Commitment**
 - High quality environment
 - Adequate assurance that the required (minimum of 75%) effort of the candidate
 - Research facilities and educational opportunities

Scoring

Make it easy for the reviewer so they can develop their bullet points and the bullets will take advantage of your own words:

Three reviewers recommend scores.
All members vote privately.
Voted scores are averaged and multiplied by 10

- Explain the Significance clearly
- Ditto with Innovation
- Write the paragraph on the Biosketch to make their Candidate section easy too
- Include key info on the Environment in your Facilities pages
- Think about how everything looks from a reviewer's point of view

Scale is 10 to 90 with 10 as the best

Scoring Descriptions

Impact	Score	Descriptor	Strengths/Weaknesses
High Impact	1	Exceptional	Strengths
	2	Outstanding	
	3	Excellent	
Moderate Impact	4	Very Good	
	5	Good	
	6	Satisfactory	
Low Impact	7	Fair	Weaknesses
	8	Marginal	
	9	Poor	

Non-numeric score options: NR = Not Recommended for Further Consideration, DF = Deferred, AB = Abstention, CF = Conflict, NP = Not Present, ND=Not Discussed

21

What Happens after Your Application is Reviewed

Institute Level

- Grant management staff
 - The major person you should call about a pending grant
- Percentile, funding cut off, and “gray area”
 - Cut off score varies by Institute, branch, cycle, and year
 - Gray area will mean a score that may be funded but they will have to let you know later...
- Institute Council meeting is final decision on funding
- “Just-in-Time” will request updated Human/Animal Subjects, Other support, etc., just before funding.