Grant Writing: Tips and Pointers From a Personal Perspective

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rogress in the science and practice of medicine requires leveraging financial resources to pursue ideas, achieve new goals, and extend professional objectives. These resources are generally allocated through agencies that function through peer review. The need to

convince a reviewing body, funding agency, or philanthropic foundation that these collective plans merit support is, therefore, a rate-limiting step. Herein I outline perspectives gained over years of writing and reviewing grants, and suggest themes to incorporate and traps to avoid in navigating this process. I focus the discussion on federal grant applications—specifically, independent investigator-initiated (R01) applications—commenting where relevant on mentored-type (K) award applications. The commonalities among these applications serves as a focal point.

Preparation

One of the great myths of successful academic careers is that grant writing is easy and can be accomplished quickly. Neither is true. If possible, plan to allocate \geq 6 months to the preparation phase, particularly for R applications. Other applications, such as K or trainingtype awards, also require advanced planning and preparation. Preparatory time allocation is crucial to solidifying and aligning preliminary data and ensuring their seamless integration into the aims. Grant writing requires thoughtful planning and preparation to set in place several key requirements, including publications; verification of resource allocation (important for K applications); having in place letters and collaborative arrangements; and, most important, creating the time to review and refine, organize, and integrate the hypotheses and aims while allowing time for expert colleagues/mentors to read the grant and provide feedback. Of note, some institutions offer to pay reviewers to critique grants before submission, which, if available, is worth taking advantage of. Publications are crucial because they establish a key confidence metric for reviewers: The ability of the applicant to progress from idea to data to finished product. Publications are also an important indicator of the overall merit of the science as viewed by peers. Another important aspect of preparation, sometimes overlooked, is to read the National Institutes of Healthprovided instructions and then assemble a "needs list" in the early stages of preparation.

Planning and Anticipation

In preparing a grant application, it is helpful to anticipate the questions that reviewers will ask, and to frame the approach with these concerns in mind. There are ≥ 3 distinct types of questions that the reviewers ask.

General Questions

Is there a clearly stated, central hypothesis? Are the hypothesis and its underlying rationale interesting and timely? Will the findings from the proposed studies really advance the field? Are the aims arranged with a logical flow and matched to the preliminary data and approach?

Feasibility Questions

Can you do what you propose? Do your experiments use state-of-the-art approaches? If you are proposing new and untested approaches, do you have the technical and institutional resources to accomplish the stated goals? Have you enlisted collaborators to assist in the technical and conceptual framework of your proposal? Are the experiments you propose possible to complete with the reagents (such as animals or cell lines) in hand? Are these experiments feasible in the time frame you propose? For clinical research proposals, do you have access to the populations and patient material you propose?

Questions Predominantly for Junior Investigators

Does the applicant have strong mentorship in place? What is the applicant's past performance and recent productivity? Are the studies feasible within the

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time frame proposed? If completed as outlined, will these studies build on an independent trajectory?

Core Questions

Impact. Impact is a major determinant of the overall score of an application and it is helpful to solicit perspective from senior colleagues or mentors to align the goals and aims of the application. Will the aims, if accomplished as outlined, have a sustained and important influence on the field? Will the findings advance knowledge of the pathogenesis, treatment or prevention of disease?

Significance. It is worth committing several lines of text to summarize the significance of the application. This material could be placed in a brief section either as an introduction to the background or between the background and approach sections. Why are the questions important and how do they address problems relevant to disease prevention, pathogenesis, treatment or outcomes?

Hypothesis. This is the primary driver. It is important to identify and emphasize an integrative hypothesis in both the abstract and on the specific aims page (see below). This core hypothesis must provide standalone rationale that is based on current information and which ideally directly implies overarching significance of the proposal. Following from this, the core hypothesis should be embedded in each of the aims. Each of the aims may have its own distinctive hypothesis, but it is important that the application have a central theme that provides linkage between the aims.

Preliminary Data. Is there a compelling foundation of preliminary and/or published data and does it lead the reviewer seamlessly into the aims of the proposal?

Organization and Flow. Is there a predictable and linear flow to the proposal? Are the aims linked thematically with thoughtful contingencies and alternative outcomes?

Environment. Are the facilities, resources, and mentorship adequate to the tasks proposed? Junior investigators should consider using the biosketch section to emphasize details of institutional resources, collaborative support, and mentorship.

Specific Aims

Simply stated, the specific aims page is the centerpiece of the entire application. This is the road map for reviewers and the specific aims page will be among the most closely scrutinized of the entire application. It is crucial that it be thoughtfully arranged, clearly written, and flawlessly organized. It is also worth noting that its most important beneficiary is not the reviewers, but rather the applicant. This is your template for the next 3–5 years of work. There are no hard and fast rules in organizing the specific aims page, but some general guidelines may help. Key sentences from the specific aims page can be used as the framework for the abstract, which should capture the essence of the proposal without wordfor-word duplication.

Provide a Framework

Begin with a concise statement of general purpose that leads to an overarching hypothesis. This is an opportunity to introduce the significance of your proposal. Use the active voice, as for example, "We will examine signal transduction pathways that lead to pancreatic cancer." A general figure summarizing the aims and illustrating the overall integration of the application is very helpful. This figure could be placed either within the specific aims page or in the background section.

Summarize Key Preliminary/Background Data

Focus on key observations that inform the current objectives and avoid a comprehensive summary of past accomplishments. Use short declarative sentences, for example, "We have recently found that patients with XX disease show decreased circulating serum levels of yy. In aim 1, I/we will determine how levels of yy influence the outcome and response to treatment." Organize the specific aims in sequential, numerical format. Each aim should have a self-contained statement that is embedded within a testable hypothesis. Returning to the example above, aim 1 might be phrased, "Determine how the levels of yy predict the outcome and response to treatment in patients with XX?" Avoid framing questions for specific aims to which the answer is either "yes" or "no"; for example, "Are levels of yy predictive of patient outcomes in XX disease?" The yes/no-types of specific aims are by definition descriptive and are not viewed favorably. Provide enough general information about the approaches to be used in each aim so the reviewer understands the general themes and experimental objectives.

Keep It Simple

Are the questions organized in a logical and hierarchical manner? Can you simply and efficiently describe to a colleague who is not an expert in the field what you propose and why it is important? Short, declarative sentences of intent, supported by a brief rationale, work best. Avoid too much experimental detail in the specific aims page. Reviewers focus on the big picture.

Background and Significance

The current space limitations preclude lengthy background descriptions but this is an important component of the application and it is worth understanding both the general and more specific objectives for this section. The general objectives include the following.

• Demonstrating your understanding of the field, recognizing contributions of others:

- Identifying the next, most logical steps for research in the field; and
- Illustrating how your proposal will expand understanding of the field.

The more specific objectives include:

- Relating your preliminary findings to testable hypotheses in the context of the current application;
- Making direct and plausible connections between your most compelling findings and your current aims; and
- Leaving the reviewer with the sense that you have built a proposal whose foundation and goals are seamlessly intertwined and which now represents the next, most logical direction for the field.

Approach

The approach is the meat of the application and reviewers focus attention on the presentation and flow of this section as a primary determinant of the overall impact. Key components to the approach section are the preliminary studies and experimental design and, as in prior sections, there are important objectives to accomplish for each.

Preliminary Studies

The core objectives include, first, to convince reviewers that your preliminary data lead to testable hypotheses that are reasonable, novel, timely, and interesting. A second set of objectives is to convince the reviewer that all the proposed methods are feasible and ideally in hand. For junior investigators, the preliminary studies section provides an opportunity to establish core competence in the approaches and to verify the feasibility of the aims. A third objective is to link the preliminary findings with the aims, specifically by illustrating how the outcomes from preliminary data will be pursued through a specific aim or subaim. It is important that the preliminary data be presented from the viewpoint of testable implications for the current aims and that the data include alternative interpretations and caveats. Reviewers pay particular attention to the analyses associated with the data sets in addition to the quality and clarity of the data.

Other General Tips

For fundamental or basic research applications, particularly for new investigators, it is important that all of the aims have at least some preliminary support. For clinical research applications, preliminary data are less critical than providing evidence for the feasibility of the approach and documenting your ability to reach beyond conventional boundaries (ie, division/department) and to have fully exploited local resources by enlisting complementary support. It is helpful to organize the preliminary data sets around the relevant specific aim. In other words, preliminary findings that inform the approach for aim 1 should be embedded within the text allocated to aim 1. This organizational framework makes it easier for the reviewer to visualize the hypotheses and aims in the context of preliminary findings and anticipated outcomes.

Key Tips for Figures

Figures are of central importance to the application. An overarching model figure is very helpful and might include pathways and hypotheses for each aim. The figures should use color if possible for impact and ideally should be able to stand alone. The legends should be readable (no smaller than 9-point font) and should detail what the data show rather than summarizing the experimental approaches used. Figure legends for grant applications are distinct in their construction from figure legends in manuscripts. Do not cut and paste from manuscripts. The goal is to demonstrate to the reviewer that you understand how to interpret your own findings and to frame the results with caveats and alternatives that will inform your approach.

Key Tips for Formatting

Do not overcrowd pages. White space provides visual appeal and is much easier on reviewers. Avoid lengthy paragraphs with dense text. Use identical fonts for both figure legends and text.

Experimental Design

Organize each aim and subaim exactly as detailed in the specific aims page and abstract. It is very helpful to organize each aim in a templated modular fashion in which the preliminary data that substantiate the rationale are placed adjacent to the relevant aim or subaim.

A useful template to consider is rationale/experimental approach/anticipated results with potential caveats/pitfalls and alternative considerations. Outline new methods/concepts and emphasize innovation and environment. For new investigators, much of the methodologic validation and environmental resources can be emphasized in the expanded biosketch section. Secure letters of support for components of the proposal that you are not an expert in (eg, a pathologist to help read the histopathology of proposed animal models; a biostatistician to aid with computational aspects). Provide a time-line for each aim and, particularly for new investigators, add a sentence outlining possible future directions. Try to achieve balance across all the aims. There is a phenomenon of applicant fatigue in which the first aim occupies 3 or 4 pages, the second aim occupies 2 to 3 pages, and the third aim occupies a single page. Bear in mind that 1 weak aim will sink an application. Try to balance the

space allocation so that all aims are allocated equal attention.

Other Tips and Pointers for the Approach Section

Use a modular template. This structure is not only appealing to reviewers, but also very useful for applicants. Reviewers rarely have uninterrupted hours to review an entire application and the modular framework provides natural breakpoints. The modular template also provides a guideline for applicants to compose a structured proposal with a thoughtful blend and balance across all the aims.

Discuss Anticipated Outcomes

Have you provided a thoughtful and linear analysis of the possible outcomes and related these to your a priori hypotheses? Have you verified that the predicted outcomes will advance the field and yield significant impact? Reviewers will try to make these connections. Discuss alternative outcomes: What if your results differ from the predicted outcomes? It is important to detail contingencies for all possible outcomes and to frame these outcomes in a context that emphasizes fluidity of the approaches.

Other Considerations and Additional Review Criteria

There are several additional components to the application that require consideration. Certain of these components are additional review criteria that the reviewers will consider, but none is assigned a numerical score. These include protections for human subjects, vertebrate animal use, statistical considerations, and welfare and biohazards. There are also sections to justify applications from foreign organizations, a section to describe resource sharing (for unique reagents that may be generated in the course of the studies proposed), and a section for justification of joint principal investigator applications in which the oversight and management of the project must be detailed and mechanisms for resolving conflict should be discussed. Finally, there is a section in which the budget should be justified. For modular budgets (applications requesting \leq \$250,000) it is helpful for the reviewers to understand how these funds will be allocated (percent effort and months allocated by key personnel and others). For applications requesting more than the modular budget, reviewers expect a detailed accounting of all the categories of expense allocation. Although there is opportunity to include material in an appendix, reviewers are not obligated to review this material and it is highly recommended that such key information be included in the body of the application. The bibliography is not included in the page limit, but it is recommended that applicants constrain themselves to literature citations that are representative and inclusive without being overwhelming.

Introduction to Revised Applications

There are several important components to the structure and content of the response to prior review. It is helpful to begin by thanking the reviewers for their suggestions and, in a few lines, to summarize the major changes in response to the previous critique. This structure allows you to acknowledge and incorporate the reviewers' comments and to demonstrate that the revised application is now correspondingly improved. It is then helpful to provide a point-by-point response to the major concerns of each reviewer. Be selective. This is an opportunity to emphasize positive changes and to suggest how these now strengthen the application. Summarize new preliminary data and indicate how this strengthens a new specific aim or subaim. Indicate where relevant that these new findings are included in Figure X in the revised application. Because space is precious, I would not recommend placing preliminary data in the introduction section. Do not waste space with a lengthy discussion of material that you have eliminated, particularly in response to the reviewers' suggestions.

Useful Tips and Resources

The Office of Extramural Research (http://grants. nih.gov/grants/oer.htm) has many useful suggestions and a regularly updated service with blogs and updates on peer review (http://nexus.od.nih.gov/all/nexus-by-date).

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