An Introduction to Obtaining Extramural Funding

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The ability to obtain extramural funding is a critical part of developing a successful academic career. This manuscript provides an introduction to the sources of funding, the process by which a research proposal is developed, and the process by which a research proposal is reviewed and funding. Emphasis is placed on the process of grant review is performed at the National Institutes of Health. © 2005 Elsevier Inc. All rights reserved.

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INTRODUCTION

The mechanism by which academic programs are funded is an arduous process. The key portion of this process is the writing of the research proposal or grant. Grant writing has been described as the worst kind of writing. If lucky, three people will read the proposal, or at least parts of it. The readers can’t actually tell anyone that they have read the proposal! They can’t even tell the authors of the proposal they have read it. The readers can critique the writing, make suggestions for correcting any sentence, or insist that the writer go back and do all of the work again (many months from now, in the hope that most of the work will become so outdated that the reviewer will never have to read it again) [1].

There are several resources available to help the young researcher in their quest to fund their research program(s). Additionally, there are multiple funding agencies interested in funding the work of young investigators. The most important funding agencies are the federal funding agencies including the National Institutes of Health (NIH), the Department of Veterans Affairs (VA), the National Science Foundation (NSF), and the Department of Defense (DOD). These agencies have numerous career development grants. The national specialty societies, including the American Heart Association, American Cancer Society, and the American Diabetes Association, have young investigator programs. Many of the surgical societies, including the Association for Academic Surgery (AAS) have grant funding mechanisms for junior faculty investigators. The AAS has a resident research award, as well as the Joel J. Roslyn faculty research award. Additionally, the AAS has expanded the Fundamentals of Surgical Research Course. This course will be held just before the start of the Annual Clinical Congress of the American College of Surgeons. The funding rates for career development awards are usually higher than for other awards; up to 50% of NIH submissions will eventually be funded. The granting agencies provide significant information to help in the funding process. There is a wealth of resources available on the Internet. The NIH Web site (www.nih.gov) has information on grant writing, proposal preparation, and areas of research focus. The American College of Surgeons (ACS) provides investigators with a significant amount of support and information. The ACS sponsors an annual Young Investigators Conference designed to teach young surgeons about grant writing and the resources available. The slides from this conference, and other outstanding reference material regarding grant writing are posted on the ACS Web site (http://web.facs.org/research/index.html). Additionally, this site has information concerning attendance at the Young Investigators Conference.

CAREER DEVELOPMENT AWARDS

Grants from the federal funding agencies are the most important types of awards with grants from the NIH being the most prestigious. The NIH has numer-
ous training awards. NRSAs are individual awards targeted toward students or residents doing work in the lab of a mentor. T32s are training grants that are given to institutions to train both residents and students. The K-series of grants are training grants given to faculty early in their academic career. In the K grant series are K-08 grants for investigators involved in basic science research. There are also clinical training grants (K-23) that are targeted to junior investigators engaged in translational or clinical research. After the NIH training grants come the most important of the NIH grants, the R-01 grant. This grant is given to independent investigators. The NIH also has larger grants such as program project awards and specialized programs of research excellence (SPORE). The VA has similar types of grants to the NIH. There are associate investigator awards available for residents working in the lab of a mentor. There are VA career development awards that parallel the K grant series from the NIH. The VA equivalent of the NIH R-01 is the Merit Review Grant. Both NIH and VA awards are peer reviewed and very competitive. Current funding rates for both agencies are between 15 to 22%. Funding rates for training grants are usually higher.

**REVIEW OF TRAINING GRANTS**

The first item all grant reviewers are instructed to consider is the importance of the work. Specifically the research proposed needs to be interesting and novel; however, the work does not need to create a paradigm shift. The proposed work should add to the body of work that is published; however, it should be separate and distinct from what others are doing. The next consideration in review of a training grant is the qualifications of the trainee and their ability to become an independent investigator. This can be demonstrated by the training record, publication record, and preliminary data of the trainee. Deficits in qualifications or preliminary data can be addressed in training grants through discussion of additional planned training and through the expertise of identified mentors. The work of the trainee should be related to the work of the chosen mentors. Additionally, it is important for clinicians to have work that is directly relevant to patient care. This will help to distinguish surgical scientists from basic scientists. A surgical question or a surgical model will further help in distinguishing the trainee as a surgical investigator. For surgical investigators it is important to document that adequate time will be provided to accomplish the research plan and the training plan. The third consideration when reviewing a training grant is the qualifications of the mentor(s). The mentor(s) should be experienced with a proven track record of successful research funding and productivity, as well as, previous success in mentoring residents and students. In addition to the mentor, reviewers will evaluate the institution and the training environment. It is important to document the facilities and the core labs available. The final part of the grant to be reviewed is the actual training plan for the duration of the grant. It is important to outline what didactic and practical training will be obtained and how progress will be monitored.

**THE GRANT REVIEW PROCESS**

The review of a grant at NIH takes several months. Initially the application goes to the Center for Scientific Review (CSR) at the NIH. Training grants then go directly to one of the relevant institutes such as the National Cancer Institute, The National Heart, Lung, and Blood Institute, etc. For non-training grants CSR assigns the grant to a relevant institute and decides which Independent Review Group (IRG) is responsible for the review. Within each IRG there are usually 5 to 6 study sections of 20 members each. The study section is where the work of peer review occurs. Regardless of where the grant is reviewed the grant is assigned a primary reviewer and two secondary reviewers. These assigned reviewers are required to read the grant in depth and provide written comments. All members of the review committee receive the grant and have an opportunity to read it. Most of the committee members will read the abstract and introduction. If a study section member has a particular interest in the field they may read the grant further. The review committee then meets for 1 to 2 days and reviews and scores all of the grants. Most grants are usually reviewed at the committee meeting in a period of 15 min. The grant is scored. Scores are now available within 2 days on the NIH eRA Commons. Within 6 to 8 weeks a critique of the grant is sent to the investigator. Subsequently, the Council of the relevant Institute examines all of the scores and decides whether the grant will be funded or not funded. If a grant is not funded the investigator has three options; respond to the critiques and resubmit, appeal the determination of the reviewers, or submit a completely new proposal. The entire process from submission to final decision is a lengthy one. For example, if an R-01 grant is submitted on February 1 initial peer review will take place in June or July of that year. The total process takes 7 to 8 months from submission to final decision. It is important to continue work on the research project during the review process to effectively answer criticisms from the reviewers. Grant review deadlines and the timeline of the review process are available on the NIH Web site.

Grant reviewers are provided with very specific review criteria. The criteria are usually consistent across funding agencies. As discussed above reviewers are told to evaluate the significance of the research. The next review criteria is the methodological approach, or how the investigator goes about doing the particular
experiments proposed. Reviewers are asked to assess if the ideas are innovative and if state of the art techniques are used. Reviewers will critically evaluate the investigators themselves. Specifically reviewers will evaluate the investigators track record, where they have trained, what training they have had, and what data and literature they have published. Publications related to the field of investigation are particularly important. Reviewers also evaluate the research environment. Is the environment conducive to research? Is there the necessary time, resources, and mentors/collaborators to get the work done? Reviewers are also required to evaluate the budget. Furthermore, reviewers are asked to weigh in on ethical issues such as equity, human subject research, and animal care issues.

GETTING READY TO WRITE

The first step in formulating a research proposal is a complete assessment of the field through performance of a thorough literature search. The goal is to make certain that all of the relevant literature in the field is cited, to demonstrate an understanding of the field, and to avoid repeating experiments where the outcome is known. In addition to checking the literature it is important to know what other grants are funded in the proposed area of interest, and to know the expertise of the study section that will evaluate the research proposal. The NIH Web site has a searchable database of all their funded grants. This database is called CRISP. This database can be queried by keyword, author, institution, year, etc. After completing a thorough assessment of the field the next step is to formulate a hypothesis. Generating a hypothesis is one of the most important and difficult parts of the grant writing process. The hypothesis must be stated clearly and in one sentence. The hypothesis must be easily tested and with results that can be interpreted in regards to the hypothesis.

When writing a training grant it is important for the investigator to identify their strengths and weaknesses. Additionally, it is critical to account for all of the resources to perform the proposed work. In a training grant it is not expected that the investigator will have all of the knowledge and tools to complete the proposal at the start of the grant period. However, the investigator must account for their knowledge and technical deficits and assure the reviewers that they will obtain appropriate training and assistance to fill in the gaps. Specifically, if a new technique is proposed it is crucial to document that the expertise is available at the institution from a willing collaborator. Mentorship is critical in the success of training grants. A mentor should be chosen based on their previous funding record and their mentorship of others. The grant will be graded, in part, on the mentor. All grant ideas should be discussed with the mentor(s). In addition to having a good idea and the resources to accomplish the hypothesis, it is important to understand what the funding agencies are looking for. Surfing the Institutes’ Web sites can be helpful. Most Institutes at NIH post their research priorities on their sites. A call to the funding agency to discuss ideas is helpful. There are program officers and Senior Research Administrators (SRAs) at both NIH and VA who know what grants are being funded by that institute. The SRAs are willing to help new investigators. The SRAs will discuss with an investigator the importance of their research in terms of the institute’s priorities. The SRAs will often provide advice as to the relevant study section for a research proposal. It is possible to steer a grant to a specific study section through the title of the grant and the cover letter. Surgical investigators should focus on a surgical question or a surgical model.

WRITING THE PROPOSAL

It is important to allow for plenty of time to write a first grant. Grant writing takes 4 to 6 months of serious work. There are some basic tips for writing a grant or writing a manuscript. The grant must be focused. The grant must be written in proper English, free of spelling and grammatical mistakes. It is important to write to the audience; this can be facilitated by knowing who is on the study section. The goal of the proposal is to sell the grant to the reviewers. Specifically the investigator should be able to persuade the reviewers as to why this idea, why this investigator, why this department. The writing should be a balance of technical and non-technical. It is essential to make life easy for the reviewer. Reviewers are accomplished, busy people who have several grants to review. If the reviewer’s work is made miserable by poor organization or poor writing, they will make the investigator’s life miserable as well. It is important to use strong active verbs in the text. The best method to get started is with an outline, topic sentences for each main topic, and one paragraph per point. The use of sections and subsections with proper breaks in between facilitates the reading of the proposal. The worst thing for a reviewer to see when reviewing a grant is a narrative that starts on page 1 and goes through page 25 with no indentations, no subject headings, and no graphics. Include bullets and lists. Graphics and pictures are wonderful. One of my mentors told me if you condense your hypothesis into a picture on a 3 × 5 card you are half way home. Make sure there is good transition from one part of the grant to the next. Keep the related parts of the grant together. Make certain the elements of the grant are consistent from the hypotheses and specific aims, to the background, to the preliminary data, to experimental plan. Sloppiness in the grant’s figures and tables suggests carelessness to the reviewer. The figures
and figure legends must match and figures must be cited in the correct order within the text. Proofread with care, start with the spellchecker, but don’t end with the spellchecker. Someone outside the research group who is not intimately familiar with the work should read the application. It is helpful to have a layperson read and edit the proposal. If a layperson can understand what is written then the reviewers should have no problem. General issues such as poor layout and the use of jargon are cited as major review issues in up to 25% of grant submissions [2]. There are several administrative and technical issues to pay attention to when writing a grant. The grant must be sent to the correct place. It is important to consult with the program officer, especially for submission of a training grant. All grant writers should solicit feedback from as many people possible. Listen to mentors and experienced investigators. These people have done it before, they have written grants, and gotten funded, and they serve on study sections.

There are often many versions of the application forms. Make certain to use the most recent version of the application. Training grants have different instructions and deadlines than do other grants. Make certain the directions match the type of proposal to be submitted. Follow the directions to the letter. Strong research departments and institutions will have people to assist with the process. The stated page limit is absolute. Grants submitted that do not adhere to the directions will be returned unreviewed. NIH officials giving talks on grant writing emphasize the importance of following the printed directions repeatedly. Reading the directions and following them to the letter should receive equal emphasis to writing the hypothesis.

PARTS OF THE PROPOSAL

All grant proposals include the same basic components; the Abstract, the Introduction and Specific aims, the Background and Significance, the Preliminary Data, the Research Plan, the special issues such as human subjects, animals, etc., the bibliography, and the letters of support.

The abstract is the first impression reviewers will get of a grant. A significant proportion of the review board will only read the abstract and introduction. The abstract should have the hypothesis clearly stated as well as the specific aims. A concise statement of the importance of the work should be included. Additionally, the abstract should include a concise description of the methodological approach. The abstract should not be a copy of the introduction condensed to nine-point font to fit in the text box provided. The abstract should not be the last thing done on grant submission day. Remember this is a chance to make a positive first impression; take the appropriate amount of time.

The second part of the grant is the Introduction and the Specific Aims. This the most important section of the grant. Up to 45% of grants will have an issue with the specific aims identified as a problem during peer review. These critiques from reviewers include statements that the aims are overly ambitious, the aims are poorly focused, or the hypotheses are poorly stated [2]. The Introduction should be a statement of the importance of the clinical problem under study and what is unknown about the problem. The introduction should finish with the hypothesis, as well as, the long-term goals of the research. As mentioned above the hypothesis is crucial. The hypothesis must be clearly stated, preferably in one sentence. The hypothesis must be testable. A simple diagram of the hypothesis is often helpful. The specific aims, are one of the most important parts of the proposal, in that they shape the research plan. Three to four specific aims are appropriate. The aims should address the hypothesis stated. The aims should be related to each other and follow a logical order. However, each aim should be independent. Aim 3 should not be completely dependent on the successful execution of aim 1. If the reviewers feel aim 1 cannot be accomplished, they will not fund aim 3. These aims must be focused, clearly stated, and feasible. The Introduction section is critical because this may be the only section many members of the study section will read. Although this section alone will not get a grant funded, a poorly written Introduction and Specific Aims will cause a grant to not be funded. The reviewers should have an accurate idea of what is planned in the grant through review of this section; no additions or surprises should appear later [2]. An excellent review of writing Specific Aims is provided by Inouye and Fiellin [2]. These authors include examples of how this section should appear.

The next section of the research proposal is the Background section. This section needs to be a detailed review of the current state of the field under investigation. This section is an opportunity to demonstrate to the reviewers the investigator’s detailed knowledge of the problem. In this section it is important to point out the holes in the current body of literature and to address briefly how the proposal will add to the current knowledge. It is helpful to know the members of the study section reviewing the grant including their expertise. This provides the investigator with the opportunity to cite the important contributions of potential reviewers.

The purpose of the Preliminary Data section is to demonstrate that the research plan is feasible. Specifically, the investigator needs to demonstrate they have the antibody, the mouse model, and the skills to perform the experiments to be described in the experimental design. The Preliminary Data section is also an opportunity to demonstrate that the hypothesis is sound and based on experimental evidence. How the
preliminary data are presented and the accompanying figures are critical. The preliminary data included in the grant should be of manuscript quality. Carelessness and sloppiness in the presentation of the preliminary data will suggest to the reviewers that the investigator doesn’t possess the necessary training and ability to successfully execute the research plan.

The Research Plan is the most important part of the grant submission. This is the section that will be most scrutinized by the assigned reviewers. Many experienced investigators will work on the Research Plan first and build the remainder of the grant around this section. The Research Plan must closely follow the outline of the specific aims. Justify all of the choices made in terms of the time points, treatment doses, patient characteristics, and controls. If a technique is proposed that the investigator is not familiar with they must indicate who will be providing the necessary expertise. More detail should be provided for techniques that are new to the investigator. It is essential to describe what the positive and negative controls will be. For human studies detail how the necessary number of patients will be accrued. There should be a section describing statistical methods to be used. Furthermore, there should be an acknowledgment of the potential pitfalls of the experimental approach (there will always be something). Potential alternative approaches for addressing the pitfalls should be included.

At the beginning of each part of this section a general discussion of the experimental approach and the relationship to the specific aims is appropriate. A discussion of expected results is placed at the end of each section. A timeline for completion of the specific aims should be placed at the completion of the research plan. Additionally, a concluding paragraph discussing the long-range research plans and the implications of the proposed work on the field is helpful in establishing context.

REVISING THE PROPOSAL

What should you do if, or when, your grant is rejected? It is important to take a deep breath, and don’t get angry. The reviewers’ comments are not a personal attack on the investigator. The comments are a thoughtful discussion of the merits of the proposal. The vast majority of successful investigators had their first grants rejected. The road to successfully obtaining peer reviewed funding can be a difficult one. Winston Churchill defined success as “...the ability to go from one failure to another with no loss of enthusiasm”. After the initial disappointment of a grant rejection, review the summary sheet, put it down, read it again, put it down, and read it again. For NIH grants it is important to call the program director or SRA, and ask if they feel the grant has fatal flaws or if the criticisms can be addressed with appropriate revision. If the issues raised by the reviewers can be addressed, the mentor should read the summary sheet. An excellent table of the most frequent review issues in NIH grant proposals is included in the review by Inouye and Fiellin. Correctable errors include poor writing, or an overly ambitious, but not focused proposal. If the review states say there is insufficient preliminary data, if the research is not shown to be feasible by the proposed staff, or if there is insufficient discussion of obstacles and alternatives, these problems can be addressed by a well written revised proposal and rebuttal letter. Fatal flaws in a grant include comments that state the work is not important, the hypothesis is not sound, the work has already been done, or the methods proposed are not suitable for testing the hypothesis. Comments such as these indicate the grant should be completely rewritten.

There are three avenues for responding to a grant review. The best approach is to revise and resubmit the application to the same study section. A thorough cover letter is essential. The tone of the letter and the revised application should be cordial and complete. All criticisms should be addressed in the letter and all revisions indicated in the revised proposal. Another option for responding to an unfavorable review is to revise the application and to try to send it to a different study section. This approach is usually not productive unless a clear conflict of interest existed in the initial review. Additionally, if a new study section reviews the revised grant reviewers with different expertise from the original group are likely to review the proposal. These new reviewers will find different elements of the proposal to critique. The third option is to write a new proposal with a different title. This approach should be reserved for grants whose reviews have demonstrated fatal flaws. I cannot state strongly enough, if a review does not identify fatal flaws the best approach is to revise and resubmit.

In conclusion, there are several important points to keep in mind when writing a research grant. Select the study section wisely, know the members of the study section and understand their expertise, and keep in contact with the SRA. The hypothesis and aims are the key to a successful proposal. This section of your grant alone won’t get your grant funded but it can certainly prevent your grant from being funded. The research plan is the section of the grant reviewers will spend the most time reading, make it logical and easy to follow. Controls, statistical analysis, expected results, and potential problems need to be explained in detail. Figures and graphs that illustrate the hypothesis are extremely helpful. Make certain the grant is easy to read. Avoid typographical errors and poor grammar. The secret to success in grant writing is persistence. Revise and resubmit as often as is necessary, don’t give up.
Press on: nothing in the world can take the place of perseverance. Talent will not: nothing is more common than unsuccessful men with talent. Genius will not; unrewarded genius is almost a proverb. Education will not; the world is full of educated derelicts. Persistence and determination are omnipotent.”

Calvin Coolidge (1872-1933)

REFERENCES