IBGS 503
Grant Writing

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Reduction of a scientific problem of clinical significance to an NIH grant.

General intro

How is an NIH grant constructed?
Abstract
Budget
Biosketches
Environment and Resources

Background and significance
Specific aims: one page
Preliminary studies/progress report
Research Plan
Timetable
Literature cited
Letters of collaboration

How is an NIH grant evaluated?
Significance: Why is problem important for human health?
Approach: specific aims
Innovation: What is new or novel: approach, paradigm shift?
Investigator: Are you qualified to perform proposed studies?
Environment: Do you have the necessary resources?

Funding or not: Why this is a good plan to follow?

* Introduction of the problem

* Assign students to review specific areas.

* Break out into research topics that might be specific aims.

* Meet in groups to discuss potential specific aims.

* Develop specific aims

* What preliminary data would be needed?

* Draft of Materials and Methods (Research Plan)

* Assemble the complete grant draft.

Grading and Expectations: It is unlikely that the information presented in this class can be found elsewhere. Therefore attendance is essential. Grades will be based upon contribution and participation. The grade will reflect the result of a peer evaluation as well as evaluation by faculty who have participated.

The partnership between the National Institutes of Health (NIH) and America's medical schools and teaching hospitals is a national investment in improving health and quality of life, and strengthening the nation's long-term economy.

NIH-funded research drives scientific innovation and develops new and better diagnostics, prevention strategies, and more effective treatments.

NIH-funded research also contributes to the nation's economic strength by creating skilled, high-paying jobs; new products and industries; and improved technologies.

R01 Planning to Award Timeline by Review Cycle

Preparation Steps	**Timing**		
1. Prepare application.	2 months: Planning and writing; 1 month: Getting feedback; 2 weeks: Checks and edits.		
Submission	**Date**		
	Review Cycle 1	**Review Cycle 2**	**Review Cycle 3**
2. Organization submits the application by the receipt date.	New submission: February 5 Resubmission: March 5	New submission: June 5 Resubmission: July 5	New submission: October 5 Resubmission: November 5
Review	**Review Cycle 1**	**Review Cycle 2**	**Review Cycle 3**
3. Assignment.	Within two weeks	Within two weeks	Within two weeks
4. NIH assigns applications to reviewers.	May	September	January
5. Applications undergo initial peer review.	June or July	October or November	February or March
After Review	**Review Cycle 1**	**Review Cycle 2**	**Review Cycle 3**
6. Advisory Council Round .	October	January	May
7. Earliest project start date.	December	April	July

How is a NIH grant constructed?

- Title
- Project Description (Summary)
- Public Health Relevance Statement (Narrative)
- Facilities and Equipment (Environment and Resources)
- Biographical Sketch
- Modular Budget
- Budget Justification
- Specific Aims
- Research Strategy
    - Significance
    - Innovation
    - Approach
        - Preliminary Studies
        - Proposed Studies
        - Timetable
- Protection of Human Subjects
- Vertebrate animals
- References Cited
- Letters of Collaboration

For R01, R03, R21, and all other Applications

Section of Application	Activity Codes	Page Limits * (if different from FOA, FOA supersedes)
Introduction to Resubmission and Revision Applications	For all Activity Codes, and for each project and core of multi-component applications	1
Specific Aims	For all Activity Codes that use an application form with the Specific Aims section	1
Research Strategy	For Activity Code DP1	5
	For Activity Codes R03, R13, U13, R13/U13, R21, R36, R41, R43, SC2, SC3, X01[1]	6
	For Activity Code DP2	10
	For Activity Codes R01, R10, R15, R18, U18, R21/R33, R24, R33, R34, U34, R42, U42, R44, U44, DP3, DP5, G08, G11, G13, SC1, SI2, single project U01, UH2, UH3, UH2/UH3, X01[1], X02	12
	For UM1 Applications	6, 12, or 30 pages
	For each project and core of multi-component applications, such as Program Project/Center (P) and multi-component U applications.	Generally 6 or 12 pages**
	For all other Activity Codes	Follow FOA instructions
Commercialization Plan	For R42 and R44	12
Biographical Sketch	For all Activity Codes except DP1 and DP2	4
	For DP1 and DP2	2

Writing a successful NIH grant proposal

Choosing a high-impact research topic, one that is highly significant and that you are likely to accomplish

Decide on a well-focused and testable hypothesis

Define specific aims as achievable objectives with clear endpoints, which can test your hypothesis

Design appropriate and sufficient experiments to fully complete each aim include alternative pathways for exciting new leads and/or negative results

How to Pick a Project?

1. **Hatch a Plan**
   see the big picture, find the gaps with high impact, follow new scientific leads, and focus on one area with the goal of becoming the expert in a field
2. **Plot Your Strategy**
   Choose a topic where you can make a high impact on a narrowly focused area: Can your research move the field forward? Can the research make a difference, e.g., will it open up a new area of discovery or develop a new approach to a major problem
   Assess gaps and opportunities in your field: Create your own space and avoid crowded areas where it's harder to make a difference.
   Be an expert in the field: Be sure to have first-hand experience with the science and most of the methods. you can recruit collaborators to fill some gaps.
   Assess the importance of potential research areas to NIH: Find how you can capitalize on Institute priorities even with an investigator-initiated application
   Write a sentence showing how your project is well focused, can make an impact, and has a testable hypothesis: The hypothesis is testable using your proposed aims and methods and the science can be tied to the cause, diagnosis, prevention, or cure of human disease.
   Rate your project: NIH program officer, colleagues

One of the most common mistakes of new investigators is overly ambitious by proposing too much: a Research Plan that has too many Specific Aims, work that is too complex for their skill level, studies that require resources they don't have access to, work that is too much to accomplish within the timeframe of the award.

Facilities and Equipment (Environment and Resources)

To succeed in peer review, you must convince reviewers you have the resources you'll need to conduct the research, including equipment and space.

Build in all the expertise necessary to complete the experiments, including consultants and collaborators as needed.

Working on Your Research Plan

To create a top-quality Research Plan, you will need to do more planning than writing.

Start by choosing a hypothesis that is the destination for your research.

Define your Specific Aims as objectives you could achieve within the time you are planning to request.

In your Research Strategy, map out experiments and alternatives, making sure they track with your aims.

1. **Decide on a hypothesis.**

2. **Define Specific Aims to test your hypothesis.**

3. **Choose experiments that support your aims.**

1. Decide on a hypothesis

The hypothesis is your destination that all research roads must lead to.

Key Points: high impact, well-focused, and testable

Examples:

This proposal seeks to test the hypothesis that the capacity of *Mycobacterium tuberculosis* to inhibit infection-induced apoptosis of macrophages is a major pathway of the bacteria to avoid the host's innate and adaptive immune response.

Understanding the strategies of *Escherichia coli* to subvert host cells will allow for improved ways of preventing and treating *E. coli* -related diseases.

A wide range of molecules can inhibit HIV infection.

2. Define Specific Aims to test your hypothesis

Key Points:

can test the hypothesis

doable

concrete and well-focused

defined endpoints that can be assessed by the reviewers

3. Design appropriate experiments to support your aims

design appropriate and sufficient experiments to fully complete each aim

make sure that you are qualified to execute the experiments

you have required resources to do the work

Key Points:

include alternative pathways for exciting new leads and/or negative results

Writing your grant application

1. Create a provisional title.
2. Write a draft of your Specific Aims.
3. Write your Research Strategy:
   Start with your significance and innovation sections.
   Then draft the Approach section considering the personnel and skills you'll need for each step.
4. Evaluate your Specific Aims and methods in light of your expected budget (for a new PI, it should be modest, probably under the $250,000 for NIH's modular budget).
5. As you progress in designing your experiments, reevaluate your hypothesis, aims, and title to make sure they still reflect your plans.
6. Prepare your Abstract (Project Description).
7. Complete the other forms.

1. Create a Title (81 characters)
Key points: unique and specific

specific and detailed, indicating at least the research area and the goals of project.
81 characters or less.
lay language to the extent possible.
use a different title for each of applications
has appropriate keywords.

Project Description (Summary)

significance and novelty
hypothesis
specific aims
Methods (brief and major approach, or an animal model if you use one)
long-term objectives
both a scientist and a lay person can understand

Analysis of Examples:

Title
Project Description
Public Health Relevance Statement

Why are you doing the study?
What are you going to do?
How are you doing it?

Why?
Heart disease is a significant public health concern (common and lethal disease)
Current medications for heart disease are not effective in all patients, more options for medication therapy are needed

What?
Inhibiting G-protein signaling shows promise in animal models for treating heart disease, and G-protein signaling pathways may be novel drug targets for developing additional pharmaceuticals to treat heart disease.

Hypothesis: Over-activation of G-protein signaling pathways alters protein kinase regulation of sympathetic excitability resulting in increased excitability that progresses to heart disease.

How?

Goals of the proposed research are:

- Test for the effects of various protein kinase activators and inhibitors on cardiac function
- Use gene expression methods to show role of protein kinases in altering sympathetic excitability and cell morphology

Measure electrophysiological changes in heart cells in response to protein kinase activity

TITLE: THE ROLE OF ABNORMAL G-PROTEIN SIGNALING IN HEART DISEASE

DESCRIPTION: Congestive heart failure is a common and lethal disease in the U.S. Current medications for treating heart disease improve survival in some, but not all, patients. Therefore, additional medications are needed to treat individuals who do not respond to current medications. Research using animal models suggests that abnormal G-protein signaling may be a biochemical mechanism that may be one of the factors that cause heart disease. However, it is unknown how altered G-protein activity would cause this disorder. It has been shown that G-proteins can regulate the activities of several protein kinases. It is also thought that protein kinase activity in turn modulates sympathetic nervous system function. As a first step to determine whether this sequence of events could lead to heart disease, this project will use pharmacological and molecular genetic approaches to establish whether a G-protein-regulated protein kinase can modulate cardiac physiology in vivo and cardiac cell activity in vitro. Possible protein kinases to be tested that are regulated by G-proteins include G-protein coupled receptor kinase 2 (GRK2), PI3K, and ERK1/2. This research will enhance our understanding of the cellular and molecular mechanisms underlying sympathetic neuron dysfunction that may progress to heart disease, and may identify a possible novel pharmaceutical target for future experiments to develop therapeutic compounds to treat this disease.

PUBLIC HEALTH RELEVANCE: Heart disease is a leading cause of death in the U.S. Medications currently being used to treat heart disease are helpful to many individuals but do not work on all patients. Therefore, there is a vital need to develop additional drug treatments that will provide multiple approaches for treating all individuals afflicted with this debilitating illness. This research should provide important information that can be used in developing new heart disease therapies.

2. Writing your Specific Aims (one page)

Write a narrative to present and provide context for your planned research (1/2 page).

State your project's goals

Describe the significance of your research.

Give your rationale for choosing the project

Briefly describe your aims and show how they build on your preliminary studies and your previous research.

To target a study section with broad expertise, summarize the status of research in your field and explain how your project fits in.

State your hypothesis.

2. Writing your Specific Aims (cont.)

List your aims

State your plans using strong verbs like *identify, define, quantify, establish, determine.*

Describe each aim in one to three sentences.

Consider including bullets under each aim to refine your objectives.

2. Writing your Specific Aims (cont.)

Checkpoint

the one-page limit
each aim is a narrowly focused, concrete objective that can be achieved during the grant
highlight the significance of the research to science and health
give a clear picture of how the project can generate knowledge that may improve human health
show the project's importance to science, how it will close a gap in the field
state how the work is innovative
describe the biology to the extent needed for the reviewers
give a rationale for choosing the topic and approach
tie the project to the preliminary data and other new findings in the field
explicitly state the hypothesis and why testing it is important
the aims can test the hypothesis and are logical
you can design and can lead the execution of two or three sets of experiments that will strive to prove each aim
use language that an educated non-expert can understand, to the extent possible
the text has bullets, bolding, or headers so reviewers can easily spot your aims *(and other key items).*

3. Writing your Research Strategy (12 pages)

Significance

This is the section you state the importance of the research to improving human health as well as to the scientific field.

1) the state of the field you choose to research

2) your long-term research plans

3) your preliminary data

describe the importance of the hypothesis to the field and human disease

show that you are aware of opportunities, gaps, roadblocks, and research underway in the field you choose to research

state how your research will advance the field, highlighting knowledge gaps and showing how your project fills one or more of them and will significantly move the filed forward.

how the work is new and unique

don’t stop here, point out the project's significance throughout the application

3. Writing your Research Strategy (cont.)

Innovation

How your proposed research is new and unique, e.g., explores new scientific avenues, has a novel hypothesis

1. How your project's research can refine, improve, or propose a new application of an existing concept, method, instrumentation, or clinical intervention

2. Shift a current paradigm
   Make a very strong case for challenging the existing paradigm
   Have data to support the innovative approach
   Have strong evidence that you can do the work

Not all studies can have a paradigm shift. More commonly, innovation can be achieved by using new approaches or models, working in new areas, or testing innovative ideas.

3. Writing your Research Strategy (cont.)

Approach:

- create a separate section for Preliminary Studies to support the concept and the ability that you can do the experiments proposed
- restate your specific aims
- lay out a few sets of experiments to address each aim
- enough detail to convince reviewers (cite publications for some methods)
- clearly state what you do well and what unique skills you and your team (collaborators) bring to the research. If you think reviewers may have doubts, you need to explicitly state your team's resources and expertise
- describe the expected results and their implications
- describe potential pitfalls and how do you deal with them
- lay out alternative experiments and approaches in case you get negative or surprising results
- show timeline when you expect to complete your aims

3. Writing your Research Strategy (cont.)

Referencing Publications:

- cite relevant important publications for the concepts underlying your research and your approach and methods throughout your Research Plan thoroughly but not excessively (fewer than 100 citations if possible)
- don’t leave out an important work
- cite current and relevant publications
- cite relevant publications from potential reviewers
- don’t forget your own or your collaborators’ publications relevant to your project (concept and methods)
- your citations and other references in your Approach should highlight your expertise and that of your colleagues
- cite important unpublished work through personal contacts
- list all citations in Bibliography and References Cited

How is a NIH grant evaluated?

1. Can your research move the field forward?

2. Is the field important -- will progress make a difference to human health?

3. Can you and your team carry out the work?

Other more specific questions the reviewer may ask

Will the investigators be able to get the work done within the project period, or is the proposed work overly ambitious?

Did the PI describe potential pitfalls and possible alternatives?

Will the experiments generate meaningful data?

Could the resulting data prove the hypothesis?

Are others already doing the work, or has it been already completed?

Review Criteria

Significance. Does the project address an important problem or a critical barrier to progress in the field? 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?

Investigators. Are the PIs, collaborators, and other researchers well suited to the project? If early-stage investigators, new investigators, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance, and organizational structure appropriate for the project?

Review Criteria (cont.)

Innovation. 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?

Approach. Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? 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?
If the project involves clinical research, are the plans for 1) protection of human subjects from research risks, and 2) inclusion of minorities, members of both genders, and children justified in terms of the scientific goals and research strategy proposed?

Review Criteria (cont.)

Environment. Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Review Scoring

Impact	Score	Descriptor	Additional Guidance on Strengths / Weaknesses
High	**1**	**Exceptional**	**Exceptionally strong with essentially no weaknesses**
	2	**Outstanding**	**Extremely strong with negligible weaknesses**
	3	**Excellent**	**Very strong with only some minor weaknesses**
Medium	**4**	**Very Good**	**Strong but with numerous minor weaknesses**
	5	**Good**	**Strong but with at least one moderate weakness**
	6	**Satisfactory**	**Some strengths but also some moderate weaknesses**
Low	**7**	**Fair**	**Some strengths but with at least one major weakness**
	8	**Marginal**	**A few strengths and a few major weaknesses**
	9	**Poor**	**Very few strengths and numerous major weaknesses**
Non-numeric score options: NR = Not Recommended for Further Consideration, DF = Deferred, AB = Abstention, CF = Conflict, NP = Not Present, ND = Not Discussed			
Minor Weakness: An easily addressable weakness that does not substantially lessen impact **Moderate Weakness:** A weakness that lessens impact **Major Weakness:** A weakness that severely limits impact			

<u>The primary outcome of a grant review is an OVERALL IMPACT SCORE</u>

1. **Importance.** Innovation and significance of research problem.

2. **Likelihood.** Experimental design, the expertise of the PI and the team, and the resources and environment.

Overall Impact vs Significance

Significance: Does the project address an important problem or critical barrier to progress in the field? 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 of the project is evaluated within the context of a research field. For example, autism is a significant field of study but not all studies of autism are significant

Overall Impact: Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following five core review criteria, and additional review criteria (as applicable for the project proposed).

Overall Impact is not the arithmetic mean of the scores for the scored review criteria.

Case Study:

An investigator proposes using a novel method of viral vector-mediated siRNA delivery to knock-down the gene for a particular CNS receptor subtype in specific brain regions he/she hypothesizes to be involved in cognitive aspects of a rare mental illness. He/she proposes to use this method to examine disruption of this receptor subtype on cognitive performance in three animal models of the illness.

Review

Both reviewers agree that the application addresses an important problem and that the hypothesis and methods are highly innovative. They believe that if the proposed aims were achieved, the project would significantly advance knowledge in the field and promote substantially new research directions in research on the rare mental illness as well as the broader field of mental health. Therefore, they rate Significance as high. They have strong reservations, however, about the application relative to other review criteria. The investigator and his/her colleagues do not appear to have the relevant training and expertise to successfully accomplish the work and there are some flaws in the approach that may reflect their inexperience with critical methods. Therefore, they rate the Overall Impact as moderate.

CASE STUDY #2

An application proposes to disrupt a well-known signal transduction pathway in mice and see if it results in an increased incidence of a particular type of breast cancer in mice.

Significance: Breast cancer is an important disease in women. Is this alone sufficient to say that this project has high significance? Provide a couple of scenarios in which the proposed studies could be significant or not significant.

Overall Impact: What is the likelihood that this project conducted by these investigators in their environment, with this level of innovation and the proposed approaches, will have a sustained powerful influence on the field? Provide a couple of scenarios for the possible outcomes of the overall impact.

Significance

Although breast cancer is a very important disease, the reviewers will evaluate whether the proposed signaling pathway and the work in mice will be important for understanding, treating, or preventing human breast cancer.

If the signaling pathway under study is also important in another disease, such as colon cancer, the Significance might be higher, since the results of the project will be more broadly applicable.

A project that addresses a slow growing type of breast cancer that responds well to existing therapies/treatments would be of lower significance because it is less likely to change clinical practice.

Overall Impact

If the proposed work in mice will strongly predict what is happening in humans, the investigators are highly qualified, the environment is strong, the approach to disrupting the pathway is innovative, and the approach is flawless the project may be likely to have high Overall Impact.

Even if the pathway and the mouse model are very significant for breast cancer in humans, the investigators are very experienced and in a great environment, and the approaches are sound, if the proposed work is not innovative or is confirmatory and duplicates many other published reports, the Overall Impact of the project on breast cancer research might be only moderate to low.

Even if the topic is very significant for breast cancer in humans, the investigators are very experienced and in a great environment, and the project is innovative, the approach may be flawed, reducing the chance of generating useful data, which would reduce the likely Overall Impact on breast cancer research.

Even if this project is very innovative, well conceived, and likely to have high overall impact, a subsequent project to clone and characterize receptor subtypes for this family of signal transduction molecules may be viewed as having less Overall Impact, since it might not be as innovative. Conversely, such a project might be viewed as having a greater Overall Impact, since the work is essential to develop a new drug treatment for breast cancer.

CASE STUDY #3

An application proposes to develop and test an antidote for a chemical agent in an animal model.

Significance: The potential use of chemical agents in wars or related to terrorist activities is of national security concern. Is this alone sufficient to say that this project has high significance? Provide a couple of scenarios in which the proposed studies could be significant or not significant.

Overall Impact: What is the likelihood that this project conducted by these investigators in their environment, with this level of innovation and the proposed approaches, will have a sustained powerful influence on the field? Provide some scenarios for the possible outcomes of the overall impact.

Significance

Although such agents may directly affect a very limited number of individuals and the therapeutic agent(s) may have no other uses, the project has the strong likelihood of yielding life saving therapeutic agents should an exposure occur; thus the significance is very high.

However, if well established clinical practices and multiple effective antidotes are widely available, contribution to the field of development therapeutics for chemical agent exposure will be lower and significance diminished.

Overall Impact

The project resolves an unmet need; there are no effective therapies for this chemical exposure with high mortality. The reviewers might note the highly qualified investigators, flawless methods, an excellent animal model, and therapeutic compounds that will work on various chemical agents - High Overall Impact

While other therapeutic agents exist, the proposed compounds have numerous advantages in terms of side effect, ease of use and efficacy and will likely be the treatment of choice - High Overall Impact

The project contributes to the enhancement of the therapeutic arsenal but will not result in major changes to current clinical/therapeutic practices - Medium Overall Impact

While the idea is significant and sound, methodologies are flawed and investigators have very limited experience in the field. The probability of achieving the goals is low - Low Overall Impact

Technically sound with good investigators but the animal model has no relevance to human condition - Low Overall Impact