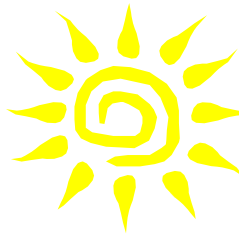# NIH-SPECIFIC GRANT WRITING WORKSHOP:
Writing a Compelling Grant Proposal to NIH

Sunshine Consultants, International
… specializing in research competitiveness

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There are Lots of NIH-specific Resources Out There

http://funding.niaid.nih.gov/researchfunding/grant/pages/appsamples.aspx
Examples of successful RO1s in the 12-page format, annotated with what is positive. A MUST STUDY.

http://sciencecareers.sciencemag.org/career_development/tools_resources/how_to_guides/how_to_get_funding
AAAS very useful site. Read: How Not to Kill a Grant Application.

http://grants1.nih.gov/grants/grant_tips.htm
Tip guide from NIH. Includes tips for new investigators and SBIR/STTR. All you wanted to know about NIH and were afraid to ask.

http://www.ninds.nih.gov/funding/grantwriting_mistakes.htm
Five common mistakes in NIH grant applications.

For Example, Take a Look at *Only One Part of* the Contents of:

http://grants1.nih.gov/grants/grant_tips.htm

- All About Grants Tutorials - Including information to help investigators
- plan and write grant applications and manage their awards.
- Applying for an NHGRI Grant
- Choosing an Appropriate NIH Funding Instrument and Funding Mechanism
- Peer Review Guidelines and Information
- Peer Review Meetings - Meeting dates, descriptions, rosters, guidelines, etc.
- Preparing Grant Applications
- Quick Guide for the Preparation of Grant Applications (Complementary and
- Alternative Medicine)
- SBIR/STTR Policy and Grantsmanship Information
- Tips for New NIH Grant Applicants
- Writing a Grant

Outline

Resources

Identifying the Proper Study Section for Your Application

Learning Who is on the Study Section (and Making Sure they Show up in the Reference List)

Understanding the Inner Workings of NIH's Peer Review Process and what Priority Scores Mean

Playing to Your Strengths

Writing the Section on Specific Aims with an Emphasis on Hypothesis-driven Research

Writing the First Two Sentences

Writing the First Two Pages (Significance, Innovation, Team)

Organizing and Writing the Approach Section

Dealing with Potential Pitfalls and Alternative Approaches

Conveying a Project Timeline

Human Subjects, Invertebrate Animals, Risks, Letters of Collaboration

Writing the Project Description

Fatal Flaws

Writing an introduction to a Revised Proposal

Summary and Wrap-up

Outline

Identifying the Proper Study Section for Your Application

Contact NIH by Web and by phone to reach people who want to help you:

1. NIH--http://www.nih.gov
2. Center for Scientific Review--http://www.csr.nih.gov
3. National Institute of General Medical Sciences--
http://www.nigms.nih.gov
4. Reserch Portfolio Online Reporting Tool (RePORT, a searchable database of federally funded biomedical research projects)--
http://projectreporter.nih.gov/reporter.cfm

Outline

Learning Who is on the Study Section (and Making Sure they Show Up on the Reference List)

Advice from a Member of the National Academy of Science

Q:"Dr. Stern, how did you do it. What is your secret?"

A: "I referenced everybody!"

Melvin Stern, Department of Oceanography, Florida State University

Adapted from Florida CRC Grants Workshop presentation by Bill Landing

Outline

Understanding the Inner Workings of the NIH Peer Review Process and What Priority Scores Mean

Peer Review Prior to the Panel Meeting → **Panel Meeting** → **Priority Score and Percentile**

Significance (Overall Impact) 1-9
Investigators 1-9
Innovation 1-9
Approach 1-9
Environment 1-9

1 is good; 9 is bad

There is Even a YouTube Video for Understanding the Inner Workings of the NIH Peer Review Process

NIH Peer Review Revealed
Provides a front-row seat to a peer review meeting.

http://cms.csr.nih.gov/ResourcesforApplicants/
InsidetheNIHGrantReviewProcessVideo.htm

Understanding the Inner Workings of the NIH Peer Review Process and What Priority Scores Mean

Peer Review Prior to the Panel Meeting → **Panel Meeting (Scientific Review Group)** → **Priority Score and Percentile**

Funded!

Priority score: 10
Percentile: 2

… At the meeting, the more meritorious applications were discussed and given final impact/priority scores; also, by concurrence of the full SRG, the remaining applications, including this application, were not discussed…

Funded!

Priority score: 20
Percentile: 7

CODE FOR "YOUR PROPOSAL FELL INTO THE BOTTOM HALF OF APPLICATIONS"

Not Funded

Priority score: 60
Percentile: 50

Understanding the Inner Workings of the NIH Peer Review Process and What Priority Scores Mean

Peer Review Prior to the Panel Meeting → **Panel Meeting** → **Priority Score and Percentile**

Sometimes it is Two Strikes and You're Out

See Guide Notice NOT-OD-10-080 at http://grants.nih.giv/grants/guide/notice-files/NOT-OD-10_080.html

Outline

Playing to Your Strengths

Outline

Writing the Section of Specific Aims with an Emphasis on Hypothesis-driven Research

Before You Start: Answer the 3 Key Questions

What are you going to do?   STRONG research question

Why is it important to do this?   Who cares? So what? What happens if you do this?

Why is your approach innovative?   How is your approach creative? How are you going to do it?

Let's Work on Your Specific Aims Page

Specific Aims

Microscopy has emerged as one of the most powerful and informative ways to analyze cell-based high-throughput screening (HTS) samples in experiments designed to uncover novel drugs and drug targets. However, many diseases and biological pathways can be better studied in whole animals–particularly diseases that involve organ systems and multicellular interactions, such as metabolism and infection. The worm Caenorhabditis elegans is a well-established ==Priority score: 10== nism that can be robotically prepared and imaged, but existing image-analysis methods are insufficient for most assays. ==Percentile: 2== lop algorithms for the analysis of high-throughput C. elegans images, validating them in three specific experiments to identify infections and genetic regulators of host response to pathogens and fat metabolism. Novel computational tools for automated ns assays will make whole-animal screening possible for a variety of biological questions not approachable by cellbased assays. Building on our expertise in developing image processing and machine learning algorithms for high-throughput screening, and on our established collaborations with leaders in C. elegans research, we will:

Aim 1: Develop algorithms for C. elegans viability assays to identify modulators of pathogen infection
Challenge: To identify individual worms in thousands of two-dimensional brightfield images of worm populations infected by Microsporidia, and measure viability based on worm body shape (live worms are curvy whereas dead worms are straight).
Approach: We will develop algorithms that use a probabilistic shape model of C. elegans learned from examples, enabling segmentation and body shape measurements even when worms touch or cross.
Impact: These algorithms will quantify a wide range of phenotypic descriptors detectable in individual worms, including body morphology as well as subtle variations in reporter signal levels.

Aim 2: Develop algorithms for C. elegans lipid assays to identify genes that regulate fat metabolism
Challenge: To detect worms versus background, despite artifacts from sample preparation, and detect subtle phenotypes of worm populations.
Approach: We will improve well edge detection, illumination correction, and detection of artifacts (e.g. bubbles and aggregates of bacteria) and enable image segmentation in highly variable image backgrounds using level-set segmentation. We will also design feature descriptors that can capture worm population phenotypes.
Impact: These algorithms will provide detection for a variety of phenotypes in worm populations. They will also improve data quality in other assays, such as those in Aims 1 and 3.

Aim 3: Develop algorithms for gene expression pattern assays to identify regulators of the response of the C. elegans host to Staphylococcus aureus infection
Challenge: To map each worm to a reference and quantify changes in fluorescence localization patterns.
Approach: We will develop worm mapping algorithms and combine them with anatomical maps to extract atlas-based measurements of staining patterns and localization. We will then use machine learning to distinguish morphological phenotypes of interest based on the extracted features.
Impact: These algorithms will enable addressing a variety of biological questions by measuring complex morphologies within individual worms. In addition to discovering novel anti-infectives and genes involved in metabolism and pathogen resistance, this work will provide the C. elegans community with (a) a versatile, modular, open-source toolbox of algorithms readily usable by biologists to quantify a wide range of important high-throughput whole-organism assays, (b) a new framework for extracting morphological features from C. elegans populations for quantitative analysis of this organism, and (c) the capability to discover disease-related pathways, chemical probes, and drug targets in high-throughput screens relevant to a variety of diseases.

Primary collaborators
Gary Ruvkun and Fred Ausubel, MGH/Harvard Medical School: Development, execution, and follow-up of large-scale C. elegans screens probing metabolism and infection. **Polina Golland and Tammy Riklin-Raviv,** MIT Computer Science and Artificial Intelligence Lab: Illumination/bias correction, model-based segmentation, and statistical image analysis. **Anne Carpenter, Broad Imaging Platform: Software engineering and support.**

Aim 1: Develop algorithms for C. elegans viability assays to identify modulators of pathogen infection

Challenge: To identify individual worms in thousands of two-dimensional brightfield images of worm populations infected by Microsporidia, and measure viability based on worm body shape (live worms are curvy whereas dead worms are straight).

Approach: We will develop algorithms that use a probabilistic shape model of C. elegans learned from examples, enabling segmentation and body shape measurements even when worms touch or cross.

Impact: These algorithms will quantify a wide range of phenotypic descriptors detectable in individual worms, including body morphology as well as subtle variations in reporter signal levels.

Carolina Wahlby, Broad Institute
http://funding.niaid.nih.gov/researchfunding/grant/documents/wahlbyresplan.pdf

Outline

Now Let's Write the First Two Sentences of Your Proposal

Example of the First Two Sentences of a Winning Proposal

Research Strategy
(A) Significance
Apicomplexa are important human pathogens responsible for numerous severe diseases around the World. These include the various forms of malaria (1-3) as well as opportunistic infections associated with AIDS (4, 5).

Priority score: 18
Percentile: 6

http://www.niaid.nih.gov/researchfunding/grant/pages/appsamples.aspx
Boris Striepen, University of Georgia

Outline

Now Let's Work on the First Two Pages of Your Grant and then Organize the Rest of It

The Secret is to Organize and "Write to the Peer Review Criteria"

Project Description – write last
Specific Aims – 1 page
Significance – 1 page or so
Innovation – ½ page or so
Investigators – 1 paragraph or so
Approach (repeat for Aims 1, 2, and 3)
   Specific Aim 1
      Hypothesis
      Background and Preliminary Data
         Supporting Specific Aim 1
      Approach to Specific Aim 1, Including
         Experiments and Interpretations
      Potential Pitfalls and Alternative
         Approaches
Timetable – 1/3 page
Environment – not in page count

Now Let's Write the First Two Pages of Your Proposal

A Significance

The NIH is committed to translating basic biomedical research into clinical practice and thereby impacting global human health[1], and Francis Collins identifies high-throughput technology as one of five areas of focus for the NIH's research agenda[2]. For many diseases, researchers have identified successful novel therapeutics or research probes by applying technical advances in automation to high-throughput screening (HTS) using either biochemical or cell-based assays[3–6]. Researchers are using genetic perturbations such as RNA interference or gene overexpression in cell-based HTS assays to identify genetic regulators of disease processes as potential drug targets[7-9]. However, the molecular mechanisms of many diseases that deeply impact human health worldwide are not well-understood and thus cannot yet be reduced to biochemical or cell-based assays.

Carolina Wahlby, Broad Institute
http://funding.niaid.nih.gov/researchfunding/grant/documents/wahlbyresplan.pdf

B Innovation

In response to the strong demand for C. elegans screening, we propose to build on our technological innovations in sample preparation and imaging and our computational innovations for cells and brains to now create a novel technology for C. elegans. Our proposed work to develop novel algorithms for identifying and characterizing worms in microscopy images will bridge the final gap, for the first time enabling widespread identification of genetic and chemical regulators of human biological processes and diseases via whole-organism screening.

C Approach
Overview of the team and the approach
The proposed project is founded on several multi-year existing collaborations between groups studying infection and metabolism using C. elegans (Ausubel and Ruvkun), and computational groups focused on developing algorithms for biomedical research (Wahlby, Carpenter, and Golland), making us uniquely situated to accomplish the proposed aims. As shown in Figure C.1, our interdisciplinary team is highly interactive and our approach to image assay development is a highly iterative process; typically the majority of the work is in multiple rounds of validation and testing of novel or existing algorithms while optimizing sample preparation protocols to ensure robust real-world performance. Each proposed aim is independent, but in several instances, improvements made for one aim will benefit the others. Later sections detail our proposed algorithm development for each aim, which will occur in the rich, collaborative, interdisciplinary environment of algorithm and software development at the Broad Institute and MIT. Here we outline the team and the approach.

Outline

Now Let's Organize Your Approach

The Secret is to Organize and "Write to the Peer Review Criteria"

Project Description – write last
Significance – 1 page or so
Investigators – 1 paragraph
Innovation – ½ page
Approach (repeat for Aims 1, 2, and 3)
- **Specific Aim 1**
  - Hypothesis
  - Background and Preliminary Data Supporting Specific Aim 1
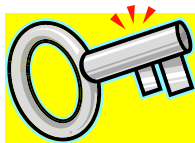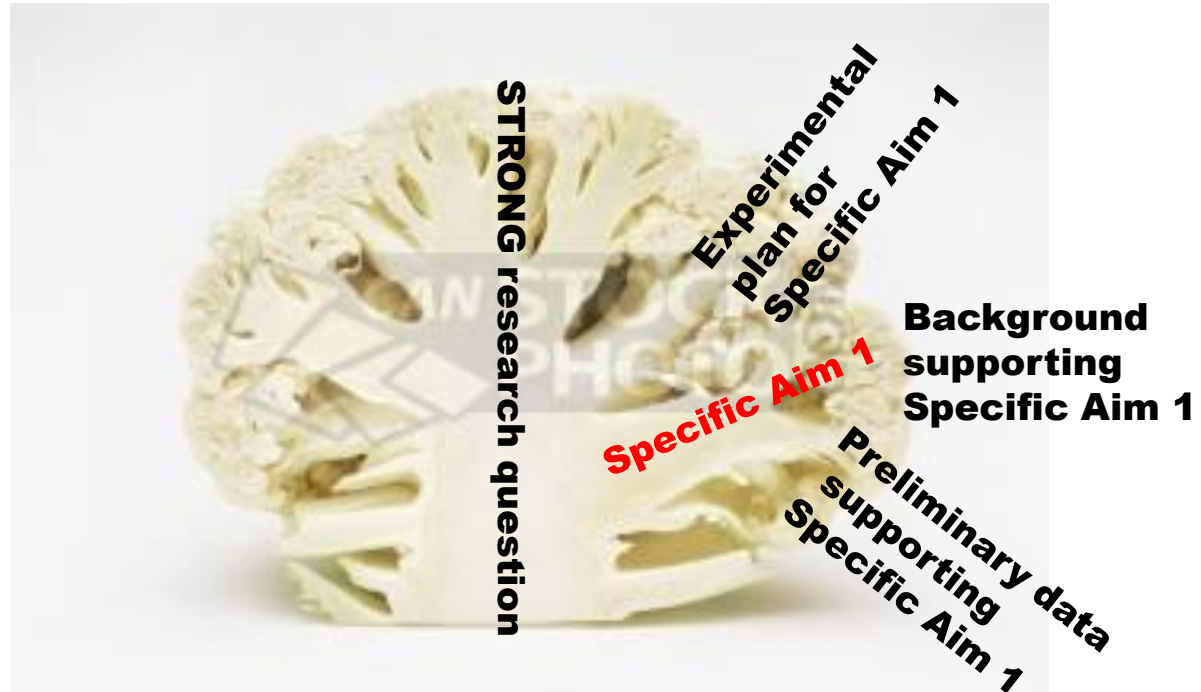 - Approach to Specific Aim 1, Including Experiments and Interpretations
  - Potential Pitfalls and Alternative Approaches

Timetable – 1/3 page
Environment – not in page count

The Cauliflower Method for Developing a Grant

EVERYTHING should relate to the central question: What are you going to do? Pare away anything else.

The Importance of Preliminary Data

Make sure at least once in your proposal you say "We will build on our preliminary data to do thus-and-so." Or better, "Building on our intriguing preliminary results, we will do thus-and-so."

Ideally, you should have at least one figure of preliminary data to support each of your specific aims/hypotheses.

What To Do if You Don't Have Preliminary Data?

Use your start-up funds to generate preliminary data.

Collaborate to generate preliminary data.

NIH has exploratory/developmental research grants (R21).

Beg your department chair for funds.

Outline

The Section on Potential Pitfalls and Alternative Interpretations

Outline

Don't Forget Your Project Timeline – Here's a Template

Specific Aims and Sub Aims	Year 1				Year 2				Year 3				Year 4				Year 5			
1.1	█	█	█	█																
1.2			█	█	█	█	█													
1.3									█	█	█	█								
1.4													█	█	█	█	█			
1.5																	█	█	█	█
2.1	█	█	█	█																
2.2	█	█	█	█	█	█														
2.3						█	█	█	█	█										
2.4									█	█	█	█	█							
2.5													█	█	█	█	█			
3.1					█	█	█	█	█											
3.2					█	█	█	█	█											
3.3									█	█	█	█	█							
3.4														█	█	█	█			

Outline

Human Subjects, Invertebrate Animals, Biological Hazards, Letters of Collaboration

Outline

Now Let's Write Your Project Description

An Example of a Winning Project Description

Sentence 1: What will you do?
Sentence 2: Why is it important?
Sentence 3: What has already been done?
Sentence 4: How are you going to do it and how
is your approach special?

Here we seek to understand how structural flexibility and variation in parvoviral capsids control their ability to bind receptors leading to cell infection and also to variation in host range, and also how capsid structures control antibody binding and neutralization. Those areas of study are significant because they are features of all animal and human viruses. While parvovirus capsids appear structurally simple, they are clearly sophisticated biomolecular machines that carry out many functions using variants of a single capsid protein, and the features controlling many functions have now been mapped to specific mutations and capsid structures, presenting an opportunity to gain a complete understanding of how virus-host interactions occur in fine detail. ..

Colin Parish, Cornell University, http://funding.niaid.nih.gov/researchfunding/grant/documents/parrishfull.pdf

Outline

Fatal Flaws

Problems with significance:
- Not significant nor exciting nor new research
- Lack of compelling rationale
- Incremental and low impact research

Problems with specific aims:
- Too ambitious, too much work proposed
- Unfocused aims, unclear goals
- Limited aims and uncertain future directions

Problems with experimental approach:
- Too much unnecessary experimental detail
- Not enough detail on approaches, especially untested ones
- Not enough preliminary data to establish feasibility
- Feasibility of each aim not shown
- Little or no expertise with approach
- Lack of appropriate controls
- Not directly testing hypothesis
- Correlative or descriptive data
- Experiments not directed towards mechanisms
- No discussion of alternative models or hypotheses
- No discussion of potential pitfalls
- No discussion of interpretation of data

Problems with investigator:
- No demonstration of expertise or publications in approaches
- Low productivity, few recent papers
- No collaborators recruited or no letters from collaborators

Problems with environment:
- Little demonstration of institutional support
- Little or no start up package or necessary equipment

Fatal Flaws, Continued

Insufficient innovativeness
Failure to cite important literature
Problems with protections for human subjects:
- Inadequate protection of identity
- Unacceptable risks

Problems with use of vertebrate animals
Annoying the reviewer

From Jelinski observations

Outline

Now Lets Look at How to Write the One-page "Introduction to Revised Application"

Identifying the Alpha Reviewer

–noun

A dominant dog; a dog that is an alpha male or alpha female. Often used figuratively.

The Alpha Reviewer is the one whose critique is repeated most obviously in the Summary Statement. The Alpha Reviewer will likely be assigned to review your grant again.

Pay careful attention BOTH to the Summary Statement and the critique by the Alpha Reviewer in revising your grant.

How to Go About Writing the One-page "Introduction to Revised Application"

Paragraph 1

Priority score: 10
Percentile: 2

INTRODUCTION TO RESUBMISSION APPLICATION

This is the second (A2) resubmission of application R01 HD061371-01, *"Gardnerella vagina/is:*toxin production and pathogenesis," which was reviewed in February 2009 and then in June 2009 at the HIBP study section. The initial submission received a 35.5 percentile (priority score 203) and the A1 resubmission a 15 percentile (impact/priority score 28 .) Under FY10 paylines, it was not funded by NICHD or NIAID . As a new investigator, I am grateful for the opportunity to present this revised application. I have made every effort to address the critique thoroughly, and I believe that the proposed studies have emerged considerably stronger and more focused on relevant aspects of pathogenesis. This resubmission has undergone very substantial revision, both in response to the reviewers' comments and in order to meet the new page limit guidelines for R01 applications. For that reason, changes are not marked in the text.

Adam Rainer, Columbia University

"Introduction to Revised Application," Continued

Paragraph 2

My impression from the summary statement for the A1 application was that the reviewers found the subject matter of interest, and there was substantial enthusiasm for studies of pathogenic mechanisms of G. *vagina/is focused on the new human-specific cytolysin (vaginolysin, VL Y)* and its receptor, human CD59. The summary of discussion described the strengths of the application as *"the expertise and productivity of the investigator in the field, the supportive preliminary data ensuring feasibility, the innovative approach, the adequate response to previous critiques, and the significance of this understated female problem." The weaknesses* identified were *"the ambitious nature of the project, the lack of a transgenic model, and the relevance to humans." However, the proposed research was felt to be* "potentially very important with a high probability of it being successful."

"Introduction to Revised Application," Continued

Paragraph 3 and following paragraphs

The major concern of the reviewers surrounded the hCD59-transgenic murine lines for the in vivo studies in Aim 2. I have approached this problem in three ways. First, I provide data…

Outline

Summary and Wrap-up

Summary: How to Write a Winning Grant

STRONG research question

Who cares? So what? What happens if you do this?

How is your approach creative? How are you going to do it?

1. **Answer the 3 Key Questions**
   - ❖ **Answers generate hypothesis**
   - ❖ **Answers generate specific aims**
   - ❖ **Answers generate broader impacts**
2. **Write Elevator Conversation**
3. **Write first 2 sentences**
4. **Write first 2 pages**
5. **Use the "Cauliflower Method" to develop the full proposal**
6. **Use 4-sentence formula to write the abstract**
7. **Ask a colleague to read it before submission**

Sentence 1: What will you do?
Sentence 2: Why is it important?
Sentence 3: What has already been done?
Sentence 4: How are you going to do it and how is your approach special?
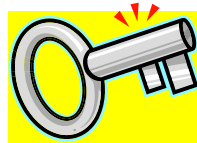
STRONG research question
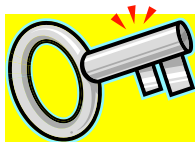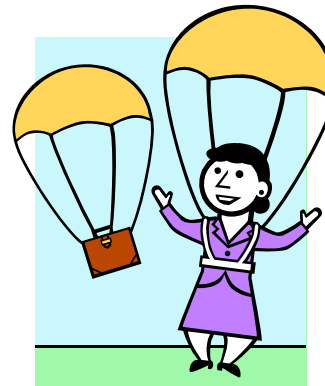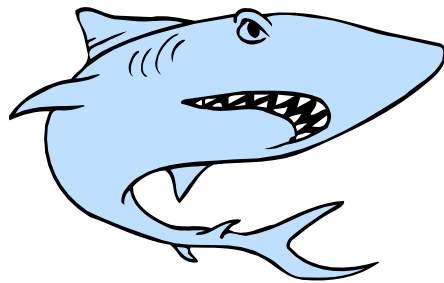
Experimental plan for Specific Aim 1

Specific Aim 1

Background supporting Specific Aim 1

Preliminary data supporting Specific Aim 1

Summary: How to Write a Winning Grant

EVERYTHING should derive from a STRONG research question.

Put yourself in the reviewer's frame of mind and don't expose your soft underbelly.

Writing a Winning NIH Grant is a Prickly but Beautiful Process