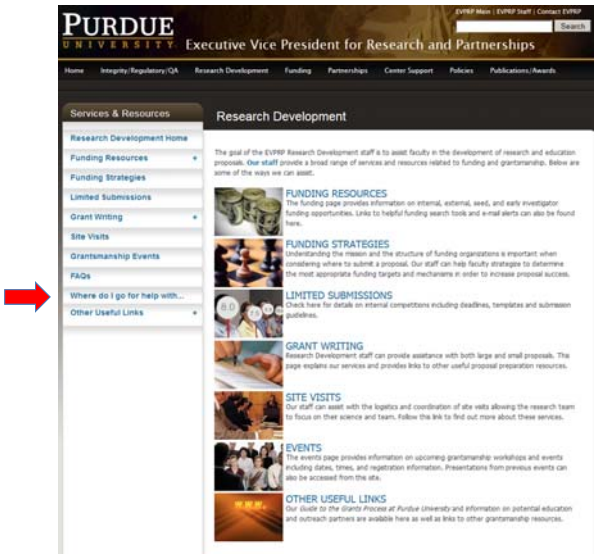
How to Write an NIH Proposal

Sally Bond
Assistant Director of Research Development Services
Proposal Coordination
Office of the Executive Vice President for Research and Partnerships

PURDUE UNIVERSITY

Purdue Research Development Services

Office of the Executive Vice President for Research and Partnerships



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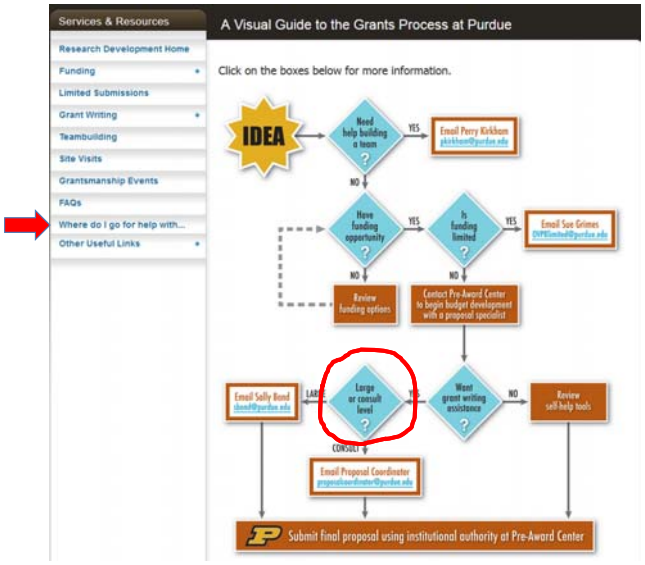
Where Do I Go for Help?

Hyperlinked "help" flowchart



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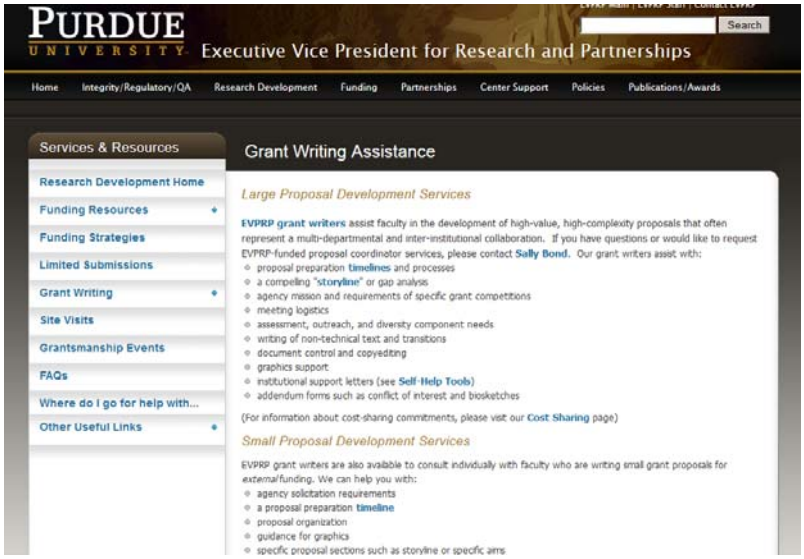
Large-Scale Proposal Coordination

High-value, higher-complexity, interdisciplinary



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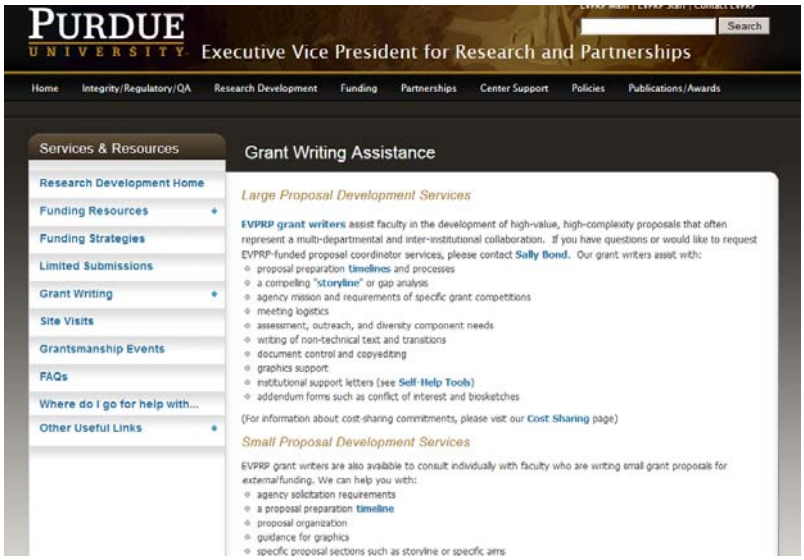
Smaller Proposal Consultation

Help is available for proposals of all sizes.



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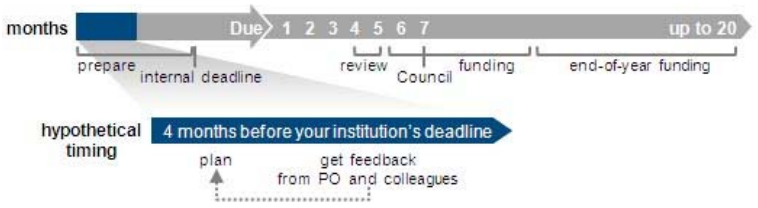
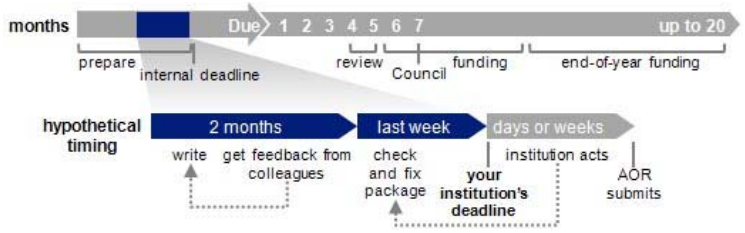
Proposal Preparation Timeline

Not a bad idea to start six months ahead of time!

NIH Planning Timeline



NIH Writing Timeline



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Reviewers Want to Know

Specific aims page is key. Reviewers ask themselves three questions….

- Are you solving something that is critical to solve?
- Are you solving it the right way?
- Are you the right person to do this work?

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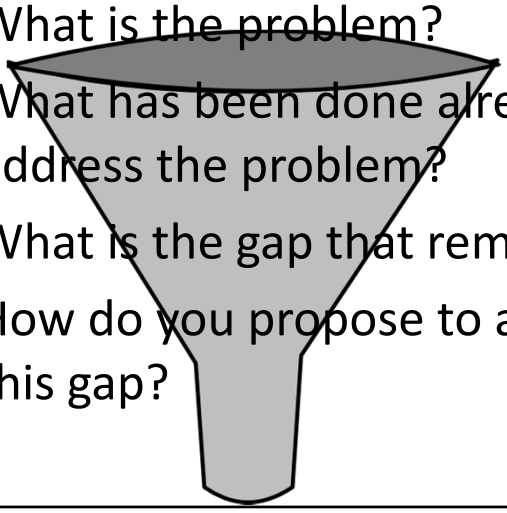
Build the Storyline

Logic flow goes from broad to narrower

- What is the problem?
- What has been done already to address the problem?
- What is the gap that remains?
- How do you propose to address this gap?



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Build the Storyline

What does this look like in NIH submission? Specific aims page template

Example of NIH-Style Outline

Specific Aims Page (1 page limit)

- State what is the human health problem. Write a compelling first sentence.
- Summarize what has been done already to address this problem.
- Clearly articulate the gap that still exists
- State how you propose to address this gap?
  - Can have overarching hypothesis at this point and put the word ***hypothesis*** in bold italics.
  - May be appropriate to: state technologies you plan to use, describe expertise to do a task, map past accomplishments to your proposed work, explain the biology further, state how your aims work together
  - State how this work is innovative

Aim 1: List your concrete objective here in bold run-on header starting with strong verbs such as *identify, quantify, establish, determine*

- Describe each aim in one to three sentences.
- Can have working hypothesis if needed (Aim must test hypothesis)
- Can tie to preliminary data
- Convey the "why" this work needs to be done as well as the "what" will be done

Aim 2: List your concrete objective here in bold run-on header starting with strong verbs such as *identify, quantify, establish, determine*

- Describe each aim in one to three sentences.
- Can have working hypothesis if needed (Aim must test hypothesis)
- Can tie to preliminary data
- Convey the "why" this work needs to be done as well as the "what" will be done

Aim 3: List your concrete objective here in bold run-on header starting with strong verbs such as *identify, quantify, establish, determine*

- Describe each aim in one to three sentences.
- Can have working hypothesis if needed (Aim must test hypothesis)
- Can tie to preliminary data
- Convey the "why" this work needs to be done as well as the "what" will be done

- End with final paragraph on the expected outcomes of the research. What will you deliver/enable when you are successful? Should be at least one outcome per specific aim but also a general outcome

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Build the Storyline

Specific aims page is critical. You must make a good first impression.

- State what is the human health problem. Write a compelling first sentence.
- Summarize what has been done already to address this problem.
- Clearly articulate the gap that still exists
- State how you propose to address this gap?
  - Can have overarching hypothesis at this point and put the word ***hypothesis*** in bold italics.
  - May be appropriate to: state technologies you plan to use, describe expertise to do a task, map past accomplishments to your proposed work, explain the biology further, state how your aims work together
  - State how this work is innovative

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Build the Storyline

Example storyline starts your specific aims page

What is the problem?
What has been done already to address this problem?
What is the gap that remains?
How do you propose to address this gap?

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 and effective model organism that can be robotically prepared and imaged, but existing image-analysis methods are insufficient for most assays. We propose to develop algorithms for the analysis of high-throughput C. elegans images, validating them in three specific experiments to identify chemicals to cure human infections and genetic regulators of host response to pathogens and fat metabolism. Novel computational tools for automated image analysis of C. elegans assays will make whole animal screening possible for a variety of biological questions not approachable by cell-based 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:

Carolina Wählby of the Broad Institute
http://www.niaid.nih.gov/researchfunding/grant/pages/appsamples.aspx

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Writing Your Aims

What you will accomplish, your approach, and impact. Two to four aims.

Aim 1: List your concrete objective here in bold run-on header starting with a strong verb

Describe each aim in one to three sentences.

- Can have working hypothesis if needed
- Can tie to preliminary data
- Convey the “why” this work needs to be done as well as the “what” will be done

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Writing Your Aims

Strong vs weak specific aim verbs

Weak: Investigate, study, correlate, describe

Strong: identify, determine, define, establish, quantify

Weak tends to not have a definitive end point.

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Writing Your Aims

What you will accomplish, your approach, and impact

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 and effective model organism that can be robotically prepared and imaged, but existing image-analysis methods are insufficient for most assays. We propose to develop algorithms for the analysis of high-throughput C. elegans images, validating them in three specific experiments to identify chemicals to cure human infections and genetic regulators of host response to pathogens and fat metabolism. Novel computational tools for automated image analysis of C. elegans assays will make whole animal screening possible for a variety of biological questions not approachable by cell-based 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.

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Innovation and Impact

Summarize long-term impact at end of specific aims page

Carolina Wählby's paragraph after her three specific aims:

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)……, (b)…., and (c)….

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Specific Aims Page is the Master Plan

Provides a map of the rest of your proposal

- Significance **STORYLINE INTRO**
- Innovation
- Approach

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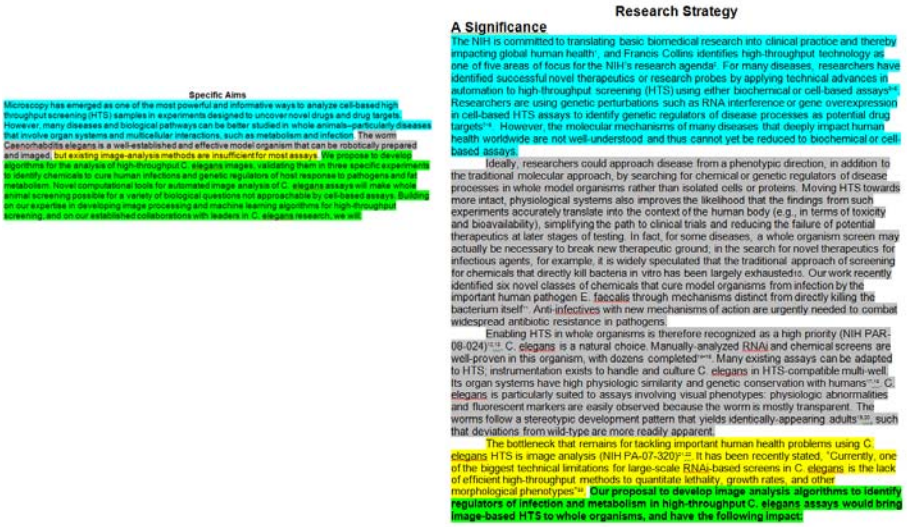
Significance Section Elaborates on Story

Storyline in specific aims serves as a preview.



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 and effective model organism that can be robotically prepared and imaged, but existing image-analysis methods are insufficient for most assays. We propose to develop algorithms for the analysis of high-throughput C. elegans images, validating them in three specific experiments to identify chemicals to cure human infections and genetic regulators of host response to pathogens and fat metabolism. Novel computational tools for automated image analysis of C. elegans assays will make whole animal screening possible for a variety of biological questions not approachable by cell-based 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

Research Strategy

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.

Ideally, researchers could approach disease from a phenotypic direction, in addition to the traditional molecular approach, by searching for chemical or genetic regulators of disease processes in whole model organisms rather than isolated cells or proteins. Moving HTS towards more intact, physiological systems also improves the likelihood that the findings from such experiments accurately translate into the context of the human body (e.g., in terms of toxicity and bioavailability), simplifying the path to clinical trials and reducing the failure of potential therapeutics at later stages of testing. In fact, for some diseases, a whole organism screen may actually be necessary to break new therapeutic ground; in the search for novel therapeutics for infectious agents, for example, it is widely speculated that the traditional approach of screening for chemicals that directly kill bacteria in vitro has been largely exhausted[10]. Our work recently identified six novel classes of chemicals that cure model organisms from infection by the important human pathogen E. faecalis through mechanisms distinct from directly killing the bacterium itself[11]. Anti-infectives with new mechanisms of action are urgently needed to combat widespread antibiotic resistance in pathogens.

Enabling HTS in whole organisms is therefore recognized as a high priority (NIH PAR-08-024)[12,13]. C. elegans is a natural choice. Manually-analyzed RNAi and chemical screens are well-proven in this organism, with dozens completed[14-16]. Many existing assays can be adapted to HTS; instrumentation exists to handle and culture C. elegans in HTS-compatible multi-well. Its organ systems have high physiologic similarity and genetic conservation with humans[17,18]. C. elegans is particularly suited to assays involving visual phenotypes: physiologic abnormalities and fluorescent markers are easily observed because the worm is mostly transparent. The worms follow a stereotypic development pattern that yields identically-appearing adults[19,20], such that deviations from wild-type are more readily apparent.

The bottleneck that remains for tackling important human health problems using C. elegans HTS is image analysis (NIH PA-07-320)[21]. It has been recently stated, "Currently, one of the biggest technical limitations for large-scale RNAi-based screens in C. elegans is the lack of efficient high-throughput methods to quantitate lethality, growth rates, and other morphological phenotypes"[22]. **Our proposal to develop image analysis algorithms to identify regulators of infection and metabolism in high-throughput C. elegans assays would bring image-based HTS to whole organisms, and have the following impact.**

Specific Aims Page is the Master Plan

Provides a map of the rest of your proposal

- Significance **STORYLINE INTRO**
- Innovation **CLOSING PARAGRAPH**
- Approach

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Innovation and Impact

Summarize long-term impact at end of specific aims page

Carolina Wählby's paragraph after specific aims:

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.

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Specific Aims Page is the Master Plan

Provides a map of the rest of your proposal

- Significance **STORYLINE INTRO**
- Innovation **CLOSING PARAGRAPH**
- Approach **AIMS**

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Writing Your Aims

What you will accomplish, your approach, and impact

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

Your research must solve a critical problem

- write for a broad scientific audience
- Answers the "**so what?**" not the "**how**." If your research works as proposed, will your results be important for the field?
- addressing the gap should be a natural extension of your research

22

Innovation

Not status quo but enabling a new direction to the research area

- innovation can be in your new theory or in your novel methods and tools
- best if you include both

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Approach

Describes your experimental design

- Is your project workable as described?
- When you are done, will the results be clear?
- relate each specific aim back to your storyline and show how results will help address gap

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Preliminary Data

Purpose is extension and feasibility

- naturally extends your existing research but not merely incremental advances
- assures reviewers that what you propose will be feasible

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Two Options for Preliminary Data

Outline to be consistent in format for a well-structured approach section

Title of Specific Aim #1

Introduction to Approach

Justification and Feasibility

Review of relevant literature

Preliminary studies

Research Design

Expected Outcomes

Potential Problems and Alternative Strategies

26

Two Options for Preliminary Data

Outline to be consistent in format for a well-structured approach section

Preliminary Studies (for all the aims together)

Title of Specific Aim #1 (verbatim from your specific aims section)

– Introductory paragraph

Research Design

Expected Outcomes

Potential Problems and Alternative Strategies

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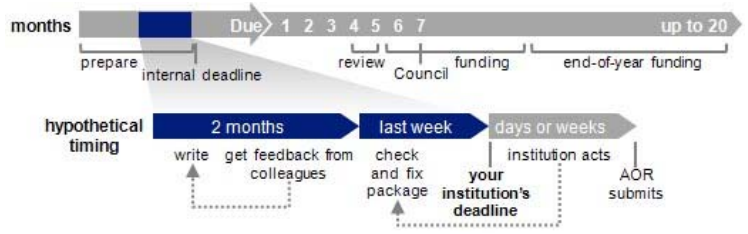
Internal Review

We can help find experienced reviewers to provide feedback

NIH Writing Timeline



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Questions?

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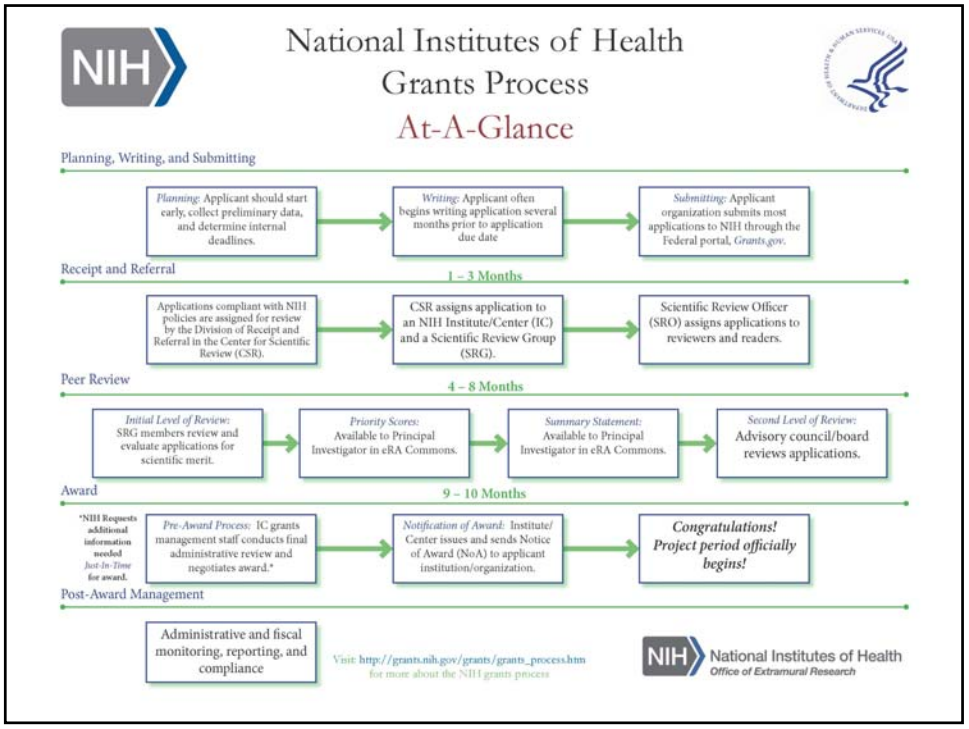
More about NIH

Perry Kirkham



Scientific Review

From submission through review

Scientific Review Officers

1. Center for Scientific Review
   - Standing study sections
   - Special Emphasis Panels
2. Internal IC reviews
   - Standing study sections
   - Special Emphasis Panels

Center for Scientific Review

Twofold Mission:

1. Assign proposals

Receipt and referral –

a. read as much of the proposal as necessary to make an appropriate assignment (suitability, IC, dual assignment, review)

b. consider the PI request

Center for Scientific Review

Twofold Mission:

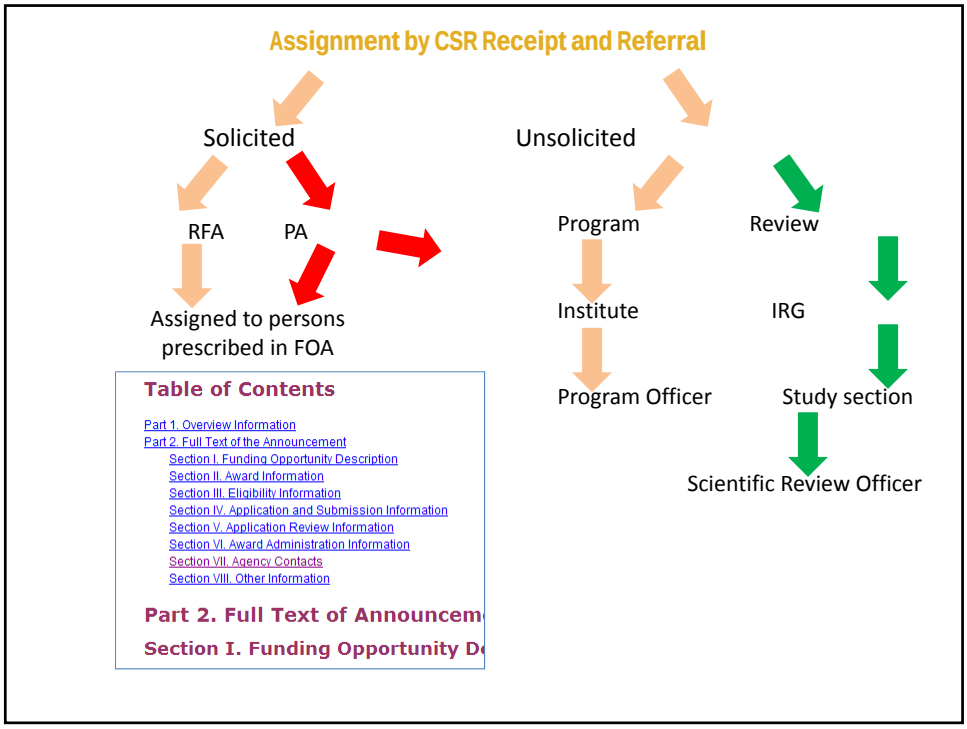
2. achieve optimal peer review

Peer Review – IRG (study section)

http://cms.csr.nih.gov/PeerReviewMeetings/CSRIRGDescriptionNew/

CB – Cell Biology (IRG)

- BDPE – biology and diseases of the posterior eye (SS)
- NCSD – nuclear and cytoplasmic structure/function and dynamics (SS)
- CMAD – cellular mechanisms in aging and development (SS)
- CSRS – cellular signaling and regulatory systems (SS)
- DEV1- development 1 (SS)
- DEV2 – development 2 (SS)


Assignment by CSR Receipt and Referral
Solicited
Unsolicited
RFA
PA
Program
Review
Assigned to persons prescribed in FOA
Institute
IRG
Program Officer
Study section
Scientific Review Officer
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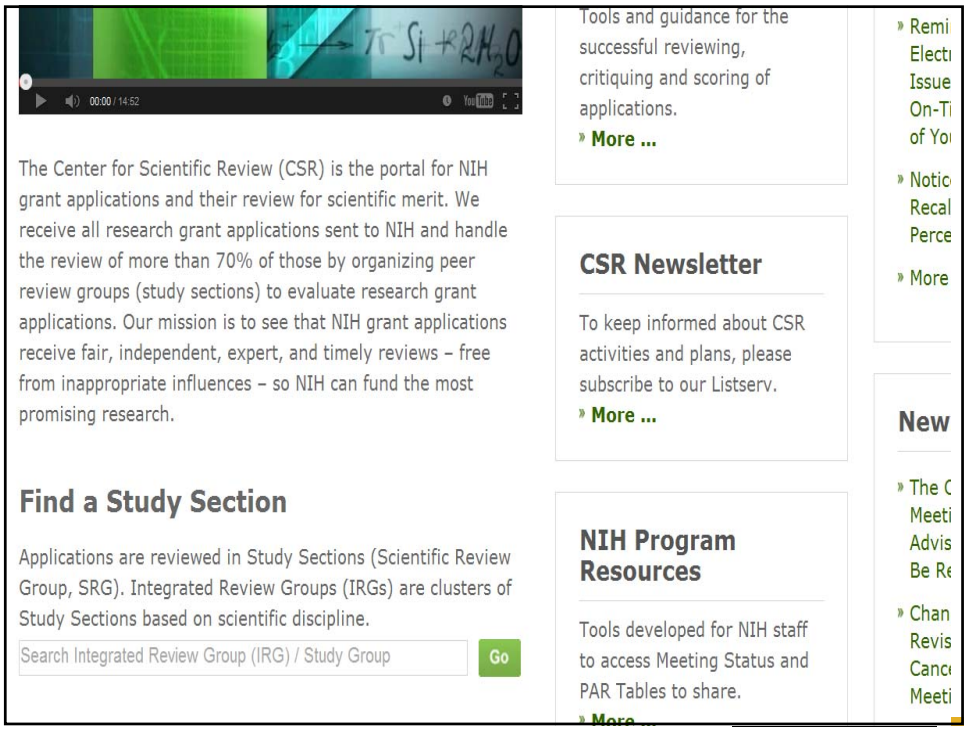
Part 2. Full Text of Announcem
Section I. Funding Opportunity D


The Center for Scientific Review (CSR) is the portal for NIH grant applications and their review for scientific merit. We receive all research grant applications sent to NIH and handle the review of more than 70% of those by organizing peer review groups (study sections) to evaluate research grant applications. Our mission is to see that NIH grant applications receive fair, independent, expert, and timely reviews – free from inappropriate influences – so NIH can fund the most promising research.
Find a Study Section
Applications are reviewed in Study Sections (Scientific Review Group, SRG). Integrated Review Groups (IRGs) are clusters of Study Sections based on scientific discipline.
Search Integrated Review Group (IRG) / Study Group
Go
Tools and guidance for the successful reviewing, critiquing and scoring of applications.
More ...
CSR Newsletter
To keep informed about CSR activities and plans, please subscribe to our Listserv.
More ...
NIH Program Resources
Tools developed for NIH staff to access Meeting Status and PAR Tables to share.
New

Center for Scientific Review

Study Section

BDPE

http://cms.csr.nih.gov/PeerReviewMeetings/CSRIRGDescriptionNew/CBIRG/BDPE.htm

Topics covered

Membership roster (standing members) **

Meeting roster (reviewers for a specific meeting)

SRA (SRO)

Study sections with areas of similar science

Scientific Review

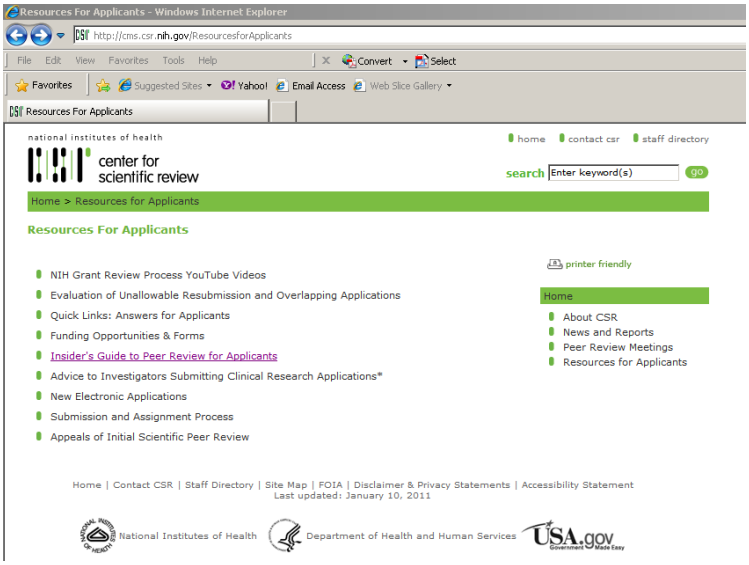
Choosing a study section

Not always necessary

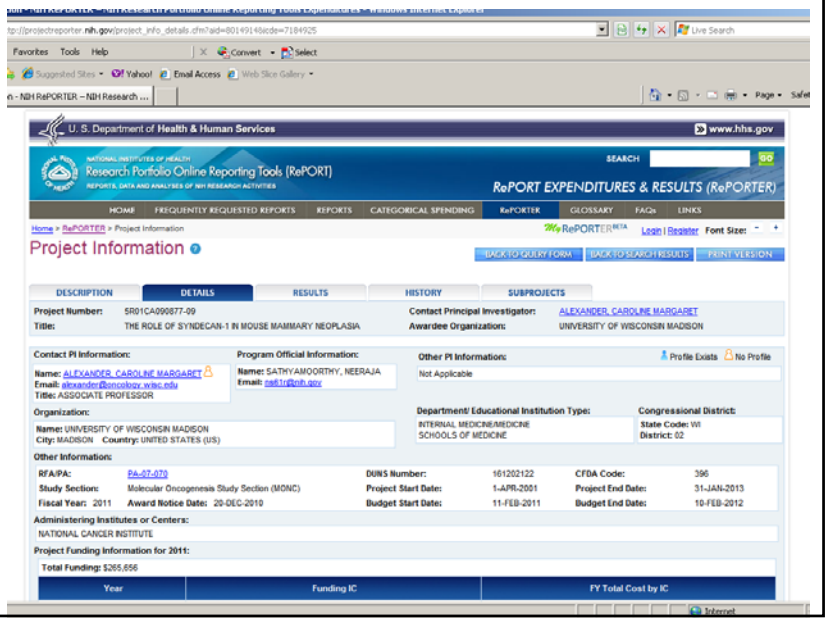
If desired, do your homework well!

- CSR website – look for keywords
- RePorter – look for keywords
  - look for topics
  - look for colleagues

What are they looking for?



What are they looking for?



Response to Scientific Review

Summary Statement

- Who is the program officer?
- What are the salient points?
- Who made the salient points?
- Which of those can you address easily?
- Which must you address?
- What do you do if you disagree?
- What is not in the text?
- What is the "tenor" of the discussion

SUMMARY STATEMENT
(Privileged Communication)

PROGRAM CONTACT:
JOSEPH GINDHART JR
301-594-0828
gindhartjg@mail.nih.gov

Release Date: 06/09/2010

Application Number: 1 R01 GM095672-01

Principal Investigator

WAHLBY, CAROLINA EWA ASA PHD

Applicant Organization: BROAD INSTITUTE, INC.

Review Group: MI
Microscopic Imaging Study Section

Meeting Date: 06/03/2010
Council: OCT 2010
Requested Start: 12/01/2010

RFA/PA: PA10-067
PCC: C104GJ

Project Title: Image analysis for high-throughput C. elegans infection and metabolism assay

SRG Action: Impact/Priority Score: 10 Percentile: 2
Human Subjects: 10-No human subjects involved
Animal Subjects: 10-No live vertebrate animals involved for competing appl.

Response to Scientific Review

What next?

- Go forward with a revision?
- Go forward with a new application?
- Revise but request a different study section?
- Write a new application using the same study section?

Office of Proposal Development Tufts University 9/15/2010

"It was generally seen that integrating preliminary data with the appropriate aim was an effective approach. Both too little preliminary data and too much preliminary data were seen as ineffective. "Shortchanging" preliminary data hurt scores, particularly if the data were relevant to the innovation. Even with published data, including enough context is key. The proposal should be able to stand on its own, and the burden is on the applicant to make certain that there is enough information for the reviewers."

"The most consistently effective strategy for the Approach was to treat each aim like a story. These proposals integrated necessary background information and preliminary data into the approach for each aim.:

"Some investigators chose to "save space" by not using any figures. This was considered a major failing. Lack of figures or tables and lack of white space indicated that the grant writer was having difficulty adapting to the new format, and this approach was not viewed favorably."