Grant Writing 101 - Clear and Compelling Scientific Aims Pages
What about me?

University of Virginia
PhD in Biology 1996

Cleveland Clinic
Postdoc ‘97–‘02

Professor, Biochemistry and Molecular Biology
RWJMS ‘02 – present
  • continuous NIH funding since 2003.
Director of Research Development since 2015

- Grantwriting support for new faculty
- Run internal funding programs
- Facilitate large interdisciplinary grant submissions
- Core Facility Strategic Plan
NIH Funded Training Program to train Grant-writing Coaches

• Rick McGee, PhD, Professor of Medical Education
  • Associate Dean for Professional Development
Basics of Grant Writing...

in a word:

Clarity
What do you have to achieve in a proposal?

- Demonstrate the research you are proposing is important, feasible, a logical next step, and hopefully innovative/novel.
- Show that you really understand the field, both the broad topic and the precise niche you are in – including best techniques.
- Show that you are actually working in the field (preliminary data).
- Demonstrate your prior research accomplishments are excellent and appropriate for your career stage.
- Write in a way that is crystal clear with every word serving a purpose – and for multiple types of reviewers.
- Convince the reviewers that you are a legitimate member of the elite NIH-funded research community (conform!)
Understanding the Review Process

In science we write for reviewers. To be a successful writer you have to start from an understanding of:

- What reviewers are used to seeing
- What they want to see
- The criteria they are using to judge what they read
- Their likely approaches to their task
  - Knowing and writing to these shows you are legitimate

Your task is to turn the reviewer into your advocate:

- Make the work of the reviewer as simple as possible
- Convince them your work is VERY important
- Convince them you know what you are doing and you can conduct the research you propose
Review in numbers: A typical study section might get 70 grants. Each grant is reviewed by 3 people. The primary reviewer is usually an expert in the field, but the others may not be. Only about half of the grants get discussed. The entire panel submits a numerical score based on discussion. Approximately 10-15% will be funded.
Writing for different types of reviewers

The expert, someone who knows as much, or more, about the topic as you do

The sophisticated non-expert

The skilled scientist who knows almost nothing about your specific topic

The technical expert – e.g. biostatistician or epidemiologist

KNOW YOUR REVIEWERS!!! You are writing for THEM.
Specific Aims
- a one page summary of the entire project.

Significance
- A concise description of why your research is important in the context of human health – why should this be funded by NIH?

Innovation
- A concise description of innovative methods or approaches – how is this cutting edge research?

Approach
- Detailed experimental plan including context, preliminary data, hypothesis and proposed experiments.
Why Focus on Specific Aims?

Specific Aims • a one page summary of the entire project.

If a reviewer only reads one thing, it will be the Specific Aims Page
Describe a good one page summary

- **Clear**
  - Simple flowing narrative

- **Compelling**
  - Amazing ideas and preliminary data

- **Story**
  - Reviewer starts reading full proposal immediately and with joy
The Writing is Key

Clear

- Write short, active, logically placed sentences

Compelling

- Amazing ideas and preliminary data

Story

- Use topic sentences and fiercely maintain logical flow
What does a reviewer expect to get from the Specific Aims Page?

Evidence that you are an expert in the field

A clearly stated significant problem and testable hypotheses

A series of creative experiments that expertly test the hypotheses

Enough information to make a preliminary determination about score

Evidence that the rest of the grant will be easy to read and interesting
The beginning of a specific aims page is comprised of rhetorical (repeating) patterns

- Broad Context
- Narrow Context
- Problem
- Testable Hypothesis

Expert audience – funnel has steep sides (get to the meat of it quickly)
General audience – funnel has shallow sides (more context is needed)
The rhetorical pattern can be expressed as questions. Write a draft of the first paragraph by answering these questions:

- **Broad Context – What is known?**
  - Just enough background to set the stage

- **Narrow Context – How has your work contributed to what is known?**
  - Key prior findings

- **Problem – What are the outstanding problems?**
  - While $x$ is known, $y$ is not

- **Testable Hypothesis – How do you propose to solve the problem?**
  - Our overarching hypothesis is…

The second paragraph – same pattern just with narrowing context (more detail)
The rhetorical pattern can be expressed as questions

- **Broad Context – What is known?**
  - Precise state of the art relevant to the project

- **Narrow Context – How has your work contributed to what is known?**
  - Sneak peak at preliminary data

- **Problem – What are the outstanding problems?**
  - More specific statement of scientific premise

- **Testable Hypothesis – How do you propose to solve the problem?**
  - Our specific overall hypothesis is…
    - The specific hypotheses will appear in the aims themselves
The first sentence is unique and important— which is best?

1. Basic principles of material transport indicate that the spatial structure of biofilm infections must impact intercellular signaling, virulence, and antibiotic resistance.

2. Most chronic bacterial infections are caused by biofilms, aggregated bacteria that are embedded in a matrix of polymer and protein.

3. Bacterial infections are deadly manifestations of microbial growth.

First sentence should establish significance without being too general or too specific
Anatomy of a Specific Aims Page

Specific Aims
Selenium is an essential trace element that is incorporated into 25 human proteins as the amino acid selenocysteine (Sec). The proteins that contain Sec (selenoproteins) are essential for many cellular functions including combatting oxidative stress, thyroid hormone production and protein folding. Sec is incorporated at specific UGA codons that would otherwise signal translation termination. A specialized set of factors are known to be required for Sec incorporation: a specialized elongation factor that delivers the Sec-IRNAsec to the ribosome and unique RNA binding proteins that bind to a Sec insertion sequence (SECIS) in selenoprotein mRNA 3’ UTRs. This SECIS-protein complex signals the ribosome to incorporate Sec instead of translation termination. Our prior work has provided molecular characterization of each of the required factors, but the mechanism by which they interact with each other and other cellular components to allow Sec incorporation remains unknown. In addition, we provide preliminary evidence that the processive incorporation of 10 Sec residues into the selenium transport protein Selenoprotein P (SELENOP) requires a unique mechanism and additional factors. The overall goals for this proposal are to determine the mechanism by which SECIS binding proteins promote single and multiple Sec incorporation events.

All vertebrates possess two SECIS binding proteins encoded by separate genes: SECISBP2 (SBP2) and SECISBP2L. While the mechanism of action for SBP2 is coming into focus, the role for SECISBP2L in Sec incorporation has not been deciphered. Our preliminary data shows that SECISBP2L is essential for the processive incorporation of Sec into Selenoprotein P. As such, we have established three model systems to study the synthesis of SELENOP: in vitro translation, expression in transfected mammalian cells and a zebrafish system that will allow unprecedented access to the role of selenoprotein function during development. These are also leveraged and combined with structural biology and transcriptomics to determine how synthesis of the entire selenoproteome is regulated by SECIS binding proteins.

Aim 1: Decipher the mechanism by which SECIS elements and SECIS binding proteins enable processive Sec incorporation into the selenium transport protein, SELENOP.

We have identified a discrete sequence in the SELENOP SECIS element that is absolutely required for processive Sec incorporation. We propose to determine all of the features that allow a SECIS element to promote processive Sec incorporation via the following:

a) Identify and characterize the RNA binding proteins that interact specifically with processive SECIS elements.
b) Reconstitute processive Sec incorporation in the plant based system that we established to determine the fundamental requirements for Sec incorporation in vitro.
c) Determine the structures of processive and non-processive SECIS elements by X-ray crystallography.

Aim 2: Utilize a zebrafish model system to determine the function of SECISBP2L and the mechanism of SELENOP synthesis in vivo.

We present preliminary data that loss of SECISBP2L in zebrafish results in defects in SELENOP synthesis and the appearance of vascular defects in early zebrafish embryos. Using this highly tractable vertebrate model system in combination with CRISPR modified cells, we propose to:

a) Analyze selenoprotein expression and developmental defects in SECISBP2L null fish and use SECISBP2L null mammalian cells to characterize its role in processivity.
b) Perform transcriptomics and sequencing of ribosome protected fragments in SECISBP2L null fish.
c) Generate SELENOP knockout fish to lay the groundwork for the study of SELENOP synthesis and function in vivo.

Aim 3: Determine the molecular basis for differential selenoprotein expression.
Although mammalian SECIS sequences are very diverse, sequence alignments of individual SECIS elements across vertebrates reveal conserved sequences that have not been characterized. We predict that these sequences impact the binding of SBP2 and/or SECISBP2L. Thus, we will:

a) Test the functions of novel conserved sequences in all human SECIS elements.
b) Identify selenoproteins whose expression persists in the absence of SBP2 and determine mechanism of expression.

Understanding the mechanism of Sec incorporation is an essential part of deciphering the molecular basis for the biological effects of selenium: defining its role in redox homeostasis, metabolism, cancer and male fertility.
Five Principles of Clear Writing

1. **Sequence Old to New**
   • Proper connection between concepts

**BAD:**
All experiments will be conducted with stromal cells isolated from normal endometrium and diseased endometriotic tissue. Informed consent will be obtained under a protocol approved by the IRB to acquire the tissue.

**GOOD:**
All experiments will be conducted with stromal cells isolated from normal endometrium and diseased endometriotic tissue. The tissue will be obtained under informed consent under a protocol approved by the IRB.
2. Sequence Light to Heavy

• Put the subject early and succinctly – get to the point quickly

BAD:
High resolution, simple phasing and selection of stable states are the three benefits of Xray crystallography.

GOOD:
Xray crystallography provides three benefits, which include high resolution, simple phasing and selection of stable states.
3. Use Transitional Words to improve flow

**Addition:** Also, too, again, in addition, next, finally, last  
**Comparison:** Similarly, likewise, like  
**Contrast:** But, yet, however, on the other hand, on the contrary  
**Enumeration:** first, second, third  
**Illustration:** That is, for example, for instance  
**Place:** Here, there, just to the right of  
**Result:** Therefore, thus, consequently  
**Summary:** In other words, in fact, in summary  
**Time:** Immediately, then, soon after, later

BAD:  
Researchers have made great strides in diagnosing Alzheimer’s disease early and accurately. Physicians who examined an older patient who seemed out of touch with reality used to have to guess whether the person was senile or had Alzheimer’s. Physicians are able to use new and more reliable tests. These tests raise their own problems.

GOOD:  
In recent years, researchers have made great strides in diagnosing Alzheimer’s disease early and accurately. Not too long ago, when a physician examined an older patient who seemed out of touch with reality, the physician had to guess whether the person was senile or had Alzheimer’s. In the past few years, however, physicians have been able to use new and more reliable tests. Nevertheless, these tests raise their own problems.
4. Use Echo Words

• Consider prior and subsequent sentence - be consistent – don’t be artistic

BAD:
Histological examination of biological and medical specimens has gained its universality and undisputed significance through distinct staining techniques and microscopical evaluation. Discrimination of tissue types after specific staining and labeling is an essential prerequisite for histopathological investigation, for example in accurate diagnosis of cancer. Histochemical staining techniques can only be used in a targeted manner for known compounds, and only a limited number of such targets can be visualized from a given sample at the same time. Another limitation of classical histology lies in the fact that a considerable amount of experience is required and that even well-trained pathologists often interpret histologically stained sections differently.

GOOD:
Histological examination of tissue has gained its universality and undisputed significance through distinct staining techniques and interpretation with microscopical visualization. Discrimination of tissue types after specific staining and visualization is an essential prerequisite for histopathological investigation, for example in accurate diagnosis of cancer. But histochemical staining techniques have two limitations. First, the techniques can only be used in a targeted manner for known compounds, and only a limited number of such targets can be visualized from a given tissue sample at the same time. Second, interpreting a histochemically stained tissue requires a considerable amount of experience, and even well-trained pathologists often interpret histologically stained sections differently.
5. Use Strong Verbs

- Find important concept and use verb to describe what happens
- When possible, use the active voice
- Identify the real actors

BAD:
In a study of mouse tumor models, previously characterized tumor-penetrating peptide iRGD was shown to increase vascular and tissue permeability in a tumor-specific and neuropilin-1-dependent manner.

BETTER:
A study of mouse tumor models showed that previously characterized tumor-penetrating peptide iRGD increased vascular and tissue permeability in a tumor-specific and neuropilin-1-dependent manner.

BEST:
Prior work demonstrated that the tumor penetrating peptide iRGD increase vascular and tissue permeability in a tumor-specific and neuropilin-1-dependent manner.
Paragraph Structure – Use a Topic Sentence and Stick to the Topic

- Topic Sentence: Sets the stage - defines the subject of a paragraph
- Supporting Sentence: Logical Flow
What about the rest of the grant?

<table>
<thead>
<tr>
<th>Significance</th>
<th>~2 pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Essential background that tells a story about the importance of your project in the context of human health.</td>
<td></td>
</tr>
<tr>
<td>• Try starting by writing the 10 or so topic sentences that will outline the whole section</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Innovation</th>
<th>~1 page</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lays out key innovation in your project. Avoid trying to make something ordinary sound innovative.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Approach</th>
<th>~up to the 12 page max</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Essential background, preliminary data, hypothesis and experimental plan for each sub-aim.</td>
<td></td>
</tr>
<tr>
<td>• End each sub-aim with an “expected results and potential pitfalls” section.</td>
<td></td>
</tr>
</tbody>
</table>
Beneath the Writing: Other Key Points

- Get feedback on your ideas BEFORE honing the writing
- Read the Call (for proposals)
- Avoid dependence – don’t make the second part completely dependent on the first
- Find joy in the creative process – use the writing process to help ideas flow (don’t sweat the details on the first pass).
- Sell (but don’t oversell) your ideas and their impact.
- Read the Call again.
Opportunity is missed by most people because it is dressed in overalls and looks like work.

Thomas A. Edison
Other Resources

- Sample NIH grants (from NIDDK)
- NIH Peer Review Videos
- Rutgers Research Portal – links to research resources at Rutgers
- NIH Grantwriting for Success
- Budget Development Tips
- List of NIH Grant Types
- NIH Study Section Information
- Northwestern CLIMB program
Your turn!
NIH Information and Videos on Grant Review

• Videos worth spending 20 minutes viewing!!

• Guidelines for Reviewers