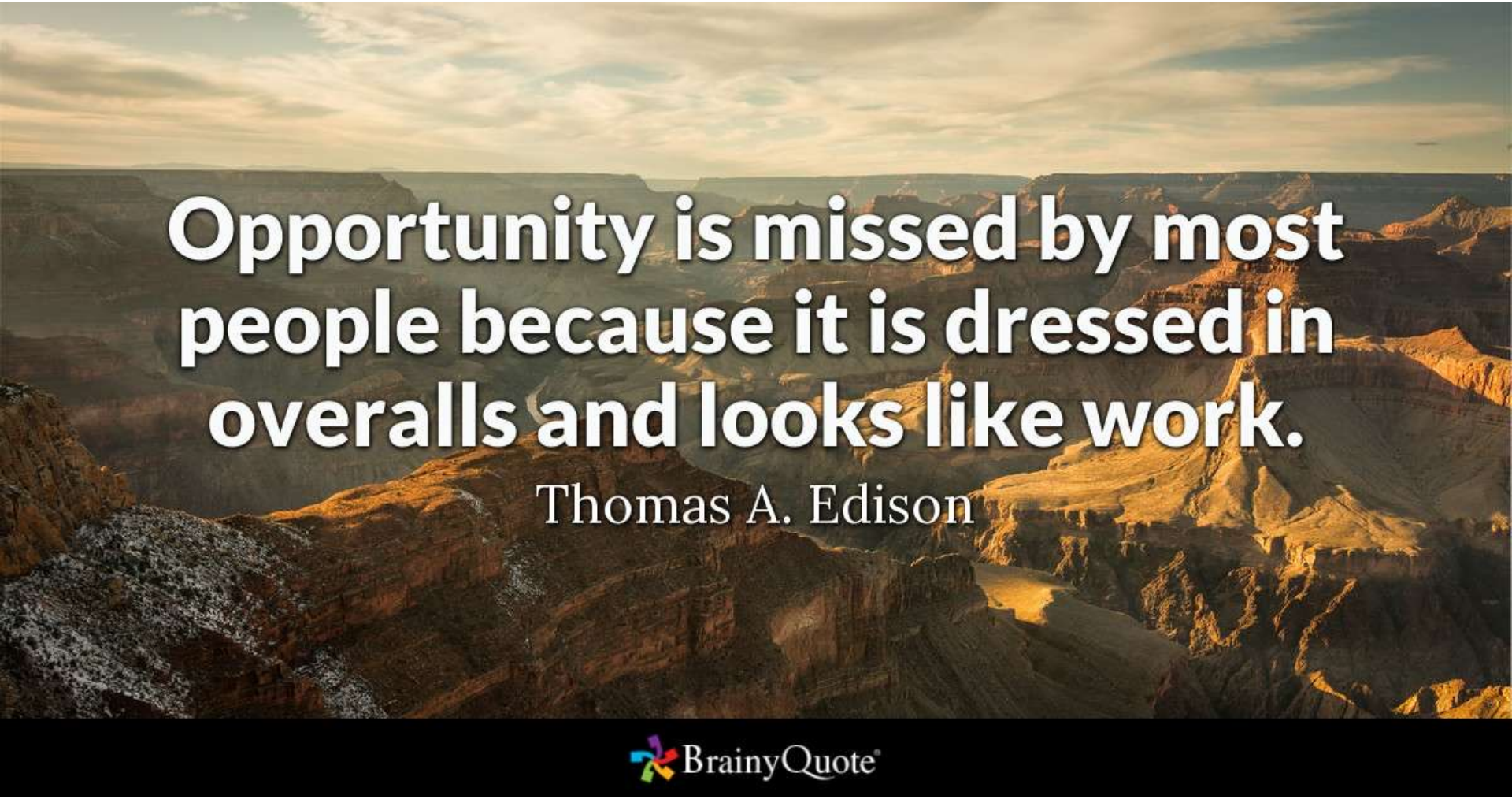
Grant Writing 101 - Clear and Compelling Scientific Aims Pages


Opportunity is missed by most people because it is dressed in overalls and looks like work.
Thomas A. Edison
BrainyQuote

This program originated at Northwestern

NIH Funded Training Program to train Grant-writing Coaches

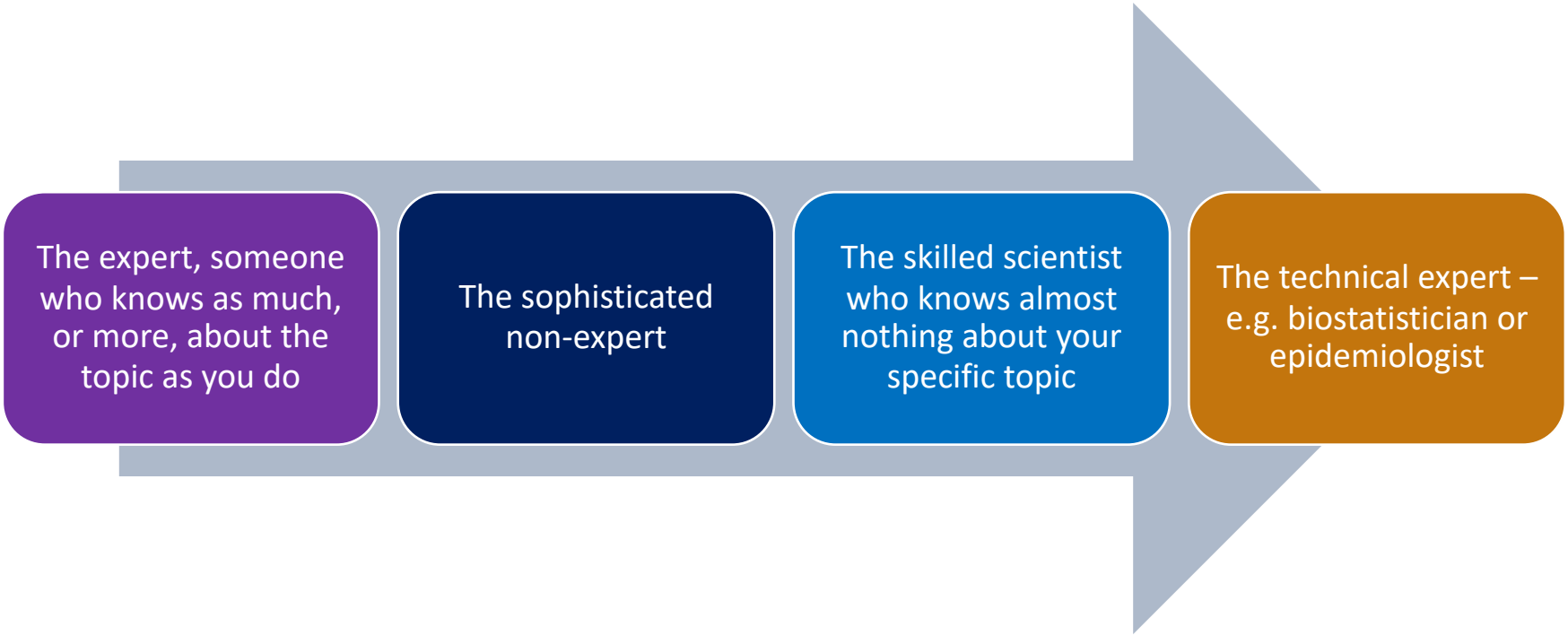
- Rick McGee, PhD, Professor of Medical Education
  - Associate Dean for Professional Development

Basics of Grant Writing…
in a word:

What do you have to achieve in a proposal?

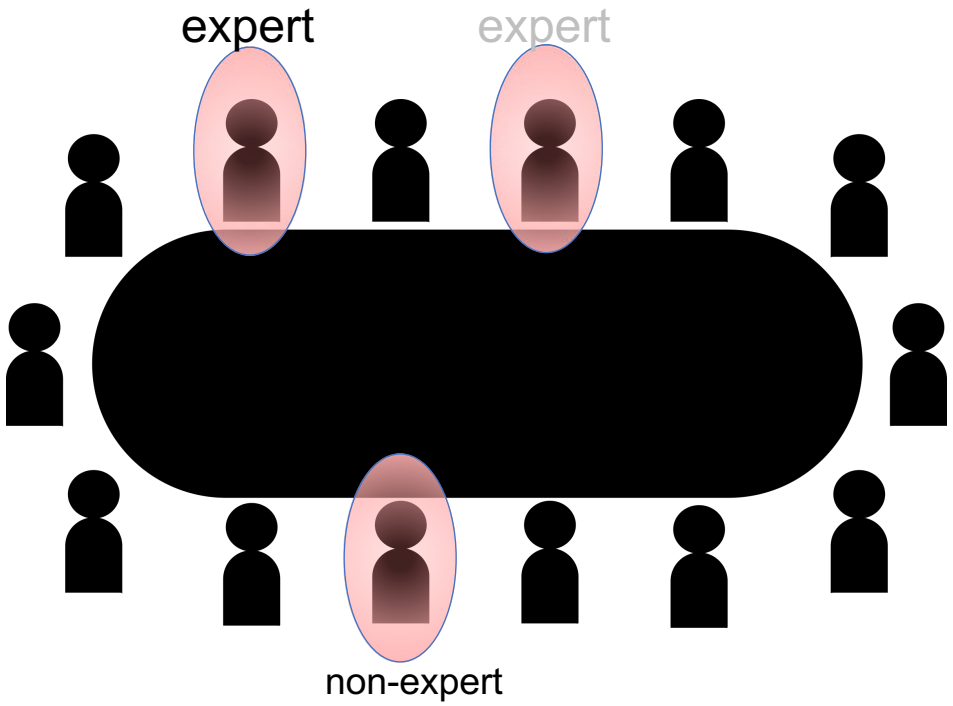
- Demonstrate the research you are proposing is important, feasible, a logical next step, and hopefully innovative/novel **(good idea!).**
- Show that you really understand the field, both the broad topic and the precise niche you are in – including best techniques **(you are an expert!).**
- Show that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

Writing for different types of reviewers



KNOW YOUR REVIEWERS!!! You are writing for THEM.

Understanding the Review Process



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.

Who are your reviewers

- Primary Reviewer
  - verbally presents your project to the group
  - Usually an expert in the field
- Secondary Reviewer
  - Supports or rebuts primary reviewer comments – adds more
  - May or may not be an expert
- Tertiary Reviewer
  - Also supports or rebuts primary reviewer
  - Often not an expert
- After discussion, all members of the the group submits scores and “vote their conscience.”
- Any reviewer who voices strong negative opinions can often sway the group and send scores down.

NIH Grant Sections

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.

Our focus will be on the Specific Aims Page
(Similar to Project Summary for NSF)

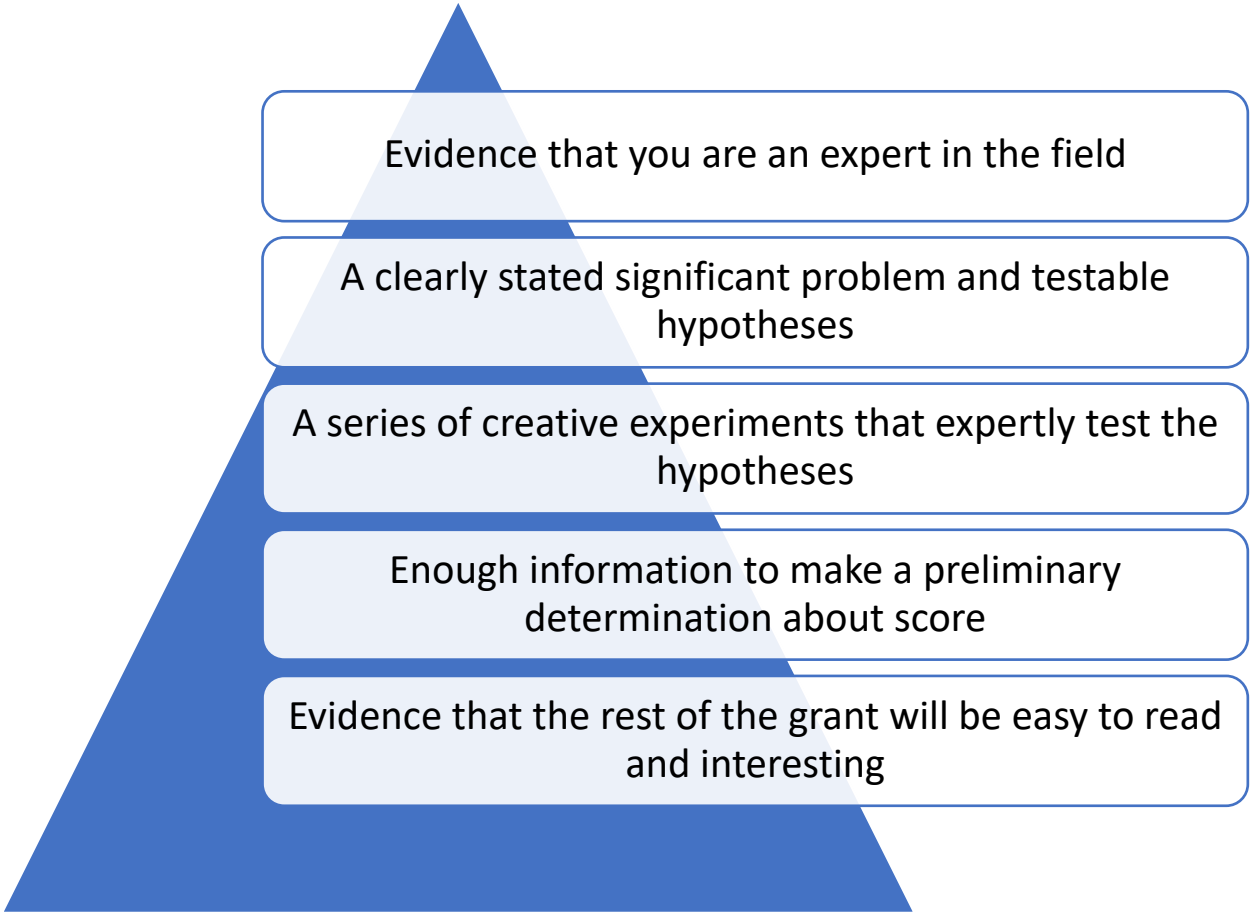
Why Focus on Specific Aims?

Specific Aims

- a one page summary of the entire project.

If a reviewer only reads one thing, it will be the Specific Aims Page

What does a reviewer expect to get from 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

How do you do it?

Clear

- Write short, active, logically placed sentences

Compelling

- Amazing ideas and preliminary data

Story

- Use topic sentences and fiercely maintain logical flow

The Writing is Key

The beginning of a specific aims page is comprised of rhetorical (repeating) patterns

- Broad Context
- Narrow Context
- Problem
- Testable Hypothesis

General

Specific

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 same questions shape the second paragraph

- 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

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-tRNA^{Sec} 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.

Broad Context and Plan

Narrower Context and Plan

AIMS

- What are you going to do and how are you going to do it?
- Use of subaim bullet points allows some whitespace which improves readability

The first sentence is unique and important– which is best?

1. LVAD implantation significantly improves inpatient rehabilitation when compared to the same procedure performed in an outpatient setting.

2. End stage heart failure is often treated with a left ventricular assist device (LVAD), but the success of this treatment depends on the length of postoperative care.

3. Patient outcomes are affected by the length of hospital stay.

First sentence should establish significance without being too general or too specific

ART

Six Principles of Clear Writing

1. Sequence Old to New

- Proper connection between concepts

LESS CLEAR:
All analyses will be conducted with survey data derived from interviews. Instrument design was conducted using the minimum item articulation method.

MORE CLEAR:
All analyses will be conducted with survey data derived from interviews. The survey instrument design was conducted using the minimum item articulation method.

2. Sequence Light to Heavy

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

LESS CLEAR:
Mild to moderate upper limb impairment and loss of facial motor control are outcomes often experienced by patients who suffer from ischemia caused by stroke, and these symptoms are tightly correlated with specific brain imaging analyses.

MORE CLEAR:
Brain imaging can be used to quantify the severity of stroke outcomes such as mild to moderate upper limb impairment and loss of facial motor control.

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

LESS CLEAR:
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.

MORE CLEAR:
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

LESS CLEAR:
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 pre-requisite 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.

MORE CLEAR:
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

LESS CLEAR:
In a study of patients with recent ischemic stroke, previously analyzed patient data was shown to be coincidentally linked to prior exposure to hypoxia.

MORE CLEAR:
Exposure to hypoxia was recently linked to the incidence of ischemic stroke.

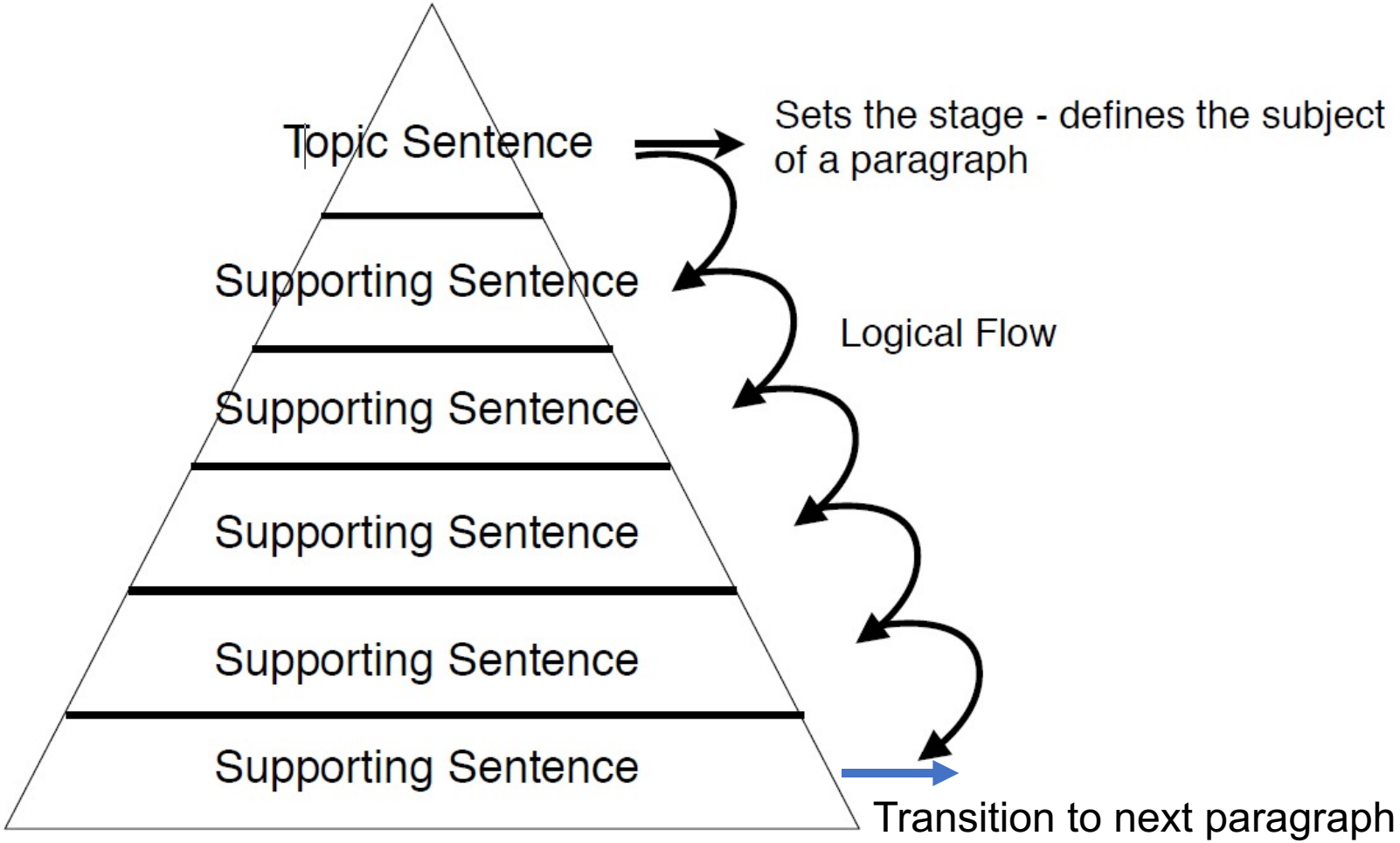
6. Avoid Parentheticals

- Keep sentences short and focused.
- Don't introduce tangential topics that won't be pursued in the current paragraph

LESS CLEAR:
Autism, a disease that affects more than 1.5 million children in the US alone, is a complex multi-dimensional disease that is commonly mis-diagnosed, and it is has recently been found to be more prevalent in people with mutations in the NDM1 gene

MORE CLEAR:
Autism is a prevalent and complex disease that has an unknown etiology. Recent evidence suggests that mutations in the NDM1 gene may correlate with autism diagnosis.

Paragraph Structure – Use a Topic Sentence and Stick to the Topic



What about the rest of the grant?

Significance ~1-2 pages

- Essential background that tells a story about the importance of your project in the context of human health.
  - Try starting by writing the 10 or so topic sentences that will outline the whole section

Innovation ~0.5 page

- Lays out key innovation in your project. Avoid trying to make something ordinary sound innovative.

Approach ~up to the 6-12 page max

- Essential background, preliminary data, hypothesis and experimental plan for each sub-aim.
  - End each sub-aim with an “expected results and pitfalls/alternatives” section.

Beneath the Writing: Other Key Points

Get feedback on your ideas BEFORE honing the writing – no amount of good writing can salvage bad science

Read the RFP (aka FOA, PA, CFP, etc)

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).

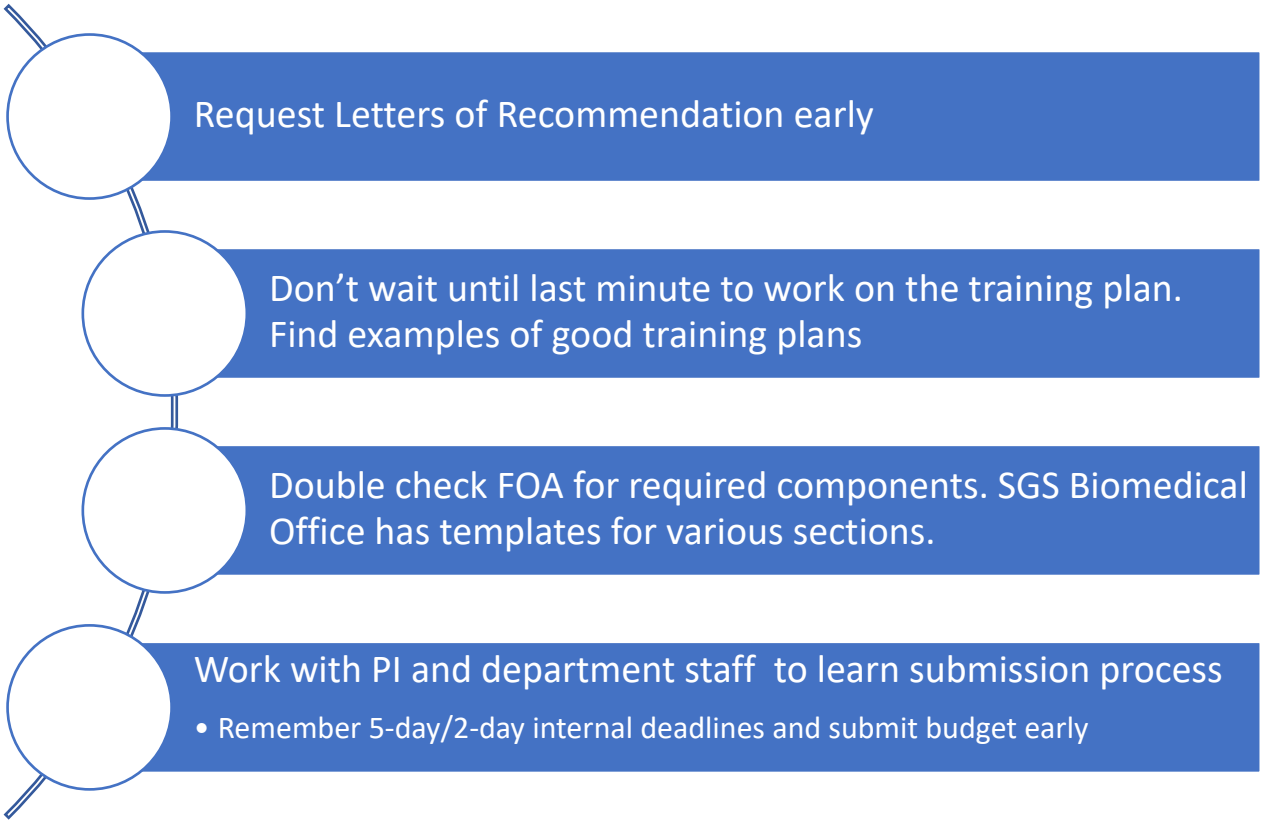
Use Figures liberally – an introductory model Figure can really help orient the reviewer.

Talk to the Program Officer – make sure your ideas are a good fit!

Other Resources

- Sample NIH grants (from NIDDK)
- Gradfund
- 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

Reminders for Fellowships



Grant Writing Class 2022 (1 credit)
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Phase 1

- Outline Experimental Plan
  - Get feedback on science

Phase 2

- Draft SA PAGE
  - Peer and mentor feedback
  - Sessions are recorded

Phase 3

- Draft an Aim
- Draft the Significance Section
  - Start with topic sentences

How do Grant Writing Groups Work?

- 2-4 months ahead of deadline, gather group of at most 6 people planning to submit
- Meet every other week or weekly
- Everyone brings hard copies of their Specific Aims page (enough for everyone)
- The entire group reads each SA page, one paragraph at a time and reacts to the writing (and the science)
- No need to pre-read SA pages ahead of time
- Each round of feedback is audio-recorded
- Simultaneously be working on other grant sections, applying concepts from SA page