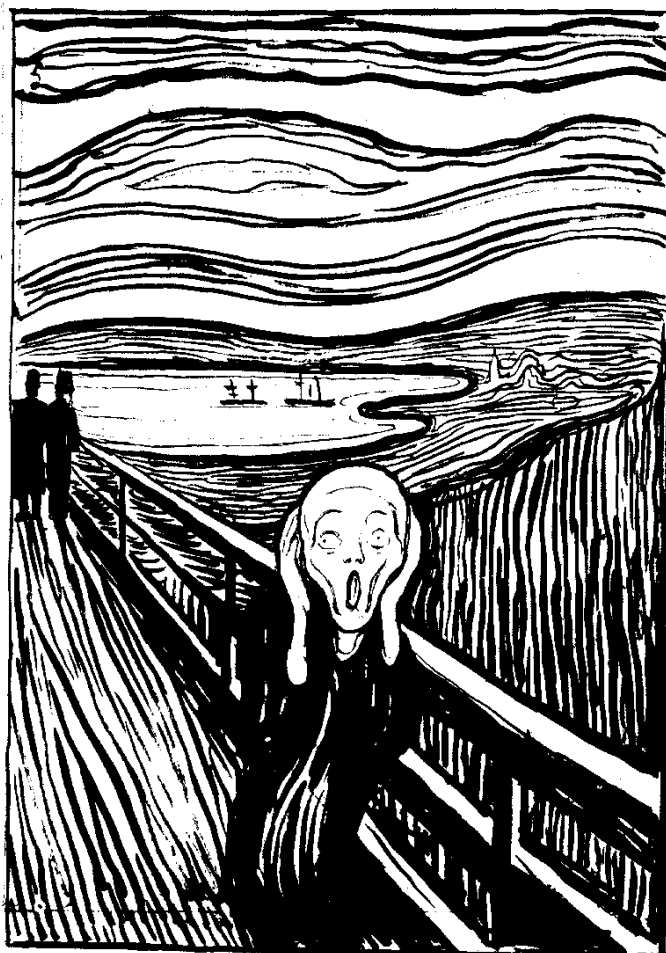


Course syllabus and reading materials

BIOC712: Scientific Writing

or... “Grant writing for grad students”



http://en.wikipedia.org/wiki/File:Munch_The_Scream_lithography.png

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BIOC 712: Scientific Writing Course (or... “Grant writing for grad students”)

Specific Aims of the course. Learn the craft of grantsmanship. Learn what it means to propose a research project that is significant, innovative and feasible.

Hypothesis. The ability to express your ideas clearly is one of the most important (and overlooked) attributes of a successful scientist.

Significance and Innovation. If you want to do important science, you must ask important questions. But if you want to do science at all, you will need to convince your audience that your work merits funding, and that your results are worth publishing. Grant reviewers must be able to understand your research objectives and their potential for new advances. Journal editors and reviewers must understand what you have accomplished and why anyone should care.

Approach. To get grant funding you need to publish. To publish you need grant funding. All of this demands good writing skills. Good writing can be learned but there is no substitute for lots of practice. This course will help you develop your scientific writing skills through (i) classroom instruction, (ii) reading and critiquing grant applications, (iii) writing a draft research proposal, (iv) responding to critiques of your proposal and revising it to make it better. All students *and their faculty advisors* are expected to participate in the course. Everyone is expected to participate in a manner that is constructive and respectful.

Few people are able to improve when they are feeling defensive or insulted on a personal level. Inappropriate comments will not be tolerated.

Anticipated results. Many of you will write a research proposal in preparation for the department qualifying examination. Some of you will also be submitting applications for a predoctoral fellowship award (a grant). Accordingly, you will be asked to write a proposal in the format used by the National Institute of Health (NIH F31 grants). Post-doctoral fellowships (NIH F32 grants) use a similar format. In addition you may elect to submit your proposal to other government agencies such as the National Science Foundation (NSF) or Department of Defense (DoD) or private foundations (there are many out there). Most funding agencies use a format that is similar in style and length to that used by the NIH. Thus it will be relatively simple for you to reformat your proposal for multiple agencies, and to use your current proposal as a model for future grant applications. Regardless of the requirements, writing a research proposal will prompt you to review the literature and it will provide a road map for your thesis research. There will likely be unexpected delays and detours, but at least you will have a destination in mind.

For an updated list of funding sources for graduate students visit:
<http://tibbs.unc.edu/resources/funding-opportunities/>

Organization

The course consists of (i) formal lectures with discussion and homework exercises, (ii) small group meetings to refine your draft proposal, and (iii) final review using the criteria of an NIH review panel. All students are expected to attend each class and to participate fully. If you must be absent it is your obligation to notify the course director in advance. Arriving unprepared, or not arriving at all, will result in a grade no better than P. A second instance of non-participation will result in a grade of L. A third instance will result in a failing grade and dismissal.

Before each lecture, material will be distributed electronically and posted on the course web site. Lectures are meant to complement the written material, and to serve as a springboard for extensive discussion. The goal is to keep lectures under 30 minutes with up to an additional 60 min for discussion.

CLASS SCHEDULE

Class 1: Introduction and overview:

To orient you, be aware that the scientific component of an NIH grant has four sections:

- **Project Summary** = consists of an abstract and statement of relevance to public health
- **Specific Aims** = consists of a one page overview of your proposal
These will be discussed in class 2.
- **Bibliography & References Cited** = no page limit
Although it comes at the end of the proposal, the topic will be discussed in class 3, along with a discussion of plagiarism.
- **Research Strategy** = 6 pages for an F31 (12 pages for an R01), consists of three sections: Significance, Innovation and Approach
This will be discussed in the remaining 6 classes.

Class 2: “Specific Aims” and “Project Summary”:

What is the question? What is the hypothesis?

Specific Aims. According to NIH guidelines, “*the purpose of the specific aims is to describe concisely and realistically the goals of the proposed research and summarize the expected outcome(s), including the impact that the results of the proposed research will exert on the research field(s) involved.*”

Project Summary. The first component of the Project Summary is an abstract, no longer than 30 lines of text. This is often an abridged version of the Specific Aims page.

The second component describes the relevance of the proposed research to public health, presented in plain language.

Both should include the following:

- Background. What is known already?
- Question. What is not known? Pose a hypothesis.
- Approach. How will you answer the question? Enumerate your aims.
- Result. What is the likely outcome of your experiments?
- Conclusion. What will you have learned. What comes next?

Homework to be completed 48 hours before class:

- Read about preparing an NIH grant from the source (http://grants.nih.gov/grants/writing_application.htm).
- Using the NIH Reporter website (<http://projectreporter.nih.gov/reporter.cfm>), find an abstract related to your own research and for that project write down the five items listed above (are any

missing? can they be improved?). **Restrict your search to R01 grants** (<http://grants.nih.gov/grants/funding/r01.htm>)

- Highlight the following, as done on p. 22.
 - Background. What is known already?
 - Question. What is not known? Pose a hypothesis.
 - Approach. How will you answer the question? Enumerate your aims.
 - Result. What is the likely outcome of your experiments?
 - Conclusion. What will you have learned. What comes next?
- Post the abstract to the class website.
- (optional) Look up a Nobel prize winning discovery (<http://www.nobelprize.org/>). Write an abstract that anticipates that discovery.

In class exercise: We will discuss a few of the abstracts submitted as homework.

For any grant that is funded by NIH, the Project Summary is posted on the NIH Reporter website. This is a wonderful resource for examples of research proposals that have survived the scrutiny of NIH.

Class 3: “Bibliography & References Cited”:

Do you give credit where credit is due?

According to NIH guidelines you must “*Provide a **bibliography** of any references cited in the Project Narrative. Each reference must include the names of all authors (in the same sequence in which they appear in the publication), the article and journal title, book title, volume number, page numbers, and year of publication.*”

Failing to reference the work of others can be seen as research misconduct.

According to NIH guidelines “*Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results... Plagiarism is the appropriation of another person’s ideas, processes, results, or words without giving appropriate credit.*”

For additional reading about plagiarism (not required for the class):

- <http://ori.hhs.gov/sites/default/files/plagiarism.pdf>

Homework to be completed 48 hours before class:

- Read these articles describing some of the consequences of plagiarism:
 - <http://www.nature.com/news/2008/080206/full/451619b.html>
 - <http://www.thecrimson.com/article/2009/3/13/hms-professor-simon-resigns-a-harvard/>
 - [http://www.nature.com/news/image-search-triggers-italian-police-probe-1.14295 -](http://www.nature.com/news/image-search-triggers-italian-police-probe-1.14295)
 - <http://www.sciencemag.org/content/245/4914/120.long>
 - <http://www.apnewsarchive.com/1989/Biologist-To-Appeal-Plagiarism-Charge-By-National-Institutes-of-Health/id-54c175b72b0c1be66f96877de44a309e>
 -
- Read this article describing ways to address the problem of plagiarism:
 - <http://www.nature.com/nature/journal/v481/n7379/full/481021a.html>

In class exercise: We will discuss **the last three articles** at length. Be prepared to speak up.

- Write and post a Specific Aims page based on your own research. Provide at least two, and preferably three, aims. Check that you have provided adequate background, **a hypothesis**, anticipated results and conclusion. **Length should be 600-800 words**. There are usually no citations in this section.
 - I suggest modeling your document after the **examples provided on pages 47 and 49 of the syllabus**. You can start by following the same outline and rewriting the text to fit your own work. I'm Ok with you copying the **outline** and **format** but not more than a few words of the **text**.
 - When you are done, read the checklist on p. 21, and revise accordingly. It might also help to read ahead.

Class 4 (Small Group):

Improving the Specific Aims page

Homework to be completed 48 hours before the first small group meeting:

- Read the Specific Aims pages of two assigned classmates and prepare comments. Do you understand what is being proposed and why? Does it make sense? Is anything missing?
- Prepare a powerpoint that contains the following five items (one slide per item). This is to help orient your group members. Use bullet points. Keep it short.
 1. Background (what is already known?)
 2. Hypothesis (what is the question?)
 3. Specific Aims (approach, how will you answer the question?).
 4. Anticipated results and conclusions
 5. Statements of Significance and Innovation

Class 5: “Research Strategy”: “Significance”, “Innovation” and “Approach”:

Is the question worth answering? Do your aims answer the question?

According to the NIH, the **Approach** section should “describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project... discuss potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims.”

The **Significance** section “should explain the importance of the problem or describe the critical barrier to progress in the field that is being addressed. Explain how the proposed research project will improve scientific knowledge... (and how the) field will be changed if the proposed aims are achieved.”

The **Innovation** section should “explain how the application challenges and seeks to shift current research or clinical practice paradigms.”

Homework to be completed 48 hours before class:

- Revise and post your Specific Aims section.
- Write and post the Significance and Innovation sections of your Research Strategy. Total length should be 300-500 words.
- Read the Significance and Innovation sections of two assigned classmates to help guide the discussion in class.

In class exercise: We will read and discuss a few of the documents submitted as homework.

Class 6: Reading and Writing part 1:

How your proposal will be read.

Homework to be completed 48 hours before class:

- Revise and post your Significance and Innovation sections.
- Write and post Aim 1 of the Approach section (through Aim 1) of your Research Strategy.

Class 7 (Small Group):

Improving the Approach section.

Homework to be completed 48 hours before the small group meeting:

- Read the Approach section of two assigned classmates and prepare comments. Use the final checklist to evaluate Aim 1.

Class 8: Reading and Writing part 2:

How to express your ideas clearly.

Homework to be completed 48 hours before the final class:

- Revise and post the Approach section (through Aim 1) of your Research Strategy.
- Include one or two examples of preliminary data (from you or your lab) that demonstrate feasibility (they can be included in any portion of the proposal but are usually under "Approach").
- Write and post your Project Summary section.

Class 9 (Small Group):

Final review.

Homework to be completed 48 hours before the final small group meeting:

- Read the assembled Project Summary, Specific Aims, Significance, Innovation, and Approach (through Aim 1) for each of your classmates, and prepare comments. Use the final checklist to evaluate Aim 1.

ONLINE SUBMISSION OF DOCUMENTS

Authors.

Upload your documents names using the format: **Author_Section_Version** (for example: "Dohlman_Approach_v1.doc").

Revised documents (with changes visible, using "track changes") must be posted before the next meeting. Documents must use Arial or Helvetica font, 11 points or larger, and half-inch margins. For figures and figure legends, a smaller font size may be used if it is clearly legible. Draft proposals will be double-spaced. Final proposals will be single-spaced. The assembled proposal can be no longer than seven pages including figures (one page for Specific Aims, approximately one or two pages for Significance and Innovation, approximately four or five pages for the Approach section). Include page numbers (note these are added automatically for submissions to NIH). Your final proposal should have at least two aims but you are required to provide text for one (in such case your assembled document will be less than seven pages!). There is no limit on references but they should be done according to NIH guidelines.

Reviewers. Every document will be reviewed by two of your fellow students. Your reviewers will post their comments before class using "track changes" and "comments". Selected assignments will be projected and discussed by the group. Faculty facilitators will read all proposals in their group so that they can guide the discussion, but need not provide detailed comments or edits. Small Group Sessions should last no more than 90 minutes.

Grading: The final grade will be based on the following criteria:

1. Attendance and preparation
2. Quality of the written critiques
3. Class participation and professionalism
4. Final evaluation of your proposal.

Class 2: “Specific Aims” and “Project Summary”

Homework to be completed 48 hours before class:

- Read about preparing an NIH grant from the source. Familiarize your self with sections related to the parts about science. You do not need to read every page. (http://grants.nih.gov/grants/writing_application.htm).
- Using the NIH Reporter website (<http://projectreporter.nih.gov/reporter.cfm>), find an abstract related to your own research and for that project **write down the five items listed above** (are any missing? can they be improved?). **Restrict your search to R01 grants** (<http://grants.nih.gov/grants/funding/r01.htm>)
- Highlight text in the abstract, following the example on p. 22.
 - Background. What is known already?
 - Question (or challenge statement). What is not known? **Pose a hypothesis.**
 - Approach. How will you answer the question? **Enumerate your aims.**
 - Result. Preliminary data to illustrate the approach. **What is the likely outcome of your experiments?**
 - Conclusion. What will you have learned. Anticipated results. What comes next?
- Post the abstract to the class website.
- (optional) Look up a Nobel prize winning discovery (<http://www.nobelprize.org/>). Write an abstract that anticipates that discovery.

In class exercise: We will discuss a few of the abstracts submitted as homework.

Overview

“I can’t talk right now, I’m working on a grant”

By now each of you has heard these words. What is a grant proposal and why does it matter so much?

A grant proposal is a plan for work on a specific problem. A competitive grant is one that is focused on a problem of real and potential significance, and is likely to advance the field. A grant is an instrument of persuasion because you must convince the reviewer panel and the funding agency that money is better spent to support your proposal over the 80-90% of proposals that are not funded. Finally, a grant proposal is a promise to the funding agency that the proposed work (or something similar) will be done.

Let us consider these statements in turn.

Significance

Any research proposal must first *state the problem* and then *outline the path to a solution*. A competitive project must address a problem that is both significant and is limiting progress. So ask yourself, your labmates or your thesis committee, what are the *most important unanswered questions* in your field? Why haven’t they been answered yet? *Has there been some conceptual or technological advance that now makes it possible to answer the question?* Are you the right person to do the work? Your proposal should capitalize on your unique experience and expertise, and the resources you have

available to you. Can you do the work in a reasonable amount of time? Your proposal must demonstrate that the question is answerable within the timeframe of the funding period (or of a PhD thesis). All of this requires that you have a thorough understanding of the literature and of the experimental approaches available to you.

Persuasion

Once submitted to a funding agency, a grant proposal is reviewed by a group of scientists called the Initial Review Group (IRG, or “study section”) who are broadly knowledgeable about the subject area of the proposal. Unlike peer reviewers of research manuscripts or members of your thesis committee, *grant reviewers may have little expertise in the precise subject of your proposal*. To convince reviewers to give your proposal a “fundable” score, you must provide enough information to convince them that the question is important and that you will be able to answer the question. They will be prone to skepticism. They will want to know that you have considered potential problems and that you have alternative strategies available. After the study section evaluates the science, your proposal will be reviewed by administrators from the funding agency. They are likely to be even less familiar with the topic of your proposal. Their job is to judge whether your project fits the mission of the funding agency. They also have the power to fund “high priority” projects that may not be in the topmost group. You must persuade all of these people that your work is important (significant) and exciting (innovative).

Promise

If your proposal is approved and funded, you are expected to carry out the work within the timeframe indicated in your proposal. However most funding agencies, like most thesis committees, recognize that a lot can change from the time a proposal is written to when the work is actually done. NIH is a remarkably flexible organization, staffed by experienced scientists, and is willing to accept a change in research direction provided that it is well justified and that you are being productive (that is, you are publishing!). If in doubt, ask the officials at NIH, it is their job to help you.

Some things to think about when planning your proposal:

- Is it significant? Can you convince others that the problem is **important** and worth solving?
- Is it **innovative**? Can you point to a recent **breakthrough** (conceptual or technical) in your field?
- Are you qualified? Does the project take advantage of **your special skills** as a scientist?
- Is it **feasible**? Can the project be completed in a reasonable amount of time? Do you have a backup?

Discussion point: What is the breakthrough behind the abstract you selected for homework?

Scientific Writing - Major Considerations

Writing a research proposal is an enormous undertaking. It is a learned skill that requires practice. The good news is that most major universities are likely to be filled with successful grant writers and experienced grant reviewers, and they are usually happy to share their knowledge.

Even if you have no interest in an academic career or in competing for research grants in the future, your proposal will serve as a roadmap that will help to ensure your success as a graduate student. Moreover, the experience you gain will be useful in almost any endeavor that requires the powers of

persuasion. Perhaps you want to start a company; in such case you will need to convince investors that your business plan is sound and that your company is likely to be profitable in the future. Perhaps you want to work for a charitable foundation; in such case you will need to convince donors that your cause is worthy of their support and the money will be well spent.

This course is about articulating your ideas and goals for the future. Such skills are transferable.

Hypothesis-driven projects

The word “hypothesis” comes from the Greek word *hypotithenai*, meaning “to suppose”. Most research proposals in the life sciences are designed to test a specific hypothesis, or supposition. By now you probably have heard various descriptions of what a hypothesis is, but here is one that I like:

A good hypothesis provides a reasonable **explanation** for the available data and can be tested experimentally.

A hypothesis is not a theory. A theory is an accepted explanation based on a body of evidence. A hypothesis is a placeholder until a tenable theory is established. A hypothesis requires evaluation. A hypothesis is an educated guess. A good hypothesis is directional, so that predictions flow naturally from it. Experimenters may test and reject several hypotheses before solving the problem. *Many hypotheses are shown to be wrong.* That is the nature of experimental science.

A hypothesis does not have to be correct. However it has to make sense given existing knowledge.

To summarize the ideas of Schick and Vaughn (Theodore Schick and Lewis Vaughn (2002). *How to think about weird things: critical thinking for a New Age*. Boston: McGraw-Hill Higher Education. ISBN 0-7674-2048-9), researchers weighing alternative hypotheses may take into consideration the following:

- **Conservatism** – does it agree with current knowledge?
- **Parsimony** – is it the simplest explanation of the available data?
- **Testability** – can it be proven or disproven through experimentation?
- **Scope** – can it be applied to different types of experiments?
- **Fruitfulness** – can it be used to predict future experiments?

Your job as an investigator is not to prove that your hypothesis is correct; rather it is to test your hypothesis and to come up with a new one if you are wrong. If this is confusing, substitute the word “model” for “hypothesis”. If you were going to build a car, you would start with a model based upon a foundation of existing knowledge. If your model does not work properly, create a new one. Once the car is built, most likely you would start working on the next new model.

For some advice on developing a strong hypothesis, and its importance:

<http://www.niaid.nih.gov/researchfunding/newsletter/2013/pages/0123.aspx#a00>

Discussion point: What is the hypothesis in the abstract you selected for homework? If it is not explicitly stated in the abstract (this is common) can you do so?

Discovery-driven projects

A second type of research proposal is a discovery-driven or data-driven project. Instead of designing an experiment to test a defined model or hypothesis, the investigator proposes to collect large amounts of new data and to then identify patterns that could point to new biological insights. This is akin to saying “if I do a lot of experiments something interesting will emerge,” or “if I cast a wide net I’m bound to catch some fish.” Reviewers often refer to this type of proposal as a “fishing expedition” and funding

agencies are generally very reluctant to fund this type of research unless the writer is able to explain how the work might benefit the larger scientific community or speed the pace of discovery.

Examples of data-driven projects include sequencing the DNA of human tumors to identify the disease-causing genes, conducting a large-scale RNAi screen for genes important in development, or screening a library of natural products for those with pharmacological activity.

For some thoughts on a role for discovery-driven projects:
<http://www.sciencemag.org/content/335/6075/1439.1.long>

Discussion point: What are some discovery-driven projects that benefitted your own research? Or of the field generally?

Technology-driven projects

A third type of research proposal is the technology-driven or technology-development project. The basic premise (sometimes called “the enabling assumption”) is that creating a new technology, or substantially improving an existing technology, will enhance our ability to address specific types of scientific questions.

In the life sciences a technology-driven proposal cannot exist in a vacuum; that is, it is important to provide examples of experiments that utilize the new technology, and explain how the technology will address an important question.

Examples of technology-driven research include the development of new DNA sequencing technology, new bioinformatic tools, or the development of new fluorescent reporters of protein activity.

Although the general format is the same for all three types of projects, the emphasis is different in critical areas that will affect how you write the proposal. Before starting you must decide what type of proposal you are going to write. *Bear in mind that most NIH-funded research is hypothesis-driven.* A thesis committee is likely to be more receptive to a technology-driven project, or even a discovery-driven project, particularly if they recognize the potential for new breakthroughs. If you have an idea for a clever new screen, or a useful device, consider how these ideas might be incorporated with a larger hypothesis-driven project. Find a collaborator if needed.

Technology-driven projects, like hypothesis-driven projects, need to be significant, innovative and feasible.

Discussion point: What are some technology-driven projects that benefitted your own research? Or of the field generally?

The Proposal

You will use the format of the NIH F31 National Research Service Awards for Individual Predoctoral Fellows (that is, graduate students). Their guidelines follow. In brief there are four parts:

1. Project Summary/Abstract (half page), includes:
 - a. ‘abstract’
 - b. ‘relevance to public health’
2. Specific Aims (one page), includes an overview of your project

3. Research Strategy (six pages), includes:
 - a. Significance
 - b. Innovation
 - c. Approach.
4. Bibliography and References Cited (no page limit).

The italicized text is copied from NIHSF424 (R&R) Application Guide for NIH and Other PHS Agencies (<http://grants.nih.gov/grants/funding/424/>):

Project Summary/Abstract

“The Project Summary must contain a summary of the proposed activity suitable for dissemination to the public. It should be a self-contained description of the project and should contain a statement of objectives and methods to be employed. It should be informative to other persons working in the same or related fields and insofar as possible understandable to a scientifically or technically literate lay reader. This Summary must not include any proprietary/confidential information.

The Project Summary is meant to serve as a succinct and accurate description of the proposed work when separated from the application. State the application’s broad, long-term objectives and specific aims, making reference to the health relatedness of the project (i.e., relevance to the mission of the agency). Describe concisely the research design and methods for achieving the stated goals. This section should be informative to other persons working in the same or related fields and insofar as possible understandable to a scientifically or technically literate reader. Avoid describing past accomplishments and the use of the first person. Finally, please make every effort to be succinct.

The second component of the Project Summary/Abstract (i.e., “Description”) is Relevance. Using no more than two or three sentences, describe the relevance of this research to public health. In this section, be succinct and use plain language that can be understood by a general, lay audience.”

If your proposal is funded by the NIH, the Project Summary is published online: (<http://projectreporter.nih.gov/reporter.cfm>).

The Relevance statement is meant to inform government officials and other laypersons about your work.

The Abstract is used in assigning the application to an Institute within NIH, to the Initial Review Group (study section) and to specific reviewers. Each of the institutes within NIH has its own set of funding priorities, and each has different levels of funding (paylines). The application is then assigned to a study section, each of which has its own areas of scientific expertise. F31s in particular are usually reviewed by a panel with broad expertise, and there may be only one or two individuals at most with specific knowledge of your research topic. You may request a specific review panel, and if you do it is usually best if the reviewers know you and your work (or the work of your advisor). The rosters are published on the NIH website (<http://public.csr.nih.gov/StudySections/Standing/Pages/default.aspx>), although late substitutions and additions are common.

Specific Aims

“State concisely the goals of the proposed research and summarize the expected outcome(s), including the impact that the results of the proposed research will exert on the research field(s) involved. List succinctly the specific objectives of the research proposed, e.g., to test a stated hypothesis, create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, or develop new technology.”

There is no second chance at making a good first impression. The Specific Aims page gives the first impression, and it is your best opportunity to excite the reader. Much of your time in this course will be focused on getting it right. Doing so will be a challenge. You will need to provide lots of critical information in a small amount of space. You will need to pose an interesting question. You will need to provide a clear and testable hypothesis.

There are other competing considerations. It should be obvious that the work needs doing, but then why hasn't it been done already? Perhaps there has been some technical breakthrough or new discovery, ideally one that comes from your own work? The approach must be sufficiently detailed so as to seem well-planned, but not so detailed as to bore the reader or obscure the bigger picture. You will need to propose aims that relate well to one another, yet each aim should stand alone (so the success of one aim does not depend on the success of another aim). The approach should be simple enough to appear feasible, but sufficiently comprehensive so as to warrant several years of support, but not so complex as to appear unrealistic or overly ambitious. You will need to give enough background information to provide a strong rationale for doing the work, but still leave enough space to explain what you are actually going to do.

Research Strategy

Six single-spaced pages that build the case for your proposed research and for you as the best person to do it. There are three subsections: Significance, Innovation, and Approach.

“Organize the Research Strategy in the specified order and using the instructions provided below. Start each section with the appropriate section heading – Significance, Innovation, Approach. Cite published experimental details in the Research Strategy section and provide the full reference in the Bibliography and References Cited section (Part I Section 4.4.9).

Follow the page limits for the Research Strategy in the table of page limits (Table 2.6-1), unless specified otherwise in the FOA. Note that the page limit for this attachment will be validated as a single file.

(a) Significance

- *Explain the importance of the problem or critical barrier to progress in the field that the proposed project addresses.*
- *Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields.*
- *Describe how the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field will be changed if the proposed aims are achieved.*

(b) Innovation

- *Explain how the application challenges and seeks to shift current research or clinical practice paradigms.*
- *Describe any novel theoretical concepts, approaches or methodologies, instrumentation or interventions to be developed or used, and any advantage over existing methodologies, instrumentation, or interventions.*
- *Explain any refinements, improvements, or new applications of theoretical concepts, approaches or methodologies, instrumentation, or interventions.”*

A competitive proposal must address a problem that is meaningful and is limiting progress. What are the most important (significant) unanswered questions in your field? Why haven't they been answered yet? Has there been some conceptual or technological advance (innovation) that now makes it possible to answer the question?

“(c) Approach

- Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project. Unless addressed separately in Item 15 (Resource Sharing Plan), include how the data will be collected, analyzed, and interpreted as well as any resource sharing plans as appropriate.
- Discuss potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims.
- If the project is in the early stages of development, describe any strategy to establish feasibility, and address the management of any high risk aspects of the proposed work.
- Point out any procedures, situations, or materials that may be hazardous to personnel and precautions to be exercised. A full discussion on the use of select agents should appear.

If an applicant has multiple Specific Aims, then the applicant may address Significance, Innovation and Approach for each Specific Aim individually, or may address Significance, Innovation and Approach for all of the Specific Aims collectively.”

The Approach section includes the overall strategy as well as the specific methodology used to carry out the Specific Aims, any important preliminary data that you have (or will need) to demonstrate the feasibility of your project, potential pitfalls and alternative strategies (should your planned approach fail), interpretation of results, and benchmarks for success.

Note that if you are proposing a technology-driven project, it is particularly important that you describe the unmet need that your proposal will address. Any technology, no matter how nifty, needs to address a problem worth solving. This statement should include your own assessment of need as well as citations or letters from others that describe the need. *Any project must provide a solution to an important question.* Provide a specific timeline for each step of your approach, and describe the benchmarks of success. Finish with an impact statement indicating what will be possible when your work is done.

Bibliography and References Cited

“Provide a bibliography of any references cited in the Project Narrative. Each reference must include the names of all authors (in the same sequence in which they appear in the publication), the article and journal title, book title, volume number, page numbers, and year of publication... Include only bibliographic citations. Provide the PubMed Central (PMC) reference number (e.g., PMCID234567) for each article... While there is not a page limitation, it is important to be concise and to select only those literature references pertinent to the proposed research.”

Include all references cited in the Research Plan including books, journal articles, web sites, databases and unpublished information. References should be indicated by number in the body of the text, and then listed by number in the Bibliography.

Be careful to give credit where credit is due. Not doing so may be seen as plagiarism, a serious form of scientific misconduct. We will discuss plagiarism in the second class.

Other sections. If you are planning an application to NIH, particularly one that uses human subjects, select agents (hazardous biological agents and toxin), animals or outside consultants, there are lots of regulations and approvals are needed. Refer to the NIH website and your department business office for guidance.

Outlining your proposal

The foundation of a good grant is a well-designed plan (an outline) and the best of materials (clear writing). Imagine building a house. It is possible to start laying the bricks without a blueprint. You might get lucky and get it right the first time, but chances are you will spend valuable time tearing down much of what you have built and starting over. Or worse, the reviewers will notice the flaws and condemn the whole construction.

This section focuses on the outline. A later class will focus on the writing.

The importance of the Specific Aims section cannot be overstated. This section stands alone. This is the first section that your reviewers will see. It is perhaps the only section of your grant that other members of the review panel will read. It is here that you first state the question and where it comes from. It is here that you outline your approach and what it is likely to yield. The significance and innovation should be evident.

This same order and wording will be used in later sections of the proposal. For this reason you will likely have write and rewrite this section many times until you are satisfied (I spend about a third of my grant writing time on this one page!).

The writing must be clear.

Start by defining the question. Writing a grant proposal starts with recognizing an important research problem and identifying ways to solve that problem. Even the most senior investigators will consult with other investigators (including their own students) for advice and feedback. In addition you will need to make sure that you are up to date with the literature in your field, so that you are familiar with what has been done before. Your advisor and other colleagues can help get you started by recommending important papers in your field. A PubMed search is essential to know you haven't missed anything (has someone already done the experiment?). Do not discount papers older than 10 years. Do not ignore older papers from your own lab! Sometimes you will find important observations (or unanswered questions) buried within these papers that could influence your approach. Do not limit your reading to just the system or organism you work in. For example, if you are working on a specific protein kinase in yeast, knowing how a homologous enzyme works in mouse or human cells may be helpful in guiding your work and demonstrating significance to health. Making these connections demonstrates that you think broadly and know your discipline.

Start big. Begin with a mile-high view of the problem and then drill down to the specifics that are important for solving the problem.

How would you complete these sentences?:

- "The overall question is..."
- "If successful, our experiments will demonstrate..."

Once you have defined the problem and identified a solution it is time to begin writing your proposal. Start with an outline. This will allow you to see clearly the relationships between the various parts of your proposal, spot gaps or inconsistencies in your logic, and avoid unnecessary repetition. Presenting your proposal in a logical manner will help to convince reviewers that you have thought ahead and that you will be able deal with the unexpected events that often accompany research.

Most reviewers cannot distinguish unclear writing from muddled thinking.

Below is guide for this section, along with a brief explanation of what you need to accomplish in each subsection. When you first outline the proposal you can use bullet-points, but you should have something for each of the sections. Don't start writing the Approach section until you are satisfied with your outline and you have completed your Specific Aims section.

Background. What is known already?

A great beginning. The first sentence and the first paragraph of each section should grab the attention of the reader. Explain why readers should care about the topic of your research. Stick to the most important information, you have later sections to provide necessary details.

- Begin with a general statement to indicate the topic of your proposal. Generate interest!
 - Provide a simple (“take home message”) statement. Then qualify your statement as needed.
 - Offering a generalization provokes a desire to know more. Then satisfy that desire by providing information and data.
 - Do not attempt to provide a comprehensive review of the literature (especially in the first sentence!)! KEEP IT SIMPLE.
 - Examples of the opening statement from several funded grants are provided below.

“The most important sentence in any article is the first one. If it doesn't induce the reader to proceed to the second sentence, your article is dead.... Therefore your lead must capture the reader immediately and force him to keep reading. It must cajole him with freshness, or novelty, or paradox, or humor, or surprise or with an unusual idea, or an interesting fact, or a question. Anything will do, as long as it nudges his curiosity and tugs at his sleeve.” – from *On Writing Well*, by William Zinsser

Question. What is not known? What is the problem you hope to solve.

- State the question up front
 - What is the gap in our knowledge that your work will address?
 - Create some tension!
 - Is the question worth answering? (If you want to do important science, you must ask important questions!). Provide *one or two relevant examples* to support your statement. These can come from your own work.
 - Avoid examples that are too broad to be useful (e.g. “my protein is involved in cancer, development and heart disease”).
 - Avoid generalities that essentially say “I'm very curious and more knowledge is good” (this does not make you unique).
- Show your enthusiasm. If you don't appear to care about your work, no one else will either!

Examples of an opening sentence (the topic) and a challenge statement (the question), taken from the abstracts of highly competitive R37 grants.

- *Acquired immunodeficiency syndrome (AIDS) is one of the most destructive epidemics in medical history. ... While darunavir has become a front line therapy against HIV/AIDS, it is far from ideal as an effective long-term treatment option. R37GM053386*
- *Glycosaminoglycans (GAGs) are complex acidic polysaccharides that are located at the interface between virtually every eukaryotic cell and its extracellular matrix (ECM).... However, decoding GAG structure function relationships has been traditionally complicated by the chemical complexity, heterogeneity and polydispersity of GAGs. R37GM057073*
- *Pain signals enter the nervous system in the spinal cord, where these signals are processed before being transmitted to the brain.... This grant seeks to understand how that processing goes awry after injury, leading to constant pain without stimulation and burning pain when the skin is lightly touched. R37GM048085*
- *Natural products are regaining their traditional importance as drug candidates, leads for drug candidates and biological probes... Complex natural products typically contain many stereocenters, but only one or at most a handful of stereoisomers are available for study. R37GM033372*
- *Dosage compensation is a striking example of the interplay between gene-specific regulation and chromosomal architecture. Our focus in the coming grant period will be to understand how chromatin activation is targeted and spread along a chromosome. R37GM045744*

State the hypothesis.

But what constitutes a good hypothesis?

- It is conservative. It agrees with current knowledge. If it doesn't, explain why not.
- It is parsimonious. It provides a simple explanation for the available data. If there is another equally simple explanation, provide a second alternative hypothesis.
- It is testable. It can be proven or disproven through experimentation.
- It has a broad scope. It can be applied to the different types of experiments in your proposal. It applies to all of your aims.
- It is likely to be fruitful later. It can it be used to predict future experiments and eventually lead to a theory.

Why the hypothesis is important

- A hypothesis allows you to determine what information is *relevant* to solving the problem.
- By predicting and anticipating outcomes, a good hypothesis will lead naturally to the right experiments and to a yes/no answer. Your aims test the hypothesis and reveal either of the following:
 - "yes our model is correct"

- “no our model is not correct”.
- A hypothesis allows you to judge the quality of the data and connect the information available.
 - Mere observation does not allow this.

Examples of an overall hypothesis, taken from the abstracts of funded NIH R01 grants

- *Our central **hypothesis** is that the interactions responsible for tight junction protein anchoring and trafficking are the primary determinants of paracellular barrier function. R01DK061931*
- *The central **hypothesis** is that the plasma membrane of endothelial cell acts as a mechanosensitive element; i.e. changes in physical properties of the membrane under mechanical stress can regulate activity of membrane proteins coupled to intracellular signaling pathways. R01HL086943*
- *Our preliminary studies support the **hypothesis** that the circadian histone acetyltransferase activity of CLOCK is a co-activator of NFkB-dependent gene expression, and that NFkB, in turn, directly mediates repression of CLOCK/BMAL1-dependent transcription presumably through posttranslational mechanisms. R01GM095874*
- *This proposal will test the **hypothesis** that mathematical techniques developed for studying dynamical systems can explain how pathway components interpret and translate spatial cues outside the cell to evoke appropriate responses inside the cell. R01GM073180*

Approach.

How will you answer the question?

- List your aims.
- Each aim should be set apart as a single short paragraph
- Each aim should begin with a simple declarative sentence that begins with “we”. (“I” is acceptable if you are writing an individual fellowship application and recommended if you are writing a thesis proposal).
- *The question always comes before the approach.* Avoid starting by saying “we will use such-and-such-method to investigate...”. That puts the emphasis on the methodology instead of the question where it belongs.

Methods are constantly being replaced but a good question could last an entire career. Even if your proposal is technology-driven, or your long-standing hypothesis can now be tested because of a technical breakthrough, it is always best to start with the question. If the question is not exciting, nobody will care about the approach or the answer.

What constitutes a good approach?

- Can you answer the question using the approach?
- Is it the *best* approach to take?

- Can you do it as well or better than anyone else? If you the best person to do the work, say why.
- Does each aim test some aspect of the central hypothesis?
- Does each aim stand alone? In no case should the success of one aim depend on the success of another!
- It is common for the aims to become progressively more risky. If you are proposing a risky aim or sub-aim, acknowledge this and explain why you think it is a risk worth taking. Risky does not mean reckless!
- Avoid aims that sound descriptive, not mechanistic.
 - It must do more than answer the question “lets see what happens?”
 - No aim should sound like a “fishing expedition” (even if that is what it is)!
- You must propose to do the obvious experiment. If you don’t, explain why you don’t.
- Acknowledge any paradox or conflicting data. Don’t leave this out.

Results.

What is the likely outcome of your experiments? (includes preliminary data)

- This part of the proposal demonstrates your ability to arrange complex facts into a logical and cohesive story.
 - Support your statements with a summary of the most relevant data.
 - How did you (or how will you) do each experiment?
- The order of presentation need not correspond to the actual order of experiments, and in fact rarely does.
 - “It is better to be logical than chronological”
- Your results can still be written as if they were obtained in chronological order.
 - This helps the reader follow transitions from one experiment to another.
 - "Having established that the protein is phosphorylated, we then sought to determine the consequence of the modification."
- Above all it should make sense.
 - By moving from simple concepts to complex results allows the reader to build on the information that has come before. Using this approach, no mental leaps are required.
- Conclusion. What have you learned (what do hope to learn)? What comes next?
 - Provide a simple (“take home message”) statement. What is the likely payoff? How will the work have a significant impact on the field? What is the best possible outcome?
 - How do the results fit with existing knowledge? Present a model
 - Emphasize any novel or innovative aspects of the work. It is OK to say “This work is innovative because...”
 - Provide a definite ending that clearly completes the presentation. End with a bang.
 - *A full circle ending:* "These results prove our original hypothesis, that RGS proteins are required for desensitization."

- *A future action ending:* "These findings suggest that homologous proteins in other organisms will also prove essential for desensitization."

Example of a Project Summary abstract (hypothesis-driven) courtesy of Henrik Dohlman

Many chemical and sensory signals act via cell surface receptors coupled to G proteins. The G protein is composed of three subunits, and the $G\alpha$ subunit is comprised of two domains: the Ras-like domain and the helical domain. The Ras-like domain binds to guanine nucleotides, GTPase activating proteins, effectors and the G protein $\beta\gamma$ subunits. By comparison the helical domain has few known binding partners and has received far less attention. In recent years we have shown that the helical domain is phosphorylated, mono-ubiquitinated and poly-ubiquitinated. Our central hypothesis is that these post-translational modifications regulate G protein signaling. The proposed research will establish the structural basis and functional consequences of helical domain phosphorylation, ubiquitination and interaction with novel protein binding partners. The approach will include biochemical analysis as well as cell-based assays of modified and unmodified G protein in yeast (Gpa1).

Aim 1. Functional analysis of monoubiquitinated Gpa1/ $G\alpha$. We have shown that the helical domain of Gpa1 is monoubiquitinated, and that monoubiquitination is mediated by the ubiquitin ligase Rsp5. To establish the function of monoubiquitinated Gpa1, we will determine its catalytic activity and its ability to bind guanine nucleotides, the receptor, the $G\beta\gamma$ subunits, the GTPase activating protein and downstream effectors.

Aim 2. Functional analysis of Gpa1/ $G\alpha$ phosphorylation. We have shown that the helical domain is phosphorylated by the three AMPK "glucose-sensing" kinases. To establish the function of phosphorylated Gpa1, we will determine the ability of each kinase to alter G protein ubiquitination, catalytic activity and signaling functions, both in vivo and in vitro.

Aim 3. Functional analysis of proteins that target monoubiquitinated Gpa1/ $G\alpha$. We have shown that monoubiquitination of the helical domain promotes Gpa1 endocytosis, and that endocytosis requires at least four ubiquitin-binding domain proteins. We will determine the ability of each "ubiquitin receptor" to alter G protein trafficking, catalytic activity and signaling functions, both in vivo and in vitro.

These experiments will reveal additional mechanisms of signal regulation, including new G protein kinases and binding partners involved in trafficking, and will establish a direct link between the nutrient-sensing and G protein signaling pathways. A deeper understanding of how cells transmit their signals could lead to new treatments for disease. Delineating such new mechanisms is the central objective of this research program.

A single aim from the Specific Aims page

Aim 1. Functional analysis of monoubiquitinated Gpa1/ $G\alpha$. We have shown previously that Gpa1 is monoubiquitinated, that monoubiquitination occurs within the helical domain and that monoubiquitination alters G protein signaling and trafficking *in vivo*. Our hypothesis is that monoubiquitination of $G\alpha$ promotes nucleotide exchange and propagation of the signal. Our recent preliminary data show the feasibility of purifying, for the first time, large quantities of monoubiquitinated protein, suitable for detailed biochemical and biophysical analysis. To establish the function of monoubiquitinated Gpa1, we will determine its catalytic activity and its ability to bind guanine nucleotides, the receptor, the $G\beta\gamma$ subunits, the GTPase activating protein and downstream effectors.

Key to highlights for each of these items in the abstract:

- Background (what is already known?)
- Question (or challenge statement) and hypothesis
- Specific Aims (approach, how will you answer the question?)
- Preliminary data to illustrate the approach.
- Anticipated results and conclusions

Example of a Project Summary abstract (technology-driven) courtesy of Brian Kuhlman

Inducible systems that perturb the activity of cell signaling molecules are powerful tools for probing pathway dynamics and dependencies in living cells and animals. Photoactivation, or caging, is an excellent method for inducing changes because it can be nearly instantaneous and activation can be spatially localized. Photoactivation of proteins has generally required site-specific chemical modification that is performed *in vitro*, generating analogs that are often difficult to add to cells and are irreversibly activated. Our goal is to create photoactivatable proteins that are genetically encodable, and therefore, can be readily introduced into living cells by DNA transfection. Our design strategy makes use of the naturally photoreactive LOV2 domain from the plant protein phototropin. When activated with blue light, the flavin chromophore in the LOV2 domain forms a covalent bond with cysteine 450, creating a structural perturbation that leads to the unfolding of the C-terminal helix of the LOV2 domain (the α -helix). We will test if the light mediated unfolding of the LOV2 α -helix can be used to control the activities of proteins or peptides that are either fused to or embedded within the α -helix. We will focus on caging proteins and peptides that activate critical signaling pathways in cell migration.

In **aim 1**, fusions with the LOV2 domain will be used to create photoactivatable variants of the small GTPases Rac1, Cdc42 and RhoA. Preliminary studies indicate that caging requires favorable interactions between surface residues on the GTPase and the LOV2 domain. A crystal structure of a LOV2-Rac1 fusion will be used as a template for protein design simulations to identify mutations that stabilize the caged state of LOV2-GTPase fusions.

In **aim 2**, multi-state protein design simulations will be used to vary the sequences of naturally occurring peptide activators and inhibitors so that they can be embedded in the folded α -helix in the dark state, but still bind their target proteins in the lit state.

In **aim 3**, we will test if photoactivatable LOV2 variants and their binding partners can be used as modules for inducing the dimerization of signaling molecules. These studies will reveal general strategies for the photoactivation of proteins with the LOV2 domain as well as provide powerful tools for studying a variety of cellular processes.

Narrative. The correct timing and localization of signal transduction is critical to a variety of biological processes, including differentiation, growth and migration. We are developing new strategies for the rapid and reversible activation of signaling pathways in living cells and animals. These methods will allow biologists to gain a better understanding of pathways linked to a variety of diseases, including cancer, cardiovascular disease, and developmental disorders.

A single aim from the Specific Aims page:

A.1 Design and optimize genetically encodable photoactivatable variants of the GTPases Rac1, Cdc42 and RhoA. GTPases from the Rho family regulate actin and adhesion formation and control the formation of lamellipodia and filopodia. Two separate modeling protocols from Rosetta will be used to stabilize the closed state of GTPase-LOV2 fusions. (1) Using the crystal structure of the Rac1-LOV2 fusion as a template, protein design simulations will be used to identify LOV2 mutations that create favorable contacts with the GTPases. (2) A simultaneous search of sequence and conformational space will be used to design N-terminal extensions to the LOV2 domain that make favorable contacts with the GTPases. In designing the extensions we will also make use of known interaction motifs for GTPases.

Exercise: Highlight each item in the abstract as done above

Checklist for the Specific Aims page.

The questions listed below are designed to help guide you in evaluating the Specific Aims pages of your colleagues.

- Is there a hypothesis? Is it testable?
- Does your outline follow a logical progression from what is known, what is not known (the challenge problem, the question or the gap in knowledge or technology limiting progress), the approach (how your proposal will fill this gap), and the likely outcome (anticipated results and conclusion)?
- Is your question worth answering? Is it important? Significant?
- Is the work innovative?
- Do all of your aims test the hypothesis?
- Do each of your aims stand alone. Does the success of one depend on the success of any other?
- Do you explain what you hope to learn (with anticipated results), rather than emphasizing the method that will be used?
- Is the work feasible? Can you do the experiments? Do you need the help of a collaborator? Does the technology exist?
- Have you checked the document for errors in grammar, spelling, font size, and page format?

We will use the checklist above as a guide in discussing homework assignments.

Class 3: “Bibliography & References Cited”.

How to give credit where credit is due.

Homework to be completed 48 hours before class:

- Read these articles describing some of the consequences of plagiarism:
 - <http://www.nature.com/news/2008/080206/full/451619b.html>
 - <http://www.thecrimson.com/article/2009/3/13/hms-professor-simon-resigns-a-harvard/>
 - [http://www.nature.com/news/image-search-triggers-italian-police-probe-1.14295 -](http://www.nature.com/news/image-search-triggers-italian-police-probe-1.14295)
 - <http://www.sciencemag.org/content/245/4914/120.long>
 - <http://www.apnewsarchive.com/1989/Biologist-To-Appeal-Plagiarism-Charge-By-National-Institutes-of-Health/id-54c175b72b0c1be66f96877de44a309e>
 - <http://www.nature.com/nature/journal/v481/n7379/full/481021a.html>

In class exercise: We will discuss **the last three articles** at length. Be prepared to speak up.

- Write and post a Specific Aims page based on your own research. Provide at least two, and preferably three, aims. Check that you have provided adequate background, **a hypothesis**, anticipated results and conclusion. **Length should be 600-800 words**. There are usually no citations in this section.
 - I suggest modeling your document after the **examples provided on pages 47 and 49 of the syllabus**. You can start by following the same outline and rewriting the text to fit your own work. I'm Ok with you copying the **outline** and **format** but not more than a few words of the **text**.
 - When you are done, read the checklist on p. 21, and revise accordingly. It might also help to read ahead.

For additional reading about plagiarism:

- <http://ori.hhs.gov/sites/default/files/plagiarism.pdf>

The following definition applies to NIH-funded research, and is taken directly from

<http://ori.hhs.gov/education/products/ucla/chapter8/default.htm>

<http://grants.nih.gov/training/responsibleconduct.htm>

“Sec. 93.103 *Research misconduct*.

Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

- **Fabrication** is making up data or results and recording or reporting them.
- **Falsification** is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.
- **Plagiarism** is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.
- *Research misconduct does not include honest error or differences of opinion.*

Sec. 93.104 Requirements for findings of research misconduct.

A finding of research misconduct made under this part requires that--

- There be a significant departure from accepted practices of the relevant research community; and
- The misconduct be committed intentionally, knowingly, or recklessly; and
- The allegation be proven by a preponderance of the evidence.”

For additional information on plagiarism:

http://wps.prenhall.com/hss_understand_plagiarism_1/6/1668/427064.cw/index.html

Although the topic of this class is the bibliography and references cited, we will focus on the topic of plagiarism. Plagiarism is the type of misconduct that is most likely to occur in a thesis proposal or grant application. In general, you must always be honest, accurate and objective in presenting your work and your ideas. *That means giving credit where credit is due.*

Most definitions of misconduct sound as if they were written by lawyers, and perhaps they were. I am not a lawyer, so allow me to translate:

Do not copy.

Do not lie.

If you are unsure what this means, ask your instructor or an experienced coworker such as your thesis advisor or a thesis committee member. If you are not satisfied with the answer, ask someone else. *You are responsible for your own actions*, but your actions can damage the reputation of others. Bad behavior on the part of others, including an unethical collaborator or even a thesis advisor, can damage your own reputation and the reputation of your labmates forever. If you suspect misconduct, it is your responsibility to voice your concerns directly, without making accusations (“I am uncomfortable with this action... can you help?”). Remember, *research misconduct does not include honest error or differences of opinion*. If you are not satisfied with the response, speak with your thesis advisor, members of your thesis committee, director of graduate studies, or ultimately with the department chair.

“Anyone having reason to believe that a member of the faculty or staff has engaged in misconduct in research should consult informally and in confidence with his or her own department chair or equivalent unit head regarding the situation. If the results of such discussions confirm the seriousness of the report, then the matter should be reported, in writing, by that department chair to the Dean.”

(source: <http://policies.unc.edu/policies/research-ethics/>)

Research misconduct includes fabrication, falsification, or plagiarism in research.

Plagiarism

Plagiarism is copying another person's words, ideas, or results without giving that person due credit.

- Do not copy the *words* (that is, whole phrases or sentences) of others.
 - Summarize instead, and cite the original source.
 - When summarizing take care to keep the original meaning.
 - If you must copy, clearly indicate the copied sections using quotation marks and/or italics (as I have done above), and cite the original source.
 - Same rules apply to published and unpublished texts, including grants. You must have permission to cite unpublished work, and you must cite the source.

- Do not copy the *ideas* of others.
 - Summarize instead, and cite the original source.
 - When summarizing take care to keep the original meaning.
 - When summarizing take care to identify which ideas are your own and which are from another source.
 - Do not ignore facts that conflict with your own ideas or results. Cite the relevant work and state that there is disagreement. Conflicting data is a part of science.
 - Same rules apply to published and unpublished texts, including grants. You must have permission to cite unpublished work, and you must cite the source.
- Examples of plagiarism in a grant or thesis proposal:
 - Copying portions of your thesis advisor's review article.
 - Copying portions of a lab mate's research proposal.
 - Copying portions of your thesis advisor's grant application
- Exceptions:
 - "Textbook knowledge". Truly common knowledge that can be found in a basic textbook. For example: "Proteins are made up of amino acids."
 - You might copy sentences describing highly technical information, such as experimental methods, but only when needed to be clear and consistent with previously published work. You must still give credit, so it is usually best to cite the source and simply describe any modifications to the published method.
 - When in doubt, provide a citation, even if it is a textbook or laboratory manual.

What is wrong with plagiarism?

- Plagiarism is fake knowledge. It misrepresents your understanding of a subject and your contribution to the field.
- Fake knowledge is just as serious as fake data.
- Plagiarized publications must be retracted by the journal. This is not always enforced, but it is becoming more common.
- All of your other work – and that of your coauthors and coworkers, past and present - may be seen as suspect.
- You may be dismissed from your position (this has happened).
- You may be prevented from receiving research funding (this has happened).
- You may lose your degree (this has happened).
- You may face legal penalties (and the cost of hiring a lawyer) for misusing federal research funds. Even jail is a possibility (this has happened).
- It is getting easier to detect, and will likely be discovered eventually
 - <http://dejavu.vbi.vt.edu/dejavu/>

How is misconduct handled?

- Faculty and postdocs will be reported to the Research Integrity Officer of the university, who is

required to investigate and report his/her findings to the NIH.

- Students will be reported to the honor court and in some cases to the Research Integrity Officer, particularly if federal research funds were used to support the plagiarized work.
- Your notebooks and data files belong to the university. Failing to keep accurate records of your data may be seen as “evidence of research misconduct.”

Exercise: the consequences of plagiarism:

You have read these articles as homework.

- <http://www.nature.com/news/2008/080206/full/451619b.html>
- <http://www.thecrimson.com/article/2009/3/13/hms-professor-simon-resigns-a-harvard/>

Here is an analysis of the Harvard case, from the dejavu website:

<http://dejavu.vbi.vt.edu/dejavu/duplicate/46778/>

“Roughly 55% of the text in the duplicate is present in the original. Most of the original text in the duplicate is present in the introduction and summary sections. There is some additional information in the duplicate which is not present in the original. The duplicate does not cite the original. The original article has 205 references, the duplicate 161, 159 of which are present in the original's set of references (99%) and appear in the same order (not alphabetical). Published in 2 different journals 1 year apart by different authors.”

Two additional examples of plagiarism in research publications:

1. Another example of duplicated text, different authors, retracted:

<http://dejavu.vbi.vt.edu/dejavu/duplicate/39892/>

“>99% of the text in the duplicate is present in the original articles. Both articles are reviews and present the exact same information. There are 2 figures in the duplicate which are highly similar to those in the original, and have been redrawn. The later article does not cite the original article. The earlier paper has 77 references. All of the duplicate's 64 references are shared with the original (100%). The later article was retracted in 2006.”

2. An example of duplicated text, different authors, *different language*, retracted:

<http://dejavu.vbi.vt.edu/dejavu/duplicate/73804/>

“Roughly 80% of the text in the later article is present in the earlier article, including almost all of the Discussion section. The two case reports are similar in nature but have some differing clinical features. The tumor in the earlier article was caused by a tentorial meningioma while the tumor in the later article was caused by a schwannoma. There are 4 pictures in the later article which are different from those in the earlier article. The earlier paper has 19 references. The later article cites the earlier earlier article. It has 6 references, 5 of which are shared with the original article (83%).”

We will now turn to the topic of **fabrication and falsification**. In this case I can be brief. Fabrication means faking data, which is forbidden. Fabrication and falsification can include:

- Fake data
 - Changing the brightness or contrast of only part of a photographic image
- Real data that is labeled falsely

- Splicing together different images so to appear as one image
- Reporting data that support your conclusion but failing to report data that do not support your conclusion. For example:
 - Showing only a very small part of an image, and removing other parts, in a way that changes the interpretation of the experiment

Exercise: The examples described above might apply to a western blot. Think of some other examples of fabrication and falsification. Are some harder than others to judge?

Discussion points for this class.

Culliton BJ. NIH sees plagiarism in vision paper. *Science*. 1989 245:120-2.

1. This was a watershed event in how scientists viewed research misconduct. What was Bridges accused of doing?
2. What is a “priority dispute”?
3. How was Bridges found out?
4. How was it investigated? Is this a good use of resources?
5. The facts:

“The manuscript reached Bridges' lab in July, but it was not until September that he returned it to Dowling with a handwritten note saying he could not be an expert reviewer because he was working on a nearly identical experiment.”

“When Rando learned about the two abstracts, he called Dowling. Had Dowling sent Bridges his paper to referee? Dowling, in what the NIH panel calls a ‘departure from accepted procedure,’ honestly said that he had.”

“departure from accepted procedure,” - what does this mean?

6. *“Bridges contends that he began the crucial vitamin A isomerase experiments, using frogs, on 14 May 1986. His lab technician and coauthor, Richard A. Alvarez, says the experiments were not begun until the 6th of August-after Bridges had seen the Rando manuscript...”*

“According to the panel, there is no good evidence that Bridges was doing studies that would be logical precursors to the isomerase experiments.”

“Is the Bridges case of alleged theft of intellectual property really unusual, or if NIH's indictment proves out, is it only the fact that Bridges got caught that stands out?”

7. *“The NIH panel declared the Baylor was wrong to conclude that the principal investigator owns his primary data and has authority to destroy them.”*

Who owns primary data?

8. *“Science knew that the Bridges paper was in dispute (though not accused of plagiarism) before publishing it.”*

Should Science have acted differently?

9. Bridges was “convicted” of the following:

“plagiarized privileged information from a draft manuscript sent to him in confidence for peer review”

What does plagiarism mean in this instance?

10. *“failed to promptly decline to act as a peer reviewer, with the possible effect of delaying the manuscript's publication”*

What is wrong with being slow?

11. *“failed to make available to the grantee institution and to the grantor agency adequate primary data related to the scientific research in question”*

Did the grantor (NIH) have a right to ask for the primary data? What’s wrong with discarding data?

12. *“violated accepted standards of conduct for scientific research”*
“violated standards of conduct applicable to principal investigators on federally supported projects”

What does this mean? Are standards different depending on the source of funding?

13. *“disregarded standards of conduct with which he was well familiar in order to deceive others about the conduct of his experiments.”*

What does this mean? What is the difference between “deceive” and “not telling”.

14. **How was Bridges punished?**

15. **What does it mean to be “debarred”?**

16. **What other punishments might have been appropriate?**

17. *“And Bridges is preparing yet another response to NIH. He and his lawyer will argue that a lack of due process precluded them from knowing all of the allegations as the NIH panel was moving along and responding completely to all of the evidence. ‘If I had gone out into the street and murdered someone in full view of 50 people, I would be accorded more safeguards than I got from NIH,’ Bridges contends.”*

Was the process ethical?**Science publishing: How to stop plagiarism.** Nature. 2012 481:21-3.

1. **Harold Garner says:** *“Editors and researchers will also need to agree on a clear definition of plagiarism. Detection software does not define it — instead, it can say only whether a scanned text exceeds a threshold of similarity to another text.”*

Is this a realistic goal? How would you define plagiarism?

2. **Melissa Anderson writes:** *“Getting past a plagiarism checker is simple: change the text just enough to pass detection. Students... keep modifying the text until the checker no longer links it with the original passage. The process, they say, takes the guesswork out of text alteration.”*

What, if anything, is wrong with this approach?

3. **John Loadsman writes:** *“Authors preparing a scientific manuscript in a non-native language sometimes use ‘patch writing’, surrounding their own data with words taken, usually without attribution, from the work of others. This form of plagiarism is among the most common.”*

Is ‘patch writing’ really plagiarism?

4. Bernd Pulverer writes: *“Authors don’t always realize that repeating their own text can be considered plagiarism... The unattributed rehashing of original ideas in an author’s own words is much harder to detect.”*

Miguel Roig writes: *“Some offenders rationalize the practice by claiming ignorance about what distinguishes acceptable paraphrasing from plagiarism, or by complaining that ‘there are only so many ways to say the same thing’.”*

Is there ever an instance where copying is not plagiarism? Is it really possible to self-plagiarize? What is rehashing?

What about this online comment: *“I believe research procedure descriptions, if properly attributed should be actually repeated as verbatim as possible for the repeatability sake.”*

5. Harvard Professor Lee Simon resigned as a result of plagiarism. His response to the accusation: *“I’m very sorry that I’ve been so targeted for something like a review article.”*

What do you think about this? Isn’t a review article a rehash of ideas anyway?

6. Yuehong Zhang & Ian McIntosh write: *“Clearly, the current system of policing plagiarism isn’t sufficient... We propose an additional measure: an international database that blacklists frequent offenders.”*

How would this work? Is it fair to everyone?

7. Sandra Titus writes: *“If I had to choose between buying software to detect plagiarism and directing resources to prevent it, I would choose the latter. That is not to say that detection is unimportant, but honesty and integrity are better served if plagiarism and cheating are prevented.”*

Is time better spent preventing or punishing offenders?

8. The title of the article is “how to stop plagiarism”. Does it provide a solution?

Class 4: Small group.

Class 4 (Small Group). Improving the Specific Aims page

Homework to be completed 48 hours before the first small group meeting:

- Read the Specific Aims pages of two assigned classmates and prepare comments. Do you understand what is being proposed and why? Does it make sense? Is anything missing?
- Prepare a Powerpoint that contains the following five items (one slide per item). This is to help orient your group members. Use bullet points. Keep it short.
 1. Background (what is already known?)
 2. Hypothesis (what is the question?)
 3. Specific Aims (approach, how will you answer the question?).
 4. Anticipated results and conclusions (include preliminary data if you have it).
 5. Statements of Significance and Innovation

Checklist for the Specific Aims page.

The questions listed below are designed to help guide you in evaluating the Specific Aims pages of your colleagues.

- Is there a hypothesis? Is it testable?
- Does your outline follow a logical progression from what is known, what is not known (the challenge problem, the question or the gap in knowledge or technology limiting progress), the approach (how your proposal will fill this gap), and the likely outcome (anticipated results and conclusion)?
- Is your question worth answering? Is it important?
- Do all of your aims test the hypothesis?
- Do each of your aims stand alone. Does the success of one depend on the success of any other?
- Do you explain what you hope to learn (with anticipated results), rather than emphasizing the method that will be used?
- Can you do the experiments? Do you need the help of a collaborator? Does the technology exist?

Class 5: “Research Strategy: Significance, Innovation, Approach”

Is the question worth answering?
Do your aims answer the question?

Homework to be completed 48 hours before class:

- Revise and post the “Specific Aims” section.
- Write and post the “Significance” and “Innovation” sections of your “Research Strategy”. Total length should be 300-500 words.
- Read the “Significance” and “Innovation” sections of two assigned classmates to help guide the discussion in class.

In class exercise: We will read and discuss a few of the documents submitted as homework.

There are three sub-sections within the Research Strategy section: Significance, Innovation, and Approach.

We will begin with the Significance and Innovation sections. We will discuss the Approach section later.

For many of you the Approach will be the easiest part to write. This is where you get to describe what you have already been doing or plan to do in the near future.

It is also relatively easy to evaluate. If something is missing it will be obvious to the reviewers, and they will be sure to let you know. Thus it is an excellent opportunity to derail an otherwise solid proposal.

The Significance and Innovation sections can be the hardest sections to write and are the hardest to evaluate, since there is no objective measure of what is important or exciting. *It is particularly important that you provide your assessment of why the work is innovative and significant.* This will make it easier for the reviewers to appreciate your work and “sell” your proposal to the rest of the review panel.

Research Strategy: Significance and Innovation

According to the NIH, the Significance section “*should explain the importance of the problem or describe the critical barrier to progress in the field that is being addressed. Explain how the proposed research project will improve scientific knowledge... (and how the) field will be changed if the proposed aims are achieved.*” The Innovation section should “*explain how the application challenges and seeks to shift current research or clinical practice paradigms.*”

Every scientist believes that his or her own work is significant. But most scientists don’t spend much time thinking about why other people’s work is significant. Thus you will need to spell it out for the reader. It helps to start with a summary of what is already known, and what remains to be discovered (don’t assume that your reviewers know the status of your field!). *What have been the roadblocks to progress?* You do not have to provide a comprehensive review, but just enough to convince the reviewer that you are knowledgeable in your own area and to show how your research fits into the broader picture. *Then explain how your work will overcome those roadblocks.* It does not have to be a leap forward, but it needs to substantially improve on existing technology or understanding.

Because this section is short, some writers do not take it seriously. Don't make this mistake. If you do not convince reviewers that your work needs to be done, it really doesn't matter if the experiments are carefully planned and well designed. The proposal will not be funded.

The stakes are not as high for a thesis proposal, but the words you use here can be used later to increase the impact of your proposal, your thesis, your thesis seminar, your research publications and your reputation among your colleagues.

Some hypothetical examples of “significance”, some good, some bad...

Enzyme X is likely to be important in multiple diseases.

Critique: Important how? What diseases? Provide an example.

Enzyme X is overexpressed in multiple diseases including diabetes, heart disease and cancer. Thus enzyme X is a potential drug target for the treatment of these conditions.

Critique: Are you going to study all of these diseases? How would such a drug work? How will your research advance the goal?

Enzyme X is a potential drug target for the treatment of diabetes and other conditions. By mapping the substrate-binding pocket of enzyme X (Aim 1), we expect to learn how candidate drugs inhibit enzyme activity (Aim 2). By studying mutants resistant to these inhibitors we will establish the precise cellular function of the enzyme (Aim 3). Given that the activity of enzyme X is elevated in diabetes, our work could pave the way to improved treatments for the disease.

Research Strategy: Approach

In the Approach section you will:

- Describe the background leading to your research
- Restate your hypothesis
- Outline your experimental strategy
- Explain the rationale for your approach
- Describe expected outcomes as well as possible alternative outcomes and how they might affect your plans.
- Include preliminary data supporting the feasibility of your approach (these can be recently published or unpublished results from your lab, and preferably data that you have collected yourself).
- Provide a reasonable estimate of how long it will take, and the order in which things will be done.
- Note any potential pitfalls and provide some alternative approaches.

In writing about your experiments the reviewers will expect you to answer the following questions:

- What will you do? Why are you doing it that way?
- What do you hope to learn? Why are you doing it?
- What might go wrong along the way, and what will you do if it does?

It is your job to answer these questions in a straightforward manner using simple language. The logic should be sound. The organization should be clear. You must do all this in six single-spaced pages. You must not bore the reader.

This brings us to two key questions. How much detail should you include? How do you make sure that reviewers don't lose track of important points? How do you strike a balance between being overly detailed (and potentially dull) and being superficial?

As you write the aims, imagine that you are drawing a roadmap that shows the reviewers where you have been, where you are now, and where you are going. Then you will describe the path to your destination. List the major milestones along the way. Avoid detours that are not important to reaching your goal (which is to test the hypothesis).

Don't take a chance that the reviewer will miss something important along the way. **If it is really important, use bold or italic font to draw attention to it.** Use this device only when it is really important. If you overdo it, the reviewer will stop paying attention.

Summarize the most important points whenever appropriate. How is the information relevant to the hypothesis, the aims, and the overall goals of the project?

Organizing the Approach section

The Approach section will follow the same outline that you used in the Specific Aims section (one more reason to get it right first!). There will be one subsection for each aim.

It is unlikely that your document will be read in one sitting. Each section and each subsection (each aim) of the proposal should stand alone. Don't assume that the reader remembers what you said four pages earlier. So, for each aim it is a good idea to write a brief introduction (a sentence or so) reminding the reviewer of how the aim relates to your hypothesis. If possible, follow with a sub-hypothesis relating to that specific aim. Then provide a brief overview of the experimental strategy, as well as the likely outcome, for that aim. The advantage of this approach is that it helps orient the reader to the broader elements of the proposal.

It is important that you use the same wording for the hypothesis and aims in the Abstract, Specific Aims, and Approach. Changing the wording may confuse your reviewer or, worse yet, it may lead the reviewer to think that you are the one who is confused.

Follow the introduction of each aim with a more detailed description of the experiments. The description must include specific techniques, controls, a plan for data analysis (including an honest assessment of the sensitivity and specificity of each technique), the critical reagents and any specialized instrumentation that you will be using. It must also include a description of the expected outcomes and how these relate to your aims and hypothesis. Finally *you must mention potential pitfalls and alternative approaches.*

At the end provide a brief statement of what you would do next assuming your experiment works or does not work. If you have done a good job of designing your experiments you will always learn something even if it isn't what you expected. *You can't predict every outcome, but you can provide an **example** of a possible outcome and what it would mean.* Better yet, provide specific examples of how similar approaches have yielded new insights before. Reading technical material is usually quite boring. By stressing the potential importance of your anticipated results you are more likely to keep the attention of the reader.

This same pattern should be followed for all of the Specific Aims.

Future directions

At the end of the Approach section you should summarize what you hope to have learned and where you will go from there. This is your last chance to convince the reviewer that your work is worth doing, and that it may lead to even bigger discoveries in the future. In any case it is best not to finish your entire proposal with a technical description of the last experiment of the last aim!

Example

The following structure is the one I use in organizing my aims. Again, make sure that the information here is consistent with that used elsewhere in the proposal (Specific Aims and Abstract). Note that the title of each section is in bold, which helps the reviewer find this specific information easily. Note the use of white space and bold face type to make it visually appealing. Note the use of italics to emphasize the key points.

APPROACH**Aim 1. Functional analysis of monoubiquitinated Gpa1/G α .**

Hypothesis: Monoubiquitination of G α promotes nucleotide exchange and propagation of the signal.

Approach: Our recent preliminary data show the feasibility of purifying – for the first time - large quantities of ubiquitinated protein suitable for detailed biochemical and biophysical analysis. To establish the function of monoubiquitinated Gpa1, we will determine its catalytic activity as well as its ability to bind guanine nucleotides, the receptor, the G $\beta\gamma$ subunits, the GTPase-activating protein and downstream effectors.

Rationale: G α proteins undergo a variety of modifications including myristoylation, palmitoylation and phosphorylation. Gpa1 is also monoubiquitinated, and ubiquitin-site mutants are less able to transmit the pheromone signal. The next step is to establish how monoubiquitination modulates Gpa1 activity. A long term goal is to examine similar events in mammals, since inappropriate activation of G proteins can lead to cancer as well as neurological and cardiovascular diseases.

Anticipated results: We have shown previously that Gpa1 is monoubiquitinated, that monoubiquitination occurs within the helical domain and that monoubiquitination regulates G protein signaling and trafficking *in vivo*. We now seek to investigate the biochemical properties of the modified vs. unmodified protein. To this end we have devised an innovative method for chemical ubiquitination of proteins. In our pilot experiments using Ras we established that monoubiquitination preserves its biochemical properties but severely disrupts the response to GTPase activating proteins (Fig. 5). Monoubiquitinated Ras was shown previously to bind preferentially to GTP, and to promote transformation in cultured cells and in an animal model (50). These results are particularly striking, given the relatively low abundance of monoubiquitinated Ras in cells. These findings are significant because Ras mutations found in cancer also impair GAP-mediated GTP hydrolysis and populate Ras in the GTP-bound activated state (51). *Our findings suggest an entirely new mode of Ras activation, in which Ras signaling can occur in the absence of an extracellular stimulus or gene mutation, through a post-translational modification.*

We will now apply our chemical ubiquitination method to generate monoubiquitinated Gpa1 and analyze all aspects of G protein function. Ras and Gpa1 have distinct binding partners, and are modified in different domains (Ras lacks a helical domain), and so investigation of Gpa1 will provide new and complementary information about cell signal regulation through protein monoubiquitination. Aside from the chemical ubiquitination method (alternative approaches exist), all of the proposed methods are firmly established and are used routinely in the lab, indicating a high likelihood of success.

Detailed methods... <blah blah blah>

For comparison, here is the corresponding text for Aim 1 in the abstract:

Aim 1. Functional analysis of monoubiquitinated Gpa1/G α . We have shown that the helical domain of Gpa1 is monoubiquitinated, and that monoubiquitination is mediated by the ubiquitin ligase Rsp5. To establish the function of monoubiquitinated Gpa1, we will determine its catalytic activity and its ability to bind guanine nucleotides, the receptor, the G $\beta\gamma$ subunits, the GTPase activating protein and downstream effectors.

For comparison, here is the corresponding text for Aim 1 in the Specific Aims page:

Aim 1. Functional analysis of monoubiquitinated Gpa1/G α . We have shown previously that Gpa1 is monoubiquitinated, that monoubiquitination occurs within the helical domain and that monoubiquitination alters G protein signaling and trafficking *in vivo*. *Our hypothesis is that monoubiquitination of G α promotes nucleotide exchange and propagation of the signal.* Our recent preliminary data show the feasibility of purifying, for the first time, large quantities of monoubiquitinated protein, suitable for detailed biochemical and biophysical analysis. To establish the function of monoubiquitinated Gpa1, we will determine its catalytic activity and its ability to bind guanine nucleotides, the receptor, the G $\beta\gamma$ subunits, the GTPase activating protein and downstream effectors....

Note that the language is identical for each section.

In preparing your own Approach section, I recommend the outline I used above:

APPROACH

Start with a paragraph summarizing the previous section.

Aim 1. Restate the aim.

Hypothesis – A one sentence sub-hypothesis relating to this aim.

Approach – A few sentences outlining the overall strategy.

Rationale – A few sentences outlining how the aim fits into existing knowledge. Note any technical or conceptual breakthroughs that have allowed you to do the work proposed.

Anticipated Results – A few sentences outlining the hoped-for results.

Detailed Methods – A page or more providing the experimental details, examples (preliminary data), pitfalls and alternative approaches.

A note about preliminary data

Preliminary data are used as **examples** of the kind of data you will collect. They show that you can do the proposed experiments and interpret the results correctly. They show feasibility. They also show how planned experiments build on past experience. However you must relate the results specifically to your proposed work. Together they help to convince the reviewer that you know what you are doing, and that your research plan makes good use of your special skills and knowledge (or those of your lab group). As you interpret your preliminary results, make sure that you consider alternative interpretations; this shows reviewers you have thought deeply about the approach and you are prepared to meet future roadblocks.

Quality matters. If your gels are overexposed, poorly labeled, or lacking controls, you will invite even greater scrutiny of your research plan. If the data are truly awful, leave them out.

Preliminary data does not necessarily mean unpublished data. Use recently published data if it helps to illustrate your experimental plan. If you can make the same point by referencing a publication, use the space for something more important. On the other hand **you cannot expect that the reviewer will**

look at any referenced article. If the approach or result is uniquely important, put it in the proposal.

You can put your preliminary data anywhere in the Research Strategy but don't make the reviewers hunt for it. Best to put it close to the text where it is first referenced, or wherever it will do the most good, but you must relate the results specifically to your proposed work.

Experimental details

The amount of detail you include depends upon several factors including the background of your reviewers and your experience with the approach. The amount of experimental detail almost never approaches that seen in a scientific publication. For standard techniques it is usually sufficient to provide a summary and reference the published literature. For non-standard methods it is especially important that you provide evidence that the method works as advertised. Discuss the advantages and limitations of the approach. For example: is your method sufficiently sensitive to measure the changes you are looking for? How reproducible are the results obtained with the technique? If there is any chance whatsoever that the approach will not work you must propose a back-up strategy.

More about figures

Cartoon models and preliminary data help an application in other ways: they can illustrate complex information in a small space and they can break up large blocks of text in your application, adding visual interest. If your experimental plan is complex or involves numerous decision points, consider adding a timetable, flowchart or decision tree. Figure legends are also a good place to include less important experimental detail because the fonts can be smaller (they must still be legible!). In designing your figures, remember that some reviewers still prefer to print out proposals so you must be certain that yours can be read on a printed page.

The following is an example from a hypothesis-driven grant proposal on a GTPase (from Henrik Dohlman)

SPECIFIC AIMS

Many chemical and sensory signals act via cell surface receptors, heterotrimeric G proteins and effector enzymes. The G protein is composed of three subunits (α , β and γ), and the α subunit is comprised of two domains: the Ras domain and the helical domain. Of these, it is the Ras-like domain that binds to guanine nucleotides, GTPase activating proteins, effector enzymes and the $G\beta\gamma$ subunits. The helical domain is composed of an all- α -helical structure but has few known binding partners and has received scant consideration. Recent analysis, using a variety of experimental systems, has drawn new attention to the $G\alpha$ helical domain. These studies have revealed that the helical domain can undergo conformational changes and post-translational modifications with profound effects on signaling. The proposed research will establish the structural basis and functional consequences of helical domain phosphorylation, ubiquitination, and interaction with novel protein binding partners.

The most dramatic evidence for the importance of the helical domain comes from recent structural and biophysical studies of a receptor/G protein complex. X-ray crystallography and electron microscopy studies revealed that receptor activation triggers a major reorientation of the helical domain away from the Ras-like domain. Our own crystallographic, biochemical and molecular-dynamics analyses have focused on a spontaneously activating (receptor-independent) G protein in plants (*Arabidopsis thaliana*). We found that a portion of the helical domain is especially dynamic, and that plant-animal chimeras containing the most dynamic segments from the plant G protein are likewise self-activating. In particular the αA helix is almost entirely responsible for the differences in activation. These results were particularly surprising given that the αA helix is quite distant from regions involved in receptor coupling, effector activation, nucleotide binding and hydrolysis. Together these findings indicate that helical domain dynamics are important for G protein activation.

Finally our analysis has revealed a number of post-translational modifications within the helical domain. Our analysis of a G protein α subunit in yeast (Gpa1) revealed that the helical domain is mono-ubiquitinated and poly-ubiquitinated. Each of these modifications requires a distinct ubiquitin ligase, and they have distinct consequences for G protein trafficking and degradation. We showed further that the helical domain is phosphorylated and that phosphorylation triggers polyubiquitination. Cells lacking the Gpa1 kinase or ubiquitin ligase, or that express a Gpa1 mutant protein that is not phosphorylated or ubiquitinated, exhibit altered signaling properties *in vivo*. *Taken together these findings suggest a functional link between helical domain dynamics, protein-protein interactions, post-translational modifications and proper signal transduction.*

More broadly, these recent findings have elevated the status of the G protein helical domain. Long considered to be devoid of major function, our hypothesis is that the helical domain serves as a dynamic regulator of G protein activity, and that post-translational modifications of the helical domain regulate G protein activity. Our approach will include biochemical analysis as well as cell-based assays of modified and unmodified G protein in yeast (Gpa1). Through existing collaborations we will, in the longer term, investigate parallel processes in plant and animal cells.

Aim 1. Functional analysis of monoubiquitinated Gpa1/ $G\alpha$. We have shown previously that Gpa1 is monoubiquitinated, that monoubiquitination occurs within the helical domain and that monoubiquitination alters G protein signaling and trafficking *in vivo*. *Our hypothesis is that monoubiquitination of $G\alpha$ promotes nucleotide exchange and propagation of the signal.* Our recent preliminary data show the feasibility of purifying, for the first time, large quantities of monoubiquitinated protein, suitable for detailed biochemical and biophysical analysis. To establish the function of monoubiquitinated Gpa1, we will determine its catalytic activity and its ability to bind guanine nucleotides, the receptor, the $G\beta\gamma$ subunits, the GTPase activating protein and downstream effectors.

Aim 2. Functional analysis of Gpa1/ $G\alpha$ phosphorylation. We have shown that Elm1 phosphorylates Gpa1 directly, that Gpa1 is phosphorylated in the helical domain, and that phosphorylation triggers Gpa1 poly-ubiquitination. Thus Elm1 is a G protein kinase. Moreover, Elm1 is expressed primarily in G2/M phase of the cell cycle. Thus Elm1 regulates the G protein in a dynamic, cell cycle-dependent manner. Our recent preliminary data reveal that the helical domain is also phosphorylated under low-glucose conditions, and that phosphorylation in this case is mediated by the three AMPK ("glucose-sensing") kinases in yeast. *Our hypothesis is that the helical domain is phosphorylated by multiple protein kinases, depending on receptor stimulus and nutrient availability, thereby altering the catalytic and binding properties of the G protein.* To establish the function of phosphorylated Gpa1, we will determine the ability of each kinase to alter G protein ubiquitination, catalytic activity and signaling functions, both *in vivo* and *in vitro*.

Aim 3. Functional analysis of proteins that target monoubiquitinated Gpa1/ $G\alpha$. We have shown previously that monoubiquitination promotes Gpa1 endocytosis and delivery to the vacuole/lysosome compartment. Our recent preliminary data reveal several "ubiquitin-binding domain" (UBD) proteins that are also necessary for the endocytosis of Gpa1; we will investigate the subset of UBD proteins that target Gpa1 specifically. *Our hypothesis is that UBD proteins bind directly to the monoubiquitinated helical domain of Gpa1, and thus alter G protein function.* We will determine the ability of each binding partner to alter G protein trafficking, catalytic activity and signaling functions, both *in vivo* and *in vitro*.

SIGNIFICANCE:**Overview**

Our recent investigations have revealed new and surprising modes of cell regulation. These include dynamic post-translational modifications of the G protein Gpa1. We have shown that the helical domain of Gpa1 is phosphorylated by Elm1 (1), mono-ubiquitinated by Rsp5 (2), and poly-ubiquitinated by the SCF^{Cdc4} protein complex (3). In this proposal we will establish the functional consequences of these modifications. Below we highlight results leading up to this proposal, and why we consider the work to be significant.

If successful, our experiments will reveal additional mechanisms of signal regulation including new G protein kinases (Aim 2) and binding partners involved in trafficking (Aim 3). Further, they will establish a direct link between the nutrient-sensing and G protein signaling pathways (Aim 2). A deeper understanding of how cells transmit their signals, particularly those that act in new and unexpected ways, could eventually lead to fundamentally new treatments for human disease. Delineating such new mechanisms is the central objective of our research program.

G proteins in pharmacology and physiology.

G protein-coupled receptors are significant because they mediate critical physiological processes such as blood pressure and heart rate (e.g. by epinephrine), perception of pain (opioids), mood (serotonin), movement and motivation (dopamine), cell proliferation (trophic factors), inflammation (histamine, prostaglandins, chemokines), coagulation (thrombin) and diuresis (vasopressin). Approximately one-third of all drugs act by binding directly to receptors of this class (4). Many of these drugs compete with endogenous hormones and neurotransmitters (e.g. beta-blockers, anti-histamines). Others work indirectly, through the inhibition of pro-hormone processing or neurotransmitter reuptake (ACE inhibitors, SSRIs). Still others act by slowing the degradation of intracellular second messengers (Viagra). Remarkably, the targets for most of these drugs have been known for 30 years or more. Our broad goal is to identify new proteins and processes that regulate G protein signaling.

Thus the proposed research is significant because it investigates new pathway components that could eventually reveal new drug targets. Generally speaking, G protein-coupled receptors act by binding to a G protein heterotrimer, thereby promoting exchange of GDP for GTP on the G α subunit and dissociation from the G $\beta\gamma$ subunit complex (5) (Fig. 1A). Depending on the system, either G α or G $\beta\gamma$ (or both) can activate effector enzymes within the cell. Upon GTP hydrolysis the G protein subunits re-associate and signaling stops. Regulators of G protein signaling (RGS proteins) accelerate GTP hydrolysis, further promoting signal inactivation (6, 7). In this proposal we will consider the role of newly identified G protein-binding proteins, and in particular those acting on the G α helical domain.

Upon GTP hydrolysis the G protein subunits re-associate and signaling stops. Regulators of G protein signaling (RGS proteins) accelerate GTP hydrolysis, further promoting signal inactivation (6, 7). In this proposal we will consider the role of newly identified G protein-binding proteins, and in particular those acting on the G α helical domain.

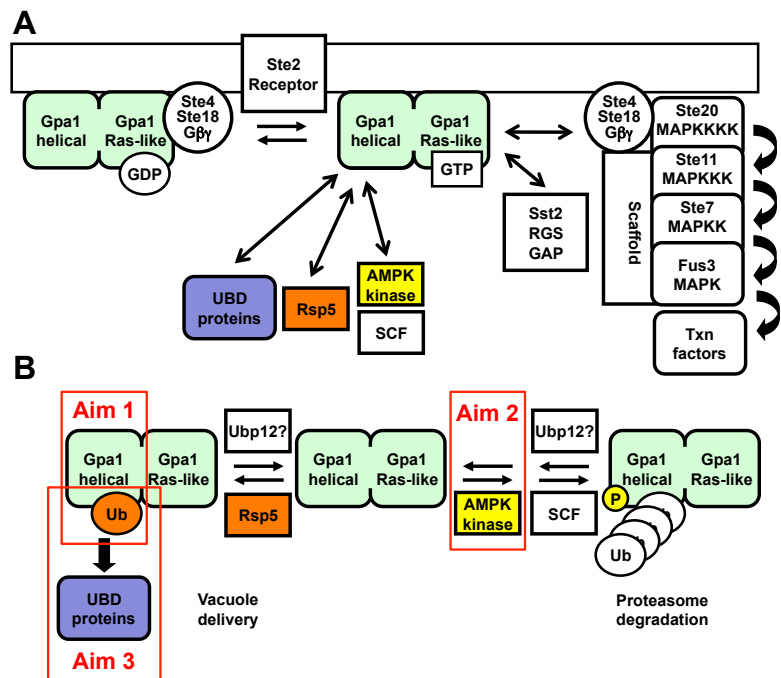


Fig 1. G protein signaling in yeast. **A**, Activation of the pheromone receptor triggers GDP-GTP exchange and dissociation of the G protein α (Gpa1) and $\beta\gamma$ (Ste4/Ste18) subunits. G $\beta\gamma$ activates a kinase scaffold and MAP kinase cascade. G α subunits are composed of a Ras-like domain and an all-helical domain. Some components omitted for brevity. **B**, Newly identified components of the signaling pathway that act via the helical domain of the G protein. These include AMPK kinases Elm1, Tos3 and Sak1 (yellow, **Aim 2**). Elm1 phosphorylation promotes polyubiquitination by SCF and degradation by the proteasome. Rsp5 promotes monoubiquitination (orange, **Aim 1**), endocytosis requiring ubiquitin-binding domain proteins Ede1, Bul1, Rup1 and Ddi1 (UBD proteins) (purple, **Aim 3**) and delivery to the vacuole. Ubp12, presumed ubiquitin protease

An example from a technology-driven grant proposal on a GTPase (from Brian Kuhlman)

SPECIFIC AIMS

Inducible systems that perturb the activity of cell signaling molecules are powerful tools for probing pathway dynamics and dependencies in living cells and animals. Photoactivation, or caging, is an excellent method for inducing changes because it can be nearly instantaneous and activation can be spatially localized. Photoactivation of proteins has generally required site-specific chemical modification that is performed *in vitro*, generating analogs that are often difficult to add to cells and are irreversibly activated. Our goal is to create photoactivatable proteins that are genetically encodable, and therefore, can be readily introduced into living cells by DNA transfection. Our design strategy makes use of the naturally photoreactive LOV2 domain from the plant protein phototropin. When activated with blue light, the flavin chromophore in the LOV2 domain forms a covalent bond with cysteine 450, creating a structural perturbation that leads to the unfolding of the C-terminal helix of the LOV2 domain (the J α -helix).

We will use the light mediated unfolding of the LOV2 J α -helix to control the activities of proteins or peptides that are either fused to or embedded within the J α -helix. In preliminary studies with Klaus Hahn's laboratory at UNC we have created a genetically encodable variant of the small GTPase Rac1, called PARac1. In this design, Rac1 is fused directly to the LOV2 J α -helix and there is a 10-fold change in binding affinity for the Rac1 effector CRIB between the lit and dark states. A crystal structure of the fusion protein in the dark state shows that the LOV2 domain makes direct contacts with Rac1, sterically blocking binding to the CRIB domain. Here, we will use the molecular modeling program Rosetta to further stabilize the closed state of PA-Rac1 by identifying mutations that stabilize the interaction between LOV2 and Rac1 in the fusion protein. Additionally, we will extend this strategy to other small GTPases. To further test the caging capacity of the LOV2 domain we will use multistate design simulations to create sequences that can be partially embedded in the J α -helix and are still competent to bind their targets when the J α -helix is unfolded by light activation. Biophysical testing will be used to identify promising designs, which will be used by our collaborator, Klaus Hahn, in live cell experiments studying cell migration.

A.1 Design and optimize genetically encodable photoactivatable variants of the GTPases Rac1, Cdc42 and RhoA. GTPases from the Rho family regulate actin and adhesion formation and control the formation of lamellipodia and filopodia. Two separate modeling protocols from Rosetta will be used to stabilize the closed state of GTPase-LOV2 fusions. (1) Using the crystal structure of the Rac1-LOV2 fusion as a template, protein design simulations will be used to identify LOV2 mutations that create favorable contacts with the GTPases. (2) A simultaneous search of sequence and conformational space will be used to design N-terminal extensions to the LOV2 domain that make favorable contacts with the GTPases. In designing the extensions we will also make use of known interaction motifs for GTPases.

A.2 Cage peptide-binders by embedding them in the J α -helix of the LOV2 domain. Multistate design simulations will be used to vary the sequences of naturally occurring peptide activators and inhibitors so that they can be embedded in the folded J α -helix in the dark state, but still bind their target proteins in the lit state. We will test our approach with an activator of vinculin and an inhibitor of calpain. Vinculin and calpain regulate the assembly and disassembly of focal adhesions, a critical process in cell migration. To generalize this approach to any target protein of interest, we will design a peptide library that is compatible with caging by the J α -helix, and can be screened for sequences that bind target protein. To test our designed library, we will use phage display to identify binders to the PAK1 kinase, and then insert the candidate sequences into the J α -helix to test for caging.

A.3 Use the LOV2 domain for the photoactivatable dimerization of signaling proteins. Induced dimerization can increase the local concentration of signaling molecules and activate signaling pathways. In preliminary results we have created a variant of the LOV2 domain that binds the N-terminal domain of the protein vinculin with an affinity of ~30 nM in the lit state, and >5 μ M in the dark state. Our hypothesis is that this can be used as a general dimerizer by attaching the LOV2 variant to protein X, and the domain of vinculin to protein Y. However, for this to be a useful reagent for studies in mammalian cells we will need to redesign the pair so that there is little affinity for endogenous vinculin and vinculin binding peptides, but still strong affinity between the designed pair. We will use Rosetta to design this orthogonal pair and validate the designs with biophysical testing and the yeast two-hybrid assay.

Class 6: Reading and Writing part 1. How your proposal will be read.

Homework to be completed 48 hours before class:

- Revise and post the Significance and Innovation sections.
- Write and post Aim 1 of the Approach section (at least through Aim 1) of your Research Strategy.

In class exercise: We will read and discuss a few of the documents submitted as homework.

Any NIH proposal, and by extension almost any research proposal, will be evaluated on the basis of

- **Overall Impact**
- **Significance**
- **Investigator**
- **Innovation**
- **Approach**
- **Environment**

Any substantial weakness can kill a grant, but lack of impact or significance is the most common cause of death. A proposal that is solid but unexciting will fail. Ask yourself, are you addressing the most important questions in your field? This should be obvious after reading just the first page (Specific Aims section).

Here is how NIH defines each of the criteria.

Source: http://grants.nih.gov/grants/peer_review_process.htm

The mission of the NIH is to support science in pursuit of knowledge about the biology and behavior of living systems and to apply that knowledge to extend healthy life and reduce the burdens of illness and disability. As part of this mission, applications submitted to the NIH for grants or cooperative agreements to support biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system.

Overall Impact. Reviewers will provide an overall impact/priority 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 review criteria, and additional review criteria (as applicable for the project proposed).

Scored Review Criteria. Reviewers will consider each of the review criteria below in the determination of scientific and technical merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example,

a project that by its nature is not innovative may be essential to advance a field.

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?*

Investigator(s). *Are the PD/PIs, collaborators, and other researchers well suited to the project? If Early Stage Investigators or 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-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?*

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 and members of both sexes/genders, as well as the inclusion of children, justified in terms of the scientific goals and research strategy proposed?*

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?*

We'll now go through the evaluation criteria **in approximate order of importance.**

Impact/Significance

If you can relate your work to human health, do so, but don't force it. Your proposal will be evaluated by like-minded scientists. If you find your work significant and innovative - and hopefully you do - use language that any fellow scientist can understand.

Perhaps the health benefits are indirect or long term. For example a climatologist could relate his/her research to human health because of the impact of drought on hunger, poverty and conflict. Perhaps you're not certain where your work will lead. In this case you might provide an example of how similar work in the past has led to health-related discoveries.

Keep it simple. Remember that most reviewers, particularly for foundation grants and even at NSF or NIH, will be intelligent but not necessarily knowledgeable about the subject of your proposal.

Even if you are lucky enough - or unlucky enough - to have three expert referees reviewing your application, they will need your help to explain your work to the rest of the review panel. Give them the ammunition they need to convey the significance and the potential impact of the proposal.

What kind of ammunition?

First, you need to state why the work is important. Applicants often say the proposal is "important for understanding such-and-such a disease", but fail to make a connection between the proposed research and the disease. Be specific. Use examples to bolster your case.

Second, you must write for a broad audience. Make it easy for the non-expert to understand your goals, and why they are important. Provide "quotable" statements that the reviewer can use in preparing his/her critique.

In my own applications I have gone so far as to begin sentences with: "The proposed research is significant because..." or "There are several innovative aspects of the proposed work. They are..."

Approach

This is your best opportunity to screw things up by making technical errors or leaving out important information. Don't do it.

State a hypothesis. One could argue about whether any project needs to be hypothesis-driven, but in my experience the most successful applications have a strong central hypothesis. Even a technology- or discovery-driven proposal can have a hypothesis. How has sequencing of the human genome affected your research? Could that have been anticipated? Can you state a hypothesis to that effect?

The hypothesis should be clearly stated in the specific aims page. Use as few words as possible. Then elaborate if necessary. Finish the following (quotable) sentence: "Our overall hypothesis is..."

Describe your rationale, complementary methods, critical controls, pitfalls, alternative approaches, anticipated results and interpretation.

Aims should be interrelated, but one aim should not depend on the success of another.

Rationale. *Explain why the question you are about to answer has now become answerable.* Justify your choice of experimental system or approach. If you are using assay X, cell line Y, or organism Z, explain your choice.

Complementary methods. The strongest grants are multi-dimensional. That is, they use multiple complementary approaches to address the question. For example, a protein crystal structure is most informative if you can make predictions about how structure dictates function, and then test those predictions. Other integrated approaches might include molecular and cellular analysis, genetics and physiology, or experimental and computational approaches.

Controls and potential pitfalls. Describe the limitations of each method or reagent. What are the biggest challenges that you will face with each aim? You might worry that highlighting the limitations of each approach will weaken your proposal. Quite the contrary, it shows that you are aware of the potential problems, and you have made a reasoned choice based on the pros-and-cons of each method. That said, you should explain how you plan to confirm or corroborate your findings using complementary methods and appropriate controls. If you don't mention the pitfalls, your reviewers will point them out for you, and then you are in trouble.

Alternative approaches. In describing alternative methods, **use an "inverse pyramid" structure.** Describe the primary approach in greatest detail, an alternate approach in just a paragraph or less, others in just a few sentences. Again, include the key controls. Do not describe buffer conditions, oligo

sequences etc. You will only bore your audience. For each key method provide a reference, ideally to a paper you or your lab has published already, to prove that you can do it.

Anticipated results and interpretation. Be explicit about what you hope to learn. Perhaps you expect a mutation to affect organ development or gene expression. What do you mean by “affect”? Will gene expression go up or down? How will you interpret that change? **How does it test the hypothesis?** In the broader sense, how will this new knowledge transform our understanding of the subject (if the work is truly important, this should be easy!). Again, avoid statements that are overly vague (“we expect to gain important insights”) or descriptive (“measurements will reveal changes in the strengths of interactions”).

Investigator

Convince the panel that you have the experience to do the experiments properly. The best evidence is to cite your publications, or preliminary data, where you have used the proposed methods (“These experiments are similar to those we conducted previously, as described in Ref. # and in Fig. #”). Obtain letters from expert collaborators when needed, expressing their precise role and their commitment to the project. Letters from collaborators do not need to be long, but they need to indicate a genuine understanding of what you are proposing, and *specifics* about how they will help the project succeed.

Publications matter greatly. Journals can choose any qualified reviewers to evaluate a manuscript. NIH is more limited, and must rely on a review panel of individuals who are broadly knowledgeable about the subject; they may not have specific knowledge about you or what you do. For this reason, grant reviewers will look at your publication record and make a judgment based on where you publish. A strong publication record is the best evidence of competence, experience, and the ability to “deliver” on your great ideas. Similarly, a history of high profile publications is the best evidence of significance and impact. A weak publication record (in *either* quantity or quality) will be a concern.

Publications - unlike grants - are subject to “real peer review”, and are often the best predictor of future productivity.

Innovation

You need to explain why the work is **innovative**. Finish the sentence “This approach is innovative because...” It will help if you can say (with complete honesty and due humility) that you are the first to do something or especially well qualified to do it.

However “new” does not always mean “innovative”. Maybe nobody has done it because nobody cares.

Many investigators claim that their grant was scored poorly because it lacked innovation. In my experience (don’t hate me for saying this), when reviewers cite a lack of innovation they were uninterested in the proposal and needed something to complain about.

Environment

You have little control over your physical environment, but it is also rarely a factor. It never hurts to list the equipment available to you, any animal or equipment core facilities you will use. You can also highlight the intellectual environment. Describe what great colleagues or collaborators you have, including thesis committee members, who are available to help you succeed. Describe the journal clubs and seminars that you attend and that enrich your environment.

Discussion points for this class.

Top ten reasons a grant is not funded – all are “weaknesses”. Do any of these “reviewer complaints” apply to your proposal?

1. “Key statements are not referenced.” Can you point to high-impact publications as the foundation of your proposal?
2. “There are numerous spelling and grammatical errors.” If you are not willing to carefully check the accuracy of your own proposal, why should I bother to read it carefully?
3. “The specific aims are not closely related.” If all your aims address a central hypothesis, this should never be an issue.
4. “The rationale is unclear.” Tell me exactly why you think your work is worth doing. Don’t make me guess.
5. “The applicant does not have experience with the proposal methods.” Provide preliminary data, find a collaborator, or change the approach. Convince me that you can do the work.
6. “Potential pitfalls and alternative approaches are not discussed.” “The limitations of the method are not adequately addressed.” Has it occurred to you that some of your experiments will fail? What will you do when that happens.
7. “The success of this aim depends on the success of a previous aim.”
8. “The proposal is descriptive, not mechanistic.” What do you hope to discover? Be specific. Provide examples of possible outcomes.
9. “There are insufficient preliminary data.” Prove to me that you can do the work.
10. “The study is methods-driven, not hypothesis-driven.” By this point in the class, this should not be an issue with your proposal.

Can you come up with a top ten list of “strengths”? Some will be the opposite of the 10 statements listed above.

Source: http://grants.nih.gov/grants/peer_review_process.htm

The following guidance is given to reviewers to determine individual review criterion and overall impact scores. The same guidelines will be used in the final review of your proposal.

High Impact Table

Score	Descriptor	Additional Guidance on Strengths/Weaknesses
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 Impact Table

Score	Descriptor	Additional Guidance on Strengths/Weaknesses
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 Impact Table

Score	Descriptor	Additional Guidance on Strengths/Weaknesses
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 = Abstinence, 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

How R01 grants and F31 fellowship scoring systems differ

In an NIH F31 predoc fellowship application, the research project is integrated with the training plan and the five review criteria are different. As I have done above, the review criteria are listed in approximate order of importance; you will note that **the actual research plan is less important than the training environment and training plan**. In writing their critiques, the reviewers are asked to comment on “*the applicant’s potential for an independent, scientific research career, the applicant’s need for the proposed training, and the degree to which the research project and training plan, the sponsor(s), and the environment will satisfy those needs.*” If you describe a training plan or career goals that don’t include research, your proposal will do poorly. The specific F31 criteria (<http://grants.nih.gov/grants/guide/pa-files/PA-14-147.html>) are shown in Italics.

F31: Fellowship Applicant (vs. R01: **Investigator(s)**).

Since your publications are likely to be few in number, the reviewers will want to know about your past academic record (grades, but not GREs) and research experience. In addition you will need to describe your commitment and potential to develop into an independent and productive researcher.

F31: Sponsors, Collaborators, and Consultants.

- *Are the sponsor(s)’ research qualifications (including recent publications) and track record of mentoring individuals at a similar stage appropriate for the needs of the applicant?*
- *Is there evidence of a match between the research interests of the applicant and the sponsor(s)? Do the sponsor(s) demonstrate an understanding of the applicant’s training needs as well as the ability and commitment to assist in meeting these needs?*
- *Is there evidence of adequate research funds to support the applicant’s research project and training for the duration of the fellowship?*
- *If a team of sponsors is proposed, is the team structure well justified for the mentored training plan, and are the roles of the individual members appropriate and clearly defined?*
- *Are the qualifications of any collaborator(s) and/or consultant(s), including their complementary expertise and previous experience in fostering the training of fellows, appropriate for the proposed research project?*

F31: Research Training Plan (vs. R01: **Approach, Significance and Innovation**).

- *Is the proposed research plan of high scientific quality, and is it well integrated with the applicant’s training plan?*
- *Is the research project consistent with the applicant’s stage of research development?*
- *Is the proposed time frame feasible to accomplish the proposed research training?*
- *Based on the sponsor’s description of his/her active research program, is the applicant’s proposed research project sufficiently distinct from the sponsor’s funded research for the applicant’s career stage?*

F31: Training Potential

- *Do the proposed research project and training plan have the potential to provide the applicant with the requisite individualized and mentored experiences that will develop his/her knowledge and research and professional development skills?*
- *Does the training plan take advantage of the applicant’s strengths, and address gaps in needed skills? Does the training plan document a clear need for, and value of, the proposed training?*
- *Does the proposed research training have the potential to serve as a sound foundation that will facilitate the applicant’s transition to the next career stage and enhance the applicant’s ability to develop into an independent and productive research scientist?*

F31: Institutional Environment & Commitment to Training (vs. R01: **Environment**).

In addition to describing the research facilities, resources (e.g., equipment, laboratory space, computer time, subject populations), it is important to describe any research training opportunities (e.g. seminars, workshops, professional development opportunities) provided by the institution and the department.

How NSF and NIH scoring systems differ

Overall Impact scores for NIH should be assigned on the basis of five main considerations, which are similar to those that are addressed in NSF Criterion 1, "**What is the intellectual merit of the proposed activity?**" The weight given to each criterion is determined by the reviewer and may vary from one application to another, depending on the nature of the application and its relative strengths.

The specific NIH criteria are shown in *Italics* following the NSF considerations.

1. NSF: How important is the proposed activity to advancing knowledge and understanding within its own field or across different fields?

NIH: **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?*

2. NSF: How well qualified is the proposer (individual or team) to conduct the project? (If appropriate, the reviewer will comment on the quality of the prior work.)

NIH: **Investigator(s):** *Are the PD/PIs, collaborators, and other researchers well suited to the project? If Early Stage Investigator or New Investigators, 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-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project??*

3. NSF: To what extent does the proposed activity suggest and explore creative and original concepts?

NIH: **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?*

4. NSF: How well conceived and organized is the proposed activity?

NIH: **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 and members of both sexes/genders, as well as the inclusion of children, justified in terms of the scientific goals and research strategy proposed?*

5. NSF: Is there sufficient access to resources?

NIH: **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?*

Class 7: Small group.

Class 7 (Small Group). Improving the Approach section.

Homework to be completed 48 hours before the small group meeting:

- Read the Approach section of two assigned classmates and prepare comments. Use the final checklist to evaluate Aim 1.

Checklist for the Approach section.

The questions listed below are designed guide you in evaluating the Approach section.

- Do you clearly explain the significance of the work? Is your question worth answering? Is it important?
 - Will the reviewer be able to complete the sentence “This work is **significant** because...”
- Do you clearly explain how the work is innovative?
 - Will the reviewer be able to complete the sentence “This work is **innovative** because...”
- Is there a hypothesis? Is it testable? Is it clear how each aim and each experiment relates to the hypothesis.
- Have you stated the **anticipated results**?
 - For each experiment do you explain what you hope to learn, rather than emphasizing the method that will be used (anticipated results)?
 - Will the reviewer be able to complete the sentence “This experiment will determine...”
- Is it clear that you are **qualified** to do the work.
 - Do you demonstrate feasibility for each of your experiments, either by citing your own published work or providing preliminary data?
 - If not, do you enlist the help of a collaborator?
- Have you explained potential **pitfalls** (how major experiments might fail) and the **alternatives** available.
 - Does the technology exist?
 - For each, can you complete the sentence “One potential pitfall of this approach is...”
 - For each, can you complete the sentence “If we do not succeed using this approach, we will instead...”

Class 8: Reading and Writing part 2.

How to express your ideas clearly.

Homework to be completed 48 hours before the final class:

- Revise and post the Approach section (at least through Aim 1) of your Research Strategy.
- Include one or two examples of preliminary data (from you or your lab) that demonstrate feasibility (they can be included in any portion of the proposal but are usually under Approach).
- Write and post your Project Summary.

In class exercise: We will read and discuss a few of the documents submitted as homework.

In the first class we discussed the outline of your proposal. As I said then, the foundation of a good grant is a well-designed plan (an outline) and the best of materials (clear writing). The following section focuses on clear writing. It starts with the building blocks (the words that make up a sentence) and works its way through paragraphs and the overall document. It is best if you have an outline before you start so you can be most efficient in your writing.

What is clear writing?

Clear writing is writing that is incapable of being misunderstood. It is much more than *writing that is able to be understood.* Clear writing exposes faulty reasoning and inconsistencies. It will force you to propose better experiments.

The Sentence

Writing for science is a special skill. The language is highly technical, and there are usually severe limits on space and structure. It is a challenge to compress a multiyear research plan – including background, experimental approach, anticipated results and alternative approaches – all into six pages. Since you don't have room to spare, you will need to convey information with few words. Your language must be clear and precise! The information needs to be presented in the proper order. That doesn't mean scientific writing has to be boring - above all you don't want to bore your audience.

Here's how.

Be clear. Be direct.

- Avoid **abbreviations** and acronyms unless they are REALLY common (DNA, ATP, AIDS etc). They save space, but they also require the reader to stop, translate, and restart the process of reading your document. They are also exceedingly dull to read.
 - "We used the mAb to detect each MAP3K by sequential IP, SDS-PAGE and WB followed by ECL."
- Avoid **vague (or obscure) words** that require the reader to pause and guess your true meaning.
 - "HIV is *involved* in the development of AIDS.
 - "HIV *promulgates* AIDS.
 - "HIV *causes* AIDS."

- Avoid **jargon**, contractions and colloquialisms (“lab lingo”). Avoid giving inanimate objects the power of possession. Avoid “get”. These sound unprofessional.
 - “The mutant receptor **can’t be** phosphorylated.”
 - “The mutant **receptor’s** inability to **get** phosphorylated.”
 - “The mutant receptor cannot be phosphorylated.”
 - “The cells were **spun down**.” “The cells were **pelleted**.”
 - “The cells were collected by centrifugation.”
- Avoid redundant or any other **unnecessary words**. Be direct.
 - “Pharmacologic modulation of HIV infectivity could potentially be of therapeutic benefit in the treatment of AIDS.”
 - “Drugs that block HIV infection are likely to prevent AIDS.”
 - “The treated animals engaged in greater consumptive behavior.”
 - “The treated animals ate more.”
- Use strong, simple and **direct verbs and adjectives**. Avoid too many verbs or adjectives in one sentence. Avoid adverbs altogether.
 - “Current evidence is **consistent** with AIDS **being due** to infection of individuals with the human retrovirus HIV.”
 - “HIV **causes** AIDS.”
 - “**The reason why** he has an immune deficiency is because he is infected with HIV.”
 - “He has an immune deficiency because he is infected with HIV.”

“Most adverbs are unnecessary. You will clutter your sentence and annoy the reader if you choose a verb that has a specific meaning and then add an adverb that carries the same meaning. Don’t tell us that the radio blared loudly; ‘blare’ connotes loudness... strong verbs are weakened by redundant adverbs.” – from *On Writing Well*, by William Zinsser

Word order

- Place the **subject** near the beginning or end of the sentence. Be direct.
 - “It is **by binding** to cell surface receptors that most **hormones** act.”
 - “Many **hormones act by binding** to cell surface receptors.”
- Keep **related things** together. Keep subjects and verbs together.
 - “**RGS proteins**, through their ability to bind to G proteins and to accelerate their GTPase activity, **promote desensitization**.”
 - “**RGS proteins promote desensitization** by binding to G proteins and accelerating their GTPase activity.”
- If you absolutely must interrupt the sentence, use a pair of commas to keep the meaning clear.
 - “We analyzed blood samples from **12 patients that had been frozen for up to a week**.”
 - “We analyzed blood samples, collected from 12 patients, that had been frozen for up to a week.”
- Be specific.
 - “The receptor then undergoes a conformational change leading to phosphorylation.” (what is being phosphorylated?)
 - The receptor then undergoes a conformational change leading to **its** phosphorylation.”
 - “The receptor must first bind to **a hormone**. **It** then undergoes a conformational change leading to its phosphorylation.” (as written, “it” refers to “hormone”)

- “The receptor must first bind to a hormone. The **receptor** then undergoes a conformational change leading to its phosphorylation.”
- Avoid overly long sentences. This is particularly important at the beginning and end of a paragraph. Split into two sentences to help the reader keep track of the main point. **Start with a simple and general statement.** Then qualify the statement if needed. Likewise, conclude with a simple sentence.
 - “Most hormones act by binding to cell surface receptors, although some hormones act instead by binding to receptors that shuttle in and out of the nucleus.”
 - “Most hormones act by binding to cell surface receptors. Another class of hormones binds to receptors that shuttle in and out of the nucleus.”
- Vary sentence length. Use **transitions** to avoid short and choppy sentences or to indicate a change in direction. Keep it interesting.
 - However... although... therefore... thus... also... whereas... because....
 - Taken together... for example... in addition... in contrast...
 - Vary word order and sentence length.
 - Avoid reusing the same words repeatedly.

“Learn to alert the reader as soon as possible to any changes in mood from the previous sentence. At least a dozen words will do this job for you: ‘but’, ‘yet,’ however,’ ‘nevertheless,’ ‘still,’ ‘instead,’ ‘thus,’ ‘therefore,’ ‘meanwhile,’ ‘now,’ ‘later,’ ‘today,’ ‘subsequently’ and several more. I can’t overstate how much easier it is for readers to process a sentence if you start with ‘but’ when you’re shifting direction. Or conversely, how much harder it is if they must wait until the end to realize that you have shifted.”— from *On Writing Well*, by William Zinsser.

Transition words are great, but do minimize vague or weak verbs (and adverbs) such as “notably”, “Interestingly,” “surprisingly”, “lastly”.

Transition words can also be used to create tension or conflict, which often makes for interesting reading.

- “We know that HIV causes AIDS. However we don’t know how HIV gains entry to the cell.”

Avoid word clusters that explain how you will go about doing the explaining. There are better alternative to common phrases like “until such time as” (until), “due to the fact that” (because), and “for the purpose of” (for). Instead of saying “it is interesting to note,” tell me why it is interesting. Instead of saying “it should be pointed out,” **tell me what I need to know and why.**

- **Be positive.** Positive statements are usually the most clear and succinct. **Negative statements are usually the least clear and succinct (unsuccinct?).**
 - “Not being positive usually makes statements less clear and less succinct.”
 - “All of the data do not support the model”
 - “Most of the data support the model.”
 - “Some of the data support an alternative model”
- With **well-chosen words**, several ideas can be expressed together in a clear and interesting manner. It helps you avoid reusing words.
 - “RGS proteins are required for desensitization. RGS proteins bind to G proteins. RGS proteins accelerate G protein GTPase activity.”
 - “RGS proteins promote desensitization by binding to G proteins and accelerating their GTPase activity.”

- Use **parallel sentence structure** when you want to highlight similarities and differences. Contrasts are easiest to see if you **vary the variable and keep the constant constant**.
 - “Receptors activate G proteins. RGS proteins inactivate G proteins.”
 - “That’s one small step for a man, one giant leap for mankind.”
 - “Ask not what your country can do for you. Ask what you can do for your country.”
- **More about long sentences, parallel structure and transition words.** Sentences that are overloaded with names or actions (nouns or verbs) usually sound dense and can be difficult to understand. Think of “noun clusters” like abbreviations, something that is tiresome and to be avoided at all costs.
 - “The seven-transmembrane domain plasma membrane G protein-coupled adrenergic receptor undergoes rapid phosphorylated and desensitization.”
 - “Adrenergic receptors have a seven-transmembrane domain topology and are expressed at the cell surface. When these receptors are phosphorylated they undergo desensitization and are no longer coupled to the G protein.”

Likewise sentences that are overloaded with ideas (long sentences that string multiple ideas together) are also difficult to follow. By focusing on one object doing one thing, there can be no doubt about what is important.

The main exception is when several things are equally important. Examples include a list of objects that do something similar, one object that does a number of related things, or two things that have opposing actions. In these instances transition words can allow you to combine short sentences and at the same time emphasize the important similarities and differences. This is particularly useful when you come to the end of a list and a concluding statement is needed.

Consider the following examples with and without transition words:

- “Unphosphorylated receptor is active. Phosphorylated receptor is inactive. Phosphorylation desensitizes the receptor.”
- “The unphosphorylated receptor is active and the phosphorylated receptor is inactive. Thus we conclude that phosphorylation results in desensitization.”

“The period. There’s not much to be said about the period except that most writers don’t reach it soon enough. If you find yourself hopelessly mired in long sentence, it’s probably because you’re trying to make the sentence do more than it can reasonably do – perhaps express two dissimilar thoughts. The quickest way out is to break the long sentence into two short sentences, or even three.” – from *On Writing Well*, by William Zinsser.

Voice

- It is more interesting, and easier to write clearly, in the **active voice**. The active voice tells the reader who did what, and keeps the sentence moving along.
 - “Enzyme activity **was measured**.”
 - “**We measured** enzyme activity.”
- You might use the **passive voice** when you are out of the picture, as in the methods section or figure legend.
 - “The enzyme assay was done using a Model B1000 Spectrofluorimeter”
- Keep it personal. Use the **first person** whenever possible.

It was once commonplace to avoid the use of ‘I’ or ‘we’ in scientific writing. The thinking was that scientific knowledge should be based on hard data and objective analysis. This practice makes sense in a textbook where the authors are conveying knowledge acquired by others (it is perhaps one reason that textbooks are exceedingly dull!). The practice makes much less sense in a grant application where investigators are describing what they have done, what they will do, and why.

Consider the following examples. The first is not only tedious and difficult to follow, it is unclear who did what and when:

- “In contrast to the old method, the new method allowed detection of very low levels of enzyme activity. It is concluded that the new method is more sensitive than the old method.”
- “Using the new method we were able to detect very low levels of enzyme activity. Based on our findings we conclude that the new method is more sensitive than the old method.”

“...getting writers to use ‘I’ is seldom easy. They think they must earn the right to reveal their emotions or their thoughts. Or that it’s egotistical. Or that it’s undignified – a fear that afflicts the academic world. Hence the professorial use of ‘one’ (‘One finds oneself not wholly in accord with Dr. Maltby’s view of the human condition.’), or of the impersonal ‘it is’ (‘It is to be hoped that Professor Felt’s monograph will find the wider audience it most assuredly deserves’). I don’t want to meet ‘one’ – he’s a boring guy. I want a professor with a passion for his subject to tell me why it fascinates *him*.” – from *On Writing Well*, by William Zinsser.

Grammar

- Do not use nouns as verbs. Do not use verbs as nouns.
 - “HIV **impacts** the immune system in several ways.”
 - “HIV **effects** the immune system in several ways.”
 - “HIV **affects** the immune system in several ways”
- Make sure subjects and verb agree. A singular subject requires a singular verb.
 - “**Each** of these receptors **is** phosphorylated.”
- The subject nearest the verb determines the number of the verb.
 - “**All** receptors but only **one** G protein **is** phosphorylated.”

The paragraph

- Use short paragraphs. Start with basic ideas, progressing to more complex ones.
- Limit each paragraph to one topic.
 - Each paragraph should have a topic sentence and a concluding sentence.
 - If a topic sentence seems out of place, use a transition sentence.
- Start the paragraph with a topic sentence that introduces the subject of the paragraph.
 - The order of topic sentences can help the reader see the overall outline of your presentation.
 - Topic sentences allow readers familiar with the topic to skip ahead to the next paragraph.
- Finish the paragraph with a concluding sentence. For example, after each paragraph of background information I look for ways to make a direct connection to one of my specific aims. If

I devote a paragraph to describing a new method I will end by saying that “in Aim 1 we will use this approach to determine.” A paragraph cannot simply stop.

Content

- There are two ways to confuse the reader. One is with too little information. The other is with too much information all at once. Keep it simple.
-
- If you try to cover too many subjects in one paragraph, the reader is likely to misunderstand their relevance to the topic of the paragraph or their relevance to one another.
- *The best way to emphasize important information is to omit or condense unimportant information.* Go through your document word by word and line by line. In each case ask yourself, do I need to include this? Am I repeating myself? Can this information be provided best in a table or figure? Can I simply summarize and provide an appropriate reference instead? (Is the same information covered in the topic or concluding sentences?). Save the lengthy review of the literature for the first chapter of your thesis or a review article. The space that you gain can be used to elaborate on what is most useful to the reader. What is left should be obviously relevant to the rest of the document.
- If a concept or finding is really important, you will probably want to repeat it. Key information might be repeated in the abstract, the specific aims, in a header, in a topic sentence, and in a summary statement. This advice might sound contradictory since repetition could be considered as unnecessary (see the previous bullet point!). However if it is really important you want to make sure the reader doesn't miss it.

Think of it as maximizing the signal-to-noise. Extra words and dull facts are the “noise”. Key terms and concepts are the “signal”. Emphasize what is important.

On the other hand, don't be afraid to break the rules, if it helps you to make a point. One of my favorite writers is Tracy Kidder, who gave the following advice on brevity:

*“Omit needless words” goes the advice from *Elements of Style*, by Strunk and White, and no one would disagree. On the other hand: How do you recognize a needless word? Should Lincoln have written not ‘Four score and seven’ but ‘eighty seven’? In *King Lear*’s dying speech – ‘Never, never, never, never, never’ – which word would you cut?*

The familiar rules about writing turn out to be more nearly half-truths, dangerous if taken literally. They are handy as correctives, but not very useful as instruction.”

From: *Good Prose: The Art of Nonfiction*

So there you have it, omit needless words, but not all the time. When in doubt, always follow your instincts. Always, always, always.

- When emphasizing the most important information, *tell them what you're going to tell them, tell them, then tell them what you told them.* Or, topic sentence, information, summary sentence.

The document

Think like a reviewer. A reviewer at NIH must often read 10 or more applications, and then writes a critique for each. Help the reader do the best job of summarizing the key points in your proposal.

- Again... avoid using acronyms and specialized language (jargon). If reviewers have to stop and translate, you risk losing their interest.
- Make sure the proposal is organized in the format suggested by NIH. Reviewers are accustomed to finding information in specific sections of the application. Don't confuse them or make them work to find what they are looking for. Provide headers to make the application as easy to navigate as possible. This is not the time or place to be innovative!
- State the strengths of your proposal. It can be as direct as completing the sentence "this work is innovative because..." or "I am qualified to conduct these experiments because..."
- Avoid a "wall of text". Make the proposal visually attractive by using bold subject headers and spaces between sections. Distribute figures throughout the document. Use non-justified text (no block text).
- Provide a cartoon that identifies the key "players" of your proposal, such as the names of the proteins in your pathway and how they connect. If possible, box areas of your cartoon that relate to each aim. Provide a legend for each figure.
- Make sure the figures and legends are large enough that they can be read without difficulty. Remember that most grant reviewers are well over 40 and are likely to need reading glasses. Most of them aren't happy about it. You can make them feel young again by using readable fonts and font sizes.
- Check that there are no spelling errors, grammatical mistakes, missing information, or errors in figures and tables.
- Check that you have referenced the key papers in the field, including those of potential reviewers, and any that conflict with your hypothesis. Check that each method has a reference.
- Check that you provide the source of any unpublished work. If you are showing unpublished data, get permission and cite the source.
- Check that the figures are in order and the text refers to the correct figure number. No missing figures!!
- **Sloppy writing or sloppy editing may be seen as a sign of sloppy science.**

Cadence.

There are many advantages to reading your work aloud. It will reveal duplicate information, missing connections and confusing transitions. It will also help you to listen to your own words and reveal how to make them more pleasing to the eyes and ears.

"Also bear in mind, when you're choosing words and stringing them together, how they sound. This may seem absurd: readers read with their eyes. But in fact they hear what they are reading far more than you realize. Therefore such matters as rhythm and alliteration are vital to every sentence. ... Such considerations of sound and rhythm should be woven through everything you write. If all your sentences move at the same plodding gait, which even you recognize as

deadly but don't know how to cure, read them aloud. (I write entirely by ear and read everything aloud before letting it go out into the world). You'll begin to hear where the trouble lies. See if you can gain variety by reversing the order of a sentence, or by substituting a word that has freshness or oddity, or by altering the length of your sentences so they don't all sound as if they came out of the same mold. An occasional short sentence can carry a tremendous punch. It stays in the reader's ear." – from *On Writing Well*, by William Zinsser.

To borrow an example from E. B. White's *The Elements of Style*, listen (don't read) the consequences of rearranging the familiar literary phrase, "These are the times that try men's souls" (Thomas Paine)

Times like these try men's souls
How trying it is to live in these times!
These are trying times for men's souls.
Soulwise, these are trying times.

In the original there is no formula that I can point to, only a tempo that pleases the ear. You'll see what I mean if you read it aloud. If you read it aloud you'll see what I mean. *Read it aloud and you'll see.*

Logic. The power of persuasion

Your hypothesis may challenge current knowledge. This can often make for an exciting proposal, but your arguments must be presented logically and without drama. There are lots of ways to derail your efforts with confrontational language or false logic. If that is your goal, there are plenty of options:

- **Red Herring** – Introducing an irrelevant fact.
 - I would have mentioned alternative models but I was in a rush to complete my proposal.
 - Reviewers rejected my model because I'm (fill in the blank) and they were not objective.
- **Non Sequiter** - Statements that do not logically follow one another.
 - The model was tested computationally and therefore does not need to be tested experimentally.
 - We know that model cannot apply to humans because the original work was done in yeast.
- **Appeal to pity** - Something bad will happen if you do not accept the argument.
 - If my proposal is not funded, it will delay finding a cure for the disease.
 - If my grant is denied, my lab will close and I won't get tenure.
- **Circular argument** - assuming the thing to be true that you are trying to prove.
 - I will demonstrate that the model is correct using these approaches.
- **False Dilemma** - Two choices are given when in actuality there could be more choices possible.
 - Since we used the same method and got different results, the model must be false.
- **Double standard** - applying a different standard to another that is applied to oneself.
 - Given my track record I did not think it necessary to provide preliminary data to support my model.
- **Appeal to the popular** – Holding a position simply because a majority of people share it.
 - My model is widely accepted.

Ten tips for clear writing.

- Be specific
 - Avoid vague terms like “involved in” or “important insights”
 - Use the active voice to identify who did what.
- Be brief
 - Omit needless words
 - Omit needless text
- Keep it simple
 - Start with a broad statement.
 - Follow up with important details, as needed.
- Limit each sentence to a single subject.
 - Place the subject first and keep the verb nearby.
 - If several things are equally important, list them.
- Limit each paragraph to a single topic.
 - Start with a topic sentence
 - Follow with the question, approach and results, in that order.
 - End with a concluding or summary sentence.
- Avoid lab jargon and colloquialisms.
- Avoid acronyms and abbreviations.
- Summarize key points.
 - State how different sections are related to each other and to the aims.
 - Use parallel sentence structure to emphasize similarities and differences.
- Listen to your words. Read your text aloud.
- Triple check grammar and spelling.

Additional reading

- Any grants (ideally fellowship grants in your field, which were funded) that you can lay your hands on.
- Strunk and White: *The Elements of Style*
- William Zinsser: *On Writing Well* *
- Tracy Kidder and Richard Todd: *Good Prose: The Art of Nonfiction*
- A dictionary.
- A thesaurus.
- Journal articles in your field

* *purchase the most recent edition, the cultural references will be more familiar*

Class 9: Small group.

Class 9 (Small Group): Final review.

Homework to be completed 48 hours before the final small group meeting:

- Read the assembled Project Summary, Specific Aims, Significance, Innovation, and Approach (through Aim 1) for each of your classmates, and prepare comments.
- Use the final checklist to evaluate Aim 1.

Final Checklist

Big picture items:

- I explain the significance of the work to public health.
 - Will the reviewer be able to complete the sentence “This work is **important** because...”
- I explain the significance of the work to progress in my field.
 - Will the reviewer be able to complete the sentence “This work is **significant** because...”
- I explain how my project is innovative.
 - Will the reviewer be able to complete the sentence “This work is **innovative** because...”
- I explain how each aim relates to the **hypothesis**.
- I explain how each experiment relates to the aim.
 - For each experiment do you explain what you hope to learn, rather than emphasizing the method that will be used (anticipated results)?
 - For each, can you complete the sentence “This experiment will reveal...”
- I explain why I am **qualified** to do the work. Can you do the experiments?
 - Do you demonstrate feasibility for each of your experiments, either by citing your own published work or providing preliminary data?
 - If not, do you enlist the help of a collaborator?
- I explain potential **pitfalls** (how major experiments might fail) and the **alternatives** available.
 - Does the technology exist?
 - For each, can you complete the sentence “One potential pitfall of this approach is...”
 - For each, can you complete the sentence “If we do not succeed using this approach, we will instead...”

Details:

- I have referenced the key papers in the field, including those that conflict with my hypothesis.
- Each method has a reference.
- I cite the source of unpublished work.
- I avoid using acronyms and specialized language (jargon).
- The figures are in order and the text points to the correct figure number.
- There are no spelling errors, grammatical mistakes, missing information, or errors in figures and tables.

Final review:

- After I finish writing, I set the application aside for a few days.
- I have received opinions from peers and mentors who are not necessarily knowledgeable about the topic of my proposal.
- I allow at least two weeks for colleagues to read my application and for me to incorporate their suggestions.
- I asked them to list the strong and weak points of my proposal. It is better to hear this from a colleague than from a funding agency.
- I conduct a final check for errors.
- I conduct yet another final check for errors.

As I mentioned above, the review criteria for an NIH R01 and F31 (predoctoral fellowship) are different. For the F31 research training potential is the major focus (the approach is not scored separately!). Preliminary data are not required.

The following is a checklist designed to help you prepare the F31 application.

F31 Checklist:

- Does your personal statement detail your training goals for a career in **research** (NIH wants to support research!).
- Is the sponsor's training plan detailed and tailored to the applicant ("individualized" and not generic)? Does it include information about institutional resources for career development? Does it describe participation (or planned participation) at research meetings? Does it include specialized course work if appropriate?
- Does the sponsor have an established track record of student mentoring (if not, try to enlist a more senior co-sponsor). Where have past students landed?
- If you enlist a co-sponsor, is the role justified and the clearly defined?
- Does the sponsor's grant support last for the duration of the fellowship? If not is there a plan for sustained research support after, for example from a co-sponsor?
- Does your proposal complement, but not duplicate, the sponsor's funded project?
- Does your truly project provide new training. Fellowships to support years 4, 5 and 6 require extra justification.
- You will need to provide a transcript. Have you addressed any blemishes or gaps in your academic record?
- Have you provided the required information about responsible conduct of research (NIH RCR) training? This includes description of format, subject matter, faculty participation, duration, and frequency as required. Don't neglect this.

For more guidance on writing a predoctoral fellowship, look up this excellent article from ASBMB Today: <http://www.asbmb.org/asbmbtoday/201405/ProfessionalDevelopment/Grants/>

Happy writing, and good luck on your journey.
-Henrik

BIOC 712: Scientific Writing Course final homework

Please complete the following and include 1-3 bullet point responses for each of evaluation criteria. Have the document signed by your thesis advisor and the chair of your thesis committee to indicate that they approve of the content (do this even if you have already defended your proposal). Please turn in a paper copy of this document and submit an electronic copy of your proposal for my final review.

Student name: _____

Student signature and date: _____

Thesis advisor signature: _____

Thesis committee chair signature: _____

1. By signing this document the student pledges that the proposal is free of plagiarism.

Plagiarism is copying another person's words, ideas, or results without giving that person credit. Examples of plagiarism in a thesis proposal include copying portions of a thesis advisor's article or research proposal.

2. Evaluation of Significance, Innovation, and Approach (to be completed by the student based on comments from the thesis committee following the examination, and approved by at least one member of the committee)

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? **

Strengths: _____

Weaknesses: _____

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? **

Strengths: _____

Weaknesses: _____

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 and members of both sexes/genders, as well as the inclusion of children, justified in terms of the scientific goals and research strategy proposed? **

Strengths:

Weaknesses:

Examples of strengths:

- Clear **significance** of the work to public health and to progress in the field.
- Clearly explains how the project is **innovative**.
- The **approach** explains how each aim relates to the hypothesis.
- The **approach** explains how each experiment relates to the aim.
- The **approach** demonstrates feasibility by citing published work or providing preliminary data.
- The **approach** clearly describes potential pitfalls and the alternatives available.

Examples of weaknesses:

- Key statements/methods are not referenced.
- There are spelling errors, grammatical mistakes, missing information, errors in figures and tables.
- The specific aims are not closely related.
- The success of one aim depends on the success of a previous aim.
- The rationale is unclear.
- The applicant does not demonstrate a clear understanding of the proposed methods, or does not provide sufficient preliminary data, or does not enlist a collaborator where needed.
- Potential pitfalls and alternative approaches are not discussed.
- The limitations of the method are not adequately addressed.
- The proposal is descriptive, not mechanistic.
- **The document does not follow the format required for the NIH F31 National Research Service Awards for Individual Predoctoral Fellows.** Specifically:
 - **Project Summary:**
 - includes an **Abstract** (no more than 30 lines of text, with aims listed) and statement of **Relevance to Public Health** (no more than two or three sentences)
 - **Specific Aims** (no more than 1 page)
 - **Research Strategy** (no more than 6 pages, including figures)
 - Includes sections on a. **Significance**, b. **Innovation**, and c. **Approach**
 - **References** (no page limit)
 - Includes the names of all authors, article title, journal title, volume number, page numbers, and year of publication.
 - **Proper formatting**
 - Arial or Helvetica font, 11 points or larger, half-inch margins, single spaced

*source: NIH