

Writing a Research Proposal



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Why write a proposal?

- Initiate dialogue with your mentors and committee
- Assure that you have a good grasp of the field, including important questions, current controversies, gaps, etc
- Assure that you know (or can learn) techniques required to succeed
- Helps you envision potential problems and devise solutions in advance
- To develop writing skills
- Begin understanding the grant writing process

Getting started: programmatic issues

- Start by reading the instructions CAREFULLY
- Find 2-3 examples from senior students
- Talk with program leadership here and/or at your University
- Communicate with your mentors and let them know WHAT help you will need and WHEN you will need it

Getting started: science issues

- Read the literature broadly - not deeply - save important papers for a deeper read later
- Engage your lab and your mentors in the brainstorming process
- Find outside experts to talk with - but go prepared
- Work early to define, organize, and plan the content

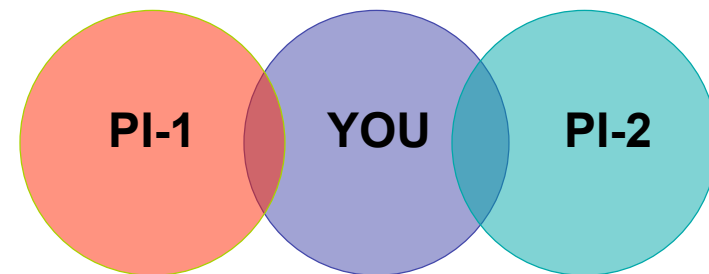
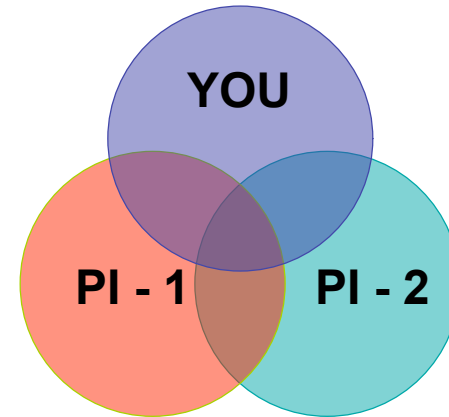
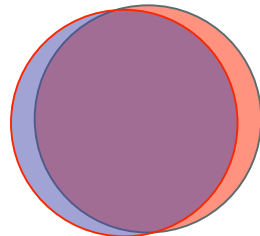
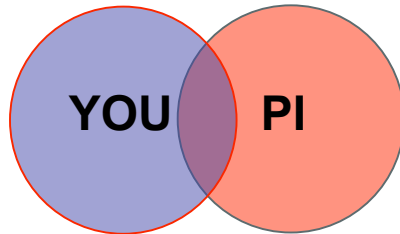
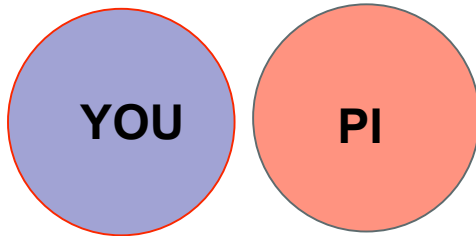
Getting started: personal issues

- Find resources to improve your writing style
- Set a daily writing schedule
- Form a writing group to help with proof-reading, procrastination, writer's block, etc

Negotiating content

- Talk with your mentor(s) before you get too far along
- Agree on the Aims first
- The proposal is not a contract written in stone - compromise

Whose project is it?



Example #1

My interest: regulation of CFTR trafficking by NHERF-family PDZ proteins

Bill's interest: identification of protein-protein interactions using mass spectrometry

Bill's thesis: Using mass spectrometry to identify novel regulators Of CFTR trafficking, turn-over, and activity

Example #2

My interest: regulation of CFTR activity by protein kinases

Larry's interest: regulation of ciliary beat frequency

Pat's interest: compartmentalization of cell signaling pathways

Pat's thesis project: Identification and characterization of signaling proteins in human respiratory axonemes

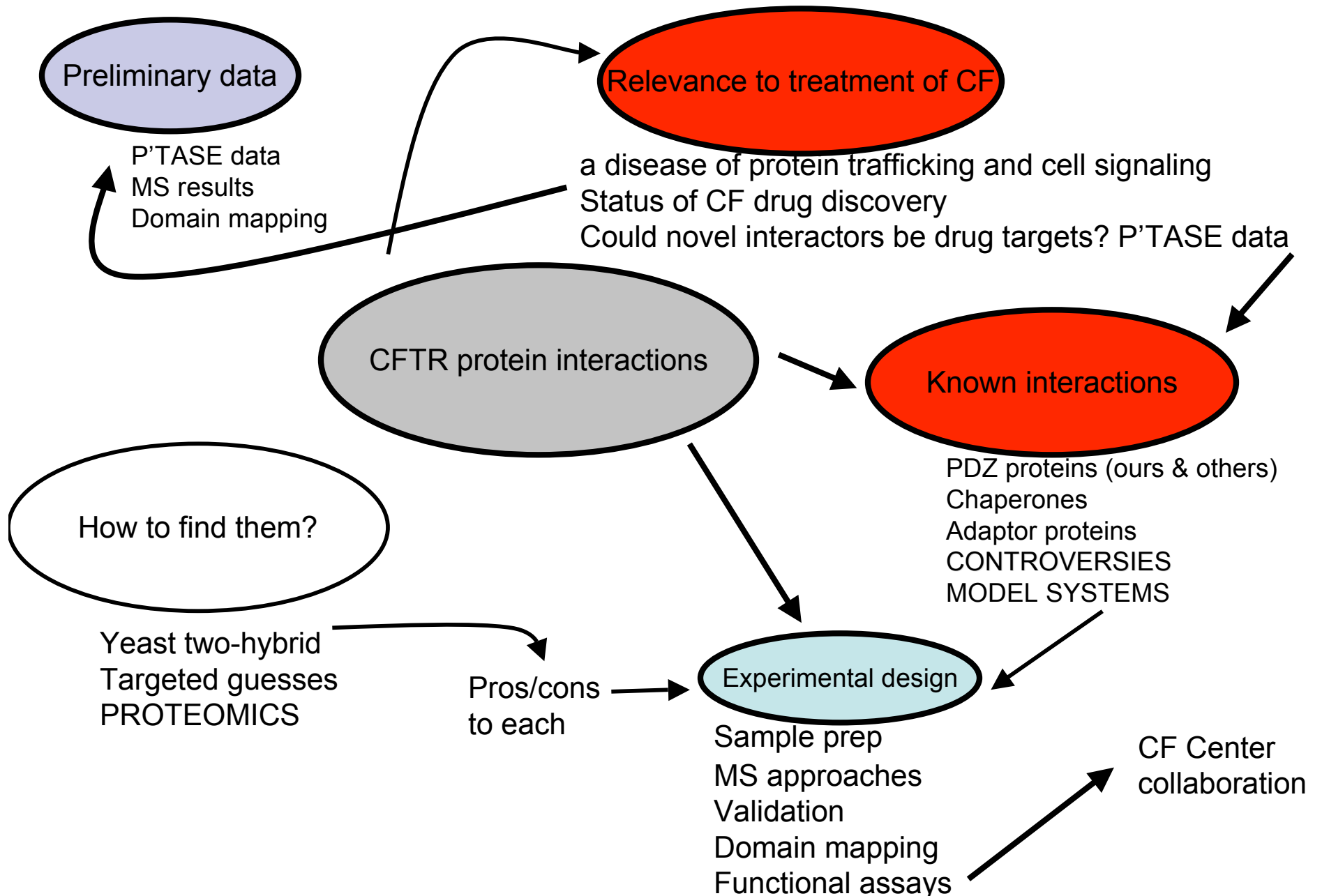
The organizational process

“Many of us when confronted by a writing deadline, skip the organizational phase of writing. This is akin to leaving on a trip to unknown parts without a road map, hotel reservations, or plans of any sort.”

Approaching the first draft

- Don't start writing immediately - spend time thinking & talking first
- Brain-storm and make lists of the issues you hope to address
- Make lists of methods you need to learn and reagent, cell type, animal, or human subject issues you need to deal with
- Use an outline or a concept map to help you prepare to write

Getting started with a concept map



Parts of a typical thesis proposal

- Title
- Abstract
- Specific aims
- Background & significance
- [Preliminary data]
- Research design & methods
- [Timeline]
- References

Abstract

- The Reader's Digest condensed version of your story
- Begin by stating the problem & end by stating the impact of the work if successful
- Should stand alone
- Should not contain abbreviations or jargon
- May follow strict word limits

Cystic fibrosis (CF) is caused by mutation in the gene coding for the cystic fibrosis transmembrane conductance regulator (CFTR), an apical membrane Cl⁻ channel. Despite extensive study, there are significant gaps in our understanding of how CFTR is synthesized and processed and how CFTR is regulated and functions at the apical membrane. CFTR associates with a number of proteins that facilitate its trafficking or function, but our understanding of these interactions and how they are altered in CF is relatively poor. Furthermore, it is likely that additional proteins associate with CFTR. We find that the actin-binding protein filamin associates directly with residues 1-25 of CFTR and a known disease-causing mutation in the N-terminus of CFTR (S13F) significantly diminishes the affinity of the interaction. In addition, S13F CFTR is inefficiently trafficked to the membrane in epithelial cell lines. Based on these preliminary data we propose to fully characterize the biological significance of the CFTR-filamin interaction in airway epithelial cells. We will also use similar approaches to identify additional N- and C-terminal CFTR-interacting proteins. We will critically test whether the interacting proteins are co-expressed and co-localized with CFTR in human airway and will study their function using a battery of cellular and electrophysiological assays. Taken together our experiments will help define novel CFTR-interacting proteins in airway, will help determine how these interactions are affected by known disease-causing mutations in CF, and will determine the function of each interaction. The identification of proteins that associate with CFTR along the secretory pathway or at the cell surface, provide one prospect for new therapies to optimize the trafficking and activity of CFTR and will increase our understanding of this complex epithelial ion channel.

Specific aims

- The “opening statement” -- tells what your proposal is about
- Generates enthusiasm & excitement for your ideas
- The reader **MUST** finish this section convinced that the work you propose is significant and that you have a feasible approach
- Should list Aims and include subaims
- No more than one page

Example 1- aim 2

AIM 1. Study the role of the CFTR-FLN interaction at the cell surface: Our localization studies suggest that FLN is accumulated at the apical cell surface and biochemical data in CalU3 cells suggests that FLN associates with mature CFTR. FLN typically regulates the stability or function of plasma membrane ion channels and receptors. Therefore, we will:

- A. Compare basal state and regulation of CFTR currents in cells expressing WT and mutant CFTR
- B. Disrupt the CFTR-FLN interaction in mammalian cells and assess the changes in CFTR activity and regulation at the PM
- C. Use RNAi strategies to study CFTR maturation and function in cells depleted of specific FLN isoforms

Example 1 - aim 3

AIM 2. Use mass spectrometry to identify other novel CFTR-associated proteins and assess the function of the interactions we identify: Our preliminary data indicate that affinity chromatography coupled with LC-MS/MS can be used to identify novel CFTR-interacting proteins. Therefore, we will use these same screening and validation strategies to more fully define the cohort of N- and C-terminal CFTR-interacting proteins in airway. We will:

- A. Use affinity chromatography and LC-MS/MS to identify additional proteins that associate with CFTR
- B. Study the cellular and subcellular distribution of CFTR-associated proteins
- C. Use biochemical assays to validate and further characterize novel interactions
- D. Determine the functional role of protein interactions that are fully validated

Background & Significance

- The place to clearly state the importance of the proposed research
- Looks both backward & forward
- Should be appropriately referenced with an honest & balanced discussion of others' work
- Points out controversies and discrepancies that your work will address
- Convinces the reader that you know what you are talking about & that your proposed work is the OBVIOUS next step
- 2 - 3 pages; no more than one or two figures

Preliminary data

- Key pieces of data to generate excitement and enthusiasm for the proposed studies
- Demonstrates feasibility
- Shows you are a careful scientist who does controls and does not over-interpret data
- Important to include data and to make the data easily viewed and interpreted
- Ranges from 2 - 8 pages depending on overall proposal length
- Typically contains several figures with clear legends

Research plan

- Organized by Aims
- Can put general methods at the end or leave them out
- Should be balanced between over-view of approaches, rationale for specific experiments, & the specific details of each experiment
- Clearly discuss controls (positive & negative) for all experimental approaches
- Show you have thought through issues of feasibility, sample size, data analysis, etc
- Include sections discussing expected outcomes, data interpretation, potential pitfalls & alternate approaches
- Include a timeframe & discussion of critical collaborators if appropriate
- Include detailed discussion of animal use or human subjects

Writing is all about revising drafts & seeking feedback

Proof-readers and editors



Scientists in your field



Scientists in peripheral/related fields



Scientists who write and review grants

What makes a research project outstanding?

- Addresses an important problem clearly
- Potential to lead to seminal new observations or new ways of thinking
- Lays the foundation for further research in the field
- Addresses a difficult problem in a way that seems simple in retrospect
- All aspects of the project are clearly linked

Common criticisms

- Diffuse, unfocused or superficial examination of the field
- Competent but unexciting science
- Lack of knowledge of published work
- Mediocre preliminary data that is over-hyped
- Lack of experience in required methodologies
- Unrealistic amount of work
- Lack of experimental detail
- Too many irrelevant experimental details
- Not enough discussion of potential pitfalls & alternate approaches
- Poorly written with typographical errors and grammatical mistakes

“Psychology” of the review process

Committee members are:

- over-committed, over-worked and tired
- inherently skeptical and critical
- often only peripherally interested in your work

Make their job easier with:

- Well organized, clearly written prose
- Lots of section headings and breaks in the writing
- Well designed flow diagrams, charts, figures

And avoid irritating them by:

- exceeding page limits, using small fonts and narrow margins
- putting information in the wrong section
- omitting or mislabeling references/figures
- submitting a sloppy application

Strong writing can not compensate for bad ideas, but weak writing can easily ruin good ideas



Writing hints

- Write from the perspective of the reader - make sure there is a logical starting point & a flow to your “story”
- Start all paragraphs with a topic sentence - this tells the reader what the paragraph is about
- End each paragraph with a transition sentence to lead to the next section
- Pay attention to the stress position in each sentence and paragraph - readers naturally emphasize material that arrives at the end of a sentence or paragraph
- Avoid passive voice, especially in the Aims, background & preliminary data sections
- Avoid long-winded sentences, & big words when simpler words would work just as well