BMB/Bi/Ch 174

Proposal Writing 101

Spring, 2018

Basic Composition of A Proposal

Front Page
Abstract
Specific Aims

Research Narrative
Background (Significance)
Research Plans (Approach)
References

Visual of proposal structure

1. State Goals and Objectives

2. Establish Importance

2.a Identify the research area

2.b Develop the research story

Explain fundamental concepts

Provide essential background

3. Introduce the Proposed Research

3.a A Identify gaps in the field

3.b Introduce your project to fill the gap

The front page is the most important page of the proposal

Start with a brief description of the overall objectives of the proposal, then list the specific goals of the research proposed, e.g., to test a hypothesis, create a novel assay, solve a specific problem, etc. In general, 2-3 specific aims are recommended. Note that different aims should not go in disparate directions, but rather connect with each other cohesively to address the overall objective.

- Reviewers often quickly assess the quality of the overall proposal by the front page.
- Read by all the reviewers in the panel.

Make it perfect!

Abstract

- What is the overarching question, hypothesis, and goal of the proposed research?
- How will the projected outcome impact the specific field and related, broader fields?

Sample abstract

"Accurate localization of proteins is essential for the proper functioning of all cells. Understanding the molecular strategies by which post-translational protein targeting pathways escort highly hydrophobic membrane proteins to their correct target site is a fundamental mechanistic challenge. The recently discovered Guided Entry of Tail-anchor (GET) pathway, in which a sophisticated cascade of protein interactions mediate the delivery of tail-anchored (TA) proteins to the ER, provides an excellent opportunity to address these fundamental questions. Our general goal is to decipher, at a biochemical and biophysical level, the molecular mechanisms underlying the post-translational targeting of TA proteins by this novel pathway. Our specific goal is to understand how Get3, the central ATPase in this pathway, uses its ATPase cycles to drive highly efficient and accurate targeting of TA proteins.

Get3 is the only eukaryotic ATPase in the SIMIBI (SRP, MinD, and BioD) family of NTPases, whose members regulate a variety of essential cellular functions… In addition to providing a deeper understanding of the GET pathway, these studies will allow us to gain deeper insights into the evolution, mechanism, regulation, and biological logic of this growing class of nucleotide hydrolases."

Specific Aims

- Breakdown the overall goal into concrete tasks / objectives, each with deliverable outcomes

- Each specific aim should include:

- A focused hypothesis or objective
- Discrete experimental approach to test the hypothesis or complete the objective
- Predicted outcomes

** Significance of aim outcomes with regard to the overall goal should be clear

- Aims should relate to each other and together build a strong story

Sample Aims

Aim 1. Establish a precise framework for the Get3 ATPase cycle.

To understand how the Get3 ATPase drives TA protein targeting, we first need to know about its enzymatic properties. To this end, we will use mechanistic enzymology, fluorescence spectroscopy, and single molecule FRET to establish a kinetic and thermodynamic framework for the ATPase cycle of Get3, and to identify global conformational changes that occur during this cycle. The results will reveal properties of Get3 that can be harnessed for TA protein targeting and generate powerful tools/assays, and thus pave the way for understanding how its ATPase cycle drives TA protein targeting in the subsequent Aims.

Aim 2. Delineate how upstream and downstream components regulate the ATPase cycle of Get3.

Using the reagents, tools and knowledge from Aim 1, we will define whether, when and how other components in the GET pathway – the Sgt2•Get4/5 TA loading complex, the TA substrate, and the Get1/2 receptor on the ER membrane – regulate the ATPase cycle of Get3. We propose that upstream and downstream components of the pathway promote or inhibit distinct steps in the Get3 ATPase cycle, thus ensuring the precise timing of ATP binding and hydrolysis during TA protein targeting.

Background (Significance)

- Describe the overall objective in both the broader and more specific context.
- Explains the open research questions that motivate the work, and convince readers about their importance.
- Impact refers to both advances within the specific field and across broader fields
- Provides the necessary technical background for readers to understand the objective and the proposed research

Pick A Good Problem

- An evolutionarily conserved phenomena
- Essential pathway
- Conceptual advance – paradigm shifts that changes the way we think
- Fundamental – insights or concepts permeate a broad spectrum of phenomena or molecules
- Technological advance – enables previously impossible experiments for many scientists
- A good proposal often contain multiple of these elements

Important Problems should not:

(1) Be a vague question or null hypothesis

(2) Be the obvious next step or elaboration of previous work

(3) Be ‘anything’ in a currently ‘hot’ field

(4) Be a fancy tinker tool you make

(5) Be a highly esoteric problem

Scientific Premise

- Refers to the body of existing knowledge (e.g., preliminary data, literature evidence) or reasoning upon which the hypothesis / proposal is based.

- Make clear, evidence-based claims to persuade reviewers that the proposal has sound scientific merit, but avoid speculation and hyperbole.

An example of Premise

(Gorlich and Rapoport, Cell 1993)

The actual membrane transfer of a polypeptide, following the targeting process, is assumed to occur through a protein-conducting channel, a view that is supported by electrophysiological data (Simon and Blobel, 1991). Several candidates for constituents of the putative channel have been proposed. Of particular importance is Sec61p, a multi-spanning membrane protein of the ER. It was initially found in Saccharomyces cerevisiae via genetic screening for translocation defects and is encoded by an essential gene (Deshaies and Schekman, 1987; Rothblatt et al., 1989; Stirling et al., 1992). Homologs of Sec61p are now known to be present in mammals as well as in other vertebrates (Gorlich et al., 1992b). Furthermore, Sec61p has sequence homology to SecYp (Gorlich et al., 1992b), a key component of the protein export apparatus in bacteria. Several of the putative membrane-spanning segments of Sec61p contain hydrophilic or even charged amino acid residues, suggesting that they may contribute to a hydrophilic interior of the membrane channel. Sec61p is adjacent to polypeptide chains passing across the membrane of the mammalian or yeast ER (Gorlich et al., 1992b; Miisch et al., 1992; Sanders et al., 1992). In mammals, it is tightly associated with membrane-bound ribosomes (Gorlich et al., 1992b), suggesting that the nascent chain is transferred directly from the ribosome into a protein-conducting channel that includes Sec61p. However, its requirement for protein translocation in mammals has, until now, not been demonstrated.

Research Plans (Approach)

- Expand on each of the specific aims on the front page.
- Explain the experimental design and approach, not protocols
- Contain sufficient detail for educated reviewers to assess the appropriateness and feasibility of the approach
- Identify potential pitfalls and provide suitable alternatives

Approach: Calculated Risk

- Starting with your overarching goal, break it down into a subset of complementary goals, each experimentally addressable
- Assess the availability of appropriate assays, technology, or defined model organisms
- Be an expert on the techniques you propose to use
- How will you interpret the results (in light of your hypothesis)? What are the appropriate controls?
- What is the worst case scenario? What are the backup plans?

Important Tips on Approach:

- Describe experimental design, not protocol

- As much as possible, be hypothesis driven:
  "If xx were observed, this would imply that….
If not, this suggests that…"

- Before the dream experiment, identify pilot experiments that provide proof-of-principle

- Describe benchmarks for success

- Assess risks and describe how they will be managed

Good proposals should:

(1) Have clear logic and reasoning

(2) Be hypothesis driven

(3) Significantly advance the understanding in a field

(4) Opens up new avenues of thoughts and/or research

(5) Elegance = Simplicity and incisiveness of experimental design

Good approaches should not:

(1) Be a fancy tinker tool you make

(2) Doing what you can do

(3) Be brutal force fishing

(4) Generate a stamp collection without mechanistic insight

Criteria for Proposal Evaluation

The three C’s:
Creativity, credibility, competence

Overall Impact Score

Definition of Overall Impact: Assessment of the ***likelihood*** for the project to exert a ***sustained, powerful influence*** on the research fields involved.

My translation: how far will the proposed experiments advance the field, given its likelihood of success?

Overall Impact is influenced by all 4 Scored Review Criteria

1. Significance

- Refers to the **project**, not the scientific field.

Does the project address an important problem or a critical barrier to progress in the field?
If so, what is it?

- If all the aims are achieved, what new knowledge / concepts will emerge? How will this knowledge advance the specific field and the broader scientific community?

Relevance to human disease or translational potential are NOT required for high Significance in GM or NSF

2. Innovation

- Creative ideas should be out-of-box but still feasible
- Technical: new methods / tools / assays. How broadly applicable are these new tools?
- Conceptual: new, broadly applicable models / concepts

3. Approach

How likely will the aims be achieved?

- Are the experimental approaches appropriate for the problem / objective? What is the premise for its intellectual soundness?
- Is the proposal writer knowledgeable on the experimental approach (including interpretation of the results)?
- Are key controls and alternative approaches in place?

Genre

Proposal writing is persuasive writing that uses technical information as evidence to support the specified research objective and approach.

Clear, concise, precise

Do’s

Make your reviewer’s life as easy as possible

Give your reviewer the tools to support you

- Make clear, evidence-based claims to persuade readers that the proposal has scientific merit.

- Make explicit statements to highlight significance, innovation, and expected outcome

- Make sure that all sections are internally consistent, and the aims dovetail but are not exclusively dependent on one another

Examples

"My general goal is to use the GET pathway as a model system to decipher, at a biochemical and biophysical level, the molecular mechanisms that underlie the post-translational targeting of membrane proteins. My specific goal is to understand how the central Get3 ATPase in this pathway use its ATP binding and hydrolysis cycles to drive and coordinate the targeted delivery of TA proteins."

"The outcome of this aim is the complete structure of the inner ring complex of the nuclear pore complex at atomic resolution."

Do-not's

"I spent an entire day reading this proposal, and I had no idea what he/she wants to do."

" A one-trick pony. "

"The models in Aim 1 and Aim 3 contradict one another…"

"The preliminary data and their interpretation give a sense of sloppiness that makes me uncomfortable…"

"All subsequent aims are dependent on Aim 1. What if it doesn't work?"

Writing Proposal Evaluation

Giving Constructive Critique

The Review Form

Proposal title:

OVERALL IMPACT/PRIORITY

Overall Impact	Please limit text to ¼ page

SCORED REVIEW CRITERIA

Significance	Please limit text to ¼ page
Strengths **Weaknesses**	

Innovation	Please limit text to ¼ page
Strengths **Weaknesses**	

Approach	Please limit text to ¼ page
Strengths **Weaknesses**	

Giving constructive critiques

(1) Write notes in the specific criteria (significance, innovation, approach) as you read along

(2) Emphasize the strengths and weaknesses under each criterion

(3) Re-read the proposal for a more complete, informed evaluation

(4) Modify your critiques: are previous questions addressed in subsequent parts of the proposal?

(5) Distinguish between major and minor weaknesses; don’t get hung up on a detail unless it is critical to the success or interpretation of the overall aim / key experiment

(6) Write your overall evaluation of the proposal outlining major strengths and weaknesses that drive the overall impact score

Scoring system

Criterion Strength	Score	Descriptor	qualification
High	1	Exceptional	Strongest, negligible weaknesses
	2	Outstanding	Extremely strong, 1-2 minor weaknesses
	3	Excellent	Very strong, 2 or more minor weaknesses
Medium	4	Very Good	Strong, 1-2 substantial weaknesses
	5	Good	Overall good, a number of substantial weaknesses
	6	Satisfactory	1-2 major weaknesses that could cripple the proposal
Low	7	Fair	Significant numbers of major weaknesses
	8	Marginal	
	9	Poor	

Hixon Writing Center

http://writing.caltech.edu

Susan Hall, campus writing coordinator
Will visit on April 26

Christina Birch, STEM writing specialist
Ph.D., BE, MIT

Writing Research Proposals to Plan and Persuade

This handout offers students an introduction to writing research or grant proposals in order to persuade an audience of the credibility, feasibility, and impact of their ideas. Students working with this writing genre as part of a course assignment may have guidelines or requirements that differ from those described here.