Strategic planning for research grant applications

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ABSTRACT I am honored to receive the 2019 ASCB Public Service Award. It has been a true privilege to work with the cell biology community; I thank them for their collegiality in their interactions with me over the years. In this essay I offer some perspectives on constructing goals and strategy for research grant and fellowship applications in basic cell biology. They are based on my observations as a program officer for grants and applications in cell biology in the National Institute of General Medical Sciences (NIGMS) from 1991 to 2019.

STRATEGIC PLANNING FOR RESEARCH GRANT APPLICATIONS

Goals and strategy are foundational concepts in research planning, and communicating them effectively can markedly improve the competitiveness of grant applications. In this essay I outline a planning exercise that a number of applicants have found helpful. This exercise is different from (re)writing the application, and should be performed as a separate activity.

Begin by thinking about where your project lies on a continuum from discovery to mechanism. At the discovery end of the spectrum, exploratory and descriptive inquiries aim to uncover or define new behaviors, organization, and processes. The corresponding research designs are focused on building a knowledge base or acquiring selected items of information to lay a foundation for future mechanistic studies and understanding. At the mechanistic end of the spectrum, inquiries have advanced to a stage where they can pose and answer specific questions about the molecular basis of cellular processes. Corresponding research designs can follow question-based formats, in which mechanistic hypotheses are tested and eliminated to arrive at working models for function. You should examine the current understanding of your system and assess where you can realistically position your goals on the spectrum. To do this, work through the steps below, which should give you an idea of whether mechanistic goals are feasible for your project.

The first step is to separate background, strategy, and tactics. Background and strategy should be framed and expressed strictly in terms of biology, and experiments should be confined to tactics. At the background level, we have a topic, prior knowledge, and long-term goals and motivations. At the strategic level, we have foundational assumptions and decisions (e.g., what is known and what is not, what is highest priority), specific project goals (to deliver descriptions and/or explanations of biology), questions to answer about biology, and the derivation of the sought-after biological conclusions from the answers. At the tactical level, we have the implementation of questions about biology as sets of experiments, experimental outcomes, and the translation of experimental outcomes into answers at the level of biology.

Specific project goals that define a contribution to biological knowledge and/or an understanding to be delivered during the project period are the cornerstone of strategy. Specific project goals should be framed in terms of biology, like a graduate/advanced-undergraduate cell biology textbook or a scientific review article.
intended for a general scientific audience (e.g., components, responses, dependencies, causes and effects). They should not reference experiments or experimental results (i.e., the kind of content in research papers). Specific project goals may be descriptive (to define a response, identify components and interactions in a process, determine a high-resolution structure) or mechanistic (to explain how a process works at some specified level of detail). If a goal is mechanistic, the definition of the goal should be clear about what aspects of the process or function the research plans to explain, for example inputs, outputs, responses, dependencies, components, interactions, locations, and/or structures. Identifying a topic or process of study is not the same as defining a goal. Long-term goals, intentions, and motivations should be clearly distinguished from specific project goals.

In this exercise, when defining specific project goals, do not reference experiments or the performing of research. Applicants tend to view their projects from the perspective of the research process, while reviewers are focused on outcomes. The distinction between goals and process is often blurred. For example, Specific Aims may briefly reference a topic, and then elaborate on it with sentences built around “activity words” (action words that reference the process of research rather than its goals/aims/purpose). Examples of these include investigate, study, examine, characterize, analyze, define, evaluate, elucidate, assess, describe, monitor, probe, test, clarify, explore, dissect, compare, understand, enhance understanding of, systematically dissect, shed light on, provide/gain insights, quantify, measure, determine the role/function/relationship/effects/contribution. These constructs can be replaced in their sentences by the phrase “do research on” without significant loss of information. Such sentences identify those aspects of the topic that the applicant intends to pursue, but often convey little beyond this. When these words are cleared from Specific Aims and the residual biological content is examined, sometimes there is very little of substance remaining. If you have difficulty expressing your goals without using these words, you should revisit and further develop the biological rationale for your project.

When defining your goals, describe molecular functions and mechanisms using specific biochemical terms like bind, activity, inhibit, activate, required, and essential, or more specific cell biological terms like localize. Descriptions are often imprecise, employing vague words used in social and economic contexts, for example: contributes to, interacts, regulates, affects (effects of), facilitates, mediates, modulates, coordinates, controls, enhances, promotes, participates in, drives, is involved in, functions in. These words often convey little beyond a general sense of involvement, causation, or dependence. Note that although the word regulate may take on a specific meaning from its context, it is often used in applications in a vague sense of “has an effect on.”

Implicit in the definition of goals should be the specification of an endpoint or solution, that is, what it means to accomplish the goal. Defined endpoints for goals are a critical element of significance. There should also be a strategy to reach the specified endpoint during the project period. In the absence of a defined endpoint and/or a strategy, a goal may be perceived more as an aspiration than a deliverable.

The next phase of this exercise is to (re)construct the strategy behind your project. Applicants often assume that their strategy is obvious from their experiments, but in practice it is difficult for reviewers to deduce the applicant’s intent and predict project outcomes from experiments. In thinking about strategy, remember that if you have experiments, they came from questions; work backward to recover them. Here are some suggestions for thinking back and reconstructing the full chain of reasoning you followed in developing your project:

Begin by examining your foundational assumptions about what is known and what is to be learned. Decisions that you make (or sidestep) at this stage determine whether your strategy will stand on a stable foundation. You should be clear about those ground truths that will not be further tested or questioned in the research plan. In a competitive research environment, choosing one’s starting point requires judgment calls and calculated risk. A too-conservative choice of starting point may seem safe, but timid goals will not significantly advance the field. More aggressive assumptions allow one to prioritize selected lines of inquiry and set more ambitious goals, but an overreach that bases strategy on questionable assumptions can introduce unacceptable risk.

Explain your reasons for choosing and excluding specific project goals. Try to capture prior inside knowledge that you unconsciously incorporated into decisions. Think about decisions that you made without a conscious awareness that a decision was being made, for example, excluding models that you judged were wrong or lines of inquiry that you judged would be unproductive.

Work your way downward from your specific project goals, which ask big questions like What is it? What does it do? How does it work? Next are second- and third-level questions that you ask to answer the big questions. For example, questions may seek to uncover cause and effect relationships by querying aspects of behavior such as dependencies and responses. For a mechanistic goal, questions may test predictions a model makes about behavior. Although these questions will be answered by performing experiments, once again frame them only in terms of biology like in a textbook, without referencing the experiments.

Next outline the reasoning connecting questions and goals: How will you stage and prioritize your questions? What kinds of answers can you foresee? How will answering your questions take you to your goals? The majority of applications in basic cell biology cite long-term goals of explaining functions or determining mechanisms. However, many of them gather information using unstructured approaches without clear endpoints. When you set goals, specify endpoints; to connect your questions to the endpoints, organize them into a systematic strategy.

If your system is well-enough described to identify in advance the models that you will need to test, designing structured strategies is relatively straightforward: The specific project goal is a mechanism that explains a process. The strategy is to challenge competing mechanistic hypotheses by testing the predictions they make for behaviors under certain conditions in wild-type and experimental systems. A question-driven process of elimination is followed to arrive at a working model.

In real life, projects are often less mature, and strategies must be staged. If you do not yet have enough information to formulate advanced models to test, perhaps you can develop strategies to systematically narrow the possibilities (e.g., by testing more general models) and guide the project efficiently through its earlier descriptive stages. If your project is too preliminary even for this, you should question whether mechanistic goals are feasible. It is common to see speculative strategies that aim to collect information about poorly characterized systems with the expectation that the findings will later be sufficient to define mechanisms. However, these often do not stand up well to critical scrutiny in peer review.

If your project goal is discovery, you will need to extrapolate to predict the biological conclusions and understanding that you expect will result from your findings. For exploratory research, what is the basis for believing that important unknown biology may be
Questions about hypotheses arise whenever we think about research strategies, so I would like to consider some uses and misuses of the term. There is an idea that hypotheses should be included in applications because “hypothesis-driven” approaches are positively viewed by reviewers. However, the term hypothesis-driven refers to a kind of structured question-based research strategy; the presence of hypotheses in an application does not make it hypothesis-driven. Unless they are organized in a systematic framework that structures (“drives”) the research, phrasing questions as hypotheses does not contribute substance to a strategy. I recommend that you consider the points about hypotheses made by Jon Lorsch in his essay “Hypothesis Overdrive” in the NIGMS Feedback Loop (https://loop.nigms.nih.gov/2014/03/hypothesis-overdrive/).

Oddly, the word hypothesis is often involved when applications are ambivalent about foundational assumptions. Sometimes the word “hypothesis” is used for an apparent premise upon which a Specific Aim seems to be based, and it is not made clear (perhaps intentionally) whether it is assumed to be correct, or is considered to be in question, or both. Sometimes a foundational proposition upon which an entire project is based is identified as an “overarching hypothesis.” To avoid confusion, I suggest using the term “hypothesis” only to refer to a specific conjecture that will be tested, and not as a synonym for a premise or assumption. More generally, it is important to decide upon and to be clear about what will be treated as ground truth that will not be tested or questioned in the research.

A concluding caution about hypotheses concerns a widespread but questionable practice noted by Jon Lorsch: basing Specific Aims on a single hypothesis. Its potential hazards are reflected in a wide range of reviewer concerns, for example: If the hypothesis is refuted, is the line of inquiry at a dead end without backup plans? If the hypothesis is not refuted, what about other hypotheses that were not considered? If the reviewers are skeptical of the hypothesis, will they consider the aim to be incomplete because alternative possibilities are not considered? If the applicant succeeds in convincing the reviewers that the hypothesis is the only reasonable possibility that needs to be addressed, will they conclude that the aim will only reinforce a preexisting understanding, rather than advancing the field to the next level of understanding? Will the reviewers worry that the plan may only amass results consistent with the hypothesis, rather than challenging it? In thinking about your strategy and goals, keep in mind that one does not “prove” a hypothesis; rather one establishes it as a working model by disproving the reasonable alternative possibilities.

My experience has been that when applications do poorly in peer review, the goals and strategy are usually missing, poorly developed, or not effectively communicated. These deficiencies may not be the only problem with an application, and they may not be remarked upon in the summary statement, but I have found it useful to begin by addressing them. To make the most of this guidance, I recommend that it be undertaken as an exercise separate from (re)writing your application. The most difficult part is to formulate goals and strategies directly in terms of biology, rather than trying to convey them indirectly in terms of experiments. However, this is important for effectively communicating the purpose and significance of your research plans.

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