Successful Grant Writing

Grantsmanship Course – 23 July, 2015
Israel Society for Biological Psychiatry

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Why Write a Grant?

- To protect your time and give you scientific freedom
- Resources to pursue a question that you believe is important
  - Salaries for students
- A measure of academic accomplishment
What keeps us from doing grants?

- Fear of rejection
- Not enough time

It can be fun!

- Seeing the bigger picture
  - Planning ahead to realize your dream projects.
- Establish fruitful collaborations that can advance your ideas and scientific enthusiasm
- Pride and accomplishment satisfaction when all your hard efforts finally get rewarded
- Acknowledgment from your reviewers and peers
“Where shall I begin?” He asked.

“Begin at the beginning,” the King said, “and stop when you get to the end.”

Lewis Carroll, Alice in Wonderland
“There is no grantsmanship that will turn a bad idea into a good one, but there are many ways to disguise a good idea.”
Scientific Parts

- Abstract
- Background
- Significance
- General Objectives & Hypothesis
- Specific aims
- Methodology
- Research plan
- Timeline
The Abstract is the first part of the proposal the reviewers will read and first impressions count.

This may decide how much time and how closely the reviewer will look at your proposal.

Get your point across:
  - What is the innovation/Breakthrough?
  - How does it exceed the State of the art?
  - What is the impact?
Background

- Not a comprehensive review of literature
  - Tell what is known relevant to hypotheses
  - What is NOT known and how you will determine the answer

- Background establishes the need for your project
  - Important and interesting
  - Explain the problem, creating the need for your program funded by the requested grant.

- A readily identified need, consistent with the priorities of the program ..... make sure you say it in the proposal!
Significance

Apicomplexa are important human pathogens responsible for numerous severe diseases around the World. These include the various forms of malaria (1-3) as well as opportunistic infections associated with AIDS (4, 5).

Researchers are using genetic perturbations such as RNA interference or gene overexpression in cell-based HTS assays to identify genetic regulators of disease processes as potential drug targets. However, the molecular mechanisms of many diseases that deeply impact human health worldwide are not well-understood and thus cannot yet be reduced to biochemical or cell-based assays.
Significance
(Needs or Problem Statement)

- Critically important, and often poorly written
- Convince the funding source that you understand the need and can help them solve the problem
  - Demonstrate that the need is pressing
    - cite evidence
    - illustrate with graphs and charts
Significance cont.

Children are exhibiting violent and disruptive behavior.

The harsh truth is that growing numbers of children in America are exhibiting violent and disruptive behavior or externalizing behavior (also referred to as antisocial behavior, challenging behavior, defiance, noncompliance, aggressive behavior, acting-out, etc.) beyond the occasional minor incident typical of most children during the normal course of development. Such behavior has become one of the most pressing issues in schools.

- The first sentence is the problem.
- Then clarify the problem by defining both the behavior and what is normal
- States that this is a pressing need which is hopefully the need the funder is addressing
General Objectives & Hypothesis

- The “Background and Significance” section should set the stage for your objective.

- **State of the art and objectives:**
  - Specify clearly the objectives of the proposal, in the context of the state of the art in the field.
  - When describing the envisaged research, indicate **how and why the proposed work is important for the field and what impact it will have** if successful (ie: how it may open up new horizons or opportunities for science, technology, medicine...)
  - Specify challenging or unconventional aspects of the proposal, including multi or interdisciplinary aspects, collaborations between basic scientists and clinicians...
The cytochrome bc₁ complex is an energy-transducing enzyme that participates in cell respiration in oxygen utilizing eukaryotic cells and is located in the inner mitochondrial membrane. A similar bc₁ complex is located in the plasma membrane of many bacteria, where it takes part in respiration, denitrification, nitrogen fixation, and cyclic photosynthetic electron transfer, depending on the species. In all of these organisms the bc₁ complex oxidizes a membrane-localized quinol and reduces a water-soluble, c-type cytochrome and links this electron transfer reaction to translocation of protons across the membrane in which the bc₁ complex resides. The bc₁ complexes from mitochondria of several species have been crystallized and the mechanism of the enzyme, the protonmotive Q cycle, is partly understood.

The long term objectives of this research are to understand the mechanism of the cytochrome bc₁ complex and to elucidate the pathway by which the subunits of this oligomerич enzyme complex are assembled into the inner mitochondrial membrane. The specific aims of the current research project are to answer the following questions regarding the mechanism:

- Is ubiquinol oxidation a concerted or sequential reaction?
- What is the structural basis of negative cooperativity in the binding of ubiquinol?
- How are protons conducted to and from the ubiquinone and ubiquinol reaction sites?
- How does ubisemiquinone stability affect the rate of ubiquinone reduction?

We plan to investigate these questions in the cytochrome bc₁ complex of the yeast *Saccharomyces cerevisiae*, since this enzyme can be modified by molecular genetics methods and isolated in quantities sufficient for biochemical and biophysical characterization.
Develop an overarching Hypothesis:

- A testable idea or notion
- Basic premise for the proposal
- Once formed and focused, it should drive the rest of the proposal
General Objectives and Hypothesis cont.

- Not in the form of a question

- Hypothesis should be repeated in “Abstract”, “Background” and “Specific Aims”

- Stated exactly the same way throughout, same applies for Specific Aims
Specific Aims

Writing the Section of Specific Aims with an Emphasis on Hypothesis-driven Research

Before You Start: Answer the 3 Key Questions

What are you going to do? STRONG research question

Why is it important to do this? Who cares? So what? What happens if you do this?

Why is your approach innovative? How is your approach creative? How are you going to do it?
Specific Aims

- Clearly hypothesis-driven
- Not names of experiments
- Aims should be independent of each other
Limit to 3-5 aims per project period.

State each aim in one sentence

Supplement each aim with a two or three sentence summary of approach.

Each aim should:
- Be experimentally feasible
- Have a realistic time frame
- Have a definitive outcome
Cancer cells are characterized by ......., form larger and more vascularized tumors and readily metastasize to distant organs. These findings are reinforced by clinical observations demonstrating a highly significant correlation between enhanced gene expression and metastatic potential, tumor vascularity and reduced postoperative survival of cancer patients. These results and the anti-cancerous effect of ....... gene silencing and inhibitory molecules indicate that this protein is a promising tumor marker and target for anti-cancer drug development..................................

Our recent studies/ preliminary results indicate that apart of its enzymatic activity, the .....protein exerts non-enzymatic functions that further promote tumor......... The proposed research focuses on basic and clinical aspects of ..................................

Aim 1. Impact of gene x on regulation and function of cancer progression, focusing on
i) Inflammation associated colon carcinoma;
ii) Radiation-induced by ... expression in pancreatic carcinoma;
iii) Contribution of ... on the tumor microenvironment.
Altogether, Aim 1 emphasizes the impact of..... on cancer progression.

Aim 2. non-enzymatic activities of ....: i)......................................................................................................

...Aim 3........................................

The proposed research stems from studies performed during the last 3 years of research supported by the......and the development of molecular tools (i.e., .........) and collaborative arrangements (i.e., ........ ) to carry out and accomplish each of the proposed specific aims. Precise structure/function analysis of the ....... protein will pave the way for rational design of inhibitory molecules directed against its enzymatic and non-enzymatic functions.
Specific Aims cont.

RESEARCH PLAN

A. Specific Aims

The objective of this research is to understand the mechanism of the cytochrome bc₁ complex. The bc₁ complex transfers electrons from ubiquinol to cytochrome c and from this electron transfer to proton translocation by the proton motive Q cycle. The specific aims of the research are to answer the following questions regarding the Q cycle mechanism.

A1. Is ubiquinol oxidation a concerted or sequential reaction?

To address this question we plan to examine the rate of ubiquinol oxidation under presteady state conditions and determine how the rate is affected by the midpoint potential of the Rieske iron-sulfur cluster and the midpoint potential of the cytochrome b₈ heme. If ubiquinol oxidation is a sequential reaction, the rate will be affected only by the midpoint potential of the Rieske iron-sulfur cluster. If ubiquinol oxidation is a concerted reaction the rate will be affected by the midpoint potentials of the Rieske iron-sulfur cluster and the cytochrome b₈ heme.

A2. What is the structural basis of negative cooperativity in the oxidation of ubiquinol?

We plan to identify amino acids that transmit conformational changes between the ubiquinol oxidation pocket at center P in one monomer and that in the other monomer. Residues suspected of involvement in the cooperative interaction will be modified by site-directed mutagenesis. Mutations that disrupt the cooperativity should change the titer for ligand binding in the ubiquinol oxidation pocket.

A3. How are protons conducted to and from the ubiquinone and ubiquinol reaction sites?

We plan to test a putative pathway for conduction of a proton out of the ubiquinol oxidation site at center P and two putative pathways for conduction of protons into the ubiquinone reduction site at center N by site-directed mutagenesis of the putative proton conducting amino acids. If these residues are involved in proton conduction, we expect the rates of ubiquinone reduction and ubiquinol oxidation to decrease significantly, with the bc₁ complex perhaps becoming completely inactive.

A4. How does ubisemiquinone stability affect the rate of ubiquinone reduction?

We plan to determine how the stability of ubisemiquinone at center N affects the rate of ubiquinone reduction. Since the EPR signal from the center N semiquinone is eliminated by antimycin, amino acid changes that confer resistance to antimycin are likely to change the stability of the semiquinone. Similar reasoning applies to funiculosin and illicolin, two less well characterized center N ligands. We will examine the stability of the EPR detectable semiquinone in bc₁ complexes with antimycin, illicolin, or funculosin resistance mutations and measure rates of cytochrome b₈ oxidation/reduction by ubiquinone/ubiquinol through center N in these mutants.

“A grant in a page” encourages the reviewer to structure the review around this page.
Microscopy has emerged as one of the most powerful and informative ways to analyze cell-based high-throughput screening (HTS) samples in experiments designed to uncover novel drugs and drug targets. However, many diseases and biological pathways can be better studied in whole animals—particularly diseases that involve organ systems and multicellular interactions, such as metabolism and infection. The worm Caenorhabditis elegans is a well-established organism that can be robotically prepared and imaged, but existing image-analysis methods are insufficient for most assays.

We will develop algorithms for the analysis of high-throughput C. elegans images, validating them in three specific experiments to identify infections and genetic regulators of host response to pathogens and fat metabolism. Novel computational tools for automated image analysis will make whole-animal screening possible for a variety of biological questions not approachable by cell-based assays. Building on our expertise in developing image processing and machine learning algorithms for high-throughput screening, and on our established collaborations with leaders in C. elegans research, we will:

Aim 1: Develop algorithms for C. elegans viability assays to identify modulators of pathogen infection
Challenge: To identify individual worms in thousands of two-dimensional brightfield images of worm populations infected by Microsporidia, and measure viability based on worm body shape (live worms are curvy whereas dead worms are straight).
Approach: We will develop algorithms that use a probabilistic shape model of C. elegans learned from examples, enabling segmentation and body shape measurements even when worms touch or cross.
Impact: These algorithms will quantify a wide range of phenotypic descriptors detectable in individual worms, including body morphology as well as subtle variations in reporter signal levels.

Aim 2: Develop algorithms for C. elegans lipid assays to identify genes that regulate fat metabolism
Challenge: To detect worms versus background, despite artifacts from sample preparation, and detect subtle phenotypes of worm populations.
Approach: We will improve well edge detection, illumination correction, and detection of artifacts (e.g. bubbles and aggregates of bacteria) and enable image segmentation in highly variable image backgrounds using level-set segmentation. We will also design feature descriptors that can capture worm population phenotypes.
Impact: These algorithms will provide detection for a variety of phenotypes in worm populations. They will also improve data quality in other assays, such as those in Aims 1 and 3.

Aim 3: Develop algorithms for gene expression pattern assays to identify regulators of the response of the C. elegans host to Staphylococcus aureus infection
Challenge: To map each worm to a reference and quantify changes in fluorescence localization patterns.
Approach: We will develop worm mapping algorithms and combine them with anatomical maps to extract atlas-based measurements of staining patterns and localization. We will then use machine learning to distinguish morphological phenotypes of interest based on the extracted features.
Impact: These algorithms will enable addressing a variety of biological questions by measuring complex morphologies within individual worms. In addition to discovering novel anti-infectives and genes involved in metabolism and pathogen resistance, this work will provide the C. elegans community with (a) a versatile, modular, open-source toolbox of algorithms readily usable by biologists to quantify a wide range of important high-throughput whole-organism assays, (b) a new framework for extracting morphological features from C. elegans populations for quantitative analysis of this organism, and (c) the capability to discover disease-related pathways, chemical probes, and drug targets in high-throughput screens relevant to a variety of diseases.

Primary collaborators

Aim 1: Develop algorithms for C. elegans viability assays to identify modulators of pathogen infection

Challenge: To identify individual worms in thousands of two-dimensional brightfield images of worm populations infected by Microsporidia, and measure viability based on worm body shape (live worms are curvy whereas dead worms are straight).

Approach: We will develop algorithms that use a probabilistic shape model of C. elegans learned from examples, enabling segmentation and body shape measurements even when worms touch or cross.

Impact: These algorithms will quantify a wide range of phenotypic descriptors detectable in individual worms, including body morphology as well as subtle variations in reporter signal levels.

Carolina Wahlby, Broad Institute
Specific Aims cont.

- **Aim 1**: To examine the relation of dairy food intake and alcohol consumption to the risk of recurrent gout attacks

  **Hypothesis 1a**: Dairy product intake decreases the risk of recurrent gout attacks;

  **Hypothesis 1b**: Alcohol consumption, irrespective of type of alcoholic beverage, increases the risk of recurrent gout attacks;

- **Aim 2**: To assess the association between systemic inflammation induced by acute infection and immunization with the risk of recurrent gout attacks

  **Hypothesis**: Acute infection and active immunization trigger recurrent gout attacks;

- **Aim 3**: To evaluate the effect of climatic factors on the risk of recurrent gout attacks

  **Hypothesis**: Low temperature, high humidity and high barometric pressure increase the risk of recurrent gout attacks;
Methodology

- Describe the proposed methodology, including key intermediate goals.

- Explain and justify the methodology in relation to the “State-of-the-art”, including any particularly novel or unconventional aspects.

- Highlight any intermediate stages where results may require adjustments to the project planning.

- Highlight any high risk areas of the research and how you will deal with them; if possible provide an alternative low risk methodology.
Talk with your Statistician
EARLY & OFTEN!

- How many subjects will you need?
- Will revising your approach to the question make numbers less intimidating?
- Do you need to revise your plans because of numbers problems?
- What’s the best analysis plan?
Writing a Detailed Research Plan

- Organization of the research plan should parallel specific aims and be easy to follow
- Should be the longest part of the grant
- Document extensively with figures, etc
- Demonstrate ability of PI to execute methods
Writing a Detailed Research Plan cont.

- Demonstrate a deep awareness of the problems
  - Understanding the scientific question
  - Recognition of the challenges you will have to overcome

- Provide chronology and time frame

- Include multiple alternate strategies

- ‘The devil is in the details’
Approach (repeat for Aims 1, 2, and 3)
Specific Aim 1
Hypothesis
Background and Preliminary Data
Supporting Specific Aim 1
Approach to Specific Aim 1, Including Experiments and Interpretations
Potential Pitfalls and Alternative Approaches

The Importance of Preliminary Data

Make sure at least once in your proposal you say “We will build on our preliminary data to do thus-and-so.” Or better, “Building on our intriguing preliminary results, we will do thus-and-so.”

Ideally, you should have at least one figure of preliminary data to support each of your specific aims/hypotheses.
Timeline

The reviewer wants to see answers to the following question:

**WHAT & WHEN** the program plans to accomplish milestones

A *timeline* or *Gantt chart* tells the grant reader when major project milestones will begin and end during the grant’s funding period.

- Key tasks or activities that will be carried out to implement the program successfully?

- Are all tasks, from the day funding is awarded to the last day of the project’s funding time frame included?

- Can each task realistically begin and end in the proposed time frame?
## Timeline Template

<table>
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<th>Specific Aims and Sub Aims</th>
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Administrative Parts

- Budget
- CV or BioSketch
- Collaboration and support letters
- Overlapping funding
Ask for Help with the Administrative Sections of the Grant

- 40% of a grant application is unrelated to a grant’s scientific merit (Ex. CVs; other support; human studies; budget; resources and environment; abstract)

- Leverage your mentor(s) and the experienced support staff in your department (or grant office) to help with these parts.

Ask for help EARLY!
A budget is a key element of most grant proposals and serves as a blueprint for spending the project’s funds.

Budget information about activities planned and personnel who will serve on the project provides reviewers with an in-depth picture of how the project will be structured and managed. Budget details usually reveal whether a proposed project has been carefully planned and may ultimately be feasible.

The proposed budget must give an accurate assessment of all cost items and cost amounts that are necessary and reasonable. It should be complete and include all the costs of any personnel, supplies, and activities required by the project.

The project needs to be feasible within the budget presented (realistic, don’t inflate). If major cost areas are omitted or underestimated, the project, as proposed, will not be considered feasible.
The funding agency will provide guidelines for the funding proposal and will state any budgetary restrictions. A budget template is often provided as well.

Important to identify any limitations
- Salary, supplies, equipment, computers, and travel are common direct cost expenses with restrictions
- Often, indirect cost limits are applied
- Total allowable funding limits, and cost share requirements, all of which must first be taken into consideration are common.

Solicitations will state whether the budget is flexible or restricted. It is imperative that the budget be as accurate as possible.

A reasonable budget is one that is based upon actual costs when possible.

If the project is funded, this budget will become the financial plan used by the funding agency to provide support. If there is a difference between the budget and actual expenses, indicative of a change in scope, this may require sponsor approval.
Two Main Parts to a Budget

- Budget Form which breaks the budget into specific categories

- Budget Narrative (justification) that explains how you arrived at these figures and why you need the money
Budget Categories

Most budgets are composed of two kinds of costs:

Direct & Indirect

- **Direct costs** are costs that can be identified specifically with a particular sponsored project. These costs include expenditures for project personnel; salaries and employee benefits, supplies and materials, travel, equipment. All direct cost items must be included in the budget.

- **Indirect costs** are incurred by a grantee that cannot be identified specifically with a particular project or program. They include the costs of many services the institution provides (procurement, administrative, library, Technology Transfer Office (TTO), accounting/finance) as well as building maintenance and utilities. These costs are often referred to as overhead, or Facilities and Administrative Costs (F&A).

*It is important to ensure that all costs meet the criteria of allowable and reasonable.*
Budget Justification

- A breakdown of your proposed budget in a narrative format, and is used to "justify" the expenses for the project. In short, the budget justification should:
  - Follow funding agency guidelines.
  - Provide as much detail and justification as necessary.
  - Be organized in the order of the line items in the detailed budget (spreadsheet).
  - Explain why each of the items is needed to accomplish the scope of work.
  - Make it clear that all budget requests are reasonable and consistent.
  - Make it clear that the Principal Investigator has the experience and authority to defend that the budget is reasonable and thorough.
Budget Justification cont.

We request a total of $100,000 to undertake the study described above. The majority of funds will go towards …

Main categories of most budgets:

I. Salaries (Personnel) – include employers cost for each of the personnel involved in the project per year and its role in the project.

II. Materials and supplies – identify general categories such as: consumables, disposables, animal purchase, husbandry and maintenance cost. Provide estimates and explanations for the number of animals needed per year.

III. Equipment – explain why it is essential to the study and provide accurate costs.

IV. Travel - Specify WHO, WHAT, WHEN, WHERE, and WHY. We request support for the PI and the Co-PI to attend an annual conference in Washington D.C. for each year of the project to present research results. This can include the registration fee.
Budget Justification cont.

V. Other Direct Costs
- Publication/Dissemination Costs
- Annual membership and professional literature
- Consultant Services
- Computers, printers and software
- Payment for project participants
- Other (shipping samples and similar project-specific costs)

VI. Indirect Costs - Administrative or other expenses NOT directly associated with a particular activity or project; but are related to overall general operations and are shared among projects and/or functions (also referred to as overhead) ie: accounting, utilities, technology support, and facility maintenance.
Curriculum vitae
The professional presentation of YOU

- Summary of educational and academic background
- Teaching and research experience
- Publications & presentations
- Awards, honors awards
- Generally preferred in the EU, Middle East, Africa, Asia
- In USA (and elsewhere), used for academic, education, scientific, research positions and grant/fellowship applications
Curriculum Vitae cont.

- Usually funding agencies specify their preferred standard. Yes, the instructions may differ depending on the grant type!

- Always follow the instructions

- Place locator information in headers and footers (your name, page numbers, date last updated)

* In the USA, a professional CV should NOT include your date of birth; army service is also not needed unless professionally relevant
Consistency is Important

Which reference is correct?


Curriculum vitae cont.

- English!

- Times New Roman, 12 Point Font

- Page numbers

- 1.5 spacing between lines!

- Avoid use of bold, italics, underline except for sections headings and your name in publications

- Chronological order should begin with the earliest date to the current date
Publications should be listed from earliest (first) to latest (last) and includes Theses.

Do not use abbreviations such as Dept., Inst., or Prof.

Academic Degree relates ONLY to MD, PhD, MSc, MPH, or MBA (do not list theses here).

Professional experience includes your residency, specialization, specialty, and studies abroad.
Collaboration and support letters

Choose the Right Collaborators: Who are they?

- Experts that bring to the project something you do not have
- Collaborators who are researchers and have written papers in the field
- Collaborators who get the work done and are easy to work with
- Ask Mentor or other senior investigators about potential collaborator
- Letters from experts expressing support and willingness to help
Overlap between grant proposals

Resources: credibility..
Describe all current existing resources & grants
Do NOT hide it, because the referees will dig it out.

Existing resources are VERY helpful in establishing credibility