Successful Grantsmanship for New Investigators

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Successful Grantsmanship for New Investigators

- Develop your career path
- When will I get my first grant?
- Grant writing – Step #1
- Stay focused and on target
- Keep it clear and simple
- It is possible to propose too much
- Anticipate reviewers’ questions
- Summary
- More questions?
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Develop your Career Path

• Learn about research in labs or in clinics

• Learn about research carried out by
  o Individuals
  o Collaborative efforts
  o Established consortia of clinical investigators

• Learn about “big data” projects and “omics” approaches to research

• Learn about the varied sources of funding available
Develop your Career Path

• Choose mentors who will give you personal advice about your career options

• Initiate ongoing discussions with mentors who can impart clinical and scientific expertise

• Ask if you may study their successful applications and the grant reviews they have received.
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When will I get my first grant?

(Well, sometimes it just feels that way...)
When will I get my first grant?

- When your application will:
  - Tell a succinct and coherent story
  - Clearly delineate the significance and novelty of the proposed studies
  - Be based on hypothesis-driven specific aims
  - Demonstrate your expertise in rheumatology research
Should you apply?

- Maybe! Maybe NOT! Maybe not at this time!
- You may need more preliminary data
- Perhaps you would be well advised to wait until you stand a better chance of success
Anatomy of a Grant Application

An application for an NIH R01 grant consists of these sections, which are submitted electronically on the SF 424 forms.

This presentation will deal mainly with two sections:
• Specific Aims – 1 separate page
• Research Strategy – 12 pages
  o A- Significance
  o B- Innovation
  o C- Approach
    ▪ C1- Preliminary Studies/Progress report
    ▪ C2- Research Design and Methods

It is a challenge to pack all of the salient information about your project within 12 pages.
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Grant Writing – Step #1

“It sort of makes you stop and think, doesn’t it.”
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Stay Focused and on Target
When you Start to Write

• Make use of all your available resources when you do write the grant

• Get help from colleagues who are willing to read the draft of your grant application and provide constructive criticism

• Read the literature, attend appropriate conferences, speak to experts, and learn about the state of the art in the area proposed
The Investigator Needs to Have

• Independence from previous mentor(s) that includes a take-away project

• The ability to communicate and collaborate with experts in the field

• A position at an institution that provides sufficient time and technical resources for research

• A publication record demonstrating successful research in an area that is relevant, if not identical, to the topic proposed in the grant application
The Investigator Needs to Have

• Evidence that the research proposed is an extension of ongoing efforts

• Letter(s) of collaboration from investigators helping with specialized methods

• A well-argued personal statement of enthusiasm for the project

• Organizational skills to plan and execute the project

• Intelligence, wisdom, and street-smarts to excel in a competitive environment

• Strong writing skills
The Project Needs to Have

• Significance that provides a reason for expert reviewers to support your plans

• An explanation of the specific ways in which the project would extend basic molecular or cellular knowledge in the field, or ways in which it would increase what is known about the prevention, diagnosis, or treatment of rheumatologic disease

• A balance of state-of-the-art knowledge and plans to significantly extend what is known
The Project Needs to Have

- An overall scientific hypothesis to be tested
- Hypotheses to be tested within each specific aim
- Well-understood research questions and medical problems
- Well-established experimental methods in a novel formulation to answer these questions and solve these problems
If your plans do not satisfy each of these requirements, you will not get funded.
Pitfalls of Project Design

• Merely incremental progress planned along a safe, experimental trajectory

• Parts of the experimental design with no preliminary data

• Study of human samples or human subjects proposed as the last Specific Aim with only a tenuous connection to the rest of the project based on animal or cellular experimentation

• Use of an animal model of disease that poorly represents a particular aspect of the human disease or condition
Pitfalls of Project Design

• Parts of the proposal that are highly significant but with a poorly justified, experimental approach

• Conversely, parts of the proposal that are technically sophisticated but have no clear significance in relation to the human disease in question

• A project that was already superseded by results in the literature

• Conversely, design that is too forward-looking and not linked to currently accepted ideas
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“I lift, you grab. … Was that concept just a little too complex, Carl?”
Experimental Design

• What are you going to do?

• How are you going to do it?

• What is the rationale?

• How are you going to analyze the data?

• What are your alternative approaches?
Experimental Design

• Controls, controls, controls

• How much experimental detail is necessary?
  o Details usually necessary for non-standard assays
  o Detailed methods are often included at the end of the ED section

• Discriminate between direct and indirect effects
  o A given response may have a direct effect at early time points, but an indirect effect later on

• Use pharmacological inhibitors with caution
  o Specificity is only relative and changes with dose
  o Controls: vehicle alone and inactive drug in vehicle
Experimental Design

• Feasibility
  o What resources are needed?

• Size does matter
  o Is there a need for a statistical analysis plan?
  o What is the correct sample size (power)?
  o How can I accommodate for variability in the study population?

• Ask mentor/peers to evaluate experimental plan and preliminary data
  o Don’t be afraid to ask (stupid) questions
In vivo veritas?

• **Mouse vs. man**
  o Profound differences exist
  o TG/KO mice are usually not good models for multigenic human disease

• **Primary cells from mouse and man**
  o Insufficient numbers
  o Phenotype changes *ex vivo*
  o Not easy to manipulate
In vivo veritas?

• Questions to consider when using clinical samples:
  o Do primary cells/tissues studied ex vivo retain their phenotype and function in vivo?
  o Do primary cells need to be expanded in culture before being used in an experiment?
  o What is the limit of sensitivity of an assay that uses primary cells/tissues/fluids?
  o Has the clinical phenotype of the subjects from which the samples were obtained been sufficiently characterized?
In vivo veritas?

• Benefits and limitations of TG/KO mice
  o Ideal means to evaluate the contribution of a single gene product in vivo
  o TG/KO mice can often be purchased, or generated by a company
  o KO mice can be affected by compensatory mechanisms that arise during ontogeny
  o Backbreeding can alter the original phenotype
Cell Lines – Not Normal Cells

• Ease of manipulation vs. relevance
  o Don’t expect an AML cell line to be identical to a macrophage
  o Cell cycle regulation isn’t the only thing abnormal in a cell line
  o Cell lines often mutate rapidly and phenotypes vary from lab to lab, and during continual passage in vitro

• Over-expression systems – a Faustian deal
  o What happens when the proteins of interest are expressed at normal levels? If you do not know, the data will always be suspect
  o Does over-expression (or the presence of epitope tags) alter intracellular localization, and/or protein stability?
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It is possible to propose too much?

“Mr. Osborne, may I be excused? My brain is full.”
It is possible to propose too much?

• Easy criticisms for reviewers to make
  o “The application is unfocused/diffuse”
  o “The application is overly-ambitious”

• More is not necessarily better
  o Quality trumps quantity
  o Multiple experimental approaches are good, but not if they test a hypothesis in the same manner
Impact vs. Ease

- Easy descriptive experiments often lack impact. That is, they don’t elucidate a mechanism, or test a hypothesis.

- A decision to propose ambitious experiments should be based on preliminary data that support the need for such experiments. Beware of seductive new technology.
Seduction by Technology

- Cell type-specific TG and cre/lox KO mice
- DNA microarrays and protein microarrays
- Robots & high-throughput screening
- SNPchips & population genetics
- RNAseq

Using one of these sophisticated methods will generate a lot of data, but perhaps little knowledge, unless it is used to test a sophisticated hypothesis!
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Anticipate Reviewers’ Questions

“Yes ... I believe there’s a question there in the back.”
What reviewers look for*

- Are the specific aims sound?
- Do the preliminary data support the central hypothesis?
- Are the proposed studies feasible?
- Are the proposed studies important and innovative?
- Is there a better experimental approach that could be used (or better controls)?

*NIH grant reviewers are instructed to judge the following: significance, innovation, approach, qualifications of the PI and co-investigators, and institutional resources.
Background & Preliminary Data

• How significant is the question to be addressed?

• What is known and where are the gaps?

• How does your hypothesis move the field forward?

• How do your preliminary data support your central hypothesis? Proof of principle?

• Do you have data to support each specific aim?
Inside Information from the NIH

• Not only new, but also some established, investigators submit an NIH grant application that fails to meet one or more of the essential criteria that reviewers demand

• Some investigators submit multiple, weak applications on topics that are only peripherally related to their publication record and/or technical expertise, and such applications usually fail to get funding
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Summary

- Grantsmanship is a specialized skill but alone it does not ensure success.
- Combine it with your scientific and/or clinical expertise
- Build a team of supporters to get the job done
- Write an exceptionally strong grant application!
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More questions?

“Sure, we need more research in alchemy, necromancy, and sorcery, but where is the money going to come from?”
More Answers

• Grant Writing
  o All About Grants Tutorials
  
o New Investigator Guide to NIH Funding
  
o NIAID Funding Opportunities and Concepts
  
o NIAMS Funding Opportunities List
    http://www.niams.nih.gov/Funding/Funding_Opportunities/filter.asp
  
o How to Write a Human Subjects Application
More Answers

• Electronic Submission
  o Electronic Application Resources  
  o Finding Help – eRA Commons  
    http://grants.nih.gov/support/index.html
  o Finding Help – Grants.gov  
    http://www.grants.gov/help/help.jsp

• Grant Review
  o Center for Scientific Review - Overview of Peer Review Process  
    http://grants.nih.gov/grants/peer_review_process.htm
More Answers

• **Grant Management**
  - How to Manage Your NIAID Grant Award
    [http://www.niaid.nih.gov/researchfunding/grant/Pages/gm.aspx](http://www.niaid.nih.gov/researchfunding/grant/Pages/gm.aspx)
  - NIAMS Grant Policies & Guidelines

• **Other Topics**
  - Advice on Research Training, Career Awards, and Research Supplements
  - NIH Loan Repayment Programs

• **Example of a Useful University Web Site**
  - UPitt Web Page - Writing and Grantsmanship
    [http://www.oorhs.pitt.edu/Resources/WritingGrantsmanshipResources.aspx](http://www.oorhs.pitt.edu/Resources/WritingGrantsmanshipResources.aspx)