Grantsmanship

November 12, 2011

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NIH R01-HL60590
NIH R01-HL34579
NIH R01-AG33283
NIH R01-HL107211
NIH S10-RR25596
PHS U26-IHS300292
NIH P01-HL85577
NIH R43-HL95199

Practice & Persistence

- Read other people's grants!
- Practice makes perfect: submit 3 / year
- Keep doing it—refine your craft
- Allow enough time: 4 hr/d for 6 weeks
  - Preliminary data may take a year before that
- Allow 1-2 weeks for mentor to review
- Allow 1 more week to revise
- Take care of routing paperwork early

Pursue Your Passion

- Passion for your work is the #1 prerequisite for success
- Surround yourself with passionate people
- Share your enthusiasm and inspire others

General Strategies

- Establish your reputation as a credible scientist
- Develop your strengths
- Collaborate productively
- Hire the best and most passionate people
- Be persistent
- Don’t take failure personally: learn from it

New NIH Guidelines

- Grant application is shorter: 25 -> 12 pages
- Less room for experimental detail
  - How do you demonstrate your ability to do it?
- Preliminary data matters even more
- Background must be focused, clear
- Use bullets, tables, boxes
- DON’T sv spc by abbrev evrthg
- DON’T cheat on fonts, margins, micro-figs

NIH Scoring Criteria

What really happens in peer review?

- Grants received 6-8 wk before SS
- Review takes 2-6hr/grant
- Detailed critique on 5 criteria
- Assessment of 3 reviewers presented to group followed by discussion of merits and faults (Total discussion <15min)
- Advocacy and randomness
- Scoring, normalization, council
- Payline and NOGA

- Significance
- Innovation
- Approach
- Investigator
- Environment
- Other

- **IMPACT**

NIH Scoring Criteria: Significance

Is this an important problem? Will the results change the field? How will it advance our understanding of the problem?

Clinical relevance, magnitude of problem, ways in which new information will affect patient care (management, diagnosis, new therapy possible, breakthrough knowledge)

Poor score from failure to make a compelling argument for your science

NIH Scoring Criteria: Investigator

Does the investigator have a proven track record? What is his/her productivity in recent years? Are the publications in solid journals? Are there appropriate collaborators? Are the letters of support strong? Does the reviewer know (and like) the investigator?

Poor score: Lack of independence, low productivity, no track record for doing the experiments proposed (expertise)

Spread the Gospel

- Good science isn't -- until you preach
- Accept all speaking opportunities, and ask for invitations to specific meetings
- Ask good questions at talks; be memorable
- Introduce yourself to others, exchange cards, emails; follow up
- Get to know the power brokers
- Most science happens outside the room
- NETWORK

NIH Scoring Criteria: Innovation

Is the hypothesis novel? Are the techniques state-of-the-art? Is a new approach being developed? Is this a COOL idea? Does this grant excite me, or am I yawning?

Poor score: Incremental science, standard approaches, old ideas

Risk: too much novelty can raise doubts about feasibility

NIH Scoring Criteria: Approach

Will the experimental plan actually yield clear crisp answers? Is the approach logical and easy to understand? Are all of the methods in place? Do the preliminary data support the hypothesis and methodology? Is it feasible?

Poor score: Experimental design messy, complicated, vague, hard-to-follow

Most common cause of poor overall score

Easiest to nit-pick

Common Criticisms of Approach

- "Over-ambitious"
  - Too many hard experiments
- "Fishing expedition"
  - Gene arrays or proteomics without a plan to validate key findings, or without other mechanistic or hypothesis-based work
- "Descriptive" or "Insufficiently mechanistic"
  - Hypothesis not clearly stated, or experiments will not test hypothesis
- "Pitfalls not addressed"
  - Missing preliminary data to show feasibility

NIH Scoring Criteria: Environment

Are the necessary resources available in terms of equipment, space, support services, and collaborators? Is the institution supportive of this young investigator?

Poor score: No independent lab space; in some cases, absence of local expertise

This is an opportunity to elaborate on the strengths of your institution: describe cores, resources, special strengths, etc.

NIH Scoring Criteria: Other

- Vertebrate animals
- Human subjects
- Biohazards
- Resource sharing plan

These are almost never a cause for poor overall score, but can factor in as a reason to not like the grant, especially the vertebrate animals section. Don't use this as a way to sneak in additional experimental details.

NIH Scoring Criteria: Budget

Is it enough money to do the work?

Is the budget padded with too many salaries?

- Nobody thinks about whether it is a bargain, or what the indirect costs are
- Non-modular budgets are scrutinized and often reduced: justification is very important
- Personnel justification is a place to elaborate on the specific skills are of each member of your team (brag a little!)

What About Revisions?

- Only one revision allowed
- Read the critiques 3 times over a few weeks—leave your ego at the door
- Highlight the good things in one color and the bad things in another
- Call your program officer for advice
- Make a list of what is needed—then do it!
- Write your Intro (response to critiques) early so you can modify grant accordingly, the re-write it at final edits
- BE RESPONSIVE!

NIH Scoring Criteria: Grantsmanship

Is the grant sloppily prepared, not proofread?

Don’t waste the reviewer’s time with a half-baked submission

Is it hard to understand because of syntax?

Read every sentence out loud or have a fluent colleague edit

Are figures unclear, mislabeled?

Double-check every figure and legend

Is it too densely written, with too many ideas?

Clarity, brevity, and formatting are your allies

Don’t cheat on the font! **It angers reviewers**

Clarity, Brevity, and Focused Plan

Overarching Hypothesis

2-4 crisp sub-hypotheses (Specific Aims)

3-5 crisp experiments to test each idea

You are telling a pretty story

Take the reader by the hand

Don’t assume they can mind-read

Neatness counts and details matter

One Possible Formula

- Aim 1: Develop novel methodology or system
  - (fulfills innovation requirement, excites reviewer)
- Aims 2 (and 3): Understand fundamental biology of the process
  - (don't make it dependent on success of Aim 1)
- Aim 4: Apply the knowledge and tools from Aims 1-3 to a disease
  - (translational relevance)

Syntax and Layout

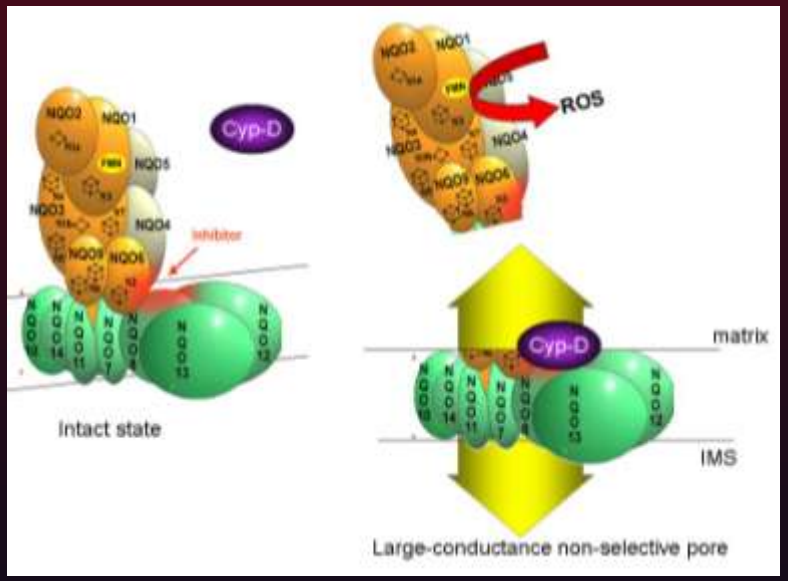
- Sentence structure matters: K.I.S.S.
- The easier it is for them to understand, the smarter they feel and the more they like you
- Avoid abbreviations
- White spaces are nice
- Boxes and tables and diagrams help
- Make figures legible

A Picture Is Worth a Thousand Words

mitochondrial depolarization, diminished ROS production, and prevented mitochondrial swelling (assessed by electron microscopy)[25]. In studies with Jeff Molkentin, we found that transgenic mice overexpressing cyclophilin D exhibited Complex I activity that was decreased by 50% (see Preliminary Data). We initially hypothesized that downregulation of Complex I was a compensatory response to allow survival in the face of extreme susceptibility to PT pore opening due to the superabundance of cyclophilin D. A suitable analogy is this: **If cyclophilin D functions as the match that lights the MPTP fire, the only way to avoid getting burned is to limit the amount of fuel provided by Complex I.**

However, further analysis has led to a far more elegant hypothesis:

Cyclophilin D causes dissociation of the peripheral subcomplex of Complex I, thereby exposing the hydrophobic core which functions as the MPTP.



A proposed model is shown in the diagram at left. In the intact state, peripheral and hydrophobic subcomplexes are in contact and capable of electron transfer and proton pumping. Changes in the matrix environment, prolyl isomerase activity of cyclophilin D, or post-translational modification (proteolysis or phosphorylation) of select subunits of Complex I result in dissociation of the peripheral subunits and exposure of the hydrophobic core, which functions as a large-conductance non-selective pore. Additional testable implications of this model will be discussed in Aim 3.

Mammalian Complex I is a membrane-bound assembly of 45 polypeptides with a combined molecular mass approaching 1 MDa together with noncovalently bound FMN and eight iron-sulfur clusters. It has an L shape with one arm embedded in the membrane and another, the peripheral arm, protruding into the mitochondrial matrix. The complex can be dissociated under mild conditions into subcomplexes. Subcomplex 1λ, which corresponds to the peripheral arm, contains 15 subunits and all the known redox cofactors and the NADH binding site. The cell death protein GRIM-19 (B16.6) is also contained within this subcomplex [26]. Subcomplex Iα is subcomplex Iλ plus nine additional subunits. Subcomplexes Iβ (13 subunits) and Iγ (6 subunits) provide most of the rest of the membrane arm. 14 of the subunits are regarded as providing the catalytic "core" of the enzyme, and the remaining subunits were defined as being "supernumerary," having no bacterial counterparts, and with functions unrelated to the electron transfer and proton pumping activities of the enzyme, or with no known function[27].

Two subunits contained within subcomplex 1α, MWFE and ESSS, have been shown to be phosphorylated in a cAMP-dependent fashion[28]. Mutation of the phosphorylation sites interferes with assembly of the full complex [29]. It is conceivable that this represents another mechanism to regulate association/ dissociation of the MPTP [30].

Convoluted Sentences

I predict that blocking exocytosis with NEM, acetylcholine-induced hyperpolarization will be greater in cells isolated from young adult mice because these cells will have more SK3 channel reservoir and will be able to mobilize the channels more readily.

I predict that cells from young adult mice have a larger reservoir of SK3 channels that can be readily mobilized; therefore acetylcholine-induced hyperpolarization will be greater when exocytosis is blocked with NEM.

Unclear Referents

This difference will contribute to the decreased acetylcholine-induced hyperpolarization in aged mice.

The reduction in SK3 reserves with aging may contribute to the decreased acetylcholine-induced hyperpolarization in aged mice.

Vague Plans

The age-related subcellular distribution will be looked at in Experiment 4 below.

In Experiment 4, we will map the subcellular distribution of SK3 channels as a function of age.

Target Audience (Study Section)

- Who is on study section?
- Talk with a former study section member
- Cite the work of study section members
- Be high-profile (in a good way) at meetings

- Remember, it is not enough to **do** good science, you must also **sell** it.

Responsibilities of Mentors

- Provide environment and opportunities for successful independent launch
- Provide introductions and speaking opportunities
- Review and provide guidance on grant opportunities, grant preparation, and scientific design
- Your best mentor isn't necessarily your boss—find somebody (or two) who can fulfill this special role

Share the Enthusiasm: Mentor Others

Thanks and kudos to my mentors along the way:

Mike Beer
Doug Murphy
Steve Buescher
Bill Lennarz
Genie Kleinerman
Michael Karin
Bernie Babior
Bob Engler
Ernie Beutler
Robert Mentzer

Failure and Success

- Persistence and improvement = success
- Don’t be discouraged—learn from the critiques—don’t take it personally
- DO take *success* personally
- Reward yourself and your team
- Remember life is cyclical; plan ahead
- **NIH works best by reimbursing for good science largely completed**

Intellectual Property

- Protect your intellectual property
- Patented discoveries are more likely to make it to clinical products
- Ideas, methods, discoveries have VALUE
- Sometimes you have to be single-minded
- Nobody else cares as much as you do

TENETS of Grant-writing

- CLEAR FOCUS
- HYPOTHESIS-DRIVEN RESEARCH
- FEASIBILITY
- STATE-OF-THE-ART METHODOLOGY
- IMAGINATIVE APPROACHES
- Discuss potential problems and solutions
- NO FISHING! NO VAGUENESS!

ABOVE ALL, HAVE FUN

- Science is fun, exciting, challenging
- Enjoy it every step of the way
- If it gets stale, re-invent yourself
- The goal is the best science: there is plenty to go around