A Winner’s Approach to Grant Writing
Taking Advantage of Both Sides of the Brain

Bruce Freeman, PhD
Ed Jackson, PhD
Pharmacology and Chemical Biology
NIH Scoring System

Need 1’s and 2’s for $$ … 3’s need revision
50% of apps not discussed
Learn and use today’s lessons and you will be well scored!

<table>
<thead>
<tr>
<th>Impact</th>
<th>Score</th>
<th>Descriptor</th>
<th>Additional Guidance on Strengths and Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>1</td>
<td>Exceptional</td>
<td>Exceptionally strong with essentially no weaknesses</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Outstanding</td>
<td>Extremely strong with negligible weaknesses</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Excellent</td>
<td>Very strong with only some minor weaknesses</td>
</tr>
<tr>
<td>Medium</td>
<td>4</td>
<td>Very Good</td>
<td>Strong but with numerous minor weaknesses</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Good</td>
<td>Strong but with at least one moderate weakness</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Satisfactory</td>
<td>Some strengths but also some moderate weaknesses</td>
</tr>
<tr>
<td>Low</td>
<td>7</td>
<td>Fair</td>
<td>Some strengths but with at least one major weakness</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Marginal</td>
<td>A few strengths and a few major weaknesses</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Poor</td>
<td>Very few strengths and numerous major weaknesses</td>
</tr>
</tbody>
</table>

Minor Weakness: An addressable weakness, does not substantially lessen impact
Moderate Weakness: A weakness that lessens impact
Major Weakness: A weakness that severely limits impact
Rejection Goes With The Territory
We will help you avoid with it!

What did we promise Mommy about leaving our rejected NIH grant applications and empty bourbon bottles on the stairs?

New Yorker, 10-5-15
Hard Skills
Preparing to Write a Grant

• Why? How to get over the activation energy barrier?
• Discuss grant ideas with mentor, colleagues
• Anticipate/resolve “personal issues”: visa status, team building, time at your computer, stress
• Organize your grant toolbox – do key experiments, obtain critical reagents, ID co-investigators, internal and external consultants (do their letters for them!)

**Begin 4 months before deadline**

• Draft Specific Aims by then
• Seek peer critique of Specific Aims
• Complete Pitt regulatory requirements
• Send out consultant letter drafts
Pitt Regulatory Requirements

The PI and those considered an “investigator” on the submission must complete:

- **ISER Research Integrity or CITI Responsible Conduct of Research** (All Investigators). ISER Res. Integrity never expires and CITI RCR every 3 yrs.
- **CITI Responsible Conduct of Research** (All investigators working with human subjects). Every 3 yrs.
- **CITI Human Subjects Module** (All investigators working with human subjects). Every 3 yrs.
- **ISER Use of Lab Animals in Research and Education-Formerly Module 3** (All investigators working with animal subjects). Every 4 yrs.

All investigators must also complete:
- **Conflict of Interest Disclosure Form (PHS-Funded)**. Every year.

All **PIs** must also complete:
- **IP Agreement Form**. Doesn’t expire.

The OOR chart that outlines the required modules:
http://www.rcco.pitt.edu/ResearchTrainingRequirements.htm
Scientific/Clinical Diligence is Crucial!

- **Is the idea original?**
  - Search the literature and the NIH RePORTER database to minimize overlap, maximize novelty.

- Use this and other databases to assess the competition
- Obtain, understand and cite the most recent literature in your application
Scientific/Clinical Diligence is Crucial!

Critical links for assembling the perfect application:
The NIH Center for Scientific Review
http://public.csr.nih.gov/ApplicantResources/Pages/default.aspx

Jeremy Somers, PhD, Office of Research in the Health Sciences
www.oorhs.pitt.edu

- The Office of Research, Health Sciences (OORHS) employs PhD/Faculty-level Scientist Administrators to provide reviews of grant applications prepared by faculty members from all six schools of the Health Sciences
  - Scientific review of specific aims and study design
  - Grantsmanship advice
  - Editorial review for language and clarity
  - Review for consistency with funding announcement focus and funding agency priorities

- Scientist Administrators also provide assistance with the development of multi-investigator and multi-disciplinary grant applications and research programs
Strategic Plan
Composition of a Highly Competitive Grant Application

SPECIFIC AIMS

SIGNIFICANCE
Why this project, what is its value?

INNOVATION
What’s new and different?

APPROACH
How the hypothesis will be tested with validated approaches

RESEARCH STRATEGY
Specific Aims

Most crucial part of the application, do in sequence:

1. Provide short summary of research question
2. Identify gaps in knowledge
3. State an overall hypothesis
4. Identify experimental goals
5. Convey why the overall study is important
6. Include a “grand scheme” graphic

Do in one page with no references!
Hypothesis

This “gap in understanding” … “new concept regarding XXX” … “recently-identified XXX” will be explored by ….. testing the hypothesis that X regulates Y via ZZZZZ.

Avoid vague “waffle” words!
(might be, may, could, in some cases)

State hypothesis in bold font

We dislike personal pronouns
Experimental Goals (Specific Aims)

• 2-4 per project, generally 3
• Each Specific Aim covers one research focus
• Thematically related, fit together logically
Make Your Aims …

• **Hypothesis-driven**
  – Based on a hypothesis to be substantiated or refuted
  – Mechanistically-oriented
  – Should yield important information even if disproven

**NOT …**

• **Descriptive**
  – Exploratory without a specific hypothesis
  – Used to obtain useful data about a specific mechanism
  – Should only be attempted as initial exploration of an important question
  – Goal is to get data for future hypothesis building
Once the Specific Aims Page is Drafted

SOLICIT FEEDBACK!

- Ask mentors, mentor team and colleagues to review a draft of your specific aims very early in the development process, at T minus 4 months.

- Make sure that your Specific Aims can be accomplished within the proposed grant life-cycle and with available resources.

- Make sure you have supporting preliminary data for each specific aim.

- Make sure you have evidence that challenging experimental goals can be accomplished.
Specific Aims. Defects in the bioavailability and signaling actions of nitric oxide (NO) are central to cardiovascular and metabolic disorders stemming from obesity-induced metabolic syndrome, in particular systemic and pulmonary hypertension. Obesity induces chronic inflammatory responses characterized by impaired adipokine signaling, pro-inflammatory cytokine production, mitochondrial dysfunction and enhanced generation of oxygen and nitrogen oxide-derived reactive species. Reactions of nitrogen oxides [including NO, nitrite (NO\textsubscript{2}) and nitrate (NO\textsubscript{3})] with partially-reduced oxygen species yields a spectrum of secondary oxidizing, nitrosating and nitrating species in biological milieu. At high concentrations, these species induce oxidative injury, but at more physiological concentrations these products can a) act as a metabolable NO reserve that signals via cGMP-dependent mechanisms and b) react with and structurally modify susceptible target molecules (e.g., unsaturated fatty acids, protein and nucleic acid modifications (PTMs)) and signaling responses. In particular, Cys is a nucleophilic amino acid that defines the selectivity of proteins for reduction-oxidation (redox)-dependent PTMs that include oxidation, glutathionylation, S-nitrosation, and alkylation reactions. These reactions intimately link metabolic and inflammatory status with changes in cell and organ function, since many enzymes, receptors and transcriptional regulatory proteins mediating metabolic and inflammatory responses contain functionally-significant hyperreactive Cys moieties.

Past perspective held that NO\textsubscript{2}/NO\textsubscript{3} were either inert end-products of endogenous NO metabolism or, on the other end of the spectrum, undesirable dietary constituents that promoted genotoxic responses. Contemporary biochemical and epidemiologic data has shifted both perceptions 180°. We now know that NO\textsubscript{2}/NO\textsubscript{3} are metabolized by commensal bacteria, metalloproteins and digestive processes, yielding NO and secondary nitrogen oxides that elicit unique redox signaling and metabolic responses (Fig. 1). The nature and amounts of various nitrogen oxides are dependent on inflammatory status, diet, acidic microenvironments and NO\textsubscript{3}-reducing enterosporal bacterial populations. Many of these products are chemically-reactive and generate potent NO-heme complexes, protein Cys-NO adducts (RSNO) and electrophilic fatty acid nitroalkenoids (NO\textsubscript{2}-FA) that readily and reversibly alkylate susceptible protein thiols.

Recent murine model studies reveal that modulation of the nitrogen oxide signaling axis in obesity-induced pulmonary arterial hypertension (PAH) can be of therapeutic value. In particular, the cGMP-independent pleiotropic signaling actions of NO\textsubscript{3}-FA s induce adaptive tissue responses that include beneficial shifts in adipokine and cytokine expression, restoration of insulin sensitivity and inhibition of pathological pulmonary vascular remodeling. This motivated the hypothesis that the promotion of nitro-fatty acid signaling alleviates metabolic syndrome-induced hypertension and its pulmonary complications. To test this concept, a de-risked new drug strategy is evaluated by pursuing mechanistically-revealing model system and clinically-based specific aims:

**Aim #1 - Bench** Define the molecular targets, biochemical responses and physiological actions of a) NO\textsubscript{2}-FA generated by the dietary precursors NO\textsubscript{2}, NO\textsubscript{3} and conjugated linoleic acid and b) pure NO\textsubscript{2}-FA in rodent models of obesity-induced pulmonary hypertension.

**Aim #2 - Bedside** Evaluate the clinical response of Group I pulmonary arterial hypertension patients to the orally administered NO\textsubscript{2}-FA, 10-nitro-octadec-9-enoic acid (NO\textsubscript{2}-OA). Focus will be placed on identifying sites of NO\textsubscript{2}-FA-induced PTM, for example redox-sensitive transcription factor (TF) and enzyme targets. Preliminary studies reveal that NO\textsubscript{2}-FA-mediated PTMs will promote salutary responses by complementing and expanding the actions of dietary and endothelial NO synthase (NOS)-derived nitrogen oxides, especially when NOS signaling is compromised. These responses include the modulation of gene expression via inhibition of NFκB-dependent pro-inflammatory mediator generation, the activation of PPARα and Nrf2-regulated responses and the instigation of additional beneficial metabolic and anti-inflammatory signaling actions. These protein targets all have in common functionally-significant Cys residues that sense changes in redox state by undergoing PTMs that, in turn, induce changes in catalytic and transcriptional regulatory activities important for maintaining physiologic homeostasis. This research strategy is readily deployable in humans, as NO\textsubscript{2}-FA and their precursors a) are endogenously present in humans at low concentrations, b) have already undergone extensive preclinical toxicology and pharmacokinetics evaluation, c) have been characterized by FDA-approved phase I/IIa clinical tracer studies and d) are in FDA-approved Phase 1 testing of both IV and oral formulations in humans. Unbiased NO\textsubscript{2}-FA-target protein ID and gene expression profiling is designed to provide detailed insight into the MOA of NO\textsubscript{2}-FA in vivo and reveal the pharmacologic potential of NO\textsubscript{2}-FA for treating a pulmonary vascular disease having limited therapeutic options. The pulmonary vascular responses to NO\textsubscript{2}-FA are anticipated to be more efficacious than many single-target drugs, because the pleiotropic signaling actions of NO\textsubscript{2}-FA strike a chord, rather than a note.
Significance

• State what is important about your research problem
• Identify the barriers to progress in the area
• How your research will knock down these barriers to improve knowledge and address controversies in the area
• How will you contribute to the evolution of the field
  — Aim for 1 page maximum, ½ - 3 pages OK
  — Use graphics, data OK if helpful for key points
  — Summarize with terse sentences, bullet points
• The above summary can be entitled “Scientific Premise”. This is a new review criteria where one emphasizes the strong “scientific premise” for the proposed research plan - the published cited and preliminary data you present, the strengths, weaknesses (lack of rigor) and gaps in knowledge coming from prior work.
Significance (2)

• Can use this section to provide key background information
  – Significance used to be called “Background”, but focus has shifted towards brevity and relevance of the project plans
• Serves as a foundation for your scientific ideas
  – Leads the reader down a logical path of knowledge to convince them that your specific aims are worthwhile
• Emphasize what is known and unknown
• May or may not require data, schemes always helpful.
Priorities of Significance

• Conveys the importance of research goals
• Provide a clear context for your project
• Demonstrates your knowledge in the area of research as it relates to your project – this means citing very current references and key foundational publications
• Explains the impact of the work on human health and on the research theme in general

“A Guide to Effective Grant Writing”, Otto O. Yang
Innovation

• A new idea is novel, not innovative
• Innovation uses new approaches for testing your hypothesis
• Describe how your work will shift current research paradigms
• Identify the useful application of your innovation and your results to understanding basic biology, and how this might relate to pathobiology and treating disease

Remember, it’s the National Institutes of Health
Examples of **Innovation**

1. The questions you are asking are new, even if the issue has been highly studied
2. The overall hypothesis poses a new theory that others have not considered
3. The hypothesis tests old concepts in a new and more revealing manner
4. Your project employs unique reagents, model systems or patient populations not generally available.

“A Guide to Effective Grant Writing”, Otto O. Yang
B. Research Strategy

Significance. The over-arching significance of the research plan is the evaluation of electrophilic NO2-FA, as a new therapeutic strategy for obesity-related asthma. We also address critical gaps in knowledge regarding the generation, specific molecular targets, gene expression, and pleiotropic signaling actions of NO2-FA. These studies will be performed at the bench using the pure synthetic NO2-FA regioisomer 10-NO2-octadeca-9-enolic acid (NO2-OA) given to a HFD-fed murine model of obesity-related asthma. Then, we go to the bedside to conduct a blinded, placebo-controlled, cross-over design study of NO2-FA therapeutics in asthma associated with obesity. This investigation will define a) the impact of obesity-induced pro-inflammatory conditions on NO2/N02/OA metabolism and FA nitration, b) the population of pulmonary proteins that react with NO2-FA [by applying an unbiased NO2-FA-protein adduct “click chemistry”-based affinity labeling strategy (Figs. 9, 11), in combination with mass spectrometry (MS)-based lipidomic, proteomic and informatics analyses], c) enzymatic and cell signaling responses of relevance to the obesity-related asthmatic phenotype and d) unbiased gene regulatory changes induced by NO2-FA, using next-generation sequencing (NGS) strategies. First, DNAse digestion will identify regions protected from digestion (DNameq), revealing in high resolution the active gene regulatory elements impacted by NO2-FA. Then, RNAseq and chromatin immunoprecipitation followed by sequencing (ChIP-seq) will interrogate the NO2-FA-regulated gene regulatory events in more detail, with initial focus placed on Nrf2, HSF1, NFkB and PPARγ-regulatory mechanisms. These analyses will be done in whole mouse lung and blood mononuclear cells, alveolar macrophages and airway epithelium obtained from a murine obesity/airway hyperreactivity (AHR) model and clinical study subjects. These data, combined with identification of the NO2-FA proteome, will annotate the predominant signaling pathways modulated by the pleiotropic signaling actions of NO2-OA. This research strategy will illuminate the role of unsaturated fatty acids in transducing nitric oxide signaling and define the mechanisms underlying the pulmonary responses to NO2-FA administration in both a murine model of obesity/AHR and obese asthma.

Innovation. The proposed research plan, built upon our NHLBI-supported discoveries, evaluates an endogenous mediator-based pleiotropic drug strategy that is mechanistically-aligned for deployment against a pulmonary disease having a complex pathogenesis - the obese asthmatic phenotype. Multiple indices attest to the novelty of this precept. For example, the applicants have been issued several US and International patents related to the composition of matter and methods of use of natural and non-natural electrophiles for treating metabolic and inflammatory diseases (p. 2. To date, Tocilex, a first electrophile-based anti-inflammatory drug strategy (Tocilex, dimethylfumarate, Biogen) has broken down barriers to FDA approval of covalent modifier drug strategies and opened up new pathways for related drug candidates. Previously, both covalent modifiers and the generation of electrophilic drug metabolites were negative attributes in drug development, eliminating many promising new candidates. In contrast, reversibly-reactive “soft” electrophiles, the pharmacologic strategies capitalizing on soft electrophiles are both safe and innovative, in that a multitude of adaptive signaling responses become induced that are of relevance to asthma and obesity therapeutics. Presently, Complexa, Inc. is moving NO2-FA through FDA new drug approval steps as IV and oral drug candidates for treating both acute and chronic metabolic and inflammatory-induced renal disorders.

The proposed covalent modifier drug strategy, designed for the treatment of obesity-related asthma, will be mechanistically evaluated using novel MS-based proteomic and lipidomic strategies. These approaches led to the discovery that “free”, complex lipid-esterified and protein-adducted fatty acid electrophiles are endogenously present under basal conditions and become more abundant during both oxidative inflammatory responses and upon consuming diets rich in precursors (e.g., unsaturated fatty acids and nitrogen oxides). This insight comes from a unique application of electrophilic lipid “fishing” strategies. For example the “hooks” for “fishing out” electrophilic lipids involve using low molecular weight thiol reagents for electrophile capture and LC-MS/MS analysis identifies “the catch” in a manner that differentiates between free and protein-adducted electrophilic lipids. The PTM of proteins (e.g., phosphorylation, acetylation, ubiquitination, SUMOylation) is a central mechanism of cell signaling that profoundly influences protein structure and function. This research plan capitalizes on a novel aspect of redox-induced PTMs by developing a pharmacologic strategy that promotes electrophile-mediated thiol alkylations for treating an inflammatory condition - obesity-related asthma. We view that this drug strategy will transiently modify the proteome in a manner that promotes tissue repair and suppresses obesity-induced pro-inflammatory responses, pulmonary inflammation and AHR.
Approach

- **Restate Specific Aim**

- **General approach and rationale** (1 para to 1 pg, references not important and can distract)

- **Preliminary data** – include key data/legends (several Figures/Tables per Aim)

- **Specific experimental approach**
  - Group global methods
  - Give experimental details (1-2 pages)
  - Either here or next section, note the steps taken to assure that proposed studies will yield *rigorous and reproducible data*

- **Anticipated results and potential pitfalls** (1-2 para)
Pointers for Research Plan

• At the end of each aim, summarize key pursuits and questions that will be answered – this can be part of Anticipated Results/Potential Pitfalls

• Reinforce with key preliminary data (Legend title states what data shows, have a very terse, minimalist legend, 8 pt arial minimum

• Avoid death by Western blot!! Avoid annoying and distracting use of .......... bold font, colored letters, italics and underlined words. Your words are ALL important and you only need this language “art” to organize and identify key elements of the story you are telling

Fig. 6. Kinetics of fatty acid (CLA) nitration in healthy humans after consumption of $^{15}$NO$_2$ and CLA

Fig. 15. Pharmacokinetics of NO$_2$-OA in humans at different doses given PO, daily. Data are actual PK measurements by LC-MS/MS of parent drug, computationally-modeled for 1000 humans (1 ng/ml = 3 nM).
Tie a Ribbon Around Your Grant Application

Statistical Analysis (3-6 lines) and Timetable (3-6 lines)

... and a personal favorite ...

Overall Summary

Insert a summary of the impact, novel approaches and innovation that comes from pursuing your research objectives – in other words, this is your chance to compose the “Overall Impact” section of your critique.

Overall Summary. This proposed translational investigation of a new therapeutic strategy for PAH is based upon strong rationale and deep understanding of the biochemical reactions, endogenous generation, cell signaling actions, pharmacokinetics and physiological actions of fatty acid nitroalkene derivatives. Innovative click chemistry-based affinity strategies will reveal the principal protein targets of thiol-reactive NO₂-FA. Unbiased genetic approaches will define transcriptional and signaling network responses in both murine models of PAH and healthy and PAH humans after the administration of a) a synthetic homolog of an endogenous NO₂-FA and b) fatty acid and nitrogen oxide precursors that promote the endogenous formation of NO₂-FA. This project is well-positioned to yield a sustained and powerful influence, as it is supported by an already productive and highly interactive tPPG network that was designed to integrate a) the discoveries and analytical expertise of innovative basic and physician-scientist teams, b) the small molecule metabolic and inflammatory disease drug development interests of a well-evolved university-spawned biopharmaceutical company and c) the highly-integrated and extensive clinical care and translational research programs of Cardiology, Pulmonary and Pharmacology-based investigators at the University of Pittsburgh/UPMC. Consequently, this research plan has a strong likelihood for discovering a new platform of drug candidates for treating not only PAH, but also other chronic metabolic and inflammatory disorders.
Tie a Ribbon Around Your Grant
… so it doesn’t fall apart at the last minute!

PI and Co-I: Compose Informative, Flawless Biosketches
http://www.sph.emory.edu/research/documents/NewNIHBiosketch.pdf

Have detailed Vertebrate Animals, Human Subjects, Resource Sharing, Multiple PI (leadership plans), Budget Justification (especially personnel) sections

Vertebrate Animals

Humans

Multiple PIs
http://grants.nih.gov/grants/multi_pi
## Rigor, Reproducibility and Transparency of Research

<table>
<thead>
<tr>
<th></th>
<th>Applies to which applications?</th>
<th>Where to include it in the application?</th>
<th>Affects overall impact score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scientific Premise</strong></td>
<td>All</td>
<td>Research Strategy (Significance)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Scientific Rigor</strong></td>
<td>All</td>
<td>Research Strategy (Approach)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Consideration of Relevant Biological Variables, Such as Sex</strong></td>
<td>Projects with vertebrate animals and/or human subjects</td>
<td>Research Strategy (Approach)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Authentication of Key Biological and/or Chemical Resources</strong></td>
<td>Project involving key biological and/or chemical resources</td>
<td>New Attachment</td>
<td>No</td>
</tr>
</tbody>
</table>
“rigor in designing and performing research and an ability to reproduce research”

To assure R&R, add the following information and phrases in application:

Significance: note the strong “scientific premise” for your proposed research, with the support for this statement being the published and preliminary data you present, the strengths of your approach and gaps/weaknesses (lack of rigor) in prior work.

Experimental Approach: note the steps taken to assure the proposed research plan will be executed with “scientific rigor”. Mention the steps you are taking to make sure results are robust and unbiased. This includes routine lab group presentations, blinded studies, extensive controls, statistical approaches for determining group sizes, replicates of studies and data analysis, specific “consideration of sex, genetic strain, age and weight as biological variables”. Male + Female studies important!

New Attachment: “Authentication of key biological and chemical resources”, summarize how you are validating cell line ID/purity/effects of passaging, antibody specificity, sequence of key gene constructs, chemical/drug purity, etc.
General Pointers

• Set a realistic submission timeline with mentor/colleagues (scientific and administrative)
• Draft Specific Aims ASAP, seek feedback
• Begin active writing 4 months before deadline. Allow 1 month for “diligence”, 1.5 for initial draft, 1.5 for peer input and revisions
• Every time application doc is opened, edit Specific Aims and if you are tough enough, Significance and Innovation

• This presentation: http://pharmacology.medicine.pitt.edu/Links
General Pointers

Etiquette Guide

• Draft letters for non-Co-Investigator collaborators and consultants, and send to them 6 weeks before deadline so they can edit and personalize.

• When requesting input from colleagues and it is “critical”, be open-minded and don’t argue!

• Continue to eat, work in lab, exercise, socialize, be “normal”, avoid stress as it impacts focus

• Give colleagues a pdf of the final submitted grant with thanks.

• Meet or beat your departmental and school submission timelines.

• Thank or do something nice for the administrative staff who spent hours-to-days organizing your budget, allied submission docs and uploading
Study Section Review of an NIH Grant

Study Section IDs the Strengths and Weaknesses of:

Significance, Innovation, Approach – Each is crucial!

Investigators, Environment – If weak, this can hurt

The above are integrated to give:
Overall impact - the likelihood for the project to exert a sustained, powerful influence on research field(s)

Make sure when doing your diligence (ask Colleagues, use NIH RePORTER tools) that you ID a Study Section with the correct expertise to do review

Provide a cover letter with the submission to the Center for Scientific Review asking for this review committee.

No whining then, as you have gamed the system the best you can!
Thank reviewers for positive comments

Provide global statement re the major revisions you made

Mention new publications, new data in revised application

Include some new Figs in revised application, cite them

Synopsize major criticisms and provide a highly compliant response

Respond professionally: do not disagree, and also “stand your ground” with solid justification when necessary
The Seven Wonders of a Competitive Application

• Hypothesis-driven experimental aims
• Overall novel, innovative, exciting goals and approaches
• Goals challenge existing views – transformational.
• Technically innovative, feasible and not overambitious.
• Grows out of your previous peer-reviewed work.
• Addresses a recognized and important topic.
• Produces relevant information that significantly advances knowledge …… for the NIH, this means disease-relevance and potential for translational studies.

These points, and how solidly you achieve them, reveal to the reviewers your passion and scientific intellect
Soft Skills
Mechanics of Grant Writing
Involving Rules That Are:
- Highly Visible
- Readily Mastered
- Left Brain Oriented
- Formulaic

Art of Grant Writing
Involving Psychological Aspects That Are:
- Hidden
- Require Practice
- Right Brain Oriented
- No Standard Recipe
Soft Skills Influence the Way People Process Information

*Including Grant Applications!!*

What Is the Best Method for Developing the Soft Skills of Grant Writing?

We Need A Good METAPHOR to Guide Our Reasoning!
THE BEST METAPHOR FOR DEVELOPING THE SOFT SKILLS OF GRANT WRITING IS:

The Heisenberg Uncertainty Principle

\[ \sigma_X \cdot \sigma_P \geq \frac{h}{4} \cdot \pi \]

Complementarity Principle

BUT WHY IS COMPLEMENTARITY PRINCIPLE USEFUL WITH REGARD TO STRATEGIZING GRANT APPLICATIONS?
Complementarity Principle
Applies to Many Fundamental Tradeoffs
A Grant Writer’s Greatest Challenge is Managing **Fundamental Tradeoffs** In Planning and Describing a Research Program.
TRADEOFFS AND GRANT WRITING

What do TRADEOFFS have to do with grant strategy?

Whether a Study Section considers X more important than Y vs Y more important than X is a subjective score-driving factor!!

An ever-changing social/cultural issue!!
The more precise and complete you attempt to be, the more difficult it becomes for the reviewers to understand what you are trying to communicate.

However, the more you strive for clarity the more difficult it becomes to include the fine details, nuances, and caveats of your hypotheses and experimental strategies.
SOLUTION?

ACCURACY versus CLARITY

Favor CLARITY in the Specific Aims page

Favor CLARITY in the Significance section

Favor CLARITY in the Innovation section

Favor CLARITY when describing the Overall Impact of your project

Favor ACCURACY in the Approach section

Summarize these in bullets that the reviewer can cut and paste into the review!!
FUNDAMENTAL TRADEOFFS
In GRANT WRITING

INNOVATION versus FEASIBILITY

The more innovative the application is, the less feasible it will seem.

The more feasible the project is, the less innovative it will seem.

Reviewers’ Critique: Project is premature!

Reviewers’ Critique: Outcomes are too predictable!
INNOVATION versus FEASIBILITY

(Too risky)

INNOVATIVE IDEAS

- Unconventional thinking
- Little extant literature
- Low a priori probability of success

(Too incremental)

HIGH PROBABILITY OF SUCCESS

Conventional thinking
- Large extant literature
- High a priori probability of success
SOLUTION?

INNOVATION versus FEASIBILITY

Favor INNOVATION

Deal with FEASIBILITY with preliminary data!

Strive for preliminary data of n=2 (not n=1 AND not n>2) for every specific aim!

Do not publish concept or data before grant is reviewed!
Although experiments in reductionistic systems can yield solidly valid conclusions, the conclusions are usually of questionable physiological significance.

Although experiments in complex biology systems can yield highly relevant conclusions, the validity of the conclusions are usually less secure.
STRENGTH OF INFERENCE versus PHYSIOLOGICAL SIGNIFICANCE

(Irrelevant)

STRENGTH OF INFERENCE

- Isolated molecules
- Isolated organelles
- Isolated cells

PHYSIOLOGICAL SIGNIFICANCE

- Isolated tissues
- Isolated organ systems

Intact animals
Intact humans

(Scientifically weak)
SOLUTION?

STRENGTH OF INFERENCE versus SIGNIFICANCE

Design 2 to 3 aims to favor STRENGTH OF INFERENCE

Design at least 1 aim to support SIGNIFICANCE
FUNDAMENTAL TRADEOFFS
In GRANT WRITING

FOCUS versus SCOPE

An application that is highly focused may thoroughly test a small subset of hypotheses, yet will leave unaddressed a subset of related issues.

An application that explores a more inclusive set of related questions will yield more, but less secure, knowledge.

Reviewers’ Critique: The PI has tunnel vision!

Reviewers’ Critique: The application is too diffuse!
FOCUS versus SCOPE

FOCUS

Aims address one hypothesis
Aims approach problem from several angles
Aims ignore related but interesting questions

SCOPE

Aims address several hypotheses
Aims approach each problem from one angle
Aims answer more questions but more superficially

(Too narrow)
(Too diffuse)
Deal with limited **SCOPE** by acknowledging the existence of many interesting and important questions and that these will be addressed in the next competing renewal.
Because of the Complementarity Principle, A Perfect Grant Application is Impossible!

However, Using the Complementarity Principle, A Close Match Of Your Application’s Priorities With Your Study Section’s Priorities is Possible.

Niels Bohr
Good References and Resources