Secrets of Superlative Specific Aims

What’s the problem?
Why should we care? &
How are you going to fix it?

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DOM Research Day, UMMC 4/12/2012

Top Massive Advertising Failures

LifeLock
LifeLock is an identity theft prevention company that detects fraudulent applications for credit cards, mortgages...

LifeLock CEO Todd Davis was so confident in the company’s ability to protect sensitive information that it publicized its services with a television advertisement, in which a van drives by with his real, actual Social Security Number

A number of thieves used the information successfully multiple times. Davis knew nothing until collection agencies started calling him.

BAD IDEA
Top Massive Advertising Failures

Lipitor

In 2006, Pfizer rolled out a television advertisement starring Robert Jarvik, inventor of the Jarvik-7 artificial heart, and he instantly lent a degree of gravitas to the spots, saying: "Just because I'm a doctor, doesn't mean I don't worry about my cholesterol."

One small problem — Jarvik had never been licensed to practice medicine, completed a residency or even an internship. The ads became the subject of a congressional investigation; lawmakers determined that the spots amounted to medical advice from someone who was not a practicing physician. Pfizer withdrew the ads.

GOOD IDEA, BAD CHOICE

No amount of grantsmanship will turn a bad idea into a good one...
But there are many ways to disguise a good idea.
- Dr. William Raub; Past Deputy Director, NIH

<table>
<thead>
<tr>
<th>Science</th>
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<tr>
<td>Investigator</td>
<td>+</td>
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<tr>
<td>50% of applications: Bad idea, and poorly prepared investigator.</td>
<td>30% of applications: Good idea, but investigator unprepared to do the work.</td>
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<tr>
<td>10% of applications: Bad idea, but capable investigator.</td>
<td>10% of applications: Great idea, well proposed by the perfect person to test it.</td>
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Modified from orig. Table by James Ferrara, M.D.; http://health.usnews.com/top-doctors/
General Guidelines: Grant Writing

CHARACTERISTICS OF A GOOD GRANT WRITER
(SALESPERSON)

• Makes a good first impression
• Is well-prepared
• Is credible
• Delivers a clear message
• Provides supporting documentation
• Has appropriate endorsements
• Has something special to offer
• Is persistent
• Plans (lead time and quality time)
• Is clever and logical
• Perspires

It’s about Selling your ideas

General Guidelines: Grant Structure

IDEAS

SUPPORTING IDEAS, CONCEPTS

DETAILS OF THE PLAN

APPENDICES

Specific Aims
If you do not draw readers in here, they will not make it to the details
General Guidelines: Grab Attention

- Set your grant apart from the rest
  - Write grant as though for a newspaper
- Characteristics of a Good News Article
  - Concise
  - Good Headlines
  - Visually appealing
  - Easy to read
  - Comprehensible to wide audience
  - Effective use of illustrations/figures
- Remember your audience: ALL the reviewers

General Guidelines: Care and feeding of reviewers

They are...
- Overworked
  - (will spend at most a few hours reviewing your grant)
- Mature & Mindful of the need to further their own careers
  - Translation: they will be upset with you if they feel you are wasting their time AT ALL
- Intelligent and savvy about research...
  - but perhaps have little in-depth experience in your area of interest.
  - and are not interested in doing outside ‘homework’ in a new topic area just so they can understand your proposal
- Avoid jargon and topic-specific abbreviations.
- Many reviewers will read only the abstract and/or specific aims.

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General Guidelines: Care and feeding of reviewers (2)

• Make the reviewer like you and your study from page 1 (Specific Aims)
  – Teach them something new (we all like to learn)
  – Convince them that you are the best person in the world to do this terrific study

  • Science Fiction Novel approach – the world will be a better place after this study is done (and you are captain Kirk)

  • Disneyland approach – make them smile while you are sucking money out of their wallets (and you hold the keys to the kingdom)
Specific Aims
The single most important section of your grant

You describing the experiments  The reviewer reading them
Scientific Sections

• **Specific aims (1 Page)** ← **Today!**
  • Significance
  • Innovation
  • Approach

(Other: References, Human subjects, animals)

• (Project summary/abstract)

usually written last

I have a bad feeling about this
Obi Wan
Deardorff

http://grants.nih.gov/grants/forms_page_limits.htm

Specific Aims: General Guidelines

• Template / master plan for the rest of the proposal
  • The most important section in the grant application
    – Similar for other, non-grant research proposals
  • This section works very well as a **pre-proposal**
    – Draft often sent to SRO for discussion
    – Draft is excellent to bring to first design meetings
  • It is the **most difficult** section to write
    – Good ones commonly go through many, many, many revisions
  • The flow and logic must be **connected** and **compelling**
  • It must be comprehensible to a wide audience
  • It must **quickly** engender enthusiasm for your ideas
    – You will not somehow finally convince reviewers on page 9
    – You must sell them on page 1 (SAs)
  • Full application is simply an expanded version of the SAs
SPECIFIC AIMS PAGE CONTENTS: 1) Intro

**Introductory Paragraph:** Convince all reviewers that there is a significant unknown (problem). This problem provides the argument of a critical need relevant to the mission of the funding agency.

- **Opening Sentence** - identifies what the proposal is generally about, and immediately relates to the mission of the funding agency
- **Knowns** - brings the reviewer up to speed re: state of the art in the field in 3-4 sentences; all key points MUST be introduced here (conceptual framework)
- **Unknowns** - the problem to be addressed
- **Frame the problem/need** - the problem points to the critical need that is the driving force for the proposal. Conclude with why the lack of a solution is an issue for the funding agency

SPECIFIC AIMS PAGE CONTENTS: 2) WWW

**What, Why, Whom Paragraph:** convince all reviewers that YOU and YOUR TEAM has the solution to the problem

- **Long-range goal** - (broad) PI’s career goal, which should match the mission of the funding agency
- **Objective in this application** - (narrow) purpose of the project, described to match the critical need; must have a well-defined end point
- **Central hypothesis** - (narrowest)
- **Rationale** - what will become possible after project is finished that is not possible now; underlying reason for pursuing the project, which relates to funding agency’s mission
- **Well-Prepared** - collective basis for our competitive advantage (qualifications, prelim data, unique skills, technologies, past successes)
SPECIFIC AIMS PAGE CONTENTS: 3) SAs

**Aims Paragraph:** provide a logical, step-by-step development of key hypotheses and activities by which you will fulfill the objective to address the critical need. Each should: flow logically into the next and collectively address objectives; be conceptual, not descriptive if possible; avoid being completely dependent upon other aims.

- **Specific Aim 1 - brief, focused IDEA statement**
  - Subtext with more details including measurements and comparisons that tie into specific hypotheses

- **Specific Aim 2 - brief, focused IDEA statement**
  - Subtext with more details including measurements and comparisons that tie into specific hypotheses

- **Specific Aim 3 - brief, focused IDEA statement**
  - Subtext with more details including measurements and comparisons that tie into specific hypotheses

Note: This section will be used as the springboard for design discussions.

SPECIFIC AIMS PAGE CONTENTS: 4) Payoff

**Payoff Paragraph:** identify the ROI to the funding agency

- **Innovation/Transformative**—statement should directly follow the aims/goals/objectives and build advocacy for the project
- **Expectations**—must be specific and credible
- **Impact**—how these outcomes will fill the identified need
- **Inspirational**—how this will change the world (w/o overreaching 😊)

“There are some things worth dying for.”

“All our dreams can come true, if we have the courage to pursue them.”
Example: 1) JHS Ancillary Study

### Intro:
Why do we care? Framing the Problem.

### What, Why Whom?:
Goals, Objectives, People

### Aims (1/2 page):
Key Activities

### Payoff:
Innovation & Impact

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Example: 2) Molecular Mechanisms of Glaucoma
INTRODUCTION

Glaucoma is the leading cause of irreversible blindness worldwide and the second most common cause of blindness in developed countries. The most common form, primary open-angle glaucoma, is often associated with elevated intraocular pressure (IOP), which develops as a result of increased resistance to aqueous humor outflow through the conventional drainage pathway. Clinical trials have established that IOP reduction in open-angle glaucoma helps preserve vision. Thus, glaucoma patients, whether having elevated IOP or not, are managed clinically with the objective of lowering IOP. Initial treatments utilize pharmaceutical agents that lower IOP by targeting aqueous secretion and/or uveoscleral outflow; functions not directly responsible for elevated IOP in glaucoma. This is partly because the molecular and cellular mechanisms responsible for reducing conventional outflow facility, thereby elevating IOP, are currently unknown. Lacking this knowledge is a significant obstacle because understanding the molecular mechanisms that underlie the regulation of outflow in the conventional drainage pathway will facilitate the development of more appropriate and effective therapies for people with glaucoma.

What, Why and Whom

Our long-range goal is to identify novel targets in the human conventional drainage pathway for the treatment of ocular hypertension, and hence glaucoma. The objective of the present proposal, as the next step towards attaining this goal, is to examine how homotypic binding of cadherin-5 may contribute to generating outflow resistance in the conventional drainage pathway. Our central hypothesis is that cadherin-5 junctions between human Schlemm’s canal (SC) endothelial cells significantly influence resistance to conventional outflow. We have formed this hypothesis based upon (i) published data demonstrating the involvement of calcium-sensitive structures in conventional outflow resistance; (ii) published data from our laboratory locating cadherin-5 between cells of SC’s inner wall, a structure thought to contribute to conventional outflow resistance; and (iii) published data showing the pivotal role of cadherin-5 in vascular endothelial permeability/barrier function.
The rationale that underlies the proposed research is that understanding the contribution of SC endothelial cells to total outflow resistance, and specifically the role of cadherin-5 binding between SC endothelial cells, will enable the identification of novel ways to modulate outflow resistance and consequently to control IOP in people with glaucoma. **We are particularly well prepared** to undertake the proposed study because our research team includes uniquely qualified individuals with combined experience in molecular and cellular biology, glaucoma, cadherin junction biology, biomechanics and anterior segment ocular perfusion. Our team members are leaders in their respective research areas, and have the technical expertise and a history of productive scientific interactions needed to successfully complete the proposed work.

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**What, Why and Whom (cont.)**

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**Specific Aims**

We plan to test our central hypothesis and accomplish the overall objective of this proposal by pursuing the following three specific aims:

**Specific Aim 1:** Assess the extent to which adherens junctions between Schlemm’s canal endothelial cells influence total outflow resistance in the human conventional outflow pathway.

*Working hypothesis:* Homotypic, extracellular interactions and cytoplasmic associations of cadherin-5 in human Schlemm’s canal endothelial cells mediate resistance to aqueous humor outflow.

**Specific Aim 2:** Evaluate the effect of mechanical forces on adherens proteins in human Schlemm’s canal endothelial cells.

*Working hypothesis:* Mechanical forces on human Schlemm’s canal endothelial cells regulate expression, distribution and/or phosphorylation of cadherin-5/catenins, and hence outflow resistance.

**Specific Aim 3:** Evaluate the role of Edg (endothelial differentiation gene) receptor signaling in Schlemm’s canal endothelial cell-cell adhesion and outflow facility.

*Working hypothesis:* Regulation of resistance to outflow at the level of adhesion between human Schlemm’s canal endothelial cells occurs in part via activation of Edg receptors.
**Payoff**

Our approach, designed to better understand the mechanisms that underpin the generation and regulation of resistance to drainage of aqueous humor in the conventional pathway, is innovative for three reasons: (i) we have the ability (via specific molecular tools) to regulate protein expression solely in human Schlemm’s canal endothelial cells; (ii) we can study cadherin function in three complementary model systems that have been validated and optimized; (iii) we will for the first time examine the dynamic relationship between cadherin function, Edg receptor activation, and mechanical force application, and determine how they interact to influence to conventional outflow function. As outcomes of this line of research, we expect to first demonstrate the specific contribution of cadherin-5 and associated proteins to the generation of total outflow resistance. Second, we plan to determine the dynamic relationship between outflow facility and cadherin function. Last, we expect to show the ability to modulate outflow facility by modulating cadherin function. Results obtained from these investigations will provide a fundamental understanding of the role of cadherin proteins in aqueous outflow resistance and uncover novel therapeutic targets for glaucoma therapy.

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**Example 3) SA – Environmental Exposure**

*Specific Aim 1: Obtain repeated measurements of PBDEs (Polybrominated Diphenyl Ethers) in consumer products (source), dust samples (microenvironments), personal air and hand-wipe samples (personal exposure), and human serum (total absorbed dose):*

- a. Recruit a cohort of 50 adults from different households in the Boston (MA) metropolitan area;
- b. Develop and administer a questionnaire on potential PBDE sources in three microenvironments (home, workplace, car) and other potential determinants of PBDE exposure (e.g., age, diet, activity patterns);
- c. Estimate PBDEs in potential sources (e.g., furniture, carpet, electronics) from three microenvironments using a portable X-ray fluorescence (XRF) analyzer to measure bromine as a surrogate for PBDEs;
- e. Measure PBDEs in personal air samples and hand-wipe samples collected from each participant;
- f. Collect a venous blood sample for the analysis of PBDEs as a measure of total absorbed dose, and for the analysis of hormone levels as a potential measure of early effect;
- g. Repeat sub-aims (b) through (f) twice more at six month intervals for a total of three sampling rounds;
General Guidelines: Grant Structure

What’s the Problem?
Why do we Care?
What will you Do?

Specific Aims Page
If you do not draw readers in here, they will not make it to the details

IDEAS

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APPENDICES

Sell your ideas Well

From This, All Good Things Come...

• Specific aims (1 Page) ← Today!
• Significance
• Innovation
• Approach
  (12 pages)

All are now just expansions of your Specific Aims

This helps us avoid
Advice from NIH: FAQ

• Were applicants advised on **how to organize the Research Strategy section** to address the Significance, Innovation, and Approach for each Specific Aim, assuming they had more than one Specific Aim?

• Applicants were advised to use their discretion in organizing the information to best convey the desired information to the reviewers. For example, if an application had two specific aims, an applicant might choose to organize the Research Strategy in one of the following two ways:

  • Significance: Specific Aim 1, Specific Aim 2  
  Innovation: Specific Aim 1, Specific Aim 2  
  Approach: Specific Aim 1, Specific Aim 2  
  **OR:**

  • Specific Aim 1: Significance, Innovation, Approach  
  Specific Aim 2: Significance, Innovation, Approach

http://enhancing-peer-review.nih.gov/faqs.html#3035

Write, Discuss, Revise; Lather, Rinse, Repeat...

"I know some very great writers, writers you love who write beautifully and have made a great deal of money, and not one of them sits down routinely feeling wildly enthusiastic and confident. **Not one of them writes elegant first drafts.** All right, one of them does, but we do not like her very much. We do not think that she has a rich inner life or that God likes her or can even stand her."...Anne Lamott
Your Goal: Be the Best at Selling Your Ideas

Then Comes the REALLY Hard Part!

This is the easy part. The Challenge will be figuring out the Indirect Cost Rates!