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Writing Specific Aims

November 11, 2020

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Agenda



- **Refining Your Idea**
- **Specific Aims:**
 - **Why this is the MOST important piece of your grant**
 - **Anatomy of an aims page**
- **Reviewing Examples**
- **Questions**



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Refining your idea

1. Define the niche you are systematically trying to develop- should move the field forward
2. Collect and critically analyze background information
3. Generate a preliminary idea that is pertinent to your research problem
4. Assess your idea's potential for success and modify as necessary
5. Seek constructive criticism
6. Refine idea to maximize potential impact



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Refining your idea

Heilmeier Catechism

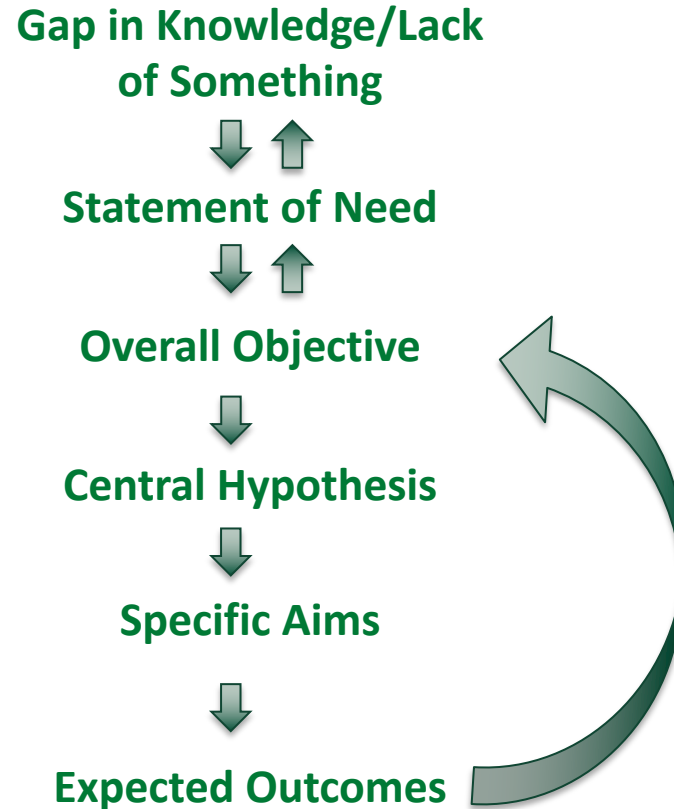
- What are you trying to do? Articulate your objectives using absolutely no jargon.
- How is it done today, and what are the limits of current practice?
- What is new in your approach and why do you think it will be successful?
- Who cares? If you are successful, what difference will it make?
- What are the risks?
- How much will it cost?
- How long will it take?
- What are the mid-term and final “exams” to check for success?



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Developing a Proposal Outline



Specific Aims

The MOST important piece of your grant for review:

- **Only 2-3 reviewers will have read your full proposal; your aims page needs to convince everyone else**
- **Likely the document you will edit and refine more than any other**
- **Draft, Vet, Edit....and repeat!**



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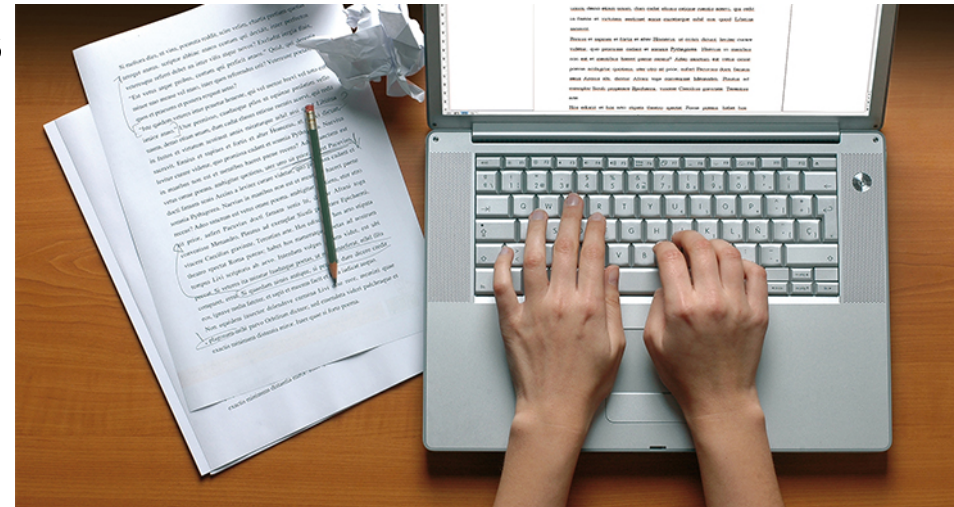
Specific Aims Outline

Paragraph 1: Introduction

Paragraph 2: What, Why, Who

Paragraph 3: Specific Aims

Paragraph 4: Pay Off



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Paragraph 1: Introduction

- **Opening Sentence:** Capture attention and highlight NIH-relevant area your application will address; focus on something the reviewers will *not* know
- **Current Knowledge:** 4-6 sentences to frame why what you propose to do is needed; progression from older knowledge to what currently is the “edge” of the field
- **Gap in Knowledge/Lack of Something:** what is the next piece of of knowledge to advance the field vertically
- **Statement of Need and Consequences of Not Meeting that Need:** Frame the gap in knowledge as a problem that demands a solution; what, explicitly, is needed?



Paragraph 1: Example (source: Bioscience Writers)

Viruses are thought to be involved in 15% to 20% of human cancers worldwide, thus providing critical tools to reveal common mechanisms involved in human malignancies. As the etiologic agent of adult T cell leukemia/lymphoma (ATLL), human T cell leukemia virus type I (HTLV-1) is just such a virus. HTLV-1 encodes a potent oncoprotein, Tax, which regulates important cellular pathways including gene expression, proliferation, apoptosis, and polarity. Over the years, Tax has proven to be a valuable model system in which to interrogate cellular processes, revealing pathways and mechanisms that play important roles in cellular transformation. Although the Tax oncoprotein has been shown to transform cells in culture and to induce tumors in a variety of transgenic mouse models, the *mechanism by which Tax transforms cells is not well understood*. A large number of Tax mutants have been generated and their biological activities have been thoroughly characterized, primarily in cell culture systems. *Currently, a major obstacle in the field is that the transforming activity of Tax mutants cannot be compared using available transgenic models due to random transgene integration sites, variable transgene copy number, and inconsistent transgene expression levels, making it difficult to link the biological activities of Tax mutants with their transforming potential.*

Color Key: **Hook** **Known Information** **Gap in Knowledge** **Critical Need**

Paragraph 2: What, Why, Who

Go from broadest to narrowest focus in terms of scope

- **Long-term goal:** establish the continuum of research that you will be pursuing over multiple periods of grant support
- **Overall objective:** must meet the need you identify in P1; emphasize the product you aspired to provide- not the process that will produce it
- **Central Hypothesis and How Formulated:** must relate directly to overall objective and your preliminary data
- **Rationale:** what is possible at the completion of the research that is not possible now; the WHY of this paragraph



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Paragraph 2: Example (source: Bioscience Writers)

To solve this problem we will develop an innovative mouse model system in which to study Tax tumorigenesis using targeting vectors containing wild-type or mutant Tax genes that are silenced by a preceding floxed stop cassette. These vectors will be knocked in to the *Rosa26* locus of recipient mice by recombination. After crossing these mice with Lck-CRE mice, the stop cassette will be specifically excised in developing thymocytes where the Lck promoter is active, allowing conditional expression of wild-type or mutant Tax proteins in T cells, the natural target of HTLV-1 infection. The feasibility of our proposed mouse model is supported by the fact that Lck-Tax transgenic mice have been developed and produce a leukemia that closely resembles ATLL. Thus, targeting of Tax expression in cells in which the Lck promoter is active is expected to produce a similar disease in our model. In our improved model system, insertion into the *Rosa26* locus will eliminate random integration sites and standardize gene copy number resulting in consistent levels of wild-type and mutant Tax protein expression.

Color Key: Long-term goal

Hypothesis

Payoff

Proposal Objective

Rationale

Paragraph 3: Specific Aims

- Aims must test all parts of your central hypothesis
- Aims should flow logically, but not be dependent
- Brief, informative, attention getting “headlines” to convey why that part of the research is being proposed (not what is being done)
- Should be global and open-ended to allow for alternative strategies if necessary (working hypothesis focuses the aim)



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Paragraph 3: Example (source: Bioscience Writers)

Aim 1 will establish an innovative mouse model for HTLV-1 Tax tumorigenesis. Targeting vectors containing silenced wild-type or mutant Tax genes will be knocked in to the Rosa26 locus of C57BL/6 mice. These mice will then be crossed with homozygous Lck-CRE mice, thereby excising the stop cassette and generating mice that express wild-type or mutant Tax proteins specifically in T cells.

Aim 2 will examine the effect of mutations that disable specific biological functions of Tax on Tax-mediated tumorigenesis. Tax can bind to and regulate the activity of members of the SRF, CREB, NF-kB and PBM protein families, each of which has been implicated in oncogenesis. Mice established in Aim 1 will allow us to compare for the first time the tumorigenic potential of wild-type and mutant Tax proteins in an effort to identify pathways that are required for Tax tumorigenesis.

Color Key: **Aim Title** **Experimental Strategy** **Outcome/Impact**

Paragraph 4: Pay-Off

- Expected outcomes of the research
- Generality regarding positive impact (segue into significance section of the proposal)



Paragraph 4: Example (source: Bioscience Writers)

The proposed studies will establish a new mouse model that will overcome current limitations and provide greater insight into the mechanism of HTLV-1 Tax tumorigenesis, knowledge that is currently lacking and that promises to yield novel insights into viral and cellular biology. The new and improved mouse model for Tax tumorigenesis will provide a valuable resource for the wider scientific community to pursue a multitude of studies that have not previously been possible due to limitations of existing mouse models of Tax.

Color Key:

Innovation

Expected Outcomes

Impact/Pay-off

Specific Aims: Do's and Don'ts

(Source: American Society of Rheumatology)

Well-designed Aims:

More than one possible outcome is acceptable
Success is not dependent on any single outcome

Unacceptable Aims:

Only one possible outcome is interesting
Success of a subsequent aim is dependent on this outcome

Fatally flawed Aims:

Descriptive, unfocused, obvious, naïve, or uninterpretable



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Example 1: We will identify [cytokine A] gene polymorphisms in biosv tissues obtained from a cohort of

Example 1: Descriptive; “Fishing Expedition”

Example 2: We will determine if [cytokine A] plays a critical role in [disease B]

Example 2: Descriptive, rather than hypothesis-testing

Example 3: We will compare the roles of [cytokine A] in [disease B and disease C]

Example 3: Allows multiple outcomes; Preliminary data involving [cytokine A] in disease support both the hypothesis and demonstrate the expertise of the investigator

(Source: American Society of Rheumatology)



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Two Examples

Helpful “Deconstruction” Tutorials here:

<https://www.northwestern.edu/climb/resources/written-communication/aims-pages-part-1-the-rhetorical-pattern-of-introductions-in-aims-pages.html>



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You've drafted your aims...now what?

- Are my Specific Aims written clearly and easy to understand?
- Would my reviewers see my proposed project as tackling an important problem in a significant field?
- Would they view my Specific Aims as capable of opening up new discoveries in the field?
- Would my reviewers regard the work as new and unique?
- Would they view my Specific Aims as likely to exert a significant influence on the research field(s) involved?



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Writing for Reviewers

- **Hierarchical Formatting**
- **Persuasive, clear, direct language**
 - Simple, declarative sentences
 - Brevity
 - Avoid:
 - ✓ Empty generalities (i.e., “State-of-the-art”)
 - ✓ Nouns as adjectives
 - ✓ Weak qualifying words
 - ✓ Whether (or not)
 - Repetition is good



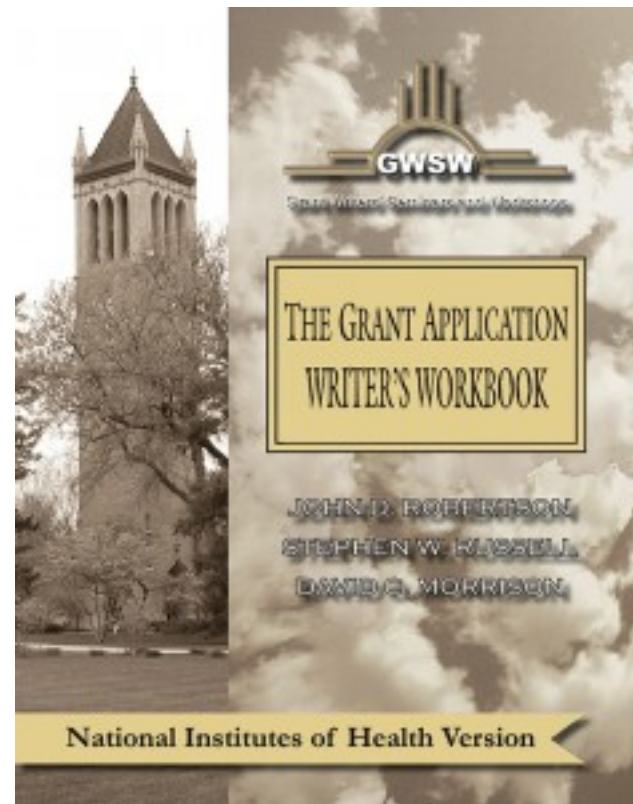
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rds@uoregon.edu



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