NIH Specific Aims Preparation

Prepared for Temple University

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NIH SPECIFIC AIMS: GENERAL CONSIDERATIONS

Specific Aims: Description

The *Specific Aims* section is arguably the most important part of the application.

- Different sources describe it as an overview of project, the template or master plan for the rest of your Research Plan, or central element of proposal.
- Due to its nature and significance, experts frequently recommend that this be the initial section of an NIH proposal that is generated.
- It is often noted that producing a clear, precise, concise statement of specific aims is a challenge. Multiple revisions are required and input from colleagues and team members can be helpful.

Sources: BioScience Writers (April 9, 2015); Dresbeck (2013); Giddings (n.d.); NIH (November 25, 2015); Univ. of Washington (n.d.)

Specific Aims: Importance

The importance of the Specific Aims page can't be overstated as...

- It will be used by the SRO to recruit reviewers for your application.
- Most members of the study section will only read the *Specific Aims* (and Project Summary/Abstract).

Sources: BioScience Writers (April 9, 2015); Dresbeck (2013); Giddings (n.d.); NIH (November 25, 2015); Univ. of Washington (n.d.)

Specific Aims: Purposes

The Specific Aims page should...

- …persuade reviewers that the project is important,
- …that you have the right team to do it,
- …that your research proposes the next logical step to advance the field,
- …and that completing the project will advance the state of science regarding human health.

Sources: BioScience Writers (April 9, 2015); Dresbeck (2013); Giddings (n.d.); NIH (November 25, 2015); Univ. of Washington (n.d.)

NIH SPECIFIC AIMS: INITIAL STEPS

Specific Aims: First Step

Start with a bullet-point concept outline that includes at least these four points…

- Issue or concern that is background of project.
- Strong research question.
- Statement(s) regarding why the project is important.
- Statement(s) regarding why the project is innovative.

Sources: Colson (2009); Dresbeck (2013); Giddings (n.d.); Jelinski (n.d.); NIH (November 25, 2015); Univ. of Washington (n.d.)

Specific Aims: Organizational Structure

Organize bullet pointed content in *four* distinct categories that will become four paragraphs.

- Introductory paragraph – definition of problem/critical need
- Proposed solution paragraph – objective(s) and rationale (what, who, how, why)
- Specific Aims list – steps to meeting objective (s) and thereby addressing critical need
- Significance paragraph – novelty, expectations, and impact

Sources: Colson (2009); Dresbeck (2013); Giddings (n.d.); Jelinski (n.d.); NIH (November 25, 2015); Univ. of Washington (n.d.)

NIH SPECIFIC AIMS: INTRODUCTORY PARAGRAPH

Introductory Paragraph

There are *four* key elements in the introductory paragraph

- An interest-grabbing and context-setting opening sentence
- A brief statement of what is known about the topic
- A brief statement of an existing gap in knowledge
- A statement of a critical need associated with the topic and the gap in knowledge

Sources: Colson (2009); Dresbeck (2013); Univ. of Washington (n.d.)

Introductory Paragraph: First Sentence

Introduces research subject to readers and quickly capture their attention

- Immediately identifies the project's focus, establishes the relevance of the proposal to human health (conveys why it is important to conduct the research), and relates these to the goals of the funding agency.

> FORMULA: There is a significant problem or unknown associated with a critical need and solving this problem is aligned with the mission of the funding agency.

- This can involve establishing the health problem, establishing the science problem, and/or or referencing the gap in knowledge and why is it important to fill.
- You want to convey that, by supporting your proposal, the reviewers will be advancing knowledge in a way that will address a critical need and help NIH accomplish its goals.

Sources: BioScience Writers (April 9, 2015); Colson (2009); Dresbeck (2013); Univ. of Washington (n.d.)

Example First Sentences

- 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.

- Microscopy has emerged as one of the most powerful and informative ways to analyze cell-based high-throughput screening (HTS) samples in experiments designed to uncover novel drugs and drug targets.

- Failure to identify regional lymph node metastases in the 40,000 US patients a year with surgically resected lung cancer is associated with a 3-fold increase in recurrence and decreased overall survival.

Sources: BioScience Writers (April 9, 2015); Colson (2009) ; Jelinski (n.d.)

Introductory Paragraph: Statement of What is Known

A statement of *current knowledge* helps the members of the panel orient themselves in respect to what is known about the topic of the application.

- Limited to 3-5 sentences that ground the reader in the subject of your research.
- Provide only the details necessary to understand why you are proposing the work.
- Save statements about what is holding back the field for the subsequent portions of the proposal.

Sources: BioScience Writers (April 9, 2015); Colson (2009); Dresbeck (2013); Univ. of Washington (n.d.)

Example “What is Known” Statement

Establishing the state of *current knowledge* requires careful selection of content and a minimalist approach.

However, many diseases and biological pathways can be better studied in whole animals–particularly diseases that involve organ systems and multicellular interactions, such as metabolism and infection. The worm Caenorhabditis elegans is a well-established and effective model organism that can be robotically prepared and imaged…

Sources: Wahlby (n.d.)

Example of a More Complex “What is Known”

Careful selection of content does not preclude precise, field-specific language or detail at points critical to understanding the discipline-specific context of the project.

> *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.*
>
> *A large number of Tax mutants have been generated and their biological activities have been thoroughly characterized, primarily in cell culture systems.*

Sources: BioScience Writers (April 9, 2015)

Introductory Paragraph: Gap in Knowledge

The gap in knowledge is a piece of information that is presently missing in the field.

- Clearly state the gap in knowledge that needs to be addressed.
- Make sure there is direct alignment between the project topic, the gap, the critical need to be addressed, and funder's priorities.
- Convey that your research will fill this gap.
- The most critical piece of the gap in knowledge or other Specific Aims content may be italicized. This technique can be useful to emphasize words or phrases but should you choose to use *italics* or <u>underline</u> to emphasize key points, remember to do so judiciously. Too much italicized text or underlining can be distracting.

Sources: BioScience Writers (April 9, 2015); Colson (2009); Dresbeck (2013); Univ. of Washington (n.d.)

Example “Gap” Statement

Stating the gap in current knowledge can be accomplished in one sentence, although it is not necessary to limit it to one sentence.

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*.

Sources: BioScience Writers (April 9, 2015)

Introductory Paragraph: Critical Need

State a critical problem that must be solved and explain why project is important to funding agency.

- The critical need is the issue or concern in the topic area the proposal seeks to address.
- The critical need is not just an interesting unknown to solve.
- The critical need acts as the background and driver of your proposal as it is the issue to be addressed and the significance of that issue within the field is the reason your proposal should be funded.
- Show how this need is important to increase medically relevant knowledge or improve health care (emphasize the significance of the problem you are trying to address).

Sources: BioScience Writers (April 9, 2015); Colson (2009); Dresbeck (2013)

Example Critical Need Statement

Critical need should also be stated concisely but with clarity and precision.

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.

Sources: BioScience Writers (April 9, 2015)

Specific Aims: Example First Full Paragraph

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.

Sources: BioScience Writers (April 9, 2015)

NIH SPECIFIC AIMS: PROPOSED SOLUTION

Proposed Solution

Introduce the solution that will fill the gap in knowledge thereby addressing the critical need. This paragraph will take a variety of forms depending on the focus of the project but should include a number of elements:

- Long term goal of application or lab
- Central hypothesis and project purpose
- Rationale
- Qualifications (including new data or advances to be utilized)

This is the "What, Why, Who, How" paragraph

Sources: BioScience Writers (April 9, 2015); Colson (2009); Dresbeck (2013); Giddings (n.d.); NIH (November 25, 2015); Univ. of Washington (n.d.)

Proposed Solution: Long-Term Goal

The long term goal summarizes the research trajectory that you will pursue over the course of multiple periods of grant support. It positions the objective of the application within a long-term research agenda.

- State this is as an overarching research goal.
- Ensure that your long-term goals align with the mission of the funding agency.
- Keep your wording general in this sentence—you are stating your long-term plans, and the reviewers understand that the specifics may be subject to change.
- It is possible for this to be shorter than a full sentence.

Sources: BioScience Writers (April 9, 2015); Colson (2009); Dresbeck (2013); Univ. of Washington (n.d.)

Example Long-Term Goal

The statement of the long-term goal can be short, even less than a full sentence.

To solve this problem we will develop an innovative mouse model system in which to study Tax tumorigenesis…

Sources: BioScience Writers (April 9, 2015)

Proposed Solution: Hypothesis and Purpose

Both of these components, hypothesis and project objective, relate to the long-term goal, the gap in knowledge, and the critical need.

- The purpose is a simple statement of what the project seeks to accomplish.
- Use NIH categories, as applicable (test hypothesis, create novel design, solve a specific problem, challenge a paradigm or practice, address a critical barrier, develop a new technology).
- State your central hypothesis in relationship to the project purpose, clearly, specifically, and with simple language.
- Preliminary data or the work of others supporting the proposed approach becomes important at this point.

Sources: BioScience Writers (April 9, 2015); Colson (2009); Dresbeck (2013); NIH (November 25, 2015); Univ. of Washington (n.d.)

Proposed Solution: Hypothesis and Purpose (2)

- Use language that demonstrates to reviewers that you have a hypothesis-driven proposal that is reasonable (improve X vs. cure cancer) and testable (the purpose will be accomplished by testing the hypothesis).
- Describe how your project addresses the critical need and gap in knowledge, while clearly stating the proposed solution.
- Avoid vague or general statements because reviewers will interpret lack of precision as poor planning of or limited clarity regarding what you expect to determine with the proposed research.
- Emphasize the product and not the process (unless the product is development of a process).

Sources: BioScience Writers (April 9, 2015); Colson (2009); Dresbeck (2013); NIH (November 25, 2015); Univ. of Washington (n.d.)

Example of a “Simple” Project Purpose Statement

The project purpose can be stated in a single sentence but needn’t be restricted to that length.

We propose to develop algorithms for the analysis of high-throughput C. elegans images, validating them in three specific experiments to identify chemicals to cure human infections and genetic regulators of host response to pathogens and fat metabolism.

Sources: Jelinski (n.d.); Wahlby (n.d.)

Example of a “Simple” Project Hypothesis

The hypothesis can also be stated in a single sentence but its length will depend on project specifics.

Novel computational tools for automated image analysis of C. elegans assays will make whole-animal screening possible for a variety of biological questions not approachable by cell-based assays.

NB – the positioning of hypotheses is flexible in this document. They can often occur associated with the project aims.

Sources: Jelinski (n.d.); Wahlby (n.d.)

“More Complex” Project Purpose and Its Associated Hypothesis

PURPOSE – …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.

HYPOTHESIS – Thus, targeting of Tax expression in cells in which the Lck promoter is active is expected to produce a similar disease in our model.

Sources: BioScience Writers (April 9, 2015)

Example with More than One Project Purpose

PURPOSE 1 – The proposed research seeks to examine the relationship between *neurotransmitter A* and *neurotransmitter B* signaling in B*rain Region of Interest* and in vivo electrophysiological measures of B*rain ROI* output during the transition from chronic morphine exposure to morphine withdrawal….

PURPOSE 2 – …additionally seeks to determine whether putative *Brain ROI* projection neurons exhibit altered basal and behaviorally-correlated firing profiles during these states…

PURPOSE 3 – …finally seeks to determine whether the observed behavioral, neurochemical, and neurophysiological indices associated with morphine dependence and withdrawal are dependent on *Neurotransmitter A* projections to the B*rain ROI.*

Sources: Dresbeck (2013)

Proposed Solution: Rationale

The final component, **rationale**, conveys *why* you want to conduct the proposed research. Your *rationale* should tell the reviewers what will become possible after the research is conducted that is not possible now.

- Explain how you arrived at your central hypothesis (for example, using past studies and published literature).
- Briefly, state what your project's completion would make possible (e.g., new therapeutics).
- Associate the desired outcome with the funding entity's mission.

Sources: BioScience Writers (April 9, 2015); Colson (2009); NIH (November 25, 2015); University of Washington (n.d.)

Example Rationale Statement

The rationale is yet another element that can be stated briefly, even a single sentence, and its length will be determined by project specifics.

The feasibility of our proposed mouse model is supported by Lck-Tax transgenic mice having been developed and producing a leukemia that closely resembles ATLL.

Sources: BioScience Writers (April 9, 2015); Dresbeck (2009); Jelinski (n.d.)

Proposed Solution: Qualifications

Briefly state why your experimental design and your team are the best for accomplishing the research goals. You can mention factors such as

- Unique qualifications of team members
- Quality or quantity of preliminary data
- Availability of rare or special laboratory equipment
- Unusual access to a population or sample
- Other special qualifications

Sources: BioScience Writers (April 9, 2015); Colson (2009)

Specific Aims: Example Second Paragraph

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 Lck-Tax transgenic mice having been developed and producing 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.

NB – this example does not include a statement of qualifications and the hypothesis is the last sentence, illustrating the ability of the author to flex the model to meet descriptive needs/preferences.

Sources: BioScience Writers (April 9, 2015)

SPECIFIC AIMS: THE AIMS STATEMENTS

Aims Statement “Do’s”

Aims are the actions to be taken to test the hypothesis (the key steps necessary to fulfill the objective and address the critical need). They should:

- Be a natural extension of the hypothesis
- Be brief, informative, and attract the reviewer’s attention.
- Convey why each part of the research is being done, but should not detail methodology.
- Ideally result in something measurable.
- Be related but not interdependent.

Sources: BioScience Writers (April 9, 2015); Dersbeck (2013); Giddings (n.d.); NIH (November 25, 2015); Univ. of Washington (n.d.)

Aims Statement "Don'ts"

Specific Aims should not:

- Introduce new ideas
- Be sequentially dependent
- Be descriptive
- Be unrealistic (the goal is ambitious but attainable)
- Be non-commital (i.e., determine whether)

Sources: BioScience Writers (April 9, 2015); Dersbeck (2013); Giddings (n.d.); NIH (November 25, 2015); Univ. of Washington (n.d.)

Expressing Specific Aims

A typical NIH R01 grant will have between 2 and 4 aims describing the experimental approach and how each step will help answer your larger hypothesis.

- Give your aim an active title that clearly states the intention in relationship to the hypothesis.
- Include a brief summary of the experimental approach and anticipated outcomes for each aim.
- Consider including a sub-hypothesis (the small portion of the overall hypothesis) and a small description of the impact of each aim (establishes each aim as valuable, testable, and independent of the others).
- Link aims to the critical need.
- Have a logical flow from one aim to the next.
- Each aim can cover several related experimental questions
- Use bullets point formatting to delineate specific aims.

Sources: BioScience Writers (April 9, 2015); Colson (2009)

Examples of “Pithy” Specific Aims

Some researchers prefer very short Specific Aims while others use statements like this as a headers.

- Determine the extent to which AH1 is downregulated by NEURO1 ablation
- Determine the extent to which insulin resistance is affected by NEURO1 ablation.
- Measure whether NEURO1 null mice are more susceptible to inflammation.

Source: Dresbeck (2013)

Examples of Sentence-Length Aims without Headers

Some successful NIH researchers use numbered Specific Aims without descriptive headers.

- AIM 1. *Establish safety, feasibility and accuracy of NIR fluorescence image-guided SLN dissection in patients with Stage I and II lung cancer.*
- AIM 2. *Compare detection of NIR fluorescence image-guided SLN identification and excision with conventional staging lymphadenectomy.*
- AIM 3. *Assess the predictive value of the detection of "occult" nodal metastatic disease on subsequent disease recurrence.*

Source: Colson (2009)

Examples of Paragraph-Length Aims without Headers

Numbered Specific Aims without descriptive headers are also fairly common.

- 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.

Sources: BioScience Writers (April 9, 2015)

Specific Aim with Headers and Explicative Information

The goal of Specific Aims is to provide a brief summary of research intention, approach, and anticipated outcomes. An explicit ordering of information in this sequence can be helpful.

Aim 1: Develop algorithms for C. elegans viability assays to identify modulators of pathogen infection

- *Challenge:* To identify individual worms in thousands of two-dimensional bright field images of worm populations infected by Microsporidia, and measure viability based on worm body shape (live worms are curvy whereas dead worms are straight).
- *Approach:* We will develop algorithms that use a probabilistic shape model of C. elegans learned from examples, enabling segmentation and body shape measurements even when worms touch or cross.
- *Impact:* These algorithms will quantify a wide range of phenotypic descriptors detectable in individual worms, including body morphology as well as subtle variations in reporter signal levels.

Sources: Jelinski (n.d.); Wahlby (n.d.)

SPECIFIC AIMS: THE SIGNIFICANCE PARAGRAPH

Significance Paragraph

Explains the overall significance of the project – why it's an important project and how it will advance the state of the science, be of value to society, and aid the agency.

- One purpose of this section to develop advocates for your proposal among the majority of reviewers who will not, in all likelihood, have read the complete application.
- The expected elements are
  - Innovation/novelty
  - Expected outcomes
  - Impact

Innovation/novelty: Plainly state what is innovative about your project. What would completion of this proposal bring to the field that is not currently present (see innovation and creativity content in NSF presentation)? This is a key review criterion.

Sources: BioScience Writers (April 9, 2015); Colson (2009); Dresbeck (2013); NIH (November 25, 2015); University of Washington (n.d.)

Significance Paragraph (2)

Expected outcomes: State your expected outcomes for this project using plain language.

- What do you expect to see at the completion of each aim (there should be at least one for each aim)?
- State how the outcomes will address the critical need and/or the knowledge gap.
- Include this information only if you have not placed it in the Aims. If it is in the aims, summarize it here as possible.

Impact: State how your project would help those who need it, (i.e. the development of a new treatment, vaccine, disease model or diagnostic tool).

- Include a broad impact statement about how your proposal will benefit the people or address the other subjects that you mentioned in the opening paragraph.

The final part of the *Specific Aims* section must summarize the general impact of the expected outcomes.

- This *positive impact* statement should make clear that, collectively, the outcomes will advance your field vertically, as well as contribute to the mission of the NIH Institute/Center that you are targeting.

Sources: BioScience Writers (April 9, 2015); Colson (2009); Dresbeck (2013); NIH (November 25, 2015); University of Washington (n.d.)

Example Significance Paragraph

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.

Sources: BioScience Writers (April 9, 2015)

REVIEW OF LEARNING REGARDING NIH SPECIFIC AIMS

Specific Aims Review

Specific Aims focus the reviewer (and you) on the main points of the grant.

- **Introduction –** *opening sentence, what is known, gap in knowledge & definition of critical need*
- **Hypothesis and Solution –** *long-term goal, hypothesis, objectives, rationale & qualifications*
- **Specific Aims –** *Actions taken to address the hypothesis*
- **Significance –** *innovation/novelty, expected outcomes & impact*

Sources

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