Specific Aim Advice and Examples

Although the following advice and examples have similarities between them, the differences evidence the large art component in grant writing. Reviewers expect the similarities; otherwise pick the style you like.

YL Colson - PowerPoint handout

Focus reviewer on main points in ~1 page

- Introduction – Definition of Problem/Critical Need
- Proposed Solution – Your Objectives & Rationale
- Specific Aims – Steps to addressing critical need
- Significance – Novelty, Expectations & Impact

Reviewer will form general conclusion by the end of the Specific Aims

Examples:

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

Emory U - Specific Aims Template handout - pdf

Concisely name a single, critical gap, hurdle, or bottleneck that is slowing or stopping progress toward solving the big picture names in the first sentence. THIS IS THE MOST CRITICAL PART OF YOUR SPECIFIC AIMS! You must have a single, clear problem that needs solving in order to have a good proposal.

“We are proposing to test the hypothesis that [state solution to gap/problem from above] with the following specific aims:

For the aims, repeat the following 1-4 times, as required:

“Aim #: To X, we will Y.” This forces you to clearly state WHAT you will do (X) and HOW you will do it (Y).

Divide the (Y) into sub-steps in a numbered/lettered list as needed

1-4 sentences stating how clearing the hurdle fits into the big picture. The more patients afflicted, the deadlier the disease, the easier it is to establish the importance of the project.

MC Giddings - specific aims template - pdf (3 pages)

1-2 sentences: Set the big picture, central challenge of your field that lots of people are interested in solving.

2-3 sentences: Elaborate on the problem, and what has been going on in your field to solving it. This is the introduction to the “What,” i.e. the theory behind what you’re trying to do. But keep it interesting and for a general audience! Do not get bogged down in heavy factual details here, or your reviewer will become lost and uninterested.

1-2 sentences: Name a general bottleneck in your field that is slowing or stopping progress towards achieving the big picture named in the first sentence. This is a critical part of your aims! You must have a single, clear Gap that needs solving [clearing], in order to have a good proposal.

1-3 sentences: Elaborate on the Gap, making it more specific and focused

1-2 sentences: Propose an approach to solving the roadblock. If you are working in a hypothesis-driven area of work, this is where you’ll state your hypothesis. If you can tie this in with the “Who” your proposal will be stronger. From the Four Steps To Funding model, this is your “What” - i.e. your model of how the world works (within the area of your proposal).

1 sentence: “We are proposing to accomplish goal [or test this hypothesis] with the following specific aims:”
“Aim #: To X we will Y.”

Example:
“Aim 1: To improve the identification of post-translational modifications and amino acid substitutions on proteins by combining top-down and bottom-up mass spectrometry data, we will enhance our PROCLAME software to use a Markov chain Monte Carlo algorithm that can incorporate: a) intact-mass mass data from top-down analysis, b) peptide data from bottom-up analysis, and c) context-sensitive rules that use but are not limited by knowledge of where modifications are likely to occur. We will further enhance the program’s assessment of modification frequency by ongoing analyses of protein databases like UniProt.” The Why is underlined and the How boldfaced, a good aim having both.

U Wash Grantsmanship 101 - [pdf](#)

The Specific Aims page, arguably the most important of the application, should be written to create a partnership with the assigned reviewers: You provide the conceptual framework upon which they hang the details of what will be done. Consider organizing bullets within four distinct paragraphs:

**Introductory paragraph**
- The opening interest-grabbing sentence immediately establishes the relevance of the proposal
- A statement of current knowledge helps less expert panel members on what is known about the topic
- Identify the gap in knowledge that is holding back the field and addressed by this application

**“What, Why, Who” paragraph**
- The long term goal projects the continuum of your research over multiple grant support periods
- This is followed by the objective of this application, which defines what you seek to accomplish
- The central hypothesis that links to the objective, which will be accomplished by testing the hypothesis
- The rationale conveys why you want to conduct the research, telling the reviewers what will become possible that isn’t now!

**Specific Aims “paragraph”**
- There must be complete concordance between the aims and the parts of your central hypothesis
- The aims should be brief, informative, headlines that attract the reviewer’s attention
- Each aim should convey why that part of the research is being done, not what will be done
- Your aims should not be descriptive or use words that connote description: “compare”, “correlate”, “describe”, “investigate”

**“Payoff” paragraph**
- This paragraph develops advocacy among the reviewers who will not read the complete application
- The expected outcomes articulate the expected research products, detailing the payoff that the reviewers can expect if they vote to fund your application
- There should be at least one important expected outcome for each aim
- The final part of the Specific Aims section must summarize the general impact of the expected outcomes. The positive impact statement makes clear that the outcomes advance your field vertically

U Mississippi - M Griswold “Secrets of Superlative Specific Aims” - 16 page PowerPoint handout

**What’s the problem? Why should we care? & How are you going to fix it?**
You must quickly engender enthusiasm for your ideas – You will not somehow finally convince reviewers on page 9 – You must sell them on page 1 (Specific Aims)

Your goal: **Be the best at selling your ideas**
- No amount of grantsmanship will turn a bad idea into a good one...
- But there are many ways to disguise a good idea. **W Raub, NIH**
**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

**What, Why, Whom Paragraph:** convince all reviewers that YOU have 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)

**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 complete dependence 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

**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 :-))

Examples:

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 . . .

**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.
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):

1. Recruit a cohort of 50 adults from different households in the Boston (MA) metropolitan area;
2. Develop and administer a questionnaire on potential PBDE sources in 3 microenvironments (home, work, car) and other potential determinants of PBDE exposure (e.g., age, diet, activity patterns);
3. 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;
4. Measure PBDEs in personal air samples and hand-wipe samples collected from each participant;
5. 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;
6. Repeat sub-aims (2) through (6) twice more at 6 month intervals for a total of three sampling rounds;

You engage or lose the reviewer here, so tell a compelling story. Each Specific Aim should take ~the same amount of time and effort and be of ~ equal importance

Good Aims can be tested against the “SMARTL” criteria:

- **Specific** – includes elements such as why, who, what, how, where, when, which, how much
- **Measurable** – can be tested empirically; will know if Aim is accomplished
- **Attainable** – you and colleagues have the expertise and resources; you can accomplish the objectives with the resources and time you are requesting
- **Relevant** – the field cares about it, it is right for you as an investigator
- **Time-bound** – doable within grant period
- **Learning** – the field learns something interesting and not trivial; you learn something that contributes to your research development

Verbs for writing Specific Aims—a list to get you started

<table>
<thead>
<tr>
<th>Probably good</th>
<th>Probably good</th>
<th>May be too descriptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apply</td>
<td>Discover</td>
<td>Correlate</td>
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<tr>
<td>Ascertain</td>
<td>Establish</td>
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<td>Characterize</td>
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<td>Understand</td>
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Delineate your specific aims in a bulleted list.

- Ensure that specific aims correlate with your central hypothesis
- Ensure that all specific aims relate to and support your overall project goal
- Provide conceptual rather than descriptive specific aims
- Delineate a reasonable number of specific aims, presented in a logical order
- “Why” aims are generally stronger than “what” aims
- Define a clear purpose, working hypothesis or statement of need, and expected outcome for each specific aim
- Make sure no specific aim is dependent on the successful outcome of another aim.
Aim 1. To define the structural variation in parvovirus capsids, and to determine the effects on capsid functions and DNA release. Hypothesis: That the capsids of paroviruses undergo structural variation that is important for infection. That occurs through the binding or release of divalent ions, by site-specific proteolysis, or by variation in specific intra- or inter-chain bonds.

a) Further define the structural flexibility in the capsid through analysis of the structures and to identify sources of variation using specific peptide and protease analysis.
b) Determine the functions of specific capsid structures by preparing mutants with altered inter-chain bonds, divalent ion binding sites, or protease cleavage sites.
c) Compare the functions of capsid structures in mutant or naturally variant viruses to reveal the structures and interactions that are critical for capsid stability, TfR binding, and the processes of cell infection.

Aim 2. To define the structural interactions between various parvovirus capsids and variants of the transferrin receptor or artificial receptors. Hypothesis: That specific binding of capsids to the feline or canine TfRs is required for successful cell infection, and those interactions are controlled by viral structures varying in structure and flexibility.

a) Determine the interactions of the feline and canine TfRs with different parvovirus capsids, examining cryoEM structures of receptor-capsid complexes at moderately high resolution. By correlating residues on the capsid and TfR that affect binding, identify the interacting structures.
b) Identify functional sites on the capsids by selecting for mutants of CPV or FPV by growth on TfRs with mutant binding domains, or on receptors with artificial binding ligands.
c) Prepare capsids with insertions that bind alternative cell receptors, and test for cell infection.
d) Examine how flexibility of capsid loops controls interactions with different host TfR - in particular receptors with additional glycans within the attachment face of the receptor.

Aim 3. Use antibodies to probe the capsid structure, and also to determine how binding to overlapping sites leads to variable neutralization. Hypothesis: That antibodies can be used to detect variant structures in the viral capsid, and that the specific position and orientation of binding controls the likelihood of competition with the TfR, and neutralization of infection.

a) Examine antibodies with known capsid binding sites for their effects on TfR binding, including the effects of cleavage with proteinases or after other asymmetrically or symmetrically displayed modifications.
b) Determine the effects on viral functions of antibody variants engineered with increased binding affinities. Identify sites on the virus that do not bind antibodies but that bind TfR, for example those subunits with cleavages in surface loops.

Aim 1: Define determinants of Gardnerella vaginalis virulence using new genetic techniques.
A. Determine genes required for production and regulation of VLY.
B. Construct and evaluate specific G. vaginalis strains with altered species specificity.
C. Determine genes required for biofilm formation in G. vaginalis.

Aim 2: Determine the role of VLY in G. vaginalis at the host-pathogen interface in vitro and in vivo.
A. Determine the role of VLY-induced membrane blebbing as a mechanism for protection of vaginal epithelial cells from toxin pores and as a pathway sensitizing cells to complement.
B. Define the role of the VLY-hCD59 interaction in G. vaginalis pathogenesis in vivo.
C. Evaluate candidate inhibitors of the VLY-hCD59 interaction in vivo.

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 brightfield 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.

**Aim 2: Develop algorithms for C. elegans lipid assays to identify genes that regulate fat metabolism**

**Challenge:** To detect worms versus background, despite artifacts from sample preparation, and detect subtle phenotypes of worm populations.

**Approach:** We will improve well edge detection, illumination correction, and detection of artifacts (e.g. bubbles and aggregates of bacteria) and enable image segmentation in highly variable image backgrounds using level-set segmentation. We will design descriptors that can capture worm population phenotypes.

**Impact:** These algorithms will provide detection for a variety of phenotypes in worm populations. They will also improve data quality in other assays, such as those in Aims 1 and 3.

**Aim 3: Develop algorithms for gene expression pattern assays to identify regulators of the response of the C. elegans host to Staphylococcus aureus infection**

**Challenge:** To map each worm to a reference and quantify changes in fluorescence localization patterns.

**Approach:** We will develop worm mapping algorithms and combine them with anatomical maps to extract atlas-based measurements of staining patterns and localization. We will then use machine learning to distinguish morphological phenotypes of interest based on the extracted features.

**Impact:** These algorithms will enable addressing a variety of biological questions by measuring complex morphologies within individual worms.

[IMO the next one is too verbose, the last too sparse]

**Specific Aim 1: Dissect the mechanism of apicoplast protein import.** The bulk of the ~500 apicoplast proteins is nuclear encoded and post-translationally imported across four membranes. We (and others) have described three mechanistically distinct candidate protein translocons that reside in the three inner membranes of complex plastids. In the current funding period we will focus on a newly discovered mechanism that was derived from the ER-associated degradation system (ERAD) of the algal endosymbiont. We will use conditional gene disruptions and complementation assays to establish the importance of individual components and to define the energy source of the translocation process.

**Specific Aim 2: Understand the function of the apicoplast ubiquitination pathway.** The ER-localized ERAD pathway goes hand in hand with the ubiquitination and subsequent proteasomal degradation of translocated proteins. Our preliminary data indicates that aspects of this protein modification pathway are still present in the apicoplast. What is the enzymatic machinery involved in this process? What are its substrates? And most importantly, what is the molecular function of apicoplast ubiquitination? A combination of genetic and biochemical approaches will be used to answer these important questions.

**Specific Aim 3: Discover a comprehensive set of apicoplast proteins and characterize their function.** Mining comparative and functional genomic information we have assembled an extensive list of proteins for which we hypothesize a role in apicoplast biology. We will establish the localization of their protein products for a comprehensive set of these candidate genes by epitope tagging. In the previous funding period we have found conditional null mutants to be highly informative to study apicoplast protein function and we have developed phenotypic assays to detect defects in apicoplast protein import, apicoplast division, and apicoplast metabolism. We will apply this genetic approach to a prioritized list of validated candidates. To increase analytical throughput, we will develop and test a new mutagenesis approach based on promoter replacement.

**Aim 1. Determine whether enteropathogenicity is a general feature of all or only some B. pseudomallei isolates.**

**Aim 2. Identify intestinal target cells for B. pseudomallei during acute and chronic enteric infection.**

**Aim 3. Determine how B. pseudomallei disseminates from the GI tract following oral inoculation.**