How to Write your NIH SBIR/STTR Specific Aims Page

Grant Writing for Success

Presented by
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My background

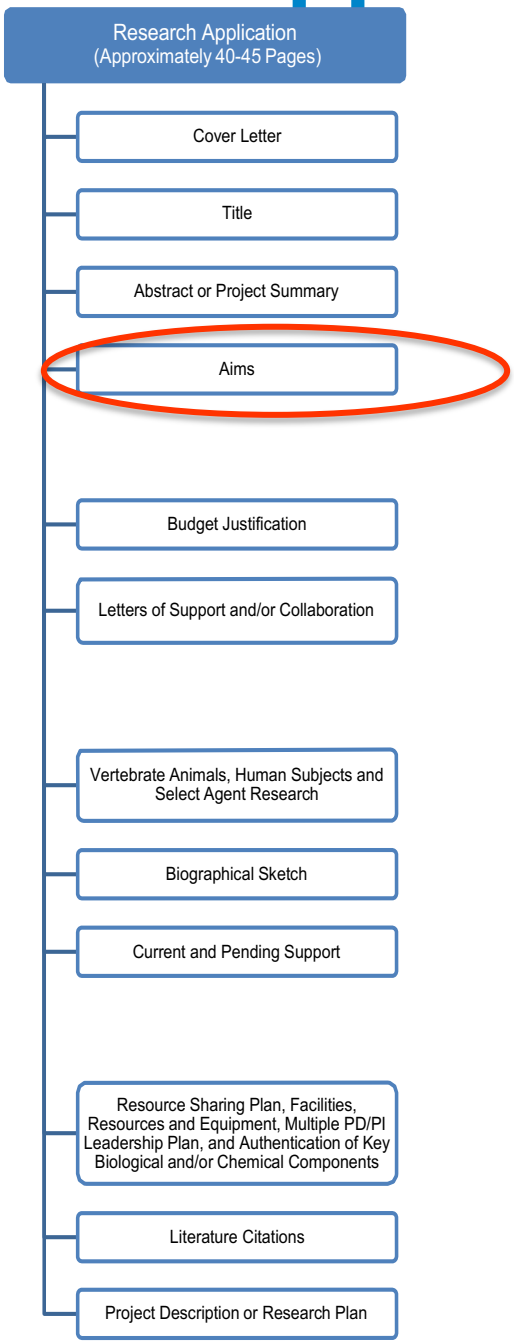
- 25+ years in the Federal Government
  - NIH: SBIR/STTR Program Manager; Researcher
    - Office of the Director
    - National Cancer Institute
  - FDA
  - USDA
  - Interagency policies/initiatives (DOD, NSF, DOE, NASA, DHS, etc.)
- 10+ years in non-profit and for-profit environments
  - Jackson Laboratory, Director of Sponsored Research
  - Small TX biotech company, VP Research
  - Small FL-based consulting company, Program Manager
- Scientific Background
  - Microbiology and immunology
  - Cancer genetics

Today's Objectives

- Brief anatomy lesson- grant application
- Understand How (And Why!) To Fit The Specific Aims Page Into Your Grant Planning Timeline
- Learn the primary components of a strong Specific Aims page
- Know your audience – Peer Reviewer
- Learn about common problems of Specific Aims
- Leave you with some relevant resources

Brief Anatomy Lesson – Grant Application

Grant Application Components



TITLE

PROJECT SUMMARY

SPECIFIC AIMS

RESEARCH PLAN
SIGNIFICANCE

INNOVATION

APPROACH
(Experimental Design)

LITERATURE CITATIONS

BIOSKETCH

FACILITIES/EQUIPMENT

Understand How (And Why!) To Fit The Specific Aims Page Into Your Grant Planning Timeline

Writing A Grant Application Is A Major Commitment

Pre-submission Planning Timeline

Months Prior

PLANNING | WRITING | SUBMITTING

8 7 6 5 4 3 2 1 mo.

Receipt Date

Brainstorm;
Research idea;
Assess resources;
Contact NIH Program Staff

Draft Specific Aims

Outline Research Plan; write; write; write!

Admin pieces

1. Preliminary budget
2. Preliminary budget justification
3. Define key personnel, % effort
4. Biosketches
5. Facilities/Resources
6. Collaboration Letters
7. Etc

Meet internal deadlines

Get feedback; edit; proofread; edit; proofread

Specific Aims

Before You Begin: Answer these 3 Questions….

1. **What are you going to do?**

STRONG research question

2. **Why is it important to do this?**

Who cares? So what?
What happens if you do this?

3. **How are you going to do it?**

How is your approach creative?

Some Basics About Specific Aims

- **THE** most important part of the application
- Reviewers have to like your idea by the time they finish reading this page.
- Provides a technical overview of the project.
- Serves as a roadmap for the entire proposal.
- You must persuade reviewers that:
  - this project is important/strong scientific premise
  - project has high impact, novelty, feasibility
  - you are the right person (or team) to do it
  - the project has high impact to advance science.

Key Rules

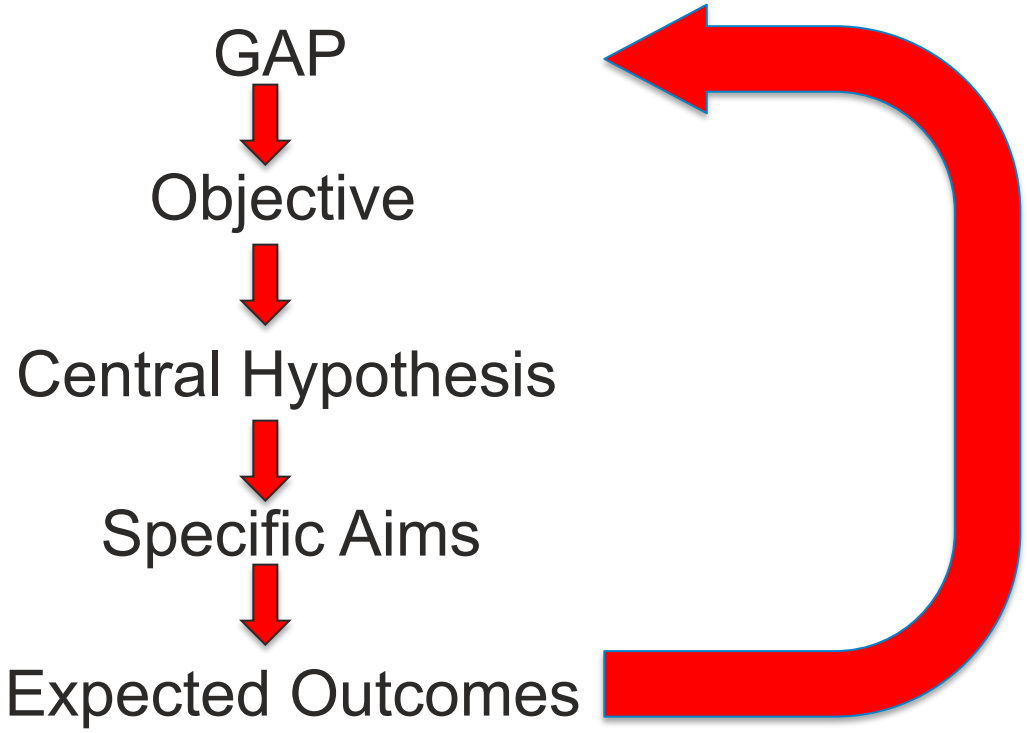
- Aims development is an iterative process!
  - Write it first… and keep revising as Research Plan develops
- Aims should test the hypothesis/support objective.
- Aims should have some detail --but not too much.
- Aims must result in something you can measure.
- Aims must be related/logical but independent of one another.
- Outcome is informative regardless of outcome.

Writing Your Aims Is Akin To A Salesperson With An Innovative Idea

1. Is well prepared
2. Is credible
3. Makes a good first impression
4. Provides supporting documentation
5. Has something special to offer
6. Presents logical, well thought out plan
7. Inspires
8. Conveys confidence in approach
9. Knows the background of the idea

Santen et al. The Jewel in the Crown: Specific Aims Section of Investigator-Initiated Grant Proposals. Journal of the Endocrine Society 2017 1:1194-1202
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5686640/

Specific Aims:
A Linear Progression of Logic



The Primary Components Of A Strong Specific Aims Page

Structure of the Aims Page

1-page document with 4 paragraphs

Opening

1. Hook

What is the research problem and why should we care?

2. State of knowledge

Concisely explain what we know about the problem (3-5 sentences).

3. Gaps in knowledge

What is the gap that needs to be filled? (hint: your study should fill this gap)

4. Critical need

Explain why this gap exists and why it is a significant problem.

What, Why, Who

1. Long-term goal

What is the "big picture" for your work? The critical need from the first paragraph needs to be the first step on this longer journey.

2. Main obj/central hyp

Explain the first step. What do you plan to achieve with the proposed study? If you are using a hypothesis-testing framework, spell out your central hypothesis.

3. Rationale

Why do you want to do this research? What will be possible if you are successful? Link your ideas back to the critical needs.

4. Team

Convey that you/team have the the expertise to conduct the work

Aims

1. Title for aim

Write brief, active headlines that link back to the central hypothesis and main objective.

HYPOTHESIS TESTING: Aims should NOT be descriptive (i.e., avoid words like compare, correlate, describe, investigate, a.k.a. "look and see")

NEEDS-BASED: It is OK to for the aims to describe what will be done

2. Supporting details

If the aim is to test a hypothesis, state working hypothesis, scientific approach, and expected outcome. If need-driven, describe process for achieving the aim.

Payoff

1. Expected outcomes

What is the expected payoff for "investing" in this proposal? There should be an outcome for each aim.

2. Impact

Make it clear that this proposal will answer an important question, fill a gap, and advance the field.

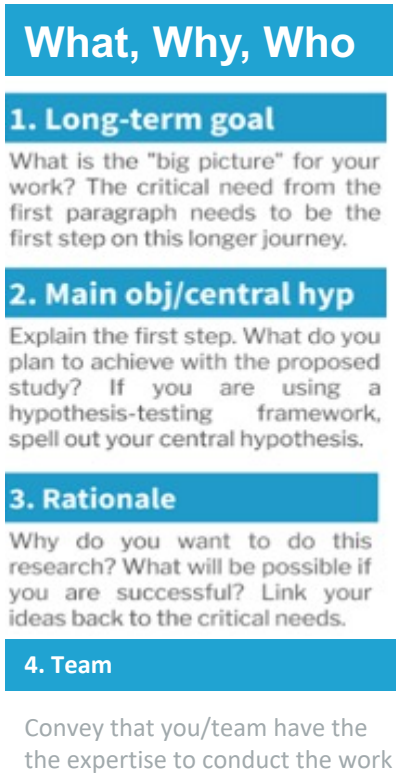
Specific Aims – Opening Paragraph

- Establish the science problem
  - Create an exciting first sentence as the *hook"* to quickly capture reviewers' attention.
- State what is currently known to ground the readers.
- Explain the gap(s) in knowledge
  - Convey that your research will fill this gap
  - Convey a sense of importance or urgency.
- State the critical unmet need
  - Emphasize the significance of the problem you are addressing.
  - Convey that your research is logical to advance the field.

At this point, reviewers should understand the medical relevance, be up to speed with current knowledge, and understand that there is a gap in the knowledge base that constitutes an important problem.

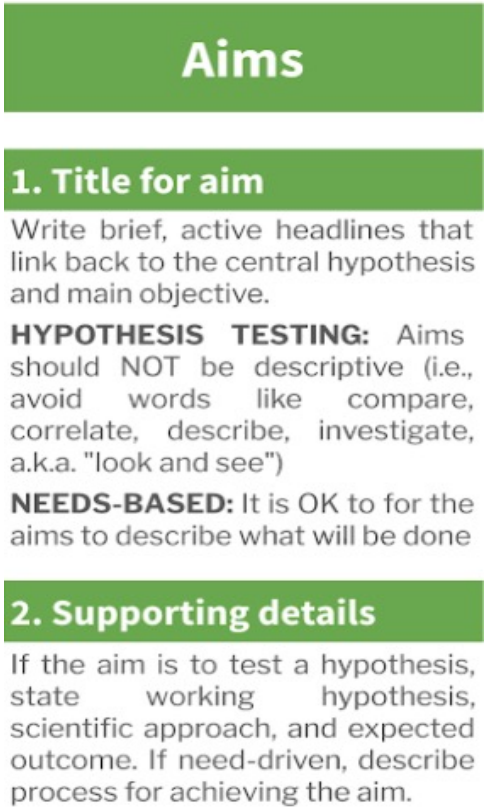
Specific Aims – Second Paragraph

- State your *long-term goal*.
  - What is your proposed solution/expected product of the research that will fill the knowledge gap?
- State your main objective (or *hypothesis)*.
  - What do plan to achieve in this proposal?
- Explain your *rationale and scientific. premise*
  - How did you arrive at your objective/hypothesis published literature, past studies).
  - Briefly, state what successful completion of the proposed work would make possible.
- *Qualifications*
  - Why is your experimental design and team the best to accomplish the research goals?



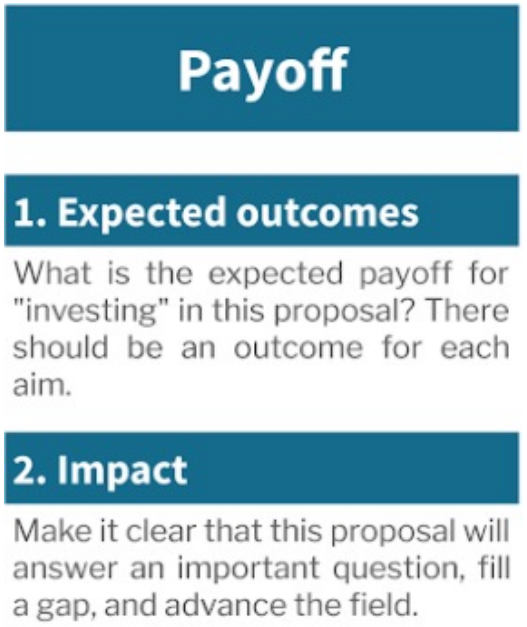
Specific Aims – Aims "Paragraph"

- State each of the aims
  - Give your aims active titles that clearly state. the objective.
  - Each should tie to your objective/test your hypothesis.
  - Aims should be related, but *must not be* dependent upon each other.
    - The failure of one aim *must not* prevent the completion of the other aims.
- Describe the experimental approach (2-4 sentences each).
  - Include a brief summary of the your technical approach.
  - Include milestone(s) for each aim.
- Specifically state for each aim the expected outcome.



Specific Aims – Payoff Paragraph

- Often overlooked, but vital for impact.
- Creates firm, broad base to support entire proposal.
- *Innovation:* Plainly state what is innovative about your project. What would your technology bring to the field that is not present currently?



- *Expected Outcomes:* Specifically state your expected outcomes for this project.
- *Impact:* Include a positive impact statement about how your results will address the knowledge gap.

Example Specific Aims (Ph I STTR)

Title: Lead Compound Discovery from Engineered Analogs of Occidiofungin

Opening

1. Hook

What is the research problem and why should we care?

2. State of knowledge

Concisely explain what we know about the problem (3-5 sentences).

3. Gaps in knowledge

What is the gap that needs to be filled? (hint: your study should fill this gap)

4. Critical need

Explain why this gap exists and why it is a significant problem.

Occidiofungins, isolated from Burkholderia *contaminans* MS14, are a newly discovered class of antifungals. From our structural characterization studies, occidiofungin was determined to have a unique chemical composition. These studies revealed four main analogs, occidiofungins A-D, and the presence of two distinct diastereomers. All analogs are composed of eight amino acids and a novel C18 fatty amino acid (NAA) containing a xylose sugar, and a 2,4- diaminobutyric acid (DABA). The structural analogs differ by an addition of oxygen to asparagine 1 (Asn1) forming a β-hydroxy asparagine 1 (BHN1) and by the addition of chlorine to β-hydroxy tyrosine 4 (BHY) forming 3-chloro β-hydroxy tyrosine 4 (chloro-BHY). So far, a mixture of occidiofungin A-D analogs show promise for developing a novel therapeutic option for treating life threatening fungal infection. There is a ***critical need*** to isolate and characterize the bioactivity and toxicity of each of these natural analogs, as well as semi-synthetically produced analogs. The potential to develop new clinically useful approaches to mitigate human susceptibility to infections caused by fungal pathogens like *Candida albicans* will likely remain limited, unless we further understand the therapeutic potential for each of these compounds.

Ref: https://www.niaid.nih.gov/sites/default/files/R41-Smith-Application.pdf

Example Specific Aims (Ph I STTR)

Title: Lead Compound Discovery from Engineered Analogs of Occidiofungin

Who, What, Why

1. Long-term goal

What is the "big picture" for your work? The critical need from the first paragraph needs to be the first step on this longer journey.

2. Main obj/central hyp

Explain the first step. What do you plan to achieve with the proposed study? If you are using a hypothesis-testing framework, spell out your central hypothesis.

3. Rationale

Why do you want to do this research? What will be possible if you are successful? Link your ideas back to the critical needs.

4. Team

Convey that you/team have the the expertise to conduct the work

Our *long-term goal* is to develop an alternative treatment option for serious fungal infections, in which currently available antifungals are failing too many people. Our *objective in this application* is to characterize the naturally produced and semi-synthetically made analogs of occidiofungin. Our *central hypothesis* is that one of these analogs has a superior set of qualities for preclinical development and that these analogs need to be evaluated to identify a lead compound. This hypothesis was based on our preliminary data showing a difference in the spectrum of activity for some of these structural analogs. The *rationale* for the proposed research is that a lead compound needs to be identified in order to ensure success with the required preclinical studies before we have our pre-IND meeting with the FDA. We propose the following aims:

Example Specific Aims (Ph I STTR)

Title: Lead Compound Discovery from Engineered Analogs of Occidiofungin

Aims

1. Title for aim

Write brief, active headlines that link back to the central hypothesis and main objective.

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NEEDS-BASED: It is OK to for the aims to describe what will be done

2. Supporting details

If the aim is to test a hypothesis, state working hypothesis, scientific approach, and expected outcome. If need-driven, describe process for achieving the aim.

Objective: Develop a novel therapeutic approach to treat life-threatening fungal infections. The occidiofungin analogs in this application will be screened based on their bioactivity in the presence of serum and toxicity against a mouse cell line. A lead drug candidate for therapeutic development will be identified from this study.

Specific Aim 1: Synthesize, engineer, and isolate structural analogs of occidiofungin.

Given our structural characterization and understanding of occidiofungin biosynthesis, we are able to engineer the synthesis of natural analogs of occidiofungin. The disruption and overexpression of gene products in the biosynthetic pathway will provide means to produce a homogenous culture of analogs of interest. Furthermore, we propose to screen semi-synthetic analogs by modifying an available amine in the molecule. Lastly, we propose to evaluate the possibility of producing occidiofungins by solid phase peptide synthesis. These studies are aimed to expand our understanding of the bioactivity of the naturally occurring analogs, while simultaneously evaluating the utility of chemically synthesizing novel analogs.

Specific Aim 2: Characterize the bioactivity of each structural analogs.

Microorganisms do not normally expend additional energy unless there is a good reason. It is likely that each naturally produced analog has a distinct set of bioactivities and toxicity. Fundamentally, we hope to understand the structure activity relationships (SAR) of the different structural elements found within occidiofungins A-D and the semi-synthetic analogs. Towards this aim, the bioactivity of each occidiofungin analog shall be determined using several methods to evaluate the spectrum of activity, serum binding, and time-kill kinetics. Occidiofungin analogs shall also be tested for differences in their *in vitro* toxicity profile using a rat hepatoma (H4IIE) cell line. These studies will expand our understanding of the biological activity and toxicity of each occidiofungin analog.

Example Specific Aims (Ph I STTR)

Title: Lead Compound Discovery from Engineered Analogs of Occidiofungin

Payoff

1. Expected outcomes

What is the expected payoff for "investing" in this proposal? There should be an outcome for each aim.

2. Impact

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At the completion of these studies, it is our *expectation* that we will have identified a lead compound of occidiofungin that has the best attributes for preclinical testing. These results are expected to have an important *positive impact* because current antifungals have limitations in use and are failing a significant population of susceptible patients. Occidiofungin is rapidly fungicidal, which may improve the therapeutic outcome for these patients. We are well equipped with the knowledge and experience to successfully complete this proposal.

Example Specific Aims (Ph I SBIR)

Title: PANDAA for universal, pan-lineage molecular detection of Lassa fever infection

Opening

1. Hook

What is the research problem and why should we care?

2. State of knowledge

Concisely explain what we know about the problem (3-5 sentences).

3. Gaps in knowledge

What is the gap that needs to be filled? (hint: your study should fill this gap)

4. Critical need

Explain why this gap exists and why it is a significant problem.

Background and Significance: Lassa virus (LASV), the causative agent of Lassa hemorrhagic fever (LHF), causes 2 million infections and 10,000 deaths each year, and further threatens global health security as a potential cause of epidemics and pandemics. Rapid and accurate diagnosis is critical to global health efforts, with a clear effect on LASV treatment, vaccine development and outbreak containment. The efficacy of current antiviral treatment strategies is limited to early stage infection and thus requires diagnostics capable of delivering results during this time. While the WHO has prioritized the development of a vaccine against Lassa, they have also recognized that the first step towards this goal is an improvement of Lassa diagnostics, as the current diagnostics do not provide reliable incidence or distribution data and are insufficient for any future vaccine efficacy study. Lastly, the failings of diagnostics for outbreak containment became clear during the 2018 Nigeria LASV outbreak, the largest of its kind on record. Burdensome and time-consuming diagnostic protocols delay results reporting (e.g. 4 days from sample collection), unnecessarily expose healthcare workers to infection, and, by delaying diagnosis in LASV-negative cases, push the healthcare infrastructure beyond its capacity.

Of the molecular assays available for LASV, qPCR offers the greatest potential for creating a rapid and sensitive clinical diagnostic tool. However, the genetic diversity of the virus has precluded a pan-lineage, universal diagnostic that sensitively and specifically detects all clades of LASV with equal performance. This shortcoming is well-documented in the literature and is addressed in the clinic by employing multiple assays targeting different genomic regions, in an attempt to mitigate viral genetic variability. Even with this approach, dubious results occur and thus multiple, independent, time-consuming diagnostic protocols need to be employed.

Note: Much of 1- 4 are better described in Significance section of Research Plan.

Ref: https://www.niaid.nih.gov/sites/default/files/R43-Application_MacLeod-1R43AI145704-01.pdf

Example Specific Aims (Ph I SBIR)

Title: PANDAA for universal, pan-lineage molecular detection of Lassa fever infection

Who, What, Why

1. Long-term goal

What is the "big picture" for your work? The critical need from the first paragraph needs to be the first step on this longer journey.

Described at end in “Payoff” section

Innovation: Aldatu Biosciences has pioneered the use of PANDAA technology, which enables probe-based qPCR for target detection in highly variable genomic regions by simultaneously adapting and amplifying diverse templates. PANDAA uniquely mitigates the presence of target-proximal polymorphisms to allow otherwise divergent templates to be detected with consensus fluorescent probes with similar sensitivities. Our experience in reaction buffer optimization further enables PANDAA to maximize assay sensitivity and specificity.

3. Rationale

Why do you want to do this research? What will be possible if you are successful? Link your ideas back to the critical needs.

Preliminary Feasibility: Aldatu Biosciences is uniquely positioned to deliver a rapid pan-lineage qPCR-based LASV diagnostic. Our technology has been successfully applied to development of subtype-independent drug resistance mutation (DRM) detection in HIV. We have designed assays for more than fifteen DRM targets covering all major HIV drug classes. Analytical and clinical validation studies have shown quantification of DRMs at very low frequency (<1%) and low copy number (>5 copies) across HIV subtypes. Excitingly, we have performed preliminary studies with LASV templates from multiple lineages, showing that even our as-yet unoptimized PANDAA reagents detect at least five lineages with near equal sensitivity and outperform the current gold standard assay by greater than an order of magnitude in terms of cross-lineage sensitivity.

2. Main obj/central hyp

Explain the first step. What do you plan to achieve with the proposed study? If you are using a hypothesis-testing framework, spell out your central hypothesis.

Approach: We propose to leverage the unique capabilities of PANDAA to develop a rapid, sensitive molecular diagnostic assay for LASV detection, and the first with pan-lineage coverage, through the following specific aims:

Example Specific Aims (Ph I SBIR)

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2. Supporting details

If the aim is to test a hypothesis, state working hypothesis, scientific approach, and expected outcome. If need-driven, describe process for achieving the aim.

Aim 1 Design of PANDAA-LASV primers and probes and reaction optimization **Months 0 - 6**

We will draw on our experience and optimized workflows to develop PANDAA-LASV primers and probes against a novel target in highly conserved regions of the LASV genome, as well as a custom reaction buffer. Reagent sensitivity will be analyzed on LASV reference sequences and empirically optimized. Milestone: Optimized PANDAA primers/probes and buffer with limit of detection (LoD) $\leq$10 RNA cps/reaction for LASV strain Josiah.

Aim 2 Refinement of PANDAA-LASV reagents on divergent genotypes **Months 6 - 9**

Reagents from our preliminary studies and Aim 1 will be evaluated on divergent LASV templates encompassing all circulating lineages. Iterative designs incorporating pre-established molecular techniques, such as PANDAA ProAmp and/or universal bases, will be evaluated to normalize sensitivity across lineages. Milestone: Refined PANDAA-LASV assay for which LoD $\leq$10 RNA cps/reaction and sensitivity deviation <25% between lineages.

Aim 3 Analytical and clinical validation of PANDAA-LASV diagnostic prototype **Months 9 - 12**

A pan-lineage analytical validation panel and probit analysis will be used to determine 95% detection limit. Serial dilutions of spiked serum will quantify LoD for purified samples. Specificity evaluation will be carried out with LASV-negative human serum, related arenaviruses, and other pathogens that cause febrile illness. Clinical sensitivity will be quantified with diverse-lineage LASV clinical isolates obtained via partnerships with FIND/BNI. Milestone: Prototype PANDAA-LASV assay with the following specifications: pan-lineage 95% detection limit of $\leq$10 RNA cps/rxn, negative signal from non-LASV templates (Cq >37 cycles), and clinical sensitivity >95%.

Example Specific Aims (Ph I SBIR)

Title: PANDAA for universal, pan-lineage molecular detection of Lassa fever infection

Payoff

1. Expected outcomes

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2. Impact

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Long-Term Goal: Successful development and validation of the PANDAA-LASV assay will precede a clinical diagnostic product that could significantly improve LHF diagnosis, management, and outbreak response, effectively reducing the testing algorithm from two tests to one. This novel, pan-lineage detection assay could ultimately be deployed in any endemic region on pre-existing qPCR equipment in central labs, and/or integrated into a closed, point-of-care system with sample processing to radically improve the LHF diagnostic workflow.

Example Specific Aims (Ph I SBIR)

Title: High-throughput, multiplexed characterization and modeling of antibody:antigen binding, with application to HSV

Opening

1. Hook

What is the research problem and why should we care?

2. State of knowledge

Concisely explain what we know about the problem (3-5 sentences).

3. Gaps in knowledge

What is the gap that needs to be filled? (hint: your study should fill this gap)

4. Critical need

Explain why this gap exists and why it is a significant problem.

Antibodies are central to modern biomedicine, with their discovery, characterization, and engineering experiencing explosive growth, yielding powerful new treatments, and enabling breakthroughs in both biotherapeutic and vaccine development. Understanding how antibodies interact with their antigens is critical to defining and distinguishing mechanisms of action and even developing improved versions of therapeutic antibodies as well as the antigen components of vaccines. While structure determination by x-ray crystallography or cryo-EM can define antibody:antigen interactions at atomic resolution, these techniques (and other related and even less detailed methodologies) are too expensive and time consuming to support studies with large sets of antibodies from polyclonal samples or engineered libraries, or likewise large sets of antigen variants from diverse populations. At the same time, more experimentally tractable methods, such as alanine scanning and pairwise antibody blocking, do not provide nearly as rich or robust information.

Ref: https://www.niaid.nih.gov/sites/default/files//R43-Brooks-Application.pdf

Example Specific Aims (Ph I SBIR)

Title: High-throughput, multiplexed characterization and modeling of antibody:antigen binding, with application to HSV

Who, What, Why

1. Long-term goal

What is the "big picture" for your work? The critical need from the first paragraph needs to be the first step on this longer journey.

2. Main obj/central hyp

Explain the first step. What do you plan to achieve with the proposed study? If you are using a hypothesis-testing framework, spell out your central hypothesis.

3. Rationale

Why do you want to do this research? What will be possible if you are successful? Link your ideas back to the critical needs.

In order to scale detailed characterization of antibody:antigen binding to handle entire panels of antibody and antigen variants, we seek here to integrate two complementary high-throughput approaches: the experimental measurement of binding via multiplexed Wasatch Microfluidics Surface Plasmon Resonance (SPR) and the computational modeling and design of interactions. Glycoprotein D (gD) from herpes simplex virus (HSV) provides an ideal focus for development, testing, and application of the new approaches, due to the availability of a wide variety of antibody and antigen variants and extensive prior low-throughput data for assessing results from the new methods. GD also still poses interesting biological questions suitable for study with the new methods, regarding variation in two HSV serotypes that resulted in failure of a vaccine trial.

Example Specific Aims (Ph I SBIR)

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Aims

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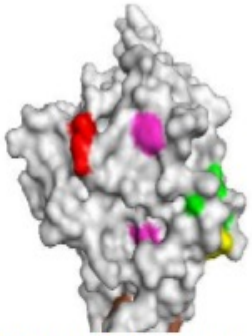
2. Supporting details

If the aim is to test a hypothesis, state working hypothesis, scientific approach, and expected outcome. If need-driven, describe process for achieving the aim.

The proposed methodologies will address two distinct levels of characterization:

Aim 1. **Define communities of antibodies with similar antigen binding patterns**. Here, we seek broad strokes across a wide range of antibodies, not being too sensitive to small differences, and requiring limited experimental effort. By analyzing patterns of antibody blocking with a set of antigen variants, our approach will identify functionally-related antibodies to infer the general binding regions on the antigen.

Aim 2. **Localize antibody epitopes**. Here, we seek to tease apart key contributors that can explain and predict subtle but significant impacts on interaction, requiring relatively more experimental effort to gain this level of detail. By analyzing binding between a panel of antibodies and a panel of natural and computationally designed antigen variants, our approach will identify hot-spot residues mediating binding.



Positions on HSV gD targeted by a few different antibodies.

The methods will be tested retrospectively against existing low-throughput data, and applied prospectively to predict binding of new antibodies and binding modes to be confirmed by x-ray crystallography.

Strength of the Premise: Other experimental techniques either do not scale or do not robustly provide the desired richness of information required to address these aims. Computational techniques are improving but are not yet by themselves able to reliably map interactions. The Wasatch SPR instrument provides a wealth of data and scales to large panels, but the panels need to be appropriately defined and analyzed. By combining computational modeling with Wasatch multiplexed SPR experimental measurement, this proposal thus builds on solid technologies and promises to hurdle limitations of existing techniques.

Reviewer comment: The two aims are clearly articulated and build on each other: first the investigators will define clusters of antibodies with similar antigen binding patterns, and then seek to map the epitopes onto specific hot-spot residues.

Example Specific Aims (Ph I SBIR)

Title: High-throughput, multiplexed characterization and modeling of antibody:antigen binding, with application to HSV

Payoff

1. Expected outcomes

What is the expected payoff for "investing" in this proposal? There should be an outcome for each aim.

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4. Team

Convey that you/team have the the expertise to conduct the work

Proposed Innovation: The project will chart as-yet unexplored territory in analyzing data across large panels of antibodies and antigens, both carefully defining general binding patterns and specifically localizing binding regions. It will integrate computational and experimental methods to rationally design antigenic variants (beyond simple alanine scans and natural variants) so as to improve resulting experimental information.

Unmet Clinical Need and Potential Health Impact: The methods will be broadly applicable in the development of vaccines and antibody therapeutics. The specific application to HSV will provide deeper insights into vaccine studies and neutralizing antibodies that may be effective against different serotypes.

Team and Outlook: The project brings together investigators with the necessary complementary expertise in the instrument (Brooks), the experimental system (Cohen), and the computational methods (Bailey-Kellogg), along with collaborators to generate variants (Integral Molecular) and to structurally validate models (Felix Ray, Pasteur Institute), see Letters of Support. The successful completion of Phase I will lay the foundation for application to additional antigens from HSV and other targets, scale up and engineering of the analysis platform for commercial distribution, and incorporation of both more detailed kinetics data and even broader antibody and antigen sequence data from next-generation sequencing.

Example Specific Aims (Ph II SBIR)

Title: Point-of-Care HIV Antigen/Antibody Diagnostic Device

Opening

1. Hook

What is the research problem and why should we care?

2. State of knowledge

Concisely explain what we know about the problem (3-5 sentences).

4. Critical need

Explain why this gap exists and why it is a significant problem.

3. Gaps in knowledge

What is the gap that needs to be filled? (hint: your study should fill this gap)

HIV infection remains a major public health crisis both in the United States and worldwide. There is increasing awareness that acutely infected individuals disproportionately contribute to disease spread (1). Yet these individuals remain the most difficult to identify, as infectivity is highest prior to the appearance of the HIV antibodies that serve as the basis for serological diagnostics (2). There are currently no FDA-approved point-of-care (POC) tests that are sensitive to acutely infected individuals. An HIV-1/2 antigen/antibody (Ag/Ab) combination assay – the so-called "4th generation" immunoassay – in an inexpensive, simple to use, POC format would fundamentally improve HIV-1/2 screening efforts in the United States and worldwide (3, 4).

for point-of-care use. Inverness Medical recently launched a point-of-care, lateral flow based p24/antibody combo assay (Determine® HIV-1 Ag/Ab Combo, not currently approved in the US). Recent results suggest that the antigen feature of the Determine® test provides an advantage over antibody-only HIV-1/2 rapid tests, but that the antigen sensitivity is inferior to the clinical analyzers (6-9), and the specificity of the antigen line is a concern (10). PCR-based methods deliver the sensitivity required for acute infection diagnosis, but current PCR-based molecular tests do not meet the cost, turnaround time, or ease-of-use requirements needed for the large-scale public health screening.

Figure 1. MBio multiplexed immunoassay system, including a reader and disposable cartridges.

[While PCR and lab-based methods provide outstanding sensitivity, they will be limited in impact in high disease burden, resource-limited settings where cost and ease-of-use are major drivers. The system proposed here addresses a major unmet public health screening need.]

Note this paragraph is in Significance section - some could have been included in Aims page

Ref: https://www.niaid.nih.gov/sites/default/files/2r44ai093289-02a1_lochhead_0.pdf

Example Specific Aims (Ph II SBIR)

Title: Point-of-Care HIV Antigen/Antibody Diagnostic Device

Who, What, Why

1. Long-term goal

What is the "big picture" for your work? The critical need from the first paragraph needs to be the first step on this longer journey.

2. Main obj/central hyp

Explain the first step. What do you plan to achieve with the proposed study? If you are using a hypothesis-testing framework, spell out your central hypothesis.

3. Rationale

Why do you want to do this research? What will be possible if you are successful? Link your ideas back to the critical needs.

MBio Diagnostics, Inc. is developing a point-of-care infectious disease testing platform for multiplexed HIV and coinfection serodiagnostic screening. Prototype devices have been placed in field sites in San Diego, Mozambique, Kenya, and Brazil. Due to cost and labor constraints, current acute infection diagnosis is typically based on pooled sample nucleic acid amplification testing algorithms, with 7 to 14 day turnaround times. 4th gen Ag/Ab assays in the clinical laboratory have been approved recently (Abbott ARCHITECT HIV Ag/Ab combo, Bio-Rad GS HIV 1/2 Ag/Ab Combo), but the 4th gen clinical analyzers do not offer the improved linkage to care associated with rapid, POC HIV testing. Here we propose an inexpensive device that delivers the performance of lab-based 4th gen Ag/Ab combo assays in a simple, POC package. We build on successes of our Phase I SBIR program and propose continuation of our translational research on a novel system with high commercial potential, offering:

- Parallel HIV-1/2 antibody and p24 antigen detection on a single point-of-care platform.
- Workflow and ease-of-use comparable to conventional HIV rapid tests.
- Robust, low cost, minimally instrumented system for use in emergency departments, public health labs, STD clinics, and targeted outreach programs.

Example Specific Aims (Ph II SBIR)

Title: Point-of-Care HIV Antigen/Antibody Diagnostic Device

Aims

1. Title for aim

Write brief, active headlines that link back to the central hypothesis and main objective.

HYPOTHESIS TESTING: Aims should NOT be descriptive (i.e., avoid words like compare, correlate, describe, investigate, a.k.a. "look and see")

NEEDS-BASED: It is OK to for the aims to describe what will be done

2. Supporting details

If the aim is to test a hypothesis, state working hypothesis, scientific approach, and expected outcome. If need-driven, describe process for achieving the aim.

Aim 1*: *Assay Development. Combine the Phase I p24 antigen detection assay with the MBio multiplexed serology assay cartridge, addressing issues of final monoclonal antibody (mAb) pair selection, HIV-1 Ag and HIV-2 Ag selection, reagent conjugations, cross-reactivity, and minimization of assay steps and complexity. The Aim 1 milestone is an HIV-1/2 antigen/antibody detection assay with performance equivalent to FDA-approved laboratory 4th gen Ag/Ab combo assays for the MBio early/acute sample collection [a set of 5 commercially available HIV-1 seroconversion/performance panels, two anti-HIV-1/2 combo performance panels, an anti-HIV-2 performance panel, and a unique collection of acute samples from San Diego.]

Aim 2*: *Cartridge Integration. Modify the MBio Cartridge, Rack, Reader, and Software to deliver an automated HIV-1/2 Ag/Ab combo result, and incorporate heat stable assay reagents into the MQ cartridge. The Aim 2 milestone is a portable, integrated system delivered to clinical collaborators that meets FDA CLIA waiver guidance requirements.

Aim 3*: *Assay Validation. Validate system using well characterized early HIV infection specimens including a panel of 200 HIV positive specimens comprised of 20 acute infection samples (RNA+ / Ab -), early seroconversion (Western Blot indeterminate) and seropositive (HIV-1 and HIV-2) samples. 200 HIV-negative samples will be used for specificity testing. The Aim 3 milestone is a dataset demonstrating performance equivalent to FDA-approved laboratory 4th gen HIV-1/2 Ag/Ab assays.

Aim 4*: *Pre-Market Field Evaluation. Place systems in intended use setting and capture operational and usability feedback in advance of design lock; and generate a preliminary dataset on capillary whole blood samples from 100 study participants in San Diego. The Aim 3 and 4 milestone is a system design and dataset for an FDA investigational device exemption (IDE) meeting in advance of clinical trials.

Example Specific Aims (Ph II SBIR)

Title: Point-of-Care HIV Antigen/Antibody Diagnostic Device

Payoff

4. Team

Convey that you/team have the the expertise to conduct the work

1. Expected outcomes

What is the expected payoff for "investing" in this proposal? There should be an outcome for each aim.

2. Impact

Make it clear that this proposal will answer an important question, fill a gap, and advance the field.

Note these 2 paragraphs are in Comm'n Plan - some could have been included in Aims page

The assembled group of investigators is uniquely capable of executing this project in a timely and cost efficient manner. The PI, Michael Lochhead, Ph.D. has led successful life science product commercialization efforts and manages MBio R&D programs, including several NIH grants projects. The MBio team includes established diagnostics industry veterans, development engineers, and bioassay scientists. Complementing the MBio group is a world class clinical team at the University of California, San Diego, with a well-established early HIV infection research program.

Expected Outcomes

The direct outcome of this program is a highly sensitive, specific, and affordable technology for detecting and quantifying proteins in a biological sample in a clinic or other point-of-care setting. This technology enables multiple products, including a 4th generation HIV test, a p24 antigen quantification test for ART therapy monitoring, a cardiac troponin test, an improved hepatitis B screening test, and a combination test for antenatal screening including HIV, hepatitis B, and syphilis, all on a single device. Each of these tests can make a significant impact on health, both in the US and in a global context.

Impact

To understand the impact of this proposal, it is necessary to put the resulting products in the context of the overall platform under development at MBio. While each test we develop has intrinsic value, there is an even greater value for an overall platform that delivers a menu of tests at the point of care. In the case of HIV, the MBio platform can simultaneously screen for multiple diseases including HIV, then provide a confirmation test that separately reports each of several markers for HIV, then perform a CD4 test, screen for multiple co-infections, and measure viral load for a confirmed case of HIV. Each of these indications is under development at MBio, and shows how a single platform can provide a comprehensive set of diagnostic information. A successful completion of this development, followed by commercialization and market acceptance, would lead to critical enabling of HIV ART therapy throughout the world. It would permit wider distribution of such therapy, helping to limit the tragedy wrought by HIV. In the US, an improved HIV screening technology that is sensitive during the viremic stage of the disease can have a real impact on the ongoing epidemic and its human and financial costs.

Common Problems with Specific Aims

- Poorly written- reviewers won't read/reread
- Dependent upon one another
- Too ambitious, too much work proposed
- Unfocused aims, unclear goals
- Weak scientific premise
- Lack of compelling rationale
- Low significance/Incremental low impact research
- Innovation is unclear

Know Your Audience – Peer Reviewer

Ideally reviewers demonstrate the following to ensure the best review of your application:

- Scientific expertise
- Mature judgement
- Ability to work effectively in a group
- Breadth of perspective
- Impartiality
- Diversity
- Geographic distribution

Know Your Audience – Peer Reviewer

Keep this thought front and center:

What will make the reviewer look forward to reviewing the rest of your grant application??

Reviewer phenotype:

- Overworked and busy
- Tired
- Multi-tasking
- May not be familiar or expert in the specific area of the grant
- Inherently skeptical
- Likely past recipients of grants from the NIH
- Accomplished, dedicated, knowledgeable and conscientious but don't want to waste their time

Know Your Audience – Peer Reviewer

- **Remember this:** Reviewer often comes to a conclusion about you, the importance of your ideas, and the clarity of your thinking after reading only the first page – The Specific Aims page!!
- Reviewers do not have time to reread to understand the intent.
- Each reviewer is assigned multiple (3-5) applications (that's hundreds of pages to consume).
- A reviewer wants to be thorough but also want to move quickly and efficiently
- They spend 3-4 hours reviewing each application - don't make it hard.

Know Your Audience – Peer Reviewer

- Reviewers not assigned to your proposal need to "catch up" during presentation by assigned reviewers.
  - Abstract, **Specific Aims,** Significance and Innovation will provide that information

- The Aims provide a conceptual framework for the assigned reviewers.
  - The flow of logic must be compelling so other reviewers can follow while someone else is talking.

Know Your Audience – Peer Reviewer

What do you think is the core or fundamental attribute that reviewers look for in Specific Aims or a Grant?

OVERALL IMPACT

The likelihood for the project to exert a sustained, powerful influence on the research field(s) involved!

$$$

Good return on investment!

Overall Impact

The likelihood for the project to exert a sustained, powerful influence on the research field(s) involved:

- in consideration of 5 core review criteria
- additional review criteria (as applicable)

Your Specific Aims page needs to be focused on this core realization!

More in next week's webinar: Understanding the NIH SBIR/STTR Peer Review Process

Takeaways and Summary

- Aims become template for rest of Research Plan
- Include everything about proposal that is exciting and compelling but without detail
- Logic must be clear and compelling and readily flow from each component
- Start with outline and bullets to ensure flow and no unnecessary detail
- Create a “hook” starter sentence that grabs interest of reviewers and establishes relevance of proposal and alignment with NIH mission

Takeaways and Summary (2)

- **Current knowledge** component grounds less knowledgeable reviewers on your topic and sets up gap/unmet need
- Include only key citations
- The **Gap in Knowledge/Unmet need** must tie back to current knowledge
- The **What, Why, Who** section takes reviewer from broadest to narrowest focus of application; has a credible long-term “big picture” goal; has an objective that describes product of research and fills gap/meets the need
- **Central hypothesis** links to objective, provides focus to your research, sets up aims

Takeaways and Summary (3)

- **Scientific premise** is clear
- **Rationale** describes what will be possible after research is conducted (advances field) – the part that excites reviewers!
- **Specific Aims** paragraph describes tasks to accomplish objective - brief, informative, attention-getting headlines or what will be done
- **Payoff** paragraph highlights expected results of research; should be at least one important outcome for each aim
- **Final part of Specific Aims** section summarizes general impact of expected outcomes; segues to Significance and Innovation sections

Become the Audience – Peer Reviewer

Contact the SRO to share your CV

Resources

Grantsmanship Assistance

- **Writing Your Specific Aims**
  - **Introduction to the Specific Aims Page of a Grant Proposal: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6133727/**
  - **Specific Aims (UTexas)**
- **NIH Research Portfolio Online Reporting Tools Expenditures and Results (RePORTER) database.**
  https://projectreporter.nih.gov
  - Search this database of funded NIH grants, using key terms of interest, or an activity code (e.g., R43, R44). In the resulting list of projects, click on the title of each to see its abstract, which usually includes the project's specific aims.
- **Sample SBIR/STTR Applications**
  - **https://www.niaid.nih.gov/grants-contracts/sample-applications**
- **Center for Scientific Review Guidance:**
  https://public.csr.nih.gov/ForApplicants/InitialReviewResultsAndAppeals/InsidersGuide
- **Yours truly!**
  - **Joanne.goodnight@gmail.com**

Today's Objectives

- ✓ Brief anatomy lesson- grant application
- ✓ Understand How (And Why!) To Fit The Specific Aims Page Into Your Grant Planning Timeline
- ✓ Learn the primary components of a strong Specific Aims page
- ✓ Know your audience – Peer Reviewer
- ✓ Learn about common problems of Specific Aims
- ✓ Leave you with some relevant resources

Thank You

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