How to Write your NIH SBIR/STTR Specific Aims Page and Commercialization Plan

Presented by
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USC Webinar 3

Grant Writing for Success

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

- Learn the primary components of a strong Specific Aims page
- Know your audience – Peer Reviewer
- Learn about common problems of Specific Aims
- Preparing your Commercialization Plan
- Leave you with some relevant resources

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 – SBIR/STTR

Before You Begin: Answer these 3 Questions….

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

Design a STRONG proof of concept study that will lead to a commercial product

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?**

What methods?
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

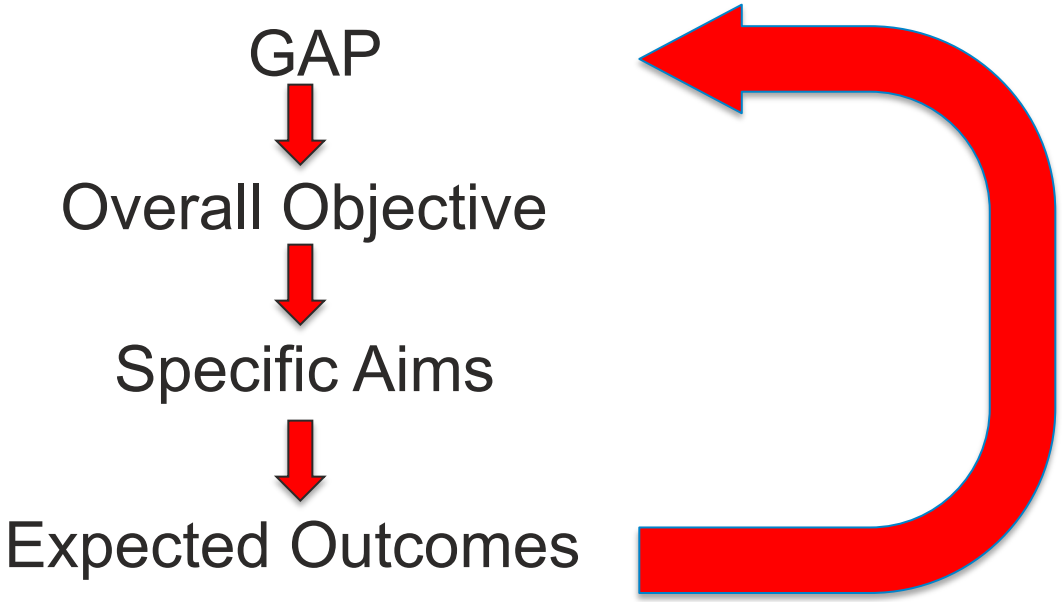
- Aims development is an iterative process!
  - Write it first… and keep revising as Research Strategy develops
- Aims should test the feasibility study/support objective.
- Aims should have some detail--but not too much.
- Aims must result in something you can measure.
- Aims must be related/logical but be independent of one another.
- Outcome is product focused to fill an unmet medical need.

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

Opening

1. Hook

What is the research problem that your technology is addressing and why should we care?

2. State of Knowledge

Concisely explain what is known about the problem (3-5 sentences)

3. Gaps in Knowledge

What is the gap to be filled? (Hint: Your study will fill this gap)

4. Critical Need

Explain why the gap exists and why it's a significant problem

What, Why, Who

1. Overall goal

What is the "big picture" goal? The critical need must align with the goal.

2. Main objective

What do plan to achieve with the proposed study?

3. Rationale

Why do you want to do this study? Link your ideas back to the critical need.

4. Team

Convey you/your team has expertise to conduct the work.

Aims

1. Title for aim

Write brief, active headlines that link back to your main objective.

2. Supporting details

Describe methods and process for achieving the aims.

3. Milestones

Include clear, measurable, quantifiable milestones for each aim.

Payoff

1. Expected Outcomes

What is the expected payoff for the government investing in this project?

2. Impact

If successful, explain how this project will fill an unmet medical need.

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 technology is logical to advance the field.

Opening

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At this point, reviewers should understand the medical relevance, be up to speed with current knowledge, and understand that there is an unmet medical need 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.
  - What do plan to achieve in this proposal?

  e.g. Demonstrate feasibility and proof of concept that product can do x, y, z
- Explain your *rationale and scientific. premise*
  - How did you arrive at your objective (e.g., 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?

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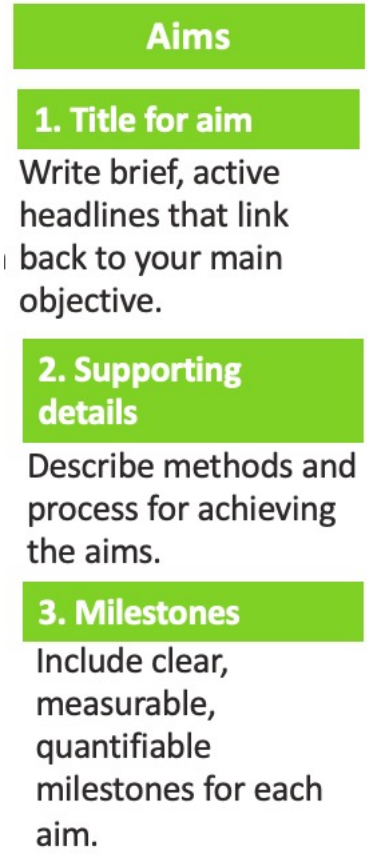
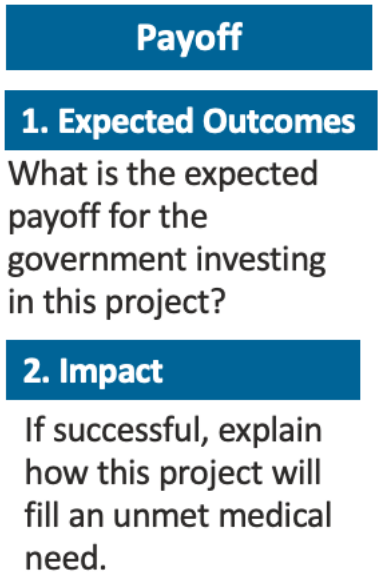
Specific Aims – Aims "Paragraph"

- State each of the aims
  - Give your aims active titles that clearly state. the objective.
  - Aims should be related, but they *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 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

Opening

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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

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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

Aims

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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

Payoff

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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

Opening

1. Hook

What is the research problem that your technology is addressing and why should we care?

2. State of Knowledge

Concisely explain what is known about the problem (3-5 sentences)

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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

What, Why, Who

What, Why, Who

1. Overall goal

What is the "big picture" goal? The critical need must align with the goal.

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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.

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.

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:

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Describe methods and process for achieving the aims.

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Include clear, measurable, quantifiable milestones for each 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) ≤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 ≤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 ≤10 RNA cps/rxn, negative signal from non-LASV templates (Cq >37 cycles), and clinical sensitivity >95%.

Example Specific Aims (Ph I SBIR)

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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

Opening

1. Hook

What is the research problem that your technology is addressing and why should we care?

2. State of Knowledge

Concisely explain what is known about the problem (3-5 sentences)

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What is the gap to be filled? (Hint: Your study will fill this gap)

4. Critical Need

Explain why the gap exists and why it's 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)

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What, Why, Who

What, Why, Who

1. Overall goal

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Convey you/your team has expertise to conduct the work.

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

Describe methods and process for achieving the aims.

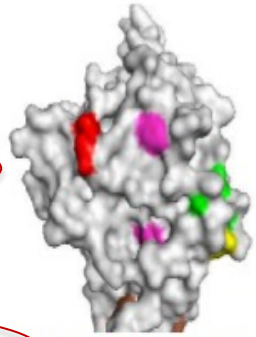
3. Milestones

Include clear, measurable, quantifiable milestones for each 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)

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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

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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

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4. Team

Convey you/your team has expertise to conduct the work.

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

Aims

1. Title for aim

Write brief, active headlines that link back to your main objective.

2. Supporting details

Describe methods and process for achieving the aims.

3. Milestones

Include clear, measurable, quantifiable milestones for each 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 you/your team has expertise to conduct the work.

Payoff

1. Expected Outcomes

What is the expected payoff for the government investing in this project?

2. Impact

If successful, explain how this project will fill an unmet medical need.

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 -- you don't want to waste their time

Know Your Audience – Peer Reviewer

- **Remember this:** Reviewer often reaches a conclusion about you, the importance of your ideas, and the clarity of your thinking after reading only one 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 they also want to move quickly and efficiently.
- They spend 3-4 hours reviewing each application - make it easy for them.

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.

Takeaways and Summary

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

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.
- **Overall Goal/Main Objective** sets up aims and provides focus to your research strategy.

Takeaways and Summary (3)

- **Scientific premise** must be clear.
- **Rationale** describes what will be possible after feasibility is demonstrated (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. Should be at least one important outcome for each aim.
- **Payoff** paragraph summarizes general impact of expected outcomes; segues to Significance and Innovation sections.

Become the Audience – Peer Reviewer

Contact the SRO to share your CV

Today's Objectives

- ✓ Learn the primary components of a strong Specific Aims page
- ✓ Know your audience – Peer Reviewer
- ✓ Learn about common problems of Specific Aims
- ➢ Preparing your Commercialization Plan
- ➢ Leave you with some relevant resources

Writing your Commercialization Plan

- **Components**
  - Value of the SBIR / STTR Project, Expected Outcomes, and Impact
  - Company
  - Market, Customer, and Competition
  - Intellectual Property (IP) Protection
  - Finance Plan
  - Production and Marketing Plan
  - Revenue Stream

Writing your Commercialization Plan

Value of the SBIR / STTR Project, Expected Outcomes, and Impact

- State the product, process, or service to be commercialized.
- Clarify the need that is addressed, specifying weaknesses in the current approaches to meet this need.
- Describe the commercial applications of the research and the innovation inherent in this application.
- Specify the potential societal, educational, and scientific benefits of this work.
- Explain the noncommercial impacts to the overall significance of the project.
- Explain how the SBIR / STTR project integrates with the overall business plan of the company.

Example

Value, Expected Outcomes and Impact

Background

Neurodegenerative disease is an encompassing term for a set of over 600 diseases in which the nervous system progressively and irreversibly deteriorates. Alzheimer's disease (AD), the most prevalent of the neurodegenerative diseases, affects approximately 15 million people worldwide[1]. Estimates expect the incident rate to triple in America[2] and Europe[3] by 2050.

The FDA has recently released a draft guidance document for the development of drugs to treat early Alzheimer's disease[4] which states that a *biomarker* alone is a sufficient endpoint for a successful clinical trial. This is a prominent departure from previous guidelines which required that a drug also demonstrate a clinical improvement. A *biomarker* is a reliable way to determine the medical state of a patient[5]. The biomarker market is expected to exceed [redacted] by 2021[12].

A major pain point in current *longitudinal neuroradiology workflows* is the time radiologists spend manually aligning the most recently acquired imaging data to the baseline so that an accurate assessment of change can be made. This severely impacts radiology report turnaround times (RTAT).

FreeSurfer is the leading software package in the research community to automatically generate *MR neuromorphometrics* from MRI data. It is in use by over 32,000 researchers worldwide. FreeSurfer's existing …

Proposal

CorticoMetrics is currently translating FreeSurfer into a clinical tool to automatically generate neuromorphometry reports from MRI imaging data. An initial prototype of this neuromorphometry report is appended to the end of this document. We expect to file our first 510(k) submission for our class II software-only medical device in the fall of 2018 (predicate: K170981). **The goal of this proposal is to augment our device with longitudinal neuromorphometric analysis capabilities** by translating, and seeking 510(k) approval for, FreeSurfer's longitudinal analysis stream.

Impact

A clinical device capable of automatically generating longitudinal neuromorphometric reports will increase the quality of patient care. Integrating this proposed device with AutoRegister, another device under development at corticometricis, will alleviate the pain point in current longitudinal neuroradiology workflows of manually aligning recent imaging data to baseline. This has the potential to drastically reduce longitudinal neuroradiology report turnaround times.

Our unbiased statistical methods will increase the power available to clinical trials affording the detection of more subtle changes or alternatively the enrolment of fewer subjects.

Quantitative imaging at a massive scale coupled with modern approaches to "big data" could revolutionize the understanding of neurodegenerative diseases and human biology more generally.

Brief overview of problem…

Discussion of pain point

Description of Company's product and impact it will have

Writing your Commercialization Plan

Company

- Describe briefly your company, including corporate objectives, core competencies, present size, history of previous federal and non-federal funding, regulatory experience, commercialization, and any current products / services that have significant sales.
- Describe the origins of the company.
- Indicate your vision for the future, how you will grow / maintain a sustainable business entity, and how you will meet critical management functions as your company evolves from a small technology R&D business to a successful commercial entity.

Example

Company

Vision

CorticoMetrics believes that the **future of healthcare** lies at the intersection of **personalized medicine** and **machine intelligence for decision support**. We are well positioned with expert domain knowledge and working collaborations in both these areas and are passionate about revolutionizing the field of medicine. With deep and longstanding connections to the neuroimaging research community, CorticoMetrics understands that clinical care is at least 2 decades behind the research community. We have made it our business to remedy this.

Presents company vision

History

CorticoMetrics was co-founded by Dr. Bruce Fischl and Mr. Nick Schmansky in 2012. Dr. Fischl has devoted his career to advancing the state of neuroimaging research. He co-developed FreeSurfer, an open-source software package currently licensed to more than 32,000 clinicians and neuroscientists. Hundreds of papers have been published using results from FreeSurfer that have led to deeper understandings of dozens of neurologic conditions and disorders.

Status

Today, CorticoMetrics employs 4 full-time employees. Dr. Wighton joined the company in November 2015, and has assumed the role of lead software engineer. He is co-PI on this application and AutoRegister, a funded STTR proposal with mutually beneficial points of integration with this proposal. Mr Sang Lee joined the company in April 2016, bringing with him experience in project management and clinical trial management and assuming the role of regulatory lead. Mr Lee Tirrell joined the team in June 2017, brining hands on experience with the FreeSurfer software and software QA experience.

To date, CorticoMetrics has secured approximately 5 million dollars in funding from the NIH. Working closely with regulatory consultants, we have created a quality management system (QMS), drafted standard operating procedures (SOPs), identified modern technologies and developed a cloud-based infrastructure harmonized with IEC 62304 so that all current and future work will be FDA 21 CFR 820 compliant.

Discussion company establishment and status

Strategy

At RSNA 2017, CorticoMetrics announced a signed distribution deal with EnvoyAI to integrate our initial product, THNIQ, into the EnvoyAI platform. Also at RSNA 2017, TeraRecon announced a distribution partnership with EnvoyAI to sell and market the EnvoyAI platform. TeraRecon is the largest independent, vendor neutral medical image viewing solution provider with a focus on advanced image processing innovation.

CorticoMetrics plans to leverage partnerships like this to distribute our products and generate revenue. Once we have established an initial revenue stream, however small, we intend to seek private investment, possibly in conjunction with a Phase IIB application to fund operations not possible to fund under this granting

Presents strategy for moving product to the market

Writing your Commercialization Plan

Market, Customer, and Competition

- Describe the market and / or market segments you are targeting and provide a brief profile of the potential customer.
- Explain what significant advantages your innovation will bring to the market (e.g., better performance; lower cost; faster, more efficient or effective, new capability).
- Explain the hurdles you will have to overcome in order to gain market / customer acceptance of your innovation.
- Describe any strategic alliances, partnerships, or licensing agreements you have in place to get FDA approval (if required) and to market and sell your product.
- Describe your marketing and sales strategy.
- Give an overview of the current competitive landscape and any potential competitors over the next several years.

Example

Markets, Customers, and Competition

Markets

There are 2 major market segments we are targeting with this device: the clinical market and the drug development market. . . .

Competition

There are 3 FDA cleared neuromorphometry reporting devices: NeuroQuant, Icobrain and NeuroReader. All 3 devices have been cleared as Class II software only medical devices (product code: LLZ)

NeuroQuant

NeuroQuant (K061855/K170981) was the first MR neuromorphometry reporting device to receive FDA clearance in 2006. Their validation plan submitted to the FDA relies heavily on reference data generated from FreeSurfer: the source from which CorticoMetrics' technology is derived. NeuroQuant automatically generates several reports containing various volumetric subcortical metrics and associated normative ranges, stratified by use case. In September 2017, they received approval to augment their device with longitudinal reporting functionality.

NeuroReader

NeuroReader (K140828) was FDA cleared in February 2015. Unlike NeuroQuant and IcoBrain, NeuroReader only offers a single neuromorphometry report containing volumetric subcortical metrics and associated normative ranges. NeuroReader does not currently offer longitudinal reporting functionality.

Icobrain

Icobrain (K161148) was FDA cleared in August 2016. Like neuroquant, they offer a variety of reports stratified by use case which contain a selection of volumetric subcortical metrics and associated normative ranges. They also offer longitudinal reporting functionality.

CorticoMetrics' Competitive Advantage

CorticoMetrics considers our proposed device to be substantially equivalent to both NeuroQuant and IcoBrain. We too intend to deliver a neuromorphometry report with associated normative data and support for longitudinal analysis. We believe, however, that our product will have 2 notable advantages over the competition. First, in addition to providing the subcortical volumetrics with normative ranges, as our competitors do, we will also provide various metrics of cortical thickness with normative ranges. **Our product will be the only one on the market capable of performing longitudinal analysis of surface based neuromorphometrics**. Also, a considerable amount of research has been invested into our longitudinal

Discussion of clinical and drug development markets

Discussion of competitors

Discusses competitive advantages

Writing your Commercialization Plan

Intellectual Property (IP) Protection

- Describe how you are going to protect the IP that results from your innovation.
- Note other actions you may take that will constitute at least a temporal barrier against others aiming to provide a solution similar to yours.

Example

Discussion IP-relatively brief.

Intellectual Property (IP) Protection

CorticoMetrics does not currently hold, nor plan to submit, patent claims on any of its current or proposed technology. The FreeSurfer code is not subject to any patent claims, and is licensed under a 'BSD/MIT-like' open-source license, where the software is free to use for commercial use, and does contain 'viral' provisions (i.e. those found in the GNU license).

CorticoMetrics is often asked about the danger of working with open-source code, where conceivably a competitor could 'take' the FreeSurfer functionality and incorporate into their own product. In principle this is true, but in practice is impractical, as neuroimage processing pipelines are quite complex, and algorithm (and its coding) expertise must be internal to the company. Each competitor has their own scientists and engineers who 'own' and maintain the algorithms they have selected (those not based on FreeSurfer). CorticoMetrics has the distinct advantage of having as co-founders the primary algorithm developer (Dr. Bruce Fischl) and software engineer (Mr. Nick Schmansky) of the FreeSurfer software package.

Writing your Commercialization Plan

Finance Plan

- Describe the necessary financing you will require to commercialize the product, process, or service, and when it will be required.
- Describe plans to raise the requisite financing to launch your innovation into Phase III and begin revenue stream.
- Plans for this financing stage may be demonstrated in one or more of the following ways:
  - Letter of commitment of funding.
  - Letter of intent or evidence of negotiations to provide funding, should the Phase II project be successful, and the market need still exist.
  - Letter of support for the project and/or some in-kind commitment (e.g., to test or evaluate the innovation).
  - Specific steps you are going to take to secure Phase III funding.

Example

Finance Plan

In early 2017, CorticoMetrics participated in the NIH 'Commercialization Accelerator Program' (NIH-CAP), for selected Phase II awardees. Mr. Nick Schmansky and Mr. Sang Lee received training in necessary Phase III activities, culminating in a presentation of proposed product offerings to a 'shark-tank'-like committee. Valuable feedback was received and highlighted the need to establish a strong product differentiator from competitors, the necessity of establishing industry contacts well-before Phase II completion, and the need to achieve a concrete 'milestone' (ie. 510(k) clearance) prior to approaching investors.

Mr. Nick Schmansky and Mr. Sang Lee have also participated in several events sponsored by a Boston-area organization called 'The Capital Network', which provides fundraising education for startups. The events have provided instruction on funding approaches, as well as one-on-one meetings with Angel and VC investors. Several informal contacts with local investors were established. More recently, Dr. Wighton submitted our complementary product (AutoRegister) to NCI's Investor Initiatives Program to seek investor funding and additional strategic partners

Discussion of commercialization programs the company has participated in

CorticoMetrics recognizes the critical importance of the Phase III stage. While we are confident we can secure 510(k) approval, and equally confident of an immediate revenue stream after approval through our distribution deal with EnvoyAI, we will lack the funds to properly scale operations post-approval. CorticoMetrics believes that private investor funds are critical to accelerate and successfully commercialize our products. Once a proof-of-principle revenue stream has been established, we intend to seek private funding, possibly in conjunction with a phase IIB bridge application, to build out the following areas: business development, sales & marketing, executive management, regulatory activities, and production and support.

Discussion of other NIH SBIR programs they intend to pursue

Writing your Commercialization Plan

Production and Marketing Plan

- Describe how the production of your product/process/ service will occur (e.g., in-house manufacturing, contract manufacturing).
- Describe the steps you will take to market and sell your product/process/service (e.g., plans for licensing, Internet sales, strategic partner)

Example

Production and Marketing Plan

Production costs of software are generally realized in the following areas: sales support, tech support, advertising, packaging and distribution, licensing agreements, liability insurance, sales processing and periodic product updates. Additionally, the FDA requires medical device manufacturers involved in the distribution of devices (including software devices) to follow certain requirements and regulations once devices are on the market. These include such things as tracking systems, reporting of device malfunctions, and registering the establishments where devices are produced or distributed. Postmarket requirements also include postmarket surveillance studies. Currently, the CorticoMetrics team has the skills and resources necessary to address these activities sufficiently for a first product sale. However, investor funding will be necessary to fully address the capital and personnel needs to achieve successful commercial growth.

CorticoMetrics is bringing its initial neuromorphetry reporting device, THINQ, to clinical markets in Fall 2018 (these efforts are outside the scope of this proposal; the incorporation of the functionality proposed in this project will happen at a later date). Introduction of our products has already begun through collaborations at MGH and an initial prototype of THINQ has already been integrated into EnvoyAI's platform for testing and non-clinical use. We are currently seeking to establish pilot projects to develop case studies and return on investment (ROI) stories to support further marketing of the product. We have planned two initial case studies for the proposed project. The first case study involves crafting a dataset specifically designed to look for methodological biases. We will then run this dataset through our product as well as our competitors to demonstrate our ability to generate more statistical power. The second case study involves measuring radiology report turnaround times (RTAT) before and after integrating the proposed product into a radiology workflow.

.....

We anticipate that additional funding will be needed for the hiring of sales and support staff to undertake the commercialization of the technology, and to support the sales efforts that potential channels have with their existing and prospective end users to target both advanced visualization capabilities and quantitative biomarker capabilities of CorticoMetrics tools. Additional funding will also be required for the support of acquired customers.

Discussion of anticipated timing for moving product to market and specific marketing efforts that the Company will undertake.

Writing your Commercialization Plan

Revenue Stream

- Explain how you plan to generate a revenue stream for your company should this project be a success (e.g., manufacture and direct sales, sales through distributors, joint venture, licensing, and service.)
- Describe how your staffing will change to meet your revenue expectations.
- Phase III funding may be from different sources such as:
  - the SBIR/STTR firm itself; private investors or “angels;”
  - VC firms; investment companies; joint ventures;
  - strategic alliances; research contracts;
  - sales of prototypes (built as part of this project);
  - public offering; state finance programs; non SBIR-funded R&D

Examples

Revenue Stream

Once the proposed device obtains 510(k) approval, a revenue stream becomes instantly available through the already established distribution deal with EnvoyAI. CorticoMetrics expects to have several additional distribution deals established by the end of this proposed project. CorticoMetrics is currently exploring efficient means to bring our product to the clinical trial/cro market to serve as an additional revenue stream.

Very brief…. Typically Company will include a chart to show the various sources of funding that are expected.

Another example…

Revenue Stream: Based on our expected development timelines and other assumptions, we project a profit of ~$5 million for GvaX12® in 2030. License and milestone payments will primarily drive revenues through 2022. After 2022 (projected launch) royalties (projected at ~5%) on sales will drive top-line revenue growth. Projections are based upon (1) the known female patient populations indicated above; (2) vaccination rates of 5% in year 1, growing steadily to 25% by year 5 (2030); and an average cost of $300 per vaccine. The financial forecasts do not include the commercialization of additional pre-clinical stage projects that could impact the revenue growth of the company as early as 2020. Operating expenses include anticipated development costs.

($000s)	2020	2021	2022	2023	2025	2026	2027	2028	2029	2030
Licensing Fees & Royalties	$0	$0	$500	$500	$1000	$1,800	$3,500	$5,500	$7,500	$10,000
Grants	$500	$1,000	$1,000	$1,000	$400	$400	$850	$850	$850	$850
Investments	$0	$2,625	$0	$0	$0	$0	$0	$0	$0	$0
Revenue	$0	$3,625	$1,500	$1,500	$1,400	$2,200	$4,350	$6,350	$8,350	$10,850
Operating Expenses	$400	$1,000	$1,000	$1,000	$1,000	$1,500	$2,000	$3,000	$4,000	$5,000
EBIT	$100	$2,625	$500	$500	$400	$700	$2,350	$3,350	$4,350	$5,850

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/**
- **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.
- **Center for Scientific Review Guidance: https://public.csr.nih.gov/ForApplicants/InitialReviewResultsAndAppeals/InsidersGuide**
- **Sample Funded NIH applications:**
  - **https://www.niaid.nih.gov/grants-contracts/sample-applications**
  - **https://www.nia.nih.gov/research/sbir/nia-small-business-sample-applications**
- **Yours truly!**
  - **joanne.goodnight@gmail.com**

Today's Objectives

- ✓ 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
- ✓ Preparing your Commercialization Plan
- ✓ Leave you with some relevant resources

Thank You

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