Grant Writing 101: The Nuts and Bolts

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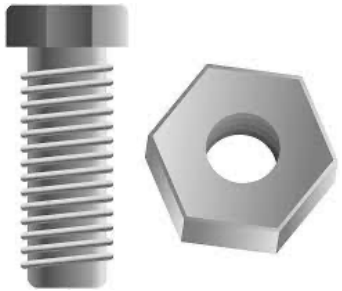


Overview of Discussion

- Planning the grant
- Writing the grant
  - How to draft the specific aims page
  - Tips for the research strategy

- Slides are formatted for NIH but can apply to all grants

- Slides will be sent to Barbara Kilbourne for reference but please do not distribute without permission

The most common mistake is not allowing enough time

- Assess yourself, your field and your resources
- Brainstorm and research the idea
- Draft specific aims
- Call NIH Program Officer

- Notify the institution that you are submitting
- Outline general application structure
- Write the application – break off small parts, one at a time
- Get feedback

- Meet institutional deadlines for budget and routing
- Correct minor errors
- Final submission

Planning Phase	Writing Phase	Submission Phase
12 to 7 months before deadline	6 to 2 months before deadline	1 to 0 months before deadline

Step 1. Plan the rough concept

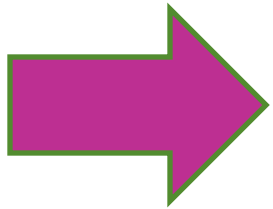
- Is the topic compelling, with a connection to patients (or does it have a clear public health impact)?
- Is the project a new idea that follows from your work and/or preliminary data (a logical progression)?
- Does the project duplicate an existing project that is funded?
  - NIH Reporter: http://reporter.nih.gov
- Are there 2-3 aspects of the project that are new to the field?

Step 1. Plan the rough concept

- Does the project align with NIH Institute Strategic Plans?
- What kind of mechanisms does the Institute support and are there
- What kinds of grant mechanisms can be used and are there priorities for certain mechanisms?
- Is there a request for this research?
  - Weekly NIH Funding Opportunities and Notices: https://grants.nih.gov/grants/guide/WeeklyIndexMobile.cfm?WeekEnding=04-09-2021

Am I ready?

- Compelling topic
- Logical idea
- Advances the field
- Aligned with funding priorities



Writing Phase

Draft Specific Aims Page

Step 2. Draft the The Specific Aims Page

- The Specific Aims page should follow a TEMPLATE
- The **Introductory paragraph** should quickly capture attention

Introductory Paragraph structure:

Sentence	What it is	Description
First sentence	HOOK	Conveys the importance of the research and why it is critical to do it
Next sentences	WHAT IS KNOWN	What is currently known in the field – be concise and focus only on the key points
Next sentences	GAP IN KNOWLEDGE	The piece of information that is not known
Final sentence	THE CRITICAL NEED	The knowledge you propose to develop and why you should be funded

Example

(https://www.biosciencewriters.com/NIH-Grant-Applications-The-Anatomy-of-a-Specific-Aims-Page.aspx)

HOOK

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

GAP

CRITICAL NEED

Example with Introductory paragraph split – Fitzpatrick R01

HOOK

The prevalence of wheezing among preschool children has tripled in the United States between 1980 and 2015. Currently, nearly 50% of all preschool children experience at least one episode of wheezing before 6 years of age and nearly 20% of all preschool children have **recurrent wheezing episodes** resulting in significant morbidity. Compared to older children, preschool children with recurrent wheezing also have twice the rate of outpatient and emergency department visits and more than five times the rate of hospitalization, resulting in substantial personal and societal economic burden.

Current treatment guidelines recommend the same pharmacotherapy be utilized for all preschool children with recurrent wheezing. However, it is increasingly recognized that recurrent wheezing in preschool children is **heterogeneous,** with many underlying biological mechanisms that likely contribute to differing temporal disease trajectories. These biological mechanisms have not been properly studied and remain poorly understood. As a result, the clinical course of preschool children with recurrent wheezing remains an enigma that is difficult to predict; there is also little evidence available to direct pharmacotherapy and a sizeable knowledge gap.

GAP

CRITICAL NEED

Step 2. Draft the Specific Aims Page

- The **second paragraph** introduces the solution that fills the gap in knowledge
- There is more flexibility here
- But should still address the following:
  - The goal of the research
  - The objective (how the project will achieve the goal)
  - Overarching (central) hypothesis to be tested
  - Consider adding your qualifications here!

Example

(https://www.biosciencewriters.com/NIH-Grant-Applications-The-Anatomy-of-a-Specific-Aims-Page.aspx)

GOAL

OBJECTIVE

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

HYPOTHESIS – but could be stronger

Example with qualifications stated – Fitzpatrick R01

We have considerable expertise in the conduct of pediatric asthma and wheezing research. We recently completed two clinical trials of preschool children with recurrent wheezing: the APRIL study (Fitzpatrick co-I, N=607, NCT01272653) and the INFANT study (Fitzpatrick MPI, N=300, NCT01606306), which advanced knowledge of wheezing triggers and preventative treatments. The INFANT study in particular identified **phenotypes** of preschool children who differed in features of allergic sensitization and future exacerbation probabilities; however, **endotyping** studies such as cytokine, metabolomic and cell-based immunologic analyses were not performed. Given our goal to advance personalized medicine for children with respiratory disorders, we propose a 50-week phenotype-stratified cohort study (N=145) to test the overarching hypothesis that **phenotypic and associated endotypic features predict wheeze exacerbation and related outcomes in preschool children age 12-59 months with recurrent wheezing**.

GOAL

OBJECTIVE

HYPOTHESIS

Example with qualifications stated – Grunwell K23

- While the exact biological mechanisms underlying pediatric acute respiratory distress syndrome (PARDS) remain unknown, neutrophils are thought to play a key role in the resolution or progression of the disorder. Neutrophils are the main innate immune cell recruited to the airways of children with viral and bacterial pneumonia and are one of the main drivers of lung injury in PARDS. During the course of my K12 training, I developed an ex vivo model to investigate of the mechanistic behavior of airway neutrophils from intubated children with acute respiratory failure. Using this model, I made the exciting observation that viral and/or bacterial coinfections (primary triggers of PARDS) promote neutrophil primary granule exocytosis, yet these same neutrophils are neither primed to mount a respiratory burst nor can they efficiently kill bacteria. These preliminary studies highlight a unique paradox whereby airway neutrophils from children at risk for PARDS are highly activated yet dysfunctional in their response to respiratory infection. The mechanisms responsible for neutrophil dysfunction in these patients are unclear but may influence suppression of T cell or macrophage function through cytokine Th1/Th2 skewing, T cell apoptosis, or inhibition of T cell proliferation through checkpoint inhibitor pathways or arginase depletion of arginine. Building upon these preliminary studies, this K23 application will test the central hypothesis that we can identify clinical phenotypic features and endotypic features of neutrophil dysfunction that can predict prolonged acute hypoxemic respiratory failure and new morbidity in children 0-17 years who develop PARDS. Through additional training in clinical research methodology, this is K23 award will investigate novel pathobiological mechanisms of potential importance to the onset and progression of PARDS and link these endotypic features with clinical phenotypes, which will lay critical groundwork for an NIH R01 proposal.

GOAL

HYPOTHESIS

OBJECTIVE

Step 2. Draft the Specific Aims Page

- The **aims section** will describe the specific aims that will test the hypothesis or achieve the objective
- Typically three aims
- Aims should:
  - Be concise
  - Be tied to the hypothesis (TESTABLE)
  - Be similar in scope
  - Be independent of each other (avoid aims that depend critically on the success of another aim)
  - Have a clear endpoint
  - Be achievable/feasible
  - Yield useful information regardless of outcome

Use strong verbs that convey a clear endpoint

WEAK VERBS
Study
Explore
Investigate
Perform
Measure
Characterize
Describe
Catalog

	STRONG VERBS
Isolate	Compare
Determine	Assess
Identify	Refine
Define	Establish
Discover	Quantify
Elucidate	Evaluate
Ascertain	
Examine	

Features of poorly developed aims

- **Unacceptable aims**
  - Only one possible outcome is interesting
  - Success of a subsequent aim is dependent on this outcome

- **Fatally-flawed aims**
  - Descriptive
  - Unfocused
  - Obvious
  - Naïve
  - Uninterpretable

Which is the strongest specific aim?

1. Compare the function of protein X in disease A and disease B
2. Determine if protein X plays a role in disease A
3. Identify protein X gene polymorphisms in biopsy tissues from a cohort of 20 patients with disease A

Which is the strongest specific aim?

1. Compare the function of protein X in disease A and disease B

   This is the strongest aim.

2. Determine if protein X plays a role in disease A

   This aim is too descriptive and does not test a specific hypothesis. Only one result is interesting. If the protein does not play a role, you can't publish the results and won't learn anything.

3. Identify protein X gene polymorphisms in biopsy tissues from a cohort of 20 patients with disease A

   This aim is too descriptive and does test a specific hypothesis. It is more of a method than an aim. It is also a "fishing" expedition and will not generate useful knowledge – sample size is so small that results cannot be published.

Example of interrelated aims

Mote AA & Libby AM, Academic Emergency Medicine April 2018

- Aim 1: Develop a new assay for Disease A
- Aim 2: Assess prevalence of Disease A in population X using new assay

- If assay development fails, aim 2 is doomed!
- An alternative proposal may seek to measure the utilization of the current assay, test three alternative methods to detect the condition in question, and pilot the test with the highest sensitivity assay for the condition. In this way, the study will generate knowledge regardless of the success with the new assay.

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Other example of Aims – Fitzpatrick R01

- **Aim 1. Determine whether wheezing phenotype predicts exacerbation occurrence (primary outcome).** Hypotheses: A phenotype distinguished by Type-2 inflammatory clinical features (i.e., eosinophils, sensitization, IgE) will be identified by latent class analysis; a higher proportion of children with this phenotype, compared to other phenotypes, will experience an exacerbation over 12 months.

- **Aim 2. Determine whether wheezing phenotype predicts episode-free days (EFDs) and response to treatment with systemic corticosteroids (secondary outcomes).** Hypothesis: The phenotype with Type-2 inflammatory clinical features, compared to other phenotypes, will have fewer EFDs and a greater response to systemic corticosteroid treatment.

- **Aim 3. Refine the prediction model for wheeze exacerbation with endotyping approaches (cytokines, metabolomics and immune cell studies)**. Hypothesis: Identified phenotypes will have distinguishing cytokine profiles, metabolomic biomarkers and markers of neutrophil and eosinophil activation and function.

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Other example of Aims – Grunwell K23

- **Aim 1. Determine the phenotype of recruited airway neutrophils and response to secondary insult.**
  - Hypothesis: Children with bacterial coinfection will have impaired Type1 interferon responses and impaired NETosis in response to: 1) NADPH oxidase activation and 2) secondary viral insult.

- **Aim 2. Determine whether recruited airway neutrophils suppress T cell function through an arginine depletion mechanism.**
  - Hypothesis: Activated neutrophils deplete arginine in the airway fluid of children with bacterial coinfection and this depletion suppresses airway T cell function.

- **Aim 3. Determine whether endotype-phenotype clusters predict clinical outcomes**
  - Hypothesis: A phenotype class distinguished by clinical features (i.e. bacterially coinfected acute viral LRTI-triggered PARDS) will be identified by latent class analysis (LCA); a higher proportion of children with this phenotype, compared to other phenotypes, will experience prolonged acute hypoxemic respiratory failure (primary outcome) and a change in functional status score (ΔFSS) of three or greater (secondary outcome)

Step 2. Draft the Specific Aims Page

- The final step is a brief statement about:
  - Innovation – what would successful completion of the project bring to the field?
  - Expected Outcomes – only if not placed in the aims
  - Impact – how does this project help those who need it (the people you mention in the first paragraph)

Example

(https://www.biosciencewriters.com/NIH-Grant-Applications-The-Anatomy-of-a-Specific-Aims-Page.aspx)

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

IMPACT

Example – Fitzpatrick R01

- This project involves a multidisciplinary team with a history of collaboration and addresses a key area in the NINR Strategic Plan: *to explore mechanisms underlying symptoms of illness and develop personalized treatments that address these mechanisms through symptom science research.* The study population, preschool children with recurrent wheezing, is understudied and the knowledge gap is quite large. This project is expected to lay critical groundwork to: 1) refine knowledge of wheeze exacerbation and associated mechanisms, 2) improve clinical prediction of exacerbation and related outcomes, and 3) identify biomarkers or features of exacerbation that can be targeted with personalized approaches, to reduce the high morbidity.

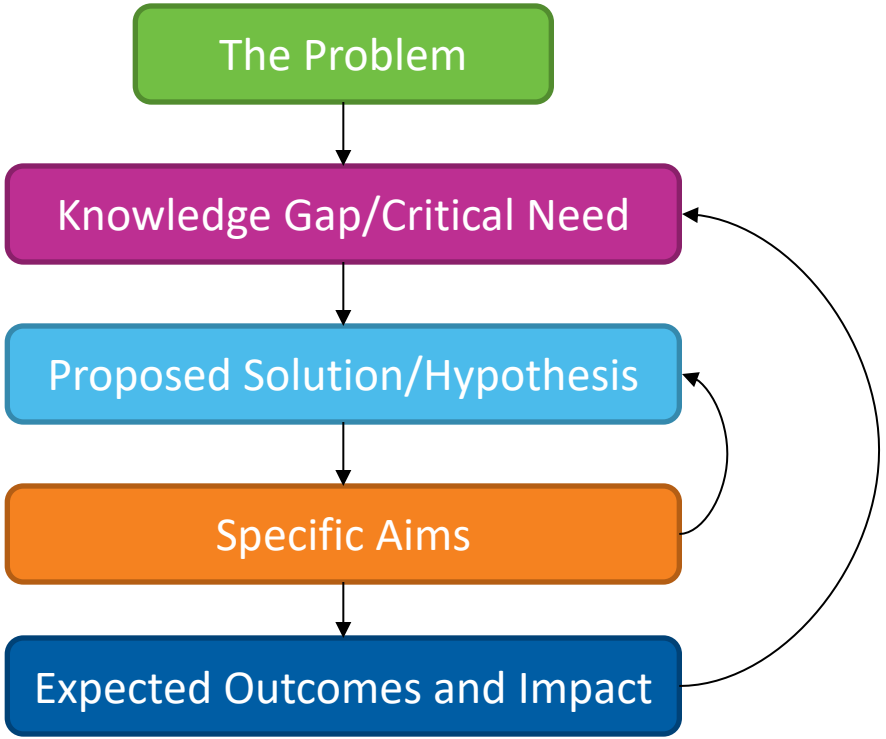
IMPACT

Example - Grunwell K23

- This K23 award describes a focused training plan in advanced biostatistical methods, big data management, and sound clinical trial study design that along with experienced and strategic mentorship will enable me to expose clinically hidden endotype classes of children with acute respiratory failure due to lower respiratory tract infections. With the career development plan and research strategy described, I will be poised to become an independently-funded physician-scientist striving to bring precision medicine to critically ill children with PARDS.

IMPACT

Summary of Specific Aims Page



Step 3: Draft the Research Strategy

- Three main sections:
  - Significance
  - Innovation
  - Approach
    - Preliminary data/feasibility
    - Methods

Significance – Reviewer criteria

- Does the project address an important problem or a critical barrier to progress in the field?
- Is the prior research that serves as the key support for the proposed project rigorous?
- If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?
- How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Innovation – Reviewer Criteria

- Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions?
- Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense?
- Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach – Reviewer Criteria

- Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?
- Have the investigators included plans to address weaknesses in the rigor of prior research that serves as the key support for the proposed project?
- Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?
- Are potential problems, alternative strategies, and benchmarks for success presented?
- If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?
- Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?
- If the project involves human subjects and/or NIH-defined clinical research, are the plans to address 1) the protection of human subjects from research risks, and 2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion or exclusion of individuals of all ages (including children and older adults), justified in terms of the scientific goals and research strategy proposed?

Thoughts about preliminary data

- Data should be relevant and supportive
- Present evidence that you have conducted smaller-scale feasibility studies
- Data should demonstrate momentum over your training/career and should show a good track record of productivity in the field
- Don’t let co-investigators appear in name only. If possible, show established working relationships with them through co-authored publications, co-presentations, or an established mentoring relationship
- If YOU didn’t generate the data, don’t say “WE did this.” Be clear about who generated what data.
- State how each result impacts your proposed approach and/or overall project

Other thoughts about the Approach

- Match your methods to your aims (don't include additional methods that aren't relevant)
- Clearly state how you will analyze your data to address specific aims and test your hypothesis - articulate the outcomes or endpoints
- A statistical analysis section is essential
- Don't forget to discuss pitfalls and alternative approaches (preferably in its own section)
- Sex as a biological variable must be discussed in the Approach
  - "NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies. Strong justification from the scientific literature, preliminary data, or other relevant considerations must be provided for applications proposing to study only one sex. Investigators are strongly encouraged to discuss these issues with NIH program staff prior to submission of applications."

Children's Healthcare of Atlanta

EMORY UNIVERSITY

Questions/Discussion