Specific Aims & Narrative Sections:

Grab NIH Reviewers Attention, Get Your Grant Funded

Presented by: Christopher Dant, PhD

Provided by:

Principal Investigators Leader

Principal Investigators Leader

1200 Pennsylvania Ave NW #7601
Suite 26526
Washington, DC 20044
www.pileader.com

[DISCLAIMER]

This webinar is an independent product of Principal Investigators Leader. It is not endorsed by nor has it any official connection with any other organization, insurance carrier, vendor, or company. Reasonable attempts have been made to provide accuracy in the content. However, of necessity, examples cited and advice given in a national periodical such as this must be general in nature and may not apply to any particular case. The publisher, editors, board members, contributors, nor consultants warrant or guarantee that the information contained herein on coding or compliance will be applicable or appropriate in any particular situation.

Principal Investigators Leader, 1200 Pennsylvania Ave NW #7601, Suite 26526, Washington, DC 20044.
Phone: 800-303-0129 • Fax: 800-230-2794 • E-mail: info@pileader.com • Website: www.pileader.com

NIH Grant: Writing Specific Aims and Narrative

PRESENTED BY: CHRISTOPHER DANT PHD

Grantsmanship

There is no grantsmanship that will turn a bad idea into a good one…

…but there are *many* ways to disguise a good idea!

Reasons Grants Fail

- Not filling a critical knowledge gap or unmet need—that is, no clear public health relevance or significance
- No clear impact on the field
- Idea not relevant to mission of NIH/Institute

Grantsmanship

"One reason for peer reviewers' lack of enthusiasm on a grant is often that it does not address the primary scientific mission or interest of the funding agency."

Dr. Jane Scott, Program Officer NHLBI

Before You Write Anything

- Before you begin outlining your grant, knowing what NIH does and does not fund is critical
- You can find this information
- This should start 6-8 months before you start

NIH DOES NOT Fund:

- Research with no significance or impact towards understanding, diagnosing, treating diseases
- Basic research ideas with no clear path to clinical translation
- Extensively pursued, well-worn ideas or incremental research that add little to what's known

Research NIH DOES Fund

- Grants aligning with NIH research priorities—either *unsolicited* aligned with NIH's stated priorities or *solicited* through specific PA/RFA
- Grants with high significance and large impact—those that clearly can move the field forward to address a specific unmet medical need

Target Your Grant to NIH

- In the specific aims page, in significance, in innovation, and approach, begin with language that looks like this:

This proposed research addresses two specific objectives of the NIH National Cancer Institute, namely:

1. Understanding specific properties of cells that inhabit a pre-malignant lung cancer, and
2. Understanding how mitochondrial heterogeneity within lung cancers influence progression or tumorigenesis

This Class

- What does the NIH reviewer expect on a grant Specific Aims Page?
- What is significance and impact?
- What is the grant Narrative and how does that relate to your Aims and Research Strategy?

NIH 5 Review Criteria

- **Significance**: relevance to human health and disease (significance to NIH)
- **Innovation**: originality of approach
- **Approach**: feasibility of your methods (will it answer aims?)
- **Investigator**: PI training and experience
- **Environment**: suitability of facilities and adequacy of support from your institution

- Overall **Impact:** Synthesis/integration of 5 criteria scored from 1-9. Overall, *the likelihood for project to exert a sustained, powerful influence on the research field(s) involved*, in consideration of these criteria (and others if applicable)

5 Review Criteria Alignment to Application

Review Criteria	Where in Application?
1. Significance	**Abstract Narrative** **Aims** Research strategy: **Significance**
2. Investigators	Biosketch: Personal Statement + Contrib. Science Research Strategy: **Approach**
3. Innovation	**Aims** Research strategy: **Innovation**
4. Approach	**Aims** Research strategy: **Approach**
5. Environment	Resources: Environment

Your Overall Impact

Is my research important (significant) to health/disease?

Plus

Can I do it…and qualified to do it?

Plus

Will it have impact on the field?

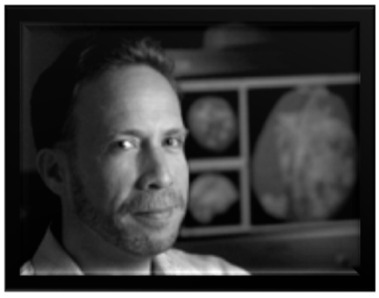
And ultimately,

Relevance to public health?

Specific Aims

What problem or gap in knowledge are you solving and how will that impact research going forward?

Specific Aims



"Most reviewers will form a general conclusion and make up their minds after reading this page…

…they then read the rest of the proposal looking for support of their opinion…"

-Allan Reiss, MD Stanford

The Specific Aims

- All successful grant writers know a basic secret to writing a winning grant
- Yet many applicants do not know this
- It's the FIRST PAGE of your grant: The Specific Aims
- Most reviewers can assign an 85%-90% accuracy score just by reading this page

The Specific Aims

- The most important but most difficult to write
- MUST quickly engender robust enthusiasm for your project
- The flow of logic must be compelling
- The template for your entire grant
- Write first and then revise as you write the rest of your grant

The Specific Aims

- The aims contain 4 key things about your proposal:
  - **why** you want to do the work--why significant?
  - **what** you want to do?
  - **how** you will do it?
  - **what impact** it will have?
- If these can't be pinned down within the one-page specific aims, they certainly can't be pinned down in a larger proposal.
- In fact, trying to write a proposal without clearly understanding those four things is a waste of time.

The Specific Aims

Assess your Specific Aims by asking yourself:

1. Would reviewers see my proposal as tackling an important problem in a significant field?
2. Would they view my Specific Aims as capable of opening up new discoveries in my field?
3. Would reviewers regard my work as new and unique?
4. Would they view my Specific Aims as likely to exert a significant influence on the research field(s) involved?
5. Are my Specific Aims written clearly and are they easy to understand?

Specific Aims
NIH Instructions:

1. State concisely the goals of the proposed research and summarize the expected outcome(s), including the impact that the results of the proposed research will exert on the research field(s) involved.

2. List succinctly the specific objectives of the research proposed, e.g.

   - test a stated hypothesis
   - create a novel design
   - solve a specific problem
   - challenge an existing paradigm or clinical practice
   - address a critical barrier to progress in the field, or
   - develop new technology

Specific Aims:
The 4-Paragraph Template

1. Identify the problem/need (knowledge gap)

2. Your solution to fill the need/gap

3. Spell out your objectives/approach you will take

4. What do you expect to find and how will it impact medical research and fill the gap?

Detailed Structure by Paragraph

1 Define problem/critical need and gap(s) in knowledge: short background (current knowledge) leading to the important problem and the knowledge gap (the "need") you will solve

2 Objective of your research to solve stated problem and fill gap by proposing central hypothesis(es) and Rationale that will fit into your long-term research goal for this work

3 Specific Aims –Objectives that test your hypotheses addressing the critical need

4 Payoff for NIH: Expected Outcomes leading to impact on the field

Addressing an NIH need? If grant is unsolicited

Impact — probability your study will be successful and will exert a powerful sustained influence on the field

- If it won't work, it has no impact, even with strong significance
- Address the grant goal AND your long-term goal(s)

Paragraph 1

Important Knowns

Unknowns

Gap in knowledge=Unmet Medical Need

The BASIS for your project

Paragraph 1: Opening Sentence

CRITICAL!

Convince your reviewers (by educating them) that there is a significant medical gap in knowledge

The knowledge gap/problem becomes the basis for a critical need that is relevant to the NIH

Paragraph 1: Opening Sentence

Paragraph must get reviewer to be your advocate to your proposal

MUST address:

1. Hook: Research topic and why it is critical that you conduct the research
2. Known information
3. Gap in knowledge (what we don't yet know)
4. The critical need

Do not state knowledge that is obvious to any reviewer

Paragraph 1

- The opening sentence must be an *interest-grabbing* sentence that immediately establishes the relevance of the proposal to human health.
- Convey that, by supporting your proposal, the reviewers will be helping NIH accomplish its goals.
- A statement of current knowledge will help the less expert members of the panel get up to speed with what's known about the topic of the application.
- Identify the gap in knowledge that is holding back the field and is what you will address in the application.

Paragraph 1: Opening Sentence

NO—This is not the problem or gap

-Cigarette smoking is a well-recognized causal factor of lung cancer, which costs the healthcare system $3B…

-Lung cancer is the leading cause of deaths among men and women in the USA and responsible for 109,302 deaths in 2015…

YES—Identifies the problem/gap

-Although overall rates of cigarette smoking in the U.S. have decreased in the past 20 years, smoking rates have actually increased among low-income women of child bearing age in the past 10 years

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

Paragraph 1

HOOK your reviewer in the first sentence!

- Background of what is currently known, what's unknown, leading to GAP in knowledge.
- The problem is NOT the disease itself but the gaps in our knowledge for diagnosing or treating the disease.

This is NOT your problem:

"Type II Diabetes currently affects more than 12% of the U.S. population, and is responsible for over 100,000 deaths and $1,000,000 in direct healthcare costs each year.

This is:

"Screening and control of risks typically associated with Diabetes (hyperglycaemia, raised blood pressure (BP), and dyslipidaemia) have been incorporated into evidence-based guidelines BUT achieving these risk factors to target levels to date remains elusive in clinical practice."

Paragraph 1: FRAME

- Important knowns lead to conclusion that there is important unknowns
- Without unknowns -- gap in knowledge -- there is NO BASIS for your project
- The gap in knowledge must make the case for a real problem and the argument that there is a critical need—the driving force for your application
- Why the lack of a solution to this problem is an issue to the funding agency rather an issue for your own research

Paragraph 1 Example

Known ➡ Re-establishing the skin's protective barrier through wound healing is significantly compromised in certain common chronic diseases such as Type II Diabetes. Open wounds lead to serious infections if not effectively treated (1). Steroids and antimicrobial hydrogels are currently the standard of care in open wounds after surgical debridement (1-3). However, these treatments result in adequate wound closure in only 32% of

Unknown ➡ serious infectious wounds (3), leading to systemic complications and death in 80,000 patients yearly (4), which is not yet fully understood. The reasons for poor wound healing involve wound microenvironmental changes in pH (6); Ca++ and Mg++ (7); and alterations in microvasculature (8-10), which have not yet been studied in wound healing. This critical gap in our understanding of wound healing has been

Gap, Unmet Need ➡ recently identified as one of the central goals of the NIDDK and the subject of NIDDK RFA 12-124. Addressing this unmet medical need will have help us better understand how wounds heal in order for researchers to identify therapeutic targets and strategies.

Paragraph 2: Your Solution

You have the solution to the stated problem/gap in knowledge, a "fix" for the critical need identified in Paragraph 1

Paragraph 2

- Solution to this problem in filling the gap lead to aims must be hypothesis-based
- What is your overall objective with this specific application addressing the critical need? (e.g., Develop a map of wound microenvironment leading to biomarkers of healing status)
- Should also include longer-term goal you identify (e.g., develop effective biomarkers of wound healing and identify treatments that target each)

Paragraph 2: Hypothesis

- Must be compatible with all known facts and evidence
- It must be specific
- It must be testable (i.e., there's at least 2 outcomes)
- Your aims will test your hypothesis

We hypothesize that …

Your hypothesis should be formulated through the existing literature and your preliminary findings

Paragraph 2

- Takes reviewer from the broad to the narrow focus
- Long-term goal—continuum of your research over multiple periods of grant support—the big picture that encompasses the gap identified
- Objective of this application—to fill the knowledge gap or meet the need you identified
- Central hypothesis links to your aims/objectives
- Rationale—what will become possible after the research is completed that is not possible now?
- After reading this paragraph, reviewers should know the continuum of your research, what the next step in that continuum is, why you want to take the next step, and what's your best bet in how to take that step

Paragraph 3: Specific Aims

Here, you provide the reviewer a step-by-step development of the key objectives (Specific Aims) that will address the problem and address the "critical need"

Paragraph 3: Specific Aims

- Aims must test your hypothesis
- Aims address the problem and fill the gap
- Aims are SPECIFIC, measurable, and do-able in time frame of the grant
- Be related, but not dependent on each other

Paragraph 3: Specific Aims

- For each aim, summarize experimental approach in 2-4 sentences: SHORT
- Each aim should show a part of how you answer your original hypothesis
- R03, R21: 1-2 Aims; R01: 3-4 Aims

Specific Aims are SPECIFIC

Do NOT write Aims with non-specific and vague unsupported statements:

To study the effects of…
To explore the reasons for…
To better understand the effects of…
To investigate the causes of…
To research why…

Specific Aims are SPECIFIC

Aims use SPECIFIC language:

Specific Aim 1. Measure levels of calcium and magnesium in the wound microenvironment over 21 days in an established rodent wound healing model. Male Wistar EK-21 rats with incisional dorsum skin wounds will be blindly scored daily for evidence of hemorrhage, ulceration, fibroblast contraction, and scab formation using standardized assays. Wound extracellular Ca^{++} and Mg^{++} and pH in wounds will be measured daily and matched to the patterns of wound changes over 21 days.

Paragraph 4

- What are my expected outcomes?
- What is the probability my study will be successful and exert a powerful sustained influence on the field(s) specifically and more generally—impact
- The NIH Payoff paragraph—why should they fund this work?
- Perhaps you are developing a new treatment, vaccine, disease model, or diagnostic tool

Paragraph 4

- Expected outcomes must be specific and credible—it's the return on investment for NIH
- Do not write in the future tense—*"this is what we believe that we will have accomplished…"* but direct present tense— *"We expect to determine…"*
- Impact — How will these stated outcomes fill the identified need and thereby advance research (and the mission of the agency, if possible)?

Paragraph 4

Expected Outcomes: By the end of our study, we expect to more fully characterize the wound microenvironmental changes in pH; Ca and Mg levels; and changes in microvasculature, providing an in-depth insights into wounds as they heal.

Innovation: This will the first study using an established wound model to correlate wound healing parameters to specific wound microenvironmental changes in pH, Ca++ and Mg++, and alterations in microvasculature using novel high-throughput assays.

Impact/Payoff: Insights into the mechanisms of wound healing will provide knowledge for the wider scientific community and clinicians to identify specific therapeutic targets and strategies to more effectively managing wounds.

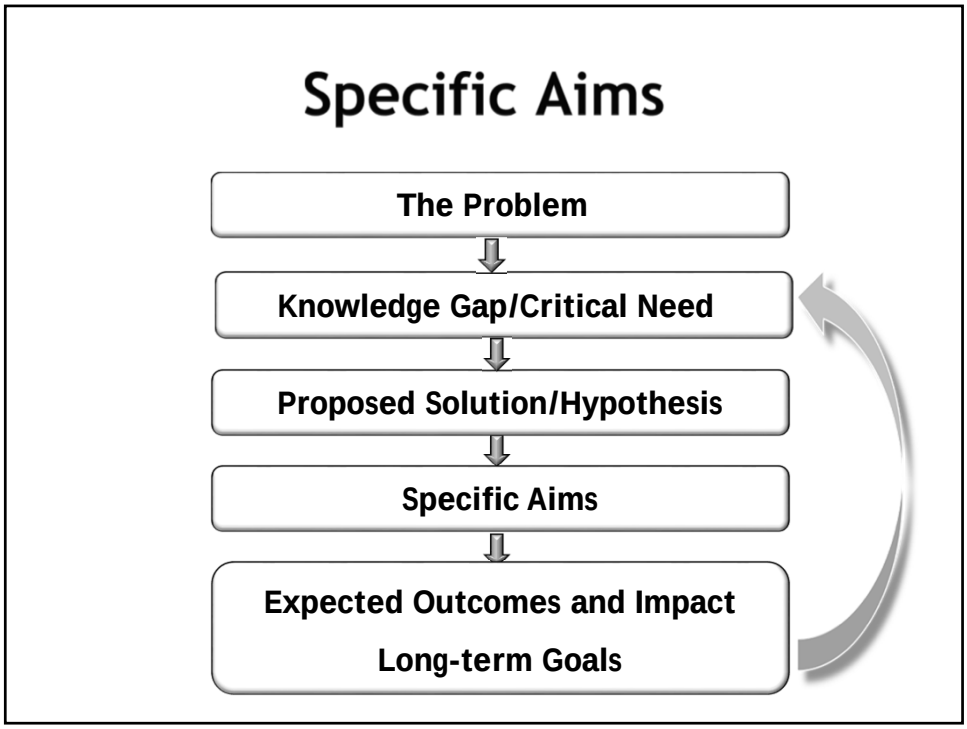
The Grant Targets NIH

In **specific aims** page, **significance,** and **approach** use specific language such as:

Our proposal addresses the 3 objectives of NCI RFA-CA-15-008…

Our specific aims address two objectives of the National Institute of General Medical Sciences (NIGMS), namely…

This research is in direct response to the NIH 2016-2020 Strategic Initiative for *Brain Research through Advancing Innovative Neurotechnologies (BRAIN)* that addresses "next-gen invasive devices to record and modulate the central nervous system of patients with spinal damage.



Specific Aims Dissected

- The Problem Colon cancer is a fatal disease if not detected early. Current medical practice in the US is screening colonoscopies for all over age 50, but colonoscopies are expensive and invasive. Screening for occult blood in stool is inexpensive but ineffective, and many cancers are missed. A blood test that could accurately detect colon cancer very early would save lives.
- Gaps in Knowledge Current approaches for measuring proteins in blood are relatively insensitive, and unlikely to detect cancers early enough. Human variability and low signal means many independent patient samples must be measured.

Specific Aims Dissected

- The Solution New proteomic technologies developed by my group offer both the sensitivity and throughput needed to identify and validate blood biomarkers for early detection of colon cancer.
- Long-term Goal Using bioinformatic methodologies, we will develop key biomarkers for other cancer types (e.g., lung, pancreatic, brain) for high-throughput proteonmics
- Hypothesis We hypothesize that colon cancers can be more effectively detected using sensitive blood biomarkers.

Specific Aims Dissected

- Action Plan

Specific Aim 1: To identify plasma proteins associated with early stages of colon cancer using novel mass spectrometric approaches that provide absolute protein abundance measurements down to pg/ml levels. These measurements will be applied to a unique cohort of colon cancer patients available from clinical collaborators

Specific Aim 2: To carry out a novel bioinformatic analysis of over-represented proteins for enrichment of specific functions using a variety of innovative software tools including KEGG, BIND, and MetaCor

Specific Aim 3: To select and validate candidate biomarkers

Candidate biomarkers selected on the basis of functions known to be associated with carcinogenesis will be verified by orthogonal approaches. The top ten ten verified candidates will be assessed in 1000 prospectively collected plasma samples from early stage colon cancer patients, using a novel high throughput proteomics approach

Specific Aims Dissected

- Expected Outcomes and Impact

The end product of this research will be an affordable accurate blood test for early detection of colon cancer without colonoscopy. Our approach will use many previously successful methods (preliminary studies) to increase the probably of success in this proposal.

Successful demonstration of this approach in colon cancer will enable application to other cancers in need of early detection biomarkers. Future directions of this research also include the application of a systems biology approach to the large datasets generated in the discovery phase that will provide new insights about the earliest stages of colon cancer. Developing such a novel treatment program for CRC directly addresses one NCI Provocative Questions and is a central mission of the NIDDK, namely…

Specific Aims:
Common Errors

- Lack of original or innovative ideas
- Unrealistic or unfocused
  - Are the aims specific and focused?
  - If there are risks, justify why it's important to pursue and how knowledge would move the field if the aim was not met
- Poorly justified
  - Relationship of aims to what's known and what's unknown should be obvious
- Purely descriptive, not hypothesis-driven
  - "This proposal looks more like a collection of experiments in which the applicants are simply listing experiments according to their expertise in specific techniques instead of testing an underlying hypothesis"
  - "Our enthusiasm was dampened by lack of a hypothesis driven by a specific mechanism"

Specific Aims:
Common Errors

- Lack of cohesiveness
  - Must be thematically related and form a cohesive unit
  - Think of a central hypothesis unifying aims
- Interdependence of aims
  - Avoid interdependent aims unless there is no doubt that the early goal will be achieved
  - Avoid "look and see" structure of an aim

Specific Aims:
Common Errors

- Describing techniques
  - Do not provide details of methods in Aims
- Overly ambitious
  - 2-4 Aims (R01), 1-2 Aims (R03,R21)
  - Gives impression proposal is unfocused or you have not thought the proposal through
- No significant impact on the field even if aims achieved

Specific Aims
Evidence of Problems in 66 Grants

Review Problem	%
Goals overstated, overly ambitious, unrealistic	45
Poorly focused, inadequately conceptualized	38
Hypotheses not clearly articulated	50

Inouye S. Evidence-based guide to writing grant proposals for clinical research. Ann Int. Med 142:274, 2005

Abstract: 2 Parts

1. Project Summary

- Project Summary — succinct and accurate description of the proposed work
- Informative to other persons working in the same/related field and for scientifically/technically literate reader
- ≤30 lines of text

2. Project Narrative

- This is the second component of the "abstract" that defines the "relevance"
- Using no more than 2-3 sentences, describe the relevance of this research to public health
- Use plain language understood by the general public (Congress)

Project Narrative

- Write AFTER the Aims Page
- Often the first thing read by reviewers and by congress
- Potential funders will read to determine if the project fits with the agency's mission and support
- Project potential to improve public health must be clearly articulated

Narrative: Use Lay Language

- **Your project will not be of interest unless it grabs their attention—and often it written *too* technically**
- How to describe the relevance to human health in lay language?
  - Start with what disease state or problem you're tackling
  - What you plan to do to overcome the problem
  - How this will help diagnose/treat people with the disease
  - Ultimately, FOCUS on how is your work relevant to public health

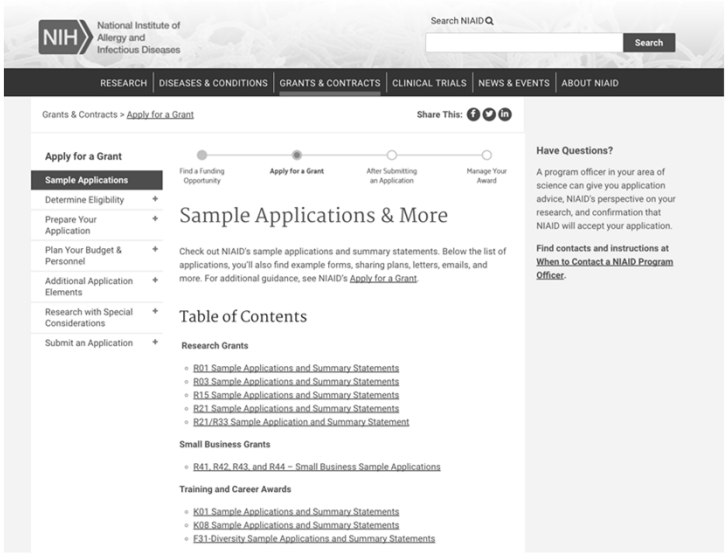
Project Narrative—too technical

Legionella pneumophila uses a specialized type IV secretion apparatus, also known as the Dot/Icm system, to secrete over 150 effector proteins directly into the host cell. The translocated bacterial effectors establish a vacuolar niche that supports replication of L. pneumophila in eukaryotic cells. While there is an extensive literature describing how several of these effectors alter host cell functions, the targets of most have remained elusive….

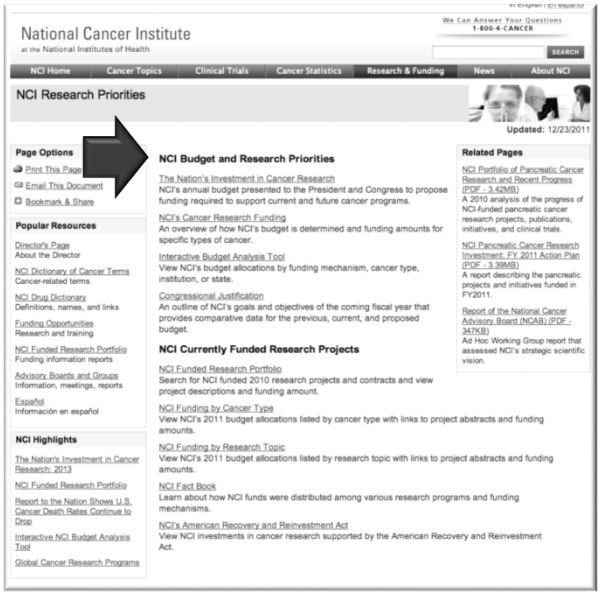
Project Narrative—lay version

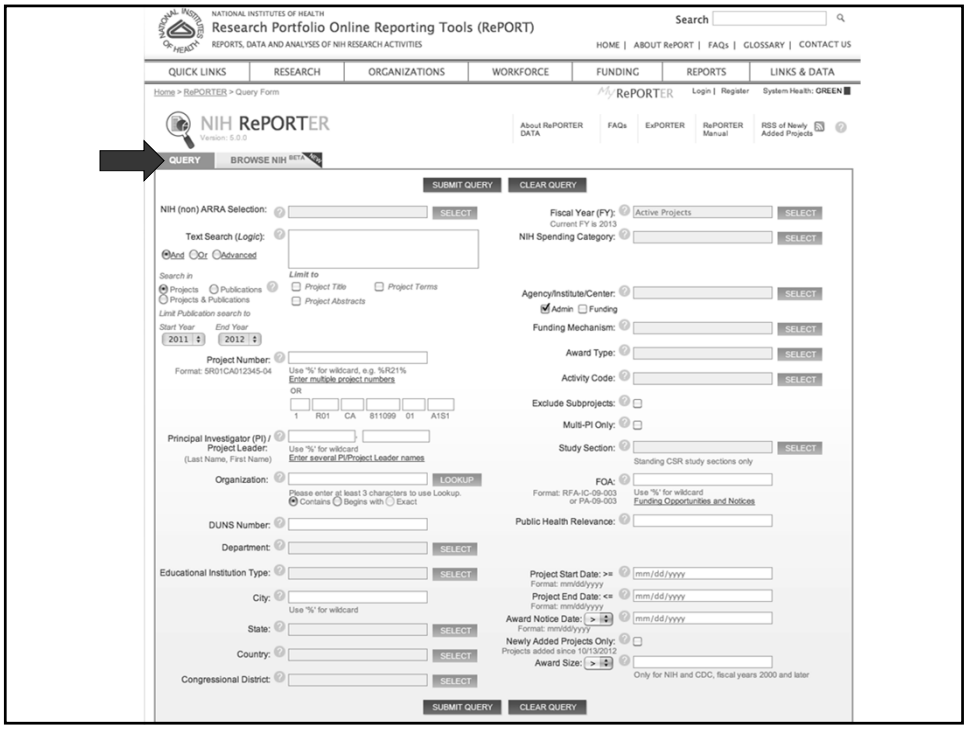
Legionnaires' disease is a rapidly progressive, deadly disease caused by the bacteria *Legionella pneumophila,* which replicates in cells of infected individuals (host). To replicate itself inside the host cell, bacteria injects ~150 proteins. Our research will use a large-scale approach to identify the targets of these injected bacterial proteins, thereby identifying the host cell proteins that are destabilized by the injected bacterial proteins. Once we identify which bacterial proteins are manipulating which host proteins, we can disrupt these interactions, halting the disease. This study will lead to new highly effective classes of antibiotics to treat bacterial infection responsible for Legionnaires' disease.

Read Sample Grants at NIAID



Institute Research Priorities





NIH Reporter

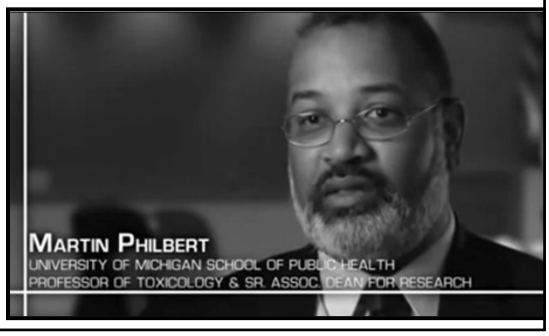
Search By:

- Keywords
- PI names
- Institution
- Project name/number
- Type of award (K, P, R, F, etc)
- Study section

Peer Reviewer Advice

NIH Advice

- "If you do not immediately convey the essence of why this work is important, then no matter how good the idea is, it's lost!"
- "Use grantsmanship—conveying clearly and repetitively what you want to do, why it's important, and how it will advance the science."



NIH Advice

- "Most common error, particularly with new investigators is over ambitiousness—trying to *cover too much territory with the time allotted, reflected in their aims page"*

Follow an Outline

- Consider the grant as a unit to establish a logical progression from Specific Aims through Approach
- Eliminates disorganized, illogical thought and poor transitions
- Eliminates redundancies and omissions
- Provides fixed points of reference that reduces complex revisions and eliminates redundancies
- Forces brevity, clarity, and a cohesive application

Thank You

Christopher Dant
medcomconsul@gmail.com