NIH Grants: The Overall Process

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H.A. and Edna Benning Presidential Professor of Pediatrics
Professor of Biomedical Informatics
University of Utah School of Medicine

Grant Writing Workshop
Outline of Presentation

- Why the NIH?
- Types of NIH grants
- Overall process of NIH grants
  - Criteria for selection
- NIH Study Section
Why go to the NIH for EMSC?

- EMSC program total budget approximately $20,000,000
- NIH total budget approximately $32,000,000,000
- The NIH budget is 1,600 times the EMSC budget

- Go where the money is.
NIH Budget Since 2008

NIH Total Funding (dollars in billions)

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<tr>
<th>Fiscal Year</th>
<th>Funding (in billions)</th>
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<td>2008</td>
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<td>2009</td>
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<td>2009 (ARRA)</td>
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<tr>
<td>2010</td>
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<td>2011</td>
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## NIH Budget Details

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<td><strong>NIEHS Interior Appropriation (Superfund)</strong></td>
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<td><strong>Total, Program Level</strong></td>
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http://grants.nih.gov/grants/oer.htm
Grants Process At-A-Glance

Planning, Writing, Submitting

Planning: Applicant should start early, collect preliminary data, and determine internal deadlines. → Writing: Applicant often begins writing application several months prior to application due date. → Submitting: Applicant organization submits most applications to NIH through Federal portal, Grants.gov.

Receipt and Referral

Months 1-3

Applications compliant with NIH policies are assigned for review by the Division of Receipt and Referral in the Center of Scientific Review (CSR). → CSR assigns application to an NIH Institute/Center (IC) and a Scientific Review Group (SRG). → Scientific Review Officer (SRO) assigns applications to reviewers and readers.

Peer Review

Months 4-8

Initial Level of Review: SRG members review and evaluate applications for scientific merit. → Priority Scores: Available to Principal Investigator on eRA Commons. → Summary Statement: Available to Principal Investigator on eRA Commons. → Second Level of Review: Advisory council/board reviews applications.

Award

Months 9-10

Pre-Award Process: IC grants management staff conducts final administrative review and negotiates award.* → Notification of Award: NIH Institute/Center (IC) issues and sends Notice of Award (NoA) to applicant institution/organization. → Congratulations! Project period officially begins!

*NIH Requests additional information needed just-in-time for award.

Post-Award Management

Administrative and fiscal monitoring, reporting, and compliance.
Primordial Soup from which You Write Grants
Relevant types of NIH grants

- R01 NIH Research Project Grant Program
- R03 NIH Small Grant Program
- R21 NIH Exploratory/Developmental Research Grant Award
- K08/K23 Mentored Clinical Scientist/Patient-Oriented Career Development Award
- K12 Mentored Clinical Scientist Development Program Awards
R01 - Research Project Grants

* This is the “staple” grant designed to fund a long-running program of research.

* Requires significant productivity, significant experience and expertise, and is highly competitive

* Amount up to $500,000 direct expenses per year without special permission, average amounts are probably $300,000 per year

* Five years duration, renewable.
Understanding the codes ... 
R01    DK    -30

Project Information

Project Number: 5R01DK020503-30
Title: PORPHYRIN BIOSYNTHESIS IN NORMAL AND DISEASE STATES

Abstract Text:
DESCRIPTION (provided by applicant): Porphyria cutanea tarda (PCT), the most common form of medicinal estrogen use. PCT is due to a reduction in the specific activity of the heme biosynthetic catalytic activity of URO-D is caused by a competitive inhibitor designated uroporphomethene, ar rings. Oxidation of the bridge carbon is mediated by P450 and iron dependent reactions. Our first which then cyclizes non- enzymatically or by oxidation of uroporphyrinogen, the fully reduced sub porphyrins by interfering wild type and mutant yeast with functional human P450 systems.
R03 Small Grants

- Limited funding for two years to support pilot or feasibility studies, collection of preliminary data, secondary analysis of existing data, small self-contained research projects

- Direct costs generally up to $50,000 per year for two years

- Not renewable
R21 Exploratory Grants

- New, exploratory and developmental research projects
- Designed for early stages of project development, can be used to generate pilot and feasibility studies
- Limited to two years of funding
- Combined direct expenses for the two year period $275,000
- No preliminary data is generally required (as advertised)
K08/K23 Career Development

- K08 is for laboratory focused research
- K23 is for patient oriented research
- Within five years of last fellowship
- Requires 75% academic protection, pays about $135,000 directs per year for up to 5 years
- Requires (really!) high quality mentor and institutional commitment to the trainee
- Large part of the grant deals with didactic training component
K12 Development Programs

* Institutional (usually) grants that subsequently give out K08/K23 type of support to selected candidates

* Pediatric CHRCDA is based in pediatric departments

* Pediatric Scientist Development Program

* Pediatric Critical Care Physician Scientist Development Program

* NHLBI Research Career Development Programs in Emergency Medicine Research (new)
Review Criteria

- Significance
- Investigator(s) - are you able to do it?
- Innovation
- Approach
- Environment - is your institution good enough?
Page Limits Are Important

✦ Monitored and enforced by the computer system

✦ Less is more - remember your reviewers are reading a lot of grants.

✦ Arial 11 Font is the smallest that you should use; many people use a 12 Font for drafts, or for final submissions

✦ Margins are 0.5 inches on all sides

✦ Don’t bother with appendices in normal circumstances.
<table>
<thead>
<tr>
<th>Section of Application</th>
<th>Activity Codes</th>
<th>Page Limits *</th>
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</thead>
<tbody>
<tr>
<td>Introduction to Revision Application</td>
<td>For all Activity Codes</td>
<td>1 page</td>
</tr>
<tr>
<td>Introduction to Resubmission Application</td>
<td>For all Activity Codes, EXCEPT Training T, D43, D71, K12, and R25 applications</td>
<td>1 page</td>
</tr>
<tr>
<td>Introduction to Revision or Resubmission Applications</td>
<td>For each project and core of multi-component applications</td>
<td>1 page</td>
</tr>
<tr>
<td>Specific Aims</td>
<td>For all Activity Codes that use an application form with the Specific Aims section</td>
<td>1 page</td>
</tr>
<tr>
<td>Research Strategy</td>
<td>For Activity Codes R03, R13/U13, R21, R36, R41, R43, Fellowships (F), SC2, SC3, X01</td>
<td>6 pages</td>
</tr>
<tr>
<td></td>
<td>For Activity Codes R01, single project U01, R10, R15, R18, U18, R21/R33, R24, R33, R34, U34, R42, R44, DP3, G08, G11, G13, UH2, UH3, SC1, X01</td>
<td>12 pages</td>
</tr>
<tr>
<td></td>
<td>For each project and core of multi-component applications, such as Program Project/Center (P)</td>
<td>Generally 6 or 12 pages**</td>
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<tr>
<td></td>
<td>For all other Activity Codes</td>
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<tr>
<td>Research Education Program Plan (uploaded via the Research Strategy)</td>
<td>For Research Education Grant Applications (R25)</td>
<td>25 pages</td>
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<tr>
<td>Combined: First four items of Candidate Information (Candidate’s Background, Career Goals and Objectives, Career Development/Training Activities During Award Period, and Training in the Responsible Conduct of Research) and Research Strategy</td>
<td>For Individual Career Development Award (K) Applications</td>
<td>12 pages</td>
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<td>Combined: Items 2-5 of Research Training Program Plan</td>
<td>For Institutional Career Development and Research Training Applications, including K12, T, D43, and D71</td>
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Thank you!
NIH Page Limits

Kurt H. Albertine, Ph.D.
University of Utah
Department of Pediatrics
## Page Limits

NIH revised 2010

<table>
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<td>12 pages</td>
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<td>Generally 6 or 12 pages**</td>
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<td>25 pages</td>
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<tr>
<td>Strategy)</td>
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<td>12 pages</td>
</tr>
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<td>Combined: First four items of Candidate Information (Candidate's Background, Career Goals and Objectives, Career Development/Training Activities During Award Period, and Training in the Responsible Conduct of Research) and Research Strategy</td>
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<td>25 pages</td>
</tr>
</tbody>
</table>

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Research Strategy

❖ Sections
- Specific Aims (1-page limit)
- Significance
- Innovation
- Impact
- Approach

Grant type-specific (e.g., K, R): 6- or 12-page limit
Thank you
Specific Aims

Kurt H. Albertine, Ph.D.
University of Utah
Department of Pediatrics
Advice for the Specific Aims Page

❖ First impression
  ● Make it count!
    ● Like a first date: you would like a second date...
  ● Often the only part that is read by most of the review panel members
  ● For these reasons, the Specific Aims page is typically the most important, and difficult, part of your proposal
Anatomy of the Specific Aims Page

✦ Purpose: Compelling synopsis of your study
✦ Organization
  ● Topic and its essential knowns
  ● Essential unknowns that are the focus
  ● Sprinkle-in your most tantalizing new datum
  ● State the overall hypothesis
  ● State the Specific Aims (only 2-4)
  ● Identify the significance, innovation, and impact of your results for the field
Guide for the Specific Aims Page

- 2-4 paragraphs: Introduce the topic, identify the problem, and describe rationale for your solution/hypothesis (main goal is to achieve a solution or test an hypothesis)
- List of 2-4 specific aims (strive for 3): These should be independent yet related (hypothesis-driven statements of scientific studies)
- State the significance, innovation, and impact of the proposal for the field
The Specific Aims Should Be

- Concise and clear
- Focused
- Hypothesis-driven
- Independent yet related
- Worthwhile, even exciting!
Why Concise and Clear?

- Concise because reviewers have little time to read and understand your grant proposal.
- Clear because reviewers have to sell your proposal to the review panel, so reviewers need to understand your proposal quickly.
- Value of being clear and concise: “Everyone is famous for 15 minutes,” but only for 15 minutes!
Be Focused: Don’t Go on a Fishing Trip!

“In addition to proposing a research design that is a fishing expedition, the applicant also proposes to use every type of bait and piece of tackle known to mankind.”
Why Hypothesis-Driven?

❖ Because this is the gold-standard of science
  ● Observation
  ● Hypothesis
  ● Test the hypothesis
    ● Experiments/controls
❖ Bottom line: one of the best things to hear at study section is “this is hypothesis-driven science!”
Why Independent Yet Related?

- Fatal flaw (aka, the kiss of death): success of a specific aim depends on success of a previous specific aim -- the aims are dependent
- Another fatal flaw: if the specific aims are not related, then the grant is viewed as unfocused
Why Worthwhile, Even Exciting?

❖ National Institutes of Health
   ● Should be relevant to improving health
   ● “Significance” criterion

❖ Grant scores reflect enthusiasm
   ● Should change the field
   ● “Impact” criterion

❖ “If all works as planned, will anyone care?”
   ● Test of significance and impact

❖ Bottom line: review panels act as advocate for society for expenditure of society’s money
Specific Aims

Specific Aim #1. To conduct a randomized double blinded trial of the efficacy of 3 agents, naltrexone, dextromethorphan and trimetazidine, to prevent neurological deficits in rats acutely poisoned with the sarin analogue diisopropylfluorophosphate (DFP).

Specific Aim #2. To conduct a randomized double blinded trial of the efficacy of naltrexone, dextromethorphan and trimetazidine to reverse the neurological deficits induced by acute poisoning with DFP.

Specific Aims

Chlorine (Cl2) is a highly irritant and reactive gas produced in large quantities throughout the world. When inhaled, Cl2, hydrolyzes to hypochlorous acid (HOCl) and its conjugate base (OCl-) that react with components of the epithelial lining fluid and epithelial cells. Products of these reactions (chloramines, lipid hydroperoxides) have considerable toxicity resulting in the formation of additional toxic intermediates and activation of inflammatory cells that mediate the injurious effects of Cl2/OCl to biological targets (reviewed in [37, 49]). When inhaled at concentrations exceeding 300 ppm, Cl2 molecules cause severe reactive airway disease (35), pulmonary edema and even death from respiratory failure (4, 5, 26, 27, 36, 44, 49, 50). In addition, exposure of rats to Cl2 causes systemic injury characterized by inflammation and endothelial dysfunction due in part to the inactivation of endothelial nitric oxide synthase an event linked to neointima formation (21).

Exciting preliminary data generated by the laboratories of the two PI’s (Drs. Pittet and Matzlou) show that exposure of mice to Cl2 concentrations that either associated with significant morbidity but no mortality (400 ppm for 30 min) or 40% mortality within 24 h post exposure (600 ppm for 45 min) result in activation of coagulation in the distal lung spaces and in the plasma, as indicated by the appearance of thrombin-antithrombin complexes in the BAL fluid and plasma, and in secondary activation of fibrinolysis in the plasma that causes hypocoagulation, as shown by a significant prolongation of clotting time. Thrombin is a well-known mediator of acute lung injury resulting in increased lung vascular permeability (18) and compromised vascular sodium transport and alveolar fluid clearance (41). In addition, it may act synergistically with reactive intermediates to activate the small GTPase RhoA and suppress Rac1 that also contribute to increased alveolar permeability and pulmonary edema (6, 10, 19). Thus, we will test the central hypothesis that exposure to Cl2 gas causes the intraalveolar and systemic activation of the coagulation cascade that plays an important role in the development of lung and other organ injury. We hypothesize that Cl2 damages lung epithelial, endothelial and inflammatory cells leading to the release of tissue factor and procoagulant microparticles, as well as the shedding of thrombomodulin and endothelial protein C receptor (EPCR) via a metalloprotease-dependent mechanism (45). This results in airspace thrombin production leading to increased alveolar and microvascular permeability to plasma proteins and pulmonary edema that contribute to death from respiratory failure. Furthermore, we hypothesize that Cl2 intermediates upregulate the expression of tissue factor on endothelial cells and monocytes causing the release of circulating procoagulant microparticles via a metalloprotease-dependent mechanism (38) that results in the systemic activation of the coagulation cascade and the development of a secondary hyperfibrinolysis. Finally, we propose that post-exposure administration of activated protein C (aPC) or one of its mutant forms which either lacks anticoagulant (6) or cytoprotective (c) activity will decrease lung epithelial and vascular permeability, development of pulmonary edema and mortality. By using these mutant forms of mouse aPC, we will determine whether the protective effect of aPC depends on its anticoagulant effect or on its cytoprotective properties via the activation of the sphingosine-1-phosphate pathway in the lung endothelium (17, 46) and alveolar epithelium (34) and by direct engagement of CD11b on alveolar macrophages (9). We thus propose the following two specific aims:

Specific Aim 1. To identify the mechanisms by which Cl2 activates the alveolar and systemic coagulation cascades. Wild-type or MPO null C57BL6 mice will be exposed to Cl2 gas (600 ppm for 45 min) and returned to room air. At various intervals post-exposure, we will measure levels of tissue factor, procoagulant microparticles, thrombin-antithrombin complexes, tissue plasminogen activator, fibrin split products formation, soluble thrombomodulin and EPCR, protein C and aPC in the BAL fluid and plasma and levels of RhoA and Rac1 in lung tissues. Activation of blood coagulation and development of secondary fibrinolysis will be measured by thromboelastometry. These measurements will be correlated with physiological indices of injury including levels of cytokines, plasma proteins in the BAL fluid (as an index of alveolar permeability), sodium-driven alveolar fluid clearance and lung wet to dry weight ratio and protein permeability (as indices of lung vascular permeability).

Specific Aim 2. To determine the mechanisms by which post-exposure of activated protein C decreases Cl2-mediated activation of the coagulation cascade, lung endothelial and epithelial permeability and apoptosis and mortality of mice exposed to Cl2. For the in vitro studies, using primary cultures of rat microvascular lung endothelial and alveolar epithelial cells, we will determine the role of a wild type and two mouse aPC mutants (3kDa mutant with severely reduced anticoagulant properties and a hyperantithrombotic G3357A mutant with anti-inflammatory properties) in mediating Cl2-induced lung endothelial and epithelial permeability, inhibition of vectorial epithelial ion transport, apoptosis and activation of alveolar macrophages. For the in vivo studies, wild-type or CD11b null C57BL6 mice will be injected intramuscularly with the wild type or one of the mutant forms of aPC within 30-45 min post exposure. We will then measure survival during the next 72h and repeat the measurements outlined in Specific Aim #1.
Specific Aims:

TRPV1 channels are ion channels and polymodal nociceptors with well-established functions in sensory neurons. Pharmacological blockade of TRPV1 by agonists and desensitization of TRPV1, by agonists, are strategies in clinical use. The treatment of various medical conditions associated with neuropathic and chronic pain. However, current research has focused on developing novel therapeutic approaches to address these issues. For example, in a recent study, it was reported that the novel TRPV1 antagonist had a therapeutic effect in the treatment of neuropathic pain. This indicates the potential of TRPV1 in the development of new therapeutic strategies for pain management.

Specific Aim 1:
To design and test the activity of small molecule TRPV1 antagonists for the treatment of neuropathic pain. A novel small molecule antagonist, (1S,2R)-N-(3,4-dihydroxyphenyl)-3-phenylpropan-2-amine, was designed using computational methods and validated in in vitro and in vivo models. The results showed a significant reduction in pain behaviors, indicating the potential of this small molecule as a novel therapeutic approach for the treatment of neuropathic pain.

Specific Aim 2:
To design and test the activity of small molecule TRPV1 antagonists in preclinical models of neuropathic pain. A novel small molecule antagonist, (1S,2R)-N-(3,4-dihydroxyphenyl)-3-phenylpropan-2-amine, was designed using computational methods and validated in preclinical models. The results showed a significant reduction in pain behaviors, indicating the potential of this small molecule as a novel therapeutic approach for the treatment of neuropathic pain.
Specific Aims Page: Examples

1. Specific Aims

We have just discovered that amodiaquine (1), a well-established anti-malarial and anti-inflammatory agent, acts at low-to-sub micromolar concentrations as a non-competitive reactivator of acetylcholinesterase (ACHE) from its adducts with organophosphorous compounds (OPCs). In our preliminary results, we demonstrated this activity on two organophosphates, paraoxon and disopropyl phosphorofluoridate (DFP). A structurally unrelated anti-malarial agent, chloroquine (2) was also identified to have significantly less effective ("neutral") reactivating ability.

The central hypothesis of our proposal is that amodiaquine will be useful in vivo as a post-exposure treatment of organophosphorous poisoning. This hypothesis is supported by what is already known about the tolerable doses of amodiaquine, its pharmacokinetics, lipophilicity, ability to cross blood-brain barrier, distribution and peak concentrations, and by extrapolation of our in vitro results. The secondary hypothesis of our proposal is that amodiaquine and chloroquine provide a platform for delivery of catalytic functionalities within the active site of ACHE and, therefore, are leads for the design of second-generation reactivation agents with broad activity and low toxicity. Through the following three aims, we will obtain support for these hypotheses and for the proposed mechanism of reactivation (or we will be led to propose an alternative mechanism), providing firm foundations for development of generic agents for both prophylaxis and treatment of exposure to OPCs.

In Aim 1 we will provide a detailed characterization of the interactions of amodiaquine and its close structural analogs with acetylcholinesterase and the different adducts (ACHE-OPC) that ACHE forms with a panel of organophosphorous compounds. In order to facilitate biomedical applications and initiate the optimization processes leading to improved agents (e.g., efficacy recovery from aged adducts), we need to develop an understanding of the scope and limitations of our reactivators and of their interactions with ACHE and ACHE-OPC. In the effort described in this aim we will (i) synthesize the initial family of analogs necessary for mechanistic studies, and (ii) perform full traditional kinetic characterization of the original leads and these analogs with human, murine, and guinea pig ACHE.

In Aim 2 we will obtain crystal structures of amodiaquine and its selected analogs with ACHE. Herein, we will determine the position and orientation of amodiaquine and analogs in complexes with ACHE. In addition, we will obtain structures of chosen analogs with ACHE-OPC.

In Aim 3 we will study the ability of amodiaquine to reverse the effects of organophosphorous compounds in vivo. Using rodent models of organophosphate poisoning, we will test amodiaquine as a reactivator post-exposure to OPCs (e.g., on paraoxon or DFP). Results of these experiments will unambiguously determine whether or not amodiaquine is able to reverse inhibition of ACHE in brain tissue in vivo.

Our goal for this funding period is to establish amodiaquine as the first member of a new class of reactivators of ACHE, through the development of pre-clinical studies of post-exposure treatment. The results of our mechanistic studies will also allow us to focus medicinal chemistry efforts on generating analogs suitable for chronic administration (pre-treatment), that is, analogs without the side effects reported when amodiaquine is used for prolonged prophylaxis.

Specific Aims:
The class of chemical threat agents known as vesicants includes mustard agents, arsenicals, etc. (Smith et al, 2002). Topical exposure to these agents causes maculopapular skin lesions, blisters, and severe cutaneous inflammation. Lewisite is one of the most important vesicants, having been synthesized as a potential threat chemical in World War I. CounterACT (NITN) notes lewisite to be an important war threat chemical for which antidote/protective agents are urgently needed. This currently known antidote, British anti-lewisite (BAL) is not fully effective in diminishing lewisite's toxic effects. The exact biological mechanism by which lewisite manifests its toxicity remains undefined. Understanding this mechanism of action may lead to the development of a target-based antidote. It has been shown that lewisite exposure induces DNA alkylation, glutathione scavenging and stress response regulatory pathways (Noot et al, 2002). The process of vesication, involves facile penetration into the skin, destruction of subepidermal tissue followed by progressive digestion of anchoring filament at the epidermal-dermal junctions with concomitant capillary leakage resulting in fluid-filled microvesicles and cutaneous blisters. Percutaneous exposure may also result in systemic toxicity.

Hypothesis: We will test whether lewisite acts by rupturing cutaneous barrier functions as a result of the disruption of tight junctions and water/glycerol transport. These effects are mediated via activation of the Hippo signaling pathway, focal adhesion kinase (FAK), ubiquitin ligases, proteases such as cathepsin, and other lysosomal proteases. The acute inflammation is mediated through activation of the unfolded protein response (UPR) signaling triggered by production of lewisite-dependent reactive oxygen species (ROS) and activation of DNA damage response signaling. Crosstalk between these intricate signaling pathways results in the pathogenesis of painful blisters and necrosis. Blocking these molecular targets may therefore prevent vesication/inflammation by lewisite.

Specific Aim 1: To investigate the effects of lewisite on skin barrier function disruption, blistering and inflammation. Tight junction proteins such as claudins, occludin, zonula occulunda (ZO), etc. in epidermis and the outermost layer of hair follicles are known to be important for barrier formation. Our preliminary data show that these targets ZO through activation of the Hippo signaling pathway. In addition, proteins involved in the regulation of water/glycerol transport, aquaporins, may be disrupted in lewisite-treated animals. Here we will investigate the involvement of these proteins in lewisite-mediated skin barrier disruption and blistering. Similarly, lewisite-mediated acute inflammation may be intractable from other acute inflammatory responses induced by aberrant reactive chemicals and may involve infiltration of leukocytes, mastophages, mast cell degranulation and the release of potent common effectors such as ROS, reactive nitrogen species (RNS), chemokines, cytokines, vasoactive amines, eicosanoids, and products of proteolytic degradation. These reactions together promote painful inflammation characterized by erythema, increase in bioid skin thickness edema and blistering. The kinetics of these inflammatory responses will be determined. At the peak of the inflammatory response, we will take skin biopsies from percutaneously lewisite-treated Pithch17/SK1/H1 hairless mice to assess hyperplasia, inflammatory cells and assays of IL-6, interferon-γ, prostaglandin E2, ROS, RNS (using DCFDA), etc. We will also investigate whether UPR signaling mediates acute inflammatory effects. The murine model Pithch17/SK1/H1 hairless is highly sensitive to inflammatory agents and recapitulates the multiple pathophysiological effects of these chemicals that occur in humans.

Specific Aim 2: To screen natural/synthetic agents for potential to attenuate expression of biomarkers depicting barrier function, blistering, and inflammation and to establish their in vivo efficacy. We have selected a series of natural/synthetic chemical agents based on their known potential to block molecular targets involved in barrier function, blistering, and inflammation. Their relative ability to block these multiple molecular targets will be ranked employing in vivo normal and immunized skin keratinocytes-based assays. The two agents most efficacious in attenuating lewisite toxicity in vivo culture systems will be further evaluated in vivo in our murine model. The therapeutic window within which the selected agents block ROS production and abrogate alterations in molecular targets associated with barrier function, blistering and inflammation will be determined.

The PI and co-PI have a longstanding interest in the fields of dermatology, toxicology, biomarker assessment and molecular biology as they relate to cutaneous toxicity and inflammation. This hypothesis-driven translational research proposal focuses on agents that can block formation of lewisite-induced acute skin lesions. Furthermore the novel animal model developed as a part of the PI’s previous arsenic-related R21 award may faithfully capture the pathophysiological effects of lewisite that occur in human skin. This proposal as succinctly formulated in the RFA provides a unique opportunity to test other vesicant as well as other war threat chemicals (utilizing future submissions), and to develop a mechanism-based antidote/therapy employing this unique murine model.
Thank you
Significance and Innovation

Lenora Olson
Leaving the Specific Aim Page

Starting the Research Strategy which includes Significance, Innovation, and Approach sections
Significance

• Explain the importance of the problem or critical barrier to progress in the field that your proposed project addresses.

• Does the project address an important problem or a critical barrier to progress in the field?

• Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields.

• If the aims are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?

• Describe how the concepts, methods, technologies, treatments, services or preventative interventions that drive your field will be changed if the proposed aims are achieved.

• How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive the field?
Innovation

- Explain how
  - The proposed work challenges and seeks to shift current research or clinical practice paradigms, or
  - any refinements, improvements, or new applications of theoretical concepts, approaches, methods, instrumentation, or interventions
- Describe any novel theoretical concepts, approaches, methods, instrumentation, or interventions to be developed or used and their advantages over existing ones.
- Does application challenge/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?
In general

The Significance and Innovation Section are one paragraph each.
Significance and Innovation

• This study is significant because *lorem ipsum dolor sit amet, consectetur adipiscing elit.* *Vivamus in tristique leo.* *Praesent convallis mi vel velit ultricies nec bibendum mi sollicitudin.* *Praesent vel enim lacus, quis volutpat dui.* *Duis sit amet consectetur ipsum.* *Nulla cursus quam id sapien congue vulputate.* *Nullam vitae nunc in elit laoreet suscipit.* *Sed quis lectus tellus, vitae ullamcorper tellus.*

• This study is novel by proposing *fusce sodales nulla dui, id pellentesque urna.* *Pellentesque luctus ultricies tristique.* *Proin ante sapien, tempor a aliquet id, sollicitudin eu lorem.* *Etiam et erat at dui aliquam eleifend nec ut purus.* *Donec pulvinar, ligula eget porta malesuada, leo dui ullamcorper nunc, ullamcorper semper magna libero at velit.* *Nulla vitae condimentum sem.*
Complete this sentence

This study is significant because........
Complete this sentence

This study is innovative because........
Or
This study is novel by proposing.....
What is the difference between Significance and Impact?
Significance and Impact

• Significance addresses:
  – Why is this problem so important that it must be addressed?

• Impact addresses:
  – Probability of whether the research will exert a sustained and powerful influence on the research field.
Overall Impact

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field involved, in consideration of the five core review criteria.

How will your work change the field?
How do you get some IMPACT?

For Significance: Assume that all the experiments work-then how important will the results be?

*Is the research worth doing?*

Overall Impact: *This includes the likelihood that the experiments will actually be successful.*

*If it won’t work, it won’t have any impact, EVEN if the problem has high significance.*
IMPACT-the bottom line

Each reviewer will weigh the individual core criteria differently in coming with an assessment of Overall Impact so.....

There is no magic formula

Appeal to the reviewers and the funding agency by using language that stresses the significance and impact of your proposed work.
Impact-Examples from NIH

• This research should provide important information that can be used in developing new heart disease therapies.

• This research will contribute to the development of clinically-effective methods for reducing substance use that are provided at low or minimal cost, which will be of medical and economic benefit to all.
Significance, Innovation, and Impact Paragraphs

Kurt H. Albertine, Ph.D.
University of Utah
Department of Pediatrics
Advice for Clear Statement of Significance, Innovation, and Impact

- The easiest proposals to read and understand
  - Use subtitled heading for each topic
  - One paragraph each, 3-4 sentences, 20 words or less
  - e.g., This study is significant because…
Advice for Clear Statement of Significance, Innovation, and Impact

Place in the application?
- Be flexible
  - Where the story is the clearest
- A frequently used layout of subheadings
  - **Significance**: after the Specific Aims page
  - **Background**: next
  - **Innovation**: next (set-up Preliminary data)
  - **Preliminary data**: next
  - **Impact**: next; last paragraph before Approach section (set-up Approach)
Example of Significance and Innovation
Sections Blended with Background

A. Significance
A.1. Inflammation and its contribution to chemical injury mechanisms
Exposed to chemical threat agents, individuals often experience strong inflammatory tissue responses that contribute to morbidity and prevent tissue repair and recovery. Pulmonary exposure to chlorine triggers a toxic inflammatory response resulting in vascular leakage, cardiopulmonary depression, neutrophil infiltration, and a pulmonary edema with elevated pulmonary vein blood flow. However, inflammatory responses also occur following cutaneous exposure to these agents and to other reactive threats (10-13).

Inflammation plays an especially important role in the mechanisms of injury following exposures to threat agents with delayed health effects such as phosgene or mustard gases. While mustard gas is usually an acute and corrosive and irritating, exposure results in the buildup of oxidative tissue stress that triggers an exaggerated inflammatory response leading to the release of the skin and severe pulmonary injury (13). Authors of this study report an increase in the inflammatory response for the pre-exposure cytokine, TNF-alpha, which diminished inflammatory responses and pulmonary injury following inhalation exposure to mustard gas (14). Non-steroidal anti-inflammatory agents were shown to attenuate cutaneous inflammatory response to the skin (15).

Inhibition of pulmonary neutrophil infiltration greatly diminished injury markers and decreased mortality in rats exposed to phosgene (16). Pre-inflammatory T-cell subpopulations were shown to contribute to the inflammatory response to chlorine and phosgene (10).

Taken together, these reports support the idea that exaggerated inflammation is a major driver of progressive tissue injury hours and (even days) after the chemical threat exposure has ended. In mass casualty situations, it may not be possible to treat all exposure victims with these anti-inflammatory treatments immediately after exposure. In these cases, and as a supportive therapy, sustained anti-inflammatory treatment may prevent progression of injury and increase survival rates.

A.2. Inflammation resolution: An active mechanism driven by newly discovered omega-3 fatty acid derived mediators
The inflammatory response is divided into three temporal phases: initiation, amplification, and resolution. Classical anti-inflammatory treatments have focused on interference with target pathways involved in the maintenance and resolution of inflammation. These strategies have only been partially successful, due to the large variety of pathways and pathways involved. Our clinical approaches with cytokine inhibitors, steroids, or NSAIDs have resulted in better outcomes, suggesting continued demand for development of new strategies counteracting inflammation.

Figure 1. Structures of fatty-acid derived inflammation resolving mediators. a) Lipoxin; b) Resolvins, represented by Resolvins E1; c) protectin, represented by Protectin D1 (also known as neuroprotectin D1), adapted from (21).

A new area of inflammation research has focused on the process of inflammation resolution (22). Inflammation resolution was thought to occur due to lack of inflammatory drive when concentrations of inflammation-initiating and maintaining mediators are in decline. However, recent studies have shown that the resolution of inflammation is an active mechanism involving the activation of anti-inflammatory pathways during inflammation and the later generation of fatty-acid derived mediators that activate resolution mechanisms. These mediators include lipoxins, resolvins, and protectins (Fig. 1).

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Resolvins and protectins are omega-3 fatty acids derived from DHA (docosahexaenoic acid; 22:6n-3) or EPA (eicosapentaenoic acid; 20:5n-3), two dietary fatty acids widely consumed due to their reported anti-inflammatory effects (23). These mediators are produced enzymatically in human blood by neutrophils with increased concentrations observed following aspirin treatment. A range of G-protein-coupled receptors and ion channels were identified that bind resolvins and mediate some of their anti-inflammatory effects (24).

A.3. Therapeutic potential and clinical development of inflammation resolving mediators
Inflammation-resolving lipid mediators, when administered exogenously, have shown potent anti-inflammatory effects in a wide range of animal disease models, including lung injury models, asthma models, and models of arthritis and colitis induced by severe chemical stimuli (lipopolysaccharides, or LPS, and tumor necrosis factor alpha, TNF, respectively) (25-33). The development of inflammation resolvins and epoxyeicosatrienoic acids (EETs) is currently in Phase II or Phase III trials. In addition to anti-inflammatory effects, inflammation, and oxidative stress, inflammation-resolving agents have been shown to improve survival of sepsis, inflammation, and oxidative stress, and to modulate the immune response in murine models. Differences in the effects of these agents to those in vivo in mice may be due to the absence of the inflammatory stress response, and because of the low dosages required to initiate inflammation resolution, it is expected that these agents will display minimal side effects and toxicity.

B. Innovation
B.1. Innovative team
These studies take advantage of the expertise of the Jori laboratory at Yale University in the development and characterization of chemical hept-induced injury models and their analysis. The Jori laboratory has been funded through the CounterACT program since 2000, and was the first to identify chemoattractant TRP ion channels as direct targets for chlorate, nitric oxide, and industrial threats such as 134/135 xenon. The Jori laboratory has also discovered that the inflammation-resolving lipid mediators are produced by the body in response to inflammatory stimuli and can be used to reduce inflammation.

B.2. Innovative hypothesis: treatments and animal models
We hypothesize that accelerating inflammation resolution will attenuate the exaggerated inflammatory response following chemical threat exposure, leading to decreased morbidity and improved recovery. Our proposed studies, if funded, will be the first to investigate the role of inflammation resolution in the mechanism of chemical threat injury by threat agents. Accelerating inflammation resolution research is an exciting area of rapidly developing field showing great potential for innovative therapeutic approaches to combat exaggerated inflammatory responses occurring following chemical exposure. At this time, research conducted in the Jori laboratory has focused on threat-mitigating agents that are being used for their anti-inflammatory properties (steroids, NSAIDs, antagonists, cytokine antagonists), with mixed results, calling for clinical trials in other directions. In addition to exposure models to chlorate, nitric oxide, and other agents, we will also establish a model using human (endothelial cells) as a chemical threat to the respiratory system. This model is a significant challenge to this laboratory's experience and expertise in using human tissues and cells for modeling in vitro and in vivo toxicology and disease models.

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References

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Times NR, 11 pt
Example of Significance and Innovation
Sections Blended with Background

RESEARCH STRATEGY

1. Significance

C34 is essential to global industry and to global public health. According to the World Chlorine Council (http://www.world-chlorinecouncil.com), 32.1 million metric tons were produced globally in the United States. Roughly 100,000 tanks filled with C34 travel on U.S. railroads each year (Spill late Tribune). The accidental release of large amounts of C34 in thirty large chemical-worldwide during the last twenty years (see for example [52]) and the deliberate release of C34 during acts of terrorism by insurgents in the Iraq conflict (3, 28), caused significant mortality and morbidity to humans and animals. C34 generated from the mixing of household products (bleach with acids) as well as swimming pool accidents resulted in incidents of mild to severe bronchoconstriction especially in people with pre-existing lung diseases (49, 56). Clinical observations suggest that even casual exposure to C34 exacerabates the clinical outcome of a number of pulmonary diseases including asthma and chronic obstructive pulmonary disease (33). There were about 9,000 cases for C34 related injuries to U.S. poison control centers each year from 2000-2005 (2). Producing C34 is considered by the Department of Homeland Security to be of high risk with respect to a terrorist attack with an estimated 17.5 million 1000 hospitalizations and damages of millions of dollars (The Homeland Security Council. Planning Scenarios: Executive Summaries, 2004. 8-1).

The seventy of C34 induces lung injury varies with the level and duration of exposure (49, 54, 56). People and animals that inhale C34 at concentrations less than 30 ppm developed reversible increased mucous production driven by increased bronchoconstriction and a decreased respiratory rate (56). Predicted concentrations of C34 fluctuations at the accident site are not possible. In the Graniteville, SC accidents (52), average C34 concentrations during a 28 min exposure period were estimated to be about 0.6 ppm at 1.1 ppm down from 1.8 ppm at 6 min after the C34 release resulting in moderate to severe lung injury with lingering pulmonary dysfunction (53). Thus to mimic sublethal injury, we plan to expose mice to 200 or 400 ppm C34 which results in significant airway hyperresponsiveness (AHR) lasting up to seven days post exposure as well as distal lung injury but less than 10% mortality (14, 45, 47). AHR usually precedes airway remodeling, causing lasting airway obstruction and the development of asthma (23, 24, 30), herein we propose a series of innovative studies to understand the basic mechanisms by which C34 exposures leads to airway remodeling and develop new types of treatment. Thus we believe that the subject matter this is of high significance to the quality of C34 Research Network.

While we spent a lot of effort in designing in vivo and in vitro studies to identify novel mechanisms, we are cognizant of the fact that the emphasis of the C34 Research Program is to develop therapeutic agents capable of reversing C34 induced injury. Currently, patients exposed to C34 and developing AHR are treated with B2 agonists; however, the effectiveness of B2 agonists may be diminished in patients with viral infections (19). Furthermore, post exposure administration of B2 agonists or antagonists partially impaired AHR and airway morphological changes (14, 45, 57). Thus, there is need for the development of more targeted therapies which may be eventually combined with antivirals and B2 agonists. Based on exciting preliminary data we are exploring the possibility of targeting low molecular weight hyaluronan (LMWH), an antithrombotic agent, (48) as a potential new therapeutic for C34 induced lung injury. In addition, we have previously demonstrated that the administration of LMWH in combination with antioxidant and anti-inflamatory agents significantly reduced the severity of C34 induced lung injury (39).

Sections Blended with Background

3. Approach

Below, we will outline each Specific Aim, followed by pertinent preliminary data, rationale, experimental approach, milestones and potential problems and solutions. Because of space limitations, we will summarize briefly published findings pertinent to the aims of this application and present some key unpublished observations.

SA 1: Low/HA and reactive species contribute to the development of AHR in C34 exposed mice.

- Preliminary Data
  - A. Detection of reactive species post C34 exposure in vivo and in vitro.
    - (a) FAD-analogues and malondialdehyde (MDA) protein adducts were detected in lungs of mice exposed to C34 (400-600 ppm) and returned to room air for 4-72 h (57, 60).
    - (b) Similarly reactive intermediates were detected in cytoplasm and organelles of cells in alveolar type II epithelial cells exposed to C34 (200 ppm) and returned to room air for 1 and 24 h.
  - B. Exposure to post exposure administration of ascorbate and desferal decreased reactive intermediates to control levels, improved survival of mice and decreased injury to ATII cells (51, 60).
  - C. Exposure of rodents to C34 leads to AHR and airway injury which was ameliorated by post exposure administration of B2 agonists and antioxidants. Mice (C34-exposed) or (SpragueDawley) were exposed to C34 (400 ppm for 30 min) and returned to room air for up to 7 days. Mice and rats developed AHR (i.e. increased airway resistance following challenge with methacholine) and morphological injury to airway epithelium which persisted for 7 days later. Post exposure administration of B2 agonists or desferal, or catalase, or reactions catalase, and desferal mitigated AHR and airway injury (14, 45).

4. Innovation

In recently published studies, we and others have shown that post exposure administration of antioxidants mitigates AHR in C34 exposed mice, most likely by enhancing repair (14, 60, 41). Furthermore, studies from Dr. Johnson’s laboratory established the importance of the Transient Receptor Potential vanilloid 1 (TRPV1) channels, present in sensory airway neurons, in the development of AHR in response to low (10 ppm) concentrations of C34 (4). However, the mechanisms by which exposure to C34 to concentrations likely to be encountered in the workplace (200-400 ppm) result in the lung of mouse exposed to 400 ppm C34 (30 min) result in the lung of mouse exposed to 400 ppm C34 (30 min) as well as C34 exposed mice (30 min).

The results indicated that the interaction between low/HA with TRPV1 of alveolar macrophages and epithelial cells contributes to inflammation and airway remodeling in asthma (32), the development of AHR following ozone inhalation (16) and even the development of lung fibrosis (18, 35). Currently, the role of low/HA, TRPV1 and RhoA as well as changes in membrane potential of airway smooth muscle cells in the development of AHR in C34 exposed mice have not been elucidated. Thus we feel that our approach is highly innovative.
Example of Significance and Innovation
Sections as Distinct, Short Paragraphs

Research Strategy
A. Significance: Data on the mechanism of action underlying the chemical threat vesicant lewisite and other similar arsenicals is limited (1,2). Our proposal to investigate its effects on molecular signaling pathways including Hippo signaling and UPR that regulate tight junctions, glycerol transport, barrier disruption, and inflammation is novel and important (3). In recent studies (3), we observed that arsenic-induced cutaneous inflammation was accompanied by alterations in UPR signaling pathway and that attenuation of UPR signaling resulted in the reduction of inflammation. As requested by the RFA, the selection of small molecules in this application is based on the broad based nature of their pharmacological activities, ability to block certain key biomolecules or signaling pathways likely to involve cutaneous lesions and easy availability. The translational component of this study is an additional aspect of significance. Once proved effective in preclinical settings, the lead small molecule candidates can be tested clinically in a timely manner as they are currently approved for medical use in humans (and their toxicity profile is thus already established). We believe that our approach will be highly rewarding leading to a prospective grant application expanding the scope of this study.

B. Innovation: The signaling pathways which have been linked to the regulation of junctional proteins involved in cutaneous barrier development, if found disrupted by lewisite, will provide a highly innovative mechanism of action. The selected lead candidates with their known history of human usage if proved effective will be a novel category of mechanism-based antioxidants for lewisite and other similar arsenicals.

C. Preliminary Studies

C1. Generation and characterization of Pch1"/SKH-1 mice: Exposure to arsenicals in humans leads to various pathophysiologic alterations that may be mediated by activation of Sonic hedgehog (Shh) signaling (4), a fundamental signaling pathway (5). Recently, it has been shown that arsenic activates Shh signaling in human and murine systems (5). To recapitulate the multiple toxic manifestations of arsenicals, we hypothesized that mice carrying active Shh signaling may provide a faithful murine model for the pathogenesis of arsenicals-induced conditions in humans. C57BL/6 genetic background is resistant to chemical toxicity. We therefore crossed the Pch1"/C57BL/6 haired mice onto the SKH-1 hairless background for more than 10 generations. SKH-1 is a widely used murine model for investigating cutaneous pathophysiology. We compared Pch1"/C57BL/6 mice with Pch1"/SKH-1 (Fig. 1A) and observed that Pch1"/SKH-1 mice are uniquely susceptible to cutaneous inflammation (Fig. 1B/C) following UVB and arsenic exposure. We observed that the cutaneous inflammatory responses to various inflammatory in hamsters and hairless Pch1"/SKH-1 littersmates is qualitatively identical but differs quantitatively (Fig. 1C & data not shown), suggesting that Pch1"/SKH-1 mice are highly sensitive to even minor inflammatory triggers and can be employed to assess inflammatory signatures of even weak inflammatory. A single nucleotide polymorphism (SNP) in the terminus of Pch1 gene (Fig. 1D) was identified and found responsible for this enhanced susceptibility (6, & our unpublished data). Significantly, we determined that inflammation/cancer susceptible mouse strains to chemicals carry this SNP whereas those resistant carry wild-type Pch1 gene.

As our initial research involved creating a mouse model for environmental/industrial arsenic exposure, our preliminary data primarily address chronic effects of arsenic. However, since many of the effects of vesicating arsenicals have been found to be dependent on the presence of arsenic, and agents that chelate arsenic reduce toxic manifestation of arsenicals (4,7), we are confident that acutely altered molecular targets have significant similarities with those identified during chronic arsenic exposure. To demonstrate our ability to conduct the proposed acute studies we obtained samples (tissue lysates and paraffin fixed tissue slides) from Dr. R. Agawal (Denver) which were generated following cutaneous acute exposure of SKH-1 and C57BL/6 (shaved) mice following acute exposure (Figs. 2B & 3A). However, these effects were much weaker in C57BL/6 than in SKH-1, confirming that C57BL/6 mouse is also resistant to arsenicals and other vesicants. In addition, skin & lung tissues obtained from Dr. S. Palmiter (Birmingham) following acute whole body exposure of Balb/c mice to chlorine (6 ppm) showed the induction of identical signaling pathways These data suggest that vesicants/inflammogens-induced inflammatory signaling does not depend qualitatively on mouse strains.

Preliminary data utilizing lewisite is lacking as its access is restricted. We propose to conduct studies utilizing lewisite at Battelle Memorial Institute, Columbus, Ohio, as they have necessary clearances/appropriate government approvals. Thus, we provide evidence for our ability to successfully conduct studies investigating effects of lewisite, developing strong preliminary data for future R01/U01 submissions.

C.1. Effects of arsenic, NM and chlorine on Hippo signaling and tight junctions proteins 2012: The Hippo signaling pathway (Fig. 2E) which controls tissue growth and "organ size" checkpoint (8), has also been linked to the regulation of tissue barrier forming junctional proteins and the pathogenesis of inflammation and...
Thank you
Meeting With Your Statistician

Larry Cook, MStat, PhD
Purpose

• At some point in the grant writing process you will want to meet with a statistician
  – Discuss analytical strategies
  – Sample size/power estimation

• Describe the process
  – What to bring/be prepared to talk about
  – What to expect as your final outcome
Meeting Preparation

• Study population

• Experimental design
  – Experimental
  – Observational

• Variables, measurements, and data collections instruments
Study Population

• What is the target population?
  – Children (5 – 18) presenting to the ED with …

• How will cases be diagnosed and selected?

• If enrolling subjects
  – How will patients be identified and recruited?

• If a retrospective study
  – What data sources will be utilized?
Study Designs

• Experimental study
  – Researcher imposes a treatment/intervention
  – Clinical trials
  – Community trials

• Observational study
  – Assignment to treatment groups is outside of our control
  – Prospective
  – Retrospective
Measurements and Variables

- Define each variable and how it is measured/collected
- Variables should be specific, objective, and clearly defined
  - Example: outcome = disease remission
    - Remission will be defined as …
- Applied consistently to all study subjects
- Measured at uniform follow-up points
Meeting Results

Statistical Analysis Plan, Sample Size, and Power Analysis
Statistical Analysis Plan

• Provide a rationale and description of all analyses that will be performed (simple to complex)
  – Descriptive
  – Inferential
    • Effect Estimation and Confidence Intervals
    • Hypothesis testing
    • Statistical modeling
Statistical Analysis Plan

• What assumptions are required for the method?
  – How will assumptions be verified?
  – Is there an alternate method if assumptions are not met?

• Model selection
  – What method will be used to identify model variables?
  – How will model adequacy be measured?
Power and Sample Size Calculations

• **Power** is the ability to detect a meaningful study result if one truly exists
  – We want our tests to have high power
  – Calculate the needed sample size to achieve desired power

• Power, significance level, and sample size are all connected
  – If two are fixed then so is the third
  – ‘I want 80% power and alpha = 0.05 …’
  – ‘I will enroll 100 patients and set alpha at 0.05 …’
**Increasing Power**

- The power of a study depends on
  - $\uparrow N = \uparrow$ power
  - $\downarrow$ variability = $\uparrow$ power
  - The difference you want to be able to detect between groups (effect size)
    - $\uparrow$ effect size = $\uparrow$ power
    - The effect size should be clinically meaningful AND achievable
    - Example - the smallest difference in average cholesterol level between the intervention and control groups that is clinically meaningful
## Example Power Table

Table 5: Power estimates for Aim 1b

<table>
<thead>
<tr>
<th>% with improved household risk factors</th>
<th>5%</th>
<th>8%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td>0.46</td>
<td>0.88</td>
<td>0.99</td>
</tr>
<tr>
<td>20%</td>
<td>0.37</td>
<td>0.78</td>
<td>0.94</td>
</tr>
<tr>
<td>10%</td>
<td>0.23</td>
<td>0.53</td>
<td>0.75</td>
</tr>
<tr>
<td>5%</td>
<td>0.14</td>
<td>0.31</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Difference in repeat abuse between subjects with and without improvement in household risk factors.
Additional Analytic Considerations

• Methods for handling of missing data

• Adjustment for clustering
  – Data from multi-center studies
  – Longitudinal studies

• Adjustment for multiple comparisons
Other Things to Consider

- How will data be collected?
- How will data be stored?
  - Description of computer resources available
- Who will be responsible for ensuring data quality?
- How will HIPPA and data confidentiality regulations be met?
Remember

- Meet with your statistician early and often
- Crafting of the analysis plan and power calculations are collaborative efforts
- Care and planning up front will prevent heartache and hassles later
It’s Not All About Crunching Numbers

Care in design and implementation will be rewarded with useful and clear study conclusions .... Elaborate analytical methods will not salvage poor design or implementation of a study.

- Paul R Rosenbaum
Two More Quotes

We must decide on the way data will be collected BEFORE observing the outcome
- Thomas E. Love

The hypothesis should drive the analysis – not the other way around.
What Went Wrong?

• Waited to last second?
• Patient population?
  – Sub groups?
• Study design?
• Variables?
• Outcome?
  – How is it measured?
  – What characteristics?
Approach Section

Kurt H. Albertine, Ph.D.
University of Utah
Department of Pediatrics

The University of Utah
Division of Neonatology
Anatomy of the Approach Section

- Copy and paste the Specific Aims (do not use a thesaurus)
- Describe the methods in a general manner
  - Option: Weave-in preliminary/published data
- Describe statistical methods
- Identify anticipated results
- Identify limitations, pitfalls, and alternative approaches
- Describe detailed methods, if not published
Advice for the Approach Section

- Present detailed methods
  - If methods are standard, cite and move on
  - If methods are used by you and/or your research team members, cite and move on
  - If you do not have experience with methods, get collaborators and include their letters of support
    - Describe the methods
Example of an Approach Section

- Key Preliminary Datum Prefaces Approach -

D. APPROACH

Our approach is based on the novel discovery that prolonged MV of preterm lambs leads to epigenetic changes in the lung, notable genomic-wide hypomethylation of H3. This approach may lead to DNA hypomethylation (Figure 14, m2m2 mice) compared to HNIV or VARA mice (m1m2 mice). Accompanying DHNA hypomethylation is an apparent greater abundance of an enzyme that adds methyl groups to DNA. DNA methyltransferase 1 (DNMT1). H3 hypomethylation and DNA hypomethylation are related to altered silencing and poor epigenetic gas exchange.

![Image](https://via.placeholder.com/150)

**Figure 14** Left panel: APV appears to increase provided DNA hypomethylation in the lungs compared to HNIV or VARA/HNIV. (m1m2 mice)

In contrast, three rescue studies (m2m2, HNIV, DACM) appear to share common outcomes. The concept is represented by the red area in Figure 15. For each rescue approach, the common epigenetic outcomes with genomic-wide H3 hypomethylation and DNA hypomethylation. Improved airflow formation and better respiratory gas exchange are accomplishments. Based on these opposing outcomes with HNIV, we propose that epigenetic characteristics are likely to be important in adaptation responses to preterm birth and MV, as well as persistence of phenotype take a role. The only way to assess this idea is to use a well-characterized, chronic, long-term model of neonatal LID.

![Image](https://via.placeholder.com/150)

**Figure 15** Concept of three different interventions that share common epigenetic characteristics of prematurity outcomes (red zone). Three shared common outcomes are distinct from those of HNIV.

With the foregoing content, our proposal will test three independent, yet related, specific aims.

---

**Specific Aim 1:**

MV causes genome-wide hypomethylation of H3 and covariant modifications and DNA methylation in the lung. We hypothesize that dysregulation of genome-wide epigenetic modifications will affect the balance between mesenchymal cell proliferation and apoptosis, which will disrupt alveolar formation, and respiratory gas exchange and mechanics. Lambs will be managed by MV or HNIV for 32 hours or allowed to breathe spontaneously and recovered for up to 10 weeks. We further hypothesize that reprogramming of VARA during MV will prevent the dysregulation of pulmonary genome-wide epigenetics, histology, and respiratory gas exchange and mechanics.

**Specific Aim 2:**

MV dysregulates IGFB-1 baseline covariant modifications and DNA methylation at functionally important regions that determine gene recognition sites and transcription initiation, gene expression, and processing. We hypothesize that the histone code in pulmonary IGFB-1 will be different between MV and VARA mice. We will compare genome-wide H3K4me1 of IGFB-1 expression and loss of function of IGFB-1 during HNIV. This code will reflect the relevance of IGFB-1.

**Specific Aim 3:**

Elevated pulmonary IGFB-1 expression during MV contributes to pulmonary histological and respiratory gas exchange and mechanics. We will compare IGFB-1 expression and loss of function of IGFB-1 during HNIV. This code will reflect the relevance of IGFB-1.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Specific Aim 1</th>
<th>Specific Aim 2</th>
<th>Specific Aim 3</th>
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<tr>
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</tr>
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<td>VARA and HNIV.</td>
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**Table 2 | Specific Aim 1 | Specific Aim 2 | Specific Aim 3 |
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<td>VARA and HNIV.</td>
</tr>
</tbody>
</table>

**Data Collection and Analysis:** Outcome variables will be molecular, morphological, and physiological. Assessment will be performed daily (of ventilation) and late (3 to 5 h after ventilation) to provide important insights into initial responses and long-term consequences. Our team includes expert clinical scientists, neocardiologists, and cell and molecular biologists. We also are supported by Dr. Tony Crum (School of Medicine) and Dr. Ambrose (Hajala School of Medicine), who will guide and perform the statistical analyses. Dr. Brian M. Hyde (School of Medicine) will conduct the histopathological and statistical analyses. Their support is acknowledged.

**Anticipated Outcomes:**

We do not anticipate major problems using the preterm lambs based on our past experience. **At this stage, our success rate for 3 and 5 h is 75%.** To obtain 8-10 complete experimental groups, 10 preterm lambs will be required. Reasons for 2-4 incomplete experimental groups have been reported, premature death, and persistent hypoxia. For Specific Aim 3, we anticipate that VARA will cause genome-wide hypomethylation of IGFB-1 covariant modifications and DNA methylation in the lung. Similarly, we anticipate that VARA will cause more mesenchymal cell proliferation and less apoptosis, which will disrupt alveolar formation, respiratory gas exchange, and lung mechanics. For Specific Aim 3, we anticipate that VARA will upregulate IGFB-1 through c-kit receptor modifications and DNA methylation fully functionally important regions that determine gene recognition sites and gene transmission/interaction, and gene expression and translation. For Specific Aim 3, we anticipate that VARA will upregulate IGFB-1 expression during MV will be characterized by increased IGFB-1 expression in the lung that will disrupt lung structural and ventilatory outcomes.

**Pitfalls and Their Solutions:**

A potential limitation of the study is temporal variation in the phenotype. We will address this by evaluating the effects of VARA and VARA in rats during different stages of development. For Specific Aim 3, we anticipate that VARA will cause genome-wide hypomethylation of IGFB-1 covariant modifications and DNA methylation in the lung. Similarly, we anticipate that VARA will cause more mesenchymal cell proliferation and less apoptosis, which will disrupt alveolar formation, respiratory gas exchange, and lung mechanics. For Specific Aim 3, we anticipate that VARA will upregulate IGFB-1 through c-kit receptor modifications and DNA methylation fully functionally important regions that determine gene recognition sites and gene transmission/interaction, and gene expression and translation. For Specific Aim 3, we anticipate that VARA will upregulate IGFB-1 expression during MV will be characterized by increased IGFB-1 expression in the lung that will disrupt lung structural and ventilatory outcomes.

**Detailed Methods:** We have not present detailed methods for the preterm lamb model because we have 2 decades of experience with this species and more than a decade of experience in epigenetic research using CHIL, PT2C, RPA, and soil in the in situ methylation assays.

**Timeline:**

- Aim 1 will be accomplished in year 1.
- Aim 2 will be phased in toward the end of year 1 and completed in year 4.
- Aim 3 will be accomplished in years 3-5.
Example of an Approach Section
- Preliminary Data Blended with Approach -

C. Approach

C.1 Preliminary Data

Using RDA we measured for concentrations of cytokine expression in patients with chronic disease (CD) and for cytokine (CYT) (serum) concentrations in patients with acute disease (AD) and for cytokine (CYT) (serum) concentrations in patients with acute disease (AD). We performed a repeated measures ANOVA in order to determine if there was a significant difference between the groups. We found that the concentrations of cytokine were significantly different between the groups (p < 0.05). Both groups showed a decrease in concentration of cytokines following treatment with a specific cytokine inhibitor. The results were consistent with previous studies showing that cytokine inhibitors can decrease the production of cytokines.

C.2 Determination of key inflammatory markers in the blood

We determined the concentrations of key inflammatory markers in the blood of patients with CD and AD. The results showed that the concentrations of inflammatory markers were significantly different between the groups (p < 0.05). The cytokine inhibitor treatment significantly decreased the concentrations of inflammatory markers in both groups.

D. Preliminary data

We conducted preliminary experiments to determine the effects of the cytokine inhibitor treatment on inflammatory markers. The results showed that the treatment significantly decreased the concentrations of inflammatory markers in both groups.

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R21; 4 of 4 pages (2 pages are Preliminary Data) Times NR, 11 pt
Putting Your Grant Together

J. Michael Dean, M.D., M.B.A.
H.A. and Edna Benning Presidential Professor of Pediatrics
Professor of Biomedical Informatics
University of Utah School of Medicine

Grant Writing Workshop
What have you accomplished?

- First draft of the hardest part of the grant
  - Specific aims
  - Significance and innovation
  - Approach
- Biosketch
- Downloaded the electronic submission package
What’s next?

• If you go home and forget about this for a couple months, then you just wasted your time

• Go home and take your specific aims to colleagues

• Sit in a room and explain your specific aims to strangers

• Spend two to three weeks working on those aims until they are virtually perfect
While writing specific aims ...

- Take a leisurely break once in a while and work on the innovation paragraphs
- Work on the significance paragraphs
- These things often have some language overlap with your specific aims page, so you are really conceptually working on the same thing
- BIG PICTURE intellectual work
How much time on specific aims?

- For me I estimate I spend at least a third of my entire grant writing on the specific aims

- Not true for special program announcements where you are responding to specific requirements

- If your specific aims are good and well written, the rest of the grant will almost write itself
After the aims seem good ...

- Revise the outline of your approach section - do not use your current draft for this

- After the outline makes sense, show it to someone who has read your specific aims

- When outline makes sense to you and someone else, then take your draft material and put the pieces into the outline

- Then edit

- At this point, you should still have three or four weeks left!
While colleagues are reviewing ..

- Go over your budget carefully
- You may be able to submit your budget to your institution well before the narrative is done so they can review it well in advance
- This can speed up the submission process significantly
- Write your biosketch
- Reread the literature
- Don’t look at your grant while it is being reviewed
When should colleagues read?

- Three stages are appropriate
  - Specific aims page
  - Outline of approach in context of specific aims
  - Final draft (not a real junky draft, a near FINAL draft)

- The latter can only be read helpfully if you have left enough time for them to read it and for you to then take their advice into account and make changes

- Four weeks before deadline should be your minimum goal
After submission

- After you submit the grant, make sure it arrives
- For the NIH you must check era Commons
- After confirmation of submission, forget about the grant for a couple months
The Biosketch and its Purposes
Biosketches have new uses

- The top section is similar
- By the way, you NEED an eraCommons ID! Get one.
- Restriction to 15 relevant publications (used to be as many publications as you could fit in four pages)
- Grants that are current or within three years
- What is new? (Actually, several years old!)
Biosketch Top Section

Program Director/Principal Investigator (Last, First, Middle): BYINGTON, Carrie

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2. Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

<table>
<thead>
<tr>
<th>NAME</th>
<th>POSITION TITLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dean, Jonathan Michael</td>
<td>Professor and Vice Chairman, Department of Pediatrics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>eRA COMMONS USER NAME</th>
<th>EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIKEDEAN</td>
<td>INSTITUTION AND LOCATION</td>
</tr>
<tr>
<td></td>
<td>Northwestern University, Evanston, IL</td>
</tr>
<tr>
<td></td>
<td>Northwestern University Medical School, Chicago, IL</td>
</tr>
<tr>
<td></td>
<td>Children's Hospital of Los Angeles, Los Angeles, CA</td>
</tr>
<tr>
<td></td>
<td>The Johns Hopkins Medical Institutions</td>
</tr>
<tr>
<td></td>
<td>The Wharton School, University of PA, Philadelphia, PA</td>
</tr>
</tbody>
</table>
Personal Statements

* The biosketch is now the area where you describe why YOU are good for this project

* In past, people would somehow bury this in the narrative somewhere

* In the present, you have potentially about two full pages of your biosketch if it is appropriate

* For K awards, the biosketch is where you will put your scientific biography because there is no room in the narrative
A. Personal Statement.

I am well suited to participate as a mentor for Tellen Bennett. I have been involved with mentoring fellows and young faculty for 25 years, and have had the perspectives of department chairman, division chief, K12 program director, K12 advisory committee, and the director mentor of five K23 awardees. I participate actively in our institutional CTSA K12 efforts at faculty development, and the advisory committee of our Departmental CHRCDA K12. I am also the PI for the data coordinating centers for the NICHD Collaborative Pediatric Critical Care Research Network (CPCCRN), the HRSA Pediatric Emergency Care Applied Research Network (PECARN), and the NHLBI Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) Trials. I am the PI and director of the K12 program funded by NICHD for pediatric critical care (Pediatric Critical Care Scientist Development Program, or PCCSDP), which has funded 17 scholars over the last seven years, in multiple institutions across the United States.

Dr. Bennett has academic goals that will require probabilistic database linkage, and I have extensive experience with this technology. Dr. Larry Cook is one of my colleagues and will also provide important expertise in this area of information technology. We have published a number of papers that have used probabilistic linkage, and our center has 20 years of experience with relatively large datasets. Dr. Bennett will also benefit from exposure to randomized clinical trial design, and my role as PI of multiple network data centers will provide him access to Steering Committee meetings, when appropriate, at which he can observe the complexities of multi-institutional study design, including randomized controlled trials (RCTs). I believe it is important that he understand not only the research methods in which he concentrates (propensity adjusted association studies with large data sets), but also the alternative strategies (RCT) that are sometimes feasible.
A. Personal Statement.

I am well suited to participate in this proposal as the Principal Investigator for the Data Coordinating Center (DCC) of the NICHD Collaborative Pediatric Critical Care Research Network. I have been involved with the network's studies of critical pertussis since inception in 2005, and supervise all aspects of the DCC function for all network studies. I have collaborated with Dr. Carcillo on several projects, including a recent RCT looking at prevention of nosocomial sepsis. Since the network inception in 2005, we have implemented more than a dozen prospective critical studies, including critical pertussis, have done all the database design and statistical analyses for all projects, and have assisted network investigators with publication of over 25 peer-reviewed manuscripts.

Personal Statement.

I am well suited to participate on the proposed project concerning standardized follow up with parents after the demise of a child in the pediatric intensive care unit, with the goal of reducing negative outcomes for those parents. I have been the Principal Investigator for the Data Coordinating Center (DCC) for the NICHD Collaborative Pediatric Critical Care Research Network (CPCCRN) since its inception in April 2005, and have worked closely with Dr. Meert on a series of CPCCRN investigations concerning bereavement. The DCC has a substantial information technology infrastructure that permits highly secure transmission and storage of audio and video data that will be collected in this project, as well as a dedicated staff of project managers, data managers, and statisticians to assist with the analyses. I am also a board certified Pediatric Critical Care Medicine specialist, chief of the Division of Pediatric Critical Care, and have played leadership roles in pediatric critical care for more than 20 years.
A. Personal Statement.

I am well suited to participate as a mentor and serve on the Advisory Committee for the CHRCDA in the Department of Pediatrics. I have been involved with mentoring fellows and young faculty for 25 years, and have had the perspectives of department chairman, division chief, K12 program director, K12 advisory committee, and the direct mentor of five K23 awardees. I participate actively in our institutional CTSA K12 efforts at faculty development, and have served on the advisory committee of our Departmental CHRCDA K12 (current application) for five years. I am also the PI for the data coordinating centers for the NICHD Collaborative Pediatric Critical Care Research Network (CPCCRN), the HRSA Pediatric Emergency Care Applied Research Network (PECARN), and the NHLBI Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) Trials. I am the PI and director of the K12 program funded by NICHD for pediatric critical care (Pediatric Critical Care Scientist Development Program, or PCCSDP), which has funded 17 scholars over the last seven years, in multiple institutions across the United States. I am also on the Advisory Committee for a K12 program in emergency medicine (PI: Kuppermann, UC Davis) and a T32 program in critical care (PI: Fineman, UC San Francisco).
A. Personal Statement.

I am well suited to participate on Dr. Khemani’s advisory committee. I have been involved with mentoring fellows and young faculty for 25 years, and have had the perspectives of department chairman, division chief, K12 program director, K12 advisory committee, and the director mentor of five K23 awardees. I participate actively in our institutional CTSA K12 efforts at faculty development, and the advisory committee of our Departmental CHRCDA K12. I am also the PI for the data coordinating centers for the NICHD Collaborative Pediatric Critical Care Research Network (CPCCRN), the HRSA Pediatric Emergency Care Applied Research Network (PECARN), and the NHLBI Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) Trials. I am the PI and director of the K12 program funded by NICHD for pediatric critical care (Pediatric Critical Care Scientist Development Program, or PCCSDP), which has funded 17 scholars over the last seven years, in multiple institutions across the United States.

Dr. Khemani has academic goals that will require facility with multi-institutional clinical studies, and it is important for him to get exposure to the realities of data management and coordination in this complex setting. I am prepared to guide him through this process by allowing him to regularly visit and participate in functions at the data coordinating center in Utah, so that he will develop a complete understanding concerning data quality, integrity, completeness, and accuracy across institutions in network studies.
Write Your Personal Statement (20 Minutes)
Budgets - YOU are Responsible
Purpose of talk

• Don’t let budgets be a black box - you are responsible and can go to jail

• Most NIH grants use modules of $25,000 amounts and the budget process is too simple for us to talk about in terms of submission

• Complex grants require detailed budgets - do them in Excel first, and then have someone transfer to forms

• But how do you plan a budget? When?
How to plan budgets

- What are the categories of expenses?
  - Personnel (salary and benefits)
  - Travel
  - Equipment
  - Supplies
  - Subcontracts
  - Other expenses
Personnel

- You need (should) to identify people by name if possible

- Indicate time commitment in months - this is to eliminate any idea that you can work a 60 hour week and have 150% grant support.

- NIH owns the percent of the months regardless of your chosen number of hours in a workweek

- Benefits are generally a rate that your institution will tell you, unless you know precisely what the benefits are for specific people
Travel

- Not a major part of most grants but attend one meeting to present results is reasonable thing to think about

- If you are doing a project that requires meetings of stakeholders, you need a travel budget

- Do not forget conference expenses at hotels
What are indirect expenses?

- Expenses needed by your institution to keep the lights on in your building, provide sidewalks, and maintain football teams
- Indirect expenses are not our enemy
- Your institutional prestige will RISE if you bring in indirect dollars
- At NIH, indirect expenses are usually simply added on top of the direct expenses.
- Rarely (NIH), the TOTAL award is capped. EMSC always caps TOTAL award.
What if there is a total award cap?

• Let’s pretend your indirect rate is 50%.

• The total award possible amount is $150,000.

• How much money can you use in your budget for direct expenses?
Let’s try another one

- Your indirect rate is 25%.
- The total award amount is restricted to $250,000.
- How much money do you have available for direct expenses?
Budget narrative

- Not normally subject to page limitations
- Do not ignore this section - it is necessary for funding agency to understand your expenses
- Luckily, for modular budget, not much has to be written
- Complicated budgets need thorough narratives
General calculation rule

- Total award divided by (One plus your indirect rate)
  - $250,000 / (1.00 + 0.25) = $250,000 / 1.25 = $200,000
  - $150,000 / (1.00 + 0.50) = $150,000 / 1.50 = $100,000
When do you do the budget?

- Early

- Your initial scope of work may be impossible if it does not fit inside a reasonable budget

- I generally do a budget after I have written specific aims so that I can make sure the specific aims will fit inside the grant limitations

- Work on the detailed budget when your brain is fried from working on the grant narrative
NIH Electronic Submissions, Or,
Don’t Let This Be A Black Box
Electronic submissions

- Submission goes from your institutional authorized individual
- This does NOT mean you should trust your institution to put together the package
- Allow some extra time for review
- Download the package and put it together yourself and then give the whole package to your authorized individual to finish
- Today, we will review the entire process so it is not foreign to you
The other purpose: Putting the whole thing together

✦ We have emphasized grant writing, but there are a lot of pieces

✦ You are the investigator and you need to know the pieces

✦ If the pieces are missing, your grant might not get reviewed, AND you might not even know it is not getting reviewed.

✦ Bottom line: Your institution has to submit it, but YOU are the only one who actually cares.
NIH and other agencies serviced by eRA Commons want your investment must be submitted in response to a Funding Opportunity Announcement use by applicants who wish to submit what were formerly termed in the electronic application package for your chosen mechanism, listed Announcements. Not all Institutes and Centers participate in all FOAs participation.

The following Parent Announcements are available (sorted by Activity Announcement

[ Research (R) | Research Training (T) | Career Development ]

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<tr>
<th>Activity Code(s)</th>
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<th>Announcement Number</th>
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<td>Research Project Grant (Parent R01)</td>
<td>PA-10-067</td>
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<tr>
<td>R03</td>
<td>NIH Small Research Grant Program (Parent R03)</td>
<td>PA-10-064</td>
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<tr>
<td>R13,U13</td>
<td>NIH Support for Conferences and Scientific Meetings (Parent R13/U13)</td>
<td>PA-10-071</td>
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<td>R15</td>
<td>Academic Research Enhancement Award (Parent R15)</td>
<td>PA-10-070</td>
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</table>
This Funding Opportunity Announcement (FOA) is a reissue of PA-09-012.

Program Announcement (PA) Number: PA-10-04


This FOA must be read in conjunction with the application guidelines.
Grants.gov is your source to FIND and APPLY for federal grants. The U.S. Department of Health and Human Services is proud to be the managing partner for Grants.gov, an initiative that is having an unparalleled impact on the grant community. Learn more about Grants.gov and determine if you are eligible for grant opportunities offered on this site.

Grants.gov does not provide personal financial assistance. To learn where you may find personal help, check Government Benefits, Student Loans and Small Business Start-up Loans.

What’s New at Grants.gov

New Opportunities This Week: ...
DOWNLOAD APPLICATION PACKAGE

Note: You will need to download and install PureEdge Viewer / Adobe Reader, please click on "PureEdge Viewer" to download.

To download an application package, enter the appropriate CFDA Number and click the "Download Package" button.

CFDA Number: 

Funding Opportunity Number: PA–10–067

Funding Opportunity Competition ID:

Download Package

If you do not remember the Funding Opportunity Number for the grant opportunity, please click on the "Find Grant Opportunity" section to locate the grant opportunity and then return to this screen to enter the Funding Opportunity Number.
Download Grant Applications

Home » Applicants » Apply for Grants »

&NBSPSELECTED GRANT APPLICATIONS FOR DOWNLOAD

Download the application and its instructions by selecting the corresponding download link. Save these files to your computer for future reference and use. You do not need Internet access to read the instructions or to complete the application once you save them to your computer.

READ BELOW BEFORE YOU APPLY FOR THIS GRANT!

Before you can view and complete an application package, you MUST have the PureEdge Viewer or compatible Adobe Reader installed. Application packages are posted in either PureEdge or Adobe Reader format. You may receive a validation error using incompatible versions of Adobe Reader. To prevent a validation error, it is now recommended you uninstall any earlier versions of Adobe Reader and install the latest compatible version of Adobe Reader.

If more than one person is working on the application package, ALL applicants must be using the same software version.

Click here to download the required PureEdge Viewer and Adobe Reader if you do not have it installed already.

Additional Resources:
• Sign-up for Grants.gov Updates for the latest issues and news.
• Download Adobe Reader and PureEdge Viewer for free.
• Visit Help for FAQs and more information on Applying for grants.

Below is a list of the application(s) currently available for the CFDA and/or Funding Opportunity Number that you entered.

To download the application instructions or package, click the corresponding download link. You will then be able to save the files on your computer for future reference and use.

<table>
<thead>
<tr>
<th>CFDA</th>
<th>Opportunity Number</th>
<th>Competition ID</th>
<th>Competition Title</th>
<th>Agency</th>
<th>Instructions &amp; Application</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>PA-10-067</td>
<td>ADOBE-FORMS-B</td>
<td>Use for submissions intended for due dates of January 25, 2010 and beyond</td>
<td>National Institutes of Health</td>
<td>download</td>
</tr>
</tbody>
</table>
Please fill out the following form. You can save data typed into this form.

Grant Application Package

Opportunity Title: Research Project Grant (Parent R01)
Offering Agency: National Institutes of Health
CFDA Number: 
CFDA Description: 
Opportunity Number: PA-10-067
Competition ID: ADOBE-FORMS-B
Opportunity Open Date: 01/05/2010
Opportunity Close Date: 01/07/2013
Agency Contact: Grants Info
E-mail: GrantsInfo@nih.gov
Phone: 301-435-0714

This electronic grants application is intended to be used to apply for the specific Federal funding opportunity referenced here.

If the Federal funding opportunity listed is not the opportunity for which you want to apply, close this application package by clicking on the "Cancel" button at the top of this screen. You will then need to locate the correct Federal funding opportunity, download its application and then apply.

This opportunity is only open to organizations, applicants who are submitting grant applications on behalf of a company, state, local or tribal government, academia, or other type of organization.

* Application Filing Name: 

Mandatory Documents
- SF424 (R & R)
- Project/Performance Site Location(s)
- Research And Related Other Project Information
- Research And Related Senior/Key Person Profile
- PHS 398 Cover Page Supplement
- PHS 398 Research Plan
- PHS 398 Checklist

Optional Documents
- PHS Cover Letter
- PHS 398 Modular Budget
- Research & Related Budget
- R & R Subaward Budget Attachment(s) Form

Instructions

1. Enter a name for the application in the Application Filing Name field.
   - This application can be completed in its entirety offline; however, you will need to login to the Grants.gov website during the submission process.
   - You can save your application at any time by clicking the "Save" button at the top of your screen.
   - The "Save & Submit" button will not be functional until all required data fields in the application are completed and you clicked on the "Check Package for Errors" button and confirmed all data required fields are completed.

2. Open and complete all of the documents listed in the "Mandatory Documents" box. Complete the SF-424 form first.
   - It is recommended that the SF-424 be the first form completed for the application package. Data entered on the SF-424 will populate data fields in other mandatory and optional forms and the user cannot enter data in these fields.
   - The forms listed in the "Mandatory Documents" box and "Optional Documents" may be predefined forms, such as SF-424, forms where a document needs to be attached, such as the Project Narrative or a combination of both. "Mandatory Documents" are required for this application. "Optional Documents" can be used to provide additional support for this application or may be required for specific types of grant activity. Reference the application package instructions for more information regarding "Optional Documents."
Select documents to work on

This opportunity is only open to organizations, applicants who are submitting grant applications on behalf of a company, state, local or tribal government, academia, or other type of organization.

* Application Filing Name:

Mandatory Documents
- SF424 (R & R)
- Project/Performance Site Location(s)
- Research And Related Other Project Information
- Research And Related Senior/Key Person Profile
- PHS 398 Cover Page Supplement
- PHS 398 Checklist

Mandatory Documents for Submission
- PHS 398 Research Plan

Optional Documents
- PHS Cover Letter
- PHS 398 Modular Budget
- Research & Related Budget
- R & R Subaward Budget Attachment(s) Form

Optional Documents for Submission

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# PHS 398 Research Plan

## 1. Application Type:

From SF 424 (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is repeated for your reference, as you attach the appropriate sections of the Research Plan.

*Type of Application:

- [ ] New
- [ ] Resubmission
- [ ] Renewal
- [ ] Continuation
- [ ] Revision

## 2. Research Plan Attachments:

Please attach applicable sections of the research plan, below.

1. **Introduction to Application**
   
   (for RESUBMISSION or REVISION only)

2. **Specific Aims**

3. **Research Strategy**

4. **Inclusion Enrollment Report**

5. **Progress Report Publication List**

### Human Subjects Sections

6. **Protection of Human Subjects**

7. **Inclusion of Women and Minorities**

8. **Targeted/Planned Enrollment Table**

9. **Inclusion of Children**

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### Other Research Plan Sections

<table>
<thead>
<tr>
<th>Section</th>
<th>Add Attachment</th>
<th>Delete Attachment</th>
<th>View Attachment</th>
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</thead>
<tbody>
<tr>
<td>10. Vertebrate Animals</td>
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<td>11. Select Agent Research</td>
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<td>12. Multiple PD/PI Leadership Plan</td>
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<td>13. Consortium/Contractual Arrangements</td>
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<td>14. Letters of Support</td>
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<td>15. Resource Sharing Plan(s)</td>
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<td>16. Appendix</td>
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Summary

- Virtually all NIH grants are submitted electronically
- I have shown you the web trail to get started
- You MUST use Adobe Reader or Acrobat to open the package - other PDF readers do not work
- You should NOT trust your institutional officials to put this together though they must submit the application
- CHECK in era Commons to make sure it got submitted properly
NIH Reporter Demonstration
http://report.nih.gov
NIH Critique Document

Application #:
Principal Investigator(s):

**Overall Impact**

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following five scored review criteria, and additional review criteria. An application does not need to be strong in all categories to be judged likely to have major scientific impact.

<table>
<thead>
<tr>
<th>Overall Impact</th>
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<tbody>
<tr>
<td>Strengths</td>
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<td>Weaknesses</td>
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<tr>
<th>Scored Review Criteria</th>
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<tr>
<td>Reviewers will consider each of the five review criteria below in the determination of scientific and technical merit, and give a separate score for each.</td>
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<table>
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<tr>
<th>1. Significance</th>
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<td>Strengths</td>
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<td>Weaknesses</td>
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<th>2. Investigator(s)</th>
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<th>3. Innovation</th>
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<td>Strengths</td>
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<td>Weaknesses</td>
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</tbody>
</table>
4. **Approach**

**Strengths**
- 

**Weaknesses**
- 

5. **Environment**

**Strengths**
- 

**Weaknesses**
- 

**Additional Review Criteria**
As applicable for the project proposed, reviewers will consider the following additional items in the determination of scientific and technical merit, but will not give separate scores for these items.

- Responses for Protections for Human Subjects, Vertebrate Animals, and Biohazards are **required for all applications**.
- A response for Inclusion of Women, Minorities and Children is **required** for applications proposing Human Subjects Research.

**Protection of Human Subjects**

**Inclusions (women, minorities, children)**

**Vertebrate Animals**

**Biohazards**

**Resubmission**

**Renewal**

**Revision**

**Additional Review Considerations**

- Applications from Foreign Countries
- Select Agents
- Resource Sharing Plan
- Budget and Period of Support

**Additional Comments to Applicant**
Reviewers’ Bottom Line: Overall Impact

- Significance and Innovation
- Investigators
- Approach
- Environment
Be a Thoughtful Writer

- Each reviewer has 10-15 grants assigned
- Be thoughtful: reviewers have a life, too (clinical service, teaching, research, family; their manuscripts and grant applications)
- Reviewers hope that at least 1, or 2 if they are lucky, of “their” grants will receive a fundable priority score
Thank you