Scientific Grant Writing
August 22-24, 2012

NEDARC
The National EMSC Data Analysis Resource Center
NIH Grants: The Overall Process

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
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)

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>2008</th>
<th>2009</th>
<th>2009 (ARRA)</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
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<tbody>
<tr>
<td></td>
<td>29.6</td>
<td>30.6</td>
<td>10.4</td>
<td>31.2</td>
<td>30.9</td>
<td>32.0</td>
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</table>
FY 2012 NIH Budget

$32.0 Billion – Estimated Percent Total by Mechanism

- Research Centers: 9.5%
- Intramural Research: 10.6%
- Research & Development Contracts: 11.1%
- Research Training: 2.5%
- Research Management and Support: 4.8%
- Other Research, Superfund, Office of the Director: 8.2%
- Facilities Construction: 0.4%
- Research Project Grants: 52.9%
## NIH Budget Details

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>2010</th>
<th>2011 *</th>
<th>2012</th>
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<tr>
<td>Research Project Grants (dollars)</td>
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<td>[ # of Non-Competing Grants ]</td>
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<td>[25,936]</td>
<td>[26,019]</td>
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<td>[ # of New/Competing Grants]</td>
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<td>[8,734]</td>
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<td>[544]</td>
<td>[557]</td>
</tr>
<tr>
<td>Buildings and Facilities</td>
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<td>108</td>
<td>134</td>
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<tr>
<td>NIEHS Interior Appropriation (Superfund)</td>
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<td>79</td>
<td>81</td>
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<tr>
<td><strong>Total, Program Level</strong></td>
<td><strong>31,243</strong></td>
<td><strong>30,943</strong></td>
<td><strong>31,987</strong></td>
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</table>
http://grants.nih.gov/grants/oer.htm
Grants Process At-A-Glance

The following NIH "Grants Process At-A-Glance" chart is provided as a sample of the general time element necessary for a competing application to proceed from Receipt and Referral through the Peer Review process to negotiation and award.

**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
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>
</tr>
</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>Research Education Program Plan (uploaded via the Research Strategy)</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>Research Education Program Plan (uploaded via the Research Strategy)</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>
</tr>
<tr>
<td>Research Education Program Plan (uploaded via the Research Strategy)</td>
<td>For all other Activity Codes</td>
<td>Follow FOA instructions</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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<tr>
<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>
<td>25 pages</td>
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</tbody>
</table>
Thank you!
NIH Page Limits

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

The University of Utah
Division of Neonatology
# Page Limits

NIH revised 2010

| Section of Application | Activity Codes | Page Limits *
|------------------------|----------------|-----------------
| Introduction to Revision Application | For all Activity Codes | 1 page
| Introduction to Resubmission Application | For all Activity Codes, EXCEPT Training T, D43, D71, K12, and R25 applications | 1 page
| For institutional Training (T), International Training (D43, D71), Insitit Career Awards (K12), and Research Education Apps (R25) | 3 pages
| Introduction to Revision or Resubmission Applications | For each project and core of multi-component applications | 1 page
| Specific Aims | For all Activity Codes that use an application form with the Specific Aims section | 1 page
| Research Strategy | For Activity Codes R03, R13/U13, R21, R36, R41, R43, Fellowships (F), SC2, SC3, X01 | 6 pages
| 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 | 12 pages
| For each project and core of multi-component applications, such as Program Project/Center (P) | Generally 6 or 12 pages**
| Commercialization Plan | For R42 and R44 | 12 pages
| Biographical Sketch | For all Activity Codes except DP1 and DP2 | 4 pages
| For DP1 and DP2 | 2 pages
| Education Program Plan and via the Research Strategy | Follow FOA instructions
| 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 | For Research Education Grant Applications (R25) | 25 pages
| Combined: Items 2-5 of Research Training Program Plan | For Individual Career Development Award (K) Applications | 12 pages
| For Institutional Career Development and Research Training Applications, including K12, T, D43, and D71 | 25 pages

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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

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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 tramcinolone 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 tramcinolone 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/ClO⁻/OCl⁻ to biological targets (reviewed in [37, 48]). 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 to the inactivation of endothelin nitric oxide synthase an event linked to atherosclerosis and hypertension (21). Existing preliminary data generated by the laboratories of the two PI’s (Drs. Pittet and Motakun) 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 vasoconstrictor 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 end-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 receptors (EPCR) via a metalloprotease-dependent mechanism (43). 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 myeloperoxidase (MPO)-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, 49) 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 aPC null C57BL/6 mice will be exposed to Cl₂ gas (600 ppm for 45 min) and returned them 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 vivo 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 (3K3A mutant with severely reduced anticoagulant properties and a hyperantithrombotic Cl₅₄/Δ9Aala mutant without 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 C57BL/6 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.
Novel Dual-Acute Molecules for the Treatment of Nerve Agent and Organophosphate Exposure

This application is in response to PAR-10-019, Countermeasures Against Chemical Threats (CounterACT) Exploratory / Developmental Projects in Translational Research (R21). Organophosphate (OP) nerve agents have been deployed as weapons of mass destruction in warfare arenas and in recent terrorist attacks; posing significant risks to military personnel, civilians, first responders and healthcare providers. These toxins irreversibly bind to acetylcholinesterase (AChE), thereby deactivating AChE and rendering it unable to process acetylcholine in the synapse; resulting in excitotoxic levels of acetylcholine and hypersensitization of muscarinic and nicotinic receptors. This overload of excitotoxic chemicals incapacitates the victim via cholinergic toxidrome. Currently available countermeasures for OP poisoning involve the simultaneous administration of different agents: (1) an anticholinergic agent, (2) an anticonvulsant agent, and (3) a pyridinium oxime-bearing AChE reactivator. Significant deficiencies in current OP countermeasures include: (1) the requirement for simultaneous multi-therapeutic modality treatments with implicated dosing regimens, (2) poor CNS-permeability of currently used pyridinium oximes, and (3) the complete lack of efficacy in any of the current treatments to counteract the long-term neurodegenerative sequelae that manifest after prolonged exposure to nerve agents. It has been established that inhibitors of poly(ADP-ribose)polymerase-1 (PARP-1) are useful neuroprotective agents especially when the neurodegeneration is caused by excitotoxic insult.

Specific Aim 1 To design and synthesize ligands that are dual AChE reactivators and PARP-1 inhibitors (AChE Read · PARP-1 Inh) by using the knowledge-based pharmacophore linking and merging drug discovery strategy approach (Hager Biosciences). Historically, the generation of therapeutic leads possessing multiple receptor activities has occurred either from empirical screening approaches or through specific knowledge-based design [25]. The knowledge-based approach relies on a thorough understanding of the pharmacophoric requirements of marketed drugs and historical compounds while the screening approach relies on serendipitous discovery through traditional diversity or focused screening campaigns [25]. Using this knowledge-based approach, we have designed several novel scaffold classes of small molecules that can display the pharmacophoric requirements of both the acetylcholine-reactivating activity and PARP-1 inhibition in the same small molecules. These dual pharmacophore molecules have been designed to maximize the drug design and pharmacokinetic parameters in mind synthetic feasibility and with the goal of developing chemical matter with intellectual property and freedom to operate. During this exploratory R21 grant period, we will synthesize and fully characterize (HIVAR, LCMS) prototype compounds within selected provided scaffolds (1-2 prototypes per scaffold) and have them assessed for their ability to reactivate OP-poisoned AChE at the US Army Medical Research Institute of Chemical Defense (USAMRICD) and for their ability to inhibit PARP-1. Upon identification of appropriate starting hit compounds with dual activity, we will immediately focus on probing and establishing SAR while addressing the refinement of pharmacological properties with iterative small library syntheses (10–20 compounds each library) based on selected initial dual-acting hits. Hager Biosciences has the expertise for achieving this aim as the CSO has over 25 years experience in drug discovery, where he served as Director of Medicinal Chemistry at Pfizer (legacy Wyeth); and the CEO has 18 years drug discovery experience including at Pfizer (legacy Wyeth), as a Project Team Leader.

Specific Aim 2 To design and synthesize small molecule dual ligands (AChE Read · PARP-1 Inh) that possess suitable pharmacological properties to cross the blood-brain barrier. Working strategically and stepwise through the design of both “linked” and “merged” dual-acting PARP-1 Inh compounds, a key goal in this campaign is to generate dual acting compounds with well-balanced calculated and pharmacological properties; the ADMET profiling will be outsourced to Cerep, Inc. In addition, having identified suitable dual acting biological leads and to further enhance their CNS penetration, the third design aspect will be deployed during this R21 grant period is implementing the “Bodor Principal” [62, 65] in the design of potential brain-targeting delivery chemical systems (CDs) as a metabolic “pro-drug” approach to enhance brain penetrability of our emerging leads.
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 organophosphorus compounds (OPCs). In our preliminary results, we demonstrated this activity on two organophosphates, paraxon and diisopropylphosphorofluoridate (DIPF). A structurally similar antimalarial agent, chloroquine (2) was also identified to have significantly less effective "partial" reactivating ability.

The central hypothesis of our proposal is that amodiaquine will be useful in vivo as a post-exposure treatment of organophosphate 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 general 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 organophosphorus compounds. In order to facilitate biomedical applications and initiate the optimization process leading to improved agents (e.g., efficient recovery from aged adducts), we need to develop an understanding of the scope and limitations of our reactivators and 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 those 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 complex 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 organophosphorus compounds in vivo. Using rodent models of organophosphate poisoning, we will test amodiaquine as a reactivator post-exposure to OPCs (e.g., on paraxon or DIPF). 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, thus enabling subsequent pre-clinical and 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, 2003). Topical exposure to these agents causes microvesicular skin lesions, blisters, and severe cutaneous inflammation. Lewisite is one of the most important arsenicals, having been synthesized as a potential threat chemical in World War I. CounterACT (NIH) notes lewisite to be an important war threat chemical for which antidotes/protection agents are urgently needed. The currently known antidote, British anti-lewisite (BAL) is not fully effective and does not protect against all effects. The exact biological mechanism by which lewisite mediate 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 oxidative stress regulatory pathways (Noort et al, 2002). The process of vesication, involves facile penetration of the skin, destruction of subcutaneous tissue followed by protease digestion of anchoring filaments 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/glycerin transport. These effects are mediated via activation of the Hippo signaling pathway, focal adhesion kinase (FAK), ubiquitin ligases, proteases such as cathepsin, and also 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 inflammation. Blocking these molecular targets may therefore prevent vesicant 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 occcludens (ZO), etc. in epidermis and in the outermost layer of hair follicles are known to be important for barrier formation. Our preliminary data show that arsenic targets ZO through activation of the Hippo signaling pathway. In addition, proteins involved in the regulation of water/glycerin 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 indistinguishable from other acute inflammatory responses invoked by abrasive toxic chemicals and may involve infiltration of leukocytes, macrophages, mast cell degradation and the release of potent common effectors such as ROS, reactive nitrogen species (RNS), chemokines, cytokines, vasoactive amines, eosinocides, and products of proteolytic degradation. These reactions together promote painful inflammation characterized by erythema, increase in 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 percutaneous lewisite-treated PchII†SKH-1 hairless mice to assess hyperplasia, inflammatory cells and assays of IL-6, interferon-γ, prostaglandin E2, ROS, RNS (quantitate what), SKH-1 hairless mice are only investigated whether UPR signaling plays a role in lewisite-mediated acute inflammatory effects. The murine model PchII†SKH-1 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 rated employing in vitro normal and immortalized skin keratinocytes-based assays. The agents two most efficacious in attenuating lewisite toxicity in vitro 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 program is the first of its kind to 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 fully capture the pathophysiological effects of lewisite that occur in human skin. This proposal as pre-competitive in the RFA provides a unique opportunity to uncover the true mechanism of lewisite as we as other war threat chemicals (utilizing future submissions), and to develop a mechanism-based antidote/therapy employing this unique murine model.
Thank you
Impression of Specific Aims Page

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

The University of Utah
Division of Neonatology
Strengths

- Layouts provide white space
- The “known” is identified
- Good ideas for science!
- Specific aims are obvious in the layout
Weaknesses

❖ Too much foreplay
Analogy for Focus
Weaknesses

- Missing “…the overall hypothesis/objective/purpose/question is…”
- Missing final paragraph that states the significance, innovation, and impact
- Technology looking for science
Weaknesses

- Changing (using synonyms for) keywords
  - *Low birth weight* changed to *preterm infants*

- Parallel construction
  - Ok if both/all specific aims do not have their own hypothesis
  - Not ok to change order of presentation

- Choice grammar and punctuation leads to unclear meaning

- Use of abbreviations

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What is the…

❖ Question?

❖ Answer to the question?

❖ Why is the answer important?

❖ What is innovative?
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

- Placement 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 (sets-up Approach)
A. Significance

A.1. Inflammation and its contribution to chemical injury mechanisms

Exposure to chemical threat agents often induces strong inflammatory tissue responses that contribute to morbidity and protracted repair and recovery. Pulmonary exposure to chlorides triggers a potent inflammatory response resulting in vascular leakage, cardiopulmonary depression, neutrophil infiltration and a pulmonary and systemic hypercytokinemia comparable to the cytokine storm observed in sepsis (x). Similar inflammatory responses are observed after inhalation exposure to acides (HCl) or alkaline gases (ammonia) and reactive industrial chemicals such as acrolein, and to toxic control agents (CS, CN or CS2 (8-10)). Inflammatory responses also occur following cutaneous and ocular exposures to these agents and to other reactive threats (11-15).

Inflammation plays an especially important role in the mechanisms of injury following exposures to threat agents with delayed health effects such as phosgene or sulfur mustard. While sulfur mustard is highly an acutely corrosive and irritating, exposure results in the buildup of oxidative tissue stress that triggers a highly exaggerated inflammatory response leading to vasodilation of the skin and severe pulmonary injury (4, 16). The acetic acid in the gas toxic in the pre-inflammatory cytokine, TGF-α, also diminished inflammatory responses and pulmonary injury following inhalation exposure to sulfur mustard (19). Non-steroidal anti-inflammatory agents were shown to attenuate sulfur mustard injury to the skin (19). Inhibition of pulmonary neutrophil infiltration greatly diminished pulmonary injury markers and decreased mortality in rats and mice exposed to phosgene (20). Pro-inflammatory T-cell subpopulations were shown to contribute to the inflammatory response to chlorine and acrolein (21).

Taken together these reports suggest that exaggerated inflammation is a mediator of progressive tissue injury hours (and even days) after the chemical threat exposure has ended. In many cases it is not feasible to test all exposure scenarios with threat-relevant treatments immediately after exposure. In these cases, and as a supportive therapy, sustained anti-inflammatory treatment may prevent progression of injury and improve 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 maintenance, resolution. Classical anti-inflammatory treatments have focused on interference with target pathways involved in the initiation and maintenance phases of inflammation. These strategies have only been partially successful, due to the large variety of pathways and pathologies involved. For many inflammatory conditions with symptoms resembling the outcomes of chemical threat injuries (such as, ARDS or dermatitis), clinical trials using cytokine inhibitors, steroids or NSAIDS have resulted in mixed outcomes, suggesting continued demand for development of new clinical strategies countering inflammation.

Figure 1. Structures of fatty-acid derived inflammation resolving mediators. a) A Lipoxin, b) Resolvin, represented by Resolin E1; c) a protectin, represented by Protein D1 (also named neuropotin D1), adapted from (21).

A new area of inflammation research has focused on the process of inflammation resolution (24). Inflammation resolution was thought to occur due to lack of inflammatory drive when concentrations of inflammatory mediators involved in the initiation and maintenance phases of inflammation are declining. However, recent studies have shown that the resolution of inflammation is an active mechanism involving the activation of signaling pathways during inflammation and the later generation of fatty acid-derived resolution mediators that activate resolution mechanisms. These mediators include lipoxins, resolvins and protectins (Fig. 1).

Research Strategy
Page 20

Resolvins and protectins are omega-3 fatty acids derived from DHA (docosahexaenoic acid; DHA) or EPA (eicosapentaenoic acid; EPA), two dietary fatty acids widely consumed due to their reported anti-inflammatory effects (21). 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 has been identified that bind resolvins and mediate some of their inflammation-resolving 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 (gadocedarsate, or 2,4,6-trinitrobenzene sulfonic acid, TNBS, respectively) (25-28). The development of inflammation-resolving agents as therapeutics is an active area of pharmaceutical research, with agents currently in trials in clinical trials for treatment of inflammatory eye conditions, asthma, inflammatory bowel disease, rheumatoid arthritis and cardiovascular conditions (33). Some agents, including resolvins (Resolin E1) are currently in Phase II or Phase III trials. In addition to bioavailable small molecules, new resolvins have been synthesized with improved stability and specificity (34, 35). Due to the similarity of these agents to endogenous mediators, and because of the low dose required to initiate inflammation resolution, it is hoped 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 Jorde laboratory at Yale University in the establishment and characterization of chemical threat agent-induced injury models and their analysis. Thus, Jorde’s laboratory has been funded through the CounterACT program since 2000, and was the first to identify chemoattractant TRP ion channels as direct targets for chlorine, riot control agents and industrial threats such as acrolein and inorganic, leading to CounterACT-sponsored publications in the Journal of Clinical Investigation and FASEB Journal (16, 30, 37). Current studies focus on the role of other TRP channels (TRP5 and TRPV) and kinase pathways in cutaneous and pulmonary chemical injury.

Due to the role of the pharmacological profile of lipid derived mediators (prostaglandins, sphingosine) similar to the inflammation-resolving agents to be used in the proposed study, the project will facilitate the analysis of unique inflammatory exposure models. Our subcontractor, Dr. Salih Matalon at UAB, is a long-time collaborator, and will assist access and training for the use of his high level chlorine exposure system and instrumentation for injury analysis.

B.2. Innovative hypothesis, treatments and animal models

We hypothesize that accelerating inflammation resolution may attenuate the exaggerated inflammatory response following chemical threat exposure, leading to decreased morbidity and improved recovery. We propose studies, if funded, will be the first to investigate the role of inflammation resolution in the mechanism of chemical injury by threat agents. Inflammation resolution research is an exciting new and rapidly developing field showing great potential for interventional therapies approaches to combat exaggerated inflammatory response occurring following chemical exposure. At this time, research in the CounterACT program has focused on threat-mediating agents (for example nerve agents, sulfur mustard) or anti-inflammatory treatments such as resolvins, steroids, NSAIDS, antihistamines, cytokine antagonists, with mixed results, calling for research in other directions.

In addition to exposure to chlorine, riot control agents and vesicants, we will also establish a model using capsaicin (a chemical irritant to the respiratory system. HCl is a significant chemical threat and is widely used and transported for industrial chemical processes, finishing of metal, disinfection, cleaning and construction. HCl has been released frequently following train derailments, and has been used in the preparation of terrorist attacks (44-45). However, scale exposure threats have so far not been a focus of CounterACT-supported research. The introduction of this model would close this gap and will allow testing of a variety of countermeasures candidate treatments.
Example of Significance and Innovation

Sections Blended with Background

RESEARCH STRATEGY

1. Significance

Ct is essential to global industry and to global public health. According to the World Chlorine Council (http://www.worldchlorinecouncil.com), 62.8 million metric tons were produced globally in the United States. Roughly 100,000 tonnes were produced in the United States. The accidental release of large amounts of C4 in thirty large cities worldwide during the last twenty years (see, for example, Section 5.2) and the deliberate release of C4 during acts of terrorism by insurgents in the Iraq conflict (3, 26), caused significant mortality and morbidity to humans and animals. C4 contributed to the mixing of household products (alcohol and acidic solutions) as well as swimming pool accidents resulting 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 C4 exacerbates the clinical outcome of a number of pulmonary diseases including asthma and chronic obstructive pulmonary disease (63). There were about 8,000 calls for C4-related injuries to U.S. poison control centers each year from 2000-2005 (2). Poisoning producing C4 is considered by the Department of Homeland Security to be of high risk with respect to a terrorist attack with an estimated 17,500 deaths, 125,000 hospitalizations and damage of $15 billions of dollars (http://www.ChlorineSecurity.com. Planning Scenarios: Executive Summaries. 2004; 8-1).

The severity of C4-induced lung injury varies with the level and duration of exposure (49, 54, 56). People and animals that inhale C4 at concentrations less than 100 ppm develop reversible increased mucociliary production, intracytoplasmic debris, and an increased respiratory rate (56). Precordinal measurements of C4 concentrations at the accident scene are not possible. In the Granvilleville, SC accident (52), average C4 concentrations during a 2-s exposure period were estimated to be about 560 ppm at 6.5 km from the accident site. Concentrations of the C4 release resulting in moderate to severe lung injury with lingering pulmonary dysfunction (53). Thus, while sub-lethal inhalation, we plan to expose mice to 200 or 400 ppm C4 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, 57). AHR usually precedes airway remodeling, causing lasting airway obstruction and the development of asthma (23, 34, 35). Hence we propose a series of innovative studies to understand the basic mechanisms by which C4 exposures leads to AHR and develop new forms of treatment. Thus we believe that the subject matter of this R21 is of high significance to the mission of the National Institutes of Health.

While we spent a lot of effort in designing in vivo and in vitro studies to identify novel mechanisms, we are cognizant to the fact that the emphasis of the National Institutes program is to develop therapeutic agents capable of reversing C4 induced injury. Currently, patients exposed to C4 and developing AHR are treated with B2 agonists, however the effectiveness of B2 agonists may be diminished in patients with viral infections (15). Furthermore, post exposure administration of B2 agonists to B2 agonists partially reversed AHR and did not lead to the emergence of low molecular weight hyaluronan (LWAN) and high molecular weight hyaluronan, which when administered intranasally may prevent the increase of AHR by blocking the binding of low molecular weight hyaluronan to its receptor. High molecular weight hyaluronan (1,000 kDa) has been shown to have antioxidant properties and to prevent exercise-induced bronchoconstriction in patients with asthma (43). Overall, the combination of in vivo and in vitro studies with airway smooth muscle cells, the translational studies with genetically altered mice and the new approach for the treatment of AHR based on lessons from basic studies will yield novel information likely to benefit patients exposed to C4.

2. Innovation

In recently published studies, we and others have shown that post exposure administration of antioxidants mitigates AHR in C4 exposed mice, most likely by enhancing repair (14, 45, 41). Furthermore, studies from Dr. Jordan’s laboratory established the importance of the Tight Receptor Potential Kinase 1 (TRPA1) channel in present sensory neurons in the development of AHR in response to low (50 ppm) concentrations of C4 (4). However, the mechanisms by which exposure to C4 in concentrations likely to be encountered in the workplace or in vitro (200 ppm or 400 ppm for 30 min) may result in AHR are not well understood. We suggest that interaction of iowisA with TRLA of alveolar macrophages and epithelial cells contributes to inflammation and airway remodeling in asthma (33), the development of AHA following ozone irritation (16).
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 levulose 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, glycan transport, barrier disruption, and inflammation is novel and important. 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. The optimized 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 recently been the focus of research on the regulation of junctional proteins involved in cutaneous barrier development, if found disrupted by levulose, will provide a highly innovative mechanism of action. The selected candidates are with their known history of human usage if proved effective will be a novel category of mechanism-based anticancer for levulose and other similar arsenicals.

C1. Preliminary Studies

C1.1. Generation and characterization of Pch1Tg(SKH-1) mice: Exposure to arsenicals in humans leads to various pathophysiological alterations that may be mediated by the 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 marine 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 Pch1Tg/C57BL6J 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 Pch1Tg/C57BL6J mice with Pch1Tg/SKH-1 (Fig. 1A) and observed that Pch1Tg/SKH-1 mice are uniquely susceptible to cutaneous inflammation (Fig. 1B,1C) following UVB and arsenic exposure. We observed that the cutaneous inflammatory responses to various immunogens in hairless and hairied Pch1Tg/SKH-1 littermates is qualitatively identical but differs quantitatively (Fig. 1D & data not shown), suggesting that Pch1Tg/SKH-1 mice are highly sensitive to even minor inflammatory triggers and can be employed to assess inflammatory signatures of even weak immunogens. A single nucleotide polymorphism (SNP) in the c-terminus of Perch gene (Fig. 1D) was identified and found responsible for this enhanced susceptibility (6 & our unpublished data). Significantly, we determined that immunobacterial susceptible mouse strains to chemicals carry this SNP whereas these 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 elate 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 the proposed acute studies we obtained samples (tissue lysates and paraffin fixed tissue slides) from Dr. R. Agarwal (Denver) which were generated following cutaneous acute exposure of SKH-1 and C57BL6J (shaved) mice to nitrogen mustards (NM). We showed that some of the pathways induced following chronic arsenic exposure and related to inflammation were also induced following NM exposure (Figs. 2B & 3A). However, these effects were much weaker in C57BL6 than in SKH-1, confirming that C57BL6 mouse is also resistant to arsenicals and other vesicants. In addition, skin & lung tissues obtained from Dr. S. Mahalan (Birmingham) generated following acute whole body exposure of Balb/c albino hair (shaved) mice to chlorine (6 ppm) showed the induction of identical signaling pathways. These data suggest that vesicants/denaturators-triggered inflammatory signaling does not depend qualitatively on mouse strains.

Preliminary data utilizing levulose is lacking as its access is restricted. We propose to conduct studies utilizing levulose 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 levulose, developing strong preliminary data for future R01U01 submissions.

C1.2. Effects of arsenic, NM and chlorine on Hippo signaling and tight junction 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
  – $\uparrow N = \uparrow \text{power}$
  – $\downarrow \text{variability} = \uparrow \text{power}$
  – The difference you want to be able to detect between groups (effect size)
    • $\uparrow \text{effect size} = \uparrow \text{power}$
    • 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>
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<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>
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.
Approach Section

Kurt H. Albertine, Ph.D.
University of Utah
Department of Pediatrics
Anatomy of the Approach Section 1

❖ 1st paragraph
● Briefly remind the reviewers of your proposal’s uniqueness (e.g., “Our approach is based on the novel discovery that prolonged MV [mechanical ventilation] of preterm lambs leads to epigenetic changes in the lung.”) [I define “briefly” as 1 paragraph, 3-4 sentences, with each sentence ≤ 20 words, using Arial 12-point font]

❖ 2nd paragraph
● Copy-and-paste the Specific Aims from the Specific Aims page
Anatomy of the Approach Section 2

3rd paragraph
● Provide a table/flow chart of the Specific Aims to give the reviewers a big-picture view of study design (let the reviewers see the forest)

4th paragraph
● If human subjects are involved, 1 overview paragraph about recruitment, selection, inclusion, exclusion. Place details in “Section E: Human Subjects” because Section E has no page limit
Anatomy of the Approach Section 3

- 5th, 6th, (7th) paragraphs
  - Specific Aim 1
    - Approach; may place preliminary data here to demonstrate feasibility
    - Statistics
    - Expected results
    - Pitfalls, limitations, alternative approaches
  - Subsequent Specific Aims: Repeat the outline
    - If elements are common to Specific Aim 1, so state and refer to that aim

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Anatomy of the Approach Section 4

n\textsuperscript{th} paragraph

- Detailed methods
  - If you and/or co-I\-s published the methods, so state, with citation(s); move on
  - If methods are new for you and your group, describe in detail or
  - Recruit collaborators, in which case get letters of support and cite their papers; move on

Next-to-final paragraph

- Timeline (graphic or words)
Final paragraph

● End on a positive note about feasibility and impact
  ● May copy the final paragraph from the Specific Aims page and paste here
Example of an Approach Section

- Key Preliminary Datum Prefaces Approach

D. APPROACH

Our approach is based on the novel discovery that prolonged MV of prem tonal leads to epigenetic changes in the lung, notable gene expression regulation. Key findings include:

1. MV induces a unique epigenetic signature in the lung that is associated with changes in gene expression.
2. MV alters DNA methylation patterns, leading to altered gene expression.
3. MV changes the micro-environment in the lung, affecting cell growth and differentiation.

In contrast, there is evidence that MV without exposure to hyperoxia does not cause similar changes.

Is this the end of the story? We believe not. Further studies are needed to fully understand the mechanisms underlying these changes.

Specific Aim 1: MV causes genome-wide dysregulation of 4370 covalent modifications and DNA methylation at the lung.

Specific Aim 2: MV induces an increase in DNA methylation at 1181 sites, leading to changes in gene expression.

Specific Aim 3: MV alters the expression of 1159 genes, with potential implications for lung function.

Details for each specific aim are listed in Table 1. This table summarizes the key findings and implications.

<table>
<thead>
<tr>
<th>Specific Aim 1</th>
<th>Specific Aim 2</th>
<th>Specific Aim 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analyze lung tissue samples for DNA methylation patterns.</td>
<td>Assess gene expression changes induced by MV.</td>
<td>Examine micro-environmental changes in the lung.</td>
</tr>
<tr>
<td>Quantify DNA methylation levels at specific sites.</td>
<td>Use RNA sequencing to identify gene expression changes.</td>
<td>Use imaging techniques to assess lung micro-environment.</td>
</tr>
<tr>
<td>Correlate DNA methylation patterns with gene expression changes.</td>
<td>Analyze changes in gene expression in response to MV.</td>
<td>Measure changes in micro-environmental factors.</td>
</tr>
</tbody>
</table>

Important caveat: We recognize that our study design does not take into account the possible confounding factors that could influence our findings. Further studies are needed to confirm our results.

The potential implications of these findings are vast. Understanding the mechanisms underlying these changes could lead to new therapeutic strategies for lung diseases.

Detailed Methods: We have developed novel methodologies to analyze lung tissue samples. Our approach includes sophisticated imaging techniques and advanced computational tools. We are confident that these methods will provide valuable insights into the mechanisms underlying MV-induced epigenetic changes.

Timeline: Aim 1 will be completed in years 1 and 2. Aim 2 will be phased in toward the end of year 3. Aim 3 will be completed in years 4-5.

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Example of an Approach Section

- Preliminary Data Blended with Approach -
Thank you
D. APPROACH

1st paragraph
Briefly remind the reviewers of your proposal’s innovation/novelty (e.g., “Our approach is based on the novel discovery that prolonged MV [mechanical ventilation] of preterm lambs leads to epigenetic changes in the lung.”). [I define “briefly” as 1 paragraph, 3-4 sentences, and each sentence ≤20 words, using Arial 12-point font]

2nd paragraph
Copy-and-paste the Specific Aims from the Specific Aims page

3rd paragraph
Provide a table/flow chart of the Specific Aims to give the reviewers a big-picture view of study design (let the reviewers see the forest)

4th paragraph
If human subjects are involved, 1 overview paragraph about recruitment, selection, inclusion, exclusion. Place details in “Section E: Human Subjects” because Section E has no page limit

5th paragraph
Specific Aim 1
Approach; may place preliminary data here to demonstrate feasibility
Statistics
Expected results
Pitfalls, limitations, alternative approaches

Repeat outline for each subsequent Specific Aim
If elements are common to Specific Aim 1, so state and refer to that aim

nth paragraph
Detailed methods
If methods are published by you (PI) and/or your co-Is, so state, with citation(s); move on
If methods are new for you and your group, describe in detail or recruit collaborators, in which case get letters of support and cite their papers; move on

Next-to-final paragraph
Timeline (graphic or words)

Final paragraph
End on a positive note about feasibility or impact (may copy the final paragraph from the Specific Aims page and paste here; that paragraph [see my definition, above] succinctly stated the significance, innovation, and impact of the proposal)

* Caveat for layout: Preliminary results may be placed in the Approach section, if they make a linear story. Reiterate significance, innovation, and impact where appropriate to be helpful to the reviewers (helpful reminders)
Impression of Approach
Section

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

- Consistent layout, aided by headings, subheadings, etc. that are obvious (bold, underline, italics)
- Good roadmap, using conversational explanation of plan and layout
- Use of white space
- Strong wrap-up paragraph
Weaknesses

- Use of prepositions to start sentences or clauses
  - It – Reader’s response: what?
  - There – Reader’s response: where?
  - They – Reader’s response: who?
  - This – Reader’s response: which/what?

- Change keywords or keyword phrases
Clarification

- Purpose of a study summary table in the Approach section
  - To show the key experiments and outcomes
    - Purpose: Simplify a complex study design
    - Purpose: Focus on important outcomes
    - Value: Juxtapose the experiments and results (they must be related) and the results to the hypotheses (the hypotheses must be tested)
Purpose of a study summary table in the Approach section, continued

- If your study design is not complex, probably do not need to make a study summary table
Thank you
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>EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dean, Jonathan Michael</td>
<td>INSTITUTION AND LOCATION</td>
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<td></td>
<td>NORTHWESTERN UNIVERSITY, EVANSTON, IL</td>
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<td>THE JOHN HOPKINS MEDICAL INSTITUTION</td>
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<td>POSITION TITLE</td>
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<td></td>
<td>PROFESSOR AND VICE CHAIRMAN, DEPARTMENT OF PEDIATRICS</td>
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<td>PEDIATRIC CRITICAL CARE</td>
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<td></td>
<td>BUSINESS ADMINISTRATION</td>
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</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.
About Grants

Grants Process
- Grant Application Basics
- Grants Process Overview
- Types of Grant Programs
- How to Apply
- Peer Review Process
- Award Management
- Foreign Grants Information
- NIH Financial Operations (w/Funding Strategies)

Funding

Funding Opportunities

Search Funding Opportunities:
NIH Guide for Grants and Contracts

- Funding Opportunities (RFAs, PAs) & Notices
- Unsolicited Applications (Parent Announcements)
NIH and other agencies serviced by eRA Commons want your investigation 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 Code(s))

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

Research (R) Announcements

<table>
<thead>
<tr>
<th>Activity Code(s)</th>
<th>Title</th>
<th>Announcement Number</th>
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<tbody>
<tr>
<td>R01</td>
<td>Research Project Grant (Parent R01)</td>
<td>PA-10-067</td>
</tr>
<tr>
<td>R03</td>
<td>NIH Small Research Grant Program (Parent R03)</td>
<td>PA-10-064</td>
</tr>
<tr>
<td>R13,U13</td>
<td>NIH Support for Conferences and Scientific Meetings (Parent R13/U13)</td>
<td>PA-10-071</td>
</tr>
<tr>
<td>R15</td>
<td>Academic Research Enhancement Award (Parent R15)</td>
<td>PA-10-070</td>
</tr>
</tbody>
</table>
This Funding Opportunity Announcement (FOA) is a reissue of PA-09-102.

Program Announcement (PA) Number: PA-10-003


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.

To download an application package, enter the appropriate CFDA Number and then 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 refer to the opportunity section to locate the grant opportunity and then return to this screen to enter the number.
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](https://apply07.grants.gov) 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](https://apply07.grants.gov) for the latest issues and news.
- Download [Adobe Reader](https://www.adobe.com/products/reader) and [PureEdge Viewer](https://www.pureedgeviewer.com) for free.
- Visit [Help](https://apply07.grants.gov) 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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<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>
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.

<table>
<thead>
<tr>
<th>Section</th>
<th>Add Attachment</th>
<th>Delete Attachment</th>
<th>View Attachment</th>
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<tr>
<td>1. Introduction to Application</td>
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<tr>
<td>(for RESUBMISSION or REVISION only)</td>
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<td>2. Specific Aims</td>
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<tr>
<td>3. *Research Strategy</td>
<td><strong>Highlighted</strong></td>
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<tr>
<td>4. Inclusion Enrollment Report</td>
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<tr>
<td>5. Progress Report Publication List</td>
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**Human Subjects Sections**

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<td>6. Protection of Human Subjects</td>
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<td>7. Inclusion of Women and Minorities</td>
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<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
the End!
NIH Grant Applications: Reviewers’ Perspective

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

- Significance – is the problem important?
- Investigator(s) - are you able to do it?
- Innovation – not always present
- Approach – reasonable, feasible, limitations?
- Environment - is your institution good enough?
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.

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<tr>
<th>Overall Impact</th>
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<td><strong>Strengths</strong></td>
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<td><strong>Weaknesses</strong></td>
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Scored Review Criteria

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.

1. **Significance**

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2. **Investigator(s)**

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3. **Innovation**

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4. **Approach**

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5. **Environment**

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**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

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Be a Thoughtful Writer

- Each reviewer has 10-15 grants assigned
- Reviewers have a life, too (clinical service, teaching, research, family; their manuscripts and grant applications)
- Reviewers hope that at least 1, or 2 if lucky, of “their” grants will get a fundable priority score
  - Reviewers cannot say the “F” word (not that “F” word!) in their written critique or oral presentation

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Thank you