NIH Study Sections:
What They Are and How They Function

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Director, Orthopaedic Hospital Research Center
Associate Director, Clinical and Translational Research Institute
Departments of Orthopaedic Surgery, Medicine and Molecular,
Cell & Developmental Biology
UCLA
Today’s Agenda

• The NIH peer-review process
• Your resubmission
  – Analyzing your summary statement
  – Writing your “Introduction”
The NIH Peer Review Process

OER

CSR

most R grants
SBIRs
some PAs
some RFAs

I/C

PPGs
training (T & F) grants
K grants
some PAs and RFAs

some RAs
RO Grant Path Through CSR

CSR → IRG → SRG or Study Section → Institute Council → Institute Director
Grant Path Through I/C

1. I/C
2. SRG or Study Section
3. Institute Council
4. Institute Director
Scientific Review Group (SRG)

• Membership
  – Reviewers (may include foreign reviewers)
  – Sometimes lay members

• Types of SRGs
  – “chartered”
    • Formal appointment process
    • Multiyear terms of service (usually 4-6)
  – Special Emphasis Panel (SEP)
    • Ad hoc membership
    • Usually meet on a single occasion
Scientific Review Officer (SRO)

- Works for the federal government
- Extramural scientist
- Identifies and recruits reviewers
- Manages conflict of interest
- Arranges and presides at SRG meeting
- Prepares and releases summary statements
Usual Study Section

- Usual grant load per study section: 100
- Mean grant load per reviewer:
  - Permanent member mean load: 10-13
  - Mean grant load for temporary reviewers: 4
  - Mean grant load per reviewer: 8
- Mean number of reviewers per grant: 3.5
- Average number of reviewers at each study section meeting: \(100 \times 3.5 \div 8 = 44\)
  - 15 permanent
  - 29 temporary
Study Section Composition
[ratio of experienced:junior reviewers in JSA’s study section]
Alternate Styles of Review

• Study sections
• Teleconferences
• Video-enhanced discussions
• Asynchronous electronic review
• Editorial-style review
What Happens to Your Application Before Study Section

• ~10 weeks before:
  – SRO sends a roster of apps to reviewers to identify conflicts

• ~9 weeks before:
  – SRO sends disc with all apps and assignments
  – ≥3 reviewers per app
  – Assignments based on expertise and C-of-I

• ~1 week before:
  – Reviewers post reviews and preliminary scores for all of the reviewers of the app to see
Study Section Proceedings

- Call to order by study section chair
- Introductions of reviewers and NIH staff
- SRO delivers instructions for review
- Application review [7A-6P with lunch]
  - Cluster new investigator grants, R21s and RO1s
  - Review only top half in each category
  - Start with grant having the highest preliminary score
- Call for initial scores, discussion by all reviewers, call for final scores, all study section members vote
- Discuss budget, human subject and animal use, resource sharing, overlap, etc.
- Bottom half “not discussed” unless requested
SRG or Study Section Meeting
Study Section Proceedings

- Call to order by study section chair
- Introductions of reviewers and NIH staff
- SRO delivers instructions for review
- Application review [7A-6P with lunch]
  - Cluster new investigator grants, R21s and RO1s
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- Discuss budget, human subject and animal use, resource sharing, overlap, etc.
# New Review Format

## OVERALL IMPACT

<table>
<thead>
<tr>
<th>Overall Impact</th>
<th>Please limit text to ¼ page</th>
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<tbody>
<tr>
<td>Strengths</td>
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<tr>
<td>Weaknesses</td>
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## SCORED REVIEW CRITERIA

1. **Significance**

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<tr>
<th>Strengths</th>
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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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### Bullet Point Review Format

**OVERALL IMPACT**

<table>
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<tr>
<th>Strengths</th>
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<tbody>
<tr>
<td>The most appealing experiments are those found in Specific Aim 2 (SAII) to determine if pharmacological amounts of vitamin D, 25D and 1,25D can prevent or rescue the EAE phenotype.</td>
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</table>

**Weaknesses**

- The Preliminary Studies section is virtually devoid of explanatory text for the presented figures; exactly how the reader is supposed to make use of this information as sound rationale for the presented experiments is unclear.
- The application suffers from a lack of explanation of abbreviations and jargon; examples include: MOGTCR, 2D2 mice, HUT102 cells, RGR, EL-4 cells, CD4+ CD25-T cells, FOXP3, aCD3, and aCD28.
- Preliminary data also lacks simple descriptive details like n and p values; there is not a summation of what the preliminary data purport to mean.
- The application appears to be “pasted” together; different parts display different fonts.
- Many of the outcomes in SAI experiments will be observational in nature and out of context with what is occurring within genomic DNA.
- Inclusion of experiments gauging the effects of dietary vitamin D deficiency on EAE expression would have strengthened the translational component of this work.

### SCORED REVIEW CRITERIA

1. **Significance**

   **Strengths**
   - The fairly recent discovery of IL-17 and a specialized subset of T cells that make IL-17 and an application to a study of the immunomodulatory action in the vitamin D hormone is of substantial significance.
   - Uncovering a 1,25D-IL-17 regulatory mechanism that might limit progression of mouse models of MS would also be of great significance.

   **Weaknesses**
   - The fact that vitamin D insufficiency actually increases MS risks suggests that 1,25-D must be made locally as low 25D levels will be associated with secondary hyperparathyroidism and increased production of 1,25D made by the kidney.

2. **Investigator(s)**

   **Strengths**
   - Mouse modeling of observations made “in vitro” is a major strength of Dr. Christakos.

3. **Innovation**

   **Strengths**
   - The hypotheses that 1,25D directed inhibition of IL-17 is immunosuppressive in MS is innovative.

4. **Approach**

   **Strengths**
   - The general approach here is to: 1) identify regulatory elements and their transactors in the proximal 1L-17 promoter that mediate its decreased expression under the influence of 1,25D; and 2) manipulate upward dietary vitamin D and metabolite intake and administration to alter expression of the EAE-like MS syndrome in mice.

   **Weaknesses**
   - The applicant focuses solely in the proximal 1L-17 promoter, ignoring the possible presence and function of important distant 5’, 3 and intrinsic VDREs in and around the 1L-17 gene; re-evaluation identification of such elements to “future studies” disregards the state-of-the-art VDR cis-trans relationship controlling gene expression.
   - A simple schematic in the Background and Significance or Preliminary Results section summarizing the connection among different cells, cytokines, vitamin D metabolites, and disease activity would have been very helpful to the reader.
   - In the crucial Figure 1, the disease suppressive affect of 1,25D requires doses of the hormone 10-fold greater than that which would be safe in humans; there is no indication as whether mice treated with such high doses developed hypercalcemia, hypercalciemia or died.
   - In SAI the applicant plans to study the effects of chromatin remodeling on expression of a transiently-transfected, truncated promoter-reporter construct in an extra genomic context. Should not an endogenous gene in its naturally “chromatinized” environment be the focus of study?

5. **Environment**

   **Strengths**
   - SAII and human cell experiments will take place in the Steinman Laboratory; these appear to be the most interesting experiments.
<table>
<thead>
<tr>
<th>Application #</th>
<th>Principal Investigator(s)</th>
<th>Significance</th>
<th>Investigator(s)</th>
<th>Innovation</th>
<th>Approach</th>
<th>Environment</th>
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eRA Commons
http://era.nih.gov/commons/index.cfm

• Impact/priority score posted by SRO 3 days post study section completion
• Impact/priority score calculation
  – Mean overall impact score x 10
  – Example: 2.7 x 10 = 27
The Current Timelines
“What to expect and when to expect it”

Months

0  1  2  3  4  5  6  7  8  9

OCT  NOV  DEC  JAN  FEB  MAR  APR  MAY  JUN  JUL

Submission to OER
CSR gives SRG, I/C and PD assignment

supplementary material to SRO
SRG review
score
summary statement
Council
resubmission
revision
Today’s Agenda

- The NIH peer-review process
- Your resubmission
  - Analyzing your summary statement
  - Writing your “Introduction”
Summary Statement

• Available 4-8 weeks post study section in your eRA Commons account
• “not discussed” and new investigator applications processed first
• Available only to:
  – PI of program director of the grant
  – NIH officials
  – Council members
Summary Statement Contents

• First page
  – Program officer (name and contact info)
  – Final impact/priority score or ND
  – Percentile rank if applicable
  – Budget request

• Subsequent pages
  – Description (applicant’s abstract)
  – Resume (if discussed)
  – Individual critiques (unedited) in bullet format
  – Administrative notes; budget, human subjects, etc
  – Study Section roster
SUMMARY STATEMENT

PROGRAM CONTACT: (Privileged Communication)  
Gail Jacobs  
301-435-5021  
ggjacobs@niaid.nih.gov  

Application Number: [Redacted]

Principal Investigator: [Redacted]

Applicant Organization: UNIVERSITY OF CALIFORNIA LOS ANGELES

Review Group: MID  
Microbiology and Infectious Diseases Research Committee

Meeting Date: 06/25/2009  
Council: OCT 2009  
Requested Start: 12/01/2009  

RFA/PA: PAR09-068  
PCC: M33A

Project Title: Mechanism of retinoic acid receptor induced innate immune responses

SRG Action: Impact/Priority Score: 20

Human Subjects: 30-Human subjects involved - Certified, no SRG concerns
Animal Subjects: 10-No live vertebrate animals involved for competing appl.
Gender: 1A-Both genders, scientifically acceptable
Minority: 1A-Minorities and non-minorities, scientifically acceptable
Children: 3A-No children included, scientifically acceptable
Clinical Research - not NIH-defined Phase III Trial

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<tr>
<th>Year</th>
<th>Direct Costs Requested</th>
<th>Estimated Total Cost</th>
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<tr>
<td>1</td>
<td>150,000</td>
<td>162,000</td>
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<tr>
<td>2</td>
<td>100,000</td>
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<tr>
<td>TOTAL</td>
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ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

NOTE TO APPLICANT: A new scoring system is in use for NIH grant applications [(<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-024.html>) and (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-025.html>).] The new system requires new percentile bases. Some of the new percentile bases will not be calculated until June 22, 2009. If your application is eligible for percentiling, but no percentile is currently shown, that percentile will be available in the eRA Commons after June 22, 2009.
Summary Statement Contents

• First page
  – Program officer (name and contact info)
  – Final impact/priority score or ND
  – Percentile rank if applicable
  – Budget request

• Subsequent pages
  – Description (applicant’s abstract)
  – Resume (if discussed)
  – Individual critiques (unedited) in bullet format
  – Administrative notes; budget, human subjects, etc
  – Study Section roster
Resubmissions

• Due in March, July or November for R grants
• Uses the SF424 format
  – Contains *clearly* marked revisions to the original submission
• Introduction or Section 1
  – Limited to 1 page for all R and most K grants
  – Delineates substance and sites of revisions
Adams Method for “Pink Sheet” Analysis

- Tabulate strengths (black) and weaknesses (red).
  - Be comprehensive, but
  - Don’t count the same criticism twice
  - Black:red ratios
    - >1:1; score ≤20
    - ~1:2; score ≤30
    - ~1:3; score ≤40
    - <1:4; score ≤50
    - <1:5; unscored
- Most important criticisms are those levied by more than a single reviewer.
NEW INVESTIGATOR

RESUME AND SUMMARY OF DISCUSSION: [Redacted] currently at University of California, Los Angeles, CA submitted this outstanding Research Scholar Development Award (K22) entitled “Mechanism of Retinoic Acid Receptor Induced Innate Immune Responses”. The applicant proposes to study the regulation and function of the vitamin D-mediated host defense and the role of retinoic acid and toll-like receptors (TLRs) in the innate immune response against intracellular *Mycobacteria*. The principal strengths of the application noted include: 1. outstanding candidate; the candidate has an excellent publication record and research productivity; 2. strong and clearly written research plan; 3. significance of the proposed study; 4. strong letters of reference; and 5. overall excellent career development plan.

The committee expressed enthusiasm for the candidate, who shows great potential to develop into an independent researcher. Weaknesses discussed included: 1. a paucity of human samples to be analyzed, which could lead to misinterpretation of the results; 2. concerns about the applicant’s independence since he has been in his current environment for a long time; and 3. lack of clarity in what elements of the project he can develop into an R01 grant application; whether the candidate’s project is independent of his mentors’ projects; and whether he can move to another institution with the project. The review committee recommended support of this application for two years.

DESCRIPTION (provided by applicant): Previous studies have demonstrated that activation of the RAR results in antimicrobial activity against intracellular *Mycobacterium tuberculosis*. Our preliminary work suggests that this antimicrobial activity could be mediated through activation of the vitamin D metabolic system. In addition, our data indicate that concurrent TLR and RAR activation results in amplification of both macrophage differentiation and increase in the antimicrobial response. These data suggest an important role of RAR in the innate immune response and is suggestive of a potential mechanism by which vitamin A deficiency is correlated to increase susceptibility to disease in humans. The data generated from this study should provide new avenues of research into the host defense mechanisms against *M. tuberculosis*, as well as potential therapeutic targets. This application is submitted by Dr. Philip T. Liu, an investigator in the field of immunology whose objective is to transition into an independent researcher. As part of his career development, he will receive training in translational immunology and molecular endocrinology through co-mentorship by Dr. Robert L. Modlin and Dr. John S. Adams. Also, Dr. Genhong Cheng and Dr. Martin Hewison will provide additional mentorship in their respective fields of expertise. This proposal also outlines the coursework through the K30 program at UCLA that will help Dr. Liu increase his knowledge base and improve his ability to execute translational clinical research. In the interim, Dr. Liu will be provided research space and resources with Dr. Modlin’s laboratory at the University of California at Los Angeles where Dr. Liu will have all the necessary resources to successfully complete his training. In summary, this application will serve not only to address immediate and long term scientific questions, but also the career development of Dr. Liu into a successful independent researcher.
1. Candidate:

**Strengths**

- Dr. Liu is an outstanding candidate.
- The candidate has potential to become a successful independent investigator. This is supported by a strong publication record with papers in the *Journal of Immunology* and *Science* that are related to the area of the proposed work.
- The candidate is an author on 18 research publications and six review articles. He is first-author on five of the research articles and one review article. Since 2007, 19 manuscripts were published or in press, and three are as a first-author in the *Journal of Immunology*. Thus, the candidate is productive, and his work is published in peer-reviewed, high-quality journals.
- The reference letters are very good. The candidate’s letters are highly complimentary, and they suggest the making of a strong independent scientist.
Weaknesses

2 A minor weakness is that the candidate has done both Ph.D. and post-doctoral work in the same laboratory. However, he has made an effort to broaden interactions with other scientists, which minimizes the potential for a narrow training experience.

2. Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring:

Strengths

6 The career development program for this candidate appears to be excellent. It has included needed coursework and participation in a K30 program to provide a more interdisciplinary training to investigators with an emphasis on translation research, etc.

8 The group of scientists that has advised this candidate is excellent and composed of researchers whose expertise complement the candidate’s expertise for the proposed research.

Weaknesses

- No weaknesses are noted.

3. Research Plan:

Strengths

4 The area of study is highly significant, focusing on the role of vitamin D and innate immunity against *M. tuberculosis*.

3 The research plan is clearly written, and it provides needed details that demonstrate the feasibility of the approaches proposed.

7 The research project is focused and appropriate for this candidate’s stage of research development, and the project will likely provide a foundation for a future productive independent research career.

7 The research plan will provide the candidate an opportunity to pursue his career objectives.

Weaknesses

- No weaknesses are noted.

4. Mentor(s), Consultant(s), Collaborator(s):

Strengths

9 The mentors are outstanding.

Weaknesses

- No weaknesses are noted.
Adams Method for “Pink Sheet” Analysis

• Tabulate strengths (black) and weaknesses (red).
  – Be comprehensive, but
  – Don’t count the same criticism twice
  – Black:red ratios
    • ~2:1; score ≤20  ratio: 20:10  score: 20
    • ~1:1; score ≤30
    • ~1:2; score ≤40
    • <1:3; score ≤50
    • <1:4; unscored
• Most important criticisms are those levied by more than a single reviewer.
Worth of “Pink Sheet” Analysis

• Will objectify the rationale for your score
• Provides a comprehensive “roadmap for response” in the ‘Introduction’
• Prevents you from missing individual points of critique that must be addressed in the resubmission
Writing the Introduction

• Thank the SRG for their work
• Begin on a positive note
  – Briefly “recount” the strengths noted by the SRG
• “Recount” each weakness
  – Start with most frequently noted and substantial
  – Move to least common and serious
  – Identify the site of revisions in response to stated weaknesses
• End on a positive note
Introduction to Application. The long-term objective of this proposal is to gain insight into mechanisms of innate immunity to infectious agents in humans, with particular emphasis on the role of vitamin D\textsuperscript{1} in host defense. Our own published investigation was: 1) the first to delineate a crucial role for circulating 25-hydroxyvitamin D (25D) in host defense against microbial pathogens; 2) the first to link 25D to the function of Toll-like receptors; and 3) the first to show effects of naturally-occurring variations in serum 25D levels on normal human immune responses (1). Serum 25D by its conversion to 1,25-dihydroxyvitamin D (1,25D) in macrophages acts in an intracrine fashion to orchestrate human innate immune responses to microbial pathogens, "providing the basis for a new paradigm" as stated by the reviewers. We have also shown that cathelicidin expression is required for 1,25D-induced antimicrobial activity in a macrophage cell line (2). We now propose to define the mechanism(s) by which TLR activation leads to antimicrobial activity, the role of the adaptive immune response in modulating this pathway and whether in vivo supplementation intervention of 25D-deficient individuals with a standard regimen of oral vitamin D can restore TLR-induced antimicrobial activity in vitro.

We thank the reviewers and the SRO for their helpful comments and the prompt return of the Summary Statement. The aims of our proposal were generally lauded for strengths in rationale, preliminary data and experimental design. There were several criticisms (in italics below) to which we have responded point-by-point with reference to revised or added text. In response to the major criticisms, we have extensively revised the application to: 1) expand the range of 25D and 1,25D to encompass infra- and supra-physiologic concentrations, 2) provide more mechanistic studies by adding aim 1.3 to investigate the spatiotemporal relationship of antimicrobial mediators, aim 1.2 to examine the role of T cell cytokines in modulating serum vitamin D binding protein (DBP) uptake and aim 2.3 to examine how T cell cytokines affect CYP24 regulation of 1,25D levels, 3) include more details on the clinical experiment, and 4) compare the in vitro response to 25D3 to that of 25D2. The revisions to the original review are indicated in the left column; the revisions to the A1 review are noted in the right column.

RESUME AND SUMMARY OF DISCUSSION:

1. "A major weakness is the narrow range of vitamin D (presumably 25D) to be used in studies." In response to the reviewer's concerns, we will now expand the range of our dose-response experiments with both 25D and 1,25D to cover the physiological (i.e. circulating) as well as the infra- and supra-physiological concentration (0.01-1000 nM) of both metabolites to make sure that we have covered the range of metabolite concentrations that are below and beyond that recognized to have a threshold and saturated bioresponse, respectively.

2. "Aims 1 and 2 can be more mechanistic." The research environment for this work has been greatly enhanced by the recent recruitment of John S. Adams, M.D. as director of the newly created, interdisciplinary Musculoskeletal Research Institute at UCLA. In January 2008, we will be neighbors in the just-completed Biomedical Sciences Research Building with RLM part of the Microbiology, Immunology and Molecular Genetics space equipped with a BSL3 facility. As suggested, we have included new experiments in the revised Aim 1.3 to examine the spatiotemporal regulation of antimicrobial mediators. In Aim 2 we have added new rationale and strategies to address the mechanism for cytokine regulation of the TLR-induced 25D-dependent antimicrobial pathway including regulation of the 1) the cellular uptake of 25D substrate for use by the CYP27b1-hydroxylase (revised Aim 2.2), as well as 2) expression of splice variants and activity of CYP24 gene products that influence both the catabolism of substrate 25D and product 1,25D along the non-biologically-active 24-hydroxylase pathway (revised Aim 2.3). These new experiments are focused on two novel mechanisms by which substrate 25D-to-product-1,25D are controlled. We have added more experimental detail as suggested.
4. "The use of 25(OH)D3 in all the studies described in Aims 1 and 2 contrasting with 25(OH)D2, the major circulating form in humans, was also discussed by members of the Committee." In response, we have added experiments in Aim 1.1 to compare the bioeffectiveness of D3 and D2 metabolites at similar concentrations in order to mirror that which will be occurring in the human reconstitution experiments set forth in Specific Aim 3.1. If differences are found between 25D2 and 25D3 in the TLR-induction of cathelicidin mRNA and antimicrobial activity, the two metabolites will be compared throughout Aims 1 and 2 as required. As outlined in Aim 3, we would be prepared to perform the clinical intervention experiment using vitamin D3.

CRITIQUE 1:

1. "The rationale for the aim 3.2 is not well justified." In response, we have eliminated this subaim. New preliminary data (see new Aim 3.1. and new Figures 7 and 11) strongly suggests that we will succeed in accomplishing the revised pilot "clinical experiment" set forth in new Aim 3. This will also provide leeway for the modest expansion and more mechanistically-directed experiments in Aims 1 and 2 suggested by the reviewers. To reiterate from the response to the summary of the discussion, we have added aim 1.3 to investigate the spatiotemporal relationship of antimicrobial mediators, aim 2.2 to examine the role of T cell cytokines in modulating DPB uptake and aim 2.3 to examine how T cell cytokines affect CYP24 regulation of 1,25D levels.

CRITIQUE 2:

1. Aim 1.1. "The concern on the actual ligand to be used (the Mtb 19 kDa lipoprotein) is lessened by the proposed concentration range. Are there any other ligands that could be used such as the related synthetic lipopeptide Pam3CSK4?" In addition to the synthetic M. tb. 19 kD lipopeptide, we now propose in Aim 1.1 to compare the TLR2/1-induced response with the native M. tb. 19 kD lipoprotein, the rLprG M. tb. lipoprotein, and the synthetic lipopeptide Pam3CysK4.

2. Aim 1.2. "It would have added additional insights to have considered in vitro experiments using purified components (e.g., LL37) to test its antimicrobial activity against extracellular Mtb in combination with pre-or post-treatments with in vitro-systems generating ROI/ROS. Then, experiments with infected macrophages could be designed to follow the spatiotemporal events associated with the various bactericidal actions of CDL, NO, ROS, and their dependence on TLR and D25 activation (e.g., using reporter constructs)." We appreciate this excellent suggestion by the reviewer. We have added a new Aim 1.3 to investigate the spatiotemporal relationship of antimicrobial mediators. Experiments are proposed 1) in Aim 1.1 and 1.2 regarding the time-course for the induction of mRNAs for cathelicidin, iNOS and NADPH oxidase as well as cathelicidin protein, NO and ROS, 2) in Aim 1.3 to determine whether blocking combinations of cathelicidin, NO and ROS have a synergistic effect on the antimicrobial response, and 3) in Aim 1.3 to determine the synergistic ability of cathelicidin, NO and ROS to kill extracellular M. tb.

3. "There is a descriptor that in some cases subjects would make verbal statements. It is not clear in the proposal whether written signed records would then be required." As now pointed out clearly in the Human Subjects Section 8.2.a. of the application, all signed records of consent will be written.

4. "The actual number of expected subjects to be recruited in this category is not indicated." As stated in the revised Section 11, <10% of volunteers will be between the ages of 12 and 18 years of age.

5. Biohazard safety. The Modlin lab is moving into the BSRB building 1/08, which contains a new BSL3 facility with institutional approval and training as detailed in the revised resources and environment page.
Your Resubmission

**Do:**

- Follow SF424 instructions precisely.
- Assume *all* of the initial study section comments were correct.
- Respond to *all* criticisms.
- Assume the same reviewer(s) will be seeing your revised application.
  - try to identify “your reviewer(s)” from the summary statement roster
  - write the resubmission with your reviewers’ research/expertise in mind
Your Resubmission

Do Not:

• assume you’re smarter than your reviewers
• argue with the reviewers in your response
• leave out a consideration of any criticism, regardless of how “minor” it might seem to you
• fail to have your colleague and/or mentor review your revision before resubmission
• fight with your:
  – grants and contract officer
  – IRB office
  – IACUC representative
Your Resubmission

*Fatal Flaws*

- Not marking points of revision in your resubmission
- Writing a “non-responsive” Introduction
- Writing an antagonistic (i.e. condescending) Introduction
- Resubmitting before you have the additional preliminary data requested
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