NIH Study Sections: What They Are and How They Function

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Today’s Agenda

• The NIH peer-review process and the SRG
• 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
RO Grant Path Through CSR

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

I/C

SRG or Study Section

Institute Council

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]

- Permanent: 33% [80:20]
- Temporary: 66% [50:50]
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 applications to reviewers to identify conflicts

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

• ~1 week before:
  – Reviewers post reviews and preliminary scores for all of the reviewers of the application to see
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 working lunch]
  - Order: new invest R01; established invest R01; R21
  - Review only top 40% 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 60% “not discussed” unless requested
# 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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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

Overall Impact

Strengths
- The most appealing experiments are those found in Specific Aim 2 (SALII) to determine if pharmacological amounts of vitamin D, 25D, and 1,25D can prevent or rescue the EAE phenotype.
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.

Modification of DNA by UV light

Weaknesses
- The inclusion of Dr. Lawrence Steinman, a world-leading expert in human autoimmunity especially neurologic disease, is a real strength to the application.

3. Innovation

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

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 intronic VDREs in and around the 1L-17 gene; redefining identification of such elements to “future studies” disregards the state-of-the-art VDR cis-trans relationship controlling gene expression.
- The applicant does not really test the effect of vitamin D insufficiency/deficiency on expression of the EAE phenotype.
- 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 effect 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, hypercalcemia 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
- SALI and human cell experiments will take place in the Steinman Laboratory, these appear to be the most interesting experiments.

Weaknesses

Investigator(s)

Strengths
- Mouse modeling of observations made “in vitro” is a major strength of Dr. Christakos.
# JSA SBDD Study Section Scores

<table>
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<th>Application #</th>
<th>Principal Investigator(s)</th>
<th>Significance</th>
<th>Investigator(s)</th>
<th>Innovation</th>
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*Significance: 2*
*Innovation: 1*
*Approach: 1*
*Environment: 1*
*Overall Score: 2*

*Significance: 1*
*Innovation: 3*
*Approach: 2*
*Environment: 1*
*Overall Score: 2*

*Significance: 1*
*Innovation: 2*
*Approach: 2*
*Environment: 1*
*Overall Score: 2*

*Significance: 8*
*Innovation: 7*
*Approach: 8*
*Environment: 4*
*Overall Score: 8*

*Significance: 7*
*Innovation: 8*
*Approach: 8*
*Environment: 5*
*Overall Score: 8*

*Significance: 3*
*Innovation: 3*
*Approach: 4*
*Environment: 1*
*Overall Score: 4*
eRA Commons
http://era.nih.gov/commons/index.cfm

• Impact/priority score posted by SRO ≤3 days post study section completion

• Overall impact 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
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)
  – “Overall impact” score (10-90) or ND
  – Percentile rank if applicable (1-50)
  – 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) Release Date: 07/14/2009
Gail Jacobs
301-435-5021
ggjacobsl@naiid.nih.gov

Application Number:

Principal Investigator

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: PAR09-088
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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<th>Project 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>
<td>108,000</td>
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<tr>
<td>TOTAL</td>
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<td>270,000</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)
  – “Overall impact” score (10-90) or ND
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  – 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’s publication record and research product, 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 has potential to develop into an independent researcher. Weaknesses discussed included: 1) 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, 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 data suggest 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 course work 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.
CRITIQUE 1:

Criterion Scores Table

| Candidate: | 1 |
| Career Development Plan/Career Goals & Objectives: | 1 |
| Research Plan: | 1 |
| Mentor(s), Consultant(s), Collaborator(s): | 1 |
| Environment and Institutional Commitment to the Candidate: | |

Overall Impact:

Strengths

1. Dr. Liu is an outstanding candidate for this award.
2. Strong research productivity and letters of reference.
6. Career development program for this candidate appears to be excellent.
3. Research plan is clearly written, and it appears to be well within the candidate's expertise and experience.
4. The area of study is highly significant, focusing on the role of vitamin D and innate immunity against *M. tuberculosis*.

Weaknesses

- No weaknesses are noted.

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 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 Summary Statement [‘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
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