Application Number: 1 K08 AI130357-01

Principal Investigator
LU, LENETTE

Applicant Organization: MASSACHUSETTS GENERAL HOSPITAL

Review Group: MID-B
Microbiology and Infectious Diseases B Subcommittee
MID-B November 2016

Meeting Date: 11/04/2016
Council: JAN 2017
Requested Start: 04/01/2017

Project Title: Antibody Mediated Mechanisms of Immune Modulation in Tuberculosis

SRG Action: Impact Score:
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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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.

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RESUME AND SUMMARY OF DISCUSSION: This exceptional new application for a Mentored Clinical Scientist Research Career Development Award (K08) entitled “Antibody Mediated Mechanisms of Immune Modulation in Tuberculosis” was submitted by Lenette Lu, MD/PhD from Massachusetts General Hospital.

The goal of this K08 submission is to provide the applicant with a career development/training opportunity while focusing on the potential contribution of humoral immunity to the control of *M. tuberculosis* in humans. The application is based on a first author publication recently accepted by *Cell*. In this K08 application she proposes to probe potential mechanisms that might account for a protective effect she has observed with certain antibodies in patients with contained (latent) *M. tuberculosis* infection that are not present in patients with uncontrolled disease. She notes that while neutralizing antibodies to *M. tuberculosis* do not correlate with protection, she has presented evidence that antibodies that recruit cellular responses might be important contributors to the immune response to this global pathogen. This application aims to unravel how Ab Fc domains contribute to immune protection against Mtb infection at the cellular level. The three aims are to 1) define the Ag specificity of functional Mtb specific Abs; 2) dissect the role of Fc/FcR mediated intracellular Mtb restriction and 3) identify macrophage effector mechanisms of Ab dependent intracellular Mtb restriction.

Among strengths are the qualifications and experience of this superior candidate. She has received both an MD and PhD and has been well trained in global Tb work. Furthermore, she has been highly productive with several first author papers in high impact journals. The project of probing differential immune responses and the role of humoral immunity against *M. tuberculosis* is one of great significance to public health. The research plan is innovative and well supported by preliminary data. The mentoring team as well as the resources of the institution and institutional commitment are first rate and she has access to an important sample cohort.

Minor weaknesses were identified in the research and career development plans. The panel questioned how patients with latent disease would be identified. Moreover, the career development plan lacks coursework in key areas such as host microbial interactions, host immunity or biostatistics, all critical to the application. However, the panel’s enthusiasm for this highly productive candidate with a commitment to TB research outweighed these weaknesses. Based upon the evaluation of scientific and technical merit, this application received an Overall Impact/Priority score of 17.

DESCRIPTION (provided by applicant):

Project Summary/Abstract This proposal presents a five year research career development program focused on the study of antibody mediated immune modulation in tuberculosis to expand the breadth and depth of understanding the role of humoral immunity in this disease. The candidate is currently an Instructor of Medicine at Harvard Medical School in the Division of Infectious Diseases at the Massachusetts General Hospital. The outlined proposal builds on the candidate's previous research and clinical experience in host pathogen interactions by integrating two new domains of expertise represented by her mentor team of Drs Sarah Fortune and Galit Alter at the Harvard School of Public Health and the Ragon Institute of MGH, MIT and Harvard: tuberculosis and antibody mediated mechanisms of innate immune effector functions. The proposed experiments and didactic work will position the candidate with a unique set of cross disciplinary skills that will enable her transition to independence as a physician scientist in antibody mediated host pathogen interactions in tuberculosis. One third of the world’s population carries the burden of tuberculosis (TB). Efforts to reduce this burden have been hindered by the lack effective diagnostics and a protective vaccine underpinned by gaps in
the understanding of the immune response in TB disease. While cellular immunity is important, the antibody (Ab) or humoral landscape is poorly understood. Ab function is determined by the combination of antigen specificity via the Fab and ability to recruit functional responses via the Fc domain. Ab Fc mediated recruitment of cellular responses is a promising underexplored potential for immune control. The foundation for this proposal is based on preliminary studies evaluating differences in antibody profiles from a systems serological approach in a cohort of individuals with latent and active TB that suggest a potential protective role for antibodies in TB disease. How exactly antibodies might function in this context and its physiological relevance are questions that this proposal begins to address. More specifically, the aims of this proposal are 1: Define the antigen specificity of functional M. tuberculosis (Mtbc) specific antibodies, 2: Dissect the role for Fc/FcR mediated intracellular Mtbc restriction and 3: Identify the macrophage effector mechanisms through which Ab restrict intracellular Mtbc. The scientific objective of this proposal is to begin to define the Ab Fab and Fc features with the capacity to mediate effector function against intracellular Mtbc with the vision that antibody features may be harnessed to expand the repertoire for immune correlates/diagnostics and rational vaccine design.

PUBLIC HEALTH RELEVANCE
Project Narrative One third of the world's population carries the burden of tuberculosis. Efforts to reduce this burden have been hindered by the lack effective diagnostics and a protective vaccine underpinned by gaps in the understanding of the immune response in tuberculosis disease. The proposed research will explore the role of humoral immunity in tuberculosis disease! with the vision that antibody features may be harnessed to expand the repertoire for immune correlates, diagnostics and rational vaccine design.

CRITIQUE: The comments in the CRITIQUE section were prepared by the reviewers assigned to this application and are provided without significant modification or editing by staff. They are included to indicate the range of comments made during the discussion, and may not reflect the final outcome. The RESUME AND SUMMARY OF DISCUSSION section summarizes the final opinion of the committee after the discussion and is the basis for the assigned Impact/Priority score.

Critique 1

Candidate: 1
Career Development 5
Plan/Career Goals /Plan to Provide Mentoring: 2
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 1
Environment Commitment to the Candidate: 1

Overall Impact:
This innovative K08 studies how Mtbc specific antibody Fc mediated interactions may contribute to protection from active TB. Impact score is largely driven by the clear dedication of the applicant to TB pathogenesis evident from strong preliminary data for all proposed aspects of the application. The
premise is based on intriguing preliminary serum studies in cohorts with latent and active TB, which have been recently been accepted for publication in Cell. The overall research approach is well rationalized and laid out with progressive analysis of several players in the Fc mediated pathway of Mtb restriction in macrophages. The team of mentors, advisors and collaborators, as well as the environment and local TB expertise are outstanding to successfully pursue the proposed studies. The innovative nature of the application based on clinical samples has excellent potential for future applications to small molecule or vaccine based therapeutics. The innovation and high impact potential of the application outweigh the very modest career development plan.

1. Candidate:

Strengths

- The applicant is well trained in microbial pathogenesis, specifically virus host innate responses and more recently TB. After receiving her MD/PhD in 2010 from Case Western Reserve University School of Medicine, she completed her residency in Internal Medicine at Weill Cornell in 2013 and fellowship in infectious disease at Massachusetts General Hospital in 2015. She is presently a postdoctoral fellow and teachers assistant at Harvard School of Public Health. Her interest in clinical microbiology with a focus on TB and expertise in cellular host pathogen interactions provide an excellent background to expand her studies to antibody-Fc mediated mechanisms of protection from Tb.

- Productivity is excellent with six primary authored publications, including one in J Biol Chem from her PhD, 4 clinical reports since 2010, and a recently accepted publication in Cell, which is the basis of the application. The studies on divergent humoral profiles in patients with different TB disease states and consequences for Mtb restriction accepted in ‘Cell’ are likely to have high impact.

- During her residency the applicant gained experience in global health from rotations in Thailand, Haiti and Tanzania.

- She was supported by a T32 training grant in the past 2 years (p92).

- The referee letters are exceptionally laudatory, emphasizing the applicant’s passion for teaching and learning, thoughtfulness, intellectual vibrancy and extraordinary potential.

Weaknesses

- None noted

2. Career Development Plan/ Career Goals & Objectives:

Strengths

- The long term goal is to pursue a career in infectious disease basic research to apply insights to patient care in resource limited areas.

Weaknesses

- A formal career development plan is lacking. The applicant lists progress in learning new skills in several areas during her present fellowship, but it is unclear how the KO8 mechanism will be used to strengthen expertise in host microbial interactions at the cellular, host immunity or biostatistics, all critical to the application.
• There are no plans for formal coursework in specialty areas critical to the application. Career development activities and training are also lacking.

3. Research Plan:
Strengths

• The concept that antigen specific Ab plays a role in restricting Mtb infection via FcRs is largely unexplored and may lead to new strategies of vaccine design. This application aims to unravel how Ab Fc domains contribute to immune protection against Mtb infection at the cellular level. The three aims to 1) define the Ag specificity of functional Mtb specific Abs; 2) dissect the role of Fc/FcR mediated intracellular Mtb resytriction and 3) identify macrophage effector mechanisms of Ab dependent intracellular Mtb restriction, are well integrated and conceptually straightforward.

• Preliminary data is supportive. It demonstrates that a link between distinct humoral serum signatures (Ag specificity, Ig subclass, FcR affinity, glycosylation state, FcR activity) with low and high bacterial burden also correlates with antimicrobial activity in an in vitro macrophage infection model.

• Expansion of studies to an additional patient cohort is essential to validate preliminary findings using ATB and LTB patient cohorts from South Africa.

• Approaches in aim 1 are well rationalized and promise to reveal extensive new insights into Ag specific Mtb humoral responses. Studies will characterize the spectrum of Ag specificity of IgG mediating protective FcR mediated function using MTb proteome array encompassing 4262 proteins (>95%). IgG activities will be assessed using functional Fc signatures (e.g.ADCC) and validated via Ag mediated IgG depletion.

• Aim 2 constitutes a best effort approach to identify the activating FcgRIIIa as the prominent FcR mediating intracellular Mtb restriction. Results are verified using complimentary knockdown, enzymatic, and microscopic approaches to interfere with FcR engagement.

• Aim 3 linking phagosomal fusion and inflammasome activation as mechanisms contributing to intracellular Mtb control is critical to ultimately target specific pathways enhancing Mtb restriction. A variety of reagents and inhibitors will test the role of the IL-1b pathway and autophagy. While these pathways may be difficult to dissect, the expertise of the mentors and collaborators is expected to be invaluable for interpretation.

• Biological resources are appropriately authenticated.

Weaknesses

• Aim 1: Fig. 2 indicates that IgG from normal serum provides protection similar to ATB derived IgG. Additional protection specifically by LTB derived IgG is significant, but less than 40%. It is unclear how the apparent non specific protection is accounted for. Aim 1 also provides no strategy to prioritize between multiple possible Ag reactivities of IgG to vast amounts of Mtb proteins.

• There are no efforts to take advantage of insights from aim 1 for studies in aims 2 and 3.

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

Strengths
The mentor team is composed of Drs Fortune, MD, and Alter (PhD). Dr Fortune is an expert in studying mechanisms underlying heterogeneity in TB disease and treatment outcomes using genetics and high throughput technologies. Dr Alter complements Dr Fortune’s expertise by studying innate immune responses to chronic viral infection and more recently antibody and Fc profiling in TB patients. This is a superb scientific team for the application’s success.

The scientific advisory committee including Drs Iwasaki, Nummerjahn and Batista, is headed by Dr Rubin, another expert in TB microbiology, with an excellent mentorship record. Their complementary expertise in innate immunity, inflammasome activation, FcR function, cell biology and microbiology, will be crucial in data interpretation and ongoing experimental design.

Dr Restrepo (Univ Texas) will be a resource for clinical samples and Dr. Hayden (MGH) will provide statistical support.

An extensive letter is provided by the mentors to support and monitor the candidate’s progress at all levels (p105).

Weaknesses

- None noted

5. Environment and Institutional Commitment to the Candidate:

Strengths

- A letter of support by the Chief of Infectious Diseases guarantees 75% protected research time with clinical activities restricted to 10%. Space and K08 independent resources are guaranteed.

- The environment at the Ragon Institute and Harvard School of Public Health is superb to pursue mechanistic studies of antibody Fc mediated effector functions in TB. The TB research community in Boston is outstanding. Access to all services including state of the art high throughput profiling, systems serology and imaging is in place.

Weaknesses

- None noted

Critique 2

Candidate: 2
Career Development 2
Plan/Career Goals /Plan to Provide Mentoring:
Research Plan: 2
Mentor(s), Co-Mentor(s), 1
Consultant(s),
Collaborator(s):
Environment Commitment 1
to the Candidate:

**Overall Impact:**
The candidate’s background in biology and immunology is excellent. The research experiences and publications are adequate to this stage of the candidate’s career. The facilities available and mentorships are excellent. The research plan is novel, well written and interesting. The candidate’s recent publication in a high impact factor journal demonstrate the significance of his research to the tuberculosis community. The research plan shows minor weaknesses on details such as a lack of definition for patients with latent disease. With adequate mentorship the candidate is on a path to become an independent researcher in this field.

1. **Candidate:**
   **Strengths**
   - The candidate is an MD, PhD with a good background in biology, molecular virology, immunology and infectious disease.
   - The research in *Saccharomyces cerevisiae* DNA replication and signaling in innate immunity demonstrate the candidate adequate training experience for this award. The recent publication in *Cell* on the role for antibodies in tuberculosis makes the candidate highly qualified for this application.
   - The letters of support are excellent and enthusiastically support candidate’s potential to develop as an independent researcher.

   **Weaknesses**
   - None

2. **Career Development Plan/ Career Goals & Objectives:**
   **Strengths**
   - The role of humoral immune response to *M. tuberculosis* is an area in tuberculosis research that has not been extensively explored, and the role of antibodies in signaling via FC domain has become more attractive in recent past. The investigator is highly qualified to successfully execute the goals of this project.
   - Humoral immunity and the role of FC domain in *M. tuberculosis* pathogenesis has potential to develop into a long term research career.

   **Weaknesses**
   - None

3. **Research Plan:**
   **Strengths**
   - The candidate aims to study the humoral immunity and the role of the FC domain in *M. tuberculosis* pathogenesis. This is a novel and very stimulating new area of research in the tuberculosis.
The investigator experience in immunology and dsRNA signaling clearly indicate the ability to carry on this project.

Weaknesses

The candidate’s application aim to study the humoral signature associated with different TB disease states. Preliminary results have shown differences in FC effectors and macrophage restriction to *M. tuberculosis* between active and latent disease. It is not clear how patients with latent disease will be identified in this application. Are these patients TST positive? IGRA positive? Both? Have they ever developed disease? Were they ever treated?

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

Strengths

- The candidate’s mentors are excellent with a vast experience in tuberculosis and immunology.
- The mentors are fully supportive of the candidate and able to guide the candidate to develop as an independent researcher in the tuberculosis field.

Weaknesses

- None

5. Environment and Institutional Commitment to the Candidate:

Strengths

- The institutions are outstanding and clearly committed to provide and facilitate the candidate to accomplish the research project.
- The institution is supportive and committed to help the candidate to a career development which may lead to an independent scientific career.

Weaknesses

- None

Critique 3

| Candidate: | 1 |
| Career Development | 1 |
| Plan/Career Goals/Plan to Provide Mentoring: | |
| Research Plan: | 2 |
| Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): | 1 |
Environment Commitment 1 to the Candidate:

Overall Impact:
An exceedingly well trained Instructor in Medicine from the Massachusetts General Hospital, Harvard Medical School and the Ragon Institute has applied for K08 support to continue her career development as a physician/scientist. Her application includes three very well integrated aims that seek to define antigen specificity and the potential role of Fc/FcR mediated intracellular *M. tuberculosis* restriction and to identify key macrophage effector mechanisms responsible for this control. Enthusiasm for the application is based on the track record of the applicant, the strength and novelty of the preliminary data, the expertise and commitment of the mentors and the critical importance of developing a deeper understanding of the role of humoral immunity in the pathogenesis of mycobacterial infection.

1. Candidate:
Strengths
- Dr. Lu is extremely well trained in both laboratory science and clinical medicine. Research training includes an honors thesis at Swarthmore focused on cell cycle regulation in *Saccharomyces cerevisiae* and a very productive investigation of IRF3 regulation by dsRNA during her MD/PhD studies at the Cleveland Clinic.
- Her interest in tuberculosis was stimulated by a very positive experience at GHESKIO in Haiti during her residency at Cornell.
- She has continued to build her research skills during her fellowship in the laboratories of Galit Alter and Sarah Fortune with studies of the role of humoral responses to *M. tuberculosis* in protection from disseminated mycobacterial infection. Her first manuscript in this area is in press in *Cell*.

Weaknesses
- No major weaknesses

2. Career Development Plan/ Career Goals & Objectives:
Strengths
- Dr. Lu has outlined a very well reasoned pathway forward that will prepare her for a productive career as a physician scientist.
- The project she has outlined is a logical extension of the work she has undertaken as a fellow. She is appropriately poised to move from describing the differences in antibody profiles from patients with contained (latent) vs. active *M. tuberculosis* infection to studies that seek to understand the mechanisms that might underlie effector functions of these antibodies.
- She has already undertaken and has outlined additional formal coursework in immunology and biostatistics that will complement her experiential training extremely well.

Weaknesses
It will be important for the applicant to maintain engagement with the clinical community engaged in care for patients with *M. tuberculosis* infection during the five years of this K08. She might benefit from scientific or clinical engagement with GHESKIO, PIH, K-RITH or any number of Harvard’s multiple clinical tuberculosis programs.

3. Research Plan:
   **Strengths**
   - The research plan builds on the work undertaken during her fellowship and takes full advantage of the deep bench of researchers focused on *M. tuberculosis* in the Boston area as well as the cutting edge immunologic expertise at the Ragon Institute.
   - The proposed research focuses on an area of mycobacterial immunity that has been traditionally neglected compared to studies of innate and cellular immunity.
   - If successful, the research might provide useful insights into the pathogenesis of mycobacterial infection as well as to lead toward the discovery of biomarkers that could be useful for diagnosis and prognosis.
   - Should humoral immunity be more central to the pathobiology of mycobacterial infection than has traditionally been posited, the work could lead toward novel approaches to mycobacterial vaccine development.
   - The research plan is logically organized and the specific aims are well integrated.
   - The focus on FcR mediated antibody (as opposed to neutralization-based) antibody activity is novel and highly testable.

   **Weaknesses**
   - Although it is highly innovative to focus this work on humoral immune responses to mycobacterial infection, one potential wrinkle that should be considered (in view of the FcR emphasis of the proposal) is whether changes in effector cell characteristics in patients with cellular immunodeficiency could undermine the effectiveness of humoral effectors. For example, FcR mediated mechanisms might be very important in defense from *M. tbc.* Infection in patients with functional mononuclear cell repertoires but non-functional in environments in which HIV has distorted effector populations. If a role for FcR-Ab mediated protection is noted, is there a plan to see whether these functions are affected in the cells obtained from patients with advanced HIV infection?

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):
   **Strengths**
   - Drs. Alter and Fortune are outstanding mentors for this early career scientist. Their complementary expertise in immunology and in mycobacterial pathogenesis will provide mentorship in both aspects of Dr. Lu’s highly innovative project.
   - Her advisory committee is likewise very well constituted with the involvement of Drs. Batista, Iwaski, Nimmerjahn and Rubin.
   - Research samples from Dr. Restrepo’s very well characterized cohort will also be extremely valuable to Dr. Lu.

   **Weaknesses**
5. Environment and Institutional Commitment to the Candidate:

Strengths

- The Ragon Institute is a superb location for training in all aspects of immunology and, as noted above, the Harvard milieu for mycobacterial research is outstanding.
- The applicant’s letter of support from her Division Head is unequivocal. She already has a faculty appointment and will be asked to devote no more than 10% of her time to clinical activities.

Weaknesses

- None

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): Code: 30 ACCEPTABLE
The study enrolls individuals with latent or active TB who are willing and able to give informed consent and are adult males and females aged 18-75. Study sites take place in University of Texas Health Science Center at Houston-School of Public Health-Brownsville Regional Campus in association with Hidalgo County Health Department and Cameron County Health Department and or MGH Infectious disease clinical sites as noted above.

Projects to be undertaken with support of this training grant, which involve human subjects, must conform to the NIH policies on the protection of human subjects. Guidance can be found in PHS398 application materials and the NIH Office of Extramural Research web site http://grants.nih.gov/grants/policy/hs/index.htm.

DATA AND SAFETY MONITORING PLAN: ACCEPTABLE

INCLUSION OF WOMEN PLAN (Resume): Code: G1A ACCEPTABLE
Eligible adult males and females from all ethnic backgrounds are included in the cohorts utilized in this study.

Projects to be undertaken with support from this training grant, which involve clinical research studies, must conform to the NIH policies on the inclusion of women in study populations. See http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. Details of such studies, including a description of the population and rationale for inclusion/exclusion, must be provided to the NIH program administrator of this training grant prior to undertaking the studies.

INCLUSION OF MINORITIES PLAN (Resume): Code: M1A ACCEPTABLE
Eligible adult males and females from all ethnic backgrounds are included in the cohorts utilized in this study.

Projects to be undertaken with support from this training grant, which involve clinical research studies, must conform to the NIH policies on the inclusion of minorities in study populations. See http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. Details of such studies, including a description of the population and rationale for inclusion/exclusion, must be provided to the NIH program administrator of this training grant prior to undertaking the studies.

Comments or Concerns: No concerns. Most or all biological specimens will come from established specimen repositories. Furthermore, since M. tuberculosis disproportionately affects members of traditionally underrepresented groups, it would be expected that samples from this population will be well represented.

INCLUSION OF CHILDREN PLAN (Resume): Code: C3A ACCEPTABLE
No children will be included.

Projects to be undertaken with support from this training grant, which involve clinical research studies, must conform to the NIH policies on the inclusion of children in study populations. See http://grants.nih.gov/grants/funding/children/children.htm. Details of such studies, including a description of the population and rationale for inclusion/exclusion, must be provided to the NIH program administrator of this training grant prior to undertaking the studies.

VERTEBRATE ANIMALS (Resume): Code: 10 NOT APPLICABLE
No vertebrate animals will be used in this application.

BIOHAZARD COMMENT: ACCEPTABLE
Biohazards, if present, are named and appropriate responses and handling procedures given.

Comments or Concerns: The applicant has access BSL 3 space both at the Ragon Institute and at the Harvard School of Public Health. Procedures for working with mycobacteria are in place and there are no concerns.

TRAINING IN THE RESPONSIBLE CONDUCT OF RESEARCH: ACCEPTABLE
Format:
Subject Matter:
Faculty Participation:
Duration:
Frequency:

Comments:
Format: Experiential, didactic and seminar based
Subject Matter: research ethics, regulatory requirements, subject privacy and other key areas of instruction.
Faculty Participation (Not applicable for mid-career (K24) and senior-candidate awards): full
participation of mentorship committee
Duration: Initial coursework involving 16 hours of face time.
Frequency: Biannual discussions with her advisory committee about

FOREIGN INSTITUTION: NOT APPLICABLE

SELECT AGENTS: NOT APPLICABLE

RESOURCE SHARING PLANS: ACCEPTABLE
Data Sharing Plan Comments (if >$500,000/year):
Sharing Model Organisms Comments:
Genomic Data Sharing (GDS) Comments:
Consistent with NIH and institutional guidelines

AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES: ACCEPTABLE

BUDGET AND PERIOD OF SUPPORT: The budget was recommended as requested.

Footnotes for 1 K08 AI130357-01; PI Name: Lu, Lenette

NIH has modified its policy regarding the receipt of resubmissions (amended applications).
14-074.html. The impact/priority score is calculated after discussion of an application by
averaging the overall scores (1-9) given by all voting reviewers on the committee and
multiplying by 10. The criterion scores are submitted prior to the meeting by the individual
reviewers assigned to an application, and are not discussed specifically at the review meeting
or calculated into the overall impact score. Some applications also receive a percentile
ranking. For details on the review process, see
http://grants.nih.gov/grants/peer_review_process.htm#scoring.