

SUMMARY STATEMENT

PROGRAM CONTACT:
Tonu Wali
240-627-3389
twali@mail.nih.gov

(Privileged Communication)

Release Date: 12/02/2016
Revised Date:

Application Number: 1 K08 AI125682-01A1

Principal Investigator

TRAN, TUAN MANH

Applicant Organization: INDIANA UNIV-PURDUE UNIV AT INDIANAPOLIS

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
RFA/PA: PA16-191
PCC: M44

Project Title: Defining clinical and sterile immunity to Plasmodium falciparum infection using systems biology approaches

SRG Action: Impact Score:17

Next Steps: Visit http://grants.nih.gov/grants/next_steps.htm

Human Subjects: E4-Human subjects involved - Exemption #4 designated

Animal Subjects: 10-No live vertebrate animals involved for competing appl.
Clinical Research - not NIH-defined Phase III Trial

| Project Year | Direct Costs Requested | Estimated Total Cost |
|--------------|------------------------|----------------------|
| 1 | [REDACTED] | [REDACTED] |
| 2 | [REDACTED] | [REDACTED] |
| 3 | [REDACTED] | [REDACTED] |
| 4 | [REDACTED] | [REDACTED] |
| 5 | [REDACTED] | [REDACTED] |
| TOTAL | [REDACTED] | [REDACTED] |

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.

1K08AI125682-01A1 **Tran, T**

**BIOHAZARD COMMENT
FOREIGN INSTITUTION**

RESUME AND SUMMARY OF DISCUSSION: This exceptional resubmission application for a Mentored Clinical Scientist Research Career Development Award (K08) entitled “Defining clinical and sterile immunity to *Plasmodium falciparum* infection using systems biology approaches” was submitted by Tuan Tran, MD, PhD of Indiana University.

This K08 award will provide the candidate, Dr. Tuan Manh Tran, with training and resources to further develop his career expertise in the field of malaria-systems biology. The main goal of this application is to use systems biology methods to elucidate correlates and mechanisms of both clinical and sterile immunity to *P. falciparum* infection. A well-characterized cohort of Malian children living in an area of intense, seasonal malaria transmission will be utilized. The work will be performed under two specific aims. Aim 1: Identify immune parameters predictive of clinical immunity to Pf infection and sterile immunity to Pf infection. Aim 2: Compare cellular, molecular, and Pf-specific IgG reactivity profiles in the blood of children with clinical vs sterile immunity and relate these profiles and immune outcomes to the in vitro parasite-inhibitory activity of their plasma.

Among strengths is a significant but challenging project to examine the correlates and mechanisms of clinical and sterile immunity to *Plasmodium falciparum* (Pf) infection. Currently an assistant professor in the Indiana University School of Medicine, this highly qualified candidate has received both MD and PhD degrees and training from an internship and residency at the Johns Hopkins Hospital and a research fellowship in NIAID. In addition to his immunology and infectious disease experience, the candidate has computational and systems biology skills. This resubmission is markedly improved with minor issues remaining in the research plan mainly because of the nature of the project. The mentoring team is well qualified and patient samples from Mali provide a well-characterized source of clinical data for the applicant’s systems biology approaches.

Among weaknesses primarily in the research plan, are the questionable rigor and statistical power of the project, the host genetic background issue, and the observation that this project may not result in a substantial publication output. Despite these weaknesses, the panel had great enthusiasm for the candidate’s potential impact in clinical research. 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 Malaria afflicts ~198 million people yearly, with 438,000 malaria deaths due to *Plasmodium falciparum*, underscoring the need for a highly effective malaria vaccine. The first licensed malaria vaccine, RTS,S, may provide much-needed reductions in morbidity and mortality, but its modest efficacy in reducing clinical malaria in the target population of African infants leaves ample margin for improvement. A better understanding of immunity to *P. falciparum* in naturally exposed populations can inform efforts to improve malaria vaccine design. To date, there are no reliable correlates of protection from either symptomatic *P. falciparum* infection (clinical immunity) or parasitemia (sterile immunity). Systems biology utilizes computational modeling of large- scale data sets to elucidate complex biological networks and has the potential to reveal novel predictors and mechanisms of malaria protection when applied to well-designed clinical cohort studies. In this project, the candidate proposes to assess immune predictors of natural protection from *P. falciparum* infection

using systems biology approaches. By analyzing clinical data and blood specimens collected from a well-characterized, prospective cohort of Malian children who differ in their degree of immunity to *P. falciparum* infection, the candidate will address two main research aims: 1) determine immune parameters predictive of protection from symptomatic infection (clinical immunity) and protection from *P. falciparum* infection (sterile immunity) and 2) relate these immune parameters and outcomes to the ability of plasma obtained from these children to inhibit parasite invasion into liver and red blood cells in vitro. The practical implications of this work include identifying novel immune predictors and mechanisms of protection from *P. falciparum* infection and disease within the vaccine target population that could provide rational benchmarks for candidate malaria vaccines. The candidate is firmly committed to a career in translational malaria research and systems biology and is strongly supported in his career and research goals by his mentors and his division at the Indiana University School of Medicine. He currently holds a position as an Assistant Professor of Medicine with 80% protected time for research, independent laboratory and office space, and funding for equipment. The current proposal includes a comprehensive mentorship and didactic plan to advance the candidate's skills and knowledge in biostatistics and computational biology required for developing expertise in systems biology. Under the guidance of his primary mentor, Dr. Chandy John, and his co-mentors, Dr. Wanzhu Tu, Dr. Lang Li, and Dr. Peter Crompton, he will advance his bioinformatics skills and learn predictive modeling methodologies that will be directly applied to this proposal. Completion of this comprehensive training plan will provide the candidate with the skills and experience necessary to become a successful independent investigator specializing in computational systems biology with a focus on host immunity to *Plasmodium* infection.

PUBLIC HEALTH RELEVANCE

Project Narrative Each year malaria afflicts ~200 million people and causes over 430,000 deaths, primarily among African infants. Although a first-generation malaria vaccine is now available, it is only modestly effective in the target population of African infants; thus, a better understanding of natural immunity to *Plasmodium falciparum*, the deadliest of malaria parasites, in young African children can inform efforts to develop the next generation of malaria vaccines. Using samples collected from young Malian children before and during natural *P. falciparum* infections, this study aims to identify predictors and mechanisms of malaria immunity that aid the development of future malaria vaccines.

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 Plan/Career Goals /Plan to Provide Mentoring: | 1 |
| Research Plan: | 3 |
| Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): | 1 |
| Environment Commitment to the Candidate: | 1 |

Overall Impact:

The candidate is a talented researcher with outstanding training in infectious diseases (esp. malaria), immunology, and applied bioinformatics. This project aims to use systems biology approaches to address an important and challenging question, i.e., what are the correlates and mechanisms of both clinical and sterile immunity to *Plasmodium falciparum* (Pf) infection. From a well-collected cohort, data from various arrays (e.g., transcriptomics, flow cytometry data, Pf genetic differences) will be generated and used. Statistical modeling and analysis are proposed to utilize these data. This is a resubmission. The candidate has improved this application by appropriately addressing most comments from the previous submission. However, the host genetic background issue, as commented previously, could be better addressed. Other research design methods could also be improved with more convincing details. To ensure future R01 submission, the candidate is also advised to systematically analyze detailed immune pathways and identify potential novel hypotheses.

1. Candidate:

Strengths

- The candidate is currently an assistant professor in the Indiana University School of Medicine (IUSM), Indianapolis. He got his MD, PhD in Immunology and Molecular Pathogenesis, Internship and residency in the John Hopkins Hospital, and fellowship in NIAID.
- The candidate learned computational and systems biology methods during his fellowship training in NIAID.
- He has published over 20 peer-reviewed articles, with 12 focusing on naturally acquired immune responses to malaria in endemic populations. His malaria research started from the Graduate School.

Weaknesses

- No significant weaknesses were noted.

2. Career Development Plan/ Career Goals & Objectives:

Strengths

- The candidate's long term goal is to become an expert in the field of systems biology of malaria. He is interested in studying host immune responses to *Plasmodium* infection in the endemic setting using systems-based analysis.
- His short term K proposal goal is to determine the immune parameters for predicting the outcomes of a child protected from malaria symptoms or parasitemia.
- The candidate's long term and short term goals fit very well with the candidate's interdisciplinary trainings in infectious diseases, immunology, field research, and bioinformatics.

Weaknesses

- The candidate will need more knowledge and skills in biostatistics and mathematical modeling. This is an objective from this K grant.

3. Research Plan:

Strengths

- Systems biology approaches are proposed. Such approaches are appropriate to elucidate correlates and mechanisms of both clinical and sterile immunity to Pf infection.
- A well-characterized, prospective cohort of Malian children living in an area of intense, seasonal malaria transmission will be used. The cohort includes longitudinally collected biospecimens (plasma/whole-blood RNA/DBS/PBMCs) linked to >3 years of prospective clinical, parasitological, and epidemiological data.
- In Aim 1, data from different assays, such as whole-blood transcriptomics, multi-parameter flow cytometry, multiplex cytokine analysis, and pathogen genetic differences will be used. These provide a broad range of data sets for predicting immune correlates of clinical or sterile protection from Pf infection.
- Different Multi-parameter statistical modeling and machine learning methods will be used for predicting clinical and sterile immunity.
- As suggested by the review comments from the first submission, this application has combined the original aims into a single Aim 1 and introduced a revised Aim 2 that comparatively analyzes clinical and sterile immunity and integrates data from functional assays.

Weaknesses

- A major comment from previous submission is the lack of genetic analysis of human hosts. The current proposal proposes to perform ABO blood group typing, and genotype for most common α -thalassemia, and G6PD deficiency variants of erythrocytes (3.2.2b). It partially addresses the previous comment. The previous comment also suggested possible new layers of “omic” data for host genetic background to determine significant molecular signatures to clinical and sterile immunity. Such host genetic background omic data is not proposed or discussed in the current proposal. Considering that a huge amount of data have already been included, this is considered a relatively minor issue for this application; however, an omics data analysis of host genetic background to identify susceptible genetic variability may be an important task to perform in the future.
- Aim 1 statistical modeling for predicting clinical or sterile immunity has its weaknesses. In Aim 1, machine learning approaches are used to determine which variables (features) from demographic (i.e. age, gender), epidemiological, erythrocyte variant, parasitological, transcriptomic, FACS, multiplex cytokine, and Pf-specific IgG data could best predict clinical or sterile immunity. This is not a trivial task. Although it is possible to find individual features able to predict the outcomes, it is very likely that in this complex system, many features are required together in a combinatory set to predict the outcomes. However, it can be very tricky to find what combinations of features to use and the sizes of features in such combinations. Also, instead of looking for individual features, we may often want to examine the interaction pathways (another layer) among these features that may become better predictors of clinical or sterile immunity. These aspects have not been discussed.
- Other than predicting clinical or sterile immunity, an important part of the study would be to identify the immune pathway mechanisms. Predictors (as emphasized in the current proposal) may predict well; however, they may not be able to well illustrate the mechanisms or it may be hard to explain the functions of these predictors. The identification of key immune factors and related pathways for future hypothesis generation and verification

would be important for extended research. Such aspect is not emphasized in the current proposal.

- The above weaknesses are considered addressable.

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

Strengths

- The candidate has assembled a strong mentoring team to support various aspects of training.
- Dr. Chandy C. John, a professor of pediatrics as well as Microbiology and Immunology at IUSM, will act as the primary mentor. He has received continuous NIH funding since 1999 to study malaria immuno-epidemiology and malaria pathogenesis in Africa.
- Dr. Wanzhu Tu, a professor of biostatistics at IUSM, will serve as a co-mentor. Dr. Tu has strong background in using statistical methods to model biological processes and understand diseases.
- Dr. Lang Li, a professor and Director of the Center for Computational Biology and Bioinformatics at IUSM, will serve as a co-mentor. He will provide the guidance and resources to properly execute predictive modeling algorithms.
- Dr. Peter D. Crompton, Chief of the Malaria Infection Biology and Immunity Unit at NIAID will also serve as a co-mentor. Dr. Crompton was the candidate's primary research mentor during his fellowship at NIAID. Dr. Crompton will provide expertise in human immunity to *Plasmodium* infection.

Weaknesses

- No significant weaknesses were noted.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- The environment for conducting the proposed research is excellent.

Weaknesses

- Not observed.

Critique 2

| | |
|--|---|
| Candidate: | 1 |
| Career Development Plan/Career Goals /Plan to Provide Mentoring: | 2 |
| Research Plan: | 4 |
| Mentor(s), Co-Mentor(s), | 3 |

Consultant(s),
Collaborator(s):
Environment Commitment 2
to the Candidate:

Overall Impact:

This resubmission of an application for a Mentored Clinical Scientist Research Career Development Award (K08) provides further evidence of an outstanding candidate, supported by a team of well-qualified mentors and collaborators. A strength of the application is its documentation of a candidate suitably-prepared for this career development step and the training program and mentorship in place for him to achieve that. The research plan itself almost assures that the candidate will gain valued experience with theory, new methods, and computational approaches that will advance his stated research goals. What remains insufficiently addressed in the resubmission is the concern that the research project in the end will largely be inconclusive, mainly because it was under-powered for the wide-ranging scope. This may leave the candidate in a vulnerable position near the end of the CDA, and the inattention to this possibility has to reflect on the quality of the mentorship.

1. Candidate:

Strengths

- The candidate, Tuan Tran, MD, PhD, an Assistant Professor of Medicine at Indiana University since 2015, has had excellent training and experience in clinical medicine and laboratory research at such institutions as Emory University, Johns Hopkins, and the intramural program of the National Institutes of Health.
- For a young physician-scientist who has much of his time devoted to full-time clinical activities, Dr. Tran's publication record is excellent.
- The background and present skill-set of the candidate prepares him well for moving beyond the domains of clinical research and laboratory research to a more integrative discipline. Dr. Tran is an outstanding prospect for a successful career in clinical and translational research.

Weaknesses

- A minor detracting point is the needless use of the third person singular instead of first person by the candidate in the abstract and the frequent use of "we" elsewhere. It gives the impression of either a reluctance of the candidate to assume ownership or some well-meaning but bad advice.

2. Career Development Plan/ Career Goals & Objectives:

Strengths

- The K08 mechanism is highly appropriate for this candidate at this stage in his career.
- The candidate and mentors have identified suitable didactic and tutorial experiences for the goals of the career development and

Weaknesses

- This may be "systems" biology in the sense of utilizing data sets of different types of information (e.g. the immunology "system"), but it is not really "systems biology" as the term is most commonly used currently, i.e. "...the focus on the dynamics of the studied systems is

the main conceptual difference between systems biology and bioinformatics" (Wikipedia entry). The research plan seems to be more devoted to identifying informative predictors across different data sets than characterizing the interactions themselves. That's fine, as discussed below, but it may be doing the candidate a disservice to promote a description that others (including potential recruiters) would assign another name to.

- While the training aspects fit well with the candidate's career development goals, but it is harder to see how the research project could realistically evolve to a competitive R01 application. This was a concern that a previous reviewer had brought up.

3. Research Plan:

Strengths

- The study's overall goal to identify transcriptomics, serum biomarkers, antigen reactivity profiles, and other molecular signatures that predict and distinguish between clinical immunity and apparent sterile immunity is meritorious.
- The candidate clearly has his research tools in place to carry out these types of studies, either through his own lab or others in Indiana or through collaborations, such as with Dr. Felgner in California.
- The research plan without doubt will provide the candidate with "priceless" research experiences that will serve him well for design and implementation of studies in the future.

Weaknesses

- A previous reviewer wrote that "weaknesses that reduce enthusiasm are concerns regarding the lack of genetic analysis of human hosts." The reviewer had in mind specifically certain hemoglobinopathies and glucose-6-phosphate dehydrogenase deficiency. New research plan incorporates these as characters, but there was little consideration of the genetics of the host or of the target population beyond that limited set of genotypes. Although some genome scan or candidate gene studies have proven to be inconclusive or unreplicable with respect to malaria susceptibility and disease outcome, there is a growing literature on candidate variants associated with large or small effect sizes as well as biological plausibility. Stratification on the basis of this or that allele would, of course, add to the challenge of attaining sufficient sample sizes. But if the goal is a project that extends more than a couple of years into the future--and to be funded, greater incorporation of the host genetics parameter into the model would seem to be an essential.
- Although it seems there has been an increase in the sample sizes from the first application, the provisional sample sizes of less than 100 for each group (Table 3) still seem to pose a substantial risk of ending up with an under-powered study (even if there is the disclaimer of it being "exploratory"). This is especially a concern given (a) the huge number of "tests" that will be performed by transcriptomics, protein arrays, and biomarkers, (b) the heterogeneity of the study population in age (7 to 18 years), sex, and ethnicity, and (c) the not-discounted possibility of assignment of some of the subjects to the wrong group. There was no mention of the nutritional state of the children as a consideration or anything about the population structure in the study. Importantly, what about other infections the children may have at the time of the blood sample?
- The machine learning approach in addition to standard regression models is reasonable, but how will the "winner" output algorithms of the machine learning be interpreted? Obviously they would need to be tested with an independent dataset, but the algorithm may still be

effectively incomprehensible. In other words, it works great as a predictor, but it's not clear to us humans why it works.

- There was insufficient consideration of some possible pitfalls. The most worrying one is that, for one reason or another, the candidate will not have access to that study population in Mali. Is there a backup study site? On pg. 110 sites in Uganda and Kenya are mentioned, but these are not explicitly referenced as alternative study sites for this particular study. Another, more minor concern is whether for RNA-seq 25 million paired-end reads of globlin- and rRNA-depleted cDNAs can be achieved from a single fingerstick sample.

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

Strengths

- The primary mentor, Dr. Chandy John (Indiana University), and co-mentors Wanzhu Tu (Indiana University), Lang Li (Indiana University), and Peter Crompton (NIH) were well-qualified to serve in these roles.
- The collaborators Sangeeta Bhatia (MIT), Philip Felgner (UC Irvine), Scott Michaels (Indiana University), and Kara Wools-Kaloustian (Indiana University) provide complementary expertise and resources to the research project.

Weaknesses

- The short-comings of the research plan of this resubmission raises a question about the quality of the mentorship to date.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- The environments of Indiana University as well as the collaborating institutions for carrying

Weaknesses

- The expertise and resources of the institutions are particularly suited for a bioinformatics, computation science, and biostatistics oriented training program and research project, but not demonstrably "systems biology", as it is usually thought of. This may not be important for what the candidate proposes to actually do, but it is another example of how the application title could be misleading.

Critique 3

| | |
|--|---|
| Candidate: | 1 |
| Career Development Plan/Career Goals /Plan to Provide Mentoring: | 1 |
| Research Plan: | 3 |
| Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): | 1 |

Environment Commitment 1
to the Candidate:

Overall Impact:

This resubmission K08 from a highly productive Assistant Professor at Indiana University proposes to study the mechanisms of immunity to malaria in Mali using a systems biology approach. The resubmitted proposal has done much to strengthen an already solid proposal. The candidate and institutional commitment is outstanding, and the mentorship team is likewise exceptional. There exist minor concerns about the research strategy, but given the many strengths of this application, there is high enthusiasm that it will lead to substantial overall impact.

1. Candidate:

Strengths

- Academic productivity (with >20 manuscripts already published, only one year after completing fellowship) is exceptional.
- All letters recommend the applicant with utmost enthusiasm.
- Easy to see how this applicant's unique skill set in systems biology and application to a disease of great global importance will lead to a productive and potentially transformative career.

Weaknesses

- None noted

2. Career Development Plan/ Career Goals & Objectives:

Strengths

- Training plan is well thought-out and includes a nice blend of mentored training, didactic activities, and hands-on experience with skills such as writing.
- Need for further training is well articulated, and it is clear how that additional training will further the applicant's research career.
- Very feasible timeline ending in submission of R01 proposal in Year 4-5.

Weaknesses

- None noted

3. Research Plan:

Strengths

- Appropriate methodology outlined, with high likelihood of success in answering important questions.
- Completing these analyses will provide the applicant important experience in the methods he proposes to master.
- Clear path identified to how this research plan will result in continued academic productivity on the part of the applicant.

- Revised plan (with a new Aim 2) is well justified and, if successful, will result in major advances in knowledge.

Weaknesses

- Sample size/power remains an issue, with a relatively small number of clinical isolates available (especially of infants who are clinically immune) – though approaches to address this limitation seem appropriate.
- Revised proposal now includes a tremendous body of work, with many combinatorial analyses – may be difficult for the applicant to complete all of this within the course of his K (though even a valiant attempt to do so would arguably be worthwhile).

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

Strengths

- Exceptionally strong mentorship team, with the complementary expertise needed to help the applicant succeed.
- Applicant has a good history of collaboration with Dr. Crompton and an emerging relationship with other mentors on his team.
- Dr. John is a distinguished mentor and clearly dedicated to the applicant's career development.

Weaknesses

- None noted

5. Environment and Institutional Commitment to the Candidate:

Strengths

- Strong combination of personnel and facilities that are necessary to facilitate the applicant's eventual transition to independence
- Patient samples from Mali provide a well-characterized source of clinical data, as necessary for the applicant's systems biology approaches
- Institution is very highly committed to this applicant, having already offered a tenure-track faculty position. The applicant is in prime position to benefit from a K08 award.

Weaknesses

- None noted

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: E4 ACCEPTABLE

This application qualifies as Exempt Human Subjects Research. The current proposal will only utilize existing, "in-the-freezer" human biological specimens and existing clinical data from an ongoing cohort study on naturally acquired malaria immunity in Kalifabougou, Mali.

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>.

INCLUSION OF WOMEN PLAN (Resume):

This proposal qualifies as Exempt Human Subjects Research. The current proposal will only utilize existing, "in-the-freezer" human biological specimens and existing clinical data from an ongoing cohort study on naturally acquired malaria immunity in Kalifabougou, Mali.

INCLUSION OF MINORITIES PLAN (Resume):

This proposal qualifies as Exempt Human Subjects Research. The current proposal will only utilize existing, "in-the-freezer" human biological specimens and existing clinical data from an ongoing cohort study on naturally acquired malaria immunity in Kalifabougou, Mali.

INCLUSION OF CHILDREN PLAN (Resume):

This proposal qualifies as Exempt Human Subjects Research. The current proposal will only utilize existing, "in-the-freezer" human biological specimens and existing clinical data from an ongoing cohort study on naturally acquired malaria immunity in Kalifabougou, Mali.

VERTEBRATE ANIMALS (Resume): Code: 10 NOT APPLICABLE

No vertebrate animals will be used in this application.

BIOHAZARD COMMENT: UNACCEPTABLE

No biohazards were addressed.

RESUBMISSION:

Comments:

The candidate has appropriately addressed most comments from the previous submission. Overall, this is a much improved application. However, the host genetic background issue could be better addressed or discussed. The statistical modeling methods for the immune prediction could also be improved.

Comments: The original application was judged as "outstanding" with the greatest enthusiasm reserved for the candidate himself, his accomplishments to date, and his promise. Minor weaknesses were identified in the training and career development aspects. Most of the more substantive criticisms were about the research plan, with four different reviewers identifying weaknesses, some of which were the same in more than one review (such as a call for combining of Aims 1 and 2), but many that were unique to each reviewer. The Introduction summarizes the modifications, including combining of the original Aims 1 and 2 and adding a new Aim 2. Some of the remaining criticisms were satisfactorily addressed by modifications in the research design, but to my eye many were not. These are discussed in the relevant sections above. But a particularly cogent comment by one reviewer remains a concern for me as well: "It seems a shame to take such a highly productive junior investigator and place him into a situation where he is not expected to generate any research manuscripts for two years – and then,

the manuscripts proposed could end up being relatively low impact [journal] due to concerns over sample size and repetition of similar analyses in the same epidemiological cohort.”

Comments: The applicant has done a very good job of responding to the initial concerns raised about the scope of the research strategy, ability to maintain academic productivity, and appropriateness of the methods.

TRAINING IN THE RESPONSIBLE CONDUCT OF RESEARCH: ACCEPTABLE

Format:

Subject Matter:

Faculty Participation:

Duration:

Frequency:

Training in the Responsible Conduct of Research: ACCEPTABLE

Comments:

Format: online and classroom

Subject Matter: conflicts of interest, misconduct, authorship, ethics, science and society

Faculty Participation: faculty at Indiana University

Duration: 22.5 contact hours

Frequency:

FOREIGN INSTITUTION: JUSTIFIED

Comments:

Dr. Boubacar Traore from [Malaria Research Training Center (MRTC), University of Sciences, Techniques, and Technology of Bamako (USTTB), Malian International Center for Excellence in Research, Bamako, Mali] will be a collaborator. Dr. Traore and the candidate's co-mentor Dr. Peter Crompton at NIAID have allowed the candidate access to human biological samples and clinical data from the Kalifabougou cohort for the current proposal.

|

SELECT AGENTS: NOT APPLICABLE

RESOURCE SHARING PLANS: NOT APPLICABLE

Data Sharing Plan Comments (if >\$500,000/year):

Sharing Model Organisms Comments:

Genomic Data Sharing (GDS) Comments:

AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES: ACCEPTABLE,

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

Footnotes for 1 K08 AI125682-01A1; PI Name: Tran, Tuan Manh

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-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.

MEETING ROSTER
Microbiology and Infectious Diseases B Subcommittee
Microbiology, Infectious Diseases and AIDS Initial Review Group
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
MID-B November 2016
MID-B
11/04/2016 - 11/07/2016

CHAIRPERSON(S)

DENISON, MARK R., MD
PROFESSOR OF PEDIATRICS
DEPARTMENT OF PEDIATRICS
VANDERBILT UNIVERSITY MEDICAL CENTER
NASHVILLE, TN 37232

DOWDY, DAVID WESLEY, PHD, MD *
ASSISTANT PROFESSOR
DEPARTMENT OF EPIDEMIOLOGY
BLOOMBERG SCHOOL OF PUBLIC HEALTH
JOHNS HOPKINS UNIVERSITY
BALTIMORE, MD 21205

ACTING CHAIR

LUKEHART, SHEILA A., PHD
PROFESSOR
DEPARTMENT OF MEDICINE
HARBORVIEW MEDICAL CENTER
UNIVERSITY OF WASHINGTON
SEATTLE, WA 98104

ENGEL, JOANNE N., MD, PHD
PROFESSOR OF MEDICINE
MEDICINE, MICROBIOLOGY AND IMMUNOLOGY
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
SAN FRANCISCO, CA 94143

MEMBERS

BARBOUR, ALAN G., MD
PROFESSOR
DEPARTMENT OF MICROBIOLOGY AND MOLECULAR
GENETICS
SCHOOL OF MEDICINE
UNIVERSITY OF CALIFORNIA, IRVINE
IRVINE, CA 92697

FOWLER, VANCE G. JR, MD, MHS
PROFESSOR OF MEDICINE
DIVISION OF INFECTIOUS DISEASES
DEPARTMENT OF INTERNAL MEDICINE
DUKE UNIVERSITY MEDICAL CENTER
DURHAM, NC 27710

BERGMANN, CORNELIA, PHD
PROFESSOR
DEPARTMENT OF NEUROSCIENCES
LERNER RESEARCH INSTITUTE
THE CLEVELAND CLINIC FOUNDATION
CLEVELAND, OH 44195

HE, YONGQUN, DVM, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY
CENTER FOR COMPUTATIONAL MEDICINE
AND BIOINFORMATICS
UNIVERSITY OF MICHIGAN MEDICAL SCHOOL
ANN ARBOR, MI 48109

COLANGELI, ROBERTO, PHD *
ASSISTANT PROFESSOR
DEPARTMENT OF MEDICINE
RUTGERS NEW JERSEY MEDICAL SCHOOL
MEDICAL SCIENCE BUILDING (MSB)
NEWARK, NJ 07101

HUANG, SUSAN S., MD, MPH
PROFESSOR
DIVISION OF INFECTIOUS DISEASES
UNIVERSITY OF CALIFORNIA, IRVINE
ORANGE, CA 92868

DIRITA, VICTOR J., PHD
PROFESSOR
RUDOLPH HUGH ENDOWED CHAIR IN MICROBIAL
PATHOGENESIS
CHAIR, DEPT. OF MICROBIOLOGY & MOLECULAR GENETICS
MICHIGAN STATE UNIVERSITY
EAST LANSING, MI 48824

KIMA, PETER E., PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF MICROBIOLOGY
AND CELL SCIENCES
UNIVERSITY OF FLORIDA
GAINESVILLE, FL 32611

MESHNICK, STEVEN RICHARD, MD, PHD
PROFESSOR AND ASSOCIATE CHAIR
DEPARTMENTS OF EPIDEMIOLOGY AND MICROBIOLOGY
AND IMMUNOLOGY
GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, NC 27599

PARRISH, COLIN R., PHD
PROFESSOR
DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY
JAMES A. BAKER INSTITUTE
COLLEGE OF VETERINARY MEDICINE
CORNELL UNIVERSITY
ITHACA, NY 14853

* Temporary Member. For grant applications, temporary members may participate in the entire meeting or may review only selected applications as needed.

Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.

ROY, CRAIG R., PHD
PROFESSOR AND VICE CHAIR
SECTION OF MICROBIAL PATHOGENESIS
BOYER CENTER FOR MOLECULAR MEDICINE
YALE UNIVERSITY
NEW HAVEN, CT 06536

SCHOOLEY, ROBERT TURNER, MD *
PROFESSOR
DIVISION OF INFECTIOUS DISEASES
UNIVERSITY OF CALIFORNIA, SAN DIEGO
SAN DIEGO, CA 92023

STEVENSON, BRIAN, PHD
PROFESSOR
DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY
UNIVERSITY OF KENTUCKY COLLEGE OF MEDICINE
LEXINGTON, KY 40536

TORTORELLA, DOMENICO, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF MICROBIOLOGY
MOUNT SINAI SCHOOL OF MEDICINE
NEW YORK, NY 10029

ZWICK, MICHAEL EDWARD, PHD *
ASSOCIATE PROFESSOR
DEPARTMENT OF HUMAN GENETICS
EMORY UNIVERSITY SCHOOL OF MEDICINE
ATLANTA, GA 30322

SCIENTIFIC REVIEW OFFICER

BUCZKO, ELLEN S., PHD
SCIENTIFIC REVIEW OFFICER
SCIENTIFIC REVIEW PROGRAM
DIVISION OF EXTRAMURAL ACTIVITIES
NATIONAL INSTITUTES OF HEALTH/NIAID
BETHESDA, MD 20892

EXTRAMURAL SUPPORT ASSISTANT

CRAWFORD, KAMESHA C.
PROGRAM SPECIALIST
SCIENTIFIC REVIEW PROGRAM
DIVISION OF EXTRAMURAL ACTIVITIES, NIAID/NIH/DHHS
ROCKVILLE, MD 20892

PROGRAM REPRESENTATIVE

ROBBINS, CHRISTIANE M.
PROGRAM OFFICER
OFFICE OF THE DIRECTOR
DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES
NIAID/NIH/DHHS
5601 FISHERS LANE, ROOM 7G44 MSC 9826
BETHESDA, MD 20892