SUMMARY STATEMENT

PROGRAM CONTACT: (Privileged Communication)

Release Date: 10/25/2010

Application Number: 1R21 AI094009-01

Mercy Prabhudas

Principal Investigator

MCCUNE, JOSEPH M, MD, PHD

Applicant Organization: UNIVERSITY OF CALIFORNIA SAN FRANCISCO

Review Group: IHD

Immunity and Host Defense Study Section

Meeting Date: 10/14/2010

RFA/PA: PA10-069

Council: JAN 2011

PCC: I2H

Requested Start: 04/01/2011

Project Title: Human immune system layering and the neonatal response to vaccines

SRG Action: Impact/Priority Score: 14

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: 1A-Both Children and Adults, scientifically acceptable

Clinical Research - not NIH-defined Phase III Trial

<table>
<thead>
<tr>
<th>Project Year</th>
<th>Direct Costs Requested</th>
<th>Estimated Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

Time has passed since the application was reviewed. This sample may not reflect the latest format for summary statements. NIAID posts new samples periodically: [https://www.niaid.nih.gov/grants-contracts/sample-applications](https://www.niaid.nih.gov/grants-contracts/sample-applications)

The text from the application is copyrighted. You may use it only for nonprofit educational purposes provided the document remains unchanged and the PI, the grantee organization, and NIAID are credited.

Contact information. If you have any questions, email the NIAID Office of Knowledge and Educational Resources at deaweb@niaid.nih.gov.
RESUME AND SUMMARY OF DISCUSSION: The investigator proposes in this application to test his hypothesis that human fetal and adult hematopoietic stem/progenitor cells (HSPC) give distinct lymphocyte lineages to yield a range of fetal/adult T cells ratio at birth. Neonates with a high ratio will generate predominant Th2 responses to routine childhood immunizations. To test this hypothesis, the investigator will analyze cord blood from infants and correlate this profile with vaccine response to hepatitis B virus (HBV). The Committee felt that the proposed work will provide new information on neonatal immune regulation. Although high risk, the work can provide the foundation to identify those newborns at risk to serious infections and to develop personalized immunization strategies relevant to the immune maturity status. Other strengths include the outstanding investigator; his accomplished collaborators; the excellent research environment and resource; the well laid-out system; the innovative techniques; and, the intriguing supporting data. Despite of minor issues with some approaches, the enthusiasm of the Committee for this application is outstanding because of its feasibility.

DESCRIPTION (provided by applicant): The development of the mammalian immune system is typically thought to occur in a linear fashion, from immaturity to maturity as a function of antigen exposure. Previous findings in birds and in mice, however, indicate that this view is oversimplified. Thus, in these species, the developing immune system appears to be "layered" in a manner that is independent of antigen exposure, beginning as a multilineage fetal system that is replaced by an anatomically and biologically distinct multilineage system after birth. If so, then developmentally ordered and unique hematopoietic stem/progenitor cells (HSPC) could give rise to distinct lymphocyte lineages at different stages of development. In ongoing experiments, we have found that such immune system "layering" occurs in humans. Our preliminary data show that a vigorous human fetal immune response to exogenous antigens can be actively suppressed by antigen-specific Tregs, that these fetal Tregs are derived from a fetal-specific lineage of T cells, and that this lineage is generated by an HSPC that is distinct from that found in adults. These data suggest that the human immune system is comprised of two distinct waves: one generated from a "fetal" HSPC that exists in utero in the fetal liver and bone marrow, and another generated from a superseding "adult" HSPC that resides in the bone marrow at later time points. The former gives rise to an immune system that is prone to deliver a tolerogenic response to foreign antigens. The latter gives rise to an immune system that is more likely to generate an immunoreactive response (e.g., one including cytotoxic T cells and neutralizing antibodies). Given these findings, we hypothesize that physiologic layering of immune system ontogeny leads to a normal range in the ratio of fetal- to adult-type T cells at birth, with some neonates exhibiting a higher fraction of fetal T cells than others; and that those with a high ratio of fetal/adult T cells will generate predominant Th2 responses to routine childhood immunizations. These hypotheses will be addressed in the experiments of the following Specific Aims: (1) to determine the normal range of fetal to adult T cells in the umbilical cord blood of the full term neonate; and (2) to determine whether those full term neonates with a high ratio of fetal/adult T cells are more likely to generate a Th2-polarized immune response to routine childhood vaccines. Should this exploratory study reveal normal variation in the ratio of fetal to adult T cells at birth and should such variation be directly related to a Th2 skew after childhood vaccination, modalities aimed at changing this ratio more towards the adult lineage at birth may provide benefit to a substantial number of newborns.

PUBLIC HEALTH RELEVANCE: These exploratory studies are relevant to public health for two reasons. First, they may provide proof-of- concept evidence for the existence of a range in the extent of immune system "layering" in human neonates. Secondly, they may demonstrate that this range is itself related to (and possibly causal of) differences in the ability of neonates to withstand infections and to respond to vaccines.

CRITIQUE 1:

Significance: 2
Investigator(s): 1
Overall Impact:
The research in this application should lead to a paradigm shift in our understanding of the development of the neonatal immune system, particularly the shift from a tolerogenic phenotype in utero to a highly responsive phenotype after birth. The hypothesis is clearly presented, and the experiments are expected to unequivocally prove or disprove the hypothesis. Either way, the results will be of great interest. If the hypothesis proves to be true, it may become possible to identify those newborns at the highest risk for serious or life-threatening infections, and to tailor immunization strategies to an individual’s immune maturity status.

1. Significance:
Strengths
- The limited ability of the neonatal immune system to effectively resist infections is a major cause of morbidity and mortality. Understanding the reasons for this would allow us to identify infants at the highest risk for infections, might allow us to tailor organization approaches appropriately, and might ultimately lead to immune modulatory approaches.
- The clear demonstration of layering in the human developing immune system would greatly alter the prevailing paradigms of immune system development.

Weaknesses

2. Investigator(s):
Strengths
- The PI has a long and highly accomplished record in this field, and is exceptionally well-suited for these studies.

Weaknesses

3. Innovation:
Strengths
- The application of the concept of layering to the developing human immune system is innovative.
- The hypothesis that temporal differences in the layering process might lead to variations in the balance of Th1 vs Th2 type responses is highly innovative.
- The development of a transcriptional signature for fetal versus adult lineage T cells is highly innovative.

Weaknesses

4. Approach:
Strengths
- The extensive preliminary data, all of which is highly relevant to this proposal, is a clear strength of the application.
The extremely clear presentation of the experimental approach is another strength.
The inclusion of multiple collaborators at different sites as sources for cord blood is good.
The well-thought-out and clear data analysis plan is a strength.
The overall synergy between the aims and between the sub aims is remarkable.
The expected results and their interpretation are clearly presented.

Weaknesses

5. Environment:
Strengths
- The environment at UCSF and the associated clinical sites is essentially perfect for this study.

Weaknesses

Protections for Human Subjects:
Acceptable Risks and/or Adequate Protections
- No concerns

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Inclusion of Women, Minorities and Children:
G1A - Both Genders, Acceptable
M1A - Minority and Non-minority, Acceptable
C1A – Children Included, Acceptable
- no concerns

Vertebrate Animals:
Not Applicable (No Vertebrate Animals)

Biohazards:
Acceptable
- no concerns

CRITIQUE 2:
Significance: 1
Investigator(s): 1
Innovation: 1
Approach: 2
Environment: 1

Overall Impact:
This is an interesting and highly translational study proposed by a seasoned investigator, proposing to comprehensively define the phenotypic, transcriptional and functional analyses of cord blood in 200 infants of normal full term delivery, and to correlate this profile with vaccine response to HBV. The strength is the available resources and collaborators, a productive and accomplished PI as well as preliminary results that lend support to the proposed work. The proposed work will provide novel information about neonatal immune regulation that can then be correlated with vaccine response. One concern was the follow-up immune analysis using blood from neonates that may be difficult due to blood volume restrictions and parental consent. Further details in this regard would be helpful.

1. Significance:
Strengths
• The proposed work is highly translational and may provide important new information regarding vaccine response and immune regulation in infants.
Weaknesses

2. Investigator(s):
Strengths
• Dr. McCune is a well-established and well-funded investigator in the field of HIV immunology with a strong track record of productivity. Dr. McCune also has expertise in examining maternal/fetal immune regulation. Also somewhat related, he is RO-1 funded to study maternal/fetal transmission of HIV, relevant for this proposal.
• There are active ongoing interactions with Drs Thyne and Burt in patient enrollment and sample collection.
Weaknesses

3. Innovation:
Strengths
• The approach to examine immune regulation (‘layering’) in neonates and to correlate it to vaccine response (and possibly other outcome in the future) is innovative.
Weaknesses

4. Approach:
Strengths
• The cord blood has been collected and most infants receive HBV immunization. There is an established collaboration with Dr. Thyne and involvement of Dr. Burt that facilitates the recruitment/sample collection process and the overall feasibility.
• Certain transcriptional profiles for adult vs. fetal T cells have been defined based on preliminary results that can be applied.
• Methods are largely established in the lab and state-of-the-art.
Weaknesses
• While standard phenotyping should be feasible with blood drawn from the babies at 6 and 12 months, some estimation for overall cell need would be helpful for feasibility given that blood draw will be limited in neonates. As proposed, there will be standard phenotyping, proliferation assay with and without CD25+ T cell depletion stimulated with polyclonal activator, HepB
antigen and HepB peptides and intracellular cytokine staining for antigen-specific Th1/Th2 cytokine response.

- Would all parents agree to blood draws in their neonates? Would this be coordinated with other clinically indicated blood draws? Some feasibility and logistics consideration would be helpful in this regard, even if the investigators are experienced in this sort of work.

5. Environment:

Strengths

- The scientific environment and resources at UCSF are outstanding.

Weaknesses

Protections for Human Subjects:
Acceptable Risks and/or Adequate Protections

Inclusion of Women, Minorities and Children:
G1A - Both Genders, Acceptable
M1A - Minority and Non-minority, Acceptable
C1A – Children Included, Acceptable

Vertebrate Animals:
Not Applicable (No Vertebrate Animals)

Biohazards:
Not Applicable (No Biohazards)

CRITIQUE 3:

Significance: 1
Investigator(s): 1
Innovation: 1
Approach: 2
Environment: 1

Overall Impact:
The proposal is high risk but potentially outstanding in impact for understanding and manipulating immune response to childhood vaccination. Significance, investigative team, innovation and environment are outstanding. Minor issues with approach do not detract from overall Impact.

1. Significance:

Strengths
• Translating concept of “immune system layering” to evaluate the impact on immune responses of children to vaccination has potential long-term significance for human health.

Weaknesses

2. Investigator(s):
Strengths
• Outstanding PI and consultants.

Weaknesses

3. Innovation:
Strengths
• High risk, high reward project.
• Identification of molecular signatures of fetal and adult HSPC derived T cells is promising.
• Translational relevance to understanding and potentially manipulating vaccine response in children.

Weaknesses

4. Approach:
Strengths
• Intriguing preliminary data supporting concept, approach and feasibility.
• Multiple sources of cord blood for analysis.
• Well-described prospective study to track vaccine responses in context of fetal/adult T cell ratios in children.
• Powered to provide sufficient evidence to support (or not) future efforts in this area.

Weaknesses
• Identification of a cell surface marker to evaluate along with selected gene markers would improve resolution.
• The possibility that selected markers will not show co-ordinate restriction to T cells from fetal or adult HSPC between individuals is not discussed.

5. Environment:
Strengths
• Outstanding

Weaknesses

Protections for Human Subjects:
Acceptable Risks and/or Adequate Protections

Inclusion of Women, Minorities and Children:
G1A - Both Genders, Acceptable
M1A - Minority and Non-minority, Acceptable
C1A - Children and Adults, Acceptable

Vertebrate Animals:
Not Applicable (No Vertebrate Animals)

Biohazards:
Acceptable
  • Human blood products, acceptable

Budget and Period of Support:
Recommend as Requested

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): ACCEPTABLE

INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE

INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE

INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.


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. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.
MEETING ROSTER
Immunity and Host Defense Study Section
Immunology Integrated Review Group
CENTER FOR SCIENTIFIC REVIEW
IHD
October 14, 2010 - October 15, 2010

CHAIRPERSON
FINBERG, ROBERT WILLIAM, MD
PROFESSOR AND CHAIR
DEPARTMENT OF MEDICINE
UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL
WORCESTER, MA 01605

MEMBERS
BOYAKA, PROSPER N, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF VETERINARY BIO SCIENCES
THE OHIO STATE UNIVERSITY
COLUMBUS, OH 43210

BROSSAY, LAURENT, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF MOLECULAR MICROBIOLOGY AND IMMUNOLOGY
BROWN UNIVERSITY
PROVIDENCE, RI 02912

CAMPOS-NETO, ANTONIO, MD, PHD *
DIRECTOR
GLOBAL INFECTIOUS DISEASE RESEARCH CENTER
THE FORSYTH INSTITUTE
CAMBRIDGE, MA 02142

CHANG, KYONG-MI, MD
ASSOCIATE PROFESSOR
DIVISION OF GASTROENTEROLOGY
DEPARTMENT OF MEDICINE
UNIVERSITY OF PENNSYLVANIA
AND PHILADELPHIA VAMC
PHILADELPHIA, PA 191046144

CHEN, ZHENG W, PHD
PROFESSOR OF MICROBIOLOGY AND IMMUNOLOGY
DIRECTOR
CENTER FOR PRIMATE BIOMEDICAL RESEARCH
UNIVERSITY OF ILLINOIS AT CHICAGO
CHICAGO, IL 60612

CROTTY, SHANE P, PHD
ASSOCIATE MEMBER
DIVISION OF VACCINE DISCOVERY
LA JOLLA INSTITUTE OF ALLERGY AND IMMUNOLOGY
LA JOLLA, CA 92037

HARTY, JOHN T, PHD
ENDOWED PROFESSOR OF MICROBIOLOGY
DEPARTMENT OF MICROBIOLOGY
CARVER COLLEGE OF MEDICINE
UNIVERSITY OF IOWA
IOWA CITY, IA 52242

HARVILL, ERIC T, PHD *
ASSOCIATE PROFESSOR
DEPARTMENT OF VETERINARY SCIENCE
Pennsylvania State University
University Park, PA 16802

HUBER, BRIGITTE T, PHD
PROFESSOR
DEPARTMENT OF PATHOLOGY
TUFTS UNIVERSITY SCHOOL OF MEDICINE
BOSTON, MA 02111

HUNTER, CHRISTOPHER A, PHD
PROFESSOR AND CHAIR
DEPARTMENT OF PATHOBIOLOGY
SCHOOL OF VETERINARY MEDICINE
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PA 19104

INGALLS, ROBIN R, MD *
ASSOCIATE PROFESSOR OF MEDICINE
DEPARTMENT OF INFECTIOUS DISEASES
BOSTON UNIVERSITY SCHOOL OF MEDICINE
BOSTON, MA 02118

JEROME, KEITH R, MD, PHD *
ASSOCIATE MEMBER
DEPARTMENT OF INFECTIOUS DISEASES
FRED HUTCHINSON CANCER RESEARCH CENTER
SEATTLE, WA 98109

KANNEGANTI, THIRUMALA-DEVI, PHD *
ASSISTANT MEMBER
DEPARTMENT OF IMMUNOLOGY
ST. JUDE CHILDREN'S RESEARCH HOSPITAL
MEMPHIS, TN 38105

KAZURA, JAMES WALTER, MD
PROFESSOR AND DIRECTOR
CENTER FOR GLOBAL HEALTH AND DISEASES
SCHOOL OF MEDICINE
CASE WESTERN RESERVE UNIVERSITY
CLEVELAND, OH 44106

KOLLS, JAY K, MD *
PROFESSOR
DEPARTMENT OF GENETICS
LOUISIANA STATE UNIVERSITY HEALTH SCIENCE CENTER
NEW ORLEANS, LA 70112

LIU, YANG, PHD
DENANCREDE CHAIR OF IMMUNOLOGY
DIVISION OF IMMUNOTHERAPY
UNIVERSITY OF MICHIGAN
ANN ARBOR, MI 48109
METZGER, DENNIS W, PHD  
PROFESSOR AND DIRECTOR  
CENTER FOR IMMUNOLOGY AND  
MICROBIAL DISEASE  
ALBANY MEDICAL COLLEGE  
ALBANY, NY 12208-3479

MILLIGAN, GREGG N, PHD *  
PROFESSOR  
SEALY CENTER FOR VACCINE DEVELOPMENT  
UNIVERSITY OF TEXAS MEDICAL BRANCH  
GALVESTON, TX 77590-0436

PITHA-ROWE, PAULA M, PHD  
PROFESSOR  
DEPARTMENT OF BIOLOGY  
JOHNS HOPKINS UNIVERSITY  
BALTIMORE, MD 21218

PRINCE, ALICE S, MD *  
PROFESSOR  
DIVISION OF INFECTIOUS DISEASES  
DEPARTMENT OF PEDIATRICS  
COLUMBIA UNIVERSITY  
NEW YORK, NY 10032

REINECKER, HANS-CHRISTIAN, MD *  
ASSOCIATE PROFESSOR OF MEDICINE  
GASTROENTEROLOGY UNIT  
MASSACHUSETTS GENERAL HOSPITAL  
BOSTON, MA 02114

SCHLEISS, MARK R, MD *  
PROFESSOR AND DIRECTOR  
DIVISION OF INFECTIOUS DISEASES  
DEPARTMENT OF PEDIATRICS  
UNIVERSITY OF MINNESOTA  
MINNEAPOLIS, MN 55455

SIGAL, LUIS J, DVM, PHD  
MEMBER  
FOX CHASE CANCER CENTER  
PHILADELPHIA, PA 19111

SCIENTIFIC REVIEW ADMINISTRATOR
LAI, PATRICK K, PHD  
SCIENTIFIC REVIEW OFFICER  
CENTER FOR SCIENTIFIC REVIEW  
NATIONAL INSTITUTES OF HEALTH  
BETHESDA, MD 20892

GRANTS TECHNICAL ASSISTANT
WASHINGTON, WENDY M  
LEAD GRANTS TECHNICAL ASSISTANT  
CENTER FOR SCIENTIFIC REVIEW  
NATIONAL INSTITUTES OF HEALTH  
BETHESDA, MD 20892

* 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.