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SUMMARY STATEMENT
(Privileged Communication)

Release Date: 10/25/2010

Application Number: 1 R21 AI094009-01

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
Council: JAN 2011
Requested Start: 04/01/2011

RFA/PA: PA10-069
PCC: I2H

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

Project Year	Direct Costs Requested	Estimated Total Cost
1		
2		
TOTAL		

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.

We selected these applications as sound examples of good grantsmanship. That said, time has passed since these grantees applied, and so the samples may not reflect the latest application format or rules. Therefore, always follow your funding opportunity's instructions for application format. We post new samples periodically.

Please note that the application text may be used only for nonprofit educational purposes provided the document remains unchanged and the PI, the grantee organization, and NIAID are credited.

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1R21AI094009-01 MCCUNE, JOSEPH

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

Innovation: 1
Approach: 1
Environment: 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.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-10-080 at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-080.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. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

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October 14, 2010 - October 15, 2010

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* 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.