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TITLE: Battlefield Acquired Immunogenicity to Metals Affects Orthopedic Implant Outcome

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14. ABSTRACT The effects of battlefield injuries on the immune system are currently unknown, especially to metals such as shrapnel. Previous studies have link exposure to metal with increased immune responses (allergy). Thus battlefield injuries resulting in increased exposure to metal may sensitize individuals and lead to excessive immune responses to orthopedic implants, which many soldiers will need. The short term goal of this project is to understand whether soldiers with battle field injury and traumatic exposure to metal debris have increased immune system reactivity to metals (such as metal allergy or immune hypersensitivity alterations). We will compare the metal reactivity of immune cells isolated during a typical blood draw (6 regular blood draw tubes totaling 60mL) from soldiers exposed to metals in battle and compared with immune cell reactivity of 3 other groups of people (injured soldiers without exposure to metals fragments, non-injured healthy soldiers and non-soldiers of similar background). We expect to find that soldiers with injuries involving metal fragments will show elevated reactivity to metals and will thus be at greater risk of poor orthopedic implant outcome (e.g. Aluminum, Chromium, Cobalt Iron, Molybdenum, Nickel, Vanadium and Zirconium).					
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INTRODUCTION

The effects of battlefield injuries on the immune system are currently unknown, particularly those that involve exposure to metal, e.g. shrapnel. We have previously linked increased exposure to metal with increased incidence of metal reactivity. This, together with past reports of metal reactivity associated with decreased implant performance, suggests that battlefield injuries resulting in increased exposure to metal will sensitize the individual and lead to excessive immune responses to orthopedic implants, thus compromising their long term performance. The short term goal of this project is to understand whether soldiers with battle field injury and traumatic exposure to metal debris have increased reactivity to metals and thus establish if excessive immune responses to implant debris may affect long term orthopedic implant performance.

RESEARCH PLAN: If metal fragment exposure during trauma is enough of a stimulus to significantly change immune system reactivity, then soldiers exposed to this in battle will demonstrate altered metal-reactivity profiles when compared to injured soldiers without exposure to metals fragments and age/gender matched soldiers and non-combatants of similar background that have not been exposed to injury or metal debris.

Subject Groups: We will compare metal immune (T-cell) reactivity profiles of 4 different groups of soldiers, using metal-Lymphocyte Transformation Testing (metal-LTT) assays, flow cytometry and cytokine analysis (Table 1, Groups: 1) control soldiers with no injury, 2) soldiers with metal-fragment injury (6 months to 5 years post-injury, 3) soldiers with non-metal fragment injury, and 4) non-soldier matched controls (n=25 in each group). Subject involvement is limited to a 60mL blood draw, which will be sent to the PI's institution for analysis. All subjects will be recruited by self referral via flyers put up at medical centers that treat wounded soldiers. The consent process is described in the following paragraph. All blood draws will be the responsibility of the subject once they receive the kit, and as stated in the consent form will have to have their blood drawn at their local VA, Rush University Medical Center, your primary care physician or a local qualified phlebotomist.

Table 1. Number of subjects in Groups 3a-3d for lymphocyte and monocyte responses at a single time point (6month-5 years post-operative).

Subgroups	Subjects in Group
Group 1 Soldiers no injury (healthy)	25
Group 2 Soldiers w/ metal-fragment injury	25
Group 3 Soldiers w/ non-metal injury	25
Group 4 Controls (healthy non-soldiers)	25

BODY: Current Status:

The Study is finalizing the recruitment procedures for human soldier subjects because final approval for subject recruitment has not been obtained from the DOD. Procedural difficulties have resulted from 1) the inability to partner with an appropriate Army medical doctor co-investigator at medical facilities such as WRAMC for reasons detailed in the following sections and, 2) the eventual changing of the the study protocol to adapt to this situation such that soldiers can self recruit where the entire study is now conducted at Rush University Medical Center.

Original protocols, consent forms etc were approved by the Rush University Medical Center IRB. Subsequently they needed amending to change the recruitment site to exclusively that of the PI, Rush University Medical Center. These amended consents and protocols were then reviewed by the Human Research Protection Office at the U.S. Army Medical Research & Materiel Command and a list of changes were requested. These requested changes were then made and the amended protocols and consents were again processed and preliminarily approved by the Human Research Protection Office at the U.S. Army Medical Research & Materiel Command, pending Rush IRB approval. These provisionally approved amendments to the original approved protocols and consents and been re-approved by the PIs institutional review board (Rush University Medical Center) and these amended protocols have been sent to the Human Research Protection Office at the U.S. Army Medical Research & Materiel Command for final approval prior to the putting up of fliers and beginning the recruitment of subjects.

Past Year Effort:

The following details our good faith efforts to attempts to conduct the study on time while trying to accommodate the changing ground conditions and requirements.

- 1) Attempts to find an ARMY PI were not met with success due to:
 - a. Tours of duty for qualified personal
 - b. Lack of enough fiscal support for dedicated staff for study
 - c. Hurdles associated with obtaining local WRAMC and Army approval for officers to recruit lower ranking soldier subject, even for minimal risk (blood draw) limited studies.

- d. The closing of WRAMC
- 2) The protocol and consent forms were changed considerably from the original approved process. These changes are summarized below.

Updated Protocol and consent forms per the request of the US Army and DOD IRB review: changes are limited to clarifications in the protocol and consent forms/questionnaire requested by the Army, and the risks to subjects remain the same:

Consent Form

- 1) Kyron McAllister has been added as a contact.
- 2) "(6 months to 5 years post-injury)" was added as a wounded soldier participant condition
- 3) Walter Reed Army Medical Center was deleted as a study site.
- 4) Study group descriptions were clarified.
- 5) Subjects are now asked to sign and send back the consent form before blood collection tubes/kit are sent out.
- 6) A questionnaire about basic health and immunological status has been added.
- 7) Subjects have been further directed that they will need to have their blood drawn at their local VA center or referred by their primary care doctor.
- 8) The "benefits of taking part in this study" has been clarified to state "We will conduct some routine immunologic testing that will be made available to you, where this test may indicate that you have a metal allergy, this may be of value to you or your orthopedic surgeon in selection of implant component in any pending or future surgeries but it may not be of any value to you."

Protocol

- 1) A title page has been added
- 2) Added text specifying subject groups has been added.
- 3) Added text specifying how subjects will self recruit with via a flyer, has been added.
- 4) A section on Eligibility has been added, specifying that because soldiers will not be recruited by doctors in the armed services (officers), they are not considered vulnerable populations.
- 5) Specimen collection and storage has been clarified that none of the samples will be stored for long term use.
- 6) A data collection and storage section has been added to describe how all data will be protected and transmitted securely.
- 7) A privacy/sensitive Information section has been added to explain how no sensitive health information will be obtained from the subjects regarding legal status or participation in illegal activities.
- 8) A key personnel section has been added to describe the key personnel involved in the study and the role for each.
- 9) An analysis section has been added to clarify what information will collected, measured and compared.
- 10) Shipping instructions included in the blood collection kits sent out have been added, Appendix A.
- 11) A general information sheet for the subjects about metal-LTT testing has been added to the protocol and will be included in the kits sent to subjects.
- 12) Example results of the testing performed on the subjects has been included in the protocol.
- 13) A 2-page questionnaire that will be included with the consent forms sent to subjects has been included in the protocol, Appendix B.

KEY RESEARCH ACCOMPLISHMENTS: Pending.

We have over the past year determined means to start recruitment without a dedicated Army physician.

REPORTABLE OUTCOMES: Pending start of recruitment of subjects.

CONCLUSION: The Study is finalizing the recruitment procedures for human soldier subjects due to procedural difficulties in mechanistically involving a Army physician (officer) to recruit soldiers (vulnerable subjects). Unavoidable procedural difficulties have resulted from 1) the inability to partner with an appropriate Army medical doctor co-

investigator at medical facilities such as WRAMC for reasons detailed in the following sections and, 2) the eventual changing of the study protocol to adapt to this situation such that soldiers can self recruit where the entire study is now conducted at Rush University Medical Center. Scientific findings are pending.

REFERENCES: None

APPENDICES:

- 1) The approval process for human subjects involved the coordination of three approval bodies, Rush University IRB, Human Research Protection Office at the U.S. Army Medical Research & Materiel Command and Grants Management for Directed Medical Research Programs U.S. Army Medical Research and Materiel Command. The details of this last email interaction requiring protocol and consent changes are provided below:

Classification: UNCLASSIFIED

Caveats: NONE

Dear Dr. Hallab,

I have received and reviewed these materials this morning (everything looks good). Please wait until you get my official email before submitting the changes to your IRB. Hopefully, Caryn will have a chance to approve my recommendation over the next several days to send you back to your local IRB.

Best regards,

Pat

-----Original Message-----

From: Nadim J Hallab [<mailto:Nadim.Hallab@rush.edu>]

Sent: Friday, September 30, 2011 9:44 PM

To: Shank, Patricia A CTR US USA

Subject: RE: A-16570.a, Follow-up Administrative Review (Proposal No. OR090690, Award No. W81XWH-10-2-0138 (UNCLASSIFIED))

Hi Pat

Many thanks. These look like important issues to address prior to starting recruitment and we are more than happy to clarify these in the protocol, consent and Hipaa forms.

Attached are the changed forms that are specified in the answers to your questions, listed below.

Let me know if there is anything I have missed.

We hope this will move us closer to approval and appreciate all your efforts.

Many thanks
Best Regards
Nadim

Dr Nadim James Hallab

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ANSWERS TO QUESTIONS:

1. Required Information/Documentation

The sections on recruitment and consent of subjects in the protocol state that "The consent process will be started on the phone when the subjects call and continued with a written consent form given to the participants with the blood collection kit to be administered by the primary physician." Please clarify what is meant by "administered by their primary physician." Please confirm that the intent is that the local physician or laboratory will provide the service of the blood draw only. It reads as if the primary physician will both consent subjects and obtain the blood draw. If the local physician is obtaining consent for research, he/she would be considered engaged in research and would need local IRB approval, etc. If this is not the intent, please explain this and consider revising the protocol to state who on the research team is obtaining informed consent for the study and whether the consent must be signed and returned to the research staff prior to obtaining the blood for the study.

ANSWER: "ADMINISTERED BY THEIR PRIMARY PHYSICIAN" HAS BEEN DELETED AND THE PROTOCOL NOW STATES IN A SIMILAR FASHION TO THE CONSENT THAT "the consent process will continue by phone including reminding the subjects they can contact us at any time to answer their questions and that their blood draw can be conducted by any trained/qualified phlebotomist (including their primary care center) and a reminder that their blood must be delivered to a Fed-Ex drop-off immediately after the blood draw" (PROTOCOL; page3-para 4). ADDITIONALLY WE HAVE INCLUDED IN THE PROTOCOL THE FOLLOWING " All blood draws will be the responsibility of the subject once they receive the kit, and as stated in the consent form will have to have their blood drawn at their local VA, Rush University Medical Center, your primary care physician or a local qualified phlebotomist. (PROTOCOL: PAGE3-PARA3) THE STUDY PERSONNEL THAT WILL OBTAIN INFORMED

CONSENT IS IDENTIFIED NOW INCLUDED IN THE PROTOCOL..."The consent process will be conducted by Kyron McAllister and/or Dr Nadim Hallab (contact numbers are included in the consent documents)."(PROTOCOL PAGE 3 PARA 4).

While consent is implied by having the blood draw, please give consideration to obtaining signed, informed consent prior to sending the kit to ship the blood so that written consent is received prior to the blood draw as subjects may not always be compliant in returning the form.

ANSWER: THIS IS A GREAT IDEA, AND THE PROTOCOL AND THE CONSENT HAVE BEEN CHANGED TO REFLECT THIS MINOR BUT IMPORTANT CHANGE IN PROCEDURE "The consent process will be conducted by Kyron McAllister and/or Dr Nadim Hallab. The consent process will be started when the subjects initiate contact with us on the phone and express interest in being a subject. Once we explain the study (as stated in the consent form) and answer any questions, if they express a desire to be in the study then a consent form and questionnaire will be mailed to the prospective subject, where they can review the forms at their leisure and decide if they wish to be a subject. After receipt of subject-signed consent forms and questionnaires, the subjects will be sent return shipping instructions, a kit containing blood draw tubes, shipping containers and return shipping labels. (PROTOCOL: PAGE 3 PARA 4)

AND "...Use the tubes in the provided kit we will send to you after we receive this signed consent to have your blood drawn at your location (your local VA, Rush University Medical Center, your primary care physician or a local qualified phlebotomist). Approximately 60mL (approximately 4 tablespoons) of your blood will be collected into six (provided) 10mL vacutainer tubes." (consent: page 2 para 2).

2. Revisions to be made to the consent form and HIPAA:

a. Please revise the section entitled, "How many people are expected to take part in the study?" The first sentence states that all subjects will be "self-enrolled"... Please correct the language to state that all subjects will be "self-referred"...

ANSWER: THE CHANGES TO THE CONSENT HAVE BEEN MADE BY CHANGING "SELF-ENROLLED" TEXT TO READ "SELF-REFERRED".

b. Please remove Walter Reed Army Medical Center from the HIPAA Authorization Confidentiality section of the form if they are not longer getting information as they are not a discreet research site.

ANSWER: THE CHANGES TO THE HIPAA HAVE BEEN MADE (deleting Walter Reed Army Medical Center).

thanks again

From: Shank, Patricia A CTR US USA [patricia.a.shank.ctr@us.army.mil]

Sent: Friday, September 30, 2011 2:38 PM

To: Nadim J Hallab

Cc: Bennett, Jodi H Ms CIV USA MEDCOM USAMRMC; Shankle, Jennifer E Ms CIV USA MEDCOM USAMRAA;

Darnell, Miriam R Dr DoD Af US USA MEDCOM CDMRP; Brosch, Laura R Dr CIV USA MEDCOM USAMRMC;

Duchesneau, Caryn L Ms CIV USA MEDCOM USAMRMC; Marshall, Peter J Mr CTR US USA MEDCOM USAMRMC

Subject: A-16570.a, Follow-up Administrative Review (Proposal No. OR090690, Award No. W81XWH-10-2-0138 (UNCLASSIFIED))

Classification: UNCLASSIFIED

Caveats: NONE

Subject: Protocol, "Battlefield Acquired Immunogenicity to Metals Affects Orthopedic Implant Outcome," Submitted by Nadim Hallab, PhD, Rush University Medical Center, Chicago, Illinois, Proposal Number OR090690, Award Number W81XWH-10-2-0138, HRPO Log Number A-16570.a

Dear Dr. Hallab,

The research protocol and supportive documents for your research project, received by the US Army Medical Research and Materiel Command on 3 and 6 September 2011 have been reviewed for compliance with human subjects' protection requirements. Below you will find a list of requests for clarification, documents, and revisions that need to be addressed to continue the review process in our office. Please provide the clarifications, documents, and revisions as requested within thirty (30) days.

Your critique is welcome. If I have misunderstood any item, please let me know.

Modifications to the protocol, consent form, and supporting documents will required review the IRB; however, I would suggest waiting to return to the IRB until my review is complete.

You are reminded not to initiate the study until you receive approval from this office.

1. Required Information/Documentation

The sections on recruitment and consent of subjects in the protocol state that "The consent process will be started on the phone when the subjects call and continued with a written consent form given to the participants with the blood collection kit to be administered by the primary physician." Please clarify what is meant by "administered by their primary physician." Please confirm that the intent is that the local physician or laboratory will provide the service of the blood draw only. It reads as if the primary physician will both consent subjects and obtain the blood draw. If the local physician is obtaining consent for research, he/she would be considered engaged in research and would need local IRB approval, etc. If this is not the intent, please explain this and consider revising the protocol to state who on the research team is obtaining informed consent for the study and whether the consent must be signed and returned to the research staff prior to obtaining the blood for the study. While consent is implied by having the blood draw, please give consideration to obtaining signed, informed consent prior to sending the kit to ship the blood so that written consent is received prior to the blood draw as subjects may not always be compliant in returning the form.

2. Revisions to be made to the consent form and HIPAA:

a. Please revise the section entitled, "How many people are expected to take part in the study?" The first sentence states that all subjects will be "self-enrolled"... Please correct the language to state that all subjects will be "self-referred"...

b. Please remove Walter Reed Army Medical Center from the HIPAA Authorization Confidentiality section of the form if they are not longer getting information as they are not a discreet research site.

Additionally, be advised that the following are reporting requirements and responsibilities of the Principal Investigator to the United States Army Medical Research and Materiel Command's (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO):

1. The protocol will be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP HRPO and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP HRPO.

2. Accurate and complete study records will be maintained and made available to representatives of the U.S. Army Medical Research and Materiel Command as a part of their responsibility to protect human subjects in research. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.
3. All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study will be promptly reported by phone (301-619-2165), by email (hsrrb@amedd.army.mil <blockedmailto:hsrrb@amedd.army.mil> <<mailto:hsrrb@amedd.army.mil> <blockedmailto:hsrrb@amedd.army.mil> >), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RP, 504 Scott Street, Fort Detrick, Maryland 21702-5012.
4. Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the IRB, the institution, the Sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.
5. Any deviation to the protocol that may have an adverse effect on the safety or rights of the subject or the integrity of the study will be reported to the USAMRMC ORP HRPO as soon as the deviation is identified.
6. Major modifications to the research protocol and any modifications that could potentially increase risk to subjects will be submitted to the USAMRMC ORP HRPO for approval prior to implementation. All other amendments will be submitted with the continuing review report to the USAMRMC ORP HRPO for acceptance.
7. A copy of the approved continuing review report and the local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the USAMRMC ORP HRPO as soon as these documents become available.
8. The knowledge of any pending compliance inspection/visit by the FDA, OHRP, or other government agency concerning this clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements that relate to this clinical investigation or research will be reported immediately to USAMRMC ORP HRPO.

If you have any questions, please feel free to contact me.

Regards,

Patricia A. Shank, RN, BSN, CCRP, PMP
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Caveats: NONE

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Caveats: NONE

SUPPORTING DATA: Pending final data.