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TITLE: Battlefield-Acquired Immunogenicity to Metals Affects Orthopaedic 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).

**15. SUBJECT TERMS**
Battlefield injury, metal allergy, immune reactivity , Delayed Type Hypersensitivity, Trauma, orthopedic, implants, lymphocyte, metal-LTT, ions, implant debris

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**Battlefield Acquired Immunogenicity to Metals Affects Orthopedic Implant Outcome Rush University Medical Center**

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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:** ***Final Status:***

**Section II. Final Report: This study is under no-cost extention due to delay and difficulties in achieving approved consent form for recruiting soldier subjects. Extensive good faith efforts to recruit soldiers have been pursued over the last 6 months (after final approval of study and consenting documents) to obtain soldier volunteer subjects (self recruited via flyer) to enroll in the study. To date we have contacted over 30 facilities and soldier organizations including the Toxic Embedded Fragment Center, and have not been able to recruit a single wounded soldier into the study (the core study group). We did not budget for this time and effort and thus have volunteered this extra time to try to recruit subjects and have kept the funding in place and reserved for subject testing.**

**Final Report Phase 2: We plan to make further financial commitments to this study and sacrifice current funding to put in place a financial incentive of $75 for each soldier/subject to provide us the required approximately 60mL (6 tubes) of blood. This additional $9375 will be deducted from our current funding and we will be forced to slightly reduce the scope of testing, supplies and or effort but will**

**gladly incur the loss financially if it results in a successful recruitment of soldiers to complete this study.**

### *Current Status: 6 of 125 subjects recruited (study pending recruitment approval)*

The Study has begun recruiting and testing subjects for the past 4 months. While we have recruited and tested control subjects, we have not recruited any soldier subjects into this study. We have been contacting VAs and veterans groups around the country and have been told our recruiting flyer is up at several institutions (detailed in following). However, we have not recruited any soldiers to date. The following section details our efforts to recruite soldier subjects.

**KEY RESEARCH ACCOMPLISHMENTS:** Pending.

We have start collecting control subject and results are as expected. We have not been able to recruit a single wounded souldier despite aggressive recruiting via Army and Ruch University approved flyer. .

**REPORTABLE OUTCOMES:** Pending results of no-cost extension.

**CONCLUSION:** The Study requires additional resourses or sacrifices within the current budget in order provide recruitement incentive for soldier subjects. Current amendent procedures are underway to ofer this incentive. In additions Dr David Schroder, Director of clinical operations in the Dept of Orthopedic Surgery at WRNMC has recently (04-23-2012) indicated his willingness to participate in our study and we are in the process of adding him to our study and obtaining approval in the no-cost extension period. The involvement of a clinical military co-investigator that we can provide with sufficient funding to support a non-officer research staff is crucial to the timely success this project. We currently lack the ability to recruit patients at a military trauma center and lack personnel help to facilitate blood draws and the organize requisite mailing of samples to our laboratory overnight. This is an apparent necessity to facilitate completion of this investigation, and a deficit of the current study..

**REFERENCES:** None

**APPENDICES:**

***Past Effort:***

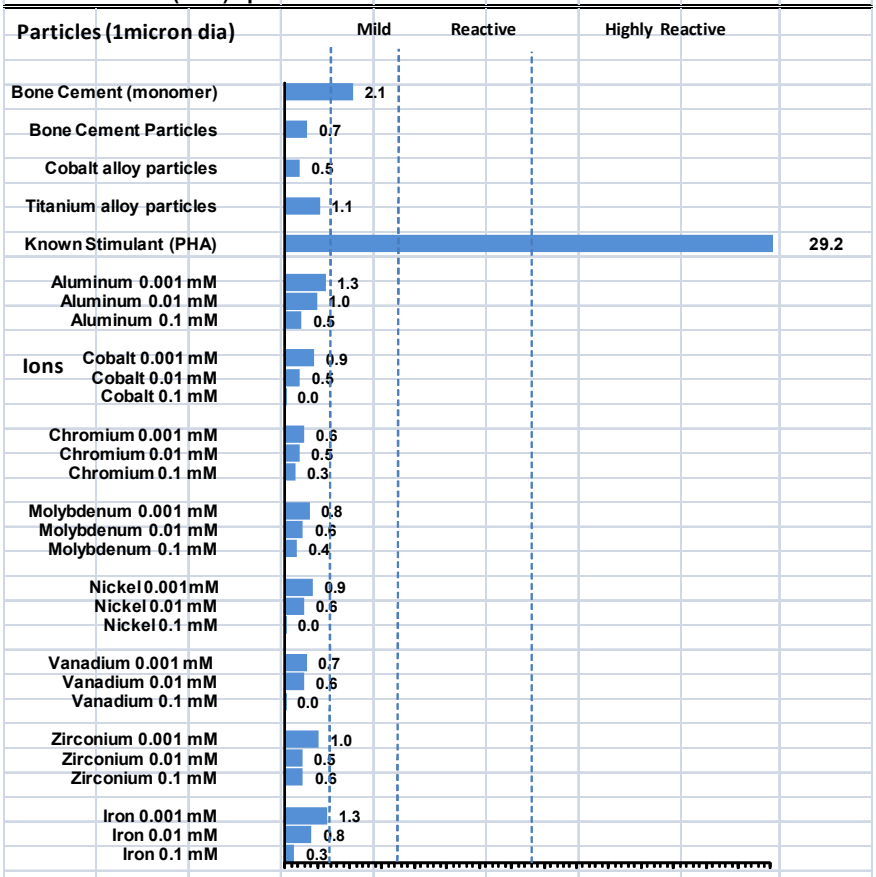
***1-Testing has begun on control groups n=7 recruited.***

***Example results are shown on the following graph and are typical for control subjects with no reactivity to metals. Postive control PHA demonstrates high reacitivity affirming that testing was conducted appropriately.***

Metal-LTT Analysis Report

**Panel 2**

| | | | |
|---|---|---|---|
| **Report Date** | 4/17/2012 | | |
| **Report Time** | 12:51 PM | **Sample Collected** #N/A | #N/A |
| **Patient ID** | 0 | **Sample Received** #N/A | #N/A |
| **Report For** | **NADIM HALLAB** | **DOB** #N/A | |
| **Attending Physician** | **#N/A** | | |
| **Control cpm** | 1308.0 | | |
| **Positive control (PHA) cpm** | 38247.3 | | |




| | |
|---|---|
| Mildly Reactive | 2 to 4 |
| Reactive | 4 to 8 |
| Highly Reactive | above 8 |

**2-The following details our good faith efforts to attempt to recruit soldier subjects that have indwelling metal fragment injury (selected points of contact):**

- Contacted angel.herrera@illinois.gov at the Illinois Army Reserve and National Guard public relations - **3-28-2012**
- Contacted 'lisa.moutria@va.gov' at the Veteran's Administration she agreed to post the flyer but when I followed -up with another V.A. office he was clear that it was against policy. - **4-20-2012**
- Contacted Harry Klemfuss who explained V.A.'s policy

"Hi Kyron,
The Veterans Health Administration has to follow Handbook 1200.05, which states:

**VHA HANDBOOK 1200.05 October 15, 2010**

n. **Advertising.** The facility Director is responsible for ensuring that recruiting documents, flyers, and advertisements for non-VA research are not posted within or on the premises of a VA facility. Posting of such documents may give the Veteran or visitors to the VA facility the impression that the non-VA study is VA-approved research, the VA supports or endorses the research, or that VA will pay for the research expenses that are incurred."

**This indicates that in general VA's will not be able to display our flyer for recruiting subjects into this research study.**

- Contacted Castillo, Carrie A SGT USAR DIV WEST PAO [carrie.castillo@usar.army.mil] who agreed to post and distribute the flyers. - **4-4-2012**
- Contacted aallred@woundedwarriorproject.org at the Wounded Warrior Project who agreed to distribute the flyer to all of their offices. **4-23-2012**
- Ft. McCoy, WI - 5-23-2012 - contacted public affairs and they would look into it.

The following places were contacted and we have not received replies:

- Indiana National Guard 3-10-2012
- San Diego Orthopedics 4-17-2012
- South Texas Veterans Health Care System - 3-18-2012
- North Carolina Veterans Affairs Office - 4-20-2012
- U.S. Naval Station Great Lakes - 4-22-2012
- Sent flyer to Ft. Bragg still waiting approval -5-3-2012
- U.S. Wounded Solders Foundation 5-23-2012

## Section IV.

In the following no-cost extention period we will conduct the following:

1) Continue to reach out to veterans groups to post current flyer.
2) If we cannot succed in enrolling soldiers in the next two monthes, we will change the flyer to add an incentive of $50 for subject volunteers (but will have to reduce the scope of test to account for this increased cost.
3) Will continue to try to find a collaborator at the The Walter Reed National Military Medical Center that has close contact with soldiers.

4) Will persue additional funding to help secure a collaborator at The Walter Reed National Military Medical Center.

**Section V.**

Administration comments: To date >95% of received funding has been retained to complete this testing in the no-cost extension period.