LSUHSC-NO IRB Protocol

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Study Title: Proteomic analysis of trauma-induced heterotopic ossification formation

Funding Agency: Department of Defense

1. Study aim, background, and design

Over the past decade, improved personal protective equipment and medical support has reduced combat fatalities substantially among wounded war fighters. As a result, survivors are more likely to present with severe trauma to their arms and legs that will need multiple reconstructive surgeries or amputation during their recovery. The orthopaedic doctors caring for these wounded service personnel have been concerned by the fact that over 60% of these patients go on to form abnormal bone within the soft tissue of their injured limbs. This condition, known as Heterotopic Ossification (HO), causes pain, loss of mobility, and often requires additional surgeries to remove the rock hard tissue that has replaced their fat and muscle. If left in place this abnormal bone can continue to grow and interfere with prosthesis placement and recovery. While there are theories to explain why HO might occur, doctors still do not fully understand the mechanism(s) causing this disorder. Without knowing the mechanism, doctors find it difficult to predict which patients might be at risk for developing HO or to decide which drugs or treatments to use that would prevent HO from happening in these patients.

The currently available treatments for HO have many undesirable side effects which can complicate the overall recovery process. The Specific Aims of this Idea Development proposal address these important questions by using blood samples collected from wounded warriors and civilians with bone injuries. The study will compare the blood samples between patients who either have or have not developed HO during the first year after their injury. The first experiments will ask, does the blood or wound fluid contain any proteins that can stimulate fat or muscle cells to form bone in the laboratory? This will test whether patients with HO have factors circulating in their blood or around the wound that specifically stimulate bone formation as compared to patients without HO. If this proves true, it will be an important step forward in understanding how HO occurs. The second experiments will ask, what is the identity of the protein(s) in the HO blood that might cause bone to form? The study will use a state of the art technique that can analyze all of the proteins in the blood and find out which ones are present. Using computer technology, researchers can then learn the name and function of these proteins of interest. This type of information will be of particular value to the orthopaedic surgeons caring for HO patients. The presence or absence of these proteins in the blood can be used to predict which patients might develop HO or to monitor HO treatment. Also, by knowing the names of the proteins involved in HO, doctors and pharmacists might be able to tell which drugs can be used to prevent HO formation at the time of injury.
Wounded warriors and civilians would benefit directly from these advances since doctors would be able to prevent HO with a pill or drug or, at the very least, reduce the number of surgeries required to treat the condition when it happens. There would be minimal risk to wounded war fighters and civilian patients enrolled in this study. Patients would only be required to provide several extra tablespoons of blood to doctors during the weeks to months following their injury. This might cause a bruise but no other complications and would not interfere with their recovery in any way. It is predicted that this information could be used to improve patient care within 5 years or less after the study is completed. As a result, war fighters recovering from blast injuries in the future will have a better outlook than today’s combat casualties. They will no longer have the same high risk of developing HO and can avoid the emotional, psychological and physical damage sustained as a result of multiple orthopaedic surgical procedures. As a result, the effort, time, and cost of wounded warrior’s recovery from life threatening orthopaedic trauma could be substantially reduced and as such, accelerate their return to active duty.

2. Subject Population
The study will recruit civilian and military patients with the following inclusion/exclusion criteria:

### Inclusion Criteria
1. Either male or female
2. Age ≥ 18 or <65 years of age
3. Orthopedic Injury involving torso or extremities secondary to trauma AND
4. Operative acetabular fracture AND/OR
5. Open femur fracture including gunshot wounds AND/OR
6. Terrible triad of the elbow AND/OR
7. Operative distal humerus AND/OR
8. Traumatic amputation of major extremity (i.e. femur, tibia, humerus, forearm) on initial hospitalization AND/OR
9. ISS score >16 with a concomitant orthopedic injury

### Exclusion Criteria
1. History of malignancy (except basal cell skin Ca)
2. Age <18 or >65 years of age
3. History of 1 month or more of the following medications associated with osteoporosis during the year prior to orthopedic injury: insulin; glucocorticoid receptor agonist (e.g. prednisone, medrol); peroxisome proliferator activated receptor γ agonist (e.g. Avandia, Actos)
4. History of osteoporosis
5. Member of a vulnerable population (pregnant women, prisoners, permanently cognitively impaired)

Samples will be collected and/or accessed from up to 300 civilian (LSUHSC-NO) and up to 500 military (Walter Reed National Military Medical Center Bethesda) over the 3 year study period. Subjects are recruited from those subjects with orthopaedic trauma meeting the inclusion/exclusion criteria who are increased risk of HO development. No subjects under the age of 18 or vulnerable populations (pregnant women, prisoners, permanently cognitively impaired) will be included in this study. Recruitment will be performed by the principal investigator and collaborating surgeons at LSUHSC-NO and by collaborators at Walter Reed National Military Medical Center Bethesda under IRB protocols and consent documents submitted at those institutions. Subjects will be approached by the Principal Investigator and his collaborating orthopaedic surgeons (Co-Investigators) at the time of the patient’s initial evaluation for the trauma injury.

3. Procedure
All research subjects will provide a serum sample (10 ml blood draw) the day of initial surgery if possible, each return to the OR, at each debridement, and at all post-op orthopedic clinic visits. Wound fluid collection will be
done at the day of initial surgery if possible, each return to the OR, at each debridement, each dressing change, and at all post-op orthopedic clinic visits if fluid is available. Patients will not be brought back to clinic more frequently than the standard of care. All subjects will be monitored for heterotopic ossification at the site of surgery by physical exam and/or radiographic analysis post operatively during follow up. Radiographic analyses will include standard radiography of the fracture site and, if necessary, CT scans to assess and document features of heterotopic ossification or other evidence of pathology (delayed union or non-union). The total time commitment for the subject for any given blood specimen collection will be approximately 10 minutes and for the radiographic examinations approximately 1 hour. Total time commitment will be extended over a period of up to 12 months. Clinical studies will be conducted at LSUHSC-NO Department of Orthopaedic Surgery (LSU University Hospital and LSU orthopedic clinics located at Poydras Ave, St Charles Ave, and Ochsner Kenner) or at the collaborating medical center (Walter Reed National Military Medical Center).

4. Risks

Subjects enrolled in the study will undergo additional phlebotomy procedures and will be at risk for the complications of hematoma, skin abrasion, and/or skin infection. The Principal Investigator and the study staff will use all routine phlebotomy precautions to minimize the risk of any complications in the patient population.

All specimens will be de-identified by the investigators at LSUHSC-NO and Walter Reed National Military Medical Center Bethesda prior to the transfer of the blood samples to the investigative team at Tulane University Center for Stem Cell Research and Regenerative Medicine. The Tulane investigative team will remain blinded to all possible information linking the specimen to a particular subject. Only the patient’s surgeon and his/her medical associates at either LSUHSC-NO or Walter Reed will be privileged with such information. Any patient identifiers will be kept exclusively in secure files of the LSUHSC-NO and Walter Reed principal investigators or their designees at the either LSUHSC-NO or Walter Reed National Military Medical Center Bethesda. Physical (paper) files will be kept secure in locked rooms or cabinets and electronic files will be kept secure under password protection.

Research data from the de-identified blood specimens obtained at the Tulane Center for Stem Cell Research and Regenerative Medicine will be kept as hard copy (paper) and electronic records by the Tulane principal investigator and his post-doctoral fellow. Both the primary data and spreadsheets compiling the total data of the project will be retained. Electronic records will be maintained under password protection and primary data will be kept in locked filing cabinets accessible only to the Tulane principal investigator and his post-doctoral fellow.

5. Benefits

There are no immediate benefits to the patients for participation in this study, but the knowledge gained from the study may benefit society in general. Study participants will be brought to the clinic for multiple follow up visits with physical exam and radiography which may exceed the number of routine visits for non-participating patients with an equivalent orthopedic condition.

6. Remuneration
There will be no remuneration to subjects for their participation in this study.

7. Academic or Extra Credit

NA.

8. Costs

There will be no costs to the subject for participation in this research study.

9. Alternatives

The alternative is that the subjects do not have to participate in the research.

10. Consent process and documentation

Consent will be obtained by the principal investigators and collaborating surgeons at LSUHSC-NO and Walter Reed National Military Medical Center Bethesda using informed consent documents reviewed and approved by the IRB of record at these institutions. All signed informed consent documents will be retained by the principal investigators at LSUHSC-NO and Walter Reed for a minimum of 3 years following the completion of the study. No details of the subject’s identity or the signed consent documents will be made available to the Tulane investigative team at any time.

11. Qualifications of the investigators

The LSUHSC-NO principal investigator (Dr. Dasa) and his co-investigators (Drs. King, Krause, and Lee) are board certified in orthopaedic surgery, are full time faculty in the Department of Orthopaedic Surgery, are licensed to practice medicine in the State of Louisiana, have collective experience as the principal investigator(s) on funded clinical trials and multiple IRB approved protocols at LSUHSC-NO, have completed the CITI Training relevant to biomedical trials, and have anywhere from 3 to 40+ years of clinical experience at the faculty level. Collectively, the investigators are well qualified to conduct this Department of Defense funded clinical study at LSUHSC-NO.

12. References
