

**SUMMARY STATEMENT**  
( Privileged Communication )

Release Date: 02/26/2010

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Application Number: 1 R01 NS067012-01A1

Principal Investigator

BRUEHL, STEPHEN PHD

Applicant Organization: VANDERBILT UNIVERSITY

Review Group: BMIO  
Behavioral Medicine, Interventions and Outcomes Study Section

Meeting Date: 02/04/2010  
Council: MAY 2010  
Requested Start: 07/01/2010

RFA/PA: PA07-282  
PCC: PORTELCN

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**Project Title:** Mechanisms of Complex Regional Pain Syndrome Following Surgical Trauma

**SRG Action:** Impact/Priority Score: 33 Percentile: 19

**Human Subjects:** 44-Human subjects involved - 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:** 3A-No children included, scientifically acceptable  
Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested	Estimated Total Cost
1	498,226	773,356
2	499,151	774,792
3	499,648	775,563
4	488,930	758,927
5	421,615	654,439
<b>TOTAL</b>	<b>2,407,570</b>	<b>3,737,077</b>

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**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.

## 1R01NS067012-01A1 BRUEHL, STEPHEN

### PROTECTION OF HUMAN SUBJECTS UNACCEPTABLE

**RESUME AND SUMMARY OF DISCUSSION:** This application proposes a prospective design assessing the natural progression of CRPS symptoms in a post-surgical TKA population, with assessments at baseline, 6 weeks, 6 months, and 12 months post surgery. Greater understanding of the mechanisms of CRPS will help to inform better future treatments. Both the environment and investigators are very good. The investigators were very responsive to prior critiques. However the committee noted a number of areas that needed further strengthening: the scope of the study is still too broad; and there are too many hypotheses for the small sample of patients likely to actually have CRPS. Additionally, poor outcomes in TKA may be due to the presence of CRPS; but could also be due to other confounds and this needs to be accounted for. In summary, the committee concluded that the current application was of moderate overall impact.

**DESCRIPTION (provided by applicant):** Complex Regional Pain Syndrome (CRPS) is an often severe chronic pain condition that can develop after acute injury to the extremities. It is characterized by persistent spontaneous pain of greater magnitude than expected given the degree of injury, allodynia, hyperalgesia, edema, and autonomic changes. Effective treatments for CRPS are lacking in part due to inadequate understanding of its pathophysiological mechanisms, which are believed to be multifactorial. The overall objective of the proposed project is to clarify the mechanisms that contribute to development of CRPS in clinical patients following acute trauma. Enhanced knowledge of mechanisms underlying CRPS will help lead to improved treatment targeting and treatment efficacy for CRPS patients, and potentially, identification of interventions to prevent CRPS following acute injury. Common surgical procedures that by their nature produce significant tissue trauma to the extremities provide a potentially useful model for prospective studies that may shed light on mechanisms underlying CRPS. For example, 13% of patients undergoing total knee arthroplasty (TKA) developed CRPS by 6-month follow-up in the only prospective study on this topic. The proposed study will enroll 400 unilateral TKA patients all experiencing similar tissue trauma during the course of surgery. Pain, function, CRPS signs and symptoms (which will be used to derive continuous CRPS scores), and hypothesized CRPS mechanisms will be systematically evaluated at pre-TKA baseline, and again at 6 weeks, 6 months, and 12 months post-TKA. Several potential CRPS mechanisms suggested by prior human and animal laboratory work will be assessed, including altered SNS function (reduced peripheral vasoconstrictive response to cold challenge), elevated proinflammatory cytokines and neuropeptides, and elevated psychological distress. Prior cross-sectional studies reveal reduced somatosensory representation of the affected limb in the brains of CRPS patients. Therefore, a subsample of 20 patients experiencing relatively low pain pre-TKA (low CRPS risk) and 55 patients experiencing relatively high pain pre-TKA (high CRPS risk) will undergo fMRI scanning at pre-TKA baseline, 6-week follow-up, and again at 6-month follow-up to prospectively evaluate the role of altered somatotopic maps in development of long-term CRPS symptomatology. Analyses will utilize the prospective nature of the data to determine the role of potential CRPS mechanisms at pre-TKA baseline and early post-TKA as contributors to the development of CRPS symptomatology at longer-term follow-up. This will be the first prospective study to systematically evaluate multiple hypothesized CRPS mechanisms concurrently in the same clinical patients. Results of the proposed project will clarify mechanisms leading to CRPS not only in post-surgical patients, but also in patients developing CRPS after acute injuries often associated with the condition (e.g., fractures, lacerations, sprains).

**PUBLIC HEALTH RELEVANCE:** Complex Regional Pain Syndrome (CRPS) is an often severe neuropathic chronic pain condition with autonomic features that can occur after tissue injury, including surgical trauma. This study will follow patients undergoing knee replacement surgery over time to clarify the mechanisms contributing to development of post-surgical CRPS. Results will help guide

development of more effective treatments for CRPS, and potentially lead to interventions to prevent CRPS following injury.

### **CRITIQUE 1:**

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

### **Overall Impact:**

#### **Strengths**

- Prospective design assessing the natural progression of CRPS symptoms in a post-surgical TKA population, assessing at baseline, 6 wks, 6 mos, and 12 mos post surgery
- Comprehensive conceptual model based on known mechanisms of CRPS
- Focused examination of four predictors: reduced SNS function, elevated proinflammatory cytokines and neuropeptides, altered brain somatotopy (reduced somatosensory representation of the operated limb), and elevated psychological distress.
- Assembled research team is excellent and experienced in CRPS, pain, and the specific mechanisms suggested for testing

### **1. Significance:**

#### **Strengths**

- CRPS is highly debilitating and the mechanisms of the pain are very poorly understood
- The very few previous prospective studies have limited their examination to demographics and medical comorbidity as predictors, and results have been negative
- Conceptual model of pathophysiological mechanisms is presented and is consistent with known mechanisms, with a priori hypotheses suggested based upon extant literature

### **2. Investigator(s):**

#### **Strengths**

- PI is a productive scholar with many publications and several funded projects in the area of pain mechanisms. His expertise in CRPS is growing rapidly, with 18 publications on CRPS in peer-reviewed journals and 8 book chapters on CRPS
- Although PI has no previous funding in the proposed area (CRPS), he has demonstrated the ability to successfully implement and manage other R01 projects as PI
- The assembled research team supplements the expertise of the PI, adding the necessary expertise in the areas of imaging, immunological/inflammatory measures, genetics, statistics, and assessment of SNS reactivity. The assembled team is excellent for this project, with the inclusion of 4 team members with specific expertise in the area of CRPS, neurobiology of pain (e.g. proinflammatory neuropeptides), brain imaging and pain, and SNS pain mechanisms.

### **3. Innovation:**

#### **Strengths**

- Prospective design, which will allow for causal inferences
- Potential pathophysiological & psychological mechanisms which may predict development of post-surgical CRPS are organized into a coherent conceptual model consistent with known mechanisms

### **4. Approach:**

#### **Strengths**

- Multiple assessments over time (baseline, 6 wks, 6 mos., 12 mos)
- Homogeneous sample (TKA) which provides some control over population variables
- Number of specific aims and number of mechanisms to be explored is based on existing literature, with specified a priori hypotheses
- Outcome variable is continuous (e.g. self-reported CRPS symptoms and clinician-observed signs) rather than dichotomous (either/or) diagnosis of CRPS, thus increasing power to test relationships
- fMRI methodology includes pre-surgical imaging (as well as follow-up imaging), with pre-surgical imaging participants selected by having either high or low risk factors for CRPS development.

### **5. Environment:**

#### **Strengths**

- Exceptionally strong and productive research environment

#### **Protections for Human Subjects:**

Acceptable Risks and/or Adequate Protections

- Well written human subjects section, details adequately described

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

Not Applicable (No Clinical Trials)

#### **Inclusion of Women, Minorities and Children:**

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C3A - No Children Included, Acceptable

- Women will be somewhat oversampled (65%) to maximize female final sample for purposes of statistical power

#### **Vertebrate Animals:**

Not Applicable (No Vertebrate Animals)

**Biohazards:**

Not Applicable (No Biohazards)

**Resubmission:**

- Proposal is much more focused, with potential confounds (e.g. certain predictor variables also being used as outcome variables) eliminated
- Multiple measures that complicated the initial proposal have been eliminated, including removing the genetic component, and dropping the examination of circulating catecholamines; furthermore, inflammatory mechanisms to be examined has been reduced and refined based on existing literature and expert consultation.
- fMRI methodology now includes pre-surgical imaging for low and high-risk subjects
- Continuous measure of CRPS symptoms rather than dichotomous diagnostic judgment now being used as outcome variable
- re-analysis of psychological predictors in existing data set pointing to importance of anxiety and depression (and subsequent inclusion of those variables in the present proposal) strengthens the psychological component of the proposal, as does the inclusion of a measure of catastrophizing.

**Budget and Period of Support:**

Recommend as Requested

**CRITIQUE 2:**

Significance: 4  
Investigator(s): 3  
Innovation: 4  
Approach: 3  
Environment: 3

**Overall Impact:**

**Strengths**

- Greater understanding of the mechanisms of CRPS will help to inform better future treatments for this condition.
- The greatest strength appears to be the individual studies of mechanisms rather than the concurrent study of multiple mechanisms (which is less well described and grounded).
- Understanding the natural history of CRPS as it relates to TKA is an important advance that could occur with this study.

**Weaknesses**

- Scope of the study is too broad. The team is trying to answer too many questions in the context of a single protocol.
- There are too many hypotheses for the relatively small sample of individuals likely to actually have CRPS; thus limiting the generalizability and confidence that can be had in the findings from this study. This limits potential impact.

## **1. Significance:**

### **Strengths**

- Topic addresses a severe pain condition for which relatively little human work has been conducted, pathophysiological mechanisms are poorly understood, and for which effective treatments are lacking.
- Current treatments are often costly and not based upon grounded pathophysiology

### **Weaknesses**

- A focused and rigorous investigation of a single mechanism upon which a program of research could be built would be more likely to significantly impact the field than a study exploring multiple moving targets each of which is poorly understood.

## **2. Investigator(s):**

### **Strengths**

- The PI appears to be productive both in terms of publishing and securing federal support for his research.
- He has studied CRPS primarily from a psychosocial and psychophysiological perspective and brings experience to the team in these areas.
- The neuroimaging team appears particularly strong and combines senior and junior investigators each with evidence of productivity (although not always in human imaging).
- Consultants appear to be highly regarded scholars in their respective fields.

### **Weaknesses**

- The majority of the team is still quite junior with somewhat limited experience in publishing and conducting sponsored research at the R01 level.

## **3. Innovation:**

### **Strengths**

- Use of a common surgical procedure as a model for CRPS is an innovative way of identifying CRPS of a common cause.
- Predictors of TKA outcome include demographics, distress, and other comorbidities but are less than perfect. To these prediction models, the current study adds SNS function, proinflammatory neuropeptides and cytokines and brain imaging so as to suggest that part of TKA failure may be due to the presence of CRPS mechanisms.
- Somatosensory mapping and identification of time course by which asymmetrical alterations in somatotopic representation occur is ground breaking work in this field.

### **Weaknesses**

- Poor outcomes in TKA may be due to the presence of CRPS; but could also be due to surgical technique, problems with the device, adherence to PT and Rehabilitation etc. These factors are mentioned but truly need to be considered as confounds to many of the hypotheses.

## **4. Approach:**

### **Strengths**

- Tests of SNS function seem reasonable
- Tests of cytokines and neuropeptides seem focused and sound

### **Weaknesses**

- While statistical benefits exist for using a continuous measure for CRPS, it would seem important to have a dichotomous research classification for purposes of this mechanistic study.
- The neuroimaging is perhaps one of the more important studies embedded in this application and perhaps the most risky given the recruitment plan. If the single pain predictor is inadequate, this entire imaging aspect of the application could fail.
- Outdated version of BDI is proposed
- Rationale is not clear for why there is significant redundancy in the outcomes assessment for pain and function.
- While the total sample is large (n=400) the actual number likely to have CRPS is small (n=52). Many predictor variables are being explored >40 when subscales are considered. A relatively small number of CRPS patients will be evaluated using a relatively large number of exploratory variables.

## **5. Environment:**

### **Strengths**

- Laboratory, clinical and informatics resources appear sufficient for the conduct of the proposed studies.
- The institution appears to be supportive of the research and of the investigator.

### **Weaknesses**

- No major weaknesses are apparent.

### **Protections for Human Subjects:**

Acceptable Risks and/or Adequate Protections

- Risks and protections are identified

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

Unacceptable

- Not mentioned

### **Inclusion of Women, Minorities and Children:**

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C3A - No Children Included, Acceptable

- Both genders included 61% female
- Minorities included 69% white, 28% African American (no outreach described)
- Study condition is rare in children (i.e, OA, total knee replacement)

### **Vertebrate Animals:**

Not Applicable (No Vertebrate Animals)

**Biohazards:**

Not Applicable (No Biohazards)

**Resubmission:**

- The PI significantly reduced the scope of the current application by dropping many of originally proposed study variables. The current application is still grand in scope but is much improved.

**Budget and Period of Support:**

Recommend as Requested

**CRITIQUE 3:**

Significance: 2

Investigator(s): 3

Innovation: 2

Approach: 5

Environment: 1

**Overall Impact:**

**Strengths**

- A longitudinal study design that is aimed at assessing the natural progression of CRPS in a post-surgical TKA population.
- Very little work that was done on the mechanisms of this disease.

**Weaknesses**

- Unclear impact on the development of a future preventive or therapeutic intervention.
- Large and not focused scope of study with no conceptual framework that ties all the domains studied.
- No preliminary data that will demonstrate the ability of the PI to execute this complex and ambitious study.
- Chance association is highly likely considering the large number of variables studied.
- A large number of co-investigators that have never worked with each other.

**1. Significance:**

**Strengths**

- Many of the components studied in this study are innovative.
- Lack of previous work in this area.

**Weaknesses**

- This is a predictive study with a questionable impact on the management of this disease. Specifically, it is not clear how any of the data obtained will be used for a future intervention.
- As indicated previously by reviewer 2. Some preliminary work and data needs to be done in order to eliminate the many factors and many associations that will be examined.



## **2. Investigator(s):**

### **Strengths**

- The PI has a long and distinguished track record looking at issues related to pain. Although his involvement in CRPS is not that extensive.

### **Weaknesses**

- There are now a (very) large number of investigators with questionable role as it relates to their set of expertise and needs of the study. This team has also never worked with each other and the management of this large team is not well described.

## **3. Innovation:**

### **Strengths**

- Each mechanism was selected carefully with many considerations.

### **Weaknesses**

- It is not clear how the data from this study will be used to develop future interventions. A priori hypothesis are needed.
- This study is mostly exploratory

## **4. Approach:**

### **Weaknesses**

- Large scope and mostly exploratory.
- Lack of preliminary data
- There is a disconnect between the inclusion criteria and the number of TKA performed per year. For example, the authors have to provide data to demonstrate how many of the patients undergoing TKA actually has osteoarthritis.
- In the preliminary study section, some of the refs cited don't reflect the statement made.

## **5. Environment:**

### **Strengths**

- Excellent

### **Weaknesses**

- Unclear If the number of subjects needed will be actually achieved.

## **Protections for Human Subjects:**

Acceptable Risks and/or Adequate Protections

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

Acceptable

## **Inclusion of Women, Minorities and Children:**

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C3A - No Children Included, Acceptable

**Vertebrate Animals:**

Not Applicable (No Vertebrate Animals)

**Biohazards:**

Not Applicable (No Biohazards)

**Budget and Period of Support:**

Recommended budget acceptable.

**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): UNACCEPTABLE**

DSMP is not adequate.

**INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE**

Both genders included 61% female.

**INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE**

Minorities included 69% white, 28% African American (no outreach described).

**INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE**

Study condition is rare in children (i.e., OA, total knee replacement).

**COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.**

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NOTICE: In 2008 NIH modified its policy regarding the receipt of resubmission (formerly termed amended) applications. Detailed information can be found by accessing the following URL address: <http://grants.nih.gov/grants/policy/amendedapps.htm>

## MEETING ROSTER

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#### BMIO

February 04, 2010 - February 05, 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.