DGIM Project Summary

Name of Project: “the Stress and Depression Study”

Investigator(s): (Include phone numbers and email address, indicate PI and primary contact)

Principal Investigator and primary contact: Heather M. Burke, PhD, Health Psychology Program, Dept. of Psychiatry, heather.burke@ucsf.edu.

Co-Investigators: Owen Wolkowitz, MD – LPPI - Dept. of Psychiatry, owen.wolkowitz@ucsf.edu and Margaret Kemeny, PhD – Health Psychology Program, Dept. of Psychiatry, KemenyM@healthpsych.ucsf.edu.

Research question(s):

The purpose of our study is to examine the effects of stress on immune system functioning in women with major depressive disorder (MDD). Specifically, we investigate a potential physiological explanation for the stress sensitization model of depression by examining cytokine responses to an acute psychological stressor as well as the integrity of the feedback effect of hypothalamic-pituitary-adrenal (HPA) axis activity on in vitro production of pro-inflammatory cytokines (eg, pro-inflammatory cytokines such as TNF-a, IL-6, and IL-1-b).

The following hypotheses will be tested:

a. Depressed women will exhibit higher baseline and stress-induced concentrations of pro-inflammatory cytokines than age-matched, non-depressed women, and women with recurrent depression will have the highest concentrations.

b. As indicative of impaired hormone-immune feedback regulation, depressed women will exhibit weaker dexamethasone suppression of in vitro cytokine production than age-matched, non-depressed women, and women with recurrent depression will exhibit the most impaired feedback regulation.

c. The degree of hormone-immune feedback impairment at baseline in depressed women will prospectively predict MDD diagnosis 12 months later.

Brief Background/Significance:

Major depressive disorder (MDD) is a worldwide public health problem, responsible for considerable disability, mortality, cost, and medical comorbidity(Organization 2001). MDD is also a chronic illness, with more than 60% of individuals exhibiting a recurrent course(Monroe and Harkness 2005). The high prevalence and profound consequences of MDD underscores the importance of identifying factors associated with its onset and course.

Psychosocial stressors have been linked with the onset, severity and course of major depressive disorder (MDD) and depressive symptoms. According to the stress-sensitization or kindling model of depression, the stress and depression association is dynamic, with more
significant stressors triggering initial depressive episodes, and less significant stressors capable of triggering subsequent depressive episodes.

While several pathophysiological mechanisms of stress sensitization have been proposed, including alterations in hypothalamic-pituitary-adrenal (HPA) and immune responses to psychological stressors (“the cytokine model of depression”), the physiological basis of the link between stressors and depression is not yet understood. Endocrine-immune interactions, specifically pro-inflammatory cytokine glucocorticoid resistance (GCR), may underlie the stress and depression association.

Thus, the purpose of this proposed study is to test a physiological explanation for the stress sensitization model of depression by examining cytokine responses to an acute psychological stressor and in vitro measures of pro-inflammatory cytokine GCR( in currently depressed and never-depressed women. Results of this study may lead to behavioral and/or novel pharmacological (e.g., anti-cytokine and/or anti-inflammatory agents) anti-depressant treatments for depression. Such treatments would not only benefit individuals with primary MDD, but may also extend to those with comorbid medical illnesses involving inflammatory processes (e.g., cardiovascular disease, coronary heart disease, rheumatoid arthritis, multiple sclerosis).

We are requesting the involvement of the General Medicine department and their patients in order to investigate hormonal and immune responses to stress in pre-menopausal depressed women.

**Inclusion/exclusion criteria (list)**

**Inclusion:**
- Pre-menopausal women between 21-50
- Major depressive disorder
- Able to understand and speak English
- General medical health

**Exclusion:**
- Males and/or transgender individuals
- Past /current post-traumatic stress disorder
- Past/current bipolar mood disorder
- Active substance abuse
- Pregnancy
- Medications that could affect the biomarkers in this study
- Medical conditions that could affect the biomarkers in this study
- Clinically significant suicidal ideation or elevated risk for suicide (eg, suicidal ideation, plan, intent, prior attempt, hopelessness)

**Method of contact/recruitment (be specific):**

We are flexible based on the departmental constraints. Our recruitment strategies specific to the GMC include placement of flyers and/or brochures in the waiting areas of the GMC and
identification of potential participants using the DGIM database.

Patients who see the flyers and/or brochures and are interested in participating will contact our study directly, either by email or phone. Patients identified in the DGIM database as potentially eligible to participate will be contacted with their preferred method of contact (eg, phone, mail, or email) by our study staff.

At the time of initial contact, our trained study interviewers will briefly explain the study and determine potential eligibility using a telephone screening interview. After the initial telephone screening interview, the interviewer will schedule an in-person Eligibility Visit during which consent will be obtained, a history and physical examination will be performed by a study physician and a psychiatric interview will be conducted to verify a depression diagnosis.

**Benefits/burden for participants**

There are no direct benefits to patients, but they will improve our understanding of the contributions of stress to the pathophysiology of depression. The major burdens to participants are the amount of time involved and inconvenience. To offset this burden, we have limited participation to 1 study visit, spread out the interviews and questionnaires over a longer period of time and will compensate individuals $175 for completing the study. Participants do not need to complete any aspects of the study that they do not want to, and payment will be prorated to the amount of completed procedures.

The primary risks associated with the study include distress from discussing sensitive topics about depressive symptoms and possible bleeding and bruising at the puncture site with a small chance of infection. Risks are minimized by restricting contact with the subjects to trained research assistants supervised by the PI, who is a licensed psychologist. Participants will be told that they do not need to answer any questions that they do not feel comfortable answering. To reduce risk of bruising and infection following the blood draw, blood will be collected in a sterile manner by experienced research nurses at the Clinical Research Center, with pressure placed on the venipuncture site following removal of the IV.

**Any benefits or burden to DGIM practitioners?**

While there are no direct or immediate benefits to DGIM practitioners, their efforts will contribute to the understanding of the biology of depression. We expect to require little effort by DGIM staff. Our study staff will bear responsibility for all study activities, and will conduct the pre-screening records review, contact potentially eligible participants who have agreed to be contacted about research projects and perform all screening interviews and testing. We will work with DGIM staff to determine the best times for the study staff to conduct the database reviews at the clinic.

**Timeline for recruitment (projected start and stop dates)**

We anticipate starting recruitment ASAP and will continue until we have at least 25 women with depression and 25 controls matched by age or up to 8/1/11 (whichever is sooner).
**Funding source**

This study funded by a NIMH Career Development Award (K08).

**Potential for DGIM collaborators? (We encourage DGIM resident and fellow involvement in particular)**

If residents, fellows and/or faculty are interested in our work, we would be happy to collaborate with any aspect of the study.

**Do you agree to notify us when recruitment is completed?**

Yes

**Date form completed**

4/16/09