**Proposal**

**Objective**

To develop a model collaboration between an Intramural Investigator in the NHGRI Social and Behavioral Research Branch, Division of Intramural Research (Bonham lab) and OBBSR.

To pilot and examine strategies for the integration of BSSR and biomedical research using an interdisciplinary health disparities research model.

To collaborate with OBBSR staff member Katherine Blizinsky, Ph.D to conduct social, behavioral and genomic research and contribute to NHGRI intramural team science health disparities program.

**Background**

The mission of the Health Disparities Unit within the Social and Behavioral Research Branch is to evaluate approaches that integrate new genomic knowledge and precision medicine into clinical settings without exacerbating inequities in healthcare delivery. This Unit conducts research related to the science of health disparities through the disciplines of social science, health services, genomics, and biopsychosocial research. Therefore, my research is conducted in partnership with a multidisciplinary team of investigators and trainees who are at the intersection of public health, medicine, and genomics. The Bonham Lab specifically focuses on examining how new genomic knowledge, technologies, and medicine may affect health disparities in underserved and ethnically diverse populations, and explores the social and clinical implications of “race” within the context of genetics and genomics.

The Bonham Lab has accepted this challenge to conduct studies that aim to understand how concepts of race and ethnicity play a role in the social and clinical implications of health, particularly within the context of genetic and genomic science. To this end, a major goal of my research program is to provide the research community with new tools and knowledge that assess how health care providers use their perceptions of race in clinical practice and in their beliefs and knowledge of genetic variation.

In 2014 the research program has expanded in scope by introducing a biopsychosocial model into our work to study the socio-ecological influence on clinical variation of sickle cell disease. This research incorporates basic genomic, clinical, and psychosocial methods to understand this disease that disproportionately affects underserved and ethnically diverse populations within the United States. We are interested both in the outcomes of this research project and examining its utility as a model for team science approaches, particularly in the area of health disparities research.

**Project**

**Examining Psychosocial, Genomic, and Clinical Implications of Sickle Cell Disease**

**Specific Aim:** *To employ microbiome, socio-ecological and genomic approaches to characterize factors that may influence clinical variation in sickle cell disease of individuals living with and without leg ulcers*

We utilize leg ulcers as a model to examine how the environment (physical and social) and the microbiome and immune system likely modulate leg ulcer formation and the healing process in SCD patients. The central goal of this study is to explore the leg ulcer microbiome, as well as the psychosocial and environmental factors that may increase one's likelihood of developing this complication. To achieve these goals, the study is characterizing the leg skin microbiome of SCD patients in the United States, collecting biomarker data, and using social science measures to assess the physical environment and psychosocial status (e.g., stress, discrimination, stigma and depression) of individuals with and without leg ulcers.

***Significance:*** This study integrates research from multiple disciplines to understand SCD and leg ulceration in SCD. To our knowledge, this is the first program of research to explore how these factors modulate leg ulcer formation and healing among SCD patients. The project investigates four distinct areas of research to uncover why SCD patients develop leg ulcers and how to intervene to reduce severity and facilitate healing.

***Innovation:*** The INSIGHTS study serves as a model for interdisciplinary research. We have integrated data, methodologies, and personnel expertise related to microbiome, clinical, environmental, and psychosocial factors to study interaction that influence formation and healing of leg ulcers. This team science model will guide our approach to investigate the etiology of leg ulceration, which is currently unknown. Our conceptual framework hypothesizes that microbes, clinical phenotype (e.g., blood pressure, Hemoglobin F, cytokines, stress levels), environmental factors (e.g., exposures at home and at work, diet), and psychosocial factors (e.g., stress, stigma, discrimination, depression) impair the immune system. (Figure 1)

Figure 1. INSIGHTS Conceptual Model

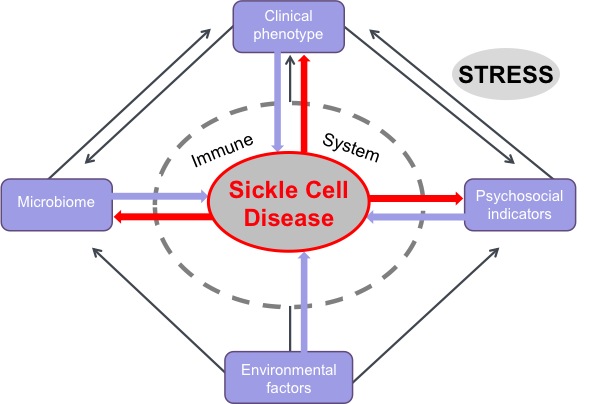


Figure Legend:

A model framework for the role of the environment and microbiome in leg ulcer formation and healing in sickle cell disease

***Preliminary Data:***

***Microbiome:*** In collaboration with Elizabeth Grice, Ph.D. at the University of Pennsylvania and postdoctoral fellow, Keisha Findley, Ph.D., we sequenced 16S rRNA bacterial sequences from the skin of the first 12 (five with active ulcers) study participants using the Illumina MiSeq Technology. Approximately 1.3 million sequences were taxonomically classified using the online molecular ecology tool, mothur, and the RDP classifier and training set (version 9).

The relative abundance of bacteria on the ankles of SCD participants with and without leg ulcers is distinct. Those with leg ulcers have lower bacterial diversity and an abundance of the skin commensal, *Staphylococcus,* while those without leg ulcers display higher bacterial diversity. This finding supports the claim that microbial diversity is higher in a healthy state and is conversely, lower in a disease state. Additionally, we conducted Principle Coordinate Analysis (PCoA) using thetayc distances comparing bacterial community structure (similarity) in participants with and without leg ulcers. This analysis confirmed that two communities differ, and we speculate that this variation could potentially explain the differences in the skin microbiome of individuals with SCD who develop leg ulcers over their life course. We are currently processing microbiome samples as they are collected and will complete the sequence analysis when the data is available.

**Microbiome Data**

**Figure Y: Bacterial relative abundance plots in participants living with sickle cell disease leg ulcers.**



Figure Legend:

Approximately 1.3 million 16S rRNA bacterial sequences were taxonomically classified using the online molecular ecology tool, mothur, and the RDP classifier and training set (version 9). Participants #0002, 0003, and 0005 are shown. Swab samples were collected from an ulcer and the contralateral leg without an ulcer and samples were sequenced.

***Clinical:*** We have examined erythrocyte sedimentation rate (ESR), hematocrit (hct) and hemoglobin (Hb), white blood cell count (WBC), fetal hemoglobin (HbF), Hemoglobin S (HgS), reticulocyte count, and C-reactive protein (CRP) levels in our preliminary analysis. For the first [56] participants recruited to the study, we compared clinical lab results in patients with (n= 40) and without leg ulcers (n= 16). We found that the hematocrit, hemoglobin, WBC, and ESR laboratory measures were significantly different between the leg ulcer and non-leg ulcer groups (p<0.1) . More specifically, the leg ulcer group had slightly higher mean values for absolute reticulocyte count, WBC, HgS, CRP and ESR (p=0.72, p<0.05, 0.87, 0.16, , and p<0.1, respectively), but lower mean values for hemoglobin (Hb) , hematocrit (hct) and fetal hemoglobin (HbF) (p<0.05, p<0.05, and p=0.22, respectively).

***Psychosocial:*** We examined psychosocial data for the first 56 participants. The following social measures were examined: discrimination experience due to SCD stigma (discrimination stigma), social withdrawal due to SCD stigma (social withdrawal stigma), resistance to SCD Stigma (stigma resistance), stress from everyday discrimination (discrimination stress), and the Cohen perceived stress measure (PSS). The Cohen stress measure is a 10-item scale that examines participant’s perception of how unpredictable, uncontrollable, and overloaded their lives are. The scale is a sum of the responses to those 10 items, ranging from 0 to 40. Data derived from a 2,387-sample study found that the mean PSS score was 13.02 (SD ± 6.35). In our study, the mean PSS score for all participants, both with and without ulcerations, was 19.60 (SD ± 7.65), thus indicating that participants with SCD reported higher levels of perceived stress than the population average.

When comparing mean values between those with and those without leg ulcers in our study, the preliminary results revealed significant differences in the stigma resistance scores, however, only minor differences were found for the remaining measures. More specifically, for the leg ulcer group, the average stigma resistance score was 2.92 (SD ± 0.46) compared with 3.13 (SD ± 0.48) in the non-leg ulcer group (p<0.1), thus indicating that those with leg ulcers are significantly less likely to resist disease stigma. The leg ulcer group also had higher average scores for the following measures: social withdrawal stigma, discrimination stress, and Cohen stress (p=0.35, 0.86, and 0.87, respectively).

***Proposed Collaboration with OBBSR:*** To collaborate with the INSIGHTS study team to participate in the analysis of the biopsychosocial (microbiome, RNA expression profiling, social and environment data). We will study many factors that may be involved in the phenotypic variation in the disease including leg ulcers. To accomplish these objectives, the INSIGHTS team requires someone with genomics, data science, and statistical skill sets, as well as an understanding of psychosocial measures. In return, OBSSR will have the opportunity to examine the process of BSSR-biomedical research integration and disseminate key strategies based on the INSIGHTS model.